Bayesian Nonparametric Inference Methods for Mean Residual Life Functions

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Outline

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Basic definitions

Survival data describe the time to a particular event

- death or infection of a patient, failure of machine, duration of unemployment, life expectancy of a product, etc.

→ Let T be a positive random variable representing survival time.

Survival function

- Defines the probability of survival beyond time t,

$$S(t) = Pr(T > t) = 1 - F(t)$$

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Functionals

Hazard rate function

- Computes the probability of a failure in the next instant given survival up to time t,

$$h(t) = \lim_{\Delta t \to 0} \frac{Pr[t < T \leq t + \Delta t | T > t]}{(\Delta t)}$$

$\rightarrow$ When T is continuous, the expression can be written as $f(t)/S(t)$, where $f(t)$ is the density function.

$\rightarrow$ The survival function can be obtained from the hazard through the following relationship:

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Functionals

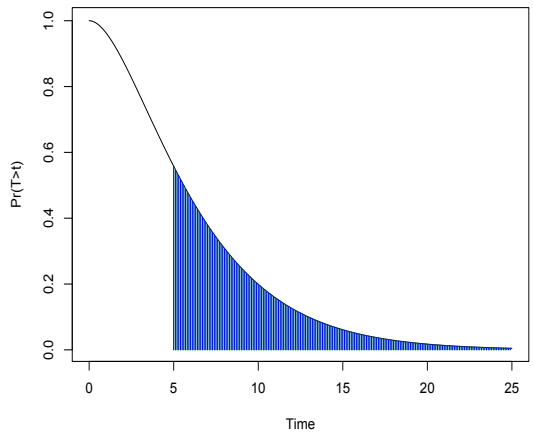
⋆ Suppose $F(0) = 0$ and $\mu \equiv E(T) = \int_0^\infty S(t)dt < \infty$.

Mean residual life (mrl) function

- Computes the expected remaining survival time of a subject given survival up to time t.

$$m(t) = E(T - t | T > t) = \frac{\int_t^\infty (u - t) f(u) du}{S(t)} = \frac{\int_t^\infty S(u) du}{S(t)}$$

and $m(t) \equiv 0$ whenever $S(t) = 0$.



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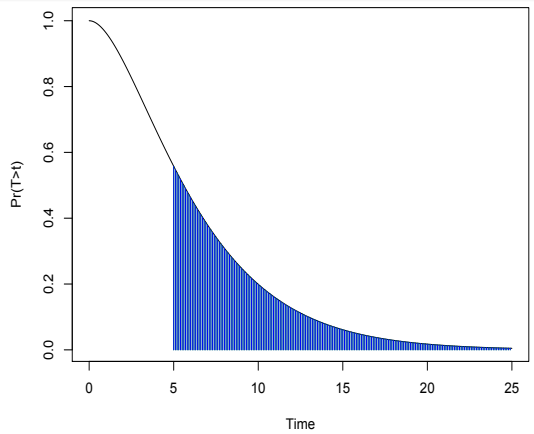

Properties of mrl functions

→ The mrl function is of particular interest in survival and reliability.

→ Characterizes the survival distribution through the Inversion Formula:

$$S(t) = \frac{m(0)}{m(t)} exp\left[-\int_0^t \frac{1}{m(u)} du\right].$$

→ Characterization theorem (Hall & Wellner, 1981) key properties: right-continuous and the function, $m(t) + t$, must be nondecreasing in t.

→ MRL function forms characterized for standard parametric distributions (Poynor, 2010).

⋆ Often limited to be monotonically increasing (INC) or decreasing (DCR).

⋆ Pham & Lai (2007) develop more flexible parametric distributions in regards to the shape (UBT and BT) of the mrl and hazard functions.

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Literature review on inference for mrl function

→ Classical framework:

⋆ Classical estimators, Yang (1978), Hall & Wellner (1979), Kochar et.al. (2000).

⋆ A class of distributions having linear mrl functions (Hall & Wellner, 1981).

⋆ Extended in a semiparametic fashion to a family having proportional mrl functions (Oakes & Dasu, 1990).

⋆ Regression setting, $m(t|z) = exp(\psi z)m_0(t)$, (Chen & Cheng, 2005)

→ Bayesian framework:

⋆ Parametric and empirical Bayes estimators with a Dirichlet process (DP) prior on the distribution function (Lahiri & Park, 1991).

⋆ Bayesian estimation method in the presence of censoring also under the DP prior for the corresponding survival distribution (Johnson, 1999).

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Objectives

Research objective:

- to develop a set of flexible inferential tools for mrl functions.

→ mrl function inference under mixture modeling

→ incorporation of covariates

- Why aren't we modeling the mrl function directly?
  - → obtaining the likelihood from the inversion formula is difficult due to the integration over the reciprocal of the mrl function.
  - → We have explored using a mixture model of a class of mrl functions for which the integration is simple. General forms were still unavailable.

Outline

DPMM for mrl function inference

Model Formulation

We use a nonparametric mixture model for the density of the survival distribution.

* Mixture models are flexible: captures general shapes in the density.
* In principal, do not have to specify a particular number of components.
* Nor specify a parametric distribution for the mixing distribution.

$$f(t; G) = \int_{\Theta} k(t; \theta) dG(\theta)$$

→ A nonparametric prior is placed on the mixing distribution, G.

* We use a Dirichlet Process (DP) prior (Ferguson, 1973).

→ We mix over the parameters of the kernel distribution with density $k(t; \theta)$.

* We discuss the choice of kernel in the spirit of obtaining desirable properties for the corresponding mrl function of the mixture.

Dirichlet Process

The DP is a stochastic process with random sample paths that are distributions.

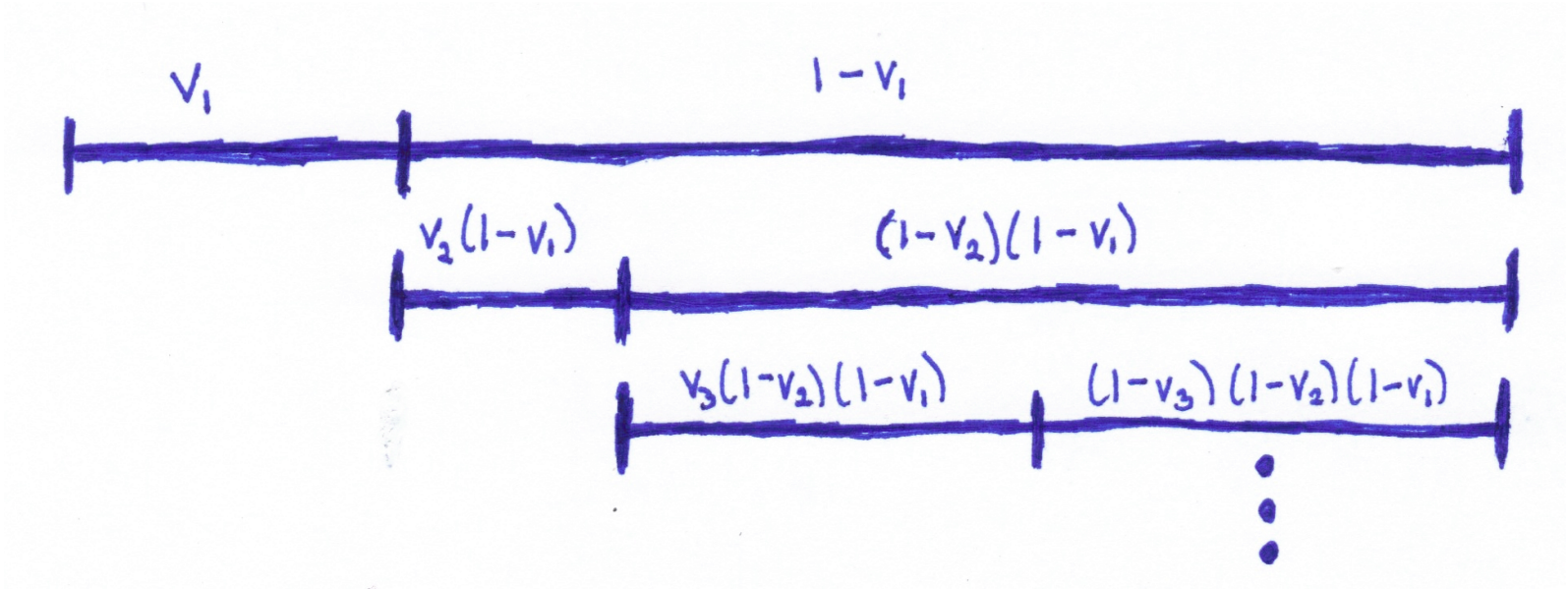
→ We use the stick-breaking (SB) constructive definition of the DP defined by Sethuraman (1994):

→ Let $\{v_r : r = 1, 2, ...\}$ and $\{\theta_l : l = 1, 2, ...\}$ be independent sequences of random variables

- $v_r \overset{iid}{\sim} Beta(1, \alpha)$, for $r = 1, 2, ...$ (where α is the precision).
- $\theta_l \overset{iid}{\sim} G_0$, for $l = 1, 2, ...$ (where G_0 is the baseline distribution).

→ Define $\omega_1 = v_1$ and $\omega_l = v_l \prod_{r=1}^{l-1}(1 - v_r)$, then a realization, G, from a $DP(\alpha, G_0)$ is almost surely of the form $G = \sum_{l=1}^{\infty} \omega_l \delta_{\theta_l}$.

→ $\sum_{l=1}^{\infty} \omega_l \overset{a.s.}{=} 1$



→ We use the truncated version of the SB constructive definition of the DP:

* $G_N = \sum_{l=1}^{N} p_l \delta_{\theta_l}$, where $\theta_l \overset{iid}{\sim} G_0$ for $l = 1, ..., N$,
* and $p_1 = v_1$ and $p_l = v_l \prod_{r=1}^{l-1}(1 - v_r)$, for $l = 2, 3, ...N - 1$ with $p_N = 1 - \sum_{l=1}^{N-1} p_l$, where $v_r \overset{iid}{\sim} Beta(1, \alpha)$ for $r = 1, ..., N - 1$.
* N is the total number of components in the mixture model. N can be specified using:

$$E(\sum_{l=1}^{N} p_l) = 1 - (\alpha/(\alpha + 1))^N$$

The model for the survival density becomes:

$$f(t; G) = \int_{\Theta} k(t; \theta) dG(\theta) \approx \sum_{l=1}^{N} p_l k(t; \theta_l)$$

→ Our interest is in the mrl function, so it is necessary that mean of the DPMM is finite, i.e., $E(T; G) < \infty$.

Sufficiency condition:

→ if $\int_{\Theta} E(T; \theta) dG_0(\theta) < \infty$, then mean of the DPMM is finite.

mrl function of the mixture

$$m(t; G_N) = \sum_{l=1}^{N} q_l(t) m(t; \theta_l)$$

where $m(t; \theta)$ is the kernel mrl function and $q_l(t) = p_l S(t; \theta_l) / \{\sum_{l=1}^{N} p_l S(t; \theta_l)\}$.

Tail behavior of the mrl function for the mixture distribution:

1. $\lim_{t \to \infty} m(t; \theta) = \infty \ \forall \theta \in \Theta \Rightarrow \lim_{t \to \infty} m(t; G_N) = \infty$.
2. $\lim_{t \to \infty} m(t; \theta) = 0 \ \forall \theta \in \Theta \Rightarrow \lim_{t \to \infty} m(t; G_N) = 0$.

Prior Specification and Posterior Inference

→ We use kernel distribution,$\Gamma(t; exp(\theta), exp(\phi))$, and baseline distribution, $N_2((exp(\theta), exp(\phi))'; \boldsymbol{\mu}, \boldsymbol{\Sigma})$.

→ The following priors are placed on the G_0 hyperparameters: $\boldsymbol{\mu} \sim N_2(a_\mu, B_\mu)$ and $\boldsymbol{\Sigma} \sim IWish(a_\Sigma, b_\Sigma)$.

→ We specify the prior parameters by using a range and midpoint/ midrange of the population, which would, in practice, be specified by the expert.

→ The number of distinct components, n^*, is large for large α and small for small α. If the sample size, n, is moderately large,

$$E(n^*|\alpha) \approx \alpha log\left(\frac{\alpha+n}{\alpha}\right)$$

can be used to suggest an appropriate range of α values.

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$\rightarrow$ We utilize a blocked Gibbs sampler (Ishwaran & James, 2001) to obtain samples from the posterior distribution $p(\boldsymbol{\theta}, \mathbf{L}, \mathbf{p}, \boldsymbol{\psi}, \alpha | data)$ where $\boldsymbol{\psi} = (a_\mu, B_\mu, B_\Sigma)$.

$\rightarrow$ The posterior samples for $G_N \equiv (\mathbf{p}, \boldsymbol{\theta})$ can be used to obtain inference for the density, survival, and hazard functions at any time point t, by directly evaluating the expressions for these functions under the gamma DPMM.

→ We can avoid having to truncate the upper bound of the integration by using the following form of the mrl function:

$$m(t) = \frac{\int_t^\infty S(u)du}{S(t)} = \frac{\int_0^\infty S(u)du - \int_0^t S(u)du}{S(t)} = \frac{\mu - \int_0^t S(u)du}{S(t)}$$

where $\mu = E(T; G_N) = \sum_{l=1}^{N} p_l E(T; \theta_l)$.

→ We evaluate over a grid of survival times, $t_{0,j}$ for $j = 1, ..., m$.

→ We evaluate the mrl at the first grid point by

$$m(t_{0,1}; G_N) = [E(T; G_N) - 0.5(t_{0,1}(1 + S(t_{0,1}; G_N))]/S(t_{0,1}; G_N)$$

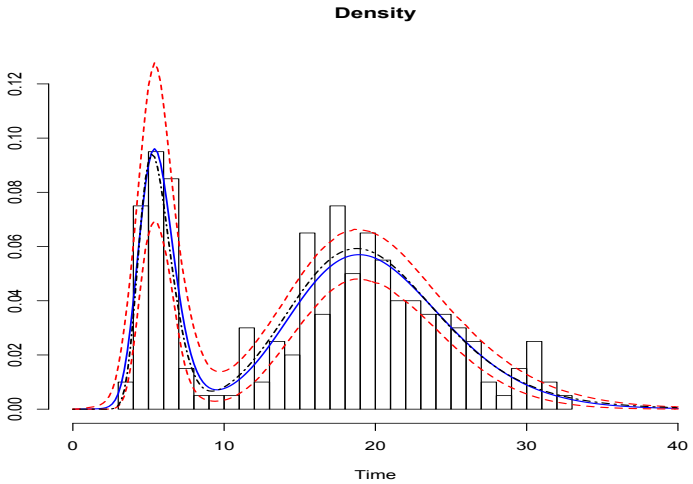
and use the following expression for $j = 2, ..., m$:

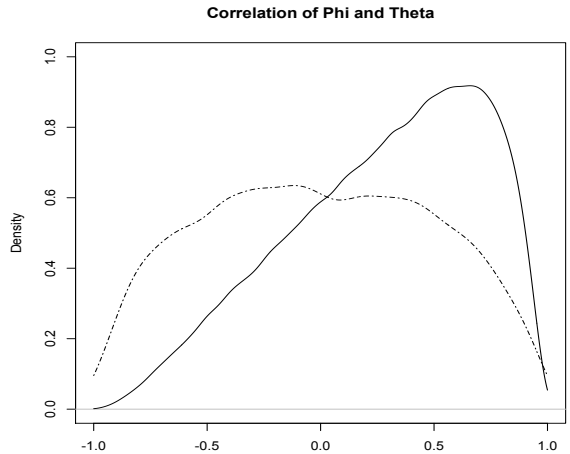
$$m(t_{0,j}; G_N) = \frac{E(T; G_N) - \frac{1}{2}\left(t_{0,1}(1 + S(t_{0,1}; G_N)) + \sum_{i=2}^{j}(t_{0,j} - t_{0,j-1})(S(t_{0,j}; G_N) + S(t_{0,j-1}; G_N))\right)}{S(t_{0,j}; G_N)}$$

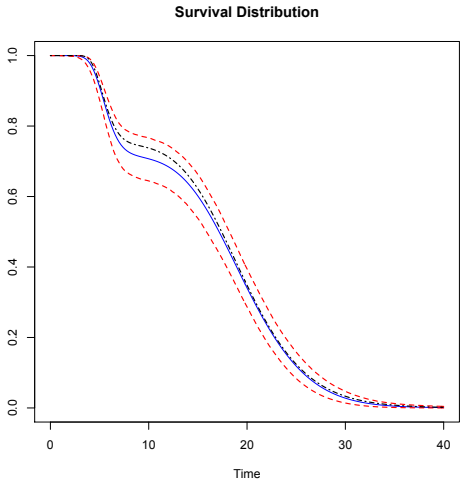
Simulation 1

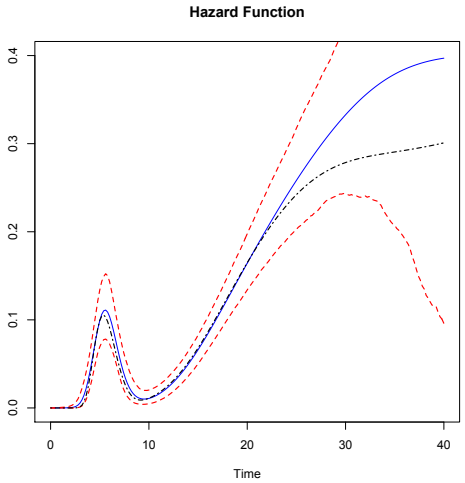
Data set consists of 200 realizations from

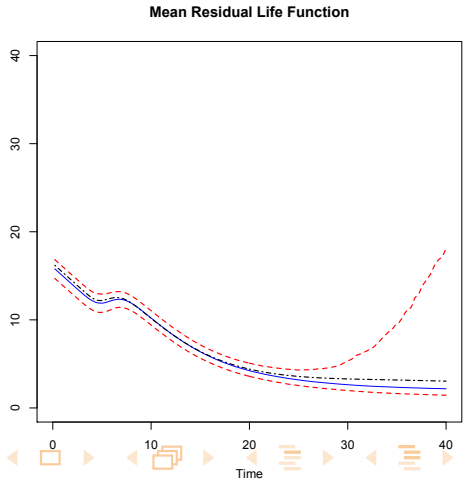
$$T_1 \sim 0.35\Gamma(10, 0.5) + 0.4\Gamma(20, 1) + 0.15\Gamma(30, 5) + 0.1\Gamma(40, 8).$$







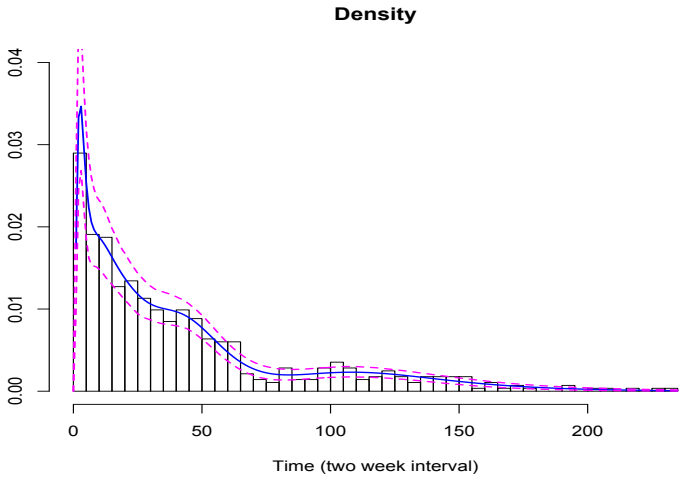


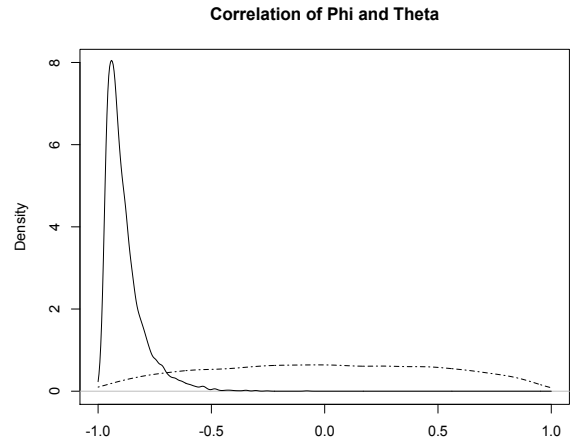


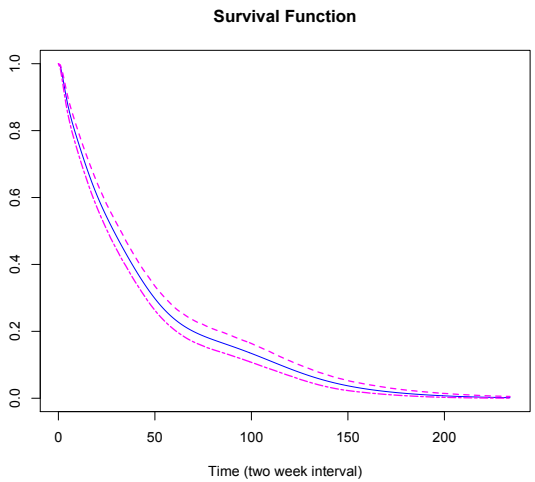
Strike Duration

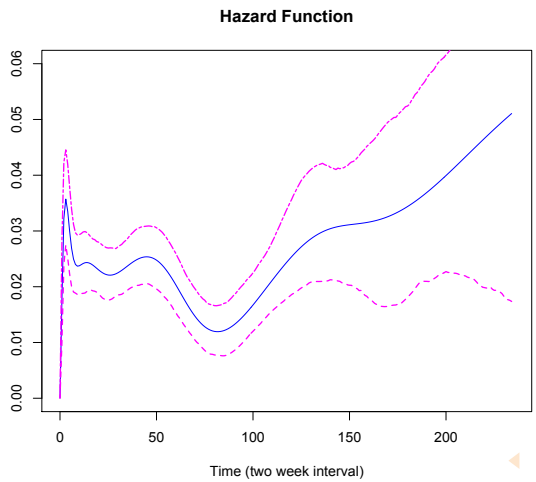
These data are from Kennan (1985) and are available in R package "Ecdat".

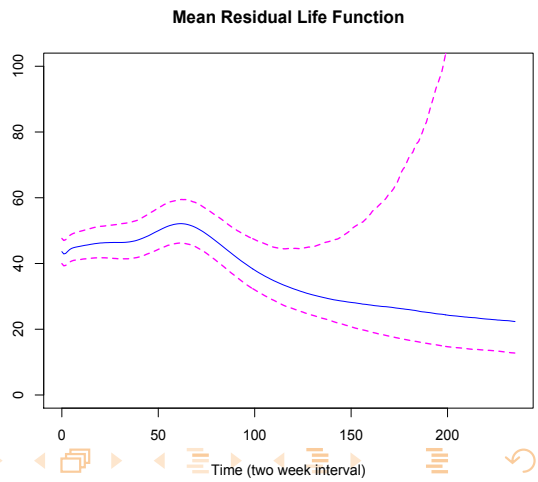
The data describe the duration of 566 strikes in U.S. manufacturing industries.





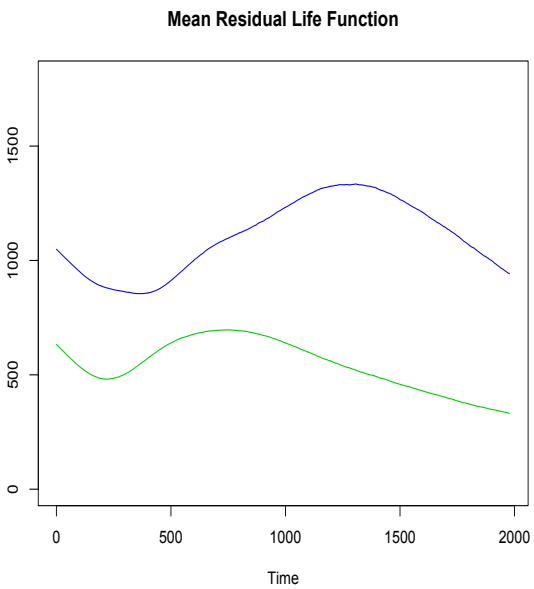


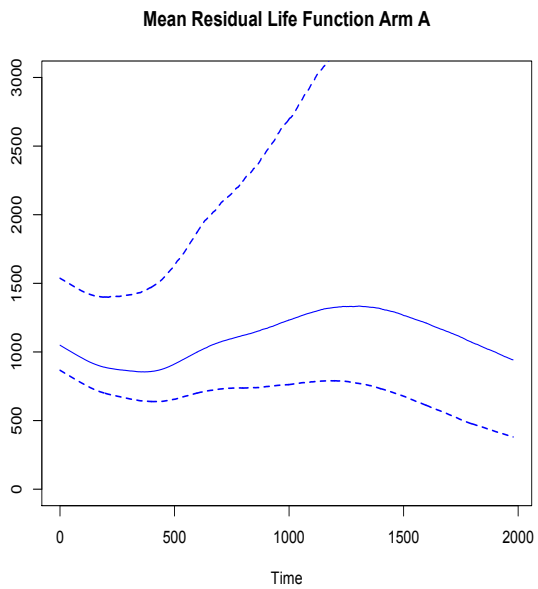


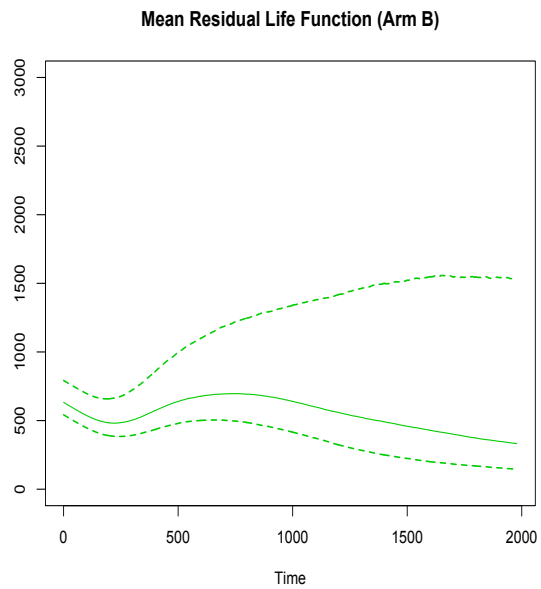


Patients with small cell lung cancer

These data, obtained from Ying et al. (1988), represent the survival time (in days) of patients with small cell lung cancer (some values are right censored). Arm A, consists of 62 patients, received cisplain (P) followed by etoposide (E) treatment. Arm B, consists of 50 patients, recieved (E) followed by (P).







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Curve fitting

Curve fitting with random covariates

→ Curve fitting has been explored in literature primarily in the case of real-valued data and a multivariate normal kernel (Müller et. al., 1996).
→ Benefits of curve fitting for survival data

- ⋆ Models non-standard/non-linear regression
- ⋆ # random covariates not unreasonably large

→ Let $\mathbf{x}$ be a vector of random covariates and $t > 0$ the survival time of a subject. We model the joint response-covariate density using a DPMM,

DPMM

$$f(t, \mathbf{x}; G) = \int_{\Theta} k(t, \mathbf{x}; \theta) dG(\theta) \approx \sum_{l=1}^{N} p_l k(t, \mathbf{x}; \theta_l)$$

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Regression interpretation of functionals:

$$E(T|\mathbf{x}_0; G_N) = \sum_{l=1}^{N} q_l(\mathbf{x}_0) E(T|\mathbf{x}_0; \theta_l)$$

where $q_l(\mathbf{x}_0) = p_l k(\mathbf{x}_0; \theta_l) / \{\sum_{l=1}^{N} p_l k(\mathbf{x}_0; \theta_l)\}$.

$$m(t|\mathbf{x}_0; G_N) = \sum_{l=1}^{N} q_l(t, \mathbf{x}_0) m(t|\mathbf{x}_0; \theta_l)$$

where $q_l(t, \mathbf{x}_0) = p_l k(\mathbf{x}_0; \theta_l) S(t|\mathbf{x}_0; \theta_l) / \{\sum_{l=1}^{N} p_l k(\mathbf{x}_0; \theta_l) S(t|\mathbf{x}_0; \theta_l)\}$.

The condition that ensures the finiteness for the mean:

- if $E_{G_0}[E(T|\mathbf{x}; \theta)] < \infty$, then $E(t|\mathbf{x}_0; G_N) < \infty$.

→ For an illustrative data example, we consider a single continuous covariate, and fit a DPMM with kernel $k(t, \mathbf{x}) = k(t)k(\mathbf{x}) = \Gamma(t_i; e^{\theta_{L_i}}, e^{\phi_{L_i}})N(x_i; \beta_{L_i}, \kappa^2_{L_i})$.

- ⋆ with baseline distribution, $G_0 = N_2((\theta_l, \phi_l)'; \boldsymbol{\mu}, \boldsymbol{\Sigma})N(\beta_l; \lambda, \tau^2)\Gamma^{-1}(\kappa^2_l; a, \rho)$.
- ⋆ We place the following priors: $\alpha \sim \Gamma(a_\alpha, b_\alpha(\text{rate}))$, $\boldsymbol{\mu} \sim N_2(a_\mu, B_\mu)$, $\boldsymbol{\Sigma} \sim IWish(a_\Sigma, B_\Sigma)$, $\lambda \sim N(a_\lambda, b_\lambda)$, $\tau^2 \sim \Gamma^{-1}(a_\tau, b_\tau)$, and $\rho \sim \Gamma(a_\rho, b_\rho)$.

→ In this model, we use an independent product kernel for the survival time and the covariate, but will explore more general kernel structures.

- ⋆ categorical covariates
- ⋆ incorporate dependency between the covariates and the survival times within the kernel, e.g.,

$$k(t|\mathbf{x}) = \Gamma(t; exp(\theta), exp(\mathbf{x}^T\beta)), \text{ such that } E(T|\mathbf{x}) = exp(\theta - \mathbf{x}^T\beta)$$

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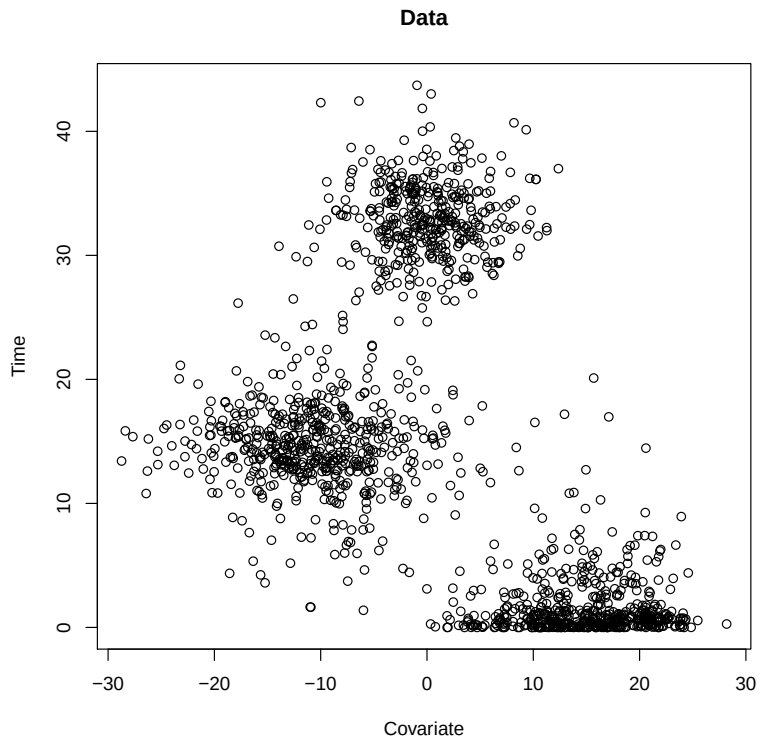
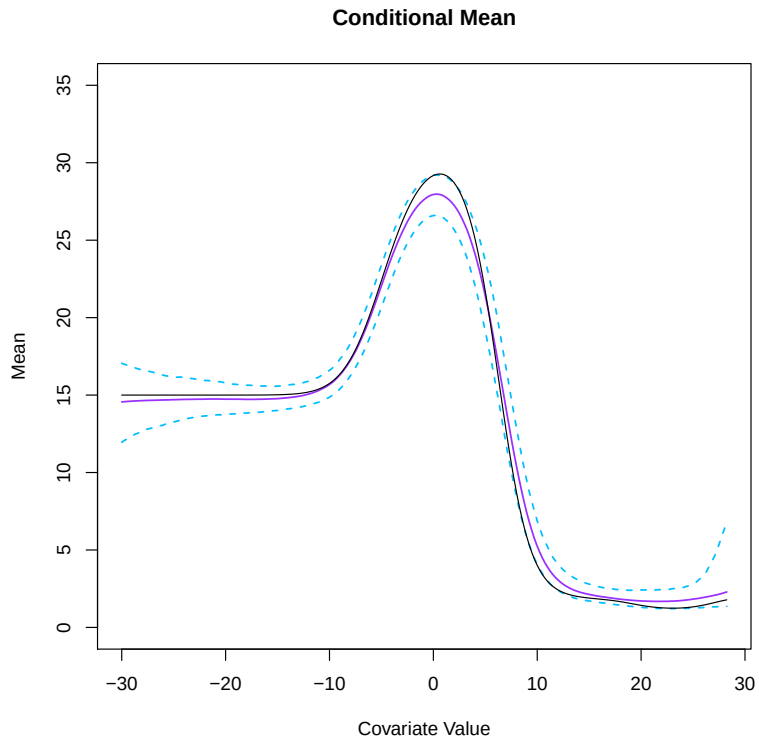
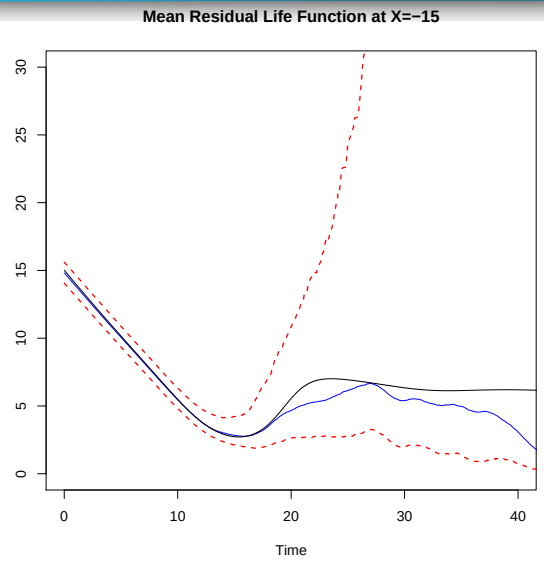
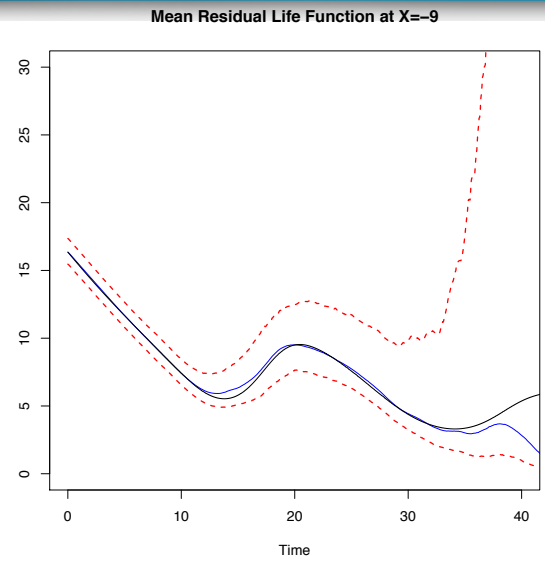
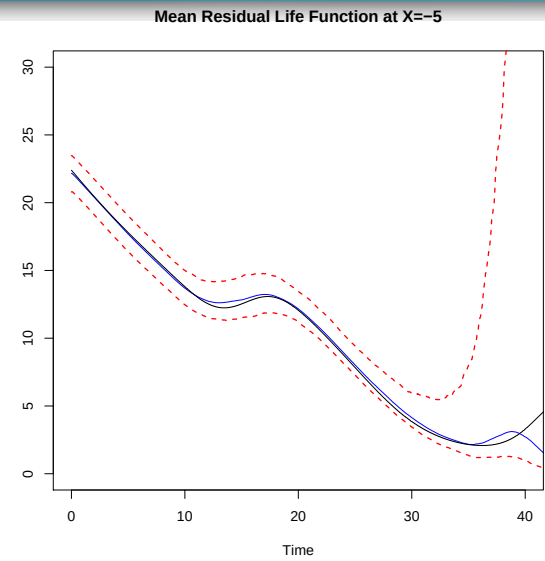
We simulate 1500 data values from a population having the following density: $f(t,x) = \sum_{l=1}^{M} q_l \Gamma(t; a_l, b_l) N(x; m_l, s_l^2)$.






Mean Residual Life Function at X=−15
Time


Mean Residual Life Function at X=−9
Time


Mean Residual Life Function at X=−5
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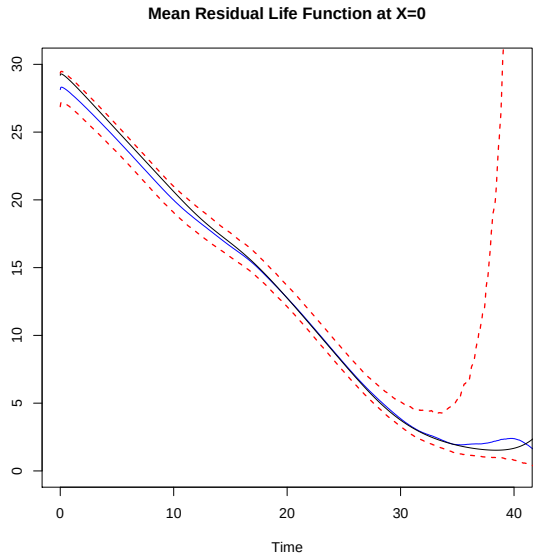
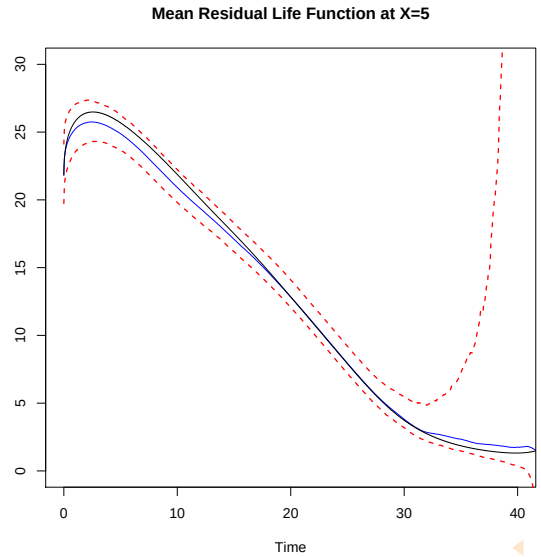
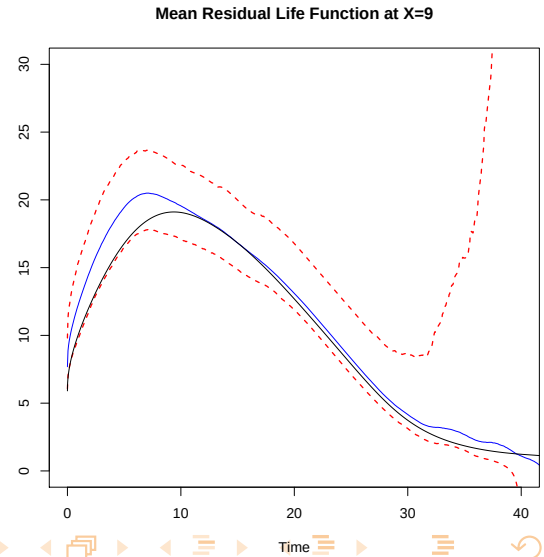

Mean Residual Life Function at X=0
Time


Mean Residual Life Function at X=5
Time


Mean Residual Life Function at X=9
Time

Outline

Closing Remarks

⋆ Often in clinical trials, researchers are interested in modeling survival times of patients under treatment and control groups.

→ Benefits in modeling dependency across groups.

→ Let $s \in S$ represent in general the index of dependence. We consider $S = \{T, C\}$ where (T) and (C) are the treatment and control groups, respectively.

→ The dependent DPMM under the regression setting,

DDPMM

$$f(t, \mathbf{x}; G_s) = \int_{\Theta} k(t, \mathbf{x}; \theta) dG_s(\theta), \text{ for } s \in S,$$

where we model a pair of dependent random mixing distributions $\{G_s : s \in S\}$.

⋆ We also propose to develop modeling for mrl ordering from a BNP point of view using random Bernstein polynomials (Petrone, 1999; Petrone & Wasserman, 2002).

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THANK YOU !!!!