The role of Frailty in survival studies

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Abstract: The focus is mainly, but not solely, on longitudinal randomised controlled clinical trials. The paper aims to delineate the role of frailty in the modern analysis of such trials and also in longitudinal survival studies. Our approach exploits recent developments in statistical modelling and in estimation methods, for example, in non-PH survival modelling, covariance modelling and in $h$-likelihood inference. We illustrate our approach and findings with examples from the literature.

Keywords: frailty; longitudinal RCTs and studies; MV responses; covariance modelling; PH & non-PH survival distributions, $h$-likelihood

1 Introduction

The importance of randomized controlled clinical trials is not in dispute. From the perspective of Scientific Method they have the status of experiments. The key feature of such experiments is that their conclusions are protected by randomization. Broadly, non-randomized studies, or observational studies control differences between groups by means of covariate adjustment, using an appropriate statistical model.

In a clinical trial the effect can be attributed to the intervention because, in principle, all other potentially confounding factors are controlled for by the randomization procedure, provided the total sample size, $n$, is large enough. Of course, in practice the sample size is always finite, and differences exist between the groups being studied and these can be controlled for using statistical modelling methods. This is particularly true of trials employing minimization which, typically, only controls for a pre-selected subset of factors (Friedman et al., 1998), and hence is considered logically inferior to a conventional, trial.

Thus, today, it is realized that there is much more information to be retrieved about the effect of treatment using a statistical modelling approach and accordingly the era of investing vast sums of money in a clinical trial only to conduct a t-test has gone. Moreover, this has led to a harmonization of methods of analysis in randomized and non-randomized studies, especially as statistical modelling methods have developed.
2 Frailty

2.1 Concept

Consider a survival regression model with failure time density $f(t|\theta,\beta)$ and basic hazard function $\lambda(t|\cdot)$ and survivor function $S(t|\cdot)$, where typically $\theta$ is a vector valued parameter and $\beta$ is a regression parameter measuring the influence of $p$ covariates $x' = (x_1, x_2, \ldots, x_p)$. Assume that the basic model is extended to a univariate multiplicative frailty model (Hougaard, 1982) with hazard

$$\lambda(t|u, x) = u\lambda(t|x)$$

(1)

where the random variable $U$, with mixing density $g(u|\sigma^2)$, denotes the unobservable individual (i.i.d.) frailties with $E(U) = 1$ and $V(U) = \sigma^2$. The frailties are person specific and may be viewed as allowing for unrecorded covariates. One example is the PH frailty model

$$\lambda(t|u, x) = \lambda_0(t) \exp(x'\beta + v)$$

(2)

where $u = \exp(v)$. A multi-component version (Ha, Lee and MacKenzie, 2007) is

$$\lambda(t|u, x) = \lambda_0(t) \exp(x'\beta + Z_1v_1 + \ldots + Z_qv_q)$$

(3)

which may be written as

$$\lambda(t|u^*, x) = u^*\lambda_0(t) \exp(x'\beta)$$

(4)

where: $u^* = \prod_{j=1}^{q} \exp(Z_jv_j)$, ie, a given function of $(u_1, u_2, \ldots, u_q)$ and the $Z_j$ are appropriate design matrices, leading naturally to

$$\lambda(t|u^*, x) = \lambda_0(t) \exp(x'\beta + Zv)$$

(5)

where $Z$ is a $n \times q$ design matrix and $v$ is a conformable ($q \times 1$) vector of random effects.

2.2 Model Choice

In the current setting this amounts to a joint choice of a basic hazard function $\lambda(t|\cdot)$ and mixing density $g(u|\cdot)$. In the multi-component version the latter quantity may be multivariate. There is a wide choice for the basic hazard function including: PH (Cox, 1972, 1975), GTDL (MacKenzie, 1996, 1997), XD (Jorgensen, 2011; Burke & MacKenzie, 2011). The latter class covers extreme distributions and is relatively new. For the mixing density the choice is usually confined to Gaussian, Log-Normal or Gamma, whence correlation structures may be more easily supported. For a basic PH hazard
the resulting marginalized frailty model is not PH (Hougaard, 2000). Moreover, in the univariate case the choice of a PH basic hazard may not always be optimal. In simulation Ha & MacKenzie (2010) report under-estimation of the regression parameter in the PH model with log-Normal frailty, when the data actually follow a GTDL model (non-PH) with log-Normal frailty. As usual, model selection is important. For multi-component models, focused model selection has been developed for selecting the frailty structure best supported by the data for a given mixer (Ha, Lee & MacKenzie, 2007).

3 Model Formulation

We develop methods in the context of time to first recurrence of disease in an EORTC randomized clinical trial of chemotherapy in invasive, non-muscle, bladder cancer patients (Ha et al, 2011). In this multi-centre trial the main interest lies in evaluating centre effects and testing for homogeneity across centres. We show how to formulate the associated multi-level frailty models, describe their properties including improved prediction of random effects and perform focused model selection in the likelihood paradigm.

In general, suppose that data consist of right censored time-to-event observations collected from $q$ centres. Let $T_{ij} (i = 1, \ldots, q, j = 1, \ldots, n_i, \sum n_i = n)$ be the survival time for the $j$th observation in the $i$th centre (or cluster) and let $C_{ij}$ be the corresponding censoring time. Then observable data become $y_{ij} = \min\{T_{ij}, C_{ij}\}$ and $\delta_{ij} = I(T_{ij} \leq C_{ij})$, where $I(\cdot)$ is the indicator function.

Denote by $v_i$ a $s$-dimensional vector of unobserved log-frailties (random effects) associated with the $i$th cluster. Given $v_i$, the conditional hazard function of $T_{ij}$ is of the form

$$\lambda_{ij}(t|v_i) = \lambda_0(t) \exp(\eta_{ij})$$

where $\lambda_0(\cdot)$ is a unknown baseline hazard function, $\eta_{ij} = x_{ij}^T \beta + z_{ij}^T v_i$ is the linear predictor for the hazards, and $x_{ij} = (x_{ij1}, \ldots, x_{ijp})^T$ and $z_{ij} = (z_{ij1}, \ldots, z_{ijp})^T$ are $p \times 1$ and $s \times 1$ covariate vectors corresponding to fixed effects $\beta = (\beta_1, \ldots, \beta_p)^T$ and log-frailties $v_i$, respectively. Here $z_{ij}$ is often a subset of $x_{ij}$. In this paper, we assume $v_i \sim N_0(0, \Sigma_i)$, which is useful for modelling multi-component or correlated frailties. Here the covariance matrix $\Sigma_i = \Sigma_i(\theta)$ depends on $\theta$, a vector of unknown parameters.

Let $v_{i0}$ be a random baseline intercept and let $v_{i1}$ be a random slope. If $z_{ij} = 1$ and $v_i = v_{i0}$ for all $i, j$, it becomes a random intercept or shared model with $\eta_{ij} = x_{ij}^T \beta + v_{i0} v_{i0} \sim N(0, \Sigma_i)$ with $\Sigma_i \equiv \sigma_0^2$ for all $i$. Let $\beta_1$ be the effect of primary covariate $x_{ij1}$ such as the main treatment effect and let $\beta_m$ ($m = 2, \ldots, p$) be the fixed effects corresponding to the
covariates \(x_{ijm}\). Our two random components lead to a bivariate model with

\[ \eta_{ij} = v_{i0} + (\beta_1 + v_{i1})x_{ij1} + \sum_{m=2}^{p} \beta_m x_{ijm} \]  

which is easily derived by taking \(z_{ij} = (1, x_{ij1})^T\) and \(v_i = (v_{i0}, v_{i1})^T\) in (1).

Here

\[ \begin{pmatrix} v_{i0} \\ v_{i1} \end{pmatrix} \sim N\left( \begin{pmatrix} 0 \\ 0 \end{pmatrix}, \Sigma_i \equiv \begin{pmatrix} \sigma_0^2 & \sigma_{01} \\ \sigma_{01} & \sigma_1^2 \end{pmatrix} \right) \]  

allowing a correlation term, \(\rho = \sigma_{01}/(\sigma_0 \sigma_1)\), between two random effects \((v_{i0} \text{ and } v_{i1})\) within a centre thus extending the independent frailty model.

### 4 Model Interpretation

In order to interpret the fixed and random effects, we consider a model with a single binary-treatment indicator, \(x_{ij}\). Then,

\[ \lambda_{ij}(t|v_{i0}, v_{i1}; x_{ij}) = \lambda_0(t) \exp\{v_{i0} + (\beta_1 + v_{i1})x_{ij}\}. \]

Now, the time-dependent relative risk for treatment becomes

\[ \psi_{ij}(t|x = 1, x = 0) = \frac{\lambda_0(t) \exp\{v_{i0} + (\beta_1 + v_{i1}) \cdot 1\}}{\lambda_0(t) \exp\{v_{i0} + (\beta_1 + v_{i1}) \cdot 0\}} = \exp(\beta_1 + v_{i1}), \]  

which is free of time \(t\) and holds for all patients in centre \(i\). Here \(\exp(\beta_1)\) is the usual expression for the relative risk in a standard PH model. Thus, \(\psi_{ij}(t|x = 1, x = 0)\) represents a random multiplicative divergence from the standard relative risk in a PH model which is homogeneous with respect to centres. Note that \(\exp(\beta_1 + v_{i1})\) is often called the treatment hazard ratio in the \(i\)th centre. We also have that

\[ \frac{\exp(\beta_1 + v_{i1})}{\exp(\beta_1)} = \exp(v_{i1}). \]

Thus \(v_{i1}\) means the random deviation of the \(i\)th centre from the overall treatment effect. Similarly, in order to interpret \(v_{i0}\) we consider the model without the covariate \(x_{ij}\) \(\lambda_{ij}(t|v_{i0}) = \lambda_0(t) \exp(v_{i0})\) whence, \(\phi_{ij}(t) = \frac{\lambda_0(t) \exp(v_{i0})}{\lambda_0(t) \exp(0)} = \exp(v_{i0})\) which is free of time \(t\) and holds for all patients in centre \(i\), and \(v_{i0}\) represents the random deviation of the \(i\)th centre from the overall underlying baseline risk.
### TABLE 1. Results for fitting the four models to the bladder cancer data

<table>
<thead>
<tr>
<th>Model</th>
<th>$\hat{\beta}_1$ (SE)</th>
<th>$\hat{\beta}_2$ (SE)</th>
<th>$\hat{\sigma}_0^2$ (SE)</th>
<th>$\hat{\sigma}_1^2$ (SE)</th>
<th>$\hat{\sigma}_{01}$ (SE)</th>
<th>$[\hat{\rho}]$</th>
</tr>
</thead>
<tbody>
<tr>
<td>M1 (Cox)</td>
<td>-0.667 (0.170)</td>
<td>0.509 (0.144)</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>M2 (Indep)</td>
<td>-0.695 (0.175)</td>
<td>0.544 (0.149)</td>
<td>0.070 (0.058)</td>
<td>$3 \times 10^{-12}$</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>M3 (Corr)</td>
<td>-0.757 (0.191)</td>
<td>0.532 (0.150)</td>
<td>0.161 (0.178)</td>
<td>0.036 (0.170)</td>
<td>-0.068 [-0.893]</td>
<td></td>
</tr>
<tr>
<td>M4 (B)</td>
<td>-0.695 (0.175)</td>
<td>0.544 (0.149)</td>
<td>0.070 (0.058)</td>
<td>-</td>
<td>-</td>
<td></td>
</tr>
</tbody>
</table>

M1: Cox model without frailties; M2: independent frailty model with $\rho = 0$; M3: correlated frailty model with $\rho \neq 0$; M4: shared frailty model with random baseline risk (B) only; $\beta_1$ and $\beta_2$, effects of treatment and tumor status, respectively; $\sigma_0^2$ and $\sigma_1^2$, the variances of random baseline risk and random treatment effect, respectively; $\sigma_{01}$ and $\rho$, the corresponding covariance and correlation with $\rho = \sigma_{01}/(\sigma_0\sigma_1)$; SE, the estimated standard error for parameters.

### 5 Analysis of EORTC Trial Data

The duration of the Disease Free Interval (DFI) in non muscle invasive bladder cancer patients, treated in various centres in Europe, is analysed. The DFI is defined as the time from randomization to the date of the first recurrence. Patients without recurrence at the end of the follow-up period were censored at their last date of follow-up. For simplicity of analysis, we consider only 410 patients from 21 centres included in EORTC trial 30791. The two covariates of interest are: CHEMO $x_{ij1}$ (0=No, 1=Yes) and TUSTAT $x_{ij2}$ (0=Primary, 1=Recurrent). Notice that $x_{ij1}$ is the main treatment covariate. The numbers of patients per centre varied from 3 to 78, with mean 19.5 and median 15. Of the 410 patients, 204 patients (49.8 per cent) without recurrence were censored at the date of last follow up. For the purpose of analysis, we consider the three submodels of (3): M1 (Cox): Cox model without frailties (basic hazard), M2 (Indep): Cox models, with two independent frailty terms ($\rho = 0$), M3 (Corr): Cox models, with two correlated frailty terms ($\rho \neq 0$).

Models M2 and M3 contain the random baseline risk $v_{i0}$ and the random treatment-by-centre interaction term, $v_{i1}x_{ij1}$. The models were fitted using SAS/IML. The results are summarized in Table 1. In all three models the two fixed effects ($\beta_j, j=1, 2$) are significant. In particular, the use of chemotherapy (CHEMO = 1) significantly prolongs the time to first recur-
rence as compared to patients who do not receive chemotherapy (CHEMO = 0). The two nested models (M1 and M2) ignoring random components or their correlation show similar results for $\beta_j$ ($j = 1, 2$). However, the absolute magnitude and SE of the estimate for the main treatment effect $\beta_1$ in M1 and M2 are smaller than those for the correlated model (M3). In M2 and M3, the variances ($\sigma_2^2$ and $\sigma_1^2$) indicate the amount of variation between centres in the baseline risk and in the treatment effect, respectively. Here, the estimate of $\sigma_2^2$ is relatively larger than that of $\sigma_1^2$. This does not seem surprising since differences in outcome according to treatment effect are typically smaller than differences due to patient characteristics which often vary across centres. However, care may be necessary in comparing the two variances because these two values should not be interpreted on the same scale.

Moreover, the correlated model M3 explains the degree of dependency between the two random components (i.e. the random centre effect $v_0$ and the random treatment-by-centre interaction $v_1$). The estimate of $\rho$ ($\hat{\rho} = -0.893$) gives a large negative value, indicating that the two predicted random components ($\hat{v}_0$ and $\hat{v}_1$) have a strong negative correlation.

6 Discussion

The methods developed lead to an interesting analysis. However, the modelling scheme described above needs to be extended in a number of important ways for use in routine biostatistical analysis. These issues which involve including individual level frailties and utilising focussed model selection will be discussed in the presentation.

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References


