Title

Generalized scale-change models for recurrent event processes under informative censoring.

Journal

Statistica Sinica, 30(4)

ISSN

1017-0405

Authors

Xu, Gongjun
Chiou, Sy Han
Yan, Jun
et al.

Publication Date

2020

DOI

10.5705/ss.202018.0224

Peer reviewed

HHS Public Access

Author manuscript

Stat Sin. Author manuscript; available in PMC 2021 August 11.

Published in final edited form as:

Stat Sin. 2020 ; 30: 1773–1795. doi:10.5705/ss.202018.0224.

Generalized scale-change models for recurrent event processes under informative censoring

Gongjun Xu[1], **Sy Han Chiou**[2], **Jun Yan**[3], **Kieren Marr**[4], **Chiung-Yu Huang**[5]

[1]University of Michigan

[2]University of Texas at Dallas

[3]University of Connecticut

[4]Johns Hopkins University

[5]University of California, San Francisco

Abstract

Two major challenges arise in regression analyses of recurrent event data: first, popular existing models, such as the Cox proportional rates model, may not fully capture the covariate effects on the underlying recurrent event process; second, the censoring time remains informative about the risk of experiencing recurrent events after accounting for covariates. We tackle both challenges by a general class of semiparametric scale-change models that allow a scale-change covariate effect as well as a multiplicative covariate effect. The proposed model is flexible and includes several existing models as special cases, such as the popular proportional rates model, the accelerated mean model, and the accelerated rate model. Moreover, it accommodates informative censoring through a subject-level latent frailty whose distribution is left unspecified. A robust estimation procedure which requires neither a parametric assumption on the distribution of the frailty nor a Poisson assumption on the recurrent event process is proposed to estimate the model parameters. The asymptotic properties of the resulting estimator are established, with the asymptotic variance estimated from a novel resampling approach. As a byproduct, the structure of the model provides a model selection approach among the submodels via hypothesis testing of model parameters. Numerical studies show that the proposed estimator and the model selection procedure perform well under both noninformative and informative censoring scenarios. The methods are applied to data from two transplant cohorts to study the risk of infections after transplantation.

gongjun@umich.edu .
Department of Statistics, University of Michigan, Ann Arbor, MI 48109, U.S.A.
Department of Mathematical Sciences, University of Texas at Dallas, Richardson, TX 75080, U.S.A.
Department of Statistics, University of Connecticut, Storrs, CT 06269, U.S.A.
Johns Hopkins University School of Medicine, Baltimore, MD 21205, U.S.A.
Department of Epidemiology and Biostatistics, University of California, San Francisco, CA 94158, U.S.A.

Supplementary Materials

The online supplementary materials contain the proof of Theorem 1, additional simulation results, and graphical diagnosis of the Weibull model.

Keywords

Accelerated failure time model; Accelerated rate model; Cox model; Frailty model; Hypothesis testing; Model selection; Resampling

1. Introduction

The importance of analyzing recurrent events data has been widely recognized in many fields such as medicine, public health, cybersecurity, engineering, and social sciences (Wei and Glidden, 1997; Cook and Lawless, 2007). Examples of recurrent events include opportunistic infections experienced by patients who undergo hematopoietic stem cell transplantation (Marr, 2012), repeated cardiovascular events in survivors of myocardial infarction (Rogers et al., 2012), episodes of schizophrenia in chronic schizophrenic patients (Eaton et al., 1992), cyber attacks on network systems (Benjamin et al., 2016), and breakdowns of repairable systems (Nelson, 2003). Various regression models have been proposed to evaluate covariate effects on the risk of recurrent events. Pepe and Cai (1993), Lawless and Nadeau (1995), and Lin et al. (2000) considered Cox-type proportional rates/intensities models that postulate multiplicative covariate effects on the baseline rate/intensity function of the recurrent event process. Lin et al. (1998) studied the accelerated mean model where covariates modify the timescale of the cumulative mean function. Chen and Wang (2000) and Ghosh (2004) presented the accelerated rate/intensity model that formulates covariate effects to change the time-scale directly on the baseline rate/intensity function. These three types of models are covered as special cases in a general class of regression models proposed by Sun and Su (2008). Other covariate effect formulations include the additive rate models (Schaubel et al., 2006) and the additive-multiplicative rate models (Liu et al., 2010). All the methods above require a noninformative censoring assumption, that is, the censoring time is conditionally independent of the recurrent event process given the observed covariates.

In many applications, an informative censoring or terminal event, such as graft failure or death, can terminate the observation. Failing to account for informative censoring can lead to substantial bias in inferences and invalid conclusions (e.g., Cook and Lawless, 1997; Ghosh and Lin, 2002; Luo et al., 2010). A popular approach to accommodate informative censoring is joint modeling, where the association between the failure event and the recurrent event process is modeled via a shared frailty (Lancaster and Intrator, 1998; Liu et al., 2004; Ye et al., 2007; Zeng and Lin, 2009; Kalbfleisch et al., 2013). One advantage of the frailty is that it accounts for heterogeneity that cannot be explained by the observed covariates. Nonetheless, inference on the shared frailty model often requires a parametric assumption on the frailty distribution and correct modeling of the terminal event, which are nuisances when the primary interest is the covariate effects on the risk of recurrent events. Formal checking for the frailty distribution and the model specification of the terminal event is essential for inferences but underdeveloped. An alternative approach is to relax the parametric assumption on the shared frailty model. For instance, Wang et al. (2001), Huang and Wang (2004) and Huang et al. (2010) considered Cox-type models and Xu et al. (2017) studied a joint scale-change model of the recurrent event process and the terminal event.

We propose an approach that allows a flexible form of informative censoring in a generalized scale-change model for recurrent event processes. Our model encompasses two types of covariate effects: a scale-change effect that alters the timescale and a multiplicative effect that modifies the risk. A similar modeling approach has been studied for univariate survival data (Chen and Jewell, 2001) and recurrent event data (Sun and Su, 2008) under conditionally independent censoring given the observed covariates. Similar to Sun and Su (2008), this flexible formulation includes Cox-type models, the accelerated mean model, and the accelerated rate model as special cases. In contrast to Sun and Su (2008), the recurrent event process is associated with the censoring time through an unobserved, subject-specific frailty, and no parametric assumption about the frailty distribution is required. Utilizing the common mean structure shared by the conditional distribution of recurrent events and the order statistics of a set of right-truncated failure times, we embed the problem into estimation with right-truncated data and develop a novel semiparametric estimation procedure that does not require information about the frailty variable. The asymptotic normality of the resulting estimator is established without the strong Poisson-type assumption for the recurrent event process or parametric assumptions for the frailty variable. The asymptotic variance is estimated from an efficient resampling-based sandwich estimator. The structure of the model facilitates model selection among the submodels via hypothesis testing of model parameters. Our numerical studies confirmed the validity of the proposed methods and the model selection procedure.

2. Model Setup

Suppose that $[0, \tau]$ is the time period of a study where recurrent events can potentially be observed up to time τ. For a subject, let $N(t)$ be the number of events in interval $[0, t]$, and X be a $p \times 1$ covariate vector. Let C be a noninformative censoring time, such as the end of the study, which is independent of $N(\cdot)$ given X. Let D be an informative censoring time, such as death, which is associated with $N(\cdot)$ even after conditioning on X. Define the follow-up time as $Y = \min(C, D, \tau)$. The observed data are independent and identically distributed copies $\{N_i(t), Y_i, X_i : t \leq Y_i, i = 1, \ldots, n\}$. Let m_i be the number of events of subject i before time Y_i. If $m_i > 0$, the jump times of $N_i(t)$ are the observed event times t_{ij}, $j = 1, \ldots, m_i$.

Our model formulates the rate function for the counting process $N_i(t)$, $\lambda_i(t)\,\mathrm{d}t = E\{\mathrm{d}N_i(t) \mid Z_i, X_i\}$, given the covariate vector X_i and an unobserved subject-specific nonnegative frailty Z_i. Specifically, we postulate that

$$\lambda_i(t) = Z_i \lambda_0\left(te^{X_i^\top \alpha}\right) e^{X_i^\top \beta}, \quad t \in [0, \tau], \tag{2.1}$$

where Z_i has an unspecified distribution with $E\left(Z_i^2\right) < \infty$, α and β are both $p \times 1$ vectors of parameters, and $\lambda_0(t)$ is an unspecified, non-Weibull baseline rate function. As in Sun and Su (2008), the Weibull baseline $\lambda_0(t) \propto t^q$, for some q, is excluded for identifiability between α and β. Define the corresponding cumulative baseline rate function $\Lambda_0(t) = \int_0^t \lambda_0(u)\,\mathrm{d}u$. For identifiability between Z_i and $\lambda(t)$, we assume $\Lambda_0(\tau) = 1$ and $E(Z_i \mid X_i) = \mu_Z$, that is, the conditional mean of Z given X does not depend on X. As Z_i has a multiplicative effect on the rate function, Model (2.1) allows the event occurrence rate to be

inflated (or deflated) by the frailty variable Z_i with an arbitrary distribution. We assume that Y_i is independent of $N_i(\cdot)$ given (Z_i, X_i). The dependence between Y_i and $N_i(\cdot)$ unconditional on (Z_i, X_i) can be either positive or negative, depending on whether the association between Y_i and Z_i is positive or negative given X_i.

Model (2.1) offers great flexibility and includes several popular semiparametric models for recurrent event processes as special cases. When $\beta = 0$, it reduces to the frailty accelerated rate model $\lambda_i(t) = Z_i\lambda_0\left(te^{X_i^\top \alpha}\right)$, the special case of which with a degenerate frailty distribution was considered in Ghosh (2004). Covariate effects under the accelerated rate model modify the timescale of the rate function and allow for identical risk at time 0, a desirable property for modeling recurrent events in randomized clinical trials. When $\alpha = \beta$, Model (2.1) reduces to the frailty accelerated mean model $\lambda_i(t) = Z_i\lambda_0\left(te^{X_i^\top \alpha}\right)e^{X_i^\top \alpha}$ proposed by Xu et al. (2017), where the covariate effects modify the time scale of the cumulative mean function of the recurrent event process by a factor of $e^{X_i^\top \alpha}$. When $\alpha = 0$, Model (2.1) reduces to the popular frailty Cox-type regression model $\lambda_i(t) = Z_i\lambda_0(t)e^{X_i^\top \beta}$; see Lancaster and Intrator (1998), Wang et al. (2001), Huang and Wang (2004). In this case, the covariate effects modify the magnitude of the rate function by a factor of $e^{X_i^\top \beta}$. Similar to Sun and Su (2008), the three submodels coincide with each other if and only if $\lambda_0(t)$ is of the Weibull form. The flexible formulation of Model (2.1) offers a new framework to test, diagnose, and compare the submodels via hypothesis tests on parameters α and β; see details in Section 3.

Interpretation of the covariate effects under Model (2.1) involves two types of modification on the rate function: a scale-change effect that alters the timescale by a factor of $e^{X_i^\top \alpha}$ and a multiplicative effect that modifies the magnitude of the rate function by a factor of $e^{X_i^\top \beta}$. The effects are easily seen when X contains a single treatment indicator. In this case, e^β characterizes the risk ratio between treated subjects ($X = 1$) at time t and untreated subjects ($X = 0$) at time te^α. When $\alpha = \beta$, the combined changes in timescale and in magnitude are in such a way that the resulting cumulative mean function has a timescale modification. This motivates a useful alternative presentation of Model (2.1). Let $\Lambda_i(t) = E\{N_i(t) \mid Z_i, X_i\}$ be the conditional cumulative mean function. Then

$$\Lambda_i(t) = Z_i\Lambda_0\left(te^{X_i^\top \alpha}\right)e^{X_i^\top \gamma}, \quad t \in [0, \tau],$$

where $\gamma = \beta - \alpha$. The parameters α and γ can then be interpreted as the scale-change effect parameter and multiplicative effect parameter on the conditional cumulative mean function, respectively. In the case of a single treatment indicator covariate, the expected number of events occurred by time t among treated subjects ($X = 1$) equals e^γ times the expected number of events by time te^α in the control group ($X = 0$).

3. Estimation and Inference

3.1 Parameter Estimation

For a p-dimensional vector a, consider the transformations $t_{ij}^*(a) = t_{ij}e^{X_i^\top a}$ and $Y_i^*(a) = Y_i e^{X_i^\top a}$. Let $R_i^*(t,a) = \sum_{j=1}^{m_i} I\{t_{ij}^*(a) \le t \le Y_i^*(a)\}$; hereafter, when $m_i = 0$, we define the summation operator $\Sigma_{j=1}^{m_i}$ to be zero. Define counting process for the transformed event times $N_i^*(t,a) = \sum_{j=1}^{m_i} I\{t_{ij}^*(a) \le t \wedge Y_i^*(a)\}$, so that $N_i^*(t,a) = N_i\left(te^{-X_i^\top a} \wedge Y_i\right)$, where $\wedge$ is the minimum operator. Under Model (2.1), for $t \le Y_i$,

$$E\{N_i(t) \mid X_i, Z_i, Y_i\} = \int_0^t Z_i \lambda_0\left(ue^{X_i^\top \alpha}\right) e^{X_i^\top \beta} \mathrm{d}u = Z_i \Lambda_0\left(te^{X_i^\top \alpha}\right) e^{X_i^\top (\beta - \alpha)},$$

and thus for $t \le Y_i^*$, $E\{N_i^*(t,a) \mid X_i, Z_i, Y_i^*\} = Z_i \Lambda_0\left\{te^{X_i^\top (\alpha - a)}\right\} e^{X_i^\top (\beta - \alpha)}$.

We develop a novel semiparametric estimation procedure that does not require a distributional assumption about the frailty variable. To motivate the procedure, we first consider the case where the true parameter is known, or $a = \alpha$. For this special case, we suppress α in the notation whenever there is no ambiguity and write, $t_{ij}^* = t_{ij}e^{X_i^\top \alpha}$, $Y_i^* = Y_i e^{X_i^\top \alpha}$, $N_i^*(t) = N_i^*(t,\alpha)$ and $R_i^*(t) = R_i^*(t,\alpha)$. When $a = \alpha$ we have $E\{N_i^*(t) \mid X_i, Z_i, Y_i\} = Z_i \Lambda_0(t) e^{X_i^\top (\beta - \alpha)}$ for $t \le Y_i$, which implies that the rate function of the underlying transformed process follows the Cox-type proportional rates model with a multiplicative frailty. Since the informative censoring time Y_i depends on both X_i and Z_i, conventional methods that require independent censoring may lead to biased estimation. Moreover, the estimation procedures in Xu et al. (2017) cannot be applied, as the transformed process remains dependent on X_i.

We now embed the problem into a seimparametric estimation with clustered right-truncated data by utilizing a common mean structure shared by the conditional distribution of recurrent events and the order statistics of a set of (possibly correlated) right-truncated failure times. Given (m_i, Y_i^*), consider a set of m_i random variables, denoted by $\tilde{t}_{i1}^*, \ldots \tilde{t}_{im_i}^*$, such that each has a *marginal* density function free of (Z_i, X_i):

$$\frac{\lambda_0(t)}{\Lambda_0(Y_i^*)}, \quad 0 \le t \le Y_i^*. \tag{3.2}$$

It follows from $\Lambda_0(\tau) = 1$ that $\Lambda_0(t)$ defines a proper distribution function and thus (3.2) can be viewed as a truncation density function (Wang et al., 2001; Xu et al., 2017). In other words, $\tilde{t}_{ij}^*$'s can be viewed as right-truncated failure times with truncation time Y_i^*. We show in Proposition 1 that the transformed recurrent event times $\{t_{i1}^*, \ldots, t_{im_i}^*\}$ of the ith individual share the same mean structure with the right-truncated failure times $\{\tilde{t}_{i1}^*, \ldots, \tilde{t}_{im_i}^*\}$.

Proposition 1.—Consider the counting process induced by the right-truncated random variables $\tilde{t}_{ij}^*$, $j = 1, \ldots, m_i$, that is, $\widetilde{N}_i^*(t) = \sum_{i=1}^{m_i} I(\tilde{t}_{ij}^* \le t)$, for $t \le Y_i^*$. Then we have $E\{\widetilde{N}_i^*(t) \mid Z_i, X_i, Y_i^*\} = E\{N_i^*(t) \mid Z_i, X_i, Y_i^*\}$.

Since $E(m_i \mid Z_i, X_i, Y_i^*) = Z_i \Lambda_0(Y^*) e^{X_i^\top(\beta - \alpha)}$, Proposition 1 follows from $E\{\widetilde{N}_i^*(t) \mid Z_i, X_i, Y_i^*\} = E\big[E\{\widetilde{N}_i^*(t) \mid m_i, Z_i, X_i, Y_i^*\} Z_i, X_i, Y_i^*\big] = E\{m_i \Lambda_0(t)/\Lambda_0(Y_i^*) \mid Z_i, X_i, Y_i^*\}$. $= Z_i \Lambda_0(t) e^{X_i^\top(\beta - \alpha)} = E\{N_i^*(t) \mid Z_i, X_i, Y_i^*\}$

Such mathematical equivalence motivates us to extend the methods for independent right-truncated survival data (Kalbfleisch and Lawless, 1991; Wang, 1989) to the context of clustered right-truncated data to construct estimating equations. Specifically, define $\widetilde{N}_{ij}^*(t) = I(\tilde{t}_{ij}^* \le t \wedge Y_i^*)$, $\widetilde{R}_{ij}^*(t) = I(\tilde{t}_{ij}^* \le t \le Y_i^*)$ and $\widetilde{R}_i^*(t) = \sum_{j=1}^{m_i} \widetilde{R}_{ij}^*(t)$. It is known that, with right-truncated data, $\widetilde{N}_{ij}^*(\tau - t) - \int_{\tau - t}^{M} \widetilde{R}_{ij}^*(u) \mathrm{d}H(u)$, where $H(u) = \log \Lambda_0(u)$, defines a martingale on $[0, \tau]$. Simple algebra with change of variable gives $E\{\mathrm{d}\widetilde{N}_{ij}^*(t) - \widetilde{R}_{ij}^*(t) \mathrm{d}H(t)\} = 0$ for $t \in [0, \tau]$ and this defines a mean zero process $\widetilde{M}_{ij}^*(t) = \widetilde{N}_{ij}^*(t) - \int_t^\tau \widetilde{R}_{ij}^*(u) \mathrm{d}H(u)$. It can be further shown that the stochastic process based on the clustered right-truncated data $\{\tilde{t}_{i1}^*, \ldots, \tilde{t}_{im_i}^*\}$,

$$\widetilde{M}_i^*(t) = \sum_{j=1}^{m_i} \widetilde{M}_{ij}^*(t) = \sum_{j=1}^{m_i} \widetilde{N}_{ij}^*(t) - \sum_{j=1}^{m_i} \int_t^\tau \widetilde{R}_{ij}^*(u) \mathrm{d}H(u) = \widetilde{N}_i^*(t) - \int_0^t \widetilde{R}_i^*(u) \mathrm{d}H(u),$$

has a zero mean. Following the above discussion, we can treat the observations $\{\tilde{t}_{i1}^*, \ldots, \tilde{t}_{im_i}^*\}$ as the order statistics of $\{\tilde{t}_{i1}^*, \ldots, \tilde{t}_{im_i}^*\}$; in this case, $N_i^*(t) = \widetilde{N}_i^*(t)$ and $R_i^*(t) = \widetilde{R}_i^*(t)$. Therefore the stochastic process $M_i^*(t) = N_i^*(t) - \int_0^t R_i^*(u) \mathrm{d}H(u)$, $t \in [0, \tau]$, though not a martingale, also has a zero mean. The proof is given in the Appendix S1 of the Supplementary Material. Moreover, for all $t \in [0, \tau]$, we have the following equations

$$E\left\{\sum_{i=1}^{n} \int_0^t \mathrm{d}M_i^*(u)\right\} = 0 \text{ and } E\left\{\sum_{i=1}^{n} \int_0^\tau X_i \mathrm{d}M_i^*(u)\right\} = 0. \tag{3.3}$$

Note that t_{ij}^*'s may be correlated but the estimating equations in (3.3) remain unbiased. The first term in (3.3) introduces a consistent estimator for H via

$$\mathrm{d}\widehat{H}(t) = \frac{\sum_{i=1}^n \mathrm{d}N_i^*(t)}{\sum_{i=1}^n R_i^*(t)}.$$

The proof of the consistency of $\widehat{H}(\cdot)$ is given in the Appendix S1 of the Supplementary Material.

Replacing H with $\widehat{H}$ in (3.3), we propose to estimate α by solving the estimating equation:

$$S_n(a) := n^{-1}\sum_{i=1}^{n}\int_0^{\tau}\left\{X_i - \frac{\mathscr{R}_n^{(1)}(u,a)}{\mathscr{R}_n^{(0)}(u,a)}\right\}\mathrm{d}N_i^*(t,a) = 0, \tag{3.4}$$

where $\mathscr{R}_n^{(k)}(t,a) = \sum_{i=1}^n X_i^k R_i^*(t,a)$ for $k \in \{0,1\}$. The estimating function $S_n(a)$ is similar to that of the accelerated failure time model with truncated data (Lai and Ying, 1991) and can be solved using, for example, the derivative-free algorithm of Barzilai and Borwein (1988) implemented in Varadhan and Gilbert (2009). Let $\hat{\alpha}_n$ be the solution to (3.4). It is easy to see that H can be estimated by

$$\widehat{H}_n(t;\hat{\alpha}_n) = -\int_t^{\tau}\frac{\sum_{i=1}^n \mathrm{d}N_i^*(u;\hat{\alpha}_n)}{\sum_{i=1}^n R_i^*(u;\hat{\alpha}_n)},$$

and thus Λ_0 can be estimated by $\widehat{\Lambda}_n(t) = \exp\left\{\widehat{H}_n(t;\hat{\alpha}_n)\right\}$.

With α estimated, we now focus on the estimation of γ, which is defined earlier as $\gamma = \beta - \alpha$. It follows from (2.1) that

$$\begin{aligned} &E\left[m_i\Lambda_0^{-1}(Y_i^*) \mid X_i\right] = E\left[E\left\{m_i \mid X_i, Y_i^*, Z_i\right\}\Lambda_0^{-1}(Y_i^*) \mid X_i\right] \\ &= E\left[Z_i\exp\left(X_i^{\top}\gamma\right) \mid X_i\right] = \exp\left(\bar{X}_i^{\top}\theta\right), \end{aligned}$$

where $\bar{X}_i^{\top} = \left(1, X_i^{\top}\right)$ and $\theta^{\top} = (\log \mu_Z, \gamma^{\top})$. This expectation suggests the following estimating equation if α and Λ_0 are known: $n^{-1}\sum_{i=1}^n \bar{X}_i^{\top}\left\{m_i\Lambda_0^{-1}(Y_i^*) - \exp\left(\bar{X}_i^{\top}\theta\right)\right\} = 0$. The estimator for θ, denotes by $\hat{\theta}_n$, can be obtained by solving the following estimating equation with α and Λ_0 replaced by their estimators from in the first step:

$$U_n(\theta;\hat{\alpha}_n) := n^{-1}\sum_{i=1}^{n}\bar{X}_i^{\top}\left[m_i\widehat{\Lambda}_n^{-1}\left\{Y_i^*(\hat{\alpha}_n)\right\} - \exp\left(\bar{X}_i^{\top}\theta\right)\right] = 0. \tag{3.5}$$

Then β can be estimated by $\hat{\beta}_n = \hat{\alpha}_n + \hat{\gamma}_n$. Given $\hat{\alpha}_n$ and $\widehat{\Lambda}_n$, the estimating equation in (3.5) is monotone and continuously differentiable with respect to θ, hence its root can be easily obtained using standard software.

3.2 Asymptotic theory and variance estimation

To study the large sample properties of the proposed estimators, we impose the following regularity conditions:

Condition 1 $\Pr(Y^* \geq \tau) > 0$, where $Y^* = Y e^{X^{\top}\alpha}$.

Condition 2 The covariate X is bounded; the latent variable Z is positive with $E(Z^2) < \infty$.

Condition 3 The conditional probability density function of Y given (Z, X) is continuous and uniformly bounded.

Condition 4 The rate function $\lambda_0(t)$, $t \in [0, \tau]$, is strictly bounded below by zero and has a bounded second derivative function.

Condition 5 The matrices J and J_2 defined in the Appendix S1 of the Supplementary Material are non-singular.

Conditions 1–5 are common assumptions in survival models. Condition 4 imposes the bounded second derivative function of $\lambda_0(t)$, which is usually required for the accelerated failure time model to evaluate the asymptotic covariance matrix. With these regularity conditions, we have the following asymptotic results, whose proof is provided in the Appendix S1 of the Supplementary Material.

Theorem 1.—Under Conditions 1–5, $n^{1/2}\left(\hat{\alpha}_n - \alpha, \hat{\beta}_n - \beta\right)$ converges weakly to a multivariate normal distribution with mean zero and covariance matrix $\Sigma(\alpha, \beta)$ specified in the Appendix S1 of the Supplementary material. Furthermore, for the estimated baseline rate function, we have $n^{1/2}\left\{\hat{\Lambda}_n(t, \hat{\alpha}_n) - \Lambda_0(t)\right\}$, $t \in [0, \tau]$, converges weakly to a mean-zero Gaussian process.

Theorem 1 allows us to use the asymptotic joint Gaussian distribution of $n^{1/2}(\hat{\alpha}_n - \alpha, \hat{\beta}_n - \beta)$ to make inferences on model parameters. Since the limiting covariance matrix $\Sigma(\alpha, \beta)$ depends on the unknown density functions of the censoring time, it may be computationally difficult and inefficient to estimate it directly from the data. We propose an efficient resampling approach to estimate the covariance matrix $\Sigma(\alpha, \beta)$.

We first describe an approach to estimate the covariance of $n^{1/2}\left(\hat{\alpha}_n - \alpha, \hat{\theta}_n - \theta\right)$ denoted by $\Sigma(\alpha, \theta)$, then use it to retrieve the estimation of $\Sigma(\alpha, \beta)$. From the proof of Theorem 1,

$$n^{1/2}\begin{pmatrix}\hat{\alpha}_n - \alpha \\ \hat{\theta}_n - \theta\end{pmatrix} = n^{1/2} J_{\alpha,\theta}^{-1}\begin{pmatrix} S_n(\alpha) \\ U_n(\theta; \alpha)\end{pmatrix} + o_p(1),$$

where $J_{\alpha,\theta}$ is the slope matrix

$$J_{\alpha,\theta} = \begin{pmatrix} J & 0 \\ J_1 & J_2\end{pmatrix},$$

with J, J_1, J_2 defined in the Appendix S1 of the Supplementary Materials. This implies $\Sigma(\alpha, \theta)$ has a sandwich form: $J_{\alpha,\theta}^{-1} V_{\alpha,\theta}\left(J_{\alpha,\theta}^{-1}\right)^{\top}$., where $V_{\alpha,\theta}$ is the limiting covariance matrix of $n^{1/2}\left\{S_n^{\top}(\alpha), U_n^{\top}(\theta; \alpha)\right\}$. The proposed resampling approach estimates the two components $V_{\alpha,\theta}$ and $J_{\alpha,\theta}$ separately, and requires neither density estimations nor intensive computation.

Step 1: Estimation of $V_{\alpha,\theta}$ Let $(\xi_1, \ldots, \xi_n)$ be a set of independent and identically distributed positive random variables with unit mean and unit variance (e.g., standard exponential), we define perturbed estimating functions as follows:

$$S_n^{\dagger}(\alpha) = n^{-1} \sum_{i=1}^{n} \sum_{j=1}^{m_i} \int_0^{\tau} \left\{ \xi_i X_i - \frac{\sum_{k=1}^{n} \sum_{l=1}^{m_k} \xi_k X_k R_{k,l}^*(t,\alpha)}{\sum_{k=1}^{n} \sum_{l=1}^{m_k} \xi_k R_{k,l}^*(t,\alpha)} \right\} \mathrm{d}N_{ij}^*(t,\alpha),$$

and

$$U_n^{\dagger}(\theta;\alpha) = n^{-1} \sum_{i=1}^{n} \xi_i \overline{X}_i^{\top} \left[\frac{m_i}{\widehat{\Lambda}_n^{\dagger}\{Y_i^*(\alpha)\}} - \exp\left(\overline{X}_i^{\top}\theta\right) \right],$$

where

$$\widehat{\Lambda}_n^{\dagger}(t) = \exp\left\{\widehat{H}_n^{\dagger}(t;\hat{\alpha}_n)\right\} \text{ and } \widehat{H}_n^{\dagger}(t;\hat{\alpha}_n) = \int_0^t \frac{\sum_{i=1}^{n} \sum_{j=1}^{m_i} \xi_i \mathrm{d}N_{ij}^*(u;\hat{\alpha}_n)}{\sum_{i=1}^{n} \sum_{j=1}^{m_i} \xi_i R_{ij}^*(u;\hat{\alpha}_n)}.$$

Following the arguments in Zeng and Lin (2008), $n^{1/2}\left\{S_n^{\dagger}(\hat{\alpha}_n), U_n^{\dagger}\left(\hat{\theta}_n;\hat{\alpha}_n\right)\right\}$ conditional on the observed data has the same asymptotic distribution as $n^{1/2}\{S_n(\alpha), U_n(\theta, \alpha)\}$ evaluated at the true parameters. Thus a consistent estimator of $V_{\alpha,\theta}$, denoted by $\widehat{V}_{\hat{\alpha}_n,\hat{\theta}_n}$, is given by the sample variance of the perturbed replicates of the derivative-free Barzilai-Borwein spectral algorithm $n^{-1/2}\left\{S_n^{\dagger}(\hat{\alpha}_n), U_n^{\dagger}\left(\hat{\theta}_n;\hat{\alpha}_n\right)\right\}$.

Step 2: Estimation of $J_{\alpha,\theta}$ Estimation of the slope matrix, $J_{\alpha,\theta}$, is challenging due to non-smoothness of the estimating functions. For a $(2p + 1)$-dimensional vector $s = (s_1, s_2) \in R^{2p+1}$ and (a, r) in a small neighborhood of (α, θ) such that $\|(a, r) - (\alpha, \theta)\| \to 0$, the proof of Theorem 1 implies that the estimating functions can be uniformly decomposed into

$$n^{1/2} \begin{pmatrix} S_n\left(a + n^{-1/2}s_1\right) - S_n(a), \\ U_n\left(r + n^{-1/2}s_2; a + n^{-1/2}s_1\right) - U_n(r;a) \end{pmatrix} = J_{\alpha,\theta} \begin{pmatrix} s_1 \\ s_2 \end{pmatrix} + o_p(1).$$

Since $S_n(\hat{\alpha}_n) = 0$ and $U_n(\hat{\gamma}_n, \hat{\alpha}_n) = 0$, we have

$$n^{1/2} \begin{pmatrix} S_n\left(\hat{\alpha}_n + n^{-1/2}s_1\right) \\ U_n\left(\hat{\theta}_n + n^{-1/2}s_2; \hat{\alpha}_n + n^{-1/2}s_1\right) \end{pmatrix} = J_{\alpha,\theta} \begin{pmatrix} s_1 \\ s_2 \end{pmatrix} + o_p(1).$$

The above equation presents an asymptotic linear relationship of the estimating equations. Motivated by the above results, the jth row of $J_{\alpha,\theta}$ can be approximated by regressing the jth component of $n^{1/2}\left\{S_n\left(\hat{\alpha}_n + n^{-1/2}s_1\right), U_n\left(\hat{\theta}_n + n^{-1/2}s_2; \hat{\alpha}_n + n^{-1/2}s_1\right)\right\}$ on s, which are generated from a $(2p + 1)$-dimensional standard normal distribution. Putting the estimated regression coefficients into a matrix gives an estimator $\hat{J}_{\hat{\alpha}_n,\hat{\theta}_n}$ of $J_{\alpha,\theta}$.

The target sandwich variance matrix $\Sigma(\alpha, \theta)$ is then estimated by $\hat{\Sigma}(\hat{\alpha}_n, \hat{\theta}_n) = \hat{J}^{-1}_{\hat{\alpha}_n, \hat{\theta}_n} \hat{V}_{\hat{\alpha}_n, \hat{\theta}_n} \left(\hat{J}^{-1}_{\hat{\alpha}_n, \hat{\theta}_n}\right)^\top$. Compare to the conventional bootstrap methods, which require solving estimating equations repeatedly, the proposed resampling procedure approach is computationally much more efficient because it only requires evaluations of (rather than solving) the perturbed estimating functions and performing least squares regressions. With $\hat{\Sigma}(\hat{\alpha}_n, \hat{\theta}_n)$, the estimated covariance matrix of $\Sigma(\alpha, \beta)$ can then be obtained by $\hat{\Sigma}(\hat{\alpha}_n, \hat{\beta}_n) = A\hat{\Sigma}(\hat{\alpha}_n, \hat{\theta}_n)A^\top$ with

$$A = \begin{pmatrix} I_p & 0_{p\times 1} & 0_{p\times p} \\ I_p & 0_{p\times 1} & I_p \end{pmatrix},$$

where I_p is the $p \times p$ identity matrix. Following the above discussion and the argument in Zeng and Lin (2008), the estimator $\hat{\Sigma}(\hat{\alpha}_n, \hat{\beta}_n)$ is consistent under Conditions 1–5.

3.3 Hypothesis testing of submodels

The asymptotic results enable model selection for the nested submodels. For example, the Cox-type proportional rates assumption can be tested through $H_0 : \alpha = 0$ vs. $H_1 : \alpha \neq 0$ under the proposed model. In this case, a test statistic can be constructed with $T_{\text{cox}} = \hat{\alpha}_n^\top \hat{\Sigma}(\hat{\alpha}_n)^{-1} \hat{\alpha}_n$, where $\hat{\Sigma}(\hat{\alpha}_n)$ is the estimated covariance matrix of $n^{1/2}(\hat{\alpha}_n - \alpha)$. Under the null hypothesis, T_{cox} converges weakly to a Chi-square distribution χ^2_p, with p degrees of freedom. To evaluate the power of the test statistics, consider the true local alternative $\alpha = n^{-1/2}h$, where $h \in R^p$, then by the central limit theorem, T_{cox} converges weakly to a noncentral Chi-square distribution with p degrees of freedom and non-centrality parameter $h^\top \Sigma(\alpha)^{-1} h$. Therefore, the power of the test goes to 1 if $h^\top \Sigma(\alpha)^{-1} h \to \infty$ or $\|n^{1/2}\alpha\| \to \infty$.

Similarly, the other two submodels can be tested and diagnosed. For the accelerated mean model, we consider $H_0 : \gamma = 0$ vs. $H_1 : \gamma \neq 0$ and the test statistic is $T_{\text{am}} = \hat{\gamma}_n^\top \hat{\Sigma}(\hat{\gamma}_n)^{-1} \hat{\gamma}_n$, where $\hat{\Sigma}(\hat{\gamma}_n)$ is the estimated covariance matrix of $n^{1/2}(\hat{\gamma}_n - \gamma)$. For the accelerated rate model, we consider $H_0 : \beta = 0$ vs. $H_1 : \beta \neq 0$ and $T_{\text{ar}} = \hat{\beta}_n^\top \hat{\Sigma}(\hat{\beta}_n)^{-1} \hat{\beta}_n$, where $\hat{\Sigma}(\hat{\beta}_n)$ is the estimated covariance matrix of $n^{1/2}(\hat{\beta}_n - \beta)$. Following similar arguments, both T_{am} and T_{ar} converge weakly to Chi-square distribution χ^2_p, and the power of the two tests go to 1 when the true parameters satisfying $\|n^{1/2}\gamma\| \to \infty$ and $\|n^{1/2}\beta\| \to \infty$, respectively.

4. Numerical Studies

Simulations were conducted to examine the performance of the proposed method. The recurrent event process was generated from a non-stationary Poisson process with intensity function $\lambda(t) = Z\lambda_0\left(te^{\alpha_1 X_1 + \alpha_2 X_2}\right)e^{\beta_1 X_1 + \beta_2 X_2}$, where $\lambda_0(t) = [2(1+t)]^{-1}$, and X_1 and X_2 were generated from independent standard normal distributions. The subject-specific latent variable Z was either set as $Z = 1$ or generated from a gamma distribution with mean 1 and variance 0.25. The latter yields a scenario of informative censoring, while the former yields

a scenario of non-informative censoring. In these settings, we used $E(Z) = 1$ as opposed to $\Lambda_0(\tau) = 1$ which was assumed in Section 2 for ease of discussion. Since we only require one of these identifiability conditions above, the proposed estimation procedure remains valid. We altered the regression coefficients α and β to generate data from whether the proposed generalized scale-change model or from the submodels discussed in Section 2. The censoring time was generated from an exponential distribution with mean $60e^{-X_1}/Z$. We set $\tau = 60$.

With $n \in \{200, 400\}$ and 1000 replications, Tables 1 and 2 summarize results under a generalized scale-change model and a Cox-type proportional rates model, respectively. Results under the accelerated rate model and accelerated mean model are presented in the Appendix S2 of the Supplementary Material. Under our settings, the average number of observed recurrent events ranges from 1.5 to 5.7. The standard errors of the proposed method were obtained from the efficient resampling approach with 200 bootstrap samples. For comparison, we also report the results of the estimator proposed by Sun and Su (2008), which requires a noninformative censoring assumption. Both the proposed estimator and the estimator proposed by Sun and Su (2008) were obtained by solving the corresponding estimating equations with the derivative-free Barzilai–Borwein spectral algorithm implemented in Varadhan and Gilbert (2009). Zero vectors were used as the initial value for the equation solver. We also present results using the true values as the initial value to investigate the stability of the estimating equations.

The proposed estimator is virtually unbiased for all scenarios considered regardless of the choice of the initial value. The average standard errors for the proposed estimators are reasonably close to the empirical counterparts, indicating that the proposed variance estimator performs well even with a moderate bootstrap sample of size 200. Furthermore, the proposed estimator yields empirical coverage probabilities that are close to the nominal level of 95%, suggesting that the normal approximation for the distribution of the proposed estimators is appropriate. When $n = 200$, the empirical coverage probabilities for $\hat{\beta}_n$ are closer to the anticipated level of 95% than that for $\hat{\alpha}_n$, suggesting that the normality approximation may require a larger sample size for $\hat{\alpha}_n$ than for $\hat{\beta}_n$. Similar trends are observed in the scenarios presented in the Appendix S2 of the Supplementary Material. The estimates of the baseline cumulative rate functions for all scenarios are also presented in the Appendix S2 of the Supplementary Material. The averages of $\hat{\Lambda}_0(t)$ are indistinguishable from the truth for all cases considered.

Through our simulation studies, the estimator of Sun and Su (2008) was found to be sensitive to the choice of the initial values. As seen in Tables 1 and 2, the estimator of Sun and Su (2008) yields large biases when the initial values were set to be zeros. The average standard errors for the estimator of Sun and Su (2008) was obtained from the classical bootstrap approach with 200 bootstrap samples. For most cases, the bootstrap standard errors are not close to the empirical counterpart. The inconsistency of the bootstrap standard errors reflect the instability in the estimator of Sun and Su (2008). As a result, the resulting coverage probabilities are far from to the nominal level. When the initial value was specified at the true value, their estimator yields small biases when $Z = 1$ but moderate biases when

the non-informative censoring assumption is not met. The estimator of Sun and Su (2008) yields smaller empirical standard errors for all cases when the initial value was specified at the true value, which is not realistic in practice.

In the Appendix S2 of the Supplementary Material, we report results from additional simulation studies. We considered gamma frailty of variance 0.5 and 1, implying a larger degree of heterogeneity among the subject. For all the settings considered, our estimator remains virtually unbiased, with estimated standard errors reasonably close to the empirical standard errors. The magnitude of the estimated standard errors seems to increase with the variance of the frailty variable, but the empirical coverage rates remain close to the nominal level in all scenarios. We also considered additional scenarios where the average number of events per subject was lower than those in the earlier settings, and scenarios where the recurrent events were generated from a non-Poisson process given the frailty by including a second latent variable in the rate model and/or altering the distribution of the interarrival time from exponential. The performance of our estimator remains satisfactory in all scenarios.

Now that the proposed estimator is robust in most practical settings, we evaluated the performance of testing the nested submodels. We considered the same simulation settings but with $\alpha_1 = \alpha_2$ and $\beta_1 = \beta_2$, and only focused on the informative censoring scenarios. Based on 1000 replications, Figure 1 displays the rejection rate at a 0.05 significance level for the tests discussed in Section 3 when fixing either α or β at $(0, 0)^\top$ and the other at $(k, k)^\top$ for some constant k. We set $k = 0$ initially, then move k away from 0 in both directions to denote gradual deviation from the accelerated mean model and migration to the Cox-type model or accelerated rate model. When $\alpha = \beta = 0$, all rejection proportions are close to the nominal level of 0.05. In Figure 1a, the rejection proportions for the T_{cox} test are close to the nominal level of 0.05 reflected by the true value of $\alpha = 0$. As β deviates from 0 in Figure 1a, both the T_{am} and T_{ar} tests increase in power, with slightly higher power for the T_{am} test. Similarly, in Figure 1b, T_{cox} test and T_{am} test increase in power as α deviates from 0 while T_{ar} test remains at the nominal level of 0.05 throughout. Among the tests, the T_{am} test appears to have the highest rejection proportion indicating that our method is more likely to reject the accelerated mean model. For a given k, the rejection proportion for the T_{ar} test is higher than that for the T_{cox} test, which is because $\hat{\beta}_n$ is usually associated with smaller standard errors.

5. Application

Serious infection is a major source of complications after transplant and is known to be associated with increased risk of allograft failure and death. A prospective cohort study was conducted at the Johns Hopkins Hospital to evaluate morbidity and mortality after transplant. In this study, patients who consented to an IRB approved protocol were contacted every 3 months to obtain information on serious infection episodes. This preliminary cohort contained 161 kidney transplant recipients and 164 patients who underwent hematopoietic stem cell transplant (HSCT) at the Johns Hopkins Hospital in the year of 2012. Patients were followed until death, graft failure, or the end of the study, whichever comes first. The median follow-up time was 20.2 months for the kidney transplant cohort and 12.2 months for the

HSCT cohort, respectively. During the study, the kidney transplant recipients experienced a total of 206 infection episodes (1.3 per recipient), and the HSCT recipients experienced a total of 290 infection episodes (1.8 per recipient). There were 42 deaths observed during the study period, among which 36 were in the HSCT cohort.

We first analyze the infection process of the kidney transplant cohort. Of the 161 kidney transplant recipients, 91 (56.5%) were white, 47 (29.2%) had hypertension, and 11 (6.8%) had diabetes at the time of transplant. The age at transplant among the kidney transplant recipients ranged from 19.7 to 81.8 years, with a median of 53.5 years. Other potential risk factors used in the analysis include the human leukocyte antigen (HLA) incompatibility and the high-risk cytomegalovirus (CMV) serostatus (CMV-negative recipients and CMV-positive donors vs. others). There were 31 (19.3%) HLA incompatible patients and 21 (13.0%) patients with high-risk CMV serostatus. The age variable was centered and scaled to have unit variance. Figure 2a depicts the longitudinal patterns of recurrent infection episodes by HLA-compatibility in the kidney transplant cohort. The plot suggests that HLA-incompatible transplant recipients tend to have a higher frequency of serious infections than HLA-compatible recipients. The upper panel of Table 3 summarizes the estimated covariate effects for the kidney transplant cohort, with standard errors estimated through the proposed resampling approach with 500 bootstraps. Using Wald's Chi-square test, p-values for testing $H_0 : \alpha = 0$, $H_0 : \beta = 0$ and $H_0 : \gamma = 0$ are all < 0.001. The hypothesis testing results suggest that none of the submodels is appropriate for the data and that the covariates modify both the timescale of the infection process and the magnitude of the rate of infections. The estimated coefficients for age and HLA incompatibility are both significantly positive, implying that patients who were older or HLA incompatible were more likely to experience infections sooner and more frequent throughout the follow-up. In particular, for one standard deviation increases in age (12.8 years), the time to infection episodes was accelerated by a factor of 0.36 in addition to an elevated risk of 1.75. Similarly, patients underwent HLA incompatible kidney transplantation had an accelerated time to infection episodes by a factor of 0.17 on top of an elevated risk of 3.95. Patients with high-risk of the CMV disease or with hypertension tend to have a decelerated time to infection episodes by a factor of 5.00 and 6.46, respectively.

A similar analysis was performed with the HSCT cohort where, instead of HLA incompatibility and CMV serostatus, the type of stem cell transplant (allogeneic vs. autologous) was included as a covariate. Among the 164 HSCT patients, 126 (76.8%) were white, 93 (56.7%) were male, 128 (78.1%) had an allogeneic transplant, and 42 (25.6%) had lymphomas disease at transplant. The age at transplant ranged from 19.2 to 75.5 years, with a median of 52.2 years. We used the standardized age in this analysis. Figure 2b depicts the longitudinal patterns of recurrent infection episodes and death by the type of HSCT transplantation. It is observed that HSCT patients who underwent an allogeneic transplant tend to experience serious infections at a higher frequency. The lower panel of Table 3 summarizes the parameter estimates and their standard errors. The p-values for testing $H_0 : \beta = 0$ is 0.37 while the p-values for testing $H_0 : \alpha = 0$ and $H_0 : \gamma = 0$ are < 0.001. The hypothesis testing results suggest that the covariates were not significantly associated with the rate of infections, and the proposed model reduces to the accelerated rate model. Since our estimating procedure estimates the timescale effect parameter without requiring the

estimation of the multiplicative effect parameter, our inferences for the regression coefficients in the accelerated rate model are still valid. The only significant risk factor is the allogeneic transplant, which decelerated the time to infection episodes by a factor of 0.13.

Finally, we considered a graphical assessment of whether the baseline rate function, $\lambda_0(t)$, is in the Weibull class. The assessment is motivated by the fact that, under the Weibull model, the proposed model reduces to the Cox-type model of Wang et al. (2001) and $\log\{\widehat{\Lambda}_0(t)\}$ is linear in $\log(t)$. Plots of $\log\{\widehat{\Lambda}_0(t)\}$ versus $\log(t)$ presented in the Appendix S3 of the Supplement Material suggests that $\lambda_0(t)$ is not Weibull.

6. Discussion

The proposed model tackles the need to characterize covariate effects in a flexible modeling framework and to account for informative censoring in recurrent event data analysis through a generalized scale-change model with an unspecified frailty. The estimation procedure is novel, without requiring information on the frailties by exploiting the model structure. The asymptotic properties of the proposed estimator are established, and inferences are based a computationally efficient resampling method. Since the model encompasses several popular models as special cases, an attractive byproduct is model specification tests for the submodels via various restrictions on the model parameters.

The proposed estimation procedure is based on a quasi-conditional likelihood, conditioning on (X_i, Z_i) and Y_i. Thus, our model is simple in the sense that model specifications for the censoring event time and the frailty are not needed as they can be treated as nuisances. For the same reason, our model is robust against the misspecification of the censoring time distribution, making it an appealing alternative to most joint modeling approaches that model the risk of recurrent events and the informative time jointly. The proposed method can be easily extended to a joint modeling framework when the joint analysis of the covariate effects on the recurrent events and the terminal event is of interest. For instance, in addition to assuming Model (2.1) for the underlying recurrent event process, we may consider the accelerated failure time model as in Xu et al. (2017) and specify the hazard function of the terminal event D as

$$h(t) = Zh_0\left(te^{X^\top\zeta}\right)e^{X^\top\zeta}, \quad t \in [0, \tau], \tag{6.6}$$

where ζ is $p\times 1$ vector of model parameters and $h_0(t)$ is the baseline hazard function. Under the joint models, the recurrent event model can still be estimated by applying the estimation procedure described in Section 3 and Model (6.6) can be estimated using the "borrow-strength" technique originally proposed in Huang and Wang (2004) and later adopted in Xu et al. (2017). This is an interesting extension to pursue in the future.

There are also several other research directions. The robustness of the proposed method comes at the cost of efficiency loss. It would be of interest to evaluate the efficiency loss in exchange of robustness by comparing the proposed methods with the likelihood-based joint analyses of recurrent and terminal events, as the latter is expected to yield the most efficient parameter estimation under correct model specifications. In particular, the current estimation

of α does not depend on the estimation of β because in our carefully devised estimation procedure, β is not involved in the embedded seimparametric estimation on clustered right-truncated data. A more efficient estimator may be constructed by incorporating the knowledge about β in the estimation of α, and, thus, to develop an iterative algorithm for estimating both β and α. Nonetheless, such procedure is difficult to derive without additional assumptions because $e^{\beta^\top X_i}$ and the unobserved frailty variable Z_i are coupled together in the rate function. It is expected that additional assumption on the distribution of Z_i will be needed in order to exploit the information about β. For instance, one may use a likelihood-based estimation approach by assuming the distribution of the frailty variable. However, such likelihood-based inference for the proposed model has not been investigated in the literature either for univariate survival data or recurrent event data, and thus warrants further research. Given that the current method can only deal with time-independent baseline covariates, it would also be of interest to extend the proposed method to allow both time-independent and time-dependent covariates (Huang et al., 2010). From the model identifiability perspective, we recommend that the Weibull model should be fitted and diagnosed first, and if rejected, the proposed model can then be fitted. As graphical diagnoses are often subjective, a formal goodness-of-fit test for the Weibull model with frailty would be a tool of important utility before applications of the proposed model.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements

Xu and Chiou contributed equally to this work. The authors acknowledge the computing time granted on the Beowulf cluster of the Department of Statistics, University of Connecticut, partially supported by NSF grant DMS 0723557. The authors also thank Dr. Shao-Hsuan Wang for his computing support in an earlier exploration of this project. This research was partially supported by NSF SES1659328 and DMS 1712717 to Xu, and NIH R01CA193888 to Huang. The transplantation cohort study was supported in part by NIH K24AI085118.

References

Barzilai J and Borwein JM (1988). Two-point step size gradient methods. IMA Journal of Numerical Analysis 8, 141–148.

Benjamin V, Zhang B, Nunamaker JF Jr, and Chen H (2016). Examining hacker participation length in cybercriminal internet-relay-chat communities. Journal of Management Information Systems 33, 482–510.

Chen YQ and Jewell NP (2001). On a general class of semiparametric hazards regression models. Biometrika 88, 687–702.

Chen YQ and Wang M-C (2000). Estimating a treatment effect with the accelerated hazards models. Controlled Clinical Trials 21, 369–380. [PubMed: 10913811]

Cook RJ and Lawless J (2007). The Statistical Analysis of Recurrent Events. New York: Wiley.

Cook RJ and Lawless JF (1997). Marginal analysis of recurrent events and a terminating event. Statistics in Medicine 16, 911–924. [PubMed: 9160488]

Eaton WW, Mortensen PB, Herrman H, Freeman H, Bilker W, Burgess P, and Wooff K (1992). Long-term course of hospitalization for schizophrenia: Part I. risk for rehospitalization. Schizophrenia Bulletin 18, 217–228. [PubMed: 1621069]

Ghosh D (2004). Accelerated rates regression models for recurrent failure time data. Lifetime Data Analysis 10, 247–261. [PubMed: 15456106]

Ghosh D and Lin D (2002). Marginal regression models for recurrent and terminal events. Statistica Sinica 12, 663–688.

Huang C-Y, Qin J, and Wang M-C (2010). Semiparametric analysis for recurrent event data with time-dependent covariates and informative censoring. Biometrics 66, 39–49. [PubMed: 19459839]

Huang C-Y and Wang M-C (2004). Joint modeling and estimation for recurrent event processes and failure time data. Journal of the American Statistical Association 99, 1153–1165. [PubMed: 24068850]

Kalbfleisch J and Lawless J (1991). Regression models for right truncated data with applications to AIDS incubation times and reporting lags. Statistica Sinica 1, 19–32.

Kalbfleisch JD, Schaubel DE, Ye Y, and Gong Q (2013). An estimating function approach to the analysis of recurrent and terminal events. Biometrics 69, 366–374. [PubMed: 23651362]

Lai TL and Ying Z (1991). Rank regression methods for left-truncated and right-censored data. The Annals of Statistics 19, 531–556.

Lancaster T and Intrator O (1998). Panel data with survival: Hospitalization of HIV-positive patients. Journal of the American Statistical Association 93, 46–53.

Lawless JF and Nadeau C (1995). Some simple robust methods for the analysis of recurrent events. Technometrics 37, 158–168.

Lin D, Wei L, Yang I, and Ying Z (2000). Semiparametric regression for the mean and rate functions of recurrent events. Journal of the Royal Statistical Society: Series B 62, 711–730.

Lin DY, Wei LJ, and Ying Z (1998). Accelerated failure time models for counting processes. Biometrika 85, 605–618.

Liu L, Wolfe RA, and Huang X (2004). Shared frailty models for recurrent events and a terminal event. Biometrics 60, 747–756. [PubMed: 15339298]

Liu Y, Wu Y, Cai J, and Zhou H (2010). Additive–multiplicative rates model for recurrent events. Lifetime Data Analysis 16, 353–373. [PubMed: 20229314]

Luo X, Wang M-C, and Huang C-Y (2010). A comparison of various rate functions of a recurrent event process in the presence of a terminal event. Statistical Methods in Medical Research 19, 167–182. [PubMed: 18445699]

Marr KA (2012). Delayed opportunistic infections in hematopoietic stem cell transplantation patients: A surmountable challenge. ASH Education Program Book 2012, 265–270.

Nelson WB (2003). Recurrent Events Data Analysis for Product Repairs, Disease Recurrences, and Other Applications. SIAM.

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

Rogers JK, McMurray JJ, Pocock SJ, Zannad F, Krum H, van Veldhuisen DJ, Swedberg K, Shi H, Vincent J, and Pitt B (2012). Eplerenone in patients with systolic heart failure and mild symptoms analysis of repeat hospitalizations. Circulation 126, 2317–2323. [PubMed: 23042980]

Schaubel DE, Zeng D, and Cai J (2006). A semiparametric additive rates model for recurrent event data. Lifetime Data Analysis 12, 389–406. [PubMed: 17031499]

Sun L and Su B (2008). A class of accelerated means regression models for recurrent event data. Lifetime Data Analysis 14, 357–375. [PubMed: 18516715]

Varadhan R and Gilbert P (2009). BB: An R package for solving a large system of nonlinear equations and for optimizing a high-dimensional nonlinear objective function. Journal of Statistical Software 32, 1–26.

Wang M-C (1989). A semiparametric model for randomly truncated data. Journal of the American Statistical Association 84, 742–748.

Wang M-C, Qin J, and Chiang C-T (2001). Analyzing recurrent event data with informative censoring. Journal of the American Statistical Association 96, 1057–1065.

Wei L and Glidden DV (1997). An overview of statistical methods for multiple failure time data in clinical trials. Statistics in Medicine 16, 833–839. [PubMed: 9160483]

Xu G, Chiou SH, Huang C-Y, Wang M-C, and Yan J (2017). Joint scale-change models for recurrent events and failure time. Journal of the American Statistical Association 112, 794–805. [PubMed: 28943684]

Ye Y, Kalbfleisch JD, and Schaubel DE (2007). Semiparametric analysis of correlated recurrent and terminal events. Biometrics 63, 78–87. [PubMed: 17447932]

Zeng D and Lin D (2009). Semiparametric transformation models with random effects for joint analysis of recurrent and terminal events. Biometrics 65, 746–752. [PubMed: 18945267]

Zeng D and Lin DY (2008). Efficient resampling methods for nonsmooth estimating functions. Biostatistics 9, 355–363. [PubMed: 17925303]

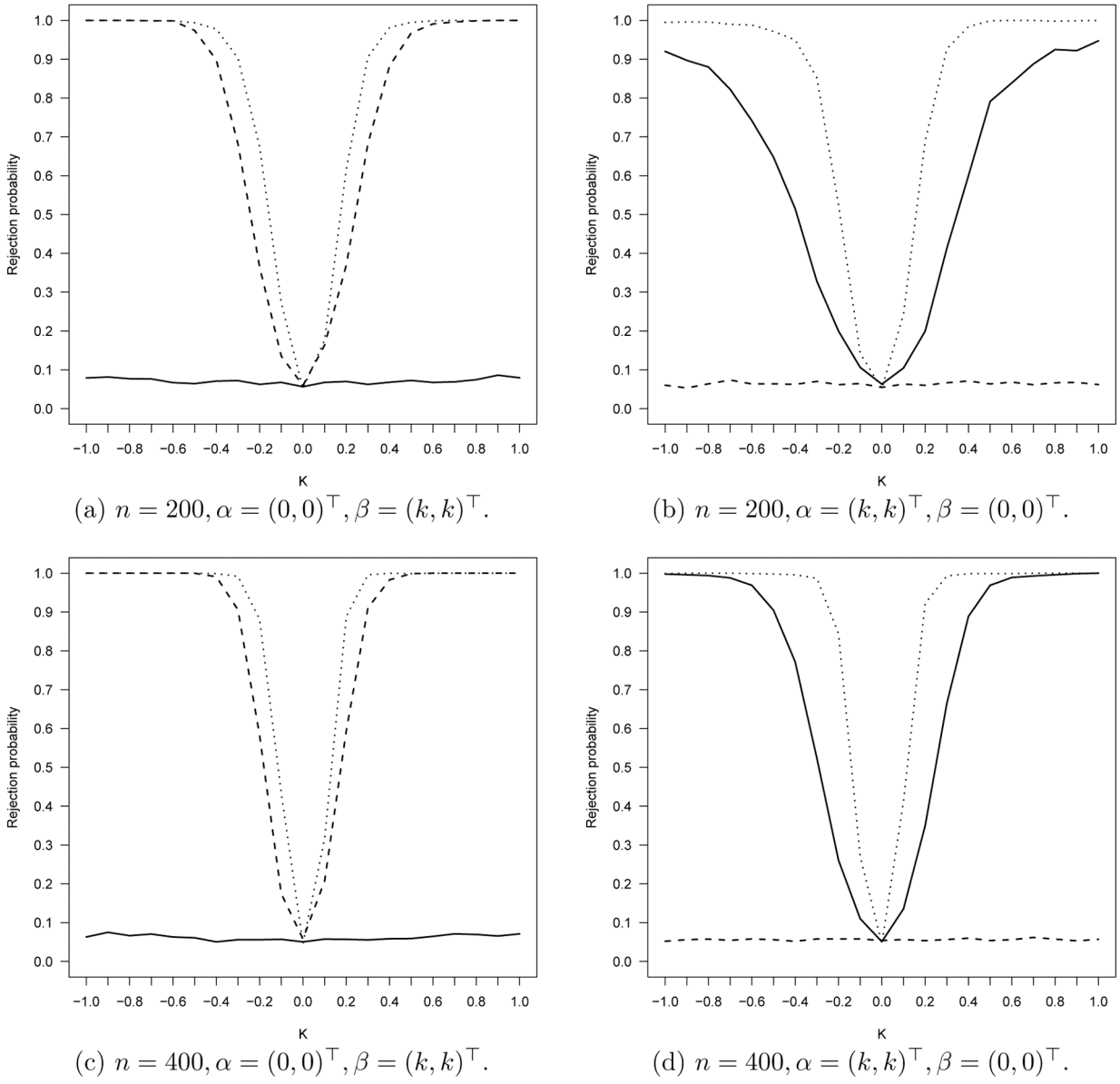
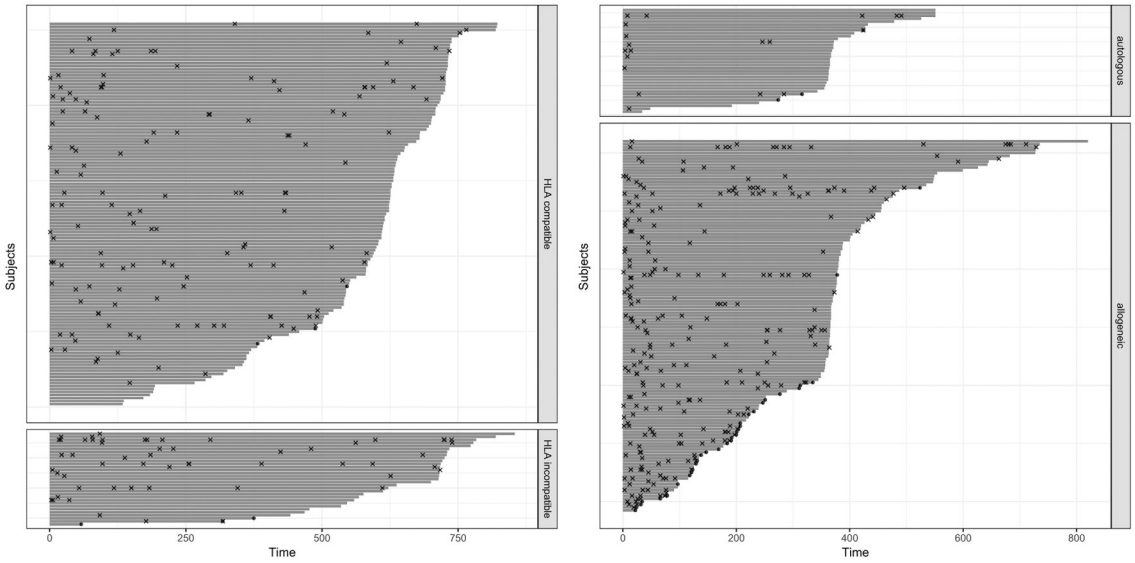


Figure 1:

Rejection rates based on 1000 replications at 0.05 significance level using the hypothesis testing procedures described in Section 3. Solid lines (—) present the rejection rates for H_0 : $\alpha = 0$, which is used to test the Cox-type proportional rates assumption; Dashed lines (- - -) present the rejection rates for H_0 : $\beta = 0$, which is used to test the accelerated rate assumption; Dotted lines (· · ·) present the rejection rates for H_0 : $\alpha = \beta$ or $\gamma = 0$, which is used to test the accelerated mean assumption.



(a) Kidney transplant c ohort by HLA compatibility.

(b) HSCT cohort by the type of stem cell transplant.

Figure 2:

Longitudinal plots of the infection data; horizontal gary lines indicate the time elapsed from transplant to end of follow-up; × represents an infection episode; • represents death.

Table 1:

Simulation results with $\alpha = (-1, -1)^\top$ and $\beta = (1, 1)^\top$. Columns without an asterisk (*) present results using the zero vector as initial value; columns with an asterisk present results using the true value as initial value; Bias is the empirical bias; ESE is the empirical standard error; ASE is the average of the standard error obtained from resampling; CP is the empirical coverage probability (%) of 95% confidence intervals.

		Proposed						Sun and Su (2008)					
n		**Bias**	**ESE**	**ASE**	**CP**	**Bias***	**ESE***	**Bias**	**ESE**	**ASE**	**CP**	**Bias***	**ESE***
						$Z = 1$							
200	α_1	0.005	0.307	0.295	93.0	−0.011	0.308	0.678	0.533	0.218	19.2	0.003	0.095
	α_2	0.007	0.277	0.264	93.1	−0.013	0.273	0.646	0.499	0.214	19.9	0.003	0.091
	β_1	0.005	0.181	0.184	93.7	0.004	0.179	0.373	0.332	0.142	33.5	−0.010	0.091
	β_2	0.005	0.175	0.174	94.2	−0.002	0.174	0.375	0.323	0.140	34.7	0.007	0.094
400	α_1	0.019	0.218	0.210	94.6	−0.004	0.217	0.218	0.251	0.161	39.5	0.001	0.086
	α_2	0.011	0.194	0.186	94.2	0.003	0.189	0.194	0.239	0.155	41.4	−0.008	0.087
	β_1	0.006	0.135	0.131	95.1	0.005	0.131	0.123	0.172	0.109	57.1	−0.001	0.077
	β_2	0.008	0.129	0.128	95.0	0.000	0.130	0.113	0.165	0.105	57.4	−0.002	0.077
						$Z \sim$ Gamma(4, 4)							
200	α_1	0.001	0.314	0.301	93.7	0.001	0.320	0.683	0.410	0.224	18.8	−0.113	0.159
	α_2	−0.010	0.281	0.267	93.3	0.023	0.281	0.536	0.386	0.230	25.1	0.095	0.146
	β_1	−0.008	0.221	0.219	93.7	−0.006	0.223	0.311	0.305	0.173	44.1	0.103	0.169
	β_2	0.003	0.213	0.209	93.5	0.013	0.214	0.311	0.301	0.180	49.6	0.096	0.168
400	α_1	0.005	0.232	0.215	94.5	−0.008	0.224	0.432	0.257	0.162	23.9	−0.147	0.156
	α_2	0.002	0.203	0.191	94.4	−0.009	0.205	0.264	0.218	0.158	41.7	−0.091	0.144
	β_1	0.005	0.163	0.158	94.4	−0.006	0.168	0.169	0.190	0.136	62.6	−0.090	0.136
	β_2	−0.001	0.151	0.151	94.7	−0.000	0.147	0.134	0.188	0.138	70.4	0.097	0.141

Table 2:

Simulation results with $\alpha = (0, 0)^\top$ and $\beta = (-1, -1)^\top$. Columns without an asterisk (*) present results using the zero vector as initial value; columns with an asterisk present results using the true value as initial value; Bias is the empirical bias; ESE is the empirical standard error; ASE is the average of the standard error obtained from resampling; CP is the empirical coverage probability (%) of 95% confidence intervals.

		Proposed						Sun and Su (2008)					
n		**Bias**	**ESE**	**ASE**	**CP**	**Bias***	**ESE***	**Bias**	**ESE**	**ASE**	**CP**	**Bias***	**ESE***
						$Z = 1$							
200	α_1	−0.004	0.161	0.155	92.5	−0.006	0.148	0.358	0.240	0.092	15.2	−0.019	0.049
	α_2	−0.001	0.153	0.151	92.5	0.005	0.150	0.394	0.237	0.097	11.6	−0.018	0.043
	β_1	−0.001	0.118	0.114	92.9	−0.003	0.109	0.241	0.154	0.081	20.3	−0.013	0.069
	β_2	−0.003	0.112	0.113	92.5	0.003	0.112	0.262	0.158	0.082	18.2	−0.012	0.072
400	α_1	0.001	0.104	0.100	94.9	0.001	0.110	0.187	0.215	0.078	33.3	−0.016	0.039
	α_2	−0.005	0.102	0.096	93.6	−0.001	0.102	0.199	0.214	0.077	30.4	0.008	0.042
	β_1	−0.001	0.078	0.073	94.8	0.001	0.081	0.127	0.145	0.064	39.8	−0.010	0.062
	β_2	−0.003	0.076	0.071	94.6	−0.001	0.076	0.135	0.148	0.063	39.4	0.005	0.058
						$Z \sim$ Gamma(4, 4)							
200	α_1	0.007	0.167	0.146	92.4	−0.011	0.169	0.414	0.219	0.118	15.0	−0.042	0.062
	α_2	0.002	0.155	0.141	94.0	−0.001	0.155	0.388	0.253	0.124	18.2	−0.045	0.077
	β_1	0.007	0.149	0.124	91.7	−0.000	0.142	0.273	0.168	0.127	35.9	−0.044	0.129
	β_2	0.003	0.146	0.123	90.7	0.005	0.143	0.255	0.202	0.131	40.5	−0.043	0.121
400	α_1	0.005	0.113	0.101	92.2	0.001	0.112	0.302	0.208	0.093	20.3	−0.051	0.071
	α_2	0.001	0.108	0.099	93.6	0.001	0.105	0.249	0.231	0.100	32.0	−0.049	0.074
	β_1	0.000	0.106	0.095	91.9	0.005	0.102	0.189	0.168	0.100	42.7	−0.044	0.096
	β_2	−0.005	0.102	0.099	91.8	0.006	0.100	0.174	0.186	0.102	49.4	−0.055	0.102

Table 3:

Summary of the infection data; $\hat{\alpha}$ and $\hat{\beta}$ are the point estimator; SE($\hat{\alpha}$) and SE($\hat{\beta}$) are the corresponding standard error; the age variable was standardized to have mean 0 and standard deviation 1.

	Proposed Model			
	$\hat{\alpha}$	SE($\hat{\alpha}$)	$\hat{\beta}$	SE($\hat{\beta}$)
Kidney transplant cohort				
Age	1.025	0.354	0.557	0.263
White	−1.729	0.952	−0.631	0.600
HLA incompatible	1.757	0.651	1.374	0.478
CMV	−1.609	0.654	−0.087	0.487
Diabetes	1.076	1.383	0.019	0.821
Hypertension	−1.864	0.918	−0.917	0.729
HSCT cohort				
Age	−0.320	0.567	0.075	0.149
White	−0.966	0.871	−0.281	0.504
Male	−2.237	2.781	−0.864	0.773
Allogeneic	−2.038	0.804	0.517	0.907
Lymphomas disease	−1.048	1.347	−0.478	0.565