Bayesian analysis of recurrent events with dependent termination: An application to heart transplant data

Elizabeth H. Slate

Florida State University
slate@stat.fsu.edu

Joint work with Bichun Ouyang, Rush University, Debajyoti Sinha, FSU and Adrian Van Bakel, MUSC
Heart Transplant Data (Sample)
Heart Transplant Data

Median follow up = 5.7 years
Number of rejections: 0 – 7

<table>
<thead>
<tr>
<th>Variable</th>
<th>N</th>
<th>Age</th>
<th>BMI</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Gender</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>221</td>
<td>52.2 (10.3)</td>
<td>27.0 (4.2)</td>
</tr>
<tr>
<td>Female</td>
<td>46</td>
<td>47.6 (13.0)</td>
<td>24.1 (4.2)</td>
</tr>
<tr>
<td><strong>Race</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Caucasian</td>
<td>201</td>
<td>52.9 (10.2)</td>
<td>26.6 (4.0)</td>
</tr>
<tr>
<td>African American</td>
<td>66</td>
<td>47.0 (11.8)</td>
<td>26.0 (5.3)</td>
</tr>
</tbody>
</table>
Modeling Goals

- Covariates associated with rejection episodes?
- Covariates associated with death?
- Death associated with rejection episodes?
- Prediction of survival? rejections?
- Tailor monitoring schedule to the patient

Assume noninformative censoring on death.
Modeling Approaches

Combine models for

- Recurrent events (rejection episodes): $N_i(t)$
- Survival time (time to death): $T_i$

Viewed as recurrent events with dependent termination.

Focus is $[N_i(t), T_i; Z_i(t)]$ where $Z_i(t) =$ covariates

We will formulate two Bayesian models:

- Generalized mixed Poisson process (GMPP)
- A “similar” coarsening at random (CAR) model
Motivation

Models

Fit Results

Prediction

Discussion

**Model Background**

**Mixed Poisson Process (MPP, Oakes 1992)**
noninformative termination, rare events

\[
\Pr[dN_i(t) = 1 | w_i, \overline{N}_i(t-); Z_i] \approx w_i \exp\{\beta_N Z_i\} \lambda_0(t)
\]

\[
\Pr[dN_i(t) > 1 | w_i, \overline{N}_i(t-); Z_i] \approx o(dt)
\]

\[
w_i \sim F(w_i | \eta), \text{iid}
\]

**Lancaster-Intrator (1998)**

\[
\lambda_N(t | w_i, \overline{N}_i(t-), T_i > t; Z_i) = w_i \exp\{\beta_N Z_i\} \lambda_0(t)
\]

\[
h_T(t | \overline{N}_i(t), w_i; Z_i) \propto w_i \exp\{\beta_T Z_i\} \lambda_0(t)
\]

\[\implies \text{risk of event } \propto \text{risk of death}\]

\[\lambda_N \text{ and } h_T \text{ depend on } \overline{N}_i(t) \text{ only through } N_i(t-)\]
Generalized MPP
(Sinha & Maiti, 2004; Liu et al., 2004; Sinha et al., 2008)

\[
\lambda_N(t \mid w_i, \overline{N}_i(t-), T_i \geq t; Z_i) = w_i \exp\{\beta_N Z_i\} \lambda_0(t)
\]
\[
h_T(t \mid w_i, \overline{N}_i(t-); Z_i) = w_i^\alpha \exp\{\beta_T Z_i\} h_0(t)
\]

Dependence parameter \( \alpha \).

- \( \lambda_N \) and \( h_T \) depend on \( \overline{N}_i(t) \) only through \( N_i(t-) \)
- \( \alpha = 0 \) implies noninformative termination.
- Taking \( w_i \sim \text{Gamma}(\eta, \eta) \) so \( \text{Var}(w_i) = \eta^{-1} \).

\[
h_T(t \mid \overline{N}_i(t-); Z_i) \approx \left\{1 + \frac{N_i(t-)}{\eta}\right\}^\alpha h_T(t \mid N_i(t-) = 0; Z_i)
\]
Coarsening at Random (CAR) Assumption

For study period \([0, \tau)\) and \(t < \tau\)

\[
h_T(t \mid \overline{N}(\tau), \overline{Z}(\tau)) = h_T(t \mid \overline{N}(t^-), \overline{Z}(t^-))
\]

Risk of death at \(t\) given all information in \([0, \tau)\) depends only on the history up to \(t\).

The GMPP model does not satisfy CAR.
A “GMPP-like” CAR Model

Car Model for Comparison with GMPP

\[
\lambda_N(t \mid \overline{N}_i(t -), T_i \geq t; Z_i) = \left\{1 + \eta^{-1} N_i(t -)\right\} e^{\beta_N Z_i} \lambda_0(t)
\]

\[
h_T(t \mid \overline{N}_i(t -); Z_i) = \left\{1 + \eta^{-1} N_i(t -)\right\}^\alpha e^{\beta_T Z_i} h_0(t)
\]

Here, \(\eta^{-1} > 0\) continues to reflect heterogeneity among subjects.
Bayesian GMPP Model

Data

\(D_N = \{\text{rejection times}\} = \{R_i, i = 1, \ldots, n\}, \quad R_i = \{t_{ij}\}_{j=1}^{m_i}\)
\(D_T = \{\text{death times}\} = \{(T_i, \delta_i); i = 1, \ldots, n\}\).

GMPP

\[
\lambda_N(t \mid w_i, N_i(t-), T_i \geq t; Z_i) = w_i \exp\{\beta_N Z_i\} \lambda_0(t)
\]
\[
h_T(t \mid w_i, N_i(t-); Z_i) = w_i^\alpha \exp\{\beta_T Z_i\} h_0(t)
\]
\(w_i \sim \text{Gamma}(\eta, \eta), \text{iid}\)

Take \(\theta = (\beta_N, \beta_T, \lambda_0(\cdot), h_0(\cdot), \alpha)\)

Posterior Distribution

\[
p(\theta, w, \eta \mid D_N, D_T, Z) \propto \]
\[
L_N(\beta_N, \lambda_0, w \mid D_N, Z) L_T(\beta_T, h_0, \alpha, w \mid D_T, Z) g(w \mid \eta) \pi(\theta)
\]
Bayesian GMPP Model

Prior Distributions

\[ \pi(\theta) = \pi(\beta_N) \pi(\beta_T) \pi(\alpha) \pi(\eta^{-1}) \pi(\lambda_0) \pi(h_0) \]

- \( \beta_N, \beta_T \sim \) diffuse normal with mean 0
- Dependency parameter \( \alpha \sim \) double exponential with mean 0, variance 8; also normal
- Frailty variance \( \eta^{-1} \sim U(0, 5) \); also weakly informative half-Cauchy and informative exponential
- rejection process baseline intensity, \( \lambda_0 \) Weibull\((u, v)\), \( u, v \sim \) gamma; also nonparametric
- death time baseline hazard \( h_0 = r \), exponential, with \( r \sim \) exponential(2); also Weibull
For both GMPP Model and “GMPP-like” CAR Model

- MCMC using WinBUGS
- 3 chains to monitor convergence
- 27K burn-in iterations
- 3K iterations for inference
### Covariate Effects, 95% Credible intervals

<table>
<thead>
<tr>
<th></th>
<th>GMPP</th>
<th></th>
<th></th>
<th>CAR</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Rejections</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>gender</td>
<td>0.48</td>
<td>(-0.07, 1.02)</td>
<td>3.3</td>
<td>(-0.03, 0.70)</td>
<td></td>
</tr>
<tr>
<td>race</td>
<td>0.16</td>
<td>(-0.30, 1.16)</td>
<td>0.26</td>
<td>(-0.03, 0.55)</td>
<td></td>
</tr>
<tr>
<td>age</td>
<td>-0.03</td>
<td>(-0.05, -0.01)</td>
<td>-0.03</td>
<td>(-0.04, -0.01)</td>
<td></td>
</tr>
<tr>
<td>BMI</td>
<td>0.04</td>
<td>(-0.00, 0.07)</td>
<td>0.04</td>
<td>(0.01, 0.06)</td>
<td></td>
</tr>
<tr>
<td><strong>Death</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>gender</td>
<td>0.53</td>
<td>(-0.39, 1.43)</td>
<td>0.20</td>
<td>(-0.39, 0.76)</td>
<td></td>
</tr>
<tr>
<td>race</td>
<td>-0.06</td>
<td>(-0.88, 0.76)</td>
<td>0.12</td>
<td>(-0.40, 0.63)</td>
<td></td>
</tr>
<tr>
<td>age</td>
<td>-0.02</td>
<td>(-0.05, 0.02)</td>
<td>-0.01</td>
<td>(-0.03, 0.02)</td>
<td></td>
</tr>
<tr>
<td>BMI</td>
<td>-0.02</td>
<td>(-0.08, 0.05)</td>
<td>-0.03</td>
<td>(-0.09, 0.03)</td>
<td></td>
</tr>
<tr>
<td>$\alpha$</td>
<td>1.94</td>
<td>(1.08, 3.06)</td>
<td>1.17</td>
<td>(0.58, 2.02)</td>
<td></td>
</tr>
<tr>
<td>$\eta^{-1}$</td>
<td>1.23</td>
<td>(0.79, 1.76)</td>
<td>0.74</td>
<td>(0.35, 1.26)</td>
<td></td>
</tr>
</tbody>
</table>

Insensitive to prior specifications
Model Comparison

CPO was used to compare the best GMPP and CAR models

\[ CPO_i = \Pr(D_{N,i}, D_{T,i} \mid D_N^{(i)}, D_T^{(i)}) = \int \Pr(D_{N,i}, D_{T,i} \mid \theta^*) p(\theta^* \mid D_N^{(i)}, D_T^{(i)}) \, d\theta^* \]

Cross-validated posterior predictive probability of data observed for subject \( i \)
CPO for GMPP versus CAR

Log CPO Ratios GMPP/CAR; 94% > 0

- ● Caucasian female patient - dead
- ○ Caucasian female patient - censored
- ▲ Caucasian male patient - dead
- △ Caucasian male patient - censored
- ▲ African American female patient - dead
- △ African American female patient - censored
- ▲ African American male patient - dead
- △ African American male patient - censored

Termination time (months since transplant)

log(GMPP/CAR)
We derive predictions for a new transplant patient using the GMPP model.

Probability of death in \((t_1, t_2)\) given covariates \(Z_{new}\) and \(k\) rejections prior to \(t_1\):

\[
Pr(T_{new} \in [t_1, t_2) \mid N_{new}(t_1-) = k, T_{new} > t_1; Z_{new})
\]

At \(t\) with \(k\) rejections, probability of survival rejection-free beyond time \(t_f\):

\[
Pr(T_{new} > t_f, N_{new}(t_f-) = k \mid N_{new}(t-) = k, T_{new} > t; Z_{new})
\]
As example, rejection-free survival in \((t_1, t_f)\)

\[
\mathcal{P}(\theta; t, t_f, k | \text{Data}) = \Pr(T_{\text{new}} > t_f, N_{\text{new}}(t_f^-) = k \mid N_{\text{new}}(t^-) = k, T_{\text{new}} > t; Z_{\text{new}})
\]

can be derived and requires computation of

- expectations of functions of the frailty for the new patient given \(\theta\) and Data, \(\mathbb{E}_w\{\psi(w_{\text{new}}) \mid \text{Data}, \theta\}\)
- expectations of functions of \(\theta\) given Data

using the cumulative hazard rate functions for both the rejection and death processes
Predictions

Computing $\mathcal{P}(\theta; t, t_f, k \mid \text{Data})$

- Monte carlo posterior mean wrt $[\theta \mid \text{Data}]$
- Monte carlo expectation $E_w$ using $w \sim [w_{new} \mid \text{Data}, \theta]$

Having run our MCMC to convergence:

For $p = 1, 2, \ldots, P$
1. $\theta^p \sim [\theta \mid \text{Data}]$
2. For $q = 1, 2, \ldots, Q$, $w^q \sim [w_{new} \mid \text{Data}, \theta^p]$
3. approximate $E_w[\nu(w_{new}; \theta^p)]$ by
   $$\hat{E}_w[\nu(w_{new}; \theta^p)] = \frac{1}{Q} \sum_{q=1}^{Q} \nu(w_{new}^q; \theta^p)$$

Estimate the prediction using the posterior mean:
$$\hat{\mathcal{P}}(\theta; t, t_f, k \mid \text{Data}) = \frac{1}{P} \sum_{p=1}^{P} \mathcal{P}(\theta^p, \hat{E}_w)$$
Prediction at 12 months

Male caucasian, age 41.7 yrs., 3 rejections at 12 months, 4th rejection at 56 mos., censored at 158 mos.
Prediction at 24 months

Male caucasian, age 41.7 yrs., 3 rejections at 12 months, 4th rejection at 56 mos., censored at 158 mos.
Survival rejection-free for 6 months

12 months: 66% (.51, .83)
24 months: 77% (.66, .88)

95% credible interval
Discussion

- Flexible dependence parameterization: \( w_i, w_i^\alpha \)
- Extended GMPP: dependence of \( T_i \) on more aspects of \( N_i(t-) \) than \( w_i^\alpha \), e.g. \( \gamma N_i(t-) \)
- AFT, additive hazard form
- Interpretation critical – mean number of events? intensity?; contribution of covariates to each process (e.g. latent class)
- Importance of prediction in personalized medicine


