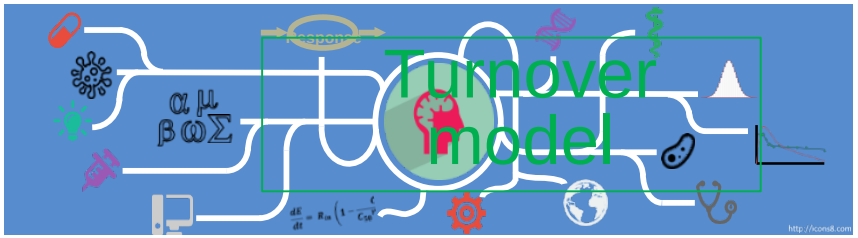

Mechanistic joint models characterizing the relationship between nonlinear prostate specific antigen kinetics and survival in prostate cancer patients

PR FRANCE MENTRÉ

UNIVERSITY PARIS DIDEROT – INSERM – UMR 1137

BIOSTATISTICAL MODELLING AND PHARMACOMETRICS

ASCPT – March 2018

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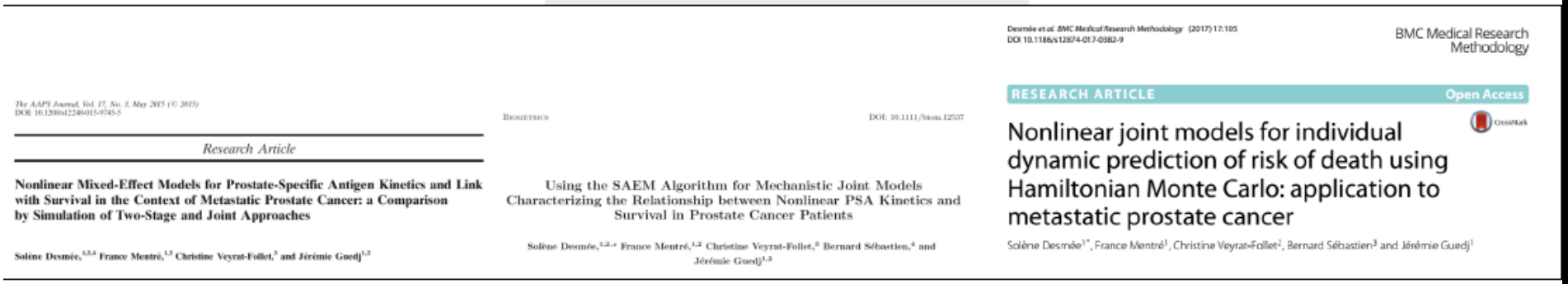


Research Article

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

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

BMC Medical Research Methodology

RESEARCH ARTICLE Open Access

Nonlinear joint models for individual dynamic prediction of risk of death using Hamiltonian Monte Carlo: application to metastatic prostate cancer

Outline

Introduction

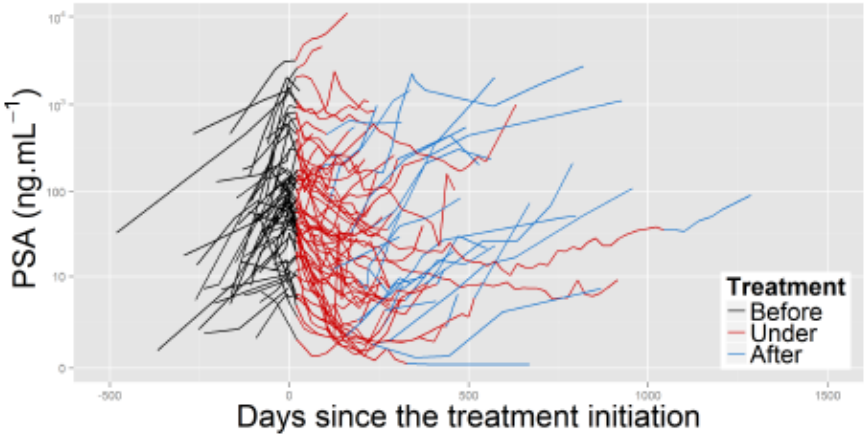
1. **Clinical Trial Simulation to Compare two-stage and joint modelling**
2. **Development of a mechanistic joint model for PSA and survival in metastatic patients**
3. **Individual dynamic prediction using joint model**

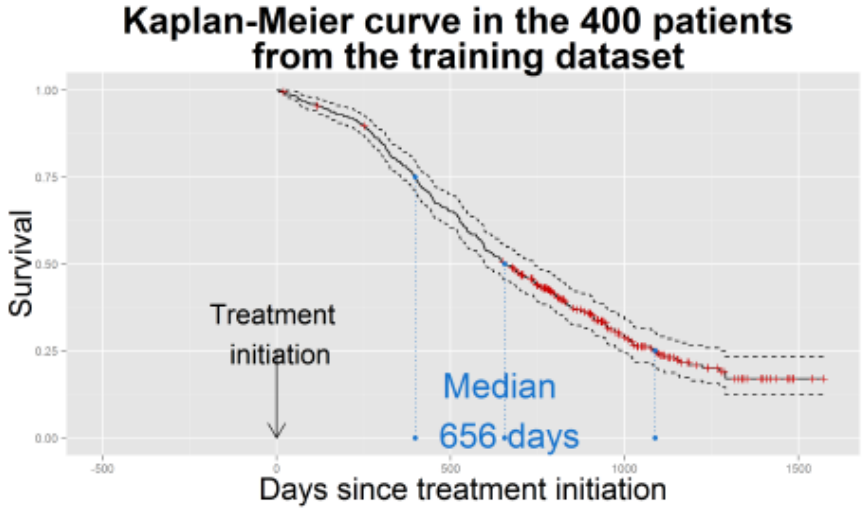
Conclusion

INTRODUCTION

- Hormono-resistant metastatic prostate cancer
  - Monitoring via Prostate Specific Antigen (PSA)
  - Reference treatment: docetaxel + prednisone

- All results presented based on the control arm of a phase III trial (Tannock et al, Lancet Oncol, 2013)
  - Training set: 400 patients randomly selected
    →Development of mechanistic joint model





  - Validation set: 196 patients
    → Model evaluation and individual predictions

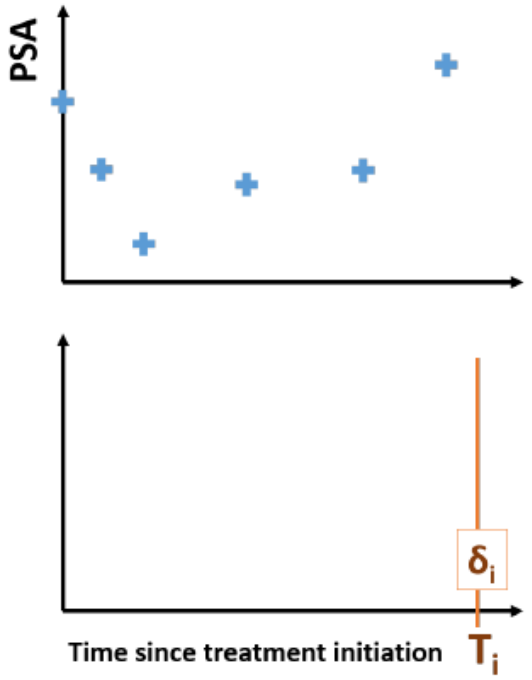
Joint modeling of longitudinal and time to event data

Longitudinal data

- y_i: vector of longitudinal measurements
- can be described by a nonlinear model

Time-to-event data

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



Two objectives

1. To characterize the (non-linear) kinetics of a biomarker in presence of a time-to-event
2. To characterize the impact of this kinetics on a time-to-event

Joint modeling of longitudinal and time to event data

→ mainly in clinical epidemiology with linear models

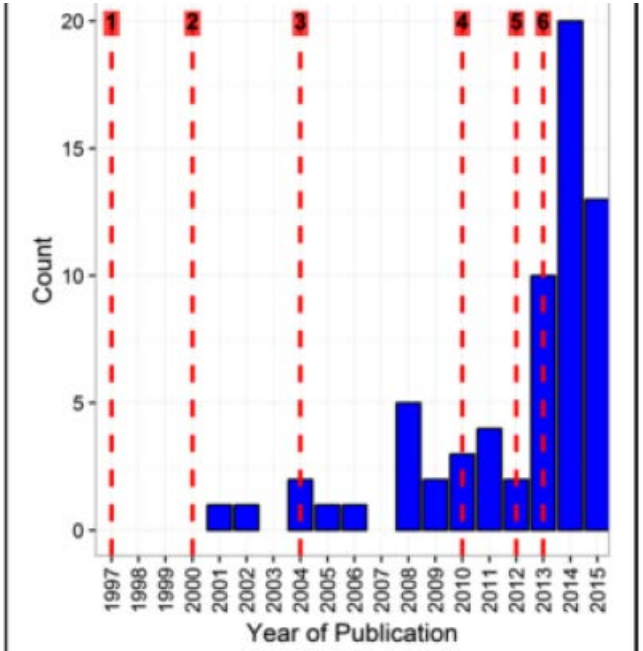
Sudell et al. BMC Medical Research Methodology (2016) 16:168
DOI 10.1186/s12874-016-0272-6

BMC Medical Research Methodology

RESEARCH ARTICLE Open Access

Joint models for longitudinal and time-to-event data: a review of reporting quality with a view to meta-analysis

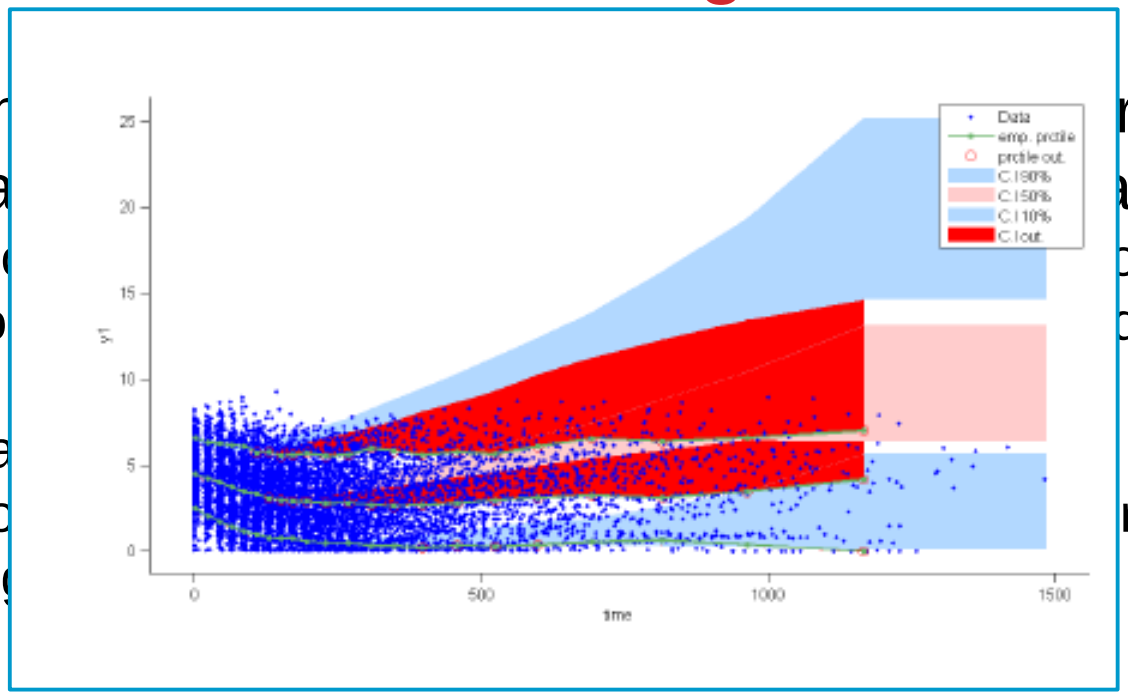
Maria Sudell*, Ruwanthi Kolamunnage-Dona† and Catrin Tudur-Smith†



	N (%)
Full text or abstract available	
Full text	63 (96.9)
Abstract	2 (3.1)
Disease Area	
Cancer related data	10 (15.4)
HIV/AIDS	9 (13.8)
Patient status after transplants	8 (12.3)
Cognitive decline	7 (10.8)
Glaucoma	4 (6.2)
Renal disease	4 (6.2)
Disability in the elderly	3 (4.6)
Heart related data	3 (4.6)
Schizophrenia	3 (4.6)
Sclerosis	3 (4.6)
Other	11 (16.9)
Journal	
Statistics in Medicine	5 (7.7)
Journal of the Royal Statistical Society. Series C: Applied Statistics	4 (6.2)
Ophthalmology	3 (4.6)
Quality of Life Research	3 (4.6)
Journal of the American Geriatrics Society	2 (3.1)
Journal of the American Statistical Association	2 (3.1)
Journals of Gerontology - Series B Psychological Sciences and Social Sciences	2 (3.1)
Statistical Methods in Medical Research	2 (3.1)
Other (only one study per journal)	45 (64.6)
Reason for joint modelling use*	
To investigate the link between longitudinal and time-to-event outcomes	43 (66.2)
To account for dropout	22 (33.8)
To include longitudinally measured variable in time-to-event model	4 (6.2)
To increase efficiency	3 (4.6)
To reduce bias	2 (3.1)
Easier to interpret	1 (1.5)

Informative censoring: Not a new issue

- Inform … rve the biom… alue
  - Po… ongitudinal data
  - Go… data
    - ➢ sa…
    - ➢ sc… rs
    - ➢ hi…



- When longitudinal and survival data analyzed separately
  - (Some) bias in longitudinal parameters
  - Problems in VPC and simulations of longitudinal data

Hu C, Sale ME. A joint model for nonlinear longitudinal data with informative dropout. *J Pharmacokinet Pharmcodyn.* 30:83–103 (2003).

Gastonguay, French, Heitjan, Rogers, Ahn, Ravva. Missing data in model-based pharmacometric applications:points to consider. J Clin Pharmacol. 50:63S–74 (2010).

Bonate & Suttle. Effect of censoring due to progressive disease on tumor size kinetic parameter estimates. *AAPS J.* 15:832–39 (2013).

Bjornsson, Friberg, Simonson. Performance of Nonlinear Mixed Effects Models in the presence of informative dropout. *AAPS J.* 17: 245–55 (2013).

Informative censoring: Not a new issue

- Informative censoring: probability to not observe the biomarker depends on current unobserved value
  - Poor responder: more likely of early event & less longitudinal data
  - Good responder: more likely of late event & more data

  - ➢ sample of longitudinal data is not representative
  - ➢ some kinetic parameters identified only in survivors
  - ➢ high shrinkage in poor responder

- When longitudinal and survival data analyzed separately
  - (Some) Bias in longitudinal parameters
  - Problems in VPC and simulations of longitudinal data
  - Bias in estimated survival parameters
  - Induced or hidden correlation between marker evolution and survival (inflated Type I error)

Ribba, Holford, Mentré. The use of Model-Based Tumor-Size metrics to predict survival. *Clin Pharmacol Ther, 96*: 133-5 (2014)
Mistry. Time dependent bias of tumor growth rate and time to tumor regrowth. *CPT:PSP, 5*: 587 (2016).
Suissa. Immortal time bias in pharmaco-epidemiology. *Am J Epidemiol,* 167: 492-9 (2008)
Mistry & Ortega. A cautionary tale on using tumour growth rate to predict survival . *BioRxiv preprint* (2017).

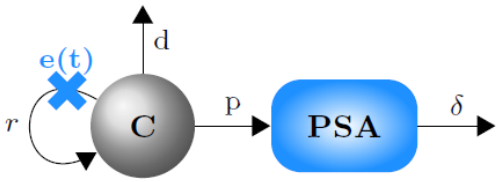
1. CTS to compare two-stage and joint modelling approaches

The AAPS Journal, Vol. 17, No. 3, May 2015 (© 2015)
DOI: 10.1208/s12248-015-9745-5

Research Article

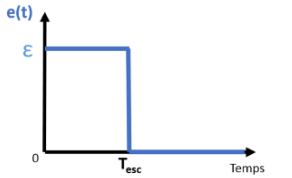
Nonlinear Mixed-Effect Models for Prostate-Specific Antigen Kinetics and Link with Survival in the Context of Metastatic Prostate Cancer: a Comparison by Simulation of Two-Stage and Joint Approaches

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



$$\begin{cases} \frac{dC}{dt} = r(1-e(t))C - dC \\ \frac{dPSA}{dt} = pC - \delta PSA \end{cases}$$

$$\psi = \{r, PSA_0, \varepsilon, T_{esc}\}$$



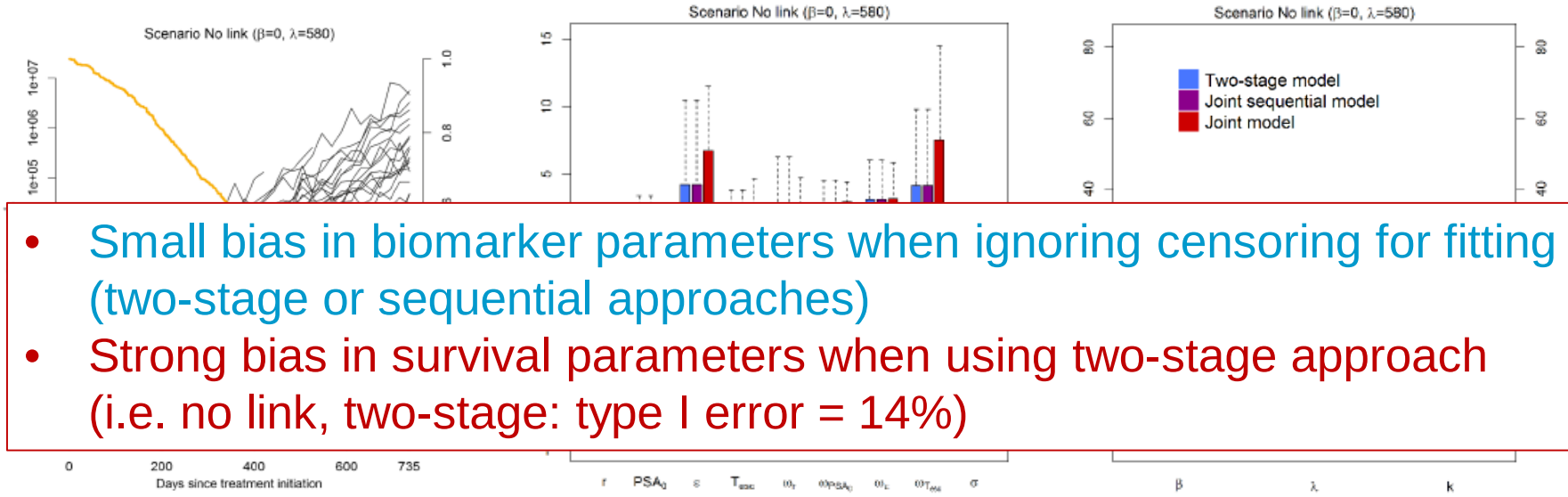
$$e(t) = \begin{cases} \varepsilon & if\ t \leqslant T_{esc} \\ 0 & if\ t > T_{esc} \end{cases}$$

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

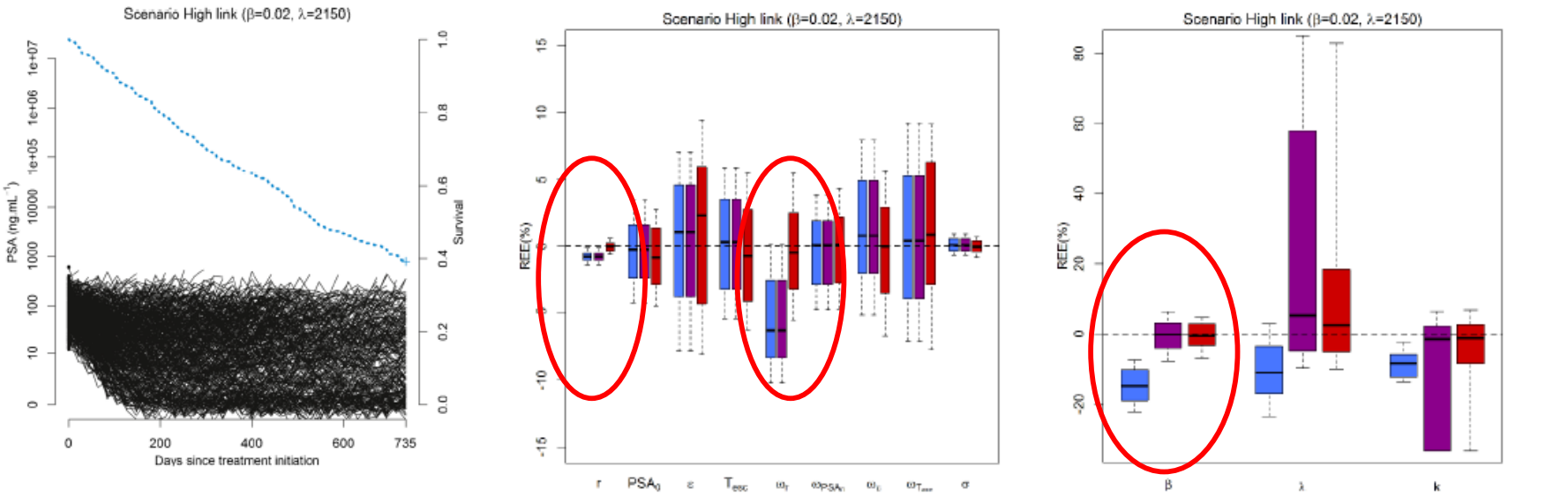
Weibull $h_0(t) = \frac{k}{\lambda}(\frac{t}{\lambda})^{k-1}$

	Scenario No link	Scenario Low link	Scenario High link
β	0	0.005	0.02
λ (day)	580	765	2150
k	1.5	1.5	1.5

Results (100 replicates, 500 patients)



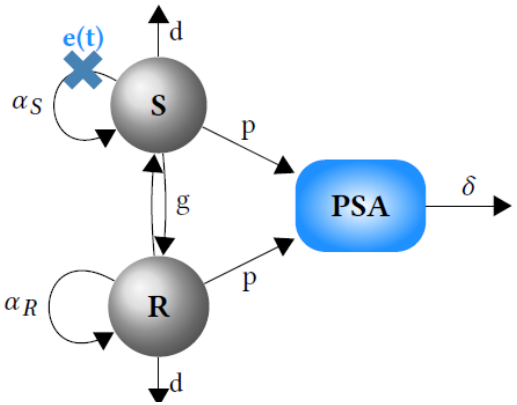
- Small bias in biomarker parameters when ignoring censoring for fitting (two-stage or sequential approaches)
- Strong bias in survival parameters when using two-stage approach (i.e. no link, two-stage: type I error = 14%)



2. Development of a mechanistic joint model for PSA and survival in metastatic patients

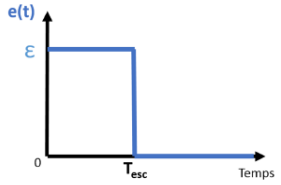
Using the SAEM Algorithm for Mechanistic Joint Models Characterizing the Relationship between Nonlinear PSA Kinetics and Survival in Prostate Cancer Patients

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



PSA is produced by 2 types of cells
- Sensitive cells (S)
- Resistant cells (R)

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



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

$$h_i(t|PSA(t,\psi_i)) = h_0(t)\exp(f(t,\psi_i))$$

$$\text{Weibull } h_0(t) = \frac{k}{\lambda}(\frac{t}{\lambda})^{k-1}$$

- Link function f
  - No link
  - Initial PSA
  - Current PSA
  - PSA slope
  - Area under PSA
  - S and R

Monolix

Results: model selection (training set, 400 patients)

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

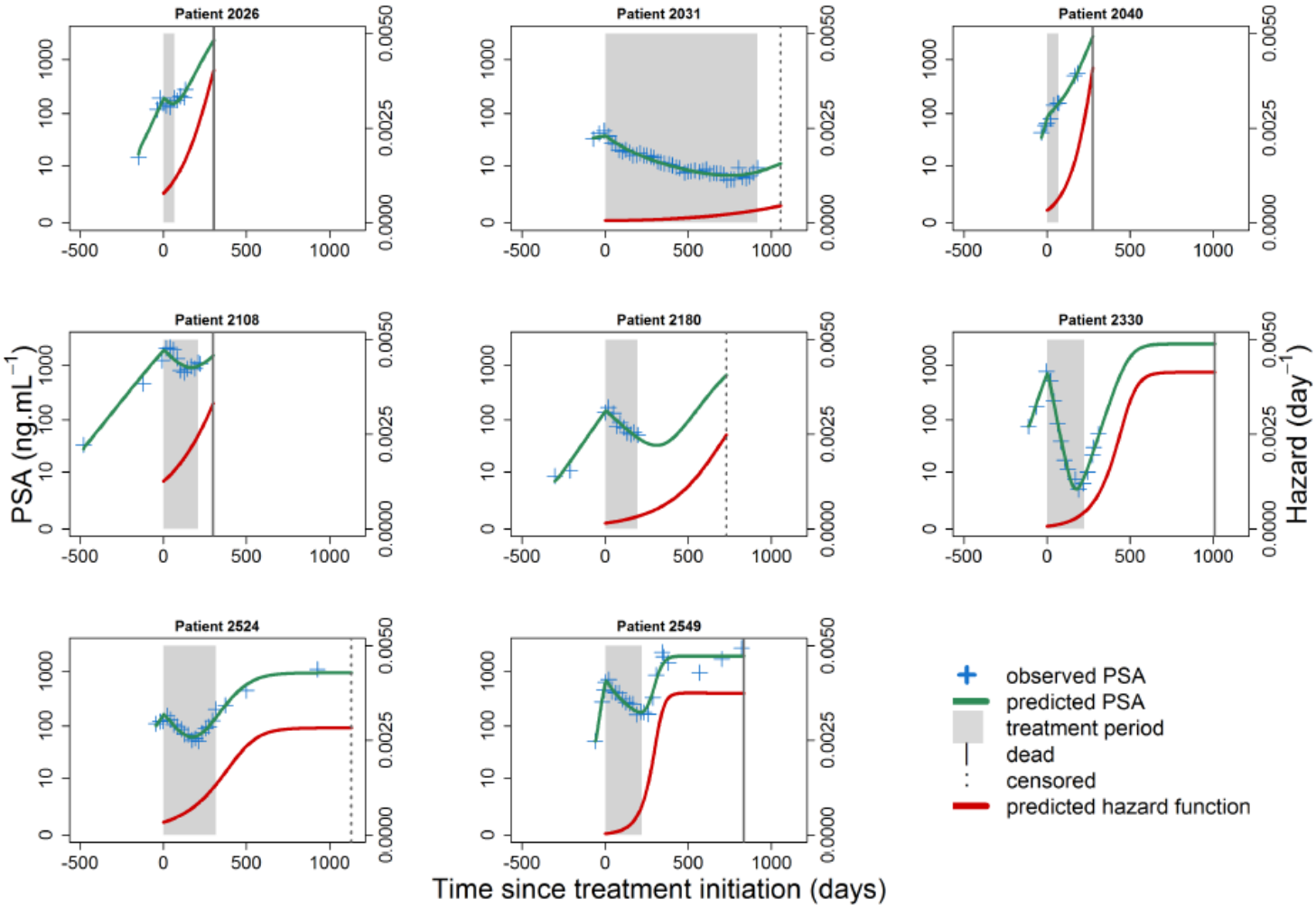
	No link	Initial PSA	PSA	PSA slope	Area under PSA	**S+R**
BIC	14598	14582	14446	14581	14575	14421
α_S	0.066 (3)	0.060 (3)	0.078 (3)	0.078 (3)	0.061 (3)	0.067 (3)
RF	0.9997 (0)	0.9996 (0)	0.9998 (0)	0.9998 (0)	0.9997 (0)	0.9998 (0)
RE	0.81 (1)	0.79 (1)	0.84 (1)	0.84 (0)	0.79 (1)	0.82 (1)
ε	0.42 (4)	0.46 (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)

➟ **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

- Delta -2LL PSA vs no link = 158 ($p<10^{-35}$)
- Delta BIC S & R vs PSA = 25

Results (training set, 400 patients)

Individual fits of PSA and hazard functions

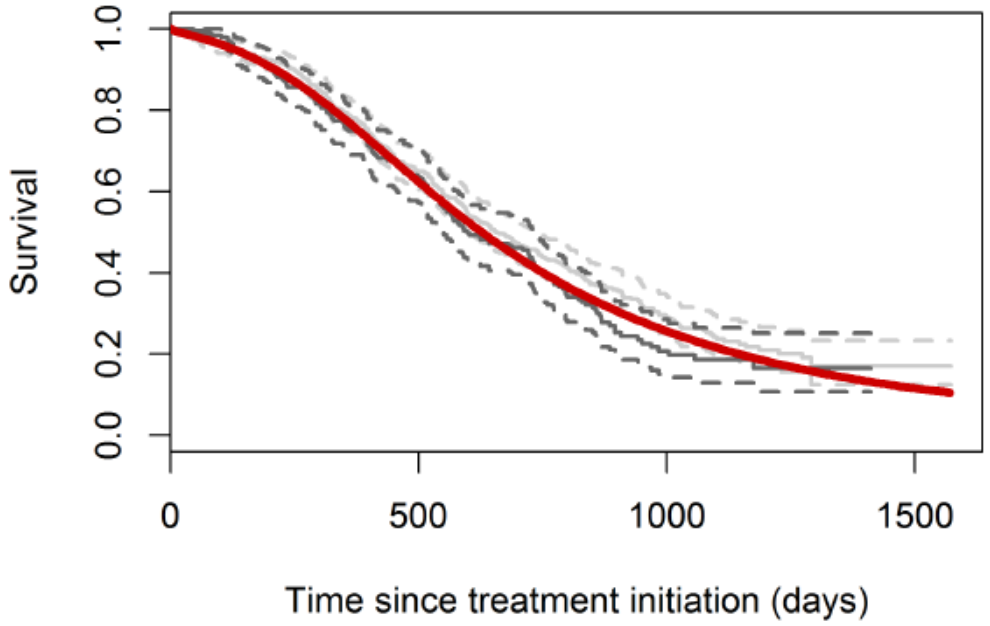


Results (validation set, 196 patients)

Prediction in the validation sample

Assumption: *true* joint model is known

- ➔ *Population parameters* θ *used as priors*
- ➔ *Individual EBEs* $\hat{\psi}_i$ *estimated using only the PSA measurements*
- ➔ *Mean survival function* $= \frac{1}{N}\sum_{i=1}^{N} S_i(t|\hat{\psi}_i, \hat{\theta})$



3. Individual dynamic prediction using joint model

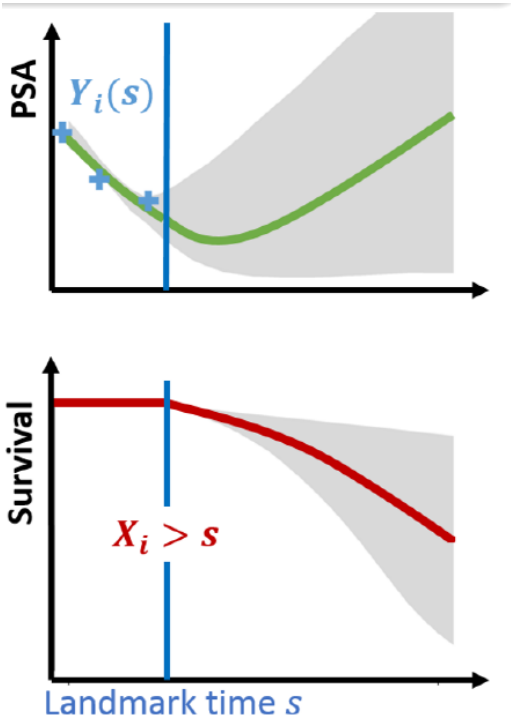
Desmée *et al. BMC Medical Research Methodology* (2017) 17:105
DOI 10.1186/s12874-017-0382-9

BMC Medical Research Methodology

RESEARCH ARTICLE Open Access

Nonlinear joint models for individual dynamic prediction of risk of death using Hamiltonian Monte Carlo: application to metastatic prostate cancer

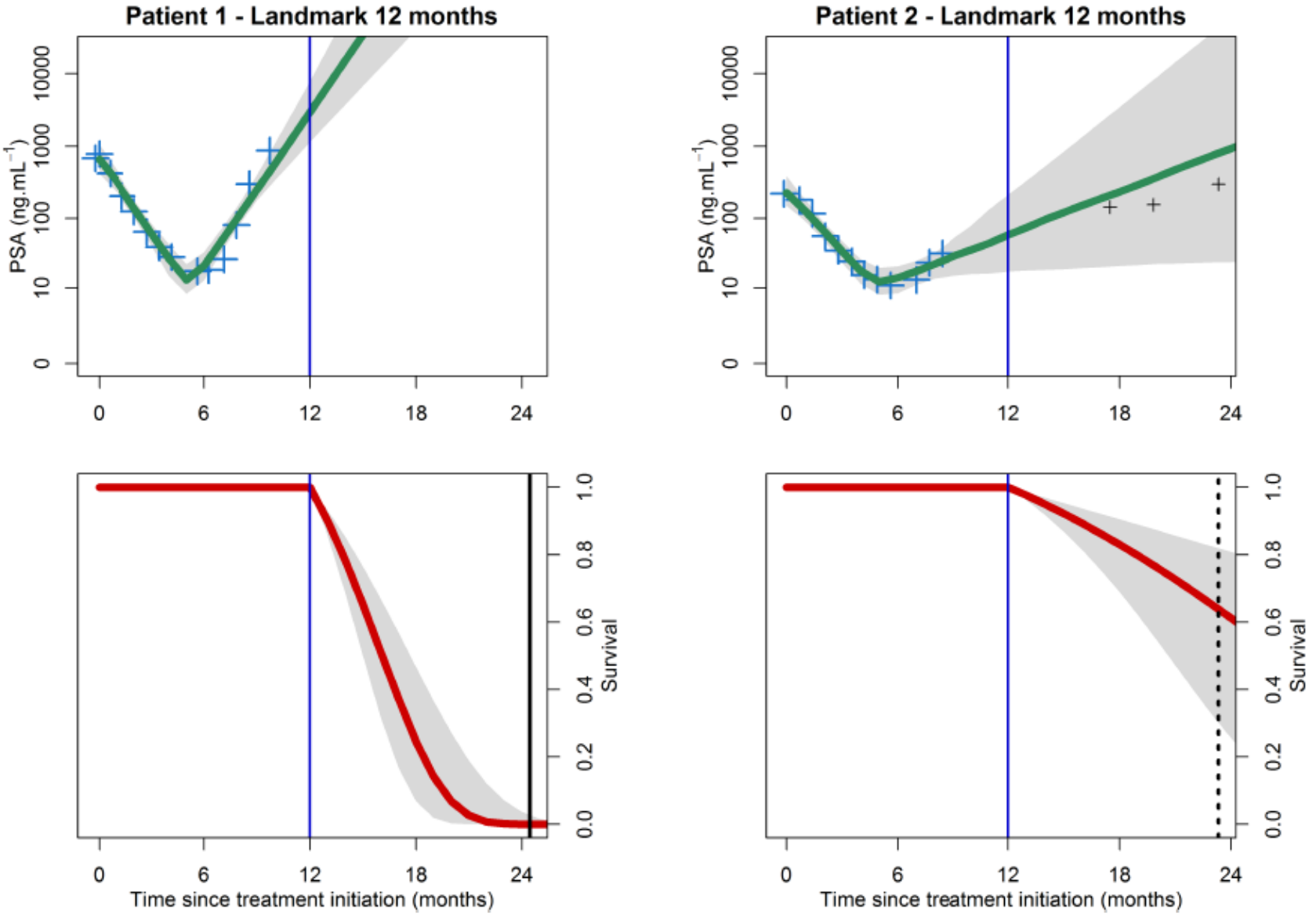
Solène Desmée[1*], France Mentré[1], Christine Veyrat-Follet[2], Bernard Sébastien[3] and Jérémie Guedj[1]



- Learning sample: prior estimates
- New patient from validation sample
  - Observed PSA data until landmark s
  - Prediction of PSA and survival after s with uncertainty
  - Using Hamiltonian Monte Carlo in STAN

Dynamic predictions for 2 patients

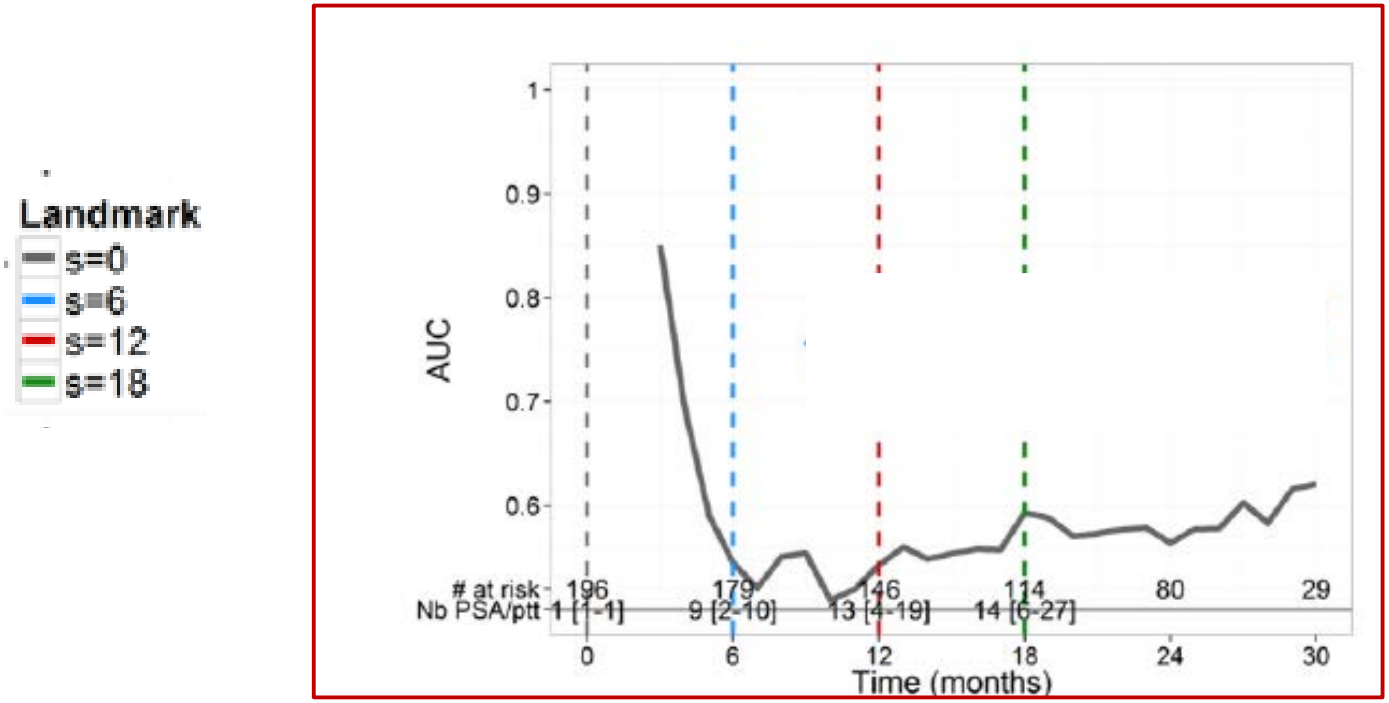
Patient 1 died at 24 months - Patient 2 was censored at 24 months



Time-dependent AUC

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

➟ **Area under the ROC curve** (AUC)



- Poor discrimination at time 0 beyond 6 months
- Good discrimination (AUC > 0.75) after 6, 12 or 18 months

CONCLUSION

- New mechanistic model of PSA during metastatic cancer
  - Use of joint modelling (here with SAEM)
  - Model building and parameter estimates in learning data set

- Use Bayesian method (here with STAN) in validation set
  - Predict PSA and survival with uncertainty
  - Various landmark times

  → Can be used for individual patient monitoring

  - Need to asses overall predictability (Time-dependent AUC)

- **Be careful** of two-stage approaches and of using model-derived metrics in survival analysis
  - Time-dependent bias
  - 'To good to be true'

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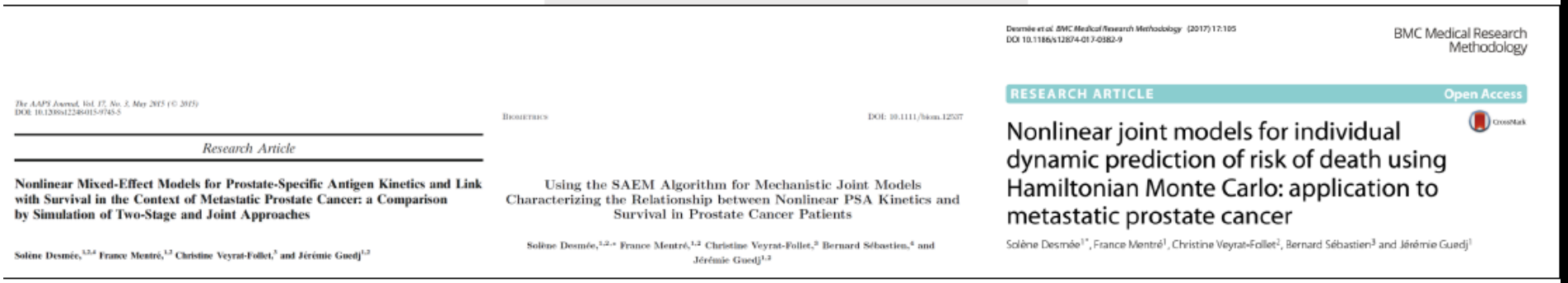

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Nonlinear joint models for individual dynamic prediction of risk of death using Hamiltonian Monte Carlo: application to metastatic prostate cancer

Citation: CPT Pharmacometrics Syst. Pharmacol. (2016) 5, 587; doi:10.1002/psp4.12145

LETTERS TO THE EDITOR

Time-Dependent Bias of Tumor Growth Rate and Time to Tumor Regrowth

To the Editor:

In a recent study by Han *et al.*[1] the authors highlight that a tumor growth inhibition metric termed time-to-tumor-growth (TTG) derived from imaging time-series data is a strong predictor of survival. The authors demonstrate the strength of TTG's correlation to survival using Kaplan-Meier curves in **Figure 2** of their article. Indeed, the relationship seems incredibly strong, maybe too good to be true. Perhaps it could well be as we now explain. One of the key forms of bias when using covariates that are time-dependent, which TTG and, in fact, any model-derived metrics are, is time-dependent (immortal time) bias.[2] In basic terms, this form of bias relates to the failure to account for the time taken to estimate a time-dependent covariate when performing a survival analysis. The Kaplan-Meier's plotted in **Figure 2** of Han *et al.*[1] assume that TTG is known at the beginning of the study; which is clearly not true. TTG can only be calculated once a certain amount of time-series data has been collected. Therefore, the Kaplan-Meier curves in **Figure 2** are incredibly misleading and biased. The article by Suissa[2]

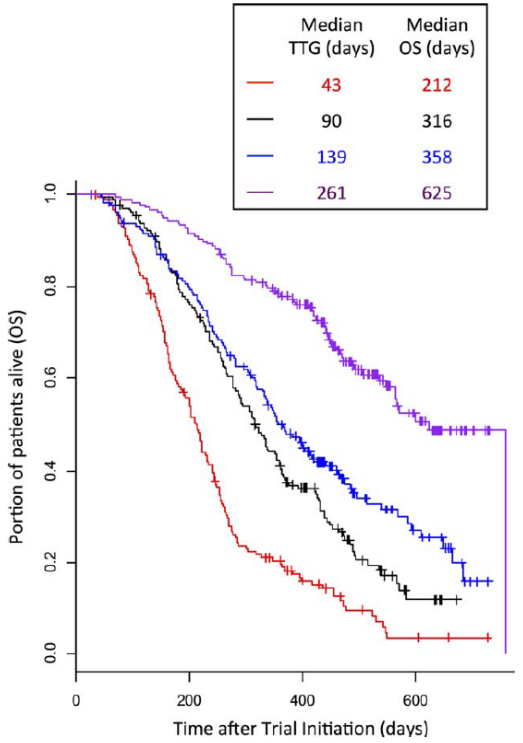


Figure 2 Survival distribution by quartiles of time to tumor growth (each group represents 25% of the patients). TTG, time to tumor growth; OS, overall survival.

1. Han, K. *et al.* Simulations to predict clinical trial outcome of bevacizumab plus chemotherapy vs. chemotherapy alone in patients with first-line gastric cancer and elevated plasma VEGF-A. *CPT Pharmacometrics Syst. Pharmacol.* **5**, 352–358 (2016).
2. Suissa, S. Immortal time bias in pharmaco-epidemiology. *Am. J. Epidemiol.* **167**, 492–499 (2008).

The Use of Model-Based Tumor-Size Metrics to Predict Survival

B Ribba[1], N Holford[2] and F Mentré[3]

CLINICAL PHARMACOLOGY & THERAPEUTICS | VOLUME 96 NUMBER 2 | AUGUST 2014

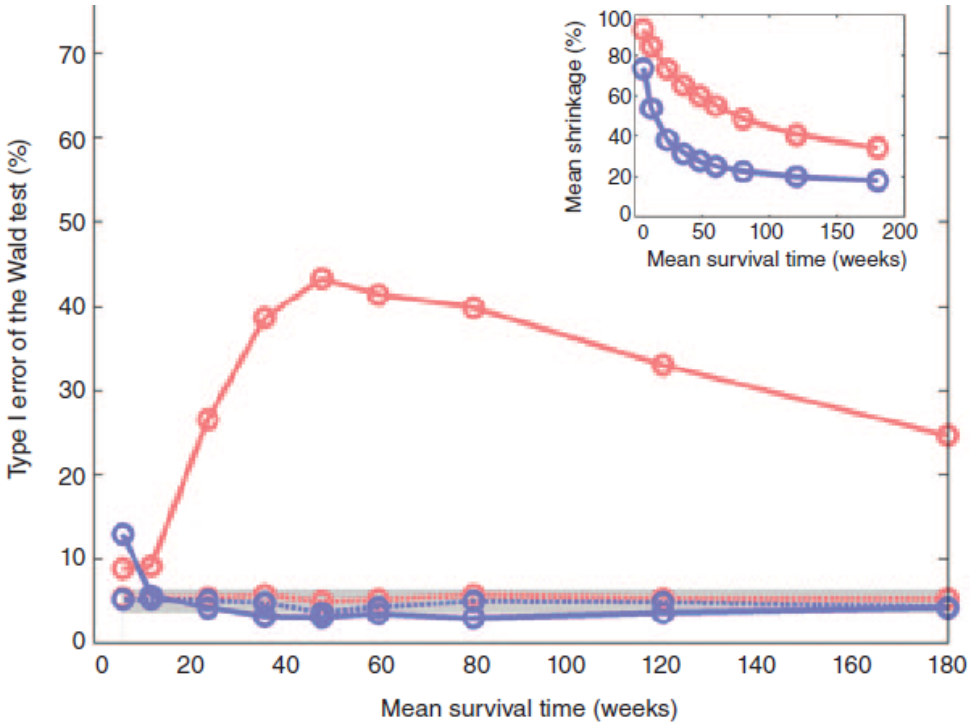


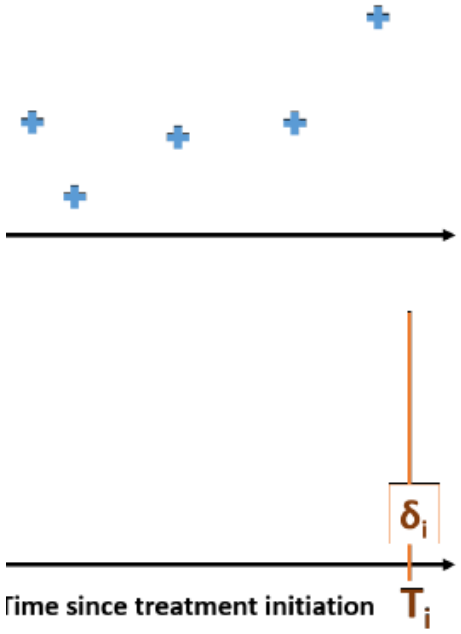
Figure 1 Relationship of the type I error of the Wald test with mean survival times for tumor-size reduction (*TSR6*, blue continuous line) and time-to-tumor-growth (*TTG*, red continuous line) metrics. The type I error of falsely concluding an association between each tumor metric and hazard was estimated from the frequency of rejecting the null hypothesis using a Wald test of size 5%. A total of 1,000 data sets were created for each of the nine survival-simulation scenarios. By design, the survival distribution was independent of tumor size, so the empirical type I error rates are all expected to fall within the 95% prediction interval. The gray band represents the 95% prediction interval around 5% type I error (for 1,000 replicates: 3.65 to 6.35%). The dashed lines represent the values of the metrics calculated using the reference "true" individual parameter values. Inset: Shrinkage of *TSR6* and *TTG* with mean survival time.

Joint model= 2 submodels

LONGITUDINAL PART: Nonlinear mixed-effect models (NLMEM)

$$y_i(t) = \log(X(t,\psi_i) + 1) + \epsilon_i(t)$$

- X: process of interest (PSA) **possibly non-linear**
- ψ_i: individual longitudinal parameters
- $e_i(t)$: residual error



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 and longitudinal model (eg., $log[PSA(t,\psi_i)]$)

Joint log-likelihood for a patient i:

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