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Statistical inference on shape and size indexes for counting processes

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Summary

Single-index models have gained increased popularity in time-to-event analysis owing to their model flexibility and advantage in dimension reduction. We propose a semiparametric framework for the rate function of a recurrent event counting process by modelling its size and shape components with single-index models. With additional monotone constraints on the two link functions for the size and shape components, the proposed model possesses the desired directional interpretability of covariate effects and encompasses many commonly used models as special cases. To tackle the analytical challenges arising from leaving the two link functions unspecified, we develop a two-step rank-based estimation procedure to estimate the regression parameters with or without informative censoring. The proposed estimators are asymptotically normal, with a root-n convergence rate. To guide model selection, we develop hypothesis testing procedures for checking shape and size independence. Simulation studies and a data example on a hematopoietic stem cell transplantation study are presented to illustrate the proposed methodology.

Keywords

Dimension reduction; Informative censoring; Kernel smoothing; Rate function; Recurrent event

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Supplementary material

Supplementary Material available at *Biometrika* online includes the proofs of Theorems 1 and 2 as well as additional simulation results and discussions.

1. Introduction

Recurrent event data have a wide application in various fields, including medicine, reliability, economics and social sciences. Compared with the conventional time-to-first-event analysis, the analysis of recurrent events better utilizes the complete event trajectory and often leads to improved statistical power and precision. However, the stochastic nature of recurrent events is more complex than a single event time, creating additional analytical challenges. Despite various regression models having been studied in the literature (see, for example, Pepe & Cai, 1993; Lawless & Nadeau, 1995; Lin et al., 1998, 2000, 2001; Ghosh, 2004; Schaubel et al., 2006; Cook & Lawless, 2007), there has been an increasing demand for flexible modelling strategies to better characterize heterogeneity across subjects. As an example, the commonly used proportional rate model assumes that all study subjects share the same baseline rate function, and thus fails to account for covariate effects in applications where the pattern of time-varying risk profile varies across subjects.

Single-index models are popular regression models because they enjoy great flexibility yet possess more structures than nonparametric methods (Härdle & Stoker, 1989; Powell et al., 1989; Härdle et al., 1993; Ichimura, 1993; Hristache et al., 2001; Xia, 2006; Cui et al., 2011; Kuchibhotla et al., 2020). In general, the models assume that a linear combination of covariates influences the outcome via an unspecified link function. Such a model structure has an attractive dimension reduction feature in that the multi-dimensional covariate information is succinctly summarized in a single index, and thus avoids the curse of dimensionality in nonparametric estimation. More recently, Balabdaoui et al. (2019) and Groeneboom & Hendrickx (2019) considered parameter estimation under a monotonicity constraint on the link function. For time-to-first-event analysis, researchers have considered Cox-type single-index hazard models, where the link function for covariate effects is left unspecified and estimated using cubic splines (Huang & Liu, 2006) or kernel smoothing (Lu et al., 2006; Wang et al., 2009); a more general setting without the proportional hazards assumption has been considered in Chiang et al. (2018).

To allow flexible modelling of the counting process, we propose a new semiparametric framework of shape- and size-index models. Our approach is formulated by decomposing the rate function into shape and size functions (Wang & Huang, 2014). We assume that the shape and size components depend on linear combinations of covariates via unknown link functions, and impose monotone constraints on the link functions to facilitate interpretation of the covariate effects. The methodological contribution of this paper is three-fold: first, existing single-index model approaches usually involve only one unspecified link function, and thus the estimation procedures are not readily applicable to our model with two unknown link functions. We develop a two-step rank-based procedure by first estimating the shape component of the rate function, and then estimating the size component by maximizing a size-targeted objective function. Second, to determine if the covariate effects modify the shape and size components of the rate function, we develop novel testing procedures to test the shape or size independence of the covariates. Third, although we derive the estimators under noninformative censoring, we show that the estimators remain valid when the counting process and the censoring time are allowed to be correlated through a latent variable.

2. Size- and shape-index models

Denote by $N^*(t)$ the number of events occurring at or before time t, and by X a p-dimensional vector of baseline covariates. Let $\lambda(t \mid X)$ be the conditional rate function of $N^*(\cdot)$ given X, that is, $\lambda(t \mid X)\mathrm{d}t = E\{\mathrm{d}N^*(t) \mid X\}$. The cumulative rate function is defined as $\Lambda(t \mid X) = \int_0^t \lambda(u \mid X)\mathrm{d}u$. Let $[0, \tau]$ be the study period of interest. Following Wang & Huang (2014), we consider decomposing the conditional rate function into the product of a shape function and a size function. The size function is the expected number of events over the entire study period, that is, $E\{N^*(\tau) \mid X\} = \Lambda(\tau \mid X)$; on the other hand, the shape function, defined by $\lambda(t \mid X)/\Lambda(\tau \mid X)$, characterizes the time-varying profile of the occurrence rate standardized by its magnitude and gives a proper probability density function on $[0, \tau]$. We consider semiparametric modelling of the size and shape components using single-index models,

$$\lambda\left(t \mid X\right) = \underbrace{f\left(t, \beta_0^{\mathrm{T}}X\right)}_{\text{shape}}\underbrace{g\left(\gamma_0^{\mathrm{T}}X\right)}_{\text{size}}, \; 0 \leqslant t \leqslant \tau, \tag{1}$$

where β_0 and γ_0 are p-dimensional vectors of regression parameters, $f(\cdot, a)$ is an unspecified density function for $a \in \mathbb{R}$, and $g(\cdot)$ is an unspecified function. The linear combinations $\beta_0^{\mathrm{T}}X$ and $\gamma_0^{\mathrm{T}}X$ are termed the shape index and the size index, respectively. Under the proposed recurrent-event modelling framework, the size index $\gamma_0^{\mathrm{T}}X$ affects the ordinate scale of the rate function, while the shape index $\beta_0^{\mathrm{T}}X$ affects the shape of the rate function, but does not stretch or shrink it along the vertical axis.

With recurrent adverse events, reducing the total event counts and postponing the occurrence of events are favourable directions. However, the single-index model does not provide directional interpretation of the regression parameters because the link function is left unspecified. To tackle this problem, we additionally impose monotone constraints on the link functions. Specifically, we impose the following monotonicity condition on the size function.

Assumption 1. We have that $g\left(\gamma_0^{\mathrm{T}}X\right)$ is increasing with the size index $\gamma_0^{\mathrm{T}}X$.

Under Assumption 1, a larger value of the size index $\gamma_0^{\mathrm{T}}X$ indicates a larger expected number of events on $[0, \tau]$. To introduce the constraints on the shape function, we define $F\left(t, a\right) = \int_0^t f\left(u, a\right)\mathrm{d}u$, $r\left(t, a\right) = f\left(t, a\right)/F\left(t, a\right)$ and $\mu\left(a\right) = \int_0^\tau \left\{1 - F\left(u, a\right)\right\}\mathrm{d}u$. Since $f(\cdot, a)$ gives a proper density function on $[0, \tau]$, $F(\cdot, a)$, $r(\cdot, a)$ and $\mu(a)$ can be viewed as the cumulative distribution, the reversed hazard function (Lagakos et al., 1988; Finkelstein, 2002) and the mean corresponding to $f(\cdot, a)$, respectively. We then impose the following condition.

Assumption 2. For any $t \in \left[0, \tau\right]$, $r\left(t, \beta_0^{\mathrm{T}}X\right)$ is decreasing with the shape index $\beta_0^{\mathrm{T}}X$.

Assumption 2 corresponds to the reversed hazard rate order (Shaked & Shanthikumar, 2007), which is stronger than the stochastic order in the sense that Assumption 2 implies $F\left(t, \beta_0^{\mathrm{T}}X\right)$ is increasing in $\beta_0^{\mathrm{T}}X$. See the Supplementary Material for a diagram illustrating the reversed hazard rate order. Under Assumption 2, a larger value of $\beta_0^{\mathrm{T}}X$ indicates that the events are likely to occur earlier.

Remark 1. Let m be the total event count on $[0, \tau]$ and T_j be the time to the jth event. It can be verified that $\mu(\beta_0^{\mathrm{T}}X) = E(\sum_{j=1}^{m} T_j \mid X)/E(m \mid X)$, and that $\mu(\beta_0^{\mathrm{T}}X)$ gives the average time to recurrent events. Moreover, in the special case where $N^*(\cdot)$ is a Poisson process, it can be shown that $\mu(\beta_0^{\mathrm{T}}X) = E(\sum_{j=1}^{m} T_j \mid X, m)/m$. Under Assumption 2, $\mu(\beta_0^{\mathrm{T}}X)$ is decreasing in $\beta_0^{\mathrm{T}}X$.

As illustrated in the following examples, model (1) with Assumptions 1 and 2 encompasses commonly used models for single-event and recurrent-event data while providing more insight into the covariate effects.

Example 1. The Cox proportional hazards model assumes $h(t \mid X) = h_0(t)\exp(b_0^{\mathrm{T}}X)$, where $h(t \mid X)$ and $h_0(t)$ are the conditional and baseline hazard functions, respectively. The size function for the single-event counting process is given by $E\{N^*(\tau) \mid X\} = 1 - s_0(\tau)^{\exp(b_0^{\mathrm{T}}X)}$, with $s_0(t) = \exp\{-\int_0^t h_0(u)\mathrm{d}u\}$. The size function is increasing in $b_0^{\mathrm{T}}X$ when $s_0(\tau) < 1$ and independent of X when $s_0(\tau) = 1$. The shape function is given by $s_0(t)^{\exp(b_0^{\mathrm{T}}X)} h_0(t)\exp(b_0^{\mathrm{T}}X)/\left\{1 - s_0(\tau)^{\exp(b_0^{\mathrm{T}}X)}\right\}$. It can be verified that the corresponding reversed hazard is decreasing in $b_0^{\mathrm{T}}X$. Hence, Assumption 2 is satisfied.

Example 2. The semiparametric transformation model $\Lambda(t \mid X) = v\{\Lambda_0(t)\exp(c_0^{\mathrm{T}}X)\}$ is a popular approach for recurrent events analysis (Lin et al., 2001), where $\Lambda_0(t)$ is an unspecified baseline cumulative rate function. A natural choice of the transformation function is the Box–Cox transformation with $v(t) = \{(t+1)^{\rho} - 1\}/\rho$ for $\rho > 0$ and $v(t) = \log(t+1)$ for $\rho = 0$. In this case, the size function is increasing in $c_0^{\mathrm{T}}X$ and Assumption 1 is satisfied. Moreover, Assumption 2 is satisfied when $\rho \neq 1$. The reversed hazard is decreasing in $c_0^{\mathrm{T}}X$ when $0 \leqslant \rho < 1$ and is decreasing in $-c_0^{\mathrm{T}}X$ when $\rho > 1$.

For any $k > 0$, the pair $\{k\beta_0, f(t, a/k)\}$ gives the same shape component as $\{\beta_0, f(t, a)\}$, leading to an identifiability problem. For convenience, we take the restricted parameter spaces $\mathscr{B} = \left\{\beta = (\beta_1, \ldots, \beta_p)^{\mathrm{T}} \in \mathbb{R}^p : \|\beta\| = 1, \beta_p > 0\right\}$ to ensure model identifiability, where $\|\cdot\|$ denotes the Euclidean norm. Similarly, for the size parameters, we focus on the restricted parameter space $\mathscr{C} = \left\{\gamma = (\gamma_1, \ldots, \gamma_p)^{\mathrm{T}} \in \mathbb{R}^p : \|\gamma\| = 1, \gamma_p > 0\right\}$. Simultaneously estimating the two sets of parameters and link functions could be computationally challenging. In what follows, we propose a two-step procedure to obtain robust and computationally stable estimators of these parameters.

3. Estimation

3.1. Estimation of the shape index

The estimation for β_0 is based on the fact that, under Assumption 2, events from subjects with a larger value of the shape index are more likely to occur earlier. We first consider the ideal case where the recurrent-event counting process can be completely observed on

$[0, \tau]$. For subjects i and j, we compare each pair of event times from the two subjects. When subject i has a larger shape index than subject j, there tend to be more pairs in which the event time from subject i is shorter than that of subject j. It can be shown that, when $\beta_0^{\mathrm{T}} X_i \geqslant \beta_0^{\mathrm{T}} X_j$, we have

$$\int_0^\tau \int_0^\tau E\{I(u < t)\mathrm{d}N_i^*(u)\mathrm{d}N_j^*(t) \mid X_i, X_j\} \geqslant \int_0^\tau \int_0^\tau E\{I(u > t)\mathrm{d}N_i^*(u)\mathrm{d}N_j^*(t) \mid X_i, X_j\},$$

where $\int_0^\tau \int_0^\tau I(u < t)\mathrm{d}N_i^*(u)\mathrm{d}N_j^*(t)$ gives the number of event time pairs in which the event from the ith subject occurs earlier than the event time from the jth subject. In the same spirit as the maximum rank correlation estimator (Han, 1987; Sherman, 1993), we propose to estimate β_0 by maximizing the following shape-targeted objective function:

$$U_1^*(\beta) = \frac{1}{n(n-1)} \sum_{i \neq j} I(\beta^{\mathrm{T}} X_i > \beta^{\mathrm{T}} X_j) \int_0^\tau \int_0^\tau I(u < t)\mathrm{d}N_i^*(u)\mathrm{d}N_j^*(t).$$

Denote the maximizer by $\hat{\beta}^* = \arg\max_{\beta \in \mathscr{B}} U_1^*(\beta)$. The estimator $\hat{\beta}^*$ can be viewed as an extension of the maximum rank correlation estimator, and it reduces to the maximum rank correlation estimator when all the subjects encounter exactly one event on $[0, \tau]$. Applying a similar argument to Han (1987), it can be shown that the true β_0 maximizes $E\{U_1^*(\beta)\}$.

In practice, the observation of the recurrent-event process is usually subject to right censoring. Let C be the time to the end of follow-up; then the process $N_i^*(\cdot)$ can only be observed up to C_i. Define the observed counting process $N(t) = N^*\{\min(t, C)\}$. The observed data $\{(N_i(t), X_i, C_i), 0 \leqslant t \leqslant C_i, i = 1, \ldots, n\}$ are assumed to be independent and identically distributed replicates of $\{(N(t), X, C), 0 \leqslant t \leqslant C\}$. We first assume that C is independent of $N^*(\cdot)$ given X. An extension to account for informative censoring is presented in § 3.4.

To estimate β_0 in the presence of right censoring, we restrict the comparison of event times from subjects i and j to the comparable regions defined by $[0, C_{ij}]$, where $C_{ij} = \min(C_i, C_j)$. As pointed out in Huang et al. (2010) and Wang & Huang (2014), the comparison of an event time pair that involves an event time outside of the comparable region does not provide information about the model parameters. It can be shown that, when $\beta_0^{\mathrm{T}} X_i \geqslant \beta_0^{\mathrm{T}} X_j$, we have

$$\int_0^\tau \int_0^\tau E\{I(C_{ij} > t > u)\mathrm{d}N_i^*(u)\mathrm{d}N_j^*(t) \mid X_i, X_j\} \geqslant \int_0^\tau \int_0^\tau E \{I(C_{ij} > u > t)\mathrm{d}N_i^*(u)\mathrm{d}N_j^*(t) \mid X_i, X_j\}. \tag{2}$$

In other words, given $\beta_0^{\mathrm{T}} X_i > \beta_0^{\mathrm{T}} X_j$, the number of concordant pairs in the comparable region is expected to be larger than the number of nonconcordant pairs. To estimate β_0, we propose to maximize the following shape-targeted objective function:

$$U_1(\beta) = \frac{1}{n(n-1)} \sum_{i \neq j} I(\beta^{\mathrm{T}} X_i > \beta^{\mathrm{T}} X_j) \int_0^{C_{ij}} \int_0^{C_{ij}} I(u < t)\mathrm{d}N_i(u)\mathrm{d}N_j(t).$$

Denote the maximizer by $\hat{\beta} = \arg\max_{\beta \in \mathscr{B}} U_1(\beta)$. The construction of the objective function $U_1(\beta)$ does not require knowing the size component, because the pairwise comparison removes the impact of size. The large-sample property of $\hat{\beta}$ is established in Theorem 1, with the proof given in the Supplementary Material. In this paper we use V^- to denote the Moore–Penrose inverse of a matrix V. Denote by f_1 the density function of $\beta_0^{\mathrm{T}} X$ and by $\dot{r}(t, a)$ the partial derivative of $r(t, a)$ with respect to a. Define $Q_k(t, a) = E\{X^{\otimes k} I(C \geqslant t) g(\gamma_0^{\mathrm{T}} X) \mid \beta_0^{\mathrm{T}} X = a\}$ for $k = 0, 1, 2$, where $v^{\otimes 0} = 1, v^{\otimes 1} = v$ and $v^{\otimes 2} = vv^{\mathrm{T}}$.

Theorem 1. *Under Conditions (C1)–(C6) in the* Supplementary Material, $n^{1/2}(\hat{\beta} - \beta_0)$ *converges in distribution to a zero-mean normal distribution* $N(0, V_1^- \Sigma_1 V_1^-)$ *as* $n \to \infty$, *where* $\Sigma_1 = E(\phi\phi^{\mathrm{T}})$ *with* $\phi = \int_0^\tau \{XQ_0(t, \beta_0^{\mathrm{T}} X) - Q_1(t, \beta_0^{\mathrm{T}} X)\}\{I(C \geqslant t) N(t) f(t, \beta_0^{\mathrm{T}} X)\mathrm{d}t - F(t, \beta_0^{\mathrm{T}} X)\mathrm{d}N(t)\} f_1(\beta_0^{\mathrm{T}} X)$, *and* $V_1 = E\left[f_1(\beta_0^{\mathrm{T}} X)\int_0^\tau \left\{Q_2(t, \beta_0^{\mathrm{T}} X)Q_0(t, \beta_0^{\mathrm{T}} X) - Q_1(t, \beta_0^{\mathrm{T}} X)Q_1(t, \beta_0^{\mathrm{T}} X)^{\mathrm{T}}\right\}\dot{r}(t, \beta_0^{\mathrm{T}} X)F(t, \beta_0^{\mathrm{T}} X)^2 \mathrm{d}t\right]$.

Remark 2. The estimator $\hat{\beta}$ is related to the maximum rank correlation estimation for truncated data (Abrevaya, 1999; Wang & Chiang, 2019). Consider a special case where each subject experiences one event on $[0, \tau]$. Since the events occurring after C are not observed, the observed event times can be viewed as right-truncated data, where the event time is truncated by C. Then, maximizing $U_1(\beta)$ is mathematically equivalent to the maximum rank correlation estimation for truncated data.

3.2. Estimation of the shape function

We next consider the estimation of the link function $F(t, a) = \int_0^t f(u, a)\mathrm{d}u$. It can be shown that the cumulative shape function $F(t, a)$ and the reversed hazard function $r(t, a)$ have a one-to-one correspondence relationship: $F(t, a) = \exp\{-\int_t^\tau r(u, a)\mathrm{d}u\}$. As pointed out in Wang et al. (2001) and Xu et al. (2020), shape estimation can be reformulated as a right truncation problem. Motivated by the estimating equation proposed in Xu et al. (2020), we define the stochastic process $\mathscr{M}(t, a) = N(t) - \int_0^t I(C \geqslant u)N(u)r(u, a)\mathrm{d}u$. Under (1), we have $E\{\mathscr{M}(t, \beta_0^{\mathrm{T}} X) \mid X\} = 0$ for all $t \geqslant 0$. Define $K_h(\cdot) = K(\cdot/h)/h$, where $K(\cdot)$ is a second-order kernel function with bounded support on $[-1, 1]$ and h is the bandwidth parameter. As $h \to 0$, the expected value of $K_h(a - \beta_0^{\mathrm{T}} X)\mathscr{M}(t, a)$ tends to zero. When β_0 is known, for any given a, one can construct a local estimating equation, $n^{-1}\sum_{i=1}^n K_h(a - \beta_0^{\mathrm{T}} X_i)\mathscr{M}_i(\mathrm{d}t, a) = 0$, using subjects whose shape index is in a small neighbourhood of a. Solving the local estimating equation for $r(t, a)$ yields

$$r(t, a)\mathrm{d}t = \frac{\sum_{i=1}^n K_h(\beta_0^{\mathrm{T}} X_i - a)\mathrm{d}N_i(t)}{\sum_{i=1}^n K_h(\beta_0^{\mathrm{T}} X_i - a)N_i(t)I(C_i \geqslant t)}.$$

Therefore, if β_0 is known, one can estimate $F(t, a)$ by the kernel-type estimator $\hat{F}_h(t, a; \beta_0)$, where

$$\hat{F}_h\left(t, a; \beta\right) = \exp\left\{-\int_t^\tau \frac{\sum_{i=1}^n K_h\left(a - \beta^{\mathrm{T}} X_i\right) \mathrm{d}N_i\left(u\right)}{\sum_{i=1}^n K_h\left(a - \beta^{\mathrm{T}} X_i\right) N_i\left(u\right) I(C_i \geqslant u)}\right\}.$$

Let $f_1(a)$ denote the density function of the shape index $\beta_0^{\mathrm{T}} X$. As $n \to \infty, h \to 0$ and $nh^2 \to \infty$, the kernel-type estimator $n^{-1} \sum_{i=1}^n K_h(a - \beta_0{}^{\mathrm{T}} X_i) N_i\left(u\right)$ converges in probability to $\int_0^u E\{I(C \geqslant s) g(\gamma_0^{\mathrm{T}} X) \mid \beta_0^{\mathrm{T}} X = a\} f(s, a) \mathrm{d}s \cdot f_1(a)$, while $n^{-1} \sum_{i=1}^n K_h\left(a - \beta^{\mathrm{T}} X_i\right) N_i\left(u\right) I(C_i \geqslant u)$ converges in probability to $F(u, a) E\{I(C \geqslant u) g(\gamma_0^{\mathrm{T}} X) \mid \beta_0^{\mathrm{T}} X = a\} \cdot f_1(a)$. By applying the continuous mapping theorem, $\hat{F}_h(t, a; \beta_0)$ converges in probability to $F(t, a)$. The proof is given in the Supplementary Material. Since β_0 is unknown, one can plug in the estimator $\hat{\beta}$ and estimate $F(t, a)$ by $\hat{F}_h\left(t, a; \hat{\beta}\right)$.

3.3. Estimation of the size index

To facilitate discussion, we begin with the ideal case where $N^*(\cdot)$ can be completely observed on $[0, \tau]$. The estimation procedure is motivated by the fact that $\gamma_0^{\mathrm{T}} X_i > \gamma_0^{\mathrm{T}} X_j$ implies

$$E\{N_i^*(\tau) \mid X_i, X_j\} \geqslant E\{N_j^*(\tau) \mid X_i, X_j\}.$$

In other words, a larger size index is associated with a larger number of events on $[0, \tau]$. In the same spirit as monotone rank estimation (Cavanagh & Sherman, 1998), we propose to estimate γ_0 by maximizing a size-targeted objective function,

$$U_2^*\left(\gamma\right) = \frac{1}{n(n-1)} \sum_{i \neq j} I\left(\gamma^{\mathrm{T}} X_i > \gamma^{\mathrm{T}} X_j\right) N_i^*\left(\tau\right).$$

Maximum rank correlation estimation is not used here because monotonicity on the conditional expectation is weaker than monotonicity on the reversed hazard function. Based on the fact that $E\{N^*(\tau) \mid X\} = g(\gamma_0^{\mathrm{T}} X)$, one may also consider other estimators for monotone single-index models, for example, Xia (2006) and Balabdaoui et al. (2019). The results of a numerical simulation study comparing different methods in estimating γ_0 under complete follow-up are reported in the Supplementary Material. The numerical study shows that monotone rank estimation performs well and is computationally stable.

In the presence of censoring, the value of $N^*(\tau)$ is unknown and the objective function $U_2^*(\gamma)$ cannot be maximized directly. Heuristically, if we can estimate the projected number of events on $[0, \tau]$ based on what is observed before C, then $N_i^*(\tau)$ in $U_2^*(\gamma)$ can be replaced with the projected event number. Based on (1), a natural attempt is to divide the observed event count by the cumulative shape function evaluated at the follow-up time C. Specifically, we consider the ratio $N_i(C_i)/F(C_i, \beta_0^{\mathrm{T}} X_i)$, which projects the observed event number onto $[0, \tau]$. It can be shown that $E\{N_i(C_i)/F(C_i, \beta_0^{\mathrm{T}} X_i) \mid X_i\} = g(\gamma_0^{\mathrm{T}} X_i)$. Therefore, for $\gamma_0^{\mathrm{T}} X_i > \gamma_0^{\mathrm{T}} X_j$, we have

$$E\left\{\frac{N_i(C_i)}{F\left(C_i, \beta_0^{\mathrm{T}} X_i\right)} \mid X_i, X_j\right\} \geqslant E\left\{\frac{N_j(C_j)}{F\left(C_j, \beta_0^{\mathrm{T}} X_j\right)} \mid X_i, X_j\right\}. \tag{3}$$

When $F\left(t, \beta_0^{\mathrm{T}} X\right)$ is known, we can estimate γ_0 by maximizing

$$\frac{1}{n(n-1)} \sum_{i \neq j} I\left(\gamma^{\mathrm{T}} X_i > \gamma^{\mathrm{T}} X_j\right) \frac{N_i(C_i)}{F(C_i, \beta_0{}^{\mathrm{T}} X_i)}. \tag{4}$$

In practice, we can replace the unknown quantities in (4) with the corresponding estimates. Thus, we estimate γ_0 by $\hat{\gamma} = \arg\max_{\gamma \in \mathscr{C}} U_2(\gamma)$, where

$$U_2\left(\gamma\right) = \frac{1}{n(n-1)} \sum_{i \neq j} I\left(\gamma^{\mathrm{T}} X_i > \gamma^{\mathrm{T}} X_j\right) \frac{N_i(C_i)}{\hat{F}_h\left(C_i, \hat{\beta}^{\mathrm{T}} X_i; \hat{\beta}\right)}.$$

The large-sample property of the proposed estimator is stated in Theorem 2, with the proof given in the Supplementary Material. Denote by f_2 the density function of $\gamma_0^{\mathrm{T}} X$ and by $\dot{g}$ the derivative of g. Define $\delta\left(X\right) = f_2\left(\gamma_0^{\mathrm{T}} X\right)\left\{X - E\left(X \mid \gamma_0^{\mathrm{T}} X\right)\right\}$ and $\mathscr{N} = N\left(C\right)/F\left(C, \beta_0^{\mathrm{T}} X\right)$.

THEOREM 2. *Under Conditions (C1)-(C9) in the* Supplementary Material, $n^{1/2}(\hat{\gamma} - \gamma_0)$ *converges in distribution to a zero-mean normal distribution* $N(0, V_2^{-}\Sigma_2 V_2^{-})$ *as* $n \to \infty$, *where* $\Sigma_2 = E\left(\psi\psi^{\mathrm{T}}\right), V_2 = -E\left[\left\{X - E\left(X \mid \gamma_0^{\mathrm{T}} X\right)\right\}\left\{X - E\left(X \mid \gamma_0^{\mathrm{T}} X\right)\right\}^{\mathrm{T}} \dot{g}(\gamma_0 X) f_2\left(\gamma_0^{\mathrm{T}} X\right)\right]$ *and*
$\psi = \delta\left(X\right)\left\{\mathscr{N} - g\left(\gamma_0^{\mathrm{T}} X\right)\right\} + E\left[\int_C^\tau \dot{r}\left(t, \beta_0^{\mathrm{T}} X\right)\mathrm{d}t \cdot \delta\left(X\right)\mathscr{N}\left\{X - E\left(X \mid \beta_0^{\mathrm{T}} X\right)\right\}^{\mathrm{T}}\right] V_1^{-}\phi + \int_0^\tau E.$
$\left\{\delta(X)\mathscr{N} I(C \leqslant t) \mid \beta_0^{\mathrm{T}} X\right\}\left\{Q_0\left(t, \beta_0^{\mathrm{T}} X\right) F\left(t, \beta_0^{\mathrm{T}} X\right)\right\}^{-1} \mathscr{M}\left(\mathrm{d}t, \beta_0^{\mathrm{T}} X\right) f_1\left(\beta_0^{\mathrm{T}} X\right)$

3.4. Extensions to informative censoring

In many applications, a correlated failure event such as death can terminate the observation of recurrent events. For example, the censoring time C can be written as $C = \min(D, C^*)$, where D is the time to death and C^* is the time to dropout or the end of the study. Failing to account for the correlation between the failure event and the underlying recurrent-event process can lead to substantial bias and invalid conclusions. In the literature, frailty models have been used to deal with informative censoring. Let Z be an unobserved, nonnegative variable that is independent of the observed covariates X. We relax the independent censoring assumption in § 3.1 by assuming that C is independent of $N^*(\cdot)$ conditioning on both the observed covariate X and the unobserved frailty Z, so that $N^*(\cdot)$ and C are allowed to be correlated through Z. Consider the model

$$\lambda\left(t \mid Z, X\right) = f\left(t, \beta_0^{\mathrm{T}} X\right) h\left(\gamma_0^{\mathrm{T}} X, Z\right), \tag{5}$$

where the link function $h(a, z)$ is monotonically increasing in a and $f(t, a)$ satisfies Assumption 2. As argued in Ghosh & Lin (2003) and Huang & Wang (2004), the process after death can be considered latent and modelled as if they could have occurred after death. After integrating out the frailty Z, we have $\lambda\left(t \mid X\right) = f\left(t, \beta_0^{\mathrm{T}} X\right) \int_0^\infty h\left(\gamma_0^{\mathrm{T}} X, z\right) F_Z\left(\mathrm{d}z\right)$, where F_Z is the cumulative distribution function of Z, and the marginalized size function $\int_0^\infty h(\gamma_0^{\mathrm{T}} X, z) F_Z(\mathrm{d}z)$ is increasing in $\gamma_0^{\mathrm{T}} X$.

Under (5), the frailty variable Z affects the rate function only through its size component. In fact, this structural assumption has been adopted in many existing works for recurrent-event data with informative censoring (Wang et al., 2001; Huang & Wang, 2004; Liu et al., 2004; Ye et al., 2007), where the occurrence rate is inflated by a multiplicative factor Z. In this case, we have $h(\gamma_0^{\mathrm{T}} X, Z) \propto Z \exp(\gamma_0^{\mathrm{T}} X)$ and the marginalized size function is the product of $E(Z)$ and a monotone transformation of the linear predictor of X. Under (5), the key inequalities in (2) and (3) that motivate the rank-based estimation still hold. Hence, applying the same estimation procedure as § 3.1–§ 3.3 yields consistent and asymptotically normal estimators for β_0 and γ_0 under (5). The asymptotic distributions are given in the Supplementary Material.

4. Testing shape and rate independence

Existing methods for recurrent-event data postulate different assumptions on the association between the shape component and the covariates X. To guide model selection, it is essential to check whether the covariates modify the shape or size function. Following the definitions given in Wang & Huang (2014), a rate function is said to be rate independent of X if the rate function does not depend on X, and is shape/size independent of X if its shape/size function does not depend on X. Rate independence holds if and only if both shape independence and size independence hold. When shape independence holds, the Cox-type models for recurrent events are an appropriate choice for regression models, as they are shape independent. Wang & Huang (2014) developed nonparametric tests for checking shape and size independence with a single variable; however, it is not clear how their testing procedures can be extended to handle multiple covariates. In what follows, we consider nonparametric tests for shape and rate independence in the general setting.

For testing shape independence, we consider Kendall's tau-type rank correlation coefficient

$$\kappa\left(b\right) = \frac{2}{n(n-1)} \sum_{i<j} \int_0^{C_{ij}} \int_0^{C_{ij}} \operatorname{sgn}\left(b^{\mathrm{T}} X_i - b^{\mathrm{T}} X_j\right) \operatorname{sgn}\left(u - t\right) \mathrm{d}N_i\left(u\right) \mathrm{d}N_j\left(t\right),$$

where b is a p-dimensional vector in $\mathscr{B}$ and $\operatorname{sgn}(a)$ is −1,0 or 1 if a is negative, zero or positive, respectively. As before, the statistic $\kappa(b)$ removes the impact of size by applying pairwise comparison, and thus can work without additional assumptions on size. Moreover, the comparison of recurrent event times is restricted to the comparable region $[0, C_{ij}]$ to account for censoring. When $p = 1, \kappa(b)$ reduces to the shape-independence test proposed in Wang & Huang (2014). Under shape independence, for any given $b, \kappa(b)$ converges in probability to 0 as $n \to \infty$. Naturally, one can construct a Kolmogorov–Smirnov-type test statistic $\sup_{b \in \mathscr{B}} n^{1/2} \kappa\left(b\right)$. We note that $\kappa(b)$ is a nonsmooth function in b, and the optimization on $\mathscr{B}$ is numerically challenging. To overcome the computational challenge, we consider the numerical approximation and evaluate the supremum on a finite, uniform grid on the unit sphere, denoted by $\mathscr{B}^*$. Under the null hypothesis, $\sup_{b \in \mathscr{B}^*} n^{1/2}\kappa(b)$ converges in distribution to a random variable $\sup_{b \in \mathscr{B}^*} G(b)$ as $n \to \infty$, where $G(b)$ is a zero-mean Gaussian process with covariance $\mathrm{cov}(G(b_1), G(b_2)) = 4E\{\xi(O_1, O_2, b_1)\xi(O_1, O_3, b_2)\}, \xi(O_i, O_j, b) = \int_0^{C_{ij}}\int_0^{C_{ij}} \mathrm{sgn}\left(b^{\mathrm{T}}X_i - b^{\mathrm{T}}X_j\right)\mathrm{sgn}\left(u - t\right)\mathrm{d}N_i\left(u\right)\mathrm{d}N_j\left(t\right)$ with O_i representing the observed data of subject i. In practice, one can approximate the null distribution $\sup_{b \in \mathscr{B}^*} G(b)$ using bootstrap methods. Specifically, for the mth bootstrap sample $(1 \leqslant m \leqslant M)$, we calculate the statistic $\kappa_m(b)$ for $b \in \mathscr{B}^*$. Given a nominal level α, the critical value c_κ is the $100 \times (1 - \alpha)$ percentile of $\left\{\sup_{b \in \mathscr{B}^*} n^{1/2}\{\kappa_m(b) - \kappa(b)\}, m = 1, \ldots, M\right\}$. Thus, we reject the null hypothesis when $n^{1/2}\sup_{b \in \mathscr{B}^*}\kappa\left(b\right) > c_\kappa$.

Next, we consider an extension of the size-independence test in Wang & Huang (2014),

$$\kappa_2\left(b\right) = \frac{2}{n(n-1)}\sum_{i<j} \mathrm{sgn}\left(b^{\mathrm{T}}X_i - b^{\mathrm{T}}X_j\right)\{N_i(C_{ij}) - N_j(C_{ij})\}.$$

When both shape and size independence hold, $\kappa_2(b)$ converges in probability to 0 as $n \to \infty$ for each b. Moreover, the Kolmogorov–Smirnov-type test statistic $\sup_{b \in \mathscr{B}^*}\kappa_2(b)$ converges in distribution to $\sup_{b \in \mathscr{B}^*} G_2(b)$ as $n \to \infty$, where $G_2(b)$ is a zero-mean Gaussian process. As before, bootstrap methods can be applied to construct the rejection region. Similar to the two-step testing procedure proposed in Wang & Huang (2014), the size-independence test is performed only when shape independence holds. The shape-independence test can be used alone or in combination with the size-independence test for rate independence. Bonferroni correction can be applied to maintain the overall Type I error rate when both tests are applied for testing rate independence.

5. Simulation studies

Simulations studies were conducted to evaluate the finite-sample performance of the proposed estimation and test procedures. The recurrent event process was generated from a non-homogeneous Poisson process, of which the rate function can depend on a subject-specific latent variable, Z. Specifically, we generated the recurrent events from the following rate functions:

$$\lambda\left(t \mid X, Z\right) = Z\left(1 + t\right)^{-1} + 0.5Z\exp\left(b^{\mathrm{T}}X\right), \beta_0 = -b, \gamma_0 = b; \quad \text{(M1)}$$

$$\lambda\left(t \mid X, Z\right) = Z\exp\left\{-0.5t\exp\left(-b^{\mathrm{T}}X\right)\right\}, \beta_0 = b, \gamma_0 = -b; \quad \text{(M2)}$$

$$\lambda\left(t \mid X, Z\right) = 0.5Z\log\left[\exp\left(b^{\mathrm{T}}X\right) + 1\right]\left(1 + 0.5t\right)^{\left\{\log\left[\exp\left(b^{\mathrm{T}}X\right) + 1\right] - 1\right\}}, \beta_0 = -b, \gamma_0 = b; \quad \text{(M3)}$$

$$\lambda(t \mid X, Z) = Z f_{\mathrm{B}}(t, \beta_0^{\mathrm{T}} X)\exp(\gamma_0^{\mathrm{T}} X), \text{ for } t \in [0,1], \text{ where } f_{\mathrm{B}}(\cdot, a) \propto x(1-x)^{\exp(a)} \text{ is a Beta density function, } \beta_0 = (0.6, 0.8)^{\mathrm{T}}, \text{ and } \gamma_0 = (0.28, 0.96)^{\mathrm{T}}. \quad \text{(M4)}$$

It can be shown that Assumptions 1 and 2 are satisfied under (M1)–(M4). We set $b = (0.6,0.8)$ in (M1)–(M3). For each setting, we consider two covariates and $X = (X_1, X_2)^{\mathrm{T}}$, where X_1 and X_2 are independent standard normal random variables. The censoring time was generated from an exponential distribution with mean $10(1 + |X_1|)/Z$, where the subject-specific latent variable Z was either set as $Z \equiv 1$ or generated from an exponential distribution with mean 1 . Thus, in the latter case, the censoring time is correlated with the recurrent-event process through both X and Z. The average number of observed recurrent events ranges from two to eight with these settings. For each configuration, we simulated 1000 datasets with sample sizes of 200 and 400.

We considered a spherical parameterization of the shape and size parameters to account for the unit norm restriction (see, for example, Balabdaoui et al., 2019). The objective functions are not smooth functions of the parameters, and thus we applied the Nelder–Mead method to maximize the objective function. The initial values were obtained using the induced smoothing technique (Brown & Wang, 2005). More details are given in the Supplementary Material. Nonparametric bootstrap with 200 iterations was used to obtain the standard error of the proposed estimators. The resulting summary statistics are reported in Table 1, with the induced smoothing counterparts given in the Supplementary Material.

For all settings, our estimators exhibit small absolute values of bias. The average standard errors obtained from nonparametric bootstrap are in close agreement with the empirical standard errors. The associated 95% confidence intervals based on the bootstrap standard errors had empirical coverage percentages reasonably close to the nominal level. In general, the absolute values of bias and standard errors decrease as n increases. The proposed estimators yield slightly smaller absolute values of bias and standard errors under the independent censoring scheme, but compatible coverage probabilities across the two censoring schemes. Overall, these findings indicate that the proposed estimators exhibit good performance for a broad range of rate functions, and remain satisfactory when the correlation between recurrent events and the censoring time is characterized by a frailty variable in the size component.

We next generated data from (M4) with different magnitudes of β_0 and γ_0 to evaluate the Type I error rates and powers of the proposed tests in § 4. The test statistics were computed based on 300 equally spaced points on the unit sphere. Rejection proportions based on 1000 replications at 0.05 significance level are reported in Table 2; the powers for more β_0 and γ_0 values are given in the Supplementary Material. Under rate independence, the Type I error rates of the shape, size and combined tests are close to the nominal level of 0.05. For the shape-/size-dependent scenarios, the powers increase as the sample size increases.

6. Data example

Infectious complications are one of the major challenges after hematopoietic stem cell transplantation, HSCT, and cause significant morbidity. We evaluated morbidity risks among HSCT recipients in a prospective cohort study conducted at the Johns Hopkins Hospital. The cohort consists of 164 recipients who were contacted every 3 months until death or loss to follow-up to obtain information on serious infection episodes. The median follow-up time was 12.2 months, and a total of 290 infection episodes and 36 deaths were observed during the study. The average age at the time of transplantation was 52.2 years and ranged from 19.2 to 75.4 years. In our analysis, we standardize age to have zero mean and unit variance. Among all the HSCT recipients, 78% had an allogeneic HSCT, 58% had cytomegalovirus positive, 57% were female, and 77% were white. In our analysis, we focus on the first 500 days after transplant, and $N^*(t)$ counts the underlying recurrent infections in the absence of censoring. Based on 1000 bootstrap samples, the p-values for the shape test and the size test are 0.048 and < 0.001, respectively.

We applied the proposed estimating procedures to obtain the shape and size indexes. To accommodate the potential nonlinear effect of age, we include a hinge function $x^+ = \max(x, 0)$ of the standardized age as covariates, and the knot was set as zero. In addition, we also included transplant type, recipient cytomegalovirus status, gender and race for a total of six covariates. A summary of the parameter estimates and their standard errors obtained from the nonparametric bootstrap with 1000 bootstrap samples are presented in Table 3. The results show that allogeneic transplant and age have a significant effect on shape; allogeneic transplant has a significant effect on size. To provide more substantive interpretation, one can report the effect sizes, defined as expected changes in the average time to events $\mu(\beta_0^{\mathrm{T}}X)$ and the expected number of events $g(\gamma_0^{\mathrm{T}}X)$ resulting from changing the covariate values. The effect sizes generally depend on the original values of the indexes. The average time to infections in a subgroup of 45-year-old, nonwhite, female patients who were free of cytomegalovirus and received allogeneic transplants was 84.6 days longer than their counterparts who received autologous transplants; meanwhile, the expected number of events in the allogeneic group is 0.4 more than that in the autologous group. This is because autologous patients tended to experience infections earlier, while allogenic patients are susceptible to infections throughout the time interval of interest. In the above autologous subgroup, a ten-year increase in age is associated with an increase of 27.4 days in average time to infections. The link functions g and μ were estimated using kernel smoothing, with details given in the Supplementary Material.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1.

Summary of simulation results based on 1000 replications. The estimates were obtained by maximizing the unsmoothed rank objective functions with the induced smoothing estimators as the initial value. The bootstrap size is 200 for each replication. Of the 1000 replications, the average numbers of observed recurrent events are 8.2 (6.9), 2.1 (1.9), 2.5 (2.3), 6.3 (6.2) for the four scenarios under independent censoring (informative censoring) |Bias|, the absolute value of the empirical bias (×1000); ESE, the empirical standard error (× 1000); ASE, the average bootstrap standard error (× 1000); CP, the 95% empirical coverage probability (%).

		Independent censoring				Informative censoring			
Scenario		**|Bias|**	**ESE**	**ASE**	**CP**	**|Bias|**	**ESE**	**ASE**	**CP**
				$n = 200$					
(M1)	β_1	25	218	222	92.2	24	207	205	94.2
	β_2	29	165	160	92.7	39	162	167	94.6
	γ_1	1	49	54	96.3	14	111	114	96.3
	γ_2	1	37	42	96.7	1	82	86	95.5
(M2)	β_1	3	95	99	94.3	2	105	112	96.1
	β_2	7	73	77	95.1	9	80	81	96.0
	γ_1	1	67	72	96.0	3	115	125	95.4
	γ_2	5	50	53	95.9	11	86	91	94.6
(M3)	β_1	1	142	151	95.8	10	170	207	96.4
	β_2	19	111	129	95.6	21	126	171	96.5
	γ_1	1	55	61	96.4	3	91	106	95.5
	γ_2	2	41	47	96.0	6	69	83	95.4
(M4)	β_1	0	39	46	95.7	3	44	51	95.2
	β_2	2	30	33	95.3	4	34	40	95.7
	γ_1	1	37	44	96.6	2	94	102	95.7
	γ_2	1	11	13	96.4	4	28	32	95.5
				$n = 400$					
(M1)	β_1	18	150	153	94.6	3	166	171	95.2
	β_2	11	115	116	94.2	20	131	136	95.8
	γ_1	1	35	39	95.9	2	76	83	95.9
	γ_2	0	26	29	95.8	4	57	63	95.4
(M2)	β_1	2	63	68	95.5	2	71	79	95.7
	β_2	2	48	52	95.6	3	53	58	96.0
	γ_1	1	46	51	95.5	2	83	87	94.9
	γ_2	2	35	39	95.3	5	63	67	94.3
(M3)	β_1	3	98	104	95.5	5	118	134	95.0
	β_2	7	73	85	95.4	10	90	100	95.4
	γ_1	1	39	44	95.8	2	65	67	95.4

Scenario		Independent censoring				Informative censoring			
		|Bias|	ESE	ASE	CP	|Bias|	ESE	ASE	CP
	γ_2	2	29	32	95.3	3	48	53	95.6
(M4)	β_1	1	26	30	95.8	1	31	34	95.6
	β_2	0	19	23	96.4	1	23	26	95.5
	γ_1	1	26	31	95.7	6	69	73	95.6
	γ_2	0	8	9	95.5	1	20	21	95.6

Table 2.

Summary of rejection proportions of the shape- and size-independence tests, and the combined test for rate independence, based on 1000 replications at the 0.05 nominal level. When the test statistics for shape and size independence are combined to test rate independence, the significance levels of individual tests were set as 0.025. In all settings where β_0 or γ_0 are nonzero, we have $\beta_0/\| \beta_0 \| = (0.6,0.8)^{\mathrm{T}}$ and $\gamma_0/\| \gamma_0 \| = (0.28,0.96)^{\mathrm{T}}$

		$n = 200$			$n = 400$		
$\|\beta_0\|$	$\|\gamma_0\|$	**Shape**	**Size**	**Rate**	**Shape**	**Size**	**Rate**
Independent censoring							
0	0	0.044	0.052	0.053	0.044	0.056	0.050
0	0.2	0.038	0.999	0.997	0.043	1.000	1.000
0.2	0.2	0.745	0.997	0.998	0.955	1.000	1.000
Informative censoring							
0	0	0.044	0.051	0.040	0.053	0.051	0.051
0	0.2	0.042	0.490	0.559	0.051	0.803	0.854
0.2	0.2	0.598	0.531	0.659	0.946	0.861	0.987

Table 3.

Summary of the infection data

	$\hat{\beta}$	$\mathrm{SE}(\hat{\beta})$	$\hat{\gamma}$	$\mathrm{SE}(\hat{\gamma})$
Age	0.209	0.081	−0.143	0.224
Age^{+}	−0.537	0.114	0.539	0.350
Allogeneic	−0.768	0.105	0.683	0.158
Cytomegalovirus positive	−0.087	0.099	0.312	0.285
Male	−0.102	0.105	0.348	0.182
Nonwhite	0.246	0.153	0.068	0.270

$\hat{\beta}$ and $\hat{\gamma}$ are the point estimators obtained from optimizing the rank-based objective functions; $\mathrm{SE}(\hat{\beta})$ and $\mathrm{SE}(\hat{\gamma})$ are the corresponding standard errors obtained from 1000 bootstrap samples; Age is standardized to have zero mean and unit variance; Age^{+} is the positive part of the standardized age.