Stan for Pharmacometrics day

Hierarchical Nonlinear Joint Modelling in Oncology - a simulation study

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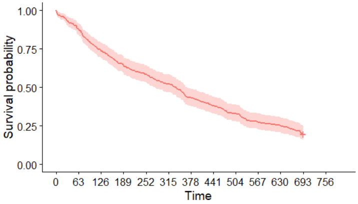
Marion Kerioui (INSERM, UMR 1137 - IAME)

8th June 2023

Treatment response assessment in oncology

Primary endpoint: Survival



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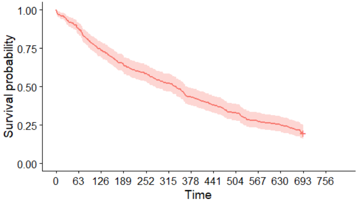
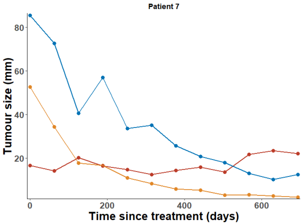


Secondary endpoint:
Tumour size evolution



- Modelling survival and tumour size **together** allows:
  - To identify the patients most at risk
  - To refine the assessment of treatment efficacy

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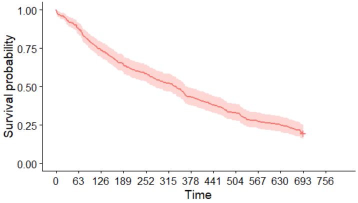

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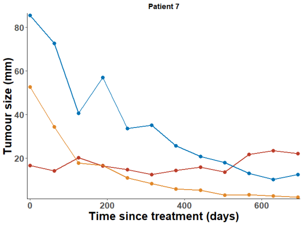

- Modelling survival and tumour size **together** allows:
  - To identify the patients most at risk
  - To refine the assessment of treatment efficacy
- **Joint models** are needed to avoid bias in the estimation:
  - Of the parameters of the longitudinal sub-model[1]
  - Of the association parameter[1]

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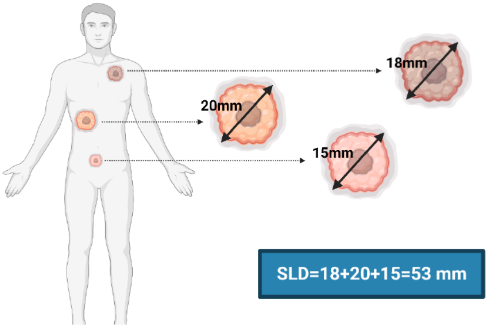
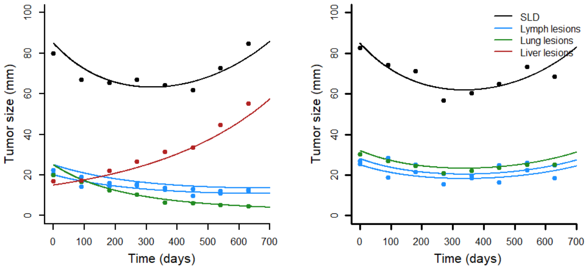
Monitoring the Sum of the Longest Diameters (SLD)



- Selection of target lesions
- Representative of the patient's health status
- Monitoring the dynamics of the sum of the size of these lesions

The limits of SLD



- Aggregates information
- Hides inter-lesion variability
- In immunotherapy, the risk of dissociated response is increased[2]
- Tumour kinetics and response to treatment could be location-specific[3]

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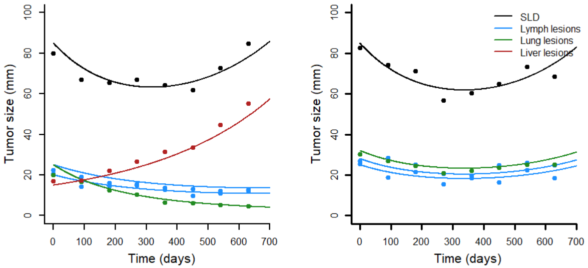

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⇒ These reasons motivated Dr Kerioui to work on the joint modelling of survival and individual lesions during her thesis.

[2] Vaflard et al, *Drugs in R&D* (2021)

[3] Kerioui et al, *European Society for Medical Oncology* (2022)

Multilevel joint modelling in metastatic bladder cancer

- Based on data from a phase III clinical trial: IMvigor211[4]
- Patients with metastatic bladder cancer
- Treatment with immunotherapy (atezolizumab)

[4] Powels et al, *The Lancet* (2018)

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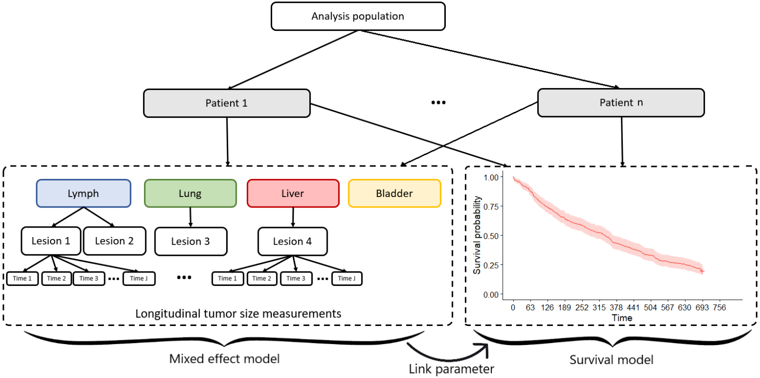

[4] Powels et al, *The Lancet* (2018)

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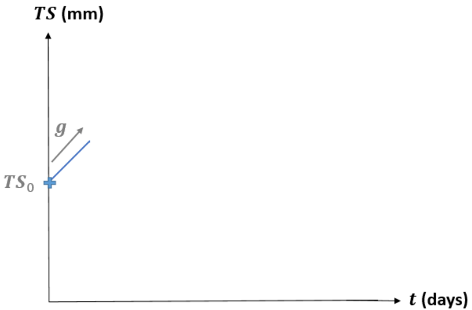
Mechanistic model of tumour dynamics

Structural model of tumour size[6]:

$$TS(t, \psi) = \begin{cases} TS_0 \times e^{g \times t} & t < t_x \end{cases}$$

with t_x the treatment initiation time



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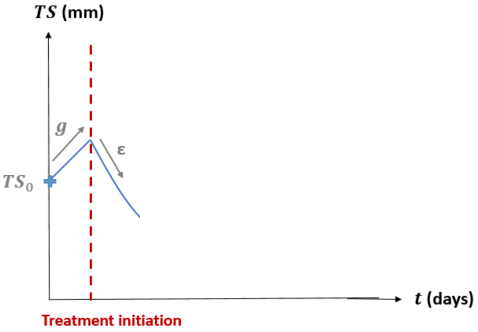

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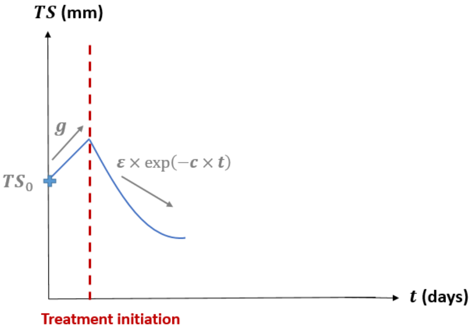

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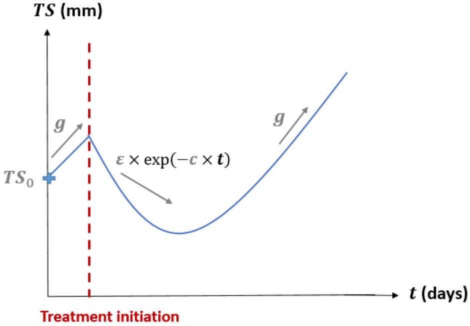

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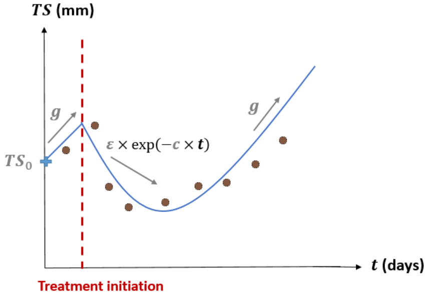
Multilevel nonlinear joint model

Longitudinal submodel: **Nonlinear mixed effect model** to describe measures of **tumour size** of individual lesions

$$y_{i,j,k,l} = TS\left(t_{i,j,k,l}, \psi_{i,j,k}\right) + \left(\sigma_j \times TS\left(t_{i,j,k,l}, \psi_{i,j,k}\right)\right) e_{i,j,k,l}$$



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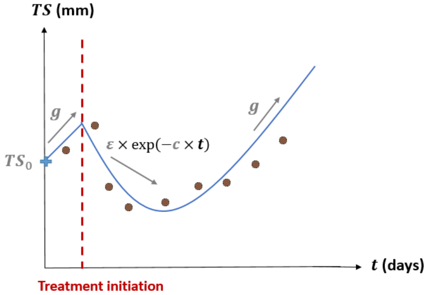
$$\text{with } \log\left(\psi_{i,j,k}\right) = \log\left(\mu\right) + \xi_j + \eta_i + \rho_{i,j,k}$$

- μ: **fixed effect**
- ξ_j: **fixed effect of location**
- η_i: **patient-specific random effect** $\sim \mathcal{N}(0, \omega_1^2)$
- $\rho_{i,j,k}$: **lesion-specific random effect** $\sim \mathcal{N}(0, \omega_2^2)$



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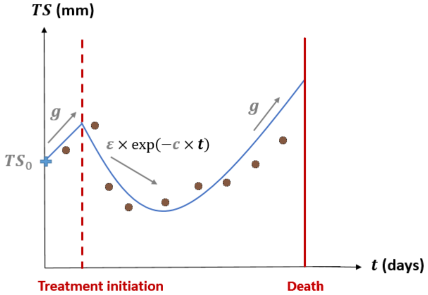

Survival submodel: **Individual hazard function**

$$h_i\left(t \mid \theta, \psi_i\right) = h_0(t) \exp\left(\sum_{j=1}^{4} \sum_{k=1}^{K_{i,j}} \beta_j \times \mathrm{TS}\left(t, \psi_{i,j,k}\right)\right)$$

with $h_0(t)$ a Weibull baseline hazard function

Bayesian inference framework

- Use of the HMC NUTS algorithm[7] implemented on the Stan software[8]
- Algorithm adapted to hierarchical models[9]
- Use of **informative priors** for population parameters μ
- The other parameters admit **weak or non-informative priors**
- From previous works[3]
- Posterior distribution:

$$p\left(\boldsymbol{\theta}, \boldsymbol{\eta}, \boldsymbol{\rho} | \boldsymbol{y}, \boldsymbol{T}, \boldsymbol{\delta}\right) \propto \prod_{i=1}^{N} \prod_{j=1}^{4} \prod_{k=1}^{K_{i,j}} \prod_{l=1}^{L_{i,j,k}} p^{L}(y_{i,j,k,l} | \boldsymbol{\theta}, \boldsymbol{\psi_{i,j,k}}) p^{S}(T_i, \delta_i | \boldsymbol{\theta}, \boldsymbol{\psi_i}) p(\boldsymbol{\rho_{i,j,k}} | \boldsymbol{\theta}) p(\boldsymbol{\eta_i} | \boldsymbol{\theta}) p(\boldsymbol{\theta})$$

[7] Hoffman et Gelman, *Journal of Machine Learning Research* (2014)
[8] Carpenter et al, *Journal of Statistical Software* (2017)
[9] Betancourt et Girolami, *arXiv* (2013)
[3] Kerioui et al, *European Society for Medical Oncology* (2022)

Objectives

Simulation study

To study the estimation properties of the model depending on the amount of information available and the level of heterogeneity in the data

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Application to a real-life data set[2]

Less informative and more heterogeneous study population compared to IMvigor211

[2] Vaflard et al, *Drugs in R&D* (2021)

Simulation scenarios

- Inspired from the IMvigor211 data[5]:
  - 50 simulated data sets
  - Target lesions in 4 locations: lymph nodes, lungs, liver, bladder
  - Study duration of 700 days, one tumour size measurement every 9 weeks

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	Number of patients	**Number of target lesions per patient**	**Inter-patient variability ω_1^2**	**Inter-lesion variability ω_2^2**
Scenario n°1 (reference)	300	1 to 5	$>$	
Scenario n°2	$\searrow$ 150	1 to 5	$>$	
Scenario n°3	$\searrow$ 150	$\nearrow$ 1 to 10	$>$	
Scenario n°4	$\searrow$ 150	1 to 5	$<$	

[5] Kerioui et al, *Under Review* (2022)

Evaluation

- **Chains convergence**: *R-hat*[10]
  - Ratio of intra-chain to inter-chain variance
  - Must be less than 1.2 for each parameter

[10] Gelman et al, *Bayesian Data Analysis* (1995)

[11] Morris et al, *Statistics in Medicine* (2018)

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$$REE(\hat{\theta}^k) = \frac{\hat{\theta}^k - \theta^*}{\theta^*} \times 100$$

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- **Estimation accuracy**: (*Coverage rate*[11], CR)

$$CR_{(1-\alpha)}(\theta) = \frac{1}{K} \sum_{k=1}^{K} \mathbb{1}_{\left\{\theta^* \in \hat{\mathrm{CI}}^k_{(1-\alpha)}\right\}}$$

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- **Goodness of fit**: (Individual fit plots)

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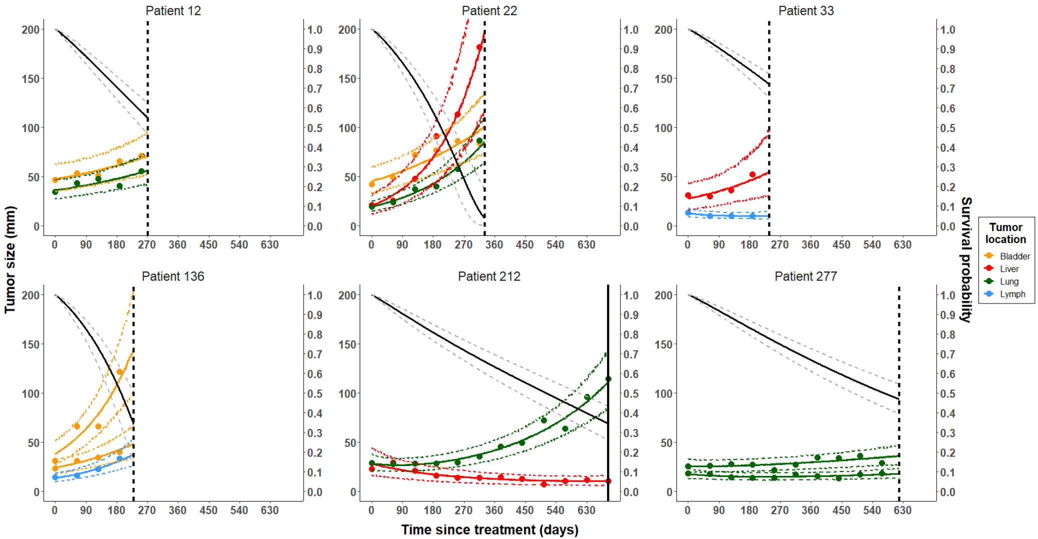
Convergence

	Scenario	n°1	n°2	n°3	n°4
1^{st} run (500 iterations)	Number of data sets (%)	50 (100)	50 (100)	50 (100)	50 (100)
	Average computation time per data set (h)	29	13	15	14
	Number of data sets converging (%)	**43 (86)**	**36 (72)**	**39 (78)**	**25 (50)**
Follow-up run (1000 iterations + another seed)	Number of data sets	7	14	11	25
	Average computation time per data set (h)	58	24	30	29
	Number of data sets converging	5	8	6	10
	Final number of data set evaluated (%)	**48 (96)**	**44 (88)**	**45 (90)**	**35 (70)**

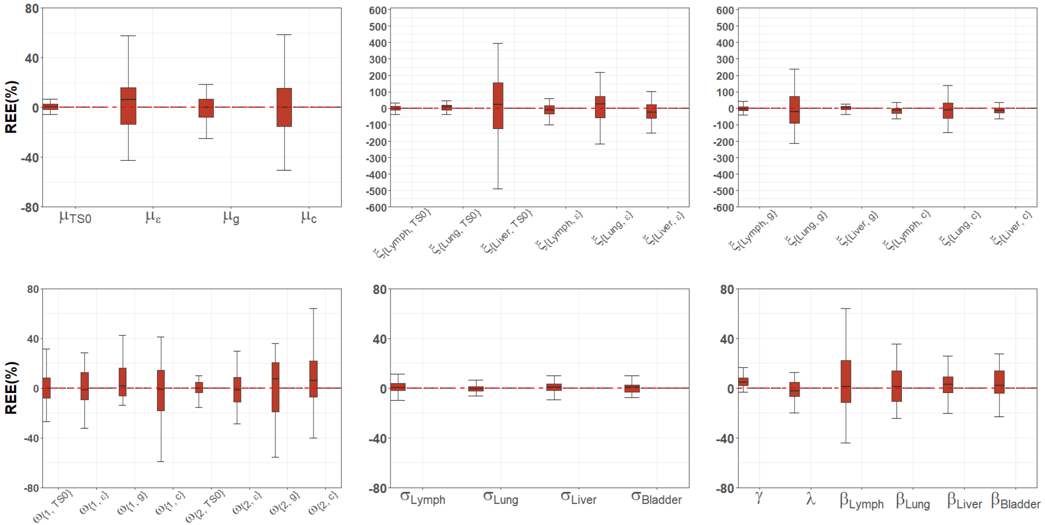
Individual fits

From a dataset of scenario n°1



Analysis of the relative estimates error

Boxplot of the *REEs* of each data set



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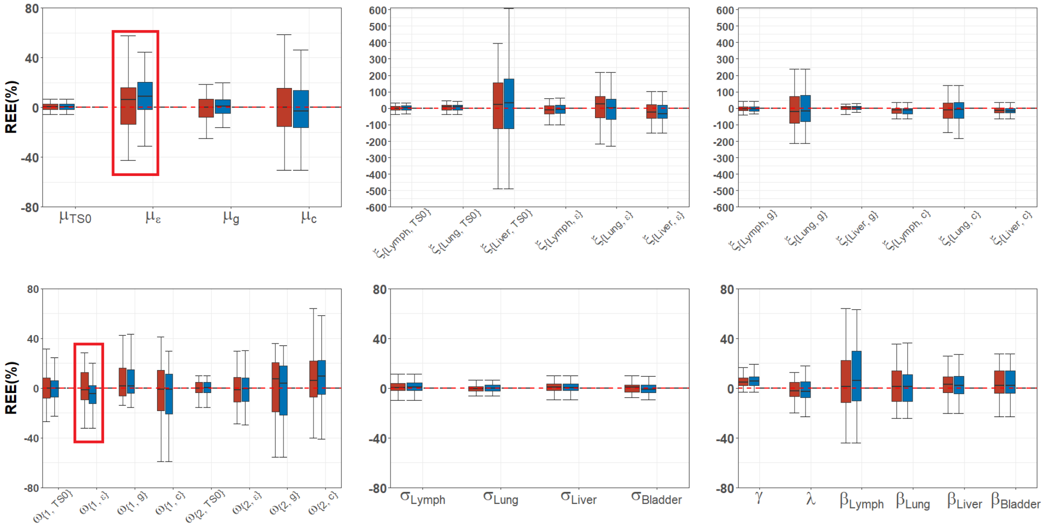

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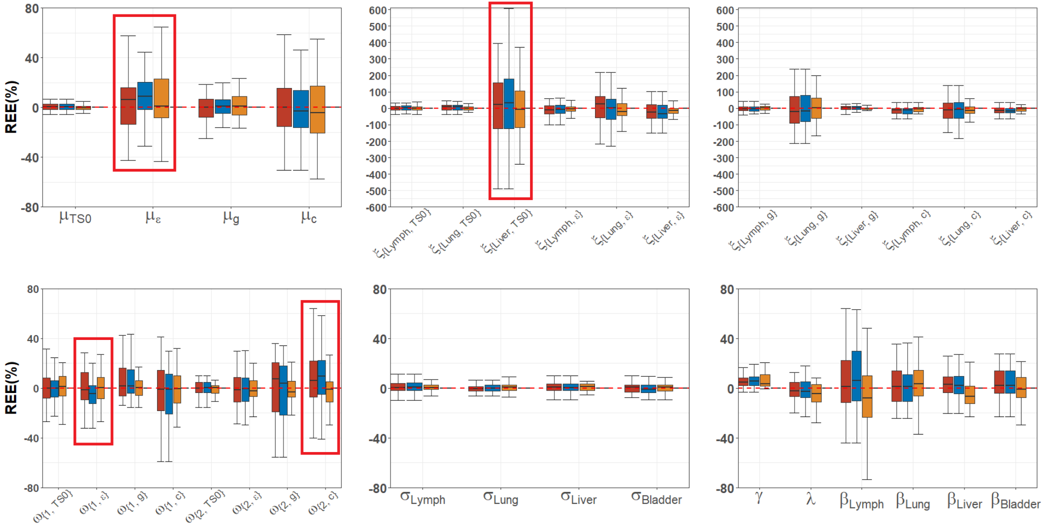

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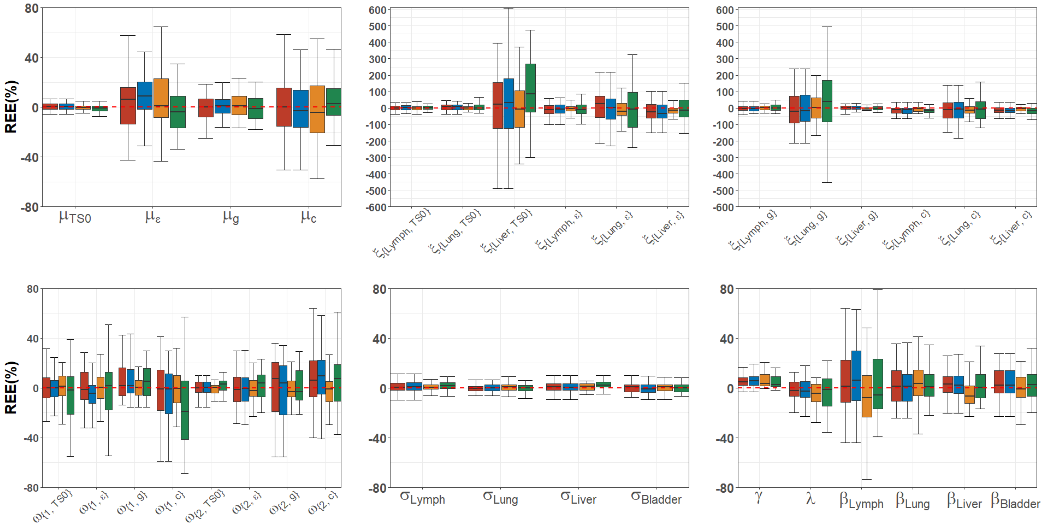
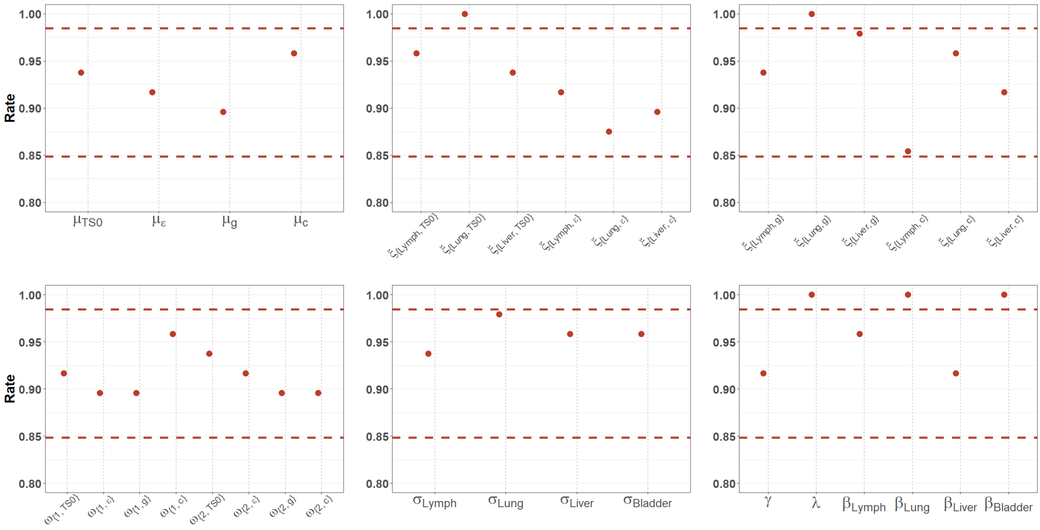


Coverage rate of parameters



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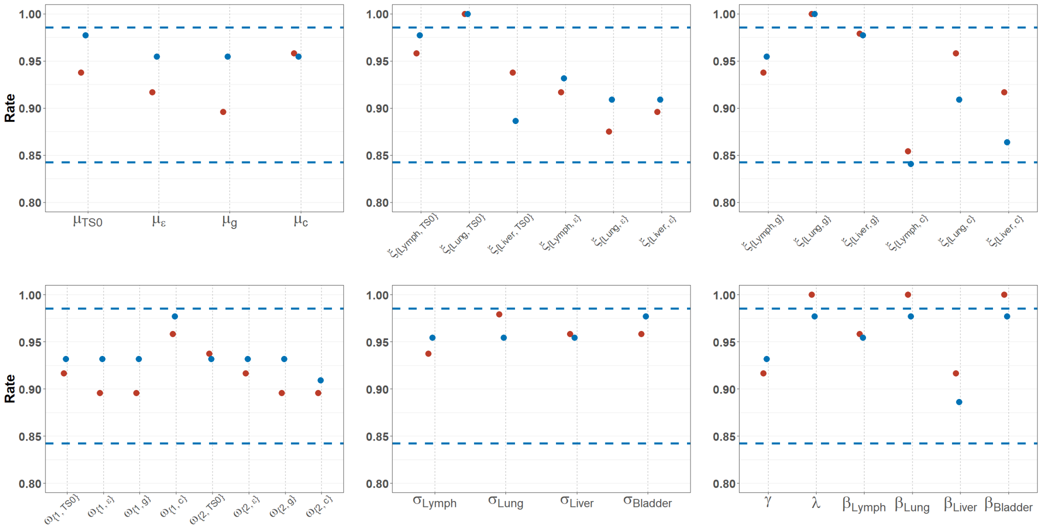

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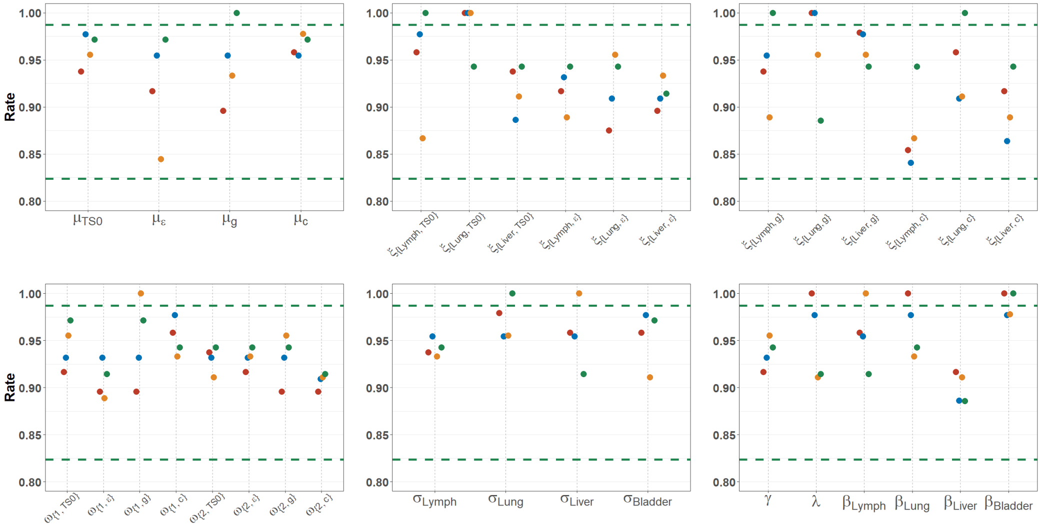


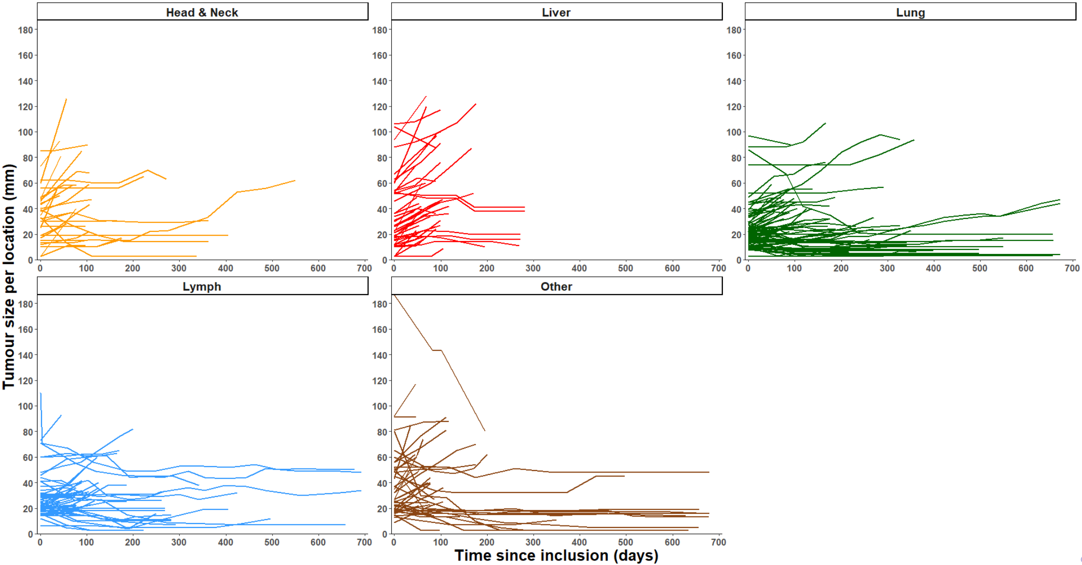
A real-life data set from the Institut Curie[2]

Baseline characteristics	
Number of patients	100
Female sex	41
Age at inclusion (min-max)	59 (21-90)
Data description	
Death	54
Number of target lesions	272
Number of measurements	1200
Number of measurements per patient median (min-max)	3 (2-16)
Number of target lesion patient	
2	43
3	43
4	13
5	1
Organ-specific data	
Locations of target lesions (%)	
Lungs	95 (35)
Lymph nodes	59 (22)
Liver	43 (16)
Head & Neck	31 (11)
Other	44 (16)
Number of measurements of target lesion per location (%)	
Lungs	464 (39)
Lymph nodes	269 (22)
Liver	131 (11)
Head & Neck	118 (10)
Other	218 (18)
Proportion of death in patients with at least one target lesion in	
Lungs	45
Lymph nodes	65
Liver	64
Head & Neck	60
Other	43

- Principal Investigator: C. Le Tourneau
- Retrospective cohort
- Highly heterogeneous population:
  - $\neq$ cancers
  - $\neq$ stages of the disease
  - 18 histological subtypes of tumour
  - $\neq$ immunotherapy treatments
- 5 target lesion locations
- Survival median after 14 months of study

[2] Vaflard et al, *Drugs in R&D* (2021)

Tumour dynamics of the patients in the cohort



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- All parameters have an *R-hat* less than 1.04
- Computation time of 18 hours

Parameters estimation

- Estimation of **location fixed effects**

	Head & Neck	Liver	Lymph nodes	Lungs	Other
$TS_0(mm)$	32.6 [25.3;41.6]	28.3 [22.6;34.7]	24.6 [20.9;29.0]	21.2 [18.6;24.2]	32.5 [27.6;38.0]
ϵ (day^{-1})	0.0006 [0.0002;0.0016]	0.0006 [0.0001;0.0016]	0.0023 [0.0007;0.0045]	0.0013 [0.0004;0.0024]	0.0014 [0.0005;0.0029]
g (day^{-1})	0.0025 [0.0013;0.0042]	0.0027 [0.0014;0.0044]	0.0026 [0.0016;0.0038]	0.0019 [0.0012;0.0027]	0.0020 [0.0011;0.0031]
c (day^{-1})	0.0058 [0.0005;0.0241]	0.0039 [0.0003;0.0162]	0.0040 [0.0015;0.0090]	0.0077 [0.0031;0.0149]	0.0030[0.0013;0.0056]

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$TS_0(mm)$	32.6 [25.3;41.6]	28.3 [22.6;34.7]	24.6 [20.9;29.0]	21.2 [18.6;24.2]	32.5 [27.6;38.0]
ϵ (day^{-1})	0.0006 [0.0002;0.0016]	0.0006 [0.0001;0.0016]	0.0023 [0.0007;0.0045]	0.0013 [0.0004;0.0024]	0.0014 [0.0005;0.0029]
g (day^{-1})	0.0025 [0.0013;0.0042]	0.0027 [0.0014;0.0044]	0.0026 [0.0016;0.0038]	0.0019 [0.0012;0.0027]	0.0020 [0.0011;0.0031]
c (day^{-1})	0.0058 [0.0005;0.0241]	0.0039 [0.0003;0.0162]	0.0040 [0.0015;0.0090]	0.0077 [0.0031;0.0149]	0.0030[0.0013;0.0056]

Parameters estimation

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g (day^{-1})	0.0025 [0.0013;0.0042]	0.0027 [0.0014;0.0044]	0.0026 [0.0016;0.0038]	0.0019 [0.0012;0.0027]	0.0020 [0.0011;0.0031]
c (day^{-1})	0.0058 [0.0005;0.0241]	0.0039 [0.0003;0.0162]	0.0040 [0.0015;0.0090]	0.0077 [0.0031;0.0149]	0.0030[0.0013;0.0056]

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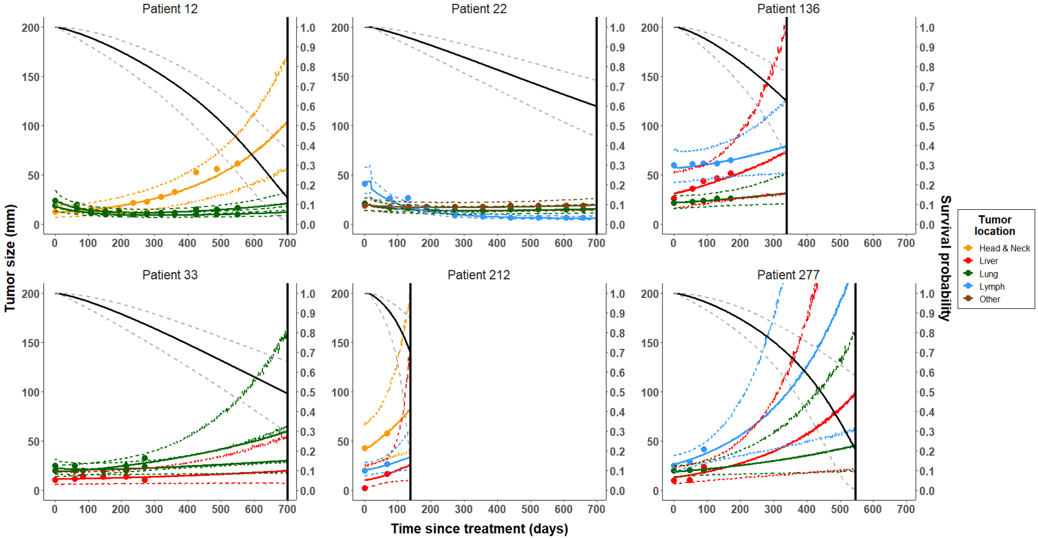
- **Head and neck** lesions are strongly associated with the instantaneous risk of death

	Head & Neck	Liver	Lymph nodes	Lungs	Other
β (mm^{-1})	0.0248 [0.0152;0.0346]	0.0093 [0.0041;0.0143]	0.0061 [0.0001;0.0137]	0.0050 [0.0005;0.0105]	0.0017 [0.0003;0.0038]
Increased instantaneous risk of death following a 10 mm increase in tumour size (%)	**28.3** [16.4;41.4]	**9.8** [4.2;15.4]	**6.4** [-0.1;14.7]	**5.2** [-0.5;11.1]	**1.7** [0.3;3.9]

Individual fits



Discussion

Conclusions

- Good estimation properties and robustness of the model in:
  - A small sample size
  - Heterogeneous population

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- Sensitivity to priors not investigated
- High computation time $\rightarrow$ future work on parallelization

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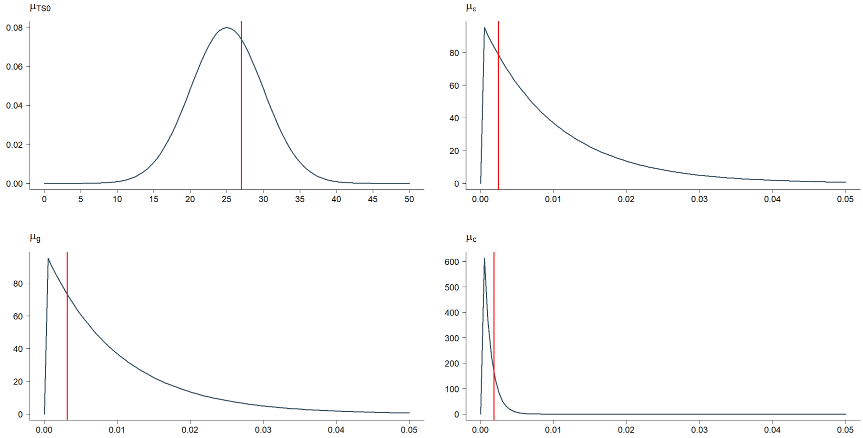
Perspectives

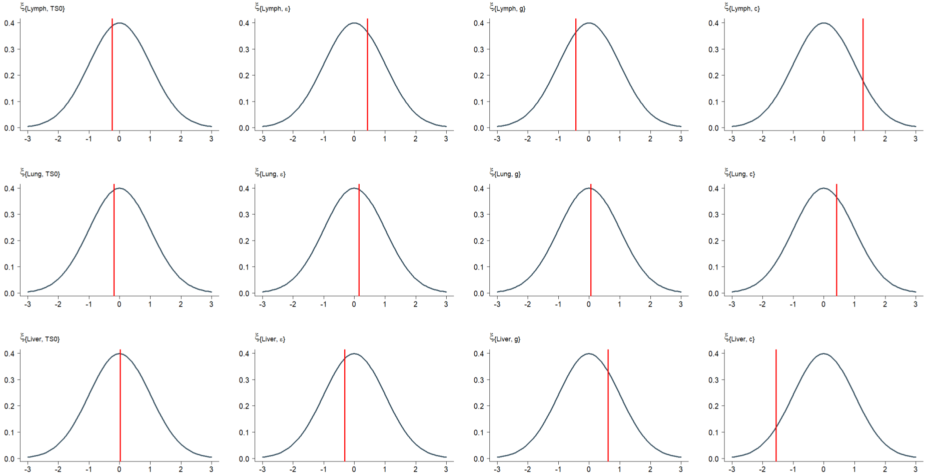
- Application of the model to:
  - Improving patient follow-up
  - Assisting in the development of therapeutic treatments

Priors for μ



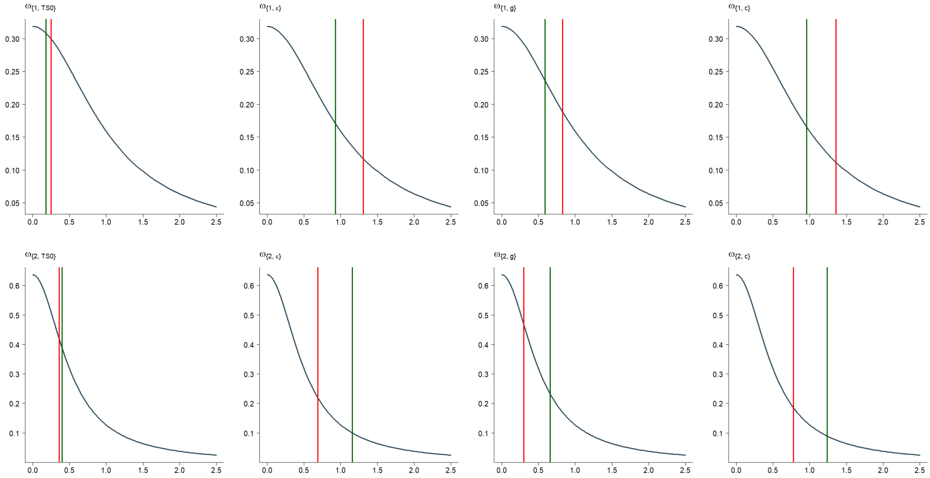
- $\mu_{TS0} \sim \mathcal{N}(25, 5)$
- $\mu_g \sim \Gamma(1, 100)$
- $\mu_\epsilon \sim \Gamma(1, 100)$
- $\mu_c \sim \Gamma(1, 1000)$

Priors for ξ



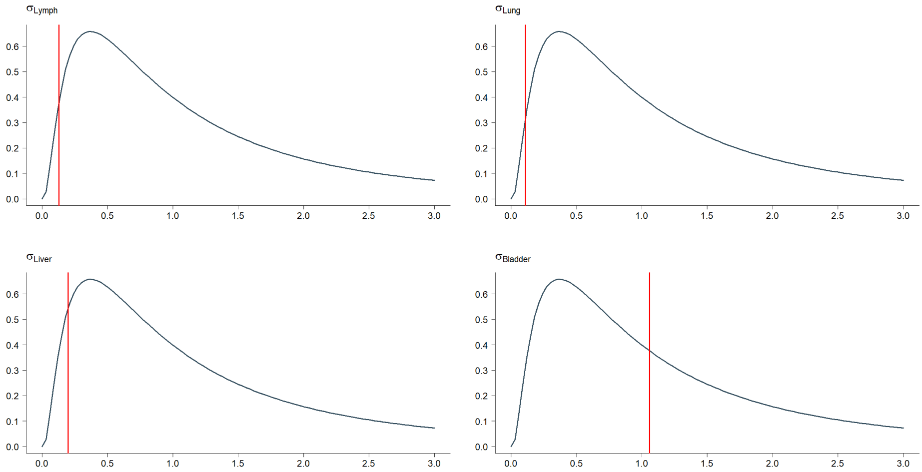
- $\xi_j \sim \mathcal{N}(0, 1)$

Priors for ω



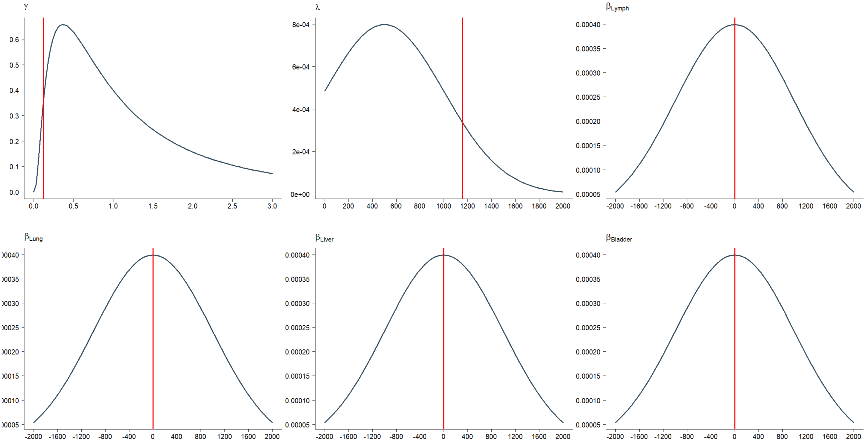
- $\omega_1 \sim Cauchy(0,1)^+$ et $\omega_2 \sim Cauchy(0,1)^+$

Priors for σ



- $\sigma_j \sim LN(0, 1)$

Priors for the parameters of the survival sub-model



- $\gamma \sim LN(0, 1)$
- $\lambda \sim \mathcal{N}(500, 500)^+$
- $\beta_j \sim \mathcal{N}(0, 1000)$

Credibility intervall at 95% for each data set of Scenario n°1 (β_{Lymph},β_{Lung},β_{Liver} and, $\beta_{Bladder}$)