Bayesian Semiparametric Cure Rate Model with an Unknown Threshold

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Outline

- Background and motivation
- Nonparametric prior specification
- Semiparametric model
- Posterior distributions
- Simulation studies
- Example
- Concluding remarks

Cure Rate Model

- In time-to-event analysis for certain diseases, there exists a fraction of the population that is cured of or insusceptible to the disease, who thus will never experience the failure.
- The standard (mixture) cure rate model of Berkson and Gage (1952)

$$S_{pop}(t) = \pi + (1 - \pi)S(t),$$

where $\pi \in (0, 1)$ and $S(t)$ is a proper survival function.

Hazard Functions

- The cumulative hazard function is

$$H_{pop}(t) = -\log S_{pop}(t) = -\log\{\pi + (1-\pi)S(t)\},$$

which satisfies that $\lim_{t\to 0} H_{pop}(t) = 0$ and $\lim_{t\to\infty} H_{pop}(t) = -\log\pi > 0$.

- The hazard rate is

$$h_{pop}(t) = \frac{\mathrm{d}}{\mathrm{d}t} H_{pop}(t) = \frac{(1-\pi)f(t)}{\pi + (1-\pi)S(t)},$$

where $f(t)$ is the density function corresponding to $S(t)$.

Alternative Cure Model

- The alternative cure rate model of Yakolev and Tsodikov (1996) is defined by

$$S_{pop}(t) = \exp\{-\theta F(t)\},$$

where $\theta > 0$ and $F(t)$ is a proper cumulative distribution function.

- This model satisfies the conditions that $\lim_{t\to 0} S_{pop}(t) = 1$ and $\lim_{t\to\infty} S_{pop}(t) = e^{-\theta}$, therefore $S_{pop}(t)$ is not a proper survival function.

Hazard Functions

- The cumulative hazard function is given by

$$H_{pop}(t) = -\log S_{pop}(t) = \theta F(t).$$

- The hazard rate is

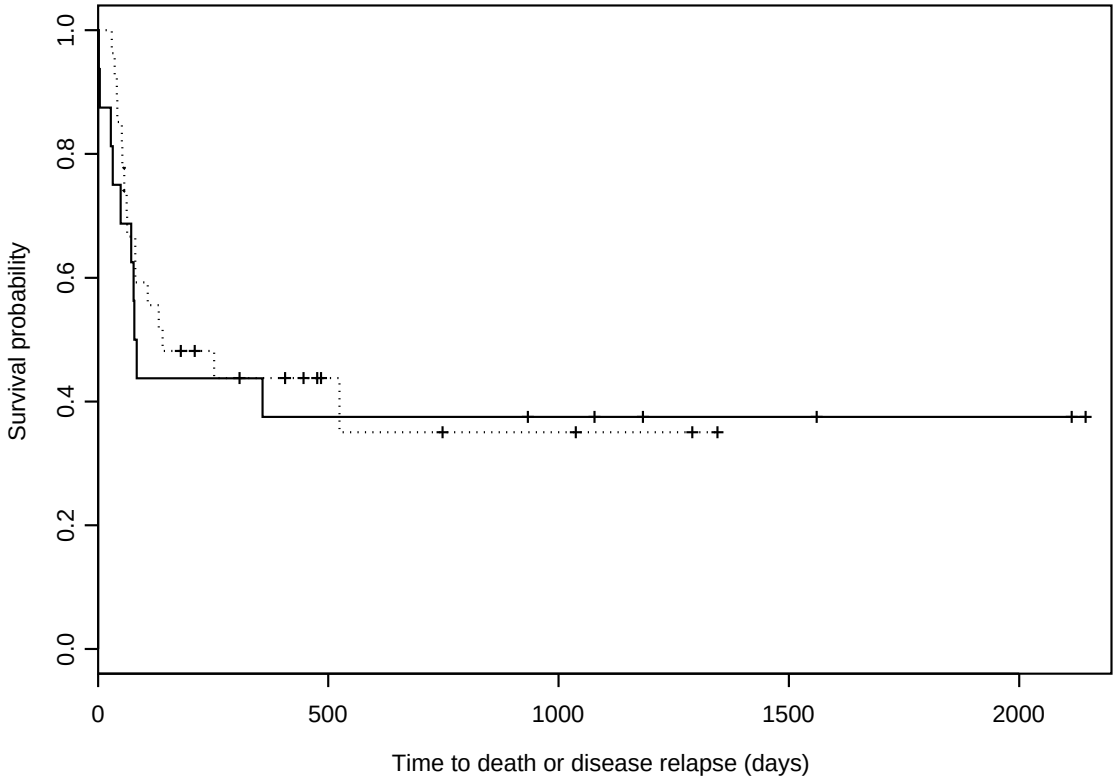
$$h_{pop}(t) = \frac{\mathrm{d}}{\mathrm{d}t} H_{pop}(t) = \theta f(t).$$

- Researchers often model a cure probability, but do not explicitly quantify the finite cure time, which would provide useful information with direct application to the clinical management of the disease.

BMT Example

- Patients had been diagnosed with Hodgkin's disease or with non-Hodgkin's lymphoma.
- Allogeneic BMT (infusion of bone marrow from a matched sibling donor), or autogeneic BMT (reinfusion of the patient's own marrow that had been removed prior to marrow-destroying treatment).
- Of 43 BMT patients, 16 had undergone an allogeneic transplant and 27 an autogeneic transplant.
- To evaluate the leukemia-free survival difference between the two BMT groups.

Figure 1: Kaplan-Meier survival curves stratified by transplant groups: (—) allogeneic group, and (· · ·) autogeneic group.



Conditions for Cure Rate Model

- Conditions required for the hazard function of the entire population in cure rate models:
  (i) $\lim_{t\to 0} H_{pop}(t) = 0$;
  (ii) $\lim_{t\to\infty} H_{pop}(t) = const. < \infty$.
- If we define $h_{pop}(t) = \mathrm{d}H_{pop}(t)/\mathrm{d}t$, a necessary condition for (i) and (ii) to be satisfied is that $\lim_{t\to\infty} h_{pop}(t) = 0$.

An Unknown Threshold

- We propose a new cure rate model for the population hazard rate function that vanishes when t exceeds a certain threshold, say τ,

$$h_{pop}(t) = h(t)I(t \leq \tau),$$

  with $h(t)$ a nonnegative function.

- It is reasonable to let the hazard rate drop to zero after the cure threshold as the subjects who have survived up to τ would become risk-free of the event.

Nonparametric Prior

- We define a nonparametric prior for $h(t)$,

$$h(t) = \sum_{k=1}^{\infty} \lambda_k I(\tau_{k-1} < t \leq \tau_k)$$

- Note that $0 = \tau_0 < \tau_1 < \cdots$ forms a partition of the time axis, and $\lambda_k \sim \text{Ga}(\alpha_k, \beta_k)$.

- Denoting τ_z as the discretized cure time, then $t \leq \tau_z$ can be replaced by $k \leq z$,

$$h_{pop}(t) = \sum_{k=1}^{\infty} \lambda_k I(k \leq z) I(\tau_{k-1} < t \leq \tau_k).$$

Mixture Prior

- If we denote the prior on z by $f(z)$, then the new process $\{\lambda_k^*\}$ with $\lambda_k^* = \lambda_k I(k \leq z)$, can be characterized by

$$f(\lambda_k^*|z) = \text{Ga}(\lambda_k^*|\alpha_k, \beta_k)I(k \leq z) + I(\lambda_k^* = 0)I(k > z).$$

- Marginalizing over z, the prior distribution of λ_k^* is

$$f(\lambda_k^*) = \eta_k \text{Ga}(\lambda_k^*|\alpha_k, \beta_k) + (1 - \eta_k)I(\lambda_k^* = 0),$$

with $\eta_k = \text{P}(z \geq k)$, i.e., λ_k^* has a prior distribution given by a mixture of a gamma distribution and a point mass at zero.

Enhancing Correlations

- To enhance the dependence in the process $\{\lambda_k\}$ we can consider the Markov gamma process of Nieto-Barajas and Walker (2002) for the λ_k's.
- The Markov gamma process $\{\lambda_k\}$ is defined through a latent process $\{u_k\}$:

$$\begin{aligned} \lambda_1 &\sim \text{Ga}(\alpha_1, \beta_1) \\ u_k|\lambda_k &\sim \text{Poi}(c_k\lambda_k) \\ \lambda_{k+1}|u_k &\sim \text{Ga}(\alpha_{k+1} + u_k, \beta_{k+1} + c_k) \end{aligned}$$

for $k = 1, 2, \ldots$.

Cure Fraction

- The cure fraction π is defined as the proportion of the population that will never experience the failure,

$$\pi = \lim_{t \to \infty} S_{pop}(t) = \exp\left\{ -\sum_{k=1}^{z} \lambda_k (\tau_k - \tau_{k-1}) \right\},$$

since λ_k is taken to be zero for $k > z$.

Semiparametric Model

- We propose the hazard function to be of the form

$$h_i(t|\mathbf{x}_i, z_i) = h(t|z_i)e^{\boldsymbol{\gamma}'\mathbf{x}_i(t)},$$

- We assign $h(t|z_i)$ a nonparametric mixture prior to model a cure fraction and a cure time,

$$h(t|z_i) = \sum_{k=1}^{\infty} \lambda_k I(k \leq z_i) I(\tau_{k-1} < t \leq \tau_k),$$

where $\{\lambda_k\}$ is a Markov gamma process common to all subjects and z_i is the cure threshold index for subject i.

Prior on z

- The prior distribution for z, with a support on $\{1, 2, \ldots\}$, can be a positive Poisson distribution, i.e., $z \sim \text{Poi}^+(\mu)$, for $\mu > 0$, that is, if $z \sim \text{Poi}^+(\mu)$ then $z - 1 \sim \text{Poi}(\mu)$.
- To estimate the subject-specific threshold, we assign a prior distribution $f(z_i)$ dependent on the covariates,

$$z_i \sim \text{Poi}^+(e^{\boldsymbol{\delta}' \mathbf{y}_i}),$$

where $\boldsymbol{\delta}$ is a vector of unknown coefficients and $\mathbf{y}_i$ is a $(q+1)$-vector of fixed covariates whose first component is 1.

Cumulative Hazard

- The cumulative hazard function becomes

$$H_i(t|\mathbf{x}_i, z_i) = \sum_{k=1}^{\infty} \lambda_k I(k \le z_i) w_{ki}(t, \mathbf{x}_i, \boldsymbol{\gamma}),$$

where

$$w_{ki}(t, \mathbf{x}_i, \boldsymbol{\gamma}) = \begin{cases} \int_{\tau_{k-1}}^{\tau_k} \exp\{\boldsymbol{\gamma}' \mathbf{x}_i(s)\} \mathrm{d}s, & t > \tau_k \\ \int_{\tau_{k-1}}^{t} \exp\{\boldsymbol{\gamma}' \mathbf{x}_i(s)\} \mathrm{d}s, & t \in (\tau_{k-1}, \tau_k] \\ 0, & \text{otherwise} \end{cases}.$$

- Let $(T_1, \ldots, T_{n_u})$ be the event times, and $(T_{n_u+1}, \ldots, T_n)$ be right-censored.

Likelihood

- The likelihood function is

$$\text{lik}(\boldsymbol{\lambda}, \mathbf{u}, \mathbf{z}, \boldsymbol{\gamma}|\text{data}) = \left\{\prod_{i=1}^{n_u} h_i(t_i|\mathbf{x}_i, z_i)\right\}\left\{\prod_{i=1}^{n} e^{-H_i(t_i|\mathbf{x}_i, z_i)}\right\}$$

$$= \exp\left\{\sum_{i=1}^{n_u} \boldsymbol{\gamma}'\mathbf{x}_i(t_i)\right\} \prod_{k=1}^{\infty}\left[\lambda_k^{r_k} e^{-m_k(\boldsymbol{\gamma},\mathbf{Z})\lambda_k} \prod_{i=1}^{n_u} I(k \le z_i)^{I(\tau_{k-1}<t_i\le\tau_k)}\right],$$

where

$$r_k = \sum_{i=1}^{n_u} I(\tau_{k-1} < t_i \le \tau_k),\ m_k(\boldsymbol{\gamma}, \mathbf{z}) = \sum_{i=1}^{n} I(k \le z_i) w_{ki}(t_i, \mathbf{x}_i, \boldsymbol{\gamma}).$$

Full Conditionals

- The full conditional distributions of λ_k

$$f(\lambda_k|\text{rest}) = \text{Ga}(\lambda_k|\alpha_k+u_{k-1}+u_k+r_k, \beta_k+c_{k-1}+c_k+m_k(\boldsymbol{\gamma}, \mathbf{z})),$$

with $c_0 = 0$ and $u_0 = 0$ w.p.1.

- For u_k, $f(u_k|\text{rest}) \propto$

$$\frac{1}{\Gamma(1+u_k)\Gamma(\alpha_{k+1}+u_k)}\{c_k(\beta_{k+1}+c_k)\lambda_k\lambda_{k+1}\}^{u_k} I_{\{0,1,\ldots\}}(u_k)$$

- For z_i, $f(z_i|\text{rest}) \propto$

$$\exp\left\{-\sum_{k=1}^{\infty}\lambda_k I(k \le z_i) w_{ki}(t_i, \mathbf{x}_i, \boldsymbol{\gamma})\right\} \text{Poi}^+(z_i|e^{\boldsymbol{\delta}'\mathbf{y}_i}) I(k_i \le z_i).$$

Full Conditionals

- The full conditional distribution of $\boldsymbol{\gamma}$

$$f(\boldsymbol{\gamma}|\boldsymbol{\lambda}, \mathbf{z}, \text{data}) \propto f(\boldsymbol{\gamma}) \exp\left\{\sum_{i=1}^{n_u} \boldsymbol{\gamma}'\mathbf{x}_i(t_i) - \sum_{k=1}^{\infty} m_k(\boldsymbol{\gamma}, \mathbf{z})\lambda_k\right\}.$$

- That of $\boldsymbol{\delta}$ only depends on z_i,

$$f(\boldsymbol{\delta}|\mathbf{z}) \propto f(\boldsymbol{\delta}) \exp\left\{\sum_{i=1}^{n} \left(\boldsymbol{\delta}'\mathbf{y}_i(z_i - 1) - e^{\boldsymbol{\delta}'\mathbf{y}_i}\right)\right\}.$$

- The probability of cure is $\pi_i = \lim_{t\to\infty} S_i(t|\mathbf{x}_i, z_i)$,

$$\pi_i = \exp\left\{-\sum_{k=1}^{z_i} \lambda_k \int_{\tau_{k-1}}^{\tau_k} e^{\boldsymbol{\gamma}'\mathbf{x}_i(s)} \mathrm{d}s\right\}.$$

Simulation I

- We simulated data from the cure rate model

$$S_{pop}(t) = \exp\{-\theta F(t)\}.$$

- We took a triangular distribution Tri$(0, 1, 4)$ as the baseline density, which puts a probability of one to the interval $[0, 4]$ and the mode at 1.
- The censoring time was independently generated from a uniform distribution to yield a 30% censoring rate.
- We took the sample size $n = 100$ and the cure proportion $e^{-\theta} = 0.20$.

Simulation Setup

- We took a fixed time partition with $\tau_0 = 0$ and $\tau_k = \tau_{k-1} + \Delta$, with $\Delta = 0.10$, for $k = 1, \ldots, 100$.
- We considered different values of (α_k, β_k, c_k) and for the hyperprior distribution on μ we took $\mu \sim \text{Ga}(.01, .01)$ to be vague.
- In all scenarios, we ran the Gibbs sampler for 10,000 iterations with a burn-in period of 1,000.
- The logarithm of the pseudo-marginal likelihood (LPML) statistic is used as a model selection criterion, the summary of CPO statistics.

Table 1: Posterior estimates of LPML, cure threshold, posterior mean and 95% credible interval (CI) for π, for a simulated sample of size $n = 100$ with a triangular baseline density.

α_k	β_k	c_k	LPML	$\tau_{\hat{z}}$	$\hat{\pi}$	95% CI
0.01	0.01	0	-153.11	7.1	0.188	(0.110,0.272)
0.1	0.1	0	-149.91	4.2	0.176	(0.105,0.259)
1	1	0	-134.42	3.6	0.133	(0.082,0.193)
1	1	5	-130.35	3.8	0.169	(0.103,0.246)
1	1	20	-127.33	4.0	0.173	(0.098,0.254)
1	1	50	-125.48	4.1	0.178	(0.111,0.259)

Figure 2: Posterior hazard rate estimates (solid line) with 95% credibility intervals (dotted line), $c_k = 0, 5, 20$ and 50.

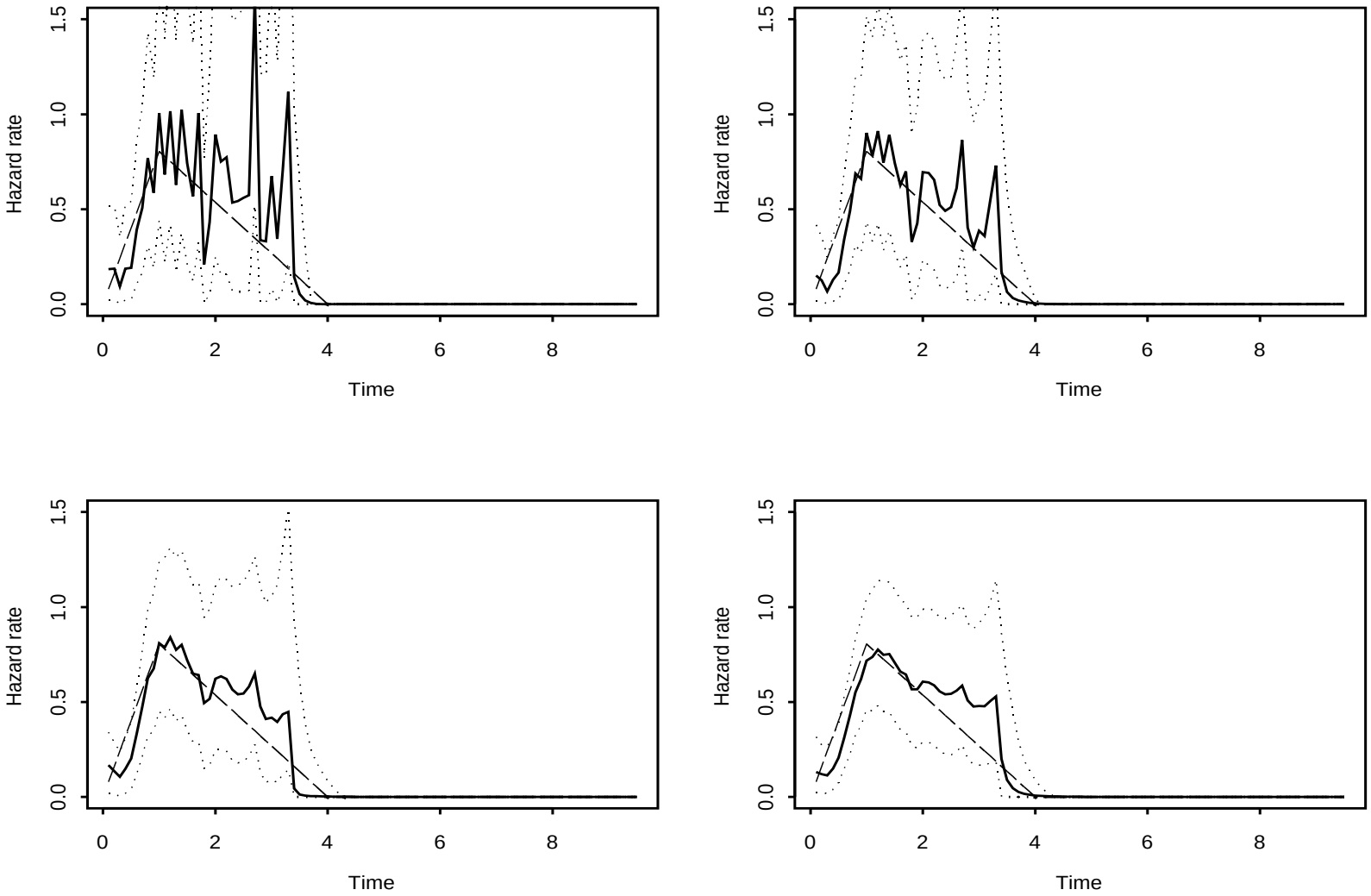


Figure 3: Posterior distributions: μ (left panel) and z (right panel).

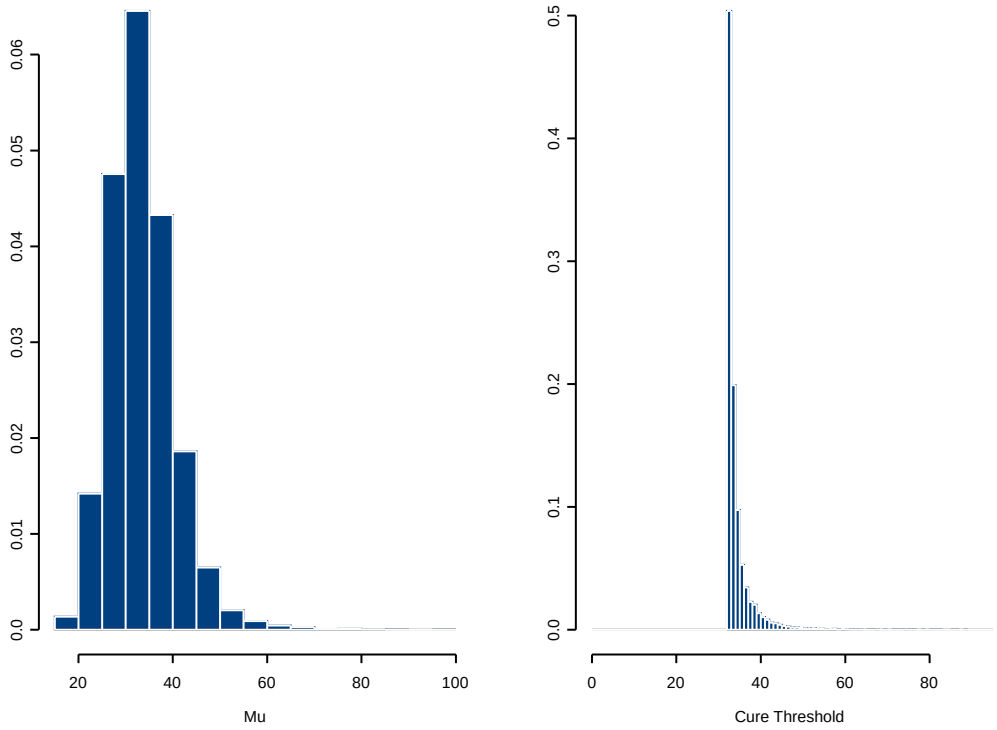
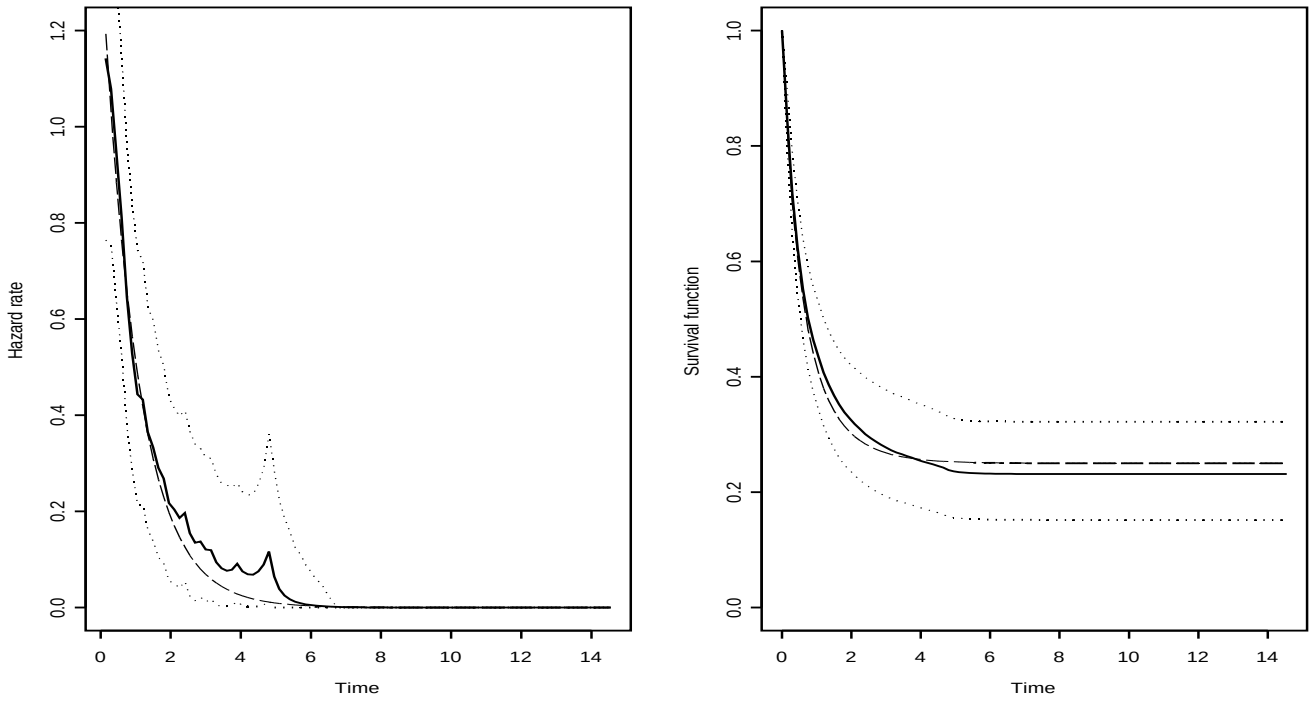


Figure 4: Posterior estimates (solid line) and 95% CI (dotted line): Hazard rate (left panel) and survival function (right panel). The dashed linea are the true functions.



Simulation II

- We simulated data from the same cure model with the baseline density given by an exponential distribution with mean 1.
- The censoring time was independently generated from a uniform distribution to yield 25% of the censoring times.
- We took a sample size of $n = 100$ and a cure proportion $e^{-\theta} = 0.25$.
- We partitioned the time axis by setting $\tau_0 = 0$ and $\tau_k = \tau_{k-1} + \Delta$, with $\Delta = 0.15$, for $k = 1, \ldots, 100$.

Table 2: Posterior estimates of LPML, cure threshold, posterior mean and 95% CI for π, for a simulated sample of size $n = 100$ with an exponential baseline density.

α_k	β_k	c_k	LPML	$\tau_{\hat{z}}$	$\hat{\pi}$	95% CI
0.01	0.01	0	-120.73	10.2	0.249	(0.166,0.340)
0.1	0.1	0	-120.13	5.9	0.229	(0.151,0.317)
1	1	0	-117.40	5.1	0.124	(0.075,0.182)
1	1	5	-111.09	5.4	0.193	(0.127,0.269)
1	1	20	-108.77	5.9	0.219	(0.143,0.302)
1	1	50	-107.47	6.3	0.232	(0.152,0.321)

BMT Data

- The covariates appear in our semiparametric model via two different ways: 1) in a multiplicative manner affecting the "baseline" hazard, and 2) in the Poisson mean of z_i affecting the cure threshold.
- We have also included the estimated covariate effects when fitting the model of Chen, Ibrahim and Sinha. (1999).

Table 3: Posterior estimates of the LPML statistics for the BMT data set.

α_k	β_k	c_k	LPML
1	1	0	-160.25
2	2	0	-159.52
2	2	5	-159.22
2	2	20	-158.21
2	2	50	-158.07
Model of Chen et al.			-165.50

Table 4: Estimated covariate effects in the hazard for the BMT data.

	Our model		Model of Chen, et al.	
Covariate	Mean	95% CI	Mean	95% CI
Intercept	-	-	4.59	(2.79, 6.42)
Trans. type	0.13	(-0.78,1.02)	0.27	(-0.62, 1.14)
Hodgkin	1.20	(0.28,2.22)	1.02	(0.0003, 2.05)
Karnofsky	-0.06	(-0.08,-0.04)	-0.06	(-0.08, -0.04)
Waiting	-0.01	(-0.03,0.004)	-0.01	(-0.03, 0.006)

Table 5: Estimated covariate effects in the cure threshold for the BMT data.

Covariate	Post. Mean	95% CI
Intercept	2.90	(1.19,4.20)
Transplant type	-0.56	(-1.30,0.29)
Hodgkin's disease	-1.10	(-2.08,-0.22)
Karnofsky score	-0.34	(-1.94,1.75)
Waiting time	0.63	(-0.71,1.85)

Table 6: Predictive cure thresholds and cure proportions for new autogeneic transplant patients with Hodgkin's disease ($x_2 = 1$) or non-Hodgkin's lymphoma ($x_2 = 0$) in the BMT data.

Patient	τ_z	π
(x_1, x_2, x_3, x_4)	95% quantile	Post. Mean
$(0, 0, 90, 36)$	14 months	0.40
$(0, 1, 90, 36)$	7 months	0.44
$(0, 0, 60, 36)$	12 months	0.13
$(0, 1, 60, 36)$	6 months	0.14

Figure 5: Predictive hazard estimates for patients with covariates $(0, 0, 90, 36)$ solid line, $(0, 1, 90, 36)$ dotted line, $(0, 0, 60, 36)$ dashed-dotted line and $(0, 1, 60, 36)$ dashed line.

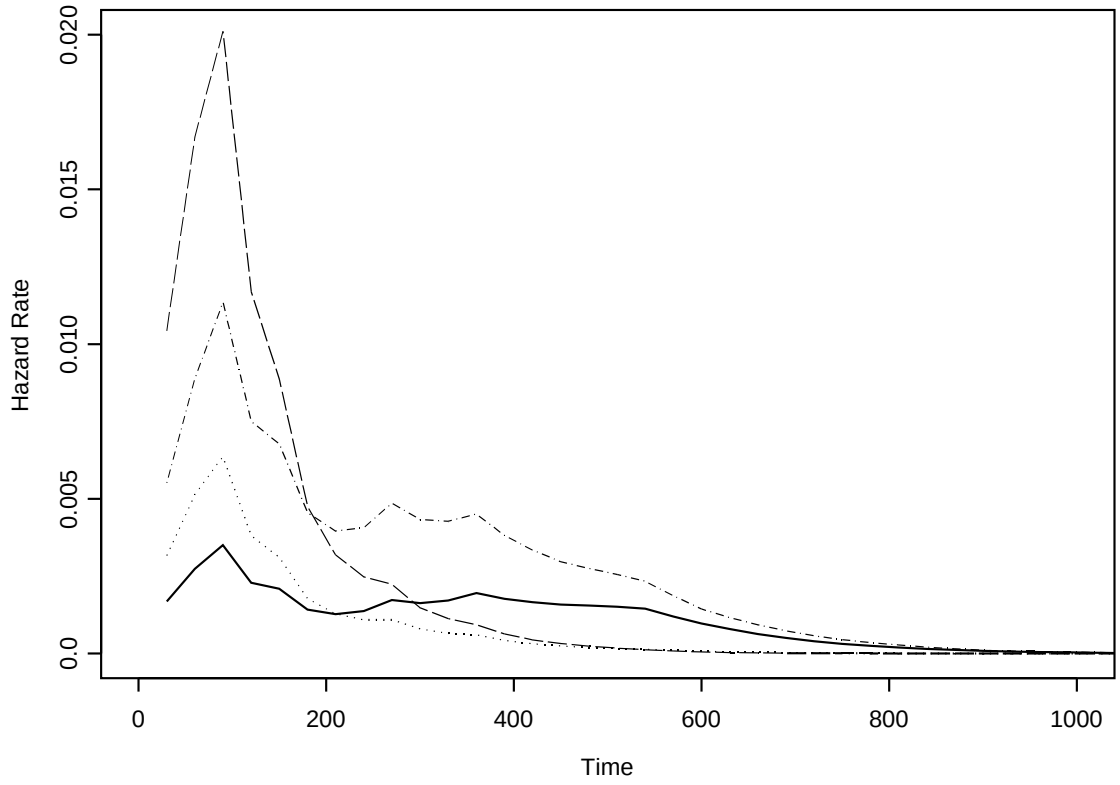
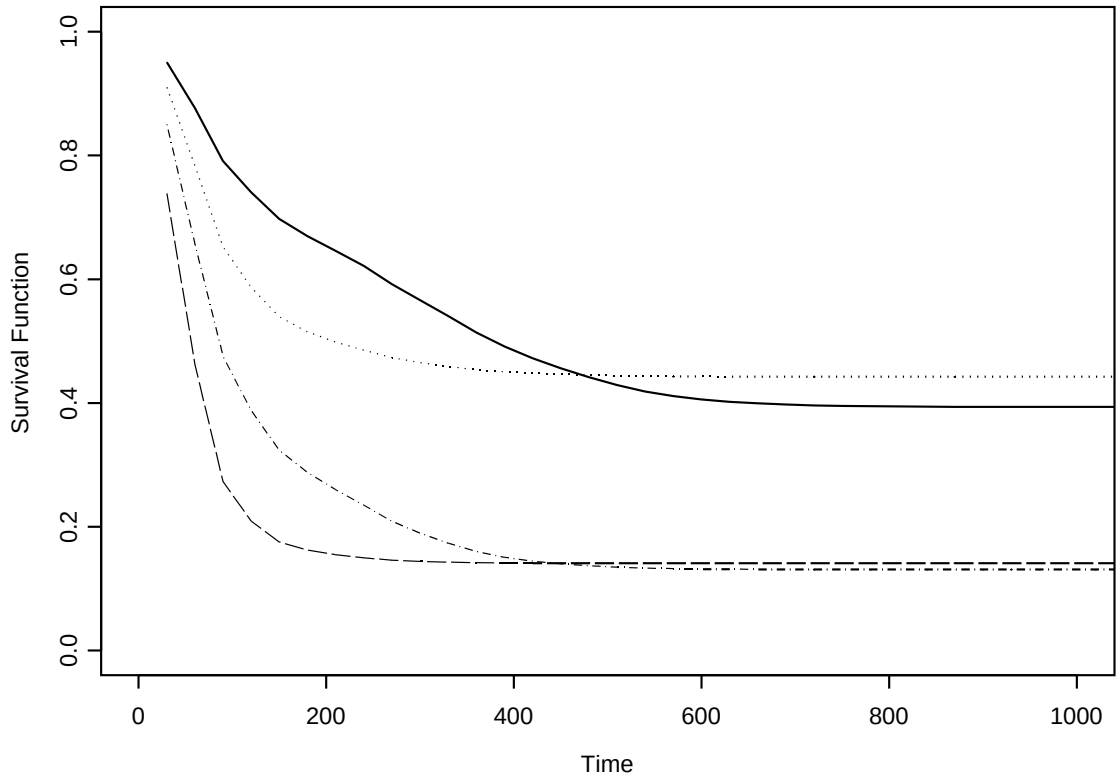


Figure 6: Predictive survival estimates for patients with covariates $(0, 0, 90, 36)$ solid line, $(0, 1, 90, 36)$ dotted line, $(0, 0, 60, 36)$ dashed-dotted line and $(0, 1, 60, 36)$ dashed line.



Summary

- We have proposed a new cure rate model that explicitly incorporates a cure threshold.
- After the cure threshold, the hazard drops to zero, while other cure rate models in the literature allow the hazard to slowly decay to zero.
- We have proposed a mixture prior of a Markov gamma process and a point mass at zero.
- Our semiparametric model uses an exponential link function and allows each patient to have a different cure time depending on covariates.

Thank You!