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A Class of Accelerated Means Regression Models for Multiple Type Recurrent Event Data

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Abstract. Recurrent events are frequently observed in biomedical studies, and often more than one type of event is of interest. In this paper, we first propose a general class of accelerated means regression models for multiple type recurrent event data. We then formulate estimating equations for the model parameters, and finally examine asymptotic properties of the parameter estimators.

1. Introduction

In many studies, the event of interest can be experienced more than once per subject. Such outcomes have been termed recurrent event, which are commonly encountered in longitudinal follow-up studies. Medical examples of recurrent events are multiple infection episodes and tumor recurrences. Other examples of recurrent events include repeated breakdowns of a certain machinery in reliability testing and repeated purchases of a certain product in marketing research. Therefore, it is important to study the recurrent events.

As is well-known, many survival models have been proposed to handle recurrent event, and most of the methods are based on modeling the mean function. For example, Pepe and Cai [14] presented a semi-parametric procedure of making inference about the mean function without the Poisson-type assumption. Lawless and Nadeau [6] proposed a class of marginal means models, and Lin et al. [9] studied the proportional means and rates models for counting precesses. Lin and Ying [10] suggested a marginal model for repeated outcomes. Sun, Sun and Liu [16], Liang, Lu and Ying [7] considered some joint models for repeated outcomes and recurrent events via latent variables. Moreover, a class of models which has been developed in many contexts is a time-transformation model, in which all subjects have similar trajectories and the effect of covariates is to alter the time scale of the trajectories. For example, Lin et al.[11] developed an accelerated failure time model to formulate the effects of covariates on the mean function of the counting process for recurrent events. Ghosh [4] presented an accelerated rates model for counting processes in which the effect of covariates is to transform the time scale for a baseline rate function. Sun and Su [17] proposed the accelerated means regression models for recurrent event data. Liu, Mu and Sun [13] presented a class of additive-accelerated means regression models for recurrent event data. Han et al. [5] developed an additive-multiplicative mean model for recurrent event with an informative.

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Often, because subjects' health is assessed in several ways, more than one type of recurrent event may be of interest. For example, in a study of infection following bone marrow transplantation, it is interesting to study different types of recurrent infection simultaneously. Note that several papers have been devoted to the analysis of data involving multiple type recurrent event. Cai and Schaubel [1] presented the marginal means/rates models for multiple type recurrent event data. Dai et al.[2, 3] discussed the general additive-multiplicative rates models and a flexible additive multiplicative rates models for multiple type recurrent event data. In this paper, we formulate a class of semi-parametric means regression model for analysing the multiple type recurrent event data, which includes the proportional means model, the accelerated failure time model and the accelerated rate model as special case.

The reminder of the paper is organized as follows. In Section 2, we present a semi-parametric formulation of the general model and propose an estimating procedure for the model parameters. In Section 3, we study the asymptotic properties of the proposed estimators. Finally, we conclude this paper in Section 4.

2. Model and Estimation Procedure

Suppose that a total of n subjects are observed over time. There are K different types of events of interest, each potentially recurrent and subject to right censoring. Let N^*_{ik} be the number of events of type k that occur over the interval [0, t] for subject i, and Z_{ik} be a $p \times 1$ covariates vector. Let C_{ik} express the follow-up or censoring time. In practice, censoring times for different event types are usually the same for a subject, i.e., $C_{ik} = C$, although this might not always be the case. Assume that C_{ik} is independent of N^*_{ik} conditional on Z_{ik}. Define $N_{ik}(t) = N^*_{ik}(t \wedge C_{ik})$ and $Y_{ik}(t) = I(C_{ik} \geq t)$, where $a \wedge b = \min(a, b)$, and $I(\cdot)$ is an indicator function. The observable data consist of $\{N_{ik}(\cdot), Y_{ik}(\cdot), Z_{ik}\}(i = 1, 2, \cdots, n, k = 1, 2, \cdots, K)$.

The proposed accelerated means regression model for multiple type recurrent event data takes the form

$$E\{N^*_{ik}(t)|Z_{ik}\} = \mu_{0k}(te^{\beta'_{10}Z_{ik}})g(\beta'_{20}Z_{ik}), \tag{1}$$

where β_{10} and β_{20} are p-vector of parameters of interest, and $\mu_{0k}(t)$ is an unspecified baseline mean function for type k of subject i. The link function $g(\cdot)$ is pre-specified and twice continuously differentiable with $g(\cdot) \geq 0$.

Note that, model (1) is a proportional means model when $\beta_{10} = 0$ and $g(x) = e^x$. The choice of $g(x) = 1$ yields the accelerated failure time model for counting processes. When $g(x) = e^x$ and $\beta_{20} = -\beta_{10}$, model (1) reduces to an accelerated rates regression model for multiple type recurrent events.

Let $\tilde{N}_{ik}(t; \beta_1) = N_{ik}(te^{-\beta'_1 Z_{ik}})$ and $Y_{ik}(t; \beta_1) = I(C_{ik} \geq te^{-\beta'_1 Z_{ik}})$. Define:

$$M_{ik}(t; \beta) = \tilde{N}_{ik}(t; \beta_1) - \int_0^t Y_{ik}(s; \beta_1)g(\beta'_2 Z_{ik})d\mu_{0k}(s),$$

where $\beta = (\beta'_1, \beta'_2)'$. Under model (1), $M_{ik}(t; \beta_0)$ are zero-mean stochastic processes where $\beta_0 = (\beta'_{10}, \beta'_{20})'$. For a given β, thus a reasonable estimator for $\mu_{0k}(t)$ is the solution to

$$\sum_{i=1}^n [\tilde{N}_{ik}(t; \beta_1) - \int_0^t Y_{ik}(s; \beta_1)g(\beta'_2 Z_{ik})d\mu_{0k}(s)] = 0, \qquad 0 \leq t \leq \tau$$

where τ is a prespecified constant such that $P(C_{ik} \geq \tau e^{-\beta'_{10}Z_{ik}}) > 0$.

Denote this estimator by $\hat{\mu}_{0k}(t; \beta)$, which is written as:

$$\hat{\mu}_{0k}(t; \beta) = \sum_{i=1}^n \int_0^t \frac{d\tilde{N}_{ik}(s; \beta_1)}{\sum_{i=1}^n Y_{ik}(s; \beta_1)g(\beta'_2 Z_{ik})}. \tag{2}$$

To estimate β_0, using the generalized estimating equation methods [8] and replacing $\mu_{0k}(t)$ with $\hat{\mu}_{0k}(t; \beta)$, we consider two estimating functions for β_{10} and β_{20} as follows:

$$U_1(\beta) = \sum_{i=1}^n \sum_{k=1}^K \int_0^\tau \{Z_{ik} - \bar{Z}_k(t; \beta)\}d\tilde{N}_{ik}(t; \beta_1), \tag{3}$$

and

$$U_2(\beta) = \sum_{i=1}^{n}\sum_{k=1}^{K}\int_0^{\tau}\{W(t, Z_{ik}; \beta) - \bar{W}_k(t, \beta)\}d\tilde{N}_{ik}(t; \beta_1), \tag{4}$$

where $W(t, Z_{ik}; \beta)$ is a known p-dimensional weight function of t, Z_{ik}, β, not in the span of the functions 1 and Z_{ik},

$$\bar{Z}_k(t; \beta) = \frac{\sum_{i=1}^{n} Y_{ik}(t; \beta_1)g(\beta_2' Z_{ik})Z_{ik}}{\sum_{i=1}^{n} Y_{ik}(t; \beta_1)g(\beta_2' Z_{ik})},$$

and

$$\bar{W}_k(t; \beta) = \frac{\sum_{i=1}^{n} Y_{ik}(t; \beta_1)g(\beta_2' Z_{ik})W(t, Z_{ik}; \beta)}{\sum_{i=1}^{n} Y_{ik}(t; \beta_1)g(\beta_2' Z_{ik})}.$$

Let $Z^*_{ik}(t; \beta) = (Z'_{ik}, W(t, Z_{ik}; \beta)')'$, $\bar{Z}^*_k(t; \beta) = (\bar{Z}_k(t; \beta)', \bar{W}_k(t; \beta)')'$, and $U(\beta) = (U_1(\beta)', U_2(\beta)')'$. Then, (3) and (4) can be rewritten as:

$$U(\beta) = \sum_{i=1}^{n}\sum_{k=1}^{K}\int_0^{\tau}\{Z^*_{ik}(t; \beta) - \bar{Z}^*_k(t; \beta)\}d\tilde{N}_{ik}(t; \beta_1).$$

Since $U(\beta)$ is a discrete function of β_1, we define the estimator $\hat{\beta} = (\hat{\beta}_1', \hat{\beta}_2')$ as a zero-crossing of $U(\beta)$ or as a minimiser of $\| U(\beta) \|$ [4, 11] where $\|\nu\| = (\nu'\nu)^{1/2}$ for a vector ν. Many methods are proposed to solve this equation, e.g. direct grid search, the bisection method or the technique of simulated annealing (SA). When there are only a small number of covariates, direct grid search, and the bisection method are recommended. For the high-dimensional covariate vectors, the SA method, which is a generic probabilistic meta-algorithm for the global optimum problem [12], may be more efficient.

When $\hat{\beta} = (\hat{\beta}_1', \hat{\beta}_2')'$ is available, the baseline mean function $\mu_{0k}(t)$ is estimated by the Nelson-Aalen-type estimator $\hat{\mu}_{0k}(t) \equiv \hat{\mu}_{0k}(t; \hat{\beta})$ which is defined in (2).

3. Asymptotic Properties

In order to establish asymptotic properties of the estimators, suppose that the following regularity conditions hold:

(C1) $(N^*_{ik}, C_{ik}, Z_{ik})$ are independent and identically distributed for $i = 1, 2, \cdots, n$.

(C2) $P(Y_{ik}(\tau; \beta_{10}) = 1) > 0$.

(C3) $N_{ik}(t)$, Z_{ik} and $W(t, Z_{ik}; \beta_0)$ are bounded on $[0, \tau]$ for $i = 1, 2, \cdots, n, k = 1, 2, \cdots, K$.

(C4) $g(\cdot)$ is twice continuously differentiable with $g(\cdot) \geq 0$, and $g(\beta_{20}' Z_{ik})$ is locally bounded away.

(C5) $C_{ik}e^{\beta_{10}' Z_{ik}}$ has a bounded density and $\mu_{0k}(t)$ has a bounded second derivative.

(C6) A is nonsingular and is defined as follows:

$$A = \begin{pmatrix} A_{11} & A_{12} \\ A_{21} & A_{22} \end{pmatrix},$$
$$A_{11} = \sum_{k=1}^{K}\int_0^{\tau}[s^{(2)}_{zk}(t) - \bar{z}_k(t)^{\otimes 2}s^{(0)}_k(t)]d\{\lambda_{0k}(t)t\},$$
$$A_{12} = \sum_{k=1}^{K}\int_0^{\tau}[s^{(3)}_{zk}(t) - \bar{z}_k(t)^{\otimes 2}s^{(1)}_k(t)']d\{\mu_{0k}(t)\}, \tag{1}$$

$$A_{21} = \sum_{k=1}^{K} \int_0^{\tau} [s_{wk}^{(2)}(t) - \bar{w}_k(t)\bar{z}(t)s_k^{(0)}(t)']d\{\lambda_{0k}(t)t\},$$

$$A_{22} = \sum_{k=1}^{K} \int_0^{\tau} [s_{wk}^{(3)}(t) - \bar{w}_k(t)s_k^{(1)}(t)']d\{\mu_{0k}(t)\},$$

where $\lambda_{0k}(t) = du_{0k}(t)/dt$, $v^{\otimes 2} = vv'$, $s_k^{(0)}(t)$, $s_k^{(1)}(t)$, $s_{zk}^{(2)}(t)$, $s_{zk}^{(3)}(t)$, $s_{wk}^{(2)}(t)$, $s_{wk}^{(3)}(t)$, $\bar{z}_k(t)$ and $\bar{w}_k(t)$ are respectively the limits of $S_k^{(0)}(t;\beta_0)$, $S_k^{(1)}(t;\beta_0)$, $S_{zk}^{(2)}(t;\beta_0)$, $S_{zk}^{(3)}(t;\beta_0)$, $S_{wk}^{(2)}(t;\beta_0)$, $S_{wk}^{(3)}(t;\beta_0)$, $\bar{Z}_k(t;\beta_0)$ and $\bar{W}_k(t;\beta_0)$, $\dot{g} = dg(t)/dt$ and

$$S^{(0)}(t;\beta) = n^{-1}\sum_{i=1}^{n} Y_{ik}(t;\beta_1)g(\beta_2' Z_{ik}),$$

$$S^{(1)}(t;\beta) = n^{-1}\sum_{i=1}^{n} Y_{ik}(t;\beta_1)\dot{g}(\beta_2' Z_{ik})Z_{ik},$$

$$S_z^{(2)}(t;\beta) = n^{-1}\sum_{i=1}^{n} Y_{ik}(t;\beta_1)g(\beta_2' Z_{ik})Z_{ik}^{\otimes 2},$$

$$S_z^{(3)}(t;\beta) = n^{-1}\sum_{i=1}^{n} Y_{ik}(t;\beta_1)\dot{g}(\beta_2' Z_{ik})Z_{ik}^{\otimes 2},$$

$$S_w^{(2)}(t;\beta) = n^{-1}\sum_{i=1}^{n} Y_{ik}(t;\beta_1)g(\beta_2' Z_{ik})W(t,Z_i;\beta)Z_{ik}',$$

$$S_w^{(3)}(t;\beta) = n^{-1}\sum_{i=1}^{n} Y_{ik}(t;\beta_1)\dot{g}(\beta_2' Z_{ik})W(t,Z_i;\beta)Z_{ik}'.$$

To establish the asymptotic properties of $\hat{\beta}$, we first need to establish the asymptotic properties of $U(\beta_0)$.

Theorem 1 Under conditions (C1-C4), $n^{-1/2}U(\beta_0)$ is asymptotically normal with mean zero and covariance matrix $\Sigma = E\{d_i d_i'\}$ where $d_i = \sum_{k=1}^{K}\int_0^{\tau}[Z_{ik}^*(t;\beta_0) - \bar{z}_k^*(t)]dM_{ik}(t;\beta_0)$ and $\bar{z}_k^*(t) = (\bar{z}_k(t)', \bar{w}_k(t)')'$.

Proof A simple algebraic manipulation yields

$$U(\beta_0) = \sum_{i=1}^{n}\sum_{k=1}^{K}\int_0^{\tau}[Z_{ik}^*(t;\beta_0) - \bar{Z}^*(t;\beta_0)]dM_{ik}(t;\beta_0).$$

Using arguments similar to those in the proof of Theorem 1 of Lin et al. [11], it is easy to obtain that

$$n^{-1/2}U(\beta_0) = n^{-1/2}\sum_{i=1}^{n} d_i + o_p(1).$$

Utilizing the multivariate central limit theorem, $n^{-1/2}U(\beta_0)$ converges in distribution to a normal random variable with mean zero and variance matrix $\Sigma = E\{d_i d_i'\}$. This completes the proof. □

Let $\mathcal{U}(\beta)$ be the limit of $n^{-1}U(\beta)$, and $\mathcal{N}$ be a compact neighborhood of β_0 on which $\|U(\beta)\|$ is minimized to obtain $\hat{\beta}$.

Theorem 2 Assume that conditions (C1-C6) hold, and $\mathcal{U}(\beta) \neq 0$ for all $\beta \in \mathcal{N}$ but $\beta \neq \beta_0$. Then $\hat{\beta}$ is strongly consistent and $n^{1/2}(\hat{\beta} - \beta_0)$ converges in distribution to zero-mean normal with covariance matrix $A^{-1}\Sigma(A^{-1})'$.

Proof Clearly, $U(\beta) = (U_1(\beta)', U_2(\beta)')'$. Firstly, we establish the asymptotic properties of $U_1(\beta)$.

$$U_1(\beta) - U_1(\beta_0) = [U_1(\beta_1,\beta_2) - U_1(\beta_1,\beta_{20})] + [U_1(\beta_1,\beta_{20}) - U_1(\beta_{10},\beta_{20})]. \quad (5)$$

For the first term on the right-hand side of (5), using the Taylor series expansion, we can get that

$$U_1(\beta_1,\beta_2) - U_1(\beta_1,\beta_{20}) = \dot{U}_1(\beta_1,\beta_{20})(\beta_2-\beta_{20}) + o_p(n\|\beta_2-\beta_{20}\|),$$

where $\dot{U}_1(\beta_1,\beta_2)$ is the derivative of $U_1(\beta_1,\beta_2)$ with respect to β_2.
It is easy to check that

$$\dot{U}_1(\beta_1,\beta_{20}) = -n\sum_{k=1}^{K}\int_0^\tau [S_z^{(3)}(t;\beta_1,\beta_{20}) - \bar{Z}(t;\beta_1,\beta_{20})S^{(1)}(t;\beta_1,\beta_{20})]d\mu_{0k}(t).$$

For any sequence $\epsilon_n \to 0$ and $\|\beta-\beta_0\| \le \epsilon_n$, by uniform strong law of large numbers [15], we have

$$U_1(\beta_1,\beta_2) - U_1(\beta_1,\beta_{20}) = -nA_{12}(\beta_2-\beta_{20}) + o_p(n\|\beta_2-\beta_{20}\|).$$

For the second term of (5), we have

$$\begin{aligned}
&U_1(\beta_1,\beta_{20}) - U_1(\beta_{10},\beta_{20})\\
&= \sum_{i=1}^{n}\sum_{k=1}^{K}\int_0^\tau [Z_{ik}(t;\beta_1,\beta_{20}) - \bar{Z}(t;\beta_1,\beta_{20})]dM_{ik}(t;\beta_1,\beta_{20})\\
&\quad - \sum_{i=1}^{n}\sum_{k=1}^{K}\int_0^\tau [Z_{ik}(t;\beta_{10},\beta_{20}) - \bar{Z}(t;\beta_{10},\beta_{20})]dM_{ik}(t;\beta_{10},\beta_{20})\\
&= \Big\{\sum_{i=1}^{n}\sum_{k=1}^{K}\int_0^\tau [Z_{ik}(t;\beta_1,\beta_{20}) - \bar{Z}(t;\beta_1,\beta_{20})][d\tilde{N}_{ik}(t;\beta_1) - Y_{ik}(t;\beta_1)g(\beta_{20}'Z_{ik})d\mu_{0k}(te^{(\beta_{10}-\beta_1)'Z_{ik}})]\\
&\quad - \sum_{i=1}^{n}\sum_{k=1}^{K}\int_0^\tau [Z_{ik}(t;\beta_{10},\beta_{20}) - \bar{Z}(t;\beta_{10},\beta_{20})][d\tilde{N}_{ik}(t;\beta_{10}) - Y_{ik}(t;\beta_{10})g(\beta_{20}'Z_{ik})d\mu_{0k}(t)]\Big\}\\
&\quad + \sum_{i=1}^{n}\sum_{k=1}^{K}\int_0^\tau [Z_{ik}(t;\beta_1,\beta_{20}) - \bar{Z}(t;\beta_1,\beta_{20})]Y_{ik}(t;\beta_1)g(\beta_{20}'Z_{ik})d[\mu_{0k}(te^{(\beta_{10}-\beta_1)'Z_{ik}}) - \mu_{0k}(t)]. \qquad (6)
\end{aligned}$$

Applying the technique of Ying [18] and Lin et al. [11], we can find that the first term on the right-hand side of (6) is of order $o_p(n^{1/2})$.
Moreover, it follows from a Taylor series expansion that

$$\mu_{0k}(te^{(\beta_{10}-\beta_1)'Z_{ik}}) - \mu_{0k}(t) = \{\lambda_{0k}(t) + o_p(1)\}t(\beta_{10}-\beta_1)'Z_{ik}.$$

Then, the second term on the right-hand side of (6) is rewritten as:

$$\begin{aligned}
&n\sum_{k=1}^{K}\int_0^\tau [S_z^{(2)}(t;\beta_1,\beta_{20}) - \bar{Z}(t;\beta_1,\beta_{20})^{\otimes 2}S^{(0)}(t;\beta_1,\beta_2)]d\{t\lambda_{0k}(t)\}(\beta_{10}-\beta_1) + o_p(n\|\beta_{10}-\beta_1\|)\\
&= -nA_{11}(\beta_1-\beta_{10}) + o_p(n\|\beta_1-\beta_{10}\|).
\end{aligned}$$

Therefore, for any sequence $\epsilon_n \to 0$, it follows that

$$\sup_{\|\beta-\beta_0\|\le\epsilon_n} \frac{\|U_1(\beta) - U_1(\beta_0) + n(A_{11},A_{12})(\beta-\beta_0)\|}{n^{1/2} + n\|\beta-\beta_0\|} = o_p(1)$$

almost surely.
Similarly, for any sequence $\epsilon_n \to 0$, we have

$$\sup_{\|\beta-\beta_0\|\le\epsilon_n} \frac{\|U_2(\beta) - U_2(\beta_0) + n(A_{21},A_{22})(\beta-\beta_0)\|}{n^{1/2} + n\|\beta-\beta_0\|} = o_p(1)$$

almost surely.

For any sequence $\epsilon_n \to 0$, using the last two equalities, we find that

$$\sup_{\|\beta-\beta_0\|\le\epsilon_n} \frac{\|U(\beta)-U(\beta_0)+nA(\beta-\beta_0)\|}{n^{1/2}+n\|\beta-\beta_0\|} = o_p(1) \tag{7}$$

almost surely.

Furthermore, it is easy to show that $\mathcal{U}(\beta_0)=0$. Note that $n^{-1}U(\beta)\to\mathcal{U}(\beta)$ uniformly in N and $\mathcal{U}(\beta_0)\neq 0$ for all $\beta\neq\beta_0$.

Following the argument used in Theorem 2 of Lin et al. [11], we can get that $\hat\beta$ is strongly consistent under the regularity conditions (C1)-(C5).

In addition, by the definition of $\hat\beta$ and condition (C6), it follows from (7) that $n^{1/2}(\hat\beta-\beta_0)$ is asymptotically normal with mean zero and covariance matrix $A^{-1}\sum(A^{-1})'$. This completes the proof. □

Theorem 3 Under conditions (C1-C6), $n^{1/2}(\hat\mu_{0k}(t)-\mu_{0k}(t))$ converges weakly to a zero-mean Gaussian process with covariance function $\Gamma_{kl}(s,t;\beta_0)=E\{\Psi_{1k}(s;\beta_0)\Psi_{1l}(t;\beta_0)\}$, where

$$\Psi_{ik}(t;\beta_0)=\int_0^t \frac{dM_{ik}(u;\beta_0)}{s^{(0)}(u)} - h_k(t)'A^{-1}\int_0^t [Z^*_{ik}(u;\beta_0)-\bar z^*_k(u)]dM_{ik}(u;\beta_0),$$

$$h_{1k}(t)=\int_0^t \bar z^*_k(u)d[\lambda_{0k}(u)u],\qquad h_{2k}(t)=\int_0^t \frac{s^{(1)}(u)}{s^{(0)}(u)}d\mu_{0k}(u),$$

and $h(t)=(h_{1k}(t)',h_{2k}(t)')'$.

Proof Note that

$$\begin{aligned}\hat\mu_{0k}(t)-\mu_{0k}(t) &= [\hat\mu_{0k}(t;\hat\beta_1,\hat\beta_2)-\hat\mu_{0k}(t;\hat\beta_1,\beta_{20})]+[\hat\mu_{0k}(t;\hat\beta_1,\beta_{20})-\hat\mu_{0k}(t;\beta_{10},\beta_{20})]\\ &\quad +[\hat\mu_{0k}(t;\beta_{10},\beta_{20})-\mu_{0k}(t;\beta_{10},\beta_{20})].\end{aligned} \tag{8}$$

Using a Taylor expansion and the uniform strong law of large number [15], we obtain that

$$\hat\mu_{0k}(t;\hat\beta_1,\hat\beta_2)-\hat\mu_{0k}(t;\hat\beta_1,\beta_{20}) = -h_{2k}(t)'(\hat\beta_2-\beta_{20})+o_p(n^{-1/2})$$

uniformly in $t\in[0,\tau]$.

For the second term on the right-hand side of (8), we have

$$\hat\mu_{0k}(t;\hat\beta_1,\beta_{20})-\hat\mu_{0k}(t;\beta_{10},\beta_{20}) = -h_{1k}(t)'(\hat\beta_1-\beta_{10})+o_p(n^{-1/2})$$

uniformly in $t\in[0,\tau]$.

It is easy to verify that

$$\hat\mu_{0k}(t;\beta_{10},\beta_{20})-\mu_{0k}(t;\beta_{10},\beta_{20}) = n^{-1}\sum_{i=1}^n\int_0^t \frac{dM_{ik}(\mu;\beta_0)}{s^{(0)}(\mu)}+o_p(n^{-1/2})$$

uniformly in $t\in[0,\tau]$.

Thus, it follows from Theorem 1 that

$$n^{1/2}(\hat\mu_{0k}(t)-\mu_{0k}(t)) = n^{-1/2}\sum_{i=1}^n \Psi_{ik}(t;\beta_0)+o_p(1)$$

uniformly in $t\in[0,\tau]$.

Since $\Psi_{ik}(t;\beta_0)$ are independent zero-mean random variables for each t, the multivariate central limit theorem implies that $n^{-1/2}\sum_{i=1}^n\Psi_{ik}(t;\beta_0)$ converges in finite dimensional distributions to a zero-mean Gaussian process.

Using the modern empirical theory as in Lin et al. [9], we can show that $n^{-1/2}\sum_{i=1}^n\Psi_{ik}(t;\beta_0)$ is tight. Thus, $n^{1/2}(\hat\mu_{0k}(t)-\mu_{0k}(t))$ converges weakly to a zero-mean Gaussian process with covariance function $\Gamma_{kl}(s,t;\beta_0)$. This completes the proof. □

4. Conclusion

In this paper, the multiple type recurrent event data is considered. We first propose a general class of accelerated means regression models which are flexible and include some commonly used models as special cases for such a data. We then formulate estimating equations for the model parameters. Finally, we examine asymptotic properties of the parameter estimators.

References

[1] J.W. Cai, D.E. Schaubel, Marginal means/rates models for multiple type recurrent event data, Lifetime Data Analysis 10 (2004) 121–138.

[2] J.J. Dai, S. He, General additive-mulitiplicative rates models for multiple type recurrent event data, Chinese Journal of Engineering Mathematics (in Chinese) 25 (2008) 979–988.

[3] J.J. Dai, H.B. Liu, Z.H. Yang, Flexible additive multiplicative rates model for multiple type recurrent event data, Acta Mathematicae Applicatae Sinica (in Chinese) 32 (2009) 939–950.

[4] D. Ghosh, Accelerated rates regression models for recurrent failure data, Lifetime Data Analysis 10 (2004) 247–261.

[5] M. Han, X. Song, L. Sun, L. Liu, An additive-multiplicative mean model for marker data contingent on recurrent event with an informative terminal event, Statistica Sinica 1 (2014) 1-32.

[6] J.F. Lawless, C. Nadeau, Some simple robust methods for the analysis of recurrent events, Technometrics 37 (1995) 158–168.

[7] Y. Liang, W. Lu, Z. Ying, Joint modeling and analysis of longitudinal data with informative observation times, Biometrics 65 (2009) 377–384.

[8] K.Y. Liang, S.L. Zeger, Longitudinal data analysis using generalized linear models, Biometrika 73 (1986) 13–22.

[9] D.Y. Lin, L.J. Wei, I. Yang, Z. Ying, Semiparametric regression for the mean and rate function of recurrent events, Journal of the Royal Statistical Society: Series B (Statistical Methodology) 69 (2000) 711–730.

[10] D.Y. Lin, Z. Ying, Semiparametric and nonparametric regression analysis of longitudinal data, Journal of the American Statistical Association 96 (2001) 103–126.

[11] D.Y. Lin, L.J. Wei, Z. Ying, Accelerated failure time models for counting processes, Biometrika 85 (1998) 609–618.

[12] D.Y. Lin, C. J. Geyer, Computational methods for semiparametric linear regression with censored dada, Journal of Computational and Graphical Statistics 1 (1992) 77–90.

[13] L. Liu, X. Mu, L. Sun, A class of additive-accelerated means regression models for recurrent event data, Science China Mathematics 53 (2010) 3139–3151.

[14] M.S. Pepe, J. Cai, Some graphical displays and marginal regression analyses for recurrent failure times and time-dependent covariates, Journal of the American Statistical Association 88 (1993) 811–820.

[15] D. Pollard, Empirical processes: theory and applications, Institute of Mathematical Statistics, Hayward, California, 1990.

[16] J. Sun, L. Sun, D. Liu, Regression analysis of longitudinal data in the presence of informative observation and censoring times, Journal of the American Statistical Association 102 (2007) 1397–1406.

[17] L.Q. Sun, B. Su, A class of accelerated means regression models for recurrent event data, Lifetime Data Analysis 14 (2008) 357–375.

[18] Z. Ying, A large sample study of rank estimation for censored regression data, The Annals of Statistics 21 (1993) 76–99.