A Comparison of Methods for Analysing Interval-Censored and Truncated Survival Data

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Summary

This thesis examines three methods for analysing right-censored data: the Cox proportional hazards model (Cox, 1972), the Buckley-James regression model (Buckley and James, 1979) and the accelerated failure time model. These models are extended to incorporate the analysis of interval-censored and left-truncated data. The models are compared in an attempt to determine whether one model performs better than the others in terms of goodness-of-fit and in terms of predictive power. Plots of the residuals and random effects from the Cox proportional hazards model are also examined.

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1. Introduction

In survival analysis, subjects are followed over time in order to observe a specific event. Survival analysis is most commonly used to analyse medical data, and typical events include death, or the onset or remission of a particular disease or set of symptoms. Survival analysis can also be applied in other fields, for example examining the lifetimes of machinery, or the times between economic events such as strikes or periods of unemployment.

One of the distinguishing features of survival data is that the occurrence of the event of interest is not always observed for each subject. This feature of the data is known as censoring. Typically a large proportion of the events will have been observed.

The most common form of censoring is right-censoring. This occurs when some subjects have not experienced the event of interest at the final time of observation. There are numerous, widely used techniques for analysing this type of data, especially with respect to the effect of covariates on the survival time.

Another form of censoring is interval-censoring, which can be viewed as a generalisation of right-censoring. When the data is interval-censored, the event of interest is known to have occurred between two time points, but the exact time that the event occurred is usually unknown. Analysis of interval-censored data is more complex than that of right-censored data as each subject has two observed times, each of which represents different information about the time of the occurrence of the event of interest.

Various models have been proposed for the analysis of interval-censored data. Finkelstein (1986), Alioum and Commenges (1996) and Pan and Chappell (2002) consider a proportional hazards model. Farrington (1996), Carstensen (1996) and Scallan (1999) examine the use of generalised linear models to fit interval-censored data. Other models have been considered by Sun (1997) and Li and Pu (1999). Lindsey and Ryan (1998) provide a comparison of methods for analysing interval-censored data.

Another possible feature of survival data is truncation, which occurs when a subject is not under observation for the entire length of a study. If there is truncation, then the data is analysed conditional on observation of the subject being possible. The most common form of truncation is left-truncation, in which the subjects are only first observed at a time after the start of a study. Analysis of their data then becomes conditional on their having survived beyond the time of truncation, as any subjects for whom the event occurred before the truncation time would not have been included in the study. Modelling truncated data also increases the complexity of the various models, but to a lesser extent than that of interval-censored data.

The aim of this thesis is to examine and compare various models that can be used to analyse interval-censored and left-truncated data. The aspects of the models used for comparison are the overall fit of each model and the predictive power of each model.

Chapter 2 describes the four data sets used for analysis, and Chapter 3 lists the notation used throughout this thesis.

Chapters 4, 7 and 8 examine three models for right-censored data: the Cox proportional hazards model (Cox, 1972), the Buckley-James regression model (Buckley and James, 1979), and the parametric accelerated failure time model.

Chapter 9 compares the models based on Heller and Simonoff's comparison of the Cox proportional hazards and Buckley-James models (Heller and Simonoff, 1992).

Following the work of Finkelstein (1986) and Smith (2002), these models are extended in order to analyse interval-censored data (Chapter 10), and then further extended to incorporate the analysis of left-truncated data (Chapter 11).

In Chapter 12, the models are fitted to a large data set that is both interval-censored and left-truncated. A discussion of the results is presented in Chapter 13.

During the development of this thesis, residuals from the Cox proportional hazards were examined, as well as the effect of frailty. The investigation of these two aspects resulted in some unusual plots. Eventually, this investigation was discontinued as the

focus shifted towards interval-censoring and left-truncation. The plots and the explanations of the unusual patterns have still been included in Chapters 5 and 6.

The Appendix consists of the four data sets.

Statistical analysis was performed in S-Plus. For models not supported by S-Plus such as the interval-censored proportional hazards and Buckley-James models, programs were written using Borland Delphi.

2. Data sets

Four sets of data have been used to demonstrate the various methods of analysing survival data that have been compared in this thesis. The first three were taken from Klein and Moeschberger (1997), and all four are given in the Appendix.

The first data set consists of 90 males diagnosed with laryngeal cancer. The times recorded are the intervals in years between the first treatment and either death or the end of the study. Also recorded are each patient's age at the time of diagnosis, the year of diagnosis, and the stage of the disease (1 to 4). This data set is used to demonstrate the analysis of right-censored data.

The second data set is from a study carried out to test the effect of radiotherapy and chemotherapy against radiotherapy alone on 94 women with breast cancer. The event of interest was the time to the first appearance of breast retraction. The patients were initially observed at regular intervals, but the length of time between intervals increased as their recovery progressed. Therefore the exact time of breast retraction is known only to fall between the times of successive visits. The data recorded is the interval in months consisting of the last time at which breast retraction was known not to have occurred, and the first time at which it was observed. This data set is used to demonstrate the analysis of interval-censored data.

The third data set is taken from a group of 120 patients who underwent bone marrow transplants as a treatment for leukaemia. The data recorded is the time in days to death, relapse or the end of the study, the time in days to platelet recovery, the disease group (lymphoblastic leukaemia, low-risk myeloctic leukaemia or high-risk myeloctic leukaemia), and their FAB classification. Patients with an FAB classification of grade 4 or 5 were considered to have a possible elevated risk of relapse or death. This data set is used to demonstrate the analysis of left-truncated data.

The final data set is a left-truncated and interval-censored data set consisting of 447 patients between the ages of 15 and 69 who attended the clinic at Somerset Hospital, Cape Town who had been diagnosed with the human immuno-deficiency virus (HIV). Patients were observed at irregular intervals, and the stage of the disease was recorded

at each observation. The data also consisted of personal details such as the age and sex of the patient, along with other demographic details. This data set will be used to demonstrate a combined analysis of interval-censored and left-truncated data.

3. Notation

T_i - a random variable representing the time to the event of interest for the ith subject, also referred to as the survival time.

t_i - the observed value of T_i

δ_i - an indicator variable equal to 1 if the ith subject is uncensored (the event was observed to happen), and 0 if they are censored.

$f(t)$ - the density function of T

$F(t)$ - the distribution function of T

$S(t)$ - the survival function of T, defined as $\Pr[T > t]$, and equal to $1 - F(t)$

$\lambda(t)$ - the hazard function of T, defined as $\lim_{h \to 0} \Pr[t \le T \le t + h \mid T \ge t]$, the instantaneous probability of the event occurring, and equal to $\frac{f(t)}{S(t)}$

$\mathbf{X}_i$ - a row vector of covariates for the ith subject. For the proportional hazards model, this is a $1 \times p$ vector, $[x_{i1} \quad x_{i2} \quad \dots \quad x_{ip}]$. For the accelerated failure time and Buckley-James models, this is a $1 \times (p+1)$ vector, $[x_{i0} \quad x_{i1} \quad \dots \quad x_{ip}]$, with $x_{i0} = 1$.

β - a vector of coefficients. For the proportional hazards model, this is a $1 \times p$ vector, $[\beta_1 \quad \beta_2 \quad \dots \quad \beta_p]^T$. For the accelerated failure time and Buckley-James models, this is a $1 \times (p+1)$ vector, $[\beta_0 \quad \beta_1 \quad \dots \quad \beta_p]^T$.

D - the total number of observed events, equal to $\sum \delta_i$

$\mathbf{Z}$ - a design matrix for the random effects

ω - a vector of random effects

$[l_i, r_i]$ - an interval within which the event of interest for the ith subject is known to have occurred

$[u_i, v_i]$ - the truncation interval, the time period for which the ith subject is able to be observed.

4. Cox proportional hazards model

One of the most widely used models used to analyse survival data with regard to the effect of covariates is the Cox proportional hazards model (Cox, 1972).

In a proportional hazards model, the *i*th subject has the hazard function

$$\lambda(t \mid \mathbf{X}_i) = \lambda_0(t) e^{\mathbf{X}_i \beta}$$

where $\lambda_0(t)$ is a function of time known as the baseline hazard. It is possible to define a parametric proportional hazards model that assumes that $\lambda_0(t)$ comes from a specific distribution, such as the Weibull distribution. However, for the Cox proportional hazards model, no assumptions are made about the functional form of $\lambda_0(t)$.

A proportional hazards model has the property that the ratio of the hazards functions for two subjects is constant.

$$\frac{\lambda(t \mid \mathbf{X}_i)}{\lambda(t \mid \mathbf{X}_j)} = \frac{\lambda_0(t) e^{\mathbf{X}_i \beta}}{\lambda_0(t) e^{\mathbf{X}_j \beta}} = e^{(\mathbf{X}_i - \mathbf{X}_j)\beta}$$

The survival function for the *i*th subject is given by

$$S(t \mid \mathbf{X}_i) = S_0(t)^{\exp(\mathbf{X}_i \beta)}$$

where $S_0(t)$ is a survival function with unspecified covariates known as the baseline survival function.

Estimation of β is performed as follows. Let $t_{(1)} < t_{(2)} < \ldots < t_{(D)}$ denote the ordered times of the events of interest, with D being the number of events. Let $\mathbf{X}_{(i)}$ be the vector of covariates for the subject whose event occurs at time $t_{(i)}$, and $R_{(i)}$ the set of subjects at risk prior to time $t_{(i)}$. A partial likelihood is set up, defined as

$$L_p(\beta) = \prod_{i=1}^{D} \frac{e^{\mathbf{X}_{(i)} \beta}}{\sum_{h \in R_{(i)}} e^{\mathbf{X}_h \beta}}$$

Although the partial likelihood is not a true likelihood, it has many of the properties of a full likelihood. The log partial likelihood is

$$l_p(\beta) = \sum_{i=1}^{D} \left[\mathbf{X}_{(i)}\beta - \log\left(\sum_{h \in R_{(i)}} e^{\mathbf{X}_h \beta} \right) \right]$$

The derivative of the log partial likelihood with respect to β is

$$\frac{\partial l_p(\beta)}{\partial \beta_j} = \sum_{i=1}^{D} \left[\mathbf{X}_{(i)j} - \frac{\sum_{h \in R_{(i)}} \mathbf{X}_{hj} e^{\mathbf{X}_h \beta}}{\sum_{h \in R_{(i)}} e^{\mathbf{X}_h \beta}} \right]$$

The maximum partial likelihood estimate, $\hat{\beta}$, is found in the usual manner, by setting this derivative equal to zero and solving for β.

The variance of an estimate is found from the information matrix which has element (j,k) given by

$$-\frac{\partial l_p(\beta)}{\partial \beta_j \partial \beta_k} = \sum_{i=1}^{D} \left[\frac{\sum_{h \in R_{(i)}} \mathbf{X}_{hj} \mathbf{X}_{hk} e^{\mathbf{X}_h \beta}}{\sum_{h \in R_{(i)}} e^{\mathbf{X}_h \beta}} \right] - \sum_{i=1}^{D} \left[\frac{\sum_{h \in R_{(i)}} \mathbf{X}_{hj} e^{\mathbf{X}_h \beta}}{\sum_{h \in R_{(i)}} e^{\mathbf{X}_h \beta}} \right] \left[\frac{\sum_{h \in R_{(i)}} \mathbf{X}_{hk} e^{\mathbf{X}_h \beta}}{\sum_{h \in R_{(i)}} e^{\mathbf{X}_h \beta}} \right]$$

The proportional hazards model was applied to the laryngeal cancer data, and the results, which are also found in Klein and Moeschberger (1997), are given in Table 1.

Table 1. Results of applying Cox proportional hazards model to the laryngeal cancer data

Variables	Parameter estimates	Standard errors	p-values	95% Confidence Intervals
Stage 2	0.1399	0.4625	0.7623	(-0.7666, 1.0464)
Stage 3	0.6422	0.3561	0.0713	(-0.0558, 1.3402)
Stage 4	1.7062	0.4219	<0.0001	(0.8793, 2.5331)
Age	0.0190	0.0143	0.1820	(-0.0089, 0.0470)
Log likelihood	-187.7074			
Likelihood ratio test	18.3122 ($p = 0.0011$)			
R^2	0.1864			

The only significant variable is that of Stage 4. The parameter estimate is greater than 0, indicating that a subject in Stage 4 has an increased risk of dying, compared with subjects in other stages. However, since the stage of the disease is essentially a factor with four different levels, the stage of the disease is significant, specifically for subjects in Stage 4.

The R^2 statistic used is the one proposed by Nagelkerke (1991), defined as $R^2 = 1 - \exp\left[-\frac{2}{n}\{l(\hat{\beta}) - l(0)\}\right]$ where $l(\hat{\beta})$ and $l(0)$ are the log-likelihoods of the fitted and the null model respectively. Since l in the Cox proportional hazards model is the logarithm of a partial likelihood, it is necessary to make an adjustment, with the R^2 statistic becoming $R^2 = \left(1 - \exp\left[-\frac{2}{n}\{l(\hat{\beta}) - l(0)\}\right]\right) \Big/ \left(1 - \exp\left[-\frac{2}{n} l(0)\right]\right)$.

This definition is an extension of the R^2 statistic used in linear regression, and has the similar interpretation of being the proportion of variation explained by the model.

5. Residuals from the proportional hazards model

Residuals based on the Cox proportional hazards model can be defined as

$$\hat{r}_i = \hat{\Lambda}(t_i \mid \mathbf{X}_i) = \hat{\Lambda}_0(t_i)e^{\mathbf{X}_i\hat{\beta}}$$

Where $\hat{\Lambda}_0(t) = \int_0^t \hat{\lambda}_0(s)ds$ is the estimate of the cumulative baseline hazard function.

These residuals are known as the Cox-Snell residuals (Cox and Snell, 1968). However, in practice, it has been found that these residuals do not have an exponential distribution, a necessary assumption for their use (Klein and Moeschberger, 1997).

Martingale residuals (Therneau, Grambsch and Fleming, 1990) are a transformation of the Cox-Snell residuals

$$\hat{M}_i = \delta_i - \hat{\Lambda}_0(t_i)e^{\mathbf{X}_i\hat{\beta}}$$

These can be viewed as the observed number of events, δ_i, less the expected number of events, $\hat{\Lambda}_0(t_i)e^{\mathbf{X}_i\hat{\beta}}$.

The martingale residuals can be used to assess the accuracy of the fit of the model for individual subjects. However, since the residuals are skew, with a maximum value of 1 and a minimum of $-\infty$, a transformation of them is more appropriate.

Deviance residuals are a normalising transformation of the martingale residuals (Therneau *et al.*, 1990), and are defined as

$$\hat{d}_i = \text{sign}(\hat{M}_i) * \left(-2\left[\hat{M}_i + \delta_i \log\left(\left\{\delta_i - \hat{M}_i\right\}/\delta_i\right)\right]\right)^{1/2}$$

Therneau *et al.* (1990) note that a percentage of censoring greater than 40% will produce a large group of deviance residuals close to zero, distorting the normal approximation. However, the transformation will still symmetrise the residuals.

Shown below are the residuals produced by applying the Cox proportional hazards model to the laryngeal cancer data.

Figure 1. Plot of the martingale residuals

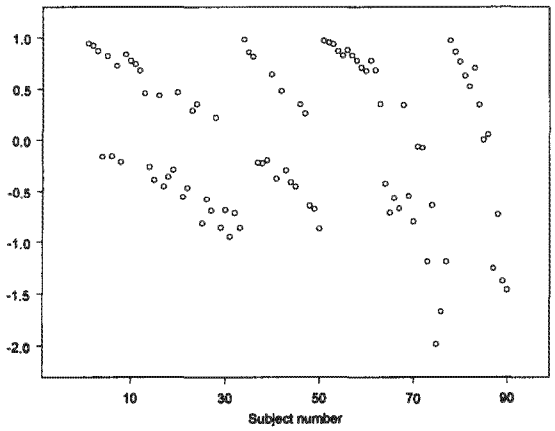
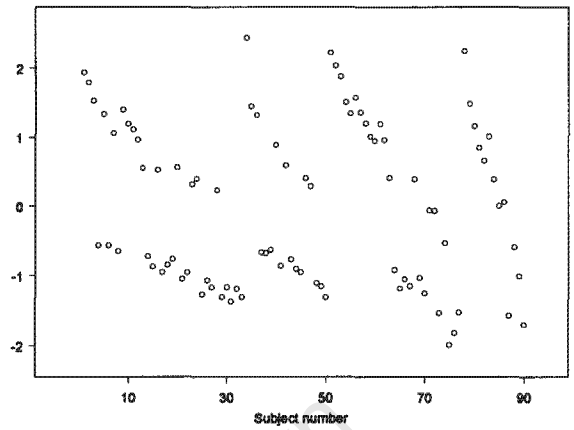


Figure 2. Plot of the deviance residuals



From the graph of the martingale residuals, there are seven subjects with residuals less than –1 that may be outliers. These are subjects numbered 73, 75, 76, 77, 87, 89 and 90. Examining their respective deviance residuals, it can be seen that these are not outliers. In particular, subject 89 has a deviance residual of –1.014. This demonstrates that the martingale residuals are not as useful as the deviance residuals in assessing the fit of the model.

In both plots, it appears that there are two groups of residuals, one consisting of positive residuals, and one of negative residuals. This feature is not confined to this set of data, and becomes even more apparent with a larger data set. An examination of the two groups reveals that they correspond to the uncensored and censored subjects. This can been seen in Figures 3 and 4.

Figure 3. Plot of the martingale residuals

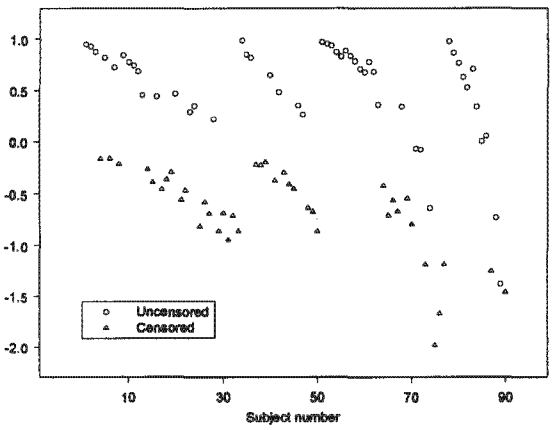
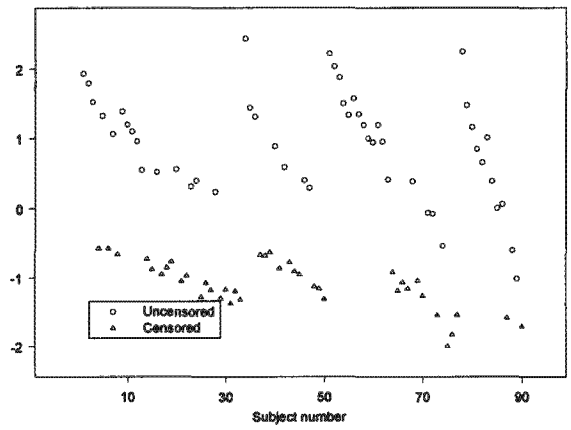


Figure 4. Plot of the deviance residuals



The reason for the separation into two groups can be explained by examining the definition of the residuals. The martingale residuals are

$$\hat{M}_i = \delta_i - \hat{\Lambda}_0(t_i)e^{\mathbf{x}_i\hat{\boldsymbol{\beta}}}$$

δ_i is defined as 0 if the ith subject is censored, and 1 if they are not. This means that the martingale residuals will have two different forms:

Censored subjects: $\hat{M}_i = -\hat{\Lambda}_0(t_i)e^{\mathbf{x}_i\hat{\boldsymbol{\beta}}}$

Uncensored subjects: $\hat{M}_i = 1 - \hat{\Lambda}_0(t_i)e^{\mathbf{x}_i\hat{\boldsymbol{\beta}}}$

This will lead to the martingale residuals consisting of two groups, with the residuals for the censored patients all being negative.

Since the deviance residuals are

$$\hat{d}_i = \text{sign}(\hat{M}_i) * \left(-2\left[\hat{M}_i + \delta_i \log\left(\left\{\delta_i - \hat{M}_i\right\}/\delta_i\right)\right]\right)^{1/2}$$

a subject's deviance residual will have the same sign as their martingale residual, and so the deviance residuals will also consist of two groups.

Despite the fact that there are the two groups, it appears that the separation is just a feature of the residuals, and has no effect on their use and interpretation.

6. Frailty model

The frailty, or random effects, model is an extension of the proportional hazards model. Frailty is an unobserved random effect present for a single subject or shared by a group of subjects. Assume that there are q groups, and each subject i is a member of one of these groups. The proportional hazards model then becomes

$$\lambda(t \mid \mathbf{X}_i) = \lambda_0(t) e^{\mathbf{X}_i\beta + \mathbf{Z}\omega}$$

where ω is a vector containing the q random effects, and $\mathbf{Z}$ is a design matrix indicating which group the ith subject belongs to. z_{ij} is 1 if the ith subject is a member of the jth group, and 0 otherwise. If the number of groups is less than the number of subjects, then the model is known as a shared frailty model.

One method of estimating the random effects is through the use of a penalised Cox model (Therneau and Grambsch, 2000). This is a model with a penalised partial likelihood

$$PL_p(\beta, \omega, \theta) = l_p(\beta, \omega) - g(\omega, \theta)$$

where $l_p(\beta, \omega)$ is the log partial likelihood for the Cox model with frailty, and $g(\omega, \theta)$ is a function of the random effects and some other parameter, θ.

The two most common choices for $g(\omega, \theta)$ are

$$g(\omega, \theta) = \frac{1}{\theta} \sum_{j=1}^{q} \left[\omega_j - e^{\omega_j} \right]$$

and

$$g(\omega, \theta) = \frac{1}{2\theta} \sum_{j=1}^{q} \omega_j^2$$

The first function describes a gamma frailty model. In this model, the ω_js are distributed as the logs of iid gamma random variables. The second function describes a normal frailty model. In this model, the ω_js have a normal distribution with variance θ. In both cases, the expected value of the ω_js is 0, and their variance is θ. The relationship between the gamma frailty model and the penalised likelihood model only holds for the shared frailty model, but the normal frailty model relationship holds for a general $\mathbf{Z}$ (Therneau and Grambsch, 2000).

A normal frailty model was applied to the laryngeal cancer data, and the results are given in Table 2, with Table 3 giving the results from Chapter 4, of the proportional hazards model without frailty.

Table 2. Result of applying a Cox proportional hazards model with individual normal random effects to the laryngeal cancer data

Variables	Parameter estimates	Standard errors	p-values	95% Confidence Intervals
Stage 2	0.1526	0.5534	0.7800	(-0.9321, 1.2373)
Stage 3	0.9000	0.4468	0.0440	(0.0243, 1.7757)
Stage 4	2.1125	0.5404	<0.0001	(1.0534, 3.1716)
Age	0.0201	0.0176	0.2500	(-0.0143, 0.0545)
Log likelihood	-196.8635			
Likelihood ratio test	73.9096 ($p < 0.0001$)			
R^2	0.5675			
Variance of random effects	0.8333			

Table 3. Results of applying Cox proportional hazards model with no random effects to the laryngeal cancer data

Variables	Parameter estimates	Standard errors	p-values	95% Confidence Intervals
Stage 2	0.1399	0.4625	0.7623	(-0.7666, 1.0464)
Stage 3	0.6422	0.3561	0.0713	(-0.0558, 1.3402)
Stage 4	1.7062	0.4219	<0.0001	(0.8793, 2.5331)
Age	0.0190	0.0143	0.1820	(-0.0089, 0.0470)
Log likelihood	-187.7074			
Likelihood ratio test	18.3122 ($p = 0.0011$)			
R^2	0.1864			

Introducing the random effects has altered the parameter estimates and caused Stage 3 to become significant, and has increased the value of the R^2 statistic. This indicates that the individual random effects account for nearly 40% of the variation in the data.

Figures 5 to 7 show plots from the proportional hazards model with individual random effects applied to the laryngeal cancer data.

Figure 5. Plot of the martingale residuals

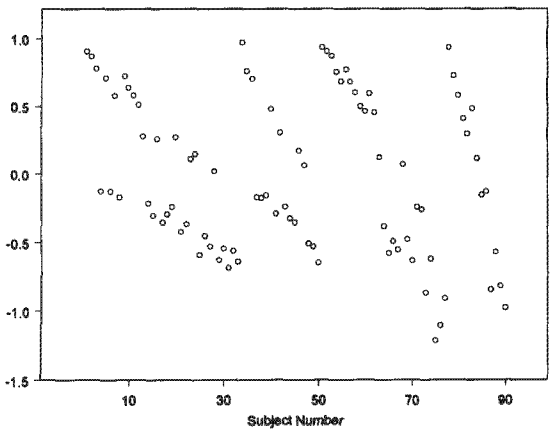


Figure 6. Plot of the individual random effects

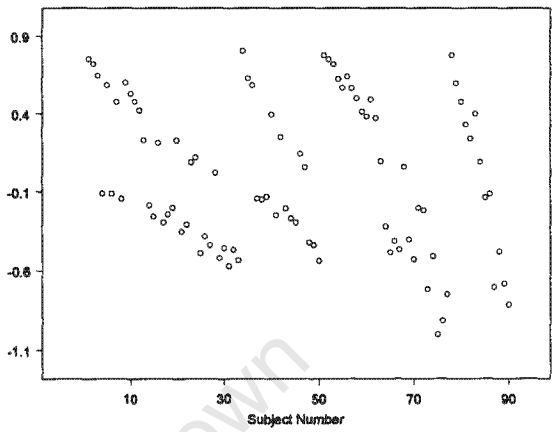
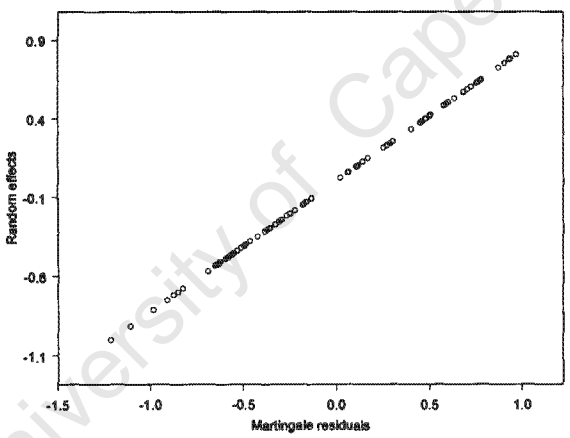


Figure 7. Plot of the random effects against the martingale residuals



With the exception of the scale, the plots of the martingale residuals and the random effects appear identical, while a plot of the random effects against the martingale residuals appears to result in a straight line. This suggests that the random effects are the martingale residuals scaled by a constant factor. An explanation can be found by examining the estimating equations.

The penalised partial likelihood is

$$PL_p(\beta,\omega,\theta)=l_p(\beta,\omega)-g(\omega,\theta)$$

Therefore the random effects are the solutions to the set of equations

$$\frac{\partial PL_p}{\partial \omega_j}=\frac{\partial l_p(\beta,\omega)}{\partial \omega_j}-\frac{\partial g(\omega,\theta)}{\partial \omega_j}=0\,,j=1\ldots q$$

From Chapter 4, the partial log likelihood function for a proportional hazards model without frailty is

$$l_p(\beta)=\sum_{i=1}^{D}\left[\mathbf{X}_{(i)}\beta-\log\left(\sum_{h\in R_{(i)}}e^{\mathbf{X}_h\beta}\right)\right]$$

Introducing an individual frailty term, this becomes

$$l_p(\beta)=\sum_{i=1}^{D}\left[\mathbf{X}_{(i)}\beta+\omega_{(i)}-\log\left(\sum_{h\in R_{(i)}}e^{\mathbf{X}_h\beta+\omega_h}\right)\right]$$

$$=\sum_{i=1}^{n}\delta_i\left[\mathbf{X}_i\beta+\omega_i\right]-\sum_{i=1}^{D}\log\left(\sum_{h\in R_{(i)}}e^{\mathbf{X}_h\beta+\omega_h}\right)$$

$$\Rightarrow\frac{\partial l_p(\beta)}{\partial \omega_j}=\delta_j-\sum_{t_{(i)}\le t_j}\frac{e^{\mathbf{X}_j\beta+\omega_j}}{\sum_{h\in R_{(i)}}e^{\mathbf{X}_h\beta+\omega_h}}$$

For a normal frailty model, $g(\omega,\theta)=\frac{1}{2\theta}\sum_{i=1}^{n}\omega_i^2$, where θ is the variance of the random effects. So $\frac{\partial g(\omega,\theta)}{\partial \omega_j}=\frac{\omega_j}{\theta}$

Therefore, $\frac{\partial PL_p(\beta)}{\partial \omega_j}=\delta_j-e^{\mathbf{X}_j\beta+\omega_j}\sum_{t_{(i)}\le t_j}\frac{1}{\sum_{h\in R_{(i)}}e^{\mathbf{X}_h\beta+\omega_h}}-\frac{\omega_j}{\theta}$, and from $\frac{\partial PL_p}{\partial \omega_j}=0$

$$\omega_j=\theta\left(\delta_j-e^{\mathbf{X}_j\beta+\omega_j}\sum_{t_{(i)}\le t_j}\frac{1}{\sum_{h\in R_{(i)}}e^{\mathbf{X}_h\beta+\omega_h}}\right)$$

Replacing β and ω_j with their maximum partial likelihood estimates gives

$$\omega_j = \theta\left(\delta_j - e^{\mathbf{X}_j\hat{\beta}+\hat{\omega}_j}\sum_{t_{(i)}\le t_j}\frac{1}{\sum_{h\in R_{(i)}} e^{\mathbf{X}_h\hat{\beta}+\hat{\omega}_h}}\right)$$

Since $\hat{\Lambda}_0(t_j) = \sum_{t_{(i)}\le t_j}\frac{1}{\sum_{h\in R_{(i)}} e^{\mathbf{X}_h\hat{\beta}+\hat{\omega}_h}}$ (Klein and Moeschberger, 1997), this means that

$$\begin{aligned}\omega_j &= \theta\left(\delta_j - e^{\mathbf{X}_j\beta+\hat{\omega}_j}\hat{\Lambda}_0(t_j)\right)\\ &= \theta\times\hat{M}_j\end{aligned}$$

From this, it can be seen that the random effects are equal to the martingale residuals scaled by a constant, which is the variance of the random effects. This comes from the fact that the normal frailty model was used, and does not affect the use and interpretation of the random effects. This result is analogous to that of a linear mixed model, where the random effects are also a scaled version of the average residual of the observations.

The residuals and random effects were examined during the development of this thesis. The focus later shifted to that of the comparison of interval-censored analysis techniques, and examination of the residuals and random effects was discontinued. The investigation of the patterns of the plots was still included partly as a curiosity, and partly due to the fact that no explanation for these patterns had been found in any relevant literature.

7. Buckley-James regression model

The Buckley-James regression model (Buckley and James, 1979) is an alternative approach to regression analysis of censored data. It has its basis in the linear regression model

$$T_i = \mathbf{X}_i\beta + \varepsilon$$

The error term ε comes from an unspecified distribution, with expected value 0.

For ease of notation, define c_i to be the observed time for all censored subjects. A response variable, y_i is defined as

$$y_i = \delta_i t_i + (1-\delta_i)c_i$$

Because c_i is an observed time, y_i is an observed variable. The Buckley-James method replaces c_i, allowing a random response variable Y_i^* to be defined as

$$Y_i^* = \delta_i T_i + (1-\delta_i)E[T_i \mid T_i > c_i]$$

Y_i^* is known as the renovated response (Smith and Zhang, 1995).

In order to find $E[T_i \mid T_i > c_i]$, $Y_i^*(\mathbf{b})$, the estimate of Y_i^*, is written as

$$\begin{aligned} Y_i^*(\mathbf{b}) &= \delta_i(\mathbf{X}_i\mathbf{b} + \varepsilon_i(\mathbf{b})) + (1-\delta_i)E[\mathbf{X}_i\mathbf{b} + \varepsilon_i(\mathbf{b}) \mid T_i > c_i] \\ &= \delta_i(\mathbf{X}_i\mathbf{b} + \varepsilon_i(\mathbf{b})) + (1-\delta_i)E[\mathbf{X}_i\mathbf{b} + \varepsilon_i(\mathbf{b}) \mid \varepsilon_i(\mathbf{b}) > v_i(\mathbf{b})] \\ &= \mathbf{X}_i\mathbf{b} + [\delta_i\varepsilon_i(\mathbf{b}) + (1-\delta_i)E[\varepsilon_i(\mathbf{b}) \mid \varepsilon_i(\mathbf{b}) > v_i(\mathbf{b})]] \end{aligned}$$

where $\mathbf{b}$ is a vector of parameter estimates, $\varepsilon_i(\mathbf{b}) = T_i - \mathbf{X}_i\mathbf{b}$ and $v_i(\mathbf{b}) = c_i - \mathbf{X}_i\mathbf{b}$

$E[\varepsilon_i(\mathbf{b}) \mid \varepsilon_i(\mathbf{b}) > v_i(\mathbf{b})]$ can be written as a weighted linear combination

$$E[\varepsilon_i(\mathbf{b}) \mid \varepsilon_i(\mathbf{b}) > v_i(\mathbf{b})] = \sum_{k=1}^{n} w_{ik}(\mathbf{b})\varepsilon_i(\mathbf{b})$$

with the weights defined as

$$w_{ik}(\mathbf{b}) = \begin{cases} \dfrac{d\hat{F}(e_{(k)}(\mathbf{b}))\delta_k(1-\delta_i)}{\hat{S}(e_{(i)}(\mathbf{b}))} & \text{if } k > i \\ 0 & \text{otherwise} \end{cases}$$

where $\hat{S}$ is a Kaplan-Meier estimator applied to $e_{(k)}(\mathbf{b})$, the observed ordered residuals, and $\hat{F} = 1 - \hat{S}$, with $d\hat{F}(e_{(k)}(\mathbf{b}))$ the probability mass assigned to $e_{(k)}(\mathbf{b})$.

Since $w_{ik}(\mathbf{b})(1-\delta_i) = w_{ik}(\mathbf{b})$, $\hat{\mathbf{Y}}^*(\mathbf{b})$, the vector of renovated responses, can be written as

$$\hat{\mathbf{Y}}^*(\mathbf{b}) = \mathbf{X}\mathbf{b} + \mathbf{W}(\mathbf{b})(\mathbf{Y} - \mathbf{X}\mathbf{b})$$

where $\mathbf{X}$ is a design matrix with the ith row equal to $\mathbf{X}_i$ and

$$\mathbf{W}(\mathbf{b}) = \mathrm{diag}(\delta) + [w_{ik}(\mathbf{b})] = \begin{pmatrix} \delta_i & w_{12}(\mathbf{b}) & \cdots & w_{1n}(\mathbf{b}) \\ 0 & \delta_2 & \cdots & w_{2n}(\mathbf{b}) \\ \vdots & \vdots & \ddots & \vdots \\ 0 & 0 & \cdots & \delta_n \end{pmatrix}$$

The Buckley-James estimate of β is the value of $\mathbf{b}$ that satisfies the equation

$$\mathbf{b} = (\mathbf{X}'\mathbf{X})^{-1}\mathbf{X}'\mathbf{Y}^*(\mathbf{b})$$

An iterative procedure is used to find this value, with $\mathbf{b}_n$, the estimate after n iterations equal to $(\mathbf{X}'\mathbf{X})^{-1}\mathbf{X}'\mathbf{Y}^*(\mathbf{b}_{n-1})$.

Smith (2002) gives further details as well as S-Plus code. Because other survival models such as the proportional hazards model and accelerated failure time model are multiplicative in $\mathbf{X}$, the logarithms of the observed times are usually used (Heller and Simonoff, 1992).

An estimate of the variance of β_k is given by

$$\frac{\sum_i^u \mathrm{var}(y_i)(x_{ik} - \bar{x}_{uk})^2}{\left(\sum_i^u (x_{ik} - \bar{x}_{uk})^2\right)^2}$$

where $\sum_i^u$ indicates a summation over uncensored observations, and $\bar{x}_{uk}$ is the mean of the uncensored x values for the kth variable (Buckley and James, 1979).

Table 4 gives the results of applying a Buckley-James model to the laryngeal cancer data.

Table 4. Results of applying Buckley-James model to the laryngeal cancer data

Variables	Parameter estimates	Standard errors	p-values	95% Confidence Intervals
Intercept	3.1989			
Stage 2	-0.2083	0.4347	0.3159	(-1.0604, 0.6437)
Stage 3	-0.9205	0.3184	0.0019	(-1.5446, -0.2963)
Stage 4	-1.8357	0.3642	<0.0001	(-2.5495, -1.1220)
Age	-0.0170	0.0134	0.1028	(-0.0432, 0.0093)
R^2	0.2905			

An R^2 statistic can be obtained by making use of the fact that

$$\mathbf{b}_n = (\mathbf{X}'\mathbf{X})^{-1}\mathbf{X}'\mathbf{Y}^*(\mathbf{b}_{n-1})$$

which is a linear regression performed on the renovated responses.

For the Buckley-James model, a positive value for a coefficient means that an increase in the value of the respective covariate will lead to a longer time till death. This is in contrast to the proportional hazards model where a positive coefficient means a greater chance of death, and therefore a shorter survival time. For that reason, the parameter estimates from the Buckley-James model and proportional hazards model will have opposing signs.

One of the useful features of the Buckley-James method is that the renovated responses are either the observed survival time for uncensored observations, or the expected survival time for censored observations. This means that it is possible to compare the original responses and the renovated responses by means of a scatterplot (Smith and Zhang, 1995).

Figure 8 and Table 5 show the original and the renovated responses for the laryngeal cancer data set. The vertical lines in Figure 8 show the extent of the renovation.

Figure 8. Plot of original and renovated responses

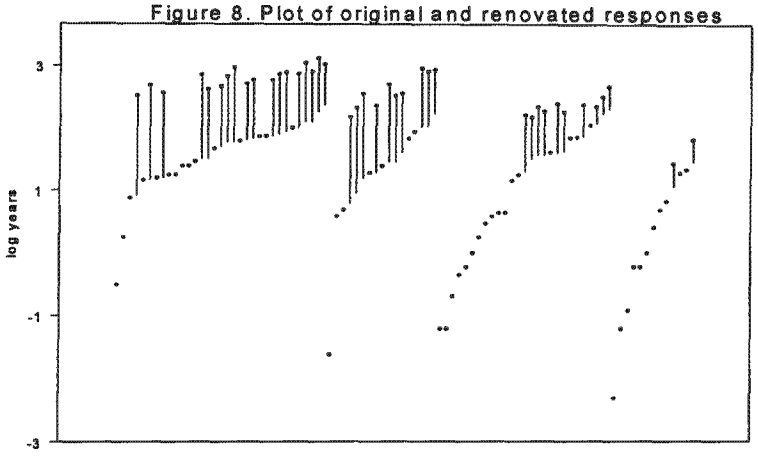


Table 5. Comparison of observed responses with renovated responses

Stage 1		Stage 2		Stage 3		Stage 4	
Original	Renovated	Original	Renovated	Original	Renovated	Original	Renovated
-0.5108	-0.5108	-1.6094	-1.6094	-1.2040	-1.2040	-2.3026	-2.3026
0.2624	0.2624	0.5878	0.5878	-1.2040	-1.2040	-1.2040	-1.2040
0.8755	0.8755	0.6931	0.6931	-0.6931	-0.6931	-0.9163	-0.9163
0.9163*	2.5199	0.7885*	2.1754	-0.3567	-0.3567	-0.2231	-0.2231
1.1632	1.1632	0.9555*	2.3251	-0.2231	-0.2231	-0.2231	-0.2231
1.1632*	2.6831	1.1939*	2.5548	0	0	0	0
1.1939	1.1939	1.2809	1.2809	0.2624	0.2624	0.4055	0.4055
1.1939*	2.5593	1.2809*	2.3642	0.4700	0.4700	0.6931	0.6931
1.2528	1.2528	1.3863	1.3863	0.5878	0.5878	0.8329	0.8329
1.2528	1.2528	1.4586*	2.7041	0.6419	0.6419	1.0647*	1.4360
1.3863	1.3863	1.4586*	2.5206	0.6419	0.6419	1.2809	1.2809
1.3863	1.3863	1.6094*	2.5723	1.1632	1.1632	1.3350	1.3350
1.4586	1.4586	1.8245	1.8245	1.2528	1.2528	1.4586*	1.8106
1.5041*	2.8556	1.9459	1.9459	1.3083*	2.2171		
1.5041*	2.6198	2.0149*	2.9639	1.5041*	2.1785		
1.6677	1.6677	2.0281*	2.9130	1.5686*	2.3438		
1.7047*	2.6703	2.2300*	2.9379	1.5686*	2.2741		
1.7750*	2.8305			1.6094	1.6094		
1.7750*	2.9761			1.6094*	2.3929		
1.7918	1.7918			1.6292*	2.2647		
1.8083*	2.7140			1.8405	1.8405		
1.8245*	2.7721			1.8563	1.8563		
1.8563	1.8563			1.8718*	2.3801		
1.8718	1.8718			2.0541	2.0541		
1.8718*	2.7706			2.0794*	2.3515		
1.9021*	2.8653			2.2300*	2.5042		
1.9459*	2.9006			2.3125*	2.6745		
2.0015	2.0015						
2.0015*	2.8724						
2.0919*	3.0444						
2.0919*	2.9067						
2.2618*	3.1269						
2.3702*	3.0273						

* denotes censored observation

8. Accelerated Failure Time model

Like the Buckley-James model, the accelerated failure time (AFT) model has its basis in the linear regression model

$$\log T_i = \mathbf{X}_i\beta + \varepsilon$$

where T_i is the ith subject's failure time random variable, $\mathbf{X}_i$ and β are vectors of covariates and coefficients respectively, and ε is an error variable independent of $\mathbf{X}$ with expected value 0. Taking exponents gives

$$T_i = T_0 e^{\mathbf{X}_i\beta}$$

where $T_0 = e^{\varepsilon}$ is a baseline failure time. The role of $\mathbf{X}$ is to accelerate or decelerate the time to death, hence the name of the model.

The AFT model rewrites the linear regression model as

$$Y = \log T = \mathbf{X}\beta + \sigma W$$

The distribution of the random variable W determines the distribution of T. For example, if W has an extreme value distribution with density function $f_W(w) = \exp(w - e^w)$, then the density function of Y is

$$f_Y(y) = \frac{1}{\sigma}\exp\left(\frac{y-\mathbf{X}\beta}{\sigma} - e^{\frac{y-\mathbf{X}\beta}{\sigma}}\right)$$

and the density function of T is

$$f_T(t) = \frac{1}{\sigma}t^{\frac{1}{\sigma}-1}e^{\frac{-\mathbf{X}\beta}{\sigma}}e^{-t^{\frac{1}{\sigma}}e^{\exp\left(\frac{-\mathbf{X}\beta}{\sigma}\right)}}$$

$$= \alpha t^{\alpha-1}\lambda e^{-\lambda t^{\alpha}} \qquad \alpha = \frac{1}{\sigma}, \lambda = e^{\frac{-\mathbf{X}\beta}{\sigma}}$$

which is the density function from a Weibull distribution. If $\sigma = 1$, then T will have an exponential distribution.

The estimate of β is found by maximising the likelihood

$$L = \prod_{i=1}^{n}[f_Y(y_i)]^{\delta_i}[S_Y(y_i)]^{(1-\delta_i)}$$

$$= \prod_{i=1}^{n}[f_Y(\log t_i)]^{\delta_i}[S_Y(\log t_i)]^{(1-\delta_i)}$$

Other distributions can be placed on W, including the normal distribution, which leads to T having a log-normal distribution and the logistic distribution, which has the density function $f_W(w) = \frac{e^w}{(1+e^w)^2}$, and leads T having a log-logistic distribution with density function $f_T(t) = \frac{\alpha\lambda t^{\alpha-1}}{(1+\lambda t^{\alpha-1})^2}$, where as before, $\alpha = \frac{1}{\sigma}$ and $\lambda = \exp\left(\frac{-\mathbf{X}\beta}{\sigma}\right)$.

The results of applying the Weibull and log-logistic models to the laryngeal cancer data are shown in Tables 6 and 7.

Table 6. Results of applying a Weibull AFT model to the laryngeal cancer data

Variables	Parameter estimates	Standard errors	p-values	95% Confidence Intervals
Intercept	3.5288	0.9041	<0.0001	(1.7568, 5.3008)
Stage 2	-0.1477	0.4076	0.7170	(-0.9466, 0.6512)
Stage 3	-0.5866	0.3199	0.0668	(-1.2136, 0.0404)
Stage 4	-1.5441	0.3633	<0.0001	(-2.2562, -0.8320)
Age	-0.0175	0.0128	0.1717	(-0.0426, 0.0076)
Log likelihood	-141.4234			
Likelihood ratio test	19.3734 ($p < 0.0001$)			
R^2	0.1937			
Scale	0.8848			

Table 7. Results of applying a Log-logistic AFT model to the laryngeal cancer data

Variables	Parameter estimates	Standard errors	p-values	95% Confidence Intervals
Intercept	3.1022	0.9527	0.0011	(1.2349, 4.9695)
Stage 2	-0.1257	0.4152	0.7621	(-1.9395, 0.6881)
Stage 3	-0.8057	0.3539	0.0228	(-1.4993, -0.1121)
Stage 4	-1.7661	0.4257	<0.0001	(-2.6005, -0.9317)
Age	-0.0151	0.0138	0.2734	(-0.0421, -0.0151)
Log likelihood	-141.5890			
Likelihood ratio test	20.0743 ($p < 0.0001$)			
R^2	0.1999			
Scale	0.7152			

The scale is the parameter σ from the equation $Y = \log T = \mathbf{X}\beta + \sigma W$, and the value of R^2 is calculated using Nagelkerke's formula (Nagelkerke, 1991).

Like the Buckley-James model, in the AFT model a positive value for a coefficient means that an increase in the value of the respective covariate will lead to a longer time till death. Therefore, the parameter estimates from the AFT model and Buckley-James model will have the same sign, which is the opposing sign to the respective estimate from the proportional hazards model.

In comparing the two models, it can be seen that the two models produce similar estimates. The main difference is that of the estimate for Stage 3, which is not quite significant in the Weibull model, but is significant in the log-logistic model. Comparing the R^2 values suggests that the log-logistic model fits slightly better, although the difference is negligible. These results suggest that for this data, neither model performs better than the other one. Models from other distributions could be fitted, but the Weibull and log-logistic models have been chosen as they have relatively simple expressions for the median survival time, which will be used for comparisons with other models in Chapter 9.

9. Comparison of models

So far, four different models have been considered. The results of the parameter estimates for the laryngeal cancer are summarised in Table 8.

Table 8. Summary of results of analysis of laryngeal cancer data

	Proportional hazards			Buckley-James		
Variables	Parameter estimates	Standard errors	p-values	Parameter estimates	Standard errors	p-values
Stage 2	0.1399	0.4625	0.7623	-0.2083	0.4347	0.3159
Stage 3	0.6422	0.3561	0.0713	-0.9205	0.3184	0.0019
Stage 4	1.7062	0.4219	<0.0001	-1.8357	0.3642	<0.0001
Age	0.0190	0.0143	0.1820	-0.0170	0.0134	0.1028
	Weibull AFT			Log-logistic AFT		
Variables	Parameter estimates	Standard errors	p-values	Parameter estimates	Standard errors	p-values
Stage 2	-0.1477	0.4076	0.7170	-0.1257	0.4152	0.7621
Stage 3	-0.5866	0.3199	0.0668	-0.8057	0.3539	0.0228
Stage 4	-1.5441	0.3633	<0.0001	-1.7661	0.4257	<0.0001
Age	-0.0175	0.0128	0.1717	-0.0151	0.0138	0.2734

As noted earlier, the estimates from the proportional hazards model will have the opposite sign to that of the Buckley-James and AFT models. This is due to the fact that proportional hazards model measures how the variables affect the risk of dying, while the other models measure how the variables affect the time to death, and an increased risk of dying will result in a shorter time to death.

For all four models, the variable Stage 4 is significant. For the Buckley-James and log-logistic models, the variable Stage 3 is also significant. It is almost significant for the other two models, so its significance is not entirely unrealistic due to the differing model formulations.

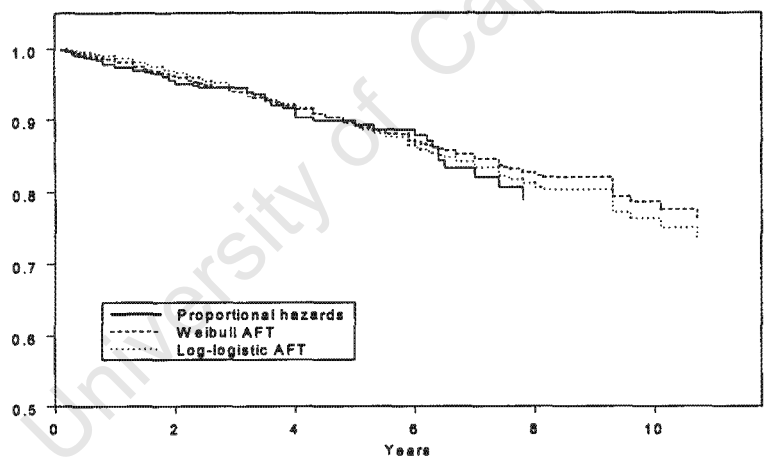
The estimated baseline survival curves can also be compared. For the proportional hazards model, an estimate of the survival curve is given by $\hat{S}_0(t) = \exp\left(-\hat{\Lambda}_0(t)\right)$, with $\hat{\Lambda}_0(t) = \sum_{t_{(i)} \le t} \frac{1}{\sum_{h \in R_{(i)}} e^{\mathbf{x}_h \hat{\boldsymbol{\beta}}}}$.

Since the AFT model is parametric, estimates of the baseline survival curve can easily be obtained. For the Weibull model, an estimate of the baseline survival curve is $\hat{S}_0(t) = e^{-t^{1/\sigma}\exp(-\hat{\beta}_0/\sigma)}$, and for the log-logistic model it is $\hat{S}_0(t) = \frac{1}{1+t^{1/\sigma}\exp(-\hat{\beta}_0/\sigma)}$.

The Buckley-James model is not based on a likelihood, so it is not possible to obtain an estimate of the baseline survival that is directly comparable to that of the proportional hazards and AFT models.

Figure 9 shows the three baseline survival curves from the proportional hazards and AFT models, and it can be seen that the three models produce very similar curves. The survival curve estimate from the proportional hazards model is based on observed survival times. As the largest uncensored survival time was 7.8, the survival curve estimate can only be calculated up to that time.

Figure 9. Estimates of baseline survival curves



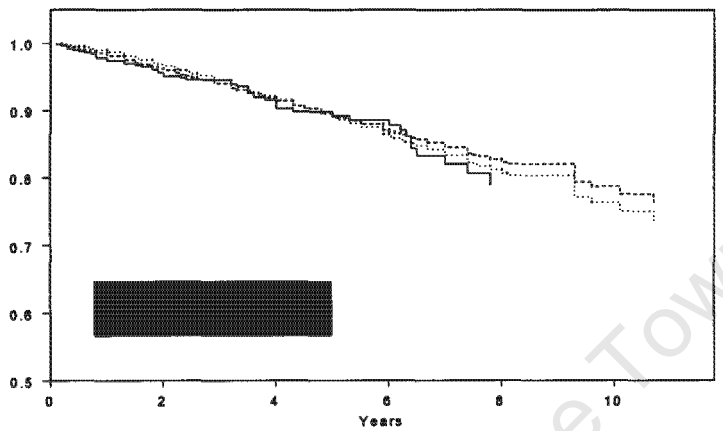
These two methods of comparison can be used to examine the results of estimation for similarities in the results. What they do not do is indicate whether one model performs better than the other models. Even if the results from one model were significantly different, these would not give an indication as to whether that the model performs better or worse than the other models.

A non-graphical means of comparing the estimates is based on Heller and Simonoff's comparison of the Cox proportional hazards model and the Buckley-James model

Since the AFT model is parametric, estimates of the baseline survival curve can easily be obtained. For the Weibull model, an estimate of the baseline survival curve is $\hat{S}_0(t) = e^{-t^{1/\sigma}\exp(-\hat{\beta}_0/\sigma)}$, and for the log-logistic model it is $\hat{S}_0(t) = \frac{1}{1+t^{1/\sigma}\exp(-\hat{\beta}_0/\sigma)}$.

The Buckley-James model is not based on a likelihood, so it is not possible to obtain

Figure 9. Estimates of baseline survival curves



an estimate of the baseline survival that is directly comparable to that of the proportional hazards and AFT models.

The following plot shows the three baseline survival curves

From Figure 9, it can be seen that the three models produce very similar curves. The survival curve estimate from the proportional hazards model is based on observed survival times. As the largest uncensored survival time was 7.8, the survival curve estimate can only be calculated up to that time.

These two methods of comparison can be used to examine the results of estimation for similarities in the results. What they do not do is indicate whether one model performs better than the other models. Even if the results from one model were significantly different, these would not give an indication as to whether that the model performs better or worse than the other models.

A non-graphical means of comparing the estimates is based on Heller and Simonoff's comparison of the Cox proportional hazards model and the Buckley-James model

(Heller and Simonoff, 1992). Simulation was used in order to determine which model would be the better choice in a given situation. The two models were compared by finding $\hat{t}_i$, the predicted value of the survival time. For the proportional hazards model, the median survival time was used, and for the Buckley-James model, $\hat{t}_i = e^{\mathbf{x}_i\hat{\boldsymbol{\beta}}}$. The predicted values were compared to the true survival times by the criterion $P = \sum\left[\left(t_i - \hat{t}_i\right)/t_i\right]^2$, with the smaller value of P indicating the better performing model. Table 9 summarises their results.

Table 9. Results from Heller and Simonoff (1992)

Censoring proportion	Strength of regression (R^2 from Cox model)	Model choice
<40%		Buckley-James
40%-60%	0.00 – 0.25	Buckley- James
	0.25 – 0.65	Cox
	0.65 – 1.00	Buckley-James
>60%		Cox

As Heller and Simonoff used simulation, all the survival times were known. Their method has to be adapted slightly in order to compare the estimates for the laryngeal cancer data. P was calculated by summing over only the uncensored subjects, as the true survival times of the censored subjects are not known. The median survival times from the AFT models were used to find $\hat{t}_i$.

The survival function from the Weibull AFT model is

$$S(t) = e^{-t^{1/\sigma}\exp\left(\frac{-\mathbf{x}\boldsymbol{\beta}}{\sigma}\right)}$$

which gives a median survival time of $(-\log 0.5)^{\sigma} e^{\mathbf{x}\boldsymbol{\beta}}$.

The survival function from the log-logistic AFT model is

$$S(t) = \frac{1}{1 + t^{\frac{1}{\sigma}} e^{\frac{-\mathbf{x}\boldsymbol{\beta}}{\sigma}}}$$

which gives a median survival time of $e^{\mathbf{x}\boldsymbol{\beta}}$.

The survival function from the Cox model is

$$S(t) = S_0(t)^{\exp(X\beta)}$$

where $S_0(t)$ is the baseline survival function. The median survival time is the value of t such that

$$S_0(t) = 0.5^{\exp(-X\beta)}$$

The values of P and R^2 from the four models are given in Table 10.

Table 10. Comparison of models

Model	Value of P	Value of R^2
Proportional hazards	1940.308	0.1841
Buckley-James	1150.82	0.2905
Weibull AFT	1604.385	0.1937
Log-logistic AFT	1487.193	0.1999

The values of P indicate that the Buckley-James model performs the best on the laryngeal cancer data. The laryngeal cancer data set has a censoring proportion of 44.44% and an R^2 value of 0.1841. The results of Heller and Simonoff suggest that the Buckley-James model should perform better than the Cox model, a fact that is borne out by the above results. The value of P for the Buckley-James model is lower than that of the other three models, and the value of R^2, which is the percentage of explained variation, is larger. Both these values suggest that the Buckley-James model is the best choice for this set of data.

10. Modelling interval-censored data

If the data is interval-censored, then instead of observing t_i, as was the case previously, the interval $[l_i, r_i]$ is observed, with $l_i \leq t_i \leq r_i$. If $l_i = r_i$, then the event of interest has been observed exactly. If the subject is left-censored, meaning that the event of interest occurred at some time before the beginning of the study, then l_i will be 0, although $-\infty$ can also be used. If $r_i = \infty$, then the subject is right-censored, which is the censoring scheme considered previously.

One approach to modelling interval-censored data is to make an assumption about when the event occurred during the interval $[l_i, r_i]$. The three most logical choices are the left-hand endpoint (l_i), the right-hand endpoint (r_i), or the midpoint of the interval ($\frac{l_i + r_i}{2}$). An alternative approach is to adapt the models which have already been considered.

10.1 Proportional hazards model

Finkelstein (1986) proposed a proportional hazards model for interval-censored data. The likelihood function for this model is

$$L = \prod_{i=1}^{n} [S(l_i \mid \mathbf{X}_i) - S(r_i \mid \mathbf{X}_i)]$$

A set C is constructed as the union of disjoint closed intervals whose left endpoints lie in the set $L = \{l_i; 1 \leq i \leq n\}$ and whose right endpoints lie in the set $R = \{r_i; 1 \leq i \leq n\}$. C is written as $\bigcup_{j=1}^{m} [q_j, p_j]$, where $q_1 \leq p_1 < q_2 \leq p_2 < \ldots < q_m \leq p_m$. Also constructed, for ease of notation, is the set $G = \{0\} \cup \{q_j, p_j; 1 \leq j \leq m$, which has elements indexed as $g_0, g_1, \ldots, g_m$, such that $0 = g_0 \leq g_1 \leq \ldots \leq g_m$. The likelihood can then be written as

$$L = \prod_{i=1}^{n} \sum_{j=1}^{m} a_{ij} [S(q_j \mid \mathbf{X}_i) - S(p_j \mid \mathbf{X}_i)]$$

where $a_{ij} = 1$ if $[q_j, p_j] \subseteq [l_i, r_i]$ and 0 otherwise.

From the proportional hazards assumption, $S(t \mid \mathbf{X}_i) = S_0(t)^{\exp(\mathbf{X}_i\beta)}$, where $S_0(t)$ is the baseline survival function. The likelihood is then reparameterised by $\gamma_j = \log(-\log S_0(g_j))$, and the log likelihood can be written as

$$\sum_{i=1}^{n} \log \sum_{j=1}^{m} a_{ij} \left[\exp\left(-\exp(\mathbf{X}_i\beta + \gamma_{j-1})\right) - \exp\left(-\exp(\mathbf{X}_i\beta + \gamma_j)\right) \right]$$

A Newton-Raphson procedure is used to find the MLE's of γ and β, and Finkelstein (1986) gives the equations for the score statistic and the information matrix. Pan and Chappell (2002) examine alternative methods of estimation for this model.

If no covariates are specified, then this model produces a survival curve that is identical to that of Turnbull (1976), but has the advantage of being produced by an iterative procedure that has a faster rate of convergence.

10.2 AFT model

Owing to its parametric nature, the AFT model can easily be adapted to analyse interval-censored data. The likelihood previously given becomes

$$L = \prod_{i=1}^{n} \left[f_Y(\log t_i) \right]^{\delta_i} \left[S_Y(\log l_i) - S_Y(\log r_i) \right]^{(1-\delta_i)}$$

where, as before, δ_i is 1 if the ith subject's event is observed to have happened, and 0 if the subject is censored in any way.

10.3 Buckley-James model

Using the Buckley-James model to analyse interval-censored data requires that δ_i be defined as for the AFT model.

An initial estimate of the parameters, **b**, is found by performing a least squares regression using the left-hand endpoints of the time intervals as a response variable. Residual intervals $J_i(\mathbf{b}) = [l_i - \mathbf{X}_i\mathbf{b}, r_i - \mathbf{X}_i\mathbf{b}]$ are created, and the weights matrix becomes

$$w_{ij}(\mathbf{b}) = \begin{cases} \delta_i & j = i \\ \dfrac{d\hat{F}(e_j(\mathbf{b}))\delta_j(1-\delta_i)}{\int_{J_i(\mathbf{b})} d\hat{F}(u)} & e_j(\mathbf{b}) \in J_i(\mathbf{b}) \\ 0 & \text{otherwise} \end{cases}$$

Smith (2002) suggests using the Kaplan-Meier estimate applied to the residuals to obtain $\hat{F}$, which requires some of the responses to be observed exactly, preferrably at least half of them (Smith, 2002). If this is not the case, then an alternative estimate such as Turnbull's (1976) estimate of the survival function must be used, although as noted above, Finkelstein's estimate can be used instead.

10.4 Comparison

As noted earlier, comparing the parameter estimates from the three models will not reveal much. What can be meaningfully compared for each model are the estimates obtained from the interval-censored model, and the estimates obtained from the equivalent right-censored models using the left-hand endpoint, right-hand endpoint and midpoint as the observed time.

Each of the models was used to analyse the interval-censored breast cancer data. Four analyses were performed for each model, the three approximations given above, and an analysis using the time intervals. The effect of the use of chemotherapy was investigated, and results are given in the Table 11.

Table 11. Results of applying models to breast cancer data

Proportional hazards model				
Model	Effect of chemotherapy	Standard errors	p-values	R^2
Left endpoint	0.9237	0.2871	0.0013	0.1099
Midpoint	0.9059	0.2854	0.0015	0.1070
Right endpoint	0.7765	0.2859	0.0066	0.0789
Interval	0.7903	0.2887	0.0063	0.1142
Buckley-James model				
Model	Effect of chemotherapy	Standard errors	p-values	R^2
Left endpoint	-0.4788	0.2670	0.0729	0.0330
Midpoint	-0.3041	0.1866	0.1030	0.0362
Right endpoint	-0.1912	0.1635	0.2434	0.0170
Interval	-0.5930	0.2090	0.0046	0.1242
Weibull AFT model				
Model	Effect of chemotherapy	Standard errors	p-values	R^2
Left endpoint	-0.7571	0.2376	0.0014	0.1066
Midpoint	-0.5527	0.1697	0.0012	0.1047
Right endpoint	-0.4117	0.1419	0.0037	0.0913
Interval	-0.5644	0.1737	0.0012	0.1104
Log-logistic AFT model				
Model	Effect of chemotherapy	Standard errors	p-values	R^2
Left endpoint	-0.6352	0.2652	0.0166	0.0598
Midpoint	-0.4649	0.1915	0.0152	0.0598
Right endpoint	-0.3657	0.1607	0.0228	0.0518
Interval	-0.4865	0.1940	0.0122	0.0638

From the results it can be seen that the choice of the method of approximation can affect the parameter estimates. Of particular interest is the Buckley-James model, where none of the estimates using the approximations are significant, while the estimate using the interval is significant. This shows that approximating the survival time can lead to misleading results.

The interval-censoring models were compared using the method described in the previous chapter, by calculating $P = \sum\left[(t_i - \hat{t}_i)/t_i\right]^2$. The midpoint of $[l_i, r_i]$ was used as t_i. The values of P and R^2 are given in Table 12.

Table 12. Comparison of models

Model	Value of P	Value of R^2
Proportional hazards	171.826	0.1142
Buckley-James	46.322	0.1242
Weibull AFT	344.785	0.1104
Log-logistic AFT	387.945	0.0638

The values of P and R^2 of suggest that the Buckley-James model is the better model. However, for this data set, there is only one explanatory variable, which is a binary variable. Therefore for each model, there are only two different values for $\hat{t}_i$, which means that calculating P is not as effective a means of comparing models for this data set as it is for other data.

11. Truncation

Truncation occurs if there exists some time interval $[u_i, v_i] \subseteq [0, \infty)$ for which if the ith subject had not been observed in that interval, an investigator would not have been aware of them and would not have included them in a study. For example, subjects could enter a study at a random time after the origin for the event of interest, and then be observed until the event occurs or the study ends. If a subject's event had occurred before they were able to enter the study, the investigator would have been unaware of them. If $u_i = 0$ and $v_i = \infty$, then there is no truncation. If $u_i > 0$, then the subject is said to be left-truncated, and if $v_i < \infty$, then the subject is said to be right-truncated.

The three models discussed previously can be adapted fairly easily for truncated data. In practice, data sets are more likely to be right-censored than interval-censored. The interval-censored forms of each model are given below, but they can easily be simplified for right-censored data.

11.1 Proportional Hazards model

The contribution of the ith subject to the likelihood is now conditional on the truncation interval, and so the likelihood now becomes

$$L = \prod_{i=1}^{n} \{[S(l_i \mid \mathbf{X}_i) - S(r_i \mid \mathbf{X}_i)] / [S(u_i \mid \mathbf{X}_i) - S(v_i \mid \mathbf{X}_i)]\}$$

Sets C and G are constructed in a similar manner to that of the interval-censored approach, however as noted by Frydman (1994), the sets L and R used to construct C and G must be defined as $L = \{l_i; 1 \le i \le n\} \cup \{v_i; 1 \le i \le n\} \cup \{0\}$ and $R = \{r_i; 1 \le i \le n\} \cup \{u_i; 1 \le i \le n\} \cup \{\infty\}$.

Based on Finkelstein (1986) and Alioum and Commenges (1996), the likelihood can be written as

$$L = \prod_{i=1}^{n} \frac{\sum_{j=1}^{m} a_{ij} [S(q_j \mid \mathbf{X}_i) - S(p_j \mid \mathbf{X}_i)]}{\sum_{j=1}^{m} b_{ij} [S(q_j \mid \mathbf{X}_i) - S(p_j \mid \mathbf{X}_i)]}$$

where $a_{ij}=1$ if $[q_j, p_j] \subseteq [l_i, r_i]$ and 0 otherwise and $b_{ij}=1$ if $[q_j, p_j] \subseteq [u_i, v_i]$ and 0 otherwise. Estimation is performed in a similar manner to that of the interval-censored approach.

11.2 AFT model

Like the proportional hazards model, the contribution of the *i*th subject is conditional on their truncation interval, and so the contributions to the likelihood for the *i*th subject with truncation interval $[u_i, v_i]$ become $\frac{f_Y(\log t_i \mid \mathbf{X}_i)}{S_Y(\log u_i \mid \mathbf{X}_i) - S_Y(\log v_i \mid \mathbf{X}_i)}$ for exactly observed data and $\frac{S_Y(\log l_i \mid \mathbf{X}_i) - S_Y(\log r_i \mid \mathbf{X}_i)}{S_Y(\log u_i \mid \mathbf{X}_i) - S_Y(\log v_i \mid \mathbf{X}_i)}$ for censored data, and the likelihood becomes

$$L = \prod_{i=1}^{n} \left[\frac{f_Y(\log t_i)}{S_Y(\log u_i) - S_Y(\log v_i)} \right]^{\delta_i} \left[\frac{S_Y(\log l_i) - S_Y(\log r_i)}{S_Y(\log u_i) - S_Y(\log v_i)} \right]^{(1-\delta_i)}$$

11.3 Buckley-James model

In order to analyse interval-censored data, residual intervals were created, defined as $J_i(\mathbf{b}) = [l_i - \mathbf{X}_i\mathbf{b}, r_i - \mathbf{X}_i\mathbf{b}]$. Following a similar reasoning, it is possible to define residual truncation intervals $K_i(\mathbf{b}) = [u_i - \mathbf{X}_i\mathbf{b}, v_i - \mathbf{X}_i\mathbf{b}]$. $K_i(\mathbf{b})$ and $J_i(\mathbf{b})$ (if required) would then be used in the estimate of F to create the weights matrix. In this case, the Kaplan-Meier estimate can no longer be used, and either the Turnbull or Finkelstein estimate of the survival curve must be used.

11.4 Comparison

To illustrate the effect of truncation, the bone marrow transplant data is used. This data is right-censored and left-truncated, as only those patients for whom platelet recovery had occurred are included in the analysis. Models were fitted both with and without taking the truncation into account, and the results are shown in Table 13

Table 13. Results of applying models to bone marrow transplant data

Proportional hazards model				
	Parameter estimates	Standard errors	p-values	R^2
No truncation				0.2105
FAB	1.1264	0.3209	0.0004	
Low-risk AML	-1.3368	0.3752	0.0003	
High-risk AML	-0.3817	0.3737	0.3070	
Truncation				0.2125
FAB	1.1322	0.3207	0.0004	
Low-risk AML	-1.3460	0.3753	0.0003	
High-risk AML	-0.3816	0.3733	0.3067	
Buckley-James model				
	Parameter estimates	Standard errors	p-values	R^2
No truncation				0.3275
FAB	-1.4832	0.2238	<0.0001	
Low-risk AML	1.9582	0.2475	<0.0001	
High-risk AML	0.4484	0.2275	0.0487	
Truncation				0.3283
FAB	-1.4794	0.2238	<0.0001	
Low-risk AML	1.9574	0.2475	<0.0001	
High-risk AML	0.4477	0.2275	0.0478	
Weibull AFT model				
	Parameter estimates	Standard errors	p-values	R^2
No truncation				0.2374
FAB	-1.7161	0.4392	<0.0001	
Low-risk AML	2.0650	0.5169	<0.0001	
High-risk AML	0.7558	0.4969	0.1282	
Truncation				0.2427
FAB	-1.6687	0.4222	0.0001	
Low-risk AML	2.0246	0.5320	<0.0001	
High-risk AML	0.7814	0.5165	0.1796	
Log-logistic AFT model				
	Parameter estimates	Standard errors	p-values	R^2
No truncation				0.2462
FAB	-1.5117	0.4190	0.0003	
Low-risk AML	1.9996	0.4622	<0.0001	
High-risk AML	0.5505	0.5026	0.2733	
Truncation				0.2503
FAB	-1.4909	0.4371	0.0006	
Low-risk AML	2.0740	0.4743	<0.0001	
High-risk AML	0.5350	0.5484	0.3292	

Examining Table 13, it appears that if the effect of truncation is ignored, it does not seem to have a large impact on the parameter estimates. The reason for this is most likely to be that for this data set, the truncation times for each subject are relatively small when compared with their survival times. This means that $S(u_i)$ will be tend to be close to 1, and so incorporating it into the likelihood will not have a great impact on the final results.

The models were compared using the same method of comparison as described previously, and the values of P and R^2 are given in Table 14.

Table 14. Comparison of models

Model	Value of P	Value of R^2
Proportional hazards	2217.663	0.2125
Buckley-James	4142.833	0.3283
Weibull AFT	3964.894	0.2427
Log-logistic AFT	3002.286	0.2503

This data has a censoring proportion of 55.83%. According to Heller and Simonoff (1992), the value of the proportional hazards R^2 should be examined. A value less than 0.25 indicates that the Buckley-James model is the better model. This is not borne out by the calculated values of P. There are a number of possible explanations for this.

The difference in the expected results of comparison and the results obtained may be due to the effect of truncation, as Heller and Simonoff did not use truncated data in their analysis. However, this is unlikely to be the case, as ignoring the effect of truncation results in similar parameter estimates, and therefore the values of P would be similar. The value of P for the proportional hazards model is almost 2000 less than that of the Buckley-James model. Therefore, if P were to be calculated for the models ignoring truncation, it would be unlikely that the value of the Buckley-James model would be less that that of the proportional hazards model.

Another reason for the discrepancy in the predicted behaviour and the observed behaviour is that the variables for this data set consist of three binary variables. Therefore there are only a limited number of possibilities for the value of $\hat{t}_i$, which as with the breast cancer data, limit the effectiveness of P for comparing models.

A final reason may be that this data set is an exception to the general rules proposed by Heller and Simonoff.

12. Applying Models to HIV data

The HIV data set comprises of patients observed from 1984 to 1997. The patients were observed at irregular intervals, and at each observation, the stage of infection was recorded. The event of interest for the analysis performed here is the development of clinical AIDS. The variables considered in the analysis were the age of the patient at the date of diagnosis of HIV; the year of diagnosis; the weight of the patient at their first visit to the clinic; the sex of the patient; the racial classification of the patient (White, Black, Coloured or Asian); and the presence of tuberculosis. Also recorded for each patient was the medication that they had used. The use of each separate type of medication was considered in the analysis, but none of them were significant. It was decided to combine these into a single variable indicating whether any medication was used, and this variable was also considered in the analysis.

The data is interval-censored, as the exact date of the development of AIDS is unknown, and all that is observed is time of the last visit before and the first visit after the development of AIDS. The data is also left-truncated, as the patients were observed after they had contracted HIV, and the date of the start of the infection is unknown. For the majority of patients, the date of diagnosis of HIV occurred before their first recorded visit to the clinic. Therefore the date of diagnosis was used as the start of the infection, and all times were calculated in months relative to this time, with the time of the first visit becoming the truncation time. The date of diagnosis is not the true start of the infection, however there was no other date available, and because of the fact that there is a window period following infection for which HIV is undetectable, the true date of infection will remain unknown.

Each of the four models was fitted, and the results are shown in Table 15. The variables that were not significant in any of the models have been discarded, and any variables that were significant in at least one of the models were included in order to make a valid comparison between the different models.

Table 15. Results of applying models to HIV data

Proportional hazards model				
	Parameter estimates	Standard errors	p-values	R^2
Weight	-0.0279	0.0084	0.0009	0.0602
Age	1.1749	0.3306	0.0004	
Black	-0.4537	0.2215	0.0405	
Medication	-0.2581	0.1992	0.1950	
Buckley-James model				
	Parameter estimates	Standard errors	p-values	R^2
Weight	0.0323	0.0124	0.0092	0.1140
Age	-1.8637	0.5083	0.0002	
Black	0.3248	0.2376	0.1716	
Medication	0.4574	0.2293	0.0461	
Weibull AFT model				
	Parameter estimates	Standard errors	p-values	R^2
Weight	0.0355	0.0095	0.0002	0.0556
Age	-1.3154	0.3753	0.0005	
Black	0.3715	0.2481	0.1342	
Medication	0.1959	0.2160	0.3646	
Log-logistic AFT model				
	Parameter estimates	Standard errors	p-values	R^2
Weight	0.0344	0.0096	0.0003	0.0604
Age	-1.6176	0.4066	<0.0001	
Black	0.3483	0.2490	0.1620	
Medication	0.3283	0.2305	0.1545	

The estimates from each model are consistent in the fact that the estimates from the Buckley-James and AFT models all have the same sign, and the opposite sign from that of the proportional hazards model. As noted before, this is due to the fact that the models measure two different aspects of the data, namely the time to the occurrence of the even, and the risk of the event occurring.

For all four models, the variables Weight and Age are significant. The estimates of Age indicate that older people are more likely to develop AIDS sooner than younger people. This is probably due to the fact that, in general, younger people are healthier and less susceptible to diseases than older people.

The estimates of Weight suggest that a patient initially weighing more that another patient would not be as likely to develop AIDS. This may be due to a larger weight indicating in certain circumstances better health and living conditions.

The results suggest that Black patients have a decreased risk of developing AIDS, albeit that it was only significant in the proportional hazards model. This is unexpected, as due to socio-economic conditions in South Africa, if Black patients were to be different from those of other racial groups, it would be expected that Black patients would be more likely to develop AIDS.

The final significant variable was that of Medication, which was only significant in the Buckley-James model. It has the expected effect, in that the use of medication prolongs the time until the development of AIDS. Over the period for which the patients have been observed, new types of medication have been developed, which led to a variety of medications being prescribed. For this reason it was decided to combine medication use into a single variable.

The results of the Heller-Simonoff approach are shown in the Table 16. As in Chapter 10, the midpoint of $[l_i, r_i]$ was used as t_i.

Table 16. Comparison of models

Model	Value of P	Value of R^2
Proportional hazards	233040	0.0602
Buckley-James	372034	0.1140
Weibull AFT	760347	0.0556
Log-logistic AFT	841894	0.0604

The value of P suggests that the proportional hazards model is the best model, and the value of R^2 suggests that the Buckley-James model is the best model. Therefore, as also occurred with the bone marrow data, the use of these statistics does not provide a clear indication of the better performing model.

13. Discussion

While right-censoring is the more common form of censoring, interval-censoring also occurs with sufficient frequency to make an investigation like this worthwhile.

The simplest approach to analysing interval-censored data is to make an approximation of the survival time based on the observed interval and then use methods for right-censored data. The drawback to this approach is that there are three different approximations that can be made, and as shown in Chapter 10, they can produce differing parameter estimates. As the left-hand endpoint is the last time a subject was observed before the event of interest occurred, using this as the observed time will tend to under-estimate survival probabilities. Similarly, using the right-hand endpoint will tend to over-estimate the survival. If the intervals are sufficiently small, then the over or under estimation will not have a significant affect on the estimates. The use of the midpoint of the interval will also tend to distort the survival pattern, particularly if the intervals are of differing lengths. Once again, with sufficiently small intervals, the distortion will not have too great an effect on the parameter estimates.

13.1 Proportional hazards models

The interval-censored proportional hazards model has the same interpretation as the Cox proportional hazards model, and also has similar properties, making consideration of this model worthwhile. The disadvantage of using this model is that its convergence rate is slow for large data sets. It may be possible to improve the rate of convergence through the choice of the initial estimates for the iterative procedure, however this becomes a circular argument, as it is difficult to know what constitutes a good initial estimate without knowing the final estimates. The use of a different algorithm from that of the Newton-Raphson algorithm to find the estimates may improve the rate of convergence, but Pan and Chappell (2002) note that the algorithms considered by them also converge slowly.

It may be the case that the assumption of proportional hazards is not valid. In that case other models, such as the Buckley-James or AFT models must be considered.

13.2 Buckley-James model

The Buckley-James model produces renovated responses, which are the expected survival times for censored observations. A plot of these responses is a useful visual aid to the interpretation of the model. Also, as estimation is based on least squares regression, there is the potential of incorporating extensions of the linear regression model, such as mixed effects models.

If the Buckley-James model is extended to the analysis of interval-censored data, then the choice of the method of estimation of the survival function becomes important. The Kaplan-Meier estimate can be used if a sufficiently large proportion of the subjects are uncensored (Smith, 2002). If this is not the case, then it is necessary to use the Turnbull estimate of the survival function. This estimate has the same disadvantage as the proportional hazards model in that the convergence rate is slow for large data sets, even if Finkelstein's method is used instead of Turnbull's. The problem of a slow rate of convergence is compounded by the fact that an estimate of the survival function must be calculated for each iteration of the Buckley-James estimation algorithm.

13.3 Accelerated failure time model

The accelerated failure time model is a fully parametric model, meaning that various quantities, such as the survival curve, can be calculated fairly easily. A necessary assumption for the use of this model is that the survival times follow a specified distribution. This is an assumption that may not always be valid, but it is one that is difficult to test for as not all of the survival times are known. This fact must be borne in mind if the AFT model is used.

13.4 Truncation

Introducing truncation into each of these models does not raise any major problems other than the slow rates of convergence for the proportional hazards model and Buckley-James model, which have already been noted. S-Plus has the capability to analyse truncated data with the Cox proportional hazards model, so the slow convergence problem can be overcome, unless the data is also interval-censored, in which case the Finkelstein approach would have to be used. If the truncation times are relatively small, as in the bone marrow data, then ignoring the effect of truncation

does not have a significant impact on the parameter estimates. This is not likely to be the case for every set of truncated data, and so if truncation is present, then it is recommended that it be modelled, otherwise an unrealistic analysis of the data may occur.

13.5 Comparison of models through the calculation of statistics

It is difficult to assess whether any of the models outperforms the others in terms of fitting the data or providing predictions from the model. Comparing the baseline survival curves would only indicate any differences between the models, and not give any guide to the performance of the model. In addition, it is not possible to generate a survival curve from the Buckley-James model comparable to that of the proportional hazards and AFT models.

The estimates of the parameters are also not directly comparable. The proportional hazards models estimates changes to the risk of the event occurring, whereas the Buckley-James and AFT models estimates changes to the time of the event occurring. Lindsey and Ryan (1998) note that the estimates should have the same order of magnitude. With all the analyses performed here, that has been the case, and the standard errors have also all been reasonably similar, resulting in the consistency of significant variables throughout all the models. As with the comparison of the survival curves, differing parameter estimates would only highlight differences between the models, and would not give an indication of model performance.

One method of comparing the models is to compare the values of the R^2 statistics. This gives an indication of the amount of variation explained by each of the models, and the model with the largest R^2 could be deemed the best-fitting model. The disadvantage in comparing these is that the R^2 statistic obtained for the Buckley-James model was the R^2 statistic obtained by performing a least squares regression on the renovated responses. Using this value will give an indication of how well the parameter estimates fit the renovated responses, and not how well the renovated responses fit the original responses. This may mean that the R^2 value is misleading in terms of assessing the fit of the Buckley-James model, and therefore may not be directly comparable with that of the other models.

The other criterion considered was Heller and Simonoff's P criterion, defined as $P = \sum \left[\left(t_i - \hat{t}_i \right) / t_i \right]^2$ (Heller and Simonoff, 1992). This is an assessment of the predictive power of the models, and may be a more reliable method of comparison than the R^2 statistic for the reasons already stated. However, there are also problems associated with its use. The first is in the use of t_i. For censored observations, the true value of t_i is unknown, and thus they cannot be included in the calculation of P. This may have an impact when comparing the values of P for each model if a large proportion of the data is censored.

If the data is interval-censored, then any interval-censored observations could be included in the calculation of P by using an approximation of the true survival time, such as the left and right endpoints or the midpoint of the interval. If this is done, then the choice of the method of approximation will have an impact on the value of P, perhaps significantly.

The other issue associated with the use of P is the calculation of $\hat{t}_i$. The median survival time from the proportional hazards model was used as it is easier to obtain than the expected survival time. Because of this, the median survival times from the two AFT models were used in order to retain consistency. The expected survival times could be calculated for the AFT models, and if they were used, this may also have an impact on the value of P when compared with the other models.

Heller and Simonoff compared the proportional hazards and Buckley-James models through the use of simulation in order to determine the factors that cause one model to perform better than the other. Extending this simulation to include AFT models would not produce meaningful results. The method employed by Heller and Simonoff generated survival times from various survival distributions, and as the AFT model is parametric then two situations would occur. If the distribution of the survival times is the same as the distribution of the AFT model, then the AFT model will definitely fit better than the proportional hazards or Buckley-James models and provide more accurate predictions. If the distribution of the survival times differs

from that of the AFT model, then that AFT model would not be appropriate for those survival times.

This means that P and R^2 and cannot be used as strict indicators of the best performing model, but rather as guidelines unless further simulation is done in order to determine factors that affect the value of P for interval-censored and truncated data. Such simulation may prove impractical, as it is necessary to fit a large number of models in order to obtain meaningful results. The size of the data sets and the length of time taken to fit the models becomes an issue. Because of the lack of conclusive evidence to suggest that one model performs better than the others, the decision over which model to be used must be based on practical issues such as the needs of the study and the ease of fitting the model.

13.6 Analysis of model-fitting procedures

For right-censored data, it is possible to fit the Cox proportional hazards and AFT models using a number of statistical packages. Smith (2002) provides S-Plus code for fitting the Buckley-James model, which means that the Buckley-James model can be fitted fairly easily in S-Plus, and the Buckley-James method could probably be implemented in other statistical packages without too much difficulty.

If the data is interval-censored, then the size of the data set becomes an issue. As noted earlier, the interval-censored proportional hazards model has a slow rate of convergence for large data sets. This would also affect the Buckley-James model if the interval-censored survival curve was used instead of the Kaplan-Meier estimate. If the data set is not too large, then the length of time taken to fit the proportional hazards and Buckley-James would not be so excessive as to make the fitting impractical. With a large data set, the choices become using an approximation of the actual survival, which may create a distorted view of the survival, or using the AFT model, which can be done easily in S-Plus.

If the data is left-truncated, then once again, the issue of the size of the data set becomes important. This time, there is the option of using the Cox model rather than the Finkelstein model to analyse the data, as this is supported by S-Plus. If the data is

interval-censored as well as left-truncated then the option of using the Cox model is no longer available.

13.7 Other possibilities

S-Plus was the only statistical package used to analyse the data sets. Other statistical packages such as SAS support the fitting of interval-censored data, and may provide support for other models than the three considered. However, these packages were unavailable for use in this thesis.

Borland Delphi was used to write programs to fit the interval-censored proportional hazards and Buckley-James model. Other programming languages may have been better suited for this task, but as Delphi was available, it was decided to use this rather than learn a new programming language.

Other models such as the generalised linear models of Carstensen (1996), Farrington (1996) and Scallan (1999), and the models of Sun (1997) and Li and Pu (1999) could also be considered. The decision to use the proportional hazards, Buckley-James and AFT models instead of other models was based on the fact that these models are widely used to analyse right-censored data, and were either supported by S-Plus, or it was relatively easy to write programs that fitted these models.

In order to compare models effectively, it may be necessary to derive other statistics that do not have the problems associated with the P and R^2 statistics. However, there still remains the problem that simulation would probably be necessary in order to determine the behaviour of any new statistics.

13.8 Conclusions

No conclusive evidence was found to suggest that one model should be preferred over another. The difficulties in comparing the models in terms of the fit and the predictive power have been analysed. If predictions are not required from the model, and only the general effect of the parameters, then the choice of the model is not as important. If that is the case, it may be advisable to fit more than one model, since the different models may produce different sets of significant variables, as was shown with the HIV data.

Ultimately there is no easy solution to dealing with the problem of interval-censored data. The AFT model is the easiest of the three models to fit, both in terms of the availability of the model in computer packages, and in the length of time that it takes to fit the model. However, the proportional hazards and Buckley-James models have features that make them worth considering if it is practical to fit them.

Future developments in computer technology may result in a decrease of the length of time taken to fit the interval-censored proportional hazards and Buckley-James models, and therefore become a viable option for analysing interval-censored data.

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Appendix: Data Sets

Laryngeal cancer data

Stage 1			Stage 2			Stage 3			Stage 4		
Time	Age	Year	Time	Age	Year	Time	Age	Year	Time	Age	Year
0.6	77	1976	0.2	86	1974	0.3	49	1972	0.1	65	1972
1.3	53	1971	1.8	64	1977	0.3	71	1976	0.3	71	1976
2.4	45	1971	2.0	63	1975	0.5	57	1974	0.4	76	1977
2.5*	57	1978	2.2*	71	1978	0.7	79	1977	0.8	65	1976
3.2	58	1974	2.6*	67	1978	0.8	82	1974	0.8	78	1977
3.2*	51	1977	3.3*	51	1977	1.0	49	1976	1.0	41	1977
3.3	76	1974	3.6	70	1977	1.3	60	1976	1.5	68	1973
3.3*	63	1977	3.6*	72	1977	1.6	64	1972	2.0	69	1976
3.5	43	1971	4.0	81	1971	1.8	74	1971	2.3	62	1971
3.5	60	1973	4.3*	47	1976	1.9	72	1974	2.9*	74	1978
4.0	52	1971	4.3*	64	1976	1.9	53	1974	3.6	71	1975
4.0	63	1976	5.0*	66	1976	3.2	54	1975	3.8	84	1974
4.3	86	1974	6.2	74	1972	3.5	81	1974	4.3*	48	1976
4.5*	48	1976	7.0	62	1973	3.7*	52	1977			
4.5*	68	1976	7.5*	50	1973	4.5*	66	1976			
5.3	81	1972	7.6*	53	1973	4.8*	54	1976			
5.5*	70	1975	9.3*	61	1971	4.8*	63	1976			
5.9*	58	1975				5.0	59	1973			
5.9*	47	1975				5.0*	49	1976			
6.0	75	1973				5.1*	69	1976			
6.1*	77	1975				6.3	70	1972			
6.2*	64	1975				6.4	65	1972			
6.4	77	1972				6.5*	65	1974			
6.5	67	1970				7.8	68	1972			
6.5*	79	1974				8.0*	78	1973			
6.7*	61	1974				9.3*	69	1971			
7.0*	66	1974				10.1*	51	1971			
7.4	68	1971									
7.4*	73	1973									
8.1*	56	1973									
8.1*	73	1973									
9.6*	58	1971									
10.7*	68	1970									

* denotes censored observation

Breast cancer data

Chemotherapy and Radiotherapy	Radiotherapy alone
(8, 12)	(45, ∞)
(0, 22)	(6, 10)
(24, 31)	(0, 7)
(17, 27)	(46, ∞)
(17, 23)	(46, ∞)
(24, 30)	(7, 16)
(16, 24)	(17, ∞)
(13, ∞)	(7, 14)
(11, 13)	(37, 44)
(16, 20)	(0, 8)
(18, 25)	(4, 11)
(17, 26)	(15, ∞)
(32, ∞)	(11, 15)
(23, ∞)	(22, ∞)
(44, 48)	(46, ∞)
(14, 17)	(46, ∞)
(0, 5)	(25, 37)
(5, 8)	(46, ∞)
(12, 20)	(26, 40)
(11, ∞)	(46, ∞)
(33, 40)	(27, 34)
(31, ∞)	(36, 44)
(13, 39)	(46, ∞)
(19, 32)	(36, 48)
(34, ∞)	(37, ∞)
(13, ∞)	(40, ∞)
(16, 24)	(17, 25)
(35, ∞)	(46, ∞)
(15, 22)	(11, 18)
(11, 17)	(38, ∞)
(22, 32)	(5, 12)
(10, 35)	(37, ∞)
(30, 34)	(0, 5)
(13, ∞)	(18, ∞)
(10, 17)	(24, ∞)
(8, 21)	(36, ∞)
(4, 9)	(5, 11)
(11, ∞)	(19, 35)
(14, 19)	(17, 25)
(4, 8)	(24, ∞)
(34, ∞)	(32, ∞)
(30, 36)	(33, ∞)
(18, 24)	(19, 26)
(16, 60)	(37, ∞)
(35, 39)	(34, ∞)
(21, ∞)	(36, ∞)
(11, 20)	
(48, ∞)	

Bone marrow transplant data

Acute lymphoblastic leukaemia (ALL)			Low-risk acute myeloctic leukaemia (AML)			High-risk acute myeloctic leukemia (AML)		
T_1	T_P	*FAB*	T_1	T_P	*FAB*	T_1	T_P	*FAB*
2081*	13	0	2569*	21	1	2640*	22	0
1602*	18	0	2506*	17	0	2430*	14	0
1496*	12	0	2409*	16	0	2252*	17	0
1462*	13	0	2218*	11	1	2140*	18	0
1433*	12	0	1857*	15	0	2133*	17	0
1377*	12	0	1829*	19	0	1238*	18	0
1330*	17	0	1562*	18	0	1631*	40	1
996*	12	0	1470*	14	0	2024*	16	1
226*	10	0	1363*	12	0	1345*	14	0
1199*	29	0	1030*	14	0	1136*	15	0
1111*	22	0	860*	15	0	845*	20	1
530*	34	0	1258*	66	0	162	13	0
1182*	22	0	2246*	15	0	100	65	1
418	21	0	1870*	16	0	47	11	1
383	16	0	1799*	12	0	242	14	1
276	21	0	1709*	19	1	456	24	1
104	20	0	1674*	24	1	268	17	0
609	26	0	1568*	14	0	318	12	1
172	37	0	1527*	13	1	32	16	0
487	22	0	1324*	15	0	467	20	1
662	17	0	957*	69	0	47	28	1
194	25	0	932*	7	1	390	31	1
230	9	0	847*	16	0	183	21	1
526	11	0	848*	16	0	115	12	1
122	13	0	1850*	9	0	93	51	1
129	22	0	1843*	19	0	120	12	1
74	49	0	1535*	21	1	80	0	1
122	23	0	1447*	24	0	677	8	1
466	100	0	1384*	19	0	64	38	1
192	59	0	414	27	1	168	48	1
109	40	0	2204	12	0	74	24	0
55	24	0	1063	16	1	157	52	1
110	27	0	481	24	1	625	18	1
332	33	0	105	15	0	48	30	1
			641	11	0	273	24	0
			390	11	0	63	16	1
			421	20	1	113	59	0
			748	18	0	363	19	0
			486	11	0			
			48	14	1			
			272	12	1			
			1074	19	1			
			381	16	1			
			248	9	0			
			704	18	0			
			211	23	1			
			219	52	1			
			606	14	1			
T_1 = time to death, relapse or the end of the study * denotes the subject survived until the end of the study			T_P = time to platelet recovery			*FAB* = 1 if FAB Grade 4 or 5 = 0 otherwise		

HIV Data

- Times are given in months
- * indicates a right-censored subject
- The four racial classifications are White, Coloured, Black and Asian

Year of diagnosis	Age at diagnosis	First visit	Last visit prior to AIDS	First visit with AIDS	Sex	Race	Weight	TB	Medication used
1985	31	1.37	132.27	*	M	W	59	N	Y
1985	27	1.60	56.20	56.40	M	W	68	N	Y
1986	30	37.67	80.60	*	M	W	88	N	Y
1985	36	1.20	4.30	5.03	M	W	51	N	N
1986	32	0.47	30.10	30.37	M	W	70	N	Y
1986	28	0.70	8.53	*	M	W	72	N	N
1985	41	7.97	13.10	105.50	M	W	83	N	N
1986	33	3.67	14.30	14.93	M	W	60	N	Y
1986	28	0.50	0.53	96.70	M	W	77	N	N
1986	44	6.33	79.17	*	M	W	78	N	Y
1987	40	0.47	3.97	4.43	M	W	65	N	N
1987	24	15.07	15.10	15.43	M	W	63	N	N
1988	31	2.60	109.93	*	M	W	65	N	Y
1988	44	0.83	2.60	*	M	W	62	N	Y
1988	40	0.17	1.10	1.27	M	W	69	N	Y
1988	30	2.97	3.67	3.90	M	W	74	N	N
1988	48	0.90	4.80	5.57	M	W	84	N	N
1986	30	32.80	33.50	*	M	W	63	N	Y
1988	27	5.07	26.23	*	M	W	62	N	N
1988	33	3.47	7.63	7.70	M	W	63	N	N
1987	34	2.57	46.07	46.47	M	W	98	N	Y
1989	31	2.10	26.00	28.00	M	C	63	N	Y
1989	61	1.53	76.23	*	M	W	62	N	Y
1987	52	30.90	32.03	*	M	W	61	N	Y
1988	47	11.87	17.83	18.47	M	W	75	N	Y
1985	23	52.80	55.27	*	M	W	71	N	Y
1987	31	33.57	62.20	*	M	W	67	N	Y
1987	34	34.03	64.60	65.77	M	W	73	N	Y
1989	39	1.50	7.10	9.13	M	W	74	N	Y
1988	31	13.57	78.43	*	M	W	87	N	Y
1989	28	0.63	19.77	*	M	W	70	N	Y
1988	52	1.10	54.80	*	M	W	84	N	Y
1990	43	1.00	45.10	47.20	M	W	78	N	Y
1985	41	61.30	62.27	63.40	M	W	69	N	Y
1988	23	22.03	31.63	32.53	M	W	60	N	Y
1990	33	3.70	16.53	16.97	M	W	53	N	Y
1989	30	8.07	28.67	28.77	M	W	66	N	Y
1990	34	2.07	5.80	7.43	M	W	68	N	N
1990	36	24.47	24.53	25.40	M	W	76	N	N
1989	26	10.00	28.43	*	M	W	60	N	N
1986	28	52.73	66.03	*	M	W	82	N	Y
1988	25	20.50	32.87	33.10	M	W	63	N	Y
1988	28	29.20	43.87	44.97	M	W	59	N	Y
1990	29	0.60	34.23	*	M	W	78	N	N
1988	38	18.87	26.80	*	M	W	77	N	Y
1985	23	67.07	101.70	*	M	W	87	N	Y
1989	25	19.03	19.17	*	M	W	67	N	N
1991	33	3.63	17.87	18.57	F	B	78	Y	Y
1989	37	0.90	92.60	*	M	C	58	Y	Y
1985	28	0.03	47.23	52.90	M	C	48	N	N
1985	21	0.57	50.97	51.23	M	A	56	N	Y
1988	32	58.33	89.13	*	M	C	84	N	N
1987	34	1.20	3.07	3.73	M	C	58	Y	Y
1988	41	0.93	27.10	*	M	A	53	N	N
1988	40	0.23	1.20	1.30	M	C	56	N	N
1988	24	1.23	61.43	61.47	M	C	54	N	Y
1989	25	0.53	2.57	3.10	M	A	60	N	N
1989	26	7.27	15.20	15.57	M	B	57	Y	Y
1989	20	2.13	71.90	*	M	C	66	N	Y
1989	33	1.67	71.20	*	F	B	62	N	Y
1989	29	5.60	11.70	*	F	C	46	Y	Y
1990	26	3.47	25.87	26.13	M	C	60	N	Y
1986	36	50.03	116.30	*	M	C	74	N	Y
1990	45	1.00	1.03	5.00	M	W	74	N	N
1990	32	2.73	3.60	*	M	B	52	Y	Y
1990	45	8.00	13.20	*	M	W	90	N	N
1990	37	5.00	5.93	*	M	B	55	Y	Y

1989	22	16.40	72.87	*	M	C	75	N	Y
1986	21	9.40	88.50	*	M	W	83	N	Y
1990	30	4.13	5.30	*	M	B	73	N	Y
1990	52	1.40	2.57	3.50	M	W	60	N	Y
1990	49	3.13	3.27	*	M	C	34	N	Y
1990	42	0.67	65.30	*	M	C	60	Y	Y
1990	37	5.90	16.50	17.20	M	C	47	Y	Y
1990	28	0.03	0.20	*	F	B	67	N	Y
1990	24	1.13	2.30	*	M	C	54	N	Y
1990	29	1.37	70.20	*	M	C	72	Y	Y
1989	28	17.70	17.80	*	M	W	66	N	Y
1991	25	0.20	63.73	66.10	F	W	53	N	Y
1990	26	5.60	19.83	21.47	M	W	70	N	Y
1991	26	0.13	20.23	22.10	M	C	54	N	N
1990	23	4.87	57.60	*	M	C	54	Y	Y
1991	30	1.57	2.27	*	M	W	60	Y	Y
1991	34	1.33	2.50	*	M	C	69	Y	Y
1991	22	0.40	8.00	8.83	M	C	56	Y	Y
1986	47	64.40	91.93	92.07	M	W	68	N	Y
1991	25	0.77	34.60	*	F	B	65	Y	Y
1990	36	7.87	8.77	9.23	M	C	48	N	Y
1988	41	35.97	36.17	36.87	M	W	64	N	Y
1990	23	14.33	30.40	30.73	M	C	61	Y	Y
1991	18	0.13	65.23	*	F	B	46	N	N
1991	38	0.37	54.97	56.83	F	B	52	N	Y
1985	35	74.53	80.40	*	M	W	77	N	Y
1990	28	15.83	50.13	51.30	M	W	66	N	Y
1991	31	0.23	4.57	*	M	B	57	Y	Y
1990	40	18.40	18.43	*	M	W	61	N	N
1991	34	0.53	1.23	2.10	M	C	61	Y	Y
1991	40	0.70	10.10	*	M	W	62	N	Y
1991	36	0.77	24.33	42.53	F	W	53	N	Y
1991	50	0.70	46.50	47.43	M	W	65	N	Y
1991	31	0.23	5.53	*	M	W	72	N	Y
1991	39	0.43	14.43	15.17	M	C	56	Y	Y
1991	18	2.70	47.03	*	M	C	56	Y	Y
1986	20	63.57	76.40	*	M	W	72	Y	N
1991	56	0.63	0.67	0.90	M	B	48	N	Y
1991	34	20.27	39.63	*	F	B	98	N	N
1991	27	2.30	8.60	*	M	B	67	Y	Y
1991	31	0.50	10.53	*	M	W	75	N	Y
1990	56	20.27	52.23	*	M	W	67	N	N
1989	31	26.93	26.97	27.00	M	C	55	N	Y
1991	40	0.97	32.70	34.33	M	A	86	N	Y
1991	32	1.17	1.67	*	F	B	76	N	Y
1991	22	0.40	0.63	*	M	B	72	N	N
1991	22	0.43	60.60	*	M	C	73	N	Y
1991	18	1.67	26.63	*	M	C	86	N	N
1991	50	0.87	23.73	*	M	W	68	N	Y
1991	23	7.47	52.73	*	M	C	57	N	N
1993	26	0.07	22.17	27.07	F	B	55	Y	Y
1991	41	12.60	17.23	*	M	W	64	N	Y
1991	27	1.73	1.97	*	F	B	61	Y	Y
1991	31	3.00	15.57	*	M	C	60	N	Y
1991	35	2.20	56.33	56.57	M	C	60	N	Y
1987	50	59.03	63.93	65.80	M	W	72	N	Y
1991	26	2.20	5.47	6.37	M	C	66	N	N
1992	39	1.17	2.33	*	M	A	62	N	N
1991	29	4.20	30.83	*	M	B	72	N	Y
1992	35	0.83	40.50	43.30	F	C	53	N	Y
1992	30	0.83	1.77	*	M	B	62	Y	Y
1989	33	39.30	74.07	*	M	W	74	N	Y
1991	22	5.07	35.17	*	M	W	71	N	N
1987	32	59.33	117.90	*	M	W	66	N	N
1991	46	12.90	18.73	*	F	W	57	N	Y
1992	29	0.90	0.93	*	M	A	67	N	N
1992	55	1.40	11.20	11.43	M	C	61	N	N
1992	41	1.03	34.63	*	F	B	98	N	N
1992	25	3.20	11.80	*	M	C	68	N	N
1992	28	2.43	2.67	*	M	B	81	N	N
1987	26	56.20	59.20	59.50	M	W	73	N	Y
1992	45	1.03	13.93	*	M	W	74	N	Y
1989	28	36.60	40.33	*	M	W	85	N	N
1992	25	1.10	5.57	*	M	C	40	N	N
1992	49	0.47	1.63	2.57	M	W	68	N	Y
1992	29	0.47	55.53	*	M	B	67	Y	Y
1989	22	40.20	43.93	64.23	M	W	63	N	N

1992	28	4.97	16.10	*	M	B	40	Y	Y
1992	22	0.77	1.90	*	M	C	74	Y	Y
1992	47	2.97	3.27	3.47	M	B	56	Y	Y
1992	44	0.97	3.13	*	M	W	79	N	Y
1992	33	6.87	38.37	39.53	F	B	63	Y	Y
1992	35	0.90	30.77	*	F	B	48	N	Y
1986	48	78.07	99.03	100.90	M	W	72	N	Y
1991	17	22.67	38.77	39.33	M	C	43	Y	Y
1989	21	44.70	44.93	44.97	M	W	57	N	Y
1992	30	4.73	5.27	*	M	W	63	N	N
1992	31	0.73	6.10	*	M	W	87	N	Y
1992	49	0.73	33.40	*	M	W	74	N	Y
1992	27	0.73	30.33	30.60	M	B	53	Y	Y
1992	31	8.53	8.57	8.80	M	C	61	N	N
1992	22	5.40	22.67	*	F	C	44	Y	Y
1993	31	0.10	0.23	*	F	B	45	Y	Y
1993	22	0.50	13.10	*	M	C	48	N	Y
1993	31	0.30	20.83	*	M	W	77	N	N
1993	45	1.00	1.23	1.30	M	W	64	N	N
1993	18	1.47	36.47	*	M	C	53	Y	Y
1993	30	1.70	30.17	*	M	B	59	Y	Y
1993	39	3.43	25.13	*	M	C	77	N	N
1993	38	2.33	19.83	*	F	C	57	N	Y
1993	31	0.20	1.73	2.03	M	C	56	Y	Y
1992	24	16.10	21.47	*	F	C	45	Y	Y
1993	20	1.97	39.73	*	M	B	40	Y	Y
1990	30	39.87	82.80	*	F	B	50	N	N
1992	32	13.13	14.30	*	M	B	69	Y	Y
1993	38	0.17	20.23	20.70	M	C	47	Y	Y
1994	45	0.83	35.60	*	M	W	82	Y	N
1993	37	0.90	3.23	3.70	M	C	59	N	N
1993	49	0.67	3.47	3.50	M	W	80	N	Y
1992	26	16.33	36.87	*	F	B	78	N	Y
1991	38	26.07	33.93	*	M	C	68	N	Y
1994	28	0.83	11.10	*	M	B	52	Y	Y
1992	23	14.77	49.07	*	F	C	55	N	Y
1993	33	0.40	1.57	*	M	B	66	Y	Y
1993	32	0.50	0.97	*	M	B	61	Y	Y
1993	24	1.03	1.27	*	F	B	49	N	N
1993	30	1.27	43.97	*	M	B	60	Y	Y
1991	39	28.67	28.70	29.17	M	W	50	N	Y
1993	44	0.43	7.57	*	M	W	76	N	N
1993	41	4.57	26.03	*	M	C	60	N	N
1994	26	5.80	16.93	*	M	B	78	N	N
1993	20	6.43	14.13	*	M	B	55	N	N
1993	23	3.00	3.23	9.17	F	B	65	Y	Y
1991	33	28.37	53.57	*	F	W	59	N	Y
1993	40	1.40	38.27	*	M	B	50	Y	Y
1993	29	3.20	3.23	3.97	F	C	47	Y	Y
1995	34	0.77	4.50	*	M	B	50	Y	Y
1993	29	2.43	25.77	*	F	B	72	N	Y
1994	58	1.10	32.20	*	M	C	88	N	N
1993	41	0.43	6.00	6.67	F	B	55	Y	Y
1993	23	0.43	2.97	*	F	B	66	Y	N
1993	34	0.47	18.37	20.23	F	B	47	Y	Y
1993	32	3.20	19.30	*	M	C	62	N	N
1992	58	16.83	16.87	*	M	B	53	Y	Y
1996	35	1.10	7.87	10.90	F	B	51	N	Y
1994	43	1.20	1.23	*	M	W	66	Y	Y
1991	31	6.37	7.43	8.23	F	B	82	N	N
1989	29	39.40	44.53	*	M	W	62	N	Y
1995	25	0.67	2.07	*	F	B	39	N	N
1996	23	0.30	9.87	*	F	B	41	Y	Y
1996	47	1.50	1.97	*	F	B	79	N	N
1994	29	0.63	1.53	*	F	C	35	N	Y
1993	33	1.33	9.77	*	M	B	76	N	N
1993	32	1.30	26.07	*	M	B	67	N	Y
1993	43	1.80	2.03	2.27	M	W	72	N	Y
1993	29	0.77	6.60	*	M	C	53	Y	Y
1993	31	4.07	8.50	*	F	C	40	Y	N
1993	51	0.03	0.07	0.67	M	B	45	N	N
1992	31	13.37	13.40	13.43	M	C	40	N	N
1993	39	4.13	6.27	8.13	M	B	88	Y	N
1993	46	0.47	7.93	*	M	W	53	N	Y
1993	31	0.40	6.53	*	M	W	71	Y	Y
1993	30	0.47	40.60	*	M	C	62	N	Y
1993	69	1.13	1.17	2.80	M	W	51	N	Y

1994	35	0.07	5.23	*	F	B	59	N	Y
1990	26	37.93	62.90	*	M	W	81	N	N
1993	36	2.40	14.77	*	F	C	91	N	N
1993	19	0.97	24.30	26.40	F	B	53	Y	N
1989	21	56.37	78.37	*	M	W	78	N	N
1994	43	0.60	14.13	*	M	W	50	N	Y
1994	34	0.63	3.70	*	M	B	48	Y	Y
1994	25	0.87	1.27	*	M	B	69	N	Y
1993	22	3.90	14.63	*	F	B	56	N	N
1984	34	117.67	120.10	*	M	W	65	N	N
1996	48	0.17	1.80	*	M	B	86	N	N
1993	29	4.73	5.67	*	M	W	71	N	N
1994	40	0.43	2.60	*	M	B	60	N	Y
1993	62	3.57	4.43	*	M	C	50	Y	Y
1994	42	0.30	33.37	*	F	C	50	N	N
1994	31	0.93	0.97	1.20	M	C	49	N	N
1994	31	0.50	0.73	*	M	B	58	Y	N
1994	45	0.47	0.50	*	F	B	67	N	N
1994	24	1.20	7.97	*	M	C	57	N	Y
1994	51	1.20	16.13	*	M	W	79	N	Y
1994	23	0.33	6.33	*	F	B	29	Y	Y
1996	44	0.37	1.77	2.47	M	B	56	N	N
1994	32	0.67	20.20	*	M	B	71	Y	Y
1991	29	39.23	45.07	*	M	W	57	N	N
1993	39	6.23	6.27	6.53	F	B	44	N	N
1994	42	1.43	20.10	*	F	B	93	N	Y
1994	37	1.43	15.67	*	M	W	68	N	Y
1994	39	1.60	2.13	*	M	C	64	N	N
1994	25	2.60	37.60	*	F	C	75	N	N
1994	31	1.67	7.73	*	F	B	74	N	Y
1991	39	35.60	35.83	*	M	W	74	N	N
1994	29	3.07	38.07	*	M	C	61	N	Y
1994	27	0.43	0.67	*	F	B	51	N	N
1994	29	2.13	33.63	*	M	C	66	N	N
1994	32	3.07	16.97	*	F	B	44	N	Y
1989	21	59.93	60.63	63.43	M	W	74	N	Y
1994	20	1.10	14.63	*	M	W	69	N	N
1993	20	11.37	19.87	*	M	B	57	N	Y
1994	30	0.53	7.10	*	F	B	56	N	Y
1994	26	1.33	10.67	*	M	C	66	N	N
1994	30	1.03	32.77	*	F	B	58	N	N
1993	52	7.50	11.70	*	M	B	73	Y	N
1996	53	1.77	2.00	*	M	B	65	Y	Y
1994	22	1.07	1.27	*	M	B	57	N	Y
1994	21	4.00	13.10	*	M	C	50	Y	Y
1993	35	10.37	10.60	*	M	B	61	N	Y
1990	28	49.10	53.13	55.00	M	W	73	N	Y
1994	34	1.50	25.57	*	M	W	61	N	Y
1994	30	0.47	0.70	*	F	B	49	N	N
1994	24	1.00	1.47	*	F	B	87	N	N
1994	22	0.63	31.43	*	F	B	66	N	N
1994	35	0.87	17.67	19.77	F	B	55	N	Y
1994	34	1.87	6.07	*	M	B	73	N	N
1993	40	13.50	25.40	26.17	M	W	85	N	N
1994	29	2.17	14.00	17.20	F	B	65	Y	Y
1996	30	1.13	2.30	*	M	B	61	Y	Y
1994	19	2.13	6.23	*	M	C	54	Y	Y
1994	43	1.23	29.00	31.13	M	C	56	Y	Y
1994	24	4.30	22.50	32.07	M	W	64	N	Y
1994	40	1.23	27.60	*	F	B	51	Y	Y
1994	23	1.47	12.67	*	F	C	58	N	N
1994	27	1.47	30.17	*	F	B	69	N	N
1994	25	0.67	30.53	*	F	B	77	N	Y
1994	24	3.73	3.97	*	F	B	63	N	N
1994	26	0.67	25.87	*	M	B	82	N	Y
1994	28	6.80	12.87	*	M	B	65	N	N
1994	39	0.67	26.80	*	M	B	73	N	N
1993	38	15.90	16.83	17.53	F	B	66	N	N
1994	44	2.17	4.73	*	F	B	58	N	Y
1994	39	4.67	7.70	*	M	B	55	N	N
1994	54	4.63	4.67	5.13	M	C	59	Y	N
1994	34	0.23	15.43	*	M	W	69	N	N
1994	19	3.57	17.80	*	F	B	59	N	Y
1994	29	5.83	17.97	*	M	W	62	Y	Y
1993	30	22.23	22.47	*	M	C	67	N	N
1994	49	6.07	31.73	*	M	B	52	Y	Y
1996	27	1.30	2.93	*	M	W	73	N	N

1994	42	9.37	30.60	*	F	B	59	N	Y
1994	32	0.17	17.93	*	F	C	58	N	Y
1994	32	0.67	26.80	*	M	C	80	N	Y
1994	28	0.93	26.80	*	M	B	81	N	N
1995	31	0.23	7.00	*	M	B	60	Y	Y
1994	32	7.17	26.57	*	F	B	76	N	N
1994	36	1.57	29.10	*	M	W	63	N	N
1995	39	0.57	19.00	*	M	B	55	Y	Y
1989	31	69.80	84.07	*	M	W	66	N	Y
1995	25	5.30	8.57	*	M	C	59	N	Y
1994	37	3.07	10.53	*	F	B	56	Y	Y
1995	35	1.27	24.60	*	M	C	44	N	N
1995	37	1.27	22.50	*	F	B	77	N	N
1995	44	0.90	8.33	10.97	M	W	51	N	Y
1995	24	7.00	8.33	*	M	B	59	N	Y
1995	45	0.73	7.97	*	F	C	39	N	Y
1995	23	1.23	2.17	*	M	B	66	Y	Y
1995	19	0.23	7.70	*	F	C	45	N	N
1995	48	1.17	1.40	*	M	C	59	N	N
1995	34	1.17	22.40	*	M	B	74	N	N
1994	29	11.87	30.97	*	F	B	50	Y	Y
1995	22	0.20	6.27	*	F	B	70	Y	N
1995	35	0.93	9.83	*	F	C	54	N	N
1995	50	0.93	3.03	*	M	W	92	N	N
1995	38	0.63	1.10	*	F	C	51	N	N
1994	30	8.70	25.50	*	F	B	58	N	Y
1995	19	2.57	3.50	4.10	M	C	56	Y	N
1995	49	0.83	22.77	*	M	B	45	Y	Y
1994	23	14.03	17.07	*	M	C	60	N	Y
1995	38	6.63	12.70	*	F	B	50	Y	Y
1995	24	0.20	10.70	*	F	B	56	N	N
1993	24	23.60	26.87	*	F	B	60	N	N
1994	37	7.37	25.80	*	M	B	47	Y	Y
1995	17	0.07	0.97	1.20	F	B	89	N	N
1995	28	0.43	4.70	*	F	B	59	N	N
1995	22	0.30	19.67	*	F	B	69	N	N
1995	39	0.67	0.90	*	F	B	70	N	N
1995	39	1.47	13.37	*	F	B	45	Y	Y
1995	63	0.67	0.90	*	M	B	55	Y	Y
1992	32	37.37	37.40	*	M	B	57	Y	N
1995	30	1.10	16.77	*	F	B	70	N	Y
1994	39	7.77	29.23	*	M	B	64	N	Y
1995	37	2.00	2.47	*	F	B	69	N	N
1995	45	0.60	2.70	*	M	B	62	Y	N
1995	31	2.87	22.93	*	F	C	84	N	N
1995	38	2.00	20.67	*	F	B	75	N	N
1995	27	1.77	15.77	*	M	W	62	N	N
1995	36	2.53	3.23	*	M	B	57	Y	Y
1996	41	1.53	5.27	*	M	C	87	N	N
1995	35	0.97	14.73	*	M	C	53	Y	N
1995	37	1.20	10.33	*	M	W	64	N	Y
1995	23	2.23	5.27	*	M	C	72	N	N
1994	20	21.00	34.30	*	F	B	55	Y	Y
1995	29	2.20	4.53	*	M	B	76	N	Y
1995	32	1.57	9.27	*	M	W	68	N	Y
1994	25	17.07	27.07	*	F	B	52	N	Y
1995	45	0.93	16.80	*	M	C	62	N	N
1995	35	0.47	11.43	*	F	C	66	Y	Y
1995	47	1.50	4.53	*	M	B	50	Y	Y
1995	28	0.47	0.70	*	F	B	63	N	N
1995	35	1.50	1.73	*	F	B	51	Y	Y
1995	37	3.53	18.00	*	M	B	70	N	N
1995	34	1.50	3.93	*	M	B	64	N	N
1995	23	1.50	1.73	*	F	B	66	N	N
1995	24	2.33	5.83	*	F	B	41	Y	Y
1996	30	1.13	3.47	*	F	B	61	N	N
1994	21	14.37	28.37	*	F	B	67	N	N
1995	38	1.33	3.67	*	F	W	67	N	Y
1989	27	79.77	95.17	*	M	W	69	N	N
1995	45	10.50	10.53	11.97	M	B	49	N	N
1995	57	5.17	5.40	*	F	W	65	N	N
1996	34	0.77	1.00	*	M	W	60	N	N
1996	31	0.77	3.10	*	M	B	60	Y	Y
1996	24	1.13	6.73	*	F	B	63	N	N
1996	20	0.30	3.30	*	F	C	48	Y	Y
1996	19	0.27	11.30	*	M	B	68	N	N
1996	33	0.90	1.13	*	F	B	78	N	N

1996	32	1.60	3.23	*	M	B	71	N	N
1994	26	21.70	32.90	*	M	C	51	Y	Y
1995	30	9.00	18.80	*	M	C	73	N	N
1996	42	1.17	1.40	*	F	B	54	Y	Y
1996	30	1.57	5.53	*	F	B	52	N	N
1996	36	0.90	4.43	*	M	B	62	N	Y
1995	38	5.30	5.53	*	M	C	37	N	Y
1996	32	1.47	9.87	*	M	W	67	N	N
1996	20	0.27	4.93	*	F	B	55	N	N
1986	38	121.90	128.43	*	M	W	58	N	Y
1996	33	1.63	3.50	*	F	B	45	Y	Y
1996	15	1.40	7.00	*	F	B	67	N	Y
1996	28	1.43	11.20	*	F	B	53	Y	N
1995	25	7.70	8.63	8.87	M	B	69	N	Y
1996	24	1.37	1.83	*	M	B	63	Y	Y
1992	19	49.70	56.07	*	M	B	70	N	Y
1996	31	1.27	3.13	*	F	B	59	N	Y
1996	31	0.77	1.70	4.97	F	B	52	N	Y
1996	33	0.77	1.47	*	F	B	67	N	N
1996	20	5.30	5.77	*	F	B	58	Y	Y
1996	25	2.23	4.80	*	M	B	60	Y	Y
1996	42	1.43	1.83	*	M	C	62	N	N
1996	21	0.80	1.73	*	M	B	51	Y	Y
1996	28	2.87	3.10	*	M	B	62	N	N
1996	27	0.10	4.00	*	F	B	56	Y	Y
1996	39	1.03	6.17	*	F	B	57	N	N
1996	37	2.30	7.20	*	F	B	62	N	Y
1995	27	16.53	16.77	*	M	C	58	N	Y
1996	31	2.53	8.60	*	M	W	86	Y	N
1995	37	16.97	17.97	*	M	W	74	N	N
1996	39	3.00	3.23	*	M	B	58	Y	Y
1996	47	1.20	1.43	*	M	B	72	N	N
1996	33	8.33	8.57	*	M	B	50	Y	Y
1996	24	0.40	3.43	*	F	B	52	N	Y
1996	21	1.43	4.47	*	F	B	59	N	N
1996	24	0.87	5.77	*	F	C	42	N	N
1996	16	1.90	2.13	*	F	B	47	N	N
1996	33	4.17	4.40	*	M	B	56	N	N
1996	39	1.10	3.43	*	M	B	72	N	N
1996	45	2.20	2.43	4.30	M	W	59	N	N
1995	19	0.40	5.50	*	F	B	57	Y	Y
1994	32	0.23	16.80	*	F	B	79	N	N
1993	35	0.47	24.97	36.87	M	C	54	Y	N
1992	34	0.40	1.10	*	M	B	56	N	N
1993	54	24.30	35.97	*	M	B	65	N	N
1995	23	2.03	12.53	*	F	B	64	N	Y
1995	42	1.60	3.13	3.70	F	C	45	Y	Y
1993	29	1.37	8.83	*	F	B	43	Y	Y
1992	40	2.50	15.33	17.87	M	C	54	Y	N
1993	26	0.17	11.83	*	F	B	53	N	Y
1994	38	0.13	0.17	2.27	M	B	46	N	N
1995	39	0.97	1.00	5.67	F	C	73	Y	Y
1994	33	0.67	23.53	*	F	B	50	Y	Y
1992	35	23.83	40.87	45.53	F	B	50	Y	Y
1994	34	1.40	4.43	5.83	M	B	69	N	Y
1992	32	10.07	15.43	*	M	B	58	N	N
1992	22	0.50	20.53	*	F	B	50	N	Y
1993	38	1.27	1.30	6.90	M	B	70	Y	Y
1993	52	1.17	29.63	32.23	M	C	72	N	Y
1992	41	3.97	7.47	*	F	C	53	N	N
1993	37	0.33	14.80	26.20	M	W	68	N	Y
1995	22	1.17	3.27	*	F	C	35	Y	Y
1993	22	1.13	1.37	*	F	B	47	N	Y
1995	40	0.23	12.13	*	F	B	46	N	N
1994	40	0.93	12.13	*	M	B	72	N	Y
1994	40	3.03	13.53	*	F	A	80	N	N
1995	23	7.73	8.67	*	F	C	48	Y	Y
1995	18	0.23	4.93	6.60	F	B	52	N	N
1995	36	1.23	2.17	*	M	B	76	N	Y
1995	21	0.20	1.37	*	F	B	56	Y	Y
1995	25	0.43	9.07	*	F	B	53	N	Y
1992	53	14.33	26.93	*	M	C	72	N	N