

SEQUENTIAL MONTE CARLO METHODS IN BAYESIAN JOINT MODELS FOR LONGITUDINAL AND TIME-TO-EVENT DATA

Danilo Alvares

Departamento de Estadística
Pontificia Universidad Católica de Chile

Joint work with



Carmen Armero (Universitat de València)

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This talk is based on

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Sequential Monte Carlo methods in Bayesian joint models for longitudinal and time-to-event data

Danilo Alvares¹, Carmen Armero², Anabel Forte², and Nicolas Chopin³

¹Department of Statistics, Pontificia Universidad Católica de Chile, Macul, Chile.

¹Department of Statistics and O.R., Universitat de València, Burjassot, Spain.

¹Centre for Research in Economics and Statistics, ENSAE, Palaiseau, France.

Abstract: The statistical analysis of the information generated by medical follow-up is a very important challenge in the field of personalized medicine. As the evolutionary course of a patient's disease progresses, his/her medical follow-up generates more and more information that should be processed immediately in order to review and update his/her prognosis and treatment. Hence, we focus on this update process through sequential inference methods for joint models of longitudinal and time-to-event data from a Bayesian perspective. More specifically, we propose the use of sequential Monte Carlo (SMC) methods for static parameter joint models with the intention of reducing computational time in each update of the full Bayesian inferential process. Our proposal is very general and can be easily applied to most popular joint models approaches. We illustrate the use of the presented sequential methodology in a joint model with competing risk events for a real scenario involving patients on mechanical ventilation in intensive care units (ICUs).

Key words: Bayesian analysis, IBIS algorithm, joint models, sequential inference.

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Outline

- 1 Background
- 2 Sequential learning
- 3 Sequential methods for Bayesian joint models
- 4 Application in ICU discharge data
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Definition (National Academy of Science)

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- 2 Risk of an event considering a time-varying endogenous covariate, typically modeled through a longitudinal process.

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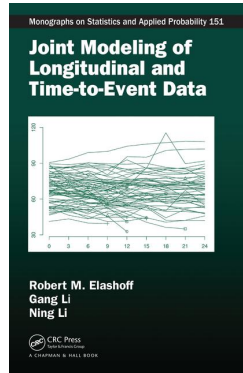
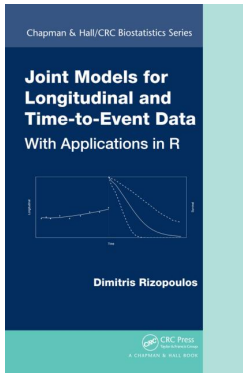
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Literature

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- 3 Full joint probability distribution [Armero et al., 2018]:

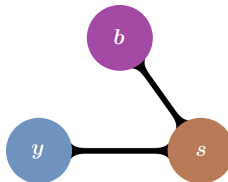
$$f(\mathbf{y}, \mathbf{s}, \mathbf{b}, \theta) = f(\mathbf{y}, \mathbf{s} \mid \mathbf{b}, \theta) f(\mathbf{b} \mid \theta) \pi(\theta)$$

- \mathbf{y} : longitudinal; \mathbf{s} : survival; \mathbf{b} : random-effects; θ : parameters.
- $f(\mathbf{y}, \mathbf{s} \mid \mathbf{b}, \theta)$: conditional joint distribution of (\mathbf{y}, \mathbf{s}) given \mathbf{b} and θ .
- $f(\mathbf{b} \mid \theta)$: conditional distribution of \mathbf{b} given θ .
- $\pi(\theta)$: prior distribution of θ .

Connection structures for joint models [Alvares, 2017]

Pattern-mixture models

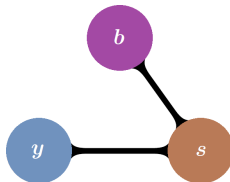
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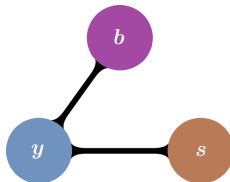
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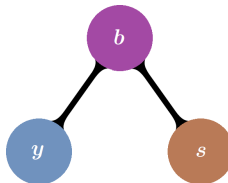
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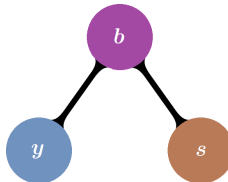
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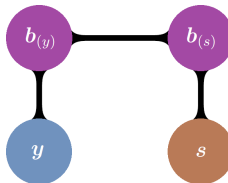
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Random-effects models

$$f(\mathbf{y}, \mathbf{s} \mid \mathbf{b}, \theta) = f(\mathbf{y} \mid \mathbf{b}_{(y)}, \theta) f(\mathbf{s} \mid \mathbf{b}_{(s)}, \theta)$$



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We propose and implement dynamic procedures based on sequential Monte Carlo methods to make quick inference and prediction

Outline

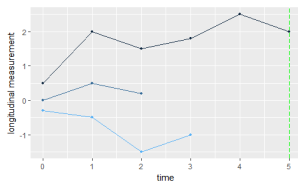
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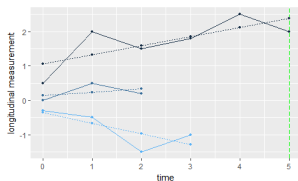
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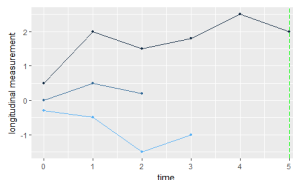
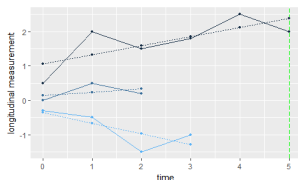
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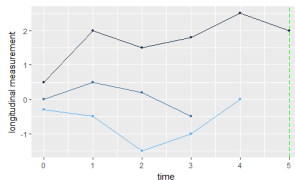
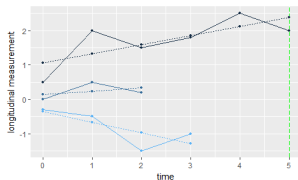
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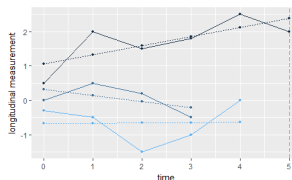
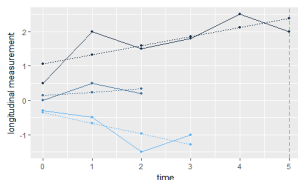
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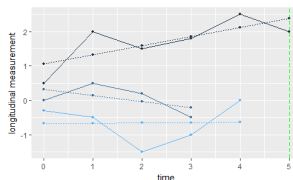
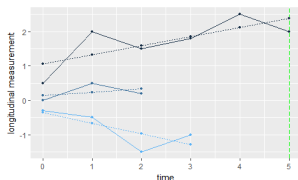
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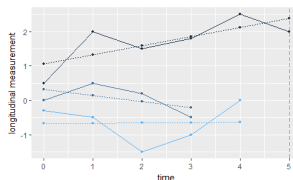
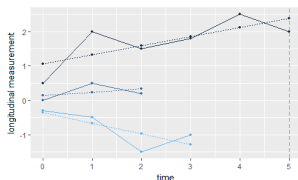
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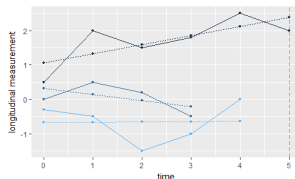
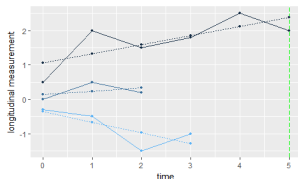


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It becomes advisable to use the Bayes' theorem to update the relevant information as it is recorded:

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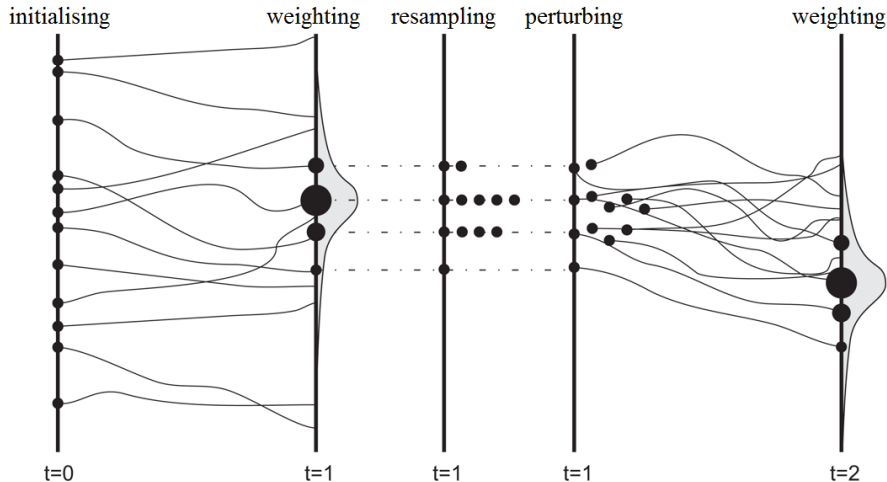
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Other related names: particle filtering, Monte Carlo filter, survival of the fittest, sequential imputations, condensation, bootstrap filter, sequential importance resampling [Cappé et al., 2007].

Sequential Monte Carlo scheme



Source: C. Montzka, V. R. N. Pauwels, H. J. H. Franssen, X. Han, and H. Vereecken. Multivariate and multiscale data assimilation in terrestrial systems: a review. *Sensors*, 12(12): 16291 - 16333, 2012.

SMC methods for models of static parameters

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Iterated Batch Importance Sampling (IBIS) [Chopin, 2002]

SMC algorithm for models of static parameters

Iterated Batch Importance Sampling (IBIS) algorithm

Step 1. Draw $\theta^{(k)} \sim \pi(\theta \mid \mathcal{D}_1)$ and set $w^{(k)} \leftarrow 1/K$, $k = 1, \dots, K$.

Step 2. From new data \mathcal{D}_2 , calculate

$$\tilde{w}^{(k)} \leftarrow f(\mathcal{D}_2 \mid \mathcal{D}_1, \theta^{(k)}) w^{(k)},$$

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if ($ESS < K_T$) then

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SMC algorithm for models of static parameters

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LIMITATION: standard IBIS does not work for random effects models

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- 2 Sequential learning
- 3 Sequential methods for Bayesian joint models**
- 4 Application in ICU discharge data
- 5 Conclusions

Updating the inference on θ

Standard IBIS works

$$\pi(\theta \mid \mathcal{D}_1, \mathcal{D}_2) \propto f(\mathcal{D}_1, \mathcal{D}_2 \mid \theta) \pi(\theta)$$

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Integration methods used:

- Monte Carlo
- Quasi-Monte Carlo

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Metropolis-Hastings algorithm based on posterior samples of $\boldsymbol{\theta}$

Sequential Monte Carlo algorithm for joint models

SMC-JM algorithm [Alvares et al., 2020]

Step 1. Draw $\theta^{(k)} \sim \pi(\theta \mid \mathcal{D}_1)$ and set $w^{(k)} \leftarrow 1/K$, $k = 1, \dots, K$.

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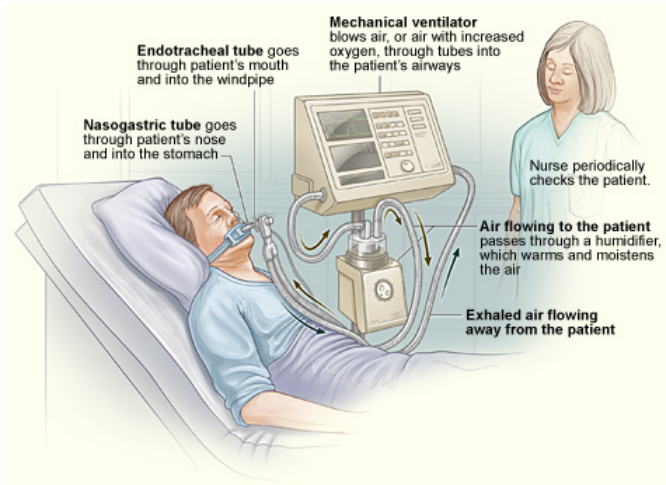
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- 2 Sequential learning
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Context



Source: <http://www.dentistryiq.com/articles/2014/03/boomers-and-the-greatest-generation.html>

Goal

Analysis of the association between a severity marker and the events *alive discharge* and *death* for patients receiving mechanical ventilation in intensive care units (ICU) during 30 days

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- 2 139 patients: 97 (69.8%) were discharged alive, 28 (20.1%) died, and 14 (10.1%) were administratively censored
- 3 Covariate: Age
- 4 Biomarker: Sequential Organ Failure Assessment (SOFA) score

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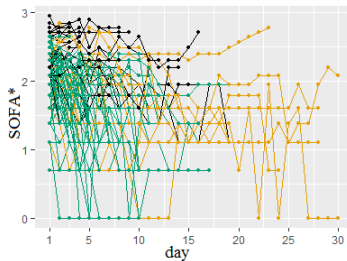
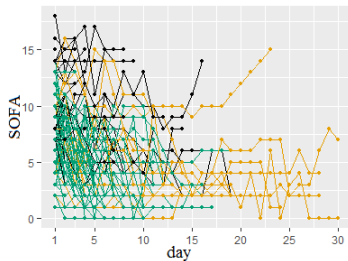
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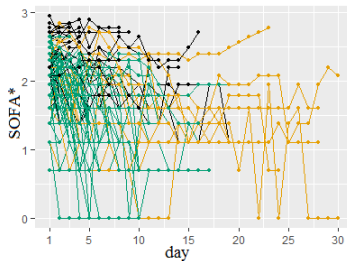
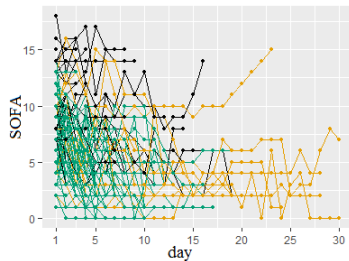
Data description

$$\text{SOFA}^* = \log(\text{SOFA} + 1)$$



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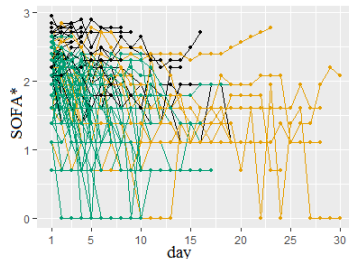
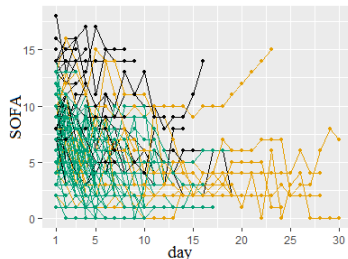
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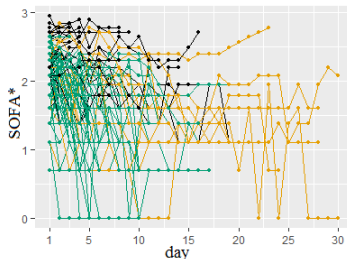
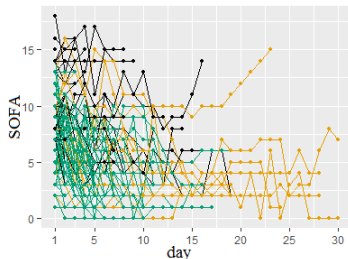


Removing observations:

- 1 **Patient 12:** 71 years old, discharged alive from the ICU at day 6, and its SOFA scores, from day 1 to 6, were 9, 9, 9, 4, 2, and 2.
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Bayesian joint modeling and preliminary results

- T_{iv} : time to event v for patient i .
- $v = 1$: *alive discharge*, $v = 2$: *death*, and $i = 1, \dots, 138$.
- $y_i(t)$: log(SOFA+1) of patient i at time t .
- $\theta = (\alpha_1, \alpha_2, \lambda_1, \lambda_2, \nu_1, \nu_2, \gamma_1, \gamma_2, \beta, \sigma, \sigma_0, \sigma_1)^\top$.

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Competing risks submodel

$$h_{iv}(t \mid b_{0i}, b_{1i}, \theta) = \lambda_v \nu_v t^{\nu_v - 1} \exp \left[\gamma_v \text{age}_i + \alpha_{0v} b_{0i} + \alpha_{1v} b_{1i} t \right]$$

$$(b_{0i}, b_{1i} \mid \sigma_0, \sigma_1) \sim \mathcal{N} \left((0, 0)^\top, \text{diag}(\sigma_0^2, \sigma_1^2) \right)$$

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- T_{iv} : time to event v for patient i .
- $v = 1$: *alive discharge*, $v = 2$: *death*, and $i = 1, \dots, 138$.
- $y_i(t)$: log(SOFA+1) of patient i at time t .
- $\theta = (\alpha_1, \alpha_2, \lambda_1, \lambda_2, \nu_1, \nu_2, \gamma_1, \gamma_2, \beta, \sigma, \sigma_0, \sigma_1)^\top$.

Competing risks submodel

$$h_{iv}(t \mid b_{0i}, b_{1i}, \theta) = \lambda_v \nu_v t^{\nu_v - 1} \exp \left[\gamma_v \text{age}_i + \alpha_{0v} b_{0i} + \alpha_{1v} b_{1i} t \right]$$

$$(b_{0i}, b_{1i} \mid \sigma_0, \sigma_1) \sim \mathcal{N} \left((0, 0)^\top, \text{diag}(\sigma_0^2, \sigma_1^2) \right)$$

Longitudinal submodel

$$(y_i(t) \mid b_{0i}, b_{1i}, \theta) \sim \mathcal{N}(\mu_i(t), \sigma^2)$$

$$\mu_i(t) = \beta_0 + b_{0i} + (\beta_1 + b_{1i})t + \beta_2 \text{age}_i$$

Bayesian joint modeling and preliminary results

- T_{iv} : time to event v for patient i .
- $v = 1$: *alive discharge*, $v = 2$: *death*, and $i = 1, \dots, 138$.
- $y_i(t)$: log(SOFA+1) of patient i at time t .
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Prior distribution

$$\pi(\alpha_{01}) = \pi(\alpha_{02}) = \pi(\alpha_{11}) = \pi(\alpha_{12}) = \mathcal{N}(0, 1000)$$

$$\pi(\log(\lambda_1)) = \pi(\log(\lambda_2)) = \mathcal{N}(0, 1000)$$

$$\pi(\nu_1) = \pi(\nu_2) = \mathcal{G}(0.01, 0.01)$$

$$\pi(\gamma_1) = \pi(\gamma_2) = \mathcal{N}(0, 1000)$$

$$\pi(\beta_0) = \pi(\beta_1) = \pi(\beta_2) = \mathcal{N}(0, 1000)$$

$$\pi(\sigma) = \pi(\sigma_0) = \pi(\sigma_1) = \mathcal{U}(0, 100)$$

Bayesian joint modeling and preliminary results

θ	Mean	SD	2.5%	50%	97.5%	$P(\cdot > 0 \mid \mathcal{D})$
<i>Competing risks process - Alive</i>						
γ_1	0.001	0.007	-0.012	0.001	0.016	0.563
α_{01}	-0.203	0.323	-0.846	-0.208	0.468	0.259
α_{11}	-1.012	0.256	-1.582	-0.998	-0.549	0.000
ν_1	1.525	0.151	1.247	1.516	1.834	—
λ_1	0.015	0.009	0.004	0.013	0.040	—
<i>Competing risks process - Death</i>						
γ_2	0.022	0.017	-0.009	0.021	0.058	0.917
α_{02}	3.367	0.948	1.756	3.307	5.456	1.000
α_{12}	0.745	0.472	-0.173	0.750	1.605	0.943
ν_2	1.172	0.250	0.740	1.157	1.733	—
λ_2	0.002	0.004	0.000	0.001	0.012	—
<i>Longitudinal process - SOFA*</i>						
β_0	1.844	0.155	1.537	1.844	2.141	1.000
β_1	-0.086	0.009	-0.105	-0.086	-0.067	0.000
β_2	0.005	0.002	0.000	0.005	0.009	0.973
σ	0.311	0.008	0.295	0.310	0.328	—
σ_0	0.407	0.032	0.349	0.405	0.476	—
σ_1	0.067	0.008	0.052	0.066	0.084	—

Conditional cumulative incidence function (CIF)

$$P(T_i \leq t, \delta_i = v \mid y_{i,1:n_i+g}, T_i \geq t_{i,n_i+g}, \mathbf{b}_i, \boldsymbol{\theta}), \quad t > t_{i,n_i+g}$$

Conditional cumulative incidence function (CIF)

$$P(T_i \leq t, \delta_i = v \mid \underline{y_{i,1:n_i+g}}, T_i \geq t_{i,n_i+g}, \mathbf{b}_i, \boldsymbol{\theta}), \quad t > t_{i,n_i+g}$$

Conditional cumulative incidence function (CIF)

$$\begin{aligned}
 P(T_i \leq t, \delta_i = v \mid \underline{y_{1:n_i+g}}, T_i \geq t_{i,n_i+g}, \mathbf{b}_i, \theta) \\
 = F_{iv}(t \mid T_i \geq t_{i,n_i+g}, \mathbf{b}_i, \theta), \quad t > t_{i,n_i+g}
 \end{aligned}$$

Conditional cumulative incidence function (CIF)

$$\begin{aligned}
 P(T_i \leq t, \delta_i = v \mid \overline{y_{i,1:n_i+g}}, T_i \geq t_{i,n_i+g}, \mathbf{b}_i, \theta) \\
 = F_{iv}(t \mid T_i \geq t_{i,n_i+g}, \mathbf{b}_i, \theta), \quad t > t_{i,n_i+g}
 \end{aligned}$$

Bayesian approach:

$$E(F_{iv}(t \mid T_i \geq t_{i,n_i+g}, \mathbf{b}_i, \theta) \mid \mathcal{D}) = \int F_{iv}(t \mid T_i \geq t_{i,n_i+g}, \mathbf{b}_i, \theta) \pi(\mathbf{b}_i, \theta \mid \mathcal{D}_i^g, \mathcal{D}) d(\mathbf{b}_i, \theta),$$

where $\mathcal{D}_i^g = [y_{i,n_i+1:n_i+g}, (t_{i,n_i+g}, \delta_i)]^\top$.

$$E(F_{iv}(t \mid T_i \geq t_{i,n_i+g}, \mathbf{b}_i, \theta) \mid \mathcal{D}) \approx \frac{1}{L} \sum_{l=1}^L F_{iv}(t \mid T_i \geq t_{i,n_i+g}, \mathbf{b}_i^{(l)}, \theta^{(l)}),$$

where $\mathbf{b}_i^{(l)}$ and $\theta^{(l)}$ are drawn from $\pi(\mathbf{b}_i, \theta \mid \mathcal{D}_i^g, \mathcal{D})$, for $l = 1, \dots, L$ and $v = 1, 2$.

Individual estimation of the dynamic conditional CIF

SMC for Bayesian joint models

Step 1. INITIALIZING.

Step 2. WEIGHTING.

if ($ESS < K_T$) then

Step 3. RESAMPLING.

Step 4. MOVE.

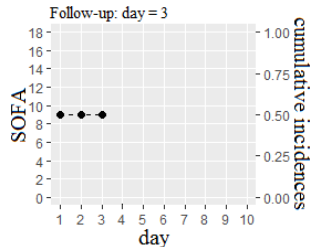
end

Step 5. PERSONALIZE.

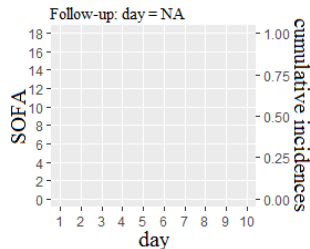
Update the conditional CIF.

If new data available, return to **Step 2.**

Patient 12



Patient 131



Individual estimation of the dynamic conditional CIF

SMC for Bayesian joint models

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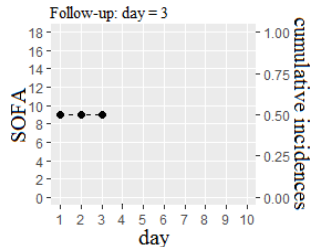
end

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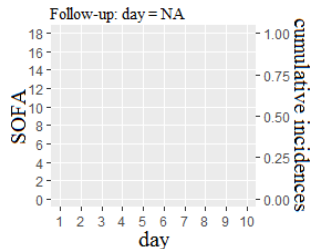
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Patient 12



Patient 131



Individual estimation of the dynamic conditional CIF

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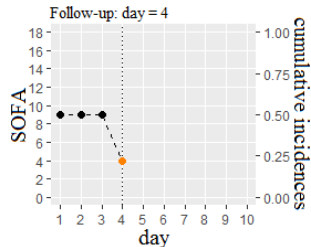
end

Step 5. PERSONALIZE.

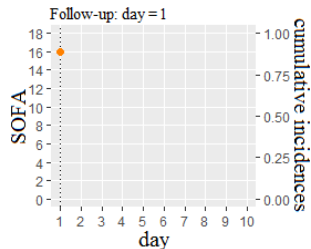
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Patient 12



Patient 131



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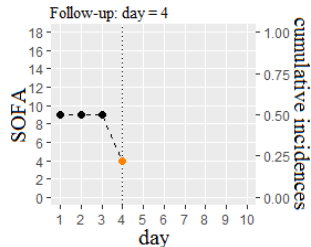
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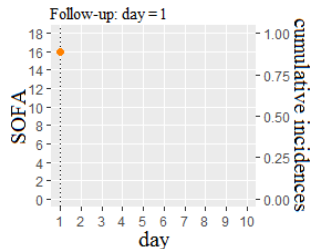
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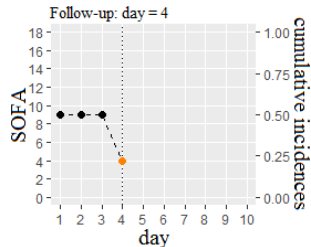
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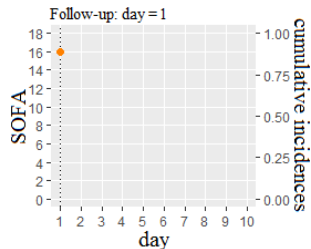
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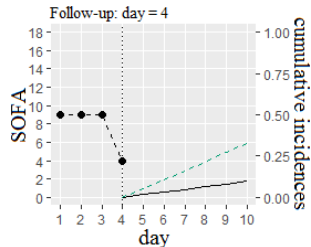
end

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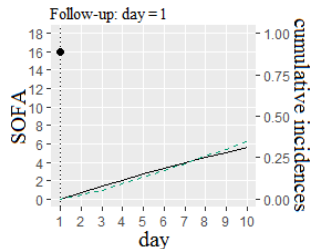
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Patient 131



Individual estimation of the dynamic conditional CIF

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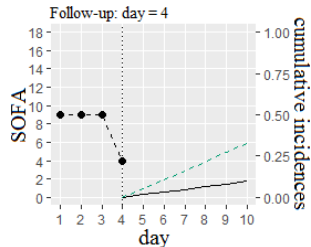
end

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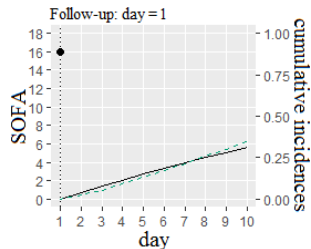
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Patient 131



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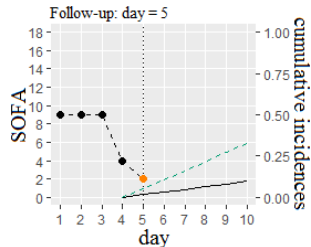
end

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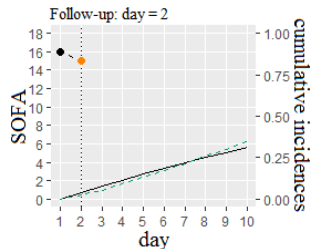
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Patient 131



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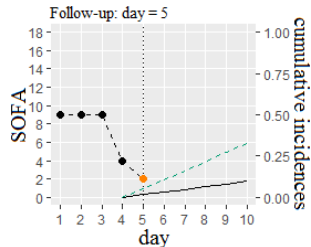
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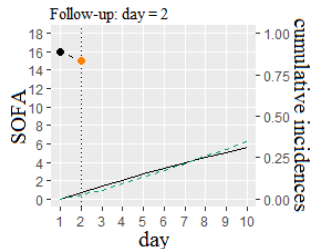
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Patient 131



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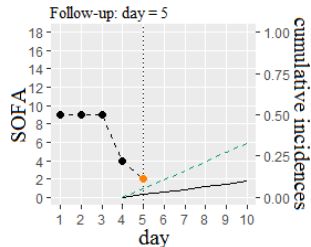
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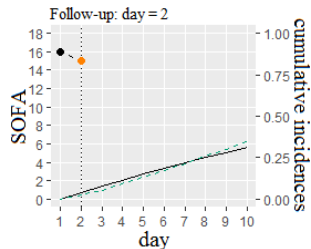
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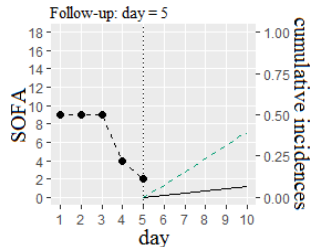
end

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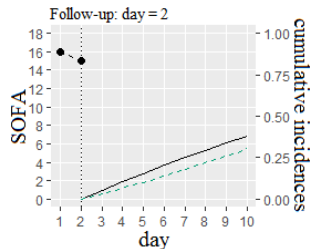
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Patient 131



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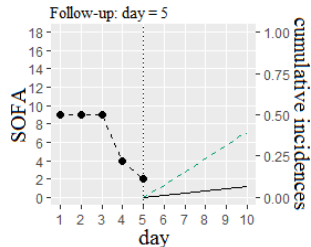
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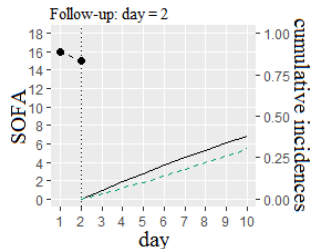
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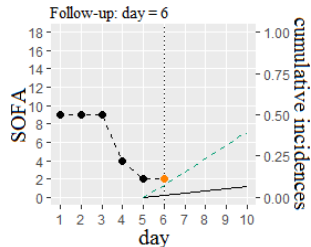
end

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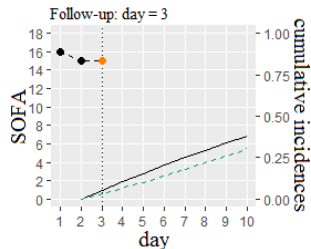
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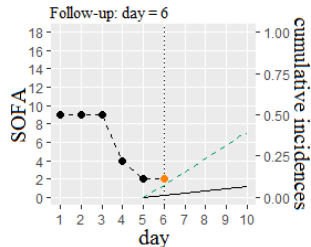
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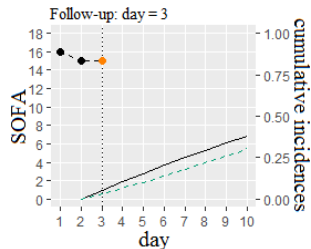
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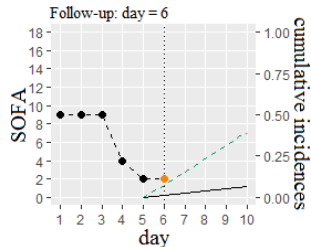
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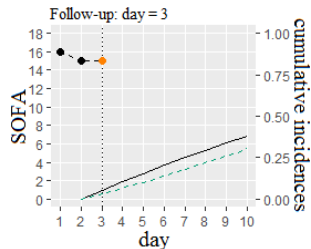
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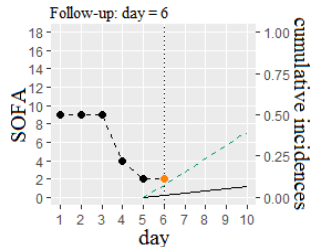
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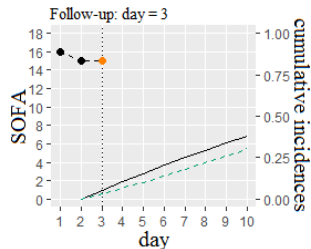
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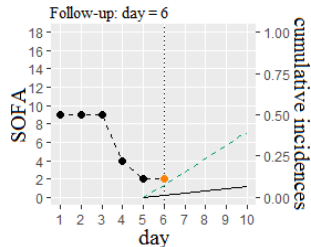
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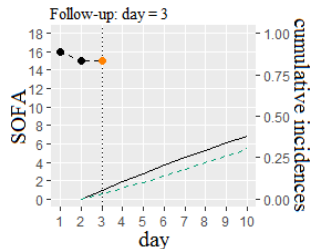
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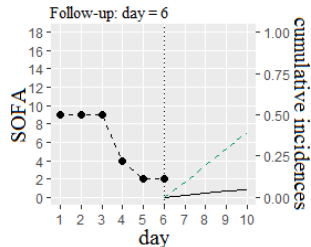
end

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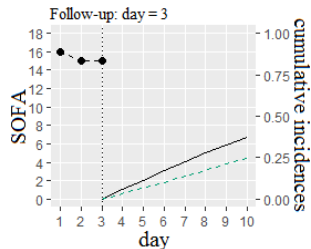
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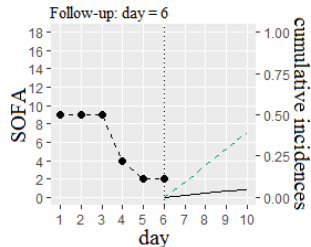
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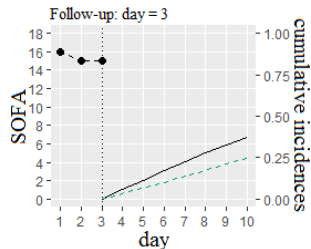
Update the conditional CIF.

If new data available, return to **Step 2.**

Patient 12



Patient 131



Updating the posterior information

θ	Initial		SMC-JM		JAGS	
	Mean	SD	Mean	SD	Mean	SD
<i>Competing risks process - Alive</i>						
α_{01}	-0.203	0.323	-0.221	0.313	-0.222	0.316
α_{11}	-1.012	0.256	-0.998	0.253	-0.999	0.255
λ_1	0.015	0.009	0.015	0.009	0.015	0.009
ν_1	1.525	0.151	1.538	0.146	1.537	0.151
γ_1	0.001	0.007	0.002	0.007	0.002	0.007
<i>Competing risks process - Death</i>						
α_{02}	3.367	0.948	3.272	0.858	3.278	0.861
α_{12}	0.745	0.472	0.717	0.453	0.716	0.454
λ_2	0.002	0.004	0.002	0.003	0.002	0.004
ν_2	1.172	0.250	1.176	0.248	1.178	0.249
γ_2	0.022	0.017	0.022	0.016	0.022	0.017
<i>Longitudinal process - SOFA*</i>						
β_0	1.844	0.155	1.851	0.149	1.851	0.154
β_1	-0.086	0.009	-0.088	0.009	-0.088	0.009
β_2	0.005	0.002	0.005	0.002	0.005	0.002
σ	0.311	0.008	0.311	0.007	0.311	0.008
σ_0	0.407	0.032	0.410	0.031	0.410	0.031
σ_1	0.067	0.008	0.069	0.009	0.068	0.009
Time (min)	867		121		869	

Outline

- 1 Background
- 2 Sequential learning
- 3 Sequential methods for Bayesian joint models
- 4 Application in ICU discharge data
- 5 **Conclusions**

SMC methods in Bayesian joint models

- Improve statistical efficiency by using all the data simultaneously in a single model.
- “Complete” inference and quick update.
- Adaptations involving analytically intractable integrals.
- Incorporation of the step of update of the random effects.

SMC methods in Bayesian joint models

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- “Complete” inference and quick update.
- Adaptations involving analytically intractable integrals.
- Incorporation of the step of update of the random effects.

ICU discharge data:

- Individual estimation of the dynamic CIF of each event.
- Reduction of 867 minutes to 121 minutes.

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Thank you for your attention