Lecture - Discussion

A Flexible Bayesian Survival Model
Statistics 255 - Survival Analysis

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Motivating example

Lymphoma and renal transplantation

End stage renal disease (ESRD)

- **Post-transplant lymphoma**
  - immune system is suppressed to avoid rejection of new organ
  - Epstein-Barr virus $\rightarrow$ B cell proliferation $\rightarrow$ lymphoma
Motivating example

Lymphoma and renal transplantation

  - variety of known risk factors
  - little known about timing of onset
  - goal is to provide information to help guide post-transplant monitoring schedules

- United States Renal Data System (USRDS)
  - demographic and clinical information
  - survived > 90 days from start of therapy
  - 89,260 patients placed on transplant waiting list: 01/01/1990 - 12/31/1999

- Kidney recipients censored at 3 years post-transplant
  - ≤ 65 years with successful transplant no longer eligible for Medicare
  - not uniformly included in USRDS database from that date forward
Motivating example

**Lymphoma and renal transplantation**

- Cox regression analysis
  - transplant ‘exposure’ defined on six 6-month time-intervals

- Adjustment for age
  - four groups; < 25 yrs, 25-44 yrs, 45-59 yrs and ≥ 60 yrs
  - interaction between exposure and age group

- Other confounders
  - gender, race, time on dialysis prior to placement on waiting list
  - common adjustment across age groups
Motivating example

Lymphoma and renal transplantation

- Select published results:

<table>
<thead>
<tr>
<th></th>
<th>Relative Risk (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Age &lt; 25 yrs</td>
</tr>
<tr>
<td>Wait List</td>
<td>1.00</td>
</tr>
<tr>
<td>Transplant &lt; 6 mnths</td>
<td>13.82 (3.96, 48.15)</td>
</tr>
<tr>
<td>Transplant 6 to 12 mnths</td>
<td>9.25 (2.49, 34.32)</td>
</tr>
<tr>
<td>Transplant 12 to 18 mnths</td>
<td>7.49 (1.92, 29.18)</td>
</tr>
<tr>
<td>Transplant 18 to 24 mnths</td>
<td>3.29 (0.66, 16.47)</td>
</tr>
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<td>Transplant 24 to 30 mnths</td>
<td>3.87 (0.86, 17.51)</td>
</tr>
<tr>
<td>Transplant 30 to 36 mnths</td>
<td>3.46 (0.69, 17.44)</td>
</tr>
</tbody>
</table>

Motivating example

Lymphoma and renal transplantation

- Potential issues:
  - discretization of transplant effect
  - arbitrary choice of interval cut-points/lengths
  - accounting for all sources of uncertainty
Bayesian hierarchical model

Issues

► Challenge:
  ► flexible characterization of the model
  ► cannot be completely arbitrary but we do have a large sample size

► Hierarchy can provide structure within which complex models can be accommodated.
  ► requires **complete** specification

► Quantification of uncertainty via the posterior
  ► relatively straightforward; computational tools such as MCMC
  ► useful in high-dimensional problems
Bayesian hierarchical model

Three-stage Bayesian specification

- Stage 1: Likelihood for observed data
- Stage 2: Structural assumptions for likelihood parameters
  - framework which permits ‘flexibility’
- Stage 3: Prior assumptions
Bayesian hierarchical model

<table>
<thead>
<tr>
<th>Notation</th>
</tr>
</thead>
<tbody>
<tr>
<td>$T_i$ and $C_i$, true survival and censoring times for subject $i$, $i = 1, \ldots, n$</td>
</tr>
<tr>
<td>$X_i = \min(T_i, C_i)$ observed survival time</td>
</tr>
<tr>
<td>$\delta_i$ failure indicator</td>
</tr>
<tr>
<td>$Z_i$ vector of time-invariant adjustment covariates</td>
</tr>
<tr>
<td>measured at time of entry</td>
</tr>
<tr>
<td>$R_i(\cdot)$ time-dependent indicator of transplant status</td>
</tr>
<tr>
<td>$T_i^*$ time of transplantation</td>
</tr>
<tr>
<td>set to $\infty$ if no transplant during follow-up</td>
</tr>
</tbody>
</table>
Bayesian hierarchical model

**Multiplicative hazard model**

\[ h(t; \mathbf{z}, r(t), t^*) = h_0(t) \exp\{\mathbf{z}^T \gamma + r(t) \beta(t - t^*)\} \]

- \( h_0(\cdot) \) baseline hazard function
- \( \gamma \) vector of log-hazard ratio parameters
  - assumed to satisfy proportional hazards
- \( \beta(\cdot) \) time-varying effect of transplant (possibly!)
- A key challenge is that there are two functions which we would expect to be smooth
  - avoid strong assumptions about their functional form
  - each is defined on their own time scale
Bayesian hierarchical model

Two time scales

- **Study time;** $t$
  - baseline hazard, $h_0(\cdot)$
  - origin is the time of placement on waiting list

- **Transplant time;** $t - t^*$
  - transplant effect, $\beta(\cdot)$
  - origin is time of transplantation
  - censored at 3 years
Bayesian hierarchical model

Likelihood

- Assuming independent censoring

\[
L^S(h_0(\cdot), \gamma, \beta(\cdot)) = \prod_{i=1}^{n} h(x_i; z_i, r_i(x_i), t_i^\ast) \delta_i \exp \left\{ - \int_0^{x_i} h(s; z_i, r_i(s), t_i^\ast) \, ds \right\}
\]

- Characterization of continuous functions

  - The approach taken here is to consider mixtures of piecewise constant functions
  - For a given knot sequence, consider a piecewise constant specification
  - Allow the number of knots and their positions to be unknown parameters
  - Ultimately, we can average over the uncertainty in the knots to obtain a smooth specification
### Bayesian hierarchical model

#### Details for transplant time

- Let $\tau_{\text{max}}^B$ = maximum observed time post-transplant
  - 3 years for the PTLD data

- Consider a partition of $(0, \tau_{\text{max}}^B]$ into $K^B$ intervals
  
  $$(\tau_1^B, \tau_2^B] \cup (\tau_2^B, \tau_3^B] \cup \ldots \cup (\tau_{K^B}^B, \tau_{K^B+1}^B],$$

  where $\tau_1^B = 0$ and $\tau_{K^B+1}^B = \tau_{\text{max}}^B$

- Let $\tau^B = \{\tau_1^B, \ldots, \tau_{K^B}^B, \tau_{K^B+1}^B\}$. Then given $(K^B, \tau^B)$ assume

  $$\beta(t - t^*) = \sum_{b=1}^{K^B} 1_{[\tau_b^B < t - t^* \leq \tau_{b+1}^B]} \beta_b,$$

  where $\beta_b$ is the height of the transplant effect on $(\tau_b^B, \tau_{b+1}^B]$
## Details for transplant time

- Could work with individual $\beta_b$ heights:
  - $\beta(\cdot)$ likely a smooth function of time
  - reasonable to incorporate correlation between components of

\[
\beta = (\beta_1, \ldots, \beta_K)
\]

- permit borrowing of information
Bayesian hierarchical model

Details for transplant time

- First order autoregressive process; $\beta_b | \beta_{b-1}$
  - Gamerman (1991); Arjas & Gasbarra (1994)

- One-dimensional spatial problem

$$\beta | K^B, \tau^B \sim \text{MVN}_{K^B}(\mu_\beta, \sigma_\beta^2 \Sigma_\beta)$$

- Gaussian conditional autoregression

$$\beta_b | \beta_{-b} \sim \text{Normal}(\nu_{\beta b}, \sigma_{\beta b}^2)$$

- Conditional mean

$$\nu_{\beta b} = \mu_\beta \beta_b + \sum_{k \neq b} W_{bk}(\beta_k - \mu_\beta k)$$
Bayesian hierarchical model

Details for transplant time

- Interval-specific influence function of width:

\[ \Delta_b^B = \tau_{b+1}^B - \tau_b^B \]

- \( \Delta_0^B = \Delta_{K^B+1}^B = 0 \)

\[ W_{b(b-1)} = \frac{(\Delta_{b-1}^B + \Delta_b^B)c_\beta}{\Delta_{b-1}^B + 2\Delta_b^B + \Delta_{b+1}^B} \]

\[ W_{b(b+1)} = \frac{(\Delta_b^B + \Delta_{b+1}^B)c_\beta}{\Delta_{b-1}^B + 2\Delta_b^B + \Delta_{b+1}^B} \]

- \( c_\beta \in [0, 1] \) dictates the extent of dependence (and hence smoothing)
Bayesian hierarchical model

Details for transplant time

▶ Conditional variance:

$$\sigma_{\beta b}^2 = \sigma_\beta^2 Q_b$$

where

$$Q_b = \frac{2}{\Delta^B_{b-1} + 2\Delta^B_b + \Delta^B_{b+1}}$$

▶ Correlation matrix: $$\Sigma_\beta = (I - W)^{-1}Q$$

▶ symmetry and positive-definiteness (Besag & Kooperberg, 1995)

$$W_{bk} Q_k = W_{kb} Q_b, \quad \sum_{k=1}^{K^B} W_{bk} \leq 1.$$ 

▶ at least one strict inequality for the latter
▶ conditions satisfied for all $$c_\beta \in [0, 1]$$
Bayesian hierarchical model

Representation of baseline hazard function

- Analogous specification for $\lambda(\cdot) = \log h_0(\cdot)$

- For fixed $K^L$ and $\tau^L$, we assume the log-baseline hazard function, $\lambda(\cdot) = \log h_0(\cdot)$, to be piecewise constant as follows:

  $$\lambda(t) = \sum_{k=1}^{K^L} 1_{[\tau_k^L < t \leq \tau_{k+1}^L]} \lambda_k,$$

  where $h_{0k} = \exp\{\lambda_k\}$ is the height of the baseline hazard function on the $k^{th}$ study time interval $(\tau_k^L, \tau_{k+1}^L]$

- Similar first-order autoregressive structure for prior distribution on $\tau^L$
Bayesian hierarchical model

Likelihood representation

- Discretization leads to a (computationally) convenient form

\[
\exp \left\{ \sum_{k=1}^{K^L} \left[ \lambda_k D_k + \gamma Z_k + W_k(\tau^B, \beta) - \exp\{\lambda_k\} S_k(\tau^L, \gamma, \tau^B, \beta) \right] \right\}
\]

- contributions during \(k^{th}\) interval

- \(D_k\) is the number of events

- \(Z_k = (Z_{1k}, \ldots, Z_{Pk})\) are covariate totals, among subjects that have an event

- \(W_k\) total contributions of subject-specific \(\beta(\cdot)\) functions, among subjects that have an event

- Survival contributions among all subjects

\[
S_k(\tau^L, \gamma, \tau^B, \beta) = \sum_{i: x_i > \tau_k^L} \min(x_i, \tau_{k+1}^L) \int_{\tau_k^L}^{\tau_{k+1}^L} \exp\{z_i \gamma + r_i(s) \beta(s - t_i^*)\} \, ds
\]
Bayesian hierarchical model

Prior distributional assumptions

- Proportional hazards parameters, $\gamma$
  - improper flat priors

- Partition, $\tau$
  - time-homogeneous Poisson process with rate $\alpha$
  - Poisson process determines number of split times, $N$
  - given $K$ intervals, locations are uniformly distributed on $(0, \tau_{\text{max}}]$

- Second stage overall trend, $\mu$
  - improper flat prior
Prior distributional assumptions

- Second stage overall variability, $\sigma^2$
  
  - Gamma($a, b$) for precision

  - baseline choice: Gamma(0.5, 0.01)
    
    - induced prior for $\sigma$ has 95% of central mass between 0.06 and 4.54

- exploit conjugacy in the posterior
**Bayesian hierarchical model**

**Posterior distribution**

- For fixed \( K^L \) and \( K^B \), let
  \[
  \theta(K^L, K^B) = (\tau^L, \lambda, \mu_\lambda, \sigma_\lambda^2, \gamma, \tau^B, \beta, \mu_\beta, \sigma_\beta^2)
  \]
  
  - \((4 + P + 2(K^L + K^B))\)-dimensional parameter

- Posterior distribution:
  \[
  \pi(K^L, K^B, \theta(K^L, K^B)) = L^S(\theta; \text{data}) \times \text{MVN}_{K^L} (\lambda | \mu_\lambda, \sigma_\lambda^2 \Sigma_\lambda) \times \text{MVN}_{K^B} (\beta | \mu_\beta, \sigma_\beta^2 \Sigma_\beta) \times \text{Poisson}(N_\lambda | \alpha_\lambda) \times \text{Poisson}(N_\beta | \alpha_\beta) \times \text{Gamma}(\sigma_\lambda^{-1} | a_\lambda, b_\lambda) \times \text{Gamma}(\sigma_\beta^{-1} | a_\beta, b_\beta)
  \]

where \( N_\lambda = K^L - 1 \) and \( N_\beta = K^B - 1 \)
Bayesian hierarchical model

Reversible jump MCMC scheme

- Use Markov Chain Monte Carlo to extract features of the posterior distribution

- MCMC scheme proceeds by updating subsets of the parameter vector, conditional on the remaining components

- Full parameter space: $\mathbb{Z}^+ \times \mathbb{Z}^+ \times \Theta(K^L, K^B)$
  - $\mathbb{Z}^+$ is the set of positive integers

- Updating components of $\theta(K^L, K^B)$
  - relatively straightforward
  - exploit conjugacies for $\mu$ and $\sigma^2$ parameters
  - Metropolis-Hastings step for remaining components
Bayesian hierarchical model

Reversible jump MCMC scheme

- Updating $K^L$ or $K^B$
  - requires change in dimension of parameter space
  - Metropolis-Hastings-Green step

- See Hanuese, Rudser, and Gillen (2008) for details
# Application to transplant data

## Updated USRDS data

- Additional follow-up/subjects, through 12/31/2010.

- Modifications to previous model:
  - < 25 year olds only
  - whites only
  - additional (linear) adjustment for age

- Interpretation of baseline hazard function $h_0(\cdot)$:
  - white, male, 20-year old with 6 months of prior dialysis
Application to transplant data

Posterior sampling

- Posterior samples:
  - two simultaneous chains; 2 million scans each
  - 25% burnin
Dimension parameters; $K_L$ and $K_B$

**Posterior Median 5; 95% CI (2, 8)**

**Posterior Median 4; 95% CI (2, 8)**
Second-stage parameters; $\mu_\lambda$, $\log(\sigma_\lambda)$, $\mu_\beta$, $\log(\sigma_\lambda)$

- Posterior Median $-7.49$; 95% CI $(-9.21, -6)$
- Posterior Median $-1.81$; 95% CI $(-4.04, 0.35)$
- Posterior Median $1.95$; 95% CI $(0.24, 3.89)$
- Posterior Median $-1.3$; 95% CI $(-3.97, 0.33)$
Introduction
PTLD following renal transplantation
Limitations of previous work

A Flexible Bayesian Survival model
Bayesian hierarchical model

Application to transplant data

Discussion
Log-hazard ratio associated with transplant
Comparison with maximum partial likelihood (Cox model)

Transplant time, years

Transplant hazard ratio, exp{β(t)}

0 5 10 15 20

0.0 0.5 1.0 1.5 2.0 2.5 3.0

Lecture - Discussion
Stat 255 - D. Gillen

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Discussion
## Application to transplant data

### Point estimates

<table>
<thead>
<tr>
<th>Covariate</th>
<th>Maximum PL</th>
<th>Bayesian Model</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>0.94 (0.91, 0.97)</td>
<td>0.94 (0.91, 0.98)</td>
</tr>
<tr>
<td>Female</td>
<td>1.19 (0.71, 1.99)</td>
<td>1.17 (0.66, 2.02)</td>
</tr>
<tr>
<td>Duration</td>
<td>1.27 (1.02, 1.59)</td>
<td>1.27 (0.99, 1.56)</td>
</tr>
<tr>
<td>Transplant Wait List</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>&lt; 6 mths</td>
<td>7.71 (3.50, 16.98)</td>
<td>4.74 (1.54, 14.38)</td>
</tr>
<tr>
<td>6 to 12 mths</td>
<td>4.65 (1.89, 11.44)</td>
<td>4.45 (1.57, 13.11)</td>
</tr>
<tr>
<td>12 to 18 mths</td>
<td>1.96 (0.65, 5.89)</td>
<td>2.72 (0.98, 8.03)</td>
</tr>
<tr>
<td>18 to 24 mths</td>
<td>2.54 (0.89, 7.23)</td>
<td>2.49 (0.89, 7.23)</td>
</tr>
<tr>
<td>24 to 30 mths</td>
<td>1.93 (0.57, 6.50)</td>
<td>2.43 (0.85, 7.31)</td>
</tr>
<tr>
<td>30 to 36 mths</td>
<td>2.72 (0.81, 9.19)</td>
<td>2.46 (0.74, 8.26)</td>
</tr>
</tbody>
</table>
Log-hazard ratio associated with transplant by age strata

(a) Less than 25 years
(b) 25 to 44 years
(c) 45 to 59 years
(d) 60 years and older
### Application to transplant data

#### Selected sensitivity analysis results (age < 25)

<table>
<thead>
<tr>
<th>Covariate</th>
<th>Full</th>
<th>Restricted</th>
</tr>
</thead>
<tbody>
<tr>
<td>$K^L$</td>
<td>6 (3, 10)</td>
<td>6</td>
</tr>
<tr>
<td>$K^B$</td>
<td>5 (2, 9)</td>
<td>6</td>
</tr>
</tbody>
</table>

**Second-stage**

<table>
<thead>
<tr>
<th></th>
<th>Full</th>
<th>Restricted</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\mu_\lambda$</td>
<td>-6.80 (-9.40, -3.84)</td>
<td>-6.99 (-7.86, -6.21)</td>
</tr>
<tr>
<td>$\sigma_\lambda$</td>
<td>0.85 (0.11, 3.54)</td>
<td>0.16 (0.06, 0.70)</td>
</tr>
<tr>
<td>$\mu_\beta$</td>
<td>1.15 (-0.76, 2.89)</td>
<td>1.46 (0.19, 2.79)</td>
</tr>
<tr>
<td>$\sigma_\beta$</td>
<td>0.38 (0.09, 1.52)</td>
<td>0.30 (0.10, 0.77)</td>
</tr>
</tbody>
</table>

**Transplant**

<table>
<thead>
<tr>
<th>Time</th>
<th>Full</th>
<th>Restricted</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wait List</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>&lt; 6 mths</td>
<td>4.74 (1.54, 14.38)</td>
<td>6.52 (3.03, 15.20)</td>
</tr>
<tr>
<td>6 to 12 mths</td>
<td>4.45 (1.57, 13.11)</td>
<td>4.42 (2.11, 9.96)</td>
</tr>
<tr>
<td>12 to 18 mths</td>
<td>2.72 (0.98, 8.03)</td>
<td>2.90 (1.21, 6.87)</td>
</tr>
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<td>24 to 30 mths</td>
<td>2.43 (0.85, 7.31)</td>
<td>2.54 (1.01, 6.23)</td>
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<td>30 to 36 mths</td>
<td>2.46 (0.74, 8.26)</td>
<td>2.87 (1.14, 7.06)</td>
</tr>
</tbody>
</table>
Application to transplant data

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</tr>
<tr>
<td>$K^B$</td>
<td>5 (2, 9)</td>
<td>5 (2, 9)</td>
</tr>
<tr>
<td>Second-stage</td>
<td></td>
<td></td>
</tr>
<tr>
<td>$\mu_\lambda$</td>
<td>-6.80 (-9.40, -3.84)</td>
<td>-6.80</td>
</tr>
<tr>
<td>$\sigma_\lambda$</td>
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Application to transplant data

Selected sensitivity analysis results (age < 25)

<table>
<thead>
<tr>
<th>Covariate</th>
<th>Gamma(0.5, 0.01)</th>
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</tr>
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<tbody>
<tr>
<td>$K^L$</td>
<td>5 (2, 8)</td>
<td>5 (3, 10)</td>
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<td>$K^B$</td>
<td>4 (2, 8)</td>
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Second-stage

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Transplant

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Discussion

Final comments

- Random split-times provides a useful tool for flexibly modeling both the baseline hazard function and covariate effects
  - Easily extendable to allow for time-dependent covariates

- Can be a bit computationally intensive
  - M-H-G to account for changing dimension of the parameter space
  - Approx 6 hrs for full analysis (with 2 million scans) on a large dataset ($N = 85,056$)
  - Overall 40% acceptance rate

- Current work is an extension to joint longitudinal-survival modeling