Prediction of Time to a Terminal Event (TTTE) of New Units in a Dynamic Recurrent Competing Risks Model

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Abstract

In this paper, we propose a simulation approach to predict time to terminal event (TE) that arises from joint dynamic modelling. Many joint dynamic models have found applications in medical research. Predicting terminal event times is often in the most interest due to its value as a prognostic tool in medical treatments and the complexity in developing appropriate prediction methodology. When a joint dynamic model gets more complicated, the computational aspect of predicting TE can be particularly challenging. An alternative, which is simulating censored event times according to history of data accrual has not been considered in previous works, to our knowledge. Based on the class of joint dynamic models of recurrent competing risks (RCR) and terminal event (TE) in \[9\], we demonstrate how to predict terminal event (TE) times by the simulation approach. We also point out the size-biased sampling related to gap time that traverses monitoring time.

1 Introduction

In recent years, joint dynamic modelling that deals with predicting time to terminal event (TE) has gained increasing attention (\[11\], \[13\] and \[16\]). The ability to make individual predictions based on an observational unit’s history is very attractive in a wide variety applications, in particular, precision medicine. Many of the joint dynamic models deal with simultaneously modeling a longitudinal marker process and a survival outcome (\[18\], \[17\], and \[12\]). There has been fewer joint dynamic models that link a recurrent event and a survival status (\[8\]). However, besides biomedical applications, a variety of disciplines have main interest in studying the time to occurrence of some kind of terminal event (TE), which is often associated with some kind of recurrent event. When TE happens, all data accrual stops. Examples of TE include but not limited to deaths, onset of cancer, exit hospital and bankruptcy of a company. For instance, a patient died of cardiovascular disease may have experienced multiple (recurrent) strokes before passing away. When considering a single recurrent event, previous works (\[14\]) discussed the impact of past event occurrences and their accumulative effects on future event occurrences. To model interventions, which could happen after one occurrence of a recurrent event (cf. \[6\] and \[4\]), effective ages (perfect vs. partial repairs) were introduced. In \[9\], the authors proposed a class of joint dynamic models for time-to-occurrences of recurrent competing risks (RCR) and the time to terminal (TE) event. In the paper, the authors model a TE and several recurrent (competing) events (RCR) simultaneously, taking into account of impact of past event occurrences, and investigate the association between recurrent competing risks (RCR) and the terminal event (TE).

For a given joint dynamic model, how to develop appropriate methodology to predict time to a terminal event (TE) is an important statistical question. In this paper, we propose a simulation approach to predict time to terminal event (TTTE) according to the joint dynamic models in \[9\]. In Section 1, we introduce the data and relevant stochastic processes. In Section 2, we describe the joint dynamic models with frailty. In Section 3, we motivate the prediction problem of time to
TE (TTTE) by introducing model estimation of the joint dynamic models with frailty. In Section 4, we describe our simulation methodology. In Section 5, we describe empirical Brier score as the measure of predictive accuracy of the proposed method. Lastly, we demonstrate the model parameter estimates and proposed prediction method on a synthetic dataset and present measures of predictive accuracy on a test set in Section 6.

1.1 Data and the Stochastic Processes

Let \((\Omega, \mathcal{F}, P)\) be some probability space. Define \(F = \{\mathcal{F}_s|0 \leq s \leq s^*\}\) a history or filtration on the same probability space. \((N_q^t(s), q = 1, 2, \cdots, Q)\) and \(N_0^t(s)\) are counting processes and \(Y_t^q(s)\) are predictable processes with respect to \(\mathcal{F}_s\). For a single unit \(i\), the stochastic processes are

1. \(\{N_q^t(s) : s \geq 0\}\) : counting process for the \(q\)th competing risk.
2. \(\{N_0^t(s) : s \geq 0\}\) : counting process for the terminal event.
3. \(\{Y_t^q(s) : s \geq 0\}\) : at-risk process.
4. \(\{\varepsilon_q^t(s) : s \geq 0\}\) : the effective age process.

For unit \(i\), and \(q = 1, 2, \cdots, Q\), the observables are

\[
D_i(s) = \{(Y_t^q(s), N_q^t(s^-), \varepsilon_q^t(s), N_0^t(s^-) : q = 1, 2, \cdots, Q, s \geq 0), X_i, \tau_i\} \tag{1}
\]

\(X_i\) is the covariate vectors associated with the RCRs and TE. \(\tau_i\) is the random monitoring time and is independent of RCRs and TE. In Figure \(a\) we show an example of an observation under partial repair with frailty. The unit experiences TE by the end of monitoring period \(\tau\), and the occurrence of TE is indicated by a red cross. Let \(T\) denote the time to TE (TTTE). The observed time to TE is \(T'\), where \(T' = \min(T, \tau)\). In this example, \(T' = 3\).
Figure 2: Many Observational Units in a Training Set
2 Model Description

Since the proposed prediction method of time to TE (TTTE) obtain parameter estimates from the joint models proposed in [9], we describe the cumulative intensity process of risk $q, q = 1, 2, \cdots, Q$

$$A_{qi}^f(s|Z_i) = Z_i \int_0^s Y_{qi}^f(v) \rho_q(N_{qi}^f(v-); \alpha_q) \exp(X_i^\alpha \beta_q \lambda_{q0}(\xi_q(v)))dv$$

where $Z_i$ is the frailty, and we assume $Z_i \overset{iid}{\sim} Ga(\xi, \xi)$. The frailty term is a latent variable and unobserved. This term is introduced to the model other unobserved factors which induce the association between the RCRs and TE. The cumulative intensity process of TE is

$$A_{qi}^0(s|Z_i) = Z_i \int_0^s Y_{qi}^0(v) \rho_0(N_{qi}^f(v-); \gamma) \exp(X_i \beta_0 \lambda_0(v))dv$$

The $\rho_q(.)$ and $\rho_0(.)$ are functions capturing effects of past event occurrences on the instantaneous probability of event occurrence conditional on history.

Frailty $Z$ is latent, and assumed to follow a Gamma distribution $Ga(\xi, \xi)$. Let $\Theta = \{ \xi, \gamma, \beta_0, (\alpha_q, \beta_q; q = 1, 2, \cdots, Q) \} \cup \{ (\Lambda_q(s), q = 1, 2, \cdots, Q), \Lambda_0(s)|0 \leq s \leq s^* \}$ denote the vector of parameters in the aforementioned joint model. $\hat{\Theta}$ is the estimator of the parameter estimator. After obtaining $\hat{\Theta}$, the prediction problem becomes predicting the residual time to TE given a new unit, say unit 0, of interest has survived up to the monitoring period $\tau_0$.

3 Model Estimation

Conditional on frailty $Z_i$, the likelihood of the frailty case for the $i$th unit is

$$L_c(s, \Theta|Z_i) = \prod_{v=0}^s P \{ \bigcap_{q=1}^Q [dN_{qi}^f(v) = dn_{qi}(v)]; [dN_{0i}^f(v) = dn_{0i}(v)]; \mathcal{F}_{v-}, Z_i \}$$

$$= \prod_{q=1}^Q \big\{ \int [dA_{qi}(v|Z_i)]^{dn_{qi}(v)} [1 - dA_{qi}(v|Z_i)]^{1 - dn_{qi}(v)} \big\}$$

where $dn_{qi}(v), dn_{0i}(v) \in \{0, 1\}$ and $\sum_{q=1}^Q dn_{qi}(v) + dn_{0i}(v) \leq 1$.

3.1 Generalized At-risk Processes

We define some new aggregated generalized at-risk processes. For $q = 1, 2, \cdots, Q,$

$$S_{qi}(s, w|\alpha_q, \beta_q, z_i) = \sum_{i=1}^n Y_{qi}(s, w|\alpha_q, \beta_q, z_i)$$

$$= \sum_{i=1}^n \sum_{j=1}^{N_{qi}^f(s \wedge \tau_i - \tau_i) + 1} z_i I[w \in (\xi_q(s_{ij} - 1), \xi_q(s_{ij} - 1))] \frac{\kappa_q(i, \xi_q^{-1}(s_{ij}))}{\xi_q^{-1}(s_{ij})}$$

$$+ \sum_{i=1}^n \sum_{j=1}^{N_{qi}^f(s \wedge \tau_i - \tau_i) + 1} z_i I[w \in (\xi_q(s_{ij} - 1), \xi_q(s_{ij}))] \frac{\kappa_q(i, \xi_q^{-1}(s_{ij}))}{\xi_q^{-1}(s_{ij})}$$

$$\cdot \frac{\xi_q^{-1}(s_{ij}) - (s_{ij} - 1)}{\xi_q^{-1}(s_{ij}) - s_{ij} + 1}$$

$$\cdot \frac{\xi_q^{-1}(s_{ij} - 1) - (s_{ij} - 1)}{\xi_q^{-1}(s_{ij} - 1) - s_{ij} + 1}$$
where \( \kappa_qi(\phi_q^{-1}(u)) = \rho_q(N_{qi}^l(\phi_q^{-1}(u))−; \alpha_q) \exp(X_i^T \beta_q) \). For the terminal event process,
\[
S_0(v|\gamma, \beta_0, z) = \sum_{i=1}^n Y_i^T(v|\gamma, \beta_0, z_i) = \sum_{i=1}^n z_i[I(\tau_i \wedge S_i \geq v)\kappa_{0i}(v)]
\]
where \( \kappa_{0i}(v) = \rho_0(N_{0i}^l(v−); \gamma) \exp(X_i^T \beta_0) \) with \( S_i \) being time-to-terminal event.
Following the approach in [13], given values of the finite-dimensional parameters and frailty \( Z = z \), we estimate baseline hazards of the recurrent competing risks and the terminal event with frailty using the expressions below
\[
\hat{\Lambda}_0(s, t|z, \alpha_q, \beta_q) = \int_0^t \frac{\sum_{i=1}^n N_{qi}(s, dw)}{S_0(s, w|z, \alpha_q, \beta_q)}; \quad \hat{\Lambda}_0(t|z, \gamma, \beta_0) = \int_0^t \frac{\sum_{i=1}^n N_{0i}(dv)}{S_0(v|z, \gamma, \beta_0)}.
\]
Plugging in the estimates of the finite-dimensional parameters, the PLEs of the baseline survival functions of the recurrent competing risks \( (q = 1, 2, \cdots, Q) \) and the terminal event processes, conditional on \( Z = z \), are
\[
\hat{F}_0(s, t|z) = \prod_{w=0}^t [1 - \hat{\Lambda}_0(s, dw|z)]; \quad \hat{F}_0(t|z) = \prod_{w=0}^t [1 - \hat{\Lambda}_0(dw|z)].
\]

### 3.2 An EM Algorithm

We develop an EM algorithm (cf. [2]) to estimate the finite-dimensional parameters since the frailty \( Z \) is latent and hence, unobserved. Assuming \( Z = z \) is known, we obtain the full likelihood process as below
\[
\mathcal{L}^f[s^*|\Theta, Z = z, D(s^*)] = \prod_{i=1}^n \left\{ \frac{\xi^k_i}{\Gamma(k)} z_i^{k_i-1} \exp(-\xi z_i) \right. \\
\times \prod_{\tau=0}^s \prod_{q=1}^Q \left( z_i Y_i^T(v) \lambda_{q0}(\phi_q(v)) \rho_q \left[ N_{qi}^l(v−); \alpha_q \right] \exp(X_i^T \beta_q) \right) N_{qi}^l(dv) \\
\times \exp \left( -\int_0^s z_i Y_i^T(v) \lambda_{q0}(\phi_q(v)) \rho_q \left[ N_{qi}^l(v−); \alpha_q \right] \exp(X_i^T \beta_q) dv \right) \\
\times \left( z_i Y_i^T(v) \lambda_0(v) \rho_0 [N_{0i}^l(v−); \gamma] \exp(X_i^T \beta_0) \right) N_{0i}^l(dv) \\
\times \exp \left( -\int_0^s z_i Y_i^T(v) \lambda_0(v) \rho_0 [N_{0i}^l(v−); \gamma] \exp(X_i^T \beta_0) dv \right) \right\}
\]
To compute conditional distribution of \( Z_i, i = 1, 2, \cdots, n \), we use the fact that
\[
Z_i|\Theta, D(s^*) \propto \mathcal{L}^f[s^*|\Theta, Z = z, D(s^*)] \prod_{i=1}^n f(Z_i|\xi).
\]
We then obtain \( Z_i|D(s^*), \Theta \overset{iid}{\sim} \operatorname{Ga}(\alpha, \beta) \), with
\[
\alpha(s^*) = \xi + \sum_{q=1}^Q N_{qi}^l(s^*−) + N_{0i}^l(s^*−)
\]
The EM algorithm is described as follows:

\[ \gamma = \frac{\sum_{q=1}^{Q} N_{q1}^+(t-) + N_{01}^+(t-)}{\xi + \sum_{q=1}^{Q} \int_0^t A_{q1}^+(dv) + \int_0^t A_{01}^+(dv)} \]

For \( i = 1, 2, \ldots, n \), the conditional expectation of \( Z_i | D(t), \Theta \) is

\[ \mathbf{E}[Z_i | \mathcal{F}_t, X_i, \Theta] = \frac{\alpha(t)}{\beta(t)} = \frac{\xi + \sum_{q=1}^{Q} N_{q1}^+(t-) + N_{01}^+(t-)}{\xi + \sum_{q=1}^{Q} \int_0^t A_{q1}^+(dv) + \int_0^t A_{01}^+(dv)} \]

\[ \mathbf{E} [\log(Z_i) | \mathcal{F}_t, X_i, \Theta] = \text{DG}(\xi + \sum_{q=1}^{Q} \int_0^t A_{q1}^+(dv) + \int_0^t A_{01}^+(dv)) + \log(\mathbf{E}[Z_i | \mathcal{F}_t, X_i, \Theta]) - \log(\xi + \sum_{q=1}^{Q} \int_0^t A_{q1}^+(dv) + \int_0^t A_{01}^+(dv)) \]

where \( \text{DG}(\alpha) = \frac{d}{d\alpha} \log \Gamma(\alpha) \).

The EM algorithm is described as follows:

**E-step:** Obtain conditional expectation of the full log-likelihood with respect to \( Z | (D(t), \Theta) \). Let

\[ \hat{Z}_i = \mathbf{E}[Z_i | \mathcal{F}_t, X_i, \Theta]; \quad \text{log}\hat{Z}_i = \log(\mathbf{E}[Z_i | \mathcal{F}_t, X_i, \Theta]) \]

\[ \mathbf{E} (\log L_{i | s^*} | Z, D(s^*)) = n \xi \log \xi - n \log \Gamma(\xi) + \sum_{i=1}^{n} \log \hat{Z}_i (\sum_{q=1}^{Q} N_{q1}^+(s^*) + N_{01}^+(s^*) + \xi - 1) - \sum_{i=1}^{n} \hat{Z}_i (\xi + \int_0^{s^*} (\sum_{q=1}^{Q} A_{q1}^+(dv) + A_{01}^+(dv)))] + \sum_{i=1}^{n} (\sum_{q=1}^{Q} \int_0^{s^*} \log a_{q1}^+(v) N_{q1}^+(dv) + \int_0^{s^*} \log a_{01}^+(v) N_{01}^+(dv)) \]

**M-step:** When values of the finite-dimensional parameters in \( \Theta \) and the frailty variables \( Z \) are given, baseline hazards of the recurrent competing risks and the terminal event can be estimated non-parametrically as in equation (4). We obtain the estimating equations below to estimate the finite-dimensional parameters. For \( \alpha_q \) and \( \beta_q, q = 1, 2, \ldots, Q \):

\[ \sum_{i=1}^{n} \int_0^{\tau_i} \left[ \frac{\partial}{\partial \alpha_q} \rho_q(N_{q1}^+(v^-) | \alpha_q) - \frac{\partial}{\partial \alpha_q} \frac{S_{q0}(s,\alpha_q,v) | \alpha_q, \beta_q, Z)}{S_{q0}(s,\alpha_q,v) | \alpha_q, \beta_q, Z)} \right] N_{q1}^+(dv) = 0; \]

\[ \sum_{i=1}^{n} \int_0^{\tau_i} \left[ X_i - \frac{\partial}{\partial \beta_q} \frac{S_{q0}(s,\alpha_q,v) | \alpha_q, \beta_q, Z)}{S_{q0}(s,\alpha_q,v) | \alpha_q, \beta_q, Z)} \right] N_{q1}^+(dv) = 0. \]

For \( \gamma \) and \( \beta_0 \):

\[ \sum_{i=1}^{n} \int_0^{\tau_i} \left[ \frac{\partial}{\partial \gamma} \rho_0(N_{q1}^+(v^-) | \gamma) - \frac{\partial}{\partial \gamma} \frac{S_0(s,\gamma,\beta_0, Z)}{S_0(s,\gamma,\beta_0, Z)} \right] N_{01}^+(dv) = 0; \]

\[ \sum_{i=1}^{n} \int_0^{\tau_i} \left[ X_i - \frac{\partial}{\partial \beta_0} \frac{S_0(s,\gamma,\beta_0, Z)}{S_0(s,\gamma,\beta_0, Z)} \right] N_{01}^+(dv) = 0. \]
We follow the algorithm described below to estimate all parameters:

1. Initialize \( \hat{Z}^{(0)} = I_{n 	imes 1}, \hat{\alpha}^{(0)}_q, \hat{\beta}^{(0)}_q, \hat{\gamma}^{(0)}, \hat{\beta}_0^{(0)} \).
2. Obtain \( \hat{\Lambda}^{(0)}_{q0}(\cdot), q = 1, 2, \ldots, Q \) and \( \hat{\Lambda}^{(0)}_0(\cdot) \).
3. Update to \( \hat{Z}^{(1)} \) using \( \{ \hat{\Lambda}^{(0)}_{q0}(\cdot), \hat{\alpha}^{(0)}_q, \hat{\beta}^{(0)}_q, q = 1, 2, \ldots, Q, \hat{\gamma}^{(0)}, \hat{\beta}_0^{(0)}, \hat{\Lambda}^{(0)}_0(\cdot) \} \).
4. Obtain \( \hat{\xi}^{(0)} \). Define \( \mathcal{L}_{\hat{\xi}}[s^*|\Theta, D(s^*)] = E(\log Z_{\hat{\xi}}^c[s^*|\Theta, Z, D(s^*)]) \) as in the E step.
5. With \( \hat{Z}^{(1)}, \hat{\Lambda}^{(0)}_{q0}(\cdot) \) and \( \hat{\Lambda}^{(0)}_0(\cdot) \), we obtain \( \hat{\alpha}^{(1)}_q, \hat{\beta}^{(1)}_q, \hat{\gamma}^{(1)}(\cdot), \hat{\beta}^{(1)}_0 \).
6. Reset \( \hat{Z}^{(1)} \) to \( \hat{Z}^{(0)}, \hat{\alpha}^{(1)}_q, \hat{\beta}^{(1)}_q, \hat{\gamma}^{(1)}(\cdot), \hat{\beta}^{(1)}_0 \) to \( \hat{\alpha}^{(0)}_q, \hat{\beta}^{(0)}_q, \hat{\gamma}^{(0)}, \hat{\beta}_0^{(0)} \).

Repeat steps 2 - 5 until \( ||(Z^{(0)}, \Theta^{(0)}) - (Z^{(1)}, \Theta^{(1)})|| < \text{tol} \). For example, \( \text{tol} = 10^{-7} \). The convergence criterion only applies to the finite-dimensional parameters in \( \Theta \).

4 Predicting Time to Terminal Event

A focal interest of joint dynamic modeling is predicting survival probabilities of time to terminal event (TE) ([11], [1], [7]) for new units which are previously unseen from the training data and at-risk by the end of monitoring time. Using our proposed simulation method, we are able to make personalized predictions of time to the TE as well as survival probabilities of the TE based on the history of a particular observational unit. Many existing methods discussed in detail dynamic predictions of TE survival probabilities (cf. [11], [7]). In our setting, we naturally only consider predicting TEs for observational units who are still at-risk by end of their respective monitoring time \( \tau \). Based on parameter estimates \( \hat{\Theta} \) of the joint dynamic models described in Section 2 and Section 3, we propose a simulation approach to 1) predict occurrences of the RCRs after \( \tau \) in a dynamic fashion where each predicted RCR occurrence is generated given data history up to the end of the last RCR occurrence. RCR occurrences are generated until the occurrence of the simulated TE; 2) we dynamically simulate a distribution of time To TE (TTTE) ; 3) compute the predicted survival probability of TE beyond \( \tau \) within some time window \( t, t > 0 \). A contribution our approach makes to existing methodology is that we allow the simulated RCR occurrences and TE times to depend on the most recent history as the simulated event processes evolve. For example, the end of monitoring time \( \tau \) is often the time stamp when data accrual stops updating for units that are still-at-risk, and predictions of TE times or survival probabilities of TE beyond \( \tau \) are made based on such history only. In our approach, potential event occurrences of RCR between \( \tau \) and the time to TE contribute to the estimated instantaneous conditional probabilities of new RCR occurrences and TE.

4.1 Frailty \( Z \) Estimates

For a new unit \( i \), still-at-risk by the end of its monitoring time \( \tau_0 \), we predict its time to TE based on its history and parameter estimate \( \hat{\Theta} \). \( \hat{\Theta} \) is estimated from the training observations. Under the joint dynamic models (See Section 2 and 3) with frailty, although we cannot estimate the value of the frailty term \( Z_0 \), we can use its conditional mean as an estimate. Let \( Z^0 \) denote the predicted frailty value of the new unit. The conditional mean of \( Z^0 \) given history and model parameter is

\[
E[Z^0|\Theta, D_0(\tau_0)] = \frac{\xi + \sum_{q=1}^{Q} N^+_q(\tau_0) + N^+_0(\tau_0)}{\xi + A^+_q(\tau_0) + A^+_0(\tau_0)}
\]
Subject with Covariate $X = (0, 0.49, 1.41)$ under Repair Type Partial Time

Figure 3: Data History of Unit 0
where $A_{q0}^\dagger(\tau_0)$ and $A_{q0}(\tau_0)$ are the cumulative intensity process without the frailty term as described in Section 2. For risk $q$, 

$$A_{q0}^\dagger(s) = \int_0^s Y_{q0}^\dagger(v)\rho_q(N_{q0}^\dagger(v-); \alpha_q)\exp(X_0\beta_q)\lambda_q(\mathcal{E}_{q0}(v))dv.$$  

(6)

For TE of the new unit, 

$$A_{00}(s) = \int_0^s Y_{00}^\dagger(v)\rho_0(N_{00}^\dagger(v-); \gamma)\exp(X_0\beta_0)\lambda_0(v)dv.$$  

(7)

In the simulation approach, we estimate $A_{q0}^\dagger(\tau_0)$ and $A_{00}(\tau_0)$ by summing over their respective estimated values at event times in the training observations, $\hat{Z}^0$, or the estimated conditional mean of $Z^0$ is then computed following equation 5 by inputting event history of the unit as well as $\hat{A}_{q0}^\dagger(\tau_0)$ and $\hat{A}_{00}(\tau_0)$.

4.2 Estimating $A_{q0}(s, dw)$ and $A_{00}(dw)$

For a new unit 0 that has not experienced the TE by the end of the corresponding monitoring time $\tau_0$, the simulation method makes predictions on time interval $[\tau_0, \tau_0 + t], t > 0$. Denote time to occurrence of the TE as $T_0, T_0 > \tau_0$. We use $D_0(s)$ to denote the data history of unit 0:

$$D_0(s) = \{(Y_{q0}^\dagger(s), N_{q0}^\dagger(s-), \mathcal{E}_{q0}(s), N_{00}^\dagger(s-), s \geq 0, q = 1, 2, \cdots, Q), X_0, \tau_0\}$$  

(8)

Let $T^*$ be the maximum observed time to TE of the training observations, $T^* = \max\{T_1, T_2, \cdots, T_n\}$. $N_{q0}^\dagger(T^*)$ and $N_{00}^\dagger(T^*)$ are the total number of observed $q_{th}$ RCR occurrences and TE occurrences from the training observations, respectively. Then 

$$N_{q0}^\dagger(T^*) = \sum_{i=1}^n N_{q0}^\dagger(T_i); \quad N_{00}^\dagger(T^*) = \sum_{i=1}^n N_{00}^\dagger(T_i).$$

For training observations, the compensator processes values of the RCRs are estimated at observed effective ages in Section 3. They can be interpreted as the conditional instantaneous probability of a RCR event occurrence corresponding to a particular effective age. Conditional on the history of a new unit 0, we need to estimate its instantaneous probabilities of new event occurrences for each risk. For risk $q$, the observed effective ages of unit 0 almost always do not coincide with the observed effective ages from training observations. This leads to an zero estimate of $\hat{A}_{q0}(s, dw)$, $w = (w_1, w_2, \cdots, w_{N_{q0}^\dagger(\tau_0)})$. To estimate the compensator process values of unit 0 beyond $\tau_0$, we use observed effective ages of risk $q$ from the training set, where $w_i, i = 1, 2, \cdots, N_q^\dagger(T^*)$. For $q = 1, 2, \cdots, Q$, we estimate the generalized at-risk process of unit 0 is 

$$\hat{Y}_{q0}(s, w) = \sum_{j=1}^{N_q^\dagger(\tau_0)} I\{w \in \mathcal{E}_{q0}(S_{0j-1}), \mathcal{E}_{q0}(S_{0j})\} \times \frac{\rho_q(N_{q0}^\dagger(\mathcal{E}_{q0}^{-1}(w))-; \alpha_q)}{\mathcal{E}_{q0}(\mathcal{E}_{q0}^{-1}(w))}$$  

(9)

To simulate a single RCR event, we compute $\hat{A}_{q0}(s, dw_1)$, 

$$\hat{A}_{q0}(s, dw_1) = \hat{Y}_{q0}(s, w_1)\hat{A}_{q0}(s, dw_1)$$  

(10)
where \( \hat{\Lambda}_{q0}(s, dw) \) is the Nelson-Aalen type of estimates of baseline hazard we obtain from training data. Notice \( \hat{\Lambda}_{q0}(s, dw) \) are combinations of parameter estimates and data histories from the training set as well as individual data history of unit 0 (see equation (10)). The value of the \( \rho_q(.) \) function will update dynamically as the simulated data accrual of unit 0 happens. Therefore, earlier simulated RCR event occurrences between \( \tau \) and time to TE contributes to the estimated conditional instantaneous probabilities of later RCR event occurrences.

To simulate an event occurrence for the TE, we also estimate the conditional instantaneous probability of TE, \( \hat{A}_{q0}(dw) \) is then

\[
\hat{A}_{q0}(dw) = Y_{\hat{w}}^1(w)\rho_0(N_0^1(w-); \hat{\gamma}) \exp(X_0\hat{\beta}_0)\hat{\Lambda}_{q0}(dw) \quad (11)
\]

### 4.3 The Simulation Algorithm

We simulate occurrences of the RCRs and the TE for unit 0 according to the following algorithm:

1. Let \( \bar{T}_0 \) be the calendar time. Set \( \bar{T}_0 = \tau_0 \). \( \mathcal{E}(\bar{T}_0) = (\mathcal{E}_{10}(\bar{T}_0), \mathcal{E}_{20}(\bar{T}_0), \cdots, \mathcal{E}_{Q0}(\bar{T}_0)) \) is the vector of observed effective ages of unit 0 by \( \bar{T}_0 \). We begin with \( k = 0 \), the total number of simulated RCRs; let \( k' \) indicate that the unit has not experienced the TE.

2. Simulate an occurrence of RCR:
   (a) For \( q = 1, 2, \cdots, Q \):
      i. Create vector \( \mathbf{w} = (w_{k_1}, w_{k_2}, \cdots, w_{k_L}) \) where \( w_{k_i} \)’s are in ascending order, and \( w_{k_1} > \mathcal{E}_q(\bar{T}_0) \), and \( \{k_1, k_2, \cdots, k_L\} \subseteq \{1, 2, \cdots, N_q^1(T^*)\} \),
      ii. Compute \( \hat{A}_q(s, dw_{k_l}) \), \( l = 1, 2, \cdots, L \).
      iii. For \( k_1, k_2, \cdots, k_L, l = 1, 2, \cdots, L \):
         - Generate a Bernoulli random variate \( B_l \) with success probability \( \hat{A}_q(s, dw_{k_l}) \):
            If \( B_l = 1, t_q = w_{k_l} \), else \( l = l+1 \);
            If \( l = L, t_q = w_{k_L} \).
   (b) \( \min t_q = \min(t_1, t_2, \cdots, t_Q) \). Go to step 3.

3. Simulate an occurrence of TE:
   (a) Create vector \( \mathbf{T} = (T_{k_1'}, T_{k_2'}, \cdots, T_{k_M'}) \), where \( T_{k_m} \)’s are in ascending order, and \( T_{k_m} > \bar{T}_0 \), and \( \{k_1', k_2', \cdots, k_M'\} \subseteq \{1, 2, \cdots, N_0^1(T^*)\} \).
   (b) Compute \( \hat{A}_0(dT_{k_m}) \), \( m = 1, 2, \cdots, M \).
   (c) For \( k_1', k_2', \cdots, k_M', m = 1, 2, \cdots, M \):
      - Generate a Bernoulli random variate \( B_{k_m} \) with success probability \( \hat{A}_{00}(dT_{k_m}) \):
          If \( B_m = 1, T_0^* = T_{k_m'} - \bar{T}_0 \), else \( m = m+1 \)
          If \( m = M, T_0^* = T_{k_M'} - \bar{T}_0 \).
4. Simulate a single TE path:

If $T_0^* < \min t_q$,

(a) Stop.
(b) Update $\tilde{T}_0 = \tilde{T}_0 + T_0^*$.
(c) Update $\mathbf{e}(\tilde{T}_0)$, according to the type of repair (perfect vs. partial).
(d) Set $T_0 = \tilde{T}_0$.

Else:

(a) Update $\tilde{T}_0 = \tilde{T}_0 + T_0^*$.
(b) Update $\mathbf{e}(\tilde{T}_0)$ and $N_{q_0}(\tilde{T}_0), q = 1, 2, \cdots, Q$, according to the type of repair (perfect vs. partial).
(c) Repeat steps 2, 3 and 4.

5 Predictive Accuracy

To measure predictive performance of the simulation method in Section 4, we use empirical Brier Score. The Brier Score is a version of expected squared-error loss for evaluating difference between observed and predicted values. Previous works on this topic have detailed description of this measure of predictive accuracy ([5], [3], [11], [1]). The empirical Brier Score is

$$
\hat{EBS}(v,t) = \frac{1}{\#\{i : Y_i^+(v) = 1\}} \sum_{(i : Y_i^+(v) = 1)} \hat{w}_i(v+t, \hat{F}) \left[ I(T_i > v+t) - \hat{P}(T_i > v+t|\hat{\Theta}, \mathcal{F}_{v-}) \right]^2
$$

(12)

and the weight $\hat{w}_i(v+t, \hat{F})$ is

$$
\hat{w}_i(v+t, \hat{F}) = \frac{I(T_i \leq v+t) \{N_{q_0}(\{v+v+t\}) = 1\}}{\hat{F}(T_i)/\hat{F}(v)} + \frac{I(T_i > v+t)}{\hat{F}(v+t)/\hat{F}(v)}.
$$

(13)

Only observations that are still at-risk at time $v$ will be considered for prediction, and $\hat{F}(\cdot)$ is the Kaplan - Meier estimator of the monitoring time distribution $\tau_i$. When the TE happens on the interval $(v, v+t], N_{q_0}(\{v+v+t\}) = 1$.

A validation set approach is used to generate the test error of the prediction method.

6 An Example on Synthetic Data

In this section, we demonstrate parameter estimation of the joint dynamic modeling in Section 2 and 3 and the proposed prediction of time to TE (TTTE) on synthetic datasets.
6.1 Parameter Estimates of the Dynamic Joint Model Under Frailty

Applying the model estimation procedure in Section 3 to a training set of 50 units (See Figure 2), we obtain $\hat{\Theta}$. The finite-dimensional parameters in Table 1, $\xi$, the frailty variable parameter, is estimated to be 1.506, and the true $\xi$ value is 2.

| Risk($q$) | $\hat{\alpha}_q$       | $\hat{\beta}_q$       |
|-----------|-------------------------|-------------------------|
| TE (0)    | (-0.04, 0.007, 0.038, 0.657) | (0.028, -0.714, 1.076) |
| 1         | -0.106                  | (-0.34, -0.03, 0.40)   |
| 2         | 0.150                   | (-0.07, 0.11, -0.03)   |
| 3         | 0.103                   | (0.05, -0.17, 0.39)    |
| 4         | -0.020                  | (-0.18, 0.82, -0.44)   |

Table 1: Finite-Dimensional Parameter Estimates (with Frailty)

The Product Limit Estimates of the survival functions for RCRs and TE are displayed in Figure 4. Since the estimates are obtained on a synthetic dataset, we plot the true survival functions using smooth red lines. The blue wiggly lines are the estimates.

Figure 4: Left: PLE Survival function of Recurrent Competing Risks; Right: PLE Survival function of Terminal Event

6.2 Predicting Time to TE of a New Unit

To illustrate our proposed prediction method, we use unit 0 (see Figure 3) as an example. The data accrual is generated under partial repair. The algorithm in Section 4.3 is applicable in the case of
perfect repair, as one only needs to alter the update of effective ages in the algorithm. We only demonstrate the case of partial repair in this paper.

In Figure 7, under partial repair, we show simulated effective ages of unit 0 as a result of one single simulated time to TE path. Solid orange dots represent simulated RCRs, and purple lines are used to indicate length of effective ages. In total, six RCRs are simulated beyond $\tau_0$. In Figure 8, observed RCRs of unit 0 and the six simulated RCRs are plotted together. Solid purple dots represent event occurrences. We observe that no risk 3 event is simulated, and two events are simulated for each of the other risks.

From a single simulated path of TE, we obtain one realization of predicted time to TE. From a large number of simulated paths, we will be able to obtain a distribution of simulated time to TE, denoted by $\hat{T}_0$. In Figure 5, histogram of $M = 10,000$ paths of the simulated time to TE is shown. Mode of the distribution is between 1 and 1.2. The histogram is right-skewed.
6.3 Predicted Survival Probability of the TE

For unit 0, we obtain the predicted survival probability of TE on \((\tau_0, \tau_0 + t]\) according to,

\[
\hat{P}(T_0 > \tau_0 + t|\hat{\Theta}, \mathcal{F}_{s-}) = \frac{\sum_{i=1}^{M} I(T_0 > \tau_0 + t)}{M}
\]  

(14)

where \(s = \max\{s_{0j}|\tau_0 < s_{01} < \cdots < s_{0j} < \tau_0 + t, N^T_{0s}(ds_{0j}) = 1, q = 1, 2, \cdots, Q\}\).

In our proposed simulation approach, we simulate a large number of paths of the TE. The predicted survival probability of TE greater than \(\tau_0 + v\) is the percentage of simulated TE paths which are greater than \(\tau_0 + t\). In Figure 6(a) we show \(M = 300\) simulated TE paths, where the red crosses indicated TE occurrences of unit 0. Lengths of the horizontal lines represent the simulated lengths of time to TE. When \(t = 0.394\), the predicted probability of unit 0 surviving after \(\tau_0 + 0.394\) is the percentage of red crosses out of \(M\) appearing after the vertical redline in Figure 6(a). \(\tau_0 + 0.394 = 1.2\) in this case. For this \(M = 300\) simulations, there are about 11% of the paths greater than 1.2. Consequently, the predicted probability is about 0.11. When the number of paths \(M\) gets very large, we obtain a predictive distribution of the TE. In Figure 6(b), predicted survival probabilities can be plotted at different time windows of interest after \(\tau_0\) (see the right panel of Figure 6b). We can also obtain the empirical distribution of the \(M\) simulated TE paths.

We summarize the average number of total predicted RCR occurrences to be 29 per path for a particular \(M = 10,000\) TE paths. For each RCR, the average number of simulated risks are 3, 2, 22, 2 per path, respectively.
Figure 7: Simulated Effective Ages of Unit 0 Under Partial Repair

| Average Event Occurrences | Average Simulated Event Occurrences |
|---------------------------|-------------------------------------|
| 38                        | 29                                  |

Table 2: Average Simulated Total Event Occurrences of Unit 0

| q = 1 | q = 2 | q = 3 | q =4 |
|-------|-------|-------|------|
| 3     | 2     | 22    | 2    |

Table 3: Average Simulated RCRs of Unit 0

| Ave. TE | 2.5th Percentile | 97.5th Percentile |
|---------|------------------|-------------------|
| 1.043   | 0.812            | 1.296             |

Table 4: Summary Stats of Simulated TEs of Unit 0
Subject with Covariate $X = (0,0.49,1.41)$ under Repair Type Partial

Figure 8: Data History of Unit 0 and Simulated RCRs
7 Simulation Studies

7.1 Empirical Brier Score

A test set of size 20 is simulated to evaluate predictive accuracy of the prediction method. The average observed time to TE is 1.04. $v$ in equation (12) is set to be 1.5. At different time windows, $t$ ranges from 0.4 to 0.7 with 0.05 as the increment. We found the empirical Brier score to be very small (See Figure 9), and increases as $t$ gets larger. This is not surprising as less accurate predictions are expected when predicting further into the future.

7.2 Size-biased Sampling

In existing literature, for example, [10], size-biased sampling in recurrent event analysis is illustrated using homogenous Poisson process (HPP). Although the probabilistic data generating mechanism does not change, gap times that cover the end of monitoring time tend to be longer than other inter-event times, on average. In the proposed joint dynamic models, if a unit has not experienced the TE by the end of monitoring time, the inter-event times of RCRs that traverse the monitoring time are censored. These inter-event times that traverse the end of monitoring time also tend to be longer compared to all other inter-event times. In Figure 10, we overlay the empirical distribution of the inter-event time that cover $\tau_0$ with that of the other inter-event times. The number of simulated TE paths is $M = 10,000$ in this demonstration. For each of the four RCRs, we show that the inter-event time covering $\tau_0$ exhibit the size-biased sampling phenomenon. For each risk, a side-by-side boxplot is created to compare the empirical distributions of the two types inter-event times. Medians of the inter-event times covering $\tau$, in other words, the censored inter-event times, are larger.
8 Concluding Remarks

In this paper, we propose a simulation method to predict time to TE (TTTE) according to a class of joint dynamic models of recurrent competing risks and terminal event ([9]). By estimating the conditional instantaneous probability of a RCR event, the simulation method combines individual data history of a new unit and parameter estimates obtained on a training set like the new unit to make individualized prediction of time to TE (TTTE). Using the proposed method, simulated paths of time to TE (TTTE) after the end of monitoring time mimic the natural progress of data accrual for censored RCR occurrences leading up to the TE. The censored RCR event occurrences
are generated dynamically as the estimated conditional instantaneous probabilities of such events are updated up to the most recent simulated RCR event, not restricting to $\tau$, the end of monitoring time. Distribution of time to TE (TTTE) and predicted survival probabilities of TE are obtained by simulating a large number of paths. Predictive accuracy of the proposed method is evaluated using empirical Brier score. We also point out the curious aspect of size-biased sampling that manifests itself in predicting time to TE (TTTE). Such phenomenon may have important implications in decision making. Although the proposed prediction method arises from a particular class of joint dynamic models with frailty, which uses parameter estimates from the models for prediction, the simulation approach to predicting time to terminal event (TTTE) can be adopted by other joint dynamic models. As data structures calling for joint dynamic modeling can potentially become much more complicated than the one considered in this project, our ongoing work is to apply and extend the simulation method in predicting time to TE (TTTE) to adapt to more challenging data situations.

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