Joint modelling for nonlinear longitudinal PSA kinetics and survival data in metastatic prostate cancer patients

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Lewis Sheiner Student Session · PAGE 2016 · Lisbon

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SANOFI

Clinical context: Prostate cancer

- Major public health issue in the world in 2012 [1]
  - 2^{nd} most frequently diagnosed cancer of men
  - 5^{th} leading cause of death from cancer in men

- In case of advanced disease and metastatic castration-resistant prostate cancer (mCRPC) patients, reference treatment is a chemotherapy: docetaxel associated to prednisone [2]

[1] Ferlay et al (2013) http://globocan.iarc.fr

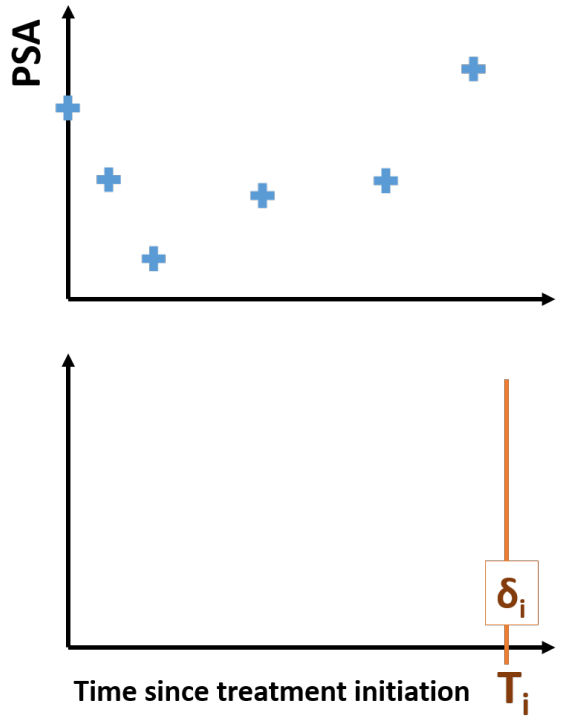
[2] Heidenreich et al (2014) EAU Guidelines on Prostate Cancer. Eur. Urol.

Methodological question

- Primary endpoint: survival

  For each patient i, $i = 1, ..., N$:

  - T_i: observed event time
  - δ_i: Event indicator
    $= \begin{cases} 1 & if\ death \\ 0 & if\ censored \end{cases}$
- Longitudinal measurements of Prostate-Specific Antigen (PSA)
  - y_i: vector of longitudinal measurements



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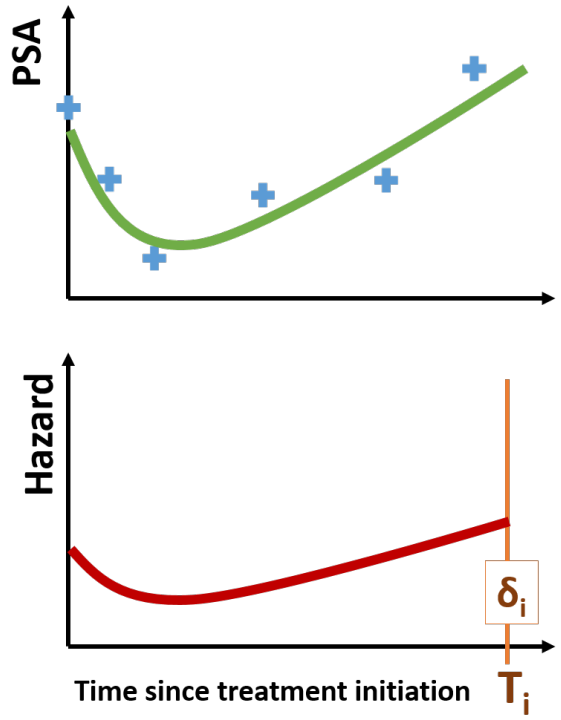

How can we make the best use of all available longitudinal PSA measurements for survival prediction ?

Model specification

➔ 2 submodels:

Longitudinal part: Nonlinear mixed-effect models (NLMEM)

$$y_i(t) = \log(PSA(t, \psi_i) + 1) + e_i(t)$$

- ψ_i: individual parameters
- $e_i(t)$: residual error

Survival part: Hazard function for patient i:

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

- Baseline hazard function $h_0(t)$
- Link function f depends on individual longitudinal parameters ψ_i

Estimation methods

- Two-stage approach (sequential approach)
  1. Estimation of the longitudinal parameters using the NLMEM
     Computation of the individual Empirical Bayes Estimates (EBEs)
  2. Estimation of the survival parameters using EBEs as regressors in the survival model

[3] Rizopoulos et al (2009) J. R. Stat. Soc.
[4] Holford (2005) PAGE poster
[5] Mbogning et al. (2015) JSCS

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- Joint approach: **Simultaneous** estimation of the longitudinal and survival parameters by maximization of the joint likelihood [3]
  - In the NLMEM framework
    - Laplacian approximation of Nonmem [4]
    - SAEM algorithm of Monolix: recently extended to joint models [5]

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- Joint sequential approach
  1. Estimation of the longitudinal parameters using the NLMEM
  2. Estimation of the survival parameters using the joint likelihood fixing longitudinal population parameters to the values obtained at step 1.
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Methods: Simulation design

Longitudinal part: $M = 100$ simulated datasets of PSA measured every 3 weeks in $N = 500$ patients

➔ NLMEM for PSA kinetics

- Structural model described by a biexponential function
  ➔ 4 parameters with random effects
- Constant error model on the logarithm of PSA+1

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Survival part: $h_i(t|\psi_i) = h_0(t)\exp(\beta PSA(t, \psi_i))$

- Weibull baseline hazard function $h_0(t) = \frac{k}{\lambda}(\frac{t}{\lambda})^{k-1}$
- β: strength of the link between predicted PSA and risk of death

  ➔ Simulation of 3 scenarios with increasingly high link

  - No link: $\beta = 0$
  - Low link: $\beta = 0.005$
  - High link: $\beta = 0.02$

Methods: Parameter estimation and evaluation criteria

Using the SAEM algorithm of Monolix 4.2.2

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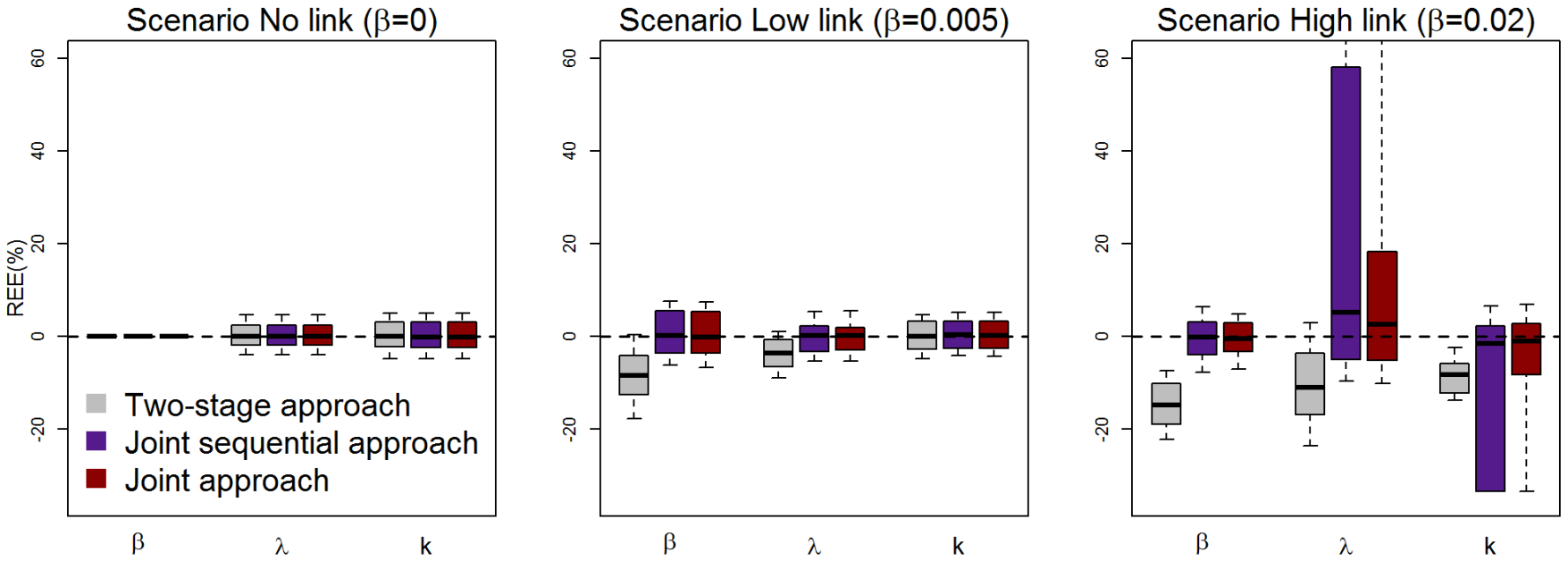
For the 3 approaches, for each dataset m and for each population parameter θ:

- Relative estimation errors: $REE(\hat{\theta}_m) = \frac{\hat{\theta}_m - \theta^*}{\theta^*} \times 100$
  - θ^* true parameter value
  - $\hat{\theta}_m$ estimates in the dataset m

Main results

Survival parameters



- Two-stage approach ➟ Increasing bias when β increased
- Joint sequential approach ➟ Limit biases on survival parameters
- Joint approach ➟ Unbiased estimates in all scenarios

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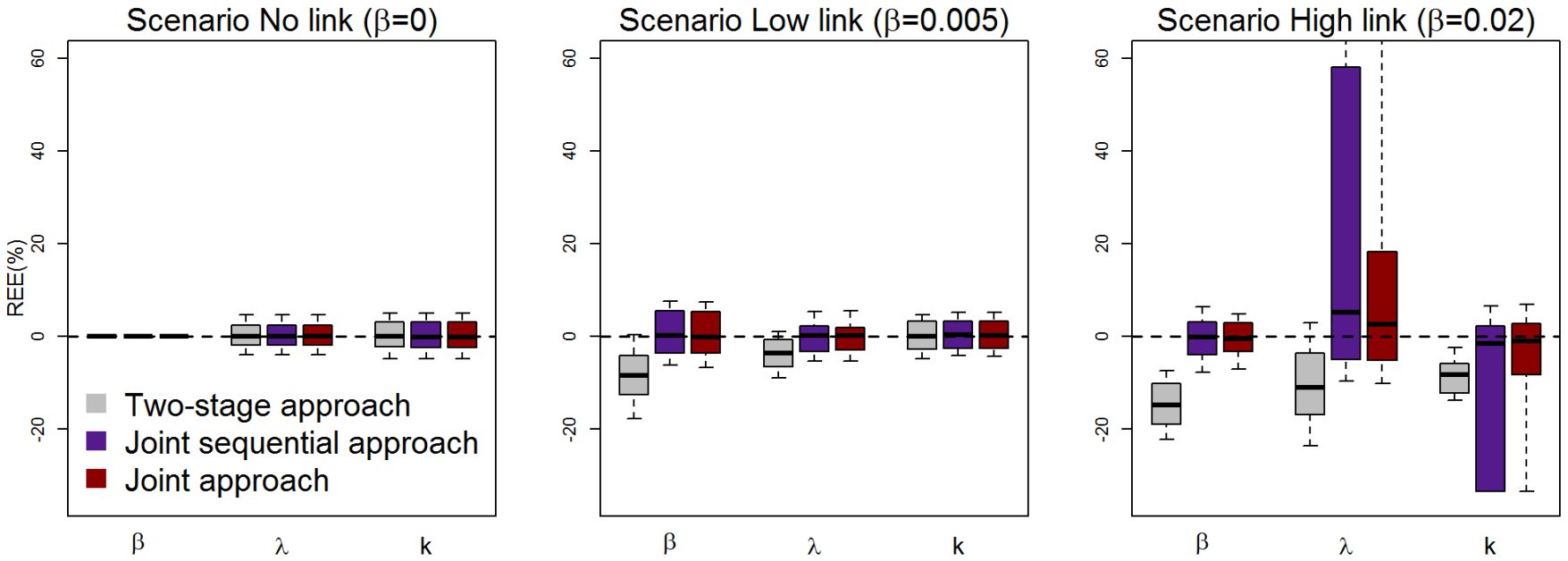

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➔ Joint modelling provides precise estimates for both longitudinal (not shown) and survival parameters in a NLMEM framework

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Research Article

Nonlinear Mixed-Effect Models for Prostate-Specific Antigen Kinetics and Link with Survival in the Context of Metastatic Prostate Cancer: a Comparison by Simulation of Two-Stage and Joint Approaches

Solène Desmée,[1,2,4] France Mentré,[1,2] Christine Veyrat-Follet,[3] and Jérémie Guedj[1,2]

Objectives

1. Compare by simulations the 3 estimation methods using the SAEM algorithm
2. Develop a mechanistic joint model to characterize the relationship between PSA kinetics and survival
3. Provide individual dynamic predictions and assess the predictive performances

Data

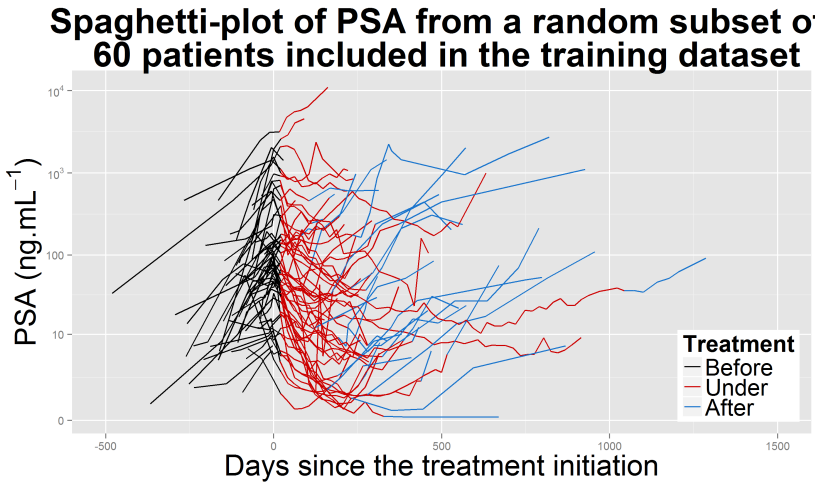
596 mCRPC patients from the control arm of a phase 3 clinical trial treated with the standard first-line chemotherapy: docetaxel every 3 weeks and oral prednisone [6]

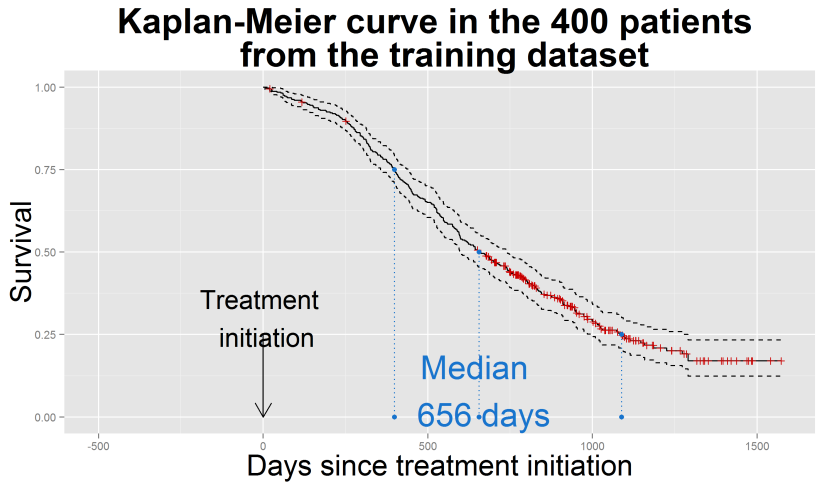
- A training dataset of 400 randomly selected patients

  ➔ Development of a mechanistic joint model

- A validation dataset of the 196 remaining patients

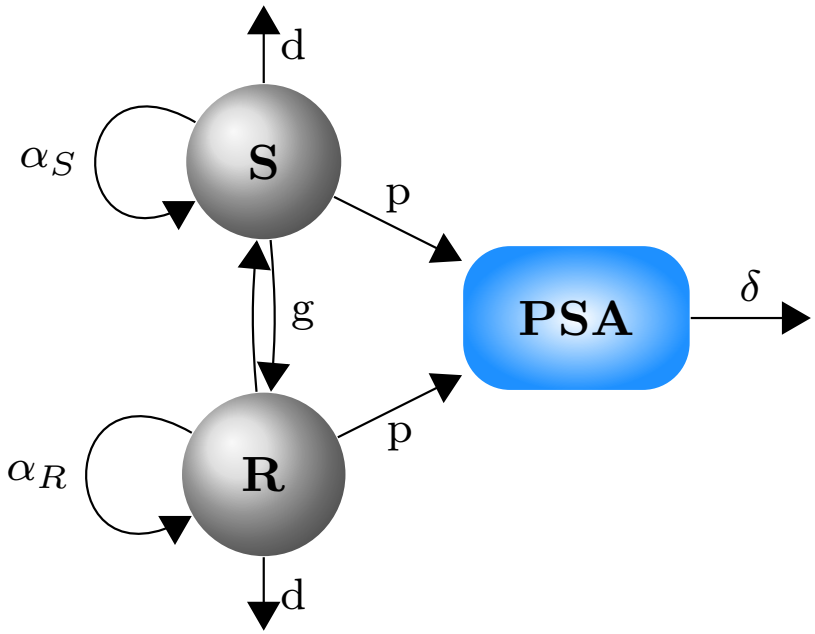
  ➔ Individual dynamic prediction





[6] Tannock et al. (2013) Lancet Oncol.

Mechanistic model for PSA kinetics



PSA is produced by 2 types of cells [7]:

- Sensitive cells (S)
- Resistant cells (R)

$$\begin{cases} \frac{dS}{dt} = \alpha_S(1 - \frac{S+R}{N_{max}})S + g(R-S) - dS \\ \frac{dR}{dt} = \alpha_R(1 - \frac{S+R}{N_{max}})R + g(S-R) - dR \\ \frac{dPSA}{dt} = pS + pR - \delta PSA \end{cases}$$

[7] Seruga et al (2011) Nat. Rev. Clin. Oncol.

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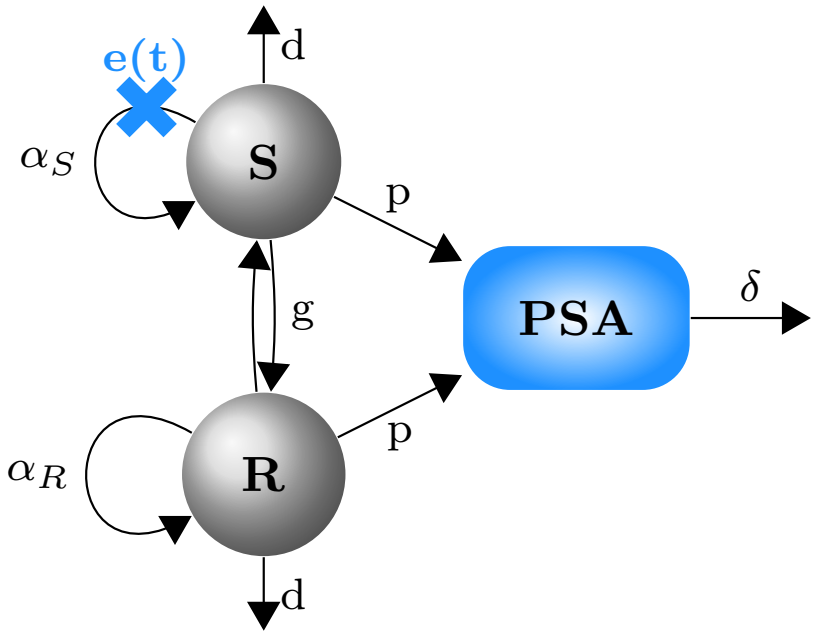

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Treatment initiation at time t=0
➔ Inhibition of the proliferation of S

$$e(t) = \begin{cases} 0 & if\ t \leqslant 0 \\ \varepsilon & if\ t > 0 \end{cases}$$

$$\begin{cases} \frac{dS}{dt} = \alpha_S(1 - e(t))(1 - \frac{S+R}{N_{max}})S + g(R - S) - dS \\ \frac{dR}{dt} = \alpha_R(1 - \frac{S+R}{N_{max}})R + g(S - R) - dR \\ \frac{dPSA}{dt} = pS + pR - \delta PSA \end{cases}$$

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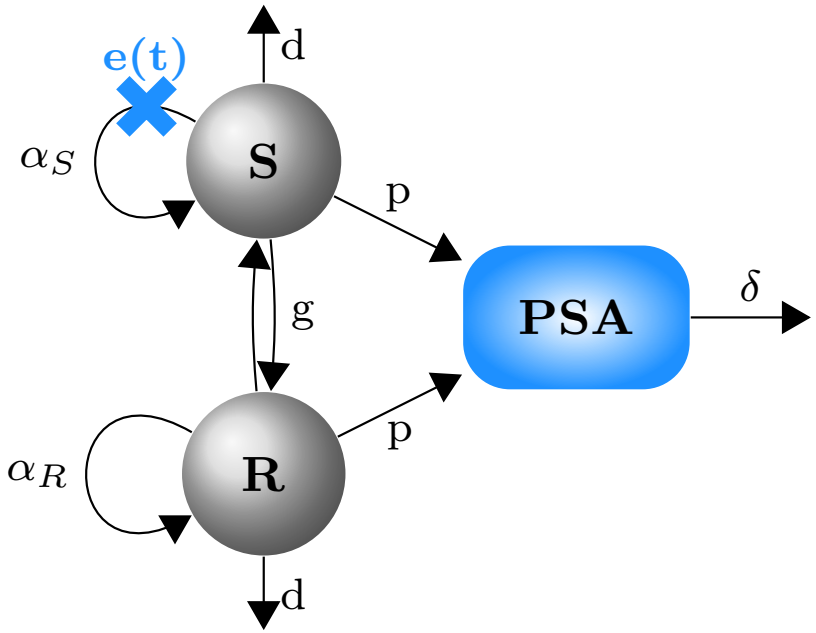

For the sake of identifiability

- δ, p and g fixed

Initial conditions:
At baseline = time of first PSA measurement

- PSA_b
- $S_b = \frac{\delta}{p} PSA_b$
- $R_b = \frac{g}{d - RF \times (g+d)} \times \frac{\delta}{p} PSA_b$

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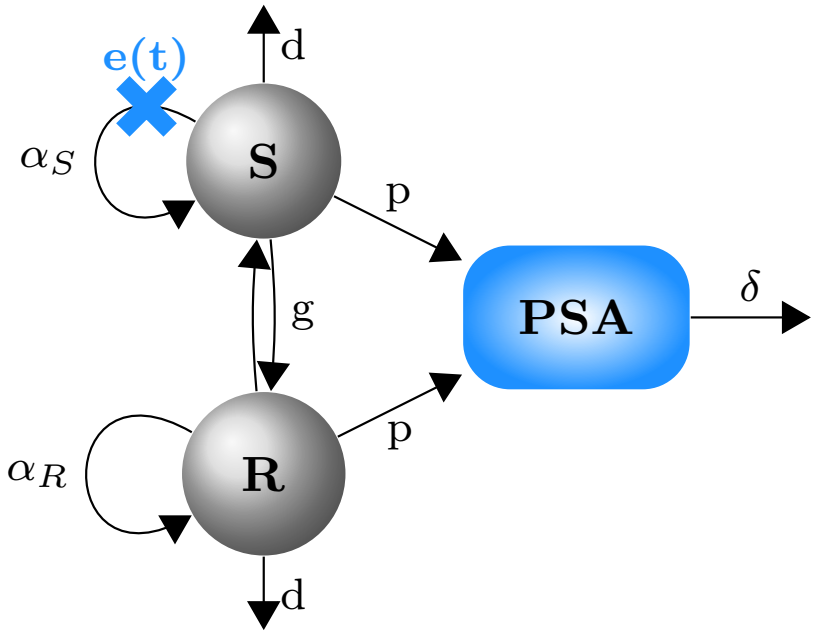

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$\rightarrow$ 6 model parameters with random effects:

α_S, $RF = \frac{\alpha_R}{\alpha_S}$, $RE = \frac{d}{\alpha_R}$, ε, PSA_b, N_{max}

$$\begin{cases} \frac{dS}{dt} = \alpha_S(1 - e(t))(1 - \frac{S+R}{N_{max}})S + g(R - S) - dS \\ \frac{dR}{dt} = \alpha_R(1 - \frac{S+R}{N_{max}})R + g(S - R) - dR \\ \frac{dPSA}{dt} = pS + pR - \delta PSA \end{cases}$$

Comparison of different link functions

Survival part: Hazard function for patient i:

$$h_i(t|PSA(t,\psi_i)) = h_0(t)\exp(f(t,\psi_i)) \qquad \text{for } t \geqslant 0$$

- Weibull baseline hazard function $h_0(t)$
- Link function f depends on PSA kinetics of patient i

➠ Selection by BIC

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  - Area under PSA: $f = \beta \int_0^t \log(PSA(u,\psi_i) + 1)du$

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  - Area under PSA: $f = \beta \int_0^t \log(PSA(u,\psi_i) + 1)du$
  - S+R: $f = \beta \log(S(t,\psi_i)) + \beta' \log(R(t,\psi_i))$

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Results: Model selection

BIC and parameters estimates (r.s.e.(%)) of PSA kinetics and survival in the 400 patients of the training dataset

	No link	Initial PSA	PSA	PSA slope	Area under PSA	S+R
BIC	14598	14582	14446	14581	14575	14421
α_S	0.066 (3)	0.060 (3)	0.078 (3)	0.078 (3)	0.061 (3)	0.067 (3)
RF	0.9997 (0)	0.9996 (0)	0.9998 (0)	0.9998 (0)	0.9997 (0)	0.9998 (0)
RE	0.81 (1)	0.79 (1)	0.84 (1)	0.84 (0)	0.79 (1)	0.82 (1)
ε	0.42 (4)	0.46 (4)	0.35 (4)	0.35 (5)	0.47 (4)	0.43 (3)
PSA_b	22.2 (8)	22.2 (8)	22.0 (8)	22.5 (8)	22.2 (8)	21.9 (8)
N_{max}	56 (4)	57 (4)	81 (4)	77 (4)	57 (4)	120 (4)
λ	885 (4)	1615 (8)	4259 (15)	920 (4)	1435 (7)	906 (7)
k	1.52 (5)	1.53 (3)	1.28 (2)	1.48 (2)	1.19 (2)	1 (-)
β	-	0.21 (12)	0.40 (7)	17 (17)	0.00023 (8)	0.00032 (21)
β'	-	-	-	-	-	0.39 (7)

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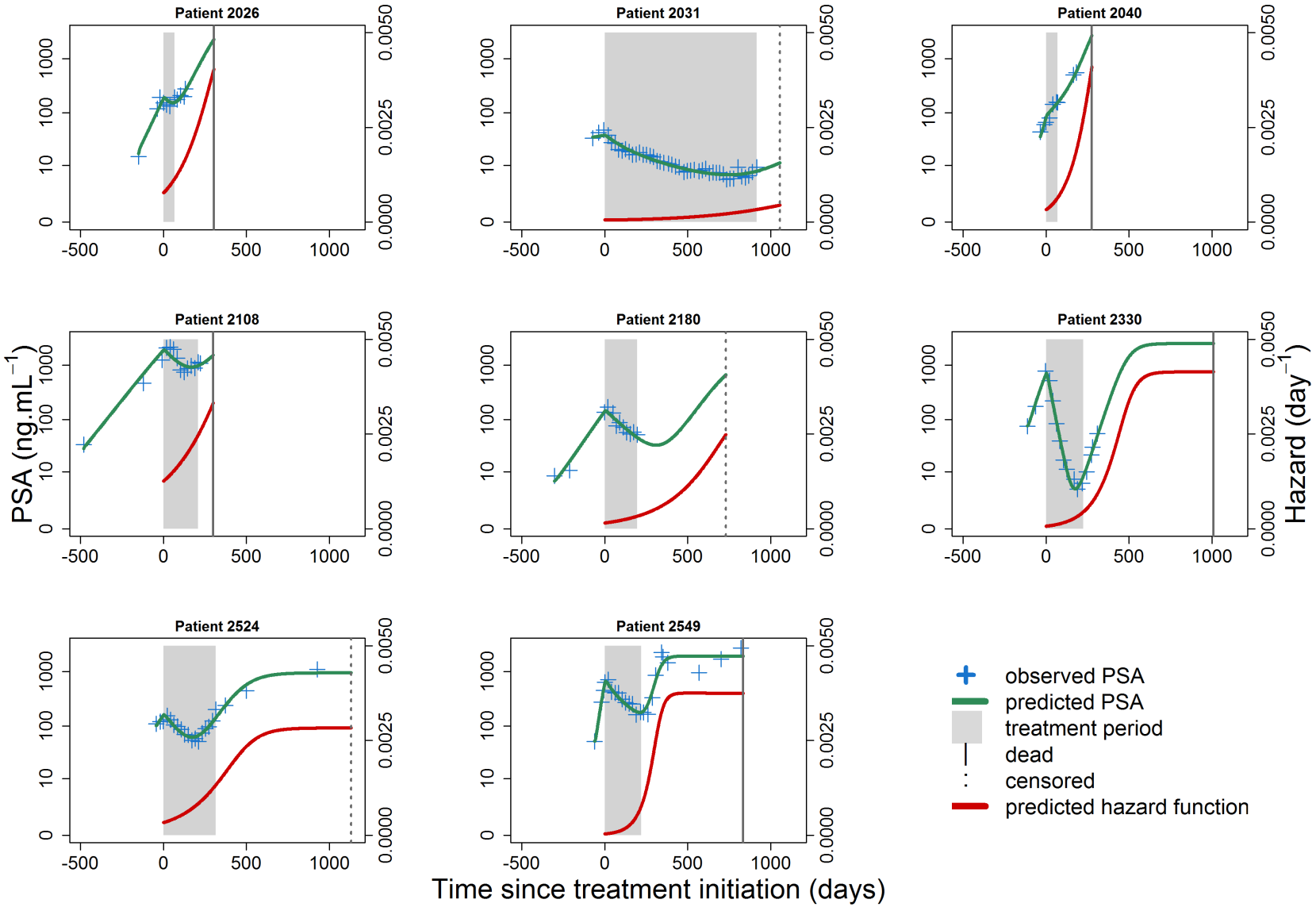
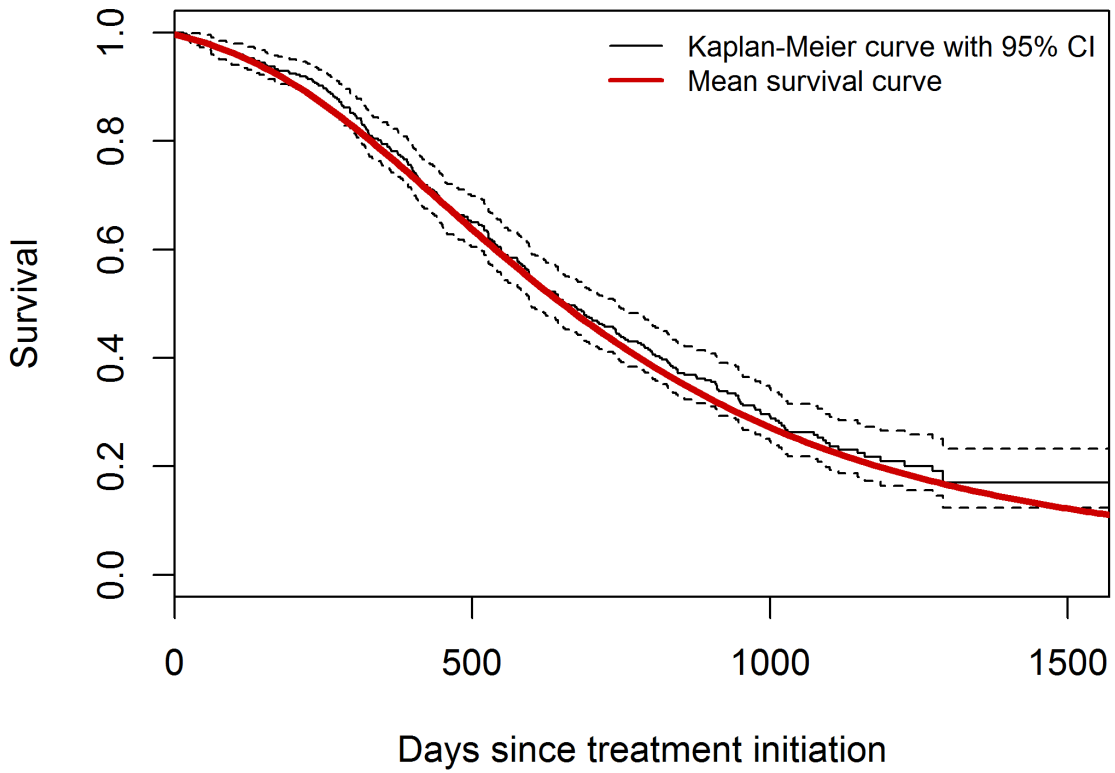
➟ **S+R model**: $f(t, \psi_i) = \beta \log(S(t, \psi_i)) + \beta' \log(R(t, \psi_i))$ with a constant baseline hazard function ($k = 1$) provided the smaller BIC

Individual fits of PSA and hazard functions



Mean survival curve

Mean survival function $= \frac{1}{N}\sum_{i=1}^{N} S_i(t|\hat{\psi}_i, \hat{\theta})$
obtained using the individual EBEs $\hat{\psi}_i$ estimated using only the PSA measurements and the final joint model



Biometrics DOI: 10.1111/biom.12537

Using the SAEM Algorithm for Mechanistic Joint Models Characterizing the Relationship between Nonlinear PSA Kinetics and Survival in Prostate Cancer Patients

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Assumption: *true* nonlinear joint model

➔ *Population parameters θ used as priors*

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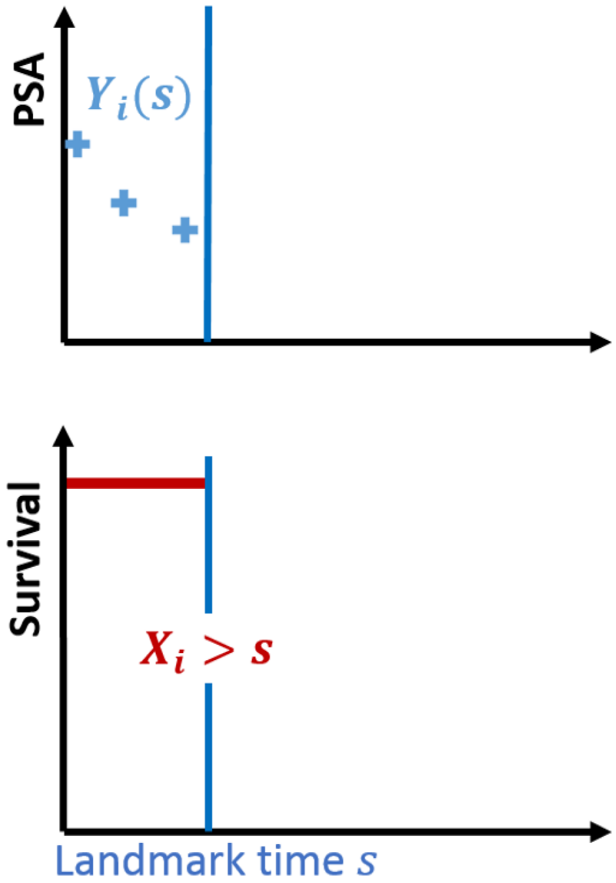

Methods for individual dynamic prediction

➔ Predict $S_i(s+t|s) = \mathbb{P}(X_i > s+t | X_i > s, \mathcal{Y}_i(s))$ the conditional survival probability up to the prediction horizon $s+t$ with $t > 0$

Assumption: *true* nonlinear joint model

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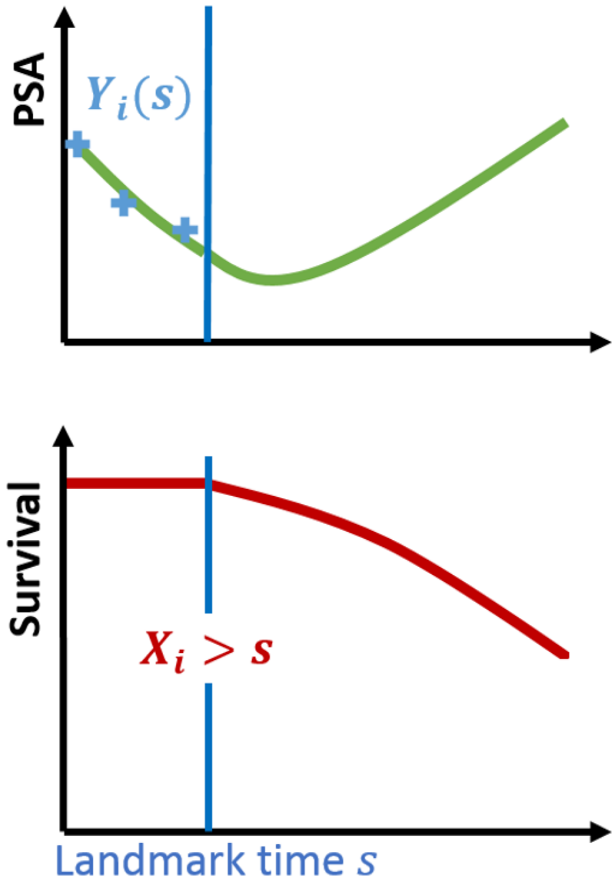

[8] Rizopoulos, CRC press (2012)

[9] Stan development team, Version 2.8.0 (2015)

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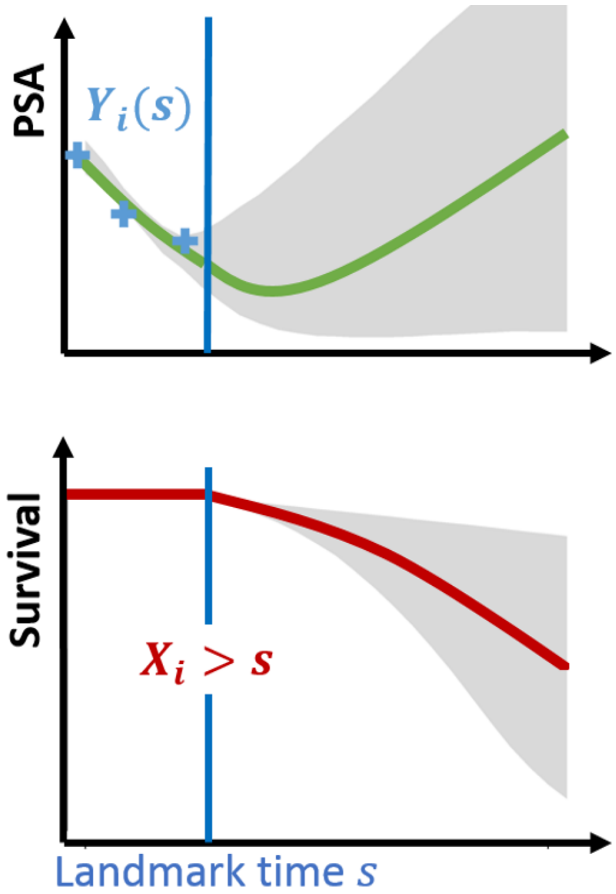
For $\ell = 1, ..., L$[8]:

1. Draw in the *a posteriori* distribution of the individual parameters $\psi_i^{(\ell)} \sim \{\psi_i | X_i > s, \mathcal{Y}_i(s), \theta\}$ using STAN software[9]
2. Compute $S_i^{(\ell)}(s+t|s)$



[8] Rizopoulos, CRC press (2012)

[9] Stan development team, Version 2.8.0 (2015)

Methods for individual dynamic prediction

➔ Predict $S_i(s+t|s) = \mathbb{P}(X_i > s+t | X_i > s, \mathcal{Y}_i(s))$ the conditional survival probability up to the prediction horizon $s+t$ with $t > 0$

Assumption: *true* nonlinear joint model

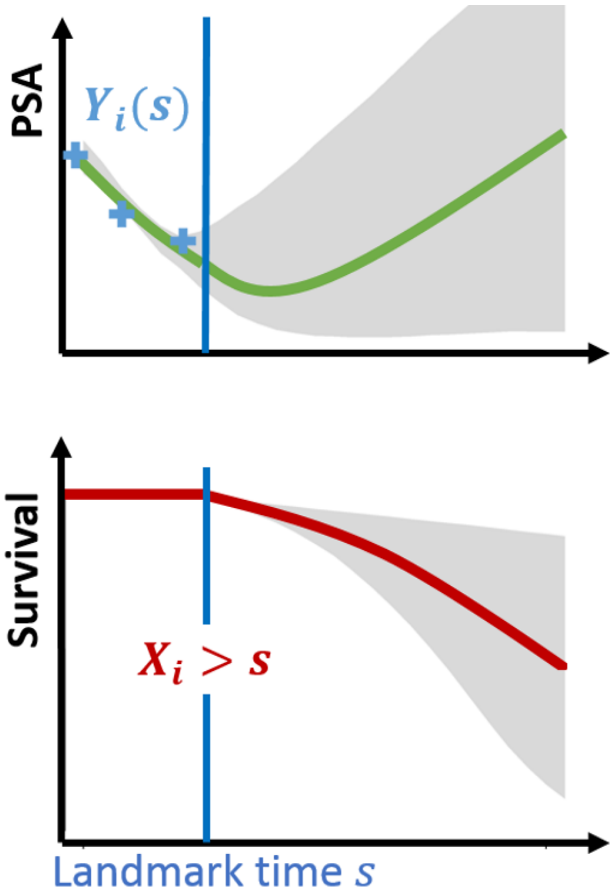
➔ *Population parameters* θ *used as priors*

For $\ell = 1, ..., L$[8]:

1. Draw in the *a posteriori* distribution of the individual parameters $\psi_i^{(\ell)} \sim \{\psi_i | X_i > s, \mathcal{Y}_i(s), \theta\}$ using STAN software[9]
2. Compute $S_i^{(\ell)}(s+t|s)$

➔ $\hat{S}_i(s+t|s) = median\{S_i^{(\ell)}(s+t|s)\}_{\ell=1,...,L}$

+ percentiles for 95% prediction interval



[8] Rizopoulos, CRC press (2012)

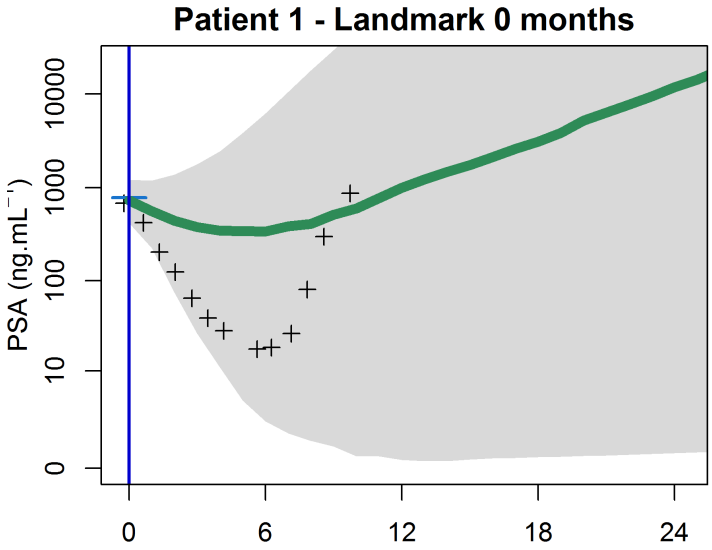
[9] Stan development team, Version 2.8.0 (2015)

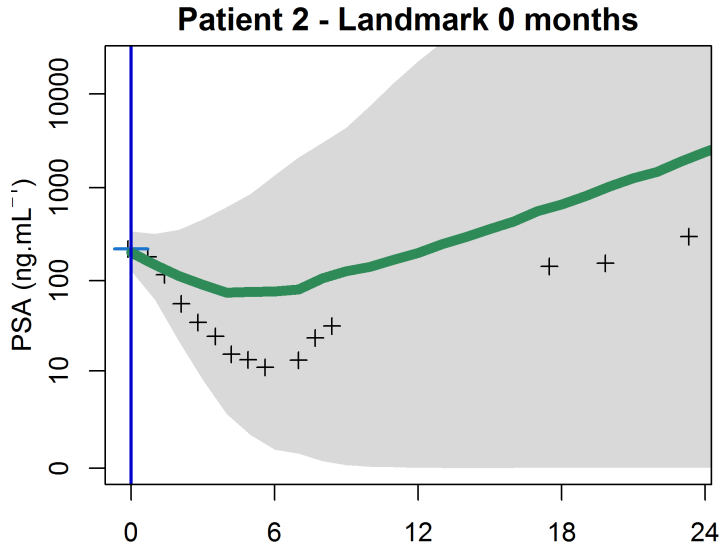
Methods

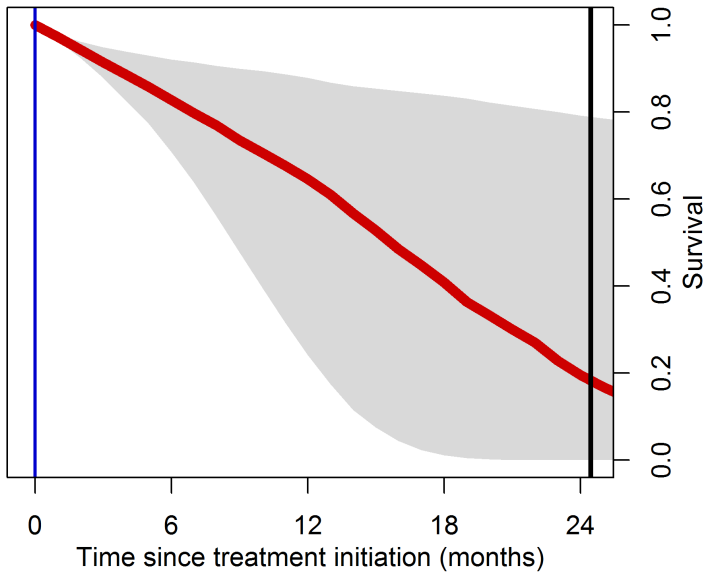
- Nonlinear joint model
  - Longitudinal part: Structural model described by a biexponential function
  - Survival part: Link between the current PSA value and risk of death
- Estimation of the population parameters θ
  - Using Monolix
  - In the training dataset
- Individual dynamic predictions
  - In the 196 patients of the validation dataset
  - For landmark times $s = \{0, 6, 12, 18\}$ months

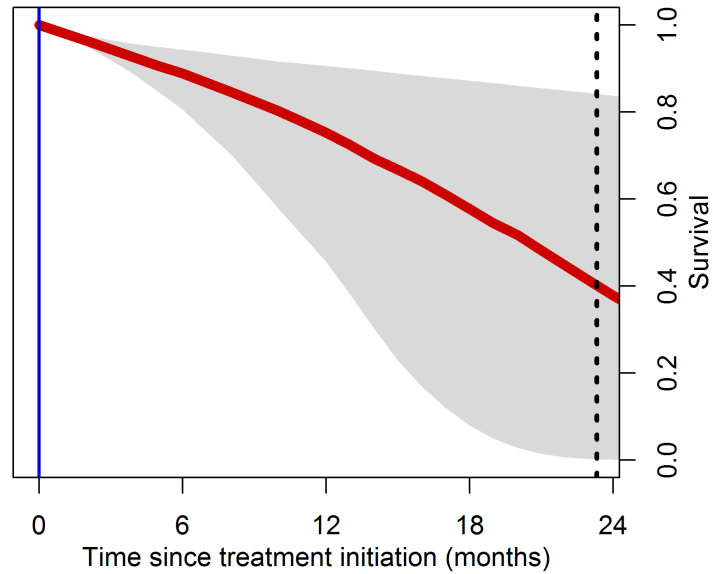
Dynamic predictions for 2 patients

Patient 1 died after 24 months - Patient 2 was censored after 24 months









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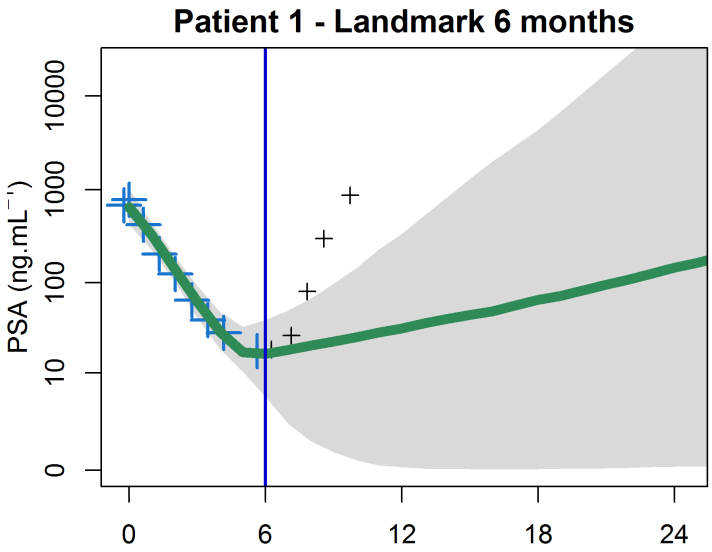

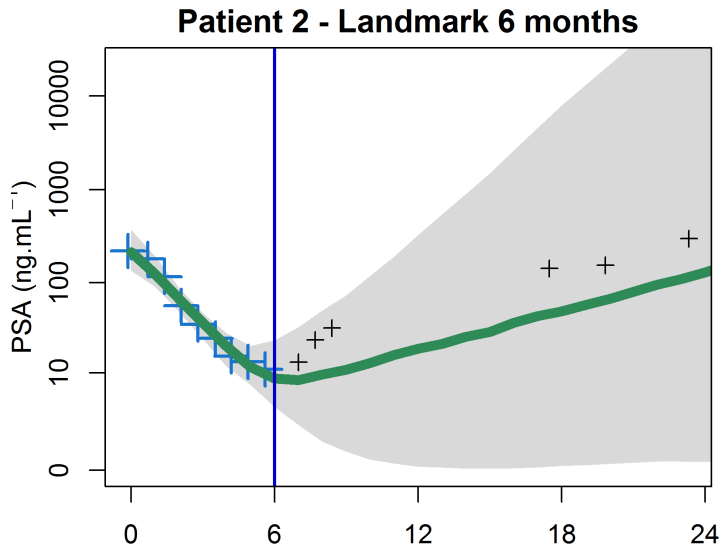

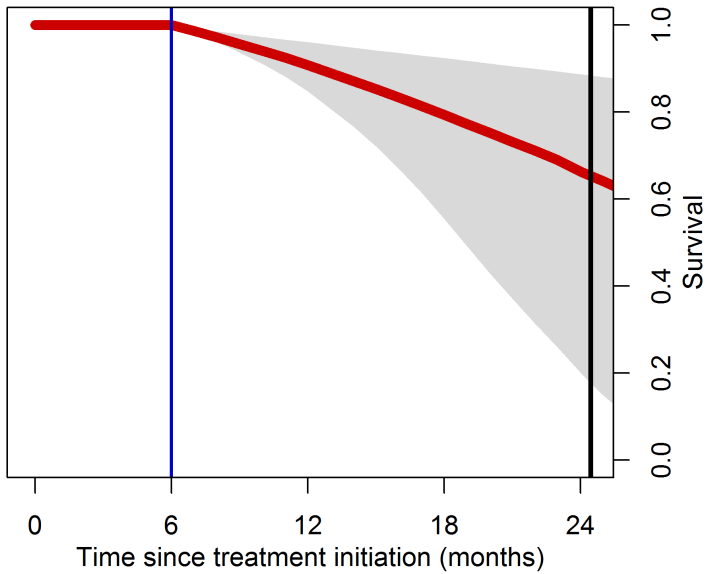

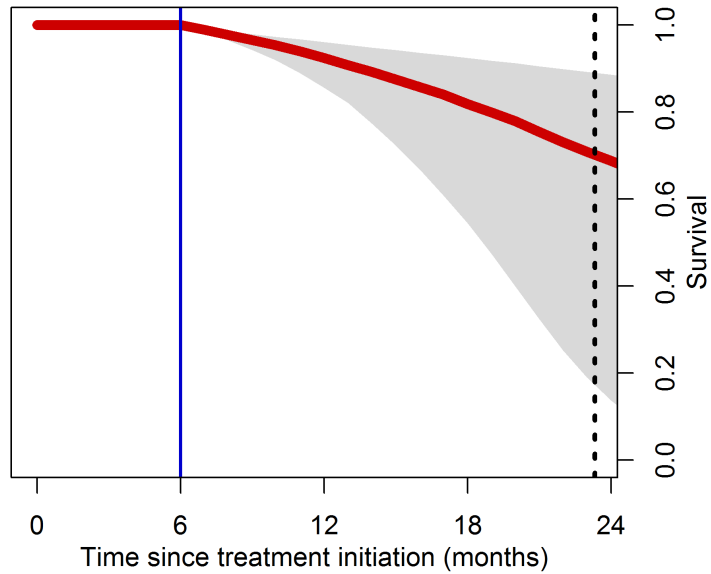

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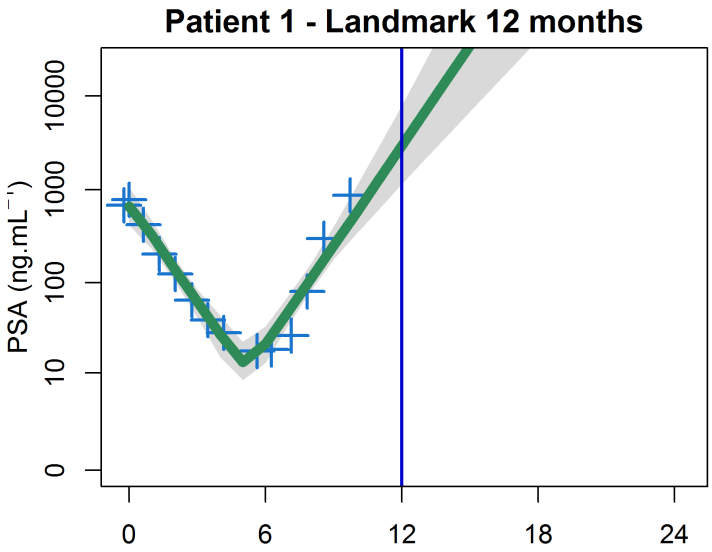

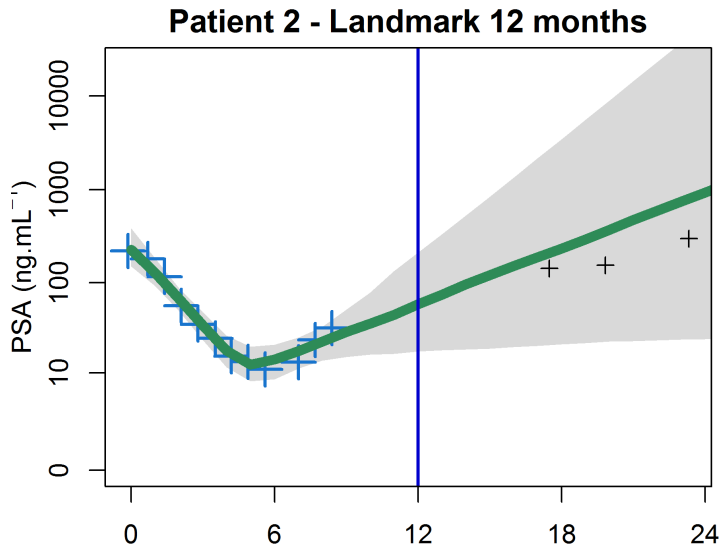

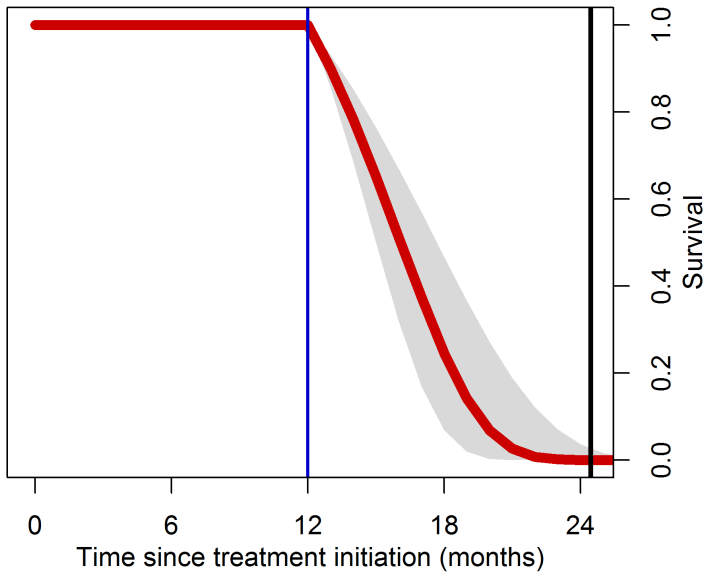

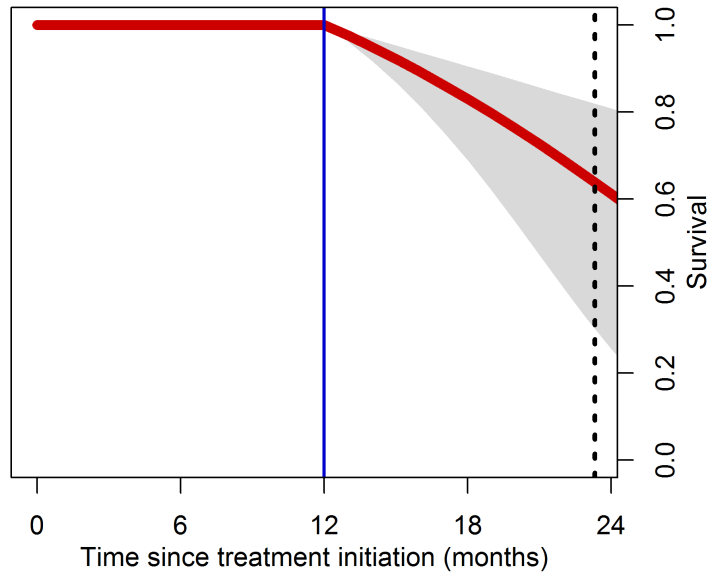

Dynamic predictions for 2 patients

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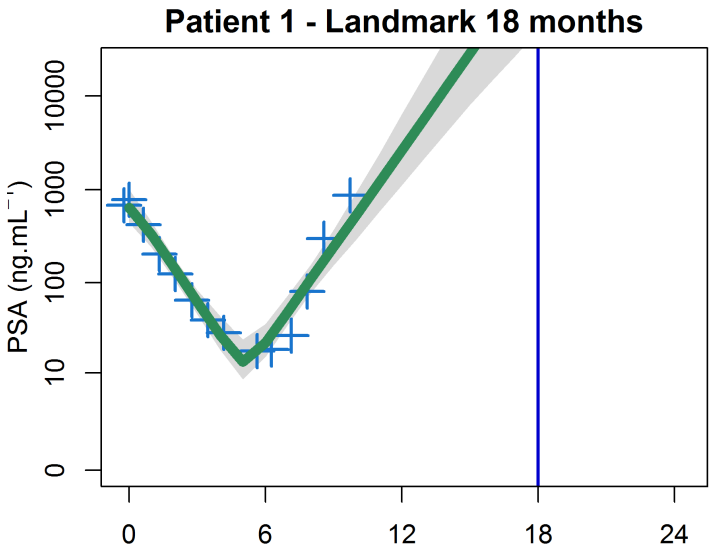
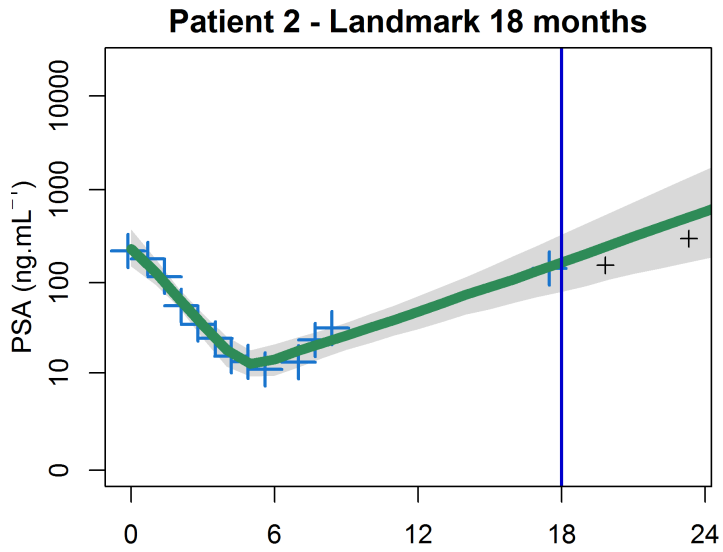
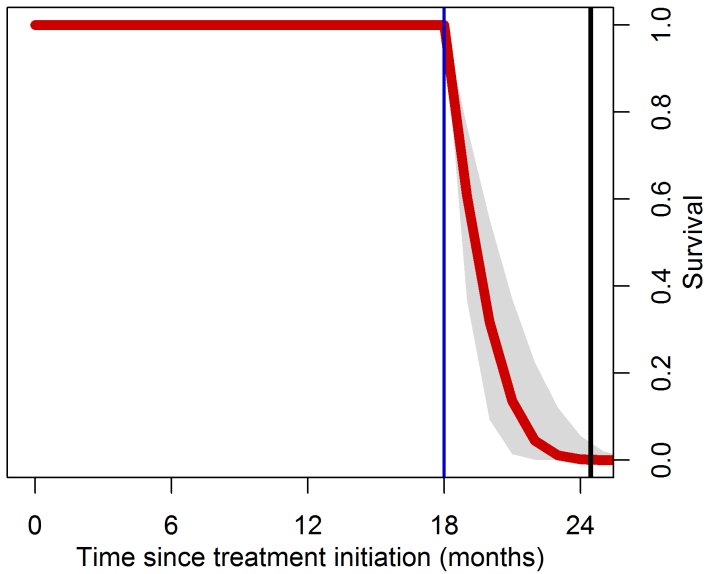
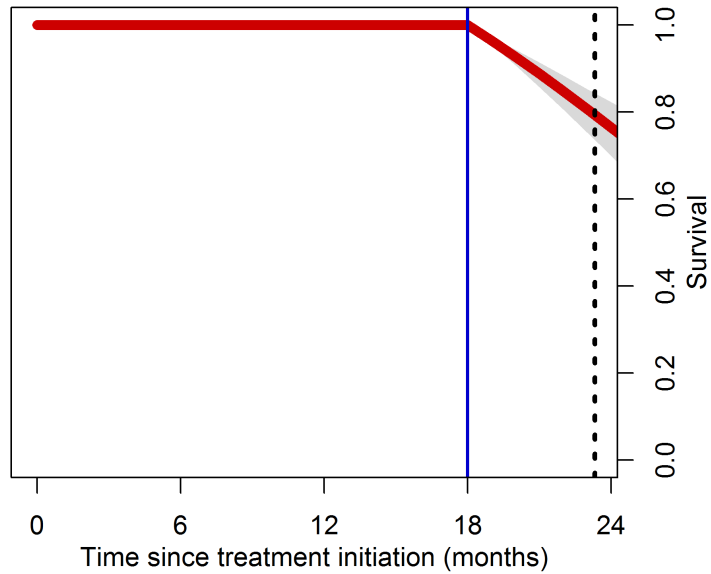








Discrimination and calibration metrics

Discrimination: ability of the model to distinguish patients of low and high risk of death

Calibration: ability of the model to predict future events

Discrimination and calibration metrics

Discrimination: ability of the model to distinguish patients of low and high risk of death

➠ **Area under the ROC curve** (AUC)

$AUC(s,t) =$
$\mathbb{P}(S_i(s+t|s) < S_j(s+t|s) | \mathbf{1}_{\{X_i<s+t\}} = 1, \mathbf{1}_{\{X_j<s+t\}} = 0, X_i > s, X_j > s)$

The higher the better

Calibration: ability of the model to predict future events

Discrimination and calibration metrics

Discrimination: ability of the model to distinguish patients of low and high risk of death

➠ **Area under the ROC curve** (AUC)

$$AUC(s,t) = \mathbb{P}(S_i(s+t|s) < S_j(s+t|s) | \mathbf{1}_{\{X_i<s+t\}} = 1, \mathbf{1}_{\{X_j<s+t\}} = 0, X_i > s, X_j > s)$$

The higher the better

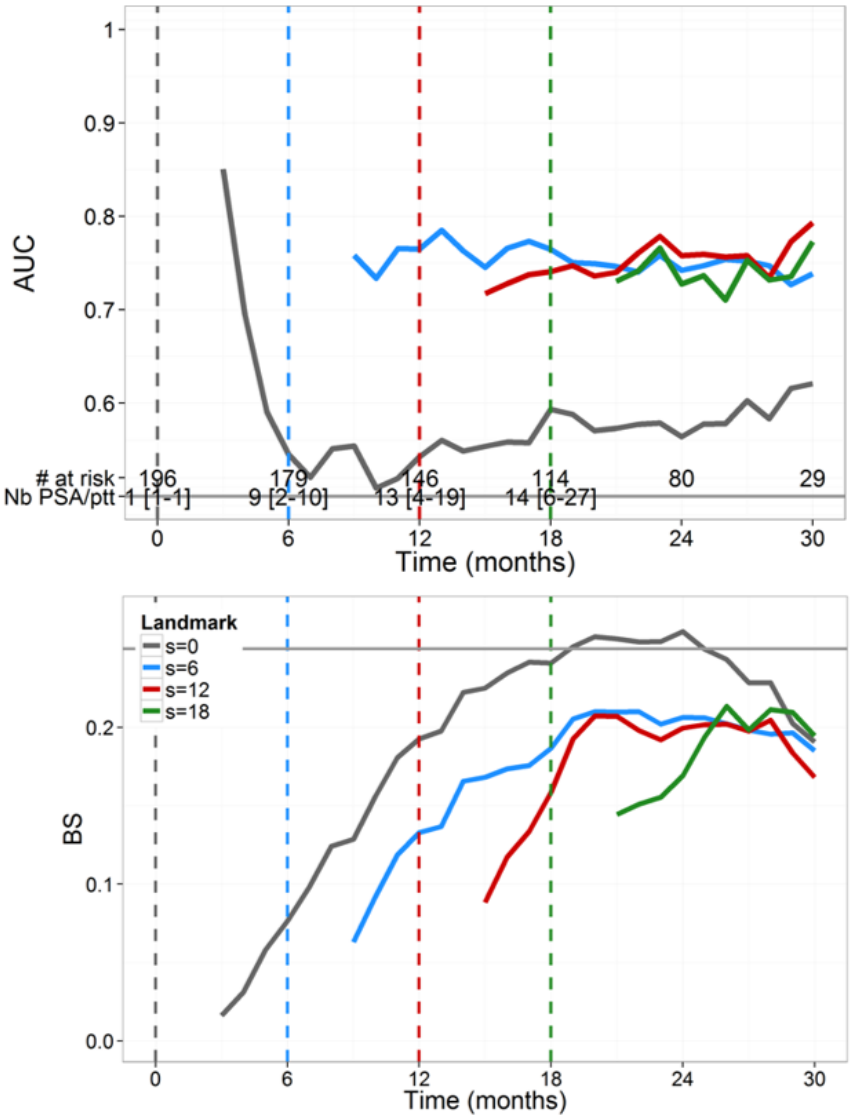
Calibration: ability of the model to predict future events

➠ **Brier score** (BS)

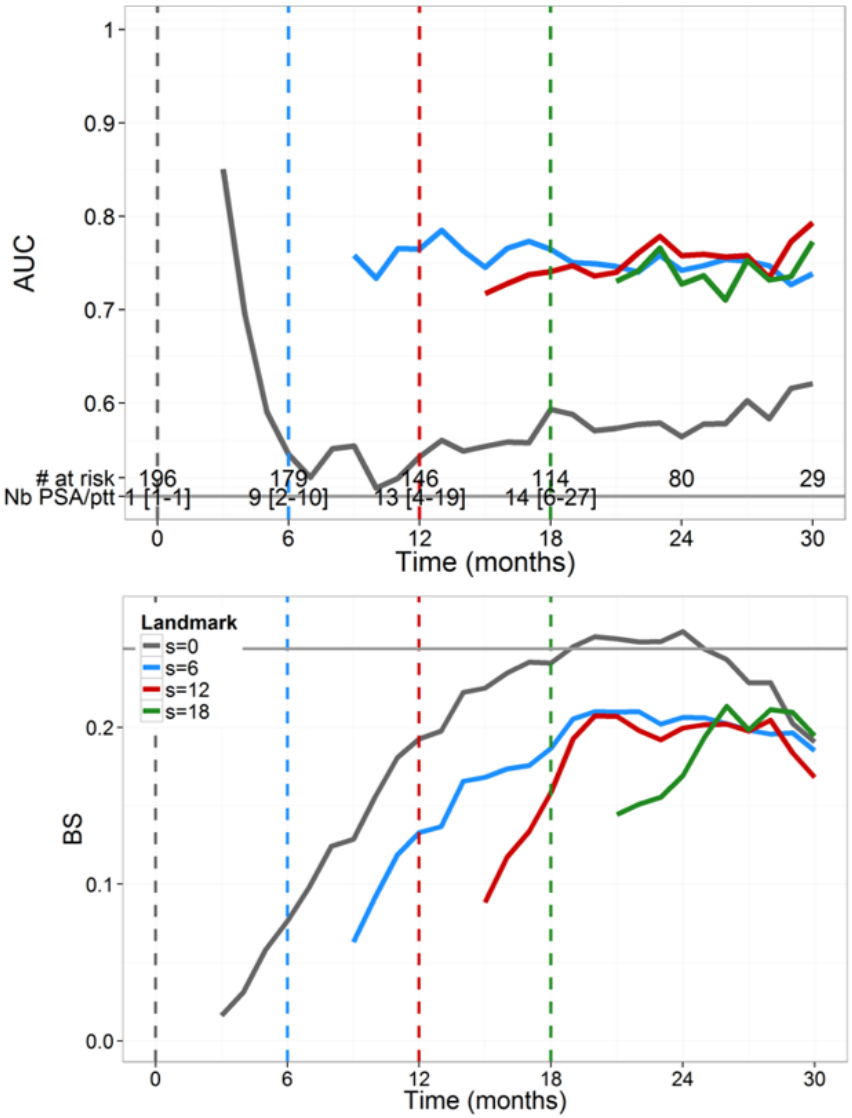
$$BS(s,t) = \mathbb{E}[(\mathbf{1}_{\{X>s+t\}} - S(s+t|s))^2 | X > s]$$

The lower the better

Time-dependent AUC and Brier score

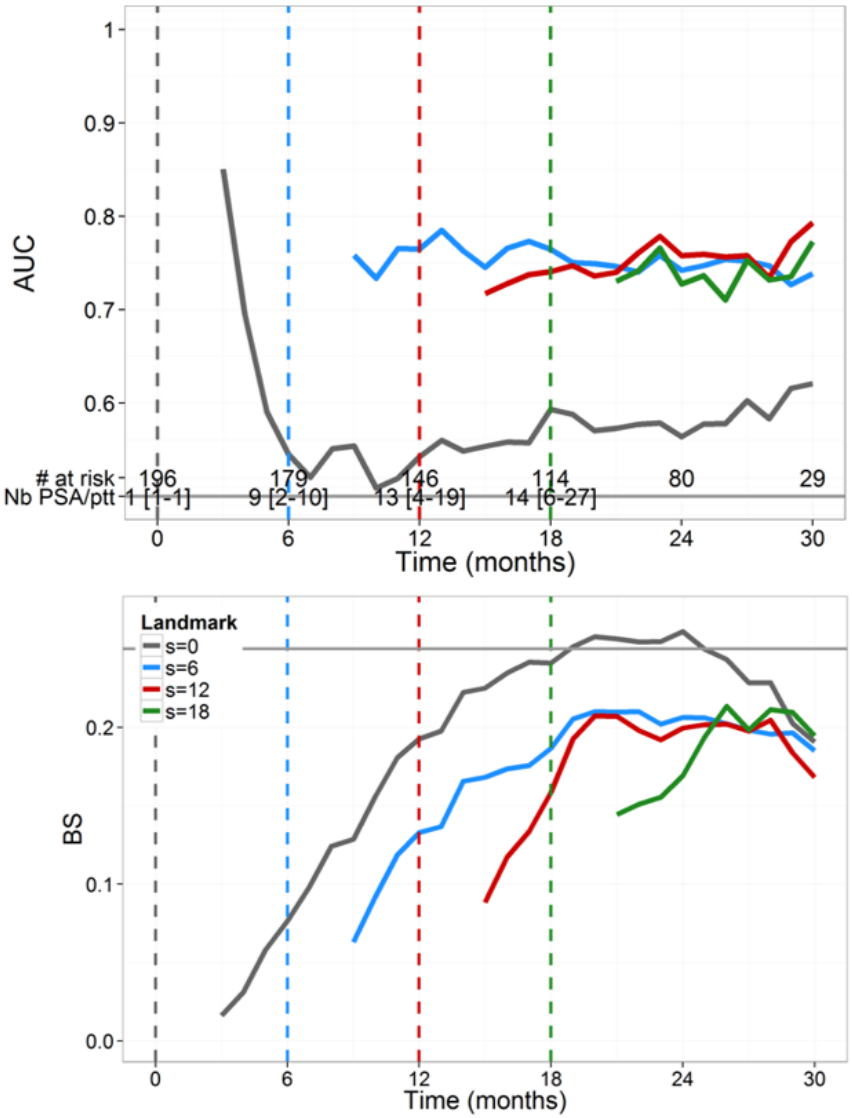


Time-dependent AUC and Brier score



- Metrics improve when s increase

Time-dependent AUC and Brier score



- Metrics improve when s increase
- Here, $s = 12$ months provides the best tradeoff between
  - Follow-up duration
  - Prediction accuracy
    - $AUC(12, t) \simeq 0.75 \ \forall t$
    - $BS(12, t) \leqslant 0.21 \ \forall t$

Conclusions

Nonlinear joint modelling

- Unbiased parameter estimations using SAEM algorithm [10]
- Characterization of the relationship between biomarker kinetics and survival [11]
- Individual dynamic predictions

➠ To develop more complex and physiological joint models
  - Several longitudinal biomarkers ➔ based on differential equations

➠ To apply these approaches and evaluate their benefit in clinical context for decision making

[10] Desmée S, Mentré F, Veyrat-Follet C, Guedj J (2015) *The AAPS Journal*

[11] Desmée S, Mentré F, Veyrat-Follet C, Sébastien B, Guedj J (2016) *Biometrics*

Thank you for your attention !

Acknowledgements

IAME team

Sanofi R & D

PAGE committee

Back-up

Estimation method: The joint approach

Simultaneous estimation of the longitudinal and survival parameters by maximization of the joint likelihood [12]

Joint log-likelihood for a patient i:

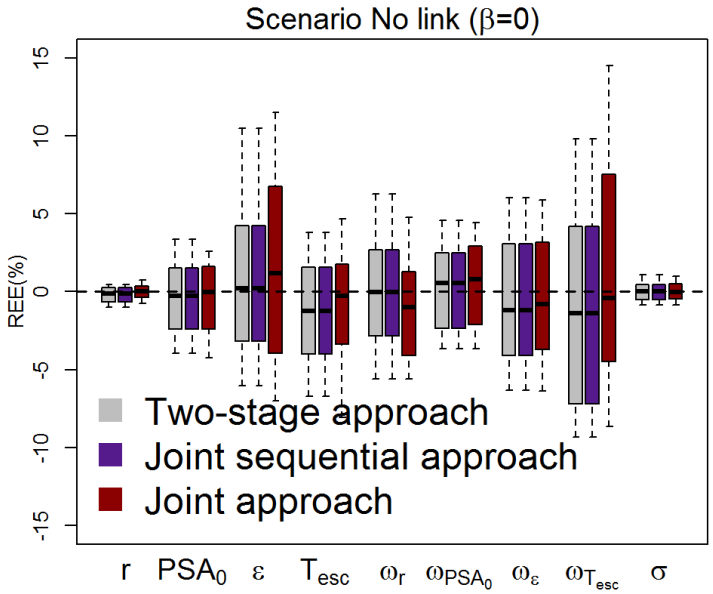
$$LL_i(\theta) = \log \int p(y_i|\eta_i;\theta)\{h_i(T_i|\eta_i;\theta)^{\delta_i} S_i(T_i|\eta_i;\theta)\}p(\eta_i;\theta)d\eta_i$$

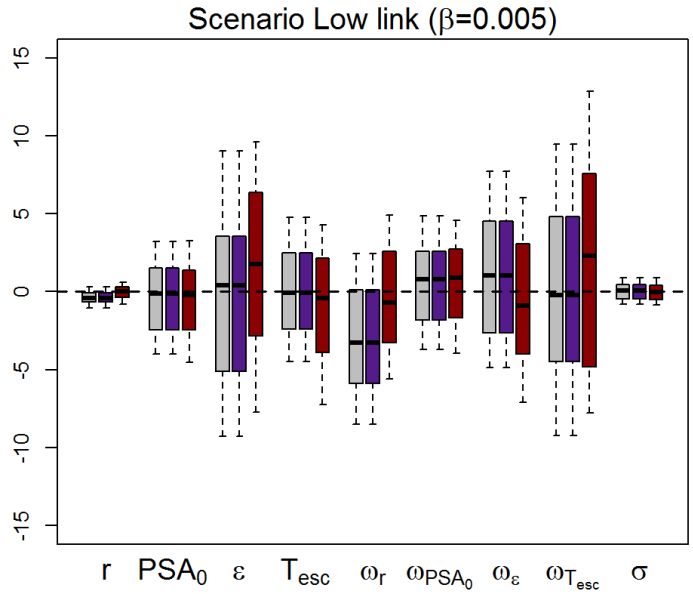
where

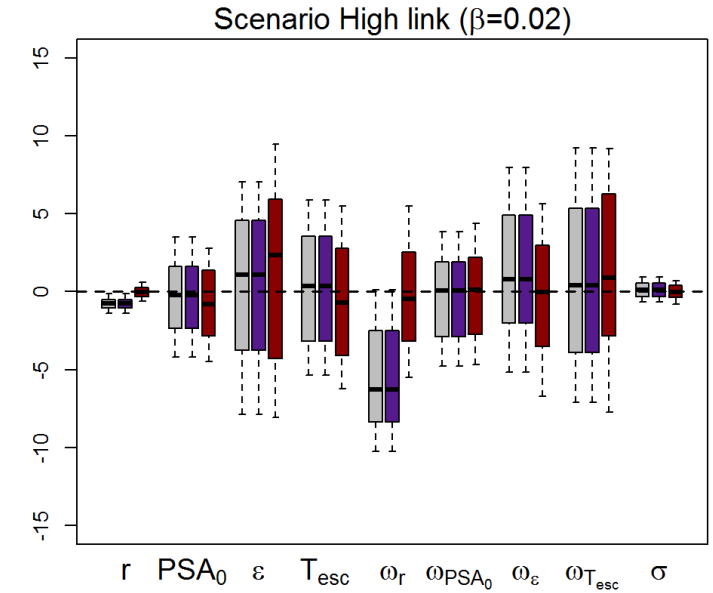
- θ vector of longitudinal and survival parameters to estimate
- η_i vector of random effects
- p density function of the longitudinal processus
- $S_i(t|\eta_i;\theta) = \exp(-\int_0^t h_i(s|\eta_i;\theta)ds)$ survival function

[12] Rizopoulos et al (2009) J. R. Stat. Soc.

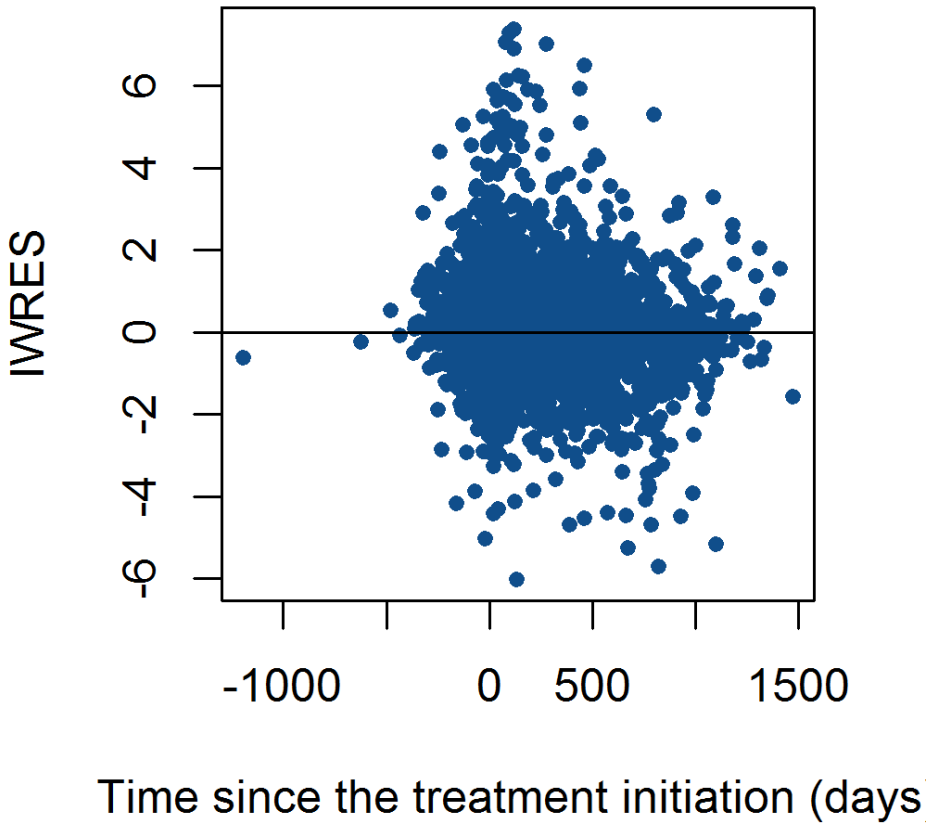
REE for the longitudinal parameters

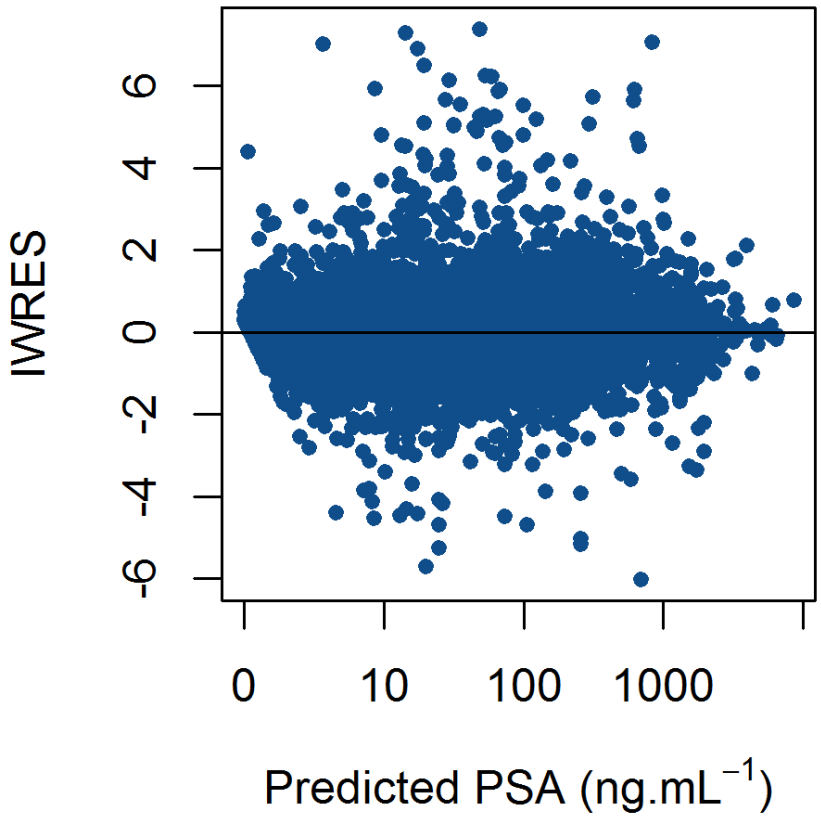




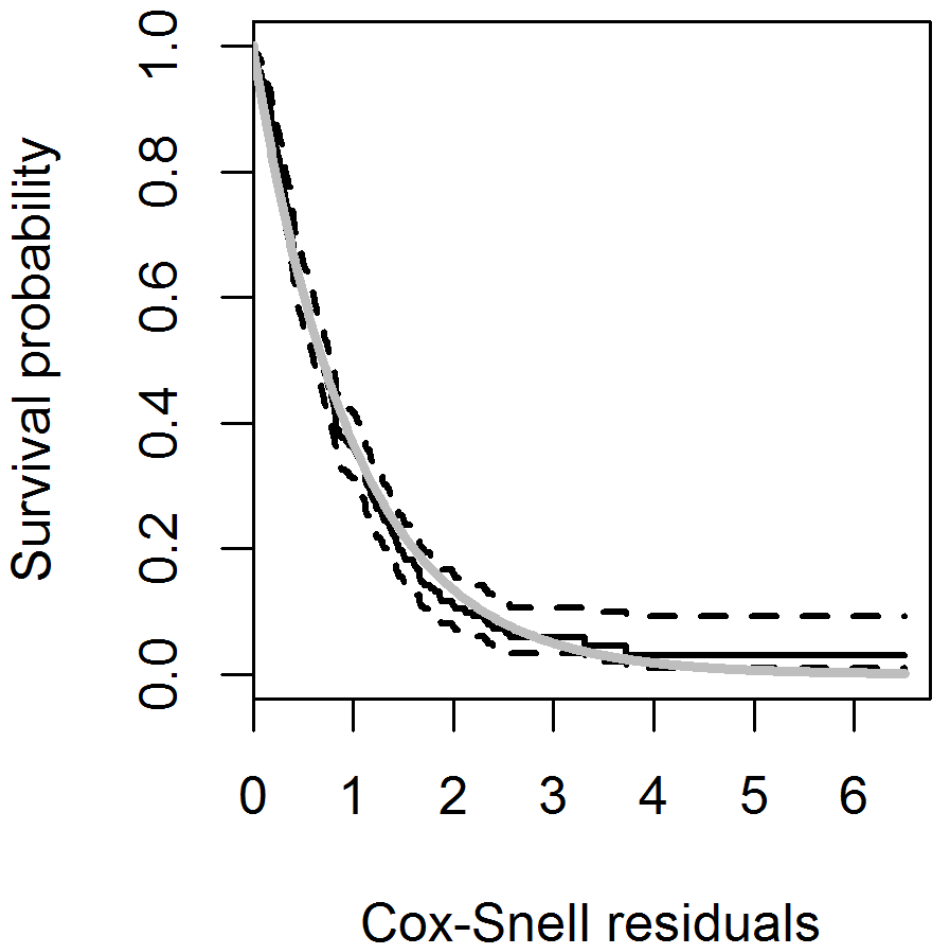


Individual Weighted Residuals (IWRES)

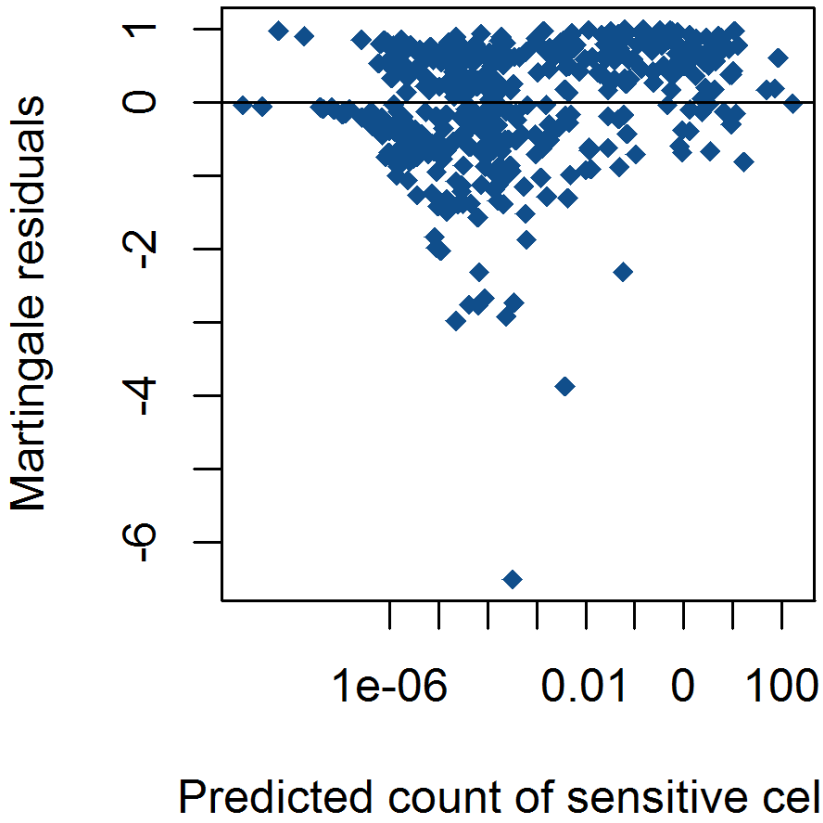


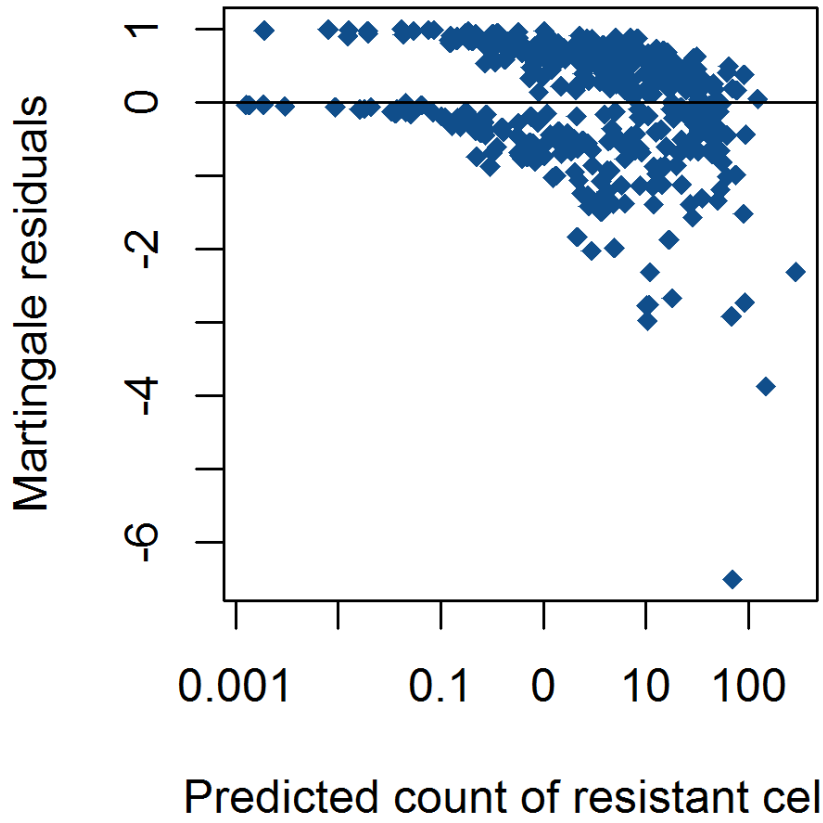


Cox-Snell residuals

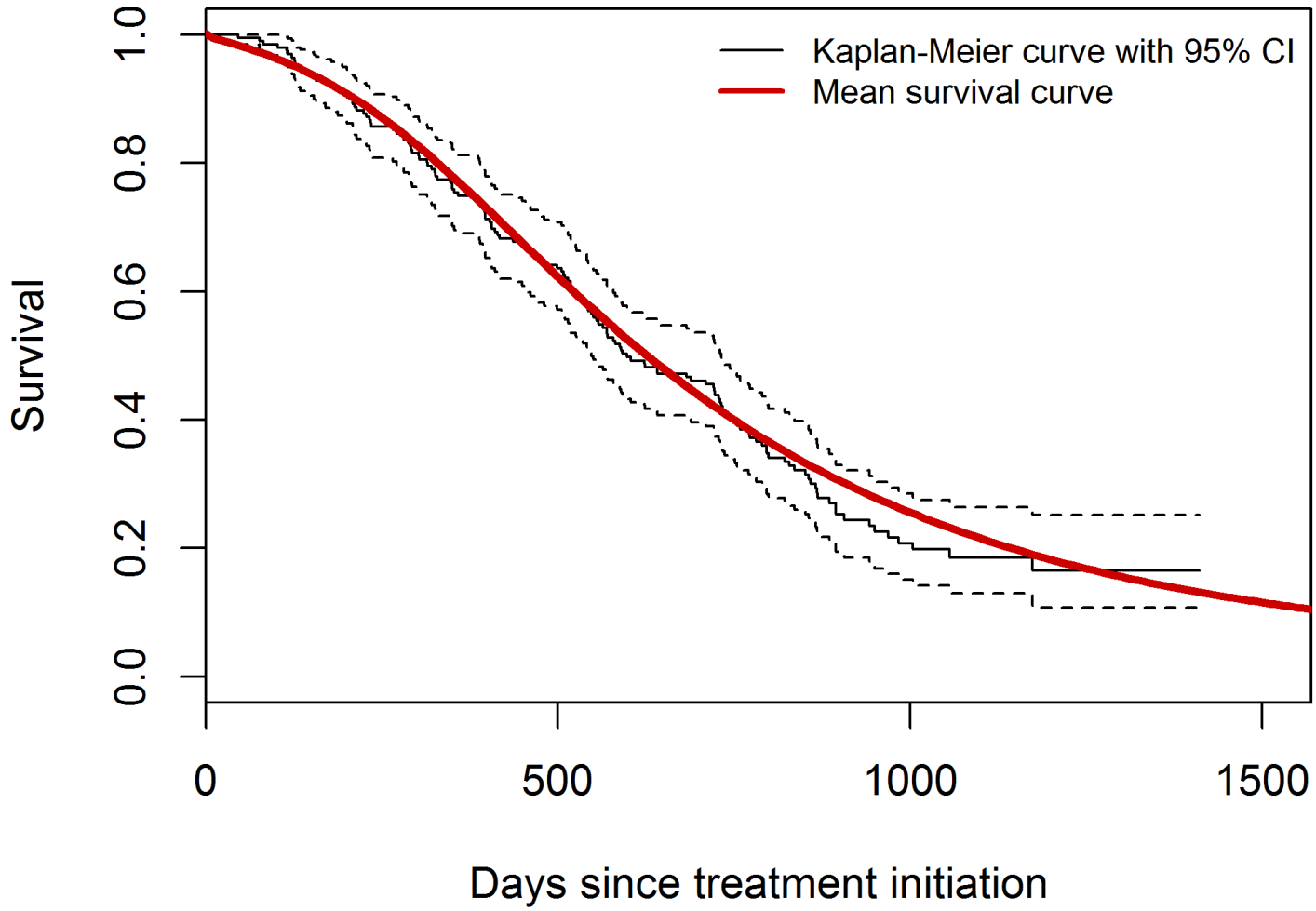


Martingale residuals





Mean survival curve in the validation dataset



AUC, BS and scaled BS

$$AUC(s,t) = \mathbb{P}(S_i(s+t|s) < S_j(s+t|s) | \mathbf{1}_{\{X_i<s+t\}} = 1, \mathbf{1}_{\{X_j<s+t\}} = 0, X_i > s, X_j > s)$$

$$BS(s,t) = \mathbb{E}[(\mathbf{1}_{\{X>s+t\}} - S(s+t|s))^2 | X > s]$$

$$sBS = 1 - \frac{BS(s,t)}{BS_{KM}(s,t)}$$

Time-dependent calibration metrics: scaled Brier score