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An Estimating Function Approach to the Analysis of Recurrent and Terminal Events

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Summary. In clinical and observational studies, the event of interest can often recur on the same subject. In a more complicated situation, there exists a terminal event (e.g., death) which stops the recurrent event process. In many such instances, the terminal event is strongly correlated with the recurrent event process. We consider the recurrent/terminal event setting and model the dependence through a shared gamma frailty that is included in both the recurrent event rate and terminal event hazard functions. Conditional on the frailty, a model is specified only for the marginal recurrent event process, hence avoiding the strong Poisson-type assumptions traditionally used. Analysis is based on estimating functions that allow for estimation of covariate effects on the recurrent event rate and terminal event hazard. The method also permits estimation of the degree of association between the two processes. Closed-form asymptotic variance estimators are proposed. The proposed method is evaluated through simulations to assess the applicability of the asymptotic results in finite samples and the sensitivity of the method to its underlying assumptions. The methods can be extended in straightforward ways to accommodate multiple types of recurrent and terminal events. Finally, the methods are illustrated in an analysis of hospitalization data for patients in an international multi-center study of outcomes among dialysis patients.

Key words: Cox model; Frailty; Marginal rate function; Multivariate survival; Relative risk; Semiparametric methods.

1. Introduction

In many medical studies, subjects can experience multiple events or failures. Examples in the literature include multiple recurrences of bladder tumors, coughing and wheezing episodes in bronchial asthma patients, and repeated hospitalizations among renal failure patients. Many methods have been proposed for the analysis of repeated events. One approach is to use point processes to model the complete intensity function, where complete intensity refers to the event rate conditional on the complete preceding covariate and event history; for example, Prentice, Williams, and Peterson (1981), and Lawless (1987). Various authors have reviewed available methods for the analysis of recurrent events; for example, Kalbfleisch and Prentice (2002);Therneau and Grambsch (2000), Cook and Lawless (2002); Cai and Schaubel (2004). Cook and Lawless (2007) give an excellent synthesis and overview.

Recent approaches have been more focused on modeling the marginal rate conditional on baseline covariates, but not conditioning on the preceding event history. This marginal rate is of particular interest when the study goals relate to population aspects of failure rates and covariate effects. Lawless and Nadeau (1995) suggest Cox-type models for the marginal rate and obtain asymptotic results under a discrete failure time model. Lin et al. (2000) use empirical process theory to extend these methods to absolutely continuous event times, based on approaches analogous to the generalized estimating equation methods for longitudinal data.

In many instances, there exists a separate terminal event, death for example, which precludes the occurrence of additional repeated events. Further, it is often the case that the terminal event is strongly correlated with the recurrent event process. More explicitly, if the rate of the recurrent event is unusually high (low) in an individual, that individual is also subject to an increased (decreased) death hazard.

Methods for recurrent/terminal event data can also be classified as complete intensity or marginal. Shared random effects or frailty models incorporate the dependence between the recurrent and the terminal event by allowing a common frailty variable to have a multiplicative effect on their respective rates. These models are based on the assumption that the complete intensity of the recurrent events and the terminal event is fully specified by the observed covariates and the unobserved frailty; for example, Wang, Qin, and Chiang (2001); Huang and Wang (2004); Liu, Wolfe, and Huang (2004). In all of the existing frailty models, it is assumed that given the frailty, the recurrent event process is a nonhomogeneous Poisson process. Since this assumption is involved in all aspects of the estimation, the estimation procedures would generally be sensitive to deviations from the Poisson assumption. Ye, Kalbfleisch, and Schaubel (2007)proposed a joint semiparametric model in which the event rate is essentially a marginal model in that it is conditional only on the covariates and the frailty, but not on the previous event history of the process. However, Ye et al. (2007) used a likelihood approach to estimate the frailty parameter, which utilizes a Poisson process assumption.

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As an alternative to complete intensity models, several authors have proposed marginal models in which the rate functions correspond to average rates that would arise across the population; for example, Cook and Lawless (1997); Ghosh and Lin (2002). Such marginal methods are robust to deviations from the Poisson assumption, but the regression parameters are somewhat hard to interpret.

In this article, we develop estimating equation-based methods to estimate the marginal and association parameters in a joint frailty model. The proposed method has at least three important advantages over related approaches in existing literature. First, under the proposed approach, parameter estimation is carried out completely in the absence of the Poisson process assumption, which leads to greatly increased robustness. Second, the estimate of the common frailty distribution relates directly and only to the association between the recurrent and terminal event processes. Third, the analysis allows simple incorporation of defined time-dependent covariates that are obtained as interactions between functions of time and fixed covariates.

2. Proposed Methods: Expectation-Based Analysis

Let $N_i^{R*}(t)$ and $N_i^{D*}(t)$ denote the processes that count the true (possibly unobserved) recurrent and death events, respectively for the ith subject ($i = 1, 2, \ldots, n$) in the time interval $(0, t]$, and let D_i be the terminal event time. The censoring time is denoted by C_i, with τ being the end-of-study time. The observation time is then given by $X_i = \min(C_i, D_i, \tau)$, with $Y_i(t) = I(X_i \geqslant t)$ representing the at-risk indicator. The counting processes for the observed recurrent event and death processes are, respectively $N_i^R(t) = \int_0^t Y_i(u)\, \mathrm{d}N_i^{R*}(u)$ and $N_i^D(t) = \int_0^t Y_i(u)\, \mathrm{d}N_i^{D*}(u)$ for $t > 0$. We suppose also that a vector of fixed covariates $\boldsymbol{Z} = (Z_1, Z_2, \ldots)^{\mathrm{T}}$ is observed (at $t = 0$) on each individual and consider a vector $\boldsymbol{Z}(t) = [Z_1(t), \ldots, Z_p(t)]^{\mathrm{T}}$ of possibly time dependent modeled covariates comprised of elements of $\boldsymbol{Z}$ and interactions of components of $\boldsymbol{Z}$ with specified functions of time. Note that $\boldsymbol{Z}(t)$ is a particular example of an external time-dependent covariate (Kalbfleisch and Prentice, 2002).

Consider a (partial) marginal rate of the recurrent event process given the terminal event time $D = s$ and frailty variable γ as

$$\mathrm{d}\Lambda_R(t|\gamma) = P\big\{\mathrm{d}N^{R*}(t) = 1|\boldsymbol{Z}, D = s, \gamma\big\}, \quad s \geqslant t. \tag{1}$$

Note that $\mathrm{d}\Lambda_R(t|\gamma, \boldsymbol{Z})$ may depend on $\boldsymbol{Z}$ and the frailty γ, but as the notation indicates, it does not depend on the given death time $D = s \geqslant t$. As a consequence, this specifies that (conditional on covariates, $\boldsymbol{Z}$) γ accounts for the correlation between the recurrent events and death. Note that we also specify that $P\{\mathrm{d}N^{R*}(t) = 1|\boldsymbol{Z}, D = s, \gamma\} = 0$, $s < t$, which explicitly acknowledges that the terminal event stops the recurrent event process.

It is easy to see that a consequence of the definition (1) is that

$$\mathrm{d}\Lambda_R(t|\gamma) = P\big\{\mathrm{d}N^{R*}(t) = 1|\boldsymbol{Z}, D \geqslant t, \gamma\big\}, \tag{2}$$

so that, given γ, (1) or (2) specifies the marginal rate of the recurrent event process among those surviving to time t. In addition, we specify the hazard function for the terminal event as

$$\mathrm{d}\Lambda_D(t|\gamma) = P\big\{\mathrm{d}N^{D*}(t) = 1|\boldsymbol{Z},\ D \geqslant t, \gamma\big\}. \tag{3}$$

These marginal rates given γ, (2) and (3), could be modeled in many ways, but we consider Cox or relative risk models of the form

$$\mathrm{d}\Lambda_R(t|\gamma) = \gamma \exp\big\{\boldsymbol{\beta}^T \boldsymbol{Z}(t)\big\}\mathrm{d}\Lambda_0^R(t), \tag{4}$$

$$\mathrm{d}\Lambda_D(t|\gamma) = \gamma \exp\big\{\boldsymbol{\alpha}^T \boldsymbol{Z}(t)\big\}\mathrm{d}\Lambda_0^D(t), \tag{5}$$

where $\mathrm{d}\Lambda_0^D(t)$ and $\mathrm{d}\Lambda_0^R(t)$ are unspecified baseline hazard and rate functions for the death and recurrent event processes, respectively. We assume that the frailty γ has a gamma distribution with mean 1, variance θ, and density

$$g_\theta(\gamma) = \left\{\Gamma\left(\frac{1}{\theta}\right)\theta^{1/\theta}\right\}^{-1} \exp\left\{\frac{-\gamma}{\theta}\right\}\gamma^{1/\theta - 1}. \tag{6}$$

As is usually the case for frailty models, the mean is fixed at $E[\gamma] = 1$ for identifiability and the distribution of γ is assumed to be independent of $\boldsymbol{Z}$.

We proceed by analyzing the average rates obtained by taking the conditional expectation of (4) and (5) with respect to γ given $D \geqslant t$ and $\boldsymbol{Z}$. With the gamma frailty model, this yields the marginal rates,

$$\begin{aligned}\mathrm{d}\Lambda_R(t) &= P\big\{\mathrm{d}N^{R*}(t) = 1|D \geqslant t, \boldsymbol{Z}\big\} \\ &= w(t) \exp\big\{\boldsymbol{\beta}^T \boldsymbol{Z}(t)\big\}\mathrm{d}\Lambda_0^R(t),\end{aligned} \tag{7}$$

$$\begin{aligned}\mathrm{d}\Lambda_D(t) &= P\big\{\mathrm{d}N^{D*}(t) = 1|D \geqslant t, \boldsymbol{Z}\big\} \\ &= w(t) \exp\big\{\boldsymbol{\alpha}^T \boldsymbol{Z}(t)\big\}\mathrm{d}\Lambda_0^D(t),\end{aligned} \tag{8}$$

where the "weight function" is given by

$$w(t) = E[\gamma|D \geqslant t, \boldsymbol{Z}] = \frac{1}{1 + \theta \int_0^t \lambda_0^D(u) \exp\{\boldsymbol{\alpha}^T \boldsymbol{Z}(u)\}\, \mathrm{du}}. \tag{9}$$

Derivations of (7), (8), and (9) are provided in the Supplementary Materials.

Models (7) and (8) pertain to the underlying unobserved counting processes N^{R*} and N^{D*}, respectively. It is assumed throughout that the censoring time is conditionally independent of both the recurrent and terminal events, such that $P\{\mathrm{d}N_i^{R*}(t) = 1|D_i \geqslant t, C_i \geqslant t, \boldsymbol{Z}_i\} = P\{\mathrm{d}N_i^{R*}(t) = 1|D_i \geqslant t, \boldsymbol{Z}_i\}$ and $P\{\mathrm{d}N_i^{D*}(t) = 1|D_i \geqslant t, C_i \geqslant t, \boldsymbol{Z}_i\} = P\{\mathrm{d}N_i^{D*}(t) = 1|D_i \geqslant t, \boldsymbol{Z}_i\}$. Thus, with respect to the observed-data counting processes, we have

$$P\big\{\mathrm{d}N_i^R(t) = 1|Y_i(t), \boldsymbol{Z}_i\big\} = Y_i(t) w_i(t) \exp\big\{\boldsymbol{\beta}^T \boldsymbol{Z}_i(t)\big\}\mathrm{d}\Lambda_0^R(t), \tag{10}$$

$$P\left\{\mathrm{d}N_i^D(t)=1|Y_i(t),\boldsymbol{Z}_i\right\}=Y_i(t)w_i(t)\exp\left\{\boldsymbol{\alpha}^T\boldsymbol{Z}_i(t)\right\}\mathrm{d}\Lambda_0^D(t). \tag{11}$$

For specified $w(t)$, models (7) and (8) have a standard proportional rate/hazard form. Under independent censoring, unbiased estimating equations for $\boldsymbol{\alpha}$ and $\boldsymbol{\beta}$ can, therefore be obtained by taking the first derivatives of the pseudo partial likelihood arising from (10) and (11), treating $w_i(t)$ as a known function. Similarly, simple estimates or estimating functions are available for the underlying cumulative baseline rate and hazard, $\Lambda_0^R(t)$ and $\Lambda_0^D(t)$, again treating $w_i(t)$ as a known function. Of course, the weight function $w(t)$ in (9) must also be estimated, but we develop a recursive technique in which $w_i(t)$ is updated on each iteration in solving a set of joint estimating equations. We explicitly outline this approach shortly.

We estimate θ by constructing a separate estimating equation. For this purpose, we consider the previous number of recurrent events for a subject known to die at time t, compared to that for a subject known to be at risk of dying at time t. Along these lines, we define $r_{1i}(t)=E[N_i^{R*}(t)|\boldsymbol{Z}_i, D_i=t]$ and $r_{2i}(t)=E[N_i^{R*}(t)|D_i>t,\boldsymbol{Z}_i]$. Under the assumed models,

$$r_{1i}(t)=(\theta+1)w_i(t)\int_0^t\exp\left\{\boldsymbol{\beta}^T\boldsymbol{Z}_i(u)\right\}\mathrm{d}\Lambda_0^R(u), \tag{12}$$

$$r_{2i}(t)=w_i(t)\int_0^t\exp\left\{\boldsymbol{\beta}^T\boldsymbol{Z}_i(u)\right\}\mathrm{d}\Lambda_0^R(u), \tag{13}$$

which provides a convenient way of describing θ as an association measure, since

$$\theta+1=\frac{r_{1i}(t)}{r_{2i}(t)}. \tag{14}$$

For instance, if $\theta=1$, the expected number of recurrent events in $(0,t]$ for an individual with $D=t$ is twice the expected number for a randomly chosen individual with identical covariates but $D_i\geqslant t$. On the other hand, if $\theta=0$, the expectations for the two subjects would be equal, which indicates a lack of association between the death and recurrent event processes, conditional on the covariates.

The relationship (14) leads to the following estimating function for θ,

$$\sum_{i=1}^n\int_0^\tau\left\{N_i^R(t)-(\theta+1)\overline{G}(t)r_{2i}(t)\right\}\mathrm{d}N_i^D(t), \tag{15}$$

where we define

$$\overline{G}(t)=\frac{\sum_{j=1}^n r_{2j}(t)^{-1}Y_j^*(t)N_j^R(t)}{\sum_{j=1}^n Y_j^*(t)}. \tag{16}$$

where $Y_j^*(t)=Y_j(t)\{1-N_j^D(t)\}$ is an indicator that j is at risk at t and fails after t. Note that when the modeled covariates are time-independent, $\boldsymbol{Z}_i(t)=\boldsymbol{Z}_i$, the estimating function simplifies considerably since $\overline{G}(t)r_{2i}(t)$ no longer depends on $\Lambda_0^R(t)$. A demonstration of the unbiasedness of (15) is provided in the Supplementary Materials.

In summary, $\boldsymbol{\beta}$ can be estimated using a weighted version of the estimating function proposed in Lin et al. (2000), while $\boldsymbol{\alpha}$ can be estimated through a weighted partial likelihood score function. The baseline hazard and rate functions are estimated using weighted Breslow-type estimators. In addition, θ can be estimated as the solution to an unbiased estimating equation. Since estimation of each parameter depends on knowledge of at least a subset of the remaining parameters, the proposed estimating equations must be solved iteratively.

First, for a parameter ϕ (e.g., $\phi=\boldsymbol{\alpha}$), define

$$S_1^{(d)}(\phi,t)=n^{-1}\sum_{i=1}^n Y_i(t)w_i(t)\boldsymbol{Z}_i^{\otimes k}(t)\exp\left\{\phi^T\boldsymbol{Z}_i(t)\right\},$$

for d=0,1,2, where $a^{\otimes 0}=1$, $a^{\otimes 1}=a$, and $a^{\otimes 2}=aa^T$. Further, let $t_1^R,\ldots,t_{n_R}^R$ be the n_R ordered *observed* distinct recurrent event times (across all subjects) and $t_1^D,\ldots,t_{n_D}^D$ be the n_D ordered distinct *observed* failure times. Standard estimates of the baseline recurrent event rates and the baseline hazard are discrete with jumps at the distinct event times. Let $\lambda_0^R=(\lambda_{01}^R,\lambda_{02}^R,\ldots,\lambda_{0n_R}^R)^T$ and $\lambda_0^D=(\lambda_{01}^D,\lambda_{02}^D,\ldots,\lambda_{0n_D}^D)^T$, where $\lambda_{0j}^R=\mathrm{d}\Lambda_0^R(t_j^R)$, $j=1,\ldots,n_R$ and $\lambda_{0j}^D=\mathrm{d}\Lambda_0^D(t_j^D)$, $j=1,\ldots,n_D$. Let d_j^R and d_j^D be the number of recurrent events at t_j^R and the number of deaths at t_j^D, respectively.

Letting $\eta=(\boldsymbol{\beta}^T,\boldsymbol{\alpha}^T,\theta,[\lambda_0^D]^T,[\lambda_0^R]^T)^T$, the unbiased estimating equations are

$$U(\eta)=\left(U_1^T,U_2^T,U_3,U_4^T,U_5^T\right)^T=0,$$

where we have

$$U_1=\sum_{i=1}^n\int_0^\tau\left\{\boldsymbol{Z}_i-\frac{S_1^{(1)}(\boldsymbol{\beta},t)}{S_1^{(0)}(\boldsymbol{\beta},t)}\right\}\mathrm{d}N_i^R(t),$$

$$U_2=\sum_{i=1}^n\int_0^\tau\left\{\boldsymbol{Z}_i-\frac{S_1^{(1)}(\boldsymbol{\alpha},t)}{S_1^{(0)}(\boldsymbol{\alpha},t)}\right\}\mathrm{d}N_i^D(t),$$

$$U_3=\sum_{i=1}^n\int_0^\tau\left\{N_i^R(t)-(\theta+1)r_{2i}(t)\overline{G}(t)\right\}\mathrm{d}N_i^D(t),$$

whereas the jth elements of U_4 and U_5 are,

$$U_{4j}=d_j^D-nS_1^{(0)}(\boldsymbol{\alpha},t_j^D)\lambda_{0j}^D,\quad j=1,\ldots,n_D$$

$$U_{5j}=d_j^R-nS_1^{(0)}(\boldsymbol{\beta},t_j^R)\lambda_{0j}^R,\quad j=1,\ldots,n_R.$$

Our numerical approach to solving $U(\eta)=0$ can be summarized as follows:

(i) Let $\eta^{(0)}=(\boldsymbol{\alpha}^{(0)},\boldsymbol{\beta}^{(0)},\theta^{(0)},\lambda_0^{D(0)},\lambda_0^{R(0)})$ be initial estimates, an issue address below.
(ii) Let $w_i^{(0)}(u)=w_i(u;\lambda_0^{D(0)},\boldsymbol{\alpha}^{(0)},\theta^{(0)})$.

(iii) Replace $w_i(u)$ with $w_i^{(0)}(u)$ in $U_1 = 0$, $U_2 = 0$, $U_4 = 0$, and $U_5 = 0$ and solve for updated estimates $\boldsymbol{\beta}^{(1)}$, $\boldsymbol{\alpha}^{(1)}$, $\lambda_0^{D(1)}$, and $\lambda_0^{R(1)}$.

(iv) Given $\boldsymbol{\alpha}^{(1)}$, $\boldsymbol{\beta}^{(1)}$, $\lambda_0^{D(1)}$, and $\lambda_0^{R(1)}$, $w_i^{(1)}(u) = w_i(u; \lambda_0^{D(1)}, \boldsymbol{\alpha}^{(1)}, \theta^{(0)})$, obtain $\theta^{(1)}$ by solving $U_3 = 0$.

(v) Replace $\eta^{(0)}$ with $\eta^{(1)}$ and repeat step (ii) to (iv) until convergence is obtained.

For initial values, one could take $\theta^{(0)} = 1$, $\boldsymbol{\alpha}^{(0)} = 0$, $\boldsymbol{\beta}^{(0)} = 0$, and set $\lambda_0^{D(0)}$ and $\lambda_0^{R(0)}$ to their respective Nelson–Aalen type estimates. An alternative (which reduces the number of required iterates somewhat) is to set $\boldsymbol{\alpha}^{(0)} = \widetilde{\boldsymbol{\alpha}}$ and $\boldsymbol{\beta}^{(0)}$ to $\widetilde{\boldsymbol{\beta}}$, where $\widetilde{\boldsymbol{\alpha}}$ and $\widetilde{\boldsymbol{\beta}}$ are based on separately fitted Cox-type models which ignore the frailty; then set $\lambda_0^{D(0)}$ and $\lambda_0^{R(0)}$ to the increments of the corresponding Breslow-type estimators. Either way, the above algorithm has been found to converge quite quickly based on simulations and various real-data applications.

Typically, the parameter vector $(\boldsymbol{\beta}^T, \boldsymbol{\alpha}^T, \theta)^T$ will be of chief interest, with $\Lambda_0^D(\cdot)$ and $\Lambda_0^R(\cdot)$ treated as nuisance parameters. We propose that the variance of $(\widehat{\boldsymbol{\beta}}^T, \widehat{\boldsymbol{\alpha}}^T, \widehat{\theta})^T$ be estimated by the appropriate submatrix of the robust variance estimator, $\hat{A}^{-1}\hat{\Sigma}(\hat{A}^{-1})^{\mathrm{T}}$, where $\hat{\eta}$ is the estimator of η, $\hat{A} = A(\hat{\eta})$, $A(\eta) = -n^{-1}\partial U(\eta)/\partial \eta^T$, $\hat{\Sigma} = \Sigma(\hat{\eta})$, and $\Sigma(\eta) = n^{-1}\sum_{i=1}^n \widehat{\xi}_i(\eta)^{\otimes 2}$. The vector $\xi_i = (\xi_{i1}^T, \xi_{i2}^T, \xi_{i3}, \xi_{i4}^T, \xi_{i5}^T)^T$ represents the asymptotic score function contributions, with

$$\xi_{i1} = \int_0^\tau \left\{ \boldsymbol{Z}_i - \frac{s_1^{(1)}(\boldsymbol{\beta}, t)}{s_1^{(0)}(\boldsymbol{\beta}, t)} \right\} \mathrm{d}M_i^R(t),$$

$$\xi_{i2} = \int_0^\tau \left\{ \boldsymbol{Z}_i - \frac{s_1^{(1)}(\boldsymbol{\alpha}, t)}{s_1^{(0)}(\boldsymbol{\alpha}, t)} \right\} \mathrm{d}M_i^D(t),$$

$$\xi_{i3} = \int_0^\tau \left\{ N_i^R(t) - (\theta+1) r_{2i}(t) \overline{g}(t) \right\} \mathrm{d}N_i^D(t),$$

$$\xi_{i4j} = \mathrm{d}M_i^D(t_j^D), \quad j = 1, \ldots, n_D \tag{17}$$

$$\xi_{i5k} = \mathrm{d}M_i^R(t_k^R), \quad k = 1, \ldots, n_R \tag{18}$$

where $s_1^{(d)}(\phi, t)$ is the limiting value of $S_1^{(d)}(\phi, t)$ for $d = 0, 1, 2$ and $\phi = \boldsymbol{\beta}, \boldsymbol{\alpha}$, $\mathrm{d}M_i^D(t) = \mathrm{d}N_i^D(t) - Y_i(t) w_i(t) \exp\{\boldsymbol{\alpha}^T \boldsymbol{Z}_i(t)\} \mathrm{d}\Lambda_0^D(t)$, $\mathrm{d}M_i^R(t) = \mathrm{d}N_i^R(t) - Y_i(t) \exp\{\boldsymbol{\beta}^T \boldsymbol{Z}_i(t)\} w_i(t) \mathrm{d}\Lambda_0^R(t)$, and $\overline{g}(t)$ is the limiting value of $\overline{G}(t)$. To obtain $\widehat{\xi}_i$ $(i = 1, \ldots, n)$, one merely substitutes empirical values in place of their respective limiting values. Having obtained standard error estimates, confidence intervals could be computed and Wald tests conducted via the normal approximation.

A rigorous derivation of the asymptotic properties of the proposed estimators appears to be quite involved and, hence, is outside the scope of the current article. A proof of asymptotic normality could proceed by demonstrating that $n^{1/2}(\widehat{\eta} - \eta_0) = A^{-1} n^{-1/2} \sum_{i=1}^n \xi_i + o_p(1)$, where A is as defined above and the ξ_i $(i = 1, \ldots, n)$ are independent and identically distributed mean zero variates with structure given above. Under such asymptotic linearity, the proposed robust variance estimator would be valid. Note that the inference we consider only applies to the subvector, $(\widehat{\boldsymbol{\beta}}^T, \widehat{\boldsymbol{\alpha}}^T, \widehat{\theta})^T$. The proposed inference procedures make sense intuitively from two angles. First, suppose that the baseline hazard and rate functions were parametric depending on a finite set of real valued parameters, $\boldsymbol{\kappa}$ say. Then, under differentiability conditions, unbiased estimating equations for the components of $\boldsymbol{\kappa}$ can be obtained to replace those in (17) and (18). The resulting estimating equations would then be of fixed dimension and usual asymptotic results would hold under assumptions of finite variance and differentiability. The resulting asymptotic normal distribution for the estimators would have an estimated covariance matrix of the sandwich type. Further, as the parametric model for the rate functions became richer, one would expect estimates of $\boldsymbol{\beta}$, $\boldsymbol{\alpha}$, and θ to become close to those obtained from the semi-parametric analysis discussed above. Second, in the semiparametric setting, it would appear that results analogous to those of Murphy (1995) and Parner (1998) for nonparametric maximum likelihood could be used to demonstrate the consistency and asymptotic normality of the finite-dimensional component of $\widehat{\eta}$. However, the estimating equations we propose are not likelihood-based.

The dimension of A can be large since there would be a component at each observed failure or recurrent event time, but at least in moderate sized problems can be easily handled with current software. Calculation difficulties for large samples can be addressed by using the fact that the matrix of partial derivatives of U_5 with respect to the λ_0^R components is diagonal. Let $\eta_1^T = (\boldsymbol{\beta}^T, \boldsymbol{\alpha}^T, \theta, [\lambda_0^D]^T)$, $\eta_2 = \lambda_0^R$, $U^{(1)}(\eta) = (U_1^T, U_2^T, U_3, U_4^T)$, and $U^{(2)}(\eta) = U_5^T$. It follows that

$$A = \begin{pmatrix} A_{11} & A_{12} \\ A_{21} & A_{22} \end{pmatrix} = -n^{-1} \begin{pmatrix} \partial U^{(1)}(\eta)/\partial \eta_1^T & \partial U^{(1)}(\eta)/\partial \eta_2^T \\ \partial U^{(2)}(\eta)/\partial \eta_1^T & \partial U^{(2)}(\eta)/\partial \eta_2^T \end{pmatrix}.$$

The dimension of A is $2p + 1 + n_R + n_D$, which may be large as the sample size increases and direct numerical inversion may be time consuming. Computation is simplified, however, by utilizing the diagonal structure of A_{22}

$$A^{-1} = \begin{pmatrix} J^{-1} & -J^{-1}F_2 \\ -F_1 J^{-1} & A_{22}^{-1} + F_1 J^{-1} F_2 \end{pmatrix},$$

where $F_1 = A_{22}^{-1} A_{21}$, $F_2 = A_{12} A_{22}^{-1}$, and $J = A_{11} - A_{12} F_1$. Thus, a matrix of dimension only $2p + 1 + n_D$ needs to be inverted directly. A further simplification is also possible by utilizing the fact that the partial derivatives of U_4 with respect to Λ_0^D is upper triangular and again simple to invert.When there are no time dependent covariates, the computation is further simplified since λ_0^R does not need to be estimated simultaneously.

3. Robustness of the Expectation-Based Method

In this section, we evaluate the robustness properties of the approach proposed in Section 2, which we refer to as the expectation-based method. Specifically, we examine the effect of departures from the Poisson process assumption.

Ye et al. (2007) considered a model similar to that outlined here, but employed maximum likelihood for the purposes of

estimating θ. As such, a complete intensity model was required, and it was assumed that, given γ and $\boldsymbol{Z}$, the recurrent event process $N^{R*}(t)$ was a nonhomogeneous Poisson process with conditional intensity $\mathrm{d}\Lambda_R(t|\gamma)$ with the same form as in (4).

Unlike existing shared-frailty models, the semiparametric analysis we propose completely drops the Poisson process assumption. Instead of modeling the complete intensity, $E[\mathrm{d}N^{R*}(t)|\mathcal{F}_{t-}]$, where $\mathcal{F}_t$ is the σ-field generated by $\{N^{R*}(u), N^{D*}(u), \boldsymbol{Z}, \gamma : 0 \le u \le t\}$, the marginal rate $E[\mathrm{d}N^{R*}(t)|\boldsymbol{Z}, \gamma, D \geqslant t]$ is modeled. Thus, given γ, the proposed approach allows for arbitrary dependence structure among the recurrent events. The influence of the prior events on the recurrent process or any possibly unknown factors is no longer required to be captured by the covariates $\boldsymbol{Z}(t)$ or γ in the model.

In both the expectation-based analysis and the likelihood analysis, θ can be interpreted in terms of the ratio of $r_{1i}(t)/r_{2i}(t) = \theta + 1$. In the expectation-based method, however, this relationship is the basis of the estimating function (15) and the estimate of θ reflects the association between the recurrent and terminal event processes only. In the likelihood analysis and the related score function. However, the magnitude of $\hat{\theta}$ not only reflects the association between the recurrent and terminal event processes, but also measures the correlation among the recurrent events. Thus, for example, if the two processes are weakly associated but the recurrent events are highly correlated with each other, then the association between recurrent and terminal event processes will tend to be overestimated by $\hat{\theta}$.

To illustrate this point, let $\mathcal{F}_t = \sigma\{N_i^R(u), N_i^D(u), Y_i(u), \boldsymbol{Z}_i,\ i = 1, \ldots, n; 0 \le u \le t\}$ record the full history of the recurrent event and failure time processes and consider a frailty model for complete intensities given by

$$\begin{aligned}\mathrm{d}\Lambda_R^{\dagger}(t;\boldsymbol{Z}) &= P\left\{\mathrm{d}N^R(t) = 1|\mathcal{F}_{t^-}, \gamma\right\} \\ &= \gamma\delta\mathrm{d}\Lambda_0^R(t)\exp\left\{\boldsymbol{\beta}^T\boldsymbol{Z}(t)\right\}, \qquad (19)\\ \mathrm{d}\Lambda_D^{\dagger}(t;\boldsymbol{Z}) &= P\left\{\mathrm{d}N^{R*}(t) = 1|\mathcal{F}_{t^-}, \gamma\right\} \\ &= \gamma\mathrm{d}\Lambda_0^D(t)\exp\left\{\boldsymbol{\alpha}^T\boldsymbol{Z}(t)\right\}, \qquad (20)\end{aligned}$$

where γ is a shared gamma frailty as before and δ is a second frailty variable with unit mean and positive variance that is distributed independently of $\boldsymbol{Z}$, D, and γ. Thus, given γ and δ, the process N^{R*} is a Poisson process that is stopped by the death time D. Note that the marginal event rate for $N^{R*}(t)$ given only $\boldsymbol{Z}, \gamma$, and $D \geqslant t$ is still given by $\gamma\mathrm{d}\Lambda_0^R(t)\exp\{\boldsymbol{\beta}^T\boldsymbol{Z}(t)\}$ as in (4). On the one hand, the Poisson process assumption for the recurrent event process in a shared frailty model with γ only is not valid in this case since the recurrent events will be correlated (even given γ and $\boldsymbol{Z}$) due to the frailty δ. Therefore, the methods based on complete intensities described in Wang et al. (2001), Huang and Wang (2004), Liu et al. (2004), or Ye et al. (2007) are no longer valid. On the other hand, the expectation analysis of Section 2 builds an estimating equation in which θ reflects only the correlation between the two processes and would be fully valid for the situation described in (19) and (20).

Some discussion of model checking is in order. Arguably our strongest assumption is that of proportionality, which applies to both the recurrent event model (10) and the terminating event hazard model (11). In both cases, although the baseline rate function is flexibly specified, covariate effects are assumed to be constant across follow-up time. For each model, this assumption can be evaluated using techniques analogous to those typically employed for the proportional hazards model. For example, by appropriately expanding the covariate vector, one can allow for covariate functions which vary parametrically over time; for example, as described in Kalbfleisch and Prentice (2002). For instance, see Schaubel and Cai (2005) for an example in the context of a recurrent event rate model similar to (10). Proportionality can then be tested using Wald tests of the corresponding additional parameters. With respect to the Gamma frailty assumption, the estimating function for θ, given in (15), is derived by taking the mean for fixed t, then integrating over $(0, \tau]$, as detailed in the Supplementary Materials. In principle, one could partition $(0, \tau]$ into subintervals (e.g., quintiles, based on the observed deaths), then compute quintile-specific $\widehat{\theta}_j$ values ($j = 1, \ldots, 5$), fixing $\widehat{\boldsymbol{\alpha}}$ and $\widehat{\boldsymbol{\beta}}$ at their originally estimated values. Considerably disparate $\{\widehat{\theta}_1, \ldots, \widehat{\theta}_5\}$ would indirectly provide evidence that the Gamma frailty assumption is not satisfied.

4. Extension to Terminating Events with Competing Risks

The proposed method can be extended to more complicated settings, including cases where there is more than one type of terminating event. Suppose there are two competing risks for the terminal event and for simplicity, we consider only time-independent covariates, $\boldsymbol{Z}$, in the model. Note that time-dependent covariates can be easily handled as in Section 2. As before, let D_i and C_i be the terminal event time and the censoring time for individual i. Let Δ_i be the terminal event type, taking the value ℓ if subject i has a type ℓ failure, $\ell = 1, 2$. Conditional on $\boldsymbol{Z}_i$ and γ, C_i is assumed independent of D_i and the recurrent event process. Let $X_i = \min(D_i, C_i, \tau)$ and, as before, let $Y_i(t) = I(X_i \geqslant t)$ be the at risk process. In this case, we define counting processes for the underlying (possibly unobserved due to censoring) recurrent events and failure types as $N^{R*}(t)$ and $N^{D_{\ell}*}(t)$, $\ell = 1, 2$. The corresponding observed counting processes are $N^R(t)$ and $N^{D_\ell}(t)$, $\ell = 1, 2$. Let γ_1 and γ_2 be independent gamma frailty variables with unit mean and variances θ_1 and θ_2, respectively; it is assumed that γ_1 and γ_2 are distributed independently of $\boldsymbol{Z}_i$. The models we consider are

$$P\left\{\mathrm{d}N^{R*}(t) = 1|D \geqslant t, \gamma, \boldsymbol{Z}\right\} = \gamma_1\gamma_2\mathrm{d}\Lambda_0^R(t)\exp\left\{\boldsymbol{\beta}^T\boldsymbol{Z}\right\}, \qquad (21)$$

$$P\left\{\mathrm{d}N^{D_{\ell}*}(t) = 1|D \geqslant t, \gamma, \boldsymbol{Z}\right\} = \gamma_\ell\mathrm{d}\Lambda_{0\ell}^D(t)\exp\left\{\boldsymbol{\alpha}_\ell^T\boldsymbol{Z}\right\}\ \ \ell = 1, 2. \qquad (22)$$

Note that (22) defines cause-specific hazard functions (Kalbfleisch and Prentice, 2002; p. 251) and specify the rate (given γ) of type 1 and type 2 failures, respectively among individuals alive at time t. In this, γ_ℓ models the correlation between the type ℓ failure rates and the recurrent event process, $\ell = 1, 2$. Taking expectations of (21), (22) and given $D \geqslant t$

and $\boldsymbol{Z}$ yields the corresponding marginal models,

$$P\left\{\mathrm{d}N_i^R(t)=1|Y_i(t),\boldsymbol{Z}_i\right\} = Y_i(t)w_1(t)w_2(t)\mathrm{d}\Lambda_0^R(t)\exp\left\{\boldsymbol{\beta}^T\boldsymbol{Z}_i\right\}, \quad (23)$$

$$P\left\{\mathrm{d}N_i^{D_\ell}(t)=1|Y_i(t),\boldsymbol{Z}_i\right\} = Y_i(t)w_\ell(t)\mathrm{d}\Lambda_{0\ell}^D(t)\exp\left\{\boldsymbol{\alpha}_\ell^T\boldsymbol{Z}_i\right\} \quad \ell=1,2. \quad (24)$$

In these expressions,

$$w_\ell(t) = E\left[\gamma_\ell|D\geqslant t,\boldsymbol{Z}\right] = \left[1+\theta_\ell\Lambda_{0\ell}^D(t)\exp\left\{\boldsymbol{\alpha}_\ell^T\boldsymbol{Z}\right\}\right]^{-1}, \quad \ell=1,2$$

$$w_3(t) = E\left[\gamma_1\gamma_2|D\geqslant t,\boldsymbol{Z}\right] = w_1(t)w_2(t).$$

Let $r_{1i}^\ell(t)=E[N_i^R(t)|\mathrm{d}N_i^{D_\ell}(t)=1,\boldsymbol{Z}_i]$, $\ell=1,2$ and $r_{2i}(t)=E[N_i^R(t)|Y_i(t)=1,\boldsymbol{Z}_i]$. Then it can be seen that $r_{1i}^\ell(t)/r_{2i}(t)=\theta_\ell+1$, $\ell=1,2$ and, in this sense, θ_1 and θ_2 measure the association between the recurrent event process and the two failure types. This relationship also leads to simple estimating equations for θ_1 and θ_2 as discussed below.

Analysis now proceeds very much as in the case of a single failure type as discussed in Section 2. Details are provided in the Supplementary Materials.

5. Simulation Studies

Simulations were carried out using a single binary covariate, Z, taking values 1 or 0 with probability 0.5, and various settings labeled A–F, which are listed in Table 1. The censoring time was taken to follow a continuous uniform distribution on $[1,10]$. Given the frailty γ and the covariate Z, a subject's recurrent events were generated from a Poisson process with intensity function $\mathrm{d}\Lambda_R(t|\gamma,Z)=\gamma\exp(\beta Z)\mathrm{d}t$. The terminal event time was generated from an exponential distribution with hazard $\mathrm{d}\Lambda_D(t)=0.2\gamma\exp(\alpha Z)\mathrm{d}t$. Thus $\Lambda_0^R(t)=t$ and $\Lambda_0^D(t)=0.2t$.

In settings A, B, C, and D, the frailty variate γ followed a gamma distribution with unit mean and variance θ. In Settings E and F, we examined the performance of the proposed estimators when the gamma distribution is misspecified. In setting E, γ has a lognormal distribution with unit mean and variance 0.65. In setting F, γ is generated as one-tenth of a Poisson variable with mean 10.

From Table 2, it can be seen that the estimators are nearly unbiased for α and β in all cases considered, including settings E and F when γ does not follow a gamma distribution. There is also no evidence of bias for θ when the frailty distribution is correctly specified (settings A–D). The variance estimates are accurate and the associated coverage probabilities are close to the nominal level of 0.95 in all settings, including those in which the distribution of γ was misspecified (E and F). The final column in each setting of Table 2 gives the estimated standard errors from Ye et al. (2007). The empirical standard errors for $\hat{\alpha}$ and $\hat{\beta}$ are only slightly larger for the expectation-based analysis. This is important since α and β are usually of primary interest. The variance of $\hat{\theta}$ increases substantially as a result of dropping the Poisson assumption.

Table 1
Settings for the simulation study $n=200$

Settings	A	B	C	D	E	F
α	0.5	0.5	0	0	0.5	0.5
β	0.5	0.5	0	0	0.5	0.5
θ	0.5	1	0.5	1	NA	NA
$E[m_i]$	3.05	2.73	2.72	2.45	3.05	3.38
$E[\Delta_i]$	61.2%	54.5%	54.3%	49%	61.1%	67.4%

$E[m_i]$: average number of recurrent events per subject.
$E[\Delta_i]$: average percentage of subjects who experience the terminal event.
For setting E, the frailty followed a lognormal distribution.
For setting F, the frailty was generated as a scaled Poisson variate.

The potential increase in efficiency offered by the likelihood analysis, with respect to $\widehat{\theta}$, needs to be judged in light of the facts that θ will often be of secondary interest, and that the increased precision is due in large measure to the fact that θ also measures correlations among the recurrent events in that model. Note that the maximum likelihood estimates were also approximately unbiased (data not tabulated).

We also simulated some data configurations where extra between subject variation is allowed for the recurrent event process, as described in (19) and (20). For example, in setting G, the frailty variables, γ and δ, were generated from independent gamma distributions with unit mean and variances $\theta=0.5$ and $\theta=1$, respectively. Other aspects were as described by setting A in Table 1 with $\beta=0.5$, $\alpha=0.5$, $\Lambda_0^R(t)=t$, and $\Lambda_0^D(t)=0.2t$ and recurrent events were generated from the Poisson process (given γ and δ). Table 3 summarizes results under setting G by comparing the expectation-based analysis with the likelihood analysis in Ye et al. (2007). As anticipated, the likelihood method substantially overestimates $var(\gamma)=\theta$. On the other hand, the marginal analysis is more robust since the estimate of θ does not reflect the correlation among recurrent events, but only measures the association between the two processes.

6. Application

The Dialysis Outcomes and Practice Patterns Study (DOPPS) is a well-known international study of end-stage renal disease patients receiving hemodialysis. The DOPPS has now gone on for many years and includes several phases. Detail regarding the design of the DOPPS study have been described by Young et al. (2000). Subjects receiving dialysis are typically patients whose kidney function has declined to the point that they would be unable to survive without some form of renal replacement therapy. Although death is arguably the most important endpoint studied in this patient population, hospitalizations are also very important. First, hospital admissions reflect morbidity and therefore quality of life. Second, hospitalization are inextricably tied to health care costs. Relatively few analyses of end-stage renal disease patients have used hospitalization as the outcome.

We applied the proposed methods to jointly analyze the death hazard and hospitalization rate given survival among patients in the European component of the DOPPS

Table 2
Simulation results for the expectation-based method in the marginal rate (MR) model (n=200)

Based on 1000 simulated samples										
	Setting *A*					Setting *B*				
MR model	Bias	CSE	ESE	95% CP	ESE*	Bias	CSE	ESE	95% CP	ESE*
$\hat{\beta}$	−0.007	0.150	0.160	0.926	0.149	−0.004	0.205	0.207	0.945	0.220
$\hat{\alpha}$	0.001	0.228	0.233	0.942	0.229	−0.003	0.277	0.266	0.964	0.275
$\hat{\theta}$	0.006	0.131	0.129	0.936	0.091	0.013	0.210	0.221	0.927	0.154
	Setting *C*					Setting *D*				
MR model	Bias	CSE	ESE	95% CP	ESE*	Bias	CSE	ESE	95% CP	ESE*
$\hat{\beta}$	−0.005	0.153	0.159	0.935	0.160	−0.007	0.205	0.204	0.948	0.206
$\hat{\alpha}$	−0.006	0.231	0.233	0.946	0.242	−0.008	0.278	0.272	0.964	0.277
$\hat{\theta}$	0.002	0.135	0.141	0.931	0.091	0.016	0.211	0.221	0.942	0.154
	Setting *E*					Setting *F*				
MR model	Bias	CSE	ESE	95% CP	ESE*	Bias	CSE	ESE	95% CP	ESE*
$\hat{\beta}$	0.007	0.152	0.157	0.940	0.145	0.005	0.089	0.096	0.925	0.098
$\hat{\alpha}$	0.004	0.215	0.220	0.947	0.213	0.004	0.181	0.186	0.950	0.185

CSE, mean of calculated standard error; ESE, empirical standard error; 95% CP, 95% confidence interval coverage probability.
ESE*, empirical standard error from likelihood method, Ye et al. (2007).
For setting *E*, the frailty followed a lognormal distribution.
For setting *F*, the frailty was generated as a scaled Poisson variate.

(Euro-DOPPS). Euro-DOPPS consisted of 101 facilities from Germany, France, Italy, Spain, and the United Kingdom. For the cohort used in the current analysis, data collection began in 1998 and follow-up information was available until December 31, 2002. In an attempt to reconstruct an incident cohort, the study population in this analysis only included patients who had been on dialysis for less than 1 month at the time of entering the study ($n = 1158$).

The primary objective of our analysis was to compare hospitalization rates and mortality hazards by country. In particular, each of Germany, France, Italy, Spain were compared to the United KingdomU.K., which served as the reference. Adjustment covariates included age (5-year increments), sex (ref: female), diabetes (yes/no; ref: non-diabetic), education level (some college vs. lower), body mass index (BMI; categorized), as well as various comorbid conditions coded as yes/no (ref: no): cerebral vascular disease, congestive heart failure, coronary heart or artery disease, hypertension, and peripheral vascular disease.

Table 4 lists results based on our first model, in which all deaths were combined. DOPPS patients from Italy experienced an all-cause mortality hazard of more than double ($e^{0.780} = 2.18$) that of patients from the U.K. (p=0.041). Relative to the U.K., the hospitalization rate was significantly decreased by approximately 1/3 for patients from Germany $e^{-0.372} = 0.69$; p=0.037) and by about 1/2 for patients from Spain ($e^{-0.666} = 0.51$; $p < 0.001$). The impact of age appeared to be much stronger for death (25% increase per 5-year increase) than for hospitalization (3% increase). Covariate effects are interpreted as conditional on the unobserved frailty γ as in the models,(4) and (5). Thus, conditional on γ and among the comorbidities evaluated, cerebral vascular disease, hypertension, and peripheral vascular disease were significant predictors of mortality; while, again conditional on γ, only hypertension and peripheral vascular disease significantly predicted the hospitalization rate.

The frailty parameter was estimated to be $\hat{\theta} = 1.33$ with an estimated standard error of 0.22 (p<0.001). From (14),

Table 3
Simulation results for the MR model under setting G: robustness issues when extra variation presents in recurrent event process (n = 200)

	Likelihood method				Expectation method			
MR model	Bias	CSE	ESE	95% CP	Bias	CSE	ESE	95% CP
$\hat{\beta}$	0.164	0.214	0.292	0.695	−0.013	0.232	0.246	0.930
$\hat{\alpha}$	0.175	0.242	0.319	0.716	0.006	0.233	0.231	0.952
$\hat{\theta}$	0.761	0.142	0.266	0	0.015	0.233	0.210	0.951

Table 4
Expectation-based analysis of Euro-DOPPS data based on a single mode of failure (all-cause mortality)

	Death			Hosptilization		
Covariate	$\hat{\boldsymbol{\alpha}}$	$\widehat{SE}$	p	$\hat{\boldsymbol{\beta}}$	$\widehat{SE}$	p
Diabetes	−0.082	0.281	0.771	0.177	0.128	0.167
Sex = M	−0.133	0.229	0.562	−0.102	0.109	0.349
Educ: ⩾college	−0.619	0.539	0.251	−0.269	0.168	0.110
Country						
France	0.578	0.398	0.146	0.180	0.162	0.264
Germany	−0.295	0.456	0.517	−0.372	0.178	0.037
Italy	0.780	0.382	0.041	−0.222	0.176	0.207
Spain	0.261	0.406	0.521	−0.666	0.165	<0.001
U.K.	0	—	—	0	—	—
Age per 5 years	0.221	0.050	<0.001	0.028	0.021	0.180
Body mass index						
< 20	0.209	0.316	0.508	0.033	0.146	0.823
⩾ 30	−0.441	0.386	0.254	0.046	0.165	0.782
∈ [20, 30)	0	—	—	0	—	—
Comorbid conditions						
Cerebral vascular disease	0.859	0.276	0.002	0.155	0.133	0.241
CHF	0.479	0.256	0.062	0.122	0.132	0.357
CHD/CAD	0.410	0.264	0.120	0.159	0.123	0.195
Hypertension	−0.938	0.256	<0.001	−0.324	0.138	0.019
PVD	0.744	0.281	0.008	0.310	0.131	0.018

this estimate suggests that a patient who is known to die at time t is expected to have more than twice (2.33) as many hospitalizations as a patient with identical covariates who has not died at time t.

Further analyses of the DOPPS data that take account of competing risks for death of CVD or non-CVD can be found in the Supplementary Materials.

7. Discussion

There are many areas in the proposed method which can possibly be improved or investigated further. The estimating equation for θ, (15), is built by using the ratio of the two moments, $E[N^{R*}(t)|Y(t) = 1, Z(t), \mathrm{d}N^{D*}(t) = 1]$ and $E[N^{R*}(t)|Y(t) = 1, Z(t), \mathrm{d}N^{D*}(t) = 0]$. The idea is simple and natural. However, the estimating equation could be built differently. For example, we could use ratios of different moments, such as the ratio between $E[N^{R*}(t)|Y(t) = 1, Z, \mathrm{d}N^{D*}(s) = 1]$ and $E[N^{R*}(t)|Y(t) = 1, Z, \mathrm{d}N^{D*}(s) = 0]$, where $s \geqslant t$. How to combine all the information available to build an estimating equation to increase efficiency and reach optimality remains an open question.

It should be noted that the methods in this article can be extended to allow for negative association between the terminal and recurrent event rates as might arise, for example, if the recurrent events were vaccinations and the terminal event was the occurrence of disease. To do this, we specify γ^{-1} as the frailty in the recurrent event process and retain γ as the frailty in the death process, where γ has a gamma distribution with mean 1 and variance θ as before and it is assumed that $\theta < 1$ for finite expectation of γ^{-1}. In this case, it can be seen that $r_{1i}(t) = (1 - \theta)r_{2i}(t), i = 1, \ldots, n; t > 0$. Thus, the same estimating Equation (14) with $1 + \theta$ replaced with $1 - \theta$ can be used. If $\theta = 1/3$ for example, an individual failing at t would be expected to have $1 - \theta = 2/3$ as many failures as one with the same covariates who survives past time t. This reflects a measure of the negative association between the rates. More detail is given in the Supplementary Material where it is also noted that the approach can be generalized to accommodate simultaneously both positive and negative correlation.

8. Supplementary Materials

Web Appendices referenced in Sections 2, 4, 6, and 7 are available with this article at the *Biometrics* website on Wiley Online Library.

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