Beyond Cox: 2.multilevel parametric models for time-to-failure data

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Summary
One way of dealing with correlated observations in time-to-event data is by including random terms (also called frailties) in the model. The objectives of this study were to evaluate the performance of these statistical procedures when fitting accelerated failure time parametric survival models and to compare the effect of various random effects distributions on the model estimates.

The use of random effects models in medical and veterinary research has increased greatly with the availability of user-friendly computer programs to fit these models. However, only recently have user-friendly computer programs for analyzing time-to-event data been integrated into those statistical packages. Correlations among survival times may arise from a hierarchical structure in the data (e.g. lactations within animals, and animals within herds), or due to the possibility of multiple recurrence times of a disease in the same subject.

One way of dealing with correlated observations in time-to-event data is by including random terms (also called frailties) in the model. These random effects generate dependency between survival times of the individuals, which are conditionally independent given the frailty, and these common (shared) random effects can be used to model the intragroup correlation. Various distributions (e.g. gamma, inverse-Gaussian and normal) can be used for the random effects. However, there are no clear criteria to select a specific distribution and ultimately the decision will depend on the knowledge of the specific situation and on the statistical package used. The choice of frailty distribution will not only influence the estimates of correlations but also the estimates of regression coefficients for the fixed effects (1). Moreover, some differences in these estimates may be observed according to the statistical approach used. In relation to this, maximum likelihood and Bayesian algorithms are available to analyze survival data. The objectives of this study were to evaluate the performance of these statistical procedures when fitting accelerated failure time parametric survival models and to compare the effect of various random effects distributions on the model estimates.

Methods

A simulated dataset and a cow-survival dataset were used in this analysis. The simulated dataset consisted of 2000 observations generated assuming a Weibull distribution (scale parameter = 0.05 shape parameter = 1.5) and a gamma distribution for the random effects (mean=1 and variance = 0.66) as described previously in Dohoo et al., (2). These observations were clustered in 40 groups of size 50 and they were followed for 100 days. A fixed effect (treatment) was simulated to have a value of –0.46 (ie accelerating the probability of failing). The cow-survival dataset consisted of 2403 cows from 90 dairy herds. The follow-up time represented the time (days) to when a cow was culled or censored after she was tested for Enzootic Bovine

Leukosis (EBL) antibodies. The cow's EBL status and if the cow was in the 5th or greater lactation at the time of testing were included in the model as independent variables.

Accelerated failure time models assuming a Weibull distribution for the baseline hazard were fit as follows: maximum likelihood estimates using a gamma and inverse-Gaussian multiplicative frailty were fit using Stata ver. 8, quasi-likelihood estimates using a normal additive frailty (on log time scale) were fit in MlwiN and Markov Chain Monte Carlo estimates using the Gibbs sampling were applied to multiplicative gamma and additive normal frailties in WinBugs.

Results

Simulated dataset

Out of the 2000 individuals, 1629 failed and they had a median survival time of 40 days. The results of the survival models are presented in Table 1. All these models had similar fixed effect results. As it was expected, the treatment effect accelerated the probability of failing (~ -0.46) and the shape parameter of the frailty models was approximately 1.5. Contrarily, the frailty variances depended on the distribution and model used. However, all these models reported significant variances between the cluster variable (eg. herds)

Table 1. Fixed and random effects coefficients and standard errors from the parametric Weibull survival models from the simulated dataset (n = 2000, 40 herds, gamma frailty mean=1 and variance ~- 0.66, expected treatment effect ~- 0.46).

		Stata		MLwiN	WinBugs	
Fixed effects	No Frailty	Gamma [1]	Inverse Gaussian [1]	Normal[2]	Gamma [1]	Normal [2]
Treatment	-0.45 (0.04)	-0.49 (0.03)	-0.49 (0.03)	-0.46 (0.04)	-0.49 (0.03)	-0.49 (0.03)
Intercept (SE)	4.31 (0.03)	4.05 (0.09)	4.05 (0.13)	3.97 (0.13)	4.02 (0.13)	4.27 (0.14)
Shape parameter	1.18	1.49	1.49	1.48	1.49	1.49
Frailty variance (SE)	-	0.67 (0.14)	1.49 (0.48)	0.69 [3] (0.16)	0.71 (0.15)	1.02 [3] (0.13)

[1] Multiplicative frailty, [2] Additive frailty, [3] Log time scale

The frailty models had similar values and they were similar to the non-frailty model. However, the non-frailty model produced a biased estimate of the shape of the Weibull hazard. The Stata (gamma) and WinBugs (gamma) reported similar values for the frailty variance and they were close to the simulated value. Contrarily, the Inverse Gaussian distribution tended to overestimate the frailty variance. The additive models reported different frailty variance estimates. However, they cannot be compared with the multiplicative frailty models because they refer to the log time scale.

Cow survival data

Out of 2403 cows 1819 were culled during the follow-up period, the median time-at-risk was 671 days. The observed (population) hazard (determined from a actuarial life

table) supported the assumption of a Weibull hazard for this dataset. The results from the statistical models are presented in Table 2.

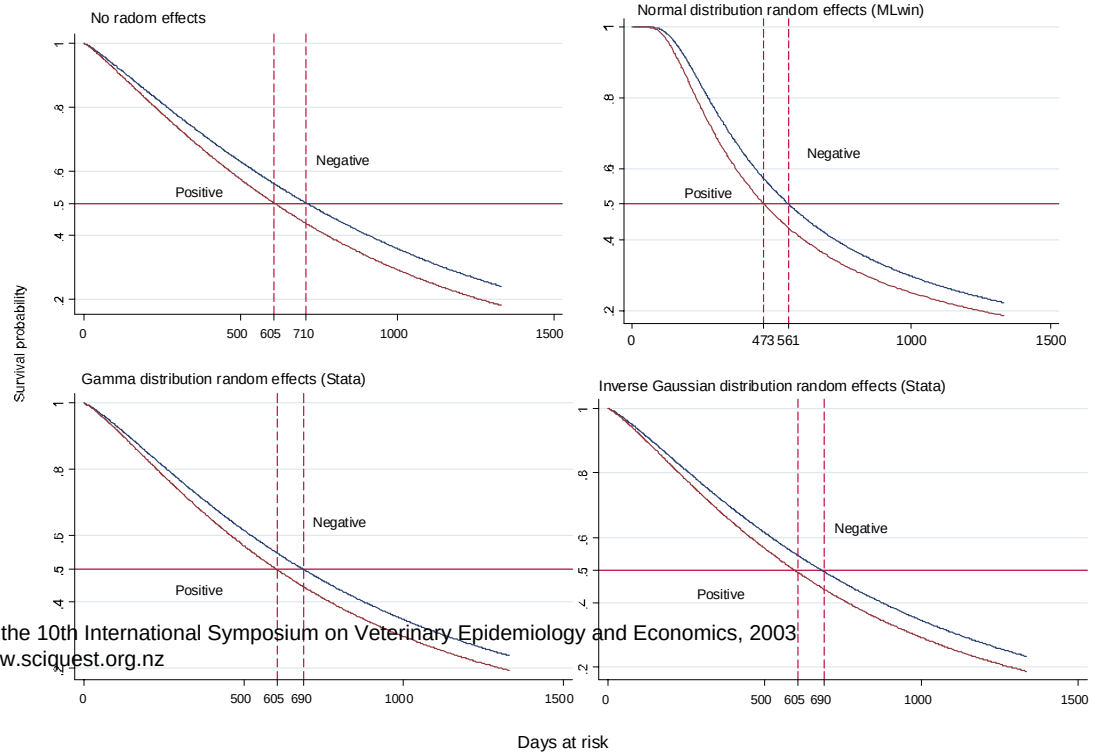
Table 2. Fixed and random effects coefficients and standard errors from the parametric Weibull survival models from the cow-survival dataset (n = 2403, 90 herds).

		Stata		MlwiN	WinBugs	
Fixed effects	No Frailty	Gamma [1]	Inverse Gaussian [1]	Normal [2]	Gamma [1]	Normal [2]
Lact 5+ (SE)	-0.43 (0.05)	-0.48 (0.05)	-0.47 (0.05)	-0.59 (0.06)	-0.47 (0.06)	-0.47 (0.05)
EBL status (SE)	-0.16 (0.05)	-0.13 (0.06)	-0.13 (0.06)	-0.17 (0.07)	-0.13 (0.06)	-0.13 (0.06)
Intercept (SE)	6.95 (0.02)	6.83 (0.05)	6.81 (0.05)	6.51 (0.05)	6.81 (0.13)	6.92 (0.14)
Shape parameter	1.15	1.24	1.24	1.24	1.24	1.24
Frailty variance (SE)	-	0.25 (0.05)	0.29 (0.06)	0.15 [3] (0.03)	0.26 (0.05)	0.26 [3] (0.05)

[1] Multiplicative frailty, [2] Additive frailty, [3] Log time scale

Similarly, the non-frailty model tended to underestimated the shape parameter. Animals in the 5th or greater lactation at the time of testing were culled earlier compared with cows in the 4th or less lactation and EBL positive cows were culled earlier compared with negative animals (Figure 1). The multiplicative frailty models (Stata and WinBugs) reported similar frailty variances regardless of the distribution used for the frailty. On the other hand, the WinBugs model using a normal frailty distribution reported a larger variance compared with MlwiN. The effect of different frailty distributions was also evaluated by estimating the predicted survival time. Although, Stata estimated similar predicted values for both gamma and inverse-Gaussian frailties, MlwiN predicted survival time 120 days shorter compared with Stata (Figure 1).

Figure 1. Predicted median survival times for the cow-survival models in Table 2.



Curves represent survival time for cows in the 4th or less lactation by EBL status.

Overall, the results from these statistical packages were similar, however some differences were observed for the models with additive frailties. Stata and MlwiN models were easier to fit, but WinBugs is more flexible and can fit a wide range of distributions for either additive or multiplicative models.

(1) Hougaard P. Life table methods for heterogeneous populations: distributions describing heterogeneity. Biometrika 1984; 71(1):75-83.

(2) Dohoo, I.; Stryhn, H. , Sanchez, J. Beyond Cox: 1. Hazard functions and time varying effects in parametric survival models. Proceedings of the 2003 annual meeting of the CAVEPM, Montreal, Canada.