The Weibull MPR model for interval censored survival data

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Summary. The Weibull multi-parameter regression (MPR) model with frailty is developed for interval censored survival data. The basic MPR model which is wholly parametric with non-proportional hazards was developed by Burke and MacKenzie in their 2016 Biometrics paper. We describe the basic model, develop the interval-censored likelihood and extend the model to include Gamma frailty. We present a simulation study and re-analyse data from the Signal Tandmobiel study. The MPR model is shown to be superior to a proportional hazards competitor.

Keywords: Interval Censoring; MPR survival models; Weibull MPR model.

1 Introduction

The concept of multi-parameter regression (MPR) survival modelling was introduced by Burke & MacKenzie (2013) and developed in Burke & MacKenzie (2017). MPR survival models model the *scale* and *shape* parameters simultaneously: they are parametric and more flexible than classical proportional hazards (PH) survival models. In their first papers the technique was developed for right-censored survival data. Burke & MacKenzie (2017) reanalysed the survival of 855 incident cases of lung cancer (Wilkinson, 1995) and the MPR Weibull provided a better fit to the data. Here we develop MPR models for interval censored survival data arising in longitudinal studies and use a MPR model with frailty to analyse data from the Signal Tandmobiel study (Gomez et al., 2009).

2 MPR Models

There is a wide class of two-parameter parametric survival models with scale and shape parameters. Here, we specialize to the MPR Weibull model because it has proved useful

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in other work and has the advantage of defaulting to a standard proportional hazards model when the shape parameter is a constant.

2.1 Weibull MPR survival model

The Weibull multi-parameter survival regression model is defined by

$$\lambda(t_i;\beta,\alpha) = \lambda\gamma t_i^{\gamma-1}, \tag{1}$$

where, λ is the *scale* parameter and γ is the *shape* parameter (Collett, 2003). It follows that the basic survival function is $S(t_i;\beta,\alpha) = \exp\big[-\lambda t_i^{\gamma}\big]$. Next let

$$\lambda_i = \exp(x_i^T\beta) \quad \text{and} \quad \gamma_i = \exp(z_i^T\alpha) \tag{2}$$

where $x_{0i} = 1 = z_{0i}\ \forall i$ are intercept terms in each regression and x and z are same covariates, in the same order, but labelled differently in the two linear predictors, for ease of exposition.

2.2 Interval Censoring

From MacKenzie and Peng (2013) a general likelihood for interval censored data is

$$L_1(\theta) = \Pi_{i=1}^{n}[S(t_{i,k-1};\theta) - S(t_{ik};\theta)]^{\delta_i}[S(t_{ci};\theta)]^{1-\delta_i}, \tag{3}$$

where the *actual times* at which the ith patient presents for examination are utilized in the likelihood. Here, $\theta = (\beta^T,\alpha^T)^T$, from equation (2), and typically the ith patient fails in the interval $(t_{i,k-1}, t_{ik}]$ such that there are n_{ic} interval censored patients and n_c censored or withdrawn at specific times such that $n_{ic} + n_c = n$, the total sample size. In (3), the interval censored observations play the role of "failures".

2.3 Frailty Extension

The Weibull multi-parameter survival regression model with Gamma frailty is defined by $\lambda(t_i;\alpha,\beta,u) = u\lambda\gamma t_i^{\gamma-1}$, whence, $S(t_i;\alpha,\beta,u) = \exp\big[-u\lambda t_i^{\gamma}\big]$, where, $\lambda = \exp(x^T\beta), \gamma = \exp(z^T\alpha)$, and u is an unobserved frailty term and the random variable $U \sim \text{Gamma}(a,b)$. When $a = b = 1/\phi$, $E(U) = 1$ and $V(U) = \phi$. Then, after some algebra, we may show that $S(t_i;\alpha,\beta) = [1+\phi\Lambda(t_i)]^{-1/\phi}$, where, $\Lambda(t_i) = \lambda t^{\gamma}$, $\lambda = \exp(x^T\beta), \gamma = \exp(z^T\alpha)$, whence

$$L(\theta|t_i,\delta_i,x_i,z_i) = \prod_{i=1}^{n}\Big\{[1+\phi\Lambda(t_{i,k-1})]^{-1/\phi} - [1+\phi\Lambda(t_{ik})]^{-1/\phi}\Big\}^{\delta_i} \times \Big\{[1+\phi\Lambda(t_{ic})]^{-1/\phi}\Big\}^{1-\delta_i}.$$

Table 1: Simulation: MPR Weibull Model: 50% censoring

Covariates	$\hat{\beta}$	SE	$\%bias$	$\hat{\alpha}$	SE	$\%bias$
$n = 200$						
Intercept	2.0612	0.1658	3.0612	2.0483	0.1050	2.4140
x_1	0.5167	0.2533	3.3469	0.2496	0.1469	-0.1485
x_2	0.3263	0.2600	8.7530	-0.0883	0.1498	-11.7465
$n = 500$						
Intercept	2.0330	0.0981	1.6487	2.0188	0.0626	0.9397
x_1	0.5072	0.1577	1.4425	0.2532	0.0924	1.2604
x_2	0.2999	0.1484	-0.0223	-0.1014	0.0873	1.4095
$n = 1000$						
Intercept	2.0099	0.0720	0.4965	2.0101	0.0461	0.5066
x_1	0.5067	0.1097	1.3426	0.2498	0.0649	-0.0749
x_2	0.3062	0.1076	2.0646	-0.0979	0.0631	-2.1102

True values: scale=(2, 0.5, 0.3), shape=(2, 0.25, -0.1)

2.4 Structural Dispersion

In the structural dispersion (SD) paradigm we allow the frailty variance to be person-specific via another regression model. Thus

$$\phi_i = \exp(w_i^T \psi), \tag{4}$$

where the vector w_i contains the same covariates as x and z and the $w_{0i} = 1\nabla i$ is the intercept term.

When the frailty variance is unstructured the model defaults to the standard SPR or MPR Weibull gamma frailty model with $\phi = \exp(\psi_0)$

3 Simulation study

We conducted a simulation study to assess the performance of the interval-censored Weibull MPR model. Emergence times were generated from the Weibull regression model (with or without frailty) with two covariates: x_1, a binary covariate (1 = New treatment and 0 = Old treatment: 50% split) mimicking the treatment effect, and x_2 a continuous baseline covariate distributed as $N(0, 0.25)$. The results in Table 1 are based on $\lambda = 2.0, \beta_1 = 0.5, \beta_2 = 0.3; \alpha = 2.0, \alpha_1 = 0.25, \alpha_2 = -0.1; \phi = 1.0$, for sample sizes ($n = 200, 500, 1000$) and a censoring rate of 50%. The number of replications is 1000. The results show that the bias of the mle estimators is acceptably low. The results for the frailty model were similar (not shown). There was some bias in the frailty variance for $n = 200$ which disappeared at the larger sample sizes. Overall, the results suggest that the underlying MPR model is recoverable for reasonable sample sizes.

4 Data Analysis

The Signal Tandmobiel study is a longitudinal prospective oral health study conducted in Flanders (Belgium) from 1996 to 2001. The response was time (yrs.-5) to the

Table 2: Selected models fitted and information criteria

Model	Scale	Shape	SD	$\ell(\hat{\theta})$	AIC
M5 SPR	c,full	c	-	-5520.08	11048.34
M6 SPR +GF	c,full	c	c	-5486.08	10982.15
M7 SPR+GF+SD	c,full	c	c, full	-5483.46	10982.91
M11 MPR	c,main	c,main	-	-5501.69	11011.39
M13 MPR	c,full	c,full	-	-5493.68	11003.36
M14 MPR+GF	c,full	c,full	c	-5466.07	10950.13
M15 MPR+GF+SD	c,full	c,full	c,full	-5465.62	10943.24
Separate Sexes					
M18 MPR+GF+SD Girls	c,dmf	c,dmf	c,dmf	-2742.16	5494.32
M6 SPR+GF Boys	c,dmf	c	c	-2740.17	5490.35

NB: c=intercept, full=gender+dmf+interaction, main=gender+dmf
GF=Gamma Frailty, SD= Structural Dispersion
Some 24 models fitted overall

emergence of the permanent upper left first premolars. Two covariates were analysed gender (sex): $0 = \text{boy}\,(52\%), 1 = \text{girl}\,(48\%)$ and dmf coded: 0 (57%) if the primary predecessor was sound and 1 (43%) if it was decayed, missing or filled. The data were analysed using R programmes and packages including `nlm` and `icfit` (R Development Team, 2012; Fay and Shaw, 2010).

Table 2 shows a selection of models fitted to the data. In general, as judged by the AIC, the MPR models were superior to the equivalent SPR models. Gamma frailty models were superior to the equivalent non-frailty models and the SD models sometimes outperformed the equivalent Gamma frailty model. Overall, Model 15 (M15) provided the best fit as judged by the AIC. This is the "full" model containing three separate regressions - scale, shape and structural dispersion - with gender, dmf and their interaction in each model. The fit obtained by Model 15 is shown in Figure 1.

Thus, it transpires that within each sex, the time to emergence does not follow a proportional hazard model. It is fortunate that the toothdata are sufficiently extensive to allow these additional investigations and tests of model fit against non-parametric alternatives to be undertaken. We conclude that both sex and dmf are important and that time to emergence of the permanent upper left first premolars is significantly earlier in girls and those children in whom the predecessor was decayed, missing, or filled and that, likely, there are other unmeasured covariates.

5 Discussion

MPR models are relatively new and are of increasing interest to statisticians working in survival analysis. To the best of our knowledge this is the first time that the effect of interval censoring has been investigated in the MPR survival model setting and the first time that MPR models have been used with Gamma frailty and SD. The models performed well yielding an interesting analysis of the Signal Tandmobiel study data.

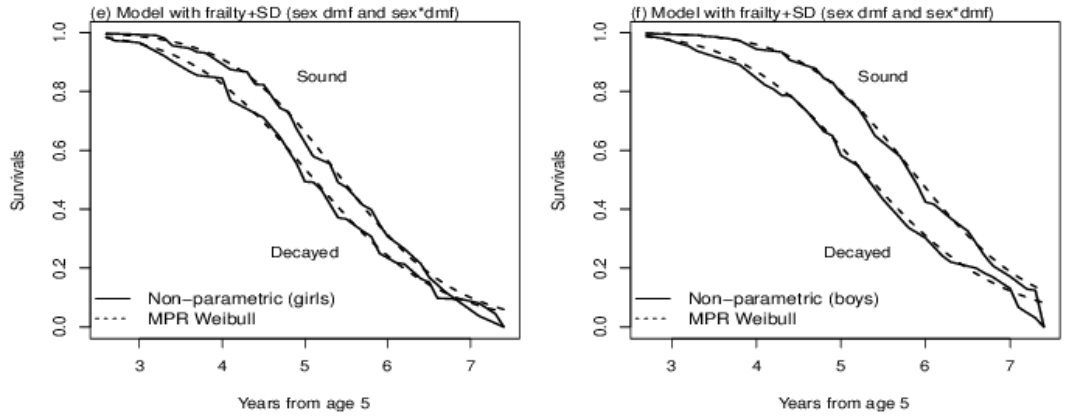

Figure 1 Comparisons of survival curves: Model 15 v NPMLE; left panel girls and right panel boys

Key References

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