Modelling Survival Data with Crossing Hazards

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Abstract: We revisit the crossing hazards problem in survival analysis and compare the use of Cox's semi-parametric model with a parametric non-PH model from the generalised time-dependent logistic family(GTDL). A set of gastric cancer data is analysed and a GTDL gamma-frailty model is shown to explain the observed data well. The role of heterogeneity in the crossing hazards problem is discussed.

Keywords: Crossing Hazards, GTDL family, non-PH survival modelling

1 Introduction

Despite the ubiquity of Cox's proportional hazards (PH) model it is being realised increasingly that not all survival data obey the PH assumption. In multi-factor studies the effect of one or more covariates may be noticeably non-PH. A clear signal is that of crossing hazards. A classical example is the well-known data set of 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 (Figure 1). The question then arises as to how best to model these effects. Sometimes, in practice, non-PH covariates are ignored and they are analysed as being PH in a larger model, but the optimality of this expediency is unclear.

An alternative approach is to adopt a model which can cope with non-PH and PH effects. The Generalised Time-Dependent Logistic family of survival models contains two non-PH parametric models which are potential competitors for Cox's model, namely, the GTDL model (MacKenzie, 1996) and the logistic accelerated life model, the LAL (Al-tawarah & MacKenzie, 2003). Recently, the family has been extended to incorporate frailty (Blagojevic, MacKenzie & Ha, 2003) and to more general multivariate forms (Blagojevic & MacKenzie, 2007).

In relation to tests and models developed specifically for crossing hazards situations *per se* we refer the reader to Stablein & Koutrouvelis (1985), Aalen(1994), Hseish (2001) and Bagdonavicius *et al* (2005).

2   Models & Interpretations

Here we take a rather simpler approach when comparing some PH and non-PH models in the GTDL family in the analysis of crossing hazards data. In particular, we consider fitting the following set of models to the gastric cancer data:

$$\lambda(t|x) = \lambda_0(t)\exp(x\beta) \tag{1}$$
$$\lambda(t|u,x) = u\lambda_0(t)\exp(x\beta) \tag{2}$$
$$\lambda(t|x) = \lambda p(t|x) \tag{3}$$
$$\lambda(t|u,x) = u\lambda p(t|x) \tag{4}$$

where $\lambda_0(\cdot)$ is an unspecified baseline hazard function, β is a $p \times 1$ vector of regression parameters associated with fixed covariates, x, $\lambda > 0$ is a scalar, $U \sim$ Gamma with $E(U) = 1$, $V(U) = \sigma^2$ and $p(t|x) = \exp(t\alpha + x'\beta)/1 + \exp(t\alpha + x'\beta)$.

2.1   Interpreting $\lambda_0(t)$

Consider the two group case with a single binary covariate, x. First we note that in the PH model (1), $\lambda_0(t)$ emerges when $x = 0$, as the baseline hazard function. However, it also emerges when $\beta = 0$, whence there is no PH regression. Then the subscript '0' is redundant and $\lambda_0(t)$ should be denoted $\lambda(t)$, since the hazard is now arbitrary. When $\beta \neq 0$ we may proceed to estimate $\lambda_0(t)$, eg, via Breslow's method, and compare the resulting (marginal) survival function with the KM estimator as a check on the goodness of fit of the model. However, as here, we are dealing with one covariate indicating two-groups the comparison with KM is not available when $\beta = 0$.

By contrast, the interpretation of parametric models is much clearer, as when $x = 0$ or $\beta = 0$ the hazard typically reduces to a specific function of time eg, $\lambda \exp(t\alpha)/(1 + \exp(t\alpha))$ in model (3) above, and the corresponding parametric survival function can always be tested against the KM estimator as a check on fit.

3   Results

We re-analysed the survival times of the 90 patients with gastric cancer. Figure 1 shows the KM survival functions in the chemotherapy and combined therapy groups. The crossing survival functions are a clear sign of non-proportionality and survival is lower in patients receiving combined therapy for the first three years and thereafter it is better. We fitted the sequence of models (1)-(4) presented above using (marginal) maximum likelihood estimation and the results are shown in Table 1. As expected the PH
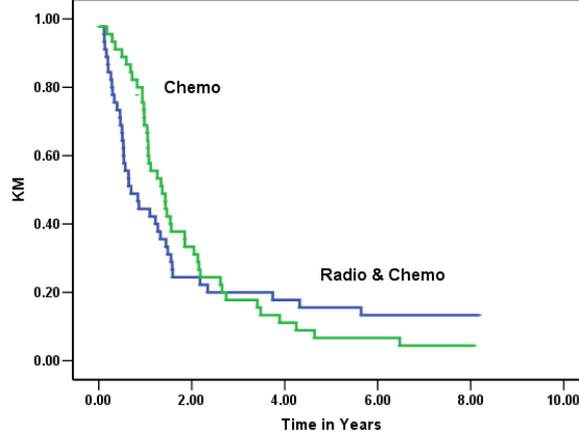
FIGURE 1. KM Survival Functions in Treatment Groups

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)	
GTDL	-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)	

model cannot cope with this situation - the log-rank test is non-significant - as indicated by $\hat{\beta}_1$ /se$(\hat{\beta}_1)$. On the other hand, the generalised Wilcoxon statistic is $(\chi^2 = 3.96, \mathrm{df} = 1, \mathrm{p} < 0.05)$. In a two group comparison with no explanatory covariates we should examine the role of heterogeneity, via frailty. Here again the semi-parametric PH model is uninformative. The GTDL model with separate time parameters for each group $(\alpha_0$ & $\alpha_1)$ is equally unhelpful, but when the GTDL model is extended to Gamma frailty, all of the resulting parameters are statistically significant, suggesting that the GTDL frailty model provides a satisfactory explanation of the data. The resulting fit is shown in Figure 2.
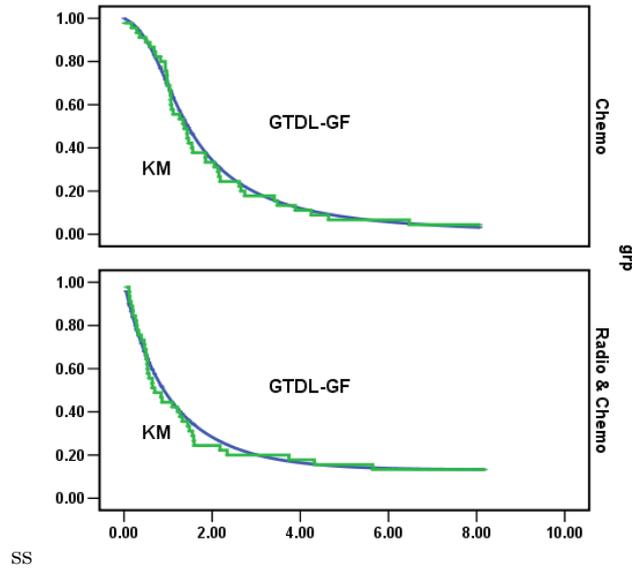
FIGURE 2. KM Survival & Fitted GTDL Gamma Frailty Model

4   Discussion

The use of parametric models is convenient when dealing with crossing hazards data. It is natural, in these circumstances, to consider a non-PH family such as the GTDL. It might be have been thought that the use of separate time parameters, which is always a viable strategy with parametric models, would have been sufficient to capture the structure of the data. However, our analysis shows clearly the important role of heterogeneity modelled via the Gamma distribution. In the main paper we will discuss these issues further and consider alternative frailty distributions including h-likelihood.

References

Cox DR (1972) Regression models and life-tables (with discussion). *J. R. Statist. Soc.* B, **34**, 187-220.

Hougaard, P. (1994). Heterogeneity Models of Disease Susceptibility, with Applications to Diabetic Nephropathy. populations. *Biometrics*, 50, 1178-1188.

MacKenzie, G. (1996) Regression models for survival data: the generalised time dependent logistic family. *JRSS Series D*, 45, 21-34.

Stablein DM I. & Koutrouvelis, IA (1985). A Two-Sample Test Sensitive to Crossing Hazards in Uncensored and Singly Censored Data *Biometrics*, Vol. 41, No. 3, 643-652.