Joint Modeling for Cognitive Trajectory and Risk of Dementia in the Presence of Death (Supplementary Document)

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SUMMARY: This supplementary note describes the likelihood function for joint modeling for cognitive trajectory and competing risk survival data. (Yu and Ghosh; Submitted to Biometrics 2008).

KEY WORDS: Change point; competing risks; dementia; Markov chain Monte Carlo.
1. Application

In the application, the Weibull model was used for dementia-onset age and dementia-free death age. Although this model has been proposed to model dementia incidence rate Brookmeyer et al. (2007), the model fit should be checked in the current application.

For competing risk data, the cumulative sub-incidence function for event type $d$ is defined as:

$$ F_d(t|x) = P(T < t; D = d|x) $$

In the application, the cumulative incidence function for dementia onset is estimated by

$$ F_1(t|x) = P(D = 1|x)S_1(t|x), $$

where $P(D = 1|x)$ is the probability of having dementia and $S_d(t|x)$ is the Weibull model for dementia onset age. Fine and Gray (1999) proposed directly modeling the sub-distribution of a competing risk with a Cox type model. The Fine and Gray’s method was implemented in R function crr (R Development Core Team, 2007). Because the crr function does not allow left truncation, the subjects are classified into four 5-year age groups.

[Figure 1 about here.]

Figure 1 compares the estimates of $F_d(t|x), d = 1, 2$, from equation 1 and the Fine and Gray’s method by age and education level. The smoothed dotted curves are based on the Weibull model and the step function along with 95% confidence bands are based on the Fine and Gray’s method. This shows that the Weibull model fit the data well.

2. BUGS code

The BUGS code of fitting the model for competing risk survival data with longitudinal markers is attached. The description of the BUGS code is as follows:

When we fit the Weibull model for left-truncated and interval-censored dementia on-
set data, we used the "zeros trick" (http://mathstat.helsinki.fi/openbugs/data/Docu/Tricks.html) to use a non-standard sampling distribution, in which an observation contributes a likelihood term.

In the program, the parameter $\eta_1$ for the survival function of dementia onset is denoted by array $\text{eta}$ and the parameter $\eta_2$ for the survival function of dementia-free death is denoted by array $\text{rho}$.

3. Simulation

A single binary covariate $x$ is considered and the cognitive function is given by

$$Y(t) = \alpha_0 + \beta_0 x + (\alpha_1 + \beta_1 x)t + (\alpha_2 + \beta_2 x)(t - \tau)^+ + \epsilon_Y, \quad \epsilon_Y \sim N(0, \sigma_Y^2),$$

where the change point $\tau$ takes a mixture distribution with dementia probability $P(D = 1) = 1/[1 + \exp\{-(\delta_0 + \delta_1 x)\}]$ and the mean of $\tau$ is $\mu_\tau = \gamma_0 + \gamma_1 x$. The parameter values are based on the application and are specified as follows: $\alpha_0 = 2.4$, $\alpha_1 = 0.04$, $\alpha_2 = 0.02$, $\beta_0 = -0.4$, $\beta_1 = 0.01$, $\beta_2 = 0.02$, $\gamma_1 = 5$, $\gamma_2 = 8$, $\delta_0 = -1.4$, $\delta_1 = -0.5$. The standard deviation of the cognitive function $\sigma_Y = 0.1$ or 0.05. The original cognitive score is calculated as $101 - \exp(Y)$. Figure 2 shows the trajectories of $Y$ and the original cognitive scores by dementia status and education level used in the simulation.

[Figure 2 about here.]

The survival function for dementia onset is $S_1(t) = \exp(-\lambda_1 t^{r_1})$ with $\lambda_1 = \exp(\eta_{11} + \eta_{12} x + \zeta \log \tau)$. The parameter values are $\eta_{11} = -4.6$, $\eta_{12} = 1.5$, $\zeta = -1.5$, $r_1 = 2.4$. The survival function of dementia-free death is $S_2(t) = \exp(-\lambda_2 t^{r_2})$ with $\lambda_2 = \exp(\eta_{21} + \eta_{22} x)$. We set $(\eta_{21}, \eta_{22}) = (-9.2, -1)$ or $(-10.2, 0)$ and $r_2 = 3.5$. We assume the maximum follow-up time is 10 years and the cognitive functions are observed every 2 years until the event, i.e., dementia onset or death occurs.
Each dataset consists of 200 observations and \( x = 0 \) or 1 for half of the data. Both the proposed method (PM) and the Jacqmin-Gadda et al’s method (JGM) are applied to each dataset. The simulation shows the parameters for cognitive trajectories are unbiased for both methods. Of primary interest are the parameters for the risk of dementia onset \((\eta_{11}, \eta_{12}, \zeta, r_1)\) and for the change point \((\gamma_0, \gamma_1)\). For each dataset, 1000 burn-ins are excluded and the estimates are based on the extra 2000 MCMC simulations.

References


Figure 1. Cumulative incidence functions of dementia onset and death from Fine and Gray's method and the Weibull model.
Figure 2. Trajectories of mean cognitive scores by education level and dementia status.