Bayesian inference using Hamiltonian Monte-Carlo algorithm for non-linear joint modelling in the context of cancer immunotherapy

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Clinical context

Clinical data IMvigor210 (phase 2) and IMvigor211 (phase 3) trials: patients suffering from advanced or metastatic bladder cancer who did not respond to chemotherapy and treated with Atezolizumab immunotherapy treatment.

Immunotherapy:

- New treatments based on immune system stimulation (Atezolizumab targets PD-L1 to prevent its interaction with its receptor on immune cell),
- Showed impressive results in several cancer, including bladder cancer,
- But also apparition of new types of response (*Hyper-progression*, *Pseudo-progression*), higher variability in response than with chemotherapy.

Clinical Context

Challenges induced by immunotherapy in clinical development:

- Define characteristics of patients to treat and predictive biomarkers of the response to treatment,
- Combinations with other treatments,
- New endpoints to evaluate treatment adapted to the diversity of responses.

⇒ There is a **need to develop mathematical models** that can characterize the kinetics of response to **immunotherapies** in order to optimize **clinical development** and improve **patients follow-up** and care.

Modeling longitudinal and survival data

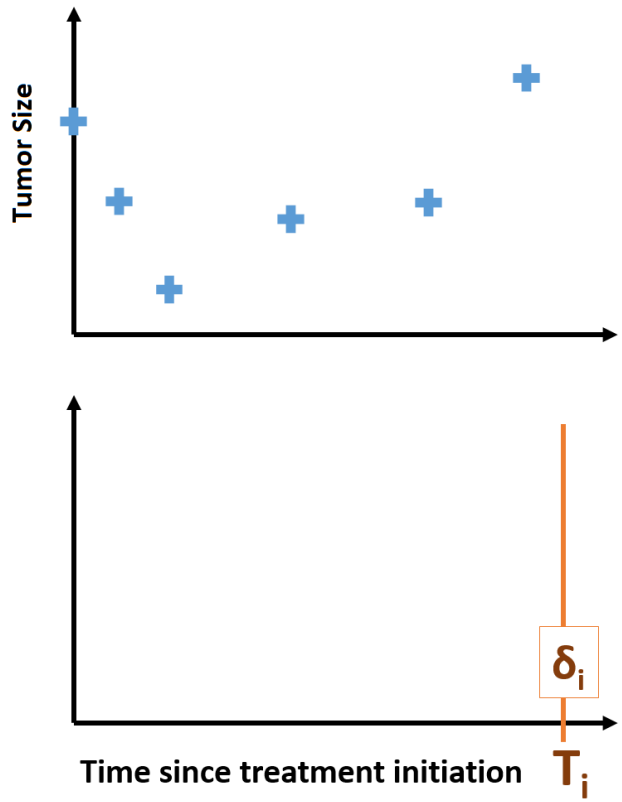
Two main observed responses to treatment:

Longitudinal data

- y_i: vector of longitudinal measurements,
- Contains early information in response to treatment,
- Can be modelled in a mixed-effects model framework.

Time-to-event data

- T_i: observed event time
- δ_i: event indicator $= \begin{cases} 1 & \text{if event observed} \\ 0 & \text{if event not observed} \end{cases}$



Joint Models

The probability to not observe the biomarker depends on current (unobserved) biomarker value

- "Poor responders" are more likely to drop out or to experience the event
- "Good responders" are overrepresented as time goes by

→ Sample is not representative (informative censoring), induce bias

⇒ **Joint modelling**[1,2]

[1] Tsiasis et al. (1995) Journal of the American Statistical Association

[2] Rizopoulos et al. (2012) Chapman and Hall/CRC

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Longitudinal part - Mixed-effect models

$$y_i(t) = X(t, \psi_i) \times (1 + e_i(t))$$

- X: process of interest (Tumor size) **possibly non-linear**
- $\psi_i = \tau(\mu, \eta_i)$: individual longitudinal parameters
- $e_i(t) \sim \mathcal{N}(0, \sigma^2)$ residual error

[1] Tsiasis et al. (1995) Journal of the American Statistical Association

[2] Rizopoulos et al. (2012) Chapman and Hall/CRC

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Survival part - Hazard function for patient i

$$h_i(t|\psi_i) = h_0(t) \exp(\beta \times f(t, \psi_i)) \qquad \text{for } t \geq 0$$

$$S_i(t|\psi_i) = P(T_i \geq t) = \exp\left[-\int_0^t h_i(u|\psi_i)du\right]$$

- Link function f depends on ψ_i

[1] Tsiasis et al. (1995) Journal of the American Statistical Association

[2] Rizopoulos et al. (2012) Chapman and Hall/CRC

Non-Linear Joint Model

Use of mechanistic models can be suited to characterize biomarker kinetics:

- **Many measurements** of biomarker in the context of clinical trial[1],
- High **biological complexity** of the tumor size kinetics,
- Exacerbated in the context of **immunotherapy** by the complex interaction between the drug, the immune response and the tumor.

⇒ Biomarker kinetics is described by a **non-linear mixed-effects model**,

- Increase of the likelihood expression complexity,
- Requires high performance algorithm.
- Inference in a frequentist framework can be done by maximum likelihood using SAEM (Stochastic Approximation of EM Algorithm)[2,3].

[1] Desmée et al. (2016) Biometrics
[2] Desmée et al. (2015) AAPS
[3] Tardivon et al. (2018) CPT

Bayesian Inference and HMC algorithm

The **complex likelihood expression** of non-linear joint models already requires **high-performance algorithm** for inference:

- **Bayesian approach** offers a natural framework to include prior information to increase identifiability,
- A new inference tool could help to **go further in modelisation** ?

Stan[1] bayesian software:

- **Hamiltonian Monte-Carlo algorithm**[2] known to have good convergence properties for complex models (Hamiltonian dynamics),
- **No-U-Turn Sampler Version**[3] optimized version of HMC algorithm.

Until now:

- Joint model inference with Stan **limited to linear** description of the longitudinal process (R package `rstanarm`),
- No published work using Stan in nonlinear joint model or nonlinear mixed-effects model inference.

⇒ **We aim to assess HMC for non-linear joint model parameters inference**

[1] Carpenter et al. (2017) Journal of statistical software
[2] Neal (2011) Handbook of Markov Chain Monte Carlo
[3] Hoffman & Gelman (2014) Journal of Machine Learning Research

Simulation Study

Simulation framework build on real data:

- Pattern of the simulated trial,
- Maximum Likelihood estimates for simulation values.

Evaluation Criteria:

- Relative Estimates Error on Posterior mode, mean and median,
- Coverage Rates.

↳ **To assess HMC algorithm for non-linear joint modeling population parameters inference**

Clinical Data Analysis

Cross-Validation method for link function selection

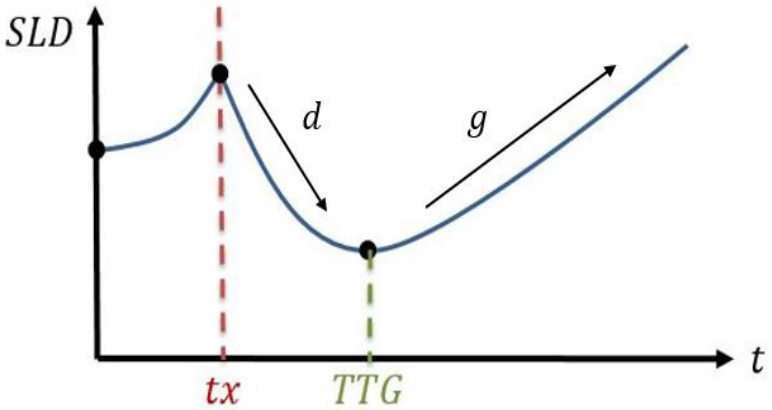
Posterior Analysis:

- Estimated posterior density of population parameters,
- Characteristics of the final posterior distribution (mean, median, maximum, standard deviation, credibility interval),
- Individual fits of tumor size and survival probability, with 95% credibility intervals.

Mechanistic model for tumor size kinetics

Longitudinal part

We rely on the **Sum of the Longest Diameters (SLD)** of the target lesions as a marker of the tumor size kinetics.



t : time since inclusion (days)
tx : time elapsed between inclusion and treatment onset

BSLD : SLD at inclusion time (mm)
d : tumor decreasing parameter (day^{-1})
g : tumor growth parameter (day^{-1})
ϕ : proportion of cells that responds to treatment

Stein-Fojo model[1]

$$SLD(t) = \begin{cases} BSLD\, e^{g\, t} & \text{if } t < tx \\ BSLD\, e^{g\, tx} \times (\phi e^{-d(t-tx)} + (1-\phi) e^{g(t-tx)}) & \text{if } t \geq tx \end{cases}$$

$$\Rightarrow TTG = \frac{\log\left(\frac{d\phi}{g(1-\phi)}\right)}{g+d} + tx$$

[1] Chatterjee et al. (2017) CPT Pharmacomet Syst Pharmacol

Building a simulation framework

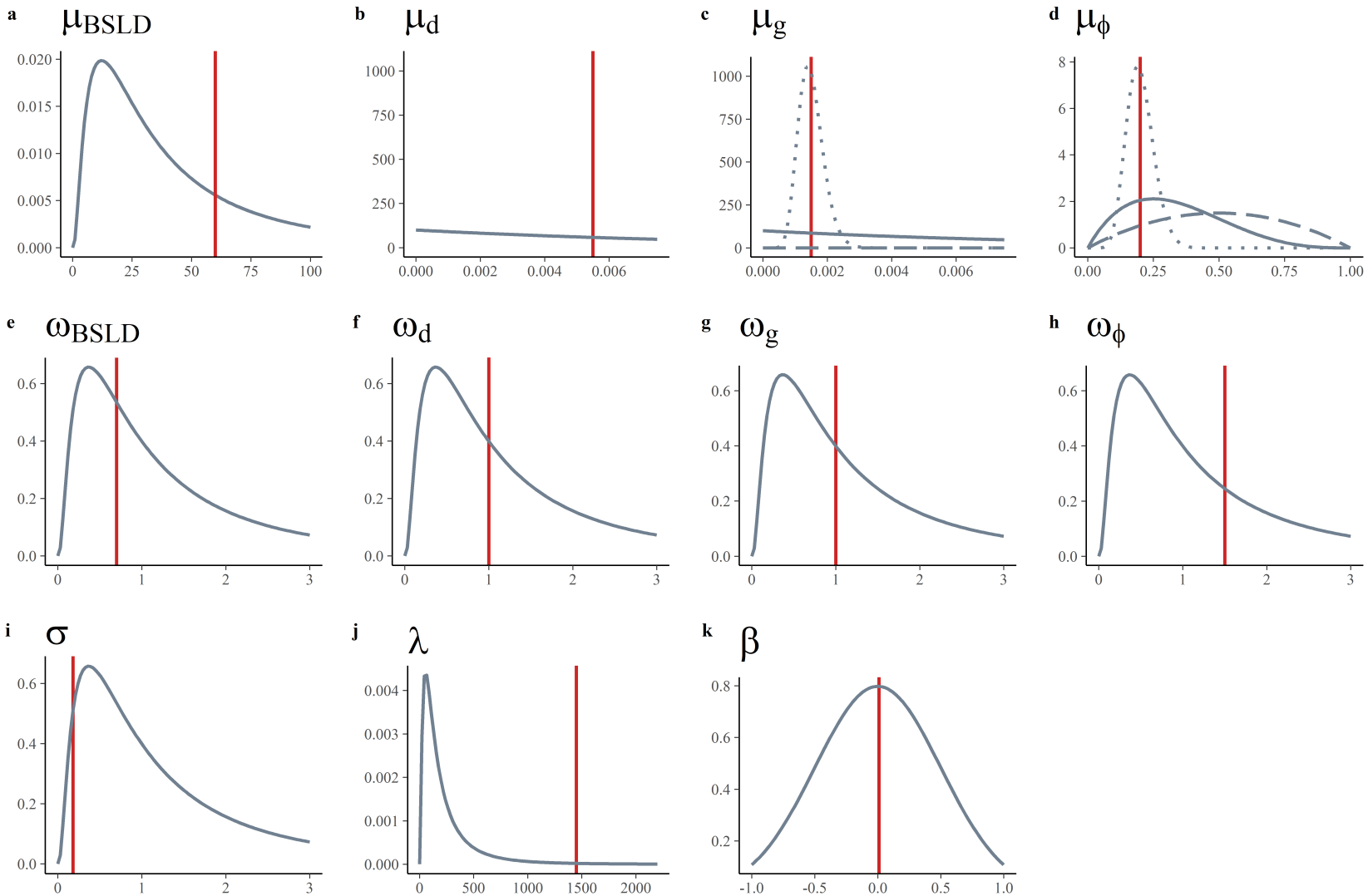
Simulation of **tumor size** and **survival** data based on IMvigor210 Phase 2 clinical trial:

- $y_{i,j} = \text{SLD}(t_{i,j}, \psi_i) \times (1 + e_{i,j})$, $e_{i,j} \sim \mathcal{N}(0, \sigma^2)$,
- $h_i(t|\text{SLD}(t, \psi_i)) = \frac{1}{\lambda} \exp(\beta \times \text{SLD}(t, \psi_i))$, exponential base hazard function.

	Fixed effects μ	Transformation	Standard deviation ω
BSLD(mm)	60	log-normal	0.7
$d(\text{day}^{-1})$	0.0055	log-normal	1
$g(\text{day}^{-1})$	0.0015	log-normal	1
ϕ	0.2	logit-normal	1.5
σ	0.18	-	-
λ	1450	-	-
β	0.01	-	-

100 datasets of 100 patients, measurements every 9 weeks for 2 years

Sensitivity analysis to prior distributions



Evaluation Criteria

Relative Estimates Error of a population parameter θ estimated on dataset k:

$$\text{REE}^k = \frac{\widehat{\theta^k} - \theta^*}{\theta^*} \times 100. \tag{1}$$

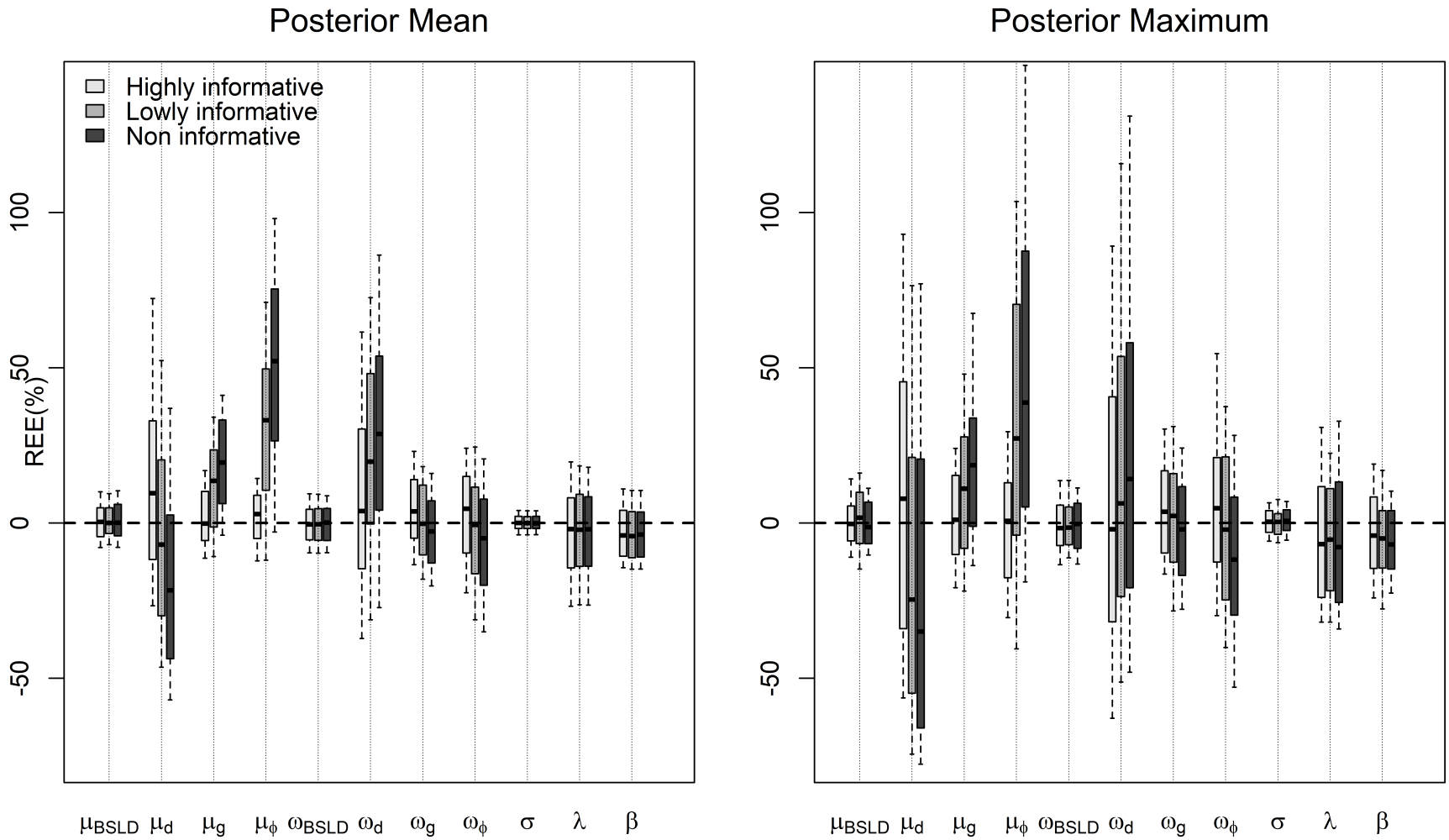
Credibility intervals based on ordered posterior sample of size L $\left(\hat{\theta}^k_{(l)}\right)_{l\in\{1,\dots,L\}}$:

$$\hat{\text{CI}}^k_\alpha = \left[\hat{\theta}^k_{(L\times\alpha/2)}; \hat{\theta}^k_{(L\times(1-\alpha/2))}\right] \tag{2}$$

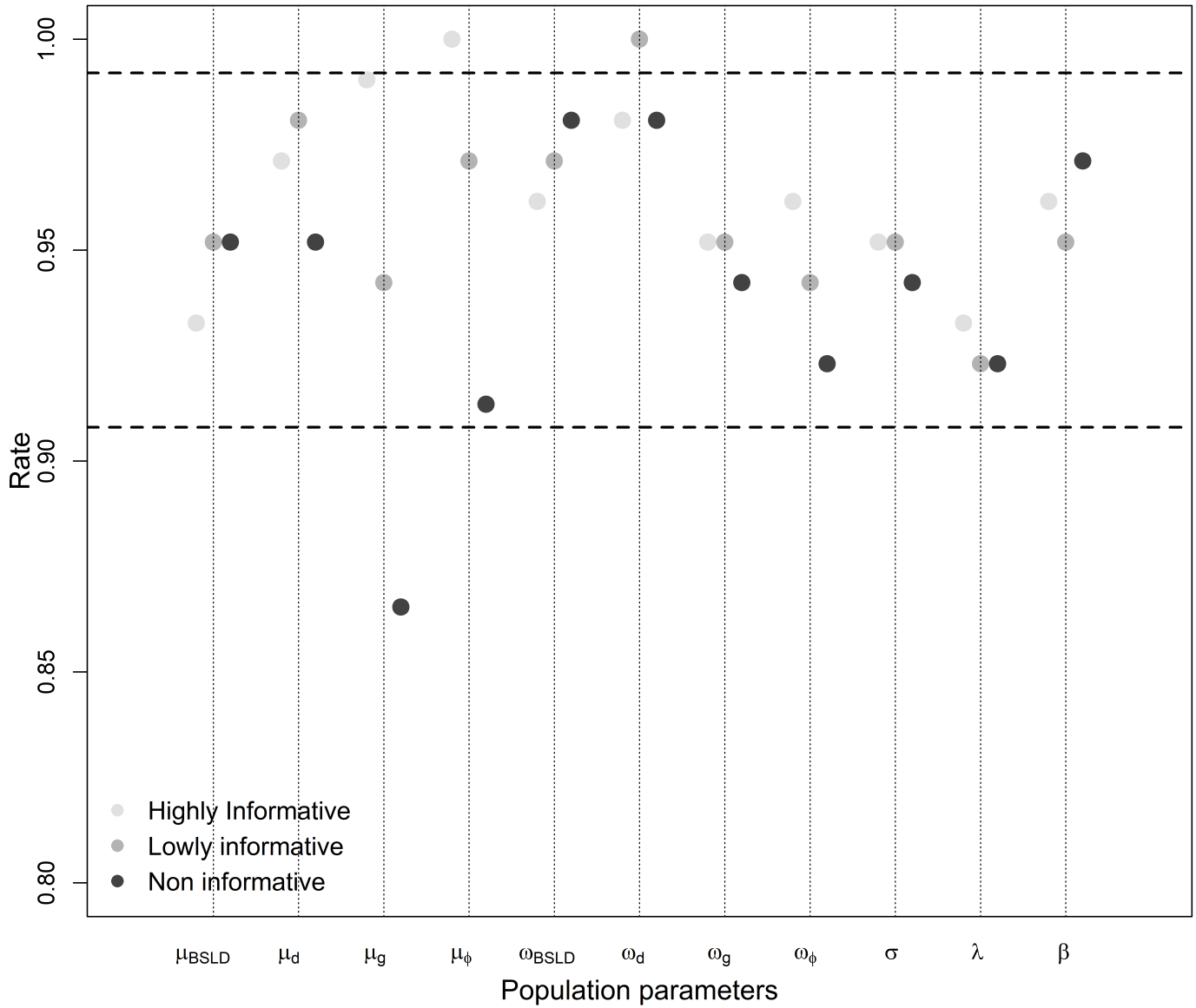
Coverage rates:

$$\text{Coverage Rate}_\alpha = \frac{1}{K}\sum_{k=1}^{K} 1_{\{\theta^*\in\hat{\text{CI}}^k_\alpha\}} \tag{3}$$

Relative Estimate Errors on point estimates



Coverage rates of 95% credibility intervals



Clinical Data

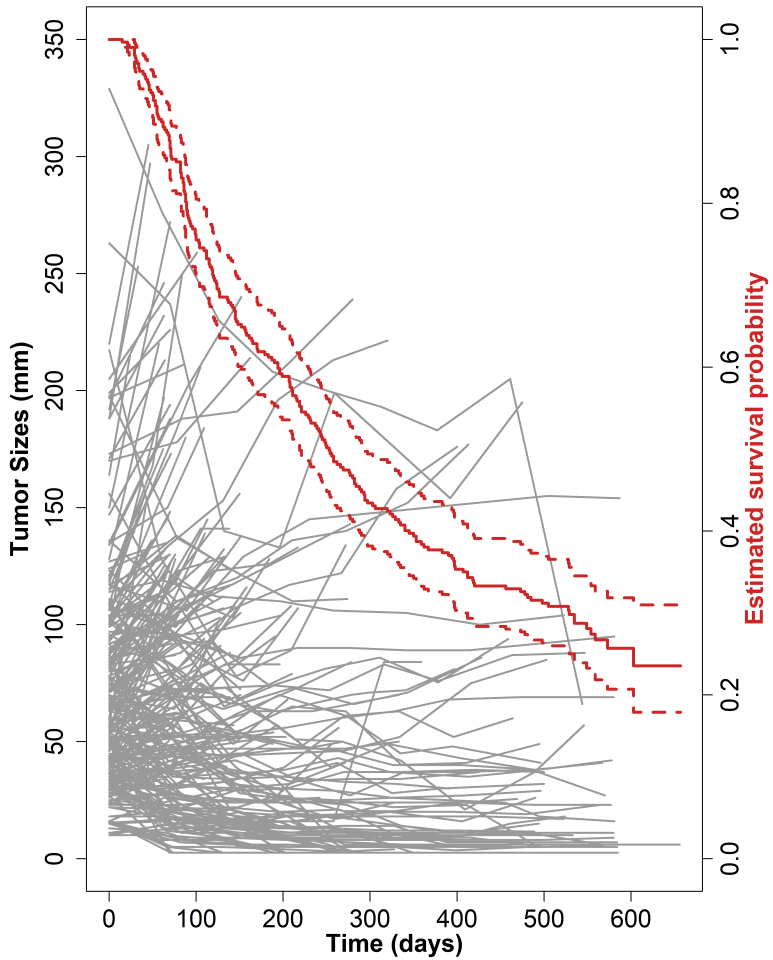
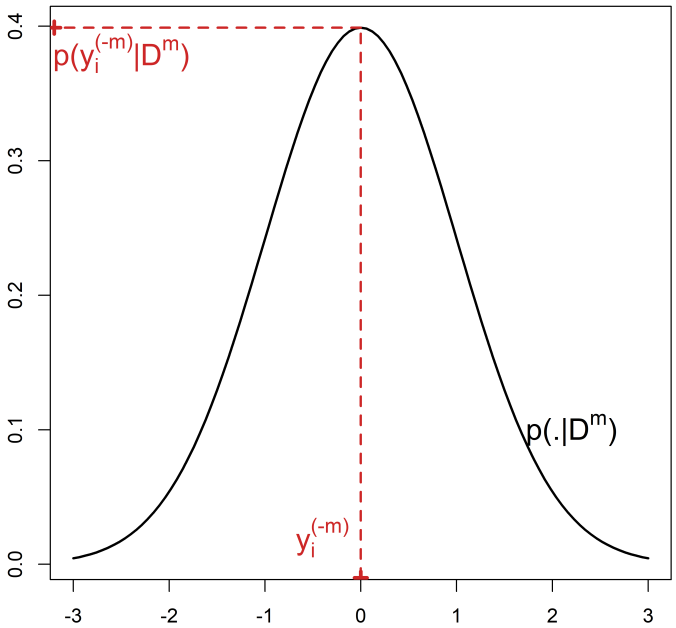


Figure: Spaghettis-plot of the tumor sizes, estimated overall survival probability by Kaplan-Meier and its 95% confidence interval on clinical data.

Cross-Validation for link function selection

Cross-Validation on patients using the posterior predictive density[1]:

$$p\left(y_i^{(-m)}|D^m\right) = \int p\left(y_i^{(-m)}|\theta\right) p\left(\theta|D^m\right) d\theta$$



- Monte-Carlo approximation on population parameters $p\left(y_i, T_i, \delta_i|D^{(-m)}\right) = \frac{1}{L}\sum_{l=1}^{L} p\left(y_i, T_i, \delta_i|\theta_l^{(-m)}\right)$,
- Inference on random effects $p\left(\eta_i|\theta_l^{(-m)}, y_i, T_i, \delta_i\right)$,
- Monte-Carlo approximation on random effects $p\left(y_i, T_i, \delta_i|\theta_l^{(-m)}\right) = \frac{1}{S}\sum_{s=1}^{S}\left[\prod_{j=1}^{n_i} p\left(y_{ij}|\theta_l^{(-m)}, \eta_i^s\right) p\left(T_i, \delta_i|\theta_l^{(-m)}, \eta_i^s\right)\right]$.

$\Rightarrow$ Selection of the link function which maximized score.

[1] Vehtari & Lampinen (2002) Neural Computation

Cross-Validation procedure results

Joint Model for clinical data analysis:

- $y_{i,j} = \text{SLD}(t_{i,j}, \psi_i) \times (1 + e_{i,j})$, $e_{i,j} \sim \mathcal{N}(0, \sigma^2)$,
- $h_i(t|\text{SLD}(t, \psi_i)) = \frac{\kappa}{\lambda}\left(\frac{t}{\lambda}\right)^{\kappa-1} \exp(\beta \times f(\text{SLD}(t, \psi_i)))$.

Selection between the 4 following link functions:

- No link model $f(\text{SLD}(t, \psi)) = 0$,
- Current SLD value $f(\text{SLD}(t, \psi)) = \text{SLD}(t, \psi)$,
- Current Slope of SLD $f(\text{SLD}(t, \psi)) = \frac{\partial \text{SLD}(t,\psi)}{\partial t}$,
- Time-to-growth, $f(\text{SLD}(t, \psi)) = \text{TTG}(\psi) = \frac{\log(\frac{d\phi}{g(1-\phi)})}{g+d} + t_x$,

	Models			
	No Link	Current SLD	**Current Slope**	Time-To-Growth
CV Score	-23.44	-22.68	**-22.23**	-23.11
Link parameter	0	0.01 (0.001) mm^{-1}	**2.56 (0.70) day.mm^{-1}**	-0.009 (0.001) day^{-1}

Posterior density on real data

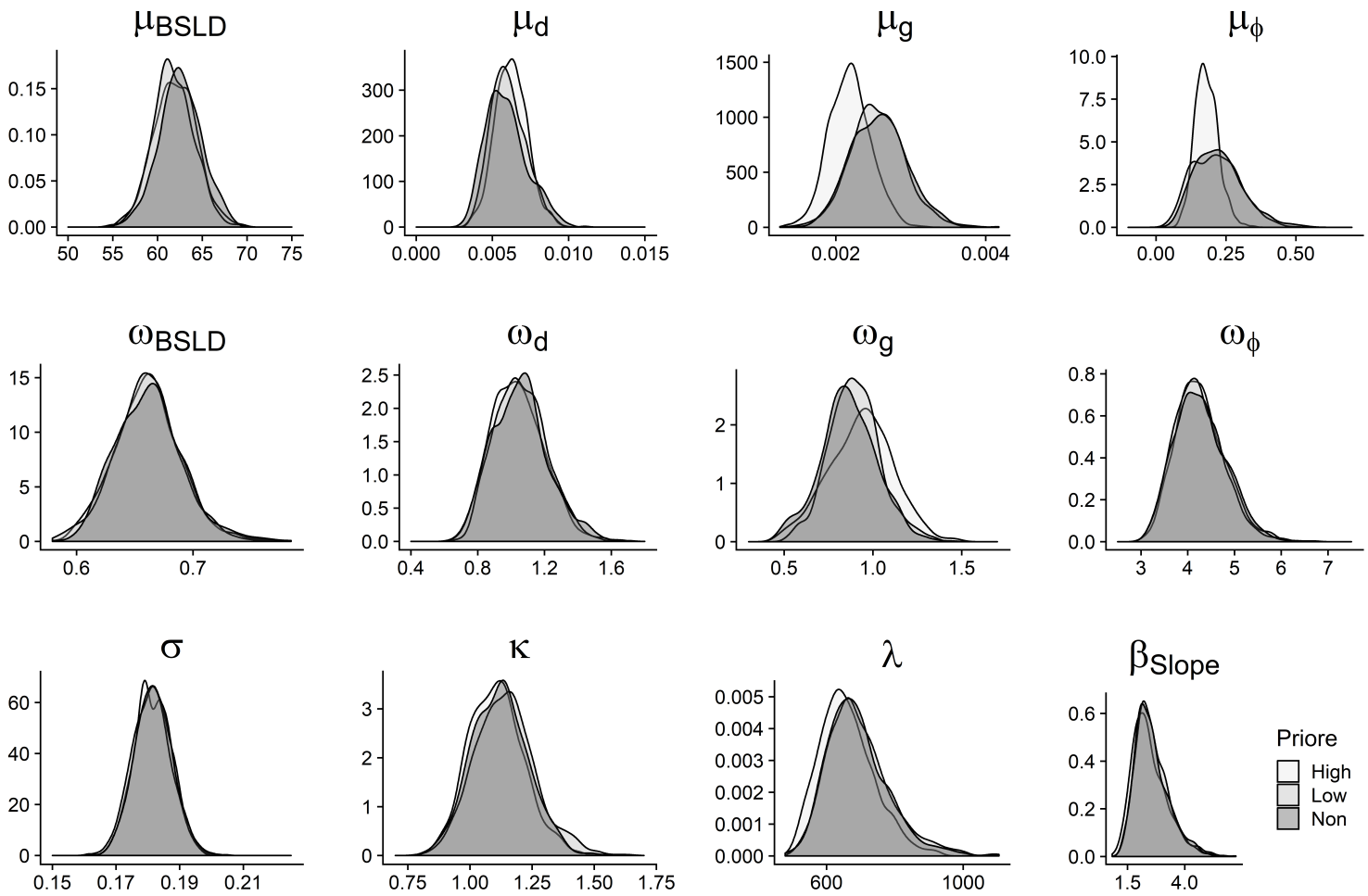


Figure: Posterior density of current SLD slope model population parameters on clinical data depending on the prior information scenario.

Posterior density characteristics on real data

			Posterior				
			Maximum	Mean	Median	Sd	RSd(%)	95% CI
		Longitudinal						
Fixed	effects μ	BSLD (mm)	61.43	61.77	61.63	2.25	3.65	[57.34;66.29]
		d (day^{-1})	0.0059	0.0060	0.0059	0.0011	18.79	[0.0040;0.0084]
		g (day^{-1})	0.0025	0.0025	0.0025	0.00036	14.01	[0.0010;0.0021]
		ϕ	0.17	0.21	0.21	0.083	38.99	[0.074;0.39]
Standard	deviations ω	BSLD (mm)	0.66	0.66	0.66	0.028	4.22	[0.60;0.72]
		d (day^{-1})	1.09	1.06	1.05	0.15	14.34	[0.80;1.37]
		g (day^{-1})	0.86	0.89	0.89	0.14	16.02	[0.60;1.21]
		ϕ	4.05	4.23	4.18	0.52	12.2	[3.36;5.35]
		σ	0.18	0.18	0.18	0.0059	3.28	[0.17;0.19]
		Survival						
		κ	1.19	1.14	1.14	0.12	10.7	[0.922;1.41]
		λ (day)	659	694	679	91	13.1	[549;915]
		β (day.mm^{-1})	2.06	2.56	2.45	0.70	27.2	[1.47;4.24]

Table: Posterior density characteristics of current SLD slope model parameters with inference under the low prior information scenario

Individual fits and 95% credibility intervals[1]

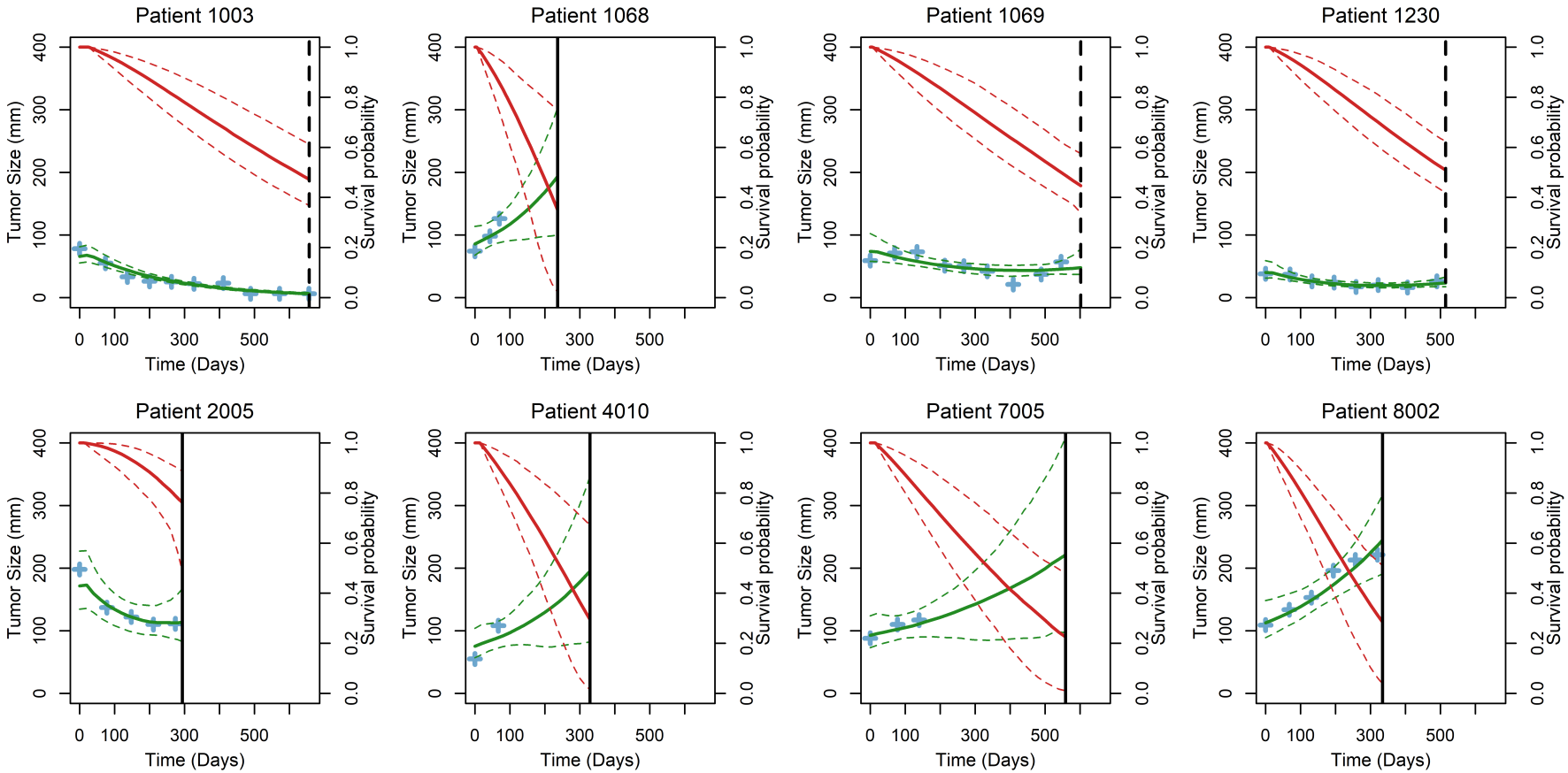


Figure: Individual fits and 95% credibility intervals of real data patients under the current SLD slope model with inference under the low prior information scenario on population parameters.

[1] Kerioui et al. (2019) *preprint version*

Discussion

⇒ A full Bayesian inference for non-linear joint model is now possible.

- Some remaining talking points:
  - Sensitivity to prior information,
  - Integration method for survival probability computation,
  - Further exploration for Bayesian model selection.

[1] Krol et al (2018) Stat in Med

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- Some remaining talking points:
  - Sensitivity to prior information,
  - Integration method for survival probability computation,
  - Further exploration for Bayesian model selection.
- These results open the way to further work for a better understanding of the large variability between patients in the response to **atezolizumab**:
  - Impact of new lesions appearance on survival (recurrent events)[1],
  - Modelling individual lesions and intra-patients variability in response to treatment,
  - Comparison with chemotherapy arm,
  - Prediction of the phase 3 outcome.

[1] Krol et al (2018) Stat in Med

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