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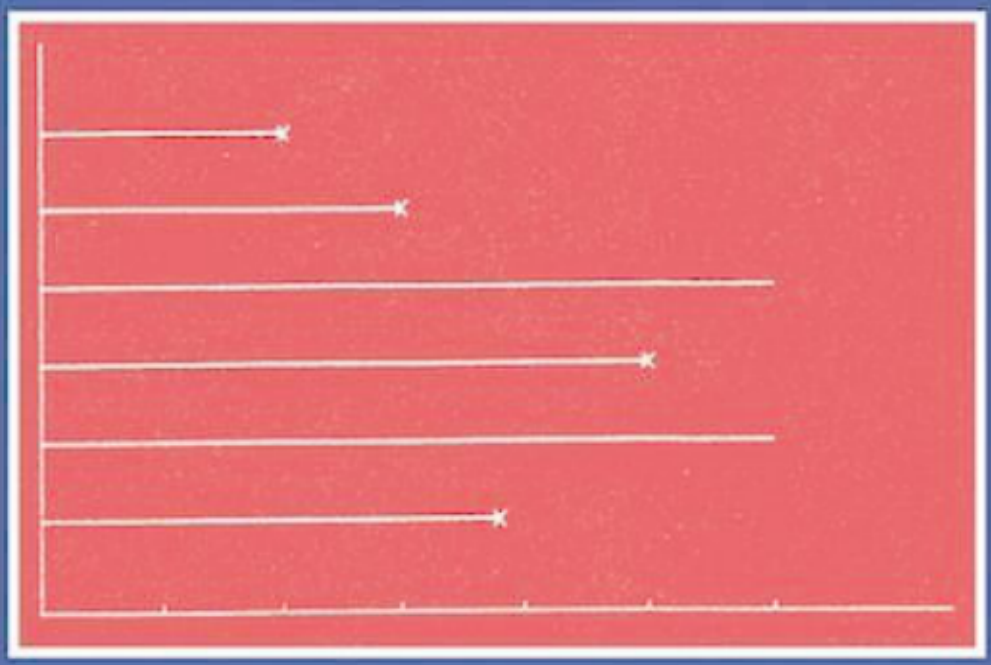


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Statistical Methods for Survival Data Analysis

Third Edition



Elisa T. Lee
John Wenyu Wang

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WILEY SERIES IN PROBABILITY AND STATISTICS

Statistical Methods for Survival Data Analysis

Statistical Methods for Survival Data Analysis

Third Edition

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To the memory of our parents

Mr. Chi-Lan Tan and Mrs. Hwei-Chi Lee Tan
(E.T.L.)

Mr. Beijun Zhang and Mrs. Xiangyi Wang
(J.W.W.)

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Preface

Statistical methods for survival data analysis have continued to flourish in the last two decades. Applications of the methods have been widened from their historical use in cancer and reliability research to business, criminology, epidemiology, and social and behavioral sciences. The third edition of *Statistical Methods for Survival Data Analysis* is intended to provide a comprehensive introduction of the most commonly used methods for analyzing survival data. It begins with basic definitions and interpretations of survival functions. From there, the reader is guided through methods, parametric and nonparametric, for estimating and comparing these functions and the search for a theoretical distribution (or model) to fit the data. Parametric and nonparametric approaches to the identification of prognostic factors that are related to survival are then discussed. Finally, regression methods, primarily linear logistic regression models, to identify risk factors for dichotomous and polychotomous outcomes are introduced.

The third edition continues to be application-oriented, with a minimum level of mathematics. In a few chapters, some knowledge of calculus and matrix algebra is needed. The few sections that introduce the general mathematical structure for the methods can be skipped without loss of continuity. A large number of practical examples are given to assist the reader in understanding the methods and applications and in interpreting the results. Readers with only college algebra should find the book readable and understandable.

There are many excellent books on clinical trials. We therefore have deleted the two chapters on the subject that were in the second edition. Instead, we have included discussions of more statistical methods for survival data analysis. A brief summary of the improvements made for the third edition is given below.

1. Two additional distributions, the log-logistic distribution and a generalized gamma distribution, have been added to the application of parametric models that can be used in model fitting and prognostic factor identification (Chapters 6, 7, and 11).

2. In several sections (Sections 7.1, 9.1, 10.1, 11.2, and 12.1), discussions of the asymptotic likelihood inference of the methods covered in the chapters are given. These sections are intended to provide a more general mathematical structure for statisticians.
3. The Cox–Snell residual method has been added to the chapter on graphical methods for survival distribution fitting (Chapter 8). In addition, the sections on probability and hazard plotting have been revised so that no special graphical papers are required to make the plots.
4. More tests of goodness of fit are given, including the BIC and AIC procedures (Chapters 9 and 11).
5. For Cox's proportional hazards model (Chapter 12), we have now included methods to assess its adequency and procedures to estimate the survivorship function with covariates.
6. The concept of nonproportional hazards models is introduced (Chapter 13), which includes models with time-dependent covariates, stratified models, competing risks models, recurrent event models, and models for related observations.
7. The chapter on linear logistic regression (Chapter 14) has been expanded to cover regression models for polychotomous outcomes. In addition, methods for a general $m:n$ matching design have been added to the section on conditional logistic regression for case–control studies.
8. Computer programming codes for software packages BMDP, SAS, and SPSS are provided for most examples in the text.

We would like to thank the many researchers, teachers, and students who have used the second edition of the book. The suggestions for improvement that many of them have provided are invaluable. Special thanks go to Xing Wang, Linda Hutton, Tracy Mankin, and Imran Ahmed for typing the manuscript. Steve Quigley of John Wiley convinced us to work on a third edition. We thank him for his enthusiasm.

Finally, we are most grateful to our families, Sam, Vivian, Benedict, Jennifer, and Annelisa (E.T.L.), and Alice and Xing (J.W.W.), for the constant joy, love, and support they have given us.

ELISA T. LEE
JOHN WENYU WANG

Oklahoma City, OK
April 18, 2001

CHAPTER 1

Introduction

1.1 PRELIMINARIES

This book is for biomedical researchers, epidemiologists, consulting statisticians, students taking a first course on survival data analysis, and others interested in survival time study. It deals with statistical methods for analyzing survival data derived from laboratory studies of animals, clinical and epidemiologic studies of humans, and other appropriate applications.

Survival time can be defined broadly as the time to the occurrence of a given event. This event can be the development of a disease, response to a treatment, relapse, or death. Therefore, survival time can be tumor-free time, the time from the start of treatment to response, length of remission, and time to death. Survival data can include survival time, response to a given treatment, and patient characteristics related to response, survival, and the development of a disease. The study of survival data has focused on predicting the probability of response, survival, or mean lifetime, comparing the survival distributions of experimental animals or of human patients and the identification of risk and/or prognostic factors related to response, survival, and the development of a disease. In this book, special consideration is given to the study of survival data in biomedical sciences, although all the methods are suitable for applications in industrial reliability, social sciences, and business. Examples of survival data in these fields are the lifetime of electronic devices, components, or systems (reliability engineering); felons' time to parole (criminology); duration of first marriage (sociology); length of newspaper or magazine subscription (marketing); and worker's compensation claims (insurance) and their various influencing risk or prognostic factors.

1.2 CENSORED DATA

Many researchers consider survival data analysis to be merely the application of two conventional statistical methods to a special type of problem: *parametric* if the distribution of survival times is known to be normal and *nonparametric*

if the distribution is unknown. This assumption would be true if the survival times of all the subjects were exact and known; however, some survival times are not. Further, the survival distribution is often skewed, or far from being normal. Thus there is a need for new statistical techniques. One of the most important developments is due to a special feature of survival data in the life sciences that occurs when some subjects in the study have not experienced the event of interest at the end of the study or time of analysis. For example, some patients may still be alive or disease-free at the end of the study period. The exact survival times of these subjects are unknown. These are called *censored observations* or *censored times* and can also occur when people are lost to follow-up after a period of study. When these are not censored observations, the set of survival times is *complete*. There are three types of censoring.

Type I Censoring

Animal studies usually start with a fixed number of animals, to which the treatment or treatments is given. Because of time and/or cost limitations, the researcher often cannot wait for the death of all the animals. One option is to observe for a fixed period of time, say six months, after which the surviving animals are sacrificed. Survival times recorded for the animals that died during the study period are the times from the start of the experiment to their death. These are called *exact* or *uncensored observations*. The survival times of the sacrificed animals are not known exactly but are recorded as at least the length of the study period. These are called *censored observations*. Some animals could be lost or die accidentally. Their survival times, from the start of experiment to loss or death, are also censored observations. In *type I censoring*, if there are no accidental losses, all censored observations equal the length of the study period.

For example, suppose that six rats have been exposed to carcinogens by injecting tumor cells into their foot pads. The times to develop a tumor of a given size are observed. The investigator decides to terminate the experiment after 30 weeks. Figure 1.1 is a plot of the development times of the tumors. Rats A, B, and D developed tumors after 10, 15, and 25 weeks, respectively. Rats C and E did not develop tumors by the end of the study; their tumor-free times are thus 30-plus weeks. Rat F died accidentally without tumors after 19 weeks of observation. The survival data (tumor-free times) are 10, 15, 30+, 25, 30+, and 19+ weeks. (The plus indicates a censored observation.)

Type II Censoring

Another option in animal studies is to wait until a fixed portion of the animals have died, say 80 of 100, after which the surviving animals are sacrificed. In this case, *type II censoring*, if there are no accidental losses, the censored observations equal the largest uncensored observation. For example, in an experiment of six rats (Figure 1.2), the investigator may decide to terminate the study after four of the six rats have developed tumors. The survival or tumor-free times are then 10, 15, 35+, 25, 35, and 19+ weeks.

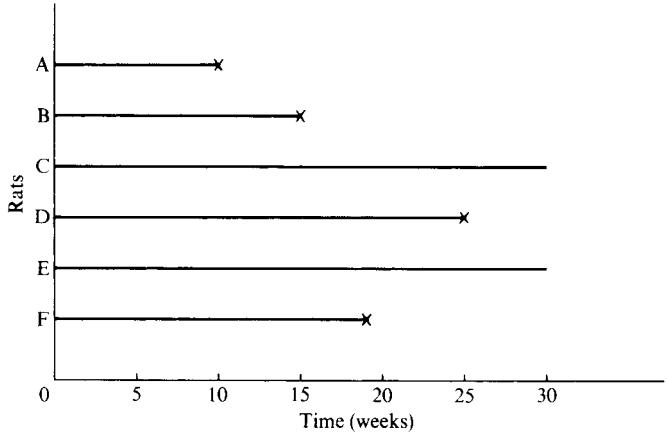


Figure 1.1 Example of type I censored data.

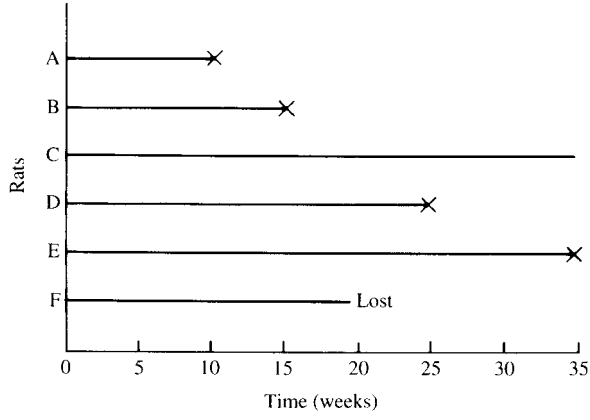


Figure 1.2 Example of type II censored data.

Type III Censoring

In most clinical and epidemiologic studies the period of study is fixed and patients enter the study at different times during that period. Some may die before the end of the study; their exact survival times are known. Others may withdraw before the end of the study and are lost to follow-up. Still others may be alive at the end of the study. For "lost" patients, survival times are at least from their entrance to the last contact. For patients still alive, survival times are at least from entry to the end of the study. The latter two kinds of observations are censored observations. Since the entry times are not simultaneous, the censored times are also different. This is *type III censoring*. For example, suppose that six patients with acute leukemia enter a clinical study

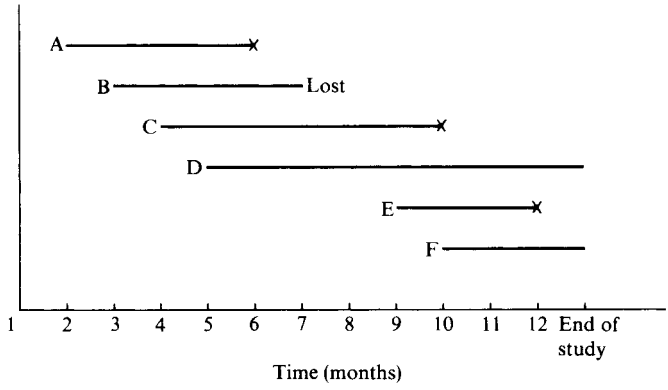


Figure 1.3 Example of type III censored data.

during a total study period of one year. Suppose also that all six respond to treatment and achieve remission. The remission times are plotted in Figure 1.3. Patients A, C, and E achieve remission at the beginning of the second, fourth, and ninth months, and relapse after four, six, and three months, respectively. Patient B achieves remission at the beginning of the third month but is lost to follow-up four months later; the remission duration is thus at least four months. Patients D and F achieve remission at the beginning of the fifth and tenth months, respectively, and are still in remission at the end of the study; their remission times are thus at least eight and three months. The respective remission times of the six patients are 4, 4+, 6, 8+, 3, and 3+ months.

Type I and type II censored observations are also called *singly censored data*, and type III, *progressively censored data*, by Cohen (1965). Another commonly used name for type III censoring is *random censoring*. All of these types of censoring are *right censoring* or *censoring to the right*. There are also left censoring and interval censoring cases. *Left censoring* occurs when it is known that the event of interest occurred prior to a certain time t, but the exact time of occurrence is unknown. For example, an epidemiologist wishes to know the age at diagnosis in a follow-up study of diabetic retinopathy. At the time of the examination, a 50-year-old participant was found to have already developed retinopathy, but there is no record of the exact time at which initial evidence was found. Thus the age at examination (i.e., 50) is a left-censored observation. It means that the age of diagnosis for this patient is *at most* 50 years.

Interval censoring occurs when the event of interest is known to have occurred between times a and b. For example, if medical records indicate that at age 45, the patient in the example above did not have retinopathy, his age at diagnosis is between 45 and 50 years.

We will study descriptive and analytic methods for complete, singly censored, and progressively censored survival data using numerical and graphical

techniques. Analytic methods discussed include parametric and nonparametric. Parametric approaches are used either when a suitable model or distribution is fitted to the data or when a distribution can be assumed for the population from which the sample is drawn. Commonly used survival distributions are the exponential, Weibull, lognormal, and gamma. If a survival distribution is found to fit the data properly, the survival pattern can then be described by the parameters in a compact way. Statistical inference can be based on the distribution chosen. If the search for an appropriate model or distribution is too time consuming or not economical or no theoretical distribution adequately fits the data, nonparametric methods, which are generally easy to apply, should be considered.

1.3 SCOPE OF THE BOOK

This book is divided into four parts.

Part I (Chapters 1, 2, and 3) defines survival functions and gives examples of survival data analysis. Survival distribution is most commonly described by three functions: the survivorship function (also called the cumulative survival rate or survival function), the probability density function, and the hazard function (hazard rate or age-specific rate). In Chapter 2 we define these three functions and their equivalence relationships. Chapter 3 illustrates survival data analysis with five examples taken from actual research situations. Clinical and laboratory data are systematically analyzed in progressive steps and the results are interpreted. Section and chapter numbers are given for quick reference. The actual calculations are given as examples or left as exercises in the chapters where the methods are discussed. Four sets of data are provided in the exercise section for the reader to analyze. These data are referred to in the various chapters.

In Part II (Chapters 4 and 5) we introduce some of the most widely used nonparametric methods for estimating and comparing survival distributions. Chapter 4 deals with the nonparametric methods for estimating the three survival functions: the Kaplan and Meier product-limit (PL) estimate and the life-table technique (population life tables and clinical life tables). Also covered is standardization of rates by direct and indirect methods, including the standardized mortality ratio. Chapter 5 is devoted to nonparametric techniques for comparing survival distributions. A common practice is to compare the survival experiences of two or more groups differing in their treatment or in a given characteristic. Several nonparametric tests are described.

Part III (Chapters 6 to 10) introduces the parametric approach to survival data analysis. Although nonparametric methods play an important role in survival studies, parametric techniques cannot be ignored. In Chapter 6 we introduce and discuss the exponential, Weibull, lognormal, gamma, and log-logistic survival distributions. Practical applications of these distributions taken from the literature are included.

An important part of survival data analysis is model or distribution fitting. Once an appropriate statistical model for survival time has been constructed and its parameters estimated, its information can help predict survival, develop optimal treatment regimens, plan future clinical or laboratory studies, and so on. The graphical technique is a simple informal way to select a statistical model and estimate its parameters. When a statistical distribution is found to fit the data well, the parameters can be estimated by analytical methods. In Chapter 7 we discuss analytical estimation procedures for survival distributions. Most of the estimation procedures are based on the maximum likelihood method. Mathematical derivations are omitted; only formulas for the estimates and examples are given. In Chapter 8 we introduce three kinds of graphical methods: probability plotting, hazard plotting, and the Cox–Snell residual method for survival distribution fitting. In Chapter 9 we discuss several tests of goodness of fit and distribution selection. In Chapter 10 we describe several parametric methods for comparing survival distributions.

A topic that has received increasing attention is the identification of prognostic factors related to survival time. For example, who is likely to survive longest after mastectomy, and what are the most important factors that influence that survival? Another subject important to both biomedical researchers and epidemiologists is identification of the risk factors related to the development of a given disease and the response to a given treatment. What are the factors most closely related to the development of a given disease? Who is more likely to develop lung cancer, diabetes, or coronary disease? In many diseases, such as cancer, patients who respond to treatment have a better prognosis than patients who do not. The question, then, relates to what the factors are that influence response. Who is more likely to respond to treatment and thus perhaps survive longer?

Part IV (Chapters 11 to 14) deals with prognostic/risk factors and survival times. In Chapter 11 we introduce parametric methods for identifying important prognostic factors. Chapters 12 and 13 cover, respectively, the Cox proportional hazards model and several nonproportional hazards models for the identification of prognostic factors. In the final chapter, Chapter 14, we introduce the linear logistic regression model for binary outcome variables and its extension to handle polychotomous outcomes.

In Appendix A we describe a numerical procedure for solving nonlinear equations, the Newton–Raphson method. This method is suggested in Chapters 7, 11, 12, and 13. Appendix B comprises a number of statistical tables.

Most nonparametric techniques discussed here are easy to understand and simple to apply. Parametric methods require an understanding of survival distributions. Unfortunately, most of survival distributions are not simple. Readers without calculus may find it difficult to apply them on their own. However, if the main purpose is not model fitting, most parametric techniques can be substituted for by their nonparametric competitors. In fact, a large percentage of survival studies in clinical or epidemiological journals are analyzed by nonparametric methods. Researchers not interested in survival

model fitting should read the chapters and sections on nonparametric methods. Computer programs for survival data analysis are available in several commercially available software packages: for example, BMDP, SAS, and SPSS. These computer programs are referred to in various chapters when applicable. Computer programming codes are given for many of the examples.

Bibliographical Remarks

Cross and Clark (1975) was the first book to discuss parametric models and nonparametric and graphical techniques for both complete and censored survival data. Since then, several other books have been published in addition to the first edition of this book (Lee, 1980, 1992). Elandt-Johnson and Johnson (1980) discuss extensively the construction of life tables, model fitting, competing risk, and mathematical models of biological processes of disease progression and aging. Kalbfleisch and Prentice (1980) focus on regression problems with survival data, particularly Cox's proportional hazards model. Miller (1981) covers a number of parametric and nonparametric methods for survival analysis. Cox and Oakes (1984) also cover the topic concisely with an emphasis on the examination of explanatory variables.

Nelson (1982) provides a good discussion of parametric, nonparametric, and graphical methods. The book is more suited for industrial reliability engineers than for biomedical researchers, as are Hahn and Shapiro (1967) and Mann et al. (1974). In addition, Lawless (1982) gives a broad coverage of the area with applications in engineering and biomedical sciences.

More recent publications include Marubini and Valsecchi (1994), Kleinbaum (1995), Klein and Moeschberger (1997), and Hosmer and Lemeshow (1999). Most of these books take a more rigorous mathematical approach and require knowledge of mathematical statistics.

CHAPTER 2

Functions of Survival Time

Survival time data measure the time to a certain event, such as failure, death, response, relapse, the development of a given disease, parole, or divorce. These times are subject to random variations, and like any random variables, form a distribution. The distribution of survival times is usually described or characterized by three functions: (1) the survivorship function, (2) the probability density function, and (3) the hazard function. These three functions are mathematically equivalent — if one of them is given, the other two can be derived.

In practice, the three functions can be used to illustrate different aspects of the data. A basic problem in survival data analysis is to estimate from the sampled data one or more of these three functions and to draw inferences about the survival pattern in the population. In Section 2.1 we define the three functions and in Section 2.2, discuss the equivalence relationship among the three functions.

2.1 DEFINITIONS

Let T denote the survival time. The distribution of T can be characterized by three equivalent functions.

Survivorship Function (or Survival Function)
This function, denoted by $S(t)$, is defined as the probability that an individual survives longer than t:

$$\begin{aligned} S(t) &= P \text{ (an individual survives longer than } t) \\ &= P(T > t) \end{aligned} \tag{2.1.1}$$

From the definition of the cumulative distribution function $F(t)$ of T,

$$\begin{aligned} S(t) &= 1\text{-}P \text{ (an individual fails before } t) \\ &= 1 - F(t) \end{aligned} \tag{2.1.2}$$

Here $S(t)$ is a nonincreasing function of time t with the properties

$$S(t) = \begin{cases} 1 & \text{for } t = 0 \\ 0 & \text{for } t = \infty \end{cases}$$

That is, the probability of surviving at least at the time zero is 1 and that of surviving an infinite time is zero.

The function $S(t)$ is also known as the *cumulative survival rate*. To depict the course of survival, Berkson (1942) recommended a graphic presentation of $S(t)$. The graph of $S(t)$ is called the *survival curve*. A steep survival curve, such as the one shown in Figure 2.1*a*, represents low survival rate or short survival time. A gradual or flat survival curve such as in Figure 2.1*b* represents high survival rate or longer survival.

The survivorship function or the survival curve is used to find the 50th percentile (the median) and other percentiles (e.g., 25th and 75th) of survival time and to compare survival distributions of two or more groups. The median survival times in Figure 2.1*a* and *b* are approximately 5 and 36 units of time, respectively. The mean is generally used to describe the central tendency of a distribution, but in survival distributions the median is often better because a small number of individuals with exceptionally long or short lifetimes will cause the mean survival time to be disproportionately large or small.

In practice, if there are no censored observations, the survivorship function is estimated as the proportion of patients surviving longer than t:

$$\hat{S}(t) = \frac{\text{number of patients surviving longer than } t}{\text{total number of patients}} \tag{2.1.3}$$

where the circumflex denotes an *estimate* of the function. When censored observations are present, the numerator of (2.1.3) cannot always be determined. For example, consider the following set of survival data: 4, 6, 6+, 10+, 15, 20.

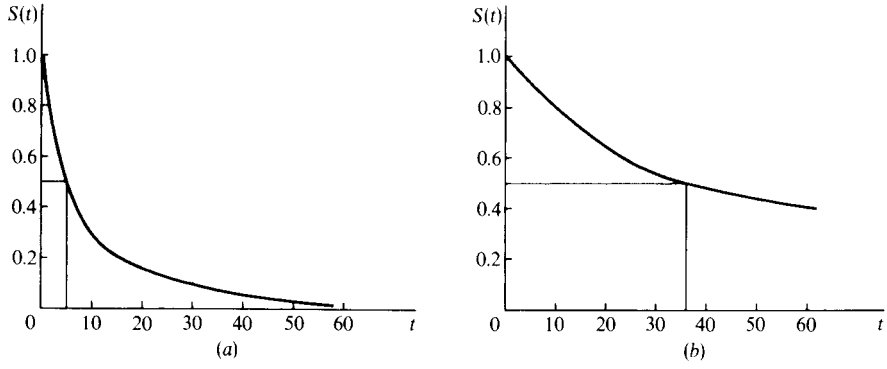


Figure 2.1 Two examples of survival curves.

Using (2.1.3), we can compute $\hat{S}(5) = 5/6 = 0.833$. However, we cannot obtain $\hat{S}(11)$ since the exact number of patients surviving longer than 11 is unknown. Either the third or the fourth patient (6+ and 10+) could survive longer than or less than 11. Thus, when censored observations are present, (2.1.3) is no longer appropriate for estimating $S(t)$. Nonparametric methods of estimating $S(t)$ for censored data are discussed in Chapter 4.

Probability Density Function (or Density Function)

Like any other continuous random variable, the survival time T has a probability density function defined as the limit of the probability that an individual fails in the short interval t to $t + \Delta t$ per unit width Δt, or simply the probability of failure in a small interval per unit time. It can be expressed as

$$f(t) = \frac{\lim_{\Delta t \to 0} P[\text{an individual dying in the interval } (t,\ t + \Delta t)]}{\Delta t} \tag{2.1.4}$$

The graph of $f(t)$ is called the *density curve*. Figure 2.2*a* and *b* give two examples of the density curve. The density function has the following two properties:

1. $f(t)$ is a nonnegative function:

$$\begin{aligned} f(t) &\geqslant 0 \qquad \text{for all } t \geqslant 0 \\ &= 0 \qquad \text{for } t < 0 \end{aligned}$$

2. The area between the density curve and the t axis is equal to 1.

In practice, if there are no censored observations, the probability density function $f(t)$ is estimated as the proportion of patients dying in an interval per

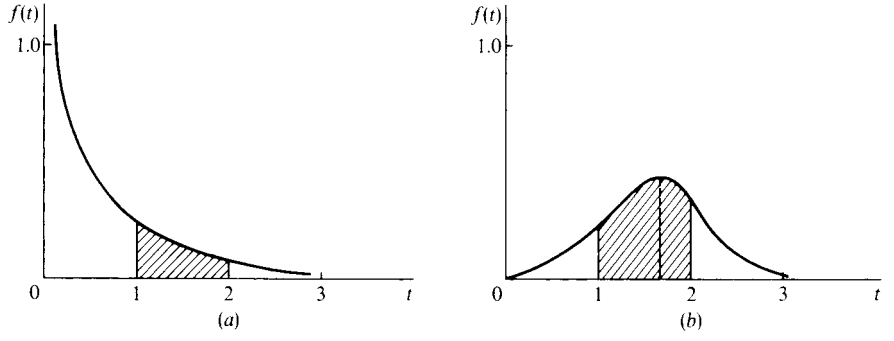


Figure 2.2 Two examples of density curves.

unit width:

$$\hat{f}(t) = \frac{\text{number of patients dying in the interval beginning at time } t}{(\text{total number of patients}) \times (\text{interval width})} \tag{2.1.5}$$

Similar to the estimation of $S(t)$, when censored observations are present, (2.1.5) is not applicable. We discuss an appropriate method in Chapter 4.

The proportion of individuals that fail in any time interval and the peaks of high frequency of failure can be found from the density function. The density curve in Figure 2.2*a* gives a pattern of high failure rate at the beginning of the study and decreasing failure rate as time increases. In Figure 2.2*b*, the peak of high failure frequency occurs at approximately 1.7 units of time. The proportion of individuals that fail between 1 and 2 units of time is equal to the shaded area between the density curve and the axis. The density function is also known as the *unconditional failure rate*.

Hazard Function

The hazard function $h(t)$ of survival time T gives the *conditional failure rate*. This is defined as the probability of failure during a very small time interval, assuming that the individual has survived to the beginning of the interval, or as the limit of the probability that an individual fails in a very short interval, $t + \Delta t$, given that the individual has survived to time t:

$$h(t) = \frac{\lim_{\Delta t \to 0} P\left[\begin{array}{c}\text{an individual fails in the time interval } (t,\ t + \Delta t) \\ \text{given the individual has survived to } t\end{array}\right]}{\Delta t} \tag{2.1.6}$$

The hazard function can also be defined in terms of the cumulative distribution function $F(t)$ and the probability density function $f(t)$:

$$h(t) = \frac{f(t)}{1 - F(t)} \tag{2.1.7}$$

The hazard function is also known as the *instantaneous failure rate*, *force of mortality*, *conditional mortality rate*, and *age-specific failure rate*. If t in (2.1.6) is age, it is a measure of the proneness to failure as a function of the age of the individual in the sense that the quantity $\Delta t h(t)$ is the expected proportion of age t individuals who will fail in the short time interval $t + \Delta t$. The hazard function thus gives the risk of failure per unit time during the aging process. It plays an important role in survival data analysis.

In practice, when there are no censored observations the hazard function is estimated as the proportion of patients dying in an interval per unit time, given

that they have survived to the beginning of the interval:

$$\hat{h}(t) = \frac{\text{number of patients dying in the interval beginning at time } t}{(\text{number of patients surviving at } t) \times (\text{interval width})}$$
$$= \frac{\text{number of patients dying per unit time in the interval}}{\text{number of patients surviving at } t} \tag{2.1.8}$$

Actuaries usually use the average hazard rate of the interval in which the number of patients dying per unit time in the interval is divided by the average number of survivors at the midpoint of the interval:

$$\hat{h}(t) = \frac{\text{number of patients dying per unit time in the interval}}{(\text{number of patients surviving at } t) - (\text{number of deaths in the interval})/2} \tag{2.1.9}$$

The actuarial estimate in (2.1.9) gives a higher hazard rate than (2.1.8) and thus a more conservative estimate.

The hazard function may increase, decrease, remain constant, or indicate a more complicated process. Figure 2.3 is a plot of several kinds of hazard function. For example, patients with acute leukemia who do not respond to treatment have an increasing hazard rate, $h_1(t)$, $h_2(t)$ is a decreasing hazard function that, for example, indicates the risk of soldiers wounded by bullets who undergo surgery. The main danger is the operation itself and this danger decreases if the surgery is successful. An example of a constant hazard function, $h_3(t)$, is the risk of healthy persons between 18 and 40 years of age whose main risks of death are accidents. The *bathtub curve*, $h_4(t)$, describes the process of

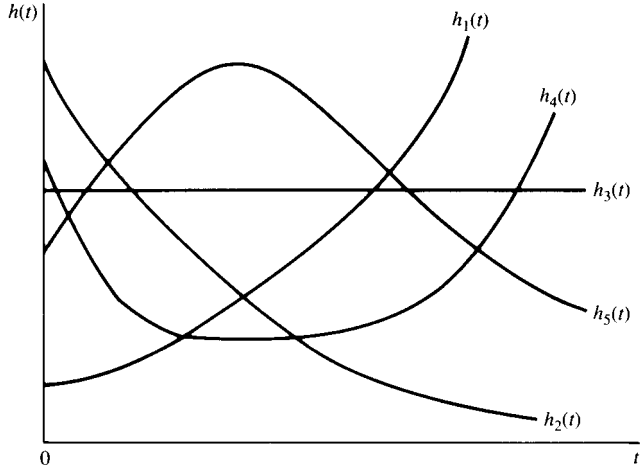


Figure 2.3 Examples of the hazard function.

human life. During an initial period, the risk is high (high infant mortality). Subsequently, $h(t)$ stays approximately constant until a certain time, after which it increases because of wear-out failures. Finally, patients with tuberculosis have risks that increase initially, then decrease after treatment. Such an increasing, then decreasing hazard function is described by $h_5(t)$.

The *cumulative hazard function* is defined as

$$H(t) = \int_0^t h(x)\,dx \tag{2.1.10}$$

It will be shown in Section 2.2 that

$$H(t) = -\log S(t) \tag{2.1.11}$$

Thus, at $t = 0$, $S(t) = 1$, $H(t) = 0$, and at $t = \infty$, $S(t) = 0$, $H(t) = \infty$. The cumulative hazard function can be any value between zero and infinity. All log functions in this book are natural logs (base e) unless otherwise indicated.

The following example illustrates how these functions can be estimated from a complete sample of grouped survival times without censored observations.

Example 2.1 The first three columns of Table 2.1 give the survival data of 40 patients with myeloma. The survival times are grouped into intervals of five months. The estimated survivorship function, density function, and hazard function are also given, with the corresponding graphs plotted in Figure 2.4*a–c*.

Table 2.1 Survival Data and Estimated Survival Functions of 40 Myeloma Patients

Survival Time t (months)	Number of Patients Surviving at Beginning of Interval	Number of Patients Dying in Interval	$\hat{S}(t)$	$\hat{f}(t)$	$\hat{h}(t)$
0–5	40	5	1.000	0.025	0.027
5–10	35	7	0.875	0.035	0.044
10–15	28	6	0.700	0.030	0.048
15–20	22	4	0.550	0.020	0.040
20–25	18	5	0.450	0.025	0.065
25–30	13	4	0.325	0.020	0.072
30–35	9	4	0.225	0.020	0.114
35–40	5	0	0.125	0.000	0.000
40–45	5	2	0.125	0.010	0.100
45–50	3	1	0.075	0.005	0.080
$\geqslant 50$	2	2	0.050	—	—

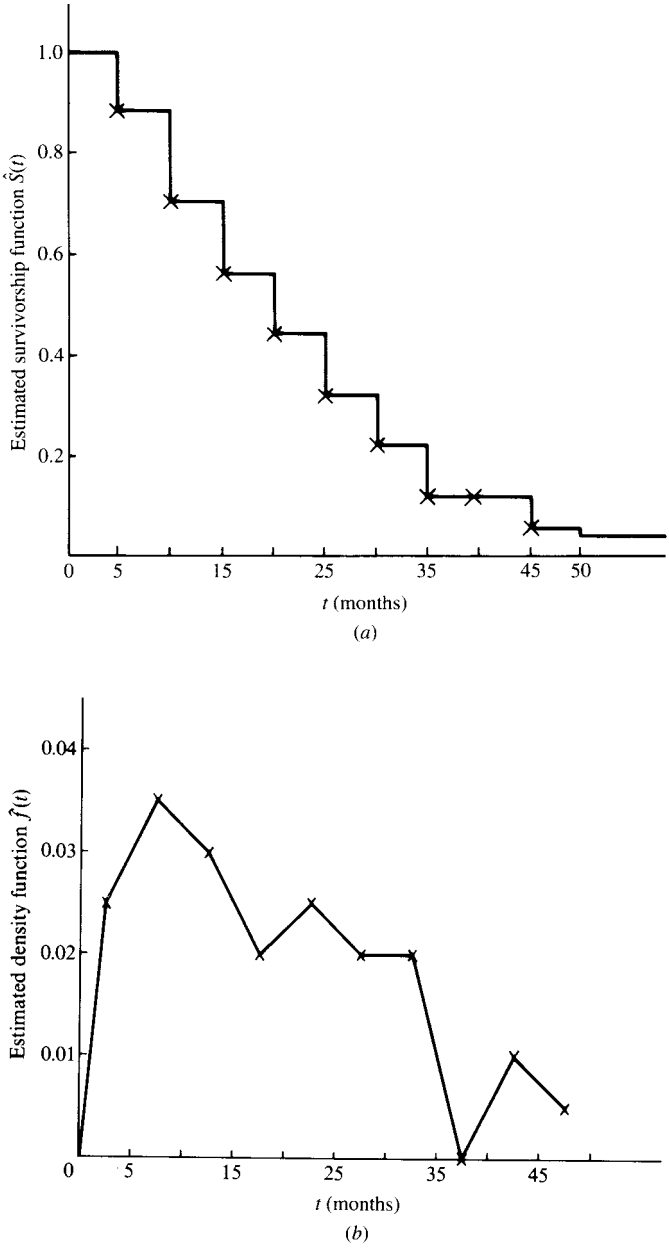


Figure 2.4 Estimated survival functions of myeloma patients.

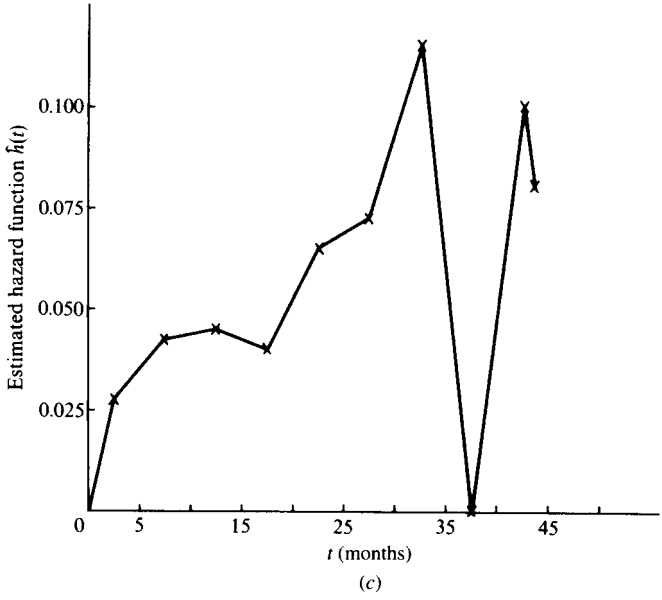


Figure 2.4 ***(Continued).***

The estimated survivorship function, $\hat{S}(t)$, is calculated following (2.1.3) at the beginning or the end of each interval. For example, at the beginning of the first interval, all 40 patients are alive, $\hat{S}(0) = 1$, and at the beginning of the second interval, 35 of the 40 patients are still alive, $\hat{S}(5) = 35/40 = 0.875$. Similarly, $\hat{S}(10) = 28/40 = 0.700$. The estimated density function $\hat{f}(t)$ is computed following (2.1.5). For example, the density function of the first interval (0–5) is $5/(40 \times 5) = 0.025$, and that of the second interval (5–10) is $7/(40 \times 5) = 0.035$. The estimated density function is plotted at the midpoint of each interval (Figure 2.4*b*). The estimated hazard function, $\hat{h}(t)$, is computed following the actuarial method given in (2.1.9). For example, the hazard function of the first interval $5/[5(40 - 5/2)] = 0.027$ and that of the second interval is $7/[5(35 - 7/2)] = 0.044$. The estimated hazard function is also plotted at the midpoint of each interval (Figure 2.4*c*).

From Table 2.1 or Figure 2.4*a*, the median survival time of myeloma patients is approximately 17.5 months, and the peak of high frequency of death occurs in 5 to 10 months. In addition, the hazard function shows an increasing trend and reaches its peak at approximately 32.5 months and then fluctuates.

2.2 RELATIONSHIPS OF THE SURVIVAL FUNCTIONS

The three functions defined in Section 2.1 are mathematically equivalent. Given any one of them, the other two can be derived. Readers not interested in the mathematical relationship among the three survival functions can skip this

section without loss of continuity.

1. From (2.1.2) and (2.1.7),

$$h(t) = \frac{f(t)}{S(t)} \tag{2.2.1}$$

   This relationship can also be derived from (2.1.6) using basic definitions of conditional probabilities.

2. Since the probability density function is the derivative of the cumulative distribution function,

$$f(t) = \frac{d}{dt}\,[1 - S(t)] = -S'(t) \tag{2.2.2}$$

3. Substituting (2.2.2) into (2.2.1) yields

$$h(t) = -\frac{S'(t)}{S(t)} = -\frac{d}{dt}\log S(t) \tag{2.2.3}$$

4. Integrating (2.2.3) from zero to t and using $S(0) = 1$, we have

$$-\int_0^t h(x)\,dx = \log S(t)$$

   or

$$H(t) = -\log S(t)$$

   or

$$S(t) = \exp[-H(t)] = \exp\left[-\int_0^t h(x)\,dx\right] \tag{2.2.4}$$

5. From (2.2.1) and (2.2.4) we obtain

$$f(t) = h(t)\exp[-H(t)] \tag{2.2.5}$$

Hence, if $f(t)$ is known, the survivorship function can be obtained from the basic relationship between $f(t)$, $F(t)$, and (2.1.2). The hazard function can then be determined from (2.2.1). If $S(t)$ is known, $f(t)$ and $h(t)$ can be determined from (2.2.2) and (2.2.1), respectively, or $h(t)$ can be derived first from (2.2.3) and then $f(t)$ from (2.2.1). If $h(t)$ is given, $S(t)$ and $f(t)$ can be obtained, respectively, from (2.2.4) and (2.2.5). Thus, given any one of the three survival functions, the other two can easily be derived. The following example illustrates these equivalence relationships.

Example 2.2 Suppose that the survival time of a population has the following density function:

$$f(t) = e^{-t} \qquad t \geqslant 0$$

Using the definition of the cumulative distribution function,

$$F(t) = \int_0^t f(x)\,dx = \int_0^t e^{-x}\,dx = -e^{-x}\Big|_0^t = 1 - e^{-t}$$

From (2.1.2) we obtain the survivorship function

$$S(t) = e^{-t}$$

The hazard function can then be obtained from (2.2.1):

$$h(t) = \frac{e^{-t}}{e^{-t}} = 1$$

A complete treatment of this distribution is given in Section 6.1.

Bibliographical Remarks

The three survival functions and their equivalents are discussed in every text cited in the Bibliographical Remarks in Chapter 1.

EXERCISES

2.1 Consider the survival data given in Exercise Table 2.1. Compute and plot the estimated survivorship function, the probability density function, and the hazard function.

Exercise Table 2.1

Year of Follow-up	Number Alive at Beginning of Interval	Number Dying in Interval
0–1	1100	240
1–2	860	180
2–3	680	184
3–4	496	138
4–5	358	118
5–6	240	60
6–7	180	52
7–8	128	44
8–9	84	32
$\geqslant 9$	52	28

2.2 Exercise Table 2.2 is a life table for the total population (of 100,000 live births) in the United States, 1959–1961. Compute and plot the estimated survivorship function, the probability density function, and the hazard function.

Exercise Table 2.2

Age Interval	Number Living at Beginning of Age Interval	Number Dying in Age Interval
0–1	100,000	2,593
1–5	97,407	409
5–10	96,998	233
10–15	96,765	214
15–20	96,551	440
20–25	96,111	594
25–30	95,517	612
30–35	94,905	761
35–40	94,144	1,080
40–45	93,064	1.686
45–50	91,378	2,622
50–55	88,756	4,045
55–60	84,711	5,644
60–65	79,067	7,920
65–70	71,147	10,290
70–75	60,857	12,687
75–80	48,170	14,594
80–85	33,576	15,034
85 and over	18,542	18,542

Source: U.S. National Center for Health Statistics, Life Tables 1959–1961, Vol. 1, No. 1, "United States Life Tables 1959–61," December 1964, pp. 8–9.

2.3 Derive (2.2.1) using (2.1.6) and basic definitions of conditional probability.

2.4 Given the hazard function

$$h(t) = c$$

derive the survivorship function and the probability density function.

2.5 Given the survivorship function

$$S(t) = \exp(-t^{\gamma})$$

derive the probability density function and the hazard function.

CHAPTER 3

Examples of Survival Data Analysis

The investigator who has assembled a large amount of data must decide what to do with it and what it indicates. In this chapter we take several sets of survival data from actual research situations and analyze them. In Example 3.1 we analyze two sets of data obtained, respectively, from two and three treatment groups to compare the treatment's abilities to prolong life. Example 3.2 is an example of the life-table technique for large samples. Example 3.3 gives remission data from two treatments; the investigator seeks a well-known distribution for the remission patterns to compare the two groups. In Example 3.4 we study survival data and several other patient characteristics to identify important prognostic factors; the patient characteristics are analyzed individually and simultaneously for their prognostic values. In Example 3.5 we introduce a case in which the interest is to identify risk factors in the development of a given disease. Four sets of real data are presented in the exercises so that the reader can plan analysis.

3.1 EXAMPLE 3.1: COMPARISON OF TWO TREATMENTS AND THREE DIETS

3.1.1 Comparison of Two Treatments

Thirty melanoma patients (stages 2 to 4) were studied to compare the immunotherapies BCG (*Bacillus* Calmette-Guerin) and *Corynebacterium parvum* for their abilities to prolong remission duration and survival time. The age, gender, disease stage, treatment received, remission duration, and survival time are given in Table 3.1. All the patients were resected before treatment began and thus had no evidence of melanoma at the time of first treatment.

The usual objective with this type of data is to determine the length of remission and survival and to compare the distributions of remission and survival time in each group. Before comparing the remission and survival

Table 3.1 Data for 30 Resected Melanoma Patients

Patient	Age	Gender[a]	Initial Stage	Treatment Received[b]	Remission Duration[c]	Survival Time[c]
1	59	2	3B	1	33.7+	33.7+
2	50	2	3B	1	3.8	3.9
3	76	1	3B	1	6.3	10.5
4	66	2	3B	1	2.3	5.4
5	33	1	3B	1	6.4	19.5
6	23	2	3B	1	23.8+	23.8+
7	40	2	3B	1	1.8	7.9
8	34	1	3B	1	5.5	16.9+
9	34	1	3B	1	16.6+	16.6+
10	38	2	2	1	33.7+	33.7+
11	54	2	2	1	17.1+	17.1+
12	49	1	3B	2	4.3	8.0
13	35	1	3B	2	26.9+	26.9+
14	22	1	3B	2	21.4+	21.4+
f15	30	1	3B	2	18.1+	18.1+
16	26	2	3B	2	5.8	16.0+
17	27	1	3B	2	3.0	6.9
18	45	2	3B	2	11.0+	11.0+
19	76	2	3A	2	22.1	24.8+
20	48	1	3A	2	23.0+	23.0+
21	91	1	4A	2	6.8	8.3
22	82	2	4A	2	10.8+	10.8+
23	50	2	4A	2	2.8	12.2+
24	40	1	4A	2	9.2	12.5+
25	34	1	3A	2	15.9	24.4
26	38	1	4A	2	4.5	7.7
27	50	1	2	2	9.2	14.8+
28	53	2	2	2	8.2+	8.2+
29	48	2	2	2	8.2+	8.2+
30	40	2	2	2	7.8+	7.8+

Source: Data courtesy of Richard Ishmael.

[a] 1, male; 2, female.

[b] 1, BCG; 2, *C. parvum.*

[c] Remission and survival times are in months.

distributions, we attempt to determine if the two treatment groups are comparable with respect to prognostic factors. Let us use the survival time to illustrate the steps. (The remission time could be analyzed similarly.)

1. *Estimate and plot the survival function of the two treatment groups.* The resulting curves are called survival curves. Points on the curve estimate the proportion of patients who will survive at least a given period of time. For such small samples with progressively censored observations, the Kaplan–Meier product-limit (PL) method is appropriate for estimating the survival function.

Table 3.2 Kaplan–Meier Product-Limit Estimate of Survival Function $S(t)$

	BCG Patients				
Death time (t)	3.9	5.4	7.9	10.5	19.5
$\hat{S}(t)$	0.909	0.818	0.727	0.636	0.477
	C. parvum Patients				
Death time (t)	6.9	7.7	8.0		
$\hat{S}(t)$	0.947	0.895	0.839		

It does not require any assumptions about the form of the function that is being estimated. We discuss this method in detail in Section 4.1. Computer programs for the method can be found in BMDP (Dixon et al. 1990), SPSS Version 10.1 (2000), and SAS Version 8.1 (2000). Examples for computer codes will be given in Section 4.1.

Table 3.2 gives the PL estimate of the survival function $\hat{S}(t)$ for the two treatment groups. Note that $\hat{S}(t)$ is estimated only at death times; however, the censored observations were used to estimate $S(t)$. The *median survival time* can be estimated by linear interpolation. For BCG patients the median survival time was about 18.2 months. The median survival time for the *C. parvum* group cannot be calculated since 15 of the 19 patients were still alive. Most computer programs give not only $\hat{S}(t)$ but also the standard error of $\hat{S}(t)$, and the 75-, 50-, and 25-percentile points.

Figure 3.1 plots the estimated survival function $\hat{S}(t)$ for patients receiving the two treatments: The median survival time (50-percentile point) for the BCG group can also be determined graphically. The survival curves clearly show that *C. parvum* patients had slightly better survival experience than BCG patients. For example, 50% of the BCG patients survived at least 18.2 months, whereas about 61% of the *C. parvum* patients survived that long.

2. *Examine the prognostic homogeneity of the two groups.* The next question to ask is whether the difference in survival between the two treatment groups is statistically significant. Is the difference shown by the data significant or simply random variation in the sample? A statistical test of significance is needed. However, a statistical test without considering patient characteristics makes sense only if the two groups of patients are homogeneous with respect to prognostic factors. It has been assumed thus far that the patients in the two groups are comparable and that the only difference between them is treatment. Thus, before performing a statistical test it is necessary to examine the homogeneity between the two groups.

Although prognostic factors for melanoma patients are not well established, it has been reported that women and the young have a better survival

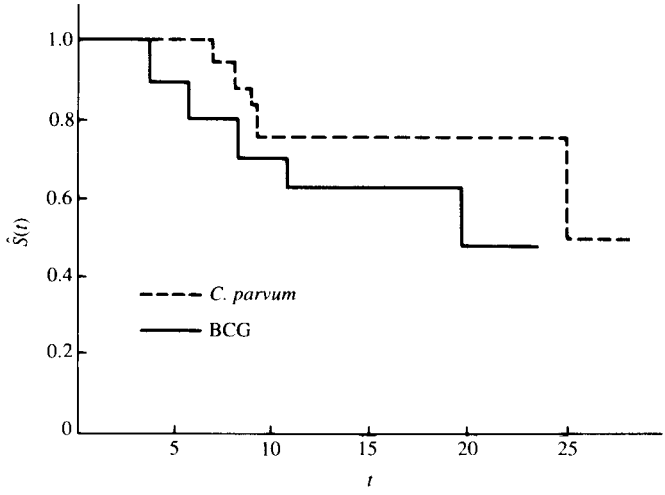


Figure 3.1 Survival curves of patients receiving BCG and *C. parvum*.

experience than men and the elderly. Also, the disease stage plays an important role in survival. Let us check the homogeneity of the two treatment groups with respect to age, gender, and disease stage.

The age distributions are estimated and plotted in Figure 3.2. The median age is 39 for the BCG group and 43 for the *C. parvum* patients. To test the significance of the difference between the two age distributions, the two-sample *t*-test (Armitage, 1971; Daniel, 1987) or nonparametric tests such as the Mann–Whitney *U*-test or the Kolmogorov–Smirnov test (Marascuilo and McSweeney, 1977) are appropriate. However, the generalized Wilcoxon tests given in Section 5.1 can also be used, since they reduce to the Mann–Whitney *U*-test. Using Geham's generalized Wilcoxon test, the difference between the two age distributions is not found to be statistically significant. More about the test will be given in Section 5.1.

The number of male and female patients in the two treatment groups is given in Table 3.3. Sixty-four percent of the BCG patients and 42% of the *C. parvum* patients are women. A chi-square test can be used to compare the two proportions (see Section 14.1). It can be used only for $r \times c$ tables in which the entries are frequencies, not for tables in which the entries are mean values or medians of a certain variable. For a 2×2 table, the chi-square value can be computed by hand. Computer programs for the test can be found in many computer program packages, such as BMDP (Dixon et al., 1990), SPSS Version 10.1 (2000), and SAS Version 8.1 (SAS Institute, 2000).

The chi-square value for treatment by gender in Table 3.3 is 1.29 with 1 degree of freedom, which is not significant at the 0.05 or 0.10 level. Therefore, the difference between the two proportions is not statistically significant. The number of stage 2 patients and the number of patients with more advanced

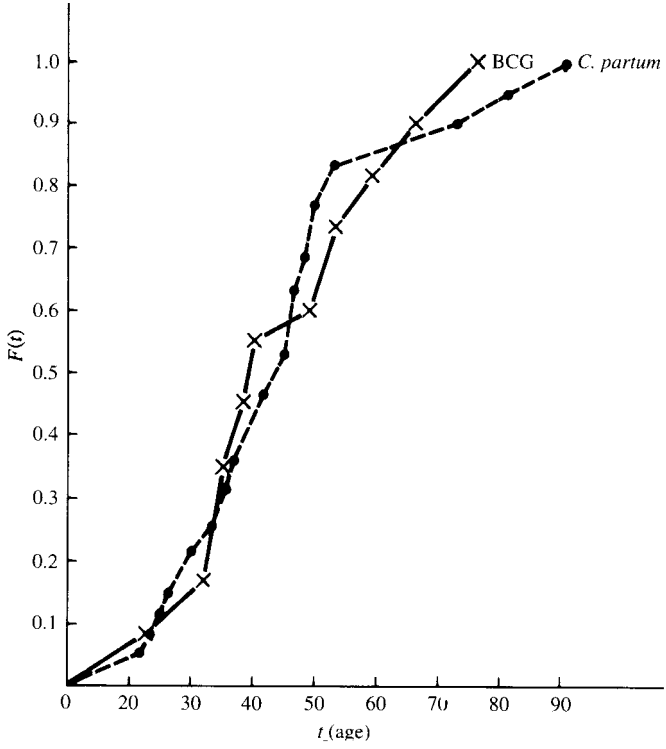


Figure 3.2 Age distribution of two treatment groups.

disease in the two treatment groups are also given in Table 3.3. Eighteen percent of the BCG patients are at stage 2 against 21% of the *C. parvum* patients. However, a chi-square test result shows that the difference is not significant.

Thus we can say that the data do not show heterogeneity between the two treatment groups. If heterogeneity is found, the groups can be divided into subgroups of members who are similar in their prognoses.

Table 3.3 Treatment by Gender and Disease Stage

	BCG		*C. parvum*				BCG		*C. Parvum*		
Gender	Number	%	Number	%	Total	Disease Stage	Number	%	Number	%	Total
Male	4	36	11	58	15	2	2	18	4	21	6
Female	7	64	8	42	15	3 and 4	9	82	15	79	24
	11		19		30		11		19		30

3. *Compare the two survival distributions.* There are several parametric and nonparametric tests to compare two survival distributions. They are described in Chapters 5 and 10. Since we have no information of the survival distribution that the data follow, we would continue to use nonparametric methods to compare the two survival distributions. The four tests described in Sections 5.1.1 to 5.1.4 are suitable. The performance of these tests is discussed at the end of Section 5.1. We chose Gehan's generalized Wilcoxon test here to demonstrate the analysis procedure only because of its simplicity of calculation.

In testing the significance of the difference between two survival distributions, the hypothesis is that the survival distribution of the BCG patients is the same as that of the *C. parvum* patients. Let $S_1(t)$ and $S_2(t)$ be the survival function of the BCG and *C. parvum* groups, respectively. The null hypothesis is

$$H_0: S_1(t) = S_2(t)$$

The alternative hypothesis chosen is two-sided:

$$H_1: S_1(t) \neq S_2(t)$$

since we have no prior information concerning the superiority of either of the two treatments. The slight difference between the two estimated survival curves could be due to random variation. The one-sided alternative $H_1: S_1(t) < S_2(t)$ should be considered inappropriate.

Using Gehan's generalized Wilcoxon test, the difference in survival distribution of the two treatment groups is found to be insignificant ($p = 0.33$). Therefore, we do not reject the null hypothesis that the two survival distributions are equal. Although our conclusion is that the data do not provide enough evidence to reject the hypothesis, "not to reject the null hypothesis" does not automatically mean "to accept the null hypothesis." The difference between the two statements is that the error probability of the latter statement is usually much larger than that of the former.

3.1.2 Comparison of Three Diets

A laboratory investigator interested in the relationship between diet and the development of tumors divided 90 rats into three groups and fed them low-fat, saturated fat, and unsaturated fat diets, respectively (King et al., 1979). The rats were of the same age and species and were in similar physical condition. An identical amount of tumor cells were injected into a foot pad of each rat. The rats were observed for 200 days. Many developed a recognizable tumor early in the study period. Some were tumor-free at the end of the 200 days. Rat 16 in the low-fat group and rat 24 in the saturated group died accidentally after 140 days and 170 days, respectively, with no evidence of tumor. Table 3.4 gives the tumor-free time, the time from injection to the time that a tumor develops or to the end of the study. Fifteen of the 30 rats on the low-fat diet developed a tumor before the experiment was terminated. The rat that died had a tumor-free time of at least 140 days. The other 14 rats did not develop any

Table 3.4 Tumor-Free Time (Days) of 90 Rats on Three Different Diets

Rat	Low-Fat	Rat	Saturated Fat	Rat	Unsaturated Fat
1	140	1	124	1	112
2	177	2	58	2	68
3	50	3	56	3	84
4	65	4	68	4	109
5	86	5	79	5	153
6	153	6	89	6	143
7	181	7	107	7	60
8	191	8	86	8	70
9	77	9	142	9	98
10	84	10	110	10	164
11	87	11	96	11	63
12	56	12	142	12	63
13	66	13	86	13	77
14	73	14	75	14	91
15	119	15	117	15	91
16	140+	16	98	16	66
17	200+	17	105	17	70
18	200+	18	126	18	77
19	200+	19	43	19	63
20	200+	20	46	20	66
21	200+	21	81	21	66
22	200+	22	133	22	94
23	200+	23	165	23	101
24	200+	24	170+	24	105
25	200+	25	200+	25	108
26	200+	26	200+	26	112
27	200+	27	200+	27	115
28	200+	28	200+	28	126
29	200+	29	200+	29	161
30	200+	30	200+	30	178

Source: King et al. (1979). Data are used by permission of the author.

tumor by the end of the experiment; their tumor-free times were at least 200 days. Among the 30 rats in the saturated fat diet group, 23 developed a tumor, one died tumor-free after 170 days, and six were tumor-free at the end of the experiment. All 30 rats in the unsaturated fat diet group developed tumors within 200 days. The two early deaths can be considered losses to follow-up. The data are singly censored if the two early deaths are excluded.

The investigator's main interest here is to compare the three diets' abilities to keep the rats tumor-free. To obtain information about the distribution of the tumor-free time, we can first estimate the *survival* (tumor-free) function of the three diet groups. The three survival functions were estimated using the

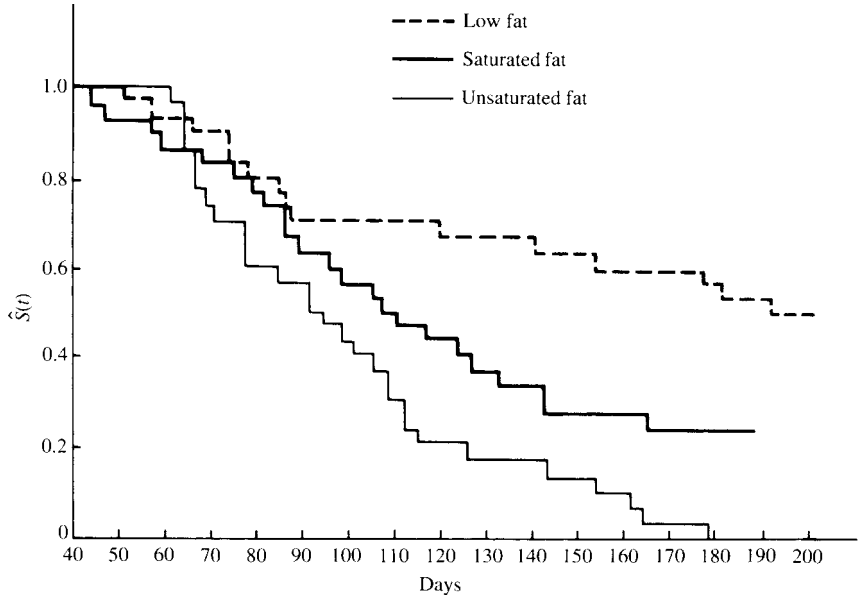


Figure 3.3 Survival curves of rats in three diet groups.

Kaplan–Meier PL method and plotted in Figure 3.3. The median tumor-free times for the low-fat, saturated fat, and unsaturated fat groups were 188, 107, and 91 days, respectively. Since the three groups are homogeneous, we can skip the step that checks for homogeneity and compare the three distributions of tumor-free time.

The K-sample test described in Section 5.3.3 can be used to test the significance of the differences among the three diet groups. Using this test, the investigator finds that the differences among the three groups are highly significant ($p = 0.002$). Note that the K-sample test can tell the investigator only that the differences among the groups are statistically significant. It cannot tell which two groups contribute the most to the differences—whether the low-fat diet produces a significantly different tumor-free time than the saturated fat diet or whether the saturated fat diet is significantly different from the unsaturated fat diet. All one can conclude is that the data show a significant difference among the tumor-free times produced by the three diets.

3.2 EXAMPLE 3.2: COMPARISON OF TWO SURVIVAL PATTERNS USING LIFE TABLES

When the sample of patients is so large that their groupings are meaningful, the life-table technique can be used to estimate the survival distribution. A method developed by Mantel and Haenszel (1959) and applied to life

tables by Mantel (1966) can be used to compare two survival patterns in the life-table analysis.

Consider the data of male patients with localized cancer of the rectum diagnosed in Connecticut from 1935 to 1954 (Myers, 1969). A total of 388 patients were diagnosed between 1935 and 1944, and 749 patients were diagnosed between 1945 and 1954. For such large sample sizes the data can be grouped and tabulated as shown in Table 3.5. The 10 intervals indicate the number of years after diagnosis. For the tabulated life tables the survival function $S(t_i)$ can be estimated for each interval t_i. In Section 4.2 we discuss the estimation procedures of $S(t_i)$ and density and hazard functions. The survival, density, and hazard functions are the three most important functions that characterize a survival distribution.

The $\hat{S}(t_i)$ column in Table 3.5 gives the estimated survival function for the two time periods; these are plotted in Figure 3.4. Patients diagnosed in the 1945–1954 period had considerably longer survival times (median 3.87 years) than did patients diagnosed in the 1935–1944 period (median 1.58 years). The five-year survival rate is frequently used by cancer researchers and can easily be determined from a life table. Patients diagnosed in 1935–1944 had a five-year survival rate of 0.2390, or 23.9%. The patients diagnosed in 1945–1954 had a rate of 0.4446, or 44.5%. In comparing two sets of survival data, one can compare the proportions of patients surviving some stated period, such as five years, or the five-year survival rates. However, one cannot anticipate that two survival patterns will always stand in a superior–inferior

Table 3.5 Life Table for Male Patients with Localized Cancer of Rectum Diagnosed in Connecticut, 1935–1944 and 1945–1954[a]

Interval	1935–1944					1945–1954				
(t_i)	n_i'	d_i	w_i+l_i	n_i	$\hat{S}(t_i)$	n_i'	d_i	w_i+l_i	n_i	$\hat{S}(t_i)$
1	388	167	2	387.0	0.5685	749	185	10	744.0	0.7513
2	219	45	1	218.5	0.4514	554	88	10	549.0	0.6309
3	173	45	1	172.5	0.3336	456	55	10	451.0	0.5539
4	127	19	0	127.0	0.2837	391	43	10	386.0	0.4922
5	108	17	0	108.0	0.2390	338	32	14	331.0	0.4446
6	91	11	1	90.5	0.2100	292	31	52	266.0	0.3928
7	79	8	0	79.0	0.1887	209	20	38	190.0	0.3514
8	71	5	0	71.0	0.1754	151	7	24	139.0	0.3337
9	66	6	1	65.5	0.1593	120	6	25	107.5	0.3151
10	59	7	0	59.0	0.1404	89	6	24	77.0	0.2905

Source: Myers (1969).

[a] Symbols: n_i', number of patients alive at beginning of interval t_i; d_i, number of patients dying during interval t_i; w_i+l_i, number of patients withdrawn alive or lost to follow-up during interval t_i; $n_i = n_i' - \frac{1}{2}(w_i+l_i)$; $\hat{S}(t_i)$, cumulative proportion surviving from beginning of study to end of interval t_i.

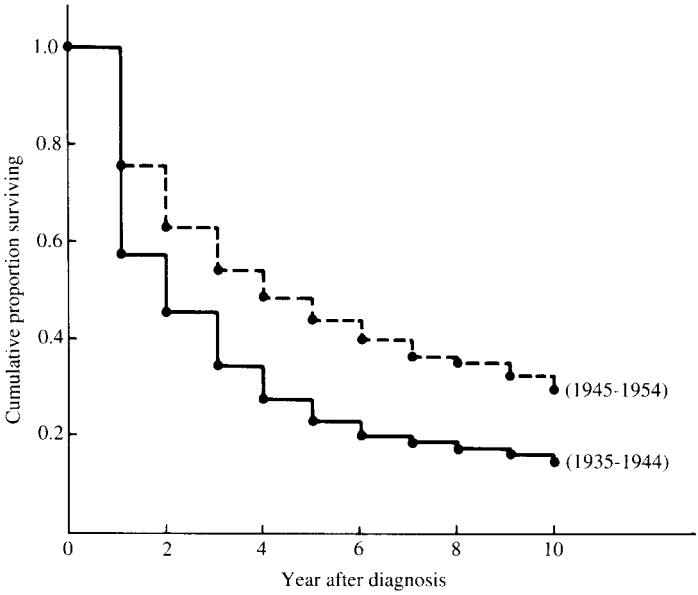


Figure 3.4 Survival curves for male patients with localized cancer of the rectum, diagnosed in Connecticut, 1935–1944 versus 1945–1954.

relationship. It is more desirable to make a whole-pattern comparison (see Sections 4.3 and 5.2).

The Mantel–Haenszel method described in Section 5.2 is a whole-pattern comparison and can be used to compare two survival patterns in life tables. Application of this method to the data in Table 3.5 results in a chi-square value of 51.996 with 1 degree of freedom. We can conclude that the difference between the two survival patterns is highly significant ($p < 0.001$).

Estimates of the survival function or survival rate depend on the life-table interval used. If each interval is very short, resulting in a large number of intervals, the computation becomes very tedious and the life-table advantage is not fully taken. One assumption underlying the life table is that the population has the same survival probability in each interval. If the interval length is long, this assumption may be violated and the estimates inaccurate; this should be avoided except for rough calculations. Although the length of each interval and the total number of intervals are important, they will not cause trouble in most clinical studies since the study periods normally cover a short period of time, such as one, two, or three years. Life tables with about 10 to 20 intervals of several months to one year each are reasonable. The investigator should also consider the disease under study. If the variation in survival is large in a short period of time, the interval length should be short. However, in some demographic or other studies it is often of interest to cover a life span from birth to age 85 or more. The number of intervals would be

very large if short intervals were used. In this case five-year intervals are sufficient to take into account the important variations in survival rate estimates (Shryock et al., 1971).

3.3 EXAMPLE 3.3: FITTING SURVIVAL DISTRIBUTIONS TO REMISSION DATA

The remission times of 42 patients with acute leukemia were reported by Freireich et al. (1963) in a clinical trial undertaken to assess the ability of 6-mercaptopurine (6-MP) to maintain remission.[1] Each patient was randomized to receive 6-MP or a placebo. The study was terminated after one year. The following remission times, in weeks, were recorded:

6-MP (21 patients): 6, 6, 6, 7, 10, 13, 16, 22, 23, 6+, 9+, 10+, 11+, 17+, 19+, 20+, 25+, 32+, 32+, 34+, 35+

Placebo (21 patients): 1, 1, 2, 2, 3, 4, 4, 5, 5, 8, 8, 8, 8, 11, 11, 12, 12, 15, 17, 22, 23

Suppose that we are interested in a distribution to describe the remission times of these patients but that no information is available as to which distribution will fit. We need to find a distribution that fits the data well. If we can find one, the remission experience can then be described by the properties of the distribution, and the remission time of new patients can be predicted. Parametric tests can be used to compare the effectiveness of the two treatments, but since there are a large number of well-known functions and distributions to choose from, the search becomes an art as much as a scientific task.

The simplest and most efficient tool is the graph. Probability plotting can be done for complete data; for data that include censored observations, hazard plotting and the Cox–Snell method are more appropriate. It is not difficult to use the computer to generate these plots. Detailed discussions of probability plotting and hazard plotting are presented in Chapter 8. In both probability and hazard plotting, a linear configuration indicates that the distribution fits well and its parameters can be estimated from the graph.

Let us begin by trying to fit a distribution to the remission duration of 6-MP patients. Since the data consist of both censored and uncensored observations, we use the technique of hazard plotting. In this example we limit ourselves to three distributions: the exponential, Weibull, and lognormal. In practice, more distributions may need to be considered. Figures 3.5, 3.6, and 3.7 give the hazard plots for the exponential, Weibull, and lognormal distributions, respectively. A straight line is fitted to the points by eye in each of the plots. Among these graphs, the Weibull distribution appears to provide the best fit to the remission data. The straight line fits the points fairly closely. The estimates of

[1] Data are used by permission of the publisher.

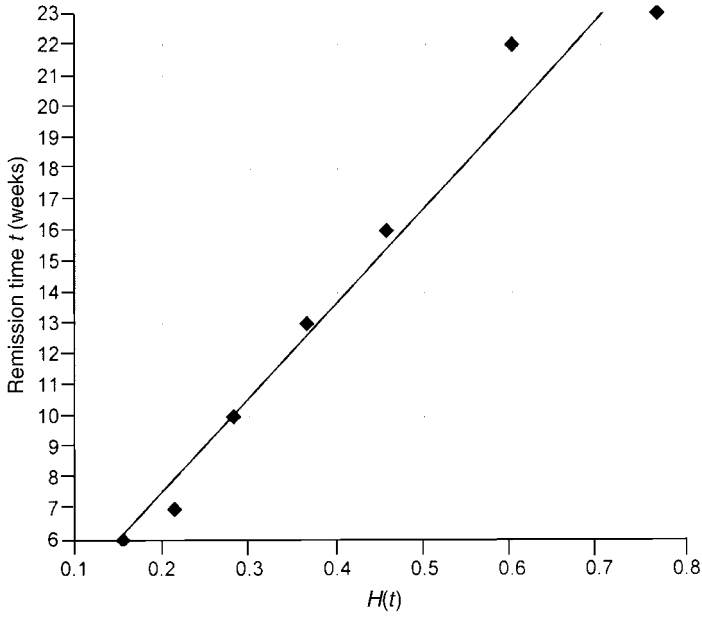


Figure 3.5 Exponential hazard plot of the remission times of 21 leukemia patients who received 6-MP.

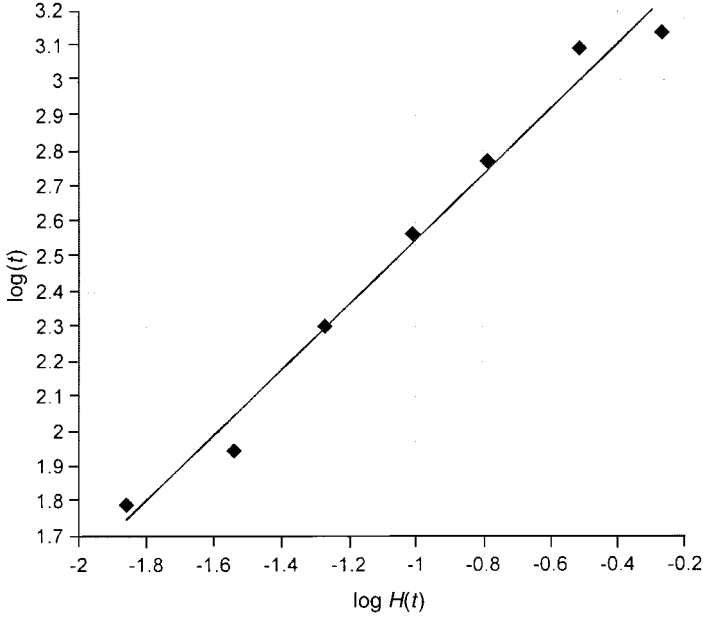


Figure 3.6 Weibull hazard plot of the remission times of 21 leukemia patients who received 6-MP.

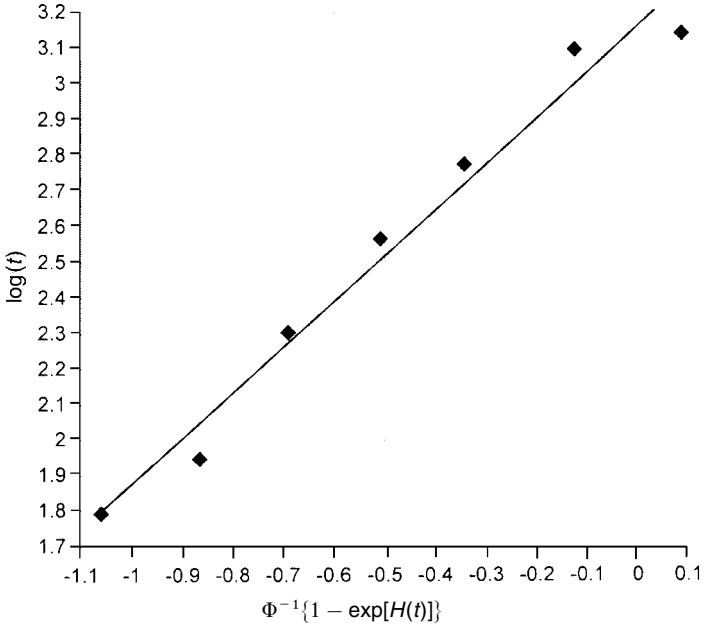


Figure 3.7 Log-normal hazard plot of the remission times of 21 leukemia patients who received 6-MP.

the parameters λ and γ of the Weibull distribution obtained from the line are equal to 0.033 and 1.143, respectively (methods discussed in Chapter 8). After knowing that the Weibull distribution provides a good fit, we can use an analytical method, the maximum likelihood method, to obtain a more accurate estimate of the parameters. Following the procedures discussed in Chapter 7, the maximum likelihood estimates of λ and γ are $\hat{\lambda} = 0.03$ and $\hat{\gamma} = 1.354$, which are quite close to the graphical estimates.

After an appropriate distribution has been identified and parameters estimated, we can estimate the probability of having a given duration of remission and other probabilities. For example, the probability of having a remission time longer than 10 weeks can be predicted as

$$P(T > 10) = e^{-(10\hat{\lambda})^{\hat{\gamma}}} = e^{-(10*0.03)^{1.354}} = 0.822$$

For the placebo group, we can use the probability plotting technique since the data are complete. Figures 3.8, 3.9, and 3.10 give the exponential, Weibull, and lognormal probability plots. Comparing the three graphs, again, the straight line in the Weibull plot appears to give the best fit. From the Weibull plot, estimates of λ and γ are found to be 0.111 and 1.250, respectively. The maximum likelihood estimates of λ and γ are, respectively, 0.105 and 1.371. Again, the graphical estimates are very close to the maximum likelihood estimates. Based on the maximum likelihood estimates of the parameters, we

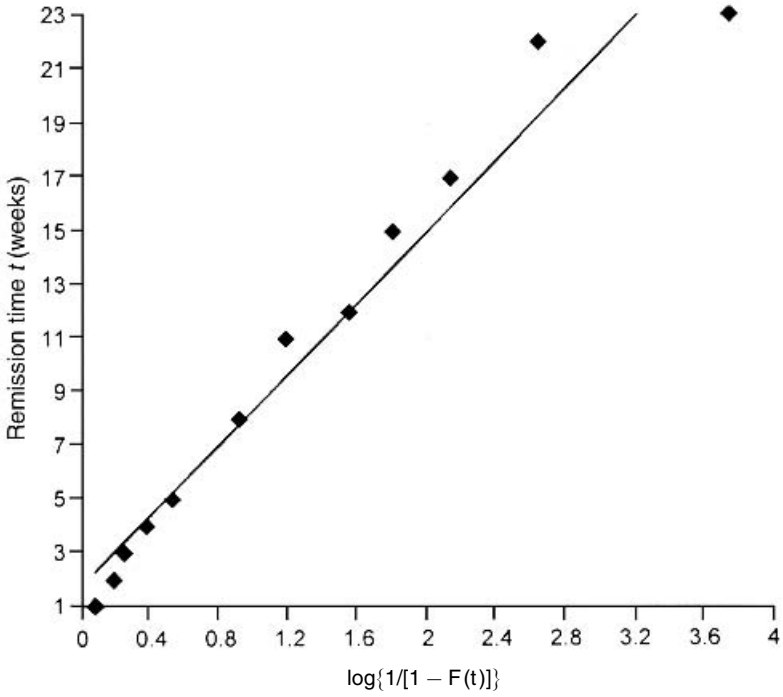


Figure 3.8 Exponential probability plot of the remission times of 21 leukemia patients who received placebo.

can estimate the probability of having a remission time longer than 10 weeks. Using the same formula as given above, the probability for a patient receiving placebo to have a remission duration longer than 10 weeks is found to be 0.34, which is smaller than that of a patient receiving 6-MP.

These graphical methods are subjective. The judgment as to whether the assumed distribution fits the data is based on a visual examination rather than on an objective statistical test. However, the methods are very simple and do provide a great deal of information. Even in a case where none of the distributions discussed in this book fit well, graphs can help find the reasons and thus help modify the model. Therefore, graphical methods are usually recommended as the first thing to try.

3.4 EXAMPLE 3.4: RELATIVE MORTALITY AND IDENTIFICATION OF PROGNOSTIC FACTORS

One thousand and twelve Oklahoma Indians (379 men and 633 women) with non-insulin-dependent diabetes mellitus (NIDDM) were examined in

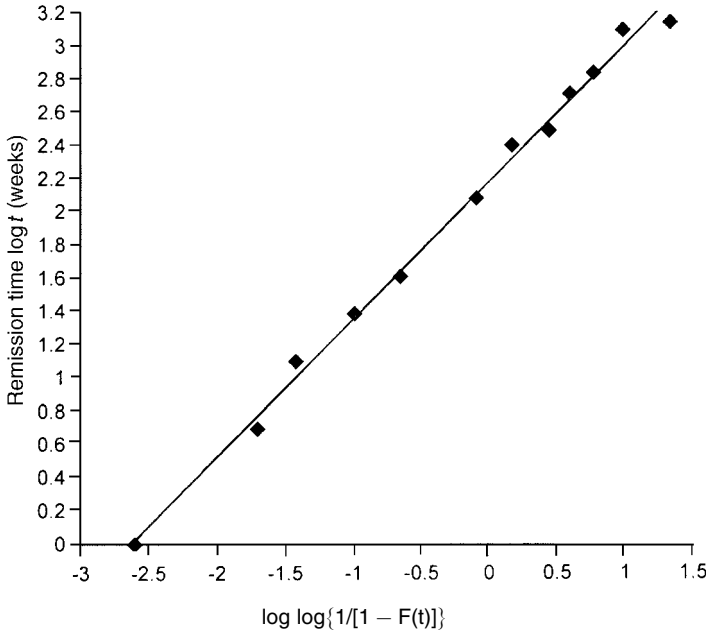


Figure 3.9 Weibull probability plot of the remission times of 21 leukemia patients who received placebo.

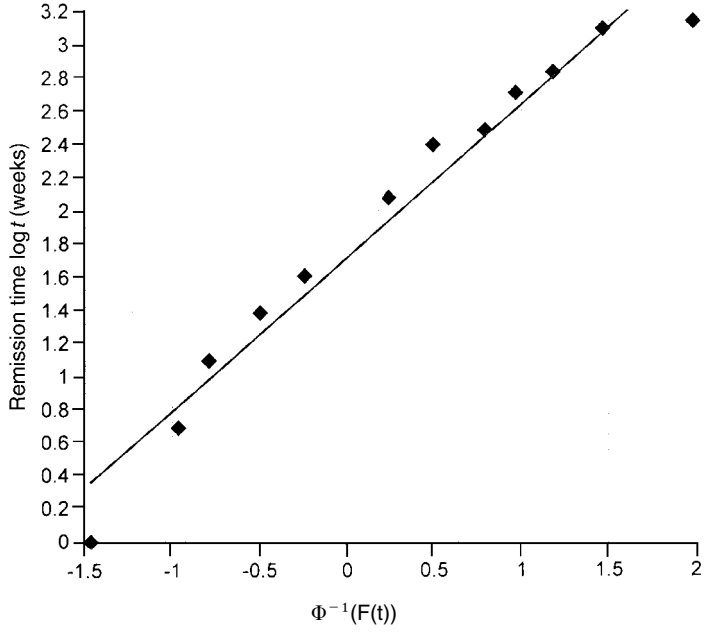


Figure 3.10 Log-normal probability plot of the remission times of 21 leukemia patients who received placebo.

1972–1980 and a mortality follow-up study was conducted in 1986–1989 (Lee et al., 1993). The mean [standard deviation (SD)] age and duration of diabetes at baseline examination were 52 (11) and 7 (6) years. The average duration of follow-up was 10 (SD 4) years. As of December 31, 1989, 548 patients were alive, 452 (187 men and 265 women) were dead, and 12 could not be traced. Table 3.6 gives the survival time in years (T) of the first 40 male patients along with 12 potential prognostic factors: age, duration of diabetes (DUR) in years, family history of diabetes (FAM), use of insulin within one year of diagnosis (INS), use of diuretics (DIU), hypertension (HBP), retinopathy (EVD), proteinuria (PRO), fasting plasma glucose (GLU) in milligrams per deciliter, cholesterol (TC) in milligrams per deciliter, triglyceride (TG) in milligrams per deciliter, and body mass index (BMI), which is defined as weight in kilograms divided by height in meters squared.

Among other things, the authors compared the mortality experience of the diabetic patients with that of the general population in Oklahoma over the follow-up period. Taking changes in age distribution into consideration, the patients were divided into five groups according to their age at baseline examination: <35, 35–44, 45–54, 55–64, and $\geqslant 65$. The expected survival rates were calculated on a yearly basis following the methods described in Section 4.3 and using the death rates given in the 1970 and 1980 Oklahoma population life tables. Death rates for the years between 1970 and 1980 and between 1980 and 1989 were estimated based on the 1970 and 1980 statistics and the assumption that changes in death rates between 1970 and 1980 and after 1980 follow a linear trend. The observed and expected survival curves for the groups were plotted (Figure 3.11), and ratios of the observed and expected number of deaths (O/E ratios) by age were tabulated (Table 3.7).

Figure 3.11 shows that the diabetic patients had a much lower survivorship than the general Oklahoma population for this age–gender distribution. At the beginning of the fifteenth year after baseline examination, the relative survival for the diabetic Oklahoma Indians was only 60%. The overall O/E ratios in Table 3.7 are 2.92 [or standardized mortality ratio (SMR) 292] for men and 4.09 (or SMR 409) for women, which indicates a significantly higher mortality rate in the diabetic Oklahoma Indians than in the general population. Although patients in every group experienced excessive mortality, the younger patients had the highest rate.

The relationship between the 12 potential prognostic variables and the survival time of men was examined using univariate and multivariate methods. The procedures are summarized below.

1. *Examine the individual relationship of each variable to survival.* One way to analyze the data is first to determine which of the 12 variables could be considered of significant prognostic importance. In addition to correlation analysis of these variables, the survival times in subcategories are compared (Table 3.8). Patients are grouped into subgroups in a meaningful way or in a way that maximizes the observed difference in survival time between the

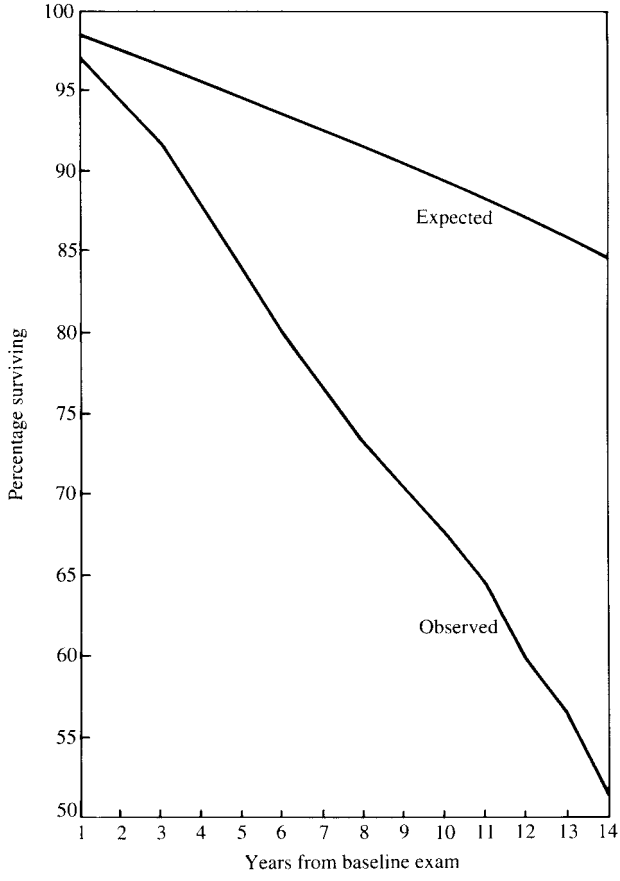


Figure 3.11 Observed and expected survivorship from baseline examination for dabetic Oklahoma Indians.

subgroups (subject to the constraint that each subgroup contains at least 10% of the total number of patients).

The survivorship function for every subgroup of each variable was estimated using the Kaplan–Meier method (discussed in Chapter 4) and plotted. Figure 3.12 gives an example. Survival functions among the subgroups were compared by the logrank test (one of the available tests discussed in Chapter 5). Table 3.8 shows that except cholesterol and triglyceride, every one of the 12 variables is significant. The median survival time decreases as age and duration of diabetes increase. Patients with a family history of diabetes, elevated fasting plasma glucose, hypertension, or retinopathy have significantly shorter survival durations than those without these characteristics. Patients with baseline BMI values greater than or equal to 30 had much better survivorship than did patients with a lower BMI value.

Table 3.6 Data of First 40 Male Patients Enrolled in Mortality Study of Oklahoma Diabetic Indians

Patient	Status[a]	T	Age	DUR	FAM[b]	INS[b]	DIU[b]	HBP[b]	EVD[b]	PRO[b]	GLU	TC	TG	BMI
1	1	12.4	44.0	3	1	0	0	0	0	1	242	392	538	34.2
2	1	14.1	43.5	1	0	0	0	0	0	0	94	158	94	42.2
3	0	14.4	47.6	4	1	0	1	1	0	0	100	195	405	33.1
4	0	14.2	36.3	3	1	0	0	0	0	0	171	212	218	38.5
5	0	14.4	54.4	7	0	0	0	0	0	0	112	204	77	31.7
6	0	12.4	50.8	4	1	0	1	0	0	0	83	206	178	41.5
7	0	12.4	50.0	2	1	0	0	0	0	0	104	178	100	39.5
8	1	7.0	66.9	8	0	0	0	0	0	1	161	189	99	29.7
9	1	13.6	40.2	14	1	0	0	1	1	0	262	241	301	27.5
10	0	14.4	54.1	4	1	0	1	0	1	0	115	183	392	24.4
11	0	12.4	38.9	3	1	0	0	1	0	1	108	237	49	32.4
12	1	9.8	51.2	4	1	0	0	0	0	1	184	114	118	26.5
13	1	0.0	53.0	6	0	0	1	0	0	1	126	206	480	34.5
14	1	12.1	45.0	5	0	0	1	1	0	0	115	238	177	18.9
15	0	14.4	38.3	2	1	0	0	0	0	0	110	204	180	31.2
16	0	12.4	40.0	5	1	0	1	1	1	1	227	159	337	39.2
17	0	14.4	44.4	9	1	0	0	0	0	0	182	193	332	32.7
18	0	14.2	48.2	5	1	0	1	1	1	1	184	171	238	33.5
19	0	12.4	36.3	6	1	0	0	0	0	0	238	196	162	24.2
20	0	13.7	41.9	3	1	0	0	0	1	0	284	170	125	30.7

21	1	13.4	49.7	15	0	0	0	0	0	0	248	217	234	28.0
22	1	12.6	51.5	9	1	0	1	1	1	0	96	174	144	24.2
23	0	14.0	44.1	1	1	0	0	0	0	0	116	251	153	33.3
24	0	12.4	35.9	3	1	0	0	0	0	0	120	129	76	30.1
25	0	12.9	50.4	1	0	0	0	1	0	0	128	190	123	27.7
26	0	12.4	48.0	1	0	0	1	1	0	0	95	207	59	28.1
27	0	14.5	40.1	3	0	0	0	0	0	0	89	252	112	31.7
28	0	13.4	54.5	0	0	1	0	1	0	0	104	490	540	30.8
29	1	13.9	69.3	6	1	0	1	1	0	0	122	162	209	24.2
30	1	12.0	38.5	0	1	0	1	1	0	1	225	183	343	43.1
31	1	3.6	63.7	18	0	0	0	1	1	0	211	217	124	25.1
32	1	15.4	71.8	12	1	0	0	0	0	0	150	227	137	26.0
33	0	10.3	59.5	3	1	0	1	1	0	0	180	188	308	28.1
34	1	5.8	50.1	1	1	0	0	0	0	0	400	200	166	26.1
35	1	2.5	75.4	18	1	0	0	1	0	1	281	692	364	49.7
36	0	15.0	29.6	1	1	0	0	0	0	1	167	154	157	60.2
37	1	5.5	60.2	18	0	0	0	0	1	0	351	206	141	26.0
38	1	4.5	63.9	4	1	0	0	1	0	1	127	180	131	21.8
39	1	6.8	57.4	17	1	0	0	1	1	0	153	786	466	34.1
40	1	3.6	71.3	18	1	1	1	1	1	1	179	488	364	25.6

[a] 1, dead; 0, alive.
[b] 1, yes; 0, no.

Table 3.7 Observed and Expected Number of Deaths and O/E Ratios During Follow-up Period by Gender and Age at Baseline

Age at Baseline (yr)	Males			Females		
	Observed	Expected	O/E	Observed	Expected	O/E
⩽44	34	6.48	5.25	31	5.51	5.63
45–54	79	25.64	3.08	85	18.40	4.62
55–64	32	11.67	2.74	69	15.03	4.59
65+	42	20.32	2.06	80	25.86	3.09
Total	187	64.11	2.92	265	64.80	4.09

2. *Examine the simultaneous relationship of the variables to survival.* Examination of each variable can give only a preliminary idea of which variables might be of prognostic importance. The simultaneous effect of the variables must be analyzed by an appropriate multivariate statistical method to determine the relative importance of each. Cox's (1972) proportional hazards model

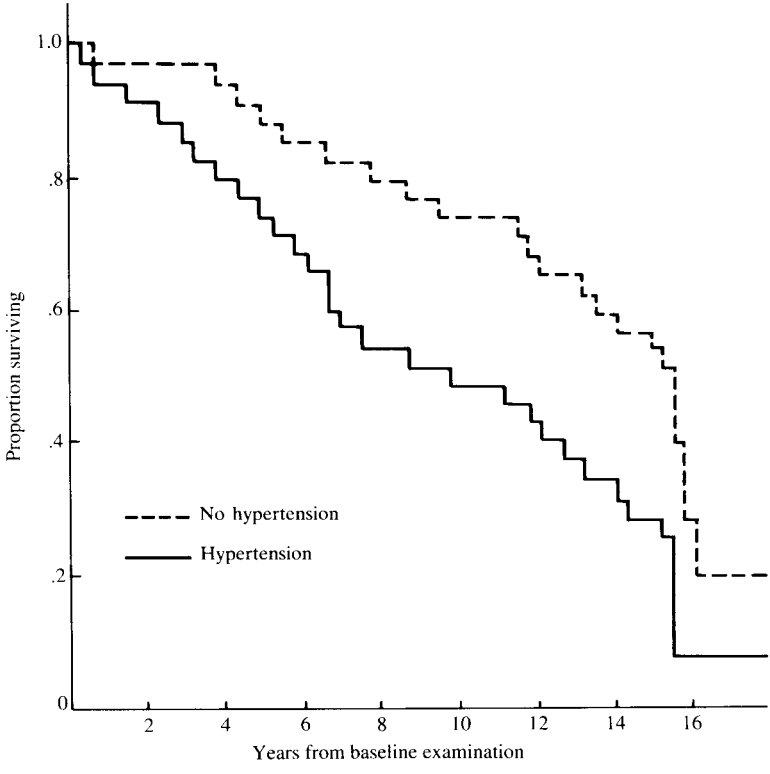


Figure 3.12 Survival curves of diabetic patients by hypertension status at baseline.

Table 3.8 Survival Time by Potential Prognostic Variable for Male Diabetic Patients

Variable	Number of Patients	Number of Deaths	Median Survival Time (yr)	p Value
Age (yr)				
<45	102	34	15.2	
45–54	173	79	14.2	<0.001
55–64	53	31	9.1	
$\geqslant 65$	46	43	5.1	
Family history of diabetes				
No	104	62	11.4	<0.01
Yes	238	104	14.8	
Duration of diabetes (yr)				
<7	207	84	15.2	
7–13	91	49	12.2	<0.001
$\geqslant 14$	58	48	7.9	
Use of diuretics				
No	254	117	14.5	<0.001
Yes	102	64	10.0	
Use of insulin <1 year of diagnosis				
No	317	157	13.9	<0.05
Yes	39	24	11.9	
Hypertension				
No	211	84	15.3	<0.001
Yes	151	99	9.8	
Retinopathy				
No	332	163	13.9	<0.001
Yes	24	18	6.5	
Proteinuria				
Negative	250	112	14.5	
Slight	54	27	12.4	<0.001
Heavy	57	44	8.0	
Fasting plasma glucose				
<200	235	106	11.9	<0.05
$\geqslant 200$	139	81	8.4	
Cholesterol				
<240	300	144	14.8	0.12
$\geqslant 240$	64	38	12.2	
Triglyceride				
<220	223	105	14.1	0.44
$\geqslant 220$	141	77	13.2	
BMI				
<30	189	114	11.8	<0.001
$\geqslant 30$	184	73	15.4	

can be applied. This model, presented in Chapter 12, is a regression model that relates patient characteristics directly to the risk of failure and thus indirectly to survival. The assumption of this model is that the hazards for different strata of each independent (or prognostic) variable are proportional over time. This assumption was verified by a graphical method (discussed in Chapter 12) using each of the variables. Figure 3.13 gives an example of the graph of $\log[-S(t)]$ versus t for the two hypertension groups. The two almost parallel curves indicate that the hazards of dying are proportional. Therefore, the assumption of the proportional hazards model is satisfied and the model appropriate.

This model can be fitted by a stepwise procedure that results in a ranking of the prognostic variables. The first variable selected to enter the model is the most important single variable in predicting the risk of dying. The second variable is the second most important, and so on. A significance level can be obtained from a likelihood ratio test at each step, which indicates the level of contribution given by the additional variable.

Using the proportional hazards model and a stepwise procedure, seven of the 12 variables were identified as significant at the 0.05 level based on the likelihood ratio test at each step. These variables, the regression coefficients, and the significance levels based on the Ward test, which uses the regression coefficient and its standard error (S.E.) are given in Table 3.9. The sign of the coefficient indicates whether the variable is positively or negatively related to the hazard of dying. For example, age and duration of diabetes are both positively related to the risk of dying and therefore negatively related to the survival time. Table 3.9 also gives the ratio of risk (or hazard) for values of each variable unfavorable to survival to values of that variable favorable to survival. For example, patients who were 60 years of age at baseline had a 3.05 times higher risk of dying during the follow-up period (10–16 years, average 13 years) than did patients who were only 40 years old at baseline. For dichotomous variables, the ratio of risk is equal to exp(coefficient), which is also interpreted as the relative risk of the variable adjusting for the other variables. Consequently, the confidence interval for the relative risk can be calculated (not shown in Table 3.9). Based on this set of data, the authors conclude that age, hypertension, duration of diabetes, fasting plasma glucose, BMI, proteinuria, and use of diuretics are significantly related to survival. The multivariate method also showed that high values of BMI might be protective.

3.5 EXAMPLE 3.5: IDENTIFICATION OF RISK FACTORS

A study of the incidence of retinopathy in Oklahoma Indians with NIDDM was conducted in 1987–1990 as part of a prospective study of diabetic complications (Lee et al., 1992). Among the 312 patients who were free of retinopathy at initial examination in the 1970s, 228 were found to have

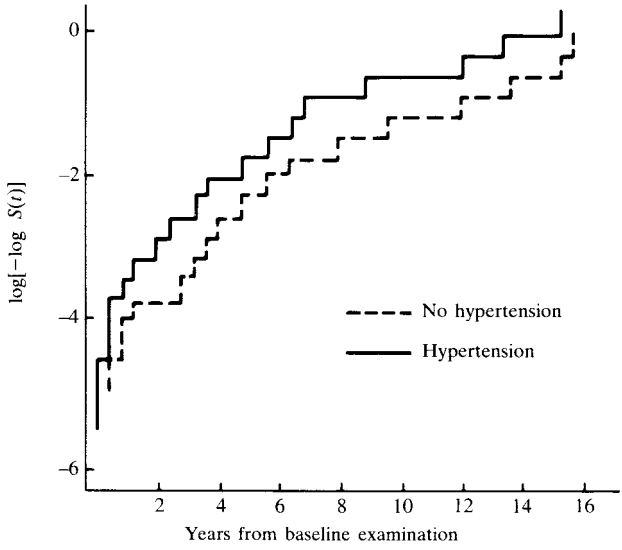


Figure 3.13 Curves of $\log[-\log S(t)]$ for the two hypertension groups.

Table 3.9 Significant Variables (at 0.05 Level) Identified by Proportional Hazards Model

Variable[a]	Regression Coefficient	p Value (Ward Test)	Relative Risk[b]		Ratio of Risk
			Favorable	Unfavorable	
Age	0.0558	<0.001	9.32	28.45	3.05
Hypertension: 1, yes, 0, no	0.6360	<0.001	1.00	1.89	1.89
Duration of diabetes	0.0559	<0.001	1.32	2.19	1.66
Fasting plasma glucose	0.0023	<0.010	1.35	1.58	1.17
BMI	−0.0330	0.035	0.32	0.44	0.72
Proteinuria: 1, yes, 0, no	0.3744	0.025	1.00	1.45	1.45
Use of diuretics: 1, yes; 0, no	0.4191	0.030	1.00	1.52	1.52

[a] Variables are listed in order of entry into model with a p-value limit for entry of 0.05.
[b] Favorable categories are 40 years of age, no hypertension, duration of diabetes 5 years, fasting plasma glucose 130 mg/dL, BMI 35, no proteinuria, and no diuretics use. Unfavorable categories are 60 years of age, hypertensive, duration of diabetes 14 years, fasting plasma glucose 200 mg/dL, BMI 25, having proteinuria, and diuretics use.

developed the eye disease during the 10 to 16-year follow-up period (average follow-up time 12.7 years). Twelve potential factors (assessed at time of baseline examination) were examined by univariate and multivariate methods for their relationship to retinopathy (RET): age, gender, duration of diabetes (DUR), fasting plasma glucose (GLU), initial treatment (TRT), systolic (SBP) and diastolic blood pressure (DBP), body mass index (BMI), plasma cholesterol (TC), plasma triglyceride (TG), and presence of macrovascular disease (LVD) or renal disease (RD). Table 3.10 gives the data for the first 40 patients. Among other things, the authors related these variables to the development of retinopathy.

1. *Examine the individual relationship of each variable to the development of diabetic retinopathy*. Table 3.11 gives some summary statistics of the eight continuous variables for patients who have developed retinopathy and for those who have not. Notice that patients who have developed the disease were younger at baseline and had much higher fasting plasma glucose, systolic and diastolic blood pressure, and plasma triglyceride than did patients who have not. Table 3.12 summarizes the contingency table analysis of retinopathy incidence rates. The number of patients at risk of developing retinopathy and the number of patients who developed the disease (and rate) are given by subcategory of each potential risk factor. Using the chi-square test, it is found that there was a significant difference in the retinopathy rate among the subcategories of several variables using a significance level of 0.05: duration of diabetes, fasting plasma glucose, systolic and diastolic blood pressure, and treatment. It appears that patients with poor glucose control or high blood pressure or treated with oral agents or insulin have a higher incidence of retinopathy. In addition, patients with high triglyceride levels tend to have higher incidence of retinopathy ($p = 0.064$). However, patients who had developed macrovascular disease at the time of baseline examination had a lower retinopathy incidence. The authors state that this may be due to the fact that 68% of the patients who had macrovascular disease either died (54%) during the follow-up period or were lost to follow-up (14%). Many of these patients may have developed retinopathy, particularly the patients who have died, but were not included. Therefore, the lower incidence of retinopathy in patients who had macrovascular disease at baseline is probably the result of a selection bias. Similarly, the large number of death plus the losses to follow-up may also contribute to the drop in retinopathy rate in patients who had had diabetes for more than 12 years at baseline. Among the 80 patients in this duration of diabetes category, 56% have died and 10% did not participate in the follow-up examination. The large number of deaths may also be responsible for the finding that patients who survived long enough to develop retinopathy were younger at baseline. The deceased patients were significantly older (mean 57 years) than the survivors who participated in the follow-up examination (mean 48 years).

Table 3.10 First 40 Patients Involved in Study of Risk Factors in Development of Diabetic Retinopathy

Patient	RET[a]	Age	Gender	DUR	TRT[b]	GLU	SBP	DBP	TC	TG	BMI	LVD[a]	RD[a]
1	1	47.6	M	4	2	100	156	98	195	405	33.1	0	0
2	0	54.4	M	7	1	112	112	78	204	77	31.7	0	0
3	0	50.8	M	4	2	83	134	80	206	178	41.5	1	0
4	1	49.4	F	5	2	276	102	70	190	222	24.1	0	0
5	1	50.0	M	2	2	104	142	86	178	100	39.5	0	0
6	1	50.7	F	7	2	242	142	78	217	268	31.6	0	1
7	1	35.3	F	2	2	130	134	80	390	564	47.0	0	0
8	0	50.2	F	5	2	130	100	70	174	128	29.8	0	0
9	1	45.0	M	5	2	115	134	100	238	177	18.9	1	0
10	0	38.3	M	2	2	110	132	80	204	180	31.2	1	0
11	0	45.8	F	5	3	130	118	68	185	316	26.6	1	0
12	1	51.6	F	3	2	141	112	78	152	77	31.2	0	1
13	1	36.3	M	6	2	238	142	94	194	162	24.2	0	0
14	1	44.7	F	16	2	190	152	90	132	161	32.0	0	0
15	1	37.2	F	1	2	126	136	90	133	211	32.7	0	0
16	1	52.6	F	9	2	159	140	76	151	132	26.7	0	0
17	1	44.1	M	1	1	116	126	76	251	153	33.3	0	0
18	1	35.9	M	3	1	120	132	80	129	76	30.1	0	0
19	1	50.4	M	1	2	128	144	90	190	123	27.7	0	0
20	1	48.0	M	1	2	95	128	74	207	59	28.1	1	0
21	0	47.5	F	1	2	85	124	82	161	190	31.6	1	0
22	1	50.1	F	6	2	138	106	72	181	135	30.5	0	1

(*Continued overleaf*)

Table 3.10 *Continued*

Patient	RET[a]	Age	Gender	DUR	TRT[b]	GLU	SBP	DBP	TC	TG	BMI	LVD[a]	RD[a]
23	0	43.3	F	1	1	104	128	86	204	198	26.1	0	0
24	1	54.5	M	0	3	104	142	84	490	540	30.8	1	0
25	1	52.2	F	3	3	304	132	84	192	119	36.9	1	0
26	1	53.3	F	3	2	249	128	72	120	85	35.5	0	0
27	1	64.3	F	6	2	297	138	80	145	64	30.1	1	0
28	1	44.6	F	4	1	139	112	80	156	111	36.1	0	1
29	1	47.1	F	2	2	169	130	84	198	99	39.0	0	1
30	1	46.5	F	7	1	159	128	78	238	157	34.5	0	0
31	0	51.5	F	3	1	147	128	78	185	182	32.0	0	0
32	1	59.5	M	3	2	180	132	78	188	308	28.1	1	0
33	1	52.0	F	6	2	183	142	84	175	68	37.6	0	0
34	1	45.7	F	6	2	180	138	80	179	189	44.1	1	0
35	1	48.2	F	18	2	267	158	100	195	112	25.2	1	0
36	1	57.4	M	0	1	159	172	108	219	294	33.7	0	1
37	1	42.0	F	4	2	158	106	68	224	157	33.6	0	0
38	1	50.7	F	1	2	211	142	84	390	645	37.1	0	0
39	1	53.8	F	0	1	177	154	80	175	208	35.3	0	1
40	0	56.9	M	1	1	98	116	70	146	97	26.5	0	1

[a] 1, yes; 0, no.
[b] 1, diet only; 2, oral agent; 3, insulin.

Table 3.11 Summary Statistics for Eight Variables by Retinopathy Status at Follow-up

	Retinopathy Status				
	No		Yes		
Variable	Mean	S.D.	Mean	S.D.	p Value
Age	50.0	9.0	47.2	7.4	0.01
Duration of diabetes	4.2	4.5	4.8	4.4	0.34
Fasting plasma glucose	141.8	65.6	196.3	76.6	<0.0001
Systolic blood pressure	128.0	15.7	132.6	17.3	0.04
Diastolic blood pressure	80.3	10.8	84.9	10.1	<0.001
Body mass index	32.3	6.3	32.5	5.9	0.76
Cholesterol	204.4	66.0	206.8	58.7	0.76
Triglyceride	180.5	111.1	234.4	273.3	0.01

2. *Examine the simultaneous relationship of the variables to the development of retinopathy*. Univariate analysis of each variable using the contingency table or the chi-square test gives a preliminary idea of which individual variable might be of prognostic importance. The simultaneous effect of all the variables can be analyzed by the linear logistic regression model (discussed in Section 14.2) to determine the relative importance of each.

The 12 variables were fitted to the linear logistic regression model using a stepwise selection procedure. The variables most significantly related to the development of retinopathy were found to be initial treatment, fasting plasma glucose, age, and diastolic blood pressure ($p \leqslant 0.001$). Table 3.13 gives the regression coefficients of the four most significant variables ($p \leqslant 0.05$), the standard errors, and adjusted odds ratios [exp(coefficient)]. The p values used here are the significance levels based on the likelihood ratio test or the improvement in the maximum likelihood due to the addition of the variable in the stepwise procedure. This method is more powerful than the Wald test, which is based on the standardized regression coefficients (Chapter 14). The results are consistent with those in the univariate analysis.

On the basis of the regression coefficients, the probability of developing retinopathy during a 10 to 16-year follow-up can be estimated by substituting values of the risk factors into the regression equation,

$$\log \frac{P}{1-P} = -2.373 + 1.495\,(\text{oral agent}) + 0.882\,(\text{insulin}) + 0.014\,(\text{GLU}) - 0.074\,(\text{age}) + 0.048\,(\text{DBP})$$

For example, for a 50-year-old patient who is on oral agents and whose fasting plasma glucose and diastolic blood pressure are 170 mg/dl and 95 mmHg,

Table 3.12 Cumulative Incidence Rates of Retinopathy by Baseline Variables

Variable	Number of Persons at Risk	Developed Retinopathy		p value
		Number	Percent	
Gender				
Female	211	151	71.6	0.384
Male	101	77	76.2	
Age (yr)				
<35	13	10	76.9	
35–44	101	77	76.2	0.242
45–54	155	115	74.2	
$\geqslant 55$	43	26	60.5	
Duration of diabetes (yr)				
<4	153	105	68.6	
4–7	113	86	76.1	0.033
8–11	23	22	95.7	
$\geqslant 12$	23	15	65.2	
Fasting plama glucose (mg/dl)				
<140	117	62	53.0	
140–199	90	74	82.2	<0.001
$\geqslant 200$	105	92	87.6	
Systolic blood pressure (mmHg)				
<130	145	95	65.5	
130–159	149	115	78.8	0.016
$\geqslant 160$	20	18	85.7	
Diastolic blood pressure (mmHg)				
<85	179	118	65.9	
85–94	87	73	83.9	0.004
$\geqslant 95$	46	37	80.4	
Plasma cholesterol (mg/dl)				
<240	267	193	72.3	0.442
$\geqslant 240$	45	35	77.8	
Plasma triglyceride (mg/dl)				
<250	237	167	70.5	0.064
$\geqslant 250$	75	61	81.3	
Body mass index (kg/m^2)				
<28	73	49	67.1	
28–33	121	94	77.7	0.261
$\geqslant 34$	118	85	72.0	
Renal disease				
No	251	179	71.3	0.155
Yes	61	49	80.3	
Macrovascular disease				
No	205	157	76.6	0.053
Yes	107	71	66.4	
Treatment (initial)				
Diet alone	115	62	53.9	
Oral agent	158	136	86.1	<0.001
Insulin	37	29	78.4	

Table 3.13 Results of Logistic Regression Analysis

Variable	Coefficient	Standard Error	exp(coefficient)	Coefficient/S.E.
Constant	−2.373	1.557		
Initial treatment				
Oral agent	1.495	0.330	4.459	4.53
Insulin	0.882	0.488	2.416	1.81
Fasting plasma glucose	0.014	0003	1.014	4.67
Age	−0.074	0019	0.929	−3.89
Diastolic blood pressure	0.048	0.015	1.049	3.20

respectively, the chance of developing retinopathy in the next 10 to 16 years is 91%.

The linear logistic regression model is useful in identifying important risk factors. However, complete measurements of all the variables are needed; missing data are a problem. In this example, complete data are available on most of the patients. This may not always be the case. Although there are methods of coping with missing data (discussed in Section 11.1), none is perfect. Thus it is extremely important for investigators to make every effort to obtain complete data on every subject.

Bibliographical Remarks

It is impossible to cite all the published examples of survival data analysis similar to those in this chapter. Other similar studies can be found in the literature: for example, *Biometrics*, *Biometrika*, *Cancer*, *Journal of Chronic Disease*, *Journal of the National Cancer Institute*, *American Journal of Epidemiology*, *Journal of the American Medical Association*, and *New England Journal of Medicine*. An easy way to find examples is to use the National Library of Medicine's Web site and search the file PubMed with appropriate keywords.

EXERCISES

The four sets of data below are taken from actual research situations. Although the data can be used for various analyses throughout the book, the reader is asked here only to describe in detail how the data can be analyzed. The data appear in examples and other exercises in subsequent chapters.

3.1 Thirty-three patients with hypernephroma were treated with combined chemotherapy, immunotherapy, and hormonal therapy. Exercise Table 3.1

Exercise Table 3.1 Data for 33 Patients with Hypernephroma

Patient	Age	Gender	Date Treatment Started	Response[a]	Date of Death or Last Follow-up	Status[b]	Skin Test Results[c]				
							Monilia	Mumps	PPD	PHA	SK-SD
1	53	F	3/31/77	1	10/1/77	0	7 × 7	23 × 23	0 × 0	25 × 25	0 × 0
2	61	M	6/18/76	0	8/21/76	1	10 × 10	15 × 20	0 × 0	13 × 13	9 × 9
3	53	F	2/1/77	3	10/1/77	0	0 × 0	7 × 7	0 × 0	25 × 25	0 × 0
4	48	M	12/19/74	2	1/15/76	1	0 × 0	0 × 0	0 × 0	0 × 0	0 × 0
5	55	M	11/10/75	0	1/15/76	1	12 × 12	ND	10 × 10	8 × 8	5 × 5
6	62	F	10/7/74	2	4/5/75	1	10 × 10	5 × 5	0 × 0	7 × 7	5 × 5
7	57	M	10/28/74	0	1/6/75	1	15 × 15	15 × 15	0 × 0	0 × 0	10 × 10
8	53	M	10/6/75	2	6/18/77	1	0 × 0	ND	0 × 0	12 × 12	0 × 0
9	45	M	4/11/77	0	10/1/77	0	6 × 4	4 × 4	0 × 0	0 × 0	0 × 0
10	58	M	8/4/76	3	2/11/77	1	13 × 13	13 × 13	22 × 22	23 × 23	0 × 0
11	61	F	1/1/77	3	10/1/77	0	0 × 0	8 × 8	17 × 17	11 × 11	0 × 0
12	61	M	7/25/76	1	10/1/77	0	9 × 9	12 × 12	0 × 0	20 × 20	0 × 0
13	77	M	5/8/75	0	9/26/75	1	0 × 0	0 × 0	0 × 0	0 × 0	0 × 0
14	55	M	4/27/77	2	10/1/77	0	0 × 0	0 × 0	15 × 15	10 × 10	0 × 0
15	50	M	4/20/77	3	10/1/77	0	0 × 0	14 × 14	5 × 5	32 × 32	21 × 21
16	42	M	8/24/76	0	10/1/77	0	11 × 11	7 × 7	0 × 0	12 × 12	0 × 0

17	50	F	1/8/75	0	6/30/75	1	0 × 0	0 × 0	0 × 0	0 × 0	0 × 0
18	66	F	9/8/76	3	10/1/77	0	9 × 9	10 × 10	6 × 6	15 × 15	11 × 11
19	58	M	2/18/75	0	10/1/77	0	0 × 0	0 × 0	0 × 0	0 × 0	ND
20	62	M	5/12/76	0	10/17/76	1	2 × 2	ND	ND	3 × 3	2 × 2
21	71	F	10/22/76	3	12/12/76	1	10 × 10	6 × 6	0 × 0	12 × 12	0 × 0
22	44	M	6/6/77	3	10/1/77	0	10 × 10	10 × 10	0 × 0	20 × 20	0 × 0
23	69	M	6/21/76	0	10/13/76	1	0 × 0	15 × 15	25 × 25	25 × 25	0 × 0
24	56	M	6/7/77	2	10/1/77	0	0 × 0	7 × 7	0 × 0	0 × 0	0 × 0
25	57	M	11/16/76	0	12/10/76	1	11 × 11	5 × 5	0 × 0	20 × 20	0 × 0
26	69	M	5/10/77	0	7/25/77	1	0 × 0	0 × 0	0 × 0	15 × 15	0 × 0
27	60	M	6/29/77	0	7/7/77	1	0 × 0	0 × 0	0 × 0	26 × 26	0 × 0
28	60	M	7/21/75	3	10/1/77	0	11 × 11	20 × 20	10 × 10	18 × 18	0 × 0
29	72	M	7/19/75	0	10/18/75	1	10 × 10	0 × 0	7 × 7	10 × 10	0 × 0
30	42	F	3/3/75	0	4/23/75	1	0 × 0	ND	0 × 0	0 × 0	0 × 0
31	57	M	2/24/77	2	10/1/77	0	5 × 5	8 × 8	0 × 0	25 × 15	0 × 0
32	66	M	6/15/77	3	10/1/77	0	0 × 0	15 × 15	0 × 0	10 × 10	0 × 0
33	59	M	3/4/77	0	4/2/77	1	0 × 0	0 × 0	0 × 0	16 × 16	0 × 0

Source: Data courtesy of Richard Ishmael.

[a] 0, no response; 1, complete response; 2, partial response; 3, stable.

[b] 0, alive; 1, dead.

[c] ND, not done.

gives the age, gender, date treatment began, response status, date of death or last follow-up, survival status, and results of five pretreatment skin tests. The investigator is interested in the response and survival of the patients and in identifying prognostic factors. How would you analyze the data?

3.2 In a study undertaken to compare the treatments given to hypernephroma patients and to relate response and survival to surgery, metastasis, and treatment time, data from 58 patients were collected (Exercise Table 3.2). How would you analyze the data to answer these questions?

(a) Do patients who had nephrectomy have a higher response rate?
(b) Is the time of nephrectomy related to response and survival?
(c) Are there significant differences between the treatments?
(d) What are the most important variables related to response and survival?

3.3 Exercise Table 3.3 gives the age, gender, family history of melanoma, remission duration, survival time, stage, and results of six pretreatment skin tests (the larger diameter is given) of 102 stage 3 and 4 melanoma patients (Lee et al., 1982).

(a) Study the immunocompetence of melanoma patients by investigating skin test results.
(b) Determine if age, gender, or pretreatment skin test results are predictive to remission and survival time.
(c) Find theoretical distributions that describe the survival and remission patterns.

3.4 One hundred and forty-nine diabetic patients were followed for 17 years (a subset of data from Lee et al., 1988). Exercise Table 3.4 gives the survival time from baseline examination, survival status, and several potential prognostic factors at baseline: age, body mass index (BMI), age at diagnosis of diabetes, smoking status, systolic blood pressure (SBP), diastolic blood pressure (DBP), electrocardiogram reading (ECG), and whether the patient had any coronary heart disease (CHD). Identify the important prognostic factors that are associated with survival.

Exercise Table 3.2 Data of 58 Patients with Hypernephroma

Patient	Gender	Age	Nephrectomy[b]	Time of Nephrectomy[c]	Treatment[d]	Response[c]	Survival Time	Status[f]	Lung Metastasis[b]	Bone Metastasis[b]
1	2	53	1	0.0	1	1	77	0	1	0
2	1	69	1	4.0	1	2	18	1	0	1
3	1	61	0	−9.0	1	0	8	1	1	0
4	2	52	1	2.0	1	2	68	1	1	0
5	1	46	1	2.0	1	2	35	1	0	1
6	1	55	1	0.0	1	0	8	1	1	0
7	2	62	1	0.0	1	2	26	1	1	0
8	1	53	1	0.0	1	2	84	1	0	1
9	1	70	0	−9.0	1	0	17	1	1	0
10	1	48	1	0.0	1	3	52	1	1	0
11	1	58	1	1.5	1	0	26	1	1	1
12	1	61	1	5.0	1	1	108	0	1	0
13	1	77	1	4.0	1	0	18	1	1	0
14	1	56	1	0.0	1	3	72	1	0	1
15	1	55	1	0.0	1	2	38	1	1	1
16	1	50	1	4.0	1	3	−99	9	1	0
17	1	75	1	0.0	1	0	9	1	1	0
18	1	43	1	2.0	1	3	56	1	0	0
19	1	69	1	1.0	1	2	36	1	1	1
20	2	59	1	1.5	1	2	108	1	0	1
21	2	71	1	0.0	1	2	10	1	1	0
22	1	56	1	0.0	1	2	36	1	1	0
23	1	57	0	−9.0	1	0	6	1	1	0
24	1	69	1	8.0	1	0	9	1	1	0

(*Continued overleaf*)

Exercise Table 3.2 *Continued*

Patient	Gender	Age	Nephrectomy[b]	Time of Nephrectomy[c]	Treatment[d]	Response[c]	Survival Time	Status[f]	Lung Metastasis[b]	Bone Metastasis[b]
25	1	72	0	−9.0	1	0	12	1	1	0
26	1	67	1	0.0	1	9	5	0	1	0
27	1	41	1	2.0	1	2	104	0	1	0
28	1	77	1	10.0	1	0	6	1	1	0
29	2	63	1	2.0	1	3	115	1	0	1
30	2	42	1	12.0	1	0	9	1	0	0
31	1	59	0	−9.0	1	0	21	1	0	0
32	1	62	1	5.0	1	0	14	1	1	0
33	1	65	1	0.0	1	0	52	1	1	0
34	2	53	0	−9.0	1	0	9	1	0	1
35	1	57	1	0.0	1	2	48	1	1	0
36	2	60	0	−9.0	1	0	15	1	1	1
37	1	59	1	0.0	1	0	5	1	1	0
38	1	75	1	0.0	2	3	28	0	1	0
39	2	53	1	0.0	2	2	25	0	1	0
40	2	67	1	5.0	2	3	25	0	0	1
41	1	58	1	8.0	2	3	40	1	1	1
42	1	62	1	8.0	2	0	16	1	1	1
43	1	69	0	−9.0	2	0	8	1	1	1

44	1	44	1	0.0	2	2	70	0	1	0
45	1	60	1	1.0	2	0	6	1	0	1
46	1	57	0	−9.0	2	0	8	1	1	1
47	1	45	1	2.0	2	4	12	1	1	0
48	2	50	1	1.0	2	4	20	1	1	0
49	1	58	0	−9.0	2	4	8	1	1	0
50	1	51	1	0.0	2	3	−99	0	0	1
51	1	59	1	3.0	2	3	12	1	1	0
52	1	53	1	0.0	2	1	181	0	1	0
53	1	70	1	0.5	2	0	20	1	1	1
54	1	69	1	3.0	2	0	14	1	1	0
55	1	62	1	0.0	2	3	26	1	0	0
56	1	52	1	2.0	2	0	16	1	1	0
57	1	77	1	2.0	2	2	30	1	1	0
58	1	61	1	8.0	2	0	20	1	1	0

Source: Data courtesy of Richard Ishmael.

[a] 1, male; 2, female.

[b] 1, yes; 0, no.

[c] Number of years prior to treatment; negative value — no nephrectomy.

[d] 1, combined chemotherapy and immunotherapy, 2, others.

[e] 0, no response; 1, complete response; 2, partial response; 3, stable; 4, increasing disease; 9, unknown.

[f] 1, dead; 0, alive; 9, unknown.

Exercise Table 3.3 Data of 102 Patients with Stages 3 and 4 Melanoma

Patient	Age	Gender	Family History of Melanoma[b]	Remission Time (months)[c]	Remission Status[d]	Survival Time (months)	Survival Status[e]	Stage	Skin Tests[f]					
									Monilia	Mumps	PPD	PHA	SK-SD	Tricophyton
1	58	2	9	42.0	0	42.0	0	3B	18	16	0	20	14	99
2	50	2	0	3.3	1	3.9	1	3B	7	8	0	0	7	0
3	76	1	0	6.1	1	10.5	1	3B	0	15	0	0	99	0
4	66	2	9	2.3	1	6.0	0	3B	8	0	0	10	0	0
5	33	1	9	5.1	1	20.6	1	3B	17	10	0	5	18	99
6	55	2	0	11.1	0	21.8	0	4B	99	99	99	99	99	99
7	25	2	0	36.5	0	36.5	0	3B	7	5	0	8	90	99
8	23	1	0	24.3	0	24.3	0	3B	10	20	0	7	30	0
9	30	1	0	28.7	0	28.7	0	3B	8	99	0	6	10	17
10	34	1	9	7.7	0	7.7	0	3B	15	99	0	0	0	0
11	34	1	0	29.3	0	29.3	0	3B	15	99	0	7	10	0
12	26	2	0	5.9	1	19.3	1	3AB	0	99	0	42	25	0
13	27	1	9	2.6	1	6.9	1	3AB	15	99	0	10	10	0
14	72	2	9	16.7	0	18.0	0	4B	10	99	99	15	0	7
15	70	2	0	14.6	0	14.6	0	3B	0	99	0	16	0	20
16	82	2	0	−99.0	9	23.6	0	4B	9	99	99	17	10	0
17	43	1	9	−99.0	9	3.9	1	4B	25	0	0	7	20	5
18	52	1	9	−99.0	9	7.3	1	4B	12	99	0	5	15	0
19	34	1	9	−99.0	9	9.8	1	4B	13	20	0	15	30	30
20	48	1	0	26.5	0	26.5	0	4A	10	99	0	88	5	0
21	62	1	9	18.0	1	25.4	0	3AB	5	99	0	10	0	24
22	49	1	9	4.3	1	8.0	1	3B	0	99	8	3	0	0
23	46	1	0	0.3	1	13.8	1	3B	0	5	0	7	0	0
24	53	2	1	21.5	0	21.5	0	3A	16	20	14	14	18	12
25	21	2	9	−99.0	9	9.3	1	4B	10	5	0	10	15	0
26	25	1	9	−99.0	9	1.2	1	4B	15	10	5	18	10	5
27	35	2	0	−99.0	9	20.0	1	4B	11	7	0	10	0	2

28	66	2	9	−99.0	9	12.5	0	4B	99	99	99	99	99	99
29	54	2	0	−99.0	9	7.4	1	4B	99	99	99	99	99	99
30	43	2	0	−99.0	9	4.7	0	4B	13	19	9	11	30	0
31	40	1	0	13.3	0	13.3	0	3B	0	5	25	12	10	0
32	16	1	0	0.0	0	0.0	0	3B	7	10	14	10	0	0
33	59	1	0	−99.0	9	25.8	0	4B	0	99	0	18	0	35
34	64	1	9	16.5	0	16.5	0	3B	8	7	0	0	0	0
35	52	1	9	−99.0	9	2.5	1	4B	9	14	0	12	5	0
36	−99	2	8	−99.0	9	13.8	1	4B	30	75	0	35	0	12
37	27	1	0	−99.0	9	4.2	1	4B	10	12	10	10	0	3
38	60	2	0	5.4	1	11.4	1	4B	20	10	0	10	0	0
39	73	1	9	−99.0	9	5.8	1	4B	0	9	0	40	0	30
40	50	2	0	13.5	0	13.5	0	3B	0	8	0	10	5	0
41	63	2	0	−99.0	9	2.7	1	4B	0	10	0	15	0	10
42	56	1	0	−99.0	9	0.9	1	4B	6	6	0	15	0	0
43	62	2	0	2.1	1	8.0	1	3A	0	8	0	32	0	20
44	57	1	9	−99.0	9	0.0	0	3AB	0	24	11	20	0	0
45	56	2	0	12.1	1	16.1	0	3B	0	5	0	25	6	30
46	41	2	1	−99.0	9	13.3	1	4B	99	99	99	99	99	99
47	40	2	0	10.1	0	10.1	0	4A	0	15	0	15	17	20
48	81	2	0	−99.0	9	0.0	0	4B	99	99	99	99	99	99
49	61	1	0	8.4	0	8.4	0	3B	0	4	0	10	0	8
50	62	2	0	7.7	0	7.7	0	3AB	0	11	0	16	23	0
51	34	1	0	15.1	1	24.4	1	3B	0	9	15	5	20	0
52	62	2	9	1.1	1	10.5	1	4A	8	99	0	99	0	0
53	63	2	9	−99.0	9	22.2	1	4B	0	0	0	8	3	0
54	56	1	9	−99.0	9	7.4	1	4B	0	99	0	6	0	0
55	66	2	9	−99.0	9	1.3	1	4B	0	0·	0	22	0	0
56	62	1	0	11.1	0	20.5	1	4B	25	20	0	10	15	18
57	68	2	0	−99.0	9	13.8	1	4B	20	99	0	17	15	15
58	45	1	0	−99.0	9	6.3	1	4B	28	15	0	10	17	50
59	58	1	9	−99.0	9	8.5	0	3B	10	17	0	25	30	25
60	55	1	9	−99.0	9	5.8	0	4B	99	99	99	99	99	99

(*Continued Overleaf*)

Exercise Table 3.3 ***Continued***

Patient	Age	Gender	Family History of Melanoma[b]	Remission Time (months)[c]	Remission Status[d]	Survival Time (months)	Survival Status[e]	Stage	Skin Tests[f]					
									Monilia	Mumps	PPD	PHA	SK-SD	Tricophyton
61	63	2	1	7.3	1	8.7	0	3B	0	9	0	23	12	15
62	53	1	9	36.4	0	36.4	0	3B	5	35	20	17	6	0
63	45	1	0	−99.0	9	5.9	1	4B	0	0	0	0	0	0
64	41	1	0	−99.0	9	1.7	1	4B	0	99	0	5	0	6
65	43	1	9	−99.0	9	3.9	1	4B	25	0	0	7	20	5
66	80	1	0	5.8	0	11.0	1	4B	99	99	99	99	99	99
67	75	2	9	−99.0	9	3.8	1	4B	0	99	0	6	0	0
68	47	2	9	−99.0	1	15.9	0	3B	0	0	0	20	15	0
69	64	2	9	6.7	0	6.7	0	3AB	0	5	0	18	0	0
70	38	1	9	−99.0	9	1.6	1	4B	99	99	99	99	99	99
71	27	1	0	6.0	0	6.0	0	3B	8	15	20	27	20	10
72	56	1	9	−99.0	9	4.1	0	4B	0	0	0	0	0	0
73	60	2	9	−99.0	9	2.8	0	3A	99	99	99	99	99	99
74	80	2	9	−99.0	9	0.2	0	4B	0	20	99	40	0	20
75	38	1	9	−99.0	9	7.0	0	4B	0	0	0	15	12	12
76	71	1	9	6.2	0	6.2	0	4A	99	99	99	99	99	99
77	57	2	0	6.1	0	6.1	0	4B	28	20	0	19	20	20
78	69	1	0	−99.0	9	2.1	0	4B	15	15	15	10	0	0
79	17	2	9	4.9	0	4.9	0	3B	99	99	99	99	99	99
80	64	2	0	−99.0	9	1.6	0	4B	99	99	99	99	99	99
81	91	1	0	6.5	0	8.3	1	4A	99	99	99	99	99	99
82	40	2	0	1.7	1	4.6	0	3B	99	99	99	99	99	99

83	63	1	0	7.3	0	28.0	1	3A	99	99	99	99	99	99
84	40	1	9	−99.0	9	16.1	1	4B	99	99	99	99	99	99
85	53	1	9	−99.0	9	4.5	1	4B	99	99	99	99	99	99
86	41	1	0	21.2	0	21.2	0	3A	99	99	99	99	99	99
87	27	1	9	−99.0	9	4.0	1	4B	99	99	99	99	99	99
88	−99	−9	0	−99.0	9	7.8	1	4B	99	99	99	99	99	99
89	45	2	9	−99.0	9	4.4	0	4B	99	99	99	99	99	99
90	50	2	9	−99.0	9	4.2	1	4B	99	99	99	99	99	99
91	47	1	9	−99.0	9	1.5	1	4B	99	99	99	99	99	99
92	63	1	9	−99.0	9	3.5	0	4B	99	99	99	99	99	99
93	52	1	9	−99.0	9	0.4	1	4B	99	99	99	99	99	99
94	53	1	9	−99.0	9	2.5	1	4B	99	99	99	99	99	99
95	60	2	9	−99.0	9	1.1	0	4B	99	99	99	99	99	99
96	35	1	9	−99.0	9	11.1	1	4B	99	99	99	99	99	99
97	24	2	9	1.2	0	1.2	0	3B	99	99	99	99	99	99
98	80	2	0	−99.0	9	1.9	0	3A	99	99	99	99	99	99
99	−99	−9	0	4.6	1	6.7	0	3B	99	99	99	99	99	99
100	60	2	9	0.9	0	0.9	0	3AB	99	99	99	99	99	99
101	60	2	9	−99.0	9	4.3	0	4B	99	99	99	99	99	99
102	35	1	0	5.2	0	5.2	0	3B	99	99	99	99	99	99

Source: Lee et al. (1979)

[a] 1, male; 2, female; −9, unknown.

[b] 1, yes; 0, No; 9, unknown.

[c] −99; never in remission during study period.

[d] 1, relapsed; 0, still in remission; 9, never in remission during study period.

[e] 1, dead; 0, still alive.

[f] In millimeters; 99, unknown.

Exercise Table 3.4 Data of 149 Diabetic Patients

			Variable at Baseline							
Patient	Status[a]	Survival Time (yr)	Age (yr)	BMI	Age at Diagnosis (yr)	Smoking Status[b]	SBP (mmHg)	DBP (mmHg)	ECG[c]	CHD[d]
1	1	12.4	44	34.2	41	0	132	96	1	0
2	1	12.4	49	32.6	48	2	130	72	1	0
3	1	9.6	49	22.0	35	2	108	58	1	1
4	1	7.2	47	37.9	45	0	128	76	2	1
5	1	14.1	43	42.2	42	2	142	80	1	0
6	1	14.1	47	33.1	44	0	156	94	1	0
7	1	12.4	50	36.5	48	0	140	86	2	1
8	1	14.2	36	38.5	33	2	144	88	1	0
9	1	12.4	50	41.5	47	1	134	78	1	1
10	1	14.5	49	34.1	45	0	102	68	1	0
11	1	12.4	50	39.5	48	2	142	84	1	0
12	1	10.8	54	42.9	43	0	128	74	1	0
13	0	10.9	42	29.8	36	2	156	86	1	0
14	1	10.3	44	33.2	43	2	102	58	1	0
15	0	13.6	40	27.5	26	2	146	98	1	0
16	1	11.9	48	25.3	48	0	120	68	2	1
17	1	12.5	50	31.6	44	1	142	76	1	0
18	1	5.9	47	26.3	38	1	144	82	1	0
19	1	12.4	38	32.4	36	2	150	98	2	1
20	1	14.1	35	47.0	33	1	134	78	1	0
21	0	9.8	51	26.5	47	2	130	76	1	0
22	1	7.2	40	43.9	34	0	122	92	1	0

23	1	3.5	54	32.3	52	1	132	80	1	0
24	1	0.0	53	34.5	47	2	150	88	3	1
25	0	12.1	45	18.9	40	1	134	98	1	0
26	1	1.9	41	32.0	31	1	142	90	2	1
27	1	8.6	34	33.9	30	2	124	66	1	0
28	1	14.0	38	23.7	28	0	102	60	1	0
29	1	14.3	43	24.8	43	0	134	80	1	0
30	1	12.4	45	26.6	41	2	118	66	2	1
31	1	12.4	40	39.2	35	2	192	108	1	0
32	1	14.4	44	32.7	36	2	122	78	1	0
33	1	14.2	48	33.5	43	1	122	92	1	0
34	1	14.5	51	32.2	49	2	112	74	1	0
35	1	12.4	36	24.2	30	2	142	90	1	0
36	1	14.3	52	31.6	48	1	152	96	1	0
37	0	13.7	41	30.7	39	2	112	74	1	0
38	1	13.4	49	28.0	35	2	118	84	1	0
39	1	12.5	44	32.0	29	0	152	88	1	0
40	1	14.4	37	32.7	36	2	136	88	1	0
41	1	12.6	51	24.2	42	2	134	90	1	0
42	1	13.8	47	18.7	42	0	130	78	2	1
43	1	14.0	45	25.6	36	0	108	72	1	0
44	1	6.8	38	22.8	27	2	126	66	2	1
45	1	12.4	35	30.1	33	0	132	78	1	0
46	1	12.9	50	27.7	49	1	144	88	1	0
47	1	8.9	53	27.6	49	2	126	68	1	0
48	1	12.4	48	28.1	47	1	128	70	1	0
49	1	14.5	40	31.7	37	2	132	82	1	0
50	1	13.0	43	26.1	42	2	128	80	1	0
51	1	13.4	54	30.8	54	1	142	80	2	1
52	1	10.6	52	36.9	50	1	132	80	2	1
53	1	13.9	69	24.2	63	1	148	78	1	0

(*Continued overleaf*)

Exercise Table 3.4 *Continued*

			Variable at Baseline							
Patient	Status[a]	Survival Time (yr)	Age (yr)	BMI	Age at Diagnosis (yr)	Smoking Status[b]	SBP (mmHg)	DBP (mmHg)	ECG[c]	CHD[d]
54	1	16.9	38	27.5	26	2	170	100	1	0
55	1	3.6	50	27.3	44	1	140	90	1	0
56	1	10.2	64	30.1	58	0	138	76	2	1
57	1	15.7	44	36.1	41	0	112	78	1	0
58	1	12.0	38	43.1	39	2	140	78	1	0
59	0	6.7	62	34.6	58	0	138	78	3	1
60	1	11.6	47	39.0	45	0	130	82	1	0
61	0	2.0	78	28.7	77	0	178	86	2	1
62	1	10.2	49	28.2	43	2	158	80	1	0
63	1	3.6	63	25.1	46	1	168	88	3	1
64	1	15.4	71	26.0	59	0	146	88	1	0
65	1	11.3	51	32.0	49	2	128	76	1	0
66	1	10.3	59	28.1	57	1	132	76	1	1
67	1	5.8	50	26.1	49	1	154	80	1	0
68	0	8.0	66	45.3	49	0	154	92	1	0
69	1	14.6	42	30.0	41	1	122	80	1	0
70	1	11.4	40	35.7	36	2	144	76	2	1
71	1	7.2	67	28.1	61	0	178	96	1	0
72	1	5.5	86	32.9	61	0	162	60	1	0
73	1	11.1	52	37.6	46	1	142	80	1	0
74	1	16.5	42	43.4	37	0	120	76	1	0
75	1	10.9	60	25.4	60	0	124	64	1	0
76	1	2.5	75	49.7	57	1	174	82	2	1

77	0	10.8	81	35.2	81	0	142	88	1	0
78	1	4.7	60	37.3	39	0	160	78	1	0
79	0	5.5	60	26.0	42	0	122	68	3	1
80	1	4.5	63	21.8	60	2	162	98	1	1
81	1	9.0	62	18.2	43	0	132	72	2	1
82	1	6.8	57	34.1	41	2	116	60	3	1
83	0	3.6	71	25.6	54	1	152	84	3	1
84	1	12.1	58	35.1	45	0	144	68	2	1
85	1	8.1	42	32.5	28	1	98	68	3	1
86	1	11.1	45	44.1	40	0	138	76	1	1
87	0	7.0	66	29.7	59	1	138	78	1	0
88	1	1.5	61	29.2	54	0	184	80	2	1
89	1	11.7	48	25.2	30	2	158	98	1	0
90	1	0.3	82	25.3	50	0	176	96	1	1
91	1	13.6	35	25.8	34	1	118	72	1	0
92	1	15.0	57	33.7	57	2	172	98	1	0
93	1	11.2	56	39.5	55	1	182	100	1	1
94	1	3.0	49	32.9	48	0	144	90	2	1
95	1	13.7	50	37.1	50	0	142	80	1	0
96	1	10.2	53	35.3	53	2	154	76	1	0
97	1	12.4	71	29.3	70	0	122	60	1	0
98	1	1.1	55	22.1	33	2	222	102	2	1
99	1	16.3	69	23.6	43	0	150	80	1	1
100	1	6.7	59	26.1	55	2	142	66	1	0
101	1	15.4	47	32.5	45	2	128	82	1	0
102	0	7.6	75	29.8	67	0	122	76	3	1
103	0	3.6	80	24.4	80	1	162	88	2	1
104	1	11.5	57	26.3	54	0	172	82	2	1
105	1	13.5	52	30.8	46	2	132	70	1	1
106	1	10.6	48	29.4	46	0	112	68	1	0

(*Continued overleaf*)

Exercise Table 3.4 ***Continued***

			Variable at Baseline							
Patient	Status[a]	Survival Time (yr)	Age (yr)	BMI	Age at Diagnosis (yr)	Smoking Status[b]	SBP (mmHg)	DBP (mmHg)	ECG[c]	CHD[d]
107	0	6.5	57	29.1	47	1	138	92	2	1
108	0	14.3	58	30.1	56	0	128	74	1	0
109	1	11.6	51	31.0	37	2	132	78	1	1
110	1	15.4	33	34.0	33	2	120	78	1	0
111	1	11.0	36	38.1	33	1	122	70	1	0
112	0	11.0	52	37.0	46	0	140	98	1	0
113	0	4.8	64	31.2	57	2	172	88	3	1
114	1	14.8	31	38.8	29	1	136	76	1	0
115	1	1.8	69	22.3	56	0	152	74	3	1
116	1	15.8	59	25.0	58	0	126	80	1	0
117	1	14.1	38	31.3	38	2	104	58	1	0
118	1	4.6	49	59.7	49	1	142	82	1	0
119	1	15.5	49	34.0	41	0	128	76	1	0
120	0	7.2	68	29.4	66	1	122	58	3	1
121	1	14.5	40	43.2	41	1	122	70	1	0
122	1	10.5	36	35.1	32	2	122	68	1	0
123	1	14.3	60	37.0	54	0	122	70	1	0
124	0	2.2	74	27.1	54	1	168	84	2	1
125	1	5.0	61	27.6	51	0	162	82	1	0
126	1	12.4	54	25.2	51	0	116	76	1	0

127	1	1.1	35	25.8	34	2	126	82	1	0
128	1	15.4	46	32.2	42	2	180	98	1	0
129	1	14.3	40	41.6	41	2	132	98	1	0
130	1	15.6	53	39.8	52	0	150	88	1	0
131	0	12.5	66	26.6	54	1	106	70	1	1
132	1	12.3	61	33.3	55	0	154	88	1	0
133	1	14.8	41	27.7	38	1	122	76	1	0
134	1	10.2	64	26.6	51	2	130	68	1	0
135	1	12.3	41	25.0	38	2	120	58	1	0
136	1	10.3	46	54.3	45	1	144	86	1	0
137	1	8.5	80	29.4	79	1	134	60	1	1
138	1	10.2	63	33.1	60	1	148	80	2	1
139	0	10.0	72	27.3	68	1	170	78	3	1
140	1	7.3	41	36.9	33	0	160	92	2	1
141	0	15.3	52	40.2	36	0	154	96	1	0
142	1	14.0	53	32.7	48	2	124	76	2	1
143	1	15.8	61	33.2	57	1	130	70	1	0
144	1	11.4	53	41.4	47	1	156	78	1	0
145	0	5.5	75	35.8	66	0	162	78	1	0
146	1	11.0	40	34.0	38	2	132	76	1	0
147	1	7.3	61	19.9	37	0	120	60	2	1
148	0	10.6	62	30.6	49	0	160	86	2	1
149	1	10.5	49	30.8	47	1	146	86	1	0

[a] Status: 0, dead; 1, alive.
[b] 0, no; ex-smoker; 2, current.
[c] 1, normal; 2, borderline; 3, abnormal.
[d] 0, no; 1, yes.

CHAPTER 4

Nonparametric Methods of Estimating Survival Functions

In this chapter we discuss methods of estimating the three survival (survivorship, density, and hazard) functions for censored data. Unfortunately, the simple method of Example 2.1 cannot be applied if some of the patients are alive at the time of analysis and therefore their exact survival times are unknown. Nonparametric or distribution-free methods are quite easy to understand and apply. They are less efficient than parametric methods when survival times follow a theoretical distribution and more efficient when no suitable theoretical distributions are known. Therefore, we suggest using nonparametric methods to analyze survival data before attempting to fit a theoretical distribution. If the main objective is to find a model for the data, estimates obtained by nonparametric methods and graphs can be helpful in choosing a distribution.

Of the three survival functions, survivorship or its graphical presentation, the survival curve, is the most widely used. Section 4.1 introduces the product-limit (PL) method of estimating the survivorship function developed by Kaplan and Meier (1958). With the increased availability of computers, this method is applicable to small, moderate, and large samples. However, if the data have already been grouped into intervals, or the sample size is very large, say in the thousands, or the interest is in a large population, it may be more convenient to perform a life-table analysis. Section 4.2 is devoted to the discussion of population and clinical life tables. The PL estimates and life-table estimates of the survivorship function are essentially the same. Many authors use the term *life-table estimates* for the PL estimates. The only difference is that the PL estimate is based on individual survival times, whereas in the life-table method, survival times are grouped into intervals. The PL estimate can be considered as a special case of the life-table estimate where each interval contains only one observation.

In Section 4.3 we discuss three other measures that describe the survival experience: the relative survival rate, the five-year survival rate, and the corrected survival rate. In Section 4.4 we describe two methods, direct and indirect standardization, to adjust rates to eliminate the effect of differences in population composition with respect to age and other variables. In addition, it introduces the standardized mortality rate and standardized incidence rate.

4.1 PRODUCT-LIMIT ESTIMATES OF SURVIVORSHIP FUNCTION

Let us first consider the simple case where all the patients are observed to death so that the survival times are exact and known. Let $t_1, t_2, \ldots, t_n$ be the exact survival times of the n individuals under study. Conceptually, we consider this group of patients as a random sample from a much larger population of similar patients. We relabel the n survival times $t_1, t_2, \ldots, t_n$ in ascending order such that $t_{(1)} \leqslant t_{(2)} \leqslant \cdots \leqslant t_{(n)}$. Following (2.1.2) and (2.1.3), the survivorship function at $t_{(i)}$ can be estimated as

$$\hat{S}(t_{(i)}) = \frac{n-i}{n} = 1 - \frac{i}{n} \tag{4.1.1}$$

where $n - i$ is the number of people in the sample surviving longer than $t_{(i)}$. If two or more $t_{(i)}$ are equal (tied observations), the largest i value is used. For example, if $t_{(2)} = t_{(3)} = t_{(4)}$, then

$$\hat{S}(t_{(2)}) = \hat{S}(t_{(3)}) = \hat{S}(t_{(4)}) = \frac{n-4}{n}$$

This gives a conservative estimate for the tied observations.

Since every person is alive at the beginning of the study and no one survives longer than $t_{(n)}$,

$$\hat{S}(t_{(0)}) = 1 \quad \text{and} \quad \hat{S}(t_{(n)}) = 0 \tag{4.1.2}$$

In practice, $\hat{S}(t)$ is computed at every *distinct* survival time. We do not have to worry about the intervals between the distinct survival times in which no one dies and $\hat{S}(t)$ remains constant. Equations (4.1.1) and (4.1.2) show that $\hat{S}(t)$ is a step function starting at 1.0 and decreasing in steps of $1/n$ (if there are no ties) to zero. When $\hat{S}(t)$ is plotted versus t, the various percentiles of survival time can be read from the graph or calculated from $\hat{S}(t)$. The following example illustrates the method.

Example 4.1 Consider a clinical trial in which 10 lung cancer patients are followed to death. Table 4.1 lists the survival times t in months. The function

Table 4.1 Computation of $\hat{S}(t)$ for 10 Lung Cancer Patients

t	i	$\hat{S}(t)$
4	1	$\frac{9}{10} = 0.9$
5	2	$\frac{8}{10} = 0.8$
6	3	$\frac{7}{10} = 0.7$
8	4	$\frac{4}{10} = 0.4$
8	5	$\frac{4}{10} = 0.4$
8	6	$\frac{4}{10} = 0.4$
10	7	$\frac{2}{10} = 0.2$
10	8	$\frac{2}{10} = 0.2$
11	9	$\frac{1}{10} = 0.1$
12	10	$\frac{0}{10} = 0.0$

$\hat{S}(t)$ is computed following (4.1.1) and plotted as a step function in Figure 4.1*a* and as a smooth curve in Figure 4.1*b*. The estimated median survival time is 8 months from Figure 4.1*a* or 7.6 months from Figure 4.1*b*. A more accurate estimate can be obtained using linear interpolation:

t	$\hat{S}(t)$
6	0.7
m	0.5
8	0.4

$$\frac{8-6}{0.4-0.7} = \frac{8-m}{0.4-0.5}$$

$$m = 8 - \frac{2(0.1)}{0.3} = 7.3(\text{months})$$

Theoretically, $\hat{S}(t)$ should be plotted as a step function since it remains constant between two observed exact survival times. However, when the median survival time must be estimated from a survival curve, a smooth curve (such as Figure 4.1*b*) may give a much better estimate than a step function, as indicated in the example.

This method can be applied only if all the patients are followed to death. If some of the patients are still alive at the end of the study, a different method of estimating $\hat{S}(t)$, such as the PL estimate given by Kaplan and Meier (1958), is required. The rationale can be illustrated by the following simple example.

Suppose that 10 patients join a clinical study at the beginning of 2000;

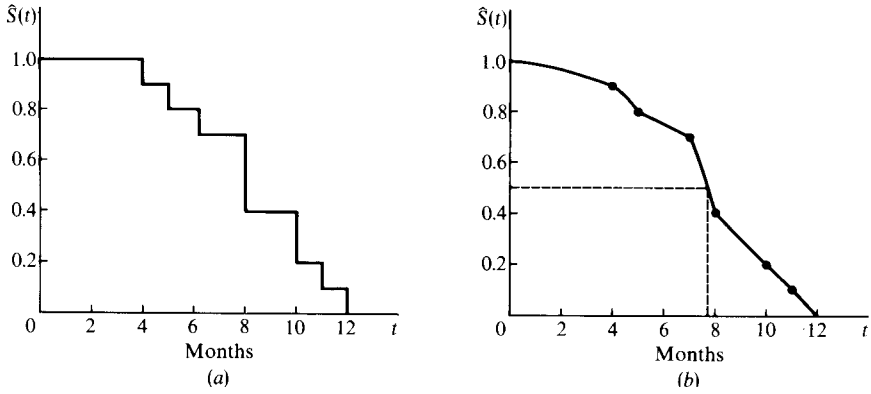


Figure 4.1 Function $\hat{S}(t)$ of lung cancer patients in Example 4.1.

during that year 6 patients die and 4 survive. At the end of the year, 20 additional patients join the study. In 2001, 3 patients who entered in the beginning of 2000 and 15 patients who entered later die, leaving one and five survivors, respectively. Suppose that the study terminates at the end of 2001 and you want to estimate the proportion of patients in the population surviving for two years or more, that is, $S(2)$.

The first group of patients in this example is followed for two years; the second group is followed for only one year. One possible estimate, the *reduced-sample estimate*, is $\hat{S}(2) = 1/10 = 0.1$, which ignores the 20 patients who are followed only for one year. Kaplan and Meier believe that the second sample, under observation for only one year, can contribute to the estimate of $S(2)$.

Patients who survived two years may be considered as surviving the first year and then surviving one more year. Thus, the probability of surviving for two years or more is equal to the probability of surviving the first year and then surviving one more year. That is,

$$S(2) = P(\text{surviving first year and then surviving one more year})$$

which can be written as

$$S(2) = P(\text{surviving two years given patient has survived first year}) \times P(\text{surviving first year}) \tag{4.1.3}$$

The Kaplan–Meier estimate of $S(2)$ following (4.1.3) is

$$\hat{S}(2) = \begin{pmatrix}\text{proportion of patients surviving two years} \\ \text{given they survive for one year}\end{pmatrix} \times (\text{proportion of patients surviving one year}) \tag{4.1.4}$$

For the data given above, one of the four patients who survived the first year survived two years, so the first proportion in (4.1.4) is $\frac{1}{4}$. Four of the 10 patients who entered at the beginning of 2000 and 5 of the 20 patients who entered at the end of 2000 survived one year. Therefore, the second proportion in (4.1.4) is $(4 + 5)/(10 + 20)$. The PL estimate of $S(2)$ is

$$\hat{S}(2) = \frac{1}{4} \times \frac{4 + 5}{10 + 20} = 0.25 \times 0.3 = 0.075$$

This simple rule may be generalized as follows: The probability of surviving k ($\geqslant 2$) or more years from the beginning of the study is a product of k observed survival rates:

$$\hat{S}(k) = p_1 \times p_2 \times p_3 \times \cdots \times p_k \tag{4.1.5}$$

where p_1 denotes the proportion of patients surviving at least one year, p_2 the proportion of patients surviving the second year after they have survived one year, p_3 the proportion of patients surviving the third year after they have survived two years, and p_k the proportion of patients surviving the kth year after they have survived $k - 1$ years.

Therefore, the PL estimate of the probability of surviving any particular number of years from the beginning of study is the product of the same estimate up to the preceding year, and the observed survival rate for the particular year, that is,

$$\hat{S}(t) = \hat{S}(t - 1)p_t \tag{4.1.6}$$

The PL estimates are maximum likelihood estimates.

In practice, the PL estimates can be calculated by constructing a table with five columns following the outline below.

1. Column 1 contains all the survival times, both censored and uncensored, in order from smallest to largest. Affix a plus sign to the censored observation. If a censored observation has the same value as an uncensored observations, the latter should appear first.
2. The second column, labeled i, consists of the corresponding rank of each observation in column 1.
3. The third column, labeled r, pertains to uncensored observations only. Let $r = i$.
4. Compute $(n - r)/(n - r + 1)$, or p_i, for every uncensored observation $t_{(i)}$ in column 4 to give the proportion of patients surviving up to and then through $t_{(i)}$.

5. In column 5, $\hat{S}(t)$ is the product of all values of $(n-r)/(n-r+1)$ up to and including t. If some uncensored observations are ties, the smallest $\hat{S}(t)$ should be used.

To summarize this procedure, let n be the total number of patients whose survival times, censored or not, are available. Relabel the n survival times in order of increasing magnitude such that $t_{(1)} \leqslant t_{(2)} \leqslant \cdots \leqslant t_{(n)}$. Then

$$\hat{S}(t) = \prod_{t_{(r)} \leqslant t} \frac{n-r}{n-r+1} \tag{4.1.7}$$

where r runs through those positive integers for which $t_{(r)} \leqslant t$ and $t_{(r)}$ is uncensored. The values of r are consecutive integers $1, 2, \ldots, n$ if there are no censored observations; if there are censored observations, they are not.

The estimated median survival time is the 50th percentile, which is the value of t at $\hat{S}(t) = 0.50$. The following example illustrates the calculation procedures.

Example 4.2 Suppose that the following remission durations are observed from 10 patients ($n = 10$) with solid tumors. Six patients relapse at 3.0, 6.5, 6.5, 10, 12, and 15 months; 1 patient is lost to follow-up at 8.4 months; and 3 patients are still in remission at the end of the study after 4.0, 5.7, and 10 months. The calculation of $\hat{S}(t)$ is shown in Table 4.2.

The survivorship function $\hat{S}(t)$ is plotted in Figure 4.2; the estimated median remission time is $m = 9.8$ months. From the calculation we notice that $\hat{S}(t)$ at

Table 4.2 Calculation of the PL Estimate of $\hat{S}(t)$ for Data in Example 4.2

Remission Time t	Rank i	r	$(n-r)/(n-r+1)$	$\hat{S}(t)$
3.0	1	1	$\frac{9}{10}$	$\frac{9}{10} = 0.900$
4.0+	2	—	—	—
5.7+	3	—	—	—
6.5	4	4	$\frac{6}{7}$	$\frac{9}{10} \times \frac{6}{7} = 0.771^a$
6.5	5	5	$\frac{5}{6}$	$\frac{9}{10} \times \frac{6}{7} \times \frac{5}{6} = 0.643^a$
8.4+	6	—	—	—
10.0	7	7	$\frac{3}{4}$	$\frac{9}{10} \times \frac{6}{7} \times \frac{5}{6} \times \frac{3}{4} = 0.482$
10.0+	8	—	—	—
12.0	9	9	$\frac{1}{2}$	$\frac{9}{10} \times \frac{6}{7} \times \frac{5}{6} \times \frac{3}{4} \times \frac{1}{2} = 0.241$
15.0	10	10	0	0

[a] 0.643 is used as $\hat{S}(6.5)$. It is a conservative estimate.

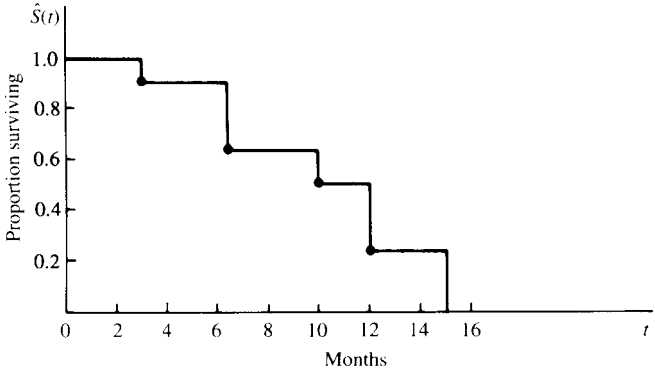


Figure 4.2 Function $\hat{S}(t)$ of Example 4.2.

$t = t_{(i)}$ is related to $\hat{S}(t)$ at $t = t_{(i-1)}$ and (4.1.6) can be rewritten as

$$\hat{S}(t_{(i)}) = \hat{S}(t_{(i-1)}) \frac{n-i}{n-i+1} \tag{4.1.8}$$

where $t_{(i)}$ and $t_{(i-1)}$ are uncensored observations. For example,

$$\hat{S}(12) = \hat{S}(10) \times \tfrac{1}{2} = 0.482 \times \tfrac{1}{2} = 0.241$$

If there are no censored observations or losses before t, (4.1.7) is equivalent to (4.1.1).

The variance of the PL estimate of $\hat{S}(t)$ is approximated by

$$\text{Var}[\hat{S}(t)] \simeq [\hat{S}(t)]^2 \sum_r \frac{1}{(n-r)(n-r+1)} \tag{4.1.9}$$

where r includes those positive integers for which $t_{(r)} \leqslant t$ and $t_{(r)}$ corresponds to a death. For the data in Example 4.2, for example,

$$\begin{aligned}\text{Var}[\hat{S}(10)] &= (0.482)^2 \left(\frac{1}{9 \times 10} + \frac{1}{6 \times 7} + \frac{1}{5 \times 6} + \frac{1}{3 \times 4}\right) \\ &= 0.0352\end{aligned}$$

and the estimated standard error is 0.1876. In Example 4.1,

$$\text{Var}[\hat{S}(6)] = (0.7)^2 \left(\frac{1}{9 \times 10} + \frac{1}{8 \times 9} + \frac{1}{7 \times 8}\right) = 0.0210$$

and the estimated standard error is 0.145. The variance may be used to obtain confidence intervals for $S(t)$.

Calculation of the PL estimate of $S(t)$ in Example 4.2 can also be obtained by using statistical software. Let t denote the observed remission time (uncensored or censored) in Table 4.2 and CENS denote an index (or dummy) variable with CENS = 0 if t is censored and 1 otherwise. Assume that the data have been saved in "C:\D4d2.DAT" as a text file, which contains two columns, t and CENS, separated by a space.

The following SAS code can be used to obtain the PL estimate of $S(t)$ in Table 4.2. One can adopt this code to obtain the PL estimate of $S(t)$ for any observed uncensored or censored survival time data.

```
data w1;
  infile 'c:\d4d2.dat' missover;
  input t cens;
run;
proc lifetest data = w1 outsurv = wa;
  time t*cens(0);
run;
title 'PL estimate of survival function';
proc print data = wa;
run;
```

If BMDP 1L is used, the following code can be used.

```
/input      file = 'c:\d4d2.dat'.
            variables = 2.
            format = free.
/variable   names = t, cens.
/form       time = t.
            status = cens.
            response = 1.
/estimate   method = product.
            Print.
/end
```

If the SPSS KM procedure is used, the following code can be used.

```
data list file = 'c:\d4d2.dat' free
        / t cens.
km t
        /status = cens event (1)
        /print.
```

Example 4.3 Consider the tumor-free time in days of the 30 rats on a low-fat diet in Table 3.4. Table 4.3 gives the calculations of the PL estimates of $S(t)$ and the standard error of $\hat{S}(t)$. The estimated $S(t)$ is plotted in Figure 3.3. The median tumor-free time is approximately 189 days.

Table 4.3 Calculation of $\hat{S}(t)$ and Standard Error of $\hat{S}(t)$ for 30 Rats on a Low-Fat Diet in Table 3.4

Rat Number	Tumor-free Time t	i	r	$\frac{n-r}{n-r+1}$	$\hat{S}(t)$	Standard Error of $\hat{S}(t)$
3	50	1	1	$\frac{29}{30}$	$\frac{29}{30} = 0.967$	$\left[(0.967)^2\left(\frac{1}{29\times 30}\right)\right]^{1/2} = 0.033$
12	56	2	2	$\frac{28}{29}$	$0.967\times\frac{28}{29} = 0.933$	$\left[(0.933)^2\left(\frac{1}{29\times 30}+\frac{1}{28\times 29}\right)\right]^{1/2} = 0.046$
4	65	3	3	$\frac{27}{28}$	$0.933\times\frac{27}{28} = 0.900$	$\left[(0.900)^2\left(\frac{1}{29\times 30}+\frac{1}{28\times 29}+\frac{1}{27\times 28}\right)\right]^{1/2} = 0.055$
13	66	4	4	$\frac{26}{27}$	$0.900\times\frac{26}{27} = 0.867$	0.062
14	73	5	5	$\frac{25}{26}$	0.833	0.068
9	77	6	6	$\frac{24}{25}$	0.800	0.073
10	84	7	7	$\frac{23}{24}$	0.767	0.077
5	86	8	8	$\frac{22}{23}$	0.733	0.081
11	87	9	9	$\frac{21}{22}$	0.700	0.084
15	119	10	10	$\frac{20}{21}$	0.667	0.086
1	140	11	11	$\frac{19}{20}$	0.633	0.088
16	140+	12	—	—	—	

6	153	13	13	$\frac{17}{18}$	$0.633 \times \frac{17}{18} = 0.598$	0.090
2	177	14	14	$\frac{16}{17}$	$0.598 \times \frac{16}{17} = 0.563$	0.091
7	181	15	15	$\frac{15}{16}$	0.528	0.092
8	191	16	16	$\frac{14}{15}$	0.493	0.092
17	200+	17	—	—	—	—
18	200+	18	—	—	—	—
19	200+	19	—	—	—	—
20	200+	20	—	—	—	—
21	200+	21	—	—	—	—
22	200+	22	—	—	—	—
23	200+	23	—	—	—	—
24	200+	24	—	—	—	—
25	200+	25	—	—	—	—
26	200+	26	—	—	—	—
27	200+	27	—	—	—	—
28	200+	28	—	—	—	—
29	200+	29	—	—	—	—
30	200+	30	—	—	—	—

The mean survival time μ can be shown to equal the area under the estimated survivorship function. To estimate μ, we can use

$$\hat{\mu} = \int_0^\infty \hat{S}(t)\, dt$$

that is, $\hat{\mu}$ is equal to the area under the estimated survivorship function. Thus, if the times to death are ordered as $t^{(1)} \leqslant t^{(2)} \leqslant \cdots \leqslant t^{(m)}$ (if there are m uncensored observations) and $t^{(m)}$ is the largest observation of all n observations [i.e., $t^{(m)} = t_{(n)}$ when $t_{(n)}$ is an uncensored observation], μ can be estimated as

$$\hat{\mu} = 1.000t^{(1)} + \hat{S}(t^{(1)})(t^{(2)} - t^{(1)}) + \hat{S}(t^{(2)})(t^{(3)} - t^{(2)}) + \cdots + \hat{S}(t^{(m-1)})(t^{(m)} - t^{(m-1)}) \tag{4.1.10}$$

which is the sum of the areas of the rectangles under the survival curve formed by the uncensored observations. Consider the data in Example 4.2: $m = 6$, $t^{(1)} = 3.0$, $t^{(2)} = 6.5$, $t^{(3)} = 6.5$, $t^{(4)} = 10$, $t^{(5)} = 12$, and $t^{(6)} = 15$. The mean survival time is estimated using (4.1.10) as

$$\begin{aligned}\hat{\mu} &= 1.000 \times 3.0 + 0.900(6.5 - 3.0) + 0.643(10 - 6.5) \\ &\quad + 0.482(12 - 10) + 0.241(15 - 12) \\ &= 3.000 + 3.150 + 2.251 + 0.964 + 0.723 \\ &= 10.088 \text{ months}\end{aligned}$$

However, if the largest observation in the data is censored and is used as $t^{(m)}$ in (4.10), μ so obtained may be a low estimate. In such cases, Irwin (1949) suggests that instead of estimating the mean survival time, one should choose a time limit L and estimate the "mean survival time limited to a time L," say $\mu_{[L]}$, by using L for $t^{(m)}$ in (4.1.10). For example, if in Example 4.2 the largest observation is censored, that is, 15+, and if we let $L = 16$, then

$$\begin{aligned}\mu_{[16]} &= 3.000 + 3.150; + 2.251 + 0.964 + 0.241(16 - 12) \\ &= 10.329 \text{ months}\end{aligned}$$

which is the mean survival time limited to 16 months.

The variance of $\hat{\mu}$ is estimated by

$$\text{Var}(\hat{\mu}) = \sum_r \frac{A_r^2}{(n - r)(n - r + 1)} \tag{4.1.11}$$

where r runs through those integers for which t_r corresponds to a death, and

A_r is the area under the curve $\hat{S}(t)$ to the right of $t_{(r)}$. The kth A_r in terms of the m uncensored observations is

$$\hat{S}(t^{(k)})(t^{(k+1)} - k^{(k)}) + \hat{S}(t^{(k+1)})(t^{(k+2)} - t^{(k+1)}) + \cdots + \hat{S}(t^{(m-1)})(t^{(m)} - t^{(m-1)}) \tag{4.1.12}$$

If there are no censored observations, (4.1.10) reduces to the sample mean $\bar{t} = \Sigma t_i/n$, and (4.1.11) reduces to

$$\text{Var}(\hat{\mu}) = \text{Var}(\bar{t}) = \frac{\sum (t_i - \bar{t})^2}{n^2} \tag{4.1.13}$$

which is not an unbiased estimate. Kaplan and Meier suggest that (4.1.11) and (4.1.13) be multiplied by $m/(m-1)$ and $n/(n-1)$, respectively, to correct the bias.

Consider the survival times in Example 4.1: The sample mean is $\bar{t} = \hat{\mu} = 8.2$ months and the estimated variance of $\hat{\mu}$, by (4.1.13), is 0.616. If the factor $n/(n-1) = 10/9$ is multiplied, the estimated variance of μ becomes 0.684.

To compute the variance of $\hat{\mu}$ in Example 4.2, we first compute the five A_r's: A_1, A_4, A_5, A_7, and A_9. The first A_r is

$$\begin{aligned} A_1 &= \hat{S}(t^{(1)})(t^{(2)} - t^{(1)}) + \hat{S}(t^{(2)})(t^{(3)} - t^{(2)}) + \cdots + \hat{S}(t^{(5)})(t^{(6)} - t^{(5)}) \\ &= 3.150 + 2.251 + 0.964 + 0.723 = 7.088 \end{aligned}$$

The second A_r is

$$\begin{aligned} A_4 &= \hat{S}(t^{(2)})(t^{(3)} - t^{(2)}) + \cdots + \hat{S}(t^{(5)})(t^{(6)} - t^{(5)}) \\ &= 2.251 + 0.964 + 0.723 = 3.938 \end{aligned}$$

The third, fourth, and fifth A_r's are, respectively,

$$\begin{aligned} A_5 &= 2.251 + 0.964 + 0.723 = 3.938 \\ A_7 &= 0.964 + 0.723 = 1.687 \\ A_9 &= 0.723 \end{aligned}$$

Thus,

$$\widehat{\text{Var}}(\hat{\mu}) = \frac{(7.088)^2}{9 \times 10} + \frac{(3.938)^2}{6 \times 7} + \frac{(3.928)^2}{5 \times 6} + \frac{(1.687)^2}{3 \times 4} + \frac{(0.723)^2}{1 \times 2} = 1.942$$

The estimated standard error of $\hat{\mu}$ is 1.394. If the factor $m/(m-1) = 6/5$ is included, these results become 2.330 and 1.526, respectively.

The Kaplan–Meier method provides very useful estimates of survival probabilities and graphical presentation of survival distribution. It is the most

widely used method in survival data analysis. Breslow and Crowley (1974) and Meier (1975b) have shown that under certain conditions, the estimate is consistent and asymptomatically normal. However, a few critical features should be mentioned.

1. The Kaplan–Meier estimates are limited to the time interval in which the observations fall. If the largest observation is uncensored, the PL estimate at that time equals zero. Although the estimate may not be welcomed by physicians, it is correct since no one in the sample lives longer. If the largest observation is censored, the PL estimate can never equal zero and is undefined beyond the largest observation.
2. The most commonly used summary statistic in survival analysis is the median survival time. A simple estimate of the median can be read from survival curves estimated by the PL method as the time t at which $\hat{S}(t) = 0.5$. However, the solution may not be unique. Consider Figure 4.3*a*, where the survival curve is horizontal at $\hat{S}(t) = 0.5$; any t value in the interval t_1 to t_2 is a reasonable estimate of the median. A practical solution is to take the midpoint of the interval as the PL estimate of the median. Figure 4.3*b* presents a different case in which the straightforward estimate (t_1) tends to overestimate the median. A practical way to handle this problem is to connect the points and locate the median.
3. If less than 50% of the observations are uncensored and the largest observation is censored, the median survival time cannot be estimated. A practical way to handle the situation is to use probabilities of surviving a given length of time, say 1, 3, or 5 years, or the mean survival time limited to a given time t.
4. The PL method assumes that the censoring times are independent of the survival times. In other words, the reason an observation is censored is unrelated to the cause of death. This assumption is true if the patient is

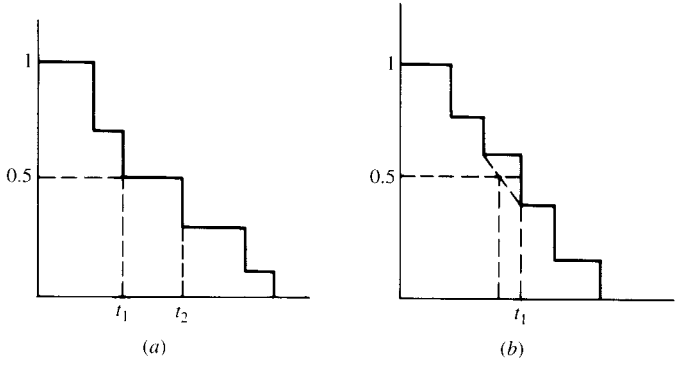


Figure 4.3 Kaplan–Meier estimate of median survival time.

still alive at the end of the study period. However, the assumption is violated if the patient develops severe adverse effects from the treatment and is forced to leave the study before death or if the patient died of a cause other than the one under study (e.g., death due to automobile accidents in a cancer survival study). When there is inappropriate censoring, the PL method is not appropriate. In practice, one way to alleviate the problem is to avoid it or to reduce it to a minimum.

5. Similar to other estimators, the standard error (S.E.) of the Kaplan–Meier estimator of $S(t)$ gives an indication of the potential error of $\hat{S}(t)$. The confidence interval deserves more attention than just the point estimate $\hat{S}(t)$. A 95% confidence interval for $S(t)$ is $\hat{S}(t) \times 1.96\,\text{S.E.}[\hat{S}(t)]$.

4.2 LIFE-TABLE ANALYSIS

The life-table method is one of the oldest techniques for measuring mortality and describing the survival experience of a population. It has been used by actuaries, demographers, governmental agencies, and medical researchers in studies of survival, population growth, fertility, migration, length of married life, length of working life, and so on. There has been a decennial series of life tables on the entire U.S. population since 1900. States and local governments also publish life tables. These life tables, summarizing the mortality experience of a specific population for a specific period of time, are called *population life tables*. As clinical and epidemiologic research become more common, the life-table method has been applied to patients with a given disease who have been followed for a period of time. Life tables constructed for patients are called *clinical life tables*. Although population and clinical life tables are similar in calculation, the sources of required data are different.

4.2.1 Population Life Tables

There are two kinds of population life tables: the cohort life table and current life table. The *cohort life table* describes the survival or mortality experience from birth to death of a specific cohort of persons who were born at about the same time, for example, all persons born in 1950. The cohort has to be followed from 1950 until all of them die. The proportion of death (survivor) is then used to construct life tables for successive calendar years. This type of table, useful in population projection and prospective studies, is not often constructed since it requires a long follow-up period.

The *current life table* is constructed by applying the age-specific mortality rates of a population in a given period of time to a hypothetical cohort of 100,000 or 1,000,000 persons. The starting point is birth at year 0. Two sources of data are required for constructing a population life table: (1) census data on

the number of living persons at each age for a given year at midyear and (2) vital statistics on the number of deaths in the given year for each age. For example, a current U.S. life table assumes a hypothetical cohort of 100,000 persons that is subject to the age-specific death rates based on the observed data for the United States in the 1990 census. The current life table, based on the life experience of an actual population over a short period of time, gives a good summary of current mortality. This type of life table is regularly published by government agencies of different levels. One of the most often reported statistics from current life tables is the life expectancy. The term *population life table* is often used to refer to the current life table.

In the United States, the National Center for Health Statistics publishes detailed decennial life tables after each decennial census. These complete life tables use one-year age groups. Between censuses, annual life tables are also published. The annual life tables are often seen in five-year age intervals and are called *abridged life tables*. Tables 4.4 and 4.5 are, respectively, a complete decennial life table for the total U.S. population for 1989–1991 and an abridged life table for the same population for 1998. The abridged table in Table 4.5 was constructed based on a complete life table.

Current life tables usually have the following columns:

1. *Age interval* $[x \text{ to } x + t)$. This is the time interval between two exact ages x and $x + t$; t is the length of the interval. For example, the interval 20–21 includes the time interval from the 20th birthday up to the 21st birthday (but not including the 21st birthday).
2. *Proportion of persons alive at beginning of age interval but dying during the interval* $({}_tq_x)$. The information is obtained from census data. For example, $({}_tq_x)$ for age interval 20–21 is the proportion of persons who died on or after their 20th birthday and before their 21st birthday. It is an estimate of the conditional probability of dying in the interval given the person is alive at age x. This column is usually calculated from data of the decennial census of population and deaths occurring in the given time interval. For example, the mortality rates in Table 4.4 are calculated from the data of the 1990 Census of Population and deaths occurring in the United States in the three years 1989–1991. This column is the foundation of the life table from which all of the other columns are derived.
3. *Number living at beginning of age interval* (l_x). The initial value of l_x, the size of the hypothetical population, is usually 100,000 or 1,000,000. The successive values are computed using the formula

$$l_x = l_{x-1}(1 - {}_tq_{x-t}) \tag{4.2.1}$$

where $1 - {}_tq_{x-t}$ is the proportion of persons who survived the previous age interval. For example, in Table 4.4, $t = 1$, $l_{20} = l_{19}(1 - {}_1q_{19}) =$

98,314(1 − 0.00101) = 98,215, which is the number of persons living at the beginning of age 20.

4. *Number dying during age interval* ($_td_x$)

$$_td_x = l_x(_tq_x) = l_x - l_{x+1} \tag{4.2.2}$$

For example, the number of persons dying during age interval 20–21, $_td_{20} = 98{,}215(0.00104) = 102$ (or $_1d_{20} = 98{,}215 - 98{,}113 = 102$).

5. *Stationary population* ($_tL_x$ and T_x). Here $_tL_x$ is the total number of years lived in the ith age interval or the number of person-years that l_x persons, aged x exactly, live through the interval. For those who survive the interval, their contribution to $_tL_x$ is the length of the interval, t. For those who die during the interval, we may not know exactly the time of death and the survival time must be estimated. The conventional assumption is that they live one-half of the interval and contribute $t/2$ to the calculation of $_tL_x$. Thus,

$$_tL_x = t(l_{x+1} + \tfrac{1}{2}\,{}_td_x) \tag{4.2.3}$$

For example, in Table 4.4, $_1L_{20} = 98{,}113 + 102/2 = 98{,}164$. If we do know the exact survival time of those who die in the interval, $_tL_x$ should be computed accordingly.

The symbol T_x is the total number of person-years lived beyond age t by persons alive at that age, that is,

$$T_x = \sum_{j \geqslant x} {}_tL_j \tag{4.2.4}$$

and

$$T_x = {}_tL_x + T_{x+t} \tag{4.2.5}$$

For example, in Table 4.4, $T_0 = 7{,}536{,}614$, which is the sum of all $_tL_x$ values in column 5, and $T_1 = 7{,}437{,}356$, which is
$T_0 - {}_1L_0 = 7{,}536{,}614 - 99{,}258$.

6. *Average remaining lifetime or average number of years of life remaining at beginning of age interval* ($\mathring{e}_i$). This is also known as the *life expectancy* at a given age, which is defined as the number of years *remaining* to be lived by persons at age x:

$$\mathring{e}_x = \frac{T_x}{l_x} \tag{4.2.6}$$

The expected age at death of a person aged x is $x + \mathring{e}_x$. The $\mathring{e}_x$ at $x = 0$ is the life expectancy at birth. For example, according to the U.S. life

Table 4.4 Life Table for the Total Population, United States, 1989–1991

Age Interval Period of Life Between Two Ages	Proportion Dying Proportion of Persons Alive at Beginning of Age Interval Dying During Interval	Of 100,000 Born Alive Number Living at Beginning of Age Interval	 Number Dying During Age Interval	Stationary Population In the Age Interval	 In This and All Subsequent Age Intervals	Average Remaining Lifetime Average Number of Years of Life Remaining at Beginning of Age Interval
x to $x + t$	${}_tq_x$	l_x	${}_td_x$	${}_tL_x$	T_x	$\mathring{e}_0$
Days						
0–1	0.00351	100,000	351	274	7,536,614	75.37
1–7	0.00135	99,649	134	1,637	7,536,340	75.63
7–28	0.00104	99,515	104	5,722	7,534,703	75.71
28–365	0.00349	99,411	347	91,625	7,528,981	75.74
Years						
0–1	0.00936	100,000	936	99,258	7,536,614	75.37
1–2	0.00073	99,064	72	99,028	7,437,356	75.08
2–3	0.00048	98,992	48	98,968	7,338,328	74.13
3–4	0.00037	98,944	37	98,926	7,239,360	73.17
4–5	0.00030	98,907	30	98,892	7,140,434	72.19
5–6	0.00027	98,877	27	98,863	7,041,542	71.22
6–7	0.00025	98,850	24	98,839	6,942,679	70.23
7–8	0.00023	98,826	23	98,814	6,843,840	69.25
8–9	0.00020	98,803	20	98,794	6,745,026	68.27
9–10	0.00018	98,783	17	98,774	6,646,232	67.28

10–11	0.00016	98,766	16	98,758	6,547,458	66.29
11–12	0.00016	98,750	16	98,742	6,448,700	65.30
12–13	0.00022	98,734	21	98,723	6,349,958	64.31
13–14	0.00032	98,713	32	98,697	6,251,235	63.33
14–15	0.00047	98,681	46	98,658	6,152,538	62.35
15–16	0.00063	98,635	62	98,604	6,053,880	61.38
16–17	0.00077	98,573	76	98,534	5,955,276	60.41
17–18	0.00089	98,497	88	98,453	5,856,742	59.46
18–19	0.00096	98,409	95	98,362	5,758,289	58.51
19–20	0.00101	98,314	99	98,265	5,659,927	57.57
20–21	0.00104	98,215	102	98,164	5,561,662	56.63
21–22	0.00109	98,113	107	98,060	5,463,498	55.69
22–23	0.00112	98,006	110	97,951	5,365,438	54.75
23–24	0.00114	97,896	112	97,840	5,267,487	53.81
24–25	0.00116	97,784	113	97,727	5,169,647	52.87
25–26	0.00117	97,671	115	97,614	5,071,920	51.93
26–27	0.00119	97,556	115	97,499	4,974,306	50.99
27–28	0.00121	97,441	119	97,381	4,876,807	50.05
28–29	0.00126	97,322	123	97,261	4,779,426	49.11
29–30	0.00133	97,199	129	97,135	4,682,165	48.17
30–31	0.00140	97,070	136	97,002	4,585,030	47.23
31–32	0.00147	96,934	143	96,862	4,488,028	46.30
32–33	0.00154	96,791	149	96,717	4,391,166	45.37
33–34	0.00162	96,642	157	96,563	4,294,449	44.44
34–35	0.00170	96,485	163	96,404	4,197,886	43.51
35–36	0.00178	96,322	172	96,236	4,101,482	42.58
36–37	0.00188	96,150	181	96,060	4,005,246	41.66
37–38	0.00198	95,969	189	95,874	3,909,186	40.73
38–39	0.00207	95,780	199	95,681	3,813,312	39.81
39–40	0.00217	95,581	208	95,477	3,717,631	38.90

(*Continued overleaf*)

Table 4.4 *Continued*

Age Interval	Proportion Dying	Of 100,000 Born Alive		Stationary Population		Average Remaining Lifetime
Period of Life Between Two Ages	Proportion of Persons Alive at Beginning of Age Interval Dying During Interval	Number Living at Beginning of Age Interval	Number Dying During Age Interval	In the Age Interval	In This and All Subsequent Age Intervals	Average Number of Years of Life Remaining at Beginning of Age Interval
x to $x + t$	${}_tq_x$	l_x	${}_td_x$	${}_tL_x$	T_x	$\mathring{e}_0$
40–41	0.00228	95,373	217	95,265	3,622,154	37.98
41–42	0.00240	95,156	228	95,042	3,526,889	37.06
42–43	0.00254	94,928	241	94,808	3,431,847	36.15
43–44	0.00271	94,687	257	94,559	3,337,039	35.24
44–45	0.00292	94,431	277	94,292	3,242,480	34.34
45–46	0.00318	94,154	299	94,005	3,148,188	33.44
46–47	0.00348	93,855	327	93,692	3,054,183	32.54
47–48	0.00380	93,528	355	93,350	2,960,491	31.65
48–49	0.00414	93,173	386	92,980	2,867,141	30.77
49–50	0.00449	92,787	417	92,579	2,774,161	29.90
50–51	0.00490	92,370	452	92,144	2,681,582	29.03
51–52	0.00537	91,918	494	91,671	2,589,438	28.17
52–53	0.00590	91,424	539	91,155	2,497,767	27.32
53–54	0.00647	90,885	588	90,591	2,406,612	26.48
54–55	0.00708	90.297	639	89.978	2,316,021	25.65
55–56	0.00773	89,658	693	89,311	2,226,043	24.83

56–57	0.00844	88,965	751	88,589	2,136,732	24.02
57–58	0.00926	88,214	817	87,806	2,048,143	23.22
58–59	0.01019	87,397	891	86,951	1,960,337	22.43
59–60	0.01120	86,506	679	86,021	1,873,386	21.66
60–61	0.01223	85,537	1,047	85,013	1,787,365	20.90
61–62	0.01328	84,490	1,122	83,930	1,702,352	20.15
62–63	0.01439	83,368	1,199	82,768	1,618,422	19.41
63–64	0.01560	82,169	1,282	81,527	1,535,654	18.69
64–65	0.01691	80,887	1,368	80,203	1,454,127	17.98
65–66	0.01827	79,519	1.453	78,793	1,373,924	17.28
66–67	0.01967	78,066	1,535	77,298	1,295,131	16.59
67–68	0.02121	76,531	1,624	75,719	1,217,833	15.91
69–69	0.02297	74,907	1,721	74,047	1,142,114	15.25
69–70	0.02499	73,186	1,829	72,272	1,068,067	14.59
70–71	0.02727	71,357	1,946	70,384	995,795	13.96
71–72	0.02979	69,411	2,067	68,377	925,411	13.33
72–73	0.03251	67,344	2,190	66,249	857,034	12.73
73–74	0.03534	65,154	2,302	64,003	790,785	12.14
74–75	0.03824	62,852	2,403	61,651	726,782	11.56
75–76	0.04126	60,449	2,494	59,201	665,131	11.00
76–77	0.04455	57,955	2,582	56,664	605,930	10.46
77–78	0.04819	55,373	2,669	54,039	549,266	9.92
78–79	0.05239	52,704	2,761	51,323	495,227	9.40
79–80	0.05723	49,943	2.859	48,514	443,904	8.89
80–81	0.06277	47,084	2,955	45,607	395,390	8.40
81–82	0.06885	44,129	3,038	42,609	349,783	7.93
82–83	0.07535	41,091	3,097	39,543	307,174	7.48
83–84	0.08207	37,994	3,118	36,435	267,631	7.04
84–85	0.08907	34,876	3,106	33,324	231,196	6.63
85–86	0.09705	31,770	3,083	30,228	197,872	6.23

(*Continued overleaf*)

Table 4.4 *Continued*

Age Interval	Proportion Dying	Of 100,000 Born Alive		Stationary Population		Average Remaining Lifetime
Period of Life Between Two Ages	Proportion of Persons Alive at Beginning of Age Interval Dying During Interval	Number Living at Beginning of Age Interval	Number Dying During Age Interval	In the Age Interval	In This and All Subsequent Age Intervals	Average Number of Years of Life Remaining at Beginning of Age Interval
x to $x + t$	${}_tq_x$	l_x	${}_td_x$	${}_tL_x$	T_x	$\mathring{e}_0$
86–87	0.10627	28,687	3,049	27,163	167,644	5.84
87–88	0.11625	25,638	2,980	24,148	140,481	5.48
88–89	0.12688	22,658	2,875	21,220	116,333	5.13
89–90	0.13834	19,783	2,737	18,415	95,113	4.81
90–91	0.15135	17,046	2,580	15,757	76,698	4.50
91–92	0.16591	14,466	2,400	13,266	60,941	4.21

92–93	0.18088	12,066	2,182	10,975	47,675	3.95
93–94	0.19552	9,884	1,933	8,918	36,700	3.71
94–95	0.21000	7,951	1,669	7,116	27,782	3.49
95–96	0.22502	6,282	1,414	5,575	20,666	3.29
96–97	0.24126	4,868	1,174	4,281	15,091	3.10
97–98	0.25689	3,694	949	3,219	10,810	2.93
98–99	0.27175	2,745	746	2,372	7,591	2.77
99–100	0.28751	1,999	575	1,711	5,219	2.61
100–101	0.30418	1,424	433	1,208	3,508	2.46
101–102	0.32182	991	319	832	2,300	2.32
102–103	0.34049	672	229	557	1,468	2.19
103–104	0.36024	443	159	364	911	2.05
104–105	0.38113	284	109	229	547	1.93
105–106	0.40324	175	70	140	318	1.81
106–107	0.42663	105	45	83	178	1.70
107–108	0.45137	60	27	46	95	1.59
108–109	0.47755	33	16	25	49	1.49
109–110	0.50525	17	8	13	24	1.39

Source: U.S. Decennial Life Tables for 1989–1991, Vol. 1, No. 1, *U.S. Life Tables*, DHHS Publication PHS-98-1150-1, National Center for Health Statistics, Washington, DC, 1997.

Table 4.5 Abridged Life Table for the Total Population, United States, 1998

Age	Proportion Dying During Age Interval, ${}_tq_x$	Number Living at Beginning of Age Interval, l_x	Number Dying During Age Interval, ${}_td_x$	Stationary Population in the Age Interval, ${}_tL_x$	Stationary Population in This and All Subsequent Age Intervals, T_x	Life Expectancy at Beginning of Age Interval, $\mathring{e}_x$
0–1	0.00721	100,000	721	99,370	7,671,400	76.7
1–5	0.00139	99,279	138	396,786	7,572,030	76.3
5–10	0.00089	99,141	88	495,473	7,175,244	72.4
10–15	0.00110	99,053	109	495,057	6,679,771	67.4
15–20	0.00353	98,944	349	493,926	6,184,714	62.5
20–25	0.00476	98,595	469	491,820	5,690,788	57.7
25–30	0.00487	98,126	478	489,450	5,198,968	53.0
30–35	0.00600	97,648	586	486,840	4,709,518	48.2
35–40	0.00819	97,062	795	483,428	4,222,678	43.5
40–45	0.01176	96,267	1,132	478,670	3,739,250	38.8
45–50	0.01728	95,135	1,644	471,811	3,260,580	34.3
50–55	0.02564	93,491	2,397	461,839	2,788,769	29.8
55–60	0.04009	91,094	3,652	446,966	2,326,930	25.5
60–65	0.06302	87,442	5,511	424,280	1,879,964	21.5
65–70	0.09437	81,931	7,732	391,364	1,455,684	17.8
70–75	0.14239	74,199	10,565	345,660	1,064,320	14.3
75–80	0.20604	63,634	13,111	286,484	718,660	11.3
80–85	0.31641	50,523	15,986	213,526	432,176	8.6
85–90	0.46104	34,537	15,923	131,897	218,650	6.3
90–95	0.61502	18,614	11,448	62,020	86,753	4.7
95–100	0.75426	7,166	5,405	20,150	24,733	3.5
100+	1.00000	1,761	1,761	4,583	4,583	2.6

Source: U.S. Life Tables, 1998. National Vital Statistics Reports, Vol. 48, No. 18, National Center for Health Statistics, Washington, DC, 2001.

table for 1989–1991 the life expectancy at birth is 75.37 years and that at age 40 is 37.98 years. This means that according to the mortality rates of 1989–1991 newborns are expected to live 75.37 years and those at age 40 are expected to live another 37.98 years. The life expectancy of a population is a general indication of the capability of prolonging life. It is used to identify trends and to compare longevity. Table 4.5 shows that according to the mortality rates of 1998, the newborns and those at age 40 are expected to live 76.7 and 38.8 years, respectively. The overall life expectancy indicates an improvement in longevity in the United States over the time period.

Population life tables can be constructed for various subgroups. For example, there are published life tables by gender, race, cause of death, as well as those which eliminate certain causes of death.

4.2.2 Clinical Life Tables

The actuarial life table method has been applied to clinical data for many decades. Berkson and Gage (1950) and Cutler and Ederer (1958) give a life-table method for estimating the survivorship function; Gehan (1969) provides methods for estimating all three functions (survivorship, density, and hazard).

The life-table method requires a fairly large number of observations, so that survival times can be grouped into intervals. Similar to the PL estimate, the life-table method incorporates all survival information accumulated up to the termination of the study. For example, in computing a five-year survival rate of breast cancer patients, one need not restrict oneself only to those patients who have entered on study for five or more years. Patients who have entered for four, three, two, and even one year contribute useful information to the evaluation of five-year survival. In this way, the life-table technique uses incomplete data such as losses to follow-up and persons withdrawn alive as well as complete death data.

Table 4.6 shows the format of the clinical life table. The columns are described below.

1. *Interval* $[t_i + t_{i+1})$. The first column gives the intervals into which the survival times and times to loss or withdrawal are distributed. The interval is from t_i up to but *not* including t_{i+1}, $i = 1, \ldots, s$. The last interval has an infinite length. These intervals are assumed to be fixed.
2. *Midpoint* (t_{mi}). The midpoint of each interval, designated t_{mi}, $i = 1, \ldots, s - 1$, is included for convenience in plotting the hazard and probability density functions. Both functions are plotted as t_{mi}.
3. *Width* (b_i). The width of each interval, $b_i = t_{i+1} - t_i$, $i = 1, \ldots, , s - 1$, is needed for calculation of the hazard and density functions. The width

Table 4.6 Format of a Life Table

Interval	Midpoint	Width	Number Lost to Follow-up	Number Withdrawn Alive	Number Dying	Number Entering Interval	Number Exposed to Risk	Conditional Proportion Dying	Conditional Proportion Surviving	Cumulative Proportion Surviving	Probability Density $f(t_{mi})$	Hazard $\hat{h}(t_{mi})$
$t - t_2$	t_{m1}	b_1	l_1	w_1	d_1	n'_1	n_1	$\hat{q}_1$	$\hat{p}_1$	$\hat{S}(t_1) = 1.00$	$\hat{f}(t_{m1})$	$\hat{h}(t_{mi})$
$t_2 - t_3$	t_{m2}	b_2	l_2	w_2	d_2	n'_2	n_2	$\hat{q}_2$	$\hat{p}_2$	$\hat{S}(t_2)$	$\hat{f}(t_{m2})$	$\hat{h}(t_{m2})$
⋮	⋮	⋮	⋮	⋮	⋮	⋮	⋮	⋮	⋮	⋮	⋮	⋮
$t_i = t_{i+1}$	t_{mi}	b_i	l_i	w_i	d_i	n'_i	n_1	$\hat{q}_i$	$\hat{p}_i$	$\hat{s}(t_i)$	$\hat{f}(t_{mi})$	$\hat{h}(t_{mi})$
⋮	⋮	⋮	⋮	⋮	⋮	⋮	⋮	⋮	⋮	⋮	⋮	⋮
$t_{s-1} - t_s$	$t_{m,s-1}$	b_{s-1}	l_{s-1}	w_{s-1}	d_{s-1}	n'_{s-1}	n_{s-1}	$\hat{q}_{s-1}$	$\hat{p}_{s-1}$	$\hat{S}(t_{s-1})$	$\hat{f}(t_{m,s-1})$	$\hat{h}(t_{m,s-1})$
$t_s - \infty$	—	—	l_s	w_s	d_s	n'_s	n_s	1	0	$\hat{S}(t_s)$	—	—

of the last interval, b_s, is theoretically infinite; no estimate of the hazard or density function can be obtained for this interval.

4. *Number lost to follow-up* (l_i). This is the number of people who are lost to observation and whose survival status is thus unknown in the ith interval ($i = 1, \ldots, s$).
5. *Number withdrawn alive* (w_i). People withdrawn alive in the ith interval are those known to be alive at the closing date of the study. The survival time recorded for such persons is the length of time from entrance to the closing date of the study.
6. *Number dying* (d_i). This is the number of people who die in the ith interval. The survival time of these people is the time from entrance to death.
7. *Number entering the* ith *interval* (n_i'). The number of people entering the first interval n_1' is the total sample size. Other entries are determined from $n_i' = n_{i-1}' - l_{i-1} - w_{i-1} - d_{i-1}$. That is, the number of persons entering the ith interval is equal to the number studied at the beginning of the preceding interval minus those who are lost to follow-up, withdrawn alive, or have died in the preceding interval.
8. *Number exposed to risk* (n_i). This is the number of people who are exposed to risk in the ith interval and is defined as $n_i = n_i' - \frac{1}{2}(l_i + w_i)$. It is assumed that the times to loss or withdrawal are approximately uniformly distributed in the interval. Therefore, people lost or withdrawn in the interval are exposed to risk of death for one-half the interval. If there are no losses or withdrawals, $n_i = n_i'$.
9. *Conditional proportion dying* ($\hat{q}_i$). This is defined as $q_i = d_i/n_i$ for $i = 1, \ldots, s-1$, and $\hat{q}_s = 1$. It is an estimate of the conditional probability of death in the ith interval given exposure to the risk of death in the ith interval.
10. *Conditional proportion surviving* ($\hat{q}_i$). This is given by $\hat{p}_i = 1 - \hat{q}_i$, which is an estimate of the conditional probability of surviving in the ith interval.
11. *Cumulative proportion surviving* [$\hat{S}(t_i)$]. This is an estimate of the survivorship function at time t_i; it is often referred to as the *cumulative survival rate*. For $i = 1$, $\hat{S}(t_{1i}) = 1$ and for $i = 2, \ldots, s$, $\hat{S}(t_i) = \hat{p}_{i-1}\hat{S}(t_{i-1})$. It is the usual life-table estimate and is based on the fact that surviving to the start of the ith interval means surviving to the start of and then through the $(i-1)$th interval.
12. *Estimated probability density function* [$\hat{f}(t_m)$]. This is defined as the probability of dying in the ith interval per unit width. Thus, a natural estimate at the midpoint of the interval is

$$\hat{f}(t_m) = \frac{\hat{S}(t_i) - \hat{S}(t_{i-1})}{b_i} = \frac{\hat{S}(t_i)\hat{q}_i}{b_i} \qquad i = 1, \ldots, s-1 \tag{4.2.7}$$

13. *Hazard function* $[\hat{h}(t_{mi})]$. The hazard function for the ith interval, estimated at the midpoint, is

$$\hat{h}(t_{mi}) = \frac{d_i}{b_i(n_i - \frac{1}{2}d_i)} = \frac{2\hat{q}_i}{b_i(1 + \hat{p}_i)} \qquad i = 1, \ldots, s-1 \tag{4.2.8}$$

It is the number of deaths per unit time in the interval divided by the average number of survivors at the midpoint of the interval. That is, $\hat{h}(t_{mi})$ is derived from $\hat{f}(t_{mi})/\hat{S}(t_{mi})$ and $\hat{S}(t_{mi}) = \frac{1}{2}[\hat{S}(t_{i+1}) + \hat{S}(t_i)]$ since $S(t_i)$ is defined as the probability of surviving at the beginning, not the midpoint, of the ith interval:

$$\hat{h}(t_{mi}) = \frac{\hat{f}(t_{mi})}{\hat{S}(t_{mi})} = \frac{\hat{S}(t_i)\hat{q}_i/b_i}{\frac{1}{2}\hat{S}(t_i)(\hat{p}_i + 1)} \tag{4.2.9}$$

which reduces to (4.2.8).

Sacher (1956) derives an estimate of the hazard function by assuming that hazard is constant within an interval but varies among intervals. His estimate is

$$\hat{h}(t_{mi}) = \frac{-\log \hat{p}_i}{b_i} \tag{4.2.10}$$

In a Monte Carlo study, Gehan and Siddiqui (1973) show that (4.2.9) is less biased than (4.2.10).

The large-sample approximate variances of the estimated survival functions, $\hat{S}(t_i)$, $\hat{f}(t_{mi})$, and $\hat{h}(t_{mi})$ in the ith interval are

$$\mathrm{Var}[\hat{S}(t_i)] \simeq [\hat{S}(t_i)]^2 \sum_{j=1}^{i-1} \frac{\hat{q}_j}{n_j \hat{p}_j} \tag{4.2.11}$$

$$\mathrm{Var}[\hat{f}(t_{mi})] \simeq \frac{[\hat{S}(t_i)\hat{q}_i]^2}{b_i} \left(\sum_{j=1}^{i-1} \frac{\hat{q}_j}{n_j \hat{p}_j} + \frac{\hat{p}_i}{n_j \hat{q}_j} \right) \tag{4.2.12}$$

and

$$\mathrm{Var}[\hat{h}(t_{mi})] \simeq \frac{[\hat{h}(t_{mi})]^2}{n_i \hat{q}_i} \left\{ 1 - \left[\frac{1}{2} \hat{h}(t_{mi}) b_i \right]^2 \right\} \tag{4.2.13}$$

Equation (4.2.11) is given by Greenwood (1926); Gehan (1969) derived (4.2.12) and (4.2.13). These may be used to obtain approximate confidence intervals for the various survival functions.

The graph of $\hat{S}(t_i)$ can be used to find an estimate of the median. Or let (t_j, t_{j+1}) be the interval such that $\hat{S}(t_j) \geqslant 0.5$ and $\hat{S}(t_{j+1}) < 0.5$. Then the

median survival time t_m can be estimated by linear interpolation:

$$\hat{t}_m = t_j + \frac{[\hat{S}(t_j) - 0.5]b_j}{\hat{S}(t_j) - \hat{S}(t_{j+1})} = t_j + \frac{\hat{S}(t_j) - 0.5}{\hat{f}(t_{mj})} \tag{4.2.14}$$

where $\hat{f}(t_{mj})$ is defined in (4.2.7).

Another interesting measure that can be obtained from the life table is the *median remaining lifetime* at time t_j, denoted by $t_{mr}(i)$, $i = 1, \ldots, s-1$. If at t_i the proportion of individual survival is $\hat{S}(t_i)$, the proportion of individual survival at $t_{mr}(i)$ is $\frac{1}{2}\hat{S}(t_i)$. That is, one-half of the people who are alive at time t_i are expected to be alive at time $t_{mr}(i)$. Let (t_j, t_{j+1}) be the interval in which $\frac{1}{2}\hat{S}(t_i)$ falls; that is, $\hat{S}(t_j) \geqslant \frac{1}{2}\hat{S}(t_i)$ and $\hat{S}(t_{j+1}) < \frac{1}{2}\hat{S}(t_i)$. Then an estimate of $t_{mr}(i)$ is

$$\hat{t}_{mr}(i) = (t_j - t_i) + \frac{b_j[\hat{S}(t_j) - \frac{1}{2}\hat{S}(t_i)]}{\hat{S}(t_j) - \hat{S}(t_{j+1})} \tag{4.2.15}$$

Here $\hat{S}(t_j)$ is the estimated proportion surviving beyond the lower limit of the interval containing the median.

The variance of $t_{mr}(i)$ is approximately

$$\mathrm{Var}[\hat{t}_{mr}(i)] = \frac{[\hat{S}(t_i)]^2}{4n_i[\hat{f}(t_{mj})]^2} \tag{4.2.16}$$

Example 4.4 The following survival data for 2418 males with angina pectoris, originally reported by Parker et al. (1946), were also included in Gehan's (1969) paper. Survival time is computed from time of diagnosis in years. The life table uses 16 intervals of one year. Table 4.7 gives estimates of the various survival functions, the median remaining lifetime, and their standard errors. The survivorship function, $\hat{S}(t)$, is plotted at t and the hazard and density functions, $\hat{h}(t)$ and $\hat{f}(t)$, are plotted at the midpoint of the interval (Figure 4.4).

The graph of the estimated hazard function shows that the death rate is highest in the first year after diagnosis. From the end of the first year to the beginning of the tenth year, the death rate remains relatively constant, fluctuating between 0.09 and 0.12. The hazard rate is generally higher after the tenth year. Hence, the prognosis for a patient who has survived one year is better than that for a newly diagnosed patient if factors such as age, gender, and race are not considered. A similar interpretation is reached by examining the estimated median remaining lifetimes. Initially, the estimated median remaining lifetime is 5.33 years. It reaches a peak of 6.34 years at the beginning of the second year after diagnosis and then decreases. The median survival time, either read from the survival curve or using (4.2.14), is 5.33 years and the five-year survival rate is 0.5193 with a standard error of 0.0103.

Table 4.7 Life-Table Analysis of 2418 Males with Angina Pectoris

Year after Diagnosis	Midpoint	Width	Number Lost to Follow-up	Number Withdrawn Alive	Number Dying	Number Entering Interval	Number Exposed to Risk	Conditional Proportion Dying	Conditional Proportion Surviving	$\hat{S}(t_i)$	$\hat{f}(t_{mi})$	$\hat{h}(t_{mi})$	$\sqrt{\text{Var}[\hat{S}(t_i)]}$	$\sqrt{\text{Var}[\hat{f}(t_{mi})]}$	$\sqrt{\text{Var}[\hat{h}(t_{mi})]}$	$\hat{t}_{mr}(i)$	$\sqrt{\text{Var}[\hat{t}_{mr}(i)]}$
0	0.5	1.0	0	0	456	2418	2418.0	0.1886	0.8114	1.0000	0.1886	0.2082	—	0.0080	0.0097	5.33	0.17
1	1.5	1.0	39	0	226	1962	1942.5	0.1163	0.8837	0.8114	0.0944	0.1235	0.0080	0.0060	0.0082	6.35	0.20
2	2.5	1.0	22	0	152	1697	1686.0	0.0902	0.9098	0.7170	0.0646	0.0944	0.0092	0.0051	0.0076	6.34	0.24
3	3.5	1.0	23	0	171	1523	1511.5	0.1131	0.8869	0.6524	0.0738	0.1199	0.0097	0.0054	0.0092	6.23	0.24
4	4.5	1.0	24	0	135	1329	1317.0	0.1025	0.8975	0.5786	0.0593	0.1080	0.0101	0.0049	0.0093	6.22	0.19
5	5.5	1.0	107	0	125	1170	1116.5	0.1120	0.8880	0.5193	0.0581	0.1186	0.0103	0.0050	0.0106	5.91	0.18
6	6.5	1.0	133	0	83	938	871.5	0.0952	0.9048	0.4611	0.0439	0.1000	0.0104	0.0047	0.0110	5.60	0.19
7	7.5	1.0	102	0	74	722	671.0	0.1103	0.8897	0.4172	0.0460	0.1167	0.0105	0.0052	0.0135	5.17	0.27
8	8.5	1.0	68	0	51	546	512.0	0.0996	0.9904	0.3712	0.0370	0.1048	0.0106	0.0050	0.0147	4.94	0.28
9	9.5	1.0	64	0	42	427	395.0	0.1063	0.8937	0.3342	0.0355	0.1123	0.0107	0.0053	0.0173	4.83	0.41
10	10.5	1.0	45	0	43	321	298.5	0.1441	0.8559	0.2987	0.0430	0.1552	0.0109	0.0063	0.0236	4.69	0.42
11	11.5	1.0	53	0	34	233	206.5	0.1646	0.8354	0.2557	0.0421	0.1794	0.0111	0.0068	0.0306	4.00+	—
12	12.5	1.0	33	0	18	146	129.5	0.1390	0.8610	0.2136	0.0297	0.1494	0.0114	0.0067	0.0351	3.00+	—
13	13.5	1.0	27	0	9	95	81.5	0.1104	0.8896	0.1839	0.0203	0.1169	0.0118	0.0065	0.0389	2.00+	—
14	14.5	1.0	23	0	6	59	47.5	0.1263	0.8737	0.1636	0.0207	0.1348	0.0123	0.0080	0.0549	1.00+	—
15	—	—	0	0	0	30	30.0	1.0000	0.0000	0.1429	—	—	0.0133	—	—	—	—

Source: Gehan (1969).

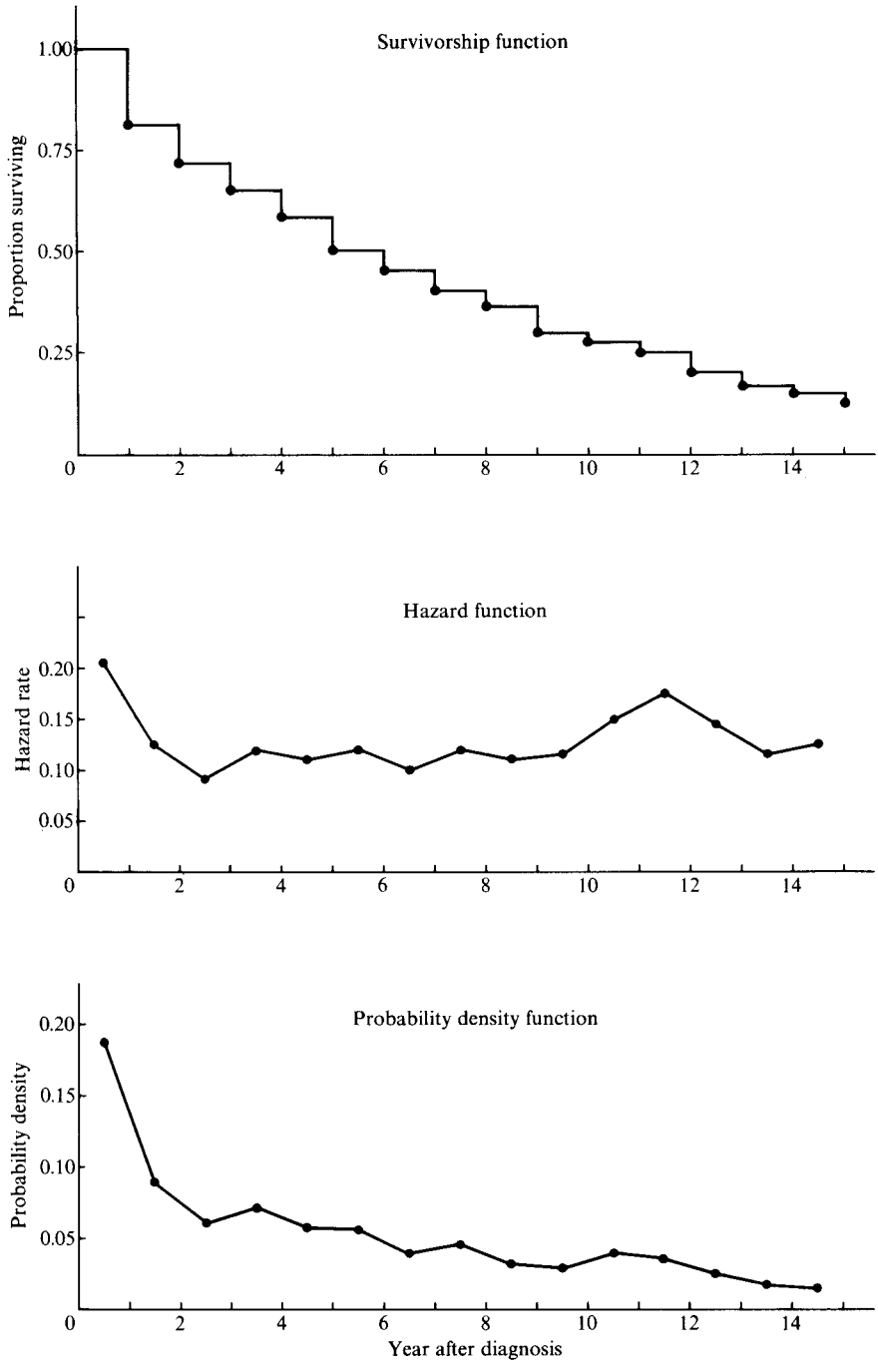


Figure 4.4 Survival functions of male patients with angina pectoris.

Assume that survival time t (year) from each of 2418 males with angina pectoris in Example 4.4 has the same format as the data file "C:\D4d2.DAT" defined in Example 4.2 and is saved in "C:\D4d4.DAT". Then the following SAS code can be used to produce a clinical life table such as Table 4.7.

```
data w1;
  infile 'c:\d4d4.dat' missover;
  input t cens;
run;
proc lifetest data = w1 outsurv = wa method = life intervals = 0 to 15 by 1;
  time t*cens(0);
run;
title 'Life table of the survival times';
proc print data = wa;
run;
```

If BMDP 1L is used, the respective code is

```
/input      file = 'c:\d4d4.dat' .
            variables = 2.
            format = free.
/variable   names = t, cens.
/form       unit = year.
            time = t.
            status = cens.
            response = 1.
/estimate   method = life.
            Print.
/end
```

If the SPSS SURVIVAL procedure is used, the respective code is

```
data list file = 'c:\d4d4.dat' free
          / t cens.
survival tables = t
          /status  =  cens (1) for t
          /intervals = thru 15 by 1
          /print.
```

4.3 RELATIVE, FIVE-YEAR, AND CORRECTED SURVIVAL RATES

Another approach to large-scale survival data is the calculation of the *relative survival rate or annual survival ratio*. The relative survival rate evaluates the survival experience of patients in terms of the general population. Greenwood (1926) first suggested this approach for evaluating the efficacy of cancer treatment: If the average survival time of the patients treated equals that of a

random sample of persons of the same age, gender, occupation, and so on, the patients could be considered "cured." Cutler et al. (1957, 1959, 1960*a*, *b*, 1967) adopted Greenwood's idea of comparing the survival experience of cancer patients with that of the general population to ascertain (1) the ratio of observed to expected survival rates and (2) whether, in time, the mortality rate declines to a "normal" level.

The relative survival rate is defined as the ratio of the survival rate (probability of surviving one year) for a patient under study (*observed rate*) to someone in the general population of the same age, gender, and race (*expected rate*) over a specified period of time. To provide a more precise measure of the relationship of the observed and expected survival rates, Cutler et al. suggest computing the ratio for each individual follow-up year. A relative rate of 100% means that during a specific follow-up year the mortality rates in the patient and in the general population are equal. A relative rate of less than 100% means that the mortality rate in the patients is higher than that in the general population. Cutler et al. use the survival rates in the Connecticut and U.S. life tables for the general population.

Using the notations in Table 4.6, the survival rate observed at time t_i is $\hat{p}_i$, the expected survival rate can be computed as follows: Suppose that at time t_i there are n_i' individuals alive for whom age, gender, race, and time of observation are known. Let p_{ij}^* be the survival rate of the jth individual from general population life tables (with corresponding age, gender, and race). The expected survival rate is

$$p_i^* = \frac{1}{n_i'} \sum_{j=1}^{n_i'} p_{ij}^* \tag{4.3.1}$$

Then the relative survival rate at time t_i is defined by

$$r_i = \frac{\hat{p}_i}{p_i^*} \tag{4.3.2}$$

Example 4.5 *taken from Cutler et al.* (1957) *illustrates the interpretation of relative survival rates.*

Example 4.5 A total of 9121 breast cancer cases were diagnosed in Connecticut hospitals from 1935 to 1953. The Connecticut life table for white females, 1939–1941, is used in calculation of the expected survival rate. Table 4.8 gives the observed and expected survival rates as well as the relative survival rates. Figure 4.5*a* graphically shows these data: the survival curves for the breast cancer patients and the general population. The relative survival rates are plotted in Figure 4.5*b*. For this group of patients, the relative survival rates, although increasing during 13 successive years, are less than 100% throughout the 15 years of follow-up. During each of the 15 years, the

Table 4.8 Relative Survival Rates of Breast Cancer Patients in Connecticut, 1935–1953

Years after Diagnosis	Survival Rates (%)		Relative Survival Rate (%)
	Observed	Expected	
0–1	82.9	97.2	85
1–2	83.3	97.1	86
2–3	85.9	96.9	89
3–4	86.8	96.7	90
4–5	89.2	96.6	92
5–6	90.0	96.4	93
6–7	89.9	96.4	93
7–8	91.6	96.2	95
8–9	92.0	96.1	96
9–10	92.7	96.1	96
10–11	92.9	95.9	97
11–12	94.0	95.8	98
12–13	94.1	95.3	99
13–14	91.5	95.3	96
14–15	90.6	94.9	95

Source: Cutler et al. (1957).

breast cancer patient mortality rate is greater than that of the general population.

Other measures of describing survival experience of cancer patients are the five-year survival rate and the corrected rate. The *five-year survival rate* is simply the cumulative proportion surviving at the end of the fifth year. For example, the five-year survival rate for the males with angina pectoris in Example 4.4 is 0.5193. The five-year survival rate is no longer a measure of treatment success for patients with many types of cancer since the survival of cancer patients has improved considerably in the last few decades.

Berkson (1942) suggests using a *corrected survival rate*. This is the survival rate if the disease under study alone is the cause of death. In most survival studies, the proportion of patients surviving is usually determined without considering the cause of death, which might be unrelated to the specific illness. If p_c denotes the survival rate when cancer alone is the cause of death, Berkson proposes that

$$p_c = \frac{p}{p_0} \tag{4.3.3}$$

where p is the observed total survival rate in a group of cancer patients and p_0 is the survival rate for a group of the same age and gender in the general

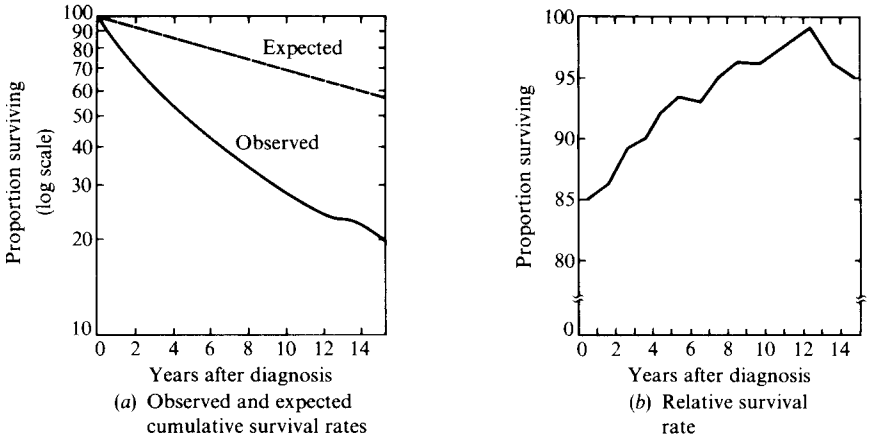


Figure 4.5 Survival rates of breast cancer patients in Connecticut, 1935–1953.

population. Rate p_c may be computed at any time after the initiation of follow-up; it provides a measure of the proportion of patients that escaped a death from cancer up to that point. If a five-year survival rate is 0.5 and it is corrected for noncancer deaths and if we find that five-year survival rate of the general population is 0.9, the corrected survival rate is 0.5/0.9, or 0.56.

4.4 STANDARDIZED RATES AND RATIOS

Rates and ratios are often used in demography and epidemiology to describe the occurrence of a health-related event. For example, the standardized mortality (or morbidity) ratio (SMR) is frequently used in occupational epidemiology as a measure of risk, and the standardized death rate is commonly used in comparing mortality experiences of different populations or the same population at different times.

The concept of the SMR is very similar to that of the relative survival rate described above. It is defined as the ratio of the observed and the expected number of death and can be expressed as

$$\text{SMR} = \frac{\text{observed number of deaths in study population}}{\text{expected number of deaths in study population}} \times 100 \qquad (4.4.1)$$

where the expected number of deaths is the sum of the expected deaths from the same age, gender, and race groups in the general population. The standardized morbidity ratio can similarly be calculated simply by replacing the word *deaths* by *disease cases* in (4.4.1). If only new cases are of interest, we call the ratio the *standardized incidence ratio* (SIR).

Table 4.9 Population and Deaths of Sunny City and Happy City by Age

	Sunny City			Happy City		
Age	Population	Deaths	Age-Specific Rates (per 1000)	Population	Deaths	Age-Specific Rates (per 1000)
<25	25,000	25	1.00	55,000	110	2.0
25–44	40,000	50	1.25	20,000	50	2.5
45–64	20,000	200	10.00	21,000	315	15.0
$\geqslant 65$	15,000	1,200	80.00	4,000	650	162.5
Total	100,000	1,475		100,000	1,125	

The standardized death rate is only one of the many rates used to describe the health status of a population or to compare the health status of different populations. If the populations are similar with respect to demographic variables such as age, gender, or race, the *crude rate*, or ratio of the number of persons to whom the event under study occurred to the total number of persons in the population, can safely be used for comparison.

The level of the crude rate is affected by demographic characteristics of the population for which the rate is computed. If populations have different demographic compositions, a comparison of the crude rates may be misleading. As an example consider the two hypothetical populations, Sunny City and Happy City, in Table 4.9. The crude death rate of Sunny City is 1000(1475/100,000) or 14.7 per 1000. The crude death rate of Happy City is 1000(1125/100,000), or 11.25 per 1000, which is lower than that of Sunny City even though all age-specific rates in Happy City are higher. This is mainly because there is a large proportion of older people in Sunny City. A crude death rate of a population may be relatively high merely because the population has a high proportion of older people; it may be relatively low because the population has a high proportion of younger people. Thus, one should adjust the rate to eliminate the effects of age, gender, or other differences. The procedure of adjustment is called *standardization* and the rate obtained after standardization is called the *standardized rate*.

The most frequently used methods for standardization are the direct method and the indirect method.

Direct Method

In this method a standard population is selected. The distribution across the groups with different values of the demographic characteristic (e.g., different age groups) must be known. Let $r_1, \ldots, r_k$, where k is the number of groups, be the specific rates of the different groups for the population under study. Let $p_1, \ldots, p_k$ be the proportions of people in the k groups for the standard population. The direct standardized rate is obtained by multiplying the specific

rates r_i by p_i in each group. The formula for the direct standardized rate is

$$R_{\text{direct}} = \sum_{i=1}^{k} r_i p_i \tag{4.3.2}$$

As an example, consider the data in Table 4.9. If we choose a standard population whose distribution is shown in the second column of Table 4.10, the direct standardized death rate for Sunny City and Happy City is, respectively, 9.37 and 17.84 per 1000. These standardized rates are more reliable than the crude rates for comparison purposes.

Indirect Method

If the specific rates r_i of the population being studied are unknown, the direct method cannot be applied. In this case, it is possible to standardize the rate by an indirect method if the following are available:

1. The number of persons to whom the event being studied occurred (D) in the population. For example, if the death rate is being standardized, D is the number of deaths.
2. The distribution across the various groups for the population being studied, denoted by $n_1, \ldots, n_k$.
3. The specific rates of the selected standard population, denoted by $s_1, \ldots, s_k$.
4. The crude rate of the standard population, denoted by r.

The formula for indirect standardization is

$$R_{\text{indirect}} = \frac{D}{\sum_{i=1}^{k} n_i s_i} r \tag{4.3.3}$$

The summation in (4.3.3) is the expected number of persons to whom the event occurred on the basis of the specific rates of the standard population. Thus, the indirect method adjusts the crude rate of the standard population by the ratio of the observed to expected number of persons to whom the event occurred in the population under study.

Table 4.11 represents an example for the death rate in the states of Oklahoma and Arizona in 1960 (data are from Grove and Hetzel, 1963). The U.S. population in 1960 is used as the standard population. The crude death rate of Oklahoma (9.7 per thousand) is higher than that of Arizona (7.8 per thousand). However, the indirect standardized rates show a reverse relationship (8.6 for Oklahoma and 9.6 for Arizona). This, again, is because of the differences in age distribution. There is a higher proportion of people below the age of 25 in Arizona and a higher proportion of people above the age of 54 in Oklahoma.

Table 4.10 Standardized Death Rates by Direct Method for Sunny City and Happy City

Age	Standard Population	Proportion, p_i	Sunny City		Happy City	
			Age-Specific Death Rates, r_i	Age-Standardized Death Rates, $p_i r_i$	Age-Specific Death Rates, r_i	Age-Standardized Death Rates, $p_i r_i$
<25	420,000	0.42	1.00	0.42	2.0	0.84
25–44	280,000	0.28	1.25	0.35	2.5	0.70
45–64	220,000	0.22	10.00	2.20	15.0	3.30
$\geqslant 65$	80,000	0.08	80.00	6.40	162.5	13.00
Total	1,000,000			9.37 (R_{direct})		17.84 (R_{direct})

Table 4.11 Standardized Death Rates by Indirect Method for Oklahoma and Arizona, 1960

Age	Standard Population (U.S. Population, 1960) Age-Specific Death Rates, s_i	Oklahoma		Arizona	
		Population, n_i	Expected Deaths, $n_i s_i$	Population, n_i	Expected Deaths, $n_i s_i$
<1	0.0270	49,103	1,325.78	34,599	934.17
1–4	0.0011	193,644	213.01	132,367	145.60
5–14	0.0005	454,972	227.49	285,830	142.92
15–24	0.0011	329,230	362.15	186,789	205.47
25–34	0.0015	279,327	418.99	169,873	254.81
35–44	0.0030	287,994	863.98	173,029	519.09
45–54	0.0076	269,147	2,045.52	136,573	1,037.95
55–64	0.0174	216,036	3,759.03	92,871	1,615.96
65–74	0.0382	157,385	6,012.11	63,634	2,430.82
75–84	0.0875	74,848	6,549.20	22,499	1,968.66
85+	0.1986	16,598	3,296.36	4,092	812.67
Total		2,328,284	25,074	1,302,161	10,068
Crude rates (per thousand)	9.5	9.7		7.8	
Observed deaths		22,584		10,157	
Expected deaths[a]		25,074		10,068	
Standardized rate (per thousand)		$\left(\frac{22{,}584}{25{,}074}\right) 9.5 = 8.6$		$\left(\frac{10{,}157}{10{,}068}\right) 9.5 = 9.6$	

Source: Data from Grove and Hetzel (1963).

[a] $\Sigma n_i s_i$.

Results for the adjusted rates depend on the standard population selected. Hence, this selection should be done carefully. When discussing death rate by age, Shryock et al. (1971) suggest that a population with similar age distribution to the various populations under study be selected as a standard. If the death rate of two populations is being compared, it is best to use the average of the two distributions as a standard.

It should be remembered that specific rates are still the most accurate and essential indicators of the variations among populations. No matter which method is used, standardized rates are meaningful only when compared with similarly computed rates. Kitagawa (1964) also criticizes the standardized rate because if the specific rates vary in different ways between the two populations being compared, standardization will not indicate the differences and sometimes will even mask the differences. Nevertheless, if the specific rates are not available, if a single rate for a population is desired, or if the demographic composition of the population being compared is different, the standardized rate is useful.

Bibliographical Remarks

Kaplan and Meier's (1958) PL method is the most commonly used technique for estimating the survivorship function for samples of small and moderate size. However, with the aid of a computer, it is not difficult to use the method for large sample sizes.

Berkson (1942), Berkson and Gage (1950), Cutler and Ederer (1958), and Gehan (1969) have written classic reports on life-table analysis. Peto et al. (1976) published an excellent review of some statistical methods related to clinical trials. The term *life-table analysis* that they use includes the PL method. Other references on life tables are, for example, Armitage (1971), Shryock et al. (1971), Kuzma (1967), Chiang (1968), Gross and Clark (1975), and Elandt-Johnson and Johnson (1980).

Relative survival rates and corrected survival rates have been used by Cutler and co-workers in a series of survival studies on cancer patients in Connecticut in the 1950s and 1960s (Cutler et al., 1957, 1959, 1960*a*, *b*, 1967; Ederer et al., 1961). Discussions of SMR, standardized rates, and related topics can be found in many standard epidemiology textbooks: for example, Mausner and Kramer (1985), Kahn (1983), Kelsey et al. (1986), Shryock et al. (1971), Chiang (1961), and Mantel and Stark (1968).

EXERCISES

4.1 Consider the survival time of the 30 melanoma patients in Table 3.1.

(a) Compute and plot the PL estimates of the survivorship functions $\hat{S}(t)$ of the two treatment groups and check your results with Table 3.2 and Figure 3.1.

(b) Compute the variance of $\hat{S}(t)$ for every uncensored observation.
(c) Estimate the median survival times of the two groups.

4.2 Do the same as in Exercise 4.1 for the remission durations of the two treatment groups in Table 3.1.

4.3 Compute and plot the PL estimates of the tumor-free time distributions for the saturated fat and unsaturated fat diet groups in Table 3.4. Compare your results with Figure 3.4.

4.4 Consider the remission data of 42 patients with acute leukemia in Example 3.3.
(a) Compute and plot the PL estimates of $S(t)$ at every time to relapse for the 6-MP and placebo groups.
(b) Compute the variances of $\hat{S}(10)$ in the 6-MP group and of $\hat{S}(3)$ in the placebo group.
(c) Estimate the median remission times of the two treatment groups.

4.5 **(a)** Compute the survival time for each patient in Exercise Table 3.1.
(b) Estimate and plot the overall survivorship function using the PL method. What is the median survival time?
(c) Divide the patients into two groups by gender. Compute and plot the PL estimates of the survivorship functions for each group. What is the median survival time for each?

4.6 Consider the skin test results in Exercise Table 3.1. For each of the five skin tests:
(a) Divide patients into two groups according to whether they had a positive reaction. Measurements less than 10×10 (5×5 for mumps) are considered negative.
(b) Estimate and plot the survivorship functions of the two groups.
(c) Can you tell from the plots if any skin tests might predict survival time?

4.7 Consider the data of patients with cancer of the ovary diagnosed in Connecticut from 1935 to 1944 (Cutler et al. 1960b). Exercise Table 4.1

Exercise Table 4.1

Time from Diagnosis (yr)	Number Lost to Follow-up, l_i	Number Withdrawn Alive, w_i	Number Dying, d_i	Number Entering, n_i'
0–5	18	0	731	949
5–10	16	0	52	200
10–15	8	67	14	132
15–20	0	33	10	43

reproduces the data in life-table format. Provide a life-table like Table 4.5. What do you find out?

4.8 Do a complete life-table analysis for the two sets of data given in Table 3.5. Plot the three survival functions.

4.9 Do a complete life-table analysis of the data given in Exercise Table 4.2. Plot the three survival functions.

Exercise Table 4.2 Survival Data of Female Patients with Angina Pectoris

Year After Diagnosis	Number Entering Interval	Number Lost to Follow-up	Number Dying
0–1	555	0	82
1–2	473	8	30
2–3	435	8	27
3–4	400	7	22
4–5	371	7	26
5–6	338	28	25
6–7	285	31	20
7–8	234	32	11
8–9	191	24	14
9–10	153	27	13
10–11	113	22	5
11–12	86	23	5
12–13	58	18	5
13–14	35	9	2
14–15	24	7	3
15+	14	11	3

Source: R. L. Parker et al., *JAMA*, **131**(2), 95–100 (1946). Copyright 1946. American Medical Association.

4.10 Consider the survival times of the melanoma patients in Exercise Table 3.4. Do a complete life-table analysis of the survival time. Plot the three survival functions.

4.11 Consider the data given in Exercise Table 4.3. Compute the direct standardized death rate for the states of Oklahoma and Montana using the U.S. population of 1960 as the standard.

4.12 Given the population of Japan and Chile (Exercise Table 4.4), compute the indirect standardized death rate for the two countries using the U.S. death rate of 1960 in Table 4.11 as the standard.

Exercise Table 4.3

Age	U.S. Population, 1960 (thousands)	Proportion, p_i	Oklahoma Average Death Rate (per 1000) r_i	Montana Average Death Rate (per 1000) r_i
<1	4,112	0.023	25.5	25.8
1–4	16,209	0.091	1.2	1.2
5–14	35,465	0.198	0.5	0.5
15–24	24,020	0.134	1.2	1.6
25–34	22,818	0.127	1.6	1.8
35–44	24,081	0.134	2.9	3.1
45–54	20,486	0.114	6.9	7.5
55–64	15,572	0.087	14.8	16.3
65–74	10,997	0.061	32.4	37.3
75–84	4,634	0.026	79.0	87.3
85+	929	0.005	190.4	202.8
Total	179,323	1.000		

Source: Grove and Hetzel (1963).

Exercise Table 4.4

	Population (thousands)	
Age	Japan	Chile
<1	1,577	228
1–4	6,268	876
5–14	20,223	1,817
15–24	17,627	1,323
25–34	15,727	1,034
35–44	11,057	779
45–54	9,018	603
55–64	6,573	395
65–74	3,724	212
75–84	1,438	83
⩽85	188	22
Total	93,419	7,374
Observed deaths	706,599	95,486

Source: Shryock et al. (1971).

CHAPTER 5

Nonparametric Methods for Comparing Survival Distributions

The problem of comparing survival distributions arises often in biomedical research. A laboratory researcher may want to compare the tumor-free times of two or more groups of rats exposed to carcinogens. A diabetologist may wish to compare the retinopathy-free times of two groups of diabetic patients. A clinical oncologist may be interested in comparing the ability of two or more treatments to prolong life or maintain health. Almost invariably, the disease-free or survival times of the different groups vary. These differences can be illustrated by drawing graphs of the estimated survivorship functions, but that gives only a rough idea of the difference between the distributions. It does not reveal whether the differences are significant or merely chance variations. A statistical test is necessary.

In Section 5.1 we introduce five nonparametric tests that can be used for data with and without censored observations. Section 5.2 is devoted to the Mantel–Haenszel test, which is particularly useful in stratified analysis, a method commonly used to take account of possible confounding variables. In Section 5.3 we discuss the problem of comparing three or more survival distributions with or without censoring.

5.1 COMPARISON OF TWO SURVIVAL DISTRIBUTIONS

Suppose that there are n_1 and n_2 patients who receive treatments 1 and 2, respectively. Let $x_1, \ldots, x_{r_1}$ be the r_1 failure observations and $x_{r_1+1}^+, \ldots, x_{n_1}^+$ the $n_1 - r_1$ censored observations in group 1. In group 2, let $y_1, \ldots, y_{r_2}$ be the r_2 failure observations and $y_{r_2+1}^+, \ldots, y_{n_2}^+$ the $n_2 - r_2$ censored observations. That is, at the end of the study $n_1 - r_1$ patients who received treatment 1 and $n_2 - r_2$ patients who received treatment 2 are still alive. Suppose that the observations in group 1 are samples from a distribution with survivorship function $S_1(t)$ and the observations in group 2 are samples from a distribution

with survivorship function $S_2(t)$. Then null hypothesis to consider is

$$H_0: S_1(t) = S_2(t) \qquad \text{(treatments 1 and 2 are equally effective)}$$

against the alternative

$$H_1: S_1(t) > S_2(t) \qquad \text{(treatment 1 more effective than 2)}$$

or

$$H_2: S_1(t) < S_2(t) \qquad \text{(treatment 2 more effective than 1)}$$

or

$$H_3: S_1(t) \neq S_2(t) \qquad \text{(treatments 1 and 2 not equally effective)}$$

When there are no censored observations, standard nonparametric tests can be used to compare two survival distributions. For example, the Wilcoxon (1945) test or the Mann–Whitney (1947) U-test can test the equality of two independent populations, and the sign test can be used for paired (or dependent) samples (Marascuilo and McSweeney, 1977). In the following we introduce five nonparametric tests: Gehan's generalized Wilcoxon test (Gehan, 1965*a*, *b*), the Cox–Mantel test (Cox 1959, 1972; Mantel, 1966), the logrank test (Peto and Peto, 1972), Peto and Peto's generalized Wilcoxon test (1972), and Cox's F-test (1964). All the tests are designed to handle censored data; data without censored observations can be considered a special case.

5.1.1 Gehan's Generalized Wilcoxon Test

In Gehan's generalized Wilcoxon test every observation x_i or x_i^+ in group 1 is compared with every observation y_j or y_j^+ in group 2 and a score U_{ij} is given to the result of every comparison. For the purpose of illustration, let us assume that the alternative hypothesis is $H_1: S_1(t) > S_2(t)$, that is, treatment 1 is more effective than treatment 2.

Define

$$U_{ij} = \begin{cases} +1 & \text{if } x_i > y_j \text{ or } x_i^+ \geqslant y_j \\ 0 & \text{if } x_i = y_j \text{ or } x_i^+ < y_j \text{ or } y_j^+ < x_i \text{ or } (x_i^+, y_j^+) \\ -1 & \text{if } x_i < y_j \text{ or } x_i \leqslant y_j^+ \end{cases}$$

and calculate the test statistic

$$W = \sum_{i=1}^{n_1} \sum_{j=1}^{n_2} U_{ij} \tag{5.1.1}$$

where the sum is over all $n_1 n_1$ comparisons. Hence, there is a contribution to

the test statistic W for every comparison where both observations are failures (except for ties) and for every comparison where a censored observation is equal to or larger than a failure. The calculation of W is laborious when n_1 and n_2 are large. Mantel (1967) shows that it can be calculated in an alternative way by assigning a score to each observation based on its relative ranking. In Gehan's computation each observation in sample 1 is compared with each in sample 2. If the two samples are combined into a single pooled sample of $n_1 + n_2$ observations, it is the same as comparing each observation with the remaining $n_1 + n_2 - 1$. Let U_i, $i = 1, \ldots, n_1 + n_2$, be the number of remaining $n_1 + n_2 - 1$ observations that the ith is definitely greater than *minus* the number that it is definitely less than. The $n_1 + n_2$ U_i's define a finite population with mean 0 and it is true that Gehan's

$$W = \sum_{i=1}^{n_1} U_i \tag{5.1.2}$$

where summation is over the U_i of sample 1 only. From either (5.1.1) or (5.1.2), it is clear that W would be a large positive number if H_1 is true. Mantel also suggests that the permutational variance of W be used instead of the more complicated variance formula derived by Gehan. The permutational distribution of W can be obtained by considering all[1]

$$\binom{n_1 + n_2}{n_2} = \frac{(n_1 + n_2)!}{n_1!\, n_2!}$$

ways of selecting n_1 of the U_i at random. The test statistic W under H_0 can be considered approximately normally distributed with mean 0 and variance[2]

$$\mathrm{Var}(W) = \frac{n_1 n_2 \sum_{i=1}^{n_1+n_2} U_i^2}{(n_1 + n_2)(n_1 + n_2 - 1)} \tag{5.1.3}$$

Since W is discrete, an appropriate continuity correction of 1 is ordinarily used when there are neither ties nor censored observations. Otherwise, a continuity correction of 0.5 would probably be appropriate.

Since W has an asymptotically normal distribution with mean zero and variance in (5.1.3), $Z = W/\sqrt{\mathrm{Var}(W)}$ has standard normal distribution. The rejection regions are $Z > Z_\alpha$ for H_1, and $Z < -Z_\alpha$ for H_2, and $|Z| > Z_{\alpha/2}$ for H_3 where $P(Z > Z_\alpha \mid H_0) = \alpha$.

[1] $n!$ is read *n factorial:* $n! = n(n-1)(n-2)\cdots 3.2.1$.

[2] This is called the *permutational variance* because it is obtained by considering the per mutational distribution of all $(n_1 + n_2)!/n_1!\, n_2!$ W's

The number U_i can be computed in two stages. For each observation, the first stage yields, unity plus the number of remaining observations that it is definitely larger than, that is, R_{1i}. The second stage yields R_{2i}, which is unity plus the number of remaining observations that the particular observation is definitely less than. Then $U_i = R_{1i} - R_{2i}$. The computations of R_{1i} and R_{2i} can be accomplished systematically in steps, as illustrated in the following hypothetical example.

Example 5.1 Ten female patients with breast cancer are randomized to receive either CMF (cyclic administration of cyclophosphamide, methatrexate, and fluorouracil) or no treatment after a radical mastectomy. At the end of two years, the following times to relapse (or remission times) in months are recorded:

CMF (group 1): 23, 16+, 18+, 20+, 24+

Control (group 2): 15, 18, 19, 19, 20

The null hypothesis and the alternatives are

$H_0: S_1 = S_2$ (the two treatments are equally effective)

$H_1: S_1 > S_2$ (CMF more efficient than no treatment)

The computations of R_{1i}, R_{2i}, and U_i are given in Table 5.1. Thus, $W = 1 + 2 + 5 + 4 + 6 = 18$, $\text{Var}(W) = (5)(5)(208)/[(10)(9)] = 57.78$, and $Z = 18/\sqrt{57.78} = 2.368$. Suppose that the significance level used is $\alpha = 0.05$, $Z_{0.05} = 1.64$; then the Z value computed is in the rejection region. Therefore, we reject H_0 at 0.05 level and conclude that the data show that CMF is more effective than no treatment. In fact, the approximate p value corresponding to $Z = 2.368$ is 0.009.

Note that the sum of all $n_1 + n_2$ U_i's equals zero. This fact can be used to check the computation.

5.1.2 Cox–Mantel Test

Let $t_{(1)} < \cdots < t_{(k)}$ be the distinct failure times in the two groups together and $m_{(i)}$ be the number of failure times equal to t_i, or the multiplicity of t_i, so that

$$\sum_{i=1}^{k} m_{(i)} = r_1 + r_2 \tag{5.1.4}$$

Further, let $R(t)$ be the set of people still exposed to risk of failure at time t, whose failure or censoring times are at least t. Here $R(t)$ is called the *risk set* at time t. Let n_{1t} and n_{2t} be the number of patients in $R(t)$ that belong to

Table 5.1 Mantel's Procedure of Calculating U_i for Gehan's Generalized Wilcoxon Test

Observations of Two Samples in Ascending Order	15	16^+	18	18^+	19	19	20	20^+	23	24^+
Computation of R_{1i}										
Step 1. Rank from left to right, omitting censored observations	1		2		3	4	5		6	
Step 2. Assign next-higher rank to censored observations		2		3				6		7
Step 3. Reduce the rank of tied observations to the lower rank for the value						3				
Step 4. R_{1i}	1	2	2	3	3	3	5	6	6	7
Computation of R_{2i}										
Step 5. Rank from right to left	10	9	8	7	6	5	4	3	2	1
Step 6. Reduce the rank of tied observations to the lowest rank for the value					5					
Step 7. Reduce the rank of censored observations to 1		1		1				1		1
Step 8. R_{2i}	10	1	8	1	5	5	4	1	2	1
$U_i = R_{1i} - R_{2i}$	-9	1^a	-6	2^a	-2	-2	1	5^a	4^a	6^a

[a] From group 1.

treatment groups 1 and 2, respectively. The total number of observations, failure or censored in $R(t_{(i)})$, is $r_{(i)} = n_{1t} + n_{2t}$. Define

$$U = r_2 - \sum_{i=1}^{k} m_{(i)} A_{(i)} \tag{5.1.5}$$

$$I = \sum_{i=1}^{k} \frac{m_{(i)}(r_{(i)} - m_{(i)})}{r_{(i)} - 1} A_{(i)}(1 - A_{(i)}) \tag{5.1.6}$$

where $r_{(i)}$ is the number of observations, failure or censored, in $R(t_{(i)})$ and $A_{(i)}$

is the proportion of $r_{(i)}$ that belong to group 2. An asymptotic two-sample test is thus obtained by treating the statistic $C = U/\sqrt{I}$ as a standard normal variate under the null hypothesis (Cox, 1972). The following example illustrates the procedure.

Example 5.2 Consider the remission data and the hypotheses in Example 5.1. There are $k = 5$ distinct failure times in the two groups, $r_1 = 1$ and $r_2 = 5$. To perform the Cox–Mantel test, Table 5.2 is prepared for convenience:

$$\begin{aligned} U &= 5 - (0.5 + 0.5 + 2 \times 0.5 + 0.25) \\ &= 5 - 2.25 \\ &= 2.75 \end{aligned}$$

$$\begin{aligned} I &= \frac{1 \times 9}{9}(0.5 \times 0.5) + \frac{1 \times 7}{7}(0.5 \times 0.5) + \frac{2 \times 4}{5}(0.5 \times 0.5) + \frac{1 \times 3}{3}(0.25 \times 0.75) \\ &= 0.25 + 0.25 + 0.4 + 0.1875 \\ &= 1.0875 \end{aligned}$$

Therefore, $C = 2.75/\sqrt{1.0875} = 2.637 > Z_{0.05} = 1.64$ and we reject H_0 at 0.05 level and reach the same conclusion as in Example 5.1. The p value corresponding to $Z = 2.637$ is approximately 0.004.

5.1.3 Logrank Test

Mantel's (1966) generalization of the Savage (1956) test, often referred to as the *logrank test* (Peto and Peto, 1972), is based on a set of scores w_i assigned to the observations. The scores are functions of the logarithm of the survival

Table 5.2 Computations of Cox–Mantel Test

		Number in Risk Set of:			
Distinct Failure Time, t_i	$m_{(i)}$	Sample 1 n_{1t}	Sample 2 n_{2t}	$r_{(i)}$	$A_{(i)}$
15	1	5	5	10	0.5
18	1	4	4	8	0.5
19	2	3	3	6	0.5
20	1	3	1	4	0.25
23	1	2	0	2	0

function. Altshuler (1970) estimates the log survival function at $t_{(i)}$ using

$$-e(t_{(i)}) = -\sum_{j \leqslant t_{(i)}} \frac{m_{(j)}}{r_{(j)}} \tag{5.1.7}$$

where $m_{(j)}$ and $r_{(j)}$ are as defined in Section 5.1.2. The scores suggested by Peto and Peto are $w_i = 1 - e(t_{(i)})$ for an uncensored observation $t_{(i)}$ and $-e(T)$ for an observation censored at T. In practice, for a censored observation t_i^+, $w_i = -e(t_{(j)})$, where $t_{(j)}$ is the largest uncensored observation that $t_{(j)} \leqslant t_i^+$. Thus, the larger the uncensored observation, the smaller its score. Censored observations receive negative scores. The w scores sum identically to zero for the two groups together. The logrank test is based on the sum S of the w scores of the two groups. The permutational variance of S is given by

$$\text{Var}(S) = \frac{n_1 n_2 \sum_{i=1}^{n_1+n_2} w_i^2}{(n_1 + n_2)(n_1 + n_2 - 1)} \tag{5.1.8}$$

which can be rewritten as

$$V = \left[\sum_{j=1}^{k} \frac{m_{(j)}(r_{(j)} - m_{(j)})}{r_{(j)}}\right] \frac{n_1 n_2}{(n_1 + n_2)(n_1 + n_2 - 1)} \tag{5.1.9}$$

The test statistic $L = S/\sqrt{\text{Var}(S)}$ has an asymptotically standard normal distribution under the null hypothesis. If S is obtained from group 1, the critical region is $L < -Z_\alpha$, and if S is obtained from group 2, the critical region is $L > Z_\alpha$, where α is the significance level for testing $H_0: S_1 = S_2$ against $H_1: S_1 > S_2$. The following example illustrates the computational procedures.

Example 5.3 Consider the data and hypotheses in Example 5.1. The test statistic of the logrank test can be computed by tabulating $m_{(i)}$, $r_{(i)}$, $m_{(i)}/r_{(i)}$, and $e(t_{(i)})$ as in Table 5.3. Since every observation in the two samples, censored or not, is assigned a score, it is convenient to list them in column 1. Columns 2 to 5 pertain only to the failure times; $e(t_{(i)})$ is the cumulative value of $m_{(i)}/r_{(i)}$, Altshuler's (1970) estimate of the logarithm of the survivorship function multipled by -1. For example, at $t_{(i)} = 18$, $e(t_{(i)}) = 0.100 + 0.125 = 0.225$; at $t_{(i)} = 19$, $e(t_{(i)}) = 0.225 + 0.333 = 0.558$. The last column, w_i, gives the score for every observation. For an uncensored observation $w_i = 1 - e(t_{(i)})$, for example, at $t_i = 18$, $w_i = 1 - 0.225 = 0.775$. Since $e(t_{(i)})$ is an estimate of a function of the survivorship function, which we assume to be constant between two consecutive failures, $e(t_i^+)$ is equal to $e(t_{(j)})$ for $t_{(j)} \leqslant t_i^+$. Thus w_i for censored observations t_i^+ equals $-e(t_{(j)})$, where $t_{(j)} \leqslant t_i^+$. For example, w_i for 16^+ is $-e(15)$, or -0.100, and that for 18^+ is $-e(18)$, or -0.225. Tied observations like the two 19's receive the same score: 0.442. The 10 scores w_i sum to zero, which can be used to check the computation.

Table 5.3 Computations of Logrank Test

Remission Times in Both Samples, t_i	$m_{(i)}$	$r_{(i)}$	$m_{(i)}/r_{(i)}$	$e(t_{(i)})$	w_i
15	1	10	0.100	0.100	0.900[a]
16+	—	—	—	—	−0.100
18	1	8	0.125	0.225	0.775[a]
18+	—	—	—	—	−0.225
19	2	6	0.333	0.558	0.442[a]
20	1	4	0.250	0.808	0.192[a]
20+	—	—	—	—	−0.808
23	1	2	0.500	1.308	−0.308
24+	—	—	—	—	−1.308

[a] From sample 2.

The statistic $S = 0.900 + 0.775 + 0.442 + 0.442 + 0.192 = 2.751$. The variance of S, computed by (5.8) is 1.210. Hence, the test statistic $L = 2.751/\sqrt{1.210} = 2.5$ and the p value is approximately 0.0064, data showing that CMF treatment is superior. The logrank statistic S can be shown to equal the sum of the failures observed minus the conditional failures expected computed at each failure time, or simply the difference between the observed and expected failures in one of the groups. A similar version of the logrank test is a chi-square test which compares the observed number of failures to the expected number of failures under the hypothesis. Let O_1 and O_2 be the observed numbers and E_1 and E_2 the expected numbers of death in the two treatment groups. The test statistic

$$X^2 = \frac{(O_1 - E_1)^2}{E_1} + \frac{(O_2 - E_2)^2}{E_2} \tag{5.1.10}$$

has approximately the chi-square distribution with 1 degree of freedom. A large X^2 value (e.g., $\geqslant X^2_{1,.05}$) would lead to the rejection of the null hypothesis in favor of the alternative that the two treatments are not equally effective ($\alpha = 0.05$).

To compute E_1 and E_2, we arrange all the uncensored observations in ascending order and compute the deaths expected at each uncensored time and sum them. The number of deaths expected at an uncensored time is obtained by multiplying the deaths observed at that time by the proportion of patients exposed to risk in the treatment group. Let d_1 be the number of deaths at time t and n_{1t} and n_{2t} be the numbers of patients still exposed to risk of dying at time up to t in the two treatment groups. The deaths expected for groups 1

and 2 at time t are

$$e_{1t} = \frac{n_{1t}}{n_{1t} + n_{2t}} \times d_t \qquad e_{2t} = \frac{n_{2t}}{n_{1t} + n_{2t}} \times d_t \tag{5.1.11}$$

Then the total numbers of deaths expected in the two groups are

$$E_1 = \sum_{\text{all } t} e_{1t} \qquad E_2 = \sum_{\text{all } t} e_{2t}$$

In practice, we only need to compute the total number of deaths expected in one of the two groups, for example, E_1, since E_2 is the total observed number of deaths minus E_1. The following example illustrates the calculation procedure.

Example 5.4 Let us use the hypothetical data in Example 5.1 again. The remission times in months are:

CMF (group 1): 23, 16+, 18+, 20+, 24+

Control (group 2): 15, 18, 19, 19, 20.

Consider the following null and alternative hypotheses:

$H_0: S_1 = S_2$ (the two treatments are equally effective)

$H_1: S_1 \neq S_2$ (the two treatments are not equally effective)

Table 5.4 gives the calculation of E_1. For example, at $t = 18$, four patients in group 1 and four in group 2 are still exposed to the risk of relapse, and there is one relapse. Thus, $d_t = 1$, $n_{1t} = n_{2t} = 4$, and $e_{1t} = 0.5$.

The total number of relapses expected is $E_1 = 3.75$. Since there are a total of six deaths ($O_1 = 1$, $O_2 = 5$) in the two groups, $E_2 = 6 - 3.75 = 2.25$. Using

Table 5.4 Computation of E_1 of Logrank Test

Relapse time, t	d_t	n_{1t}	n_{2t}	e_{1t}	e_{2t}
15	1	5	5	0.5	0.5
18	1	4	4	0.5	0.5
19	2	3	3	1.0	1.0
20	1	3	1	0.75	0.25
23	1	2	0	1.0	0
Total				3.75	2.25

(5.1.10), we have

$$X^2 = \frac{(1 - 3.75)^2}{3.75} + \frac{(5 - 2.25)^2}{2.25} = 5.378$$

Using Table C-2, the p value corresponding to this X^2 value is less 0.05 ($p \simeq 0.02$). Therefore, we reach the same conclusion: that there is a significant difference in remission duration between the CMF and control groups.

Computer software is available to perform a number of two-sample tests with censored observations. For example, SAS, SPSS, and BMDP provide procedures for the logrank and Cox–Mantel tests. We use the remission time of the 10 breast cancer patients in Example 5.1 to illustrate the use of these software packages. To compare the two groups, we create the following three variables: t, remission time; CENS = 0 if t is censored and 1 otherwise; and TREAT = 1 if receiving CMF and = 2 if no treatment. Assume that the data have been saved in "C:\D5d1.DAT" as a text file, which contains three columns, separated by a space (t is in the first column, CENS the second column, and TREAT the third column), and the data in each row are for the same patient. The following SAS code can be used to perform the logrank test.

```
data w1;
  infile 'c:\d5d1.dat' missover;
  input t cens treat;
run;
proc lifetest data = w1;
  time t*cens(0);
  strata treat;
run;
```

If BMDP procedure 1L is used, the following code can be used to perform the Cox–Mantel test.

```
/input      file = 'c:\d5d1.dat' .
            variables = 3.
            format = free.
/variable   names = t, cens, treat.
/form       time = t.
            status = cens.
            response = 1.
/group      codes(treat) = 1, 2.
            Names(treat) = treated, control.
/estimate   method = product.
            Group = treat.
            Stat = mantel.
/end
```

If procedure KM in SPSS is used, the following code can be used to perform the Cox–Mantel test.

```
data list file = 'c:\d5d1.dat' free
        / t cens treat.
km t by treat
            /status = cens event (1)
            /test = logrank.
```

These codes can be modified to perform tests comparing more than two groups simply by replacing TREAT in the codes with the group variable defined.

5.1.4 Peto and Peto's Generalized Wilcoxon Test

Another generalization of Wilcoxon's two-sample rank sum test is described by Peto and Peto (1972). Similar to the logrank test, this test assigns a score to every observation. For an uncensored observation t, the score is $u_i = \hat{S}(t+) + \hat{S}(t-) - 1$, and for an observation censored at T, the score is $u_i = \hat{S}(T) - 1$, where $\hat{S}$ is the Kaplan–Meier estimate of the survival function. If we use the notation of Section 5.1.2, the score for an uncensored observation $t_{(i)}$ is $u_i = \hat{S}(t_{(i)}) + \hat{S}(t_{(i-1)}) - 1$ and $\hat{S}(t_{(0)}) = 0$ and that for a censored observation is t_j^+ is $u_j = \hat{S}(t_{(i)}) - 1$, where $t_{(i)} \leqslant t_j^+$. These generalized Wilcoxon scores sum to zero. The test procedure after the scores are assigned is the same as for the logrank test. The following example illustrates the computational procedures.

Example 5.5 Using the same data and hypotheses as in Example 5.1, the calculations of the scores u_i for Peto and Peto's generalized Wilcoxon test are given in Table 5.5. Using the scores of group 1, we obtain

$$S = -0.100 - 0.212 - 0.605 - 0.408 - 0.803 = -2.128$$

$$\text{Var}(S) = (5)(5)\ \frac{(0.9)^2 + \cdots + (-0.803)^2}{10 \times 9} = 0.765$$

Thus, $Z = -2.128/\sqrt{0.765} = -2.433 < -Z_{0.05} = -1.64$. We reject H_0 at the 0.05 level and reach the same conclusion as in the last three examples: that the data show that CMB is more effective than no treatment.

5.1.5 Cox's *F*-test

Cox's F-test (Cox, 1964) is based on ordered scores from the exponential distribution. It is for singly censored or complete samples; it is not applicable to progressively censored data. The procedure is as follows:

Table 5.5 Computations of Peto and Peto's Generalized Wilcoxon Test

$t_{(i)}$	$\hat{S}(t)$	u_i
15	0.900	$1 + 0.900 - 1 = 0.900$
16+	—	$0.900 - 1 = -0.100^a$
18	0.788	$0.900 + 0.788 - 1 = 0.688$
18+	—	$0.788 - 1 = -0.212^a$
19	0.657	$0.788 + 0.657 - 1 = 0.445$
19	0.526	$0.526 + 0.657 - 1 = 0.183$
20	0.395	$0.395 + 0.526 - 1 = -0.079$
20+	—	$0.395 - 1 = -0.605^a$
23	0.197	$0.197 + 0.395 - 1 = -04.08^a$
24+	—	$0.197 - 1 = -0.803^a$

[a] Group 1.

1. Rank the observations in the combined sample.
2. Replace the ranks by the corresponding expected order statistics in sampling the unit exponential distribution $[f(t) = e^{-t}]$. Denote by t_{rn} the expected value of the rth observation in increasing order of magnitude,

$$t_{rn} = \frac{1}{n} + \cdots + \frac{1}{n-r+1} \qquad r = 1, \ldots, n \tag{5.1.12}$$

where n is the total number of observations in the two samples. In particular,

$$\begin{aligned} t_{1n} &= \frac{1}{n} \\ t_{2n} &= \frac{1}{n} + \frac{1}{n-1} \\ &\vdots \\ t_{nn} &= \frac{1}{n} + \frac{1}{n-1} + \cdots + 1 \end{aligned} \tag{5.1.13}$$

For n not too large, they can easily be computed by using tables of reciprocals. When two or more observations are tied, the average of the scores is used.

3. For data without censored observations, the entire set of n observations is replaced by the set of scores $\{t_{rn}\}$ so obtained. The sample mean scores denoted by $\bar{t}_1$ and $\bar{t}_2$ of the two samples with n_1, n_2 observations are then computed. The ratio $\bar{t}_1/\bar{t}_2$ has been shown to follow an F distribution with $(2n_1, 2n_2)$ degrees of freedom. Critical regions for testing $H_0: S_1 = S_2$

against $H_1(S_1 > S_2)$, $H_2(S_1 < S_2)$, and $H_3(S_1 \neq S_2)$ are, respectively, $\bar{t}_1/\bar{t}_2 > F_{2n_1,2n_2,\alpha}$, $\bar{t}_1/\bar{t}_2 < F_{2n_1 2n_2,1-\alpha}$, and $\bar{t}_1/\bar{t}_2 > F_{2n_1,2n_2,\alpha/2}$ or $\bar{t}_1/\bar{t}_2 < F_{2n_1,2n_2,1-\alpha/2}$.

4. The calculation of F is slightly different for singly censored data. Let r_1 and r_2 be the number of failures and $n_1 - r_1$ and $n_2 - r_2$ the number of censored observations in the two samples. Then there are $p = r_1 + r_2$ failures in the combined sample and $n - p$ censored observations. Cox (1964) suggests using the scores $t_{1n}, \ldots, t_{pn}$ as before for the failures and $t_{(p+1)n}$ for all censored observations. The mean score, for example, for the first group is

$$\bar{t}_1 = \frac{r_1 \bar{t}'_1 + (n_1 - r_1) t_{(p+1)n}}{r_1} \tag{5.1.14}$$

where $\bar{t}'_1$ is the mean score of the failures. The mean score for the second group is calculated in a similar way. The F-statistic $\bar{t}_1/\bar{t}_2$, has an approximate F-distribution with $(2r_1, 2r_2)$ degrees of freedom.

This test is for the hypothesis that the two samples are from populations with equal means. It can also determine if the second population mean is k times the first population mean, for a given k, by dividing the observations in the second sample by k before ranking and applying the test. The set of all values k not rejected in such a significance test forms a confidence interval. The following example illustrates the computation.

Example 5.6 In an experiment comparing two treatments (A and B) for solid tumor, suppose that the question is whether treatment B is better than treatment A. Six mice are assigned to treatment A and six to treatment B. The experiment is terminated after 30 days. The following survival times in days are recorded. Our null and alternative hypotheses are $H_0: S_A = S_B$ and $H_1: S_A < S_B$.

Treatment A: 8, 8, 10, 12, 12, 13

Treatment B: 9, 12, 15, 20, 30+, 30+

That is, all the mice receiving treatment A die within 13 days and two mice receiving treatment B are still alive at the end of the study. Do the data provide sufficient evidence that treatment B is more effective than treatment A?

To compute the test statistic, it is convenient to set up a table like Table 5.6. The first column lists all the observations in the two samples. The second column contains the ordered exponential scores t_{rn}. In this case, $n_1 = 6$, $n_2 = 6$, $n = 12$, $r_1 = 6$, and $r_2 = 4$. The scores are computed following (5.1.12) and (5.1.13). For example, t_{rn} for $t_i = 10$ is equal to $1/12 + 1/11 + 1/10 + 1/9$ or simply the previous t_{rn} plus $1/9$, that is, $0.274 + 1/9 = 0.385$. The tied observations receive an average score: for example, for $t_i = 12$,

Table 5.6 Computations of Cox's *F*-Test for Data in Example 5.6

t_i	t_{rn}	t_{rn} of Sample A	t_{rn} of Sample B
8	$\frac{1}{12} = 0.0831$ } 0.129	0.129	—
8	$\frac{1}{12} + \frac{1}{11} = 0.174$ }	0.129	—
9	$\frac{1}{12} + \frac{1}{11} + \frac{1}{10} = 0.174 + 0.100 = 0.274$	—	0.274
10	$0.274 + \frac{1}{9} = 0.385$	0.385	—
12	$0.385 + \frac{1}{8} = 0.510$ }	0.661	—
12	$0.510 + \frac{1}{7} = 0.661$ } 0.661	0.661	—
12	$0.653 + \frac{1}{6} = 0.820$ }	—	0.661
13	$0.820 + \frac{1}{5} = 1.020$	1.020	—
15	$1.020 + \frac{1}{4} = 1.270$	—	1.270
20	$1.270 + \frac{1}{3} = 1.603$	—	1.603
30+	$1.603 + \frac{1}{2} = 2.103$	—	2.103
30+	2.103	—	2.103
		2.985	8.014

$t_{rn} = \frac{1}{3}(0.510 + 0.653 + 0.820) = 0.661$. The last two columns of Table 5.6 give the scores for the two samples and the sums are entered at the bottom. Thus $\bar{t}_A = 2.985/6 = 0.498$ and $\bar{t}_B = 8.014/4 = 2.004$ according to (5.1.14) and

$$F = \frac{\bar{t}_A}{\bar{t}_B} = \frac{0.498}{2.004} = 0.249$$

with (12, 8) degrees of freedom. The critical region is $F < F_{12,8,0.95} = 1/F_{8,12,0.05} = 1/2.8486 = 0.351$ for $\alpha = 0.05$.[3] Hence, the data provide strong evidence that treatment B is superior to treatment A.

5.1.6 Comments on the Tests

The tests presented in Sections 5.1.1 to 5.1.5 are based on rank statistics obtained from scores assigned to each observation. The first four tests are applicable to data with progressive censoring. They can be further grouped into two categories: generalization of the Wilcoxon test (Gehan's and Peto and Peto's) and the non-Wilcoxon test (Cox–Mantel and logrank test). In the logrank test, if the statistic S is the sum of w scores in group 2, it is the same as U of the Cox–Mantel test. This can be seen in Examples 5.2 ($U = 2.75$) and 5.3 ($S = 2.751$); the small discrepancy is due to rounding-off errors.

[3] $F_{r_1,r_2,\alpha} = 1/F_{r_2,r_1,1-\alpha}$.

The only reason to choose one test over another in a given circumstance is if it will be more powerful, that is, more likely to reject a false hypothesis. When sample sizes are small ($n, n_2 \leqslant 50$), Gehan and Thomas (1969) show that Cox's F-test is more powerful than Gehan's generalized Wilcoxon test if samples are from exponential or Weibull distributions and if there are no censored observations or the observations are singly censored. Comparisons of Gehan's Wilcoxon test to several other tests are reported by Lee et al. (1975). They show that when samples are from exponential distributions, with or without censoring, the Cox–Mantel and logrank tests are more powerful and more efficient than the generalized Wilcoxon tests of Gehan and Peto and Peto. There is little difference between the Cox–Mantel and logrank tests and between the two generalized Wilcoxon tests. When the samples are taken from Weibull distributions with a constant hazard ratio (i.e., the ratio of the two hazard functions does not vary with time), the results are essentially the same as in the exponential case. However, when the hazard ratio is nonconstant, the two generalizations of the Wilcoxon test have more power than the other tests. Thus, the logrank test is more powerful than the Wilcoxon tests in detecting departures when the two hazard functions are parallel (proportional hazards) or when there is random but equal censoring and when there is no censoring in the samples (Crowley and Thomas, 1975). The generalized Wilcoxon tests appear to be more powerful than the logrank test for detecting many other types of differences, for example, when the hazard functions are not parallel and when there is no censoring and the logarithm of the survival times follow the normal distribution with equal variance but possibly different means.

The generalized Wilcoxon tests give more weight to early failures than later failures, whereas the logrank test gives equal weight to all failures. Therefore, the generalized Wilcoxon tests are more likely to detect early differences in the two survival distributions, whereas the logrank test is more sensitive to differences in the right tails. Prentice and Marek (1979) show that Gehan's Wilcoxon statistic is subject to a serious criticism when censoring rates are high. If heavy censoring exists, the test statistic is dominated by a small number of early failures and has very low power.

There are situations in which neither the logrank nor Wilcoxon test is very effective. When the two distributions differ but their hazard functions or survivorship functions cross, neither the Wilcoxon nor logrank test is very powerful, and it will be sensible to consider other tests. For example, Tarone and Ware (1977) discuss general statistics of similar form (using scores) and Fleming and Harrington (1979) and Fleming et al. (1980) present a two-sample test based on the maximum of a Smirnov-type statistic designed to measure the maximum distance between estimates of two distributions. The latter approach is shown to be more effective than the logrank or Wilcoxon tests when two survival distributions differ substantially for some range of t values, but not necessarily elsewhere. These statistics have not been widely applied. Interested readers are referred to the original papers.

5.2 MANTEL–HAENSZEL TEST

The Mantel–Haenszel (1959) test is particularly useful in comparing survival experience between two groups when adjustments for other prognostic factors are needed. The test has been used in many clinical and epidemiological studies as a method of controlling the effects of confounding variables. For example, in comparing two treatments for malignant melanoma, it would be important to adjust the comparison for a possible confounding variable such as stage of the disease. In studying the association of smoking and heart disease, it would be important to control the effects of age. To use the Mantel–Haenszel test, the data are stratified by the confounding variable and cast into a sequence of 2×2 tables, one for each stratum.

Let s be the number of strata, n_{ji} be the number of individuals in group j, $j = 1, 2$, and stratum i, $i = 1, \ldots, s$, and d_{ji} be the number of deaths (or failures) in group j and stratum i. For each of the s strata, the data can be represented by a 2×2 contingency table:

Group	Number of Deaths	Number of Survivors	Total
1	d_{1i}	$n_{1i} - d_{1i}$	n_{1i}
2	d_{2i}	$n_{2i} - d_{2i}$	n_{2i}
Total	D_i	S_i	T_i

The null hypothesis to be tested can be stated as

$$\begin{aligned} H_0: p_{11} &= p_{12} \\ p_{21} &= p_{22} \\ &\vdots \\ p_{s1} &= p_{s2} \end{aligned}$$

where $p_{ij} = P$ (death | group j, stratum i). Thus, the test permits simultaneous comparison over all the s contingency tables of the difference in survival or death probabilities for the two groups.

The chi-square test statistic without continuity correction[4] is given by

$$X^2 = \frac{[\Sigma_{i=1}^{s} d_{1i} - \Sigma_{i=1}^{s} (d_{1i})]^2}{\Sigma_{i=1}^{s} \operatorname{Var}(d_{1i})} \tag{5.2.1}$$

[4] According to Grizzle (1967), the distribution of X^2 without continuity correction is closer to the chi-square distribution than the X^2 with continuity correction. His simulations show that the probability of Type I error (rejecting a true hypothesis) is better controlled without the continuity correction at $\alpha = 0.01, 0.05$.

where

$$E(d_{1i}) = \frac{n_{1i} D_i}{T_i} \tag{5.2.2}$$

$$\text{Var}(d_{1i}) = \frac{n_{1i} n_{2i} D_i S_i}{T_i^2 (T_i - 1)} \tag{5.2.3}$$

are the mean and variance, respectively, of the number of deaths in group i computed conditionally on the contingency table marginal totals. This statistic follows the chi-square distribution with 1 degree of freedom. Thus, a computed chi-square value larger than the table chi-square value for the significance level chosen indicates a significant difference in survival between the two groups. The following two examples illustrate the use of the test.

Example 5.7 Five hundred and ninety-five persons participate in a case control study of the association of cholesterol and coronary heart disease (CHD). Among them, 300 persons are known to have CHD and 295 are free of CHD. To find out if elevated cholesterol is significantly associated with CHD, the investigator decides to control the effects of smoking. The study subjects are then divided into two strata: smokers and nonsmokers.

The following tables give the data for smokers:

Elevated Cholesterol?	With CHD	Without CHD	Total
Yes	120	20	140
No	80	60	140
Total	200	80	280

and for nonsmokers:

Elevated Cholesterol?	With CHD	Without CHD	Total
Yes	30	60	90
No	70	155	255
Total	100	215	315

Using (5.2.2) and (5.2.3), we obtain

$$E(d_{11}) = \frac{140 \times 200}{280} = 100 \qquad E(d_{12}) = \frac{90 \times 100}{315} = 28.571$$

$$\text{Var}(d_{11}) = \frac{140 \times 140 \times 200 \times 80}{(280)^2(280 - 1)} = 14.337$$

$$\text{Var}(d_{12}) = \frac{90 \times 225 \times 100 \times 215}{(315)^2(315 - 1)} = 13.974$$

Using (5.2.1) and $d_{11} = 120$, $d_{12} = 30$, we have

$$X^2 = \frac{(150 - 128.571)^2}{14.337 + 13.974} = 16.220$$

which is significant at the 0.001 level. Thus, elevated cholesterol is significantly associated with CHD after adjusting for the effects of smoking.

Example 5.8 Table 5.7 gives survival data in life-table format of male cases with localized cancer of the rectum in Connecticut for 1935–1944 and 1945–1954. We use Mantel and Haenszel's chi-square test to see if the survival distribution of patients diagnosed in 1935–1944 is the same as for patients diagnosed in 1945–1954. The null hypothesis is that the two survival distributions are the same. It is not necessary to set up 10 contingency tables for the 10 intervals. The chi-square value is easily calculated by constructing columns 7 to 12 directly from the life table. Using the sums in columns 1, 10, and 12, we obtain

$$X^2 = \frac{(330.0 - 246.50)^2}{132.491} = 52.624$$

which is significant at the 0.001 level. Thus, the data show a significant difference between the survival distributions of patients diagnosed in 1935–1944 and 1945–1954.

It should be noted that this chi-square test statistic, when applied to life tables, gives more weight to those deaths that occur in an early time interval rather than later. That is, if the two groups are subject to the same probability of surviving through the entire study period, (5.2.1)–(5.2.3) will give high mortality for the group in which early deaths occur. Mantel (1966) gives the following illustration.

Consider two groups of 100 persons each. Both have 50 deaths. In group 1 all deaths occur in the first interval, and in group 2 all deaths occur in the

Table 5.7 Computational Procedure for Comparing Two Survival Distributions: Male Cases with Localized Cancer of Rectum in Connecticut

	(1)	(2)	(3)	(4)	(5)	(6)	(7)	(8)	(9)	(10)	(11)	(12)
	1935–1944			1945–1954			Combined Time Periods			$E(d_{1i})$	$n_{2i}S_i/T_i$	$\text{Var}(d_{1i})$
Internal	Deaths, d_{1i}	Survivors, $n_{1i}-d_{1i}$	Total, n_{1i}	Deaths, d_{2i}	Survivors, $n_{2i}-d_{2i}$	Total, n_{2i}	Deaths, D_i	Survivors, S_i	Total, T_i	$\frac{(3)\times(7)}{(9)}$	$\frac{(6)\times(8)}{(9)}$	$\frac{(10)\times(11)}{(9)-1.0}$
1	167	220.0	387.0	185	559.0	744.0	352	779.0	1131.0	120.45	512.45	54.624
2	45	173.5	218.5	88	461.0	549.0	133	634.5	767.5	37.86	453.86	22.418
3	45	127.5	172.5	55	396.0	451.0	100	523.5	623.5	27.67	378.67	16.832
4	19	108.0	127.0	43	343.0	386.0	62	451.0	513.0	15.35	339.35	10.174
5	17	91.0	108.0	32	299.0	331.0	49	390.0	439.0	12.05	294.05	8.090
6	11	79.5	90.5	31	235.0	266.0	42	314.5	356.5	10.66	234.66	7.036
7	8	71.0	79.0	20	170.0	190.0	28	241.0	269.0	8.22	170.22	5.221
8	5	66.0	71.0	7	132.0	139.0	12	198.0	210.0	4.06	131.06	2.546
9	6	59.5	65.5	6	101.5	107.5	12	161.0	173.0	4.54	100.04	2.641
10	7	52.0	59.0	6	71.0	77.0	13	123.0	136.0	5.64	69.64	2.909
	330									246.50		132.491

second interval. The contingency table for the first interval is:

Group	Deaths	Survivors	Total
1	50	50	100
2	0	100	100
Total	50	150	200

and for the second interval is:

Group	Deaths	Survivors	Total
1	0	50	50
2	50	50	100
Total	50	100	150

From these two tables we have $E(d_{11}) = 100 \times 50/200 = 25$ and $E(d_{12}) = 100 \times 50/150 = 16.67$. The total deaths expected is $25 + 16.67 = 41.67$, so the 50 deaths in group 1 is 20% larger than expected. Thus, a significant chi-square value may be obtained if early survival patterns differ significantly in the two groups.

5.3 COMPARISON OF K ($K > 2$) SAMPLES

In this section the two-sample problem is generalized to a situation in which the data consist of K ($K > 2$) samples, one sample from each of the K treatment populations. The problem is to decide whether the K independent samples can be regarded as coming from the same population, or in practical terms, to see if the survival data from patients receiving the K treatments provide enough evidence to conclude that the K treatments are not equally effective. This problem has been considered by many statisticians: for example, Kruskal and Wallis (1952), Mantel and Haenszel (1959), Breslow (1970), and Peto and Peto (1972). In this section two nonparametric tests for the problem are presented. The first is Kruskal and Wallis's (1952) H-test for uncensored data. The second is a generalization of the H-test for censored data (Peto and Peto, 1972). Both use ranks instead of the original observations and are simple to apply.

5.3.1 Kruskal–Wallis Test

The Kruskal–Wallis H-test (Kruskal and Wallis, 1952; Hollander and Wolfe, 1973; Marascuilo and McSweeney, 1977), analogous to the F-test in the usual analysis of variance, uses ranks rather than original observations; it is also called the Kruskal–Wallis one-way analysis of variance by ranks. It assumes

that the variable (survival time) under study has an underlying continuous distribution.

Let N be the total number of independent observations in the K samples, n_j the number of observations in the jth sample, $j = 1, \ldots, K$, and t_{ij} the ith observation in the jth sample. The null hypothesis H_0 states that the K samples come from the same population (or clinically, the K treatments are equally effective).

In computation of the Kruskal–Wallis H-test, we first rank all N observations from smallest to largest. Let r_{ij} be the rank of t_{ij}. Compute, for $j = 1, \ldots, K$,

$$R_j = \sum_{i=1}^{n_j} r_{ij} \qquad \bar{R}_j = \frac{R_j}{n_j} \qquad \bar{R} = \frac{1}{2}(N+1) \tag{5.3.1}$$

where R_j and $\bar{R}_j$ are, respectively, the sum of the ranks and the average rank of the jth treatment, and $\bar{R}$ is the overall average rank. Then the Kruskal–Wallis H-statistic is

$$H = \frac{12}{N(N+1)} \sum_{j=1}^{K} n_j(\bar{R}_j - \bar{R})^2 \tag{5.3.2}$$

$$= \frac{12}{N(N+1)} \sum_{j=1}^{K} \frac{R_j^2}{n_j} - 3(N+1) \tag{5.3.3}$$

Under the null hypothesis, H has an asymptotic (n_j's approaching infinity or n_j's are large) chi-square distribution with $K-1$ degrees of freedom. Thus, for large n_j's, the approximate test procedure at the α level is to reject H_0 if $H \geqslant \chi^2_{(k-1),\alpha}$. When $K = 3$ and the number of observations in each of the three samples is 5 or fewer, the chi-square approximation is not sufficiently close. For such cases, exact permutational distributions of H are available and percentage points χ_k are given in Table B-4 of Appendix B. The test procedure is to reject H_0 if $H \geqslant \chi_{k,\alpha}$, where $\chi_{k,\alpha}$ satisfies the equation $P(H \geqslant \chi_{k,\alpha} \mid H_0) = \alpha$.

When there are tied observations, each is assigned the average of the ranks. To correct for the effects of ties, H is computed by (5.3.3) and then divided by

$$1 - \frac{1}{N^3 - N} \sum_{j=1}^{g} T_j \tag{5.3.4}$$

where g is the number of tied groups, and $T_j = t_j^3 - t_j$, with t_j being the number of tied observations in a tied group. In counting g, an untied observation is considered as a tied group of size 1. Thus, a general expression of H corrected for ties is

$$H = \frac{[12/N(N+1)]\,\Sigma_{j=1}^{k}(R_j^2/n_j) - 3(N+1)}{1 - \Sigma_{j=1}^{g} T_j/(N^3 - N)} \tag{5.3.5}$$

Table 5.8 Cholesterol Values of 12 Subjects on Three Different Diets

Diet 1	Diet 2	Diet 3
229	145	231
176	181	208
187	147	217
208	187	199

Note that when there are no ties, $g = N$, $t_j = 1$ for all j, and $T_j = 0$, and (5.3.5) reduces to (5.3.3). The following example illustrates the use of the test.

Example 5.9 In a study of the relationship between cholesterol level and diet, three diets are given randomly to 12 men whose initial cholesterol levels are almost the same. Table 5.8 shows the cholesterol levels of the 12 people after having their assigned diet for a given period of time. The purpose of the study is to decide if the three diets are equally effective in controlling cholesterol level.

The null hypothesis H_0 states that there is no difference in cholesterol level of men having the three diets, and the alternative H_1 says that the cholesterol levels of men having the three different diets are different. To compute the H-statistic, we first rank the observations as in Table 5.9 and compute R_j. In this case $N = 12$, $n_1 = n_2 = n_3 = 4$, $g = 10$, and $T_j = 0$ except for $j = 5, 7$.

Table 5.9 Computation of H for Data in Example 5.9

Ordered Observations	Ranks	Ranks of Diet 1	Ranks of Diet 2	Ranks of Diet 3
145	1	—	1	
147	2	—	2	
176	3	3		
181	4	—	4	
187	5.5	—	5.5	
187	5.5	5.5		
199	7	—	—	7
208	8.5	8.5		
208	8.5	—	—	8.5
217	10	—	—	10
229	11	11		
231	12	—	—	12
R_j		28	12.5	37.5

Hence, $\Sigma_{j=1}^{g} T_j = 2(8-2) = 12$, and by (5.3.5),

$$H = \frac{[12/(12\times 13)](784/4 + 156.25/4 + 1406.25/4) - 3(13)}{1 - 12/(1728-12)} = 6.168$$

From Table B-4 we find that $P(H \geqslant 6.038 \mid H_0) = 0.037$ and $P(H \geqslant 6.269 \mid H_0) = 0.033$; we reject H_0 at the $\alpha \approx 0.035$ level. There is evidence of significant differences among the diets.

5.3.2 Multiple Comparisons Based on the Kruskal–Wallis Test

If the null hypothesis that the K samples are from the same distribution is rejected, we might ask which particular samples are from different distributions. In Example 5.9 we reject the null hypothesis that the three diets are similar. The investigator may also be interested in knowing which particular diets differ from one another. In this section we introduce some nonparametric methods for multiple comparison based on Kruskal–Wallis rank sums. An excellent treatment of multiple comparisons is given by Miller (1966).

To decide which treatments differ from one another, there are $\frac{1}{2}K(K-1)$ decisions to make, one for each pair of treatments. The null hypothesis can be written as

$$H_0: \text{samples } i \text{ and } j \text{ are from the same population for}$$
$$i = 1, \ldots, K-1, j = i+1, \ldots, K, i < j$$

Let the probability of at least one wrong decision when H_0 is true be controlled by α and the probability of making all correct decisions when H_0 is true be $1-\alpha$. To make the $\frac{1}{2}K(K-1)$ decisions, we introduce the following comparison procedures.

1. When sample sizes are equal, that is, $n_1 = n_2 = \cdots = n_K = n$, and n is small, we reject the hypothesis that the ith and jth samples, $i < j$, are from the same distribution if

$$|R_i - R_j| \geqslant y(\alpha, K, n) \tag{5.3.6}$$

   where $y(\alpha, K, n)$ satisfies the equation

$$P(|R_i - R_j| \geqslant y(\alpha, K, n) \mid H_0, i < j) = 1 - \alpha \tag{5.3.7}$$

   and $R_1, R_2, \ldots, R_K$ are given in (5.3.1). Some approximate values of y are given in Table B-5.
2. When sample sizes are equal to n and n is large, we introduce Miller's (1966) procedure, that is, to reject the hypothesis that the ith and jth

Table 5.10 Multiple Comparisons for Data in Example 5.9

i	j	$\lvert R_i - R_j \rvert$	Decision
1	2	$\lvert 28 - 12.5 \rvert = 15.5$	Not significant
1	3	$\lvert 28 - 37.5 \rvert = 9.5$	Not significant
2	3	$\lvert 12.5 - 37.5 \rvert = 25.0$	Significant

samples, $i < j$, are from the same distribution if

$$|\bar{R}_i - \bar{R}_j| \geqslant q(a,\ K)[\tfrac{1}{12}K(Kn + 1)]^{1/2} \tag{5.3.8}$$

where $\bar{R}_1, \ldots, \bar{R}_K$ are given in (5.3.1) and $q(\alpha, K)$ is the upper α percentile point of the range of K independent standard normal variables. Table B-6 gives the $q(\alpha, K)$ values for some K and α.

3. For cases of small unequal sample sizes $n_1, \ldots, n_K$, a conservative procedure is to reject the hypothesis that the ith and jth samples, $i < j$, are from the same distribution if

$$|\bar{R}_i - \bar{R}_j| \geqslant (x_{\alpha,K})^{1/2} \left[\frac{1}{12}\, N(N + 1)\right]^{1/2} \left(\frac{1}{n_i} + \frac{1}{n_j}\right)^{1/2} \tag{5.3.9}$$

where N is the total number of observations. Values of $x_{a,K}$ are given in Table B-4.

4. When $n_1, \ldots, n_K$ are large, Dunn (1964) suggests the following procedure. Reject the hypothesis that the ith and jth samples, $i < j$, are from the same distribution if

$$|\bar{R}_i - \bar{R}_j| \geqslant Z_{\alpha/[K(K-1)]} \left[\frac{1}{12}\, N(N + 1)\right]^{1/2} \left(\frac{1}{n_i} + \frac{1}{n_j}\right)^{1/2} \tag{5.3.10}$$

where $Z_{\alpha/[K(K-1)]}$ is the upper $100\alpha/[K(K-1)]$ percentage point of the standard normal distribution (see Table B-1).

Example 5.10 Let us use the data in Example 5.9. To examine which particular diets differ from one another, we apply (5.3.6). Since $K = 3$, there are three possible comparisons. The calculation is shown in Table 5.10. For $K = 3$, $n = 4$, and from Table B-5, $y(0.045, 3, 4) = 24$; hence for $(i, j) = (2, 3)$, (5.3.6) is satisfied. Thus, at $\alpha \simeq 0.045$, we conclude that diets 2 and 3 are significantly different.

5.3.3 Test for Censored Data

In Section 5.1 we introduced three nonparametric tests based on scores for comparing two samples with censored observations; Gehan's generalized Wilcoxon test (if Mantel's procedure is used), Peto and Peto's generalized Wilcoxon test, and the logrank test. The K-sample test discussed in this section can be considered an extension of these tests and the Kruskal–Wallis test.

Suppose that we have a set of N scores $w_1, w_2, \ldots, w_N$ obtained according to the manner of scoring in one of the three tests mentioned above. The sum of the N scores is zero. Let S_j be the sum of the scores in the jth sample. The null hypothesis H_0 states that the K samples are from the same distribution. To test H_0 we calculate

$$X^2 = \frac{\Sigma_{j=1}^{K} (S_j^2/n_j)}{s^2} \tag{5.3.11}$$

where

$$s^2 = \frac{\Sigma_{i=1}^{N} w_i^2}{N-1} \tag{5.3.12}$$

Under the null hypothesis X^2 has approximately chi-square distribution with $K-1$ degrees of freedom (Peto and Peto, 1972). Thus, we reject H_0 if X^2 exceeds the upper 100α percentage point of the chi-square distribution with $K-1$ degrees of freedom, that is, if $X^2 \geqslant \chi^2_{(k-1),\alpha}$.

Example 5.11, using the scoring method of Mantel (1967) for Gehan's generalized Wilcoxon test, illustrates the K-sample test for censored data.

Example 5.11 Consider the initial remission times of leukemia patients (in days) induced by three treatments as given in Table 5.11. In this case, $K = 3$, $N = 66$, $n_1 = 25$, $n_2 = 19$, and $n_3 = 22$. A table similar to Table 5.1 may be set up to compute the score for every observation. The computation is left to the reader as an exercise. The sums of scores in the three samples are $S_1 = -273$, $S_2 = 170$, and $S_3 = 103$. The sum of squares of the scores $\Sigma w_i^2 = 89{,}702$. Hence, from (5.3.11) and (5.3.12), $X^2 = 3.612$. From Table B-2, $\chi^2_{2,0.05} = 5.991$;

Table 5.11 Initial Remission Times of Leukemia Patients

1	2	3
4, 5, 9, 10, 12, 13, 10, 23, 28, 28, 28, 29 31, 32, 37, 41, 41, 57, 62, 74, 100, 139, 20+, 258+, 269+	8, 10, 10, 12, 14, 20, 48, 70, 75, 99, 103, 162, 169, 195, 220, 161+, 199+, 217+, 245+	8, 10, 11, 23, 25, 25, 28, 28, 31, 31, 40, 48, 89, 124, 143, 12+, 159+, 190+, 196+, 197+, 205+, 219+

thus we do not reject H_0. The data do not show significant differences among the three initial treatments.

Bibliographical Remarks

Gehan's test was first proposed in 1965. The Cox–Mantel test was first discussed by Cox in 1959, then by Mantel in 1966, and finally, by Cox again in 1972. The scores for the logrank test was proposed by Peto and Peto in 1972 along with another generalization of the Wilcoxon test. In the same paper, they also discuss the K-sample test for censored data. The logrank test is also discussed in Peto et al. (1977). Cox's F-test was developed in 1964 and the Mantel–Haenszel chi-square test can be found in Mantel and Haenszel (1959) and Mantel (1966). The Kruskal–Wallis one-way analysis of variance can be found in most standard textbooks under nonparametric methods. Readers who are interested in the theoretical development or more properties of these tests should read the original papers cited above. Applications of these tests are given in the original papers or can easily be found in medical and epidemiological journals.

EXERCISES

The first five exercises are continuations of Exercises 4.1 to 4.4 and 4.6.

5.1 For the survival times given in Table 3.1, compare the survival distributions of the two treatment groups using:
(a) Gehan's generalized Wilcoxon test
(b) The Cox–Mantel test

5.2 For the remission data given in Table 3.1, compare the remission time distributions of the two treatment groups using:
(a) The logrank test
(b) Peto and Peto's generalized Wilcoxon test

5.3 For the data given in Table 3.4, compare the tumor-free time distributions of the three diet groups.

5.4 For the remission data of 42 leukemia patients given in Example 3.3, use the two generalized Wilcoxon tests to see if 6-MP is more effective than placebo in prolonging remission time.

5.5 For the first four skin tests given in Exercise Table 3.1, use the Cox–Mantel and logrank tests to see if there is a significant difference in survival between patients with positive ($\geqslant 5$ mm for mumps, $\geqslant 10$ mm for others) and negative (< 5 mm for mumps, < 10 mm for others) reactions.

5.6 Compute the test statistic W of Gehan's generalized Wilcoxon test by using (5.1.1) for the data in Example 5.1. Do you get the same result as in Example 5.1?

5.7 Consider the data in Example 5.11. Use Mantel's procedure for Gehan's generalized Wilcoxon test to compute a score for each observation and the sum of scores for each of the three treatment groups.

5.8 Using the data in Table 3.1, compare the age distributions of the two treatment groups using Cox's F-test.

5.9 Consider the data in Exercise Table 5.1. Is elevated percent standard BMI associated with renal cell carcinoma after controlling the effects of gender?

Exercise Table 5.1

Percentage of Standard BMI[a]	Male		Female	
	Case	Control	Case	Control
<140	130	160	60	65
$\geqslant 140$	85	55	55	50

[a] Standard BMI: male, 22.1; female, 20.6. Percentage of standard BMI = (observed BMI/standard BMI) $\times$ 100.

5.10 Consider the survival data of men with angina pectoris in Table 4.6 and women with the same disease in Exercise Table 4.2. Is there a significant difference between the survival distributions of men and women?

5.11 In a study of noise level and efficiency, 18 students were given a very simple test under three different noise levels. It is known that under

Exercise Table 5.2

1	2	3
10.5	10.0	12.0
9.0	12.0	13.0
9.5	12.5	15.5
9.0	11.0	14.0
8.5	12.0	12.5
10.0	10.5	15.0

normal conditions, they should be able to finish the test in 10 minutes. The students were randomly assigned to the three levels. Exercise Table 5.2 gives the time required to finish the test. Are the three noise levels significantly different? If they are, determine which levels differ from one another.

5.12 Exercise Table 5.3 gives the survival time in weeks of 30 brain tumor patients receiving four different treatments. Are the four treatments equally effective?

Exercise Table 5.3

1	2	2	3
4	1	3	5
5	4	7	15
9	9	14	20
12	12	20	31
20+	15	27	39
25	23	30	47
30+	30	32+	55+
		50+	67+

CHAPTER 6

Some Well-Known Parametric Survival Distributions and Their Applications

Usually, there are many physical causes that lead to the failure or death of a person at a particular time. It is very difficult, if not impossible, to isolate these physical causes and account mathematically for all of them. Therefore, choosing a theoretical distribution to approximate survival data is as much an art as a scientific task. In this chapter, several theoretical distributions that have been used widely to describe survival time are discussed, their characteristics summarized, and their applications illustrated.

6.1 EXPONENTIAL DISTRIBUTION

The simplest and most important distribution in survival studies is the exponential distribution. In the late 1940s, researchers began to choose the exponential distribution to describe the life pattern of electronic systems. Davis (1952) gives a number of examples, including bank statement and ledger error, payroll check errors, automatic calculating machine failure, and radar set component failure, in which the failure data are well described by the exponential distribution. Epstein and Sobel (1953) report why they select the exponential distribution over the popular normal distribution and show how to estimate the parameter when data are singly censored. Epstein (1958) also discusses in some detail the justification for the assumption of an exponential distribution. The exponential distribution has since continued to play a role in lifetime studies analogous to that of the normal distribution in other areas of statistics.

The exponential distribution is often referred to as a purely random failure pattern. It is famous for its unique "lack of memory," which requires that the age of the animal or person does not affect future survival. Although many

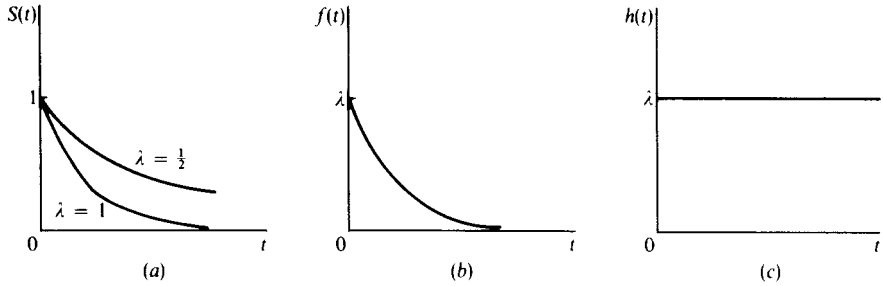


Figure 6.1 Exponential distribution: (*a*) survivorship function; (*b*) probability density function; (*c*) hazard function.

survival data cannot be described adequately by the exponential distribution, an understanding of it facilitates the treatment of more general situations.

The exponential distribution is characterized by a constant hazard rate λ, its only parameter. A high λ value indicates high risk and short survival; a low λ value indicates low risk and long survival. Figure 6.1 depicts the survivorship function, the density function, and the hazard function of the exponential distribution with parameter λ. When $\lambda = 1$, the distribution is often referred to as the *unit exponential distribution.*

When the survival time T follows the exponential distribution with a parameter λ, the probability density function is defined as

$$f(t) = \begin{cases} \lambda e^{-\lambda t} & t \geqslant 0, \quad \lambda > 0 \\ 0 & t < 0 \end{cases} \tag{6.1.1}$$

The cumulative distribution function is

$$F(t) = 1 - e^{-\lambda t} \qquad t \geqslant 0 \tag{6.1.2}$$

and the survivorship function is then

$$S(t) = e^{-\lambda t} \qquad t \geqslant 0 \tag{6.1.3}$$

So that, by (2.2.1), the hazard function is

$$h(t) = \lambda \qquad t \geqslant 0 \tag{6.1.4}$$

a constant, independent of t. Figure 6.1 gives the graphical presentation of the three functions.

Because the exponential distribution is characterized by a constant hazard rate, independent of the age of the person, there is no aging or wearing out,

and failure or death is a random event independent of time. When natural logarithms of the survivorship function are taken, $\log S(t) = -\lambda t$, which is a linear function of t. Thus, it is easy to determine whether data come from an exponential distribution by plotting $\log \hat{S}(t)$ against t, where $\hat{S}(t)$ is an estimate of $S(t)$. A linear configuration indicates that the data follow an exponential distribution and the slope of the straight line is an estimate of the hazard rate λ.

The mean and variance of the exponential distribution with parameter λ are, respectively, $1/\lambda$ and $1/\lambda^2$. The median is $(1/\lambda)\log 2$. The coefficient of variation is 1.

A more general form of the exponential distribution is the *two-parameter exponential distribution* with probability density function

$$f(t) = \begin{cases} \lambda e^{-\lambda(t-G)} & t \geqslant G \\ 0 & t < G \end{cases} \tag{6.1.5}$$

Then

$$F(t) = \begin{cases} 1 - e^{-\lambda(t-G)} & t \geqslant G \\ 0 & t < G \end{cases} \tag{6.1.6}$$

$$S(t) = \begin{cases} e^{-\lambda(t-G)} & t \geqslant G \\ 0 & t < G \end{cases} \tag{6.1.7}$$

and

$$h(t) = \begin{cases} 0 & 0 \leqslant t < G \\ \lambda & t < G \end{cases} \tag{6.1.8}$$

The term G is a *guarantee time* within which no deaths or failures can occur, or a minimum survival time. If $G = 0$, (6.1.5)–(6.1.8) reduce to (6.1.1)–(6.1.4) for the one-parameter exponential. The mean and the median of the two-parameter exponential distribution are, respectively, $G + 1/\lambda$ and $(\log 2 + \lambda G)/\lambda$.

Example 6.1 In a study of new anticancer drugs in the L1210 animal leukemia system, Zelen (1966) used the exponential distribution successfully as the model for survival time. The system consists of injecting a tumor inoculum into inbred mice. These tumor cells then proliferate and eventually kill the animal, but survival time may be prolonged by an active drug. Figure 6.2 shows the survival curve in a semilogarithmic scale of the untreated mice inoculated at different cell dilutions. Twenty-five mice were inoculated at each dilution. The reasonably linear configurations suggest that the survival distributions follow the exponential distribution quite well. The four straight lines fitted to the points are almost parallel, indicating that the hazard rate was independent of the inoculum size. Table 6.1 gives the estimated values of the

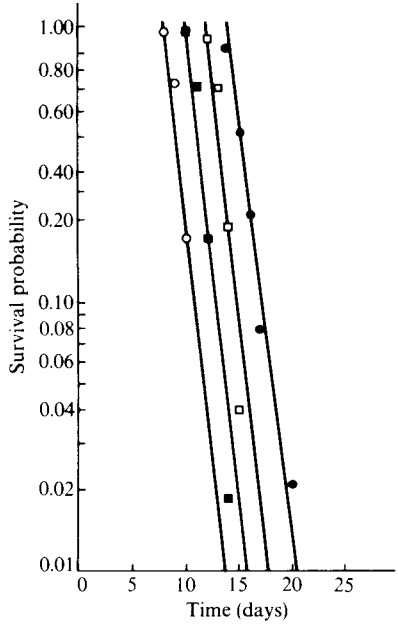


Figure 6.2 Survival curves of untreated mice inoculated with serial 10-fold dilutions of leukemia L1210: (○) 10^5 cells; (■) 10^4 cells; (□) 10^3 cells; (●) 10^2 cells. (From Zelen, 1966.)

guarantee times G, hazard rates λ, and the mean survival times (in days) for the various dilutions. (Estimation procedures are discussed in Chapter 7.) Note that the estimated hazard rates, λ, are very close.

The probability that a mouse receiving 10^5 cells of inoculum will survive more than 20 days is, from (6.1.7),

$$S(20) = e^{-0.78(20-8)} \simeq 0.0001$$

and the median survival time is 8.9 days.

Table 6.1 Estimates of G, λ, and Mean Survival Time for Untreated Mice with Serial Leukemia Dilutions

Dilution	$\hat{G}$	$\hat{\lambda}$	Mean Survival Time
10^5	8.0	0.78	9.3
10^4	10.0	0.78	11.3
10^3	11.9	0.76	13.2
10^2	13.9	0.67	15.4

Source: Zelen (1966).

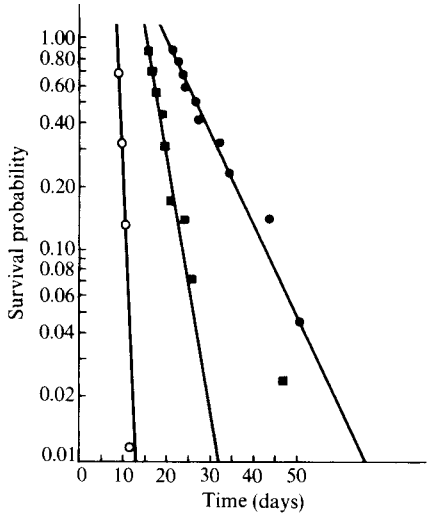


Figure 6.3 Survival curves of mice treated with cyclophosphamide on day 3 after inoculation of 10^5 tumor cells: (○) control; (■) 80 mg/kg; (●) 160 mg/kg. (From Zelen, 1966.)

Figure 6.3 gives the survival curves of mice treated with different doses of cyclophosphamide on day 3 after receiving a 10^5 tumor inoculum. Table 6.2 gives the estimates of G, λ, and the mean survival time. Mice receiving 160 mg/kg of the drug show a remarkably improved surivival pattern over the control group.

The probability that a mouse receiving 80 mg/kg of cyclophosphamide will survive more than 20 days is, from (6.1.7),

$$S(20) = e^{-0.29(20-15.6)} = 0.279$$

The median survival time is approximately 18 days.

6.2 WEIBULL DISTRIBUTION

The Weibull distribution is a generalization of the exponential distribution. However, unlike the exponential distribution, it does not assume a constant hazard rate and therefore has broader application. The distribution was proposed by Weibull (1939) and its applicability to various failure situations discussed again by Weibull (1951). It has then been used in many studies of reliability and human disease mortality.

The Weibull distribution is characterized by two parameters, γ and λ. The value of γ determines the shape of the distribution curve and the value of λ

Table 6.2 Estimates of G, λ, and Mean Survival Time for Treated Mice on Day 3

Dose (mg/kg)	$\hat{G}$	$\hat{\lambda}$	Mean Survival Time
Control	8.7	1.12	9.6
80	15.6	0.29	19.0
160	21.5	0.10	31.5

Source: Zelen (1966).

determines its scaling. Consequently, γ and λ are called the *shape* and *scale parameters*, respectively. The relationship between the value of γ and survival time can be seen from Figure 6.4, which shows the hazard rate of the Weibull distribution with $\gamma = 0.5, 1, 2, 4$. When $\gamma = 1$, the hazard rate remains constant as time increases; this is the exponential case. The hazard rate increases when $\gamma > 1$ and decreases when $\gamma < 1$ as t increases. Thus, the Weibull distribution may be used to model the survival distribution of a population with increasing, decreasing, or constant risk. Examples of increasing and decreasing hazard rates are, respectively, patients with lung cancer and patients who undergo successful major surgery.

The probability density function and cumulative distribution functions are, respectively,

$$f(t) = \lambda\gamma(\lambda t)^{\gamma-1}e^{-(\lambda t)^{\gamma}}\, t \geqslant 0, \quad \gamma, \lambda > 0 \tag{6.2.1}$$

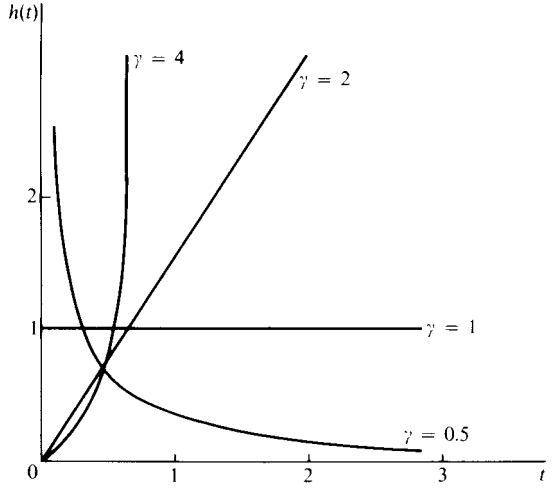


Figure 6.4 Hazard functions of Weibull distribution with $\lambda = 1$.

and

$$F(t) = 1 - e^{-(\lambda t)^{\gamma}} \tag{6.2.2}$$

The survivorship function is, therefore,

$$S(t) = e^{-(\lambda t)^{\gamma}} \tag{6.2.3}$$

and the hazard function, the ratio of (6.2.1) to (6.2.3), is

$$h(t) = \lambda\gamma(\lambda t)^{\gamma - 1} \tag{6.2.4}$$

Figure 6.5 gives the Weibull density function with scale parameter $\lambda = 1$ and several different values of the shape parameter γ.

For the survival curve, it is simple to plot the logarithm of $S(t)$,

$$\log S(t) = -(\lambda t)^{\gamma} \tag{6.2.5}$$

Figure 6.6 gives $\log S(t)$ for $\lambda = 1$ and $\gamma = 1, >1, <1$. When $\gamma = 1$ is a straight line with negative slope. When $\gamma < 1$, negative aging, $\log S(t)$ decreases very slowly from 0 and then approaches a constant value. When $\gamma > 1$, positive aging, $\log S(t)$ decreases sharply from 0 as t increases. Equation (6.2.5) can also

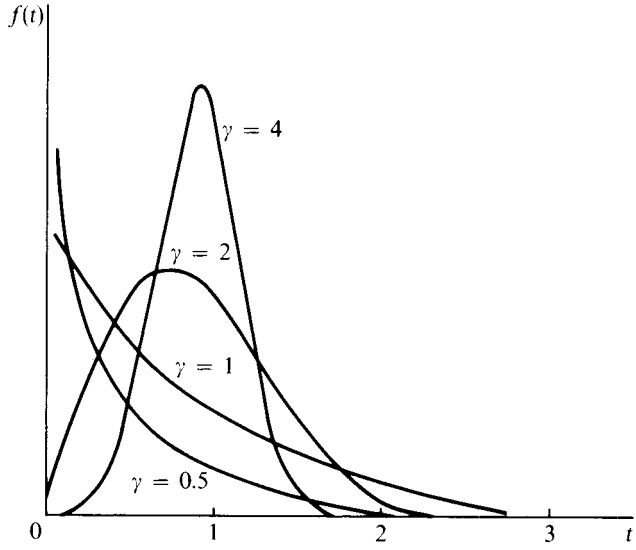


Figure 6.5 Density curves of Weibull distribution with $\lambda = 1$.

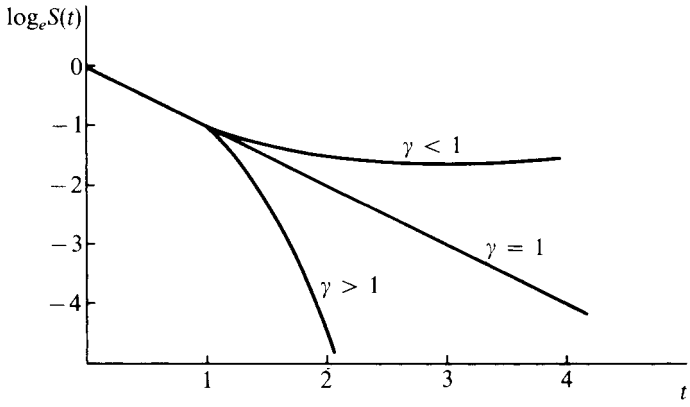


Figure 6.6 Curves of $\log_e S(t)$ of Weibull distribution with $\lambda = 1$.

be written as

$$\log[-\log S(t)] = \gamma \log_e \lambda + \gamma \log_e t \tag{6.2.6}$$

The mean of the Weibull distribution is

$$\mu = \frac{\Gamma(1 + 1/\gamma)}{\lambda} \tag{6.2.7}$$

and the variance is

$$\sigma^2 = \frac{1}{\lambda^2}\left[\Gamma\left(1 + \frac{2}{\gamma}\right) - \Gamma^2\left(1 + \frac{1}{\gamma}\right)\right] \tag{6.2.8}$$

where $\Gamma(\gamma)$ is the well-known gamma function defined as

$$\begin{aligned}\Gamma(\gamma) &= \int_0^\infty x^{\gamma-1} e^{-x}\,dx \\ &= (\gamma - 1)! \qquad \text{when } \gamma \text{ is a positive integer}\end{aligned} \tag{6.2.9}$$

Values of $\Gamma(\gamma)$ can be found in Abramowitz and Stegun (1964). The coefficient of variation is then

$$\text{CV} = \left[\frac{\Gamma(1 + 2/\gamma)}{\Gamma^2(1 + 1/\gamma)} - 1\right]^{1/2} \tag{6.2.10}$$

The Weibull distribution can also be generalized to take into account a guarantee time G during which no deaths or failures can occur. The three-

parameter Weibull probability density function is

$$f(t) = \lambda^{\gamma}\gamma(t - G)^{\gamma - 1} \exp[-\lambda^{\gamma}(t - G)^{\gamma}] \tag{6.2.11}$$

Consequently,

$$S(t) = \exp[-\lambda^{\gamma}(t - G)^{\gamma}] \tag{6.2.12}$$

and

$$h(t) = \lambda^{\gamma}\gamma(t - G)^{\gamma - 1} \tag{6.2.13}$$

Example 6.2 Pike (1966) applied the Weibull distribution to a two-group experiment on vaginal cancer in rats exposed to the carcinogen DMBA. The two groups were distinguished by pretreatment regime. The times in days, after the start of the experiment, at which the carcinoma was diagnosed for the two groups of rats were as follows:

Group 1: 143, 164, 188, 188, 190, 192, 206, 209, 213, 216, 220, 227, 230, 234, 246, 265, 304, 216+, 244+

Group 2: 142, 156, 173, 198, 205, 232, 232, 233, 233, 233, 233, 239, 240, 261, 280, 280, 296, 296, 323 204+, 344+

Assuming that $G = 100$ and $\gamma = 3$, Pike obtained $\hat{\lambda}_1 = (4.51 \times 10^{-7})^{1/3}$ for group 1 and $\hat{\lambda}_2 = (2.38 \times 10^{-7})^{1/3}$ for group 2. Analytical estimation procedure is discussed in Chapter 7. Figure 6.7 plots the survival curves of the two groups. The step functions are nonparametric estimates similar to the Kaplan–Meier

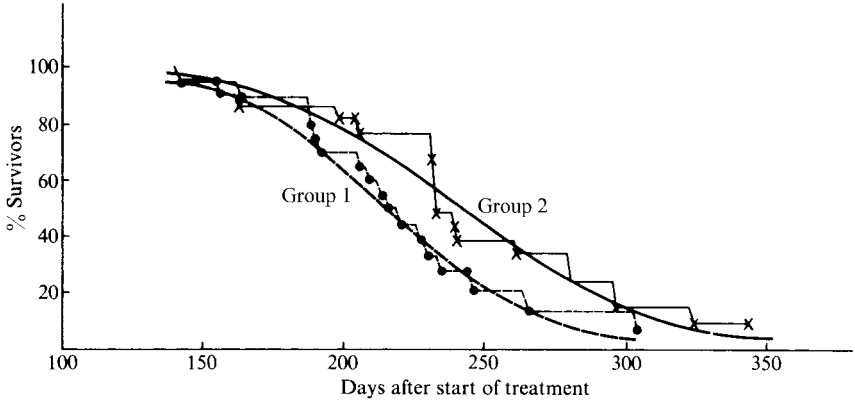


Figure 6.7 Survival curves of rats exposed to carcinogen DMBA. (From Pike, 1966. Reproduced with permission of the Biometrics Society.)

Table 6.3 Calculation of Survivorship Functions for Group 2 of Rats Exposed to DMBA

Time	r	$n-r+1$	$\frac{n-r}{n-r+1}$	Kaplan–Meier Estimates, $\hat{S}(t)$	Modified Kaplan–Meier Estimates[a], $\hat{S}(t)$ Plotted	$\hat{S}(t)$ Obtained from Weibull Fit
142	1	21	0.9524	0.9524	0.9546	0.9825
156	2	20	0.9500	0.9048	0.9091	0.9590
163	3	19	0.9474	0.8572	0.8637	0.9421
198	4	18	0.9444	0.8095	0.8182	0.7990
204+	—	17	1.0000	0.8095	0.8182	0.7647
205	6	16	0.9375	0.7589	0.7700	0.7588
232	7	15	0.9333	0.7083	0.7218	0.5778
232	8	14	0.9286	0.6577	0.6737	0.5778
232	9	13	0.9231	0.6071	0.6255	0.5706
233	10	12	0.9167	0.5565	0.5773	0.5706
233	11	11	0.9091	0.5059	0.5292	0.5706
233	12	10	0.9000	0.4553	0.4810	0.5706
239	13	9	0.8888	0.4047	0.4320	0.5271
240	14	8	0.8750	0.3541	0.3847	0.5198
261	15	7	0.8571	0.3035	0.3365	0.3697
280	16	6	0.8333	0.2529	0.2883	0.2489
280	17	5	0.8000	0.2023	0.2402	0.2489
296	18	4	0.7500	0.1517	0.1920	0.1660
296	19	3	0.6667	0.1011	0.1439	0.1660
323	20	2	0.5000	0.0506	0.0958	0.0710
344+	—	1	1.0000	0.0506	0.0958	0.0313

[a] Instead of $(n-r)/(n-r+1)$, Pike uses $(n-r+1)/(n-r+2)$ in the Kaplan–Meier product-limit estimate to avoid $(n-r)/(n-r+1)=0$.

Source: Pike (1966). Reproduced with permission of the Biometric Society.

estimate. The smooth curves are obtained from the Weibull fits. Table 6.3 shows the calculation of the plotting points for group 2.

It is obvious that the Weibull distributions with $G=100$, $\gamma=3$, $\hat{\lambda}_1=(4.51\times10^{-7})^{1/3}$, and $\hat{\lambda}_1=(2.38\times10^{-7})^{1/3}$ fit the carcinoma-free time of the two groups of rats very well.

6.3 LOGNORMAL DISTRIBUTION

In its simplest form the lognormal distribution can be defined as the distribution of a variable whose logarithm follows the normal distribution. Its origin may be traced as far back as 1879, when McAlister (1879) described explicitly a theory of the distribution. Most of its aspects have since been under study. Gaddum (1945*a*, *b*) gave a review of its application in biology, followed by

Boag's (1949) applications in cancer research. Its history, properties, estimation problems, and uses in economics have been discussed in detail by Aitchison and Brown (1957). Later, other investigators also observed that the age at onset of Alzheimer's disease and the distribution of survival time of several diseases such as Hodgkin's disease and chronic leukemia could be rather closely approximated by a lognormal distribution since they are markedly skewed to the right and the logarithms of survival times are approximately normally distributed.

Consider the survival time T such that $\log T$ is normally distributed with mean μ and variance σ^2. We then say that T is lognormally distributed and write T as $\Lambda(\mu, \sigma^2)$. It should be noted that μ and σ^2 are *not* the mean and variance of the lognormal distribution. Figure 6.8 gives the hazard function of the lognormal distribution with different values for the parameters. The hazard function increases initially to a maximum and then decreases (almost as soon as the median is passed) to zero as time approaches infinity (Watson and Wells 1961). Therefore, the lognormal distribution is suitable for survival patterns with an initially increasing and then decreasing hazard rate. By a central limit theorem, it can be shown that the distribution of the product of n independent positive variates approaches a lognormal distribution under very general conditions: for example, the distribution of the size of an organism whose growth is subject to many small impulses, the effect of each of which is proportional to the momentary size of the organism.

The popularity of the lognormal distribution is due in part to the fact that the cumulative values of $y = \log t$ can be obtained from the tables of the standard normal distribution and the corresponding values of t are then found by taking antilogs. Thus, the percentiles of the lognormal distribution are easy to find.

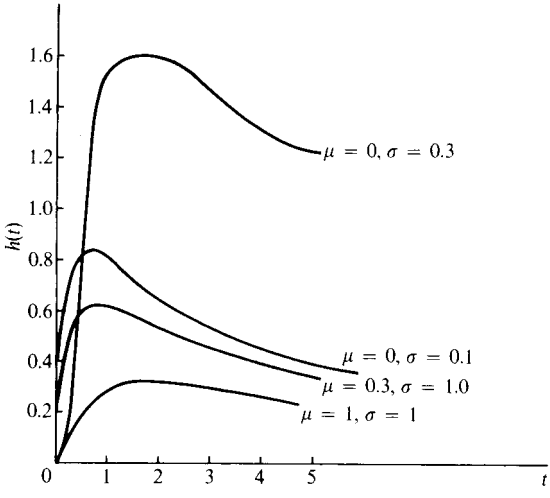


Figure 6.8 Hazard of the lognormal distribution with different parameters.

The probability density function and survivorship function are, respectively,

$$f(t) = \frac{1}{t\sigma\sqrt{2\pi}} \exp\left[-\frac{1}{2\sigma^2} (\log t - \mu)^2 \right] \qquad t > 0, \quad \sigma > 2 \tag{6.3.1}$$

and

$$S(t) = \frac{1}{\sigma\sqrt{2\pi}} \int_t^\infty \frac{1}{x} \exp\left[-\frac{1}{2\sigma^2} (\log x - \mu)^2 \right] dx \tag{6.3.2}$$

Let $a = \exp(-\mu)$. Then $-\mu = \log a$, (6.3.1) and (6.3.2) can be written as

$$f(t) = \frac{1}{t\sigma\sqrt{2\pi}} \exp\left[-\frac{1}{2\sigma^2} (\log at)^2 \right] \tag{6.3.3}$$

and

$$S(t) = \frac{1}{\sigma\sqrt{2\pi}} \int_t^\infty \frac{1}{x} \exp\left[-\frac{1}{2\sigma^2} (\log ax)^2 \right] dx \tag{6.3.4}$$

$$= 1 - G\left(\log \frac{at}{\sigma} \right) \tag{6.3.5}$$

where $G(y)$ is the cumulative distribution function of a standard normal variable

$$G(y) = \frac{1}{\sqrt{2\pi}} \int_0^y e^{-u^2/2}\, du \tag{6.3.6}$$

The lognormal distribution is specified completely by the two parameters μ and σ^2. Time T cannot assume zero values since $\log T$ is not defined for $T = 0$. Figure 6.9 gives the lognormal frequency curves for $\mu = 0$, $\sigma^2 = 0.1, 0.5, 2$, from which an idea of the flexibility of the distribution may be obtained. It is obvious that the distribution is positively skewed and that the greater the value of σ^2, the greater the skewness. Figure 6.10 shows the frequency curves for $\sigma^2 = 0.5$, $\mu = 0, 0.5, 1$. It is obvious that μ and σ^2 are, respectively, scale parameters and *not* location and scale parameters as in the normal distribution. The hazard function, from (6.3.3) and (6.3.5), has the form

$$h(t) = \frac{(1/t\sigma\sqrt{2\pi}) \exp[-(\log at)^2/2\sigma^2]}{1 - G(\log at/\sigma)} \tag{6.3.7}$$

and is plotted in Figure 6.8.

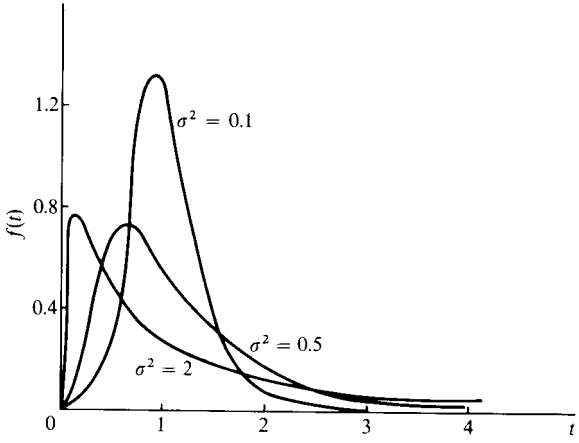


Figure 6.9 Lognormal density curves with $\mu = 0$.

The mean and variance of the two-parameter lognormal distribution are, respectively, $\exp(\mu + \frac{1}{2}\sigma^2)$ and $[\exp(\sigma^2) - 1]\exp(2\mu + \sigma^2)$. The coefficient of variation of the distribution is then $[\exp(\sigma^2) - 1]^{1/2}$. The median is e^{μ} and the mode is $\exp(\mu + \sigma^2)$.

The two-parameter lognormal distribution can also be generalized to a three-parameter distribution by replacing t with $t - G$ in (6.3.1). In other words, the survival time $\log(T - G)$ follows the normal distribution with mean μ and variance σ^2. In certain situations the value of G may be determined a priori and should not be regarded as an unknown parameter that requires estimation. If this is so, the variable $T - G$ may be considered in place of T and the distribution of $T - G$ has all the properties of the two-parameter lognormal distribution. However, the estimation procedures developed for the two-parameter case are not directly applicable to the distribution of $T - G$.

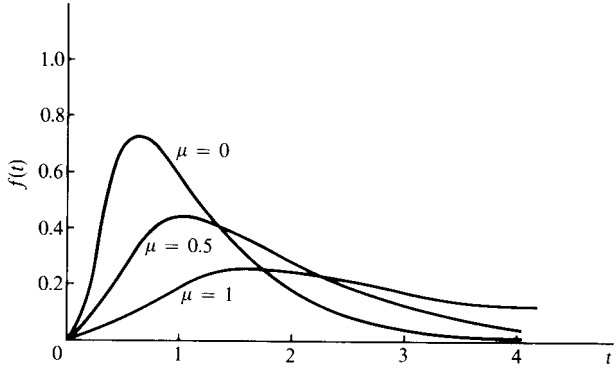


Figure 6.10 Lognormal density curves with $\sigma^2 = 0.5$.

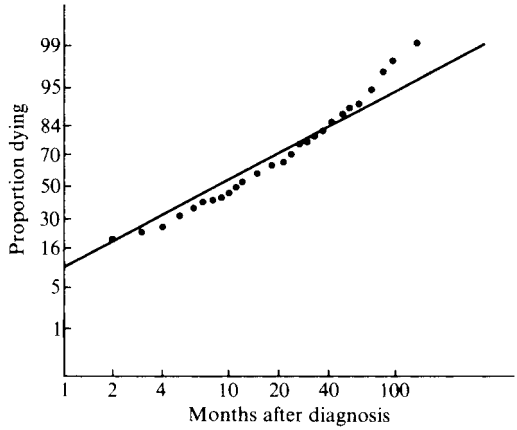


Figure 6.11 Lognormal probability plot of the survival time of 234 male patients with chronic lymphocytic leukemia. (From Feinleib and MacMahon, 1960. Reproduced by permission of the publisher.)

Example 6.3 In a study of chronic lymphocytic and myelocytic leukemia, Feinleib and MacMahon (1960) applied the lognormal distribution to analyze survival data of 649 white residents of Brooklyn diagnosed from 1943 to 1952. The analysis of several subgroups of patients follows. The survival time of each patient is computed from the date of diagnosis in months. Analytical method is used to fit the lognormal distribution to the data. The method is discussed in Chapters 7 and 8.

Figure 6.11 gives the probability plot of the survival time of 234 male patients with chronic lymphocytic leukemia, in which the horizontal axis for the survival time is in logarithmic scale and the vertical axis is in normal probability scale. When plotting $1 - S(t)$ on this graph paper, a straight line is obtained when the data follow a two-parameter lognormal distribution. An inspection of the graph shows that the distribution is concave. Gaddum (1945*a*, *b*) has pointed out that such a deviation can be corrected by subtracting an appropriate constant from the survival times. In other words, the three-parameter lognormal distribution can be used. Figure 6.12 gives a similar plot in which the survival time of every patient plus 4 is plotted. The configuration is linear and hence empirically it seems valid to assume that the lognormal distribution is appropriate.

Similar graphs for male patients with chronic myelocytic leukemia and for female patients with chronic lymphocytic or myelocytic leukemia are given in Figures 6.13 and 6.14. Parameters of the lognormal distribution are estimated. Feinleib and MacMahon report that the agreement between the observed and calculated distributions is striking for each group except for women with chronic lymphocytic leukemia. The corresponding p values for the chi-square

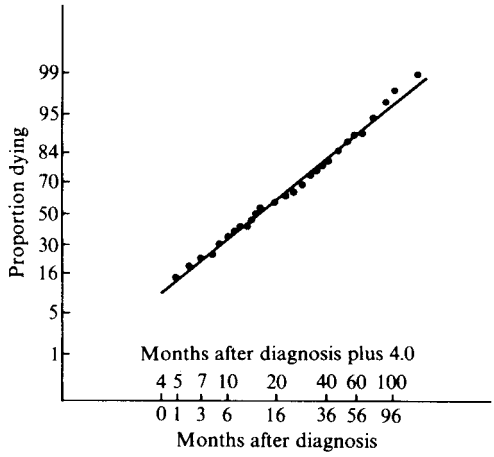


Figure 6.12 Lognormal probability plot of the survival time in months plus 4 of 234 male patients with chronic lymphocytic leukemia. (From Feinleib and MacMahon, 1960. Reproduced by permission of the publisher.)

goodness-of-fit test are as follows:

	Chronic Myelocytic	Chronic Lymphocytic
Male	0.86	0.73
Female	0.57	0.016

Since a large p value indicates close agreement, it is concluded that the three-parameter lognormal distribution adequately describes the distribution of survival times for each subgroup except women with chronic lymphocytic leukemia. The shape of the observed distribution for the latter group suggests that it might actually be composed of two dissimilar groups, each of whose survival times might fit a lognormal distribution.

6.4 GAMMA AND GENERALIZED GAMMA DISTRIBUTIONS

The gamma distribution, which includes the exponential and chi-square distribution, was used a long time ago by Brown and Flood (1947) to describe the life of glass tumblers circulating in a cafeteria and by Birnbaum and Saunders (1958) as a statistical model for life length of materials. Since then, this distribution has been used frequently as a model for industrial reliability problems and human survival.

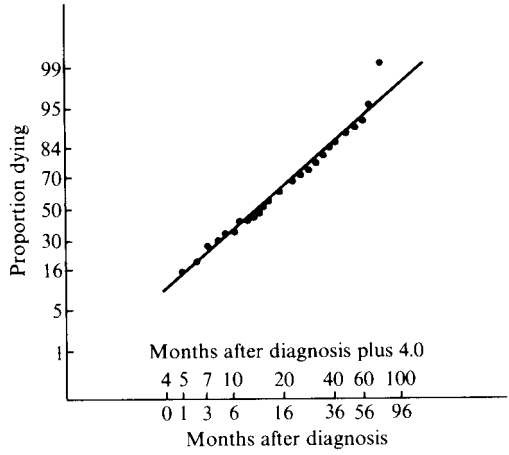


Figure 6.13 Lognormal probability plot of the survival time in months plus 4 of 162 male patients with chronic myelocytic leukemia. (From Feinleib and MacMahon, 1960. Reproduced by permission of the publisher.)

Suppose that failure or death takes place in n stages or as soon as n subfailures have happened. At the end of the first stage, after time T_1, the first subfailure occurs; after that the second stage begins and the second subfailure occurs after time T_2; and so on. Total failure or death occurs at the end of the nth stage, when the nth subfailure happens. The survival time, T, is then $T_1 + T_2 + \cdots + T_n$. The times $T_1, T_2, \ldots, T_n$ spent in each stage are assumed to

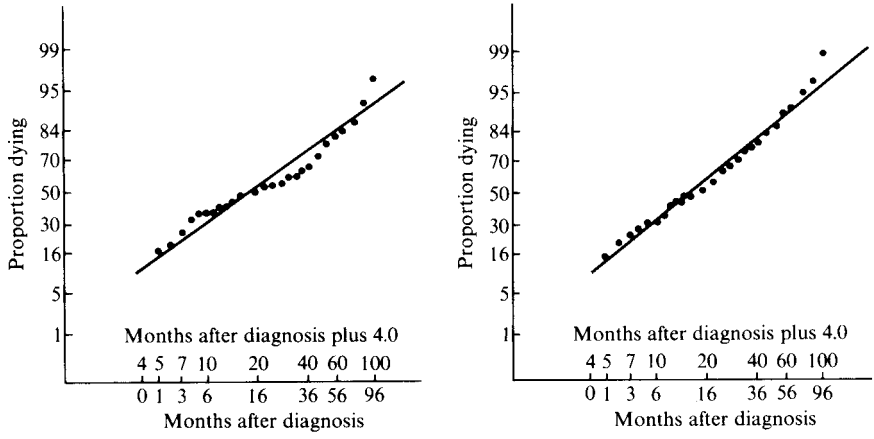


Figure 6.14 Lognormal probability plot of the survival time in months plus 4 of female patients with two types of leukemia. (From Feinleib and MacMahon, 1960. Reproduced by permission of the publisher.)

be independently exponentially distributed with probability density function $\lambda \exp(-\lambda t_i)$, $i = 1, \ldots, n$. That is, the subfailures occur independently at a constant rate λ. The distribution of T is then called the *Erlangian distribution.* There is no need for the stages to have physical significance since we can always assume that death occurs in the n-stage process just described. This idea, introduced by A. K. Erlang in his study of congestion in telephone systems, has been used widely in queuing theory and life processes.

A natural generalization of the Erlangian distribution is to replace the parameter n restricted to the integers 1, 2,... by a parameter γ taking any real positive value. We then obtain the *gamma distribution.*

The gamma distribution is characterized by two parameters, γ and λ. When $0 < \gamma < 1$, there is negative aging and the hazard rate decreases monotonically from infinity to λ as time increases from 0 to infinity. When $\gamma > 1$, there is positive aging and the hazard rate increases monotonically from 0 to λ as time increases from 0 to infinity. When $\gamma = 1$, the hazard rate equals λ, a constant, as in the exponential case. Figure 6.15 illustrates the gamma hazard function for $\lambda = 1$ and $\gamma < 1$, $\gamma = 1$, 2, 4. Thus, the gamma distribution describes a different type of survival pattern where the hazard rate is decreasing or increasing to a constant value as time approaches infinity.

The probability density function of a gamma distribution is

$$f(t) = \frac{\lambda}{\Gamma(\gamma)} (\lambda t)^{\gamma - 1} e^{-\lambda t} \qquad t > 0, \quad \gamma > 0, \quad \lambda > 0 \tag{6.4.1}$$

where $\Gamma(\gamma)$ is defined as in (6.2.9). Figures 6.16 and 6.17 show the gamma density function with various values of γ and λ. It is seen that varying γ changes the shape of the distribution while varying λ changes only the scaling. Consequently, γ and λ are shape and scale parameters, respectively. When $\gamma > 1$, there is a single peak at $t = (\gamma - 1)/\lambda$.

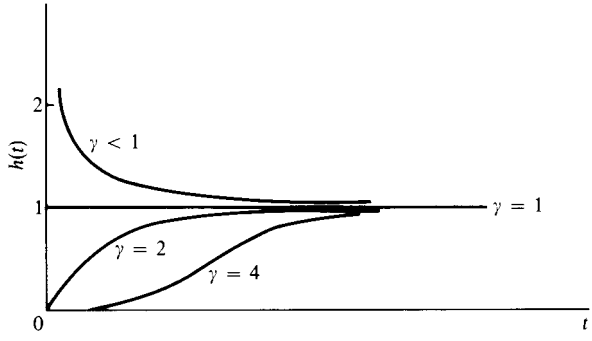


Figure 6.15 Gamma hazard functions with $\lambda = 1$.

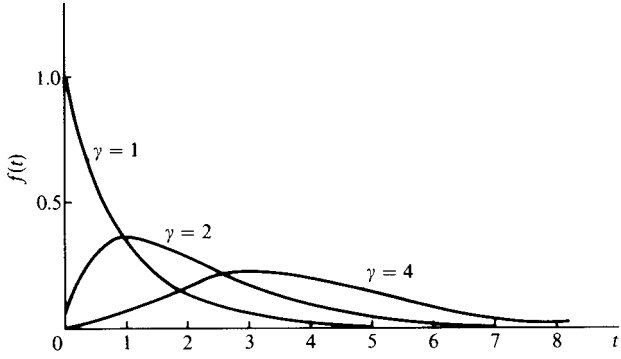


Figure 6.16 Gamma density functions with $\lambda = 1$.

The cumulative distribution function $F(t)$ has a more complex form:

$$F(t) = \int_0^t \frac{\lambda}{\Gamma(\gamma)} (\lambda x)^{\gamma-1} e^{-\lambda x}\, dx \tag{6.4.2}$$

$$= \frac{1}{\Gamma(\gamma)} \int_0^{\lambda t} u^{\gamma-1} e^{-u}\, du$$

$$= I(\lambda t, \gamma) \tag{6.4.3}$$

where

$$I(s, \gamma) = \frac{1}{\Gamma(\gamma)} \int_0^s u^{\gamma-1} e^{-u}\, du \tag{6.4.4}$$

known as the *incomplete gamma function*, is tabulated in Pearson (1922, 1957).

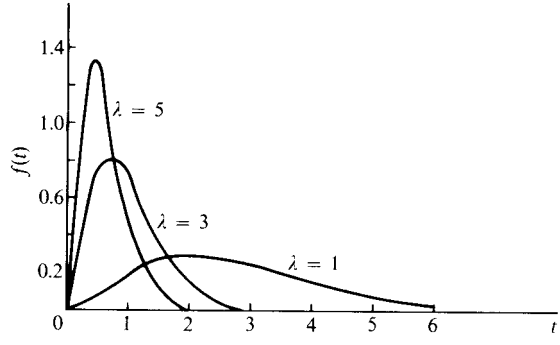


Figure 6.17 Gamma density functions with $\gamma = 3$.

For the Erlangian distribution, it can be shown that

$$F(t) = 1 - \sum_{k=0}^{n-1} \frac{e^{-\lambda t}(\lambda t)^k}{k!} \tag{6.4.5}$$

Thus, the survivorship function $1 - F(t)$ is

$$S(t) = \int_t^{\infty} \frac{\lambda}{\Gamma(\gamma)} (\lambda x)^{\gamma - 1} e^{-\lambda x}\, dx \tag{6.4.6}$$

for the gamma distribution or

$$S(t) = e^{-t} \sum_{k=0}^{n-1} \frac{(\lambda t)^k}{k!} \tag{6.4.7}$$

for the Erlangian distribution.

Since the hazard function is the ratio of $f(t)$ to $S(t)$, it can be calculated from (6.4.1) and (6.4.7). When γ is an integer n,

$$h(t) = \frac{\lambda(\lambda t)^{n-1}}{(n-1)!\, \Sigma_{k=0}^{n-1} (1/k!)(\lambda t)^k} \tag{6.4.8}$$

When $\gamma = 1$, the distribution is exponential. When $\lambda = \frac{1}{2}$ and $\gamma = \frac{1}{2}v$, where v is an integer, the distribution is chi-square with v degrees of freedom. The mean and variance of the standard gamma distribution are, respectively, γ/λ and γ/λ^2, so that the coefficient of variation is $1/\sqrt{\gamma}$.

Many survival distributions can be represented, at least roughly, by suitable choice of the parameters λ and γ. In many cases, there is an advantage in using the Erlangian distribution, that is, in taking γ integer.

The exponential, Weibull, lognormal, and gamma distributions are special cases of a generalized gamma distribution with three parameters, λ, α, and γ, whose density function is defined as

$$f(t) = \frac{\alpha \lambda^{\alpha\gamma}}{\Gamma(\gamma)} t^{\alpha\gamma - 1} \exp[-(\lambda t)^{\alpha}] \qquad t > 0, \quad \gamma > 0, \quad \lambda > 0, \quad \alpha > 0 \tag{6.4.9}$$

It is easily seen that this generalized gamma distribution is the exponential distribution if $\alpha = \gamma = 1$, the Weibull distribution if $\gamma = 1$; the lognormal distribution if $\gamma \to \infty$, and the gamma distribution if $\alpha = 1$.

In later chapters (e.g., Chapters 7 and 9), we discuss several parametric procedures for estimation and hypothesis testing. To use available computer software such as SAS to carry out the computation, we use the distributions adopted by the software. One of the very few software packages that include the gamma or generalized gamma distribution is SAS. In SAS, the generalized

Table 6.4 Lifetimes of 101 Strips of Aluminum Coupon

370	1085	1293	1522	1792
706	1102	1300	1522	1820
716	1102	1310	1530	1868
746	1108	1313	1540	1881
785	1115	1315	1560	1890
797	1120	1330	1567	1893
844	1134	1355	1578	1895
855	1140	1390	1594	1910
858	1199	1416	1602	1923
886	1200	1419	1604	1940
886	1200	1420	1608	1945
930	1203	1420	1630	2023
960	1222	1450	1642	2100
988	1235	1452	1674	2130
990	1238	1475	1730	2215
1000	1252	1478	1750	2268
1010	1258	1481	1750	2440
1016	1262	1485	1763	
1018	1269	1502	1768	
1020	1270	1505	1781	
1055	1290	1513	1782	

Source: Birnbaum and Saunders (1958).

gamma distribution is defined as having the following density function:

$$f(t) = \frac{|\alpha|\gamma^{\gamma}\lambda^{\alpha\gamma}}{\Gamma(\gamma)}\, t^{\alpha\gamma-1} \exp\left[-\gamma(\lambda t)^{\alpha}\right], \qquad t > 0, \quad \gamma > 0, \quad \lambda > 0 \tag{6.4.10}$$

To differentiate this form of the generalized gamma distribution from the generalized gamma in (6.4.9), we refer to this distribution as the *extended generalized gamma distribution*. It can be shown that the extended generalized gamma distribution reduces to the Weibull distribution when $\alpha > 0$ and $\gamma = 1$, the lognormal distribution when $\gamma \to \infty$, the gamma distribution when $\alpha = 1$, and the exponential distribution when $\alpha = \gamma = 1$.

Example 6.4 Birnbaum and Saunders (1958) report an application of the gamma distribution to the lifetime of aluminum coupon. In their study, 17 sets of six strips were placed in a specially designed machine. Periodic loading was applied to the strips with a frequency of 18 hertz and a maximum stress of 21,000 pounds per square inch. The 102 strips were run until all of them failed. One of the 102 strips tested had to be discarded for an extraneous reason, yielding 101 observations. The lifetime data are given in Table 6.4 in ascending order. From the data the two parameters of the gamma distribution were

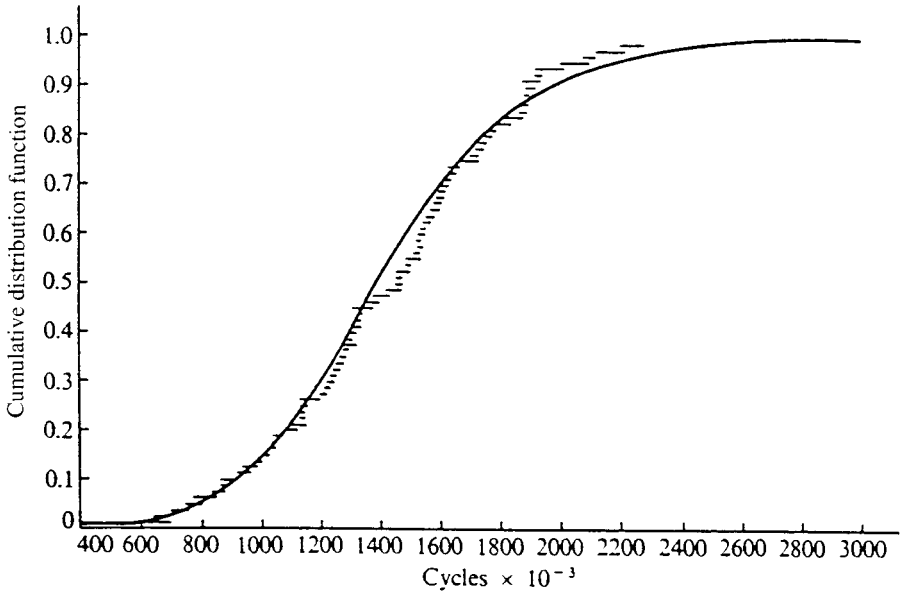


Figure 6.18 Graphical comparison of observed and fitted cumulative distribution functions of data in Example 6.4. (From Birnbaum and Saunders, 1958.)

estimated (estimation methods are discussed in Chapter 7). They obtained $\hat{\gamma} = 11.8$ and $\hat{\lambda} = 1/(118.76 \times 10^3)$.

A graphical comparison of the observed and fitted cumulative distribution function is given in Figure 6.18, which shows very good agreement. A chi-square goodness-of-fit test (discussed in Chapter 9) yielded a χ^2 value of 4.49 for 6 degrees of freedom, corresponding to a significance level between 0.5 and 0.6. Thus, it was concluded that the gamma distribution was an adequate model for the life length of some materials.

6.5 LOG-LOGISTIC DISTRIBUTION

The survival time T has a log-logistic distribution if $\log(T)$ has a logistic distribution. The density, survivorship, hazard, and cumulative hazard functions of the log-logistic distribution are, respectively,

$$f(t) = \frac{\alpha\gamma t^{\gamma-1}}{(1 + \alpha t^{\gamma})^2} \tag{6.5.1}$$

$$S(t) = \frac{1}{1 + \alpha t^{\gamma}} \tag{6.5.2}$$

$$h(t) = \frac{\alpha\gamma t^{\gamma-1}}{1+\alpha t^{\gamma}} \tag{6.5.3}$$

$$H(t) = \log(1+\alpha t^{\gamma}) \tag{6.5.4}$$

$$t \geqslant 0, \quad \alpha > 0, \quad \gamma > 0$$

The log-logistic distribution is characterized by two parameters α, and γ. The median of the log-logistic distribution is $\alpha^{-1/\gamma}$. Figure 6.19(*a*) to (*c*) show the log-logistic hazard, density, and survivorship functions with $\alpha = 1$ and various values of $\gamma = 2.0$, 1, and 0.67.

When $\gamma > 1$, the log-logistic hazard has the value 0 at time 0, increases to a peak at $t = (\gamma - 1)^{1/\gamma}/\alpha^{1/\gamma}$, and then declines, which is similar to the lognormal hazard. When $\gamma = 1$, the hazard starts at $\alpha^{1/\gamma}$ and then declines monotonically. When $\gamma < 1$, the hazard starts at infinity and then declines, which is similar to the Weibull distribution. The hazard function declines toward 0 as t approaches infinity. Thus, the log-logistic distribution may be used to describe a first increasing and then decreasing hazard or a monotonically decreasing hazard.

Example 6.5 Byers et al. (1988) used the log-logistic distribution to describe the rate of spread of HIV between 1978 and 1986. Between 1978 and 1980, over 6700 homosexual and bisexual men in San Francisco were enrolled in studies of the prevalence and incidence of sexually transmitted hepatitis B virus (HBV) infections. Blood specimens were collected from the participants. Four hundred and eighty-eight men who were HBV-seronegative were randomly selected to participate in a study of HIV infection later. These men agreed to allow the investigators to test the specimens collected previously together with a current specimen. For those who convert to positive, the infection time is only known to have occurred between the previous negative test and the time of the first positive one. The exact time is unknown. The time to infection is therefore interval censored. The investigators tried to fit several distributions to the interval-censored data, including the Weibull and log-logistic by maximum likelihood methods (discussed in Chapter 7). Based on the Akaike information criterion (discussed in Chapter 9), the log-logistic distribution was found to provide the best fit to the data. The maximum likelihood estimates of the two parameters are $\hat{\alpha} = 0.003757$ and $\hat{\gamma} = 1.424328$. Based on the log-logistic model, the median infection time is estimated to be 50.4 months, and the hazard function approaches its peak at 27.6 months.

6.6 OTHER SURVIVAL DISTRIBUTIONS

Many other distributions can be used as models of survival time, three of which we discuss briefly in this section: the linear exponential, the Gompertz (1825),

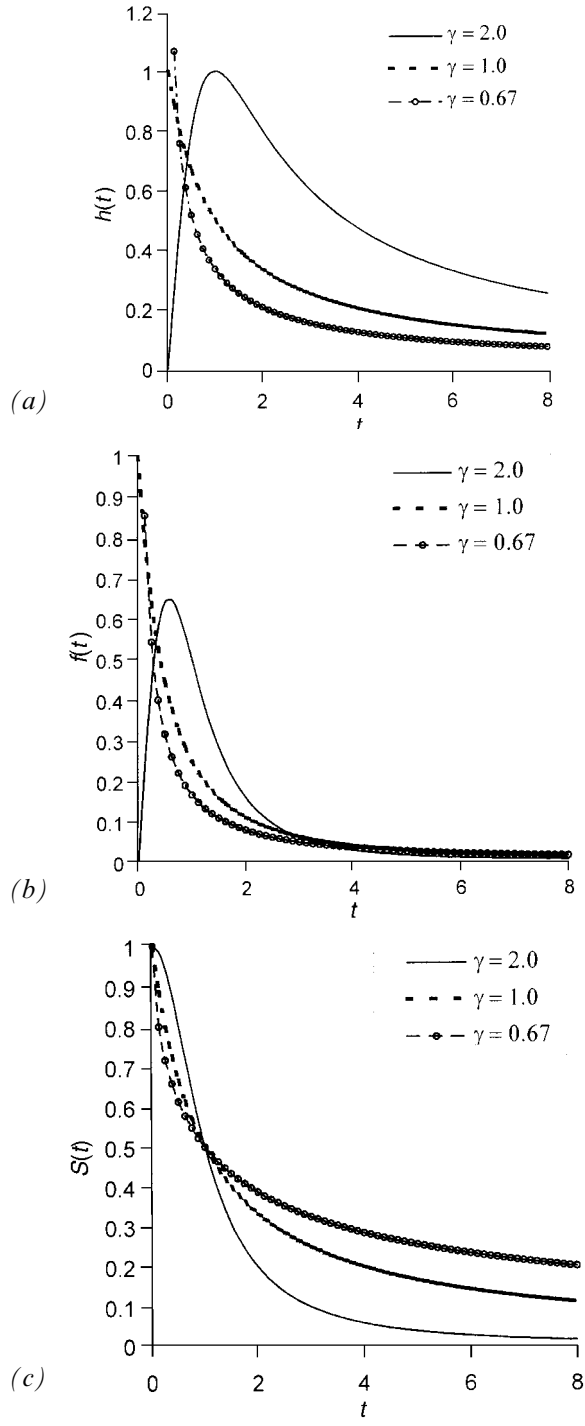


Figure 6.19 (*a*) Hazard function of the log-logistic distribution; (*b*) density function of the log-logistic distribution; (*c*) Survivorship function of the log-logistic distribution.

and a distribution whose hazard rate is a step function. The linear-exponential model and the Gompertz distribution are extensions of the exponential distribution. Both describe survival patterns that have a constant initial hazard rate. The hazard rate varies as a linear function of time or age in the linear-exponential model and as an exponential function of time or age in the Gompertz distribution.

In demonstrating the use of the linear-exponential model, Broadbent (1958), uses as an example the service of milk bottles that are filled in a dairy, circulated to customers, and returned empty to the dairy. The model was also used by Carbone et al. (1967) to describe the survival pattern of patients with plasmacytic myeloma. The hazard function of the linear-exponential distribution is

$$h(t) = \lambda + \gamma t \tag{6.6.1}$$

where λ and γ can be values such that $h(t)$ is nonnegative. The hazard rate increases from λ with time if $\gamma > 0$, decreases if $\gamma < 0$, and remains constant (an exponential case) if $\gamma = 0$, as depicted in Figure 6.20.

The probability density function and the survivorship function are, respectively,

$$f(t) = (\lambda + \gamma t) \exp[-(\lambda t + \tfrac{1}{2}\gamma t^2)] \tag{6.6.2}$$

and

$$S(t) = \exp[-(\lambda t + \tfrac{1}{2}\gamma t^2)] \tag{6.6.3}$$

The mean of the linear-exponential distribution is $-(\lambda/\gamma) + (\gamma/2)^{-1/2} L(\lambda^2/2\gamma)$, where

$$L(x) = e^x \int_x^\infty y^{1/2} e^{-y}\, dy$$

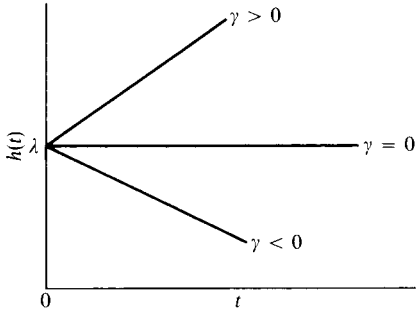


Figure 6.20 Hazard function of linear-exponential model.

Table 6.5 Values of $L(x)$ and $G(x)$

x	$L(x)$	$G(x)$
0	0.886	∞
0.1	0.951	2.015
0.2	1.012	1.493
0.3	1.067	1.223
0.4	1.119	1.048
0.5	1.168	0.923
0.6	1.214	0.828
0.7	1.258	0.753
0.8	1.300	0.691
0.9	1.341	0.640
1	1.381	0.596
2	1.712	0.361
3	1.987	0.262

Source: Broadbent (1958).

is tabulated in Table 6.5. A special case of the linear-exponential distribution, the Rayleigh distribution, is obtained by replacing γ by $\frac{1}{2}\gamma$ (Kodlin, 1967). That is, the hazard function of the Rayleigh distribution is $h(t) = \lambda + \frac{1}{2}\gamma t$.

The Gompertz distribution is also characterized by two parameters, λ and γ. The hazard function,

$$h(t) = \exp(\lambda + \gamma t) \tag{6.6.4}$$

is plotted in Figure 6.21. When $\gamma > 0$, there is positive aging starting from e^{λ}; when $\gamma < 0$, there is negative aging; and when $\gamma = 0$, $h(t)$ reduces to a constant, e^{λ}. The survivorship function of the Gompertz distribution is

$$S(t) = \exp\left[-\frac{e^{\lambda}}{\gamma} (e^{\gamma t} - 1) \right] \tag{6.6.5}$$

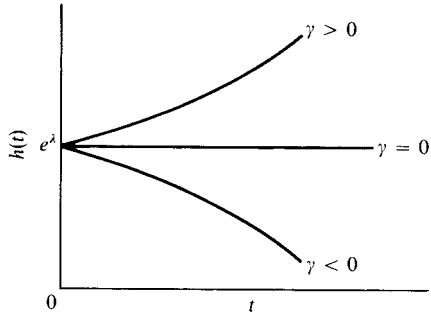


Figure 6.21 Gompertz hazard function.

and the probability density function, from (6.6.4) and (2.2.5), is then

$$f(t) = \exp\left[(\lambda + \gamma t) - \frac{1}{\gamma}(e^{\lambda+\gamma t} - e^{\lambda})\right] \tag{6.6.6}$$

The mean of the Gompertz distribution is $G(e^{\lambda}/\gamma)/e^{\lambda}$, where

$$G(x) = e^{x}\int_{x}^{\infty} y^{-1}e^{-y}\,dy$$

is tabulated in Table 6.5.

Finally, we consider a distribution where the hazard rate is a step function:

$$h(t) = \begin{cases} a_1 & 0 \leqslant t < t_1 \\ a_2 & t_1 \leqslant t < t_2 \\ \vdots & \\ a_{k-1} & t_{k-2} \leqslant t < t_{k-1} \\ a_k & t \geqslant t_{k-1} \end{cases} \tag{6.6.7}$$

where $t_1, t_2, \ldots, t_k$ are different time points. Figure 6.22 shows a typical hazard function of this nature for $k = 5$. Using (2.2.4), the survivorship function can be derived:

$$S(t) = \begin{cases} \exp(-a_1 t) & 0 \leqslant t < t_1 \\ \exp[-a_1 t_1 - a_2(t - t_1)] & t_1 \leqslant t < t_2 \\ \quad\vdots & \\ \exp[-a_1 t_1 - a_2(t_2 - t_1) - \cdots - a_k(t - t_{k-1}) & t \geqslant t_{k-1} \end{cases} \tag{6.6.8}$$

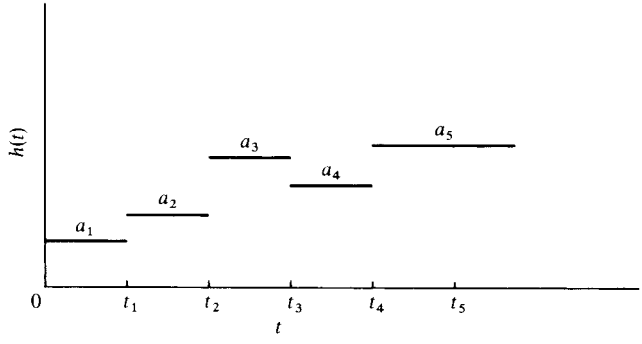


Figure 6.22 Step hazard function.

The probability density function $f(t)$ can then be obtained from (6.6.7) and (6.6.8) using (2.2.5):

$$f(t) = \begin{cases} a_1 \exp(-a_1 t) & 0 \leqslant t < t_1 \\ a_2 \exp[-a_1 t_1 - a_2(t - t_1)] & t_1 \leqslant t < t_2 \\ \vdots & \\ a_k \exp[-a_1 t_1 - a_2(t_2 - t_1) - \cdots - a_k(t - t_{k-1})] & t \geqslant t_{k-1} \end{cases} \tag{6.6.9}$$

One application of this distribution is the life-table analysis discussed in Chapter 4. In a life-table analysis, time is divided into intervals and the hazard rate is assumed to be constant in each interval. However, the overall hazard rate is not necessarily constant.

The nine distributions described above are, among others, reasonable models for survival time distribution. All have been designed by considering a biological failure, a death process, or an aging property. They may or may not be appropriate for many practical situations, but the objective here is to illustrate the various possible techniques, assumptions, and arguments that can be used to choose the most appropriate model. If none of these distributions fits the data, investigators might have to derive an original model to suit the particular data, perhaps by using some of the ideas presented here.

Bibliographical Remarks

In addition to the papers on the distributions cited in this chapter, Mann et al. (1974), Hahn and Shapiro (1967), Johnson and Kotz (1970*a*, *b*), Elandt-Johnson and Johnson (1980), Lawless (1982), Nelson (1982), Cox and Oakes (1984), Gertsbakh (1989), and Klein and Moeschberger (1997) also discuss statistical failure models, including the exponential, Weibull, gamma, lognormal, generalized gamma, and log-logistic distributions. Applications of survival distributions can be found easily in medical and epidemiological journals. The following are a few examples: Dharmalingam et al. (2000), Riffenburgh and Johnstone (2001), and Mafart et al. (2002).

EXERCISES

6.1 Summarize the distributions discussed in this chapter, answering the following questions.

- **(a)** What distributions describe constant hazard rates? Give the range of parameter values.
- **(b)** What distributions describe increasing hazard rates? If there are more than one, discuss the differences between them.
- **(c)** What distributions describe decreasing hazard rates? If there are more than one, discuss the differences between them.

6.2 Suppose that the survival distribution of a group of patients follows the exponential distribution with $G = 0$ (year), $\lambda = 0.65$. Plot the survivorship function and find:
(a) The mean survival time
(b) The median survival time
(c) The probability of surviving 1.5 years or more

6.3 Suppose that the survival distribution of a group of patients follows the exponential distribution with $G = 5$ (years) and $\lambda = 0.25$. Plot the survivorship function and find:
(a) The mean survival time
(b) The median survival time
(c) The probability of surviving 6 years or more

6.4 Consider the following two Weibull distributions as survival models:
(i) $G = 0$, $\lambda = 1$, $\gamma = 0.5$
(ii) $G = 0$, $\lambda = 0.5$, $\gamma = 2$
For each distribution, plot the survivorship function and the hazard function and find:
(a) The mean
(b) The variance
(c) The coefficient of variation
Which distribution gives the larger probability of surviving at least 3 units of time?

6.5 Suppose that the survival time follows the lognormal distribution with $\mu = 1$ and $\sigma = 0.5$. Find:
(a) The mean survival time
(b) The variance
(c) The coefficient of variation
(d) The median
(e) The mode

6.6 Suppose that pain relief time follows the gamma distribution with $\lambda = 1$, $\gamma = 0.5$. Find:
(a) The mean
(b) The variance
(c) The coefficient of variation

6.7 Suppose that the survival distribution is (1) Gompertz and (2) linear-exponential, and $\lambda = 1$, $\gamma = 2.0$. Plot the hazard function and find:
(a) The mean
(b) The probability of surviving longer than 1 unit of time

6.8 Consider the survival times of hypernephroma patients given in Exercise Table 3.1. From the plot you obtained in Exercise 4.5, suggest a distribution that might fit the data.

CHAPTER 7

Estimation Procedures for Parametric Survival Distributions without Covariates

In this chapter we discuss some analytical procedures for estimating the most commonly used survival distributions discussed in Chapter 6. We introduce the maximum likelihood estimates (MLEs) of the parameters of these distributions. The general asymptotic likelihood inference results that are most widely used for these distributions are given in Section 7.1. We begin to used the general symbol $\mathbf{b} = (b_1, b_2, \ldots, b_p)$ to denote a set of parameters. For example, in discussing the Weibull distribution, b_1 could be λ and b_2 could be γ, and $p = 2$. $\mathbf{b}$ is called a *vector* in linear algebra. Readers who are not familiar with linear algebra or are not interested in the mathematical details may skip this section and proceed to Section 7.2 without loss of continuity. In Sections 7.2 to 7.7 we introduce the MLEs for the parameters of the exponential, Weibull, lognormal, gamma, log-logistic, and Gompertz distributions for data with and without censored observations. The related BMDP or SAS programming codes that may be used to obtain the MLE are given in the respective sections.

7.1 GENERAL MAXIMUM LIKELIHOOD ESTIMATION PROCEDURE

7.1.1 Estimation Procedures for Data with Right-Censored Observations

Suppose that persons were followed to death or censored in a study. Let t_1, $t_2, \ldots, t_r$, $t_{r+1}^+, \ldots, t_n^+$ be the survival times observed from the n individuals, with r exact times and $(n - r)$ right-censored times. Assume that the survival times follow a distribution with the density function $f(t, \mathbf{b})$ and survivorship function $S(t, \mathbf{b})$, where $\mathbf{b} = (b_1, \ldots, b_p)$ denotes unknown p parameters $b_1, \ldots, b_p$ in the distribution. As shown in Chapter 6, an exponential distribution has one ($p = 1$) parameter λ, the Weibull distribution has two ($p = 2$)

parameters λ and γ, and so on. If the survival time is discrete (i.e., it is observed at discrete time only), $f(t, \mathbf{b})$ represents the probability of observing t and $S(t, \mathbf{b})$ represents the probability that the survival or event time is greater than t. In other words, $f(t, \mathbf{b})$ and $S(t, \mathbf{b})$ represent the information that can be obtained from an observed uncensored survival time and an observed right-censored survival time, respectively. Therefore, the product $\Pi_{i=1}^{n} f(t_i, \mathbf{b})$ represents the joint probability of observing the uncensored survival times, and $\Pi_{i=r+1}^{n} S(t_i^+, \mathbf{b})$ represents the joint probability of those right-censored survival times. The product of these two probabilities, denoted by $L(\mathbf{b})$,

$$L(\mathbf{b}) = \prod_{i=1}^{r} f(t_i, \mathbf{b}) \prod_{i=r+1}^{n} S(t_i^+, \mathbf{b})$$

represents the joint probability of observing $t_1, t_2, \ldots, t_r, t_{r+1}^+, \ldots, t_n^+$. A similar interpretation applies to continuous survival. $L(\mathbf{b})$ is called the *likelihood function* of $\mathbf{b}$, which can also be interpreted as a measure of the likelihood of observing a specific set of survival times $t_1, t_2, \ldots, t_r, t_{r+1}^+, \ldots, t_n^+$, given a specific set of parameters $\mathbf{b}$. The method of the MLE is to find an estimator of $\mathbf{b}$ that maximizes $L(\mathbf{b})$, or in other words, which is "most likely" to have produced the observed data $t_1, t_2, \ldots, t_r, t_{r+1}^+, \ldots, t_n^+$. Take the logarithm of $L(\mathbf{b})$ and denote it by $l(\mathbf{b})$,

$$l(\mathbf{b}) = \log L(\mathbf{b}) = \sum_{i=1}^{r} \log[f(t_i, \mathbf{b})] + \sum_{i=r+1}^{n} \log[S(t_i^+, \mathbf{b})] \tag{7.1.1}$$

Then the MLE $\hat{\mathbf{b}}$ of $\mathbf{b}$ is the set of $\hat{b}_1, \ldots, \hat{b}_p$ that maximizes $l(\mathbf{b})$:

$$l(\hat{\mathbf{b}}) = \max_{\text{all b}} (l(\mathbf{b})).$$

It is clear that $\hat{\mathbf{b}}$ is a solution of the following simultaneous equations, which are obtained by taking the derivative of $l(\mathbf{b})$ with respect to each b_j:

$$\frac{\partial l(\mathbf{b})}{\partial b_j} = 0 \qquad j = 1, 2, \ldots, p \tag{7.1.2}$$

The exact forms of (7.1.2) for the parametric survival distributions discussed in Chapter 6 are given in Sections 7.2 to 7.7. Often, there is no closed solution for the MLE $\hat{\mathbf{b}}$ from (7.1.2). To obtain the MLE $\hat{\mathbf{b}}$, one can use a numerical method. A commonly used numerical method is the Newton–Raphson iterative procedure, which can be summarized as follows.

1. Let the initial values of $b_1, \ldots, b_p$ be zero; that is, let

$$\mathbf{b}^{(0)} = 0$$

2. The changes for $\mathbf{b}$ at each subsequent step, denoted by $\Delta^{(j)}$, is obtained by taking the second derivative of the log-likelihood function:

$$\Delta^{(j)} = \left[-\frac{\partial^2 l(\mathbf{b}^{(j-1)})}{\partial \mathbf{b}\, \partial \mathbf{b}'} \right]^{-1} \frac{\partial l(\mathbf{b}^{(j-1)})}{\partial \mathbf{b}} \tag{7.1.3}$$

3. Using $\Delta^{(j)}$, the value of $\mathbf{b}^{(j)}$ **at** jth step is

$$\mathbf{b}^{(j)} = \mathbf{b}^{(j-1)} + \Delta^{(j)} \qquad j = 1, 2, \ldots$$

The iteration terminates at, say, the mth step if $\|\Delta^{(m)}\| < \delta$, where δ is a given precision, usually a very small value, 10^{-4} or 10^{-5}. Then the MLE $\hat{\mathbf{b}}$ is defined as

$$\hat{\mathbf{b}} = \mathbf{b}^{(m-1)} \tag{7.1.4}$$

The estimated covariance matrix of the MLE $\hat{\mathbf{b}}$ is given by

$$\hat{V}(\hat{\mathbf{b}}) = \hat{\mathrm{Cov}}(\hat{\mathbf{b}}) = \left[-\frac{\partial^2 l(\hat{\mathbf{b}})}{\partial \mathbf{b}\, \partial \mathbf{b}'} \right]^{-1} \tag{7.1.5}$$

One of the good properties of a MLE is that if $\hat{\mathbf{b}}$ is the MLE of $\mathbf{b}$, then $g(\hat{\mathbf{b}})$ is the MLE of $g(\mathbf{b})$ if $g(\mathbf{b})$ is a finite function and need not be one-to-one. The concept of the Newton–Raphson method for $p = 1$ is illustrated in detail in Appendix A.

The estimated $100(1 - \alpha)\%$ confidence interval for any parameter b_i is

$$(\hat{b}_i - Z_{\alpha/2}\sqrt{v_{ii}},\ \hat{b}_i + Z_{\alpha/2}\sqrt{v_{ii}}) \tag{7.1.6}$$

where v_{ii} is the ith diagonal element of $\hat{V}(\hat{\mathbf{b}})$ and $Z_{\alpha/2}$ is the $100(1 - \alpha/2)$ percentile point of the standard normal distribution $[P(Z > Z_{\alpha/2}) = \alpha/2]$. For a finite function $g(b_i)$ of b_i, the estimated $100(1 - \alpha)\%$ confidence interval for $g(b_i)$ is its respective range R on the confidence interval (7.1.6), that is,

$$R = \{g(b_i) : b_i \in (\hat{b}_i - Z_{\alpha/2}\sqrt{v_{ii}},\ \hat{b}_i + Z_{\alpha/2}\sqrt{v_{ii}})\} \tag{7.1.7}$$

In case $g(b_i)$ is monotone in b_i, the estimated $100(1 - \alpha)\%$ confidence interval for $g(b_i)$ is

$$[g(\hat{b}_i - Z_{\alpha/2}\sqrt{v_{ii}}),\ g(\hat{b}_i + Z_{\alpha/2}\sqrt{v_{ii}})] \tag{7.1.8}$$

7.1.2 Estimation Procedures for Data with Right-, Left-, and Interval-Censored Observations

If the survival times $t_1, t_2, \ldots, t_n$ observed for the n persons consist of uncensored, left-, right-, and interval-censored observations, the estimation procedures are similar. Assume that the survival times follow a distribution with the density function $f(t, \mathbf{b})$ and the survivorship function $S(t, \mathbf{b})$, where $\mathbf{b}$ denotes all unknown parameters of the distribution. Then the log-likelihood function is

$$l(\mathbf{b}) = \log L(\mathbf{b}) = \sum \log[f(t_i, \mathbf{b})] + \sum \log[S(t_i, \mathbf{b})] + \sum \log[1 - S(t_i, \mathbf{b})] + \sum \log[S(v_i, \mathbf{b}) - S(t_i, \mathbf{b})] \qquad (7.1.9)$$

where the first sum is over the uncensored observations, the second sum over the right-censored observations, the third sum over the left-censored observations, and the last sum over the interval-censored observations, with v_i as the lower end of a censoring interval. The other steps for obtaining the MLE $\hat{\mathbf{b}}$ of $\mathbf{b}$ are similar to the steps shown in Section 7.1.1 by substituting the log-likelihood function defined in (7.1.1) with the log-likelihood function in (7.1.9).

The computation of the MLE $\hat{\mathbf{b}}$ and its estimated covariance matrix is tedious. The following example gives the general procedure for using SAS to carry out the computation.

Example 7.1 If the survival time observed contains uncensored, right-, left-, and interval-censored observations, one needs to create a new data set from the observed data to use SAS to obtain the estimates of the parameters in the distribution. For an observed survival time t (uncensored, right-, or left-censored), we define two variables LB and UB as follows: If t is uncensored, take LB = UB = t; if t is left-censored, LB = . and UB = t; and if t is right-censored, then LB = t and UB = ., where "." means "missing" in SAS. If a survival time is interval-censored, [i.e., one observed two numbers t_1 and t_2, $t_1 < t_2$ and the survival time is in the interval (t_1, t_2)], let LB = t_1 and UB = t_2. Assume that the new data set (in terms of LB and UB) has been saved in "C:\EXAMPLEA.DAT" as a text file, which contains two columns (LB in the first column and UB the second column) separated by a space.

As an example, the following SAS code can be used to obtain the estimated covariance matrix defined in (7.1.5) and the MLE of the parameters of the Weibull distribution for the survival data observed in the text file "C:\EXAMPLEA.DAT". One can replace d = weibull in the following code with the respective distribution in Sections 7.2 to 7.6 (see the SAS code in these sections for details) to obtain the estimate.

```
data w1;
  infile 'c:\examplea.dat' missover;
  input lb ub;
run;
proc lifereg;
  model (lb,ub)=/covb d = weibull;
run;
```

7.2 EXPONENTIAL DISTRIBUTION

7.2.1 One-Parameter Exponential Distribution

The one-parameter exponential distribution has the following density function;

$$f(t) = \lambda e^{-\lambda t} \tag{7.2.1}$$

survivorship function;

$$S(t) = e^{-\lambda t} \tag{7.2.2}$$

and hazard function;

$$h(t) = \lambda \tag{7.2.3}$$

where $t \geqslant 0$, $\lambda > 0$. Obviously, the exponential distribution is characterized by one parameter, λ. The estimation of λ by maximum likelihood methods for data without censored observations will be given first followed by the case with censored observations.

Estimation of λ for Data without Censored Observations

Suppose that there are n persons in the study and everyone is followed to death or failure. Let $t_1, t_2, \ldots, t_n$ be the exact survival times of the n people. The likelihood function, using (7.2.1) and (7.1.1), is

$$L = \prod_{i=1}^{n} \lambda e^{-\lambda t_i}$$

and the log-likelihood function is

$$l(\lambda) = n \log \lambda - \lambda \sum_{i=1}^{n} t_i \tag{7.2.4}$$

From (7.1.2), the MLE of λ is

$$\hat{\lambda} = \frac{n}{\Sigma_{i=1}^{n} t_i} \tag{7.2.5}$$

Since the mean μ of the exponential distribution is $1/\lambda$ and a MLE is invariant under an one-to-one transformation, the MLE of μ is

$$\hat{\mu} = \frac{1}{\hat{\lambda}} = \frac{\Sigma_{i=1}^{n} t_i}{n} = \bar{t} \tag{7.2.6}$$

It can be shown $2n\hat{\mu}/\mu$ has an exact chi-square distribution with $2n$ degrees of freedom (Epstein and Sobel, 1953). Since $\lambda = 1/\mu$ and $\hat{\lambda} = 1/\hat{\mu}$, an exact $100(1-\alpha)\%$ confidence interval for λ is

$$\frac{\hat{\lambda}\chi^2_{2n,1-\alpha/2}}{2n} < \lambda < \frac{\hat{\lambda}\chi^2_{2n,\alpha/2}}{2n} \tag{7.2.7}$$

where $\chi^2_{2n,\alpha}$ is the 100α percentage point of the chi-square distribution with $2n$ degrees of freedom, that is, $P(\chi^2_{2n} > \chi^2_{2n,\alpha}) = \alpha$ (Table B-2). When n is large ($n \geqslant 25$, say), $\hat{\lambda}$ is approximately normally distributed with mean λ and variance λ^2/n. Thus, an approximate $100(1-\alpha)\%$ confidence interval for λ is

$$\hat{\lambda} - \frac{\hat{\lambda}Z_{\alpha/2}}{\sqrt{n}} < \lambda < \hat{\lambda} + \frac{\hat{\lambda}Z_{\alpha/2}}{\sqrt{n}} \tag{7.2.8}$$

where $Z_{\alpha/2}$ is the $100\alpha/2$ percentage point, $P(Z > Z_{\alpha/2}) = \alpha/2$, of the standard normal distribution (Table B-1).

Since $2n\hat{\mu}/\mu$ has an exact chi-square distribution with $2n$ degrees of freedom, an exact $100(1-a)\%$ confidence interval for the mean survival time is

$$\frac{2n\hat{\mu}}{\chi^2_{2n,\alpha/2}} < \mu < \frac{2n\hat{\mu}}{\chi^2_{2n,1-\alpha/2}} \tag{7.2.9}$$

The following example illustrates the procedures.

Example 7.2 Consider the following remission times in weeks for 21 patients with acute leukemia: 1, 1, 2, 2, 3, 4, 4, 5, 5, 6, 8, 8, 9, 10, 10, 12, 14, 16, 20, 24, and 34. Assume that remission duration follows the exponential distribution. Let us estimate the parameter λ by using the formulas given above.

According to (7.2.5), the MLE of the relapse rate, λ, is

$$\hat{\lambda} = \frac{21}{198} = 0.106 \text{ per week}$$

The mean remission time μ is then $198/21 = 9.429$ weeks. Using the analytical procedures given above, confidence intervals for λ and μ can also be obtained.

A 95% confidence interval for the relapse rate λ, following (7.2.7), is approximately

$$\frac{(0.106)(24.433)}{42} < \lambda < \frac{(0.106)(59.342)}{42}$$

or (0.062, 0.150). A 95% confidence interval for the mean remission time,

following (7.2.9), is

$$\frac{(42)(9.429)}{59.342} < \mu < \frac{(42)(9.429)}{24.433}$$

or (6.673, 16.208).

Once the parameter λ is estimated, other estimates can be obtained. For example, the probability of staying in remission for at least 20 weeks, estimated from (7.2.2), is $\hat{S}(20) = \exp[-0.106(20)] = 0.120$. Any percentile of survival time t_p may be estimated by equating $S(t)$ to p and solving for t_p, that is, $t_p = -\log p/\hat{\lambda}$. For example, the median (50th percentile) survival time can be estimated by $t_{0.5} = -\log 0.5/\hat{\lambda} = 6.539$ weeks.

Estimation of λ for Data with Censored Observations

We first consider singly censored and then progressively censored data. Suppose that without loss of generality, the study or experiment begins at time 0 with a total of n subjects. Survival times are recorded and the data become available when the subjects die one after the other in such a way that the shortest survival time comes first, the second shortest second, and so on. Suppose that the investigator has decided to terminate the study after r out of the n subjects have died and to sacrifice the remaining $n - r$ subjects at that time. Then the survival times for the n subjects are

$$t_{(1)} \leqslant t_{(2)} \leqslant \cdots \leqslant t_{(r)} = t^{+}_{(r+1)} = \cdots = t^{+}_{(n)}$$

where a superscript plus indicates a sacrificed subject, and thus $t^{+}_{(i)}$ is a censored observation. In this case, n and r are fixed values and all of the $n - r$ censored observations are equal.

The likelihood function, using (7.1.1), (7.2.1), and (7.2.2), is

$$L = \frac{n!}{(n-r)!} \prod_{i=1}^{r} \lambda e^{-\lambda t_{(i)}} (e^{-\lambda t_{(r)}})^{n-r}$$

and from (7.1.2), the MLE of λ is

$$\hat{\lambda} = \frac{r}{\Sigma_{i=1}^{r} t_{(i)} + \Sigma_{i=r+1}^{n} t^{+}_{(i)}} \tag{7.2.10}$$

The mean survival time $\mu = 1/\lambda$ can then be estimated by

$$\hat{\mu} = \frac{1}{\hat{\lambda}} = \frac{\Sigma_{i=1}^{r} t_{(i)} + \Sigma_{i=r+1}^{n} t^{+}_{(i)}}{r} \tag{7.2.11}$$

It is shown by Halperin (1952) that $2r\lambda/\hat{\lambda}$ has a chi-square distribution with $2r$

degrees of freedom. The mean and variance of $\hat{\lambda}$ are $r\lambda/(r-1)$ and $\lambda^2/(r-1)$, respectively. The $100(1-\alpha)\%$ confidence interval for λ is

$$\frac{\hat{\lambda}\chi^2_{2r,1-\alpha/2}}{2r} < \lambda < \frac{\hat{\lambda}\chi^2_{2r,\alpha/2}}{2r} \tag{7.2.12}$$

When n is large, the distribution of $\hat{\lambda}$ is approximately normal with mean λ and variance $\lambda^2/(r-1)$. An approximate $100/(1-\alpha)\%$ confidence interval for λ is then

$$\hat{\lambda} - \frac{\hat{\lambda}Z_{\alpha/2}}{\sqrt{r-1}} < \lambda < \hat{\lambda} + \frac{\hat{\lambda}Z_{\alpha/2}}{\sqrt{r-1}} \tag{7.2.13}$$

Epstein and Sobel (1953) show that $2r\hat{\mu}/\mu$ has a chi-square distribution with $2r$ degrees of freedom. Thus a $100/(1-\alpha)\%$ confidence interval for μ (see also Epstein, 1960b) is

$$\frac{2r\hat{\mu}}{\chi^2_{2r,\alpha/2}} < \mu < \frac{2r\hat{\mu}}{\chi^2_{2r,1-\alpha/2}} \tag{7.2.14}$$

They also develop test procedures for the hypothesis $H_0: \mu = \mu_0$ against the alternative $H_1: \mu < \mu_0$. One of their rules of action is to accept H_0 if $\hat{\mu} > c$ and reject H_0 if $\hat{\mu} < c$, where $c = (\mu_0\chi^2_{2r,\alpha})/2r$ and α is the significance level. Or if the estimated mean survival time calculated from (7.2.11) is greater then c, the hypothesis H_0 is rejected at the α level. The following example illustrates the procedure.

Example 7.3 Suppose that in a laboratory experiment 10 mice are exposed to carcinogens. The experimenter decides to terminate the study after half of the mice are dead and to sacrifice the other half at that time. The survival times of the five dead mice are 4, 5, 8, 9, and 10 weeks. The survival data of the 10 mice are 4, 5, 8, 9, 10, 10+, 10+, 10+, 10+, and 10+. Assuming that the failure of these mice follows an exponential distribution, the survival rate λ and mean survival time μ are estimated, respectively, according to (7.2.10) and (7.2.11) by

$$\lambda = \frac{5}{36+50} = 0.058 \text{ per week}$$

and $\hat{\mu} = 1/0.058 = 17.241$ weeks. A 95% confidence interval for λ by (7.2.12) is

$$\frac{(0.058)(3.247)}{(2)(5)} < \lambda < \frac{(0.058)(20.483)}{(2)(5)}$$

or (0.019, 0.119). A 95% confidence interval for μ following (7.2.13) is

$$\frac{2(5)(17.241)}{20.483} < \mu < \frac{2(5)(17.241)}{3.247}$$

or (8.417, 53.098).

The probability of surviving a given time for the mice can be estimated from (7.2.2). For example, the probability that a mouse exposed to the same carcinogen will survive longer than 8 weeks is

$$\hat{S}(8) = \exp[-0.058(8)] = 0.629$$

The probability of dying in 8 weeks is then $1 - 0.629 = 0.371$.

A slightly different situation may arise in laboratory experiments. Instead of terminating the study after the rth death, the experimenter may stop after a period of time T, which may be six months or a year. If we denote the number of deaths between 0 and T as r, the survival data may look as follows:

$$t_{(1)} \leqslant t_{(2)} \leqslant \cdots \leqslant t_{(r)} \leqslant t^{+}_{(r+1)} = \cdots = t^{+}_{(n)} = T$$

Mathematical derivations of the MLE of λ and μ are exactly the same and (7.2.10) can still be used. The sampling distribution of $\hat{\mu}$ for singly censored data is also discussed by Bartholomew (1963).

Progressively censored data come more frequently from clinical studies where patients are entered at different times and the study lasts a predetermined period of time. Suppose that the study begins at time 0 and terminates at time T and there are a total of n people entered. Let r be the number of patients who die before or at time T and $n - r$ the number of patients who are lost to follow-up during the study period or remain alive at time T. The data look as follows: $t_1, t_2, \ldots, t_r, t^{+}_{r+1}, t^{+}_{r+2}, \ldots, t^{+}_{n}$. Ordering the r uncensored observations according to their magnitude, we have

$$t_{(1)} \leqslant t_{(2)} \leqslant \cdots \leqslant t_r, t^{+}_{r+1}, t^{+}_{r+2}, \ldots, t^{+}_{n}$$

The likelihood function, using (7.1.1), (7.2.1), and (7.2.2), is

$$L = \prod_{i=1}^{r} \lambda e^{-\lambda t_{(i)}} \prod_{i=r+1}^{n} e^{-\lambda t_i^{+}}$$

and the log-likelihood function is

$$l(\lambda) = n\lambda - \lambda \sum_{i=1}^{r} t_i - \lambda \sum_{i=r+1}^{n} t_i^{+} \tag{7.2.15}$$

and from (7.1.2), the MLE of the parameter λ is

$$\hat{\lambda} = \frac{r}{\Sigma_{i=1}^{r} t_{(i)} + \Sigma_{i=r+1}^{n} t_i^+} \tag{7.2.16}$$

Consequently,

$$\hat{\mu} = \frac{1}{\hat{\lambda}} = \frac{\Sigma_{i=1}^{r} t_{(i)} + \Sigma_{i=r+1}^{n} t_i^+}{r} \tag{7.2.17}$$

is the MLE of the mean survival time. The sum of all of the observations, censored and uncensored, divided by the number of uncensored observations, gives the MLE of the mean survival time. To overcome the mathematical difficulties arising when all of the observations are censored ($r = 0$), Bartholomew (1957) defines

$$\hat{\mu} = \sum_{i=1}^{n} t_i^+ \tag{7.2.18}$$

In practice, this estimate has little value.

Distributions of the estimators are discussed by Bartholomew (1957). The distribution of $\hat{\lambda}$ for large n is approximately normal with mean λ and variance:

$$\mathrm{Var}(\hat{\lambda}) = \frac{\lambda^2}{\sum_{i=1}^{n} (1 - e^{-\lambda T_i})} \tag{7.2.19}$$

where T_i is the time that the ith person is under observation. In other words, T_i is computed from the time the ith person enters the study to the end of the study. If the observation times T_i are not known, the following quick estimate of $\mathrm{Var}(\hat{\lambda})$ can be used:

$$\widehat{\mathrm{Var}}(\hat{\lambda}) = \frac{\hat{\lambda}^2}{r} \tag{7.2.20}$$

Thus an approximate $100(1 - \lambda)\%$ confidence interval for λ is, by (7.1.6),

$$\hat{\lambda} - Z_{\alpha/2}\sqrt{\widehat{\mathrm{Var}}(\hat{\lambda})} < \lambda < \hat{\lambda} + Z_{\alpha/2}\sqrt{\widehat{\mathrm{Var}}(\hat{\lambda})} \tag{7.2.21}$$

The distribution of $\hat{\mu}$ is approximately normal with mean μ and variance:

$$\mathrm{Var}(\hat{\mu}) = \frac{\mu^2}{\Sigma_{i=1}^{n} (1 - e^{-\lambda T_i})} \tag{7.2.22}$$

Again, a quick estimate is

$$\widehat{\text{Var}}(\hat{\mu}) = \frac{\hat{\mu}^2}{r} \tag{7.2.23}$$

An approximate $100(1-\alpha)\%$ confidence interval for μ is then, by (7.1.6),

$$\hat{\mu} - Z_{\alpha/2}\sqrt{\widehat{\text{Var}}(\hat{\mu})} < \mu < \hat{\mu} + Z_{\alpha/2}\sqrt{\widehat{\text{Var}}(\hat{\mu})} \tag{7.2.24}$$

The exact distribution of $\hat{\mu}$ derived by Bartholomew (1963) is too cumbersome for general use and thus is not included here.

Example 7.4 Consider the remission duration of the 21 leukemia patients receiving 6-MP in Example 3.3. The remission times in weeks were 6, 6, 6, 7, 10, 13, 16, 22, 23, 6+, 9+, 10+, 11+, 17+, 19+, 20+, 25+, 32+, 32+, 34+, and 35+. The hazard plot given in Figure 3.6 shows that the exponential distribution fits the data very well. Maximum likelihood estimates of the relapse rate and the mean remission time can be obtained, respectively, from (7.2.16) and (7.2.17):

$$\hat{\lambda} = \frac{9}{109 + 250} = 0.025 \text{ per week} \qquad \hat{\mu} = \frac{1}{0.025} = 40 \text{ weeks}$$

The graphical estimate of λ obtained in Example 3.3 is 0.027, which is very close to the MLE. Thus, the remission duration of leukemia patients receiving 6-MP can be described by an exponential distribution with a constant weekly relapse rate of 2.5% and a mean remission time of 40 weeks. The probability of staying in remission for one year (or 52 weeks) or more is estimated by

$$\hat{S}(52) = \exp[-0.025(52)] = 0.273$$

Using (7.2.20) and (7.2.23) for the variance of $\hat{\lambda}$ and $\hat{\mu}$, the 95% confidence intervals for λ and μ are, respectively, (0.009, 0.041) and (13.867, 66.133).

Example 7.5 The results in Examples 7.2 to 7.4 can also be obtained by using available statistical software. Let t denote the observed survival time (exact or censored) and CENS be an index (or dummy) variable with CENS = 0 if t is censored and 1 otherwise. Assume that the data have been saved in "C:\EXAMPLE.DAT" as a text file, which contains two columns (t in the first column and CENS in second column for the same study subject), separated by a space.

The following SAS code for procedure LIFEREG can be used to obtain the estimated covariance matrix defined in (7.1.5) and the MLE of the parameter of the exponential distribution for the observed survival data in "C:\EXAMPLE.DAT".

```
data w1;
  infile 'c:\example.dat' missover;
  input t cens;
run;
proc lifereg;
  model t*cens(0) = /covb d = exponential;
run;
```

The respective BMDP code for program 2L is

```
/input      file = 'c:\example.dat' .
            variables = 2.
            format = free.
/print      level = brief.
            cova. survival.
/variable   names = t, cens.
/form       time = t.
            status = cens.
            response = 1.
/regress    accel = exponential.
/end
```

If SAS is used, the estimated parameter of the exponential distribution can be obtained by

$$\hat{\lambda} = \exp(-\text{INTERCEPT}),$$

where INTERCEPT is the name of output estimated parameter in SAS procedure LIFEREG. In BMDP 2L,

$$\hat{\lambda} = \exp(-\text{CONSTANT})$$

where CONSTANT is given by the program.

7.2.2 Two-Parameter Exponential Distribution

In the case where a two-parameter exponential distribution is more appropriate for the data (Zelen, 1966), the density and survivorship functions are defined, respectively, as

$$f(t) = \begin{cases} \lambda e^{-\lambda(t-G)} & t \geqslant G \geqslant 0, \quad \lambda \geqslant 0 \\ 0 & t < G \end{cases} \tag{7.2.25}$$

and

$$S(t) = \begin{cases} e^{-\lambda(t-G)} & t \geqslant G \geqslant 0, \quad \lambda \geqslant 0 \\ 1 & t < G \end{cases} \tag{7.2.26}$$

where G is called the *guarantee time*, the minimum survival time before which no deaths occur.

Estimation of λ and G for Data without Censored Observations

If $t_1, t_2, \ldots, t_n$ are the survival times of the n patients, using (7.1.1), (7.1.2), (7.2.25), and (7.2.26), the MLE of λ is

$$\hat{\lambda} = \frac{n}{\sum_{i=1}^{n} (t_i - \hat{G})} \tag{7.2.27}$$

where $\hat{G}$ is an estimate of G that is the smallest observation in the data,

$$\hat{G} = \min(t_1, t_2, \ldots, t_n) \tag{7.2.28}$$

and the mean survival time is estimated by $\hat{\mu} = \hat{G} + 1/\hat{\lambda}$.

Example 7.6 Consider the survival times in months of 11 patients following initial pulmonary metastasis from ostenogenic sarcoma considered by Burdette and Gehan (1970). The data were 11, 13, 13, 13, 13, 13, 14, 14, 15, 15, and 17. Suppose that the two-parameter exponential distribution is selected. The guarantee time G is estimated by the smallest observation (i.e., $\hat{G} = 11$), and the hazard rate $\hat{\lambda}$ estimated by (7.2.27) is

$$\hat{\lambda} = \frac{11}{(11-11) + (13-11) + \cdots + (17-11)} = 0.367$$

Thus, the exponential model tells us that the minimum survival time is 11 months, and after that the chance of death per month is 0.367. Similarly, the probability of surviving a given amount of time can then be estimated from (7.2.26). For example, the estimated probability of surviving 18 months or longer is

$$\hat{S}(18) = \exp[-0.367(18-11)] = 0.077$$

Estimation of λ and G for Data with Censored Observations

We first consider singly censored data. Suppose that an experiment begins with n animals and terminates as soon as the first r deaths occur. For this case, we introduce the estimation procedures derived by Epstein (1960a).

Let the first r survival times be $t_{(1)} \leqslant t_{(2)} \leqslant \cdots \leqslant t_{(r)}$ and let T^* be the total survival observed between the first and the rth death:

$$\begin{aligned} T^* &= (n-1)(t_{(2)} - t_{(1)}) + (n-2)(t_{(3)} - t_{(2)}) + \cdots + (n-r+1)(t_{(r)} - t_{(r-1)}) \\ &= -(n-1)t_{(1)} + t_{(2)} + t_{(3)} + \cdots + t_{(r-1)} + (n-r+1)t_{(r)} \\ &= \sum_{i=1}^{r} t_{(i)} - nt_{(1)} + (n-r)t_{(r)} \end{aligned} \tag{7.2.29}$$

The best estimates for G and μ in the sense that they are unbiased and have minimum variance are given by

$$\hat{G} = t_{(1)} - \frac{\hat{\mu}}{n} \tag{7.2.30}$$

and

$$\hat{\mu} = \frac{T^*}{r-1} \tag{7.2.31}$$

Then λ can then be estimated by $\hat{\lambda} = 1/\hat{\mu}$.

Confidence intervals for the mean survival time μ are easy to obtain from the fact that $2(r-1)\hat{\mu}/\mu = 2T^*/\mu$ has a chi-square distribution with $2(r-1)$ degrees of freedom. Thus, for $r > 1$, the $100(1-\alpha)\%$ confidence interval for μ is

$$\frac{2(r-1)\hat{\mu}}{\chi^2_{2(r-1),\alpha/2}} < \mu < \frac{2(r-1)\hat{\mu}}{\chi^2_{2(r-1),1-\alpha/2}} \tag{7.2.32}$$

or

$$\frac{2T^*}{\chi^2_{2(r-1),\alpha/2}} < \mu < \frac{2T^*}{\chi^2_{2(r-1),1-\alpha/2}} \tag{7.2.33}$$

To find confidence intervals for G, we use the fact that $x_1 = 2n(t_{(1)} - G)/\mu$ and $x_2 = 2(r-1)\hat{\mu}/\mu$ are independent and have a chi-square distribution with 2 and $2(r-1)$ degrees of freedom, respectively. Thus the ratio

$$Y = \frac{x_1/2}{x_2/2(r-1)} = \frac{n(t_{(1)} - G)}{\hat{\mu}} = \frac{n(r-1)(t_{(1)} - G)}{T^*} \tag{7.2.34}$$

follows the F-distribution with 2 and $2(r-1)$ degrees of freedom. Let $F_{2,2(r-1),\alpha}$ be the 100α percentage point of the $F_{2,2(r-1)}$ distribution [i.e., $P(Y \geqslant F_{2,2(r-1),\alpha}) = \alpha$] (Table B-3 in Appendix B), and then a $100(1-\alpha)\%$ confidence interval for G is

$$t_{(1)} - \frac{\hat{\mu}}{n} F_{2,2(r-1),\alpha} < G < t_{(1)} \tag{7.2.35}$$

or

$$t_{(1)} - \frac{T^*}{n(r-1)} F_{2,2(r-1),\alpha} < G < t_{(1)} \tag{7.2.36}$$

Epstein and Sobel (1953) show that this interval is the shortest in the class of intervals being used. If for some particular values of r and α the value $F_{2,2(r-1),\alpha}$ is not tabulated in the F-table, Epstein (1960a) suggests using the following

confidence intervals for G:

$$t_{(1)} - \frac{\hat{\mu}(r-1)}{n} g_{1-\alpha} < G < t_{(1)} \tag{7.2.37}$$

or

$$t_{(1)} - \frac{T^*}{n} g_{1-\alpha} < G < t_{(1)} \tag{7.2.38}$$

where

$$g_{1-\alpha} = \left(\frac{1}{\alpha}\right)^{1/(r-1)} - 1 \tag{7.2.39}$$

is computable for any α and r. Example 7.7 illustrates the procedures.

Example 7.7 In a laboratory experiment 20 mice are injected with a tumor inoculum. These tumor cells multiply and eventually kill the animal. Suppose that the investigator decides to terminate the experiment after 10 deaths. The first occurs 30 days after the experiment starts. The total survival observed between the time when the first and tenth deaths occur is 600 animal days. Assuming that the survival distribution of these mice is exponential, the shortest 95% confidence interval for G can be obtained by (7.2.36). Since $F_{2,18,0.05} = 3.555$, the interval is

$$30 - \frac{600}{(20)(9)} (3.555) < G < 30$$

or (18.150, 30).

The mean survival time estimated by (7.2.31) is $\hat{\mu} = 66.667$ days, and the 95% confidence interval for μ computed from (7.2.33) is

$$\frac{2(600)}{31.526} < \mu < \frac{2(600)}{8.231}$$

or (38.064, 145.790).

When data are progressively censored, Gehan (1970) derives an estimate for G and a modified MLE for the hazard rate λ. Suppose that r out of the n individuals in the study die before the end of the study and $n - r$ individuals are alive at the time of the last follow-up or termination. The n survival times are denoted by

$$t_{(1)} \leqslant t_{(2)} \leqslant \cdots \leqslant t_{(r)}, t^+_{(r+1)}, \ldots, t^+_{(n)}$$

An estimate of G obtained by

$$\hat{G} = \max\left(t_{(1)} - \frac{1}{n\hat{\lambda}}, 0\right) \tag{7.2.40}$$

and the variance of $\hat{G}$ is

$$\text{Var}(\hat{G}) = \frac{1}{(n\hat{\lambda})^2}\left(1 + \frac{1}{r-1}\right) \tag{7.2.41}$$

When n is large, G and $\text{Var}(\hat{G})$ can be estimated by

$$\hat{G} \simeq t_{(1)} \tag{7.2.42}$$

and

$$\widehat{\text{Var}}(\hat{G}) \simeq \frac{1}{(n\hat{\lambda})^2} \tag{7.2.43}$$

A modified MLE for λ is

$$\hat{\lambda} = \frac{r-1}{\Sigma_{i=1}^{r} t_{(i)} + \Sigma_{i=r+1}^{n} t_{(i)}^{+} - nt_{(1)}} \tag{7.2.44}$$

with variance

$$\text{Var}(\hat{\lambda}) = \frac{\lambda^2}{r-1} \tag{7.2.45}$$

Any percentile of survival time t_p may be estimated by equating $S(t)$ to p and solving for $\hat{t}_p$; that is, $\hat{t}_p = -(\log_e p)/\hat{\lambda} + \hat{G}$.

The following example illustrates the procedures.

Example 7.8 Suppose that 19 patients with brain tumor are followed in a clinical trial for a year. Their survival times in weeks are 3, 4, 6, 8, 8, 10, 12, 16, 17, 30, 33, 3+, 8+, 13+, 21+, 26+, 35+, 44+, and 45+. In this case $n = 19$, $r = 11$, $t_{(1)} = 3$, $\Sigma_{i=1}^{11} t_{(i)} = 147$, and $\Sigma_{i=12}^{19} t_{(i)}^{+} = 195$. The hazard rate λ per week and its variance may be estimated by (7.2.44) and (7.2.45) as

$$\hat{\lambda} = \frac{10}{147 + 195 - 19(3)} = 0.035$$

and

$$\widehat{\text{Var}}(\hat{\lambda}) = \frac{(0.035)^2}{10} = 0.0001$$

The guarantee time G and its variance may then be estimated by (7.2.40) and (7.2.41):

$$\hat{G} = \max\left(3 - \frac{1}{19 \times 0.035}, 0\right) = 1.496$$

and

$$\widehat{\mathrm{Var}}(\hat{G}) = \frac{1}{(19 \times 0.035)^2}\left(1 + \frac{1}{10}\right) = 2.487$$

Thus, after a guarantee time of approximately 1.5 weeks, the chance of death per week is 0.035. The estimated median survival time is

$$\hat{t}_{0.5} = -\frac{\log\ 0.5}{0.035} + 1.496 = 21.3 \text{ weeks}$$

The probability of surviving at least six months (or 26 weeks) is estimated by

$$\hat{S}(26) = \exp[-0.35(26 - 1.496)] = 0.424$$

7.3 WEIBULL DISTRIBUTION

The Weibull distribution has the density and survivorship functions

$$\begin{aligned} f(t) &= \gamma\lambda^{\gamma}t^{\gamma-1}\exp[-(\lambda t)^{\gamma}] \\ S(t) &= e^{-(\lambda t)^{\gamma}} \qquad t \geqslant 0, \quad \gamma > 0, \quad \lambda > 0 \end{aligned} \tag{7.3.1}$$

The MLE of the parameters λ and γ involves equations to be solved simultaneously. Numerical methods such as the Newton–Raphson iterative procedure (7.1.13) can be applied. We begin with the case where no censored observations are presented.

Let $t_1, t_2, \ldots, t_n$ be the exact survival times of n individuals under investigation. If their survival times follow the Weibull distribution, the log-likelihood function is

$$l(\lambda, \gamma) = n\log\gamma + n\gamma\log\lambda + \sum_{i=1}^{n}[(\gamma - 1)\log t_i - \lambda^{\gamma}t_i^{\gamma}] \tag{7.3.2}$$

The MLE of λ and γ in (7.3.1) can be obtained by solving the following two equations simultaneously:

$$n - \hat{\lambda}^{\hat{\gamma}}\sum_{i=1}^{n} t_i^{\hat{\gamma}} = 0 \tag{7.3.3}$$

$$\frac{n}{\hat{\gamma}} + n\log\hat{\lambda} + \sum_{i=1}^{n}\log t_i - \hat{\lambda}^{\hat{\gamma}}\sum_{i=1}^{n} t_i^{\hat{\gamma}}(\log\hat{\lambda} + \log t_i) = 0 \tag{7.3.4}$$

Next, let us consider a typical laboratory experiment in which subjects are entered at the same time and the experiment is terminated after r of the n subjects have failed (or after a fixed period of time T). In both of these cases the data collected are singly censored. The ordered survival data are

$$t_{(1)} \leqslant t_{(2)} \leqslant \cdots \leqslant t_{(r)} = t^{+}_{(r+1)} = \cdots = t^{+}_{(n)}$$

If the time to failure follows the Weibull distribution with the density function given in (7.3.1), the MLE of λ and γ may be obtained by solving the following two equations simultaneously:

$$r - \hat{\lambda}^{\hat{\gamma}} \left[\sum_{i=1}^{r} t_i^{\hat{\gamma}} + (n-r) t_{(r)}^{\hat{\gamma}} \right] = 0 \tag{7.3.5}$$

$$\frac{r}{\hat{\gamma}} + r \log \hat{\lambda} + \sum_{i=1}^{r} \log t_i + \hat{\lambda}^{\hat{\gamma}} \left[\sum_{i=1}^{r} t_i^{\hat{\gamma}} (\log \hat{\lambda} + \log t_i) + (n-r) t_{(r)}^{\hat{\gamma}} (\log \hat{\lambda} + \log t_{(r)}) \right] = 0 \tag{7.3.6}$$

When data are progressively censored, we have

$$t_{(1)} \leqslant t_{(2)} \leqslant \cdots \leqslant t_{(r)}, t^{+}_{(r+1)}, \ldots, t^{+}_{(n)}$$

If the survival distribution is Weibull defined by (7.3.1), the log-likelihood function is

$$l(\lambda, \gamma) = r \log \gamma + r\gamma \log \lambda + \sum_{i=1}^{r} [(\gamma - 1) \log t_{(i)} - \lambda^{\gamma} t_{(i)}^{\gamma}] - \sum_{i=r+1}^{n} \lambda^{\gamma} t_{(i)}^{+\gamma} \tag{7.3.7}$$

The MLE of λ and γ may be obtained by solving the following two equations simultaneously:

$$r - \hat{\lambda}^{\hat{\gamma}} \left(\sum_{i=1}^{r} t_i^{\hat{\gamma}} + \sum_{i=r+1}^{n} t_i^{+\hat{\gamma}} \right) = 0 \tag{7.3.8}$$

$$\frac{r}{\hat{\gamma}} + r \log \hat{\lambda} + \sum_{i=1}^{r} \log t_i - \hat{\lambda}^{\hat{\gamma}} \sum_{i=1}^{r} t_i^{\hat{\gamma}} (\log \hat{\lambda} + \log t_i) - \hat{\lambda}^{\hat{\gamma}} \sum_{i=r+1}^{n} t_i^{+\hat{\gamma}} (\log \hat{\lambda} + \log t_i^{+}) = 0 \tag{7.3.9}$$

The following example illustrates the use of available computer software to obtain the MLE of λ and γ.

Example 7.9 Referring to Example 7.5, for the observed survival data in the file "EXAMPLE.DAT", we can use either SAS or BMDP to obtain the estimated parameters of the Weibull distribution. The codes given in Example 7.5 can be used except that d = exponential in the SAS code must be changed to d = weibull and accel = exponential in BMDP code be changed to accel = weibull. If SAS is used, the estimated parameters of the Weibull distribution are

$$\hat{\lambda} = \exp(-\text{INTERCEPT}) \quad \text{and} \quad \hat{\gamma} = \frac{1}{\text{SCALE}}$$

where INTERCEPT and SCALE are produced by SAS procedure LIFEREG. If BMDP is used,

$$\hat{\lambda} = \exp(-\text{INTERCEPT}) \quad \text{and} \quad \hat{\gamma} = \frac{1}{\text{SCALE}}$$

where CONSTANT and SCALE are given by procedure 2L.

7.4 LOGNORMAL DISTRIBUTION

If the survival time T follows the lognormal distribution with density function

$$f(t) = \frac{1}{t\sigma\sqrt{2\pi}} \exp\left[-\frac{1}{2\sigma^2} (\log t - \mu)^2 \right] \tag{7.4.1}$$

the mean and the variance are $\exp(\mu + \frac{1}{2}\sigma^2)$ and $[\exp(\sigma^2) - 1]\exp(2\mu + \sigma^2)$, respectively. Estimation of the two parameters μ and σ^2 has been investigated either by using (7.4.1) directly or by using the fact that $Y = \log T$ follows the normal distribution with mean μ and variance σ^2. In the following, we discuss the estimation of μ and σ^2 for samples with and without censored observations.

7.4.1 Estimation of μ and σ^2 for Data without Censored Observations

Estimations of μ and σ^2 for complete samples by maximum likelihood methods have been studied by many authors: for example, Cohen (1951) and Harter and Moore (1966). But the simplest way to obtain estimates of μ and σ^2 with optimum properties is by considering the distribution of $Y = \log T$. Let t_1, $t_2, \ldots, t_n$ be the survival times of n subjects. The MLE of μ is the sample mean of Y given by

$$\hat{\mu} = \frac{1}{n} \sum_{i=1}^{n} \log t_i \tag{7.4.2}$$

The MLE of σ^2 is

$$\hat{\sigma}^2 = \frac{1}{n} \left[\sum_{i=1}^{n} (\log t_i)^2 - \frac{(\Sigma_{i=1}^{n} \log t_i)^2}{n} \right] \tag{7.4.3}$$

The estimate $\hat{\mu}$ is also unbiased but $\hat{\sigma}^2$ is not. The best unbiased estimates of μ and σ^2 are $\hat{\mu}$ and the sample variance $s^2 = \hat{\sigma}^2[n/(n-1)]$. If n is moderately large, the difference between s^2 and $\hat{\sigma}^2$ is negligible.

One of the properties of the MLE is that if $\hat{\theta}$ is the MLE of θ, $g(\hat{\theta})$ is the MLE of $g(\theta)$ if $g(\theta)$ is a finite function. Therefore, the MLEs of the mean and variance of T are, respectively, $\exp(\hat{\mu} + \frac{1}{2}\hat{\sigma}^2)$ and $\exp[(\hat{\sigma}^2 - 1)] \exp(2\hat{\mu} + \hat{\sigma}^2)$.

It is known that $\hat{\mu} = \bar{y}$ is normally distributed with mean μ and variance σ^2/n. Hence, if σ is known, a $100(1-\alpha)\%$ confidence interval for μ is $\hat{\mu} \pm Z_{a/2}\sigma/\sqrt{n}$. If σ is unknown, we can use Student's t-distribution. A $100(1-\alpha)\%$ confidence interval for μ is $\hat{\mu} \pm t_{\alpha/2,(n-1)}S/\sqrt{n-1}$, where $t_{\alpha/2,(n-1)}$ is the $100\alpha/2$ percentage point of Student's t-distribution with $n-1$ degrees of freedom (Table B-7).

Confidence intervals for σ^2 can be obtained by using the fact that $n\hat{\sigma}/\sigma^2$ has a chi-square distribution with $n-1$ degrees of freedom. A $100(1-\alpha)\%$ confidence interval for σ^2 is

$$\frac{n\hat{\sigma}^2}{\chi^2_{(n-1),\alpha/2}} < \sigma^2 < \frac{n\hat{\sigma}^2}{\chi^2_{(n-1),1-\alpha/2}} \tag{7.4.4}$$

The following hypothetical example illustrates the procedures.

Example 7.10 Five melanoma (resected) patients receiving immunotherapy BCG are followed. The remission duration in weeks are, in order of magnitude, 8, 16, 23, 27, and 28. Suppose that the remission times follow a lognormal distribution. In this case, parameters are estimated by (7.4.2) and (7.4.3) as follows:

t	$\log t$	$(\log t)^2$
8	2.079	4.322
16	2.773	7.690
23	3.135	9.828
27	3.296	10.864
28	3.332	11.102
	14.615	43.806

$$\hat{\mu} = \frac{14.615}{5} = 2.923$$

$$\hat{\sigma}^2 = \frac{1}{5}\left[43.806 - \frac{1}{5}(14.615)^2\right] = 0.217$$

$$s^2 = \frac{5\hat{\sigma}^2}{5-1} = 0.271$$

The mean remission time is exp(2.923 + 0.217/2), or 20.728, weeks and the standard deviation of the remission time is $\{[\exp(0.217) - 1]\exp(5.846 + 0.217)\}^{1/2}$, or 10.204, weeks. A 95% confidence interval for μ is

$$2.923 - 2.776\left(\frac{0.521}{\sqrt{4}}\right) < \mu < 2.923 + 2.776\left(\frac{0.521}{\sqrt{4}}\right)$$

or (2.200,3.646). A 95% confidence interval for σ^2, following (7.4.4), is

$$\frac{5(0.217)}{11.1433} < \sigma^2 < \frac{5(0.217)}{0.4844}$$

or (0.097, 2.240).

7.4.2 Estimation of μ and σ^2 for Data with Censored Observations

We first consider samples with singly censored observations. The data consist of r exact survival times $t_{(1)} \leqslant t_{(2)} \leqslant \cdots \leqslant t_{(r)}$ and $n - r$ right-censored survival times that are at least $t_{(r)}$, denoted by $t_{(r)}^{+}$. Again, we use the fact that $Y = \log T$ has normal distribution with mean μ and variance σ^2. Estimates of μ and σ^2 can be obtained from the transformed data $y_i = \log t_i$. Many authors have investigated the estimation of μ and σ^2: for example, Gupta (1952), Sarhan and Greenberg (1956, 1957, 1958, 1962), Saw (1959), and Cohen (1959, 1961). We shall discuss the methods of Sarhan and Greenberg and Cohen because of the available table that reduces computation time and efforts.

The best linear estimates of μ and σ proposed by Sarhan and Greenberg are linear combinations of the logarithms of the r exact survival times:

$$\hat{\mu} = \sum_{i=1}^{r} a_i \log t_{(i)} \tag{7.4.5}$$

and

$$\hat{\sigma} = \sum_{i=1}^{r} b_i \log t_{(i)} \tag{7.4.6}$$

where the coefficients a_i and b_i are calculated and tabulated by Saharan and Greenberg for $n \leqslant 20$ and are partially reproduced in Table B-8. The variance and covariance of $\hat{\mu}$ and $\hat{\sigma}$ are tabulated in Table B-9.

The following example illustrates the procedure.

Example 7.11 Suppose that in a study of the efficacy of a new drug, 12 mice with tumors are given the drug. The experimenter decides to terminate the study after 9 mice have died. The survival times are, in weeks, 5, 8, 9, 10, 12, 15, 20, 21, 25, 25+, 25+, and 25+. Assume that the times to death of these

mice follow the lognormal distribution. In this case $n = 12$, $r = 9$, and $n - r = 3$. Using (7.4.5), (7.4.6), and Table B-8, $\hat{\mu}$ and $\hat{\sigma}$ can be calculated as

$$\begin{aligned}\hat{\mu} &= 0.036\log 5 + 0.0581\log 8 + 0.0682\log 9 + 0.0759\log 10 + 0.0827\log 12 \\ &\quad + 0.0888\log 15 + 0.0948\log 20 + 0.1006\log 21 + 0.3950\log 25 \\ &= 2.811 \\ \hat{\sigma} &= -0.2545\log 5 - 0.1487\log 8 - 0.1007\log 9 - 0.0633\log 10 \\ &\quad - 0.0308\log 12 - 0.0007\log 15 + 0.0286\log 20 + 0.0582\log 21 \\ &\quad + 0.5119\log 25 \\ &= 0.747\end{aligned}$$

The variance of $\hat{\mu}$ and $\hat{\sigma}$ given in Table B-9 are, respectively, 0.0926 and 0.0723 and the covariance of $\hat{\mu}$ and $\hat{\sigma}$ is 0.0152.

Cohen's (1959, 1961) MLEs for the normal distribution can be used for $n > 20$. Let

$$\bar{y} = \frac{1}{r}\sum_{i=1}^{r} \log t_{(i)} \tag{7.4.7}$$

and

$$s^2 = \frac{1}{r}\left[\sum (\log t_{(i)})^2 - \frac{(\Sigma \log t_{(i)})^2}{r}\right] \tag{7.4.8}$$

Then the MLEs of μ and σ^2 are

$$\hat{\mu} = \bar{y} - \hat{\lambda}(\bar{y} - \log t_{(r)}) \tag{7.4.9}$$

and

$$\hat{\sigma}^2 = s^2 + \hat{\lambda}(\bar{y} - \log t_{(r)})^2 \tag{7.4.10}$$

where the value of $\hat{\lambda}$ has been tabulated by Cohen (1961) as a function of a and b. The proportion of censored observations, b, is calculated as

$$b = \frac{n - r}{n}$$

and

$$a = \frac{1 - Y(Y - c)}{(Y - c)^2}$$

where $Y = [b/(1 - b)]\, f(c)/F(c)$, $f(c)$ and $F(c)$ being the density and distribu-

tion functions, respectively, of the standard normal distribution, evaluated at $c = (\log t_{(r)} - \mu)/\sigma$. Table 7.1 gives values of $\hat{\lambda}$ for $b = 0.01$ to 0.90 and $a = 0.00$ to 1.00. For a censored sample, after computing $a = s^2/(\bar{y} - \log t_{(r)})^2$, and $b = (n - r)/n$, enter Table 7.1 with these values of a and b to obtain $\hat{\lambda}$. For values not tabulated, two-way linear interpolation can be used.

The asymptotic variances and covariance are the following:

$$\begin{aligned} \text{Var}(\hat{\mu}) &\sim \frac{\sigma^2}{n} m_1 \\ \text{Var}(\hat{\sigma}) &\sim \frac{\sigma^2}{n} m_2 \\ \text{Cov}(\hat{\mu}, \hat{\sigma}) &\sim \frac{\sigma^2}{n} m_3 \end{aligned} \tag{7.4.11}$$

where m_1, m_2, and m_3 are also tabulated by Cohen (1961). The table is reproduced in Table 7.2. For any censored sample, compute $\hat{c} = (\log t_{(r)} - \hat{\mu})/\hat{\sigma}$ and then enter the appropriate columns of Table 7.2 with $y = -\hat{c}$, and interpolate to obtain the required values of m_i, $i = 1, 2, 3$, if the experiment was terminated after a predetermined time. If the experiment was terminated after a given proportion of animals have died, enter Table 7.2 through the percent censored column with percentage censored $= 100b$ and interpolate to obtain the required value of m_i.

To illustrate the use of Tables 7.1 and 7.2 for the computation of $\hat{\mu}$, $\hat{\sigma}^2$, $\text{Var}(\hat{\mu})$, $\text{Var}(\hat{\sigma})$, and $\text{Cov}(\hat{\mu}, \hat{\sigma})$, consider Example 7.12, adapted from Cohen (1961).

Example 7.12 Suppose that in a laboratory experiment 300 insects were followed until 119 died within seconds, $\bar{y} = 1{,}304.832$ seconds, $s^2 = 12{,}128.250$, and $\log t_{(119)} = 1{,}450.000$ seconds. In this case $n = 300$ and $r = 119$. Accordingly,

$$\hat{a} = \frac{12{,}128.25}{(1{,}304.832 - 1{,}450)^2} = 0.575 \qquad b = \frac{300 - 119}{300} = 0.603$$

From Table 7.1, $\hat{\lambda}$ is approximately 1.36. Using (7.4.9) and (7.4.10), we obtain

$$\hat{\mu} = 1{,}304.832 - 1.36(1{,}304.832 - 1{,}450) = 1{,}502.26 \text{ seconds}$$
$$\hat{\sigma}^2 = 12{,}128.250 + 1.36(1{,}304.832 - 1{,}450)^2 = 40{,}788.55$$

and $\hat{\sigma}^2 = 201.96$ seconds.

For the variance and covariance of $\hat{\mu}$ and $\hat{\sigma}$, we enter Table 7.2 with percentage censored $100b = 60.3$ and interpolate linearly to obtain $m_1 = 2.002$,

Table 7.1 Estimated Values for $\hat{\mu}$ and σ^2

	b																							
a	.01	.02	.03	.04	.05	.06	.07	.08	.09	.10	.15	.20	.25	.30	.35	.40	.45	.50	.55	.60	.65	.70	.80	.90
.00	.010100	.020400	.030902	.041583	.052507	.063627	.074953	.086488	.09824	.11020	.17342	.24268	.31862	.4021	.4941	.5961	.7096	0.8368	0.9808	1.145	1.336	1.561	2.176	3.282
.05	.010551	.021294	.032225	.043350	.054670	.066189	.077909	.089834	.10197	.11431	.17935	.25033	.32793	.4130	.5066	.6101	.7252	0.8540	0.9994	1.166	1.358	1.585	2.203	3.314
.10	.010950	.022082	.033398	.044902	.056596	.068483	.080568	.092852	.10534	.11804	.18479	.25741	.33662	.4233	.5184	.6234	.7400	0.8703	1.017	1.185	1.379	1.608	2.229	3.345
.15	.011310	.022798	.034466	.046318	.058356	.070586	.038009	.095629	.10845	.12148	.18985	.26405	.34480	.4330	.5296	.6361	.7542	0.8860	1.035	1.204	1.400	1.630	2.255	3.376
.20	.011642	.023459	.035453	.047629	.059990	.072539	.085280	.098216	.11135	.12469	.19460	.27031	.35255	.4422	.5403	.6483	.7678	0.9012	1.051	1.222	1.419	1.651	2.280	3.405
.25	.011952	.024076	.036377	.048858	.061522	.074372	.087413	.10065	.11408	.12772	.19910	.27626	.35993	.4510	.5506	.6600	.7810	0.9158	1.067	1.240	1.439	1.672	2.305	3.435
.30	.012243	.024658	.037249	.050018	.062969	.076106	.089433	.10295	.11667	.13059	.20338	.28193	.36700	.4595	.5604	6.713	.7937	0.9300	1.083	1.257	1.457	1.693	2.329	3.464
.35	.012520	.025211	.038077	.051120	.064345	.077756	.091355	.10515	.11914	.13333	.20747	.28737	.37379	.4676	.5699	.6821	.8060	0.9437	1.098	1.274	1.476	1.713	2.353	3.492
.40	.012784	.025738	.038866	.052173	.065660	.079332	.093193	.10725	.12150	.13595	.21139	.29260	.38033	.4755	.5791	.6927	.8179	0.9570	1.113	1.290	1.494	1.732	2.376	3.520
.45	.013036	.026243	.039624	.053182	.066921	.080845	.094958	.10926	.12377	.13847	.21517	.29765	.38665	.4831	.5880	.7029	.8295	0.9700	1.127	1.306	1.511	1.751	2.399	3.547
.50	.013279	.026728	.040352	.054153	.068135	.082301	.096657	.11121	.12595	.14090	.21882	.30253	.39276	.4904	.5967	.7129	.8408	0.9826	1.141	1.321	1.528	1.770	2.421	3.575
.55	.013513	.027196	.041054	.055089	.069306	.083708	.098298	.11308	.12806	.14325	.22235	.30725	.39870	.4976	.6051	.7225	.8517	0.9950	1.155	1.337	1.545	1.788	2.443	3.601
.60	.013739	.027649	.041733	.055995	.070439	.085068	.099887	.11490	.13011	.14552	.22578	.31184	.40447	.5045	.6133	.7320	.8625	1.007	1.169	1.351	1.561	1.806	2.465	3.628
.65	.013958	.028087	.042391	.056874	.071538	.086388	.10143	.11666	.13209	.14773	.22910	.31630	.41008	.5114	.6213	.7412	.8729	1.019	1.182	1.366	1.577	1.824	2.486	3.654
.70	.014171	.028513	.043030	.057726	.072605	.087670	.10292	.11837	.13402	.14987	.23234	.32065	.41555	.5180	.6291	.7502	.8832	1.030	1.195	1.380	1.593	1.841	2.507	3.679
.75	.014378	.028927	.043652	.058556	.073643	.088917	.10438	.12004	.13590	.15196	.23550	.32489	.42090	.5245	.6367	.7590	.8932	1.042	1.207	1.394	1.608	1.858	2.528	3.705
.80	.014579	.029330	.044258	.059364	.074655	.090133	.10580	.12167	.13773	.15400	.23858	.32903	.42612	.5308	.6441	.7676	.9031	1.053	1.220	1.408	1.624	1.875	2.548	3.730
.85	.014755	.029723	.044848	.060153	.075642	.901319	.10719	.12325	.13952	.15599	.24158	.33307	.43122	.5370	.6515	.7761	.9127	1.064	1.232	1.422	1.639	1.892	2.568	3.754
.90	.014967	.030107	.045425	.060923	.076606	.092477	.10854	.12480	.14126	.15793	.24452	.33703	.43622	.5430	.6586	.7844	.9222	1.074	1.244	1.435	1.653	1.908	2.588	3.779
.95	.015154	.030483	.045989	.061676	.077549	.0093611	.10987	.12632	.14297	.15983	.24740	.34091	.44112	.5490	.6656	.7925	.9314	1.085	1.255	1.448	1.668	1.924	2.607	3.803
1.00	.015338	.030850	.046540	.062413	.078471	.094720	.11116	.12780	.14465	.16170	.25022	.34471	.44592	.5548	.6724	.8005	.9406	1.095	1.267	1.461	1.682	1.940	2.626	3.827

Source: Cohen (1961).

[a] For all values $0 \leqslant a \leqslant 1$, $\lambda = 0$.

Table 7.2 Estimated Values of m_1, m_2. and m_3 for Var($\hat{\mu}$), Var($\hat{\sigma}$), and Cov($\hat{\mu}, \hat{\sigma}$)

y	m_1	m_2	m_3	Percentage Censored
−4.0	1.00000	0.500030	0.000006	0.00
−3.5	1.00001	0.500208	0.000052	0.02
−3.0	1.00010	0.501180	0.000335	0.13
−2.5	1.00056	0.505280	0.001712	0.62
−2.4	1.00078	0.506935	0.002312	0.82
−2.3	1.00107	0.509030	0.003099	1.07
−2.2	1.00147	0.511658	0.004121	1.39
−2.1	1.00200	0.514926	0.005438	1.79
−2.0	1.00270	0.518960	0.007123	2.28
−1.9	1.00363	0.523899	0.009266	2.87
−1.8	1.00485	0.529899	0.011971	3.59
−1.7	1.00645	0.537141	0.015368	4.46
−1.6	1.00852	0.545827	0.019610	5.48
−1.5	1.01120	0.556186	0.024884	6.68
−1.4	1.01467	0.568417	0.031410	8.08
−1.3	1.01914	0.582981	0.039460	9.68
−1.2	1.02488	0.600046	0.049355	11.51
−1.1	1.03224	0.620049	0.061491	13.57
−1.0	1.04168	0.643438	0.076345	15.87
−0.9	1.05376	0.670724	0.094501	18.41
−0.8	1.06923	0.702513	0.116674	21.19
−0.7	1.08904	0.739515	0.143744	24.20
−0.6	1.11442	0.782574	0.176698	27.43
−0.5	1.14696	0.832691	0.217183	30.85
−0.4	1.18876	0.891077	0.266577	34.46
−0.3	1.24252	0.959181	0.327080	38.21
−0.2	1.31180	1.03877	0.401326	42.07
−0.1	1.40127	1.13198	0.492641	46.02
0.0	1.51709	1.24145	0.605233	50.00
0.1	1.66743	1.37042	0.744459	53.98
0.2	1.86310	1.52288	0.917165	57.93
0.3	2.11857	1.70381	1.13214	61.79
0.4	2.45318	1.91942	1.40071	65.54
0.5	2.89293	2.17751	1.73757	69.15
0.6	3.47293	2.48793	2.16185	72.57
0.7	4.24075	2.86318	2.69858	75.80
0.8	5.2612	3.3192	3.3807	78.81
0.9	6.6229	3.8765	4.2517	81.59
1.0	8.4477	4.5614	5.3696	84.13
1.1	10.903	5.4082	6.8116	86.43
1.2	14.224	6.4616	8.6818	88.49
1.3	18.735	7.7804	11.121	90.32
1.4	24.892	9.4423	14.319	91.92

Table 7.2 *Continued*

y	m_1	m_2	m_3	Percentage Censored
1.5	33.339	11.550	18.539	93.32
1.6	44.986	14.243	24.139	94.52
1.7	61.132	17.706	31.616	95.54
1.8	83.638	22.193	41.664	96.41
1.9	115.19	28.046	55.252	97.13
2.0	159.66	35.740	63.750	97.72
2.1	222.74	45.930	99.100	98.21
2.2	312.73	59.526	134.08	98.61
2.3	441.92	77.810	182.68	98.93
2.4	628.58	102.59	250.68	99.18
2.5	899.99	136.44	346.53	99.38

Source: Cohen (1961).

$m_2 = 1.635$, and $m_3 = 1.051$. Substituting these values and $\hat{\sigma}^2 = 40{,}788.55$ into (7.4.11), we obtain

$$\text{Var}(\hat{\mu}) \simeq \frac{40{,}788.55(2.022)}{300} = 274.91$$

$$\text{var}(\hat{\sigma}) \simeq \frac{40{,}788.55(1.635)}{300} = 222.30$$

$$\text{Cov}(\hat{\mu}, \hat{\sigma}) \simeq \frac{40{,}788.55(1.051)}{300} = 142.90$$

When the data are progressively censored, let $t_1, t_2, \ldots, t_r$ be the uncensored and $t_{r+1}^+, t_{r+2}^+, \ldots, t_n^+$ be the censored observations, the likelihood function, using (7.4.1) and (7.1.1), is

$$l(\mu, \sigma^2) = -\frac{r\log(2\pi\sigma^2)}{2} - \sum_{i=1}^{r}\left(\log t_i + \frac{(\log t_i - \mu)^2}{2\sigma^2}\right) + \sum_{i=r+1}^{n}\log\left\{\int_{t_i^+}^{\infty}\frac{1}{x\sqrt{2\pi\sigma^2}}\exp\left[-\frac{1}{2\sigma^2}(\log x - \mu)^2\right]dx\right\}$$

and the MLE of μ and σ^2 can be obtained by solving the following two

equations:

$$\sum_{i=1}^{r} \frac{\log t_i - \mu}{\sigma^2} + \sum_{i=r+1}^{n} \frac{\displaystyle\int_{t_i^+}^{\infty} \frac{\log x - \mu}{x\sigma^2\sqrt{2\pi\sigma^2}} \exp\left[-\frac{1}{2\sigma^2}(\log x - \mu)^2 \right] dx}{\displaystyle\int_{t_i^+}^{\infty} \frac{1}{x\sqrt{2\pi}\sigma} \exp\left[-\frac{1}{2\sigma^2}\ (\log x - \mu)^2 \right] dx} = 0$$

$$-\frac{n}{2\sigma^2} + \sum_{i=1}^{r} \frac{(\log t_i - \mu)^2}{2\sigma^4} + \sum_{i=r+1}^{n} \frac{\displaystyle\int_{t_i^+}^{\infty} \frac{(\log x - \mu)^2}{x2\sigma^4\sqrt{2\pi\sigma^2}} \exp\left[-\frac{1}{2\sigma^2}(\log x - \mu)^2 \right] dx}{\displaystyle\int_{t_i^+}^{\infty} \frac{1}{x\sqrt{2\pi\sigma^2}} \exp\left[-\frac{1}{2\sigma^2}\ (\log x - \mu)^2 \right] dx} = 0$$

Again, this can be done by applying the Newton–Raphson iterative procedure.

The following example illustrate the use of SAS and BMDP to obtain estimates of the lognormal parameters.

Example 7.13 Referring to Example 7.5, for the observed survival data in the file "EXAMPLE.DAT", by changing d = exponential in SAS code to d = lnormal and accel = exponential in BMDP code to accel = lnormal we can obtain the estimated parameters of the lognormal distribution. If SAS is used, the estimated parameters of the lognormal distribution are

$$\hat{\mu} = \text{INTERCEPT} \quad \text{and} \quad \hat{\sigma}^2 = \text{SCALE}^2$$

where INTERCEPT and SCALE are the names of output estimated parameters in SAS procedure LIFEREG. If BMDP is used,

$$\hat{\mu} = \text{CONSTANT} \quad \text{and} \quad \hat{\sigma}^2 = \text{SCALE}^2$$

where CONSTANT and SCALE are given by procedure 2L.

7.5 STANDARD AND GENERALIZED GAMMA DISTRIBUTIONS

The density function of the standard gamma distribution is

$$f(t) = \frac{\lambda}{\Gamma(\gamma)} (\lambda t)^{\gamma - 1} \exp(-\lambda t) \qquad t \geqslant 0, \quad \lambda, \gamma > 0 \tag{7.5.1}$$

where

$$\Gamma(\gamma) = \begin{cases} \int_0^\infty x^{\gamma-1} e^{-x}\, dx \\ (\gamma - 1)! \qquad \text{if } \gamma \text{ is an integer} \end{cases} \tag{7.5.2}$$

In this section we discuss the MLE of λ and γ for data with and without censored observations.

7.5.1 Estimation of λ and γ for Data without Censored Observations

Suppose that the n patients under study are followed to death and their exact survival times $t_1, t_2, \ldots, t_n$ are known. The MLE of λ and γ can be obtained by solving simultaneously the two equations

$$\frac{n\hat{\gamma}}{\hat{\lambda}} - \sum_{i=1}^{n} t_i = 0 \tag{7.5.3}$$

and

$$n \log \hat{\lambda} - \frac{n\Gamma'(\hat{\gamma})}{\Gamma(\hat{\gamma})} + \sum_{i=1}^{n} \log t_i = 0 \tag{7.5.4}$$

where $\Gamma'(\gamma)$ is the derivative of $\Gamma(\gamma)$,

$$\Gamma'(\gamma) = \int_0^\infty x^{\gamma-1} \log(x) e^{-x}\, dx \tag{7.5.5}$$

From (7.5.3), we have

$$\hat{\lambda} = \frac{n\hat{\gamma}}{\Sigma_{i=1}^{n} t_i} \tag{7.5.6}$$

On eliminating λ, we substitute (7.5.6) into (7.5.4) and obtain

$$\frac{\Gamma'(\hat{\gamma})}{\Gamma(\hat{\gamma})} - \log \hat{\gamma} - \log \frac{(\Pi_{i=1}^{n} t_i)^{1/n}}{\Sigma_{i=1}^{n} t_i/n} = 0 \tag{7.5.7}$$

to solve for $\hat{\gamma}$. This can be done by using the Newton–Raphson iterative procedure. Tables for the solution of (7.5.7) for $\hat{\gamma}$ as a function of R are given by Greenwood and Durand (1960), where R is the ratio of the geometric mean to the arithmetic mean of the n observations:

$$R = \frac{(\Pi_{i=1}^{n} t_i)^{1/n}}{\Sigma_{i=1}^{n} t_i/n} \tag{7.5.8}$$

Wilk et al. (1962a) show that the relationship between $\hat{\gamma}$ and $1/(1-R)$ is linear. A table of $\hat{\gamma}$ values of as a function of $1/(1-R)$ given in their paper is reproduced in Table B-10. Thus if R and $1/(1-R)$ are computed from the sample, a MLE of γ can be found from Table B-10. For values not tabulated, linear interpolation can be used. Having $\hat{\gamma}$ so determined, $\hat{\lambda}$ can be obtained from (7.5.6).

In the method of moments (Fisher, 1922), the estimators are obtained simply by equating the population mean and variance to the sample mean and variance. The moment estimators of γ and λ are

$$\lambda^* = \frac{\Sigma_{i=1}^n t_i}{\Sigma_{i=1}^n (t_i - \bar{t})^2} \tag{7.5.9}$$

and

$$\gamma^* = \frac{(\Sigma_{i=1}^n t_i)^2}{n \Sigma_{i=1}^n (t_i - \bar{t})^2} \tag{7.5.10}$$

Both types of estimators give biased estimates. The moment estimators are easy to calculate but are inefficient in the sense that their variances are larger than the variance of the MLE. To reduce the bias, Lilliefors (1971) suggests correction factors for these two types of estimators. The corrected MLE of γ and λ are, respectively,

$$\hat{\gamma}_c = \frac{\hat{\gamma}}{1 + 3/n} \tag{7.5.11}$$

and

$$\hat{\lambda}_c = \frac{\hat{\gamma}_c}{\bar{t}} \left(1 - \frac{1}{n\hat{\gamma}_c}\right) \tag{7.5.12}$$

The corrected moments estimators of γ and λ are

$$\gamma_c^* = \frac{\gamma^*}{1 + 2/n} - \frac{3}{n} \tag{7.5.13}$$

and

$$\lambda_c^* = \frac{\gamma_c^*}{t} \left(1 - \frac{1}{n\gamma_c^*}\right) \tag{7.5.14}$$

Lilliefors shows by the Monte Carlo method that the corrected MLE and the method-of-moment estimates are approximately unbiased. In addition, as long as $\gamma \geqslant 2$, the corrected moments estimators have no more bias than the corrected MLE and for $n = 10$ have considerably less bias. For $n = 10$, 20 and $\gamma \geqslant 2$, the variance is close to that of the MLE.

Example 7.14 Ten patients with melanoma achieve remission after surgery and therapy. They are followed to relapse. The durations of remission in months are recorded as follows: 5, 8, 10, 11, 15, 20, 21, 23, 30, and 40. Assuming that the distribution of remission duration is standard gamma, we first calculate the MLE of γ and λ according to Wilk et al. (1962a). To compute R, we obtain $\Sigma_{i=1}^{n} t_i = 183$ and $(\Pi_{i=1}^{n} t_i)^{1/10} = 15.43$. Therefore $R = 0.84$ and $1/(1-R) = 6.25$. From Table B-10, $\hat{\gamma} = 2.89830$ for $1/(1-R) = 6.0$ and $\hat{\gamma} = 3.14984$ for $1/(1-R) = 6.5$. By linear interpolation, for $1/(1-R) = 6.25$, $\hat{\gamma} = 3.02407$. From (7.5.6), $\hat{\lambda} = 0.16525$. The corrected MLEs obtained from (7.5.11) and (7.5.12) are $\hat{\gamma}_c = 2.326$ and $\hat{\lambda}_c = 0.122$. The moment estimates of γ and λ following (7.5.9) and (7.5.10) are $\lambda^* = 0.173$ and $\gamma^* = 3.171$. With the correction factors, $\lambda_c^* = 0.1225$ and $\gamma_c^* = 2.3425$, which are very close to the corrected MLE.

7.5.2 Estimation of γ and λ for Data with Censored Observations

When data are singly censored, the survival times can be ordered as

$$t_{(1)} \leqslant t_{(2)} \leqslant \cdots \leqslant t_{(r)} \leqslant t^{+}_{(r+1)} = \cdots = t^{+}_{(n)}$$

where r persons in the study have exact survival times recorded and $n-r$ others have their lives terminated after the rth death occurs. In this case, the maximum likelihood procedure becomes much more complicated.

Let $\eta = \lambda t_{(r)}$, $P = [\Pi_{i=1}^{r} t_{(i)}]^{1/r}/t_{(r)}$, and $S = \Sigma_{i=1}^{r} t_{(i)}/r t_{(r)}$. The MLE of η and γ and can be obtained by solving simultaneously

$$\log P = \frac{n\Gamma'(\gamma)}{r\Gamma(\gamma)} - \frac{n}{r}\log\eta - \left(\frac{n}{r} - 1\right)\frac{J'(\gamma,\ \eta)}{J(\gamma,\ \eta)} \tag{7.5.15}$$

and

$$S = \frac{\gamma}{\eta} - \frac{1}{\eta}\left(\frac{n}{r} - 1\right)\frac{e^{-\eta}}{J(\gamma,\ \eta)} \tag{7.5.16}$$

where

$$J(\gamma,\ \eta) = \int_1^{\infty} t^{\gamma-1} e^{-\eta t}\, dt \tag{7.5.17}$$

and

$$J'(\gamma,\ \eta) = \frac{\partial}{\partial\gamma} J(\gamma,\ \eta) = \int_1^{\infty} t^{\gamma-1}\log t e^{-\eta t}\, dt \tag{7.5.18}$$

Wilk et al. (1962a) generate, for a grid of values of P and S and n/r, tables of values of $\hat{\gamma}$ and $\hat{\mu} = \hat{\gamma}/\hat{\eta}$ based on the solutions of (7.5.15) and (7.5.16). The tables are reproduced in Table B-11. Thus, to find $\hat{\gamma}$ and $\hat{\lambda}$, one needs to

compute P and S first. For specific values of P, S, and n/r, $\hat{\gamma}$ and $\hat{\mu}$ may be looked up from Table B-11. Then $\hat{\lambda}$ can be obtained from $\hat{\lambda} = \hat{\gamma}/[\hat{\mu}t_{(r)}]$. Interpolations may be needed when any of the values of P, S, and n/r are not tabulated.

Example 7.15, adapted from Wilk et al. (1962a), illustrates the procedure of calculating $\hat{\gamma}$, $\hat{\mu}$, and $\hat{\lambda}$ when Table B-11 is used. This method can also be used in the case of a complete sample (no censored observations); that is, $r = n$. If it is obvious that some of the observations may be outliers (too large or too small), it is reasonable not to use them in estimation. In this case, r is the number of observations used in the estimation procedure.

Example 7.15 Consider an experiment with $n = 34$ animals. The following data are the lifetimes t_i in weeks of 34 animals: 3, 4, 5, 6, 6, 7, 8, 8, 9, 9, 9, 10, 10, 11, 11, 11, 13, 13, 13, 13, 13, 17, 17, 19, 19, 25, 29, 33, 42, 42, 52, 52+, 52+, and 52+. The study is terminated when 31 animals have died and the other 3 are sacrificed. In our notation, $n = 34$ and $r = 31$.

1. Compute n/r, P, and S:

$$\frac{n}{r} = \frac{34}{31} = 1.10$$

$$S = \frac{\Sigma t_i}{rt_{(r)}} = \frac{487}{(31)(52)} = 0.30$$

   To compute P, it is easier first to compute $\log P$:

$$\log P = \frac{1}{r}\sum \log t_{(i)} - \log t_{(r)} = \frac{1}{31} \times 33.90207 - 1.716 = -0.622385$$

   Hence $P = 0.24$.

2. Consider the entries for $n/r = 1.10$ and $P = 0.24$ in Table B-11:

$$S = 0.28: \qquad \hat{\gamma} = 1.986 \quad \hat{\mu} = 0.365$$

$$S = 0.32: \qquad \hat{\gamma} = 1.449 \quad \hat{\mu} = 0.410$$

   Using linear interpolation, approximate estimates of γ and μ are $\hat{\gamma} = 1.72$ and $\hat{\mu} = 0.39$.

3. Finally, $\hat{\lambda} = 1.72/(0.39 \times 52) = 0.085$.

For a more accurate two-way interpolation, the reader is referred to Wilk et al. (1962a).

When the data are progressively censored, let $t_1, t_2, \ldots, t_r$ be the uncensored and $t_{r+1}^+, t_{r+2}^+, \ldots, t_n^+$ be the censored observations; the likelihood function is

$$l(\lambda, \gamma) = \log L(\lambda, \gamma) = n\gamma \log \lambda - n \log \Gamma(\gamma) + \sum_{i=1}^{r} [(\gamma - 1) \log t_i - \lambda t_i] + \sum_{i=r+1}^{n} \log \left(\int_{t_i^+}^{\infty} x^{\gamma - 1} e^{-\lambda x} dx \right)$$

and the MLE of λ and γ can be obtained by solving the two equations

$$\frac{n\gamma}{\lambda} - \sum_{i=1}^{r} t_i - \sum_{i=r+1}^{n} \frac{\displaystyle\int_{t_i^+}^{\infty} x^{\gamma} e^{-\lambda x} dx}{\displaystyle\int_{t_i^+}^{\infty} x^{\gamma - 1} e^{-\lambda x} dx} = 0$$

$$n \log \lambda - \frac{n\Gamma'(\gamma)}{\Gamma(\gamma)} + \sum_{i=1}^{r} \log t_i + \sum_{i=r+1}^{n} \frac{\displaystyle\int_{t_i^+}^{\infty} x^{\gamma - 1} e^{-\lambda x} \log(x)\, dx}{\displaystyle\int_{t_i^+}^{\infty} x^{\gamma - 1} e^{-\lambda x} dx} = 0$$

using the Newton–Raphson iterative procedure.

7.5.3 Estimation of λ, γ, and α in the Extended Generalized Gamma Distribution for Data with or without Censored Observations

The extended generalized gamma distribution has density function defined in (6.4.10),

$$f(t) = |\alpha| \gamma^{\gamma} \lambda^{\alpha\gamma} t^{\alpha\gamma - 1} \frac{\exp[-\gamma(\lambda t)^{\alpha}]}{\Gamma(\gamma)} \qquad t > 0, \quad \gamma > 0, \quad \lambda > 0 \qquad (7.5.19)$$

Let us consider the case $\alpha > 0$. Let $t_1, t_2, \ldots, t_r$ be the uncensored and $t_{r+1}^+, \ldots, t_n^+$ the censored observations from n persons and the survival times follow the generalized gamma distribution. Then the likelihood function is

$$l(\lambda, \gamma, \alpha) = n\alpha\gamma \log \lambda + n \log \alpha + n\gamma \log \gamma - n \log \Gamma(\gamma) + \sum_{i=1}^{r} [(\alpha\gamma - 1) \log t_i - \gamma(\lambda t_i)^{\alpha}] + \sum_{i=r+1}^{n} \log \left\{ \int_{t_i^+}^{\infty} x^{\alpha\gamma - 1} \exp[-\gamma(\lambda x)^{\alpha}]\, dx \right\}$$

and the MLE of λ, γ, and α can be obtained by solving the three equations

$$\frac{n\alpha\gamma}{\lambda} - \gamma\alpha\lambda^{\alpha-1}\sum_{i=1}^{r} t_i^{\alpha} - \gamma\alpha\lambda^{\alpha-1}\sum_{i=r+1}^{n}\frac{\displaystyle\int_{t_i^+}^{\infty} x^{\alpha\gamma-1+\alpha}\exp(-\gamma(\lambda x)^{\alpha})\,dx}{\displaystyle\int_{t_i^+}^{\infty} x^{\alpha\gamma-1}\exp(-\gamma(\lambda x)^{\alpha})\,dx} = 0 \qquad (7.5.20)$$

$$n\alpha\log\lambda + n\log\gamma + n - \frac{n\Gamma'(\gamma)}{\Gamma(\gamma)} + \sum_{i=1}^{r}[\alpha\log t_i - (\lambda t_i)^{\alpha}] + \sum_{i=r+1}^{n}\frac{\displaystyle\int_{t_i^+}^{\infty} x^{\alpha\gamma-1}\exp[-\gamma(\lambda x)^{\alpha}][\alpha\log(x) - (\lambda x)^{\alpha}]\,dx}{\displaystyle\int_{t_i^+}^{\infty} x^{\alpha\gamma-1}\exp(-\gamma(\lambda x)^{\alpha})\,dx} = 0 \qquad (7.5.21)$$

$$n\gamma\log\lambda + \frac{n}{\alpha} + \sum_{i=1}^{r}[\gamma\log t_i - \gamma(\lambda t_i)^{\alpha}\log(\lambda t_i)] + \sum_{i=r+1}^{n}\frac{\displaystyle\int_{t_i^+}^{\infty} x^{\alpha\gamma-1}\exp[-\gamma(\lambda x)^{\alpha}][\gamma\log_e(x) - \gamma(\lambda x)^{\alpha}\log(\lambda x)]\,dx}{\displaystyle\int_{t_i^+}^{\infty} x^{\alpha\gamma-1}\exp[-\gamma(\lambda x]^{\alpha})\,dx} = 0 \qquad (7.5.22)$$

using the Newton–Raphson iterative procedure.

If all the observed survival times are uncensored, the respective equations for the MLE of λ, γ, and α can be obtained simply by replacing r with n in (7.5.20)–(7.5.22). The SAS procedure LIFEREG can be used to obtain the MLE of λ, γ, and α in the extended generalized gamma distribution.

Example 7.16 Referring to Example 7.5, for the observed survival data in the file "EXAMPLE.DAT', by changing d = exponential in the SAS code to d = gamma, one can obtain the MLE of the parameters of the extended generalized gamma distribution:

$$\hat{\lambda} = \exp(-\text{INTERCEPT}) \qquad \hat{\alpha} = \frac{\text{SHAPE1}}{\text{SCALE}} \qquad \hat{\gamma} = \frac{1}{\text{SHAPE1}^2}$$

where INTERCEPT, SHAPE1, and SCALE are given by the SAS LIFEREG procedure.

7.6 LOG-LOGISTIC DISTRIBUTION

The log-logistic distribution has the density function

$$f(t) = \frac{\alpha\gamma t^{\gamma-1}}{(1+\alpha t^{\gamma})^2} \tag{7.6.1}$$

and survivorship function

$$S(t) = \frac{1}{1+\alpha t^{\gamma}} \tag{7.6.2}$$

where $t \geqslant 0$, $\alpha > 0$, $\gamma > 0$. Let $t_1, t_2, \ldots, t_r$ be the uncensored and t_{r+1}^{+}, $t_{r+2}^{+}, \ldots, t_n^{+}$ the censored observations from n persons and the survival times follow the log-logistic distribution. Then the MLE of α and γ can be obtained from solving the following two simultaneous equations:

$$r - \alpha\left(2\sum_{i=1}^{r}\frac{t_i^{\gamma}}{1+\alpha t_i^{\gamma}} + \sum_{i=r+1}^{n}\frac{t_i^{+\gamma}}{1+\alpha t_i^{+\gamma}}\right) = 0 \tag{7.6.3}$$

$$\frac{r}{\gamma} + \sum_{i=1}^{r}\log(t_i) - \alpha\left[2\sum_{i=1}^{r}\frac{t_i^{\gamma}\log(t_i)}{1+\alpha t_i^{\gamma}} + \sum_{i=r+1}^{n}\frac{t_i^{+\gamma}\log(t_i^{+})}{1+\alpha t_i^{+\gamma}}\right] = 0 \tag{7.6.4}$$

using the Newton–Raphson iterative procedure. If all the survival times observed are uncensored, the respective equations for the MLE of α and γ can be obtained simply by replacing r with n in (7.6.3) and (7.6.4).

Example 7.17 Referring to Example 7.5, for the observed survival data in file "EXAMPLE.DAT', replacing d = exponential in the SAS code by d = llogistic and accel = exponential in the BMDP code by accel = llogistic, we can obtain the estimated parameters of the log-logistic distribution. If SAS is used, the estimated parameters of the log-logistic distribution are

$$\hat{\alpha} = \exp\left(-\frac{\text{INTERCEPT}}{\text{SCALE}}\right) \quad \text{and} \quad \hat{\gamma} = \frac{1}{\text{SCALE}}$$

where INTERCEPT and SCALE are given by the SAS LIFEREG procedure. If BMDP is used,

$$\hat{\alpha} = \exp\left(-\frac{\text{CONSTANT}}{\text{SCALE}}\right) \quad \text{and} \quad \hat{\gamma} = \frac{1}{\text{SCALE}}$$

where CONSTANT and SCALE are produced by the BMDP procedure 2L.

Example 7.18 Assume that the tumor-free time of the 30 rats in the low-fat diet group in Table 3.4 follows the log-logistic distribution. The estimates of the two parameters from either SAS or BMDP are $\hat{\alpha} = 0.000025484$ and $\hat{\gamma} = 2.01866$. Therefore, from Section 6.5, the median survival time for this group is 188.64 days, and the hazard function approach the peak at 190.37 days.

7.7 OTHER PARAMETRIC SURVIVAL DISTRIBUTIONS

The Gompertz distribution (Section 6.6) has the following survivorship and probability density functions:

$$S(t) = \exp\left[-\frac{e^{\lambda}}{\gamma}(e^{\gamma t} - 1)\right] \tag{7.7.1}$$

$$f(t) = \exp\left[(\lambda + \gamma t) - \frac{1}{\gamma}(e^{\lambda + \gamma t} - e^{\lambda})\right] \tag{7.7.2}$$

7.7.1 Estimation of λ and γ for Data with or without Censored Observations

Assume that $t_1, t_2, \ldots, t_n$ are the observed survival times from n individuals and the survival times follow the Gompertz distribution, without loss of generality, and assume that $t_1, t_2, \ldots, t_r$ are uncensored and $t_r^+, t_{r+2}^+, \ldots, t_n^+$ right-censored. The MLE of λ and γ can be obtained by solving the equations

$$r + \frac{e^{\lambda}}{\gamma}\left\{\sum_{i=1}^{r}[1 - \exp(\gamma t_i)] + \sum_{i=r+1}^{n}[1 + \exp(\gamma t_i^+)]\right\} = 0 \tag{7.7.3}$$

$$\sum_{i=1}^{r} t_i - \frac{e^{\lambda}}{\gamma^2}\left\{\sum_{i=1}^{r}[1 + (\gamma t_i - 1)\exp(\gamma t_i)] + \sum_{i=r+1}^{n}[1 + (\gamma t_i^+ - 1)\exp(\gamma t_i^+)]\right\} = 0 \tag{7.7.4}$$

using the Newton–Raphson iterative procedure.

If all $t_1, t_2, \ldots, t_n$ are uncensored, the MLE of λ and γ can be obtained similarly by replacing r with n in (7.7.3) and (7.7.4). The MLE of the parameters of the other models in Section 6.6 can be obtained in a similar manner.

Bibliographical Remarks

In addition to the papers cited in this chapter, Gross and Clark (1975) have chapters on estimation and inference in the exponential distribution and on the estimation of parameters of three distributions, including the Weibull and

gamma. Mann et al. (1974), Lawless (1982), and Nelson (1982) also provide a chapter on the estimation procedures for survival distributions, including the exponential, Weibull, gamma, and lognormal. A more recent book is by Klein and Moeschberger (1997). Readers with a background in mathematical statistics and an interest in mathematical treatment of estimation procedures are referred to these books.

EXERCISES

7.1 Consider the survival times given in Exercise 8.2. Assuming that they follow the one-parameter exponential distribution, obtain:
(a) The MLE of λ
(b) The MLE of μ
(c) The 95% confidence intervals for λ and μ

7.2 Assuming that the correct entries between errors in Exercise 8.3 follow the two-parameter exponential distribution, obtain:
(a) An estimate of G
(b) The MLE of λ
(c) The MLE of μ
(d) The probability of 100 correct entries between two errors

7.3 Consider the survival data in Exercise 8.5. Obtain the MLE of the parameter(s) and mean survival times, assuming:
(a) A one-parameter exponential distribution
(b) A Weibull distribution

7.4 In a study of deep venous thrombosis, the following blood clot lysis times in hours were recorded from 20 patients: 2, 3, 4, 5.5, 9, 13, 16.5, 17.5, 12.5, 7, 6, 17.5, 11.5, 6, 14, 25, 49, 37.5, 49, and 28. Assume that the blood clot lysis times follow the lognormal distribution.
(a) Obtain MLEs of the parameters μ and σ^2.
(b) Obtain 95% confidence intervals for μ and σ^2.

7.5 Consider the following tumor-free times in days of 10 animals: 2, 3.5, 5, 7, 9, 10, 15, 20, 30, and 40. Assume that the tumor-free times follow the log-logistic distribution. Estimate the parameters α and γ.

CHAPTER 8

Graphical Methods for Survival Distribution Fitting

The use of probability models for survival experience has played an increasingly important role in biomedical sciences. Survival models summarize the survival pattern, suggest further studies, and generate hypotheses. In this chapter we introduce three graphical methods for survival distribution fitting.

In Section 8.1 we discuss the advantages of the graphical techniques. In Section 8.2 we discuss probability plotting, including how to make probability plots and how to estimate parameters from them. In Section 8.3 we discuss the theory and applications of hazard plotting for censored data. In Section 8.4 we introduce the Cox–Snell residual method.

8.1 INTRODUCTION

Graphical methods have long been used for display and interpretation of data because they are simple and effective. Often used in place of or in conjunction with numerical analysis, a plot of data serves a number of purposes simultaneously that no numerical method can. The basic idea of the three graphical methods is to see if the survival time itself, or a function of it, has a linear relationship with the distribution function and the cumulative hazard function of a given parametric distribution, or a function of the distribution function and the cumulative hazard function. If such a linear relationship exists, it can be demonstrated graphically as a straight line. Thus, if one chooses the appropriate distribution and makes a probability, or hazard, plot, the result will be a straight line fit to the data. Parameters of the distribution chosen can be estimated from the probability or hazard plots without tedious numerical calculations. Such estimates may be adequate and useful for preliminary purposes. However, prior information is often not sufficient to choose a suitable distribution, and the plot may not be a straight line. If the plot is not a straight line, there is no need to estimate the parameters and an alternative

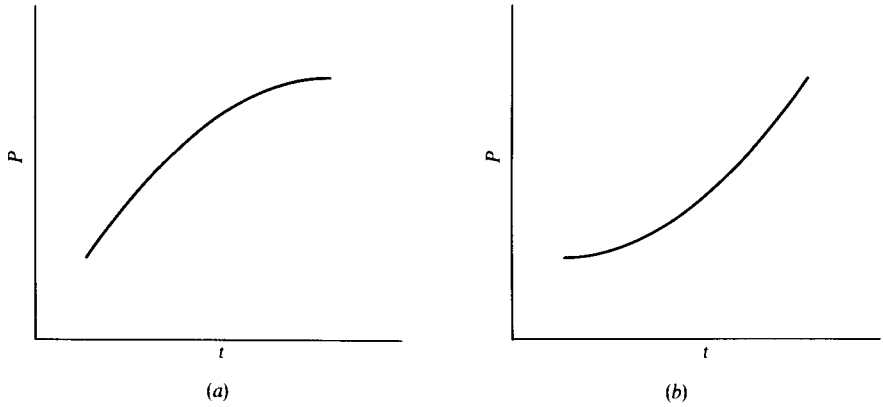


Figure 8.1 Two curved normal probability plots.

distribution may be selected. If the Cox–Snell residual plotting method is used, estimates of the parameters must be obtained first.

A nonlinear plot can provide insight into the data. There are several possible interpretations. First, the wrong theoretical distribution might have been used. Second, the sample might be from a mixture of populations. In the latter case, it is necessary to separate the data accordingly and make a separate plot for each population. If one or two points are way out of line, they might be the results of errors in collecting and recording the data or they might not be from the same population. Other reasons for peculiar looking plots and interpretations of them are discussed by King (1971) and Hahn and Shapiro (1967).

Consider the normal probability plots in Figures 8.1*a* and *b*. The plot in Figure 8.1*a* is convex, indicating that the data have a long tail to the left and could be from a distribution with a negatively skewed density function such as in Figure 8.2*a*. On the contrary, the concave plot in Figure 8.1*b* indicates that

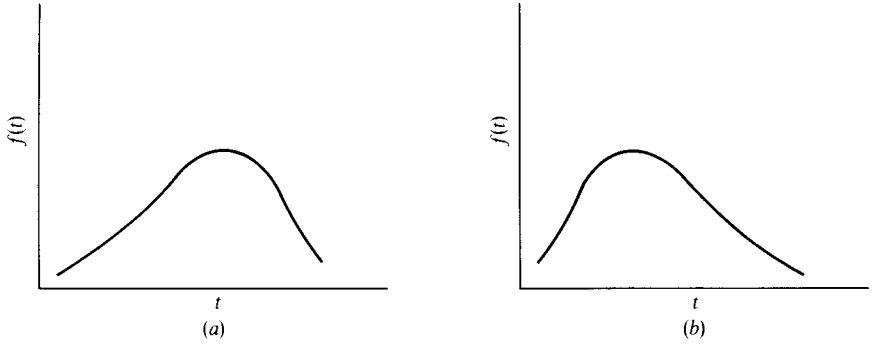


Figure 8.2 Two skewed density functions.

the data have a long tail to the right and could be from a distribution with a positively skewed density function such as in Figure 8.2*b*. From the discussion in Chapter 6, we may try to fit a lognormal or gamma distribution.

The advantages of graphical methods can be summarized as follows:

1. They are fast and simple to use, in contrast with numerical methods, which may be computationally tedious and require considerable analytical sophistication. The additional accuracy of numerical methods is usually not great enough in practice to warrant the effort involved.
2. Probability and hazard plots provide approximate estimates of the parameters of the distribution by simple graphical means.
3. They allow one to assess whether a particular theoretical distribution provides an adequate fit to the data.
4. Peculiar appearance of a plot or points in a plot can provide insight into the data when the reasons for the peculiarities are determined.
5. A graph provides a visual representation of the data that is easy to grasp. This is useful not only for oneself but also in presenting data to others, since a plot allows one to assess conclusions drawn from the data by graphical or numerical means.

8.2 PROBABILITY PLOTTING

The basic ideas in probability plotting are illustrated by the following example.

Example 8.1 Consider the white blood cell counts (WBCs) of 23 pediatric leukemia patients given in Table 8.1, ranging from 8000 to 120,000. A *sample cumulative distribution* is constructed by ordering the data from smallest to largest, as shown in Table 8.1. A sample cumulative distribution curve can then be made by plotting each WBC value versus the percentage of the sample equal to or less than that value. That is, the ith ordered data value in a sample of n values is plotted against the percentage $100i/n$. Note that for tied observations, we compute and plot the sample distribution only for the one with the largest i value. This gives a conservative estimate of the survivorship function. For example, the third value of WBC, 10, is plotted against a percentage of $100 \times 3/23 = 13\%$.

A plot of the cumulative distribution function for most large populations contains many closely spaced values and can be well approximated by a smooth curve drawn though the points. In contrast, a sample cumulative distribution function has a relatively small number of points and thus somewhat ragged appearance. To approximate the population cumulative distribution function, one draws a smooth curve through the data points, obtaining a best fit by eye. Such a curve from the WBC data is given in Figure 8.3. It is an

Table 8.1 Ordered WBCs Data and Sample Cumulative Distribution for Example 8.1

WBC (10^3)	Order, i	Sample Distribution		
		$i/23$	$(i-0.5)/23$	$\Phi^{-1}(F)^a$
8	1			
8	2	0.087	0.065	−1.512
10	3	0.130	0.109	−1.233
15	4	0.174	0.152	−1.027
20	5	0.217	0.196	−0.857
30	6	0.261	0.239	−0.709
50	7			
50	8			
50	9			
50	10			
50	11	0.478	0.457	−0.109
60	12			
60	13	0.565	0.543	0.109
75	14			
75	15	0.652	0.630	0.333
80	16			
80	17	0.739	0.717	0.575
90	18			
90	19			
90	20	0.870	0.848	1.027
100	21	0.913	0.891	1.233
110	22	0.957	0.935	1.512
120	23	1.000	0.978	2.019

[a] $\Phi^{-1}(\cdot)$ denotes the inverse of the standard normal distribution function.

estimate of the cumulative distribution function of the population and is used to obtain estimates and other information about the population.

An estimate of the population median (50th percentile) is obtained by entering the plot on the percentage scale at 50% going horizontally to the fitted line and then vertically down to the data scale to read the estimate of the median. For the WBC data, an estimate of the population median is 65,000. The median is a representative of nominal value for the population since half of the population values are above it and half below. An estimate of any other percentile can be obtained similarly by entering the plot at the appropriate point on the percentage scale going horizontally to the fitted line and then vertically down to the data scale where the estimate is read. For example, an estimate for the 25th percentile is 40,000.

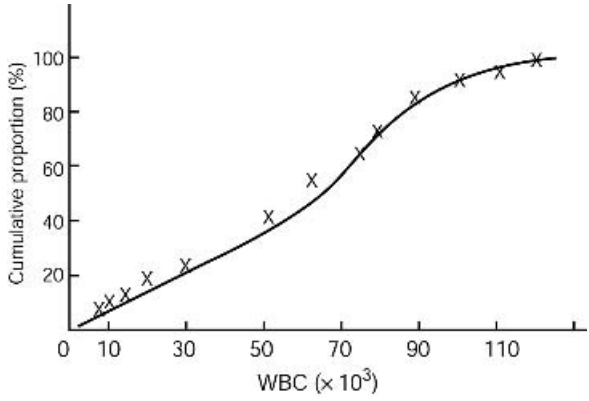


Figure 8.3 Sample cumulative distribution curve of the WBC data.

One can obtain an estimate of the proportion of the population that has a WBC below a specific value in a similar way. For example, to find the proportion of the population with a WBC of 10,000 or less, you enter the plot on the horizontal axis at the given value, 10, go vertically up to the line fitted to the data, and then horizontally to the probability scale, where the estimate of the population proportion is read, 8%. An estimate of the proportion of a population between two given values is obtained by first getting an estimate of the proportion below each value and then taking the difference. For example, the estimate of the population proportion with WBC between 10,000 and 65,000 is $50 - 8 = 42\%$.

As mentioned above, a smooth curve can be fitted by eye to a sample cumulative distribution function to obtain an estimate of the population distribution function. Also, one can fit data with a theoretical cumulative distribution function by using a probability plot and then use this plot to estimate the parameters in the theoretical cumulative distribution function. The distribution may be the normal, lognormal, exponential, Weibull, gamma, or log-logistic. To make a probability plot, one generally uses $(i - 0.5)/n$ or $i/(n + 1)$ to estimate the sample cumulative distribution function at the ith ordered value of the n observations in the sample. The $(i - 0.5)/n$ for the WBC data are given in Table 8.1.

The probability plot is so constructed that if the theoretical distribution is adequate for the data, the graph of a function of t (used as the y-axis) versus a function of the sample cumulative distribution function (used as the x-axis) will be close to a straight line. The parameters of the theoretical distribution can then be estimated from a fitted line. This is carried out as follows.

Step 1. A theoretical distribution for the survival time t has to be selected.

Step 2. The sample cumulative distribution function is estimated by using $(i - 0.5)/n$ or $i/(n + 1)$, $i = 1, 2, \ldots, n$, for the ith ordered t value. For tied

observations have the same value, the sample cumulative distribution function is plotted against only the t with the largest i value.

Step 3. Plot t or a function of it versus the estimated sample cumulative distribution or a function of it.

Step 4. Fit a straight line through the points by eye. The position of the straight line should be chosen to provide a fit to the bulk of the data and may ignore outliers or data points of doubtful validity.

Figure 8.4 gives a normal probability plot of the WBC versus $\Phi^{-1}(F)$, where $\Phi^{-1}(\cdot)$ is the inverse of the standard normal distribution function. The values of $\Phi^{-1}(\hat{F}(\text{WBC}_{(i)}))$ are shown in Table 8.1. The plot is reasonably linear. The straight line fitted by eye in a probability plot can be used to estimate percentiles and proportions within given limits in the same manner as for the sample cumulative distribution curve. In addition, a probability plot provides estimates of the parameters of the theoretical distribution chosen. The mean (or median) WBC estimated from the normal probability plot in Figure 8.4 is 56,000 [at $\Phi^{-1}(F) = 0$, $F = 0.5$ and WBC $= 56{,}000$]. At $\Phi^{-1}(F) = 1$, WBC $= 91{,}000$, which corresponds to the mean plus 1 standard deviation. Thus, the standard deviation is estimated as 35,000.

We now discuss probability plots of the exponential, Weibull, lognormal, and log-logistic distributions.

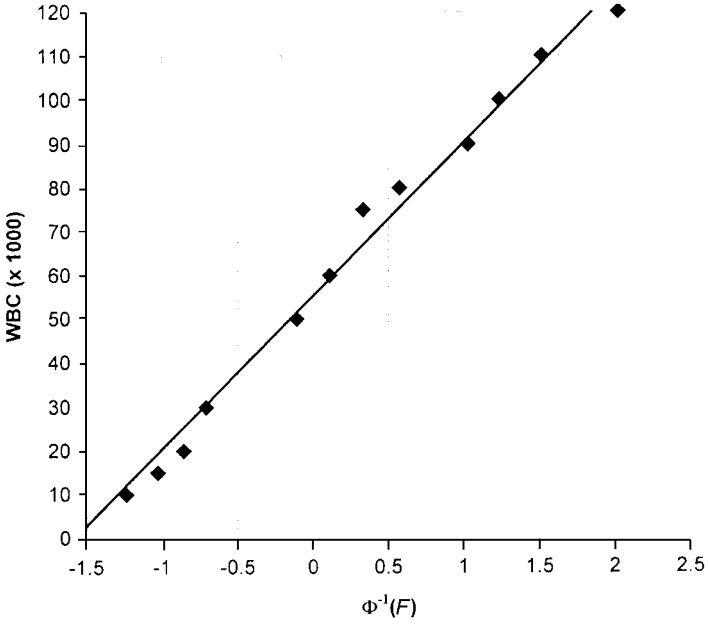


Figure 8.4 Normal probability plot of the WBC data in Example 8.1.

Exponential Distribution

The exponential cumulative distribution function is

$$F(t) = 1 - \exp[-(\lambda t)] \qquad t > 0 \tag{8.2.1}$$

The probability plot for the exponential distribution is based on the relationship between t and $F(t)$, from (8.2.1),

$$t = \frac{1}{\lambda} \log \frac{1}{1 - F(t)} \tag{8.2.2}$$

This relationship is linear between t and the function $\log[1/(1 - F(t))]$. Thus, an exponential probability plot is made by plotting the ith ordered observed survival time $t_{(i)}$ versus $\log[1/(1 - \hat{F}(t_{(i)}))]$, where $\hat{F}(t_{(i)})$ is an estimate of $F(t_{(i)})$, for example, $(i - 0.5)/n$, for $i = 1, \ldots, n$.

From (8.2.2), at $\log\{1/[1 - F(t)]\} = 1$, $t = 1/\lambda$. This fact can be used to estimate $1/\lambda$ and thus λ from the fitted straight line. That is, the value t

Table 8.2 Probability Plotting for Example 8.2

t	Order, i	F, $(i - 0.5)/21$	$\log[1/(1 - F)]$
1	1		
1	2	0.071	0.074
2	3		
2	4	0.167	0.182
3	5	0.214	0.241
4	6		
4	7	0.310	0.370
5	8		
5	9	0.405	0.519
6	10	0.452	0.602
8	11		
8	12	0.548	0.793
9	13	0.595	0.904
10	14		
10	15	0.690	1.173
12	16	0.738	1.340
14	17	0.786	1.540
16	18	0.833	1.792
20	19	0.881	2.128
24	20	0.929	2.639
34	21	0.976	3.738

corresponding to $\log\{1/[1 - F(t)]\} = 1$ is an estimate of the mean $1/\lambda$ and its reciprocal is an estimate of the hazard rate λ.

Example 8.2 Suppose that 21 patients with acute leukemia have the following remission times in months: 1, 1, 2, 2, 3, 4, 4, 5, 5, 6, 8, 8, 9, 10, 10, 12, 14, 16, 20, 24, and 34. We would like to know if the remission time follows the exponential distribution. The ordered remission times $t_{(i)}$ and the $\log\{1/[1 - F(t)]\}$ are given in Table 8.2. The exponential probability plot is shown in Figure 8.5. A straight line is fitted to the points by eye, and the plot indicates that the exponential distribution fits the data very well. At the point $\log[1/(1 - F(t))] = 1.0$, the corresponding t, approximately 9.0 months, is an estimate of the mean $1/\lambda$ and thus an estimate of the hazard rate is $\hat{\lambda} = 1/9 = 0.111$ per month. An alternative is to use (7.2.5) to estimate λ, $\hat{\lambda} = 21/198 = 0.107$, which is very close to the graphical estimate.

Weibull Distribution

The Weibull cumulative distribution function is

$$F(t) = 1 - \exp[-(\lambda t)^{\gamma}] \qquad t > 0, \quad \gamma > 0, \quad \lambda > 0 \tag{8.2.3}$$

The probability plot for the Weibull distribution is based on the relationship

$$\log t = \log\frac{1}{\lambda} + \frac{1}{\gamma}\log\left[\log\frac{1}{1 - F(t)}\right] \tag{8.2.4}$$

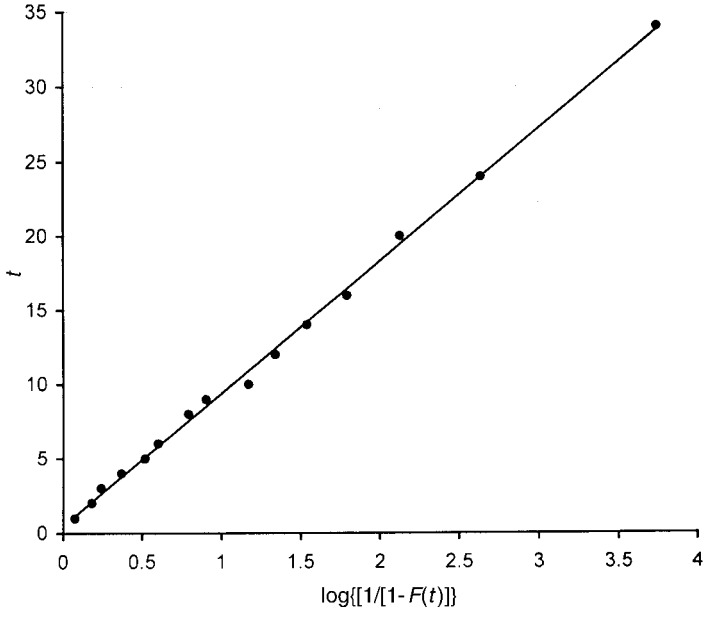


Figure 8.5 Exponential probability plot of the data in Example 8.2.

between t and the cumulative distribution function F of t obtained from (8.2.3). This relationship is linear between $\log t$ and the function $\log(\log\{1/[1-F(t)]\})$. Thus, a Weibull probability plot is a graph of $\log(t_{(i)})$ and $\log(\log\{1/[1-\hat{F}(t_{(i)})]\})$, where $\hat{F}(t_{(i)})$ is an estimate of $F(t_{(i)})$, for example, $(i-0.5)/n$, for $i=1,\ldots,n$.

The shape parameter γ is estimated graphically as the reciprocal of the slope of the straight line fitted to the graph. If the fitted line is appropriate, then at $\log(\log\{1/[1-F(t)]\})=0$, the corresponding $\log(t)$ is an estimate of $\log(1/\lambda)$ from (8.2.4). This fact can be used to estimate $1/\lambda$ and thus λ graphically from a Weibull probability plot. At $\log(\log\{1/[1-F(t)]\})=0.5$, (8.2.4) reduces to $\log t=\log(1/\lambda)+0.5/\gamma$. This equation can be used to estimate γ.

Estimates of the parameters can also be obtained from the method described in Chapter 7 if the Weibull distribution appears to be a good fit graphically. The following hypothetical example illustrates the use of the Weibull probability plot. The small number of observations used in the example is only for illustrative purposes. In practice, many more observations are needed to identify an appropriate theoretical model for the data.

Example 8.3 Six mice with brain tumors have survival times, in months of 3, 4, 5, 6, 8, and 10. $\text{Log}(t_{(i)})$ plotted against $\log(\log\{1/[1-(i-0.5)/6]\})$ for $i=1,\ldots,6$ is shown in Figure 8.6. A straight line is fitted to the data point by eye. From the fitted line, at $\log(\log\{1/[1-F(t)]\})=0$, the corresponding $\log(t)=1.9$, and thus an estimate of $1/\lambda$ is approximately 6.69 $[=\exp(1.9)]$ months and an estimate of λ is 0.150. At $\log(\log\{1/[1-F(t)]\})=0.5$, the corresponding $\log(t)=2.09$, and thus an estimate of $\gamma=0.5/(2.09-1.9)=2.63$. The maximum likelihood estimates of γ and λ obtained from the SAS procedure LIFEREG are 2.75 and 0.148, respectively. The graphical estimates of γ and λ are close to the MLE.

Lognormal Distribution

If the survival time t follows a lognormal distribution with parameters μ and σ^2, $\log t$ follows the normal distribution with mean μ and variance σ^2. Consequently, $(\log t-\mu)/\sigma$ has the standard normal distribution. Thus, the lognormal distribution function can be written as

$$F(t)=\Phi\left(\frac{\log t-\mu}{\sigma}\right)\qquad t>0 \tag{8.2.5}$$

where $\Phi(\cdot)$ is the standard normal distribution function and μ and σ are, respectively, the mean and standard deviation of $\log t$.

A probability plot for the lognormal distribution is based on the following relationship obtained from (8.2.5):

$$\log t=\mu+\sigma\Phi^{-1}(F(t)) \tag{8.2.6}$$

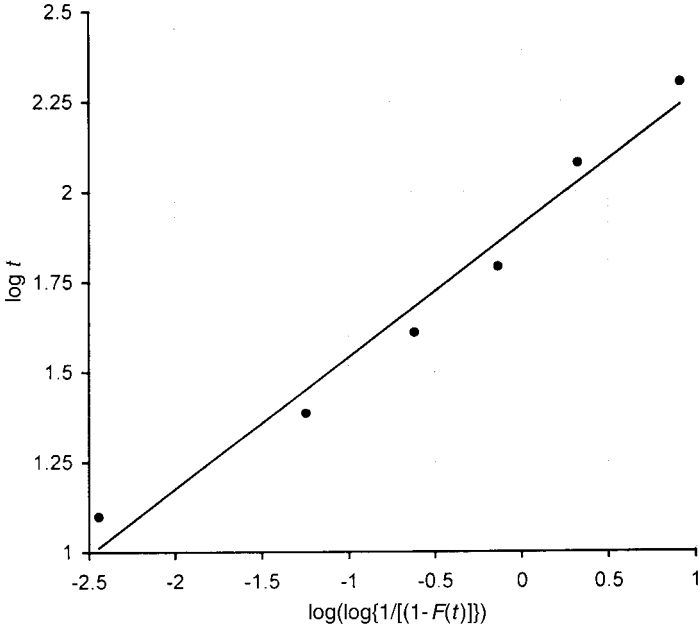


Figure 8.6 Weibull probability plot of the data in Example 8.3.

The function $\Phi^{-1}(\cdot)$ is the inverse of the standard normal distribution function or its $100F$ percentile. This relationship is linear between the value $\log t$ and the function $\Phi^{-1}(F(t))$. Thus, a log-normal probability plot is a graph of $\log(t_{(i)})$ versus $\Phi^{-1}(\hat{F}(t_{(i)}))$, where $\hat{F}(t_{(i)})$ is an estimate of $F(t_{(i)})$. From (8.2.6), at $\Phi^{-1}(F(t)) = 0$, $\log t = \mu$; and at, $\Phi^{-1}(F(t)) = 1$, $\sigma = \log t - \mu$. These facts can be used to estimate μ and σ from a straight line fitted to the graph.

Example 8.4 In a study of a new insecticide, 20 insects are exposed. Survival times in seconds are 3, 5, 6, 7, 8, 9, 10, 10, 12, 15, 15, 18, 19, 20, 22, 25, 28, 30, 40, and 60. Suppose that prior experience indicates that the survival time follows a lognormal distribution; that is, some insects might react to the insecticide very slowly and not die for a long time. The $\log(t_{(i)})$ versus $\Phi^{-1}[(i - 0.5)/20]$, $i = 1, \ldots, 20$, are plotted in Figure 8.7. The plot shows a reasonably straight line. From the fitted line, at $\Phi^{-1}(F(t)) = 0$, $\log t$ is an estimate of μ, which is equal to 2.64, and at $\Phi^{-1}(F(t)) = 1$, $\log t = 3.4$ and thus $\sigma = 3.4 - 2.64 = 0.76$. $\Phi^{-1}(F(t))$ can be obtained by applying Microsoft Excel function NORMSINV.

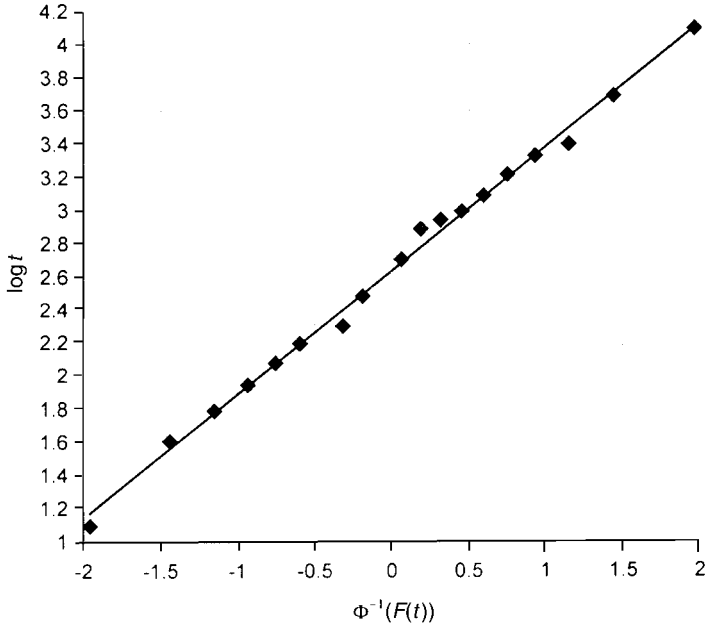


Figure 8.7 Lognormal probability plot of the data in Example 8.4.

Log-Logistic Distribution

The log-logistic distribution function is

$$F(t) = \frac{\alpha t^{\gamma}}{1 + \alpha t^{\gamma}} \qquad t > 0, \quad \gamma > 0, \quad \alpha > 0 \tag{8.2.7}$$

A probability plot for the log-logistic distribution is based on the following relationship obtained from (8.2.7):

$$\log t = \frac{1}{\gamma} \log \left[\frac{1}{1 - F(t)} - 1 \right] - \frac{1}{\gamma} \log \alpha \tag{8.2.8}$$

Thus, a log-logistic probability plot is a graph of $\log(t_{(i)})$ versus $\log(\{1/[1 - \hat{F}(t_{(i)})]\} - 1)$, where $\hat{F}(t_{(i)})$ is an estimate of $F(t_{(i)})$, for example, $(i - 0.5)/n$, for $i = 1, \ldots, n$. From (8.2.8), at $\log\{[1/(1 - F)] - 1\} = 0$, $\log t = -(1/\gamma) \log \alpha$; and at $\log\{[1/(1 - F)] - 1\} = 1$, $\log t = (1/\gamma)(1 - \log \alpha)$. These facts can be used to estimate γ and α. The following example illustrates the log-logistic probability plot.

Example 8.5 Consider the following survival times of 10 experimental rats in days: 8, 15, 25, 30, 50, 90, 95, 100, 150, and 300. Figure 8.8 plots $\log(t_{(i)})$

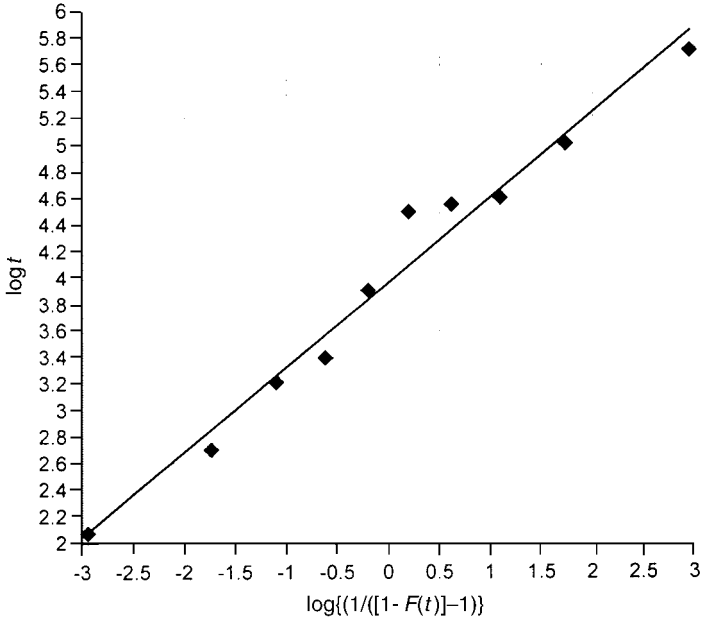


Figure 8.8 Log-logistic probability plot of the data in Example 8.5.

against $\log(\{1/[1-(i-0.5)/10]\}-1)$ for $i=1,\ldots,10$. To estimate γ and α, from the fitted line, at $\log(\{1/[1-F(t)]\}-1)=0$, $\log t=4.0$; and at $\log(\{1/[1-F(t)]\}-1)=1$, $\log t=4.6$. Thus, we have two equations:

$$4.0=-\frac{1}{\gamma}\log\alpha \quad \text{and} \quad 4.6=\frac{1}{\gamma}(1-\log\alpha)$$

From these two equations, $\hat{\gamma}=1.667$ and $\hat{\alpha}=0.0013$.

8.3 HAZARD PLOTTING

Hazard plotting (Nelson 1972, 1982) is analogous to probability plotting, the principal difference being that the survival time (or a function of it) is plotted against the cumulative hazard function (or a function of it) rather than the distribution function. Hazard plotting is designed to handle censored data. Similar to probability plotting, estimates of parameters in the distribution can be determined from the hazard plot with little computational effort.

To determine if a set of survival time with censored observation is from a given theoretical distribution, we construct a hazard plot by plotting the survival time (or a function of it) versus an estimation cumulative hazard (or

a function of it). The cumulative hazard function can be estimated by following the steps below.

Step 1. Order the n observations in the sample from smallest to largest without regard to whether they are censored. If some uncensored and censored observations have the same value, they should be listed in random order. In the list of ordered values, the censored data are each marked with a plus.

Step 2. Number the ordered observations in reverse order, with n assigned to the smallest data value, $n-1$ to the second smallest, and so on. The numbers so obtained are called K *values* or *reverse-order numbers*. For the uncensored observation, K is the number of subjects still at risk at that time.

Step 3. Obtain the corresponding hazard value for each uncensored observation. Censored observations do not have a hazard value. The hazard value for an uncensored observation is $1/K$. This is the fraction of the K individuals who survived that length of time and then failed. It is an observed conditional failure probability for an uncensored observation.

Step 4. For each uncensored observation, calculate the cumulative hazard value. This is the sum of the hazard values of the uncensored observation and of all preceding uncensored observations. For tied uncensored observations, the cumulative hazard is evaluated only at the smallest K among the uncensored observations.

The table in the following example illustrates the procedure.

Example 8.6 Consider the remission data of the 21 leukemia patients receiving 6-MP in Example 3.3. Table 8.3 illustrates the procedure for estimating the cumulative hazard function.

We now discuss the basic idea underlying hazard plotting for the exponential, Weibull, lognormal, and log-logistic distributions.

Exponential Distribution

The exponential distribution has constant hazard function $h(t) = \lambda$. Thus, the cumulative hazard function is

$$H(t) = \lambda t \tag{8.3.1}$$

From (8.3.1), the time can be written as a linear function of the cumulative hazard H,

$$t = \frac{1}{\lambda} H(t) \tag{8.3.2}$$

Thus, t plots as a straight-line function of H. The slope of the fitted line is the

Table 8.3 Estimation of Cumulative Hazard

t	Reversed Order, K	Hazard, $1/K$	Cumulative Hazard, $\hat{H}(t)$
6	21	0.048	
6+	20		
6	19	0.053	
6	18	0.056	0.156
7	17	0.059	0.215
9+	16		
10	15	0.067	0.281
10+	14		
11+	13		
13	12	0.083	0.365
16	11	0.091	0.456
17+	10		
19+	9		
20+	8		
22	7	0.143	0.598
23	6	0.167	0.765
25+	5		
32+	4		
32+	3		
34+	2		
35+	1		

mean survival time $1/\lambda$ of the distribution. More simply, $1/\lambda$ is the value of t when $H(t) = 1$. This fact is used to estimate $1/\lambda$ from an exponential hazard plot.

Example 8.7 Using the estimated cumulative hazard values $\hat{H}(t)$ in Table 8.3, we construct the exponential hazard plot in Figure 3.5 by plotting each exact time t against its corresponding $\hat{H}(t)$. The configuration appears to be reasonably linear, suggesting that the exponential distribution provides a reasonable fit. In Chapter 3 we see that the Weibull distribution gives a better fit than the exponential. We use the data here just to demonstrate how the parameter can be estimated.

To find an estimate for the mean remission time of the leukemia patients, we can use $H(t) = 0.5$ since the time for which $H = 1$ is out of the range of the horizontal axis. At $H(t) = 0.5$, $t = 16.9$, from (8.3.2), an estimate of λ is $0.5/16.9 = 0.0296$. Thus, an estimate of the mean remission time is 34 weeks.

Weibull Distribution

The Weibull distribution has the hazard function

$$h(t) = \lambda\gamma(\lambda t)^{\gamma-1} \qquad t > 0$$

The cumulative hazard function is

$$H(t) = (\lambda t)^{\gamma} \qquad t > 0 \tag{8.3.3}$$

and is plotted in Figure 8.9 for four different values of γ: 0.5, 1, 2, and 4. From (8.3.3), the time t can be written as a function of the cumulative hazard function, that is,

$$t = \frac{1}{\lambda}[H(t)]^{1/\gamma} \tag{8.3.4}$$

Taking the logarithm of (8.3.4), we obtain

$$\log t = \log\frac{1}{\lambda} + \frac{1}{\gamma}\log H(t) \tag{8.3.5}$$

Since $\log t$ is a linear function of $\log H(t)$, a plot of $\log t$ against $\log H(t)$ is a straight line. For $\log H(t) = 0$ or $H(t) = 1$, (8.3.5) reduces to $\log t = \log(1/\lambda)$, and thus the corresponding time t equals $1/\lambda$. This fact is used to estimate $1/\lambda$ and consequently, λ. The slope of the fitted straight line is $1/\gamma$, or at $\log H(t) = 1$, (8.3.5) can be written as $\gamma = 1/(\log t + \log\lambda)$. This equation can be used to estimate γ.

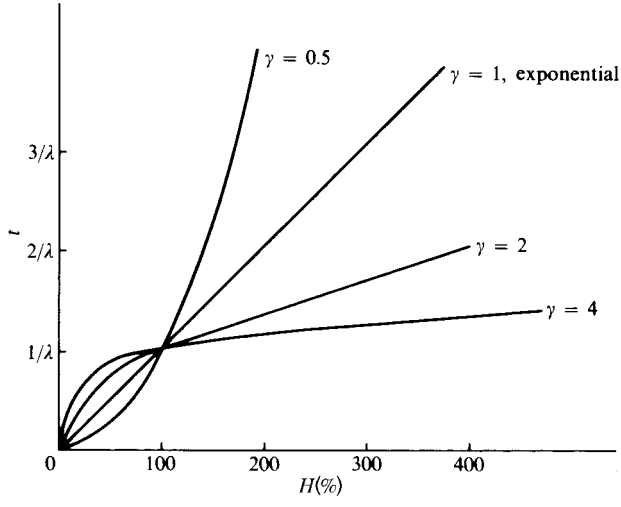


Figure 8.9 Cumulative hazard functions of the Weibull distribution with $\gamma = 0.5, 1, 2, 4$.

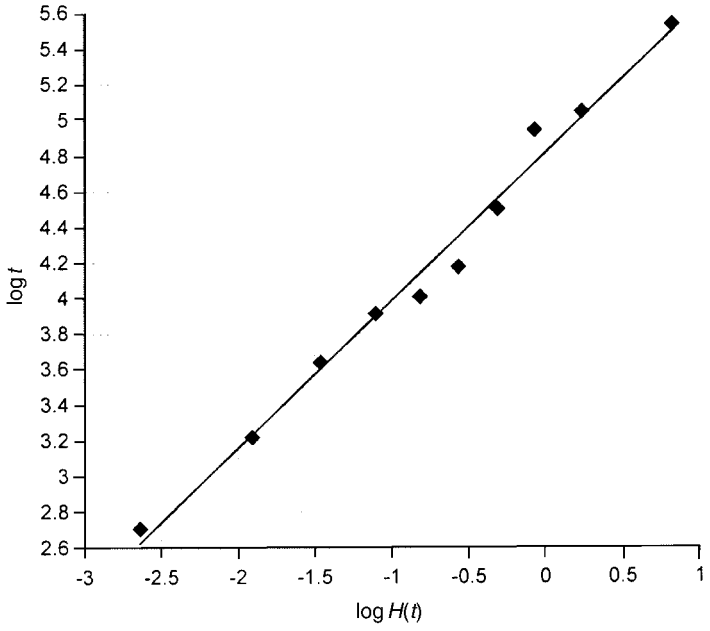


Figure 8.10 Weibull hazard plot of the data in Example 8.8.

Example 8.8 Consider the following survival times in months of 14 patients: 15, 25, 38, 40+, 50, 55, 65, 80+, 90, 140, 150+, 155, 250+, 252. Figure 8.10 is the hazard plot with $\log t$ versus $\log H(t)$ of the data. From the fitted line, at $\log H(t) = 0$, $\log t = 4.8$. Thus, $t = 121.5$ and the estimate of λ is $\hat{\lambda} = 1/t = 0.0082$. Similarly, at, $\log H(t) = 1$, $\log t = 5.6$, and thus $\hat{\gamma} = 1/(5.6 - 4.8) = 1.25$.

Lognormal Distribution

The density function of a lognormal distribution is

$$f(t) = \frac{1}{t\sigma\sqrt{2\pi}} \exp\left[-\frac{1}{2\sigma^2} (\log t - \mu)^2 \right]$$
$$= \frac{1}{t\sigma} g\left(\frac{\log t - \mu}{\sigma} \right) \qquad t > 0 \tag{8.3.6}$$

where $g(x)$ is the standard normal density function. The lognormal cumulative distribution function is

$$F(t) = \Phi\left(\frac{\log t - \mu}{\sigma} \right) \qquad t > 0 \tag{8.3.7}$$

where $\Phi(\cdot)$ is the standard normal distribution function. Thus, by (2.10), the hazard function can be written as

$$h(t) = \frac{\dfrac{1}{t\sigma}\, g\left(\dfrac{\log t - \mu}{\sigma}\right)}{1 - \Phi\left(\dfrac{\log t - \mu}{\sigma}\right)} \tag{8.3.8}$$

The cumulative hazard function, plotted in Figure 8.11 for three values of σ, is

$$H(t) = -\log\left[1 - \Phi\left(\frac{\log t - \mu}{\sigma}\right)\right] \tag{8.3.9}$$

From (8.3.9), the logarithm of the survival time t as a function of the cumulative hazard H is

$$\log t = \mu + \sigma\Phi^{-1}[1 - e^{-H(t)}] \tag{8.3.10}$$

where $\Phi^{-1}(\cdot)$ is the inverse of the standard normal distribution function.

Thus, $\log t$ is a linear function of $\Phi^{-1}[1 - e^{-H(t)}]$. The log-normal hazard plot is a graph of $\log t$ versus $\Phi^{-1}[1 - e^{-H(t)}]$. From (8.3.10), at $\Phi^{-1}[1 - e^{-H(t)}] = 0$, $\log t = \mu$; and at $\Phi^{-1}[1 - e^{-H(t)}] = 1$, $\log t = \mu + \sigma$. These facts can be used to estimate μ and σ.

Example 8.9 Consider the following remission times in months of 18 cancer patients: 4, 5, 6, 7, 8, 9+, 12, 12+, 13, 15, 18, 20, 25, 26+, 28+, 35, 35+, 56. Figure 8.12 gives the log-normal hazard plot. From the fitted line by eye, at $\Phi^{-1}[1 - e^{-H(t)}] = 0$, $\log t = 2.8$; and at $\Phi^{-1}[1 - e^{-H(t)}] = 1$,

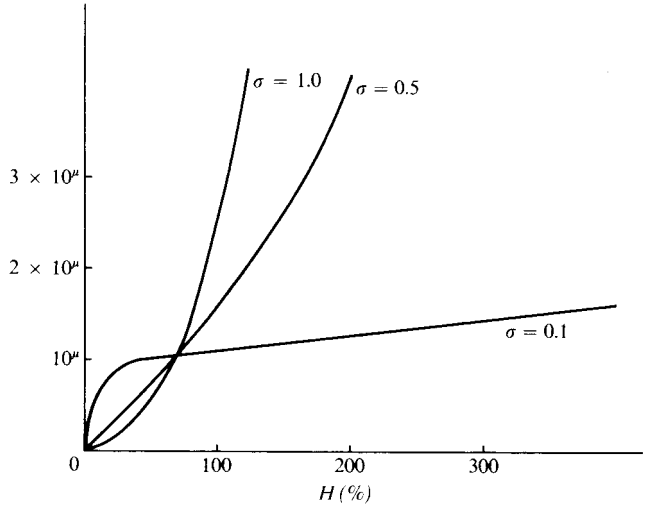


Figure 8.11 Cumulative hazard functions of the lognormal distribution with $\sigma = 0.1$, 0.5, 1.0.

$\log t = 3.76$. Thus, the estimate of μ is 2.8 and the estimate of σ is $3.76 - 2.8 = 0.96$.

Log-Logistic Distribution

The cumulative hazard function of the log-logistic distribution is

$$H(t) = \log(1 + \alpha t^{\gamma})$$

This equation can be written as

$$\log t = \frac{1}{\gamma}\log\{\exp[H(t)] - 1\} - \frac{1}{\gamma}\log\alpha \tag{8.3.11}$$

Thus, $\log t$ is a linear function of $\log\{\exp[H(t)] - 1\}$. A log-logistic hazard plot is a graph of $\log t$ versus $\log\{\exp[H(t)] - 1\}$. From (8.3.11), at $\log\{\exp[H(t)] - 1\} = 0$, $\log t = -(1/\gamma)\log\alpha$; and at $\log\{\exp[H(t)] - 1\} = 1$, $\log t = (1/\gamma) - (1/\gamma)\log\alpha$. These facts can be used to estimate γ and α.

8.4 COX–SNELL RESIDUAL METHOD

The Cox–Snell (1968) residual method can be applied to any parametric model. The Cox–Snell residual r_i for the ith individual with observed survival time t_i, uncensored or censored, is defined as

$$r_i = -\log\hat{S}(t_i) \qquad i = 1, 2, \ldots, n \tag{8.4.1}$$

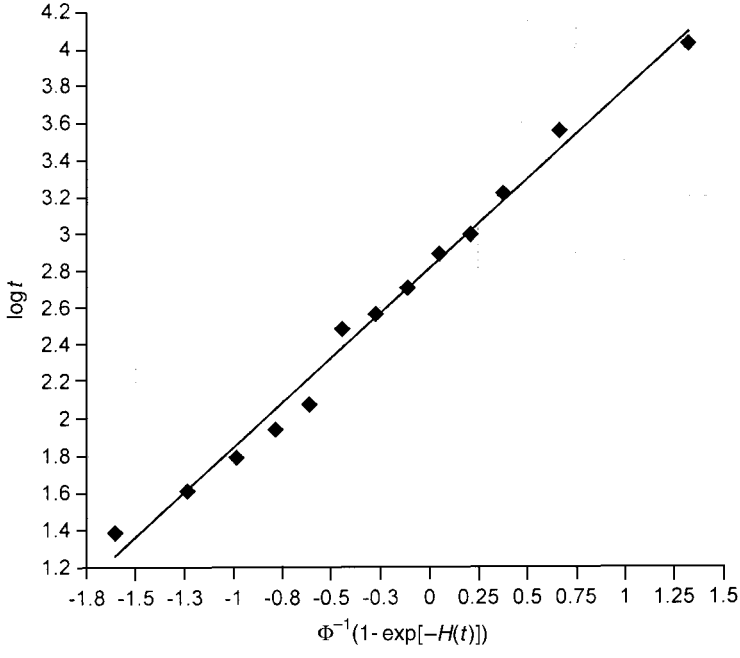


Figure 8.12 Lognormal hazard plot of the data in Example 8.9.

where $\hat{S}(t)$ is the estimated survival function based on the MLE of the parameters. If the observed t_i is censored, the corresponding r_i is also censored. Since the cumulative hazard function $H(t) = -\log S(t)$, the Cox–Snell residual r_i is an estimated cumulated hazard value at t_i. The important property of the Cox–Snell residual is that if the model selected fits the data, r_i's follow the unit exponential distribution with density function $f_R(r) = e^{-r}$.

Let $S_R(r)$ denote the survival function of the Cox–Snell residual r_i. Then $S_R = \int_r^\infty f_R(x)\,dx = \int_r^\infty e^{-x}\,dx = e^{-r}$, and

$$-\log S_R(r) = -\log(e^{-r}) = r \tag{8.4.2}$$

Let $\hat{S}_R(r)$ denote the Kaplan–Meier estimate of $S_R(r)$. It is clear from (8.4.2) that the plot of r_i versus $-\log \hat{S}_R(r_i)$ should be a straight line with unit slope and zero intercept if the fitted survival distribution is appropriate, regardless of the form of the distribution.

The procedure for using Cox–Snell residuals can be summarized as follows.

1. Use the methods shown in Sections 7.1 to 7.7 to find the MLE of the parameters of the selected theoretical distribution.
2. Calculate Cox–Snell residuals $r_i = -\log \hat{S}(t_i)$, $i = 1, 2, \ldots, n$, where $\hat{S}(t_i)$ is the estimated survival function with the MLE of the parameters.
3. Apply the Kaplan–Meier method to estimate the survival function $S_R(r)$ of the Cox–Snell residuals r_i's obtained in step 2, then using the estimate $\hat{S}_R(r)$, calculate $-\log \hat{S}_R(r_i)$, $i = 1, 2, \ldots, n$.
4. Plot r_i versus $-\log \hat{S}_R(r_i)$, $i = 1, 2, \ldots, n$. If the plot is closed to a straight line with unit slope and zero intercept, the fitted distribution is appropriate.

From (8.4.1), if an individual survival time is right-censored, say, t_i^+ and the fitted model is correct, the corresponding Cox–Snell residual $-\log S(t_i^+) = H(t_i^+)$ is smaller than the residual evaluated at an uncensored observation with the same value t_i since $H(t)$ is a monotone-increasing function of t. To take this into account, two modified Cox–Snell residuals have been proposed for censored observations (Crowley and Hu, 1977). One is based on the mean, and the other is based on the median ($=\log 2 = 0.693$) of the unit exponential distribution by assuming that difference between $H(t_i)$ and $H(t_i^+)$ also follows the unit exponential distribution. For a censored observation t_i^+, the modified residual r_i^+ is defined as

$$r_i^+ = r_i + 1 \tag{8.4.3}$$

or

$$r_i^+ = r_i + 0.693 \qquad \text{where } r_i = -\log \hat{S}(t_i) \tag{8.4.4}$$

Example 8.10 Consider the tumor-free time data observed from rats fed with saturated diets in Table 3.4. We select the lognormal distribution for this

set of data for illustrative purposes. Using methods discussed in Chapter 7, the MLE of the parameters obtained are $\mu = 4.76458$ and $\sigma = 0.56053$. We then calculate the Cox–Snell residuals $r_i = -\log S(t_i) = -\log[1 - F(t_i)]$, where $F(t)$ is the distribution function of the lognormal distribution. An easy way to compute r_i for the lognormal distribution is to use the relationship between the normal and lognormal distributions, i.e., the distribution function of the lognormal distribution, $F(t)$, is equivalent to $\Phi[(\log t - \mu)/\sigma]$, where $\Phi(\ )$ is the distribution function of the standard normal distribution. We can use Microsoft Excel function NORMSDIST to calculate $\Phi(t)$. Thus, for the lognormal distribution,

$$S(t_i) = 1 - \Phi([\log(t_i) - 4.76458]/0.56053)$$

Using the specific notation of NORMSDIST, ln for log,

$$r_i = -\ln(1 - \text{normsdist}\{[\ln(t_i) - 4.76458]/0.56053\})$$

The r_i's so obtained are given in Table 8.4. The next step is to obtain the Kaplan–Meier estimate of the survival function $S(r_i)$, and compute $-\log S(r_i)$. These values are also given in Table 8.4.

Figure 8.13 gives the graph of r_i versus $-\log \hat{S}_R(r_i)$, $i = 1, \ldots, 22$. The graph is close to a straight line with unit slope and zero intercept. Therefore, a

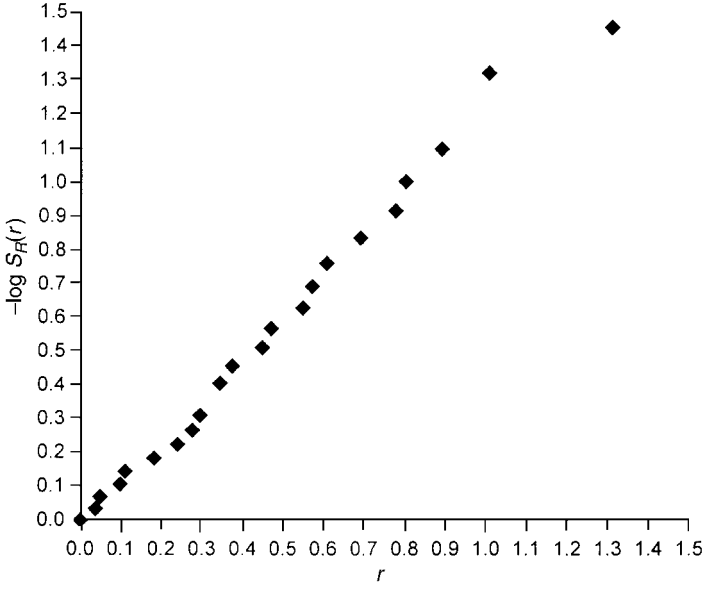


Figure 8.13 Cox–Snell residual plot for the fitted lognormal model on the tumor-free time data for rats fed with saturated diets.

Table 8.4 Kaplan–Meier Estimate of Survivorship Function for the Cox–Snell Residuals from the Fitted Lognormal Model on Tumor-Free Time Data for Rats Fed with Saturated Diets

t	r^a	$\hat{S}_R(r)^b$	$-\log \hat{S}_R(r)$
	0.000	1.000	0.000
43	0.037	0.967	0.034
46	0.049	0.933	0.069
56	0.098	0.900	0.105
58	0.110	0.867	0.143
68	0.181	0.833	0.182
75	0.239	0.800	0.223
79	0.275	0.767	0.266
81	0.294	0.733	0.310
86	0.342	0.667	0.405
86	0.342	0.667	0.405
89	0.373	0.633	0.457
96	0.447	0.600	0.511
98	0.469	0.567	0.568
105	0.548	0.533	0.629
107	0.571	0.500	0.693
110	0.606	0.467	0.762
117	0.690	0.433	0.836
124	0.776	0.400	0.916
126	0.800	0.367	1.003
133	0.889	0.333	1.099
142	1.004	0.267	1.322
142	1.004	0.267	1.322
165	1.305	0.233	1.455
170+	1.371+		
200+	1.769+		
200+	1.769+		
200+	1.769+		
200+	1.769+		
200+	1.769+		
200+	1.769+		

[a] r, ordered Cox–Snell residuals from the fitted lognormal model.
[b] $S_R(r)$, Kaplan–Meier estimate of survivorship function for the Cox–Snell residuals.

lognormal model may be appropriate for the tumor-free times observed. In Chapter 9 (Example 9.2) we will see that the lognormal model was not rejected based on a goodness-of-fit test. Thus the result is consistent with those obtained by using the analytical method. A weakness of the Cox–Snell residual method is that the plot does not indicate the kind of departure the data have from the model selected if the configuration is not linear.

Bibliographical Remarks

Probability plotting has been widely used since Daniel's (1959) classical work on the use of half-normal plot. A quite complete and excellent treatment of probability plotting is given by King (1971). Although examples given are applications to industrial reliability, its interpretation of probability plots of many distributions, such as the uniform, lognormal, Weibull, and gamma, are applicable to biomedical research. Recent applications of probability plotting include Leitner et al. (1986), Horner (1987), Waters et al. (1991), and Tsumagari et al. (2000).

Hazard plotting was developed by Nelson (1972, 1982). Applications included Gore (1983) and Wurpel et al. (1986).

EXERCISES

8.1 Show that the Cox–Snell residuals defined in (8.4.1) follow the unit exponential distribution with density function $f(r) = \exp(-r)$.

8.2 Consider the following survival times of 16 patients in weeks: 4, 20, 22, 25, 38, 38, 40, 44, 56, 83, 89, 98, 110, 138, 145, and 27.

(a) Does the exponential distribution provide a reasonable fit to the survival data? Use the probability plotting technique.

(b) Estimate graphically the parameter λ of the exponential distribution and consequently, the mean survival time.

8.3 To computerize patients' records, a data clerk is hired to transcribe medical data from the patients' charts to computer coding forms. The number of correct entries between errors is listed in chronological order of occurrence over a period of five days as follows: 73, 12, 40, 65, 100, 15, 70, 40, 110, 64, 200, 6, 90, 102, 20, 102, 90, 34. The assumption is that the data clerk, during the five days, would not change her error rate appreciably. Use the technique of probability plotting to evaluate the assumption above. What is your conclusion?

8.4 Twenty-five rats were injected with a give tumor inoculum. Their times, in days, to the development of a tumor of a certain size are given below.

30	53	77	91	118
38	54	78	95	120
45	58	81	101	125
46	66	84	108	134
50	69	85	115	135

Which of the distributions discussed in this chapter provide a reasonable fit to the data? Estimate graphically the parameters of the distribution chosen.

8.5 In a clinical study, 28 patients with cancer of the head and neck did not respond to chemotherapy. Their survival times in weeks are given below.

1.7	8.3	14.0	22.7	6.0+	13.1+
5.1	9.6	15.9	33.0	7.4+	13.4+
5.3	11.3	16.7	3.7+	8.0+	16.1+
6.0	12.1	17.0	5.0+	8.3+	
8.3	12.3	21.0	5.9+	9.1+	

(a) Make a hazard plot for each of the following distributions: exponential, Weibull, lognormal, and log-logistic.
(b) Which distribution provides a reasonable fit to the data? Estimate graphically the parameters of the distribution chosen.

8.6 Thirty-one patients with advanced melanoma treated with combined chemotherapy, immunotherapy, and hormonal therapy have survival times as given below.

26.3+	16.1	24.0	4.3	31.3+
94.0	49.6	77.9	97.6+	17.6+
9.1	27.3	16.6+	7.3	16.3
34.6+	61.9+	3.4	75.6+	
9.4	46.6+	10.9	14.3	
25.7	22.4+	13.0	56.4	
88.7	7.1	64.4+	9.1	

(a) Make a hazard plot for each of the following distributions: exponential, Weibull, lognormal, and log-logistic.
(b) Which distribution provides a reasonable fit to the data? Estimate the parameters of the distribution chosen.

8.7 Consider the survival times of the hypernephroma patients in Exercise Table 3.1 (see Exercise 4.5). Make a hazard plot for the distribution you chose in Exercise 6.8. Did you make a good selection? If not, try two other distributions.

8.8 Consider the following survival times in weeks of 10 mice with injection of tumor cells: 5, 16, 18+, 20, 22+, 24+, 25, 30+, 35, 40+. Make an exponential hazard plot. Does the exponential distribution provide a reasonable fit? If not, is the lognormal distribution better?

8.9 Consider the following survival times in months of 25 patients with cancer of the prostate. Use a graphical method to see if the survival time of prostate cancer patients follows the exponential distribution with $\lambda = 0.01$: 2, 19, 19, 25, 30, 35, 40, 45, 45, 48, 60, 62, 69, 89, 90, 110, 145, 160, 9+, 10+, 20+, 40+, 50+, 110+, 130+.

8.10 Make a log-logistic hazard plot of the following data and estimate the two parameters: 20, 30, 32+, 40, 60, 100, 150, 200+, 300.

CHAPTER 9

Tests of Goodness of Fit and Distribution Selection

In Chapter 8 we discuss three graphical methods for checking if a parametric distribution fits the observed data. Parametric distributions can be grouped into families. First, any given distribution with different parameter values forms a family. Second, if a distribution includes other distributions as its special cases, this distribution is a nesting (larger) family of these distributions. For example, the distributions introduced in Chapter 6 belong to more than one nested family. First, the Weibull distribution reduces to the exponential when $\gamma = 1$. Therefore, the exponential distribution is a special case of the Weibull and the two distributions are said to belong to one family, the Weibull family. Second, consider the standard gamma distribution; when $\gamma = 1$, it reduces to the exponential, and when $\lambda = \frac{1}{2}$ and $\gamma = \frac{1}{2}v$, it becomes the chi-square distribution with v degrees of freedom. Thus, the gamma distribution includes the exponential and chi-square as a family. Now let us consider the generalized gamma distribution. It reduces to the exponential if $\alpha = \gamma = 1$, the Weibull if $\gamma = 1$, the lognormal if $\gamma \to \infty$, and the gamma if $\alpha = 1$. Thus, the generalized gamma distribution includes these four distributions and represents a large family of distributions. The relationship of the generalized gamma distribution to the exponential, Weibull, lognormal, and gamma distributions allows us to evaluate the appropriateness of these distributions relative to each other and to a more general distribution. It is known that the generalized gamma distribution is a special case of the generalized F-distribution and therefore belongs to the generalized F family (Kalbfleisch and Prentice, 1980) Because of its complexity, we do not cover the generalized F family.

In this chapter we discuss several analytical procedures for comparing parametric distributions and assessing goodness of fit. In Section 9.1 we introduce several widely used statistics for testing the appropriateness of a distribution. Readers who are not familiar with linear algebra or are not interested in the mathematical details may skip this section without loss of continuity. In Section 9.2 we discuss statistics for testing whether a distribution

is appropriate by comparing it with other distributions in the same family or a more general family. Section 9.3 covers the selection of a distribution based on Baysian information criteria. Section 9.4 covers the statistics for testing whether a given distribution with known parameters is appropriate. All the test statistics discussed in Sections 9.1 to 9.4 are based on asymptotic likelihood inferences. In Section 9.5 we introduce the test statistic of Hollander and Proschan (1979) for testing whether a distribution with given parameters is appropriate. Computer codes for BMDP or SAS that can be used to carry out the test procedures are provided.

9.1 GOODNESS-OF-FIT TEST STATISTICS BASED ON ASYMPTOTIC LIKELIHOOD INFERENCES

We take the exponential distribution as an example to see how to construct statistics to test whether it is appropriate for the observed survival times. As noted in Chapter 6, the Weibull family with $\gamma = 1$, the gamma family with $\gamma = 1$, and the generalized gamma family with $\alpha = \gamma = 1$ reduce to the exponential distribution. Therefore, to test if the exponential distribution is appropriate for the observed survival time, we can first fit a Weibull distribution and test if $\gamma = 1$, or fit a gamma distribution, then test if $\gamma = 1$, or fit a generalized gamma distribution, then test if $\alpha = \gamma = 1$. Similarly, to test whether the family of Weibull distributions, or the gamma distributions, or the lognormal distributions is appropriate for the survival data observed, we can fit a generalized gamma distribution (their nesting distribution) and then test if $\gamma = 1$, or $\alpha = 1$, or with $\gamma \to \infty$, respectively. Thus, testing the appropriateness of a family of distributions is equivalent to testing whether a subset of the parameters in its nesting distribution equal to some specific values. If the data can be assumed to follow a certain distribution but the values of its parameters are uncertain, we need to test only that the parameters are equal to certain values. In the following, we separately introduce test statistics for testing whether some of the parameters in a distribution are equal to certain values and whether all parameters in a distribution are equal to certain values. Readers who are interested in a detailed discussion of these statistics are referred to Kalbfleisch and Prentice (1980).

9.1.1 Testing a Subset of Parameters in a Distribution

Let $\mathbf{b} = (\mathbf{b}_1, \mathbf{b}_2)$ denote all the parameters in a parametric distribution, where $\mathbf{b}_1$ and $\mathbf{b}_2$ are subsets of parameters, and let the hypothesis be

$$H_0: \mathbf{b}_2 = \mathbf{b}_0 \tag{9.1.1}$$

where $\mathbf{b}_0$ is a vector of specific numbers. Let $\hat{\mathbf{b}}$ be the MLE of $\mathbf{b}$, $\hat{\mathbf{b}}_1(\mathbf{b}_0)$ the MLE of $\mathbf{b}_1$ given $\mathbf{b}_2 = \mathbf{b}_0$, and $\hat{V}_2(\hat{\mathbf{b}})$ the submatrix of the covariance matrix in

(7.1.5), $\hat{V}(\hat{\mathbf{b}})$, corresponding to $\mathbf{b}_2$. Under H_0 and some mild assumptions, both of the following two statistics have an asymptotic chi-square distribution with degrees of freedom equal to the dimension of (or the number of parameters in) $\mathbf{b}_2$.

Log-likelihood ratio statistic:

$$X_L = 2[l(\hat{\mathbf{b}}) - l(\hat{\mathbf{b}}_1(\mathbf{b}_0), \mathbf{b}_0)] \tag{9.1.2}$$

Wald statistic:

$$X_W = (\hat{\mathbf{b}}_2 - \mathbf{b}_0)' \hat{V}_2^{-1}(\hat{\mathbf{b}})(\hat{\mathbf{b}}_2 - \mathbf{b}_0) \tag{9.1.3}$$

If the number of parameters in $\mathbf{b}_2$ is equal to q, for a given significant level α, H_0 is rejected if $X_L > \chi^2_{q,a}$ when the likelihood ratio statistic is used; or if $X_W > \chi^2_{q,\alpha/2}$ or $X_W < \chi^2_{q,1-\alpha/2}$, (two-sided test) or $X_W > \chi^2_{q,\alpha}$ (one-sided test) when the Wald's statistic is used, where $\chi^2_{q,\alpha}$, $\chi^2_{q,\alpha/2}$ and $\chi^2_{q,1-\alpha/2}$ are the $100(1-\alpha)$, $100(1-\alpha/2)$, and $100\alpha/2$ percentile points of the chi-square distribution with q degrees of freedom; that is,

$$P(\chi^2_q > \chi^2_{q,\alpha}) = \alpha \quad \text{and} \quad P(\chi^2_q > \chi^2_{q,\alpha/2}) = P(\chi^2_q < \chi^2_{q,1-\alpha/2}) = \frac{\alpha}{2}$$

Example 9.1 Suppose that we wish to test whether the observed data are from an exponential distribution. We can use a Weibull distribution and test whether its shape parameter, γ, is equal to 1. The Weibull distribution has two parameters, λ and γ; thus $\mathbf{b} = (\lambda, \gamma)$ and the null and alternative hypotheses are:

$$H_0: \gamma = 1 \text{ (the underlying distribution is an exponential distribution)} \tag{9.1.4}$$

$$H_1: \gamma \neq 1 \text{ (the underlying distribution is a Weibull distribution)}$$

Let $\hat{\mathbf{b}} = (\hat{\lambda}, \hat{\gamma})$ be the MLE of $\mathbf{b}$, $l_W(\hat{\mathbf{b}}) = l_W(\hat{\lambda}, \hat{\gamma})$ and $l_E(\hat{\lambda})$ be the log-likelihood of the Weibull and exponential distributions, respectively, $l_E(\hat{\lambda}) \equiv l_W(\hat{\lambda}(1), 1)$, where $\hat{\lambda}(1)$ is the MLE of λ in the Weibull distribution given $\gamma = 1$. The log-likelihood ratio and Wald statistics defined in (9.1.2) and (9.1.3) in this case become

$$X_L = 2[l_W(\hat{\lambda}, \hat{\gamma}) - l_W(\hat{\lambda}(1), 1)] \tag{9.1.5}$$

and

$$X_W = (\hat{\gamma} - 1)\hat{V}_2^{-1}(\hat{\lambda}, \hat{\gamma})(\hat{\gamma} - 1) \tag{9.1.6}$$

respectively, where $\hat{V}_2(\hat{\lambda}, \hat{\gamma})$ is the second diagonal element of the covariance matrix

$$\hat{V}(\hat{\lambda}, \hat{\gamma}) = -\begin{pmatrix} \dfrac{\partial^2 l_W(\hat{\lambda}, \hat{\gamma})}{\partial \lambda^2} & \dfrac{\partial^2 l_W(\hat{\lambda}, \hat{\gamma})}{\partial \lambda \, \partial \gamma} \\ \dfrac{\partial^2 l_W(\hat{\lambda}, \hat{\gamma})}{\partial \gamma \, \partial \lambda} & \dfrac{\partial^2 l_W(\hat{\lambda}, \hat{\gamma})}{\partial \gamma^2} \end{pmatrix}^{-1} \tag{9.1.7}$$

and

$$\hat{V}_2^{-1}(\hat{\lambda}, \hat{\gamma}) = -\frac{[\partial^2 l_W(\hat{\lambda}, \hat{\gamma})/\partial \lambda^2][\partial^2 l_W(\hat{\lambda}, \hat{\gamma})/\partial \gamma^2] - (\partial^2 l_W(\hat{\lambda}, \hat{\gamma})/\partial \lambda \, \partial \gamma)^2}{\partial^2 l_W(\hat{\lambda}, \hat{\gamma})/\partial \lambda^2} \tag{9.1.8}$$

For a given significant-level α, H_0 is rejected if $X_L > \chi^2_{1,\alpha}$, when the likelihood ratio statistic is used; or if $X_W > \chi^2_{1,\alpha/2}$ or $X_W < \chi^2_{1,1-\alpha/2}$, when the Wald statistic is used.

It must be pointed out that failure to reject H_0 in (9.1.4) does not imply that an exponential distribution provides the best fit to the data. On the other hand, rejection of H_0 does not indicate that a Weibull distribution is the choice either. Further testing of other distributions is needed. The details and examples are given in Section 9.2.

Since the gamma and generalized gamma distribution also include the exponential as a special case, similar test statistics can be constructed to test the null hypothesis that the data are from the exponential distribution by using the gamma, the generalized gamma, or the extended generalized gamma distribution.

9.1.2 Testing All Parameters in a Distribution

To test whether all of the parameters in $\mathbf{b}$ equal a given set of known values $\mathbf{b}_0$, the null hypothesis is

$$H_0: \mathbf{b} = \mathbf{b}_0 \tag{9.1.9}$$

and the following three test statistics can be used.

Log-likelihood ratio statistic:

$$X_L = 2[l(\hat{\mathbf{b}}) - l(\mathbf{b}_0)] \tag{9.1.10}$$

Wald statistic:

$$X_W = -(\hat{\mathbf{b}} - \mathbf{b}_0)' \frac{\partial^2 l(\mathbf{b}_0)}{\partial \mathbf{b} \, \partial \mathbf{b}'} (\hat{\mathbf{b}} - \mathbf{b}_0) \qquad \left[\text{or} = -(\hat{\mathbf{b}} - \mathbf{b}_0)' \frac{\partial^2 l(\hat{\mathbf{b}})}{\partial \mathbf{b} \, \partial \mathbf{b}'} (\hat{\mathbf{b}} - \mathbf{b}_0) \right] \tag{9.1.11}$$

Score statistic:

$$X_S = \left[\frac{\partial l(\mathbf{b}_0)}{\partial \mathbf{b}}\right]' \left[-\frac{\partial^2 l(\mathbf{b}_0)}{\partial \mathbf{b}\,\partial \mathbf{b}'}\right]^{-1} \frac{\partial l(\mathbf{b}_0)}{\partial \mathbf{b}} \qquad \left(\text{or} = \left[\frac{\partial l(\mathbf{b}_0)}{\partial \mathbf{b}}\right]' \hat{V}(\hat{\mathbf{b}}) \frac{\partial l(\mathbf{b}_0)}{\partial \mathbf{b}}\right) \tag{9.1.12}$$

where $\hat{V}(\hat{\mathbf{b}})$ is the estimated covariance matrix in (7.1.5). Under H_0 and the assumption that $\hat{\mathbf{b}}$ has approximately multinormal distribution, each of the three statistics has an asymptotic chi-square distribution with p (the dimension of $\mathbf{b}$ or the number of parameters in $\mathbf{b}$) degrees of freedom.

For a given significant-level α, H_0 is rejected if $X_L > \chi^2_{p,\alpha}$, when the likelihood ratio statistic is used; or if $X_W > \chi^2_{p,\alpha/2}$ or $X_W < \chi^2_{p,1-\alpha/2}$, when the Wald statistic is used; or if $X_S > \chi^2_{p,\alpha/2}$ or $X_S < \chi^2_{p,1-\alpha/2}$, when the score statistic is used.

It must be pointed out that rejection of H_0 in (9.1.9) means only that the given distribution with the known parameters $\mathbf{b}_0$, not the family of distributions to which the given distribution belongs, is not appropriate for the observed data. It is possible that a distribution with different $\mathbf{b}_0$ in the family may be appropriate.

9.2 TESTS FOR APPROPRIATENESS OF A FAMILY OF DISTRIBUTIONS

The usual method for testing whether a distribution is appropriate for the observed data is to compare the distribution with a larger or more general family that includes the distribution of interest as a special case (Hagar and Bain, 1970).

Let $l_E(\lambda)$, $l_W(\lambda, \gamma)$, $l_G(\lambda, \gamma)$, $l_{LN}(\mu, \sigma^2)$, and $l_{GG}(\alpha, \lambda, \gamma)$ denote, respectively, the log-likelihood function defined in (7.1.1) based on the exponential, Weibull, gamma, lognormal, and extended generalized gamma distribution, and $l_E(\hat{\lambda})$, $l_W(\hat{\lambda}, \hat{\gamma})$, $l_G(\hat{\lambda}, \hat{\gamma})$, $l_{LN}(\hat{\mu}, \hat{\sigma}^2)$, and $l_{GG}(\hat{\alpha}, \hat{\lambda}, \hat{\gamma})$ denote the respective log-likelihood values where $\hat{\lambda}$, $(\hat{\lambda}, \hat{\gamma})$, $(\hat{\lambda}, \hat{\gamma})$, $(\hat{\mu}, \hat{\sigma}^2)$, and $(\hat{\alpha}, \hat{\lambda}, \hat{\gamma})$ are the MLE. For example, the log-likelihood of the exponential distribution can be obtained from

$$l_E(\hat{\lambda}) = \sum_{i=1}^{r} \log(\hat{\lambda} e^{-\hat{\lambda} t_i}) + \sum_{i=r+1}^{n} \log(e^{-\lambda t_i^+}) = r \log \hat{\lambda} - \hat{\lambda} \sum_{i=1}^{r} t_i - \hat{\lambda} \sum_{i=r+1}^{n} t_i^+$$

for a set of observed survival times $t_1, \ldots, t_r, t_{r+1}^+, \ldots, t_n^+$. The log-likelihood value and the estimated covariance matrix in (7.1.5) and parameters for each of the distributions discussed in Sections 7.2 to 7.6 can be obtained from SAS or BMDP. The results can be used to construct the log-likelihood ratio statistic and the Wald statistic defined in (9.1.2) and (9.1.3). In the following, we

introduce several tests for the appropriateness of a family of distributions based on the log-likelihoods. Construction of the respective Wald statistics is left to the reader as exercises.

1. *Testing the hypothesis that the underlying distribution is exponential.* The null hypothesis is

$$H_0\text{: The underlying distribution is an exponential distribution}$$

If the Weibull distribution is used, testing the null hypothesis above is equivalent to testing the following null and alternative hypotheses:

$H_0: \gamma = 1$ (the underlying distribution is an exponential distribution)

$H_1: \gamma \neq 1$ (the underlying distribution is a Weibull distribution)

Let $\hat{\lambda}(1)$ be the MLE of λ in the Weibull distribution given $\gamma = 1$, the log-likelihood ratio statistic is

$$X_L = 2[l_W(\hat{\lambda}, \hat{\gamma}) - l_W(\hat{\lambda}(1), 1)] \tag{9.2.1}$$

which has an asymptotic chi-square distribution with 1 degree of freedom. For a given level of significance α, H_0 is rejected if $X_L > \chi^2_{1,\alpha}$. Note that $l_W(\hat{\lambda}(1), 1) \equiv l_E(\hat{\lambda})$.

Similarly, a log-likelihood ratio statistic can be constructed by using the gamma or the extended generalized gamma distribution. These will be left to the reader as exercises.

2. *Testing the hypothesis that the underlying distribution is Weibull.* The null hypothesis is

$$H_0\text{: The underlying distribution is a Weibull distribution}$$

We can use the extended generalized gamma distribution and test whether its parameter γ equals 1. Thus the null and alternative hypotheses can be stated as

$H_0: \gamma = 1$ (the underlying distribution is a Weibull distribution)

$H_1: \gamma \neq 1$ (the underlying distribution is an extended generalized gamma distribution)

Let $\hat{\lambda}(1)$ and $\hat{\alpha}(1)$ be the MLE of λ and α in the extended generalized gamma distribution given $\gamma = 1$. According to Section 6.4, an extended generalized

gamma distribution with $\gamma = 1$ is a Weibull distribution. The likelihood ratio statistic is

$$X_L = 2[l_{GG}(\hat{\alpha}, \hat{\lambda}, \hat{\gamma}) - l_{GG}(\hat{\alpha}(1), \hat{\lambda}(1), 1)] \tag{9.2.2}$$

which follows asymptotically the chi-square distribution with 1 degree of freedom. H_0 is rejected at a significance level of α if $X_L > \chi^2_{1,\alpha}$. Note that $l_{GG}(\hat{\alpha}(1), \hat{\lambda}(1), 1) \equiv l_W(\hat{\lambda}, \hat{\gamma})$.

3. *Testing the hypothesis that the underlying distribution is standard gamma.* The null hypothesis is

H_0: The underlying distribution is a gamma distribution

Following the same logic in Section 6.4, the null hypothesis above is equivalent to the following if the extended generalized gamma distribution is used.

$H_0: \alpha = 1$ (the underlying distribution is a standard gamma distribution)

$H_1: \alpha \neq 1$ (the underlying distribution is a generalized gamma distribution).

The likelihood test statistic is

$$X_L = 2[l_{GG}(\hat{\alpha}, \hat{\lambda}, \hat{\gamma}) - l_{GG}(1, \hat{\lambda}(1), \hat{\gamma}(1))] \tag{9.2.3}$$

where $\hat{\gamma}(1)$ and $\hat{\lambda}(1)$ are the MLE of γ and λ given $\alpha = 1$, which has an asymptotic chi-square distribution with 1 degree of freedom under H_0. The rejection rule is the same as that for the exponential or Weibull distribution. Note that $l_{GG}(1, \hat{\lambda}(1), \hat{\gamma}(1)) \equiv l_G(\hat{\lambda}, \hat{\gamma})$.

4. *Testing the hypothesis that the underlying distribution is lognormal.* The null hypothesis is

H_0: the underlying distribution is a lognormal distribution

The log-likelihood test statistic is

$$X_L = 2[l_{GG}(\hat{\alpha}, \hat{\lambda}, \hat{\gamma}) - l_{LN}(\hat{\mu}, \hat{\sigma}^2)]$$

which has an asymptotic chi-square distribution with 1 degree of freedom under H_0. The rejection rule is the same as that for the exponential or Weibull distribution.

For the log-logistic and extended generalized gamma distributions, it can be shown that a generalized F-distribution (Kalbfleisch and Prentice, 1980) includes the exponential, Weibull, lognormal, gamma, generalized gamma,

Table 9.1 Summary of Goodness-of-Fit Tests for Testing Whether a Family of Models Is Appropriate for the Observed Data[a]

Hypothesized Model	LL	X_L	df
Generalized gamma	l_{GG}		
Lognormal	l_{LN}	$2(l_{GG} - l_{LN})$	1
Gamma	l_G	$2(l_{GG} - l_G)$	1
Weibull	l_W	$2(l_{GG} - l_W)$	1
Exponential	l_E	$2(l_{GG} - l_E)$	2
Exponential	l_E	$2(l_G - l_E)$	1
Exponential	l_E	$2(l_W - l_E)$	1

[a] LL, log-likelihood; X_L, likelihood ratio chi-square statistic; df, degrees of freedom.

extended generalized gamma, and log-logistic distributions as special cases. Therefore, one can follow the same logic to construct either the log-likelihood ratio or the Wald statistic to test the appropriateness of a family of generalized gamma or log-logistic distributions. However, methods for testing the appropriateness of a generalized F-distribution remain unknown. Unless we can find a more general distribution that includes the generalized F-distribution as a special case, there is no formal way to check whether the generalized F-distribution is appropriate. However, the generalized gamma distribution is a rich family and includes a considerable number of distributions. It should be sufficient for most applications. All the tests introduced in this section are summarized in Table 9.1.

As pointed out in Section 9.1, when using any of the testing procedures above, failure to reject H_0 does not imply that the hypothesized distribution provides a perfect fit to the data. On the other hand, rejection of H_0 does not mean that the distribution under the alternative hypothesis is the best choice either. In practice, with the help of available computer software, it is easy to fit several distributions simultaneously and then select the most appropriate one, usually the simplest one, as the final choice for the data. The following examples illustrate the procedure.

Example 9.2 Consider the tumor-free times of the 30 rats that are fed with a saturated diet in Table 3.4. Using SAS, we obtain the MLE of the parameters and the log-likelihoods for the exponential, Weibull, lognormal, and generalized gamma distributions. The results are given in Table 9.2. For example, the MLE of λ in the exponential distribution is 5.054 and the corresponding log-likelihood is -35.359, and the MLE of the two parameters in the Weibull distribution are $\hat{\lambda} = 5.002$ and $\hat{\gamma} = 0.500$ and the corresponding log-likelihood

Table 9.2 Goodness-of-Fit Tests Based on Asymptotic Likelihood Inference for the Tumor-Free Time Data from Rats Fed with Saturated Diet in Table 3.4[a]

Model	Estimated Parameters			LL	X_L	p Value	BIC	AIC
	A[b]	B[c]	C[d]					
Exponential	5.054	—	—	−35.359	11.922[e]	<0.001	—	—
Exponential	5.054	—	—	−35.359	19.762[f]	<0.001	−37.060	−37.359
Weibull	5.002	0.500	—	−29.398	7.840[f]	0.005	−32.800	−33.398
Lognormal	4.765	0.561	—	−26.641	2.326[f]	0.127	−30.042	−30.641
Extended generalized gamma	4.495	0.527	−1.088	−25.478	—	—	−30.580	−31.478
Log-logistic	4.739	0.332	—	−26.867	—	—	−30.268	−30.867

[a] LL, log-likelihood; X_L, likelihood ratio statistic; p value, $P(X^2 > X_L)$.
[b] $A = -\log \lambda$ for the exponential and the extended generalized gamma, $= -(1/\gamma)\log \lambda$ for the Weibull, $= \mu$ for the lognormal, and $= -(1/\gamma)\log \alpha$ for the log-logistic distribution.
[c] $B = 1/\gamma$ for the Weibull and log-logistic, $= \sigma$ for the lognormal, and $= 1/(\alpha\gamma^{0.5})$ for the extended generalized gamma distribution.
[d] $C = 1/\gamma$ for the extended generalized gamma distribution.
[e] Relative to the Weibull.
[f] Relativew to the extended generalized gamma.

is -29.398. To test the null hypothesis that the underlying distribution is an exponential distribution versus the alternative hypothesis that the underlying distribution is Weibull (or extended generalized gamma), the likelihood ratio test statistic $X_L = 2(35.359 - 29.398) = 11.922$ [or $2(35.359 - 25.478) = 19.762$]. The probability of observing such a chi-square value is < 0.001; therefore, the exponential distribution is rejected and the Weibull or the generalized gamma is preferred.

However, the Weibull distribution is also rejected at the 0.001 level relative to the extended generalized gamma distribution ($X_L = 7.840$, $p < 0.001$). This implies that the extended generalized gamma distribution may be better. However, the extended generalized gamma distribution is not significantly better than the lognormal distribution ($X_L = 2.326$, $p = 0.127$). Thus, among these distributions, the lognormal and extended generalized gamma distributions are our choices. Because of its simplicity, we may select the lognormal distribution as the choice for this set of data.

Example 9.3 Table 9.3 contains a set of remission times from 137 cancer patients. These remission times are a subset of the data from a bladder cancer study and are used here only for illustrative purposes. The results of goodness of fit tests based on asymptotic likelihood inferences are shown in Table 9.4. From this table, we see that the exponential distribution is not rejected relative to the Weibull distribution based on the statistic defined in (9.2.1) ($X_L = 0.638$, $p = 0.425$). The hypothesis that the underlying distribution is exponential versus the alternative hypothesis that the distribution is the extended generalized gamma is rejected ($X_L = 6.772$, $p = 0.034$). Furthermore, the Weibull and lognormal distributions are also rejected in favor of the extended generalized gamma ($X_L = 6.135, 8.120$, $p = 0.013$ and 0.004, respectively). This implies that the exponential distribution may not be an appropriate distribution since the Weibull distribution (its nesting distribution) is rejected. Therefore, we may accept the extended generalized gamma as our final choice of distribution for the data.

9.3 SELECTION OF A DISTRIBUTION USING BIC OR AIC PROCEDURES

The test procedures discussed in Section 9.2 require knowledge of the distribution family to which the distribution of interest belongs. In this section we introduce a simpler selection procedure called the *Baysian information criterion* (BIC; Schwarz, 1978). This criterion is based on the log-likelihood $l(\hat{\mathbf{b}})$, the number of parameters in the distribution (p), and the total number of observations (n). For each candidate distribution, compute

$$r = l(\hat{\mathbf{b}}) - \frac{p}{2}\log n \tag{9.3.1}$$

Table 9.3 Remission Times (Months) of 137 Cancer Patients

t	t	t	t
4.50	32.15	3.88	13.80
19.13	4.87	3.02+	5.85
14.24	5.71	19.36+	7.09
7.87	7.59	20.28	5.32
5.49	3.02	46.12	4.33+
2.02	4.51	5.17	2.83
9.22	1.05	0.20	8.37
3.82	9.47	36.66	14.77
26.31	79.05	10.06	8.53
4.65+	2.02	4.98	11.98
2.62	4.26	5.06	1.76
0.90	11.25	16.62	4.40
21.73	10.34	12.07	34.26
0.87+	10.66	6.97	2.07
0.51	12.03	0.08	17.12
3.36	2.64	1.40	12.63
43.01	14.76	2.75	7.66
0.81	1.19	7.32	4.18
3.36	8.66	1.26	13.29
1.46	14.83	6.76	23.63
24.80+	5.62	8.60+	3.25
10.86+	18.10	7.62	7.63
17.14	25.74	3.52	2.87
15.96	17.36	9.74	3.31
7.28	1.35	0.40	2.26
4.33	9.02	5.41	2.69
22.69	6.94	2.54	11.79
2.46	7.26	2.69	5.34
3.48	4.70+	8.26	6.93
4.23	3.70	0.50	10.75
6.54	3.64	5.32	13.11
8.65	3.57	5.09	7.39
5.41	11.64	2.09	
2.23	6.25	7.93	
4.34	25.82	12.02	

where $\hat{\mathbf{b}}$ denotes the MLE of all the parameters in the distribution. The candidate distribution with the largest r value is the distribution that fits the data the best. It has been shown that for some distribution families and under mild assumptions, for sufficiently large n, the distribution selected by the BIC procedure approaches the true underlying distribution, if it exists.

Table 9.4 Goodness-of-Fit Tests Based on Asymptotic Likelihood Inference for Data in Table 9.3[a]

Model	Estimated Parameters			LL	X_L	p Value	BIC	AIC
	A[b]	B[c]	C[d]					
Exponential	2.303	—	—	−198.234	0.638[e]	0.425	—	—
Exponential	2.303	—	—	−198.234	6.772[f]	0.034	−200.694	−200.234
Weibull	2.322	0.949	—	−197.915	6.134[f]	0.013	−202.835	−201.915
Lognormal	1.821	1.090	—	−198.908	8.120[f]	0.004	−203.828	−202.908
Extended generalized gamma	2.087	0.999	0.520	−194.848	—	—	−202.228	−200.848
Log-logistic	1.866	0.591	—	−195.344	—	—	−200.264	−199.344

[a] LL, log-likelihood; X_L, likelihood ratio statistic; p value, $P(X^2 > X_L)$.
[b,c,d] See the footnotes in Table 9.2.
[e] Relative to the Weibull.
[f] Relative to the extended generalized gamma.

In general, the larger the number of parameters p in a distribution, the larger the log-likelihood $l(\hat{\mathbf{b}})$ in (9.3.1). Thus the first term represents the gain by using a distribution with more parameters. But the larger the p, the larger the second term in (9.3.1) is, which represents a penalty by having more parameters in the distribution. Therefore, the BIC provides a balance between the gain and the penalty.

Another widely used criterion is called an *information criterion* (AIC; Akaike, 1969), in which r is defined as

$$r = l(\hat{\mathbf{b}}) - 2p \tag{9.3.2}$$

Example 9.4 The values of the BIC and AIC for the various distributions considered in Examples 9.2 and 9.3 are listed in the last two columns in Tables 9.2 and 9.4. Based on Table 9.2, the lognormal distribution would be selected by either the BIC or AIC procedure, which is consistent with the results obtained in Example 9.2. The results in Table 9.4 show that the log-logistic distribution, rather than the extended generalized gamma distribution, should be selected based on either the BIC or AIC procedure.

9.4 TESTS FOR A SPECIFIC DISTRIBUTION WITH KNOWN PARAMETERS

In this section we introduce the likelihood ratio statistic for testing if the survival data observed follow a given distribution with known parameters. We use the same notations as in Section 9.2. In addition to the exponential, Weibull, lognormal, gamma, generalized gamma distributions, we also consider the log-logistic distribution. Let $l_{LL}(\alpha, \gamma)$ and $l_{LL}(\hat{\alpha}, \hat{\gamma})$ denote its log-likelihood function and the log-likelihood with $(\hat{\alpha}, \hat{\gamma})$, the MLE of (α, γ).

1. *Testing the hypothesis that the underlying distribution is exponential with known parameter* λ_0. The null hypothesis is

H_0: the underlying distribution is the exponential distribution with $\lambda = \lambda_0$

The likelihood ratio test statistic based on (9.1.10) is

$$X_L = 2[l_E(\hat{\lambda}) - l_E(\lambda_0)] \tag{9.4.1}$$

X_L has an asymptotic chi-square distribution with 1 degree of freedom under H_0. H_0 is rejected if $X_L > X^2_{1,\alpha}$, where α is the significance level. Similarly, the Wald test statistic and the score statistic can be derived by following (9.1.11) and (9.1.12). This is left to the reader as exercises.

Example 9.5 Consider the following survival times in weeks of 10 mice with a given tumor: 1, 3, 5, 8, 10+, 15, 18, 19, 22, 25+. We test the following

null hypothesis:

H_0: the underlying distribution of the observed data is exponential with $\lambda = 0.06$

In this case, $n = 10$, $r = 8$, $\Sigma_{i=1}^{r} t_i = 91$, and $\Sigma_{i=r+1}^{n} t_i^+ = 35$. The MLE of λ based on (7.2.16) is

$$\hat{\lambda} = \frac{8}{91 + 35} = 0.0635$$

and $l_E(\hat{\lambda}) = 8(\log 0.0635) - 0.0635(91) - 0.0635(35) = -30.055$. Under H_0, $l_E(\lambda_0) = 8(\log 0.06) - 0.06(91) - 0.06(35) = -30.067$. Thus, following (9.4.1), $X_L = 2[-30.055 - (-30.067)] = 0.024$. $X^2_{1,0.05} = 3.84$; therefore, we cannot reject the null hypothesis that the data are from the exponential distribution with $\lambda = 0.06$.

2. *Testing the hypothesis that the underlying distribution is Weibull with known parameters λ_0 and γ_0.* The null hypothesis is

H_0: the underlying distribution is Weibull with known parameters $\lambda = \lambda_0$ and $\gamma = \gamma_0$

Based on (9.1.10), the likelihood ratio test statistic is

$$X_L = 2[l_W(\hat{\lambda}, \hat{\gamma}) - l_W(\lambda_0, \gamma_0)] \tag{9.4.2}$$

Under H_0, X_L has an asymptotic chi-square distribution with 2 degrees of freedom. H_0 is rejected if $X_L > X^2_{2,\alpha}$ where α is the significance level.

3. *Testing the hypothesis that the underlying distribution is lognormal with known parameters μ_0 and σ_0^2.* Similar to the procedures above, the likelihood ratio test statistic is

$$X_L = 2[l_{LN}(\hat{\mu}, \hat{\sigma}^2) - l_{LN}(\mu_0, \sigma_0^2)] \tag{9.4.3}$$

Under H_0, X_L has an asymptotic chi-square distribution with 2 degrees of freedom.

4. *Testing the hypothesis that the underlying distribution is standard gamma with known parameters λ_0 and γ_0.* The likelihood ratio test statistic is

$$X_L = 2[l_G(\hat{\lambda}, \hat{\gamma}) - l_G(\lambda_0, \gamma_0)] \tag{9.4.4}$$

Under H_0, X_L is asymptotically chi-square distributed with 2 degrees of freedom.

5. *Testing the hypothesis that the underlying distribution is generalized gamma with known parameters* α_0, λ_0, *and* γ_0. The likelihood ratio test statistic is

$$X_L = 2[l_{GG}(\hat{\alpha}, \hat{\lambda}, \hat{\gamma}) - l_{GG}(\alpha_0, \lambda_0, \gamma_0)] \tag{9.4.5}$$

Under H_0, X_L is asymptotically chi-square distributed with 3 degrees of freedom.

6. *Testing the hypothesis that the underlying distribution is log-logistic with known parameters* α_0 *and* γ_0. The likelihood ratio test statistic is

$$X_L = 2[l_{LL}(\hat{\alpha}, \hat{\gamma}) - l_{LL}(\alpha_0, \gamma_0)] \tag{9.4.6}$$

Under H_0, X_L has an asymptotic chi-square distribution with 2 degrees of freedom.

Note that the respective Wald and score statistics can be constructed for these tests by following (9.1.11) and (9.1.12). These are left to the reader as exercises. As noted in Section 9.3, the log-likelihood and estimated covariance matrix and parameters in (9.1.10)–(9.1.12) for each of the distributions discussed in Sections 7.2 to 7.6 can be obtained from SAS or BMDP. The other terms in these test statistics can also be obtained by using SAS or BMDP. The following example illustrates the use of SAS and BMDP.

Example 9.6 To use the likelihood ratio statistic (9.4.1) to test the null hypothesis in Example 9.5, H_0: $\lambda = \lambda_0 = 0.06$, we need to calculate the log-likelihood $l_E(\hat{\lambda})$ and $l_E(\lambda_0)$. $l_E(\hat{\lambda})$ can be obtained by applying either the SAS or BMDP codes in Example 7.5. We now show how to use SAS or BMDP to calculate $l_E(\lambda_0)$. Suppose that the survival data of the 10 mice in Example 9.5 are saved in the file "C:\EXAMPLE.DAT". If SAS is used, we specify that the distribution is exponential by using D = EXPONENTIAL in the "model" statement and letting INTERCEPT = 2.813 $[= -\log \lambda_0 = -\log(0.06)]$. If BMDP is used, we specify the distribution by letting ACCEL = EXPONENTIAL and CONSTANT = 2.813. The following SAS or BMDP codes can be used to obtain the $l_E(\lambda_0)$ and the terms needed for the Wald and score statistics in (9.1.11) and (9.1.12).

SAS code:

```
data w1;
  infile 'c:\example.dat' missover;
  input t cens;
run;
proc lifereg;
  model t*cens(0) = /maxit = 0 covb itprint d = exponential intercept = 2.813;
run;
```

BMDP code:

```
/input      file = 'c:\example.dat' .
            variables = 2.
            format = free.
/print      level = brief.
            cova. iterations.
/variable   names = t, cens.
/form       time = t.
            status = cens.
            response = 1.
/regress    iteration = 0.
            accel = exponential.
            constant = 2.813.
/end
```

Similarly, to obtain the log-likelihood ratio statistic, the Wald and the score statistics in (9.1.10)–(9.1.12) for testing null hypotheses about the parameters of other distributions, we can follow the same procedure but change the D= and ACCEL= statements to reflect the distribution under the null hypothesis. We also need to provide values for the input variables INTERCEPT and SCALE, for Weibull, lognormal, and log-logistic distributions, if SAS is used. For the extended generalized gamma distribution, we need to provide a value for SHAPE1. BMDP does not have a procedure for the gamma distribution. For the Weibull, lognormal, and log-logistic distributions, we need to provide values for CONSTANT and SCALE. All of these input variables are based on the distribution and their relationship to the parameters under the null hypothesis (see notes at the end of each of the SAS or BMDP codes in Section 7.2 to 7.6).

9.5 HOLLANDER AND PROSCHAN'S TEST FOR APPROPRIATENESS OF A GIVEN DISTRIBUTION WITH KNOWN PARAMETERS

Another test for the appropriateness of a parametric distribution with known parameters was proposed by Hollander and Proschan (1979). Let $0 = t_{(0)} < t_{(1)} < t_{(2)} < \cdots < t_{(n)}$ be a set of distinct ordered survival times and some of the $t_{(i)}$'s may be censored. If censored observations are tied with uncensored observations, treat the censored observations of tie as being greater than the uncensored of the tie. Let $S(t)$ be the underlying survivorship function and $S_0(t)$ the survivorship function of the specific distribution. The null hypothesis is

$$H_0: S(t) = S_0(t)$$

Using the Kaplan–Meier product-limit method, $S(t)$ is estimated as

$$\hat{S}(t) = \begin{cases} \prod_{j=1}^{k-1} \left(\dfrac{n-j}{n-j+1} \right)^{\delta_{(j)}} & t_{(k-1)} < t \leqslant t_{(k)}, \quad k = 1, \ldots, n \\ 0 & t > t_{(n)} \end{cases} \tag{9.5.1}$$

where $\delta_{(j)} = 1$ if $t_{(j)}$ is uncensored and $\delta_{(j)} = 0$ if $t_{(j)}$ is censored. Hollander and Proschan's test statistic for the null hypothesis that the data are from a distribution with survivorship function $S(t)$ is

$$C = \sum_{\substack{\text{all uncensored} \\ \text{observations}}} S_0(t_{(i)}) \hat{f}(t_{(i)}) \tag{9.5.2}$$

where $\hat{f}(t_{(i)})$ is the jump of the Kaplan–Meier estimates at consecutive uncensored observation and at the largest observation, uncensored or not,

$$\hat{f}(t_{(i)}) = \frac{1}{n} \prod_{j=1}^{i-1} \left(\frac{n-j+1}{n-j} \right)^{1-\delta_{(j)}}. \tag{9.5.3}$$

Under the null hypothesis,

$$C^* = \frac{\sqrt{n}(C - 0.5)}{\hat{\sigma}} \tag{9.5.4}$$

follows approximately the standard normal distribution, where $\hat{\sigma}$ is an estimate of the standard deviation of C and

$$\hat{\sigma}^2 = \frac{1}{16} \sum_{i=1}^{n} \frac{n}{n-i+1} [S_0^4(t_{(i-1)}) - S_0^4(t_{(i)})] \tag{9.5.5}$$

To test $H_0: S = S_0$ versus $H_1: S > S_0$, we reject H_0 if $C^* < -Z_\alpha$; to test H_0 versus $H_1: S < S_0$, we reject H_0 if $C^* > Z_\alpha$; and to test H_0 versus $H_1: S \neq S_0$, we reject H_0 if $C^* < -Z_{\alpha/2}$ or $C^* > Z_{\alpha/2}$, where Z_α is the upper α percentile point of the standard normal distribution.

The procedure for the calculation of C^* can be summarized as follows.

1. Compute the Kaplan–Meier estimate $\hat{S}(t)$ for each uncensored observation.
2. Compute the jump of the Kaplan–Meier distribution at each $t_{(i)}$ uncensored, that is, $\hat{f}(t_{(i)})$, which is the difference of $\hat{F}(t) = 1 - \hat{S}(t)$ at two consecutive uncensored observations.
3. Compute $S_0(t_{(i)})$ for each observation.

4. Multiply $S_0(t_{(i)})$ by $\hat{f}(t_{(i)})$ and sum over all uncensored $t_{(i)}$'s to obtain C.
5. Compute $\hat{\sigma}^2$ according to (9.5.5) and consequently, C^* according to (9.5.4).

Example 9.7 Consider the survival times in weeks of 10 mice in Example 9.5: 8, 5, 10+, 1, 3, 18, 22, 15, 25+, and 19. We wish to test that the survival time follows an exponential distribution with $\lambda = 0.06$. The null and alternative hypotheses are

$$H_0: S(t) = S_0(t)$$
$$H_1: S(t) \neq S_0(t)$$

where $S_0(t) = \exp(-0.06t)$.

Following the procedure outlined above, we first arrange the observations in ascending order and compute the Kaplan–Meier estimates as shown in column (d) of Table 9.5. The jumps are given in column (e). For example, the first jump is between $\hat{S}(0)$ and $\hat{S}(1)$ or $1 - 0.9 = 0.1$. Column (f) gives the survival function under the null hypothesis, for example, $S_0(3) = \exp(-0.06 \times 3) = 0.835$. Following (9.5.2), column (g) gives the value of $C = 0.4808$. The last three columns are for calculation of the estimated variance of C. Thus,

$$\hat{\sigma}^2 = \frac{1}{16}(1.3166) = 0.0823$$

and

$$C^* = \frac{\sqrt{10}(0.4808 - 0.5)}{\sqrt{0.0823}} = -0.2116$$

For $\alpha = 0.05$, $Z_{\alpha/2} = 1.96$, C^* does not fall in the rejection region. From Table B-1 we obtain that the p value corresponding to $C^* = -0.2116$ is approximately 0.84. Therefore, we conclude that there is insufficient evidence to say that the data are not from an exponential distribution with $\lambda = 0.06$. Figure 9.1, which plots the Kaplan–Meier estimates and the hypothesized theoretical distribution $S_0(t) = \exp(-0.06t)$, demonstrates a close agreement between the two. The result is consistent with that obtained in Example 9.5, where the likelihood ratio test is used.

Bibliographical Remarks

Readers with a background in mathematical statistics and an interest in mathematical details about asymptotic likelihood theory, likelihood ratio, Wald's, and score statistics are referred to Cox (1961, 1962*a*), Atkinson (1970), Hagar and Bain (1970), Cox and Hinkley (1974), and Kalbfleisch and Prentice

Table 9.5 Calculation of Test Statistic C^* for Data in Example 9.7

(a)	(b)	(c)	(d)	(e)	(f)	(g)	(h)	(i)	(j)
$t_{(i)}$	i	$\frac{n-i}{n-i+1}$	$\widehat{S}(t)$	$\widehat{f}(t_{(i)})$	$S_0(t_{(i)})$	(e) × (f)	$S_0^4(t_{(i)})$	$S_0^4(t_{(i-1)}) - S_0^4(t_{(i)})$	$\frac{n}{n-i+1} \times$ (i)
1	1	0.900	0.900	0.100	0.941	0.0941	0.7841	0.2159[a]	0.2159
3	2	0.889	0.800	0.100	0.835	0.0835	0.4861	0.2980	0.3311
5	3	0.875	0.700	0.100	0.741	0.0741	0.3015	0.1846	0.2308
8	4	0.857	0.600	0.100	0.619	0.0619	0.1468	0.1547	0.2210
10+	5	—	—	0	0.549	0	0.0908	0.0560	0.0933
15	6	0.800	0.480	0.120	0.407	0.0560	0.0274	0.0634	0.1268
18	7	0.750	0.360	0.120	0.340	0.0408	0.0134	0.0140	0.0350
19	8	0.667	0.240	0.120	0.320	0.0384	0.0105	0.0029	0.0097
22	9	0.500	0.120	0.120	0.267	0.0320	0.0051	0.0054	0.0270
25+	10	—	—	0	0.223	0	0.0025	0.0026	0.0260
						0.4808			1.3166

[a] $S_0^4(t_{(0)}) = S_0^4(0) = 1$.

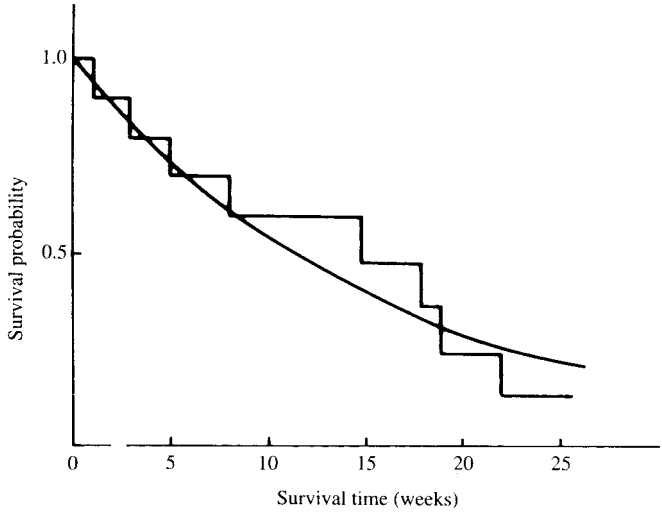


Figure 9.1 Kaplan–Meier estimator $\hat{S}(t)$ and the hypothesized survival function $S_0(t) = \exp(-0.06t)$.

(1980). There have been many papers about the AIC and BIC criteria in the literature since the introduction of AIC by Akaike (1969). The asymptotic properties of the two criteria and their relationships with other criteria were discussed by Akaike (1974), Parzen (1974), Schwarz (1978), Hannan (1979), Shibata (1980), Wang (1984, 1989), Rissanen (1986), and Wei (1992). Interested readers are referred to these papers for details.

When there are no censored observations, the chi-square goodness of fit test introduced by Karl Pearson in 1900 can be used to test any distributional assumption. In addition, tests for the exponential and lognormal (Shapiro and Wilk, 1965a, b) are available.

EXERCISES

9.1 Derive the likelihood ratio and Wald test statistics following (9.1.2) and (9.1.3) for the following null hypothesis:

$$H_0\text{: The underlying distribution is exponential}$$

versus the alternatives

(a) H_1: The underlying distribution is gamma

(b) H_1: The underlying distribution is generalized gamma

9.2 Derive the Wald test statistics following (9.1.3) for the following null and alternative hypotheses

H_0: The underlying distribution is Weibull

H_1: The underlying distribution is generalized gamma

9.3 Derive the respective Wald test statistics by following (9.1.3) for the null hypothesis that the distribution is the standard gamma versus the alternative hypothesis that the distribution is the generalized gamma.

9.4 Derive the Wald and score statistics for testing the null hypotheses in Section 9.4 by following (9.1.11) and (9.1.12).

9.5 Consider the survival time of 28 cancer patients in Exercise 8.5.

(a) Obtain the log-likelihoods for the exponential, Weibull, lognormal, and generalized gamma distributions. Perform the likelihood ratio test and select the best distribution among these four distributions.

(b) Use the BIC and AIC procedures to select the best distribution among the four distributions in part (a) plus the log-logistic distribution.

(c) Compare the results obtained in parts (a) and (b) and those obtained in Exercise 8.5.

9.6 Consider the survival time of 31 patients with advanced melanoma in Exercise 8.6.

(a) Select the best distribution using the likelihood ratio, Wald, and score statistics among the exponential, Weibull, gamma, lognormal, and generalized gamma distributions.

(b) Use the BIC and AIC procedures to do the same as in part (a) with the addition of the log-logistic distribution.

(c) Compare the results obtained in parts (a) and (b) and those obtained in Exercise 8.6.

(d) Compare the MLE of the parameters with those estimates obtained by using the graphical methods in Exercise 8.6.

9.7 Do the same as in Exercise 9.5 for the data in Exercise Table 3.1.

9.8 Consider the following survival time in weeks of 10 mice with injection of tumor cells: 5, 16, 18+, 20, 22+, 24+, 25, 30+, 35, 40+. Do the data follow the exponential distribution with $\lambda = 0.02$?

(a) Use the likelihood ratio test.

(b) Use Hollander and Proschan's test statistic.

(c) Plot the Kaplan–Meier estimator of $S(t)$ and the hypothesized distribution.

9.9 Consider the following survival time in months of 25 patients with cancer of the prostate. Test the hypothesis that the survival time of prostate cancer patients follows the exponential distribution with $\lambda = 0.01$: 2, 19, 19, 25, 30, 35, 40, 45, 45, 48, 60, 62, 69, 89, 90, 110, 145, 160, 9+, 10+, 20+, 40+, 50+, 110+, 130+.

9.10 The Gompertz distribution belongs to the Gompertz–Makeham distribution family and the Gompertz–Makeham distribution (Makeham, 1860) has the following hazard function:

$$h(t) = \alpha + \exp(\lambda + \gamma t) \qquad \alpha \geqslant 0$$

Construct a likelihood ratio statistic and Wald's statistic to test the appropriateness of a Gompertz distribution.

CHAPTER 10

Parametric Methods for Comparing Two Survival Distributions

In Chapter 5 we discussed several nonparametric tests for comparing two survival distributions. If the distributions follow a known model, parametric tests are more powerful than nonparametric tests, but their computation is more tedious. In this chapter we first discuss the likelihood ratio test in general for comparing two survival distributions in Section 10.1. Readers who are not familiar with linear algebra may skip this section without loss of continuity. In Sections 10.2 to 10.4 we present either the likelihood ratio test or other tests for the comparison of two survival patterns that follow the exponential, Weibull, and gamma distributions.

10.1 LIKELIHOOD RATIO TEST FOR COMPARING TWO SURVIVAL DISTRIBUTIONS

Let $x_1, \ldots, x_{n_1}$, and $y_1, \ldots, y_{n_2}$ be the observed exact or censored survival times of n_1 and n_2 subjects from two groups. Assume that the survival times from the two groups follow the same distribution with different parameters. We use the general notation $\mathbf{b} = (b_1, b_2, \ldots, b_p)$ to denote the set of parameters of the distribution, $p \geqslant 1$. Let $l_i(\mathbf{b}_i)$, $i = 1, 2$, denote the log-likelihood function for the observed survival times from each group, where $\mathbf{b}_i = (b_{i1}, \ldots, b_{ik}, b_{ik+1}, \ldots, b_{ip}) = (\mathbf{b}_{i1}, \mathbf{b}_{i2})$, and $\mathbf{b}_{i1} = (b_{i1}, \ldots, b_{ik})$ and $\mathbf{b}_{i2} = (b_{ik+1}, \ldots, b_{ip})$ are two subsets of the p parameters, $i = 1, 2$. Then the joint log-likelihood function for the two groups is $l(\mathbf{b}_1, \mathbf{b}_2) = l_1(\mathbf{b}_1) + l_2(\mathbf{b}_2)$. Let $\hat{\mathbf{b}}_i$ denote the MLE of $\mathbf{b}_i$, and $\hat{\mathbf{b}}_{i2}(\mathbf{b}_0)$ denote the MLE of $\mathbf{b}_{i2}$ given $\mathbf{b}_{i1} = \mathbf{b}_0$, where $\mathbf{b}_0$ is known.

For example, if the survival time of the two groups follows the Weibull distribution with a scale parameter λ and a shape parameter γ. Then $p = 2$, $\mathbf{b}_1 = (\lambda_1, \gamma_1)$, and $\mathbf{b}_2 = (\lambda_2, \gamma_2)$, where λ_1, γ_1 and λ_2, γ_2 are the respective parameters in the two Weibull distributions. Let $l_1(\lambda_1, \gamma_1)$ and $l_2(\lambda_2, \gamma_2)$ denote the log-likelihood functions of the observed survival times from two groups;

then the joint log-likelihood function for the two groups is

$$l(\lambda_1, \gamma_1, \lambda_2, \gamma_2) = l_1(\lambda_1, \gamma_1) + l_2(\lambda_2, \gamma_2)$$

In this case, $\mathbf{b}_{i1}$ may be a singleton λ_i, and similarly, $\mathbf{b}_{i2}$ may be γ_i.

The following tests are widely used in comparing two survival distributions.

Case 1. All parameters are unknown. When $\mathbf{b}_i$, $i = 1, 2$, are unknown, we test the hypothesis

$$H_0: \mathbf{b}_1 = \mathbf{b}_2 = \mathbf{b} \tag{10.1.1}$$

that is, that the two groups have the same survival distribution with equal but unknown parameters $\mathbf{b}$. The log-likelihood ratio test statistic

$$\begin{aligned} X_L &= -2[l(\hat{\mathbf{b}}, \hat{\mathbf{b}}) - l(\hat{\mathbf{b}}_1, \hat{\mathbf{b}}_2)] \\ &= 2[l_1(\hat{\mathbf{b}}_1) + l_2(\hat{\mathbf{b}}_2) - l(\hat{\mathbf{b}}, \hat{\mathbf{b}})] \end{aligned} \tag{10.1.2}$$

has an asymptotic chi-square distribution with p degrees of freedom. For a given significance level α, H_0 is rejected if

$$X_L > \chi^2_{p,\alpha} \tag{10.1.3}$$

or equivalently, if

$$P(\chi^2_p > X_L) < \alpha \tag{10.1.4}$$

where χ^2_p denotes the chi-square random variable with p degrees of freedom, and $\chi^2_{p,\alpha}$ is its $100(1-\alpha)$ percentile points, $P(\chi^2_p > \chi^2_{p,\alpha}) = \alpha$.

In the case of comparing two Weibull distributions, it reduces to

$$H_0: \lambda_1 = \lambda_2 = \lambda \text{ and } \gamma_1 = \gamma_2 = \gamma$$

where λ and γ are unknown,

$$X_L = 2[l_1(\hat{\lambda}_1, \hat{\gamma}_1) + l_2(\hat{\lambda}_2, \hat{\gamma}_2) - l(\hat{\lambda}, \hat{\gamma}, \hat{\lambda}, \hat{\gamma})]$$

and H_0 is rejected if $X_L > \chi^2_{2,\alpha}$, or equivalently, if $P(\chi^2_2 > X_L) < \alpha$.

Case 2. A subset of the parameters of the two survival distributions are known and equal, say, $\mathbf{b}_{11} = \mathbf{b}_{21} = \mathbf{b}_0$, where the values of $\mathbf{b}_0$ are known. The null hypothesis is the equality of the remaining parameters, or

$$H_0: \mathbf{b}_{12} = \mathbf{b}_{22} = \mathbf{b}_{\cdot 2} \tag{10.1.5}$$

where $\mathbf{b}_{\cdot 2}$ is unknown. The log-likelihood ratio statistic is

$$X_L = 2[l_1(\mathbf{b}_0, \hat{\mathbf{b}}_{12}(\mathbf{b}_0)) + l_2(\mathbf{b}_0, \hat{\mathbf{b}}_{22}(\mathbf{b}_0)) - l((\mathbf{b}_0, \hat{\mathbf{b}}_{\cdot 2}(\mathbf{b}_0)), (\mathbf{b}_0, \hat{\mathbf{b}}_{\cdot 2}(\mathbf{b}_0)))] \tag{10.1.6}$$

where $\hat{\mathbf{b}}_{12}(\mathbf{b}_0)$ is the MLE of $\mathbf{b}_{12}$ given $\mathbf{b}_{11} = \mathbf{b}_0$, and so are the others. X_L has an asymptotic chi-square distribution with degrees of freedom equal to the number of parameters in $\mathbf{b}_{12}$ (or $\mathbf{b}_{22}$).

In the case of comparing two Weibull distributions, we may assume that $\lambda_1 = \lambda_2 = \lambda_0$ (or $\gamma_1 = \gamma_2 = \gamma_0$), where the value of λ_0 (or γ_0) is known, and test the null hypothesis

$$H_0: \gamma_1 = \gamma_2 = \gamma \text{ (or } \lambda_1 = \lambda_2 = \lambda)$$

Then

$$X_L = 2[l_1(\lambda_0, \hat{\gamma}_1(\lambda_0)) + l_2(\lambda_0, \hat{\gamma}_2(\lambda_0)) - l(\lambda_0, \hat{\gamma}(\lambda_0), \lambda_0, \hat{\gamma}(\lambda_0))]$$
$$\text{(or } X_L = 2[l_1(\hat{\lambda}_1(\gamma_0), \gamma_0) + l_2(\hat{\lambda}_2(\gamma_0), \gamma_0) - l(\hat{\lambda}(\gamma_0), \gamma_0, \hat{\lambda}(\gamma_0), \gamma_0)]$$

and H_0 is rejected if $X_L > \chi^2_{1,\alpha}$, equivalently, if $P(\chi^2_1 > X_L) < \alpha$.

Case 3. A subset of the parameters of the two survival distributions are equal but unknown, say, if $\mathbf{b}_{11} = \mathbf{b}_{21} = \mathbf{b}_{\cdot 1}$ and the values of $\mathbf{b}_{\cdot 1}$ are unknown. The null hypothesis is the equality of the remaining parameters, or

$$H_0: \mathbf{b}_{12} = \mathbf{b}_{22} = \mathbf{b}_{\cdot 2} \tag{10.1.7}$$

where $\mathbf{b}_{\cdot 2}$ is unknown and needs to be estimated. In addition, $\mathbf{b}_{\cdot 1}$ also needs to be estimated. The log-likelihood ratio statistic,

$$X_L = 2[l((\hat{\mathbf{b}}_{\cdot 1}, \hat{\mathbf{b}}_{12}), (\hat{\mathbf{b}}_{\cdot 1}, \hat{\mathbf{b}}_{22})) - l(\hat{\mathbf{b}}, \hat{\mathbf{b}})] \tag{10.1.8}$$

has an asymptotic chi-square distribution with degrees of freedom equal to the number of parameters in $\mathbf{b}_{12}$ (or $\mathbf{b}_{22}$).

For the case of comparing two Weibull distributions, the derivation of X_L in (10.1.8) is left to the reader as an exercise.

Case 4. A subset of the parameters of the two survival distributions are known but not equal, say, if $\mathbf{b}_{11} = \mathbf{b}_{10}$, $\mathbf{b}_{21} = \mathbf{b}_{20}$, and $\mathbf{b}_{10}$ and $\mathbf{b}_{20}$ are known

but $\mathbf{b}_{10} \neq \mathbf{b}_{20}$. The null hypothesis is the equality of the remaining parameters, or

$$H_0: \mathbf{b}_{12} = \mathbf{b}_{22} = \mathbf{b}_{\cdot 2} \tag{10.1.9}$$

The log-likelihood ratio statistic

$$\begin{aligned} X_L = 2[&l_1(\mathbf{b}_{10}, \hat{\mathbf{b}}_{12}(\mathbf{b}_{10})) + l_2(\mathbf{b}_{20}, \hat{\mathbf{b}}_{22}(\mathbf{b}_{20})) \\ &- l((\mathbf{b}_{10}, \hat{\mathbf{b}}_{\cdot 2}(\mathbf{b}_{10}, \mathbf{b}_{20})), (\mathbf{b}_{20}, \hat{\mathbf{b}}_{\cdot 2}(\mathbf{b}_{10}, \mathbf{b}_{20})))] \end{aligned} \tag{10.1.10}$$

has an asymptotic chi-square distribution with degrees of freedom equal to the number of parameters in $\mathbf{b}_{12}$ or $\mathbf{b}_{22}$.

For the case of comparing two Weibull distributions, the derivation of X_L in (10.1.10) is left to the reader as an exercise.

10.2 COMPARISON OF TWO EXPONENTIAL DISTRIBUTIONS

Suppose that two survival distributions follow the exponential model with parameters λ_1 and λ_2, respectively. Two tests can compare the distributions: the likelihood ratio test and an F-test suggested by Cox (1953). These two tests can test the hypothesis that the two exponential distributions are equal whether or not the samples include censored observations.

10.2.1 Likelihood Ratio Test

Suppose that there are n_1 and n_2 individuals in groups 1 and 2, respectively, $x_1, \ldots, x_{r_1}$ uncensored and $x_{r_1+1}^+, \ldots, x_{n_1}^+$ censored in group 1, and $y_1, \ldots, y_{r_2}$ uncensored and $y_{r_2+1}^+, \ldots, y_{n_2}^+$ censored in group 2. Thus, in group 1, there are r_1 uncensored and $n_1 - r_1$ censored observations. In group 2, there are r_2 uncensored and $n_2 - r_2$ censored observations. If it is known that the survival times of the two groups follow the exponential distribution with density function $f_i(t) = \lambda_i e^{-\lambda_i t}$, $i = 1, 2$, testing the equality of two exponential distributions is equivalent to testing the hypothesis $H_0: \lambda_1 = \lambda_2$. This is because the two exponential distributions are characterized by the two parameters λ_1 and λ_2. Thus, the null hypothesis is $H_0: \lambda_1 = \lambda_2 = \lambda$ and the alternative hypothesis is $H_1: \lambda_1 \neq \lambda_2$. According to (10.1.2), the test statistic for the likelihood ratio test is

$$X_L = -2 \log \frac{L(\hat{\lambda}, \hat{\lambda})}{L(\hat{\lambda}_1, \hat{\lambda}_2)} \tag{10.2.1}$$

where the denominator is the likelihood function for the two groups combined,

$$L(\hat{\lambda}_1, \hat{\lambda}_2) = \hat{\lambda}_1^{r_1}\hat{\lambda}_2^{r_2}\exp\left[-\hat{\lambda}_1\left(\sum_{i=1}^{r_1} x_i + \sum_{i=r_1+1}^{n_1} x_i^+\right) - \hat{\lambda}_2\left(\sum_{i=1}^{r_2} y_i + \sum_{i=r_2+1}^{n_2} y_i^+\right)\right] \tag{10.2.2}$$

and $\hat{\lambda}_1$ and $\hat{\lambda}_2$ are the MLE of λ_1 and λ_2, respectively, from groups 1 and 2. From Section 7.2,

$$\hat{\lambda}_1 = \frac{r_1}{\sum_{i=1}^{r_1} x_i + \sum_{i=r_1+1}^{n_1} x_i^+} \qquad \hat{\lambda}_2 = \frac{r_2}{\sum_{i=1}^{r_2} y_i + \sum_{i=r_2+1}^{n_2} y_i^+} \tag{10.2.3}$$

The numerator in (10.2.1) is the likelihood function for the combined sample under the null hypothesis, that is, $\lambda_1 = \lambda_2 = \lambda$,

$$L(\hat{\lambda}, \hat{\lambda}) = \hat{\lambda}^{r_1+r_2}\exp\left[-\hat{\lambda}\left(\sum_{i=1}^{r_1} x_i + \sum_{i=r_1+1}^{n_1} x_i^+ + \sum_{i=1}^{r_2} y_i + \sum_{i=r_2+1}^{n_2}\right)\right] \tag{10.2.4}$$

where $\hat{\lambda}$ is the MLE of λ obtained from the combined sample,

$$\hat{\lambda} = \frac{r_1 + r_2}{\sum_{i=1}^{r_1} x_i + \sum_{i=r_1+1}^{n_1} x_i^+ + \sum_{i=1}^{r_2} y_i + \sum_{i=r_2+1}^{n_2} y_i^+} \tag{10.2.5}$$

From Section 10.1, X_L has an approximate chi-square distribution with 1 degree of freedom for samples of at least 25 ($n_1 + n_2 \geqslant 25$) under the null hypothesis. For a given significance level α, H_0 is rejected if $X_L > \chi^2_{1,\alpha}$, or equivalently, if $P(\chi_1^2 > X_L) < \alpha$.

The test procedure can be summarized as follows:

1. Compute $\hat{\lambda}_1$ and $\hat{\lambda}_2$ following (10.2.3).
2. Compute $L(\hat{\lambda}_1, \hat{\lambda}_2)$ in (10.2.2) using the given data and $\hat{\lambda}_1$ and $\hat{\lambda}_2$ obtained in step 1.
3. Compute $\hat{\lambda}$ following (10.2.5).
4. Compute $L(\hat{\lambda}, \hat{\lambda})$ in (10.2.4).
5. Compute X_L in (10.2.1). If $X_L > \chi^2_{1,\alpha}$ (Table B-2), reject H_0 and conclude that the two exponential survival distributions are not equal. Otherwise, the data do not provide enough evidence to reject the null hypothesis.

If there are no censored observations in the data, (10.2.1)–(10.2.5) are also applicable simply be letting $n_1 = r_1$, $n_2 = r_2$ and omitting the terms involving

x_i^+ and y_i^+. The likelihood ratio test is primarily for two-sided tests and is difficult to apply to a one-sided test. It is approximate and should be used with caution when the sample size is small. The power of the test, similar to that of other likelihood tests, is not high. That is, if the likelihood ratio test is used regularly, one is more likely not to reject the null hypothesis when the two survival distributions are not equal.

Example 10.1 Consider the remission data of the two treatment groups given in Example 5.1. The remission times in months are as follows:

CMF:	23, 16+, 18+, 20+, 24+
Control:	15, 18, 19, 19, 20

Assume that the two distributions are exponential with parameters λ_1 and λ_2, respectively. Using the likelihood ratio test, we test the following null hypothesis

$$H_0: \lambda_1 = \lambda_2 = \lambda \text{ (the two treatments are equally effective)}$$

against

$$H_1: \lambda_1 \neq \lambda_2 \text{ (the two treatments are not equally effective)}$$

Following the above, we proceed as follows:

1. Compute $\hat{\lambda}_1$ and $\hat{\lambda}_2$ in (10.2.3): In this case, $n_1 = n_2 = 5$, $r_1 = 1$, $r_2 = 5$, $\sum_{i=1}^{r_1} x_i = 23$, $\sum_{i=r_1+1}^{n_1} x_i^+ = 78$, $\sum_{i=1}^{r_2} y_i = 91$, $\sum_{i=r_2+1}^{n_2} y_i^+ = 0$,

$$\hat{\lambda}_1 = \frac{1}{23 + 78} = \frac{1}{101} = 0.0099$$

$$\hat{\lambda}_2 = \frac{5}{91} = 0.0549$$

2. Compute $L(\hat{\lambda}_1, \hat{\lambda}_2)$ in (10.2.2):

$$\begin{aligned} L(\hat{\lambda}_1, \hat{\lambda}_2) &= (0.0099)(0.0549)^5 \exp[-0.0099(101) - 0.0549(91)] \\ &= 1.2290(10)^{-11} \end{aligned}$$

3. Compute $\hat{\lambda}$ in (10.2.5):

$$\hat{\lambda} = \frac{1 + 5}{23 + 78 + 91} = \frac{6}{192} = 0.0313$$

4. Compute $L(\hat{\lambda}_1, \hat{\lambda}_2)$ in (10.2.4):

$$L(\hat{\lambda}_1, \hat{\lambda}_2) = (0.0313)^6 \exp[-0.0313(192)] = 2.3085(10)^{-12}$$

5. Compute X_L in (10.2.1):

$$X_L = -2\log \frac{2.3085(10)^{-12}}{1.2290(10)^{-11}} = -2\log(0.1878) = 3.344$$

From Table B-2 we obtain $\chi^2_{1,0.05} = 3.84$. Thus we cannot reject H_0 at the 0.05 level. Recall that in Chapter 5 the null hypothesis was rejected at the 0.05 level by using the four nonparametric tests.

10.2.2 Cox's *F*-Test for Exponential Distributions

If the times to failure can be assumed to follow the exponential distribution in both treatment groups, an F-test suggested by Cox (1953) can be used to test for treatment differences whether or not censored observations are present. Suppose that we wish to test the hypothesis $H_0: \lambda_1 = \lambda_2$ against either the one-sided alternative $H_1: \lambda_1 < \lambda_2$ (or $H_2: \lambda_1 > \lambda_2$) or the two-sided alternative $H_3: \lambda_1 \neq \lambda_2$. An efficient test is to take $\bar{t}_1/\bar{t}_2$ as having an F-distribution with $(2r_1, 2r_2)$ degrees of freedom, where

$$\bar{t}_1 = \frac{\sum_{i=1}^{r_1} x_i + \sum_{i=r_1+1}^{n_1} x_i^+}{r_1} \tag{10.2.6}$$

$$\bar{t}_2 = \frac{\sum_{i=1}^{r_2} y_i + \sum_{i=r_2+1}^{n_2} y_i^+}{r_2} \tag{10.2.7}$$

The test procedures are (1) for H_1, reject H_0 if $\bar{t}_1/\bar{t}_2 > F_{2r_1,2r_2,\alpha}$; (2) for H_2, reject H_0 if $\bar{t}_1/\bar{t}_2 < F_{2r_1,2r_2,1-\alpha}$; and (3) for H_3, reject H_0 if $\bar{t}_1/\bar{t}_2 > F_{2r_1,2r_2,\alpha/2}$ or $\bar{t}_1/\bar{t}_2 < F_{2r_1,2r_2,1-\alpha/2}$, where α is the significance level and $F_{2r_1,2r_2,\alpha}$ is the upper 100α percentage point of the F-distribution with $(2r_1, 2r_2)$ degrees of freedom. Similarly, the hypothesis that $\lambda_1/\lambda_2 = k$ can be tested by referring $k\bar{t}_1/\bar{t}_2$ to the table of the F-distribution.

When there are no censored observations, that is, $n_1 = r_1$, $n_2 = r_2$, the second terms of the numerators in (10.2.6) and (10.2.7) are zero. Then the test statistic $\bar{t}_1/\bar{t}_2$ has an F-distribution with $(2n_1, 2n_2)$ degrees of freedom.

Confidence intervals for the ratio λ_1/λ_2 can be obtained from the fact that $\lambda_1\bar{t}_1/\lambda_2\bar{t}_2$ has the F-distribution with $(2n_1, 2n_2)$ degrees of freedom. It follows that a $100(1-\alpha)\%$ confidence interval for the ratio of two hazard rates λ_1/λ_2 is

$$\frac{\bar{t}_2}{\bar{t}_1} F_{2r_1,2r_2,1-\alpha/2} < \frac{\lambda_1}{\lambda_2} < \frac{\bar{t}_2}{\bar{t}_1} F_{2r_1,2r_2,\alpha/2} \tag{10.2.8}$$

Example 10.2 Thirty-six patients with glioblastoma multiforme were divided into two groups; the experimental group contained 21 patients who had surgery and chemotherapy, and the control group contained 15 patients who had surgery only. The survival times in weeks are available about one year after the start of the study (Burdette and Gerhan, 1970):

Experimental: 1, 2, 2, 2, 6, 8, 8, 9, 13, 16, 17, 29, 34, 2+,9+, 13+, 22+, 25+, 36+, 43+, 45+

Control: 0, 2, 5, 7, 12, 42, 46, 54, 7+, 11+, 19+, 22+, 30+, 35+, 39+

The hypotheses are

$H_0: \lambda_1 = \lambda_2$ (no difference in survival between experimental and control groups)

$H_1: \lambda_1 < \lambda_2$ (difference in survival favoring experimental group)

In this case, $n_1 = 21$, $n_2 = 15$, $r_1 = 13$, $r_2 = 8$, $\Sigma x_i = 147, \Sigma x_i^+ = 195$, $\Sigma y_i = 168$, and $\Sigma y_i^+ = 163$. Hence

$$\bar{t}_1 = \frac{147 + 195}{13} = 26.308 \qquad \bar{t}_2 = \frac{168 + 163}{8} = 41.375$$

and $\bar{t}_1/\bar{t}_2 = 0.636$ with (26,16) degrees of freedom. For $\alpha = 0.05$, $F_{26,16,0.05}$ is approximately 2.23; hence the hypothesis H_0 is not rejected and the data do not provide enough evidence that the survival time is longer in the experimental group. A 95% confidence interval for the ratio λ_1/λ_2 is

$$\frac{41.375}{26.308}(0.419) < \frac{\lambda_1}{\lambda_2} < \frac{41.375}{26.308}(2.625)$$

or (0.659, 4.128). The estimate of $\hat{\lambda}_1/\hat{\lambda}_2$ according to (10.2.3) is 1.58. Hence the data show that the death rate per week of the experimental group is close to that of the control group.

In Example 10.2, the guarantee time in both groups is zero. In the case where a group has a nonzero guarantee time, it can be subtracted from every observation in the group and the test then applied. Monte Carlo studies (Gehan and Thomas, 1969; Lee et al., 1975) show that when samples are from exponential distributions, with or without censoring, the F-test is the most powerful test among the parametric or nonparametric tests discussed in this chapter and Chapter 5.

10.3 COMPARISON OF TWO WEIBULL DISTRIBUTIONS

It is well known that if the survival time T has a Weibull distribution with shape parameter γ, then T^{γ} has an exponential distribution. Thus, if γ_1 and γ_2 for the two groups are known, the most powerful Cox's F-test described in Section 10.2 can be applied to the transformed observations. However, in practice, γ_1 and γ_2 are probably unknown, and so are the scale parameters, λ_1 and λ_2. In this case, the likelihood ratio tests described in Section 10.1 can be applied to test whether the observed survival times from the two groups have the same Weibull distribution. To test the equality of two Weibull distributions, it suffices to test $\gamma_1 = \gamma_2$ and $\lambda_1 = \lambda_2$. If the hypothesis $\gamma_1 = \gamma_2$ is rejected, we need not test the hypothesis $\lambda_1 = \lambda_2$. If the hypothesis $\gamma_1 = \gamma_2$ is not rejected, we do need to test $\lambda_1 = \lambda_2$. In the following, we introduce an additional two-sample test proposed by Thoman and Bain (1969) for uncensored samples.

Assume that independent random samples of equal size ($n_1 = n_2 = n$) are obtained from Weibull distributions $f_1(t)$ and $f_2(t)$, where

$$f_i(t) = \lambda_i \gamma_i (\lambda_i t)^{\gamma_i - 1} \exp[-(\lambda_i t)^{\gamma_i}] \qquad i = 1, 2 \tag{10.3.1}$$

To test $\gamma_1 = \gamma_2$, we use the property of the maximum likelihood estimator $\hat{\gamma}$ (Thoman et al., 1969; Thoman and Bain, 1969). To test the null hypothesis $H_0: \gamma_1 = \gamma_2$ against $H_1: \gamma_1 > \gamma_2$, we use the fact that $(\hat{\gamma}_1/\gamma_1)/(\hat{\gamma}_2/\gamma_2) = \hat{\gamma}_1/\hat{\gamma}_2$ under H_0. The percentage points of $\hat{\gamma}_1/\hat{\gamma}_2$ are given in Table B-12. We compute the MLE of γ_1 and γ_2, that is, $\hat{\gamma}_1$ and $\hat{\gamma}_2$, and compare $\hat{\gamma}_1/\gamma_2$ with the percentage points for a given α in Table B-12. Reject H_0 at α level if $\hat{\gamma}_1/\hat{\gamma}_2 > l_\alpha$. For example, if $n_1 = n_2 = n = 10$, a computed $\hat{\gamma}_1/\hat{\gamma}_2 > 1.897$ would lead to rejection of H_0 at a significance level of 0.05. For $\alpha \geqslant 0.50$, percentage points l_α can be calculated by using the relationship $l_\alpha = 1/l_{1-\alpha}$.

The procedure described above can be generalized to test $H_0: \gamma_1 = k\gamma_2$ against $H_1: \gamma_1 = k'\gamma_2$. For the case when $k < k'$, the rejection region becomes $\hat{\gamma}_1/\hat{\gamma}_2 > kl_\alpha$, where α is the significance level.

If the hypothesis $H_0: \gamma_1 = \gamma_2$ is rejected, the two Weibull distributions are not the same. However, if the hypothesis is not rejected, we need to test the equality of the two scale parameters λ_1 and λ_2. A test of $H_0: \lambda_1 = \lambda_2$ against $H_1: \lambda_1 < \lambda_2$ suggested by Thoman and Bain (1969) rejects H_0 if

$$G = \tfrac{1}{2}(\hat{\gamma}_1 + \hat{\gamma}_2)(\log \hat{\lambda}_2 - \log \hat{\lambda}_1) > z_\alpha \tag{10.3.2}$$

where z_α is such that $P(G < z_\alpha \mid H_0) = 1 - \alpha$ and $\hat{\gamma}_1$, $\hat{\gamma}_2$, $\hat{\lambda}_1$, and $\hat{\lambda}_2$ are the MLEs of γ_1, γ_2, λ_1, and λ_2 respectively. The percentage points z_α are given in Table B-13. For example, if the common sample size is 10, the hypothesis $H_0: \lambda_1 = \lambda_2$ is rejected if $G \geqslant 0.918$ at significance level 0.05. A test of $H_0: \lambda_1 = \lambda_2$ against $H_1: \lambda_1 > \lambda_2$ can be constructed in a similar fashion. The critical points z_α can be obtained from Table B-13 by using the fact that $z_\alpha = -z_{1-\alpha}$.

Table 10.1 Survival Times of Patients in Two Treatment Groups

Treatment 1	Treatment 2
5, 10, 17, 32, 32, 33, 34, 36, 43, 44, 44, 48, 48, 61, 64, 65, 65, 66, 67, 68, 82, 85, 90, 92, 92, 102, 103, 106, 107, 114, 114, 116, 117, 124, 139, 142, 143, 151, 158, 195	20.9, 32.2, 33.2, 39.4, 40.0, 46.8, 57.3, 58.0, 59.7, 61.1, 61.4, 54.3, 66.0, 66.3, 67.4, 68.5, 69.9, 72.4, 73.0, 73.2, 88.7, 89.3, 91.6, 93.1 94.2, 97.7, 101.6, 101.9, 107.6, 108.0, 109.7, 110.8, 114.1, 117.5, 119.2, 120.3, 133.0, 133.8, 163.3, 165.1

Example 10.3 illustrates the test procedures. The data are adapted and modified from Harter and Moore (1965). Forty observations are generated from a Weibull distribution with $\lambda_1 = 0.01$ and $\gamma_1 = 2$ and another 40 from a Weibull distribution with $\lambda_2 = 0.01$ and $\gamma_2 = 3$. The resulting data are shown in Table 10.1. For illustrative purposes, we consider the two samples as two treatment groups.

Example 10.3 Consider the survival times of the patients in the two treatment groups in Table 10.1. The null hypothesis is that the two populations have the same shape parameter; that is, $H_0: \gamma_1 = \gamma_2$ against $H_1: \gamma_1 < \gamma_2$.

The MLEs are $\hat{\gamma}_1 = 1.945$, $\hat{\gamma}_2 = 2.715$, and hence $\hat{\gamma}_2/\hat{\gamma}_1 = 1.396$, which is significant at the 0.05 level ($l_{0.05} = 1.342$ for $n = 40$) but not significant at the 0.02 level ($l_{0.02} = 1.453$ for $n = 40$). If we choose $\alpha = 0.05$ and reject H_0, the decision is correct. An error of not rejecting H_0 would be committed if an α of 0.02 or 0.01 is chosen. This is because the two shape parameters are very close ($\gamma_1 = 2$, $\gamma_2 = 3$).

To illustrate the procedure of testing the equality of the scale parameters, let us assume that the hypothesis $H_0: \gamma_1 = \gamma_2$ is not rejected. To test $H_0: \lambda_1 = \lambda_2$ against $H_1: \lambda_1 > \lambda_2$, we need the MLEs of λ_1 and λ_2. Harter and Moore obtain $\hat{\lambda}_1 = 0.010776$ and $\hat{\lambda}_2 = 0.010471$. From (10.3.2) we obtain

$$G = \tfrac{1}{2}(1.945 + 2.715)(4.559 - 4.530) = 0.068$$

From Table B-13, the critical region for $n = 40$ is $G > 0.404$. Hence we do not reject H_0. This decision is correct since $\lambda_1 = \lambda_2 = 0.01$. Note that the MLEs of γ_1, γ_2, λ_1, and λ_2 are very close to their real values.

10.4 COMPARISON OF TWO GAMMA DISTRIBUTIONS

Suppose that $x_1, \ldots, x_n$, and $y_1, \ldots, y_n$ are the survival times of patients receiving two different treatments and that they follow the gamma distribution with the density function given in (6.4.1). Let λ_1 and γ_1 be the parameters of

the x population and λ_2 and γ_2 be those of the y population. The likelihood ratio tests introduced in Section 10.1 can be used to test whether the survival times observed from the x population and the y population have different gamma distributions. The estimation of the parameters is quite complicated but can be obtained using commercially available computer programs. In the following we introduce an F-test for testing the null hypothesis $H_0: \lambda_1 = \lambda_2$ against $H_1: \lambda_1 \neq \lambda_2$, under the assumptions that the x_i's and y_i's are exact (uncensored) survival times, and that γ_1 and γ_2 are known (usually assumed equal).

Let $\bar{x}$ and $\bar{y}$ be the sample mean survival times of the two groups. The test is based on the fact that $\bar{x}/\bar{y}$ has the F-distribution with $2n\gamma_1$ and $2n\gamma_2$ degrees of freedom (Rao, 1952). Thus the test procedure is to reject H_0 at the α level if $\bar{x}/\bar{y}$ exceeds $F_{2n\gamma_1, 2n\gamma_2, \alpha/2}$, the $100(\alpha/2)$ percentage point of the F-distribution with $(2n\gamma_1, 2n\gamma_2)$ degrees of freedom. Since the F-table gives percentage points for integer degrees of freedom only, interpolations (linear or bilinear) are necessary when either $2n\gamma_1$ or $2n\gamma_2$ is not an integer.

The following example illustrates the test procedure. The data are adapted and modified from Harter and Moore (1965). They simulated 40 survival times from the gamma distribution with parameters $\gamma_1 = \gamma_2 = \gamma = 2$, $\lambda = 0.01$. The 40 individuals are divided randomly into two groups for illustrative purposes.

Example 10.4 Consider the survival time of the two treatment groups in Table 10.2. The two populations follow the gamma distributions with a common shape parameter $\gamma = 2$. To test the hypothesis $H_0: \lambda_1 = \lambda_2$ against $H_1: \lambda_1 \neq \lambda_2$, we compute $\bar{x} = 181.80$, $\bar{y} = 173.55$, and $\bar{x}/\bar{y} = 1.048$. Under the null hypothesis, $\bar{x}/\bar{y}$ has the F-distribution with (80,80) degrees of freedom. Use $\alpha = 0.05$, $F_{80,80,0.025} \simeq 1.45$. Hence, we do not reject H_0 at the 0.05 level of significance. The result is what we would expect since the two samples are simulated from the same overall sample of 40 with $\lambda = 0.01$.

To test the equality of two lognormal distributions, we use the fact that the logarithmic transformation of the observed survival times follows the normal distributions, and thus we can use the standard tests based on the normal distribution. In general, for other distributions, such as log-logistic and the generalized gamma, the log-likelihood ratio statistics defined in Section 10.1

Table 10.2 Survival Times of 40 Patients Receiving Two Different Treatments

Treatment 1(x)	Treatment 2(y)
17, 28, 49, 98, 119	26, 34, 47, 59, 101,
133, 145, 146, 158, 160,	112, 114, 136, 154, 154,
174, 211, 220, 231, 252,	161, 186, 197, 226, 226,
256, 267, 322, 323, 327	243, 253, 269, 308, 465

can be applied to test whether the survival times observed from two groups have the same distribution. Readers can follow Example 10.2.1 in Section 10.2 and use the respective likelihood functions derived in Chapter 7 to construct the needed tests.

Bibliographical Remarks

In addition to the papers cited in this chapter, readers are referred to Mann et al. (1974), Gross and Clark (1975), Lawless (1982), and Nelson (1982).

EXERCISES

10.1 Derive the likelihood ratio tests in (10.1.8) and (10.1.10) for testing the equality of two Weibull distributions.

10.2 Derive the likelihood ratio test in (10.1.2) for testing the equality of two log-logistic distributions with unknown parameters.

10.3 Consider the remission data of the leukemia patients in Example 3.3. Assume that the remission times of the two treatment groups follow the exponential distribution. Test the hypothesis that the two treatments are equally effective using:
(a) The likelihood ratio test
(b) Cox's F-test
Obtain a 95% confidence interval for the ratio of the two hazard rates.

10.4 For the same data in Exercise 10.3, test the hypothesis that $\lambda_2 = 5\lambda_1$.

10.5 Suppose that the survival time of two groups of lung cancer patients follows the Weibull distribution. A sample of 30 patients (15 from each group) was studied. Maximun likelihood estimates obtained from the two groups are, respectively, $\hat{\gamma}_1 = 3$, $\hat{\lambda}_1 = 1.2$ and $\hat{\gamma}_2 = 2$, $\hat{\lambda}_2 = 0.5$. Test the hypothesis that the two groups are from the same Weibull distribution.

10.6 Divide the lifetimes of 100 strips (delete the last one) of aluminum coupon in Table 6.4 randomly into two equal groups. This can be done by assigning the observations alternately to the two groups. Assume that the two groups follow a gamma distribution with shape parameter $\gamma = 12$. Test the hypothesis that the two scale parameters are equal.

10.7 Twelve brain tumor patients are randomized to receive radiation therapy or radiation therapy plus chemotherapy (BCNU) in a one-year clinical trial. The following survival times in weeks are recorded:

1. Radiation + BCNU: 24, 30, 42, 15+, 40+, 42+
2. Radiation: 10, 26, 28, 30, 41, 12+

Assuming that the survival time follows the exponential distribution, use Cox's F-test for exponential distributions to test the null hypothesis $H_0: \lambda_1 = \lambda_2$ versus the alternative $H_1: \lambda_1 < \lambda_2$.

10.8 Use one of the nonparametric tests discussed in Chapter 5 to test the equality of survival distributions of the experimental and control groups in Example 10.2. Compare your result with that obtained in Example 10.2.

CHAPTER 11

Parametric Methods for Regression Model Fitting and Identification of Prognostic Factors

Prognosis, the prediction of the future of an individual patient with respect to duration, course, and outcome of a disease plays an important role in medical practice. Before a physician can make a prognosis and decide on the treatment, a medical history as well as pathologic, clinical, and laboratory data are often needed. Therefore, many medical charts contain a large number of patient (or individual) characteristics (also called *concomitant variables*, *independent variables*, *covariates*, *prognostic factors*, or *risk factors*), and it is often difficult to sort out which ones are most closely related to prognosis. The physician can usually decide which characteristics are irrelevant, but a statistical analysis is usually needed to prepare a compact summary of the data that can reveal their relationship. One way to achieve this purpose is to search for a theoretical model (or distribution), that fits the observed data and identify the most important factors. These models, usually regression models, extend the methods discussed in previous chapters to include covariates. In this chapter we focus on parametric regression models (i.e., we assume that the survival time follows a theoretical distribution). If an appropriate model can be assumed, the probability of surviving a given time when covariates are incorporated can be estimated.

In Section 11.1 we discuss briefly possible types of response and prognostic variables and things that can be done in a preliminary screening before a formal regression analysis. This section applies to methods discussed in the next four chapters. In Section 11.2 we introduce the general structure of a commonly used parametric regression model, the accelerated failure time (AFT) model. Sections 11.3 to 11.7 cover several special cases of AFT models. Fitting these models often involves complicated and tedious computations and requires computer software. Fortunately, most of the procedures are available in software packages such as SAS and BMDP. The SAS and BMDP code that

can be used to fit the models are given at the end of the examples. Readers may find these codes helpful. Section 11.8 introduces two other models. In Section 11.9 we discuss the model selection methods and goodness of fit tests.

11.1 PRELIMINARY EXAMINATION OF DATA

Information concerning possible prognostic factors can be obtained either from clinical studies designed mainly to identify them, sometimes called *prognostic studies*, or from ongoing clinical trials that compare treatments as a subsidiary aspect. The dependent variable (also called the *response variable*), or the outcome of prediction, may be dichotomous, polychotomous, or continuous. Examples of dichotomous dependent variables are response or nonresponse, life or death, and presence or absence of a given disease. Polychotomous dependent variables include different grades of symptoms (e.g., no evidence of disease, minor symptom, major symptom) and scores of psychiatric reactions (e.g., feeling well, tolerable, depressed, or very depressed). Continuous dependent variables may be length of survival from start of treatment or length of remission, both measured on a numerical scale by a continuous range of values. Of these dependent variables, response to a given treatment (yes or no), development of a specific disease (yes or no), length of remission, and length of survival are particularly common in practice. In this chapter we focus our attention on continuous dependent variables such as survival time and remission duration. Dichotomous and multiple-response dependent variables are discussed in Chapter 14.

A *prognostic variable* (or independent variable) or factor may be either numerical or nonnumerical. Numerical prognostic variables may be discrete, such as the number of previous strokes or number of lymph node metastases, or continuous, such as age or blood pressure. Continuous variables can be made discrete by grouping patients into subcategories (e.g., four age subgroups: <20, 20–39, 40–59, and $\geqslant 60$). Nonnumerical prognostic variables may be unordered (e.g., race or diagnosis) or ordered (e.g., severity of disease may be primary, local, or metastatic). They can also be dichotomous (e.g., a liver either is or is not enlarged). Usually, the collection of prognostic variables includes some of each type.

Before a statistical calculation is done, the data have to be examined carefully. If some of the variables are significantly correlated, one of the correlated variables is likely to be a predictor as good as all of them. Correlation coefficients between variables can be computed to detect significantly correlated variables. In deleting any highly correlated variables, information from other studies has to be incorporated. If other studies show that a given variable has prognostic value, it should be retained.

In the next eight sections we discuss multivariate or regression techniques, which are useful in identifying prognostic factors. The regression techniques involve a function of the independent variables or possible prognostic factors.

The variables must be quantitative, with particular numerical values for each patient. This raises no problem when the prognostic variables are naturally quantitative (e.g., age) and can be used in the equation directly. However, if a particular prognostic variable is qualitative (e.g., a histological classification into one of three cell types A, B, or C), something needs to be done. This situation can be covered by the use of two dummy variables, e.g., x_1, taking the value 1 for cell type A and 0 otherwise, and x_2, taking the value 1 for cell type B and 0 otherwise. Clearly, if there are only two categories (e.g., sex), only one dummy variable is needed: x_1 is 1 for a male, 0 for a female. Also, a better description of the data might be obtained by using transformed values of the prognostic variables (e.g., squares or logarithms) or by including products such as x_1x_2 (representing an interaction between x_1 and x_2). Transforming the dependent variable (e.g., taking the logarithm of a response time) can also improve the fit.

In practice, there are usually a larger number of possible prognostic factors associated with the outcomes. One way to reduce the number of factors before a multivariate analysis is attempted is to examine the relationship between each individual factor and the dependent variable (e.g., survival time). From the univariate analysis, factors that have little or no effect on the dependent variable can be excluded from the multivariate analysis. However, it would be desirable to include factors that have been reported to have prognostic values by other investigators and factors that are considered important from biomedical viewpoints. It is often useful to consider model selection methods to choose those significant factors among all possible factors and determine an adequate model with as few variables as possible. Very often, a variable of significant prognostic value in one study is unimportant in another. Therefore, confirmation in a later study is very important in identifying prognostic factors.

Another frequent problem in regression analysis is missing data. Three distinctions about missing data can be made: (1) dependent versus independent variables, (2) many versus few missing data, and (3) random versus nonrandom loss of data. If the value of the dependent variable (e.g., survival time) is unknown, there is little to do but drop that individual from analysis and reduce the sample size. The problem of missing data is of different magnitude depending on how large a proportion of data, either for the dependent variable or for the independent variables, is missing. This problem is obviously less critical if 1% of data for one independent variable is missing than if 40% of data for several independent variables is missing. When a substantial proportion of subjects has missing data for a variable, we may simply opt to drop them and perform the analysis on the remainder of the sample. It is difficult to specify "how large" and "how small," but dropping 10 or 15 cases out of several hundred would raise no serious practical objection. However, if missing data occur in a large proportion of persons and the sample size is not comfortably large, a question of randomness may be raised. If people with missing data do not show significant differences in the dependent variable, the problem is not serious. If the data are not missing randomly, results obtained from dropping

subjects will be misleading. Thus, dropping cases is not always an adequate solution to the missing data problem.

If the independent variable is measured on a nominal or categorical scale, an alternative method is to treat individuals in a group with missing information as another group. For quantitatively measured variables (e.g., age), the mean of the values available can be used for a missing value. This principle can also be applied to nominal data. It does not mean that the mean is a good estimate for the missing value, but it does provide convenience for analysis.

A more detailed discussion on missing data can be found in Cohen and Cohen (1975, Chap. 7), Little and Rubin (1987), Efron (1994), Crawford et al. (1995), Heitjan (1997), and Schafer (1999).

11.2 GENERAL STRUCTURE OF PARAMETRIC REGRESSION MODELS AND THEIR ASYMPTOTIC LIKELIHOOD INFERENCE

When covariates are considered, we assume that the survival time, or a function of it, has an explicit relationship with the covariates. Furthermore, when a parametric model is considered, we assume that the survival time (or a function of it) follows a given theoretical distribution (or model) and has an explicit relationship with the covariates. As an example, let us consider the Weibull distribution in Section 6.2. Let $\boldsymbol{x} = (x_1, \ldots, x_p)$ denote the p covariates considered. If the parameter λ in the Weibull distribution is related to $\mathbf{x}$ as follows:

$$\lambda = e^{-(a_0 + \sum_{i=1}^{p} \boldsymbol{a}_i \boldsymbol{x}_i)} = \exp[-(a_0 + \boldsymbol{a}'\boldsymbol{x})]$$

where $\mathbf{a} = (a_1, \ldots, a_p)$ denote the coefficients for $\mathbf{x}$, then the hazard function of the Weibull distribution in (6.2.4) can be extended to include the covariates as follows:

$$h(t, \boldsymbol{x}) = \lambda^{\gamma}\gamma t^{\gamma-1} = \gamma t^{\gamma-1} e^{-(a_0 + \sum_{i=1}^{p} a_i x_i)\gamma} = \gamma t^{\gamma-1} \exp[-(a_0 + \boldsymbol{a}'\boldsymbol{x})\gamma] \qquad (11.2.1)$$

The survivorship function in (6.2.3) becomes

$$S(t, \boldsymbol{x}) = (e^{-t^{\gamma}})^{\exp(-\gamma(a_0 + \boldsymbol{a}'\boldsymbol{x}))} \qquad (11.2.2)$$

or

$$\log[-\log S(t, \boldsymbol{x})] = -\gamma(a_0 + \boldsymbol{a}'\boldsymbol{x}) + \gamma \log t \qquad (11.2.3)$$

which presents a linear relationship between $\log[-\log S(t, \boldsymbol{x})]$ and $\log t$ and the covariates. In Sections 11.2 to 11.7 we introduce a special model called the *accelerated failure time model.*

Analogous to conventional regression methods, survival time can also be analyzed by using the accelerated failure time (AFT) model. The AFT model

for survival time assumes that the relationship of logarithm of survival time T and the covariates is linear and can be written as

$$\log T = a_0 + \sum_{j=1}^{p} a_j x_j + \sigma\varepsilon \tag{11.2.4}$$

where x_j, $j = 1, \ldots, p$, are the covariates, a_j, $j = 0, 1, \ldots, p$ the coefficients, σ ($\sigma > 0$) is an unknown scale parameter, and ε, the error term, is a random variable with known forms of density function $g(\varepsilon, \mathbf{d})$ and survivorship function $G(\varepsilon, \mathbf{d})$ but unknown parameters $\boldsymbol{d}$. This means that the survival is dependent on both the covariate and an underlying distribution g.

Consider a simple case where there is only one covariate x with values 0 and 1. Then (11.2.4) becomes

$$\log T = a_0 + a_1 x + \sigma\varepsilon$$

Let T_0 and T_1 denote the survival times for two individuals with $x = 0$ and $x = 1$, respectively. Then, $T_0 = \exp(a_0 + \sigma\varepsilon)$, and $T_1 = \exp(a_0 + a_1 + \sigma\varepsilon) = T_0 \exp(a_1)$. Thus, $T_1 > T_0$ if $a_1 > 0$ and $T_1 < T_0$ if $a_1 < 0$. This means that the covariate x either "accelerates" or "decelerates" the survival time or time to failure—thus the name *accelerated failure time models* for this family of models.

In the following we discuss the general form of the likelihood function of AFT models, the estimation procedures of the regression parameters (a_0, $\mathbf{a}$, σ, and $\mathbf{d}$) in (11.2.4) and tests of significance of the covariates on the survival time. The calculations of these procedures can be carried out using available software packages such as SAS and BMDP. Readers who are not interested in the mathematical details may skip the remaining part of this section and move on to Section 11.3 without loss of continuity.

Let $t_1, t_2, \ldots, t_n$ be the observed survival times from n individuals, including exact, left-, right-, and interval-censored observations. Assume that the log survival time can be modeled by (11.2.4) and let $\mathbf{a}' = (a_1, a_2, \ldots, a_p)$, and $\mathbf{b}' = (\mathbf{a}', \mathbf{d}', a_0, \sigma)$. Similar to (7.1.1), the log-likelihood function in terms of the density function $g(\varepsilon)$ and survivorship function $G(\varepsilon)$ of ε is

$$\begin{aligned} l(\mathbf{b}) = \log L(\mathbf{b}) &= \sum \log[g(\varepsilon_i)] + \sum \log[G(\varepsilon_i)] \\ &\quad \sum \log[1 - G(\varepsilon_i)] + \sum \log[G(\eta_i) - G(\varepsilon_i)] \end{aligned} \tag{11.2.5}$$

where

$$\varepsilon_i = \frac{\log t_i - a_0 - \sum_{j=1}^{p} a_j x_{ji}}{\sigma} \tag{11.2.6}$$

$$\eta_i = \frac{\log v_i - a_0 - \sum_{j=1}^{p} a_j x_{ji}}{\sigma} \tag{11.2.7}$$

The first term in the log-likelihood function sums over uncensored observations, the second term over right-censored observations, and the third term over left-censored observations, and the last term over interval-censored observations with v_i as the lower end of a censoring interval. Note that the last two summations in (11.2.5) do not exist if there are no left- and interval-censored data.

Alternatively, let

$$\mu_i = a_0 + \sum_{j=1}^{p} a_j x_{ji} \qquad i = 1, 2, \ldots, n \tag{11.2.8}$$

Then (11.2.4) becomes

$$\log T = \mu + \sigma\varepsilon \tag{11.2.9}$$

The respective alternative log-likelihood function in terms of the density function $f(t, \mathbf{b})$ and survivorship function $S(t, \mathbf{b})$ of T is

$$\begin{aligned} l(\mathbf{b}) = \log L(\mathbf{b}) &= \sum \log[f(t_i, \mathbf{b})] + \sum \log[S(t_i, \mathbf{b})] \\ &+ \sum \log[1 - S(t_i, \mathbf{b})] + \sum \log[S(v_i, \mathbf{b}) - S(t_i, \mathbf{b})] \end{aligned} \tag{11.2.10}$$

where $f(t, \mathbf{b})$ can be derived from (11.2.4) through the density function $g(\varepsilon)$ by applying the density transformation rule

$$f(t, \mathbf{b}) = \frac{g((\log t - \mu)/\sigma)}{\sigma t} \tag{11.2.11}$$

and $S(t, \mathbf{b})$ is the corresponding survivorship function. The vector $\mathbf{b}$ in (11.2.10) and (11.2.11) includes the regression coefficients and other parameters of the underlying distribution.

Either (11.2.5) or (11.2.10) can be used to derive the maximum likelihood estimates (MLEs) of parameters in the model. For a given log-likelihood function $l(\mathbf{b})$, the MLE $\hat{\mathbf{b}}$ is a solution of the following simultaneous equations:

$$\frac{\partial(l(\mathbf{b}))}{\partial b_i} = 0 \qquad \text{for all } i \tag{11.2.12}$$

Usually, there is no closed solution for the MLE $\hat{\mathbf{b}}$ from (11.2.12) and the Newton–Raphson iterative procedure in Section 7.1 must be applied to obtain $\hat{\mathbf{b}}$. By replacing the parameters $\mathbf{b}$ with its MLE $\hat{\mathbf{b}}$ in $S(t_i, \mathbf{b})$, we have an estimated survivorship function $S(t, \hat{\mathbf{b}})$, which takes into consideration the covariates.

All of the hypothesis tests and the ways to construct confidence intervals shown in Section 7.1 can be applied here. In addition, we can use the following tests to test linear relationships among the regression coefficients $a_1, a_2, \ldots, a_p$.

To test a linear relationship among $x_1, \ldots, x_p$ is equivalent to testing the null hypothesis that there is a linear relationship among $a_1, a_2, \ldots, a_p$. H_0 can be written in general as

$$H_0: \mathbf{La} = \mathbf{c} \tag{11.2.13}$$

where $\mathbf{L}$ is a matrix or vector of constants for the linear hypothesis and $\mathbf{c}$ is a known column vector of constants. The following Wald's statistics can be used:

$$X_W = (\mathbf{L}\hat{\mathbf{a}} - \mathbf{c})'[\mathbf{L}\hat{V}_a(\hat{\mathbf{a}})\mathbf{L}']^{-1}(\mathbf{L}\hat{\mathbf{a}} - \mathbf{c}) \tag{11.2.14}$$

where $\hat{V}_\alpha(\hat{\mathbf{a}})$ is the submatrix of the covariance matrix $\hat{V}(\hat{\mathbf{b}})$ corresponding to $\mathbf{a}$. Under the H_0 and some mild assumptions, X_W has an asymptotic chi-square distribution with v degrees of freedom, where v is the rank of $\mathbf{L}$. For a given significance level α, H_0 is rejected if $X_W > \chi^2_{v,\alpha/2}$ or $X_W < \chi^2_{v,1-\alpha/2}$.

For example, if $p = 3$ and we wish to test if x_1 and x_2 have equal effects on the survival time, the null hypothesis is $H_0: a_1 = a_2$ (or $a_1 - a_2 = 0$). It is easy to see that for this hypothesis, the corresponding $\mathbf{L} = (1, -1, 0)$ and $\mathbf{c} = 0$ since

$$\mathbf{La} = (1, \ -1, \ 0)(a_1, a_2, a_3)' = a_1 - a_2$$

Let the (i, j) element of $\hat{V}_a(\hat{\mathbf{a}})$ be v_{ij}; then the X_W defined in (11.2.14) becomes

$$X_W = (\hat{a}_1 - \hat{a}_2)\left[(1, \ -1, \ 0)\begin{pmatrix} v_{11} & v_{12} & v_{13} \\ v_{21} & v_{22} & v_{23} \\ v_{31} & v_{32} & v_{33} \end{pmatrix}\begin{pmatrix} 1 \\ -1 \\ 0 \end{pmatrix}\right]^{-1}(\hat{a}_1 - \hat{a}_2)$$

$$= \frac{(\hat{a}_1 - \hat{a}_2)^2}{v_{11} + v_{22} - 2v_{12}}$$

X_W has an asymptotic chi-square distribution with 1 degree of freedom (the rank of $\mathbf{L}$ is 1).

In general, to test if any two covariates have the same effects on T, the null hypothesis can be written as

$$H_0: a_i = a_j \ (\text{or } a_i - a_j = 0) \tag{11.2.15}$$

The corresponding $\mathbf{L} = (0, \ldots, 0, \ 1, \ 0, \ldots, 0, \ -1, \ 0, \ldots, 0)$ and $\mathbf{c} = 0$, and the X_W in (11.2.14) becomes

$$X_W = \frac{(\hat{a}_i - \hat{a}_j)^2}{v_{ii} + v_{jj} - 2v_{ij}} \tag{11.2.16}$$

which has an asymptotic chi-square distribution with 1 degree of freedom. H_0 is rejected if $X_W > \chi^2_{1,\alpha/2}$ or $X_W < \chi^2_{1,1-\alpha/2}$.

To test that none of the covariates is related to the survival time, the null hypothesis is

$$H_0: \mathbf{a} = \mathbf{0} \tag{11.2.17}$$

The respective test statistics for this overall null hypothesis are shown in Section 9.1. For example, the log-likelihood ratio statistics there becomes

$$X_L = -2[l(\mathbf{0}, \hat{\mathbf{d}}(\mathbf{0}), \hat{a}_0(\mathbf{0}), \hat{\sigma}(\mathbf{0})) - l(\hat{\mathbf{b}})] \tag{11.2.18}$$

which has an asymptotic chi-square distribution with p degrees of freedom under H_0, where p is the number of covariates; $\hat{\mathbf{d}}(\mathbf{0})$, $\hat{a}_0(\mathbf{0})$, and $\hat{\sigma}(\mathbf{0})$ are the MLE of $\mathbf{d}$, a_0, and σ given $\mathbf{a} = \mathbf{0}$.

11.3 EXPONENTIAL REGRESSION MODEL

To incorporate covariates into the exponential distribution, we use (11.2.4) for the log survival time and let $\sigma = 1$:

$$\log T_i = a_0 + \sum_{j=1}^{p} a_j x_{ji} + \varepsilon_i = \mu_i + \varepsilon_i, \tag{11.3.1}$$

where $\mu_i = a_0 + \Sigma_{j=1}^{p} a_j x_{ji}$, ε_i's are independently identically distributed (i.i.d.) random variables with a double exponential or extreme value distribution which has the following density function $g(\varepsilon)$ and survivorship function $G(\varepsilon)$:

$$g(\varepsilon) = \exp[\varepsilon - \exp(\varepsilon)] \tag{11.3.2}$$

$$G(\varepsilon) = \exp[-\exp(\varepsilon)] \tag{11.3.3}$$

This model is the exponential regression model. T has the exponential distribution with the following hazard, density, and survivorship functions.

$$h(t, \lambda_i) = \lambda_i = \exp\left[-\left(a_0 + \sum_{j=1}^{p} a_j x_{ji}\right)\right] = \exp(-\mu_i) \tag{11.3.4}$$

$$f(t, \lambda_i) = \lambda_i \exp(-\lambda_i t) \tag{11.3.5}$$

$$S(t, \lambda_i) = \exp(-\lambda_i t) \tag{11.3.6}$$

where λ_i is given in (11.3.4). Thus, the exponential regression model assumes a linear relationship between the covariates and the logarithm of hazard. Let

$h_i(t, \lambda_i)$ and $h_j(t, \lambda_j)$ be the hazards of individuals i and j; the hazard ratio of these two individuals is

$$\frac{h_i(t,\ \lambda_i)}{h_j(t,\ \lambda_j)} = \frac{\lambda_i}{\lambda_j} = \exp[-(\mu_i - \mu_j)] = \exp\left[-\sum_{k=1}^{p} a_k(x_{ki} - x_{kj})\right] \quad (11.3.7)$$

This ratio is dependent only on the differences of the covariates of the two individuals and the coefficients. It does not depend on the time t. In Chapter 12 we introduce a class of models called *proportional hazard models* in which the hazard ratio of any two individuals is assumed to be a time-independent constant. The exponential regression model is therefore a special case of the proportional hazard models.

The MLE of $\mathbf{b} = (a_0, a_1, \ldots, a_p)$ is a solution of (11.2.12), using (11.2.10), where $f(t, \lambda)$ and $S(t, \lambda)$ are given in (11.3.5) and (11.3.6). Computer programs in SAS or BMDP can be used to carry out the computation.

In the following we introduce a practical exponential regression model. Suppose that there are $n = n_1 + n_2 + \cdots + n_k$ individuals in k treatment groups. Let t_{ij} be the survival time and $x_{1ij}, x_{2ij}, \ldots, x_{pij}$ the covariates of the jth individual in the ith group, where p is the number of covariates considered, $i = 1, \ldots, k$, and $j = 1, \ldots, n_i$. Define the survivorship function for the jth individual in the ith group as

$$S_{ij}(t) = \exp(-\lambda_{ij} t) \quad (11.3.8)$$

where

$$\lambda_{ij} = \exp(-\mu_{ij}) \quad \text{and} \quad \mu_{ij} = -\left(a_{0i} + \sum_{l=1}^{p} a_l x_{lij}\right) \quad (11.3.9)$$

This model was proposed by Glasser (1967) and was later investigated by Prentice (1973) and Breslow (1974). The term $\exp(-a_{0i})$ represents the underlying hazard of the ith group when covariates are ignored. It is clear that μ_{ij} defined in (11.3.9) is a special case of (11.3.4) by adding a new index for the treatment groups. To construct the likelihood function, we use the following indicator variables to distinguish censored observations from the uncensored:

$$\delta_{ij} = \begin{cases} 1 & \text{if } t_{ij} \text{ uncensored} \\ 0 & \text{if } t_{ij} \text{ censored} \end{cases}$$

According to (11.2.10) and (11.3.8), the likelihood function for the data can then be written as

$$L(\lambda_{ij}) = \sum_{i=1}^{k} \prod_{j=1}^{n_i} (\lambda_{ij})^{\delta_{ij}} \exp(-\lambda_{ij} t_{ij})$$

Substituting (11.3.9) in the logarithm of the function above, we obtain the log-likelihood function of $\mathbf{a}_0 = (a_{01}, a_{02}, \ldots, a_{0k})$ and $\mathbf{a} = (a_1, a_2, \ldots, a_p)$:

$$l(\mathbf{a}_0, \mathbf{a}) = \sum_{i=1}^{k} \sum_{j=1}^{n_i} \left[\delta_{ij} \left(a_{0i} + \sum_{l=1}^{p} a_l x_{lij} \right) - t_{ij} \exp\left(a_{0i} + \sum_{l=1}^{p} a_l x_{lij} \right) \right]$$
$$= \sum_{i=1}^{k} \left[a_{0i} r_i + \sum_{l=1}^{p} a_l s_{il} - \exp(a_{0i}) \sum_{j=1}^{n_i} t_{ij} \exp\left(\sum_{l=1}^{p} a_l x_{lij} \right) \right] \quad (11.3.10)$$

where

$$s_{il} = \sum_{j=1}^{n_i} \delta_{ij} x_{lij}$$

is the sum of the lth covariate corresponding to the uncensored survival times in the ith group and r_i is the number of uncensored times in that group.

Maximum likelihood estimates of a_{0i}'s and a_l's can be obtained by solving the following $k + p$ equations simultaneously. These equations are obtained by taking the derivative of $l(\boldsymbol{a}_0, \boldsymbol{a})$ in (11.3.10) with respect to the k a_{0i}'s and p a_l's:

$$r_i - \exp(\hat{a}_{0i}) \sum_{j=1}^{n_i} t_{ij} \exp\left(\sum_{l=1}^{p} \hat{a}_l x_{lij} \right) = 0 \qquad i = 1, \ldots, k \quad (11.3.11)$$

$$\sum_{i=1}^{k} \left[s_{il} - \exp(\hat{a}_i) \sum_{j=1}^{n_i} t_{ij} x_{lij} \exp\left(\sum_{l=1}^{p} \hat{a}_l x_{lij} \right) \right] = 0 \qquad l = 1, \ldots, p \quad (11.3.12)$$

This can be done by using the Newton–Raphson iterative procedure in Section 7.1. The statistical inferences for the MLE and the model are the same as those stated in Section 7.1. Let $\hat{\mathbf{a}}_0$ and $\hat{\mathbf{a}}$ be the MLE of $\mathbf{a}_0$ and $\mathbf{a}$ in (11.3.10), and $\hat{\mathbf{a}}_0(\mathbf{0})$ be the MLE of $\mathbf{a}_0$ given $\mathbf{a} = \mathbf{0}$. According to (11.2.18), the difference between $l(\hat{\mathbf{a}}_0, \hat{\mathbf{a}})$ and $l(\hat{\mathbf{a}}_0(\mathbf{0}), \mathbf{0})$ can be used to test the overall null hypothesis (11.2.17) that none of the covariates is related to the survival time by considering

$$X_L = -2(l(\hat{\mathbf{a}}_0(\mathbf{0}), \mathbf{0}) - l(\hat{\mathbf{a}}_0, \hat{\mathbf{a}})) \quad (11.3.13)$$

as chi-square distributed with p degrees of freedom. A X_L greater than the 100α percentage point of the chi-square distribution with p degrees of freedom indicates significant covariates. Thus, fitting the model with subsets of the covariates $x_1, x_2, \ldots, x_p$ allows selection of significant covariates of prognostic variables. For example, if $p = 2$, to test the significance of x_2 after adjusting for x_1, that is, $H_0: a_2 = 0$, we compute

$$X_L = -2[l(\hat{\mathbf{a}}_0(0), \hat{a}_1(0), 0) - l(\hat{\mathbf{a}}_0, \hat{a}_1, \hat{a}_2)]$$

Table 11.1 Summary Statistics for the Five Regimens

Regimen	Additive Therapy: 6-MP Cycle	Additive Therapy: MTX Cycle	Number of Patients	Number in Remission	Geometric Mean[a] of WBC	Mean Age (yr)	Median Remission Duration
1	A-D	NM	46	20	9,000	4.61	510
2	A-D	A-D	52	18	12,308	5.25	409
3	NM	NM	64	18	15,014	5.70	307
4	NM	A-D	54	14	9,124	4.30	416
5	None	None	52	17	13,421	5.02	420
1, 2, 4	—	—	152	52	10,067	4.74	435
3, 5	—	—	116	35	14,280	5.40	340
All	—	—	268	87	11.711	5.02	412

Source: Breslow (1974). Reproduced with permission of the Biometric Society.

[a] The geometric mean of $x_1, x_2, \ldots, x_n$ is defined as $(\Pi_{i=1}^{n} x_i)^{1/n}$. It gives a less biased measure of central tendency than the arithmetic mean when some observations are extremely large.

where $\hat{\mathbf{a}}_0(0)$ and $\hat{a}_1(0)$ are, respectively, the MLE of $\mathbf{a}_0$ and a_1 given $a_2 = 0$. X_L follows the chi-square distribution with 1 degree of freedom. A significant X_L value indicates the importance of x_2. This can be done automatically by a stepwise procedure. In addition, if one or more of the covariates are treatments, the equality of survival in specified treatment groups can be tested by comparing the resulting maximum log-likelihood values. Having estimated the coefficients a_{0i} and a_l, a survivorship function adjusted for covariates can then be estimated from (11.3.9) and (11.3.8).

The following example, adapted from Breslow (1974), illustrates how this model can identify important prognostic factors.

Example 11.1 Two hundred and sixty-eight children with newly diagnosed and previously untreated ALL were entered into a chemotherapy trial. After successful completion of an induction course of chemotherapy designed to induce remission, the patients were randomized onto five maintenance regimens designed to maintain the remission as long as possible. Maintenance chemotherapy consisted of alternating eight-week cycles of 6-MP and methotrexate (MTX) to which actinomycin-D (A-D) or nitrogen mustard (NM) was added. The regimens are given in Table 11.1. Regimen 5 is the control. Many investigators had a prior feeling that actinomycin-D was the active additive drug; therefore, pooled regimens 1, 2, and 4 (with actinomycin-D) were compared to regimens 3 and 5 (without actinomycin-D). Covariates considered were initial WBC and age at diagnosis. Analysis of variance showed that differences between the regimens with respect to these variables were not significant. Table 11.1 shows that the regimen with lowest (highest) WBC geometric mean has the longest (shortest) estimated remission duration. Figure

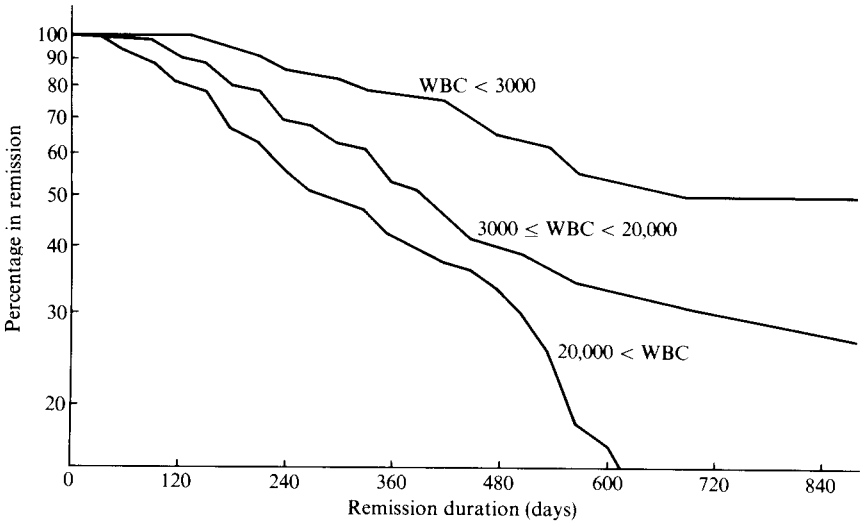


Figure 11.1 Remission curves of all patients by WBC at diagnosis. (From Breslow, 1974. Reproduced with permission of the Biometric Society.)

11.1 gives three remission curves by WBC; differences in duration were significant. It is well known that the initial WBC is an important prognostic factor for patients followed from diagnosis; however, it is interesting to know if this variable will continue to be important after the patient has achieved remission.

To identify important prognostic variables, model (11.3.9) was used to analyze the effect of WBC and age at diagnosis. Previous studies (Pierce et al., 1969; George et al., 1973) showed that survival is longest for children in the middle age range (6–8 years), suggesting that both linear and quadratic terms in age be included. The WBC was transformed by taking the common logarithm. Thus, the number of covariates is $p = 3$. Let x_1, x_2, and x_3 denote $\log_{10}$(WBC), age, and age squared, and a_1, a_2, and a_3 be the respective coefficients. Instead of using a stepwise fitting procedure, the model was fitted five times using different numbers of covariates. Table 11.2 gives the results.

The estimated regression coefficients were obtained by solving (11.3.11) and (11.3.12). Maximum log-likelihood values were calculated by substituting the regression coefficients with the estimates in (11.3.10). The X_L values were computed following (11.3.13), which show the effect of the covariates included. The first fit did not include any covariates. The log-likelihood so obtained is the unadjusted value $l(\hat{\mathbf{a}}_0(\mathbf{0}), \mathbf{0})$ in (11.3.13). The second fit included only x_1 or $\log_{10}$(WBC), which yields a larger log-likelihood value than the first fit. Following (11.3.13), we obtain

$$X_L = -2(l(\hat{\mathbf{a}}_0(0), 0) - l(\hat{\mathbf{a}}_0, \hat{a}_1)) = -2(-1332.925 + 1316.399) = 33.05$$

Table 11.2 Regression Coefficients and Maximum Log-Likelihood Values for Five Fits

Fit	Covariates Included	Maximum Log-Likelihood	Regression Coefficient			χ^2	df
			b_1	b_2	b_3		
1	None	−1332.925					
2	x_1 ($\log_{10}$WBC)	−1316.399	0.72			33.05	1
3	x_1, x_2 (age)	−1316.111	0.73	0.02		33.63	2
4	x_2, x_3 (age squared)	−1327.920		−0.24	0.018	10.01	2
5	x_1, x_2, x_3	−1314.065	0.67	−0.14	0.011	37.72	3

Source: Breslow (1974). Reproduced with permission of the Biometric Society.

with 1 degree of freedom. The highly significant ($p < 0.001$) X_L value indicates the importance of WBC. When age and age squared are included (fit 4) in the model, the X_L value, 10.01, is less than that of fit 2. This indicates that WBC is a better predictor than age as the only covariate. To test the significance of age effects after adjusting for WBC, we subtract the log-likelihood value of fit 2 from that of fit 5 and obtain

$$X_L = -2(-1316.399 + 1314.065) = 4.668$$

with $3 - 1 = 2$ degrees of freedom. The significance of this X_L value is marginal ($p = 0.10$). Comparing the maximum log-likelihood value of fit 2 to that of fit 5, we find that log WBC accounts for the major portion of the total covariate effect. Thus, log(WBC) was identified as the most important prognostic variable. In addition, subtracting the maximum log-likelihood value of fit 5 from that of fit 3 yields

$$X_L = -2(-1316.111 + 1314.065) = 4.092$$

with 1 degree of freedom. This significant ($p < 0.05$) value indicates that the age relationship is indeed a quadratic one, with children 6 to 8 years old having the most favorable prognosis. For a complete analysis of the data, the interested reader is referred to Breslow (1974).

To use SAS to perform the analysis, let T be the remission duration, TG an indicator variable (TG = 1 if in regimen groups 1, 2, and 4; 0 otherwise), CENS a second indicator variable (CENS = 0 when t is censored; 1 otherwise), and x1, x2, and x3 be $\log_{10}$(WBC), age, and age squared, respectively. Assume that the data are saved in "C:\RDT.DAT" as a text file, which contains six columns, and that each row (consisting of six space-separated numbers) gives the observed T, CENS, TG, x1, x2, and x3 from a child. For instance, a first row

in RDT.DAT may be

```
500   1   0   4.079   5.2   27.04
```

which represents that a 5.2-year-old child with initial $\log_{10}(\text{WBC}) = 4.079$ who received regimen 3 or 5 relapsed after 500 days [i.e., $t = 500$, CENS = 1, TG = 0, x1 = 4.079, x2 = 5.2, and x3 (age squared) = 27.04].

For this data set, the following SAS code can be used to perform fits 1 to 5 in Table 11.2 by using procedure LIFEREG.

```
data w1;
  infile 'c:\rdt.dat' missover;
  input t cens tg x1 x2 x3;
run;
proc lifereg;
  model 1: model t*cens(0) = tg / d = exponential;
  model 2: model t*cens(0) = tg x1/ d = exponential;
  model 3: model t*cens(0) = tg x1 x2/ d = exponential;
  model 4: model t*cens(0) = tg x2 x3/ d = exponential;
  model 5: model t*cens(0) = tg x1 x2 x3/ d = exponential;
run;
```

For BMDP procedure 2L the following code can be used for fit 5.

```
/input      file = 'c:\rdt.dat'.
            variables = 6.
            format = free.
/print      level = brief.
/variable   names = t, cens, tg, x1, x2, x3.
/form       time = t.
            status = cens.
            response = 1.
/regress    covariates = tg, x1, x2, x3.
            accel = exponential.
/end
```

11.4 WEIBULL REGRESSION MODEL

To consider the effects of covariates, we use the model (11.2.4); that is, the log-survival-time of individual i is

$$\log T_i = a_0 + \sum_{k=1}^{p} a_k x_{ki} + \sigma\varepsilon_i = \mu_i + \sigma\varepsilon_i \tag{11.4.1}$$

where $\mu_i = a_0 + \Sigma_{k=1}^{p} a_k x_{ki}$ and ε has the distribution defined in (11.3.2) and

(11.3.3). This model is the Weibull regression model. T has the Weibull distribution with

$$\lambda_i = \exp\left(-\frac{\mu_i}{\sigma}\right) \quad \text{and} \quad \gamma = \frac{1}{\sigma} \tag{11.4.2}$$

and the following hazard, density, and survivorship functions that are related with covariates via λ_i in (11.4.2):

$$h(t, \lambda_i, \gamma) = \lambda_i \gamma t^{\gamma - 1} \tag{11.4.3}$$

$$f(t, \lambda_i, \gamma) = \lambda_i \gamma t^{\gamma - 1} \exp(-\lambda_i t^{\gamma}) \tag{11.4.4}$$

$$S(t, \lambda_i, \gamma) = \exp(-\lambda_i t^{\gamma}) \tag{11.4.5}$$

The hazard ratio of any two individuals i and j, based on (11.4.3) and (11.4.2), is

$$\frac{h_i}{h_j} = \exp\left(-\frac{\mu_i - \mu_j}{\sigma}\right) = \exp\left(-\frac{1}{\sigma}\sum_{k=1}^{p} a_k(x_{ki} - x_{kj})\right)$$

which is not time-dependent. Therefore, similar to the exponential regression model, the Weibull regression model is also a special case of the proportional hazard models.

The following example illustrates the use of the Weibull regression model and of computer software packages.

Example 11.2 Consider the tumor-free time in Table 3.4. Suppose that we wish to know if three diets have the same effect on the tumor-free time. Let T be the tumor-free time; CENS be an index (or dummy) variable with CENS = 0 if T is censored and 1 otherwise; and LOW, SATU, and UNSA be index variables indicating that a rat was fed a low-fat, saturated fat, or unsaturated fat diet, respectively (e.g., LOW = 1 if fed a low-fat diet; 0 otherwise). The data from the 90 rats in Table 3.4 can be presented using these five variables. For example, the three observations in the first row of Table 3.4 can be rearranged as

T	CENS	LOW	SATU	UNSA
140	1	1	0	0
124	1	0	1	0
112	1	0	0	1

Assume that the rearranged data are saved in the text file "C:\RAT.DAT", which contains the data from the 90 rats in five columns as above and the five numbers in each row are space-separated. This data file is ready for almost all

of the statistical software packages for parametric survival analysis currently available, such as SAS and BMDP. Suppose that the tumor-free time follows the Weibull distribution and the following Weibull regression model is used:

$$\log T_i = a_0 + a_1 \text{SATU}_i + a_2 \text{UNSA}_i + \sigma\varepsilon_i = \mu_i + \sigma\varepsilon_i \tag{11.4.6}$$

where ε_i has a double exponential distribution as defined in (11.3.2) and (11.3.3). Note that from (11.4.3) and (11.4.2),

$$\begin{aligned} \log h(t, \lambda_i, \gamma) &= \log \lambda_i + \log(\gamma t^{\gamma-1}) \\ &= -\frac{\mu_i}{\sigma} + \log(\gamma t^{\gamma-1}) \\ &= \frac{-a_0 - a_1 \text{SATU}_i - a_2 \text{UNSA}_i}{\sigma} + \log(\gamma t^{\gamma-1}) \end{aligned} \tag{11.4.7}$$

Denote the hazard function of a rat fed an unsaturated, saturated, and low-fat diet as h_u, h_s, and h_l, respectively. From (11.4.7), $\log h_u = (-a_0 - a_2)/\sigma + \log(\gamma t^{\gamma-1})$, $\log h_s = (-a_0 - a_1)/\sigma + \log(\gamma t^{\gamma-1})$, and $\log h_l = -a_0/\sigma + \log(\gamma t^{\gamma-1})$. Thus, the logarithm of the hazard ratio of rats fed a low-fat diet and those fed a saturated fat diet is $\log(h_l/h_s) = a_1/\sigma$, and the similar ratios of rats fed a low-fat diet and those an unsaturated fat diet, and of rats fed a saturated fat diet and those fed an unsaturated fat diet are, respectively, $\log(h_l/h_u) = a_2/\sigma$ and $\log(h_s/h_u) = (a_2 - a_1)/\sigma$. These ratios are constants and are independent of time. Therefore, to test the null hypothesis that the three diets have an equal effect on tumor-free time is equivalent to testing the following three hypotheses: $H_0: h_l/h_s = 1$ or $a_1 = 0$, $H_0: h_l/h_u = 1$, or $a_2 = 0$, and $H_0: h_s/h_u = 1$ or $a_2 = a_1$. The statistic defined in Section 9.1.1 can be used to test the first two null hypotheses, and the statistic defined in (11.2.16) can be used for the third one. Failure to reject a null hypothesis implies that the corresponding log-hazard ratio is not statistically different from zero; that is, there are no statistically significant differences between the two corresponding diets. For example, failure to reject $H_0: a_1 = 0$ means that there are no significant differences between the hazards for rats fed a low-fat diet and rats fed a saturated fat diet. When all three hypotheses $H_0: a_1 = 0$, $H_0: a_2 = 0$, and $H_0: a_2 = a_1$ are rejected, we conclude that the three diets have significantly different effects on tumor-free time. Furthermore, a positive (negative) estimated implies that the hazard of a rat fed a low-fat diet is $\exp(a_1/\sigma)$ times higher (lower) than that of a rat fed a saturated fat diet. Similarly, a positive (negative) estimated a_2 and $(a_2 - a_1)$ imply, respectively, the hazard of a rat fed a low-fat diet is $\exp(a_2/\sigma)$ times higher (lower) than that of a rat fed an unsaturated fat diet, and the hazard of a rat fed a saturated fat diet is $\exp[(a_2 - a_1)/\sigma]$ times higher (lower) than that of a rat fed an unsaturated fat diet.

To estimate the unknown coefficients, a_1, a_2, a_0, and σ, we construct the log-likelihood function by replacing μ in (11.4.2), (11.4.4), and (11.4.5) with (11.4.6). Next, place the resulting $f(t_i, \lambda_i, \gamma)$ and $S(t_i, \lambda_i, \gamma)$ in the log-likelihood function (11.2.10). The log-likelihood function for the observed 90 exact or right-censored tumor-free times, $t_1, t_2, \ldots, t_{90}$, in the three diet groups is

$$\begin{aligned} l(a_0, a_1, a_2, \gamma) &= \sum \log[f(t_i, \lambda_i, \gamma)] + \sum \log[S(t_i, \lambda_i, \gamma)] \\ &= \sum [\log \gamma + (\gamma - 1)\log t_i - \gamma \mu_i - t_i^{\gamma} \exp(-\gamma \mu_i)] \\ &\quad + \sum [-t_i^{\gamma} \exp(-\gamma \mu_i)] \\ &= \sum \{\log \gamma + (\gamma - 1)\log t_i - \gamma(a_0 + a_1 \mathrm{SATU_i} + a_2 \mathrm{UNSA_i}) \\ &\quad - t_i^{\gamma} \exp[-\gamma(a_0 + a_1 \mathrm{SATU_i} + a_2 \mathrm{UNSA_i})]\} \\ &\quad + \sum \{-t_i^{\gamma} \exp[-\gamma(a_0 + a_1 \mathrm{SATU_i} + a_2 \mathrm{UNSA_i})]\} \end{aligned}$$

The first term in the log-likelihood function sums over the uncensored observations, and the second term sums over the right-censored observations. The MLE $(\hat{a}_1, \hat{a}_2, \hat{a}_0, \hat{\sigma})$ of (a_1, a_2, a_0, σ) where $\sigma = 1/\gamma$ is a solution of (11.2.12) with the above log-likelihood function by applying the Newton–Raphson iterative procedure. The results from SAS are shown in Table 11.3, where INTERCPT $= a_0$ and SCALE $= \sigma$. The MLE $\hat{\sigma} = 0.43$, $\hat{a}_1 = -0.394$, $\hat{a}_2 = -0.739$, and $\hat{a}_2 - \hat{a}_1 = -0.345$. $H_0: a_1 = 0$ (or $h_l/h_s = 1$), $H_0: a_2 = 0$ (or $h_l/h_u = 1$), and $H_0: a_2 - a_1 = 0$ (or $h_s/h_u = 1$) are rejected at significance level $p = 0.0065$, $p = 0.0001$, and $p = 0.0038$, respectively. The conclusion that the data indicate significant differences among the three diets is the same as that obtained in Chapter 3 using the k-sample test. Furthermore, both $\hat{a}_1$ and $\hat{a}_2$ are negative and $\hat{h}_l/\hat{h}_s = \exp(\hat{a}_1/\hat{\sigma}) = \exp(-0.916) = 0.40$, $\hat{h}_l/\hat{h}_u = \exp(\hat{a}_2/\hat{\sigma}) = \exp(-1.719) = 0.18$, and $\hat{h}_s/\hat{h}_u = \exp((\hat{a}_2 - \hat{a}_1)/\hat{\sigma}) = \exp(-0.802) = 0.45$. Thus, based on the data observed, the hazard of rats fed a low-fat diet is 40% and 18% of the hazard of rats a saturated fat diet and an unsaturated fat diet, respectively, and the hazard of rats fed a saturated fat diet is 45% of that of rats fed an unsaturated fat diet.

The survivorship function in (11.4.5) can be estimated by using (11.4.2) and the MLE of a_0, a_1, a_2, and σ:

$$\begin{aligned} \hat{S}(t, \lambda, \gamma) &= \exp(-\hat{\lambda} t^{\hat{\gamma}}) \\ &= \exp\left\{-\exp\left[-\frac{1}{\hat{\sigma}}(\hat{a}_0 + \hat{a}_1 \mathrm{SATU} + \hat{a}_2 \mathrm{UNSA})\right] t^{1/\hat{\sigma}}\right\} \\ &= \exp[-\exp(-12.56 + 0.92 \times \mathrm{SATU} + 1.72 \times \mathrm{UNSA}) t^{2.33}] \end{aligned}$$

Based on $\hat{S}(t, \lambda_i, \gamma)$, we can estimate the probability of surviving a given time for rats fed with any of the diets. For example, for rats fed a low-fat diet,

Table 11.3 Analysis Results for Rat Data in Table 3.4 Using a Weibull Regression Model

Variable	Regression Coefficient	Standard Error	X_L	p	$\exp(\hat{a}_i/\hat{\sigma})$
INTERCPT ($\hat{a}_0$)	5.400	0.113	2297.610	0.0001	
TRTSA($\hat{a}_1$)	−0.394	0.145	7.407	0.0065	0.40
TRTUS($\hat{a}_2$)	−0.739	0.140	28.049	0.0001	0.18
SCALE($\hat{\sigma}$)	0.430	0.043			
$\hat{a}_2 - \hat{a}_1$	−0.345	0.119	8.355	0.0038	0.45

(SATU = 0 and UNSA = 0), the probability of being tumor-free for 200 days is

$$\begin{aligned}\hat{S}_{\text{LOW}}(200) &= \exp[-\exp(-12.56)(200)^{2.33}] \\ &= \exp[-0.00000353(200)^{2.33}] = 0.132\end{aligned}$$

and for rats fed an unsaturated fat diet, (SATU = 0 and UNSA = 1), the probability is 0.011.

Following is the SAS code used to obtain Table 11.3, based on the Weibull regression model in (11.4.6).

```
data w1;
  infile 'c:\rat.dat' missover;
  input t cens low satu unsa;
run;
proc lifereg covout;
  model t*cens(0) = satu unsa / d = weibull;
run;
```

The respective BMDP procedure 2L code based on (11.4.6) is

```
/input      file = 'c:\rat.dat'.
            variables = 5.
            format = free.
/print      level = brief.
/variable   names = t, cens, low, satu, unsa.
/form       time = t.
            status = cens.
            response = 1.
/regress    covariates = satu, unsa .
            accel = weibull.
/end
```

11.5 LOGNORMAL REGRESSION MODEL

Let ε in (11.2.4) be the standard normal random variable with the density function $g(\varepsilon)$ and survivorship function $G(\varepsilon)$,

$$g(\varepsilon) = \frac{\exp(-\varepsilon^2/2)}{\sqrt{2\pi}} \tag{11.5.1}$$

$$G(\varepsilon) = 1 - \Phi(\varepsilon) = 1 - \frac{1}{\sqrt{2\pi}} \int_{-\infty}^{\varepsilon} e^{-x^2/2}\, dx \tag{11.5.2}$$

where Φ is the cumulative distribution function of the standard normal distribution. Then the model defined by (11.2.4) for the survival time T of individual i,

$$\log T_i = a_0 + \sum_{k=1}^{p} a_k x_{ki} + \sigma\varepsilon_i = \mu_i + \sigma\varepsilon_i$$

is the lognormal regression model. T has the lognormal distribution with the density function

$$f(t,\ \mu_i,\ \sigma^2) = \frac{\exp[-(\log t - \mu_i)^2/2\sigma^2]}{\sqrt{2\pi}\,\sigma t} \tag{11.5.3}$$

and the survivorship function

$$S(t,\ \mu_i,\ \sigma^2) = 1 - \Phi\left(\frac{\log t - \mu_i}{\sigma}\right) \tag{11.5.4}$$

It can be shown that the hazard function $h(t, \sigma, a_0, a_1, \ldots, a_p)$ of T with covariate $x_1,\ x_2, \ldots, x_p$ and unknown parameters and coefficients $\sigma,\ a_0,\ a_1, \ldots, a_p$ can be written as

$$\log h(t,\ \sigma,\ a_0,\ a_1, \ldots, a_p) = \log h_0[t\exp(-\mu)] - \mu \tag{11.5.5}$$

where $h_0(\cdot)$ is the hazard function of an individual with all covariates equal to zero. Equation (11.5.5) indicates that $h(t, \sigma, a_0, a_1, \ldots, a_p)$ is a function of h_0 evaluated at $t\exp(-\mu)$, not independent of t. Thus, the lognormal regression model is not a proportional hazards model.

Example 11.3 Consider the survival time data from 30 patients with AML in Table 11.4. Two possible prognostic factors or covariates, age, and cellular-

Table 11.4 Survival Times and Data for Two Possible Prognostic Factors of 30 AML Patients

Survival Time	x_1	x_2	Survival Time	x_1	x_2
18	0	0	8	1	0
9	0	1	2	1	1
28+	0	0	26+	1	0
31	0	1	10	1	1
39+	0	1	4	1	0
19+	0	1	3	1	0
45+	0	1	4	1	0
6	0	1	18	1	1
8	0	1	8	1	1
15	0	1	3	1	1
23	0	0	14	1	1
28+	0	0	3	1	0
7	0	1	13	1	1
12	1	0	13	1	1
9	1	0	35+	1	0

ity status are considered:

$$x_1 = \begin{cases} 1 & \text{if patient is } \geqslant 50 \text{ years old} \\ 0 & \text{otherwise} \end{cases}$$

$$x_2 = \begin{cases} 1 & \text{if cellularity of marrow clot section is 100\%} \\ 0 & \text{otherwise} \end{cases}$$

Let us use the lognormal regression model

$$\log T_i = a_0 + a_1 x_{1i} + a_2 x_{2i} + \sigma \varepsilon_i \tag{11.5.6}$$

and

$$\mu_i = a_0 + a_1 x_{1i} + a_2 x_{2i} \tag{11.5.7}$$

The unknown coefficients and parameter a_1, a_2, a_0, σ need to be estimated. We construct the log-likelihood function by replacing μ in (11.5.3) and (11.5.4) with (11.5.7), then replacing $f(t_i, \mu, \sigma^2)$ and $S(t_i, \mu, \sigma^2)$ in the log-likelihood function (11.2.5) with their expression (11.5.3) and (11.5.4), respectively. The resulting log-likelihood function for the exact and right-censored survival times

observed from the 30 patients with AML is

$$l(a_0, a_1, a_2, \sigma) = \sum \left[-\frac{(\log t_i - \mu_i)^2}{2\sigma^2} - \log(\sqrt{2\pi}\,\sigma t_i) \right] + \sum \left\{ \log \left[1 - \Phi \left(\frac{\log t_i - \mu_i}{\sigma} \right) \right] \right\}$$

$$= \sum \left\{ -\frac{[\log t_i - (a_0 + a_1 x_{1i} + a_2 x_{2i})]^2}{2\sigma^2} - \log(\sigma t_i \sqrt{2\pi}) \right\} + \sum \left\{ \log \left[1 - \Phi \frac{(\log t_i - (a_0 + a_1 x_{1i} + a_2 x_{2i})}{\sigma} \right] \right\}$$

The first term in the log-likelihood function sums over the uncensored observations, and the second sums over the right-censored observations. The MLE $(\hat{a}_1, \hat{a}_2, \hat{a}_0, \hat{\sigma})$ of (a_1, a_2, a_0, σ) can be obtained by applying the Newton–Raphson iterative procedure. The hypothesis-testing procedures discussed in Section 9.1.2 can be used to test whether the coefficients a_1 and a_2 are equal to zero. Table 11.5 shows that a_1 is significantly ($p = 0.0039$) different from zero, while a_2 is not ($p = 0.4514$). The signs of the regression coefficients indicate that age over 50 years has significantly negative effects on the survival time, while a 100% cellularity of marrow clot section also has a negative effect; however, the effect is not of significant importance to the survival time.

Let T be the survival time and CENS be an index (or dummy) variable with CENS = 0 if T is censored and 1 otherwise. Assume that the data are saved in a text file "C:\AML.DAT" with four numbers in each row, space-separated, which contains successively T, CENS, x1, and x2.

Let T be the survival time and CENS be an index (or dummy) variable with CENS = 0 if T is censored and 1 otherwise. Assume that the data are saved in a text file "C:\AML.DAT" with four numbers in each row, space-separated, which contains successively T, CENS, x1, and x2. The following SAS code is used to obtain the results in Table 11.5.

Table 11.5 Asymptotic Likelihood Inference for Data on 30 AML Patients Using a Lognormal Regression Model

Variable[a]	Regression Coefficient	Standard Error	X_L	p
INTERCPT (a_0)	3.3002	0.3750	77.4675	0.0001
x_1 (a_1)	−1.0417	0.3605	8.3475	0.0039
x_2 (a_2)	−0.2687	0.3568	0.5672	0.4514
SCALE (σ)	0.9075	0.1409		

[a] $x_1 = 1$ if patient $\geqslant 50$ years old, and 0 otherwise; $x_2 = 1$ if cellularity of marrow clot section is 100%, and 0 otherwise.

```
data w1;
  infile 'c:\aml.dat' missover;
  input t cens x1 x2;
run;
proc lifereg;
  model 1: model t*cens(0) = x1 x2 / d = lnormal;
run;
```

If BMDP is used, the following 2L code is suggested.

```
/input      file = 'c:\aml.dat'.
            variables = 4.
            format = free.
/print      level = brief.
/variable   names = t, cens, x1, x2.
/form       time = t.
            status = cens.
            response = 1.
/regress    covariates = x1, x2.
            accel = lnormal.
/end
```

11.6 EXTENDED GENERALIZED GAMMA REGRESSION MODEL

In this section we introduce a regression model that is based on an extended form of the generalized gamma distribution defined in Section 6.4. Assume that the survival time T of individual i and covariates $x_1, \ldots, x_p$ have the relationship given in (11.4.1), where ε has the log-gamma distribution with the density function $g(\varepsilon)$ and survivorship function $G(\varepsilon)$:

$$g(\varepsilon) = \frac{|\delta|[\exp(\delta\varepsilon)/\delta^2]^{1/\delta^2}\exp[-\exp(\delta\varepsilon)/\delta^2]}{\Gamma(1/\delta^2)} \tag{11.6.1}$$

$$G(\varepsilon) = \begin{cases} I\left[\dfrac{\exp(\delta\varepsilon)}{\delta^2}, \dfrac{1}{\delta^2}\right] & \text{if } \delta < 0 \qquad (11.6.2) \\ 1 - I\left[\dfrac{\exp(\delta\varepsilon)}{\delta^2}, \dfrac{1}{\delta^2}\right] & \text{if } \delta > 0 \qquad (11.6.3) \end{cases} \quad -\infty < \varepsilon < +\infty$$

This model is the extended generalized gamma regression model. It can be shown that T has the extended generalized gamma distribution with the density function

$$f(t, \alpha, \lambda, \gamma) = \frac{|\alpha|\gamma^\gamma \lambda_i^{\alpha\gamma} t^{\alpha\gamma - 1}\exp[-\gamma(\lambda_i t)^\alpha]}{\Gamma(\gamma)} \tag{11.6.4}$$

and survivorship function

$$S(t, \alpha, \lambda, \gamma) = \begin{cases} I(\gamma(\lambda_i t)^\alpha, \gamma) & \text{if } \alpha < 0 \qquad (11.6.5) \\ 1 - I(\gamma(\lambda_i t)^\alpha, \gamma) & \text{if } \alpha > 0 \qquad (11.6.6) \end{cases}$$

where

$$\lambda_i = \exp(-\mu_i) \qquad \alpha = \frac{\delta}{\sigma} \qquad \gamma = \frac{1}{\delta^2} \tag{11.6.7}$$

$\Gamma(x)$ is the complete gamma function defined in (6.2.9), $I(a, x)$ is the incomplete gamma function defined in (6.4.4), and δ is a shape parameter. We used the extended generalized gamma distribution in (11.6.4) here because it is the distribution used in SAS. The derivation is left to the reader as an exercise (Exercise 11.12).

The estimation procedures for the parameters, regression coefficients, and the covariate adjusted survivorship function are similar to those discussed in Sections 11.3 and 11.4.

Example 11.4 Consider the survival times (T) in days and a set of prognostic factors or covariates from 137 lung cancer patients, presented in Appendix I of Kalbfleisch and Prentice (1980). The covariates include the Karnofsky measure of the overall performance status (KPS) of the patient at entry into the trial, time in months from diagnosis to entry into the trial (DIAGTIME), age in years (AGE), prior therapy (INDPRI, yes or no), histological type of tumor, and type of therapy. There are four histological types of tumor: adeno, small, large, and squamous cell and two types of therapies: standard and experimental. The values of KPS have the following meanings: 10–30 completely hospitalized, 40–60 partial confinement, 70–90 able to care for self. Assume that the survival time follows the extended generalized gamma regression model, we wish to identify the most significant prognostic variables.

First we define several index (or dummy) variables for the categorical variables and the censoring status. Let CENS = 0 when the survival time T is censored and 1 otherwise; INDADE = 1, INDSMA = 1, and INDSQU = 1 if the type of cancer cell is adeno, small, and squamous, respectively, and 0 otherwise; INDTHE = 1 if the standard therapy is received and 0 otherwise; and INDPRI = 1 if there is a prior therapy and 0 otherwise. The model is

$$\begin{aligned}\log T_i = {} & a_0 + a_1\mathrm{KPS}_i + a_2\mathrm{AGE}_i + a_3\mathrm{DIAGTIME}_i + a_4\mathrm{INDPRI}_i \\ & + a_5\mathrm{INDTHE}_i + a_6\mathrm{INDADE}_i + a_7\mathrm{INDSMA}_i + a_8\mathrm{INDSQU}_i + \sigma\varepsilon_i\end{aligned} \tag{11.6.8}$$

where the density function of ε_i is defined in (11.6.1). Thus,

$$\begin{aligned}\mu_i = {} & a_0 + a_1\mathrm{KPS}_i + a_2\mathrm{AGE}_i + a_3\mathrm{DIAGTIME}_i + a_4\mathrm{INDPRI}_i + a_5\mathrm{INDTHE}_i \\ & + a_6\mathrm{INDADE}_i + a_7\mathrm{INDSMA}_i + a_8\mathrm{INDSQU}_i\end{aligned} \tag{11.6.9}$$

To estimate $a_1, \ldots, a_8$, δ, a_0, and σ, we construct the log-likelihood function by replacing μ in (11.6.7) and (11.6.4)–(11.6.6) with (11.6.9), then replacing $f(t_i, \mathbf{b})$ and $S(t_i, \mathbf{b})$ in the likelihood function (11.2.10) by those in (11.6.4) and (11.6.5) or (11.6.6). The MLE $(\hat{a}_1, \ldots, \hat{a}_8, \hat{\delta}, \hat{a}_0, \hat{\sigma})$ of $(a_1, \ldots, a_8, \delta, a_0, \sigma)$ can be

Table 11.6 Asymptotic Likelihood Inference on Lung Cancer Data Using a Generalized Gamma Regression Model

Variable	Regression Coefficient	Standard Error	X_L	p
INTERCPT (a_0)	2.176	0.719	9.143	0.003
INDADE (a_6)	−0.759	0.286	7.034	0.008
INDSMA (a_7)	−0.594	0.264	5.059	0.025
INDSQU (a_8)	0.150	0.291	0.266	0.606
KPS (a_1)	0.034	0.005	46.443	0.000
AGE (a_2)	0.008	0.009	0.845	0.358
DIAGTIME (a_3)	0.000	0.009	0.001	0.980
INDPRI (a_4)	−0.089	0.216	0.171	0.679
INDTHE (a_5)	0.168	0.185	0.823	0.364
SCALE (σ)	1.000	0.071		
SHAPE (δ)	0.450	0.223		
INTERCPT (a_0)	2.748	0.396	48.247	0.000
INDADE (a_6)	−0.766	0.280	7.492	0.006
INDSMA (a_7)	−0.534	0.258	4.284	0.039
INDSQU (a_8)	0.144	0.280	0.264	0.608
KPS (a_1)	0.033	0.005	45.497	0.000
SCALE (σ)	1.004	0.070		
SHAPE (δ)	0.473	0.206		

obtained in a manner similar to that used in Examples 11.2 and 11.3. The hypothesis-testing procedure defined in Section 11.2 can be used to test whether the coefficients $a_1, a_2, \ldots, a_8$ are equal to zero. The first part of Table 11.6 shows the results from SAS (where INTERCPT $= a_0$, SCALE $= \sigma$, and SHAPE $= \delta$).

Table 11.6 shows that a_1, a_6, and a_7 are significantly ($p < 0.05$) different from zero, whereas the other covariates are not ($p > 0.05$). That is, only KPS and the type of cancer cell have significant effects on the survival time. In particular, adeno cell carcinoma and small cell carcinoma have significant negative effects on survival time. Patients who have better Karnofsky performance status have a longer survival time. If we wish to include only KPS and cell type in the model, the lower part of Table 11.6 gives the results.

Assume that the coded data are saved in "C:\LCANCER.DAT" as a text file with 10 numbers in a row, space-separated, which contains data for T, CENS, KPS, AGE, DIAGTIME, INDPRI, INDTHE, INDADE, INDSMA, and INDSQU, in that order. The SAS code used to obtain Table 11.6 is

```
data w1;
  infile 'c:\lcancer.dat' missover;
  input t cens kps age diagtime indpri indthe indade indsma indsqu;
run;
```

```
proc lifereg;
   Model 1: model t*cens(0) = kps age diagtime indpri indthe indade indsma indsqu /
d = gamma;
   Model 2: model t*cens(0) = kps indade indsma indsqu / d = gamma;
run;
```

11.7 LOG-LOGISTIC REGRESSION MODEL

Assume that the relationship between the survival time T_i for individual i and a set of covariates, $x_1, \ldots, x_p$ can be expressed by the AFT model in (11.4.1), where ε_i has a logistic distribution with the density function

$$g(\varepsilon) = \frac{\exp(\varepsilon)}{[1 + \exp(\varepsilon)]^2} \tag{11.7.1}$$

and survivorship function

$$G(\varepsilon) = \frac{1}{1 + \exp(\varepsilon)} \tag{11.7.2}$$

This model is the log-logistic regression model. Then T has the log-logistic distribution defined in Section 6.5. The parameter α in the distribution is a function of the covariates:

$$\alpha_i = \exp\left(-\frac{\mu_i}{\sigma}\right) \qquad \gamma = \frac{1}{\sigma} \tag{11.7.3}$$

Substituting (11.7.3) in the survivorship function in (6.5.2), we obtain

$$\log \frac{S(t,\ \mathbf{b})}{1 - S(t,\ \mathbf{b})} = -\log(\alpha t^{\gamma}) = \frac{\mu}{\sigma} - \gamma \log t \tag{11.7.4}$$

or

$$\log \frac{S(t,\ \mathbf{b})}{1 - S(t,\ \mathbf{b})} = \frac{a_0}{\sigma} + \frac{1}{\sigma} \sum_{k=1}^{p} a_k x_k - \gamma \log t \tag{11.7.5}$$

where $\mathbf{b} = (a_0, a_1, \ldots, a_p, \sigma)$. Since $S(t_i, \mathbf{b})$ is the probability of surviving longer than t, $S(t_i, \mathbf{b})/[1 - S(t_i, \mathbf{b})]$ is the odds of surviving longer than t. Let OR_i and OR_j denote the odds of surviving longer than t for individuals i and j, respectively. The logarithm of the odds ratio is

$$\log \frac{\mathrm{OR}_i}{\mathrm{OR}_j} = \frac{1}{\sigma} \sum_{k=1}^{p} a_k (x_{ki} - x_{kj}) \tag{11.7.6}$$

This ratio is independent of time. Therefore, the log-logistic regression model is a proportional odds model, not a proportional hazards model.

Example 11.5 We fit the log-logistic regression model above to the data in Example 11.6.1 using only KPS and the three cancer cell type index variables. That is,

$$\log T_i = a_0 + a_1\text{KPS}_i + a_2\text{INDADE}_i + a_3\text{INDSMA}_i + a_4\text{INDSQU}_i + \sigma\varepsilon_i \tag{11.7.7}$$

where the density function of ε_i is defined in (11.7.1). Thus,

$$\mu_i = a_0 + a_1\text{KPS}_i + a_2\text{INDADE}_i + a_3\text{INDSMA}_i + a_4\text{INDSQU}_i \tag{11.7.8}$$

To estimate $\mathbf{b} = (a_0, a_1, \ldots, a_4, \sigma)'$, we construct the log-likelihood function by using the α and γ in (11.7.3) as parameters in the density and survivorship functions of the log-logistic distribution in Section 6.5. The resulting log-likelihood function for the 137 observed exact or right-censored survival times is

$$\begin{aligned}
l(\mathbf{b}) &= \sum \left\{ \frac{-\mu_i}{\sigma} - \log\sigma + \frac{1-\sigma}{\sigma}\log t_i - 2\log\left[1 + \exp\left(\frac{-\mu_i}{\sigma}\right) t_i^{1/\sigma}\right]\right\} \\
&\quad + \sum \left\{ -\log\left[1 + \exp\left(\frac{-\mu_i}{\sigma}\right) t_i^{1-\sigma}\right]\right\} \\
&= \sum \Bigg(-\frac{1}{\sigma}(a_0 + a_1\text{KPS}_i + a_2\text{INDADE}_i + a_3\text{INDSMA}_i + a_4\text{INDSQU}_i) \\
&\quad - \log\sigma + \frac{1-\sigma}{\sigma}\log t_i \\
&\quad - 2\log\Bigg\{1 + \exp\Bigg[-\frac{1}{\sigma}(a_0 + a_1\text{KPS}_i + a_2\text{INDADE}_i + a_3\text{INDSMA}_i \\
&\qquad + a_4\text{INDSQU}_i)\Bigg] t_i^{1/\sigma}\Bigg\}\Bigg) \\
&\quad - \sum \Bigg(\log\Bigg\{1 + \exp\Bigg[-\frac{1}{\sigma}(a_0 + a_1\text{KPS}_i + a_2\text{INDADE}_i + a_3\text{INDSMA}_i \\
&\qquad + a_4\text{INDSQU}_i)\Bigg] t_i^{1/\sigma}\Bigg\}\Bigg)
\end{aligned}$$

The first term in the log-likelihood function sums over the uncensored observations, and the second sums over the right-censored observations. The MLE $(\hat{a}_1, \ldots, \hat{a}_4, \hat{a}_0, \hat{\sigma})$ of $(a_1, \ldots, a_4, a_0, \sigma)$ are given in Table 11.7, with their

Table 11.7 Asymptotic Likelihood Inference on Lung Cancer Data Using a Log-Logistic Regression Model

Variable	Regression Coefficient	Standard Error	X_L	p	$\exp(a_i/a)$
INTERCPT (a_0)	2.451	0.344	50.911	0.000	—
INDADE (a_2)	−0.749	0.261	8.217	0.004	0.275
INDSMA (a_3)	−0.661	0.240	7.565	0.006	0.321
INDSQU (a_4)	0.029	0.264	0.012	0.913	1.051
KPS (a_1)	0.036	0.004	66.885	0.000	1.064
SCALE (σ)	0.581	0.043	—	—	—

standard errors, likelihood ratio test statistics (X_L), and p values. The results are similar to those obtained from fitting the general gamma regression model in Example 11.4.

In addition, using (11.7.5) and (11.7.6), we can obtain odds ratios for the covariates. For example, let the odds of surviving to time t for four patients with the same KPS but different cell type (adeno, small, squamous and large) be denoted by OR_{AD}, OR_{SM}, OR_{SQ}, and OR_{LA}, respectively; then the log-odds ratios of the individuals with adeno, small, and squamous cell types to the one with large cell type are, respectively,

$$\log\frac{\mathrm{OR}_{AD}}{\mathrm{OR}_{LA}} = \frac{a_2}{\sigma} \qquad \log\frac{\mathrm{OR}_{SM}}{\mathrm{OR}_{LA}} = \frac{a_3}{\sigma} \qquad \log\frac{\mathrm{OR}_{SQ}}{\mathrm{OR}_{LA}} = \frac{a_4}{\sigma}$$

Replacing a_2, a_3, a_4, and σ with their estimates, we have

$$\frac{\mathrm{OR}_{AD}}{\mathrm{OR}_{LA}} = \exp\left(\frac{\hat{a}_2}{\hat{\sigma}}\right) = 0.275$$

$$\frac{\mathrm{OR}_{SM}}{\mathrm{OR}_{LA}} = \exp\left(\frac{\hat{a}_3}{\hat{\sigma}}\right) = 0.321$$

$$\frac{\mathrm{OR}_{SQ}}{\mathrm{OR}_{LA}} = \exp\left(\frac{\hat{a}_4}{\hat{\sigma}}\right) = 1.051$$

These results mean that in lung cancer patients, persons with adeno and small cell type have odds of only about one-fourth and one-third, respectively, of those with large cell type. The odds of persons with large cell carcinoma are not significantly different from those of patients with squamous cell carcinoma. Further, when ignoring cell type, $\exp(\hat{a}_1/\hat{\sigma})$ represents an increase (or decrease) in the odds for any 1-unit increase in the KPS measure. In this case,

$\exp(\hat{a}_1/\hat{\sigma}) = 1.064$; thus for a 1-unit increase in the KPS measure, the odds increase by 6.4%. The results are, in general, consistent with those obtained in Example 11.4.

The following SAS code can be used to obtain the results in Table 11.7.

```
data w1;
  infile 'c:\lcancer.dat' missover;
  input t cens kps age diagtime indpri indthe indade indsma indsqu;
run;
proc lifereg;
  model t*cens(0) = kps indade indsma indsqu / d = llogistic;
run;
```

The following BMDP 2L code is also applicable.

```
/input      file = 'c:\lcancer.dat'.
            variables = 10.
            format = free.
/print      level = brief.
/variable   names = t, cens, kps, age, diagtime, indpri, indthe, indade, indsma, indsqu.
/form       time = t.
            status = cens.
            response = 1.
/regress    covariates = kps, indade, indsma, indsqu.
            accel = llogistic.
/end
```

11.8 OTHER PARAMETRIC REGRESSION MODELS

In this section we discuss two models in which the survival time T is assumed to follow the exponential distribution with density and survivorship functions as defined in (6.1.1) and (6.1.3), respectively, and the mean survival time $1/\lambda$ or hazard rate λ has the following linear relationship with the covariates:

$$\text{Model 1:} \quad \frac{1}{\lambda_i} = a_0 + \sum_{j=1}^{p} a_j x_{ji}$$

$$\text{Model 2:} \quad \lambda_i = a_0 + \sum_{j=1}^{p} a_j x_{ji}$$

Model 1 is considered by Feigl and Zelen (1965) and extended to include censored data by Zippin and Armitage (1966). Model 2 is used by Byar et al. (1974).

Model 1

Suppose that n patients are entered in a study; r of these die and $s = n - r$ are still alive at the end of the study. Let $t_1, \ldots, t_r$ be the exact survival times of the r deaths and $t_1^+, \ldots, t_s^+$ be the s censoring times. Furthermore, let x_{ji}, $i = 1, \ldots, n$, $j = 1, \ldots, p$, be the observed value of the jth covariate of the ith patient. The model assumes that the mean survival time is linearly related to the covariates:

$$\frac{1}{\lambda_i} = a_0 + \sum_{j=1}^{p} a_j x_{ji} = \sum_{j=0}^{p} a_j x_{ji} \tag{11.8.1}$$

where $x_{0i} \equiv 1$. The term a_0 represents the underlying hazard in the sense that $1/a_0$ is the hazard rate λ_i when covariates are ignored or all x_{ji}'s are zero. Then the likelihood function of the n survival times under the model (11.8.1) can be written as

$$\begin{aligned} L(a_0, a_1, \ldots, a_p) = \prod_{i=1}^{r} \left(\sum_{j=0}^{p} a_j x_{ji} \right)^{-1} \exp\left[-t_i \left(\sum_{j=0}^{p} a_j x_{ji} \right)^{-1} \right] \\ \times \prod_{k=1}^{s} \exp\left[-t_k^+ \left(\sum_{j=0}^{p} a_j x_{jk} \right)^{-1} \right] \end{aligned} \tag{11.8.2}$$

The log-likelihood is then

$$\begin{aligned} l(a_0, a_1, \ldots, a_p) = -\sum_{i=1}^{r} \log\left(\sum_{j=0}^{p} a_j x_{ji} \right) - \sum_{i=1}^{r} t_i \left(\sum_{j=0}^{p} a_j x_{ji} \right)^{-1} \\ - \sum_{k=1}^{r} t_k^+ \left(\sum_{j=0}^{p} a_j x_{jk} \right)^{-1} \end{aligned} \tag{11.8.3}$$

The maximum likelihood estimates of a_j, $j = 0, 1, \ldots, p_j$, may be obtained by solving simultaneously the $p + 1$ equations:

$$\begin{aligned} -\sum_{i=1}^{r} \left(\sum_{j=1}^{p} a_j x_{ji} \right) + \sum_{i=1}^{r} t_i \left(\sum_{j=1}^{p} a_j x_{ji} \right)^{-2} + \sum_{k=1}^{s} t_k^+ \left(\sum_{j=1}^{p} a_j x_{jk} \right)^{-2} = 0 \\ -\sum_{i=1}^{r} x_{ji} \left(\sum_{j=1}^{p} a_j x_{ji} \right)^{-1} + \sum_{i=1}^{r} t_i x_{ji} \left(\sum_{j=1}^{p} a_j x_{ji} \right)^{-2} \\ + \sum_{k=1}^{s} t_k^+ x_{jk} \left(\sum_{j=1}^{p} a_j x_{jk} \right)^{-2} = 0 \qquad j = 1, \ldots, p \end{aligned} \tag{11.8.4}$$

Again, this can be done by Newton–Raphson iterative procedures described in Section 7.1.

After obtaining the MLE, $\hat{a}_j$, $j = 0, 1, \ldots, p$, the log-likelihood function can be used to test the significance of the covariates. The procedure is exactly the same as those used in Example 11.1.

The survivorship function (for the ith patient) adjusted for the covariates can be obtained from

$$\begin{aligned}\hat{S}_i(t) &= \exp(-\hat{\lambda}_i t) \\ &= \exp\left[-t\left(\sum_{j=0}^{p} \hat{a}_j x_{ji}\right)^{-1}\right] \end{aligned} \tag{11.8.5}$$

Model 2

Byar et al. (1974) developed another exponential model relating survival time to concomitant information for prostate cancer patients in which the individual hazard is linearly related to the possible prognostic variables:

$$\lambda_i = a_0 + \sum_{j=1}^{p} a_j x_{ji} = \sum_{j=0}^{p} a_j x_{ji} \tag{11.8.6}$$

where $x_{0i} = 1$. Similar to the model of Feigl and Zelen (1965), a_0 is the underlying hazard rate when covariates are ignored, force of mortality or the intercept.

Suppose that r of the n patients are dead and $s = n - r$ are still alive at the end of the study; then the likelihood function is

$$\begin{aligned}L(a_0, a_1, \ldots, a_p) = &\prod_{i=1}^{r}\left(\sum_{j=0}^{p} a_j x_{ji}\right)\exp\left[-\left(\sum_{j=0}^{p} a_j x_{ji}\right)t_i\right] \\ &\times \prod_{k=1}^{s}\exp\left[-\left(\sum_{j=0}^{p} a_j x_{jk}\right)t_k^{+}\right] \end{aligned} \tag{11.8.7}$$

Taking the logarithms of (11.8.7), we obtain the log-likelihood function

$$l(a_0, a_1, \ldots, a_p) = \sum_{i=1}^{r}\left[\log\left(\sum_{j=0}^{p} a_j x_{ji}\right) - \left(\sum_{j=0}^{p} a_j x_{ji}\right)t_i\right] - \sum_{k=1}^{s}\left(\sum_{j=0}^{p} a_j x_{jk}\right)t_k^{+} \tag{11.8.8}$$

To obtain the MLEs of the a_j's, we need to solve simultaneously the following $p + 1$ equations:

$$\sum_{i=1}^{r}\left(\frac{x_{ji}}{\sum_{j=0}^{p} \hat{a}_j x_{ji}} - x_{ji} t_i\right) - \sum_{k=1}^{s} x_{jk} t_k^{+} = 0 \qquad j = 0, 1, \ldots, p \tag{11.8.9}$$

These equations can be solved simultaneously by using the Newton–Raphson iterative procedure.

After the MLEs of a_j, $j = 0, 1, \ldots, p$, are obtained, the log-likelihood function can be used to test the significance of the covariates by following the same procedure as that used in Example 11.1.

The survivorship function for the ith individual adjusted for the covariates can be estimated from

$$\begin{aligned} \hat{S}_i(t) &= \exp(-\hat{\lambda}_i t) \\ &= \exp\left(-t \sum_{j=0}^{p} \hat{a}_j x_{ji}\right) \end{aligned} \tag{11.8.10}$$

11.9 MODEL SELECTION METHODS

To identify important risk factors using a parametric approach, one needs to select a most appropriate parametric model and identify the most significant subset of covariates. In this section we first discuss, for a given parametric model, how to choose an optimal subset of the covariates that have statistically significant effects on the survival time. Second, we consider if the significant covariates are known, how to determine which parametric model is most appropriate. Third, we discuss a method that can be used to compare among parametric models with different subsets of covariates.

11.9.1 Selection of Most Significant Covariates for a Known Parametric Model

For a known parametric model, the following methods can be used to select an optimal subset of the covariates in the sense that the subset selected has the most statistically significant effects on the survival time among all subsets of the covariates. These methods include the forward, backward, stepwise, AIC, and BIC selection procedures commonly used in ordinary regression analyses. We give only a brief outline here. Interested readers are referred to books on ordinary regression analysis.

Forward Selection Procedure

The forward selection procedure is an adding process in which one covariate is selected and added to the model at every step. First, we have to estimate the specific parameters that define the parametric model and the coefficients of the adjusting covariates, if any, that are forced into the model. For example, to have age- and gender-adjusted results, age and gender must be included in the model, whether or not they are significant. Then the adjusted chi-square statistics for each covariate not in the model are computed and the largest of these statistics is identified. If the largest chi-square statistic is significant at the

α level specified (usually, $\alpha = 0.15$) for entry, the corresponding covariate is added to the model.

Let $\mathbf{a}_1$ be the vector of the parameters or coefficients of covariates already in the model and $l(\cdot)$ be the log-likelihood function. The forward selection procedure will select x_j, which is not yet in the model, to enter the model if the difference between the log-likelihood values with x_j and without x_j is largest among all the x_k's that are not in the model. That is, the coefficient a_j of x_j satisfies

$$\begin{aligned} X_L &= 2[(l(\hat{a}_j, \hat{\mathbf{a}}_1) - l(\hat{\mathbf{a}}_{1j}(0))] \\ &= \max_k \{2[l(\hat{a}_k, \hat{\mathbf{a}}_1) - l(\hat{\mathbf{a}}_{1k}(0))], \text{ for any } x_k \text{ that is not in the model}\} \end{aligned} \tag{11.9.1}$$

and $X_L > \chi^2_{1,\alpha}$ where a_k is the coefficient of x_k not yet in the model, $(\hat{a}_k, \hat{\mathbf{a}}_1)$, is the MLE of $(a_k, \mathbf{a}_1)$, $\hat{\mathbf{a}}_{1k}(0)$ is the MLE of $\mathbf{a}_1$ given $a_k = 0$, and $\chi^2_{1,\alpha}$ is the α-level critical point of the chi-square distribution with 1 degree of freedom. In the forward selection procedure, once a covariate is entered into the model, it will never be removed. The process is repeated until none of the remaining covariates meet the level α specified for entry or until a predetermined number of covariates have been entered.

Backward Selection Procedure

The backward selection procedure is an elimination process in which all the covariates are included in the model at the beginning and are removed one by one according to a significance criterion. The specific parameters that define the parametric model and the coefficients of all the covariates are estimated first. Then the Wald test is used to examine each covariate. The least significant covariate that does not meet the specified level α (usually, $\alpha = 0.15$) for staying in the model is removed. That is, covariate x_j will be removed from the model if

$$X_W = \frac{\hat{a}_j^2}{v_{jj}^2} = \min_k \left(\frac{\hat{a}_k^2}{v_{kk}^2} \text{ for any } x_k \text{ that is in the model} \right) \tag{11.9.2}$$

and $X_W \leqslant \chi^2_{1,\alpha}$ where a_j is the corresponding coefficient for x_j and v_{jj}^2 is the estimated variance of $\hat{a}_j$. In the backward selection procedure, once a covariate is removed from the model, it remains excluded. The process is repeated until all the covariates remained in the model meet the specified significance level α for staying or until a predetermined number of covariates remain in the model. The advantages of the backward procedure have been discussed by Mantel (1970).

Stepwise Selection Procedure

The stepwise selection procedure is a combination of forward and backward selection procedures. At first, it is similar to the forward selection procedure; however, covariates already in the model do not necessarily remain. Covariates already in the model may be removed later if they are no longer significant. The stepwise selection process terminates if no significant covariate can be added to the model or if the covariate just entered into the model is removed and no more covariates can be added.

Information Criterion (AIC and BIC) Procedures

The Baysian information criterion (BIC) selection procedure discussed in Section 9.3 can be used to select the best parametric model with covariates. This can be done easily by replacing the log-likelihood function $l(\hat{\mathbf{b}})$ in (9.3.1) with the log-likelihood function with subsets of covariates defined in previous sections of this chapter. The subset of covariates that produces the largest r value in (9.3.1) among all possible subsets is the choice. If the number of covariates is large, one may apply the forward, backward, and stepwise selection method first to reduce the number of candidate covariates, then use the BIC procedure. The AIC criterion can be applied in a similar manner.

11.9.2 Selection of a Parametric Model with a Fixed Subset of Covariates

If the most significant subset of covariates is known, selection of an appropriate parametric model can be carried out by using a procedure similar to those based on the likelihood functions and discussed in Section 9.2. The procedures are exactly the same except that all the likelihood functions are replaced by those with covariates, for example, those given in (11.3.10) and Examples 11.2 and 11.5. With computer software packages available commercially, the procedure can easily be applied. The following example illustrates the application.

Example 11.6 Consider the lung cancer patients who did not receive any prior therapy in Example 11.4. Assume that the three covariates KPS, INDADE, and INDSMA are most significant. For these three fixed covariates, the log-likelihood values based on the exponential, Weibull, lognormal, log-logistic, and generalized gamma models are given in Table 11.8. From this table, the lognormal, Weibull and exponential models (relative to the generalized gamma model), with the three covariates, are rejected at $\alpha = 0.0325$, 0.016 and 0.024, respectively. It appears that the exponential model, relative to the Weibull, is not rejected ($p = 0.194$). However, since the exponential model belongs to the Weibull distribution family and the Weibull model has been rejected, the exponential model with the three covariates is not appropriate for the data, as noted earlier in Chapter 9. Thus, we conclude that none of the three models (exponential, Weibull, and lognormal), with covariates, provide an appropriate fit to the data. In Example 11.7 we will see that the log-logistic model is the best fit among all these models.

Table 11.8 Goodness-of-Fit Tests Based on Asymptotic Likelihood Inference on Lung Cancer Data

Distribution	LL[a]	LLR[a]	p^a	BIC	AIC
Extended generalized gamma	−132.793	—	—	−146.517	−144.793
Log-logistic	−131.230	—	—	−142.667	−141.230
Lognormal	−135.022	4.459[b]	0.035	−146.459	−145.022
Weibull	−135.669	5.752[c]	0.016	−147.106	−145.669
Exponential	−136.512	7.438[d]	0.024	−145.661	−144.512
Exponential	−136.512	1.686[e]	0.194	—	—

[a] LL, log-likelihood; LLR, log-likelihood ratio statistic; p, probability that the respective chi-square random variable $>$LLR.
[b] Lognormal relative to extended generalized gamma.
[c] Weibull relative to extended generalized gamma.
[d] Exponential relative to extended generalized gamma.
[e] Exponential relative to Weibull.

Using the data file "C:\LCANCER.DAT" described in Example 11.4, the following SAS code can be used to obtain Table 11.8.

```
data w1;
  infile 'c:\lcancer.dat' missover;
  input t cens kps age diagtime indpri indthe indade indsma indsqu;
  if indpri = 0;
run;
proc lifereg;
  Model 1: model t*cens(0) = kps indade indsma / d = exponential;
  Model 2: model t*cens(0) = kps indade indsma / d = weibull;
  Model 3: model t*cens(0) = kps indade indsma / d = lnormal;
  Model 4: model t*cens(0) = kps indade indsma / d = gamma;
  Model 5: model t*cens(0) = kps indade indsma / d = llogistic;
run;
```

11.9.3 Selection of a Parametric Model and an Optimal Subset of Covariates Simultaneously: AIC and BIC Procedures

The extended AIC and BIC criteria, which include covariates, can be applied not only to select the most significant covariates for a given parametric model, but also, simultaneously, to select the best parametric model. The procedure may be tedious if the number of covariates to be considered is large. However, in practice, the number of covariates worthy of consideration in a model is usually reduced after univariate analyses, as described in Section 11.1. Therefore, the AIC or BIC procedure may not be too difficult to apply. With the aid of software packages, we can apply the forward, backward, and stepwise

selection methods in Section 11.9.1 first to fit different parametric regression models to the data and then include in the AIC or BIC procedure all or a subset of the significant covariates identified in each fit.

Example 11.7 Consider the lung cancer data of Example 11.6. We apply the methods of Section 11.9.1 to select the best subset of covariates separately for the exponential, Weibull, lognormal, log-logistic, and generalized gamma models. The same three covariates (KPS, INDADE, and INDSMA) are selected (at the 0.05 level) as the most significant covariates in every of these parametric models. The last column of Table 11.8 gives the r values of the BIC for the different parametric models with the same three covariates. Based on these values, the log-logistic model with the three covariates should be selected as the final model for the data since its BIC or AIC value is the largest among all the models. However, it is not known if the log-logistic model is significantly better than the other models.

11.9.4 Cox–Snell Residual Procedure with Covariates

The AFT models in Sections 11.2 to 11.7 assume the following linear relationship between log T and the p covariates:

$$\log T_i = a_0 + \sum_{k=1}^{p} a_k x_{ki} + \sigma\varepsilon_i = \mu_i + \sigma\varepsilon_i \tag{11.9.3}$$

where ε_i has survival function $G(\varepsilon)$. Once a specified parametric model and a subset of covariates are selected, to assess the goodness of fit of this model, one approach is to compute the regression residuals

$$\hat{\varepsilon}_i = \frac{\log t_i - \hat{\mu}_i}{\hat{\sigma}} \qquad i = 1, 2, \ldots, n \tag{11.9.4}$$

where

$$\hat{\mu}_i = \hat{a}_0 + \sum_{k=1}^{p} \hat{a}_k x_{ki}$$

and $\hat{a}_0, \hat{a}_1, \hat{a}_2, \ldots, \hat{a}_p$ and $\hat{\sigma}$ are the MLE of $a_0, a_1, a_2, \ldots, a_p$ and σ, respectively, and t_i's are observed survival times. An $\hat{\varepsilon}_i$ is taken as censored if the corresponding t_i is censored. If the model fitted is correct, the corresponding survival function $G(\varepsilon)$ is the survival function of the fitted model. For example, if T indeed follows the log-logistic regression model with a selected subset of covariates, the corresponding $\hat{\varepsilon}_i$'s should follow the log-logistic distribution. Moreover, if the fitted model is correct, the Cox–Snell residuals defined in (8.4.1) are

$$r_i = -\log G(\hat{\varepsilon}_i; \hat{\mathbf{d}}) = -\log G\left(\frac{\log t_i - \hat{\mu}_i}{\hat{\sigma}}; \hat{\mathbf{d}}\right) \qquad i = 1, 2, \ldots, n \tag{11.9.5}$$

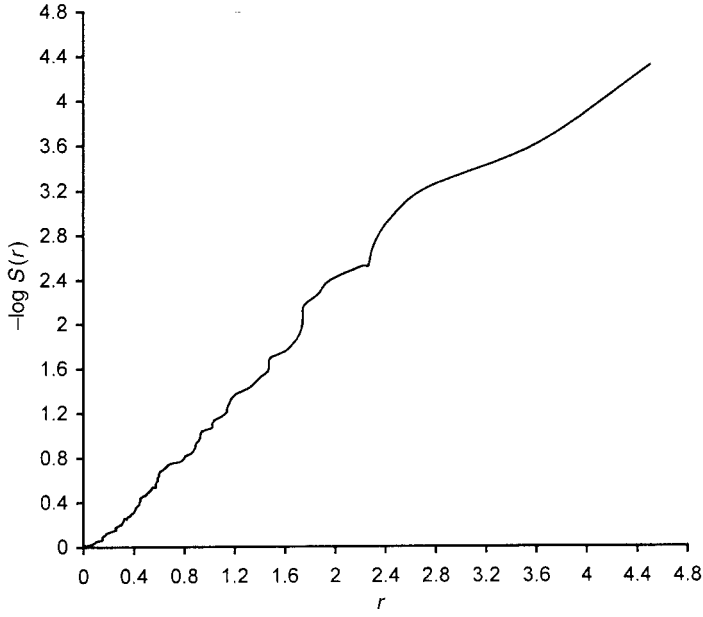


Figure 11.2 Cox–Snell residuals plot from the fitted exponential model on lung cancer data.

where $\hat{\mathbf{d}}$ is the MLE of the parameters of the distribution. Let $\hat{S}(r)$ denote the estimated survival function of r_i's. From Section 8.4, the graph of r_i versus $-\log \hat{S}(r_i)$, $i = 1, 2, \ldots, n$, should be closed to a straight line with unit slope and zero intercept if the fitted model for the survival time T is correct. This graphical method can be used to assess the goodness of fit of the parametric regression model.

Example 11.8 Figures 11.2 to 11.6 show the Cox–Snell residuals plots from fitting the exponential, Weibull, lognormal, log-logistic, and extended generalized gamma models, respectively with the three covariates KPS, INDADE, and INDSMA, to the lung cancer data in Example 11.6. The five graphs look similar, and all are close to a straight line with unit slope and zero intercept. No significant differences are observed in these graphs. The results obtained are similar to those from Examples 11.6 and 11.7. The differences among the five distributions are small with the log-logistic distribution being slightly better than the others.

Using the same data file "C:\LCANCER.DAT" as in Example 11.6.1, the following SAS code can be used to obtain the Cox–Snell residuals based on the exponential, Weibull, lognormal, log-logistic, and generalized gamma model with the three covariates, KPS, INDADE, and INDSMA.

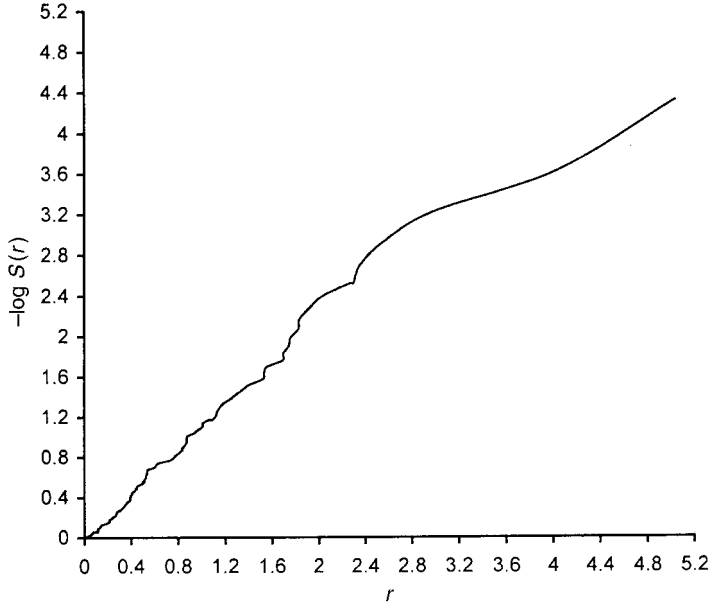


Figure 11.3 Cox–Snell residuals plot from the fitted Weibull model on lung cancer data.

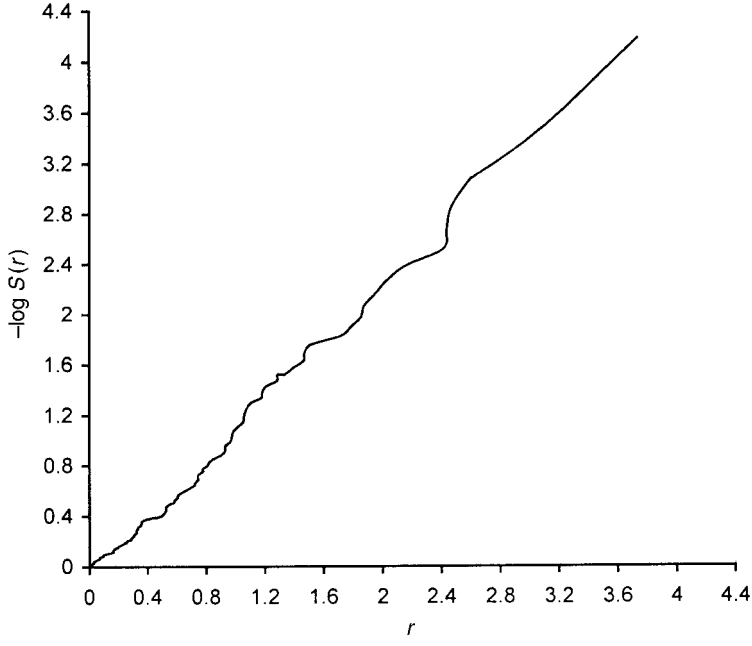


Figure 11.4 Cox–Snell residuals plot from the fitted lognormal model on lung cancer data.

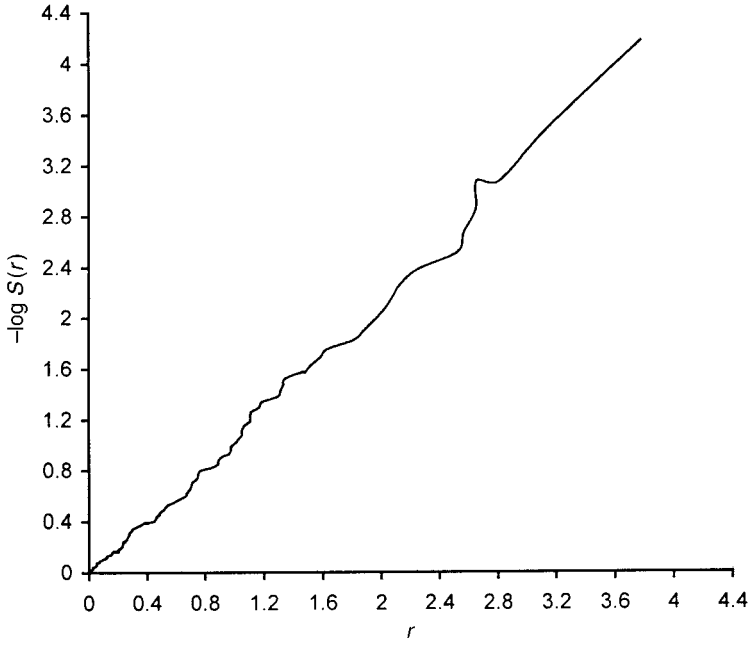


Figure 11.5 Cox–Snell residuals plot from the fitted log-logistic model on lung cancer data.

```
data w1;
   infile 'c:\lcancer.dat' missover;
   input t cens kps age diagtime indpri indthe indade indsma indsqu;
   if indpri = 0;
run;
proc lifereg noprint;
   a: model t*cens(0) = kps indade indsma / d = exponential;
   output out = wa cdf = f;
   b: model t*cens(0) = kps indade indsma / d = weibull;
   output out = wb cdf = f;
   c: model t*cens(0) = kps indade indsma / d = lnormal;
   output out = wc cdf = f;
   d: model t*cens(0) = kps indade indsma / d = gamma;
   output out = wd cdf = f;
   e: model t*cens(0) = kps indade indsma / d = llogistic;
   output out = we cdf = f;
run;
data wa;
   set wa;
   model = 'Exponential';
data wb;
```

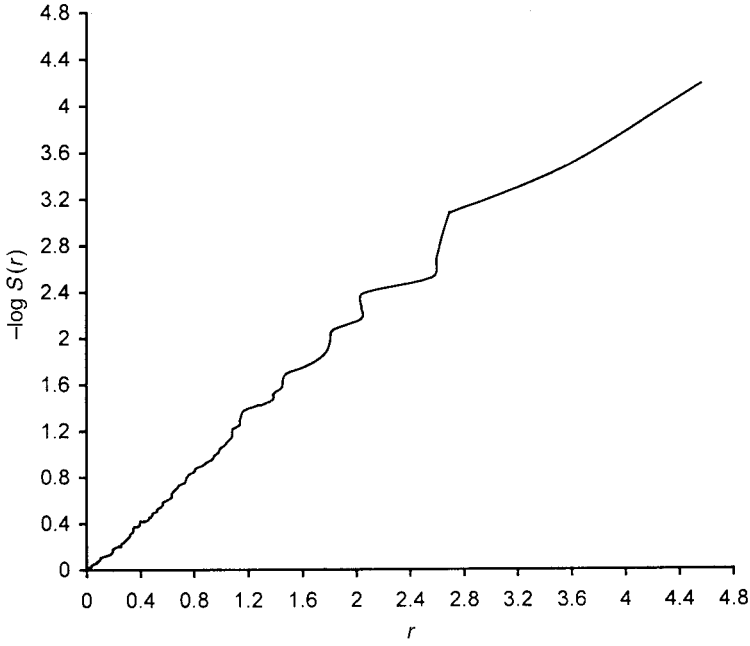


Figure 11.6 Cox–Snell residuals plot from the fitted extended generalized gamma model on lung cancer data.

```
   set wb;
   model = 'Weibull';
data wc;
   set wc;
   model = 'LNnormal';
data wd;
   set wd;
   model = 'Gamma';
data we;
   set we;
   model = 'LLogistic';
data w2;
   set wa wb wc wd we;
   rcs = −log(1 − f);
run;
proc sort;
   by model;
run;
proc lifetest notable outs = ws noprint;
   time rcs*cens(0);
   by model ;
```

```
run;
data ws;
   set ws;
   mls = −log(survival);
run;
title 'Cox-Snell Residuals (rcs) and -log(estimated survival function of rcs) (mls)';
proc print data = ws;
   var model rcs mls;
run;
```

Bibliographical Remarks

An excellent expository paper on statistical methods for the identification and use of prognostic factors has been written by Armitage and Gehan (1974). Many studies of prognostic factors have been published, including Sirott et al. (1993), Brancato et al. (1997), Linka et al. (1998), and Lassarre (2001). The accelerated failure time (AFT) model was introduced by Cox (1972). The detailed statistical inference of the AFT models and the theoretical aspects of model-selecting methods are included in the works cited in the bibliographical remarks at the end of Chapter 9 and in the papers and books cited in this chapter.

EXERCISES

11.1 Consider the data given in Exercise Table 3.1. In addition to the five skin tests, age and gender may also have prognostic value. Examine the relationship between survival and each of the seven possible prognostic variables as in Table 3.12. For each variable, group the patients according to different cutoff points. Estimate and draw the survival function for each subgroup by the product-limit method and then use the methods discussed in Chapter 5 to compare survival distributions of the subgroups. Prepare a table similar to Table 3.12. Interpret your results. Is there a subgroup of any variable that shows significantly longer survival times? (For the skin test results, use the larger diameter of the two.)

11.2 Consider the seven variables in Exercise 11.1. Use the Weibull regression model to identify the most significant variables. Compare your results with that obtained in Exercise 11.1.

11.3 Consider the data given in Exercise Table 3.3. Examine the relationship between remission duration and survival time and each of the nine possible prognostic variables: age, gender, family history of melanoma, and the six skin tests. Group the patients according to different cutoff

points. Estimate and draw remission and survival curves for each subgroup. Compare the remission and survival distributions of subgroups using the methods discussed in Chapter 5. Prepare tables similar to Table 3.8.

11.4 Perform the following analyses: (1) Use the exponential, Weibull, lognormal, generalized gamma, or log-logistic regression models separately to identify the significant variables in Exercise 11.3 for their relative importance to remission duration and survival time. (2) Select a model among these final models using the BIC or AIC method. (3) Calculate separately the respective likelihood for the exponential, Weibull, lognormal, or generalized gamma regression model with the fixed variables in the model selected in step (2), then use the method in Section 11.9.2 to choose a model and see whether this model is the model selected in step (2).

11.5 Perform the same analyses as in Exercise 11.4 for survival time in the 157 diabetic patients given in Exercise Table 3.4.

11.6 Using the notations in Example 11.2, show that if we use the following model to replace the model defined in (11.4.6), $\log T_i = a_0 + a_1\text{LOW}_i + a_2\text{UNSA}_i + \sigma\varepsilon_i = \mu_i + \sigma\varepsilon_i$, the hypothesis $H_0: h_s = h_u$ is equivalent to $H_0: a_2 = 0$.

11.7 Following Examples 11.2 and 11.3, obtain the log-likelihood function based on (11.6.8) for the 137 observed exact and right-censored survival times from the lung cancer patients.

11.8 Using the same notation as in Example 11.5, show that if we use the model $\log T_i = a_0 + a_1\text{KPS}_i + a_2\text{INDLAR}_i + a_3\text{INDSMA}_i + a_4\text{INDSQU}_i + \sigma\varepsilon_i$, where INDLAR = 1 if the type of cancer is large, and 0 otherwise, to replace the model defined in (11.7.8), the hypotheses $H_0: a_3 = 0$ and $H_0: a_4 = 0$ are equivalent to $H_0: OR_{SM} = OR_{AD}$ and $H_0: OR_{SQ} = OR_{AD}$, respectively. Moreover, if we use the model $\log T_i = a_0 + a_1\text{KPS}_i + a_2\text{INDLAR}_i + a_3\text{INDADE}_i + a_4\text{INDSQU}_i + \sigma\varepsilon_i$ to replace the model defined in (11.7.8), the hypothesis $H_0: a_4 = 0$ is equivalent to $H_0: OR_{SQ} = OR_{SM}$.

11.9 Let ε be a survival time with the density function $g(\varepsilon) = \exp[\varepsilon - \exp(\varepsilon)]$. Show that the survival time T defined by $\log T = \mu + \sigma\varepsilon$ has the Weibull distribution with $\lambda = \exp(-\mu/\sigma)$ and $\gamma = 1/\sigma$ by applying the density transformation rule in (11.2.11).

11.10 Let ε be a survival time with the standard normal distribution $N(0, 1)$. Show that the survival time T defined by $\log T = \mu + \sigma\varepsilon$ has the lognormal distribution by applying the density transformation rule in (11.2.11).

11.11 Let u be a survival time with the density function $f(u)$,

$$f(u) = \frac{\exp[u/\delta^2 - \exp(u)]}{\Gamma(1/\delta^2)}$$

where $\Gamma(\cdot)$ is the gamma function defined in (6.2.8).

(a) Show that the survival time ε defined by $\varepsilon = \mu/\delta + (\log \delta^2)/\delta$ has the following density function,

$$g(\varepsilon) = \frac{|\delta|[\exp(\delta\varepsilon)/\delta^2]^{1/\delta^2} \exp[-\exp(\delta\varepsilon)/\delta^2]}{\Gamma(1/\delta^2)} \qquad -\infty < \varepsilon < +\infty$$

and survival function,

$$G(\varepsilon) = \begin{cases} I\left(\dfrac{\exp(\delta\varepsilon)}{\delta^2}, \dfrac{1}{\delta^2}\right) & \text{if } \delta < 0 \\ 1 - I\left(\dfrac{\exp(\delta\varepsilon)}{\delta^2}, \dfrac{1}{\delta^2}\right) & \text{if } \delta > 0 \end{cases}$$

where $I(\cdot, \cdot)$ is the incomplete gamma function defined as in (6.4.4).

(b) Show that the survival time T defined by $\log T = \mu + \delta\varepsilon$ has the extended gamma density function defined in (11.6.4).

11.12 If ε has a logistic distribution with the density function

$$g(\varepsilon) = \frac{\exp(\varepsilon)}{[1 + \exp(\varepsilon)]^2}$$

show that the survival time T defined by $\log T = \mu + \sigma\varepsilon$ has the log-logistic distribution with $\alpha = \exp(-\mu/\sigma)$ and $\gamma = 1/\sigma$ by applying the density transformation rule in (11.2.11).

CHAPTER 12

Identification of Prognostic Factors Related to Survival Time: Cox Proportional Hazards Model

In Chapter 11 we discussed parametric survival methods for model fitting and for identifying significant prognostic factors. These methods are powerful if the underlying survival distribution is known. The estimation and hypothesis testing of parameters in the models can be conducted by applying standard asymptotic likelihood techniques. However, in practice, the exact form of the underlying survival distribution is usually unknown and we may not be able to find an appropriate model. Therefore, the use of parametric methods in identifying significant prognostic factors is somewhat limited. In this chapter we discuss a most commonly used model, the Cox (1972) proportional hazards model, and its related statistical inference. This model does not require knowledge of the underlying distribution. The hazard function in this model can take on any form, including that of a step function, but the hazard functions of different individuals are assumed to be proportional and independent of time. The usual likelihood function is replaced by the partial likelihood function. The important fact is that the statistical inference based on the partial likelihood function is similar to that based on the likelihood function.

12.1 PARTIAL LIKELIHOOD FUNCTION FOR SURVIVAL TIMES

The Cox proportional hazards model possesses the property that different individuals have hazard functions that are proportional, i.e., $[h(t \mid \mathbf{x}_1)/h(t \mid \mathbf{x}_2)]$, the ratio of the hazard functions for two individuals with prognostic factors or covariates $\mathbf{x}_1 = (x_{11}, x_{21}, \ldots, x_{p1})'$, and $\mathbf{x}_2 = (x_{12}, x_{22}, \ldots, x_{p2})'$ is a constant (does not vary with time t). This means that the ratio of the risk of dying of two individuals is the same no matter how long they survive. In Sections 11.3

and 11.4, we showed that the exponential and Weibull regression models possess this property. This property implies that the hazard function given a set of covariates $\mathbf{x} = (x_1, x_2, \ldots, x_p)'$ can be written as a function of an underlying hazard function and a function, say $g(x_1, \ldots, x_p)$, of only the covariates, that is,

$$h(t \mid x_1, \ldots, x_p) = h_0(t)g(x_1, \ldots, x_p) \quad \text{or} \quad h(t \mid \mathbf{x}) = h_0(t)g(\mathbf{x}) \tag{12.1.1}$$

The underlying hazard function, $h_0(t)$, represents how the risk changes with time, and $g(\mathbf{x})$ represents the effect of covariates. $h_0(t)$ can be interpreted as the hazard function when all covariates are ignored or when $g(\mathbf{x}) = 1$, and is also called the *baseline hazard function*. The hazard ratio of two individuals with different covariates $\mathbf{x}_1$ and $\mathbf{x}_2$ is

$$\frac{h(t \mid \mathbf{x}_1)}{h(t \mid \mathbf{x}_2)} = \frac{h_0(t)g(\mathbf{x}_1)}{h_0(t)g(\mathbf{x}_2)} = \frac{g(\mathbf{x}_1)}{g(\mathbf{x}_2)} \tag{12.1.2}$$

which is a constant, independent of time.

The Cox (1972) proportional hazard model assumes that $g(\mathbf{x})$ in (12.1.1) is an exponential function of the covariates, that is,

$$g(x) = \exp\left(\sum_{j=1}^{p} b_j x_j\right) = \exp(\mathbf{b}'\mathbf{x})$$

and the hazard function is

$$h(t \mid \mathbf{x}) = h_0(t) \exp\left(\sum_{j=1}^{p} b_j x_j\right) = h_0(t) \exp(\mathbf{b}'\mathbf{x}) \tag{12.1.3}$$

where $\mathbf{b} = (b_1, \ldots, b_p)$ denotes the coefficients of covariates. These coefficients can be estimated from the data observed and indicate the magnitude of the effects of their corresponding covariates. For example, if there is only one covariate treatment, let $x_1 = 0$ if a person receives placebo and $x_1 = 1$ if a person receives the experimental drug. The hazard ratio of the patient receiving the experimental drug and the one receiving placebo based on (12.1.2) and (12.1.3) is

$$\frac{h(t \mid x_1 = 1)}{h(t \mid x_1 = 0)} = \exp(b_1)$$

Thus, the two treatments are equally effective if $b_1 = 0$ and the experimental drug introduces lower (higher) risk for survival than placebo if $b_1 < 0$ ($b_1 > 0$).

It can be shown that (12.1.3) is equivalent to

$$S(t \mid \mathbf{x}) = [S_0(t)]^{\exp(\sum_{j=1}^{p} b_j x_j)} = [S_0(t)]^{\exp(\mathbf{b}'\mathbf{x})} \tag{12.1.4}$$

Thus the covariates can be incorporated into the survivorship function. The use of (12.1.3) can be exemplified as follows.

1. *Two-sample problems.* Suppose that $p = 1$; that is, there is only one *covariate*, x_1, which is an indicator variable:

$$x_{1i} = \begin{cases} 0 & \text{if the } i\text{th individual is from group 0} \\ 1 & \text{if the } i\text{th individual is from group 1} \end{cases}$$

   Then according to (12.1.3), the hazard functions of groups 0 and 1 are, respectively, $h_0(t)$ and $h_1(t) = h_0(t)\exp(b_1)$. The hazard function of group 1 is equal to the hazard function of group 0 multiplied by a constant $\exp(b_1)$, or the two hazard functions are proportional. In terms of the survivorship function,

$$S(t) = [S_0(t)]^c$$

   where the constant $c = \exp(b_1)$ (Nadas, 1970). The two-sample test developed from (12.1.3) is the Cox–Mantel test discussed in Chapter 5. It is now apparent that the test is based on the assumption of a proportional hazard between the two groups.
2. *Two-sample problems with covariates.* The covariates in (12.1.3) can either be indicator variables such as x_1 in the two-group problem above or prognostic factors. Having one or more covariates representing prognostic factors in (12.1.1) enables us to examine the relation between two groups, adjusting for the presence of prognostic factors.
3. *Regression problems.* Dividing both sides of (12.1.3) by $h_0(t)$ and taking its logarithm, we obtain

$$\log \frac{h_i(t)}{h_0(t)} = b_1 x_{1i} + b_2 x_{2i} + \cdots + b_p x_{pi} = \sum_{j=1}^{p} b_j x_{ji} = \mathbf{b}'\mathbf{x}_i \quad (12.1.5)$$

   where the x's are covariates for the ith individual. The left side of (12.1.5) is a function of hazard ratio (or relative risk) and the right side is a linear function of the covariates and their respective coefficients.

As mentioned earlier, $h_0(t)$ is the hazard function when all covariates are ignored. If the covariates are standardized about the mean and the model used is

$$\log \frac{h_i(t)}{h_0(t)} = b_1(x_{1i} - \bar{x}_1) + b_2(x_{2i} - \bar{x}_2) + \cdots + b_p(x_{pi} - \bar{x}_p) = \mathbf{b}'(\mathbf{x}_i - \bar{\mathbf{x}}) \quad (12.1.6)$$

where $\bar{\mathbf{x}}' = (\bar{x}_1, \bar{x}_2, \ldots, \bar{x}_p)$ and $\bar{x}_j$ is the average of the jth covariate for all patients, the left side of (12.1.6) is the logarithm of the ratio of risk of failure for a patient with a given set of values $\mathbf{x}_i' = (x_{1i}, x_{2i}, \ldots, x_{pi})$ to that for an average patient who has an average value for every covariate.

In this chapter we focus on the use of (12.1.5), and the main interest here is to identify important prognostic factors. In other words, we wish to identify from the p covariates a subset of variables that affect the hazard more significantly, and consequently, the length of survival of the patient. We are concerned with the regression coefficients. If b_i is zero, the corresponding covariate is not related to survival. If b_i is not zero, it represents the magnitude of the effect of x_i on hazard when the other covariates are considered simultaneously.

To estimate the coefficients, $b_1, \ldots, b_p$, Cox (1972) proposes a partial likelihood function based on a conditional probability of failure, assuming that there are no tied values in the survival times. However, in practice, tied survival times are commonly observed and Cox's partial likelihood function was modified to handle ties (Kalbfleisch and Prentice, 1980; Breslow, 1974; Efron, 1977). In the following we describe the estimation procedure without and with ties.

12.1.1 Estimation Procedures without Tied Survival Times

Suppose that k of the survival times from n individuals are uncensored and distinct, and $n - k$ are right-censored. Let $t_{(1)} < t_{(2)} < \cdots < t_{(k)}$ be the ordered k distinct failure times with corresponding covariates $\mathbf{x}_{(1)}, \mathbf{x}_{(2)}, \ldots, \mathbf{x}_{(k)}$. Let $\mathbf{R}(t_{(i)})$ be the risk set at time $t_{(i)}$. $\mathbf{R}(t_{(i)})$ consists of all persons whose survival times are at least $t_{(i)}$. For the particular failure at time $t_{(i)}$, conditionally on the risk set $\mathbf{R}(t_{(i)})$, the probability that the failure is on the individual as observed is

$$\frac{\exp\left(\sum_{j=1}^{p} b_j x_{j(i)}\right)}{\sum_{l \in \mathbf{R}(t_{(i)})} \exp\left(\sum_{j=1}^{p} b_j x_{jl}\right)} \qquad \left(= \frac{\exp(\mathbf{b}'\mathbf{x}_{(i)})}{\sum_{l \in \mathbf{R}(t_{(i)})} \exp(\mathbf{b}'\mathbf{x}_l)} \right)$$

Each failure contributes a factor and hence the partial likelihood function is

$$L(\mathbf{b}) = \prod_{i=1}^{k} \frac{\exp\left(\sum_{j=1}^{p} b_j x_{j(i)}\right)}{\sum_{l \in \mathbf{R}(t_{(i)})} \exp\left(\sum_{j=1}^{p} b_j x_{jl}\right)} \qquad \left(= \prod_{i=1}^{k} \frac{\exp(\mathbf{b}'\mathbf{x}_{(i)})}{\sum_{l \in \mathbf{R}(t_{(i)})} \exp(\mathbf{b}'\mathbf{x}_l)} \right) \tag{12.1.7}$$

and the log-partial likelihood is

$$\begin{aligned} l(\mathbf{b}) = \log L(\mathbf{b}) &= \sum_{i=1}^{k} \sum_{j=1}^{p} b_j x_{ji} - \sum_{i=1}^{k} \log\left[\sum_{l \in \mathbf{R}(t_{(i)})} \exp\left(\sum_{j=1}^{p} b_j x_{jl} \right) \right] \\ &= \sum_{i=1}^{k} \left\{ \mathbf{b}'\mathbf{x}_{(i)} - \log\left[\sum_{l \in \mathbf{R}(t_{(i)})} \exp(\mathbf{b}'\mathbf{x}_l) \right] \right\} \end{aligned} \tag{12.1.8}$$

The maximum partial likelihood estimator (MPLE) $\hat{\mathbf{b}}$ of $\mathbf{b}$ can be obtained by the steps shown in (7.1.2)–(7.1.4). That is, $\hat{b}_1, \ldots, \hat{b}_p$ are obtained by solving the following simultaneous equations:

$$\frac{\partial(l(\mathbf{b}))}{\partial \mathbf{b}} = 0$$

or

$$\frac{\partial l(\mathbf{b})}{\partial b_u} = \sum_{i=1}^{k} [x_{u(i)} - A_{ui}(\mathbf{b})] = 0 \qquad u = 1, 2, \ldots, p \tag{12.1.9}$$

where

$$A_{ui}(\mathbf{b}) = \frac{\sum_{l \in \mathbf{R}(t_{(i)})} x_{ul} \exp(\sum_{j=1}^{p} b_j x_{jl})}{\sum_{l \in \mathbf{R}(t_{(i)})} \exp(\sum_{j=1}^{p} b_j x_{jl})} = \frac{\sum_{l \in \mathbf{R}(t_{(i)})} x_{ul} \exp(\mathbf{b}'\mathbf{x}_l)}{\sum_{l \in \mathbf{R}(t_{(i)})} \exp(\mathbf{b}'\mathbf{x}_l)} \tag{12.1.10}$$

by applying the Newton–Raphson iterated procedure. The second partial derivatives of $l(\mathbf{b})$ with respective to b_u and b_v, $u, v = 1, 2, \ldots, p$, in the Newton–Raphson iterative procedure are

$$I_{uv}(\mathbf{b}) = \frac{\partial^2 l(\mathbf{b})}{\partial b_u \partial b_v} = -\sum_{i=1}^{k} C_{(uvi)}(b_1, \ldots, b_p) = -\sum_{i=1}^{k} C_{(uvi)}(\mathbf{b}) \qquad u, v = 1, 2, \ldots, p \tag{12.1.11}$$

where

$$C_{(uvi)}(\mathbf{b}) = \frac{\sum_{l \in \mathbf{R}(t_{(i)})} x_{ul} x_{vl} \exp(\sum_{j=1}^{p} b_j x_{jl})}{\sum_{l \in \mathbf{R}(t_{(i)})} \exp(\sum_{j=1}^{p} b_j x_{jl})} - A_{ui}(\mathbf{b}) A_{vi}(\mathbf{b}) \tag{12.1.12}$$

The covariance matrix of the MPLE $\hat{\mathbf{b}}$, defined similarly as $\hat{V}(\mathbf{b})$ defined in (7.1.5), is

$$\hat{V}(\hat{\mathbf{b}}) = \widehat{\mathrm{Cov}}(\hat{\mathbf{b}}) = \left[-\frac{\partial^2 l(\hat{\mathbf{b}})}{\partial \mathbf{b} \partial \mathbf{b}'} \right]^{-1} \tag{12.1.13}$$

where $-\partial^2 l(\hat{\mathbf{b}})/\partial \mathbf{b} \partial \mathbf{b}'$ is called the *observed information matrix* with $-I_{uv}(\hat{\mathbf{b}})$ as its (u, v) element and where $I_{uv}(\mathbf{b})$ is defined in (12.1.11). Let the (i, j) element of $\hat{V}(\hat{\mathbf{b}})$ in (12.1.13) be v_{ij}; then the $100(1 - \alpha)\%$ confidence interval for b_i is, according to (7.1.6),

$$(\hat{b}_i - Z_{\alpha/2}\sqrt{v_{ii}},\ \hat{b}_i + Z_{\alpha/2}\sqrt{v_{ii}}) \tag{12.1.14}$$

12.1.2 Estimation Procedure with Tied Survival Times

Suppose that among the n observed survival times there are k distinct uncensored times $t_{(1)} < t_{(2)} < \cdots < t_{(k)}$. Let $m_{(i)}$ denote the number of people

who fail at $t_{(i)}$ or the multiplicity of $t_{(i)}$; $m_{(i)} > 1$ if there are more than one observation with value $t_{(i)}$; $m_{(i)} = 1$ if there is only one observation with value $t_{(i)}$. Let $R(t_{(i)})$ denote the set of people at risk at time $t_{(i)}$ [i.e., $R(t_{(i)})$ consists of those whose survival times are at least $t_{(i)}$] and r_i be the number of such persons. For example, in the following set of survival times from eight subjects, $\{15,\ 16+,\ 20,\ 20,\ 20,\ 21,\ 24,\ 24\}$, $n = 8$, $k = 4$, $t_{(1)} = 15$, $t_{(2)} = 20$, $t_{(3)} = 21$, $t_{(4)} = 24$, $m_{(1)} = 1$, $m_{(2)} = 3$, $m_{(3)} = 1$, and $m_{(4)} = 2$. Then $R(t_{(1)})$ includes all eight subjects. $R(t_{(2)}) = \{$those subjects with survival times 20, 21, and 24$\}$, $R(t_{(3)}) = \{$those subjects with survival times 21 and 24$\}$, and $R(t_{(4)}) = \{$those subjects with survival time 24$\}$; thus, $r_1 = 8$, $r_2 = 6$, $r_3 = 3$, and $r_4 = 2$.

To discuss the methods for ties, we introduce a few additional notations. From every $R(t_{(i)})$, we can randomly select $m_{(i)}$ subjects. Donate each of these $m_{(i)}$ selections by $\mathbf{u}_{(j)}$. There are ${}_{r_i}C_{m_{(i)}} = r_i!/[m_{(i)}!\,(r_i - m_{(i)})!]$ possible $\mathbf{u}_{(j)}$'s. Let $\mathbf{U}_i$ denote the set that contains all the $\mathbf{u}_{(j)}$'s. For example, from $R(t_{(2)})$, we can randomly select any $m_{(2)} = 3$ out of the 6 ($r_2 = 6$) subjects. There are a total of ${}_6C_3 = 20$ such selections (or subsets), and one of $\mathbf{u}_{(j)}$'s is, for example, $\{$three subjects with survival times 20, 20, and 24$\}$. $\mathbf{U}_2 = \{\mathbf{u}_{(1)}, \mathbf{u}_{(2)}, \ldots, \mathbf{u}_{(20)}\}$ contains all 20 subsets. Now let us focus on the tied observations. Let $\mathbf{x}_k = (x_{1k}, x_{2k}, \ldots, x_{pk})'$ denote the covariates of the kth individual, $z_{\mathbf{u}(j)} = \sum_{k \in \mathbf{u}_{(j)}} \mathbf{x}_k = (z_{1\mathbf{u}(j)}, z_{2\mathbf{u}(j)}, \ldots, z_{p\mathbf{u}(j)})'$, where $z_{l\mathbf{u}(j)}$ is the sum of the lth covariate of the $m_{(i)}$ persons who are in $\mathbf{u}_{(j)}$. Let $\mathbf{u}^*_{(i)}$ denotes the set of $m_{(i)}$ people who failed at time $t_{(i)}$, and $\mathbf{z}_{\mathbf{u}^*(i)} = \sum_{k \in \mathbf{u}^*_{(i)}} \mathbf{x}_k = (z^*_{1\mathbf{u}^*(i)}, z^*_{2\mathbf{u}^*(i)}, \ldots, z^*_{p\mathbf{u}^*(i)})'$, where $z^*_{l\mathbf{u}^*(i)}$ be the sum of the lth covariate of the $m_{(i)}$ persons who are in $\mathbf{u}^*_{(i)}$ (failed at time $t_{(i)}$). For example, for the set of survival times above, $z^*_{1\mathbf{u}^*(2)}$ equals the sum of the first covariate values of three persons who failed at time 20. With these notations we are ready to introduce the following method for ties.

Continuous Time Scale

In the case of a continuous time scale, for the $m_{(i)}$ persons failing at $t_{(i)}$, it is reasonable to say that the survival times of the $m_{(i)}$ people are not identical since the ties are most likely to be the results of imprecise measurements. If the precise measurements could be made, these $m_{(i)}$ survival times could be ordered and we could use the likelihood function in (12.1.7). In the absence of knowledge of the true order (the real case), we have to consider all possible orders of these observed $m_{(i)}$ tied survival times. For each $t_{(i)}$, the observed $m_{(i)}$ tied survival time can be ordered in $m_{(i)}!$ ($m_{(i)}$ factorial) different possible ways. For each of these possible orders we will have a product as in (12.1.7) for the corresponding $m_{(i)}$ survival times. Therefore, when the survival time is measured at a continuous time scale, construction and computation of the exact partial likelihood function is a very tedious task if $m_{(i)}$ is larger. Readers interested in the details of the exact partial likelihood function are referred to Kalbfleisch and Prentice (1980) and Delong et al. (1994). The formula provided by Delong et al. makes computation of the partial likelihood function for tied continuous survival times more feasible. We will not discuss the exact partial likelihood function further due to its complexity. Among the statistical sof-

tware packages, SAS includes a procedure based on the exact partial likelihood function. Use of this procedure is illustrated in Example 12.3.

To approximate the exact partial likelihood function, the following two likelihood functions can be used when each $m_{(i)}$ is small compared to r_i. Breslow (1974) provided the following approximation:

$$L_B(\mathbf{b}) = \prod_{i=1}^{k} \frac{\exp(\mathbf{z}'_{\mathbf{u}^*(i)}\mathbf{b})}{[\sum_{l \in R(t_{(i)})} \exp(\mathbf{x}'_l\mathbf{b})]^{m_{(i)}}} \tag{12.1.15}$$

An alternative approximation was provided by Efron (1977):

$$L_E(\mathbf{b}) = \prod_{i=1}^{k} \frac{\exp(\mathbf{z}'_{\mathbf{u}^*(i)}\mathbf{b})}{\prod_{j=1}^{m_{(i)}} [\sum_{l \in R(t_{(i)})} \exp(\mathbf{x}'_l\mathbf{b}) - [(j-1)/m_{(i)}] \sum_{l \in \mathbf{u}^*_{(i)}} \exp(\mathbf{x}'_l\mathbf{b})]} \tag{12.1.16}$$

Discrete Time Scale

If survival times are observed at discrete times, the tied observations are true ties: that is, these events really happen at the same time. Cox (1972) proposed the following logistic model:

$$\frac{h_i(t)\,dt}{1 - h_i(t)\,dt} = \frac{h_0(t)\,dt}{1 - h_0(t)\,dt} \exp\left(\sum_{j=1}^{p} b_j x_{ji}\right) = \frac{h_0(t)\,dt}{1 - h_0(t)\,dt} \exp(\mathbf{b}'\mathbf{x}_i)$$

This model reduces to (12.1.3) in the continuous time scale. Using the model and replacing the ith term in (12.1.7) with the following term with tied observations at $t_{(i)}$:

$$\frac{\exp(\mathbf{z}'_{\mathbf{u}^*(i)}\mathbf{b})}{\sum_{\mathbf{u}_{(j)} \in \mathbf{U}_i} \exp(\mathbf{z}'_{\mathbf{u}(j)}\mathbf{b})}$$

the partial likelihood function with tied observations at a discrete time scale is

$$L_d(\mathbf{d}) = \prod_{i=1}^{k} \frac{\exp(\mathbf{z}'_{\mathbf{u}^*(i)}\mathbf{b})}{\sum_{\mathbf{u}_{(j)} \in \mathbf{U}_i} \exp(\mathbf{z}'_{u(j)}\mathbf{b})} \tag{12.1.17}$$

The ith term in this expression represents the conditional probability of observing the $m_{(i)}$ failures given that there are $m_{(i)}$ failures at time $t_{(i)}$ and the risk set $R(t_{(i)})$ at $t_{(i)}$. The number of terms in the denominator of the ith term is ${}_{r_i}C_{m_{(i)}} = r_i!/[m_{(i)}!(r_i - m_i)!]$, as noted earlier, and will be very large if the $m_{(i)}$ is large. Fortunately, a recursive algorithm proposed by Gail et al. (1981) makes the calculation manageable. Equation (12.1.17) can also be considered as an approximation of the partial likelihood function for continuous survival times with ties by assuming that the ties are true as if they were observed at a discrete time scale.

As shown in many papers in literature, in most practical situations, the three partial likelihood functions above are reasonably good approximations of the exact partial likelihood function for continuous survival time with ties. When there are no ties on the event times (i.e., $m_{(i)} \equiv 1$), (12.1.15)–(12.1.17) reduce to (12.1.7). The maximum partial likelihood estimate of **b** in (12.1.15)–(12.1.17) can be estimated using procedures similar to those in (12.1.8)–(12.1.14).

Once the coefficients are estimated, relative risk (or relative hazard) in (12.1.2) or (12.1.5) can be obtained. For example, if x_1 represents hypertension and is defined as

$$x_1 = \begin{cases} 1 & \text{if patient is hypertensive} \\ 0 & \text{otherwise} \end{cases}$$

the hazard rate for hypertensive patients is $\exp(\hat{b}_1)$ times that for normotensive patients. That is, the risk associated with hypertension is $\exp(\hat{b}_1)$ adjusting for the other covariates in the model. A $100(1-\alpha)\%$ confidence interval for the relative risk can be obtained by using the confidence interval for b_1. Let (b_{1L}, b_{1U}) be the $100(1-\alpha)\%$ confidence interval for b_1; a $100(1-\alpha)\%$ confidence interval for the relative risk is $(\exp(b_{1L}), \exp(b_{1U}))$ according to (7.1.8). This application of the proportional hazards model has been used extensively, particularly by epidemiologists.

The following three examples illustrate the use of Cox's regression model.

Example 12.1 Consider the survival data from 30 patients with AML in Table 11.4. Recall that the two possible prognostic factors are

$$x_1 = \begin{cases} 1 & \text{if patient is } \geqslant 50 \text{ years} \\ 0 & \text{otherwise} \end{cases}$$

$$x_2 = \begin{cases} 1 & \text{if cellularity of marrow clot section is 100\%} \\ 0 & \text{otherwise} \end{cases}$$

We fit the Cox proportional hazard model to the data. The results are presented in Table 12.1 In this case, Breslow's approximation in (12.1.15) is used to handle ties. The positive signs of the regression coefficients indicate that the older patients ($\geqslant 50$ years) and patients with 100% cellularity of the marrow clot section have a higher risk of dying. Furthermore, age is significantly related to survival after adjustment for cellularity. The results are consistent with those from fitting the lognormal regression model in Example 11.3. The coefficients of the binary covariates can be interpreted in terms of relative risk. The estimated risk of dying for patients at least 50 years of age is 2.75 times higher than that for patients younger than 50. Patients with 100% cellularity have a 42% higher risk of dying than patients with less than 100% cellularity.

Table 12.1 Results of a Proportional Hazards Regression Analysis of Data in Table 11.4

Covariate	Regression Coefficient	Standard Error	p Value	exp(coefficient)
x_1 (age)	1.01	0.46	0013	2.75
x_2 (cellularity)	0.35	0.44	0.212	1.42

The 95% confidence intervals for b_1 (age) and b_2 (cellularity) are 1.01 ± 1.96 (0.46) or (0.11, 1.91) and 0.35 ± 1.96 (0.44) or $(-0.51, 1.21)$, respectively. Consequently, the 95% confidence intervals for the relative risks are $(e^{0.11}, e^{1.91})$ or (1.12, 6.75) and $(e^{-0.51}, e^{1.21})$ or (0.60, 3.35), respectively. The small number of patients (30) may have contributed to the large standard errors of $\hat{b}_1$ and $\hat{b}_2$ and consequently, the wide confidence intervals. The lower bound of the confidence interval for age is only slightly above 1. This suggests that the importance of age should be interpreted carefully. In general, if the number of subjects is small and the standard errors of the estimates are large, the estimates may be unreliable.

When the two covariates are considered simultaneously, the risk for a patient with $x_1 = 1$ and $x_2 = 1$ relative to patients with $x_1 = 0$ and $x_2 = 0$ can be estimated. The relative risk is estimated as $\exp(1.01 + 0.35) = 3.90$ for a patient who is over 50 years of age and whose cellularity is 100%, compared to patients who are younger than 50 and whose cellularity is less than 100%.

Using the same data set "C:\AML.DAT" defined in Example 11.3, the following SAS code can be used to obtain the results in Table 12.1.

```
data w1;
  infile 'c:\aml.dat' missover;
  input t cens x1 x2;
run;
proc phreg;
  model t*cens(0) = x1 x2 / rl;
run;
```

If BMDP 2L is used, the following code is applicable.

```
/input      file = 'c:\aml.dat' .
            variables = 4.
            format = free.
/print      cova.
/variable   names = t, cens, x1, x2.
/form       time = t.
            status = cens.
            response = 1.
/regress    covariates = x1, x2.
```

If SPSS is used, the following code suffices.

```
data list file = 'c:\aml.dat' free
        / t cens x1 x2.
coxreg t with x1 x2
        /status = cens event (1)
        /print = all.
```

Example 12.2 In a study (Buzdar et al., 1978) to evaluate a combination of 5-flourouracil, adramycin, cyclophosphamide, and BCG (FAC-BCG) as adjuvant treatment in stage II and III breast cancer patients with positive axillary nodes, 131 patients receiving FAC-BCG after surgery and radiation therapy were compared with 151 patients receiving surgery and radiation therapy only (control group).

Cox's regression model was used to identify prognostic factors and to evaluate the comparability of the two treatment groups. The model was fitted to the data from 151 patients to determine the variables related to length of remission. The possible prognostic variables considered were age (years), menopausal status (1, premenopausal; 0, other), size of primary tumor (2, <3 cm; 4, 3–5 cm; 7, >5 cm), state of disease (2, stage II; 3, stage III), location of surgery (1, M. D. Anderson Hospital; 0, other), number of nodes involved (2, <4; 7, 4–10; 12, >10), and race (1, Caucasian; 2, other). The covariates were selected by the forward selection method outlined in Section 11.9. Three variables — number of nodes involved, state of disease, and menopausal status — were selected for use in the model, all related significantly ($p < 0.1$) to disease-free time. The regression equation including these variables only is

$$\log\frac{h_i(t)}{h_0(t)} = 0.111(\text{number of nodes} - 6.16) + 0.8122(\text{stage} - 2.39) + 0.872(\text{menopausal} - 0.26)$$

Table 12.2 gives the details of the fit. Relative risk was taken as $h_i(t)/h_0(t)$, the ratio of the risk of death per unit of time for a patient with a given set of prognostic variables to the risk for a patient whose prognostic variables were average in value. The relative risk for each variable was calculated by considering favorable or unfavorable values of that variable, assuming that other variables were at their average value. Note that the risk of relapse per unit time for a patient with 12 positive nodes is 3.04 (ratio or risk) times that for a patient with only two positive nodes. The risk of relapse per unit time for a stage III patient was 2.25 times that of a stage II patient.

The Cox's regression model was also fitted to the combined group of FAC-BCG and control patients, including type of treatment (0, control; 1, FAC-BCG), menopausal status, size of primary tumor, and number of involved nodes as potential prognostic variables. The regression equation with three

Table 12.2 Patient Characteristics Related to Disease-Free Time in Cox's Regression Model Fit to Control Patients

Prognostic Variable	Regression Coefficient	Significance Level (p)	Maximum Log Likelihood	Relative Risk[a]		Ratio of Risks
				Favorable	Unfavorable	
Number of nodes	0.1110	<0.01	-257.407	0.63	1.91	3.04
Stage	0.8122	0.016	-254.533	0.73	1.64	2.25
Menopausal status	0.8720	<0.1	-250.576	0.80	1.91	2.39

Source: Buzdar et al. (1978). Reprinted by permission of the editor.

[a] Favorable variables: number of nodes = 2, stage II, postmenopausal. Unfavorable variables: number of nodes = 12, stage III, premenopausal.

significant ($p < 0.05$) variables obtained was as follows:

$$\log \frac{h_i(t)}{h_0(t)} = -1.8792(\text{treatment} - 0.47) + 0.9644(\text{menopausal status} - 0.33) + 0.1611(\text{size of primary tumor} - 4.04)$$

Table 12.3 gives the details of the fit. The most important variable in predicting survival time was the type of treatment (FAC-BCG favorable); other significantly important variables were menopausal status and size of primary tumor. The risk of death per unit of time for a patient receiving no adjuvant treatment (control group) was 6.55 times that for a patient receiving the treatment, showing that FAC-BCG can prolong life considerably.

Table 12.3 Patient Characteristics Related to Survival, Treatment Included

Prognostic Variable	Regression Coefficient	Significance Level (p)	Maximum Log Likelihood	Relative Risks[a]		Ratio of Risks
				Favorable	Unfavorable	
Treatment	-1.8792	<0.01	-201.200	0.37	2.42	6.55
Menopausal status	0.9644	0.01	-197.719	0.73	1.91	2.62
Size of primary tumor	0.1611	0.05	-195.865	0.72	1.61	2.24

Source: Buzdar et al. (1978). Reprinted by permission of the editor.

[a] Favorable variables: treatment — FAC-BCG, postmenopausal, size of primary tumor 2 cm. Unfavorable variables: no adjuvant treatment, premenopausal, size of primary tumor 7 cm.

Example 12.3 Suppose that demographic, personal, clinical, and laboratory data are collected from an interview and physical examination of 200 participants in a study of cardiovascular disease (CVD). These participants, aged 50–79 years and free of CVD at the time of the baseline examination, are then followed for 10 years. During the follow-up period, 96 of the 200 participants develop or die of CVD. We use this set of simulated data to illustrate further the use of the proportional hazards model in identifying important risk factors. Table 12.4 gives a subset of the simulated data of 68 participants.

The event time T of interest is CVD-free time, which is defined as the time in years from baseline examination to the first time that a participant was diagnosed as having CVD or confirmed as a CVD death. CVD includes coronary heart disease (CHD) and stroke. The covariates of interest are age (AGE), gender (SEX = 1 if male and =0 if female); smoking status (SMOKE = 1 if current smoker, and 0 otherwise); body mass index (BMI = weight in kilograms divided by height in meter squared); systolic blood pressure (SBP); logarithm of ratio of urinary albumin and creatinine (LACR); logarithm of triglycerides (LTG); hypertension status (HTN = 1 if SBP $\geqslant$ 140 mmHg or DBP $\geqslant$ 90 mmHg or under treatments of hypertension, and =0 otherwise); and diabetes status (DM = 1 if fasting glucose $\geqslant$ 126 mg/dL or under the treatments of diabetes, and =0 otherwise). For the CVD outcome of interest, we let DG denote the type of CVD. DG = 0 if the participant is free of CVD at the end of the study or confirmed as a non-CVD death (thus the CVD-free time is censored), =1 if the participant had a stroke, =2 if the participant had a CHD, and =3 if the participant had other CVDs. It is of interest to compare the risk of CVD among the three age groups: 50–59, 60–69, and 70–79. We create two dummy variables: AGEA = 1 if aged 50–69, =0 otherwise; and AGEB = 1 if aged 60–69, and =0 otherwise. Thus for a 70 to 79-year-old, AGEA = 0 and AGEB = 0. We also create a variable to denote the censoring status: CENS = 0 if t is censored, and = 1 if uncensored.

To illustrate the different methods to handle ties, we fit the Cox proportional hazards model with the following six covariates: AGEA, AGEB, SEX, SMOKE, BMI, and LACR. The approximated partial likelihood function defined in (12.1.15)–(12.1.17) as well as the exact partial likelihood function (Delong et al., 1994) are applied. As noted in Sections 11.3 and 11.4, the exponential and Weibull regression models are also proportional hazard models. Therefore, for comparisons we also fit an exponential and a Weibull regression model with the same covariates to the data. The estimated regression coefficients obtained from the proportional hazards model with approximated discrete, Breslow, Efron, and exact partial likelihood functions as well as those from the exponential and Weibull regression models are given in Table 12.5. All of the estimates based on the Cox model and an approximated partial likelihood function are very closed to those based on the exact partial likelihood. Those based on Efron's approximation are almost identical to those (different only at the fourth decimal place) based on the exact partial

Table 12.4 A Subset of the Simulated Data for a Cardiovascular Disease Study in Example 12.3[a]

ID	T	CENS	DG	AGEA	AGEB	SEX	SMOKE	BMI	SBP	LACR	LTG	AGE	HTN	DM
1	7.4	0	0	0	0	0	0	31.78	141	4.23	3.94	77.8	1	0
2	7.9	0	0	0	0	0	0	25.02	124	4.31	4.66	76.9	0	1
3	6.4	0	0	0	0	0	1	26.05	111	4.38	4.27	76.3	0	0
4	7.1	0	0	0	0	0	1	26.92	140	1.11	4.51	72.2	1	0
5	6.0	0	0	0	0	0	1	34.30	146	1.19	4.82	76.0	1	0
6	6.5	0	0	0	0	0	1	31.76	142	1.20	4.88	74.5	1	0
7	8.3	0	0	0	0	1	0	25.01	154	3.53	4.10	70.7	1	1
8	7.9	0	0	0	0	1	0	28.21	136	3.73	4.12	75.2	1	0
9	7.6	0	0	0	1	0	0	28.13	127	2.92	4.24	64.9	0	0
10	8.4	0	0	0	1	0	0	25.68	118	2.47	4.41	60.2	0	0
11	7.4	0	0	0	1	0	0	34.34	118	2.37	4.46	64.4	0	1
12	7.7	0	0	0	1	0	0	28.92	127	3.58	4.55	68.8	1	1
13	6.9	0	0	0	1	0	1	24.68	100	2.11	4.33	64.4	0	0
14	7.2	0	0	0	1	0	1	21.93	121	3.39	4.64	60.8	0	1
15	6.3	0	0	0	1	0	1	29.47	98	1.96	4.69	64.4	0	0
16	7.4	0	0	0	1	0	1	28.65	150	2.59	4.95	61.6	1	0
17	4.5	0	0	0	1	1	0	32.28	128	2.99	4.73	65.3	0	0
18	7.0	0	0	0	1	1	0	29.21	117	2.17	4.91	65.7	0	1
19	2.8	0	0	0	1	1	0	28.82	136	4.04	4.92	65.4	0	1
20	7.2	0	0	0	1	1	0	30.58	121	2.84	4.94	64.5	0	1
21	7.4	0	0	1	0	0	0	27.83	95	1.85	4.44	52.0	0	0
22	5.2	0	0	1	0	0	0	26.61	128	2.87	4.51	50.7	0	0
23	7.7	0	0	1	0	0	0	30.32	96	2.41	4.60	52.5	0	1
24	7.8	0	0	1	0	0	0	30.41	130	1.45	4.73	55.9	0	0
25	7.6	0	0	1	0	0	1	29.98	140	1.88	4.51	53.4	1	0
26	7.9	0	0	1	0	0	1	26.00	118	2.34	4.53	51.0	0	0
27	7.3	0	0	1	0	0	1	29.05	110	1.44	4.67	50.6	0	0

28	8.2	0	0	1	0	0	1	27.21	131	2.50	4.68	57.7	0	0
29	3.8	0	0	1	0	1	0	36.97	141	4.60	4.25	58.7	1	0
30	6.9	0	0	1	0	1	0	29.44	115	2.89	4.26	53.6	0	1
31	6.1	0	0	1	0	1	0	33.85	154	3.48	4.48	51.2	1	0
32	7.2	0	0	1	0	1	0	32.13	122	2.92	4.48	55.2	0	0
33	8.4	0	0	1	0	1	1	27.52	135	2.39	4.42	53.7	0	0
34	5.0	0	0	1	0	1	1	30.64	114	1.39	4.45	54.9	1	0
35	6.5	0	0	1	0	1	1	29.94	120	2.96	4.49	50.7	0	0
36	6.4	0	0	1	0	1	1	29.89	115	1.68	4.52	51.3	0	0
37	2.6	1	1	0	0	0	0	30.88	189	5.38	4.72	73.9	1	1
38	2.7	1	1	0	0	0	1	25.05	200	3.37	4.86	77.2	1	1
39	2.7	1	1	0	0	1	0	26.80	130	2.31	5.10	73.5	0	0
40	3.3	1	1	0	0	1	1	21.67	111	3.53	4.18	71.1	0	0
41	2.9	1	1	0	1	0	0	36.83	114	2.64	4.52	68.2	0	0
42	0.2	1	1	0	1	0	1	21.49	125	4.61	4.69	67.3	0	0
43	2.1	1	1	0	1	1	0	31.05	131	1.38	4.48	69.1	0	0
44	6.8	1	1	0	1	1	1	26.78	134	4.36	4.90	61.0	1	0
45	5.7	1	1	1	0	0	0	35.78	132	9.93	5.11	52.5	0	1
46	1.1	1	1	1	0	0	1	28.44	134	3.54	4.32	55.7	0	0
47	6.6	1	1	1	0	1	0	24.38	124	4.16	4.00	51.8	0	1
48	1.3	1	1	1	0	1	1	34.13	126	5.87	3.95	53.1	0	1
49	4.6	1	2	0	0	0	0	43.23	128	5.08	5.25	72.2	0	1
50	6.3	1	2	0	0	0	1	38.67	126	5.16	4.50	76.8	1	1
51	2.0	1	2	0	0	1	0	34.49	130	2.69	3.95	76.7	1	1
52	4.2	1	2	0	0	1	1	20.78	127	4.40	4.54	73.1	0	0
53	3.6	1	2	0	1	0	0	28.40	118	5.43	4.66	69.3	1	1
54	3.2	1	2	0	1	0	1	28.73	154	1.94	5.24	68.9	1	1
55	4.5	1	2	0	1	1	0	44.25	97	2.01	4.40	68.6	0	1
56	4.5	1	2	0	1	1	1	32.46	141	0.74	4.39	63.5	1	0
57	6.1	1	2	1	0	0	0	39.72	118	2.39	3.93	52.6	0	1

(*Continued overleaf*)

Table 12.4 *Continued*

ID	T	CENS	DG	AGEA	AGEB	SEX	SMOKE	BMI	SBP	LACR	LTG	AGE	HTN	DM
58	3.0	1	2	1	0	0	1	27.90	117	7.45	5.61	56.0	0	1
59	2.1	1	2	1	0	1	0	27.77	119	7.03	4.71	54.3	0	1
60	1.3	1	2	1	0	1	1	31.03	151	3.94	4.43	59.2	1	1
61	4.9	1	3	0	0	0	0	25.22	129	6.69	3.90	75.4	1	0
62	2.5	1	3	0	0	0	1	45.29	130	2.46	4.40	75.7	0	1
63	3.8	1	3	0	0	1	0	25.03	188	6.25	5.63	71.7	1	1
64	5.0	1	3	0	1	1	0	46.76	96	3.93	4.12	65.6	1	0
65	1.5	1	3	0	1	1	1	28.53	126	3.09	4.65	68.6	0	1
66	4.1	1	3	1	0	0	0	23.63	144	8.24	4.82	59.4	1	1
67	0.5	1	3	1	0	1	0	31.39	134	6.96	4.11	54.2	1	0
68	2.7	1	3	1	0	1	1	30.29	115	4.70	4.98	59.1	1	1

[a] ID, participant id number; T, CVD event time (CVD-free time); CENS = 0 if censored, and =1 if uncensored; DG = 0 if non-CVD at the end of the study or non-CVD death, =1 if stroke, =2 if coronary heart disease (CHD), and =3 if the other CVDs; AGEA = 1 if aged 50–59 and =0 otherwise; AGEB = 1 if aged 60–69 and =0 otherwise; SEX = 1 if male and =0 if female; SMOKE = 1 if current smoker and 0 otherwise; BMI, body mass index; SBP, systolic blood pressure; LACR, logarithm of the ratio of urinary albumin and creatinine; LTG, logarithm of triglycerides; HTN = 1 if SBP$\geqslant$140 mmHg or DBP (diastolic blood pressure)$\geqslant$90 mmHg and =0 otherwise; DM = 1 if fasting glucose$\geqslant$126 mg/dL and =0 otherwise.

Table 12.5 Results from Fitting a Cox Proportional Hazards Model Based on Different Methods for Ties on the CVD Data

	Regression Coefficient					
Variable	Breslow	Discrete	Efron	Exact	Exponential	Weibull
AGEA	−1.3478	−1.3662	−1.3558	−1.3560	−1.2550	−1.0436
AGEB	−0.7709	−0.7828	−0.7753	−0.7755	−0.7107	−0.5966
SEX	0.7134	0.7233	0.7187	0.7189	0.6862	0.5659
SMOKE	0.3762	0.3810	0.3776	0.3776	0.3440	0.2855
BMI	0.0253	0.0256	0.0255	0.0255	0.0233	0.0194
LACR	0.1735	0.1759	0.1739	0.1740	0.1658	0.1357

likelihood function. The estimated regression coefficients based on the two parametric models, particularly the exponential regression model, are also close to those based on the Cox hazards model. From the signs of the coefficients, we see that men, current smokers, and persons with high BMI and albumin–creatinine ratios have a higher hazard (risk) of CVD and shorter CVD-free time. The coefficients of the two age variables are both negative, indicating that persons in the younger age groups have a lower hazard (risk) of CVD.

Suppose that "C:\EX12d2d1.DAT" contains eight successive columns, for T, CENS, AGEA, AGEB, SEX, SMOKE, BMI, and LACR, and that the numbers in each row are space-separated. The following code for the SAS PHREG and LIFEREG procedures can be used to obtain the results in Table 12.5.

```
data w1;
  infile 'c:\ex12d2d1.dat' missover;
  input t cens agea ageb sex smoke bmi lacr;
run;
proc phreg;
  model t*cens(0) =  agea ageb sex smoke bmi lacr / ties = breslow;
run;
proc phreg;
  model t*cens(0) =  agea ageb sex smoke bmi lacr / ties = discrete;
run;
proc phreg;
  model t*cens(0) =  agea ageb sex smoke bmi lacr / ties = efron;
run;
proc phreg;
  model t*cens(0) =  agea ageb sex smoke bmi lacr / ties = exact;
run;
proc lifereg;
  Model a: model t*cens(0) =  agea ageb sex smoke bmi lacr / d = exponential;
  Model b: model t*cens(0) =  agea ageb sex smoke bmi lacr / d = weibull;
run;
```

12.2 IDENTIFICATION OF SIGNIFICANT COVARIATES

As noted earlier, one principal interest is to identify significant prognostic factors or covariates. This involves hypothesis testing and covariate selection procedures, similar to those discussed in Chapter 11 for parametric methods. The differences are that the Cox proportional hazard model has a partial likelihood function in which the only parameters are the coefficients associated with the covariates. However, statistical inference based on the partial likelihood function has asymptotic properties similar to those based on the usual likelihood. Therefore, the estimation procedure (discussed in Section 12.1) is similar to those in Section 7.1, and the hypothesis-testing procedures are similar to those in Sections 9.1 and 11.2. For example, the Wald statistic in (9.1.4) can be used to test if any one of the covariates has no effect on the hazard, that is, to test $H_0: b_i = 0$. By replacing the log-likelihood function with the log partial likelihood function, the log-likelihood ratio statistic, the Wald statistic, and the score statistic in (9.1.10), (9.1.11), and (9.1.12) can be used to test the null hypothesis that all the coefficients are equal to zero, that is, to test

$$H_0: b_1 = 0, b_2 = 0, \ldots, b_p = 0$$

or $H_0: \mathbf{b} = \mathbf{0}$ in (9.1.9). Similarly the forward, backward, and stepwise selection procedures discussed in Section 11.9.1 are applicable to the Cox proportional hazard model.

The following example, using the SAS PHREG procedure, illustrates these procedures.

Example 12.4 We use the entire CVD data set in Example 12.3 to demonstrate how to identify the most important risk factors among all the covariates. Suppose that the effects of age, gender, and current smoking status on CVD risk are of fundamental interest and we wish to include these variables in the model. In epidemiology this is often referred to as adjusting for these variables. Thus, AGEA, AGEB, SEX, and SMOKE are forced into the model and we are to select the most important variables from the remaining covariates (BMI, SBP, LACR, LTG, HTN, and DM), adjusting for age, gender, and current smoking status.

The SAS procedure PHREG is used with Breslow's approximation for ties (default procedure) and three variable selection methods (forward, backward, and stepwise). Two covariates, BMI and LACR, are selected at the 0.05 significance level by all three selection methods. The final model, in the form of (12.1.5), including only the four covariates that we purposefully included and the two most significant ones identified by the selection method, is

$$\log\frac{h(t_i)}{h_0(t_i)} = b_1\text{AGEA}_i + b_2\text{AGEB}_i + b_3\text{SEX}_i + b_4\text{SMOKE}_i + b_5\text{BMI}_i + b_6\text{LACR}_i$$
$$= -1.3558\text{AGEA}_i - 07753\text{AGEB}_i + 0.7187\text{SEX}_i + 0.3776\text{SMOKE}_i + 0.0255\text{BMI}_i + 0.1739\text{LACR}_i \quad (12.2.1)$$

The regression coefficients, their standard errors, the Wald test statistics, p values, and relative hazards (relative risks as they are termed by many epidemiologists) are given in Table 12.6. The estimated regression coefficients $\hat{b}_i$, $i = 1, 2, \ldots, 6$, are solutions of (12.1.9) using the Newton–Raphson iterated procedure (Section 7.1). The estimated variances of $\hat{b}_i$, $i = 1, 2, \ldots, 6$, are the respective diagonal elements of the estimated covariance matrix defined in (12.1.13). The square roots of these estimated variances are the standard errors in the table. The Wald statistics are for testing the null hypothesis that the covariate is not related to the risk of CVD or $H_0: b_i = 0$, $i = 1, \ldots, 6$, respectively. For example, the Wald statistic equals 10.7457 for gender with a p value

Table 12.6 Asymptotic Partial Likelihood Inference on the CVD Data from the Final Cox Proportional Hazards Model[a]

Variable	Regression Coefficient	Standard Error	Wald Statistic	p	Relative Hazards	95% Confidence Interval	
						Lower	Upper
Final Model for the Cohort CVD Data							
AGEA	−1.3558	0.2712	24.9910	0.0001	0.258	0.151	0.439
AGEB	−0.7753	0.2618	8.7709	0.0031	0.461	0.276	0.769
SEX	0.7187	0.2193	10.7457	0.0010	2.052	1.335	3.153
SMOKE	0.3776	0.2208	2.9235	0.0873	1.459	0.946	2.249
BMI	0.0255	0.0124	4.2113	0.0402	1.026	1.001	1.051
LACR	0.1739	0.0446	15.2112	0.0001	1.190	1.090	1.299
$b_1 - b_2$	−0.580		4.9443	0.0262	0.560		
$b_3 + b_4$	1.096		11.5409	0.0007	2.993		
$b_3 - b_4$	0.341		1.3001	0.2542	1.407		
Hypothesis Testing Results (H_0: all $b_i = 0$)							
Log-partial-likelihood ratio statistic			42.1130	0.0001			
Score statistic			43.1750	0.0001			
Wald statistic			41.3830	0.0001			

[a] The covariates, except AGEA, AGEB, SEX, and SMOKE, in the final model are selected among BMI, SBP, LACR, LTG, HTN, and DM.

of 0.0010 and $b = 0.7187$. It indicates that after adjusting for all the variables in the model (12.2.1), gender is a significant predictor for the development of CVD, with men having a higher risk than women. The relative hazard (or risk) is $\exp(\hat{b}_1)$, and for the covariate gender, it is $\exp(0.7187) = 2.052$, which implies that men aged 50–79 years have about twice the risk of developing CVD in 10 years. The 95% confidence interval for the relative risk is (1.335, 3.153), which is calculated according to (7.1.8). For a continuous variable, $\exp(\hat{b}_i)$ represents the increase in risk corresponding to a 1-unit increase in the variable. For example, for BMI, $\exp(0.0255) = 1.026$; that is, for every unit increase in BMI, the risk for CVD increases 2.6%.

To compare hazards among different age groups, between genders, or between smokers and nonsmokers, let $h_{\mathrm{AGEA}}(t)$, $h_{\mathrm{AGEB}}(t)$, $h_{\mathrm{AGEC}}(t)$, $h_{\mathrm{MAL}}(t)$, $h_{\mathrm{FEM}}(t)$, $h_{\mathrm{SM}}(t)$, and $h_{\mathrm{NSM}}(t)$ denote hazard functions for participants that are 50–59, 60–69, 70–79 years old, male, female, current smoker, and not current smoker, respectively. The log hazard ratio of a person in the 50 to 59-year age group to a person in the 70 to 79-year group assuming the two people are of same gender and the same current smoking status, BMI and LACR, is $\log[h_{\mathrm{AGEA}}(t)/h_{\mathrm{AGEC}}(t)] = b_1$; similarly, $\log[h_{\mathrm{AGEB}}(t)/h_{\mathrm{AGEC}}(t)] = b_2$ and $\log[h_{\mathrm{AGEA}}(t)/h_{\mathrm{AGEB}}(t)] = b_1 - b_2$. Assuming that the two people are in the same age group and have the same BMI and LACR, the log hazard ratio of male to females is

$$\log \frac{h_{\mathrm{MAL}}(t)}{h_{\mathrm{FEM}}(t)} = b_3$$

Similarly, assuming that the two people are in the same age group, of the same gender, and have the same BMI and LACR, the hazard ratio of a smoker to a nonsmoker is

$$\log \frac{h_{\mathrm{SM}}(t)}{h_{\mathrm{NSM}}(t)} = b_4$$

Thus, testing whether risk of CVD are the same among different age groups is equivalent to testing $H_0: b_1 = 0$, $H_0: b_2 = 0$, and $H_0: b_1 - b_2 = 0$. Similarly, to test if the risk of CVD is the same between males and females or between smokers and nonsmokers is equivalent to tasting the null hypothesis $H_0: b_3 = 0$ or $H_0: b_4 = 0$, respectively.

To consider more than one covariate, we also can formulate the null hypothesis by using (12.2.1). For example, if we wish to compare male nonsmokers to female smokers, from (12.2.1),

$$\log \frac{h_{\mathrm{MAL-NSM}}}{h_{\mathrm{FEM-SM}}} = b_3 - b_4$$

assuming that they are in the same age group and have the same BMI and LACR. Thus to test if these two groups of people have the same risk of CVD, we test the null hypothesis $H_0: b_3 - b_4 = 0$. Similarly, to compare male smokers to female nonsmokers, we can test the null hypothesis $H_0: b_3 + b_4 = 0$. These null hypotheses are in the form of linear combinations of the coefficients. Using the notations in Section 11.2, the hypotheses $H_0: b_1 - b_2 = 0$ and $H_0: b_3 + b_4 = 0$ are the hypotheses in (11.2.13) with $\mathbf{c} = 0$, $\mathbf{L} = (1\ -1\ 0\ 0\ 0\ 0)$, and $\mathbf{L} = (0\ 0\ 1\ 1\ 0\ 0)$, respectively. The Wald statistics in Table 12.6 are calculated according to (11.2.14). By assuming that the patients have the same BMI and LACR, we can construct hypotheses to compare subgroups defined by age groups, gender, and current smoking status.

The last part of Table 12.6 shows the results of testing the null hypothesis that none of these covariates have any effect on the development of CVD. The log partial likelihood ratio, Wald, and score statistics, X_L, X_W, and X_S are calculated according to (9.1.10), (9.1.11), and (9.1.12), respectively. Table 12.6 indicates that the hypotheses, $H_0: b_1 = 0$, $H_0: b_2 = 0$, $H_0: b_1 - b_2 = 0$, $H_0: b_3 = 0$, $H_0: b_5 = 0$, $H_0: b_6 = 0$, and $H_0: b_3 + b_4 = 0$ are rejected at a significance level of $p = 0.05$. However, the hypotheses $H_0: b_4 = 0$ and $H_0: b_3 - b_4 = 0$ are not rejected at a 0.05 level. The null hypothesis H_0: all $b_i = 0$, $i = 1, \ldots, 6$, is rejected with $p = 0.0001$ by using any of these tests.

Assuming that the other covariates are the same, based on the relative hazards shown in the table, we conclude that (1) participants aged 50–59 and 60–69 have, respectively, about 25% and 50% lower CVD risk than those aged 70–79 ($H_0: b_1 = 0$ and $H_0: b_2 = 0$ are rejected); (2) participants aged 50–59 have 50% lower CVD risk than those aged 60–69 ($H_0: b_1 - b_2 = 0$ is rejected); (3) men's CVD risk is twice as high as that of women ($H_0: b_3 = 0$ is rejected); (4) BMI and LACR have a significant effect on CVD risk ($H_0: b_5 = 0$ and $H_0: b_6 = 0$ are rejected) and the risk increases about 3% and 19%, respectively, for every 1-unit increase in BMI and LACR, respectively; (5) male smokers have a CVD risk three times higher than that of female nonsmokers ($H_0: b_3 + b_4 = 0$ is rejected); (6) male nonsmokers have CVD risk similar to that of female smokers ($H_0: b_3 - b_4 = 0$ is not rejected); (7) considering current smoking status alone, smokers had similar CVD risk as nonsmokers ($H_0: b_4 = 0$ is not rejected). This example is solely for the purpose of illustrating the use of the proportional hazards model and the interpretation of its results. Other hypotheses of interest can be constructed in a similar manner. The construction of null hypotheses for comparisons among subgroups defined by AGEGROUP*SEX*SMOKE are left to the reader as exercises.

Suppose that "C:\EX12d4d1.DAT" is a text data file that contains 12 successive columns for T, CENS, AGEA, AGEB, SEX, SMOKE, BMI, LACR, SBP, LTG, HTN, and DM. The following SAS code is used to obtained the results in Table 12.6.

```
data w1;
  infile 'c:\ex12d4d1.dat' missover;
  input t cens agea ageb sex smoke bmi lacr sbp ltg htn dm;
run;
proc phreg data = w1;
  model t*cens(0) = agea ageb sex smoke bmi lacr sbp ltg htn dm /
                    include = 4 selection = f ;
run;
proc phreg data = w1;
  model t*cens(0) = agea ageb sex smoke bmi lacr sbp ltg htn dm /
                    include = 4 selection = b;
run;
proc phreg data = w1 outest = wcov covout;
  model t*cens(0) = agea ageb sex smoke bmi lacr sbp ltg htn dm /
                    include = 4 selection = s;
run;
proc phreg data = w1;
  model t*cens(0) = agea ageb sex smoke bmi lacr sbp ltg htn dm /
                    include = 4 selection = score best = 3;
run;
data wcov;
  set wcov;
  if _type_ = 'cov';
  keep agea ageb sex smoke bmi lacr sbp ltg htn dm;
run;
title 'The estimated covariance of the estimated coefficients';
proc print data = wcov;
run;
```

The following SPSS code can be used to select an optimal subset of covariates among all covariates by the forward and backward selection methods defined in Section 11.9.1 and to obtain the estimated coefficients and the other results in Table 12.6.

```
data list file = 'c:\ex12d4d1.dat' free
        / t cens agea ageb sex smoke bmi lacr sbp ltg htn dm.
coxreg t with agea ageb sex smoke bmi lacr sbp ltg htn dm
        /status = cens event (1)
        /method = fstep bmi lacr sbp ltg htn dm
        /criteria pin (0.05) pout (0.05)
        /print = all.
coxreg t with agea ageb sex smoke bmi lacr sbp ltg htn dm
        /status = cens event (1)
        /method = bstep bmi lacr sbp ltg htn dm
        /criteria pin (0.05) pout (0.05)
        /print = all.
```

If BMDP 2L is used, the following code is applicable when selecting an optimal subset of covariates among all covariates by the stepwise selection method defined in Section 11.9.1 and to obtain the results in Table 12.6.

```
/input      file = 'c:\ex12d4d1.dat' .
            variables = 12.
            format = free.
/print      cova.
/variable   names = t,cens, agea, ageb, sex, smoke, bmi, lacr, sbp, ltg,
            htn, dm.
/form       time = t.
            status = cens.
            response = 1.
/regress    covariates = agea, ageb, sex, smoke, bmi, lacr, sbp, ltg, htn,
              dm.
            Step = phh.
```

Example 12.5 If we do not force age, gender, and current smoking status on the model and are not interested in the three age groups, we can fit the proportional hazard model with age as a continuous variable and the other covariates: SEX, SMOKE, BMI, SBP, LACR, LTG, HTN, and DM. Using Breslow's method for ties, the stepwise selection method, and the SAS procedure PHREG, the final model with significant ($p < 0.05$) covariates is

$$\log \frac{h(t)}{h_0(t)} = 0.697\text{AGE} + 0.7528\text{SEX} + 0.1111\text{LACR} + 0.3987\text{LTG} \tag{12.2.2}$$

The details are given in Table 12.7; all four covariates in the model have positive coefficients, indicating that the risk of developing CVD increases with age, gender, albumin/creatinine ratio, and triglyceride values. The relative hazards represent the increase in risk of CVD per unit increase in the covariates. For example, for every 1-unit increase in log(albumin/creatinine), the risk of developing CVD increases 12% after adjusting for age, gender, and log triglyceride. Men have more than twice the risk of CVD as women. The global null hypothesis that all four coefficients equal zero (H_0: all $b_i = 0$) is rejected by all three tests, as given in the lower part of Table 12.7.

12.3 ESTIMATION OF THE SURVIVORSHIP FUNCTION WITH COVARIATES

When parametric regression models (Chapter 11) are used, we can estimate the survivorship function simply by replacing the parameters and coefficients in the survival function with their estimates. This is not the case when the Cox

Table 12.7 Asymptotic Partial Likelihood Inference on the CVD Data from the Final Cox Proportional Hazards Model Selected by the Stepwise Model Selection Method[a]

Variable	Regression Coefficient	Standard Error	Chi-Square Statistic	p	Relative Hazards	95% Confidence Interval for Relative Hazards	
						Lower	Upper
AGE	0.0697	0.0136	26.1393	0.0001	1.07	1.04	1.10
SEX	0.7528	0.2192	11.7893	0.0006	2.12	1.38	3.26
LACR	0.1111	0.0459	5.8602	0.0155	1.12	1.02	1.22
LTG	0.3987	0.1976	4.0722	0.0436	1.49	1.01	2.20
H_0: All coefficients equal zero							
Log-partial-likelihood ratio statistic			44.002	0.0001			
Score statistic			44.278	0.0001			
Wald statistic			42.527	0.0001			

[a] The covariates in the final model are selected among AGE, SEX, SMOKE, BMI, LACR, LTG, HTN, and DM using the stepwise selection method.

proportional hazards model is used since we do not know the exact form of the baseline hazard function or the survival function. In this section we introduce briefly two estimators of the survival function, one proposed by Breslow (1974) and the other by Kalbfleisch and Prentice (1980). These estimates are available in commercial software packages. Readers interested in details are referred to the corresponding publications.

As indicated earlier, under the Cox model, the survivorship function with covariates x_j's is

$$S(t, \mathbf{x}) = [S_0(\mathrm{t})]^{\exp(\Sigma_{j=1}^{p} b_j x_j)} \tag{12.3.1}$$

Once the regression coefficients, the b_j's, are estimated, we need only estimate the underlying survivorship function, $S_0(t)$. From the estimated survivorship function, we can easily estimate the probability of surviving longer than a given time for a patient with a given set of covariates $x_1, \ldots, x_p$.

By assuming that the baseline hazard function is constant between each pair of successive observed failure times, Breslow has proposed the following estimator of the baseline cumulative hazard function:

$$\hat{H}_0(t) = \sum_{t_{(i)} \leqslant t} \frac{m_{(i)}}{\sum_{l \in R(t_{(i)})} \exp(\mathbf{x}_l' \hat{\mathbf{b}})} \tag{12.3.2}$$

Following (2.15), the baseline survival function can be estimated as

$$\hat{S}_0(t) = \exp[-\hat{H}_0(t)] = \prod_{t_{(i)} \leqslant t} \left\{ \exp\left[\frac{m_{(i)}}{\sum_{l \in R(t_{(i)})} \exp(\mathbf{x}_l' \hat{\mathbf{b}})} \right] \right\} \tag{12.3.3}$$

and the survivorship function for a person with a set of covariates $\mathbf{x} = (x_1, \ldots, x_p)$ is

$$\hat{S}(t, \mathbf{x}) = [\hat{S}_0(t)]^{\exp(\sum_{j=1}^{p} \hat{b}_j x_j)} = [\hat{S}_0(t)]^{\exp(\hat{\mathbf{b}}'\mathbf{x})} \tag{12.3.4}$$

Under mild assumptions, $\hat{S}(t, \mathbf{x})$ has an asymptotic normal distribution with mean $S(t, \mathbf{x})$. Since $S(t, \mathbf{x}) = \exp[-H(t, \mathbf{x})]$, the variance estimator $\widehat{\mathrm{Var}}(\hat{S}(t, \mathbf{x}))$ of $\hat{S}(t, \mathbf{x})$ is

$$\widehat{\mathrm{Var}}(\hat{S}(t, \mathbf{x})) \simeq [\hat{S}(t, \mathbf{x})]^2 \, \widehat{\mathrm{Var}}(\hat{H}(t, \mathbf{x}))$$

We will not give $\hat{H}(t, \mathbf{x})$ here because of its complexity. The asymptotic confidence bands for the survivorship function is

$$\left(\hat{S}(t, \mathbf{x}) - Z_{\alpha/2} \sqrt{\widehat{\mathrm{Var}}(\hat{S}(t, \mathbf{x}))}, \; \hat{S}(t, \mathbf{x}) + Z_{\alpha/2} \sqrt{\widehat{\mathrm{Var}}(\hat{S}(t, \mathbf{x}))} \right) \tag{12.3.5}$$

where $Z_{\alpha/2}$ is the upper $100(1 - \alpha/2)$ percentile point of the standard normal distribution.

An alternative estimator has been suggested by Kalbfleisch and Prentice in which the baseline survivorship function $S_0(t)$ is estimated to be a step function and

$$\hat{S}_0(t) = \prod_{j=0}^{i-1} \hat{\alpha}_j \qquad t_{(i-1)} < t \leqslant t_{(i)}, \quad i = 1, \ldots, k+1 \tag{12.3.6}$$

where $\hat{\alpha}_0 \equiv 1$ and $\hat{\alpha}_1, \hat{\alpha}_2, \ldots, \hat{\alpha}_k$ are the solution of the following k simultaneous equations:

$$\sum_{j \in \mathbf{u}_{(i)}^*} \frac{\exp(\mathbf{x}_j' \hat{\mathbf{b}})}{1 - \hat{\alpha}_i^{\exp(\mathbf{x}_j' \hat{\mathbf{b}})}} = \sum_{l \in R(t_{(i)})} \exp(\mathbf{x}_l' \hat{\mathbf{b}}) \qquad i = 1, \ldots, k \tag{12.3.7}$$

When there are no ties,

$$\hat{\alpha}_i = \left[1 - \frac{\exp(\mathbf{x}_{(i)}' \hat{\mathbf{b}})}{\sum_{l \in R(t_{(i)})} \exp(\mathbf{x}_l' \hat{\mathbf{b}})} \right]^{\exp(-\mathbf{x}_{(i)}' \hat{\mathbf{b}})} \qquad i = 1, \ldots, k \tag{12.3.8}$$

and

$$\hat{S}_0(t) = \prod_{j=0}^{i-1} \left[1 - \frac{\exp(\mathbf{x}_{(j)}' \hat{\mathbf{b}})}{\sum_{l \in R(t_{(j)})} \exp(\mathbf{x}_l' \hat{\mathbf{b}})} \right]^{\exp(-\mathbf{x}_{(j)}' \hat{\mathbf{b}})} \qquad t_{(i-1)} \leqslant t < t_{(i)} \qquad i = 1, \ldots, k+1$$

Thus,

$$\hat{S}(t, \mathbf{x}) = [\hat{S}_0(t)]^{\exp(\hat{\boldsymbol{\beta}}'\mathbf{x})} \tag{12.3.9}$$

Under mild assumptions, the Kalbfleisch and Prentice estimator in (12.3.9) also follows an asymptotic normal distribution with mean $S(t, \mathbf{x})$ and a variance that can be estimated. Thus confidence bands for the survivorship function can also be constructed.

Using (12.3.4) with $S_0(t)$ in (12.3.3) or (12.3.6), the survivorship function can be estimated with any given values of $x_1, \ldots, x_p$. If the observed average of every covariate, $\bar{x}_1, \ldots, \bar{x}_p$ is used, the estimated survivorship function can be interpreted as the survivorship function of an "average" person.

Both the Breslow and Kalbfleisch–Prentice estimators are available in the SAS procedure PHREG. The Breslow estimator is also available in BMDP (program 2L) and SPSS (program COXREG). The following example illustrates the procedures.

Example 12.6 Again, we use the CVD data in the Example 12.3, the data set "C:\EX12d2d1.DAT", and the SAS procedure PHREG. We use the average of each of the covariates in (12.2.1), and therefore the estimated survivorship function is for an average person. The Kalbfleisch–Prentice and Breslow estimates of the survival function, defined in (12.3.9) and (12.3.4) (Efron adjustment for ties is used), and the lower and upper 95% confidence bands, calculated based on (12.3.5), are shown in Figures 12.1 and 12.2. These estimated survival functions, using all the covariates in the model with average values, are often referred to as the global covariate–adjusted survivorship functions. The two figures are almost identical, which indicates that the two methods produce very similar results for this set of data. From Figure 12.1 it appears that the global covariates–adjusted survivorship function decreases somewhat more rapidly after 3.5 years. This means that the process to develop CVD accelerates after 3.5 years.

Using the data set "C:\EX12d2d1.DAT" defined in Example 12.3, the SAS code used for this example is the following.

```
data w1;
  infile 'c:\ex12d2d1.dat' missover;
  input t cens agea ageb sex smoke bmi lacr;
run;
proc phreg data = w1 noprint;
  model t*cens(0) =  agea ageb sex smoke bmi lacr / ties = efron;
  baseline out = base1 survival = survival l= lowb u = uppb / method = pl;
run;
title 'K-P estimate of the survival function and its lower and upper bands';
proc print data = base1;
  var t survival lowb uppb;
run;
```

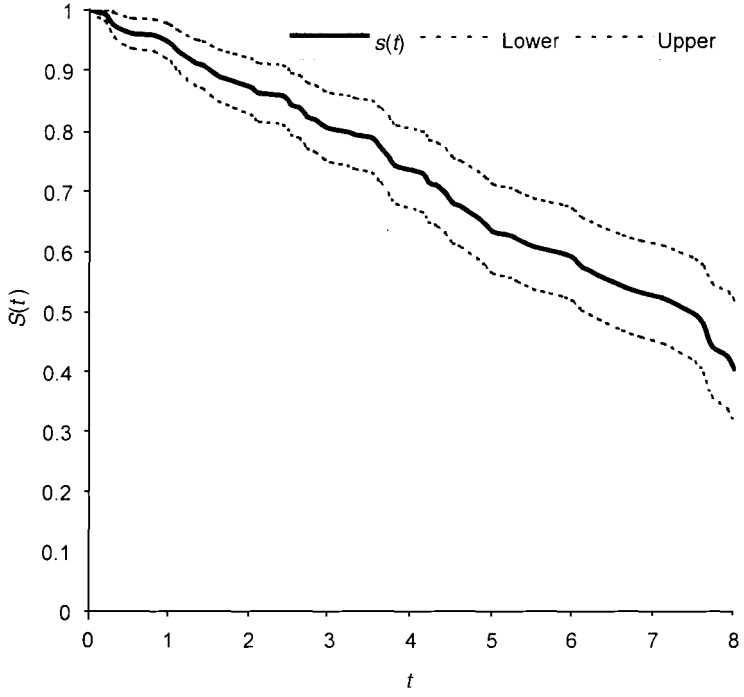


Figure 12.1 Kalbfleisch–Prentice estimate of survivorship function and its 95% confidence bands at the averages of the covariates from the fitted Cox proportional hazards model on the CVD data.

```
proc phreg data = w1 noprint;
   model t*cens(0) =  agea ageb sex smoke bmi lacr / ties = efron;
   baseline out = base1 survival = survival l = lowb u = uppb / method = ch;
run;
title 'Breslow estimate of the survival function and its lower and upper bands';
proc print data = base1;
   var t survival lowb uppb;
run;
```

The following SPSS code can be used to obtain the Breslow estimate of the survival function and its standard error at each uncensored observation. The confidence bands can then be calculated according to (12.3.5).

```
data list file = 'c:\ex12d2d1.dat' free
        / t cens agea ageb sex smoke bmi lacr.
coxreg t with agea ageb sex smoke bmi lacr
        /status = cens event (1)
        /print = all.
```

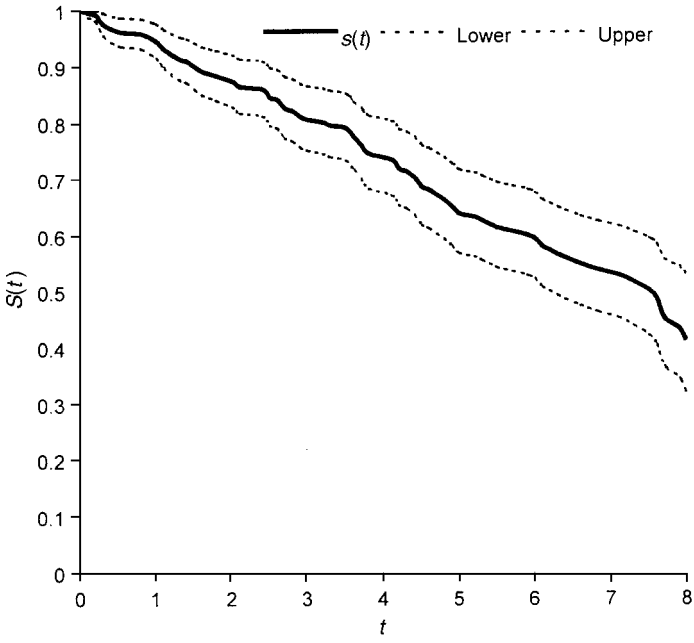


Figure 12.2 Breslow estimate of the survivorship function and its 95% confidence bands at the averages of the covariates from the fitted Cox proportional hazards model on the CVD data.

The corresponding BMDP 2L code is

```
/input      file = 'c:\ex12d2d1.dat' .
            variables = 8.
            format = free.
/print      cova.
            Survival.
/variable   names = t,cens, agea, ageb, sex, smoke, bmi, lacr.
/form       time = t.
            status = cens.
            response = 1.
/regress    covariates = agea, ageb, sex, smoke, bmi, lacr.
```

In addition to the global covariates–adjusted survivorship function defined as $\hat{S}(t, \bar{\mathbf{x}})$, where $\bar{\mathbf{x}} = (\bar{x}_1, \bar{x}_2, \ldots, \bar{x}_p)$, the survivorship function can be estimated with any specific values of one or more of the covariates and interactions. We can also estimate the probability of surviving longer than a given time for individuals with a given set of values for covariates. The following is an example.

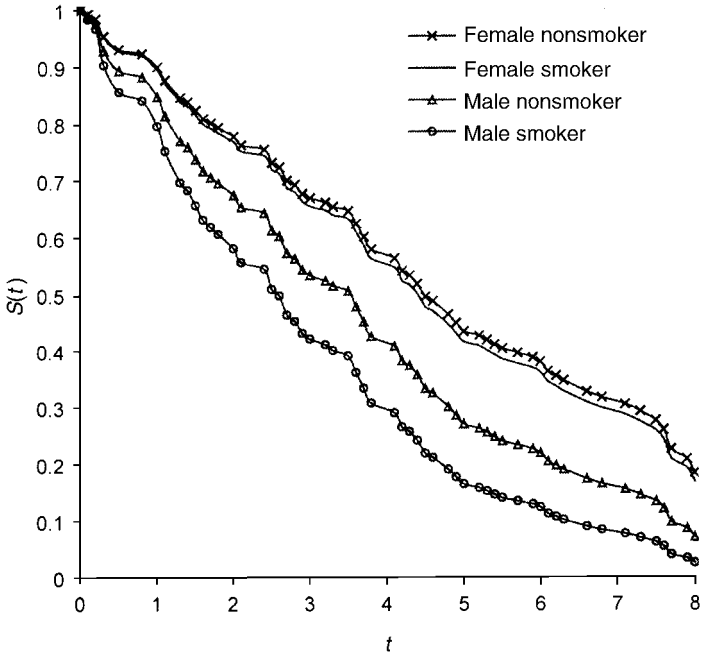


Figure 12.3 Breslow estimate of survivorship functions at the averages of BMI and LACR from SEX*SMOKER subgroups in aged 70–79 participants from the fitted Cox proportional hazards model on the CVD data.

Example 12.7 For the same model as in Example 12.6, we can estimate the covariate-specific survivorship function for female nonsmokers, female smokers, male smokers, and male nonsmokers. Let us use the 70–79 age group and assume that BMI and LACR are at the average of the respective SEX–SMOKE subgroup. Thus, the specific covariate vector (AGEA, AGEB, SEX, SMOKE, BMI, LACR) for female nonsmokers is (0, 0, 0, 0, 30.69, 4.62), where 30.69 and 4.62 are the average values of BMI and LACR for female nonsmokers. Similarly, the specific covariate vectors for female smokers, male nonsmokers, and male smokers are, respectively, (0, 0, 0, 1, 31.19, 2.67), (0, 0, 1, 0, 28.19, 3.43), and (0, 0, 1, 1, 25.76, 3.47). The estimated survival curves are shown in Figure 12.3. Similarly, Figures 12.4 and 12.5 give the estimated survival curves of the four groups in persons aged 60–69 years and 50–59 years, respectively. The groups show that in all these age groups, females have a lower risk of developing CVD (longer CVD-free time) than males. Female nonsmokers have a slightly lower risk than female smokers and the differences increase as age decreases. However, among males, the differences in the risk of CVD between smokers and nonsmokers are almost negligible in the youngest group and much larger in the two older groups. Male smokers have the highest risk of developing CVD (shortest CVD-free time) among the four groups.

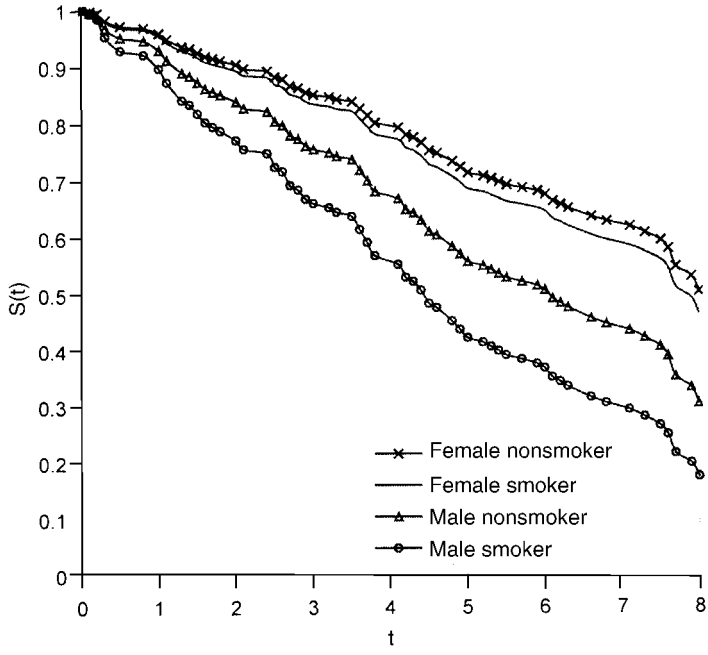


Figure 12.4 Breslow estimate of survivorship functions at the averages of BMI and LACR from SEX*SMOKER subgroups in aged 60–69 participants from the fitted Cox proportional hazards model on the CVD data.

12.4 ADEQUACY ASSESSMENT OF THE PROPORTIONAL HAZARDS MODEL

The validity of statistical inferences that leads to the identification of important risk or prognostic factors depends largely on the adequacy of the model selected. The proportional hazards model is used widely in medical and epidemiological studies. The adequacy of this model, including the assumption of proportional hazards and the goodness of fit, needs to be assessed. In this section we introduce several methods for this purpose. A major reason for selecting these methods to present here is the availability of computer software that can perform the calculations.

12.4.1 Checking the Proportional Hazards Assumption

The proportional hazards models defined in (12.1.1) and (12.1.3) assume that the hazard ratio of two people is independent of time. This requires that covariates not be time-dependent. If any of the covariates varies with time, the proportional hazards assumption is violated. This fact can be used to test the assumption by including a time–covariate interaction term in the model and

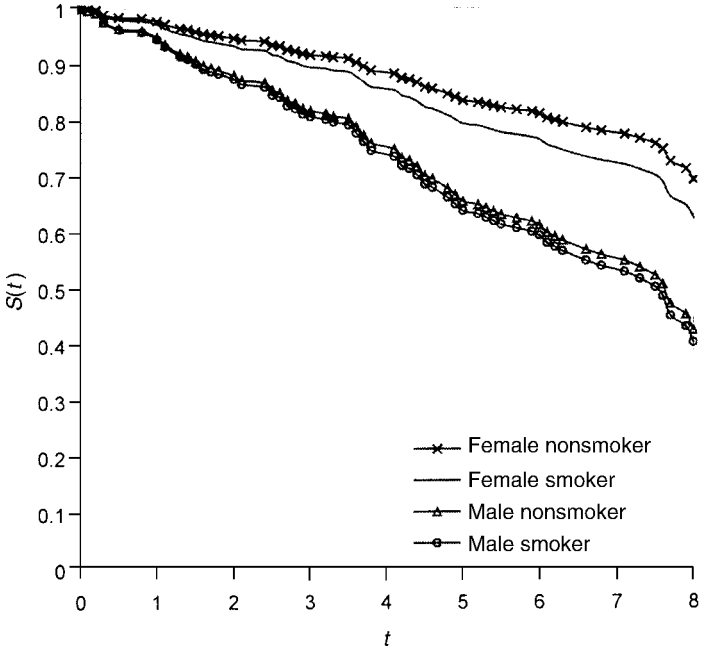


Figure 12.5 Breslow estimate of survivorship functions at the averages of BMI and LACR from SEX*SMOKER subgroups in aged 50–59 participants from the fitted Cox proportional hazards model on the CVD data.

testing if the coefficient for interaction is significantly different from zero. For example, we can add an interaction term $x_i t$ or $x_i \log t$ in the model, that is,

$$\log \frac{h(t)}{h_0(t)} = b_1 x_1 + \cdots + b_i x_i + b_{i1} x_i t + b_{i+1} x_{i+1} + \cdots + b_p x_p$$

or

$$\log \frac{h(t)}{h_0(t)} = b_1 x_1 + \cdots + b_i x_i + b_{i1} x_i \log t + b_{i+1} x_{i+1} + \cdots + b_p x_p$$

With the added interaction term, the partial likelihood function becomes more complicated. Fortunately, computer software is available to carry out the calculations. Testing procedures similar to those discussed earlier (e.g., the Wald test), can be used to test the null hypothesis $H_0: b_{i1} = 0$. If H_0 is rejected, we conclude that Cox's proportional hazard model is not appropriate for the data. The interaction term with $\log t$ can be included in the model for each of the covariates separately. If none of the corresponding p null hypotheses $H_0: b_{i1} = 0$ is rejected, we may conclude that the proportional hazards assumption is appropriate.

Example 12.8 Consider the fitted proportional hazards model in (12.2.2) for the CVD data. To check the proportional hazards assumption, we add a term $LTG \times \log(t+1)$ to the model. We use $t+1$ instead of t to avoid negative values. Table 12.8(*a*) gives the results. The p value for the interaction term is 0.1910. Similarly, the results in Table 12.9(*b*) and (*c*) suggest that LACR $\times \log(t+1)$ and AGE $\times \log(t+1)$ are not significant either. Since gender is time-independent, we may conclude that the data satisfy the proportional hazards assumption since every covariate in the model is time-independent.

Another method to check the proportional hazards assumption is to stratify the data based on some values of a covariate, fit a stratified Cox proportional hazards model (this is discussed in Chapter 13), and then construct the survivorship function separately for the each stratum and plot

$$\log(-\log(\hat{S}_j(t;\, \bar{\mathbf{x}}_j))) \qquad j = 1, 2, \ldots, m$$

Table 12.8 Asymptotic Partial Likelihood Inference on the CVD Data from the Cox Proportional Hazards Model with Time-Dependent Covariate

Regressor Variable	Regressor Coefficient	Standard Error	Wald Statistic	p	Relative Hazards	95% Confidence Interval for Relative Hazards	
						Lower	Upper
			(a)				
AGE	0.068	0.014	25.249	0.0001	1.07	1.04	1.1
SEX	0.759	0.218	12.056	0.0005	2.14	1.39	3.28
LACR	0.111	0.046	5.781	0.0162	1.12	1.02	1.22
LTG	0.915	0.435	4.420	0.0355	2.50	1.06	5.86
LTG* log($t+1$)	−0.390	0.298	1.710	0.1910	0.68	0.38	1.22
			(b)				
AGE	0.071	0.014	26.635	0.0001	1.07	1.05	1.1
SEX	0.741	0.220	11.327	0.0008	2.10	1.36	3.23
LACR	−0.087	0.120	0.519	0.4714	0.92	0.72	1.16
LTG	0.395	0.199	3.917	0.0478	1.48	1	2.19
LACR* log($t+1$)	0.143	0.079	3.269	0.0706	1.15	0.99	1.35
			(c)				
AGE	0.038	0.033	1.330	0.2488	1.04	0.97	1.11
SEX	0.764	0.220	12.020	0.0005	2.15	1.39	3.31
LACR	0.111	0.046	5.888	0.0152	1.12	1.02	1.22
LTG	0.417	0.197	4.469	0.0345	1.52	1.03	2.24
AGE*log($t+1$)	0.023	0.023	1.046	0.3064	1.02	0.98	1.07

against time t, where m is the number of strata defined by the covariate, $\bar{\mathbf{x}}_j$ is the vector of the average values of the other covariates for the jth stratum, and $\hat{S}_j(t; \bar{\mathbf{x}}_j)$ is the estimated survivorship function of the jth stratum evaluated at t and $\bar{\mathbf{x}}_j$. If the hazards are proportional, the m curves should be parallel. Nonparallel curves indicate departure from the proportional hazards assumption. This is because if hazard functions from any two people are proportional, it can be shown from (12.1.1) that, for any $j \neq k$ and $1 \leqslant j, k \leqslant m$, there exists a constant d_{jk} such that

$$\hat{S}_j(t; \bar{\mathbf{x}}_j) = (\hat{S}_k(t; \bar{\mathbf{x}}_k))^{d_{jk}} \tag{12.4.1}$$

Taking the logarithm twice, we have

$$\log[-\log(\hat{S}_j(t; \bar{\mathbf{x}}_j))] = \log d_{jk} + \log[-\log(\hat{S}_k(t; \bar{\mathbf{x}}_k))] \tag{12.4.2}$$

Thus the curves of $\log[-\log(\hat{S}_j(t; \bar{\mathbf{x}}_j))]$ and $\log[-\log(\hat{S}_k(t; \bar{\mathbf{x}}_k))]$ versus t should be parallel.

Example 12.9 Consider again the fitted model in (12.2.2); using the stratified analysis (more details are given in Chapter 13), we plot $\log[-\log \hat{S}_j(t; \bar{\mathbf{x}}_j)]$ against t for two age strata (50–64 and 65–79 years) and two gender strata separately, where $\bar{\mathbf{x}}_j$ denotes the average values of the other covariates for the jth stratum. These graphs are given in Figures 12.6 and 12.7,

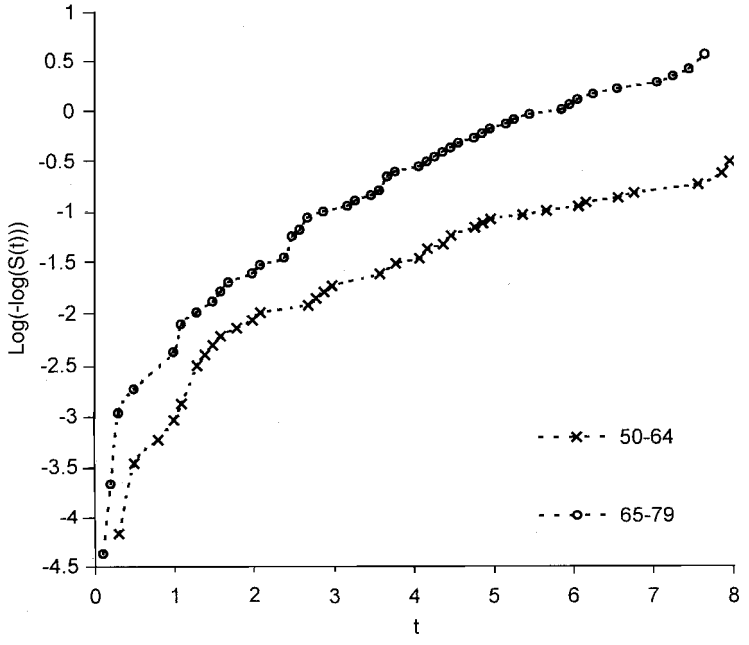


Figure 12.6 $\text{Log}[-\log(S(t))]$ plots for the age-stratified Cox proportional hazards model on the CVD data.

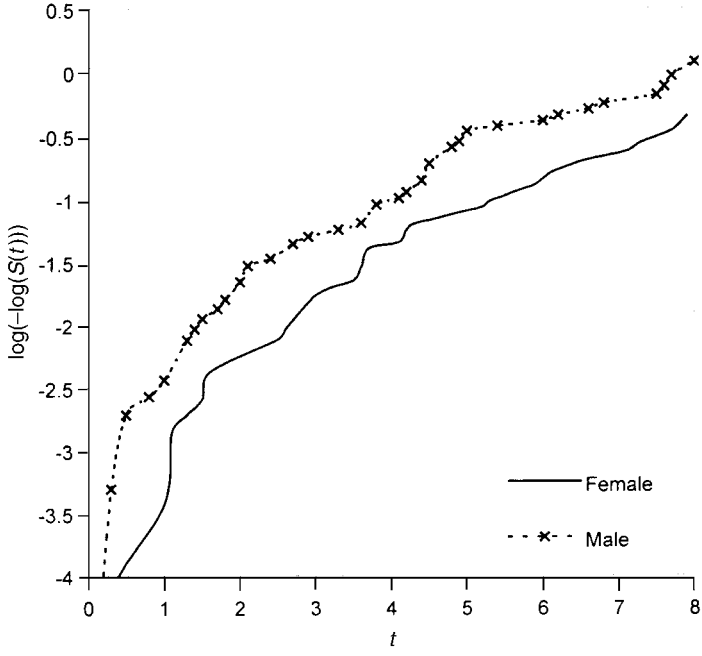


Figure 12.7 Log[$-\log(S(t))$] plots for gender-stratified Cox proportional hazards model on the CVD data.

respectively. The two curves in Figure 12.6 are roughly parallel. The two curves in Figure 12.7 are also parallel over time. The results suggest that the proportional hazards assumption holds.

In Chapter 11 we discussed several parametric models. Among these models, the exponential and the Weibull are proportional hazards models, but the others are not. Thus, if one of the other models provides a good fit to data, we would know that the data do not meet the proportional hazards assumption. This procedure can also be served as an alternative for checking the proportional hazards assumption.

12.4.2 Assessing Goodness of Fit by Residuals

There are several other graphical methods available for assessing the goodness of fit of a proportional hazards model. These graphical methods are based on residuals and are often used as diagnostic tools. In multiple regression methods, residuals are referred to as the difference between the observed and the predicted values (based on the regression model) of the dependent variable. However, when censored observations are present and only a partial likelihood function is used in the proportional hazards model, the usual concept of residuals is not applicable. In the following we introduce three different types

of residuals: the extended Cox–Snell, deviance, and Schoenfeld residuals. These can be plotted versus the survival time or a covariate. The pattern of the graph provides some information about the appropriateness of the proportional hazards model. It also provides information about outliers and other patterns. Similar to other graphical methods, interpretation of the residual plots may be subjective.

The Cox–Snell method discussed in Section 8.4 can easily be extended to the proportional hazards model. The extended Cox–Snell residual, R_i, for the ith individual with observed survival time t and covariates at values $\mathbf{x}_i$ is defined as $R_i = -\log \hat{S}(t_i; \mathbf{x}_i)$, which is the estimated accumulated hazard based on the proportional hazards model. If the t_i observed is censored, the corresponding R_i is also censored. If the proportional hazards model is appropriate, the plot of R_i and its Kaplan–Meier estimate of survival function ($\hat{S}(R)$) would appear as a 45° straight line. The Cox–Snell residual method is useful in assessing the goodness of fit of a parametric model (Section 11.9.4). However, it is not so desirable for a proportional hazards model where a partial likelihood function is used and the survivorship function is estimated by nonparametric methods.

The deviance residuals (Therneau et al., 1990) are defined as

$$R_{Di} = \text{sign}(R_{Mi})\sqrt{2[-R_{Mi} - \delta_i \log(\delta_i - R_{Mi})]} \qquad i = 1, 2, \ldots, n \quad (12.4.3)$$

where sign $(\cdot)$ is the sign function, which takes value 1 if its argument is positive, 0 if zero, and -1 if negative, R_{Mi} is the martingale residual (Fleming and Harrington, 1991) for the ith individual,

$$R_{Mi} = \delta_i - R_i \qquad i = 1, \ldots, n$$

and $\delta_i = 1$ if the observed survival time t_i is uncensored and 0 otherwise.

The martingale residuals have a skewed distribution with mean zero (Anderson and Gill, 1982). The deviance residuals also have a mean of zero but are symmetrically distributed about zero when the fitted model is adequate. Deviance residuals are positive for persons who survive for a shorter time than expected and negative for those who survive longer. The deviance residuals are often used in assessing the goodness of fit of a proportional hazards model.

Another residual method was proposed by Schoenfeld (1982) and modified by Grambsch and Therneau (1994). The original Schoenfeld residuals are defined for each person and each covariate and are based on the first derivative of the log-likelihood function in (12.1.9). A Schoenfeld residual for the jth covariate of the ith person with the observed survival time t_i is

$$R_{ji} = \delta_i \left[x_{ji} - \frac{\sum_{l \in R(t_{(i)})} x_{jl} \exp(\hat{\mathbf{b}}'\mathbf{x}_l)}{\sum_{l \in R(t_{(i)})} \exp(\hat{\mathbf{b}}'\mathbf{x}_l)} \right] \qquad j = 1, 2, \ldots, p; \quad i = 1, 2, \ldots, n \quad (12.4.4)$$

where $\hat{\mathbf{b}}$ is the maximum partial likelihood estimator of $\mathbf{b}$. The Schoenfeld residuals are defined only at uncensored survival times; for censored observations they are set as missing. Since $\hat{\mathbf{b}}$ is the solution of (12.1.9), the sum of the Schoenfeld residuals for a covariate is zero. Thus asymptotically, the Schoenfeld residuals have a mean of zero. It can also be shown that these residuals are not correlated with one another.

Grambsch and Therneau (1994) suggested that the Schoenfeld residuals be weighted by the inverse of the estimated covariance matrix of $\mathbf{R}_i = (R_{1i}, \ldots, R_{pi})'$ denoted by $\hat{V}(\mathbf{R}_i)$, that is,

$$\mathbf{R}_i^* = [\hat{V}(\mathbf{R}_i)]^{-1}\mathbf{R}_i \tag{12.4.5}$$

The weighted Schoenfeld residuals have better diagnostic power and are used more often than the unweighted residuals in assessing the proportional hazards assumption. To simplify the computations, Grambsch and Therneau (1994) suggested an approximation of $[\hat{V}(\mathbf{R}_i)]^{-1}$ in (12.4.5):

$$[\hat{V}(\mathbf{R}_i)]^{-1} \simeq r\hat{V}(\hat{\mathbf{b}})$$

where r is the number of events or the number of observed uncensored survival times and $\hat{V}(\hat{\mathbf{b}})$ is the estimated covariance matrix of $\hat{\mathbf{b}}$ in (12.1.13). With this approximation, the weighted Schoenfeld residuals in (12.4.5) can be approximated by

$$\mathbf{R}_i^* = r\hat{V}(\hat{\mathbf{b}})\mathbf{R}_i \tag{12.4.6}$$

The graphs of deviance and Schoenfeld residuals against survival time or a covariate can be used to check the adequacy of the proportional hazards model. The presence of certain patterns in these graphs may indicate departures from the proportional hazards assumption, while extreme departures from the main cluster indicate possible outliers or potential stability problems of the model.

Example 12.10 Consider the proportional hazards model (12.2.2) for the CVD data. Using the estimated survivorship function with covariates, we obtain the extended Cox–Snell residual R_i values and plot the Kaplan–Meier estimate of the survivorship function of the R_i's. Figure 12.8 gives the extended Cox–Snell residual plot. The configuration is very close to a 45° line, indicating that the proportional hazards model (12.2.2) provides a reasonable fit to the data.

Figure 12.9 plots the deviance residuals against t. Roughly speaking, the residuals are distributed symmetrically around zero between -3 and 3 with no peculiar patterns. Larger positive (negative) residuals are associated with smaller (larger) t values. The deviance residuals suggest that the proportional hazards model provides a reasonable fit to the data.

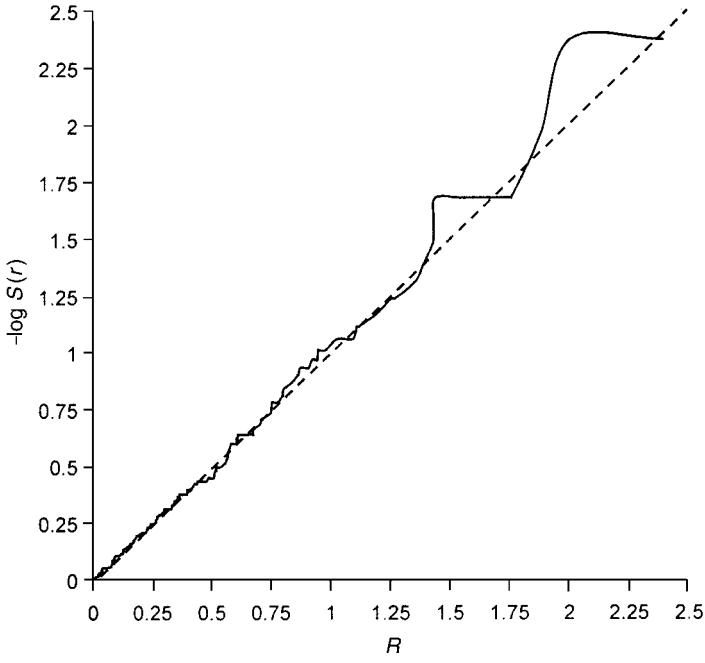


Figure 12.8 Cox–Snell residuals plot from the fitted Cox proportional hazards model on the CVD data.

The weighted Schoenfeld residuals versus AGE, LACR, and LTG are given in Figures 12.10 to 12.12. In all these graphs, the residuals are distributed symmetrically around zero except that in Figure 12.12, there are two outliers in the upper right corner. These extremely large residuals are from people with exceptionally high values of triglyceride. A large number of the residuals equal zero or are very close to zero, particularly those for AGE and LACR, suggesting that the model is accurate in predicting the risk of developing CVD for these people.

We also fit several parametric models to the data. Table 12.9 gives the goodness of fit assessments for five parametric models. The likelihood ratio test results suggest that the Weibull regression model provides an adequate fit ($p = 0.2534$). The Weibull fit also gives the largest BIC and AIC values, suggesting that the Weibull fit is best among these five models. As mentioned earlier, the Weibull model is a proportional hazards model. Thus, the parametric model fitting provides additional evidence that the proportional hazards model is adequate.

Using the data set "C:\EX12d4d1.DAT" in Example 12.4, the following SAS code is used to obtain the Cox–Snell, deviance, and weighted Schoenfeld residuals for AGE, LTG, and LACR in Example 12.10.

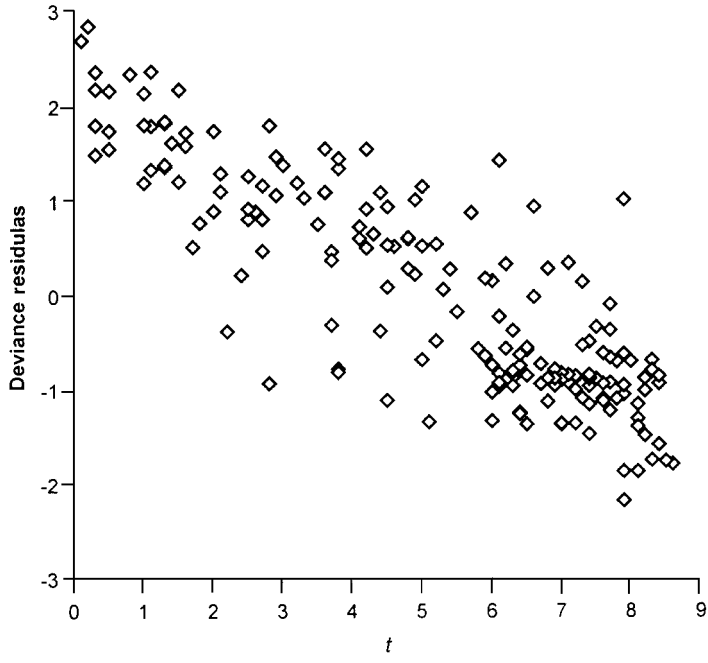


Figure 12.9 Deviance residuals from the fitted Cox proportional hazards model on the CVD data.

```
data w1;
   infile 'c:\ex12d4d1.dat' missover;
   input t cens agea ageb sex smoke bmi lacr sbp ltg age htn dm;
run;
proc phreg data = w1 noprint;
   model t*cens(0) =  age sex lacr ltg / ties = efron;
   output out = out1 logsurv = ls resdev = rdev wtressch = rage r2 rlacr rltg;
run;
data out1;
   set out1;
   rcs = -ls;
run;
proc lifetest data = out1 notable outs = ws noprint;
   time rcs*cens(0);
run;
data ws;
   set ws;
   mls = -log(survival);
run;
title 'Cox-Snell Residuals (rcs) and -log(estimated survival function of rcs) (mls)';
proc print data = ws;
   var rcs mls;
```

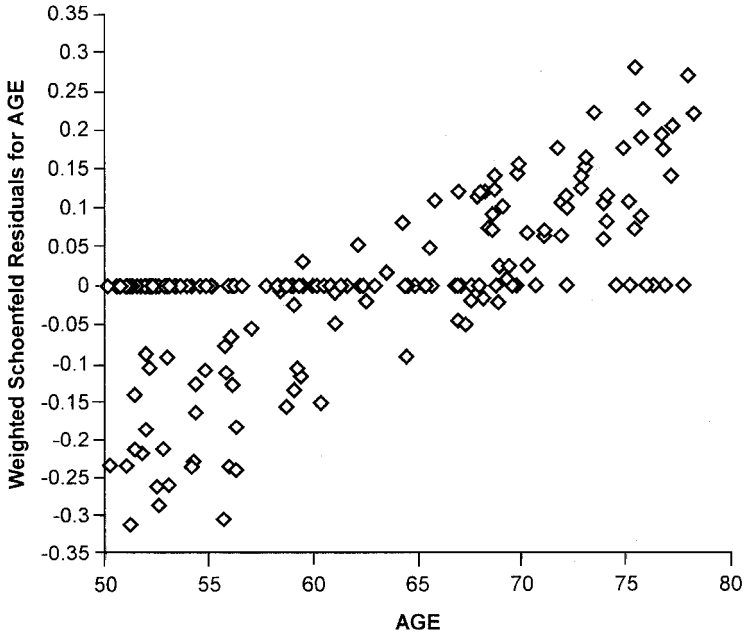


Figure 12.10 Weighted Schoenfeld residuals from the fitted Cox proportional hazards model on the CVD data.

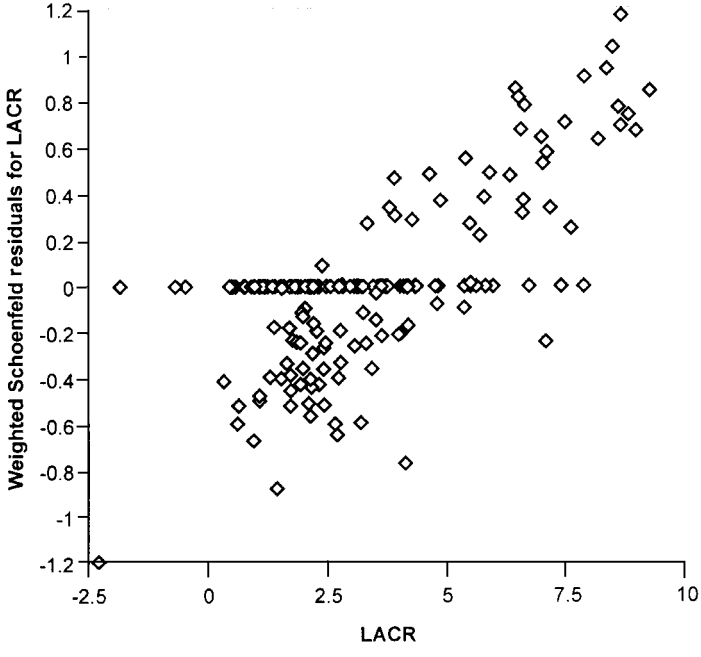


Figure 12.11 Weighted Schoenfeld residuals from the fitted Cox proportional hazards model on the CVD data.

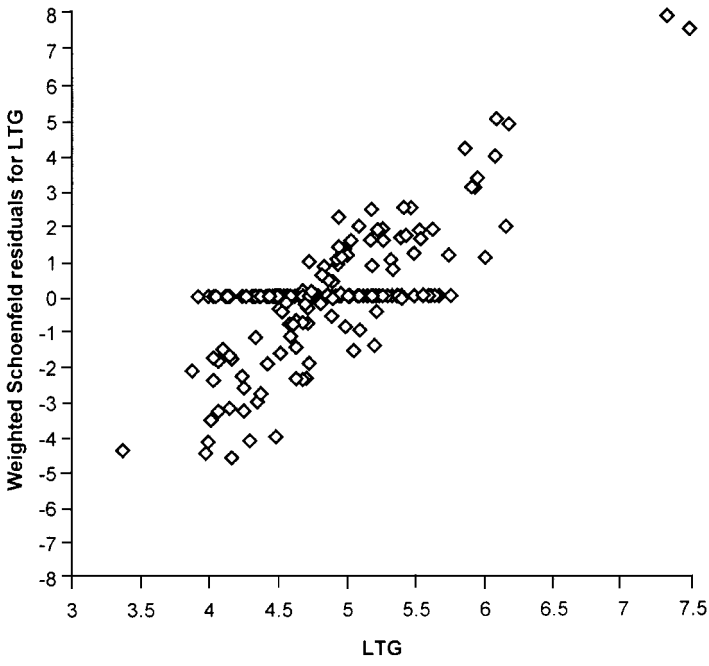


Figure 12.12 Weighted Schoenfeld residuals from the fitted Cox proportional hazards model on the CVD data.

```
run;
title 'Deviance residuals (rdev) and weighted Schoenfeld residuals for AGE, LACR and
LTG';
proc print data = out1;
   var t age lacr ltg rage rlacr rltg rdev;
run;
```

The following SPSS code can be used to obtain Cox–Snell and Schoenfeld residuals for AGE, and LACR and LTG.

```
data list file = 'c:\ex12d4d1.dat' free
        / t cens agea ageb sex smoke bmi lacr sbp ltg age htn dm
coxreg t with age sex lacr ltg
        /status = cens event (1)
        /print = all
        /save = hazard resid presid.
```

Bibliographical Remarks

An excellent expository paper on statistical methods for the identification and

Table 12.9 Goodness-of-Fit Tests Based on Asymptotic Likelihood Inference in Fitting the CVD Data[a]

Model	LL	LLR	p	BIC	AIC
Generalized gamma	−198.842	—	—	−217.113	−212.842
Log-logistic	−203.322	—	—	−218.983	−215.322
Lognormal	−206.017	14.3505	0.0002	−221.678	−218.017
Weibull	−199.494	1.3046	0.2534	−215.155	−211.494
Exponential	−203.061	8.4385[b]	0.0147	−216.112	−213.061
Exponential	−203.061	7.1339[c]	0.0076	−216.112	−213.061

[a] LL, log likelihood; LLR, log-likelihood ratio statistic; p, probability that the respective chi-square random variable $>$LLR.
[b] Compared to the generalized gamma fit.
[c] Compared to the Weibull fit.

use of prognostic factors is that of Armitage and Gehan (1974). Many studies of prognostic factors have been published. A few recent ones are cited here: Well et al. (1998), Shipley et al. (1999), Marrison and Siu (2000), Seaman and Bird (2001), Bolard et al. (2001), Vasan et al. (2001), Young et al. (2001), Meisinger et al. (2002), Feskanich et al. (2002), Williams et al. (2002), and Bliwise et al. (2002).

Cox's regression model has stimulated the interest of many statisticians. A large number of papers on this model and related areas have been published since 1972. In addition to the articles cited earlier, the following are a few examples: Sasieni (1996), Alioum and Commenges (1996), Farrington (2000), Vaida and Xu (2000), and Zhang and Klein (2001). Survival data analysis methods are closely related to counting processes, particularly the proportional hazards model and residual analysis. The counting process approach requires a strong background in probability theory and stochastic processes and is beyond the scope of this book. Interested readers are referred to Fleming and Harrington (1991) and Andersen et al. (1993).

EXERCISES

12.1 **(a)** Consider the data in Exercise Table 3.1. In addition to the five skin tests, age and gender may also have prognostic values. Examine the relationship between survival and each of seven possible prognostic variables, as in Table 3.8. For each variable, group the patients according to different cutoff points. Estimate and draw the survival function for each subgroup using the product-limit method and then use the methods discussed in Chapter 5 to compare the survival

distribution of the subgroups. Prepare a table similar to Table 3.8. Interpret your results. Is there a subgroup of any variable that shows significantly longer survival times? (For the skin test results, use the larger diameter of the two.)

(b) Consider the seven variables in part (a). Use Cox's model to identify the most significant variables. Compare your results with those obtained in part (a).

12.2 **(a)** Consider the data given in Exercise Table 3.3. Examine the relationship between remission duration and survival time for each of the nine possible prognostic variables: age, gender, family history of melanoma, and the six skin tests. Group the patients according to different cutoff points. Estimate and draw remission and survival curves for each subgroup. Compare remission and survival distribution of subgroups using the methods discussed in Chapter 5. Prepare tables similar to Table 3.8.

(b) Use Cox's regression model to identify the significant variables in part (a) for their relative importance to remission duration and survival time. Check the appropriateness of the proportional hazards model using the significant variables identified and the stratified analysis and weighted Shoenfeld residuals. Interpret the results.

12.3 Use the proportional hazards model to identify the most important factors related to survival time in the 157 diabetic patients in Exercise Table 3.4. Check the appropriateness of the model using all the methods discussed in Section 12.4 and interpret the results.

12.4 **(a)** Construct a table similar to Table 3.8 using the data given in Table 3.6.

(b) Use the proportional hazards model to identify the most important factors related to survival time.

(c) Is the proportional hazards model appropriate for this data set?

12.5 Using the data given in Table 12.4, perform similar analyses as in Examples 12.3 to 12.10 and discuss the results obtained.

CHAPTER 13

Identification of Prognostic Factors Related to Survival Time: Nonproportional Hazards Models

In Chapter 12 we discussed the proportional hazards model for the identification of important prognostic factors, in which the covariates are assumed to be independent of time. We also assume that there is only one cause of failure; that is, the event or failure is allowed to occur only once for each person, and there is no correlation among failure times of different persons. However, in practice, the covariates may be observed more than once during the study, and their values change with time, failure may be due to more than one event or cause, the same event or failure may recur during a follow-up study, and the event or failure time observed may be from related persons in a family or from the same person at different times. In this chapter we discuss several models for these situations. The first two models are extensions of the proportional hazards model to handle time-dependent covariates and to perform stratified analysis. Other models introduced in this chapter are for multiple causes of failure, recurrent events, and related observations.

13.1 MODELS WITH TIME-DEPENDENT COVARIATES

In the Cox proportional hazards model, the ratio of hazard functions for any two persons is assumed to be independent of time t, or the covariates are not time-dependent. However, it is common in practice that a study include both time-dependent and time-independent covariates. For example, in a longitudinal study of heart disease, certain demographic variables, such as gender and race, do not change with time and are usually collected only once at the baseline examination. Other variables, such as lipids, may vary with time and are often collected in subsequent examinations. The partial likelihood function allowing time-dependent covariates has the same form as that in (12.1.7) except

that the covariates are now a function of time. That is, the partial likelihood function with time-dependent covariates is

$$L(\mathbf{b}) = \prod_{i=1}^{k} \frac{\exp[\sum_{j=1}^{p} b_j x_{j(i)}(t_{(i)})]}{\sum_{l \in R(t_{(i)})} \exp[\sum_{j=1}^{p} b_j x_{jl}(t_{(i)})]} \left[= \prod_{i=1}^{k} \frac{\exp[\mathbf{b}'\mathbf{x}_{(i)}(t_{(i)})]}{\sum_{l \in R(t_{(i)})} \exp[\mathbf{b}'\mathbf{x}_l(t_{(i)})]} \right] \quad (13.1.1)$$

where k is the number of distinct failure times, $R(t_{(i)})$ is the risk set that contains all persons at risk at time $t_{(i)}$, $\mathbf{x}_l(t_{(i)}) = (x_{1l}(t_{(i)}), x_{2l}(t_{(i)}), \ldots, x_{pl}(t_{(i)}))'$ denotes the covariates observed from person l at the ordered uncensored event time $t_{(i)}$, and $\mathbf{b}' = (b_1, b_2, \ldots, b_p)'$ denotes the unknown coefficients. For covariates that are not time varying, their values are constant over time. For example, let x_{1k} denote gender of person k, then $x_{1k}(t) = x_{1k}(0) = x_{1k}$ for all t. Thus, in practice, we usually have a mixture of non-time-dependent and time-dependent covariates in the likelihood function. The estimation procedure for the coefficients, b_j, is similar to that discussed in Chapter 12. We can also apply the model selection methods mentioned in Chapter 11 to select the optimal subset of covariates as the most important prognostic or risk factors.

There are two kinds of time-dependent covariates: (1) covariates that are observed repeatedly at different follow-up time points prior to the occurrence of the event or the end of a study or the censored time; and (2) covariates that change with time according to a known mathematical function and covariates that have different values due to therapy, age, or the changes in medical conditions.

The following example illustrates how the Cox proportional hazards model is extended to fit observed survival or event time data with the first kind of time-dependent covariates, that is, covariates observed several times before the event.

Example 13.1 A study was conducted to examine whether biomarker profiles could be used for risk assessment and bladder cancer detection in a cohort of workers occupationally exposed to benzidine and at risk of bladder cancer (Hemstreet et al., 2001). These workers were free of bladder cancer at the time of initial (or baseline) examination and were reexamined at least once based on their risk assessments in a seven-year period. The event time considered in this study is the cancer-free time from baseline examination to last follow-up. To simplify the analysis, we consider only four covariates: age, level of benzidine exposure, and two biomarkers, M1 and M2. The level of benzidine exposure (LEX) is scored based on the worker's job position in the factory and is considered fixed (time independent). In addition, age (AGEB) and the two biomarkers M1B ($=0$ is negative, $=1$ if positive) and M2B ($=0$ if negative, $=1$ if positive) were measured at baseline examination (they are not changed with time). At subsequent examinations, age (AGET) and the two biomarkers, M1T and M2T, were measured again (they are changed with time) with the status of bladder cancer and the cancer-free time from baseline examination to subsequent examination (TR). We selected a subset of 61

persons from this study for this example. The data reproduced in Table 13.1 are solely for the purpose of illustrating the proportional hazards model with time-dependent covariates. Thus, the results should not be interpreted as the true findings of this large study.

Table 13.1 gives the baseline and follow-up data from the 61 participants selected from the study. We use ID numbers to distinguish the data observed from different participants. For example, the person in the table with ID = 4 had LEX = 36, diagnosed as M1 positive and M2 negative (M1B = 1 and M2B = 0), and was 47.82 years old (AGEB = 47.82) at the baseline examination (time 0). He was diagnosed with negative M1 and M2 (M1T = 0 and M2T = 0) and without cancer at 42.94 months (TR = 42.94) from the baseline examination and at 51.39 years of age (AGET = 51.39) (thus 42.94 was considered a censored event time, CS = 0). His third examination was conducted at 67.06 months (TR = 67.06) and he was still cancer free with both M1 and M2 negative (M1T = 0 and M2T = 0) at 53.40 years old (AGET = 53.40) (thus 67.06 was considered a censored event time, CS = 0). In other words, for this person, AGET = 51.39, M1T = 0, and M2T = 0 during the time interval (0, 42.94] and AGET = 53.40, M1T = 0, and M2T = 0 during the time interval (42.94, 67.06]. The event time TR was censored at the end of the first time interval (TR = 42.94 months, CS = 0) and also at the end of the second time interval (TR = 67.06 months, CS = 0). The left endpoint of a time interval is denoted as TL in the table. Thus, in this example, covariates LEX, AGEB, M1B, and M2B are fixed for all time intervals, but AGET, M1T, and M2T are time-dependent covariates, which may change from one interval to another.

To facilitate better understanding of (13.1.1.), we use only the data from the first six people to illustrate how to construct the likelihood function (13.1.1.). If we have only the data from the first six people, there are two ($k = 2$) distinct uncensored cancer-free times, $t_{(1)} = 14.65$ (observed from the person with ID = 2) and $t_{(2)} = 24.61$ (observed from the persons with ID = 1). At $t_{(1)}$, all six people are at risk and $R(t_{(1)})$ contains all six. At time $t_{(2)}$, only four people (ID = 1, 3, 4, and 6) are at risk and $R(t_{(2)})$ contains these four. The person with ID = 5 is censored at 14.78 months, prior to $t_{(2)}$. Table 13.2 gives those in the risk sets for $t_{(1)}$ and $t_{(2)}$ with values of the seven covariates.

Let

$$\mathbf{x}_l(t_{(i)}) = (\mathrm{LEX}_l,\ \mathrm{AGEB}_l,\ \mathrm{M1B}_l,\ \mathrm{M2B}_l,\ \mathrm{AGET}_l(t_{(i)}),\ \mathrm{M1T}_l(t_{(i)}),\ \mathrm{M2T}_l(t_{(i)}))'$$

denote the covariates from person l (ID = l) evaluated at the ordered uncensored event time $t_{(i)}$, $i = 1, 2$; $l = 1, 2, \ldots, 6$, and $\mathbf{b}' = (b_1, b_2, \ldots, b_7)'$ denote the unknown coefficients. Then the first term in (13.1.1) for $t_{(1)}$ is

$$\frac{\exp[\mathbf{b}'\mathbf{x}_2(t_{(1)})]}{\sum_{l=1}^{6} \exp[\mathbf{b}'\mathbf{x}_l(t_{(1)})]}$$

Table 13.1 Cancer-Free Times for Workers Exposed to Some Chemical Elements[a]

ID	LEX	AGEB	M1B	M2B	AGET	M1T	M2T	CS	TR	TL
1	180	58.64	0	0	60.70	1	0	1	24.61	0.00
2	69	40.99	0	0	42.21	1	0	1	14.65	0.00
3	36	57.14	0	0	60.72	0	0	0	42.97	0.00
4	36	47.82	1	0	51.39	0	0	0	42.94	0.00
4	36	47.82	1	0	53.40;	0	0	0	67.06	42.94
5	36	34.85	1	0	36.08	0	0	0	14.78	0.00
6	15	64.24	0	0	67.66	0	1	0	41.03	0.00
7	15	60.72	0	0	64.14	0	0	0	41.00	0.00
8	15	58.97	0	0	61.54	0	0	0	30.82	0.00
8	15	58.97	0	0	62.01	1	0	0	36.40	30.82
8	15	58.97	0	0	62.41	1	0	0	41.26	36.40
8	15	58.97	0	0	63.00	0	0	0	48.33	41.26
8	15	58.97	0	0	63.54	0	0	0	54.83	48.33
8	15	58.97	0	0	64.03	1	0	0	60.71	54.83
8	15	58.97	0	0	64.49	0	0	0	66.17	60.71
8	15	58.97	0	0	65.06	1	0	0	73.07	66.17
9	15	49.95	0	0	49.95	0	0	0	41.00	0.00
10	15	69.19	0	0	72.61	0	0	0	41.03	0.00
11	15	48.98	0	0	52.41	0	0	0	41.20	0.00
12	15	65.52	0	0	68.95	0	0	0	41.17	0.00
13	15	47.86	0	0	47.86	0	0	0	41.43	0.00
14	15	47.82	0;	0	51.28	0	1	0	41.43	0.00
14	15	47.82	0	0	52.41	0	0	0	54.97	41.43
15	15	43.49	1	0	46.53	0	0	0	36.50	0.00
15	15	43.49	1	0	46.94	0	0	0	41.43	36.50
15	15	43.49	1	0	47.53	0	0	0	48.46	41.43
15	15	43.49	1	0	48.56	0	0	0	60.85	48.46
16	15	41.28	0	0	44.74	0	1	0	41.56	0.00
16	15	41.28	0	0	45.86	0	0	0	54.93	41.56
17	15	49.09	0	0	52.54	0	0	0	41.43	0.00
18	15	46.03	0	0	49.45	0	0	0	41.03	0.00
19	15	64.41	0	0	67.85	0	0	0	41.23	0.00
20	164	52.52	0	0	53.54	1	1	1	12.32	0.00
21	15	61.51	0	0	64.94	0	0	0	41.10	0.00
22	144	64.59	0	0	68.01	1	0	0	41.13	0.00
22	144	64.59	0	0	68.60	1	1	1	48.16	41.13
23	192	62.26	0	1	64.88	1	0	0	31.47	0.00
23	192	62.26	0	1	65.27	0	0	1	36.17	31.47
24	54	57.56	0	0	57.95	1	0	1	4.67	0.00
25	264	60.03	0	0	73.03	1	0	0	36.07	0.00
25	264	60.03	0	0	73.71	1	0	0	44.19	36.07
25	264	60.03	0	0	64.17	1	0	0	49.68	44.19
25	264	60.03	0	0	65.15	1	0	1	61.44	49.68
26	40	44.30	0	0	45.48	1	0	0	14.13	0.00
26	40	44.30	0	0	46.49	1	0	1	26.25	14.13
27	265	52.84	0	1	53.98	0	0	0	13.73	0.00
27	265	52.84	0	1	55.43	0	0	0	31.18	13.73
27	265	52.84	0	1	55.83	0	0	0	35.91	31.18
27	265	52.84	0	1	56.42	0	0	1	42.97	35.91

Table 13.1 *Continued*

ID	LEX	AGEB	M1B	M2B	AGET	M1T	M2T	CS	TR	TL
28	132	68.19	0	1	69.31	0	0	1	13.50	0.00
29	24	62.22	1	1	64.39	0	0	0	26.02	0.00
29	24	62.22	1	1	64.85	0	0	0	31.54	26.02
29	24	62.22	1	1	65.22	0	0	0	36.01	31.54
29	24	62.22	1	1	65.82	0	1	0	43.27	36.01
29	24	62.22	0	1	66.89	1	0	1	56.02	43.27
30	132	68.27	0	0	70.12	0	0	1	22.14	0.00
31	178	64.07	0	0	64.07	1	0	1	21.95	0.00
32	50	65.88	0	0	65.88	0	0	0	25.43	0.00
33	50	70.82	0	1	74.40	0	0	0	42.97	0.00
34	50	60.53	0	1	63.54	0	0	0	36.14	0.00
34	50	60.53	0	1	64.67	0	0	0	49.68	36.14
34	50	60.53	0	1	66.18	0	0	0	67.88	49.68
35	50	62.99	0	0	66.00	0	0	0	36.11	0.00
36	50	63.01	1	1	65.15	0	0	0	25.76	0.00
36	50	63.01	1	1	66.01	0	0	0	36.04	25.76
36	50	63.01	1	1	66.60	0	0	0	43.07	36.04
36	50	63.01	1	1	67.68	1	0	0	56.05	43.07
37	50	63.86	0	0	66.89	0	0	0	36.40	0.00
38	50	61.15	0	0	62.33	0	0	0	14.16	0.00
38	50	61.15	0	0	63.32	0	0	0	26.02	14.16
38	50	61.15	0	0	63.78	0	0	0	31.57	26.02
38	50	61.15	0	0	64.75	0	0	0	43.20	31.57
38	50	61.15	0	0	65.30	1	0	0	49.87	43.20
39	50	61.02	0	0	64.03	1	0	0	36.14	0.00
40	50	61.08	0	0	61.08	0	0	0	36.17	0.00
41	50	49.50	0	1	52.51	0	0	1	36.14	0.00
42	50	49.81	0	0	52.81	0	0	0	35.94	0.00
43	50	49.09	0	0	52.10	0	0	0	36.17	0.00
44	50	47.07	0	0	50.08	0	0	0	36.14	0.00
45	50	63.69	0	1	64.84	0	0	0	13.90	0.00
45	50	63.69	0	1	66.30	0	0	0	31.41	13.90
45	50	63.69	0	1	66.69	0	0	0	36.01	31.41
45	50	63.69	0	1	67.28	0	0	0	43.10	36.01
46	50	55.77	0	0	58.77	0	0	0	36.01	0.00
47	50	60.84	0	1	61.99	1	0	0	13.83	0.00
47	50	60.84	0	1	64.98	0	0	0	49.71	13.83
48	50	50.09	1	1	51.24	1	0	0	13.90	0.00
48	50	50.09	1	1	52.70	0	0	0	31.41	13.90
48	50	50.09	1	1	53.09	0	0	0	36.01	31.41
48	50	50.09	1	1	54.23	0	0	0	49.77	36.01
48	50	50.09	1	1	54.76	0	0	0	56.05	49.77
48	50	50.09	1	1	55.75	0	0	0	67.98	56.05
49	50	62.41	1	0	63.53	0	0	0	13.50	0.00
49	50	62.41	1	0	65.38	0	0	0	35.61	13.50
50	50	73.88	0	1	78,03	0	0	0	49.81	0.00
51	50	44.68	0	0	47.68	1	0	0	35.98	0.00
51	50	44.68	0	0	49.36	0	0	0	56.12	35.98
52	50	62.67	0	0	65.66	0	0	0	35.91	0.00

(*Continued overleaf*)

Table 13.1 *Continued*

ID	LEX	AGEB	M1B	M2B	AGET	M1T	M2T	CS	TR	TL
53	275	74.28	0	1	75.34	1	1	0	12.75	0.00
53	275	74.28	0	1	77.28	0	0	0	36.04	12.75
53	275	74.28	0	1	77.70	1	0	0	41.07	36.04
53	275	74.28	0	1	78.26	1	0	1	47.80	41.07
54	57	39.52	0	0	43.50	0	0	0	47.80	0.00
5	57	76.22	1	0	79.23	1	0	0	36.07	0.00
5	57	76.22	1	0	79.64	0	0	0	41.10	36.07
5	57	76.22	1	0	80.21	0	0	0	47.84	41.10
5	57	76.22	1	0	81.24	0	0	0	60.29	47.84
56	57	62.41	0	0	65.83	0	0	0	41.10	0.00
57	57	67.64	0	0	71.06	0	0	0	41.10	0.00
58	57	80.61	0	0	84.03	0	1	0	41.10	0.00
58	57	80.61	0	0	85.14	0	0	0	54.37	41.10
59	57	67.78	1	0	67.68	1	0	0	72.12	0.00
60	0	47.35	0	1	47.35	0	1	0	13.83	0.00
60	0	47.35	0	1	49.84	0	0	0	43.70	13.83
61	0	40.98	1	0	42.13	0	0	0	13.83	0.00
61	0	40.98	1	0	43.59	0	0	0	31.38	13.83
61	0	40.98	1	0	44.62	0	0	0	43.70	31.38
61	0	40.98	1	0	46.55	0	0	0	66.92	43.70

[a] ID, participant ID number; LEX, level of exposure; AGEB, age at the baseline examination; M1B and M2B, index functions of measure 1 and 2 at the baseline; M1B = 1 if measure 1 is positive and 0 if not; M2B = 1 if measure 2 is positive and 0 if not; AGET, age at the end of each time interval; M1T and M2T, index functions of measure 1 and 2 at the end of each time interval; M1T = 1 if measure 1 is positive and 0 if not; M2T = 1 if measure 2 is positive and 0 if not; CS = 0 if censored and 1 if not; TR, cancer-free time in months (or the right endpoint of time interval); TL, left endpoint of time interval.

where

$$\mathbf{x}_2(t_{(1)}) = (69,\ 40.99,\ 0,\ 0,\ 42.21,\ 1,\ 0)'$$

is the column vector of covariates from person 2, whose cancer-free time is $t_{(1)} = 14.65$. The $\mathbf{x}_l(t_{(1)})$'s in the denominator are the covariate vectors observed for the six people in the risk set $R(t_{(1)})$ and are listed in Table 13.2. For example, $\mathbf{x}_3(t_{(1)}) = (36,\ 57.14,\ 0,\ 0,\ 60.72,\ 0,\ 0)$. The second and also the last term in (13.1.1) for $t_{(2)} = 24.61$ is

$$\frac{\exp[\mathbf{b}'\mathbf{x}_1(t_{(2)})]}{\exp[\mathbf{b}'\mathbf{x}_1(t_{(2)})] + \exp[\mathbf{b}'\mathbf{x}_3(t_{(2)})] + \exp[\mathbf{b}'\mathbf{x}_4(t_{(2)})] + \exp[\mathbf{b}'\mathbf{x}_6(t_{(2)})]}$$

where $\mathbf{x}_1(t_{(2)}) = (180,\ 58.64,\ 0,\ 0,\ 60.70,\ 1,\ 0)$ and $\mathbf{x}_l(t_{(2)})$'s in the denominator are the observed covariate vectors from the four persons (ID = 1, 3, 4, and 6)

Table 13.2 Construction of the Partial Likelihood for the Cancer-Free Times from the First Six People with Time-Dependent Covariates

Ordered Event time	$t_{(1)} = 14.65$ (observed from individual with ID = 2)							$t_{(2)} = 24.61$ (observed from individual with ID = 1)						
ID	LEX	AGEB	M1B	M2B	AGET	M1T	M2T	LEX	AGEB	M1B	M2B	AGET	M1T	M2T
1	180	58.64	0	0	60.70	1	0	180	58.64	0	0	60.70	1	0
2	69	40.99	0	0	42.21	1	0							
3	36	57.14	0	0	60.72	0	0	36	57.14	0	0	60.72	0	0
4	36	47.82	1	0	51.39	0	0	36	47.82	1	0	51.39	0	0
5	36	34.85	1	0	36.08	0	0							
6	15	64.24	0	0	67.66	0	1	15	64.24	0	0	67.66	0	1

Table 13.3 Asymptotic Partial Likelihood Inference on Cancer-Free Time Data from Fitted Model with Time-Dependent Covariates

Variable	Regression Coefficient	Standard Error	Chi-Square Statistic	p	Hazards Ratio	95% Confidence Interval	
						Lower	Upper
LEX	0.007	0.003	5.593	0.018	1.01	1.00	1.01
M1T	1.361	0.645	4.449	0.035	3.90	1.10	13.81

in $R(t_{(2)})$ (see Table 13.2 for details). The partial likelihood function for this reduced data set is the product of these two terms.

The partial likelihood function for the entire data set in Table 13.1 can be constructed in a similar way and estimates of the coefficients can be obtained using the Newton–Raphson method. The data format style in Table 13.1 is referred to as a counting process data format. The results of fitting this model with time-dependent covariates and a stepwise selection method are given in Table 13.3. The coefficients indicate that high levels of exposure and positive M1 at follow-up examination are positively related to the risk of a short cancer-free time. Assuming that other measures are the same, a person with a positive M1 at follow-up examination will have 3.9 times higher risk to develop bladder cancer than will someone with a negative M1. For every 1-unit increase in LEX, the risk will increase by 1%.

Suppose that the text data file "C:\EX1311.DAT" contains the data in Table 13.1 and the successive 11 columns give ID, LEX, AGEB, M1B, M2B, AGET, M1T, M2T, CS, TR, and TL. The following SAS code can be used to obtain the results in Table 13.3.

```
data w1;
  infile 'c:\ex13d1d1.dat' missover;
  input id lex ageb m1b m2b aget m1t m2t cs tr tl;
run;
title "Selected Cox proportional hazards model with time dependent covariates";
proc phreg data = w1;
  model (tl,tr)*cs(0) = lex ageb m1b m2b aget m1t m2t / rl ties = efron selection = s;
  where tl<tr;
run;
```

For the second type of time-dependent covariate (i.e., the covariate known to change with time according to a mathematical function), we simply use the known mathematical function to replace the covariate. Following is a hypothetical example to illustrate the use of SAS, SPSS, and BMDP.

Example 13.2 Suppose that we wish to fit the proportional hazards model to a set of survival data that has been saved in a text file "C:\EX1312.DAT". This set of data consists of survival time t, an indicator variable CENS ($=1$ for an uncensored observation and 0 for a censored observation) and three covariates, X1, X2, and X3. Furthermore, assume that X3 is known to change with time according to the function $X3 \times \log(t + 1)$. In this case, the following SAS, SPSS, and BMDP code can be used to incorporate this time-dependent covariate with known mathematical relationship with time into the model.

```
data w1;
  infile 'c:\ex1312.dat' missover;
  input t cens x1 x2 x3;
run;
proc phreg data = w1;
  model t*cens(0) = x1 x2 z/ rl ties = efron;
  z = x3*log(t + 1)
run;
```

If the SPSS COXREG procedure is used, the code is

```
data list file = 'c:\ex1312.dat' free
        / t cens x1 x2 x3.
time program
Compute z = x3*log(t + 1).
coxreg t with x1 x2 z
        /status = cens event (1)
        /print = all
        /save = hazard resid presid.
```

For the BMDP 2L procedure, the code is

```
/input      file = 'c:\ex1312.dat' .
            variables = 6.
            format = free.
/print      cova.
/variable   names = t,cens, x1, x2, x3.
/form       time = t.
            status = cens.
            response = 1.
/regress    covariates = x1, x2, z.
            add = z.
/function   z = x3*ln(time + 1).
```

13.2 STRATIFIED PROPORTIONAL HAZARDS MODELS

The proportional hazards model in (12.1.3) assumes that the ratio of the hazard functions of any two people with prognostic variables $\mathbf{x}_1$ and $\mathbf{x}_2$ is a constant, independent of time. This assumption may not always be met in practical situations. To accommodate the nonproportional cases, Cox's model can be generalized using the concept of stratification (Kalbfleisch and Prentice, 1980). The data can be stratified by a covariate: for example, age. If we consider two strata, say age $\geqslant 50$ and < 50 years, the model in (12.1.3) becomes two models:

$$h_i(t \mid \mathbf{x}) = \mathrm{h}_{0i}(t) \exp\left(\sum b_j x_j\right) = h_{0i}(t) \exp(\mathbf{b}'\mathbf{x}_i) \tag{13.2.1}$$

where $i = 1, 2$ for the two age strata. Notice that the underlying hazard function $h_{0i}(t)$ is assumed to be different for the two strata; however, the regression coefficients are the same for all strata. That is, we assume that the hazards for patients may be proportional within each stratum but not among different strata (or levels). The partial (marginal) likelihood function for all observations from the m strata is defined as

$$L(\mathbf{b}) = \prod_{j=1}^{m} L_j(\mathbf{b}) \tag{13.2.2}$$

where $L_j(\mathbf{b})$ is the partial (marginal) likelihood function for the jth stratum. The regression coefficients $\mathbf{b}$ can be estimated by the Newton–Raphson method. For stratified models, the baseline survivorship function for each stratum is estimated separately based on the estimated regression coefficients $\hat{\mathbf{b}}$ and the data in that stratum alone by using the methods discussed in Section 12.3.

Example 13.3 Consider the data given in Example 12.1.1. Suppose that we are not sure if the risk of dying for patients at least 50 years of age is proportional to that for patients less than 50 years and decide to do a stratified analysis. Two regression equations are therefore assumed:

$$h_1(t \mid x_2) = h_{01}(t) \exp(b_2 x_2)$$
$$h_2(t \mid x_2) = h_{02}(t) \exp(b_2 x_2)$$

where $h_1(t \mid x_2)$, the hazard function for patients under 50 years of age, and $h_2(t \mid x_2)$, the hazard function for patients at least 50 years, are functions of cellularity, and $h_{01}(t)$ and $h_{02}(t)$ are the underlying hazard functions for the two groups. The results of the stratified analysis, $\hat{b}_2 = 0.22$, $\mathrm{SE}(\hat{b}_2) = 0.44$, $p = 0.31$, and $\exp(\hat{b}_2) = 1.24$, are close to those obtained earlier in the unstratified model.

Table 13.4 Asymptotic Partial Likelihood Inference on CVD-free Time Data from Fitted Models

Variable	Regression Coefficient	Standard Error	Chi-Square Statistic	p	Hazards Ratio	95% Confidence Interval	
						Lower	Upper
Unstratified Model for All CVDs							
AGE	0.070	0.014	26.139	0.0001	1.07	1.04	1.10
SEX	0.753	0.219	11.789	0.0006	2.12	1.38	3.26
LACR	0.111	0.046	5.860	0.0155	1.12	1.02	1.22
LTG	0.399	0.198	4.072	0.0436	1.49	1.01	2.20
Gender-Stratified Model for All CVDs							
AGE	0.063	0.013	23.430	0.0001	1.07	1.04	1.09
LACR	0.149	0.043	11.828	0.0006	1.16	1.07	1.26
Gender-Specific Proportional Hazards Models							
Female							
SBP	0.022	0.006	13.962	0.0002	1.02	1.01	1.03
DM	0.986	0.373	6.973	0.0083	2.68	1.29	5.57
Male							
AGE	0.069	0.018	14.453	0.0001	1.07	1.03	1.11
LACR	0.125	0.058	4.555	0.0328	1.13	1.01	1.27

However, this may not always be the case. Because the model is stratified by age group and no specific relationship is assumed between the hazard ratio of patients at least 50 years old and those under 50, tests of significance of the regression coefficients for the other variables are adjusted for age.

Example 13.4 In Example 12.5 we used the stepwise selection method to fit the proportional hazards model to the CVD data in Example 12.3. We reanalyze the data using a gender-stratified proportional hazards model. Results from the unstratified model and the stratified model (with a stepwise selection procedure) are given in Table 13.4.

The unstratified model identifies AGE, SEX, LACR (logarithm of the ratio of urinary albumin and creatinine), and LTG (logarithm of triglycerides) as significant covariates for the time to CVD. The gender-stratified model with the stepwise selection procedure identifies AGE and LACR as the most significant covariates. The coefficients are close to those obtained in the unstratified model. The $\log[-\log(S(t))]$ at the averages of covariates AGE and LACR for the two strata are plotted in Figure 12.7. The two curves look

parallel to each other. It suggests that stratification for this set of data does not provide more information for the study. Moreover, the sex-specific proportional hazards model (at the bottom of Table 13.4) show that systolic blood pressure (SBP) and diabetes are significant covariates related to the risk of CVD in women and AGE and LACR in men. Thus, the gender-specific models provide more information and suggest that there are differences in CVD risk factors among men and women.

The method of stratification is useful in cases when the observations from different strata are considered independent, conditional on the stratified variable, or one is not interested in the effect of the stratified variable itself on the outcome but in the interactions of the stratified variable with the other covariates in the model and does not know the exact forms of the interactions. It is clear that modeling observations from different strata separately can provide more information than either stratification or unstratification if the sample size in each stratum is large enough.

Using the data file "C:\EX12d4d1.DAT" defined in Example 12.4, the following SAS code can be used to obtain the results in Table 13.4 and Figure 12.7.

```
data w1;
  infile 'c:\ex12d4d1.dat' missover;
  input t cens agea ageb sex smoke bmi lacr sbp ltg age htn dm;
run;
title "Unstratified model";
proc phreg data = w1;
  model t*cens(0) = age sex bmi lacr sbp ltg smoke htn dm / selection = b
    ties = efron;
run;
title "gender stratified model";
proc phreg data = w1;
  model t*cens(0) = age bmi lacr sbp ltg smoke htn dm / selection = b
    ties = efron;
  strata sex;
run;
proc phreg data = w1 noprint;
  model t*cens(0) = age lacr / ties = efron;
  strata sex;
  baseline out = bas1 loglogs = lmls;
run;
title "Log-logS from fitting a gender stratified model";
proc print data = bas1;
  var sex age lacr t lmls;
run;
proc sort data = w1;
  by sex;
run;
title "gender-specific models";
```

```
proc phreg data = w1;
  model t*cens(0) = age bmi lacr sbp ltg smoke htn dm / selection = b
    ties = efron;
  by sex;
run;
```

The following SPSS code can also be used. In this case, the data for women and men are assumed to be in the files "C:\EX12d4d1a.DAT" and "C:\EX12d4d1b.DAT" separately.

```
data list file = "c:\ex12d4d1.dat" free
        / t cens agea ageb sex smoke bmi lacr sbp ltg age htn dm.
coxreg t with age sex bmi lacr sbp ltg smoke htn dm
        /status = cens event (1)
        /method = bstep age sex bmi lacr sbp ltg smoke htn dm
        /criteria pin (0.05) pout (0.05)
        /print = all
coxreg t with age bmi lacr sbp ltg smoke htn dm
        /status = cens event (1)
        /strata = sex
        /method = bstep age bmi lacr sbp ltg smoke htn dm
        /criteria pin (0.05) pout (0.05)
        /print = all
coxreg t with age lacr
        /status = cens event (1)
        /strata = sex
        /print = all
        /save = lml.
data list file = "c:\ex12d4d1a.dat" free
        / t cens agea ageb sex smoke bmi lacr sbp ltg age htn dm.
coxreg t with age bmi lacr sbp ltg smoke htn dm
        /status = cens event (1)
        /method = bstep age bmi lacr sbp ltg smoke htn dm
        /criteria pin (0.05) pout (0.05)
        /print = all
data list file = "c:\ex12d4d1b.dat" free
        / t cens agea ageb sex smoke bmi lacr sbp ltg age htn dm.
coxreg t with age bmi lacr sbp ltg smoke htn dm
        /status = cens event (1)
        /method = bstep age bmi lacr sbp ltg smoke htn dm
        /criteria pin (0.05) pout (0.05)
        /print = all
```

For the BMDP 2L procedure, the following code can be used.

```
/input      file = 'c:\ex12d4d1.dat' .
            variables = 13.
            format = free.
```

```
/print      cova.
            Survival.
/variable   names = t,cens, agea, ageb, sex, smoke, bmi, lacr, sbp, ltg,
              age, htn, dm.
/form       time = t.
            status = cens.
            response = 1.
/regress    covariates = age, smoke, bmi, lacr, sbp, ltg, htn, dm.
            strata = sex.
            step = phh.

/input      file = 'c:\ex12d4d1a.dat' .
            variables = 13.
            format = free.
/print      cova.
            Survival.
/variable   names = t,cens, agea, ageb, sex, smoke, bmi, lacr, sbp, ltg,
              age, htn, dm.
/form       time = t.
            status = cens.
            response = 1.
/regress    covariates = age, smoke, bmi, lacr, sbp, ltg, htn, dm.
            step = phh.

/input      file = 'c:\ex12d4d1b.dat' .
            variables = 13.
            format = free.
/print      cova.
            Survival.
/variable   names = t,cens, agea, ageb, sex, smoke, bmi, lacr, sbp, ltg,
              age, htn, dm.
/form       time = t.
            status = cens.
            response = 1.
/regress    covariates = age, smoke, bmi, lacr, sbp, ltg, htn, dm.
            step = phh.
```

13.3 COMPETING RISKS MODEL

All the methods for prognostic factor analysis discussed so far deal with a single type of failure time for each study subject. This may be a perfectly acceptable way to proceed in many cases. However, in some situations, failure on an person may be due to several distinct causes. It may be desirable to distinguish different kinds of events that may lead to failure and treat them differently in the analysis. For example, to evaluate the efficacy of heart transplants, one would certainly want to treat deaths due to heart failure differently from deaths due to other causes, such as accident and cancer. In a

mortality study, it may be more interesting to study separately deaths due to heart disease, diabetes, cancer, and others than to combine all the causes. These different causes of failure are considered as competing events, which introduce competing risks. Thus, problems arising in the analysis of data with multiple causes are commonly referred to as *competing risk* problems. We will see later that competing risk analysis, in general, requires no inference methods other than those introduced in Chapters 11 and 12. We focus on using the proportional hazards model to identify significant prognostic or risk factors when competing risks are present. Readers interested in additional details are referred to Kalbfleisch and Prentice (1980).

Let T be the survival time, $\mathbf{x}$ the covariate vector, and J the type or cause of failure. We define a type- or cause-specific hazard function $h_j(t; \mathbf{x})$

$$h_j(t;\ \mathbf{x}) = \lim_{\Delta t \to 0} \frac{P(t \leqslant T < t + \Delta t,\ J = j \mid T \geqslant t,\ \mathbf{x})}{\Delta t}, \qquad j = 1, \ldots, m \tag{13.3.1}$$

In words, $h_j(t; \mathbf{x})$ is the instantaneous failure rate of cause j at time t given $\mathbf{x}$ and in the presence of other $(m-1)$ causes of failure. The only difference between (13.3.1) and the hazard function defined in Chapter 2 is the appearance of $J = j$. Equation (13.3.1) is a type- or cause-specific hazard function, which is very much the same as the ordinary hazard function except that the event is of a specific type. The overall hazard of failure is the sum of all the type-specific hazards, that is,

$$h(t;\ \mathbf{x}) = \sum_j h_j(t;\ \mathbf{x}) \tag{13.3.2}$$

provided that the failure types are mutually excluded. Based on (2.15), we can define the function

.

$$S_j(t;\ \mathbf{x}) = \exp\left[-\int_0^t h_j(u;\ \mathbf{x})\, du \right], \qquad j = 1, \ldots, m \tag{13.3.3}$$

However, these functions cannot, in general, be interpreted as survivorship functions when $m > 1$. *Let* $t_{j1} < t_{j2} < \cdots < t_{jk_j}$ denote the failure times for failures of type j, $j = 1, \ldots, m$. Assuming proportional hazards, the hazard function in (13.3.1) can be written as

$$h_j(t;\ \mathbf{x}) = h_{0j}(t) \exp(\mathbf{b}_j' \mathbf{x}), \qquad j = 1, \ldots, m \tag{13.3.4}$$

which can be generalized for time-dependent covariates by replacing $\mathbf{x}$ with $\mathbf{x}(t)$, that is,

$$h_j(t;\ \mathbf{x}) = h_{0j}(t) \exp[\mathbf{b}_j' \mathbf{x}(t)], \qquad j = 1, \ldots, m \tag{13.3.5}$$

The partial likelihood function for the model in (13.3.5) is

$$L = \prod_{j=1}^{m} \prod_{i=1}^{k_j} \frac{\exp[\mathbf{b}_j' \mathbf{x}_{ji}(t_{ji})]}{\sum_{l \in R(t_{ji})} \exp[\mathbf{b}_j' \mathbf{x}_l(t_{ji})]} \tag{13.3.6}$$

where $R(t_{ji})$ is the risk set at t_{ji}. The estimation of the coefficients and identification of significant covariates can be carried out exactly the same way as described in Chapters 11 and 12 by treating failure times of types other than j as censored observations. This is perhaps the most important concept in competing risks analysis. It is because the basic assumption for a competing risks model is that the occurrence of one type of event removes the person from risk of all other types of events and the person will no longer contribute to the successive risk set. Furthermore, there is nothing to prevent one from choosing different types of models for different $h_j(t; x)$'s. For example, in a mortality study we might choose a proportional hazards model for heart disease and a parametric model for diabetes.

The coefficient vector $\mathbf{b}_j$ in (13.3.6) indicates the effects of the covariates for event type j. If any covariates are not related to a particular type or cause, they may be set to 0. If $\mathbf{b}_j$ are the same for all j, the model in (13.3.5) reduces to the proportional hazards model in Chapter 12. The following example illustrates the proportional hazards model with competing risks.

Example 13.5 Let us again use the CVD data in Example 12.3. The event types are non-CVD (DG = 0), stroke (DG = 1), CHD (DG = 2), and the other CVDs (DG = 3). If one is interested in all CVD no matter whether it is stroke, CHD, or the other CVDs, the competing risks model reduces to a general CVD event model, the times (T) to CVD for DG = 1, 2, 3 are uncensored event times, and the other times are censored (DG = 0). An indicator variable, CS, can be used to indicate the censoring status; that is, CS = 1 if DG = 1, 2, 3, and CS = 0 otherwise. The result from fitting the proportional hazards model with the backward selection method is given in section (a) of Table 13.5.

If one considers strokes only, the indicator variable CS has to be defined differently; that is, CS = 1 if DG = 1 and CS = 0 if DG = 0, 2 and 3. This means that in addition to non-CVD, the event time of CHD and the other CVDs are treated as censored observations. Note that we will remove a person from the risk set after his or her first CVD event time in constructing the likelihood function for the modified data even if the event was not a fatal event. For stroke, age is the only significant variable [section (b) in Table 13.5]. We call this model a marginal model for strokes. Similarly, if only CHD, other CVDs, or either stroke or CHD are of interest, the respective modification will be CS = 1 if DG = 2 and CS = 0 otherwise (CHD only); CS = 1 if DG = 3 and CS = 0 otherwise (other CVD only); or CS = 1 if DG = 1, 2 and CS = 0 otherwise (either stroke or CHD). The results of these three fits with the backward selection method are shown in Table 13.5 (c)–(e). The results suggest

Table 13.5 Asymptotic Partial Likelihood Inference on CVD Event Time Data from the Fitted Competing Risks Models

Variable	Regression Coefficient	Standard Error	Chi-Square Statistic	p	Hazards Ratio	95% Confidence Interval	
						Lower	Upper
(a) Model for All CVDs							
AGE	0.070	0.014	26.139	0.0001	1.07	1.04	1.10
SEX	0.753	0.219	11.789	0.0006	2.12	1.38	3.26
LACR	0.111	0.046	5.860	0.0155	1.12	1.02	1.22
LTG	0.399	0.198	4.072	0.0436	1.49	1.01	2.20
(b) Marginal Model for Strokes							
AGE	0.072	0.021	12.092	0.0005	1.08	1.03	1.12
(c) Marginal Model for CHDs							
AGE	0.069	0.020	11.622	0.0007	1.07	1.03	1.12
SEX	0.970	0.329	8.716	0.0032	2.64	1.39	5.02
BMI	0.040	0.017	5.162	0.0231	1.04	1.01	1.08
LTG	1.106	0.266	17.234	0.0001	3.02	1.79	5.09
(d) Margial Model for Other CVDs							
AGE	0.087	0.033	6.874	0.0087	1.09	1.02	1.17
SEX	1.100	0.555	3.937	0.0472	3.01	1.01	8.91
LACR	0.315	1.101	9.745	0.0018	1.37	1.12	1.67
(e) Marginal Model for Strokes or CHDs							
AGE	0.072	0.015	23.555	0.0001	1.07	1.04	1.11
SEX	0.692	0.239	8.362	0.0038	2.00	1.25	3.20
LTG	0.665	0.200	11.095	0.0009	1.94	1.32	2.88

that significant risk factors differ for different types of CVD events. Age is the only factor common to all the CVD events.

Thus, competing risks models provide an opportunity to separate any one or more specific types of event or cause of death from all other types or causes. In practice, it is not necessary to fit a model to every type or cause.

Suppose that "C:\EX13d3d1.DAT" is a text data file that contains 14 columns similar to Table 12.4 and the successive columns give T, CENS, DG, AGEA, AGEB, SEX, SMOKE, BMI, LACR, SBP, LTG, AGE, HTN, and DM. The following SAS code can be used to obtain the model for stroke in Table 13.5. These codes can easily be modified to obtain the results for CHD,

other CVD, and stroke/CHD.

```
data w1;
  infile 'c:\ex13d3d1.dat' missover;
  input t cens dg agea ageb sex smoke bmi lacr sbp ltg age htn dm;
run;
title "Model for stroke event times";
proc phreg data = w1;
  model t*dg(0, 2, 3) = age sex smoke bmi lacr sbp ltg htn dm
                        / rl selection = b ties = efron;
run;
```

The following SPSS code can be used.

```
data list file = "c:\ex13d3d1.dat" free
        / t cens dg agea ageb sex smoke bmi lacr sbp ltg age htn dm.
coxreg t with age sex bmi lacr sbp ltg smoke htn dm
        /status = dg event (1)
        /method = bstep age sex bmi lacr sbp ltg smoke htn dm
        /criteria pin (0.05) pout (0.05)
        /print = all
```

The following code is for the BMDP 2L procedure.

```
/input      file = 'c:\ex13d3d1.dat' .
            variables = 14.
            format = free.
/print      cova.
            Survival.
/variable   names = t,cens, dg, agea, ageb, sex, smoke, bmi, lacr, sbp, ltg,
            age, htn, dm.
/form       time = t.
            status = dg.
            response = 1.
/regress    covariates = age, sex, smoke, bmi, lacr, sbp, ltg, htn, dm.
            step = phh.
```

13.4 RECURRENT EVENTS MODELS

So far we have considered events or failures that are allowed to occur only once. Even in competing risks models, the occurrence of one type of event removes a person from the risk set thereafter. However, in practice the failures on an individual may be recurrences of essentially the same event, such as tumor recurrences after surgeries, or may be successive events of entirely different types, such as strokes and heart attacks. When data include recurrent events, regression models such as the proportional hazards model become much more mathematically complicated and often involve counting process

theory, which is beyond the scope of this book. A number of regression models have been proposed in the literature. In this section we introduce three models that can be considered as extensions of the Cox proportional hazards model. We keep the mathematics to a minimum and use examples to show how these models can be used to identify important prognostic or risk factors with the aid of available computer software. The three models are based on Prentice et al. (1981), Andersen and Gill (1982), and Wei et al. (1989). All three models are proportional hazards models, and the likelihood functions of these models are constructed differently, primarily in the risk set at the uncensored observations. Readers interested in details are referred to the papers cited above.

Prentice et al. Model

In their 1981 paper, Prentice, Williams, and Peterson (PWP) proposed two models for recurrent events. Both PWP models can be considered as extensions of the stratified proportional hazards model with strata defined by the number and time of the recurrent events. The hazard function is extended beyond the person's first event to cover subsequent events. In the first PWP model, follow-up time starts at the beginning of the study (true time 0) and the hazard function of the ith person can be written as

$$h(t \mid \mathbf{b}_s, \mathbf{x}_i(t)) = h_{0s}(t) \exp[\mathbf{b}_s' \mathbf{x}_i(t)] \tag{13.4.1}$$

where the subscript s represents the stratum that the person is in at time t. The first stratum includes people who have at least one recurrence or are censored without recurrence, the second stratum includes people who have at least two recurrences or are censored after the first recurrence, and so on. A person moves from stratum 1 ($s = 1$) to stratum 2 ($s = 2$) following his or her first recurrent event and remains in stratum 2 until the second recurrent event takes place or becomes a censor observation (no more recurrent event). The $h_{0s}(t)$ in (13.4.1) is the stratum-specific underlying hazard. Notice that in (13.4.1), the coefficients are stratum-specific also.

Let $t_{s1} < \cdots < t_{sd_s}$ denote the d_s ordered distinct failure times in stratum s, $\mathbf{x}_{si}(t_{si})$ the covariate vector of a subject in stratum s who fails at time t_{si}, $\mathbf{x}_{sl}(t_{si})$ the covariate vector of subject l in stratum s at time t_{si}, and $R(t, s)$ the set of persons at risk in stratum s just prior to time t. Note that the risk set $R(t, s)$ includes only those persons who have experienced the first $s - 1$ recurrent events. Then the partial likelihood for the first model in (13.4.1) is

$$L(b) = \prod_{s \geqslant 1} \prod_{i=1}^{d_s} \frac{\exp[\mathbf{b}_s' \mathbf{x}_{si}(t_{si})]}{\sum_{l \in R(t_{si}, s)} \exp[\mathbf{b}_s' \mathbf{x}_{sl}(t_{si})]} \tag{13.4.2}$$

The following example illustrates the construction of the likelihood function and the necessary data arrangements for using SAS, SPSS, or BMDP to carry out the analysis.

Example 13.6 We use the tumor recurrence data from bladder cancer patients (Andrews and Herzberg, 1985; Wei et al., 1989) in a clinical trial to compare three treatments, which was conducted by the Veterans Administration Cooperative Urological Research Group (Byar, 1980). All patients had superficial bladder tumors when they entered the study. These tumors were removed and the patients were randomized into three treatment groups: placebo, thiotepa, and pyridoxine. During the follow-up period many patients had one or more recurrences of tumors and new tumors were removed when discovered. In this example we use the tumor recurrence data from 86 patients who received either placebo or thiotepa. Only the first four recurrence times are considered. The data set, reproduced in Table 13.6, includes treatment (1, placebo; 2, thiotepa) follow-up time, initial number of tumors (N), initial tumor size (S) in centimeters, and recurrent time. Each recurrent time of a patient was measured from the date of first treatment.

In this case, the event of interest is tumor recurrence and the strata are defined by the number of recurrences (NRs).To use SAS and other software to fit data with the model (13.4.1), the data must be rearranged in a certain format by stratum. To facilitate illustration, we select six patients from Table 13.6 and place the data of these six patients in Table 13.7. The follow-up and recurrence times are also shown in Figure 13.1. From the figure we see that stratum 1 includes patients 1 (censored at 9 months), 2 (censored at 59 months), 3 (first recurrent at 3 months), 4 (first recurrent at 12 months), 5 (first occurrence at 6 months), and 6 (first occurrence at 3 months). The time intervals, (TL, TR], are (0,9], (0,59], (0,3], (0,12], (0,6], and (0,3], respectively. These intervals are used to determine the risk set in the stratum-specific likelihood function in (13.4.2), and the patients in the stratum were at risk only in these time intervals. To use software packages such as SAS, BMDP, and SPSS, we need to rearrange the data by stratum. Table 13.8 gives the rearranged data. Note that the six patients in stratum 1 are arranged in ascending order according to the right end of the time interval. Also introduced in this table are T1–T4, N1–N4, and S1–S4, giving the treatment received, initial tumor number, and initial tumor size of the patients for the four strata, respectively. These variables are set to be zero in the other strata except the stratum they are in. For example, for patients in stratum 1, T2–T4, N2–N4, and S2–S4 are set to be zero because these six patients are in stratum 1, not in stratum 2, 3, or 4. Stratum 2 includes those patients who had one recurrence and had either another recurrence or were censored at end of follow-up. Therefore, stratum 2 has patients 3 (censored at 14 months after the first recurrence), 4 (second recurrence at 16 months), 5 (second recurrence at 12 months), and 6 (second recurrence at 15 months). The time intervals between successive recurrences for these four patients are (3, 14], (12,16], (6,12], and (3,15], respectively. The rearranged data in order of the right end of the intervals are given in Table 13.8. Strata 3 and 4 are constructed in a similar way. Once the data are rearranged exactly as in Table 13.8, SAS and other software can be used to perform the analysis.

This data arrangement also facilitates explanation of the likelihood function

Table 13.6 Tumor Recurrence Data for Patients with Bladder Cancer[a]

Treatment Group	Follow-up Time	Initial Number	Initial Size	Recurrence Time 1	2	3	4
1	0	1	1				
1	1	1	3				
1	4	2	1				
1	7	1	1				
1	10	5	1				
1	10	4	1	6			
1	14	1	1				
1	18	1	1				
1	18	1	3	5			
1	18	1	1	12	16		
1	23	3	3				
1	23	1	3	10	15		
1	23	1	1	3	16	23	
1	23	3	1	3	9	21	
1	24	2	3	7	10	16	24
1	25	1	1	3	15	25	
1	26	1	2				
1	26	8	1	1			
1	26	1	4	2	26		
1	28	1	2	25			
1	29	1	4				
1	29	1	2				
1	29	4	1				
1	30	1	6	28	30		
1	30	1	5	2	17	22	
1	30	2	1	3	6	8	12
1	31	1	3	12	15	24	
1	32	1	2				
1	34	2	1				
1	36	2	1				
1	36	3	1	29			
1	37	1	2				
1	40	4	1	9	17	22	24
1	40	5	1	16	19	23	29
1	41	1	2				
1	43	1	1	3			
1	43	2	6	6			
1	44	2	1	3	6	9	
1	45	1	1	9	11	20	26
1	48	1	1	18			
1	49	1	3				
1	51	3	1	35			
1	53	1	7	17			
1	53	3	1	3	15	46	51
1	59	1	1				
1	61	3	2	2	15	24	30
1	64	1	3	5	14	19	27

(*Continued overleaf*)

Table 13.6 ***Continued***

Treatment Group	Follow-up Time	Initial Number	Initial Size	Recurrence Time			
				1	2	3	4
1	64	2	3	2	8	12	13
2	1	1	3				
2	1	1	1				
2	5	8	1	5			
2	9	1	2				
2	10	1	1				
2	13	1	1				
2	14	2	6				
2	17	5	3	3	1	3	5
2	18	5	1				
2	18	1	3	17			
2	19	5	1	2			
2	21	1	1	17	19		
2	22	1	1				
2	25	1	3				
2	25	1	5				
2	25	1	1				
2	26	1	1	6	12	13	
2	27	1	1	6			
2	29	2	1	2			
2	36	8	3	26	35		
2	38	1	1				
2	39	1	1	22	23	27	32
2	39	6	1	4	16	23	27
2	40	3	1	24	26	29	40
2	41	3	2				
2	41	1	1				
2	43	1	1	1	27		
2	44	1	1				
2	44	6	1	2	20	23	27
2	45	1	2				
2	46	1	4	2			
2	46	1	4				
2	49	3	3				
2	50	1	1				
2	50	4	1	4	24	47	
2	54	3	4				
2	54	2	1	38			
2	59	1	3				

Source: Wei et al (1989) and StatLib web site: http//lib.stat.cmu.edu/datasets/tumor.

[a] Treatment group: 1, placebo; 2, thioteps. Follow-up time and recurrence time are measured in months. Initial size is measured in centimeters. Initial number of 8 denotes eight or more initial tumors.

Table 13.7 Six of 86 Bladder Cancer Patients from the Tumor Recurrence Data[a]

Patient ID	Treatment Group	Follow-up Time	Initial Number	Initial Size	Recurrence Time			
					1	2	3	4
1	1	9	1	2				
2	0	59	1	1				
3	1	14	2	6	3			
4	0	18	1	1	12	16		
5	1	26	1	1	6	12	13	
6	0	53	3	1	3	15	46	51

[a] Treatment group: 0, placebo; 1, thiotepa. Following-up time and recurrence time are measured in months. Initial size is measured in centimeters for the largest initial tumor.

in (13.4.2). We use stratum 2 to show the second product in (13.4.2). In stratum 2 ($s = 2$), $d_s = 3$ (there are three uncensored observations: patients 5, 6 and 4, according to the ordered recurrent times, 12, 15, and 16 months). Therefore, the second product is the product of three terms, one for each of these three patients. Using the notations in (13.4.2), we renumber them as patient $i = 1$, 2, and 3, respectively. The risk set at the first uncensored time t_{21} in stratum 2

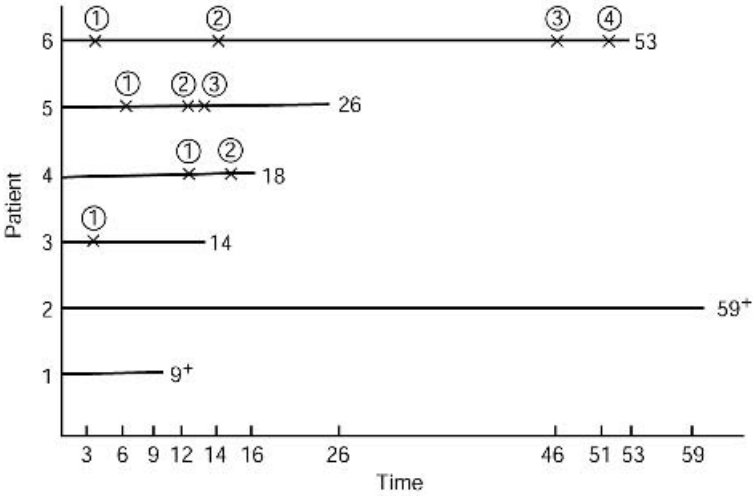


Figure 13.1 Graphical presentation of recurrence times of the six patients in Table 13.7 (numbers in circle indicate the number of recurrences).

Table 13.8 Rearranged Data from Table 13.7 for Fitting PWP Model with NR-Indexed Coefficients[a]

ID	NR	TL	TR	CS	T1	T2	T3	T4	N1	N2	N3	N4	S1	S2	S3	S4
3	1	0	3	1	1	0	0	0	2	0	0	0	6	0	0	0
6	1	0	3	1	0	0	0	0	3	0	0	0	1	0	0	0
5	1	0	6	1	1	0	0	0	1	0	0	0	1	0	0	0
1	1	0	9	0	1	0	0	0	1	0	0	0	2	0	0	0
4	1	0	12	1	0	0	0	0	1	0	0	0	1	0	0	0
2	1	0	59	0	0	0	0	0	1	0	0	0	1	0	0	0
5	2	6	12	1	0	1	0	0	0	1	0	0	0	1	0	0
3	2	3	14	0	0	1	0	0	0	2	0	0	0	6	0	0
6	2	3	15	1	0	0	0	0	0	3	0	0	0	1	0	0
4	2	12	16	1	0	0	0	0	0	1	0	0	0	1	0	0
5	3	12	13	1	0	0	1	0	0	0	1	0	0	0	1	0
4	3	16	18	0	0	0	0	0	0	0	1	0	0	0	1	0
6	3	15	46	1	0	0	0	0	0	0	3	0	0	0	1	0
5	4	13	26	0	0	0	0	1	0	0	0	1	0	0	0	1
6	4	46	51	1	0	0	0	0	0	0	0	3	0	0	0	1

[a] ID, patient ID number; NR, number of recurrence, where 1 = first recurrence, 2 = second recurrence, and so on; TL and TR, left and right ends of time interval (TL, TR) defined by the successive rcurrence times and the follow-up time, where TR denotes either the successive recurrence time or the follow-up time; CS, censoring status, where 0 = censored, 1 = uncensored; T1 to T4, treatment group; N1 to N4, initial number of tumors; S1 to S4, initial size.

(observed from patient 5), or $R(t_{21}, 2)$ includes patients in stratum 2, whose recurrent times, censored or not, are at least 12 (t_{21}) months. Therefore, $R(t_{21}, 2)$ includes all four patients in stratum 2. Similarly, the risk set at the second uncensored time t_{22} in stratum 2, $R(t_{22}, 2)$, includes two patients (patients 6 and 4), and $R(t_{23}, 2)$ includes only one patient (patient 4). Thus, using the ID in Table 13.7, let $\mathbf{x}_{23}$–$\mathbf{x}_{26}$ denote the covariate vectors for patients 3–6 in stratum 2, the second product in (13.4.2) is

$$\prod_{i=1}^{d_2} \frac{\exp[\mathbf{b}_2' \mathbf{x}_{2i}(t_{2i})]}{\sum_{l \in R(t_{2i},2)} \exp[\mathbf{b}_2' \mathbf{x}_l(t_{2i})]}$$

$$= \frac{\exp(\mathbf{b}_2' \mathbf{x}_{25})}{\exp(\mathbf{b}_2' \mathbf{x}_{23}) + \exp(\mathbf{b}_2' \mathbf{x}_{24}) + \exp(\mathbf{b}_2' \mathbf{x}_{25}) + \exp(\mathbf{b}_2' \mathbf{x}_{26})}$$

$$\times \frac{\exp(\mathbf{b}_2' \mathbf{x}_{26})}{\exp(\mathbf{b}_2' \mathbf{x}_{24}) + \exp(\mathbf{b}_2' \mathbf{x}_{26})} \times \frac{\exp(\mathbf{b}_2' \mathbf{x}_{24})}{\exp(\mathbf{b}_2' \mathbf{x}_{24})} \tag{13.4.3}$$

where the $\mathbf{x}$'s represent the covariate vector (T1, T2, T3, T4, N1, N2, N3, N4, S1, S2, S3, S4). For example, $\mathbf{x}_{25} = (0, 1, 0, 0, 0, 1, 0, 0, 0, 1, 0, 0)$. It is clear that

in this model the regression coefficients are stratum specific. They represent the importance of the coefficient for patients in different strata or patients who had different numbers of recurrent events. If the primary interest is the overall importance of the covariates, regardless of the number of recurrences or if it can be assumed that the importance of covariates is independent of the number of recurrences, T1–T4, N1–N4, and S1–S4 can be combined into a single variable. As shown in Table 13.9, the three covariates are named TRT, N, and S for the six patients, and coefficients common to all strata can be estimated. Data sets that have been so rearranged are ready for SAS and other software.

To use SAS and other software, the entire data set in Table 13.6 must first be rearranged as in Table 13.8 or 13.9. This can also be accomplished using a computer.

Table 13.10 gives the results from fitting the PWP model to the bladder tumor data in Table 13.6 with stratum-specific coefficients and common coefficients. None of the stratum-specific covariates is significant except N1, the initial number of tumors in stratum 1 patients ($p = 0.0017$). There is no significant difference between the two treatments in any stratum, and the size of the initial tumor has no significant effect on tumor recurrence. When stratification is ignored, the results are similar (the second part of Table 13.10). The number of initial tumors is the only significant prognostic factor, and the risk of recurrence increase would increase almost 13% for every one-tumor increase in the number of initial tumors.

Table 13.9 Rearranged Data from Table 13.7 for Fitting PWP Model with Common Coefficients[a]

ID	NR	TL	TR	CS	TRT	N	S
3	1	0	3	1	1	2	6
6	1	0	3	1	0	3	1
5	1	0	6	1	1	1	1
1	1	0	9	0	1	1	2
4	1	0	12	1	0	1	1
2	1	0	59	0	0	1	1
5	2	6	12	1	1	1	1
3	2	3	14	0	1	2	6
6	2	3	15	1	0	3	1
4	2	12	16	1	0	1	1
5	3	12	13	1	1	1	1
4	3	16	18	0	0	1	1
6	3	15	46	1	0	3	1
5	4	13	26	0	1	1	1
6	4	46	51	1	0	3	1

[a] TRT, treatment group; N, initial number; S, initial size.

Table 13.10 Asymptotic Partial Likelihood Inference on the Bladder Cancer Data from Fitted PWP Models with Stratum-specific or Common Coefficients

Variable	Regression Coefficient	Standard Error	Chi-Square Statistic	p	Hazards Ratio	95% Confidence Interval	
						Lower	Upper
Model with Stratum-Specific Coefficients							
T1	−0.526	0.316	2.774	0.0958	0.591	0.318	1.097
T2	−0.504	0.406	1.539	0.2148	0.604	0.273	1.339
T3	0.141	0.673	0.044	0.8345	1.151	0.308	4.305
T4	0.050	0.792	0.004	0.9493	1.052	0.223	4.963
N1	0.238	0.076	9.851	0.0017	1.269	1.094	1.472
N2	−0.025	0.090	0.075	0.7840	0.976	0.818	1.164
N3	0.050	0.185	0.072	0.7887	1.051	0.731	1.511
N4	0.204	0.242	0.712	0.3987	1.227	0.763	1.971
S1	0.070	0.102	0.470	0.4931	1.072	0.879	1.308
S2	−0.161	0.122	1.722	0.1894	0.852	0.670	1.083
S3	0.168	0.269	0.390	0.5321	1.183	0.698	2.005
S4	0.009	0.339	0.001	0.9786	1.009	0.519	1.961
Model with Common Coefficients							
TRT	−0.333	0.216	2.380	0.1229	0.716	0.469	1.094
N	0.120	0.053	5.029	0.0249	1.127	1.015	1.251
S	−0.008	0.073	0.014	0.9071	0.992	0.860	1.144

In the second PWP model, the follow-up time starts from the immediately preceding event or failure time. Analogous to (13.4.1), the second PWP model can be written in terms of a hazard function as

$$h(t \mid \mathbf{b}_s, \mathbf{x}_i(t)) = h_{0s}(t - t_{s-1}) \exp[\mathbf{b}_s' \mathbf{x}_i(t)] \tag{13.4.4}$$

where t_{s-1} denotes the time of the preceding event. The time period between two consecutive recurrent events or between the last recurrent event time and the end of follow-up is called the *gap time*.

For the lth subject, who fails at time t_{sl} in stratum s, denote the gap time as $u_{sl} = t_{sl} - t_{s-1l}$, where t_{s-1l} is the failure time of the lth subject in the stratum $s-1$. Let $u_{s(1)} < \cdots < u_{s(d_s)}$ denote the ordered observed distinct gap times in stratum s and $\tilde{R}(u, s)$ denote the set of subjects at risk in stratum s just prior to gap time u. Again, $\tilde{R}(u, s)$ includes only those subjects who have experienced the first $s-1$ strata. Then we have the partial likelihood for the second model (13.4.4):

$$L(\mathbf{b}) = \prod_{s \geqslant 1} \prod_{i=1}^{d_s} \frac{\exp[\mathbf{b}_s' \mathbf{x}_{si}(t_{s(i)})]}{\sum_{l \in \tilde{R}(u_{s(i)}, s)} \exp(\mathbf{b}_s' \mathbf{x}_{sl}(t_{s(i)})]} \tag{13.4.5}$$

Note that risk sets in (13.4.5) are defined by the ordered distinct gap times in the strata rather than by the failure times themselves.

Using the notations in Table 13.9, let GT denote the gap time, then GT = TR−TL. Replacing TR and TL in Tables 13.8 and 13.9 by GT, the data are ready for SAS and other software. Table 13.11 is the corresponding table for the same six patients in Table 13.9 using gap times. Using the notation of Example 13.6, the second product in (13.4.5) for stratum 2 is

$$\prod_{i=1}^{d_2} \frac{\exp[\mathbf{b}_2' \mathbf{x}_{2i}(t_{2i})]}{\sum_{l \in \tilde{R}(u_{2(i)},2)} \exp[\mathbf{b}_2' \mathbf{x}_{2l}(t_{2l})]}$$

$$= \frac{\exp(\mathbf{b}_2' \mathbf{x}_{24})}{\exp(\mathbf{b}_2' \mathbf{x}_{23}) + \exp(\mathbf{b}_2' \mathbf{x}_{24}) + \exp(\mathbf{b}_2' \mathbf{x}_{25}) + \exp(\mathbf{b}_2' \mathbf{x}_{26})}$$

$$\times \frac{\exp(\mathbf{b}_2' \mathbf{x}_{25})}{\exp(\mathbf{b}_2' \mathbf{x}_{23}) + \exp(\mathbf{b}_2' \mathbf{x}_{25}) + \exp(\mathbf{b}_2' \mathbf{x}_{26})} \times \frac{\exp(\mathbf{b}_2' \mathbf{x}_{26})}{\exp(\mathbf{b}_2' \mathbf{x}_{26})}$$

Note that this is different from (13.4.3), due to a different definition of the risk set.

The results from fitting the PWP gap time model to all the data in Table 13.6 with stratum-specific coefficients and common coefficients are given in Table 13.12. Again, the number of initial tumors is the only significant

Table 13.11 Rearranged Data from Table 13.9 for Fitting PWP Gap Time Model with Common Coefficients

ID	NR	GT	CS	TRT	N	S
3	1	3	1	1	2	6
6	1	3	1	0	3	1
5	1	6	1	1	1	1
1	1	9	0	1	1	2
4	1	12	1	0	1	1
2	1	59	0	0	1	1
4	2	4	1	0	1	1
5	2	6	1	1	1	1
3	2	11	0	1	2	6
6	2	12	1	0	3	1
5	3	1	1	1	1	1
4	3	2	0	0	1	1
6	3	31	1	0	3	1
6	4	5	1	0	3	1
5	4	13	0	1	1	1

Table 13.12 Asymptotic Partial Likelihood Inference on the Bladder Cancer Data from the Fitted PWP Gap Time Models with Stratum-Specific or Common Coefficients

Variable	Regression Coefficient	Standard Error	Chi-Square Statistic	p	Hazards Ratio	95% Confidence Interval	
						Lower	Upper
Model with Stratum-Specific Coefficients							
T1	−0.526	0.316	2.774	0.0958	0.591	0.318	1.097
T2	−0.271	0.405	0.448	0.5034	0.763	0.345	1.687
T3	0.210	0.550	0.146	0.7022	1.234	0.420	3.626
T4	−0.220	0.639	0.119	0.7301	0.802	0.229	2.807
N1	0.238	0.076	9.851	0.0017	1.269	1.094	1.472
N2	−0.006	0.096	0.004	0.9469	0.994	0.823	1.200
N3	0.142	0.162	0.774	0.3791	1.153	0.840	1.582
N4	0.475	0.203	5.492	0.0191	1.609	1.081	2.394
S1	0.070	0.102	0.470	0.4931	1.072	0.879	1.308
S2	−0.119	0.119	1.003	0.3166	0.888	0.703	1.121
S3	0.278	0.233	1.425	0.2326	1.321	0.836	2.086
S4	0.043	0.290	0.022	0.8822	1.044	0.592	1.842
Model with Common Coefficients							
TRT	−0.279	0.207	1.811	0.1784	0.757	0.504	1.136
N	0.158	0.052	9.258	0.0023	1.171	1.058	1.297
S	0.007	0.070	0.011	0.9157	1.007	0.878	1.156

covariates. There are no major differences between the two PWP models for this set of data. It is impossible to compare the coefficients obtained in the two models. The first model defines time from the beginning of the study and therefore is recommended if the entire course of recurrent events is of interest. The second model is the choice if the primary interest is to model the gap time between events.

Suppose that the text file "C:\EX13d4d1.DAT" contains the successive columns in Table 13.8 for the entire data set in Table 13.6: NR, TL, TR, CS, T1, T2, T3, T4, N1, N2, N3, N4, S1, S2, S3, and S4, and the text file "C:\EX13d4d2.DAT" contains the seven successive columns in Table 13.9: NR, TL, TR, CS, TRT, N, and S. The following SAS code can be used to obtain the PWP models in Table 13.10.

```
data w1;
  infile 'c:\ex13d4d1.dat' missover;
  input nr tl tr cs t1 t2 t3 t4 n1 n2 n3 n4 s1 s2 s3 s4;
run;
title "PWP model with stratified coefficients';
proc phreg data = w1;
```

```
   model (tl, tr)*cs(0) = t1 t2 t3 t4 n1 n2 n3 n4 s1 s2 s3 s4 / ties = efron;
   where tl < tr;
   strata nr;
run;
data w1;
   infile 'c:\ex13d4d2.dat' missover;
   input nr tl tr cs trt n s;
run;
title "PWP model with common coefficients';
proc phreg data = w1;
   model (tl, tr)*cs(0) = trt n s / ties = efron;
   where tl<tr;
   strata nr;
run;
```

Suppose that the text file "C:\EX13d4d3.DAT" contains 15 successive columns similar to Table 13.8 but with gap time GT. The 15 columns are NR, GT, CS, T1, T2, T3, T4, N1, N2, N3, N4, S1, S2, S3, and S4. The text file "C:EX13d4d4.DAT" contains the successive six columns from Table 13.11: NR, GT, CS, TRT, N, and S. The following SAS, SPSS, and BMDP codes can be used to obtain the PWP gap time models in Table 13.12.

SAS code:

```
data w1;
   infile 'c:\ex13d4d3.dat' missover;
   input nr gt cs t1 t2 t3 t4 n1 n2 n3 n4 s1 s2 s3 s4;
run;
title "PWP gap time model with stratified coefficients";
proc phreg data = w1;
   model gt*cs(0) = t1 t2 t3 t4 n1 n2 n3 n4 s1 s2 s3 s4 / ties = efron;
   strata nr;
run;
data w1;
   infile 'c:\ex13d4d4.dat' missover;
   input nr gt cs trt n s;
run;
title "PWP gap time model with common coefficients';
proc phreg data = w1;
   model gt*cs(0) = trt n s / ties = efron;
   strata nr;
run;
```

SPSS code:

```
data list file = 'c:\ex13d4d3.dat' free
        / nr gt cs t1 t2 t3 t4 n1 n2 n3 n4 s1 s2 s3 s4.
coxreg gt with t1 t2 t3 t4 n1 n2 n3 n4 s1 s2 s3 s4
        /status = cs event (1)
```

```
        /strata = nr
        /print = all.
data list file = 'c:\ex13d4d4.dat' free
        / nr gt cs trt n s.
coxreg gt with trt n s
        /status = cs event (1)
        /strata = nr
        /print = all.
```

BMDP 2L code:

```
/input      file = 'c:\ex13d4d3.dat' .
            variables = 15.
            format = free.
/print      cova.
            Survival.
/variable   names = nr, gt, cs, t1, t2, t3, t4, n1, n2, n3, n4, s1, s2, s3, s4.
/form       time = gt.
            status = cs.
            response = 1.
/regress    covariates = t1, t2, t3, t4, n1, n2, n3, n4, s1, s2, s3, s4.
            strata = nr.
/input      file = 'c:\ex13d4d4.dat' .
            variables = 6.
            format = free.
/print      cova.
            Survival.
/variable   names = nr, gt, cs, trt, n, s.
/form       time = gt.
            status = cs.
            response = 1.
/regress    covariates = trt, n, s.
            strata = nr.
```

Anderson–Gill Model

The model proposed by Andersen and Gill (1982), the AG model, assumes that all events are of the same type and are independent. The risk set in the likelihood function is totally different from that in the PWP models. The risk set of a person at the time of an event would contain all the people who are still under observation, regardless of how many events they have experienced before that time. The multiplicative hazard function $h(t, \mathbf{x}_i)$ for the ith person is

$$h(t, \mathbf{x}_i) = Y_i(t) h_0(t) \exp[\mathbf{b}'\mathbf{x}_i(t)]$$

where $Y_i(t)$, an indicator, equals 1 when the ith person is under observation (at risk) at time t and 0 otherwise and $h_0(t)$ is an unspecified underlying hazard

function. The partial likelihood for n independent persons is

$$L(\mathbf{b}) = \prod_{i=1}^{n} \prod_{t \geq 0} \left[\frac{Y_i(t) \exp(\mathbf{b}'\mathbf{x}_i)}{\sum_{j=1}^{n} Y_j(t) \exp(\mathbf{b}'\mathbf{x}_j)} \right]^{\delta_i(t)} \tag{13.4.6}$$

where $\delta_i(t) = 1$ if the ith person has an event at t and $=0$ otherwise. Details of this likelihood function and the estimation of the coefficients can be found in Fleming and Harrington (1991) and Andersen et al. (1993). Similar to the PWP models, software packages are available to carry out the computation provided that the data are arranged in a certain format. The following example illustrates the terms in (13.4.6) and the data format required by SAS.

Example 13.7 We use again the data in Table 13.6 to fit the AG model. To explain the terms in the likelihood function, we use the data of the six people in Table 13.7. In this model, every recurrent event is considered to be independent. Therefore, we can rearrange the data by person and by event time "within" an individual. Table 13.13 shows the rearranged data. For example, the person with ID = 4 had two recurrences, at 12 and 16, and the follow-up time ended at 18. The time intervals (TL, TR] are (0, 12], (12, 16], and (16,18], and 12 and 16 are uncensored observations and 18 censored, since there was no tumor recurrence at 18. For patients with ID = 1 and 2 ($i = 1, 2$), the respective second product terms in (13.4.6) are equal to 1 since $\delta_i(t) = 0$, $i = 1$, 2, for all t. For patient 3 ($i = 3$), $\delta_i(t) = 1$ only at $t = 3$ (the first tumor recurrence time of the patient). Thus, the respective second product has only

Table 13.13 Rearranged Data from Table 13.7 for Fitting AG Model

ID	TL	TR	CS	TRT	N	S
1	0	9	0	1	1	2
2	0	59	0	0	1	1
3	0	3	1	1	2	6
3	3	14	0	1	2	6
4	0	12	1	0	1	1
4	12	16	1	0	1	1
4	16	18	0	0	1	1
5	0	6	1	1	1	1
5	6	12	1	1	1	1
5	12	13	1	1	1	1
5	13	26	0	1	1	1
6	0	3	1	0	3	1
6	3	15	1	0	3	1
6	15	46	1	0	3	1
6	46	51	1	0	3	1
6	51	53	0	0	3	1

Table 13.14 Asymptotic Partial Likelihood Inference on the Bladder Cancer Data from the Fitted AG Model

Variable	Regression Coefficient	Standard Error	Chi-Square Statistic	p	Hazards Ratio	95% Confidence Interval	
						Lower	Upper
TRT	−0.412	0.200	4.241	0.0395	0.663	0.448	0.980
N	0.164	0.048	11.741	0.0006	1.178	1.073	1.293
S	−0.041	0.070	0.342	0.5590	0.960	0.836	1.102

one term at $t = 3$ and the denominator of this term sums over all the patients who are under observation and at risk at time $t = 3$. From Figure 13.1 it is easily seen that the sum is over all six patients; that is, the respective second product is

$$\frac{\exp(\mathbf{b}'\mathbf{x}_3)}{\sum_{j=1}^{6}\exp(\mathbf{b}'\mathbf{x}_j)} \tag{13.4.7}$$

For patient 4 ($i = 4$), the second product in (13.4.6) contains two terms. One is for $t = 12$ (the first recurrence time), and at $t = 12$, patients 2, 3, 4, 5, and 6 are still under observation, and therefore the denominator of the term sums over patients 2 to 6. The other term is for $t = 16$ (the second recurrence time) and the denominator sums over patients 2, 4, 5, and 6. Patient 3 is no longer under observation after $t = 14$. Thus, the second product term for $i = 4$ is

$$\frac{\exp(\mathbf{b}'\mathbf{x}_4)}{\sum_{j=2}^{6}\exp(\mathbf{b}'\mathbf{x}_j)} \times \frac{\exp(\mathbf{b}'\mathbf{x}_4)}{\exp(\mathbf{b}'\mathbf{x}_2) + \sum_{j=4}^{6}\exp(\mathbf{b}'\mathbf{x}_j)} \tag{13.4.8}$$

Similarly, we can construct each term in (13.4.6) and the partial likelihood function.

Using SAS, we obtain the results in Table 13.14. The AG model identifies treatment and number of initial tumor as significant covariates. Compared with placebo, thiotepa does slow down tumor recurrence.

Readers can construct the SAS codes for the AG model by using Table 13.13 and by following the codes given in Example 13.6.

Wei et al. Model

By using a marginal approach, Wei, Lin, and Weissfeld (1989) proposed a model, the WLW model, for the analysis of recurrent failures. The failures may be recurrences of the same kind of event or events of different natures, depending on how the stratification is defined. If the strata are defined by the

times of repeated failures of the same type, similar to the strata defined in the PWP models, it can be used to analyze repeated failures of the same kind. The difference between the PWP models and the WLW model is that the latter considers each event as a separate process and treats each stratum-specific (marginal) partial likelihood separately. In the stratum-specific (marginal) partial likelihood of stratum s, people who have experienced the $(s-1)$th failure contribute either one uncensored or one censored failure time depending on whether or not they experience a recurrence in stratum s, and the other subjects contribute only censored times (forced as censored times). Therefore, each stratum contains everyone in the study. This is different from the PWP models, in which subjects who have not experienced the $(s-1)$th failure are not included in stratum s. If the strata are defined by the type of failure, the WLW model acts like the competing risks model defined in Section 13.3, and the type-specific (marginal) partial likelihood for the jth type simply treats all failures of types other than j in the data as censored.

For the kth stratum of the ith person, the hazard function is assumed to have the form

$$h_{ki}(t) = Y_{ki}(t)h_{k0}(t)\exp(\mathbf{b}_k'\mathbf{x}_{ki}), \qquad t \geqslant 0 \tag{13.4.9}$$

where $Y_{ki}(t) = 1$, if the ith person in the kth stratum is under observation, 0, otherwise, $h_{k0}(t)$ is an unspecified underlying hazard function. Let $R_k(t_{ki})$ denote the risk set with people at risk at the ith distinct uncensored time t_{ki} in the kth stratum. Then the specific partial likelihood for the kth stratum is

$$L_k(\mathbf{b}_k) = \prod_{i=1}^{n}\left[\frac{\exp(\mathbf{b}_k'\mathbf{x}_{ki})}{\sum_{l\in R_k(t_{ki})}\exp(\mathbf{b}_k'\mathbf{x}_{kl})}\right]^{\delta_i} \tag{13.4.10}$$

where $\delta_i = 1$ if the ith observation in the kth stratum is uncensored and 0 otherwise. The coefficients $\mathbf{b}_k$ are stratum specific. In practice, if we are interested in the overall effect of the covariates, we can assume that the coefficients from different strata are equal (provided that there are no qualitative differences among the strata), combine the strata and draw conclusions above the "average effect" of the covariates. We again called the coefficients of these covariates common coefficients. The event time is from the beginning of the study in this model.

Similar to the PWP and AG models, the data must be arranged in a certain format in order to use available software to carry out estimation of the coefficients and tests of significance of the covariates. Using the same data as in Examples 13.6 and 13.7, the following example illustrates the terms in the stratum-specific likelihood function and the use of software.

Example 13.8 First, we use the same six patients to illustrate the components in the stratum-specific likelihood function in (13.4.10). The format the data have to be in for the available software, such as SAS, SPSS, and BMDP,

Table 13.15 Rearranged Data from Table 13.7 for Fitting WLW Model with NR-Indexed Coefficients

ID	NR	TR	CS	T1	T2	T3	T4	N1	N2	N3	N4	S1	S2	S3	S4
3	1	3	1	1	0	0	0	2	0	0	0	6	0	0	0
6	1	3	1	0	0	0	0	3	0	0	0	1	0	0	0
5	1	6	1	1	0	0	0	1	0	0	0	1	0	0	0
1	1	9	0	1	0	0	0	1	0	0	0	2	0	0	0
4	1	12	1	0	0	0	0	1	0	0	0	1	0	0	0
2	1	59	0	0	0	0	0	1	0	0	0	1	0	0	0
1	2	9	0	0	1	0	0	0	1	0	0	0	2	0	0
5	2	12	1	0	1	0	0	0	1	0	0	0	1	0	0
3	2	14	0	0	1	0	0	0	2	0	0	0	6	0	0
6	2	15	1	0	0	0	0	0	3	0	0	0	1	0	0
4	2	16	1	0	0	0	0	0	1	0	0	0	1	0	0
2	2	59	0	0	0	0	0	0	1	0	0	0	1	0	0
1	3	9	0	0	0	1	0	0	0	1	0	0	0	2	0
5	3	13	1	0	0	1	0	0	0	1	0	0	0	1	0
3	3	14	0	0	0	1	0	0	0	2	0	0	0	6	0
4	3	18	0	0	0	0	0	0	0	1	0	0	0	1	0
6	3	46	1	0	0	0	0	0	0	3	0	0	0	1	0
2	3	59	0	0	0	0	0	0	0	1	0	0	0	1	0
1	4	9	0	0	0	0	1	0	0	0	1	0	0	0	2
3	4	14	0	0	0	0	1	0	0	0	2	0	0	0	6
4	4	18	0	0	0	0	0	0	0	0	1	0	0	0	1
5	4	26	0	0	0	0	1	0	0	0	1	0	0	0	1
6	4	51	1	0	0	0	0	0	0	0	3	0	0	0	1
2	4	59	0	0	0	0	0	0	0	0	1	0	0	0	1

is similar to that in the PWP and AG models except that all six people are in each of the four strata (Table 13.15). The first stratum (NR = 1) is exactly the same as in Table 13.8. The six patients are ordered according to the magnitude of the event time (censored or not, TR). In stratum 2(NR = 2), the three people (with ID = 4, 5, and 6) whose times to the second tumor recurrence are uncensored observations. Patients 1 and 2 had censored time at 9 and 59, respectively. Patient 3, who had no second recurrence and was observed until 14 months, is considered censored at 14. The other strata are constructed in a similar manner. Using the data arrangement in Table 13.15, we can see that for the second stratum, the likelihood function in (13.4.10) has three terms, one for each of persons 5, 6, and 4, whose $\delta_i = 1$ (CS = 1 in the table). For patient 4, the risk set at time $t = 16$ has two individuals (ID = 4 and 2); for patient 5, the risk set at time $t = 12$ contains five individuals (ID = 2, 3, 4, 5, and 6); and for patient 6, the risk set at time $t = 15$ has three individuals (ID = 2, 4, and 6). Let $\mathbf{x}_{2j}$ be the covariate vector of the patient with ID = j in stratum 2; then

Table 13.16 Rearranged Data from Table 13.7 for Fitting WLW Model with Common Coefficients

ID	NR	TR	CS	TRT	N	S
3	1	3	1	1	2	6
6	1	3	1	0	3	1
5	1	6	1	1	1	1
1	1	9	0	1	1	2
4	1	12	1	0	1	1
2	1	59	0	0	1	1
1	2	9	0	1	1	2
5	2	12	1	1	1	1
3	2	14	0	1	2	6
6	2	15	1	0	3	1
4	2	16	1	0	1	1
2	2	59	0	0	1	1
1	3	9	0	1	1	2
5	3	13	1	1	1	1
3	3	14	0	1	2	6
4	3	18	0	0	1	1
6	3	46	1	0	3	1
2	3	59	0	0	1	1
1	4	9	0	1	1	2
3	4	14	0	1	2	6
4	4	18	0	0	1	1
5	4	26	0	1	1	1
6	4	51	1	0	3	1
2	4	59	0	0	1	1

the likelihood function in (13.4.10) is

$$L_2(\mathbf{b}_2) = \prod_{i=1}^{6} \left[\frac{\exp(\mathbf{b}_2'\mathbf{x}_{2i})}{\sum_{l \in R_2(t_{2i})} \exp(\mathbf{b}_2'\mathbf{x}_{2l})} \right]^{\delta_i} = \frac{\exp(\mathbf{b}_2'\mathbf{x}_{24})}{\exp(\mathbf{b}_2'\mathbf{x}_{22}) + \exp(\mathbf{b}_2'\mathbf{x}_{24})}$$
$$\times \frac{\exp(\mathbf{b}_2'\mathbf{x}_{25})}{\exp(\mathbf{b}_2'\mathbf{x}_{22}) + \exp(\mathbf{b}_2'\mathbf{x}_{23}) + \exp(\mathbf{b}_2'\mathbf{x}_{24}) + \exp(\mathbf{b}_2'\mathbf{x}_{25}) + \exp(\mathbf{b}_2'\mathbf{x}_{26})}$$
$$\times \frac{\exp(\mathbf{b}_2'\mathbf{x}_{26})}{\exp(\mathbf{b}_2'\mathbf{x}_{22}) + \exp(\mathbf{b}_2'\mathbf{x}_{24}) + \exp(\mathbf{b}_2'\mathbf{x}_{26})} \tag{13.4.11}$$

Note that (13.4.11) is different from (13.4.3). The likelihood function for the other strata and for the entire data set in Table 13.6 can be constructed in a similar manner. If we ignore the stratum-specific effect and are interested only in the average overall effect of the covariates, we combine T1–T4, N1–N4, and S1–S4. The rearranged data for the six patients are given in Table 13.16.

Table 13.17 Asymptotic Partial Likelihood Inference on the Bladder Cancer Data from the Fitted WLW Models with Stratum-Specific or Common Coefficients

Variable	Regression Coefficient	Standard Error	Chi-Square Statistic	p	Hazards Ratio	95% Confidence Interval	
						Lower	Upper
Model with Stratum-Specific Coefficients							
T1	−0.526	0.316	2.774	0.0958	0.591	0.318	1.097
T2	−0.632	0.393	2.588	0.1077	0.531	0.246	1.148
T3	−0.698	0.460	2.308	0.1278	0.496	0.202	1.225
T4	−0.635	0.576	1.215	0.2703	0.530	0.171	1.639
N1	0.238	0.076	9.851	0.0017	1.269	1.094	1.472
N2	0.137	0.902	2.229	0.1354	1.147	0.958	1.373
N3	0.174	0.105	2.750	0.0973	1.189	0.969	1.460
N4	0.332	0.125	7.112	0.0077	1.394	1.092	1.780
S1	0.070	0.102	0.470	0.4931	1.072	0.879	1.308
S2	−0.078	0.134	0.337	0.5614	0.925	0.712	1.203
S3	−0.214	0.183	1.371	0.2416	0.807	0.565	1.155
S4	−0.206	0.231	0.800	0.3712	0.813	0.517	1.279
Model with Common Coefficients							
TRT	−0.585	0.201	8.460	0.0036	0.557	0.376	0.826
N	0.210	0.047	20.230	0.0001	1.234	1.126	1.352
S	−0.052	0.070	0.548	0.4592	0.950	0.828	1.089

The results from fitting the WLW models to the entire data set in Table 13.6 are given in Table 13.17. The model with stratum-specific coefficients suggests that more initial tumors accelerate tumor recurrence and the acceleration is particularly faster for the first recurrence and the third and fourth recurrences. The signs of the coefficients for T1–T4 suggest that thiotepa may slow down tumor growth, but the evidence is not statistically significant. The model with common coefficients suggests that thiotepa is significantly more effective in prolonging the recurrence time. The results suggest that when looking at each stratum independently, there is no strong evidence that thiotepa is more effective than placebo. However, the combined estimate of the common coefficient provides stronger evidence that thiotepa is more effective over the course of the study.

13.5 MODELS FOR RELATED OBSERVATIONS

In Cox's proportional hazards model and other regression methods, a key assumption is that observed survival or event times are independent. However, in many practical situations, failure times are observed from related individuals

or from successive recurrent events or failures of the same person. For example, in an epidemiological study of heart disease, some of the participants may be from the same family and therefore are not independent. These families with multiple participants may be called *clusters*. In this case, the regression methods we introduced earlier may not be appropriate. Several types of models introduced especially for related observations are discussed by Andersen et al. (1993), Liang et al. (1995), Klein and Moeschberger (1997), and Ibrahim et al. (2001). Details about these models are beyond the scope of this book. In the following, we introduce briefly the frailty models.

The *frailty models* assume that there is an unmeasured random variable (frailty) in the hazard function. This random variable accounts for the variation or heterogeneity among individuals in a cluster. It is also assumed that the frailty is independent of censoring. Let n be the total number of participants in the study, some of them related and forming clusters. Let v_i be the unknown random variable, frailty, associated with the ith cluster, $1 \leqslant i < n$. The frailty model associated with the proportional hazards model can be written in terms of the log hazard function as

$$\log[h_{ij}(t;\, \mathbf{x}_{ij} \,|\, v_i)] = \log[h_0(t)] + v_i + \mathbf{b}'\mathbf{x}_{ij} \tag{13.5.1}$$

for $1 \leqslant j \leqslant m_i$ and $1 \leqslant i < n$, where $\mathbf{b}$ denotes the $p \times 1$ column vector of unknown regression coefficients, $\mathbf{x}_{ij}$ is the covariate vector of the jth person in the ith cluster, m_i is the number of individuals in the ith cluster, and $h_0(t)$ is an unknown underlying hazard function. Compared with the Cox proportional hazards model, the difference here is the random effect v_i. Because v_i remains the same in the ith cluster, the association between failure and covariates within each cluster in this model is assumed to have a symmetric pattern. In a family study, this model can be used, for example, to model failure times observed from siblings by treating each family as a cluster. This model was proposed by Vaupel et al. (1979) and developed and discussed by many researchers, including Clayton and Cuzick (1985). The main approach to this model is to assume that v_i follows a parametric distribution.

The frailty model in (13.5.1) can be extended to handle more complicated situations. For example, the frailty can be a time-dependent variable [replace v_i by $v_i(t)$ in (13.5.1)]. The frailty model with $v_i(t)$ can be used to model successive or recurrent failure time as an alternative to the models in Section 13.4. Another example is that there may be more than one type of frailty in each cluster, and v_i in (13.5.1) can be replaced by $v_i + u_i$ or $v_i + u_i + w_i$, and so on.

Inferences of these frailty models are also based on either a likelihood function or a partial likelihood function. Since the models involve a parametric distribution, the likelihood or partial likelihood functions are complicated and are beyond the level of this book.

The frailty models have not been used widely primarily because of the lack of commercially available software. There are some computer programs

available; for example, a SAS macro is available for a gamma frailty model at the Web site of Klein and Moeschberger (1997), and another program is described by Jenkins (1997).

Bibliographical Remarks

Most of the major references for nonproportional hazards models have been cited in the text of this chapter. Applications of these models include: *stratified models*: Vasan et al. (1997), Aaronson et al. (1997), and Yakovlev et al. (1999); *frailty models*: Yashin and Iachine (1997), Kessing et al. (1999), Siegmund et al. (1999), Albert (2000), Lee and Yau (2001), Wienke el al. (2001), and Xue (2001); *competing risks models*: Mackenbach et al. (1995), Fish et al. (1998), Albertsen et al. (1998), Blackstone and Lytle (2000), Yan et al. (2000), and Tai et al. (2001).

EXERCISES

13.1 Consider the cancer-free times from the participants with IDs 15 to 23 in Table 13.1. Follow Example 13.1 to construct the partial likelihood function based on the observed cancer-free times from these nine participants.

13.2 Consider the survival times from 30 resected melanoma patients in Table 3.1. Let AGEG denote age group, AGEG = 1 if age <45 and AGEG = 2 otherwise. Fit the survival times with an AGEG-stratified Cox proportional hazards model with the covariates age, gender, initial stage, and treatment received. Discuss the association of the treatment received with the survival time.

13.3 Using the data in Table 12.4, following Example 13.5 and the sample codes for SAS, SPSS, or BMDP, fit the competing risk model for stroke, CHD, other CVD, or STROKE/CHD separately, and discuss the results obtained.

13.4 Using the rearranged data in Tables 13.7 to 13.13 and following Examples 13.6 to 13.8, complete construction of the remaining terms in the partial likelihood function based on the PWP model (13.4.2), PWP gap time model (13.4.3), and AG model (13.4.9), and the remaining three marginal likelihood functions based on the WLW model (13.4.13).

CHAPTER 14

Identification of Risk Factors Related to Dichotomous and Polychotomous Outcomes

In biomedical research we are often interested in whether a certain survival-related event will occur and the important factors that influence its occurrence. Such events may involve two or more possible outcomes; examples are the development of a given condition and response to a given treatment. If the given condition is diabetes and we are only interested in whether someone develops the disease (yes or no), the outcome is binary or dichotomous. If we are interested in whether the person develops impaired glucose tolerance, diabetes, or remains having normal glucose tolerance, there are three possible outcomes, or we say the outcome is *trichotomous*. Similarly, response to a given treatment can have *dichotomous* (response or no response) or *polychotomous* outcomes (complete response, partial response, or no response).

To determine whether one is likely to develop a given disease, we need to know the important characteristics (or factors) related to its development. High- and low-risk groups can then be defined accordingly. Factors closely related to the development of a given disease are usually called *risk factors* or *risk variables* by epidemiologists. We shall use these terms in a broader sense to mean factors closely related to the occurrence of any event of interest. For example, to find out whether a woman will develop breast cancer because one of her relatives did, we need to know whether a family history of breast cancer is an important risk factor. Therefore, we need to know the following:

1. Of age, race, family history of breast cancer, number of pregnancies, experience of breast-feeding, and use of oral contraceptives — which are most important?
2. Can we predict, on the basis of the important risk factors, whether a woman will develop breast cancer or is more likely to develop breast cancer than another person?

In this chapter we introduce several methods for answering these questions. The general approach is to relate various patient characteristics (or independent variables, or covariates) to the occurrence of an event (dependent or response variable) on the basis of data collected from patients in each of the outcome groups. In the case of dichotomous outcomes, there are two outcome groups. For example, to relate variables such as age, race, and number of pregnancies to the development of breast cancer, we need to collect information about these variables from a group of breast cancer patients as well as from a group of healthy normal women. For an event with polychotomous outcomes, we need to collect data from each outcome group.

Often, a large number of patient characteristics deserve consideration. These characteristics may be demographic variables such as age; genetic variables such as gene variant or phenotype; behavioral variables such as smoking or drinking behavior and use of estrogen or progesterone medication; environmental variables such as exposure to sun, air pollution, or occupational dust; or clinical variables such as blood cell counts, weight, and blood pressure. The number of possible risk factors can be reduced through medical knowledge of the disease and careful examination of the possible risk factors individually.

In Section 14.1 we present two methods for examination of individual variables. One is to compare the distribution of each possible risk variable among the outcome groups. The other method is the chi-square test for a contingency table. This test is particularly useful when the risk variables are categorical: for example, dichotomous or trichotomous. In this case, a $2 \times c$ or $r \times c$ contingency table can be set up and a chi-square test performed. In Section 14.2 we discuss logistic, conditional logistic, and other regression models for binary responses and for examining the possible risk variables simultaneously. Models for multiple outcomes are discussed in Section 14.3.

14.1 UNIVARIATE ANALYSIS

14.1.1 Comparing the Distributions of Risk Variables Among Groups

When the outcome is binary, it is often convenient to call an observation a success or a failure. *Success* may mean that a survival-related event occurred, and *failure* that it failed to occur. Thus, a success may be a responding patient, a patient who survives more than five years after surgery, or a person who develops a given disease. A failure may be a nonresponding patient, a patient who dies within five years after surgery, or a person who does not develop a given disease. A preliminary examination of the data can compare the distribution of the risk variables in the success and failure groups. This method is especially appropriate if the risk variable is

Table 14.1 Ages of 71 Leukemia Patients (Years)

Responders	20, 25, 26, 26, 27, 28, 28, 31, 33, 33, 36, 40, 40, 45, 45, 50, 50, 53 56, 62, 71, 74, 75, 77, 18, 19, 22, 26, 27, 28, 28, 28, 34, 37, 47, 56, 19
Nonresponders	27, 33, 34, 37, 43, 45, 45, 47, 48, 51, 52, 53, 57, 59, 59, 60, 60, 61, 61, 61, 63, 65, 71, 73, 73, 74, 80, 21, 28, 36, 55, 59, 62, 83

Source: Hart et al. (1977). Data used by permission of the author.

continuous. If, for example, the risk factor x is weight and the dependent variable y is having cardiovascular disease, we may compare the weight distribution of patients who have developed disease to that of disease-free patients. If the disease group has significantly higher weights than those of the disease-free group, we may consider weight an important risk factor. Commonly used statistical methods for comparing two distributions are the t-test for two independent samples if the assumption of normality holds and the Mann–Whitney U-test if the normality assumption is violated and a nonparametric test is preferred.

Similarly, if there are more than two possible outcomes, we can use analysis of variance or the Kruskal–Wallis nonparametric test to compare the multiple distributions of a continuous variable. The following example compares the age distribution of responders with that of nonresponders in a cancer clinical trial.

Example 14.1 Consider the ages of 71 leukemia patients — 37 responders and 34 nonresponders (response is defined as a complete response only) — given in Table 14.1. Figure 14.1 gives us the estimated age distributions of the two groups. By using the Mann–Whitney U-test (or Gehan's generalized Wilcoxon test), we find that the difference in age between responders and nonresponders is statistically significant ($p < 0.01$). In consequence, a question may arise as to what age is critical. Can we say that patients under 50 may have a better chance of responding than do patients over 50? To answer this question, one can dichotomize the age data and use the chi-square test, discussed next.

14.1.2 Chi-Square Test and Odds Ratio

The chi-square test and the odds ratio are most appropriate when the independent variable is categorical. If the independent variable is dichotomous, a 2×2 table can be used to represent the data. Any variables that are not dichotomous can be made so (with a loss of some information) by choosing a cutoff point: for example, age less than 50 years. For multiple-outcome events, $2 \times c$ or $r \times c$ tables can be constructed. The independent

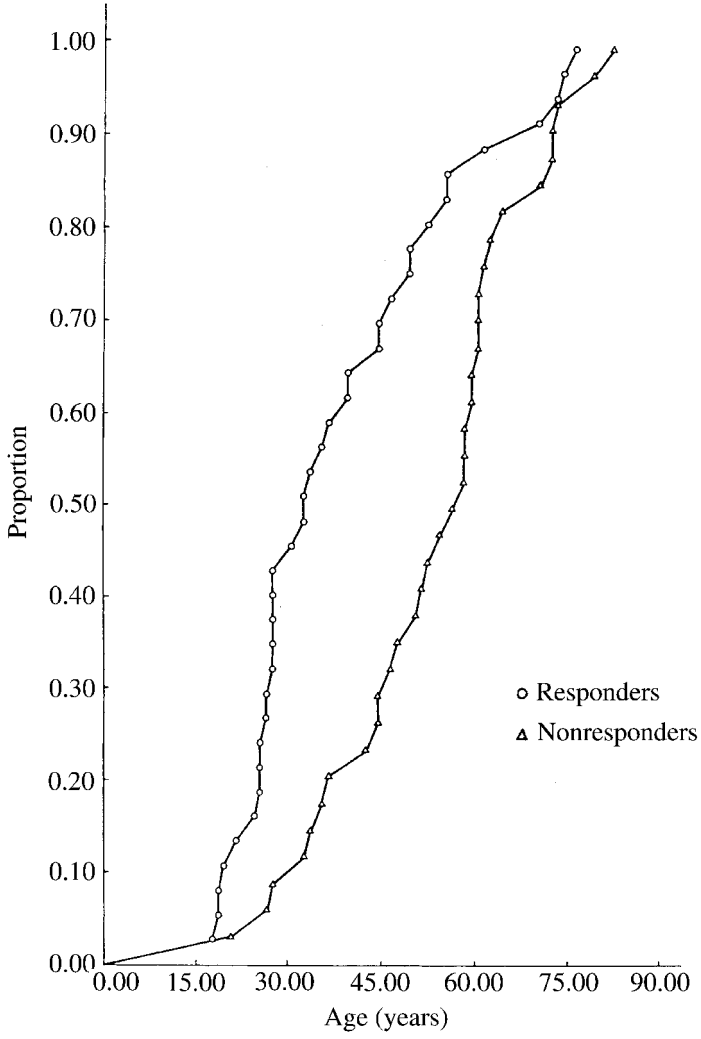


Figure 14.1 Age distribution of responders and nonresponders.

variables are then examined to find which ones (in some sense) provide the best risk associations with the dependent variable. We first consider binary outcomes and independent variables that have two categories; that is, we set up a 2×2 contingency table similar to Table 14.2 for each independent variable and look for a high degree of proportionality.

The first step is to calculate the sample proportion of successes in the two risk groups, a/C_1 and b/C_2. Further analysis of the table is concerned with the precision of these proportions. A standard chi-square test can be used.

Table 14.2 General Setup of a 2×2 Contingency Table

	Risk Factor		
	Present (E)	Absent ($\bar{E}$)	Total
Dependent variable			
Success	a	b	R_1
Failure	c	d	R_2
Total	C_1	C_2	N
Proportion of successes (success rate)	a/C_1	b/C_2	

If the rates of success for the two groups E and $\bar{E}$ are exactly equal, the *expected* number of patients in the ijth cell (ith row and jth column) is

$$E_{ij} = N \times \frac{R_i}{N} \times \frac{C_j}{N} = \frac{R_i \times C_j}{N} \tag{14.1.1}$$

For example, in the top left cell, the expected number is

$$E_{11} = \frac{R_1 \times C_1}{N}$$

since the overall success rate is R_1/N and there are C_1 individuals in the E group. Similar expected numbers can be obtained for each of the four cells. Let O_{ij} be the number of patients observed in the ijth cell. Then the discrepancies can be measured by the differences $(O_{ij} - E_{ij})$. In a rough sense, the greater the discrepancies, the more evidence we have against the null hypothesis that the success rates are the same for the two groups. The *chi-square test* is based on these discrepancies. Let

$$X^2 = \sum_{i=1}^{2} \sum_{j=1}^{2} \frac{(O_{ij} - E_{ij})^2}{E_{ij}} \tag{14.1.2}$$

Under the null hypothesis, X^2 follows the chi-square distribution with 1 degree of freedom (df). The hypothesis of equal success rates for groups E and $\bar{E}$ is rejected if $X^2 > \chi^2_{1,\alpha}$, where $\chi^2_{1,\alpha}$ is the 100α percentage point of the chi-square distribution with 1 degree of freedom. An alternative way to compute X^2 is

$$X^2 = \frac{(ad - bc)^2 N}{R_1 R_2 C_1 C_2} \tag{14.1.3}$$

The odds ratio (Cornfield, 1951) is a commonly used measure of association in 2×2 tables. The *odds ratio* (OR) is the ratio of two odds: the odds of success when the risk factor is present and the odds of success when the risk factor is absent. In terms of probabilities,

$$\text{OR} = \frac{P(\text{success} \mid E)/P(\text{failure} \mid E)}{P(\text{success} \mid \bar{E})/P(\text{failure} \mid \bar{E})} \tag{14.1.4}$$

Using the notation in Table 14.2, $P(\text{success} \mid E)$ and $P(\text{failure} \mid E)$ may be estimated by a/C_1 and c/C_1, respectively. Similarly, $P(\text{success} \mid \bar{E})$ and $P(\text{failure} \mid \bar{E})$ may be estimated, respectively, by b/C_2 and d/C_2. Therefore, the numerator and denominator of (14.1.4) may be estimated, respectively, by

$$\frac{a/C_1}{c/C_1} = \frac{a}{c}$$

and

$$\frac{b/C_2}{d/C_2} = \frac{b}{d}$$

Consequently, the OR may be estimated by

$$\widehat{\text{OR}} = \frac{a/c}{b/d} = \frac{ad}{bc} \tag{14.1.5}$$

which is also referred to as the *cross-product ratio.*

Several methods are available for an interval estimate of OR: for example, Cornfield (1956) and Woolf (1955). Cornfield's method, which requires an iterative procedure, is considered more accurate but more complicated than Woolf's method. Woolf suggests using the logarithm of OR. The standard error of $\log \widehat{\text{OR}}$ may be estimated by

$$\widehat{\text{SE}}(\log \widehat{\text{OR}}) = \left(\frac{1}{a} + \frac{1}{b} + \frac{1}{c} + \frac{1}{d}\right)^{1/2} \tag{14.1.6}$$

Then a $100(1 - \alpha)\%$ confidence interval (CI) for log OR is

$$\log \widehat{\text{OR}} \pm Z_{\alpha/2}\, \widehat{\text{SE}}(\log \widehat{\text{OR}})$$

The confidence interval for OR can be obtained by taking the antilog of the confidence limits for log OR. If $\log \text{OR}_U$ and $\log \text{OR}_L$ are the upper and lower

confidence limits for $\log \text{OR}$, $e^{\log \text{OR}_U}$ and $e^{\log \text{OR}_L}$ are the upper and lower confidence limits for OR.

Notice that in (14.1.5), if b or c is zero, $\widehat{\text{OR}}$ is undefined. If any one of the four cell frequencies is zero, the estimated standard error in (14.1.6) is also undefined. Should this occur, some statisticians (Haldane, 1956; Fleiss, 1979, 1981) suggest that 0.5 be added to each cell before using (14.1.5) and (14.1.6) to solve the computational problem. However, if the cell frequencies are as small as zero, the addition of 0.5 to each cell will substantially affect the resulting estimate of OR and its standard error (Mantel, 1977; Miettinen, 1979). The estimates so obtained must be interpreted with caution.

An odds ratio of 1 indicates that the odds of success are the same whether or not the risk factor is present. An odds ratio greater than 1 means that the odds in favor of success is higher when the risk factor is present, and therefore there is a positive association between the risk factor and success. Similarly, an odds ratio of less than 1 signifies a negative association between the risk factor and success. The interpretation should not be based totally on the point estimate. A confidence interval is always more meaningful, just as in any other estimation procedure.

The chi-square statistic in (14.1.2) may be used to test the null hypothesis that there is no association between the risk factor and success, or H_0: $\text{OR} = 1$. The following example illustrates the chi-square test and odds ratio.

Example 14.2 In the study of the response rate of 71 leukemia patients (Example 14.1), age is considered one of the possible risk variables. The following 2×2 table is constructed.

	Age < 50	Age $\geqslant 50$	Total
Response	27	10	37
Nonresponse	12	22	34
Total	39	32	71

The question is whether the response rates in the two age groups differ significantly or whether age is associated with response.

The X^2 value according to (14.1.3) is

$$X^2 = \frac{(594 - 120)^2(71)}{(37)(34)(39)(32)} = 10.16$$

with 1 degree of freedom. Reference to Table B-2 shows that the probability of

getting a X^2 value of 10.16 if the two response rates are equal in the population is less than 0.01. Hence the difference between the two response rates is significant at the 1% level.

The estimate odds ratio, according to (14.1.5), is

$$\text{OR} = \frac{(27)(22)}{(10)(12)} = 4.95$$

The data show that the odds in favor of response are almost five times higher in patients under 50 years of age than in patients at least 50 years old. The difference is significantly different, as indicated by the chi-square test above.

To obtain a confidence interval for OR, we first compute $\log \widehat{\text{OR}} = 1.60$. The estimated standard error of $\log \widehat{\text{OR}}$ following (14.1.6) is

$$\widehat{\text{SE}}(\log \widehat{\text{OR}}) = \left(\frac{1}{27} + \frac{1}{10} + \frac{1}{12} + \frac{1}{22}\right)^{1/2} = 0.515$$

A 95% confidence interval for log OR is $1.60 \pm 1.96(0.515)$, or (0.59, 2.61), and a 95% confidence interval for OR is $(e^{0.59}, e^{2.61})$, or (1.80, 13.60). The wide interval may be due to the small cell frequencies. Note that the standard error of $\log \widehat{\text{OR}}$ is inversely related to the cell frequencies.

In this example, the cutoff point, 50, was chosen arbitrarily. It is often of interest to try more than one cutoff point if the number of observations in each cell is not too small.

There are cases where the independent variable has $c > 2$ classes. The chi-square test can be extended to $2 \times c$ tables. The odds ratio method can also be extended to handle polychotomous independent variables. It is done by selecting one of the classes as the reference class (the $\bar{E}$ group) and calculating the measure of association of each of the other classes relative to the reference class. For multiple-outcome events, the chi-square test can be extended to $r \times c$ tables. The expected frequencies are computed just as in (14.1.1), and computation of X^2 [chi-square distributed with $(r-1)(c-1)$ degrees of freedom] is the same as in (14.1.2) except that the sum is over all $r \times c$ cells. For details, see Snedecor and Cocharan (1967, Sec. 9.7). The following example illustrates the procedures.

Example 14.3 Suppose that in the study of response rates of leukemia patients, another possible risk variable is the *marrow absolute leukemic infiltrate*, which is defined as the percentage of the total marrow that is either blast cells or promyelocytes. It is believed that patients should be classified into three classes: $\leqslant 45\%$, 46–90%, and $> 90\%$. The 2×3 table is given below. Numbers in parentheses are expected frequencies. For example, $18.68 = (39)(34)/71$.

	Marrow Absolute Infiltrate			
	$\leqslant 45\%$	46–90%	$>90\%$	Total
Response	4 (8.34)	20 (20.32)	13 (8.34)	37
Nonresponse	12 (7.66)	19 (18.68)	3 (7.66)	34
Total	16	39	16	71
Response rate, (%)	25	51	81	
$\widehat{\text{OR}}$	1	3.16	13.0	
95% CI for OR		(0.86, 11.52)	(2.40, 70.46)	

The question is whether the difference in marrow absolute leukemic infiltrate is related to response. The value of X^2 is

$$X^2 = \frac{(4 - 8.34)^2}{8.34} + \frac{(12 - 7.66)^2}{7.66} + \cdots + \frac{(3 - 7.66)^2}{7.66} = 10.17$$

The number of degrees of freedom is $3 - 1 = 2$. With $X^2 = 10.17$ and 2 degrees of freedom, the probability that the three absolute infiltrate groups have the same response rate is less than 0.01. The data suggest that patients with a high percentage of marrow absolute infiltrate tend to have a high response rate. Marrow absolute infiltrate may be an important factor in predicting response.

The $\widehat{\text{OR}}$s given in the table above are calculated using the $\leqslant 45\%$ class as the reference class (or group). For example, for the $>90\%$ class, the odds ratio is $13 \times 12/4 \times 3 = 13$. The 95% confidence intervals for the ORs are obtained using (14.1.6). Although the odds ratio for the 46–90% group is larger than 1, the 95% confidence intervals covers 1. Therefore, the point estimate, 3.16, cannot be taken too seriously. It appears that the major difference is between the $>90\%$ and $\leqslant 45\%$ groups.

Individual examination of each independent variable can provide only a preliminary idea of how important each variable is by itself. The relative importance of all the variables has to be examined simultaneously using multivariate methods. In the following section we discuss the linear logistic regression analysis.

14.2 LOGISTIC AND CONDITIONAL LOGISTIC REGRESSION MODELS FOR DICHOTOMOUS RESPONSES

14.2.1 Logistic Regression Model for Prospective Studies

In a typical prospective study, a random sample of subjects is taken and the values of the independent variables are measured at a given time (usually called *baseline measurements*). The subjects are then followed for a given period of

time and the outcome (dependent) variable is measured at the end of the follow-up. Therefore, for a prospective study, the independent variables are regarded as fixed quantities during the follow-up, but the outcomes are random and unknown. The purpose of a prospective study is to examine the outcomes and relate them to the baseline measurements. Examples of prospective studies are cohort epidemiologic studies and clinical trials.

Suppose that there are n subjects and to some of whom the event of interest occurred. They are called successes; the others are failures. Let $y_i = 1$ if the ith subject is a success and $y_i = 0$ if the ith subject is a failure. Suppose that for each of the n subjects, p independent variables $x_{i1}, x_{i2}, \ldots, x_{ip}$ are measured. These variables can be either qualitative, such as gender and race, or quantitative, such as blood pressure and white blood cell count. The problem is to relate the independent variables, $x_{i1}, \ldots, x_{ip}$, to the dichotomous dependent variable y_i.

Let P_i be the probability of success, $P_i = P(y_i = 1 \mid x_{i1}, \ldots, x_{ip})$, for the ith subject. The logistic regression model, proposed by Cox (1970) assumes that the dependence of the probability of success on independent variables is

$$P_i = P(y_i = 1 \mid \mathbf{x}_i) = \frac{\exp(\sum_{j=0}^{p} b_j x_{ij})}{1 + \exp(\sum_{j=0}^{p} b_j x_{ij})} \tag{14.2.1}$$

and

$$1 - P_i = P(y_i = 0 \mid \mathbf{x}_i) = \frac{1}{1 + \exp(\sum_{j=0}^{p} b_j x_{ij})} \tag{14.2.2}$$

where $\mathbf{x}_i = (x_{i0} \cdots x_{ip})$, $x_{i0} \equiv 1$, and b_j are unknown coefficients. The logarithm of the ratio of P_i and $1 - P_i$ is a simple linear function of the x_{ij}'s.

Let

$$\lambda_i = \log \frac{P_i}{1 - P_i} = \sum_{j=0}^{p} b_j x_{ij} \tag{14.2.3}$$

$\lambda_i = \log[P_i/(1 - P_i)]$ is called the *logistic transform* of P_i and (14.2.3) is a linear logistic model. Another name for λ_i is *log odds*. Thus, the model relates the independent variables to the logistic transform of P_i, or log odds. The probability of success P_i can then be found from (14.2.3) or (14.2.1). In many ways (14.2.3) is the most useful analog for dichotomous response data of the ordinary regression model for normally distributed data.

To estimate the coefficients b_j's, Cox suggests the maximum likelihood method. Let $y_1, y_2, \ldots, y_n$ be observations with dichotomous values on n subjects. The likelihood function based on the binomial distribution contains a factor (14.2.1) whenever $y_i = 1$ and (14.2.2) whenever $y_i = 0$. Thus, the likeli-

hood function is

$$L(b_0, b_1, \ldots, b_p) = \prod_{i=1}^{n} P_i^{y_i}(1 - P_i)^{1-y_i}$$
$$= \frac{\prod_{i=1}^{n} \exp(y_i \sum_{j=0}^{p} b_j x_{ij})}{\prod_{i=1}^{n}[1 + \exp(\sum_{j=0}^{p} b_j x_{ij})]} = \frac{\exp(\sum_{j=0}^{p} b_j t_j)}{\prod_{i=1}^{n}[1 + \exp(\sum_{j=0}^{p} b_j x_{ij})]} \tag{14.2.4}$$

where $t_j = \sum_{i=1}^{n} x_{ij} y_i$. The log-likelihood function is

$$l(b_0, b_1, \ldots, b_p) = \log L = \sum_{j=0}^{p} b_j t_j - \sum_{i=1}^{n} \log\left[1 + \exp\left(\sum_{j=0}^{p} b_j x_{ij}\right)\right] \tag{14.2.5}$$

The maximum likelihood estimates of b_j's that maximize the log-likelihood function in (14.2.5) can be obtained by solving the following p equations simultaneously:

$$t_j - \sum_{i=1}^{n} \frac{x_{ij} \exp(\sum_{j=0}^{p} b_j x_{ij})}{1 + \exp(\sum_{j=0}^{p} b_j x_{ij})} = 0 \qquad j = 0, 1, \ldots, p \tag{14.2.6}$$

This can be done by an iterative procedure such as the Newton–Raphson procedure. The second derivative of l in (14.2.5) is

$$I^*_{j_1 j_2} = \frac{\partial^2 l}{\partial b_{j_1} \partial b_{j_2}} = -\sum_{i=1}^{n} \frac{x_{ij_1} x_{ij_2} \exp(\sum_{j=0}^{p} b_j x_{ij})}{1 + \exp(\sum_{j=0}^{p} b_j x_{ij})}$$
$$j_1 = 0, \ldots, p; \quad j_2 = 0, \ldots, p \tag{14.2.7}$$

Let $I_{j_1 j_2} = (-1) I^*_{j_1 j_2}$. Then the estimated inverse of the I matrix, $\hat{I}^{-1}$, is the asymptotic covariance matrix of the b_j's. If we use the notation in Section 7.1 and let $\hat{\mathbf{b}} = (\hat{b}_0, \hat{b}_1, \ldots, \hat{b}_p)'$ denote the MLE of $\mathbf{b}$, the estimated covariance matrix of the MLE $\hat{\mathbf{b}}$ is $\hat{V}(\hat{\mathbf{b}}) = (v_{ij}) = (-\partial^2 l(\hat{\mathbf{b}})/\partial \mathbf{b}\, \partial \mathbf{b}')^{-1} = \hat{I}^{-1}$, where v_{ij} denotes the ijth element of $\hat{V}(\hat{\mathbf{b}})$ or the ijth element of $\hat{I}^{-1}$.

The coefficients so obtained indicate the relationships between the variables and the log odds in favor of success. For a continuous variable, the corresponding coefficient gives the change in the log odds for an increase of 1 unit in the variable. For a categorical variable, the coefficient is equal to the log odds ratio (see Section 14.1).

An approximate $100(1 - \alpha)\%$ confidence interval for b_j is

$$\hat{b}_j \pm Z_{\alpha/2} \sqrt{v_{jj}} \tag{14.2.8}$$

where $Z_{\alpha/2}$ is the $100(1 - \alpha/2)$ percentile of the standard normal distribution.

To test the hypothesis that some of the b_j's are zero, a likelihood ratio test can be used. For example, to test $H_0: b_j = 0$, the log-likelihood ratio test statistic is

$$X_L = -2[l(\hat{b}_0, \hat{b}_1, \ldots, \hat{b}_{j-1}, 0, \hat{b}_{j+1}, \ldots, \hat{b}_p) - l(\hat{b}_0, \hat{b}_1, \hat{b}_2, \ldots, \hat{b}_p)] \tag{14.2.9}$$

where the first term is the maximized log-likelihood subject to the constraint $b_j = 0$. If the hypothesis is true, X_L is distributed asymptotically as chi-square with 1 degree of freedom.

An alternative test for the significance of the coefficients is the *Wald test*, which can be written as

$$X_W = \frac{\hat{b}_j^2}{v_{jj}} \tag{14.2.10}$$

Under the null hypothesis that $b_j = 0$, X_W has an asymptotic chi-square distribution with 1 degree of freedom. Although the Wald test is used by many, it is less powerful than the likelihood ratio test (Hauck and Donner, 1977; Jennings, 1986). In other words, the Wald test often leads the user to conclude that the coefficient (consequently, the respective risk factor) is not significant when, in fact, it is significant.

Similar to earlier discussion of model selection, forward, backward, and stepwise variable selection methods can be used to select the risk factors that are significantly associated with a dichotomous response. The independent variables x_{ij} in this model do not have to be the original variables. They can be any meaningful transforms of the original variables: for example, the logarithm of the original variable, $\log x_{ij}$, and the deviation of the variable from its mean, $x_{ij} - \bar{x}_j$.

From (14.2.1) and (14.2.2), the logarithm of the odds ratio for ith and kth subjects is

$$\log \frac{P_i/(1 - P_i)}{P_k/(1 - P_k)} = \sum_{j=1}^{p} b_j(x_{ij} - x_{kj}) \tag{14.2.11}$$

Thus, an estimate of the odds ratio can be obtained by replacing b_j in (14.2.11) with its MLE, $\hat{b}_j$.

From the estimated regression equation, a predicted probability of success can be computed by substituting the values of the risk factors in the equation. Using these predicted probabilities, a goodness-of-fit test can be performed to test the hypothesis that the model fits the data adequately. Several such tests are available (Lemeshow and Hosmer, 2000): for example, the Pearson chi-square test, the Hosmer–Lemeshow (Hosmer and Lemeshow, 1980) test, a test statistic suggested by Tsiatis (1980), and the score of Brown (1982). In the following, we introduce the *Hosmer–Lemeshow* test.

Let p_i be the estimate of P_i obtained from the fitted logistic regression equation for the ith subject, $i = 1, \ldots, n$. The p_i's can be arranged in ascending order from smallest to largest. Those probabilities and the corresponding subjects are then divided into g groups according to some cutoff points of the probability. For example, let $g = 10$ and the cutoff points of the probability be equal to $k/10$, $k = 1, 2, \ldots, 10$. Thus, the first group contains all subjects whose estimated probabilities are less than or equal to 0.1, the second group contains all subjects whose estimated probabilities are less than or equal to 0.2, and so on. Let n_k be the number of subjects in the kth group. The estimated expected number of successes for the kth group is

$$E_k = \sum_{j=1}^{n_k} p_j \qquad k = 1, 2, \ldots, g$$

The Hosmer–Lemeshow test statistic is defined as

$$C = \sum_{k=1}^{g} \frac{(O_k - E_k)^2}{n_k \bar{p}_k (1 - \bar{p}_k)} \tag{14.2.12}$$

where O_k is the observed number of successes in the kth group and $\bar{p}_k$ is the average estimated probability of the kth group, that is,

$$\bar{p}_k = \frac{1}{n_k} \sum_{j=1}^{n_k} p_j$$

Under the null hypothesis that the model is adequate, the distribution of C in (14.2.12) is well approximated by the chi-square distribution with $g - 2$ degrees of freedom. The test is basically a chi-square test of the discrepancy between the observed and predicted frequencies of success. Thus, a C value larger than the 100α percentage point of the chi-square distribution (or p value less than α) indicates that the model is inadequate.

Similar to other chi-square goodness-of-fit tests, the approximation depends on the estimated expected frequencies being reasonably large. If a large number (say, far more than 20%) of the expected frequencies are less than 5, the approximation may not be appropriate and the p value must be interpreted carefully. If this is the case, adjacent groups may be combined to increase the estimated expected frequencies. However, Hosmer and Lemeshow warn that if fewer than six groups are used to calculate C, the test would be insensitive and would almost always indicate that the model is adequate.

Most statistical software packages provide programs for logistic regression analysis: for example, SAS (procedures LOGISTIC, PHREG, and CATMOD), BMDP (procedures LR and PR), and SPSS (procedures NOMREG, PROBIT, PLUM, and LOGISTIC). Most of them provide estimates of the coefficients and test statistics, variable selection procedures, and tests of goodness of fit.

Example 14.4 In a study of 238 non-insulin-dependent diabetic patients, 10 covariates are considered possible risk factors for proteinuria (the outcome variable). The logistic regression method is used to identify the most important risk factors and to predict the probability of proteinuria on the basis of these risk factors. The 10 potential risk factors are age, gender (1, male; 2, female), smoking status (0, no; 1, yes), percentage of ideal body mass index, hypertension (0, no; 1, yes), use of insulin (0, no; 1, yes), glucose control (0, no; 1, yes), duration of diabetes mellitus (DM) in years, total cholesterol, and total triglyceride. Among the 238 patients, 69 have proteinuria ($y_i = 1$).

Using the stepwise procedure in BMDP, it is estimated that at step 1, the model contains only b_0 and $\hat{b}_0 = -0.896$ and $l(\hat{b}_0)$ in (14.2.5) is -143.292. At step 2, duration of diabetes is added to the model because its maximum log-likelihood value is the largest among all the covariates. The MLEs of the two coefficients are $\hat{b}_0 = -1.467$ and $\hat{b}_1 = -0.055$, and $l(\hat{b}_0, \hat{b}_1) = -139.429$. Since

$$X_L = -2[l(\hat{b}_0) - l(\hat{b}_0, \hat{b}_1)] = 7.726$$

which is significant ($p = 0.005$), the duration of DM is related significantly to the chance of proteinuria. The Hosmer–Lemeshow test statistic for goodness of fit with only duration of DM in the model, $C = 9.814$ with 8 degrees of freedom, gives a p value of 0.278.

At step 3, gender is added to the model because its addition yields the largest maximum log-likelihood value among all the remaining covariates. The maximum log-likelihood value, $l(\hat{b}_0, \hat{b}_1, \hat{b}_2) = -137.749$, $\hat{b}_0 = -1.453$, $\hat{b}_1 = -0.060$, and $\hat{b}_2 = -0.279$. To test if gender is significantly related to proteinuria after duration of DM, we perform the likelihood ratio test

$$X_L = -2[l(\hat{b}_0, \hat{b}_1) - l(\hat{b}_0, \hat{b}_1, \hat{b}_2)] = 3.360$$

which is significant at $p = 0.067$. The stepwise procedure terminates after the third step because no other covariates are significant enough to enter the regression model; that is, none of the other covariates have a p value less than 0.15, which is set by the program (BMDP). If any covariate already in the regression becomes insignificant after some other variables are in, the insignificant variable would be removed. The p values for entering and removing a variable can be determined by the user. The default values for entering and removing a variable are, respectively, 0.10 and 0.15. Thus, the procedure identifies duration of DM and gender as the two most important risk factors based on the data given. A question that may be raised at this point is whether one should include gender in the equation since its significance level is larger than the commonly used 0.05. The recommendation is to include it since it is close to 0.05 and since the p value should not be the only basis for determining whether a covariate should be included in the model. In addition, the Hosmer–Lemeshow goodness of fit test statistic $C = 5.036$, when gender is

Table 14.3 Estimated Coefficients for a Linear Logistic Regression Model Using Data from Diabetic Patients

Variable	Estimated Coefficient	Standard Error	Coefficient/SE	exp(coefficient)
Constant	−1.453	0.264	−5.504	0.234
Duration of DM	0.060	0.020	2.956	1.062
Sex	−0.279	0.152	−1.836	0.756

included, yields a p value of 0.754. Thus, inclusion of this covariate improves considerably the adequacy of the model. Thus, the final regression equation with the two significant risk factors is

$$\log \frac{P_i}{1-P_i} = -1.453 + 0.060 \text{ (duration of DM)} - 0.279 \text{ (gender)}$$

Table 14.3 gives the details for the estimated coefficients.

The signs of the coefficients indicate that male patients and patients with a longer duration of diabetes have a higher chance of proteinuria. Furthermore, for each increase of one year in duration of diabetes, the log odds increase by 0.060. Probabilities of proteinuria can be estimated following (14.2.1). For example, the probability of developing proteinuria for a male patient who has had diabetes for 15 years is

$$P = \frac{e^{-0.832}}{1+e^{-0.832}} = 0.303$$

where -0.832 is obtained by substituting the values of the two covariates in the fitted equation; that is, $-1.453+0.060(15)-0.279(1) = -0.832$. Similarly, for a female patient who has the same duration of diabetes, the probability is 0.248.

In addition to individual variables, interaction terms can be included in the logistic regression model. If the association between an independent variable x_1 and the dependent variable y is not the same in different levels of another variable, x_2, there is interaction between x_1 and x_2. To check if there is interaction, one can include the product of x_1 and x_2 in the regression model and test the significance of this new variable. The following example illustrates the procedure.

Example 14.5 It is well known that adriamycin is effective for treating certain types of cancer. It is also well known that adriamycin is highly toxic.

Some patients develop congestive heart failure (CHF), but others who receive a similar dose of adriamycin do not. In an attempt to detect factors that would increase the risk of developing adriamycin cardotoxicity, various patient characteristics of 53 cancer patients were studied. Seventeen of these patients developed CHF and 36 patients did not. After a careful investigation, it was found that the total dose (z_1) and percentage decrease in electrocardiographic QRS voltage (z_2) are most closely related to CHF. Table 14.4 shows the data and some summary statistics. The following linear logistic regression model with transformed variables $x_1 = z_1 - \bar{z}_1$ and $x_2 = z_2 - \bar{z}_2$ is used:

$$\lambda = \log \frac{p}{1-p} = b_0 + b_1 x_1 + b_2 x_2 + b_3 x_1 x_2$$

The stepwise procedure selects percentage decrease in QRS as the most important variable, followed by the total dose (TD) and interaction (TD $\times$ QRS). The logistic regression analysis results are given in Table 14.5. The stepwise log-likelihood values given in the last column indicate that only QRS is significant since $2(-10.185 + 33.254) = 46.138$, which yields a p value less than 0.001. Neither the total dose nor the interaction is significant.

Suppose that the last three columns of Table 14.4, Y, Z1, and Z2, are stored in a text data file "C:\EX14d2d2.DAT", separated by a space. The following SAS, SPSS, or BMDP codes can be used to obtain the results in Table 14.5.

SAS code:

```
data w1;
  infile 'c:\ex14d2d2.dat' missover;
  input y z1 z2;
  x1 = z1-517.679;
  x2 = z2-26.019;
  x12 = x1*x2;
run;
proc logistic data = w1 descending;
  model y =  x1 x2 x12/ selection = s plcl plrl lackfit;
run;
```

SPSS code (forward selection method):

```
data list file = 'c:\ex14d2d2.dat' free
        / y z1 z2.
Compute x1 = z1-517.679.
Compute x2 = z2-26.019.
Compute x12 = x1*x2.
Logistic regression y with x1 x2 x12
        /method = fstep
        /print = all.
```

Table 14.4 Total Dose and Percent Decrease in QRS of 53 Patients Receiving Adriamycin

Patient	CHF[a], y	Total Dose, z_1	Percent Decrease in QRS, z_2
1	1	435	41
2	1	600	71
3	1	600	51
4	1	540	40
5	1	510	63
6	1	740	79
7	1	825	61
8	1	535	44
9	1	510	53
10	1	483	27
11	1	460	53
12	1	460	60
13	1	550	65
14	1	540	58
15	1	310	41
16	1	500	64
17	1	400	44
18	0	440	9
19	0	600	42
20	0	510	19
21	0	410	24
22	0	540	−24
23	0	575	39
24	0	564	35
25	0	450	10
26	0	570	6
27	0	480	6
28	0	585	21
29	0	420	14
30	0	470	1
31	0	540	33
32	0	585	33
33	0	600	4
34	0	570	2
35	0	570	5
36	0	510	12
37	0	470	−1
38	0	405	44
39	0	575	14
40	0	540	−10
41	0	500	−43
42	0	450	23
43	0	520	−1

(*Continued overleaf*)

Table 14.4 *Continued*

Patient	CHF[a], y	Total Dose, z_1	Percent Decrease in QRS, z_2
44	0	495	29
45	0	585	40
46	0	450	30
47	0	450	23
48	0	500	12
49	0	540	−11
50	0	440	7
51	0	480	−22
52	0	550	20
53	0	500	19

Source: Minow et al. (1977).

[a] 1, yes; 0, no; $\bar{z}_1 = 517.679$, $\bar{z}_2 = 26.019$.

BMDP codes for procedure LR:

```
/input      file = 'c:\ex14d2d2.dat' .
            variables = 3.
            format = free.
/variable   names =  y, z1, z2.
/transform  x1 = z1-517.679.
            x2 = z2-26.019.
            x12 = x1*x2.
/regress    depend = y.
            Interval = x1, x2, x12.
            Model =  x1, x2, x12.
            Start = in, in, in.
            Move = 0, 0, 0.
```

Table 14.5 Linear Logistic Regression Analysis Results of Data in Table 14.4

Variable	Estimated Coefficient	Standard Error	Coefficient/SE	Log Likelihood
Constant	−3.757	1.576	−2.384	−33.254
QRS	0.254	0.102	2.480	−10.185
TD	−0.024	0021	−1.160	−9.225
TD × QRS	0.001	0.001	0.677	−8.803

```
          Method = mlr.
/print    cell = used.
/end
```

When the independent variables are dichotomous or polychotomous, the logistic regression coefficients can be linked with odds ratios. Consider the simplest case, where there is one independent variable, x_1, which is either 0 or 1. The linear regression model in (14.2.1) and (14.2.2) becomes

$$P(y = 1 \mid x_1) = \frac{e^{b_0 + b_1 x_1}}{1 + e^{b_0 + b_1 x_1}}$$

$$P(y = 0 \mid x_1) = \frac{1}{1 + e^{b_0 + b_1 x_1}}$$

Values of the model when $x_1 = 0, 1$ are

$$P(y = 1 \mid x_1 = 0) = \frac{e^{b_0}}{1 + e^{b_0}}$$

$$P(y = 1 \mid x_1 = 1) = \frac{e^{b_0 + b_1}}{1 + e^{b_0 + b_1}}$$

$$P(y = 0 \mid x_1 = 0) = \frac{1}{1 + e^{b_0}}$$

$$P(y = 0 \mid x_1 = 1) = \frac{1}{1 + e^{b_0 + b_1}}$$

The odds ratio in (14.1.4) is

$$\text{OR} = \frac{P(y = 1 \mid x_1 = 1)/P(y = 0 \mid x_1 = 1)}{P(y = 1 \mid x_1 = 0)/P(y = 0 \mid x_1 = 0)} = \frac{e^{b_0 + b_1}}{e^{b_0}} = e^{b_1}$$

and the log odds ratio is $\log(\text{OR}) = \log(e^{b_1}) = b_1$ [this can also be derived directly from (14.2.11)]. Thus, the estimated logistic regression coefficient also provides an estimate of the odds ratio, that is, $\widehat{\text{OR}} = e^{\hat{b}_1}$. If (b_{1L}, b_{1U}) is the confidence interval for b_1, the corresponding interval for OR is $(e^{b_{1L}}, e^{b_{1U}})$.

Example 14.6 Consider the age (x) and response (y) data from the 71 leukemia patients presented in Table 14.6 (Examples 14.1 and 14.2). The logistic regression analysis results are given in Table 14.7. Notice that $\exp(b_1) = \exp(1.5994) = 4.95$, which is equal to the estimate of OR obtained in Example 14.2 using (14.1.5), and the standard error of $\hat{b}_1$ is the same as that of $\log \widehat{\text{OR}}$ except for a small rounding-off error. The confidence interval for OR can also be obtained from the logistic regression analysis results.

Table 14.6 Age and Response Data of 71 Leukemia Patients

Response	$x < 50(1)$	$x \geqslant 50(0)$	Total
Yes (1)	27	10	37
No (0)	12	22	34
Total	39	32	71

Table 14.7 Results of Logistic Regression Analysis of Data in Table 14.6

Variable	Estimated Coefficient	Standard Error	Coefficient/SE	exp(coefficient)
Constant ($\hat{b}_0$)	−0.7885	0.3814	−2.067	0.45
Age($\hat{b}_1$)	1.5994	0.5156	3.102	4.95

The relationship between the logistic regression coefficient and odds ratio can be extended to polychotomous variables by creating dummy variables (or design variables). The following example illustrates the procedure.

Example 14.7 Consider the data in Example 14.3. The variable marrow absolute infiltrate (MAI) has three levels. As in Example 14.3, the $\leqslant 45\%$ level is considered as the reference group. In this case, two design variables will be used and their values are assigned as follows:

$$D_1 = \begin{cases} 1 & \text{if MAI} = 46\text{–}90\% \\ 0 & \text{otherwise} \end{cases} \qquad D_2 = \begin{cases} 1 & \text{if MAI} > 90\% \\ 0 & \text{otherwise} \end{cases}$$

For MAI, the design variable values and the respective number of responders (Event) and total number of patient in each MAI level (N) are listed in the following table.

MAI(%)	D_1	D_2	Event	N
$\leqslant 45$	0	0	4	16
46–90	1	0	20	39
>90	0	1	13	16

Using these design variables, the logistic regression analysis gives the results in Table 14.8.

Table 14.8 Results of Logistic Regression Analysis of Data in Example 14.7 and Two Design Variables

Variable	Estimated Coefficient	Standard Error	Coefficient/SE	exp(coefficient)
Constant	−1.0986	0.5774	−1.903	0.33
MAI (D_1)	1.1499	0.6603	1.742	3.16
MAI (D_2)	2.5649	0.8623	2.974	13.00

The coefficient corresponding to D_1, 1.1499, is the log odds ratio between the 46–90% group and the $\leqslant$45% group. The odds ratio is exp(1.1499) = 3.16, which is exactly equal to the estimate obtained in Example 14.3. Similarly, the coefficient corresponding to D_2 is the log odds ratio between the $>$90% group and the $\leqslant$45% group. The odds ratio obtained from the regression coefficient, 13.00, is the same as that obtained in Example 14.3.

The estimated standard error for D_1, 0.6603, is also the standard error of $\log\widehat{\text{OR}}$. A 95% confidence interval for the coefficient is $1.1499 \pm 1.96(0.6603)$, or (−0.1443, 2.4441), and consequently, a 95% confidence interval for OR is $(e^{-0.1443}, e^{2.4441})$, or (0.86, 11.52), which is identical to that obtained in Example 14.3 using Woolf's estimate of SE(log OR).

Suppose that the data in Example 14.6 are arranged in four columns for D_1, D_2, Event, and N as in the table above and are saved in a text data file "C:\EX14d2d4.DAT". The values of D_1, D_2, Event, and N in each row are separated by a space. The following SAS, SPSS, or BMDP codes can be used to obtain the results in Table 14.8.

SAS code:

```
data w1;
  infile 'c:\ex14d2d4.dat' missover;
  input d1 d2 event n;
run;
proc logistic data = w1 ;
  model event/n =  d1 d2 / plcl plrl;
run;
```

SPSS code:

```
data list file = 'c:\ex14d2d4.dat' free
        / d1 d2 event n.
Probit event OF n WITH d1 d2
        /model = logit
        /log = 2.718
        /print = all.
```

BMDP code for procedure LR:

```
/input      file = 'c:\ex14d2d4.dat' .
            variables = 4.
            format = free.
/variable   names =  d1, d2, event, n.
/regress    count is n.
            fcount is event.
            Interval = d1, d2.
/print      cell = used.
/end
```

For a continuous independent variable, the logistic regression coefficient gives the change in log odds for an increase of 1 unit in the variable. In general, for an increase of m units in the variable, the log odds ratio is equal to m times the logistic regression coefficient. The derivation is left to the reader as an exercise.

When more than one independent variable is included in the logistic regression model, each estimated coefficient can be interpreted as an estimate of the log odds ratio statistically adjusting for all the other variables. For example, in Example 14.4, the regression coefficient for the gender variable, -0.279, is an estimate of the log odds ratio for females versus males, adjusting for duration of diabetes. Or the adjusted odds ratio for females versus males is estimated as $\exp(-0.279) = 0.76$; suggesting that female diabetic patients have a lower risk of having proteinuria than that of male patients, after adjusting for duration of diabetes. This interpretation, commonly used by epidemiologists, is appropriate if the linear relationship between the log odds and the independent variables holds.

Press and Wilson (1978) compare the logistic regression method to the discriminant analysis and find that if the independent variables are normal with identical covariance matrices, discriminant analysis is preferred. Under abnormality, the logistic regression method is preferred. In particular, if the independent variables are dichotomous, we cannot expect to predict accurately the probability of success with a discriminant function, even with a large amount of data. Their examples show that the logistic regression gives a higher correct classification rate.

14.2.2 Logistic and Conditional Logistic Regression Model for Retrospective Studies

As mentioned earlier, the logistic regression model defined in (14.2.3) is originally designed for prospective studies, where a set of covariates or independent variables are measured at a baseline examination on a group of people without the disease of interest. These subjects are then followed for a period of time and development of the disease among them are recorded during

follow-up. The model can be extended to analyze data from retrospective studies, such as a case–control study. In a *case–control study*, cases (subjects with the disease of interest) and controls (subjects without the disease) are first selected and risk factor data such as exposure variables and other covariates are collected retrospectively. For example, in a case–control study of lung cancer and cigarette smoking, a group of lung cancer patients and a group of people without lung cancer are selected. Their smoking histories are then collected along with other risk factors. Therefore, in a case–control study, participants are selected first based on their disease status, and their history of risk factor exposures is collected later. The purpose of a case–control study is to estimate the association between the risk factors and the disease under study. Using probability terms, we are dealing with the probability that the risk factors take on certain values given that a person is a case or a control. We denote this conditional probability by $P(\mathbf{x} \mid y)$, where $\mathbf{x}$ denote the covariates and y the outcome variable. Using the same notation, the probability of interest in a prospective study is $P(y \mid \mathbf{x})$. Based on conditional probability theory, $P(\mathbf{x} \mid y)$ can be written as

$$P(\mathbf{x} \mid y) = \frac{P(y \mid \mathbf{x})P(\mathbf{x})}{P(y)} \tag{14.2.13}$$

where $y = 1$ for cases and 0 for controls. Thus, $P(\mathbf{x} \mid y)$ is a function of $P(y \mid \mathbf{x})$, $P(\mathbf{x})$, and $P(y)$.

The likelihood function of the logistic regression model for a retrospective study, similar to (14.2.4), is the product of terms in the form of $P(\mathbf{x} \mid y)$ in (14.2.13) for the cases and controls selected [($P(\mathbf{x} \mid y = 1)$ from a case and $P(\mathbf{x} \mid y = 0)$ from a control)]. We introduce here two most widely used approaches to this likelihood function. One approach considers the probability of case/control selection. Since in case–control studies, the cases and controls are selected from the population and the likelihood function is based on subject selection, we introduce an indicator variable to denote whether a person is selected ($s = 1$) or is not selected ($s = 0$). Let n_1 and n_0 be, respectively, the numbers of selected cases and controls in the study. The likelihood function is

$$L_{\text{cc}} = \prod_{i=1}^{n_1} P(\mathbf{x}_i \mid y_i = 1, s = 1) \prod_{i=1}^{n_0} P(\mathbf{x}_i \mid y_i = 0, s = 1) \tag{14.2.14}$$

Define

$$\pi_1 = P(s = 1 \mid y = 1)$$

to be the probability that a diseased person is selected for the study as a case and

$$\pi_0 = P(s = 1 \mid y = 0)$$

to be the probability that a disease-free person is selected for the study as a control. Assume that the sampling probabilities depend only on disease status and not on the covariates. Using Bayes' theorem in probability theory and (14.2.1), it can be shown (the derivation is left to the reader as an exercise) that the probability that a person is diseased given that he or she has risk factors $\mathbf{x}$ and was selected for the study can be written as

$$P(y_i = 1 \mid \mathbf{x}_i, s = 1) = \frac{\exp(b_0^* + \sum_{j=1}^{p} b_j x_{ij})}{1 + \exp(b_0^* + \sum_{j=1}^{p} b_j x_{ij})} \tag{14.2.15}$$

where

$$b_0^* = b_0 + \log \frac{\pi_1}{\pi_0} \tag{14.2.16}$$

According to the conditional probability in (14.2.13), the first term in the likelihood function in (14.2.14) is

$$P(\mathbf{x}_i \mid y_i = 1, s = 1) = \frac{\exp(b_0^* + \sum_{j=1}^{p} b_j x_{ij})}{1 + \exp(b_0^* + \sum_{j=1}^{p} b_j x_{ij})} \left[\frac{P(\mathbf{x}_i \mid s = 1)}{P(y = 1 \mid s = 1)} \right] \tag{14.2.17}$$

Similarly, the second term in (14.2.14) for $y_i = 0$ can be obtained:

$$P(\mathbf{x}_i \mid y_i = 0, s = 1) = \frac{1}{1 + \exp(b_0^* + \sum_{j=1}^{p} b_j x_{ij})} \left[\frac{P(\mathbf{x}_i \mid s = 1)}{P(y = 0 \mid s = 1)} \right] \tag{14.2.18}$$

Substituting (14.2.17) and (14.2.18) into (14.2.14), we obtain the likelihood function for a case–control study:

$$L_{cc} = L(b_0^*, b_1, \ldots, b_p) \times \prod_{i=1}^{n} \frac{P(\mathbf{x}_i \mid s = 1)}{P(y \mid s = 1)} \tag{14.2.19}$$

where $n = n_0 + n_1$, $L(b_0^*, b_1, \ldots, b_p)$ is the likelihood function for prospective studies in (14.2.4) except that the intercept term b_0 is replaced by b_0^* in (14.2.16). If we assume that the probability distribution of the covariates, $P(\mathbf{x})$, contains no information about the parameters of interest, or $P(\mathbf{x})$ is independent of the coefficients b_j, and the selection is independent of $\mathbf{x}$, then maximizing L_{cc} to obtain estimates of b_j is equivalent to maximizing only $L(b_0^*, b_1, \ldots, b_p)$ since $P(y = 1 \mid s = 1) = n_1/n$ and $P(y = 0 \mid s = 1) = n_0/n$. This implies that we can use the computer program for prospective studies to analyze case–control study data except that the intercept term cannot be interpreted meaningfully unless π_1 and π_0 are known.

In most practical situations, the assumption made above about $P(\mathbf{x})$ is reasonable. Historically, in early applications of the logistic regression method, the covariates were assumed to have multivariate normal distribution. Then

estimation of the coefficients, b_j in (14.2.19), would involve the distribution $P(\mathbf{x})$ and thus became much more complicated. However, in practice, many of the covariates are categorical or discrete and are therefore distinctly nonnormal. Thus, it is appropriate to allow $P(\mathbf{x})$ to remain completely arbitrary and use simply $L(b_0^*, b_1, \ldots, b_p)$ in (14.2.19) in case–control studies.

Another approach to the likelihood function based on (14.2.13) is to consider a conditional probability instead. Suppose that n_1 cases and n_0 controls were selected in a case–control study and $n = n_1 + n_0$; let $\mathbf{x}_1$, $\mathbf{x}_2, \ldots, \mathbf{x}_n$ be the risk factor sets of the n subjects without specifying which of them pertain to the cases and which to the controls. Then the conditional probability that the first n_1 $\mathbf{x}$'s are observed from the n_1 cases and the remainder are from the n_0 controls may be written as

$$\frac{\prod_{i=1}^{n_1} P(\mathbf{x}_i \mid y=1) \prod_{i=n_1+1}^{n} P(\mathbf{x}_i \mid y=0)}{\sum_{\{l_1,\ldots,l_{n_1}\}} \left(\prod_{i=1}^{n_1} P(\mathbf{x}_{l_i} \mid y=1) \prod_{i=n_1+1}^{n} P(\mathbf{x}_{l_i} \mid y=0)\right)} \tag{14.2.20}$$

where the summation in the denominator is over the $n!/(n_1!\, n_0!)$ possible ways of selecting n_1 individuals as cases from the n subjects, with the remaining n_0 as controls. By using (14.2.13) and (14.2.1), (14.2.20) reduces to

$$\frac{\prod_{i=1}^{n_1} \exp\left(\sum_{j=1}^{p} b_j x_{ij}\right)}{\sum_{\{l_1,\ldots,l_{n_1}\}} \prod_{i=1}^{n_1} \exp\left(\sum_{j=1}^{p} b_j x_{l_i j}\right)} \tag{14.2.21}$$

Comparing with (12.1.17), (14.2.21) can be considered as a special case of (12.1.17) in which there is only one distinct uncensored failure time, say at $t = 1$, and all of the n_1 persons failed at $t = 1$. The remaining n_0 subjects survive longer than 1 and are censored, say at $t = 2$, while all n subjects are at risk at $t = 1$. This interpretation of (14.2.21) permits us to apply the method and computer software for the Cox proportional hazards model with a discrete time scale and ties to obtain an estimate of $\mathbf{b}$ in the logistic regression model and to perform the corresponding inferences. The procedure is illustrated in Example 14.8. When n_1 and n_0 are large enough, it can be shown that an analysis based on this conditional probability will produce results equivalent to those based on the likelihood function defined in (14.2.19) (Efron, 1975; Farewell, 1979; Breslow and Day, 1980). When n_1 and n_0 are large, one may prefer using (14.2.19) to (14.2.21) since the former is easier. However, for a case–control study with a matched or stratified design, analysis based on the conditional probability defined in (14.2.21) is a better choice than (14.2.19) (Efron, 1975; Farewell, 1979; Breslow and Day, 1980). In the following section we discuss the application of logistic regression analysis for two widely accepted matched designs in case–control studies.

1 : R Matched Design

A widely used case–control design is to have one or more controls matched

for each case based on matching variables such as age and gender. Suppose that for each case there are $R(\geqslant 1)$ matched controls. Let x_{ijk} denote the observed value of the jth covariate ($j = 1, \ldots, p$) from the kth subject ($k = 1$ for the case and $k = 2, \ldots, R+1$ for matched controls) in the ith matched set ($i = 1, \ldots, n$). The n matched sets are considered as the samples from the n different strata defined by the matching variables. Following (14.2.21) with $n_1 = 1$ and $n_0 = R$, the conditional probability for the matched set (1 case and R controls) in the ith stratum is

$$\frac{\exp(\sum_{j=1}^{p} b_j x_{ij1})}{\exp(\sum_{j=1}^{p} b_j x_{ij1}) + \sum_{k=2}^{R+1} \exp(\sum_{j=1}^{p} b_j x_{ijk})} = \frac{1}{1 + \sum_{k=2}^{R+1} \exp[\sum_{j=1}^{p} b_j (x_{ijk} - x_{ij1})]} \tag{14.2.22}$$

and thus the conditional likelihood function for all n strata is the product of the n terms in (14.2.22), that is,

$$\prod_{i=1}^{n} \frac{1}{1 + \sum_{k=2}^{R+1} \exp[\sum_{j=1}^{p} b_j (x_{ijk} - x_{ij1})]} \tag{14.2.23}$$

When $R = 1$, that is, a one-to-one pair matching, the conditional likelihood function obtained from (14.2.23) reduces to

$$\begin{aligned} L(b_1, \ldots, b_p) &= \prod_{i=1}^{n} \frac{1}{1 + \exp[\sum_{j=1}^{p} b_j (x_{ij2} - x_{ij1})]} \\ &= \prod_{i=1}^{n} \frac{\exp[\sum_{j=1}^{p} b_j (x_{ij1} - x_{ij2})]}{1 + \exp[\sum_{j=1}^{p} b_j (x_{ij1} - x_{ij2})]} \end{aligned} \tag{14.2.24}$$

Compared with the likelihood function for the ordinary logistic regression in (14.2.4), the conditional likelihood function (14.2.24) can be treated as a special case of (14.2.4) with $y_i \equiv 1$, $b_0 \equiv 0$, and x_{ij} can be replaced by the difference in x_{ij} between the case and its matched control. This fact permits the use of computer programs for ordinary logistic regression in one-to-one matched case–control studies. The procedure is as follows:

1. Let n be the number of case–control pairs.
2. Use $x_{ij1} - x_{ij2}$, the difference between covariates for the case (x_{ij1}) and its matched control (x_{ij2}), as the independent variable in the model.
3. Let $y_i \equiv 1$ for all pairs.
4. Delete the intercept term b_0 from the model.

$n_1 : n_0$ Matched Design or Stratified Design

Suppose that there are n_1 cases and n_0 controls in the ith stratum and $n = n_1 + n_0$. Let x_{ijk} denote the observed value of the jth covariate ($j = 1, \ldots, p$) from the kth subject ($k = 1, 2, \ldots, n_1$ for the n_1 cases and $k = n_1 + 1, \ldots, n$ for the n_0 controls) in the ith stratum ($i = 1, \ldots, m$). From (14.2.21), the contribution of the ith stratum to the conditional likelihood function is

$$\frac{\prod_{k=1}^{n_1} \exp(\sum_{j=1}^{p} b_j x_{ijk})}{\sum_{\{k_1,\ldots,k_{n_1}\}} \prod_{l=1}^{n_1} \exp(\sum_{j=1}^{p} b_j x_{ijk_l})} \tag{14.2.25}$$

where the summation in the denominator is over all the $n!/(n_1!\, n_0!)$ possible ways to select n_1 out of the n subjects as cases and the remaining n_0 as controls. The term in (14.2.25) has the same mathematical form as (14.2.21). Thus, as discussed earlier, the computer software for the proportional hazards model can be used to estimate the coefficients.

In both $1 : R$ and $n_1 : n_0$ matched designs, most of the other features in the ordinary logistic regression model fitting, including the use of design (dummy) variables and statistical inferences, remain the same. However, the goodness of fit test of Hosmer and Lemeshow is not applicable to matched designs. Readers who are interested in assessing the logistic regression model in matched case–control studies are referred to Pregibon (1984) and Moolgavkar et al. (1985).

The following example illustrates the basic procedure for the one-to-one matched design using (14.2.24).

Example 14.8 To study the effect of obesity, family history of diabetes, and level of physical activity to non-insulin-dependent diabetes (NIDDM), 30 nondiabetic persons are matched with 30 NIDDM patients by age and gender. Obesity is measured by body mass index (BMI), which is defined as weight in kilograms divided by height in meters squared. Family history of diabetes (FH) and levels of physical activity (PHY) are binary variables. Table 14.9 gives the partially fictitious data. Following the procedure given above, the results of fitting the three variables using BMDP are given in Table 14.10.

Suppose that text data file "C:\EX14d2d5.DAT" contains six successive columns of data: BMIC, FHC, PHYC, BMIN, FHN, and PHYN, as in Table 14.9, separated by a space. The following SAS, SPSS, or BMDP code can be used to generate the results in Table 14.10.

SAS code:

```
data w1;
  infile 'c:\ex14d2d5.dat' missover;
  input bmic fhc phyc bmin fhn phyn;
  bmi = bmic-bmin;
```

Table 14.9 Data of 30 Matched Case–Control Pairs

	Case (Diabetic)			Control (Nondiabetic)		
Pair	BMI	FH[a]	PHY[b]	BMI	FH[a]	PHY[b]
1	22.1	1	1	26.7	0	1
2	31.3	0	0	24.4	0	1
3	33.8	1	0	29.4	0	0
4	33.7	1	1	26.0	0	0
5	23.1	1	1	24.2	1	0
6	26.8	1	0	29.7	0	0
7	32.3	1	0	30.2	0	1
8	31.4	1	0	23.4	0	1
9	37.6	1	0	42.4	0	0
10	32.4	1	0	25.8	0	0
11	29.1	0	1	39.8	0	1
12	28.6	0	1	31.6	0	0
13	35.9	0	0	21.8	1	1
14	30.4	0	0	24.2	0	1
15	39.8	0	0	27.8	1	1
16	43.3	1	0	37.5	1	1
17	32.5	0	0	27.9	1	1
18	28.7	0	1	25.3	1	0
19	30.3	0	0	31.3	0	1
20	32.5	1	0	34.5	1	1
21	32.5	1	0	25.4	0	1
22	21.6	1	1	27.0	1	1
23	24.4	0	1	31.1	0	0
24	46.7	1	0	27.3	0	1
25	28.6	1	1	24.0	0	0
26	29.7	0	0	33.5	0	0
27	29.6	0	1	20.7	0	0
28	22.8	0	0	29.2	1	1
29	34.8	1	0	30.0	0	1
30	37.3	1	0	26.5	0	0

[a] 1, yes; 0, no.
[b] 1, physically active; 0, sedentary.

```
   fh = fhc-fhn;
   phy = phyc-phyn;
   y = 1;
run;
proc logistic data = w1;
   model y =  bmi fh phy / noint plcl plrl lackfit;
run;
```

Table 14.10 Results of a Logistic Regression Analysis of Data in Table 11.13

Variable	Estimated Coefficient	Estimated Standard Error	Coefficient/SE	exp(coefficient)
BMI	0.090	0.065	1.381	1.094
FH	0.968	0.588	1.646	2.633
PHY	−0.563	0.541	−1.041	0.569

SPSS code:

```
data list file = 'c:\ex14d2d5.dat' free
        / bmic fhc phyc bmin fhn phyn.
Compute bmi = bmic-bmin.
Compute fh = fhc-fhn.
Compute phy = phyc-phyn.
Compute y = 1.
Logistic regression y with bmi fh phy
        /origin
        /print = all.
```

BMDP LR code:

```
/input      file = 'c:\ex14d2d5.dat' .
            variables = 6.
            format = free.
/variable   names =  bmic, fhc, phyc, bmin, fhn, phyn.
/transform  bmi = bmic-bmin.
            fh = fhc-fhn.
            phy = phyc-phyn.
            y = 1.
/regress    depend = y.
            Interval =  bmi, fh, phy.
            Model =  bmi, fh, phy.
            Start = in, in, in.
            Constant = out.
            Move = 0, 0, 0.
            Method = mlr.
/print      cell = used.
/end
```

The following example illustrates the estimating procedures for the $1:R$ and $n_1:n_0$ matched case–control designs.

Example 14.9 Table 14.11 lists a subset of simulated data from a case–control diabetes study that is based on a cohort study of heart disease with a

Table 14.11 A Subset of Age-Group and Gender-Matched DM Data in Example 14.9[a]

AGE	AGEG	SEX	SBP	DBP	LACR	HDL	LINSUL	SMOKE	DMS	DM	SN
51.8	50	1	148	91	1.35	37	2.81	0	1	0	1
50.9	50	1	116	95	1.04	43	2.74	0	1	0	1
50.9	50	1	114	85	1.26	64	1.98	1	1	0	1
50.9	50	1	120	80	1.56	52	2.53	1	1	0	1
54.6	50	1	119	71	1.55	30	2.87	0	2	0	1
50.8	50	1	123	78	1.40	33	3.31	0	2	0	1
53.3	50	1	119	75	1.69	40	2.13	1	3	1	1
72.0	70	0	129	73	1.06	25	2.69	0	1	0	2
73.1	70	0	120	68	0.87	30	2.76	0	1	0	2
72.8	70	0	111	66	2.52	73	3.17	0	2	0	2
70.3	70	0	115	65	3.16	42	2.96	0	2	0	2
72.1	70	0	140	66	3.18	52	3.48	0	2	0	2
72.8	70	0	136	72	3.36	59	3.22	0	2	0	2
71.1	70	0	133	85	2.95	73	3.25	0	3	1	2
56.4	55	1	110	74	0.58	43	2.18	0	1	0	3
55.7	55	1	122	77	1.18	34	2.76	1	1	0	3
56.9	55	1	114	74	1.10	25	2.62	0	1	0	3
58.5	55	1	104	74	1.24	23	2.58	0	1	0	3
55.2	55	1	128	77	1.25	43	2.77	0	2	0	3
55.9	55	1	130	83	1.34	44	2.34	1	2	0	3
57.4	55	1	116	79	2.23	38	2.46	1	3	1	3
60.7	60	0	136	85	2.04	42	3.66	0	1	0	4
62.0	60	0	115	74	1.32	33	2.85	0	1	0	4
64.7	60	0	155	89	2.55	46	3.73	1	1	0	4
64.4	60	0	191	107	3.66	34	2.67	1	2	0	4
60.5	60	0	109	74	0.89	64	2.88	0	2	0	4
62.4	60	0	106	72	0.88	35	3.44	1	2	0	4
62.8	60	0	234	91	7.28	49	2.38	1	3	1	4
73.2	70	0	119	72	1.00	47	2.53	0	1	0	5
73.0	70	0	128	70	2.87	51	2.62	0	1	0	5
72.2	70	0	124	69	1.43	33	2.49	0	1	0	5
73.7	70	0	128	72	2.12	38	3.30	0	2	0	5
71.7	70	0	111	68	3.16	64	3.14	0	2	0	5
71.2	70	0	104	67	3.00	40	3.30	0	2	0	5
74.5	70	0	140	82	2.84	46	2.95	1	3	1	5
58.2	55	0	112	77	2.84	71	2.23	0	1	0	6
57.3	55	0	111	77	2.23	41	2.57	0	1	0	6
58.7	55	0	120	76	1.85	60	2.57	0	1	0	6
57.2	55	0	120	73	0.55	48	3.10	0	2	0	6
57.2	55	0	112	73	0.49	45	2.86	0	2	0	6
55.5	55	0	120	73	−0.53	49	3.12	0	2	0	6
59.5	55	0	156	76	3.22	59	3.14	1	3	1	6
78.4	75	0	119	75	1.28	53	1.72	1	1	0	7
77.8	75	0	112	74	1.39	44	1.80	1	1	0	7
75.5	75	0	123	74	1.41	72	1.93	0	1	0	7
78.3	75	0	149	84	0.53	40	2.84	0	1	0	7

Table 14.11 *Continued*

AGE	AGEG	SEX	SBP	DBP	LACR	HDL	LINSUL	SMOKE	DMS	DM	SN
76.9	75	0	153	75	3.78	43	2.95	0	2	0	7
75.4	75	0	144	77	4.57	45	2.54	0	2	0	7
77.9	75	0	156	86	5.38	39	3.34	0	3	1	7
68.0	65	0	123	70	1.62	48	2.49	0	1	0	8
66.2	65	0	131	72	1.71	56	2.47	0	1	0	8
65.8	65	0	136	80	3.82	56	2.84	1	1	0	8
68.8	65	0	120	66	2.20	45	2.45	0	1	0	8
68.0	65	0	162	60	2.35	62	3.86	0	2	0	8
67.9	65	0	115	54	2.33	39	3.92	0	2	0	8
67.8	65	0	132	79	2.68	42	2.47	0	3	1	8
63.1	60	1	123	80	1.81	46	1.93	1	1	0	9
61.3	60	1	122	78	1.41	85	1.88	0	1	0	9
60.8	60	1	131	83	2.43	31	1.90	1	1	0	9
61.8	60	1	109	69	1.27	61	2.35	1	2	0	9
63.1	60	1	114	73	1.04	38	2.53	0	2	0	9
60.7	60	1	130	76	0.84	46	2.59	0	2	0	9
62.2	60	1	133	85	2.10	37	3.04	0	3	1	9
78.7	75	0	147	85	0.48	58	2.62	0	1	0	10
77.4	75	0	167	84	0.92	71	2.66	0	1	0	10
78.0	75	0	165	85	0.44	49	3.02	0	1	0	10
75.2	75	0	117	70	2.05	42	2.88	0	2	0	10
77.8	75	0	151	75	4.27	41	2.76	0	2	0	10
78.5	75	0	137	74	2.13	40	2.86	0	2	0	10
78.5	75	0	156	81	5.33	52	327	0	3	1	10
56.5	55	0	108	71	1.58	41	2.27	0	1	0	11
58.8	55	0	104	73	2.55	34	2.53	0	1	0	11
55.7	55	0	135	77	2.06	106	2.32	1	1	0	11
57.8	55	0	110	74	2.59	49	2.37	0	1	0	11
57.3	55	0	153	91	0.54	44	3.13	0	2	0	11
55.4	55	0	141	94	1.47	61	3.15	0	2	0	11
56.9	55	0	123	78	3.72	40	3.18	0	3	1	11
53.3	50	0	113	74	1.19	46	2.71	0	1	0	12
50.8	50	0	143	89	3.45	78	1.84	0	1	0	12
50.3	50	0	136	79	−1.44	48	2.48	1	2	0	12
55.0	50	0	131	77	0.23	49	2.57	1	2	0	12
54.4	50	0	132	77	−0.08	34	2.45	0	2	0	12
53.3	50	0	135	77	0.48	37	2.93	1	2	0	12
50.7	50	0	114	78	2.52	41	4.37	0	3	1	12

[a] AGEG = 50 if $50 \leqslant \text{age} < 55$, = 55 if $55 \leqslant \text{age} < 60$, = 60 if $60 \leqslant \text{age} < 65$, = 65 if $65 \leqslant \text{age} < 70$, = 70 if $70 \leqslant \text{age} < 75$, = 75 if $75 \leqslant \text{age} < 80$; SEX = 1 if male and = 0 if female; SMOKE = 1 if current smoker and 0 otherwise; SBP, systolic blood pressure; DBP, diastolic blood pressure; LACR, logarithm of the ratio of urinary albumin and creatinine; HDL, high-density lipoprotein in cholesterol; LINSUL, logarithm of insuline; DM = 1 if fasting glucose $\geqslant$ 126 mg/dL and = 0 otherwise; DMS, diabetic status defined by ADA fasting glucose criterion: DMS = 1 if normal fasting glucose, = 2 if impaired fasting glucose, and = 3 if diabetic; SN, stratum number.

Table 14.12 Results from the Conditional Logistic Regression Model for the DM Data in Example 14.9

Variable	Regression Coefficient	Standard Error	Chi-Square Statistic	p	Odds Ratio	95% Confidence Interval for Odds Ratio	
						Lower	Upper
AGE	0.327	0.161	4.127	0.0422	1.39	1.01	1.90
DBP	0.046	0.020	5.639	0.0176	1.05	1.01	1.09
LACR	0.395	0.133	8.776	0.0031	1.48	1.14	1.93
LINSUL	0.860	0.288	8.900	0.0029	2.36	1.34	4.16

baseline and second examinations (about five years after the baseline examination). In this study, 33 persons with diabetes at the second examination are selected, and for each of these cases, six age group (in five-year interval)- and gender-matched diabetes-free controls are selected randomly from all participants without diabetes in the second examination. There are 33 strata and each stratum contains one case (DM = 1) and its six matched controls (DM = 0), for a total of 231 participants. The demographic, physical, blood, and urinary data collected at the baseline examination of the first 12 strata are listed in Table 14.11 and arranged by stratum. The conditional logistic model based on (14.2.20) is used for these 1:6 matched data to identify risk factors for diabetes. The stepwise selection method is used to select the significant risk factors. The results are shown in Table 14.12. AGE, DBP, LACR, and LINSUL are significant risk factors for diabetes. The larger the values of AGE, DBP, LACR, and LINSUL, the higher is the risk of being diabetic.

As noted earlier, for (14.2.21), the computer software for a Cox proportional model with discrete time scale can be used to obtain an estimate of parameter **b**. Suppose that the text data file "C:\EX14d2d6.DAT" contains 12 successive columns, separated by a space, with data as in Table 14.11: AGE, AGEG, SEX, SBP, DBP, LACR, HDL, LINSUL, SMOKE, DMS, DM, and SN. The following SAS code shows how the SAS procedure for the proportional hazards model with discrete time scale can be used to obtain an estimate of parameter **b** for the conditional logistic regression model in a matched case–control study (the results are given in Table 14.12). In the SAS code, first, we define a nominal variable (for survival time), TIME, and let TIME = 1 if a case (DM = 1), and = 2 if a control (DM = 0). This is accomplished by the statement "time = 2-dm;". Second, DM is also used to indicate censoring status, DM = 0 meaning censored, and = 1 uncensored. Thus, a case will have an uncensored time 1 and a control will have a censored time 2.

```
data w1;
  infile 'c:\ex14d2d6.dat' missover;
```

Table 14.13 Data from Example 14.9 If Stratified by Age Group Only

Stratum	AGEG	Number of DMs	Number of Non-DMs	Total
1	50–54	9	54	63
2	55–59	8	48	56
3	60–64	4	24	28
4	65–69	4	24	28
5	70–74	5	30	35
6	75–79	3	18	21
Total		33	198	231

```
   input age ageg sex sbp dbp lacr hdl linsul smoke dms dm sn;
   time = 2-dm;
run;
proc phreg data = w1 noprint;
   model time*dm(0) = age sbp dbp lacr hdl linsul smoke
                      / ties = discrete selection = s;
   strata sn;
run;
```

Using the same data, if we stratify by age group only, Table 14.13 lists the number of cases and controls in each age group (stratum). This can be considered as an example of a stratified design with a different numbers of cases and controls in each stratum: stratum 1 has a 9 : 54 match, stratum 2 an 8 : 48 match, and so on. The results from the conditional logistic regression model based on this new stratification are given in Table 14.14.

Table 14.14 Results from the Conditional Logistic Regression Model for the Data in Example 14.9 with Strata Defined by Age Groups

Variable	Regression Coefficient	Standard Error	Chi-Square Statistic	p	Odds Ratio	95% Confidence Interval for Odds Ratio	
						Lower	Upper
DBP	0.050	0.020	6.304	0.0120	1.05	1.01	1.09
LACR	0.391	0.124	9.876	0.0017	1.48	1.16	1.89
HDL	−0.037	0.019	4.034	0.0446	0.96	0.93	1.00
LINSUL	0.694	0.292	5.668	0.0173	2.00	1.13	3.55

The following SAS code can be used to generate the results in Table 14.14. The code can be modified to perform conditional logistic regression analysis for data from any $n_1 : n_0$ matched design or a stratified design.

```
data w1;
  infile 'c:\ex14d2d6.dat' missover;
  input age ageg sex sbp dbp lacr hdl linsul smoke dms dm sn;
  time = 2-dm;
run;
proc phreg data = w1 noprint;
  model time*dm(0) = age sex sbp dbp lacr hdl linsul smoke
                     / ties = discrete selection = s;
  strata ageg;
run;
```

14.2.3 Other Models for Dichotomous Outcomes

In the logistic regression model (14.2.3), the left side is a function of the probability of success, P_i, and the right side is the linear combination of covariates. The function, called a *link function*, defines the relationship between the covariates and P_i. In general, a link function represents the underlying biological, physical, or epidemiological relationship between the mean of the dependent variable (probability of success) and the covariates $x_1, x_2, \ldots, x_p$. In the logistic regression model the link function, say g, is the logit function of P_i, that is,

$$g(P_i) = \text{logit}(P_i) = \log \frac{P_i}{1 - P_i}$$

and $g(P_i)$ is assumed to be linearly related to the covariates, that is,

$$\log \frac{P_i}{1 - P_i} = \sum_{j=0}^{p} b_j x_{ij}$$

or

$$P_i = \frac{\exp(\sum_{j=0}^{p} b_j x_{ij})}{1 + \exp(\sum_{j=0}^{p} b_j x_{ij})} \tag{14.2.26}$$

Two other forms of link function $g(P)$ that assume a linear relationship with the covariates have been proposed and used in the literature. In the following, we introduce these two link functions and the corresponding regression model.

1. *The probit* (*or normit*) *function.* This is the link function defined by the inverse of the cumulative standard normal distribution function, $\Phi^{-1}(\cdot)$:

$$g(P_i) = \Phi^{-1}(P_i) \tag{14.2.27}$$

The corresponding model is

$$\Phi^{-1}(P_i) = \sum_{j=0}^{p} b_j x_{ij}$$

or

$$P_i = \Phi\left(\sum_{j=1}^{P} b_j x_{ij}\right) \tag{14.2.28}$$

2. *The complementary log-log link function.* This function is defined by

$$g(P_i) = \log[-\log(1 - P_i)] \tag{14.2.29}$$

The corresponding model is

$$\log[-\log(1 - P_i)] = \sum_{j=0}^{p} b_j x_{ij}$$

or

$$P_i = 1 - \exp\left[-\exp\left(\sum_{j=0}^{P} b_j x_{ij}\right)\right] \tag{14.2.30}$$

The logistic regression model in (14.2.26) is for binary outcomes such as diseased versus nondiseased. The model (14.2.28) can be thought of as an alternative model for binary outcome. In addition, it can be used to model those binary outcomes that are defined by a cutoff point on the basis of a normally distributed variable. For example, the cutoff point may be defined by the last quintile or quartile of a continuous measurement in an epidemiological study. When the binary outcomes are defined by a cutoff point in an asymmetric distribution, the model in (14.2.30) may be appropriate. The model (14.2.30) can also be considered as a version of the Cox proportional hazards model for grouped survival times (Kalbfleisch and Prentice, 1973).

Let $y_1, y_2, \ldots, y_n$ be the observations with dichotomous values on the n subjects: $y_i = 1$ for success and $y_i = 0$ for failure. Similar to (14.2.4), the likelihood functions for the models in (14.2.28) and (14.2.30) can be obtained by replacing the corresponding P_i in the following formula:

$$L(b_0, b_1, \ldots, b_p) = \prod_{i=1}^{n} P_i^{y_i}(1 - P_i)^{1 - y_i}$$

The MLEs of the coefficients and the asymptotic likelihood inferences are similar to those given in Section 14.2.1 for the ordinary logistic regression model except that interpretation of the odds ratio is not possible for the latter two models. The procedure LOGISTIC in SAS provides options for all three models.

Example 14.10 Consider the data in Example 14.9 as nonstratified data, Table 14.15 gives the results from the regression models defined in (14.2.26), (14.2.28), and (14.2.30) by using the stepwise selection method. Based on Hosmer–Lemeshow test statistics, the regression model with the inverse normal link function gives a good fit to the data ($p = 0.4956$), whereas the other two models do not ($p = 0.0152$ and $p = 0.0261$). All three models identify DBP, LACR, and LINSUL as significant covariates for the development of diabetes.

The following SAS, SPSS, and BMDP codes may be used to generate the results in Table 14.15.

SAS code:

```
data w1;
  infile 'c:\ex14d2d6.dat' missover;
  input age ageg sex sbp dbp lacr hdl linsul smoke dms dm sn;
run;
```

Table 14.15 Asymptotic Partial Likelihood Inference from the Regression Models with Different Link Functions for the Data in Example 14.9

Variable	Regression Coefficient	Standard Error	Chi-Square Statistic	p	Odds Ratio	95% Confidence Interval for Odds Ratio	
						Lower	Upper
Model with Logit Link Function							
INTERCPT	−8.419	1.792	22.061	<0.0001			
DBP	0.044	0.018	5.673	0.0172	1.05	1.01	1.08
LACR	0.343	0117	8.627	0.0033	1.41	1.13	1.79
LINSUL	0.870	0.287	9.191	0.0024	2.39	1.38	4.27
Hosmer–Lemeshow test statistic			18.9460	0.0152			
Model with Inverse Normal Link Function							
INTERCPT	−4.532	0.953	22.597	<0.0001			
DBP	0.023	0.010	5.302	0.0213			
LACR	0.186	0.065	8.060	0.0045			
LINSUL	0.445	0.156	8.146	0.0043			
Hosmer–Lemeshow test statistic			7.386	0.4956			
Model with Log-Log Link Function							
INTERCPT	−7.740	1.530	25.589	<0.0001			
DBP	0.038	0.016	5.919	0.0150			
LACR	0.305	0.096	10.153	0.0014			
LINSUL	0.785	0.241	10.592	0.0011			
Hosmer–Lemeshow test statistic			17.415	0.0261			

```
title "Regression model with the logit link function-generalized logistic regression";
proc logistic data = w1 descending;
  model dm = age sex sbp dbp lacr hdl linsul smoke
             / selection = s lackfit link = logit;
run;
title "Regression model with the inverse normal link function';
proc logistic data = w1 descending;
  model dm = age sex sbp dbp lacr hdl linsul smoke
             / selection = s lackfit link = probit;
run;
title "Regression model with the log-log link funtion';
proc logistic data = w1 descending;
  model dm = age sex sbp dbp lacr hdl linsul smoke
             / selection = s lackfit link = cloglog;
run;
```

SPSS code for the model in (14.2.28) with the forward selection method:

```
data list file = 'c:\ex14d2d6.dat' free
        / age ageg sex sbp dbp lacr hdl linsul smoke dms dm sn.
Logistic regression dm with age sex sbp dbp lacr hdl linsul smoke htn
        /method = fstep
        /print = all.
```

BMDP code for procedure LR and the model in (14.2.28):

```
/input      file = 'c:\ex14d2d6.dat' .
            variables = 12.
            format = free.
/variable   names = age, ageg, sex, sbp, dbp, lacr, hdl, linsul, smoke,
                    dms, dm, sn.
            Use =  age, sex to smoke.
/regress    depend = dm.
            Interval = age, sex to smoke.
            Method = mlr.
/print      cell = used.
/end
```

14.3 MODELS FOR POLYCHOTOMOUS OUTCOMES

The regression models in Section 14.2 can be extended to handle outcomes that have more than two categories. These categories may be nominal, for example, different types of heart disease or psychological conditions; or ordinal, for example, different levels of glucose intolerance or different severity of communication disorders. An outcome variable with more than two possibilities is called *polychotomous* or *polytomous*. In this section we discuss first the model for

nominal polychotomous outcomes (generalized logistic regression model), then the model for ordinal polychotomous outcomes (ordinal regression model). Details regarding these models can be found in Aitchison and Silvey (1957), McCullagh (1980), Green (1984), McCullagh and Nelder (1989), Hosmer and Lemeshow (1989, 2000), Cox and Snell (1989), Afifi and Clark (1990), Agresti (1990), Collett (1991), and Ananth and Kleinbaum (1997).

14.3.1 Models for Nominal Polychotomous Outcomes: Generalized Logistic Regression Models

Let Y_i denote the outcome for individual i. The outcome can be one of the m nominal categories, such as different cell types of lung cancer. Let $Y_i = k$ denote that Y_i belongs to the kth category and $k = 1, 2, \ldots, m$. Suppose that for each of n subjects, p independent variables $\mathbf{x}_i = (x_{i1}, x_{i2}, \ldots, x_{ip})'$ are measured. These variables can be either qualitative or quantitative. Let $P(Y_i = k \mid \mathbf{x}_i)$ be the probability that $Y_i = k$ given the p measured covariates $\mathbf{x}_i$; then $\sum_{k=1}^{m} P(Y_i = k \mid \mathbf{x}_i) = 1$. Without loss of generality, using the last catalog as the reference, the generalized logistic regression model

$$\log \frac{P(Y_i = k \mid \mathbf{x}_i)}{P(Y_i = m \mid \mathbf{x}_i)} = a_k + \sum_{j=1}^{p} b_{kj} x_{ij} \qquad k = 1, 2, \ldots, m-1 \tag{14.3.1}$$

can be used to study the association of the covariates $\mathbf{x}$ to the outcome. To simplify the notation, let $u_{ki} = a_k + \sum_{j=1}^{p} b_{kj} x_{ij}$. Similar to (14.2.1) and (14.2.2), the model in (14.3.1) assumes that the dependence on the covariates of the probability of being in the kth category is

$$P(Y_i = k \mid \mathbf{x}_i) = \begin{cases} \dfrac{\exp(u_{ki})}{1 + \sum_{j=1}^{m-1} \exp(u_{ji})} & k = 1, 2, \ldots, m-1 \\ \dfrac{1}{1 + \sum_{j=1}^{m-1} \exp(u_{ji})} & k = m \end{cases} \tag{14.3.2}$$

This model reduces to the logistic regression model in (14.2.1) and (14.2.2) when $m = 2$.

Let $k_1, \ldots, k_n$ be the outcomes observed for the n subjects. Then the log-likelihood function based on the n outcomes observed is the logarithm of the product of all $P(Y_i = k_i \mid \mathbf{x}_i)$'s from the n subjects, that is,

$$l(a_1, a_2, \ldots, a_{m-1}, \mathbf{b}_1, \mathbf{b}_2, \ldots, \mathbf{b}_{m-1}) = \log L = \log \left[\prod_{i=1}^{n} P(Y_i = k_i \mid \mathbf{x}_i) \right] \tag{14.3.3}$$

where $P(Y_i = k_i \mid \mathbf{x}_i)$ is given in (14.3.2) and $\mathbf{b}_k = (b_{k1}, \ldots, b_{kp})'$, $k = 1, 2, \ldots, m-1$. There are a total of $(m-1)(p+1)$ unknown coefficients. The estimation and hypothesis testing procedures for the coefficients are similar to

those in the logistic regression model for dichotomous outcomes. Strictly speaking, the models in (14.3.1) are not logistic regression models if $m > 2$. Therefore, the interpretation of the coefficients in these models needs to be clarified. Let us consider modeling the relationship between gender and cardiovascular disease status, NORMAL, STROKE, and CHD (coronary heart disease). Let the outcome variable Y be defined as $Y = 1$ if CHD, $= 2$ if STROKE, and $= 3$ if NORMAL, and the covariate SEX defined as SEX $= 1$ if male and $= 0$ if female. Then the two models according to (14.3.1) are

$$\log \frac{P(Y_i = 1 \mid \text{SEX}_i)}{P(Y_i = 3 \mid \text{SEX}_i)} = a_1 + b_1 \cdot \text{SEX}_i$$

$$\log \frac{P(Y_i = 2 \mid \text{SEX}_i)}{P(Y_i = 3 \mid \text{SEX}_i)} = a_2 + b_2 \cdot \text{SEX}_i$$

It is clear that neither of them is a logistic regression model. In the following, we show how to interpret the coefficients b_1 and b_2 in these models. From the first model,

$$\begin{aligned}
&\log \frac{P(Y = 1 \mid \text{SEX} = 1)/P(Y = 3 \mid \text{SEX} = 1)}{P(Y = 1 \mid \text{SEX} = 0)/P(Y = 3 \mid \text{SEX} = 0)} \\
&\quad = \log \frac{P(Y = 1 \mid \text{SEX} = 1)}{P(Y = 3 \mid \text{SEX} = 1)} - \log \frac{P(Y = 1 \mid \text{SEX} = 0)}{P(Y = 3 \mid \text{SEX} = 0)} \\
&\quad = (a_1 + b_1) - a_1 \\
&\quad = b_1
\end{aligned}$$

and thus

$$\frac{P(Y = 1 \mid \text{SEX} = 1)/P(Y = 3 \mid \text{SEX} = 1)}{P(Y = 1 \mid \text{SEX} = 0)/P(Y = 3 \mid \text{SEX} = 0)} = \exp(b_1) \tag{14.3.4}$$

Now let us cast the data into a 3×2 contingency table as in Table 14.16. The left side of (14.3.4) can be estimated by

$$\frac{(f/n_1)/(b/n_1)}{(e/n_0)/(a/n_0)} = \frac{fa}{be}$$

However, if only the data from the normal and CHD participants are used,

$$\frac{fa}{be} = \frac{[f/(b + f)]/[b/(b + f)]}{[e/(e + a)]/[a/(e + a)]}$$

Table 14.16 Nominal Cross-Classification of Cardiovascular (CVD) Status by Gender

CVD Status (Y)	SEX	
	Female (0)	Male (1)
NORMAL (3)	a	b
STROKE (2)	c	d
CHD (1)	e	f
Total	n_0	n_1

which is an estimate of

$$\frac{P(\text{CHD} \mid \text{Male})/[1 - P(\text{CHD} \mid \text{male})]}{P(\text{CHD} \mid \text{female})/[1 - P(\text{CHD} \mid \text{female})]}$$

or the ratio of the odds of a male having CHD to the odds of a female having CHD. Therefore, the $\exp(\hat{b}_1)$ obtained from the first model can be interpreted as an estimate of the ratio of the odds of a male having CHD to the odds of a female having CHD if only the data from the normal and CHD participants are used. Similarly, $\exp(\hat{b}_2)$ obtained from the second model can be interpreted as an estimate of the ratio of the odds of a male having STROKE to the odds of a female having STROKE if only the data from the normal and STROKE participants are used. The same interpretation also holds for coefficients of continuous covariates in the models of (14.3.1); that is, an exponentiated coefficient for a continuous covariate is the odds ratio of a 1-unit increase in the covariate assuming that other covariates are the same.

Example 14.11 We use the data in Example 14.9 and assume that DM ($Y = 1$), IFG ($Y = 2$), and NFG ($Y = 3$) are three nominal categories. Let the referent category be NFG. For simplicity, only two covariates, systolic blood pressure (SBP) and log insulin (LINSUL), are included. Table 14.17 gives the results from fitting these covariates to the model (14.3.1).

$$\log \frac{P(i\text{th participant is DM})}{P(i\text{th participant is NFG})} = \log \frac{P(Y_i = 1 \mid \mathbf{x}_i)}{P(Y_i = 3 \mid \mathbf{x}_i)}$$
$$= -7.648 + 0.026\text{SBP}_i + 1.047\text{LINSUL}_i$$
$$\log \frac{P(i\text{th participant is IFG})}{P(i\text{th participant is NFG})} = \log \frac{P(Y_i = 2 \mid \mathbf{x}_i)}{P(Y_i = 3 \mid \mathbf{x}_i)}$$
$$= -4.949 + 0.011\text{SBP}_i + 0.876\text{LINSUL}_i$$

Table 14.17 Asymptotic Partial Likelihood Inference from the Generalized Logistic Regression Model for Example 14.11

Order of Coefficients by SAS	k	Variable	Regression Coefficient	Standard Error	Chi-Square Statistic	p	Odds Ratio	95% Confidence Interval for Odds Ratio	
								Lower	Upper
				DM vs. NFG					
b_1	1	INTERCP	−7.648	1.648	21.530	<0.0001			
b_3	1	SBP	0.026	0.010	6.300	0.0121	1.03	1.01	1.05
b_5	1	LINSUL	1.047	0.304	11.870	00006	2.85	1.57	5.17
				IFG vs. NFG					
b_2	2	INTERCP	−4.949	1.427	12.020	00005			
b_4	2	SBP	0.011	0.010	1.410	0.2346	1.01	0.99	1.03
b_6	2	LINSUL	0.876	0.262	11.150	0.0008	2.40	1.44	4.01
				DM vs. IFG					
		INTERCP	*−2.699*	*1.850*	*2.130*	*0.1445*			
		SBP	*0.015*	*0.012*	*0.480*	*0.2239*	*1.02*	*0.99*	*1.04*
		LINSUL	*0.171*	*0.333*	*1.270*	*0.6066*	*1.19*	*0.62*	*2.28*
$H_0: b_3 = b_4$					1.48	0.2239			
$H_0: b_5 = b_6$					0.27	0.6066			

Consequently,

$$\begin{aligned}
\log \frac{P(i\text{th participant is DM})}{P(i\text{th participant is IFG})} &= \log \frac{P(Y_i = 1 \mid \mathbf{x}_i)}{P(Y_i = 2 \mid \mathbf{x}_i)} \\
&= \log \frac{P(Y_i = 1 \mid \mathbf{x}_i)}{P(Y_i = 3 \mid \mathbf{x}_i)} - \log \frac{P(Y_i = 2 \mid \mathbf{x}_i)}{P(Y_i = 3 \mid \mathbf{x}_i)} \\
&= (-7.648 + 4.949) + (0.026 - 0.011)\text{SBP}_i \\
&\quad + (1.047 - 0.876)\text{LINSUL}_i \\
&= -2.699 + 0.015\text{SBP}_i + 0.171\text{LINSUL}_i
\end{aligned}$$

Thus, the odds ratio is 1.03 [exp(0.026)] times (or 3% higher) for a 1-unit increase in SBP, and 2.85 [exp(1.047)] times (or 185% higher) for a 1-unit increase in LINSUL from the model for DM vs. NFG. The odds ratio is 2.40 [exp(0.876)] times (or 140% higher) for a 1-unit increase in LINSUL from the model for IFG versus NFG. SBP is not significant in the model for IFG versus NFG ($p = 0.2346$). Neither SBP nor LINSUL is significant in the model for DM versus IFG ($p = 0.2239$ and $p = 0.6066$, respectively). One can also follow the examples in Chapter 7, 9, 11, and 12 to perform additional statistical inferences. For instance, we can test whether the coefficients for SBP in the first two models are equal (whether the odds ratio for a 1-unit increase of SBP in the model for DM versus NFG is equal to that in the model for IFG versus NFG), that is, $H_0: b_3 - b_4 = 0$ (where the subscripts 3 and 4 are the orders of the coefficients given by SAS). From (11.2.13), under H_0, Wald's statistic, $X_W = (\hat{b}_3 - \hat{b}_4)^2/(v_{33} + v_{44} - 2v_{34})$, has an asymptotic chi-square distribution with 1 degree of freedom, where v_{33} and v_{44} are the estimated variance of b_3 and b_4, respectively, and v_{34} is the estimated covariance of b_3 and b_4. From Table 14.17, the hypothesis is not rejected ($p = 0.2239$). Similarly, the hypothesis $H_0: b_5 - b_6 = 0$ is not rejected ($p = 0.6066$); that is, there is insufficient evidence to say that the change in odds ratio for a 1-unit increase in LINSUL in the model for DM versus NFG is not equal to that in the model for IFG versus NFG.

The following SAS, SPSS, and BMDP codes can be used to obtain the results in Table 14.17.

SAS code:

```
data w1;
  infile 'c:\ex14d2d6.dat' missover;
  input age ageg sex sbp dbp lacr hdl linsul smoke dms dm sn;
  y = 4-dms;
run;
title "Generalized logistic regression model";
proc catmod data = w1;
  direct sbp linsul;
```

```
   model y = sbp linsul
         / ml covb;
   contrast 'Equal coefficients for SBP' all_parms 0 0 1 −1 0 0;
   contrast 'Equal coefficients for LINSUL' all_parms 0 0 0 0 1 −1;
run;
```

SPSS code:

```
data list file = 'c:\ex14d2d6.dat' free
         / age ageg sex sbp dbp lacr hdl linsul smoke dms dm sn.
Compute y = 4-dms.
nomreg y with sbp linsul
         /print = fit history parameter lrt.
```

BMDP PR code:

```
/input      file = 'c:\ex14d2d6.dat' .
            variables = 12.
            format = free.
/variable   names = age, ageg, sex, sbp, dbp, lacr, hdl, linsul, smoke,
                    dms, dm, sn.
            Use = age, sex to smoke.
/transform  y = 4-dms.
/group      codes(y) = 1, 2, 3.
            Names(y) =  DM, IFG, NFG.
/regress    depend = y.
            Level = 3.
            Type = nom.
            Interval = age, sex to smoke.
            enter = .05, .05.
            remove =  = .05, .05.
/print      cell = model.
/end
```

14.3.2 Model for Ordinal Polychotomous Outcomes: Ordinal Regression Models

If the outcomes involve a rank ordering, that is, the outcome variable is ordinal, several multivalued regression models are available. Readers interested in these models are referred to McCullagh and Nelder (1989), Agresti (1990), Ananth and Kleinbaum (1997), and Hosmer and Lemeshow (2000). In the following discussion, we introduce the most frequently used model, the proportional odds model. In this model, the probability of an outcome below or equal to a given ordinal level, $P(Y \leqslant k)$, is compared to the probability that it is higher than the level given, $P(Y > k)$.

Let Y_i be the outcome of the ith subject. Assume that Y_i can be classified into m ordinal levels. Let $Y_i = k$ if Y_i is classified into the kth level and

$k = 1, 2, \ldots, m$. Suppose that for each of n subjects, p independent variables $\mathbf{x}_i = (x_{i1}, x_{i2}, \ldots, x_{ip})'$ are measured. These variables can be either qualitative or quantitative. If the *logit link function* defined in Section 14.2.3 is used, similar to the logistic regression model (14.2.3), we consider the following models:

$$\text{logit}(P(Y_i \leqslant k \mid \mathbf{x}_i)) = \log \frac{P(Y_i \leqslant k \mid \mathbf{x}_i)}{1 - P(Y_i \leqslant k \mid \mathbf{x}_i)} = a_k + \sum_{j=1}^{p} b_j x_{ij}$$
$$k = 1, 2, \ldots, m-1 \tag{14.3.5}$$

or, equivalently, let $u_{ki} = a_k + \sum_{j=1}^{p} b_j x_{ij}$,

$$P(Y_i \leqslant k \mid \mathbf{x}_i) = \frac{\exp(a_k + \sum_{j=1}^{p} b_j x_{ij})}{1 + \exp(a_k + \sum_{j=1}^{p} b_j x_{ij})} = \frac{\exp(u_{ki})}{1 + \exp(u_{ki})}$$
$$k = 1, 2, \ldots, m-1 \tag{14.3.6}$$

Therefore,

$$P(Y_i = k \mid \mathbf{x}_i) = P(Y_i \leqslant k \mid \mathbf{x}_i) - P(Y_i \leqslant k-1 \mid \mathbf{x}_i)$$
$$= \begin{cases} \dfrac{\exp(u_{1i})}{1 + \exp(u_{1i})} & k = 1 \\ \dfrac{\exp(u_{ki})}{1 + \exp(u_{ki})} - \dfrac{\exp(u_{k-1\,i})}{1 + \exp(u_{k-1\,i})} & k = 2, \ldots, m-1 \\ 1 - \dfrac{\exp(u_{m-1\,i})}{1 + \exp(u_{m-1\,i})} & k = m \end{cases} \tag{14.3.7}$$

If $m = 2$, that is, there are only two outcome levels, (14.3.7) reduces to the logistic regression model in (14.2.3). The models in (14.3.5) can be thought of as having only two outcomes [$(Y \leqslant k)$ versus $(Y > k)$] and therefore are logistic regression models. Thus, interpretation of the coefficients, b_j, such as the exponentiated coefficient [$\exp(b_j)$] for a discrete or a continuous covariate is similar to that in a logistic regression model.

Let $k_1, \ldots, k_n$ be observed outcomes from n subjects. Then the log-likelihood function based on the n outcomes observed is the logarithm of the product of all $P(Y_i = k_i \mid \mathbf{x}_i)$'s from the n subjects, that is,

$$l(a_1, a_2, \ldots, a_{m-1}, b_1, b_2, \ldots, b_p) = \log L = \log \left[\prod_{i=1}^{n} P(Y_i = k_i \mid \mathbf{x}_i) \right] \tag{14.3.8}$$

where $P(Y_i = k_i \mid \mathbf{x}_i)$ is as given in (14.3.7). The maximum likelihood estimation and hypothesis-testing procedures for the coefficients are similar to those discussed previously. If the *probit link function* in (14.2.27) is used, the models

and formula corresponding to (14.3.5)–(14.3.7) are

$$\Phi^{-1}(P(Y_i \leqslant k \mid \mathbf{x}_i)) = a_k + \sum_{j=1}^{p} b_j x_{ij} \qquad k = 1, 2, \ldots, m-1$$

$$P(Y_i \leqslant k \mid \mathbf{x}_i) = \Phi(u_{ki}) \qquad k = 1, 2, \ldots, m-1$$

$$P(Y_i = k \mid \mathbf{x}_i) = P(Y_i \leqslant k \mid \mathbf{x}_i) - P(Y_i \leqslant k-1 \mid \mathbf{x}_i)$$

$$= \begin{cases} \Phi(u_{1i}) & k = 1 \\ \Phi(u_{ki}) - \Phi(u_{k-1\,i}) & k = 2, \ldots, m-1 \\ 1 - \Phi(u_{m-1\,i}) & k = m \end{cases}$$

If the *complementary log-log link function* in (14.2.29) is used, the models and formula corresponding to (14.3.5)–(14.3.7) are

$$\log[-\log(1 - P(Y_i \leqslant k \mid \mathbf{x}_i))] = a_k + \sum_{j=1}^{p} b_j x_{ij} \qquad k = 1, 2, \ldots, m-1$$

$$P(Y_i \leqslant k \mid \mathbf{x}_i) = 1 - \exp[-\exp(u_{ki})] \qquad k = 1, 2, \ldots, m-1$$

$$P(Y_i = k \mid \mathbf{x}_i) = P(Y_i \leqslant k \mid \mathbf{x}_i) - P(Y_i \leqslant k-1 \mid \mathbf{x}_i)$$

$$= \begin{cases} 1 - \exp[-\exp(u_{1i})] & k = 1 \\ \exp[-\exp(u_{k-1\,i})] - \exp[-\exp(u_{ki})] & k = 2, \ldots, m-1 \\ \exp[-\exp(u_{m-1\,i})] & k = m \end{cases}$$

The log-likelihood function based on these two models can be obtained by replacing $P(Y_i = k_i \mid \mathbf{x}_i)$ in (14.3.8) with the respective expressions above.

Example 14.12 Now consider the NFG, IFG, and DM categories in Example 14.9 that represent three levels of severity in glucose intolerance. DM (diabetes) is defined as fasting plasma glucose (FPG) $\geqslant 126$ mg/dL, IFG (impaired fasting glucose) as FPG between 110 and 125 mg/dL, and NFG (normal fasting glucose) as FPG < 110 mg/dL. Thus, it is reasonable to consider the outcome variable as ordinal. Let the outcome variable $Y = 1$ if DM, 2 if IFG, and 3 if NFG. We fit the models in (14.3.5) using the SAS procedure LOGISTIC with all the covariates. The SAS program allows users to use a variable selection method (forward, backward, and stepwise). In this case, we use the stepwise selection method, and the results are given in the first part of Table 14.18. The stepwise method identifies SBP and LINSUL as significant independent variables. For $k = 1$ [i.e., we compare diabetes with

Table 14.18 Asymptotic Partial Likelihood Inference from the Ordinal Regression Model with Different Link Functions for the Diabetic Status Data in Example 14.9

k	Variable	Regression Coefficient	Standard Error	Chi-Square Statistic	p	Odds Ratio	95% Confidence Interval for Odds Ratio	
							Lower	Upper
				Model with Logit Link Function				
1	INTERCP1	−6.753	1.183	32.571	0.0001			
2	INTERCP2	−5.485	1.151	22.708	0.0001			
	SBP	0.019	0.007	6.114	0.0134	1.02	1.00	1.03
	LINSUL	0.925	0.213	18.803	0.0001	2.52	1.67	3.90
Log-likelihood ratio statistic for $H_0: b_1 = b_2 = 0$[a]				26.831	0.0001			
				Model with Inverse Normal Link Function				
1	INTERCP1	−3.971	0.677	34.415	0.0001			
2	INTERCP2	−3.240	0.664	23.790	0.0001			
	SBP	0.011	0.004	6.311	0.0120			
	LINSUL	0.530	0.123	18.674	0.0001			
Log-likelihood ratio statistic for $H_0: b_1 = b_2 = 0$				26.261	0.0001			
				Model from Complementary Log-Log Link Function				
1	INTERCP1	−5.626	0.915	37.813	0.0001			
2	INTERCP2	−4.562	0.894	26.025	0.0001			
	SBP	0.014	0.006	5.721	0.0168			
	LINSUL	0.715	0.162	19.534	0.0001			
Log-likelihood ratio statistic for $H_0: b_1 = b_2 = 0$				25.835	0.0001			

[a] b_1 and b_2 are coefficients for SBP and LINSUL, respectively.

nondiabetes (NFG + IFG)] the estimated model in (14.3.5) is

$$\log \frac{P(Y_i \leqslant 1 \mid \mathbf{x}_i)}{1 - P(Y_i \leqslant 1 \mid \mathbf{x}_i)} = \log \frac{P(\text{participant } i \text{ is diabetic})}{P(\text{participant } i \text{ is nondiabetic})}$$
$$= -6.753 + 0.019\text{SBP}_i + 0.925\text{LINSUL}_i$$

For $k = 2$, the estimated model in (14.3.5) is

$$\log \frac{P(Y_i \leqslant 2 \mid \mathbf{x}_i)}{1 - P(Y_i \leqslant 2 \mid \mathbf{x}_i)} = \log \frac{P(\text{participant } i \text{ is either DM or IFG})}{P(\text{participant } i \text{ is NFG})}$$
$$= -5.485 + 0.019\text{SBP}_i + 0.925\text{LINSUL}_i$$

According to (14.3.7), we can estimate the probability of developing DM, IFG, or remaining NFG. For example, the probability of developing IFG is

$$P(Y_i = 2 \mid \mathbf{x}_i) = P(\text{participant } i \text{ is IFG})$$
$$= \frac{\exp(-5.485 + 0.019\text{SBP}_i + 0.925\text{LINSUL}_i)}{1 + \exp(-5.485 + 0.019\text{SBP}_i + 0.925\text{LINSUL}_i)}$$
$$- \frac{\exp(-6.753 + 0.019\text{SBP}_i + 0.925\text{LINSUL}_i)}{1 + \exp(-6.753 + 0.019\text{SBP}_i + 0.925\text{LINSUL}_i)}$$

Thus, for a person whose systolic blood pressure is 140 mmHg and whose log insulin is 3, the probability of developing IFG can be obtained by plugging these values into the preceding equation. The result is

$$P(\text{participant is IFG}) = \frac{0.951}{1 + 0.951} - \frac{0.268}{1 + 0.268}$$
$$= 0.276$$

As noted earlier, the coefficients in these models can be interpreted as those in the ordinary logistic regression model for binary outcomes. In this example, the higher SBP and LINSUL are, the higher the odds of having DM than of not having DM, or the higher the odds of having either DM or IFG than of being NFG. The odds ratio is 1.02 [exp(0.019)] times (or 2% higher) for a 1-unit increase in SBP assuming that LINSUL is the same, and 2.52 times (or 152% higher) for a 1-unit increase in LINSUL assuming that SBP is the same. From the table, SBP and LINSUL are related significantly to the diabetic status in all models with different link functions.

SAS and SPSS can also be used for the other two link functions: the inverse of the cumulative standard normal distribution and the complementary log-log

link functions introduced in Section 14.2.3. Table 14.18 includes the results from models with these two link functions. The results are very similar to those obtained using the logit link function.

The following SAS, SPSS, and BMDP codes can be used to obtain the results in Table 14.18.

SAS code:

```
data w1;
  infile 'c:\ex14d2d6.dat' missover;
  input age ageg sex sbp dbp lacr hdl linsul smoke dms dm sn;
run;
title "Ordinal regression model with logic link function";
proc logistic data = w1 descending;
  model dms = age sex sbp dbp lacr hdl linsul smoke
              / selection = s lackfit link = logit;
run;
title "Ordinal regression model with inverse normal link function';
proc logistic data = w1 descending;
  model dms = age sex sbp dbp lacr hdl linsul smoke
              / selection = s lackfit link = probit;
run;
title "Ordinal regression model with complementary log-log link function";
proc logistic data = w1 descending;
  model dms = age sex sbp dbp lacr hdl linsul smoke
              / selection = s lackfit link = cloglog;
run;
```

SPSS code:

```
data list file = 'c:\ex14d2d6.dat' free
        / age ageg sex sbp dbp lacr hdl linsul smoke dms dm sn.
Compute y = 4-dms.
plum y with sbp linsul
        /link = logit
        /print = fit history parameter.
plum y with sbp linsul
        /link =  probit
        /print = fit history parameter.
plum y with sbp linsul
        /link =  cloglog
        /print = fit history parameter.
```

BMDP PR code for the logit link function only:

```
/input      file = 'c:\ex14d2d6.dat' .
            variables = 12.
            format = free.
```

```
/variable   names = age, ageg, sex, sbp, dbp, lacr, hdl, linsul, smoke,
            dms, dm, sn.
            Use = age, sex to smoke.
/transform  y = 4-dms.
/group      codes(y) = 1, 2, 3.
            Names(y) = DM, IFG, NFG.
/regress    depend = y.
            Level = 3.
            Type = ord.
            Interval = age, sex to smoke.
            enter = .05, .05.
            remove = = .05, .05.
/print      cell = used.
/end
```

Note that the model for ordinal polychotomous outcomes in BMDP PR is defined as

$$\log \frac{P(Y_i > k \mid \mathbf{x}_i)}{1 - P(Y_i > k \mid \mathbf{x}_i)} = \tilde{\alpha}_k + \sum_{j=1}^{p} \tilde{\beta}_j x_{ij} = \tilde{u}_{ki} \qquad k = 1, 2, \ldots, m-1$$

Compared with (14.3.5), $\tilde{\alpha}_k = -a_k$, $k = 1, 2, \ldots, m-1$; $\tilde{\beta}_j = -b_j$, $j = 1, 2, \ldots, p$.

Bibliographical Remarks

The linear logistic regression method is discussed extensively in Cox (1970), Cox and Snell (1989), Collett (1991), Kleinbaum (1994), and Hosmer and Lemeshow (2000). Cox's book provides the theoretical background, and Hosmer and Lemeshow discuss broad application of the method, including model-building strategies and interpretation and presentation of analysis results. In addition to the papers and books cited in this chapter, other works on the subject include Anderson (1972), Mantel (1973), Prentice (1976), Prentice and Pyke (1979), Holford et al. (1978), and Breslow and Day (1980). Applications of the logistic regression model can easily be found in various biomedical journals.

EXERCISES

14.1 Consider the study presented in Example 3.5 and the data for the 40 patients in Table 3.10.

- **(a)** Construct a summary table similar to Table 3.11.
- **(b)** Construct a table similar to Table 3.12.
- **(c)** Use the chi-square test to detect any differences in retinopathy rates among the subgroups obtained in part (b).

(d) On the basis of these 40 patients, identify the most important risk factors using a linear logistic regression method.

14.2 Consider the data for the 33 hypernephroma patients given in Exercise Table 3.1. Let "response" be defined as stable, partial response, or complete response.

(a) Compare each of the five skin test results of the responders with those of the nonresponders.

(b) Use a linear logistic regression method to identify the most important risk factors related to response.

(i) Consider the five skin tests only.

(ii) Consider age, gender, and the five skin tests.

14.3 Consider all nine risk variables (age, gender, family history of melanoma, and six skin tests) in Exercise 3.3 and Exercise Table 3.3. Identify the most important prognostic factors that are related to remission. Use both univariate and multivariate methods.

14.4 Consider the data of 58 hypernephroma patients given in Exercise Table 3.2. Apply the logistic regression method to response (defined as complete response, partial response, or stable disease). Include gender, age, nephrectomy treatment, lung metastasis, and bone metastasis as independent variables.

(a) Identify the most significant independent variables.

(b) Obtain estimates of odds ratios and confidence intervals when applicable.

14.5 Consider the case where there is one continuous independent variable X_1. Show that the log odds ratio for $X_1 = x_1 + m$ versus $X_1 = x_1$ is mb_1, where b_1 is the logistic regression coefficient.

14.6 Using the data in Table 12.4, define the index function CVD as $\text{CVD} = 1$ if $\text{dg} \geqslant 1$, and $\text{CVD} = 0$ otherwise, and fit a logistic regression model for CVD by using the stepwise selection method to select risk factors among the same factors as those noted at the bottom of Table 12.7. Compare the results obtained with those in Table 12.7.

14.7 Assuming that $P(\text{a person is sampled} \mid y, \mathbf{x}) = P(\text{a person is sampled} \mid y)$, that is, the sampling probability is independent of the risk factors $\mathbf{x}$, derive (14.2.15).

14.8 By using (14.2.14) and (14.2.1), show that (14.2.20) reduces to (14.2.21).

14.9 Derive (14.3.2).

14.10 Consider the data in Table 12.4. Fit the generalized logistic regression model in (14.3.1) for DG with covariates AGE, SEX, LACR, and LTG by using the SAS CATMOD, SPSS NOMREG, or BMDP PR procedure. Select risk factors among those noted at the bottom of Table 12.7 using the stepwise selection method in the BMDP PR procedure. Compare the results with those given in Table 13.5.

14.11 Using the same notation and data as in Table 14.11, (1) fit the outcome variable Y with the generalized logistic regression model in (14.3.1) with SEX as the covariate; (2) fit a logistic regression for the binary outcome DM versus NFG, with SEX as the covariate, by using the data from DM and NFG participants only; (3) fit a logistic regression for the binary outcome IFG versus NFG, with SEX as the covariate, by using the data from IFG and NFG participants only; (4) compare the coefficients obtained from (2) and (3) with the coefficients obtained from (1), and (5) report what you have found.

14.12 Perform the same analyses as in Exercise 14.11 but use SBP as the covariate, and discuss your findings.

APPENDIX A

Newton–Raphson Method

The Newton–Raphson method (Ralston and Wilf, 1967; Carnahan et al., 1969) is a numerical iterative procedure that can be used to solve nonlinear equations. An iterative procedure is a technique of successive approximations, and each approximation is called an *iteration*. If the successive approximations approach the solution very closely, we say that the iterations *converge*. The maximum likelihood estimates of various parameters and coefficients discussed in Chapters 7, 9, and 11 to 14 can be obtained by using the Newton–Raphson method. In this appendix we discuss and illustrate the use of this method, first considering a single nonlinear equation and then a set of nonlinear equations.

Let $f(x) = 0$ be the equation to be solved for x. The Newton–Raphson method requires an initial estimate of x, say $\hat{x}_0$, such that $f(\hat{x}_0)$ is close to zero preferably, and then the first approximate iteration is given by

$$\hat{x}_1 = \hat{x}_0 - \frac{f(\hat{x}_0)}{f'(\hat{x}_0)} \tag{A.1}$$

where $f'(\hat{x}_0)$ is the first derivative of $f(x)$ evaluated at $x = \hat{x}_0$. In general, the $(k + 1)$th iteration or approximation is given by

$$\hat{x}_{k+1} = \hat{x}_k - \frac{f(x_k)}{f'(x_k)} \tag{A.2}$$

where $f'(\hat{x}_k)$ is the first derivative of $f(x)$ evaluated at $x = \hat{x}_k$. The iteration terminates at the kth iteration if $f(\hat{x}_k)$ is close enough to zero or the difference between $\hat{x}_k$ and $\hat{x}_{k-1}$ is negligible. The stopping rule is rather subjective. Acceptable rules are that $f(\hat{x}_k)$ or $d = \hat{x}_k - \hat{x}_{k-1}$ is in the neighborhood of 10^{-6} or 10^{-7}.

Example A.1 Consider the function

$$f(x) = x^3 - x + 2$$

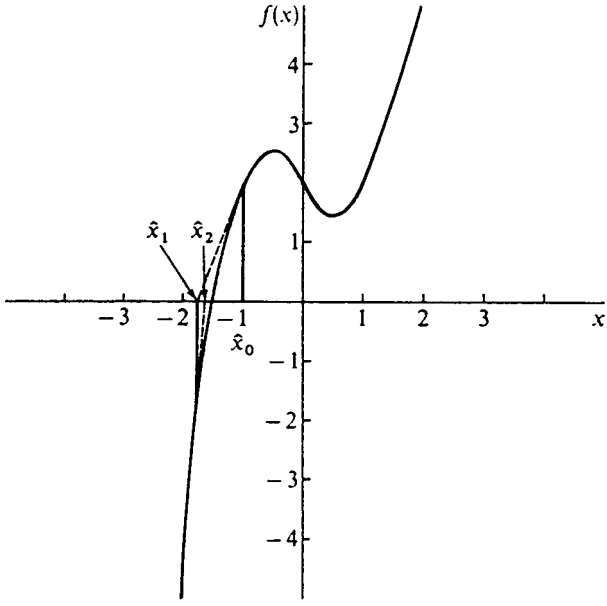


Figure A.1 Graphical presentation of the Newton–Raphson method for Example A.1.

We wish to find the value of x such that $f(x) = 0$ by the Newton–Raphson method. The first derivative of $f(x)$ is

$$f'(x) = 3x^2 - 1$$

Since $f(-1) = 2$ and $f(-2) = -4$, graphically (Figure A.1), we see that the curve cuts through the x axis $[f(x) = 0]$ between -1 and -2. This gives us a good hint of an initial value of x. Suppose that we begin with $\hat{x}_0 = -1$; $f(\hat{x}_0) = 2$ and $f'(\hat{x}_0) = 2$. Thus, the first iteration, following (A.1), gives

$$\hat{x}_1 = -1 - \frac{2}{2} = -2$$

and $f(\hat{x}_1) = -4$ and $f'(\hat{x}_1) = 11$. Following (A.2), we obtain the following:

Second iteration:

$$\hat{x}_2 = -2 + \frac{4}{11} = -1.6364$$

$$f(\hat{x}_2) = -0.7456 \qquad f'(\hat{x}_2) = 7.0334$$

Third iteration:

$$\hat{x}_3 = -1.6364 + \frac{0.7456}{7.0334} = -1.5304$$

$$f(\hat{x}_3) = -0.054 \qquad f'(\hat{x}_3) = 6.0264$$

Fourth iteration:

$$\hat{x}_4 = -1.5304 + \frac{0.054}{6.0264} = -1.52144$$

$$f(\hat{x}_4) = -0.00036 \qquad f'(\hat{x}_4) = 5.9443$$

Fifth iteration:

$$\hat{x}_5 = -1.52144 + \frac{0.00036}{5.9443} = -1.52138$$

$$f(\hat{x}_5) = 0.0000017$$

At the fifth iteration, for $x = -1.52138$, $f(x)$ is very close to zero. If the stopping rule is that $f(x) \leqslant 10^{-6}$, the iterative procedure would terminate after the fifth iteration and $x = -1.52138$ is the root of the equation $x^3 - x + 2 = 0$. Figure A.1 gives the graphical presentation of $f(x)$ and the iteration.

It should be noted that the Newton–Raphson method can only find the real roots of an equation. The equation $x^3 - x + 2 = 0$ has only one real root, as shown in Figure A.1; the other two are complex roots.

The Newton–Raphson method can be extended to solve a system of equations with more than one unknown. Suppose that we wish to find values of $x_1, x_2, \ldots, x_p$ such that

$$\begin{aligned} f_1(x_1, \ldots, x_p) &= 0 \\ f_2(x_1, \ldots, x_p) &= 0 \\ &\vdots \\ f_p(x_1, \ldots, x_p) &= 0 \end{aligned}$$

Let a_{ij} be the partial derivative of f_i with respect to x_j; that is, $a_{ij} = \partial f_i / \partial x_j$.

The matrix

$$J = \begin{bmatrix} a_{11} & \cdots & a_{1p} \\ a_{21} & \cdots & a_{2p} \\ \vdots & & \vdots \\ a_{p1} & \cdots & a_{pp} \end{bmatrix}$$

is called the *Jacobian matrix*. Let the inverse of J, denoted by J^{-1}, be

$$J^{-1} = \begin{bmatrix} b_{11} & \cdots & b_{1p} \\ b_{21} & \cdots & b_{2p} \\ \vdots & & \vdots \\ b_{p1} & \cdots & b_{pp} \end{bmatrix}$$

Let $x_1^k, x_2^k, \ldots, x_p^k$ be the approximate root at the kth iteration; let $f_1^k, \ldots, f_p^k$ be the corresponding values of the functions $f_1, \ldots, f_p$, that is,

$$\begin{aligned} f_1^k &= f_1(x_1^k, \ldots, x_p^k) \\ &\vdots \\ f_p^k &= f_p(x_1^k, \ldots, x_p^k) \end{aligned}$$

and let b_{ij}^k be the ijth element of J^{-1} evaluated at $x_1^k, \ldots, x_p^k$. Then the next approximation is given by

$$\begin{aligned} x_1^{k+1} &= x_1^k - (b_{11}^k f_1^k + b_{12}^k f_2^k + \cdots + b_{1p}^k f_p^k) \\ x_2^{k+1} &= x_2^k - (b_{21}^k f_1^k + b_{22}^k f_2^k + \cdots + b_{2p}^k f_p^k) \\ &\vdots \\ x_p^{k+1} &= x_p^k - (b_{p1}^k f_1^k + b_{p2}^k f_2^k + \cdots + b_{pp}^k f_p^k) \end{aligned} \tag{A.3}$$

The iterative procedure begins with a preselected initial approximate $x_1^0, x_2^0, \ldots, x_p^0$, proceeds following (A.3), and terminates either when $f_1, f_2, \ldots, f_p$ are close enough to zero or when differences in the x values at two consecutive iterations are negligible.

Example A.2 Suppose that we wish to find the value of x_1 and x_2 such that

$$x_1^2 + x_1 x_2 - 2x_1 - 1 = 0 \qquad x_1^3 - x_1 + x_2 - 2 = 0$$

In this case, $p = 2$:

$$f_1 = x_1^2 + x_1x_2 - 2x_1 - 1 \qquad f_2 = x_1^3 - x_1 + x_2 - 2$$

Since $\partial f_1/\partial x_1 = 2x_1 + x_2 - 2$, $\partial f_1/\partial x_2 = x_1$, $\partial f_2/\partial x_1 = 3x_1^2 - 1$, and $\partial f_2/\partial x_2 = 1$, the Jacobian matrix is

$$J = \begin{bmatrix} 2x_1 + x_2 - 2 & x_1 \\ 3x_1^2 - 1 & 1 \end{bmatrix} \tag{A.4}$$

Let the initial estimates be $x_1^0 = 0$, $x_2^0 = 1$, $f_1^0 = -1$, and $f_2^0 = -1$:

$$J = \begin{bmatrix} -1 & 0 \\ -1 & 1 \end{bmatrix} \qquad J^{-1} = \begin{bmatrix} -1 & 0 \\ -1 & 1 \end{bmatrix}$$

Iteration 1. Following (A.3), we obtain

$$x_1^1 = 0 - [(-1)(-1) + 0(-1)] = -1 \qquad x_2^1 = 1 - [(-1)(-1) + 1(-1)] = 1$$

With these values, $f_1^1 = 1$, $f_2^1 = -1$, and

$$J = \begin{bmatrix} -3 & -1 \\ 2 & 1 \end{bmatrix} \qquad J^{-1} = \begin{bmatrix} -1 & -1 \\ 2 & 3 \end{bmatrix}$$

Iteration 2. From (A.3) we obtain

$$x_1^2 = -1 - [(-1)(1) + (-1)(-1)] = -1 \qquad x_2^2 = 1 - [(2)(1) + (3)(-1)] = 2$$

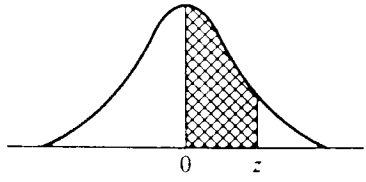
With these values, $f_1^2 = 0$ and $f_2^2 = 0$. Therefore, the iteration procedure terminates and the solution of the two simultaneous equations is $x_1 = -1$, $x_2 = 2$.

The number of iterations required depends strongly on the initial values chosen. In Example A.2, if we use $x_1^0 = 0$, $x_2^0 = 0$, it requires about 11 iterations to find the solution. Interested readers may try it as an exercise.

APPENDIX B

Statistical Tables

Table B-1 Normal Curve Areas



z	.00	.01	.02	.03	.04	.05	.06	.07	.08	.09
0.0	.0000	.0040	.0080	.0120	.0160	.0199	.0239	.0279	.0319	.0359
0.1	.0398	.0438	.0478	.0517	.0557	.0596	.0636	.0675	.0714	.0753
0.2	.0793	.0832	.0871	.0910	.0948	.0987	.1026	.1064	.1103	.1141
0.3	.1179	.1217	.1255	.1293	.1331	.1368	.1406	.1443	.1480	.1517
0.4	.1554	.1591	.1628	.1664	.1700	.1736	.1772	.1808	.1844	.1879
0.5	.1915	.1950	.1985	.2019	.2054	.2088	.2123	.2157	.2190	.2224
0.6	.2257	.2291	.2324	.2357	.2389	.2422	.2454	.2486	.2517	.2549
0.7	.2580	.2611	.2642	.2673	.2704	.2734	.2764	.2794	.2823	.2852
0.8	.2881	.2910	.2939	.2967	.2995	.3023	.3051	.3078	.3106	.3133
0.9	.3159	.3186	.3212	.3238	.3264	.3289	.3315	.3340	.3365	.3389
1.0	.3413	.3438	.3461	.3485	.3508	.3531	.3554	.3577	.3599	.3621
1.1	.3643	.3665	.3686	.3708	.3729	.3749	.3770	.3790	.3810	.3830
1.2	.3849	.3869	.3888	.3907	.3925	.3944	.3962	.3980	.3997	.4015
1.3	.4032	.4049	.4066	.4082	.4099	.4115	.4131	.4147	.4162	.4177
1.4	.4192	.4207	.4222	.4236	.4251	.4265	.4279	.4292	.4306	.4319
1.5	.4332	.4345	.4357	.4370	.4382	.4394	.4406	.4418	.4429	.4441
1.6	.4452	.4463	.4474	.4484	.4495	.4505	.4515	.4525	.4535	.4545
1.7	.4554	.4564	.4573	.4582	.4591	.4599	.4608	.4616	.4625	.4633
1.8	.4641	.4649	.4656	.4664	.4671	.4678	.4686	.4693	.4699	.4706
1.9	.4713	.4719	.4726	.4732	.4738	.4744	.4750	.4756	.4761	.4767
2.0	.4772	.4778	.4783	.4788	.4793	.4798	.4803	.4808	.4812	.4817
2.1	.4821	.4826	.4830	.4834	.4838	.4842	.4846	.4850	.4854	.4857
2.2	.4861	.4864	.4868	.4871	.4875	.4878	.4881	.4884	.4887	.4890
2.3	.4893	.4896	.4898	.4901	.4904	.4906	.4909	.4911	.4913	.4916
2.4	.4918	.4920	.4922	.4925	.4927	.4929	.4931	.4932	.4934	.4936
2.5	.4938	.4940	.4941	.4943	.4945	.4946	.4948	.4949	.4951	.4952
2.6	.4953	.4955	.4956	.4957	.4959	.4960	.4961	.4962	.4963	.4964
2.7	.4965	.4966	.4967	.4968	.4969	.4970	.4971	.4972	.4973	.4974
2.8	.4974	.4975	.4976	.4977	.4977	.4978	.4979	.4979	.4980	.4981
2.9	.4981	.4982	.4982	.4983	.4984	.4984	.4985	.4985	.4986	.4986
3.0	.4987	.4987	.4987	.4988	.4988	.4989	.4989	.4989	.4990	.4990

Source: Abridged from Table 1 of *Statistical Tables and Formulas*, by A. Hald, John Wiley & Sons, 1952. Reproduced by permission of John Wiley & Sons.

Table B-2 Percentage Points of the χ^2-Distribution

ν d.f.	99.5%	97.5%	5%	2.5%	1%	0.5%
1	392704×10^{-10}	982069×10^{-9}	3.84146	5.02389	6.63490	7.87944
2	0.0100251	0.0506356	5.99147	7.37776	9.21034	10.5966
3	0.0717212	0.215795	7.81473	9.34840	11.3449	12.8381
4	0.206990	0.484419	9.48773	11.1433	13.2767	14.8602
5	0.411740	0.831211	11.0705	12.8325	15.0863	16.7496
6	0.675727	1.237347	12.5916	14.4494	16.8119	18.5476
7	0.989265	1.68987	14.0671	16.0128	18.4753	20.2777
8	1.344419	2.17973	15.5073	17.5346	20.0902	21.9550
9	1.734926	2.70039	16.9190	19.0228	21.6660	23.5893
10	2.15585	3.24697	18.3070	20.4831	23.2093	25.1882
11	2.60321	3.81575	19.6751	21.9200	24.7250	26.7569
12	3.07382	4.40379	21.0261	23.3367	26.2170	28.2995
13	3.56503	5.00874	22.3621	24.7356	27.6883	29.8194
14	4.07468	5.62872	23.6848	26.1190	29.1413	31.3193
15	4.60094	6.26214	24.9958	27.4884	30.5779	32.8013
16	5.14224	6.90766	26.2962	28.8454	31.9999	34.2672
17	5.69724	7.56418	27.5871	30.1910	33.4087	35.7185
18	6.26481	8.23075	28.8693	31.5264	34.8053	37.1564
19	6.84398	8.90655	30.1435	32.8523	36.1908	38.5822
20	7.43386	9.59083	31.4104	34.1696	37.5662	39.9968
21	8.03366	10.28293	32.6705	35.4789	38.9321	41.4010
22	8.64272	10.9823	33.9244	36.7807	40.2894	42.7956
23	9.26042	11.6885	35.1725	38.0757	41.6384	44.1813
24	9.88623	12.4011	36.4151	39.3641	42.9798	45.5585
25	10.5197	13.1197	37.6525	40.6465	44.3141	46.9278
26	11.1603	13.8439	38.8852	41.9232	45.6417	48.2899
27	11.8076	14.5733	40.1133	43.1944	46.9630	49.6449
28	12.4613	15.3079	41.3372	44.4607	48.2782	50.9933
29	13.1211	16.0471	42.5569	45.7222	49.5879	52.3356
30	13.7867	16.7908	43.7729	46.9792	50.8922	53.6720
40	20.7065	24.4331	55.7585	59.3417	63.6907	66.7659
50	27.9907	32.3574	67.5048	71.4202	76.1539	79.4900
60	35.5346	40.4817	79.0819	83.2976	88.3794	91.9517
70	43.2752	48.7576	90.5312	95.0231	100.425	104.215
80	51.1720	57.1532	101.879	106.629	112.329	116.321
90	59.1963	65.6466	113.145	118.136	124.116	128.299
100	67.3276	74.2219	124.342	129.561	135.807	140.169

Source: "Tables of the Percentage Points of the χ^2-Distribution," by Catherine M. Thompson, *Biometrika*, Vol. 32, pp. 188–189 (1941). Reproduced by permission of the editor of *Biometrika*.

Table B-3 5% Points of the *F*-Distribution

ν_2 \ ν_1	Degrees of Freedom for Numerator								
	1	2	3	4	5	6	7	8	9
1	161.45	199.50	215.71	224.58	230.16	233.99	236.77	238.88	240.54
2	18.513	19.000	19.164	19.247	19.296	19.330	19.353	19.371	19.385
3	10.128	9.5521	9.2766	9.1172	9.0135	8.9406	8.8868	8.8452	8.8123
4	7.7086	6.9443	6.5914	6.3883	6.2560	6.1631	6.0942	6.0410	5.9988
5	6.6079	5.7861	5.4095	5.1922	5.0503	4.9503	4.8759	4.8183	4.7725
6	5.9874	5.1433	4.7571	4.5337	4.3874	4.2839	4.2066	4.1468	4.0990
7	5.5914	4.7374	4.3468	4.1203	3.9715	3.8660	3.7870	3.7257	3.6767
8	5.3177	4.4590	4.0662	3.8378	3.6875	3.5806	3.5005	3.4381	3.3881
9	5.1174	4.2565	3.8626	3.6331	3.4817	3.3738	3.2927	3.2296	3.1789
10	4.9646	4.1028	3.7083	3.4780	3.3258	3.2172	3.1355	3.0717	3.0204
11	4.8443	3.9823	3.5874	3.3567	3.2039	3.0946	3.0123	2.9480	2.8962
12	4.7472	3.8853	3.4903	3.2592	3.1059	2.9961	2.9134	2.8486	2.7964
13	4.6672	3.8056	3.4105	3.1791	3.0254	2.9153	2.8321	2.7669	2.7144
14	4.6001	3.7389	3.3439	3.1122	2.9582	2.8477	2.7642	2.6987	2.6458
15	4.5431	3.6823	3.2871	3.0556	2.9013	2.7905	2.7066	2.6408	2.5876
16	4.4940	3.6337	3.2389	3.0069	2.8524	2.7413	2.6572	2.5911	2.5377
17	4.4513	3.5915	3.1968	2.9647	2.8100	2.6987	2.6143	2.5480	2.4943
18	4.4139	3.5546	3.1599	2.9277	2.7729	2.6613	2.5767	2.5102	2.4563
19	4.3808	3.5219	3.1274	2.8951	2.7401	2.6283	2.5435	2.4768	2.4227
20	4.3513	3.4928	3.0984	2.8661	2.7109	2.5990	2.5140	2.4471	2.3928
21	4.3248	3.4668	3.0725	2.8401	2.6848	2.5727	2.4876	2.4205	2.3661
22	4.3009	3.4434	3.0491	2.8167	2.6613	2.5491	2.4638	2.3965	2.3419
23	4.2793	3.4221	3.0280	2.7955	2.6400	2.5277	2.4422	2.3748	2.3201
24	4.2597	3.4028	3.0088	2.7763	2.6207	2.5082	2.4226	2.3551	2.3002
25	4.2417	3.3852	2.9912	2.7587	2.6030	2.4904	2.4047	2.3371	2.2821
26	4.2252	3.3690	2.9751	2.7426	2.5868	2.4741	2.3883	2.3205	2.2655
27	4.2100	3.3541	2.9604	2.7278	2.5719	2.4591	2.3732	2.3053	2.2501
28	4.1960	3.3404	2.9467	2.7141	2.5581	2.4453	2.3593	2.2913	2.2360
29	4.1830	3.3277	2.9340	2.7014	2.5454	2.4324	2.3463	2.2782	2.2229
30	4.1709	3.3158	2.9223	2.6896	2.5336	2.4205	2.3343	2.2662	2.2107
40	4.0848	3.2317	2.8387	2.6060	2.4495	2.3359	2.2490	2.1802	2.1240
60	4.0012	3.1504	2.7581	2.5252	2.3683	2.2540	2.1665	2.0970	2.0401
120	3.9201	3.0718	2.6802	2.4472	2.2900	2.1750	2.0867	2.0164	1.9588
∞	3.8415	2.9957	2.6049	2.3719	2.2141	2.0986	2.0096	1.9384	1.8799

Degrees of Freedom for Denominator

ν_2 \ ν_1	Degrees of Freedom for Numerator									
	10	12	15	20	24	30	40	60	120	∞
1	241.88	243.91	245.95	248.01	249.05	250.09	251.14	252.20	253.25	254.32
2	19.396	19.413	19.429	19.446	19.454	19.462	19.471	19.479	19.487	19.496
3	8.7855	8.7446	8.7029	8.6602	8.6385	8.6166	8.5944	8.5720	8.5494	8.5265
4	5.9644	5.9117	5.8578	5.8025	5.7744	5.7459	5.7170	5.6878	5.6581	5.6281
5	4.7351	4.6777	4.6188	4.5581	4.5272	4.4957	4.4638	4.4314	4.3984	4.3650
6	4.0600	3.9999	3.9381	3.8742	3.8415	3.8082	3.7743	3.7398	3.7047	3.6688
7	3.6365	3.5747	3.5108	3.4445	3.4105	3.3758	3.3404	3.3043	3.2674	3.2298
8	3.3472	3.2840	3.2184	3.1503	3.1152	3.0794	3.0428	3.0053	2.9669	2.9276
9	3.1373	3.0729	3.0061	2.9365	2.9005	2.8637	2.8259	2.7872	2.7475	2.7067
10	2.9782	2.9130	2.8450	2.7740	2.7372	2.6996	2.6609	2.6211	2.5801	2.5379
11	2.8536	2.7876	2.7186	2.6464	2.6090	2.5705	2.5309	2.4901	2.4480	2.4045
12	2.7534	2.6866	2.6169	2.5436	2.5055	2.4663	2.4259	2.3842	2.3410	2.2962
13	2.6710	2.6037	2.5331	2.4589	2.4202	2.3803	2.3392	2.2966	2.2524	2.2064
14	2.6021	2.5342	2.4630	2.3879	2.3487	2.3082	2.2664	2.2230	2.1778	2.1307
15	2.5437	2.4753	2.4035	2.3275	2.2878	2.2468	2.2043	2.1601	2.1141	2.0658
16	2.4935	2.4247	2.3522	2.2756	2.2354	2.1938	2.1507	2.1058	2.0589	2.0096
17	2.4499	2.3807	2.3077	2.2304	2.1898	2.1477	2.1040	2.0584	2.0107	1.9604
18	2.4117	2.3421	2.2686	2.1906	2.1497	2.1071	2.0629	2.0166	1.9681	1.9168
19	2.3779	2.3080	2.2341	2.1555	2.1141	2.0712	2.0264	1.9796	1.9302	1.8780
20	2.3479	2.2776	2.2033	2.1242	2.0825	2.0391	1.9938	1.9464	1.8963	1.8432
21	2.3210	2.2504	2.1757	2.0960	2.0540	2.0102	1.9645	1.9165	1.8657	1.8117
22	2.2967	2.2258	2.1508	2.0707	2.0283	1.9842	1.9380	1.8895	1.8380	1.7831
23	2.2747	2.2036	2.1282	2.0476	2.0050	1.9605	1.9139	1.8649	1.8128	1.7570
24	2.2547	2.1834	2.1077	2.0267	1.9838	1.9390	1.8920	1.8424	1.7897	1.7331
25	2.2365	2.1649	2.0889	2.0075	1.9643	1.9192	1.8718	1.8217	1.7684	1.7110
26	2.2197	2.1479	2.0716	1.9898	1.9464	1.9010	1.8533	1.8027	1.7488	1.6906
27	2.2043	2.1323	2.0558	1.9736	1.9299	1.8842	1.8361	1.7851	1.7307	1.6717
28	2.1900	2.1179	2.0411	1.9586	1.9147	1.8687	1.8203	1.7689	1.7138	1.6541
29	2.1768	2.1045	2.0275	1.9446	1.9005	1.8543	1.8055	1.7537	1.6981	1.6377
30	2.1646	2.0921	2.0148	1.9317	1.8874	1.8409	1.7918	1.7396	1.6835	1.6223
40	2.0772	2.0035	1.9245	1.8389	1.7929	1.7444	1.6928	1.6373	1.5766	1.5089
60	1.9926	1.9174	1.8364	1.7480	1.7001	1.6491	1.5943	1.5343	1.4673	1.3893
120	1.9105	1.8337	1.7505	1.6587	1.6084	1.5543	1.4952	1.4290	1.3519	1.2539
∞	1.8307	1.7522	1.6664	1.5705	1.5173	1.4591	1.3940	1.3180	1.2214	1.0000

Degrees of Freedom for Denominator

Table B-3 2.5% Points of the *F*-Distribution

ν_2 \ ν_1	Degrees of Freedom for Numerator								
	1	2	3	4	5	6	7	8	9
1	647.79	799.50	864.16	899.58	921.85	937.11	948.22	956.66	963.28
2	38.506	39.000	39.165	39.248	39.298	39.331	39.355	39.373	39.387
3	17.443	16.044	15.439	15.101	14.885	14.735	14.624	14.540	14.473
4	12.218	10.649	9.9792	9.6045	9.3645	9.1973	9.0741	8.9796	8.9047
5	10.007	8.4336	7.7636	7.3879	7.1464	6.9777	6.8531	6.7572	6.6810
6	8.8131	7.2598	6.5988	6.2272	5.9876	5.8197	5.6955	5.5996	5.5234
7	8.0727	6.5415	5.8898	5.5226	5.2852	5.1186	4.9949	4.8993	4.8232
8	7.5709	6.0595	5.4160	5.0526	4.8173	4.6517	4.5286	4.4332	4.3572
9	7.2093	5.7147	5.0781	4.7181	4.4844	4.3197	4.1971	4.1020	4.0260
10	6.9367	5.4564	4.8256	4.4683	4.2361	4.0721	3.9498	3.8549	3.7790
11	6.7241	5.2559	4.6300	4.2751	4.0440	3.8807	3.7586	3.6638	3.5879
12	6.5538	5.0959	4.4742	4.1212	3.8911	3.7283	3.6065	3.5118	3.4358
13	6.4143	4.9653	4.3472	3.9959	3.7667	3.6043	3.4827	3.3880	3.3120
14	6.2979	4.8567	4.2417	3.8919	3.6634	3.5014	3.3799	3.2853	3.2093
15	6.1995	4.7650	4.1528	3.8043	3.5764	3.4147	3.2934	3.1987	3.1227
16	6.1151	4.6867	4.0768	3.7294	3.5021	3.3406	3.2194	3.1248	3.0488
17	6.0420	4.6189	4.0112	3.6648	3.4379	3.2767	3.1556	3.0610	2.9849
18	5.9781	4.5597	3.9539	3.6083	3.3820	3.2209	3.0999	3.0053	2.9291
19	5.9216	4.5075	3.9034	3.5587	3.3327	3.1718	3.0509	2.9563	2.8800
20	5.8715	4.4613	3.8587	3.5147	3.2891	3.1283	3.0074	2.9128	2.8365
21	5.8266	4.4199	3.8188	3.4754	3.2501	3.0895	2.9686	2.8740	2.7977
22	5.7863	4.3828	3.7829	3.4401	3.2151	3.0546	2.9338	2.8392	2.7628
23	5.7498	4.3492	3.7505	3.4083	3.1835	3.0232	2.9024	2.8077	2.7313
24	5.7167	4.3187	3.7211	3.3794	3.1548	2.9946	2.8738	2.7791	2.7027
25	5.6864	4.2909	3.6943	3.3530	3.1287	2.9685	2.8478	2.7531	2.6766
26	5.6586	4.2655	3.6697	3.3289	3.1048	2.9447	2.8240	2.7293	2.6528
27	5.6331	4.2421	3.6472	3.3067	3.0828	2.9228	2.8021	2.7074	2.6309
28	5.6096	4.2205	3.6264	3.2863	3.0625	2.9027	2.7820	2.6872	2.6106
29	5.5878	4.2006	3.6072	3.2674	3.0438	2.8840	2.7633	2.6686	2.5919
30	5.5675	4.1821	3.5894	3.2499	3.0265	2.8667	2.7460	2.6513	2.5746
40	5.4239	4.0510	3.4633	3.1261	2.9037	2.7444	2.6238	2.5289	2.4519
60	5.2857	3.9253	3.3425	3.0077	2.7863	2.6274	2.5068	2.4117	2.3344
120	5.1524	3.8046	3.2270	2.8943	2.6740	2.5154	2.3948	2.2994	2.2217
∞	5.0239	3.6889	3.1161	2.7858	2.5665	2.4082	2.2875	2.1918	2.1136

Degrees of Freedom for Denominator

ν_2 \ ν_1	Degrees of Freedom for Numerator									
	10	12	15	20	24	30	40	60	120	∞
1	968.63	976.71	984.87	993.10	997.25	1,001.4	1,005.6	1,009.8	1,014.0	1,018.3
2	39.398	39.415	39.431	39.448	39.456	39.465	39.473	39.481	39.490	39.498
3	14.419	14.337	14.253	14.167	14.124	14.081	14.037	13.992	13.947	13.902
4	8.8439	8.7512	8.6565	8.5599	8.5109	8.4613	8.4111	8.3604	8.3092	8.2573
5	6.6192	6.5246	6.4277	6.3285	6.2780	6.2269	6.1751	6.1225	6.0693	6.0153
6	5.4613	5.3662	5.2687	5.1684	5.1172	5.0652	5.0125	4.9589	4.9045	4.8491
7	4.7611	4.6658	4.5678	4.4667	4.4150	4.3624	4.3089	4.2544	4.1989	4.1423
8	4.2951	4.1997	4.1012	3.9995	3.9472	3.8940	3.8398	3.7844	3.7279	3.6702
9	3.9639	3.8682	3.7694	3.6669	3.6142	3.5604	3.5055	3.4493	3.3918	3.3329
10	3.7168	3.6209	3.5217	3.4186	3.3654	3.3110	3.2554	3.1984	3.1399	3.0798
11	3.5257	3.4296	3.3299	3.2261	3.1725	3.1176	3.0613	3.0035	2.9441	2.8828
12	3.3736	3.2773	3.1772	3.0728	3.0187	2.9633	2.9063	2.8478	2.7874	2.7249
13	3.2497	3.1532	3.0527	2.9477	2.8932	2.8373	2.7797	2.7204	2.6590	2.5955
14	3.1469	3.0501	2.9493	2.8437	2.7888	2.7324	2.6742	2.6142	2.5519	2.4872
15	3.0602	2.9633	2.8621	2.7559	2.7006	2.6437	2.5850	2.5242	2.4611	2.3953
16	2.9862	2.8890	2.7875	2.6808	2.6252	2.5678	2.5085	2.4471	2.3831	2.3163
17	2.9222	2.8249	2.7230	2.6158	2.5598	2.5021	2.4422	2.3801	2.3153	2.2474
18	2.8664	2.7689	2.6667	2.5590	2.5027	2.4445	2.3842	2.3214	2.2558	2.1869
19	2.8173	2.7196	2.6171	2.5089	2.4523	2.3937	2.3329	2.2695	2.2032	2.1333
20	2.7737	2.6758	2.5731	2.4645	2.4076	2.3486	2.2873	2.2234	2.1562	2.0853
21	2.7348	2.6368	2.5338	2.4247	2.3675	2.3082	2.2465	2.1819	2.1141	2.0422
22	2.6998	2.6017	2.4984	2.3890	2.3315	2.2718	2.2097	2.1446	2.0760	2.0032
23	2.6682	2.5699	2.4665	2.3567	2.2989	2.2389	2.1763	2.1107	2.0415	1.9677
24	2.6396	2.5412	2.4374	2.3273	2.2693	2.2090	2.1460	2.0799	2.0099	1.9353
25	2.6135	2.5149	2.4110	2.3005	2.2422	2.1816	2.1183	2.0517	1.9811	1.9055
26	2.5895	2.4909	2.3867	2.2759	2.2174	2.1565	2.0928	2.0257	1.9545	1.8781
27	2.5676	2.4688	2.3644	2.2533	2.1946	2.1334	2.0693	2.0018	1.9299	1.8527
28	2.5473	2.4484	2.3438	2.2324	2.1735	2.1121	2.0477	1.9796	1.9072	1.8291
29	2.5286	2.4295	2.3248	2.2131	2.1540	2.0923	2.0276	1.9591	1.8861	1.8072
30	2.5112	2.4120	2.3072	2.1952	2.1359	2.0739	2.0089	1.9400	1.8664	1.7867
40	2.3882	2.2882	2.1819	2.0677	2.0069	1.9429	1.8752	1.8028	1.7242	1.6371
60	2.2702	2.1692	2.0613	1.9445	1.8817	1.8152	1.7440	1.6668	1.5810	1.4822
120	2.1570	2.0548	1.9450	1.8249	1.7597	1.6899	1.6141	1.5299	1.4327	1.3104
∞	2.0483	1.9447	1.8326	1.7085	1.6402	1.5660	1.4835	1.3883	1.2684	1.0000

Degrees of Freedom for Denominator

Table B-3 1% Points of the *F*-Distribution

ν_2 \ ν_1	Degrees of Freedom for Numerator								
	1	2	3	4	5	6	7	8	9
1	4,052.2	4,999.5	5,403.3	5,624.6	5,763.7	5,859.0	5,928.3	5,981.6	6,022.5
2	98.503	99.000	99.166	99.249	99.299	99.332	99.356	99.374	99.388
3	34.116	30.817	29.457	28.710	28.237	27.911	27.672	27.489	27.345
4	21.198	18.000	16.694	15.977	15.522	15.207	14.976	14.799	14.659
5	16.258	13.274	12.060	11.392	10.967	10.672	10.456	10.289	10.158
6	13.745	10.925	9.7795	9.1483	8.7459	8.4661	8.2600	8.1016	7.9761
7	12.246	9.5466	8.4513	7.8467	7.4604	7.1914	6.9928	6.8401	6.7188
8	11.259	8.6491	7.5910	7.0060	6.6318	6.3707	6.1776	6.0289	5.9106
9	10.561	8.0215	6.9919	6.4221	6.0569	5.8018	5.6129	5.4671	5.3511
10	10.044	7.5594	6.5523	5.9943	5.6363	5.3858	5.2001	5.0567	4.9424
11	9.6460	7.2057	6.2167	5.6683	5.3160	5.0692	4.8861	4.7445	4.6315
12	9.3302	6.9266	5.9526	5.4119	5.0643	4.8206	4.6395	4.4994	4.3875
13	9.0738	6.7010	5.7394	5.2053	4.8616	4.6204	4.4410	4.3021	4.1911
14	8.8616	6.5149	5.5639	5.0354	4.6950	4.4558	4.2779	4.1399	4.0297
15	8.6831	6.3589	5.4170	4.8932	4.5556	4.3183	4.1415	4.0045	3.8948
16	8.5310	6.2262	5.2922	4.7726	4.4374	4.2016	4.0259	3.8896	3.7804
17	8.3997	6.1121	5.1850	4.6690	4.3359	4.1015	3.9267	3.7910	3.6822
18	8.2854	6.0129	5.0919	4.5790	4.2479	4.0146	3.8406	3.7054	3.5971
19	8.1850	5.9259	5.0103	4.5003	4.1708	3.9386	3.7653	3.6305	3.5225
20	8.0960	5.8489	4.9382	4.4307	4.1027	3.8714	3.6987	3.5644	3.4567
21	8.0166	5.7804	4.8740	4.3688	4.0421	3.8117	3.6396	3.5056	3.3981
22	7.9454	5.7190	4.8166	4.3134	3.9880	3.7583	3.5867	3.4530	3.3458
23	7.8811	5.6637	4.7649	4.2635	3.9392	3.7102	3.5390	3.4057	3.2986
24	7.8229	5.6136	4.7181	4.2184	3.8951	3.6667	3.4959	3.3629	3.2560
25	7.7698	5.5680	4.6755	4.1774	3.8550	3.6272	3.4568	3.3239	3.2172
26	7.7213	5.5263	4.6366	4.1400	3.8183	3.5911	3.4210	3.2884	3.1818
27	7.6767	5.4881	4.6009	4.1056	3.7848	3.5580	3.3882	3.2558	3.1494
28	7.6356	5.4529	4.5681	4.0740	3.7539	3.5276	3.3581	3.2259	3.1195
29	7.5976	5.4205	4.5378	4.0449	3.7254	3.4995	3.3302	3.1982	3.0920
30	7.5625	5.3904	4.5097	4.0179	3.6990	3.4735	3.3045	3.1726	3.0665
40	7.3141	5.1785	4.3126	3.8283	3.5138	3.2910	3.1238	2.9930	2.8876
60	7.0771	4.9774	4.1259	3.6491	3.3389	3.1187	2.9530	2.8233	2.7185
120	6.8510	4.7865	3.9493	3.4796	3.1735	2.9559	2.7918	2.6629	2.5586
∞	6.6349	4.6052	3.7816	3.3192	3.0173	2.8020	2.6393	2.5113	2.4073

Degrees of Freedom for Denominator

ν_2 \ ν_1	Degrees of Freedom for Numerator									
	10	12	15	20	24	30	40	60	120	∞
1	6,055.8	6,106.3	6,157.3	6,208.7	6,234.6	6,260.7	6,286.8	6,313.0	6,339.4	6,366.0
2	99.399	99.416	99.432	99.449	99.458	99.466	99.474	99.483	99.491	99.501
3	27.229	27.052	26.872	26.690	26.598	26.505	26.411	26.316	26.221	26.125
4	14.546	14.374	14.198	14.020	13.929	13.838	13.745	13.652	13.558	13.463
5	10.051	9.8883	9.7222	9.5527	9.4665	9.3793	9.2912	9.2020	9.1118	9.0204
6	7.8741	7.7183	7.5590	7.3958	7.3127	7.2285	7.1432	7.0568	6.9690	6.8801
7	6.6201	6.4691	6.3143	6.1554	6.0743	5.9921	5.9084	5.8236	5.7372	5.6495
8	5.8143	5.6668	5.5151	5.3591	5.2793	5.1981	5.1156	5.0316	4.9460	4.8588
9	5.2565	5.1114	4.9621	4.8080	4.7290	4.6486	4.5667	4.4831	4.3978	4.3105
10	4.8492	4.7059	4.5582	4.4054	4.3269	4.2469	4.1653	4.0819	3.9965	3.9090
11	4.5393	4.3974	4.2509	4.0990	4.0209	3.9411	3.8596	3.7761	3.6904	3.6025
12	4.2961	4.1553	4.0096	3.8584	3.7805	3.7008	3.6192	3.5355	3.4494	3.3608
13	4.1003	3.9603	3.8154	3.6646	3.5868	3.5070	3.4253	3.3413	3.2548	3.1651
14	3.9394	3.8001	3.6557	3.5052	3.4274	3.3476	3.2656	3.1813	3.0942	3.0040
15	3.8049	3.6662	3.5222	3.3719	3.2940	3.2141	3.1319	3.0471	2.9595	2.8684
16	3.6909	3.5527	3.4089	3.2588	3.1808	3.1007	3.0182	2.9330	2.8447	2.7528
17	3.5931	3.4552	3.3117	3.1615	3.0835	3.0032	2.9205	2.8348	2.7459	2.6530
18	3.5082	3.3706	3.2273	3.0771	2.9990	2.9185	2.8354	2.7493	2.6597	2.5660
19	3.4338	3.2965	3.1533	3.0031	2.9249	2.8442	2.7608	2.6742	2.5839	2.4893
20	3.3682	3.2311	3.0880	2.9377	2.8594	2.7785	2.6947	2.6077	2.5168	2.4212
21	3.3098	3.1729	3.0299	2.8796	2.8011	2.7200	2.6359	2.5484	2.4568	2.3603
22	3.2576	3.1209	2.9780	2.8274	2.7488	2.6675	2.5831	2.4951	2.4029	2.3055
23	3.2106	3.0740	2.9311	2.7805	2.7017	2.6202	2.5355	2.4471	2.3542	2.2559
24	3.1681	3.0316	2.8887	2.7380	2.6591	2.5773	2.4923	2.4035	2.3099	2.2107
25	3.1294	2.9931	2.8502	2.6993	2.6203	2.5383	2.4530	2.3637	2.2695	2.1694
26	3.0941	2.9579	2.8150	2.6640	2.5848	2.5026	2.4170	2.3273	2.2325	2.1315
27	3.0618	2.9256	2.7827	2.6316	2.5522	2.4699	2.3840	2.2938	2.1984	2.0965
28	3.0320	2.8959	2.7530	2.6017	2.5223	2.4397	2.3535	2.2629	2.1670	2.0642
29	3.0045	2.8685	2.7256	2.5742	2.4946	2.4118	2.3253	2.2344	2.1378	2.0342
30	2.9791	2.8431	2.7002	2.5487	2.4689	2.3860	2.2992	2.2079	2.1107	2.0062
40	2.8005	2.6648	2.5216	2.3689	2.2880	2.2034	2.1142	2.0194	1.9172	1.8047
60	2.6318	2.4961	2.3523	2.1978	2.1154	2.0285	1.9360	1.8363	1.7263	1.6006
120	2.4721	2.3363	2.1915	2.0346	1.9500	1.8600	1.7628	1.6557	1.5330	1.3805
∞	2.3209	2.1848	2.0385	1.8783	1.7908	1.6964	1.5923	1.4730	1.3246	1.0000

Degrees of Freedom for Denominator

Table B-3 0.5% Points of the *F*-Distribution

ν_2 \ ν_1	Degrees of Freedom for Numerator								
	1	2	3	4	5	6	7	8	9
Degrees of Freedom for Denominator									
1	16,211	20,000	21,615	22,500	23,056	23,437	23,715	23,925	24,091
2	198.50	199.00	199.17	199.25	199.30	199.33	199.36	199.37	199.39
3	55.552	49.799	47.467	46.195	45.392	44.838	44.434	44.126	43.882
4	31.333	26.284	24.259	23.155	22.456	21.975	21.622	21.352	21.139
5	22.785	18.314	16.530	15.556	14.940	14.513	14.200	13.961	13.772
6	18.635	14.544	12.917	12.028	11.464	11.073	10.786	10.566	10.391
7	16.236	12.404	10.882	10.050	9.5221	9.1554	8.8854	8.6781	8.5138
8	14.688	11.042	9.5965	8.8051	8.3018	7.9520	7.6942	7.4960	7.3386
9	13.614	10.107	8.7171	7.9559	7.4711	7.1338	6.8849	6.6933	6.5411
10	12.826	9.4270	8.0807	7.3428	6.8723	6.5446	6.3025	6.1159	5.9676
11	12.226	8.9122	7.6004	6.8809	6.4217	6.1015	5.8648	5.6821	5.5368
12	11.754	8.5096	7.2258	6.5211	6.0711	5.7570	5.5245	5.3451	5.2021
13	11.374	8.1865	6.9257	6.2335	5.7910	5.4819	5.2529	5.0761	4.9351
14	11.060	7.9217	6.6803	5.9984	5.5623	5.2574	5.0313	4.8566	4.7173
15	10.798	7.7008	6.4760	5.8029	5.3721	5.0708	4.8473	4.6743	4.5364
16	10.575	7.5138	6.3034	5.6378	5.2117	4.9134	4.6920	4.5207	4.3838
17	10.384	7.3536	6.1556	5.4967	5.0746	4.7789	4.5594	4.3893	4.2535
18	10.218	7.2148	6.0277	5.3746	4.9560	4.6627	4.4448	4.2759	4.1410
19	10.073	7.0935	5.9161	5.2681	4.8526	4.5614	4.3448	4.1770	4.0428
20	9.9439	6.9865	5.8177	5.1743	4.7616	4.4721	4.2569	4.0900	3.9564
21	9.8295	6.8914	5.7304	5.0911	4.6808	4.3931	4.1789	4.0128	3.8799
22	9.7271	6.8064	5.6524	5.0168	4.6088	4.3225	4.1094	3.9440	3.8116
23	9.6348	6.7300	5.5823	4.9500	4.5141	4.2591	4.0469	3.8822	3.7502
24	9.5513	6.6610	5.5190	4.8898	4.4857	4.2019	3.9905	3.8264	3.6949
25	9.4753	6.5982	5.4615	4.8351	4.4327	4.1500	3.9394	3.7758	3.6447
26	9.4059	6.5409	5.4091	4.7852	4.3844	4.1027	3.8928	3.7297	3.5989
27	9.3423	6.4885	5.3611	4.7396	4.3402	4.0594	3.8501	3.6875	3.5571
28	9.2838	6.4403	5.3170	4.6977	4.2996	4.0197	3.8110	3.6487	3.5186
29	9.2297	6.3958	5.2764	4.6591	4.2622	3.9830	3.7749	3.6130	3.4832
30	9.1797	6.3547	5.2388	4.6233	4.2276	3.9492	3.7416	3.5801	3.4505
40	8.8278	6.0664	4.9759	4.3738	3.9860	3.7129	3.5088	3.3498	3.2220
60	8.4916	5.7950	4.7290	4.1399	3.7600	3.4918	3.2911	3.1344	3.0083
120	8.1790	5.5393	4.4973	3.9207	3.5482	3.2849	3.0874	2.9330	2.8083
∞	7.8794	5.2983	4.2794	3.7151	3.3499	3.0913	2.8968	2.7444	2.6210

ν_1 / ν_2	Degrees of Freedom for Numerator									
	10	12	15	20	24	30	40	60	120	∞
1	24,224	24,426	24,630	24,836	24,940	25,044	25,148	25,253	25,359	25,465
2	199.40	199.42	199.43	199.45	199.46	199.47	199.47	199.48	199.49	199 51
3	43 686	43.387	43.085	42.778	42.622	42.466	42.308	42.149	41.989	41.829
4	21.967	20.705	20.438	20.167	20.030	19.892	19.752	19.611	19.468	19.325
5	13.618	13.384	13.146	12.903	12.780	12.656	12.530	12.402	12.274	12.144
6	10.250	10.034	9.8140	9.5888	9.4741	9.3583	9.2408	9.1219	9.0015	8.8793
7	8.3803	8.1764	7.9678	7.7540	7.6450	7.5345	7.4225	7.3088	7.1933	7.0760
8	7.2107	7.0149	6.8143	6.6082	6.5029	6.3961	6.2875	6.1772	6.0649	5.9505
9	6.4171	6.2274	6.0325	5.8318	5.7292	5.6248	5.5186	5.4104	5.3001	5 1875
10	5.8467	5.6613	5.4707	5.2740	5.1732	5.0705	4.9659	4.8592	4.7501	4.6385
11	5.4182	5.2363	5.0489	4.8552	4.7557	4.6543	4 5508	4.4450	4.3367	4.2256
12	5.0855	4.9063	4.7214	4.5299	4.4315	4.3309	4.2282	4.1229	4.0149	3.9039
13	4.8199	4.6429	4.4600	4.2703	4.1726	4.0727	3.9701	3.8655	3.7577	3.6465
14	4.6034	4.4281	4.2468	4.0585	3.9614	3.8619	3.7600	3.6553	3.5473	3.4359
15	4.4236	4.2198	4.0698	3.8826	3.7859	3.6867	3.5850	3.4803	3.3722	3.2602
16	4.2719	4.0991	3.9205	3.7312	3.6378	3.5388	3.4372	3.3324	3.2240	3.1115
17	4.1423	3.9709	3.7929	3.6073	3.5112	3.4124	3.3107	3.2058	3.0971	2.9839
18	4.0305	3.8599	3.6827	3.4977	3.4017	3.3030	3.2014	3.0952	2.9871	2.8732
19	3.9329	3.7631	3.5866	3.4020	3.3062	3.2075	3.1058	3.0004	2.8908	2.7762
20	3.8470	3.6779	3.5020	3.3178	3.2220	3.1234	3.0215	2.9159	2.8058	2.6904
21	3.7709	3.6024	3.4270	3.2431	3.1474	3.0488	2.9467	2.8408	2.7302	2.6140
22	3.7030	3.5350	3.3600	3.1764	3.0807	2.9821	2.8799	2.7736	2.6625	2.5455
23	3.6420	3.4745	3.2993	3.1165	3.0208	2.9221	2.8198	2.7132	2.6015	2.4837
24	3.5870	3.4199	3.2456	3.0624	2.9667	2.8679	2.7654	2.6585	2.5463	2.4276
25	3.5370	3.3704	3.1963	3.0133	2.9176	2.8187	2.7160	2.6088	2.4960	2.3765
26	3.4916	3.3252	3.1515	2.9685	2.8728	2.7738	2.6709	2.5633	2.4501	2.3297
27	3.4499	3.2839	3.1104	2.9275	2.8318	2.7327	2.6296	2.5217	2.4078	2.2867
28	3.4117	3.2160	3.0727	2.8899	2.7941	2.6949	2.5916	2.4834	2.3689	2.2469
29	3.3765	3.2111	3.0379	2.8551	2.7594	2.6601	2.5565	2.4479	2.3330	2.2102
30	3.3440	3.1787	3.0057	2.8230	2.7272	2.6278	2.5241	2.4151	2.2997	2.1760
40	3.1167	2.9531	2.7811	2.5984	2.5020	2.4015	2.2958	2.1838	2.0635	1.9318
60	2.9042	2.7419	2.5705	2.3872	2.2898	2.1874	2.0789	1.9622	1.8341	1.6885
120	2.7052	2.5439	2.3727	2.1881	2.0890	1.9839	1.8703	1.7469	1.6055	1.4311
∞	2.5188	2.3583	2.1858	1.9998	1.8983	1.7891	1.6691	1.5325	1.3637	1.0000

Degrees of Freedom for Denominator

Source: "Tables of Percentage Points of the Inverted Beta (F) Distribution," by Maxine Merrington and Catherine M. Thompson, *Biometrika*, Vol. 33, pp. 73–88 (1943). Reproduced by permission of the editor of *Biometrika*.

Table B-4 Upper Tail Probabilities for the Null Distribution of the Kruskal–Wallis H Statistic: $k = 3$, $n_1 = 1(1)5$, $n_2 = n_1(1)5$, $2 \leqslant n_3 = n_2(1)5$

For $k = 3$ and sample sizes n_1, n_2, n_3, the tabled entry for the point x is $P_0\{H \geqslant x\}$. Thus if x is such that $P_0\{H \geqslant x\} = \alpha$, then $h(\alpha, 3, (n_1, n_2, n_3)) = x$.

$n_1 = 1, n_2 = 1, n_3 = 2$

x	$P_0\{H \geqslant x\}$
.300	1.000
1.800	.833
2.700	.500

$n_1 = 1, n_2 = 1, n_3 = 3$

x	$P_0\{H \geqslant x\}$
.533	1.000
.800	.800
2.133	.700
3.200	.300

$n_1 = 1, n_2 = 1, n_3 = 4$

x	$P_0\{H \geqslant x\}$
.143	1.000
.786	.933
1.000	.800
1.286	.667
2.143	.600
2.500	.467
3.571	.200

$n_1 = 1, n_2 = 1, n_3 = 5$

x	$P_0\{H \geqslant x\}$
.257	1.000
.429	.905
1.029	.857
1.114	.762
1.457	.667
1.714	.571
2.314	.524
2.829	.333
3.857	.143

$n_1 = 1, n_2 = 2, n_3 = 2$

x	$P_0\{H \geqslant x\}$
.000	1.000
.400	.933
.600	.867
1.400	.733
2.000	.600
2.400	.467
3.000	.333
3.600	.200

$n_1 = 1, n_2 = 2, n_3 = 3$

x	$P_0\{H \geqslant x\}$
.095	1.000
.238	.933
.429	.900
.810	.833
.857	.800
1.238	.700
1.381	.600
1.952	.567
2.143	.533
2.381	.433
3.095	.267
3.524	.200
3.857	.133
4.286	.100

$n_1 = 1, n_2 = 2, n_3 = 4$

x	$P_0\{H \geqslant x\}$
.000	1.000
.161	.971
.268	.933
.321	.895
.536	.857
.643	.819
.696	.800
1.018	.781
1.071	.743
1.125	.705
1.286	.667
1.393	.629
1.446	.590
1.875	.533
2.036	.495
2.143	.476
2.250	.457
2.411	.400
2.571	.305
2.786	.286
2.893	.267
3.161	.190
3.696	.171
3.750	.133
4.018	.114
4.500	.076
4.821	.057

$n_1 = 1, n_2 = 2, n_3 = 5$

x	$P_0\{H \geqslant x\}$
.050	1.000
.133	.964
.200	.940
.450	.905
.467	.845
.583	.821
.667	.798
.717	.774
1.000	.750
1.117	.738
1.200	.714
1.250	.655
1.383	.619
1.533	.583
1.783	.560
1.800	.536
1.917	.488
2.050	.464
2.333	.429
2.450	.393
2.717	.298
2.800	.286
2.867	.214
3.133	.202
3.333	.190
3.383	.179
3.783	.131
4.050	.119
4.200	.095
4.450	.071
5.000	.048
5.250	.036

$n_1 = 1, n_2 = 2, n_3 = 5$

x	$P_0\{H \geqslant x\}$
.050	1.000
.133	.964
.200	.940
.450	.905
.467	.845
.583	.821
.667	.798
.717	.774
1.000	.750
1.117	.738
1.200	.714
1.250	.655
1.383	.619
1.533	.583
1.783	.560
1.800	.536
1.917	.488
2.050	.464
2.333	.429
2.450	.393
2.717	.298
2.800	.286
2.867	.214
3.133	.202
3.333	.190
3.383	.179
3.783	.131
4.050	.119
4.200	.095
4.450	.071
5.000	.048
5.250	.036

$n_1 = 1, n_2 = 3, n_3 = 3$

x	$P_0\{H \geqslant x\}$
.000	1.000
.143	.986
.286	.957
.571	.871
1.000	.771

Table B-4 (*continued*)

$n_1 = 1, n_2 = 3, n_3 = 3$

x	$P_0\{H \geq x\}$
1.143	.743
1.286	.600
1.571	.571
2.000	.514
2.286	.486
2.571	.329
3.143	.243
3.286	.157
4.000	.129
4.571	.100
5.143	.043

$n_1 = 1, n_2 = 3, n_3 = 4$

x	$P_0\{H \geq x\}$
.056	1.000
.097	.971
.208	.950
.333	.921
.431	.900
.500	.871
.556	.843
.764	.786
.875	.743
1.097	.721
1.208	.707
1.222	.679
1.389	.629
1.431	.557
1.764	.536
1.833	.514
1.875	.471
2.097	.457
2.208	.443
2.333	.429
2.431	.371
2.722	.300
2.764	.229
3.000	.221
3.097	.214
3.208	.200
3.222	.157

$n_1 = 1, n_2 = 3, n_3 = 4$

x	$P_0\{H \geq x\}$
3.764	.136
3.889	.129
4.056	.093
4.097	.086
4.208	.079
4.764	.071
5.000	.057
5.208	.050
5.389	.036
5.833	.021

$n_1 = 1, n_2 = 3, n_3 = 5$

x	$P_0\{H \geq x\}$
.000	1.000
.071	.992
.160	.972
.178	.952
.284	.929
.338	.889
.551	.869
.604	.853
.640	.833
.711	.770
.818	.750
.960	.730
1.084	.694
1.138	.683
1.351	.651
1.404	.611
1.440	.591
1.511	.571
1.600	.560
1.671	.520
1.778	.488
1.884	.480
1.938	.468
2.044	.452
2.204	.437
2.400	.413
2.418	.405
2.560	.341

$n_1 = 1, n_2 = 3, n_3 = 5$

x	$P_0\{H \geq x\}$
2.844	.258
2.951	.218
3.040	.210
3.218	.190
3.271	.183
3.378	.143
3.484	.135
3.804	.131
3.840	.123
4.018	.095
4.284	.083
4.338	.079
4.551	.075
4.711	.056
4.871	.052
4.960	.048
5.404	.044
5.440	.036
5.760	.028
6.044	.020
6.400	.012

$n_1 = 1, n_2 = 4, n_3 = 4$

x	$P_0\{H \geq x\}$
.000	1.000
.067	.987
.167	.968
.267	.930
.300	.911
.567	.873
.600	.835
.667	.803
.867	.759
.967	.721
1.067	.689
1.200	.676
1.367	.644
1.500	.600
1.667	.537
1.767	.498
2.167	.460

$n_1 = 1, n_2 = 4, n_3 = 4$

x	$P_0\{H \geq x\}$
2.267	.410
2.400	.384
2.467	.349
2.667	.305
2.700	.260
2.967	.235
3.000	.222
3.267	.178
3.367	.171
3.467	.152
3.867	.121
3.900	.108
4.067	.102
4.167	.083
4.267	.070
4.800	.067
4.867	.054
4.967	.048
5.100	.041
5.667	.035
6.000	.029
6.167	.022
6.667	.010

$n_1 = 1, n_2 = 4, n_3 = 5$

x	$P_0\{H \geq x\}$
.033	1.000
.060	.983
.104	.968
.186	.952
.273	.938
.278	.922
.295	.906
.360	.890
.409	.875
.540	.848
.622	.821
.731	.806
.758	.794
.796	.778
.818	.762

Table B-4 (*continued*)

$n_1 = 1, n_2 = 4, n_3 = 5$

x	$P_0\{H \geq x\}$
.906	.730
.933	.719
.976	.690
1.151	.676
1.167	.665
1.195	.651
1.233	.640
1.342	.625
1.369	.614
1.495	.606
1.500	.589
1.587	.562
1.604	.535
1.669	.517
1.778	.498
1.806	.483
1.849	.468
1.931	.460
2.040	.441
2.067	.432
2.106	.419
2.242	.406
2.286	.400
2.455	.394
2.460	.354
2.504	.346
2.591	.300
2.651	.286
2.896	.251
2.913	.222
2.940	.216
3.000	.208
3.087	.194
3.158	.187
3.240	.183
3.349	.151
3.524	.146
3.595	.138
3.682	.132
3.813	.110
3.960	.102
3.987	.098
4.206	.095
4.222	.087

$n_1 = 1, n_2 = 4, n_3 = 5$

x	$P_0\{H \geq x\}$
4.287	.071
4.549	.067
4.636	.063
4.724	.060
4.833	.059
4.860	.056
4.986	.044
5.078	.041
5.160	.038
5.515	.037
5.558	.035
5.596	.033
5.733	.027
5.776	.025
5.858	.024
5.864	.022
5.967	.021
6.431	.019
6.578	.016
6.818	.013
6.840	.011
6.954	.008
7.364	.005

$n_1 = 1, n_2 = 5, n_3 = 5$

x	$P_0\{H \geq x\}$
.000	1.000
.036	.994
.109	.982
.146	.956
.182	.944
.327	.920
.400	.885
.436	.872
.546	.847
.582	.802
.727	.792
.836	.771
.909	.752
.982	.716
1.127	.669
1.200	.646

$n_1 = 1, n_2 = 5, n_3 = 5$

x	$P_0\{H \geq x\}$
1.309	.630
1.346	.605
1.600	.584
1.636	.571
1.709	.509
1.746	.493
1.782	.468
1.927	.462
2.000	.438
2.146	.422
2.182	.411
2.327	.379
2.436	.374
2.509	.361
2.582	.314
2.727	.286
2.909	.242
2.946	.227
3.236	.188
3.346	.168
3.382	.161
3.527	.141
3.600	.132
3.636	.116
3.927	.113
4.036	.105
4.109	.086
4.182	.082
4.400	.076
4.546	.074
4.800	.056
4.909	.053
5.127	.046
5.236	.039
5.636	.033
5.709	.030
5.782	.027
6.000	.022
6.146	.019
6.509	.018
6.546	.015
6.582	.014
6.727	.012
6.836	.011

$n_1 = 1, n_2 = 5, n_3 = 5$

x	$P_0\{H \geq x\}$
7.309	.009
7.527	.008
7.746	.005
8.182	.002

$n_1 = 2, n_2 = 2, n_3 = 2$

x	$P_0\{H \geq x\}$
.000	1.000
.286	.933
.857	.800
1.143	.667
2.000	.533
2.571	.400
3.429	.333
3.714	.200
4.571	.067

$n_1 = 2, n_2 = 2, n_3 = 3$

x	$P_0\{H \geq x\}$
.000	1.000
.179	.971
.214	.895
.500	.857
.607	.800
.714	.743
.857	.686
1.179	.657
1.357	.619
1.464	.562
1.607	.524
1.929	.467
2.000	.438
2.214	.419
2.429	.381
2.464	.362
2.750	.324
2.857	.286
3.179	.267
3.429	.248

Table B-4 (*continued*)

$n_1 = 2, n_2 = 2, n_3 = 3$

x	$P_0\{H \geq x\}$
3.607	.238
3.750	.219
3.929	.181
4.464	.105
4.500	.067
4.714	.048
5.357	.029

$n_1 = 2, n_2 = 2, n_3 = 4$

x	$P_0\{H \geq x\}$
.000	1.000
.125	.971
.167	.914
.333	.890
.458	.862
.500	.814
.667	.757
.792	.733
1.000	.695
1.125	.657
1.333	.581
1.500	.552
1.792	.514
1.833	.486
2.000	.448
2.125	.410
2.458	.362
2.667	.333
2.792	.314
2.833	.295
3.000	.276
3.125	.248
3.167	.229
3.458	.210
3.667	.190
4.000	.181
4.125	.152
4.167	.105
4.458	.100
4.500	.090
5.125	.052

$n_1 = 2, n_2 = 2, n_3 = 4$

x	$P_0\{H \geq x\}$
5.333	.033
5.500	.024
6.000	.014

$n_1 = 2, n_2 = 2, n_3 = 5$

x	$P_0\{H \geq x\}$
.000	1.000
.093	.984
.133	.937
.240	.913
.360	.881
.373	.844
.533	.807
.573	.791
.773	.759
.840	.722
.893	.685
.960	.653
1.093	.638
1.200	.606
1.373	.590
1.440	.563
1.493	.542
1.533	.516
1.693	.495
1.800	.474
2.133	.452
2.160	.444
2.173	.402
2.293	.381
2.333	.365
2.373	.344
2.693	.317
2.760	.296
2.973	.275
3.093	.265
3.133	.254
3.240	.238
3.333	.206
3.360	.196
3.573	.185

$n_1 = 2, n_2 = 2, n_3 = 5$

x	$P_0\{H \geq x\}$
3.773	.175
3.840	.164
3.973	.159
4.093	.148
4.200	.138
4.293	.122
4.373	.090
4.573	.085
4.800	.063
4.893	.061
5.040	.056
5.160	.034
5.693	.029
6.000	.019
6.133	.013
6.533	.008

$n_1 = 2, n_2 = 3, n_3 = 3$

x	$P_0\{H \geq x\}$
.028	1.000
.111	.968
.222	.946
.250	.896
.472	.864
.556	.807
.694	.757
1.000	.686
1.111	.671
1.139	.600
1.361	.564
1.444	.539
1.806	.511
1.889	.446
2.000	.425
2.028	.396
2.250	.368
2.472	.357
2.694	.329
2.778	.307
2.889	.286
3.139	.243

$n_1 = 2, n_2 = 3, n_3 = 3$

x	$P_0\{H \geq x\}$
3.222	.221
3.361	.207
3.778	.200
3.806	.179
4.028	.164
4.111	.129
4.250	.121
4.556	.100
4.694	.093
5.000	.075
5.139	.061
5.361	.032
5.556	.025
6.250	.011

$n_1 = 2, n_2 = 3, n_3 = 4$

x	$P_0\{H \geq x\}$
.000	1.000
.078	.987
.100	.965
.111	.944
.244	.922
.278	.902
.311	.881
.344	.862
.400	.844
.444	.829
.544	.811
.600	.794
.611	.770
.700	.756
.778	.722
.811	.703
.900	.689
.978	.673
1.000	.660
1.078	.627
1.111	.614
1.178	.602
1.244	.586
1.344	.571

Table B-4 (*continued*)

$n_1 = 2, n_2 = 3, n_3 = 4$		$n_1 = 2, n_2 = 3, n_3 = 4$		$n_1 = 2, n_2 = 3, n_3 = 5$		$n_1 = 2, n_2 = 3, n_3 = 5$	
x	$P_0\{H \geq x\}$	x	$P_0\{H \geq x\}$	x	$P_0\{H \geq x\}$	x	$P_0\{H \geq x\}$
1.378	.559	4.378	.105	.713	.743	3.069	.243
1.411	.548	4.444	.102	.724	.714	3.167	.237
1.500	.537	4.511	.098	.767	.703	3.186	.233
1.600	.511	4.544	.086	.887	.692	3.273	.222
1.611	.502	4.611	.083	.942	.680	3.331	.211
1.678	.478	4.711	.079	1.014	.659	3.342	.206
1.711	.468	4.811	.076	1.058	.648	3.386	.201
1.778	.457	4.878	.073	1.091	.638	3.414	.193
1.844	.448	4.900	.071	1.149	.616	3.506	.189
1.944	.437	4.978	.059	1.178	.593	3.546	.183
2.144	.417	5.078	.057	1.276	.579	3.604	.175
2.178	.406	5.144	.054	1.324	.569	3.676	.171
2.200	.398	5.378	.052	1.378	.537	3.767	.167
2.211	.376	5.400	.051	1.451	.529	3.778	.159
2.244	.368	5.444	.046	1.586	.519	3.822	.156
2.378	.357	5.500	.040	1.596	.510	3.909	.152
2.400	.346	5.611	.032	1.614	.502	3.942	.146
2.411	.338	5.800	.030	1.713	.483	3.996	.139
2.444	.329	6.000	.024	1.727	.474	4.058	.137
2.500	.321	6.111	.021	1.760	.459	4.069	.132
2.778	.294	6.144	.014	1.814	.451	4.204	.129
2.800	.284	6.300	.011	1.858	.444	4.214	.125
2.911	.271	6.444	.008	1.876	.429	4.233	.122
2.944	.262	7.000	.005	2.022	.420	4.258	.120
3.011	.256			2.033	.403	4.331	.117
3.100	.251	$n_1 = 2, n_2 = 3, n_3 = 5$		2.076	.396	4.378	.113
3.111	.238			2.106	.389	4.494	.101
3.244	.232	x	$P_0\{H \geq x\}$	2.196	.382	4.651	.091
3.278	.225			2.251	.375	4.694	.089
3.300	.216	.014	1.000	2.294	.368	4.724	.087
3.311	.203	.069	.981	2.367	.362	4.727	.085
3.444	.197	.113	.966	2.454	.356	4.814	.071
3.478	.190	.131	.951	2.458	.350	4.869	.067
3.544	.184	.142	.932	2.469	.336	4.913	.063
3.600	.175	.273	.917	2.487	.330	4.942	.062
3.811	.168	.276	.901	2.546	.321	5.076	.060
3.844	.163	.306	.886	2.633	.294	5.087	.053
3.911	.159	.331	.869	2.749	.287	5.106	.052
3.978	.156	.364	.855	2.818	.279	5.251	.049
4.000	.149	.451	.823	2.894	.269	5.349	.046
4.078	.140	.549	.807	2.924	.263	5.513	.044
4.200	.137	.567	.794	2.949	.257	5.524	.043
4.278	.124	.622	.781	2.978	.252	5.542	.041
4.311	.108	.636	.769	3.022	.248	5.727	.037

Table B-4 (*continued*)

$n_1 = 2, n_2 = 3, n_3 = 5$

x	$P_0\{H \geq x\}$
5.742	.034
5.786	.033
5.804	.033
5.949	.026
6.004	.025
6.033	.024
6.091	.021
6.124	.020
6.294	.017
6.386	.016
6.414	.015
6.818	.012
6.822	.010
6.909	.009
6.949	.006
7.182	.004
7.636	.002

$n_1 = 2, n_2 = 4, n_3 = 4$

x	$P_0\{H \geq x\}$
.000	1.000
.054	.988
.082	.970
.191	.940
.218	.910
.273	.893
.327	.879
.409	.848
.491	.820
.627	.779
.736	.757
.764	.712
.873	.685
.954	.671
1.091	.651
1.146	.638
1.173	.596
1.282	.577
1.309	.559
1.364	.537
1.582	.526

$n_1 = 2, n_2 = 4, n_3 = 4$

x	$P_0\{H \geq x\}$
1.636	.510
1.718	.488
1.827	.441
1.964	.426
2.046	.400
2.236	.386
2.264	.375
2.373	.363
2.454	.338
2.509	.317
2.673	.301
2.809	.281
2.918	.272
2.946	.263
3.054	.239
3.136	.228
3.327	.220
3.354	.210
3.464	.192
3.491	.185
3.682	.180
3.764	.166
3.818	.152
4.009	.142
4.364	.125
4.418	.120
4.446	.103
4.554	.098
4.582	.094
4.691	.080
4.773	.075
4.854	.071
4.991	.065
5.127	.057
5.236	.052
5.454	.046
5.509	.044
5.536	.042
5.646	.039
5.727	.034
5.946	.028
6.082	.025
6.327	.024
6.409	.022

$n_1 = 2, n_2 = 4, n_3 = 4$

x	$P_0\{H \geq x\}$
6.546	.020
6.600	.017
6.627	.016
6.873	.011
7.036	.006
7.282	.004
7.854	.002

$n_1 = 2, n_2 = 4, n_3 = 5$

x	$P_0\{H \geq x\}$
.000	1.000
.041	.992
.064	.979
.068	.965
.141	.952
.154	.939
.164	.926
.223	.913
.254	.902
.273	.891
.300	.880
.323	.866
.368	.855
.404	.832
.504	.823
.518	.812
.541	.801
.564	.791
.573	.781
.614	.759
.618	.749
.654	.740
.723	.730
.791	.720
.841	.710
.864	.701
.891	.691
.904	.683
.914	.674
.950	.657
.954	.649
1.018	.640
1.023	.632

$n_1 = 2, n_2 = 4, n_3 = 5$

x	$P_0\{H \geq x\}$
1.050	.623
1.091	.614
1.200	.607
1.204	.599
1.268	.592
1.291	.576
1.314	.569
1.318	.562
1.391	.554
1.414	.537
1.450	.529
1.473	.521
1.518	.507
1.591	.499
1.618	.491
1.641	.485
1.664	.479
1.704	.472
1.750	.465
1.754	.459
1.814	.452
1.823	.432
1.973	.427
2.004	.420
2.018	.403
2.073	.398
2.114	.392
2.118	.387
2.141	.381
2.164	.375
2.223	.371
2.254	.366
2.291	.361
2.318	.351
2.323	.346
2.391	.335
2.454	.329
2.473	.324
2.504	.320
2.550	.315
2.618	.311
2.700	.306
2.723	.301
2.754	.296

Table B-4 (*continued*)

$n_1 = 2, n_2 = 4, n_3 = 5$		$n_1 = 2, n_2 = 4, n_3 = 5$		$n_1 = 2, n_2 = 4, n_3 = 5$		$n_1 = 2, n_2 = 5, n_3 = 5$	
x	$P_0\{H \geq x\}$	x	$P_0\{H \geq x\}$	x	$P_0\{H \geq x\}$	x	$P_0\{H \geq x\}$
2.768	.285	4.404	.110	6.564	.016	.908	.674
2.773	.273	4.500	.104	6.654	.016	.931	.661
2.868	.267	4.518	.101	6.723	.015	1.115	.638
2.891	.262	4.541	.098	6.904	.014	1.154	.611
2.904	.258	4.614	.090	6.914	.013	1.185	.593
2.914	.249	4.664	.088	7.000	.013	1.277	.569
2.973	.246	4.768	.079	7.018	.012	1.300	.558
3.023	.237	4.791	.078	7.064	.012	1.362	.552
3.050	.234	4.800	.076	7.118	.010	1.431	.539
3.064	.231	4.818	.074	7.204	.009	1.485	.528
3.118	.226	4.841	.072	7.254	.009	1.523	.516
3.164	.221	4.868	.071	7.291	.008	1.554	.506
3.268	.217	4.950	.063	7.450	.007	1.646	.496
3.314	.214	5.073	.061	7.500	.007	1.669	.486
3.341	.208	5.154	.059	7.568	.006	1.731	.463
3.364	.200	5.164	.053	7.573	.005	1.854	.445
3.414	.197	5.254	.052	7.773	.004	1.915	.434
3.454	.193	5.268	.051	7.814	.003	1.923	.424
3.523	.190	5.273	.049	8.018	.002	2.015	.407
3.564	.187	5.300	.048	8.114	.001	2.038	.398
3.568	.184	5.314	.046	8.591	.001	2.223	.379
3.573	.181	5.414	.045			2.262	.374
3.618	.178	5.518	.043	$n_1 = 2, n_2 = 5, n_3 = 5$		2.285	.363
3.641	.175	5.523	.042			2.292	.353
3.654	.170	5.564	.038	x	$P_0\{H \geq x\}$	2.385	.345
3.700	.164	5.641	.037			2.408	.330
3.704	.160	5.664	.036	.008	1.000	2.469	.323
3.791	.157	5.754	.035	.046	.988	2.538	.315
3.800	.151	5.823	.034	.069	.978	2.592	.300
3.818	.148	5.891	.032	.077	.966	2.662	.292
3.823	.145	5.954	.030	.169	.947	2.754	.286
3.864	.143	5.973	.029	.192	.928	2.777	.279
4.041	.139	6.004	.026	.254	.896	2.908	.276
4.064	.135	6.041	.025	.323	.877	2.962	.270
4.073	.133	6.068	.025	.377	.859	3.023	.243
4.091	.130	6.118	.024	.415	.830	3.031	.234
4.141	.128	6.141	.023	.446	.822	3.123	.228
4.154	.126	6.223	.022	.538	.807	3.146	.218
4.200	.123	6.368	.021	.562	.775	3.331	.210
4.223	.121	6.391	.021	.623	.759	3.369	.203
4.250	.119	6.473	.020	.692	.749	3.392	.198
4.323	.116	6.504	.020	.746	.735	3.492	.190
4.364	.114	6.541	.017	.808	.719	3.515	.186
4.368	.112	6.550	.017	.815	.688	3.577	.181

Table B-4 (*continued*)

$n_1 = 2, n_2 = 5, n_3 = 5$

x	$P_0\{H \geq x\}$
3.646	.169
3.738	.165
3.769	.163
3.862	.150
3.885	.146
4.015	.136
4.069	.132
4.131	.130
4.138	.127
4.231	.124
4.254	.114
4.438	.106
4.477	.103
4.508	.100
4.623	.097
4.685	.092
4.754	.084
4.808	.081
4.846	.073
4.877	.068
4.992	.066
5.054	.060
5.177	.057
5.238	.054
5.246	.051
5.338	.047
5.546	.045
5.585	.041
5.608	.040
5.615	.039
5.708	.037
5.731	.036
5.792	.032
5.915	.030
5.985	.028
6.077	.027
6.231	.026
6.346	.025
6.354	.021
6.446	.020
6.469	.019
6.654	.017
6.692	.016
6.815	.015
6.838	.014

$n_1 = 2, n_2 = 5, n_3 = 5$

x	$P_0\{H \geq x\}$
6.969	.013
7.023	.013
7.185	.012
7.208	.011
7.269	.010
7.338	.010
7.392	.009
7.462	.008
7.577	.007
7.762	.007
7.923	.006
8.008	.006
8.077	.006
8.131	.005
8.169	.003
8.292	.003
8.377	.002
8.562	.002
8.685	.001
8.938	.001
9.423	.000

$n_1 = 3, n_2 = 3, n_3 = 3$

x	$P_0\{H \geq x\}$
.000	1.000
.089	.993
.267	.929
.356	.879
.622	.829
.800	.721
1.067	.664
1.156	.629
1.422	.543
1.689	.511
1.867	.439
2.222	.382
2.400	.361
2.489	.339
2.756	.296
3.200	.254
3.289	.232

$n_1 = 3, n_2 = 3, n_3 = 3$

x	$P_0\{H \geq x\}$
3.467	.196
3.822	.168
4.267	.139
4.356	.132
4.622	.100
5.067	.086
5.422	.071
5.600	.050
5.689	.029
5.956	.025
6.489	.011
7.200	.004

$n_1 = 3, n_2 = 3, n_3 = 4$

x	$P_0\{H \geq x\}$
.018	1.000
.046	.984
.118	.970
.164	.941
.200	.925
.336	.895
.346	.869
.409	.842
.454	.830
.482	.817
.636	.791
.700	.764
.746	.717
.891	.690
1.064	.656
1.073	.633
1.136	.611
1.182	.602
1.209	.582
1.427	.541
1.473	.523
1.573	.513
1.618	.497
1.654	.481
1.791	.447
1.800	.433

$n_1 = 3, n_2 = 3, n_3 = 4$

x	$P_0\{H \geq x\}$
1.864	.415
2.091	.402
2.200	.389
2.227	.368
2.300	.351
2.382	.326
2.518	.314
2.527	.303
2.664	.291
2.882	.281
2.927	.273
2.954	.253
3.027	.244
3.073	.234
3.109	.220
3.254	.212
3.364	.203
3.391	.196
3.609	.188
3.682	.180
3.754	.178
3.800	.165
3.836	.150
3.973	.143
4.046	.132
4.091	.126
4.273	.123
4.336	.117
4.382	.111
4.564	.106
4.700	.101
4.709	.092
4.818	.085
4.846	.081
5.000	.074
5.064	.070
5.109	.068
5.254	.064
5.436	.062
5.500	.056
5.573	.053
5.727	.050
5.791	.046
5.936	.036

Table B-4 (*continued*)

$n_1 = 3, n_2 = 3, n_3 = 4$

x	$P_0\{H \geq x\}$
5.982	.034
6.018	.027
6.154	.025
6.300	.023
6.564	.017
6.664	.014
6.709	.013
6.746	.010
7.000	.006
7.318	.004
7.436	.002
8.018	.001

$n_1 = 3, n_2 = 3, n_3 = 5$

x	$P_0\{H \geq x\}$
.000	1.000
.048	.994
.061	.970
.133	.958
.170	.948
.194	.926
.242	.902
.315	.890
.376	.868
.412	.847
.436	.826
.533	.804
.546	.794
.594	.783
.679	.765
.776	.725
.848	.686
.970	.668
1.042	.641
1.079	.624
1.103	.609
1.200	.594
1.212	.587
1.261	.571
1.442	.539
1.503	.526

$n_1 = 3, n_2 = 3, n_3 = 5$

x	$P_0\{H \geq x\}$
1.515	.512
1.527	.505
1.576	.491
1.648	.478
1.746	.450
1.770	.437
1.867	.425
2.012	.414
2.048	.403
2.061	.393
2.133	.382
2.170	.367
2.182	.358
2.194	.352
2.315	.342
2.376	.334
2.594	.315
2.667	.306
2.679	.298
2.715	.291
2.836	.267
2.861	.258
2.970	.242
3.079	.239
3.103	.232
3.333	.218
3.382	.215
3.394	.209
3.442	.196
3.467	.184
3.503	.179
3.576	.173
3.648	.167
3.709	.162
3.879	.156
3.927	.149
4.012	.144
4.048	.139
4.170	.135
4.194	.126
4.242	.122
4.303	.117
4.315	.113
4.412	.109

$n_1 = 3, n_2 = 3, n_3 = 5$

x	$P_0\{H \geq x\}$
4.533	.097
4.679	.094
4.776	.090
4.800	.087
4.848	.085
4.861	.082
4.909	.079
5.042	.077
5.079	.069
5.103	.067
5.212	.065
5.261	.062
5.346	.058
5.442	.055
5.503	.053
5.515	.051
5.648	.049
5.770	.047
5.867	.042
6.012	.040
6.061	.033
6.109	.032
6.194	.027
6.303	.026
6.315	.021
6.376	.020
6.533	.019
6.594	.019
6.715	.014
6.776	.013
6.861	.012
6.982	.011
7.079	.009
7.333	.008
7.467	.008
7.503	.006
7.515	.005
7.636	.004
7.879	.003
8.048	.002
8.242	.001
8.727	.001

$n_1 = 3, n_2 = 4, n_3 = 4$

x	$P_0\{H \geq x\}$
.000	1.000
.046	.993
.053	.981
.144	.959
.167	.937
.182	.925
.212	.913
.326	.890
.348	.870
.386	.850
.409	.829
.477	.819
.576	.799
.598	.779
.659	.761
.667	.742
.712	.731
.727	.713
.848	.704
.894	.685
.932	.668
.962	.651
1.053	.635
1.076	.620
1.136	.604
1.144	.597
1.296	.582
1.303	.568
1.326	.553
1.394	.539
1.417	.524
1.500	.510
1.546	.503
1.598	.490
1.636	.477
1.682	.470
1.750	.457
1.803	.444
1.909	.421
1.962	.409
2.053	.388
2.144	.378
2.227	.368
2.296	.354

Table B-4 (*continued*)

$n_1 = 3, n_2 = 4, n_3 = 4$		$n_1 = 3, n_2 = 4, n_3 = 4$		$n_1 = 3, n_2 = 4, n_3 = 4$		$n_1 = 3, n_2 = 4, n_3 = 5$	
x	$P_0\{H \geq x\}$	x	$P_0\{H \geq x\}$	x	$P_0\{H \geq x\}$	x	$P_0\{H \geq x\}$
2.303	.344	5.053	.078	8.909	.001	1.062	.621
2.326	.334	5.144	.073			1.103	.615
2.394	.325	5.182	.068			1.106	.609
2.417	.315	5.212	.066	$n_1 = 3, n_2 = 4, n_3 = 5$		1.118	.602
2.598	.306	5.296	.063			1.137	.590
2.636	.290	5.303	.061	x	$P_0\{H \geq x\}$	1.164	.584
2.667	.281	5.326	.058			1.188	.578
2.712	.276	5.386	.054	.010	1.000	1.241	.572
2.848	.269	5.500	.052	.030	.990	1.246	.566
2.894	.261	5.576	.051	.060	.981	1.260	.553
2.909	.254	5.598	.049	.081	.972	1.349	.548
2.932	.250	5.667	.047	.092	.963	1.414	.542
2.962	.243	5.803	.045	.118	.953	1.445	.537
3.076	.230	5.932	.043	.138	.944	1.465	.522
3.136	.218	5.962	.041	.173	.935	1.472	.516
3.326	.212	6.000	.040	.180	.926	1.487	.506
3.386	.207	6.046	.039	.214	.917	1.506	.495
3.394	.201	6.053	.035	.241	.908	1.558	.490
3.417	.195	6.144	.032	.256	.900	1.568	.479
3.477	.190	6.167	.031	.265	.891	1.599	.475
3.576	.184	6.182	.030	.276	.882	1.615	.465
3.598	.178	6.348	.027	.323	.874	1.718	.460
3.659	.173	6.386	.026	.337	.865	1.733	.455
3.682	.162	6.394	.025	.368	.857	1.753	.450
3.727	.160	6.409	.023	.426	.841	1.780	.446
3.803	.154	6.417	.022	.430	.833	1.814	.441
3.848	.150	6.546	.021	.462	.825	1.856	.437
3.932	.145	6.659	.020	.491	.817	1.906	.427
3.962	.140	6.712	.019	.503	.809	1.927	.423
4.144	.135	6.727	.018	.542	.784	1.938	.418
4.167	.131	6.962	.017	.549	.777	1.964	.400
4.212	.129	7.000	.016	.626	.769	1.968	.396
4.296	.125	7.053	.014	.645	.754	1.985	.391
4.303	.121	7.076	.011	.692	.746	2.019	.387
4.326	.116	7.136	.011	.727	.738	2.030	.383
4.348	.113	7.144	.010	.737	.716	2.060	.379
4.409	.106	7.212	.009	.799	.709	2.103	.375
4.477	.102	7.477	.006	.830	.696	2.112	.366
4.546	.099	7.598	.004	.831	.689	2.169	.358
4.576	.097	7.636	.004	.856	.667	2.272	.354
4.598	.093	7.682	.003	.953	.660	2.308	.350
4.712	.090	7.848	.003	1.004	.654	2.337	.346
4.750	.087	8.227	.002	1.041	.641	2.349	.343
4.894	.084	8.326	.001	1.045	.628	2.368	.335

Table B-4 (*continued*)

$n_1 = 3, n_2 = 5, n_3 = 5$

x	$P_0\{H \geq x\}$
6.998	.015
7.050	.015
7.121	.014
7.209	.014
7.226	.012
7.288	.012
7.306	.012
7.314	.011
7.437	.011
7.543	.010
7.578	.010
7.622	.009
7.736	.009
7.763	.008
7.780	.008
7.859	.007
7.894	.007
7.912	.007
8.026	.006
8.079	.006
8.106	.006
8.237	.005
8.264	.005
8.316	.005
8.334	.005
8.545	.004
8.571	.004
8.580	.004
8.650	.003
8.659	.003
8.791	.002
8.809	.002
8.950	.002
9.002	.002
9.055	.001
9.284	.001
9.336	.001
9.398	.001
9.521	.000
9.635	.000
9.916	.000
10.057	.000
10.550	.000

$n_1 = 4, n_2 = 4, n_3 = 4$

x	$P_0\{H \geq x\}$
.000	1.000
.038	.994
.115	.968
.154	.941
.269	.913
.346	.864
.462	.840
.500	.815
.615	.770
.731	.746
.808	.706
.962	.667
1.038	.648
1.077	.630
1.192	.592
1.385	.557
1.423	.540
1.500	.510
1.654	.480
1.846	.452
1.885	.436
2.000	.397
2.192	.370
2.346	.348
2.423	.327
2.462	.307
2.577	.296
2.808	.277
2.885	.260
2.923	.252
3.038	.234
3.115	.219
3.231	.212
3.500	.197
3.577	.173
3.731	.162
3.846	.151
3.962	.145
4.154	.136
4.192	.131
4.269	.122
4.308	.114
4.500	.104

$n_1 = 4, n_2 = 4, n_3 = 4$

x	$P_0\{H \geq x\}$
4.654	.097
4.769	.094
4.885	.086
4.962	.080
5.115	.074
5.346	.063
5.538	.057
6.654	.055
5.692	.049
5.808	.044
6.000	.040
6.038	.037
6.269	.033
6.500	.030
6.577	.026
6.615	.024
6.731	.021
6.962	.019
7.038	.018
7.269	.016
7.385	.015
7.423	.013
7.538	.011
7.654	.008
7.731	.007
8.000	.005
8.115	.003
8.346	.002
8.654	.001
8.769	.001
9.269	.001
9.846	.000

$n_1 = 4, n_2 = 4, n_3 = 5$

x	$P_0\{H \geq x\}$
.000	1.000
.030	.996
.033	.981
.086	.974
.096	.967
.119	.952
.132	.937
.201	.930
.218	.916
.228	.903
.267	.889
.297	.875
.343	.869
.376	.862
.382	.849
.399	.836
.425	.823
.475	.811
.528	.798
.544	.792
.597	.780
.610	.768
.613	.757
.640	.745
.689	.734
.742	.723
.771	.711
.804	.706
.824	.695
.860	.690
.870	.679
.903	.668
.910	.658
.940	.647
1.019	.637
1.058	.627
1.068	.617
1.124	.607
1.167	.598
1.187	.589
1.190	.584
1.203	.574
1.256	.565
1.272	.556
1.299	.548
1.371	.539
1.404	.534
1.414	.526

Table B-4 (*continued*)

$n_1 = 4, n_2 = 4, n_3 = 5$		$n_1 = 4, n_2 = 4, n_3 = 5$		$n_1 = 4, n_2 = 4, n_3 = 5$		$n_1 = 4, n_2 = 4, n_3 = 5$	
x	$P_0\{H \geq x\}$	x	$P_0\{H \geq x\}$	x	$P_0\{H \geq x\}$	x	$P_0\{H \geq x\}$
1.454	.518	3.013	.228	4.701	.094	6.214	.034
1.503	.509	3.086	.224	4.711	.092	6.228	.033
1.530	.501	3.119	.221	4.728	.091	6.267	.032
1.533	.493	3.129	.217	4.747	.089	6.310	.031
1.586	.485	3.168	.214	4.760	.088	6.343	.030
1.596	.477	3.218	.210	4.813	.086	6.382	.029
1.615	.469	3.260	.206	4.830	.084	6.399	.028
1.668	.465	3.297	.202	4.833	.082	6.462	.027
1.701	.458	3.330	.200	4.896	.081	6.544	.027
1.718	.450	3.382	.197	4.975	.077	6.547	.026
1.744	.443	3.432	.190	5.014	.076	6.597	.026
1.810	.436	3.442	.187	5.024	.074	6.672	.024
1.876	.429	3.481	.183	5.028	.073	6.676	.024
1.899	.422	3.511	.180	5.090	.071	6.804	.023
1.929	.414	3.590	.176	5.172	.069	6.860	.022
1.942	.408	3.613	.170	5.196	.068	6.870	.022
1.958	.401	3.630	.167	5.225	.066	6.887	.021
2.047	.388	3.640	.164	5.344	.065	6.890	.021
2.110	.375	3.656	.160	5.360	.063	6.943	.020
2.140	.371	3.696	.157	5.370	.062	6.953	.020
2.143	.365	3.758	.154	5.387	.061	6.976	.019
2.176	.362	3.828	.151	5.410	.060	7.058	.018
2.196	.356	3.910	.146	5.440	.059	7.075	.017
2.275	.344	3.986	.143	5.476	.057	7.101	.017
2.387	.338	3.989	.141	5.486	.056	7.124	.016
2.390	.332	4.025	.139	5.489	.056	7.190	.016
2.403	.327	4.042	.134	5.519	.054	7.203	.015
2.440	.316	4.068	.132	5.568	.052	7.233	.015
2.443	.310	4.075	.130	5.571	.051	7.240	.014
2.453	.305	4.118	.127	5.618	.050	7.256	.014
2.558	.299	4.170	.125	5.657	.049	7.418	.014
2.575	.293	4.200	.122	5.687	.048	7.467	.013
2.601	.288	4.233	.121	5.756	.047	7.470	.013
2.667	.283	4.253	.119	5.782	.046	7.497	.013
2.670	.279	4.272	.117	5.815	.045	7.503	.012
2.733	.271	4.289	.114	5.819	.043	7.586	.012
2.756	.267	4.332	.112	5.914	.042	7.596	.012
2.799	.262	4.381	.108	6.003	.042	7.714	.011
2.881	.257	4.447	.106	6.013	.041	7.744	.011
2.904	.253	4.497	.104	6.030	.040	7.760	.009
2.918	.249	4.553	.102	6.096	.039	7.767	.009
2.967	.245	4.619	.100	6.119	.038	7.797	.009
2.987	.240	4.668	.098	6.132	.037	7.810	.009
2.997	.236	4.685	.096	6.201	.036	7.833	.008

Table B-4 (*continued*)

$n_1 = 4, n_2 = 4, n_3 = 5$

x	$P_0\{H \geq x\}$
7.942	.007
7.981	.007
8.047	.006
8.113	.006
8.130	.006
8.140	.005
8.156	.005
8.189	.005
8.403	.004
8.440	.004
8.456	.004
8.525	.003
8.558	.003
8.571	.003
8.575	.003
8.604	.003
8.703	.003
8.733	.002
8.782	.002
8.868	.002
8.997	.001
9.053	.001
9.099	.001
9.129	.001
9.168	.001
9.396	.001
9.528	.001
9.590	.001
9.613	.000
9.758	.000
10.118	.000
10.187	.000
10.681	.000

$n_1 = 4, n_2 = 5, n_3 = 5$

x	$P_0\{H \geq x\}$
.006	1.000
.020	.994
.043	.988
.051	.976
.086	.970
.111	.958
.131	.946
.143	.935
.180	.929
.203	.923
.223	.912
.226	.901
.271	.890
.280	.879
.326	.874
.360	.863
.371	.852
.386	.841
.463	.821
.500	.805
.523	.800
.543	.790
.546	.781
.591	.771
.600	.752
.691	.742
.706	.738
.726	.729
.751	.720
.771	.711
.783	.693
.843	.684
.863	.675
.866	.667
.966	.658
.980	.654
1.000	.650
1.003	.642
1.011	.626
1.046	.617
1.071	.610
1.140	.594
1.183	.587
1.186	.579
1.286	.572
1.300	.553
1.323	.547
1.331	.540
1.346	.532

$n_1 = 4, n_2 = 5, n_3 = 5$

x	$P_0\{H \geq x\}$
1.366	.525
1.411	.518
1.423	.512
1.483	.505
1.551	.498
1.560	.492
1.606	.485
1.620	.479
1.643	.470
1.651	.458
1.686	.455
1.711	.449
1.731	.443
1.743	.437
1.803	.431
1.826	.425
1.871	.420
1.963	.414
1.971	.409
1.986	.398
2.006	.393
2.031	.382
2.051	.377
2.063	.372
2.100	.369
2.143	.364
2.191	.354
2.246	.349
2.280	.344
2.306	.339
2.351	.335
2.371	.330
2.383	.326
2.420	.322
2.443	.319
2.463	.307
2.466	.302
2.511	.298
2.520	.294
2.566	.292
2.600	.288
2.626	.284
2.691	.280
2.740	.276

$n_1 = 4, n_2 = 5, n_3 = 5$

x	$P_0\{H \geq x\}$
2.783	.272
2.786	.268
2.831	.257
2.840	.254
2.886	.250
2.931	.246
2.946	.239
2.966	.236
2.991	.232
3.023	.229
3.083	.224
3.103	.221
3.160	.218
3.240	.215
3.243	.211
3.266	.209
3.286	.203
3.311	.200
3.343	.197
3.380	.188
3.403	.187
3.471	.184
3.540	.176
3.571	.174
3.586	.170
3.651	.167
3.743	.162
3.746	.160
3.791	.155
3.800	.153
3.846	.151
3.883	.148
3.891	.144
3.906	.142
3.926	.140
3.951	.137
3.971	.135
4.043	.133
4.063	.131
4.166	.127
4.200	.124
4.203	.122
4.246	.120
4.271	.118

Table B-4 (*continued*)

$n_1 = 4, n_2 = 5, n_3 = 5$		$n_1 = 4, n_2 = 5, n_3 = 5$		$n_1 = 4, n_2 = 5, n_3 = 5$		$n_1 = 4, n_2 = 5, n_3 = 5$	
x	$P_0\{H \geq x\}$	x	$P_0\{H \geq x\}$	x	$P_0\{H \geq x\}$	x	$P_0\{H \geq x\}$
4.291	.115	5.711	.048	7.183	.017	8.683	.004
4.303	.113	5.780	.048	7.220	.017	8.691	.004
4.363	.111	5.803	.047	7.243	.017	8.726	.004
4.383	.110	5.811	.046	7.266	.016	8.751	.004
4.386	.108	5.871	.045	7.311	.015	8.771	.004
4.486	.106	5.903	.043	7.320	.015	8.969	.003
4.500	.105	5.963	.042	7.426	.015	8.980	.003
4.520	.101	5.983	.042	7.446	.014	9.000	.003
4.523	.099	5.986	.041	7.471	.014	9.011	.003
4.531	.098	6.031	.040	7.491	.014	9.026	.003
4.591	.096	6.086	.040	7.503	.013	9.071	.002
4.611	.095	6.100	.038	7.563	.013	9.103	.002
4.660	.093	6.123	.037	7.586	.012	9.163	.002
4.706	.092	6.146	.037	7.631	.012	9.231	.002
4.806	.089	6.166	.035	7.640	.011	9.286	.002
4.843	.088	6.211	.035	7.686	.011	9.323	.001
4.851	.086	6.223	.034	7.720	.011	9.411	.001
4.866	.084	6.283	.034	7.766	.010	9.503	.001
4.886	.083	6.303	.033	7.791	.010	9.506	.001
4.911	.079	6.351	.032	7.823	.010	9.606	.001
4.943	.078	6.406	.031	7.860	.010	9.643	.001
4.980	.076	6.440	.030	7.903	.009	9.651	.001
5.023	.075	6.451	.029	7.906	.009	9.686	.001
5.071	.074	6.486	.029	8.006	.009	9.926	.001
5.126	.073	6.531	.028	8.043	.009	9.986	.000
5.163	.070	6.543	.028	8.051	.008	10.051	.000
5.171	.069	6.603	.027	8.066	.008	10.063	.000
5.186	.068	6.623	.026	8.086	.008	10.100	.000
5.206	.067	6.626	.026	8.131	.008	10.260	.000
5.231	.066	6.671	.025	8.143	.008	10.511	.000
5.263	.064	6.760	.025	8.223	.007	10.520	.000
5.323	.063	6.763	.024	8.226	.007	10.566	.000
5.400	.061	6.771	.024	8.271	.007	10.646	.000
5.446	.059	6.786	.023	8.280	.006	11.023	.000
5.460	.058	6.806	.022	8.340	.006	11.083	.000
5.483	.057	6.831	.022	8.363	.006	11.571	.000
5.491	.056	6.900	.021	8.371	.005		
5.526	.056	6.943	.020	8.386	.005		
5.571	.055	7.000	.019	8.431	.005		
5.583	.052	7.046	.019	8.463	.005		
5.620	.051	7.080	.018	8.523	.005		
5.643	.050	7.106	.018	8.543	.005		
5.666	.049	7.171	.018	8.546	.004		

$n_1 = 5, n_2 = 5, n_3 = 5$	
x	$P_0\{H \geq x\}$
.000	1.000
.020	.998

Table B-4 (*continued*)

$n_1 = 5, n_2 = 5, n_3 = 5$		$n_1 = 5, n_2 = 5, n_3 = 5$		$n_1 = 5, n_2 = 5, n_3 = 5$		$n_1 = 5, n_2 = 5, n_3 = 5$	
x	$P_0\{H > x\}$	x	$P_0\{H > x\}$	x	$P_0\{H > x\}$	x	$P_0\{H > x\}$
.060	.983	2.340	.330	5.120	.072	8.000	.009
.080	.968	2.420	.319	5.180	.070	8.060	.009
.140	.954	2.480	.314	5.360	.065	8.180	.008
.180	.925	2.540	.304	5.420	.063	8.240	.008
.240	.911	2.580	.294	5.460	.060	8.340	.007
.260	.898	2.660	.284	5.540	.055	8.420	.007
.320	.871	2.780	.265	5.580	.053	8.540	.006
.380	.858	2.880	.256	5.660	.051	8.640	.006
.420	.832	2.940	.252	5.780	.049	8.660	.006
.500	.807	2.960	.239	5.820	.048	8.720	.005
.540	.794	3.020	.231	5.840	.046	8.780	.005
.560	.783	3.120	.223	6.000	.044	8.820	.005
.620	.759	3.140	.216	6.020	.043	8.880	.004
.720	.736	3.260	.208	6.080	.040	8.960	.004
.740	.725	3.380	.201	6.140	.038	9.060	.004
.780	.703	3.420	.190	6.180	.036	9.140	.003
.860	.681	3.440	.184	6.260	.035	9.260	.003
.960	.660	3.500	.177	6.320	.033	9.360	.003
.980	.650	3.620	.171	6.480	.032	9.380	.003
1.040	.620	3.660	.165	6.500	.031	9.420	.002
1.140	.601	3.780	.159	6.540	.030	9.500	.002
1.220	.582	3.840	.153	6.620	.028	9.620	.002
1.260	.564	3.860	.150	6.660	.027	9.680	.001
1.280	.547	3.920	.145	6.720	.026	9.740	.001
1.340	.538	3.980	.137	6.740	.025	9.780	.001
1.460	.521	4.020	.132	6.860	.024	9.920	.001
1.500	.505	4.160	.127	6.980	.021	9.980	.001
1.520	.497	4.220	.123	7.020	.020	10.140	.001
1.580	.481	4.340	.118	7.220	.019	10.220	.001
1.620	.466	4.380	.110	7.260	.018	10.260	.000
1.680	.459	4.460	.105	7.280	.018	10.500	.000
1.820	.444	4.500	.102	7.340	.016	10.580	.000
1.860	.416	4.560	.100	7.440	.015	10.640	.000
1.940	.403	4.580	.096	7.460	.015	10.820	.000
2.000	.390	4.740	.092	7.580	.014	11.060	.000
2.060	.383	4.820	.089	7.620	.013	11.180	.000
2.160	.371	4.860	.085	7.740	.012	11.520	.000
2.180	.365	4.880	.084	7.760	.012	11.580	.000
2.220	.353	4.940	.081	7.940	.011	12.020	.000
2.240	.342	5.040	.075	7.980	.011	12.500	.000

Source: Table F of *A Nonparametric Introduction to Statistics*, by C. H. Kraft and C van Eedan, Macmillan, New York, 1968. Reproduced by permission of the Macmillan Publishing Company.

Table B-5 Selected Critical Values for All Treatments: Multiple Comparisons Based on Kruskal–Wallis Rank Sums

$k = 3, n = 2(1)6$; $k = 6, 7, 8, n = 2, 3$;
$k = 4, 5, n = 2, 3, 4$; $k = 9(1)15, n = 2$

For a given k and n, the entries in the table correspond to $P\{|R_i - R_j| < y(\alpha, k, n)$ $i = 1, \ldots, k-1, j = u+1, \ldots, k\} \approx 1 - \alpha$.

	n									
	2		3		4		5		6	
k	$y(\alpha, k, 2)$	α	$y(\alpha, k, 3)$	α	$y(\alpha, k, 4)$	α	$y(\alpha, k, 5)$	α	$y(\alpha, k, 6)$	α
3	8	.067	15*	.064	24*	.045	33*	.048	43*	.049
			16	.029	25	.031	35	.031	51*	.011
			17*	.011	27*	.011	39*	.009		
4	12	.029	22	.043	34	.049				
			23	.023	36	.026				
			24	.012	38	.012				
5	15	.048	28	.060	44	.056				
	16	.016	30	.023	46	.033				
			32	.007	50	.010				
6	19	.030	35	.055						
	20	.010	37	.024						
			39	.009						
7	22	.056	42	.054						
	23	.021	44	.026						
	24	.007	46	.012						
8	26	.041	49	.055						
	28	.005	51	.029						
			54	.010						
9	29	.063								
	30	.031								
	31	.012								
10	33	.050								
	34	.025								
	35	.009								
11	37	.040								
	38	.020								
	39	.008								
12	40	.062								
	41	.033								
	43	.006								
13	44	.052								
	45	.028								
	46	.014								
14	48	.044								
	49	.024								
	50	.012								
15	52	.038								
	54	.010								

Source: "Rank Sum Multiple Comparisons in One- and Two-Way Classification," by B. J. McDonald and W. A. Thompson, *Biometrika*, Vol. 54, pp. 487–497 (1967). Reproduced by permission of the editor of *Biometrika*. The starred values are from "Distribution-Free Multiple Comparisons," Ph.D. thesis (1963), P. Nemenyi, Princeton University, with permission of the author.

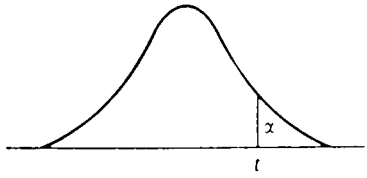
Table B-6 Selected Critical Values for the Range of k Independent $N(0, 1)$ Variables: $k = 2(1)20(2)40(10)100$

For a given k and α, the tabled entry is $q(\alpha, k, \infty)$.

	α								
k	.0001	.0005	.001	.005	.01	.025	.05	.10	.20
2	5.502	4.923	4.654	3.970	3.643	3.170	2.772	2.326	1.812
3	5.864	5.316	5.063	4.424	4.120	3.682	3.314	2.902	2.424
4	6.083	5.553	5.309	4.694	4.403	3.984	3.633	3.240	2.784
5	6.240	5.722	5.484	4.886	4.603	4.197	3.858	3.478	3.037
6	6.362	5.853	5.619	5.033	4.757	4.361	4.030	3.661	3.232
7	6.461	5.960	5.730	5.154	4.882	4.494	4.170	3.808	3.389
8	6.546	6.050	5.823	5.255	4.987	4.605	4.286	3.931	3.520
9	6.618	6.127	5.903	5.341	5.078	4.700	4.387	4.037	3.632
10	6.682	6.196	5.973	5.418	5.157	4.784	4.474	4.129	3.730
11	6.739	6.257	6.036	5.485	5.227	4.858	4.552	4.211	3.817
12	6.791	6.311	6.092	5.546	5.290	4.925	4.622	4.285	3.895
13	6.837	6.361	6.144	5.602	5.348	4.985	4.685	4.351	3.966
14	6.880	6.407	6.191	5.652	5.400	5.041	4.743	4.412	4.030
15	6.920	6.449	6.234	5.699	5.448	5.092	4.796	4.468	4.089
16	6.957	6.488	6.274	5.742	5.493	5.139	4.845	4.519	4.144
17	6.991	6.525	6.312	5.783	5.535	5.183	4.891	4.568	4.195
18	7.023	6.559	6.347	5.820	5.574	5.224	4.934	4.612	4.242
19	7.054	6.591	6.380	5.856	5.611	5.262	4.974	4.654	4.287
20	7.082	6.621	6.411	5.889	5.645	5.299	5.012	4.694	4.329
22	7.135	6.677	6.469	5.951	5.709	5.365	5.081	4.767	4.405
24	7.183	6.727	6.520	6.006	5.766	5.425	5.144	4.832	4.475
26	7.226	6.773	6.568	6.057	5.818	5.480	5.201	4.892	4.537
28	7.266	6.816	6.611	6.103	5.866	5.530	5.253	4.947	4.595
30	7.303	6.855	6.651	6.146	5.911	5.577	5.301	4.997	4.648
32	7.337	6.891	6.689	6.186	5.952	5.620	5.346	5.044	4.697
34	7.370	6.925	6.723	6.223	5.990	5.660	5.388	5.087	4.743
36	7.400	6.957	6.756	6.258	6.026	5.698	5.427	5.128	4.786
38	7.428	6.987	6.787	6.291	6.060	5.733	5.463	5.166	4.826
40	7.455	7.015	6.816	6.322	6.092	5.766	5.498	5.202	4.864
50	7.571	7.137	6.941	6.454	6.228	5.909	5.646	5.357	5.026
60	7.664	7.235	7.041	6.561	6.338	6.023	5.764	5.480	5.155
70	7.741	7.317	7.124	6.649	6.429	6.118	5.863	5.582	5.262
80	7.808	7.387	7.196	6.725	6.507	6.199	5.947	5.669	5.353
90	7.866	7.448	7.259	6.792	6.575	6.270	6.020	5.745	5.433
100	7.918	7.502	7.314	6.850	6.636	6.333	6.085	5.812	5.503

Source: "Table of Range and Studentized Range," by H. L. Harter, *Ann. Math. Statist.*, Vol. 31, pp. 1122–1147 (1960). Reproduced by permission of the editor of the *Annals of Mathematical Statistics.*

Table B-7 Percentage Points of the *t*-Distribution



d.f.	$t_{.100}$	$t_{.050}$	$t_{.025}$	$t_{.010}$	$t_{.005}$	d.f.
1	3.078	6.314	12.706	31.821	63.657	1
2	1.886	2.920	4.303	6.965	9.925	2
3	1.638	2.353	3.182	4.541	5.841	3
4	1.533	2.132	2.776	3.747	4.604	4
5	1.476	2.015	2.571	3.365	4.032	5
6	1.440	1.943	2.447	3.143	3.707	6
7	1.415	1.895	2.365	2.998	3.499	7
8	1.397	1.860	2.306	2.896	3.355	8
9	1.383	1.833	2.262	2.821	3.250	9
10	1.372	1.812	2.228	2.764	3.169	10
11	1.363	1.796	2.201	2.718	3.106	11
12	1.356	1.782	2.179	2.681	3.055	12
13	1.350	1.771	2.160	2.650	3.012	13
14	1.345	1.761	2.145	2.624	2.977	14
15	1.341	1.753	2.131	2.602	2.947	15
16	1.337	1.746	2.120	2.583	2.921	16
17	1.333	1.740	2.110	2.567	2.898	17
18	1.330	1.734	2.101	2.552	2.878	18
19	1.328	1.729	2.093	2.539	2.861	19
20	1.325	1.725	2.086	2.528	2.845	20
21	1.323	1.721	2.080	2.518	2.831	21
22	1.321	1.717	2.074	2.508	2.819	22
23	1.319	1.714	2.069	2.500	2.807	23
24	1.318	1.711	2.064	2.492	2.797	24
25	1.316	1.708	2.060	2.485	2.787	25
26	1.315	1.706	2.056	2.479	2.779	26
27	1.314	1.703	2.052	2.473	2.771	27
28	1.313	1.701	2.048	2.467	2.763	28
29	1.311	1.699	2.045	2.462	2.756	29
∞	1.282	1.645	1.960	2.326	2.576	∞

Source: "Table of Percentage Points of the *t*-Distribution," by Maxine Merrington, *Biometrika*, Vol. 32, p. 300 (1941). Reproduced by permission of the editor of *Biometrika*.

Table B-8 Coefficients (a_i and b_i) of the Best Estimates of the Mean (μ) and Standard Deviation (σ) in Censored Samples Up to $n = 20$ from A Normal Population

$n = 2$

$n - r$		$t_{(1)}$	$t_{(2)}$
0	μ	.5000	.5000
	σ	−.8862	.8862

$n = 3$

$n - r$		$t_{(1)}$	$t_{(2)}$	$t_{(3)}$
0	μ	.3333	.3333	.3333
	σ	−.5908	.0000	.5908
1	μ	.0000	1.0000	
	σ	−1.1816	1.1816	

$n = 4$

$n - r$		$t_{(1)}$	$t_{(2)}$	$t_{(3)}$	$t_{(4)}$
0	μ	.2500	.2500	.2500	.2500
	σ	−.4539	−.1102	.1102	.4539
1	μ	.1161	.2408	.6431	
	σ	−.6971	−.1268	.8239	
2	μ	−.4056	1.4056		
	σ	−1.3654	1.3654		

$n = 5$

$n - r$		$t_{(1)}$	$t_{(2)}$	$t_{(3)}$	$t_{(4)}$	$t_{(5)}$
0	μ	.2000	.2000	.2000	.2000	.2000
	σ	−.3724	−.1352	.0000	.1352	.3724
1	μ	.1252	.1830	.2147	.4771	
	σ	−.5117	−.1668	.0274	.6511	
2	μ	−.0638	.1498	.9139		
	σ	−.7696	−.2121	.9817		
3	μ	−.7411	1.7411			
	σ	−1.4971	1.4971			

$n = 6$

$n - r$		$t_{(1)}$	$t_{(2)}$	$t_{(3)}$	$t_{(4)}$	$t_{(5)}$	$t_{(6)}$
0	μ	.1667	.1667	.1667	.1667	.1667	.1667
	σ	−.3175	−.1386	−.0432	.0432	.1386	.3175
1	μ	.1183	.1510	.1680	.1828	.3799	
	σ	−.4097	−.1685	−.0406	.0740	.5448	
2	μ	.0185	.1226	.1761	.6828		
	σ	−.5528	−.2091	−.0290	.7909		
3	μ	−.2159	.0649	1.1511			
	σ	−.8244	−.2760	1.1004			
4	μ	−1.0261	2.0261				
	σ	−1.5988	1.5988				

$n = 7$

$n - r$		$t_{(1)}$	$t_{(2)}$	$t_{(3)}$	$t_{(4)}$	$t_{(5)}$	$t_{(6)}$	$t_{(7)}$
0	μ	.1429	.1429	.1429	.1429	.1429	.1429	.1429
	σ	−.2778	−.1351	−.0625	.0000	.0625	.1351	.2778
1	μ	.1088	.1295	.1400	.1487	.1571	.3159	
	σ	−.3440	−.1610	−.0681	.0114	.0901	.4716	
2	μ	.0465	.1072	.1375	.1626	.5462		
	σ	−.4370	−.1943	−.0718	.0321	.6709		
3	μ	−.0738	.0677	.1375	.8686			
	σ	−.5848	−.2428	−.0717	.8994			
4	μ	−.3474	−.0135	1.3609				
	σ	−.8682	−.3269	1.1951				
5	μ	−1.2733	2.2733					
	σ	−1.6812	1.6812					

Table B-8 (*continued*)

$n = 8$

$n-r$		$t_{(1)}$	$t_{(2)}$	$t_{(3)}$	$t_{(4)}$	$t_{(5)}$	$t_{(6)}$	$t_{(7)}$	$t_{(8)}$
0	μ	.1250	.1250	.1250	.1250	.1250	.1250	.1250	.1250
	σ	−.2476	−.1294	−.0713	−.0230	.0230	.0713	.1294	.2476
1	μ	.0997	.1139	.1208	.1265	.1318	.1370	.2704	
	σ	−.2978	−.1515	−.0796	−.0200	.0364	.0951	.4175	
2	μ	.0569	.0962	.1153	.1309	.1451	.4555		
	σ	−.3638	−.1788	−.0881	−.0132	.0570	.5868		
3	μ	−.0167	.0677	.1084	.1413	.6993			
	σ	−.4586	−.2156	−.0970	.0002	.7709			
4	μ	−.1549	.0176	.1001	1.0372				
	σ	−.6110	−.2707	−.1061	.9878				
5	μ	−.4632	−.0855	1.5487					
	σ	−.9045	−.3690	1.2735					
6	μ	−1.4915	2.4915						
	σ	−1.7502	1.7502						

$n = 9$

$n-r$		$t_{(1)}$	$t_{(2)}$	$t_{(3)}$	$t_{(4)}$	$t_{(5)}$	$t_{(6)}$	$t_{(7)}$	$t_{(8)}$	$t_{(9)}$
0	μ	.1111	.1111	.1111	.1111	.1111	.1111	.1111	.1111	.1111
	σ	−.2237	−.1233	−.0751	−.0360	.0000	.0360	.0751	.1233	.2237
1	μ	.0915	.1018	.1067	.1106	.1142	.1177	.1212	.2365	
	σ	−.2633	−.1421	−.0841	−.0370	.0062	.0492	.0954	.3757	
2	μ	.0602	.0876	.1006	.1110	.1204	.1294	.3909		
	σ	−.3129	−.1647	−.0938	−.0364	.0160	.0678	.5239		
3	μ	.0104	.0660	.0923	.1133	.1320	.5860			
	σ	−.3797	−.1936	−.1048	−.0333	.0317	.6797			
4	μ	−.0731	.0316	.0809	.1199	.8408				
	σ	−.4766	−.2335	−.1181	−.0256	.8537				
5	μ	−.2272	−.0284	.0644	1.1912					
	σ	−.6330	−.2944	−.1348	1.0622					
6	μ	−.5664	−.1521	1.7185						
	σ	−.9355	−.4047	1.3402						
7	μ	−1.6868	2.6868							
	σ	−1.8092	1.8092							

$n = 10$

$n-r$		$t_{(1)}$	$t_{(2)}$	$t_{(3)}$	$t_{(4)}$	$t_{(5)}$	$t_{(6)}$	$t_{(7)}$	$t_{(8)}$	$t_{(9)}$	$t_{(10)}$
0	μ	.1000	.1000	.1000	.1000	.1000	.1000	.1000	.1000	.1000	.1000
	σ	−.2044	−.1172	−.0763	−.0436	−.0142	.0142	.0436	.0763	.1172	.2044
1	μ	.0843	.0921	.0957	.0986	.1011	.1036	.1060	.1085	.2101	
	σ	−.2364	−.1334	−.0851	−.0465	−.0119	.0215	.0559	.0937	.3423	
2	μ	.0605	.0804	.0898	.0972	.1037	.1099	.1161	.3424		
	σ	−.2753	−.1523	−.0947	−.0488	−.0077	.0319	.0722	.4746		
3	μ	.0244	.0636	.0818	.0962	.1089	.1207	.5045			
	σ	−.3252	−.1758	−.1058	−.0502	−.0006	.0469	.6107			
4	μ	−.0316	.0383	.0707	.0962	.1185	.7078				
	σ	−.3930	−.2063	−.1192	−.0501	.0111	.7576				
5	μ	−.1240	−.0016	.0549	.0990	.9718					
	σ	−.4919	−.2491	−.1362	−.0472	.9243					
6	μ	−.2923	−.0709	.0305	1.3327						
	σ	−.6520	−.3150	−.1593	1.1263						
7	μ	−.6596	−.2138	1.8734							
	σ	−.9625	−.4357	1.3981							
8	μ	−1.8634	2.8634								
	σ	−1.8608	1.8608								

Table B-8 (*continued*)

$n = 11$

$n - r$		$t_{(1)}$	$t_{(2)}$	$t_{(3)}$	$t_{(4)}$	$t_{(5)}$	$t_{(6)}$	$t_{(7)}$	$t_{(8)}$	$t_{(9)}$	$t_{(10)}$	$t_{(11)}$
0	μ	.0909	.0909	.0909	.0909	.0909	.0909	.0909	.0909	.0909	.0909	.0909
	σ	−.1883	−.1115	−.0760	−.0481	−.0234	.0000	.0234	.0481	.0760	.1115	.1883
1	μ	.0781	.0841	.0869	.0891	.0910	.0928	.0945	.0963	.0982	.1891	
	σ	−.2149	−.1256	−.0843	−.0519	−.0233	.0038	.0309	.0593	.0911	.3149	
2	μ	.0592	.0744	.0814	.0869	.0917	.0962	.1005	.1049	.3047		
	σ	−.2463	−.1417	−.0934	−.0555	−.0220	.0095	.0409	.0736	.4349		
3	μ	.0320	.0609	.0741	.0845	.0935	.1020	.1101	.4430			
	σ	−.2852	−.1610	−.1038	−.0589	−.0194	.0178	.0545	.5562			
4	μ	−.0082	.0415	.0642	.0820	.0974	.1116	.6116				
	σ	−.3357	−.1854	−.1163	−.0621	−.0146	.0299	.6842				
5	μ	−.0698	.0128	.0504	.0797	.1049	.8220					
	σ	−.4045	−.2175	−.1317	−.0647	−.0061	.8246					
6	μ	−.1702	−.0323	.0303	.0786	1.0937						
	σ	−.5053	−.2627	−.1519	−.0657	.9857						
7	μ	−.3516	−.1104	−.0016	1.4636							
	σ	−.6687	−.3331	−.1807	1.1825							
8	μ	−.7445	−.2712	2.0157								
	σ	−.9862	−.4630	1.4402								
9	μ	−2.0245	3.0245									
	σ	−1.9065	1.9065									

$n = 12$

$n - r$		$t_{(1)}$	$t_{(2)}$	$t_{(3)}$	$t_{(4)}$	$t_{(5)}$	$t_{(6)}$	$t_{(7)}$	$t_{(8)}$	$t_{(9)}$	$t_{(10)}$	$t_{(11)}$	$t_{(12)}$
0	μ	.0833	.0833	.0833	.0833	.0833	.0833	.0833	.0833	.0833	.0833	.0833	.0833
	σ	−.1748	−.1061	−.0749	−.0506	−.0294	−.0097	.0097	.0294	.0506	.0749	.1061	.1748
1	μ	.0726	.0775	.0796	.0813	.0828	.0842	.0855	.0868	.0882	.0896	.1719	
	σ	−.1972	−.1185	−.0827	−.0548	−.0305	−.0079	.0142	.0367	.0608	.0881	.2919	
2	μ	.0574	.0693	.0747	.0789	.0825	.0859	.0891	.0923	.0956	.2745		
	σ	−.2232	−.1324	−.0911	−.0590	−.0310	−.0050	.0203	.0461	.0733	.4020		
3	μ	.0360	.0581	.0682	.0759	.0827	.0888	.0948	.1006	.3950			
	σ	−.2545	−.1487	−.1007	−.0633	−.0308	−.0007	.0286	.0582	.5119			
4	μ	.0057	.0428	.0595	.0724	.0836	.0938	.1036	.5386				
	σ	−.2937	−.1686	−.1119	−.0678	−.0296	.0058	.0400	.6259				
5	μ	−.0382	.0210	.0477	.0684	.0861	.1022	.7128					
	σ	−.3448	−.1939	−.1255	−.0726	−.0267	.0155	.7479					
6	μ	−.1048	−.0109	.0313	.0637	.0915	.9292						
	σ	−.4146	−.2274	−.1428	−.0774	−.0210	.8833						
7	μ	−.2125	−.0609	.0070	.0589	1.2075							
	σ	−.5171	−.2749	−.1659	−.0820	1.0399							
8	μ	−.4059	−.1472	−.0321	1.5852								
	σ	−.6836	−.3493	−.1996	1.2324								
9	μ	−.8225	−.3249	2.1474									
	σ	−1.0075	−.4874	1.4948									
10	μ	−2.1728	3.1728										
	σ	−1.9474	1.9474										

Table B-8 (*continued*)

$n = 13$

$n - r$		$t_{(1)}$	$t_{(2)}$	$t_{(3)}$	$t_{(4)}$	$t_{(5)}$	$t_{(6)}$	$t_{(7)}$	$t_{(8)}$	$t_{(9)}$	$t_{(10)}$	$t_{(11)}$	$t_{(12)}$	$t_{(13)}$
0	μ	.0769	.0769	.0769	.0769	.0769	.0769	.0769	.0769	.0769	.0769	.0769	.0769	.0769
	σ	−.1632	−.1013	−.0735	−.0520	−.0335	−.0164	.0000	.0164	.0335	.0520	.0735	.1013	.1632
1	μ	.0679	.0718	.0735	.0749	.0761	.0771	.0781	.0792	.0802	.0813	.0824	.1576	
	σ	−.1824	−.1122	−.0806	−.0563	−.0353	−.0160	.0026	.0212	.0404	.0612	.0850	.2724	
2	μ	.0552	.0648	.0691	.0724	.0752	.0778	.0803	.0827	.0852	.0877	.2497		
	σ	−.2043	−.1243	−.0884	−.0607	−.0368	−.0148	.0063	.0273	.0490	.0723	.3743		
3	μ	.0380	.0555	.0633	.0693	.0745	.0792	.0836	.0880	.0924	.3564			
	σ	−.2301	−.1382	−.0970	−.0653	−.0379	−.0128	.0113	.0352	.0598	.4750			
4	μ	.0144	.0430	.0557	.0655	.0739	.0816	.0888	.0958	.4813				
	σ	−.2616	−.1549	−.1071	−.0703	−.0386	−.0095	.0182	.0456	.5781				
5	μ	−.0185	.0259	.0457	.0610	.0740	.0857	.0968	.6294					
	σ	−.3011	−.1754	−.1191	−.0758	−.0386	−.0046	.0278	.6867					
6	μ	−.0659	.0020	.0322	.0553	.0750	.0928	.8055						
	σ	−.3528	−.2015	−.1339	−.0819	−.0374	.0032	.8042						
7	μ	−.1371	−.0330	.0132	.0484	.0784	1.0301							
	σ	−.4236	−.2363	−.1528	−.0888	−.0341	.9355							
8	μ	−.2516	−.0876	−.0151	.0400	1.3143								
	σ	−.5276	−.2859	−.1785	−.0964	1.0884								
9	μ	−.4561	−.1817	−.0610	1.6988									
	σ	−.6969	−.3638	−.2165	1.2773									
10	μ	−.8946	−.3753	2.2699										
	σ	−1.0266	−.5094	1.5360										
11	μ	−2.3101	3.3101											
	σ	−1.9845	1.9845											

Table B-8 (*continued*)

$n = 14$

$n-r$		$t_{(1)}$	$t_{(2)}$	$t_{(3)}$	$t_{(4)}$	$t_{(5)}$	$t_{(6)}$	$t_{(7)}$	$t_{(8)}$	$t_{(9)}$	$t_{(10)}$	$t_{(11)}$	$t_{(12)}$	$t_{(13)}$	$t_{(14)}$
0	μ	.0714	.0714	.0714	.0714	.0714	.0714	.0714	.0714	.0714	.0714	.0714	.0714	.0714	.0714
	σ	−.1532	−.0968	−.0717	−.0526	−.0362	−.0212	−.0070	.0070	.0212	.0362	.0526	.0717	.0968	.1532
1	μ	.0637	.0669	.0683	.0694	.0704	.0712	.0721	.0728	.0736	.0745	.0753	.0762	.1455	
	σ	−.1698	−.1065	−.0784	−.0568	−.0384	−.0216	−.0056	.0100	.0259	.0426	.0609	.0820	.2556	
2	μ	.0530	.0609	.0643	.0670	.0692	.0713	.0732	.0751	.0770	.0789	.0809	.2291		
	σ	−.1885	−.1171	−.0854	−.0612	−.0404	−.0215	−.0036	.0140	.0319	.0505	.0707	.3506		
3	μ	.0388	.0529	.0592	.0639	.0680	.0717	.0752	.0785	.0819	.0852	.3247			
	σ	−.2102	−.1292	−.0933	−.0658	−.0423	−.0209	−.0006	.0192	.0393	.0601	.4438			
4	μ	.0199	.0426	.0526	.0602	.0667	.0726	.0782	.0835	.0887	.4350				
	σ	−.2361	−.1434	−.1023	−.0709	−.0440	−.0196	.0035	.0260	.0487	.5382				
5	μ	−.0057	.0288	.0440	.0557	.0655	.0744	.0828	.0908	.5637					
	σ	−.2678	−.1604	−.1129	−.0765	−.0455	−.0174	.0092	.0350	.6363					
6	μ	−.0411	.0102	.0328	.0500	.0646	.0777	.0899	.7159						
	σ	−.3077	−.1815	−.1256	−.0829	−.0466	−.0137	.0172	.7407						
7	μ	−.0915	−.0158	.0175	.0429	.0643	.0835	.8992							
	σ	−.3599	−.2084	−.1414	−.0903	−.0469	−.0077	.8546							
8	μ	−.1670	−.0537	−.0040	.0338	.0655	1.1255								
	σ	−.4317	−.2444	−.1618	−.0990	−.0457	.9825								
9	μ	−.2879	−.1127	−.0360	.0218	1.4148									
	σ	−.5372	−.2959	−.1898	−.1094	1.1322									
10	μ	−.5027	−.2142	−.0886	1.8054										
	σ	−.7091	−.3771	−.2318	1.3180										
11	μ	−.9616	−.4228	2.3843											
	σ	−1.0441	−.5293	1.5734											
12	μ	−2.4378	3.4378												
	σ	−2.0182	2.0182												

$n = 15$

$n - r$		$t_{(1)}$	$t_{(2)}$	$t_{(3)}$	$t_{(4)}$	$t_{(5)}$	$t_{(6)}$	$t_{(7)}$	$t_{(8)}$	$t_{(9)}$	$t_{(10)}$	$t_{(11)}$	$t_{(12)}$	$t_{(13)}$	$t_{(14)}$	$t_{(15)}$
0	μ	.0667	.0667	.0667	.0667	.0667	.0667	.0667	.0667	.0667	.0667	.0667	.0667	.0667	.0667	.0667
	σ	−.1444	−.0927	−.0699	−.0526	−.0379	−.0247	−.0122	.0000	.0122	.0247	.0379	.0526	.0699	.0927	.1444
1	μ	.0599	.0627	.0639	.0648	.0655	.0662	.0669	.0675	.0682	.0688	.0695	.0702	.0709	.1351	
	σ	−.1590	−.1013	−.0760	−.0568	−.0404	−.0256	−.0116	.0019	.0154	.0293	.0440	.0602	.0791	.2409	
2	μ	.0508	.0574	.0602	.0624	.0642	.0659	.0675	.0690	.0704	.0719	.0735	.0751	.2116		
	σ	−.1752	−.1108	−.0825	−.0610	−.0427	−.0262	−.0106	.0044	.0195	.0349	.0512	.0690	.3100		
3	μ	.0390	.0506	.0556	.0595	.0628	.0657	.0685	.0711	.0737	.0763	.0790	.2982			
	σ	−.1937	−.1214	−.0897	−.0655	−.0450	−.0265	−.0091	.0078	.0246	.0417	.0598	.4169			
4	μ	.0234	.0418	.0498	.0560	.0611	.0658	.0701	.0743	.0784	.0824	.3969				
	σ	−.2154	−.1336	−.0977	−.0705	−.0473	−.0264	−.0068	.0122	.0310	.0502	.5042				
5	μ	.0030	.0305	.0425	.0516	.0593	.0663	.0727	.0789	.0849	.5104					
	σ	−.2414	−.1481	−.1071	−.0760	−.0496	−.0258	−.0035	.0180	.0393	.5940					
6	μ	−.0244	.0155	.0330	.0462	.0574	.0674	.0767	.0856	.6425						
	σ	−.2733	−.1654	−.1181	−.0822	−.0518	−.0244	.0012	.0258	.6882						
7	μ	−.0621	−.0046	.0205	.0395	.0555	.0698	.0830	.7983							
	σ	−.3136	−.1870	−.1315	−.0894	−.0538	−.0219	.0079	.7892							
8	μ	−.1155	−.0326	.0036	.0309	.0539	.0743	.9854								
	σ	−.3664	−.2146	−.1482	−.0979	−.0555	−.0174	.9001								
9	μ	−.1950	−.0732	−.0203	.0196	.0531	1.2157									
	σ	−.4390	−.2518	−.1700	−.1082	−.0562	1.0252									
10	μ	−.3217	−.1364	−.0560	.0043	1.5097										
	σ	−.5459	−.3050	−.2002	−.1211	1.1722										
11	μ	−.5462	−.2448	−.1148	1.9058											
	σ	−.7201	−.3892	−.2458	1.3552											
12	μ	−1.0242	−.4676	2.4918												
	σ	−1.0601	−.5477	1.6077												
13	μ	−2.5574	3.5574													
	σ	−2.0493	2.0493													

Table B-8 (*continued*)

$n = 16$

$n-r$		$t_{(1)}$	$t_{(2)}$	$t_{(3)}$	$t_{(4)}$	$t_{(5)}$	$t_{(6)}$	$t_{(7)}$	$t_{(8)}$	$t_{(9)}$	$t_{(10)}$	$t_{(11)}$	$t_{(12)}$	$t_{(13)}$	$t_{(14)}$	$t_{(15)}$	$t_{(16)}$
0	μ	.0625	.0625	.0625	.0625	.0625	.0625	.0625	.0625	.0625	.0625	.0625	.0625	.0625	.0625	.0625	.0625
	σ	−.1366	−.0889	−.0681	−.0524	−.0391	−.0272	−.0160	−.0053	.0053	.0160	.0272	.0391	.0524	.0681	.0889	.1366
1	μ	.0566	.0589	.0599	.0607	.0613	.0619	.0625	.0630	.0635	.0640	.0645	.0651	.0657	.0663	.1261	
	σ	−.1495	−.0967	−.0737	−.0563	−.0416	−.0284	−.0161	−.0042	.0075	.0193	.0316	.0447	.0593	.0763	.2279	
2	μ	.0487	.0543	.0566	.0585	.0600	.0614	.0626	.0638	.0650	.0662	.0674	.0687	.0700	.1967		
	σ	−.1637	−.1051	−.0797	−.0604	−.0441	−.0294	−.0158	−.0027	.0103	.0233	.0369	.0513	.0671	.3120		
3	μ	.0386	.0483	.0525	.0557	.0584	.0608	.0630	.0652	.0673	.0693	.0714	.0736	.2757			
	σ	−.1797	−.1145	−.0862	−.0647	−.0466	−.0303	−.0151	−.0006	.0138	.0282	.0432	.0590	.3935			
4	μ	.0257	.0408	.0474	.0524	.0566	.0604	.0638	.0671	.0704	.0736	.0768	.3649				
	σ	−.1982	−.1252	−.0935	−.0694	−.0491	−.0310	−.0140	.0022	.0182	.0343	.0508	.4748				
5	μ	.0090	.0313	.0410	.0484	.0545	.0601	.0652	.0700	.0747	.0794	.4664					
	σ	−.2200	−.1376	−.1018	−.0747	−.0518	−.0313	−.0123	.0060	.0239	.0419	.5577					
6	μ	−.0129	.0191	.0329	.0434	.0522	.0601	.0673	.0742	.0808	.5829						
	σ	−.2461	−.1523	−.1114	−.0806	−.0546	−.0313	−.0097	.0110	.0312	.6439						
7	μ	−.0420	.0030	.0225	.0373	.0496	.0606	.0707	.0803	.7180							
	σ	−.2782	−.1700	−.1229	−.0874	−.0575	−.0307	−.0059	.0177	.7350							
8	μ	−.0817	−.0185	.0089	.0295	.0467	.0621	.0762	.8769								
	σ	−.3189	−.1920	−.1369	−.0954	−.0604	−.0292	−.0004	.8333								
9	μ	−.1379	−.0484	−.0096	.0194	.0438	.0653	1.0674									
	σ	−.3723	−.2204	−.1545	−.1049	−.0632	−.0262	.9415									
10	μ	−.2211	−.0916	−.0358	.0061	.0410	1.3015										
	σ	−.4457	−.2586	−.1776	−.1167	−.0657	1.0642										
11	μ	−.3534	−.1587	−.0750	−.0125	1.5996											
	σ	−.5538	−.3134	−.2097	−.1319	1.2088											
12	μ	−.5869	−.2739	−.1398	2.0006												
	σ	−.7303	−.4004	−.2586	1.3894												
13	μ	−1.0829	−.5101	2.5931													
	σ	−1.0748	−.5645	1.6394													
14	μ	−2.6696	3.6696														
	σ	−2.0779	2.0779														

$n = 17$

$n - r$		$t_{(1)}$	$t_{(2)}$	$t_{(3)}$	$t_{(4)}$	$t_{(5)}$	$t_{(6)}$	$t_{(7)}$	$t_{(8)}$	$t_{(9)}$	$t_{(10)}$	$t_{(11)}$	$t_{(12)}$	$t_{(13)}$	$t_{(14)}$	$t_{(15)}$	$t_{(16)}$	$t_{(17)}$
0	μ	.0588	.0588	.0588	.0588	.0588	.0588	.0588	.0588	.0588	.0588	.0588	.0588	.0588	.0588	.0588	.0588	.0588
	σ	−.1297	−.0854	−.0663	−.0519	−.0398	−.0290	−.0189	−.0094	.0000	.0094	.0189	.0290	.0398	.0519	.0663	.0854	.1297
1	μ	.0536	.0596	.0565	.0571	.0577	.0582	.0586	.0590	.0595	.0599	.0603	.0607	.0612	.0617	.0622	.1183	
	σ	−.1412	−.0925	−.0715	−.0556	−.0423	−.0304	−.0194	−.0089	.0014	.0117	.0222	.0332	.0450	.0582	.0737	.2164	
2	μ	.0468	.0515	.0535	.0550	.0563	.0574	.0585	.0595	.0605	.0615	.0624	.0634	.0545	.0656	.1837		
	σ	−.1537	−.1001	−.0769	−.0595	−.0448	−.0317	−.0196	−.0080	.0033	.0146	.0261	.0381	.0510	.0653	.2962		
3	μ	.0381	.0463	.0498	.0525	.0547	.0567	.0585	.0603	.0620	.0636	.0653	.0670	.0688	.2564			
	σ	−.1677	−.1085	−.0829	−.0636	−.0474	−.0329	−.0196	−.0068	.0057	.0181	.0308	.0439	.0580	.3728			
4	μ	.0271	.0398	.0453	.0494	.0528	.0559	.0588	.0615	.0641	.0666	.0692	.0718	.3378				
	σ	−.1837	−.1179	−.0895	−.0681	−.0501	−.0341	−.0192	−.0051	.0087	.0225	.0364	.0509	.4491				
5	μ	.0131	.0317	.0397	.0457	.0507	.0552	.0593	.0632	.0670	.0707	.0744	.4294					
	σ	−.2022	−.1287	−.0969	−.0730	−.0529	−.0351	−.0185	−.0028	.0126	.0278	.0433	.5263					
6	μ	−.0047	.0214	.0327	.0411	.0482	.0545	.0603	.0658	.0710	.0762	.5334						
	σ	−.2241	−.1412	−.1055	−.0786	−.0560	−.0359	−.0173	.0004	.0176	.0346	.6059						
7	μ	−.0278	.0083	.0239	.0356	.0454	.0540	.0620	.0695	.0767	.6525							
	σ	−.2504	−.1561	−.1154	−.0849	−.0592	−.0364	−.0154	.0046	.0240	.6892							
8	μ	−.0585	−.0088	.0126	.0286	.0421	.0539	.0648	.0750	.7903								
	σ	−.2828	−.1742	−.1274	−.0922	−.0627	−.0365	−.0124	.0105	.7777								
9	μ	−.1002	−.0317	−.0022	.0199	.0383	.0545	.0694	.9521									
	σ	−.3238	−.1967	−.1419	−.1009	−.0665	−.0359	−.0079	.8736									
10	μ	−.1589	−.0633	−.0223	.0084	.0340	.0565	1.1456										
	σ	−.3777	−.2257	−.1603	−.1113	−.0704	−.0341	.9796										
11	μ	−.2457	−.1091	−.0506	−.0070	.0293	1.3831											
	σ	−.4519	−.2649	−.1846	−.1245	−.0744	1.1002											
12	μ	−.3832	−.1799	−.0932	−.0287	1.6850												
	σ	−.5612	−.3212	−.2185	−.1418	1.2427												
13	μ	−.6253	−.3014	−.1637	2.0904													
	σ	−.7398	−.4108	−.2705	1.4211													
14	μ	−1.1383	−.5506	2.6888														
	σ	−1.0885	−.5802	1.6687														
15	μ	−2.7754	3.7754															
	σ	−2.1046	2.1046															

Table B-8 (*continued*)

$n = 18$

$n-r$		$t_{(1)}$	$t_{(2)}$	$t_{(3)}$	$t_{(4)}$	$t_{(5)}$	$t_{(6)}$	$t_{(7)}$	$t_{(8)}$	$t_{(9)}$	$t_{(10)}$	$t_{(11)}$	$t_{(12)}$	$t_{(13)}$	$t_{(14)}$	$t_{(15)}$	$t_{(16)}$	$t_{(17)}$	$t_{(18)}$
0	μ	.0556	.0556	.0556	.0556	.0556	.0556	.0556	.0556	.0556	.0556	.0556	.0556	.0556	.0556	.0556	.0556	.0556	.0556
	σ	−.1235	−.0822	−.0645	−.0512	−.0401	−.0302	−.0211	−.0125	−.0041	.0041	.0125	.0211	.0302	.0401	.0512	.0645	.0822	.1235
1	μ	.0509	.0526	.0534	.0540	.0544	.0548	.0552	.0556	.0559	.0563	.0566	.0570	.0574	.0577	.0582	.0586	.1113	
	σ	−.1338	−.0887	−.0693	−.0548	−.0426	−.0318	−.0219	−.0124	−.0033	.0058	.0149	.0243	.0342	.0450	.0570	.0712	.2061	
2	μ	.0449	.0489	.0507	.0520	.0531	.0540	.0549	.0558	.0566	.0574	.0582	.0590	.0598	.0607	.0616	.1723		
	σ	−.1449	−.0955	−.0743	−.0584	−.0451	−.0333	−.0224	−.0121	−.0021	.0078	.0178	.0281	.0389	.0505	.0634	.2818		
3	μ	.0373	.0443	.0474	.0496	.0515	.0532	.0547	.0562	.0576	.0589	.0603	.0617	.0631	.0646	.2396			
	σ	−.1573	−.1030	−.0798	−.0623	−.0477	−.0347	−.0228	−.0115	−.0005	.0103	.0213	.0325	.0442	.0568	.3545			
4	μ	.0279	.0387	.0433	.0468	.0497	.0522	.0546	.0568	.0589	.0610	.0631	.0652	.0674	.3144				
	σ	−.1713	−.1114	−.0858	−.0665	−.0504	−.0361	−.0230	−.0105	.0015	.0135	.0254	.0377	.0505	.4264				
5	μ	.0161	.0317	.0384	.0434	.0475	.0512	.0546	.0578	.0609	.0639	.0669	.0698	.3979					
	σ	−.1872	−.1209	−.0925	−.0711	−.0533	−.0375	−.0230	−.0092	.0042	.0173	.0305	.0440	.4988					
6	μ	.0013	.0230	.0323	.0392	.0450	.0502	.0549	.0593	.0636	.0677	.0718	.4918						
	σ	−.2058	−.1318	−.1001	−.0763	−.0564	−.0388	−.0226	−.0073	.0075	.0221	.0367	.5728						
7	μ	−.0176	.0121	.0247	.0342	.0421	.0491	.0555	.0615	.0673	.0729	.5980							
	σ	−.2278	−.1445	−.1089	−.0821	−.0598	−.0400	−.0219	−.0047	.0119	.0282	.6497							
8	μ	−.0419	−.0019	.0153	.0281	.0387	.0482	.0568	.0648	.0726	.7194								
	σ	−.2543	−.1597	−.1191	−.0888	−.0635	−.0411	−.0205	−.0011	.0176	.7305								
9	μ	−.0741	−.0200	.0031	.0204	.0348	.0474	.0590	.0698	.8597									
	σ	−.2869	−.1781	−.1315	−.0966	−.0676	−.0418	−.0183	.0039	.8168									
10	μ	−.1176	−.0441	−.0128	.0106	.0300	.0471	.0627	1.0241										
	σ	−.3283	−.2010	−.1466	−.1059	−.0720	−.0421	−.0147	.9107										
11	μ	−.1788	−.0775	−.0343	−.0022	.0245	.0479	1.2204											
	σ	−.3827	−.2307	−.1657	−.1173	−.0770	−.0414	1.0148											
12	μ	−.2689	−.1257	−.0648	−.0195	.0180	1.4609												
	σ	−.4576	−.2707	−.1911	−.1317	−.0824	1.1335												
13	μ	−.4113	−.2001	−.1106	−.0442	1.7662													
	σ	−.5681	−.3285	−.2266	−.1509	1.2741													
14	μ	−.6615	−.3276	−.1867	2.1758														
	σ	−.7486	−.4205	−.2815	1.4505														
15	μ	−1.1905	−.5891	2.7796															
	σ	−1.1013	−.5948	1.6960															
16	μ	−2.8756	3.8756																
	σ	−2.1294	2.1294																

$n-r$		$t_{(1)}$	$t_{(2)}$	$t_{(3)}$	$t_{(4)}$	$t_{(5)}$	$t_{(6)}$	$t_{(7)}$	$t_{(8)}$	$t_{(9)}$	$t_{(10)}$	$t_{(11)}$	$t_{(12)}$	$t_{(13)}$	$t_{(14)}$	$t_{(15)}$	$t_{(16)}$	$t_{(17)}$	$t_{(18)}$	$t_{(19)}$
0	μ	.0526	.0526	.0526	.0526	.0526	.0526	.0526	.0526	.0526	.0526	.0526	.0526	.0526	.0526	.0526	.0526	.0526	.0526	.0526
	σ	−.1178	−.0792	−.0628	−.0505	−.0402	−.0312	−.0228	−.0150	−.0074	.0000	.0074	.0150	.0228	.0312	.0402	.0505	.0628	.0792	.1178
1	μ	.0485	.0500	.0506	.0511	.0515	.0519	.0522	.0525	.0528	.0531	.0534	.0537	.0540	.0543	.0547	.0550	.0554	.1052	
	σ	−.1272	−.0851	−.0672	−.0538	−.0427	−.0328	−.0238	−.0152	−.0070	.0011	.0092	.0174	.0259	.0349	.0447	.0558	.0689	.1969	
2	μ	.0431	.0467	.0482	.0493	.0502	.0511	.0518	.0525	.0532	.0539	.0546	.0552	.0559	.0566	.0574	.0581	.1623		
	σ	−.1372	−.0914	−.0719	−.0573	−.0451	−.0344	−.0245	−.0152	−.0063	.0025	.0113	.0202	.0295	.0392	.0498	.0616	.2490		
3	μ	.0365	.0426	.0451	.0471	.0457	.0501	.0514	.0526	.0538	.0550	.0561	.0572	.0584	.0596	.0608	.2249			
	σ	−.1482	−.0932	−.0769	−.0609	−.0477	−.0359	−.0252	−.0150	−.0053	.0043	.0139	.0236	.0336	.0442	.0556	.3381			
4	μ	.0283	.0376	.0415	.0445	.0469	.0491	.0510	.0529	.0547	.0564	.0582	.0599	.0616	.0634	.2940				
	σ	−.1605	−.1057	−.0823	−.0649	−.0504	−.0375	−.0257	−.0146	−.0040	.0065	.0170	.0276	.0385	.0499	.4092				
5	μ	.0182	.0315	.0371	.0413	.0448	.0479	.0507	.0534	.0559	.0584	.0609	.0633	.0658	.3707					
	σ	−.1744	−.1141	−.0884	−.0692	−.0532	−.0391	−.0262	−.0140	−.0022	.0093	.0207	.0323	.0442	.4744					
6	μ	.0057	.0240	.0318	.0376	.0424	.0467	.0506	.0542	.0577	.0611	.0644	.0678	.4561						
	σ	−.1905	−.1237	−.0952	−.0740	−.0563	−.0407	−.0264	−.0129	.0000	.0127	.0253	.0380	.5437						
7	μ	−.0100	.0147	.0253	.0331	.0396	.0453	.0506	.0554	.0601	.0647	.0691	.5520							
	σ	−.2091	−.1347	−.1030	−.0794	−.0597	−.0423	−.0264	−.0114	.0029	.0170	.0309	.6152							
8	μ	−.0298	−.0032	.0172	.0276	.0363	.0439	.0509	.0574	.0636	.0696	.6603								
	σ	−.2312	−.1476	−.1120	−.0855	−.0634	−.0439	−.0261	−.0093	.0067	.0224	.6898								
9	μ	−.0553	−.0115	.0070	.0209	.0324	.0425	.0516	.0602	.0684	.7839									
	σ	−.2578	−.1630	−.1226	−.0925	−.0675	−.0454	−.0252	−.0063	.0118	.7685									
10	μ	−.0888	−.0306	−.0059	.0125	.0277	.0411	.0532	.0646	.9264										
	σ	−.2907	−.1817	−.1353	−.1007	−.0720	−.0465	−.0237	−.0021	.8530										
11	μ	−.1341	−.0560	−.0229	.0017	.0221	.0399	.0561	1.0931											
	σ	−.3324	−.2051	−.1509	−.1106	−.0772	−.0478	−.0210	.9450											
12	μ	−.1976	−.0910	−.0459	−.0124	.0153	.0395	1.2920												
	σ	−.3873	−.2353	−.1708	−.1228	−.0831	−.0482	1.0474												
13	μ	−.2909	−.1415	−.0783	−.0316	.0070	1.5351													
	σ	−.4629	−.2762	−.1971	−.1384	−.0898	1.1645													
14	μ	−.4379	−.2194	−.1273	−.0593	1.8438														
	σ	−.5744	−.3353	−.2342	−.1594	1.3034														
15	μ	−.6958	−.3527	−.2086	2.2572															
	σ	−.7568	−.4295	−.2918	1.4761															
16	μ	−1.2401	−.6258	2.8659																
	σ	−1.1132	−.6064	1.7216																
17	μ	−2.9705	3.9705																	
	σ	−2.1527	2.1527																	

Table B-8 (*continued*)

$n = 20$

$n - r$		$t_{(1)}$	$t_{(2)}$	$t_{(3)}$	$t_{(4)}$	$t_{(5)}$	$t_{(6)}$	$t_{(7)}$	$t_{(8)}$	$t_{(9)}$	$t_{(10)}$	$t_{(11)}$	$t_{(12)}$	$t_{(13)}$	$t_{(14)}$	$t_{(15)}$	$t_{(16)}$	$t_{(17)}$	$t_{(18)}$	$t_{(19)}$	$t_{(20)}$
0	μ	.0500	.0500	.0500	.0500	.0500	.0500	.0500	.5000	.0500	.0500	.0500	.0500	.0500	.0500	.0500	.0500	.0500	.0500	.0500	.0500
	σ	−.1128	−.0765	−.0611	−.0497	−.0402	−.0318	−.0241	−.0169	−.0101	−.0033	.0033	.0101	.0169	.0241	.0318	.0402	.0497	.0611	.0765	.1128
1	μ	.0462	.0476	.0482	.0486	.0489	.0493	.0495	.0498	.0501	.0503	.0506	.0508	.0511	.0513	.0516	.0519	.0522	.0525	.0996	
	σ	−.1212	−.0819	−.0652	−.0528	−.0425	−.0335	−.0252	−.0174	−.0099	−.0026	.0046	.0119	.0193	.0271	.0354	.0444	.0546	.0667	.1884	
2	μ	.0415	.0446	.0459	.0469	.0477	.0484	.0491	.0497	.0502	.0508	.0514	.0519	.0525	.0531	.0537	.0544	.0550	.1533		
	σ	−.1303	−.0876	−.0695	−.0561	−.0449	−.0351	−.0261	−.0177	−.0096	−.0017	.0061	.0140	.0221	.0305	.0394	.0491	.0599	.2574		
3	μ	.0356	.0409	.0431	.0448	.0462	.0474	.0485	.0496	.0506	.0516	.0525	.0535	.0544	.0554	.0564	.0575	.2119			
	σ	−.1401	−.0938	−.0741	−.0595	−.0474	−.0367	−.0269	−.0178	−.0090	−.0004	.0080	.0166	.0253	.0344	.0440	.0543	.3233			
4	μ	.0284	.0365	.0399	.0424	.0445	.0463	.0480	.0496	.0511	.0526	.0540	.0554	.0569	.0584	.0599	.2762				
	σ	−.1511	−.1006	−.0792	−.0632	−.0500	−.0384	−.0277	−.0178	−.0082	.0011	.0103	.0196	.0291	.0389	.0492	.3880				
5	μ	.0197	.0311	.0359	.0395	.0425	.0451	.0475	.0497	.0519	.0539	.0560	.0580	.0600	.0621	.3470					
	σ	−.1634	−.1081	−.0847	−.0673	−.0528	−.0401	−.0285	−.0176	−.0071	.0030	.0131	.0232	.0335	.0441	.4526					
6	μ	.0090	.0246	.0312	.0361	.0402	.0438	.0470	.0501	.0530	.0558	.0586	.0613	.0640	.4254						
	σ	−.1773	−.1166	−.0908	−.0717	−.0558	−.0418	−.0291	−.0171	−.0057	.0055	.0165	.0275	.0387	.5179						
7	μ	−.0042	.0167	.0255	.0321	.0375	.0423	.0466	.0507	.0545	.0583	.0619	.0656	.5126							
	σ	−.1934	−.1262	−.0978	−.0766	−.0591	−.0437	−.0296	−.0164	−.0038	.0085	.0206	.0327	.5848							
8	μ	−.0206	.0069	.0185	.0272	.0343	.0406	.0463	.0517	.0567	.0616	.0664	.6103								
	σ	−.2121	−.1374	−.1057	−.0822	−.0627	−.0455	−.0299	−.0153	−.0013	.0123	.0257	.6541								
9	μ	−.0414	−.0053	.0099	.0213	.0306	.0388	.0463	.0532	.0598	.0662	.7205									
	σ	−.2343	−.1504	−.1149	−.0886	−.0667	−.0475	−.0300	−.0136	.0020	.0172	.7268									
10	μ	−.0680	−.0205	−.0008	.0140	.0262	.0369	.0466	.0557	.0642	.8460										
	σ	−.2612	−.1660	−.1258	−.0959	−.0712	−.0494	−.0296	−.0111	.0065	.8038										
11	μ	−.1028	−.0408	−.0146	.0048	.0209	.0349	.0476	.0594	.9905											
	σ	−.2943	−.1850	−.1389	−.1046	−.0762	−.0513	−.0287	−.0076	.8866											
12	μ	−.1498	−.0673	−.0326	−.0068	.0144	.0329	.0497	1.1595												
	σ	−.3363	−.2088	−.1550	−.1151	−.0820	−.0531	−.0268	.9771												
13	μ	−.2154	−.1039	−.0569	−.0222	.0064	.0313	1.3607													
	σ	−.3916	−.2396	−.1755	−.1280	−.0888	−.0544	1.0779													
14	μ	−.3117	−.1565	−.0914	−.0433	−.0037	1.6066														
	σ	−.4679	−.2813	−.2028	−.1447	−.0967	1.1934														
15	μ	−.4632	−.2378	−.1433	−.0738	1.9180															
	σ	−.5804	−.3417	−.2414	−.1673	1.3308															
16	μ	−.7284	−.3766	−.2298	2.3348																
	σ	−.7645	−.4380	−.3014	1.5039																
17	μ	−1.2872	−.6610	2.9482																	
	σ	−1.1244	−.6212	1.7456																	
18	μ	−3.0609	4.0609																		
	σ	−2.1745	2.1745																		

Source: "Estimation of Location and Scale Parameters by Order Statistics from Singly and Doubly Censored Samples, Parts I and II," by A. E. Sarhan and B. G. Greenberg, *Ann. Math. Statist.*, Vol. 27, pp. 427–451 (1956). Reproduced by permission of the editor of the *Annals of Mathematical Statistics*.

Table B-9 Variances and Covariances of the Best Linear Estimates of the Mean ($\hat{\mu}$) and Standard Deviation ($\hat{\sigma}$) for Censored Samples Up to Size 20 from a Normal Population

		n-r											
n		0	1	2	3	4	5	6	7	8	9	10	11	12
2	$V(\hat{\mu})$	.5000												
	$V(\hat{\sigma})$	.5708												
	$Cov(\hat{\mu}, \hat{\sigma})$	0												
3	$V(\hat{\mu})$	.3333	.4487											
	$V(\hat{\sigma})$	.2755	.6378											
	$Cov(\hat{\mu}, \hat{\sigma})$	0	.2044											
4	$V(\hat{\mu})$	.2500	.2870	.5130										
	$V(\hat{\sigma})$	.1801	.3021	.6730										
	$Cov(\hat{\mu}, \hat{\sigma})$	0	.0672	.3567										
5	$V(\hat{\mu})$	.2000	.2177	.2839	.6112									
	$V(\hat{\sigma})$	.1333	.1948	.3181	.6957									
	$Cov(\hat{\mu}, \hat{\sigma})$	0	.0330	.1234	.4749									
6	$V(\hat{\mu})$	.1667	.1769	.2068	.2999	.7186								
	$V(\hat{\sigma})$	.1057	.1428	.2044	.3292	.7119								
	$Cov(\hat{\mu}, \hat{\sigma})$	0	.0195	.0624	.1702	.5705								
7	$V(\hat{\mu})$	.1429	.1494	.1660	.2071	.3248	.8264							
	$V(\hat{\sigma})$	.0875	.1123	.1493	.2114	.3375	.7243							
	$Cov(\hat{\mu}, \hat{\sigma})$	0	.0128	.0375	.0881	.2099	.6503							
8	$V(\hat{\mu})$	.1250	.1295	.1399	.1623	.2138	.3541	.9310						
	$V(\hat{\sigma})$	.0746	.0924	.1171	.1542	.2168	.3441	.7342						
	$Cov(\hat{\mu}, \hat{\sigma})$	0	.0090	.0250	.0538	.1106	.2442	.7186						
9	$V(\hat{\mu})$	.1111	.1144	.1214	.1352	.1629	.2241	.3854	1.0313					
	$V(\hat{\sigma})$	.0650	.0784	.0960	.1207	.1581	.2212	.3494	.7423					
	$Cov(\hat{\mu}, \hat{\sigma})$	0	.0067	.0178	.0362	.0684	.1305	.2743	.7781					
10	$V(\hat{\mu})$	.1000	.1025	.1075	.1167	.1336	.1664	.2366	.4174	1.1269				
	$V(\hat{\sigma})$	.0576	.0681	.0813	.0989	.1237	.1613	.2248	.3539	.7491				
	$Cov(\hat{\mu}, \hat{\sigma})$	0	.0051	.0132	.0260	.0465	.0816	.1483	.3011	.8306				
11	$V(\hat{\mu})$	.0909	.0929	.0966	.1031	.1143	.1342	.1718	.2504	.4493	1.2179			
	$V(\hat{\sigma})$	.0517	.0601	.0704	.0836	.1013	.1262	.1640	.2279	.3577	.7550			
	$Cov(\hat{\mu}, \hat{\sigma})$	0	.0041	.0102	.0195	.0336	.0559	.0936	.1644	.3251	.8777			
12	$V(\hat{\mu})$	.0833	.0849	.0878	.0926	.1004	.1136	.1363	.1784	.2650	.4809	1.3044		
	$V(\hat{\sigma})$	.0469	.0538	.0620	.0723	.0855	.1033	.1283	.1663	.2305	.3610	.7601		
	$Cov(\hat{\mu}, \hat{\sigma})$	0	.0033	.0081	.0152	.0254	.0406	.0645	.1045	.1791	.3469	.9202		

Table B-9 (*continued*)

n		$n-r$ = 0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	
13	$V(\hat{\mu})$	.0769	.0782	.0805	.0841	.0899	.0991	.1141	.1395	.1858	.2799	.5118	1.3868						
	$V(\hat{\sigma})$	.0429	.0486	.0554	.0636	.0739	.0872	.1050	.1302	.1688	.2329	.3640	.7646						
	$\mathrm{Cov}(\hat{\mu}, \hat{\sigma})$	0	.0027	.0066	.0121	.0198	.0309	.0472	.0725	.1146	.1925	.3668	.9589						
14	$V(\hat{\mu})$	.0714	.0725	.0743	.0772	.0816	.0883	.0988	.1155	.1435	.1938	.2950	.5419	1.4654					
	$V(\hat{\sigma})$	.0395	.0444	.0500	.0568	.0650	.0753	.0886	.1065	.1318	.1702	.2350	.3666	.7687					
	$\mathrm{Cov}(\hat{\mu}, \hat{\sigma})$	0	.0023	.0055	.0099	.0159	.0242	.0360	.0533	.0799	.1239	.2048	.3851	.9945					
15	$V(\hat{\mu})$	.0667	.0676	.0691	.0714	.0748	.0799	.0875	.0992	.1176	.1480	.2022	.3101	.5713	1.5404				
	$V(\hat{\sigma})$	.0366	.0408	.0456	.0512	.0580	.0662	.0765	.0899	.1078	.1332	.1718	.2368	.3689	.7723				
	$\mathrm{Cov}(\hat{\mu}, \hat{\sigma})$	0	.0019	.0046	.0082	.0130	.0195	.0284	.0409	.0590	.0868	.1325	.2163	.4020	1.0273				

n		$n-r$ = 0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18
16	$V(\hat{\mu})$	.0625	.0633	.0645	.0664	.0692	.0731	.0789	.0874	.1002	.1202	.1529	.2107	.3250	.5998	1.6121				
	$V(\hat{\sigma})$	.0341	.0378	.0419	.0467	.0523	.0590	.0672	.0776	.0910	.1090	.1345	.1732	.2385	.3710	.7756				
	$\mathrm{Cov}(\hat{\mu}, \hat{\sigma})$	0	.0017	.0039	.0069	.0109	.0160	.0229	.0323	.0454	.0644	.0933	.1406	.2269	.4177	1.0578				
17	$V(\hat{\mu})$	.0588	.0595	.0605	.0621	.0644	.0675	.0720	.0784	.0877	.1016	.1231	.1581	.2194	.3398	.6274	1.6808			
	$V(\hat{\sigma})$	.0320	.0352	.0387	.0428	.0476	.0532	.0599	.0682	.0786	.0920	.1101	.1357	.1745	.2400	.3729	.7786			
	$\mathrm{Cov}(\hat{\mu}, \hat{\sigma})$	0	.0015	.0034	.0059	.0092	.0134	.0189	.0262	.0360	.0497	.0694	.0993	.1481	.2369	.4324	1.0862			
18	$V(\hat{\mu})$	.0556	.0561	.0570	.0584	.0602	.0628	.0664	.0713	.0784	.0885	.1034	.1264	.1635	.2282	.3544	.6543	1.7467		
	$V(\hat{\sigma})$	.0301	.0329	.0360	.0395	.0436	.0483	.0540	.0607	.0690	.0794	.0929	.1111	.1368	.1757	.2414	.3746	.7814		
	$\mathrm{Cov}(\hat{\mu}, \hat{\sigma})$	0	.0013	.0030	.0051	.0079	.0114	.0158	.0216	.0293	.0395	.0538	.0742	.1050	.1552	.2463	.4462	1.1127		

n		$n-r$ = 0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18
19	$V(\hat{\mu})$	.0526	.0531	.0539	.0550	.0566	.0587	.0616	.0656	.0710	.0787	.0895	.1055	.1299	.1691	.2369	.3687	.6804	1.8101	
	$V(\hat{\sigma})$	.0284	.0309	.0336	.0367	.0403	.0443	.0491	.0547	.0614	.0698	.0802	.0938	.1120	.1377	.1768	.2426	.3763	.7839	
	$\mathrm{Cov}(\hat{\mu}, \hat{\sigma})$	0	.0011	.0026	.0045	.0068	.0098	.0135	.0182	.0242	.0322	.0429	.0576	.0787	.1104	.1619	.2551	.4591	1.1377	
20	$V(\hat{\mu})$	.0500	.0504	.0511	.0521	.0534	.0552	.0576	.0608	.0651	.0710	.0792	.0909	.1078	.1335	.1747	.2456	.3828	.7056	1.8710
	$V(\hat{\sigma})$	.0268	.0291	.0316	.0343	.0374	.0409	.0450	.0497	.0553	.0621	.0705	.0810	.0945	.1128	.1386	.1778	.2438	.3778	.7863
	$\mathrm{Cov}(\hat{\mu}, \hat{\sigma})$	0	.0010	.0023	.0039	.0060	.0085	.0116	.0155	.0204	.0267	.0350	.0460	.0612	.0829	.1155	.1682	.2634	.4713	1.1613

Source: Up to $n = 15$ of this table is reproduced from A. E. Sarhan and B. G. Greenberg, "Estimation of Location and Scale Parameters by Order Statistics from Singly and Censored Samples, Parts I and II," *Ann. Math. Statist.*, Vol. 27, pp. 427–451 (1956), and Vol. 29, pp. 79–105 (1958), with permission of the editor of the *Annals of Mathematical Statistics*. The rest of the table is produced from A. E. Sarhan and B. G. Greenberg, "Estimation of Location and Scale Parameters by Order Statistics from Singly and Doubly Censored Samples, Part III," Tech. Rep. 4-OOR, Project 1597, U.S. Army Research Office.

Table B-10 $1/(1-R)$ and $\hat{\gamma}$ for the Estimation of the Parameters of the Gamma Distribution When There Are No Censored Observations

$1/(1-R)$	$\hat{\gamma}$	$1/(1-R)$	$\hat{\gamma}$	$1/(1-R)$	$\hat{\gamma}$
1·000	0·00000	1·11	0·29854	2·4	1·06335
1·001	0·11539	1·12	0·30749	2·5	1·11596
1·002	0·12663	1·13	0·31616	2·6	1·16833
1·003	0·13434	1·14	0·32461	2·7	1·22050
1·004	0·14043	1·15	0·33285	2·8	1·27248
1·005	0·14556	1·16	0·34090	2·9	1·32430
1·006	0·15005	1·18	0·35654	3·0	1·37599
1·007	0·15408	1·20	0·37165	3·2	1·47899
1·008	0·15775	1·22	0·38631	3·4	1·58158
1·009	0·16115	1·24	0·40060	3·6	1·68385
1·010	0·16432	1·26	0·41457	3·8	1·78585
1·012	0·17011	1·28	0·42825	4·0	1·88763
1·014	0·17535	1·30	0·44170	4·2	1·98921
1·016	0·18017	1·32	0·45492	4·4	2·09063
1·018	0·18464	1·34	0·46795	4·6	2·19191
1·020	0·18884	1·36	0·48081	4·8	2·29308
1·022	0·19282	1·38	0·49351	5·0	2·39414
1·024	0·19659	1·40	0·50608	5·5	2·64643
1·026	0·20020	1·45	0·53694	6·0	2·89830
1·028	0·20366	1·50	0·56715	6·5	3·14984
1·030	0·20700	1·55	0·59682	7·0	3·40115
1·035	0·21486	1·60	0·62604	8·0	3·90325
1·040	0·22217	1·65	0·65488	9·0	4·40482
1·045	0·22904	1·70	0·68340	10·0	4·90608
1·050	0·23554	1·75	0·71163	12·0	5·90790
1·055	0·24175	1·80	0·73961	14·0	6·90914
1·060	0·24771	1·85	0·76737	16·0	7·91005
1·065	0·25345	1·90	0·79494	18·0	8·91073
1·070	0·25899	1·95	0·82233	20·0	9·91125
1·075	0·26437	2·00	0·84957	30·0	14·91301
1·080	0·26959	2·10	0·90364	40·0	19·91401
1·090	0·27966	2·20	0·95724	50·0	24·91457
1·100	0·28928	2·30	1·01046		

Source: "Estimation of Parameters of the Gamma Distribution Using Order Statistics," by M. B. Wilk, R. Gnanadesikan, and Marilyn J. Huyett, *Biometrika*, Vol. 49, pp. 525–545 (1962). Reproduced by permission of the editor of *Biometrika*.

Table B-11 $\hat{\gamma}(P, S)$ and $\hat{\mu}(P, S)$ for Various Values of *nlr*: *nlr* = 1.0

				0·96	0·92	0·88	0·84	0·80	0·76	0·72	0·68	0·64	0·60	0·56	P/S
0·08	γ	**0·850**		12·412	6·158	4·070	3·024	2·394	1·972	1·669	1·440	1·261	1·116	0·996	1·00
	μ	**0·080**		1·000	1·000	1·000	1·000	1·000	1·000	1·000	1·000	1·000	1·000	1·000	
0·12	γ	**0·567**	**1·376**		11·912	5·908	3·903	2·898	2·293	1·888	1·596	1·376	1·203	1·063	0·96
	μ	**0·120**	**0·120**		0·960	0·960	0·960	0·960	0·960	0·960	0·960	0·960	0·960	0·960	
0·16	γ	**0·464**	**0·850**	**1·887**		11·412	5·657	3·736	2·772	2·192	1·803	1·523	1·311	1·145	0·92
	μ	**0·160**	**0·160**	**0·160**		0·920	0·920	0·920	0·920	0·920	0·920	0·920	0·920	0·920	
0·20	γ	0·408	**0·664**	**1·116**	**2·394**		10·912	5·407	3·569	2·646	2·091	1·718	1·450	1·247	0·88
	μ	0·200	**0·200**	**0·200**	**0·200**		0·880	0·880	0·880	0·880	0·880	0·880	0·880	0·880	
0·24	γ	0·372	0·567	**0·850**	**1·376**	**2·898**		10·411	5·157	3·401	2·520	1·989	1·633	1·376	0·84
	μ	0·240	0·240	**0·240**	**0·240**	**0·240**		0·840	0·840	0·840	0·840	0·840	0·840	0·840	
0·28	γ	0·346	0·506	**0·712**	**1·028**	**1·633**	**3·401**		9·911	4·906	3·234	2·394	1·888	1·547	0·80
	μ	0·280	0·280	**0·280**	**0·280**	**0·280**	**0·280**		0·800	0·800	0·800	0·800	0·800	0·800	
0·32	γ	0·327	0·464	0·626	0·850	**1·203**	**1·888**	**3·903**		9·411	4·655	3·066	2·268	1·786	0·76
	μ	0·320	0·320	0·320	0·320	**0·320**	**0·320**	**0·320**		0·760	0·760	0·760	0·760	0·760	
0·36	γ	0·312	0·432	0·567	0·740	0·984	1·376	**2·141**	**4·405**		8·911	4·405	2·898	2·141	0·72
	μ	0·360	0·360	0·360	0·360	0·360	0·360	**0·360**	**0·360**		0·720	0·720	0·720	0·720	
0·40	γ	0·300	0·408	0·524	0·664	0·850	1·116	1·547	**2·394**	**4·906**		***8·410***	4·154	2·730	0·68
	μ	0·400	0·400	0·400	0·400	0·400	0·400	0·400	**0·400**	**0·400**		***0·680***	0·680	0·680	
0·44	γ	0·289	0·388	0·490	0·609	0·758	0·957	1·247	1·718	**2·646**	***5·407***		***7·910***	3·903	0·64
	μ	0·440	0·440	0·440	0·440	0·440	0·440	0·440	0·440	**0·440**	***0·440***		***0·640***	0·640	
0·48	γ	0·281	0·372	0·464	0·567	0·691	0·850	1·063	1·376	1·888	***2·898***	***5·908***		***7·409***	0·60
	μ	0·480	0·480	0·480	0·480	0·480	0·480	0·480	0·480	0·480	***0·480***	***0·480***		***0·600***	
0·52	γ	0·273	0·358	0·442	0·534	0·641	0·771	0·939	1·168	1·505	***2·057***	***3·150***	***6·408***		
	μ	0·520	0·520	0·520	0·520	0·520	0·520	0·520	0·520	0·520	***0·520***	***0·520***	***0·520***		
0·56	γ	0·266	0·346	0·423	0·506	0·600	0·712	0·850	1·028	1·272	1·633	***2·226***	***3·401***	***6·909***	
	μ	0·560	0·560	0·560	0·560	0·560	0·560	0·560	0·560	0·560	0·560	***0·560***	***0·560***	***0·560***	
0·60	γ	0·261	0·336	0·408	0·483	0·567	0·664	0·781	0·927	1·116	1·376	1·760	***2·394***	***3·652***	
	μ	0·600	0·600	0·600	0·600	0·600	0·600	0·600	0·600	0·600	0·600	0·600	***0·600***	***0·600***	
0·64	γ	0·255	0·327	0·394	0·464	0·540	0·626	0·727	0·850	1·003	1·203	1·479	1·888	2·562	
	μ	0·640	0·640	0·640	0·640	0·640	0·640	0·640	0·640	0·640	0·640	0·640	0·640	0·640	
0·68	γ	0·251	0·319	0·382	0·447	0·516	0·594	0·683	0·789	0·917	1·078	1·290	1·582	2·015	
	μ	0·680	0·680	0·680	0·680	0·680	0·680	0·680	0·680	0·680	0·680	0·680	0·680	0·680	
0·72	γ	0·246	0·312	0·372	0·432	0·496	0·567	0·647	0·740	0·850	0·984	1·153	1·376	1·684	
	μ	0·720	0·720	0·720	0·720	0·720	0·720	0·720	0·720	0·720	0·720	0·720	0·720	0·720	
0·76	γ	0·242	0·305	0·362	0·419	0·479	0·544	0·616	0·699	0·795	0·910	1·050	1·228	1·462	
	μ	0·760	0·760	0·760	0·760	0·760	0·760	0·760	0·760	0·760	0·760	0·760	0·760	0·760	
0·80	γ	0·239	0·300	0·354	0·408	0·464	0·524	0·590	0·664	0·750	0·850	0·969	1·116	1·302	
	μ	0·800	0·800	0·800	0·800	0·800	0·800	0·800	0·800	0·800	0·800	0·800	0·800	0·800	
0·84	γ	0·236	0·294	0·346	0·397	0·450	0·506	0·567	0·635	0·712	0·800	0·904	1·028	1·181	
	μ	0·840	0·840	0·840	0·840	0·840	0·840	0·840	0·840	0·840	0·840	0·840	0·840	0·840	
0·88	γ	0·232	0·289	0·339	0·388	0·438	0·490	0·547	0·609	0·679	0·758	0·850	0·957	1·087	
	μ	0·880	0·880	0·880	0·880	0·880	0·880	0·880	0·880	0·880	0·880	0·880	0·880	0·880	
0·92	γ	0·230	0·285	0·333	0·379	0·427	0·476	0·529	0·587	0·651	0·722	0·804	0·899	1·010	
	μ	0·920	0·920	0·920	0·920	0·920	0·920	0·920	0·920	0·920	0·920	0·920	0·920	0·920	
0·96	γ	0·227	0·281	0·327	0·372	0·417	0·464	0·513	0·567	0·626	0·691	0·765	0·850	0·948	
	μ	0·960	0·960	0·960	0·960	0·960	0·960	0·960	0·960	0·960	0·960	0·960	0·960	0·960	
1·00	γ	0·225	0·277	0·322	0·365	0·408	0·452	0·499	0·549	0·604	0·664	0·732	0·808	0·895	
	μ	1·000	1·000	1·000	1·000	1·000	1·000	1·000	1·000	1·000	1·000	1·000	1·000	1·000	
S/P		0·04	0·08	0·12	0·16	0·20	0·24	0·28	0·32	0·36	0·40	0·44	0·48	0·52	

For $P \leqslant 0.52$ read S from the left-hand margin, and for $P \geqslant 0.56$ read S from the right-hand margin. Note that the figures in region 2 are printed in bold roman type and those in region 3 in bold italic type; the remainder of the table (outside of regions 2 and 3) is region 1.

Table B-11 (*continued*)

$n/r = 1.10$

		1·00	0·96	0·92	0·88	0·84	0·80	0·76	0·72	0·68	0·64	0·60	0·56	P/S
0·08	γ	0·501	12·505	6·224	4·124	3·070	2·435	2·009	1·703	1·471	1·290	1·143	1·021	1·00
	μ	0·195	1·023	1·034	1·043	1·051	1·058	1·065	1·072	1·079	1·085	1·092	1·099	
0·12	γ	0·438	0·759	11·866	5·927	3·932	2·929	2·323	1·916	1·624	1·402	1·228	1·087	0·96
	μ	0·243	0·226	0·986	0·996	1·005	1·013	1·021	1·028	1·035	1·041	1·048	1·055	
0·16	γ	0·398	0·634	1·029	11·212	5·628	3·740	2·787	2·211	1·824	1·544	1·332	1·166	0·92
	μ	0·291	0·272	0·259	0·948	0·959	0·968	0·976	0·983	0·990	0·997	1·004	1·011	
0·20	γ	0·370	0·558	0·827	1·321	10·546	5·326	3·547	2·646	2·099	1·731	1·465	1·263	0·88
	μ	0·338	0·318	0·305	0·294	0·911	0·922	0·931	0·939	0·946	0·953	0·960	0·967	
0·24	γ	0·349	0·507	0·711	1·025	1·639	9·872	5·023	3·354	2·504	1·987	1·638	1·385	0·84
	μ	0·386	0·364	0·351	0·339	0·329	0·874	0·885	0·893	0·901	0·909	0·916	0·923	
0·28	γ	0·333	0·470	0·634	0·863	1·232	1·986	9·193	4·721	3·161	2·363	1·875	1·545	0·80
	μ	0·433	0·411	0·396	0·385	0·374	0·365	0·837	0·847	0·856	0·864	0·872	0·879	
0·32	γ	0·319	0·442	0·580	0·759	1·018	1·449	2·365	8·516	4·419	2·968	2·222	1·764	0·76
	μ	0·480	0·457	0·442	0·430	0·419	0·410	0·400	0·800	0·810	0·819	0·827	0·835	
0·36	γ	0·308	0·419	0·539	0·687	0·884	1·177	1·677	2·776	7·846	4·119	2·777	2·082	0·72
	μ	0·528	0·503	0·487	0·475	0·464	0·455	0·446	0·436	0·763	0·774	0·782	0·790	
0·40	γ	0·299	0·401	0·507	0·633	0·792	1·010	1·340	1·914	3·220	*7·186*	3·821	2·588	0·68
	μ	0·575	0·549	0·533	0·520	0·509	0·500	0·491	0·482	0·472	*0·727*	0·737	0·745	
0·44	γ	0·291	0·385	0·481	0·591	0·724	0·897	1·138	1·507	2·162	*3·698*	*6·543*	3·529	0·64
	μ	0·622	0·595	0·578	0·565	0·554	0·544	0·535	0·527	0·518	*0·508*	*0·690*	0·700	
0·48	γ	0·284	0·372	0·460	0·557	0·672	0·815	1·002	1·267	1·678	*2·419*	*4·208*	*5·920*	0·60
	μ	0·669	0·641	0·623	0·610	0·599	0·589	0·580	0·571	0·563	*0·554*	*0·544*	*0·653*	
0·52	γ	0·277	0·361	0·442	0·529	0·630	0·752	0·905	1·109	1·399	*1·854*	*2·685*	*4·750*	
	μ	0·716	0·687	0·669	0·655	0·644	0·634	0·624	0·616	0·607	*0·599*	*0·590*	*0·581*	
0·56	γ	0·272	0·351	0·426	0·506	0·596	0·702	0·831	0·996	1·216	1·532	*2·033*	*2·959*	*5·321*
	μ	0·763	0·733	0·714	0·700	0·688	0·678	0·669	0·660	0·652	0·644	*0·635*	*0·627*	*0·617*
0·60	γ	0·267	0·342	0·412	0·486	0·568	0·662	0·773	0·910	1·086	1·324	1·668	*2·215*	*3·241*
	μ	0·810	0·779	0·759	0·745	0·733	0·723	0·713	0·705	0·696	0·688	0·680	*0·672*	*0·663*
0·64	γ	0·262	0·334	0·401	0·469	0·544	0·628	0·726	0·844	0·989	1·178	1·433	1·804	2·400
	μ	0·856	0·824	0·805	0·790	0·778	0·767	0·758	0·749	0·741	0·733	0·725	0·717	0·709
0·68	γ	0·258	0·327	0·390	0·454	0·523	0·600	0·687	0·790	0·914	1·068	1·269	1·543	1·942
	μ	0·903	0·870	0·850	0·835	0·822	0·811	0·802	0·793	0·785	0·777	0·769	0·761	0·754
0·72	γ	0·254	0·320	0·380	0·441	0·505	0·575	0·654	0·745	0·853	0·984	1·147	1·361	1·653
	μ	0·950	0·916	0·895	0·879	0·867	0·856	0·846	0·837	0·829	0·821	0·813	0·806	0·798
0·76	γ	0·251	0·314	0·372	0·429	0·489	0·554	0·626	0·708	0·803	0·916	1·054	1·227	1·453
	μ	0·996	0·962	0·940	0·924	0·911	0·900	0·890	0·881	0·873	0·865	0·857	0·850	0·842
0·80	γ	0·247	0·309	0·364	0·418	0·475	0·535	0·602	0·676	0·761	0·860	0·979	1·123	1·306
	μ	1·043	1·007	0·985	0·969	0·956	0·944	0·934	0·925	0·917	0·909	0·901	0·894	0·887
0·84	γ	0·244	0·304	0·357	0·409	0·462	0·519	0·580	0·648	0·725	0·814	0·917	1·041	1·193
	μ	1·089	1·053	1·030	1·014	1·000	0·989	0·978	0·969	0·961	0·953	0·945	0·938	0·931
0·88	γ	0·241	0·300	0·350	0·400	0·451	0·504	0·561	0·624	0·695	0·774	0·866	0·974	1·103
	μ	1·136	1·098	1·075	1·058	1·045	1·033	1·023	1·013	1·005	0·997	0·989	0·982	0·974
0·92	γ	0·239	0·295	0·344	0·392	0·440	0·491	0·544	0·603	0·668	0·740	0·822	0·918	1·030
	μ	1·182	1·144	1·120	1·103	1·089	1·077	1·067	1·057	1·049	1·040	1·033	1·025	1·018
0·96	γ	0·236	0·291	0·339	0·385	0·431	0·479	0·529	0·584	0·644	0·710	0·785	0·870	0·970
	μ	1·229	1·189	1·165	1·148	1·134	1·121	1·111	1·101	1·092	1·084	1·076	1·069	1·062
1·00	γ	0·234	0·288	0·334	0·378	0·422	0·467	0·515	0·567	0·623	0·684	0·752	0·830	0·918
	μ	1·275	1·235	1·210	1·192	1·178	1·166	1·155	1·145	1·136	1·128	1·120	1·113	1·106
S/P		0·04	0·08	0·12	0·16	0·20	0·24	0·28	0·32	0·36	0·40	0·44	0·48	0·52

Table B-11 (*continued*)

$n/r = 1.20$

		0·96	0·92	0·88	0·84	0·80	0·76	0·72	0·68	0·64	0·60	0·56	P/S
0·08	γ	**0·423**	12·587	6·283	**4·172**	**3·111**	2·471	2·042	1·733	1·499	1·315	1·167	1·043	1·00
	μ	**0·343**	1·044	1·065	1·082	1·098	1·112	1·126	1·140	1·153	1·167	1·180	1·194	
0·12	γ	**0·393**	**0·616**	11·827	5·945	3·958	2·956	2·350	1·942	1·648	1·425	1·249	1·107	0·96
	μ	**0·400**	**0·352**	1·009	1·030	1·047	1·063	1·078	1·092	1·106	1·119	1·133	1·147	
0·16	γ	**0·370**	**0·554**	**0·816**	11·045	5·603	3·744	2·801	2·228	1·842	1·563	1·351	1·184	0·92
	μ	**0·456**	**0·405**	**0·373**	0·974	0·995	1·013	1·028	1·043	1·058	1·072	1·086	1·100	
0·20	γ	0·352	**0·510**	**0·713**	1·033	10·248	5·259	3·529	2·646	2·107	1·742	1·478	1·277	0·88
	μ	0·512	**0·458**	**0·424**	**0·398**	0·940	0·961	0·978	0·994	1·009	1·023	1·038	1·052	
0·24	γ	0·337	0·476	**0·643**	**0·879**	**1·274**	9·447	**4·916**	3·315	2·491	1·986	1·643	1·394	0·84
	μ	0·567	0·511	**0·476**	**0·449**	**0·426**	0·906	0·926	0·944	0·960	0·975	0·990	1·004	
0·28	γ	0·325	0·450	**0·592**	**0·779**	**1·056**	**1·542**	8·651	4·574	3·103	2·338	1·866	1·545	0·80
	μ	0·623	0·564	**0·527**	**0·500**	**0·476**	**0·455**	0·872	0·892	0·910	0·926	0·941	0·956	
0·32	γ	0·315	0·429	0·553	0·708	**0·919**	**1·245**	**1·841**	7·871	4·237	2·893	2·186	1·747	0·76
	μ	0·678	0·616	0·579	0·550	**0·526**	**0·505**	**0·485**	0·838	0·858	0·876	0·892	0·908	
0·36	γ	0·307	0·412	0·522	0·654	0·825	1·066	**1·447**	**2·175**	7·116	**3·906**	2·685	2·036	0·72
	μ	0·733	0·669	0·630	0·601	0·577	0·555	**0·535**	**0·515**	0·805	0·825	0·842	0·859	
0·40	γ	0·299	0·397	0·497	0·612	0·755	0·945	1·219	**1·664**	**2·547**	***6·393***	3·583	2·482	0·68
	μ	0·788	0·721	0·681	0·651	0·626	0·605	0·585	**0·566**	**0·546**	***0·772***	0·791	0·809	
0·44	γ	0·292	0·384	0·476	0·579	0·702	0·858	1·069	1·379	**1·895**	***2·961***	***5·708***	3·270	0·64
	μ	0·842	0·774	0·732	0·701	0·676	0·654	0·634	0·616	**0·597**	***0·578***	***0·739***	0·758	
0·48	γ	0·286	0·373	0·458	0·551	0·659	0·791	0·962	1·196	1·546	***2·142***	***3·418***	***5·066***	0·60
	μ	0·897	0·826	0·783	0·751	0·726	0·704	0·684	0·665	0·647	***0·629***	***0·609***	***0·706***	
0·52	γ	0·281	0·363	0·442	0·527	0·624	0·739	0·881	1·068	1·327	***1·721***	***2·403***	***3·920***	
	μ	0·951	0·878	0·834	0·802	0·775	0·753	0·733	0·714	0·696	***0·678***	***0·661***	***0·641***	
0·56	γ	0·276	0·355	0·429	0·507	0·594	0·696	0·819	0·973	1·176	1·463	***1·902***	***2·679***	***4·470***
	μ	1·005	0·930	0·885	0·852	0·825	0·802	0·782	0·763	0·745	0·728	***0·711***	***0·693***	***0·673***
0·60	γ	0·272	0·347	0·417	0·490	0·570	0·661	0·768	0·899	1·065	1·287	**1·601**	***2·090***	***2·968***
	μ	1·059	0·982	0·935	0·901	0·874	0·851	0·830	0·811	0·794	0·777	0·760	***0·743***	***0·725***
0·64	γ	0·268	0·340	0·406	0·474	0·548	0·631	0·726	0·840	0·980	1·159	1·399	1·743	2·283
	μ	1·113	1·033	0·986	0·951	0·923	0·900	0·879	0·860	0·842	0·825	0·809	0·793	0·776
0·68	γ	0·264	0·333	0·397	0·461	0·529	0·605	0·691	0·791	0·912	1·061	1·254	1·514	1·888
	μ	1·167	1·085	1·037	1·001	0·973	0·949	0·927	0·908	0·890	0·874	0·857	0·841	0·825
0·72	γ	0·261	0·328	0·388	0·449	0·513	0·583	0·661	0·751	0·856	0·984	1·144	1·350	1·630
	μ	1·221	1·137	1·087	1·051	1·022	0·997	0·976	0·957	0·939	0·922	0·906	0·890	0·874
0·76	γ	0·257	0·322	0·380	0·438	0·498	0·563	0·635	0·716	0·810	0·922	1·057	1·226	1·447
	μ	1·274	1·188	1·137	1·100	1·071	1·046	1·024	1·005	0·987	0·970	0·954	0·938	0·923
0·80	γ	0·254	0·317	0·373	0·428	0·485	0·545	0·612	0·686	0·771	0·870	0·987	1·130	1·310
	μ	1·328	1·240	1·188	1·150	1·120	1·095	1·073	1·053	1·035	1·018	1·002	0·986	0·971
0·84	γ	0·252	0·313	0·366	0·419	0·473	0·530	0·592	0·660	0·737	0·826	0·929	1·052	1·203
	μ	1·381	1·291	1·238	1·200	1·169	1·143	1·121	1·101	1·082	1·065	1·049	1·034	1·019
0·88	γ	0·249	0·308	0·360	0·411	0·462	0·516	0·574	0·637	0·708	0·788	0·880	0·988	1·118
	μ	1·434	1·343	1·288	1·249	1·218	1·192	1·169	1·149	1·130	1·113	1·097	1·081	1·067
0·92	γ	0·247	0·304	0·355	0·403	0·452	0·503	0·558	0·617	0·682	0·755	0·839	0·935	1·048
	μ	1·487	1·394	1·338	1·298	1·267	1·240	1·217	1·197	1·178	1·161	1·144	1·129	1·114
0·96	γ	0·244	0·301	0·349	0·396	0·443	0·492	0·543	0·599	0·659	0·727	0·802	0·889	0·989
	μ	1·540	1·445	1·389	1·348	1·316	1·289	1·265	1·245	1·226	1·208	1·192	1·176	1·161
1·00	γ	0·242	0·297	0·344	0·389	0·434	0·481	0·530	0·582	0·639	0·701	0·771	0·849	0·939
	μ	1·593	1·496	1·439	1·397	1·364	1·337	1·313	1·292	1·273	1·256	1·239	1·224	1·209
S/P		0·04	0·08	0·12	0·16	0·20	0·24	0·28	0·32	0·36	0·40	0·44	0·48	0·52

Table B-11 (*continued*)

$n/r = 1.40$

		1·00	0·96	0·92	0·88	0·84	0·80	0·76	0·72	0·68	0·64	0·60	0·56	I'/S
0·08	γ	0·368		12·728	6·382	4·253	3·181	2·533	2·097	1·783	1·545	1·358	1·207	1·081	1·00
	μ	0·760		1·081	1·120	1·153	1·183	1·211	1·239	1·266	1·293	1·321	1·340	1·378	
0·12	γ	0·355	0·514		11·765	5·975	4·002	3·002	2·395	1·985	1·689	1·463	1·286	1·142	0·96
	μ	0·835	0·671		1·051	1·090	1·123	1·154	1·182	1·211	1·238	1·266	1·295	1·324	
0·16	γ	0·343	0·486	0·661		10·779	5·565	3·752	2·824	2·257	1·873	1·594	1·382	1·214	0·92
	μ	0·909	0·739	0·643		1·021	1·061	1·094	1·125	1·154	1·183	1·211	1·240	1·269	
0·20	γ	0·334	0·463	0·614	0·820		9·789	5·156	3·503	2·647	2·121	1·762	1·501	1·301	0·88
	μ	0·982	0·806	0·708	0·637		0·992	1·032	1·065	1·097	1·126	1·156	1·185	1·214	
0·24	γ	0·325	0·445	0·578	0·749	0·996		8·818	4·753	3·258	2·473	1·986	1·653	1·409	0·84
	μ	1·055	0·873	0·772	0·699	0·641		0·964	1·003	1·037	1·069	1·099	1·129	1·159	
0·28	γ	0·318	0·429	0·548	0·695	0·893	1·194		7·884	4·358	3·017	2·302	1·854	1·545	0·80
	μ	1·128	0·940	0·836	0·761	0·702	0·651		0·936	0·976	1·010	1·042	1·073	1·103	
0·32	γ	0 311	0·415	0·524	0·652	0·817	1·049	1·417		7·000	3·977	2·782	2·134	1·724	0·76
	μ	1·200	1·007	0·899	0·823	0·763	0·711	0·664		0·909	0·948	0·983	1·015	1·047	
0·36	γ	0·306	0·403	0·503	0·617	0·759	0·947	1·220	1·671		6·177	3·611	2·554	1·971	0·72
	μ	1·271	1·073	0·962	0·884	0·823	0·771	0·725	0·681		0·883	0·922	0·957	0·990	
0·40	γ	0·300	0·393	0·486	0·589	0·713	0·870	1·085	1·406	1·960		*5·423*	3·263	2·335	0·68
	μ	1·342	1·138	1·025	0·946	0·883	0·831	0·784	0·741	0·699		*0·857*	0·896	0·931	
0·44	γ	0·296	0·384	0·470	0·565	0·675	0·810	0·987	1·233	1·611	*2·290*		*4·738*	2·935	0·64
	μ	1·413	1·204	1·088	1·007	0·943	0·890	0·843	0·800	0·759	*0·719*		*0·832*	0·871	
0·48	γ	0·291	0·376	0·457	0·544	0·643	0·762	0·911	1·109	1·390	*1·834*	*2·665*		*4·124*	0·60
	μ	1·483	1·269	1·150	1·067	1·002	0·948	0·901	0·859	0·818	*0·779*	*0·740*		*0·808*	
0·52	γ	0·287	0·368	0·445	0·526	0·616	0·722	0·851	1·016	1·237	*1·558*	*2·077*	*3·092*		
	μ	1·553	1·334	1·213	1·128	1·062	1·007	0·959	0·916	0·877	*0·839*	*0·801*	*0·761*		
0·56	γ	0·283	0·361	0·434	0·510	0·593	0·689	0·803	0·943	1·124	1·372	*1·737*	*2·342*	*3·577*	
	μ	1·623	1·399	1·275	1·188	1·121	1·065	1·017	0·974	0·934	0·897	*0·860*	*0·823*	*0·784*	
0·60	γ	0·280	0·355	0·424	0·498	0·573	0·660	0·762	0·884	1·037	1·237	1·513	*1·926*	*2·627*	
	μ	1·692	1·463	1·336	1·248	1·180	1·123	1·075	1·031	0·991	0·954	0·918	*0·883*	*0·847*	
0·64	γ	0·277	0·349	0·416	0·483	0·555	0·636	0·727	0·836	0·968	1·134	1·353	1·660	2·126	
	μ	1·762	1·528	1·398	1·308	1·238	1·181	1·132	1·088	1·048	1·011	0·976	0·941	0·907	
0·68	γ	0·274	0·344	0·408	0·472	0·539	0·614	0·698	0·795	0·911	1·053	1·233	1·473	1·813	
	μ	1·830	1·592	1·460	1·368	1·297	1·239	1·189	1·145	1·105	1·067	1·032	0·998	0·965	
0·72	γ	0·271	0·339	0·400	0·461	0·525	0·595	0·672	0·760	0·863	0·987	1·140	1·335	1·597	
	μ	1·899	1·656	1·521	1·428	1·355	1·296	1·246	1·201	1·161	1·123	1·088	1·055	1·022	
0·76	γ	0·268	0·335	0·394	0·452	0·512	0·578	0·649	0·730	0·823	0·932	1·064	1·228	1·439	
	μ	1·967	1·719	1·582	1·487	1·414	1·354	1·302	1·257	1·217	1·179	1·144	1·111	1·079	
0·80	γ	0·266	0·330	0·387	0·443	0·501	0·562	0·629	0·703	0·788	0·886	1·002	1·142	1·318	
	μ	2·036	1·783	1·643	1·546	1·472	1·411	1·359	1·313	1·272	1·235	1·200	1·166	1·135	
0·84	γ	0·263	0·326	0·382	0·435	0·490	0·548	0·611	0·680	0·757	0·846	0·949	1·072	1·221	
	μ	2·104	1·846	1·704	1·606	1·530	1·468	1·415	1·369	1·328	1·290	1·255	1·222	1·190	
0·88	γ	0·261	0·323	0·376	0·428	0·480	0·535	0·595	0·659	0·731	0·812	0·904	1·013	1·143	
	μ	2·171	1·910	1·765	1·665	1·588	1·525	1·472	1·425	1·383	1·345	1·310	1·278	1·245	
0·92	γ	0·259	0·319	0·371	0·421	0·471	0·524	0·580	0·640	0·707	0·781	0·866	0·963	1·077	
	μ	2·239	1·973	1·826	1·724	1·646	1·582	1·528	1·481	1·438	1·400	1·364	1·331	1·299	
0·96	γ	0·257	0·316	0·366	0·415	0·463	0·513	0·566	0·623	0·685	0·754	0·832	0·920	1·022	
	μ	2·306	2·036	1·886	1·783	1·704	1·639	1·584	1·536	1·494	1·455	1·419	1·385	1·354	
1·00	γ	0·255	0·313	0·362	0·409	0·455	0·503	0·554	0·608	0·666	0·730	0·802	0·882	0·974	
	μ	2·374	2·099	1·947	1·842	1·761	1·696	1·640	1·592	1·548	1·509	1·473	1·440	1·408	
S/P		0·04	0·08	0·12	0·16	0·20	0·24	0·28	0·32	0·36	0·40	0·44	0·48	0·52	

Table B-11 (*continued*)

$n/r = 1.60$

		1·00	0·96	0·92	0·88	0·84	0·80	0·76	0·72	0·68	0·64	0·60	0·56	P/S
0·08	γ	0·346		12·845	6·465	4·320	3·238	2·583	2·143	1·825	1·584	1·394	1·239	1·111	1·00
	μ	1·366		1·113	1·168	1·215	1·259	1·300	1·341	1·381	1·422	1·464	1·507	1·552	
0·12	γ	0·338	0·473		11·716	6·000	4·039	3·040	2·432	2·020	1·722	1·495	1·316	1·170	0·96
	μ	1·460	1·089		1·087	1·143	1·191	1·235	1·277	1·319	1·361	1·403	1·446	1·491	
0·16	γ	0·331	0·456	0·598		10·575	5·536	3·760	2·844	2·281	1·899	1·620	1·408	1·239	0·92
	μ	1·553	1·172	0·975		1·062	1·119	1·167	1·212	1·255	1·298	1·341	1·385	1·430	
0·20	γ	0·325	0·441	0·570	0·732		9·451	5·079	3·485	2·650	2·133	1·779	1·520	1·321	0·88
	μ	1·645	1·255	1·053	0·916		1·038	1·095	1·144	1·190	1·234	1·278	1·323	1·368	
0·24	γ	0·320	0·429	0·546	0·688	0·880		8·373	4·633	3·216	2·461	1·988	1·662	1·421	0·84
	μ	1·736	1·336	1·130	0·991	0·884		1·016	1·073	1·123	1·169	1·215	1·260	1·306	
0·28	γ	0·315	0·418	0·526	0·652	0·816	1·046		7·363	4·205	2·956	2·277	1·846	1·547	0·80
	μ	1·827	1·418	1·206	1·064	0·956	0·866		0·995	1·052	1·102	1·150	1·196	1·243	
0·32	γ	0·310	0·408	0·508	0·623	0·764	0·954	1·234		6·435	3·798	2·705	2·098	1·709	0·76
	μ	1·916	1·498	1·282	1·137	1·027	0·936	0·857		0·975	1·032	1·083	1·131	1·180	
0·36	γ	0·306	0·400	0·493	0·597	0·723	0·884	1·107	1·448		5·597	3·414	2·466	1·927	0·72
	μ	2·006	1·578	1·358	1·210	1·098	1·006	0·927	0·854		0·956	1·013	1·065	1·115	
0·40	γ	0·302	0·392	0·480	0·576	0·689	0·828	1·012	1·275	1·694		*4·850*	3·057	2·239	0·68
	μ	2·094	1·658	1·433	1·282	1·168	1·075	0·996	0·924	0·856		*0·938*	0·995	1·048	
0·44	γ	0·298	0·385	0·468	0·557	0·660	0·783	0·940	1·151	1·461	*1·976*		*4·192*	2·727	0·64
	μ	2·182	1·737	1·507	1·354	1·238	1·144	1·064	0·992	0·926	*0·862*		*0·921*	0·979	
0·48	γ	0·295	0·378	0·457	0·541	0·635	0·745	0·881	1·058	1·301	*1·667*	*2·302*		*3·615*	0·60
	μ	2·269	1·816	1·582	1·425	1·307	1·212	1·131	1·060	0·994	*0·932*	*0·870*		*0·906*	
0·52	γ	0·292	0·372	0·447	0·526	0·613	0·713	0·834	0·984	1·183	*1·462*	*1·895*	*2·679*		
	μ	2·356	1·894	1·656	1·496	1·376	1·280	1·198	1·126	1·061	*1·000*	*0·940*	*0·850*		
0·56	γ	0·289	0·367	0·439	0·513	0·594	0·685	0·793	0·925	1·092	1·316	*1·637*	*2·146*	*3·114*	
	μ	2·442	1·972	1·729	1·567	1·445	1·347	1·265	1·192	1·127	1·066	*1·008*	*0·951*	*0·893*	
0·60	γ	0·286	0·361	0·430	0·501	0·577	0·661	0·759	0·876	1·020	1·205	1·457	*1·824*	*2·423*	
	μ	2·528	2·050	1·802	1·637	1·514	1·414	1·331	1·258	1·192	1·132	1·075	*1·019*	*0·964*	
0·64	γ	0·284	0·357	0·423	0·490	0·561	0·640	0·730	0·835	0·961	1·118	1·324	1·606	2·025	
	μ	2·613	2·127	1·876	1·708	1·582	1·481	1·396	1·323	1·257	1·196	1·140	1·086	1·033	
0·68	γ	0·281	0·352	0·416	0·480	0·548	0·621	0·704	0·799	0·911	1·048	1·221	1·447	1·762	
	μ	2·699	2·204	1·948	1·778	1·650	1·548	1·462	1·387	1·321	1·261	1·204	1·151	1·099	
0·72	γ	0·279	0·348	0·410	0·471	0·535	0·604	0·681	0·768	0·869	0·990	1·138	1·326	1·576	
	μ	2·783	2·281	2·021	1·847	1·718	1·614	1·527	1·452	1·385	1·324	1·268	1·215	1·164	
0·76	γ	0·277	0·344	0·404	0·463	0·524	0·589	0·661	0·741	0·833	0·941	1·070	1·230	1·435	
	μ	2·868	2·358	2·093	1·917	1·785	1·680	1·592	1·516	1·449	1·388	1·331	1·279	1·228	
0·80	γ	0·274	0·341	0·399	0·455	0·514	0·575	0·643	0·717	0·802	0·899	1·014	1·152	1·325	
	μ	2·951	2·434	2·165	1·986	1·852	1·746	1·657	1·580	1·512	1·450	1·394	1·341	1·291	
0·84	γ	0·272	0·337	0·393	0·448	0·504	0·563	0·626	0·696	0·774	0·862	0·966	1·088	1·236	
	μ	3·035	2·610	2·237	2·055	1·920	1·811	1·721	1·643	1·575	1·513	1·456	1·404	1·354	
0·88	γ	0·271	0·334	0·389	0·441	0·495	0·551	0·611	0·676	0·749	0·830	0·924	1·033	1·163	
	μ	3·118	2·685	2·308	2·124	1·987	1·877	1·785	1·707	1·638	1·575	1·518	1·465	1·416	
0·92	γ	0·269	0·331	0·384	0·435	0·487	0·540	0·597	0·659	0·727	0·802	0·888	0·986	1·101	
	μ	3·201	2·661	2·380	2·193	2·053	1·942	1·850	1·770	1·700	1·637	1·580	1·527	1·477	
0·96	γ	0·267	0·328	0·380	0·429	0·479	0·531	0·585	0·643	0·707	0·777	0·856	0·945	1·048	
	μ	3·284	2·736	2·451	2·261	2·120	2·007	1·914	1·833	1·762	1·699	1·641	1·588	1·538	
1·00	γ	0·265	0·325	0·376	0·424	0·472	0·521	0·573	0·629	0·688	0·754	0·827	0·909	1·003	
	μ	3·367	2·811	2·522	2·330	2·186	2·072	1·977	1·896	1·825	1·760	1·702	1·649	1·599	
S/P		0·04	0·08	0·12	0·16	0·20	0·24	0·28	0·32	0·36	0·40	0·44	0·48	0·52	

Table B-11 (*continued*)

$n/r_j = 1.80$

			1·00	0·96	0·92	0·88	0·84	0·80	0·76	0·72	0·68	0·64	0·60	0·56	P/S
0·08	γ	0·335		12·945	6·535	4·377	3·287	2·626	2·181	1·860	1·616	1·423	1·267	1·137	1·00
	μ	2·196		1·140	1·211	1·271	1·327	1·381	1·434	1·487	1·542	1·598	1·656	1·717	
0·12	γ	0·330	0·451		11·677	6·023	4·070	3·072	2·463	2·050	1·750	1·522	1·341	1·194	0·96
	μ	2·310	1·613		1·119	1·190	1·251	1·309	1·364	1·419	1·474	1·531	1·589	1·650	
0·16	γ	0·325	0·439	0·564		10·412	5·515	3·767	2·861	2·302	1·920	1·642	1·429	1·260	0·92
	μ	2·422	1·712	1·370		1·099	1·171	1·233	1·292	1·349	1·405	1·463	1·522	1·583	
0·20	γ	0·321	0·429	0·544	0·685		9·188	5·019	3·471	2·654	2·144	1·794	1·536	1·338	0·88
	μ	2·534	1·810	1·461	1·237		1·080	1·153	1·217	1·276	1·335	1·394	1·453	1·515	
0·24	γ	0·317	0·420	0·527	0·654	0·817		8·039	4·542	3·185	2·453	1·990	1·670	1·432	0·84
	μ	2·644	1·907	1·551	1·323	1·153		1·064	1·137	1·201	1·263	1·323	1·384	1·446	
0·28	γ	0·313	0·412	0·512	0·627	0·771	0·965		6·984	4·090	2·910	2·259	1·842	1·549	0·80
	μ	2·753	2·003	1·641	1·408	1·236	1·098		1·049	1·122	1·188	1·251	1·313	1·377	
0·32	γ	0·310	0·404	0·499	0·605	0·733	0·899	1·132		6·038	3·667	2·648	2·072	1·698	0·76
	μ	2·861	2·098	1·729	1·492	1·318	1·179	1·061		1·036	1·109	1·176	1·241	1·306	
0·36	γ	0·306	0·398	0·487	0·585	0·701	0·845	1·039	1·322		5·201	3·274	2·401	1·895	0·72
	μ	2·968	2·192	1·817	1·576	1·399	1·259	1·140	1·035		1·024	1·098	1·167	1·234	
0·40	γ	0·303	0·391	0·476	0·568	0·674	0·802	0·967	1·195	1·541		*4·471*	2·913	2·170	0·68
	μ	3·075	2·286	1·904	1·659	1·480	1·337	1·218	1·114	1·018		*1·015*	1·089	1·160	
0·44	γ	0·301	0·386	0·467	0·553	0·650	0·765	0·909	1·099	1·369	*1·795*		*3·839*	2·585	0·64
	μ	3·181	2·380	1·991	1·742	1·559	1·416	1·295	1·191	1·096	*1·007*		*1·007*	1·083	
0·48	γ	0·298	0·380	0·458	0·539	0·629	0·734	0·862	1·024	1·243	*1·562*	*2·088*		*3·296*	0·60
	μ	3·286	2·472	2·077	1·824	1·639	1·493	1·372	1·267	1·173	*1·085*	*1·000*		*1·001*	
0·52	γ	0·295	0·375	0·450	0·527	0·611	0·707	0·822	0·963	1·147	*1·399*	*1·778*	*2·431*		
	μ	3·390	2·564	2·163	1·905	1·718	1·570	1·447	1·342	1·248	*1·161*	*1·079*	*0·998*		
0·56	γ	0·293	0·371	0·442	0·515	0·595	0·684	0·788	0·913	1·071	1·278	*1·569*	*2·019*	*2·830*	
	μ	3·494	2·656	2·248	1·987	1·796	1·646	1·522	1·416	1·322	1·236	*1·155*	*1·077*	*0·998*	
0·60	γ	0·291	0·366	0·435	0·505	0·580	0·663	0·758	0·871	1·009	1·184	1·418	*1·754*	*2·287*	
	μ	3·597	2·747	2·333	2·067	1·874	1·722	1·597	1·490	1·395	1·309	1·229	*1·153*	*1·078*	
0·64	γ	0·289	0·362	0·429	0·496	0·567	0·644	0·732	0·834	0·957	1·108	1·303	1·568	1·954	
	μ	3·699	2·838	2·418	2·148	1·952	1·798	1·671	1·563	1·468	1·382	1·302	1·227	1·155	
0·68	γ	0·287	0·359	0·423	0·487	0·555	0·628	0·709	0·803	0·913	1·046	1·212	1·429	1·727	
	μ	3·802	2·928	2·502	2·228	2·029	1·873	1·745	1·635	1·539	1·453	1·374	1·300	1·229	
0·72	γ	0·285	0·355	0·418	0·479	0·544	0·613	0·689	0·775	0·875	0·993	1·138	1·320	1·560	
	μ	3·903	3·018	2·586	2·308	2·106	1·948	1·818	1·708	1·611	1·524	1·445	1·371	1·301	
0·76	γ	0·283	0·352	0·412	0·472	0·533	0·599	0·670	0·751	0·842	0·949	1·076	1·233	1·433	
	μ	4·004	3·108	2·669	2·387	2·183	2·022	1·891	1·779	1·682	1·595	1·515	1·442	1·372	
0·80	γ	0·281	0·348	0·408	0·465	0·524	0·586	0·654	0·729	0·813	0·910	1·024	1·161	1·331	
	μ	4·105	3·197	2·752	2·467	2·259	2·097	1·964	1·851	1·752	1·665	1·585	1·511	1·442	
0·84	γ	0·279	0·345	0·403	0·459	0·515	0·575	0·639	0·709	0·787	0·876	0·979	1·101	1·249	
	μ	4·205	3·286	2·835	2·545	2·335	2·171	2·036	1·922	1·823	1·734	1·654	1·580	1·512	
0·88	γ	0·278	0·343	0·399	0·452	0·507	0·564	0·625	0·691	0·764	0·846	0·940	1·050	1·180	
	μ	4·305	3·374	2·918	2·624	2·411	2·245	2·108	1·993	1·892	1·803	1·723	1·649	1·580	
0·92	γ	0·276	0·340	0·394	0·447	0·499	0·554	0·612	0·674	0·743	0·819	0·906	1·005	1·121	
	μ	4·404	3·462	3·000	2·703	2·487	2·318	2·180	2·063	1·962	1·872	1·791	1·717	1·648	
0·96	γ	0·275	0·337	0·391	0·441	0·492	0·545	0·600	0·660	0·724	0·795	0·875	0·966	1·071	
	μ	4·503	3·550	3·082	2·781	2·562	2·391	2·252	2·134	2·031	1·941	1·859	1·784	1·715	
1·00	γ	0·273	0·335	0·387	0·436	0·486	0·536	0·589	0·646	0·707	0·774	0·848	0·932	1·027	
	μ	4·601	3·638	3·164	2·859	2·637	2·465	2·323	2·204	2·100	2·009	1·926	1·861	1·782	
S/P		0·04	0·08	0·12	0·16	0·20	0·24	0·28	0·32	0·36	0·40	0·44	0·48	0·52	

Table B-11 (*continued*)

n/r = 2.0

		1·00	0·96	0·92	0·88	0·84	0·80	0·76	0·72	0·68	0·64	0·60	0·56	P/S
0·08	γ 0·328		13·029	6·596	4·426	3·329	2·663	2·215	1·890	1·644	1·449	1·291	1·159	1·00
	μ 3·287		1·165	1·249	1·321	1·389	1·455	1·520	1·586	1·654	1·724	1·798	1·875	
0·12	γ 0·325	0 437		11·643	6·042	4·097	3·100	2·490	2·076	1·774	1·545	1·362	1·214	0·96
	μ 3·420	2 252		1·147	1·233	1·307	1·376	1·444	1·512	1·581	1·651	1·725	1·803	
0·16	γ 0·321	0 429	0·543		10·278	5·497	3·774	2·875	2·319	1·939	1·661	1·447	1·277	0·92
	μ 3·552	2 366	1·830		1·132	1·218	1·294	1·365	1·435	1·506	1·577	1·652	1·730	
0·20	γ 0·318	0·421	0·528	0·655		8·977	4·971	3·461	2·657	2·154	1·806	1·550	1·352	0·88
	μ 3·683	2·479	1·934	1·596		1·119	1·206	1·283	1·357	1·429	1·502	1·577	1·656	
0·24	γ 0·315	0 414	0·515	0·631	0·777		7·776	4·470	3·160	2·446	1·993	1·677	1·442	0·84
	μ 3·812	2·591	2·037	1·694	1·449		1·108	1·196	1·275	1·350	1·426	1·502	1·581	
0·28	γ 0·312	0·408	0·503	0·611	0·742	0·913		6·695	4·000	2·874	2·245	1·838	1·552	0·80
	μ 3·940	2·702	2·139	1·791	1·542	1·348		1·099	1·188	1·269	1·347	1·425	1·505	
0·32	γ 0·309	0·402	0·493	0·593	0·712	0·862	1·067		5·741	3·566	2·604	2·053	1·690	0·76
	μ 4·067	2·812	2·240	1·886	1·634	1·438	1·276		1·093	1·182	1·265	1·346	1·428	
0·36	γ 0·307	0·396	0·483	0·577	0·686	0·820	0·994	1·242		4·913	3·168	2·352	1·871	0·72
	μ 4·193	2·921	2·340	1·981	1·726	1·527	1·364	1·223		1·089	1·180	1·265	1·349	
0·40	γ 0·305	0·391	0·474	0·563	0·663	0·784	0·936	1·142	1·443		*4·201*	2·807	2·118	0·68
	μ 4·318	3·029	2·440	2·075	1·816	1·616	1·451	1·310	1·183		*1·088*	1·180	1·267	
0·44	γ 0·302	0·387	0·466	0·550	0·643	0·753	0·889	1·064	1·306	*1·676*		*3·593*	2·481	0·64
	μ 4·442	3·137	2·539	2·169	1·906	1·703	1·537	1·395	1·269	*1·153*		*1·089*	1·183	
0·48	γ 0·300	0·382	0·459	0·538	0·626	0·727	0·848	1·001	1·202	*1·490*	*1·947*		*3·076*	0·60
	μ 4·566	3·244	2·637	2·261	1·995	1·789	1·622	1·480	1·354	*1·239*	*1·130*		*1·093*	
0·52	γ 0·298	0·378	0·452	0·528	0·610	0·704	0·814	0·949	1·121	*1·355*	*1·697*	*2·265*		
	μ 4·688	3·350	2·735	2·354	2·083	1·875	1·706	1·563	1·437	*1·323*	*1·217*	*1·113*		
0·56	γ 0·296	0·374	0·445	0·518	0·596	0·683	0·784	0·905	1·055	1·251	*1·521*	*1·929*	*2·638*	
	μ 4·810	3·455	2·832	2·445	2·171	1·961	1·790	1·645	1·519	1·405	*1·301*	*1·201*	*1·101*	
0·60	γ 0·294	0·371	0·439	0·509	0·583	0·665	0·758	0·867	1·000	1·168	1·390	*1·703*	*2·189*	
	μ 4·931	3·560	2·928	2·537	2·259	2·045	1·872	1·727	1·600	1·486	1·382	*1·284*	*1·190*	
0·64	γ 0·293	0·367	0·434	0·501	0·571	0·648	0·735	0·835	0·954	1·101	1·288	1·540	1·902	
	μ 5·051	3·664	3·024	2·627	2·346	2·130	1·955	1·807	1·680	1·566	1·462	1·366	1·274	
0·68	γ 0·291	0·364	0·429	0·493	0·560	0·633	0·714	0·806	0·914	1·044	1·206	1·415	1·700	
	μ 5·171	3·768	3·120	2·718	2·432	2·213	2·036	1·888	1·759	1·645	1·541	1·445	1·355	
0·72	γ 0·289	0·361	0·424	0·486	0·550	0·619	0·695	0·781	0·880	0·997	1·138	1·316	1·549	
	μ 5·290	3·872	3·215	2·808	2·518	2·297	2·118	1·967	1·838	1·723	1·619	1·524	1·434	
0·76	γ 0·288	0·358	0·419	0·479	0·541	0·607	0·679	0·758	0·850	0·955	1·082	1·236	1·432	
	μ 5·408	3·974	3·310	2·897	2·604	2·380	2·199	2·047	1·916	1·800	1·696	1·601	1·512	
0·80	γ 0·286	0·355	0·415	0·473	0·532	0·595	0·663	0·738	0·823	0·919	1·033	1·169	1·337	
	μ 5·526	4·077	3·404	2·986	2·690	2·462	2·279	2·126	1·993	1·877	1·772	1·677	1·588	
0·84	γ 0·285	0·352	0·411	0·467	0·524	0·585	0·649	0·720	0·798	0·888	0·991	1·112	1·259	
	μ 5·644	4·179	3·498	3·075	2·775	2·545	2·359	2·204	2·071	1·953	1·848	1·752	1·664	
0·88	γ 0·283	0·350	0·407	0·462	0·517	0·575	0·636	0·703	0·777	0·859	0·954	1·064	1·194	
	μ 5·760	4·280	3·592	3·163	2·859	2·627	2·439	2·282	2·147	2·029	1·923	1·827	1·738	
0·92	γ 0·282	0·347	0·403	0·456	0·510	0·565	0·624	0·688	0·757	0·834	0·921	1·021	1·138	
	μ 5·877	4·382	3·685	3·252	2·944	2·708	2·519	2·360	2·224	2·105	1·998	1·901	1·812	
0·96	γ 0·281	0·345	0·399	0·451	0·503	0·557	0·613	0·673	0·739	0·811	0·892	0·984	1·090	
	μ 5·993	4·482	3·778	3·339	3·028	2·790	2·598	2·437	2·300	2·180	2·072	1·975	1·886	
1·00	γ 0·279	0·342	0·396	0·447	0·497	0·549	0·603	0·660	0·722	0·791	0·866	0·951	1·047	
	μ 6·108	4·583	3·871	3·427	3·112	2·871	2·677	2·515	2·376	2·254	2·146	2·048	1·958	
S/P	0·04	0 08	0·12	0·16	0·20	0·24	0·28	0·32	0·36	0·40	0·44	0·48	0·52	

Table B-11 (*continued*)

$n/r = 2.30$

		1·00	0·96	0·92	0·88	0·84	0·80	0·76	0·72	0·68	0·64	0·60	0·56	P/S
0·08	γ	0·322	13·143	6·674	4·489	3·383	2·711	2·257	1·929	1·679	1·482	1·321	1·187	1·00
	μ	5·488	1·197	1·299	1·389	1·473	1·556	1·638	1·723	1·810	1·902	1·998	2·101	
0·12	γ	0·320	0·425	11·606	6·067	4·131	3·135	2·524	2·108	1·805	1·573	1·390	1·239	0·96
	μ	5·651	3·438	1·185	1·290	1·381	1·468	1·554	1·640	1·729	1·821	1·917	2·020	
0·16	γ	0·318	0·419	0·524	10·116	5·477	3·783	2·895	2·342	1·963	1·685	1·471	1·300	0·92
	μ	5·812	3·575	2·641	1·176	1·283	1·377	1·467	1·555	1·646	1·739	1·836	1·939	
0·20	γ	0·315	0·414	0·513	0·627	8·727	4·913	3·449	2·662	2·166	1·822	1·568	1·370	0·88
	μ	5·972	3·711	2·764	2·209	1·170	1·278	1·375	1·468	1·560	1·655	1·753	1·856	
0·24	γ	0·313	0·409	0·504	0·610	0·740	7·473	4·385	3·132	2·440	1·997	1·686	1·454	0·84
	μ	6·130	3·845	2·886	2·324	1·937	1·168	1·277	1·376	1·473	1·569	1·669	1·773	
0·28	γ	0·311	0·404	0·495	0·595	0·714	0·864	6·368	3·897	2·833	2·229	1·836	1·556	0·80
	μ	6·287	3·978	3·007	2·437	2·046	1·751	1·168	1·279	1·381	1·481	1·583	1·688	
0·32	γ	0·309	0·400	0·487	0·581	0·691	0·826	1·004	5·414	3·452	2·555	2·031	1·682	0·76
	μ	6·443	4·110	3·127	2·549	2·153	1·855	1·616	1·172	1·285	1·390	1·495	1·601	
0·36	γ	0·308	0·396	0·479	0·569	0·671	0·794	0·950	1·164	4·601	3·050	2·297	1·844	0·72
	μ	6·598	4·241	3·246	2·661	2·260	1·958	1·717	1·514	1·180	1·294	1·403	1·513	
0·40	γ	0·306	0·392	0·472	0·558	0·653	0·766	0·905	1·088	1·347	*3·914*	2·690	2·061	0·68
	μ	6·751	4·371	3·364	2·771	2·365	2·060	1·817	1·614	1·435	*1·191*	1·308	1·422	
0·44	γ	0·304	0·388	0·466	0·547	0·637	0·741	0·867	1·027	1·243	*1·559*	*3·336*	2·369	0·64
	μ	6·903	4·501	3·481	2·881	2·469	2·161	1·916	1·711	1·534	*1·373*	*1·207*	1·327	
0·48	γ	0·303	0·385	0·460	0·538	0·623	0·720	0·834	0·976	1·160	*1·416*	*1·807*	*2·851*	0·60
	μ	7·055	4·629	3·598	2·989	2·573	2·261	2·013	1·808	1·630	*1·471*	*8·324*	*1·227*	
0·52	γ	0·301	0·381	0·455	0·529	0·610	0·700	0·806	0·933	1·094	*1·308*	*1·612*	*2·099*	
	μ	7·205	4·756	3·713	3·097	2·675	2·360	2·110	1·903	1·724	*1·566*	*1·422*	*1·284*	
0·56	γ	0·300	0·378	0·449	0·521	0·598	0·683	0·781	0·896	1·039	1·222	*1·470*	*1·834*	*2·443*
	μ	7·354	4·882	3·829	3·205	2·778	2·458	2·206	1·996	1·817	1·660	*1·516*	*1·382*	*1·252*
0·60	γ	0·298	0·375	0·444	0·514	0·587	0·667	0·758	0·864	0·992	1·152	1·360	*1·648*	*2·035*
	μ	7·503	5·008	3·942	3·311	2·879	2·556	2·300	2·089	1·909	1·751	1·609	*1·477*	*1·351*
0·64	γ	0·297	0·372	0·440	0·507	0·577	0·653	0·738	0·836	0·952	1·093	1·272	1·509	1·845
	μ	7·651	5·134	4·055	3·417	2·980	2·653	2·395	2·181	2·000	1·841	1·699	1·568	1·446
0·68	γ	0·296	0·370	0·435	0·500	0·567	0·640	0·720	0·811	0·917	1·044	1·200	1·400	1·670
	μ	7·798	5·258	4·168	3·523	3·080	2·749	2·488	2·273	2·090	1·930	1·788	1·658	1·537
0·72	γ	0·294	0·367	0·431	0·494	0·559	0·628	0·704	0·789	0·886	1·001	1·140	1·313	1·537
	μ	7·944	5·382	4·281	3·628	3·180	2·845	2·581	2·364	2·179	2·019	1·876	1·746	1·626
0·76	γ	0·293	0·365	0·427	0·488	0·551	0·617	0·689	0·768	0·859	0·964	1·089	1·240	1·431
	μ	8·089	5·505	4·392	3·732	3·279	2·940	2·673	2·454	2·268	2·106	1·962	1·833	1·713
0·80	γ	0·292	0·362	0·423	0·483	0·543	0·606	0·675	0·750	0·835	0·931	1·044	1·179	1·345
	μ	8·234	5·627	4·503	3·836	3·378	3·035	2·765	2·543	2·355	2·193	2·048	1·918	1·799
0·84	γ	0·291	0·360	0·420	0·477	0·536	0·597	0·662	0·733	0·813	0·902	1·005	1·127	1·273
	μ	8·378	5·749	4·614	3·939	3·476	3·130	2·857	2·632	2·443	2·278	2·133	2·003	1·883
0·88	γ	0·290	0·358	0·416	0·473	0·529	0·588	0·650	0·718	0·793	0·876	0·971	1·082	1·212
	μ	8·521	5·871	4·724	4·042	3·574	3·224	2·948	2·721	2·530	2·364	2·218	2·086	1·967
0·92	γ	0·288	0·356	0·413	0·468	0·523	0·579	0·639	0·704	0·774	0·853	0·941	1·042	1·160
	μ	8·664	5·992	4·834	4·145	3·671	3·317	3·038	2·809	2·616	2·449	2·301	2·169	2·049
0·96	γ	0·287	0·354	0·410	0·463	0·517	0·572	0·629	0·691	0·757	0·831	0·913	1·007	1·114
	μ	8·806	6·112	4·943	4·247	3·768	3·411	3·129	2·897	2·702	2·533	2·385	2·252	2·131
1·00	γ	0·286	0·352	0·407	0·459	0·511	0·564	0·620	0·678	0·742	0·812	0·889	0·975	1·073
	μ	8·947	6·232	5·052	4·349	3·865	3·504	3·218	2·985	2·787	2·617	2·467	2·333	2·212
S/P		0·04	0·08	0·12	0·16	0·20	0·24	0·28	0·32	0·36	0·40	0·44	0·48	0·52

Table B-11 (*continued*)

$n/r = 2.60$

			1·00	0·96	0·92	0·88	0·84	0·80	0·76	0·72	0·68	0·64	0·60	0·56	P/S
0·08	γ	0·319		13·237	6·740	4·542	3·428	2·751	2·293	1·961	1·708	1·509	1·346	1·210	1·00
	μ	8·478		1·226	1·344	1·449	1·548	1·647	1·746	1·848	1·955	2·067	2·186	2·315	
0·12	γ	0·317	0·418		11·575	6·089	4·160	3·165	2·553	2·135	1·831	1·598	1·412	1·261	0·96
	μ	8·670	4·915		1·219	1·340	1·448	1·552	1·654	1·758	1·866	1·978	2·098	2·226	
0·16	γ	0·315	0·413	0·512		9·987	5·461	3·792	2·911	2·361	1·983	1·704	1·490	1·318	0·92
	μ	8·861	5·075	3·600		1·216	1·340	1·451	1·559	1·666	1·775	1·889	2·009	2·137	
0·20	γ	0·314	0·409	0·504	0·610		8·532	4·869	3·441	2·667	2·177	1·836	1·582	1·386	0·88
	μ	9·049	5·233	3·743	2·906		1·217	1·344	1·458	1·570	1·682	1·797	1·918	2·047	
0·24	γ	0·312	0·405	0·496	0·596	0·716		7·241	4·320	3·110	2·436	2·001	1·694	1·465	0·84
	μ	9·237	5·390	3·884	3·038	2·477		1·222	1·351	1·470	1·586	1·704	1·826	1·955	
0·28	γ	0·311	0·402	0·489	0·584	0·695	0·833		6·124	3·818	2·802	2·218	1·834	1·560	0·80
	μ	9·423	5·545	4·023	3·168	2·601	2·185		1·232	1·363	1·486	1·607	1·731	1·862	
0·32	γ	0·310	0·398	0·483	0·574	0·677	0·803	0·964		5·174	3·366	2·518	2·014	1·677	0·76
	μ	9·607	5·699	4·162	3·297	2·723	2·303	1·975		1·246	1·380	1·507	1·635	1·767	
0·36	γ	0·308	0·395	0·477	0·564	0·661	0·776	0·921	1·113		4·377	2·963	2·257	1·825	0·72
	μ	9·790	5·852	4·299	3·424	2·844	2·420	2·089	1·816		1·265	1·402	1·535	1·669	
0·40	γ	0·307	0·392	0·471	0·554	0·646	0·753	0·884	1·052	1·284		*3·711*	2·605	2·019	0·68
	μ	9·972	6·004	4·435	3·551	2·964	2·535	2·201	1·928	1·693		*1·289*	1·430	1·569	
0·44	γ	0·306	0·389	0·466	0·546	0·633	0·733	0·852	1·002	1·200	*1·483*		*3·157*	2·289	0·64
	μ	10·153	6·154	4·570	3·676	3·082	2·649	2·312	2·037	1·803	*1·595*		*1·318*	1·465	
0·48	γ	0·304	0·386	0·461	0·538	0·621	0·715	0·825	0·959	1·132	*1·366*	*1·714*		*2·696*	0·60
	μ	10·333	6·304	4·705	3·800	3·200	2·762	2·422	2·145	1·910	*1·704*	*1·516*		*1·355*	
0·52	γ	0·303	0·384	0·457	0·531	0·610	0·698	0·800	0·923	1·075	*1·275*	*1·554*	*1·987*		
	μ	10·512	6·453	4·838	3·924	3·317	2·874	2·530	2·251	2·015	*1·810*	*1·625*	*1·452*		
0·56	γ	0·302	0·381	0·452	0·524	0·600	0·683	0·779	0·891	1·028	1·201	*1·433*	*1·768*	*2·311*	
	μ	10·689	6·600	4·970	4·046	3·433	2·985	2·638	2·356	2·119	1·913	*1·729*	*1·560*	*1·399*	
0·60	γ	0·301	0·379	0·448	0·517	0·590	0·670	0·759	0·863	0·987	1·140	1·338	*1·609*	*2·012*	
	μ	10·866	6·747	5·102	4·168	3·548	3·095	2·744	2·460	2·221	2·015	1·831	*1·664*	*1·508*	
0·64	γ	0·300	0·376	0·444	0·511	0·581	0·657	0·741	0·838	0·951	1·088	1·261	1·487	1·804	
	μ	11·041	6·893	5·233	4·289	3·662	3·204	2·850	2·563	2·322	2·115	1·932	1·766	1·612	
0·68	γ	0·299	0·374	0·440	0·506	0·573	0·645	0·725	0·815	0·920	1·044	1·196	1·390	1·649	
	μ	11·216	7·038	5·363	4·410	3·776	3·313	2·955	2·665	2·422	2·214	2·030	1·865	1·712	
0·72	γ	0·298	0·372	0·437	0·500	0·565	0·635	0·710	0·795	0·892	1·005	1·142	1·311	1·529	
	μ	11·390	7·183	5·492	4·529	3·888	3·421	3·059	2·766	2·522	2·312	2·127	1·962	1·810	
0·76	γ	0·297	0·370	0·433	0·495	0·558	0·625	0·697	0·777	0·867	0·971	1·095	1·244	1·432	
	μ	11·563	7·326	5·621	4·649	4·001	3·528	3·163	2·867	2·620	2·408	2·223	2·057	1·906	
0·80	γ	0·296	0·368	0·430	0·490	0·551	0·615	0·684	0·760	0·845	0·941	1·054	1·188	1·352	
	μ	11·735	7·469	5·749	4·767	4·113	3·635	3·265	2·967	2·718	2·504	2·318	2·151	2·001	
0·84	γ	0·295	0·366	0·427	0·486	0·545	0·607	0·673	0·744	0·824	0·914	1·018	1·139	1·285	
	μ	11·906	7·611	5·876	4·885	4·224	3·741	3·368	3·066	2·815	2·599	2·412	2·244	2·093	
0·88	γ	0·294	0·364	0·424	0·481	0·539	0·598	0·662	0·730	0·805	0·890	0·986	1·096	1·227	
	μ	12·076	7·753	6·003	5·002	4·335	3·847	3·470	3·165	2·911	2·694	2·505	2·337	2·185	
0·92	γ	0·293	0·362	0·421	0·477	0·533	0·591	0·652	0·717	0·788	0·868	0·957	1·059	1·177	
	μ	12·246	7·894	6·129	5·119	4·445	3·952	3·571	3·263	3·007	2·788	2·597	2·428	2·276	
0·96	γ	0·292	0·361	0·418	0·473	0·528	0·583	0·642	0·705	0·773	0·847	0·931	1·025	1·134	
	μ	12·415	8·034	6·255	5·236	4·555	4·057	3·672	3·361	3·102	2·881	2·689	2·518	2·366	
1·00	γ	0·291	0·359	0·416	0·469	0·522	0·577	0·633	0·693	0·758	0·829	0·907	0·995	1·095	
	μ	12·583	8·174	6·380	5·352	4·664	4·161	3·772	3·458	3·197	2·974	2·780	2·608	2·455	
S/P			0·04	0·08	0·12	0·16	0·20	0·24	0·28	0·32	0·36	0·40	0·44	0·48	0·52

Table B-11 (*continued*)

$n/r = 3.00$

		1·00	0·96	0·92	0·88	0·84	0·80	0·76	0·72	0·68	0·64	0·60	0·56	P/S
0·08	γ 0·316		13·343	6·815	4·602	3·479	2·795	2·333	1·997	1·742	1·539	1·374	1·236	1·00
	μ 13·912		1·258	1·396	1·520	1·638	1·756	1·876	2·001	2·132	2·271	2·421	2·584	
0·12	γ 0·315	0·411		11·540	6·113	4·193	3·199	2·585	2·166	1·860	1·625	1·438	1·284	0·96
	μ 14·142	7·370		1·258	1·400	1·528	1·651	1·775	1·902	2·034	2·174	2·324	2·486	
0·16	γ 0·314	0·408	0·502		9·850	5·445	3·802	2·929	2·383	2·005	1·727	1·511	1·339	0·92
	μ 14·371	7·560	5·113		1·263	1·409	1·541	1·670	1·800	1·934	2·075	2·225	2·387	
0·20	γ 0·313	0·405	0·496	0·595		8·328	4·822	3·433	2·674	2·189	1·851	1·599	1·402	0·88
	μ 14·598	7·747	5·280	3·966		1·273	1·422	1·560	1·694	1·831	1·974	2·124	2·286	
0·24	γ 0·312	0·403	0·490	0·585	0·695		7·003	4·252	3·088	2·433	2·006	1·704	1·477	0·84
	μ 14·823	7·933	5·446	4·119	3·273		1·288	1·441	1·584	1·725	1·870	2·022	2·185	
0·28	γ 0·311	0·400	0·485	0·575	0·679	0·805		5·878	3·738	2·771	2·207	1·834	1·565	0·80
	μ 15·047	8·118	5·610	4·270	3·416	2·810		1·309	1·466	1·615	1·764	1·918	2·081	
0·32	γ 0·310	0·397	0·480	0·567	0·665	0·782	0·928		4·938	3·281	2·480	1·999	1·672	0·76
	μ 15·270	8·301	5·773	4·420	3·557	2·946	2·480		1·336	1·498	1·653	1·811	1·976	
0·36	γ 0·309	0·395	0·475	0·559	0·652	0·761	0·894	1·068		4·160	2·877	2·217	1·808	0·72
	μ 15·491	8·483	5·934	4·569	3·697	3·080	2·611	2·234		1·370	1·536	1·699	1·868	
0·40	γ 0·308	0·393	0·471	0·552	0·640	0·742	0·865	1·020	1·228		*3·518*	2·522	1·978	0·68
	μ 15·711	8·663	6·094	4·716	3·835	3·212	2·739	2·360	2·044		*1·411*	1·583	1·756	
0·44	γ 0·307	0·390	0·467	0·545	0·630	0·726	0·839	0·979	1·161	*1·413*		*2·989*	2·212	0·64
	μ 15·929	8·842	6·253	4·862	3·973	3·343	2·866	2·485	2·167	*1·893*		*1·460*	1·640	
0·48	γ 0·306	0·388	0·463	0·538	0·620	0·711	0·816	0·944	1·105	*1·320*	*1·630*		*2·552*	0·60
	μ 16·147	9·020	6·410	5·007	4·108	3·472	2·991	2·607	2·289	*2·015*	*1·771*		*1·518*	
0·52	γ 0·305	0·386	0·459	0·532	0·610	0·697	0·796	0·913	1·058	*1·244*	*1·500*	*1·886*		
	μ 16·363	9·197	6·567	5·150	4·243	3·601	3·114	2·727	2·407	*2·134*	*1·892*	*1·671*		
0·56	γ 0·304	0·384	0·455	0·527	0·602	0·684	0·777	0·886	1·017	1·182	*1·399*	*1·706*	*2·189*	
	μ 16·578	9·372	6·722	5·293	4·377	3·728	3·237	2·847	2·525	2·250	*2·009*	*1·792*	*1·588*	
0·60	γ 0·304	0·382	0·452	0·521	0·594	0·672	0·760	0·862	0·982	1·129	1·318	*1·572*	*1·942*	
	μ 16·792	9·547	6·877	5·435	4·510	3·854	3·358	2·964	2·640	2·364	2·124	*1·908*	*1·709*	
0·64	γ 0·303	0·380	0·449	0·516	0·586	0·661	0·745	0·840	0·951	1·084	1·250	1·466	1·764	
	μ 17·005	9·721	7·031	5·575	4·641	3·979	3·479	3·081	2·754	2·477	2·236	2·021	1·825	
0·68	γ 0·302	0·379	0·446	0·511	0·579	0·651	0·731	0·820	0·923	1·045	1·193	1·380	1·628	
	μ 17·217	9·893	7·183	5·715	4·772	4·104	3·598	3·197	2·867	2·588	2·346	2·132	1·937	
0·72	γ 0·301	0·377	0·443	0·507	0·572	0·642	0·718	0·802	0·898	1·010	1·144	1·309	1·521	
	μ 17·428	10·065	7·335	5·855	4·903	4·228	3·717	3·312	2·979	2·698	2·455	2·240	2·046	
0·76	γ 0·300	0·375	0·440	0·502	0·566	0·633	0·706	0·786	0·876	0·979	1·102	1·249	1·433	
	μ 17·638	10·236	7·486	5·993	5·032	4·350	3·834	3·425	3·090	2·807	2·562	2·347	2·153	
0·80	γ 0·300	0·373	0·437	0·498	0·560	0·625	0·694	0·770	0·855	0·952	1·064	1·197	1·360	
	μ 17·847	10·408	7·636	6·131	5·161	4·473	3·951	3·539	3·200	2·914	2·668	2·452	2·258	
0·84	γ 0·299	0·372	0·434	0·494	0·554	0·617	0·684	0·756	0·837	0·927	1·031	1·152	1·298	
	μ 18·055	10·575	7·788	6·268	5·289	4·594	4·068	3·651	3·309	3·021	2·773	2·556	2·361	
0·88	γ 0·298	0·370	0·432	0·490	0·549	0·610	0·674	0·743	0·820	0·905	1·001	1·113	1·244	
	μ 18·262	10·744	7·935	6·404	5·417	4·715	4·184	3·763	3·418	3·127	2·877	2·658	2·463	
0·92	γ 0·298	0·369	0·429	0·487	0·544	0·603	0·665	0·731	0·804	0·884	0·974	1·077	1·197	
	μ 18·468	10·912	8·083	6·540	5·543	4·835	4·299	3·874	3·525	3·232	2·981	2·760	2·564	
0·96	γ 0·297	0·367	0·427	0·483	0·539	0·596	0·656	0·720	0·789	0·865	0·950	1·046	1·156	
	μ 18·674	11·078	8·230	6·675	5·670	4·955	4·413	3·984	3·633	3·337	3·083	2·861	2·663	
1·00	γ 0·296	0·366	0·425	0·480	0·534	0·590	0·648	0·709	0·776	0·848	0·928	1·017	1·119	
	μ 18·878	11·245	8·377	6·809	5·795	5·074	4·527	4·094	3·739	3·441	3·185	2·961	2·762	
S/P	0·04	0·08	0·12	0·16	0·20	0·24	0·28	0·32	0·36	0·40	0·44	0·48	0·52	

Source: "Estimation of Parameters of the Gamma Distribution Using Order Statistics," by M. B. Wilk, R. Gnanadesikan, and Marilyn J. Huyett, *Biometrika*, Vol. 49, pp. 525–545 (1962). Reproduced by permission of the editor of *Biometrika*.

Table B-12 Percentage Points l_α Such That $P(\hat{\gamma}_1/\hat{\gamma}_2 < l_\alpha) = 1 - \alpha$

n \ $1-\alpha$	.60	.70	.75	.80	.85	.90	.95	.98
5	1.158	1.351	1.478	1.636	1.848	2.152	2.725	3.550
6	1.135	1.318	1.418	1.573	1.727	1.987	2.465	3.146
7	1.127	1.283	1.370	1.502	1.638	1.869	2.246	2.755
8	1.119	1.256	1.338	1.450	1.573	1.780	2.093	2.509
9	1.111	1.236	1.311	1.410	1.524	1.711	1.982	2.339
10	1.104	1.220	1.290	1.380	1.486	1.655	1.897	2.213
11	1.098	1.206	1.273	1.355	1.454	1.609	1.829	2.115
12	1.093	1.195	1.258	1.334	1.428	1.571	1.774	2.036
13	1.088	1.186	1.245	1.317	1.406	1.538	1.727	1.922
14	1.084	1.177	1.233	1.301	1.386	1.509	1.688	1.917
15	1.081	1.170	1.224	1.288	1.369	1.485	1.654	1.870
16	1.077	1.164	1.215	1.277	1.355	1.463	1.624	1.829
17	1.075	1.158	1.207	1.266	1.341	1.444	1.598	1.793
18	1.072	1.153	1.200	1.257	1.329	1.426	1.574	1.762
19	1.070	1.148	1.194	1.249	1.318	1.411	1.553	1.733
20	1.068	1.144	1.188	1.241	1.308	1.396	1.534	1.708
22	1.064	1.136	1.178	1.227	1.291	1.372	1.501	1.663
24	1.061	1.129	1.169	1.216	1.276	1.351	1.473	1.625
26	1.058	1.124	1.162	1.206	1.263	1.333	1.449	1.593
28	1.055	1.119	1.155	1.197	1.252	1.318	1.428	1.566
30	1.053	1.114	1.149	1.190	1.242	1.304	1.409	1.541
32	1.051	1.110	1.144	1.183	1.233	1.292	1.393	1.520
34	1.049	1.107	1.139	1.176	1.224	1.281	1.378	1.500
36	1.047	1.103	1.135	1.171	1.217	1.272	1.365	1.483
38	1.046	1.100	1.131	1.166	1.210	1.263	1.353	1.467
40	1.045	1.098	1.127	1.161	1.204	1.255	1.342	1.453
42	1.043	1.095	1.124	1.156	1.198	1.248	1.332	1.439
44	1.042	1.093	1.121	1.152	1.193	1.241	1.323	1.427
46	1.041	1.091	1.118	1.149	1.188	1.235	1.314	1.416
48	1.040	1.088	1.115	1.145	1.184	1.229	1.306	1.405
50	1.039	1.087	1.113	1.142	1.179	1.224	1.299	1.396
52	1.038	1.085	1.111	1.139	1.175	1.219	1.292	1.387
54	1.037	1.083	1.108	1.136	1.172	1.215	1.285	1.378
56	1.036	1.081	1.106	1.133	1.168	1.210	1.279	1.370
58	1.036	1.080	1.104	1.131	1.165	1.206	1.274	1.363
60	1.035	1.078	1.102	1.128	1.162	1.203	1.268	1.355
62	1.034	1.077	1.101	1.126	1.159	1.199	1.263	1.349
64	1.034	1.076	1.099	1.124	1.156	1.196	1.258	1.342
66	1.033	1.075	1.097	1.122	1.153	1.192	1.253	1.336
68	1.032	1.073	1.096	1.120	1.151	1.189	1.249	1.331
70	1.032	1.072	1.094	1.118	1.148	1.186	1.245	1.325
72	1.031	1.071	1.093	1.116	1.146	1.184	1.241	1.320
74	1.031	1.070	1.091	1.114	1.143	1.181	1.237	1.315
76	1.030	1.069	1.090	1.112	1.141	1.179	1.233	1.310
78	1.030	1.068	1.089	1.111	1.139	1.176	1.230	1.306
80	1.030	1.067	1.088	1.109	1.137	1.174	1.227	1.301
90	1.028	1.063	1.082	1.102	1.128	1.164	1.212	1.282
100	1.026	1.060	1.078	1.097	1.121	1.155	1.199	1.266
120	1.023	1.054	1.071	1.087	1.109	1.142	1.180	1.240

Source: "Two Sample Test in the Weibull Distribution," by D. R. Thoman and L. J. Bain, *Technometrics*, Vol. 11, pp. 805–815 (1969). Reproduced by permission of the editor of *Technometrics*.

Table B-13 Percentage Points z_α Such That $P(G < z_\alpha) = 1 - \alpha$

n \ $1-\alpha$	.60	.70	.75	.80	.85	.90	.95	.98
5	.228	.476	.608	.777	.960	1.226	1.670	2.242
6	.190	.397	.522	.642	.821	1.050	1.404	1.840
7	.164	.351	.461	.573	.726	.918	1.215	1.592
8	.148	.320	.415	.521	.658	.825	1.086	1.421
9	.136	.296	.383	.481	.605	.757	.992	1.294
10	.127	.277	.356	.449	.563	.704	.918	1.195
11	.120	.261	.336	.423	.528	.661	.860	1.115
12	.115	.248	.318	.401	.499	.625	.811	1.049
13	.110	.237	.303	.383	.474	.594	.770	.993
14	.106	.227	.290	.366	.453	.567	.734	.945
15	.103	.218	.279	.352	.434	.544	.704	.904
16	.099	.210	.269	.339	.417	.523	.676	.867
17	.096	.203	.260	.328	.403	.505	.654	.834
18	.094	.197	.251	.317	.389	.488	.631	.805
19	.091	.191	.244	.308	.377	.473	.611	.779
20	.089	.186	.237	.299	.366	.459	.593	.755
22	.085	.176	.225	.284	.347	.435	.561	.712
24	.082	.168	.215	.271	.330	.414	.534	.677
26	.079	.161	.206	.259	.316	.396	.510	.646
28	.076	.154	.198	.249	.303	.380	.490	.619
30	.073	.149	.191	.240	.292	.366	.472	.595
32	.071	.144	.185	.232	.282	.354	.455	.574
34	.069	.139	.179	.225	.273	.342	.441	.555
36	.067	.135	.174	.218	.265	.332	.427	.537
38	.065	.131	.169	.212	.258	.323	.415	.522
40	.064	.127	.165	.206	.251	.314	.404	.507
42	.062	.124	.160	.201	.245	.306	.394	.494
44	.061	.121	.157	.196	.239	.298	.384	.482
46	.059	.118	.153	.192	.234	.292	.376	.470
48	.058	.115	.150	.188	.229	.285	.367	.460
50	.057	.113	.147	.184	.224	.279	.360	.450
52	.056	.110	.144	.180	.220	.273	.353	.440
54	.055	.108	.141	.176	.215	.268	.346	.432
56	.054	.106	.138	.173	.212	.263	.340	.423
58	.053	.104	.136	.170	.208	.258	.334	.416
60	.052	.102	.134	.167	.204	.254	.328	.408
62	.051	.100	.131	.164	.201	.250	.323	.402
64	.050	.099	.129	.162	.198	.246	.317	.395
66	.049	.097	.127	.159	.195	.242	.313	.389
68	.049	.095	.125	.157	.192	.238	.308	.383
70	.048	.094	.123	.154	.190	.235	.304	.377
72	.047	.092	.122	.152	.187	.231	.299	.372
74	.046	.091	.120	.150	.184	.228	.295	.366
76	.046	.090	.118	.148	.182	.225	.291	.361
78	.045	.089	.117	.146	.180	.222	.288	.357
80	.045	.087	.115	.144	.178	.219	.284	.352
90	.042	.082	.109	.136	.168	.207	.268	.332
100	.040	.077	.103	.128	.160	.196	.255	.315
120	.036	.070	.094	.117	.147	.179	.233	.287

Source: "Two Sample Test in the Weibull Distribution," by D. R. Thoman and L. J. Bain, *Technometrics*, Vol. 11, pp. 805–815 (1969). Reproduced by permission of the editor of *Technometrics*.

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