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Semiparametric transformation models for multivariate panel count data with dependent observation process

Ni Li, Do-Hwan Park, Jianguo Sun*, and KyungMann Kim

Department of Statistics, University of Missouri, Columbia, MO 65211, USA

Abstract

This article discusses regression analysis of multivariate panel count data in which the observation process may contain relevant information about or be related to the underlying recurrent event processes of interest. Such data occur if a recurrent event study involves several related types of recurrent events and the observation scheme or process may be subject-specific. For the problem, a class of semiparametric transformation models is presented, which provides a great flexibility for modelling the effects of covariates on the recurrent event processes. For estimation of regression parameters, an estimating equation-based inference procedure is developed and the asymptotic properties of the resulting estimates are established. Also the proposed approach is evaluated by simulation studies and applied to the data arising from a skin cancer chemoprevention trial.

Key words and phrases

Counting processes; multivariate data analysis; panel count data; transformation models

1. INTRODUCTION

Recurrent event studies concern occurrence rates or patterns of recurrent events. In this article, we consider the analysis of the recurrent event studies that involve several related types of recurrent events and in which each subject is observed only at finite discrete time points instead of continuously. Furthermore, the observation times or process may be related to or contain relevant information about the underlying recurrent event processes of interest. In these situations, only the number of events that occur between observation times is known and no information is available on subjects between the observation time points. The areas that often produce such multivariate panel count data include prospective cohort studies, population-based epidemiological studies, reliability studies, and tumorigenicity experiments since in these situations, it is usually either impossible or not practical to maintain continuous observation of subjects.

An example of multivariate panel count data is given by a skin cancer chemoprevention trial conducted by the University of Wisconsin Comprehensive Cancer Center in Madison, Wisconsin. It was a double-blinded and placebo-controlled randomized Phase III clinical trial. The primary objective of this trial was to evaluate the effectiveness of 0.5 g/m²/day PO difluoromethylornithine (DFMO) in reducing new skin cancers in a population of patients with a history of non-melanoma skin cancers: basal cell carcinoma and squamous cell carcinoma. During the study, the patients were scheduled to be assessed or observed every 6

months for the development of new skin cancers. As expected, however, the real observation times differ from patient to patient and so as the follow-up times. The study consists of 291 patients randomized to either the placebo group (147) or the DFMO group (144) and the data include the numbers of occurrences of both basal cell carcinoma and squamous cell carcinoma between observation times. More details about the study will be given below. He et al. (2008) discussed another example of multivariate panel count data from a cohort study, conducted at the University of Toronto Psoriatic Arthritis Clinic, of the patients with psoriatic arthritis on the recurrences of joint damages.

A number of statistical procedures have been developed for univariate panel count data when the observation process can be regarded as being independent of the underlying recurrent event process (Sun & Kalbfleisch, 1993, 1995; Sun & Wei, 2000; & Lachin, 1988; Zhang, 2002). For the situation where the two processes may be related, among others, He, Tong, & Sun (2009), Huang, Wang, & Zhang (2006) and Sun, Tong, & He (2007) proposed some joint modelling approaches that model the relationship between the underlying recurrent event process and the observation process through the use of some random effects. However, these approaches only apply to limited situations. For multivariate panel count data, Chen et al. (2005) proposed two approaches based on a mixed Poisson model with piecewise constant baseline intensities. One approach assumes that the different types of recurrent events are related through multivariate log-normal random effects and bases inference on the resulting full likelihood, while the other makes use of the marginal model approach. He et al. (2008) also discussed the same problem and proposed a marginal model approach. However, in both cases, the methods developed only apply to situations where the recurrent event processes and the observation process are independent completely or conditional on covariates.

The remainder of the article is organized as follows. We will begin in Section 2 with defining the notation and describing the models used throughout the article. In particular, a class of semiparametric transformation models is presented for modelling covariate effects and the dependence of the underlying recurrent event processes of interest on the observation process. A proportional rates model is employed for modelling the effect of covariates on the observation process. Note that here we focus on the marginal models and one major advantage of these models is that they leave the dependence structures for related types of recurrent events completely arbitrary. More comments on this are given below. In Section 3, some estimating equations are proposed for estimation of regression parameters and the asymptotic properties of the resulting estimates are established. Section 4 presents some simulation results obtained for the evaluation of the proposed estimates and they suggest that the approach works well for practical situations. The method is applied in Section 5 to the bivariate panel count data from the skin cancer chemoprevention trial discussed above and some concluding remarks are given in Section 6.

2. STATISTICAL MODELS

Consider a study that consists of n independent subjects experiencing some recurrent events and suppose that each subject may experience K different types of events. Let $Y_{ik}(t)$ denote the point process that represents the total number of occurrences of the k th type recurrent event of interest up to time t arising from subject i and $0 < t_{ik,1} < \dots < t_{ik,m_{ik}}$ the potential time points at which subject i is observed on the k th type of recurrent event. Also let $Z_i(t)$ be a covariate process and C_i the follow-up or censoring time for subject i , $i = 1, \dots, n$. Note that here for simplicity, we assume that $Z_i(t)$ and C_i are the same for different types of

recurrent events. Define $N_{ik}(t) = \sum_{l=1}^{m_{ik}} I(t_{ik,l} \leq t)$, a counting process that records the number of observations on subject i with respect to the k th type recurrent event up to time t . Then the process $Y_{ik}(t)$ is observed only at the time points where $N_{ik}(t)$ jumps. In reality, $Y_{ik}(t)$ is

observed at $t_{ik,l}$ only if $t_{ik,l} \leq C_i - \tau$, where τ denotes the longest follow-up time. Define $\tilde{N}_{ik}(t) = N_{ik}(\min(t, C_i))$, the actual observation process for subject i with respect to the k th type recurrent event, and $m_{ik}^* = N_{ik}(C_i) = \tilde{N}_{ik}(C_i)$, the total number of actual observations on subject i with respect to the k th type recurrent event. It is easy to see that we have $\Delta_i(t) dN_{ik}(t) = d\tilde{N}_{ik}(t)$, where $\Delta_i(t) = I(C_i - t)$.

For the dependence of the observation process on covariates, following Huang, Wang, & Zhang (2006) and Sun, Tong, & He (2007), we will assume that $N_{ik}(t)$ is a nonhomogeneous Poisson process with

$$E\{dN_{ik}(t) | Z_i(t)\} = e^{\gamma' Z_i(t)} d\Lambda_{0k}(t), \quad (1)$$

$i = 1, \dots, n$. Here γ is a vector of unknown regression parameters and $\Lambda_{0k}(t)$ is an arbitrary, unknown nondecreasing function, representing the mean cumulative number of observations by time t . In the following, we will assume that $d\Lambda_{0k}(t) = \lambda_{0k}(t)dt$ and the model (1) above is often referred to as the proportional rate model (Cook & Lawless, 2007).

For subject i , define $\mathcal{F}_{ikt} = \{N_{ik}(s), 0 \leq s \leq t\}$, the history or filtration of the observation process N_{ik} up to time t , $i = 1, \dots, n$. To characterize the relationship between the recurrent event process $Y_{ik}(t)$ and covariate process $Z_i(t)$, we will assume that the mean function of $Y_{ik}(t)$ is specified by the following semiparametric transformation model

$$E\{Y_{ik}(t) | Z_i(t), \mathcal{F}_{ikt}\} = g\{\mu_{0k}(t)e^{\beta' Z_i(t) + \alpha' H(\mathcal{F}_{ikt})}\} \quad (2)$$

given $Z_i(t)$ and $\mathcal{F}_{ikt}$. In the model above, g is a known twice continuously differentiable and strictly increasing function, μ_{0k} denotes an unspecified smooth function of t , β , and α are vectors of unknown regression parameters, and $H(\cdot)$ is a vector of known functions of $\mathcal{F}_{ikt}$. Model (2) assumes that the observation process $N_{ik}(t)$ may be informative or contain relevant information about the underlying recurrent event process $Y_{ik}(t)$, and $Y_{ik}(t)$ depends on $N_{ik}(t)$ through α . The goal is to make inference about β and α .

For the function vector H in model (2), as discussed in Sun et al. (2005), it can have different forms depending on the dependence of $Y_{ik}(t)$ on $N_{ik}(t)$. For example, one may take $H(\mathcal{F}_{ikt}) = N_{ik}(t-)$ if it is believed that $Y_{ik}(t)$ may depend on the total number of the observations with respect to the k th type recurrent event up to time t . This could be the case in a medical study in which patients may pay more visits to their doctors because they feel worse than usual either with or without treatments.

3. INFERENCE PROCEDURES

In this section, we will present the estimation procedure for regression parameters β and α as well as other parameters. For this, let β_0 , α_0 , and γ_0 denote the true values of β , α , and γ . Also let $X_{ik}(t) = (Z_i(t)', H(\mathcal{F}_{ikt})')'$, $\theta = (\beta', \alpha')'$, $\theta_0 = (\beta_0', \alpha_0')'$ for easy presentation. Define

$$M_{ik}(t; \beta, \alpha, \gamma) = \int_0^t Y_{ik}(u) \Delta_i(u) dN_{ik}(u) - \int_0^t g\{\mu_{0k}(u)e^{\beta' Z_i(u) + \alpha' H(\mathcal{F}_{iku})}\} \Delta_i(u) e^{\gamma' Z_i(u)} d\Lambda_{0k}(u),$$

$i = 1, \dots, n$. Then under models (1) and (2), the $M_{ik}(t; \beta_0, \alpha_0, \gamma_0)$'s are zero-mean stochastic processes. This suggests that if β , α , γ , and Λ_{0k} are known, one can estimate $\mu_{0k}(t)$ by the solution to

$$\sum_{i=1}^n d M_{ik}(t; \beta, \alpha, \gamma) \sum_{i=1}^n \left[Y_{ik}(t) \Delta_i(t) dN_{ik}(t) - g\{\mu_{0k}(t) e^{\beta' Z_i(t) + \alpha' H(\mathcal{F}_{ikt})}\} \Delta_i(t) e^{\gamma' Z_i(t)} d\Lambda_{0k}(t) \right] = 0, 0 \leq t \leq \tau. \quad (3)$$

Also it is natural to estimate θ by the estimating equation

$$U(\theta; \gamma) = \sum_{k=1}^K \sum_{i=1}^n \int_0^\tau W(t) X_{ik}(t) \left[Y_{ik}(t) \Delta_i(t) dN_{ik}(t) - g\{\mu_{0k}(t) e^{\theta' X_{ik}(t)}\} \Delta_i(t) e^{\gamma' Z_i(t)} d\Lambda_{0k}(t) \right] = 0_4$$

where $W(t)$ is a possibly data-dependent weight function.

Of course, in general, γ and $\Lambda_{0k}(t)$ are unknown. Fortunately, we have recurrent event data on the $N_{ik}(t)$'s and in this case, a consistent estimator of γ is given by the solution, say $\hat{\gamma}$, to the estimating equation

$$\sum_{k=1}^K \sum_{i=1}^n \int_0^\tau \{Z_i(t) - \bar{Z}(t; \gamma)\} \Delta_i(t) dN_{ik}(t) = 0$$

(Andersen et al., 1993; Cook & Lawless, 2007). In the above, $\bar{Z}(t; \gamma) = S_1(t; \gamma) / S_0(t; \gamma)$ with

$$S_j(t; \gamma) = n^{-1} \sum_{i=1}^n \Delta_i(t) Z_i(t)^j e^{\gamma' Z_i(t)},$$

$j = 0, 1$. Furthermore, $\Lambda_{0k}(t)$ can be estimated by

$$\hat{\Lambda}_{0k}(t; \gamma) = \sum_{i=1}^n \int_0^t \frac{\Delta_i(u) dN_{ik}(u)}{n S_0(u; \gamma)}$$

with replacing γ by $\hat{\gamma}$.

Let $\hat{\theta} = (\hat{\beta}', \hat{\alpha}')'$, and $\hat{\mu}_{0k}(t)$ denote the estimates of θ and $\mu_{0k}(t)$ given by the estimating Equations (3) and (4) with replacing γ and $\Lambda_{0k}(t)$ by $\hat{\gamma}$ and $\hat{\Lambda}_{0k}(t; \hat{\gamma})$, respectively. Then by following the discussion used in Lin, Wei, & Ying (2001) and Sun et al. (2005), one can show that for large n , both $\hat{\theta}$ and $\hat{\mu}_{0k}(t)$ always exist and are unique and consistent. To establish the asymptotic normality of $\hat{\theta}$, define

$$\begin{aligned}
\hat{M}_{ik}(t) &= \int_0^t Y_i(u) \Delta_i(u) dN_{ik}(u) - \int_0^t g\{\hat{\mu}_{0k}(u) e^{\hat{\theta}' X_{ik}(u)}\} \Delta_i(u) e^{\hat{\gamma}' Z_i(u)} d\hat{\Lambda}_{0k}(u; \hat{\gamma}), \\
\hat{M}_{ik}^*(t) &= \int_0^t \Delta_i(u) dN_{ik}(u) - \int_0^t \Delta_i(u) e^{\hat{\gamma}' Z_i(u)} d\hat{\Lambda}_{0k}(u; \hat{\gamma}), \\
\hat{E}_{x_k}(t) &= \frac{\sum_{i=1}^n \Delta_i(t) X_{ik}(t) g\{\hat{\mu}_{0k}(t) e^{\hat{\theta}' X_{ik}(t)}\} e^{\hat{\gamma}' Z_i(t)}}{\sum_{i=1}^n \Delta_i(t) g\{\hat{\mu}_{0k}(t) e^{\hat{\theta}' X_{ik}(t)}\} e^{\hat{\gamma}' Z_i(t)}}, \\
\hat{R}_k(t) &= n^{-1} \sum_{i=1}^n \{X_{ik}(t) - \hat{E}_{x_k}(t)\} \Delta_i(t) g\{\hat{\mu}_{0k}(t) e^{\hat{\theta}' X_{ik}(t)}\} e^{\hat{\gamma}' Z_i(t)}, \\
\hat{D} &= n^{-1} \sum_{k=1}^K \sum_{i=1}^n \int_0^\tau \{Z_i(t) - \bar{Z}(t; \hat{\gamma})\}^{\otimes 2} \Delta_i(t) dN_{ik}(t),
\end{aligned}$$

and

$$\hat{P} = n^{-1} \sum_{k=1}^K \sum_{i=1}^n \int_0^\tau W(t) \Delta_i(t) g\{\hat{\mu}_{0k}(t) e^{\hat{\theta}' X_{ik}(t)}\} e^{\hat{\gamma}' Z_i(t)} \{X_{ik}(t) - \hat{E}_{x_k}(t)\} \times \{Z_i(t) - \bar{Z}(t; \hat{\gamma})\}' d\hat{\Lambda}_{0k}(u; \hat{\gamma}).$$

In the above, $\dot{g}(t) = dg(t)/dt$, and $\mathbf{v}^{\otimes 2} = \mathbf{v} \mathbf{v}'$ for a vector $\mathbf{v}$. Then it can be shown that as $n \rightarrow \infty$, $n^{1/2}(\hat{\theta} - \theta_0)$ has an asymptotically normal distribution with mean zero and the covariance matrix that can be consistently estimated by $\hat{A}^{-1} \hat{\Sigma} \hat{A}^{-1}$, where

$$\hat{A} = n^{-1} \sum_{k=1}^K \sum_{i=1}^n \int_0^\tau W(t) \Delta_i(t) \dot{g}\{\hat{\mu}_{0k}(t) e^{\hat{\theta}' X_{ik}(t)}\} \{X_{ik}(t) - \hat{E}_{x_k}(t)\}^{\otimes 2} e^{\hat{\theta}' X_{ik}(t) + \hat{\gamma}' Z_i(t)} \hat{\mu}_{0k}(t) d\hat{\Lambda}_{0k}(t; \hat{\gamma})$$

and

$$\hat{\Sigma} = n^{-1} \sum_{i=1}^n \left[\sum_{k=1}^K \int_0^\tau W(t) \left\{ X_{ik}(t) - \hat{E}_{x_k}(t) \right\} d\hat{M}_{ik}(t) - \sum_{k=1}^K \int_0^\tau \frac{W(t) \hat{R}_k(t)}{S_0(t; \hat{\gamma})} d\hat{M}_{ik}^*(t) - \hat{P} \hat{D}^{-1} \sum_{k=1}^K \int_0^\tau \{Z_i(t) - \bar{Z}(t; \hat{\gamma})\} d\hat{M}_{ik}^*(t) \right]^{\otimes 2}.$$

The proof is sketched in the Appendix.

For the determination of $\hat{\theta}$ and $\hat{\mu}_{0k}(t)$, let $s_1 < s_2 < \dots < s_J$ denote the distinct ordered observation times of $\{t_{ik,l}, l = 1, \dots, m_{ik}; i = 1, \dots, n; k = 1, \dots, K\}$. Then one can first derive $\hat{\mu}_{0k}(t, \theta, \gamma)$ from the Equation (3), which can be rewritten as

$$\sum_{i=1}^n \sum_{l=1}^{m_{ik}} Y_{ik}(t_{ik,l}) I(t_{ik,l} = s_j) - \sum_{i=1}^n \sum_{l=1}^{m_{ik}} g\{\mu_{0k}(s_j) e^{\beta' Z_i(s_j) + \alpha' H(\mathcal{F}_{iks_j})}\} \Delta_i(s_j) e^{\gamma' Z_i(s_j)} d\Lambda_{0k}(s_j) = 0$$

$j = 1, \dots, J$. With replacing $\mu_{0k}(t)$ by $\hat{\mu}_{0k}(t, \theta, \hat{\gamma})$, the Equation (4) has the form

$$\sum_{k=1}^K \sum_{i=1}^n \sum_{l=1}^{k_i^*} W(t_{ik,l}) X_{ik}(t_{ik,l}) Y_{ik}(t_{ik,l}) - \sum_{j=1}^J W(s_j) \sum_{k=1}^K \sum_{i=1}^n X_{ik}(s_j) g\{\hat{\mu}_{0k}(s_j; \theta, \hat{\gamma}) e^{\theta' X_{ik}(s_j)}\} \Delta_i(s_j) \times e^{\hat{\gamma}' Z_i(s_j)} d\hat{\Lambda}_{0k}(s_j; \hat{\gamma}) = 0.$$

It can be easily seen that in general, there are no closed forms for $\hat{\mu}_{0k}(t; \theta, \gamma)$ and $\hat{\theta}$ and some iterative algorithms have to be used to solve the equations above. For some special function g , however, the determination of these estimators is quite straightforward. For example, assume $g(t) = t^\eta$, where η is a positive constant. In this case, $\hat{\mu}_{0k}(t; \theta, \gamma)$ has an explicit expression given by

$$g\{\hat{\mu}_{0k}(t; \theta, \gamma)\} = \frac{\sum_{i=1}^n Y_{ik}(t) \Delta_i(t) dN_{ik}(t)}{\sum_{i=1}^n g\{e^{\theta' X_{ik}(t)}\} \Delta_i(t) e^{\gamma' Z_i(t)}} \cdot \frac{1}{d\Lambda_{0k}(t)}$$

and $U(\theta; \hat{\gamma}) = 0$ becomes

$$\sum_{k=1}^K \sum_{i=1}^n \int_0^\tau W(t) \{X_{ik}(t) - \bar{X}_k(t; \theta, \hat{\gamma})\} Y_{ik}(t) \Delta_i(t) dN_{ik}(t) = 0,$$

where

$$\bar{X}_k(t; \theta, \hat{\gamma}) = \frac{\sum_{j=1}^n X_{jk}(t) g\{e^{\theta' X_{jk}(t)}\} \Delta_j(t) e^{\hat{\gamma}' Z_j(t)}}{\sum_{j=1}^n g\{e^{\theta' X_{jk}(t)}\} \Delta_j(t) e^{\hat{\gamma}' Z_j(t)}}.$$

If we take $g(t) = \log(t)$, the estimator $\hat{\mu}_{0k}(t; \theta, \gamma)$ also has a closed form that can be obtained by

$$g\{\hat{\mu}_{0k}(t; \theta, \gamma)\} = \frac{\sum_{i=1}^n Y_{ik}(t) \Delta_i(t) dN_{ik}(t)}{\sum_{i=1}^n \Delta_i(t) e^{\gamma' Z_i(t)}} \cdot \frac{1}{d\Lambda_{0k}(t)} - \frac{\sum_{i=1}^n g\{e^{\theta' X_{ik}(t)}\} \Delta_i(t) e^{\gamma' Z_i(t)}}{\sum_{i=1}^n \Delta_i(t) e^{\gamma' Z_i(t)}}.$$

In this situation, we have

$$U(\theta; \hat{\gamma}) = \sum_{k=1}^K \sum_{i=1}^n \int_0^\tau W(t) \{X_{ik}(t) - \bar{X}_k(t; \hat{\gamma})\} \Delta_i(t) \left[Y_{ik}(t) dN_{ik}(t) - \theta' X_{ik}(t) e^{\hat{\gamma}' Z_i(t)} d\hat{\Lambda}_{0k}(t) \right],$$

where

$$\bar{X}_k(t; \hat{\gamma}) = \frac{\sum_{j=1}^n X_{jk}(t) \Delta_j(t) e^{\hat{\gamma}' Z_j(t)}}{\sum_{j=1}^n \Delta_j(t) e^{\hat{\gamma}' Z_j(t)}},$$

which yields

$$\hat{\theta} = \left\{ \sum_{k=1}^K \sum_{i=1}^n \int_0^{\tau} W(t) \{X_{ik}(t) - \bar{X}_k(t; \hat{\gamma})\} X'_{ik}(t) \Delta_i(t) e^{\hat{\gamma}' Z_i(t)} d\hat{\Lambda}_{0k}(t) \right\}^{-1} \times \sum_{k=1}^K \sum_{i=1}^n \int_0^{\tau} W(t) \{X_{ik}(t) - \bar{X}_k(t; \hat{\gamma})\} Y_{ik}(t) \Delta_i(t) dN_{ik}(t).$$

That is, $\hat{\theta}$ has a closed form.

4. A SIMULATION STUDY

An extensive simulation study was conducted to evaluate the performance of the proposed inference procedure with the focus on estimation of β and α . In the study, we assumed that $Z_i(t)$ was a Bernoulli random variable with 0.5 success probability and the follow-up time C_i was generated from the uniform distribution over $(\tau/2, \tau)$. For the generation of the observation process, it was assumed that $N_{i1}(t)$ and $N_{i2}(t)$ are Poisson processes satisfying model (1). In this case, given Z_i , the number of observations, m_{ik}^* , follows the Poisson distribution with mean $\Lambda(C_i | Z_i) = \Lambda_0(C_i) e^{\gamma' Z_i}$ and the observation times $(t_{ik,1}, \dots, t_{ik,m_{ik}^*})$ are the order statistics of the random sample of size m_{ik}^* from the uniform distribution over $(0, C_i)$.

To generate panel counts $Y_{ik}(t_{ik,l})$, we assumed that

$$Y_{ik}(t_{ik,l}) = Y_{ik}^*(t_{ik,1}) + Y_{ik}^*(t_{ik,2} - t_{ik,1}) + \dots + Y_{ik}^*(t_{ik,l} - t_{ik,l-1})$$

and given the Q_i 's, $Y_{ik}^*(t_{ik,l})$, and $Y_{ik}^*(t_{ik,l} - t_{ik,l-1})$ follow Poisson distributions with the mean functions

$$Q_i g \left\{ \mu_0(t_{ik,l}) e^{\beta Z_i + \alpha H(\mathcal{F}_{it_{ik,l}})} \right\}$$

and

$$Q_i g \left\{ \mu_0(t_{ik,l}) e^{\beta Z_i + \alpha H(\mathcal{F}_{it_{ik,l}})} \right\} - Q_i g \left\{ \mu_0(t_{ik,l-1}) e^{\beta Z_i + \alpha H(\mathcal{F}_{it_{ik,l-1}})} \right\},$$

respectively, $j=1, \dots, m_{ik}^*$, $k=1, 2$, $i=1, \dots, n$. Here $t_{ik,0} = 0$ and the Q_i 's are a random sample from the gamma distribution with mean 1 and variance 0.1. With respect to functions g and μ_{0k} , we considered a number of choices including $g(t) = t$, $g(t) = t^2$ and $g(t) = \log(t)$ for g and $\mu_{0k}(t) = t$, $\mu_{0k}(t) = t^{1/2}$ and $\mu_{0k}(t) = \exp(t)$ for μ_{0k} . For all situations, we took $H(\mathcal{F}_{ikt}) = N_{ik}(t-)$, $W(t) = 1$, and $n = 100$ or 300 . The results reported below are based on 500 replications.

Table 1 presents the results for estimation of β and α based on the simulated data with $g(t) = t$, $\mu_{01}(t) = t$, $\mu_{02}(t) = t^{1/2}$, $\lambda_{01}(t) = 20/\tau$, and $\lambda_{02}(t) = 15/\tau$. The results include the estimated biases (Bias) given by the sample means of the point estimates $\hat{\beta}$ and $\hat{\alpha}$ minus their true values, the sample means of the estimated standard errors of $\hat{\beta}$ and $\hat{\alpha}$ (SEE), the sampling standard deviations of $\hat{\beta}$ and $\hat{\alpha}$ (SSE), and the 95% empirical coverage probabilities (CP) for both $\hat{\beta}$ and $\hat{\alpha}$. It can be seen from the table that the point estimates seem to be unbiased and SEE and SSE are quite close to each other, indicating that the proposed variance estimation seems to work well. Also the coverage probabilities are reasonable and consistent with the

nominal levels and as expected, the estimates of variances became smaller as the sample size increased.

The results given in Tables 2 and 3 are also about the estimation of β and α obtained under the set-ups similar to those used in Table 1 except some underlying functions. Specifically, in Table 2, we employed $g(t) = \log(t)$, $\mu_{01}(t) = \mu_{02}(t) = \exp(t)$, $\lambda_{01}(t) = \lambda_{02}(t) = 10/\tau$, while for Table 3, we used $g(t) = \log(t)$, $\mu_{01}(t) = \exp(t)$, $\mu_{02}(t) = \exp(t^{1/2})$, $\lambda_{01}(t) = 10/\tau$ and $\lambda_{02}(t) = 6/\tau$. One can easily see that both Tables 2 and 3 gave similar conclusions to those given in Table 1 and again suggested that the proposed inference procedure seems to perform well for practical situations. In addition to the results presented here, we also considered other set-ups such that the Z_i 's follow the normal distribution and the observation process was generated from the nonhomogeneous Poisson process. The results obtained are similar to those described above.

5. APPLICATION TO THE SKIN CANCER CHEMOPREVENTION TRIAL

In this section, we apply the methodology proposed in the previous sections to the bivariate panel count data on the occurrences of the two types of related non-melanoma skin cancers, basal cell carcinoma and squamous cell carcinoma, from the skin cancer chemoprevention trial discussed before. As mentioned above, the study involves 291 skin cancer patients and two treatment groups, placebo group and DFMO group. For the analysis below, we will focus on the 290 patients (147 in the placebo group and 143 in the DFMO group) with at least one observation. Among these patients, the number of observations ranges from 1 to 17. With respect to the number of the recurrent events, the number of new basal cell carcinoma ranges from 0 to 16, while the number of new squamous cell carcinoma ranges from 0 to 23. In addition to the treatment indicator, for each patient, other baseline information available include patient's gender and age at the diagnosis and the number of prior skin cancers from first diagnosis to randomization. In the original analysis of the study, the two-sample t -test was used to compare the skin cancer occurrence rates, defined as the total number of new skin cancers divided by the length of follow-up period, between the two treatment groups. It is clear that a great deal of the useful information was lost in this analysis.

To analyze the bivariate skin cancer panel count data, for patient i , let $Y_{i1}(t)$ denote the total number of the occurrences of basal cell carcinoma up to time t and $Y_{i2}(t)$ the total number of the occurrences of squamous cell carcinoma. Also let $N_{i1}(t) = N_{i2}(t)$ denote the observation process on patient i , which is the same for both types of the skin cancers. Define $Z_{i1} = 0$ if patient i was in the placebo group and 1 otherwise, Z_{i2} and Z_{i3} to denote the number of prior skin cancers and the age of the patient, and $Z_{i4} = 0$ if patient i is female and 1 otherwise, $i = 1, \dots, 290$. Assume that the $N_{ik}(t)$'s and $Y_{ik}(t)$'s can be described by models (1) and (2), respectively. With respect to the function g , we considered the same three functions used in the simulation study: $g(t) = t$, $g(t) = t^2$, and $g(t) = \log(t)$. For the function $H(\mathcal{F}_{ikt})$, two situations were investigated. One is to take $H(\mathcal{F}_{ikt}) = N_{ik}(t-)$, assuming that the recurrence rate of skin cancer may depend on the total number of patient's visits, and the other is to let $H(\mathcal{F}_{ikt}) = N_{ik}(t-) - N_{ik}(t-100)$, meaning that the recurrence rate may depend only on the number of patient's visits during the 100-day period before. The latter choice was motivated by the fact that sometimes it is the most recent visits that may carry information about the response variable. For all analyses, we took $W(t) = 1$.

The analysis results are given in Tables 4 and 5. The former is for $H(\mathcal{F}_{ikt}) = N_{ik}(t-)$ and the latter is for $H(\mathcal{F}_{ikt}) = N_{ik}(t-) - N_{ik}(t-100)$. They include the point estimates of regression parameters, the estimated standard errors (SE) and the estimated 95% confidence intervals (CI). One can see from the tables that it seems that the DFMO treatment did not have any

significant effect on the recurrence of the skin cancer and also the recurrence did not seem to be significantly related to the age and gender of the patient. However, the occurrence of the skin cancer seems to be positively related to the number of prior skin cancers. It can also be seen that the analysis results seem to be consistent with respect to the choice of functions g and $H(\sigma_{ikt})$. More comments on this are given in the next section. In terms of the relationship between the recurrence process of the types of skin cancers considered here and the patient's observation process, the results suggest that the latter seems to contain some relevant information about the former. However, the information may depend on the follow-up period or timing as the results indicate that a higher total number of the observations was related to a higher recurrence rate of the skin cancer, but a higher number of the observations over a short period could cause a lower recurrence rate of the skin cancer. A possible explanation is that the more observations or visits mean the higher recurrence rate in general, but the high number of the visits over a short period would leave no time for and thus prevent the occurrence of new skin cancers.

6. CONCLUDING REMARKS

In the preceding sections, we have discussed regression analysis of multivariate panel count data when the observation process on study subjects may contain relevant information about the underlying recurrent event processes of interest. Such data naturally occur when a recurrent event study involves several related types of recurrent events and follow-up or observation processes on study subjects are subject-specific. The areas in which one often faces such data include clinical trials and medical or social follow-up studies. For the problem, we presented a class of flexible transformation models for the underlying recurrent event processes and an estimating equation-based inference procedure was developed for estimation of regression parameters. Both finite sample and asymptotic properties of the proposed estimates have been established and the simulation results indicated that the procedure seems to work well for practical situations. The methodology was applied to a set of bivariate panel count data arising from a skin cancer chemoprevention trial.

It is worth noting that both models (1) and (2) are marginal models and we took the marginal approach for the problem considered here as the main focus of the article was on estimation of covariate effects. An advantage of the proposed approach, as many other marginal approaches for multivariate data, is that it leaves the correlation between different types of recurrent events arbitrary. An alternative is to directly model the correlation structure, which would be appealing if the correlation is of main interest. In general, if the model is correct, the direct modelling of the correlation could increase the efficiency of the estimated covariate effects but has no effect on the unbiasedness of the estimate.

There exist several directions for future research. One is that in the proposed methodology, the observation process $N_{ik}(t)$ was assumed to be a nonhomogeneous Poisson process. It is clear that this may not be true in practice and it would be useful to generalize the proposed approach to situations where the assumption does not hold. Another direction is model checking and the selection of the link function g . Although both models (1) and (2) are quite general, there may exist situations where they do not hold. To assess their appropriateness for a given data set, one way is to develop some model checking procedures for the goodness-of-fit test. Note that for the situation where the main interest is on covariate effects as in the example discussed in Section 5, the selection of the function g may not be critical if different functions g give similar results. Also note that the regression parameters β corresponding to different g may have different meanings. A related problem or method is to assume that g belongs to some class of functions and to develop a procedure for its selection.

A third direction is that in the estimating function (4), we used a possibly data-dependent weight function $W(t)$ and it would be useful to develop some procedures for the selection of an appropriate weight function for a given data set. It is clear that $W(t)$ cannot be any data-dependent function as $W(t)$ needs to be chosen such that the estimating function has zero expectation. In general, one would like to choose $W(t)$ that gives the most efficient estimate of covariate effects. However, sometimes, this may not be possible and it is usually quite difficult.

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APPENDIX: JOINT ASYMPTOTIC NORMALITY OF $\hat{\beta}$ AND $\hat{\alpha}$

In this section, we will use the same notation defined above and all limits are taken as $n \rightarrow \infty$. Assume that g is a twice continuously differentiable function. Also assume that $Z_i(t)$, $H(\cdot)$, and $W(t)$ have bounded variations and $W(t)$ converges almost surely to a deterministic function $w(t)$ uniformly in $t \in [0, \tau]$. Define

$$\begin{aligned} M_{ik}(t) &= \int_0^t Y_{ik}(u) \Delta_i(u) dN_{ik}(u) - \int_0^t \Delta_i(u) g\{\mu_{0k}(u) e^{\theta' X_{ik}(u)}\} e^{\gamma' Z_i(u)} d\Lambda_{0k}(u), \\ M_{ik}^*(t) &= \int_0^t \Delta_i(u) dN_{ik}(u) - \int_0^t \Delta_i(u) e^{\gamma' Z_i(u)} d\Lambda_{0k}(u), \\ E_{X_k}(t; \theta, \gamma) &= \frac{\sum_{i=1}^n \Delta_i(t) X_{ik}(t) g\{\mu_{0k}(t) e^{\theta' X_{ik}(t)}\} e^{\gamma' Z_i(t)}}{\sum_{i=1}^n \Delta_i(t) g\{\mu_{0k}(t) e^{\theta' X_{ik}(t)}\} e^{\gamma' Z_i(t)}}, \end{aligned}$$

and

$$R_k(t; \theta, \gamma) = n^{-1} \sum_{i=1}^n \{X_{ik}(t) - E_{X_k}(t; \theta, \gamma)\} \Delta_i(t) g\{\mu_{0k}(t) e^{\theta' X_{ik}(t)}\} e^{\gamma' Z_i(t)}.$$

Let $s_0(t)$, $s_1(t)$, $e_{X_k}(t)$, and $r_k(t)$ denote the limits of $S_0(t; \gamma_0)$, $S_1(t; \gamma_0)$, $E_{X_k}(t; \theta_0, \gamma_0)$, and $R_k(t; \theta_0, \gamma_0)$, respectively. Also let $\bar{X}(t) = s_1(t)/s_0(t)$. First by the linear expansion of g , we have

$$\begin{aligned} U(\theta_0; \gamma_0) &= \sum_{k=1}^K \sum_{i=1}^n \int_0^\tau W(t) X_{ik}(t) \left[Y_{ik}(t) \Delta_i(t) dN_{ik}(t) - \Delta_i(t) g\{\mu_{0k}(t) e^{\theta' X_{ik}(t)}\} e^{\gamma' Z_i(t)} d\hat{\Lambda}_{0k}(t; \gamma_0) - \Delta_i(t) g\{\mu_k^*(t) e^{\theta' X_{ik}(t)}\} e^{\gamma' Z_i(t)} \{\hat{\mu}_{0k}(t; \theta_0, \gamma_0) - \mu_{0k}(t) \} \right] \end{aligned}$$

where μ_k^* lies between $\mu_{0k}(t)$ and $\hat{\mu}_{0k}(t; \theta_0, \gamma_0)$. Note that $\hat{\mu}_{0k}(t; \theta, \gamma)$ satisfies

$$\sum_{i=1}^n \left[Y_{ik}(t) \Delta_i(t) dN_{ik}(t) - \Delta_i(t) g\{\hat{\mu}_{0k}(t; \theta, \gamma) e^{\theta' X_{ik}(t)}\} e^{\gamma' Z_i(t)} d\hat{\Lambda}_{0k}(t; \gamma) \right] = 0. \quad (\text{A.2})$$

Likewise, the linear expansion of (A.2) with $\theta = \theta_0$ and $\gamma = \gamma_0$ yields

$$\{\hat{\mu}_{0k}(t; \theta_0, \gamma_0) - \mu_{0k}(t)\} d\hat{\Lambda}_{0k}(t; \gamma_0) = \frac{\sum_{i=1}^n \left[Y_{ik}(t) \Delta_i(t) dN_{ik}(t) - \Delta_i(t) g\{\mu_{0k}(t) e^{\theta'_0 X_{ik}(t)}\} e^{\gamma'_0 Z_i(t)} d\hat{\Lambda}_{0k}(t; \gamma_0) \right]}{\sum_{i=1}^n \Delta_i(t) g\{\mu_k^{**}(t) e^{\theta'_0 X_{ik}(t)}\} e^{\gamma'_0 X_{ik}(t) + \gamma'_0 Z_i(t)}} \quad (\text{A.3}),$$

where μ_k^{**} lies between $\mu_{0k}(t)$ and $\hat{\mu}_{0k}(t; \theta_0, \gamma_0)$. By using the functional central limit theorem (Pollard, 1990, p. 53) and noting $\sup_{0 \leq t \leq \tau} |\hat{\Lambda}_{0k}(t; \gamma_0) - \Lambda_{0k}(t)| = o_p(n^{-1/2})$, it can be seen that

$$\sum_{i=1}^n \left[Y_{ik}(t) \Delta_i(t) dN_{ik}(t) - \Delta_i(t) g\{\mu_{0k}(t) e^{\theta'_0 X_{ik}(t)}\} e^{\gamma'_0 Z_i(t)} d\hat{\Lambda}_{0k}(t; \gamma_0) \right] = o_p(n^{1/2})$$

uniformly in t . Hence, combining (A.1) and (A.3) with the uniform convergence of $\hat{\mu}_{0k}(t; \theta_0, \gamma_0)$, we have

$$U(\theta_0; \gamma_0) = \sum_{k=1}^K \sum_{i=1}^n \int_0^\tau w(t) \{X_{ik}(t) - e_{x_k}(t)\} dM_{ik}(t) - U^*(\theta_0; \gamma_0) + o_p(n^{1/2}),$$

where

$$U^*(\theta_0; \gamma_0) = \sum_{k=1}^K \sum_{i=1}^n \int_0^\tau w(t) \{X_{ik}(t) - e_{x_k}(t)\} \Delta_i(t) g\{\mu_{0k}(t) e^{\theta'_0 X_{ik}(t)}\} e^{\gamma'_0 Z_i(t)} d[\hat{\Lambda}_{0k}(t; \gamma_0) - \Lambda_{0k}(t)].$$

It is well known that

$$\hat{\Lambda}_{0k}(t; \gamma_0) - \Lambda_{0k}(t) = n^{-1} \sum_{i=1}^n \int_0^t \frac{dM_{ik}^*(u)}{s_0(u)} + o_p(n^{-1/2}).$$

Thus,

$$U^*(\theta_0; \gamma_0) = \sum_{k=1}^K \sum_{i=1}^n \int_0^\tau \frac{w(t) r_k(t)}{s_0(t)} dM_{ik}^*(t) + o_p(n^{1/2}).$$

It then follows that

$$U(\theta_0; \gamma_0) = \sum_{k=1}^K \sum_{i=1}^n \left[\int_0^\tau w(t) \{X_{ik}(t) - e_{x_k}(t)\} dM_{ik}(t) - \int_0^\tau \frac{w(t) r_k(t)}{s_0(t)} dM_{ik}^*(t) \right] + o_p(n^{1/2}). \quad (\text{A.4})$$

It can be checked that

$$\frac{\partial \hat{\Lambda}_{0k}(t; \gamma)}{\partial \gamma} = - \int_0^t \frac{S_1(u; \gamma) d\bar{N}_k(u)}{S_0(u; \gamma)^2} \quad (\text{A.5})$$

where $\bar{N}_k(t) = n^{-1} \sum_{i=1}^n \Delta_i(t) N_{ik}(t)$. Differentiation of (A.2) with respect to γ yields

$$\frac{\partial \hat{\mu}_{0k}(t; \theta, \gamma)}{\partial \gamma} d\hat{\Lambda}_{0k}(t; \gamma) = -Q_k(t; \theta, \gamma)^{-1} \sum_{i=1}^n \Delta_i(t) g\{\hat{\mu}_{0k}(t; \theta, \gamma) e^{\theta' X_{ik}(t)}\} e^{\gamma' Z_i(t)} \times \left[Z_i(t) d\hat{\Lambda}_{0k}(t; \gamma) - \frac{S_1(t; \gamma)}{S_0(t; \gamma)^2} d\bar{N}_k(t) \right],$$

where

$$Q_k(t; \theta, \gamma) = \sum_{i=1}^n \Delta_i(t) g\{\hat{\mu}_{0k}(t; \theta, \gamma) e^{\theta' X_{ik}(t)}\} e^{\theta' X_{ik}(t) + \gamma' Z_i(t)}.$$

Let $P^*(\theta, \gamma) = -n^{-1} U(\theta, \gamma) / \gamma'$. Thus it follows from (A.5) and (A.6) that $P^*(\theta, \gamma)$ converges almost surely to a nonrandom function $P(\theta, \gamma)$ uniformly in θ and γ . Denote $P(\theta_0; \gamma_0)$ by P . Then

$$P = E \left[\sum_{k=1}^K \int_0^\tau w(t) \Delta_i(t) g\{\mu_{0k}(t) e^{\theta_0' X_{ik}(t)}\} e^{\gamma_0' Z_i(t)} \{X_{ik}(t) - e_{x_k}(t)\} \{Z_i(t) - \bar{z}(t)\}' d\Lambda_{0k}(t) \right].$$

Using the Taylor expansion of $U(\theta_0; \hat{\gamma})$ at (θ_0, γ_0) , we have

$$U(\theta_0; \hat{\gamma}) = U(\theta_0; \gamma_0) - PD^{-1} \sum_{k=1}^K \sum_{i=1}^n \int_0^\tau \{Z_i(t) - \bar{z}(t)\} dM_{ik}^*(t) + o_p(n^{1/2}), \quad (\text{A.7})$$

based on the consistency of $\hat{\gamma}$ and Equation (A.5) of Lin et al. (2000), where

$$D = E \left[\sum_{k=1}^K \int_0^\tau \{Z_i(t) - \bar{z}(t)\}^{\otimes 2} \Delta_i(t) e^{\gamma_0' Z_i(t)} d\Lambda_{0k}(t) \right].$$

Hence it follows from (A.4), (A.7) and the multivariate central limit theorem that $n^{-1/2} U(\theta_0; \hat{\gamma})$ converges in distribution to a mean-0 normal random vector with covariance matrix

$$\Sigma = E \left[\sum_{k=1}^K \int_0^\tau w(t) \{X_{ik}(t) - e_{x_k}(t)\} dM_{ik}(t) - \sum_{k=1}^K \int_0^\tau \frac{w(t) r_k(t)}{s_0(t)} dM_{ik}^*(t) - PD^{-1} \sum_{k=1}^K \int_0^\tau \{Z_i(t) - \bar{z}(t)\} dM_{ik}^*(t) \right]^{\otimes 2}.$$

By using the method in Equation (A.3) of Lin et al. (2000), it is easy to see that Σ can be consistently estimated by $\hat{\Sigma}$ given in Section 3.

Differentiation of (A.2) with respect to θ gives

$$\frac{\partial \hat{\mu}_{0k}(t; \theta, \gamma)}{\partial \theta} d\hat{\Lambda}_{0k}(t; \gamma) = -E_{X_k}^*(t; \theta, \gamma) \hat{\mu}_{0k}(t; \theta, \gamma) d\hat{\Lambda}_{0k}(t; \gamma), \quad (\text{A.8})$$

where

$$E_{X_k}^*(t; \theta, \gamma) = Q_k(t; \theta, \gamma)^{-1} \sum_{i=1}^n \Delta_i(t) X_{ik}(t) \dot{g}\{\hat{\mu}_{0k}(t; \theta, \gamma) e^{\theta' X_{ik}(t)}\} e^{\theta' X_{ik}(t) + \gamma' Z_i(t)}.$$

Thus, it follows from (A.8) and some simple algebra that $-n^{-1} U(\hat{\theta}; \hat{\gamma}) / \theta'$ converges almost surely to a nonrandom function $A(\theta)$ uniformly in θ , and

$$A(\theta_0) = E \left[\sum_{k=1}^K \int_0^\tau w(t) \Delta_i(t) \dot{g}\{\mu_{0k}(t) e^{\theta_0' X_{ik}(t)}\} \{X_{ik}(t) - e_{X_k}(t)\}^{\otimes 2} e^{\theta_0' X_{ik}(t) + \gamma_0' Z_i(t)} \mu_{0k}(t) d\Lambda_{0k}(t) \right],$$

which can be consistently estimated by $\hat{A}$ given in Section 3. The Taylor expansion of $U(\hat{\theta}; \hat{\gamma})$ at $(\theta_0, \hat{\gamma})$ yields

$$n^{1/2}(\hat{\theta} - \theta_0) = A(\theta_0)^{-1} n^{-1/2} U(\theta_0; \hat{\gamma}) + o_p(1). \quad (\text{A.9})$$

Therefore, it follows from (A.7) and (A.9) that $n^{1/2}(\hat{\theta} - \theta_0)$ asymptotically follows the normal distribution with mean zero and the covariance matrix $A(\theta_0)^{-1} \Sigma A(\theta_0)^{-1}$, which can be consistently estimated by $\hat{A}^{-1} \hat{\Sigma} \hat{A}^{-1}$.

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Table 1

Results on estimation of β and α based on the simulated data with $\mathcal{G}(t) = t$, $\mu_{01}(t) = t$, $\mu_{02}(t) = t^{1/2}$, $\lambda_{01}(t) = 20/t$, and $\lambda_{02}(t) = 15/t$.

		$n = 100$						$n = 300$					
		$\tau = 1$			$\tau = 2$			$\tau = 1$			$\tau = 2$		
		$\hat{\beta}$	$\hat{\alpha}$	$\hat{\beta}$	$\hat{\alpha}$	$\hat{\beta}$	$\hat{\alpha}$	$\hat{\beta}$	$\hat{\alpha}$	$\hat{\beta}$	$\hat{\alpha}$	$\hat{\beta}$	$\hat{\alpha}$
$\theta = (0, 0)$													
	BIAS	0.0152	0.0047	0.0236	0.0028	0.0119	0.0047	0.0185	0.0038				
	SSE	0.2574	0.0244	0.2048	0.0192	0.1462	0.0133	0.1168	0.0111				
	SEE	0.2504	0.0235	0.1993	0.0187	0.1466	0.0140	0.1169	0.0110				
	CP	0.954	0.924	0.924	0.936	0.952	0.938	0.950	0.928				
$\theta = (0, 0.02)$													
	BIAS	0.0449	0.0023	0.0230	0.0030	0.0140	0.0048	0.0113	0.0032				
	SSE	0.2333	0.0210	0.1898	0.0170	0.1335	0.0127	0.1078	0.0099				
	SEE	0.2212	0.0201	0.1777	0.0157	0.1289	0.0118	0.1039	0.0095				
	CP	0.928	0.938	0.928	0.932	0.948	0.912	0.938	0.932				
$\theta = (0.5, 0)$													
	BIAS	0.0261	0.0029	0.0007	0.0049	0.0062	0.0063	0.0053	0.0040				
	SSE	0.2314	0.0212	0.1925	0.0163	0.1346	0.0121	0.1127	0.0097				
	SEE	0.2239	0.0205	0.1803	0.0162	0.1312	0.0123	0.1064	0.0098				
	CP	0.934	0.934	0.932	0.934	0.936	0.920	0.942	0.934				
$\theta = (0.5, 0.02)$													
	BIAS	0.0197	0.0029	0.0136	0.0042	0.0134	0.0040	0.0211	0.0029				
	SSE	0.1918	0.0186	0.1643	0.0145	0.1153	0.0106	0.0959	0.0084				
	SEE	0.1984	0.0172	0.1629	0.0141	0.1170	0.0104	0.0955	0.0085				
	CP	0.956	0.922	0.936	0.930	0.966	0.922	0.950	0.930				

Table 2

Results on estimation of β and α based on the simulated data with $g(\theta) = \log t$, $\mu_{01}(\theta) = \mu_{02}(\theta) = \exp(\theta)$, and $\lambda_{01}(\theta) = \lambda_{02}(\theta) = 10/\tau$.

		$n = 100$				$n = 300$			
		$\tau = 3$		$\tau = 4$		$\tau = 3$		$\tau = 4$	
		$\hat{\beta}$	$\hat{\alpha}$	$\hat{\beta}$	$\hat{\alpha}$	$\hat{\beta}$	$\hat{\alpha}$	$\hat{\beta}$	$\hat{\alpha}$
$\theta = (0, 0)$									
BIAS		0.0108	-0.0003	0.0147	-0.0001	0.0035	0.0006	-0.0059	0.0003
SSE		0.1743	0.0363	0.2066	0.0451	0.1014	0.0212	0.1222	0.0255
SEE		0.1667	0.0350	0.1992	0.0424	0.0975	0.0207	0.1176	0.0252
CP		0.924	0.942	0.950	0.938	0.950	0.942	0.934	0.956
$\theta = (0, 0.1)$									
BIAS		-0.0056	-0.0022	0.0194	-0.0020	-0.0083	0.0012	-0.0009	-0.0001
SSE		0.2112	0.0504	0.2400	0.0587	0.1289	0.0311	0.1434	0.0340
SEE		0.2116	0.0480	0.2432	0.0557	0.1229	0.0290	0.1429	0.0334
CP		0.960	0.926	0.950	0.932	0.922	0.936	0.938	0.944
$\theta = (0.5, 0)$									
BIAS		-0.0103	-0.0015	-0.0178	-0.0032	0.0084	-0.0005	-0.0050	0.0020
SSE		0.1973	0.0407	0.2256	0.0501	0.1112	0.0251	0.1392	0.0282
SEE		0.1906	0.0403	0.2239	0.0470	0.1126	0.0242	0.1316	0.0283
CP		0.942	0.936	0.936	0.924	0.954	0.948	0.922	0.952
$\theta = (0.5, 0.1)$									
BIAS		-0.0025	0.0016	0.0127	-0.0015	-0.0009	-0.0017	0.0086	0.0016
SSE		0.2301	0.0530	0.2570	0.0608	0.1329	0.0333	0.1538	0.0395
SEE		0.2308	0.0532	0.2626	0.0592	0.1374	0.0320	0.1541	0.0363
CP		0.942	0.940	0.948	0.930	0.952	0.938	0.936	0.938

Table 3

Results on estimation of β and α based on the simulated data with $\mathcal{G}(t) = \log t$, $\mu_{01}(t) = \exp(t)$, $\mu_{02}(t) = \exp(t^{1/2})$, $\lambda_{01}(t) = 10/t$, and $\lambda_{02}(t) = 6/t$.

		$n = 100$						$n = 300$					
		$\tau = 3$			$\tau = 4$			$\tau = 3$			$\tau = 4$		
		$\hat{\beta}$	$\hat{\alpha}$	$\hat{\beta}$	$\hat{\alpha}$	$\hat{\beta}$	$\hat{\alpha}$	$\hat{\beta}$	$\hat{\alpha}$	$\hat{\beta}$	$\hat{\alpha}$	$\hat{\beta}$	$\hat{\alpha}$
$\theta = (0, 0)$													
	BIAS	0.0069	0.0012	0.0012	-0.0012	0.0141	-0.0019	0.0062	-0.0004				
	SSE	0.1728	0.0414	0.1976	0.0498	0.0976	0.0230	0.1178	0.0293				
	SEE	0.1676	0.0396	0.1960	0.0473	0.0986	0.0236	0.1148	0.0282				
	CP	0.950	0.934	0.948	0.936	0.942	0.950	0.946	0.948				
$\theta = (0, 0.1)$													
	BIAS	0.0213	-0.0034	0.0224	-0.0057	0.0052	-0.0016	0.0041	-0.0011				
	SSE	0.2240	0.0553	0.2474	0.0634	0.1229	0.0340	0.1383	0.0384				
	SEE	0.2046	0.0531	0.2338	0.0608	0.1212	0.0325	0.1374	0.0370				
	CP	0.920	0.934	0.934	0.930	0.948	0.942	0.952	0.944				
$\theta = (0.5, 0)$													
	BIAS	-0.0040	-0.0053	0.0176	-0.0021	0.0056	-0.0021	0.0016	-0.0028				
	SSE	0.2002	0.0456	0.2331	0.0553	0.1114	0.0288	0.1307	0.0320				
	SEE	0.1936	0.0457	0.2211	0.0530	0.1133	0.0272	0.1287	0.0314				
	CP	0.948	0.934	0.932	0.930	0.946	0.934	0.962	0.946				
$\theta = (0.5, 0.1)$													
	BIAS	0.0323	-0.0040	0.0158	-0.0003	0.0120	-0.0029	0.0086	-0.0014				
	SSE	0.2437	0.0632	0.2692	0.0704	0.1384	0.0373	0.1483	0.0429				
	SEE	0.2318	0.0591	0.2557	0.0676	0.1342	0.0363	0.1502	0.0408				
	CP	0.934	0.932	0.934	0.932	0.946	0.938	0.950	0.928				

Table 4

Estimation of regression parameters for the skin cancer chemoprevention trial with $H(\vec{\gamma}_{it}) = N_K(t-)$.

Function $g(t)$	DFMO treatment: $\hat{\beta}_1$, SE($\hat{\beta}_1$), 95% CI for β_1	Prior skin cancer number: $\hat{\beta}_2$, SE($\hat{\beta}_2$), 95% CI for β_2	Age: $\hat{\beta}_3$, SE($\hat{\beta}_3$), 95% CI for β_3	Gender: $\hat{\beta}_4$, SE($\hat{\beta}_4$), 95% CI for β_4	Observation history: $\hat{\alpha}$, SE($\hat{\alpha}$), 95% CI for α
$g(t) = t$	-0.2629, 0.1849, (-0.6252, 0.0995)	0.0697, 0.0080, (0.0539, 0.0854)	-0.0016, 0.0085, (-0.0183, 0.0151)	0.2419, 0.1896, (-0.1297, 0.6135)	0.1657, 0.0469, (0.0738, 0.2575)
$g(t) = t^2$	-0.1314, 0.0924, (-0.3126, 0.0498)	0.0348, 0.0040, (0.0269, 0.0427)	-0.0008, 0.0043, (-0.0091, 0.0075)	0.1210, 0.0948, (-0.0648, 0.3067)	0.0828, 0.0234, (0.0369, 0.1288)
$g(t) = \log(t)$	-0.1107, 0.1111, (-0.3284, 0.1070)	0.0981, 0.0223, (0.0544, 0.1419)	-0.0035, 0.0047, (-0.0126, 0.0057)	0.1478, 0.1106, (-0.0690, 0.3647)	0.1718, 0.0736, (0.0275, 0.3162)

Estimation of regression parameters for the Skin cancer chemoprevention trial with $H(\hat{\alpha}_{it}) = N_A(t) - N_A(t - 100)$.

Table 5

Function $g(t)$	DFMO treatment $\hat{\beta}_1, SE(\hat{\beta}_1), 95\% \text{ CI for } \beta_1$	Prior skin cancer number $\hat{\beta}_2, SE(\hat{\beta}_2), 95\% \text{ CI for } \beta_2$	Age $\hat{\beta}_3, SE(\hat{\beta}_3), 95\% \text{ CI for } \beta_3$	Gender $\hat{\beta}_4, SE(\hat{\beta}_4), 95\% \text{ CI for } \beta_4$	Observation history $\hat{\alpha}, SE(\hat{\alpha}), 95\% \text{ CI for } \alpha$
$g(t) = t$	-0.3863, 0.2116, (-0.8011, 0.0284)	0.0774, 0.0095, (0.0587, 0.0960)	0.0044, 0.0094, (-0.0139, 0.0228)	0.2050, 0.2060, (-0.1987, 0.6087)	-0.7768, 0.2744, (-1.3145, -0.2391)
$g(t) = t^2$	-0.1932, 0.1058, (-0.4005, 0.0142)	0.0387, 0.0048, (0.0293, 0.0480)	0.0022, 0.0047, (-0.0070, 0.0114)	0.1025, 0.1030, (-0.0994, 0.3044)	-0.3884, 0.1372, (-0.6573, -0.1195)
$g(t) = \log(t)$	-0.1418, 0.1146, (-0.3664, 0.0829)	0.10600.0247, (0.0576, 0.1544)	-0.00080.0048, (-0.0103, 0.0087)	0.1149, 0.1108, (-0.1022, 0.3320)	-0.4621, 0.0983, (-0.6549, -0.2694)