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.

12 Inference for Parametric Regression Models

12.1 Introduction

In previous chapters, we focused on nonparametric methods for describing the survival experience of a population and regression models for survival data which do not require any specific distributional assumptions about the shape of the survival function. In this chapter, we shall discuss the use of parametric models for estimating univariate survival and for the censored-data regression problem. When these parametric models provide a good fit to data, they tend to give more precise estimates of the quantities of interest because these estimates are based on fewer parameters. Of course, if the parametric model is chosen incorrectly, it may lead to consistent estimators of the wrong quantity.

All of the models we shall consider in this chapter have an *accelerated failure-time model* representation and a *linear model* representation in log time. Let X denote the time to the event and $\mathbf{Z}$ a vector of fixed-time explanatory covariates. The accelerated failure-time model states that the survival function of an individual with covariate $\mathbf{Z}$ at time x is the same as the survival function of an individual with a baseline survival function at a time $x\exp(\boldsymbol{\theta}'\mathbf{Z})$, where $\boldsymbol{\theta}' = (\theta_1, \ldots, \theta_p)$ is a vector of regression coefficients. In other words, the accelerated failure-time

model is defined by the relationship

$$S(x \mid \mathbf{Z}) = S_0[\exp(\boldsymbol{\theta}'\mathbf{Z})x], \text{ for all } x. \tag{12.1.1}$$

The factor $\exp(\boldsymbol{\theta}'\mathbf{Z})$ is called an *acceleration factor* telling the investigator how a change in covariate values changes the time scale from the baseline time scale. One implication of this model is that the hazard rate for an individual with covariate $\mathbf{Z}$ is related to a baseline hazard rate by

$$h(x \mid \mathbf{Z}) = \exp(\boldsymbol{\theta}'\mathbf{Z})h_0[\exp(\boldsymbol{\theta}'\mathbf{Z})x], \text{ for all } x. \tag{12.1.2}$$

A second implication is that the median time to the event with a covariate $\mathbf{Z}$ is the baseline median time to event divided by the acceleration factor.

The second representation of the relationship between covariate values and survival is the linear relationship between log time and the covariate values. Here, we assume the usual linear model for log time, namely,

$$Y = \ln X = \mu + \boldsymbol{\gamma}'\mathbf{Z} + \sigma W, \tag{12.1.3}$$

where $\boldsymbol{\gamma}' = (\gamma_1, \ldots, \gamma_p)$ is a vector of regression coefficients and W is the error distribution. The regression coefficients have an interpretation similar to those in standard normal theory regression.

The two representations are closely related. If we let $S_0(x)$ be the survival function of the random variable $\exp(\mu + \sigma W)$, then, the linear log-time model is equivalent to the accelerated failure-time model with $\boldsymbol{\theta} = -\boldsymbol{\gamma}$.

A variety of models can be used for W or, equivalently, for S_0 (see Table 2.2). In section 12.2, we focus on estimation for the Weibull distribution for which W has a standard extreme value distribution. This model is very flexible because it has a hazard rate that can be either increasing, decreasing, or constant. It has the unique property that, along with the accelerated failure-time representation, it is the only parametric distribution that also has a proportional hazards representation.

In section 12.3, we focus on the log logistic distribution for which W has a standard logistic distribution. This model has a hazard rate that is hump-shaped (see Chapter 2). This model is the only accelerated failure-time model that also has a representation as a *proportional odds* model, that is, for the log logistic distribution, the odds of survival beyond time t are given by

$$\frac{S(x \mid \mathbf{Z})}{1 - S(x \mid \mathbf{Z})} = \exp(\boldsymbol{\beta}'\mathbf{Z})\frac{S_0(x)}{1 - S_0(x)}, \tag{12.1.4}$$

where $\boldsymbol{\beta} = -\boldsymbol{\gamma}/\sigma$.

In section 12.4, we will examine several other models popular for survival data. These include the log normal distribution and the generalized gamma distribution which can be used to discriminate between models.

In these sections, maximum likelihood estimation of the parameters is presented for each of these parametric models. The parameters of the log-time, linear model are estimated first and their variance-covariance matrix, readily available in most major software packages, is reported. From these values, the maximum likelihood estimates of functions of the parameters, along with their approximate variance-covariance matrix, may be obtained using the method of statistical differentials, also called the delta method.

In section 12.5, graphical methods for assessing the fit of these models are presented. For univariate problems, we use the hazard rates displayed in Table 2.2 and the Nelson–Aalen estimator of the cumulative hazard rate, to make hazard plots for each parametric model. A *hazard plot* is a plot of the appropriate function of the cumulative hazard function as the ordinate versus the appropriate function of time as the abscissa. Each distribution will have its own functions of the cumulative hazard and time. Such plots should be straight lines if the model is correct.

To assess the fit of regression models, we present analogs of the Cox–Snell, martingale and deviance residuals presented in Chapter 11. A quantile-quantile plot is also presented for checking that the accelerated failure-time model fits a set of data.

12.2 Weibull Distribution

The Weibull distribution, discussed in Chapter 2, is a very flexible model for lifetime data. It has a hazard rate which is either monotone increasing, decreasing, or constant. It is the only parametric regression model which has both a proportional hazards representation and an accelerated failure-time representation. In this section, we shall first examine estimating the parameters of the Weibull distribution in the univariate setting and, then, examine the regression problem for this model.

The survival function for the Weibull distribution is given by

$$S_X(x) = \exp(-\lambda x^{\alpha}),$$

and the hazard rate is expressed by

$$h_X(x) = \lambda\alpha x^{\alpha-1}.$$

Taking the log transform of time, the univariate survival function for $Y = \ln X$ is given by

$$S_Y(y) = \exp(-\lambda e^{\alpha y}).$$

If we redefine the parameters as $\lambda = \exp(-\mu/\sigma)$ and $\sigma = 1/\alpha$, then, Y follows the form of a log linear model with

$$Y = \ln X = \mu + \sigma W, \tag{12.2.1}$$

where W is the extreme value distribution with probability density function,

$$f_W(w) = \exp(w - e^w) \tag{12.2.2}$$

and survival function,

$$S_W(w) = \exp(-e^w). \tag{12.2.3}$$

Thus, the underlying probability density function and survival function, respectively, for Y, are

$$f_Y(y) = (1/\sigma)\exp[(y-\mu)/\sigma - e^{[(y-\mu)/\sigma]}] \tag{12.2.4}$$

and

$$S_Y(y) = \exp(-e^{[(y-\mu)/\sigma]}). \tag{12.2.5}$$

When $\alpha = 1$, or, equivalently, $\sigma = 1$, then, the Weibull distribution reduces to an exponential distribution.

The likelihood function for right-censored data, following the construction in Chapter 3, is given by

$$L = \prod_{j=1}^{n}[f_Y(y_j)]^{\delta_j}[S_Y(y_j)]^{(1-\delta_j)}$$

$$= \prod_{j=1}^{n}\left[\frac{1}{\sigma}f_W\left(\frac{y_j-\mu}{\sigma}\right)\right]^{\delta_j}\left[S_w\left(\frac{y_j-\mu}{\sigma}\right)\right]^{(1-\delta_j)}$$

where $f_Y(y)$ and $S_Y(y)$ are given in (12.2.4) and (12.2.5). Once maximum likelihood estimates of the parameters μ and σ, or equivalently, λ and α are computed (see Practical Note 1), estimates of the survival function and the cumulative hazard rate are available for the distribution of X or Y.

Estimates of μ and σ are found numerically, and routines to do so are available in most statistical packages. The variance-covariance matrix of the log linear parameters μ and σ, obtained from the observed information matrix, are also available in these packages. The invariance property of the maximum likelihood estimator provides that the maximum likelihood estimators of λ and α are given by

$$\hat{\lambda} = \exp(-\hat{\mu}/\hat{\sigma}) \text{ and } \hat{\alpha} = 1/\hat{\sigma}. \tag{12.2.6}$$

Applying the delta method (see Theoretical Notes),

$$\mathrm{Var}(\hat{\lambda}) = \exp(-2\hat{\mu}/\hat{\sigma})[\mathrm{Var}(\hat{\mu})/\hat{\sigma}^2 + \hat{\mu}^2\mathrm{Var}(\hat{\sigma})/\hat{\sigma}^4 - 2\hat{\mu}\,\mathrm{Cov}(\hat{\mu},\hat{\sigma})/\hat{\sigma}^3], \tag{12.2.7}$$

$$\mathrm{Var}(\hat{\alpha}) = \mathrm{Var}(\hat{\sigma})/\hat{\sigma}^4, \tag{12.2.8}$$

and

$$\mathrm{Cov}(\hat{\lambda},\hat{\alpha}) = \exp(-\hat{\mu}/\hat{\sigma})[\mathrm{Cov}(\hat{\mu},\hat{\sigma})/\hat{\sigma}^3 - \hat{\mu}\,\mathrm{Var}(\hat{\sigma})/\hat{\sigma}^4]. \tag{12.2.9}$$

EXAMPLE 12.1 Consider the data set described in section 1.9 and studied in Chapters 7 and 11. It compares the efficacy of autologous (auto) versus allogeneic (allo) transplants for acute myelogenous leukemia. The outcome for the 101 patients was leukemia-free survival. All patients in the sample were in their first complete remission at least one year.

The Weibull maximum likelihood estimates of the log linear parameters μ and σ are $\hat{\mu}_{\text{auto}} = 3.45$, $\hat{\sigma}_{\text{auto}} = 1.11$, $\hat{\mu}_{\text{allo}} = 4.25$, and $\hat{\sigma}_{\text{allo}} = 1.94$. The corresponding maximum likelihood estimates of the parameters $\lambda = \exp(-\mu/\sigma)$ and $\alpha = 1/\sigma$ are $\hat{\lambda}_{\text{auto}} = 0.045$, $\hat{\alpha}_{\text{auto}} = 0.900$, $\hat{\lambda}_{\text{allo}} = 0.112$, and $\hat{\alpha}_{\text{allo}} = 0.514$, respectively. The variance-covariance matrix for $\hat{\mu}_{\text{auto}}$ and $\hat{\sigma}_{\text{auto}}$ is

$$\begin{pmatrix} 0.048 & 0.010 \\ 0.010 & 0.031 \end{pmatrix},$$

and the variance-covariance matrix for $\hat{\mu}_{\text{allo}}$ and $\hat{\sigma}_{\text{allo}}$ is

$$\begin{pmatrix} 0.229 & 0.088 \\ 0.088 & 0.135 \end{pmatrix}.$$

Applying (12.2.7)–(12.2.9), the variance-covariance matrix for $\hat{\lambda}_{\text{auto}}$ and $\hat{\alpha}_{\text{auto}}$ is

$$\begin{pmatrix} 0.0004 & -0.00202 \\ -0.00202 & 0.0202 \end{pmatrix}$$

and the variance-covariance matrix for $\hat{\lambda}_{\text{allo}}$ and $\hat{\alpha}_{\text{allo}}$ is

$$\begin{pmatrix} 0.0016 & -0.0032 \\ -0.0032 & 0.0095 \end{pmatrix}.$$

To test the hypothesis that the exponential model provides as good a fit to the data as the Weibull model, we shall test the hypothesis that $\sigma = 1$ (or equivalently that $\alpha = 1$). Although any of the three types of likelihood-based tests can be performed, only the likelihood ratio and score tests are invariant under the different parameterizations. We shall perform the likelihood ratio tests. For the allo transplant data, the log likelihood for the Weibull model is -72.879 whereas for the exponential model it is -81.203. For the auto transplant data, the log likelihood for the Weibull model is -68.420 whereas, for the exponential model, it is -68.653. The likelihood ratio chi square for the allo transplant data is $2[72.879 - (-81.203)] = 16.648$ which is highly significant when compared to a chi-square percentile with one degree of freedom. For auto transplants, the likelihood ratio chi square is 0.467, which is not significant. This suggests that an exponential distribution may provide as good a fit as the Weibull distribution for auto transplants, but it is not a viable model for allo transplants.

To incorporate covariates into the Weibull model, we use a linear model (12.1.3) for log time,

$$Y = \mu + \boldsymbol{\gamma}'\mathbf{z} + \sigma W, \tag{12.2.10}$$

where W has the standard extreme value distribution (12.2.2). This model leads to a proportional hazards model for X with a Weibull baseline hazard, that is,

$$h(x \mid \mathbf{Z}) = (\alpha\lambda x^{\alpha-1})\exp(\boldsymbol{\beta}'\mathbf{Z}), \tag{12.2.11}$$

with $\alpha = 1/\sigma$, $\lambda = \exp(-\mu/\sigma)$ and $\beta_j = -\gamma_j/\sigma$, $j = 1, \ldots, p$.

Using the accelerated failure-time representation of the Weibull regression model, the hazard rate for an individual with covariate vector $\mathbf{Z}$ is given by

$$h(x \mid \mathbf{z}) = \exp(\boldsymbol{\theta}'\mathbf{Z})h_0[x\exp(\boldsymbol{\theta}'\mathbf{Z})] \tag{12.2.12}$$

where the baseline hazard, $h_0(x)$ is $\lambda\alpha x^{\alpha-1}$. The factor $\exp(\boldsymbol{\theta}'\mathbf{Z})$ is called an acceleration factor. If the covariate vector is a scalar which is the indicator of treatment group ($Z = 1$ if group 1; $Z = 0$ if group 2], the acceleration factor can be interpreted naturally. Under the accelerated failure model, the survival functions between the two groups will have the following relationship:

$$S(x \mid Z = 1) = S(xe^{\theta} \mid Z = 0), \text{ for all } t.$$

For an accelerated failure time distribution with covariate $\mathbf{Z}$

$$S(x \mid \mathbf{Z}) = S_0(x\exp[\boldsymbol{\theta}'\mathbf{Z}]) \quad \text{for all } x$$

by (12.1.1). Let X_m^0 be the median of the baseline distribution. Then $S_0(X_m^0) = 1/2$. Now let X_m^z be the median, with $Z = z$, which has $S_0(X_m^z \mid z) = S_0(X_m^z\exp[\theta z]) = 1/2$ by (12.1.1). This implies that $X_m^z\exp[\theta z] = X_m^0$ or $X_m^z = X_m^0/\exp[\theta z]$. So the median of a group with $Z = z$ is the baseline median divided by $\exp[\theta z]$. This implies that the median time in the $Z = 1$ group is equal to the median time in the $Z = 0$ group divided by e^{θ}. Comparing 12.2.11 and 12.2.12, we see that $\boldsymbol{\theta} = \boldsymbol{\beta}/\alpha$ or $\boldsymbol{\theta} = -\boldsymbol{\gamma}$. The Weibull is the only continuous distribution that yields both a proportional hazards and an accelerated failure-time model.

For the Weibull regression model, estimates must be found numerically. Routines for estimation, based on (12.2.10), are found in most statistical packages. As before, the invariance property of the maximum likelihood estimators in the log linear model provides estimates of parameters in the alternative formulation (12.2.11). Using the delta method, the following is the approximate covariance matrix for these estimates based on the estimates and their covariances in the log linear model:

$$\text{Cov}(\hat{\beta}_j, \hat{\beta}_k) = \frac{\text{Cov}(\hat{\gamma}_j, \hat{\gamma}_k)}{\hat{\sigma}^2} - \frac{\hat{\gamma}_j\,\text{Cov}(\hat{\gamma}_j, \hat{\sigma})}{\hat{\sigma}^3} - \frac{\hat{\gamma}_k\,\text{Cov}(\hat{\gamma}_k, \hat{\sigma})}{\hat{\sigma}^3} + \frac{\hat{\gamma}_j\hat{\gamma}_k\,\text{Var}(\hat{\sigma})}{\hat{\sigma}^4}, \quad j, k = 1, \ldots, p; \tag{12.2.13}$$

$$\text{Var}(\hat{\lambda}) = \exp\left(-2\frac{\hat{\mu}}{\hat{\sigma}}\right)\left[\frac{\text{Var}(\hat{\mu})}{\hat{\sigma}^2} - 2\frac{\hat{\mu}\,\text{Cov}(\hat{\mu}, \hat{\sigma})}{\hat{\sigma}^3} + \frac{\hat{\mu}^2\,\text{Var}(\hat{\sigma})}{\hat{\sigma}^4}\right] \tag{12.2.14}$$

$$\text{Var}(\hat{\alpha}) = \frac{\text{Var}(\hat{\sigma})}{\hat{\sigma}^4} \tag{12.2.15}$$

$$\text{Cov}(\hat{\beta}_j, \hat{\lambda}) = \exp\left(-\frac{\hat{\mu}}{\hat{\sigma}}\right)\left[\frac{\text{Cov}(\hat{\gamma}_j, \hat{\mu})}{\hat{\sigma}^2} - \frac{\hat{\gamma}_j\,\text{Cov}(\hat{\gamma}_j, \hat{\sigma})}{\hat{\sigma}^3} - \frac{\hat{\mu}\,\text{Cov}(\hat{\mu}, \hat{\sigma})}{\hat{\sigma}^3} + \frac{\hat{\gamma}_j\hat{\mu}\,\text{Var}(\hat{\sigma})}{\hat{\sigma}^4}\right], \quad j = 1;, \ldots, p; \tag{12.2.16}$$

$$\text{Cov}(\hat{\beta}_j, \hat{\alpha}) = \frac{\text{Cov}[\hat{\gamma}_j, \hat{\sigma}]}{\hat{\sigma}^3} - \frac{\hat{\gamma}_j\,\text{Var}[\hat{\sigma}]}{\hat{\sigma}^4} \quad j = 1, \ldots, p; \tag{12.2.17}$$

$$\text{Cov}(\hat{\lambda}, \hat{\alpha}) = \exp\left(-\frac{\hat{\mu}}{\hat{\sigma}}\right)\left[\frac{\text{Cov}(\hat{\mu}, \hat{\sigma})}{\hat{\sigma}^3} - \frac{\hat{\mu}\,\text{Var}(\hat{\sigma})}{\hat{\sigma}^4}\right]. \tag{12.2.18}$$

We shall illustrate this model on the data for times to death from laryngeal cancer.

EXAMPLE 12.2 A study of 90 males diagnosed with cancer of the larynx is described in section 1.8 and analyzed in Chapters 7 and 8. Here, we shall employ the accelerated failure-time model using the main effects of age and stage for this data. The model is given by

$$Y = \ln X = \mu + \gamma_1 Z_1 + \gamma_2 Z_2 + \gamma_3 Z_3 + \gamma_4 Z_4 + \sigma W$$

where Z_i, $i = 1, \ldots, 3$ are the indicators of stage II, III and IV disease, respectively, and Z_4 is the age of the patient. The parameter estimates, standard errors, Wald chi squares, and p-values for testing that $\gamma_i = 0$ are given in Table 12.1. Here, we see that patients with stage IV disease do significantly worse than patients with stage I disease. Note that, as opposed to the Cox model where a positive value of the risk coefficient reflects poor survival, here, a negative value of the coefficient is indicative of decreased survival.

We apply the transformation in (12.2.11)–(12.2.18) on the original time scale and obtain the parameter estimates in Table 12.2. Using these estimates and the proportional hazards property of the Weibull regression model, we find that the relative risk of death for a Stage IV patient compared to a Stage I patient is $\exp(1.745) = 5.73$. The acceleration factor for Stage IV disease compared to Stage I disease is $\exp(1.54) = 4.68$, so that the median lifetime for a Stage I patient is estimated to be 4.68 times that of a Stage IV patient.

TABLE 12.1
Analysis of Variance Table for Stage and Age for Laryngeal Cancer Patients, Utilizing the Log Linear Model, Assuming the Weibull Distribution

Variable	*Parameter Estimate*	*Standard Error*	*Wald Chi Square*	*p-Value*
Intercept $\hat{\mu}$	3.53	0.90		
Scale $\hat{\sigma}$	0.88	0.11		
Z_1: Stage II ($\hat{\gamma}_1$)	−0.15	0.41	0.13	0.717
Z_2: Stage III ($\hat{\gamma}_2$)	−0.59	0.32	3.36	0.067
Z_3: Stage IV ($\hat{\gamma}_3$)	−1.54	0.36	18.07	<0.0001
Z_4: Age ($\hat{\gamma}_4$)	−0.02	0.01	1.87	0.172

TABLE 12.2
Parameter Estimates for the Effects of Stage and Age on Survival for Laryngeal Cancer Patients, Modeling Time Directly Assuming the Weibull Distribution

Variable	*Parameter Estimate*	*Standard Error*
Intercept $\hat{\lambda}$	0.002	0.002
Scale $\hat{\alpha}$	1.13	0.14
Z_1: Stage II ($\hat{\beta}_1$)	0.17	0.46
Z_2: Stage III ($\hat{\beta}_2$)	0.66	0.36
Z_3: Stage IV ($\hat{\beta}_3$)	1.75	0.42
Z_4: Age ($\hat{\beta}_4$)	0.02	0.01

Practical Notes

1. SAS PROC LIFEREG and the S-Plus routine survreg provide maximum likelihood estimates of an intercept μ and scale parameter σ associated with the extreme value distribution, the error distribution for the Weibull model. Our parameters of the underlying Weibull distribution are the following functions of these extreme value parameters, $\lambda = \exp(-\mu/\sigma)$ and $\alpha = 1/\sigma$. SAS allows for right-, left- and interval-censored data.
2. When performing an accelerated failure time regression employing the Weibull distribution, SAS and S-Plus provide maximum likelihood estimates of an intercept μ, scale parameter σ, and regression coefficients γ_i. The parameters of the underlying Weibull distribution, when modeling time directly, are the following functions of those parameters: $\lambda = \exp(-\mu/\sigma)$, $\alpha = 1/\sigma$, and $\beta_i = -\gamma_i/\sigma$. SAS allows for right-, left- and interval-censored data.

Theoretical Notes

1. The method of statistical differentials or the delta method (Elandt–Johnson and Johnson, 1980, pp. 69–72) is based on a Taylor series expansion of a continuous function $g(.)$ of the maximum likelihood estimators of a vector of parameters. We shall illustrate how this works in the two-parameter case. Let ψ_1 and ψ_2 be the two parameters of interest, and let $\hat{\psi}_1$ and $\hat{\psi}_2$ be the maximum likelihood estimators of the parameters. Recall that, for large samples, $(\hat{\psi}_1, \hat{\psi}_2)$ has a bivariate normal distribution with mean (ψ_1, ψ_2) and a covariance matrix estimated by the inverse of the observed Fisher information observed. Let $\theta_1 = g_1(\psi_1, \psi_2)$ and $\theta_2 = g_2(\psi_1, \psi_2)$ be a reparametrization of ψ_1 and ψ_2. The invariance principle of the maximum likelihood estimator insures that the maximum likelihood estimators of θ_1 and θ_2 are $g_k(\hat{\psi}_1, \hat{\psi}_2)$, $k = 1, 2$.

   To apply the delta method, for $k = 1, 2$, we expand $g_k(\hat{\psi}_1, \hat{\psi}_2)$ in a first-order Taylor series about the true values of ψ_1 and ψ_2, that is,

$$g_k(\hat{\psi}_1, \hat{\psi}_2) = g_k(\psi_1, \psi_2) + (\hat{\psi}_1 - \psi_1)\frac{\partial g_k(\hat{\psi}_1, \hat{\psi}_2)}{\partial \hat{\psi}_1} + (\hat{\psi}_2 - \psi_2)\frac{\partial g_k(\hat{\psi}_1, \hat{\psi}_2)}{\partial \hat{\psi}_2}$$

   where the partial derivatives are evaluated at the true values of the parameters. Thus,

$$g_k(\hat{\psi}_1, \hat{\psi}_2) - g_k(\psi_1, \psi_2) = (\hat{\psi}_1 - \psi_1)\frac{\partial g_k(\hat{\psi}_1, \hat{\psi}_2)}{\partial \hat{\psi}_1} + (\hat{\psi}_2 - \psi_2)\frac{\partial g_k(\hat{\psi}_1, \hat{\psi}_2)}{\partial \hat{\psi}_2}$$

   If we let $g_k^b = \frac{\partial g_k(\hat{\psi}_1, \hat{\psi}_2)}{\partial \hat{\psi}_b}$, then, for large samples,

$$\begin{aligned}\mathrm{Cov}[g_k(\hat{\psi}_1, \hat{\psi}_2), g_m(\hat{\psi}_1, \hat{\psi}_2)] &= E\{g_k^1 g_m^1(\hat{\psi}_1 - \psi_1)^2 + [g_k^1 g_m^2 + g_k^2 g_m^1] \\ &\quad \cdot (\hat{\psi}_1 - \psi_1)(\hat{\psi}_2 - \psi_2) + g_k^2 g_m^2(\hat{\psi}_2 - \psi_2)^2\} \\ &= g_k^1 g_m^1 \mathrm{Var}[\hat{\psi}_1] + [g_k^1 g_m^2 + g_k^2 g_m^1]\mathrm{Cov}[\hat{\psi}_1, \hat{\psi}_2] \\ &\quad + g_k^2 g_m^2 \mathrm{Var}[\hat{\psi}_2], \quad k, m = 1, 2.\end{aligned}$$

12.3 Log Logistic Distribution

An alternative model to the Weibull distribution is the log logistic distribution. This distribution has a hazard rate which is hump-shaped, that is, it increases initially and, then, decreases. It has a survival function and hazard rate that has a closed form expression, as contrasted with the log normal distribution which also has a hump-shaped hazard rate.

Utilizing the notation which models time directly, as in Chapter 2, the univariate survival function and the cumulative hazard rate for X, when X follows the log logistic distribution, are given by

$$S_X(x) = \frac{1}{1 + \lambda x^\alpha} \tag{12.3.1}$$

and

$$H_X(x) = \ln(1 + \lambda x^\alpha). \tag{12.3.2}$$

Taking the log transform of time, the univariate survival function for $Y = \ln X$ is

$$S_Y(y) = \frac{1}{1 + \lambda e^{\alpha y}} \tag{12.3.3}$$

This log linear model with no covariates is, from (12.1.1),

$$Y = \ln X = \mu + \sigma W, \tag{12.3.4}$$

where W is the standard logistic distribution with probability density function,

$$f_W(w) = e^w/(1 + e^w)^2 \tag{12.3.5}$$

and survival function,

$$S_W(w) = 1/(1 + e^w) \tag{12.3.6}$$

Thus, the underlying probability density function and survival function, respectively, for Y, are given by

$$f_Y(y) = (1/\sigma)\exp[(y - \mu)/\sigma]/[1 + \exp[(y - \mu)/\sigma]^2 \tag{12.3.7}$$

and

$$S_Y(y) = 1/[1 + e^{[(y-\mu)/\sigma)}]. \tag{12.3.8}$$

Thus, one can see that the parameters of the underlying log logistic distribution for the random variable X in (12.3.1) and for the distribution of the log transformed variable Y in (12.3.3) are the following functions of the log linear parameters in (12.3.8):

$$\alpha = 1/\sigma \text{ and } \lambda = \exp(-\mu/\sigma), \tag{12.3.9}$$

the same functions as for the Weibull model (see (12.2.6)). Thus, given estimates of μ and α, estimates of λ and α and their covariance matrix are given by (12.2.6)–(12.2.9). Estimates of μ and σ are available in most statistical packages.

EXAMPLE 12.1 *(continued):* We shall continue the example on univariate estimation for the autologous (auto) versus allogeneic (allo) transplants for acute myelogenous leukemia.

The log logistic maximum likelihood estimates of the log linear parameters μ and σ are $\hat{\mu}_{\text{auto}} = 2.944$, $\hat{\sigma}_{\text{auto}} = 0.854$, $\hat{\mu}_{\text{allo}} = 3.443$, and $\hat{\sigma}_{\text{allo}} = 1.584$, and the corresponding maximum likelihood estimates of the parameters $\lambda = \exp(-\mu/\sigma)$ and $\alpha = 1/\sigma$ are $\hat{\lambda}_{\text{auto}} = 0.032$, $\hat{\alpha}_{\text{auto}} = 1.171$, $\hat{\lambda}_{\text{allo}} = 0.114$, and $\hat{\alpha}_{\text{allo}} = 0.631$, respectively. The variance-covariance matrix for $\hat{\mu}_{\text{auto}}$ and $\hat{\sigma}_{\text{auto}}$ is

$$\begin{pmatrix} 0.0531 & 0.0085 \\ 0.0085 & 0.019 \end{pmatrix},$$

and the variance-covariance matrix for $\hat{\mu}_{\text{allo}}$ and $\hat{\sigma}_{\text{allo}}$ is

$$\begin{pmatrix} 0.2266 & 0.0581 \\ 0.0581 & 0.0855 \end{pmatrix}.$$

Inserting the maximum likelihood estimates $(\hat{\mu}, \hat{\sigma})$ and their estimated variances into (12.2.7)–(12.2.9), the variance-covariance matrix for $\hat{\lambda}_{\text{auto}}$ and $\hat{\alpha}_{\text{auto}}$ is

$$\begin{pmatrix} 3.010 \times 10^{-4} & -2.861 \times 10^{-3} \\ -2.681 \times 10^{-3} & 3.518 \times 10^{-3} \end{pmatrix}$$

and the variance-covariance matrix for $\hat{\lambda}_{\text{allo}}$ and $\hat{\alpha}_{\text{allo}}$ is

$$\begin{pmatrix} 1.951 \times 10^{-3} & -3.661 \times 10^{-3} \\ -3.661 \times 10^{-3} & 1.360 \times 10^{-2} \end{pmatrix}.$$

One of three equivalent models can be used to model the effects of covariates on survival with the log logistic distribution. The first is the linear model for log time with

$$Y = \ln X = \mu + \boldsymbol{\gamma}^t \mathbf{Z} + \sigma W, \tag{12.3.10}$$

where W has the standard logistic distribution (12.3.5). The second representation is obtained by replacing λ in (12.3.3) by $\exp(\boldsymbol{\beta}^t \mathbf{Z})$. Here, the conditional survival function for the time to the event is given by

$$S_X(x \mid \mathbf{Z}) = \frac{1}{1 + \lambda \exp(\boldsymbol{\beta}^t \mathbf{Z}) x^\alpha}. \tag{12.3.11}$$

As for the Weibull distribution, the parameters are related by

$$\boldsymbol{\beta} = -\boldsymbol{\gamma}/\sigma, \tag{12.3.12}$$

$$\lambda = \exp[-\mu/\sigma],$$

and

$$\alpha = 1/\sigma.$$

Based on maximum likelihood estimates for $\mu, \boldsymbol{\gamma}, \sigma$, and their covariance matrix, estimates for $\lambda, \boldsymbol{\beta}, \alpha$, and their covariance are obtained from Eqs. (12.2.13)–(12.2.18). To interpret the factor $\exp(\boldsymbol{\beta}^t \mathbf{Z})$ for the

log logistic model, note that the odds of survival beyond time t for the logistic model is given by

$$\frac{S_X(x \mid \mathbf{Z})}{1 - S_X(x \mid \mathbf{Z})} = \frac{1}{\lambda \exp[\boldsymbol{\beta}'\mathbf{Z}]x^{\alpha}} = \exp(-\boldsymbol{\beta}'\mathbf{Z})\frac{S_X(x \mid \mathbf{Z} = \mathbf{0})}{1 - S_X(x \mid \mathbf{Z} = \mathbf{0})}.$$

So, the factor $\exp(-\boldsymbol{\beta}'\mathbf{Z})$ is an estimate of how much the baseline odds of survival at any time changes when an individual has covariate $\mathbf{Z}$. Note that $\exp(\boldsymbol{\beta}'\mathbf{Z})$ is the relative odds of dying for an individual with covariate $\mathbf{Z}$ compared to an individual with the baseline characteristics.

The third representation of a log logistic regression is as an accelerated failure-time model (12.1.1) with a log logistic baseline survival function. The log logistic model is the only parametric model with both a proportional odds and an accelerated failure-time representation.

EXAMPLE 12.2

(continued): Continuing the study of laryngeal cancer, we shall employ the log logistic model using the main effects of age and stage. The parameter estimates, standard errors, Wald chi squares and p-values for testing $\gamma_i = 0$, are given in Table 12.3. Here we see that Stage II is not significantly different from Stage I, Stages III and IV are significantly different from Stage I, adjusted for age, and, as in earlier analyses, age is not a significant predictor of death in these patients, adjusted for stage.

The estimates obtained by converting the parameters in the log linear model to those in the proportional odds model and calculating their standard errors using (12.2.13)–(12.2.18), are listed in Table 12.4. From Table 12.4, we see that the relative odds of survival for a Stage III patient compared to a Stage I patient are $\exp(-1.127) = 0.32$ and for a Stage IV patient are $\exp(-2.469) = 0.085$, that is, Stage IV patients have 0.085 times lesser odds of surviving than Stage I patients (or $1/0.085 = 11.81$ times greater odds of dying). Using the accelerated failure-time model for the log logistic model, we see that the acceleration factor for Stage III

TABLE 12.3
Analysis of Variance Table for Stage and Age for Laryngeal Cancer Patients, Utilizing the Log Linear Model, Assuming the Log Logistic Distribution

Parameter	*Parameter Estimate*	*Standard Errors*	*Wald Chi Square*	*p-Value*
Intercept $\hat{\mu}$	3.10	0.95		
Scale $\hat{\sigma}$	0.72	0.09		
Z_1: Stage II ($\hat{\gamma}_1$)	−0.13	0.42	0.09	0.762
Z_2: Stage III ($\hat{\gamma}_2$)	−0.81	0.35	5.18	0.023
Z_3: Stage IV ($\hat{\gamma}_3$)	−1.77	0.43	17.22	<0.0001
Z_4: Age ($\hat{\gamma}_4$)	−0.015	0.014	1.20	0.273

TABLE 12.4
Analysis of Variance Table for Stage And Age For Laryngeal Cancer Patients, Utilizing the Proportional Odds Model and the Log Logistic Distribution

Parameter	*Parameter Estimate*	*Standard Errors*
Intercept $\hat{\lambda}$	0.013	0.018
Scale $\hat{\alpha}$	1.398	0.168
Z_1: Stage II ($\hat{\beta}_1$)	0.176	0.581
Z_2: Stage III ($\hat{\beta}_2$)	1.127	0.498
Z_3: Stage IV ($\hat{\beta}_3$)	2.469	0.632
Z_4: Age ($\hat{\beta}_4$)	0.021	0.019

disease compared to Stage I disease is $\exp[-(-.81)] = 2.25$ and for Stage IV disease is $\exp[-(-1.77)] = 5.87$. This suggests that the median life for Stage I patients is about 5.87 times that of Stage IV patients.

Practical Notes

1. SAS PROC LIFEREG and S-Plus routine survreg provide maximum likelihood estimates of intercept μ, and scale parameter σ, associated with the logistic distribution. The parameters of the underlying log logistic distribution are the following functions of these extreme value parameters: $\lambda = \exp(-\mu/\sigma)$ and $\alpha = 1/\sigma$. SAS allows for right-, left- and interval-censored data.
2. When performing an accelerated failure time regression employing the log logistic distribution, SAS and S-Plus provide maximum likelihood estimates of intercept μ, scale parameter σ, and regression coefficients γ_i. The parameters of the underlying log logistic distribution, when modeling time directly, are the following functions of those parameters: $\lambda = \exp(-\mu/\sigma)$, $\alpha = 1/\sigma$, and $\beta_i = -\gamma_i/\sigma$. SAS allows for right-, left- and interval-censored data.

12.4 Other Parametric Models

In section 12.2, we examined the use of the Weibull distribution as a model for survival data, and, in section 12.3, we examined the use of the log logistic model. In this section, we shall look at alternative parametric

models for the survival function, focusing on the regression problem with obvious extensions to the problem of univariate estimation.

The first model to be considered is the log normal distribution. Here, given a set of covariates $\mathbf{Z} = (Z_1, \ldots, Z_p)'$, the logarithm of the time to the event follows the usual normal regression model, that is,

$$Y = \log X = \mu + \boldsymbol{\gamma}'\mathbf{Z} + \sigma W, \tag{12.4.1}$$

where W has a standard normal distribution. The general shape of the hazard rate for this model is quite similar to that of the log logistic distribution, and, in most instances, regression models based on the log normal distribution are very close to regression models based on the log logistic model.

For the log normal distribution the survival function of the time to event T is given by

$$S(x) = 1 - \Phi\{[\log(x) - (\mu + \boldsymbol{\gamma}'\mathbf{Z})]/\sigma\},$$

where $\Phi\{\}$ is the standard normal cumulative distribution function.

A second model of interest is the generalized gamma distribution. This model is very useful in selecting between alternative parametric models because it includes the Weibull, exponential, and the log normal models as limiting cases. For this model, $Y = \log X$ follows the linear model (12.4.1) with W having the following probability density function:

$$f(w) = \frac{|\theta|[\exp(\theta w)/\theta^2]^{(1/\theta^2)}\exp[-\exp(\theta w)/\theta^2]}{\Gamma(1/\theta^2)}, \quad -\infty < w < \infty. \tag{12.4.2}$$

When θ equals 1, this model reduces to the Weibull regression model, and, when θ is 0, the model reduces to the log normal distribution. When $\theta = 1$ and $\sigma = 1$ in (12.4.1), then, (12.4.1) reduces to the exponential regression model.

The generalized gamma model is most commonly used as a tool for picking an appropriate parametric model for survival data but, rarely, as the final parametric model. Wald or likelihood ratio tests of the hypotheses that $\theta = 1$ or $\theta = 0$ provide a means of checking the assumption of a Weibull or log normal regression model, respectively.

With the exception of the Weibull and log normal distribution, it is difficult to use a formal statistical test to discriminate between parametric models because the models are not nested in a larger model which includes all the regression models discussed in this chapter. One way of selecting an appropriate parametric model is to base the decision on minimum Akaikie information criterion (AIC). For the parametric models discussed, the AIC is given by

$$\text{AIC} = -2 * \log(\text{Likelihood}) + 2(p + k), \tag{12.4.3}$$

where $k = 1$ for the exponential model, $k = 2$ for the Weibull, log logistic, and log normal models and $k = 3$ for the generalized gamma model. We shall illustrate this on two examples considered in this chapter.

EXAMPLE 12.1 *(continued):* We shall reexamine the parametric models for the auto and allo transplant survival data. We will fit the exponential, Weibull, log logistic, log normal models, and generalized gamma models separately to the data on allo and auto transplants. The log likelihood and the AIC for each model are reported in Table 12.5. (Note that here $p = 0$.) Also included in this table are the estimates of θ from the generalized gamma model, their standard errors and the p-values of the Wald tests of $H_o : \theta = 0$ and $H_o : \theta = 1$. These are tests of the appropriateness of the log normal and Weibull models, respectively.

TABLE 12.5
Results of Fitting Parametric Models to the Transplant Data

		Allo Transplants	*Auto Transplants*
Exponential	Log likelihood	−81.203	−68.653
	AIC	164.406	139.306
Weibull	Log likelihood	−72.879	−68.420
	AIC	149.758	140.840
Log logistic	Log likelihood	−71.722	−67.146
	AIC	147.444	138.292
Log normal	Log likelihood	−71.187	−66.847
	AIC	146.374	137.694
Generalized gamma	Log likelihood	−70.892	−66.781
	AIC	147.784	139.562
	$\hat{\theta}$	−0.633	−0.261
	SE[$\hat{\theta}$]	0.826	0.725
	p-value for $H_o : \theta = 0$	0.443	0.719
	p-value for $H_o : \theta = 1$	0.048	0.082

From this table, we see that the log normal distribution provides the best fit to this data, and the log logistic distribution is a close second. The generalized gamma model, which has the smallest log likelihood, does not have a smaller AIC than these two models and the simpler models are preferred. The exponential distribution for Allo transplants has a much poorer fit than the Weibull model, and there is no evidence of an improved fit for auto transplants, using the Weibull rather than the exponential. A likelihood ratio chi-square test, with one degree of freedom, for testing the hypothesis that the Weibull shape parameter is equal to one has a value of 16.648 ($p < 0.0001$) for allo transplants and a value of 0.468 for auto transplants.

Using a log normal regression model with a single covariate Z_1 equal to 1 if the patient received an auto transplant, we have the following regression model:

Parameter	*Estimate*	*Standard Error*	*Wald Chi Square*	*p-Value*
Intercept: μ	3.177	0.355	80.036	<0.0001
Type of Transplant: γ_1	0.054	0.463	0.0133	0.9080
Scale: σ	2.084	0.230	—	—

Here, we see that there is no evidence of any difference in survival between the two types of transplants.

EXAMPLE 12.2 *(continued):* We shall now compare the fit of the exponential, Weibull, log normal, log logistic and generalized gamma models for the data on laryngeal cancer. Recall that, here, we have four covariates:

Z_1: 1 if Stage II cancer, 0 otherwise,

Z_2: 1 if Stage III cancer, 0 otherwise,

Z_3: 1 if Stage IV cancer; 0 otherwise, and

Z_4: Patient's age at diagnosis.

We fit the log linear model

$$Y = \ln X = \mu + \sum_{k=1}^{4} \gamma_k Z_k + \sigma W,$$

TABLE 12.6
Parametric Models for the Laryngeal Cancer Study

	Exponential		*Weibull*		*Log Logistic*		*Log Normal*		*Generalized Gamma*	
	Estimate	*SE*	*Estimate*	*SE*	*Estimate*	*SE*	*Estimate*	*SE*	*Estimate*	*SE*
μ	3.755	0.990	3.539	0.904	3.102	0.953	3.383	0.936	3.453	0.944
α_1	−0.146	0.460	−0.148	0.408	−0.126	0.415	−0.199	0.442	−0.158	0.431
α_2	−0.648	0.355	−0.587	0.320	−0.806	0.354	−0.900	0.363	−0.758	0.394
α_3	−1.635	0.399	−1.544	0.363	−1.766	0.426	−1.857	0.443	−1.729	0.449
α_4	−0.020	0.014	−0.017	0.013	−0.015	0.014	−0.018	0.014	−0.018	0.014
σ	1.000	0.000	0.885	0.108	0.715	0.086	1.264	0.135	1.104	0.257
θ									0.458	0.584
Log L	−108.50		−108.03		−108.19		−108.00		−107.68	
AIC	227.00		228.05		228.38		227.99		229.36	

where W has the appropriate distribution for each of the models. Note that the value of σ is fixed at 1 for the exponential distribution. Table 12.6 provides the estimates of the model parameters and their standard errors, the maximized likelihoods, and the AIC criterion for all five models.

In this table, we see that all three models fit equally well. The exponential model has the smallest AIC and, in that sense, is the best fitting model. For this model,

$$Y = 3.755 - 0.146Z_1 - 0.648Z_2 - 1.635Z_3 - 0.020Z_4 + W.$$

The negative values of the coefficients of Z_1, Z_2, and Z_3 in the log linear model suggest that individuals with stages II, III, and IV cancer have shorter lifetimes than individuals with Stage I disease.

Practical Note

1. SAS PROC LIFEREG has routines for fitting the generalized gamma and log normal distributions to right-, left- and interval-censored data. The S-Plus routine survreg fits the log normal model.

12.5 Diagnostic Methods for Parametric Models

In the last three sections, we have presented a variety of models for univariate survival data and several parametric models that can be used to study the effects of covariates on survival. In this section, we shall focus on graphical checks of the appropriateness of these models. As discussed in Chapter 11, we favor graphical checks of the appropriateness rather then formal statistical tests of lack of fit because these tests tend either to have low power for small-sample sizes or they always reject a given model for large samples. The graphical checks discussed here serve as a means of rejecting clearly inappropriate models, not to "prove" that a particular parametric model is correct. In fact, in many applications, several parametric models may provide reasonable fits to the data and provide quite similar estimates of key quantities.

We shall first examine the problem of checking for the adequacy of a given model in the univariate setting. The key tool is to find a function of the cumulative hazard rate which is linear in some function of time. The basic plot is made by estimating the cumulative hazard rate by the Nelson–Aalen estimator (see section 4.2). To illustrate this technique, consider a check of the appropriateness of the log logistic distribution. Here, the cumulative hazard rate is $H(x) = \ln(1 + \lambda x^{\alpha})$. This implies that, for the log logistic model,

$$\ln\{\exp[H(x)] - 1\} = \ln\lambda + \alpha \ln x, \qquad (12.5.1)$$

so, a plot of $\ln\{\exp[\hat{H}(x)] - 1\}$ versus $\ln x$ should be approximately linear. The slope of the line gives a crude estimate of α and the y intercept gives a crude estimate of $\ln\lambda$. Here, $\hat{H}$ is the Nelson–Aalen estimator. Note that, for the log logistic distribution, the quantity $\ln\{\exp[H(x)] - 1\}$ is precisely the log odds favoring survival.

For the other models discussed in this chapter, the following plots are made to check the fit of the models:

Model	*Cumulative Hazard Rate*	*Plot*	
Exponential:	λx	$\hat{H}$ versus x	(12.5.2)
Weibull:	λx^{α}	$\ln\hat{H}$ versus $\ln x$	(12.5.3)
Log normal:	$-\ln\{1 - \Phi[\ln(x) - \mu)]/\sigma\}$	$\Phi^{-1}[1-\exp(-\hat{H})]$ versus $\ln x$	(12.5.4)

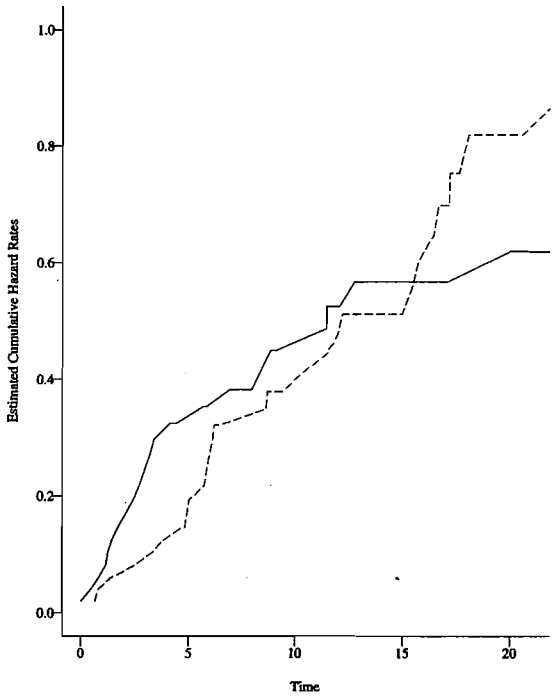

Figure 12.1 *Exponential hazard plot for the allo (solid line) and auto (dashed line) transplant groups.*

Note that the slope of the line for the Weibull hazard plot gives a crude estimate of α and, if the slope of the line is 1, then, the exponential is a reasonable model.

EXAMPLE 12.1 *(continued):* To check the adequacy of the exponential, Weibull, log logistic, and log normal models for the data on auto and allo transplants, four hazard plots are presented in Figures 12.1–12.4. If the curves do not appear linear for each figure, this is evidence that the parametric model does not provide an adequate fit to the data. From Figure 12.1, the exponential plot, we see that the curves for the allo transplant group appear to be nonlinear, suggesting that the exponential is not a good model for this set of data. The curve is roughly linear for the auto transplant data, except in the tail where the estimate of H is highly variable, suggesting that the exponential may be a reasonable model. The curves for the other three models (Figures 12.2–12.4) are roughly linear, suggesting these may be appropriate models for either groups.

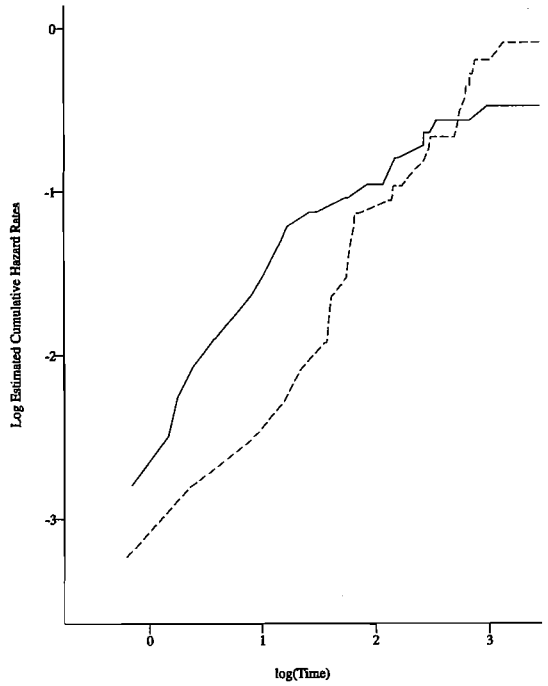

Figure 12.2 *Weibull hazard plot for the allo (solid line) and auto (dashed line) transplant groups.*

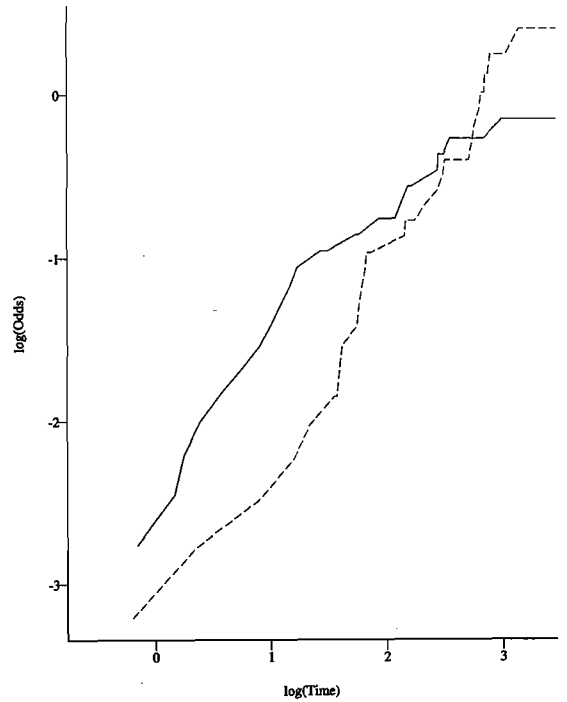

Figure 12.3 *Log logistic hazard plot for the allo (solid line) and auto (dashed line) transplant groups.*

When comparing two groups, an alternative to the proportional hazards model is the accelerated failure-time model. A *quantile-quantile* or *q-q* plot is made to check if this provides an adequate fit to the data. The plot is based on the fact that, for the accelerated failure-time model,

$$S_1(t) = S_o(\theta t), \tag{12.5.2}$$

where S_o and S_1 are the survival functions in the two groups and θ is the acceleration factor. Let t_{op} and t_{1p} be the pth percentiles of groups 0 and 1, respectively, that is

$$t_{kp} = S_k^{-1}(1-p), k = 0, 1.$$

Using the relationship (12.5.2), we must have $S_o(t_{op}) = 1-p = S_1(t_{1p}) = S_o(\theta t_{1p})$ for all t. If the accelerated failure time model holds, $t_{op} = \theta t_{1p}$. To check this assumption we compute the Kaplan–Meier estimators of the two groups and estimate the percentiles t_{1p}, t_{0p}, for various values of p. If we plot the estimated percentile in group 0 versus the estimated

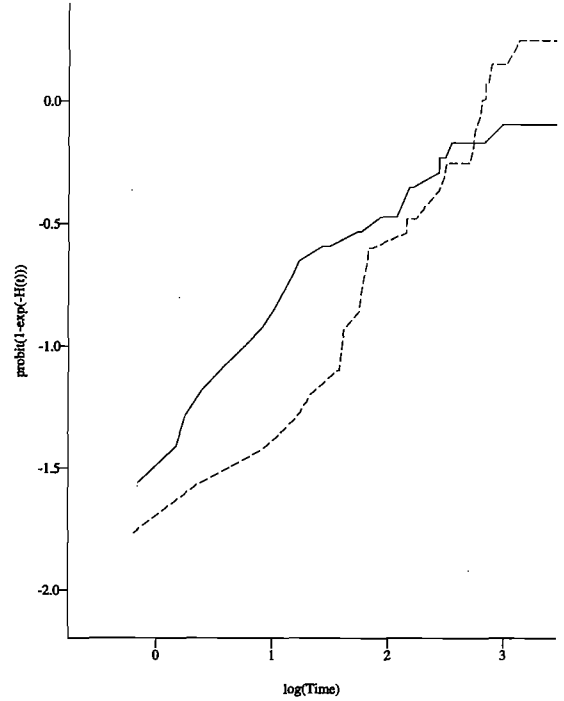

Figure 12.4 *Log normal hazard plot for the allo (solid line) and auto (dashed line) transplant groups.*

percentile in group 1 (i.e., plot the points t_{1p}, t_{0p} for various values of p), the graph should be a straight line through the origin, if the accelerated failure time model holds. If the curve is linear, a crude estimate of the acceleration factor q is given by the slope of the line.

EXAMPLE 12.1

(continued): We shall graphically check the adequacy of the accelerated failure-time model for comparing allo and auto transplants. Here, we fit the Kaplan-Meier estimator separately to each group and compute the percentiles for each group for $p = 0.05, 0.10, \ldots, 0.35$. These percentiles are in the range where the percentile could be estimated for both groups. Figure 12.5 shows the *q-q* plot for auto transplants (Group 1) versus allo transplants (Group 0). The figure appears to be approximately linear with a slope of about 0.6, which is a crude estimate of the acceleration factor θ.

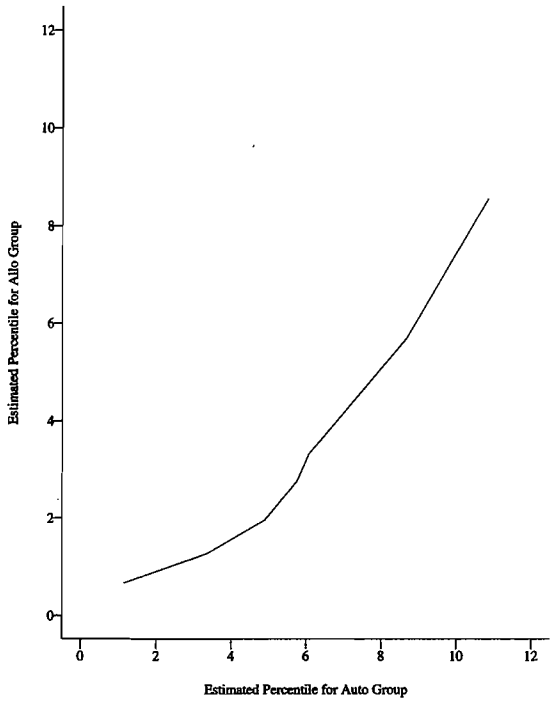

Figure 12.5 *q-q plot to check the adequacy of the accelerated failure time model for comparing Allo and Auto transplants.*

For the parametric regression problem, analogs of the residual plots described in Chapter 11 can be made with a redefinition of the various residuals to incorporate the parametric form of the baseline hazard rates. The first such residual is the Cox–Snell residual that provides a check of the overall fit of the model. The Cox–Snell residual, r_j, is defined by $r_j = \hat{H}(T_j \mid \mathbf{Z}_j)$, where $\hat{H}$ is the fitted model. If the model fits the data then the r_j's should have a standard ($\lambda = 1$) exponential distribution, so that a hazard plot of r_j versus the Nelson–Aalen estimator of the cumulative hazard of the r_j's should be a straight line with slope 1. For the four models considered in this chapter, the Cox–Snell residuals are

Exponential $\quad r_i = \hat{\lambda} t_i \exp\{\hat{\beta}'\mathbf{Z}_i\}$,

Weibull $\quad \hat{\lambda} \exp(\hat{\beta}'\mathbf{Z}_i) t_1^{\hat{\alpha}}$,

Log logistic $\quad \ln\left[\dfrac{1}{1 + \hat{\lambda} \exp(\hat{\beta}'\mathbf{Z}_i) t_j^{\hat{\alpha}}}\right]$,

and

Log normal $\quad \ln\left[1 - \Phi\left(\dfrac{\ln T_j - \hat{\mu} - \hat{\gamma}'\mathbf{Z}_j}{\hat{\sigma}}\right)\right]$.

Examination of model fit with the Cox–Snell residuals is equivalent to that done using the so-called standardized residuals based on the log linear model representation. Here, we define the standardized residuals by analogy to those used in normal theory regression as

$$s_j = \frac{\ln T_j - \hat{\mu} - \hat{\gamma}'\mathbf{Z}_j}{\hat{\sigma}}.$$

If the Weibull model holds, then, these residuals should be a censored sample from the standard extreme value distribution (12.2.2); if the log logistic distribution holds, these are a censored sample from a standard logistic distribution (12.3.1); and if the log normal distribution holds, these are a censored sample from a standard normal distribution. The hazard plot techniques discussed earlier can be used to check if the standardized residuals have the desired distribution. However, the hazard plots obtained are exactly those obtained by the exponential hazard plot for the Cox–Snell residuals.

EXAMPLE 12.2 *(continued):* In Figures 12.6–12.9, the cumulative hazard plots for the Cox–Snell residuals are shown for the exponential, Weibull, log logistic and log normal regression models for the laryngeal cancer data. We see from these plots that all four models give reasonable fits to the data, the best being the log normal and log logistic models.

In Chapter 11, the martingale and deviance residuals were defined for Cox regression models. For a parametric model, the martingale residual is defined by $M_j = \delta_j - r_j$ and the deviance residual by

$$D_j = \text{sign}[M_j]\{-2[M_j + \delta_j \ln(\delta_j - M_j)]\}^{1/2}.$$

As for the Cox model, the martingale residual is an estimate of the excess number of deaths seen in the data, but not predicted by the model. In the parametric case, note that the derivation of M_j as a martingale does not hold but, because the residuals are similar in form to those for the Cox model, the name carries through. The deviance residuals are an attempt to make the martingale residuals more symmetric about 0. If the model is correct, then, the deviance residuals should look like random noise. Plots of either the martingale or deviance residuals against time, observation number, or acceleration factor provides a check of the model's adequacy. The discussion of how to use these residuals in Chapter 11 carries over to the parametric case. We shall illustrate

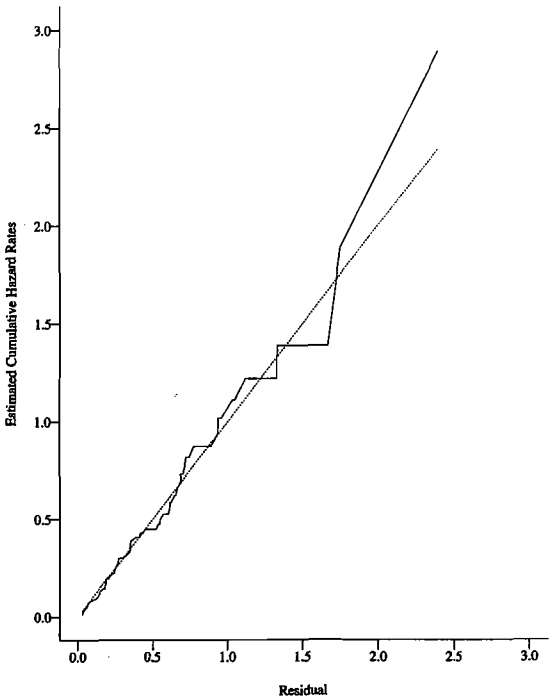

Figure 12.6 *Cox–Snell residuals to assess the fit of the exponential regression model for the laryngeal cancer data set*

the use of the deviance residuals in the following continuation of Example 12.2.

EXAMPLE 12.2 *(continued):* We shall examine the fit of the log logistic regression model to the laryngeal cancer data using the deviance residuals. Figure 12.10 is a plot of the deviance residuals versus time on study. Here, we see that the deviance residuals are quite large for small times and that they decrease with time. This suggests that the model underestimates the chance of dying for small t and overestimates this chance for large t. However, there are only a few outliers early, which may cause concern about the model. The deviance residual plots for the other three models are quite similar.

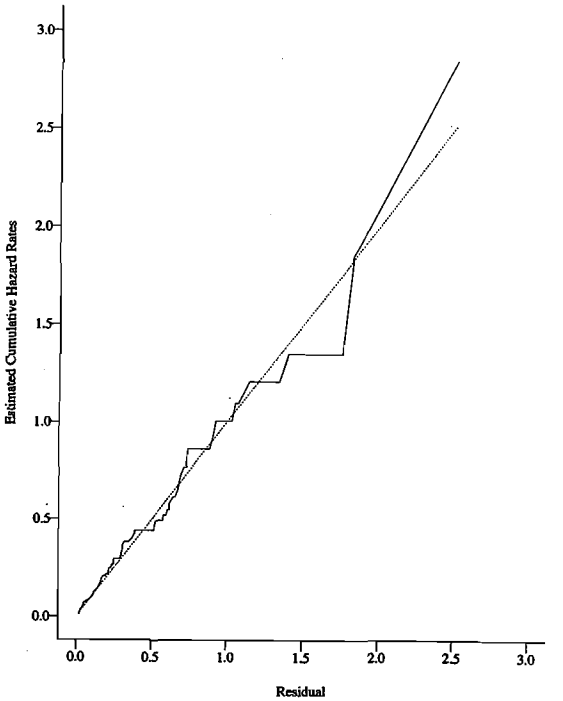

Figure 12.7 *Cox–Snell residuals to assess the fit of the Weibull regression model for the laryngeal cancer data set*

Practical Note

1. Martingale and deviance residuals for these parametric models are available in S-Plus.

Theoretical Notes

1. Further work on graphical checks for the parametric regression models can be found in Weissfeld and Schneider (1990) and Escobar and Meeker (1992).
2. It is possible to define a score residual for the various parametric models similar to that presented in section 12.6. To illustrate how

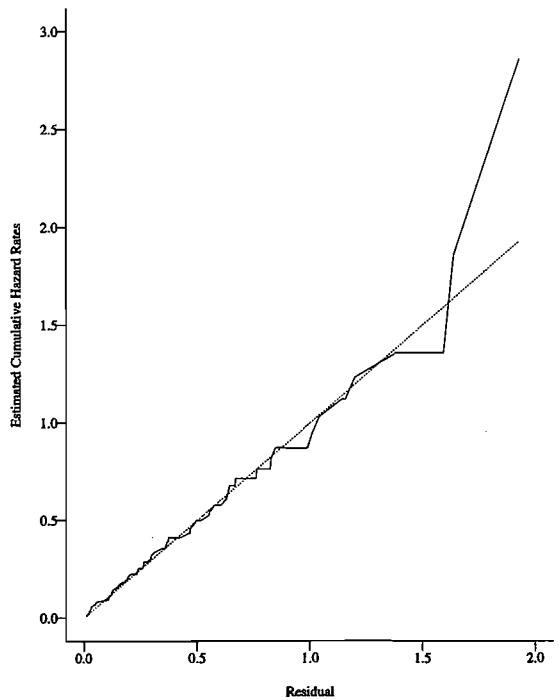

Figure 12.8 *Cox–Snell residuals to assess the fit of the log logistic regression model for the laryngeal cancer data set*

this is done, consider the Weibull regression problem with a single covariate Z. The contribution of an individual with covariate Z_j to the likelihood is given by

$$L_j = [\exp(\beta Z_j)\lambda\alpha t_j^{\alpha-1}]^{\delta_j} \exp[-\lambda \exp(\beta Z_j) T_j^{\alpha}].$$

The score residual for λ is given by

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

for α,

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

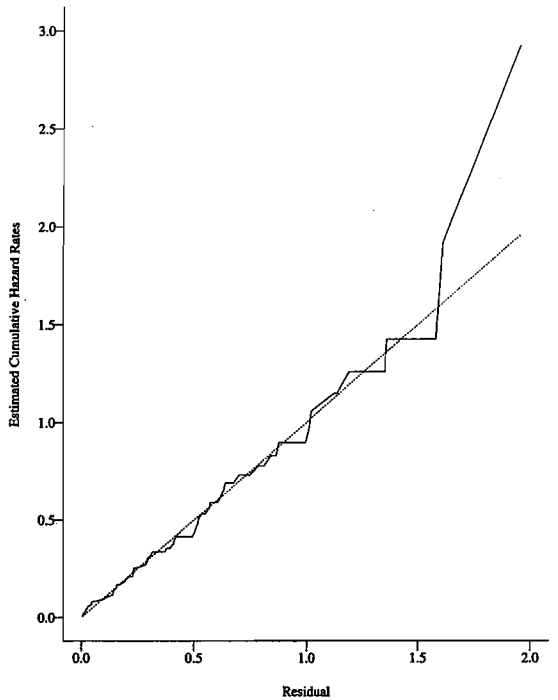

Figure 12.9 *Cox–Snell residuals to assess the fit of the log normal regression model for the laryngeal cancer data set*

and for β,

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

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.

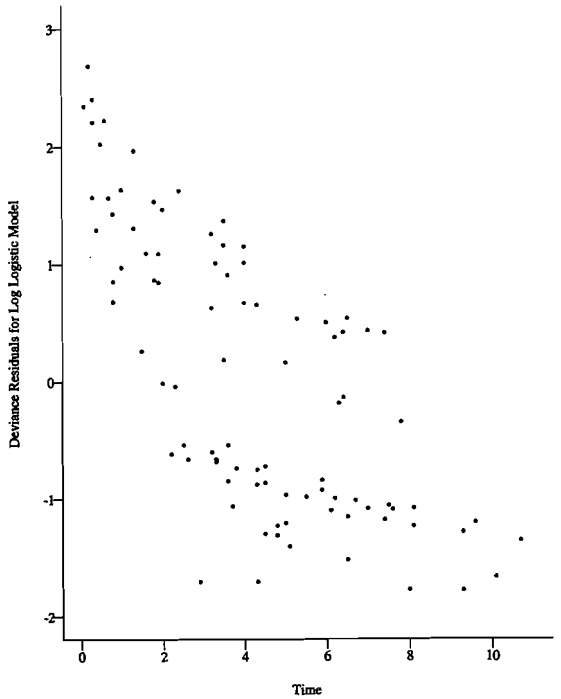

Figure 12.10 *Deviance residuals from the log logistic regression model for laryngeal cancer patients*

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

(b) For both groups, test the hypothesis that the shape parameter, α, 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 λ and α, and their standard errors.

(b) For both groups test the hypothesis that the shape parameter, α, 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_0 : $h(t \mid \text{NHL Allo}) = h(t \mid \text{NHL Auto})$ *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.