and

$$q_i(t) = \frac{d}{dt} F_i(t).$$

Knowledge of the function $\rho(t)$ and the observable information, $(T, \delta)$, is sufficient to determine uniquely the marginal distribution of $X$. The resulting estimators $\hat{S}_\rho(x)$ are decreasing functions of $\rho(\cdot)$. These resulting bounds are obtained by the investigator's specification of two functions, $\rho_i(t)[\rho_1(t) < \rho_2(t)]$, so that if the true $\rho(t)$ function is in the interval $[\rho_1(t) < \rho_2(t)]$, for all $t$, then $\hat{S}\rho_2(t) \leq S(t) \leq \hat{S}\rho_1(t)$.

2. Pepe (1991) and Pepe and Mori (1993) interpret the cumulative incidence function as a "marginal probability." Note that this function is not a true marginal distribution as discussed earlier but rather is the chance that the event of interest will occur prior to time $t$ in a system where an individual is exposed to both risks. Pepe and Mori suggest as an alternative to the cumulative incidence function the "conditional probability" of $X$, defined by

$$P(\{X \leq t, X < Y\} \mid \{Y < t, X > Y\}^c) = \frac{F_i(t)}{F_i^c(t)},$$

which they interpret as the probability of $X$'s occurring in $[0, t)$, given nonoccurrence of $Y$ in $[0, t)$, where $F^c$ denotes the complement of $F$.

# 2.8 Exercises

**2.1** The lifetime of light bulbs follows an exponential distribution with a hazard rate of 0.001 failures per hour of use.

(a) Find the mean lifetime of a randomly selected light bulb.

(b) Find the median lifetime of a randomly selected light bulb.

(c) What is the probability a light bulb will still function after 2,000 hours of use?

**2.2** The time in days to development of a tumor for rats exposed to a carcinogen follows a Weibull distribution with $\alpha = 2$ and $\lambda = 0.001$.

(a) What is the probability a rat will be tumor free at 30 days? 45 days? 60 days?

(b) What is the mean time to tumor? (Hint $\Gamma(0.5) = \sqrt{\pi}$.)

(c) Find the hazard rate of the time to tumor appearance at 30 days, 45 days, and 60 days.

(d) Find the median time to tumor.

**2.3** The time to death (in days) following a kidney transplant follows a log logistic distribution with $\alpha = 1.5$ and $\lambda = 0.01$.

(a) Find the 50, 100, and 150 day survival probabilities for kidney transplantation in patients.

(b) Find the median time to death following a kidney transplant.

(c) Show that the hazard rate is initially increasing and, then, decreasing over time. Find the time at which the hazard rate changes from increasing to decreasing.

(d) Find the mean time to death.

**2.4** A model for lifetimes, with a bathtub-shaped hazard rate, is the exponential power distribution with survival function $S(x) = \exp\{1 - \exp[(\lambda x)^{\alpha}]\}$.

(a) If $\alpha = 0.5$, show that the hazard rate has a bathtub shape and find the time at which the hazard rate changes from decreasing to increasing.

(b) If $\alpha = 2$, show that the hazard rate of $x$ is monotone increasing.

**2.5** The time to death (in days) after an autologous bone marrow transplant, follows a log normal distribution with $\mu = 3.177$ and $\sigma = 2.084$. Find

(a) the mean and median times to death;

(b) the probability an individual survives 100, 200, and 300 days following a transplant; and

(c) plot the hazard rate of the time to death and interpret the shape of this function.

**2.6** The Gompertz distribution is commonly used by biologists who believe that an exponential hazard rate should occur in nature. Suppose that the time to death in months for a mouse exposed to a high dose of radiation follows a Gompertz distribution with $\theta = 0.01$ and $\alpha = 0.25$. Find

(a) the probability that a randomly chosen mouse will live at least one year,

(b) the probability that a randomly chosen mouse will die within the first six months, and

(c) the median time to death.

**2.7** The time to death, in months, for a species of rats follows a gamma distribution with $\beta = 3$ and $\lambda = 0.2$. Find

(a) the probability that a rat will survive beyond age 18 months,

(b) the probability that a rat will die in its first year of life, and

(c) the mean lifetime for this species of rats.

**2.8** The battery life of an internal pacemaker, in years, follows a Pareto distribution with $\theta = 4$ and $\lambda = 5$.

(a) What is the probability the battery will survive for at least 10 years?

(b) What is the mean time to battery failure?

(c) If the battery is scheduled to be replaced at the time $t_o$, at which 99% of all batteries have yet to fail (that is, at $t_o$ so that $Pr(X > t_o) = .99$), find $t_o$.

**2.9** The time to relapse, in months, for patients on two treatments for lung cancer is compared using the following log normal regression model:

$$Y = \text{Ln}(X) = 2 + 0.5Z + 2W,$$

where $W$ has a standard normal distribution and $Z = 1$ if treatment A and 0 if treatment B.

(a) Compare the survival probabilities of the two treatments at 1, 2, and 5 years.

(b) Repeat the calculations if $W$ has a standard logistic distribution. Compare your results with part (a).

**2.10** A model used in the construction of life tables is a piecewise, constant hazard rate model. Here the time axis is divided into $k$ intervals, $[\tau_{i-1}, \tau_i)$, $i = 1, \ldots, k$, with $\tau_o = 0$ and $\tau_k = \infty$. The hazard rate on the $i$th interval is a constant value, $\theta_i$; that is

$$h(x) = \begin{cases} \theta_1 & 0 \le x < \tau_1 \\ \theta_2 & \tau_1 \le x < \tau_2 \\ \vdots & \\ \theta_{k-1} & \tau_{k-2} \le x < \tau_{k-1} \\ \theta_k & x \ge \tau_{k-1} \end{cases}.$$

(a) Find the survival function for this model.

(b) Find the mean residual-life function.

(c) Find the median residual-life function.

**2.11** In some applications, a third parameter, called a guarantee time, is included in the models discussed in this chapter. This parameter $\phi$ is the smallest time at which a failure could occur. The survival function of the three-parameter Weibull distribution is given by

$$S(x) = \begin{cases} 1 & \text{if } x < \phi \\ \exp[-\lambda(x-\phi)^{\alpha}] & \text{if } x \ge \phi. \end{cases}$$

(a) Find the hazard rate and the density function of the three- parameter Weibull distribution.

(b) Suppose that the survival time $X$ follows a three-parameter Weibull distribution with $\alpha = 1$, $\lambda = 0.0075$ and $\phi = 100$. Find the mean and median lifetimes.

**2.12** Let $X$ have a uniform distribution on the interval 0 to $\theta$ with density function

$$f(x) = \begin{cases} 1/\theta, & \text{for } 0 \leq x \leq \theta \\ 0, & \text{otherwise.} \end{cases}$$

(a) Find the survival function of $X$.

(b) Find the hazard rate of $X$.

(c) Find the mean residual-life function.

**2.13** Suppose that $X$ has a geometric distribution with probability mass function

$$p(x) = p(1-p)^{x-1}, x = 1, 2, \ldots$$

(a) Find the survival function of $X$. (Hint: Recall that for $0 < \theta < 1$, $\sum_{j=k}^{\infty} \theta^j = \theta^k/(1-\theta)$.

(b) Find the hazard rate of $X$. Compare this rate to the hazard rate of an exponential distribution.

**2.14** Suppose that a given individual in a population has a survival time which is exponential with a hazard rate $\theta$. Each individual's hazard rate $\theta$ is potentially different and is sampled from a gamma distribution with density function

$$f(\theta) = \frac{\lambda^{\beta}\theta^{\beta-1}e^{-\lambda\theta}}{\Gamma(\beta)}$$

Let $X$ be the life length of a randomly chosen member of this population.

(a) Find the survival function of $X$.

(Hint: Find $S(x) = E_{\theta}[e^{-\theta x}]$.)

(b) Find the hazard rate of $X$. What is the shape of the hazard rate?

**2.15** Suppose that the hazard rate of $X$ is a linear function $h(x) = \alpha + \beta x$, with $\alpha$ and $\beta > 0$. Find the survival function and density function of $x$.

**2.16** Given a covariate $Z$, suppose that the log survival time $Y$ follows a linear model with a logistic error distribution, that is,

$$Y = \ln(X) = \mu + \beta Z + \sigma W \text{ where the pdf of } W \text{ is given by}$$

$$f(w) = \frac{e^w}{(1+e^w)^2}, -\infty < w < \infty.$$

(a) For an individual with covariate $Z$, find the conditional survival function of the survival time $X$, given $Z$, namely, $S(x \mid Z)$.

(b) The odds that an individual will die prior to time $x$ is expressed by $[1 - S(x \mid Z)]/S(x \mid Z)$. Compute the odds of death prior to time $x$ for this model.

(c) Consider two individuals with different covariate values. Show that, for any time $x$, the ratio of their odds of death is independent of $x$. The log logistic regression model is the only model with this property.

**2.17** Suppose that the mean residual life of a continuous survival time $X$ is given by $\text{MRL}(x) = x + 10$.

(a) Find the mean of $X$.

(b) Find $h(x)$.

(c) Find $S(x)$.

**2.18** Let $X$ have a uniform distribution on 0 to 100 days with probability density function

$$f(x) = 1/100 \text{ for } 0 < x < 100,$$
$$= 0, \text{ elsewhere}.$$

(a) Find the survival function at 25, 50, and 75 days.

(b) Find the mean residual lifetime at 25, 50, and 75 days.

(c) Find the median residual lifetime at 25, 50, and 75 days.

**2.19** Suppose that the joint survival function of the latent failure times for two competing risks, $X$ and $Y$, is

$$S(x, y) = (1 - x)(1 - y)(1 + .5xy), \quad 0 < x < 1, \quad 0 < y < 1.$$

(a) Find the marginal survival function for $x$.

(b) Find the cumulative incidence of $T_1$.

**2.20** Let $X$ and $Y$ be two competing risks with joint survival function

$$S(x, y) = \exp\{-x - y - .5xy\}, 0 < x, y.$$

(a) Find the marginal cumulative distribution function of $X$.

(b) Find the cumulative incidence function of $X$.

For right-censored data, where $\lambda_j(t) = Y_j(t)h(t)$, with $Y_j(t) = 1$ if $t \leq t_j$, 0 if $t > t_j$, so

$$L \propto \left[\prod_{j=1}^{n} h(t_j)^{\delta_j}\right] \exp\left(-\sum_{j=1}^{n} H(t_j)\right),$$

which is exactly the same form as (3.5.1). This heuristic argument is precisely stated in Chapter 2 of Andersen et al. (1993).

The counting process techniques illustrated in this section can be used to derive a wide variety of statistical techniques for censored and truncated survival data. They are particularly useful in developing nonparametric statistical methods. In particular, they are the basis of the univariate estimators of the survival function and hazard rate discussed in Chapter 4, the smoothed estimator of the hazard rate and the models for excess and relative mortality discussed in Chapter 6, most of the $k$-sample nonparametric tests discussed in Chapter 7, and the regression methods discussed in Chapters 8, 9, and 10. A check of the martingale property is used to test model assumptions for regression models, as discussed in Chapter 11. Most of the statistics developed in the sequel can be shown to be stochastic integrals of some martingale, so large sample properties of the statistics can be found by using the predictable variation process and the martingale central limit theorem. In the theoretical notes, we shall point out where these methods can be used and provide references to the theoretical development of the methods. The books by Andersen et al. (1993) or Fleming and Harrington (1991) provide a sound reference for these methods.

## 3.7 Exercises

**3.1** Describe, in detail, the types of censoring which are present in the following studies.

(a) The example dealing with remission duration in a clinical trial for acute leukemia described in section 1.2.

(b) The example studying the time to death for breast cancer patients described in section 1.5.

**3.2** A large number of disease-free individuals were enrolled in a study beginning January 1, 1970, and were followed for 30 years to assess the age at which they developed breast cancer. Individuals had clinical exams every 3 years after enrollment. For four selected individuals described below, discuss in detail, the types of censoring and truncation that are represented.

(a) A healthy individual, enrolled in the study at age 30, never developed breast cancer during the study.

(b) A healthy individual, enrolled in the study at age 40, was diagnosed with breast cancer at the fifth exam after enrollment (i.e., the disease started sometime between 12 and 15 years after enrollment).

(c) A healthy individual, enrolled in the study at age 50, died from a cause unrelated to the disease (i.e., not diagnosed with breast cancer at any time during the study) at age 61.

(d) An individual, enrolled in the study at age 42, moved away from the community at age 55 and was never diagnosed with breast cancer during the period of observation.

(e) Confining your attention to the four individuals described above, write down the likelihood for this portion of the study.

**3.3** An investigator, performing an animal study designed to evaluate the effects of vegetable and vegetable-fiber diets on mammary carcinogenesis risk, randomly assigned female Sprague-Dawley rats to five dietary groups (control diet, control diet plus vegetable mixture, 1; control diet plus vegetable mixture, 2; control diet plus vegetable-fiber mixture, 1; and control diet plus vegetable-fiber mixture, 2). Mammary tumors were induced by a single oral dose (5 mg dissolved in 1.0 ml. corn oil) of 7,12-dimethylbenz($\alpha$)anthracene (DMBA) administered by intragastric intubation, i.e., the starting point for this study is when DMBA was given.

Starting 6 weeks after DMBA administration, each rat was examined once weekly for 14 weeks (post DMBA administration) and the time (in days) until onset of the first palpable tumor was recorded. We wish to make an inference about the marginal distribution of the time until a tumor is detected. Describe, in detail, the types of censoring that are represented by the following rats.

(a) A rat who had a palpable tumor at the first examination at 6 weeks after intubation with DMBA.

(b) A rat that survived the study without having any tumors.

(c) A rat which did not have a tumor at week 12 but which had a tumor at week 13 after inturbation with DMBA.

(d) A rat which died (without tumor present and death was unrelated to the occurrence of cancer) at day 37 after intubation with DMBA.

(e) Confining our attention to the four rats described above, write down the likelihood for this portion of the study.

**3.4** In section 1.2, a clinical trial for acute leukemia is discussed. In this trial, the event of interest is the time from treatment to leukemia relapse. Using the data for the 6-MP group and assuming that the time to relapse distribution is exponential with hazard rate $\lambda$, construct the likelihood function. Using this likelihood function, find the maximum likeli-

hood estimator of $\lambda$ by finding the value of $\lambda$ which maximizes this likelihood.

**3.5** Suppose that the time to death has a log logistic distribution with parameters $\lambda$ and $\alpha$. Based on the following left-censored sample, construct the likelihood function.

DATA: 0.5, 1, 0.75, 0.25-, 1.25-, where - denotes a left- censored observation.

**3.6** The following data consists of the times to relapse and the times to death following relapse of 10 bone marrow transplant patients. In the sample patients 4 and 6 were alive in relapse at the end of the study and patients 7–10 were alive, free of relapse at the end of the study. Suppose the time to relapse had an exponential distribution with hazard rate $\lambda$ and the time to death in relapse had a Weibull distribution with parameters $\theta$ and $\alpha$.

| Patient | Relapse Time (months) | Death Time (months) |
|---|---|---|
| 1 | 5 | 11 |
| 2 | 8 | 12 |
| 3 | 12 | 15 |
| 4 | 24 | $33^+$ |
| 5 | 32 | 45 |
| 6 | 17 | $28^+$ |
| 7 | $16^+$ | $16^+$ |
| 8 | $17^+$ | $17^+$ |
| 9 | $19^+$ | $19^+$ |
| 10 | $30^+$ | $30^+$ |

$^+$ Censored observation

(a) Construct the likelihood for the relapse rate $\lambda$.

(b) Construct a likelihood for the parameters $\theta$ and $\alpha$.

(c) Suppose we were only allowed to observe a patients death time if the patient relapsed. Construct the likelihood for $\theta$ and $\alpha$ based on this truncated sample, and compare it to the results in (b).

**3.7** To estimate the distribution of the ages at which postmenopausal woman develop breast cancer, a sample of eight 50-year-old women were given yearly mammograms for a period of 10 years. At each exam, the presence or absence of a tumor was recorded. In the study, no tumors were detected by the women by self-examination between the scheduled yearly exams, so all that is known about the onset time of breast cancer is that it occurs between examinations. For four of the eight women, breast cancer was not detected during the 10 year study period. The age at onset of breast cancer for the eight subjects was in

the following intervals:

$$(55, 56], (58, 59], (52, 53], (59, 60], \geq 60, \geq 60, \geq 60, \geq 60.$$

(a) What type of censoring or truncation is represented in this sample?

(b) Assuming that the age at which breast cancer develops follows a Weibull distribution with parameters $\lambda$ and $\alpha$, construct the likelihood function.

**3.8** Suppose that the time to death $X$ has an exponential distribution with hazard rate $\lambda$ and that the right-censoring time $C$ is exponential with hazard rate $\theta$. Let $T = \min(X, C)$ and $\delta = 1$ if $X \leq C; 0,$ if $X > C$. Assume that $X$ and $C$ are independent.

(a) Find $P(\delta = 1)$

(b) Find the distribution of $T$.

(c) Show that $\delta$ and $T$ are independent.

(d) Let $(T_1, \delta_1), \ldots, (T_n, \delta_n)$ be a random sample from this model. Show that the maximum likelihood estimator of $\lambda$ is $\sum_{i=1}^{n} \delta_i / \sum_{i=1}^{n} T_i$. Use parts a–c to find the mean and variance of $\hat{\lambda}$.

**3.9** An example of a counting process is a Poisson process $N(t)$ with rate $\lambda$. Such a process is defined by the following three properties:

(a) $N(0) = 0$ with probability 1.

(b) $N(t) - N(s)$ has a Poisson distribution with parameter $\lambda(t - s)$ for any $0 \leq s \leq t$.

(c) $N(t)$ has independent increments, that is, for $0 \leq t_1 < t_2 < t_3 < t_4$, $N(t_2) - N(t_1)$ is independent of $N(t_4) - N(t_3)$.

Let $\mathbf{F}_s$ be the $\sigma$-algebra defined by $N(s)$. Define the process $M(t) = N(t) - \lambda t$.

i. Show that $E|M(t)| < \infty$.

ii. Show that $E[M(t) \mid N(s)] = M(s)$ for $s < t$, and conclude that $M(t)$ is a martingale and that $\lambda t$ is the compensator of $N(t)$. (Hint: Write $M(t) = M(t) - M(s) + M(s)$.)

$\exp\{-\int_0^t \lambda_X(u)\,du\}$. This quantity has no interpretation as a probability.

2. The cumulative incidence estimator was first proposed by Kalbfleisch and Prentice (1980). The estimator can be derived using techniques described in Andersen et al. (1993) as a special case of a more general theory for product-limit estimators for the transitions of a non-homogeneous Markov process.
3. Pepe and Mori (1993), Pepe et al. (1993), and Gooley et al. (1999) provide a nice discussion of these three estimates and present alternative derivations of the variance estimates.

## *Practical Note*

1. A SAS macro to compute the cumulative incidence curves can be found on our web site.

# 4.8 Exercises

**4.1** In section 1.11 we discussed a study of the effect of ploidy on the survival of patients with cancer of the tongue. Using the data on aneuploid tumors found in Table 1.6.

(a) Estimate the survival function at one (12 months) and five years (60 months) after transplant. Find the standard errors for your estimates.

(b) Estimate the cumulative hazard rate, $H(t)$, at 60 months. Find the standard error of $\hat{H}(t)$. Estimate $S(60)$ by $\exp\{-\hat{H}(t)\}$ and compare to your estimate in part a.

(c) Find a 95% linear confidence interval for $S(60)$.

(d) Find a 95% log-transformed confidence interval for $S(60)$.

(e) Find a 95% arcsine-square root confidence interval for $S(60)$.

(f) Using the log transformation find a 95% EP confidence band for the survival function over the range three years to six years (i.e., 36–72 months).

(g) Using the log transformation find a 95% Hall-Wellner confidence band for the survival function over the range three years to six years (i.e., 36–72 months).

(h) Estimate the mean survival time restricted to 400 months. Also provide a 95% confidence interval for the restricted mean survival time.

(i) Estimate the median time to death and find a 95% confidence interval for the median survival time based on a linear confidence interval.

**4.2** Using the data reported in section 1.3, find the quantities specified below for the AML low risk and AML high risk groups. Note that most of these quantities are worked out in detail in Example 4.2 and its continuations for the ALL group.

(a) Estimate the survival functions and their standard errors for the AML low risk and AML high risk groups.

(b) Estimate the cumulative hazard rates and their standard errors for the AML low risk and AML high risk groups.

(c) Provide a crude estimate of the hazard rates for each group based on the estimates obtained in (b).

(d) Estimate the mean time to death and find 95% confidence intervals for the mean survival time for both the AML low risk and AML high risk groups. (Answers are given in section 4.5.)

(e) Work out estimates of the median time to death and find 95% confidence intervals for the median survival time for both the AML low risk and AML high risk groups using the linear, log-transformed, and arcsine formulas. (Answers are given in section 4.5.)

(f) Find 95% confidence intervals for the survival functions at 300 days post-transplant for both the AML low risk and AML high risk groups using the log- and arcsine-transformed formulas.

(g) Find 95% EP confidence bands for the survival functions over the range 100–400 days post-transplant for both the AML low risk and AML high risk groups using the linear, log-transformed, and arcsine-transformed formulas.

(h) Find 95% HW confidence bands for the survival functions over the range 100–400 days post-transplant for both the AML low risk and AML high risk groups using the linear, log-transformed, and arcsine-transformed formulas.

(i) Based on the results above and those discussed in Example 4.2 and its continuations, how do the survival experiences of the ALL, AML low risk, and AML high risk groups compare?

**4.3** The following table contains data on the survival times of 25 patients with inoperative lung cancer entered on a study between November 1, 1979, and December 23, 1979. Complete follow-up was obtained on all patients so that the exact date of death was known. The study had one interim analysis conducted on March 31, 1980, by which time only 13 patients had died.

(a) Estimate the survival function based on the available sample information at the time of the interim analysis on 3/31/80. Provide the standard error of your estimate.

(b) Use the Brown, Hollandar, and Kowar technique (Practical Note 2 of section 4.1) to complete the right-hand tail of the product-limit estimate found in part a.

| *Patient* | *Date of Diagnosis* | *Date of Death* | *Days to death* | *Days to 3/31/80(Status)* |
|---|---|---|---|---|
| 1 | 1/11/79 | 5/30/79 | 139 | 139(Dead) |
| 2 | 1/23/79 | 1/21/80 | 363 | 363(Dead) |
| 3 | 2/15/79 | 8/27/79 | 193 | 193(Dead) |
| 4 | 3/7/79 | 11/10/79 | 248 | 248(Dead) |
| 5 | 3/12/79 | 4/8/79 | 27 | 27(Dead) |
| 6 | 3/25/79 | 10/21/79 | 210 | 210(Dead) |
| 7 | 4/4/79 | 8/16/79 | 134 | 134(Dead) |
| 8 | 4/30/79 | 11/19/79 | 203 | 203(Dead) |
| 9 | 5/16/79 | 5/9/81 | 724 | 320 (Alive) |
| 10 | 5/26/79 | 7/15/79 | 50 | 50(Dead) |
| 11 | 5/30/79 | 10/22/80 | 511 | 306(Alive) |
| 12 | 6/3/79 | 6/25/79 | 22 | 22(Dead) |
| 13 | 6/15/79 | 12/27/80 | 561 | 290(Alive) |
| 14 | 6/29/79 | 1/29/81 | 580 | 276(Alive) |
| 15 | 7/1/79 | 11/14/79 | 136 | 136(Dead) |
| 16 | 8/13/79 | 6/16/80 | 308 | 231(Alive) |
| 17 | 8/27/79 | 4/7/80 | 224 | 217(Alive) |
| 18 | 9/15/79 | 1/9/81 | 482 | 198(Alive) |
| 19 | 9/27/79 | 4/5/80 | 191 | 186(Alive) |
| 20 | 10/11/79 | 3/3/80 | 144 | 144(Dead) |
| 21 | 11/17/79 | 1/24/80 | 68 | 68(Dead) |
| 22 | 11/21/79 | 10/4/81 | 683 | 131(Alive) |
| 23 | 12/1/79 | 8/13/80 | 256 | 121(Alive) |
| 24 | 12/14/79 | 2/27/81 | 441 | 108(Alive) |
| 25 | 12/23/79 | 4/2/80 | 101 | 99(Alive) |

(c) Compute the estimate of the survival function and an estimate of its standard error using the complete follow-up on each patient. Compare this estimate to that found in part a.

(d) Estimate the mean time to death restricted to 683 days based on the product-limit estimator found in part c.

(e) Estimate the mean time to death by finding the area under the survival curve found in part c. Find the standard error of your estimate.

(f) Compute the usual estimate of the time to death based on complete follow-up data by finding the arithmetic mean of the complete follow-up data. Find the standard error of this estimate in the usual way as the sample standard deviation divided by the square root of the sample size. Compare your answers to those obtained in part e.

**4.4** In section 1.4 the times to first exit site infection (in months) of patients with renal insufficiency was reported. In the study 43 patients had a surgically placed catheter (Group 1) and 76 patients had a percutaneous placement of their catheter (Group 0).

(a) For each group plot the estimated survival function. Which technique seems better in delaying the time to infection?

(b) Estimate the cumulative hazard rate for each group of patients. Provide a crude estimate of the hazard rate at 5 months after placement of the catheter in each group.

(c) Find a 95% confidence interval for the mean time to first exit site infection restricted to 36 months for both groups.

**4.5** Using the survival times of 59 black females given a kidney transplant at the OSU transplant center discussed in section 1.7—

(a) Estimate the distribution of the time to death, measured from transplant, for black female kidney transplant patients. Provide the standard error of the estimated survival function.

(b) Find a 95% confidence interval, based on the linear transformation, for the probability a black female will survive at least 12 months (365 days) after transplantation.

(c) Repeat b using the log-transformed confidence interval.

(d) Repeat c using the arcsine-transformed confidence interval. Compare the intervals found in parts c–e.

**4.6** In section 1.6 a study is described to evaluate a protocol change in disinfectant practice in a large midwestern university medical center. Control of infection is the primary concern for the 155 patients entered into the burn unit with varying degrees of burns. The outcome variable is the time until infection from admission to the unit. Censoring variables are discharge from the hospital without an infection or death without an infection. Eighty-four patients were in the group which had chlorhexidine as the disinfectant and 72 patients received the routine disinfectant povidone-iodine.

(a) Estimate the survival (infection-free) functions and their standard errors for the chlorhexidine and povidone-iodine groups.

(b) Estimate the cumulative hazard rates and their standard errors for the chlorhexidine and povidone-iodine groups. Plot these estimates. Does it appear that the two cumulative hazard rates are proportional to each other?

(c) Provide estimates of the median time to infection and find 95% confidence intervals for the median time to infection for both the chlorhexidine and povidone-iodine groups using the linear, log-transformed, and arcsine formulas.

(d) Find 95% confidence intervals for the survival (infection-free) functions at 10 days postadmission for both the chlorhexidine and povidone-iodine groups using the log transformed and arcsine transformed formulas.

(e) Find 95% confidence bands for the infection-free functions over the range 8–20 days postinfection for both the chlorhexidine and povidone-

iodine groups using the linear, log transformed, and arcsine transformed formulas.

(f) Find 95% HW confidence bands for the infection-free functions over the range 8–20 days postinfection for both the chlorhexidine and povidone-iodine.

(g) Based on the results above, how does the infection experience of the chlorhexidine and povidone-iodine groups compare?

**4.7** Consider a hypothetical study of the mortality experience of diabetics. Thirty diabetic subjects are recruited at a clinic and followed until death or the end of the study. The subject's age at entry into the study and their age at the end of study or death are given in the table below. Of interest is estimating the survival curve for a 60- or for a 70-year-old diabetic.

(a) Since the diabetics needed to survive long enough from birth until the study began, the data is left truncated. Construct a table showing the number of subjects at risk, $Y$, as a function of age.

(b) Estimate the conditional survival function for the age of death of a diabetic patient who has survived to age 60.

(c) Estimate the conditional survival function for the age of death of a diabetic patient who has survived to age 70.

(d) Suppose an investigator incorrectly ignored the left truncation and simply treated the data as right censored. Repeat parts a–c.

| *Entry Age* | *Exit Age* | *Death Indicator* | *Entry Age* | *Exit Age* | *Death Indicator* |
|---|---|---|---|---|---|
| 58 | 60 | 1 | 67 | 70 | 1 |
| 58 | 63 | 1 | 67 | 77 | 1 |
| 59 | 69 | 0 | 67 | 69 | 1 |
| 60 | 62 | 1 | 68 | 72 | 1 |
| 60 | 65 | 1 | 69 | 79 | 0 |
| 61 | 72 | 0 | 69 | 72 | 1 |
| 61 | 69 | 0 | 69 | 70 | 1 |
| 62 | 73 | 0 | 70 | 76 | 0 |
| 62 | 66 | 1 | 70 | 71 | 1 |
| 62 | 65 | 1 | 70 | 78 | 0 |
| 63 | 68 | 1 | 71 | 79 | 0 |
| 63 | 74 | 0 | 72 | 76 | 1 |
| 64 | 71 | 1 | 72 | 73 | 1 |
| 66 | 68 | 1 | 73 | 80 | 0 |
| 66 | 69 | 1 | 73 | 74 | 1 |

**4.8** Table 1.7 reports the results of a study on the survival times of patients admitted to a psychiatric hospital. In this data set patients were admitted to the hospital at a random age and followed until death or the end of the study. Let $X$ be the patient's age at death. Note that the data we

have on $X$ is left truncated by the patient's age at entry into the hospital and right censored by the end of the study.

(a) Plot the number at risk, $Y_i$, as a function of age.

(b) Estimate the conditional survival function for a psychiatric patient who has survived to age 30 without entering a psychiatric hospital.

**4.9** Hoel and Walburg (1972) report results of an experiment to study the effects of radiation on life lengths of mice. Mice were given a dose of 300 rads of radiation at 5–6 weeks of age and followed to death. At death each mouse was necropsied to determine if the cause of death was thymic lymphoma, reticulum cell sarcoma, or another cause. The ages of the mice at death are shown below:

| *Cause of Death* | *Age at Death (Days)* |
|---|---|
| Thymic lymphoma | 158, 192, 193, 194, 195, 202, 212, 215, 229, 230, 237, 240, 244, 247, 259, 300, 301, 337, 415, 444, 485, 496, 529, 537, 624, 707, 800 |
| Reticulum cell sarcoma | 430, 590, 606, 638, 655, 679, 691, 693, 696, 747, 752, 760, 778, 821, 986 |
| Other causes | 136, 246, 255, 376, 421, 565, 616, 617, 652, 655, 658, 660, 662, 675, 681, 734, 736, 737, 757, 769, 777, 801, 807, 825, 855, 857, 864, 868, 870, 873, 882, 895, 910, 934, 942, 1,015, 1,019 |

(a) For each of the three competing risks estimate the cumulative incidence function at 200, 300, . . . , 1,000 days by considering the two other risks as a single competing risk.

(b) Show that the sum of the three cumulative incidence functions found in part a is equal to the Kaplan-Meier estimate of the overall survival function for this set of data.

(c) Repeat part a using the complement of the marginal Kaplan-Meier estimates. What are the quantities estimating and how different from the results found in part a are these estimates?

(d) Compute the conditional probability function for thymic lymphoma at 500 and 800 days. What are the quantities estimating?

**4.10** Using the data reported in section 1.3 for the AML low risk and AML high risk groups, find the following quantities for the two competing risks of relapse and death:

(a) The estimated cumulative incidence at one year.

(b) The standard errors of the two estimates in part a.

(c) The estimated conditional probabilities of relapse and of death in remission.

(d) The standard errors of the probabilities found in part c.

(e) Graphically express the development of relapse and death in remission for these two disease groups.

parisons (in our case, $K = 3$) is used to make pairwise comparisons of the cumulative incidence curves, each test needs to be carried out at the $0.05/3 = 0.017$ level of significance. The contrasts $(1, -1, 0)$, $(1, 0, -1)$, and $(0, 1, -1)$ may be used to test each of the individual pairwise comparisons. Using the appropriate variances in (7.8.5), we get

$$\text{for} \quad H_0 : CI_1(t_0) = CI_2(t_0) \text{ at } t_0 = 1$$

we have

$$Z = 2.41, \ p\text{-value} = 0.016,$$

$$\text{for} \quad H_0 : CI_1(t_0) = CI_3(t_0) \text{ at } t_0 = 1$$

we have

$$Z = -1.17, \ p\text{-value} = 0.242,$$

and

$$\text{for} \quad H_0 : CI_2(t_0) = CI_3(t_0) \text{ at } t_0 = 1$$

we have

$$Z = -3.76, \ p\text{-value} = 0.0002.$$

Thus we conclude that the AML high-risk group is statistically different from the other two groups and that the ALL and AML low-risk groups are not statistically different from each other.

## *Practical Notes*

1. One may test a hypothesis for any linear combination of several groups. For example, if one wants to test whether the cumulative incidence curves for the ALL patients are different than those for the AML (both high-risk and low-risk) patients, then one may select the linear contrast $(2, -1, -1)$ and use the quadratic form (7.8.5).

# 7.9 Exercises

**7.1** In a study of the effectiveness of a combined drug regimen for the treatment of rheumatoid arthritis, 40 white patients were followed for a period ranging from 1 to 18 years. During the course of the study, 9 patients died. The ages at entry into the study and at death for these 9 patients were as follows:

Female deaths: (66, 74), (60, 76), (70, 77), (71, 81)
Male deaths: (50, 59), (60, 66), (51, 69), (69, 71), (58, 71)

For the 31 patients still alive at the end of the study their ages at entry and last follow-up were as follows:

Female Survivors: (50, 68), (55, 72), (56, 60), (45, 55), (48, 51), (44, 55), (33, 51), (44, 50), (60, 70), (55, 60), (60, 72), (77, 80), (70, 75), (66, 70), (59, 63), (62, 63)
Male Survivors: (53, 68), (55, 62), (56, 63), (45, 51), (48, 61), (49, 55), (43, 51), (44, 54), (61, 70), (45, 60), (63, 72), (74, 80), (70, 76), (66, 72), (54, 70)

Using the all-cause U.S. mortality table for 1989 (Table 2.1) test the hypothesis that the death rate of these rheumatoid arthritis patients is not different from that in the general population using the log-rank test.

**7.2** In Exercise 5 of Chapter 6, the survival experience of patients given an autologous transplant was compared to a postulated exponential survival rate with a hazard rate of 0.045. Using the data in Table 1.4 of Chapter 1, test the hypothesis that the hazard rate of these auto transplant patients is equal to 0.045 against the alternative that it is larger than 0.045 using the one-sample, log-rank test. Repeat this test using a weight function which gives heavier weight to departures early in time from this hazard rate.

**7.3** Consider the data reported in section 1.6 on the times until staphylococcus infection of burn patients (see our web page).

(a) Using the log-rank test, test the hypothesis of no difference in the rate of staphylococcus infection between patients whose burns were cared for with a routine bathing care method versus those whose body cleansing was initially performed using 4% chlorhexidine gluconate. Use a two-sided test and a 0.05 significance level.

(b) Repeat the test using Gehan's test.

(c) Repeat the test using the Tarone and Ware weights.

**7.4** In section 1.11, data from a study of the effect of ploidy on survival for patients with tumors of the tongue was reported.

(a) Test the hypothesis that the survival rates of patients with cancer of the tongue are the same for patients with aneuploid and diploid tumors using the log-rank test.

(b) If primary interest is in detecting differences in survival rates between the two types of cancers which occur soon after the diagnosis of the cancer, repeat part a using a more appropriate test statistic.

**7.5** Using the data on laryngeal cancers in Example 7.6, test, by the log-rank statistic, the null hypothesis of no difference in death rates among the four stages of cancer against the global alternative that at least one of the death rates differs from the others. Compare your results to those found in Example 7.6.

**7.6** One of the goals of recent research is to explore the efficacy of triple-drug combinations of antiretroviral therapy for treatment of HIV-infected patients. Because of limitations on potency and the continuing emergence of drug resistance seen with the use of currently available antiretroviral agents in monotherapy and two-drug regimens, triple-combination regimens should represent a more promising approach to maximize antiviral activity, maintain long-term efficacy, and reduce the incidence of drug resistance. Towards this end, investigators performed a randomized study comparing AZT + zalcitabine (ddC) versus AZT + zalcitabine (ddC) + saquinavir. The data, time from administration of treatment (in days) until the CD4 count reached a prespecified level, is given below for the two groups.

AZT + zalcitabine (ddC): 85, 32, 38+, 45, 4+, 84, 49, 180+, 87, 75, 102, 39, 12, 11, 80, 35, 6
AZT + zalcitabine (ddC) + saquinavir: 22, 2, 48, 85, 160, 238, 56+, 94+, 51+, 12, 171, 80, 180, 4, 90, 180+, 3

Use the log rank statistic to test if there is a difference in the distribution of the times at which patient's CD4 reaches the prespecified level for the two treatments.

**7.7** A study was performed to determine the efficacy of boron neutron capture therapy (BNCT) in treating the therapeutically refractory F98 glioma, using boronophenylalanine (BPA) as the capture agent. F98 glioma cells were implanted into the brains of rats. Three groups of rats were studied. One group went untreated, another was treated only with radiation, and the third group received radiation plus an appropriate concentration of BPA. The data for the three groups lists the death times (in days) and is given below:

| *Untreated* | *Radiated* | Radiated + BPA |
|---|---|---|
| 20 | 26 | 31 |
| 21 | 28 | 32 |
| 23 | 29 | 34 |
| 24 | 29 | 35 |
| 24 | 30 | 36 |
| 26 | 30 | 38 |
| 26 | 31 | 38 |
| 27 | 31 | 39 |
| 28 | 32 | $42^+$ |
| 30 | $35^+$ | $42^+$ |

$^+$Censored observation

(a) Compare the survival curves for the three groups.

(b) Perform pairwise tests to determine if there is any difference in survival between pairs of groups.

(c) There is a priori evidence that, if there is a difference in survival, there should be a natural ordering, namely, untreated animals will have the worst survival, radiated rats will have slightly improved survival, and the radiated rats + BPA should have the best survival. Perform the test for trend which would test this ordered hypothesis.

**7.8** In Example 7.4, we compared the disease-free survival rates of ALL patients with those of high-risk and low risk AML patients. Because acute graft-versus-host (aGVHD) disease is considered to have an antileukemic effect, one would expect lower relapse rates for patients who have developed aGVHD than for those that do not develop aGVHD. Using the data on out web page, examine the validity of this finding by

(a) testing if the hazard rate for the occurrence of aGVHD is the same for the three groups,

(b) testing if the hazard rate for relapse is the same in all three groups, and

(c) testing if the hazard rate for relapse in the three disease groups is the same for patients who have developed aGVHD. (Hint: For this test, the data is left-truncated at the time of aGVHD).

**7.9** On our web page, data is reported on the death times of 863 kidney transplant patients (see section 1.7). Here, patients can be classified by race and sex into one of four groups.

(a) Test the hypothesis that there is no difference in survival between the four groups.

(b) Provide individual tests, for each sex, of the hypothesis of no racial differences in survival rates. Also, adjusting by stratification for the sex of the patient, test the hypothesis that blacks have a higher mortality rate than whites.

**7.10** In Example 7.6 we found that the four populations of cancer patients had ordered hazard rates. Of interest is knowing which pairs of the hazard rates are different. Using the log-rank test, perform the three pairwise tests of the hypothesis $H_{0j} : h_j(t) = h_{j+1}(t)$ versus $H_{Aj} : h_j(t) < h_{j+1}(t)$, for $j = 1, 2, 3$. For each test, use only those individuals with stage $j$ or $j+1$ of the disease. Make an adjustment to your critical value for multiple testing to give an approximate 0.05 level test.

One method to making the pairwise comparisons is to base the pairwise tests on the full $\mathbf{Z}(\tau)$ vector. To perform this test, recall that this vector has an asymptotic $K$ variate normal distribution with mean 0 and covariance matrix $\hat{\Sigma}$ under the null hypothesis. Thus, the statistic $Z_j(\tau) - Z_{j+1}(\tau)$ has a normal distribution with mean 0 and variance $\hat{\sigma}_{jj} + \hat{\sigma}_{j+1j+1} - 2\hat{\sigma}_{jj+1}$ when the null hypothesis is true. Large negative values of this test statistic will suggest that the hazard rate in

sample $j$ is smaller than in sample $j+1$, so the hypothesis $H_{0j}: h_j(t) = h_{j+1}(t)$ is rejected in favor of $H_{Aj}: h_j(t) < h_{j+1}(t)$ when $[Z_j(\tau) - Z_{j+1}(\tau)]/[\hat{\sigma}_{jj} + \hat{\sigma}_{j+1j+1} - 2\hat{\sigma}_{jj+1}]^{1/2}$ is smaller than the $\alpha$th lower percentile of a standard normal. Use the information in Example 7.6 and this statistic to make the multiple comparisons.

**7.11** The data on laryngeal cancer patients was collected over the period 1970–1978. It is possible that the therapy used to treat laryngeal cancer may have changed over this nine year period. To adjust for this possible confounding fact, test the hypothesis of no difference in survival between patients with different stages of disease against a global alternative using a test which stratifies on the cancer being diagnosed prior to 1975 or not. Also perform a separate test of the hypothesis of interest in each stratum.

**7.12** (a) Repeat Exercise 3 using the log-rank version of the Renyi statistic.

(b) Repeat Exercise 4 using the Gehan version of the Renyi statistic.

**7.13** In Table 1.3 of section 1.5, the data on time to death for breast cancer-patients who where classed as lymph node negative by standard light microscopy (SLM) or by immunohistochemical (IH) examination of their lymph nodes is reported. Test the hypothesis that there is no difference in survival between theses two groups using

(a) the log-rank test,

(b) the Renyi statistic based on the log-rank test,

(c) the Cramer-von Mises statistic, and

(d) the weighted difference in the Kaplan–Meier statistic $W_{\mathrm{KM}}$.

**7.14** Repeat Exercise 7 using

(a) the Renyi statistic based on the log-rank test,

(b) the Cramer-von Mises statistic, and

(c) the weighted difference in the Kaplan–Meier statistic $W_{\mathrm{KM}}$.

**7.15** Using the data of section 1.3,

(a) compare the three survival functions for ALL, AML low-risk, and AML high-risk at one year;

(b) perform pairwise multiple comparisons for the three groups employing the Bonferroni correction for multiple tests.

5. As was the case for confidence intervals for the survival function discussed in Chapter 4, Andersen and Klein (1996) show that the log-transformed confidence interval for $S(t \mid \mathbf{Z}_0)$ seems to work best, and the arcsine-square-root confidence interval is a close second. The routine use of the linear confidence interval is not recommended.
6. Based on an extensive Monte Carlo study by Andersen and Klein (1996), it can be shown that the estimators $S_2$ and $S_4$ have the smallest bias and are recommended. The estimator $S_3$, available in SAS, seems to perform quite poorly for continuous and mixed, continuous covariate models.

# 8.9 Exercises

**8.1** In section 1.10, times to death or relapse (in days) are given for 23 non-Hodgkin's lymphoma (NHL) patients, 11 receiving an allogenic (Allo) transplant from an HLA-matched sibling donor and 12 patients receiving an autologous (Auto) transplant. Also, data on 20 Hodgkin's lymphoma (HOD) patients, 5 receiving an allogenic (Allo) transplant from an HLA-matched sibling donor and 15 patients receiving an autologous (Auto) transplant is given.

(a) Treating NHL Allo as the baseline hazard function, state the appropriate coding which would allow the investigator to test for any difference in survival functions for the four groups, treating them as four independent groups.

(b) Treating NHL Allo as the baseline hazard function, state the appropriate coding which would allow the investigator to test for an interaction between type of transplant and disease type using main effects and interaction terms.

(c) Suppose that we have the following model for the hazard rates in the four groups:

$$h(t \mid \text{NHL Allo}) = h_0(t)$$
$$h(t \mid \text{HOD Allo}) = h_0(t)\exp(2)$$
$$h(t \mid \text{NHL Auto}) = h_0(t)\exp(1.5)$$
$$h(t \mid \text{HOD Auto}) = h_0(t)\exp(.5)$$

What are the risk coefficients, $\beta_i$, $i = 1, 2, 3$, for the interaction model in part *b*?

**8.2** In section 1.6 a study is described which evaluates a protocol change in disinfectant practices in a large midwestern university medical center. Of primary interest in the study is a comparison of two methods of

body cleansing. The first method, used exclusively from January 1983 to June 1984, consisted of a routine bathing care method (initial surface decontamination with 10% povidone-iodine followed with regular bathing with Dial soap). From June 1984 to the end of the study period in December 1985, body cleansing was initially performed using 4% chlorhexidine gluconate. Eighty-four patients were in the group who received the new bathing solution, chlorhexidine, and 70 patients served as the control group who received routine bathing care, povidone-iodine. Included in the data set is a covariate that measures the total surface area burned. The data is reported on our web site.

State the appropriate coding which would allow the investigator to test for:

(a) any difference in survival functions for the two groups.

(b) any difference in survival functions for the two groups adjusting for total area burned.

**8.3** In section 1.11, a study was conducted on the effects of ploidy on the prognosis of patients with cancer of the tongue. Tissue samples were examined to determine if the tumor had a aneuploid or diploid DNA profile. Times to death for these two groups of patients are recorded in Table 1.6. To analyze this data create a single indicator variable, $Z$, which reflects the type of tumor.

(a) Find the $p$-value of a test of the hypothesis of no effect of ploidy on survival using the score test and the Breslow method of handling ties.

(b) Estimate $\beta$ and its standard error using the Breslow method of handling ties. Find a 95% confidence interval for the relative risk of death of an individual with an aneuploid tumor as compared to an individual with a diploid tumor.

(c) Repeat (a) using the likelihood test. Compare your answer to that of part a.

(d) Repeat (a) using the Wald test. Compare your answer to those in parts a and c.

**8.4** In Exercise 7 of Chapter 7, three different treatments were administered to rats who had F98 glioma cells implanted into their brains. The data for the three groups of rats lists the death times (in days) in that exercise. Create two dummy variables, $Z_1 = 1$ if animal is in the "radiation only" group, 0 otherwise; $Z_2 = 1$ if animal is in the "radiation plus BPA" group, 0 otherwise. Use the Breslow method of handling ties in the problems below.

(a) Estimate $\beta_1$ and $\beta_2$ and their respective standard errors. Find a 95% confidence interval for the relative risk of death of an animal radiated only compared to an untreated animal.

(b) Test the global hypothesis of no effect of either radiation or radiation plus BPA on survival. Perform the test using all the three tests (Wald, likelihood ratio, and score test).

(c) Test the hypothesis that the effect a radiated only animal has on survival is the same as the effect of radiation plus BPA (i.e., Test $H_0 : \beta_1 = \beta_2$).

(d) Find an estimate and a 95% confidence interval for the relative risk of death for a radiation plus BPA animal as compared to a radiated only animal.

(e) Test the hypothesis that any radiation given as a treatment (either radiation alone or with BPA) has a different effect on survival than no radiation. Use the likelihood ratio test.

(f) Repeat part (e) using a Wald test.

**8.5** Using the data set in Exercise 1, using the Breslow method of handling ties,

(a) Analyze the data by performing a global test of no effect of group as defined in Exercise 8.1(a) on survival. Construct an ANOVA table to summarize estimates of the risk coefficients and the results of the one degree of freedom tests for each covariate in the model.

(b) Repeat part (a) using the coding as described in Exercise 8.1(b). Furthermore, test the hypothesis of disease type by transplant interaction using a likelihood ratio rest based on this coding. Repeat using the Wald test.

(c) Find point estimates and 95% confidence intervals for the relative risk of death for an NHL Auto transplant patient as compared to an NHL Allo transplant patient.

(d) Find the $p$-value of a test of the hypothesis that the hazard rates are the same for HOD Allo transplants and NHL Allo patients, using the Wald test. Repeat a similar test for Auto patients.

(e) Test the hypothesis, using the Wald test, that the hazard rates for Auto transplant and Allo transplant patients are the same for each disease group against the alternative that the hazard rates for Auto transplant and Allo transplant patients for at least one group are different using a two-degree of freedom test of $H_0 : h(t \mid \text{NHL Allo}) = h(t \mid \text{NHL Auto})$ *and* $H_0 : h(t \mid \text{HOD Allo}) = h(t \mid \text{HOD Auto})$.

**8.6** In section 1.13, data on the time to hospitalization of pneumonia in young children was discussed. The data is presented on our web site. In the sample there were 3,470 annual personal interviews. An investigator is interested in assessing race, poverty status, and their interaction on time to hospitalization of pneumonia. Use the discrete method for handling ties to answer the following questions.

(a) Estimate the parameters of your model and their standard errors. Construct and interpret an "ANOVA" table for this model.

(b) Provide point estimates and 95% confidence intervals for the relative risk of hospitalization for pneumonia for a person raised in poverty relative to a person not raised in poverty for each race.

(c) Test that blacks raised in poverty have a different hospitalization for pneumonia rate than whites not raised in poverty.

**8.7** In section 1.6 a study is described which evaluates the relationship of various covariates to staphylococcus infection in a large midwestern university medical center (see Exercise 8.2). One of the covariates recorded in the data set is the total surface area burned. Use Breslow's method for handing ties to answer the following questions.

(a) Find the optimal cutpoint to categorize patients into high- or low-risk groups for staphylococcus infection based on their total surface area burned for each disinfectant practice.

(b) Test the hypothesis that there is a difference in times to infection for high- and low-risk groups using the cutpoints obtained in (a). Using the cut points obtained in (a) find the relative risk of the high-risk group compared to the low-risk group for each disinfectant practice.

(c) Analyze the data using total surface area burned as a continuous variable. Give the parameter estimate, standard error, and relative risk for total surface area burned. Compare with the answer in (b).

**8.8** In section 1.3, data gathered from a multicenter trial of patients in three groups (ALL, AML low-risk, and AML high-risk) was followed after transplantation until relapse, death, or end of study. One of the covariates recorded in the data set is the waiting time to transplant (in days). Use Breslow's method for handling ties in the following.

(a) You are asked to categorize patients into high- or low-risk groups for disease-free survival based on the waiting time to transplant variable for the ALL group.

(b) Analyze the data using waiting time to transplant as a categorized variable using the cut point obtained in (a). Give the parameter estimate, standard error, and relative risk of the high-risk group compared to the low-risk group for the ALL group.

(c) Analyze the data using waiting time to transplant as a continuous variable. Give the parameter estimate, standard error, and relative risk for waiting time to transplant for the ALL group. Compare with answer in (b).

**8.9** Use the Breslow method for handling ties and the Wald test in the following.

(a) Using the data set in section 1.6, test the hypothesis that the distributions of the times to staphylococcus infection are the same in the two disinfectant groups.

(b) Test the hypothesis that the distributions of the times to staphylococcus infection are the same in the two disinfectant groups adjust-

ing for the total area burned, $Z_4$. Compare your results to those in part a.

(c) Also available in the data set is information on other factors that may be associated with the timing of staphylococcus infection. Some of these factors are gender, race, total surface area burned, and type of burn (chemical, scald, electrical, flame). For each factor create a set of fixed-time covariates. Test the hypothesis that the times to staphylococcus infection are the same for the two disinfectant groups using a model which adjusts for each of these factors.

(d) Since one is primarily interested in comparing the two bathing solutions, interest will center upon building a model with the view of testing that particular comparison adjusting for the other noncontrollable factors in part (c). Using a forward selection approach, build such a model using the $p$-value approach. Based on the final model, test the hypothesis of primary interest.

**8.10** In section 1.3, several event times are described for patients receiving a bone marrow transplant for leukemia. Consider the time to development of acute graft-versus-host disease (AGVHD). As a prophylactic treatment, patients at two of the hospitals were given a treatment combining methotrexate (MTX) with cyclosporine and possibly methylprednisilone. Patients at the other hospitals were not given methotrexate but rather a combination of cyclosporine and methylprednisilone. Of primary interest in studying AGVHD is a test of the effectiveness of the MTX regime to prevent AGVHD. Use Breslow's method for handling ties to answer the following exercises.

(a) Using an appropriate Cox model test the hypothesis of no difference in the rate of development of AGVHD between MTX and no MTX patients. Find a point estimate and a 95% confidence interval for the relative risk of AGVHD for patients on the MTX protocol as compared to those not given MTX.

(b) Patients were also grouped into risk categories based on their status at the time of transplantation. These categories were as follows: acute lymphoblastic leukemia (ALL) with 38 patients and acute myeloctic leukemia (AML). The latter category was further subdivided into low-risk—first remission (54 patients) and high-risk—second remission or untreated first relapse or second or greater relapse or never in remission (45 patients). Test the hypothesis of interest (no effect of MTX on development of AGVHD) adjusting for the three disease categories.

(c) Test for the possibility of an interaction effect on AGVHD between the disease categories and the use MTX.

(d) Using the factors of age, sex, CMV status, FAB class, waiting time to transplant, and disease category as defined in Example 8.5, find the best model to test the primary hypothesis of no MTX effect on

the occurrence of AGVHD. Test the primary hypothesis and find an estimate of the relative risk of occurrence of AGVHD for an MTX patient as compared to a non-MTX patient.

**8.11** In section 1.13, data gathered from annual personal interviews conducted for the National Longitudinal Survey of Youth (NLSY) from 1979 through 1986 was presented. This data was used to study whether or not the mother's feeding choice protected the infant against hospitalized pneumonia in the first year of life. Ages of young children at the time they were hospitalized with pneumonia were recorded as well as the observed ages of those infants that were not hospitalized with pneumonia during the study period. The data is available from our web site, which can be reached via the authors' pages at http://www.springer-ny.com. Use the discrete method for handling ties in the following.

(a) Consider the dummy variable $Z = 1$ if infants were breast fed at birth, 0 if infants were never breast fed, and test the hypothesis $H_0 : \beta = 0$, i.e., the survival functions for the two types of breast feeding are equal, using the score, likelihood ratio, and Wald tests. Find the estimate of $\beta$, $b$, the standard error of $b$, and the relative risk using the Wald test.

(b) Also available in the data set is information on other factors that may be associated with the timing of hospitalized pneumonia. These factors are age of the mother at the infant's birth, rural-urban environment of the mother, use of alcohol by the mother (no drinks, less than one drink, 1–2 drinks, 3–4 drinks, or more than 4 drinks per month), mother's cigarette use (none, less than 1 pack/day, 1 or more pack/day), region of country (northeast, north central, south, or west), birthweight of infant (less the 5.5 lbs or 5.5 lbs or more), poverty status of mother (yes/no), race of mother (white, black, or other), or number of siblings of infant. For each factor create a set of fixed-time covariates. Test the hypothesis that the times to hospitalized pneumonia are the same for the two feeding groups adjusting for each of these factors in a separate model using the Wald test.

(c) Since one is primarily interested in comparing the two types of breast feeding, interest will center upon building a model with the view of testing the particular comparison of interest adjusting for the other noncontrollable fixed covariates in part b. Build such a model using the AIC approach and the Wald test.

(d) Summarize your findings from this data set.

**8.12** A major problem in certain sub-populations is the occurrence of sexually transmitted diseases (STD). Even if one ignores the lethal effects of the acquired immune deficiency syndrome, other STD's still have a significant impact on the morbidity of the community. Two of these STD's are the focus of this investigation—gonorrhea and chlamydia. Both of

these diseases can be prevented and effectively treated. The purpose of the study described in section 1.12 is to identify those factors which are related to time until reinfection by either gonorrhea or chlamydia given a patient with an initial infection of gonorrhea or chlamydia. The data for this study is available from our web site.

Possible factors related to reinfection are the individual's race (black/white), marital status (divorced/separated, married, single), age at time of initial infection, years of schooling, initial infection type (gonorrhea, chlamydia, both), number of partners within the last 30 days, oral sex within the last year, rectal sex within the past year, presence of symptoms (abdominal pain, discharge, dysuria, itch, lesion, rash, lymph node involvement), and condom use. If the factors that are related to a greater risk of reinfection can be identified, then interventions could be targeted to those individuals who are at greatest risk for reinfection. Use regression techniques to find those factors which are most predictive of the distribution of the time until reinfection from this list of fixed explanatory factors with no particular prior hypothesis in mind. Build such a model using the $p$-value approach. Use the Breslow method for handling ties and the Wald test in the model building.

**8.13** Find 95% confidence intervals for the survival functions for the two bathing solutions at 20 days for a patient with 25% of total surface area of body burned, using data in Section 1.6.

**8.14** (a) Estimate the survival functions of the time to AGVHD for the MTX and no MTX treatment groups discussed in Exercise 8.10, adjusted for disease category. Provide a separate estimate for each disease group.

(b) Find 95% confidence intervals for the survival functions for the two patient treatment groups at 80 days for AML high-risk patients.

where $\bar{\mathbf{Z}}_{(j)}(T_j)$ is the vector $\bar{\mathbf{Z}}(t)$ defined by (11.4.3), with the $j$th observation omitted. Simplifying this expression yields

$$(\mathbf{b} - \mathbf{b}_{(j)}) = \mathbf{I}^{-1}(\boldsymbol{\beta}_o)\{\delta_j[\mathbf{Z}_j - \bar{\mathbf{Z}}(T_j)]\} - \Sigma[\mathbf{Z}_j - \bar{\mathbf{Z}}_{(j)}(T_b)]\exp[\mathbf{b}^t\mathbf{Z}_j(t)][\hat{H}_o(T_b) - \hat{H}_o(T_{b-1})],$$

which is approximately equal to the standardized score residual $\boldsymbol{\Delta}$.

The approximation is based on an assumption that deletion of the $j$th observation does not change the value of $\mathbf{I}^{-1}(\boldsymbol{\beta}_o)$ and that $\bar{\mathbf{Z}}_{(j)}$ is close to $\bar{\mathbf{Z}}$. Storer and Crowley (1985) give an alternate approximation based on the one-step application of the Newton-Raphson approximation to the estimate of $\boldsymbol{\beta}$ which attempts to remedy the first problem. In most cases, these approximations are very close to the score residuals suggested here.

## 11.7 Exercises

**11.1** In Example 8.2, a proportional hazards model was fit to the data on the death times of 90 males diagnosed with cancer of the larynx (see section 1.8). A model with three covariates for stage of disease was considered.

(a) Determine if adding the patient's age into the model is appropriate using a martingale residual plot based on a Cox model adjusted for disease stage. If age should not enter the model as a linear term suggest a functional form for age.

(b) Repeat part a for the covariate year of transplant.

(c) Fit a model with the factor stage of disease and a linear term for age. Perform a general examination of this model using a Cox–Snell residual.

**11.2** In section 1.14 a study of the times to weaning of breast-fed newborns was presented. This data is available on our web site. Categorical variables which could explain the difference in weaning times are the mother's race (white, black, other), smoking status, and an indicator of whether the mother was in poverty. Continuous variables which could explain outcome are the mother's age at the child's birth, mother's years of education, and the child's year of birth. Using a Cox model with appropriate terms for the mother's race, smoking status, and poverty indicator, determine if each of the three continuous covariates would enter the model as a linear function.

**11.3** In section 1.8 data on the death times of patients diagnosed with cancer of the larynx was presented (see Example 8.2 and Exercise 11.1). Using

this data in a model which adjusts for age, examine the proportional hazards assumption for the stage of disease by the following graphical methods.

(a) A plot of the logarithms of the cumulative baseline hazard rates for each disease stage.

(b) A plot of the difference in the log cumulative hazard rates for the disease stages.

(c) An Andersen plot.

(d) A score residual plot.

**11.4** In Exercise 1 of Chapter 8 a Cox model was fit to data on the survival times of patients with an aneuploid or diploid DNA tumor profile.

(a) Check the proportional hazards assumption for this data by plotting the logarithms of the cumulative baseline hazard rates for each ploidy group.

(b) Check for proportional hazards by plotting the difference in the log cumulative hazard rates for the two groups.

(c) Check for proportional hazards by using an Andersen plot.

(d) Check for proportional hazards by using a score residual plot.

**11.5** In Example 8.3 and its continuation in section 8.4 a proportional hazards model was fit to the data on the time to death of 863 kidney transplant patients. (The data is presented on our web site.) Covariates in the model were gender, race, and a gender by race interaction.

(a) Check this data for possible outliers by making an appropriate plot of the deviance residuals.

(b) For each of the three covariates in this model find the four most influential observations on the estimates of the regression coefficients. Explain why these observations are so influential.

**11.6** (a) For the data on survival times of patients with an aneuploid or diploid DNA tumor profile in Exercise 4 determine which, if any, observations are outliers by making an appropriate deviance residual plot.

(b) Find the three points that have the greatest influence on the estimate of the regression effect by constructing a plot of the adjusted score residuals. Explain why these three points are so influential in light of your fitted regression model.

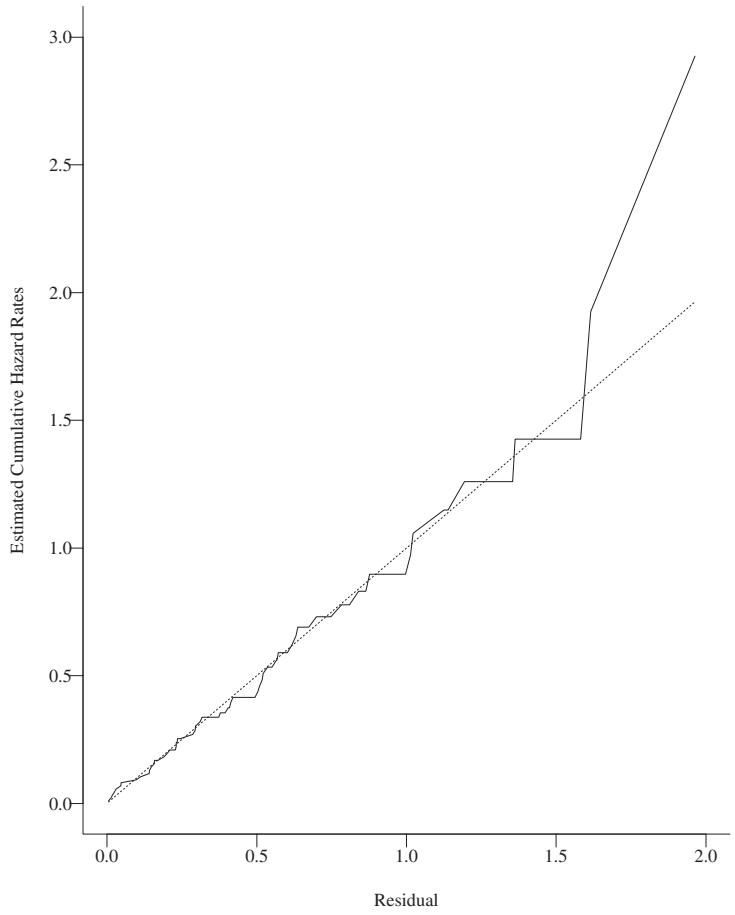


**Figure 12.9** *Cox–Snell residuals to assess the fit of the log normal regression model for the laryngeal cancer data set*

and for $\beta$,

$$\frac{\partial \ln L_j}{\partial \beta} = \delta_j Z_j - \lambda Z_j \exp(\beta Z_j) T_j^{\alpha}.$$

These residuals can be used, as in section 11.6, to examine the influence of a given observation on the estimates. See Collett (1994) for additional detail. These residuals are available in S-Plus.

# 12.6 Exercises

**12.1** In section 1.11, a study of the effects of ploidy on survival for patients with cancer of the tongue was described. In the study patients were classified as having either an aneuploid or diploid DNA profile. The data is presented in Table 1.6.

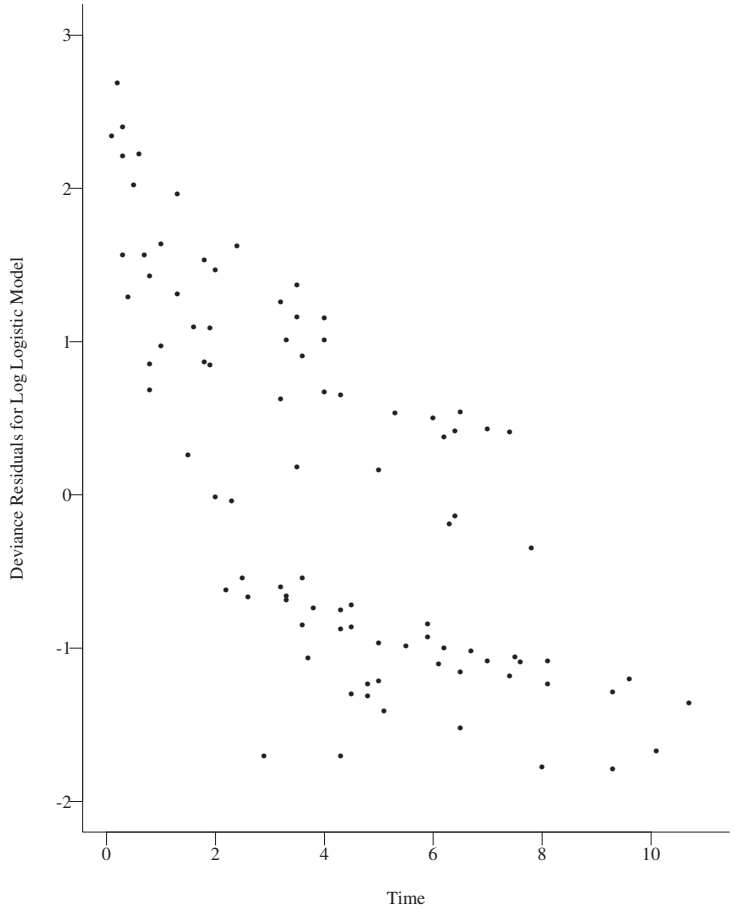


**Figure 12.10** *Deviance residuals from the log logistic regression model for laryngeal cancer patients*

(a) For both the aneuploid and diploid groups fit a Weibull model to the data. Find the maximum likelihood estimates of $\lambda$ and $\alpha$, and their standard errors.

(b) For both groups, test the hypothesis that the shape parameter, $\alpha$, is equal to 1 by both the Wald and likelihood ratio tests.

(c) Find the maximum likelihood estimates of the median survival for both groups. Use the delta method to find an estimate of the standard error of your estimates.

(d) Fit a Weibull regression model to this data with a single covariate, $Z$, that is equal to 1 if the patient had an aneuploid DNA profile and 0 otherwise. Test the hypothesis of no effect of ploidy on survival using the likelihood ratio test and the Wald test. Find a point estimate and 95% confidence interval for the relative risk of death for an aneuploid tumor as compared to a diploid tumor. Also find a point estimate and a 95% confidence for the acceleration factor. Provide an interpretation of this factor.

**12.2** In section 1.4 the times to first exit-site infection (in months) of patients with renal insufficiency were reported. In the study 43 patients had a surgically placed catheter (Group 1) and 76 patients had a percutaneous placement of their catheter (Group 0).

(a) For both groups fit a Weibull model to the data. Find the maximum likelihood estimates of $\lambda$ and $\alpha$, and their standard errors.

(b) For both groups test the hypothesis that the shape parameter, $\alpha$, is equal to 1 using the likelihood ratio test and the Wald test.

(c) Find the maximum likelihood estimates and 95% confidence intervals for the two survival functions at 5 months after placement of the catheter. Compare these estimates to those obtained using the product-limit estimator.

(d) Fit a Weibull regression model to this data with a single covariate, $Z$, that indicates group membership. Test the hypothesis of no effect of catheter placement on the time to exit site infection. Find point estimates and 95% confidence intervals for the relative risk and the acceleration factor for exit site infections. Provide an interpretation of these quantities.

**12.3** In section 1.10, times to death or relapse (in days) are given for 23 non-Hodgkin's lymphoma (NHL) patients, 11 receiving an allogeneic (Allo) transplant from an HLA-matched sibling donor and 12 patients receiving an autologous (Auto) transplant. Also, data is given in Table 1.5 on 20 Hodgkin's lymphoma (HOD) patients, 5 receiving an allogeneic (Allo) transplant from an HLA-matched sibling donor and 15 patients receiving an autologous (Auto) transplant. Because there is a potential for different efficacy of the two types of transplants for the two types of lymphoma, a model with a main effect for type of transplant, a main effect for disease type and an interactive term is of interest (coding similar to 8.1b).

(a) Using a Weibull regression model, analyze this data by performing a likelihood ratio global test of no effect of transplant type and disease state on survival. Construct an ANOVA table to summarize estimates of the risk coefficients and the results of the one degree of freedom tests for each covariate in the model.

(b) Test the hypothesis of no disease–transplant type interaction using a likelihood ratio test.

(c) Find point estimates and 95% confidence intervals for the relative risk of death for an NHL Auto transplant patient as compared to an NHL Allo transplant patient.

(d) Test the hypothesis that the death rates are the same for HOD Allo transplants and NHL Allo patients. Repeat this test for Auto patients.

(e) Test the hypothesis that the death rates for Auto transplant and Allo transplant patients are the same against the alternative they are different for at least one disease group by a 2 degree of freedom test

of $H_o$ : $h(t \mid \text{NHL Allo}) = h(t \mid \text{NHL Auto})$ *and* $h(t \mid \text{HOD Allo}) = h(t \mid \text{HOD Auto})$.

(f) Compare your results to those found in Exercise 3 of Chapter 8 by using the semiparametric proportional hazards model.

**12.4** Repeat Exercise 2 using the log logistic model. In part b use the Wald test and in part d provide point and interval estimates of the acceleration factor and the relative odds. Compare your results to those found in Exercise 2.

**12.5** Repeat Exercise 1 using the log logistic model. In part b use the Wald test and in part d provide point and interval estimates of the acceleration factor and the relative odds. Compare your results to those found in that exercise.

**12.6** Repeat Exercise 3 using the log logistic model. Compare your results to those found in that exercise. Estimate relative odds rather than relative risks in part c.

**12.7** Using the ploidy data in Exercise 1, estimate the parameters and the variance-covariance matrix for the following models for each of the two groups.

(a) A log normal model.

(b) A normal model.

(c) A generalized gamma model.

(d) Using the results of part c, test the hypothesis that $\theta = 0$. Interpret your result in terms of model selection.

(e) Using the results of part c, test the hypothesis that $\theta = 1$. Interpret your result in terms of model selection.

(f) Based on your results in this exercise and in Exercises 1 and 5, which parametric model best fits the data for each of the two ploidy groups?

**12.8** Using the information in Exercise 2, determine the best fitting parametric regression model to determine the effects of catheter placement on the time to first exit site infection by fitting the exponential, log normal, and generalized gamma models.

**12.9** For both the aneuploid and diploid groups in Exercise 1, make an appropriate hazard plot to determine if the following models fit the data:

(a) exponential,

(b) Weibull,

(c) log normal, and

(d) log logistic.

**12.10** For both catheter placement groups in Exercise 2, make an appropriate hazard plot to determine if the following models fit the data:

(a) exponential,

(b) Weibull,

(c) log normal, and

(d) log logistic.

**12.11** Check the adequacy of the accelerated failure time model for describing the effects of ploidy on survival in Exercise 1 by making a quantile-quantile plot. Provide a crude estimate of the acceleration factor and compare it to the estimate you found in Exercise 1.

**12.12** Check the adequacy of the accelerated failure time model for describing the effects of catheter placement on the time to first exit site infection in Exercise 2 by making a quantile-quantile plot. Provide a crude estimate of the acceleration factor and compare it to the estimate you found in Exercise 2.

**12.13** In Exercise 1, you fit a Weibull regression model to explain the effect of ploidy on survival.

(a) Examine the fit of this model by making the appropriate plot of the Cox–Snell residuals.

(b) Examine the fit of this model by making the appropriate plot of the deviance residuals residuals.

(c) Repeat a and b for the log logistic regression model.

**12.14** In Exercise 3 a Weibull regression model was fit to the survival times of patients given a bone marrow transplant. The model included a covariate for type of transplant, type of disease as well as an interaction term.

(a) Examine the fit of this model by making the appropriate plot of the Cox–Snell residuals.

(b) Examine the fit of this model by making the appropriate plot of the deviance residuals residuals.

(c) Repeat a and b for the log logistic regression model.