Joint Modelling of Longitudinal and Survival Data

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Summary

Data in longitudinal studies

- Multiple biomarkers, *e.g.* blood pressure or CD4 counts, are often collected repeatedly over time (longitudinal data)
- time to an event of interest, *e.g.* death from any cause (survival data)
- Examples
  - PSA repeated measures and time to a recurrence of prostate cancer
  - CD4 repeated measures and time to AIDS

Questions of interest

- Separate Analysis
  - does treatment affect survival?
  - are the average longitudinal evolutions different between males and females?
- Joint Analysis
  - what is the effect of the longitudinal evolution of CD4 cell count in the hazard rate for death?
  - how the association between markers evolves over time (evolution of the association)
  - how marker-specific evolutions are related to each other (association of the evolutions)

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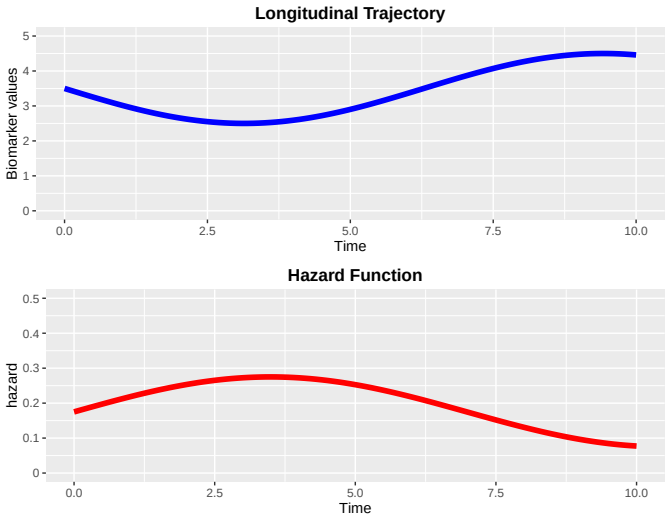
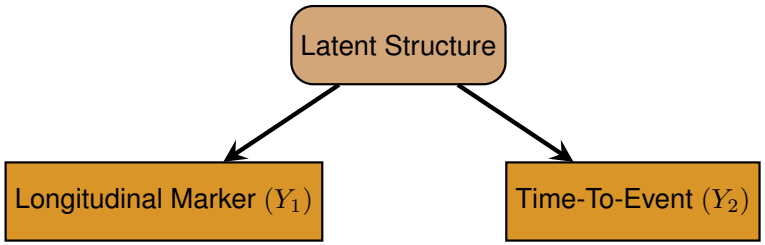
Issues

- Longitudinal studies are often affected by (informative) drop-out, e.g. due to death: MCAR, MAR, MNAR
- Biomarkers are often measured with error
- Survival analysis assumes that covariates are measured without error: Internal *vs* External covariates

Principle

Simultaneous modelling of correlated longitudinal and survival data





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

Objectives of a joint analysis

- explore the association between the two processes
- describe the longitudinal process stopped by the event
- **predict the risk of event adjusted for the longitudinal process**

Applications

- Arose primarily in the field of AIDS, relating CD4 trajectories to progression to AIDS in HIV$^+$ patients (Faucett and Thomas, 1996)
- Further developed in cancer, particularly modelling PSA levels and their association with prostate cancer recurrence (Proust-Lima and Taylor, 2009)

Joint Models to Analyse Longitudinal and Survival Data

Statistical Models

- Longitudinal model
  - mixed effects model
  - splines, etc.
  - multiple markers of progression and/or different nature
  - Gaussian, binary, Poisson
  - continuous but non Gaussian
- Survival model
  - Relative risk model (Proportional hazard model)
  - Accelerated failure time model
  - Competing risks; recurrent events; multiple events
- Linking structure
  - depends on the purposes
  - without consensus
  - *still evolving* ...

Statistical Models

Main families of joint models

- Latent classes (Proust-Lima et al., 2012)
- Shared parameters (Wulfsohn and Tsiatis, 1997; Henderson et al., 2000; Gould et al., 2014)
- random-effects models
- Pattern-mixture models
- Selection models

General idea

How to specify the joint distribution, $f(y_1, y_2)$?

- directly
- factorize

$$f(y_1, y_2) = f(y_1|y_2)f(y_2) = f(y_2|y_1)f(y_1)$$

- use latent variables

$$f(y_1, y_2) = \int f(y_1, y_2|\boldsymbol{b})f(\boldsymbol{b})d\boldsymbol{b} = \int f(y_1|\boldsymbol{b})f(y_2|\boldsymbol{b})f(\boldsymbol{b})d\boldsymbol{b}$$

$$f(y_1, y_2) = \int f(y_1, y_2|\boldsymbol{b})f(\boldsymbol{b}_1, \boldsymbol{b}_2)d\boldsymbol{b} = \int f(y_1|\boldsymbol{b}_1)f(y_2|\boldsymbol{b}_2)f(\boldsymbol{b}_1, \boldsymbol{b}_2)d\boldsymbol{b}_1 d\boldsymbol{b}_2$$

Longitudinal submodel

Assumes observations of a normally distributed longitudinal marker for each time,

$$y_i(t)|\boldsymbol{\theta} \sim \mathcal{N}\left(m_i(t), \sigma_e^2\right)$$

- the mean level trajectory (linear mixed-effects model)

$$m_i(t) = \mathbf{x}_i^\top(t)\boldsymbol{\beta}_1 + \mathbf{z}_i^\top(t)\boldsymbol{b}_i$$

- random-effects

$$\boldsymbol{b}_i \sim \mathcal{N}\left(0, \Sigma_b\right)$$

- more flexibility through polynomials or splines in $\mathbf{x}_i$ and $\mathbf{z}_i$.

Survival submodel

Estimates T_i^*, but using only $T_i = \min(T_i^*, C_i)$ and δ_i.
Assumes the following hazard model,

$$h_i(t) = h_0(t) \exp\{\mathbf{v}_i^\top \boldsymbol{\beta}_2 + \gamma \times m_i(t)\}$$

- where $h_0(t)$ is the baseline hazard function (Weibull, piecewise exponential, splines...)
- $\mathbf{v}_i$ is a vector of time-independent baseline covariates with an associated vector of log hazard ratios, $\boldsymbol{\beta}_2$
- $\gamma \times m_i(t)$ represents the linking structure.

How can we link longitudinal and survival data?

- Use the observed baseline biomarker values
  - We're ignoring all the repeated measures and measurement error
- Use the repeated measures as a time-varying covariate
  - We're still ignoring the measurement error
- Model the longitudinal outcome, and use predictions as a time-varying covariate
  - Uncertainty in the longitudinal outcome is not carried through
- Model both processes simultaneously in a joint model, defining a joint probability distribution
  - Reduce bias and maximize efficiency

Linking structure

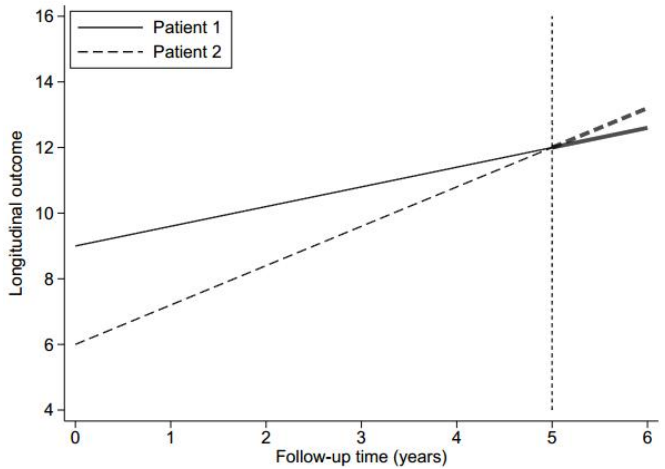
What are the main characteristics of the longitudinal trajectory associated with the Survival?

- **Current value parameterisation**

$$h_i(t) = h_0(t) \exp\{\mathbf{v}_i^\top \boldsymbol{\beta}_2 + \gamma \times m_i(t)\}$$

- **Time-dependent slope**

$$h_i(t) = h_0(t) \exp\{\mathbf{v}_i^\top \boldsymbol{\beta}_2 + \gamma_1 \times m_i(t) + \gamma_2 \times m_i'(t)\}$$



Linking structure II – shared parameters

A time-independent association

Longitudinal submodel

$$m_i(t) = (\beta_0 + b_{0i}) + (\beta_1 + b_{1i})t$$

Survival submodel

$$h_i(t) = h_0(t) \exp\{\mathbf{v}_i^\top \boldsymbol{\beta}_2 + \gamma(b_{0i} + b_{1i})\}$$

$$h_i(t) = h_0(t) \exp\{\mathbf{v}_i^\top \boldsymbol{\beta}_2 + \gamma_1 b_{0i} + \gamma_2 b_{1i}\}$$

random-effects: $\boldsymbol{b}_i = (b_{0i}, b_{1i})$ with density $f(\boldsymbol{b}_i)$; usually a Gaussian

Linking structure III – random-effects

Random-effects parameterisation

$$m_i(t) = (\beta_0 + b_{0i}) + (\beta_1 + b_{1i})t$$

$$h_i(t) = h_0(t) \exp\{\mathbf{v}_i^\top \boldsymbol{\beta}_2 + \gamma(b_{2i})\}$$

random-effects: $\boldsymbol{b}_i = (b_{0i}, b_{1i}, b_{2i})$ with density $f(\boldsymbol{b}_i)$; usually a Gaussian

Joint likelihood

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

Joint likelihood

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

where

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

Joint likelihood

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

where

$$p(T_i, \delta_i \mid \boldsymbol{\theta}, \boldsymbol{b}_i) = [h_0(T_i) \exp\{\mathbf{v}_i^\top \boldsymbol{\beta}_2 + \gamma \times m_i(T_i)\}]^{\delta_i} \times \exp\left\{ - \int_0^{T_i} h_0(u) \exp\{\mathbf{v}_i^\top \boldsymbol{\beta}_2 + \gamma \times m_i(u)\} du \right\}$$

Prediction

Probably the most "marketable" feature of Joint Models

- A growing interest in a tailored made medical decision
  - Personalized Medicine
  - Shared Decision Making
- This is of high relevance in various diseases
  - cancer research, cardiovascular diseases, HIV research ...
- Bayesian approach

Physicians are interested in accurate prognostic tools that will inform them about the future prospect of a patient to adjust medical care

Dynamic Predictions

Example: HIV/AIDS patients receiving HAART therapy

- Interest in predicting survival probabilities for a new patient i that has provided a set of CD4 measurements up to a specific time point t
- What do we know for the patient?
  - a series of CD4 and/or viral load
  - is event-free up to the last measurement
- General Questions:
  - Can we utilize CD4 or viral load measurements to predict survival?
  - When to plan the next visit for a patient?
- Survival probabilities and the visiting plan can be dynamically updated as additional information is recorded - *Dynamic Predictions* (Rizopoulos 2011)

Predictions (Bayesian)

Suppose a new individual data, $\tilde{\mathcal{D}} = \{\tilde{\mathbf{y}}, \tilde{T} = t, \tilde{\delta} = 0\}$

- **Future longitudinal values** at time $s > t$

$$p(\tilde{y}(s) \mid \mathcal{D}, \tilde{\mathcal{D}}) = \int\int p(\tilde{y}(s)|\tilde{\mathcal{D}}, \tilde{\boldsymbol{b}}, \boldsymbol{\theta})\, p(\tilde{\boldsymbol{b}}|\tilde{\mathcal{D}}, \boldsymbol{\theta})\, p(\boldsymbol{\theta}|\mathcal{D}) d\boldsymbol{\theta}\, d\tilde{\boldsymbol{b}}$$

- **Future survival probabilities** at time $s > t$

$$p(\tilde{T}^* > s \mid \mathcal{D}, \tilde{T}^* > t, \tilde{\mathbf{y}}) = \int\int \frac{\tilde{S}(s \mid \tilde{\mathbf{y}}, \tilde{\boldsymbol{b}})}{\tilde{S}(t \mid \tilde{\mathbf{y}}, \tilde{\boldsymbol{b}})}\, p(\tilde{\boldsymbol{b}}|\tilde{\mathcal{D}}, \boldsymbol{\theta})\, p(\boldsymbol{\theta}|\mathcal{D})\, d\boldsymbol{\theta}\, d\tilde{\boldsymbol{b}}$$

Software

- R - JM, joineR, frailtypack, INLA
- WinBUGS, Stan, JMBayes
- STATA - stjm command

Computationally intensive

Software

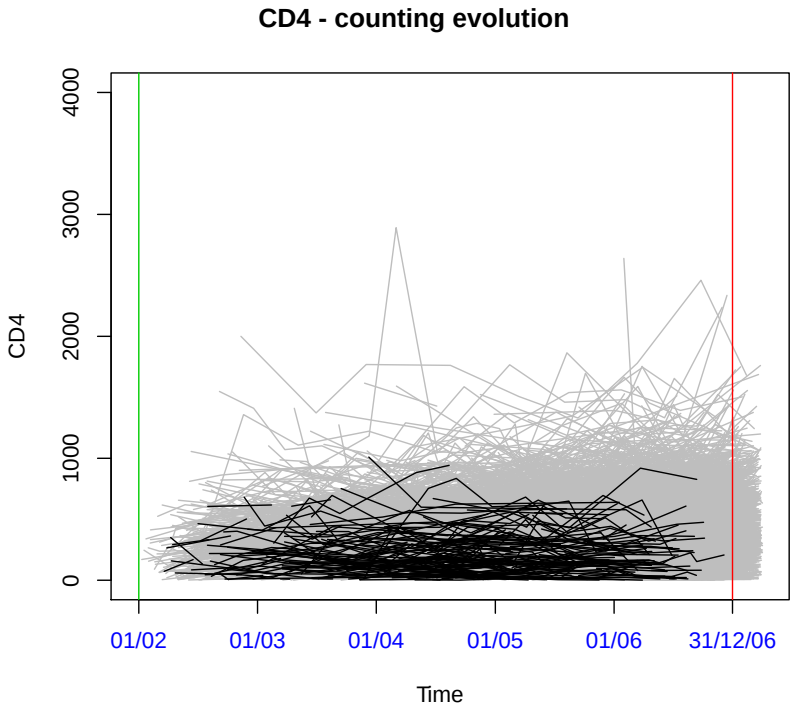
```
jointModel(lmeObject, survObject, timeVar,
  parameterization = c("value", "slope", "both"),
  method = c("weibull-PH-aGH", "weibull-PH-GH", "weibull-AFT-aGH",
    "weibull-AFT-GH", "piecewise-PH-aGH", "piecewise-PH-GH",
    "Cox-PH-aGH", "Cox-PH-GH", "spline-PH-aGH", "spline-PH-GH",
    "ch-Laplace"),
  interFact = NULL, derivForm = NULL, lag = 0, scaleWB = NULL,
  CompRisk = FALSE, init = NULL, control = list(), ...)
```

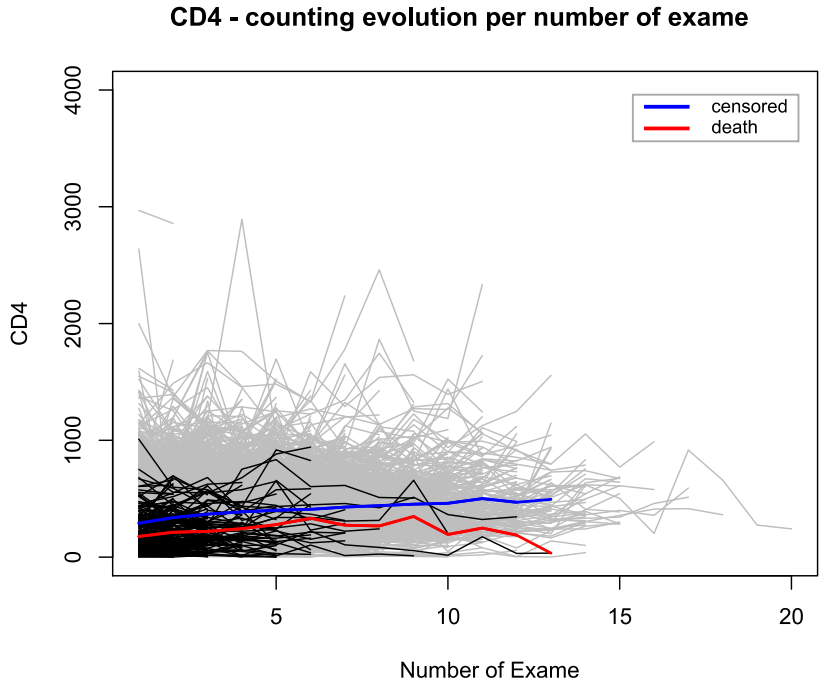
```
jointModelBayes(lmeObject, survObject, timeVar,
    param = c("td-value", "td-extra", "td-both", "shared-betasRE", "shared-RE"),
    extraForm = NULL, baseHaz = c("P-splines", "regression-splines"),
    transFun = NULL, densLong = NULL, lag = 0, df.RE = NULL,
    estimateWeightFun = FALSE, weightFun = NULL, init = NULL,
    priors = NULL, scales = NULL, control = list(), ...)
```

Database - Martins, Silva, Andreozzi (2016) Stat. Med.

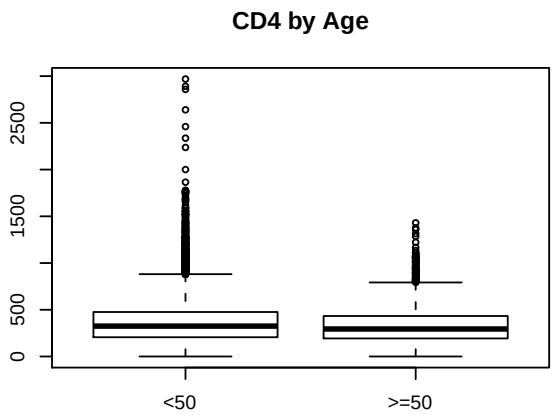
- network of 88 laboratories located in every state in Brazil during 2002–2006;
- **Sample**: $n = 4654$ individuals;
- **Outcomes**: CD4$^+$T lymphocyte counts and survival time;
- **Covariates**: age (<50=0, $\geq$50=1); gender (Female=0, Male=1); prevoi (previous opportunistic infection at study entry=1, no previous infection=0); region (the 27 states of Brazil); time;
- **Patients**: 320 deaths. 88% between 15 and 49 years old; 60% males. 61% no previous infection. Initial CD4 median: 245 cells/mm^3 (men - 226 cells/mm^3; women - 263 cells/mm^3).

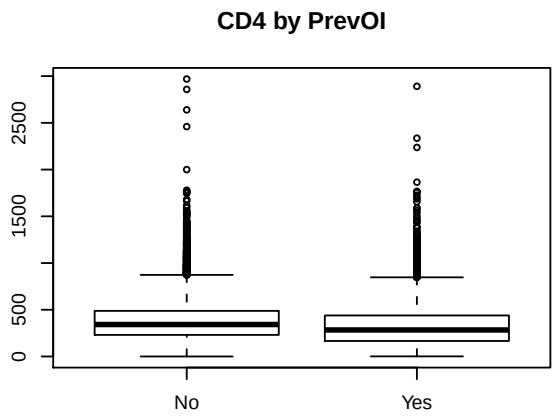
Exploratory trajectory plots

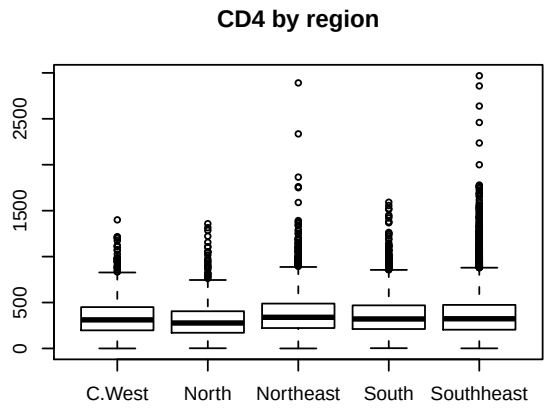


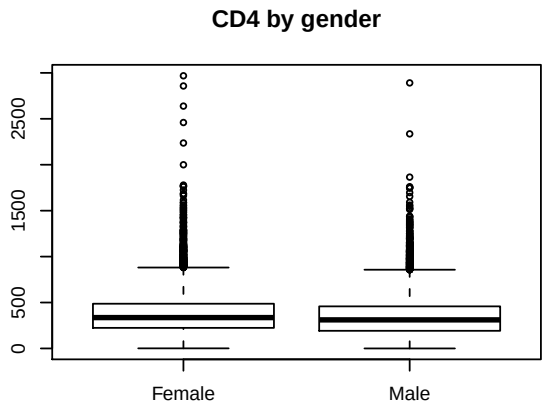


CD4 transformation









Adjusted joint model

Longitudinal specification

$$\sqrt{\text{CD4}} \mid \boldsymbol{b}_{ik}, \boldsymbol{\beta}_1, \sigma_e^2 \sim \mathcal{N}(m_{ikj}, \sigma^2)$$

$$\begin{aligned} m_{ikj} = {} & \beta_{11} + \beta_{12} t_{ikj} + \beta_{13} t_{ikj}^2 + \beta_{14} t_{ikj}^3 + \\ & b_{1ik} + b_{2ik} t_{ikj} + b_{3ik} t_{ikj}^2 + b_{4ik} t_{ikj}^3 + \\ & \beta_{15} \text{gender}_{ik} + \beta_{16} \text{age}_{ik} + \beta_{17} \text{PrevOI}_{ik} \end{aligned}$$

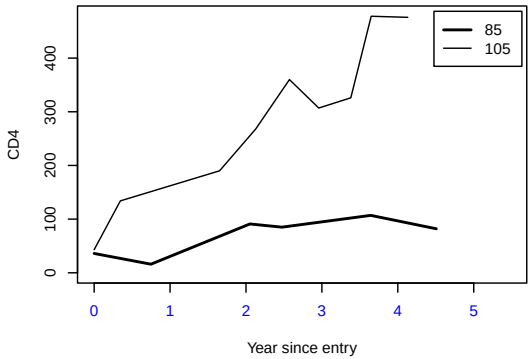
Survival specification

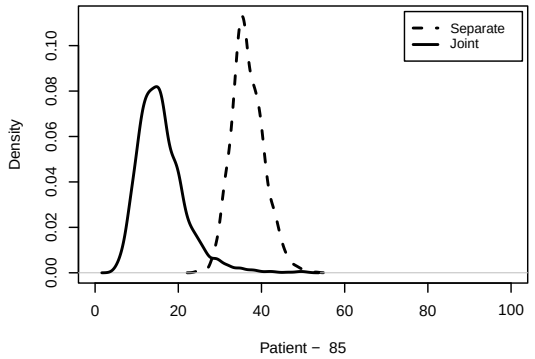
$$T_{ik} \mid \boldsymbol{b}_{ik}, \boldsymbol{\beta}_2, Q_k \sim \mathcal{W}(1, \lambda_{ik}(t)) \equiv \mathcal{E}(\lambda_{ik}(t))$$

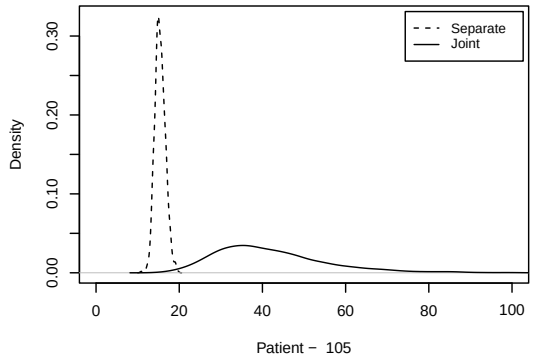
$$\lambda_{ik}(t) = \exp\{\beta_{21} + \beta_{22}\text{gender}_{ik} + \beta_{23}\text{age}_{ik} + \beta_{24}\text{PrevOI}_{ik} + \sum_{s=1}^{4} \gamma_s b_{sik} + Q_k\}$$

$$Q_k | \sigma_Q^2 \sim ICAR(\sigma_Q^2), \quad k = 1, \ldots, 27$$

Separate *vs* Joint



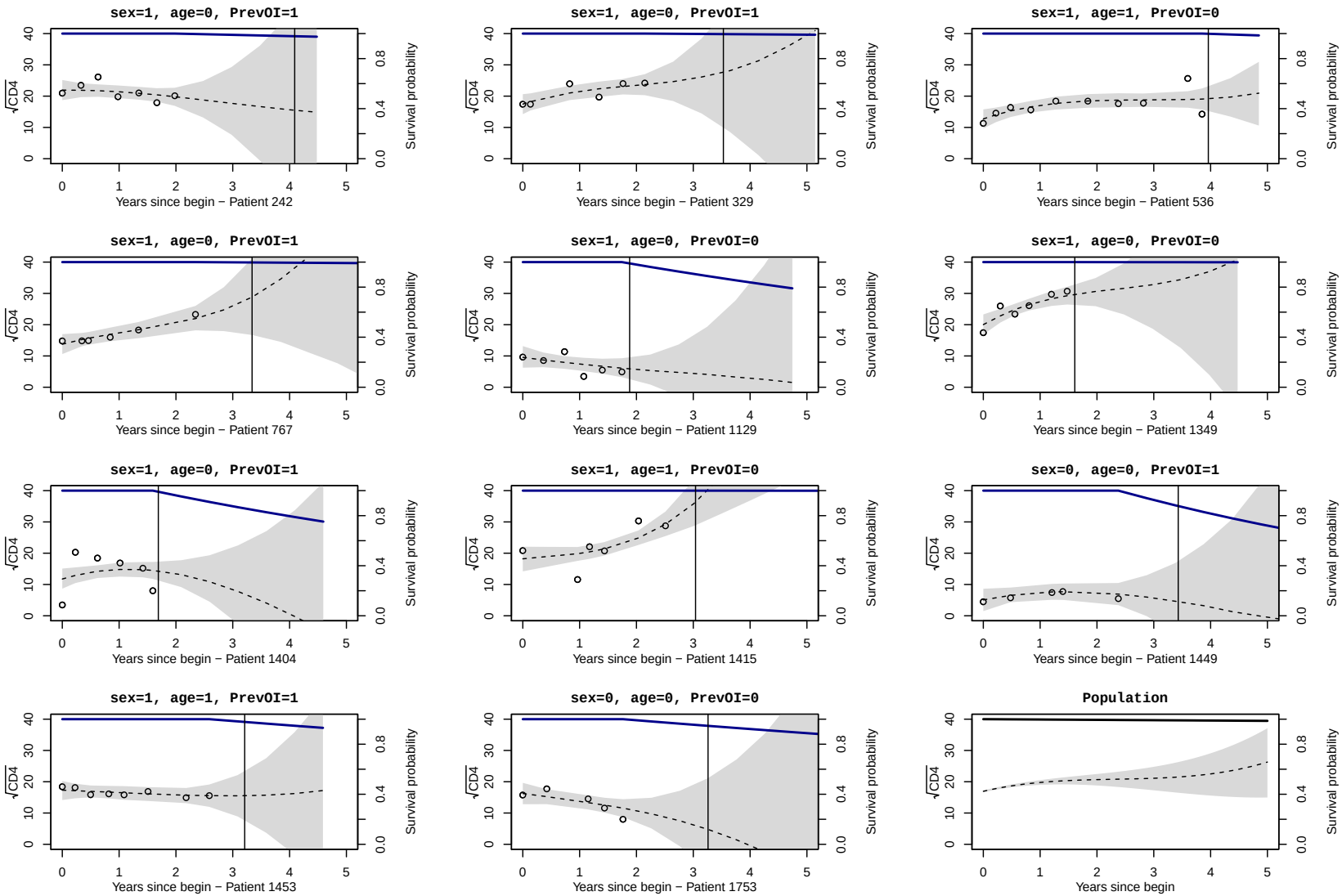




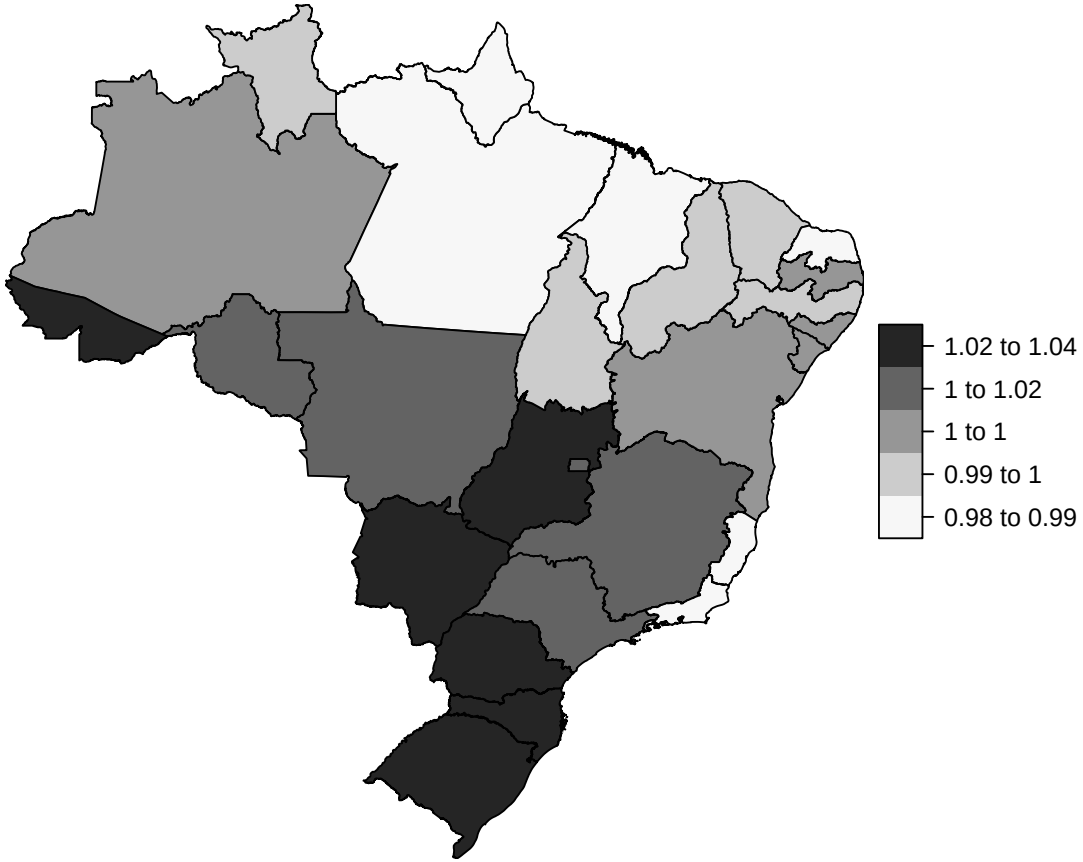
- two patients:
  - male, 31 years old, without previous opportunistic infection and censored time 1645 days
  - male, 29 years old, with previous opportunistic infection and censored time 1508 days

- **Posterior median survival time**: joint model improves the survival estimates

Predictions



Spatial relative risk



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Obrigado!