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Dynamic Regression with Recurrent Events

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SUMMARY:

Recurrent events often arise in follow-up studies where a subject may experience multiple occurrences of the same event. Most regression models with recurrent events tacitly assume constant effects of covariates over time, which may not be realistic in practice. To address time-varying effects, we develop a dynamic regression model to target the mean frequency of recurrent events. We propose an estimation procedure which fully exploits observed data. Consistency and weak convergence of the proposed estimator are established. Simulation studies demonstrate that the proposed method works well, and two real data analyses are presented for illustration.

Keywords

Counting process; Event history analysis; Marginal modeling; Multiplier bootstrap; Multivariate survival data; Varying-effects model

1. Introduction

Recurrent events are observed in event history studies where multiple episodes of the same event occur for a subject. Examples in biomedical studies include series of opportunistic infections in AIDS patients and successive pulmonary exacerbations in cystic fibrosis patients. By the multiplicity nature of recurrent events, an intra-individual correlation between events that may not be explained by covariates is often observed. Therefore it is important to accommodate such dependence in analysis of recurrent events.

Most regression models with recurrent events may be categorized as either conditional or marginal modeling. In conditional regression modeling, the intensity function of a recurrent event process is specified; see Prentice, Williams, and Peterson (1981) and Andersen and Gill (1982) among others. Thus conditional models could be more useful in making an individual-level prediction. On the other hand, in marginal regression modeling, either the overall rate or the mean frequency of recurrent event processes is specified by covariates; see Pepe and Cai (1993) and Lawless and Nadeau (1995) among others. Thus marginal models have an intuitive interpretation on covariate effects at the population level. For example, the

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Supporting Information

Web Tables referenced in Section 4 are available with this paper at the Biometrics website on Wiley Online Library. Also an R package implementing our method is available on GitHub: <https://github.com/statsoh/drrc>.

proportional means model by Lin et al. (2000) postulates constant proportional effects of covariates on a baseline mean frequency function. As an alternative, Lin, Wei, and Ying (1998) proposed the accelerated failure time model with recurrent events in which constant effects of covariates are specified through time-scale change of the mean frequency function.

Most of the existing models with recurrent events assume constant effects of covariates over time. This simplistic assumption is often unrealistic in practice. In a clinical study for AIDS patients, for example, a treatment might take time to reach its full efficacy rather than right after randomization; meanwhile, the treatment effect might also erode over time as drug resistance develops, e.g., Eshleman et al. (2001) and Wu et al. (2005). Such circumstances call for a more general model to accommodate evolving effects of covariates, as investigated in a few recent developments. In particular, the temporal process regression by Fine, Yan, and Kosorok (2004) accommodates temporal effects of covariates on a baseline mean frequency at a given time point. Chiang and Wang (2009) proposed a varying-coefficient model for the overall rate of recurrent events and developed a kernel smoothing-based estimation procedure. Both of the two marginal models are formulated on the frequency scale of recurrent events. On the other hand, Huang and Peng (2009) proposed the accelerated recurrence time model in which time-varying effects of covariates are modeled through time-scale change of the mean frequency function. Along a similar line, Sun et al. (2016) proposed a generalization of the univariate censored quantile regression of Peng and Huang (2008) for recurrent events.

In this paper, we develop a dynamic regression model to target the mean frequency of recurrent events. By allowing regression coefficients to vary over time, it generalizes the proportional means model of Lin et al. (2000). Meanwhile, our proposed model can be viewed as a special case of the temporal process regression of Fine et al. (2004). The model is described in Section 2. We propose estimation and inference procedures in Section 3, also present large sample properties of the proposed estimator. The performance of the proposed estimator is evaluated through Monte Carlo simulations in Section 4. In Section 5, two real data analyses are presented for illustration of the proposed method. We conclude with final remarks in Section 6.

2. Model

Let $N^*(t)$ denote the number of recurrent events of interest for a subject in time interval $[0, t]$ and $\mathbf{Z}$ be a p -dimensional covariate vector. We develop a dynamic regression model with recurrent events

$$E\{N^*(t) \mid \mathbf{Z}\} = \exp\{\beta_0(t)^T \tilde{\mathbf{Z}}\}, \quad \text{for all } t \geq 0, \quad (1)$$

where $\beta_0(t) = \{\log \mu_0(t), \mathbf{b}_0(t)^T\}^T$ and $\tilde{\mathbf{Z}} = (1, \mathbf{Z}^T)^T$. Here $\mu_0(t)$ denotes the baseline mean frequency of recurrent events, i.e., with all covariates being zero; and $\mathbf{b}_0(t)$ is the p -dimensional time-varying regression coefficient vector. Model (1) postulates time-varying multiplicative effects of covariates on the baseline mean frequency function. Note $\mu_0(0) = 0$ because $N^*(0) = 0$.

In many circumstances the underlying counting process $N^*(\cdot)$ for a subject is only observed up to a random follow-up time, say, C . Therefore what are observed are an observed event process $N(\cdot) = N^*(\cdot \wedge C)$ and an *at-risk* process $Y(\cdot) = I(C \geq \cdot)$, where $\wedge$ and $I(\cdot)$ are the minimization operator and the indicator function, respectively. We adopt the conditional independence assumption on the censoring mechanism

$$N^*(\cdot) \perp\!\!\!\perp C \mid \mathbf{Z}.$$

Model (1) is a structure-imposed nonparametric model as the slope coefficients depend on time. In the special case of a k -sample problem, it is a saturated model, in which no structure is actually imposed. Note that our proposed model with time-varying coefficients generalizes the proportional means model of Lin et al. (2000). Meanwhile, our model turns out to be the special case of the temporal process regression of Fine et al. (2004) when log link and recurrent events are considered.

3. Estimation and Inference

3.1 Point Estimation

Suppose an observed data set $\{N_i(\cdot); Y_i(\cdot); C_i; \mathbf{Z}_i\}_{i=1}^n$ consists of n independent replicates of $\{N(\cdot); Y(\cdot); C; \mathbf{Z}\}$. Under model (1) with the conditional independence assumption on the censoring mechanism, it follows $E\{N(t) \mid \mathbf{Z}\} = E[\int_0^t Y(s) d \exp\{\beta_0(s)^T \tilde{\mathbf{Z}}\} \mid \mathbf{Z}]$. This motivates our proposed estimating integral equation

$$n^{-1} \sum_{i=1}^n \tilde{\mathbf{Z}}_i [N_i(t) - \int_0^t Y_i(s) d \exp\{\beta(s)^T \tilde{\mathbf{Z}}_i\}] = 0, \quad \text{for all } t \geq 0. \quad (2)$$

This equation is similar to the one for the univariate survival model in Peng and Huang (2007). However, under the proposed model (1) the left-hand side of equation (2) does not have a martingale structure when $\beta(\cdot)$ is $\beta_0(\cdot)$, unlike the case for univariate survival data.

Equation (2) admits a càdlàg solution, $\hat{\beta}(t)$, which has jumps only at observed event times. Write $0 < x_1 < x_2 < \dots < x_M$ as the observed event times of all subjects in the sample, and denote $\mathbf{Z}_{(1)}, \mathbf{Z}_{(2)}, \dots, \mathbf{Z}_{(M)}$ as the associated covariate vectors. Note that one individual may have multiple contributions to $\{x_j, \mathbf{Z}_{(j)}\}_{j=1}^M$. The initial value, $\hat{\beta}(0)$, satisfies $\exp\{\hat{\beta}(0)^T \tilde{\mathbf{Z}}_i\} = 0$ for all i . Then, at time x_1 , the estimating integral equation (2) reduces to

$$\tilde{\mathbf{Z}}_{(1)} - \sum_{i=1}^n Y_i(x_1) \tilde{\mathbf{Z}}_i \exp\{\hat{\beta}(x_1)^T \tilde{\mathbf{Z}}_i\} = 0. \quad (3)$$

Sequentially at the observed event times $(x_j)_{j=2}^M$, the estimating integral equation (2) reduces to

$$\tilde{\mathbf{Z}}_{(j)} - \sum_{i=1}^n Y_i(x_j) \tilde{\mathbf{Z}}_i [\exp\{\beta(x_j)^T \tilde{\mathbf{Z}}_i\} - \exp\{\hat{\beta}(x_{j-1})^T \tilde{\mathbf{Z}}_i\}] = 0, \quad j = 2, \dots, M. \quad (4)$$

Both estimating equations (3) and (4) have good computational properties since their left-hand sides are monotone functions.

If censoring is absent up to time t , the estimating integral equation (2) implies

$$n^{-1} \sum_{i=1}^n \tilde{\mathbf{Z}}_i [N_i(t) - \exp\{\beta(t)^T \tilde{\mathbf{Z}}_i\}] = 0.$$

This estimating equation coincides with the one in Fine et al. (2004) when the natural logarithm is adopted for the link function in their model. Consequently an identical estimator is obtained. When censoring is present, however, equation (2) fully utilizes the observed data, whereas the estimating equation of Fine et al. (2004),

$\sum_{i=1}^n Y_i(t) \tilde{\mathbf{Z}}_i [N_i(t) - \exp\{\beta(t)^T \tilde{\mathbf{Z}}_i\}] = 0$, uses the data only from uncensored observation as of the given time point of interest. Therefore, our estimator tends to be more efficient as shown later in our simulation studies.

3.2 Large Sample Properties

We establish the uniform consistency and the weak convergence of the proposed estimator $\hat{\beta}(\cdot)$. Write $\|\cdot\|$ and $\text{eigmin}(\cdot)$ as the Euclidean norm and the minimum eigenvalue of a positive semidefinite matrix, respectively. Write $\beta_0(t)$ as the true value of $\beta(t)$. We postulate the following regularity conditions:

- C1. there exists a time point $\kappa > 0$ such that $Pr(C > \kappa) = 1$;
- C2. $N(\tau)$ is bounded, where τ is a fixed time point satisfying $Pr(C > \tau) > 0$ for $\kappa < \tau < \infty$;
- C3. $\|\mathbf{Z}\|$ is bounded;
- C4. $\sup_{t \in [\kappa, \tau]} \|\beta_0(t)\|$ is bounded;
- C5. $\beta_0(t)$ is continuously differentiable for $t \in (\kappa, \tau]$;
- C6. $\inf_{t \in [0, \tau]} \text{eigmin} E\{Y(t) \tilde{\mathbf{Z}} \tilde{\mathbf{Z}}^T\}$ is bounded away from zero.

The logarithm of a baseline mean frequency function is negative infinity, i.e., $\log \mu_0(0) = -\infty$, which creates a challenge in the asymptotic study. To avoid this issue, we focus on the properties of $\hat{\beta}(t)$ over $t \in [\kappa, \tau]$ for some small κ and impose condition C1. As such, $\hat{\beta}(\kappa)$ is the same as an estimator of Fine et al. (2004) and its properties follow the standard M -estimation theory. Other conditions, C2 to C6, are technical assumptions and fairly standard with varying-coefficient regression models.

THEOREM 1: Under regularity conditions C1-C6, $\sup_{t \in [\kappa, \tau]} \|\hat{\beta}(t) - \beta_0(t)\| \rightarrow 0$, almost surely.

THEOREM 2: Under regularity conditions C1-C6, $n^{1/2}\{\hat{\beta}(\cdot) - \beta(\cdot)\}$ on $(\kappa, \tau]$ weakly converges to a mean-zero Gaussian process.

The proofs are relegated to the Appendix.

3.3 Interval Estimation

Inference may be based on Theorem 2. In particular for a finite-dimensional quantity, e.g., $\beta_0(t)$ for a given t , asymptotic variance can be estimated and subsequently confidence interval may be constructed. However, this approach is difficult if not impossible to construct confidence band for infinite-dimensional quantities such as $\beta_0(\cdot)$; see related discussion in Lin et al. (1994) and Huang (2014) in different contexts. We instead propose a nonparametric bootstrap inference procedure using multiplier bootstrap; see Rubin (1981), Kosorok (2008) and Huang (2014). To be specific, we propose a bootstrap estimating integral equation

$$n^{-1} \sum_{i=1}^n \xi_i \tilde{Z}_i [N_i(t) - \int_0^t Y_i(s) d \exp\{\beta(s)^T \tilde{Z}_i\}] = 0, \quad \text{for all } t \geq 0, \quad (5)$$

where $(\xi_i)_{i=1}^n$ are independent and identically distributed, following the standard exponential distribution. Denote a solution to this equation (5) by $\beta^*(\cdot)$. Then based on B bootstrap resamples, a set of bootstrap solutions $\{\beta_b^*(\cdot)\}_{b=1}^B$ can be obtained. At any given time t , the variance of estimator $\hat{\beta}(t)$ can be estimated by the sample variance of $\{\beta_b^*(t)\}_{b=1}^B$. Provided this variance estimate, a $100(1 - \alpha)\%$ point-wise confidence interval for $\beta_0(t)$ can be constructed by the normal approximation centered at $\hat{\beta}(t)$. Alternatively, a confidence interval can be simply constructed with the $(\alpha/2)$ th and $(1-\alpha/2)$ th quantiles of the empirical distribution of $\beta^*(t)$. Given the solutions $\hat{\beta}(\cdot)$ and $\{\beta_b^*(\cdot)\}_{b=1}^B$, we propose to construct a $100(1 - \alpha)\%$ confidence band for $\{\beta_0(t) : t \in (l, u)\}$ with $\{\hat{\beta}(t) \pm \gamma_\alpha : t \in (l, u)\}$. Here γ_α is the $(1 - \alpha/2)$ th quantile of the empirical distribution of J^* , where $J_b^* = \sup_{t \in [l, u]} |\beta_b^*(t) - \hat{\beta}(t)|$ for $b = 1, \dots, B$.

3.4 Average Effect and Test for Varying Effect

Our estimator $\hat{\beta}(\cdot)$ can provide a profile of time-varying effects of covariates over time. However, one may be interested in average effects of covariates over time interval $(l, u]$ for $0 < l < u < \infty$. That is, $\bar{\beta}_0(l, u) \equiv (u - l)^{-1} \int_l^u \beta_0(t) dt$, see Peng and Huang (2008) for its usage in quantile regression. Therefore based on $\hat{\beta}(\cdot)$, we propose a natural estimator of the average effects $\bar{\hat{\beta}}(l, u) = (u - l)^{-1} \int_l^u \hat{\beta}(t) dt$.

Moreover, we consider the null hypothesis testing for constant vs. time-varying effects

$$H_0: \mathbf{c}^\top \beta_0(t) \text{ is a constant for all } t \in (l, u],$$

where $\mathbf{c}$ is a known $(p+1)$ -dimensional vector. In the special case of testing the varying effect of the i th covariate, the $(i+1)$ th component of $\mathbf{c}$ is one and zeros elsewhere. To evaluate H_0 , we propose a test statistic $\mathcal{T} = n^{1/2} \int_l^u \mathbf{c}^\top \{\hat{\beta}(t) - \bar{\beta}(l, u)\} \Xi(t) dt$, where $\Xi(t)$ is a known nonnegative weight function. The identity function $\Xi(t) = t$ is considered to be a good candidate for the weight when a linear changing effect is reasonable. Note that the limiting distribution of $\mathcal{T}$ is a Gaussian because $\mathcal{T}$ is a linear function of $\hat{\beta}(\cdot)$. For variance estimation of the limiting distribution of $\mathcal{T}$, we consider

$\mathcal{T}^* = n^{1/2} \int_l^u \mathbf{c}^\top \{\beta^*(t) - \bar{\beta}^*(l, u)\} \Xi(t) dt$ in a bootstrap sample as the counter part of $\mathcal{T}$, where $\bar{\beta}^*(l, u) = (u-l)^{-1} \int_l^u \beta^*(t) dt$. Since the limiting distribution of $\mathcal{T}$ under H_0 is equivalent to the limiting conditional distribution of $\mathcal{T}^*$ given the observed data, a p-value for a constant effect test can be computed based on the bootstrap replicates of $\mathcal{T}^*$.

4. Simulation Studies

We conducted Monte Carlo simulations to investigate finite-sample properties of the proposed estimator. Throughout the simulations, the underlying baseline mean frequency function was the identity function of time t , i.e., $\mu_0(t) = t$. To induce an intra-individual correlation, a subject-level random frailty η was generated from the unit-mean gamma distribution with $\text{Var}(\eta) = \sigma^2 = 0, 0.5, \text{ and } 1$. Note that larger σ^2 leads to higher intra-individual correlation. The sample size n in each data set was 200, and the bootstrap size B was 500. Under each frailty scenario, 1,000 Monte Carlo data sets were simulated.

For comparison with the proposed method, we also considered the temporal process regression method of Fine et al. (2004) and the proportional means model of Lin et al. (2000). For the proportional means model, we used the same estimates from the conventional estimation based on the whole observed data, regardless of the time interval under consideration for averaging.

4.1 Simulation 1: Single Covariate with Constant Effect

We first considered a single covariate with constant multiplicative effect on the baseline mean frequency. The covariate followed the uniform[0, 1] distribution, and its fixed regression coefficient $b_0(\cdot)$ was 0.5. Random follow-up time C was from the uniform[0, 3] distribution.

Table 1 reports a summary of the Monte Carlo simulations for both of the proposed method and the temporal process regression method: empirical biases, empirical standard deviations, average standard error estimates, and empirical coverage probabilities of Wald-type 95% confidence intervals at the predetermined time points. First of all, it is shown that all the estimates were close to the estimands over time. Moreover, the averages of the estimated standard errors agreed quite well with the empirical standard deviations. This indicates that

the estimated standard errors based on the proposed resampling procedure approximate the true sampling variation well. When the variance of random frailty was increased, the empirical standard deviations increased and the empirical coverage probabilities decreased on the whole. This indicates that an extra variability was introduced in estimation by the increased dependence between events. On the whole, the Monte Carlo biases of estimator of Fine et al. (2004) were comparable to the ones based on the proposed method. However, relatively large empirical standard deviations were observed for the temporal process regression estimator, even more so at the end of the follow-up. This low efficiency of the temporal process regression estimator was attributed to the fact that in its estimation procedure, the data only from uncensored observation at a given time are used in cross-sectional fashion.

Table 2 reports the three methods' estimation performance for the average effect of covariate. For each of the three intervals under consideration, the Monte Carlo empirical biases were close to zero relative to the corresponding empirical standard deviations over the different intra-individual correlation scenarios. In case of no dependence between events $\sigma^2 = 0$, the proportional means model of Lin et al. (2000) had smallest empirical standard deviations as expected. However, the Monte Carlo standard deviations increased by a great deal when an intra-individual correlation was introduced, i.e., with $\sigma^2 = 0.5$ and 1. Indeed, the finite-sample efficiency of estimator of Lin et al. (2000) became comparable to the ones based on the other two methods. On the other hand, for the time interval which includes the end of the follow-up, i.e., $(l, u] = (0, 3]$, the temporal process regression estimator of Fine et al. (2004) had larger Monte Carlo biases and big discrepancies between the empirical standard deviations and the average of the estimated standard errors. The temporal process regression is a robust method in general providing unbiased estimates in large sample. However, our simulation results with practical sample size indicate that its estimator tended to be highly variable when a time interval of interest included the end of the study time, in which less events were observed.

4.2 Simulation 2: Single Covariate with Time-Varying Effect

In the second simulation, we considered a single covariate with decreasing time-varying effect. The covariate followed the uniform[0, 1], and its time-varying coefficient $b_0(t)$ was $\exp\{-t/\exp(1)\}$. Random follow-up time C was generated from the uniform[0, 3].

Table 3 shows that the empirical biases of the considered estimators were close to zero relative to the corresponding Monte Carlo standard deviations. Notably all of the empirical standard deviations of the proposed estimator were smaller than those based on the temporal process regression method. Table 4 summarizes the simulation results for the average of the time-varying coefficient $\bar{\beta}_0(l, u)$. Regardless of degrees of intra-individual correlations, the

Monte Carlo biases of the proposed average effect estimator $\bar{\beta}(l, u)$ were close to zero relative to the empirical standard deviations. By contrast, the average estimator based on the temporal process regression had larger empirical biases and empirical standard deviations, especially when the time interval of interest contained the end-part of the study follow-up, i.e., interval $(l, u] = (0, 3]$; the similar pattern was observed in Table 2.

4.3 Simulation 3: Two Covariates with Constant and Time-Varying Effects

We further considered two covariates, one with varying effect and the other with constant effect. Covariate $Z^{(1)}$ was randomly generated from the trimmed normal distribution over range $[0, 1]$ with mean $1/3$ and variance 1 , and had time-varying coefficient $b_0^{(1)} = \exp\{-t / \exp(1)\}$. Covariate $Z^{(2)}$ was from the uniform $[0, 1]$ distribution, having the constant coefficient $b_0^{(2)}(t) = 0.5$. Random follow-up time C was generated conditionally on the second covariate such that $C|Z^{(2)} \geq 0.5$ from the uniform $[0, 3]$ and $C|Z^{(2)} < 0.5$ from the uniform $[2, 3]$.

Web Table 1 and Web Table 2 report that the simulation results were similar to the ones discussed in the previous simulations, respectively for the covariate effects over time and the averaged effects of covariates.

5. Real Data Analyses

Our proposed method is illustrated by two real data analyses of the bladder tumor study data (Byar, 1980) and the DISC study data (Tangpricha et al., 2017).

5.1 Analysis of the Bladder Tumor Study Data

Byar (1980) reported a randomized clinical trial assessing the effects of new treatments on tumor recurrence. A total of 118 patients with superficial bladder tumors entered the study after removal of their initial tumors. They were randomly assigned to three treatment arms (pyridoxine, thiotepa, and placebo). Follow-up time varied from 1 to 64 months. During the follow-up, sixty-two patients experienced tumor recurrences, and the maximum number of recurrences was 9. We applied our dynamic regression model with four baseline covariates: the size of a largest initial tumor, the number of tumors at enrollment, and two treatment indicators for pyridoxine and thiotepa.

Figure 1 shows the estimated effects of the covariates and corresponding Wald-type 95% point-wise bootstrap confidence intervals. The effects of initial number and size of tumors appeared to be changing over time. Specifically, the initial number of tumors was associated with lower recurrence rate around the middle of study follow-up but with higher recurrence rate toward the end. In contrast, the initial tumor size increased the mean frequency of tumor occurrence by about $\exp(0.1 * \text{size})$ around 5 months after the removal of initial tumors, and the size decreased the mean frequency by the same factor after 50-month of follow-up. The p-values for the proposed constant effect test were 0.105 and 0.030, respectively, for $(I, u] = (5, 53]$. On the other hand, pyridoxine and thiotepa had relatively constant effects, with p-values 0.960 and 0.691 respectively. Thiotepa appeared to reduce the tumor recurrence compared to the placebo, whereas pyridoxine did not. This observation is consistent with the results of other bladder tumor data analyses discussed in Therneau and Grambsch (2000).

5.2 Analysis of the DISC trial Data

Cystic fibrosis is a chronic genetic disorder, which occurs at a rate of 3 cases per 10,000 Caucasian newborns each year in the U.S.; see Strausbaugh and Davis (2007). Also, it is

reported that vitamin D deficiency in cystic fibrosis patients is highly prevalent, e.g., Wolfenden et al. (2008). In order to assess the effect of vitamin D on recurrence of pulmonary exacerbation, ninety-one adults with cystic fibrosis were randomly assigned to either high-dose vitamin D group or placebo group in the DISC trial of Tangpricha et al. (2017). During the follow-up, pulmonary exacerbations were observed as many as 9 times in each patient. In addition to vitamin D treatment, we considered additional five covariates in the model: gender, Caucasian, age, body mass index (BMI), and forced expiratory volume (FEV) at enrollment.

Figure 2 shows the estimated effects of covariates and corresponding Wald-type 95% point-wise bootstrap confidence intervals. The age effect appeared to vary over time on recurrence of pulmonary exacerbation although the test for the constant effect was not significant with p-value 0.163 for $(l, u] = (50, 500]$ (days). Younger people tended to have more frequent pulmonary exacerbation, perhaps even more so at the end of the study follow-up. On the other hand, the effects of the other covariates, including vitamin D treatment, did not appear to change over time in the sample. As one reviewer pointed out, the relatively constant effect estimates suggest that a time-independent coefficient model fits well. This shows another utility of the proposed methods, to provide justification for such a simpler model.

6. Concluding Remarks

In this article, we have considered right-censored recurrent events with time-independent covariates. The proposed method can be easily extended to left-truncated data, i.e., with delayed entries. Technically speaking, the method may also be generalized to accommodate external time-dependent covariates. However, the model interpretation would be difficult when both the covariates and their effects are time-varying.

Model (1) can be generalized to a class of dynamic transformation models

$$E\{N^*(t) \mid \mathbf{Z}\} = g\{\beta_0(t)\mathbf{I}\tilde{\mathbf{Z}}\}, \quad \text{for all } t \geq 0,$$

where g is a known function. Both of the estimation procedure and the resampling approach in Section 3 can be easily adapted. This class includes the additive regression model of Aalen et al. (2004) as a special case when g is the identity function, and their estimator coincides with ours.

In practice, a mixture model with constant and time-varying effects may be useful when clinical or biological knowledge implies constant effects for some of the covariates. In quantile regression framework, Qian and Peng (2010) considered such mixture modeling for univariate survival data. A method based on such mixture modeling in our context merits further investigation.

A mean frequency function of recurrent events does not decrease over time. However, lack of monotonicity respecting may arise in the estimated conditional mean frequency. Recently Huang (2017) proposed the adaptive interpolation method for restoration of monotonicity respecting. That method should be applicable to our estimator as well.

By introducing weight processes in the proposed estimating integral equation (2), a class of estimating integral equations can be developed. The weight processes may depend on covariates as well as $\beta(\cdot)$. A future research topic is to pursue more efficient estimation within this class.

As described in Section 3.1, our algorithm solves estimating integral equation (2) at each and every observed event time. Although it might appear burdensome, the estimator at the previous event time may naturally serve as the initial value and the computation is actually quite fast over a wide range of practical scenarios. Nevertheless, as one reviewer pointed out, a faster estimation may be achieved by solving estimating integral equation (2) approximately over a grid of time points. So long as the mesh size approaches 0 fast enough, the resulting estimator would be asymptotically equivalent only on a prespecified grid of time points. Thus, this algorithm can be a viable alternative especially when a data set has a large number of distinct event times.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Appendix

An Asymptotic Study with Proofs of Theorems 1 and 2

We first characterize the jump size of the proposed estimator $\hat{\beta}(\cdot)$ in Lemma 1.

LEMMA 1: Suppose $\hat{\beta}(t) \in \mathbf{B}$ for all $t \in [\kappa, \tau]$, where $\mathbf{B}$ is a compact parameter space in $\mathcal{R}^{p+1}$. Under conditions C1-C3, and C6, $\Delta \hat{\beta}(t) \equiv \hat{\beta}(t) - \hat{\beta}(t-)$ is $O(n^{-1})$, almost surely, uniformly over $t \in (\kappa, \tau]$

Proof. From the estimating integral equation (2), it follows that, for $t > 0$

$$0 = \frac{1}{n} \sum_{i=1}^n \tilde{Z}_i (dN_i(t) - Y_i(t) [\exp\{\hat{\beta}(t)^T \tilde{Z}_i\} - \exp\{\hat{\beta}(t-)^T \tilde{Z}_i\}]).$$

There may be change in $\hat{\beta}(\cdot)$ at the observed event times $(x_j)_{j=1}^M$, whereas no jump occurs in $\hat{\beta}(\cdot)$ over time between any two adjacent event times. At the j th event time, it follows that

$$\begin{aligned}
\frac{1}{n} \tilde{\mathbf{Z}}_{(j)} &= \frac{1}{n} \sum_{i=1}^n Y_i(t) \tilde{\mathbf{Z}}_i [\exp\{\hat{\beta}(t)^T \tilde{\mathbf{Z}}_i\} - \exp\{\hat{\beta}(t-)^T \tilde{\mathbf{Z}}_i\}] \\
&= \frac{1}{n} \sum_{i=1}^n Y_i(t) \tilde{\mathbf{Z}}_i \tilde{\mathbf{Z}}_i^T \exp\{\beta_i^{\otimes}(t)^T \tilde{\mathbf{Z}}_i\} \{\hat{\beta}(t) - \hat{\beta}(t-)\},
\end{aligned} \tag{A.1}$$

where $\beta_i^{\otimes}(t)^T \tilde{\mathbf{Z}}_i$ is on the line segment between $\hat{\beta}(t)^T \tilde{\mathbf{Z}}_i$ and $\hat{\beta}(t-)^T \tilde{\mathbf{Z}}_i$. Note $\beta_i^{\otimes}(t)$ satisfies $\exp\{\beta_i^{\otimes}(t)^T \tilde{\mathbf{Z}}_i\} = \int_0^1 \exp\{[\hat{\beta}(t-) + r\{\hat{\beta}(t) - \hat{\beta}(t-)\}]^T \tilde{\mathbf{Z}}_i\} dr$. Under C3, $\frac{1}{n} \tilde{\mathbf{Z}}_{(j)}$ on the left-hand side of equation (A.1) is $O(n^{-1})$. The limit of the factor $\frac{1}{n} \sum_{i=1}^n Y_i(t) \tilde{\mathbf{Z}}_i \tilde{\mathbf{Z}}_i^T \exp\{\beta_i^{\otimes}(t)^T \tilde{\mathbf{Z}}_i\}$, on the right-hand side of (A.1) has a smallest eigenvalue bounded away from zero under C6 as every $\exp\{\beta_i^{\otimes}(t)^T \tilde{\mathbf{Z}}_i\}$ is bounded away from zero. Consequently, at any $t \in [\kappa, \tau]$, the jump size $\Delta \hat{\beta}(t) = O(n^{-1})$ almost surely.

A.1. Proof of Theorem 1: the uniform consistency of $\hat{\beta}(\cdot)$.

Define classes $\mathbf{F}$ and $\mathbf{G}$ as $\mathbf{F} \equiv \{\tilde{\mathbf{Z}}N(t): t \in [0, \tau]\}$ and $\mathbf{G} \equiv \{Y(t) \tilde{\mathbf{Z}} \tilde{\mathbf{Z}}^T \exp(\beta^T \tilde{\mathbf{Z}}): t \in [0, \tau], \beta \in \mathbf{B}\}$, where $\mathbf{B}$ is a compact subset of $\mathcal{R}^{p+1}$. It is known that both $\{I(T \leq t): t \in \mathcal{R}\}$ and $\{I(C \geq t): t \in \mathcal{R}\}$ are Donsker (Kosorok, 2008, Lemma 9.10). By permanence properties of the Donsker class, $\mathbf{F}$ and $\mathbf{G}$ are Donsker. Since Donsker implies Glivenko-Cantelli, it follows that

$$\sup_{t \in [0, \tau]} \|n^{-1} \sum_{i=1}^n \tilde{\mathbf{Z}}_i [N_i(t) - \int_0^t Y_i(s) \tilde{\mathbf{Z}}_i^T \exp\{\beta_0(s)^T \tilde{\mathbf{Z}}_i\} d\beta_0(s)]\| \rightarrow 0, \tag{A.2}$$

almost surely.

Let $\psi(t) \equiv n^{-1} \sum_{i=1}^n \tilde{\mathbf{Z}}_i [N_i(t) - \int_0^t Y_i(s) d \exp\{\beta_0(s)^T \tilde{\mathbf{Z}}_i\}]$ for $t \in [0, \tau]$. With the solutions to the estimating equations (3) and (4), it follows that

$$\begin{aligned}
\psi(t) - \psi(\kappa) &= n^{-1} \sum_{i=1}^n \tilde{\mathbf{Z}}_i \int_{\kappa}^t Y_i(s) d [\exp\{\hat{\beta}(s)^T \tilde{\mathbf{Z}}_i\} - \exp\{\beta_0(s)^T \tilde{\mathbf{Z}}_i\}] \\
&= n^{-1} \sum_{i=1}^n \tilde{\mathbf{Z}}_i \tilde{\mathbf{Z}}_i^T \int_{\kappa}^t Y_i(s) d [\exp\{\beta_i^{\otimes}(s)^T \tilde{\mathbf{Z}}_i\} \{\hat{\beta}(s) - \beta_0(s)\}] \\
&= \int_{\kappa}^t n^{-1} \sum_{i=1}^n \tilde{\mathbf{Z}}_i \tilde{\mathbf{Z}}_i^T Y_i(s) \{\hat{\beta}(s-) - \beta_0(s-)\} d \exp\{\beta_i^{\otimes}(s)^T \tilde{\mathbf{Z}}_i\} \\
&\quad + \int_{\kappa}^t n^{-1} \sum_{i=1}^n \tilde{\mathbf{Z}}_i \tilde{\mathbf{Z}}_i^T Y_i(s) \exp\{\beta_i^{\otimes}(s)^T \tilde{\mathbf{Z}}_i\} d \{\hat{\beta}(s) - \beta_0(s)\},
\end{aligned} \tag{A.3}$$

where $\beta_i^{\odot(s)\top} \tilde{\mathbf{Z}}_i$ is on the line segment between $\hat{\beta}(s)^\top \tilde{\mathbf{Z}}_i$ and $\beta_0(s)^\top \tilde{\mathbf{Z}}_i$. Note that the subscript i in $\beta_i^{\odot(s)}$ indicates its dependency on $\tilde{\mathbf{Z}}_i$. Let $\hat{\mathbf{A}}(t) \equiv \int_{\kappa}^t n^{-1} \sum_{i=1}^n \tilde{\mathbf{Z}}_i \tilde{\mathbf{Z}}_i^\top Y_i(s) d \exp\{\beta_i^{\odot(s)\top} \tilde{\mathbf{Z}}_i\}$ and $\hat{\mathbf{B}}(s) \equiv n^{-1} \sum_{i=1}^n \tilde{\mathbf{Z}}_i \tilde{\mathbf{Z}}_i^\top Y_i(s) \exp\{\beta_i^{\odot(s)\top} \tilde{\mathbf{Z}}_i\}$. From equation (A.3), we have

$$d\psi(t) = \hat{\mathbf{A}}(dt)\{\hat{\beta}(t-) - \beta_0(t-)\} + \hat{\mathbf{B}}(t)d\{\hat{\beta}(t) - \beta_0(t)\}. \quad (\text{A.4})$$

By conditions C3, C4, and C6, $\hat{\mathbf{B}}(t)^{-1}$ exists almost surely for sufficiently large n . By multiplying the inverse of $\hat{\mathbf{B}}(t)$ on each side of the equation (A.4) followed by integration over $(\kappa, t]$, we have

$$\begin{aligned} \hat{\beta}(t) - \beta_0(t) &= \{\hat{\beta}(\kappa) - \beta_0(\kappa)\} + \int_{\kappa}^t \hat{\mathbf{B}}(s)^{-1} d\psi(s) - \int_{\kappa}^t \hat{\mathbf{B}}(s)^{-1} \hat{\mathbf{A}}(ds)\{\hat{\beta}(s-) \\ &\quad - \beta_0(s-)\} \end{aligned} \quad (\text{A.5})$$

Since this is a the Volterra integral equation (e.g., Andersen et al., 1993, Theorem II.6.3), unique solution $\hat{\beta}(t) - \beta_0(t)$ is obtained for $t \in [\kappa, \tau]$. That is,

$$\begin{aligned} \hat{\beta}(t) - \beta_0(t) &= [\pi_{[\kappa, t]} \{\mathbf{I} - \hat{\mathbf{A}}(du) \hat{\mathbf{B}}(u)^{-1}\}^\top \{\hat{\beta}(\kappa) - \beta_0(\kappa)\} \\ &\quad + \int_{\kappa}^t [\pi_{(s, t]} \{\mathbf{I} - \hat{\mathbf{A}}(du) \hat{\mathbf{B}}(u)^{-1}\}^\top \hat{\mathbf{B}}(s)^{-1} \psi(ds), \end{aligned} \quad (\text{A.6})$$

where π denotes the product-integral.

Suppose that almost surely $\hat{\beta}(t)$ is in a compact subset of $\mathcal{R}^{p+1}$ for $t \in [\kappa, \tau]$ for sufficiently large n . By Lemma 1 $\Delta \hat{\beta}(t)$ and $\Delta \hat{\mathbf{A}}(t)$ on $[\kappa, \tau]$ are $O(n^{-1})$, almost surely. As $\hat{\mathbf{A}}(t)$ is differentiable on intervals between the adjacent event times, the derivative of $\hat{\mathbf{A}}(t)$ is bounded. Therefore, $\hat{\mathbf{A}}(\cdot)$ and $\int_{\kappa}^t \hat{\mathbf{A}}(du) \hat{\mathbf{B}}(u)^{-1}$ are of bounded variation on $[\kappa, \tau]$. Note the product integral $\pi_{(s, t]} \{\mathbf{I} - \hat{\mathbf{A}}(du) \hat{\mathbf{B}}(u)^{-1}\}$ exists for $\kappa \leq s \leq t \leq \tau$ (Gill and Johansen, 1990, Theorem 1). Given the consistent estimator $\hat{\beta}(\kappa)$, the first term on the right-hand side of equation (A.6) is $o(1)$ almost surely; also, the second term on the right-hand side of equation (A.6) is $o(1)$ almost surely by the integration by parts. Thus, we have the result that $\sup_{t \in [\kappa, \tau]} \|\hat{\beta}(t) - \beta_0(t)\| \rightarrow 0$, almost surely.

Now it remains to show that almost surely $\sup_{t \in [\kappa, \tau]} \|\hat{\beta}(t) - \beta_0(t)\| \rightarrow 0$ if it is not true that $\hat{\beta}(t)$ is in a compact subset of $\mathcal{R}^{p+1}$ for $t \in [\kappa, \tau]$. There exists $t^* \in (\kappa, \tau]$ at which $\hat{\beta}(\cdot)$ has a jump and goes off the boundary of the compact set for the first time, since $\hat{\beta}(\kappa) - \beta_0(\kappa) \rightarrow 0$ almost surely. As $\hat{\beta}(t)$ is in the compact set for all $t \in [\kappa, t^*]$, $\|\hat{\beta}(t) - \beta_0(t)\|$ can be made arbitrarily small for $t \in [\kappa, t^*]$ with sufficiently large sample size. It implies that the jump

size of $\hat{\beta}(\cdot)$ at t^* is bounded away from 0. This would result in a contradiction in light of the equation (A.1) in Lemma 1.

A.2. Proof of Theorem 2: the weak convergence of $\hat{\beta}(\cdot)$.

Recall $\psi(\cdot)$ defined in the proof of Theorem 1. For each $t \in (\kappa, \tau]$, almost surely,

$$\begin{aligned} \psi(t) - \psi(\kappa) &= n^{-1} \sum_{i=1}^n \tilde{Z}_i \int_{\kappa}^t Y_i(s) d[\exp\{\hat{\beta}(s)\}^T \tilde{Z}_i - \exp\{\beta_0(s)\}^T \tilde{Z}_i] \\ &= n^{-1} \sum_{i=1}^n \tilde{Z}_i \int_{\kappa}^t Y_i(s) d[\exp\{\beta_0(s)\}^T \tilde{Z}_i \tilde{Z}_i^T \{\hat{\beta}(s) - \beta_0(s)\}] + \tilde{C}(t) \\ &= \int_{\kappa}^t n^{-1} \sum_{i=1}^n \tilde{Z}_i \tilde{Z}_i^T Y_i(s) \{\hat{\beta}(s) - \beta_0(s)\} d\exp\{\beta_0(s)\}^T \tilde{Z}_i \\ &\quad + \int_{\kappa}^t n^{-1} \sum_{i=1}^n \tilde{Z}_i \tilde{Z}_i^T Y_i(s) \{\exp\{\beta_0(s)\}^T \tilde{Z}_i d\{\hat{\beta}(s) - \beta_0(s)\} + \tilde{C}(t), \end{aligned}$$

for some $\tilde{C}(t) = o\{\hat{\beta}(t) - \beta_0(t)\}$. Define $\tilde{A}(t) \equiv \int_{\kappa}^t n^{-1} \sum_{i=1}^n \tilde{Z}_i \tilde{Z}_i^T Y_i(s) d\exp\{\beta_0(s)\}^T \tilde{Z}_i$ and

$\tilde{B}(s) \equiv n^{-1} \sum_{i=1}^n \tilde{Z}_i \tilde{Z}_i^T Y_i(s) \exp\{\beta_0(s)\}^T \tilde{Z}_i$. It follows that

$d\psi(t) = \tilde{A}(dt)\{\hat{\beta}(t) - \beta_0(t)\} + \tilde{B}(t)d\{\hat{\beta}(t) - \beta_0(t)\} + d\tilde{C}(t)$. Under the regularity conditions, $\tilde{B}(t)^{-1}$ exists almost surely for sufficiently large n . By virtue of the Volterra integral equation,

$$\begin{aligned} n^{1/2}\{\hat{\beta}(t) - \beta_0(t)\} &= n^{1/2}[\pi_{[\kappa, t]} \{I - \tilde{A}(du)\tilde{B}(u)^{-1}\}^T \{\hat{\beta}(\kappa) - \beta_0(\kappa)\} \\ &\quad + n^{1/2} \int_{\kappa}^t [\pi_{(s, t]} \{I - \tilde{A}(du)\tilde{B}(u)^{-1}\}^T \tilde{B}(s)^{-1} d\{\psi(s) - \tilde{C}(s)\}] \\ &= n^{1/2}[\pi_{[\kappa, t]} \{I - \tilde{A}(du)\tilde{B}(u)^{-1}\}^T \{-\tilde{B}(\kappa) + o_p(1)\}^{-1} \psi(\kappa)] \\ &\quad + n^{1/2} \int_{\kappa}^t [\pi_{(s, t]} \{I - \tilde{A}(du)\tilde{B}(u)^{-1}\}^T \tilde{B}(s)^{-1} d\{\psi(s) - \tilde{C}(s)\}] \\ &= -n^{1/2}[\pi_{[\kappa, t]} \{I - A_0(du)B_0(u)^{-1}\}^T B_0(\kappa)^{-1} \psi(\kappa)] \\ &\quad + n^{1/2} \int_{\kappa}^t [\pi_{(s, t]} \{I - \tilde{A}(du)\tilde{B}(u)^{-1}\}^T B_0(s)^{-1} \psi(ds) + o_p(n^{1/2}\{\hat{\beta}(t) - \beta_0(t)\})], \end{aligned}$$

where $A_0(t) \equiv E[\int_{\kappa}^t \tilde{Z}\tilde{Z}^T Y(s) d\exp\{\beta_0(s)\}^T \tilde{Z}]$ and $B_0(s) \equiv E[\tilde{Z}\tilde{Z}^T Y(s) \exp\{\beta_0(s)\}^T \tilde{Z}]$.

Then, $n^{1/2}\{\hat{\beta}(\cdot) - \beta_0(\cdot)\}$ weakly converges to a Gaussian process as it is a linear mapping of $\psi(\cdot)$, which is a Gaussian process itself.

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Figure 1.

The bladder tumor clinical study. Estimates for the effects of the considered covariates. The rugged solid lines and the dotted lines denote the point estimates and the Wald-type 95% point-wise bootstrap confidence intervals, respectively. The horizontal solid lines are the estimated average effects over (5, 53]. The p-values for the constant effect tests are calculated based on time interval (5, 53]. This figure appears in color in the electronic version of this article.

Figure 2.

The DISC clinical study. Estimates for the effects of covariates. The rugged solid lines and the dotted lines denote the point estimates and the Wald-type 95% point-wise bootstrap confidence intervals, respectively. The horizontal solid lines are the estimated average effects over (50, 500]. The p-values for the constant effect tests are calculated based on time interval (50, 500]. This figure appears in color in the electronic version of this article.

Table 1

Summary Results of Simulation 1 at the Prespecified Time Points

t	$h_0(t) = \log(t)$						$h_0(t) = 0.5$					
	Proposed Method			Fine et al. (2004)			Proposed Method			Fine et al. (2004)		
	B	SD	SE	Cov95	B	SD	SE	Cov95	B	SD	SE	Cov95
Zero intra-individual correlation												
0.50	0	192	194	94.7	0	200	202	94.9	-6	320	317	95.2
1.00	-4	143	144	94.8	-6	160	160	94.4	1	233	235	95.4
1.50	-3	125	126	95.7	-4	152	150	94.3	2	206	205	94.6
2.00	-3	119	118	94.7	-9	162	158	93.7	1	196	193	94.0
2.25	-4	120	118	94.1	-10	182	171	92.7	1	199	192	94.5
2.50	-6	120	120	94.8	-8	225	197	89.9	7	200	197	94.6
2.75	-10	131	127	94.7	-37	325	267	87.7	9	220	208	93.7
Gamma frailty of variance 0.5												
0.50	0	222	219	94.1	-1	233	230	93.8	-14	367	360	93.6
1.00	-3	183	179	93.5	-7	212	201	93.6	-11	311	296	93.1
1.50	-4	168	166	94.3	-10	206	205	94.9	-6	287	277	94.3
2.00	-5	167	164	95.0	-18	236	233	94.3	-7	286	275	93.3
2.25	-8	170	166	94.8	-31	276	261	93.4	-1	291	278	94.1
2.50	-7	177	170	92.9	-49	346	310	92.9	-3	302	284	92.6
2.75	-6	187	178	93.9	-67	539	421	88.6	-5	318	296	92.4
Gamma frailty of variance 1												
0.50	-20	248	240	94.9	-19	263	253	94.3	11	409	399	94.6
1.00	-25	211	206	94.0	-25	239	233	93.3	20	352	345	94.2
1.50	-17	206	197	93.9	-23	260	244	92.9	9	344	332	93.5
2.00	-13	209	197	93.0	-32	299	282	93.2	2	347	334	93.6
2.25	-18	215	200	93.6	-41	353	317	92.1	9	356	339	93.2
2.50	-15	222	205	93.5	-52	442	376	91.0	0	369	345	92.6
2.75	-20	234	212	92.6	-125	733	525	88.2	6	391	358	93.1

NOTE: B: empirical bias ($\times 1000$); SD: empirical standard deviation ($\times 1000$); SE: average standard error ($\times 1000$); Cov95: empirical coverage probability of the Wald 95% confidence interval ($\times 100$). Based on 1,000 Monte Carlo replications.

Table 2Summary Results of Simulation 1 for the Average Effect of Covariate $\bar{\beta}_0(l, u)$

	$b_0(t) = 0.5$											
	Proposed Method				Fine et al. (2004)				Lin et al. (2000)			
	B	SD	SE	Cov95	B	SD	SE	Cov95	B	SD	SE	Cov95
Interval (0, 3]												
$\sigma^2 = 0$	4	194	190	94.6	13	596	212	83.1	3	176	176	94.8
$\sigma^2 = 0.5$	-7	284	263	94.3	-4	1151	310	71.8	-6	271	265	94.0
$\sigma^2 = 1$	9	337	317	93.9	137	1580	377	61.8	7	332	328	94.4
Interval (0, 2.5]												
$\sigma^2 = 0$	4	208	203	94.4	5	230	219	94.2				
$\sigma^2 = 0.5$	-5	288	271	93.7	1	322	301	93.6				
$\sigma^2 = 1$	10	344	322	92.8	11	391	357	92.0				
Interval (0.5, 2.5]												
$\sigma^2 = 0$	1	187	185	94.5	4	218	210	94.8				
$\sigma^2 = 0.5$	-8	273	262	93.6	1	318	306	94.2				
$\sigma^2 = 1$	9	326	318	94.2	12	394	371	92.1				

NOTE: B: empirical bias ($\times 1000$); SD: empirical standard deviation ($\times 1000$); SE: average standard error ($\times 1000$); Cov95: empirical coverage probability of the Wald 95% confidence interval ($\times 100$). Based on 1,000 Monte Carlo replications. For the proportional means model of Lin et al. (2000), the same estimates from the conventional estimation were used based on the whole observed data regardless of the time interval under consideration for averaging; thus the results for intervals (0, 2.5] and (0.5, 2.5] are not presented as they are equivalent to the ones for interval (0, 3].

Table 3

Summary Results of Simulation 2 at the Prespecified Time Points

t	$h_0(t) = \log(t)$						$h_0(t) = \exp\{-t/\exp(1)\}$									
	Proposed Method			Fine et al. (2004)			Proposed Method			Fine et al. (2004)						
	B	SD	SE	Cov95	B	SD	SE	Cov95	B	SD	SE	Cov95	B	SD	SE	Cov95
Zero intra-individual correlation																
0.50	-16	190	187	94.2	-20	201	196	94.3	11	306	292	94.1	17	326	307	93.2
1.00	2	140	141	94.7	-3	160	157	94.1	-10	227	224	94.3	-4	259	249	94.6
1.50	2	125	124	95.1	2	154	149	93.9	-9	203	199	95.0	-13	253	241	94.0
2.00	0	123	118	93.6	-4	171	159	93.2	-7	198	190	94.3	-8	280	261	92.7
2.25	-3	121	117	93.9	-8	179	173	93.5	-5	196	189	93.9	-3	300	284	93.5
2.50	-4	125	119	94.2	-14	220	199	91.3	-4	203	194	93.9	3	362	330	92.2
2.75	-4	136	126	92.1	-45	327	266	88.3	-4	218	205	92.4	37	541	448	88.0
Gamma frailty of variance 0.5																
0.50	-5	213	211	94.6	-3	228	222	93.8	-10	354	340	93.4	-15	379	358	93.2
1.00	-3	178	174	94.5	-5	200	196	93.9	-12	297	286	93.5	-12	334	323	93.8
1.50	-4	166	163	94.2	-9	206	202	93.3	-10	280	271	93.7	-12	348	338	93.1
2.00	-1	166	161	94.3	-9	244	229	93.1	-14	279	269	93.7	-21	417	386	93.3
2.25	-1	164	162	94.3	-13	274	255	92.6	-15	276	271	93.1	-20	468	431	93.0
2.50	-2	167	166	94.6	-27	323	301	92.2	-13	282	276	94.3	-7	550	508	92.6
2.75	-2	178	172	94.2	-69	510	424	88.4	-15	298	286	94.2	3	859	715	90.3
Gamma frailty of variance 1																
0.50	-8	239	234	93.9	-16	250	247	94.5	-11	392	379	93.5	-1	409	400	94.4
1.00	-10	208	203	94.1	-14	235	229	93.8	-8	352	335	93.2	-3	399	380	91.9
1.50	-15	203	195	93.2	-24	261	243	92.5	3	344	326	92.6	12	442	408	92.3
2.00	-13	202	195	93.4	-35	304	280	92.6	1	344	326	92.4	18	519	473	92.9
2.25	-14	211	197	92.5	-41	363	315	90.8	2	359	330	91.3	10	620	533	91.1
2.50	-14	219	201	92.7	-53	435	371	90.0	4	369	336	91.6	8	747	630	90.0
2.75	-20	234	208	90.4	-112	688	518	88.1	12	393	347	92.0	29	1156	880	87.3

See the footnote of Table 1

Table 4Summary Results of Simulation 2 for the Average Effect of Covariate $\bar{\beta}_0(l, u)$

	$b_0(t) = \exp\{-t/\exp(1)\}$											
	Proposed Method				Fine et al. (2004)				Lin et al. (2000)			
	B	SD	SE	Cov95	B	SD	SE	Cov95	B	SD	SE	Cov95
Interval (0, 3]												
$\sigma^2 = 0$	2	199	186	93.0	18	606	209	81.7	-102	180	176	91.1
$\sigma^2 = 0.5$	-7	279	258	92.4	24	1163	316	68.5	-109	261	260	91.8
$\sigma^2 = 1$	1	339	313	92.3	-2	1834	385	59.8	-96	337	322	91.4
Interval (0, 2.5]												
$\sigma^2 = 0$	3	213	196	92.8	7	240	214	91.6	-150	180	176	85.5
$\sigma^2 = 0.5$	21	292	265	90.7	18	324	294	91.8	-130	279	261	90.7
$\sigma^2 = 1$	-1	342	317	92.5	8	399	354	90.4	-145	337	322	90.5
Interval (0.5, 2.5]												
$\sigma^2 = 0$	-7	189	182	94.7	-5	226	209	93.6	-85	180	176	92.3
$\sigma^2 = 0.5$	-14	265	257	93.8	-16	321	302	93.6	-93	261	260	92.7
$\sigma^2 = 1$	-3	333	313	93.0	6	413	368	90.6	-80	337	322	92.0

See the footnote of Table 1