

Joint Modeling of Repeated Measures and Survival Time Data

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1. Introduction

Recently, many long-term clinical trials collect both repeated measures data at a number of time points and survival time data at which times to terminating events are recorded: see Hogan and Laird (1997). For example, after a kidney transplantation clinicians usually monitor the patient's serum creatinine level, an indicator of kidney function, at many time points. However, a single terminating event may occur, for instance, failure of the kidney graft or death of the patient: see Sung et al. (1998). Thus, a patient has both repeated measures data and survival time data, so that these data may induce a dependence due to a shared random effect such as the patient's genetic or environmental effect.

In this presentation we introduce a random effect model for the joint analysis of combined repeated and survival time data of this form, and then propose an inferential method using hierarchical-likelihood (Lee and Nelder, 1996; Ha et al., 2001). Finally, our method is illustrated with kidney transplantation data presented by Sung et al. (1998).

2. The model

We consider the situation that for the i th ($i = 1, \dots, q$) patient there are both repeated measures responses y_{ij} ($j = 1, \dots, n_i$) and survival time T_i . Let $y_i = (y_{i1}, \dots, y_{in_i})^T$ denote the $n_i \times 1$ vector of the i th responses among y_{ij} 's, $X_i^{(1)} = (x_{i1}^{(1)}, \dots, x_{in_i}^{(1)})^T$ the $n_i \times p_1$ matrix of covariates corresponding to y_i , where $x_{ij}^{(1)} = (x_{ij1}^{(1)}, \dots, x_{ijp_1}^{(1)})^T$ is the $p_1 \times 1$ covariate vector corresponding to y_{ij} , and $x_i^{(2)} = (x_{i1}^{(2)}, \dots, x_{ip_2}^{(2)})^T$ the $p_2 \times 1$ covariate vector corresponding to T_i . Let C_i be the censoring time corresponding to T_i , and $t_i^* = \min(T_i, C_i)$ and $\delta_i = I(T_i \leq C_i)$, where $I(\cdot)$ is the indicator function. Denote by v_i a shared random effect for the i th patient. In this paper, we assume that y_i and T_i are conditionally independent given v_i , and that T_i and C_i are also conditionally independent given v_i .

The y_i and T_i ($i = 1, \dots, q$) are assumed to have the following models:

(i) $y_i|v_i \sim N(\mu_i^{(1)}, \phi I_{n_i \times n_i})$ with $\mu_i^{(1)} = X_i^{(1)} \beta^{(1)} + z_i \gamma_1 v_i$,

where $I_{n_i \times n_i}$ is the $n_i \times n_i$ identity matrix, $\beta^{(1)}$ is a $p_1 \times 1$ vector of regression parameters, z_i is a $n_i \times 1$ vector with one, and γ_1 is the real-valued parameter which describes the random effect, say $v_{i1}(= \gamma_1 v_i)$, of y_i .

(ii) $T_i|v_i$ has the conditional hazard function

$$\lambda_i(t|v_i) = \lambda_0(t) \exp(x_i^{(2)T} \beta^{(2)} + \gamma_2 v_i),$$

where $\lambda_0(\cdot)$ is a parametric (e.g. Weibull) or nonparametric baseline hazard function, $\beta^{(2)}$ is a $p_2 \times 1$ vector of regression parameters, and γ_2 is the real-valued parameter which describes the random effect, say $v_{i2}(= \gamma_2 v_i)$, of T_i .

(iii) $v_i \sim N(0, 1)$.

The above model is the joint of mixed linear model and frailty model. The random effect v_i models the dependence between y_i and T_i , and γ_1 and γ_2 are parameters describing the dependence. That is, if the two parameters take the same sign, then y_i and T_i have a positive correlation; otherwise they have a negative correlation.

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