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Joint modeling with integrated nested Laplace approximations

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Outline - joint modeling with INLA

- **Introduction:** Joint modeling
- **Introduction:** Why do we need INLA?
- **Detailed example:** Joint modeling one longitudinal outcome and a terminal event
- **INLAjoint:** a flexible R package to fit joint models with **INLA**

Joint modeling

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).

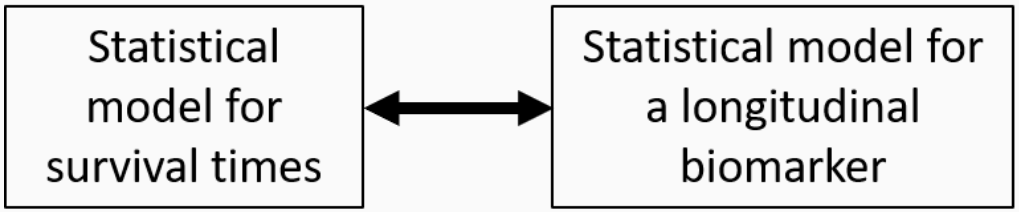
Joint models are popular in health research because it is common to observe **longitudinal markers censored by a terminal event** with interest in the analysis of the longitudinal marker trajectory and the risk of the terminal event as well as their relationship.

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 - underlying idea



A joint model can take advantage of the complementary information flowing between the outcomes.

Joint modeling offers many advantages:

- Addressing measurement error and missing data in the longitudinal process
- Can add flexibility to the proportional hazards in the survival process
- Understanding and quantifying the association between the longitudinal marker and the survival event
- Predicting the risk of event based on the longitudinal markers

Joint modeling

=> Joint modeling **reduce bias** in parameter estimation and **increase efficiency** in statistical inference by **utilizing all the available information** simultaneously.

Moreover, joint modeling allows:

- To investigate the link between the outcomes
- To account for dropout
- To include a time varying covariate in the time-to-event sub-model

An Overview of Joint Modeling of Time-to-Event and Longitudinal Outcomes. Grigorios Papageorgiou, Katya Mauff, Anirudh Tomer, and Dimitris Rizopoulos. Annual Review of Statistics and Its Application 2019

Joint modeling

A standard joint model for a longitudinal biomarker and survival times is defined as follows:

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

There are many ways to define the association between the outcomes. One of the most popular is shared random effects: $h(\cdot) = \boldsymbol{b}_i^\top \boldsymbol{\varphi}$

This model accounts for informative censoring in the longitudinal part and individual heterogeneity in the survival part.

Joseph G. Ibrahim et al. Basic Concepts and Methods for Joint Models of Longitudinal and Survival Data. Journal of Clinical Oncology 2010.

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Why do we need INLA?

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)

Joint modeling with INLA - History

INLA:

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.

Joint modeling with INLA:

Van Niekerk, Janet, Haakon Bakka, and Haavard Rue. *Joint models as latent Gaussian models-not reinventing the wheel.* arXiv preprint arXiv:1901.09365 (2019)

Comparison with Levenberg-Marquardt 1/2

$$\begin{cases} \text{Logit}[\text{Prob}(Y_{ij} > 0)] = \alpha_0 + a_i + \alpha_1 \cdot time_j + \alpha_2 \cdot trt_i + \alpha_3 \cdot time_j \cdot trt_i, \\ \mathbf{E}[\log(Y_{ij})|Y_{ij} > 0] = \beta_0 + b_{0i} + (\beta_1 + b_{1i}) \cdot time_j + \beta_2 \cdot trt_i + \beta_3 \cdot time_j \cdot trt_i + \varepsilon_{ij}, \\ \lambda_i(t|Y_{ij}) = \lambda_0(t) \exp\left(\gamma \cdot trt_i + \varphi_a \cdot a_i + \varphi_{b_0} \cdot b_{0i} + \varphi_{b_1} \cdot b_{1i}\right), \end{cases}$$

$$\begin{bmatrix} a_i \\ b_{0i} \\ b_{1i} \end{bmatrix} \sim MVN\left(\begin{bmatrix} 0 \\ 0 \end{bmatrix}, \begin{bmatrix} \boldsymbol{\Sigma}_{aa} & \boldsymbol{\Sigma}_{ab} \\ \boldsymbol{\Sigma}_{ab} & \boldsymbol{\Sigma}_{bb} \end{bmatrix}\right) \equiv MVN\left(\begin{bmatrix} 0 \\ 0 \\ 0 \end{bmatrix}, \begin{bmatrix} \sigma_a^2 & \sigma_{ab_0} & \sigma_{ab_1} \\ \sigma_{ab_0} & \sigma_{b_0}^2 & \sigma_{b_0 b_1} \\ \sigma_{ab_1} & \sigma_{b_0 b_1} & \sigma_{b_1}^2 \end{bmatrix}\right).$$

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 R-INLA: Interests for Cancer Clinical Trial Evaluation.* arXiv preprint arXiv:2010.13704 (2020)

Comparison with Levenberg-Marquardt 2/2

Approach		R-INLA Est.* (SD†) [CP‡]	frailtypack Est. (SD) [CP]
Binary part (SLD>0 versus SLD=0)			
intercept	$\alpha_0 = 4$	3.95 (0.22) [92%]	3.94 (0.25) [91%]
time (year)	$\alpha_1 = -0.5$	-0.51 (0.07) [95%]	-0.51 (0.07) [95%]
treatment (B/A)	$\alpha_2 = -0.5$	-0.50 (0.29) [95%]	-0.51 (0.31) [93%]
time:treatment (B/A)	$\alpha_3 = 0.5$	0.50 (0.11) [95%]	0.50 (0.11) [95%]
Continuous part ($\mathbb{E}[\log(Y_{ij})\|Y_{ij} > 0]$)			
intercept	$\beta_0 = 2$	2.00 (0.03) [95%]	1.99 (0.04) [86%]
time (years)	$\beta_1 = -0.3$	-0.30 (0.04) [94%]	-0.30 (0.08) [48%]
treatment (B/A)	$\beta_2 = -0.3$	-0.30 (0.05) [95%]	-0.30 (0.06) [88%]
time:treatment (B/A)	$\beta_3 = 0.3$	0.30 (0.05) [95%]	0.29 (0.09) [48%]
residual S.E.	$\sigma_\varepsilon = 0.3$	0.30 (0.00) [95%]	0.30 (0.00) [95%]
Death risk			
treatment (B/A)	$\gamma = 0.2$	0.19 (0.18) [95%]	0.19 (0.27) [84%]
Association			
intercept (binary part)	$\varphi_a = 1$	0.94 (0.11) [98%]	0.98 (1.05) [91%]
intercept (continuous part)	$\varphi_{b_0} = 1$	1.10 (0.13) [96%]	1.04 (1.00) [88%]
slope (continuous part)	$\varphi_{b_1} = 1$	1.07 (0.13) [98%]	1.10 (1.05) [87%]
Computation time			
80 CPUs (Intel Xeon E5-4627 v4 2.60 GHz)		49 sec. (5)	347 sec. (90)
Convergence rate		100%	96%

* Posterior mean, † Standard deviation of the posterior mean, ‡ Coverage probability

Comparison with MCMC

$$
\begin{cases}
Poi(Y_{i1}(t)) = (\beta_{10} + b_{i10}) + (\beta_{11} + b_{i11})t + \beta_{12}X_i^c + \beta_{13}X_i^b \\
Poi(Y_{i2}(t)) = (\beta_{20} + b_{i20}) + (\beta_{21} + b_{i21})t + \beta_{22}X_i^c + \beta_{23}X_i^b \\
Poi(Y_{i3}(t)) = (\beta_{30} + b_{i30}) + (\beta_{31} + b_{i31})t + \beta_{32}X_i^c + \beta_{33}X_i^b \\
\lambda_i(t) = \lambda_0(t)\exp\left(Poi(Y_{i1}(t))\varphi_1 + Poi(Y_{i2}(t))\varphi_2 + Poi(Y_{i3}(t))\varphi_3\right)
\end{cases}
$$

Approach:	R-INLA			rstanarm 1 (1 chain / 1000 iter.)			rstanarm 2 (4 chains / 2000 iter.)		
True value	Bias	(SD)	CP	Bias	(SD)	CP	Bias	(SD)	CP
β_{10}=4	-0.002	(0.043)	96%	-0.021	(0.469)	69%	0.017	(0.212)	93%
β_{11}=-0.1	-0.001	(0.017)	95%	-0.027	(0.131)	74%	-0.032	(0.279)	95%
β_{12}=0.1	-0.001	(0.035)	94%	0.013	(0.147)	72%	-0.009	(0.106)	93%
β_{13}=-0.2	0.004	(0.032)	96%	-0.013	(0.154)	77%	0.004	(0.067)	94%
β_{20}=2	-0.006	(0.063)	96%	0.013	(0.229)	82%	-0.018	(0.444)	96%
β_{21}=-0.1	0	(0.027)	95%	-0.027	(0.268)	81%	-0.008	(0.134)	96%
β_{22}=0.1	0.005	(0.051)	95%	-0.003	(0.112)	86%	0.013	(0.243)	97%
β_{23}=-0.2	0.001	(0.05)	95%	0.012	(0.116)	85%	0.002	(0.052)	95%
β_{30}=2	-0.001	(0.058)	95%	-0.063	(0.54)	85%	0.002	(0.067)	94%
β_{31}=-0.1	0	(0.025)	93%	-0.061	(0.49)	85%	-0.003	(0.035)	94%
β_{32}=0.1	0.003	(0.045)	95%	0.016	(0.102)	87%	0	(0.055)	96%
β_{33}=-0.2	-0.001	(0.048)	94%	0.052	(0.384)	85%	0	(0.049)	95%
Conv. rate	1			0.61			0.41		
Comp. time (sec.)	122.42 (148.46)			3327.91 (977.34)			8494.53 (2925.53)		

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

Rustand, D., van Niekerk, J., Krainski, E. T., Rue, H., Proust-Lima, C. *Fast and flexible inference approach for joint models of multivariate longitudinal and survival data using Integrated Nested Laplace Approximations.* arXiv preprint arXiv:2203.06256 (2022)

Comparison with MCMC

Approach:		R-INLA			rstanarm 1 (1 chain / 1000 iter.)			rstanarm 2 (4 chains / 2000 iter.)	
True value	Bias	(SD)	CP	Bias	(SD)	CP	Bias	(SD)	CP
σ^2_{b10}=0.16	0.007	(0.043)	96%	-0.035	(0.062)	70%	0.021	(0.279)	95%
σ^2_{b11}=0.09	0.004	(0.01)	93%	0.088	(0.187)	70%	0.057	(0.325)	92%
σ^2_{b20}=0.25	0.002	(0.021)	94%	0.053	(0.641)	79%	0.012	(0.123)	96%
σ^2_{b21}=0.16	0.004	(0.016)	97%	0.026	(0.143)	81%	0.036	(0.281)	95%
σ^2_{b30}=0.25	0.007	(0.02)	94%	0.016	(0.168)	84%	0.005	(0.025)	97%
σ^2_{b31}=0.16	0.007	(0.016)	94%	0.013	(0.084)	85%	0.002	(0.019)	97%
$\mathrm{cov}_{b10,b11}$=0.06	0	(0.015)	95%	-0.016	(0.033)	68%	-0.005	(0.028)	93%
$\mathrm{cov}_{b10,b20}$=0.02	0.001	(0.012)	94%	-0.005	(0.022)	70%	-0.001	(0.012)	94%
$\mathrm{cov}_{b10,b21}$=0.04	-0.002	(0.011)	96%	-0.01	(0.022)	74%	-0.016	(0.135)	96%
$\mathrm{cov}_{b10,b30}$=0	-0.003	(0.013)	97%	-0.002	(0.014)	75%	-0.001	(0.012)	96%
$\mathrm{cov}_{b10,b31}$=-0.04	0.004	(0.011)	96%	0.01	(0.019)	77%	0.003	(0.011)	98%
$\mathrm{cov}_{b11,b20}$=0.03	-0.001	(0.01)	93%	0.004	(0.05)	75%	-0.002	(0.019)	89%
$\mathrm{cov}_{b11,b21}$=0	-0.001	(0.008)	95%	0.005	(0.033)	81%	-0.01	(0.1)	96%
$\mathrm{cov}_{b11,b30}$=-0.06	0.004	(0.01)	94%	0.006	(0.03)	84%	0	(0.016)	95%
$\mathrm{cov}_{b11,b31}$=0	-0.003	(0.008)	97%	0	(0.037)	86%	-0.001	(0.01)	99%
$\mathrm{cov}_{b20,b21}$=0.08	-0.001	(0.014)	94%	-0.001	(0.03)	82%	0.001	(0.016)	95%
$\mathrm{cov}_{b20,b30}$=0.05	0.001	(0.015)	96%	-0.007	(0.024)	83%	0	(0.017)	97%
$\mathrm{cov}_{b20,b31}$=0.04	-0.003	(0.014)	93%	-0.007	(0.023)	78%	-0.001	(0.014)	93%
$\mathrm{cov}_{b21,b30}$=0.04	-0.001	(0.014)	93%	0.003	(0.024)	79%	0.01	(0.017)	88%
$\mathrm{cov}_{b21,b31}$=-0.04	0.003	(0.012)	95%	0.005	(0.021)	81%	0.002	(0.013)	97%
$\mathrm{cov}_{b30,b31}$=0.12	-0.008	(0.015)	91%	-0.007	(0.043)	86%	-0.001	(0.017)	94%
φ_1=0.2	-0.007	(0.09)	92%	-0.078	(0.471)	86%	-0.027	(0.121)	93%
φ_2=-0.2	0.006	(0.074)	92%	0.057	(0.415)	90%	-0.007	(0.08)	96%
φ_3=0.2	0.001	(0.071)	91%	-0.041	(0.425)	90%	0.008	(0.132)	96%
Conv. rate		1			0.61			0.41	
Comp. time (sec.)		122.42 (148.46)			3327.91 (977.34)			8494.53 (2925.53)	

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

Detailed example: Joint modeling one longitudinal outcome and a terminal event

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

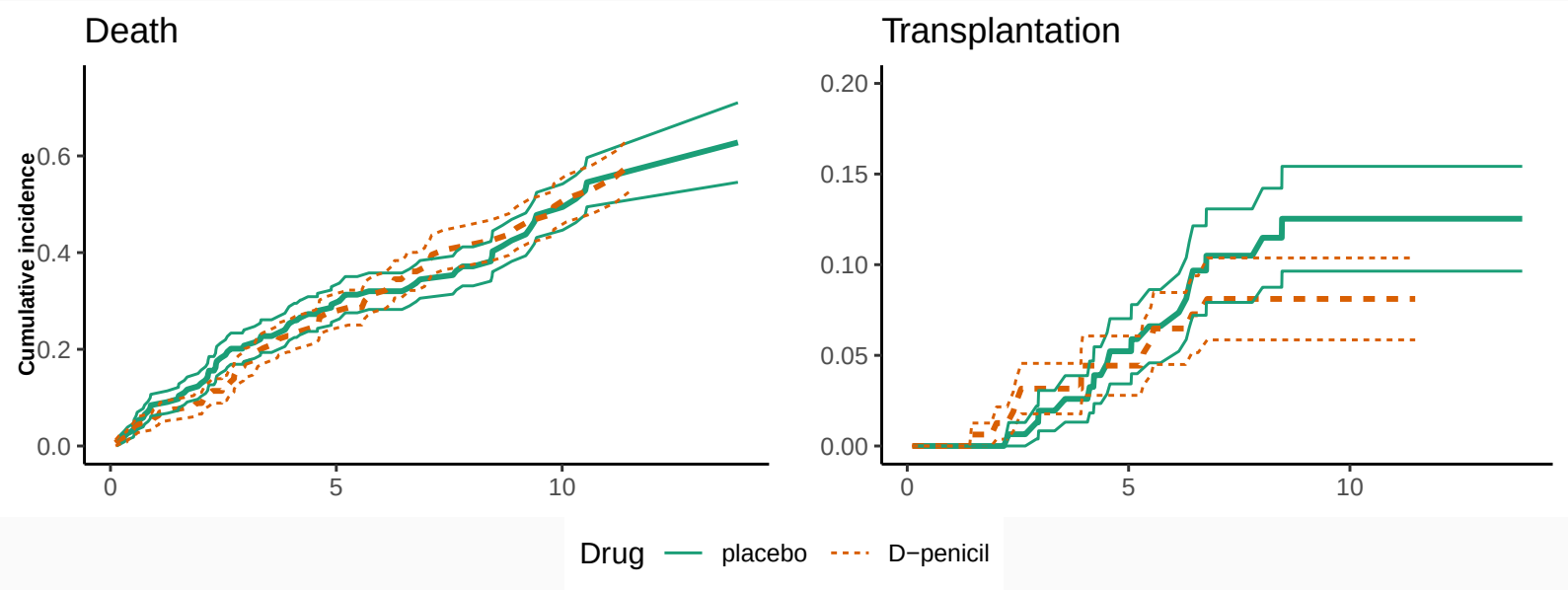
INLAjoint: a flexible R package to fit joint models with INLA

Dataset for illustrations

Primary Biliary Cholangitis (PBC)

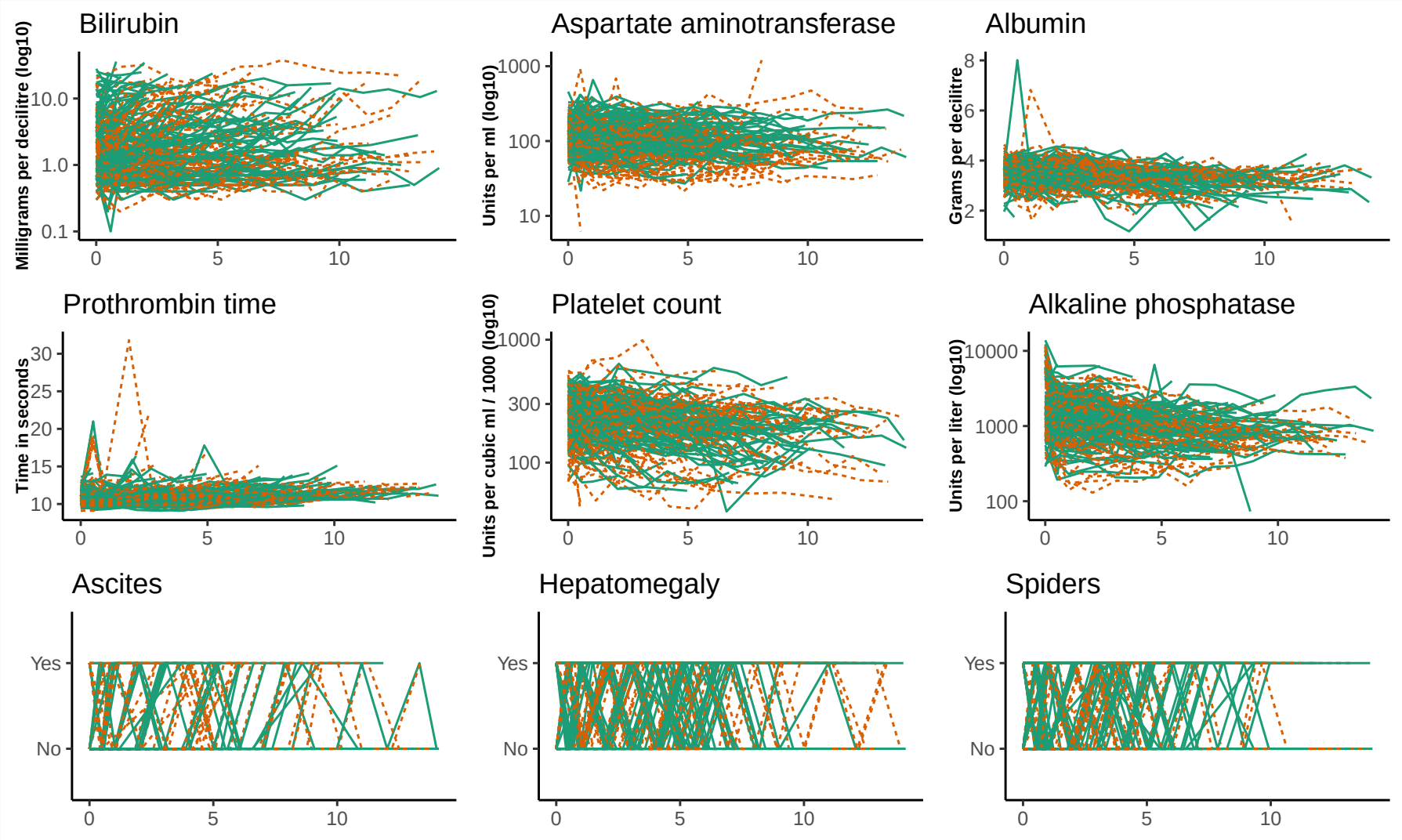
- 312 PBC patients were followed at the Mayo Clinic between 1974 and 1988 and received either a placebo or D-penicillamine.
- These data are publicly available in several software including the R package ‘JM‘.
- During the follow-up, 140 patients died and 29 patients received a liver transplantation which we consider here as a competing event of death.
- In addition, repeated measures of various longitudinal markers potentially associated with the disease progression were collected.

Primary Biliary Cholangitis - Survival outcomes



Competing risks!

Primary Biliary Cholangitis - Longitudinal outcomes



M1: SINGLE LONGITUDINAL MARKER

$$\log(serBilir_{ij}) = \beta_0 + b_{i0} + \beta_1 year_{ij} + \beta_2 drug_i + \varepsilon_{ij} \qquad \text{(L1)}$$

where β are the fixed effects, b_{i0} is an individual random intercept and ε_{ij} is the residual error term.

M2: multiple markers with different distributions

$$
\begin{cases}
\log(serBilir_{ij}) = \beta_{10} + b_{i10} + (\beta_{11} + b_{i11})year_{ij} + \beta_{12}drug_i \\
\qquad\qquad + \beta_{13}sex_i + \beta_{14}year_{ij}drug_i + \varepsilon_{ij1} & \text{(L1)} \\
\log(E[platelets_{ij}]) = \beta_{20} + b_{i20} + (\beta_{21} + b_{i21})year_{ij} + \beta_{22}sex_i \\
\qquad\qquad + \beta_{23}drug_i + \beta_{24}year_{ij}sex_i & \text{(L2)} \\
\text{logit}(E[spiders_{ij}]) = \beta_{30} + b_{i30} + (\beta_{31} + b_{i31})year_{ij} + \beta_{32}drug_i \\
\qquad\qquad + \beta_{33}year_{ij}drug_i & \text{(L3)}
\end{cases}
$$

M3: LONGITUDINAL - SURVIVAL JOINT MODEL

Back to the example!

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

- 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

M4: Comparison with MCMC

$$
\begin{cases}
albumin_{ij} = \eta_i(t_{ij}) + \varepsilon_{ij} & \text{(L1)} \\
\qquad\qquad = \beta_0 + b_{i0} + (\beta_1 + b_{i1}) year_{ij} + \beta_2 drug_i + \beta_3 year_{ij} drug_i + \varepsilon_{ij} & \\
\\
\lambda_i(t) \quad = \lambda_0(t) \exp\left(\gamma_1 sex_i + \gamma_2 drug_i + \varphi \eta_i(t)\right) & \text{(S1)}
\end{cases}
$$

Package	INLAjoint	JMbayes	rstanarm
algorithm	INLA	JAGS MCMC	Stan MCMC
comp. time	8 sec.	109 sec.	596 sec.

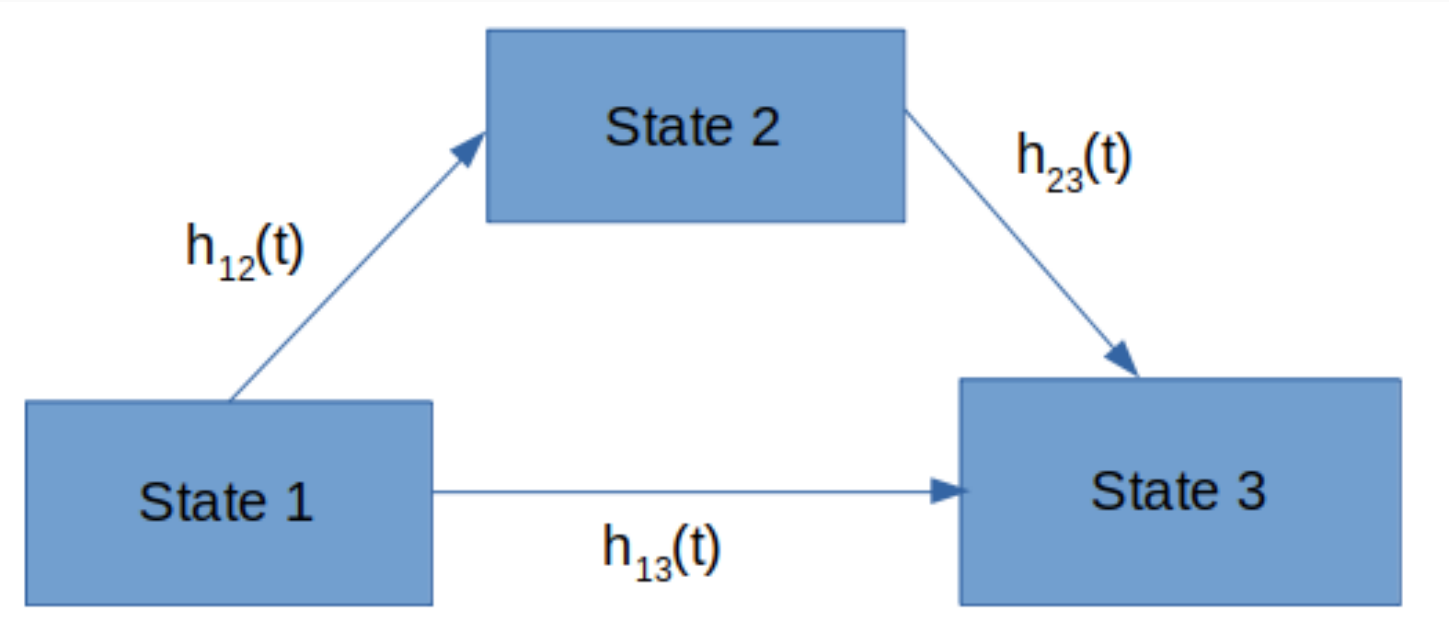
M5: JOINT WITH ONE LONGITUDINAL AND COMPETING RISKS

$$
\begin{cases}
\begin{aligned}
\log(serBilir_{ij}) &= \eta_i(t_{ij}) + \varepsilon_{ij} && \text{(L1)}\\
&= \beta_0 + b_{i0} + (\beta_1 + b_{i1}) year_{ij} + \beta_2 drug_i + \beta_3 sex_i \\
&\quad + \beta_4 year_{ij} drug_i + \beta_5 year_{ij} sex_i + \varepsilon_{ij}
\end{aligned}\\[2ex]
\lambda_{i1}^{death}(t) = \lambda_{01}(t) \exp\left(\gamma_{11} sex_i + \gamma_{12} drug_i + \varphi_{11}(b_{i0} + b_{i1} t)\right) && \text{(S1)}\\[2ex]
\begin{aligned}
\lambda_{i2}^{transpl.}(t) &= \lambda_{02}(t) \exp\left(\gamma_{21} edema\_no_i + \gamma_{22} edema\_de_i \right.\\
&\quad + \gamma_{23} sex_i + \gamma_{24} edema\_no_i sex_i \\
&\quad \left. + \gamma_{25} edema\_de_i sex_i + \varphi_{21} b_{i0} + \varphi_{22} b_{i1}\right)
\end{aligned} && \text{(S2)}
\end{cases}
$$

M6: Three longitudinal markers and competing risks

$$
\begin{cases}
\log(\mathit{serBilir}_{ij}) &= \eta_{i1}(t_{ij}) + \varepsilon_{ij1} = \beta_{10} + b_{i10} + (\beta_{11} + b_{i11})\mathit{year}_{ij} \\
&\quad + \beta_{12}\mathit{drug}_i + \beta_{13}\mathit{sex}_i + \beta_{14}\mathit{year}_{ij}\mathit{drug}_i + \varepsilon_{ij1} \qquad \text{(L1)} \\
\log(E[\mathit{platelets}_{ij}]) &= \eta_{i2}(t_{ij}) = \beta_{20} + b_{i20} + (\beta_{21} + b_{i21})\mathit{year}_{ij} \\
&\quad + \beta_{22}\mathit{sex}_i + \beta_{23}\mathit{drug}_i + \beta_{24}\mathit{year}_{ij}\mathit{sex}_i \qquad \text{(L2)} \\
\operatorname{logit}(E[\mathit{spiders}_{ij}]) &= \eta_{i3}(t_{ij}) = \beta_{30} + b_{i30} + (\beta_{31} + b_{i31})\mathit{year}_{ij} \\
&\quad + \beta_{32}\mathit{drug}_i + \beta_{33}\mathit{year}_{ij}\mathit{drug}_i \qquad \text{(L3)} \\
\lambda_{i1}^{\mathit{death}}(t) &= \lambda_{01}(t)\exp\left(\gamma_{11}\mathit{drug}_i + \varphi_{11}\eta_{i1}(t) + \varphi_{12}(b_{i20} + b_{i21}t)\right. \\
&\quad \left. + \varphi_{13}\eta_{i3}(t) + \varphi_{14}\eta'_{i3}(t)\right) \qquad \text{(S1)} \\
\lambda_{i2}^{\mathit{transpl.}}(t) &= \lambda_{02}(t)\exp\left(\gamma_{21}\mathit{drug}_i + \varphi_{21}\eta_{i1}(t) + \varphi_{22}\eta'_{i3}(t)\right) \qquad \text{(S2)}
\end{cases}
$$

M7: Multi-state model



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

M8: Joint longitudinal and multi-state model

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

M9: Application section of arXiv: 2203.06256

$$
\begin{cases}
\log(Y_{i1}(t)) &= \eta_{i1}(t) + \varepsilon_{i1}(t) \qquad \textit{(bilirubin - lognormal - L1)} \\
&= (\beta_{10} + b_{i10}) + \beta_{11}X_i + (\beta_{12} + b_{i11})\mathrm{NS}_1(t) + (\beta_{13} + b_{i12})\mathrm{NS}_2(t) + \\
&\quad (\beta_{14} + b_{i13})\mathrm{NS}_3(t) + \beta_{15}X_i\mathrm{NS}_1(t) + \beta_{16}X_i\mathrm{NS}_2(t) + \beta_{17}X_i\mathrm{NS}_3(t) + \varepsilon_{i1}(t) \\
\log(Y_{i2}(t)) &= \eta_{i2}(t) + \varepsilon_{i2}(t) \qquad \textit{(aspartate aminotransferase - lognormal - L2)} \\
&= (\beta_{20} + b_{i20}) + \beta_{21}X_i + (\beta_{22} + b_{i21})\mathrm{NS}_1(t) + (\beta_{23} + b_{i22})\mathrm{NS}_2(t) + \\
&\quad (\beta_{24} + b_{i23})\mathrm{NS}_3(t) + \beta_{25}X_i\mathrm{NS}_1(t) + \beta_{26}X_i\mathrm{NS}_2(t) + \beta_{27}X_i\mathrm{NS}_3(t) + \varepsilon_{i2}(t) \\
Y_{i3}(t) &= \eta_{i3}(t) + \varepsilon_{i3}(t) \qquad \textit{(albumin - normal - L3)} \\
&= (\beta_{30} + b_{i30}) + \beta_{31}X_i + (\beta_{32} + b_{i31})t + \beta_{33}X_it + \varepsilon_{i3}(t) \\
\log(E[Y_{i4}(t)]) &= \eta_{i4}(t) \qquad \textit{(platelet - Poisson - L4)} \\
&= (\beta_{40} + b_{i40}) + \beta_{41}X_i + (\beta_{42} + b_{i41})\mathrm{NS}_1(t) + (\beta_{43} + b_{i42})\mathrm{NS}_2(t) + \\
&\quad (\beta_{44} + b_{i43})\mathrm{NS}_3(t) + \beta_{45}X_i\mathrm{NS}_1(t) + \beta_{46}X_i\mathrm{NS}_2(t) + \beta_{47}X_i\mathrm{NS}_3(t) \\
\mathrm{logit}(E[Y_{i5}(t)]) &= \eta_{i5}(t) \qquad \textit{(spiders - binomial - L5)} \\
&= (\beta_{50} + b_{i50}) + \beta_{51}X_i + (\beta_{52} + b_{i51})t + \beta_{53}X_it \\
\lambda_{i1}(t) &= \lambda_{01}(t)\exp\big(\gamma_1X_i + \eta_{i1}(t)\varphi_1 + \eta'_{i1}(t)\varphi_3 + \eta_{i2}(t)\varphi_4 + \\
&\qquad \eta_{i3}(t)\varphi_5 + \eta_{i4}(t)\varphi_7 + \eta_{i5}(t)\varphi_9\big) \qquad \textit{(death risk - S1)} \\
\lambda_{i2}(t) &= \lambda_{02}(t)\exp\big(\gamma_2X_i + \eta_{i1}(t)\varphi_2 + \eta_{i3}(t)\varphi_6 + \eta_{i4}(t)\varphi_8\big) \qquad \textit{(transplantation risk - S2)}
\end{cases}
$$

References

D. Rustand, J. van Niekerk, E. Teixeira Krainski, H. Rue and C. Proust-Lima. *Fast and flexible inference approach for joint models of multivariate longitudinal and survival data using Integrated Nested Laplace Approximations.*
arxiv: 2203.06256.

D. Rustand, J. van Niekerk, H. Rue, C. Tournigand, V. Rondeau, L. Briollais. *Bayesian Estimation of Two-Part Joint Models for a Longitudinal Semicontinuous Biomarker and a Terminal Event with R-INLA: Interests for Cancer Clinical Trial Evaluation.*
arxiv: 2010.13704.

INLAjoint R package for joint modeling multivariate longitudinal and time-to-event outcomes with INLA.
https://github.com/DenisRustand/INLAjoint