Bayesian Inference for PVF Frailty Models

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$\boxed{\text{Outline of the Talk}}$

1. Introduction to Multivariate Times to Events Data

2. Power Variance Function Frailty Models

3. Bayesian Modeling Framework

4. Illustration

5. Local Dependence Measure

1. MV Times to Events Analysis

Frailty models are useful for modelling dependence in multivariate times to events analysis [Clayton & Cuzick,1985; Oakes,1989]. Variability of multivariate times to events arise from two sources:

1. variability explained by the hazard function
2. variability common to subjects of the same group,explained by the frailty.

Frailty is an individual random effect. Event times are conditionally independent given the frailty.

We assume the hazard for each event time follows a **multiplicative proportional hazards model** and carry out Bayesian inference.
Must specify a model for baseline hazard and frailty.

Frailty Distribution: PVF family-tilted Positive Stable [Hougaard,1986]
Baseline Hazards: Piecewise exponential hazard with correlated prior process [Arjas and Gasbarra, 1994, Gamerman,1991] or Weibull model

Multiplicative Proportional Hazards model conditional on the frailty x_i:

$$h(t_{ij}|x_i, \tilde{z}_{ij}) = \lambda_0(t_{ij}) \exp(\tilde{\beta}^t \tilde{z}_{ij}) x_i$$

t_{ij} : event time of the j^{th} subject $(i = 1, \cdots, m)$ in the i^{th} group $(j = 1, \cdots, n)$

$\tilde{z}_{ij}$ is a fixed, possibly time dependent covariate vector of dim. p

$\tilde{\beta}$ is the vector of regression parameters.

$\lambda_0(.)$ is the baseline hazard function.

$x_i \sim PVF(\alpha, \delta, \theta)$

Baseline Hazard

Piecewise exponential hazard with correlated prior process:
The time period is divided into g prespecified intervals
$I_k = (t_{k-1}, t_k)$, $k = 1, \cdots, g$, $0 = t_0 < t_1 < \cdots < t_g < \infty$
Assume that $\lambda_0(t_{ij}) = \lambda_k$ for $t_{ij} \in I_k$.
Use a discrete-time martingale process to correlate the λ_k's in adjacent intervals

$$\lambda_k | \lambda_1, \cdots, \lambda_{k-1} \sim \text{Gamma}(v_k, \frac{v_k}{\lambda_{k-1}}), k = 1, \cdots, g$$

where $\lambda_0 = 1$, so $E(\lambda_k | \lambda_1, \cdots, \lambda_{k-1}) = \lambda_{k-1}$.
Let $\tilde{\lambda} = (\lambda_1, \cdots, \lambda_g)$.
Note: v_k small implies less information for smoothing the λ_k 's; if $v_k = 0$, λ_k is independent of λ_{k-1} while if $v_k \to \infty$, $\lambda_k = \lambda_{k-1}$.
A large value of g would give unstable λ estimates; a very small g value would lead to inadequate model fitting.

2. PVF as a Tilted Positive Stable

PVF(α, δ, θ): 3 parameters PVF distribution where $\alpha \leq 1, \delta > 0$, and $\theta \geq 0$ for $\alpha > 0$ and $\theta > 0$ for $\alpha \leq 0$.

Special cases:

- $\alpha = 0$, PVF$\rightarrow$ Gamma
- $\theta = 0$,$\delta = \alpha$,PVF$\rightarrow$ Positive Stable
- α=1/2, PVF$\rightarrow$ Inverse Gaussian

For $\alpha \geq 0$, the PVF is obtained as the exponential family generated from the positive stable distributions [Jorgensen, 1987 and Hougaard, 1986]:

Suppose $W \sim P(\alpha, \alpha, 0)$, where $\alpha \in (0, 1)$ with Laplace transform

$$L(s) = E\,\mathrm{exp}\left(-sW\right) = \mathrm{exp}\left(-s^{\alpha}\right), \ \ s \geq 0,$$

[Samorodnitsky and Taqqu, 1994].
For $\delta > 0$, $\left(\frac{\delta}{\alpha}\right)^{1/\alpha} W \sim P(\alpha, \delta, 0)$, with Laplace transform

$$L(s) = E\,\mathrm{exp}[-s\left(\frac{\delta}{\alpha}\right)^{1/\alpha} W] = \mathrm{exp}\left[-s^{\alpha}\left(\frac{\delta}{\alpha}\right)\right].$$

Let $X = \left(\frac{\delta}{\alpha}\right)^{1/\alpha} W$

For fixed α, the exponential dispersion model generated by $P(\alpha, \alpha, 0)$, is PVF $P(\alpha, \delta, \theta)$, with pdf [Jorgensen, 1987]

$$\frac{f_\alpha\left(x|\zeta\right)\exp\left(-\theta x\right)}{\zeta L_\alpha(\zeta\theta)}, \text{ where } \zeta = \left(\frac{\delta}{\alpha}\right)^{1/\alpha};$$

Its Laplace transform is

$$L\left(s\right) = \exp\left[-\frac{\delta\{(\theta+s)^\alpha - \theta^\alpha\}}{\alpha}\right].$$

It helps us to study dependence properties.

Lack of closed form pdf makes inference difficult. We show an approach which is an extension of a result for stable.

$S_\alpha(\sigma, \beta, \mu)$: 4-parameter stable distribution where
α : stability parameter $\in (0, 2]$,
β : skewness parameter $\in [-1, 1]$
σ : scale parameter $\in (0, \infty)$,
μ : location parameter $\in (-\infty, \infty)$.
When $\beta = 1, 0 < \alpha < 1, \mu = 0, \sigma = 1$, the positive stable distribution $S_\alpha(1, 1, 0)$ has support $(0, \infty)$. Its density function is not available in closed form.

Let $f(w_i, y_i|\alpha)$ be a bivariate function such that it projects $(-\infty, 0)\times(-1/2, l_\alpha)\cup(0, \infty)\times(l_\alpha, 1/2)$ to $(0, \infty)$:

$$f(w_i, y_i|\alpha) = \frac{\alpha}{|\alpha - 1|} \exp\left[-\left|\frac{w_i}{\tau_\alpha(y_i)}\right|^{\alpha(\alpha-1)}\right] \times \left|\frac{w_i}{\tau_\alpha(y_i)}\right|^{\alpha/(\alpha-1)} \frac{1}{w_i},$$

where

$$\tau_\alpha(y_i) = \frac{\sin(\pi\alpha y_i + \psi_\alpha)}{\cos \pi y_i}\left[\frac{\cos \pi y_i}{\cos\{\pi(\alpha - 1)y_i + \psi_\alpha\}}\right]^{\frac{\alpha-1}{\alpha}},$$

$w_i \in (-\infty, \infty)$, $y_i \in (-1/2, 1/2)$, $\psi_\alpha = \min(\alpha, 2-\alpha)\pi/2$ and $l_\alpha = -\psi_\alpha/\pi\alpha$.

The marginal frailty distribution based on stable law is [Buckle, 1995; Ravishanker & Qiou, 1998]

$$f(w_i|\alpha) = \frac{\alpha|w_i|^{1/(\alpha-1)}}{|\alpha-1|}\int_{-1/2}^{1/2} \exp\left[-\left|\frac{w_i}{\tau_\alpha(y_i)}\right|^{\alpha/(\alpha-1)}\right] \times \left|\frac{1}{\tau_\alpha(y_i)}\right|^{\alpha/(\alpha-1)} dy_i.$$

Replacing $\int$ by MC simulation enables likelihood based inference.

Following Jorgensen (1987) and Hougaard (1986a), the density for the PVF family when $\alpha \in (0, 1]$ becomes

$$
\begin{aligned}
f(x_i|\alpha,\delta,\theta) \;=\; & \frac{\alpha|x_i|^{\frac{1}{(\alpha-1)}} \left(\frac{\alpha}{\delta}\right)^{\frac{1}{(\alpha-1)}} \exp(-\theta x_i + \frac{\delta\theta^{\alpha}}{\alpha})}{|\alpha-1|} \\
& \times \int_{-1/2}^{1/2} \exp\left[-\left|\frac{x_i}{\tau_\alpha(y_i)}\right|^{\frac{\alpha}{(\alpha-1)}} \left(\frac{\alpha}{\delta}\right)^{\frac{1}{(\alpha-1)}}\right] \\
& \times \left|\frac{1}{\tau_\alpha(y_i)}\right|^{\frac{\alpha}{(\alpha-1)}} dy_i.
\end{aligned}
$$

Considering a reparametrization $\delta = \eta^{1-\alpha}$ and $\theta = \eta$, the resulting distribution has mean 1 and variance $(1-\alpha)/\eta$. After reparametrization of δ and θ in terms of η, (in order to yield mean one), the density becomes

$$
\begin{aligned}
f(x_i|\alpha,\eta) \;\; = \;\; & \frac{\alpha^{\frac{\alpha}{(\alpha-1)}}|x_i|^{\frac{1}{(\alpha-1)}}\eta\,\text{exp}(-\eta x_i + \frac{\eta}{\alpha})}{|\alpha-1|} \\
& \times \int_{-1/2}^{1/2} \text{exp}\left[-\left|\frac{x_i}{\tau_\alpha(y_i)}\right|^{\frac{\alpha}{(\alpha-1)}} \alpha^{\frac{1}{\alpha-1}}\eta\right] \\
& \times \left|\frac{1}{\tau_\alpha(y_i)}\right|^{\frac{\alpha}{(\alpha-1)}} dy_i.
\end{aligned}
$$

3. Bayesian Modeling Framework

For subject j in group i, [$(j = 1, \cdots, m)$, $(i = 1, \cdots, n)$], we observe $(t_{ij}, \delta_{ij}, \tilde{z}_{ij})$.
t_{ij}: event time if $\delta_{ij} = 1$ and censoring time if $\delta_{ij} = 0$.

Let $\tilde{Z}$ denote all such triplets, $(t_{ij}, \delta_{ij}, \tilde{z}_{ij})$.
Frailty $\tilde{X} = x_i$: augmented data. Its distribution is based on a vector of auxiliary variables $\tilde{Y} = (y_1, \cdots, y_n)$.

$(\tilde{X}, \tilde{Y}, \tilde{Z})$:complete data. $\tilde{X}$ and $\tilde{Y}$ are treated as parameters in the Bayesian formulation.
The Bayesian specification requires a likelihood and a prior from which the posterior density is obtained as a normalized product of the likelihood and the prior.

Derivation of the likelihood

Baseline hazard-piecewise exponential with correlated prior process.

g_{ij}: number of partitions of the time interval

In interval k, given x_i, $h_{ij} = \lambda_k e^{\beta' z_{ij}} x_i$.

If $t_{ij} > t_k$, likelihood contribution for the k^{th} interval is $\exp(-\lambda_k \Delta_k e^{\beta' z_{ij}} x_i)$ where $\Delta_k = t_k - t_{k-1}$.

If $t_{k-1} < t_{ij} \leq t_k$ the likelihood contribution is $(\lambda_k e^{\beta' z_{ij}} x_i)^{\delta_{ij}} \exp\{-\lambda_k (t_{ij} - t_{k-1}) e^{\beta' z_{ij}} x_i\}$.

Therefore, the complete data likelihood is

$$l(\tilde{\beta}, \tilde{\lambda}, \alpha, \eta | \tilde{X}, \tilde{Y}, \tilde{Z}) = \prod_{i=1}^{n} \prod_{j=1}^{m} [\prod_{k=1}^{g_{ij}-1} \exp\{-\lambda_k \Delta_k e^{\beta' z_{ij}} x_i\}]$$

$$\times \exp\{-\lambda_{g_{ij}} (t_{ij} - t_{g_{ij}-1}) e^{\beta' z_{ij}} x_i\} (\lambda_{g_{ij}} e^{\beta' z_{ij}} x_i)^{\delta_{ij}}.$$

We integrate out the x_i's from the last equation using PVF density to get observed data likelihood

$$l(\tilde{\beta}, \tilde{\lambda}, \alpha, \eta | \tilde{Z}) = \prod_{i=1}^{n} \int \prod_{j=1}^{m} [\prod_{k=1}^{g_{ij}-1} \exp\{-\lambda_k \Delta_k e^{\beta' z_{ij}} x_i\}]$$
$$\times \exp\{-\lambda_{g_{ij}} (t_{ij} - t_{g_{ij}-1}) e^{\beta' z_{ij}} x_i\}.(\lambda_{g_{ij}} e^{\beta' z_{ij}} x_i)^{\delta_{ij}}$$
$$\times \frac{\alpha^{\frac{\alpha}{\alpha-1}} |x_i|^{\frac{1}{\alpha-1}} \eta \exp(-\eta x_i + \frac{\eta}{\alpha})}{|\alpha - 1|} \int_{-1/2}^{1/2} \exp\left[-|\frac{x_i}{\tau_\alpha(y)}|^{\frac{\alpha}{\alpha-1}} \alpha^{\frac{1}{\alpha-1}} \eta\right] |\frac{1}{\tau_\alpha(y_i)}|^{\frac{\alpha}{\alpha-1}} dy_i dx_i.$$

Note: Complete likelihood corresponds to the conditional model, given the frailty x_i, while observed likelihood corresponds to the marginal model with the frailty parameter is integrated out. For parsimony of notation, we suppress the subscripts on g_{ij} and denote it by g.

Prior Specification

Piecewise exponential hazard

Prior for $\lambda_k|\lambda_1, ..., \lambda k - 1 : Gamma(v_k, \frac{v_k}{\lambda_{k-1}})$

Prior for p -dimensional vector $\widetilde{\beta}$: Normal($\widetilde{e}, D$)

Prior for α: Uniform(0,1)

Prior for η: Gamma(c, c)

Assuming independence of all model parameters, The posterior density based on the observed data likelihood is proportional to the product of the likelihood and the prior, i.e.,

$$p(\tilde{\lambda}, \tilde{\beta}, \alpha, \eta|\tilde{Z}) \propto L\left(\lambda, \gamma, \widetilde{\beta}, \eta, \alpha|\widetilde{Z}\right) p(\tilde{\beta})p(\tilde{\lambda})p(\alpha)p(\eta)$$

We use a modified Gibbs sampler to generate samples from $p\left(\lambda, \gamma, \widetilde{\beta}, \eta, \alpha|\widetilde{Z}\right)$, given initial values for $\lambda, \gamma, \widetilde{\beta}, \eta, \alpha$, and the two "augmented" vectors $\widetilde{x}$ and $\widetilde{y}$.

$\boxed{\textbf{Sampling Algorithms}}$

Piecewise exponential hazard

$\tilde{\lambda}$: ratio of Uniform method

β : ratio of uniform method

α : Metropolis Hastings Algorithm with Beta proposal

η : Multiple try Metropolis Algorithm with log-normal proposal.

x: ratio of uniform method

y: rejection algorithm

4. Illustration: Kidney Infection Data

- We illustrate our approach using data on times to first and second occurrence of infection in 38 patients on portable dialysis machines (McGilchrist and Aisbett, 1991).

- Covariate to consider: gender (0 indicating male, 1 indicating female)

- Other covariates: age, disease type- insignificant so omitted

Piecewise exponential hazard with correlated prior process:
The prior for η is Gamma(0.1, 0.1).
The prior on β is Normal$(0, 10^3)$, where β is the coefficient corresponding to gender.

For lognormal proposal for the generation of η, we assume that standard deviation of normal distribution is 0.4.
We choose the value 0.01 for v_k

Using Gibbs sampling, we generate 30,000 iterates from the complete conditional distributions After monitoring convergence, we consider 20,000 additional iterates for making inference.

Table1:Posterior Estimates of Kidney Infection data:

Baseline Hazards: Piecewise Exponential Hazard with Correlated Prior Process

Frailty: PVF

	Mean	Median	95% C. I.
α	0.38301	0.35787	(0.09162, 0.79398)
η	1.0880	1.0457	(0.24814, 2.34249)
β	-1.1449	-1.1300	(-2.05725, -0.30453)
λ_1	0.00122	0.00040	(0.00001, 0.00734)
λ_2	0.00419	0.00078	(0.00002, 0.03134)
λ_3	0.00502	0.00086	(0.00002, 0.03771)
λ_4	0.00499	0.00086	(0.00002, 0.03775)
λ_5	0.00507	0.00087	(0.00002, 0.03791)
λ_6	0.00517	0.00089	(0.00002, 0.03780)
λ_7	0.00545	0.00104	(0.0003, 0.04078)
λ_8	0.00797	0.00245	(0.00012, 0.05105)
λ_9	0.03782	0.02698	(0.00597, 0.13416)
λ_{10}	2.6021	2.3686	(1.1441, 5.4127)

- The negative estimate of β in PVF frailty model: lower risk of infection for female patients

- posterior parameter estimates of δ and θ: 1.0534, 1.0880 respectively–indicating none of the estimated values of α, δ and θ falling in the restricted parameter regions corresponding to gamma or positive stable distributions.

Conditional Predictive Ordinate (CPO) plots indicate that the PVF frailty model is supported over the positive stable frailty(82.5%) models for **Piecewise Exponential baseline hazard model**.

5. Local Dependence Measure

The cross ratio function is useful measure of local dependence for bivariate event times (u_1, u_2) and has the form

$$\chi(u_1, u_2) = \frac{h(u_1|U_2 = u_2)}{h(u_1|U_2 > u_2)},$$

where

$$h(u_1|U_2 = u_2) = \frac{\partial^2 S(u_1, u_2)}{\partial u_1 \partial u_2} / \{\frac{\partial}{\partial u_2} S(u_1, u_2)\}$$

$$h(u_1|U_2 > u_2) = \frac{\partial S(u_1, u_2)}{\partial u_1 S(u_1, u_2)}$$

For bivariate times to events data with the piecewise exponential hazard with the correlated prior process, four possible cases emerge in the evaluation of the cross-ratio function.

Let u_1 and u_2 denote the event time or censored time for the first and second individuals respectively. Let z_1 and z_2 denote the respective covariate vectors for the first and second individuals, while β denotes the regression coefficient vector.

Case 1: Both individuals survive beyond the k^{th} subinterval, i.e., $u_1 > t_k$ and $u_2 > t_k$. In this case,

$$S(u_1, u_2) = \exp\Big[-\frac{\delta}{\alpha}\{\Big(\theta + \lambda_k\,(t_k - t_{k-1})\,e^{\beta' z_1} + \lambda_k\,(t_k - t_{k-1})\,e^{\beta' z_2}\Big)^{\alpha} - \theta^{\alpha}\}\Big]$$

Since this is not a function of u_1 or u_2, the cross ratio function is undefined.

Case 2: The first individual survives beyond the k^{th} interval, while for the second individual, the event time occurs within the k^{th} subinterval, i.e., $u_1 > t_k$ and $t_{k-1} < u_2 < t_k$. Then,

$$S(u_1, u_2) = \exp\Big[-\frac{\delta}{\alpha}\{\Big(\theta + \lambda_k\,(t_k - t_{k-1})\,e^{\beta' z_1} + \lambda_k\,(u_2 - t_{k-1})\,e^{\beta' z_2}\Big)^{\alpha} - \theta^{\alpha}\}\Big]$$

This is a function of u_2 but not of u_1, and the cross ratio function is again undefined in this case.

Case 3: The second individual survives beyond the k^{th} interval, while for the first individual, the event time occurs within the k^{th} subinterval, i.e., $t_{k-1} < u_1 < t_k$ and $u_2 > t_k$. then,

$$S(u_1, u_2) = \exp\Big[-\frac{\delta}{\alpha}\{\Big(\theta + \lambda_k\,(u_1 - t_{k-1})\,e^{\beta' z_1} + \lambda_k\,(t_k - t_{k-1})\,e^{\beta' z_2}\Big)^{\alpha} - \theta^{\alpha}\}\Big]$$

This is a function of u_1 but not of u_2, so that the cross ratio function is undefined.

Case 4: The event times for both individuals occur within the k^{th} subinterval, i.e., $t_{k-1} < u_1 < t_k$ and $t_{k-1} < u_2 < t_k$. In this case,

$$S(u_1, u_2) = \exp\left[-\frac{\delta}{\alpha}\{\Big(\theta + \lambda_k\left(u_1 - t_{k-1}\right)e^{\beta' z_1} + \lambda_k\left(u_2 - t_{k-1}\right)e^{\beta' z_2}\Big)^{\alpha} - \theta^{\alpha}\}\right]$$

The cross ratio function is

$$\chi(u_1, u_2) = \left[1 + \left(1 - \alpha\right)/\delta\{\theta + \lambda_k\left(u_1 - t_{k-1}\right)e^{\beta' z_1} + \lambda_k\left(u_2 - t_{k-1}\right)e^{\beta' z_2}\}^{\alpha}\right].$$

As $\theta \to 0$, $\delta = \alpha$, the cross ratio function corresponds to the survival model with positive stable frailty and the semiparametric baseline hazard function. As $\alpha \to 0$, the cross ratio function measures local dependence for the Gamma frailty and the piecewise exponential baseline hazard.

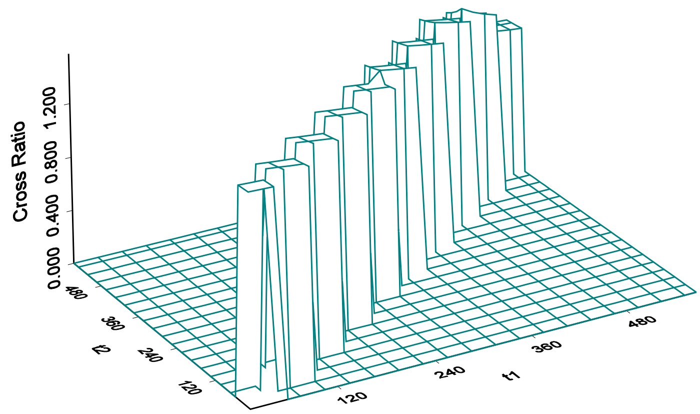

Figure 1: Estimated cross-ratio function for the PVF frailty for male

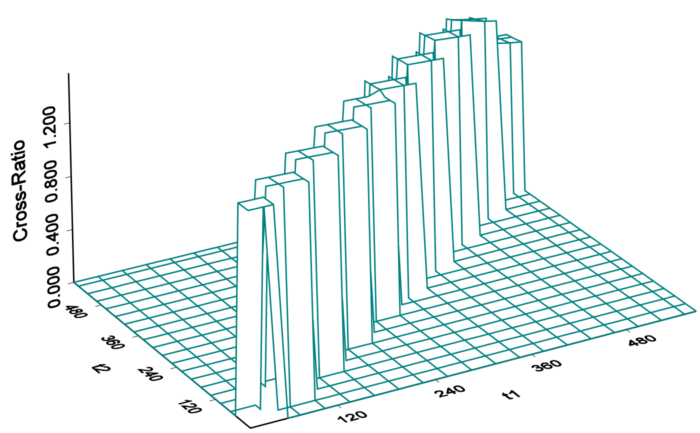

Figure:2 Estimated cross-ratio function for the PVF frailty for female

The cross ratio function is defined at distinct time. Therefore for piecewise exponential hazard with correlated prior process, this function is quite restricted. There is one empirical local dependence measure defined in time interval as follows,

$$\tau\left(u_1, u_2\right) = \frac{h\left(U_1 | U_2 \in I_k\right)}{h\left(U_1 | U_2 > t_k\right)},$$

where $U_1 \in I_i$. But after fitting the model and obtaining all model parameter estimates, empirical dependence measure is not very interesting.