A Bayesian Joint Dispersion Model With Flexible Links

Rui Martins

CENTRO DE INVESTIGAÇÃO INTERDISCIPLINAR EGAS MONIZ

Egas Moniz Health School
Egas Moniz Interdisciplinary Research Center, Portugal

Summary

1. **Background**
   - Longitudinal studies
   - Outline
2. **HIV/AIDS Application**
   - Data
   - Exploratory analysis
   - Joint Model
3. **Results**

Questions of interest

- Biomarker, Y_1
  - *e.g.* CD4 counts, collected repeatedly over time (longitudinal data)
- time to an event of interest, Y_2
  - *e.g.* death from any cause (survival data)

- Separate Analysis
  - does treatment affect survival?
  - are the average longitudinal evolutions different between males and females?
- Joint Analysis
  - what is the effect of the missing information due to drop-out in assessing the trends of the repeated measures?
  - what is the effect of the longitudinal evolution of CD4 cell count in the hazard rate for death?

Questions of interest

- Biomarker, Y_1
  - *e.g.* CD4 counts, collected repeatedly over time (longitudinal data)
- time to an event of interest, Y_2
  - *e.g.* death from any cause (survival data)

- Separate Analysis
  - does treatment affect survival?
  - are the average longitudinal evolutions different between males and females?

- Joint Analysis
  - what is the effect of the missing information due to drop-out in assessing the trends of the repeated measures?
  - what is the effect of the longitudinal evolution of CD4 cell count in the hazard rate for death?

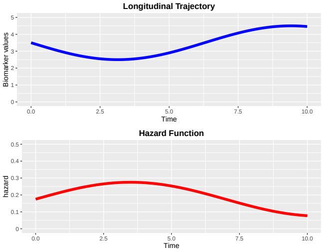
Questions of interest

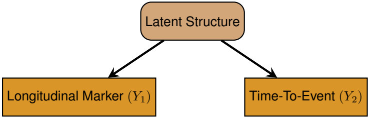
- Biomarker, Y_1
  - *e.g.* CD4 counts, collected repeatedly over time (longitudinal data)
- time to an event of interest, Y_2
  - *e.g.* death from any cause (survival data)

- Separate Analysis
  - does treatment affect survival?
  - are the average longitudinal evolutions different between males and females?

- Joint Analysis
  - what is the effect of the missing information due to drop-out in assessing the trends of the repeated measures?
  - what is the effect of the longitudinal evolution of CD4 cell count in the hazard rate for death?

Correlated data in longitudinal studies





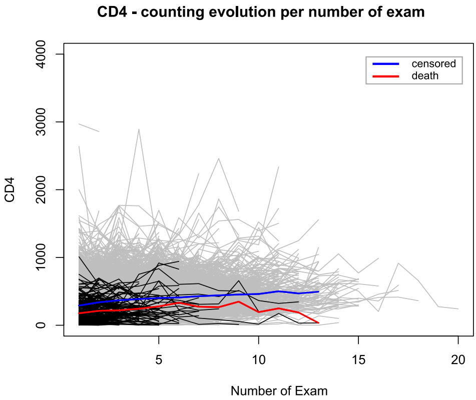
If the two processes are associated $\Rightarrow$ define a model for their joint probability distribution: $f(y_1, y_2)$

Analysing HIV/AIDS data through
A Bayesian Joint Dispersion Model with Flexible Links

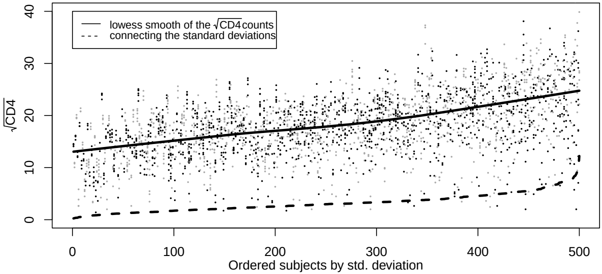
Data

- network of 88 laboratories located in every state in Brazil during Jan 2002 – Dec 2006;
- **Sample**: $n = 500$ individuals; 2757 repeated measurements;
- **Outcomes**: CD4^{+}T lymphocyte counts, Y, and time-to-death, T;
- **Covariates**: age (<50=0, $\geq$50=1); sex (Female=0, Male=1); PrevOI (previous opportunistic infection at study entry=1, no previous infection=0); measurement times; date of diagnosis; date of death; failure indicator, δ;
- **Patients**: 34 deaths. 88% between 15 and 49 years old; 60% males. 61% no previous infection. Initial CD4 median: 269 cells/mm^3 (men - 250 cells/mm^3; women - 295 cells/mm^3).

Longitudinal outcome



Intra-individual variance (dispersion)



Individuals values of the $\sqrt{\text{CD4}}$ *vs* Std. Deviation (ordered) suggests considerable **within-subject variance heterogeneity**. Individuals with higher $\sqrt{\text{CD4}}$ values are associated with a higher variability.

Longitudinal specification

- **Mixed-effects dispersion model** **(McLain et al. 2012)**

$$y_{ij}|\boldsymbol{b}_i, \sigma_i^2 \sim \mathcal{N}\Big(m_i(t_{ij}), \sigma_i^2\Big), \quad j = 1, \dots, n_i \tag{1}$$

$$m_i(t_{ij}) = \boldsymbol{\beta}_1^\top \mathbf{x}_{1i}(t_{ij}) + \boldsymbol{b}_{1i}^\top \mathbf{w}_{1i}(t_{ij}), \tag{2}$$

$$\sigma_i^2 = \sigma_0^2 \exp\{\, \boldsymbol{\beta}_2^\top \mathbf{x}_{2i}(t_{ij}) + \boldsymbol{b}_{2i}^\top \mathbf{w}_{2i}(t_{ij})\,\}, \tag{3}$$

- $\mathbf{y}_i = (y_{i1}, \dots, y_{in_i}) \rightarrow n_i$ observed repeated measures, $\sqrt{\text{CD4}}$
- $\mathbf{t}_i = (t_{i1}, \dots, t_{in_i}) \rightarrow$ visiting times
- $\mathbf{x}_{1i}$, $\mathbf{x}_{2i}$, $\mathbf{w}_{1i}$ and $\mathbf{w}_{2i}$ $\rightarrow$ individual covariates (time-dependent?)
- β_1 and β_2 $\rightarrow$ population parameters
- $(\boldsymbol{b}_{1i}^\top, \boldsymbol{b}_{2i}^\top) = \boldsymbol{b}_i|\Sigma \sim \mathcal{N}_p(\mathbf{0}, \Sigma) \rightarrow$ time-independent random-effects

Longitudinal specification

- **Mixed-effects dispersion model** (McLain et al. 2012)

$$y_{ij} | \boldsymbol{b}_i, \sigma_i^2 \sim \mathcal{N}\big(m_i(t_{ij}), \sigma_i^2\big), \quad j = 1, \ldots, n_i \tag{1}$$

$$m_i(t_{ij}) = \boldsymbol{\beta}_1^\top \mathbf{x}_{1i}(t_{ij}) + \boldsymbol{b}_{1i}^\top \mathbf{w}_{1i}(t_{ij}), \tag{2}$$

$$\sigma_i^2 = \sigma_0^2 \exp\{ \boldsymbol{\beta}_2^\top \mathbf{x}_{2i}(t_{ij}) + \boldsymbol{b}_{2i}^\top \mathbf{w}_{2i}(t_{ij}) \}, \tag{3}$$

- $\mathbf{y}_i = (y_{i1}, \ldots, y_{in_i}) \rightarrow n_i$ observed repeated measures, $\sqrt{\text{CD4}}$
- $\mathbf{t}_i = (t_{i1}, \ldots, t_{in_i}) \rightarrow$ visiting times
- $\mathbf{x}_{1i}$, $\mathbf{x}_{2i}$, $\mathbf{w}_{1i}$ and $\mathbf{w}_{2i} \rightarrow$ individual covariates (time-dependent?)
- β_1 and $\beta_2 \rightarrow$ population parameters
- $(\boldsymbol{b}_{1i}^\top, \boldsymbol{b}_{2i}^\top) = \boldsymbol{b}_i | \Sigma \sim \mathcal{N}_p(\mathbf{0}, \Sigma) \rightarrow$ time-independent random-effects

Longitudinal outcome

$$\sqrt{\text{CD4}}_{ij}|\boldsymbol{b}_i, \sigma_i^2 \sim \mathcal{N}\left(m_i(t_{ij}), \sigma_i^2\right)$$

- Longitudinal mean

$$m_i(t_{ij}) = \beta_{10} + \beta_{11}\text{sex}_i + \beta_{12}\text{age}_i + \beta_{13}\text{PrevOI}_i + \beta_{14}t_{ij} + b_{1i,1} + b_{1i,2}t_{ij} \quad (4)$$

- Dispersion model (3) may assume:

$$\sigma_i^2 = \sigma_0^2 \exp\{\beta_{21}\text{sex} + \beta_{22}\text{age} + \beta_{23}\text{PrevOI} + b_{2i}\}, \quad (5)$$

$$\sigma_i^2 = \sigma_0^2 \exp\{b_{2i}\}, \quad (6)$$

$$\sigma_i^2, \quad (7)$$

$$\sigma_i^2 = \sigma_0^2. \quad (8)$$

- **Priors**
  - $\beta_{1p} \sim \mathcal{N}(0, 100); p = 0, \ldots, 4$ and $\beta_{2q} \sim \mathcal{N}(0, 100); q = 1, \ldots, 3$
  - $\boldsymbol{b}_i|\Sigma \sim \mathcal{N}_p(\boldsymbol{0}, \Sigma); \quad \Sigma^{-1} \sim \mathcal{W}ish(R, \xi)$
  - $\log(\sigma_0) \sim \mathcal{U}(-100, 100)$; or $\log(\sigma_i) \sim \mathcal{U}(-100, 100)$
  - Other options: $1/\sigma_0^2 \sim \mathcal{G}(\epsilon, \epsilon)$ and $\sigma_0|\varpi \sim$ h-$\mathcal{C}(\varpi)$, $\varpi \sim \mathcal{U}(0, 100)$.

Longitudinal outcome

$$\sqrt{\text{CD4}}_{ij}|\boldsymbol{b}_i, \sigma_i^2 \sim \mathcal{N}\left(m_i(t_{ij}), \sigma_i^2\right)$$

- Longitudinal mean

$$m_i(t_{ij}) = \beta_{10} + \beta_{11}\text{sex}_i + \beta_{12}\text{age}_i + \beta_{13}\text{PrevOI}_i + \beta_{14}t_{ij} + b_{1i,1} + b_{1i,2}t_{ij} \quad (4)$$

- Dispersion model (3) may assume:

$$\sigma_i^2 = \sigma_0^2 \exp\{\beta_{21}\text{sex} + \beta_{22}\text{age} + \beta_{23}\text{PrevOI} + b_{2i}\}, \quad (5)$$

$$\sigma_i^2 = \sigma_0^2 \exp\{b_{2i}\}, \quad (6)$$

$$\sigma_i^2, \quad (7)$$

$$\sigma_i^2 = \sigma_0^2. \quad (8)$$

- **Priors**
  - $\beta_{1p} \sim \mathcal{N}(0, 100); p = 0, \ldots, 4$ and $\beta_{2q} \sim \mathcal{N}(0, 100); q = 1, \ldots, 3$
  - $\boldsymbol{b}_i|\Sigma \sim \mathcal{N}_p(\mathbf{0}, \Sigma); \quad \Sigma^{-1} \sim \mathcal{W}ish(R, \xi)$
  - $\log(\sigma_0) \sim \mathcal{U}(-100, 100)$; or $\log(\sigma_i) \sim \mathcal{U}(-100, 100)$
  - Other options: $1/\sigma_0^2 \sim \mathcal{G}(\epsilon, \epsilon)$ and $\sigma_0|\varpi \sim$ h-$\mathcal{C}(\varpi)$, $\varpi \sim \mathcal{U}(0, 100)$.

Survival specification

- **Time-dependent coefficients** (Penalized cubic B-Splines)

$$h_i(t|\boldsymbol{b}_i, \sigma_i) = h_0(t)\exp\{\boldsymbol{\beta}_3^\top \mathbf{x}_{3i} + \mathcal{C}_i\{\boldsymbol{b}_i, \sigma_i; \boldsymbol{g}(t)\}\} = h_0(t)\exp\{\varrho_i(t)\} \quad (9)$$

- $\mathcal{C}_i\{.\} \rightarrow$ specifies which components of the longitudinal process are related to $h_i(.)$
- Link $\rightarrow$ Shared parameters
  - $\boldsymbol{b}_i, \sigma_i$
- $\mathbf{x}_{3i} \rightarrow$ baseline covariates
- $\boldsymbol{\beta}_3 \rightarrow$ population parameters
- $h_0(t) \rightarrow$ parametric (*e.g.* Weibull); P-Splines; Piecewise constant function.
- $\boldsymbol{g}(t) = (g_1(t), \ldots, g_L(t)) \rightarrow$ suitable vector of smooth functions (P-Splines) representing the time-dependent coefficients

Survival specification

- **Time-dependent coefficients** (Penalized cubic B-Splines)

$$h_i(t|\boldsymbol{b}_i, \sigma_i) = h_0(t) \exp\{\boldsymbol{\beta}_3^\top \mathbf{x}_{3i} + \mathcal{C}_i\{\boldsymbol{b}_i, \sigma_i; \boldsymbol{g}(t)\}\} = h_0(t) \exp\{\varrho_i(t)\} \quad (9)$$

  - $\mathcal{C}_i\{.\} \rightarrow$ specifies which components of the longitudinal process are related to $h_i(.)$
  - Link $\rightarrow$ Shared parameters
    - $\boldsymbol{b}_i, \sigma_i$
  - $\mathbf{x}_{3i} \rightarrow$ baseline covariates
  - $\boldsymbol{\beta}_3 \rightarrow$ population parameters
  - $h_0(t) \rightarrow$ parametric (*e.g.* Weibull); P-Splines; Piecewise constant function.
  - $\boldsymbol{g}(t) = (g_1(t), \ldots, g_L(t)) \rightarrow$ suitable vector of smooth functions (P-Splines) representing the time-dependent coefficients

Survival specification

- **Time-dependent coefficients** (Penalized cubic B-Splines)

$$h_i(t|\boldsymbol{b}_i, \sigma_i) = h_0(t)\exp\{\boldsymbol{\beta}_3^\top \mathbf{x}_{3i} + \mathcal{C}_i\{\boldsymbol{b}_i, \sigma_i; \boldsymbol{g}(t)\}\} = h_0(t)\exp\{\varrho_i(t)\} \quad (9)$$

- $\mathcal{C}_i\{.\} \rightarrow$ specifies which components of the longitudinal process are related to $h_i(.)$
- Link $\rightarrow$ Shared parameters
  - $\boldsymbol{b}_i, \sigma_i$
- $\mathbf{x}_{3i} \rightarrow$ baseline covariates
- $\boldsymbol{\beta}_3 \rightarrow$ population parameters
- $h_0(t) \rightarrow$ parametric (*e.g.* Weibull); P-Splines; Piecewise constant function.
- $\boldsymbol{g}(t) = (g_1(t), \ldots, g_L(t)) \rightarrow$ suitable vector of smooth functions (P-Splines) representing the time-dependent coefficients

Time-to-death

$$h_i(t|\boldsymbol{b}_i, \sigma_i) = h_0(t)\exp\{\boldsymbol{\beta}_3^\top \mathbf{x}_{3i} + \mathcal{C}_i\{\boldsymbol{b}_i, \sigma_i; \boldsymbol{g}(t)\}\} = h_0(t)\exp\{\varrho_i(t)\} \quad (10)$$

- all models

$$\boldsymbol{\beta}_3^\top \mathbf{x}_{3i} = \beta_{31}\text{sex}_i + \beta_{32}\text{age}_i + \beta_{33}\text{PrevOI}_i \quad (11)$$

- $\mathcal{C}_i(.)$ may assume:

$$\mathcal{C}_i(.) = g_1(t)b_{1i,1} + g_2(t)b_{1i,2} + g_3(t)b_{2i} \quad (12)$$

$$\mathcal{C}_i(.) = g_1(t)b_{1i,1} + g_2(t)b_{1i,2} + g_3(t)\sigma_i \quad (13)$$

$$\mathcal{C}_i(.) = g_1(t)b_{1i,1} + g_2(t)b_{1i,2} \quad (14)$$

- $g_1(t)$, $g_2(t)$, $g_3(t) \rightarrow$ ***Penalized Splines*** with 19 internal knots.
  - $g_l(t) = \sum_{q=1}^{19} \gamma_{lq} B_{lq}(t), \quad l = 1, 2, 3$
  - $\gamma_{l1} \sim \mathcal{N}(0, 1000), \quad \gamma_{lq}|\tau_l^2 \sim \mathcal{N}(\gamma_{l,q-1}, \tau_l^2), \quad q = 2, \ldots, 19$
  - $1/\tau_l^2 \sim \mathcal{G}(0.001, 0.001)$, $l = 0, 1, 2, 3$.
- 3 scenarios for $h_0(t) = \log(g_0(t)) \rightarrow$ Weibull, ***Penalized Splines*** or piecewise constant

Time-to-death

$$h_i(t|\boldsymbol{b}_i,\sigma_i) = h_0(t)\exp\{\boldsymbol{\beta}_3^\top \mathbf{x}_{3i} + \mathcal{C}_i\{\boldsymbol{b}_i,\sigma_i;\boldsymbol{g}(t)\}\} = h_0(t)\exp\{\varrho_i(t)\} \quad (10)$$

- all models

$$\beta_3^\top \mathrm{x}_{3i} = \beta_{31}\text{sex}_i + \beta_{32}\text{age}_i + \beta_{33}\text{PrevOI}_i \quad (11)$$

- $\mathcal{C}_i(.)$ may assume:

$$\mathcal{C}_i(.) = g_1(t)b_{1i,1} + g_2(t)b_{1i,2} + g_3(t)b_{2i} \quad (12)$$

$$\mathcal{C}_i(.) = g_1(t)b_{1i,1} + g_2(t)b_{1i,2} + g_3(t)\sigma_i \quad (13)$$

$$\mathcal{C}_i(.) = g_1(t)b_{1i,1} + g_2(t)b_{1i,2} \quad (14)$$

- $g_1(t)$, $g_2(t)$, $g_3(t) \rightarrow$ ***Penalized Splines*** with 19 internal knots.
  - $g_l(t) = \sum_{q=1}^{19} \gamma_{lq} B_{lq}(t), \quad l = 1,2,3$
  - $\gamma_{l1} \sim \mathcal{N}(0,1000), \quad \gamma_{lq}|\tau_l^2 \sim \mathcal{N}(\gamma_{l,q-1},\tau_l^2), \quad q = 2,\ldots,19$
  - $1/\tau_l^2 \sim \mathcal{G}(0.001,0.001)$, $l = 0,1,2,3.$
- 3 scenarios for $h_0(t) = \log(g_0(t)) \rightarrow$ Weibull, ***Penalized Splines*** or piecewise constant

Time-to-death

$$h_i(t|\boldsymbol{b}_i,\sigma_i) = h_0(t)\exp\{\boldsymbol{\beta}_3^\top \mathbf{x}_{3i} + \mathcal{C}_i\{\boldsymbol{b}_i,\sigma_i;\boldsymbol{g}(t)\}\} = h_0(t)\exp\{\varrho_i(t)\} \qquad (10)$$

- all models

$$\beta_3^\top \mathrm{x}_{3i} = \beta_{31}\mathsf{sex}_i + \beta_{32}\mathsf{age}_i + \beta_{33}\mathsf{PrevOI}_i \qquad (11)$$

- $\mathcal{C}_i(.)$ may assume:

$$\mathcal{C}_i(.) = g_1(t)b_{1i,1} + g_2(t)b_{1i,2} + g_3(t)b_{2i} \qquad (12)$$

$$\mathcal{C}_i(.) = g_1(t)b_{1i,1} + g_2(t)b_{1i,2} + g_3(t)\sigma_i \qquad (13)$$

$$\mathcal{C}_i(.) = g_1(t)b_{1i,1} + g_2(t)b_{1i,2} \qquad (14)$$

- $g_1(t)$, $g_2(t)$, $g_3(t)$ $\rightarrow$ ***Penalized Splines*** with 19 internal knots.
  - $g_l(t) = \sum_{q=1}^{19} \gamma_{lq} B_{lq}(t), \quad l = 1,2,3$
  - $\gamma_{l1} \sim \mathcal{N}(0,1000), \quad \gamma_{lq}|\tau_l^2 \sim \mathcal{N}(\gamma_{l,q-1},\tau_l^2), \quad q = 2,\ldots,19$
  - $1/\tau_l^2 \sim \mathcal{G}(0.001, 0.001)$, $l = 0,1,2,3.$
- 3 scenarios for $h_0(t) = \log(g_0(t))$ $\rightarrow$ Weibull, ***Penalized Splines*** or piecewise constant

Time-to-death

$$h_i(t|\boldsymbol{b}_i, \sigma_i) = h_0(t)\exp\{\boldsymbol{\beta}_3^\top \mathbf{x}_{3i} + \mathcal{C}_i\{\boldsymbol{b}_i, \sigma_i; \boldsymbol{g}(t)\}\} = h_0(t)\exp\{\varrho_i(t)\} \quad (10)$$

- all models

$$\beta_3^\top \mathrm{x}_{3i} = \beta_{31}\mathsf{sex}_i + \beta_{32}\mathsf{age}_i + \beta_{33}\mathsf{PrevOI}_i \quad (11)$$

- $\mathcal{C}_i(.)$ may assume:

$$\mathcal{C}_i(.) = g_1(t)b_{1i,1} + g_2(t)b_{1i,2} + g_3(t)b_{2i} \quad (12)$$

$$\mathcal{C}_i(.) = g_1(t)b_{1i,1} + g_2(t)b_{1i,2} + g_3(t)\sigma_i \quad (13)$$

$$\mathcal{C}_i(.) = g_1(t)b_{1i,1} + g_2(t)b_{1i,2} \quad (14)$$

- $g_1(t)$, $g_2(t)$, $g_3(t) \rightarrow$ ***Penalized Splines*** with 19 internal knots.
  - $g_l(t) = \sum_{q=1}^{19} \gamma_{lq} B_{lq}(t), \quad l = 1, 2, 3$
  - $\gamma_{l1} \sim \mathcal{N}(0, 1000), \quad \gamma_{lq}|\tau_l^2 \sim \mathcal{N}(\gamma_{l,q-1}, \tau_l^2), \quad q = 2, \ldots, 19$
  - $1/\tau_l^2 \sim \mathcal{G}(0.001, 0.001)$, $l = 0, 1, 2, 3$.
- 3 scenarios for $h_0(t) = \log(g_0(t)) \rightarrow$ Weibull, ***Penalized Splines*** or piecewise constant

Joint likelihood

We consider:

- $\mathbf{y}_i | \boldsymbol{b}_i \perp T_i | \boldsymbol{b}_i; \quad y_{ij} | \boldsymbol{b}_i \perp y_{il} | \boldsymbol{b}_i,\ j \neq l$
- non-informative right censoring

$$L(\boldsymbol{\theta}, \mathrm{b}, \boldsymbol{\sigma} \mid \mathcal{D}) = \prod_{i=1}^{N} \left(\prod_{j=1}^{n_i} p(y_i(t_{ij}) | \boldsymbol{\theta}, \boldsymbol{b}_i, \sigma_i^2) \right) p(T_i, \delta_i | \boldsymbol{\theta}, \boldsymbol{b}_i, \sigma_i)$$

where

- $\mathcal{D} = \{\mathcal{D}_i\}_{i=1}^{N} = \{(\mathbf{y}_i, \mathbf{t}_i, T_i, \delta_i)\}_{i=1}^{N} \rightarrow$ observed data for the N independent individuals
- $\boldsymbol{\theta} \rightarrow$ other parameters;
- $p(.) \rightarrow$ suitable density function

Joint likelihood

We consider:

- $\mathbf{y}_i|\boldsymbol{b}_i \perp T_i|\boldsymbol{b}_i; \quad y_{ij}|\boldsymbol{b}_i \perp y_{il}|\boldsymbol{b}_i, \, j \neq l$
- non-informative right censoring

$$L(\boldsymbol{\theta}, \mathrm{b}, \boldsymbol{\sigma} \mid \mathcal{D}) = \prod_{i=1}^{N} \left(\prod_{j=1}^{n_i} p(y_i(t_{ij})|\boldsymbol{\theta}, \boldsymbol{b}_i, \sigma_i^2) \right) p(T_i, \delta_i|\boldsymbol{\theta}, \boldsymbol{b}_i, \sigma_i)$$

where

$$p(y_i(t_{ij}) \mid \boldsymbol{\theta}, \boldsymbol{b}_i, \sigma_i^2) = \frac{1}{\sqrt{2\pi\sigma_i^2}} \exp\left\{ -\frac{[y_i(t_{ij}) - m_i(t_{ij})]^2}{2\sigma_i^2} \right\}$$

Joint likelihood

We consider:

- $\mathbf{y}_i|\boldsymbol{b}_i \perp T_i|\boldsymbol{b}_i; \quad y_{ij}|\boldsymbol{b}_i \perp y_{il}|\boldsymbol{b}_i,\, j \neq l$
- non-informative right censoring

$$L(\boldsymbol{\theta}, \mathrm{b}, \boldsymbol{\sigma} \mid \mathcal{D}) = \prod_{i=1}^{N} \left(\prod_{j=1}^{n_i} p(y_i(t_{ij})|\boldsymbol{\theta}, \boldsymbol{b}_i, \sigma_i^2) \right) p(T_i, \delta_i|\boldsymbol{\theta}, \boldsymbol{b}_i, \sigma_i)$$

where

$$\begin{aligned} p(T_i, \delta_i \mid \boldsymbol{\theta}, \boldsymbol{b}_i, \sigma_i) =& h(T_i|\boldsymbol{\theta}, \boldsymbol{b}_i, \sigma_i)^{\delta_i} \times S(T_i|\boldsymbol{\theta}, \boldsymbol{b}_i, \sigma_i) \\ =& [h_0(T_i) \exp\{\boldsymbol{\beta}_3^\top \mathbf{x}_{3i} + \mathcal{C}_i\{\boldsymbol{b}_i, \sigma_i; \boldsymbol{g}(t)\}\}]^{\delta_i} \times \\ & \exp\left\{ -\int_0^{T_i} h_0(u) \exp\{\boldsymbol{\beta}_3^\top \mathbf{x}_{3i} + \mathcal{C}_i\{\boldsymbol{b}_i, \sigma_i; \boldsymbol{g}(t)\}\} du \right\} \end{aligned}$$

Models comparison

MCMC simulation within WinBUGS.

Longitudinal model		**Survival model**			
m_i	σ_i^2	$\varrho_i(t)$	h_0		
			Weibull	P-Spline	Piecewise
(4)	(5)	(11) + (12)	14671	12573	14317
(4)	(6)		14700	12848	14483
(4)	(5)	(11) + (13)	14307	12605	13365
(4)	(6)		14452	12917	13571
(4)	(7)		13134	**12104** ♣	12921
(4)	(8)		13956	12887	13533
(4)	(5)	(11) + (14)	14811	13334	14463
(4)	(6)		14923	13688	14599
(4)	(7)		14314	13144	13968
(4)	(8)		14627	13553	14355
(4)	(8)	(11)$+g_1 b_{1i,1} + g_2 b_{1i,2}$	16984	15779	16383

Tabela: **WAIC values** for the 33 joint models.

Best fit $\Rightarrow$ share the individual random-effects and the individual std-deviation considered as a covariate for the hazard model (Model ♣). The heteroscedasticity is related to the survival time.

Posterior estimates for the time-dependent coefficients

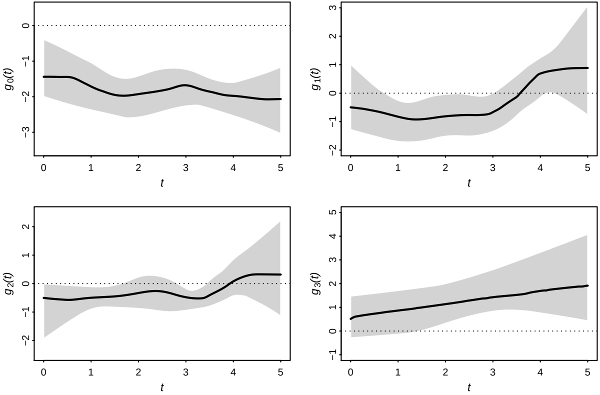


Figure 1: Posterior mean estimates, together with the corresponding 95% Credible Bands (CB), for the selected model ♣. The top left panel shows $g_0 = \log(h_0)$ and the subsequent panels have the time-varying regression coefficients as a function of time in years, t.

BREZGER, A., AND LANG, S.
Simultaneous probability statements for bayesian p-splines.
Statistical Modelling 8, 2 (2008), 141–168.

FAUCETT, C. L., AND THOMAS, D. C.
Simultaneously modelling censored survival data and repeatedly measured covariates: a gibbs sampling approach.
Statistics in Medicine 15, 15 (Aug 1996), 1663–1685.

IBRAHIM, J. G., CHEN, M. H., AND SINHA, D.
Bayesian Survival Analysis.
Springer-Verlag, 2001.

LANG, S., AND BREZGER, A.
Bayesian p-splines.
Journal of Computational and Graphical Statistics 13, 1 (2004), 183–212.

LUNN, D., THOMAS, A., BEST, N., AND SPIEGELHALTER, D.
Winbugs – a bayesian modelling framework: Concepts, structure, and extensibility.
Statistics and Computing 10 (2000), 325–337.

MCLAIN, A. C., LUM, K. J., AND SUNDARAM, R.
A joint mixed effects dispersion model for menstrual cycle length and time-to-pregnancy.
Biometrics 68, 2 (Feb 2012), 648–656.

RIZOPOULOS, D.
Joint Models for Longitudinal and Time-to-Event Data With Applications in R.
Chapman and Hall/CRC, 2012.

Thank you!