Non-PH parametric survival modelling

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Abstract: Non-PH parametric survival modelling is developed within the framework of the multiple logistic function. The family considered comprises three basic models: (a) a PH model, (b) an accelerated life model and (c) a model which is non-proportional hazards and non-accelerated life. The family is generalised by means of a Gamma frailty extension which is shown to accommodate crossing hazards data. These extensions lead naturally to the concept of a Multi-Parameter Regression model described by Burke and MacKenzie (2016). The new models are used to analyse two sets of survival data and the advantages of the methods are discussed.

Keywords: Accelerated Life, Frailty, MPR model, Non-PH Model, PH Model

2 Introduction

MacKenzie (1996) introduced a family of survival models based on the multiple logistic function. The generalised time dependent logistic family (GTDL) comprised three models (a) a PH model, (b) an accelerated life (AL) model and (c) a model which is non-PH and non-AL. Development was focussed on model (c), designated the GTDL model, and a Gamma extension demonstrated its ability to deal with crossing hazards survival data (MacKenzie and Ha, 2007). This example involved the creation of a covariate dependent shape parameter. Accordingly, the idea of modelling the shape parameter more generally intrudes and this has motivated the development of multi-parameter regression survival models (MPR models) (Burke and MacKenzie, 2013, 2016). We trace these methodological developments and illustrate the main ideas using a non-PH Weibull MPR model.

3 The GTDL family

The GTDL family was predicated on the multiple logistic function and the defining hazard functions of the three models in the family areas follows:

(a) The GTDL PH model

$$\lambda(t;x) = \pi(t\alpha + \gamma)\exp(x'\beta) \tag{1}$$

(b) The GTDL AL Model

$$\lambda(t;x) = \lambda\phi\pi(\alpha\phi t) \tag{2}$$

(c) The GTDL model
This model is not PH and not AL

$$\lambda(t;x) = \lambda_0\pi(t\alpha + \gamma^*) \tag{3}$$

In the models above $\pi(s) = \exp(s)/[1+\exp(s)]$, $\lambda_0 > 0$ and $\lambda > 0$ are scalars, $\phi = \exp(x'\beta)$ and $\gamma^* = x'\beta$. An intercept term is included in the linear predictor, γ^*, for model (c), but not in the other two models.

4 Frailty Extensions

Standard arguments involving the multiplicative random effect, u_i, on the hazard function yields, the general formulae for the marginal survivor and hazard functions

$$S_m(t) = \mathcal{L}[\Lambda(t)] = [1+\phi\,\Lambda(t)]^{-1/\phi}, \tag{4}$$

and

$$\lambda_m(t) = \lambda(t)\frac{-\mathcal{L}'[\Lambda(t)]}{\mathcal{L}[\Lambda(t)]} = \frac{\lambda(t)}{1+\phi\,\Lambda(t)}, \tag{5}$$

respectively. Here $S(t), \Lambda(t)$ and $\lambda(t)$ are the basic survival quantities. Moreover, $\mathcal{L}[\Lambda(t)]$ is the Laplace transform and U is the random effect with density $g(u) = [\phi^{\frac{1}{\phi}}\Gamma(1/\phi)]^{-1}u^{\frac{1}{\phi}-1}\exp(-u/\phi)$ with $E(U) = 1$ and $V(U) = \phi$. In the main paper we use these formulae to generalise the three models in the family and analyse the lung cancer data.

5 MPR modelling

MPR survival models model the scale and shape parameters simultaneously as a function of covariates. We develop the Non-PH MPR Weibull model which is used (below) to fit the lung cancer data. The hazard function is given by

$$\lambda(t;x,z) = \exp(x'\beta)\exp(z'\alpha)t^{\exp(z'\alpha)-1} \tag{6}$$

where the Weibull hazard is $\lambda(t) = \lambda\gamma t^{\gamma-1} \quad (\lambda > 0, \gamma > 0)$ and the MPR specification is

$$\log\lambda = x'\beta \quad \text{(scale)} \qquad \log\gamma = z'\alpha \quad \text{(shape)}$$

note that x and z may contain the same covariates.

TABLE 1. Models fitted and their marginal mles & (s.e.)

Model	$\hat{\alpha}_0$	$\hat{\alpha}_1$	$\hat{\beta}_0$	$\hat{\beta}_1$	$\hat{\sigma}^2$	$\hat{\ell}$
Cox	-	-	-	-0.106	-	-307.47
	-	-	-	(0.223)	-	
Cox GF	-	-	-	-1.146	1.717	-306.50
	-	-	-	(0.675)	(1.024)	
TDL	-0.832	-0.094	1.494	-1.380	-	-132.55
	(0.242)	(0.192)	(0.666)	(0.822)	-	
GTDL GF	-0.789	3.499	2.380	-4.612	0.400	-127.89
	(0.326)	(1.408)	(1.413)	(1.676)	(0.176)	

6 Applications

A classical motivating example is the crossing hazards data provided by the Gastrointestinal Tumor Study Group (GTSG)(1982), reporting the effects of chemotherapy and combined chemotherapy and radiotherapy on the survival times of gastric cancer patients.

The results of fitting several models is shown in Table 1. The most successful model is the GTDL Gamma frailty model involving separate shape parameters for the two groups. The other models (PH and non-PH) shown in the table are not successful. This shows that having covariate dependent shape parameters is sometimes useful.

We turn now to analyse the Lung Cancer data set.This was a multi-source population study of 855 incident cases in Northern Ireland diagnosed between Oct. 1st 1991 and Sept. 30th 1992. The patients were followed for c18 months and their survival time was computed as the time from diagnosis to death or censoring. Some 693 (77%) patients had died by the censoring date (30th May, 1993).The influence of 9 covariates were analysed: Age, Sex, Treatment, WHO Status, Cell type, Sodium level, Albumen level, Metastases and Smoking category.

The results are shown in Table 2. The presence of a β indicates a statistically significant covariate in the scale parameter while the presence of an α indicates that the covariate is statistically significant in the shape parameter. In the PH model the shape parameter is a constant, γ. The presence of an α also indicates that the covariate is formally non-PH. From the AIC information, the superiority of the non-PH MPR model is apparent, even though it fits more parameters.

TABLE 2. Multi-factor MPR model for scale and shape

Covariate	PH Weibull	MPR Weibull
Treatment	β	β, α
Age group	-	-
WHO Status	β	β
Sex	-	-
Smoker	β	α
Cell Type	β	β
Metastases	β	β, α
Sodium	β	β
Albumen	β	β, α
AIC	3723.1	3679.7
Δ-AIC	43.4	0.0
$\dim(\theta)$	22	30

7 Discussion

The GTDL family is of course not the only way to model non-PH data but it was the use of a member of this family in the crossing hazards example that led, in part, to the broader idea of modelling the shape parameter symmetrically with the usual scale parameter in survival distributions. This highlights both the importance of the frailty concept and the MPR approach. In further work we have demonstrated that, unlike the lung cancer data analysed here, both concepts can be required together which suggests that the MPR model captures a form of time dependence which classical frailty models cannot.

References

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