Joint Modelling of Two Sequential Times to Events With Longitudinal Information

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Abstract: In survival analysis, the lifetimes may be observed in some specified order, where the time to event T_k, cannot be observed until $T_1, ..., T_{k-1}$ have been observed. The present work proposes a joint model of two sequential times to events together with longitudinal information, extending the joint model of Wolfsohn and Tsiatis (1997) for one time to event and one longitudinal variable. We apply the model to the clinical trial called TIBET, in which an intermittent therapeutic strategy has been assigned to each patient. Of special clinical interest is the lifetime that a patient needs before restarting treatment given the progression of biological markers recorded during the followup period.

Keywords: Joint Modelling; Longitudinal Data; Survival Analysis; Sequential Times.

1 Joint Models in the Literature

Likelihood and Bayesian approaches rely on the specification of an appropriate likelihood for the joint model parameters; for both, much of the early literature focuses on models without autocorrelation structure for longitudinal model. Good review can be found in Tsiatis and Davidian (2004). Wulfsohn and Tsiatis (1997) proposed and EM algorithm for a simple joint model, but many proposals for more complex joint models developed recently, have based the estimating procedures in it, among others, the joint model for one time to event with multiple longitudinal variables (Lin *et al.*, 2002), a joint modelling of accelerated failure time and longitudinal data, (Tseng *et al.*, 2005), and a robust joint modelling of longitudinal measurements and competing risks failure time data (Li *et al.* 2009). In Bayesian framework, Chi and Ibrahim (2006) give a model for multivariate longitudinal and multivariate survival data by using MCMC techniques.

2 Notation

The idealized data for each subject $i = 1, ..., n$ followed over an interval $[0, \tau)$ are $\{T_{1i}, T_{2i}, R_i(u), 0 \leq u \leq \tau, X_i\}$, where T_{1i} and T_{2i} are event times, $\{R_i(u), 0 \leq u \leq \tau\}$ is the longitudinal response trajectory for all times $u \geq 0$ and $X_i = [X_{1i}^T \;\; X_{2i}^T]^T$ is a vector of baseline (time 0) covariates, X_{1i} with influence over T_1, and X_{2i} over T_2, which may have elements in common or not.
We will consider only a situation where T_1 and T_2 may be right censored by the censoring times C_1 and C_2 respectively, so instead of T_{ji} we observe (Y_{ji}, δ_{ji}), $j = 1, 2$, where $Y_{ji} = min\{T_{ji}, C_{ji}\}$ and $\delta_{ji} = I(T_{ji} \leq C_{ji})$ which indicates whether Y_{ji} is an uncensored right value of T_{ji}. On the other hand, for some set of times $t_{ij}, j = 1, ..., n_i$, instead of the true values $R_i(t_{ij})$ we observe $Z_i(t_{ij})$, then the observed data for subject i is $O_i = \{X_i, Y_i, \delta_i, Z_i, \tilde{t}_i\}$, where $\tilde{t}_i = (t_{i1}, ..., t_{in_i})^T$, $Z_i = (Z_i(t_{i1}), ..., Z_i(t_{in_i}))^T$, $Y_i = (Y_{1i}, Y_{2i})$, and $\delta_i = (\delta_{1i}, \delta_{2i})$.

3 Joint Modelling of One Time to Event Data and one Longitudinal Variable

For the longitudinal response process, a standard approach is to characterize $R_i(u)$, $u \geq 0$, only in terms of random effects b_{0i} and b_{1i} like

$$R_i(u) = b_{0i} + b_{1i}u. \tag{1}$$

Associations among the longitudinal and time to event processes and covariates, is characterized by the following semi-parametric model for the hazard risk:

$$\begin{array}{rcl} \lambda_i(u) & = & \lim_{du \to 0} \Pr(u \leq T_i < u + du \mid T_i \geq u, R_i^H(u), X_i)/du \\ & = & \lambda_0(u) \exp(\eta^T X_i + \beta R_i(u)), \end{array} \tag{2}$$

where $R_i^H(u) = \{R_i(t), 0 \leq t < u\}$ is the history of the longitudinal process up to time u, and the parameters are represented in β and the η vector. If model takes $\beta R_i(u)$ as $\beta_1 b_{0i} + \beta_2 b_{1i} + \beta_3(b_{0i} + b_{1i}u)$, the parameters β_1, β_2 and β_3 measure the association induced through the intercept, slope and current R value, respectively. Wulfsohn and Tsiatis (1997) give and EM algorithm to estimate the joint model maximizing the resultant log-likelihood.
Zeng and Cai (2005) rigorously prove under the normal assumption for the random effects, among other assumptions, the strong consistency of the maximum likelihood estimators for joint models of repeated measurements and survival time, and derive their asymptotic distributions, which is multivariate normal. Moreover, the asymptotic results hold even if the random effect, has slightly heavier tails than the normal density. The theoretical results further confirm that nonparametric maximum likelihood estimation provides efficient estimation.

4 Joint Modelling of Two Sequential Times to Events and One Longitudinal Variable

We have proposed a joint model for two sequential times to events with one longitudinal variable, as an extension of the Wulfsohn and Tsiatis's model (1997) with a model for two sequential times to events (Lawless 2003, section 11.3). The model permit us to give prognosis for a time to event given covariates, the longitudinal process and the previous event time. Usually the trend of the longitudinal variable changes with the first time to event. If we take the longitudinal variable with two piecewise linear mixed models, the knot where the slope changes is obviously the time to first event T_1, and a particular joint model in which the longitudinal and survival sub-models are linking with the current value may be as:

$$Z_{ij} = b_{0i} + (b_{1i}\ t_{ij} + b_{2i}(t_{ij} - t_{1i})I) + e_i(t_{ij}) \tag{3}$$

$$\lambda(t_1 \mid b_i; \beta_1) = \lambda_{1,0}(t_1) \exp\{\beta_1(b_{0i} + b_{1i}t_1)\} \tag{4}$$

$$\lambda(t_2 \mid t_{1i}, b_i; \beta_2, \gamma) = \lambda_{2,0}(t_2) \exp\{\beta_2(b_{0i}+b_{1i}\cdot t_{1i}+(b_{1i}+b_{2i})t_{2i})+\gamma\, t_{1i}\} \tag{5}$$

where $I = I(t_{ij} \geq t_{1i})$, β_1 and β_2 are parameters of association between the longitudinal and survival process, and γ describes the relation among the times to event. Both baseline risks $\lambda_{1,0}(\cdot)$ and $\lambda_{2,0}(\cdot)$ are left unspecified and different. In the likelihood construction we have the same assumptions made by Wulfsohn and Tsiatis (1997). The assumption of non-informative censoring extend to this case of censoring process. The errors e_i are assumed mutually independent, normally distributed with mean 0 and variance σ_ϵ^2, and independent with b_i and for all other variables conditional on (b_i, X_i). If we may assume that, given random effects and covariates, Z, T_1, and $T_2 \mid T_1$, are all independent, then the observed likelihood is:

$$L(\Omega) = \prod_{i=1}^{n} \int_{b_i} \left\{ \prod_{j=1}^{n_i} f(z_{ij} \mid b_i; \sigma_\epsilon^2) \right\} f(Y_i, \delta_i \mid b_i, X_i; \psi_{T|b}) f(b_i; B, \Gamma) \mathrm{d}b_i, \tag{6}$$

where $\Omega = (\psi_{T|b}, B, \Gamma, \sigma_\epsilon^2)$ and $\psi_{T|b} = (\eta_1, \eta_2, \beta_1, \beta_2, \gamma, \lambda_{1,0}, \lambda_{2,0})$. The vector of random effects $b_i = [b_{0i}\ b_{1i}]^T$ is taken to be normally distributed with mean B and covariance matrix Γ. The function $f_{Y,\delta}$ is defined as (omitting parameters for simplicity):

$$\begin{aligned} f(Y_i, \delta_i \mid b_i, X_i) = &\left[S(Y_{1i}, \delta_{1i} \mid b_i, X_{1i})\lambda(Y_{1i}, \delta_{1i} \mid b_i, X_{1i})^{\delta_{1i}}\right] \\ &\left[S(Y_{2i}, \delta_{2i} \mid b_i, t_{1i}, X_{2i})\lambda(Y_{2i}, \delta_{2i} \mid b_i, t_{1i}, X_{2i})^{\delta_{2i}}\right]^{\delta_{1i}}. \end{aligned} \tag{7}$$

We estimate the joint model with an EM algorithm as an extension of the algorithm developed by Wulfsohn and Tsiatis (1997). Although our problem consist of two times to different events (Restart and suspension of therapy), the proposed model could be used to model data sets where the events are similar, like the problems with disabled recurrences: the first time being the time to some disabled, and the second, the time to the same disabled from the first (having repeated measurements for some marker).

5 Application

We apply the above described technique to the TIBET clinical trial. The trial contemplates the incorporation of interruption periods in the administration of an intensive therapy *HAART* (Highly Active Antiretroviral Therapy). A cohort of 100 patients enters the study with suspension of the treatment (state *OFF*). Basal and retrospective information is gathered, and every 4 weeks there is registered information of the $CD4$ cell count. If the patient's conditions deteriorate, the therapy is restarted (state *ON*), and so on. The times to event are T_1: time to first restart of therapy, and T_2: time from the first restart of therapy to the suspension of therapy. The longitudinal variable is the evolution of the $CD4$ which is not increasing until the first time to event, and then is increasing.
The data base analysis with a set of joint models like (3) - (5) has the following principal findings: 1. the only baseline covariate significative in T_1 was the viral load pre-therapy but this effect is diluted in T_2, 2. The relationship between T_1 and T_2 is inverse, and 3. The slope of the longitudinal variable along of T_2 and the observed values of the first time to event T_1, are the only significative covariates in the survival model of T_2.

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