Application of Event Time Analysis to Replacement, Health and Reproduction Data in Dairy Cattle Research

IVER THYSEN

National Institute of Animal Science, Research Center Foulum, 8833 Orum Sonderlyng (Denmark)

(Accepted for publication 28 August 1987)

ABSTRACT


Life data statistical methods are proposed for the analysis of dairy cattle production data representing the time from one event to another. The Kaplan-Meier estimator of survival is described and its applications to dairy cattle data are exemplified with data sets of replacement times, time from calving to first case of mastitis and time from calving to first insemination. All data sets include censored data from cows for which the event had not been observed at the end of lactation or data collection period. A method for modifying replacement times to a standard calving interval is presented. A simple non-parametric test of homogeneity in two samples is described.

INTRODUCTION

Statistical methods for the analysis of life data were originally developed for the purpose of estimating and comparing probabilities of surviving a specified length of time or expected lifetimes. In cattle production, life data methods have been used in studies of replacement of dairy cows by several authors (Cannon and Hansen, 1939; Andrus et al., 1970; Sharma and Singh, 1974; Cobo-Aubreau et al., 1979; Britney et al., 1984; Dohoo and Martin, 1984) and in estimation of genetic parameters of stayability of dairy cows (Famula, 1980; Wolynetz and Binns, 1983; Smith and Quaas, 1984; Smith and Allaire, 1986). Umoh (1982) and Waltner-Toews et al. (1986) studied survival of calves by means of life data methods.

The characteristic property of life data is that the observed variable represents time from one event to another; originally the time was from birth to death, but any well-defined events may be used. Kalbfleisch and Prentice (1980) use the term 'failure time data' in order to extend the statistical methods to,
for example, tests of reliability and durability of manufactured goods. In animal science, acquirement of a specific disease is a 'failure' different from death. Life table methods were used by Agger and Willeberg (1986) to estimate the probability of acquiring subclinical mastitis subsequent to teat damage, and by Waltner-Toews et al. (1986) to estimate the risks of first treatments for scours and pneumonia during the first 20 weeks after birth of calves. The events under study need not necessarily be negative, as is implied by the term 'failure'. Sørensen et al. (1986), for instance, used life data methods to analyse the effects of artificial light during winter in cow houses on time from calving to first insemination. 'Event time data analysis', therefore, may be a more proper term in veterinary epidemiology to ensure neutrality.

There are two main reasons for considering the event time data methods in veterinary epidemiology: (1) a stochastic variable representing time from one event to another will generally not follow the normal distribution (a long tail to the right is usually found) which is required for application of analysis of variance; (2) in many empirical or prospective studies, animals are entering the herd at intervals and may be removed for several reasons, and at the end of the study a number of animals will not have experienced the event of interest (censored data). The statistical methods in event time data analysis are capable of dealing with non-normal distributions, and event incidence rates can be estimated from censored data.

In this paper, emphasis is put on computation and plot of the Kaplan-Meier estimator of survival for a descriptive analysis, and on the log-rank test for comparisons of populations; examples are given concerning the analysis of time of replacement of dairy cows, time from calving to first case of mastitis in dairy cows, time from calving to first insemination and time from birth to diagnosis of pneumonia in calves. Several more advanced methods are described in the statistical literature, but these are considered beyond the scope of this paper.

ESTIMATION OF THE SURVIVOR FUNCTION

Let $T$ be a non-negative random variable representing event time of an animal from a homogenous population. $T$ is further assumed to be discrete e.g., days, which generally will be the case in veterinary epidemiology. The probability distribution of $T$ can be specified in many ways, two of which are the hazard function and the survivor function (Kalbfleisch and Prentice, 1980). The hazard function is defined as the probability of occurrence of the event at some observed time $t_i$ conditional upon survival to that time, that is

$$g(t_i) = P(T = t_i | T \geq t_i)$$

(1)

The survivor function is defined as the probability of surviving time $t_i$

$$F(t_i) = P(T \geq t_i)$$

(2)
The relationship between the two functions is given by

\[
F(t_i) = \prod_{j=1}^{i} (1 - g(t_j))
\]

(i.e., the cumulative product of \((1 - g(t_j)), j=1,...,i\).

Let \(t_1 < t_2 < ... < t_k\) be the ordered event times in a sample of size \(n_0\) from a population with survivor function \(F(t)\), and let \(d_i\) be the number of animals for which the event occurs at \(t_i\) \((i=1,...,k)\). The number of animals at risk at time \(t_i\) then will be \(n_i = n_0 - d_1 - d_2 - ... - d_{i-1}\). A maximum likelihood estimate of \(F(t_i)\) now is given by

\[
F(t_i) = \prod_{j=1}^{i} \left(1 - \frac{d_j}{n_j}\right)
\]

By comparison to (3), it is seen that the estimate (4) is obtained by making the conditional probability of the event at each \(t_i\) agree exactly with the observed relative frequency of the event at that time. The estimate was derived by Kaplan and Meier (1958) and, as a consequence, is often referred to as the Kaplan-Meier estimator.

The standard error (s.e.) of \(F(t_i)\) is calculated by Greenwood’s formula

\[
s.e.(F(t_i)) = F(t_i) \sqrt{\frac{\sum_{j=1}^{i} d_j}{n_j(n_j-d_j)}}
\]

Censored data are accounted for by reducing the number of animals at risk by the number of animals censored prior to each discrete event time. When censoring times are tied with event times, adaptation of the convention that events occur prior to censoring maintains the estimate (4) to be a maximum likelihood estimate. Thus, if \(m_i\) represents the number of animals censored in the interval \(t_{i-1} \leq t < t_i\), then \(n_i = n_0 - m_1 - d_1 - m_2 - ... - d_{i-1} - m_i\).

Several of the authors referred to in the introduction analysed their data with the life table method. The life table is a summary of the survival data grouped in convenient intervals. The survival function is estimated by

\[
F(t_i) = \prod_{j=1}^{i} \left(1 - \frac{d_j}{n_i - 0.5m_i}\right)
\]

The 0.5\(m_i\) term in the denominator is used to adjust for not all \(n_i\) individuals being at risk during the whole of the \(i\)th interval. The standard error is estimated by (5) with \(n_i\) replaced by \(n_i - 0.5m_i\). The choice of intervals may introduce some arbitrariness into the analysis. The Kaplan-Meier estimator should, therefore, be preferred when the exact event times are known.

TIME FROM FIRST CALVING TO REPLACEMENT OF DAIRY COWS

The data in Table I were observed during 36 months in a tie-up cow house that participated in a study on dairy cow housing systems (Østergaard, 1985).
TABLE I

Analysis of the survival of dairy cows (Thysen, 1985a)

<table>
<thead>
<tr>
<th>i</th>
<th>$t_i$</th>
<th>$m_i$</th>
<th>$d_i$</th>
<th>$n_i$</th>
<th>$F_i$</th>
<th>s.e.$(F_i)$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2</td>
<td>3</td>
<td>55</td>
<td>0.945</td>
<td>0.031</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>60</td>
<td>1</td>
<td>1</td>
<td>51</td>
<td>0.927</td>
<td>0.035</td>
</tr>
<tr>
<td>3</td>
<td>163</td>
<td>0</td>
<td>1</td>
<td>50</td>
<td>0.908</td>
<td>0.039</td>
</tr>
<tr>
<td>4</td>
<td>174</td>
<td>1</td>
<td>1</td>
<td>48</td>
<td>0.889</td>
<td>0.043</td>
</tr>
<tr>
<td>5</td>
<td>236</td>
<td>2</td>
<td>2</td>
<td>45</td>
<td>0.850</td>
<td>0.049</td>
</tr>
<tr>
<td>6</td>
<td>272</td>
<td>11</td>
<td>1</td>
<td>32</td>
<td>0.823</td>
<td>0.054</td>
</tr>
<tr>
<td>7</td>
<td>404</td>
<td>4</td>
<td>1</td>
<td>27</td>
<td>0.793</td>
<td>0.060</td>
</tr>
<tr>
<td>8</td>
<td>429</td>
<td>0</td>
<td>1</td>
<td>26</td>
<td>0.762</td>
<td>0.065</td>
</tr>
<tr>
<td>9</td>
<td>473</td>
<td>1</td>
<td>1</td>
<td>24</td>
<td>0.731</td>
<td>0.070</td>
</tr>
<tr>
<td>10</td>
<td>526</td>
<td>2</td>
<td>1</td>
<td>21</td>
<td>0.696</td>
<td>0.075</td>
</tr>
<tr>
<td>11</td>
<td>571</td>
<td>1</td>
<td>1</td>
<td>19</td>
<td>0.659</td>
<td>0.079</td>
</tr>
<tr>
<td>12</td>
<td>637</td>
<td>0</td>
<td>1</td>
<td>18</td>
<td>0.623</td>
<td>0.083</td>
</tr>
<tr>
<td>13</td>
<td>668</td>
<td>0</td>
<td>1</td>
<td>17</td>
<td>0.586</td>
<td>0.086</td>
</tr>
<tr>
<td>14</td>
<td>723</td>
<td>0</td>
<td>1</td>
<td>16</td>
<td>0.549</td>
<td>0.088</td>
</tr>
<tr>
<td>15</td>
<td>766</td>
<td>5</td>
<td>1</td>
<td>10</td>
<td>0.494</td>
<td>0.095</td>
</tr>
<tr>
<td>16</td>
<td>797</td>
<td>0</td>
<td>1</td>
<td>9</td>
<td>0.439</td>
<td>0.099</td>
</tr>
</tbody>
</table>

$i=$ event time index; $t_i=$ time from calving to event (days); $m_i=$ cows censored in $t_{i-1} - t_i$; $d_i=$ cows culled at $t_i$; $n_i=$ cows at risk at $t_i$; $F_i=$ survivor function estimate; s.e.$(F_i)$ = standard error.

Fifty-five heifers entered the herd in that period, 19 of them were culled and 36 remained in the herd until the termination of the study. Each cow contributed to the data with an observation of days from first calving to either culling or the end of the study; the latter constitute the censored data.

The estimates of the survivor function were calculated by eqn. 4 as follows:

\[
F(0) = 1
\]
\[
F(1) = (1 - 3/55) = 0.945
\]
\[
F(2) = 0.945(1 - 1/51) = 0.927
\]

The standard errors were calculated by eqn. 5. It is convenient to store the sum included in eqn. 5 at each culling time before the expression is evaluated.

The estimates of the survivor function and the standard errors, calculated at each distinct culling time, are given in Table I.

In Fig 1, the estimates are plotted against time. It is seen that the survivor function is discontinuous at the observed event times and constant between event times. The plot represents the data visually and provides information on, for example, the expected median survival time in the herd until replacement and expected proportions of cows surviving 1 and 2 years, which can be read off the axes at the broken lines.

The Kaplan-Meier estimates of the probability of surviving 1 and 2 years in
the herd can be read off Table I at \( t_6 = 272 \) and \( t_{14} = 723 \) days, and they are 82 and 55%, respectively. The 95% confidence intervals of the estimates are calculated as 1.96 s.e.(\( F_t \)) and are \( \pm 11 \) and \( \pm 18\% \), respectively. If event time methods had not been used, it would have been necessary to exclude 20 heifers entering the herd during the last 12 months of the study in order to obtain an unbiased estimate of the probability of surviving 1 year in the herd. Seven of the remaining 35 heifers were culled during the first year in the herd, and the estimated probability of surviving 1 year would have been \( 28/35 = 80\% \), with a 95% confidence interval of \( 1.96 \sqrt{(0.8)(0.2)/35} = \pm 13\% \). The corresponding probability of surviving 2 years would have been \( 15/25 = 60 \pm 19\% \).

**STANDARDIZED CALVING INTERVALS**

The cyclical life of the dairy cow (calving – lactation – dry period – calving) causes the probability of any particular event to vary considerably over time. Due to variations in the length of the cycle (calving interval) between cows, a survivor function based on the age of the cow (from first calving) results in an unclear picture of the cyclical variation.

This problem may be overcome by a standardization to median calving interval and calculating time from first calving to the replacement by

\[
t = MCI \cdot (LCN - 1) + \min(MCI, t_{LCN})
\]

where \( MCI = \) median calving interval, \( LCN = \) last calving number and \( t_{LCN} = \) days from last calving to the event.
If, say, a cow is culled 217 days after the third calving and the median calving interval in the herd is 365 days, then eqn. 7 yields $t=947$ days; if the cow is culled at any time in the third lactation later than 365 days after calving, then $t=1095$.

Figure 2 shows survival curves for three herds being observed over 5 years. Time from entering the herd at first calving to replacement was calculated by eqn. 7 with $MCI=365$ days, and the survivor function estimates were calculated by eqn. 4 (Thysen, 1985b). The cyclical variation is especially evident in Herd C.

**TIME FROM CALVING TO FIRST CASE OF MASTITIS**

Mastitis is very significantly related to the lactational cycle of the dairy cow, which can be revealed by an appropriate analysis of time from calving to first case of mastitis. In Fig. 3, cumulative incidence curves of clinical mastitis are shown for three herds with different levels of mastitis, the incidence at time $t$ was estimated by $1 - F(t)$ (eqn. 4). Data from cows that were culled, or did not have clinical mastitis until the subsequent calving or the end of the observation period, were considered censored at the maximum observed time from calving. If a cow was treated <10 days before calving, the subsequent lactation was excluded from the data (Blom et al., 1985). In these curves, the standardization of the calving interval also included the dry period that was fixed to start at 48 weeks postpartum (w.p.p.) and end at 54 w.p.p. A case of clinical mastitis occurring while a cow was lactating and later than 48 w.p.p. was taken
Fig. 3. Cumulative incidence of mastitis in relation to days postpartum in three dairy herds (Blom et al., 1985).

to happen just prior to the standardized time of drying-off, and a case of clinical mastitis in the dry period was taken to happen at 48 w.p.p. plus the number of days from the observed time of drying-off that cow.

The patterns of the incidence of clinical mastitis were similar for the three herds, even though they had different levels of mastitis; approximately 50% of first cases of clinical mastitis occurred within the first 2 weeks postpartum; the risk of a first case was low in mid-lactation, but rose sharply at the time of drying-off.

REPRODUCTION DATA

Median calving to first service and calving to conception intervals are often included as targets in dairy herd fertility monitoring schemes (Esslemont et al., 1985). Median intervals calculated from cows being served or conceiving may, however, seriously overestimate the reproductive status of the herd, if a large proportion of the cows are not served or conceiving at all. Information concerning median intervals, therefore, is usually supplemented with proportions of cows not being served or pregnant at the end of given intervals from calving.

By means of event time analysis, the complete information can be provided in one analysis and presented in one chart. Figure 4 shows the cumulative percentage of cows being served by days postpartum \((1-F(t), \text{eqn. 4})\) in two herds (Thysen and Hindhede, 1985). The chart provides information on days
from calving to first allowable service and the percentage of cows being served at least once at any time thereafter. A submission or heat detection rate also may be estimated from these curves, or from the underlying estimates of $1 - F(t)$, by the proportion of cows being served during any appropriate 21-day interval. If this interval is taken to begin at the time postpartum when 10% of the cows are served, it can be seen in Fig. 4 that 55% of the cows in Herd I had been served 21 days later. Hence, the submission rate was $(55 - 10)/0.9 = 50\%$. In Herd II the submission rate was 28\%.

Cows that were not served before culling or before the data collection period ended were regarded as censored. Analysis of censored data assumes independent censoring, i.e. the cause of censoring cannot be that the censored individuals appeared to be at unusually high or low risk (Kalbfleisch and Prentice, 1980). In reproduction, the censoring mechanism is clearly not independent of the performance of the individual cow, as the probability of a cow being culled increases with the time that has passed since calving without a service. The consequence of this is that the graphs in Fig. 4 tend to overestimate the percentage of cows being served, but it is reasonable to believe that this is not biasing the results until mid-lactation because that is when culling for infertility begins.

COMPARISON OF SURVIVAL CURVES

It is often of interest to determine whether two or more samples could have arisen from identical survivor functions. One commonly used test is the log-
rank test, which is a non-parametric test that has a similarity to the familiar $\chi^2$ test for homogeneity in categorical data in the sense that the test statistic is a function of the difference between the observed number of events and the expected number of events under the null hypothesis. The log-rank test of equality of two survival curves will be demonstrated with an example in the following paragraph; a discussion of the theoretical justification of the test and the generalization to more than two samples can be found in Kalbfleisch and Prentice (1980).

To compare two survival curves, form a pooled sample of the original samples and let $t_i, i=1,...,r$, denote the ordered event times in the pooled sample. Let $d_i, d_{1i}$ and $d_{2i}$ denote the number of animals for which the event occurs at time $t_i$ in the pooled sample and the two individual samples, respectively; accordingly, let $n_i, n_{1i}$ and $n_{2i}$ denote the number of animals at risk at $t_i$ and $m_i$, $m_{1i}$ and $m_{2i}$ denote the number of censored observations in the interval $t_{i-1} \leq t < t_i$. The expected number of events at time $t_i$ in Sample 1 now is the number of animals at risk in Sample 1 multiplied by the observed hazard rate in the pooled sample

$$w_{1i} = n_{1i}(d_i/n_i)$$

The log-rank statistic $v$ is calculated by summation of the differences between the observed and the expected number of events over event times

$$v = \sum_{i=1}^r d_{1i} - w_{1i}$$

The variance of the log-rank statistic is calculated by

$$V = \sum_{i=1}^r n_{1i}(n_i - n_{1i})d_i(n_i - d_i)/n_i^2(n_i - 1)$$

The test statistic for homogeneity is

$$c = v/V$$

which can be treated as a $\chi^2$ statistic with 1 degree of freedom. It should be noted that the two samples yield identical values of the test statistic.

The test is illustrated with data from an experiment by Østergaard et al. (1986): 1-day-old Holstein Friesian calves were stocked either continuously in a large calf house or in batches (all in–all out) in a sectioned calf house, and observed for pneumonia during the first 4 months of life. Time from birth to diagnosis of pneumonia or to either death or removal from the calf house without diagnosis of pneumonia (censored observations) was recorded, and cumulative incidence curves of pneumonia were estimated.

A subset of the data consisting of observations on 12 calves on each treatment is shown in Table II, where the contributions to $v_i$ and $V$ at each event time are also shown. The $\chi^2$ statistic has value $c = 2.888^2/2.794 = 2.985$, which is just significant at the 10% level. The cumulative curves of pneumonia for the two samples are shown in Fig. 5.
TABLE II

Example of the log-rank test of homogeneity of two survival curves: age at diagnosis of pneumonia in calves (Østergaard et al., 1986)

<table>
<thead>
<tr>
<th>Pooled sample</th>
<th>Sample 1: continuous stocking</th>
<th>Sample 2: batch stocking</th>
<th>$u$</th>
<th>$V$</th>
</tr>
</thead>
<tbody>
<tr>
<td>$n_i$</td>
<td>$d_{i1}$</td>
<td>$m_{i1}$</td>
<td>$n_{i1}$</td>
<td>$d_{i2}$</td>
</tr>
<tr>
<td>27</td>
<td>1</td>
<td>24</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>49</td>
<td>1</td>
<td>23</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>72</td>
<td>1</td>
<td>22</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>79</td>
<td>2</td>
<td>21</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>89</td>
<td>1</td>
<td>19</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>90</td>
<td>1</td>
<td>18</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>101</td>
<td>1</td>
<td>17</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>113</td>
<td>2</td>
<td>15</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>117</td>
<td>1</td>
<td>9</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>123</td>
<td>1</td>
<td>6</td>
<td>2</td>
<td>0</td>
</tr>
</tbody>
</table>

See text for explanation of symbols.

Fig. 5. Cumulative incidence curves of pneumonia in calves stocked continuously or in batches (Østergaard et al., 1986).
REFERENCES


