جامعة الملك عبدالله
للعلوم والتقنية
King Abdullah University of
Science and Technology

Advancing public health statistics and data science using R-INLA

Day 3 - Time to event modeling

Denis Rustand
Post-Doctoral fellow, Statistics program
Computer, Electrical and Mathematical Sciences and Engineering Division
King Abdullah University of Science and Technology (KAUST)

Centers for Disease Control and Prevention - Atlanta - May 2024

Outline

- **Part 1:** Time-to event modeling with **INLA** - Basics
  - **Model 1:** Proportional Hazards model with parametric or semi-parametric baseline hazards
  - **INLAjoint**: a flexible and user-friendly R package to fit longitudinal, survival and joint models with **INLA**
  - **Model 2:** Competing risks
  - **Model 3:** Multi-state model
  - **Model 4:** Mixture cure model
  - **Model 5:** Shared frailty model for recurrent events
  - **Model 6:** Joint model for recurrent and terminal event

Outline

- **Part 2:** Prior sensitivity analysis
- **Part 3:** (Generalized) linear mixed effects models for multivariate longitudinal outcomes
- **Part 4:** Joint modeling one longitudinal outcome and a terminal event
- **Part 5:** Advanced joint models
  - Functions of time and parameterizations
  - Joint model for longitudinal and competing risks
  - Joint model for longitudinal and multi-state
  - Complex multivariate joint models

Integrated Nested Laplace Approximations

Integrated Nested Laplace Approximations (INLA)

INLA is a deterministic alternative to the Markov chain Monte Carlo sampling methods for Bayesian inference of latent Gaussian models.

$\rightarrow$ Approximate Bayesian inference without sampling.

A latent Gaussian model is where the data $\boldsymbol{Y}_i$ depends on the latent field $\boldsymbol{\chi}$ only through the linear predictor η_i and the latent field has a Gaussian distribution (with sparse precision).

$$\pi(\boldsymbol{\chi}, \boldsymbol{\theta}) \propto \pi(\boldsymbol{y}|\boldsymbol{\chi}, \boldsymbol{\theta})\pi(\boldsymbol{\chi}|\boldsymbol{\theta})\pi(\boldsymbol{\theta})$$

Likelihood (any distribution), latent field (Gaussian), prior (any distribution).

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Many models fit with the LGM framework and thus can be fitted with INLA:

- Survival models (AFT, Cox models, competing risks, multi-state, cure models, frailty, censoring and truncation, parametric and nonparametric hazards)
- Longitudinal models (GLMM, zero-inflated models, proportional odds, ...)
- Spatial and spatio-temporal models (CAR, ICAR, MCAR, SPDE)
- Joint models that include multiple longitudinal and survival outcomes
- and many more...

With a few exceptions (e.g., PK/PD models using ODE or SDE without analytical solution).

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Integrated Nested Laplace Approximations (INLA)

This **computationally efficient** and **accurate** algorithm is implemented in the freely available open-source R package *INLA*.

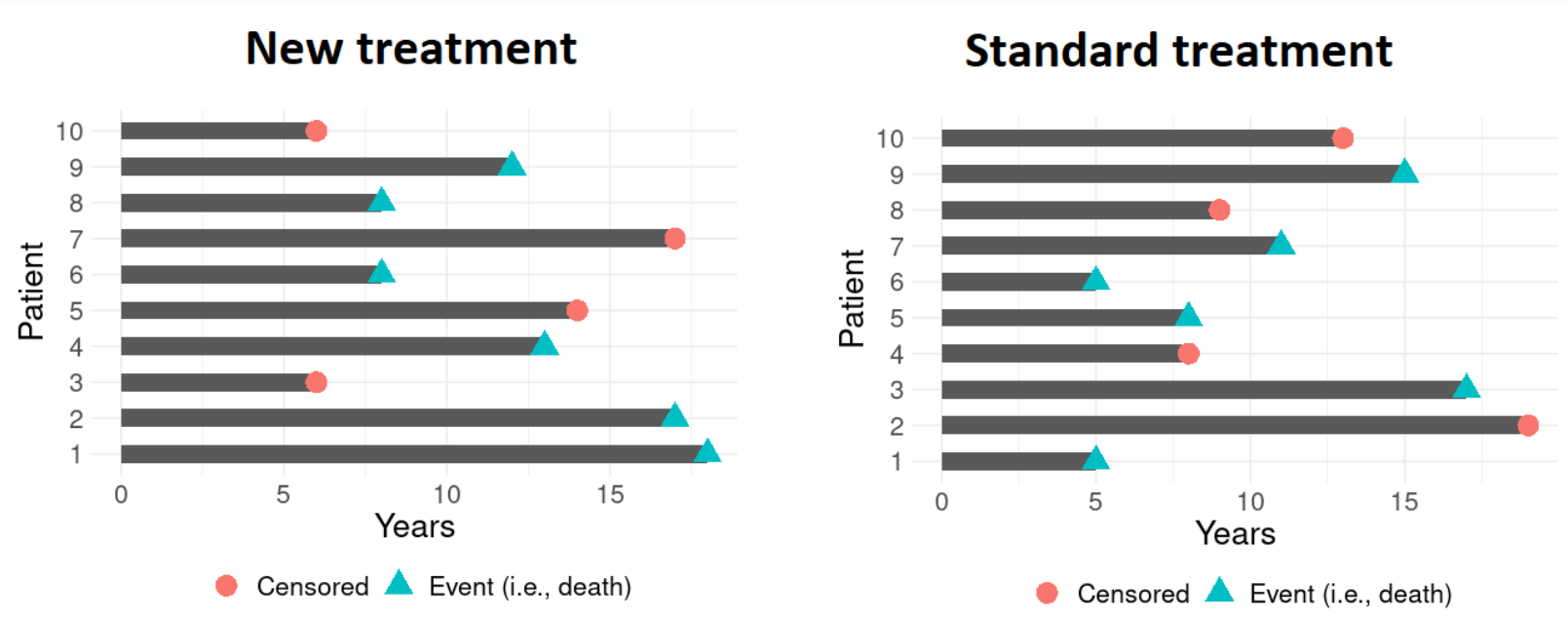
R-INLA project (*www.r-inla.org*)

Rue, Håvard, Sara Martino, and Nicolas Chopin. *Approximate Bayesian inference for latent Gaussian models by using integrated nested Laplace approximations.* Journal of the royal statistical society: Series b (statistical methodology) 71.2 (2009): 319-392.

Survival analysis

Treatment evaluation in clinical trials

The event (i.e., death) is not observed for some individuals…

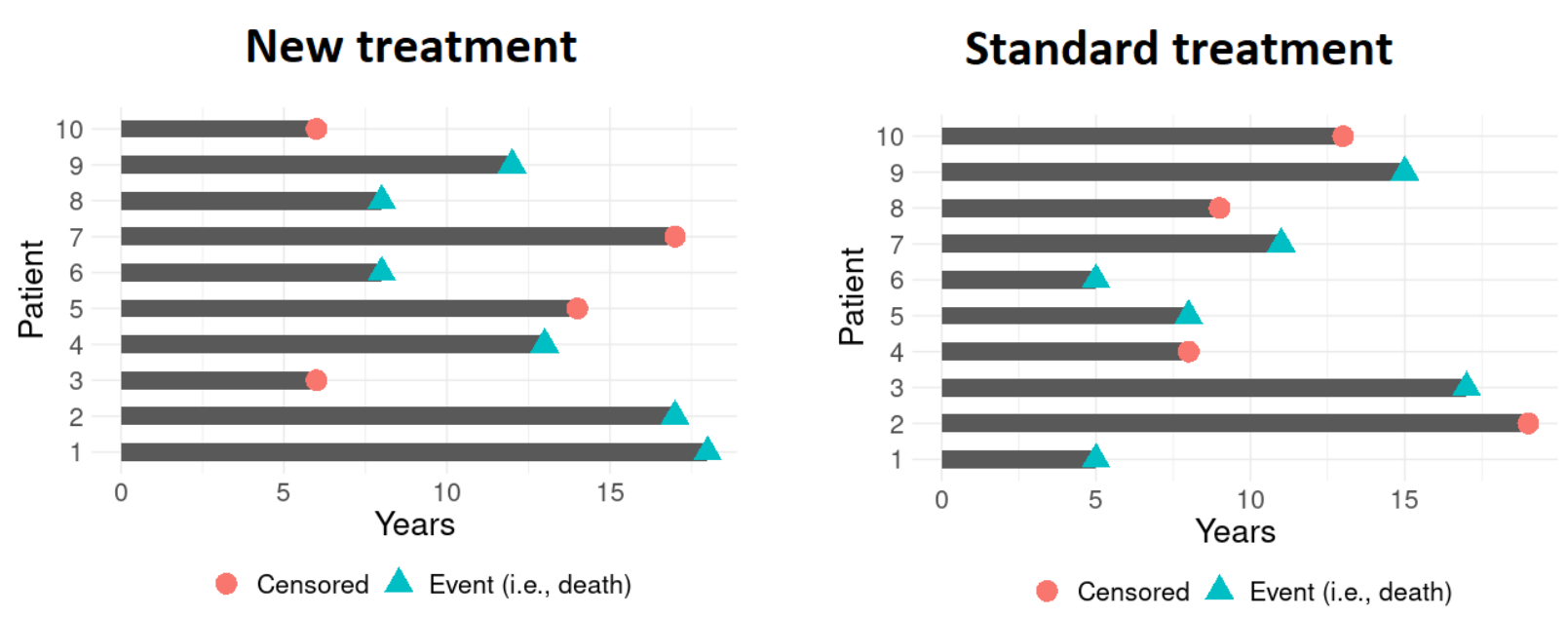


Censoring occurs when a patient withdraws from the study, is lost to follow-up, or is alive without event occurrence at last follow-up.

=> We don't know what happened to these people after censoring.

Survival data - Survival analysis

Survival analysis is used to analyze data in which the time until the event is of interest. The response is often referred to as a failure time, survival time, or event time.



=> Not easy to compare!

Quantities of interest in survival analysis

Let T denote the positive continuous response variable that represents the elapsed time between the beginning of the follow-up and the event of interest. There are many ways to represent and describe the distribution of T.

- Hazard function: Instantaneous risk of event.

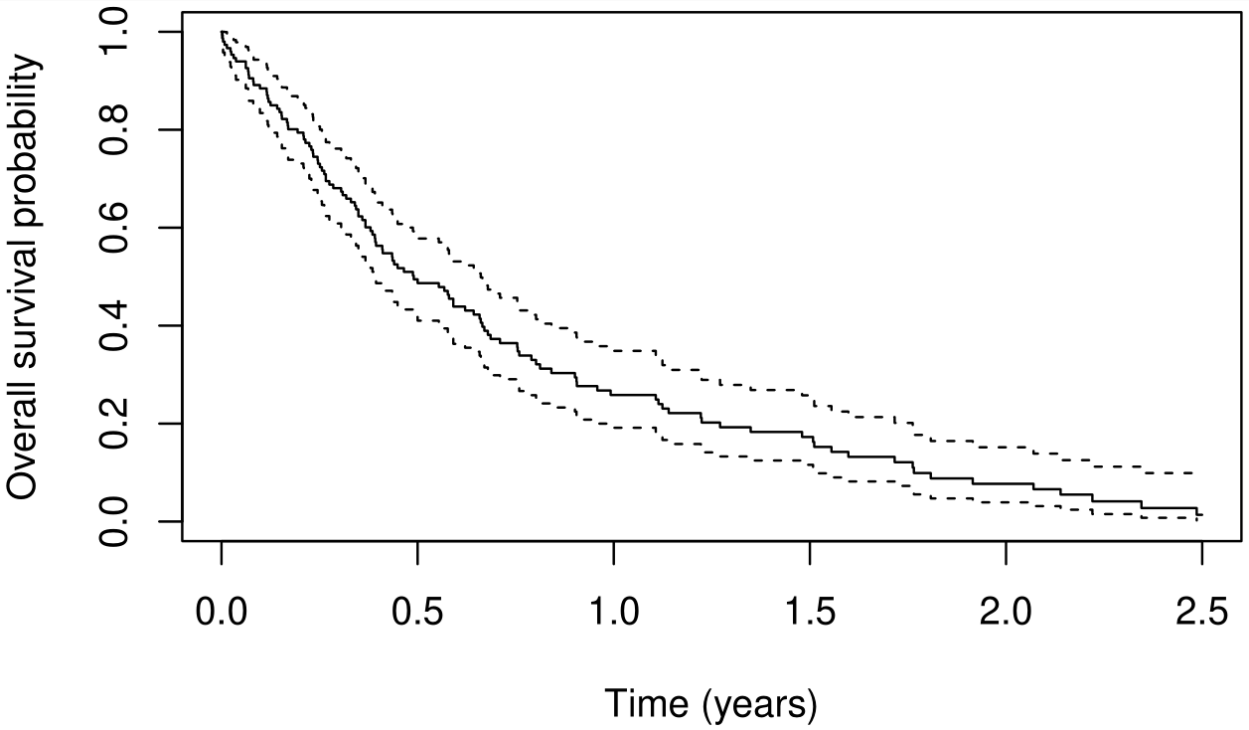
$$\lambda(t) = \lim_{h \to 0^+} \frac{P(t \leq T < t + h | T > t)}{h}$$

- Survival function: Probability of being alive up to time t (i.e., dying after t).

$$S(t) = P(T > t) = \exp(-\int_0^t \lambda(u)du)$$

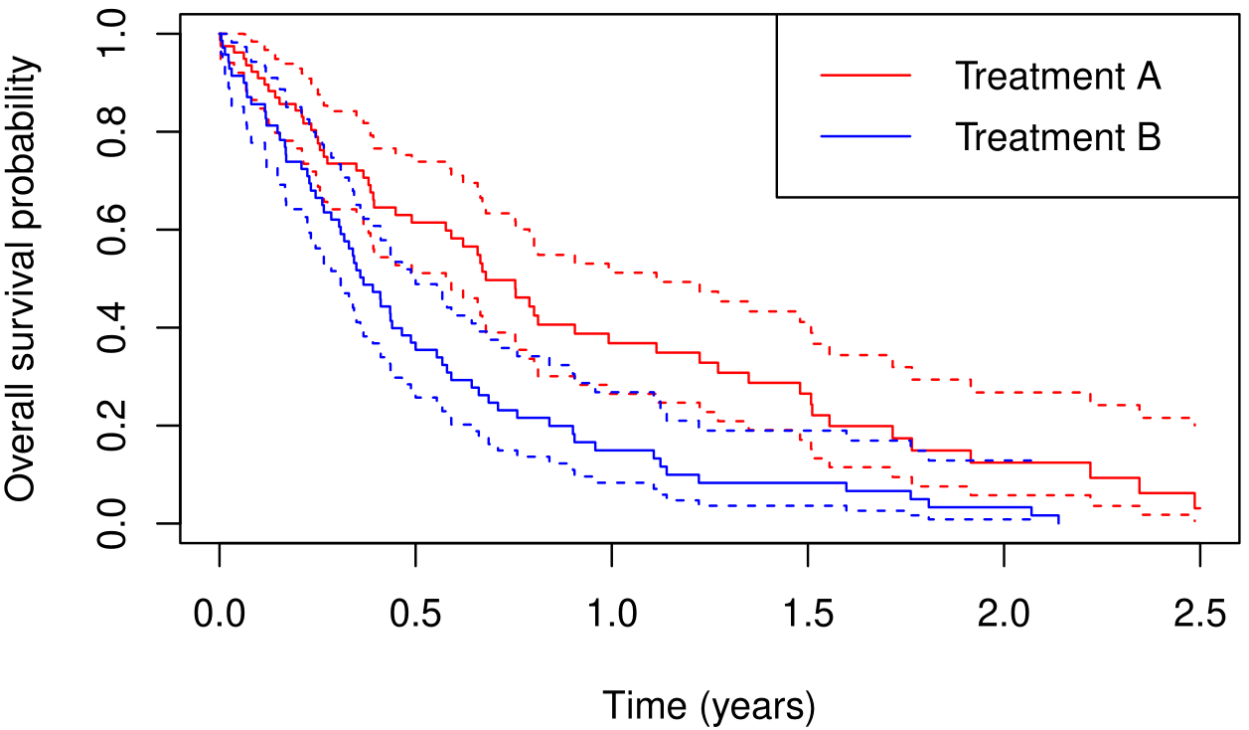
Survival curves (Kaplan-Meier)

The survival curve is one of several ways to describe and display survival data. It has the advantage of taking into account censoring over time.



The horizontal axis (x-axis) represents time and the vertical axis (y-axis) shows the probability of surviving (or the proportion of people surviving).

Survival curves - Example

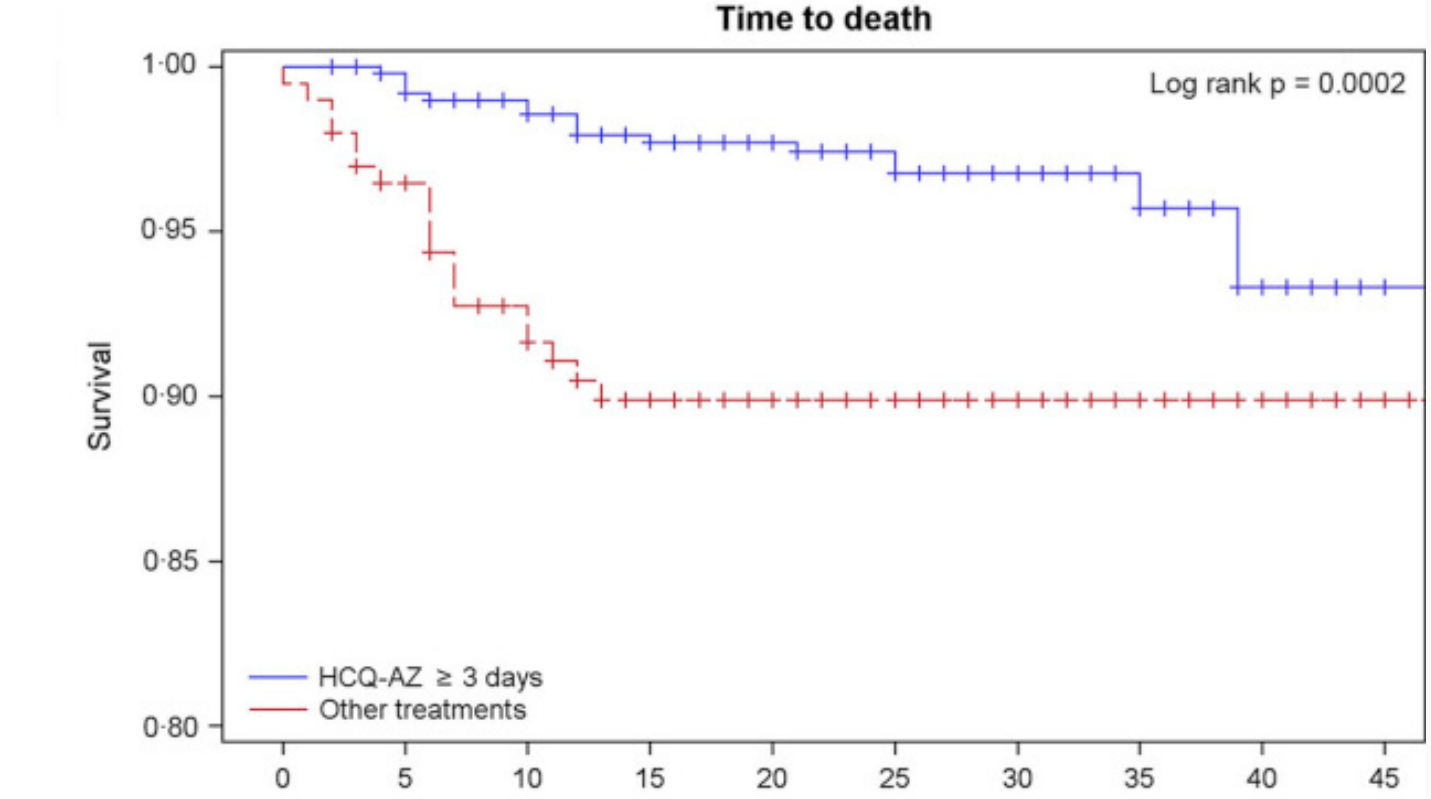


There appears to be a survival advantage for treatment A compared to treatment B. However, a formal statistical test is required to evaluate whether this difference is statistically significant.

The log-rank test is the most widely used method for comparing two or more survival curves.

Survival analysis: what could go wrong?

Example: “proof” of HCQ+AZ efficacy to treat COVID 19.



Survival analysis: what could go wrong?

- **Immortal time bias**: HCQ + AZ $\geq$ 3 days ; anyone dying in the 3 first days is assumed to be in the "other treatment group" => artificially overestimating the effect of the HCQ–AZI.

- **Imbalance between groups**: Randomization bias
  Age 18-44: 52.8% in HCQ+AZ vs. 36.4% in control
  Age >74: 3.6% in HCQ+AZ vs. 16% in control
  Patients with chronic heart diseases: 4% in HCQ+AZ vs. 15.2% in control
  etc.
  Moreover, patients with contraindications to HCQ or AZI were included in the control group (they should have been excluded)

Updated guidelines for clinical trials

Randomized clinical trials are subject to guidelines for good clinical practice defined by the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (Europe, Japan, and the United States).

These guidelines have been updated recently (ICH E9):

- Need more advanced methodology to move towards causality.
- Even RCT are subject to bias => need to account for intercurrent events (e.g., rescue medication), non-compliance with treatment, etc.

Survival regression models

The survival curves and the log-rank tests are limited to categorical variables. Moreover, the heterogeneity of the population within groups is ignored.

Regression models that describe survival as function of explanatory variables have been introduced.

Multiple independent prognosis factors can be analyzed simultaneously and treatment differences can be assessed while adjusting for heterogeneity and imbalances in baseline characteristics.

Survival regression models

The shape of the distribution of survival times justifies the requirement for specific models. (positive values, skewed shapes of distribution, censoring).

=> Statistical methods that rely on normality are not directly applicable and may produce invalid results with survival data.

Cox proportional hazards model: Most commonly used statistical model to study the relationship between the survival time of patients and predictor variables.

Cox proportional hazards regression model

The Cox PH regression model can include both categorical and quantitative variables and study their effect on the risk of event (i.e., death).

$$\lambda_i(t) = \lambda_0(t) \exp\left(X_i(t)\, \boldsymbol{\gamma}\right)$$

Baseline hazard $\lambda_0(t)$ = time-dependent intercept.

The rest of the equation is a multiple linear regression of the logarithm of the hazard on the variables X_i.

Interpretation (example):

Patients in the new treatment group at any time point during the study period were 10% [8% - 12%] less likely to die than patients in the control group.

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Survival regression models

The Cox PH regression model can also answer more complex questions:

- Effect of weight on survival? (continuous variable which we do not want to categorize).
- Effect of treatment if we control for other variables? (e.g., weight, age, history of other diseases, etc.)
- Identify specific subgroups that benefit from the treatment.

Assumptions:

- Non-informative missing data (censoring)
- Proportional hazards

Let's start with the most simple models

Motivation:

- Good scaling in computation time for large data or large number of covariates
- Required to build more complex models

Primary Biliary Cholangitis (PBC)

- 312 PBC patients were followed at the Mayo Clinic between 1974 and 1988 and received either a placebo or D-penicillamine.
- This data is publicly available in the R package 'JM'.
- During the follow-up, 140 patients died.

PBC dataset (available in R package JM):

id	years	death	drug	sex
1	1.095170	1	D-penicil	female
2	14.152338	0	D-penicil	female
3	2.770781	1	D-penicil	male
4	5.270507	1	D-penicil	female
5	4.120578	0	placebo	female
6	6.853028	1	placebo	female
⋮	⋮	⋮	⋮	⋮

Question of interest: Effect of drug and sex on the risk of death?

Model 1 - Parametric proportional hazards survival

$$\lambda_i(t) = \lambda_0(t) \exp\left(\beta_{drug} * drug_i + \beta_{sex} * sex_i\right)$$

Where $\lambda_0(t)$ can have different forms:

- Exponential (constant) baseline hazard
- Weibull baseline hazard

R: Example with **INLA**

INLAjoint, a flexible R package to fit joint models with R-INLA

R package: INLAjoint

We recently developed a **flexible** and **user-friendly** interface to fit models for survival and/or longitudinal data with INLA. The **INLAjoint** package allows to build various models with a lot of flexibility, using its main function *joint()*:

- Univariate and multivariate **survival** outcomes (i.e., frailty models, competing risks, multi-state) fitted with **proportional hazards models**
- Univariate and multivariate **longitudinal** outcomes fitted with **mixed effects models**
- Multivariate longitudinal and survival outcomes

R: Example with **INLAjoint**

Rustand, D., Teixeira Krainski, E., Rue, H., van Niekerk, J. INLAjoint: Multivariate joint modeling for longitudinal and time-to-event outcomes with INLA.
https://github.com/DenisRustand/INLAjoint

Cox model

In practice, survival distributions are complex and not well fit by any common parametric distribution, that's what makes the Cox proportional hazards model popular.

However, we may need to estimate the baseline hazard function, either for technical reasons (because the "partial likelihood" technique for the Cox PH model does not apply for more complex models) or for practical reasons (because we want to look at survival curves).

We can add more flexibility to the baseline hazard to let it fluctuate with time using functions like splines **BUT** we need to avoid overfitting as we aim for the population baseline risk, not the sample!

=> smooth functions to avoid parametric assumptions

Replicate a Cox model using Poisson regression

It is possible to write the Cox PH model as a Poisson regression.

Although the parameter estimates and standard errors are identical, the models are not technically identical. In the Poisson regression model we assume the hazards are constant within event times, an assumption that is not made with the Cox model.

However, it is possible to have more flexibility and replicate the Cox model by splitting the follow-up in many small intervals, and hence Poisson modeling of datasets with many records, each representing a small piece of the follow-up time for a person.

Model 1.2 - Semi-parametric proportional hazards

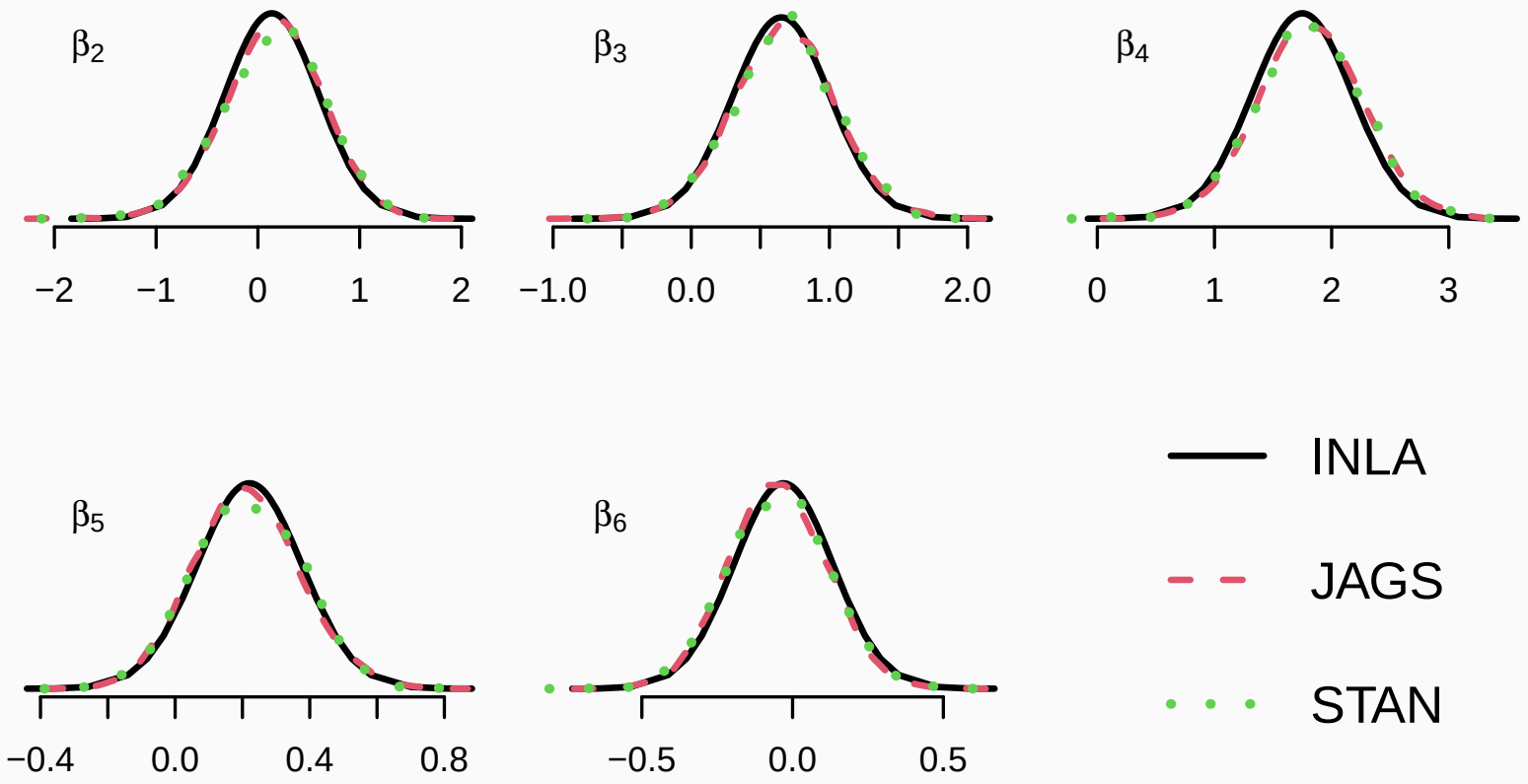
$$\lambda_i(t) = \lambda_0(t) \exp\left(\beta_{drug} * drug_i + \beta_{sex} * sex_i\right)$$

Where $\lambda_0(t)$ is fitted with **Bayesian smooth splines** (random walk order 1 or 2).

When the true **shape** of the baseline hazard is **unknown**, it is better to use semi-parametric approach.

R: Example with **INLAjoint**

Model 1 - Semi-parametric proportional hazards

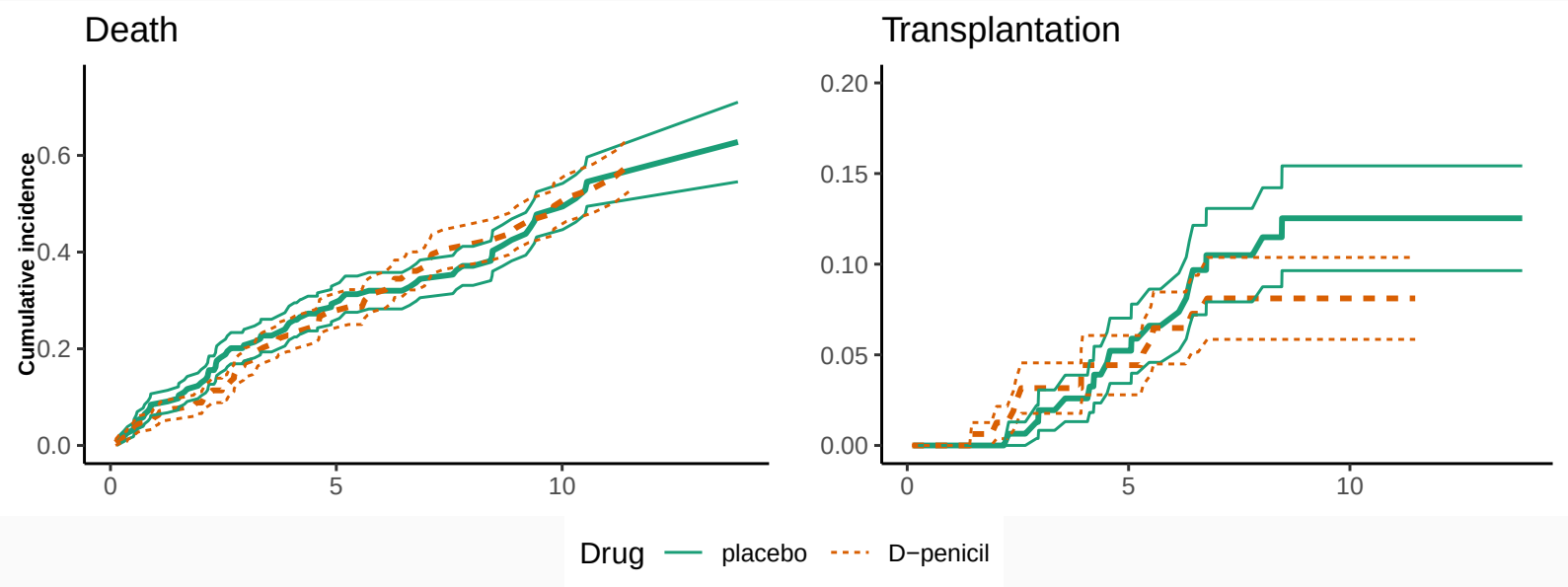


Computation time: INLA = 0.6sec. ; JAGS = 24sec. ; STAN = 67sec.

JAGS: 4 chains, 1000 burn-in and 4000 iterations

STAN: 4 chains, 1000 burn-in and 1000 iterations

Model 2 - Competing risks



Competing risks! (i.e., an individual can only experience one event type: **death** or **liver transplantation**)

id	years	death	transplantation	drug	sex
1	1.095170	1	0	D-penicil	female
2	14.152338	0	0	D-penicil	female
3	2.770781	1	0	D-penicil	male
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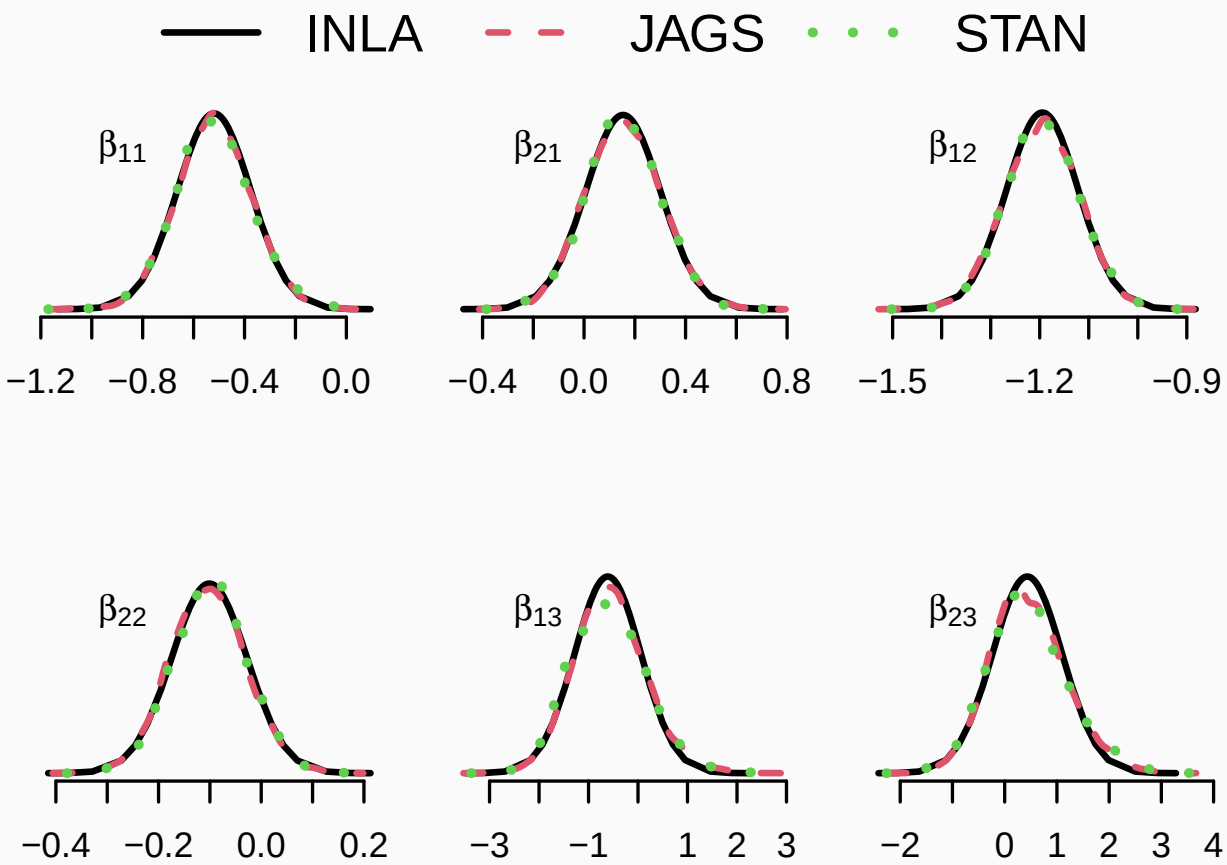
6	6.853028	1	0	placebo	female
⋮	⋮	⋮	⋮	⋮	

Cause-specific hazard functions are modelled from a PH specification:

$$\begin{cases} \lambda_{i1}^{death}(t) & = \lambda_{01}(t)\exp\left(X_{i1}(t)^\top \gamma_1\right) \\ \lambda_{i2}^{transpl.}(t) & = \lambda_{02}(t)\exp\left(X_{i2}(t)^\top \gamma_2\right) \end{cases}$$

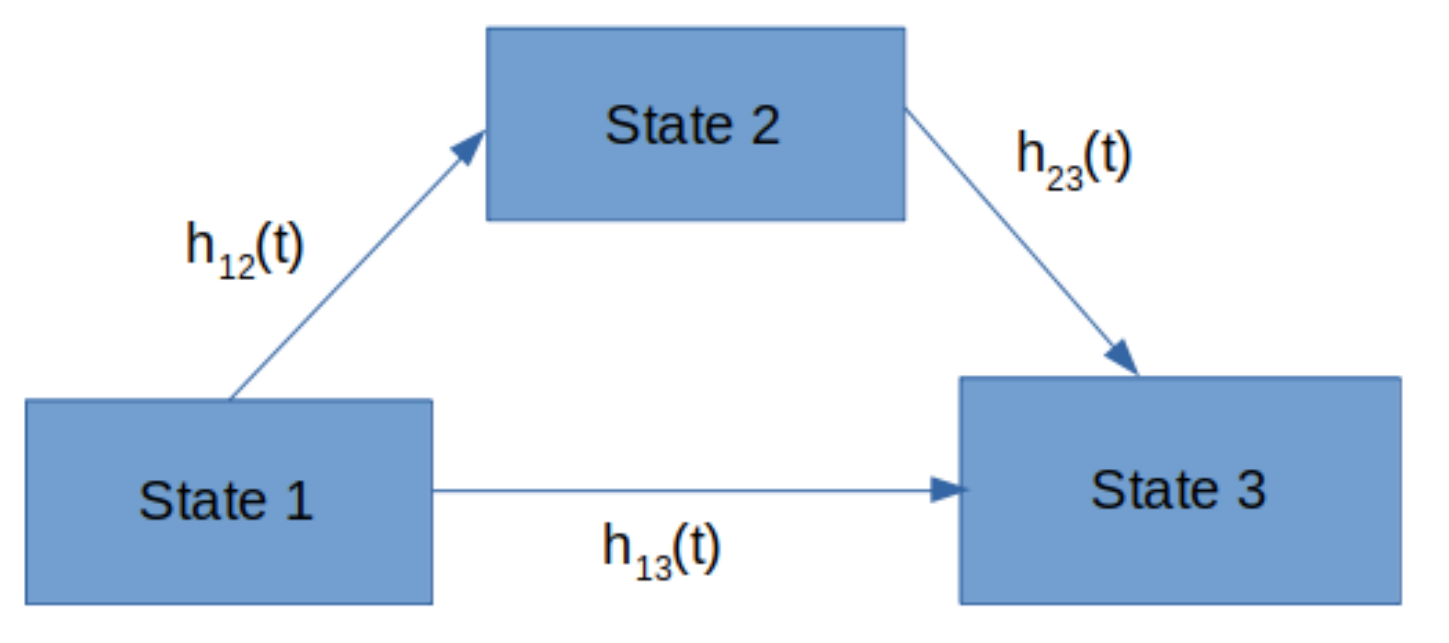
R: Example with **INLAjoint**



Computation time: INLA = 1.3sec. ; JAGS = 1272sec. ; STAN = 350sec.

JAGS: 4 chains, 1000 burn-in and 4000 iterations

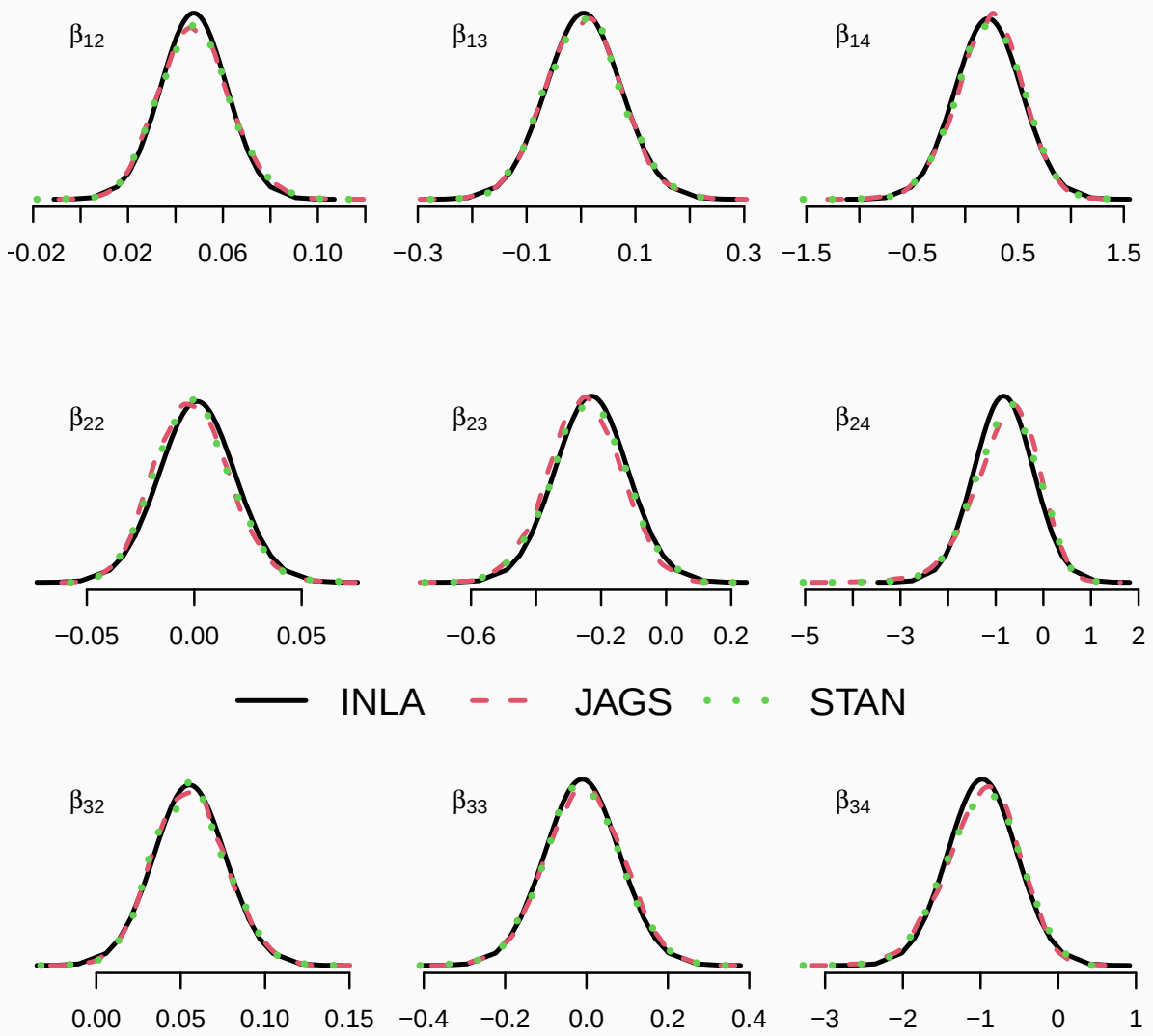
STAN: 4 chains, 1000 burn-in and 1000 iterations



$$\begin{cases} h_{i,12}(t) = h_{0,12}(t)\exp(\gamma_{12}X_i) \text{ (S1)} \\ h_{i,13}(t) = h_{0,13}(t)\exp(\gamma_{13}X_i) \text{ (S2)} \\ h_{i,23}(t) = h_{0,23}(t)\exp(\gamma_{23}X_i) \text{ (S3)} \end{cases}$$

R: Example with **INLAjoint**

Model 3 - Multi-state model



Computation time: INLA = 1sec. ; JAGS = 155sec. ; STAN = 94sec.

bmt dataset (**smcure** R package)

The **bmt** dataset contains 91 patients with refractory acute lymphoblastic leukemia who participated in a bone marrow transplant study. Each patient has the following variables:

- Time: time to death (in days).
- Status: censoring indicator (1: if patient is uncensored; 0: otherwise).
- TRT: treatment group indicator (1: autologous; 0: allogeneic).

Model specification

Let Z be a binary random variable defined as 0 for susceptible and 1 for cured or immune individuals. The incidence submodel is given by:

$$Z \sim \text{Bernoulli}(\eta), \tag{1}$$

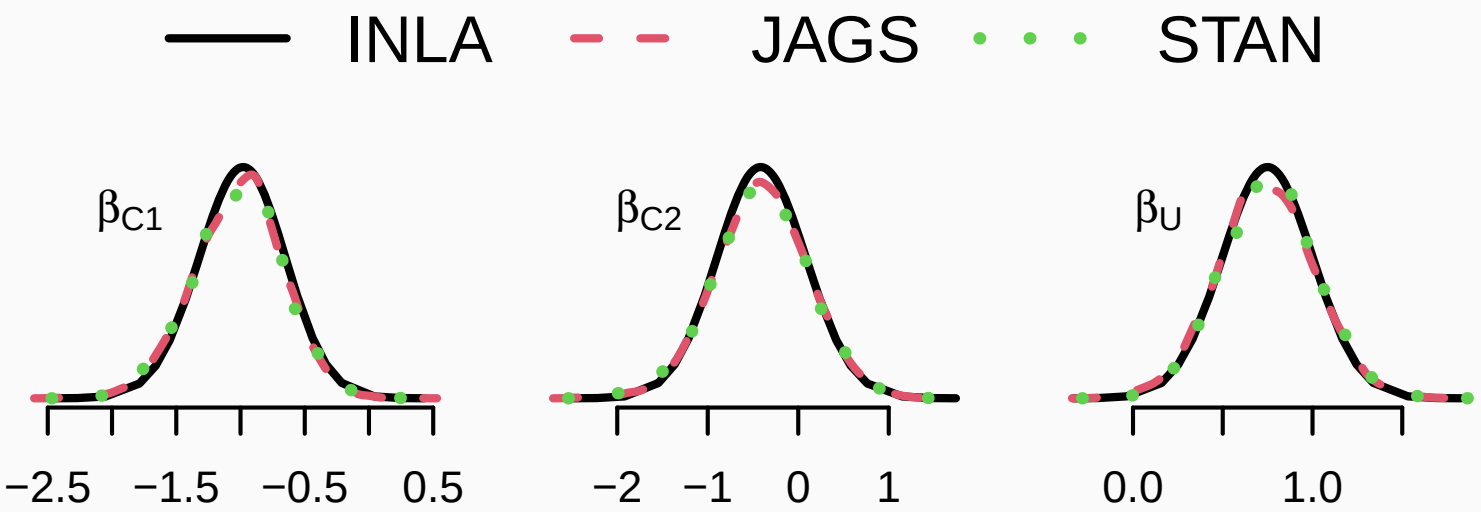
$$\text{logit}(\eta) = \beta_{C1} + \beta_{C2} TRT, \tag{2}$$

The latency submodel is expressed through a PH specification:

$$\lambda(t) = \lambda_0(t) \exp\{\beta_U TRT\}, \quad t > 0, \tag{3}$$

Note: Mixture cure is currently limited to parametric baseline.

R: Example with **INLAjoint**



Computation time: INLA = 0.6sec. ; JAGS = 62sec. ; STAN = 74sec.

JAGS: 4 chains, 1000 burn-in and 4000 iterations

STAN: 4 chains, 1000 burn-in and 1000 iterations

readmission dataset (**frailtypack** R package)

The frailty model can fit recurrent events with a gaussian distribution for the frailty term (i.e., lognormal frailty model).

$$\lambda_{i1}(t) = \lambda_{01}(t) \exp\left(\gamma_1 Chemo_i + \omega_i\right)$$

$$\omega_i \sim \mathcal{N}(\mu, \sigma^2)$$

R: Example with **INLAjoint**

readmission dataset (**frailtypack** R package)

The joint frailty model deals with recurrent events with a frailty model and shares the frailty term in a proportional hazards model for a terminal event. The parameter φ_1 is scaling the frailty term in the terminal event submodel.

$$\begin{cases} \lambda_{i1}(t) = \lambda_{01}(t)\exp\left(\gamma_{11}Chemo_i + \omega_i\right) & \text{(S1)} \\ \lambda_{i2}(t) = \lambda_{02}(t)\exp\left(\gamma_{12}Chemo_i + \varphi_1\omega_i\right) & \text{(S2)} \end{cases}$$

$$\omega_i \sim log\mathcal{N}(\mu, \sigma^2)$$

R: Example with **INLAjoint**

Longitudinal models - Mixed effects

```
# Longitudinal data

 id      year serBilir      drug
  1 0.0000000     14.5 D-penicil
  1 0.5256817     21.3 D-penicil
  2 0.0000000      1.1 D-penicil
  2 0.4983025      0.8 D-penicil
  2 0.9993429      1.0 D-penicil
  2 2.1027270      1.9 D-penicil
  2 4.9008871      2.6 D-penicil
  2 5.8892783      3.6 D-penicil
  2 6.8858833      4.2 D-penicil
  2 7.8907020      3.6 D-penicil
```

Longitudinal models - Mixed effects

Example: mixed-effects regression model for a longitudinal biomarker.

$$Y_{ij} = \beta_{10} + b_{i10} + (\beta_{11} + b_{i11})year_{ij} + \beta_{drug} * drug_i + \varepsilon_{ij}$$

- $Y1$: longitudinal outcome (continuous - lognormal)
- β_0: fixed intercept
- β_1: fixed slope
- β_2: fixed effect of drug
- b_{i0}: random individual intercept
- b_{i1}: random individual slope
- ε_{ij}: residual error

R: Example with **INLAjoint**

Prior sensitivity analysis

Prior sensitivity analysis

In **Bayesian inference**, parameters are associated to a **prior** knowledge. When there are identifiability issues, for example **data is not informative** for a parameter value, the **posterior will reflect prior** (while frequentist will have issues...).

Most parameters are not easy to interpret and flat or **non-informative priors** are **not obvious**. In case of identifiability issues or when the prior is very informative, the posterior may look fine, not showing the issue.

Prior sensitivity analysis consists in evaluating the **posteriors** obtained from **different priors** to evaluate their impact and idensify ill-defined models.

R: Prior sensitivity analysis

Part 3: Multivariate longitudinal outcomes

Two longitudinal markers

$$\begin{cases} Y_{i1j} & = \beta_{10} + b_{i10} + (\beta_{11} + b_{i11}) year_{ij} + \varepsilon_{ij} \\ \mathrm{E}[\log(Y_{i2j})] & = \beta_{20} + b_{i20} + (\beta_{21} + b_{i21}) year_{ij} \end{cases}$$

- $Y1$: longitudinal outcome (continuous - Gaussian)
- $Y2$: second longitudinal outcome (count - Poisson)
- β_0: fixed intercept
- β_1: fixed slope
- b_{i0}: random individual intercept
- b_{i1}: random individual slope
- ε_{ij}: residual error

The two submodels are linked by correlated random effects.

R: Example with **INLA** and **INLAjoint**

Time-dependent covariates in survival models

It is possible to include time-dependent covariates in a survival model, they can be classified into two categories:

- Exogeneous (or external) covariates remain measurable and their distribution is unchanged after the occurrence of the event.
- Endogeneous (or internal) covariates' distribution is affected by the event.

The proportional hazards model can handle exogeneous time-dependent covariates but the likelihood requires knowing the value of these covariates for all subjects at risk for each event time.

When covariates measurements does not coincide with event times in the sample, models are required to impute values at the times of events.

Likelihood = $\prod_{i=1}^{N} S_i(t)\lambda_i(t)^{[Eventindicator]}$
where $S(t) = \exp(-\int_0^t \lambda(u)du)$ and $\lambda_i(t) = \lambda_0(t)\exp(X_i(t)\boldsymbol{\gamma})$

However, most biomarkers of interest in clinical research are endogeneous variables, their values are affected by a change in the risk of occurrence of the event.

For example in a cancer clinical trial, if a treatment reduces both the risk of death and the size of tumors, adjusting a survival model on the tumors size may severely bias the effect of treatment on the risk of death.

Joint modeling Longitudinal and Survival data

Regression models

Regression: Effect of covariates on an outcome (continuous, counts, binary, ...).
Example: Tumors size in cancer clinical trials (outcome)
=> Effect of treatment on tumors size?

Survival analysis: time-to-event.
Example: time to death in cancer clinical trials.

Survival regression model: Evaluate the effect of covariates on the risk of event.
Example: Effect of treatment on the risk of death?

Joint modeling - underlying idea

Can we have a statistical model that evaluates simultaneously the effect of treatment on the tumors size and the risk of death?

Useful because when death occurs => no more measurements of tumors size!
Maybe we never observe big tumors because a patient with big tumors die (informative censoring).

The risk of death for a patient with big tumor is higher compared to a patient with small tumors (recorded heterogeneity of the population).

Joint modeling - underlying idea

Joint modeling consists in **simultaneously** modeling **multiple outcomes** while taking into account their **association**. The outcomes are either **longitudinal** or **time to an event** of interest (e.g., death in health research).

Joint models are popular in health research because it is common to observe **longitudinal markers censored by a terminal event** with interest in the analysis of the longitudinal marker trajectory and the risk of the terminal event as well as their relationship.

Joint modeling - Examples

A few examples of recent applications of joint models:

- Cancer tumor dynamics and the risk of death
- Analysis of CD4 lymphocytes counts and AIDS survival
- Prostate-specific antigen dynamics and the risk of cancer recurrence
- Dynamics of aortic gradient and aortic regurgitations and their relationship with the competing risks of death or reoperation in the field of cardiac surgery
- Cognitive markers's relationship with the time to onset of Alzheimer's disease
- Jointly modeling forest fires ignition, number of fires and the proportion of burned area in mainland Portugal aggregated by years and regions

Joint modeling Longitudinal and Survival data

- Can efficiently utilize all available information to limit costs and optimize outcomes.
- Dynamic risk predictions for personalized care.
- Have interesting properties for mediation analysis (decomposition of a treatment effect into direct and indirect effects (could be a promising tool in the shift toward causality in clinical trials evaluation, see ICH E9 addendum recommendations).
- Evaluation of surrogate markers.

Le Coënt, Q., Legrand, C., & Rondeau, V. (2022). *Time-to-event surrogate endpoint validation using mediation analysis and meta-analytic data.* Biostatistics, kxac044.

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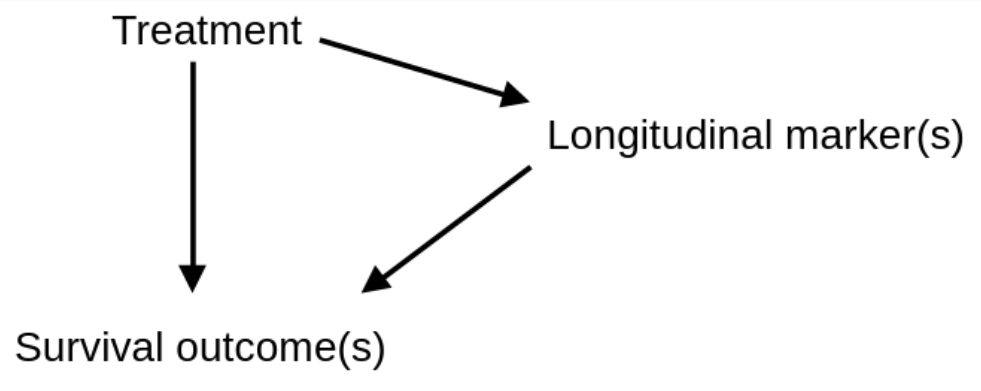

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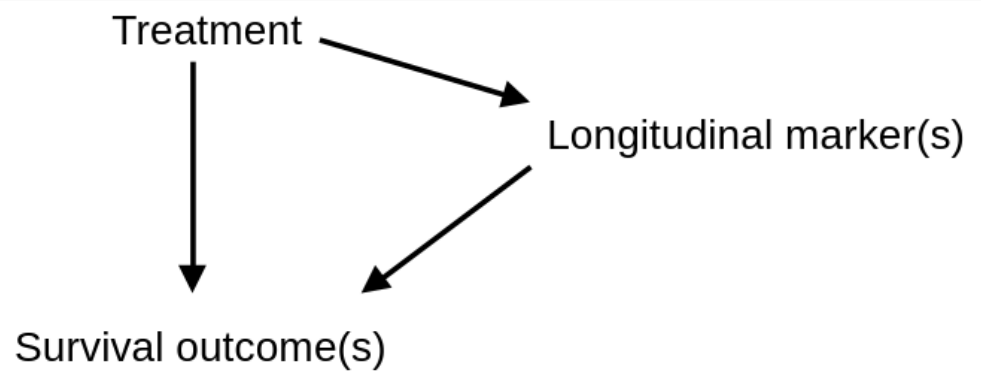

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Lack of efficient algorithm!

The multiple random effects included in joint models needs to be integrated out in the likelihood => multidimensional integral that requires numerical approximation.

Iterative algorithms (e.g., Newton-like, Monte-Carlo) have slow convergence properties, joint modeling has been limited so far by the available inference techniques and associated statistical software.

Hickey, G. L., Philipson, P., Jorgensen, A., Kolamunnage-Dona, R. *Joint modelling of time-to-event and multivariate longitudinal outcomes: recent developments and issues.* BMC medical research methodology, 16(1), 1-15. (2016)

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Simulation studies

Comparison with Levenberg-Marquardt algorithm (Newton-like algorithm):

Rustand D, van Niekerk J, Rue H, Tournigand C, Rondeau V, Briollais L. *Bayesian estimation of two-part joint models for a longitudinal semicontinuous biomarker and a terminal event with INLA: Interests for cancer clinical trial evaluation.* Biometrical Journal. 2023 Apr;65(4):2100322.

Comparison with MCMC and MCEM:

Rustand, D., van Niekerk, J., Krainski, E. T., Rue, H., Proust-Lima, C. *Fast and flexible inference for joint models of multivariate longitudinal and survival data using integrated nested Laplace approximations*, Biostatistics, 2023 Aug; kxad019, https://doi.org/10.1093/biostatistics/kxad019.

Comparison with MCMC - Simulations

$$\begin{cases} \log(E[Y_i(t)]) = \eta_i(t) = (\beta_0 + b_{i0}) + (\beta_1 + b_{i1})t + \beta_2 X_i^c + \beta_3 X_i^b & \textbf{(Counts - Poisson GLMM)} \\ \lambda_i(t) = \lambda_0(t) \exp(\eta_i(t)\varphi) & \textbf{(Survival - Cox PH)} \end{cases}$$

- $Yi(t)$: longitudinal outcome
- $\lambda_i(t)$: Terminal event risk
- $\lambda_0(t)$: Baseline risk
- β_0: fixed intercept
- b_{i0}: random intercept
- β_1: fixed slope
- b_{i1}: random slope
- X_i^c: continuous covariate
- X_i^b: binary covariate
- φ: association parameter

Comparison with MCMC

$$\begin{cases} \log(E[Y_i(t)]) = \eta_i(t) = (\beta_0 + b_{i0}) + (\beta_1 + b_{i1})t + \beta_2 X_i^c + \beta_3 X_i^b & \textbf{(Counts - Poisson GLMM)} \\ \lambda_i(t) = \lambda_0(t) \exp\left(\eta_i(t)\varphi\right) & \textbf{(Survival - Cox PH)} \end{cases}$$

Approach:	R-INLA			JMbayes2			rstanarm (1 chain / 1000 iter.)			rstanarm (4 chains / 2000 iter.)		
True value	Bias	(SD)	CP	Bias	(SD)	CP	Bias	(SD)	CP	Bias	(SD)	CP
β_{10}=4	-0.002	(0.044)	95%	0	(0.044)	95%	0.008	(0.056)	87%	0.003	(0.046)	95%
β_{11}=-0.1	0	(0.016)	95%	0.001	(0.016)	96%	-0.011	(0.042)	91%	-0.006	(0.025)	93%
β_{12}=0.1	0.001	(0.035)	96%	0	(0.035)	96%	0	(0.037)	87%	0.001	(0.036)	93%
β_{13}=-0.2	0.002	(0.034)	96%	0	(0.034)	95%	-0.002	(0.058)	91%	0.002	(0.035)	95%
σ^2_{b10}=0.16	0.002	(0.012)	94%	0.002	(0.012)	94%	-0.011	(0.042)	84%	-0.005	(0.022)	94%
σ^2_{b11}=0.09	0.004	(0.007)	95%	0.001	(0.008)	93%	0.036	(0.12)	88%	0.024	(0.059)	95%
$\mathrm{cov}_{b10,b11}$=0.06	-0.001	(0.008)	95%	0	(0.007)	92%	-0.004	(0.018)	87%	-0.002	(0.012)	92%
φ_1=0.2	-0.012	(0.097)	93%	-0.003	(0.094)	97%	-0.01	(0.095)	93%	-0.009	(0.093)	93%
Conv. rate	1			1			0.61			0.62		
Comp. time (sec.)	7.04 (1.12)			92.31 (1.94)			724.87 (508.13)			2110.49 (1287.46)		

Bias = Absolute bias, SD = Standard deviation of the absolute bias, CP = Coverage probability

Similar results are observed with multiple longitudinal markers with different distributions.

Example - INLAjoint

Example from simulations:

$$\begin{cases} \log(E[Y_i(t)]) = \eta_i(t) = (\beta_0 + b_{i0}) + (\beta_1 + b_{i1})t + \beta_2 X_i^c + \beta_3 X_i^b & \textbf{(Counts - Poisson GLMM)} \\ \lambda_i(t) = \lambda_0(t)\exp\left(\eta_i(t)\varphi\right) & \textbf{(Survival - Cox PH)} \end{cases}$$

```
JM.INLA <- joint(formLong = L1 ~ 1 + t + X_i^c + X_i^b + (1 + t |id),
                 formSurv = S1 ~ 1,
                 dataLong = Longi, dataSurv = Surv,
                 family = "poisson", id = "id",
                 timeVar = "t", assoc = "CV")
```

Association: Shared random effects

$$\begin{cases} Y_{ij} = X_{ij}^\top \boldsymbol{\beta} + Z_{ij}^\top \boldsymbol{b}_i + \epsilon_{ij} & (\text{Biomarker}) \\ \lambda_i(t) = \lambda_0(t) \exp\left(X_i(t)\,\boldsymbol{\gamma} + \boldsymbol{\varphi}^\top \boldsymbol{b}_i\right) & (\text{Time-to-event}) \end{cases}$$

We only share the variability not explained by fixed effects (therefore adjusting the survival model on population heterogeneity not related to covariates of interest).

Advantages: Hazard ratio interpretation ; account for unobserved confounders.

Association: Current value

$$\begin{cases} Y_{ij} = \eta_{ij} = X_{ij}^\top \boldsymbol{\beta} + Z_{ij}^\top \boldsymbol{b}_i + \epsilon_{ij} & (\text{Biomarker}) \\ \lambda_i(t) = \lambda_0(t) \exp\left(X_i(t)\,\boldsymbol{\gamma} + \boldsymbol{\varphi}^\top \eta_i(t)\right) & (\text{Time-to-event}) \end{cases}$$

The risk of event depends on the individual value of the longitudinal marker.

Similar to shared random effects but shares also fixed effects.

Joint modeling longitudinal - survival

$$\begin{cases} Y_{ij} = \beta_0 + b_{i0} + \beta_1 year_{ij} + \varepsilon_{ij} \\ \lambda_i(t) = \lambda_0(t) \exp\left(b_{i0}\varphi_1\right) \end{cases}$$

- Y: longitudinal outcome (continuous - Gaussian)
- $\lambda_i(t)$: Terminal event risk
- $\lambda_0(t)$: Baseline risk
- β_0: fixed intercept
- b_{i0}: random individual intercept
- β_1: fixed slope
- ε_{ij}: residual error
- φ: association parameters

R: Joint modeling

Part 5: Advanced joint models

Parameterizations

$$\begin{cases} Y_{ij} = \beta_{10} + b_{i0} + (\beta_1 + b_{i1}) year_{ij} + \varepsilon_{ij} \\ \lambda_i(t) = \lambda_0(t) \exp\left(b_{i0}\varphi_1 + b_{i1}\varphi_2\right) \end{cases}$$

- Y: longitudinal outcome (continuous - Gaussian)
- $\lambda_i(t)$: Terminal event risk
- $\lambda_0(t)$: Baseline risk
- β_0: fixed intercept
- b_{i0}: random individual intercept
- b_{i1}: random individual slope
- β_1: fixed slope
- ε_{ij}: residual error
- φ: association parameters

Joint Model - Individual deviation association

$$\begin{cases} Y1_{ij} = \eta_{ij}(year_{ij}) + \varepsilon_{ij} = \beta_0 + b_{i0} + (\beta_1 + b_{i1})year_{ij} + \varepsilon_{ij} \\ \lambda_i(t) = \lambda_0(t)\exp\left((b_{i0} + b_{i1}t)\varphi\right) \end{cases}$$

- $Y1$: first longitudinal outcome (continuous - Gaussian)
- $\lambda_i(t)$: Terminal event risk
- $\lambda_0(t)$: Baseline risk
- β_0: fixed intercept
- b_{i0}: random individual intercept
- b_{i1}: random individual slope
- β_1: fixed slope
- ε_{ij}: residual error
- φ: association parameter

Joint Model - Current value association

$$\begin{cases} Y_{ij} = \eta_{ij}(year_{ij}) + \varepsilon_{ij} = \beta_0 + b_{i0} + (\beta_1 + b_{i1})year_{ij} + \varepsilon_{ij} \\ \lambda_i(t) = \lambda_0(t)\exp\left(\eta_{ij}(t)\varphi\right) \end{cases}$$

- Y: longitudinal outcome (continuous - Gaussian)
- $\lambda_i(t)$: Terminal event risk
- $\lambda_0(t)$: Baseline risk
- β_0: fixed intercept
- b_{i0}: random individual intercept
- b_{i1}: random individual slope
- β_1: fixed slope
- ε_{ij}: residual error
- φ: association parameter

Joint Model - Current slope association

$$\begin{cases} Y_{ij} = \eta_{ij}(year_{ij}) + \varepsilon_{ij} = \beta_0 + b_{i0} + (\beta_1 + b_{i1})year_{ij} + \varepsilon_{ij} \\ \lambda_i(t) = \lambda_0(t)\exp\left(\eta_{ij}(t)'\varphi\right) \end{cases}$$

- Y: longitudinal outcome (continuous - Gaussian)
- $\lambda_i(t)$: Terminal event risk
- $\lambda_0(t)$: Baseline risk
- β_0: fixed intercept
- b_{i0}: random individual intercept
- b_{i1}: random individual slope
- β_1: fixed slope
- ε_{ij}: residual error
- φ: association parameter

LONGITUDINAL - SURVIVAL JOINT MODEL

Including some functions of time.

$$\begin{cases} log(serBilir_{ij}) = \eta_i(t_{ij}) + \varepsilon_{ij} & \text{(L1)} \\ \qquad\qquad = \beta_0 + b_{i0} + (\beta_1 + b_{i1})NS1(year_{ij}) \\ \qquad\qquad\quad + (\beta_2 + b_{i2})NS2(year_{ij}) + \beta_3 drug_i \\ \qquad\qquad\quad + \beta_4 NS1(year_{ij})drug_i + \beta_5 NS2(year_{ij})drug_i + \varepsilon_{ij} \\ \\ \lambda_{i1}(t) \quad = \lambda_{01}(t)\exp\left(\gamma_1 drug_i + \varphi_1 \eta_i(t)\right) & \text{(S1)} \end{cases}$$

Joint model for longitudinal and competing risks

$$
\begin{cases}
\log(serBilir_{ij}) = \eta_i(t_{ij}) + \varepsilon_{ij} & \text{(L1)} \\
\qquad = \beta_0 + b_{i0} + (\beta_1 + b_{i1}) year_{ij} + \beta_2 drug_i + \beta_3 sex_i \\
\qquad\quad + \beta_4 year_{ij} drug_i + \beta_5 year_{ij} sex_i + \varepsilon_{ij} \\
\lambda_{i1}^{death}(t) = \lambda_{01}(t) \exp\left(\gamma_{11} sex_i + \gamma_{12} drug_i + \varphi_{11}(b_{i0} + b_{i1} t)\right) & \text{(S1)} \\
\lambda_{i2}^{transpl.}(t) = \lambda_{02}(t) \exp\left(\gamma_{21} edema\_no_i + \gamma_{22} edema\_de_i \right. \\
\qquad\qquad + \gamma_{23} sex_i + \gamma_{24} edema\_no_i sex_i \\
\qquad\qquad \left. + \gamma_{25} edema\_de_i sex_i + \varphi_{21} b_{i0} + \varphi_{22} b_{i1}\right) & \text{(S2)}
\end{cases}
$$

Joint model for longitudinal and multi-state

$$
\begin{cases}
Y_{ij} = \eta_i(t_{ij}) + \varepsilon_{ij} = \beta_0 + b_{i0} + (\beta_1 + b_{i1}) time_{ij} + \beta_{12} X_i + \varepsilon_{ij} & \text{(L1)} \\
\lambda_{i,12}(t) = \lambda_{0,12}(t) \exp\left(\gamma_{12} X_i + \varphi_{12} \eta_i(t)\right) & \text{(S1)} \\
\lambda_{i,13}(t) = \lambda_{0,13}(t) \exp\left(\gamma_{13} X_i + \varphi_{13} \eta_i(t)\right) & \text{(S2)} \\
\lambda_{i,23}(t) = \lambda_{0,23}(t) \exp\left(\gamma_{23} X_i + \varphi_{23} \eta_i(t)\right) & \text{(S3)}
\end{cases}
$$

Joint model for 3 longitudinal and competing risks

$$
\begin{cases}
\log(serBilir_{ij}) &= \eta_{i1}(t_{ij}) + \varepsilon_{ij1} = \beta_{10} + b_{i10} + (\beta_{11} + b_{i11})year_{ij} \\
&\quad + \beta_{12} drug_i + \beta_{13} sex_i + \beta_{14} year_{ij} drug_i + \varepsilon_{ij1} \qquad \text{(L1)} \\
\log(E[platelets_{ij}]) &= \eta_{i2}(t_{ij}) = \beta_{20} + b_{i20} + (\beta_{21} + b_{i21})year_{ij} \\
&\quad + \beta_{22} sex_i + \beta_{23} drug_i + \beta_{24} year_{ij} sex_i \qquad \text{(L2)} \\
\text{logit}(E[spiders_{ij}]) &= \eta_{i3}(t_{ij}) = \beta_{30} + b_{i30} + (\beta_{31} + b_{i31})year_{ij} \\
&\quad + \beta_{32} drug_i + \beta_{33} year_{ij} drug_i \qquad \text{(L3)} \\
\lambda_{i1}(t) &= \lambda_{01}(t) \exp\left(\gamma_{11} drug_i + \varphi_{11}\eta_{i1}(t) + \varphi_{12}(b_{i20} + b_{i21}t)\right. \\
&\quad \left. + \varphi_{13}\eta_{i3}(t) + \varphi_{14}\eta'_{i3}(t)\right) \qquad \text{(S1)} \\
\lambda_{i2}(t) &= \lambda_{02}(t) \exp\left(\gamma_{21} drug_i + \varphi_{21}\eta_{i1}(t) + \varphi_{22}\eta'_{i3}(t)\right) \qquad \text{(S2)}
\end{cases}
$$

Bivariate joint model

Primary biliary cholangitis trial data

This dataset containts longitudinal information of 312 randomised patients with primary biliary cirrhosis disease, followed at the Mayo Clinic between 1974 and 1988.

id	drug	year	log_serBilir	platelets
1	D-penicil	0.00	1.87	190
1	D-penicil	0.53	2.21	183
2	D-penicil	0.00	-0.46	221
2	D-penicil	0.50	-0.74	188
2	D-penicil	1.00	-0.54	161
2	D-penicil	2.10	0.03	122

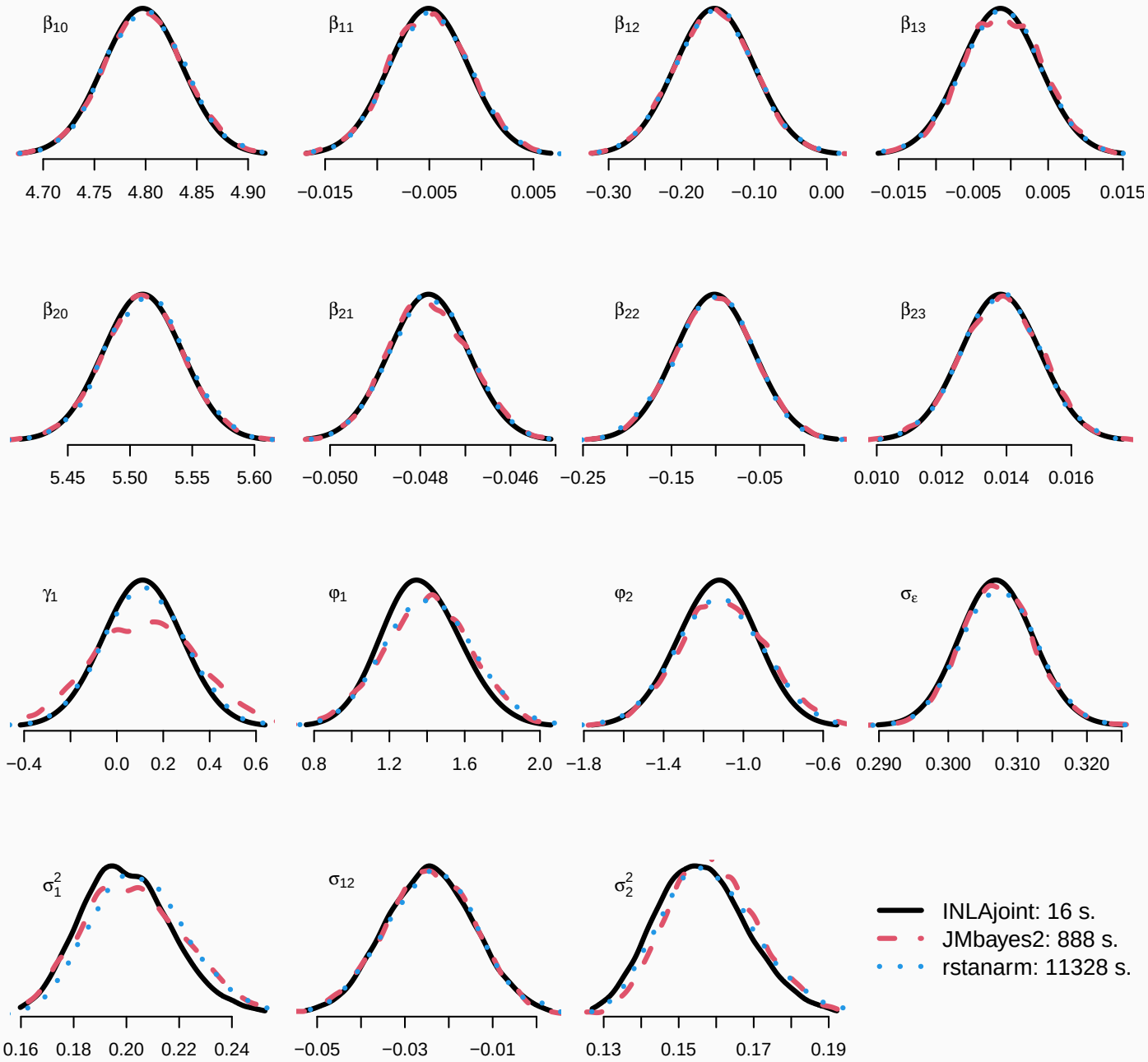
id	years	event	drug
1	1.10	1	D-penicil
2	14.15	0	D-penicil
3	2.77	1	D-penicil
4	5.27	1	D-penicil
5	4.12	1	placebo
6	6.85	1	placebo

Bivariate joint model

$$
\begin{cases}
\log(Y_{i1}(t)) &= \eta_{i1}(t) + \varepsilon_{i1}(t) \qquad \textit{(Serum bilirubin - lognormal)} \\
&= \beta_{10} + b_{i1} + \beta_{11} t + \beta_{12} drug_i + \beta_{13} t drug_i + \varepsilon_{i1}(t) \\
\\
\log(E[Y_{i2}(t)]) &= \eta_{i2}(t) \qquad \textit{(platelet - Poisson)} \\
&= \beta_{20} + b_{i2} + \beta_{21} t + \beta_{22} drug_i + \beta_{23} t drug_i \\
\\
\lambda_i(t) &= \lambda_0(t) \exp\left(\gamma_1 drug_i + \eta_{i1}(t)\varphi_1 + \eta_{i2}(t)\varphi_2\right) \qquad \textit{(event risk)}
\end{cases}
$$

Objective: comparison with software specialized in joint modeling.

Bivariate joint model



Multivariate joint model

Primary biliary cholangitis trial data

This dataset containts longitudinal information of 312 randomised patients with primary biliary cirrhosis disease, followed at the Mayo Clinic between 1974 and 1988.

id	drug	year	ascites	spiders	log_serBilir	albumin	log_SGOT	platelets	log_prothrombin
1	D-penicil	0.00	1.00	1.00	1.87	-1.57	0.49	190	1.01
1	D-penicil	0.53	1.00	1.00	2.21	-0.89	-5.08	183	0.23
2	D-penicil	0.00	0.00	1.00	-0.46	1.49	0.14	221	-0.28
2	D-penicil	0.50	0.00	1.00	-0.74	0.42	0.51	188	0.06
2	D-penicil	1.00	0.00	1.00	-0.54	0.32	0.57	161	0.55
2	D-penicil	2.10	0.00	1.00	0.03	1.05	0.57	122	-0.28

id	years	death	tsp	drug
1	1.10	1	0	D-penicil
2	14.15	0	0	D-penicil
3	2.77	1	0	D-penicil
4	5.27	1	0	D-penicil
5	4.12	0	1	placebo
6	6.85	1	0	placebo

Multivariate joint model

7 longitudinal outcomes and 2 competing risks of events.

$$
\begin{cases}
\log(Y_{i1}(t)) &= \eta_{i1}(t) + \varepsilon_{i1}(t) \qquad \textit{(serum Bilirubin - lognormal)} \\
&= (\beta_{10} + b_{i10}) + (\beta_{11} + b_{i11})\mathrm{NS}_1(t) + (\beta_{12} + b_{i12})\mathrm{NS}_2(t) + \varepsilon_{i1}(t) \\
\log(E[Y_{i2}(t)]) &= \eta_{i2}(t) \qquad \textit{(platelet - Poisson)} \\
&= (\beta_{20} + b_{i20}) + (\beta_{21} + b_{i21})t + \beta_{22} drug_i + \beta_{23} sex_i + \beta_{24} tdrug_i \\
&\quad + \beta_{25} tsex_i + \beta_{26} drug_i sex_i + \beta_{27} tdrug_i sex_i \\
Y_{i3}(t) &= \eta_{i3}(t) + \varepsilon_{i3}(t) \qquad \textit{(aspartate aminotransferase (SGOT) - lognormal)} \\
&= (\beta_{30} + b_{i30}) + \beta_{31} t + \varepsilon_{i3}(t) \\
Y_{i4}(t) &= \eta_{i4}(t) + \varepsilon_{i4}(t) \qquad \textit{(albumin - Gaussian)} \\
&= (\beta_{40} + b_{i40}) + \beta_{41} t + \varepsilon_{i4}(t) \\
\mathrm{logit}(E[Y_{i5}(t)]) &= \eta_{i5}(t) \qquad \textit{(ascites - Binomial)} \\
&= (\beta_{50} + b_{i50}) + \beta_{51} t \\
\mathrm{logit}(E[Y_{i6}(t)]) &= \eta_{i6}(t) \qquad \textit{(spiders - Binomial)} \\
&= (\beta_{60} + b_{i60}) + \beta_{61} t \\
Y_{i7}(t) &= \eta_{i7}(t) \qquad \textit{(prothrombin - Gaussian)} \\
&= (\beta_{70} + b_{i70}) + \beta_{71} t \\
\lambda_{i1}(t) &= \lambda_{01}(t) \exp\left(\eta_{i1}(t)\varphi_{11} + \eta_{i2}(t)\varphi_{12} + b_{i50}\varphi_{13} + \frac{\partial \eta_{i7}(t)}{\partial t}\varphi_{14}\right) \qquad \textit{(death risk)} \\
\lambda_{i2}(t) &= \lambda_{02}(t) \exp\left(\eta_{i2}(t)\varphi_{21} + \eta_{i3}(t)\varphi_{22} + b_{i40}\varphi_{23} + \eta_{i6}(t)\varphi_{24} + \frac{\partial \eta_{i6}(t)}{\partial t}\varphi_{25}\right) \\
& \qquad \textit{(transplantation risk)}
\end{cases}
$$

Multivariate joint model

7 longitudinal outcomes and 2 competing risks of events.

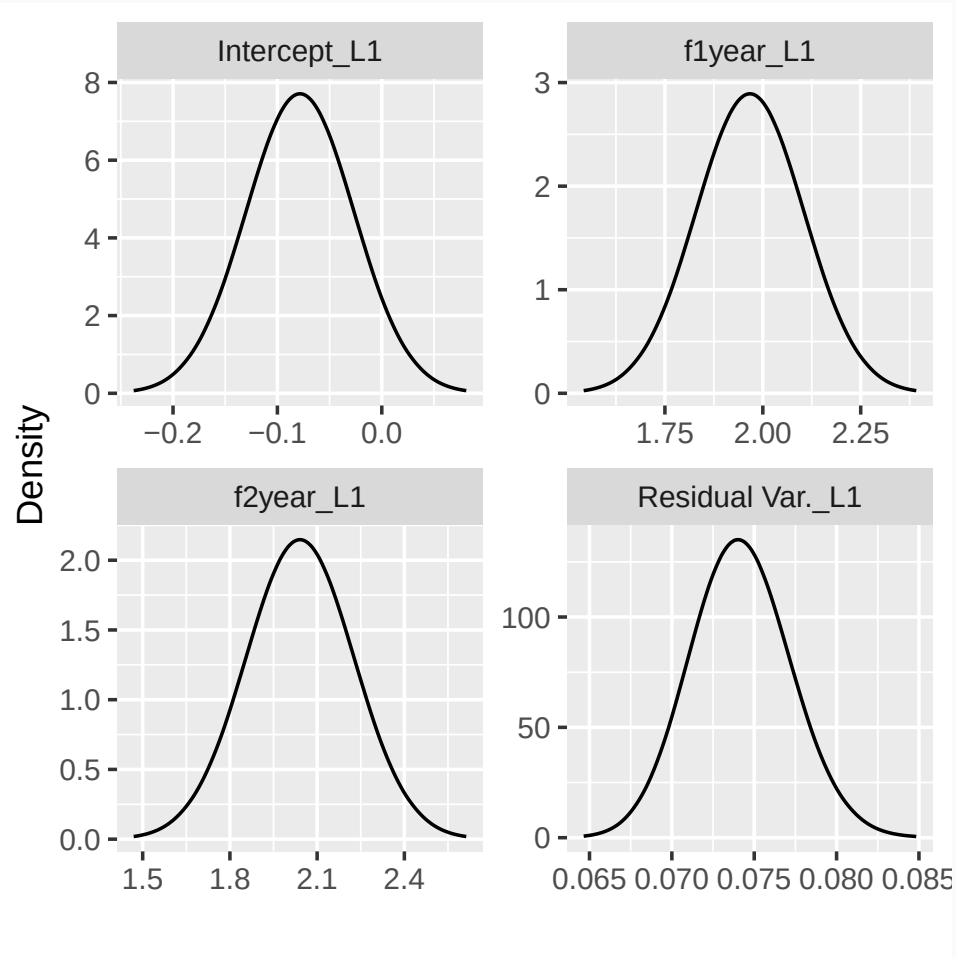
```
MD <- joint(formSurv = list(inla.surv(pbc2.id$years, pbc2.id$death) ~ 1,
                            inla.surv(pbc2.id$years, pbc2.id$tsp) ~ 1),
            formLong = list(serBilir ~  f1(year) + f2(year) +
                                        (1 + f1(year) + f2(year) |id),
                            platelets ~ year * drug * sex + (1 + year|id),
                            SGOT ~ year + (1|id),
                            albumin ~ year + (1|id),
                            ascites ~ year + (1|id),
                            spiders ~ year + (1|id),
                            prothrombin ~ year + (1|id)),
            dataLong = pbc2_2, dataSurv = pbc2.id, id = "id", corLong=FALSE,
            timeVar = "year", basRisk=c("rw2","rw1"),
            family = c("gaussian", "poisson", "gaussian", "gaussian",
                       "binomial", "binomial", "gaussian"),
            assoc = list(c("CV", ""), c("CV", "CV"), c("", "CV"), c("", "SRE"),
                         c("SRE", ""), c("", "CV_CS"), c("CS", "")),
            control=list(int.strategy="eb"))
summary(MD)
```

This would require 1000+ lines of code if fitted with INLA instead of INLAjoint.

Multivariate joint model

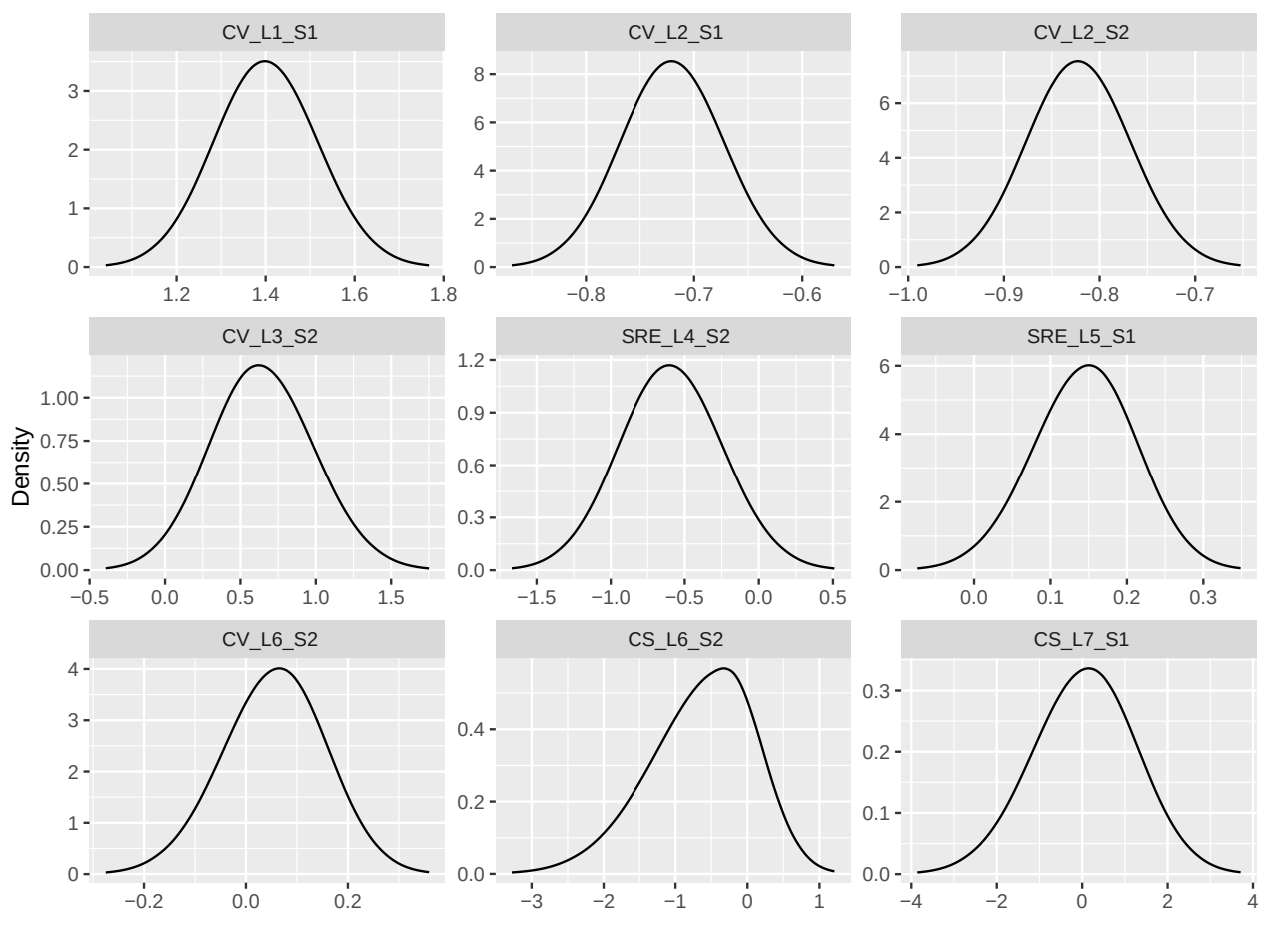
Posteriors marginals of all parameters can be plotted with the *plot()* function.

```
plot(MD)$Outcomes$L1
```



Multivariate joint model

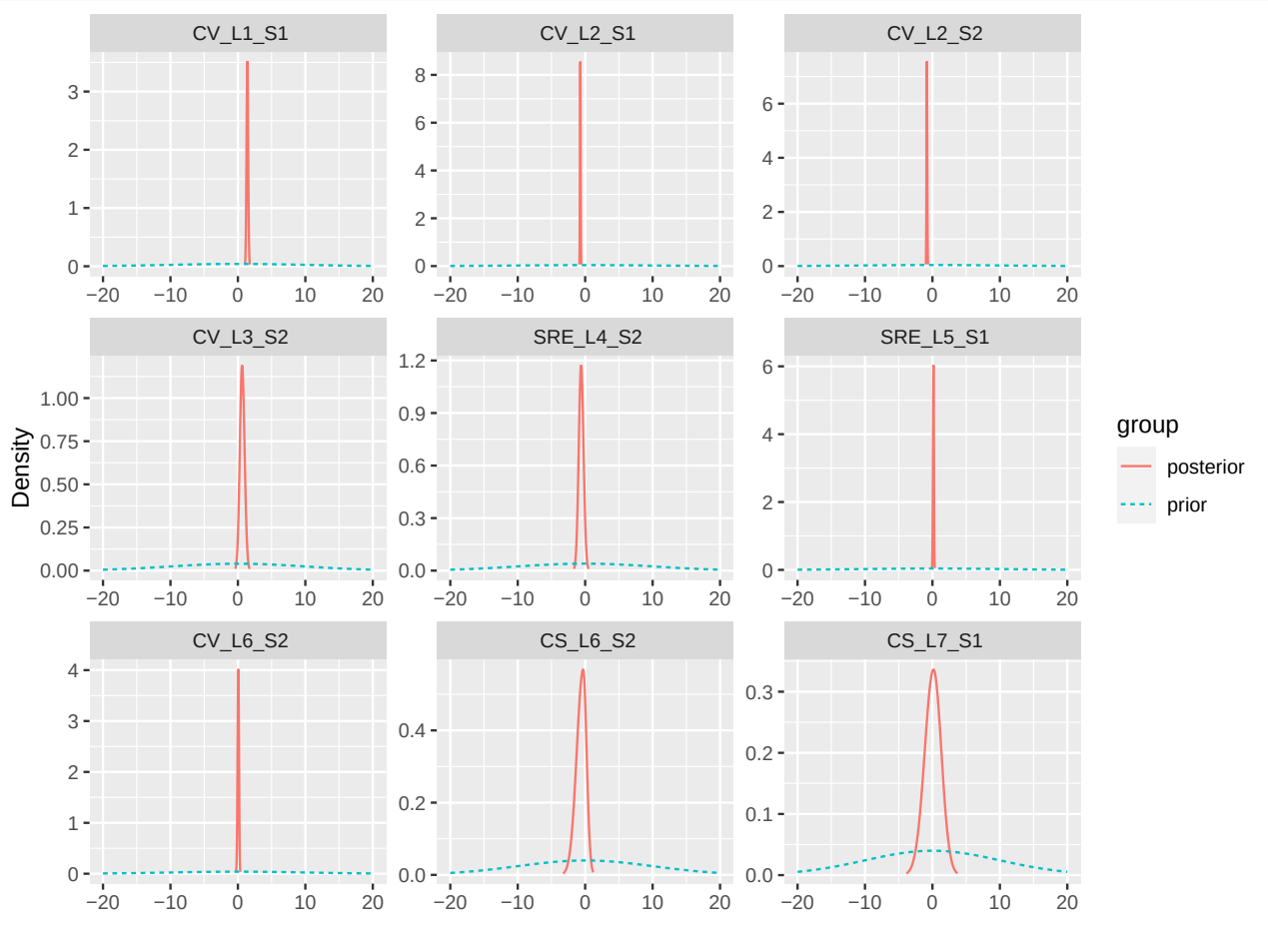
plot(MD)$Associations



Multivariate joint model

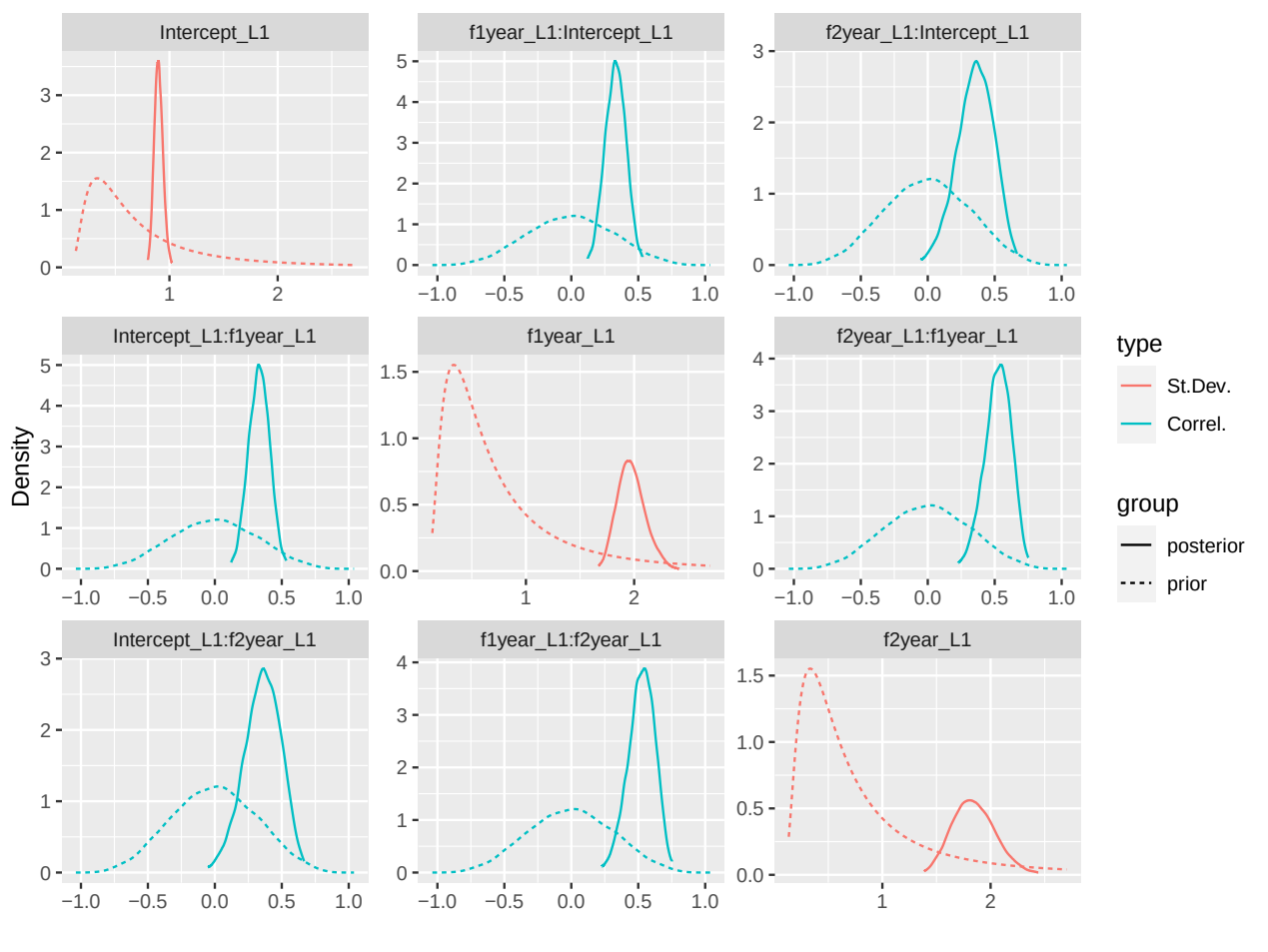
It is possible to add prior distributions on the plot (e.g., to evaluate how data informs about parameters values and for prior sensitivity analysis).

plot(MD, priors=TRUE)$Associations



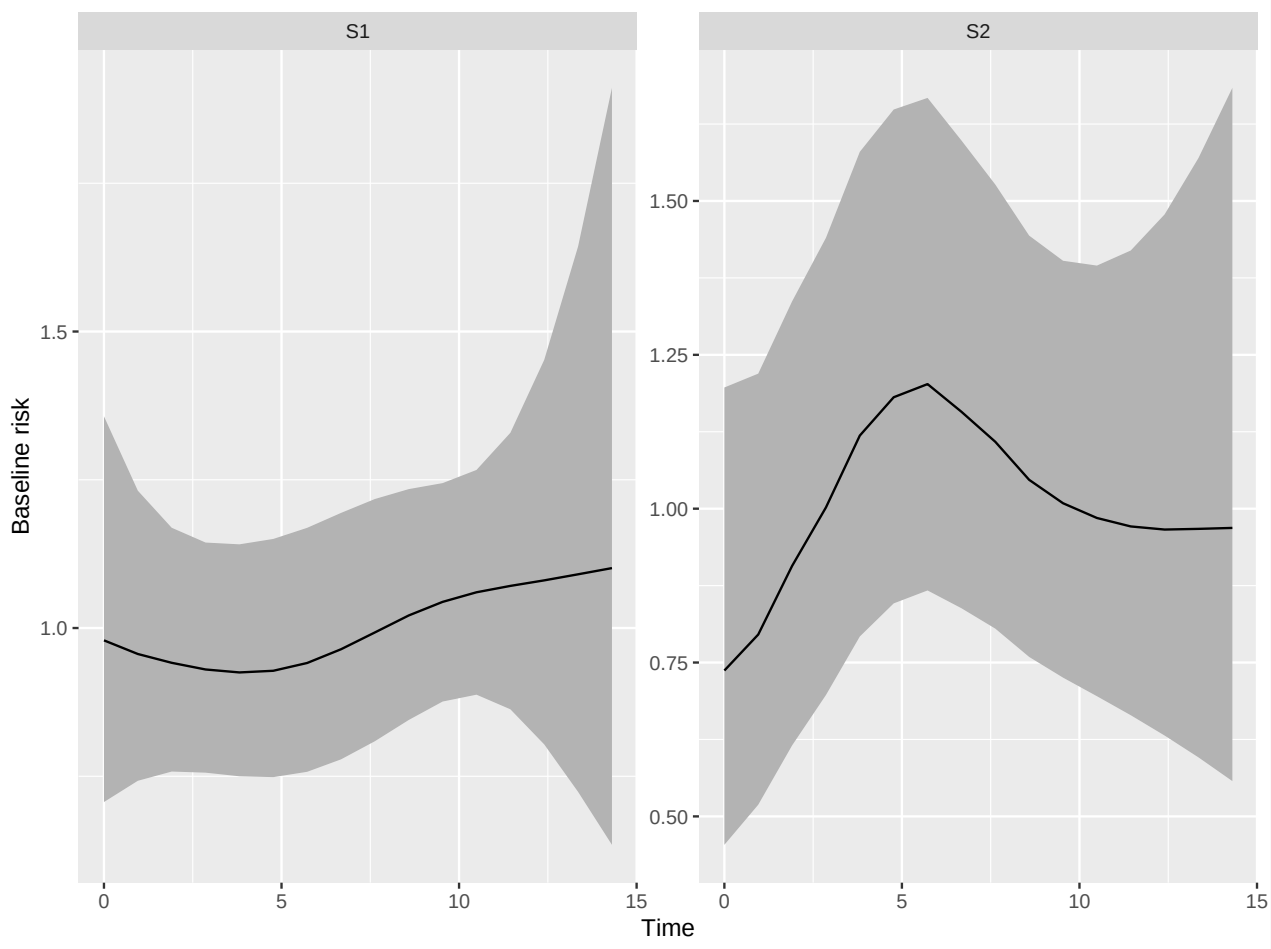
Multivariate joint model

```
plot(MD, sdcor=TRUE, priors=TRUE)$Covariances$L1
```



Multivariate joint model

```
plot(MD)$Baseline
```



Multivariate joint model

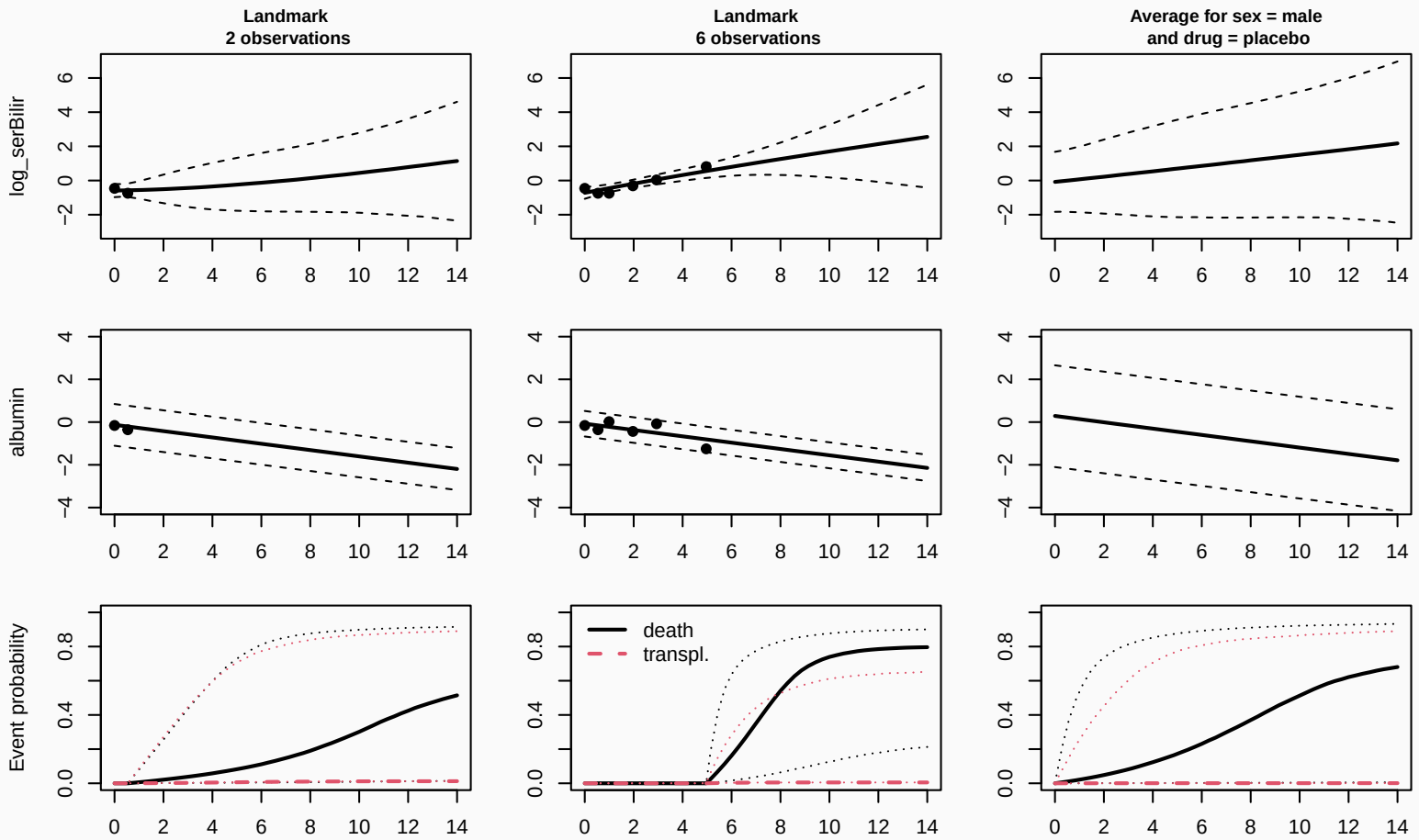
Finally, we can do imputation, prediction and inference with the *predict()* function.
First set up new dataset:

id	drug	sex	year	ascites	spiders	log_serBilir	albumin	log_SGOT	platelets	log_prothrombin
1	0	1	0.0	0	0	-0.46	-0.16	-0.19	142	0.6
1	0	1	0.5	0	0	-0.74	-0.36	0.08	120	0.6
2	0	1	0.0	0	0	-0.46	-0.16	-0.19	142	0.6
2	0	1	0.5	0	0	-0.74	-0.36	0.08	120	0.6
2	0	1	1.0	0	0	-0.74	0.02	-0.36	121	-0.1
2	0	1	2.0	1	0	-0.31	-0.44	-0.51	81	0.6
2	0	1	2.9	0	0	0.03	-0.08	-0.42	64	1.5
2	0	1	5.0	0	0	0.81	-1.25	-0.22	59	2.3
3	0	0	0.0	NA	NA	NA	NA	NA	NA	NA

We ask for prediction for an individual at 2 different landmark times and average prediction for the reference individual.

Multivariate joint model

```
PRED <- predict(m5, NewDat, horizon=14, inv.link=TRUE, CIF=TRUE)
```

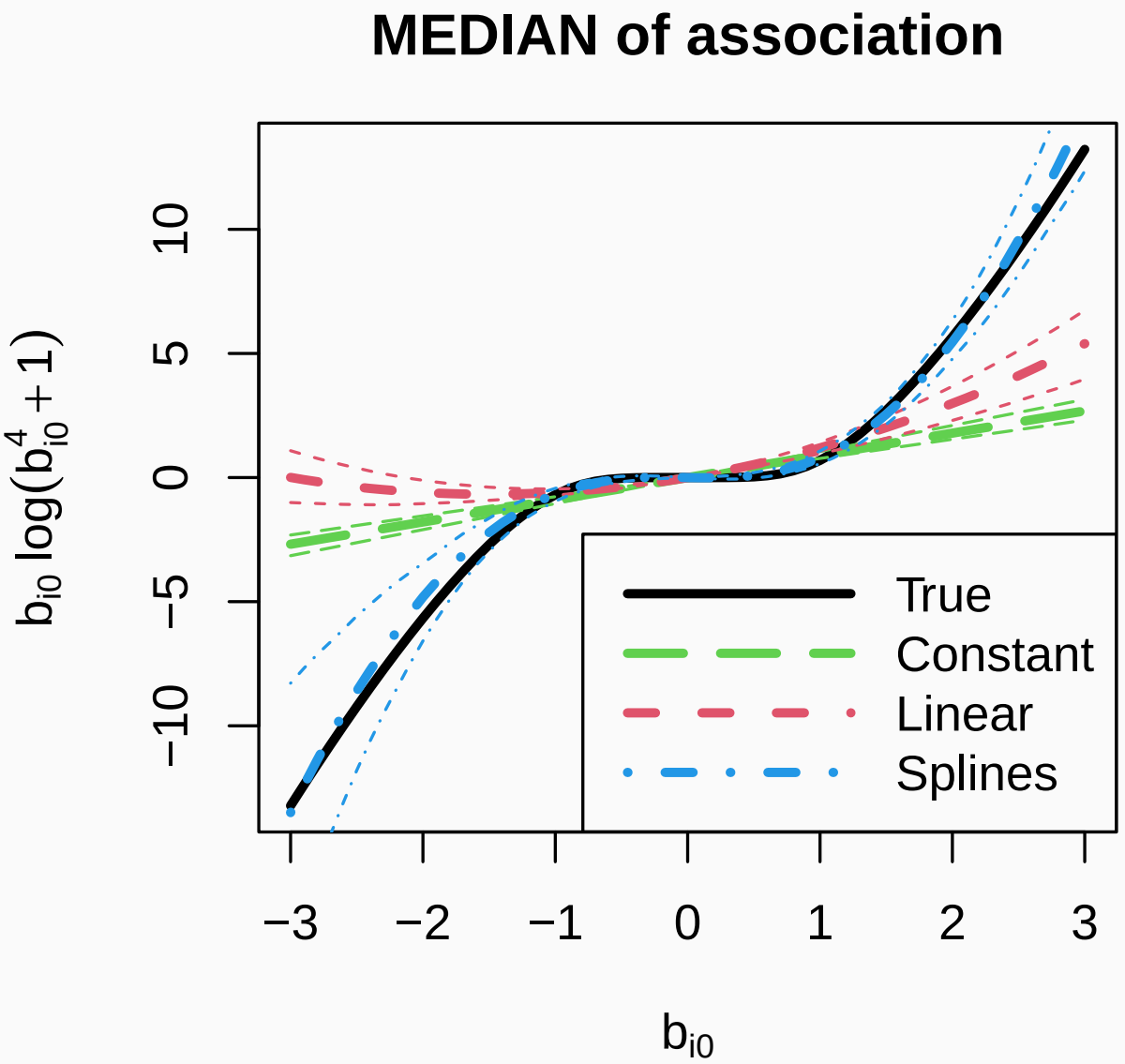


Summary

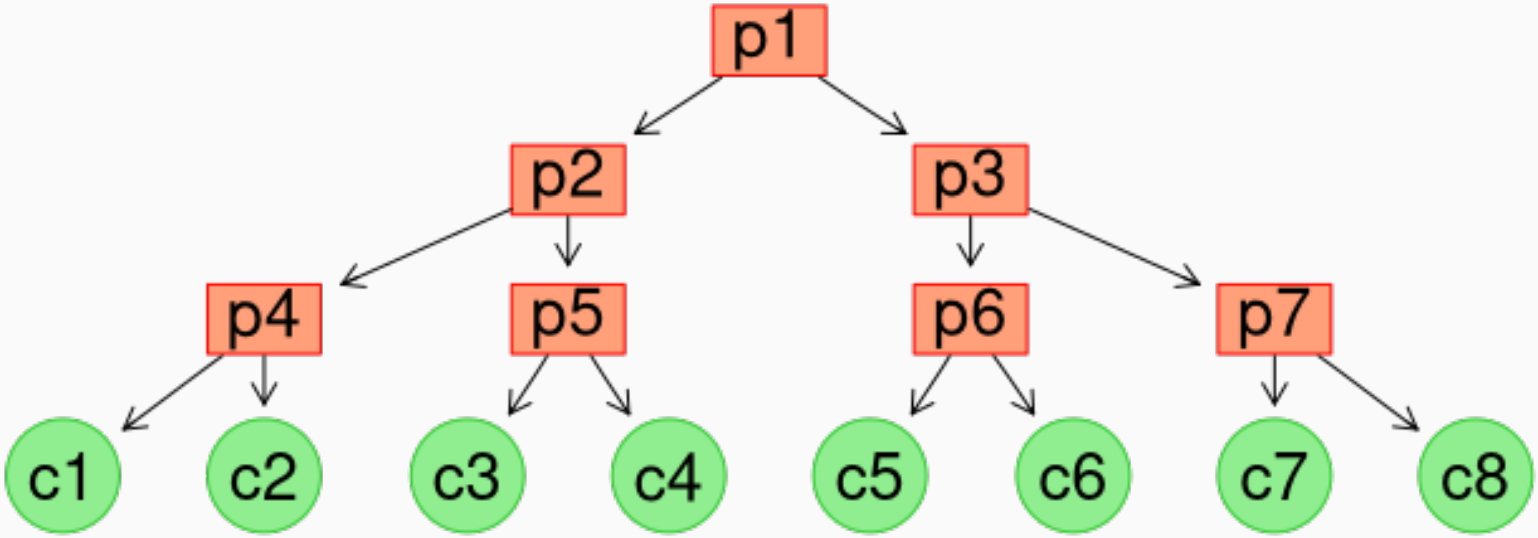
- Most survival models can be formulated as Latent Gaussian Models and thus can be fitted with INLA
- INLA provides an efficient and reliable approach to fit complex survival models.
- Its architecture allows to tailor the model to answer a given question of interest.
- User-friendly interface (INLAjoint) for longitudinal, survival and joint models
- Spatial and spatio-temporal random effects can be included in longitudinal and survival models.
- Dynamic development team, new features and improving efficiency

Ongoing development: Non-linear effects

Simulations non-linear effect



Correlation graphs



References

- Rustand D, van Niekerk J, Rue H, Tournigand C, Rondeau V, Briollais L. *Bayesian estimation of two-part joint models for a longitudinal semicontinuous biomarker and a terminal event with INLA: Interests for cancer clinical trial evaluation.* Biometrical Journal. 2023 Apr;65(4):2100322.
- Rustand, D., van Niekerk, J., Krainski, E. T., Rue, H., Proust-Lima, C. *Fast and flexible inference for joint models of multivariate longitudinal and survival data using integrated nested Laplace approximations*, Biostatistics, 2023 Aug; kxad019, https://doi.org/10.1093/biostatistics/kxad019.
- Danilo Alvares, Janet van Niekerk, Elias T. Krainski, Håvard Rue, and Denis Rustand. *Bayesian survival analysis with INLA.* arXiv preprint arXiv:2212.01900 (2023).
- Denis Rustand, Janet van Niekerk, Elias T. Krainski, and Håvard Rue. *Joint Modeling of Multivariate Longitudinal and Survival Outcomes with the R package INLAjoint.* arXiv preprint arXiv:2402.08335 (2024).