Bayesian Semi-Parametric Analysis of Semi-Competing Risks Data

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Approximately 56,000 individuals will be diagnosed with pancreatic cancer in the U.S. this year.

Unfortunately there are no effective screening modalities
  * patients are usually diagnosed at late stages

Large majority are not eligible for surgical treatment
  * chemotherapy is administered in the context of palliative care

Prognosis is very poor
  * 5-year survival rate is 9%
Ongoing collaboration

- Broad goal is to characterize and understand variation in the quality of end-of-life care for patients diagnosed with pancreatic cancer

- Quality can be measured in many ways

- Our immediate focus is on readmission
  * readmission after discharge from the hospitalization at which the diagnosis was given

- Hospital-specific readmission rates are calculated and reported by CMS
  * logistic regression
  * Readmissions Reduction Program
  * Hospital Inpatient Quality Reporting Program
  * determine, in part, a hospital's reimbursement rate for the subsequent year
Challenges

Death as a competing risk

Consider outcomes among $N = 16,051$ Medicare patients:

* between 2005-2008
* inpatient care claims, including hospitalizations

<table>
<thead>
<tr>
<th>Observed events during the first 90 days</th>
<th>2,254</th>
<th>14.0%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Readmitted and subsequently died</td>
<td>2,213</td>
<td>13.8%</td>
</tr>
<tr>
<td>Readmitted and censored prior to death</td>
<td>7,505</td>
<td>46.8%</td>
</tr>
<tr>
<td>Death without readmission</td>
<td>4,079</td>
<td>25.4%</td>
</tr>
</tbody>
</table>
- Primary interest lies with readmission or time-to-readmission
- We only observe readmission among folks who have not died
- Data that exhibit this structure is often referred to as semi-competing risks data
Naïve approaches to learning about readmission might include:

(a) logistic regression analyses
   * binary outcome
   * ignores death as a competing risk (!)

(b) Cox regression analyses
   * time-to-readmission
   * treat death as an independent censoring mechanism (!)

(c) composite endpoint analyses
   * first of either readmission or death
   * conflation changes the scientific question (!)

In the profiling context, inappropriate handling of death may be problematic because:

* a hospital may have a low readmission rates because they do a poor job of keeping patients alive
* a hospital may have a high readmission rates because they do a good job of keeping patients alive
Semi-Competing Risks Problem

- If a patient dies prior to readmission, the time to readmission will never be observed.
- Key challenge: non-identifiability

\[ T_1 < T_2 \]

\[ S(t_1, t_2) \text{ and } S_i(t_1) \text{ are not identifiable in the lower wedge, } T_1 \geq T_2 \]

(Fine et al., 2001)
An intuitive approach to analyzing semi-competing risks data is to view the data as arising from an underlying illness-death multi-state model.

Movement between the states is governed by a set of transition-specific intensity or hazard functions.
To permit the identifiability of the marginal density of $T_1$, Xu et al. (2010) set $T_1 = \infty$ if a subject experiences death prior to readmission.
Transition-Specific Hazard Functions

Modeling strategy is to place structure on the three hazard functions as follows:

\[
\begin{align*}
    h_1(t_{1i} | \gamma_i, x_i) &= \gamma_i h_{01}(t_{1i}) e^{x_i^\top \beta_1}, \quad t_{1i} > 0, \\
    h_2(t_{2i} | \gamma_i, x_i) &= \gamma_i h_{02}(t_{2i}) e^{x_i^\top \beta_2}, \quad t_{2i} > 0, \\
    h_3(t_{2i} | t_{1i}, \gamma_i, x_i) &= \gamma_i h_{03}(t_{2i}) e^{x_i^\top \beta_3}, \quad 0 < t_{1i} < t_{2i},
\end{align*}
\]

* \( \gamma_i \sim \text{Gamma}(\theta^{-1}, \theta^{-1}) \) is a shared patient-specific frailty
Our experience with both of these is that they are highly unstable
  * maximization (or root solving) over a large parameter space is tricky

Potential benefits of the Bayesian paradigm:
  * ability to incorporate substantive prior information
  * automated quantification of uncertainty
  * prediction is straightforward
  * prescriptive nature of computation

Four main challenges:
  1. specification of the three continuous baseline hazard functions
  2. prior elicitation and specification
  3. robust and efficient computational schemes
  4. user-friendly software
Baseline hazard functions

\[ h_1(t_1) = \gamma_{ji} h_{01}(t_1) \exp \left\{ \mathbf{X}_{ji1}^\top \beta_1 \right\}, \quad t_1 > 0, \]

\[ h_2(t_2) = \gamma_{ji} h_{02}(t_2) \exp \left\{ \mathbf{X}_{ji2}^\top \beta_2 \right\}, \quad t_2 > 0, \]

\[ h_3(t_2|t_1) = \gamma_{ji} h_{03}(t_2|t_1) \exp \left\{ \mathbf{X}_{ji3}^\top \beta_3 \right\}, \quad 0 < t_1 < t_2. \]

- One simple way forward would be to take the baseline hazard function from some parametric distribution
  - exponential/Weibull distribution

- Parametric modeling is often viewed in a negative light but it does have some advantages
  - estimation/inference tends to be (more) straightforward
  - typically more stable in data poor settings
  - prediction is more straightforward
Nevertheless, towards a more flexible model specification, we also consider modeling each the logarithm of $h_{0g}(t)$ as a mixture of piecewise constant functions

$$\log(h_0(t)) = \lambda(t) = \sum_{j=1}^{J} 1_{[s_j < t \leq s_{j+1}]} \lambda_j$$

* $s = \{s_1, \ldots, s_J, s_{J+1}\}$ is a partition of the observed time scale

Within the Bayesian framework we can treat $J$ and $s$ as ‘random’
* assign priors and update their values in the MCMC scheme

Result is that the value of $\lambda(t)$ in any given small interval is (marginally) a mixture of piecewise constant functions
* smooth!
The Observed Likelihood of \((\beta_1, \beta_2, \beta_3, \lambda_1, \lambda_2, \lambda_3, \gamma)\)

Then the observed data likelihood for grouped or discretized survival times for \(n\) subjects has the following form in terms of the disjoint intervals:

\[
\prod_{j=1}^{J_1+1} \prod_{k=1}^{J_2+1} \prod_{l=1}^{J_3+1} \exp \left\{ \lambda_{1j} d_{1j} - e^{\lambda_{1j}} \sum_{m \in \mathcal{R}_{1j}} \Delta_{1mj} \gamma_{m} e^{x_{m}^\top \beta_1} \right\} \\
\times \exp \left\{ \lambda_{2k} d_{2k} - e^{\lambda_{2k}} \sum_{q \in \mathcal{R}_{1k}} \Delta_{2qk} \gamma_{q} e^{x_{q}^\top \beta_2} \right\} \\
\times \exp \left\{ \lambda_{3l} d_{3l} - e^{\lambda_{3l}} \sum_{r \in \mathcal{R}_{2l}} \Delta_{3rl} \gamma_{r} e^{x_{r}^\top \beta_3} \right\} \\
\times \prod_{m' \in \mathcal{D}_{1j}} \gamma_{m'} e^{x_{m'}^\top \beta_1} \prod_{q' \in \mathcal{D}_{2k}} \gamma_{q'} e^{x_{q'}^\top \beta_2} \prod_{r' \in \mathcal{D}_{3l}} \gamma_{r'} e^{x_{r'}^\top \beta_3} ,
\]
The Prior Distributions

Our prior choices are, for $g \in \{1, 2, 3\}$:

$$\pi(\beta_g) \propto 1,$$

$$\lambda_g | J_g, \mu_{\lambda_g}, \sigma_{\lambda_g}^2 \sim \mathcal{N}_{J_g+1}(\mu_{\lambda_g} \mathbf{1}, \sigma_{\lambda_g}^2 \Sigma_{\lambda_g}),$$

$$J_g \sim \mathcal{P}(\alpha_g),$$

$$\pi(s_g | J_g) \propto \frac{(2J_g + 1)! \prod_{j=1}^{J_g+1} (s_j - s_{j-1})}{(s_g, J_g+1)(2J_g+1)},$$

$$\pi(\mu_{\lambda_g}) \propto 1,$$

$$\sigma_{\lambda_g}^{-2} \sim \mathcal{G}(a_g, b_g),$$

and

$$\gamma_i | \theta \sim \mathcal{G}(\theta^{-1}, \theta^{-1}), \quad i = 1, \ldots, n$$

$$\theta^{-1} \sim \mathcal{G}(\psi, \omega).$$
Computation and software

- MCMC via a random scan Gibbs sampling algorithm

- Most of the moves are straightforward
  * exploit conjugacies
  * Metropolis-Hastings update

- Certain moves for the baseline hazard functions requires a change in the dimension of the parameter space
  * those pertaining to the number of intervals, $J$
  * use a reversible-jump Metropolis-Hastings-Green update

- Implemented in the SemiCompRisks package for R
  * C is used as the primary work engine
  * documentation includes a series of cheat sheets specific to various models that might be of interest
To perform posterior estimation and inference, we use a random scan Gibbs sampling algorithm to generate samples from the full posterior distributions.

Updating $s_g$ and $J_g$ requires a change in the dimension of the parameter space; a reversible jump MCMC Metropolis-Hastings-Green (MHG) algorithm was developed and implemented (Green, 1995).

R-package ”SemiCompRisks” is available in CRAN.
3. Application

- The data available for this study consists of information on 100% Medicare enrollees from Jan/2005 to Nov/2008.

- A total of 16,051 individuals aged 75 years or older are considered:
  1. They were hospitalized with a diagnosis of pancreatic cancer,
  2. They did not undergo any pancreatic cancer specific procedures (i.e. their disease was sufficiently advanced that curative treatment was not a viable option).

- For both outcomes, we (administratively) censored observation time at $t = 90$ days.
Objectives

- Identifying risks factors for time to readmission
- Providing the measure of dependence between time to readmission and time to death
- Predictive probability of being readmitted
Table: Posterior medians (PM) and 95% credible intervals (CI) for hazard ratio parameters \((\exp(\beta_g), g \in \{1, 2, 3\})\) from semi-competing risks analyses based on the proposed Bayesian framework. Results are based on setting the Poisson rate parameters \(\alpha_g, g \in \{1, 2, 3\}\), to 20 for all MVN-ICAR specifications of baseline hazard functions.

<table>
<thead>
<tr>
<th></th>
<th>Readmission to readmission</th>
<th>Death prior to readmission</th>
<th>Death after readmission</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>PM (95% CI)</td>
<td>PM (95% CI)</td>
<td>PM (95% CI)</td>
</tr>
<tr>
<td>Comorbidity index(^a)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0-1</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>2-3</td>
<td>1.03 (0.96, 1.12)</td>
<td>0.99 (0.93, 1.05)</td>
<td>0.99 (0.89, 1.10)</td>
</tr>
<tr>
<td>≥ 4</td>
<td>1.26 (1.16, 1.37)</td>
<td>1.15 (1.07, 1.23)</td>
<td>1.07 (0.95, 1.21)</td>
</tr>
<tr>
<td>Race</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>Non-white</td>
<td>1.27 (1.17, 1.39)</td>
<td>0.86 (0.79, 0.93)</td>
<td>1.13 (1.01, 1.28)</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>Male</td>
<td>1.10 (1.03, 1.18)</td>
<td>1.30 (1.23, 1.38)</td>
<td>1.22 (1.12, 1.34)</td>
</tr>
<tr>
<td>Age(^b)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0.87 (0.84, 0.90)</td>
<td>1.07 (1.04, 1.10)</td>
<td>1.08 (1.03, 1.13)</td>
<td></td>
</tr>
<tr>
<td>Care after discharge</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Home</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>Home care</td>
<td>1.21 (1.12, 1.31)</td>
<td>1.53 (1.39, 1.69)</td>
<td>1.23 (1.10, 1.38)</td>
</tr>
<tr>
<td>ICF/SNF</td>
<td>0.82 (0.75, 0.91)</td>
<td>3.46 (3.19, 3.79)</td>
<td>1.76 (1.54, 2.01)</td>
</tr>
<tr>
<td>Hospice</td>
<td>0.18 (0.15, 0.21)</td>
<td>8.96 (8.25, 9.86)</td>
<td>3.08 (2.38, 3.99)</td>
</tr>
<tr>
<td>Hospital stay</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤ 2 weeks</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>&gt; 2 weeks</td>
<td>1.25 (1.12, 1.39)</td>
<td>1.09 (1.00, 1.20)</td>
<td>0.89 (0.76, 1.05)</td>
</tr>
</tbody>
</table>

\(^a\) Number of diagnosis codes given during the initial hospitalization from a list of 27 disease/disorders related to prognosis following hospital discharge.

\(^b\) Standardized so that a one-unit contrast corresponds to a difference of 5 years.
Identifying Risk Factors for Time to Readmission

- There is evidence of increased risk for readmission associated with a high comorbidity index, a long (initial) hospital stay, non-white race, male gender, and discharge to home care.

- The semi-competing risks analysis reveals nuance in how several covariates confer risk for death.
  - The semi-competing risks analysis reveals the evidence of the decreased risk of death for an individual with non-white race who have not been readmitted (HR 0.86; 95% CI 0.79, 0.93) and the evidence of the increased risk of death for an individual with non-white race after readmission (HR 1.13; 95% 1.01, 1.28).
Table: Covariate profiles of the four different individuals considered for the explanatory hazard ratio and the posterior predictive distribution

<table>
<thead>
<tr>
<th>Comorbidity index</th>
<th>Race</th>
<th>Gender</th>
<th>Age</th>
<th>Care after discharge</th>
<th>Hospital stay</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>0-1</td>
<td>White</td>
<td>Female</td>
<td>82</td>
<td>Home</td>
</tr>
<tr>
<td>Subject 1</td>
<td>≥ 4</td>
<td>Non-white</td>
<td>Male</td>
<td>92</td>
<td>Home care</td>
</tr>
<tr>
<td>Subject 2</td>
<td>0-1</td>
<td>Non-white</td>
<td>Female</td>
<td>92</td>
<td>Home</td>
</tr>
<tr>
<td>Subject 3</td>
<td>≥ 4</td>
<td>White</td>
<td>Male</td>
<td>82</td>
<td>Hospice</td>
</tr>
</tbody>
</table>
Measure of dependence between $T_1$ and $T_2$

Explanatory Hazard Ratio (EHR):

$$\frac{h_3(t_2|t_1, \gamma, x)}{h_2(t_2|\gamma, x)} = \frac{h_{03}(t_2)}{h_{02}(t_2)} \exp[x^\top (\beta_3 - \beta_2)]$$

Figure: Pointwise posterior median and 95% credible intervals for the explanatory hazard ratio (EHR) for the four individuals.
Figure: Posterior predictive distribution (conditioning on $\gamma = 1$) for four individuals; panels (a)-(d) show the posterior predictive distribution $F(t_1, t_2)$ for $t_1 \leq t_2$; panels (e)-(h) provide the posterior predictive distribution $F_\infty(t_2)$. 
Final comments

- Semi-competing risks framework provides an opportunity to think about any given line of research in a different way.
  - consider the two events jointly

- Implemented in the SemiCompRisks package for R

- Cluster-correlated data (JASA, 2016), AFT model (Biometrics, 2017)
Acknowledgements

- Sebastien Haneuse
- Francesca Dominici
- Deborah Schrag
- Yun Wang

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Figure: Estimates of the log-baseline hazard functions from the proposed Bayesian framework for semi-competing risks analysis. Three sets of analyses were performed, with values of $\alpha_g$ of 5, 20 and 50 adopted for all Poisson rate parameters.