Contributions to survival analysis

Rebecca Jean Benner
Iowa State University

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Contributions to survival analysis

by

Rebecca Jean Benner

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Signature was redacted for privacy.

Major Professor
Signature was redacted for privacy.
For the Major Program
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For the Graduate College
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1 Introduction

The common theme of this dissertation is the analysis of interval censored lifetime data. Examples of lifetime variables are time to the failure of treatment in a clinical trial, time for an insect to complete a specific stage of development, or time to first appearance of a tumor. Data are analyzed by using stochastic models to describe event times as realizations of a random variable. Models based on continuous random variables have been developed for the ideal situation where event times are observed with exact precision. In reality, life event data are often interval censored, where it is only known that an event occurred between two inspection points. One way to handle this discreetness is to initially ignore it and employ methods for a continuous time model and subsequently make adjustments for the interval censoring. This approach is examined for the proportional hazards regression model in the first paper. An alternative approach would be to adopt methods for discrete data to the counts within the inspection intervals, which is done in the second paper.

The additional literature review provided by this chapter is presented in two parts. The first part reviews procedures that have been used to apply methods for continuous event times to interval censored data. The second part reviews methods that take a discrete approach to interval censored data.

2 Proportional hazards literature review

The proportional hazards model, introduced by Cox (1972, 1975), provides a way to relate exact failure times to one or more covariates. This model is based on a continuous random variable \( T \) which measures the time to an event. The proportional hazards model is specified by

\[
h(t \mid x) = h_0(t)g(x'\beta)
\]

where \( h_0(t) \) is the baseline hazard function, \( x' = (z_1, z_2, \ldots, z_p) \) is a vector of covariates, \( \beta \) is the vector of parameters to be estimated, and \( g(\cdot) \) is a function that does not depend on \( T \). When \( x = 0 \), then we
require \( g(x' \beta) \equiv 1 \). We will restrict our attention to \( g(x' \beta) = \exp(x' \beta) \), which is commonly referred to as the Cox model.

### 2.1 Estimation in proportional hazards models

There are several possible ways of solving the problem of estimating \( \beta \) in the proportional hazards model. Let \( \theta' = (\phi' \beta') \), where \( \phi \) is a nuisance parameter associated with the unknown baseline hazard function \( h_0(t) \). Maximum likelihood estimation can be used to estimate \( \theta \), the full vector of unknown parameters. Ordering the failure times \( t(1) < t(2) < ... < t(k) \), the risk set, denoted by \( R_i \), is the set of subjects who are still alive and uncensored just before time \( t(i) \). Let \( x(i) \) denote the values of the explanatory variables associated with the \( i \)-th ordered failure time \( t(i) \). With this notation the full likelihood is given by

\[
L_f(\beta, h_0(t)) = \left[ \prod_{i=1}^{k} \frac{\exp(x'(i) \beta)}{\sum_{t \in R_i} \exp(x'(t) \beta)} \right] \left[ \prod_{i=1}^{k} \left( h_0(t(i)) \sum_{t \in R_i} \exp(x'(t) \beta) \right) \right]^{n} S_0(t_j)^{\exp(x'(j) \beta)}
\]

where \( n \) is the total number of individuals and \( S_0(t) \) is the baseline survivor function. Maximizing this function can be very complicated, however, if not impossible. If no parametric form is specified for \( h_0(t) \) then it corresponds to an infinite dimensional nuisance parameter. If a parametric form for the baseline hazard, such as the Weibull distribution, is assumed, then the maximum likelihood estimation is more straightforward.

However, often the interest centers on the value of \( \beta \), and another approach would be to condition on the nuisance parameter \( \phi \), or a sufficient statistic of it, and use the conditional distribution of \( \beta \) given \( \phi \) as the basis for inference on \( \beta \). The infinite dimensional \( h_0(t) \) makes computation of conditional distributions very difficult.

A third method uses the partial likelihood proposed by Cox (1972, 1975), which allows the estimation of \( \beta \) without the estimation of nuisance parameters related to \( h_0(t) \) or \( S_0(t) \). Often this method is called semi-parametric since the baseline hazard is not specified. Using the same notation as above, Cox's partial likelihood is given as

\[
L(\beta) = \prod_{i=1}^{k} \frac{\exp(x'(i) \beta)}{\sum_{t \in R_i} \exp(x'(t) \beta)}
\]

which is the first factor of (2). In this partial likelihood function only the ordering of the failure times come into the calculation through the risk set \( R_i \). The likelihood function compares the risk score of the \( i \)-th ordered failure, \( \exp(x'(i) \beta) \), to the sum of all of the risk scores of all the individuals that are available to fail at that particular point in time.
Cox (1975) and Fleming and Harrington (1991) give an intuitive justification for the use of the partial likelihood function. In generic notation, let Y be a continuous random variable, then the probability density function of Y can be factored as

\[ f_Y(Y, \theta) = f_{W|V}(w | v, \theta) \cdot f_V(v, \theta) \]  

by partitioning Y into two components W and V. The idea is to find a partition so that one of the factors does not contain \( \phi \), and use that factor to estimate \( \beta \). If such a partition exists, this factor is called a partial likelihood. To match the general case with the proportional hazards partial likelihood, partition of \( Y_i \), so that \( W_i \) represents the censoring in \([t_{(i-1)}, t_{(i)})\) and the information that a failure occurs at \( t_{(i)} \) and let \( V_i \) represent the individual who failed at that time \( t_{(i)} \). If the second factor in the full likelihood, \( f_Y(y_i, h_0(t)) \) of (2), does not depend on \( \beta \) then the censoring mechanism is called noninformative.

One concern with using partial likelihood methods is the potential loss of efficiency, or information about \( \beta \), due to not using the full likelihood \( L_f(\beta, h_0(t)) \). These issues are discussed by Lawless (1982), Kalbfleisch and Prentice (1980), and Efron (1977). Lawless (1982) concludes that the efficiency of the partial likelihood methods is high when the baseline hazard function \( h_0(t) \) corresponds to a Weibull distribution, the proportional hazards model is appropriate and the number of parameters in \( \beta \) is not too large. Efron (1977) comments that these methods will usually be highly efficient under any reasonable assumptions about the class of possible hazard functions.

2.2 Inference for the proportional hazards model

Andersen, et al. (1993) and Fleming and Harrington (1991) use counting processes to establish the asymptotic properties of the partial likelihood estimator \( \hat{\beta} \). Since Andersen, et al. (1993) use general counting process notation and the results given in Fleming and Harrington (1991) more closely follow the notation given here, we cite the latter. Theorem 8.3.2 of Fleming and Harrington (1991) establishes the asymptotic normality of the maximum partial likelihood estimator \( \hat{\beta} \), ie.

\[ \sqrt{n}(\hat{\beta} - \beta_0) \xrightarrow{d} N(0, \Sigma(\beta_0)). \]  

and shows that the maximum partial likelihood estimator \( \hat{\beta} \) is a consistent estimator of \( \beta_0 \). Fleming and Harrington (1991) also establish that \( n^{-1}I(\beta_0) \) and \( n^{-1}I(\hat{\beta}) \) are both consistent estimators of \( \Sigma(\beta_0) \) where \( I(\cdot) \) is the Fisher information matrix. Proofs are based on the asymptotic properties of the score function.
These results can be used to test the hypothesis $H_0 : \beta = 0$ which corresponds to the hypothesis that $m$ survivor functions are the same when $x$ is a system of $m - 1$ dummy variables indicating $m$ populations. This application is illustrated by Lawless (1982). In this special case the null hypothesis becomes

$$H_0 : S_j(t) = S_0(t)^{\exp(\beta_i)}$$

for $i = 1, \ldots, m - 1$, and $S_m(t) = S_0(t)$. Then the test statistic is

$$X^2 = U(0)'[I(0)]^{-1} U(0)$$

where $U$ is the score function and $I$ is the Fisher information which is approximately a $\chi^2_{m-1}$ variate when the null hypothesis is true. This test, according to Lawless (1982), has power to detect alternatives from equality when the proportional hazards model is correct. Inference about an element of $\beta$, say $\beta_j$, can be made via the large sample normal approximation to the marginal distribution of $\beta_j$ which has mean $\beta_j$ and variance given by the $(j, j)$ entry of $[I(\beta)]^{-1}$. Kalbfleisch and Street (1990) claim that the asymptotic approximations are reasonably accurate when the number of failures is considerably larger than the number of parameters in the model. They also recommend that the inferences based on the normal approximation to the distribution of $\beta$ be compared to inferences obtained from a chi-squared approximation to the distribution of a ratio of partial likelihoods. Theorem 8.3.4 in Fleming and Harrington (1991) demonstrates that $-2[\log L(\beta) - \log L(\beta_0)] \xrightarrow{d} \chi^2_2$ as $n \to \infty$. when the null hypothesis $\beta = \beta_0$ is true. Fleming and Harrington also discuss large sample properties of the estimator of the baseline hazard function and asymptotic relative efficiency of partial likelihood methods.

2.3 Interval censored failure times

Often there is interval censoring which produces tied failure times. When the data are interval censored it is only known that a failure or an event occurred between two specified points. If the inspection intervals are small enough so that each failure falls into a unique disjoint interval, then the ordering of the failure times is preserved and the partial likelihood can be evaluated because it depends only on the order of the failures. If there are tied failure times or two or more failures are observed in the same inspection interval, then the partial likelihood is no longer well-defined.

Consider the data in Table 1 where there are four inspection intervals and the covariate is simply an indicator of one of two treatment groups. For the first inspection interval the possible contributions to the partial likelihood are either

$$\left( \frac{\exp \beta}{5 \exp \beta + 5} \right) \left( \frac{1}{4 \exp \beta + 5} \right)$$
Table 1  An example of tied failure times

<table>
<thead>
<tr>
<th>Inspection Interval</th>
<th>1</th>
<th>1</th>
<th>2</th>
<th>2</th>
<th>2</th>
<th>3</th>
<th>3</th>
<th>3</th>
<th>4</th>
<th>4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment Group</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>0</td>
</tr>
</tbody>
</table>

or

\[
\left(\frac{1}{5 \exp \beta + 5}\right) \left(\frac{\exp \beta}{5 \exp \beta + 4}\right)
\]

depending on whether or not the failure for group 1 preceded the failure for group 0. For the second inspection interval there are three possible contributions to the partial likelihood given by

\[
\left(\frac{1}{4 \exp \beta + 4}\right) \left(\frac{1}{4 \exp \beta + 3}\right) \left(\frac{\exp \beta}{4 \exp \beta + 2}\right)
\]

\[
\left(\frac{1}{4 \exp \beta + 4}\right) \left(\frac{\exp \beta}{4 \exp \beta + 3}\right) \left(\frac{1}{3 \exp \beta + 3}\right)
\]

\[
\left(\frac{\exp \beta}{4 \exp \beta + 4}\right) \left(\frac{1}{3 \exp \beta + 4}\right) \left(\frac{1}{3 \exp \beta + 3}\right)
\]

For the third inspection interval the three possibilities are

\[
\left(\frac{1}{3 \exp \beta + 2}\right) \left(\frac{\exp \beta}{3 \exp \beta + 1}\right) \left(\frac{\exp \beta}{2 \exp \beta + 1}\right)
\]

\[
\left(\frac{\exp \beta}{3 \exp \beta + 2}\right) \left(\frac{1}{2 \exp \beta + 2}\right) \left(\frac{\exp \beta}{2 \exp \beta + 1}\right)
\]

\[
\left(\frac{\exp \beta}{3 \exp \beta + 2}\right) \left(\frac{\exp \beta}{2 \exp \beta + 2}\right) \left(\frac{1}{\exp \beta + 2}\right)
\]

Finally, the two possibilities for the fourth inspection interval are

\[
\left(\frac{\exp \beta}{\exp \beta + 1}\right) \left(\frac{1}{1}\right)
\]

and

\[
\left(\frac{1}{\exp \beta + 1}\right) \left(\frac{\exp \beta}{\exp \beta}\right)
\]
Then, if the exact failure times could be observed, the partial likelihood for $\beta$ would be one of the thirty-six possible products obtained by selecting one of the possible contributions from each of the four intervals.

As discussed in the first paper, two commonly used methods of dealing with tied failure times within an inspection interval were proposed by Breslow (1974) and Efron (1977). These methods are available in statistical computing packages such as SAS and Splus. Both of these methods use approximations to the continuous time partial likelihood for proportional hazards models. In addition to these two approximations, we consider the arithmetic mean of all possible partial likelihoods, which is proportional to the approximation proposed by Kalbfleisch and Prentice (1973) and the geometric mean of all possible partial likelihoods. If the number of tied failure times in any particular inspection interval is too large, we use a random sample of the possible orderings. Our investigation focuses on the effect of interval censoring on the accuracy of partial likelihood estimates computed with these four methods.

Our simulation results show that the Efron approximation of the partial likelihoods generally provides more accurate estimates of regression parameters in proportional hazards models than the Breslow approximation, but the Efron modification will fail to give reliable estimates if either the coefficient is too far from zero or the number of tied failure times is too large. Sample size and level of random right censoring have relatively little effect on the accuracy of these methods. We provide a general recommendation about level of tied failure times that can be tolerated in the accurate use of the Efron approximation. Maximizing the geometric mean of the partial likelihoods of all possible orderings of tied failure times produces nearly the same estimates as the Efron approximation. Maximizing the arithmetic mean of the partial likelihoods of all possible orderings of tied failure times produces estimators of regression coefficients similar to those that could be obtained from maximizing the partial likelihood for exact continuous lifetime data. Estimates from the arithmetic mean of all possible partial likelihoods are much less affected by changes in either the percentage of tied failure times or the actual values of the regression parameters than the estimates obtained from the Efron approximation.

2.4 Some alternative approaches for proportional hazards with interval censored data

Similar to our point of view that interval censored data arise from imprecise recording of realizations of a continuous random variable, other researchers have investigated estimation methods based on grouped continuous models. The grouped continuous model, discussed by Kalbfleisch and Prentice (1980) and Lawless (1982), assumes failure times are grouped into intervals which partition the con-
tinuous time scale into \( k \) intervals \([a_{j-1}, a_j)\), for \( j = 1, \ldots, k \), where \( a_0 = 0 \) and \( a_k = \infty \). All that is known about the failure times and the censoring times is the inspection interval in which they occurred. With this notation, the conditional probability of failure in the \( i \)th interval given the covariates \( x \) and survival to the beginning of the interval is

\[
\Pr(T \in [a_{i-1}, a_i) \mid T \geq a_{i-1}) = 1 - (1 - \lambda_i)^{\exp(x'\beta)}
\]

where

\[
\lambda_i = \exp \left( - \int_{a_{i-1}}^{a_i} \lambda_0(u) \, du \right)
\]

and \( \lambda_0(u) \) represents the baseline hazard. This model requires the simultaneous estimation of both the regression parameters and the baseline "hazard" values, \( \lambda_1, \ldots, \lambda_k \).

Prentice and Gloeckler (1978) extended the grouped continuous model to incorporate time-dependent covariates. They use maximum likelihood methodology to simultaneously estimate both the treatment effects and survivor function.

An alternative model for grouped continuous data was proposed by Cox (1972) and is based on a discrete distribution for the failure times. In this model \( \lambda_i \) is a contribution to the \( S_0(t) \), the baseline survivor function, which has mass points \( p_i \), and the hazard function is

\[
1 - (1 - \lambda_i)^{\exp(x'\beta)}
\]

assuming proportional hazards. This model is a linear log odds model for the hazard probability at each potential failure time. It is often referred to as Cox’s discrete logistic model. A partial likelihood function is

\[
\prod_{i=1}^{k} \left( \frac{\exp(s_i \beta)}{\sum_{\bar{R}_d(t_{ii})} \exp(s_i \beta)} \right)
\]

where \( s_i \) is the sum of the covariates associated with the \( d_i \) failure times at time \( t_{ii} \), and \( R_d(t_{ii}) \) is the set of all subsets of \( d_i \) items chosen from the risk set at \( t_{ii} \) without replacement.

Both of these models converge to a model for continuous time data as the length of the intervals becomes infinitesimally small. However, Kalbfleisch and Prentice (1980) point out that the discrete logistic model does not provide a consistent estimator of \( \beta \).

McKeague and Zhang (1996) take a slightly different approach to tied failure times in that they employ a bias correction. They use the partial likelihood estimator for grouped data as presented by Kalbfleisch and Prentice (1973) and they compare that model to a Poisson regression model. They demonstrate consistency of their estimator under a set of assumptions about the length of the intervals and covariate strata, and derive the asymptotic bias of their estimator under a slightly different set
of assumptions. In a simulation study, they use their estimator to estimate the treatment effects in a proportional hazards model, and they also estimate their bias term. They conclude that their bias estimator removes the bias from the estimator based on the grouped continuous model.

Aranda-Ordaz (1983) considers a more general class of additive and multiplicative hazard models for interval censored data. The proportional hazards model is a special case. Estimation is done via a transformation of the conditional probability of failing in an interval to get a generalized linear model format similar to the grouped continuous model. This specification is used for estimation of both the treatment effects and the survivor function. It also provides a framework for testing for departures from the proportional hazards model.

We did not consider any of these approaches in the simulation study in our first paper because these models differ from the proportional hazards model for continuous data. Our simulation study examines only the effective use of modifications of partial likelihoods to accommodate tied event times arising from interval censoring.

3 A discrete approach to interval censored data

Our second paper considers methods based on discrete distributions for counts corresponding to the observed numbers of events occurring within the various inspection intervals. We generalize this approach by allowing different sets of inspection times to be used for different cohorts of individuals. Furthermore, cohorts are assumed to be independent, but response times for members of a single cohort are allowed to be correlated. We also allow for limited failure populations where a proportion of the population either never fail or never experience some life event.

Although responses within individual cohorts may be correlated, we obtain a consistent estimator for the conditional probability of failure within each inspection interval by initially assuming all responses are independent and maximizing the corresponding multinomial likelihood function. Since inspection schedules are allowed to vary across cohorts, this procedure involves maximization of likelihoods for incompletely classified data. Similar to Kaplan-Meier estimation, estimates of survival probabilities are obtained from products of the estimates of conditional probabilities of survival for successive inspection intervals. This is also similar to Turnbull's (1976) nonparametric estimation of a cumulative distribution function.

The covariance matrix for the large sample distribution of the estimated parameters is not obtained from the Fisher information matrix for the incorrect multinomial likelihood. We use properties of the score function for the incorrect multinomial likelihood to develop a robust "sandwich" estimator for
the covariance matrix of the parameter estimates. This methodology is an application of what Zeger, et al. (1988) refer to as a "population-averaged" or marginal approach. There is no real interest in estimating within cohort correlations. A practical advantage of this approach is that it does not require the specification of a joint distribution of correlated response times. There may be some loss of efficiency relative to estimates obtained by maximizing the true likelihood function, if it could be established, but this is not likely to be substantial unless within cohort correlations are large.

Lifetable analyses of correlated failure times without covariates, analogous to Kaplan-Meier estimation, have been previously discussed by Eriksson and Adell (1994), Williams (1995), and Kang and Koehler (1997). They all propose modifications of Greenwood's formula to account for positive correlations within cohorts. None of those methods have been adapted to situations with different inspection schedules for different groups of subjects.

In analysis of the effects of temperature on the distribution of hatch times of bean leaf beetle eggs, considered in the second paper, the researchers are interested in the inverse of the median hatch time of viable eggs, which is called the "daily development rate". A shortcoming of the multinomial model is that it does not provide a unique estimate of the median of the failure time distribution. Estimation of the median event time from multinomial models is discussed by Reid (1981), Brookmeyer and Crowley (1982), Emerson (1982), and Slud et al. (1984).

We adopt an alternative semi-parametric approach that models the multinomial probability of failure in an inspection interval with the difference in the values of a parametric survivor function evaluated at the beginning and end of the inspection interval. Finkelstein (1986) uses a similar approach to deal with interval censored survival data. Estimation of the regression coefficients in proportional hazards models and parameters of the survivor function are done simultaneously via the EM algorithm. Finkelstein (1986) does not consider the possibility of correlated response times. Koehler (1994) uses the Weibull survivor function in an application of this approach to deal with correlated event times, but he uses bootstrap estimation of the covariance matrix instead of the robust covariance estimator considered in our second paper.

Another way to deal with correlated responses within cohorts is to introduce random effects for the cohorts. Then, conditional on a specific cohort, individual responses within a cohort are assumed to be independent. Zeger et al. (1988) refer to this method as a "subject-specific" approach.

An example of this approach is the frailty model proposed by Vaupel et al. (1979). The frailty is a continuous random variable corresponding to an unobserved random effect, with mean zero and positive variance, which accounts for differences among cohorts. It is assumed that the frailty acts
multiplicatively on the hazard. Then the conditional hazard function in the proportional hazards framework is

$$h_0(t \mid x, z) = z_i h_0(t) \exp(x_i \beta)$$  \hspace{1cm} (12)

where $z_i$ is the frailty, $h_0(t)$ is the baseline hazard and $x_i$ is a covariate for the $i$th cohort. Usually the distribution of $Z$ is assumed to be either gamma, inverse Gaussian, or positive stable. Often the baseline hazard is taken to be Weibull. A general review of frailty models is given by Costigan and Klein (1993). Frailty models require a detailed model specification for which the previous semi-parametric approach and evaluation of maximum likelihood estimates can be a very complex numerical task. Frailty models would be preferred if there was interest in predicting the random effects for individual cohorts. Since this is not of interest in the applications considered in the second paper, we do not give further consideration to frailty models.

Since some beetle eggs are not viable and will never hatch, we need to consider a limited failure population where some individuals are not subject to failure. In general, this model is specified by

$$S^*(t) = \xi S_1(t) + (1 - \xi)$$  \hspace{1cm} (13)

where $S_1(t)$ is a parametric survivor function and $\xi$ is the proportion of the population subject to failure. Meeker (1987) describes a limited failure Weibull model which we adopt in our semi-parametric approach. Based on simulation, he concludes that at least 80% of the population which is subject to failure must be observed to fail to obtain reliable estimates of $\xi$ and the parameters of $S_1(t)$. Koehler and McGovern (1990) and Koehler (1994) also discuss applications of limited failure Weibull models.

4 Dissertation organization

This dissertation is organized into four major parts in the paper format. The first part is the general introduction to explain the motivation behind the work, the justification for the work, and the literature review and other details which are not contained in the papers. The next two parts are two papers in the form to be submitted to journals which contain an independent list of references. The final part is the the general conclusion to unify the conclusions from the two papers. References within the two papers are given in a section at the conclusion of the paper. The references for the general introduction are given at the conclusion of the thesis.

The first paper is a simulation study dealing with the Cox proportional hazards model for interval censored data. This approach is based on adapting the underlying continuous model for the data to the grouped data.
The second paper develops a robust variance estimator for interval censored and correlated life event data. Additionally, a goodness of fit test is developed for comparison of two nested models for this type of data.
THE EFFECT OF INTERVAL CENSORING ON PARTIAL
LIKELIHOOD ANALYSIS OF PROPORTIONAL HAZARDS MODELS

Rebecca J. Benner and Kenneth J. Koehler

A paper to be submitted to Biometrics

Abstract

Methods for adjusting the effects of interval censoring on partial likelihood analysis of proportional hazards models are compared using a simulation study. The Efron approximation is shown to be superior to the Breslow approximation, but both methods tend to break down as the number of tied event times created by interval censoring increases or treatment effects increase. Estimates of treatment effects tend to be biased toward zero for both methods. The Efron method is shown to closely approximate the geometric mean of the partial likelihoods for all possible orderings of tied event times, while the arithmetic mean of all possible likelihoods more closely approximates the results that would be obtained if the exact event times were known. Geometric and arithmetic means of random samples of possible partial likelihoods are considered for situations with larger numbers of tied failure times.

KEY WORDS: Cox proportional hazards, interval censored failure times, ties.

1 Introduction

The focus of this paper is the estimation of the covariate effects in the Cox proportional hazards model. Application of partial likelihood estimation procedures depends on the assumption that the failure times are positive continuous random variables. Practical limitations of many medical and ecological studies, however, only allow subjects to be checked at regular inspection intervals, and exact failure times are often not recorded. The discreteness arising from the interval censoring of failure times leads to problems in applying partial likelihood estimation when the ordering of failure times cannot
be uniquely determined. Two popular methods for adjusting the partial likelihood have been proposed by Breslow (1974) and Efron (1977).

We first demonstrate that the Efron approximation is generally superior to the Breslow approximation. Secondly, a more extensive set of simulations are used to more carefully examine how the accuracy of the Efron approximation deteriorates as the percentage of tied failure times and size of the treatment effect increase. Finally the Efron approximation is compared to the use of either the arithmetic mean or the geometric mean of the set of partial likelihoods corresponding to all possible orderings of the failure times within inspection intervals.

1.1 Modification of the partial likelihood for tied failure times

We restrict attention to the Cox proportional hazard function $h(t \mid x) = h_0(t) \exp(x' \beta)$, where $h_0(t)$ is the baseline hazard function, $x' = (x_1, x_2, \ldots, x_p)$ is a vector of covariates, and $\beta$ is the vector of parameters to be estimated. Suppose that exact failure times are available for $k$ of the $n$ subjects in the study who are observed to fail. Times for the remaining $n - k$ subjects are right censored. Ordering the failure times $t_{(1)} < t_{(2)} < \ldots < t_{(k)}$, the risk set, denoted by $R_i$, is the set of subjects who are still alive and uncensored just before time $t_{(i)}$. Let $x_{(i)}$ denote the values of the explanatory variables associated with the $i$th ordered failure time $t_{(i)}$. To avoid specification and estimation of $h_0(t)$, Cox (1972, 1975) suggested that $\beta$ could be estimated by maximizing a portion of the full likelihood,

$$L(\beta) = \prod_{i=1}^{k} \frac{\exp(x_{(i)}' \beta)}{\sum_{t \in R_i} \exp(x_{(i)}' \beta)},$$

known as the partial likelihood. Andersen, et al. (1993) and Fleming and Harrington (1991) use the theory of counting processes to establish the consistency and asymptotic normality of the partial likelihood estimator when the exact failure times are available.

In practice, tied failure times appear in the data due to practical limitations in the ability to continuously monitor subjects. When tied failure times occur, the partial likelihood function is undefined because the ordering of tied failure times is unknown. Tied failure times occur for interval censored data whenever more than one failure occurs in a single inspection interval. Breslow's (1974) suggestion is to use

$$L_B(\beta) = \prod_{i=1}^{k} \frac{\exp(s_{(i)}' \beta)}{[\sum_{t \in R_i} \exp(x_{(i)}' \beta)]^{d_i}},$$

as the partial likelihood, where $s_{(i)} = \sum_{j=1}^{d_i} x_{(j)}$ is the sum of the covariate values for the $d_i$ subjects failing in the $i$th inspection interval. This method uses the same denominator for each member of a set of
tied failure times, which tends to make the denominator too large since no failures are removed from the risk set until the next inspection interval. However, Kalbfleisch and Prentice (1980) and Fleming and Harrington (1991) both indicate that the Breslow approximation should provide a good estimate of \( \beta \) if \( d_i \) is small compared to the number of subjects in the risk set \( R_i \) for all \( i \). Kalbfleisch and Street (1990) also claim that this method is satisfactory for small numbers of tied failure times and note that most software packages use this method as the default method due to the ease of programming. Kalbfleisch and Prentice (1980) express some concern about bias associated with the Breslow approximation and indicate that an alternative modification of the partial likelihood suggested by Efron (1977) may work better when the \( d_i \)'s are small. Therneau (1994) also suggests that the Efron approximation should work better, and it is the default for his programs.

Efron's (1977) modification to the partial likelihood is

\[
L_E(\beta) = \frac{\prod_{i=1}^{k} \prod_{j=1}^{d_i} \exp(s_i^{(j)} \beta)}{\prod_{i=1}^{k} \prod_{j=1}^{d_i} \left[ \sum_{t \in R_i} \exp(x_t^{(j)} \beta) - \frac{\sum_{t \in D_i} \exp(x_t^{(j)} \beta)}{d_i} \right]}
\]

where \( D_i \) is the set of subjects who failed in the \( i \)th inspection interval. This method does not use the same denominator for each case in a set of tied values. The denominators are arithmetic means of all possible denominators that could appear at that point in the partial likelihood. Both the Breslow and Efron approximations reduce to the partial likelihood \( L(\beta) \) in (1) when there are no tied failure times in the data. If tied failure times are numerous, Kalbfleisch and Prentice (1980) recommend using a discrete model instead of either the Breslow or Efron approximations.

Efron (1977) motivated his modification as an approximation to an average of partial likelihoods for all possible orderings of tied failure times. Using the actual mean, instead of the Breslow or Efron approximations, may provide an improved estimator of \( \beta \). We consider both the arithmetic and geometric means of all the possible partial likelihoods.

Consider the situation where subjects are inspected at \( b - 1 \) inspection times, and failure times are interval censored with respect to the resulting set of \( b \) inspection intervals. The last interval contains any subject that has not failed by the final inspection time. Let \( m_i = d_i! \) denote the number of possible orderings for the \( d_i \) failures observed in the \( i \)th inspection interval. Then the arithmetic mean of the partial likelihood for all of the possible orderings of the tied failure times in each inspection interval is

\[
L_A(\beta) = \prod_{i=1}^{b} \frac{1}{m_i} \sum_{k=1}^{m_i} L_{ik}(\beta)
\]

where \( L_{ik}(\beta) \) is given by (1) with \( k \) replaced by \( d_i \) and the risk set \( R_{ik} \) depends on the \( k \)th ordering of the failures in the \( i \)th inspection interval. This likelihood is proportional to the method proposed by
Kalbfleisch and Prentice (1973). Alternatively, using the geometric mean of the contributions to the partial likelihood for all possible orderings of the failures in each interval yields

\[ L_G(\beta) = \prod_{i=1}^{b} \left( \prod_{k=1}^{m_i} L_{ik}(\beta) \right)^{\frac{1}{m_i}}. \]  

Either (4) or (5) can be maximized to obtain an estimate for \( \beta \).

A practical limitation of either approach is that the number of partial likelihoods in the mean increases exponentially as the number of tied failure times within an inspection interval increases. This limitation can be avoided by averaging across a random sample from the set of possible orderings of the failures in any inspection interval with a large number of tied failure times. For the simple case of a treatment versus a control and no other covariates, the number of unique possible likelihoods for an inspection interval with \( y_i \) of the \( d_i \) failures in the treatment group reduces from \( d_i! \) to \( \binom{d_i}{y_i} \).

1.2 Relationships among approximations

Using the relationship between geometric and arithmetic means, it is easy to show that \( L_E(\beta) \leq L_G(\beta) \leq L_A(\beta) \) for any \( \beta \). From this perspective, the Efron approximation is a better approximation to the geometric mean of all possible partial likelihoods than to the arithmetic mean.

The proof of the result follows from the well-known fact that if \( a_j > 0 \) for all \( j = 1, \ldots, k \), then

\[ \left( \prod_{j=1}^{k} a_j \right)^{\frac{1}{k}} \leq \frac{1}{k} \sum_{j=1}^{k} a_j \]  

with equality only if \( a_j \equiv a \) for all \( j = 1, \ldots, k \). Consequently, \( L_G(\beta) \leq L_A(\beta) \). Furthermore, \( L_E(\beta) \leq L_G(\beta) \) can be established by comparing corresponding factors. Let \( d_j = \exp(x_j^T \beta) \) for the \( j = 1, \ldots, d_i \) failures recorded in the \( i \)th inspection interval, and define \( a_* = \sum_{i \in R} \exp(x_i^T \beta) \). Then the \( i \)th factor in (5) can be written as

\[ \prod_{j=1}^{d_i} a_j \]  

(7)

where \( f = \frac{2}{d_i(d_i-1)} \) and the \( i \)th factor in (3) can be written as

\[ \prod_{j=1}^{d_i} a_j \]  

(8)

Corresponding factors in the denominator of (7) and (8) are geometric and arithmetic means, respectively, of the same set of values. If follows that \( L_E(\beta) \leq L_G(\beta) \) for any \( \beta > 0 \).
Table 1  Example with six inspection intervals and five tied failure times in one inspection interval

<table>
<thead>
<tr>
<th>Interval</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>4</th>
<th>4</th>
<th>4</th>
<th>5</th>
<th>6</th>
</tr>
</thead>
<tbody>
<tr>
<td>Extreme Ordering (A)</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Extreme Ordering (B)</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
</tr>
</tbody>
</table>

Obviously, $L_E(\beta) = L_C(\beta) = L_A(\beta)$ when $\beta = 0$, and all three partial likelihoods have the same score function, but second partial derivatives differ across methods. These partial likelihoods are also equal if all cases that failed in a particular inspection interval have the same set of covariate values. In either case, the ordering of the failures within an inspection interval has no consequence. Although the Breslow approximation yields a partial likelihood that is smaller than $L_E(\beta)$, it has a shape similar to $L_E(\beta)$ when the number of tied failure times is not too large. Then the value of $\beta$ which maximizes $L_B(\beta)$ will be close to the estimate obtained by maximizing $L_E(\beta)$. Otherwise maximization of $L_B(\beta)$ can lead to an estimate of $\beta$ that tends to be biased toward zero.

To illustrate this relationship among partial likelihoods, consider the example in Table 1 with six inspection intervals and five failures occurring in one inspection interval. Treatment group failures are indicated by 1 and control group failures are indicated by 0. The true ordering of the five failures in the fourth inspection interval has been lost to interval censoring in this example. The possible ordering labeled Extreme Ordering (A) produces the minimum possible value of $\beta = -0.7175$. The possible ordering labeled Extreme Ordering (B) yields the maximum possible value of $\beta = -0.0516$. Log partial likelihoods for the orderings corresponding to the minimum and maximum of the possible values for $\beta$ are shown in Figure 1 along with the natural logarithms of $L_A(\beta), L_C(\beta), L_E(\beta)$, and $L_B(\beta)$. The maximum partial likelihood estimate for each method is shown in Table 1 and denoted by "•" in Figure 1. Note that the natural logarithms of $L_A(\beta), L_C(\beta)$, and $L_E(\beta)$ are all between the log partial likelihoods of the two extreme cases of orderings. Although $\log L_B(\beta)$ falls well below the rest of the log partial likelihoods, it is closest in shape to $L_E(\beta)$ in the sense that the ratio of the two log partial likelihoods is closest to one. Also, the value of $\beta$ obtained from the Breslow log partial likelihood is similar to the values of $\beta$ obtained from the other methods for this example.

1.3  Review of previous simulation studies

Kalbfleisch and Prentice (1973) performed a simulation study for the two sample problem with baseline exponential failure rates with $\beta = 0.50$. They compared estimates of $\beta$ obtained by maximizing
Figure 1 Log partial likelihoods for the data in Table 1
Table 2 Results for different methods of estimation for the data in Table 1

<table>
<thead>
<tr>
<th>Estimation Method</th>
<th>Estimated (\hat{\beta})</th>
<th>Variance of (\hat{\beta})</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breslow</td>
<td>-0.4088</td>
<td>0.4519</td>
</tr>
<tr>
<td>Efron</td>
<td>-0.3744</td>
<td>0.4514</td>
</tr>
<tr>
<td>Geometric</td>
<td>-0.3867</td>
<td>0.4663</td>
</tr>
<tr>
<td>Arithmetic</td>
<td>-0.4197</td>
<td>0.5059</td>
</tr>
</tbody>
</table>

\(L_A(\beta)\) with estimates obtained from the discrete logistic likelihood suggested by Cox (1972), for various sets of inspection intervals. There was no random censoring and they used total sample sizes of 80 and 400 with equal allocation to both groups. They concluded that maximizing \(L_A(\beta)\) provided a fairly stable estimator for \(\beta\) as the width of the inspection intervals increased, although it was slightly biased for small samples, and the bias of the estimator based on Cox's logistic model increased as the width of the inspection intervals increased.

Farewell and Prentice (1980) compared five maximum partial likelihood estimation methods including adaptations of the Breslow and Efron approximations for case-control studies. They generated data from the discrete logistic model proposed by Cox (1972). Except for the matched pair situation, they concluded that neither the Breslow nor the Efron approximations should be used in either case-control or prospective studies when the fraction of subjects failing at any given time is large. They also concluded that an adjusted quadratic estimator, which is a noniterative odds ratio estimator derived from a second order Taylor series approximation to the log partial likelihood from the Cox discrete logistic model for discrete failure times at \(\beta = 0\), was a better estimator for the examples they studied.

A simulation study by Costanza and Nichola (1982) examined the effects of the amount random censoring on estimates of \(\beta\) obtained from the Breslow approximation for the partial likelihood. They fit a proportional hazards model to a a large set of data with no censoring and re-analyzed the resulting simulated data sets. Then, they imposed different levels of random censoring. For large samples they concluded that estimation of \(\beta\) and any subsequent inferences are not reliable when the amount of censoring is greater than 75%. They also found that the level of random censoring had little effect on inferences about \(\beta\).

Johnson, et al. (1982) simulated the small sample behavior of maximum partial likelihood estimators for \(\beta\) in cases with treatment and control groups and the possibility of an additional covariate which could be discrete (with either two or five levels) or continuous (uniform on an interval). Overall, observed
test sizes agreed closely with nominal levels. They concluded that if the total sample size was greater than 40, then the bias of the estimators was small, asymptotic variance formulas were only slightly smaller than simulated variances, and power sizes were reasonable, provided that the treatment and control groups had the same number of subjects. They found no difference in the results due to type of variable included as the second covariate, but there tended to be more bias in the cases where the treatment and control units were not equally divided at each level of the covariate.

More recently, Hertz-Picciotto and Rockhill (1997) compared the performance of the Breslow and Efron approximations with the discrete logistic partial likelihood proposed by Cox (1972) for total sample sizes of 50, 100, 500, and 1000 with equal allocation to treatment and control groups. They varied the inspection intervals to have averages of 2.5, 5, or 10 failures per inspection interval, but considered only one value of \( \beta = 0.6931 \). and did not consider effects of random censoring. Their simulations showed that the Breslow approximation tends to underestimate \( \beta \) while the discrete logistic estimator tends to overestimate \( \beta \). Hence they recommend the Efron approximation for tied failure time data.

Our comparison of the Breslow and Efron approximations agree with the findings of these other researchers, but we have performed a more extensive investigation of the Efron approximation to determine conditions under which it begins to break down. In addition, we examine more closely the behavior of estimators of \( \beta \) based on maximizing either the arithmetic mean or the geometric mean of the partial likelihoods for all possible orderings of tied failure times.

Since interval censored data result from imprecise monitoring of a continuous random variable, we consider only methods which view the underlying failure times as continuous. Hence, the discrete logistic partial likelihood proposed by Cox (1972) was not included in our simulation study because it is intended for data which are truly discrete, and when failures can only occur at specified points in time. As previously noted, simulation studies have shown that that the estimator of \( \beta \) from the Cox's discrete logistic model does not perform as well as the Efron method for interval censored data. Furthermore, Kalbfleisch and Prentice (1973) and (1980) show that the discrete logistic model does not provide a consistent estimator of \( \beta \).

2 Averaging across all possible orderings

When the number of failures in any single inspection interval is not too large, estimates of \( \beta \) can be obtained by maximizing either \( L_A(\beta) \) or \( L_G(\beta) \). We accomplished this by modifying a version of of the Package for Survival Analysis in S written and made available from StatLib by Terry M. Therneau. For
larger numbers of tied failure times, we approximated $L_A(\beta)$ and $L_C(\beta)$ by averaging partial likelihoods for a random sample of possible orderings.

### 2.1 Numerical procedures

When there are no tied failure times, Therneau's program uses a modified Newton-Raphson Algorithm to maximize the log partial likelihood

$$\ln(L(\beta)) = \sum_{i=1}^{b} x_{(i)}' \beta - \sum_{i=1}^{b} \ln \left( \sum_{t \in R_i} \exp(x_i' \beta) \right).$$

The components of the score function are

$$\frac{\partial \ln(L(\beta))}{\partial \beta_j} = \sum_{i=1}^{b} x_{(i)} j - \sum_{i=1}^{b} \frac{\sum_{t \in R_i} x_{tj} \exp(x_i' \beta)}{\sum_{t \in R_i} \exp(x_i' \beta)}.$$  

for $j = 1, \ldots, p$, and the required second partial derivatives are

$$\frac{\partial^2 \ln(L(\beta))}{\partial \beta_j \partial \beta_r} = -\sum_{i=1}^{b} \left[ \frac{\sum_{t \in R_i} x_{tj} x_{tj}' \exp(x_i' \beta)}{(\sum_{t \in R_i} \exp(x_i' \beta))^2} - \frac{\sum_{t \in R_i} x_{tj} \exp(x_i' \beta) \sum_{t \in R_i} x_{tj}' \exp(x_i' \beta)}{(\sum_{t \in R_i} \exp(x_i' \beta))^3} \right].$$

Therneau's program uses a convergence criteria of 0.0001 applied to the absolute value of one minus the ratio of the log partial likelihoods for the previous and current values of the estimate for $\beta$. When tied failure times arise from interval censored data, failure times are simply entered as if failures only occur at the end of inspection intervals.

$$\ln(L_A(\beta)) = -\sum_{i=1}^{b} \ln(m_i) + \sum_{i=1}^{b} \ln \left( \sum_{k=1}^{m_i} L_{ik}(\beta) \right).$$

and where $L_{ik}(\beta)$ takes the same form as (9). Censored failure times are handled in a corresponding manner. The components of the score function are

$$\frac{\partial \ln(L_A(\beta))}{\partial \beta_s} = \sum_{i=1}^{b} \sum_{k=1}^{m_i} L_{ik}(\beta) \frac{\partial \ln(L_{ik}(\beta))}{\partial \beta_s} \frac{\sum_{k=1}^{m_i} L_{ik}(\beta)}{\sum_{k=1}^{m_i} L_{ik}(\beta)},$$

where $\partial \ln(L_{ik}(\beta))/\partial \beta_s$ is the same form as (10). Finally elements of the matrix of second partial derivatives of (12) are

$$\frac{\partial^2 \ln(L_A(\beta))}{\partial \beta_s \partial \beta_r} = \sum_{i=1}^{b} \left[ g_i(\beta) \sum_{k=1}^{m_i} L_{ik}(\beta) - \left( \sum_{k=1}^{m_i} L_{ik}(\beta) \frac{\partial \ln(L_{ik}(\beta))}{\partial \beta_s} \right) \right] \left( \sum_{k=1}^{m_i} L_{ik}(\beta) \right) - \left( \sum_{k=1}^{m_i} L_{ik}(\beta) \frac{\partial \ln(L_{ik}(\beta))}{\partial \beta_s} \right)^2.$$
where
\[ g_i(\beta) = \sum_{k=1}^{m_i} L_{ik}(\beta) \frac{\partial \ln(L_{ik}(\beta))}{\partial \beta_s} \frac{\partial \ln(L_{ik}(\beta))}{\partial \beta_r} + \sum_{k=1}^{m_i} L_{ik}(\beta) \frac{\partial^2 \ln(L_{ik}(\beta))}{\partial \beta_s \partial \beta_r} \] (15)
and \( \frac{\partial^2 \ln(L_{ik}(\beta))}{\partial \beta_s \partial \beta_r} \) has the same form as (11).

Similarly, the natural logarithm of the geometric mean of the partial likelihoods for all possible orderings is
\[ \ln(L_G(\beta)) = \sum_{i=1}^{b} \frac{1}{m_i} \sum_{k=1}^{m_i} \ln(L_{ik}(\beta)). \] (16)
The components of the score function are
\[ \frac{\partial \ln(L_G(\beta))}{\partial \beta_s} = \sum_{i=1}^{b} \frac{1}{m_i} \sum_{k=1}^{m_i} \frac{\partial \ln(L_{ik}(\beta))}{\partial \beta_s}, \] (17)
and the elements of the matrix of second partial derivatives are
\[ \frac{\partial^2 \ln(L_G(\beta))}{\partial \beta_s \partial \beta_r} = \sum_{i=1}^{b} \frac{1}{m_i} \sum_{k=1}^{m_i} \frac{\partial^2 \ln(L_{ik}(\beta))}{\partial \beta_s \partial \beta_r}. \] (18)

2.2 Random sampling of possible orderings

When the number of failures in an inspection interval is too large, the computational burden of evaluating partial likelihoods for all of the possible orderings may exceed available computational resources. Then, an approximation to an average across all possible orderings is obtained by averaging across a random sample of possible orderings. Kalbfleisch and Prentice (1973) recommend that a sample of possible orderings be used for inspection intervals containing seven or more tied failure times. We further modified Therneau's program to do this within any particular inspection interval where the number of failures exceeds a user specified bound.

Several data sets were analyzed to investigate how randomly sampling a subset of possible orderings affects variability in the estimation of \( \beta \). Each data set had one inspection interval with either seven or eight tied failure times, and half of the failures were from the treatment group and half were from the control group. For each data set we first computed \( \hat{\beta} \) by maximizing the arithmetic mean of all possible partial likelihoods. Next, \( \hat{\beta} \) was estimated by maximizing the arithmetic means of 1000 and 5000 randomly selected orderings. Sampling was done with replacement from the set of all possible orderings. The process was repeated so that each data set was analyzed 100 times with 100 different randomly selected subsets of the possible orderings.

The minimum and maximum deviations in the 100 samples from \( \hat{\beta} \) based on all the possible orderings are shown in Table 3. Additionally, we used the estimated value of the standard error of \( \hat{\beta} \) based on all the possible orderings to compute the percentage increase in the standard error due to random
Table 3  Effects of sampling possible orderings for the arithmetic mean of partial likelihoods

<table>
<thead>
<tr>
<th>Sample Size</th>
<th>Maximum Ties in any Interval</th>
<th>Estimated Percentage of Ties</th>
<th>Possible Orderings</th>
<th>1000 Orderings</th>
<th>5000 Orderings</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Minimum Deviation</td>
<td>Maximum Deviation</td>
</tr>
<tr>
<td>16</td>
<td>7</td>
<td>23</td>
<td>-0.8097</td>
<td>-0.0087</td>
<td>0.0075</td>
</tr>
<tr>
<td>20</td>
<td>8</td>
<td>25</td>
<td>-0.6813</td>
<td>-0.0091</td>
<td>0.0094</td>
</tr>
<tr>
<td>16</td>
<td>8</td>
<td>28</td>
<td>-0.9137</td>
<td>-0.0115</td>
<td>0.0119</td>
</tr>
<tr>
<td>12</td>
<td>7</td>
<td>38</td>
<td>0.0625</td>
<td>-0.0167</td>
<td>0.0208</td>
</tr>
<tr>
<td>12</td>
<td>7</td>
<td>39</td>
<td>-0.3184</td>
<td>-0.0081</td>
<td>0.0100</td>
</tr>
<tr>
<td>10</td>
<td>7</td>
<td>54</td>
<td>-0.0264</td>
<td>-0.0203</td>
<td>0.0234</td>
</tr>
</tbody>
</table>

sampling when compared to the standard error of \( \hat{\beta} \) including the variance due to random sampling possible orderings and found that in all cases this was one. However, the simulation variance in \( \hat{\beta} \) for selecting 1000 possible orderings was between 2 and 2.4 times larger than for selecting 5000 for the six examples studied. We conclude that if there are more than seven tied failure times in any one inspection interval, then we can replace all of the possible orderings with only a sample of 5000 possible orderings of failure times and still get a speedy, reliable estimate of \( \beta \) for one data set. The results for randomly sampling possible orderings for the geometric mean of partial likelihoods were similar.

3 Simulation studies

Simulation studies were performed to compare properties of estimators of \( \beta \) obtained from the Breslow and Efron approximations with the estimators obtained by maximizing the arithmetic and geometric means of partial likelihoods for all possible orderings of tied failure times arising from interval censoring. These estimators are denoted by \( \hat{\beta}_B, \hat{\beta}_E, \hat{\beta}_A, \) and \( \hat{\beta}_G \), respectively. The first study considers small samples with five cases in each of two treatment groups and four inspection intervals. The second study investigates larger, more realistic samples where simulated approximations to averages of partial likelihoods for all possible orderings of tied failure times are more often used.

Estimators are compared with respect to the following properties. The bias of each estimator for \( \beta \) was estimated as the difference between the average of the estimate from the simulated samples and the true \( \beta \) value. The ratio computed as the average of the estimates of variance calculated from the simulated information matrices divided by the sample variance of the estimates from the simulation
was computed to assess the accuracy of the asymptotic variance estimator. The quality of inferences is assessed by examining the coverage rates of confidence intervals for $\beta$, which is the proportion of confidence intervals computed from the simulated data sets that contain the true value of $\beta$.

3.1 Computations

All of the computations for data simulation and parameter estimation were done using Splus Version 3.1 Release 1 for DEC RISC. ULTRIX 4.3 at Iowa State University. The various estimation methods were evaluated with our modification of the Package for Survival Analysis in S written by Terry M. Therneau. This program was modified to maximize both the arithmetic mean and the geometric mean of the possible partial likelihoods for all possible orderings of tied failure times. Means of a random sample of 1000 possible orderings were used when there were more than seven tied failure times in an inspection interval.

Each run of the simulation consisted of 1000 simulated sets of exact failure times generated from a standard exponential baseline hazard function for a particular combination of sample size, true value of $\beta$, and censoring level. In each case, a proportional hazards model was fit to the simulated failure times before any interval censoring was imposed. Then, each set of simulated failure times was progressively interval censored to obtain coarser levels of interval censoring and estimates of $\beta$ were obtained from $L_B(\beta)$, $L_E(\beta)$, $L_A(\beta)$, and $L_G(\beta)$.

3.2 Monotone partial likelihood

A monotone partial likelihood occurs when either the value of the covariate at each failure time is the largest of the covariate values in the risk set at that particular point or when the covariate value at each failure time is always the smallest of the covariate values in the risk set. In such cases the maximum partial likelihood estimator for $\beta$ does not exist, and it is often detected by the failure of the estimation procedure to converge. Bryson and Johnson (1981) recommend that any simulated data exhibiting this problem should be removed and replaced, and the results of the study should be conditioned on the estimate of $\beta$ being finite. In the following simulation studies, results for samples with a monotone partial likelihood are excluded, but are not replaced, because data that are monotone with respect to the exact failure times, may no longer be monotone when higher levels of interval censoring are induced.

If the data are nearly monotone in that all the failures from one group precede those from the other group with the exception of one inspection interval which contains failures from both groups, then the Breslow and Efron approximations and geometric mean of partial likelihoods methods will provide a
finite estimate of $\beta$. If there is no such inspection interval and the data are still monotone after interval censoring, then there will be no finite estimate of $\beta$ for any of these methods. The arithmetic mean of possible partial likelihoods is more sensitive to monotone data, but in the simulations in the worst case, we dropped only seventeen data sets for this method. The estimate of $\beta$ that maximizes the arithmetic mean of partial likelihoods for a set of possible orderings of the tied failure times will not exist if any one of the possible orderings produces a monotone case. For the other methods there were only one or two data sets which were dropped.

4 Small sample simulations

The small sample behavior of $\hat{\beta}_B$, $\hat{\beta}_E$, $\hat{\beta}_A$, and $\hat{\beta}_G$, are compared for total sample size ten. These results can be compared to the results of simulations with larger, more realistic sample sizes given in Section 5. We assess the behaviors of the estimators in terms of bias, the ratio of the average asymptotic variance values to the simulation variance, and coverage rates.

Exact failure times were generated with a standard exponential as a baseline hazard for situations where five units were allocated to each of two groups. The exact failure times were grouped into four inspection intervals of equal length to provide tied failure times. Any exact failure time which exceeded the upper endpoint of the fourth inspection interval was recorded as right censored. Three values of $\lambda$ were considered: 0, 0.5, and 1.0. Any data set that exhibited a monotone partial likelihood for any estimation method was deleted and replaced for the small sample simulations. If there were nine tied failure times in an inspection interval, then we used a random sample of 5000 possible orderings of those failure times, otherwise we considered all the possible orderings.

Results from the first phase of the small sample simulations are shown in Table 4. These results agree with the simulation results for larger sample sizes presented in Section 5. Estimates of $\beta$ tend to be biased toward zero for $L_B(\beta)$, $L_E(\beta)$, and $L_G(\beta)$. In spite of the larger bias, mean squared error of the Breslow approximation was smaller than the mean squared error of the arithmetic mean of possible partial likelihoods. The last column is the percentage of 95 % confidence intervals computed from the simulated data which contain the true value of $\beta$. All of the methods provided a reasonable approximation to the nominal level of coverage.
Table 4  Bias, variance ratio, and coverage rate for 95 % confidence intervals for simulations with total sample size=10

<table>
<thead>
<tr>
<th>True Value of $\beta$</th>
<th>Estimator</th>
<th>Bias</th>
<th>Variance</th>
<th>Coverage Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>$\hat{\beta}_{\text{Exact}}$</td>
<td>-0.0017</td>
<td>0.8974</td>
<td>0.982</td>
</tr>
<tr>
<td>0.0</td>
<td>$\hat{\beta}_B$</td>
<td>0.0014</td>
<td>1.3672</td>
<td>1.000</td>
</tr>
<tr>
<td>0.0</td>
<td>$\hat{\beta}_E$</td>
<td>0.0003</td>
<td>0.9900</td>
<td>0.990</td>
</tr>
<tr>
<td>0.0</td>
<td>$\hat{\beta}_G$</td>
<td>0.0003</td>
<td>0.9624</td>
<td>0.993</td>
</tr>
<tr>
<td>0.0</td>
<td>$\hat{\beta}_A$</td>
<td>-0.0029</td>
<td>0.8926</td>
<td>0.989</td>
</tr>
<tr>
<td>0.5</td>
<td>$\hat{\beta}_{\text{Exact}}$</td>
<td>-0.0261</td>
<td>1.1029</td>
<td>0.981</td>
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<td>0.5</td>
<td>$\hat{\beta}_B$</td>
<td>-0.1454</td>
<td>1.8017</td>
<td>0.991</td>
</tr>
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<td>0.5</td>
<td>$\hat{\beta}_E$</td>
<td>-0.0726</td>
<td>1.2420</td>
<td>0.981</td>
</tr>
<tr>
<td>0.5</td>
<td>$\hat{\beta}_G$</td>
<td>-0.0515</td>
<td>1.1975</td>
<td>0.982</td>
</tr>
<tr>
<td>0.5</td>
<td>$\hat{\beta}_A$</td>
<td>0.0367</td>
<td>0.3090</td>
<td>0.982</td>
</tr>
<tr>
<td>1.0</td>
<td>$\hat{\beta}_{\text{Exact}}$</td>
<td>-0.1404</td>
<td>1.1871</td>
<td>0.960</td>
</tr>
<tr>
<td>1.0</td>
<td>$\hat{\beta}_B$</td>
<td>-0.4676</td>
<td>2.6121</td>
<td>0.950</td>
</tr>
<tr>
<td>1.0</td>
<td>$\hat{\beta}_E$</td>
<td>-0.3162</td>
<td>1.7036</td>
<td>0.940</td>
</tr>
<tr>
<td>1.0</td>
<td>$\hat{\beta}_G$</td>
<td>-0.2694</td>
<td>1.6400</td>
<td>0.940</td>
</tr>
<tr>
<td>1.0</td>
<td>$\hat{\beta}_A$</td>
<td>-0.1244</td>
<td>1.7230</td>
<td>0.940</td>
</tr>
</tbody>
</table>

5  Simulation studies with larger sample sizes

The objective of these simulation studies is to assess the effects of ties in failure times on the estimation of $\beta$, the coefficient in the proportional hazards model for the two sample problem of treatment versus control in larger, more realistic sample sizes. The first phase is the comparison of estimates from the Efron and Breslow approximations to the partial likelihood. The second phase is a more extensive investigation of the properties of the Efron approximation partial likelihood. Finally, the third phase provides a comparison of the Efron approximation with results from the arithmetic and geometric means of all possible partial likelihoods.

5.1 Study design

The following five factors were considered in this study.

Covariate Structure. The covariate structure corresponds to a treatment group and a control group with equal allocation to each group. Kalish and Harrington (1988) investigated the efficiency of this equal allocation for comparing treatments with respect to survival for the proportional hazards model. They conclude that the balanced design is slightly less efficient for larger values of $\beta$ or higher
amounts of censoring when compared to optimal designs which allocate more subjects to the treatment group, but they still recommend use of the balanced design because of the impracticality of the optimal design.

**Sample Size.** Total sample sizes of \( n = 50 \) and 100 were chosen for the initial phases of this study. These values are similar to the choices used by Johnson, et al. (1982), Loughin (1995), and Burr (1994). The final phase investigated \( n = 50 \) only.

**True Value of \( \beta \).** True values of \( \beta = 0, 1, 2 \) were examined in the first phase. The second phase considered additional values of \( \beta = 1.25, 1.50, 1.75, 2.25, \) and 2.50. The third phase focused only on the five largest values of \( \beta \).

**Censoring.** The two levels of censoring were chosen for the first two phases of the study, with Type I censoring only corresponding to the low level and, and Type I and random censoring corresponding to the high level. Zero censoring was not considered since it would seldom be observed in a clinical trial with a fixed endpoint. For the final phase only the low level of censoring was considered.

The low level censoring was implemented by right censoring of any observed failure time which exceeded an appropriate upper value considered to be the end of the trial. The low level of censoring depends on the value of \( \beta \) and ranged from about 8% to 16%. The high level of censoring was chosen to be 40% in total when considering both the Type I and random censoring, which is larger than the percentage used by Loughin (1995) and smaller than the percentage used by Burr (1994), but similar to the censoring percentages in examples considered by Fleming and Harrington (1991), Kalbfleisch and Street (1990), Lee (1992) and Lawless (1982).

The random censoring mechanism was constructed to be similar to that of Burr (1994). Censoring times were generated independently of failure times. The censoring times were generated from a Uniform \((0, c)\) distribution and the \( i \)th failure time was censored if it exceeded the corresponding censoring time. Otherwise, the uncensored simulated survival time was recorded. Values of \( c \) which gave 40% censoring were determined individually for each value of \( \beta \).

**Interval censoring.** Initially three level of interval censoring were considered, which roughly correspond to "Monthly", "Quarterly", and "Yearly" inspections in a five year study. Define a "Month" to consist of 30 days, a "Quarter" to be 90 days and a "Year" to be 360 days. The final inspection time was set at 1800 "Days", the total inspection period could be partitioned into 60 "Months", 20 "Quarters", or 5 "Years" as possible sets of inspection intervals. Interval censored data were produced by counting the number of exact failure times in each inspection interval. Additional levels of interval censoring corresponding to 15, 10, 8, 6, or 4 inspection intervals of equal length were considered in the
Table 5  Bias, variance ratio, and coverage rate for 95 % confidence intervals for exact failure times averaged over level of censoring and sample size

<table>
<thead>
<tr>
<th>True Value of $\beta$</th>
<th>Bias</th>
<th>Variance Ratio</th>
<th>Coverage Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.00</td>
<td>-0.0003</td>
<td>0.9780</td>
<td>95.4</td>
</tr>
<tr>
<td>0.50</td>
<td>0.0218</td>
<td>0.9825</td>
<td>94.9</td>
</tr>
<tr>
<td>1.00</td>
<td>0.0121</td>
<td>0.9947</td>
<td>95.3</td>
</tr>
<tr>
<td>1.25</td>
<td>0.0099</td>
<td>0.9412</td>
<td>95.0</td>
</tr>
<tr>
<td>1.50</td>
<td>0.0310</td>
<td>0.9606</td>
<td>95.3</td>
</tr>
<tr>
<td>1.75</td>
<td>0.0306</td>
<td>0.9896</td>
<td>95.9</td>
</tr>
<tr>
<td>2.00</td>
<td>0.0423</td>
<td>0.9413</td>
<td>95.0</td>
</tr>
<tr>
<td>2.25</td>
<td>0.0581</td>
<td>0.9470</td>
<td>95.8</td>
</tr>
<tr>
<td>2.50</td>
<td>0.0662</td>
<td>0.9780</td>
<td>96.2</td>
</tr>
</tbody>
</table>

second phase of the study. Only 10.8.6.5 and 4 inspection intervals of equal length were considered in the third phase of the study.

5.2 Results of simulations with larger sample sizes

The results from these simulations fall into four categories: results concerning the exact failure times, results comparing the Efron and Breslow approximation methods, results consisting of a more in-depth study of the Efron approximation, and results comparing the Efron approximation to the arithmetic and geometric means of all possible partial likelihoods.

5.2.1 Exact failures

The simulated exact failure times contain no tied failure times. Thus, the only factors are the sample size, true value of $\beta$ and level of censoring. There were no occurrences of monotone likelihood for any of the simulated data sets in the first phase of the study. Since results for bias and coverage rates for 95 % confidence intervals were similar for both levels of censoring and both sample sizes, only averages across levels of censoring and sample sizes are shown in Table 5.

These results indicate that the bias of $\hat{\beta}$ increases as $\beta$ moves away from zero. Beyond $\beta = 2$, the distribution of $\hat{\beta}$ was not well approximated by the normal distribution. However, coverage rates of asymptotic 95 % confidence intervals approximately maintained the nominal level. This matches results reported by Costanza and Nichola (1982) and Johnson, et. al (1982).
Table 6 Comparison of the Efron and Breslow approximations averaged over levels of censoring and sample sizes

<table>
<thead>
<tr>
<th>True Value of ( \beta )</th>
<th>Number of Intervals</th>
<th>Bias Efron</th>
<th>Bias Breslow</th>
<th>Variance Ratio Efron</th>
<th>Variance Ratio Breslow</th>
<th>Coverage Rate Efron</th>
<th>Coverage Rate Breslow</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>60</td>
<td>-0.0003</td>
<td>-0.0002</td>
<td>0.9791</td>
<td>1.0043</td>
<td>95.4</td>
<td>95.7</td>
</tr>
<tr>
<td>0</td>
<td>20</td>
<td>-0.0001</td>
<td>-0.0002</td>
<td>0.9814</td>
<td>1.0589</td>
<td>95.4</td>
<td>96.2</td>
</tr>
<tr>
<td>0</td>
<td>5</td>
<td>-0.0006</td>
<td>-0.0005</td>
<td>0.9907</td>
<td>1.3312</td>
<td>95.5</td>
<td>97.9</td>
</tr>
<tr>
<td>1</td>
<td>60</td>
<td>0.0084</td>
<td>-0.0136</td>
<td>0.9958</td>
<td>1.0420</td>
<td>95.3</td>
<td>95.5</td>
</tr>
<tr>
<td>1</td>
<td>20</td>
<td>0.0004</td>
<td>-0.0628</td>
<td>0.9991</td>
<td>1.1355</td>
<td>95.2</td>
<td>95.4</td>
</tr>
<tr>
<td>1</td>
<td>5</td>
<td>-0.0511</td>
<td>-0.2566</td>
<td>1.0351</td>
<td>1.6282</td>
<td>95.3</td>
<td>89.7</td>
</tr>
<tr>
<td>2</td>
<td>60</td>
<td>0.0300</td>
<td>-0.0527</td>
<td>0.9448</td>
<td>1.0141</td>
<td>95.0</td>
<td>93.9</td>
</tr>
<tr>
<td>2</td>
<td>20</td>
<td>-0.0025</td>
<td>-0.2288</td>
<td>0.9604</td>
<td>1.1637</td>
<td>94.6</td>
<td>88.8</td>
</tr>
<tr>
<td>2</td>
<td>5</td>
<td>-0.2422</td>
<td>-0.8150</td>
<td>1.0128</td>
<td>1.7282</td>
<td>86.5</td>
<td>30.4</td>
</tr>
</tbody>
</table>

5.2.2 Comparison of the Efron and Breslow approximations

In phase one of the simulation study, the Efron and Breslow approximations were compared for three levels of the true value of \( \beta \) and three levels of interval censoring. The results indicate that the most important factors for determining bias and coverage rates are the true value of \( \beta \) and the level of interval censoring. The effects of sample size and level of random censoring are relatively small. Consequently, estimates of bias, ratios of average asymptotic variance to simulation variance, and coverage rates for 95% confidence intervals are averaged over the levels of random censoring and sample size. The results are reported in Table 6.

The effects of \( \beta \) and level of interval censoring were more pronounced for the Breslow approximation than the Efron approximation. In both cases as the true value of \( \beta \) or the amount of interval censoring increased, the estimate of \( \beta \) exhibited more bias toward zero. The Efron approximation provided ratios of average asymptotic variance to simulation variance that were closer to one. The amount of interval censoring had a larger effect on this ratio for the Breslow approximation. Although a difference in the average length of 95% confidence intervals was not found between the two methods, the Efron approximation was much better at maintaining the nominal confidence level for higher levels of interval censoring and larger values of \( \beta \).

An alternative covariate structure with four treatment groups of 25 patients each was also considered. True values of \( \beta \) were (1.0, 1.5, 2.0)'. Only the low censoring level was considered. The bias and coverage rates for 95% confidence intervals for each \( \beta_i \), show in Table 7, correspond to the previous results for
the single covariate case. Properties of estimators from the Breslow approximation deteriorate more quickly as the level of interval censoring increases.

5.2.3 Further analysis of the Efron approximation

Since the Efron approximation performed considerably better than the Breslow approximation, we decided to more closely examine the Efron approximation to determine the levels of interval censoring and values of $\beta$ where it begins to seriously break down. We added additional values of $\beta$ and levels of interval censoring and kept sample sizes of 50 and 100 and the same low and high levels of censoring.

Contour plots of the simulated bias and the coverage rates of 95% confidence intervals averaged over the two levels of censoring and two sample sizes are shown in Figures 2 and 3, respectively. The cases considered in the simulation study are shown in Table 8. Both plots exhibit the same general
pattern. The Efron approximation is reasonably reliable in this case when the relative lengths of the inspection interval is less than 0.1 or the true value of $\beta$ is less than 1.5, but it is accurate for larger values of $\beta$ if the percentage of ties created by the interval censoring is sufficiently small.

The simulated variances for $\hat{\beta}_E$ are quite close to the estimates obtained by evaluating the asymptotic variance formula at $\hat{\beta}_E$. Hence, the poor coverage rates for confidence intervals derived from asymptotic normal distributions seem to largely depend on the increasing bias of $\hat{\beta}_E$ as either $\beta$ becomes large or interval censoring generates more tied observations.

To relate the relative length of the inspection intervals to the level of tied failure times, we computed the expected overall percentage of tied failure times, the expected percentage of ties within each of the treatment and control groups, and the expected percentage of tied failure times involving one member of the treatment group and one member of the control group. These expectations were based on the underlying standard exponential hazard used to generate the failure times. Results are shown in Table 9. We explored the relationship between each of these four percentages of tied failure times and the simulated bias and coverage rates of 95% confidence intervals. The best predictor of both bias and coverage rate was the overall percentage of tied failure times. Figures 4 and 5 display these relationships along with reference lines indicating zero bias and the nominal 95% coverage rate, respectively. The Efron approximation is quite good when less than 20% of the uncensored failure times are involved in ties, and the accuracy begins to rapidly deteriorate for data sets containing more than 35% tied failure times. To compute an estimate of the expected overall percentage of tied failure times for a given data set, estimate the probability of failure in an inspection interval as the observed percentage of failures in that particular inspection interval.

5.2.4 Comparison with partial likelihood averaging methods

The Efron approximation gives a very close approximation to the geometric mean of all possible partial likelihoods for $n = 50$ and the low level of censoring. The contour plots shown in Figures 6 and 7 for bias and coverage rates are nearly indistinguishable from Figures 2 and 3. Figures 8 and 9 give contour plots for the bias of $\hat{\beta}_A$ and the coverage rates of the corresponding 95% confidence intervals. The arithmetic mean of all possible partial likelihoods is more sensitive to monotone data which happens more frequently when there are fewer inspection intervals or a larger $\beta$. However, if there are many failures in one inspection interval, a possible monotone ordering is not always selected in the random sampling process. When both the true value of $\beta$ and the amount of interval censoring increase, the bias of $\hat{\beta}_A$ does not necessarily increase in absolute value as was observed for $\hat{\beta}_B$, $\hat{\beta}_E$, and
Figure 2. Contour plot of average bias of $\hat{\beta}$.
Figure 3  Contour plot of average coverage rate for 95 % confidence intervals for $\hat{\beta}_E$.
Figure 4  Relation between bias and the overall expected percentage of tied failure times among uncensored observations for $\hat{\beta}_E$
Figure 5  Relation between coverage rates for 95% confidence intervals and the overall expected percentage of tied failure times among uncensored observations for $\hat{\beta}_G$. 
Although, $\hat{\beta}_A$ tends to slightly overestimate the size of treatment effects, it exhibits little bias in the regions where the Efron approximation breaks down. The behaviors of $\hat{\beta}_A$ more closely follows the trend of the maximum partial likelihood estimates computed from exact failure times. Additionally, $\hat{\beta}_A$ exhibits larger variances than either $\hat{\beta}_B$, $\hat{\beta}_E$, or $\hat{\beta}_G$, which leads to wider confidence intervals which maintain nominal coverage rates for all levels of interval censoring considered in this study.

6 Discussion

Overall the Efron approximation provides more accurate estimates of $\beta$ and more reliable confidence intervals than the Breslow approximation for all levels of $\beta$, interval censoring, sample sizes and random censoring considered in the simulation study. The Breslow approximation to the partial likelihood tends to produce estimates of $\beta$ that are biased toward zero. The Efron approximation also deteriorates, but at larger values of $\beta$ and higher levels of interval censoring. Since the estimates of $\beta$ are biased toward zero, inferences tend to be conservative. The true value of $\beta$ and and the amount of interval censoring also has much greater impact on coverage rates than sample size of level of random censoring. Further investigation of the Efron approximation leads to the recommendation that the confidence intervals are reliable when fewer than 20% of the cases that are observed to fail are involved in ties. The Efron approximation is shown to be similar to using the geometric mean of possible partial likelihoods. Using the arithmetic mean of possible partial likelihoods provides results closest to what would be obtained from exact failure times. Since the arithmetic mean of possible partial likelihoods is more sensitive to the monotone data case, it can also be used as an indicator that a proportional hazards model may not be appropriate. This situation can also be determined simply by examining the data and noting that there is only one interval which contains overlaps of the treatment and control groups. When the number of failures in an inspection interval becomes too large, an accurate approximation to the mean of all possible partial likelihoods is obtained from the mean of a sample of at least 5000 of the possible orderings.

7 Bibliography


Figure 6: Contour plot of bias of \( \hat{\theta} \)
Figure 7  Contour plot of coverage rate of 95% confidence intervals of $\hat{\beta}_G$
Figure 9  Contour plot of coverage rate of 95% confidence intervals of $\hat{\beta}_A$
Figure 10  Relation between bias and the overall expected percentage of tied failure times among uncensored observations for $\beta_A$
Figure 11  Relation between coverage rates for 95% confidence intervals and
the overall expected percentage of tied failure times among uncensored observations for $\hat{J}_A$


Table 8  Bias, variance ratio, and coverage rates for 95% confidence intervals for Efron approximation averaged over level of censoring and sample size

<table>
<thead>
<tr>
<th>True Value of $\beta$</th>
<th>Number of Intervals</th>
<th>Bias</th>
<th>Variance Ratio</th>
<th>Coverage Rate</th>
</tr>
</thead>
<tbody>
<tr>
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<td>1.00243</td>
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</tr>
<tr>
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<td>1.00717</td>
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<td>1.01921</td>
<td>95.0</td>
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Table 9  Percentage of ties among uncensored failure times (n = 50 and low level of censoring)

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Abstract

We discuss methods for analyzing interval censored event time data where members of a cohort may provide correlated failure times and different cohorts may be subjected to different inspection schedules. Initially we ignore any correlation among response times and use a multinomial model for the counts observed in an inspection interval. Use of nonhomogeneous inspection schedules requires estimation methods for incompletely classified multinomial data. Robust variance estimation is used to obtain consistent estimates of covariance matrices for parameter estimates. Parametric models for multinomial failure probabilities are also considered, and tests for comparing the fit of nested models are developed. An application to modeling the development rate of bean leaf beetle eggs is discussed.

KEY WORDS: Correlated event times, limited failure models, multinomial distribution, incomplete classification.

1 Introduction

Estimates of survivor functions are developed for situations with complex interval censored data. We consider situations where individuals are grouped into cohorts such that response times provided by individuals from a single cohort are correlated, individuals from different cohorts respond independently, and different cohorts may be subjected to different inspection schedules. We first consider a nonparametric approach based on a multinomial model for the number of failures or life events observed in the various inspection intervals. Then, a semi-parametric approach is considered where the probability that event occurs in any particular inspection interval is obtained from a parametric model for the survivor
function. This second approach is illustrated with an application of a limited-failure Weibull model. A robust variance estimator is used to adjust for effects of within cohort correlation on the distribution of parameter estimates. Comparison of survival probability estimates for the two approaches provides a test of fit of the semi-parametric model.

This methodology is illustrated with an analysis of data from a series of experiments dealing with the effect of incubation temperature on the time to hatch of bean leaf beetle eggs. Understanding the effects of temperature on both beetle and plant development is a vital step in the development of optimal pest management strategies. The beetles do the most damage when the second generation adult beetles emerge in time to eat newly developing soybean pods. In an experiment conducted by Zeiss, et al. (1996), a cohort consists of about twenty eggs placed into rearing cups which were incubated at one of seven temperatures. Hatch times for eggs within a cup are correlated due to both varying conditions within an incubator and genetic effects, and different inspection schedules were used for different rearing cups. The analysis also accounts for non-viable eggs which never hatch.

2 Nonparametric approach

The nonparametric approach for estimating the probabilities of failures within inspection intervals utilizes a working model assumption of independence which implies that all of the individuals in any cohort respond independently. In this case we simply have an application of multinomial counts, although the combination of information from individuals subjected to different inspection schedules requires estimation methods for multinomial data with incomplete classification in the manner of Hocking and Oxspring (1971). Finally, the covariance matrix for the estimated probabilities will be adjusted to reflect the dependence among individuals within cohorts using a robust sandwich estimator.

Suppose \( r \) experiments are run at a particular combinations of levels of the covariates. Let \( y_{ijk} \) be the number of failures observed in the \( j \)th cohort in the \( i \)th experiment for the interval \([t_{ij,k-1}, t_{ijk})\). There are \( m_i \) cohorts and \( K_{ij} \) inspection times for the \( j \)th cohort in the \( i \)th experiment. Let \( \theta_{ij} = \Pr(\text{an individual fails in the interval } [t_{ij,k-1}, t_{ijk})]) \). If there are \( n_{ij} \) individuals in the \( j \)th cohort of the \( i \)th experiment, then under the working model assumption of independence, \( Y_{ij}^t = [y_{ij1}, y_{ij2}, \ldots, y_{ijK_i}, y_{ij(K_i+1)}] \), the counts for the units in the \( j \)th cohort of the \( i \)th experiment, has a multinomial distribution with vector of probabilities \( \theta_{ij}^t = [\theta_{ij1}, \theta_{ij2}, \ldots, \theta_{ijK_i}, \theta_{ij(K_i+1)}] \). To combine the information from all cohorts in the \( r \) experiments, define the primary partition of time as the finest partition of the inspection interval for which failure probabilities can be estimated. Table 1 shows a case with three cohorts in the first experiment and one cohort in the second experiment where a “Day” represents the finest in-
spection partition. Since Day 4 is always included in the same inspection interval as Day 5, the finest partition for this example is \{ [0,1), [1,2), [2,3), [3,5), and [5,oo) \}, and \( \pi_4 \) represents the probability of failure on either Day 4 or Day 5. Let \( K^* \) be the index of the last primary inspection interval. Define \( \pi_k = \Pr(\text{an individual fails in the } k\text{th primary inspection interval}) \), where \( k = 1, \ldots, K^* \). Then, \( \pi_{K^*+1} = 1 - \sum_{k=1}^{K^*} \pi_k \) denotes the probability of survival beyond the longest inspection time used for any of the cohorts. Using

\[
\theta_{ijk} = \sum_{t=t_{ijk},k-1+1}^{t_{ijk}} \pi_l,  \tag{1}
\]

the contribution of cohort \( j \) in experiment \( i \) to the log-likelihood for the working multinomial model is given by

\[
\ell_{ij}(\theta_{ij}) = \sum_{k=1}^{K_{ij}+1} y_{ijk} \log \theta_{ijk} + C  \tag{2}
\]

and the working log-likelihood for \( \pi' = (\pi_1, \ldots, \pi_K) \) is given by

\[
\ell(\pi) = \sum_{i=1}^{r} \sum_{j=1}^{m_i} \sum_{k=1}^{K_{ij}+1} y_{ijk} \log \left( \sum_{l=t_{ijk},k-1+1}^{t_{ijk}} \pi_l \right) + C  \tag{3}
\]

where \( C = \sum_i \sum_j c_{ij} \) is the sum of natural logarithms of the normalizing constants for the working multinomial model. A consistent estimator for \( \pi \) is obtained by maximizing (3). Then survival probabilities

\[
q_k = \frac{\Pr(\text{Survive first } k \text{ intervals})}{\Pr(\text{Survive first } k - 1 \text{ intervals})}  \tag{4}
\]

can be estimated by

\[
\hat{q}_k = \frac{1 - \sum_{j=1}^{k} \hat{\pi}_j}{1 - \sum_{j=1}^{K^*} \hat{\pi}_j}.  \tag{5}
\]

The estimated probability of surviving beyond the end of the \( k \)th primary interval is

\[
\hat{S}(t_k) = \prod_{j=1}^{k} \hat{q}_j  \tag{6}
\]

which is analogous to the familiar Kaplan-Meier estimator of survival probabilities. The asymptotic variance of \( \hat{q}_k \) can be computed from the covariance matrix of \( \pi \) using the Delta Method.

The score function corresponding to (3) is denoted by

\[
S(p, \pi) = \left[ \frac{\partial \ell(\pi)}{\partial \pi_1} \ldots \frac{\partial \ell(\pi)}{\partial \pi_{K^*}} \right]',  \tag{7}
\]

where

\[
\frac{\partial \ell(\pi)}{\partial \pi_l} = \sum_{i=1}^{r} \sum_{j=1}^{m_i} \sum_{k=1}^{K_{ij}+1} \frac{y_{ijk}}{\theta_{ijk}(\pi)} \frac{\partial \theta_{ijk}(\pi)}{\partial \pi_l}.  \tag{8}
\]


Table 1  Example of inspection schedule of cohorts and notation for nonparametric approach

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<th>Day 1</th>
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<th>Day 4</th>
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</table>

and \( p_{ijk} = y_{ijk}/n_{ij} \) is an observed proportion. Note that \( \frac{\partial \theta_{ijk}}{\partial \pi_i} \) is simply an indicator function, and (7) can be expressed in matrix notation as

\[
S(p, \pi) = \sum_{i=1}^{r} \sum_{j=1}^{n_i} n_{ij} A_{ij}' \Delta_{\theta_i}^{-1} p_{ij} \tag{9}
\]

where \( p_{ij} = y_{ij}/n_{ij} \),

\[
A_{ij}' = \begin{bmatrix}
\frac{\partial \theta_{ij1}}{\partial \pi_1} & \ldots & \frac{\partial \theta_{ij(K_{ij}+1)}}{\partial \pi_1} \\
\vdots & \ddots & \vdots \\
\frac{\partial \theta_{ij1}}{\partial \pi_{K_{ij}}} & \ldots & \frac{\partial \theta_{ij(K_{ij}+1)}}{\partial \pi_{K_{ij}}}
\end{bmatrix}, \tag{10}
\]

and \( \Delta_{\theta_i} \) is a diagonal matrix with the vector \( \theta_{ij} \) on the diagonal. The corresponding Fisher Information matrix is

\[
I(\pi) = -E \left[ \frac{\partial^2 \ell(\pi)}{\partial \pi_i \partial \pi_{i'}} \right] = \sum_{i=1}^{r} \sum_{j=1}^{n_i} n_{ij} A_{ij}' \Delta_{\theta_i}^{-1} A_{ij}. \tag{11}
\]

A consistent estimator \( \hat{\pi}(p) \) for \( \pi \) is obtained by solving the estimating equations

\[
S(p, \hat{\pi}(p)) = 0. \tag{12}
\]

Then \( \hat{\pi}(p) \) is the maximum likelihood estimator for the multinomial working model. As \( r \to \infty \), the distribution of \( \hat{\pi}(p) \) is approximately normal with mean \( \pi_0 \). The asymptotic covariance matrix is estimated as

\[
\text{var}(\hat{\pi}(p)) = I(\hat{\pi}(p))^{-1} \left[ \sum_{i=1}^{r} \sum_{j=1}^{n_i} n_{ij} A_{ij}' \Delta_{\theta_i}^{-1} r_{ij} \Delta_{\theta_i}^{-1} A_{ij} \right] I(\hat{\pi}(p))^{-1} \tag{13}
\]
where \( r_{ij} = p_{ij} - \hat{\theta}_{ij} \), and each \( \hat{\theta}_{ij} \) in (13) is evaluated at \( \hat{\pi}(p) \). The covariance matrix for the limiting normal distribution is not proportional to the information matrix in (11) when there is either within cohort correlation among response times for individual units or within experiment correlation among cohorts. Derivations of asymptotic results are given in Section 4.

When a solution to (12) exists, it must be unique and maximize (3) because (3) is a strictly concave function of \( \pi \). When certain \( p_{ijk} \) are zero, a solution to (12) will not exist in the formal sense that (12) will be well-defined. In such cases, at least one element of \( \hat{\pi}(p) \) will be zero and (11) will not be positive definite. This situation will occur, for example, when the observed count is zero in a particular primary inspection interval for every cohort for which that primary inspection interval is used. If the four cohorts in Table 1 comprise the entire data set, then \( \hat{\pi}(p) \) would not exist if \( y_{112} = 0 \) even though \( y_{111} > 0 \) and \( y_{121} > 0 \). This result is easily seen by examination of (3) which reveals that \( y_{132} \log(\hat{\pi}_1(p)) \) is maximized by making \( \pi_1(p) = (y_{111} + y_{121} + y_{131} + y_{211})/(n_{11} + n_{12} + n_{13} + n_{21}) \) and forcing \( \pi_2(p) \) to zero. In such cases, an extended estimator is defined by allowing some elements of \( \hat{\pi}(p) \) to be zero.

### 3 Semi-parametric approach

In this approach, \( \pi \) is considered to be a parametric function of the parameters \( \eta \), and thus \( \pi = f(\eta) \) where \( f(\cdot) \) is assumed to be a locally smooth function of \( \eta \) with continuous first and second partial derivatives at the true value of \( \eta_0 \). Additionally, we will assume that the Fisher information of the working multinomial model evaluated at \( \eta_0 \) is positive definite.

One example of a parametric function is the identity function which gives the results from the previous section. Another possibility is

\[
\pi_k = \xi \left[ S(k-1) - S(k) \right] \quad \text{for} \quad k = 1, \ldots, K^* \quad \text{and} \\
\pi_{K^*+1} = \xi S(K^*) + 1 - \xi
\]

where \( S(\cdot) \) is a parametric survivor function. An example is the limited failure Weibull model (Meeker, 1987) in which

\[
S(t) = \exp \left( - \left( \frac{t - A}{\delta} \right) ^ \gamma \right),
\]

where \( t > A \), \( A \) is a known starting time, \( \delta > 0 \) is the scale parameter, \( \gamma > 0 \) is the shape parameter, and \( \xi \) is the proportion of the population which is subject to failure. In this case \( \eta = (\delta, \gamma, \xi) \). A third possible model is to define \( \eta \) to be a set of parameters which describe the relationship with a covariate. One possibility for this set-up would be to have a proportional hazards or accelerated failure model.
A different model would be defined by
\[ \pi_k = \frac{e^{\alpha_k}}{1 + \sum_{j=1}^{K^*} e^{\alpha_j}} \quad \text{for } k = 1, \ldots, K^* \]
\[ \pi_{K^*+1} = \frac{1}{1 + \sum_{j=1}^{K^*} e^{\alpha_j}} \]
and the relationship with the covariates is specified as
\[ \alpha_k = \beta_0 \mathbf{k} + \mathbf{Z}_k \beta_k. \] (15)

In the semi-parametric model, the log-likelihood for the working multinomial model is a function of \( \eta \). The elements of the score function are
\[ \frac{\partial \ell(\eta)}{\partial \eta_i} = \sum_{i=1}^{r} \sum_{j=1}^{m_i} n_{ij} \sum_{k=1}^{K^*+1} \frac{p_{ijk}}{\theta_{ijk}(f(\eta))} \frac{\partial \theta_{ijk}(\pi)}{\partial \eta_i} \frac{\partial f(\eta)}{\partial \eta_i}. \] (16)
and using the notation from (9), the score function can be written as
\[ S(p, \eta) = \sum_{i=1}^{r} \sum_{j=1}^{m_i} n_{ij} B A_i J^{-1}_i \Delta^{-1}_{i} p_{ij} \] (17)
where \( B = \left[ \frac{\partial f(\eta)}{\partial \eta_i} \right] \). Similarly, the Fisher information matrix is
\[ I(\eta) = -E \left[ \frac{\partial^2 \ell(\eta)}{\partial \eta_i \partial \eta_j} \right] = \sum_{i=1}^{r} \sum_{j=1}^{m_i} n_{ij} B A_i J^{-1}_i \Delta^{-1}_{i} A_{i} B'. \] (18)

In Section 4 we establish asymptotic properties of \( \hat{\eta}(p) \) and derive the consistent sandwich covariance estimator
\[ \widehat{\text{var}}(\hat{\eta}(p)) = I(\hat{\eta}(p))^{-1} \left[ \sum_{i=1}^{r} \sum_{j=1}^{m_i} n_{ij} n_{ij} B A_i J^{-1}_i \Delta^{-1}_{i} r_{ij} r_{ij}' \Delta^{-1}_{i} A_{i} B' \right] I(\hat{\eta}(p))^{-1} \] (19)
for the large sample covariance matrix of \( \hat{\eta}(p) \).

4 Proof of asymptotic properties

The following theorems will be used in the proof of asymptotic properties of \( \hat{\eta}(p) \).

**Implicit Function Theorem.** Cox (1984). Let \( S: \mathbb{R}^{r+p} \rightarrow \mathbb{R}^p \) be continuously differentiable in an open set \( U \) of \( \mathbb{R}^{r+p} \) containing the point \((p, \pi)\) for which \( S(p, \pi) = 0 \). Suppose that the \( p \times p \) matrix of partial derivatives, \( \frac{\partial S}{\partial \pi} \), is nonsingular at \((p, \pi)\). Then there exists a \( t \)-dimensional neighborhood \( U_0 \) of \( p \) in \( \mathbb{R}^t \) and a unique, continuously differentiable function \( g: U_0 \rightarrow \mathbb{R}^p \) such that \( g(p) = \pi \) and \( S((p, \pi)) = 0 \) for every \( p \in U_0 \).
Properties of Convergence in Probability and Distribution. Rao (1973). Let \( \{X_n, Y_n\} \) be a sequence of pairs of random variables. If \( X_n \overset{d}{\rightarrow} X \) and \( Y_n \overset{d}{\rightarrow} Y \) then \( X_n + Y_n \overset{d}{\rightarrow} X + Y \).

Multivariate Central Limit Theorem for Independent but not Identical Random Vectors. Rao (1973). Let \( \{x_j\}_{j=1}^{\infty} \) be a sequence of independent \( p \) dimensional random vectors such that \( \mathbb{E}x_j = 0 \) and \( \text{var}(x_j) = \Sigma_j \). Suppose that as \( m \to \infty \), \( \frac{1}{m} \sum_{j=1}^{m} \Sigma_j \to \Sigma \neq 0 \) and for any \( \forall \varepsilon > 0 \),

\[
\frac{1}{m} \sum_{j=1}^{m} \int_{||x|| > \varepsilon \sqrt{m}} ||x||^2 dF_j \to 0 \tag{20}
\]

where \( F_j \) is the distribution function of \( x_j \) and \( ||x|| \) is the Euclidean norm of the vector \( x \). Then \( (\sqrt{m})^{-1}(x_1 + x_2 + \ldots + x_m) \overset{d}{\rightarrow} \mathcal{N}_p(0, \Sigma) \) as \( m \to \infty \).

Markov Inequality. \( \Pr(|X| \geq a) \leq \frac{\mathbb{E}X}{a} \).

Expected Value of a Quadratic Form. Let \( E(y) = \mu \) and \( V = \text{var}(y) \) then \( E(y'Cy) = \text{trace}(C V) + \mu'C\mu \).

Properties of Convergence in Probability and Distribution for Vectors. Fuller (1996). Let \( \{Y_n\} \) be a sequence of \( p \) dimensional random variables, and let \( \{A_n\} \) be a sequence of \( k \times k \) non-singular random matrices. If there exists a random vector \( Y \) and a fixed non-singular matrix \( A \) such that \( Y_n \overset{d}{\rightarrow} Y, A_n \overset{d}{\rightarrow} A \), then \( A_n^{-1}Y_n \overset{d}{\rightarrow} A^{-1}Y \).

The asymptotic properties of \( \hat{\eta}(p) \) follow from the smoothness of (17) since it has continuous derivatives in the neighborhood of \( p \) and \( \eta(p) \). We also assume the Fisher information matrix is non-singular. Then by the Implicit Function Theorem, \( \hat{\eta}(p) \) has continuous derivatives in the neighborhood of \( \eta_0 \) and we can expand \( \hat{\eta}(p) \) in a first order Taylor series expansion. This expansion requires a change in notation. Previously \( p' = (p_{11}, \ldots, p_{mr}, r) \), where \( p_{ij} \) are the observed proportions of failures for the \( j \)th cohort in the \( i \)th replication. Now we are going to re-arrange the observed proportions by recalling that each cohort has a potentially different inspection schedule, but note that there are only a finite number, \( Q \), of possible inspection schedules and index them by \( q = 1, \ldots, Q \). In this notation, define \( \theta_q \) to be the set of unknown true proportions for the \( q \)th possible inspection schedule and \( p_q \) as the observed proportions of failure for all subjects monitored with inspection schedule \( q \). Then

\[
p_q = \frac{\sum n_{ij} p_{ij}}{\sum n_{ij}} \tag{21}
\]

where the sum is over all cohorts subjected to the \( q \)th inspection schedule. Let \( n_q = \sum n_{ij} \) and assume that \( n_q \to \infty \) as \( r \to \infty \) such that \( \frac{n_q}{r} \to c \), a positive constant, for all \( q \). Now let \( p' = (p_1, \ldots, p_Q) \) and \( \theta' = (\theta_1, \ldots, \theta_Q) \).
The general form of the Taylor series expansion for \( \eta(p) \) about \( \eta_0 \) is

\[
\eta(p) = \eta_0 + \frac{\partial \eta(p)}{\partial p} \bigg|_{p=\theta_0} (p - \theta_0) + o(||p - \theta_0||). \tag{22}
\]

To evaluate the Taylor series approximation for this application, note that \( S(p, \eta(p)) = 0 \) when it is evaluated at the maximum likelihood estimate \( \eta(p) \), and therefore \( \eta(p) \) is an implicit function of the data. Therefore we can use implicit differentiation to obtain

\[
0 = \frac{\partial}{\partial p} [S(p, \eta(p))] = \left[ \frac{\partial S(p, \eta(p))}{\partial p} \right] + \left[ \frac{\partial S(p, \eta(p))}{\partial \eta(p)} \right] \left[ \frac{\partial \eta(p)}{\partial p} \right]. \tag{23}
\]

The first term on the right hand side of (23) is

\[
\left[ \frac{\partial S(p, \eta(p))}{\partial p} \right] = \left[ n_1 BA_1' \Delta_{\theta_1}^{-1} \right] \cdots \left[ n_Q BA_Q' \Delta_{\theta_Q}^{-1} \right]. \tag{24}
\]

and the remaining factor is

\[
\left[ \frac{\partial S(p, \eta(p))}{\partial \eta(p)} \right] \bigg|_{p=\theta_0} = - \sum_{q=1}^Q n_q BA_q' \Delta_{\theta_q}^{-1} A_q B'. \tag{25}
\]

Next we evaluate the stochastic order of the remainder term by noting first that under the assumption that \( \frac{\partial \eta}{\partial \theta} \rightarrow \infty \) as \( r \rightarrow \infty \), \( p_q \) is a weighted average of vectors of proportions from independent experiments, each with expectation \( \theta_q \). Then, \( \sqrt{r}(p_q - \theta_{q0}) \) has a limiting normal distribution and \( ||p_q - \theta_{q0}|| = o_p(r^{-\frac{1}{2}}) \). Thus \( ||p - \theta_0|| = o_p(r^{-\frac{1}{2}}) \). Combining this result with the Taylor series expansion and solving for yields

\[
\sqrt{r}(\eta(p) - \eta_0) = \sqrt{r} \sum_{q=1}^Q n_q BA_q' \Delta_{\theta_q}^{-1}(p_q - \theta_{q0}) + o_p(1). \tag{27}
\]

Consequently we only have to establish the asymptotic distribution of

\[
\sqrt{r} \sum_{q=1}^Q n_q BA_q' \Delta_{\theta_q}^{-1}(p_q - \theta_{q0}) \tag{28}
\]

Define

\[
x_i = \sum_{j=1}^{m_i} n_{ij} BA_{ij}' \Delta_{\theta_{ij0}}^{-1}(p_{ij} - \theta_{ij0}). \tag{30}
\]

Then, \( E(x_i) = 0 \) since \( Ep_{ij} = \theta_{ij0} \), and the \( x_i \) are independent since replicates are assumed to be independent. Furthermore,

\[
\var(x_i) = \sum_{j=1}^{m_i} \sum_{j'=1}^{m_i} n_{ij} n_{ij'} BA_{ij}' \Delta_{\theta_{ij0}}^{-1} E[(p_{ij} - \theta_{ij0})(p_{ij'} - \theta_{ij0}')] \Delta_{\theta_{ij0}}^{-1} A_{ij'} B'. \tag{31}
\]
Assume that
\[ \Sigma_{III} = \lim_{r \to \infty} \frac{1}{r} \sum_{i=1}^{r} \text{var}(x_i) \] (32)
is positive definite. To verify condition (20), compute

\[ \|x_i\|^2 \leq \sum_{j=1}^{m_i} n_{ij}^2 \|B A'_{ij} \Delta^{-1}_{\theta_{ij0}} (p_{ij} - \theta_{ij0})\| \]
\[ = \sum_{j=1}^{m_i} n_{ij}^2 (p_{ij} - \theta_{ij0})^T C_{ij} (p_{ij} - \theta_{ij0}) \] (34)

where
\[ C_{ij} = \Delta^{-1}_{\theta_{ij0}} A_{ij} B A'_{ij} \Delta^{-1}_{\theta_{ij0}}. \] (35)

Then \( c_{ijkl} \), the \((k,l)\)th element of \( C_{ij} \), is bounded by \( p M_\theta^2 M_B^2 \) where \( p \) is the dimension of \( \eta \), since
\[ 0 < \pi_{k0} = f_k(\eta) < 1 \) and therefore \( \frac{1}{\pi_{ij}} \leq \frac{1}{\min(\pi_{ij})} \equiv M_\theta \) and \( M_B \) is the bound on the derivatives of \( f(\eta) \). Using this notation, we have

\[ d_{ij} = \sum_{k=1}^{K_{ij}+1} c_{ij} \left| \sum_{l=1}^{K_{ij}+1} c_{ijkl} (p_{ijl} - \theta_{ij0}) (p_{ijl} - \theta_{ij0}) \right| \]
\[ \leq \sum_{k=1}^{K_{ij}+1} \| c_{ij} \| \sum_{l=1}^{K_{ij}+1} \left| c_{ijkl} (p_{ijl} - \theta_{ij0}) (p_{ijl} - \theta_{ij0}) \right| \]
\[ \leq N^2 \sum_{k=1}^{K_{ij}+1} \sum_{l=1}^{K_{ij}+1} p M_\theta^2 M_B^2 \]
\[ \leq p N^2 M_\theta^2 M_B^2 (K^* + 1)^2 \]
since \( |p_{ijl} - \theta_{ij0}| < 1 \) and \( K_{ij} \leq K^* \). Consequently,

\[ \|x_i\|^2 \leq \left( \sum_{j=1}^{m_i} n_{ij}^2 \right) M_\theta^2 M_B^2 (K^* + 1)^2. \] (36)

Then assuming that \( \sum_{j=1}^{m_i} n_{ij}^2 \) is bounded above by \( N \), we have

\[ \int_{\|x_i\| > \varepsilon \sqrt{F}} \|x_i\|^2 dF_i \leq \int_{\|x_i\| > \varepsilon \sqrt{F}} p N^2 M_\theta^2 M_B^2 (K^* + 1)^2 dF_i \]
\[ = p N^2 M_\theta^2 M_B^2 (K^* + 1)^2 \Pr(\|x_i\| > \varepsilon \sqrt{F}). \]

Now, apply the Markov Inequality to obtain

\[ \Pr(\|x_i\| > \varepsilon \sqrt{F}) \leq \left( \frac{1}{\varepsilon \sqrt{F}} \right)^2 E\|x_i\|^2 \]
\[ \leq \left( \frac{1}{\varepsilon \sqrt{F}} \right)^2 \sum_{i=1}^{r} E\|x_i\|^2. \]
We evaluate this expression by computing

\[ E[||x||^2] = \text{trace}(C_{ij} \text{ var}(p_{ij} - \theta_{ij0})) \leq pn_{ij}^2M^4_\theta M^4_\beta (K^* + 1) \]

and, since var(p_{ijk} - \theta_{ijk0}) \leq 1, and we conclude that

\[ \int_{||x|| > \epsilon}\frac{||x||^2dF_i}{r^2} \leq \frac{p^2N^4M^4_\theta M^4_\beta (K^* + 1)^3}{r^2} \quad (37) \]

Finally,

\[ 0 \leq \lim_{r \to \infty} \frac{1}{r} \sum_{i=1}^{c} \int_{||x|| > \epsilon}\frac{||x||^2dF_i}{r^2} \leq \lim_{r \to \infty} \frac{1}{r} \sum_{i=1}^{c} \frac{p^2N^4M^4_\theta M^4_\beta (K^* + 1)^3}{r^2} = 0. \]

Thus we have established that

\[ \frac{1}{\sqrt{r}} \sum_{i=1}^{m_i} \sum_{j=1}^{m_j} n_{ij}^2BA'_{ij}\Delta^{-1}_{\theta_{ij0}}(p_{ij} - \theta_{ij0}) \xrightarrow{d} N(0, \Sigma_{III}) \quad (38) \]

where \( \Sigma_{III} \) is given by (32).

We note that

\[ Y_r = \frac{1}{r}T(\eta_0) = \frac{1}{r} \sum_{i=1}^{r} \sum_{j=1}^{m_i} n_{ij}BA'_{ij}\Delta^{-1}_{\theta_{ij0}}A_{ij}B' \quad (39) \]

has no stochastic components and converges to a finite matrix of constants.

\[ \Sigma_* = \lim_{r \to \infty} \frac{1}{r} \sum_{i=1}^{r} \sum_{j=1}^{m_i} BA'_{ij}\Delta^{-1}_{\theta_{ij0}}A_{ij}B' \quad (40) \]

which we assume to exist. Therefore we conclude by the properties of convergence in probability and distribution for vectors that

\[ \sqrt{r}(\eta(p) - \eta_0) \xrightarrow{d} N(0, \Sigma_*^{-1}\Sigma_{III}\Sigma_*^{-1}) \quad (41) \]

To estimate the sandwich covariance matrix, we substitute in \( T(\eta(p)) \) for \( \eta_0 \). Thus \( \Sigma_* = rT(\eta(p)) \) where \( B \) and \( \Delta^{-1}_{\theta_{ij}} \) are evaluated at \( \eta(p) \). We estimate \( \Sigma_{III} \) by

\[ \frac{1}{r} \sum_{i=1}^{r} \sum_{j=1}^{m_i} \sum_{j'=1}^{m_j} n_{ij}n_{ij'}BA'_{ij}\Delta^{-1}_{\theta_{ij}}r_{ij}r_{ij'}\Delta^{-1}_{\theta_{ij'}}A_{ij}B' \quad (42) \]
where \( r_j = p_{ij} - \hat{r}_{ij} \). If the independence working model is correct, \( r \Sigma_{II} \) reduces to the Fisher information matrix. It can be shown that \( \Sigma_z^{-1} \Sigma_{II} \Sigma_z^{-1} \) is a consistent estimator of the limiting covariance matrix by following the arguments outlined by Zeger, Liang and Self (1985) and Liang and Zeger (1986). Actually the requirement that \( \sum i \rightarrow c \) is not a necessary condition. If, for example, the primary inspection schedule were used infinitely often, but occasionally other schedules were used, the contribution of those other schedules would converge to zero in probability. We only need to guarantee that inspection schedules needed to estimate all elements in \( \pi \) are used infinitely often.

We can apply similar arguments if \( r = 1 \) and there are \( m \) cohorts and \( m \rightarrow \infty \). Similar arguments also apply when cohorts within the same replication are independent and \( \sum r_i m_i \rightarrow \infty \). In these cases \( \eta(p) \) has a limiting normal distribution with mean \( \eta_0 \) and limiting covariance matrix \( \Sigma_z^{-1} \Sigma_{II} \Sigma_z^{-1} \) where we consistently estimate \( \Sigma_{II} \) by

\[
\frac{1}{\sum r_i m_i} \sum_{i=1}^r \sum_{j=1}^{m_i} n_{ij}^2 B A_i^j \Delta_z^{-1} r_i j r_i j A_i j B^t
\]

where \( r_{ij} = p_{ij} - \hat{r}_{ij} \).

5 Comparison of nested models

Suppose we have maximum likelihood estimators for \( \pi \) for a set of nested models, namely \( \pi_1(p) = f(\eta_1(p)) \) from the larger model I and from a model II obtained by placing some restrictions on the parameters in model I. A large sample Wald (1943) chi-square test of the null hypothesis that the restricted model II is appropriate against model I alternative is obtained from the quadratic form

\[ d'V_d^{-1}d \]

where \( d = \pi_1(p) - \pi_2(p) \) and \( V_d^{-1} \) is the generalized inverse of a consistent estimator of \( V_d = \text{var}(\pi_1(p) - \pi_2(p)) \).

We first derive the limiting normal distribution of \( d \). From (27) we have

\[ \pi_1(p) - \pi_2(p) \approx D \sum_{q=1}^Q n_q A_q^t \Delta_{\theta_{q0}}^{-1} (p_q - \theta_{q0}) + o_p(r^{-\frac{1}{2}}) \]

where

\[ D = B_1 I_1(\eta_0)^{-1} B_1' - B_2 I_2(\eta_0)^{-1} B_2. \]

which has a limiting normal distribution under the conditions specified in Section 4. The variance, switching back to the original notation, is

\[ \text{var}(\pi_1(p) - \pi_2(p)) \equiv V_d = D \left[ \sum_{i=1}^r \sum_{j=1}^{m_i} \sum_{j'=1}^{m_i} n_{ij'} n_{ij} A_i^j \Delta_{\theta_{ij0}}^{-1} \Sigma_{ijj'} \Delta_{\theta_{ij'0}}^{-1} A_i j' \right] D' \]
where all matrices are evaluated at $\eta_0$. As shown by Moore (1977), the Wald test

$$[\hat{\pi}_1(p) - \hat{\pi}_2(p)]' V_d^{-1} [\hat{\pi}_1(p) - \hat{\pi}_2(p)]$$

(47)

has a chi-squared distribution with degrees of freedom equal to the rank of $\lim_{r \to \infty} V_d$ when model II is correct.

A consistent estimator for $V_d$ is given by

$$V_d = \hat{D} \left[ \sum_{i=1}^r \sum_{j=1}^{m_i} \sum_{j'=1}^{m_i} n_{ij} n_{ij'} A_{ij}^* \Delta^{-1}_{\hat{\theta}_{ij}} (p_{ij} - \hat{\theta}_{ij})(p_{ij'} - \hat{\theta}_{ij'})' \Delta^{-1}_{\hat{\theta}_{ij'}} A_{ij'} \right] \hat{D}'.
$$

(48)

where $\hat{\theta}_{ij}$ and $\hat{D}$ are evaluated at $\hat{\pi}_2(p)$. If cohorts are assumed to be independent, then $\Sigma_{ijj'}$ is a zero matrix for $j \neq j'$ and the estimator reduces to

$$V_d = \hat{D} \left[ \sum_{i=1}^r \sum_{j=1}^{m_i} n_{ij}^2 A_{ij}^* \Delta^{-1}_{\hat{\theta}_{ij}} (p_{ij} - \hat{\theta}_{ij})(p_{ij} - \hat{\theta}_{ij})' \Delta^{-1}_{\hat{\theta}_{ij}} A_{ij} \right] \hat{D}'.
$$

(49)

which is consistent as $\sum_{i=1}^r m_i \to \infty$.

6 Application to the bean leaf beetle experiments

We will now apply our methods to a series of experiments conducted by Zeiss, et al. (1996) to examine the effect of temperature on the development rate of bean leaf beetle eggs. We first present an analysis based on the assumption that a limited failure Weibull model is correct at each temperature, and then discuss the validity of this assumption.

6.1 Description of experiments

Eggs were collected daily from cages containing adult bean leaf beetles, and placed into rearing cups. Typically all of the eggs in a single rearing cup were collected from the same cage on a single day. Consequently, some of the eggs in a single rearing cup were laid by the same female, but they could not be identified as each cage contained more than one female. The eggs in a rearing cup are treated as a cohort. There were approximately twenty eggs per cup. Rearing cups were placed in incubators maintained at prescribed temperatures, and the hatch times was monitored for each egg. Correlations among hatch times for eggs in a single cohort arise from genetic similarities among eggs laid by a single female, and temperature variation among locations within individual incubators.

Experiments were run with incubators set at 18° C, 20° C, 22° C, 25° C, 28° C, 30° C, 32° C, and each temperature was replicated three times in three different incubators. Table 2 shows the number
Table 2  Summary of the data for the bean leaf beetle experiments

<table>
<thead>
<tr>
<th>Temperature</th>
<th>Replication</th>
<th>Number of Cohorts</th>
<th>Number of Eggs</th>
<th>Number of Inspection Intervals</th>
<th>First Day with Hatching Observed</th>
<th>Percentage Observed to Hatch</th>
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<td>31</td>
<td>619</td>
<td>17</td>
<td>9</td>
<td>74.31</td>
</tr>
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<td>37</td>
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<td>17</td>
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<td>69.51</td>
</tr>
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<td>12</td>
<td>5</td>
<td>71.58</td>
</tr>
<tr>
<td>28°C</td>
<td>1</td>
<td>19</td>
<td>348</td>
<td>13</td>
<td>2</td>
<td>63.22</td>
</tr>
<tr>
<td>28°C</td>
<td>2</td>
<td>17</td>
<td>341</td>
<td>13</td>
<td>2</td>
<td>78.01</td>
</tr>
<tr>
<td>28°C</td>
<td>3</td>
<td>27</td>
<td>447</td>
<td>13</td>
<td>2</td>
<td>70.25</td>
</tr>
<tr>
<td>30°C</td>
<td>1</td>
<td>127</td>
<td>2499</td>
<td>10</td>
<td>2</td>
<td>77.51</td>
</tr>
<tr>
<td>30°C</td>
<td>2</td>
<td>22</td>
<td>444</td>
<td>10</td>
<td>2</td>
<td>70.72</td>
</tr>
<tr>
<td>30°C</td>
<td>3</td>
<td>22</td>
<td>444</td>
<td>10</td>
<td>2</td>
<td>70.50</td>
</tr>
<tr>
<td>32°C</td>
<td>1</td>
<td>27</td>
<td>633</td>
<td>12</td>
<td>2</td>
<td>55.92</td>
</tr>
<tr>
<td>32°C</td>
<td>2</td>
<td>34</td>
<td>612</td>
<td>12</td>
<td>2</td>
<td>58.50</td>
</tr>
<tr>
<td>32°C</td>
<td>3</td>
<td>14</td>
<td>236</td>
<td>12</td>
<td>2</td>
<td>92.80</td>
</tr>
</tbody>
</table>

of cohorts (rearing cups) and the total number of eggs placed in each incubator. In all cases, the eggs were exposed to fourteen hours of light and ten hours of darkness. Table 2 also shows the number of inspection days for the incubator, the day when eggs first begin to hatch, which is taken to be the first day of inspection, and the percentage of eggs which were observed to hatch. In the first few days after the eggs were laid, it is not biologically possible for eggs to hatch, and those days have been left out of the analysis since there is no probability of hatching on those days. Table 2 deviates from Zeiss, et al. (1996) only in that they used day 3 as the first inspection day at 30° and we use day 2, to match the first inspection day at 28° and 32° C.

The hatch time data include several additional complications. Rearing cups in the same incubators were not all inspected on the same schedule. Table 3 shows the data for some of the cohorts in one of the incubators set at 25°C. The first column is the number of eggs in the cohort. A period indicates that
that cohort was not inspected on that day. For almost all of the cohorts, there were eggs which were not observed to hatch, and most of these eggs, according to the researchers, would never hatch. Thus we have a situation where not all of the population is subject to the life event. There can be considerable variation of conditions within incubators set at the same temperature. Furthermore, replications at individual temperatures were conducted in different incubators and with different generations of beetles, although these are considered to be samples from a single population.

We use a robust covariance estimator to account for correlation among hatch times arising from both within and between incubator variation.
6.2 Fitting limited failure Weibull models

We first consider a model where the marginal distribution of hatch times, averaging across incubators and cohorts, has a limited failure Weibull distribution at each temperature. Our approach differs from Koehler (1994) in that we use a sandwich covariance estimator as our robust variance estimator instead of a bootstrap variance estimator.

This semi-parametric approach utilizes the model specified by (14) where $A$ is the first day where the entomologists observed an egg to hatch as shown in Table 3. They chose the last day of inspection such that almost all of the viable eggs would have hatched by that time. The entomologists were interested in the median time to hatch for the viable eggs which is

$$M = A + \delta[\ln(2)]^{1/\gamma}. \quad (50)$$

The inverse of the median hatch time is often used by entomologists as a measure of the daily rate of development.

In all of the results we present three standard errors. Standard error I is based on a multinomial working model and is included for comparison. Standard error II is based on a sandwich covariance estimator that accounts for correlations within the cohorts, but ignores variation among replicates. Standard error III is based on a sandwich covariance estimator which not only accounts for correlated hatch times within the cohorts, but also accounts for correlated hatch times within replications.

We estimated $\eta = (\delta, \gamma, \xi)$ in the semi-parametric model for each temperature and the three standard errors for each temperature as shown in Table 4. In this case, standard error II is almost three times as large as the standard error from the multinomial working model, and standard error III is about double that of standard error II. The latter reflects considerable variation among replicates, but it is based on only three replicates at each temperature. The value of $A$, the first day an egg to is observed to hatch, has an effect on the estimates of $\delta$ and $\gamma$. For example, if we used $A = 3$ at 30°C, as in Zeiss, et al. (1996), then $\delta = 3.654$ and $\gamma = 4.599$, but $\xi = 0.7614$ and the estimated median hatch time of 6.374 days are essentially the same as the estimates for $\xi$ and the median using $A = 2$. Note that the estimate of the proportion of viable eggs in the population tends to be only slightly larger than the proportion of eggs that actually were observed to hatch, indicating that the hatch times of most viable eggs were actually observed. Tables 5 to 11 show estimates of $\pi_k$, the probability of hatching on the $k$th day, counting from when the eggs were laid, along with the three standard errors. Observe that generally standard error II is about three times larger than the multinomial working model standard error, and standard error III tends to be a little more than twice as big as standard error II. This pattern was less
evident at 28°C or 30°C.

6.3 Effect of temperature on daily development rates

We also fit different limited failure Weibull models for each replicate at each temperature. Then, the sandwich covariance estimators used to account for within cohort correlations yield standard errors that are very similar to the bootstrap standard errors presented by Koehler (1994).

The relationships of the median time to hatch and the daily development rate with temperature were further explored by plotting estimates against temperature in Figures 1 to 5. In each figure, the upper panel shows estimates obtained from combining data for the three replicates and the lower panel shows estimates for individual replicates. Notice the greater variation in estimated medians and development rates at lower temperatures in the lower panels. Linear and quadratic polynomials were fit to these estimates in Figures 1 and 2 using weighted least squares with weights proportional to the standard errors of the estimated medians or daily development rates. Figure 1 shows an approximately linear relationship between daily development rate and temperature.

Figure 2 displays the relationship between the median hatch times and temperature. For the combined data we only present the weighted least squares results based on standard error III. The results using standard error II as weights were virtually indistinguishable. The first model is a quadratic polynomial with temperature while the second model is the linear model for daily development rate translated back to the scale of medians. In both cases, we see that median hatch time does not have a straight line relationship with temperature.

Figures 1 to 5 can be used as a guide to develop a semi-parametric model incorporating temperature as a covariate, where one or more of the limited failure Weibull parameters depend on temperature. Figure 5, reveals no effect of temperature on the proportion of viable eggs. This result was anticipated by the entomologists.

In accelerated failure time models, as described by Lawless (1982), the shape parameter $\gamma$ is not allowed to be affected by the values of the covariate, while the logarithm of the scale parameter $\delta$ is taken to be a linear function of the covariates. This specification also provides a proportional hazards model. This model is not supported by Panel A in Figure 4 which reveals an increasing trend in the estimates of $\gamma$ with temperature. When considering each replication separately the resulting estimates of $\gamma$ give more support for a proportional hazards model since a trend in the $\gamma$ estimates is not as apparent.
6.4 Assessing the fit of the limited failure Weibull model

Before trying to model the effects of temperature on $\delta$ and $\gamma$, we tried to assess the fit of the limited failure Weibull model at each temperature. In order to carry out the testing, we fit the nonparametric multinomial model to the combined data for the three replications at each temperature. In the nonparametric model, the proportion of non-viable eggs, which will never hatch, can not be separated from the proportion of viable eggs which were not observed to hatch.

The estimates of the daily hatch probabilities are summarized for each temperature in Tables 13 to 19. Estimates of $\pi_k$ which appear to be zero tend to occur only in either the first few days or the last few days of inspection. At lower temperatures, hatching events are spread out over more days than at the higher temperatures. Unlike estimates from the limited failure Weibull model, then nonparametric estimates of $\pi$ do not always increase as time increases at $k$ increases until the median hatch time is reached and then decrease until the final interval. At $32^\circ$ C the nonparametric method yields $\hat{\pi}_{14} = 0.0132$, while the estimated probability of hatching on the last few days of inspection is basically zero for most other temperatures. Investigation of the data reveals that only one cohort at $32^\circ$ C was inspected on day 14 and only one egg was observed to hatch. When that cohort is removed from the data, its influence is immediately seen, as $\hat{\pi}_{14}$ drops back to essentially zero. The presence of this cohort has much less of an effect when the semi-parametric method is used. Another disadvantage of the nonparametric method is that it is not straightforward to obtain a more precise estimate of the median hatch time other than the interval containing the median.

Comparison of the three standard errors for the nonparametric method reveals that standard error II is larger than the independence working standard error by a factor of roughly two, and standard error III is larger than standard error II by a factor of about 1.5, but results for higher temperatures do not follow this pattern as closely. Situations where the standard errors for $\pi_k$ do not follow this pattern, there tend to involve small estimates of $\pi_k$ with small variances.
Table 4  Estimates from a limited failure Weibull model for each temperature

<table>
<thead>
<tr>
<th>Temperature</th>
<th>Parameter</th>
<th>Point Estimate</th>
<th>Standard Error I</th>
<th>Standard Error II</th>
<th>Standard Error III</th>
</tr>
</thead>
<tbody>
<tr>
<td>18°</td>
<td>δ</td>
<td>9.824</td>
<td>0.1001</td>
<td>0.3650</td>
<td>1.3409</td>
</tr>
<tr>
<td>18°</td>
<td>γ</td>
<td>3.468</td>
<td>0.0932</td>
<td>0.2654</td>
<td>0.1934</td>
</tr>
<tr>
<td>18°</td>
<td>ξ</td>
<td>0.7513</td>
<td>0.0126</td>
<td>0.0300</td>
<td>0.0370</td>
</tr>
<tr>
<td></td>
<td>Median</td>
<td>17.839</td>
<td>0.0942</td>
<td>0.3229</td>
<td>1.2457</td>
</tr>
<tr>
<td>20°</td>
<td>δ</td>
<td>9.705</td>
<td>0.0552</td>
<td>0.1855</td>
<td>0.7144</td>
</tr>
<tr>
<td>20°</td>
<td>γ</td>
<td>4.139</td>
<td>0.0775</td>
<td>0.2539</td>
<td>0.5616</td>
</tr>
<tr>
<td>20°</td>
<td>ξ</td>
<td>0.6697</td>
<td>0.0082</td>
<td>0.0215</td>
<td>0.0283</td>
</tr>
<tr>
<td></td>
<td>Median</td>
<td>15.883</td>
<td>0.0542</td>
<td>0.1837</td>
<td>0.6000</td>
</tr>
<tr>
<td>22°</td>
<td>δ</td>
<td>7.748</td>
<td>0.0660</td>
<td>0.2318</td>
<td>0.8765</td>
</tr>
<tr>
<td>22°</td>
<td>γ</td>
<td>4.296</td>
<td>0.1190</td>
<td>0.3338</td>
<td>0.6626</td>
</tr>
<tr>
<td>22°</td>
<td>ξ</td>
<td>0.7183</td>
<td>0.0135</td>
<td>0.0397</td>
<td>0.0921</td>
</tr>
<tr>
<td></td>
<td>Median</td>
<td>12.114</td>
<td>0.0635</td>
<td>0.2255</td>
<td>0.8968</td>
</tr>
<tr>
<td>25°</td>
<td>δ</td>
<td>4.757</td>
<td>0.0232</td>
<td>0.0766</td>
<td>0.2653</td>
</tr>
<tr>
<td>25°</td>
<td>γ</td>
<td>4.383</td>
<td>0.0733</td>
<td>0.2625</td>
<td>0.7737</td>
</tr>
<tr>
<td>25°</td>
<td>ξ</td>
<td>0.7796</td>
<td>0.0069</td>
<td>0.0174</td>
<td>0.0296</td>
</tr>
<tr>
<td></td>
<td>Median</td>
<td>9.376</td>
<td>0.0232</td>
<td>0.0762</td>
<td>0.3084</td>
</tr>
<tr>
<td>28°</td>
<td>δ</td>
<td>5.164</td>
<td>0.0389</td>
<td>0.0811</td>
<td>0.1311</td>
</tr>
<tr>
<td>28°</td>
<td>γ</td>
<td>5.461</td>
<td>0.1738</td>
<td>0.5813</td>
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</tr>
<tr>
<td>28°</td>
<td>ξ</td>
<td>0.7271</td>
<td>0.0142</td>
<td>0.0331</td>
<td>0.0382</td>
</tr>
<tr>
<td></td>
<td>Median</td>
<td>6.829</td>
<td>0.0393</td>
<td>0.0783</td>
<td>0.0978</td>
</tr>
<tr>
<td>30°</td>
<td>δ</td>
<td>4.675</td>
<td>0.0158</td>
<td>0.0308</td>
<td>0.0200</td>
</tr>
<tr>
<td>30°</td>
<td>γ</td>
<td>5.823</td>
<td>0.0925</td>
<td>0.2459</td>
<td>0.2078</td>
</tr>
<tr>
<td>30°</td>
<td>ξ</td>
<td>0.7614</td>
<td>0.0059</td>
<td>0.0096</td>
<td>0.0121</td>
</tr>
<tr>
<td></td>
<td>Median</td>
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<td>0.0163</td>
<td>0.0277</td>
<td>0.0148</td>
</tr>
<tr>
<td>32°</td>
<td>δ</td>
<td>4.536</td>
<td>0.0307</td>
<td>0.0632</td>
<td>0.1503</td>
</tr>
<tr>
<td>32°</td>
<td>γ</td>
<td>5.559</td>
<td>0.1626</td>
<td>0.4790</td>
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</tr>
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<td>32°</td>
<td>ξ</td>
<td>0.6277</td>
<td>0.0128</td>
<td>0.0318</td>
<td>0.0615</td>
</tr>
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<td>Median</td>
<td>6.247</td>
<td>0.0315</td>
<td>0.0586</td>
<td>0.1311</td>
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</table>
Table 5  Estimates of daily hatch probabilities at 18°C from a limited failure
Weibull model

<table>
<thead>
<tr>
<th>Interval</th>
<th>Estimate</th>
<th>Std Error I</th>
<th>Std Error II</th>
<th>Std Error III</th>
</tr>
</thead>
<tbody>
<tr>
<td>( \pi_{10} )</td>
<td>0.0003</td>
<td>0.0001</td>
<td>0.0002</td>
<td>0.0002</td>
</tr>
<tr>
<td>( \pi_{11} )</td>
<td>0.0027</td>
<td>0.0004</td>
<td>0.0011</td>
<td>0.0018</td>
</tr>
<tr>
<td>( \pi_{12} )</td>
<td>0.0092</td>
<td>0.0010</td>
<td>0.0026</td>
<td>0.0054</td>
</tr>
<tr>
<td>( \pi_{13} )</td>
<td>0.0204</td>
<td>0.0016</td>
<td>0.0042</td>
<td>0.0107</td>
</tr>
<tr>
<td>( \pi_{14} )</td>
<td>0.0363</td>
<td>0.0020</td>
<td>0.0055</td>
<td>0.0168</td>
</tr>
<tr>
<td>( \pi_{15} )</td>
<td>0.0555</td>
<td>0.0021</td>
<td>0.0065</td>
<td>0.0221</td>
</tr>
<tr>
<td>( \pi_{16} )</td>
<td>0.0752</td>
<td>0.0022</td>
<td>0.0074</td>
<td>0.0243</td>
</tr>
<tr>
<td>( \pi_{17} )</td>
<td>0.0917</td>
<td>0.0024</td>
<td>0.0085</td>
<td>0.0213</td>
</tr>
<tr>
<td>( \pi_{18} )</td>
<td>0.1008</td>
<td>0.0028</td>
<td>0.0090</td>
<td>0.0128</td>
</tr>
<tr>
<td>( \pi_{19} )</td>
<td>0.0998</td>
<td>0.0030</td>
<td>0.0084</td>
<td>0.0072</td>
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<tr>
<td>( \pi_{20} )</td>
<td>0.0884</td>
<td>0.0028</td>
<td>0.0073</td>
<td>0.0186</td>
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<tr>
<td>( \pi_{21} )</td>
<td>0.0695</td>
<td>0.0025</td>
<td>0.0075</td>
<td>0.0283</td>
</tr>
<tr>
<td>( \pi_{22} )</td>
<td>0.0480</td>
<td>0.0025</td>
<td>0.0085</td>
<td>0.0310</td>
</tr>
<tr>
<td>( \pi_{23} )</td>
<td>0.0288</td>
<td>0.0023</td>
<td>0.0085</td>
<td>0.0268</td>
</tr>
<tr>
<td>( \pi_{24} )</td>
<td>0.0149</td>
<td>0.0019</td>
<td>0.0068</td>
<td>0.0187</td>
</tr>
<tr>
<td>( \pi_{25} )</td>
<td>0.0065</td>
<td>0.0012</td>
<td>0.0044</td>
<td>0.0106</td>
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<tr>
<td>( \pi_{26} )</td>
<td>0.0024</td>
<td>0.0006</td>
<td>0.0023</td>
<td>0.0049</td>
</tr>
<tr>
<td>( \pi_{27} )</td>
<td>0.2497</td>
<td>0.0126</td>
<td>0.0298</td>
<td>0.0353</td>
</tr>
</tbody>
</table>
Table 6  Estimates of daily hatch probabilities at 20°C from a limited failure Weibull model

<table>
<thead>
<tr>
<th>Interval</th>
<th>Estimate</th>
<th>Std Error I</th>
<th>Std Error II</th>
<th>Std Error III</th>
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</thead>
<tbody>
<tr>
<td>π₂</td>
<td>0.0001</td>
<td>0.0000</td>
<td>0.0000</td>
<td>0.0001</td>
</tr>
<tr>
<td>π₉</td>
<td>0.0009</td>
<td>0.0001</td>
<td>0.0004</td>
<td>0.0007</td>
</tr>
<tr>
<td>π₁₀</td>
<td>0.0042</td>
<td>0.0004</td>
<td>0.0013</td>
<td>0.0021</td>
</tr>
<tr>
<td>π₁₁</td>
<td>0.0117</td>
<td>0.0008</td>
<td>0.0025</td>
<td>0.0041</td>
</tr>
<tr>
<td>π₁₂</td>
<td>0.0248</td>
<td>0.0012</td>
<td>0.0039</td>
<td>0.0070</td>
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<tr>
<td>π₁₃</td>
<td>0.0439</td>
<td>0.0014</td>
<td>0.0047</td>
<td>0.0113</td>
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<tr>
<td>π₁₄</td>
<td>0.0671</td>
<td>0.0015</td>
<td>0.0049</td>
<td>0.0176</td>
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<tr>
<td>π₁₅</td>
<td>0.0898</td>
<td>0.0016</td>
<td>0.0050</td>
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<tr>
<td>π₁₆</td>
<td>0.1051</td>
<td>0.0020</td>
<td>0.0060</td>
<td>0.0257</td>
</tr>
<tr>
<td>π₁₇</td>
<td>0.1062</td>
<td>0.0022</td>
<td>0.0069</td>
<td>0.0195</td>
</tr>
<tr>
<td>π₁₈</td>
<td>0.0910</td>
<td>0.0021</td>
<td>0.0066</td>
<td>0.0095</td>
</tr>
<tr>
<td>π₁₉</td>
<td>0.0646</td>
<td>0.0019</td>
<td>0.0060</td>
<td>0.0158</td>
</tr>
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<td>π₂₀</td>
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<td>0.0018</td>
<td>0.0057</td>
<td>0.0215</td>
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<td>π₂₁</td>
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<td>0.0014</td>
<td>0.0044</td>
<td>0.0178</td>
</tr>
<tr>
<td>π₂₂</td>
<td>0.0055</td>
<td>0.0008</td>
<td>0.0025</td>
<td>0.0097</td>
</tr>
<tr>
<td>π₂₃</td>
<td>0.0013</td>
<td>0.0003</td>
<td>0.0009</td>
<td>0.0035</td>
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<td>0.0002</td>
<td>0.0008</td>
</tr>
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<td>0.0000</td>
<td>0.0000</td>
<td>0.0001</td>
</tr>
<tr>
<td>π₂₆</td>
<td>0.3303</td>
<td>0.0082</td>
<td>0.0215</td>
<td>0.0283</td>
</tr>
</tbody>
</table>
Table 7  Estimates of daily hatch probabilities at 22°C from a limited failure
Weibull model

<table>
<thead>
<tr>
<th>Interval</th>
<th>Estimate</th>
<th>Std Error I</th>
<th>Std Error II</th>
<th>Std Error III</th>
</tr>
</thead>
<tbody>
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<td>T6</td>
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<td>0.0000</td>
<td>0.0001</td>
<td>0.0002</td>
</tr>
<tr>
<td>T7</td>
<td>0.0020</td>
<td>0.0003</td>
<td>0.0010</td>
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<td>0.0033</td>
<td>0.0114</td>
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<td>0.0287</td>
<td>0.0021</td>
<td>0.0066</td>
<td>0.0262</td>
</tr>
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<td>T10</td>
<td>0.0607</td>
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<td>0.0095</td>
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<td>0.0044</td>
<td>0.0137</td>
<td>0.0307</td>
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<td>0.0132</td>
<td>0.0369</td>
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<td>0.0011</td>
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Table 8  Estimates of daily hatch probabilities at 25°C from a limited failure
Weibull model

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<td>0.0092</td>
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<td>0.0379</td>
</tr>
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<td>0.0029</td>
<td>0.0100</td>
<td>0.0117</td>
</tr>
<tr>
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<td>0.0006</td>
<td>0.0021</td>
<td>0.0010</td>
</tr>
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<td>0.0000</td>
<td>0.0001</td>
<td>0.0001</td>
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Table 9  Estimates of daily hatch probabilities at 28°C from a limited failure Weibull model

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<th>Std Error III</th>
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<tr>
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<td>0.0007</td>
<td>0.0021</td>
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<td>0.0185</td>
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<tr>
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<td>0.0142</td>
<td>0.0331</td>
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Table 10  Estimates of daily hatch probabilities at 30°C from a limited failure Weibull model

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<th>Std Error III</th>
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<tbody>
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<td>0.0000</td>
<td>0.0000</td>
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<tr>
<td>π₄</td>
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<td>0.0004</td>
<td>0.0014</td>
<td>0.0011</td>
</tr>
<tr>
<td>π₅</td>
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<td>0.0022</td>
<td>0.0058</td>
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</tr>
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<td>0.0026</td>
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<td>0.0172</td>
<td>0.0076</td>
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<td>0.0122</td>
<td>0.0100</td>
</tr>
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<td>0.0050</td>
<td>0.0041</td>
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Table 11  Estimates of daily hatch probabilities of hatching at 32°C from a limited failure Weibull model

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<th>Std Error III</th>
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<td>0.0009</td>
<td>0.0024</td>
<td>0.0010</td>
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<td>$\pi_5$</td>
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<td>0.0088</td>
<td>0.0051</td>
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<td>0.0062</td>
<td>0.0135</td>
<td>0.0293</td>
</tr>
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<td>$\pi_7$</td>
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<td>0.0088</td>
<td>0.0256</td>
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<td>$\pi_9$</td>
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<td>0.0318</td>
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Table 12  Estimates from individual limited failure Weibull models for each replication

<table>
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<th>Temperature</th>
<th>Parameter</th>
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<th>Std Error I</th>
<th>Std Error II</th>
<th>Point Estimate</th>
<th>Std Error I</th>
<th>Std Error II</th>
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<tbody>
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<td>0.1685</td>
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<td>γ</td>
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<td>0.1497</td>
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<td>ξ</td>
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<td>0.0824</td>
<td>0.7821</td>
<td>0.0184</td>
<td>0.0394</td>
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<td>M</td>
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<td>0.3725</td>
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<td>0.0788</td>
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<td>γ</td>
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Table 12 (Continued)

<table>
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<th>Std Error I</th>
<th>Std Error II</th>
</tr>
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<td>20°</td>
<td>ξ</td>
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<td>0.0092</td>
<td>0.0215</td>
</tr>
<tr>
<td>20°</td>
<td>M</td>
<td>15.5660</td>
<td>0.0487</td>
<td>0.1544</td>
</tr>
<tr>
<td>22°</td>
<td>δ</td>
<td>8.9890</td>
<td>0.0707</td>
<td>0.2572</td>
</tr>
<tr>
<td>22°</td>
<td>γ</td>
<td>8.3910</td>
<td>0.3708</td>
<td>0.6417</td>
</tr>
<tr>
<td>22°</td>
<td>ξ</td>
<td>0.5994</td>
<td>0.0227</td>
<td>0.0746</td>
</tr>
<tr>
<td>22°</td>
<td>M</td>
<td>13.6050</td>
<td>0.0685</td>
<td>0.2355</td>
</tr>
<tr>
<td>25°</td>
<td>δ</td>
<td>4.4770</td>
<td>0.0371</td>
<td>0.1046</td>
</tr>
<tr>
<td>25°</td>
<td>γ</td>
<td>3.8340</td>
<td>0.0994</td>
<td>0.3453</td>
</tr>
<tr>
<td>25°</td>
<td>ξ</td>
<td>0.7424</td>
<td>0.0102</td>
<td>0.0266</td>
</tr>
<tr>
<td>25°</td>
<td>M</td>
<td>9.0690</td>
<td>0.0367</td>
<td>0.0879</td>
</tr>
<tr>
<td>28°</td>
<td>δ</td>
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<td>0.0745</td>
<td>0.1369</td>
</tr>
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<td>28°</td>
<td>γ</td>
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<td>0.2565</td>
<td>0.8443</td>
</tr>
<tr>
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<td>ξ</td>
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<td>0.0244</td>
<td>0.0621</td>
</tr>
<tr>
<td>28°</td>
<td>M</td>
<td>6.9960</td>
<td>0.0727</td>
<td>0.1281</td>
</tr>
<tr>
<td>30°</td>
<td>δ</td>
<td>4.5360</td>
<td>0.0500</td>
<td>0.0867</td>
</tr>
<tr>
<td>30°</td>
<td>γ</td>
<td>5.9000</td>
<td>0.3004</td>
<td>0.9280</td>
</tr>
<tr>
<td>30°</td>
<td>ξ</td>
<td>0.7035</td>
<td>0.0223</td>
<td>0.0364</td>
</tr>
<tr>
<td>30°</td>
<td>M</td>
<td>6.2630</td>
<td>0.0516</td>
<td>0.0887</td>
</tr>
<tr>
<td>32°</td>
<td>δ</td>
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<td>0.0529</td>
<td>0.1127</td>
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<tr>
<td>32°</td>
<td>γ</td>
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<td>0.4835</td>
<td>1.5297</td>
</tr>
<tr>
<td>32°</td>
<td>ξ</td>
<td>0.9277</td>
<td>0.0208</td>
<td>0.0449</td>
</tr>
<tr>
<td>32°</td>
<td>M</td>
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<td>0.0539</td>
<td>0.1072</td>
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Table 13  Estimates of daily hatch probabilities at 18°C from a nonparametric model

<table>
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<tr>
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<th>Std Error II</th>
<th>Std Error III</th>
</tr>
</thead>
<tbody>
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<td>$\pi_{10}$</td>
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<td>0.0000</td>
<td>0.0000</td>
<td>0.0000</td>
</tr>
<tr>
<td>$\pi_{11}$</td>
<td>0.0081</td>
<td>0.0026</td>
<td>0.0051</td>
<td>0.0056</td>
</tr>
<tr>
<td>$\pi_{12}$</td>
<td>0.0000</td>
<td>0.0000</td>
<td>0.0000</td>
<td>0.0000</td>
</tr>
<tr>
<td>$\pi_{13}$</td>
<td>0.0030</td>
<td>0.0017</td>
<td>0.0026</td>
<td>0.0021</td>
</tr>
<tr>
<td>$\pi_{14}$</td>
<td>0.0091</td>
<td>0.0027</td>
<td>0.0064</td>
<td>0.0052</td>
</tr>
<tr>
<td>$\pi_{15}$</td>
<td>0.0769</td>
<td>0.0067</td>
<td>0.0210</td>
<td>0.0288</td>
</tr>
<tr>
<td>$\pi_{16}$</td>
<td>0.1261</td>
<td>0.0082</td>
<td>0.0239</td>
<td>0.0501</td>
</tr>
<tr>
<td>$\pi_{17}$</td>
<td>0.1113</td>
<td>0.0080</td>
<td>0.0226</td>
<td>0.0549</td>
</tr>
<tr>
<td>$\pi_{18}$</td>
<td>0.0822</td>
<td>0.0071</td>
<td>0.0165</td>
<td>0.0153</td>
</tr>
<tr>
<td>$\pi_{19}$</td>
<td>0.0991</td>
<td>0.0079</td>
<td>0.0245</td>
<td>0.0302</td>
</tr>
<tr>
<td>$\pi_{20}$</td>
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<td>0.0071</td>
<td>0.0156</td>
<td>0.0402</td>
</tr>
<tr>
<td>$\pi_{21}$</td>
<td>0.0564</td>
<td>0.0067</td>
<td>0.0162</td>
<td>0.0314</td>
</tr>
<tr>
<td>$\pi_{22}$</td>
<td>0.0346</td>
<td>0.0055</td>
<td>0.0110</td>
<td>0.0251</td>
</tr>
<tr>
<td>$\pi_{23}$</td>
<td>0.0338</td>
<td>0.0056</td>
<td>0.0121</td>
<td>0.0233</td>
</tr>
<tr>
<td>$\pi_{24}$</td>
<td>0.0214</td>
<td>0.0046</td>
<td>0.0091</td>
<td>0.0145</td>
</tr>
<tr>
<td>$\pi_{25}$</td>
<td>0.0151</td>
<td>0.0042</td>
<td>0.0086</td>
<td>0.0121</td>
</tr>
<tr>
<td>$\pi_{26}$</td>
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<td>0.0000</td>
<td>0.0000</td>
<td>0.0000</td>
</tr>
<tr>
<td>$\pi_{27}$</td>
<td>0.2500</td>
<td>0.0125</td>
<td>0.0299</td>
<td>0.0345</td>
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</tbody>
</table>
Table 14 Estimates of daily hatch probabilities at 20°C from a nonparametric model

<table>
<thead>
<tr>
<th>Interval</th>
<th>Estimate</th>
<th>Std Error I</th>
<th>Std Error II</th>
<th>Std Error III</th>
</tr>
</thead>
<tbody>
<tr>
<td>(\pi_8)</td>
<td>0.0098</td>
<td>0.0034</td>
<td>0.0128</td>
<td>0.0146</td>
</tr>
<tr>
<td>(\pi_9)</td>
<td>0.0000</td>
<td>0.0000</td>
<td>0.0000</td>
<td>0.0000</td>
</tr>
<tr>
<td>(\pi_{10})</td>
<td>0.0013</td>
<td>0.0019</td>
<td>0.0057</td>
<td>0.0021</td>
</tr>
<tr>
<td>(\pi_{11})</td>
<td>0.0033</td>
<td>0.0025</td>
<td>0.0073</td>
<td>0.0021</td>
</tr>
<tr>
<td>(\pi_{12})</td>
<td>0.0083</td>
<td>0.0024</td>
<td>0.0096</td>
<td>0.0057</td>
</tr>
<tr>
<td>(\pi_{13})</td>
<td>0.0528</td>
<td>0.0045</td>
<td>0.0155</td>
<td>0.0181</td>
</tr>
<tr>
<td>(\pi_{14})</td>
<td>0.0654</td>
<td>0.0050</td>
<td>0.0122</td>
<td>0.0161</td>
</tr>
<tr>
<td>(\pi_{15})</td>
<td>0.1046</td>
<td>0.0058</td>
<td>0.0132</td>
<td>0.0232</td>
</tr>
<tr>
<td>(\pi_{16})</td>
<td>0.1029</td>
<td>0.0057</td>
<td>0.0149</td>
<td>0.0274</td>
</tr>
<tr>
<td>(\pi_{17})</td>
<td>0.1140</td>
<td>0.0057</td>
<td>0.0138</td>
<td>0.0384</td>
</tr>
<tr>
<td>(\pi_{18})</td>
<td>0.0855</td>
<td>0.0050</td>
<td>0.0120</td>
<td>0.0099</td>
</tr>
<tr>
<td>(\pi_{19})</td>
<td>0.0645</td>
<td>0.0045</td>
<td>0.0124</td>
<td>0.0329</td>
</tr>
<tr>
<td>(\pi_{20})</td>
<td>0.0362</td>
<td>0.0036</td>
<td>0.0096</td>
<td>0.0319</td>
</tr>
<tr>
<td>(\pi_{21})</td>
<td>0.0116</td>
<td>0.0023</td>
<td>0.0058</td>
<td>0.0114</td>
</tr>
<tr>
<td>(\pi_{22})</td>
<td>0.0041</td>
<td>0.0017</td>
<td>0.0025</td>
<td>0.0015</td>
</tr>
<tr>
<td>(\pi_{23})</td>
<td>0.0050</td>
<td>0.0021</td>
<td>0.0030</td>
<td>0.0027</td>
</tr>
<tr>
<td>(\pi_{24})</td>
<td>0.0010</td>
<td>0.0012</td>
<td>0.0014</td>
<td>0.0011</td>
</tr>
<tr>
<td>(\pi_{25})</td>
<td>0.0028</td>
<td>0.0021</td>
<td>0.0021</td>
<td>0.0001</td>
</tr>
<tr>
<td>(\pi_{26})</td>
<td>0.3270</td>
<td>0.0085</td>
<td>0.0214</td>
<td>0.0308</td>
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</table>
Table 15  Estimates of daily hatch probabilities at 22°C from a nonparametric model

<table>
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<tr>
<th>Interval</th>
<th>Estimate</th>
<th>Std Error I</th>
<th>Std Error II</th>
<th>Std Error III</th>
</tr>
</thead>
<tbody>
<tr>
<td>( \pi_6 )</td>
<td>0.0029</td>
<td>0.0053</td>
<td>0.0020</td>
<td>0.0016</td>
</tr>
<tr>
<td>( \pi_7 )</td>
<td>0.0085</td>
<td>0.0060</td>
<td>0.0058</td>
<td>0.0045</td>
</tr>
<tr>
<td>( \pi_8 )</td>
<td>0.0000</td>
<td>0.0001</td>
<td>0.0000</td>
<td>0.0000</td>
</tr>
<tr>
<td>( \pi_9 )</td>
<td>0.0000</td>
<td>0.0001</td>
<td>0.0000</td>
<td>0.0000</td>
</tr>
<tr>
<td>( \pi_{10} )</td>
<td>0.0763</td>
<td>0.0074</td>
<td>0.0230</td>
<td>0.0529</td>
</tr>
<tr>
<td>( \pi_{11} )</td>
<td>0.1472</td>
<td>0.0091</td>
<td>0.0267</td>
<td>0.0972</td>
</tr>
<tr>
<td>( \pi_{12} )</td>
<td>0.1086</td>
<td>0.0085</td>
<td>0.0208</td>
<td>0.0607</td>
</tr>
<tr>
<td>( \pi_{13} )</td>
<td>0.1436</td>
<td>0.0099</td>
<td>0.0308</td>
<td>0.0316</td>
</tr>
<tr>
<td>( \pi_{14} )</td>
<td>0.1290</td>
<td>0.0099</td>
<td>0.0282</td>
<td>0.0457</td>
</tr>
<tr>
<td>( \pi_{15} )</td>
<td>0.0610</td>
<td>0.0077</td>
<td>0.0200</td>
<td>0.0282</td>
</tr>
<tr>
<td>( \pi_{16} )</td>
<td>0.0337</td>
<td>0.0064</td>
<td>0.0129</td>
<td>0.0252</td>
</tr>
<tr>
<td>( \pi_{17} )</td>
<td>0.0049</td>
<td>0.0027</td>
<td>0.0033</td>
<td>0.0031</td>
</tr>
<tr>
<td>( \pi_{18} )</td>
<td>0.0022</td>
<td>0.0021</td>
<td>0.0019</td>
<td>0.0011</td>
</tr>
<tr>
<td>( \pi_{19} )</td>
<td>0.0024</td>
<td>0.0021</td>
<td>0.0019</td>
<td>0.0010</td>
</tr>
<tr>
<td>( \pi_{20} )</td>
<td>0.0000</td>
<td>0.0000</td>
<td>0.0000</td>
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<tr>
<td>( \pi_{21} )</td>
<td>0.2797</td>
<td>0.0136</td>
<td>0.0392</td>
<td>0.0907</td>
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Table 16  Estimates of daily hatch probabilities at 25°C from a nonparametric model

<table>
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<th>Std Error I</th>
<th>Std Error II</th>
<th>Std Error III</th>
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</thead>
<tbody>
<tr>
<td>( \pi_6 )</td>
<td>0.0034</td>
<td>0.0013</td>
<td>0.0040</td>
<td>0.0031</td>
</tr>
<tr>
<td>( \pi_7 )</td>
<td>0.0112</td>
<td>0.0022</td>
<td>0.0060</td>
<td>0.0087</td>
</tr>
<tr>
<td>( \pi_8 )</td>
<td>0.0626</td>
<td>0.0043</td>
<td>0.0133</td>
<td>0.0164</td>
</tr>
<tr>
<td>( \pi_9 )</td>
<td>0.2052</td>
<td>0.0073</td>
<td>0.0225</td>
<td>0.0899</td>
</tr>
<tr>
<td>( \pi_{10} )</td>
<td>0.2912</td>
<td>0.0083</td>
<td>0.0249</td>
<td>0.0606</td>
</tr>
<tr>
<td>( \pi_{11} )</td>
<td>0.1671</td>
<td>0.0068</td>
<td>0.0222</td>
<td>0.0726</td>
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<tr>
<td>( \pi_{12} )</td>
<td>0.0254</td>
<td>0.0031</td>
<td>0.0088</td>
<td>0.0118</td>
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<tr>
<td>( \pi_{13} )</td>
<td>0.0118</td>
<td>0.0022</td>
<td>0.0055</td>
<td>0.0071</td>
</tr>
<tr>
<td>( \pi_{14} )</td>
<td>0.0005</td>
<td>0.0005</td>
<td>0.0005</td>
<td>0.0006</td>
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<tr>
<td>( \pi_{15} )</td>
<td>0.0012</td>
<td>0.0007</td>
<td>0.0008</td>
<td>0.0006</td>
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<tr>
<td>( \pi_{16} )</td>
<td>0.0000</td>
<td>0.0000</td>
<td>0.0000</td>
<td>0.0000</td>
</tr>
<tr>
<td>( \pi_{17} )</td>
<td>0.0000</td>
<td>0.0000</td>
<td>0.0000</td>
<td>0.0000</td>
</tr>
<tr>
<td>( \pi_{18} )</td>
<td>0.2205</td>
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<td>0.0174</td>
<td>0.0292</td>
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</table>
Table 17  Estimates of daily hatch probabilities at 28°C from a nonparametric model

<table>
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<th>Std Error III</th>
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<tbody>
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<td>π₃</td>
<td>0.0298</td>
<td>0.0060</td>
<td>0.0137</td>
<td>0.0032</td>
</tr>
<tr>
<td>π₄</td>
<td>0.0000</td>
<td>0.0001</td>
<td>0.0000</td>
<td>0.0000</td>
</tr>
<tr>
<td>π₅</td>
<td>0.0054</td>
<td>0.0037</td>
<td>0.0044</td>
<td>0.0006</td>
</tr>
<tr>
<td>π₆</td>
<td>0.0308</td>
<td>0.0052</td>
<td>0.0144</td>
<td>0.0208</td>
</tr>
<tr>
<td>π₇</td>
<td>0.4040</td>
<td>0.0146</td>
<td>0.0393</td>
<td>0.0337</td>
</tr>
<tr>
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<td>0.1937</td>
<td>0.0122</td>
<td>0.0293</td>
<td>0.0158</td>
</tr>
<tr>
<td>π₉</td>
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<td>0.0229</td>
</tr>
<tr>
<td>π₁₀</td>
<td>0.0082</td>
<td>0.0035</td>
<td>0.0035</td>
<td>0.0045</td>
</tr>
<tr>
<td>π₁₁</td>
<td>0.0054</td>
<td>0.0031</td>
<td>0.0040</td>
<td>0.0024</td>
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<tr>
<td>π₁₂</td>
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<td>0.0000</td>
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<td>0.0000</td>
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<tr>
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<td>0.0040</td>
<td>0.0004</td>
<td>0.0055</td>
<td>0.0036</td>
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<tr>
<td>π₁₄</td>
<td>0.0000</td>
<td>0.0000</td>
<td>0.0000</td>
<td>0.0000</td>
</tr>
<tr>
<td>π₁₅</td>
<td>0.0000</td>
<td>0.0000</td>
<td>0.0000</td>
<td>0.0000</td>
</tr>
<tr>
<td>π₁₆</td>
<td>0.2716</td>
<td>0.0144</td>
<td>0.0337</td>
<td>0.0385</td>
</tr>
</tbody>
</table>

Table 18  Estimates of daily hatch probabilities at 30°C from a nonparametric model

<table>
<thead>
<tr>
<th>Interval</th>
<th>Estimate</th>
<th>Std Error I</th>
<th>Std Error II</th>
<th>Std Error III</th>
</tr>
</thead>
<tbody>
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<td>0.0000</td>
<td>0.0000</td>
<td>0.0000</td>
</tr>
<tr>
<td>π₄</td>
<td>0.0029</td>
<td>0.0015</td>
<td>0.0019</td>
<td>0.0024</td>
</tr>
<tr>
<td>π₅</td>
<td>0.0042</td>
<td>0.0017</td>
<td>0.0036</td>
<td>0.0058</td>
</tr>
<tr>
<td>π₆</td>
<td>0.2219</td>
<td>0.0078</td>
<td>0.0216</td>
<td>0.0250</td>
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<tr>
<td>π₇</td>
<td>0.4315</td>
<td>0.0093</td>
<td>0.0223</td>
<td>0.0229</td>
</tr>
<tr>
<td>π₈</td>
<td>0.0778</td>
<td>0.0054</td>
<td>0.0122</td>
<td>0.0177</td>
</tr>
<tr>
<td>π₉</td>
<td>0.0137</td>
<td>0.0024</td>
<td>0.0029</td>
<td>0.0028</td>
</tr>
<tr>
<td>π₁₀</td>
<td>0.0063</td>
<td>0.0017</td>
<td>0.0019</td>
<td>0.0001</td>
</tr>
<tr>
<td>π₁₁</td>
<td>0.0024</td>
<td>0.0012</td>
<td>0.0012</td>
<td>0.0008</td>
</tr>
<tr>
<td>π₁₂</td>
<td>0.0000</td>
<td>0.0000</td>
<td>0.0000</td>
<td>0.0000</td>
</tr>
<tr>
<td>π₁₃</td>
<td>0.0022</td>
<td>0.0016</td>
<td>0.0017</td>
<td>0.0008</td>
</tr>
<tr>
<td>π₁₄</td>
<td>0.2371</td>
<td>0.0076</td>
<td>0.0157</td>
<td>0.0199</td>
</tr>
</tbody>
</table>
Table 19  Estimates of daily hatch probabilities at 32°C from a nonparametric model

<table>
<thead>
<tr>
<th>Interval</th>
<th>Estimate</th>
<th>Std Error I</th>
<th>Std Error II</th>
<th>Std Error III</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\pi_3$</td>
<td>0.0037</td>
<td>0.0027</td>
<td>0.0020</td>
<td>0.0003</td>
</tr>
<tr>
<td>$\pi_4$</td>
<td>0.0037</td>
<td>0.0027</td>
<td>0.0020</td>
<td>0.0003</td>
</tr>
<tr>
<td>$\pi_5$</td>
<td>0.0081</td>
<td>0.0023</td>
<td>0.0039</td>
<td>0.0044</td>
</tr>
<tr>
<td>$\pi_6$</td>
<td>0.2208</td>
<td>0.0108</td>
<td>0.0258</td>
<td>0.0606</td>
</tr>
<tr>
<td>$\pi_7$</td>
<td>0.3291</td>
<td>0.0123</td>
<td>0.0331</td>
<td>0.0705</td>
</tr>
<tr>
<td>$\pi_8$</td>
<td>0.0406</td>
<td>0.0054</td>
<td>0.0087</td>
<td>0.0081</td>
</tr>
<tr>
<td>$\pi_9$</td>
<td>0.0152</td>
<td>0.0035</td>
<td>0.0051</td>
<td>0.0040</td>
</tr>
<tr>
<td>$\pi_{10}$</td>
<td>0.0047</td>
<td>0.0021</td>
<td>0.0028</td>
<td>0.0027</td>
</tr>
<tr>
<td>$\pi_{11}$</td>
<td>0.0036</td>
<td>0.0019</td>
<td>0.0025</td>
<td>0.0023</td>
</tr>
<tr>
<td>$\pi_{12}$</td>
<td>0.0010</td>
<td>0.0011</td>
<td>0.0012</td>
<td>0.0007</td>
</tr>
<tr>
<td>$\pi_{13}$</td>
<td>0.0012</td>
<td>0.0013</td>
<td>0.0014</td>
<td>0.0013</td>
</tr>
<tr>
<td>$\pi_{14}$</td>
<td>0.0132</td>
<td>0.0124</td>
<td>0.0089</td>
<td>0.0022</td>
</tr>
<tr>
<td>$\pi_{15}$</td>
<td>0.3552</td>
<td>0.0175</td>
<td>0.0318</td>
<td>0.0582</td>
</tr>
</tbody>
</table>

Table 20  Estimated differences in hatch probabilities at 18°C for the nonparametric and limited failure Weibull models

<table>
<thead>
<tr>
<th>Interval Difference</th>
<th>Estimated Difference</th>
<th>Std Error II of Difference</th>
<th>Std Error III of Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\pi_{10} + \pi_{11} + \pi_{12}$</td>
<td>-0.0041</td>
<td>0.0039</td>
<td>0.0075</td>
</tr>
<tr>
<td>$\pi_{13} + \pi_{14}$</td>
<td>-0.0446</td>
<td>0.0097</td>
<td>0.0275</td>
</tr>
<tr>
<td>$\pi_{15}$</td>
<td>0.0215</td>
<td>0.0065</td>
<td>0.0221</td>
</tr>
<tr>
<td>$\pi_{16}$</td>
<td>0.0508</td>
<td>0.0074</td>
<td>0.0243</td>
</tr>
<tr>
<td>$\pi_{17}$</td>
<td>0.0196</td>
<td>0.0085</td>
<td>0.0213</td>
</tr>
<tr>
<td>$\pi_{18}$</td>
<td>-0.0187</td>
<td>0.0090</td>
<td>0.0127</td>
</tr>
<tr>
<td>$\pi_{19}$</td>
<td>-0.0007</td>
<td>0.0084</td>
<td>0.0071</td>
</tr>
<tr>
<td>$\pi_{20}$</td>
<td>-0.0155</td>
<td>0.0073</td>
<td>0.0185</td>
</tr>
<tr>
<td>$\pi_{21}$</td>
<td>-0.0130</td>
<td>0.0075</td>
<td>0.0283</td>
</tr>
<tr>
<td>$\pi_{22}$</td>
<td>-0.0134</td>
<td>0.0085</td>
<td>0.0310</td>
</tr>
<tr>
<td>$\pi_{23}$</td>
<td>0.0050</td>
<td>0.0085</td>
<td>0.0268</td>
</tr>
<tr>
<td>$\pi_{24}$</td>
<td>0.0065</td>
<td>0.0088</td>
<td>0.0187</td>
</tr>
<tr>
<td>$\pi_{25} + \pi_{26}$</td>
<td>0.0063</td>
<td>0.0067</td>
<td>0.0155</td>
</tr>
<tr>
<td>$\pi_{27}$</td>
<td>0.0004</td>
<td>0.0298</td>
<td>0.0353</td>
</tr>
</tbody>
</table>
Table 21 Estimated differences in hatch probabilities at 20°C for the nonparametric and limited failure Weibull models

<table>
<thead>
<tr>
<th>Interval</th>
<th>Estimate Difference</th>
<th>Std Error II of Difference</th>
<th>Std Error III of Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\pi_8 + \pi_9 + \pi_{10}$</td>
<td>0.0059</td>
<td>0.0017</td>
<td>0.0028</td>
</tr>
<tr>
<td>$\pi_{11}$</td>
<td>-0.0084</td>
<td>0.0025</td>
<td>0.0041</td>
</tr>
<tr>
<td>$\pi_{12}$</td>
<td>-0.0165</td>
<td>0.0039</td>
<td>0.0070</td>
</tr>
<tr>
<td>$\pi_{13}$</td>
<td>0.0090</td>
<td>0.0047</td>
<td>0.0113</td>
</tr>
<tr>
<td>$\pi_{14}$</td>
<td>-0.0017</td>
<td>0.0049</td>
<td>0.0175</td>
</tr>
<tr>
<td>$\pi_{15}$</td>
<td>0.0147</td>
<td>0.0050</td>
<td>0.0236</td>
</tr>
<tr>
<td>$\pi_{16}$</td>
<td>-0.0022</td>
<td>0.0059</td>
<td>0.0254</td>
</tr>
<tr>
<td>$\pi_{17}$</td>
<td>0.0077</td>
<td>0.0068</td>
<td>0.0190</td>
</tr>
<tr>
<td>$\pi_{18}$</td>
<td>-0.0055</td>
<td>0.0066</td>
<td>0.0095</td>
</tr>
<tr>
<td>$\pi_{19}$</td>
<td>-0.0001</td>
<td>0.0060</td>
<td>0.0157</td>
</tr>
<tr>
<td>$\pi_{20}$</td>
<td>-0.0006</td>
<td>0.0057</td>
<td>0.0215</td>
</tr>
<tr>
<td>$\pi_{21}$</td>
<td>-0.0048</td>
<td>0.0044</td>
<td>0.0178</td>
</tr>
<tr>
<td>$\pi_{22} + \pi_{23} + \pi_{24} + \pi_{25}$</td>
<td>0.0059</td>
<td>0.0036</td>
<td>0.0142</td>
</tr>
<tr>
<td>$\pi_{26}$</td>
<td>-0.0034</td>
<td>0.0212</td>
<td>0.0270</td>
</tr>
</tbody>
</table>

We first test the fit of a marginal Weibull model at each temperature averaging across replicates. Some primary inspection intervals are combined to obtain expected counts larger than ten. Differences, computed as $\pi_k$ for the nonparametric model minus $\pi_k$ for the limited failure Weibull model, are shown in Tables 20 to 26 along with the standard errors of the differences based on the two sandwich covariance estimators. The degrees of freedom for each goodness of fit test are also shown in these tables.

Substantial variability among replications requires the use of sandwich covariance estimators corresponding to standard error III in the goodness of fit test. The three replications available at each temperature are not sufficient for accurate use of the large sample chi-squared approximation to (47). Consequently, we also present results for tests based on the inadequate covariance matrix estimate in (49), that only accounts for correlations within cohorts. in Table 27. These test statistics have inflated type I error levels, and it is unclear if the proposed marginal Weibull model is adequate for higher temperatures.

An alternative approach is to fit a separate limited failure Weibull model to the data from each replication at each temperature. We did this for the 25°C data, and found a significant lack of fit for the replication with 111 cohorts. Although the lack of fit for the other two replications at 25°C was not significant, we observed the same for all three replications. The limited failure Weibull model yielded
Table 22  Estimated differences in hatch probabilities at 22°C for the nonparametric and limited failure Weibull models

<table>
<thead>
<tr>
<th>Interval</th>
<th>Estimate Difference</th>
<th>Std Error II of Difference</th>
<th>Std Error III of Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\pi_6 + \pi_7 + \pi_8 + \pi_9$</td>
<td>-0.0293</td>
<td>0.0108</td>
<td>0.0408</td>
</tr>
<tr>
<td>$\pi_{10}$</td>
<td>0.0156</td>
<td>0.0095</td>
<td>0.0430</td>
</tr>
<tr>
<td>$\pi_{11}$</td>
<td>0.0450</td>
<td>0.0111</td>
<td>0.0510</td>
</tr>
<tr>
<td>$\pi_{12}$</td>
<td>-0.0298</td>
<td>0.0124</td>
<td>0.0388</td>
</tr>
<tr>
<td>$\pi_{13}$</td>
<td>-0.0047</td>
<td>0.0136</td>
<td>0.0138</td>
</tr>
<tr>
<td>$\pi_{14}$</td>
<td>0.0081</td>
<td>0.0136</td>
<td>0.0306</td>
</tr>
<tr>
<td>$\pi_{15}$</td>
<td>-0.0101</td>
<td>0.0131</td>
<td>0.0369</td>
</tr>
<tr>
<td>$\pi_{16}$</td>
<td>0.0056</td>
<td>0.0100</td>
<td>0.0221</td>
</tr>
<tr>
<td>$\pi_{17} + \pi_{18} + \pi_{19} + \pi_{20}$</td>
<td>0.0015</td>
<td>0.0057</td>
<td>0.0084</td>
</tr>
<tr>
<td>$\pi_{21}$</td>
<td>-0.0020</td>
<td>0.0392</td>
<td>0.0908</td>
</tr>
</tbody>
</table>

a smaller estimate of the hatch probability in the inspection interval containing the median and higher probabilities in the other intervals.

Results presented in Tables 20 to 26 indicate that this also occurs for higher temperatures, but the Weibull model fits better at lower temperatures. It appears that an alternative to the limited failure Weibull model should be developed to concentrate greater probability near the median hatch time as temperature increases.

7 Discussion

In the application of our nonparametric and semi-parametric methods to the bean leaf beetle data, we found that the sandwich covariance estimator given by (19) when $j = j'$ provided similar estimates of standard errors to the bootstrap method used by Koehler (1994). It is very clear from this analysis that some type of robust variance estimator is needed to account for correlated hatch times within cohorts and variation among incubators. Although the limited failure Weibull model does not fit as well at the higher temperatures, it provided satisfactory estimates of the median hatch times and daily development rates. The limited failure Weibull model gives a straightforward estimate of median hatch time and also yields an estimate of the proportion of viable eggs. Unless variation among incubators can be better controlled, experiments of this type should use more replicates possibly with fewer cohorts per replicate.
Table 23  Estimated differences in hatch probabilities at 25°C for the nonparametric and limited failure Weibull models

<table>
<thead>
<tr>
<th>Interval</th>
<th>Estimate Difference</th>
<th>Std Error II</th>
<th>Std Error III</th>
</tr>
</thead>
<tbody>
<tr>
<td>( \pi_6 + \pi_7 )</td>
<td>-0.0026</td>
<td>0.0042</td>
<td>0.0150</td>
</tr>
<tr>
<td>( \pi_8 )</td>
<td>-0.0169</td>
<td>0.0092</td>
<td>0.0361</td>
</tr>
<tr>
<td>( \pi_9 )</td>
<td>0.0108</td>
<td>0.0100</td>
<td>0.0252</td>
</tr>
<tr>
<td>( \pi_{10} )</td>
<td>0.0276</td>
<td>0.0149</td>
<td>0.0372</td>
</tr>
<tr>
<td>( \pi_{11} )</td>
<td>-0.0086</td>
<td>0.0127</td>
<td>0.0546</td>
</tr>
<tr>
<td>( \pi_{12} )</td>
<td>-0.0203</td>
<td>0.0100</td>
<td>0.0117</td>
</tr>
<tr>
<td>( \pi_{13} + \pi_{14} + \pi_{15} + \pi_{16} + \pi_{17} )</td>
<td>0.0100</td>
<td>0.0022</td>
<td>0.0010</td>
</tr>
<tr>
<td>( \pi_{18} )</td>
<td>0.0001</td>
<td>0.0171</td>
<td>0.0289</td>
</tr>
</tbody>
</table>

Table 24  Estimated differences in hatch probabilities at 28°C for the nonparametric and limited failure Weibull models

<table>
<thead>
<tr>
<th>Interval</th>
<th>Estimate Difference</th>
<th>Std Error II</th>
<th>Std Error III</th>
</tr>
</thead>
<tbody>
<tr>
<td>( \pi_3 + \pi_4 + \pi_5 )</td>
<td>-0.0013</td>
<td>0.0112</td>
<td>0.0051</td>
</tr>
<tr>
<td>( \pi_6 )</td>
<td>-0.0923</td>
<td>0.0134</td>
<td>0.0028</td>
</tr>
<tr>
<td>( \pi_7 )</td>
<td>0.1510</td>
<td>0.0231</td>
<td>0.0220</td>
</tr>
<tr>
<td>( \pi_8 )</td>
<td>-0.0455</td>
<td>0.0225</td>
<td>0.0146</td>
</tr>
<tr>
<td>( \pi_9 + \pi_{10} + \pi_{11} + \pi_{12} + \pi_{13} + \pi_{14} + \pi_{15} )</td>
<td>-0.0106</td>
<td>0.0224</td>
<td>0.0376</td>
</tr>
<tr>
<td>( \pi_{16} )</td>
<td>-0.0013</td>
<td>0.0311</td>
<td>0.0362</td>
</tr>
</tbody>
</table>

8 Appendix: numerical issues

We fit both the nonparametric method and the limited failure Weibull model using a modified Fisher scoring algorithm. For convergence we required that the maximum absolute change in the parameter estimates to be less than 0.0001.

For the nonparametric method, we used a logistic reparameterization for \( \pi \) to force each \( \pi_k \) to be between zero and one, and the elements of \( \pi \) to add up to one, and to make the information matrix invertible. This reparameterization is

\[
\pi_k = \frac{e^{\alpha_k}}{1 + \sum_{j=1}^{K^*} e^{\alpha_j}} \quad \text{for } k = \ldots K^*
\]

\[
\frac{1}{(1 + \sum_{j=1}^{K^*} e^{\alpha_j})}
\]

\[\pi_{K^*+1} = \frac{1}{(1 + \sum_{j=1}^{K^*} e^{\alpha_j})}.
\]
Table 25  Estimated differences in hatch probabilities at 30°C nonparametric and limited failure Weibull models

<table>
<thead>
<tr>
<th>Interval</th>
<th>Estimate Difference</th>
<th>Std Error II of Difference</th>
<th>Std Error III of Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>( \pi_3 + \pi_4 + \pi_5 )</td>
<td>-0.0483</td>
<td>0.0056</td>
<td>0.0049</td>
</tr>
<tr>
<td>( \pi_6 )</td>
<td>0.0246</td>
<td>0.0058</td>
<td>0.0025</td>
</tr>
<tr>
<td>( \pi_7 )</td>
<td>0.0963</td>
<td>0.0128</td>
<td>0.0075</td>
</tr>
<tr>
<td>( \pi_8 )</td>
<td>-0.0852</td>
<td>0.0090</td>
<td>0.0086</td>
</tr>
<tr>
<td>( \pi_9 + \pi_{10} + \pi_{11} + \pi_{12} + \pi_{13} )</td>
<td>0.0141</td>
<td>0.0037</td>
<td>0.0033</td>
</tr>
<tr>
<td>( \pi_{14} )</td>
<td>-0.0015</td>
<td>0.0087</td>
<td>0.0106</td>
</tr>
</tbody>
</table>

Table 26  Estimated differences in hatch probabilities at 32°C nonparametric and limited failure Weibull model

<table>
<thead>
<tr>
<th>Interval</th>
<th>Estimate Difference</th>
<th>Std Error II of Difference</th>
<th>Std Error III of Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>( \pi_3 + \pi_4 + \pi_5 )</td>
<td>-0.0444</td>
<td>0.0112</td>
<td>0.0055</td>
</tr>
<tr>
<td>( \pi_6 )</td>
<td>0.0349</td>
<td>0.0120</td>
<td>0.0258</td>
</tr>
<tr>
<td>( \pi_7 )</td>
<td>0.0599</td>
<td>0.0219</td>
<td>0.0342</td>
</tr>
<tr>
<td>( \pi_8 + \pi_9 + \pi_{10} + \pi_{11} + \pi_{12} + \pi_{13} + \pi_{14} )</td>
<td>-0.0333</td>
<td>0.0199</td>
<td>0.0404</td>
</tr>
<tr>
<td>( \pi_{15} )</td>
<td>-0.0171</td>
<td>0.0261</td>
<td>0.0509</td>
</tr>
</tbody>
</table>

Then, we maximized the log-likelihood with respect to \((\alpha_1, \alpha_2, \ldots, \alpha_{K*})\). In some replications, observed zero counts resulted in attempts to estimate a boundary solution of \(\pi_k = 0\). To avoid numerical difficulties, we added a small number (0.00001) to all of the counts. Starting values used for the nonparametric method were \(\alpha = 0\) which corresponds to equally likely probabilities of hatching in all intervals, but we obtained the same maximum likelihood estimates when we used starting values computed from the observed proportions of eggs hatching on a given day.

In fitting the limited failure Weibull model, we also needed to prevent estimates of \(\pi_k\) from getting too small, to prevent overflow problems in evaluating the log-likelihood and its derivatives, on each iteration. After updating the values of \(\delta, \gamma, \) and \(\xi\), we changed the new value of the \(\pi_k\) to \(\pi_k^* = (1-\varepsilon)\pi_k + \varepsilon/(K*+1)\), where \(\varepsilon = .000001\), before evaluating the log-likelihood. Starting values for this method can also be problematic. We tried some method of moments estimators as starting values, but concluded that a grid search was necessary to find appropriate starting values.
Table 27  Assessing the goodness of fit of the limited failure Weibull model

<table>
<thead>
<tr>
<th>Temperature</th>
<th>df</th>
<th>Test Statistic Using Std Error II</th>
<th>p-value</th>
<th>Test Statistic Using Std Error III</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>18°</td>
<td>11</td>
<td>0.7386</td>
<td>1.0000</td>
<td>0.1091</td>
<td>1.0000</td>
</tr>
<tr>
<td>20°</td>
<td>11</td>
<td>0.4901</td>
<td>1.0000</td>
<td>0.0321</td>
<td>1.0000</td>
</tr>
<tr>
<td>22°</td>
<td>7</td>
<td>0.0907</td>
<td>1.0000</td>
<td>0.0112</td>
<td>1.0000</td>
</tr>
<tr>
<td>25°</td>
<td>5</td>
<td>4.7039</td>
<td>0.4531</td>
<td>0.3522</td>
<td>0.9965</td>
</tr>
<tr>
<td>28°</td>
<td>3</td>
<td>7.8391</td>
<td>0.0495</td>
<td>7.9873</td>
<td>0.0463</td>
</tr>
<tr>
<td>30°</td>
<td>3</td>
<td>77.9823</td>
<td>0.0000</td>
<td>62.3163</td>
<td>0.0000</td>
</tr>
<tr>
<td>32°</td>
<td>2</td>
<td>10.2478</td>
<td>0.0060</td>
<td>1.5556</td>
<td>0.4594</td>
</tr>
</tbody>
</table>

9  Bibliography


Figure 1  Relationship between daily development rate and temperature using weighted least squares
Figure 2  Relationship between median and temperature using weighted least squares
Figure 3  Relationship between estimated $\delta$ and temperature
Figure 4  Relationship between estimated $\gamma$ and temperature
Figure 5  Relationship between estimated $\xi$ and temperature
GENERAL CONCLUSIONS

In this dissertation we have addressed the issue of analysis of interval censored lifetime data. We have explored two different approaches. The first approach assumes that an underlying continuous time model is reasonable for the data, and uses modifications to the partial likelihood to deal with tied event times arising from the interval censoring. In the second approach we applied discrete models to the counts representing the number of failures in the inspection intervals.

We studied the effects of interval censoring on partial likelihood analysis of proportional hazards models and found that the Efron approximation to the partial likelihood produces accurate estimates of treatment effects and reliable confidence intervals provided that fewer than 20% of the cases that are observed to fail are involved in ties. This performance was superior to the Breslow approximation and almost identical to maximizing the geometric mean of all possible partial likelihoods. The behavior of the estimator that maximizes the arithmetic mean of all possible partial likelihoods is similar to the behavior of the partial likelihood estimator that would be obtained if the exact failure times were available. In the appendix we present our program for computing the geometric and arithmetic means of all possible partial likelihoods. If the tied failure times in a particular inspection interval exceed some specified bound, then we use averages of partial likelihoods for a random sample of possible orderings.

In the second paper we adopted a discrete approach to interval censored lifetime data. In addition to interval censoring, we considered cohorts with correlated survival times nested in replications where different cohorts are inspected on different schedules. Additionally, there is a proportion of the population which in not subject to failure. We explored a working model approach based on an independence multinomial model and a parametric model for multinomial probabilities. We used a sandwich covariance estimator to account for the correlated failure times within cohorts and variation among replications which uses properties of the score function of the working multinomial log-likelihood. Additionally we developed a test to compare two models a nonparametric model and a semi-parametric model where probabilities of failure within an inspection interval are modeled by a parametric function.

Finally, we presented an application of our methods to modeling the effect of temperature on de-
development rates of bean leaf beetles. Algorithms for evaluating parameter estimates were developed in S-plus. It was observed that the limited failure Weibull model did not adequately describe the data at higher temperatures. Improvements to this model is a topic for further research.
APPENDIX: PROGRAMS FOR COX PROPORTIONAL HAZARDS REGRESSION

The following listing of programs detail the modifications which we made to the version of the Package for Survival Analysis in S written and made available from StatLib by Terry M. Therneau.

We made only slight changes to the coxph.s by adding two options to the menu of choices of method for handling tied failure times. We added 'arith' and 'geo' to the line which reads method = c('efron', 'breslow', 'exact'). These options are added throughout the program in appropriate places. Additionally we added a parameter iseed = negative integer and the line m$seed <- NULL where iseed is the seed for the random number generator which randomly selects possible orderings for failures which appear in the same interval.

We used Therneau's coxfit2.c as the basis for the functions avgfit.c and geofit.c. These programs are listed below along with some additional functions which our program uses.

/* avgfit.c by Becky Benner 5/8/1997

**
** DESCRIPTION: avgfit estimates beta, the parameter vector
** for the Cox Proportional Hazards regression, using
** Newton Raphson iterations on the log partial likelihood
** where the log partial likelihood is the arithmetic mean
** of all possible log partial likelihoods (if the number of
** ties in any particular interval is less than CUTOFF) or a
** random sample of MAXORDER possible orderings of the covariates
** if the number of ties in an interval is greater than or equal to CUTOFF
**
** FUNCTIONS CALLED: Therneau: cholesky2, chsolve2, chinv2, dmatrix
** My functions: notiespl, permute, ranpermute (which calls ran2)
** factorial
** INPUTS:

- **maxiter**: number of iterations (set to be 10 in this application)
- **nused**: number of observations or people
- **nvar**: number of covariates
- **time(n)**: time of event or censoring for person i
- **status(n)**: status for the ith person 1=dead, 0=censored
- **covar(nv,n)**: covariates for person i.
  
  Note that S sends this in column major order.
- **eps**: tolerance for convergence. Iteration continues until
  the percent change in loglikelihood is <= eps.
  (set to be 0.0001 in this application)
- **sctest**: on input = 0
- **isseed**: seed for the random number generator in C which is
  used for sampling of possible orders. Must be
  a negative number.

** RETURNED VALUES:

- **means(nv)**: vector of column means of X
- **beta(nv)**: the vector of answers (at start contains initial est
  which is zero by default in this application)
- **u(nv)**: score vector
- **imat(nv,nv)**: the variance matrix at beta=final, also a ragged array
  if flag<0, imat is undefined upon return
- **loglik(2)**: loglik at beta=initial values, at beta=final
- **sctest**: the score test at beta=initial
- **flag**: success flag 1000 did not converge
  1 to nvar: rank of the solution
- **maxiter**: actual number of iterations used

** ACKNOWLEDGEMENTS:

This program has been adapted from Terry Therneau's Cox Regression
program for the Efron and Breslow methods, coxfit2.c

NOTES: I dropped the strata, offset, and weight variables from Therneau's original program.
THE DATA MUST BE SORTED BY ASCENDING TIME

GLOBALLY DEFINED VARIABLES:
- MAX = Maximum number of ties allowed
- CUTOFF = Switch point for switching from iterating through all permutations to random selection of possible orders
- ORDERMAX = Number of randomly selected permutations

LOCALLY DEFINED VARIABLES:
- i,j = Index for covariates = 0,...,nvar-1
- k = Index for possible orders, 1,..., (#ties !)
- person = Index for failure times
- ties = Indicator: 0= all failure times in interval are unique
  1 = have tied failure times
- orders = Number of possible orders is either (#ties !) or ORDERMAX
- start = Saves the original seed for the sampling of random orders from the beginning of the first iteration
- perm[MAX] = A permutation of the ordering of the failures in an interval
- mark[i] = Mark(i) contains the number of tied deaths at this point,
  for the first person of several tied times. It is zero for the second and etc of a group of tied times.
- newbeta = New parameter estimates; the update
- denom = Sum of the risks in the risk set
- org_den = Saves the value of denom when enter an interval with ties
- halving = 1 = doing step halving; 0 = not doing step halving
- a[] = Part of the score function computations
** a2 = Contribution to the score function for an interval
** cmat2 = Contribution to imat for an interval
** num_u = Part of the numerator of the score function, used in
** computations when there are ties.
** cmat3 = Used in computing imat when there are ties
** a3 = Stores what a was at the begining of an interval
** with ties
** cmat4 = Stores what cmat was at the begining of an interval
** with ties
** newlk = Contains the new value of the loglikelihood for updated beta
** pl = Contribution to the partial likelihood for an interval
** cmat = Part of the imat computations (negative of second
** partial derivatives)
**
** the work arrays are passed as a single
** vector of storage, and then broken out.
**
*/
#include <math.h>
#include <stdio.h>

#define MAX 100
#define CUTOFF 8
#define ORDERMAX 5000

double **dmatrix();

void notiespl();

long factorial();

void permute();
void ranpermute();

void avgfit(maxiter, nusedx, nvarx, time, status, covar2, iseed, means, beta, u, imat2, loglik, flag, work, eps, sctest)

long *nusedx,
*nvarx,
*maxiter,
*flag,
*iseed,
status;
double *covar2,
*imat2;
double u,
means,
*work,
beta,
time;
double loglik[2],
*sctest;
double *eps;
{
    register int i, j, k, person;
    int iter, ties;
    int nused, nvar;
    long orders, start;
    int perm[MAX];

    double **covar, **cmat, **imat; /*ragged array versions*/
    double *mark;
double *a, *newbeta;
double *a2, **cmat2;
double *num_u, **cmat3;
double *a3, **cmat4;
double denom, org_den, zbeta, risk;
double temp, temp2;
double 11[2], newlk[2], pl[2];
int halving;

nused = *nusedx;
nvar = *nvarx;

/*
 ** Set up the ragged arrays
 */
covcir= dmatrix(covcir2, nused, nvar);
imat = dmatrix(imat2, nvar, nvar);
cmat = dmatrix(work, nvar, nvar);
cmat2= dmatrix(work+nvar*nvar, nvar, nvar);
a = work + 2*nvar*nvar;
newbeta = a + nvar;
a2 = newbeta + nvar;
mark = a2 + nvar;
cmat3 = dmatrixx(mark+nused, nvar, nvar);
num_u = mark + nused + nvar * nvar;
cmat4 = dmatrix(num_u + nvar, nvar, nvar);
a3 = num_u + nvar + nvar * nvar;

/∗
 ** Compute the number of failures in each interval
 */
temp=0;
j=0;
for (i=nused-1; i>0; i--) {


if (time[i] == time[i-1]) {
    j += status[i];
    temp += status[i];
    mark[i] = 0;
}  
else {
    mark[i] = j + status[i];
    temp = 0;  j = 0;
}
mark[0] = j + status[0];
/*
  ** Subtract the mean from each covar, as this makes the regression
  ** much more stable
  */
for (i=0; i<nvar; i++) {
    temp = 0;
    for (person=0; person<nused; person++) temp += covar[i][person];
    temp /= nused;
    means[i] = temp;
    for (person=0; person<nused; person++) covar[i][person] -= temp;
}
/*
  ** Initializations for the random sampling of orders
  */
start = *isseed;
for (i=0; i < MAX; i++){
    perm[i]=0;
}
ties = 0;
/*
  ** do the initial iteration step
  */
/ ** Initialize the arrays for the sums of the risks, and the loglikelihood, ** the score function, the negative of the matrix of second partial derivatives ** and the working arrays used in computing them */
loglik[1] =0;
l1[i]=0;
p1[i]=0;
denom = 0;
org_den = 0;
for (i=0; i<nvar; i++) {
u[i] =0;
a[i] =0;
a2[i] =0;
num_u[i]=0;
a3[i] = 0;
for (j=0; j<nvar; j++){
imat[i][j] =0 ;
cmat[i][j]=0;
cmat2[i][j] =0;
cmat3[i][j] =0;
cmat4[i][j] =0;
}
}
for (person=nused-1; person >=0; person --){
  if (status[person] == 0){
/*
 ** Add the censored observations into the risk set */
  zbeta = 0;    /* form the term beta*z (vector mult) */
risk =0;
  for (i=0; i<nvar; i++)
\[ z_{\beta} += \beta[i] \cdot \text{covar}[i][\text{person}]; \]

\[ \text{risk} = \exp(z_{\beta}); \]

\[ \text{denom} += \text{risk}; \]

for (i=0; i<nvar; i++) {
    \[ a[i] += \text{risk} \cdot \text{covar}[i][\text{person}]; \]
    for (j=0; j<=i; j++)
        \[ \text{cmat}[i][j] += \text{risk} \cdot \text{covar}[i][\text{person}] \cdot \text{covar}[j][\text{person}]; \]
}

} /* end of censored portion */
else{
    if (\text{mark}[\text{person}] == 1) {
        \text{ties}=0;
        /*
        ** There is only one failure in the interval, so there is one
        ** unique contribution to the likelihood.
        */
        \text{noties}=\text{nvar}, (\text{int})\text{mark}[\text{person}] , \text{person}, \text{covar}, \text{status}, \
        \text{beta}, &\text{denom}, \text{ll}, \text{a2}, \text{cmat2}, \text{a}, \text{cmat}, \text{ties}, \text{perm});
        \text{loglik}[i] += \text{ll}[i];
        for (i=0; i<nvar; i++) {
            \text{u}[i] += \text{a2}[i];
            for (j=0; j<=i; j++)
                \[ \text{imat}[j][i] += \text{cmat2}[j][i]; \]
        }
    }
} /* end of loop for unique partial likelihood*/
else if (\text{mark}[\text{person}] > 0) {
    \text{ties}=1;
    /*
    ** There is more than one failure in the interval
    ** Decide how many possible orderings of the covariates to use.
    */
if (mark[person] >= CUTOFF) orders = ORDERMAX;
else orders = factorial((int)mark[person]);
loglik[l] -= log((double)orders);
pl[l] = 0;
for (i=0; i<nvar; i++){
    num_u[i] = 0;
    for (j=0; j<nvar; j++){
        cmat3[i][j] = 0;
    }
}
for (k=0; k < orders; k++){
    /*
     ** Compute a permutation of the orderings
     */
    if (mark[person] >= CUTOFF) {
        ranpermute(perm, (int)mark[person], &start);
    }
    else permute(perm, (int)mark[person], k, orders);
    /*
     ** Save the values of things with the risk set
     ** as it was when entering the interval.
     */
    org_den = denom;
    for (i=0; i<nvar; i++) {
        a3[i] = a[i];
        for (j=0; j<nvar; j++){
            cmat4[i][j] = cmat[i][j];
        }
    }
    /*
     ** Compute the contribution to the likelihood and etc
     ** for this particular interval
     */
notiespl(nvar, (int)mark[person], person, covar, status, beta, &denom, ll, a2, cmat2, a, cmat, ties, perm);
temp = exp(ll[i]);
pl[i] += temp;
for (i=0; i<nvar; i++) {
    num_u[i] += temp*a2[i];
    for (j=0; j<=i; j++){
        cmat3[j][i] += temp*(a2[j] * a2[i] - cmat2[j][i]);
        }
        }
if ( k != orders-1){
    
    denom = org_den;
    for (i=0; i<nvar; i++) {
        a[i] = a3[i];
        for (j=0; j<nvar; j++){
            cmat[i][j] = cmat4[i][j];
            }
            }
        }
    }
    }
    }
    
    loglik[i] += log(pl[i]);
    for (i=0; i<nvar; i++) {
u[i] += num_u[i] / pl[i];
for (j=0; j<i; j++){
    imat[j][i] -= (cmat3[j][i] * pl[i] -
    num_u[j]*num_u[j]) / (pl[1]* pl[1]) ;
}
/* end of loop for ties */
} /* end of else loop */
} /* end of loop for all people */
/*
 ** End of the initial iteration step
 */
loglik[0] = loglik[i];
/* am I done?
 ** update the betas and test for convergence
 */
for (i=0; i<nvar; i++) /*use 'a' as a temp to save u0, for the score test*/
    a[i] = u[i];
*flag= cholesky2(imat, nvar);
chsolve2(imat,nvar,a);        /* a replaced by a *inverse(i) */
*sctest=0;
for (i=0; i<nvar; i++)
    *sctest += u[i]*a[i];
/*
 ** Never, never complain about convergence on the first step. That way,
 ** if someone HAS to they can force one iter at a time.
 */
/*
 ** Update the value of beta
 */
for (i=0; i<nvar; i++) {
    newbeta[i] = beta[i] + a[i];
if (*maxiter==0) {
    chinv2(imat, nvar);
    for (i=1; i<nvar; i++)
        for (j=0; j<i; j++) imat[i][j] = imat[j][i];
    return;  /* and we leave the old beta in peace */
}

/** Main loop; the loop follows the same logic as the
** initial iteration */
halving =0 ;  /* =1 when in the midst of "step halving" */
for (iter=1; iter<=maxiter; iter++) {
    /*
    ** Resetting things which need to be reset at each iteration
    */
    start = *isep;
    newlk[i] =0;
    l1[i] =0;
    denom = 0;
    for (i=0; i<nvar; i++) {
        u[i] =0;
        a[i] =0;
        a2[i] =0;
        a3[i] =0;
        num_u[i]=0;
        for (j=0; j<nvar; j++){
            imat[i][j] =0 ;
            cmat[i][j]=0;
            cmat2[i][j] =0;
            cmat3[i][j] =0;
        }
    }
}
cmat4[i][j] = 0;
}
}
for (person=nused-1; person >=0; person --){
if (status[person] == 0){
    zbeta = 0;    /* form the term beta*z (vector mult) */
    risk = 0;
    for (i=0; i<nvar; i++)
        zbeta += newbeta[i]*covar[i][person];
    risk = exp(zbeta);
    denom += risk;
    for (i=0; i<nvar; i++) {
        a[i] += risk*covar[i][person];
        for (j=0; j<=i; j++)
            cmat[i][j] += risk*covar[i][person]*covar[j][person];
    }
}
else if (mark[person] == 1){
    ties = 0;
    notiesps1(nvar, (int) mark[person], person, covar, status,
             newbeta, &denom, ll, a2, cmat2, a, cmat, ties, perm);
    newlk[1] += ll[1];
    for (i=0; i<nvar; i++) {
        u[i] += a2[i];
        for (j=0; j<i; j++)
            imat[j][i] += cmat2[j][i];
    }
}
} /* end of loop for unique likelihood */
else if (mark[person] > 0){
    ties = 1;
    if (mark[person] >= CUTOFF) orders = ORDERMAX;
else orders = factorial((int)mark[person]);
newlk[i] -= log((double)orders);
pl[i] = 0;
for (i=0; i<nvar; i++){
    num_u[i]=0;
    for (j=0; j<nvar; j++){
        cmat3[i][j] = 0;
    }
}
for (k=0; k < orders; k++){
    if (mark[person] >= CUTOFF) ranpermute(perm, (int)mark[person], &start);
    else permute(perm, (int)mark[person], k, orders);
org_den = denom;
for (i=0; i<nvar; i++) {
    a3[i] = a[i];
    for (j=0; j<nvar; j++){
        cmat4[i][j] = cmat[i][j];
    }
}
notiespl(nvar, (int)mark[person], person, covar, status,
    newbeta, &denom, l1, a2, cmat2, a, cmat, ties, perm);
temp = exp(l1[i]);
pl[i] += temp;
for (i=0; i<nvar; i++) {
    num_u[i] += temp*a2[i];
    for (j=0; j<=i; j++){
        cmat3[j][i] += temp*(a2[j] * a2[i] - cmat2[j][i]);
    }
}
if (k != orders -1 ){
    denom = org_den;
    for (i=0; i<nvar; i++) {

a[i] = a3[i];
for (j=0; j<nvar; j++) {
    cmat[i][j] = cmat4[i][j];
}

newlk[1] += log(pl[1]);
for (i=0; i<nvar; i++) {
    u[i] += num_u[i] / pl[1];
    for (j=0; j<i; j++) {
        imat[j][i] -= (cmat3[j][i] * pl[1] -
        num_u[j]*num_u[j]) / (pl[1]*pl[1]);
    }
}

/* end of loop for ties */
/* end of loop for all people */

/* am I done? */
/* update the betas and test for convergence */

*flag = cholesky2(imat, nvar);
if (fabs(1-(loglik[1]/newlk[1]))<=*eps) { /* all done */
    loglik[1] = newlk[1];
    chinv2(imat, nvar); /* invert the information matrix */
    for (i=1; i<nvar; i++)
        for (j=0; j<i; j++) imat[i][j] = imat[j][i];
    for (i=0; i<nvar; i++)
        beta[i] = newbeta[i];
    if (halving==1) *flag= 1000; /* didn't converge after all */
    *maxiter = iter;
    return;
}
if (iter==maxiter) break; /*skip the step halving and etc */
if (newlk[i] < loglik[i]) { /*it is not converging! */
halving =1;
for (i=0; i<nvar; i++)
    newbeta[i] = (newbeta[i] + beta[i]) /2; /*half of old increment */
}
else {
    halving=0;
    loglik[i] = newlk[i];
    chsolve2(imat,nvar,u);
    j=0;
for (i=0; i<nvar; i++) {
    beta[i] = newbeta[i];
    newbeta[i] = newbeta[i] + u[i];
}
}
} /* return for another iteration */

loglik[i] = newlk[i];
chinv2(imat, nvar);
for (i=1; i<nvar; i++)
    for (j=0; j<i; j++) imat[i][j] = imat[j][i];
for (i=0; i<nvar; i++)
    beta[i] = newbeta[i];
*flag= 1000;
return;
}

/* GEOfit.c by Becky Benner 5/8/1997 */
**
** DESCRIPTION: avgfit estimates beta, the parameter vector
** for the Cox Proportional Hazards regression, using
** Newton Raphson iterations on the log partial likelihood
** where the log partial likelihood is the geometric mean
** of all possible log partial likelihoods (if the number of
ties in any particular interval is less than CUTOFF) or a
** random sample of MAXORDER possible orderings of the covariates
** if the number of ties in an interval is greater than or equal to CUTOFF
**
** FUNCTIONS CALLED: Therneau: cholesky2, chsolve2, chinv2, dmatrix
** My functions: notiespl, permute, ranpermute (which calls ran2)
** factorial
**
** INPUTS:
** maxiter :number of iterations (set to be 10 in this application)
** nused :number of observations or people
** nvar :number of covariates
** time(n) :time of event or censoring for person i
** status(n) :status for the ith person 1=dead, 0=censored
** covar(nv,n) :covariates for person i.
** Note that S sends this in column major order.
** eps :tolerance for convergence. Iteration continues until
** the percent change in loglikelihood is <= eps.
** (set to be 0.0001 in this application)
** sctest :on input = 0
** iseed :seed for the random number generator in C which is
** used for sampling of possible orders. Must be
** a negative number.
**
** RETURNED VALUES:
** means(nv) : vector of column means of X
** beta(nv) :the vector of answers (at start contains initial est
** which is zero by default in this application)
** u(nv) :score vector
** imat(nv,nv) :the variance matrix at beta=final, also a ragged array
** if flag<0, imat is undefined upon return

** loglik(2) : loglik at beta=initial values, at beta=final

** sctest : the score test at beta=initial

** flag : success flag 1000 did not converge

** 1 to nvar: rank of the solution

** maxiter : actual number of iterations used

**

** ACKNOWLEDGEMENTS:

** This program has been adapted from Terry Therneau's Cox Regression

** program for the Efron and Breslow methods, coxfit2.c

**

** NOTES: I dropped the strata, offset, and weight variables from

** Therneau's original program.

** THE DATA MUST BE SORTED BY ASCENDING TIME

**

** GLOBALLY DEFINED VARIABLES:

** MAX = Maximum number of ties allowed

** CUTOFF = Switch point for switching from iterating through all

** permutations to random selection of possible orders

** ORDERMAX = Number of randomly selected permutations

**

** LOCALLY DEFINED VARIABLES:

** i,j = Index for covariates = 0,...,nvar-1

** k = Index for possible orders, 1,..., (#ties !)

** person = Index for failure times

** ties = Indicator: 0= all failure times in interval are unique

** 1 = have tied failure times

** orders = Number of possible orders is either (#ties !) or

** ORDERMAX

** start = Saves the original seed for the sampling of random

** orders from the beginning of the first iteration

** perm[MAX]= A permutation of the ordering of the failures in
** an interval

** mark[i] = Mark(i) contains the number of tied deaths at this point,
** for the first person of several tied times. It is zero for
** the second and etc of a group of tied times.

** newbeta = New parameter estimates; the update
** denom = Sum of the risks in the risk set

** org_den = Saves the value of denom when enter an interval with ties
** halving = 1 = doing step halving; 0 = not doing step halving

** a[] = Part of the score function computations
** a2[] = Contribution to the score function for an interval
** cmat2[] = Contribution to imat for an interval

** num_u[] = Part of the numerator of the score function, used in
** computations when there are ties.
** cmat3[] = Used in computing imat when there are ties
** a3[] = Stores what a[] was at the begining of an interval
** with ties
** cmat4[] = Stores what cmat[] was at the begining of an interval
** with ties
** newlk = Contains the new value of the loglikelihood for updated beta
** pl[] = Contribution to the partial likelihood for and interval
** cmat[] = Part of the imat computations(negative of second
** partial derivatives)

** the work arrays are passed as a single
** vector of storage, and then broken out.

*/
#include <math.h>
#include <stdio.h>

#define MAX 100
#define CUTOFF 8
#define ORDERMAX 5000

double **dmatrix();

void notiespl();

long factorial();

void permute();

void ranpermute();

void geofit(maxiter, nusedx, nvarx, time, status, covar2, iseed,
            means, beta, u, imat2, loglik, flag, work,
            eps, sctest)

long *nusedx,
    *nvarx,
    *maxiter,
    *flag,
    *iseed,
    status[];
double *covar2,
    *imat2;
double u[],
    means[],
    *work,
    beta[],
    time[];
double loglik[2],
    *sctest;
double *eps;
```c
{
    register int i, j, k, person;
    int iter, ties;
    int nused, nvar;
    long orders, start;
    int perm[MAX];

    double **covar, **cmat, **imat; /*ragged array versions*/
    double *mark;
    double *a, *newbeta;
    double *a2, **cmat2;
    double *num_u, **cmat3;
    double *a3, **cmat4;
    double denom, org_den, zbeta, risk;
    double temp, temp2;
    double ll[2], newlk[2], pl[2];
    int halving;

    nused = *nusedx;
    nvar = *nvarx;
    /*
    ** Set up the ragged arrays
    */
    covar = dmatrix(covar2, nused, nvar);
    imat = dmatrix(imat2, nvar, nvar);
    cmat = dmatrix(work, nvar, nvar);
    cmat2 = dmatrix(work + nvar*nvar, nvar, nvar);
    a = work + 2*nvar*nvar;
    newbeta = a + nvar;
    a2 = newbeta + nvar;
    mark = a2 + nvar;
    cmat3 = dmatrix(mark + nused, nvar, nvar);
```
\begin{verbatim}
num_u = mark + nused + nvar * nvar;
cmat4 = dmatrix(num_u + nvar, nvar, nvar);
a3 = num_u + nvar + nvar * nvar;

/*
 ** Compute the number of failures in each interval
 */

temp=0;
j=0;
for (i=nused-1; i>0; i--) {
    if (timeCiD==timeCi-l]) {
        j += status Ci;
        temp += status Ci;
        mark[i]=0;
    }
    else {
        mark[i] = j + status[i];
        temp=0; j=0;
    }
}

mark[0] = j + status[0];

/*
 ** Subtract the mean from each covar, as this makes the regression
 ** much more stable
 */

for (i=0; i<nvar; i++) {
    temp=0;
    for (person=0; person<nused; person++) temp += covar[i][person];
    temp /= nused;
    means[i] = temp;
    for (person=0; person<nused; person++) covar[i][person] -=temp;
}

/*
\end{verbatim}
** Initializations for the random sampling of orders

start = *iseed;
for (i=0; i < MAX; i++) {
    perm[i]=0;
}
ties=0;

/**
 * do the initial iteration step
 */

/**
 * Initialize the arrays for the sums of the risks, and the loglikelihood,
 * the score function, the negative of the matrix of second partial derivatives
 * and the working arrays used in computing them
 */
loglik[1] =0;
l1[1]=0;
pl[1]=0;
denom = 0;
org_den = 0;
for (i=0; i<nvar; i++) {
    u[i] =0;
a[i] =0;
a2[i] =0;
    num_u[i]=0;
    a3[i] = 0;
    for (j=0; j<nvar; j++){
        imat[i][j] =0 ;
        cmat[i][j]=0;
        cmat2[i][j] =0;
        cmat3[i][j] =0;
        cmat4[i][j] =0;
        }
}
for (person=mised-l; person >=0; person --){
  if (status[person] == 0) {
    /*
     ** Add the censored observations into the risk set
     */
    zbeta = 0; /* form the term beta*z  (vector mult) */
    risk =0;
    for (i=0; i<nvar; i++)
      zbeta += beta[i]*covar[i][person];
    risk = exp(zbeta);
    denom += risk;
    for (i=0; i<nvcur; i++) {
      a[i] += risk*covar[i][person];
      for (j=0; j<=i; j++)
        cmat[i][j] += risk*covar[i][person]*covar[j][person];
    }
  } /* end of censored portion */
  else{
    if (mark[person] = 1) {
      ties=0;
      /*
       ** There is only one failure in the interval, so there is one
       ** unique contribution to the likelihood.
       */
      notiespl(nvar, (int)mark[person], person, covar, status,
          beta, &denom, ll, a2, cmat2, a, cmat, ties, perm);
      loglik[l] += ll[l];
      for (i=0; i<nvar; i++) {
        u[i] += a2[i];
        for (j=0; j<=i; j++){
          imat[j][i] += cmat2[j][i];
        }
      }
    }
  }
}
} /* end of loop for unique partial likelihood*/
else if (mark[person] > 0){
    ties=1;
    /*
    ** There is more than one failure in the interval
    ** Decide how many possible orderings of the covariates to use.
    */
    if (mark[person] >= CUTOFF) orders = ORDERMAX;
    else orders = factorial((int)mark[person]);
    pl[i] =0;
    for (i=0; i<nvar; i++) {
        num_u[i]=0;
        for (j=0; j<nvar; j++) {
            cmat3[i][j] =0;
        }
    }
    for (k=0; k < orders; k++) {
        /*
        ** Compute a permutation of the orderings
        */
        if (mark[person] >= CUTOFF) ranpermute(perm, (int)mark[person], &start);
        else permute(perm, (int)mark[person], k, orders);
        /*
        ** Save the values of things with the risk set
        ** as it was when entering the interval.
        */
        org_den = denom;
        for (i=0; i<nvar; i++) {
            a3[i] = a[i];
            for (j=0; j<nvar; j++) {

cmat4[i][j] = cmat[i][j];
}

/*
** Compute the contribution to the likelihood and etc
** for this particular interval
*/
notiespl(nvar, (int)mark[person], person, covar, status,
    beta, &denom, ll, a2, cmat2, a, cmat, ties, perm);
pl[i] += ll[i];
for (i=0; i<nvar; i++) {
    num_u[i] += a2[i];
    for (j=0; j<=i; j++){
        cmat3[j][i] += cmat2[j][i];
    }
}
if (k != orders-1){
    /*
    ** After finishing a possible order, set these things
    ** back to what they were before starting analyzing
    **) the interval using a particular ordering unless
    ** it is the last interval being considered.
    */
    denom = org_den;
    for (i=0; i<nvar; i++) {
        a[i] = a3[i];
        for (j=0; j<nvar; j++){
            cmat[i][j] = cmat4[i][j];
        }
    }
}
/*
 ** Update the returned values
 */

loglik[1] += pl[1]/orders;
for (i=0; i<nvar; i++) {
    u[i] += num_u[i] / orders;
    for (j=0; j<=i; j++){
        imat[j][i] += cmat3[j][i] /orders;
    }
}

} /* end of loop for ties */
} /* end of else loop */
} /* end of loop for all people */
/
/**
 ** End of the initial iteration step
 */
/**/

loglik[0] = loglik[1];
/* am I done?
 ** update the betas and test for convergence
 */

for (i=0; i<nvar; i++) /*use 'a' as a temp to save u0, for the score test*/
a[i] = u[i];

*flag= cholesky2(imat, nvar);
chsolve2(imat,nvar,a); /* a replaced by a *inverse(i) */
*sctest=0;
for (i=0; i<nvar; i++)
*sctest += u[i]*a[i];
/
/**
 ** Never, never complain about convergence on the first step. That way,
 ** if someone HAS to they can force one iter at a time.
 */
for (i=0; i<nvar; i++) {  
    newbeta[i] = beta[i] + a[i];  
}
if (*maxiter==0) {
    chinv2(imat,nvar);
    for (i=1; i<nvar; i++)
        for (j=0; j<i; j++)  imat[i][j] = imat[j][i];
    return; /* and we leave the old beta in peace */
}

halving =0 ;  /* =1 when in the midst of "step halving" */
for (iter=1; iter<=*maxiter; iter++) {
    /*
    ** Resetting things which need to be reset at each iteration
    */
    start = *iseed;
    newlk[1] =0;
    ll[1] =0;
    denom = 0;
    for (i=0; i<nvar; i++) {
        u[i] =0;
        a[i] =0;
        a2[i] =0;
        a3[i] =0;
    }
num_u[i]=0;
for (j=0; j<nvar; j++){
    imat[i][j] = 0;
    cmat[i][j]=0;
    cmat2[i][j] =0;
    cmat3[i][j] =0;
    cmat4[i][j] =0;
}
for (person=nused-1; person >=0; person --){
    if (status[person] == 0){
        zbeta = 0; /* form the term beta*z (vector mult) */
        risk =0;
        for (i=0; i<nvar; i++)
            zbeta += newbeta[i]*covar[i][person];
        risk = exp(zbeta);
        denom += risk;
        for (i=0; i<nvar; i++) {
            a[i] += risk*covar[i][person];
            for (j=0; j<i; j++)
                cmat[i][j] += risk*covar[i][person]*covar[j][person];
        }
    } else if (mark[person] == 1){
        ties = 0;
        notiespl(nvar, (int)mark[person], person, covar, status,
            newbeta, &denom, ll, a2, cmat2, a, cmat, ties, perm);
        newlk[i] += ll[1];
        for (i=0; i<nvar; i++) {
            u[i] += a2[i];
            for (j=0; j<i; j++){
                imat[j][i] += cmat2[j][i];
            }
        }
    }
}
} */ end of loop for unique likelihood */

else if (mark[person] > 0) {
    ties = 1;
    if (mark[person] >= CUTOFF) orders = ORDERMAX;
    else orders = factorial((int)mark[person]);
    pl[1] = 0;
    for (i=0; i<nvar; i++) {
        num_u[i] = 0;
        for (j=0; j<nvar; j++) {
            cmat3[i][j] = 0;
        }
    }
    for (k=0; k < orders; k++) {
        if (mark[person] >= CUTOFF) ranpermute(perm, (int)mark[person], &start);
        else permute(perm, (int)mark[person], k, orders);
        org_den = denom;
        for (i=0; i<nvar; i++) {
            a3[i] = a[i];
            for (j=0; j < i; j++) {
                cmat4[i][j] = cmat[i][j];
            }
        }
        notiespl(nvar, (int)mark[person], person, covar, status,
        newbeta, &denom, ll, a2, cmat2, a, cmat, ties, perm);
        pl[1] += ll[1];
        for (i=0; i<nvar; i++) {
            num_u[i] += a2[i];
            for (j=0; j <= i; j++) {
                cmat3[j][i] += cmat2[j][i];
            }
        }
if ( k != orders -1 ){
    denom = org_den;
    for (i=0; i<nvar; i++) {
        a[i] = a3[i];
        for (j=0; j<nvar; j++) {
            cmat[i][j] = cmat4[i][j];
        }
    }
}

} /* end of loop for orders */
newlkCl] += pi[1]/orders;
for (i=0; i<nvar; i++) {
    u[i] += num_u[i] / orders;
    for (j=0; j<=i; j++) {  |
        imat[j][i] += cmat3[j][i]/orders;
    }
}

} /* end of loop for ties */
} /* end of loop for all people */
/* am I done?  */
/** update the betas and test for convergence */
/**
*flag = cholesky2(imat, nvar);
if (fabs(1-(loglik[l]/newlk[l]))<=eps ) { /* all done */
loglik[l] = newlk[l];
chinv2(imat, nvar); /* invert the information matrix */
for (i=1; i<nvar; i++)
    for (j=0; j<i; j++) imat[i][j] = imat[j][i];
for (i=0; i<nvar; i++)
    beta[i] = newbeta[i];
if (halving=1) *flag= 1000; /*didn't converge after all */
maxiter = iter;
return;
}

if (iter==maxiter) break; /*skip the step halving and etc */

if (newlk[i] < loglik[i]) { /*it is not converging ! */
halving =1;
for (i=0; i<nvar; i++)
    newbeta[i] = (newbeta[i] + beta[i]) /2; /*half of old increment */
} else {
    halving=0;
    loglik[i] = newlk[i];
    chsolve2(imat,nvar,u);
    j=0;
    for (i=0; i<nvar; i++) {
        beta[i] = newbeta[i];
        newbeta[i] = newbeta[i] + u[i];
    }
}
} /* return for another iteration */

loglik[i] = newlk[i];
chinv2(imat, nvar);
for (i=1; i<nvar; i++)
    for (j=0; j<i; j++) imat[i][j] = imat[j][i];
for (i=0; i<nvar; i++)
    beta[i] = newbeta[i];
*flag= 1000;
return;
DESCRIPTION: notiespl evaluates the log of Cox partial likelihood and the first partial derivatives (score function) and the negative of the second partial derivatives for a given value of beta the parameter vector for Cox Proportional Hazards Regression. It works for the entire data set if there are no tied failure times or is can compute this entities for a given ordering for a given interval.

FUNCTIONS CALLED: None

INPUTS:
- nvar = Number of covariates
- nused = Number of observations to use in computations
- start = Point in data where the interval starts
- covar = Matrix of covariates
- status = Indicator of status; 1=dead, 0=censored
- beta = Current value of the parameter vector
- ties = Indicator ties=1 indicates the failure times belong to an interval with tied failure times; ties=0 indicates the failure times are in the observed order
- perm = Specifies the ordering of the failures for intervals with tied failure times

The interval is assumed to range from (start) to (nused+start-1)

RETURNED VALUES:
- denom = On entry the sum of the risks over the appropriate risk set, on return includes the additional risk that is added on due to the current interval
**loglik** = loglik[i] returns the contribution to the log partial
likelihood for the current interval (with the current
ordering of failures if they are tied)

**u** = Returns the contribution to the score function (first
partial derivatives of the log partial
likelihood for the current interval (with the current
ordering of failures if they are tied)

**imat** = Returns the contribution to the negative second
partial derivatives of the log partial
likelihood for the current interval (with the current
ordering of failures if they are tied)

**a[i]** = On entry the sum of cov[i]*risk over the risk set which
is part of the derivative of denom, on return includes
the additional risk that is added on due to the current
interval

**cmat[i][j]** = On entry the sum of cov[i]*cov[j]*risk over the risk set
which is part of the second derivative of denom, on return
includes the additional risk that is added on due to the
current interval

**ACKNOWLEDGEMENTS:**

This function is adapted from the Efron method Cox regression program
written by Terry Therneau. I took the portion of the code that evaluates
the log partial likelihood when there were no ties in the data and
re-wrote it into a function.

*/

#include <math.h>
#include <stdio.h>

void notiespl(nvar, nused, start, covar, status,

beta, denom, loglik, u, imat, a, cmat, ties, perm)
int start,
ties,
perm;
long nvar,
nused,
status;
double **covar,
**imat,
beta,
*denom,
loglik[2],
u,
*a,
**cmt;

{
    register int i, j, person;
    int index;
    double zbeta, risk, temp2;
    /**
     * Initializing the returned values to zero */
    /*
     * Initializing the returned values to zero */
    rank = 0;
    risk =0;
    temp2=0;
    loglik[1]=0;
    for (i=0; i<nvar; i++) {
        u[i] =0;
for (j=0; j<nvar; j++) {
    imat[i][j] = 0;
}

for (person=start-1; person>=start; person--) {

    /* Setting the index to be either a permuted value in the case of 
     ** ties or just letting it be the order the data is in in the case 
     ** of no ties 
     */
    if (ties==0){
        index = person;
    }
    else if (ties== 1){
        index = start - 1 + perm[person - start];
    }

    /* Updating the risk set to include failures from the current interval 
     and adding up pieces that add over the risk set. */

    zbeta = 0;       /* form the term beta*z (vector mult) */
    for (i=0; i<nvar; i++)
        zbeta += beta[i]*covar[i][index];
    risk = exp(zbeta);

    *denom += risk;
    for (i=0; i<nvar; i++) {
        a[i] += risk*covar[i][index];
        for (j=0; j<=i; j++)
            cmat[i][j] += risk*covar[i][index]*covar[j][index];
    }
}
if ((ties==1) && (nused>= 7)) rank += person *(covar[0][index] + .5);
/* Compute the returned values for this interval */
if (status[person]==1) {
  loglik[i] += zbeta;
  loglik[i] -= log(*denom);
  for (i=0; i<nvar; i++) {
    u[i] += covar[i][index];
    temp2 = a[i] / *denom;
    u[i] -= temp2;
    for (j=0; j<=i; j++) {imat[j][i] += (cmat[i][j] - temp2 * a[j])/ *denom;
    }
  }
}
return;

/* The following is a collection of functions used in
** the Cox proportional hazards regression */

#include <stdio.h>
#include <string.h>
#include <stdlib.h>
#include <math.h>

/* ran2
*
** DESCRIPTION: Portable Random Number Generator
** Long period ( > 2 * 10^-18 ) random number generator of L'Ecuyer
** with Bays-Durham shuffle and added safeguards
** Returns a uniform random deviate between 0.0 and 0.1 */

** (exclusive of the endpoint values.)

**

** FUNCTIONS CALLED: None

**

** INPUTS:

**

• idum = Address of a negative integer

**

** RETURNS: Returns a uniform random deviate between 0.0 and 0.1

**

(exclusive of the endpoint values.)

**

** ACKNOWLEDGEMENTS:

**

From Numerical Recipes in C: The Art of Scientific Computing

**

2nd ed.

**

** OTHER NOTES:

**

Call with idum a negative integer to initialize; thereafter

**

do not alter idum between successive deviates in a sequence

**

RNMX should approximate the largest floating value that is < 1

*/

#define IM1 2147483563
#define IM2 2147483399
#define AM (1.0/IM1)
#define IMM1 (IM1-1)
#define IA1 40014
#define IA2 40692
#define IQ1 53668
#define IQ2 52774
#define IR1 12211
#define IR2 3791
#define NTAB 32
#define NDIV (1+IMM1/NTAB)
#define EPS 1.2e-7
#define RNMX (1.0-EPS)

double ran2(long *idum)
{
    int j;
    long k;
    static long idum2=123456789;
    static long iy=0;
    static long iv[NTAB];
    double temp;

    if (*idum <= 0){
        if (-(•idum) < 1) •idum =1;
        else •idum = - (•idum);
        idum2 = (*idum);
        for (j=NTAB+7; j>=0; j--){
            k=(•idum)/IQ1;
            •idum=IA1*( •idum - k*IQ1) -IR1*k;
            if (•idum < 0) •idum += IM1;
            if ( j < NTAB) iv[j] = •idum;
        }
        iy = iv[0];
    }
    k=(•idum)/IQ1;
    •idum=IA1*( •idum - k*IQ1) -IR1*k;
    if (•idum < 0) •idum += IM1;
    k = idum2 / IQ2;
    idum2 = IA2*(idum2-k*IQ2) - k*IR2;
    if (idum2 < 0) idum2 += IM2;
j = iy / NDIV;
    iy = iv[j] - idum2;
    iv[j] = *idum;
    if (iy < 1) iy += IMM1;
    if ((temp=AM*iy) > RNMX) return RNMX;
    else return temp;
}

/* permute in file myfunc.c by Becky Benner 5/7/1997 */
/**
 ** DESCRIPTION: This function will produce permutations of
 ** the integers 1 up to intSize which has a max of 10.
 ** If the function is called repeatedly in a loop from
 ** 0 to intSize ! - 1 then the result would be a list
 ** of all the permutations and they are ordered such that
 ** the first place varies the slowest and the last place
 ** varies the fastest.
 **
 ** FUNCTIONS CALLED: None
 **
 ** INPUTS:
 ** intSize = Size of the permutation, the maximum
 ** allowable value is set to be 10.
 ** intWhich = Indicates which permutation to select
 ** from the list of possibles so intWhich
 ** must have a value of 0 to intSize ! - 1.
 ** intFactorial = intSize ! which before entry has been
 ** computed from the factorial function below.
 **
 ** RETURNED VALUES:
 ** perm = array containing the permutation requested
 ** in the form of p[0]...p[intSize-1] which is a
** permutation of 1...intSize

** ACKNOWLEDGEMENTS:
** Most of this algorithm was written by Charles Peterson
**
** LOCAL VARIABLES:
** MAXP = Sets the maximum size of permutation to be 10
** used = Keeps track of the numbers already used in the
** permutation.
*/

#define TRUE 1
#define FALSE 2
#define MAXP 10

void permute(int perm[], int intSize, int intWhich, long intFactorial)
{
    int intIndex,
        intRepeatFactor,
        intTmp1,
        intTmp2,
        intTmp3,
        intValue,
        intDone,
        intLowValue = 0;

    int used[MAXP];

    for(intIndex = 0; intIndex < intSize; intIndex++){
used[intIndex+1] = FALSE;
perm[intIndex] = 0;
}
intRepeatFactor = intSize;

for(intIndex = 0; intIndex < intSize-2; intIndex++){
    intTmp1 = intWhich / (intFactorial/ intRepeatFactor) + 1;
    intValue = intLowValue;

    for(intTmp2 = 1; intTmp2 <= intTmp1; intTmp2++){
        intValue++;
        intDone = 0;
        while(intDone==0){
            intDone = 1;
            for(intTmp3 = 0; intTmp3 < intIndex; intTmp3++)
                if(intValue == perm[intTmp3]){
                    intValue++;
                    intDone = 0;
                }
        }
        if(intValue > intSize){
            intValue = 1;
            intDone = 0;
            while(intDone == 0)
            {
                intDone = 1;
                for(intTmp3 = 0; intTmp3 <= intIndex; intTmp3++)
                    if(intValue == perm[intTmp3]) { intValue++; intDone = 0; }
            }
        }
    }
}
perm[intIndex] = intValue;
used[intValue] = TRUE;
intRepeatFactor *= (intSize - intIndex - 1);
}

intTmp1 = 0;
intTmp2 = 0;
intTmp3 = 0;
for (intIndex = 1; intIndex <= intSize; intIndex++){
    if ((used[intIndex] == FALSE) && (intTmp1 == 0)) {
        intTmp2 = intIndex;
        intTmp1++;
    }
    else if ((used[intIndex] == FALSE) && (intTmp1 > 0)) {
        intTmp3 = intIndex;
    }
}
if ((intWhich % 2 ==0){
    perm[intSize-2] = intTmp2;
    perm[intSize-1] = intTmp3;
}
else if ((intWhich % 2 ==1){
    perm[intSize-2] = intTmp3;
    perm[intSize-1] = intTmp2;
}
return;

/* ranpermut in file myfunc.c by Becky Benner 5/7/1997 */
DESCRIPTION: This function will produce permutations of
the integers 1 up to intSize which has a max of 100.
The permutation is randomly selected in that first
an integer between 1 to intSize. Next an integer is
randomly selected from the remaining integers and so
on until the last integer in the permutation is determined.

FUNCTIONS CALLED: ran2

Note: The function ran2 could be replaced with any random
number generator which produces uniform random numbers

INPUTS:
intSize = Size of the permutation, the maximum
allowable value is set to be 100.
iseed = Address of a negative integer. This value
is passed directly to the ran2 function.

RETURNED VALUES:
perm = array containing the permutation requested
in the form of p[0]...p[intSize-1] which is a
permutation of 1...intSize

ACKNOWLEDGEMENTS:
This function is my implementation of an algorithm
suggested by Dr. Kenneth Koehler

LOCAL VARIABLES:
MAX = largest size of permutation available
rannum = random number which results from calling ran2
avail = Keeps track of the numbers already used in the
permutation.
#define MAX 100

void ranpermute(int perm[], int intSize, int *iseed)
{

    int rannum;
    int i, j;
    int avail[MAX];

    for (j = 1; j <= MAX; j++){
        for (i=intSize-1; i >=0; i--){
            avail[i] = i+1;
        }

        for (i=intSize-1; i >=0; i--){
            rannum = floor(ran2(iseed) * (i+1));
            perm[i] = avail[rannum];
            avail[rannum] = avail[i];
        }
    }

    /* factorial in myfunc.c
    ** DESCRIPTION: Function to compute the factorial
    ** FUNCTIONS CALLED: None
    ** INPUTS: n = an integer, can correctly compute factorials
    ** up to n = 12
    ** RETURNED VALUES: returns the factorial of the inputted n
    ** ACKNOWLEDGEMENTS: Code can be found in any introductory
long factorial(n)

long n;

{  
  if ( n <= 0)
    return 1;
  else
    return n*factorial(n-1);
}
BIBLIOGRAPHY FOR GENERAL INTRODUCTION


