Joint modeling of biomarkers dynamics and survival with competing risks to predict the prognosis of patients hospitalized with severe infectious diseases

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29/06/2023

Provide every patient with a self and adapted medical treatment

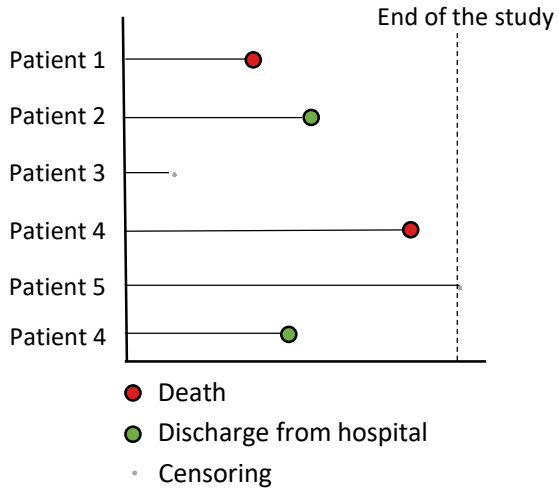
Personalized medicine

1- Rizopoulos. *Biometrics*, 2011

Provide every patient with a self and adapted medical treatment

Personalized medicine

Predict the death of hospitalized patients for severe infectious diseases



Competing risks

1- Rizopoulos. *Biometrics*, 2011

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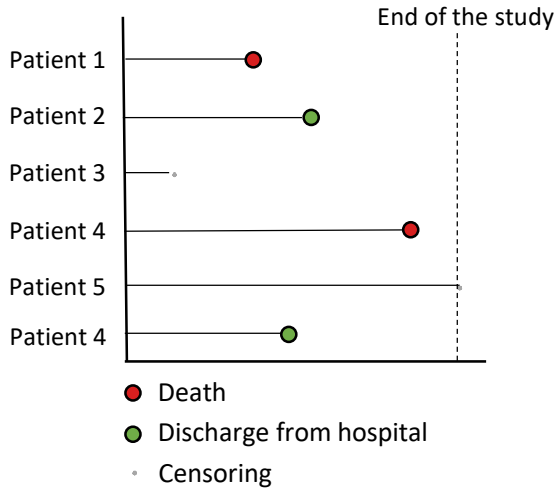
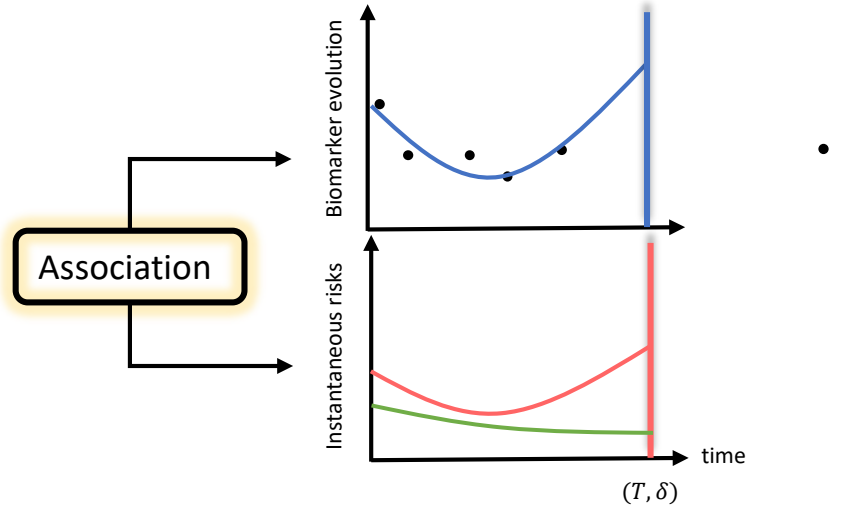


Competing risks

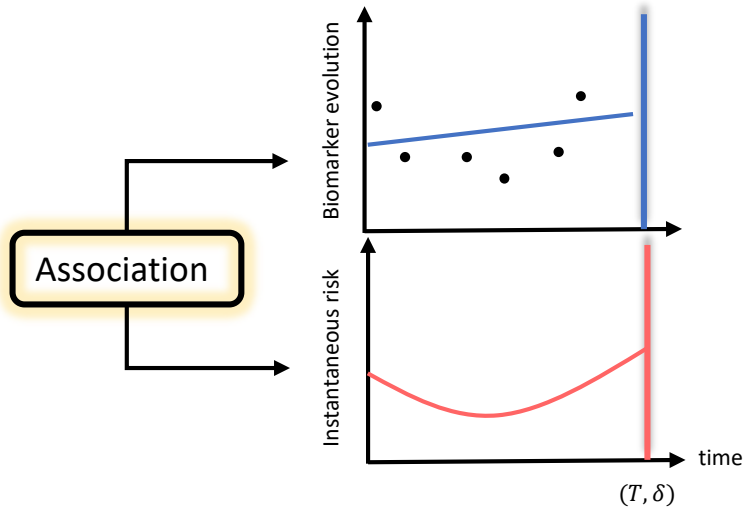
Hospitals equipped with laboratory information systems that routinely gather results of biological analyses

Consecutive biological observations can be used in a joint model to provide individual dynamic predictions[1] of patient prognosis



1- Rizopoulos. *Biometrics*, 2011

Joint modeling of **LMEM** and **single event**



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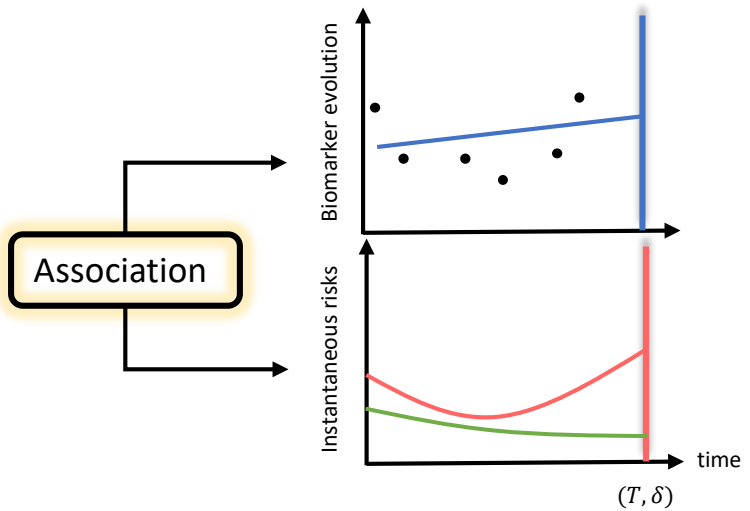
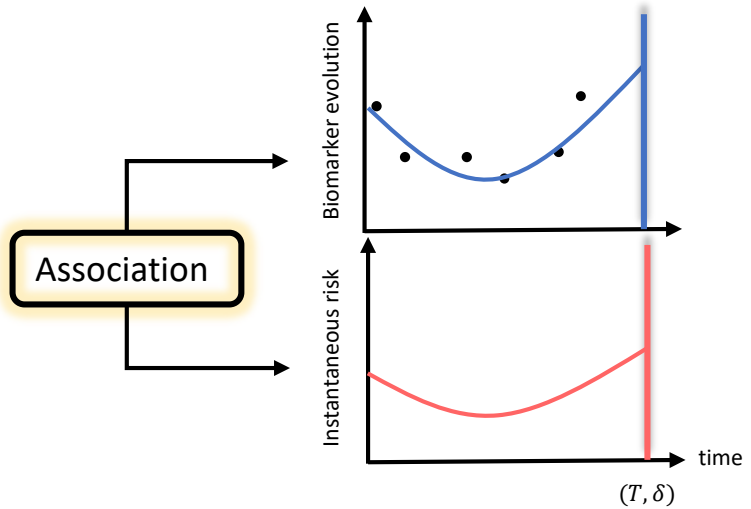


Widely developed in literature (single event[1,2,3],competing risks[4,5,6])
Estimation available in various software: (R, SAS, Monolix, NONMEM,…)

LMEM = linear mixed-effects model

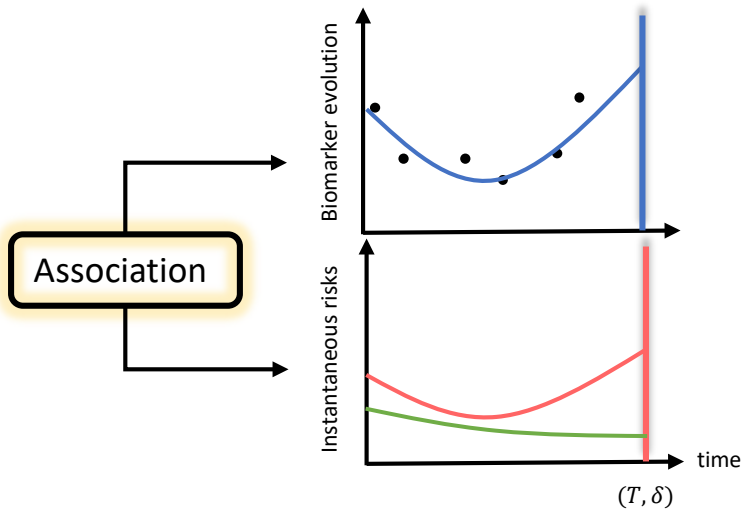
1- Rizopoulos. *Biometrics*, 2011
2- Angeli et al. *The AAPS Journal,* 2016
3- Elashoff et al. *Biometrics*, 2008
4- Deslandes and Chevret. *BMC Medical Research and Methodology*, 2010
5- Musoro et al. *Statistica Neerlandica*, 2018
6- Alvares and Rubio. *Statistics in Medicine*, 2021

Joint modeling of **NLMEM** and **single event**



Widely developed in literature[7,8,9]
Some softwares available: Monolix, NONMEM

Joint modeling of **NLMEM** and **competing risks**



Very few developed in literature (1 published work[10])
Software used: NONMEM

NLMEM = nonlinear mixed-effects model

7- Desmée et al. *The AAPS Journal*, 2015
8- Tardivon et al. *Clinical Pharmacology & Therapeutics,* 2019
9- Kerioui et al. *Statistics in Medicine*, 2020
10- Krishnan et al. *CPT:Pharmacometrics & Systems Pharmacology,* 2021

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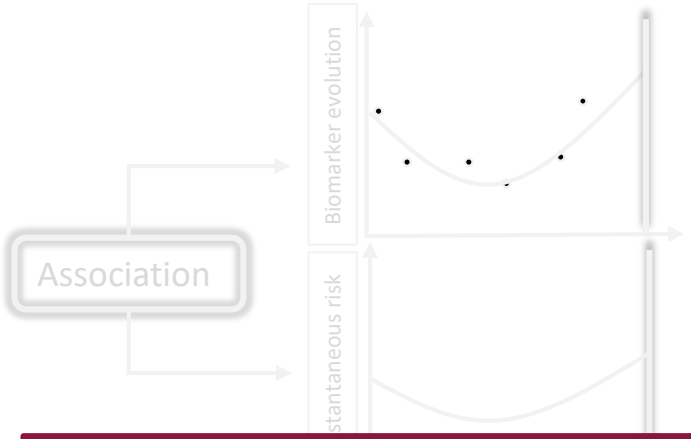
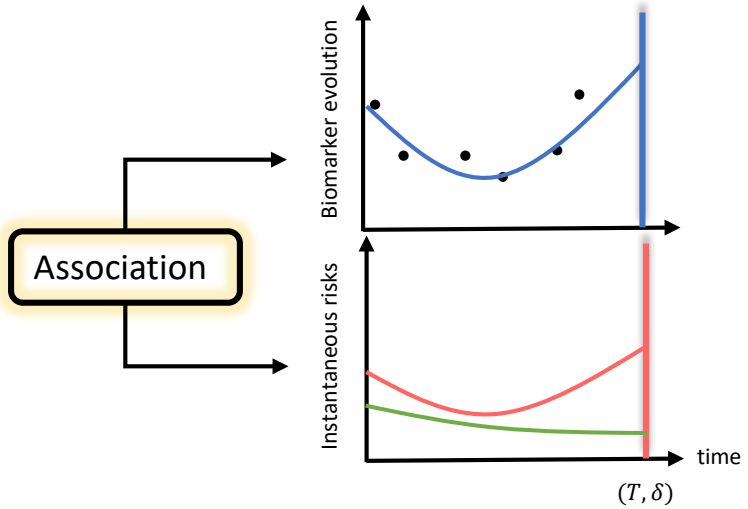


1st PhD work:

- Show that estimation well performs in **Monolix** software
- Application on sepsis patients

- Lavalley-Morelle et al. *CPT:Pharmacometrics & Systems Pharmacology*, 2022
- 29th PAGE conference (2021), "Individual dynamic predictions and their evaluation in joint analysis with nonlinear longitudinal model and parametric competing risks model: application on sepsis patients"

Joint modeling of **NLMEM** and **competing risks**



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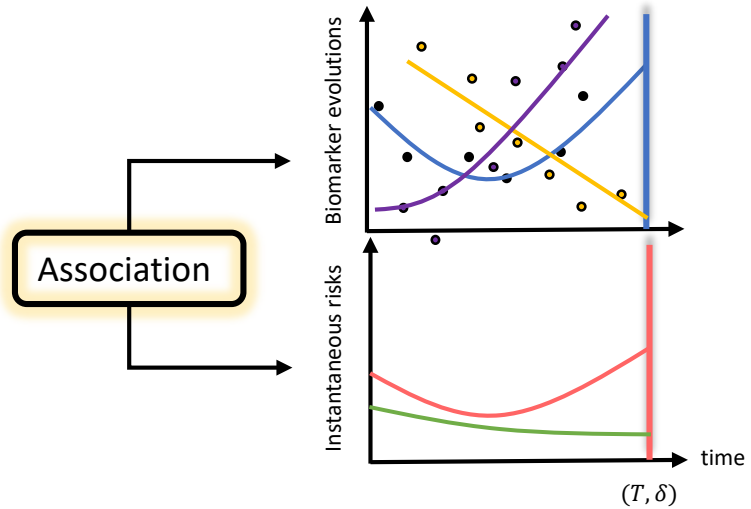
Comes with computational and identifiability issues due to the high number of random effects[11]

Published models mostly limited to longitudinal models with at most two biomarkers[12,13]

Certainly improve prediction accuracy

Shifting the modeling from one to several biomarkers

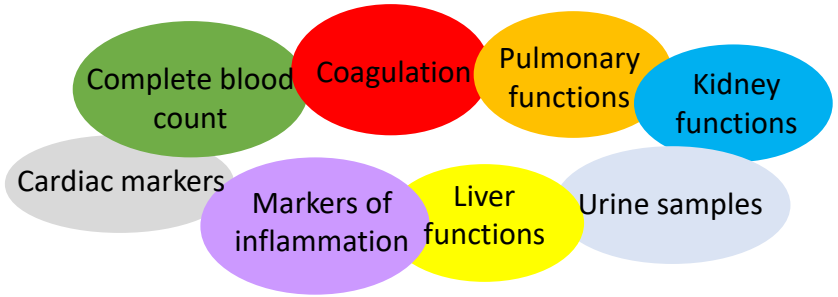
Need of methods for variable selection in this context



11- Shen et al. *Statistics in Medicine*, 2021
12- Long and Mills. *BMC Medical Research Methodology*, 2018
13- Rajeswaran et al. *Statistics in Biosciences*,2018

RisCoV database

- 327 patients hospitalized during the first wave of the COVID-19 pandemic
- 59 biomarkers (classified in 8 categories) variably followed until death or discharge
- Prognosis (death/discharge from hospital)



How to select biomarkers most associated with prognosis ?

Objectives of the work

COVID-19 case study

- Develop a multivariate joint model and a strategy to select a subset of biomarkers to predict the death of patients hospitalized for SARS-CoV-2 infection

Methodological assessment

- Evaluate the SAEM algorithm implemented in Monolix for multivariate joint models under competing risks
- Assess the validity of the proposed selection strategy

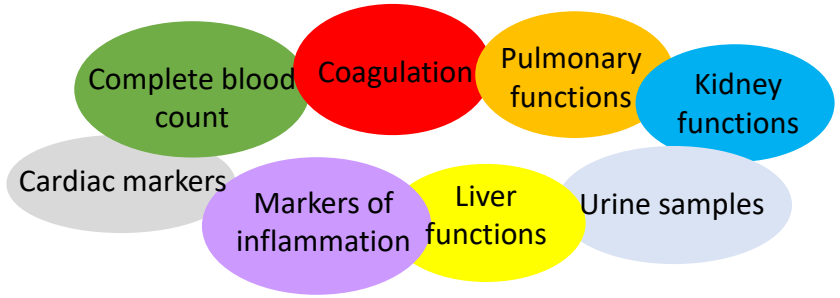
saemix extension

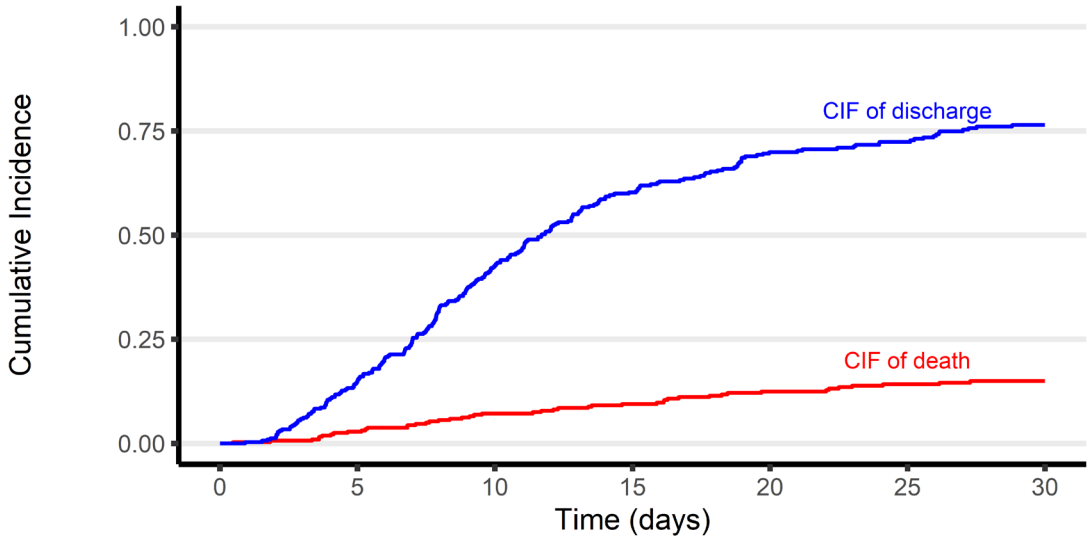
- Extend the R *saemix*[14] package to the case of multi-response and joint models

14- Comets et al. *Journal of Statistical Software*, 2017

RisCoV database

- 327 patients hospitalized in France during the first wave of the COVID-19 pandemic (January to July 2020)
- 59 biomarkers (classified in 8 categories) followed until death or discharge
- 4C Score[15] available at admission
- At D30: 14% deaths
  73% discharges





Cumulative incidence functions for both events

Components of the 4C-Score

Age, years	**< 50**	0				
	50 – 59	+2				
	60 – 69	+4				
	70 – 79	+6				
	≥ 80	+7				
Sex at birth	**Female**	0	Male	+1		
Number of commorbidities	**0**	0	**1**	+1	**≥ 2**	+2
Respiratory rate, breaths/min	**< 20**	0	**20 – 29**	+1	**≥ 30**	+2
Peripheral oxygen saturation on room air	**≥ 92%**	0	**< 92%**	+2		
Glasgow Coma Scale	**15**	0	**< 15**	+2		
Urea (mmoL/L) at admission	**< 7**	0	**7 – 14**	+1	**> 14**	+3
C-reactive protein (mg/L) at admisson	**< 50**	0	**50 – 100**	+1	**≥ 100**	+2

15- Knight et al. *British Medical Journal*, 2020

General notations

y_{ijk}: obs of marker k in patient i at time t_{ijk}
$Score_i$: baseline 4C-Score for patient i

$$y_{ijk} = \boldsymbol{m_k(\psi_{ik}, t_{ijk})} + g\left[m_k(\psi_{ik}, t_{ijk}), \sigma_k\right]\varepsilon_{ij} \longrightarrow \text{Mixed-effects model}$$

Subdistribution parametrization

$$h_{1ik}(t) = h_{01k} \times \exp(\boldsymbol{\alpha_{1k}} \times \boldsymbol{m_k(\psi_{ik}, t)} + \beta_{1k} \times Score_i) \longrightarrow \text{instantaneous risk of in-hospital death}$$

$$h_{2ik}(t) = h_{02k} \times \exp(\boldsymbol{\alpha_{2k}} \times \boldsymbol{m_k(\psi_{ik}, t)} + \beta_{2k} \times Score_i) \longrightarrow \text{instantaneous risk of discharge from hospital}$$

Linear model: $\boldsymbol{m_k(\psi_{ik}, t_{ijk})} = \psi_{0ik} + \psi_{1ik} \times t_{ijk}$

Nonlinear model: $\boldsymbol{m_k(\psi_{ik}, t_{ijk})} = \psi_{0ik} + \psi_{aik} \times \left[\exp(\psi_{1ik} \times t_{ijk}) - \exp(\psi_{2ik} \times t_{ijk})\right]$

$\psi_{.ik} = \mu_{.k} + \eta_{.ik}$

$\psi_{aik} = \mu_{ak} \times \exp(\eta_{aik})$

$\eta_{.ik} \sim \mathcal{N}(0, \Omega_k)$

$\varepsilon_{ij} \sim \mathcal{N}(0,1)$

General notations

y_{ijk}: obs of marker k in patient i at time t_{ijk}
$Score_i$: baseline 4C-Score for patient i
K: number of biomarkers involved

$$y_{ij1} = \boldsymbol{m_1(\psi_{i1}, t_{ij1})} + g\left[m_1(\psi_{i1}, t_{ij1}), \sigma_1\right]\varepsilon_{ij}$$
$$\dots$$
$$y_{ijK} = \boldsymbol{m_K(\psi_{iK}, t_{ijK})} + g\left[m_K(\psi_{iK}, t_{ijK}), \sigma_K\right]\varepsilon_{ij}$$

$$h_{1i}(t) = h_{01} \times \exp(\boldsymbol{\alpha_{11}} \times \boldsymbol{m_1(\psi_{i1}, t)} + \dots + \boldsymbol{\alpha_{1K}} \times \boldsymbol{m_K(\psi_{iK}, t)} + \beta_1 \times Score_i)$$
$$h_{2i}(t) = h_{02} \times \exp(\boldsymbol{\alpha_{21}} \times \boldsymbol{m_1(\psi_{i1}, t)} + \dots + \boldsymbol{\alpha_{2K}} \times \boldsymbol{m_K(\psi_{iK}, t)} + \beta_2 \times Score_i)$$

Linear model: $\boldsymbol{m_k(\psi_{ik}, t_{ijk})} = \psi_{0ik} + \psi_{1ik} \times t_{ijk}$

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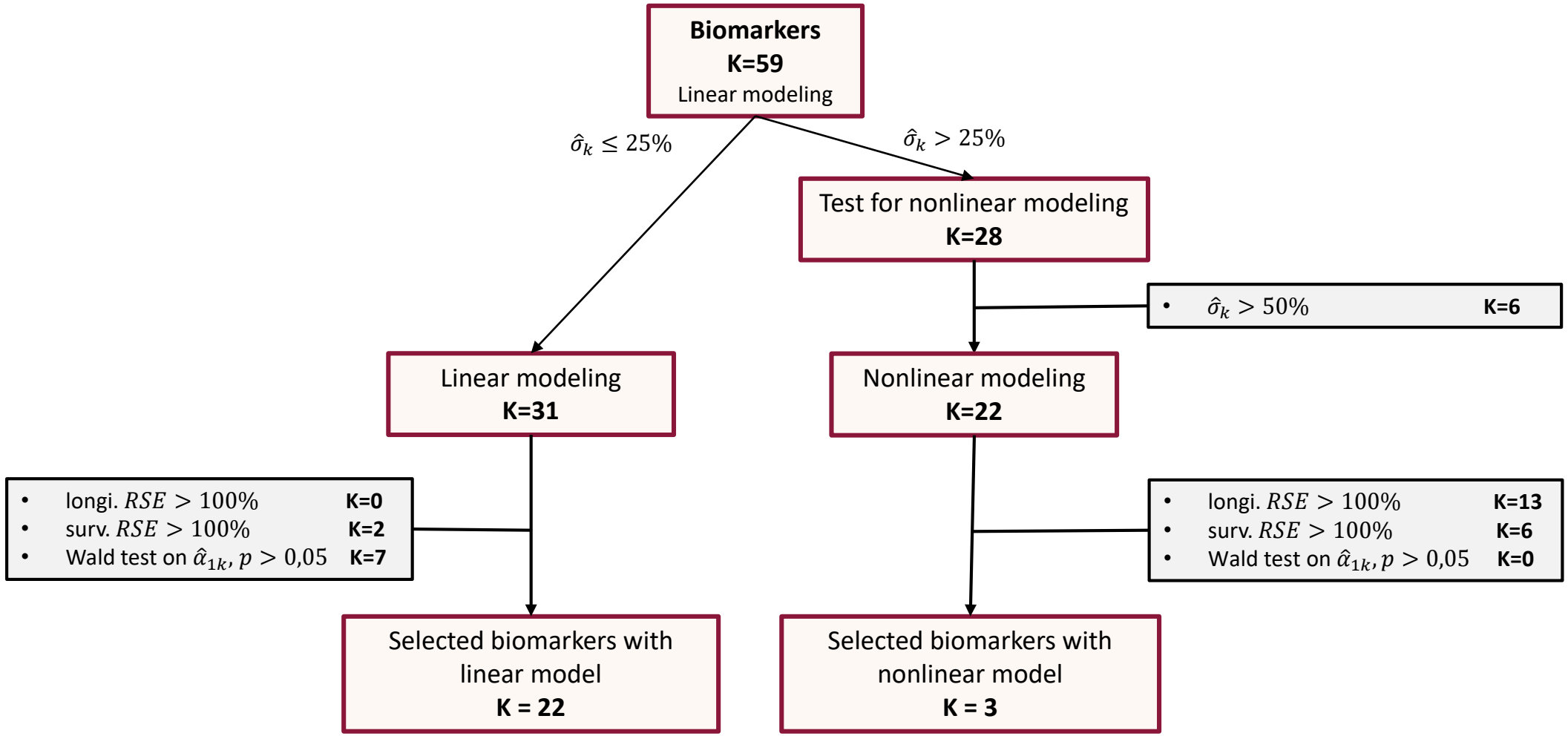
Estimation

$\theta = (\mu, \Omega, \sigma, h_{01}, h_{02}, \alpha_1, \alpha_2, \beta_1, \beta_2)$

Monolix software version 2018R2

$\mu = (\mu_1, \dots, \mu_K)$
$\Omega = diag(\omega_1, \dots, \omega_K)$
$\sigma = (\sigma_1, \dots, \sigma_K)$
$\alpha_1 = (\alpha_{11}, \dots, \alpha_{1K})$
$\alpha_2 = (\alpha_{21}, \dots, \alpha_{2K})$

Univariate joint models



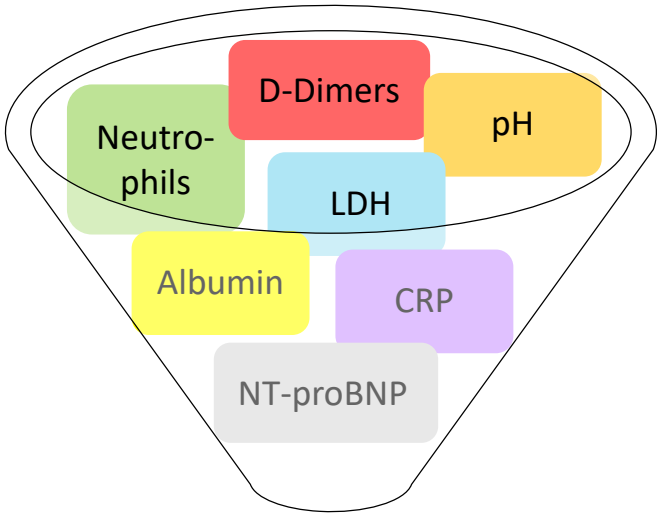
Univariate joint models

Biomarker	α_1	RSE (α_1)	-log10(p)	model
Complete blood count				
Neutrophil polynuclear cells	**0.24**	**16.17**	**9.20**	**nonlin**
Platelets	-0.004	27.66	3.52	lin
Erythrocytes	-0.44	45.28	1.57	lin
Hemoglobin	-0.14	49.06	1.38	lin
Coagulation				
D-Dimers	**1.08**	**14.86**	**10.78**	**lin**
Activated facteur V	0.04	18.40	7.26	lin
aPTT	1.50	20.00	6.24	lin
Fibrinogen	0.70	22.10	5.22	lin
Activated facteur II	-0.02	45.62	1.55	lin
Pulmonary functions				
pHa	**-20.61**	**11.18**	**18.42**	**lin**
pCO2a	0.19	12.48	14.95	lin
Oxyhemoglobin ratio	-2.04	45.23	1.57	lin
Markers of inflammation				
CRP	**1.25**	**17.63**	**7.85**	**lin**
Haptoglobin	0.42	19.03	6.83	lin
Orosomucoid	1.85	19.87	6.32	lin

Biomarker	α_1	RSE (α_1)	-log10(p)	model
Blood kidney functions/cellular lysis				
Lactate deshydrogenase (LDH)	**0.01**	**12.97**	**13.90**	**lin**
Uremia	0.07	18.11	7.48	nonlin
Kaliuresis	0.10	19.19	6.73	nonlin
Magnesium	6.65	23.96	4.52	lin
Calcemia	-6.00	25.27	4.12	lin
Creatininemia	0.003	32.27	2.71	lin
Phosphates	1.92	39.10	1.98	lin
Kalemia	0.99	44.01	1.64	lin
Urine kidney functions				
Liver/pancreatic functions				
Albuminemia	**-0.11**	**27.43**	**3.57**	**lin**
Lipasemia	0.88	17.22	8.19	lin
Cardiac markers				
NT-proBNP	**0.48**	**23.01**	**4.86**	**lin**

Multivariate joint models

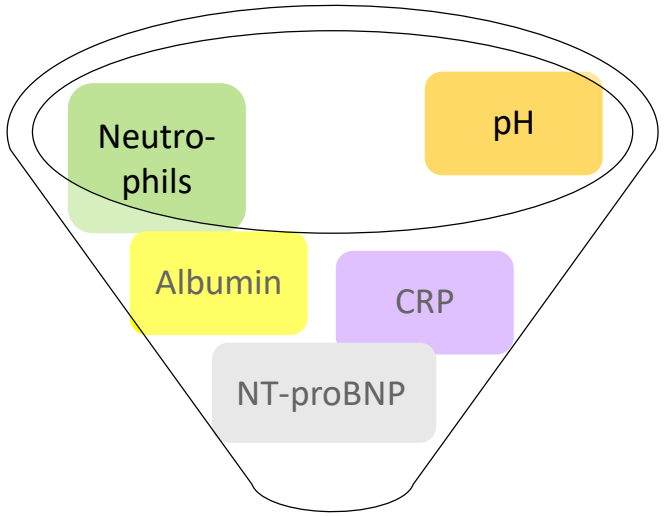
Initial multivariate joint model



death

$\hat{\alpha}_{1k}$

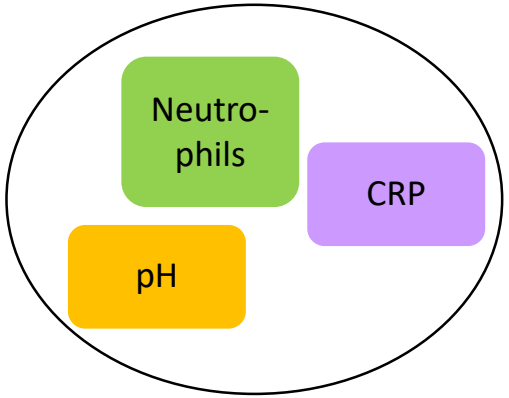
Intermediate multivariate joint model



discharge

$\hat{\alpha}_{2k}$

Final multivariate joint model

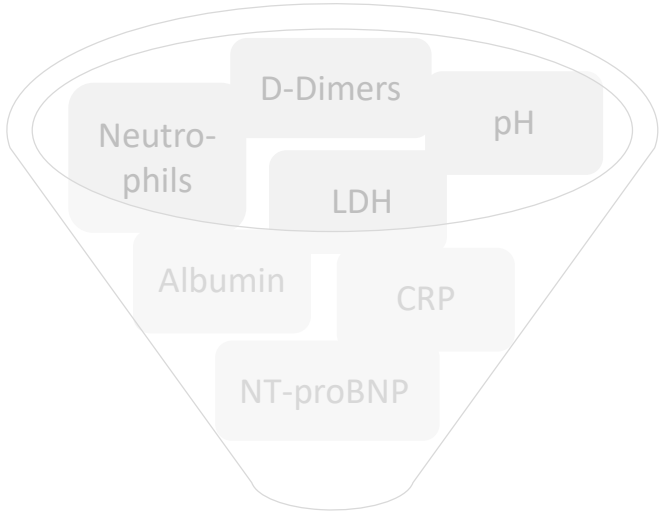


Backward selections

- Removed the highest p-value Wald test for $\hat{\alpha}_{.k}$
- Stop when all p-values for $< 5\%$

Multivariate joint models

Initial multivariate joint model



$\hat{\alpha}_{1k}$

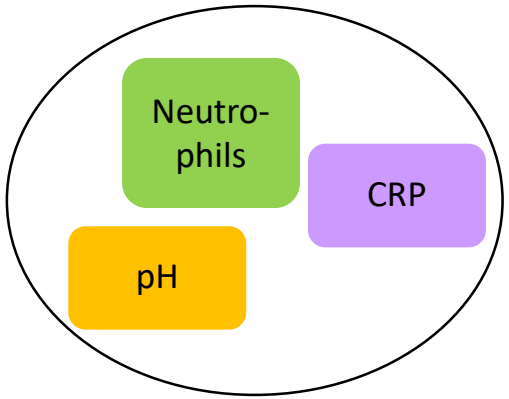
Intermediate multivariate joint model

Parameter	Value	R.S.E.(%)	p-value
Death			
α_{1neut} (L×10^{-9})	0.14	24.2	$< 10^{-4}$
α_{1pH}	-11.4	24.9	$< 10^{-4}$
α_{1CRP} (L.mg^{-1})	0.63	34.7	0.004
β_1	0.33	18.1	$< 10^{-4}$
Discharge			
α_{2neut} (L×10^{-9})	-0.14	39.1	0.01
α_{2pH}	25.2	25.2	$< 10^{-4}$
α_{2CRP} (L.mg^{-1})	-1.09	16.2	$< 10^{-4}$
β_2	-0.12	27.3	0.0002

Link and covariate parameter estimates (final multivariate joint model)

- Stop when all p-values for $< 5\%$

Final multivariate joint model

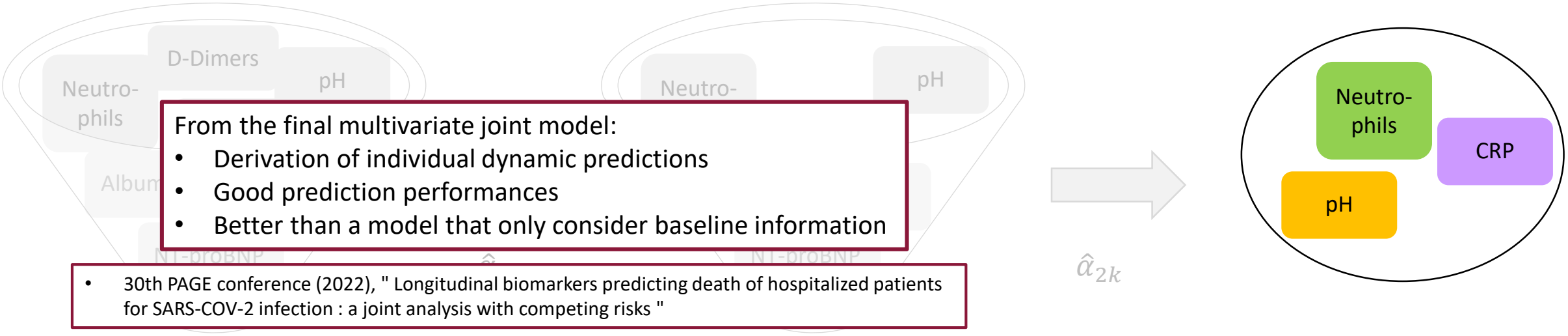


Multivariate joint models

Initial multivariate joint model

Intermediate multivariate joint model

Final multivariate joint model



From the final multivariate joint model:

- Derivation of individual dynamic predictions
- Good prediction performances
- Better than a model that only consider baseline information

- 30th PAGE conference (2022), " Longitudinal biomarkers predicting death of hospitalized patients for SARS-COV-2 infection : a joint analysis with competing risks "

Backward selections

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Objectives

- Evaluate the performances of the estimation
- Assess the validity of the proposed selection strategy

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Data generating mechanism

$M = 100$ datasets of $N = 300$ patients

$K = 7$ biomarkers (bm_1 to bm_7) simulated according to the design of the application (multivariate stage)

2 failure causes: death (event 1) and discharge (event 2)

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Biomarker	Longitudinal submodel	Error model	Measurement frequency	Association with event 1	Correlation on slopes
bm_1	Nonlinear	Proportional	Every 2 days	✓	
bm_2	Linear	Additive	Every 1.5 days	✓	
bm_3	Linear	Additive	Every 2 days	✓	
bm_4	Linear	Additive	Every 3 days		$\rho(\eta_{.4}, \eta_{.2}) = 0.8$
bm_5	Linear	Proportional	Every 3 days		$\rho(\eta_{.5}, \eta_{.3}) = 0.8$
bm_6	Linear	Proportional	Every 3 days		
bm_7	Linear	Proportional	Every 3 days		

$$h_{i1}(t, \psi_i; \theta) = \frac{p_1 g_1 \exp(-g_1 \times t)}{1 - p_1(1 - \exp(-g_1 \times t))} \exp\left(\alpha_{11} \times m_1(\psi_{i1}, t) + \cdots + \alpha_{13} \times m_3(\psi_{i3}, t)\right)$$

$$h_{i2}(t, \psi_i; \theta) = \frac{1}{b} \times \frac{(1 - F_1(\infty)) \exp(-t/b)}{1 - (1 - F_1(\infty))(1 - \exp(-t/b))}$$

Estimands and performances measures

Objective 1: assess the performances of the estimation

For a simulation $m \in \{1, \dots, M\}$:

- Estimation of θ (true model parameters)
- Performances assessed with relative estimation errors:

$$\mathrm{REE}^m(\hat{\theta}) = \frac{\hat{\theta}^m - \theta}{\theta} \times 100$$

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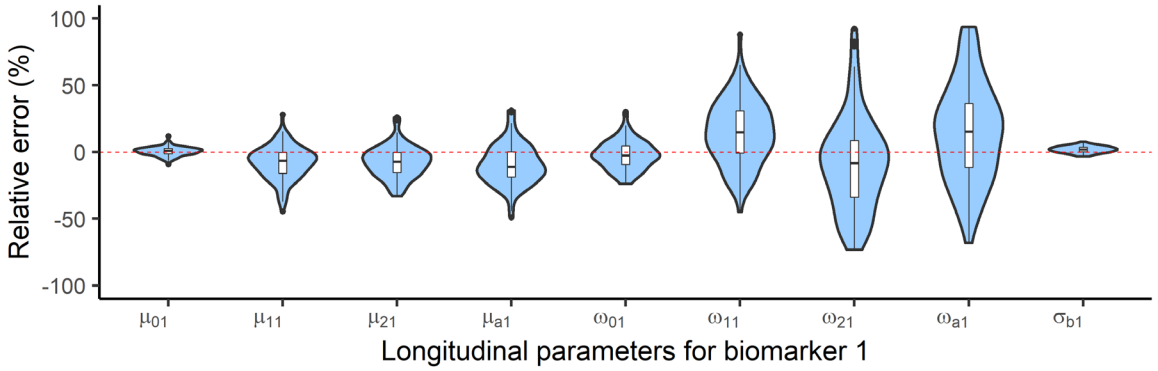
Objective 2: assess the ability of the backward strategy to find the "true" model

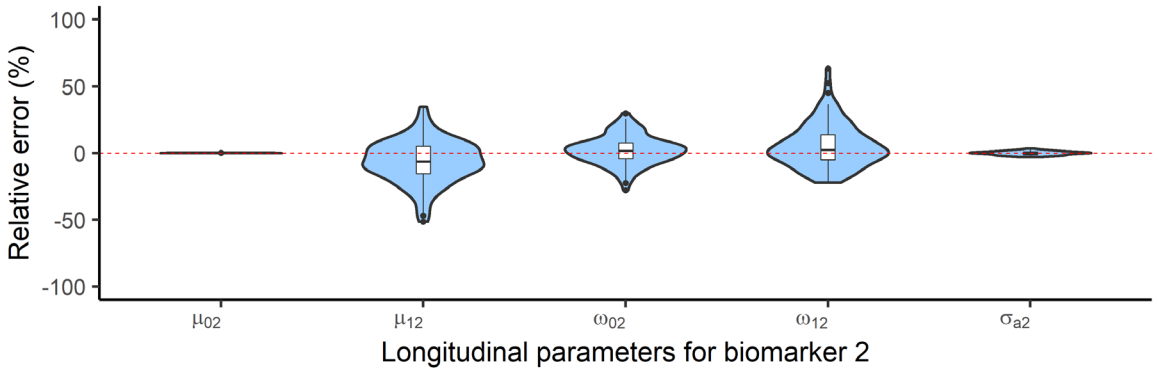
For a simulation $m \in \{1, \dots, M\}$:

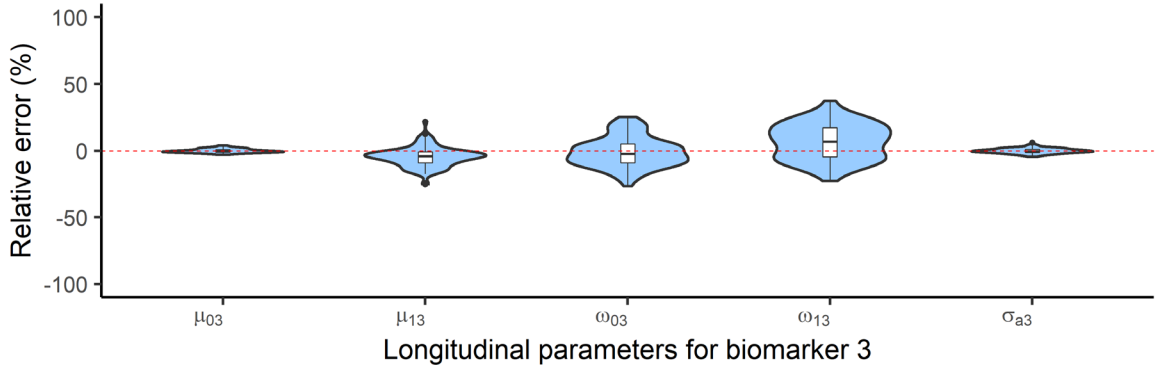
- Start with the full multivariate model (7 biomarkers)
- Backward process on $\hat{\alpha}_{1k}$ (stop when all p-values are $< 5\%$)
- Performances assessed by reporting the final set of biomarkers

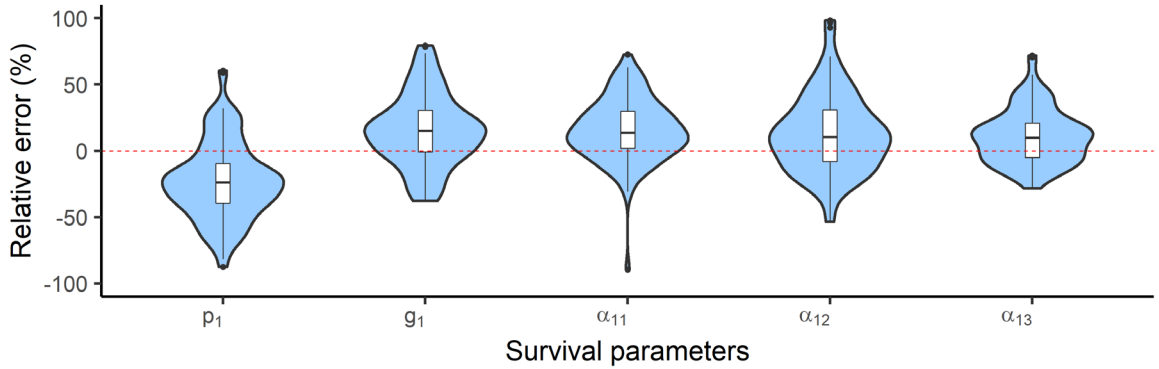
Results

Objective 1: assess the performances of the estimation





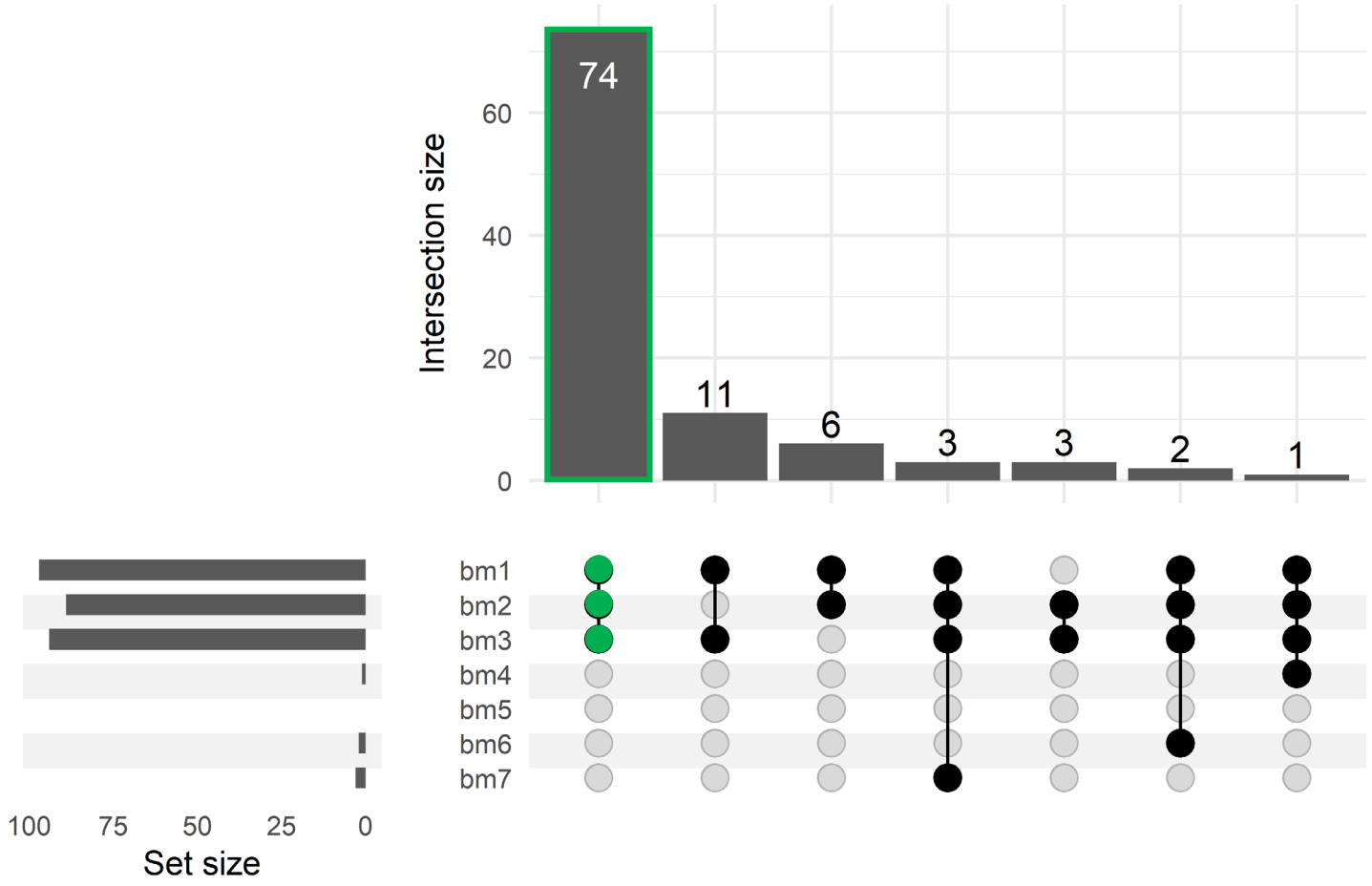




Distribution of the Relative Estimation Errors for each model parameter

Results

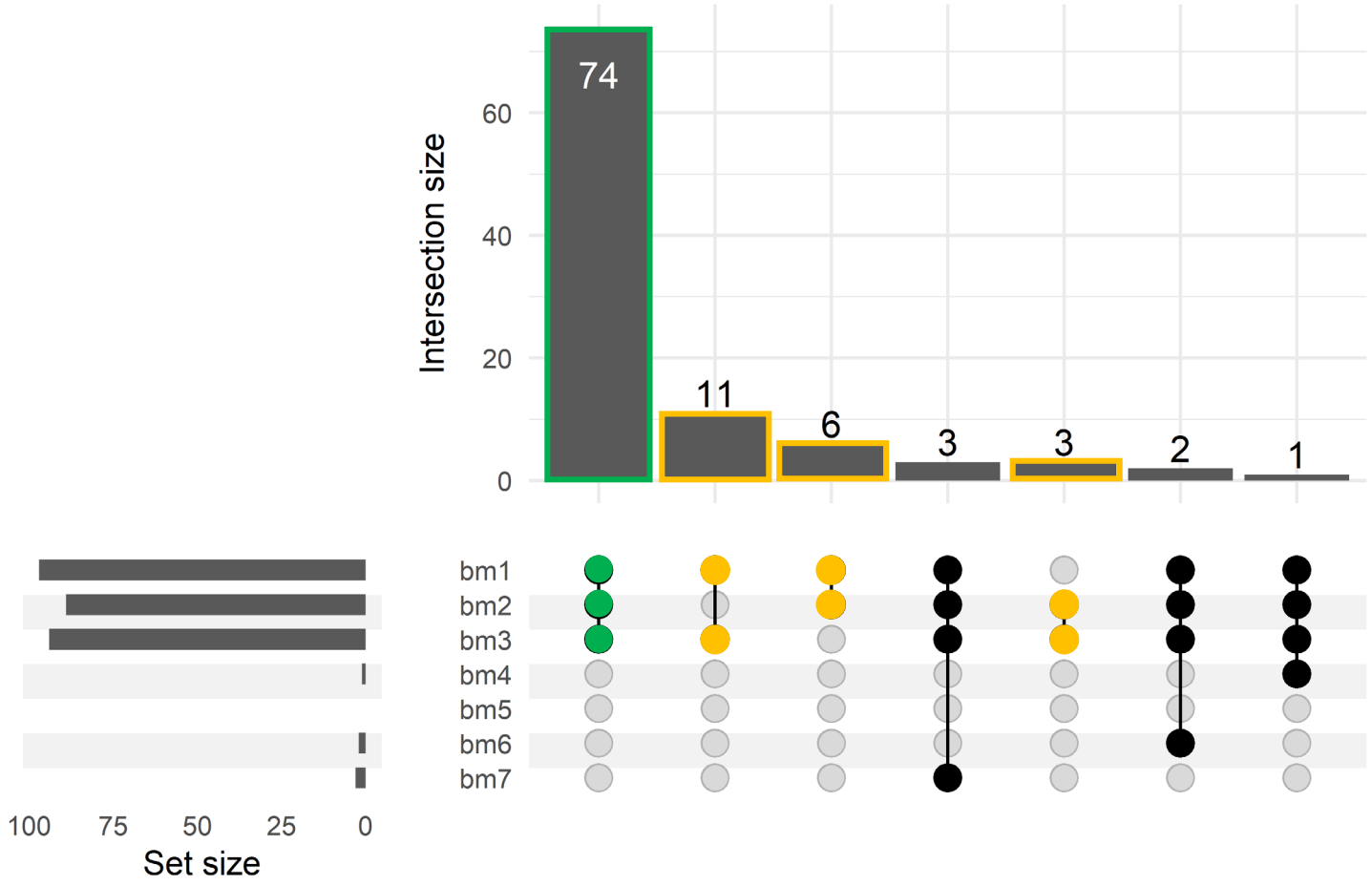
Objective 2: assess the ability of the backward strategy to find the "true" model



Final set of biomarkers selected after the backward process for each simulation

Results

Objective 2: assess the ability of the backward strategy to find the "true" model



Final set of biomarkers selected after the backward process for each simulation

Objectives: extend the *saemix* package to the case of multi-responses and joint models

- Re-defining the likelihood expression (to allow for multiple outcomes)
- Implementing an algorithm for Fisher Information Matrix (FIM) computation, noted $I(\hat{\theta})$

16- Louis, *Journal of the Royal Statistical Society*, 1982
17- Delattre and Kuhn, *hal-02285712v2,* 2023

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  - In joint model context: $I(\hat{\theta})$ computed by stochastic approximations
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  - In joint model context: $I(\hat{\theta})$ computed by stochastic approximations
  - Monolix software: Louis's method[16] (time consuming…)
  - Alternative stochastic algorithm developed by Delattre and Kuhn[17]

→ interesting properties because it is integrated in the SAEM algoritm (time saving)
→ but not currently evaluated for joint models

16- Louis, *Journal of the Royal Statistical Society*, 1982
17- Delattre and Kuhn, *hal-02285712v2,* 2023

Evaluation by simulations

Aims

1. Evaluate the SAEM algorithm extended in R *saemix* package[14] for joint models:

	Single event	2 competing risks
Linear mixed-effects model	LMEM – TTE	LMEM – CR
Nonlinear mixed-effects model	NLMEM – TTE	NLMEM – CR

2. Evaluate the algorithm developed by Delattre and Kuhn[17] for the 4 previous models (standard errors estimation)

14- Comets et al. *Journal of Statistical Software*, 2017
17- Delattre and Kuhn, *hal-02285712v2,* 2023

Evaluation by simulations

Data generating mechanism

For each of the 4 models presented, we simulate M = 100 datasets of N = 100 patients.
Biomarker measurements available each day until time-to-event for at most 30 days

LMEM – TTE

$$y_{ij} = m_l(\psi_i, t_{ij}) + \sigma\epsilon_{ij}$$
$$h_i(t, \psi_i; \theta) = h_0 \times \exp\left(\boldsymbol{\alpha} \times m_l(\psi_i, t)\right)$$

NLMEM-TTE

$$y_{ij} = m_{nl}(\psi_i, t_{ij}) + \sigma\epsilon_{ij}$$
$$h_i(t, \psi_i; \theta) = h_0 \times \exp\left(\boldsymbol{\alpha} \times m_{nl}(\psi_i, t)\right)$$

LMEM-CR

$$y_{ij} = m_l(\psi_i, t_{ij}) + \sigma\epsilon_{ij}$$
$$h_{i1}(t, \psi_i; \theta) = \frac{p_1 g_1 \exp(-g_1 \times t)}{1 - p_1(1 - \exp(-g_1 \times t))} \exp\left(\boldsymbol{\alpha_1} \times m_l(\psi_i, t)\right)$$
$$h_{i2}(t, \psi_i; \theta) = \frac{1}{b} \times \frac{(1 - F_1(\infty)) \exp(-t/b)}{1 - (1 - F_1(\infty))(1 - \exp(-t/b))}$$

NLMEM-CR

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Evaluation by simulations

Estimands

Objective 1: assess parameter estimation

JM LMEM/NLMEM – TTE

$\theta = (\mu, \Omega, \sigma, h_0, \alpha)$

JM LMEM/NLMEM – CR

$\theta = (\mu, \Omega, \sigma, p_1, g_1, \alpha, b)$

Performance measures

Relative estimation errors:

$$\mathrm{REE}^m(\hat{\theta}) = \frac{\hat{\theta}^m - \theta}{\theta} \times 100$$

Evaluation by simulations

Estimands

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Objective 2: assess standard error estimation

JM LMEM/NLMEM – TTE/CR

$\hat{\Sigma}$ = variance-covariance matrix of $\hat{\theta}$

Performance measures

Relative estimation errors:

$$\mathrm{REE}^m(\hat{\theta}) = \frac{\hat{\theta}^m - \theta}{\theta} \times 100$$

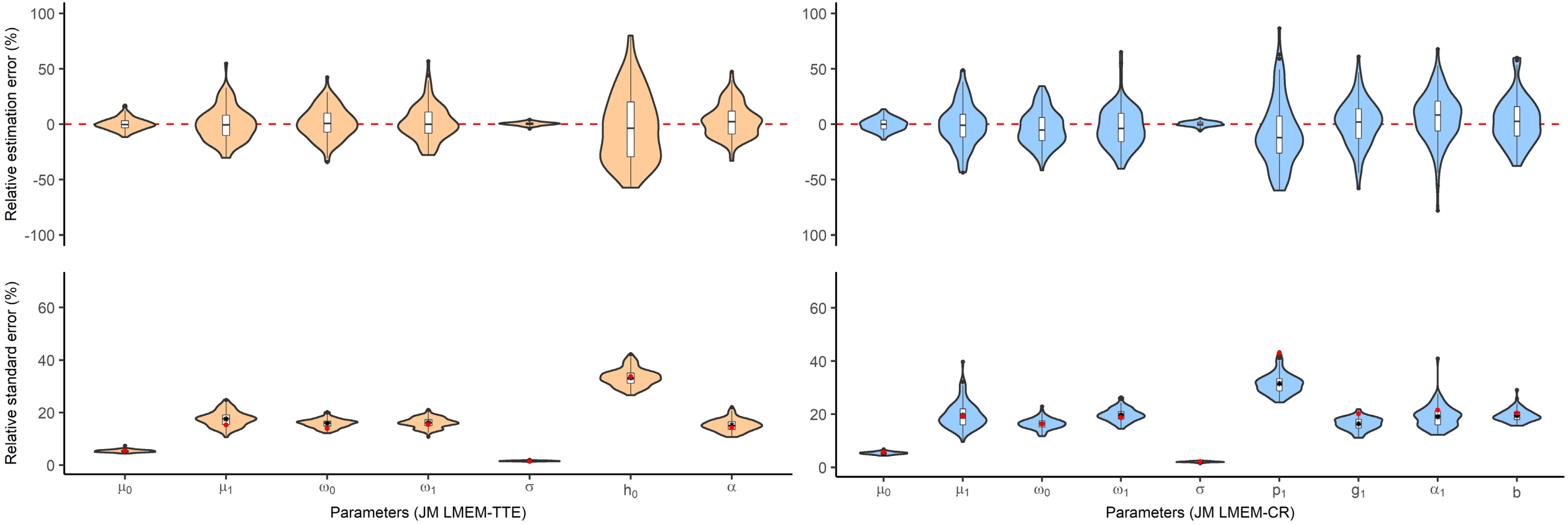
Relative standard errors:

$$\mathrm{RSE}^m(\hat{\theta}) = \frac{\sqrt{diag(\hat{\Sigma}^m)}}{\hat{\theta}^m} \times 100$$

Relative empirical error:

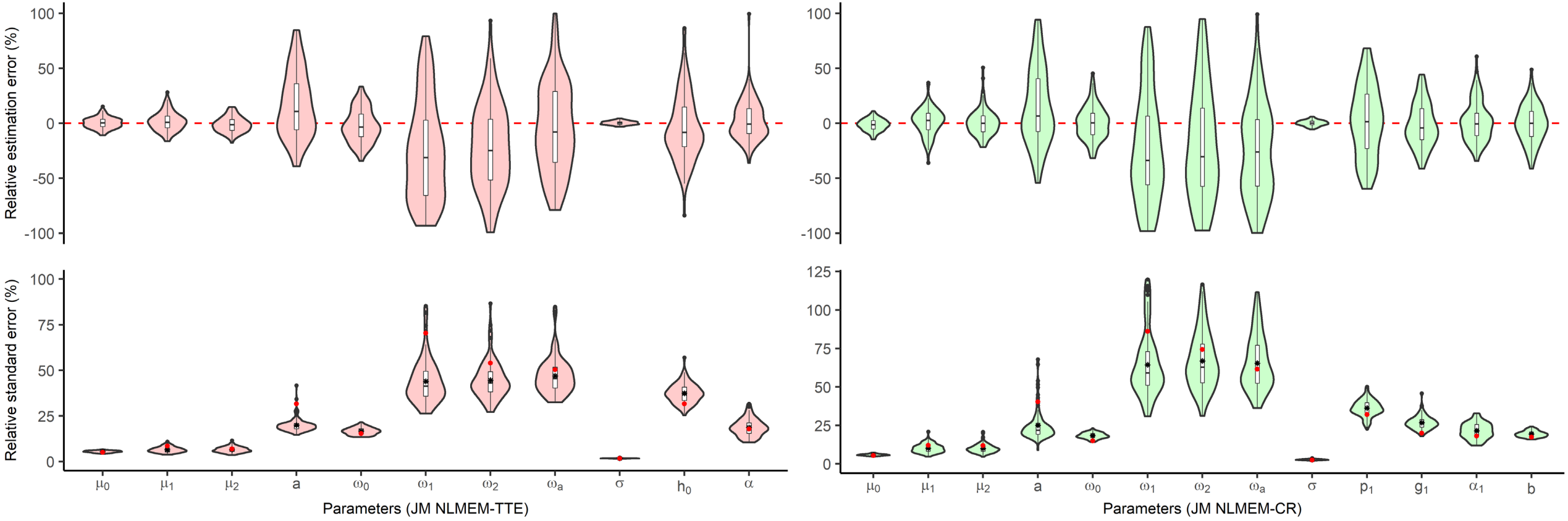
$$\mathrm{RSE}^{emp}(\hat{\theta}) = \sqrt{\frac{1}{m-1}\sum_{m=1}^{M}\left(\hat{\theta}^m - \bar{\hat{\theta}}\right)^2} \times \frac{100}{\bar{\hat{\theta}}}$$

Distribution of REE (top) and stochastic RSE versus empirical RSE (bottom) - JM LMEM-TTE and JM LMEM-CR



- Empirical RSE
- ★ Mean distribution of the stochastic RSE

Distribution of REE (top) and stochastic RSE versus empirical RSE (bottom) - JM NLMEM-TTE and JM NLMEM-CR



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- Mean distribution of the stochastic RSE

COVID-19 case study

- Developments of a multivariate joint model to predict the death of patients hospitalized for SARS-CoV-2 infection and a strategy to select among various biomarkers
- Evolution of neutrophils, pH and CRP are predictive of the death/discharge of patients
- Identify biomarkers in other emergent diseases

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- The backward strategy yields good performances

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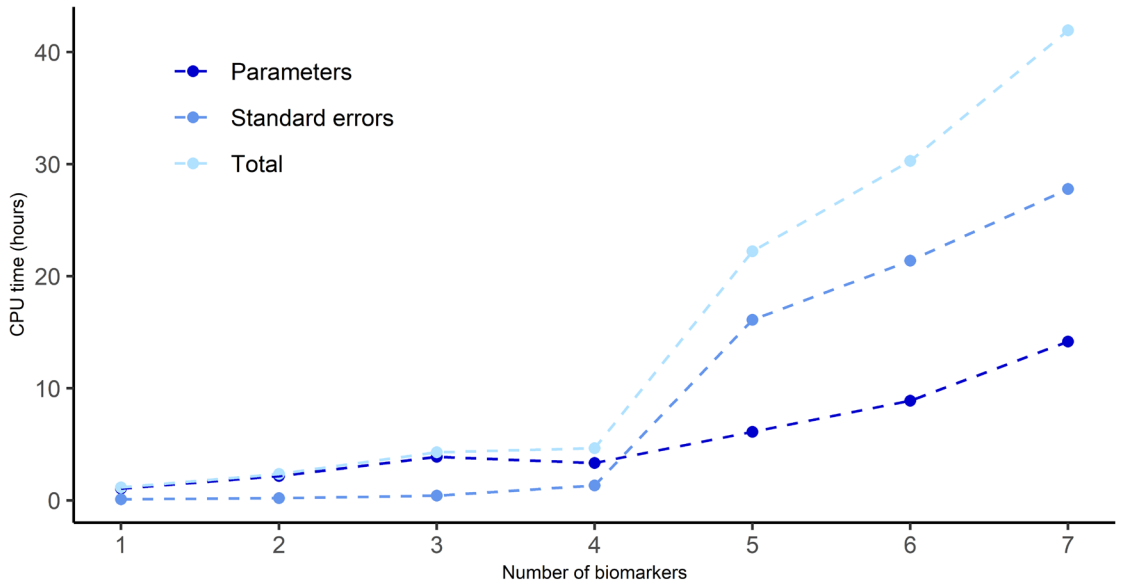
Limitations

- Limited number of biomarkers included in the multivariate analysis (computational limit)
- Backward strategy usually outperformed by penalized regression methods[18] (LASSO penalization)



CPU time spent to estimate a joint model involving a given number of biomarkers

18- Tibshirani, *Journal of the Royal Statistical Society,* 1996

saemix extension

- Extension of the R package *saemix* to the case of joint models
- Good properties for parameter and standard errors estimation
- Flexible tool in parametric joint model framework
- Users define the likelihood of the model (very specific joint models can be considered)

Perspectives

- Need to evaluate for multiple longitudinal biomarkers
- Need to develop goodness of fit tools in the package

Functions and examples available on Github:
https://github.com/saemixdevelopment/saemixextension/tree/master/joint

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Thank you for your attention !