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Joint modeling with integrated nested Laplace approximations

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Outline

- **Introduction:** Joint modeling with INLA

- **Part 1:** Fitting joint models with **INLA**
  - **Model 1:** (Generalized) linear mixed effects models for multivariate longitudinal outcomes
  - **Model 2:** Joint modeling one longitudinal outcome and a terminal event
  - **Model 3:** Joint modeling (left-censored) longitudinal, recurrent events and terminal event

- **Part 2: INLAjoint**, a flexible R package to fit joint models with **INLA**

Introduction: 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

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)

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

$$\begin{bmatrix} a_i \\ b_{0i} \\ b_{1i} \end{bmatrix} \sim MVN\left(\begin{bmatrix} \mathbf{0} \\ \mathbf{0} \end{bmatrix}, \begin{bmatrix} \mathbf{\Sigma}_{aa} & \mathbf{\Sigma}_{ab} \\ \mathbf{\Sigma}_{ab} & \mathbf{\Sigma}_{bb} \end{bmatrix}\right) \equiv MVN\left(\begin{bmatrix} 0 \\ 0 \\ 0 \end{bmatrix}, \begin{bmatrix} \sigma_a^2 & \sigma_{ab_0} & \sigma_{ab_1} \\ \sigma_{ab_0} & \sigma_{b_0}^2 & \sigma_{b_0b_1} \\ \sigma_{ab_1} & \sigma_{b_0b_1} & \sigma_{b_1}^2 \end{bmatrix}\right).$$

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

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)

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

Approach:	R-INLA 1 (Empirical Bayes)			R-INLA 2 (Full Bayesian)			rstanarm 1 (1 chain / 1000 iter.)			rstanarm 2 (4 chains / 2000 iter.)			JMbayes2		
True value	Bias	(SD)	CP	Bias	(SD)	CP	Bias	(SD)	CP	Bias	(SD)	CP	Bias	(SD)	CP
β_{10}=4	-0.002	(0.043)	95%	-0.002	(0.043)	96%	-0.021	(0.469)	69%	0.017	(0.212)	93%	-0.001	(0.043)	100%
β_{11}=-0.1	-0.001	(0.017)	95%	-0.001	(0.017)	95%	-0.027	(0.131)	74%	-0.032	(0.279)	95%	0.001	(0.017)	100%
β_{12}=0.1	-0.001	(0.035)	93%	-0.001	(0.035)	94%	0.013	(0.147)	72%	-0.009	(0.106)	93%	-0.001	(0.035)	100%
β_{13}=-0.2	0.004	(0.032)	96%	0.004	(0.032)	96%	-0.013	(0.154)	77%	0.004	(0.067)	94%	0.002	(0.032)	100%
β_{20}=2	-0.006	(0.063)	96%	-0.006	(0.064)	96%	0.013	(0.229)	82%	-0.018	(0.444)	96%	-0.007	(0.064)	100%
β_{21}=-0.1	0	(0.027)	95%	0	(0.027)	95%	-0.027	(0.268)	81%	-0.008	(0.134)	96%	0.003	(0.027)	100%
β_{22}=0.1	0.005	(0.051)	95%	0.005	(0.051)	95%	-0.003	(0.112)	86%	0.013	(0.243)	97%	0.003	(0.052)	100%
β_{23}=-0.2	0.001	(0.05)	95%	0.001	(0.05)	95%	0.012	(0.116)	85%	0.002	(0.052)	95%	0	(0.05)	100%
β_{30}=2	-0.001	(0.058)	95%	0	(0.058)	95%	-0.063	(0.54)	85%	0.002	(0.067)	94%	-0.004	(0.059)	100%
β_{31}=-0.1	0	(0.025)	93%	0.001	(0.025)	93%	-0.061	(0.49)	85%	-0.003	(0.035)	94%	0.007	(0.026)	100%
β_{32}=0.1	0.003	(0.045)	96%	0.003	(0.045)	95%	0.016	(0.102)	87%	0	(0.055)	96%	0.003	(0.045)	100%
β_{33}=-0.2	-0.001	(0.048)	94%	-0.001	(0.048)	94%	0.052	(0.384)	85%	0	(0.049)	95%	0	(0.048)	100%
Conv. rate	1			1			0.61			0.41			0.98		
Comp. time (sec.)	122.42 (148.46)			238.96 (211.98)			3327.91 (977.34)			8494.53 (2925.53)			258.16 (7.19)		

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

Comparison with MCMC

Approach:	R-INLA 1 (Empirical Bayes)			R-INLA 2 (Full Bayesian)			rstanarm 1 (1 chain / 1000 iter.)			rstanarm 2 (4 chains / 2000 iter.)			JMbayes2		
True value	Bias	(SD)	CP	Bias	(SD)	CP	Bias	(SD)	CP	Bias	(SD)	CP	Bias	(SD)	CP
σ^2_{b10}=0.16	0.007	(0.043)	96%	0.003	(0.016)	95%	-0.035	(0.062)	70%	0.021	(0.279)	95%	0.004	(0.011)	94%
σ^2_{b11}=0.09	0.004	(0.01)	93%	0.004	(0.009)	94%	0.088	(0.187)	70%	0.057	(0.325)	92%	0.005	(0.008)	92%
σ^2_{b20}=0.25	0.002	(0.021)	94%	0.001	(0.022)	95%	0.053	(0.641)	79%	0.012	(0.123)	96%	0.014	(0.022)	90%
σ^2_{b21}=0.16	0.004	(0.016)	97%	0.003	(0.016)	96%	0.026	(0.143)	81%	0.036	(0.281)	95%	0.012	(0.017)	92%
σ^2_{b30}=0.25	0.007	(0.02)	94%	0.008	(0.02)	94%	0.016	(0.168)	84%	0.005	(0.025)	97%	0.018	(0.021)	88%
σ^2_{b31}=0.16	0.007	(0.016)	94%	0.007	(0.016)	94%	0.013	(0.084)	85%	0.002	(0.019)	97%	0.01	(0.017)	94%
$\mathrm{cov}_{b10,b11}$=0.06	0	(0.015)	95%	-0.001	(0.009)	96%	-0.016	(0.033)	68%	-0.005	(0.028)	93%	-0.004	(0.007)	91%
$\mathrm{cov}_{b10,b20}$=0.02	0.001	(0.012)	94%	0.001	(0.011)	94%	-0.005	(0.022)	70%	-0.001	(0.012)	94%	0	(0.01)	94%
$\mathrm{cov}_{b10,b21}$=0.04	-0.002	(0.011)	96%	-0.002	(0.011)	96%	-0.01	(0.022)	74%	-0.016	(0.135)	96%	-0.003	(0.01)	96%
$\mathrm{cov}_{b10,b30}$=0	-0.003	(0.013)	97%	-0.002	(0.011)	97%	-0.002	(0.014)	75%	-0.001	(0.012)	96%	-0.001	(0.01)	98%
$\mathrm{cov}_{b10,b31}$=-0.04	0.004	(0.011)	96%	0.004	(0.01)	96%	0.01	(0.019)	77%	0.003	(0.011)	98%	0.003	(0.009)	97%
$\mathrm{cov}_{b11,b20}$=0.03	-0.001	(0.01)	93%	-0.001	(0.01)	94%	0.004	(0.05)	75%	-0.002	(0.019)	89%	-0.001	(0.009)	94%
$\mathrm{cov}_{b11,b21}$=0	-0.001	(0.008)	95%	-0.001	(0.008)	96%	0.005	(0.033)	81%	-0.01	(0.1)	96%	-0.001	(0.008)	96%
$\mathrm{cov}_{b11,b30}$=-0.06	0.004	(0.01)	94%	0.004	(0.01)	95%	0.006	(0.03)	84%	0	(0.016)	95%	0.003	(0.009)	96%
$\mathrm{cov}_{b11,b31}$=0	-0.003	(0.008)	97%	-0.003	(0.008)	96%	0	(0.037)	86%	-0.001	(0.01)	99%	0.001	(0.007)	98%
$\mathrm{cov}_{b20,b21}$=0.08	-0.001	(0.014)	94%	-0.001	(0.014)	95%	-0.001	(0.03)	82%	0.001	(0.016)	95%	-0.01	(0.013)	92%
$\mathrm{cov}_{b20,b30}$=0.05	0.001	(0.015)	96%	0.001	(0.015)	96%	-0.007	(0.024)	83%	0	(0.017)	97%	0	(0.014)	98%
$\mathrm{cov}_{b20,b31}$=0.04	-0.003	(0.014)	93%	-0.004	(0.014)	92%	-0.007	(0.023)	78%	-0.001	(0.014)	93%	-0.004	(0.014)	94%
$\mathrm{cov}_{b21,b30}$=0.04	-0.001	(0.014)	93%	-0.001	(0.014)	95%	0.003	(0.024)	79%	0.01	(0.017)	88%	0.001	(0.014)	97%
$\mathrm{cov}_{b21,b31}$=-0.04	0.003	(0.012)	95%	0.003	(0.012)	95%	0.005	(0.021)	81%	0.002	(0.013)	97%	0.002	(0.011)	97%
$\mathrm{cov}_{b30,b31}$=0.12	-0.008	(0.015)	91%	-0.008	(0.015)	91%	-0.007	(0.043)	86%	-0.001	(0.017)	94%	-0.013	(0.014)	85%
φ_1=0.2	-0.007	(0.09)	92%	-0.005	(0.093)	90%	-0.078	(0.471)	86%	-0.027	(0.121)	93%	0.003	(0.093)	99%
φ_2=-0.2	0.006	(0.074)	92%	0.004	(0.073)	94%	0.057	(0.415)	90%	-0.007	(0.08)	96%	0.006	(0.072)	97%
φ_3=0.2	0.001	(0.071)	91%	0	(0.069)	92%	-0.041	(0.425)	90%	0.008	(0.132)	96%	0.007	(0.07)	96%
Conv. rate	1			1			0.61			0.41			0.98		
Comp. time (sec.)	122.42 (148.46)			238.96 (211.98)			3327.91 (977.34)			8494.53 (2925.53)			258.16 (7.19)		

Part 1: Fitting joint models with INLA

Model 1: Multivariate longitudinal outcomes

$$\begin{cases} Y1_{ij} & = \beta_{10} + b_{i10} + (b_{i11} + \beta_{11}) year_{ij} + \varepsilon_{ij} \\ \mathrm{E}[\log(Y2_{ij})] & = \beta_{20} + b_{i20} + (b_{i21} + \beta_{21}) year_{ij} \end{cases}$$

- $Y1$: 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

Model 2: Joint longitudinal-survival

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

- 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

Model 2 - 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

Model 2 - Current level 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

Model 3: Joint longitudinal-recurrent-survival

$$\begin{cases} Y_{ij} = \beta_0 + b_{i0} + (b_{i1} + \beta_1) year_{ij} + \beta_2 trt_i + \beta_3 trt_i year_{ij} + \varepsilon_{ij} \\ r_{ij}(t) = r_0(t) \exp\left(\nu_i + \gamma_1^r trt_i + b_{i0}\varphi_1^r + b_{i1}\varphi_2^r\right) \\ \lambda_i(t) = \lambda_0(t) \exp\left(\alpha\nu_i + \gamma_1^d trt_i + b_{i0}\varphi_1^d + b_{i1}\varphi_2^d\right) \end{cases}$$

- Y: longitudinal outcome (continuous - Gaussian, left censored!)
- $\lambda_i(t)$: Terminal event risk
- $r_{ij}(t)$: Recurrent event risk
- $r_0(t), \lambda_0(t)$: Baseline risks
- β, γ: fixed effects
- b_i, ν_i: random effects
- β_1: fixed slope
- ε_{ij}: residual error
- φ, α: association parameters

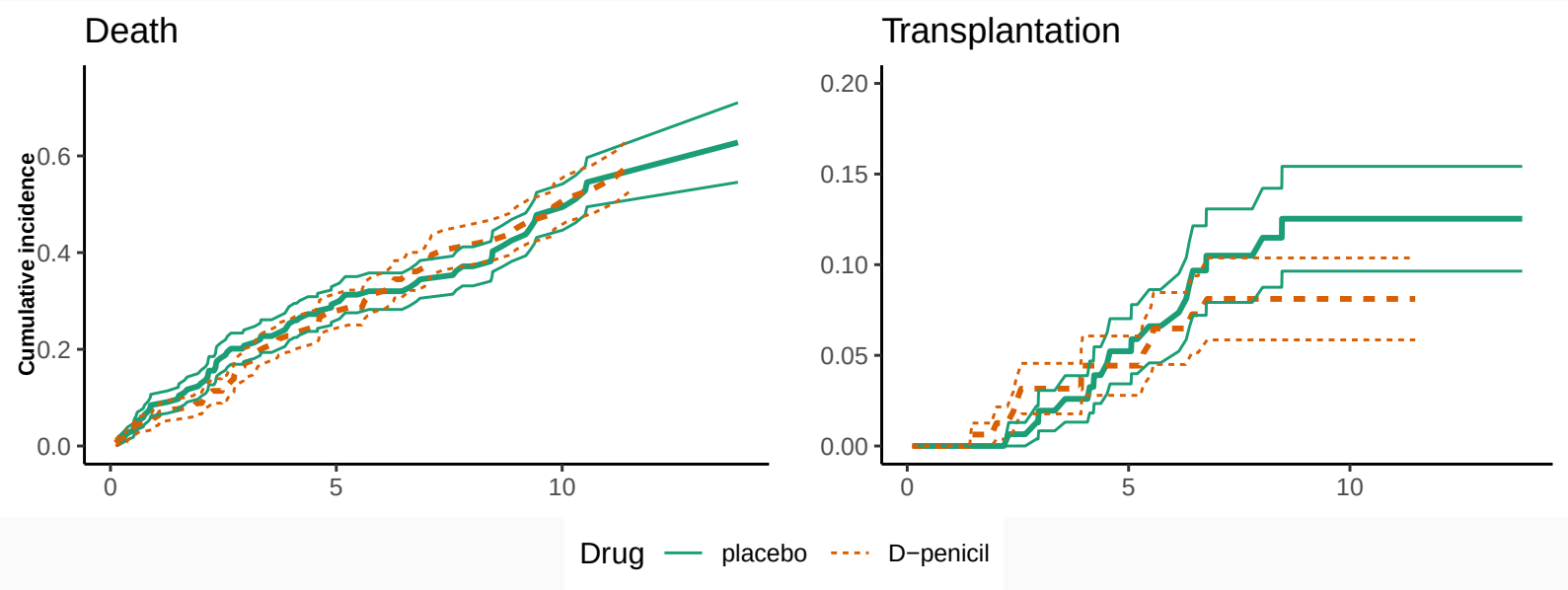
Part 2: INLAjoint, a flexible R package to fit joint models with INLA

Dataset for illustrations

Primary Biliary Cholangitis (PBC)

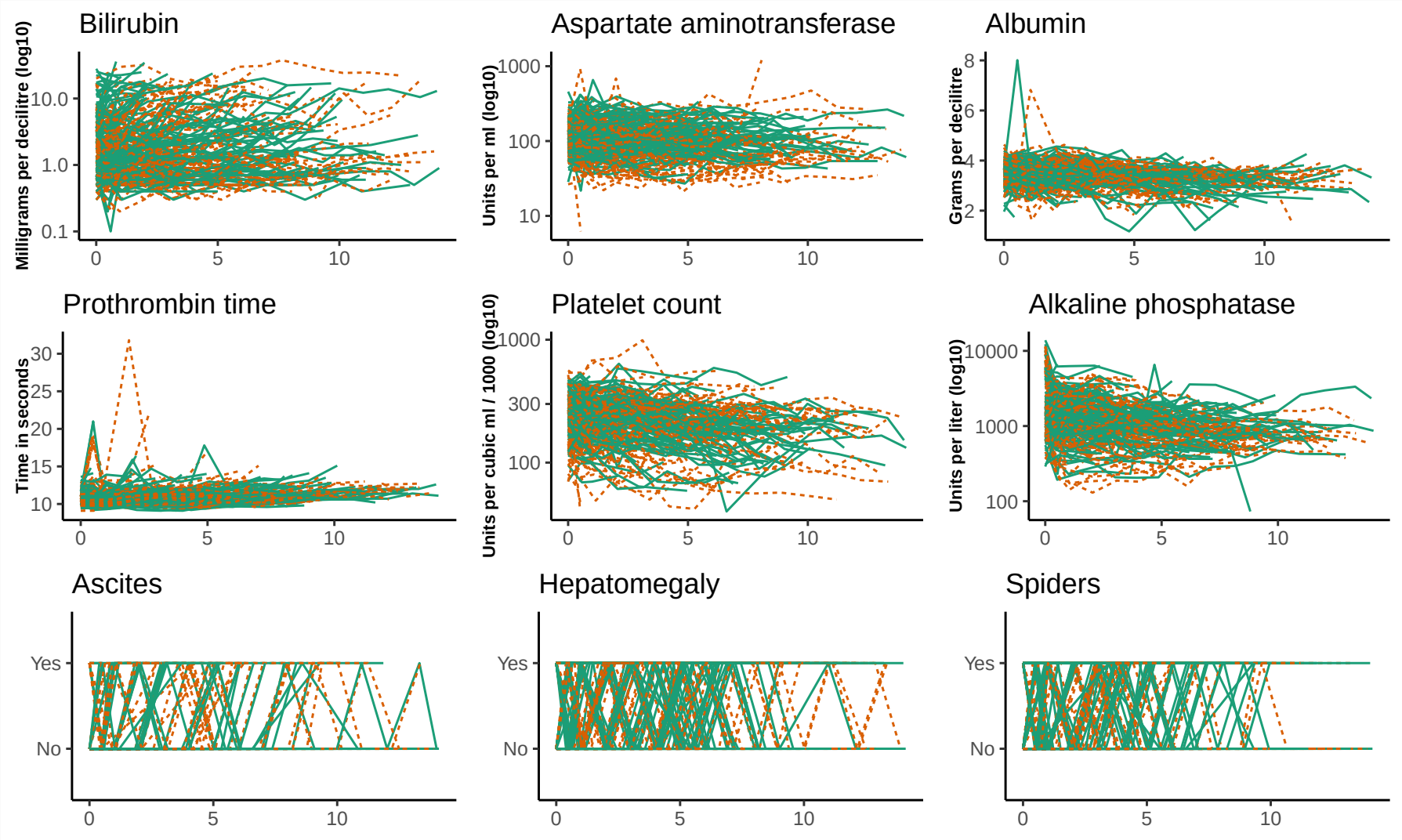
- 312 PBC patients were followed at the Mayo Clinic between 1974 and 1988 and received either a placebo or D-penicillamine.
- These data are publicly available in several software including the R package ‘JM‘.
- During the follow-up, 140 patients died and 29 patients received a liver transplantation 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

$$
\begin{cases}
\begin{aligned}
log(serBilir_{ij}) &= \eta_i(t_{ij}) + \varepsilon_{ij} && \text{(L1)} \\
&= \beta_0 + \beta_1 year_{ij} + (\beta_2 + b_{i2}) year_{ij}^2 \\
&\quad + (\beta_3 + b_{i3}) year_{ij}^3 + \beta_4 drug_i + \beta_5 year_{ij} drug_i \\
&\quad + \beta_6 year_{ij}^2 drug_i + \beta_7 year_{ij}^3 drug_i + \varepsilon_{ij} \\
\\
\lambda_{i1}(t) &= \lambda_{01}(t) \exp\left(\gamma_1 drug_i + \varphi_1 \eta_i(t) + \varphi_2 \eta_i'(t)\right) && \text{(S1)}
\end{aligned}
\end{cases}
$$

M4: Comparison with MCMC

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

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

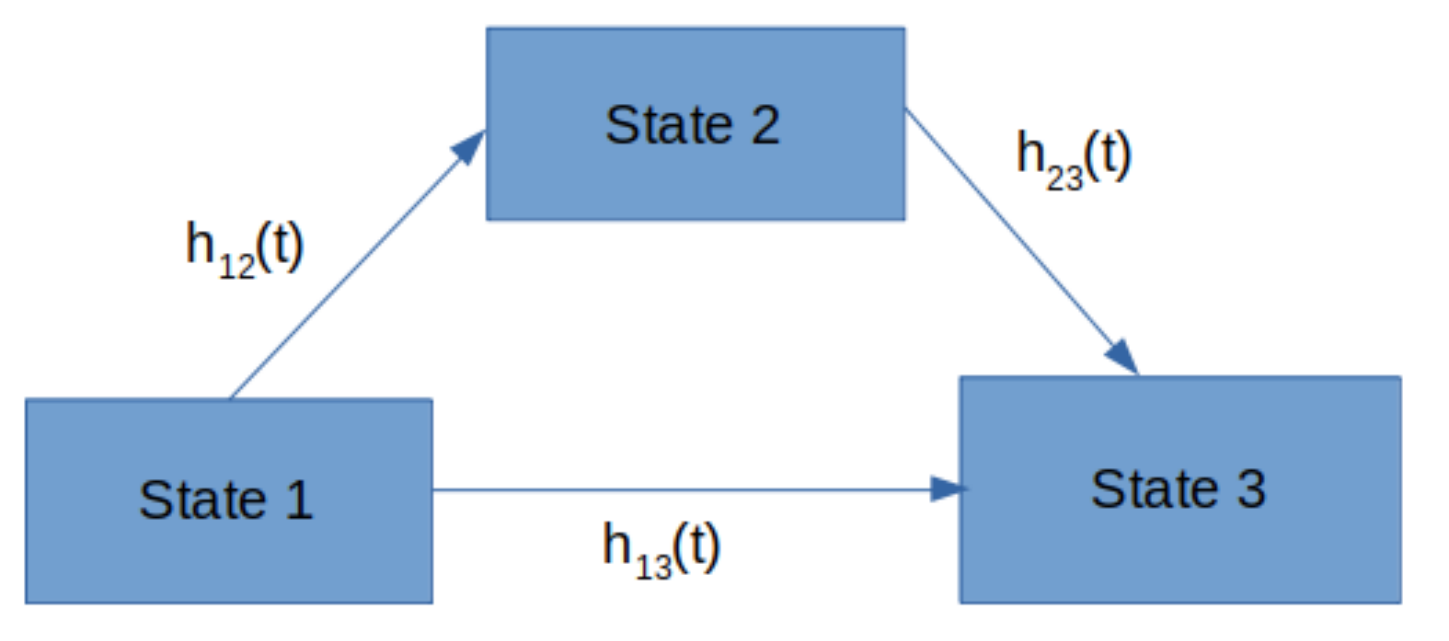
M5: JOINT WITH ONE LONGITUDINAL AND COMPETING RISKS

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

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

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