Semiparametric Spatial Model for Interval-censored Data with Time-varying Covariate Effects

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Outline

- Introduction and motivating example
- Likelihood, prior and posterior
- Simulation study and application
- Summary and future work

Survival Analysis

Survival analysis is used to analyze data in which the time until the event is of interest. The response is often referred to as a failure time, survival time, or event time, e.g.,

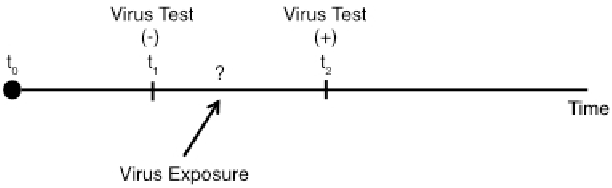
- Time until tumor recurrence
- Time until cardiovascular death after some treatment intervention
- Time until AIDS for HIV patients
- Time until a machine part fails

The survival time response

- Usually Continuous
- Incompletely observed responses are censored
- Let survival time T be a nonnegative random variable and

$$T \in (L, R] \quad \text{(Sun, 2007)}$$

  - Exact observation: $0 < L = R < \infty$
  - Right Censoring: $0 < L < R = \infty$
  - Interval Censoring: $0 < L < R < \infty$
- e.g., HIV infection time



- Ignore interval-censoring?

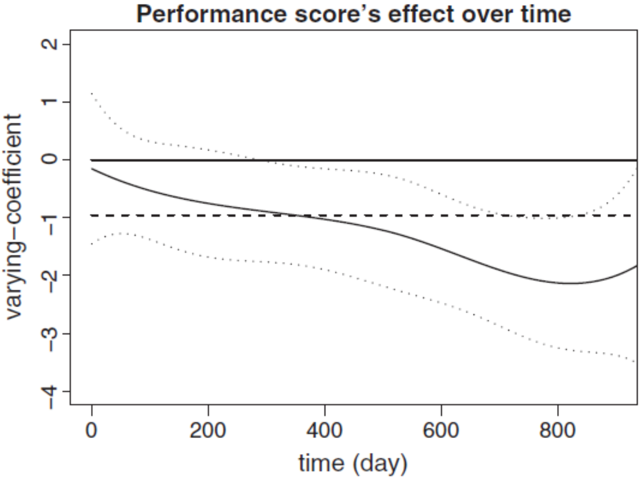
Statistical Methods

- Estimation of the survival distribution
  - Kaplan-Meier or Product Limit Estimator
  - Life-Table
- Comparison of survival curves
  - Log-Rank Test
- Regression Models with respect to hazard
  - Parametric regression models: exponential, Weibull, etc.
  - Semiparametric regression models: Cox, etc.

$$\lambda(t) = \lambda_0(t) \exp(\mathbf{x}^T \boldsymbol{\beta})$$

- Cox model, or relative risk model = proportional hazards model? $\boldsymbol{\beta}$ or $\boldsymbol{\beta}(t)$.

Time-varying coefficient example



Time-varying effect of the performance score on stroke readmission: $\beta(t)$, solid; 95% point-wise confidence interval, dotted; performance score effect in constant coefficient model, dashed (Yu et al., 2013).

Motivating example

Smoking cessation data in southeastern Minnesota

- Lung health study (Murray et al., 1998)
- Event of interest: Time to smoking relapse
- Covariates: Gender (F/M), Treatment (Intervention/Usual)

ObsLHS	SexF	Relapse	Timept1	Timept2	Zip	Treatment
4266	0	1	0.997	2.146	55009	1
4213	0	0	4.895	Inf	55009	2

Challenge

- The effect of **Treatment** may vary over time
- **Cox** model with **interval-censored** data
- The **correlation** of subjects **within/between** zip code areas

Methods

Challenge

- The effect of **Treatment** may vary over time
  Solution: Time-varying coefficient $\beta(t)$
  - Gibbs sampling with piecewise constant coefficient assumption (Sinha et al., 1999)
  - Penalized splines (Cai and Betensky, 2003; Kneib, 2006)
  - ✓ Reversible jump Markov chain Monte Carlo (Green, 1995)
- **Cox** model with **interval-censored** data
  Solution: Piecewise constant baseline and augmented likelihood (Sinha et al., 1999)
- The **correlation** of subjects **within/between** zip code areas
  - Frailty model (Yu et al., 2013; Zhang et al., 2018)
  - ✓ Spatially correlated frailty (Carlin and Louis, 1997; Banerjee et al., 2003)

Model

Cox model with time-varying coefficient and frailty:

$$\lambda(t|\omega_i, \mathbf{x}_{i,j}) = \lambda_0(t)\exp(\mathbf{x}_{i,j}^T\beta(t) + \omega_i)$$

- $i = 1, 2, ..., n$, $j = 1, 2, ..., m_i$, $N = \sum_{i=1}^{n} m_i$
- $\lambda_0(.)$ is an unknown baseline hazard function common to all subjects
- $\mathbf{x}_{i,j}$ is the covariate vector for the j^{th} subject in the i^{th} cluster
- $\beta(t)$ is the time-varying coefficient of main interest
- ω_i is the frailty of the i^{th} cluster

likelihood

Observed data likelihood of subject i

- Interval censoring: $\ell_i = \mathcal{P}(T_i > L_i) - \mathcal{P}(T_i > R_i)$
- Right censoring: $\ell_i = \lambda(t_i)^{\delta_i} S(t_i)$

Latent variables

- $dN_{i,j,k} = \mathbb{1}(T_{i,j} \in (\tau_{k-1}, \tau_k]), k = 1, 2, \dots K$
- $Y_{i,j,\ell} = 1$ for $\ell < k$, $Y_{i,j,\ell} = 0$ for $\ell > k$, and $Y_{i,j,\ell} = (T_{i,j} - \tau_{\ell-1})/\Delta_\ell$ for $\ell = k$

Augmented likelihood
Set $\Theta = \{\log \lambda_0(t), \boldsymbol{\beta}(t)\}$, $D = \{dN_{i,j,k}, Y_{i,j,k}\}$, $W = \{\omega_i\}$, $\lambda_k = \lambda_0(\tau_k)$ and $\boldsymbol{\beta}_k = \boldsymbol{\beta}(\tau_k)$ for $k = 1, 2, \dots, K$,

$$\ell_{i,j}(\Theta | D, W, \mathbf{x}_{i,j}) = \prod_{k=1}^{K} \{\lambda_k \omega_i \exp(\mathbf{x}_{i,j}^T \boldsymbol{\beta}_k)\}^{dN_{i,j,k}} \exp\{-\Delta_k \lambda_k \omega_i \exp(\mathbf{x}_{i,j}^T \boldsymbol{\beta}_k) Y_{i,j,k}\}$$

Prior specification

- Three models
  - Model 1: Fixed $\boldsymbol{\beta}$ with spatially correlated ω_i's
  - Model 2: Time-varying $\boldsymbol{\beta}(t)$ with independent ω_i's
  - Model 3: Time-varying $\boldsymbol{\beta}(t)$ with spatially correlated ω_i's
- Prior of coefficient
  - Fixed $\boldsymbol{\beta}$: $\lambda_k \sim \mathcal{G}(c_k, d_k)$, $\beta \sim \mathcal{N}(\mu_0, \sigma_0^2)$
  - Time-varying $\boldsymbol{\beta}(t)$: $\theta(\tau_p)|\theta(\tau_{p-1}) \sim \mathcal{N}(\theta(\tau_{p-1}), \nu)$, where $\theta = \{\log \lambda_0, \boldsymbol{\beta}\}$
- Prior of frailty
  - Independent ω_i: $\omega_i \overset{i.i.d.}{\sim} \mathcal{N}(0, \sigma^2)$.
  - Spatially correlated ω_i: $\omega_i|\omega_{-i} \sim \mathcal{N}(\bar{\omega}_{ii}, 1/(m_i\pi_\omega))$ Intrinsic conditional autoregressive (ICAR) model prior (Besag and Kooperberg, 1995)

Posterior computation of latent variables: $dN_{i,j,k}$ and $Y_{i,j,k}$

- Event indicator vector $(dN_{i,j,1}, dN_{i,j,2}, ..., dN_{i,j,k})$ follows a multinomial distribution with size 1 and probability vector $(e_{i,j,1}, e_{i,j,2}, ..., e_{i,j,k})$, where for $k = 1, 2, ..., K$,

$$e_{i,j,k} = \frac{p_{i,j,k}\mathbb{1}(s_k \in (L_{i,j}, R_{i,j}])}{\sum_{s_l \in (L_{i,j}, R_{i,j}]} p_{i,j,l}},$$

$$p_{i,j,k} = \begin{cases} \exp\left\{-\sum_{l=1}^{k-1} \Delta_l \lambda_l \exp(\mathbf{x}_{i,j}^T \boldsymbol{\beta}_k + \omega_i)\right\} - & \\ \exp\left\{-\sum_{l=1}^{k} \Delta_l \lambda_l \omega_i \exp(\mathbf{x}_{i,j}^T \boldsymbol{\beta}_k + \omega_i)\right\} & \text{if } k > 1 \\ 1 - \exp\left\{-\Delta_1 \lambda_1 \exp(\mathbf{x}_{i,j}^T \boldsymbol{\beta}_1 + \omega_i)\right\} & \text{if } k = 1 \end{cases}$$

- Sample failure time $T_{i,j}$, where $T_{i,j}$ follows a doubly truncated exponential distribution on $(\tau_{k-1}, \tau_k]$

$$F(u) = \frac{1 - \exp\{-\lambda_k (u - s_{k-1}) \exp(\mathbf{x}_{i,j}^T \boldsymbol{\beta}_k) + \omega_i\}}{1 - \exp\{-\lambda_k \Delta_k \exp(\mathbf{x}_{i,j}^T \boldsymbol{\beta}_k + \omega_i)\}}$$

- $Y_{i,j,k} = (T_{i,j} - \tau_{k-1})/\Delta_k$

Posterior computation: $\lambda_0(t)$, $\boldsymbol{\beta}(t)$ and ω_i

- $\theta(t) = \{\log(\lambda_0(t)), \beta(t)\}$. Reversible jump MCMC
  - Update move: Number of jumps P and jump times are fixed

$$\Pr(\theta(\tau_p)|\Theta/\{\theta(\tau_p)\}, D, \nu, W) \propto \exp\left\{-\frac{(\theta(\tau_p)-\mu_p)^2}{2\sigma_p^2}\right\}$$

$$\times \exp\left\{-\sum_{i=1}^{n}\sum_{j=1}^{m_i}\sum_{k=1}^{K} \mathbb{1}(\tau_k \in (\tau_{p-1}, \tau_p])\Delta_k \lambda_k \omega_i \exp(\mathbf{x}_{i,j}^T \boldsymbol{\beta}_k) Y_{i,j,k}\right\},$$

  - Birth move: A new jump time τ' is randomly selected from non-jump time grids
  - Death move: A current jump time τ' is randomly selected and deleted

- Sample ω_i with Metropolis-Hastings algorithm.

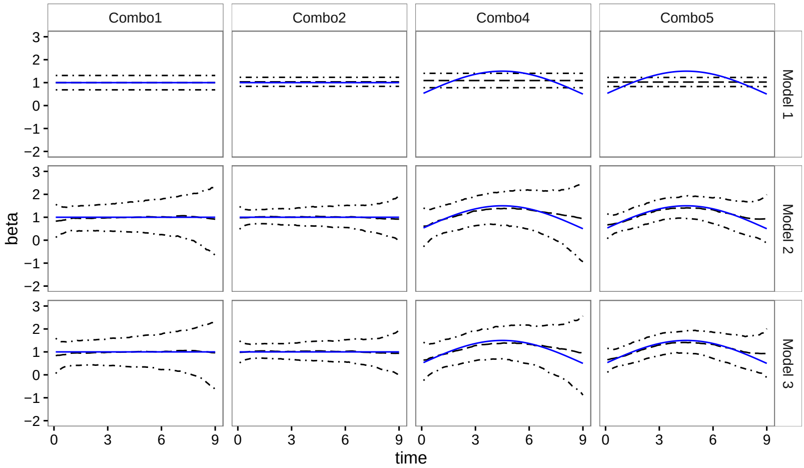
$$\Pr(\omega_i|\Theta, D, \pi_\omega, \omega_{-i}) \propto \prod_{j=1}^{J_i}\prod_{k=1}^{K}\{\lambda_k \exp(\mathbf{x}_{i,j}^T\boldsymbol{\beta}_k + \omega_i)\}^{dN_{i,j,k}}$$

$$\exp\{-\Delta_k \lambda_k \exp(\mathbf{x}_{i,j}^T\boldsymbol{\beta}_k + \omega_i) Y_{i,j,k}\}\Pr(\omega_i|\omega_{-i}).$$

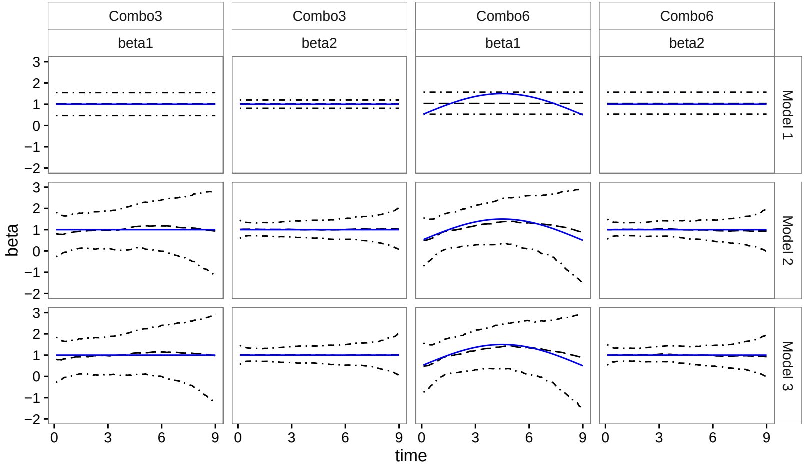
Simulation

- Six combinations
  Combo 1: $\beta_1 = 1$, $x_1 \sim \mathcal{B}(N, 0.5)$
  Combo 2: $\beta_1 = 1$, $x_1 \sim \mathcal{N}(0, 1)$
  Combo 3: $\beta_1 = 1$, $x_1 \sim \mathcal{B}(N, 0.5)$, $\beta_2 = 1$, $x_2 \sim \mathcal{N}(0, 1)$
  Combo 4: $\beta_1 = 0.5 + \sin(t\pi/9)$, $x_1 \sim \mathcal{B}(N, 0.5)$
  Combo 5: $\beta_1 = 0.5 + \sin(t\pi/9)$, $x_1 \sim \mathcal{N}(0, 1)$
  Combo 6: $\beta_1 = 0.5 + \sin(t\pi/9)$, $x_1 \sim \mathcal{B}(N, 0.5)$, $\beta_2 = 1$, $x_2 \sim \mathcal{N}(0, 1)$
- Spatial frailties are based on 45 zip code areas in Cincinnati, there are 15 subjects in each zip code area.
- Baseline hazard function: $\lambda_0(t) = 0.1\sqrt{t}$.
- Log-normal density function $\mathcal{LN}(x; 0, 0.4)$ is used to simulate follow-up times.

Coefficient estimates for combinations with one covariate



Coefficient estimates for combinations with two covariates



LPML comparison between Model 2 and Model 3

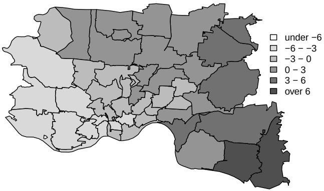
LPML comparison result between Model 2 and Model 3

	Combo 1	Combo 2	Combo 3
LPML Diff	117.6 (-139.0, 391.3)	145.8 (-287.1, 498.3)	125.5 (-92.9, 498.3)
% Diff $>$ 0	84%	79%	89%
	Combo 4	**Combo 5**	**Combo 6**
LPML Diff	116.4 (-129.5, 343.7)	115.1 (-159.9, 539.4)	100.6 (-117.9, 357.6)
% Diff $>$ 0	85%	70%	81%

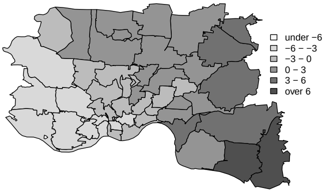
LPML Diff $=$ LPML of Model 3 $-$ LPML of Model 2. Mean and $(0.025, 0.975)$ quantile from 100 replicates are reported. % Diff $>$ 0 is calculated as percentage of LPML Diff $>$ 0 over 100 replicates.

Maps of posterior means for the 45 spatial frailties

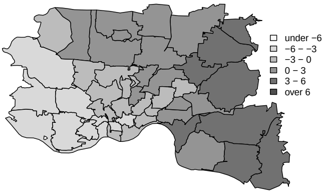
Simulated Frailties



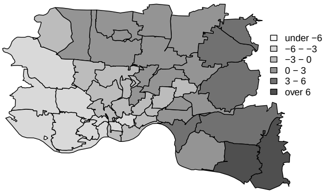
Model 1



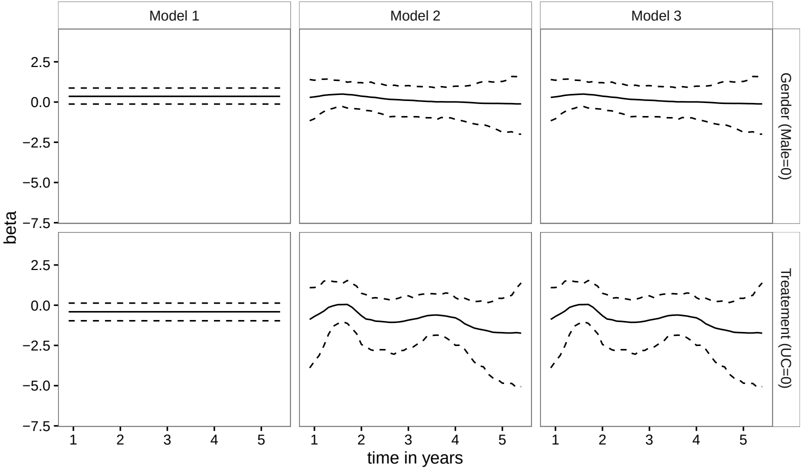
Model 2



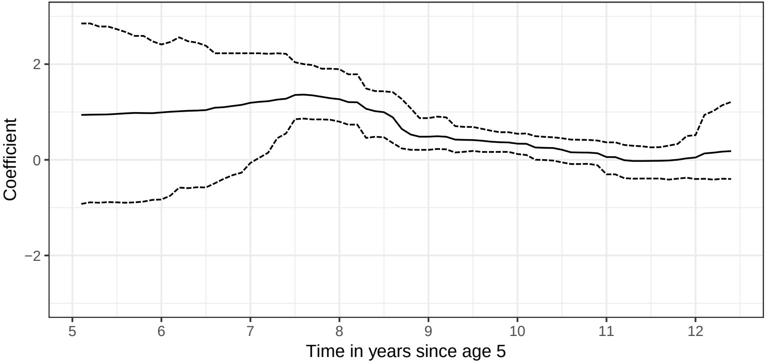
Model 3



Smoking data: Coefficient of *Gender* and *Treatment*

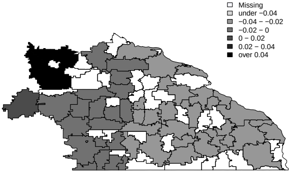


Tooth data (Zhang et al., 2018)

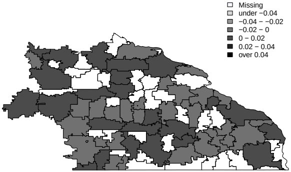


Posterior mean of frailties

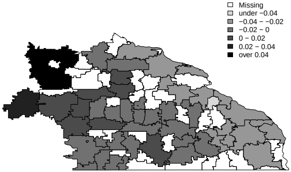
Model 1



Model 2



Model 3



Summary

- Reversible jump MCMC is a powerful tool to deal with model dimensionality, i.e., smooth the time-varying curve in this project.

- Spatial correlation needs to be considered.

- Current & future work
  - Improvement of reversible jump MCMC
  - Spline model?
  - Sample size calculation

Reference

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