T E C H N I C A L

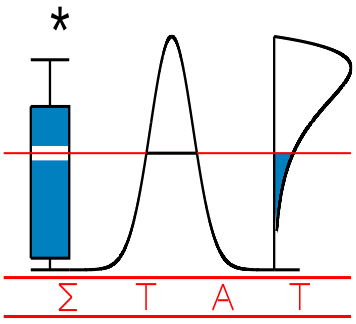
R E P O R T

0645

MODELLING INTERVAL-CENSORED, CLUSTERED COW UDDER QUARTER INFECTION TIMES THROUGH THE SHARED GAMMA FRAITLY MODEL

GOETHALS K., AMPE B., BERKVENS D., LAEVENS H., JANSSEN P.,

and L. DUCHATEAU



I A P S T A T I S T I C S

N E T W O R K

INTERUNIVERSITY ATTRACTION POLE

http://www.stat.ucl.ac.be/IAP

Modelling interval-censored, clustered cow udder quarter infection times through the shared gamma frailty model

Klara Goethals[1*], Bart Ampe[1], Dirk Berkvens[2], Hans Laevens[1], Paul Janssen[3] and Luc Duchateau[1]

[1]Department of Physiology and Biometrics, Faculty of Veterinary Medicine, Ghent University, Salisburylaan 133, 9820 Merelbeke, Belgium.

[2]Institute of Tropical Medicine, Nationalestraat 155, 2000 Antwerp, Belgium.

[3] Hasselt University, Center for Statistics, Agoralaan, 3590 Diepenbeek, Belgium.

[*] *Corresponding author, email:* Klara.Goethals@UGent.be

SUMMARY. Time to infection data are often simultaneously clustered and interval-censored. First, the time to infection is not known exactly; it is only known to have occurred within a certain interval. Second, observations often occur in clusters. As a consequence the independence assumption does not hold. We propose here an extension of the shared gamma frailty model to handle the interval-censoring and the clustering simultaneously. It is shown that the frailties can be integrated out analytically and therefore the marginal likelihood can be maximised to obtain parameter estimates. The method is applied to a longitudinal study with periodic follow-up on dairy cows to investigate the effect of parameters at the cow level (e.g. parity) and parameters that can change within the cow (e.g. front or rear udder quarter) on time to infection. Dairy cows were assessed monthly for the presence of a bacterial infection at udder quarter level, thus generating interval-censored data, and the four udder quarters are obviously clustered within the cow. Based on simulations we show that ignoring the interval-censored nature of the data can lead to biased parameter estimates.

KEY WORDS: Dairy cows; Interval-censoring; Shared gamma frailty model; Udder infection.

1 Introduction

Infectious disease data can be analysed most efficiently by survival analysis techniques if infection times of individual units are available. However, ordinary survival analysis techniques often need to be extended due to the particular data structure. We investigate a data set that has two characteristics that require extension of the currently available survival analysis techniques if they have to be dealt with simultaneously. First, infectious disease data are often hierarchically structured, with observation units grouped in clusters, so that the event times within a cluster can not be assumed to be independent. Second, the time to infection is not known exactly; it is only known that the infection happened between the last negative and first positive test, therefore the infection time is interval-censored (Finkelstein, 1986). The infectious disease data set considered in this paper, the mastitis data, corresponds to infection times of individual cow udder quarters with a bacteria (Laevens et al., 1997). Obviously, the four udder quarters are clustered within a cow (Adkinson et al., 1993) and udder quarters are sampled only monthly, generating interval-censored data. We want to investigate the effect of covariates that change within cow (e.g. front and rear udder quarters) and covariates that change between cows (e.g. parity, i.e., the number of previous calvings). But also the correlation between udder infection times within a cow is of interest because it is a measure of the infectivity of the agent which causes the disease (Barkema et al., 1997). To handle the problem of interdependence for right-censored observations different models have been used among which the frailty model is the standard. For the analysis of independent interval-censored data a number of inferential techniques have been described in the literature (Radke, 2003; Collet, 1994). But analysis methods for settings where observations are at the same time correlated and interval-censored received less attention. Bellamy et al. (2005) proposed a method to fit clustered interval-censored data assuming a normal distribution for the random effect and integrating out the random effects numerically using Gaussian Quadrature.

In Section 2 we study an extension of the parametric shared gamma frailty model to interval-censored

data. We show that a closed form of the marginal likelihood can be obtained by integrating out the gamma-distributed frailties. In Section 3, we demonstrate the method for our example. In Section 4, the performance of the method is evaluated based on a simulation study. Conclusions are given in the last section.

2 The parametric shared gamma frailty model with interval-censored data

Consider the following proportional hazard frailty model

$$h_{ij}(t) = h_0(t) w_i \exp\left(\boldsymbol{x}_{ij}^t \boldsymbol{\beta}\right), \quad i = 1, \ldots, N, j = 1, \ldots, n_i \tag{1}$$

with $h_{ij}(t)$ the hazard at time t for udder quarter j of cow i, $h_0(t)$ the baseline hazard at time t, $\boldsymbol{x}_{ij}$ the vector of covariates for the corresponding udder quarter and $\boldsymbol{\beta}$ the vector of covariate effects. We further assume that the frailties $w_1, \ldots, w_N$ are independent realizations from a one parameter gamma density with mean one and variance θ

$$f_W(w_i) = \frac{w_i^{\frac{1}{\theta}-1} \exp(\frac{-w_i}{\theta})}{\theta^{\frac{1}{\theta}} \Gamma(\frac{1}{\theta})}. \tag{2}$$

In (1) the frailty w_i acts multiplicatively on the hazard rate and is gamma-distributed. The model formulation in Bellamy et al. (2005) expresses the frailty term as $\exp b_i$ with b_i the random effect working additively on the log hazard rate and assumes a normal distribution for the random effect (see Section 3 for a comparison of these two models). In what follows we write θ for the variance of the frailty and σ^2 for the variance of the random effect. In the further discussion we assume a Weibull distributed baseline hazard, i.e., $h_0(t) = \lambda\gamma t^{\gamma-1}$.

The udder quarter infection times in the mastitis study are either right-censored or interval-censored. Cluster i consists of $n_i = 4$ observations (one observation per udder quarter) of which r_i are right-censored and d_i are interval-censored. We write R_{ij} to denote the right-censored infection time for udder quarter j of cow i. If the information on the infection time is subject to interval-censoring we denote the lower and upper bounds of the interval as L_{ij} and U_{ij}. Per cluster we define two sets of indices according to whether the infection time is right-censored or interval-censored:

$$R_i = \{j \in \{1,2,3,4\} : T_{ij} > R_{ij}\}$$
$$D_i = \{j \in \{1,2,3,4\} : L_{ij} < T_{ij} \leq U_{ij}\},$$

with $R_i \cap D_i = \phi$ and $R_i \cup D_i = \{1,2,3,4\}$ and T_{ij} the real but unobservable infection time.

Assuming that the censoring process is not informative for the survival process the conditional data likelihood contribution for cluster i consists of the product of differences of the conditional survival functions evaluated at the observed lower and upper time point for the interval-censored quarters and of the conditional survival function evaluated at the censoring time for the right-censored quarters

$$L_i(\beta, \lambda, \gamma, \theta \mid w_i) = \prod_{j \in R_i} S(R_{ij}) \prod_{j \in D_i} \{S(L_{ij}) - S(U_{ij})\}, \tag{3}$$

which results in

$$\begin{aligned} L_i(\boldsymbol{\beta}, \lambda, \gamma, \theta \mid w_i) &= \exp\left\{-\sum_{j \in R_i} \lambda R_{ij}^{\gamma} w_i \exp\left(\boldsymbol{x}_{ij}^t \boldsymbol{\beta}\right)\right\} \\ &\quad \times \prod_{j \in D_i} \left[\exp\left\{-\lambda L_{ij}^{\gamma} w_i \exp\left(\boldsymbol{x}_{ij}^t \boldsymbol{\beta}\right)\right\} - \exp\left\{-\lambda U_{ij}^{\gamma} w_i \exp\left(\boldsymbol{x}_{ij}^t \boldsymbol{\beta}\right)\right\}\right] \\ &= \exp\left(-w_i C_i\right) \times \prod_{j \in D_i} \left\{\exp\left(-w_i L_{ij}^*\right) - \exp\left(-w_i U_{ij}^*\right)\right\}, \end{aligned} \tag{4}$$

with $C_i = \sum_{j \in R_i} \lambda R_{ij}^{\gamma} \exp\left(\boldsymbol{x}_{ij}^t \boldsymbol{\beta}\right)$, $L_{ij}^* = \lambda L_{ij}^{\gamma} \exp\left(\boldsymbol{x}_{ij}^t \boldsymbol{\beta}\right)$ and $U_{ij}^* = \lambda U_{ij}^{\gamma} \exp\left(\boldsymbol{x}_{ij}^t \boldsymbol{\beta}\right)$.

To be able to write down the product in the second factor of (4) in a general way, we define the following column vector $\boldsymbol{a}_i$ of length 2^{d_i} with d_i the number of elements in D_i

$$\boldsymbol{a}_i = ({}_c a_{ik})_{k=1}^{2^{d_i}} = \bigotimes_{j \in D_i} \begin{pmatrix} \exp(-w_i L_{ij}^*) \\ -\exp(-w_i U_{ij}^*) \end{pmatrix}.$$

The first element of this column vector, for example, is $\exp\left(-w_i \sum_{j \in D_i} L_{ij}^*\right)$.

The last element is $\pm \exp\left(-w_i \sum_{j \in D_i} U_{ij}^*\right)$ with a positive sign if the number of U_{ij}^*'s in the sum of the exponent is even and a negative sign if the number is odd. The number of U_{ij}^*'s in a_{ik} will be denoted as n_{ik}.

Expression (4) can then be rewritten as

$$L_i\left(\beta, \lambda, \gamma, \theta \mid w_i\right) = \exp\left(-w_i C_i\right) \left(\sum_{k=1}^{2^{d_i}} a_{ik} \right).$$

This expression still contains the unobserved frailty term w_i. We can however integrate out the frailty term which is assumed to have the gamma density (2), we then obtain the marginal likelihood

$$\begin{aligned} L_i\left(\beta, \lambda, \gamma, \theta\right) &= \int_0^\infty \frac{w_i^{(1/\theta - 1)} \exp\left(-w_i/\theta\right)}{\theta^{1/\theta} \Gamma(1/\theta)} \exp\left(-w_i C_i\right) \left(\sum_{k=1}^{2^{d_i}} a_{ik} \right) dw_i \\ &= \frac{1}{\theta^{1/\theta} \Gamma(1/\theta)} \sum_{k=1}^{2^{d_i}} \int_0^\infty w_i^{(1/\theta - 1)} \exp\left\{ -w_i \left(C_i + \frac{1}{\theta} \right) \right\} a_{ik} dw_i \\ &= \sum_{k=1}^{2^{d_i}} \frac{(-1)^{n_{ik}}}{\left(C_i + \frac{1}{\theta} + \log p_{ik}\right)^{1/\theta} \theta^{1/\theta}}, \end{aligned} \tag{5}$$

with $\boldsymbol{p}_i$ the column vector:

$$\boldsymbol{p}_i = ({}_c p_{ik})_{k=1}^{2^{d_i}} = \bigotimes_{j \in D_i} \begin{pmatrix} \exp(L_{ij}^*) \\ \exp(U_{ij}^*) \end{pmatrix}.$$

To obtain the full marginal likelihood we take the product of the N cluster-specific marginal likelihoods $\prod_{i=1}^{N} L_i(\boldsymbol{\beta}, \theta, \lambda, \gamma)$. Maximum likelihood estimates can then be obtained by maximising the full marginal likelihood using, for instance, the Newton Raphson procedure. As the second partial derivatives can be obtained for all parameters (see Web Appendix A), an explicit expression for the information matrix is available, from which an estimate of the asymptotic variance-covariance matrix can be obtained.

3 Example

The importance of mastitis in dairy cows has been addressed previously and mastitis control is an important component of dairy herd health programs because udder infections are closely associated with reduced milk yield and impaired milk quality (Seegers, Fourichon and Beaudeau, 2003). A total of 100 cows were monthly screened at the udder quarter level for bacterial infections from the time of parturition until the end of the lactation period. Observations can be right censored if no infection has occurred before the end of the lactation period, which is roughly 300 days but different for every cow, or if the cow is lost to follow-up during the study, for example due to culling. Due to the periodic follow-up, udder quarters that experience an event are interval-censored with lower bound the last visit with a negative test and upper bound the first visit with a positive test.

In the analysis, two types of covariates are considered. Cow level covariates take the same value for every udder quarter of the cow (e.g. number of calvings or parity). Several studies have shown that prevalence as well as incidence of intra mammary infections increases with parity (Vecht, Wisselink and Defize, 1989; Weller, Saran and Zeliger, 1992). Several hypotheses have been suggested to explain these findings, e.g. teat end condition deteriorates with increasing parity (Neijenhuis et al., 2001). Because the teat end is a physical barrier that prevents organisms from invading the udder, impaired teat ends makes the udder

more vulnerable for intra mammary infections. For simplicity in the analysis, parity is dichotomized into primiparous cows (one calving) and multiparous cows (more than one calving). Udder quarter level covariates change within the cow (e.g. position of the udder quarter, front or rear). The difference in teat end condition between front and rear quarters has also been put forward to explain the difference in infection status (Adkinson et al., 1993; Barkema et al., 1997; Schepers et al., 1997). In total 317 out of 400 udder quarters were infected during the lactation period.

The parameter estimates obtained from the method proposed in the previous section and the naive models are shown in Table 1. The infection time is given in days, but as too small values for the estimate of the parameter λ typically lead to convergence problems, we transformed the time to infection from days to quarters of a year through the formula $t_Q = 4/365.25 * t_D$. Therefore the estimate $\hat{\lambda}$ in Table 1 refers to quarters of a year rather than days.

For both covariates the parameter estimate $\hat{\gamma}$ is above 1, and the hazard is thus increasing with time. The hazard ratio of multiparous cows versus primiparous cows is $\exp(0.3139) = 1.37$ with 95% confidence interval [0.72;1.88]. The hazard ratio of front versus rear udder quarters is $\exp(0.1798) = 1.20$ with 95% confidence interval [0.94;1.52]. The estimate for θ is 1.8; the corresponding estimate for Kendall's tau (Kendall, 1938) is $\hat{\theta}/(\hat{\theta} + 2) = 0.4736$ (Oakes, 1989). Thus, infection times within the cow are highly correlated.

The proposed method is now compared to the naive method of converting the interval-censored data to exact event time data by either taking the midpoint or the upper bound of the interval. Although using the midpoint gives us similar results (parameter estimates of θ, λ and γ are only slightly higher) for both covariates (see Table 1), imputation of the upper bound has a large effect on the parameter estimates $\hat{\theta}$, $\hat{\lambda}$ and $\hat{\gamma}$. Especially the overestimation of γ is eye-catching and leads to a more rapidly increasing hazard compared to the hazard obtained using imputation of midpoint or using the exact method based on interval-censored data. This can be seen clearly in Figure 1 in which the estimated hazard functions

for the three models investigating the difference between front and rear udder quarters are depicted for a cow with frailty equal to one. The choice of the upper bound as exact event time makes that no events take place within the first 30 days after calving. Therefore the model based on imputation of the upper bound leads to a faster increasing hazard function to accommodate for the fact that the hazard rate should be as low as possible in the first 30 days.

It is also interesting to compare our results with the estimates obtained from the method proposed by Bellamy et al. (2005). We consider the following model

$$h_{ij}(t) = h_0(t) \exp(b_i) \exp\left(\boldsymbol{x}_{ij}^t \boldsymbol{\beta}\right), \quad i = 1, \ldots, N, j = 1, \ldots, n_i \tag{6}$$

with $h_0(t) = \lambda\gamma t^{\gamma-1}$ and $b_i \sim \mathrm{N}\left(0, \sigma^2\right)$.

Since a normal distribution is assumed for the random effects b_i, the frailties follow a lognormal distribution and it is no longer possible to obtain a closed form expression for the marginal likelihood by integrating out the frailties exactly. So Bellamy et al. (2005) used Gaussian Quadrature to integrate out the frailties and then maximised the marginal likelihood. Compared to Bellamy et al. (2005) we use the proportional hazards (PH) model representation instead of the accelerated failure time (AFT) model representation (see Web Appendix B for the program based on the nlmixed procedure of SAS), but after appropriate parameter transformation, the PH and AFT models lead to exactly the same solution with $\hat{\sigma}^2 = 2.9136$, $\hat{\lambda} = 0.3205$, $\hat{\gamma} = 2.0084$ and $\hat{\beta} = 0.1765$ for the model investigating the difference between front and rear udder quarters.

It is not straightforward to compare the gamma frailty model (1) with model (6) with normally distributed random effects. The frailties corresponding to the random effects with mean equal to zero in the last model do not have mean one. In this particular case, the mean is estimated by $\exp\left(0.5\hat{\sigma}^2\right) = 4.29$.

A good practice to compare the two hazard models is to interpret the models in terms of a medically relevant quantity such as the median time to infection (m_i). Both the random effects model and the

frailty models induce heterogeneity in median time to infection between cows. The density function for the median time to infection in the frailty model is given by (Duchateau and Janssen, 2005)

$$f_{m_i}(m) = \alpha \left(\frac{\log 2}{\theta \lambda \exp\left(\boldsymbol{x}_{ij}^t \boldsymbol{\beta}\right)} \right)^{1/\theta} \frac{1}{\Gamma\left(1/\theta\right)} \times \left(\frac{1}{m}\right)^{1+\frac{\alpha}{\theta}} \exp\left(-\frac{\log 2}{\theta m^{\alpha} \lambda \exp\left(\boldsymbol{x}_{ij}^t \boldsymbol{\beta}\right)} \right). \tag{7}$$

In case of normally distributed random effects the density function for m_i is (Legrand et al., 2005)

$$f_{m_i}(m) = \frac{\alpha}{m_i \sqrt{2\pi\sigma^2}} \exp\left(-\frac{1}{2\sigma^2} \left(\ln\left(\frac{\ln 2}{m_i \lambda \exp\left(\boldsymbol{x}_{ij}^t \boldsymbol{\beta}\right)} \right) \right)^2 \right). \tag{8}$$

The two density functions for the model with the difference between front and rear udder quarters as covariate are shown in Figure 2. The two density functions look rather similar, but the gamma frailty model puts more emphasis on the peak, whereas the model with normally distributed random effects puts more emphasis on the skewness.

4 Simulation study

To evaluate the performance of our proposed model, a simulation study was done. Analogous to the data example 1000 datasets consisting of 100 clusters with 4 observations per cluster were simulated with parameter values equal to parameter estimates obtained in the example. The frailties (w_i) were generated from the one-parameter gamma density (2) with $\mathrm{E}(w_i) = 1$ and $\mathrm{Var}(w_i) = \theta = 1.8$. The data were simulated from the frailty model (1) assuming Weibull distributed event times with λ equal to 0.9, γ equal to 1.9 and β equal to 0.2. A binary covariate x takes the value 1 for the first two observations in a cluster and 0 for the other two.

Asynchronous intervals of 30 days are created around the simulated infection time as follows: first for each cow the number of days she was in lactation before the first visit was simulated from the uniform distribution with a minimum of 1 and a maximum of 29. Visits are held at fixed time points (0-30-60-

90-....) but since each cow entered the study at a different moment, namely the first day she was in lactation, the endpoints of the intervals are adjusted to the number of days in lactation. The end of the study was set at one year so that udder quarters with simulated infection time longer than one year become right-censored observations. The upper bound of their interval is used as the censoring time.

For each of the 1000 datasets three models were fitted: the model proposed in Section 2 using the interval-censored data and the two naive models ignoring the interval-censoring and imputing the midpoint or upper bound as exact event time.

The mean of the 1000 obtained estimates for the parameters θ, λ, γ and β is compared with their true values and differences between the three models are investigated. Standard errors are obtained by taking the inverse of the Hessian matrix at the end of the optimisation procedure. The mean of the estimated standard errors and the empirical standard error obtained from the 1000 datasets is also calculated. Finally, we also determine the coverage, defined as the percentage of the 1000 datasets that contains the true population parameter within their 95 % confidence interval. The results of the simulation suggest that the estimates obtained with our proposed model and by imputation of the midpoint are close to the true population parameters of interest (see Table 2). For the upper bound imputation, however, the estimate of λ is biased downward and the estimate of γ upward. The coverage is good if the interval-censored nature of the data is taken into account or if imputation of the midpoint is used. As can be expected because of the large bias for λ and γ, coverages for these parameters are unacceptable when the upper bound imputation is used.

Based on these simulations, it might seem that our new technique has no advantage over imputation of the midpoint. However, this is not always the case. For instance, consider the same simulation setting as before ($\lambda = 0.9$, $\beta = 0.2$, $\theta = 1.8$, 30-day intervals) but change the value of the parameter γ to 0.5. Changing the value of the parameter γ from 1.9 to 0.5 means that the hazard is no longer increasing but decreasing over time. At the start of the study all udder quarters are at risk and, in case of an increasing

hazard, few events take place in the beginning and a lot of udder quarters are still at risk towards the end of the study when more events take place. Therefore a lot of information is available throughout the study and is used to obtain parameter estimates. For a decreasing hazard ($\gamma < 1$) a lot of events take place in the beginning leaving only few udder quarters at risk near the end of the study. So, when you ignore the interval-censored nature of the data in this setting there is not enough information left to obtain adequate parameter estimates. As can be seen in Table 3 the exact method performs well in estimating all parameters including γ, but the techniques of imputing the midpoint or upper bound both fail in estimating the parameter γ and imputation also performs worse compared to the exact method in estimating the other parameters. For the considered simulation studies it is clear that the exact method outperforms the two methods based on imputation.

5 Conclusions

In this paper we propose a shared gamma frailty model for clustered, interval-censored data. Although we use a Weibull baseline hazard, the method can easily be extended to other parametric forms of the baseline hazard. Assuming a gamma distribution for the frailty with mean one and variance θ enables us to integrate out the frailties analytically and to obtain a closed form expression for the marginal likelihood, which can then be maximised with some optimisation procedure (R-program is available from Web Appendix B) to obtain parameter estimates. Furthermore exact expressions for the second derivatives of the likelihood (see Web Appendix A) and thus estimates for the variances of the parameters can be obtained by inverting the matrix of second derivatives.

In the example we compare our technique to the technique proposed by Bellamy et al. (2005). They assume a normal distribution for the random effects. Under this assumption no closed form of the likelihood can be obtained and frailties are integrated out using Gaussian Quadrature. Some of the parameters appearing in the two models can be linked (γ and β) and the estimates for these parameters

are comparable. To link the λ parameter in the proposed model to parameters in the model proposed by Bellamy et al. (2005) is more difficult. This is due to the specification of the cluster effects in terms of normally distributed random effects with mean zero, i.e. a lognormal distribution at the frailty level, but with a mean different from one. It is therefore not straightforward to compare these two hazard functions and we can expect large differences between them for large values of the variance of the lognormal and gamma distributions (Therneau and Grambsch, 2000). Indeed the larger the value of the variance parameter the more different the densities are. The two models can however be meaningfully compared when the models are translated in terms of the density function of the median infection time. The two models result in quite comparable density functions.

The first simulation setting show that accurate estimates are obtained using the proposed technique and imputation of the midpoint. However, in the second simulation setting where the parameter γ is smaller than one, imputation of the midpoint fails. Using the upper bound as an exact event time leads to biased estimates especially for λ and γ in both simulation settings. The simulation studies show that our technique outperforms the imputation techniques.

Supplementary Materials

Web Appendices referenced in Sections 2, 3 and 5 , the data and the programs are available under the Paper Information Link at the Biometrics website http://www.tibs.org/biometrics.

Acknowledgements

The first author acknowledges the financial support of the Research Fund of Ghent University, Ghent, Belgium (grant no. B/04953/01). The research of Luc Duchateau and Paul Janssen was supported by the Interuniversity Attraction Poles research network P5/24 of the Belgian State (Federal Office for Scientific,

Technical and Cultural Affairs.

References

Adkinson, R.W., Ingawa, K.H., Blouin, D.C., Nickerson, S.C. (1993). Distribution of clinical mastitis among quarters of the bovine udder. *Journal of Dairy Science* **76**, 3453-3459.

Barkema, H.W., Schukken, Y.H., Lam, T.J.G.M., Galligan, D.T., Beiboer, M.L., Brand, A. (1997). Estimation of interdependence among quarters of the bovine udder with subclinical mastitis and implications on the analysis. *Journal of Dairy Science* **80**, 1592-1599.

Bellamy, S., Li, Y., Ryan, L., Lipsitz, S., Canner, M. and Wright, R. (2005). Analysis of clustered and interval censored data from a community-based study in asthma. *Statistics in Medicine* **23**, 3607-3621.

Collet, D. (1994). *Modelling survival data in medical research*. London: Chapman & Hall.

Duchateau, L. and Janssen, P. (2005). Understanding heterogeneity in generalized mixed and frailty models. *The American Statistician* **59**, 143-146.

Finkelstein, D.M. (1986). A proportional hazards model for interval-censored failure time data. *Biometrics* **42**, 845-854.

Kendall, M.G. (1938). A new measure of rank correlation. *Biometrika* **30**, 81-93.

Laevens, H., Deluyker, H., Schukken, Y.H., De Meulemeester, L., Vandermeersch, R., De Meulenaere, E. and De Kruif, A. (1997). Influence of parity and stage of lactation on the somatic cell count in bacteriologically negative dairy cows. *Journal of Dairy Science* **80**, 3219-3226.

Legrand, C., Ducrocq, V., Janssen, P., Sylvester, R. and Duchateau, L. (2005). A Bayesian approach to jointly estimate centre and treatment by centre heterogeneity in a proportional hazards model. *Statistics in Medicine* **24**, 3789-3804.

Neijenhuis, F., Barkema, H. W., Hogeveen, H. and Noordhuizen, J. P. T. M. (2001). Relationship between teat end callosity and occurrence of clinical mastitis. *Journal of Dairy Science* **84**, 2664-2672.

Oakes, D. (1989). Bivariate survival models induced by frailties. *Journal of the American Statistical Association* **84**, 487-493.

Radke, B.R. (2003). A demonstration of interval-censored survival analysis. *Preventive Veterinary Medicine* **59**, 241-256.

Schepers, A.J., Lam, T.J.G.M., Schukken, Y.H., Wilmink, J.B.M. and Hanekamp, W.J.A. (1997). Estimation of variance components for somatic cell counts to determine thresholds for uninfected quarters. *Journal of Dairy Science* **80**, 1833-1840.

Seegers, H., Fourichon, C. and Beaudeau, F. (2003). Production effects related to mastitis and mastitis economics in dairy cattle herds. *Veterinary Research* **34**, 475-491.

Therneau, T.M. and Grambsch, P.M. (2000). *Modeling survival data: extending the Cox model.* New York. Springer Verlag. p.234.

Vecht, U., Wisselink, H. J. and Defize, P. R. (1989). Dutch national mastitis survey. The effect of herd and animal factors on SCC. *Netherlands Milk and Dairy Journal* **43**, 425.

Weller, J. I., Saran, A. and Zeliger, Y. (1992). Genetic and environmental relationships among somatic cell count, bacterial infection, and clinical mastitis. *Journal of Dairy Science* **75**, 2532-2540.

Table 1: Parameter estimates and their standard error (SE) for time to infection with parity resp. front or rear udder quarters as covariate, using the proposed method (Exact), midpoint (MP) and upperbound (UB) of the interval as exact event times and Gaussian Quadrature (GQ)

	$\hat{\theta}/\hat{\sigma}^2$ (SE)	$\hat{\lambda}$ (SE)	$\hat{\gamma}$(SE)	$\hat{\beta}$ (SE)
Proportional hazards model with parity as covariate				
Exact	1.7718 (0.3031)	0.8108 (0.2087)	1.9239 (0.1099)	0.3139 (0.3299)
MP	1.7927 (0.3043)	0.8379 (0.2145)	1.9791 (0.1064)	0.3167 (0.3284)
UB	1.8921 (0.3126)	0.5441 (0.1418)	2.4036 (0.1300)	0.2463 (0.3339)
GQ	0.7130 (0.1287)	0.2620 (0.2126)	2.0044 (0.1151)	0.4939 (0.3716)
Proportional hazards model with front-rear udder quarters as covariate				
Exact	1.7836 (0.3033)	0.8956 (0.1653)	1.9287 (0.1098)	0.1798 (0.1219)
MP	1.7981 (0.3041)	0.9264 (0.1713)	1.9807 (0.1060)	0.1774 (0.1194)
UB	1.8999 (0.3125)	0.5753 (0.1042)	2.4080 (0.1297)	0.1848 (0.1195)
GQ	0.7224 (0.1303)	0.3205 (0.2017)	2.0084 (0.1151)	0.1765 (0.1229)

Table 2: Average of estimated model parameters and their standard error (SE) from 1000 simulated datasets using the proposed method (Exact), midpoint (MP) and upperbound (UB) of the interval as exact event times. True values for the parameters are given by $\lambda = 0.9$, $\beta = 0.2$, $\theta = 1.8$ and $\gamma = 1.9$. Empirical standard errors and coverage is given on the second and third row resp.

	$\hat{\theta}$(SE)	$\hat{\lambda}$(SE)	$\hat{\gamma}$(SE)	$\hat{\beta}$(SE)
	empirical SD	empirical SD	empirical SD	empirical SD
	coverage	coverage	coverage	coverage
Exact	1.8050 (0.2845)	0.9061 (0.1593)	1.8913 (0.0998)	0.1978 (0.1215)
	0.2921	0.1584	0.1029	0.1236
	93.7	93.6	94.4	94.7
MP	1.7615 (0.2752)	0.8911 (0.1530)	1.8894 (0.0932)	0.1945 (0.1196)
	0.2832	0.1524	0.0947	0.1214
	92.4	92.5	94.2	94.6
UB	1.8801 (0.2877)	0.6029 (0.1047)	2.2680 (0.1116)	0.2015 (0.1203)
	0.2927	0.1021	0.1120	0.1262
	95.7	23.4	6	93.7

Table 3: Average of estimated model parameters and their standard error (SE) from 1000 simulated datasets using the proposed method (Exact), midpoint (MP) and upperbound (UB) of the interval as exact event times. True values for the parameters are given by $\lambda = 0.9$, $\beta = 0.2$, $\theta = 1.8$ and $\gamma = 0.5$. Empirical standard errors and coverage is given on the second and third row resp.

	$\hat{\theta}$(SE)	$\hat{\lambda}$(SE)	$\hat{\gamma}$(SE)	$\hat{\beta}$(SE)
	empirical SD	empirical SD	empirical SD	empirical SD
	coverage	coverage	coverage	coverage
Exact	1.8419 (0.3456)	0.9165 (0.1714)	0.4923 (0.0401)	0.1989 (0.1454)
	0.3585	0.1699	0.0393	0.1454
	92.7	94.5	94.2	95.3
MP	2.1413 (0.3721)	0.8781 (0.1689)	0.7353 (0.0431)	0.2123 (0.1436)
	0.3974	0.1808	0.0446	0.1559
	89.7	90.0	0	93.4
UB	2.1563 (0.3733)	0.7087 (0.1349)	0.8811 (0.0518)	0.2111 (0.1434)
	0.3979	0.1395	0.0558	0.1556
	89.3	62.1	0	93.5

Figure 1: Hazard functions for time to infection based on parameter estimates of the proposed method accommodating for interval censoring (Exact), and of the method using imputation with the midpoint (MP) and upperbound (UB). The left panel refers to the front udder quarters, the right panel to the rear udder quarters.

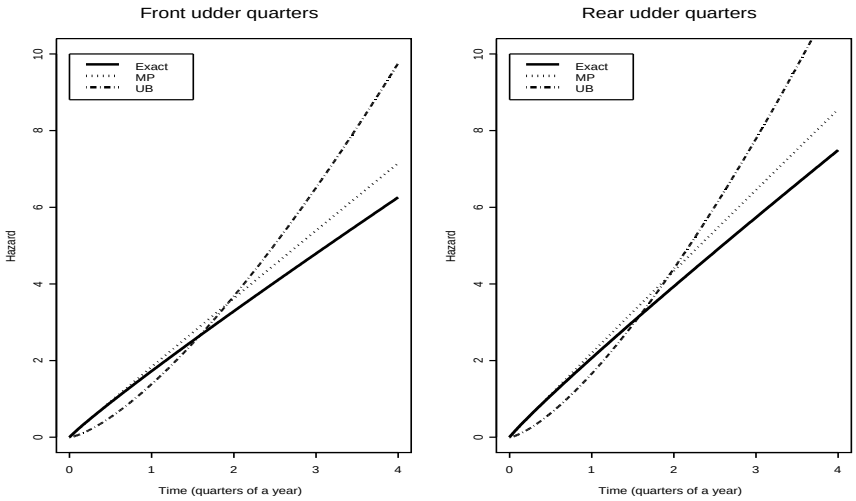


Figure 2: Density functions for median time to infection for front udder quarters with a gamma frailty (full line), and a normal random effect (dotted line)