Survival Analysis Applied to Genetic Evaluation for Female Fertility in Dairy Cattle

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ABSTRACT

The objective of this research was to study whether survival analysis results in a more accurate genetic evaluation for female fertility traits compared with the usual methodology based on linear models. The fertility trait studied was interval between calving and last insemination. A stochastic simulation describing the reproductive cycle of first-parity cows was done, in which true breeding values for conception rate were created. A model containing effects of sire and herd was used both with survival analysis and with mixed linear model analysis to predict sire breeding values. Correlations between true breeding values for conception rate and breeding values for calving to last insemination predicted by the best survival analysis model or the best linear model were 0.77 and 0.68, respectively. The results showed that when pregnancy status is known, survival analysis is a better method than linear models for genetic evaluation of conception rate when using observations on the interval between calving and last insemination.

(Key words: female fertility, genetic evaluation, survival analysis)

Abbreviation key: CLI = interval between calving and last insemination, CR = conception rate, PBV = predicted breeding value, TBV_{CR} = true breeding value for conception rate, VWP = voluntary waiting period.

INTRODUCTION

Poor reproductive performance is one of the most common reasons for culling in dairy herds (Dürr, 1997; Pryce et al., 1997; Swedish Dairy Association, 2002). The main costs associated with low fertility are higher insemination costs, lower production per day and, espe-

cially, higher replacement costs due to increased culling. Good female fertility is characterized by cows that return to cyclicity soon after calving, show strong signs of estrus, have a high probability of becoming pregnant when inseminated at the correct time, and have the ability to carry the resulting fetus to term. Among the potential measures that can be used to describe this complex trait, this study emphasizes the interval between calving and last insemination (**CLI**, also called days open). The trait CLI is a measure that is a combination of return to cyclicity, expression of estrus, and ability to conceive (conception rate). If insemination dates are available, CLI can be used in breeding programs, which is the case in some countries (Mark et al., 2001).

With field data, the pregnancy status of cows is not always available and thus one cannot be sure if cows have conceived (Weller and Ron, 1992; Roxström, 2001). However, even if pregnancy information is available, linear model methodology, the method most frequently used for the genetic evaluation of fertility, has the disadvantage that it cannot properly distinguish between pregnant and nonpregnant cows. Hence, records of pregnant and nonpregnant cows have to be treated alike (as is commonly done for interval from calving to last insemination), or the records of nonpregnant cows have to be excluded (as is commonly done for calving interval) or extended by projection. Culling for reproduction creates another problem. The worse a bull's daughter fertility is, the larger the proportion of daughters culled for reproductive failure. Thus, sires are evaluated without correct information on their daughters with poor fertility (these daughters either have missing information or observed intervals that are shorter than true intervals). Therefore, such bulls appear to be better than they really are and this is expected to lead to less efficient selection.

Survival analysis is an alternative method for analyzing reproductive traits recorded as time intervals (Lee et al., 1989; Eicker et al., 1996; Harman et al., 1996; Allore et al., 2001). Survival analysis is a statistical

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method for studying the occurrence and timing of events, where the outcome variable corresponds to a measure of time elapsed from a starting point until the occurrence of a certain event (Lee, 1992). The length of this interval is not always known, because competing events may occur before the occurrence of the event under study. For example, in our case, cows may have been culled, sold, or the study may have stopped before the cows conceived. One of the main advantages of survival analysis is that it can retain the information from cows that are culled before conception or not pregnant by the time the data recording was completed. Thus, records from pregnant (uncensored) and nonpregnant (censored) cows can be treated jointly and included in the analysis, making proper use of all the available information. Within the field of fertility in dairy cattle, survival analysis has been applied to study: 1) the effects of diseases on days to conception (Lee et al., 1989; Harman et al., 1996b), 2) the relationship between BCS and postpartum reproductive efficiency (Suriyasathaporn et al., 1998), and 3) the effect of early lactation milk yield on days open (Harman et al., 1996a). So far, no research using genetic models with survival analysis has been published for fertility traits.

The objective of this study was to investigate by simulation whether the analysis of CLI using survival analysis results in a more accurate genetic evaluation for conception rate than do the commonly used approaches based on linear models.

MATERIALS AND METHODS

A simulation was done to create phenotypic observations for CLI, some of which were censored observations, that is, cows that did not get pregnant and were culled. To avoid the possibility that the simulation itself would favor any of the ensuing statistical analysis methods, we did not simulate breeding values directly for CLI. Rather, we created 3 underlying traits: milk production, interval between calving and first ovulation, and conception rate. Then we added the effect of decision-making of farmers, such as number of inseminations allowed and voluntary waiting period. We then simulated the reproductive performance of each individual and ended up with the trait that we were interested in studying: CLI.

Simulated Data

Each replicate of the simulated data consisted of 60,000 first-parity cows, daughters of 400 unrelated sires distributed over 1200 herds. The herd size was fixed to 50 cows. The average number of daughters per sire was 150 (SD = 12.3), ranging from 104 to 201

Table 1. Heritability and genetic correlations assumed for the simulated traits (diagonal = heritability; below diagonal = genetic correlation; above diagonal = environmental correlation).

	305-d milk production	CFO	Conception rate
305-d milk production	0.30	0.00	0.00
CFO	0.10	0.20	0.00
Conception rate	-0.10	0.00	0.05

CFO = Interval between calving and first ovulation.

daughters. Fifty replicates were done. Three traits were simulated: 305-d milk production (kg), interval between calving and first ovulation (d), and conception rate (CR, %). The mean phenotypic values were 8000 kg (SD 1000) and 28 d (SD 15) for milk production and interval between calving and first ovulation, respectively.

Conception rate was simulated as a binary trait with an underlying normally distributed liability for conception with mean zero and standard deviation of unity [$\sim N(0,1)$]. Zero was chosen as the threshold; hence, all phenotypic values above 0 corresponded to pregnant cows (50% CR). Heritabilities and genetic and environmental correlations among the traits are shown in Table 1. The heritability of the interval between calving and first ovulation was chosen according to the estimates for the interval from calving to commencement of luteal activity reported by Darwash et al. (1997), Veerkamp et al. (1997), and Royal et al. (2002). For CR, we assumed a heritability value somewhat higher than the values found in the literature, which were estimated with linear model methods, because we simulated CR on the underlying scale. Herd variances as proportion of the phenotypic variance were 9% for the 3 traits. The phenotypic value for each trait was created as: phenotypic value = mean + herd effect + breeding value ($\frac{1}{2}$ sire breeding value + $\frac{1}{2}$ dam breeding value + Mendelian sampling) + environmental value.

Simulation Process

The simulation of the reproductive cycle is summarized in Figure 1. For all herds, the voluntary waiting period (VWP; the first part of the lactation during which no insemination occurs) was set to 8 wk and the heat detection rate to 60%. Heat detection was drawn from a uniform distribution between 0 and 1; if the value was below 0.6, the heat was assumed to be detected. For each herd a maximum number of inseminations (MAXHERD) was set as the integer part of a random draw from the distribution $\sim N(5,1)$. Within herd, the maximum number of inseminations (MAXINS) for each cow was calculated according to its milk yield deviation from herd mates as the integer part of (MAXHERD) +

Figure 1. Simulation process of the reproductive cycle of a first-parity cow. CR = Conception rate; nins = number of inseminations; maxins = maximum number of inseminations; maxwait = days from calving to first ovulation $\times$ maxins $\times$ 21 d. The hexagons indicate observations for CLI.

$0.0015 \times (\text{milk yield deviation, kg})$. High-producing cows were thus given the chance to have more inseminations before being culled. A maximum waiting period was also calculated for each cow as $\text{MAXWAIT} = (\text{phenotype for calving to first ovulation}) + (\text{MAXINS}) \times (21 \text{ d})$. The interval between 2 ovulations (estrous cycle) was sampled from a normal distribution [the integer part of $\sim N(21,4)$], based on the estimates reported by Royal et al. (2000). The environmental component of the phenotype for liability of conception rate was resampled in each estrous cycle. When drawing from the normal distributions, only positive values were accepted (as it happened, negative values were never drawn).

Trait Definition

In survival analysis, the CLI for a pregnant cow was defined as the interval from calving to the last known

Figure 2. Frequency distribution for days between calving and last insemination (for one replicate).

insemination, and the observation was considered as uncensored because conception was the outcome of interest.

For a nonpregnant cow, the observation was considered censored. Cows were culled for reproductive reasons only. To be culled, the cow either had had its maximum number of inseminations without becoming pregnant or the MAXWAIT was exhausted without it becoming pregnant. The CLI was calculated from the last known insemination. For those cows that were never detected in heat, and thus never inseminated, CLI was calculated from the maximum waiting period (MAXWAIT) (approximately 0.8% of the records).

For the linear model analysis, CLI was defined in the same way, except that we could not distinguish between pregnant or nonpregnant cows.

Description of Simulated Data Set

About $15.3 \pm 0.06\%$ of the records were censored, i.e., nonpregnant cows. The average for CLI was 104.2 d (SD 39.0). The average number of inseminations was 1.81 (SD 1.10). The mean failure time was 98 d after calving, and the mean censoring time was 138 d after calving. We corroborated the values of the variables created in the simulation with field data. The average number of days for CLI and the number of inseminations was similar to values reported by Lee et al. (1989) and Roxström (2001).

Figure 2 shows the distribution of CLI. As shown, the distribution was skewed and nonnormal. The time scale started at d 56 because we set a VWP of 8 wk for all cows. About 50% of the observations had an interval less than 95 d.

Survival Analysis

The following proportional hazards model was used for the analysis of CLI:

$$\lambda(t) = \lambda_0(t) \exp \{ \text{herd}_i + \text{sire}_j \} \quad [1]$$

where $\lambda(t)$ = hazard of a cow of getting pregnant; $\lambda_0(t)$ = baseline hazard function; herd_i = random effect of herd i , assumed to follow a log-gamma (γ) distribution; sire_j = random effect of sire j . Sire effects were assumed to follow a normal distribution with variance σ_s^2 . No relationship among sires was assumed.

Three models were analyzed using expression [1]: one Cox and 2 Weibull models. The Cox model (model S1) does not assume a distributional form of the baseline hazard function in expression [1] and defines a semi-parametric regression model.

For the Weibull models (model S2 and S3), a parametric form is assumed for the baseline hazard function in expression [1]; where $\lambda_0(t) = \lambda \rho (\lambda t)^{\rho-1}$, with positive scale parameter λ and positive shape parameter ρ . In model S3, the origin of the time interval analyzed was shifted to avoid a long early period without events (to account for the VWP). The new time scale (t^*) was defined as $t^* = t - 55$. This value of 55 d was chosen because the VWP was 56 d. When we tested different values (e.g., 56, 55, ..., 50 d) by regressing the log of the Kaplan-Meier estimates against the log of time, d 55 had the best fit. To evaluate the ability of survival models to account for censoring, an extra analysis was done, similar to model S3 with the only difference that all the records were considered as uncensored (model S4).

To validate that the Weibull distribution properly fitted the data, Kaplan-Meier curves were created. The suitability of the Weibull model was assessed visually from the plot of the log of the Kaplan-Meier estimates [nonparametric estimate of the survivor curve $S(t)$] against the logs of time (Figure 3). If the assumption holds, a straight line should be obtained. Two plots are shown: a) the time period analyzed starts at day of calving, and b) the time period analyzed starts at d 55 after calving. In a), the relationship results in approximately a straight line, except at the beginning of the period analyzed where no cows get pregnant; therefore it can be assumed that a Weibull distribution reasonably fits the data, at least after the VWP. In b), when the time scale was shifted such that the origin reflects when failures actually start, a straight line was obtained over the whole time scale.

Linear Model Analysis

Using the mixed linear model, the following model was used:

Figure 3. Graphical test of the Weibull assumption: linear regression of $\ln[-\ln S(t)]$ on $\ln(t)$. $S(t)$ = Kaplan-Meier estimates of the survivor function at time t : a) starting from day of calving; b) starting from d 55 after calving.

$$y_{ijk} = \mu + \text{herd}_i + \text{sire}_j + e_{ijk} \quad [2]$$

where y_{ijk} = CLI or Log CLI of cow k , in the herd i , daughter of sire j ; herd_i = random effect of herd i , assumed to follow a normal distribution with variance σ_{herd}^2 ; sire_j = random effect of sire j ; and e_{ijk} = error term. Sire effects were assumed to follow a normal distribution with variance σ_s^2 . No relationship among sires was assumed.

Three models were analyzed using expression [2]: model L1 included all the records (pregnant and non-pregnant cows) where records are treated alike, model L2 included all the records as in model L1, but we used the log transformation of CLI (Log CLI), and model L3 used CLI and excluded the nonpregnant cows from the analysis (about 15% of the records).

Table 2. Estimates of heritability and variance components from survival analysis and mixed linear model (mean and standard error based on 50 replicates).

Method ¹	Model	Heritability	Sire variance	Herd variance	Residual variance
SA	S1: Cox	0.038 ± 0.001	0.012 ± 0.000	0.088 ± 0.001	
	S2: Weibull	0.056 ± 0.001	0.019 ± 0.000	0.119 ± 0.001	
	S3: Weibull origin shifted	0.037 ± 0.001	0.012 ± 0.000	0.086 ± 0.001	
LM	L1: All records	0.040 ± 0.001	15.207 ± 0.253	105.402 ± 0.869	1402.731 ± 2.161
	L2: Log transformed	0.035 ± 0.001	0.001 ± 0.000	0.008 ± 0.000	0.117 ± 0.000
	L3: Excluding nonpregnant cows	0.024 ± 0.001	7.580 ± 0.185	49.842 ± 0.493	1209.067 ± 1.777

¹LM = Mixed linear model; SA = survival analysis.

The Survival Kit V3.12 (Ducrocq and Sölkner, 1998) and DMU (Jensen and Madsen, 1994) were used for the survival analysis and linear model analysis, respectively. Variance components and heritabilities were estimated in both analyses.

The heritability for the linear model was calculated as: $\frac{4\sigma_s^2}{\sigma_s^2 + \sigma_{herd}^2 + \sigma_e^2}$. For the survival analysis, equivalent heritability was defined as (Yazdi et al., 2002): $\frac{4\sigma_s^2}{\sigma_s^2 + \sigma_{herd}^2 + \frac{1}{1-c}}$ where c is the proportion of censored records ($c = 0.153$), σ_{herd}^2 is the herd variance calculated as $\sigma_{herd}^2 = \text{trigamma}(\gamma)$. The use of the equivalent heritability allows a direct comparison of the heritabilities for the 2 approaches.

Model Comparison

Three approaches were used to compare the methods: 1) Pearson correlations (SAS Institute, 1999) between predicted breeding values (PBV) based on CLI and true breeding values for conception rate (TBV_{CR}), 2) comparison of average true genetic merit of bulls selected based on their PBV (best 10% and worst 10%), and 3) the proportions of the truly best or worst 10% of bulls that were identified to be in the best or worst 10% based on PBV from each method.

RESULTS

Results from Statistical Analyses

The estimated Weibull parameter ρ was 2.70 for model S2 and 1.13 for model S3. The heritabilities, sire, herd, and residual variances estimated with survival analysis and linear models are presented in Table 2.

Table 3 shows the correlation between TBV_{CR} and PBV for CLI for the different models analyzed. Correlations of TBV for CR with PBV from survival analysis were higher than corresponding correlations with PBV from the linear model. Within the survival analysis

models, the Cox model and model S3 had the highest correlation with TBV_{CR}. For the linear model analysis when the log of CLI was used (model L2), the correlation with TBV_{CR} was slightly higher compared with model L1. When the information of nonpregnant cows was excluded from the analysis (model L3), the correlation of PBV with TBV_{CR} was even lower. In the survival model, when all the records were treated as uncensored (model S4, results not shown), the correlation between PBV and TBV_{CR} was very similar to the linear model analysis (model L1) (0.665 ± 0.004).

The average true genetic merit (TBV_{CR}) of bulls selected on PBV (top 10% and bottom 10% bulls for fertility) is also presented in Table 3. The average TBV_{CR} of extreme bulls for fertility shows that survival models were better to identify best and worst bulls for fertility. These results confirmed the results from the correlations between PBV and TBV_{CR}.

Another way to compare the results of the 2 methods is to calculate how large was the proportion of those bulls that are ranked among the top 10% (or bottom 10%) TBV_{CR}, that are among the top 10% (or bottom 10%) when ranked on the PBV from the 2 methods (Table 4). Survival analysis (model S3) ranked 51% of the bulls correctly in the top 10%, whereas the linear model (model L1) ranked only 42% correctly. The corresponding differences for the worst bulls were similar.

DISCUSSION

The estimated Weibull parameter ρ was 2.7 and 1.13 for model S2 and S3, respectively. The difference is a reflection of the early long period without risk of pregnancy in model S2. Even when the origin was shifted (model S3), ρ was still greater than 1, which indicates that the hazard of conception increased slightly with time (even though we simulated a constant CR). In our simulation, we had variation in the time from calving to first ovulation. Some cows would therefore have their first ovulation after d 56. This would lower the risk of getting pregnant very early, thus increasing the relative risk with time.

Table 3. Correlations between true breeding values for conception rate (TBV_{CR}) and predicted breeding values (PBV), and average TBV_{CR} of animals selected on PBV (best and worst 10%) from survival analysis and mixed linear model (mean and standard error based on 50 replicates).

Method ¹	Model	Correlation	Average TBV_{CR}	
			Best 10%	Worst 10%
SA	S1: Cox	0.767 $\pm$ 0.003	0.292 $\pm$ 0.004	-0.308 $\pm$ 0.004
	S2: Weibull	0.747 $\pm$ 0.003	0.285 $\pm$ 0.004	-0.299 $\pm$ 0.004
	S3: Weibull origin shifted	0.769 $\pm$ 0.003	0.291 $\pm$ 0.004	-0.309 $\pm$ 0.004
LM	L1: All records	0.677 $\pm$ 0.004	0.253 $\pm$ 0.004	-0.272 $\pm$ 0.004
	L2: Log transformed	0.685 $\pm$ 0.004	0.258 $\pm$ 0.004	-0.276 $\pm$ 0.004
	L3: Excluding nonpregnant cows	0.516 $\pm$ 0.006	0.198 $\pm$ 0.005	-0.202 $\pm$ 0.004

¹LM = Mixed linear model; SA = survival analysis.

The Cox model (model S1) had a higher correlation with TBV_{CR} than Weibull model S2. A feature of the Cox model is that no assumption is made about the form of the baseline hazard function. This higher correlation could be explained by the fact that Cox fits the data better at the beginning of the period analyzed. But when the origin was shifted (model S3), the correlation with TBV_{CR} was as high as for the Cox model.

In the simulation, we assumed a VWP of 56 d for all cows and herds. In field data, the VWP would be more flexible and vary between herds and possibly cows, and the appropriate scale shift should be tested (as in Figure 3).

If we compare the Weibull models S2 and S3, we can see from the lower correlation between TBV_{CR} and PBV that model S2 is not the better model. Mainly, this result occurred because it does not make sense to assume a nonzero hazard before d 56. This inconsistency also has an effect on the estimates of ρ and h^2 , which became inflated in model S2. Nevertheless, model S2 was still superior to the linear models for predicting breeding values for CR. In practice, therefore, a Weibull model with any reasonable scale shift can be expected to perform almost as well as the more computationally demanding Cox model.

In the linear model analysis, when part of the information was excluded (model L3), the correlation of PBV

with TBV_{CR} was the lowest. Therefore, if the linear model is used, it is better not to discard the nonpregnant cows. When the data was log transformed (model L2), the correlation with TBV_{CR} was only slightly higher compared with model L1. The log transformation of the data did not improve the results much, because the distribution of the data started so abruptly after the VWP (Figure 2).

The results show that survival analysis is a better method than the linear model for prediction of the genetic merit of bulls for CR when using observations on CLI. Correlations between TBV and PBV were higher for survival analysis than for LM. If selection were carried out on these PBV, this advantage of the survival analysis would also translate into greater genetic progress. This statement was also confirmed by the higher proportion of bulls that rank among the top bulls (or bottom) for CR. The main advantage of survival analysis is the ability to account for censoring. When all the records were treated as uncensored (model S4), we obtained almost the same correlation as was obtained with the linear model. Survival analysis makes proper use of information that would be otherwise discarded or treated as uncensored.

More simplified scenarios regarding variation within and between herds and without the effect of milk production on the maximum number of insemination were studied (results not shown), and survival analysis was always better than the linear model. In fact, the more complex the simulation, the greater was the advantage of survival analysis.

One potential drawback with using survival analysis is that it is currently not possible to use it together with other traits (e.g., production or other fertility traits) in a multiple-trait analysis. Such an analysis would use all the available information simultaneously, while at the same time accounting for potential bias due to culling or selection over time. However, recent work has shown that it is indeed possible to analyze a survival trait together with a normally distributed continuous

Table 4. Percentage of bulls of those that are among the best 10% (or worst 10%) (40 bulls) when ranked on true breeding value for fertility (TBV_{CR}) that are among the best 10% (or worst 10%) when ranked on predicted breeding values (mean based on 50 replicates).

Method ¹	Model	Best 10% bulls	Worst 10% bulls
SA	S1: Cox	51.0	54.0
	S2: Weibull	49.3	52.3
	S3: Weibull origin shifted	51.0	54.5
LM	L1: All records	42.0	45.8
	L2: Log transformed	43.0	46.8
	L3: Excluding nonpregnant cows	32.5	32.8

¹LM = Mixed linear model; SA = survival analysis.

trait or a threshold trait using a Bayesian approach and applying Gibbs sampling (Damgaard, 2005).

To take full advantage of survival analysis, it is necessary to have information on whether the cow is pregnant or not (e.g., confirmed by a veterinarian). Information from slaughterhouses on culled cows (pregnant or not at slaughter) could be useful as well. It is hoped that information on fertility (actual VWP, service period, pregnancy status) will be more accurately recorded in the future. Having this information and using survival analysis could be expected to give more than 10% greater genetic response than using the linear models typically used today.

CONCLUSIONS

Correlations between true breeding values for conception rate and breeding values predicted with survival analysis were higher than the corresponding correlations from the linear model. The results show that survival analysis is a better method than linear model to predict the genetic merit of bulls for conception rate when analyzing the interval between calving and last insemination. The main reason for this is that survival analysis accounts for censoring. If selection were carried out on these PBV, the higher precision would translate into higher genetic progress.

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REFERENCES

- Allore, H. G., L. D. Warnick, J. Hertl, and Y. T. Gröhn. 2001. Censoring in survival analysis: A simulation study of the effect of milk yield on conception. *Prev. Vet. Med.* 46:223–234.
- Damgaard, L. H. 2005. Quantitative genetic analysis of survival, linear Gaussian and ordered categorical traits. Ph.D. Thesis, Dept. Large Anim. Sci, The Royal Vet. and Agric. Univ., Frederiksberg, Denmark.
- Darwash, A. O., G. E. Lamming, and J. A. Woolliams. 1997. Estimation of genetic variation in the interval from calving to postpartum ovulation of dairy cows. *J. Dairy Sci.* 80:1227–1234.
- Ducrocq, V., and J. Sölkner. 1998. The Survival Kit—A Fortran package for the analysis of survival data. *Proc. 6th World Congr. Genet. Appl. Livest. Prod., Armidale, Australia.* 27: 447–448.
- Dürr, J. W. 1997. Genetic and phenotypic studies on culling in Quebec Holstein cows. Ph.D. Diss., McGill Univ., Montreal, Canada.
- Eicker, S. W., Y. T. Gröhn, and J. A. Hertl. 1996. The association between cumulative milk yield, days open, and days to first breeding in New York Holstein cows. *J. Dairy Sci.* 79:235–241.
- Harman, J. L., G. Casella, and Y. T. Gröhn. 1996. The application of event-time regression techniques to the study of dairy cow interval-to-conception. *Prev. Vet. Med.* 26:263–274.
- Harman, J. L., Y. T. Gröhn, H. N. Erb, and G. Casella. 1996a. Event-time analysis of the effect of 60-day milk production on the parturition-to-conception interval in dairy cows. *Am. J. Vet. Res.* 57:634–639.
- Harman, J. L., Y. T. Gröhn, H. N. Erb, and G. Casella. 1996b. Event-time analysis of the effect of season of parturition, parity, and concurrent disease on parturition-to-conception interval in dairy cows. *Am. J. Vet. Res.* 57:640–645.
- Jensen, J., and P. Madsen. 1994. DMU: A package for the analysis of multivariate mixed models. *Computing Strategies and Software. Proc. of 5th World Congr. Genet. Appl. Livest. Prod., Guelph, Canada.* 22:45–46.
- Lee, L. A., J. D. Ferguson, and D. T. Galligan. 1989. Effect of disease on days open assessed by survival analysis. *J. Dairy Sci.* 72:1020–1026.
- Lee, E. T. 1992. Statistical methods for survival data analysis. 2nd ed., John Wiley & Sons, Inc., New York, NY.
- Mark, T., U. S. Nielsen, J. Pösö, M. Gundel, and M. Svendsen. 2001. Genetic relationships among functional traits in the Nordic Holstein populations. *Interbull Bull.* 27:64–67.
- Pryce, J. E., R. F. Veerkamp, R. Thompson, W. G. Hill, and G. Simm. 1997. Genetic aspects of common health disorders and measures of fertility in Holstein Friesian dairy cattle. *Anim. Sci.* 65:353–360.
- Roxström, A. 2001. Genetics aspects of fertility and longevity in dairy cattle. Ph.D. Diss. Swedish University of Agricultural Sciences, Uppsala, Sweden.
- Royal, M. D., A. O. Darwash, A. P. F. Flint, R. Webb, J. A. Woolliams, and G. E. Lamming. 2000. Declining fertility in dairy cattle: Changes in traditional and endocrine parameters of fertility. *Anim. Sci.* 70:487–501.
- Royal, M. D., A. P. F. Flint, and J. A. Woolliams. 2002. Genetic and phenotypic relationships among endocrine and traditional fertility traits and production traits in Holstein-Friesian dairy cows. *J. Dairy Sci.* 85:958–967.
- SAS Institute. 1999. SAS Release V8.1. SAS Inst., Inc., Cary, NC.
- Suriyasathaporn, W., M. Nielsen, S. J. Dieleman, A. Brand, E. N. Noordhuizen-Stassen, and Y. H. Schukken. 1998. A Cox proportional-hazards model with time-dependent covariates to evaluate the relationship between body-condition score and the risks of first insemination and pregnancy in a high-producing dairy herd. *Prev. Vet. Med.* 37:159–172.
- Swedish Dairy Association. 2002. *Husdjursstatistik (cattle statistics) 2002.* Svensk Mjölk, Eskilstuna, Sweden.
- Veerkamp, R. F., J. K. Oldenbroek, and T. Van der Lende. 1997. The use of milk progesterone measurements for genetic improvement of fertility traits in dairy cattle. *Genetic Improvement of Functional Traits: Fertility.* Interbull Publ. No. 17. Interbull, Uppsala, Sweden.
- Weller, J. I., and M. Ron. 1992. Genetic analysis of fertility traits in Israeli Holsteins by linear and threshold models. *J. Dairy Sci.* 75:2541–2548.
- Yazdi, M. H., P. M. Visscher, V. Ducrocq, and R. Thompson. 2002. Heritability, reliability of genetic evaluations and response to selection in proportional hazard models. *J. Dairy Sci.* 85:1563–1577.