Joint models for a longitudinal marker and multivariate survival data

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Bordeaux

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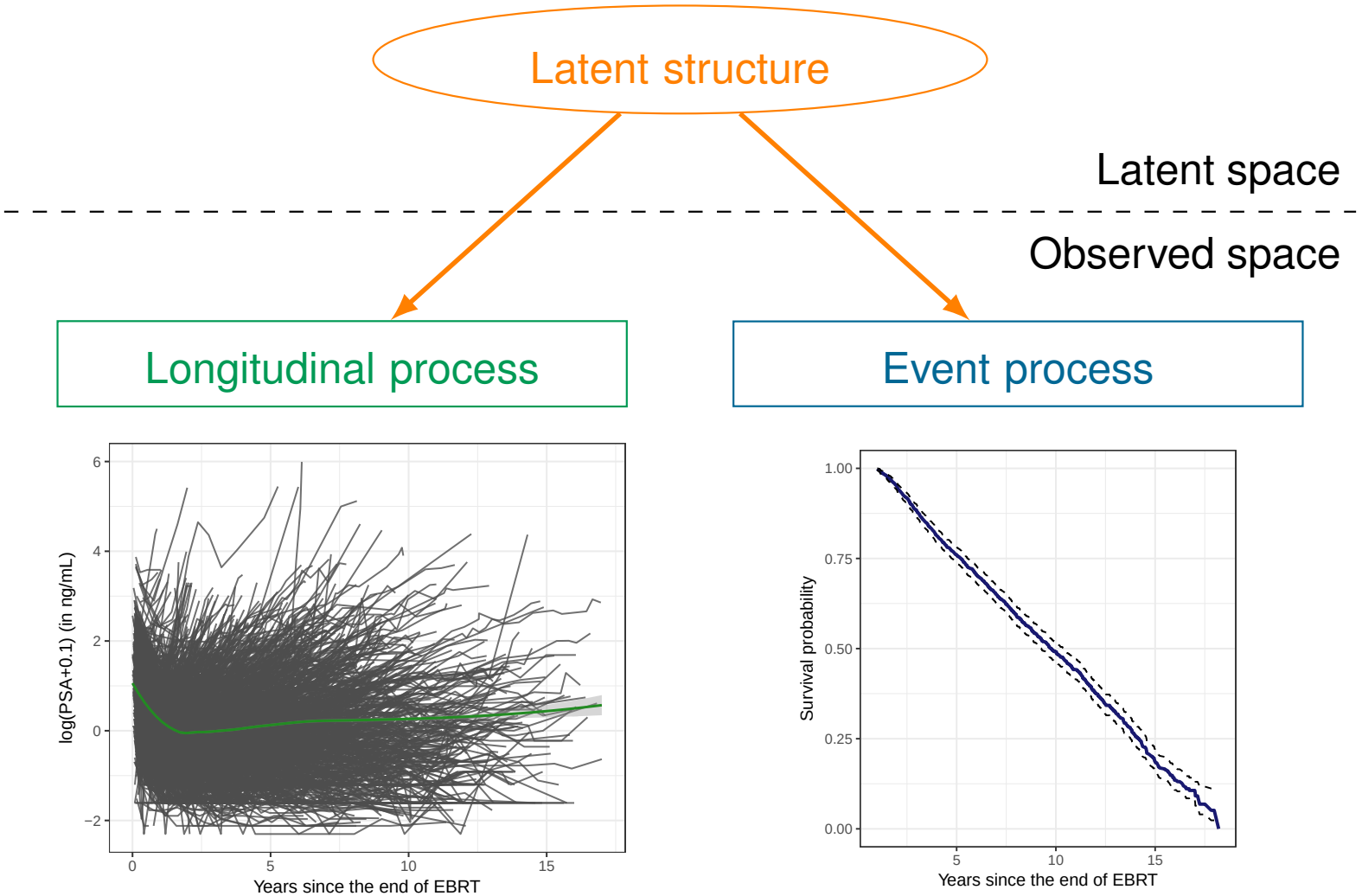
Joint modelling principle

Simultaneous modelling of correlated longitudinal and event processes



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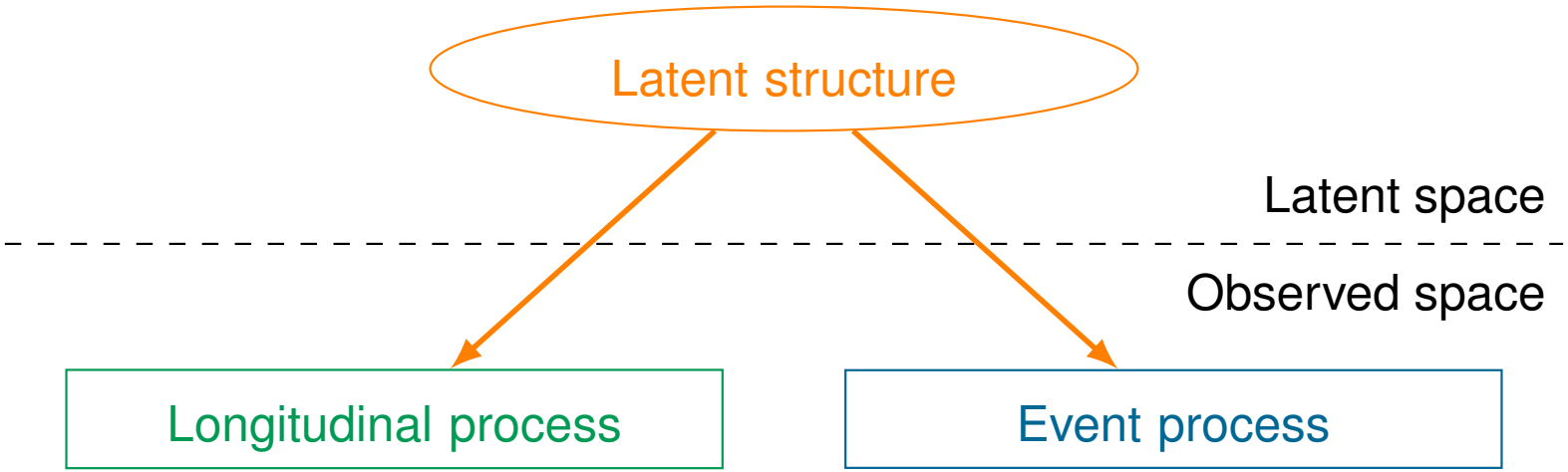

- Objectives:
  - Describe the longitudinal process stopped by the event
  - Explore the association between the two processes
  - Predict the risk of event adjusted for the longitudinal process

Joint modelling principle

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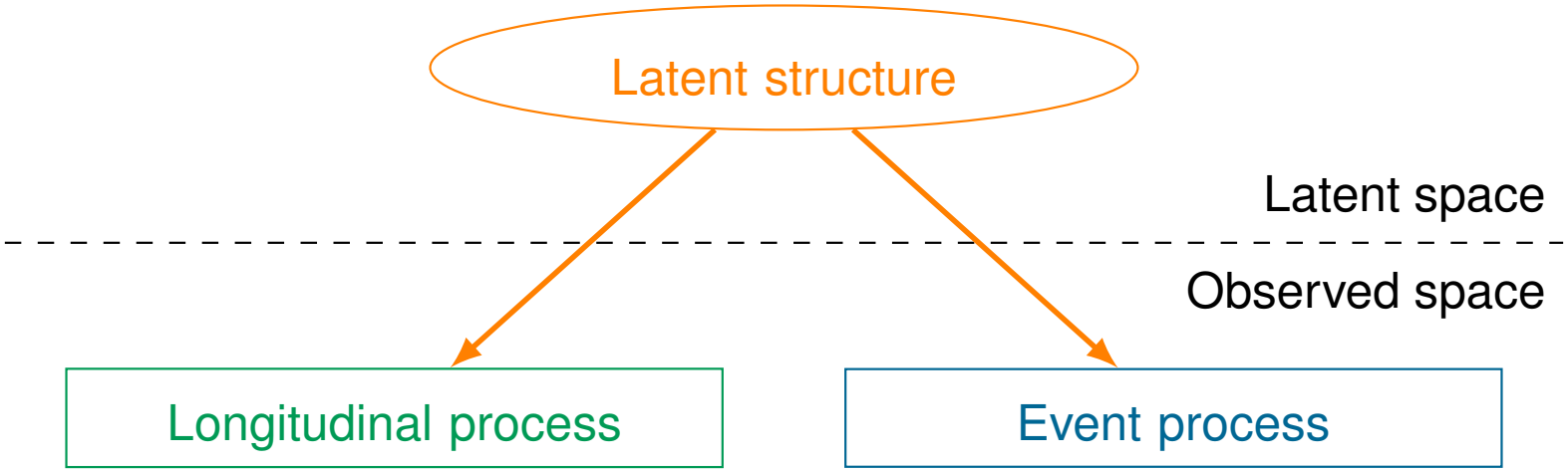
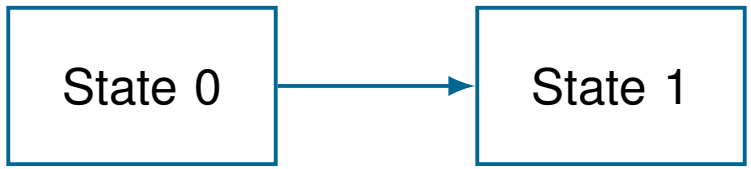


- Latent structure:
  - Function of shared random effects (shared random effect models) [1]
    - Homogeneous population
    - Specification and quantification of the association between the two processes
  - Latent classes (joint latent class models) [2]
    - Heterogeneous population
    - No assumption on the association

1. [Rizopoulos, 2012]
2. [Proust-Lima et al., 2014]

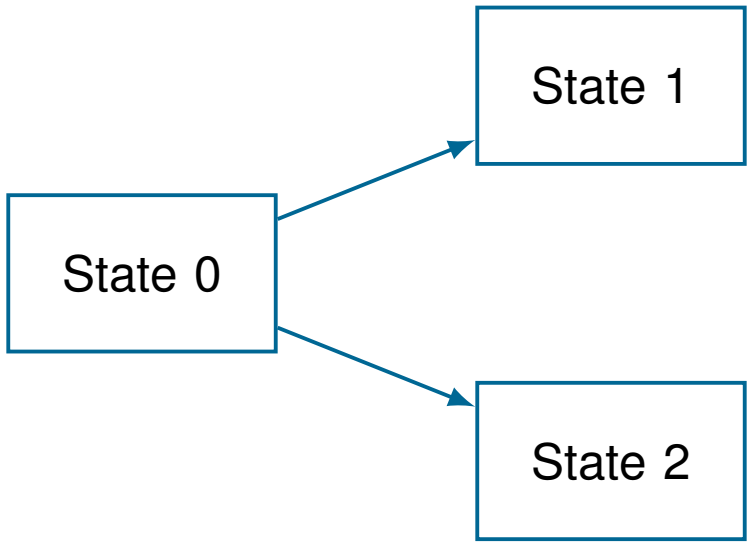
Classical joint modelling

- Classical joint models are developed for
  - A Gaussian longitudinal marker
  - Survival data with one single type of event



Extension of the classical joint models

- Many applications require joint models with
  - More complex longitudinal processes
  - More complex event processes
    - Survival data with competing events
    - Recurrent events
    - Multi-state process with possible multiple transitions



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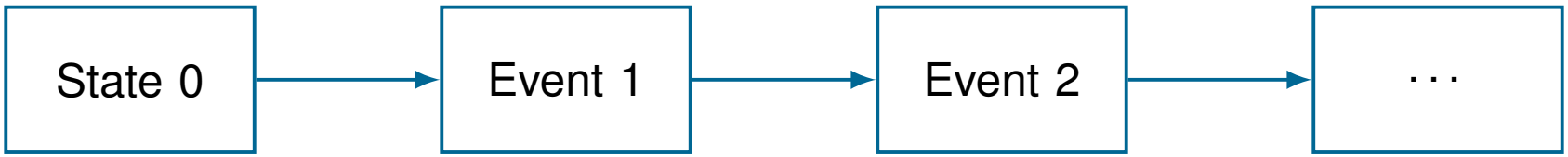

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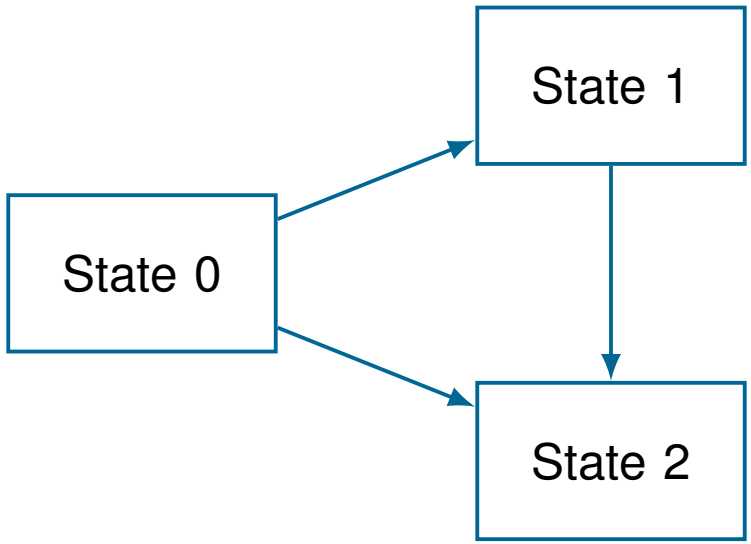

Joint multi-state models

- In the literature, very few papers have focused on the succession of events in the joint model setting [3]
- Focus on
  - A joint multi-state model with shared random effects [4]
    - application: link between PSA & multiple clinical progressions in prostate cancer
  - A joint multi-state model with latent classes [5]
    - application: distinction of profiles of cognitive decline associated with risks of dementia and death in elderly people

3. [Hickey et al., 2018]
4. [Ferrer et al., 2016]
5. [Rouanet et al., 2016]

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Joint modelling of longitudinal and multi-state processes: application to clinical progressions in prostate cancer

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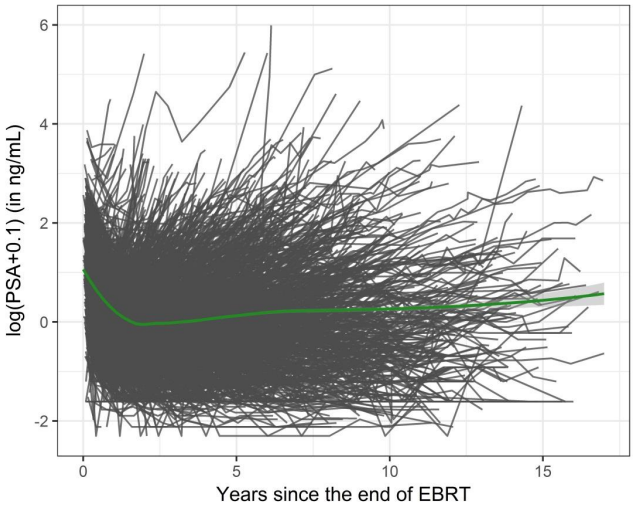
Classical modelling in prostate cancer

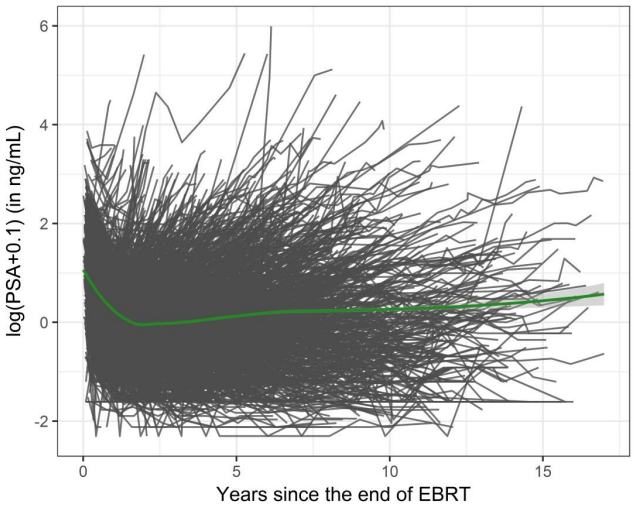
- Longitudinal PSA & clinical progression

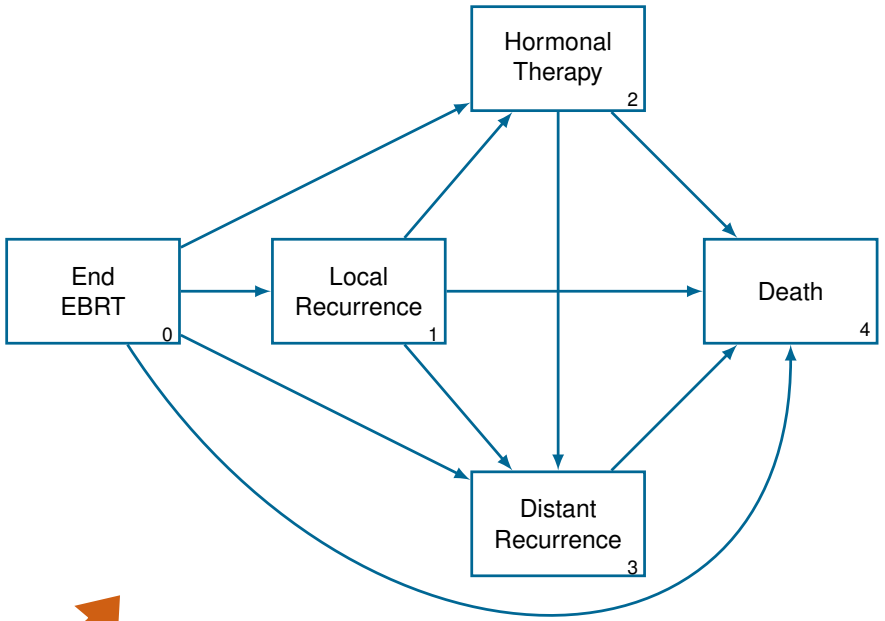


- No distinction between the clinical progressions
- No modelling of the full disease progression

Multiple clinical progressions in cancer

- Longitudinal PSA & multiple clinical progressions





- Objectives
  - → Understanding the PSA evolution during the patient's follow-up
  - → Distinguishing & evaluating the impact of PSA dynamics and other prognostic factors on disease evolution

Notations

- Let us consider two observed processes: one longitudinal and one multi-state
- Multi-state process
  - $E_i = \{E_i(t), T_{i0} \leq t \leq C_i\}$ non-homogeneous Markovian process
    - $E_i(t)$ with values in the finite state space $S = \{0, 1, \ldots, M\}$
    - T_{i0} left truncature time, C_i right censoring time
  - $T_i = (T_{i1}, \ldots, T_{im_i})^\top$ the m_i observed time(s); $T_{ir} < T_{i(r+1)}, \forall r \in S$
  - $\delta_i = (\delta_{i1}, \ldots, \delta_{im_i})^\top$ the vector of indicators of observed transition(s)
- Longitudinal process
  - $Y_i = (Y_{i1}, \ldots, Y_{in_i})^\top$ the n_i measure(s) of marker collected at time(s) $t_{i1}, \ldots, t_{in_i}$, with $t_{in_i} \leq T_{im_i}$

Joint multi-state model

$$\begin{cases} Y_{ij} &= Y_i^*(t_{ij}) + \epsilon_{ij} \\ &= X_i^L(t_{ij})^\top \beta + Z_i(t_{ij})^\top b_i + \epsilon_{ij} \\ \\ \lambda_{hk}^i(t) &= \lim_{\mathrm{d}t \to 0} \dfrac{\Pr(E_i(t+\mathrm{d}t) = k | E_i(t) = h)}{\mathrm{d}t} \\ &= \lambda_{hk,0}(t) \exp(X_{hk,i}^{E\top} \gamma_{hk} + W_{hk,i}(b_i, t)^\top \eta_{hk}), \quad \text{for } (h,k) \in S^2, \end{cases}$$

- $b_i \sim \mathcal{N}_q(0, B)$, $\epsilon_i = (\epsilon_{i1}, \ldots, \epsilon_{in_i})^\top \sim \mathcal{N}_{n_i}(0, \sigma^2 I)$, $b_i \perp\!\!\!\perp \epsilon_i$
- $\lambda_{hk,0}(t)$ parametric baseline intensity, $X_{hk,i}^E$ prognostic factors
- $W_{hk,i}(b_i, t)$ structure of dependence, e.g.
  - $W_{hk,i}(b_i, t) = Y_i^*(t)$ $\longrightarrow$ (true current level)
  - $W_{hk,i}(b_i, t) = \partial Y_i^*(t)/\partial t$ $\longrightarrow$ (true current slope)
  - $W_{hk,i}(b_i, t) = \left(Y_i^*(t), \partial Y_i^*(t)/\partial t\right)^\top$ $\longrightarrow$ (both)
  - ...

Estimation and implementation

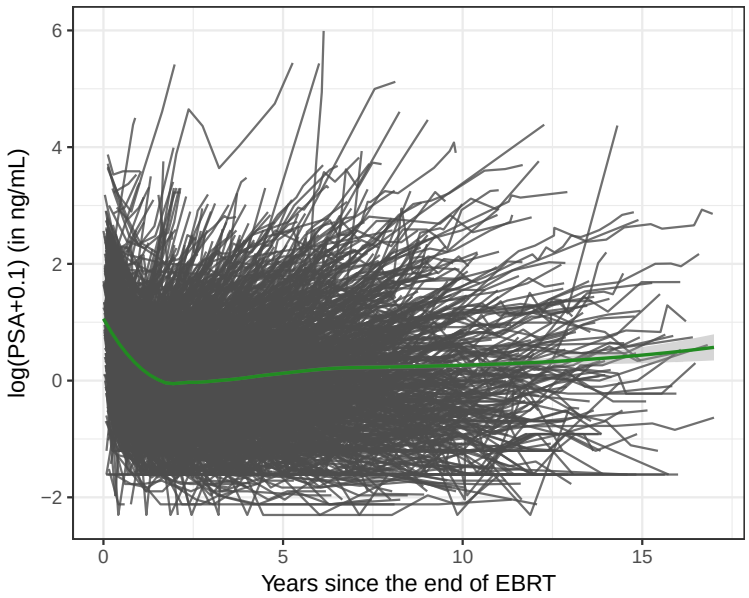
- Maximum likelihood approach
  - Using $Y_i \perp\!\!\!\perp_{b_i} E_i$
  - Likelihood function

$$L(\theta) = \prod_{i=1}^{N} \int_{\mathbb{R}^q} f_Y(Y_i|b_i;\theta)\ f_E(E_i|b_i;\theta)\ f_b(b_i;\theta)\,\mathrm{d}b_i$$

- Implementation in R
  - Combination and extension of the existing R packages `JM` and `mstate`
  - Codes with detailed examples available at `https://github.com/LoicFerrer/JMstateModel`
  - Likelihood computed and optimised using
    - numerical integration algorithms (Gaussian quadratures: multi-step pseudo-adaptive Gauss-Hermite quadratures for the integral over random effects)
    - optimisation algorithms (EM + quasi-Newton)

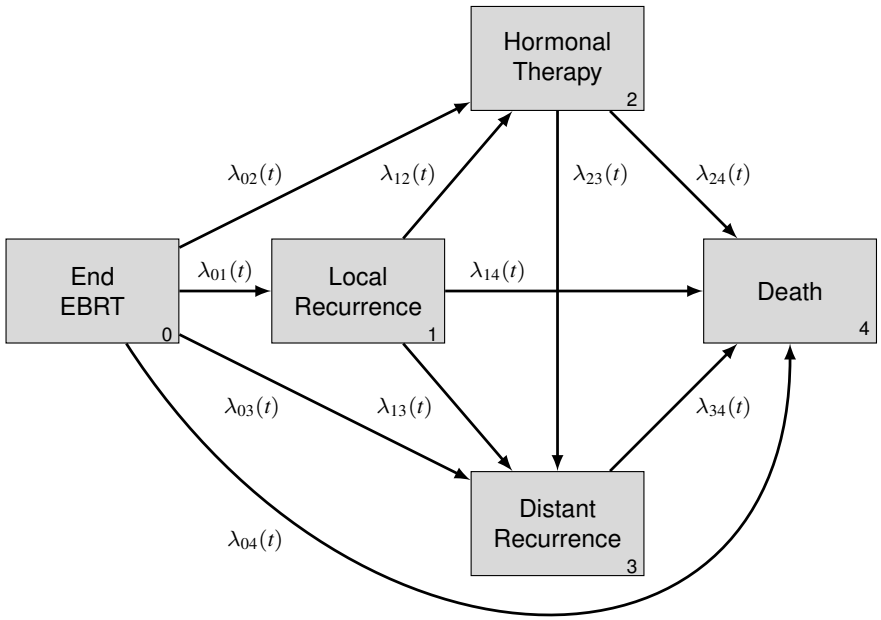
Application

- 2 cohorts of men with localised prostate cancer treated by radiotherapy (N=1474)
- Longitudinal biomarker: PSA
- Multi-state representation of the clinical progressions



10, [3–21] measures per patient

(50th, [5th – 95th] %iles)



$$\Upsilon = \begin{pmatrix} 533 & 144 & 227 & 47 & 523 \\ 0 & 20 & 90 & 10 & 24 \\ 0 & 0 & 106 & 33 & 178 \\ 0 & 0 & 0 & 13 & 77 \\ 0 & 0 & 0 & 0 & 802 \end{pmatrix}$$

matrix of direct transitions

Specification of the joint multi-state model

- Model inspired from the literature with one unique type of event

$$
\begin{cases}
\begin{aligned}
Y_{ij} &= Y_i^*(t_{ij}) + \epsilon_{ij} \\
&= \left(\beta_0 + X_i^{L0\top}\beta_{0,\texttt{cov}} + b_{i0}\right) + \\
&\quad \left(\beta_1 + X_i^{L1\top}\beta_{1,\texttt{cov}} + b_{i1}\right) \times \left((1+t_{ij})^{-1.2} - 1\right) + \\
&\quad \left(\beta_2 + X_i^{L2\top}\beta_{2,\texttt{cov}} + b_{i2}\right) \times t_{ij} + \epsilon_{ij}
\end{aligned} \\
\lambda_{hk}^i(t) = \lambda_{hk,0}(t)\exp\left(X_{hk,i}^{E\top}\gamma_{hk} + \begin{pmatrix} g(Y_i^*(t)) \\ \partial Y_i^*(t)/\partial t \end{pmatrix}^\top \begin{pmatrix} \eta_{hk,\texttt{level}} \\ \eta_{hk,\texttt{slope}} \end{pmatrix}\right)
\end{cases}
$$

- $g(Y_i^*(t)) = \text{logit}^{-1}((Y_i^*(t) - 0.71)/0.44)$
- $\epsilon_i \sim \mathcal{N}(0, \sigma^2 I_{n_i})$
- $b_i = (b_{i0}, b_{i1}, b_{i2})^\top \sim \mathcal{N}(0, D)$, D unstructured

Results

Estimates of the association parameters between the longitudinal and multi-state processes

	Value	StdErr	p-value
Level : 01	3.32	0.41	< 0.001
Level : 02	4.89	0.39	< 0.001
Level : 03	2.94	0.68	< 0.001
Level : 04	-0.41	0.23	0.071
Level : 12	1.90	0.83	0.023
Level : 13	-2.30	1.32	0.081
Level : 14	-0.07	0.88	0.939
Level : 23	-0.29	1.04	0.778
Level : 24	-0.48	0.62	0.440
Level : 34	-0.02	0.57	0.974
.....			
Slope : 01	1.33	0.33	< 0.001
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Slope : 03	1.74	0.54	0.001
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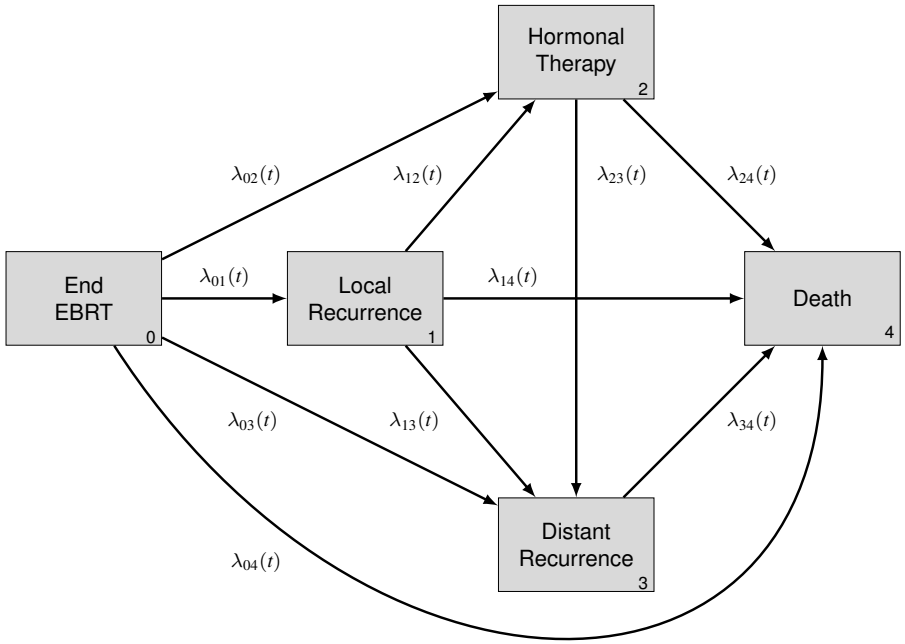
Slope : 12	0.46	0.58	0.336
Slope : 13	3.82	1.07	< 0.001
Slope : 14	0.70	1.02	0.495
Slope : 23	0.23	0.51	0.651
Slope : 24	0.64	0.23	0.005
Slope : 34	-0.56	0.42	0.186

Multi-state representation of the clinical progressions



- Prognostic factors: advanced initial stage not always associated with intensities of transitions between health states after adjustment on PSA

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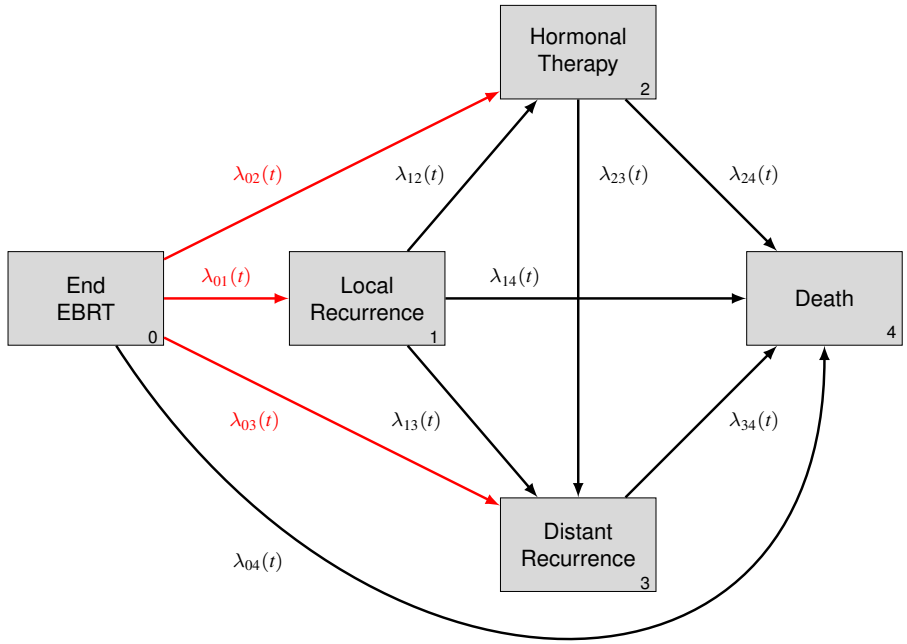

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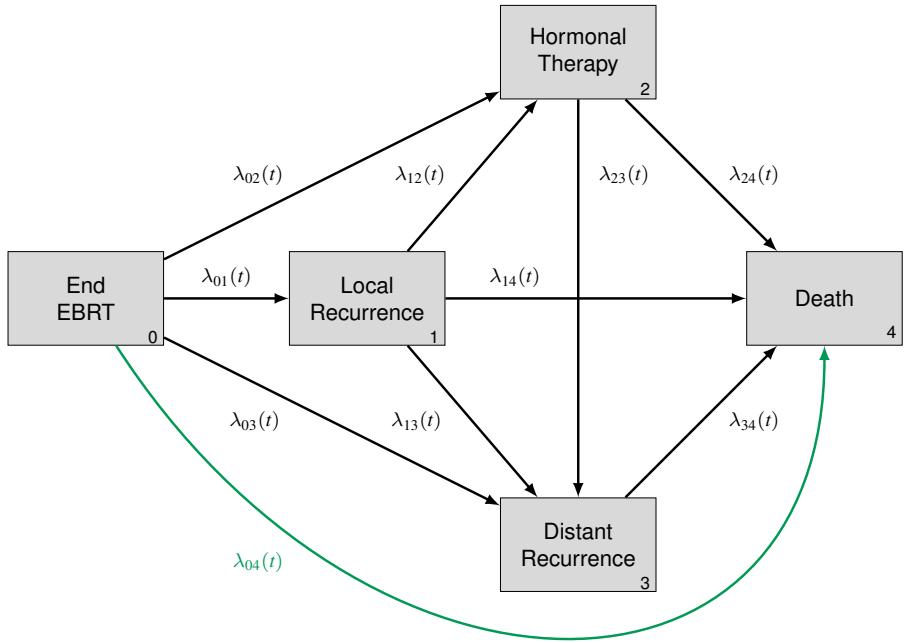

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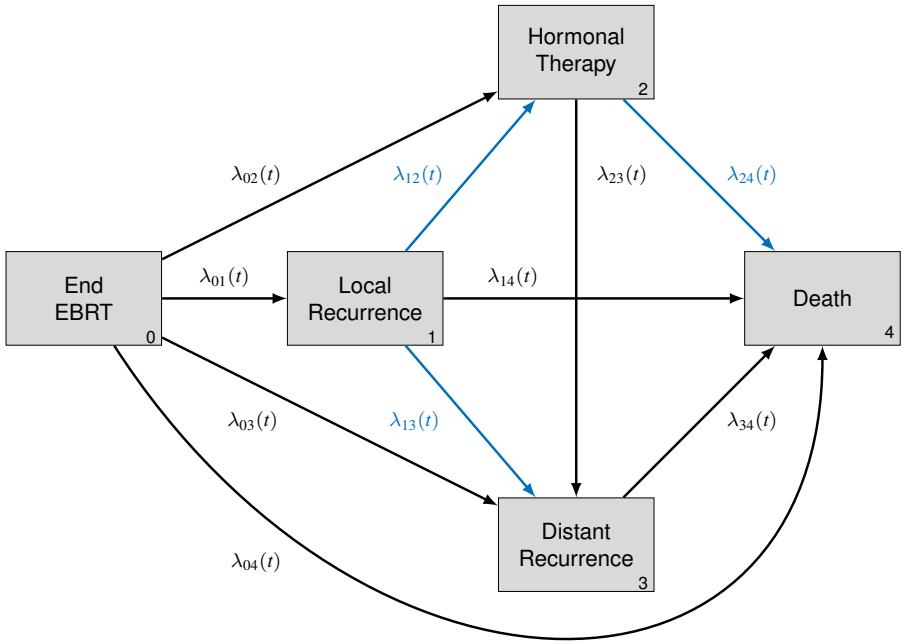

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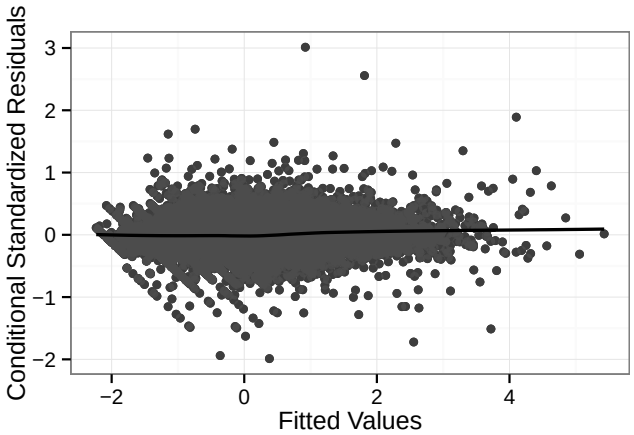
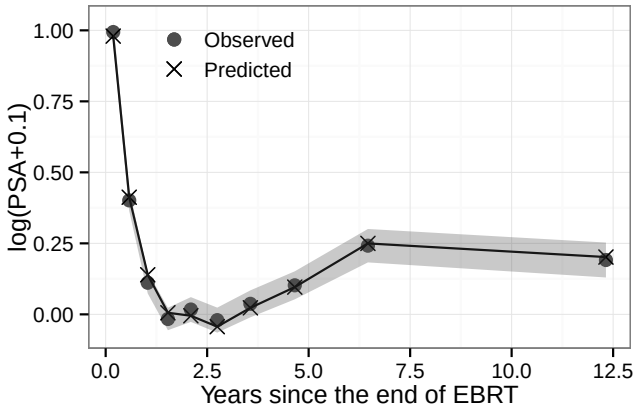
Model diagnostics

- Goodness-of-fit plots for the longitudinal process

  - Conditional standardized residuals versus fitted values

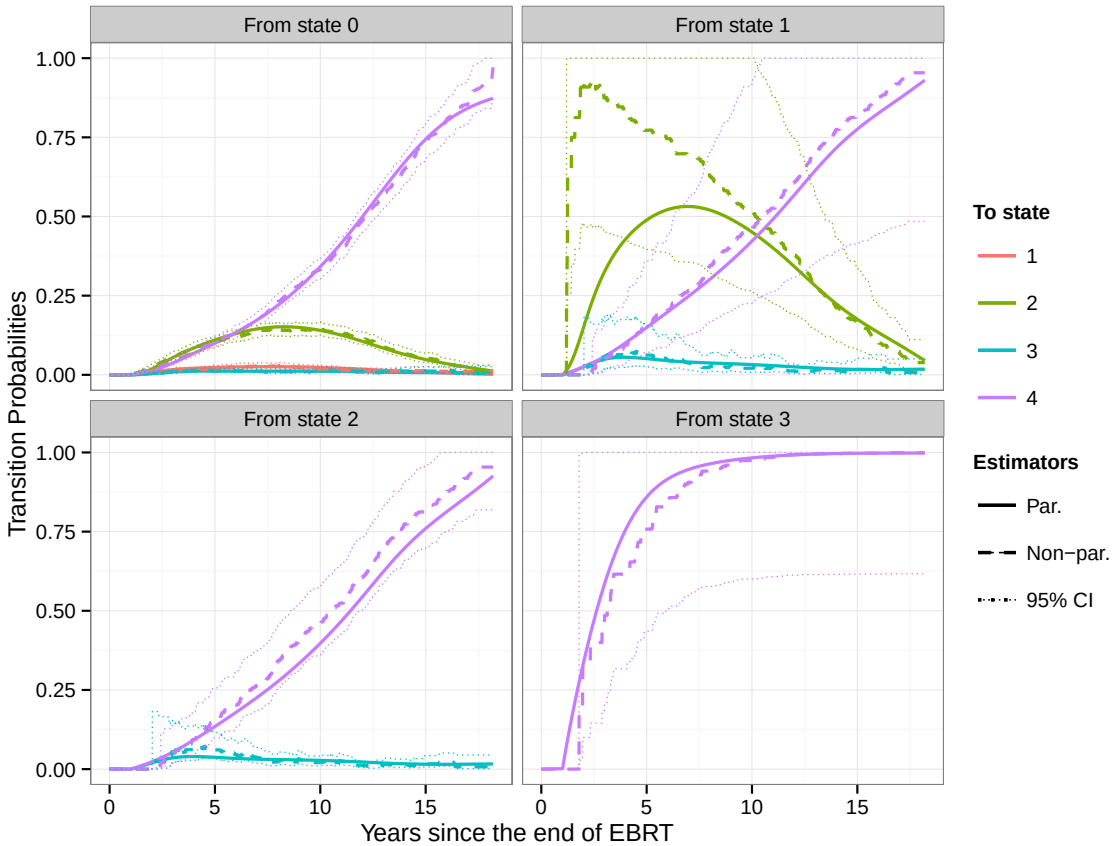


  - Observed and predicted values of the biomarker



Model diagnostics (cont'd)

- Goodness-of-fit plots for the longitudinal process
- Goodness-of-fit plot for the multi-state process
  - Predicted transition probabilities from the joint multi-state model and non-parametric probability transitions



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Joint Latent Class Model for Longitudinal Data and Interval-Censored Semi-Competing Events: Application to Dementia

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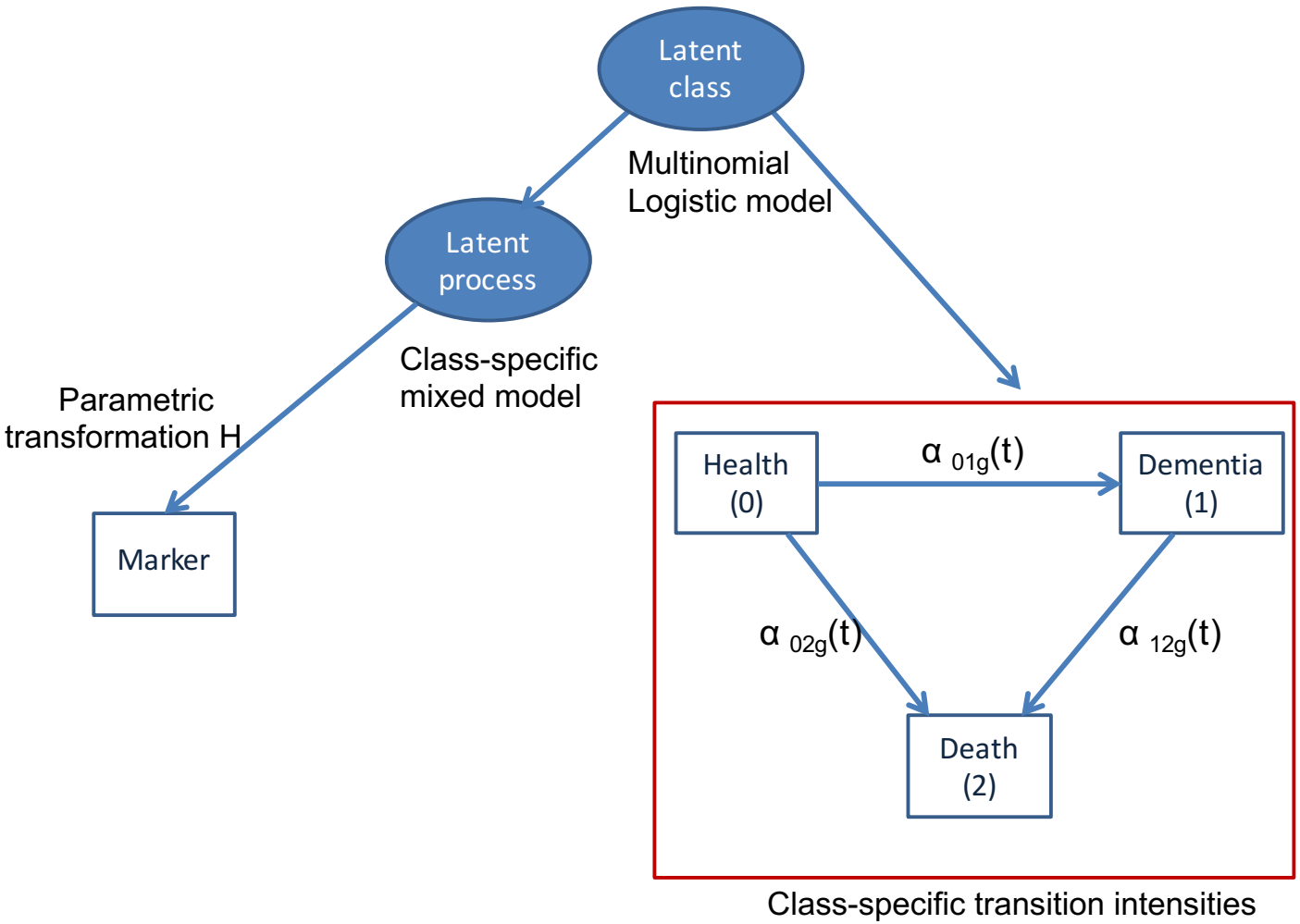
[2]Université de Bordeaux, ISPED, 146 rue Léo Saignat, F-33076 Bordeaux, France
[*]*email:* anais.rouanet@isped.u-bordeaux2.fr

Application to dementia

- Aim: To distinguish different profiles of cognitive decline associated with risks of dementia and death
- Data: Paquid Cohort (French prospective cohort: Normal and pathological brain ageing)
  - 3777 subjects from Dordogne and Gironde, aged 65 and over
  - Visits every 2/3 years during 25 years
  - Study of Isaacs Set Test [0-40], verbal fluency
- Methodological challenges
  - Heterogeneity in cognitive decline
  - Correlation between cognitive decline and occurrence of dementia
  - Competing risk of death
  - Time-to-dementia onset interval-censored

Joint latent class illness-death model



Joint model formulation

- Membership probability: $p_{ig} = P(c_i = g|X_{pi})$
- Latent process Λ_i, given the class g:

$$\begin{aligned}\Lambda_i(t_{ij}|c_i = g) &= f_1(X_{ij};\ \beta_g) + f_2(Z_{ij};\ \beta_g)\ u_{ig} \\ &= X_{ij}^T \beta_g + Z_{ij}^T u_{ig}\end{aligned}$$

f_1, f_2: (possibly nonlinear) functions of time, covariates
β_g: class-specific parameters
$u_{ig} \sim \mathcal{N}(0, \sigma_g^2 B)$

- Transformed gaussian marker $\tilde{Y}$:

$$\tilde{Y}_{ij} = H(Y_{ij}; \eta) = \Lambda_i(t_{ij}) + \epsilon_{ij} \text{ with } \epsilon_{ij} \sim \mathcal{N}(0, \sigma_e^2)$$

$H(.; \eta)$: Parametric transformation

- Transition intensity from state k to state l for subject i in class g:

$$\alpha_{klig}(t) = \alpha_{klg}^0(t)\ e^{X_{ei}^\top \gamma_{klg}}$$

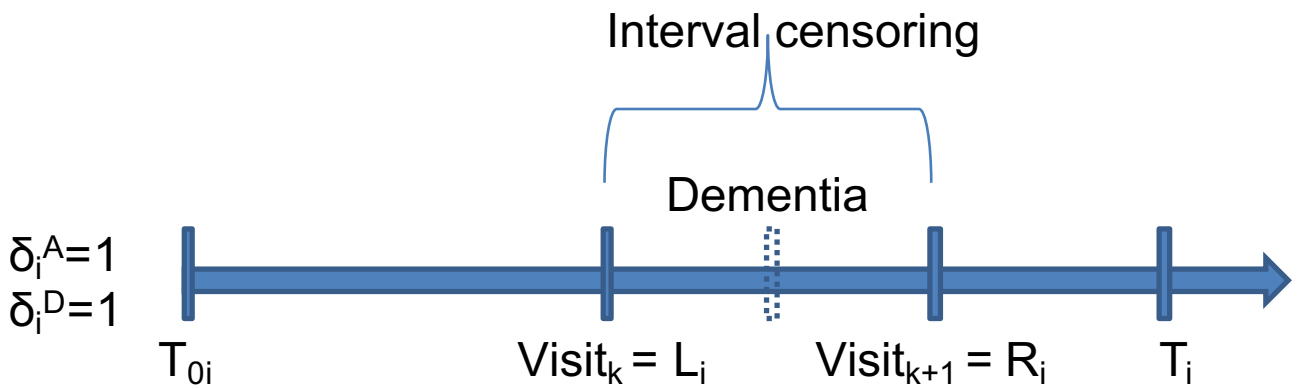
α_{klg}^0: class-specific baseline intensity
γ_{klg}: class-specific regression parameters

Estimation

- Maximum likelihood approach
  - Using $Y_i \perp\!\!\!\perp_g D_i$
  - Log-likelihood function

$$\mathcal{L}(\theta_G) = \sum_{i=1}^{N} \log \left[\sum_{g=1}^{G} p_{ig}\, f(Y_i|c_i = g;\theta_G)\; P(D_i|c_i = g;\theta_G) \right]$$

$$- \sum_{i=1}^{N} \log \left[\sum_{g=1}^{G} p_{ig}\, \mathrm{e}^{-A_{01ig}(T_{0i};\theta_G) - A_{02ig}(T_{0i};\theta_G)} \right]$$



- Marquardt algorithm for a fixed number of latent classes G
- G chosen by Bayesian Information Criterion (BIC) minimisation

Model specification

- Mixed model, given latent class g :

$$\Lambda_i(t) = \beta_{0g} + u_{ig}^{(0)} + [\beta_{1g} - \beta_{2g} + u_{ig}^{(1)}]\ (t - \tau_g) + \beta_3\ Educ_i + (\beta_4 - \beta_5)\ Educ_i\ (t - \tau_g) + \beta_6\ Sex_i \quad \text{if } t \leq \tau_g$$

$$\Lambda_i(t) = \beta_{0g} + u_{ig}^{(0)} + [\beta_{1g} + \beta_{2g} + u_{ig}^{(2)}]\ (t - \tau_g) + \beta_3\ Educ_i + (\beta_4 + \beta_5)\ Educ_i\ (t - \tau_g) + \beta_6\ Sex_i \quad \text{if } t \geq \tau_g$$

$u_{ig} = (u_{ig}^{(0)}, u_{ig}^{(1)}, u_{ig}^{(2)})^\top \sim \mathcal{N}(0, \sigma_g^2 B)$, $\epsilon_{ij} \sim \mathcal{N}(0, \sigma_\epsilon^2)$

$\tilde{Y}_{ij} = H(Y_{ij}; \eta) = \Lambda_i(t_{ij}) + \epsilon_{ij}$ with H : Beta cumulative distribution function

- Transition intensities from states $k \to l$ of the multi-state model:

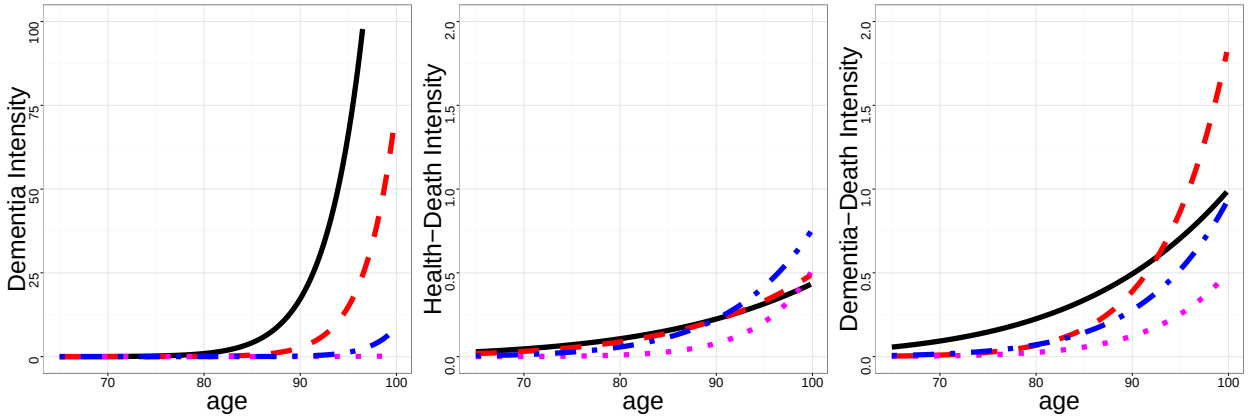
$$\alpha_{klig}(t) = \alpha_{klg}^0(t)\ \mathrm{e}^{\gamma_{kls}\ Sex_i + \gamma_{kle}\ Educ_i}$$

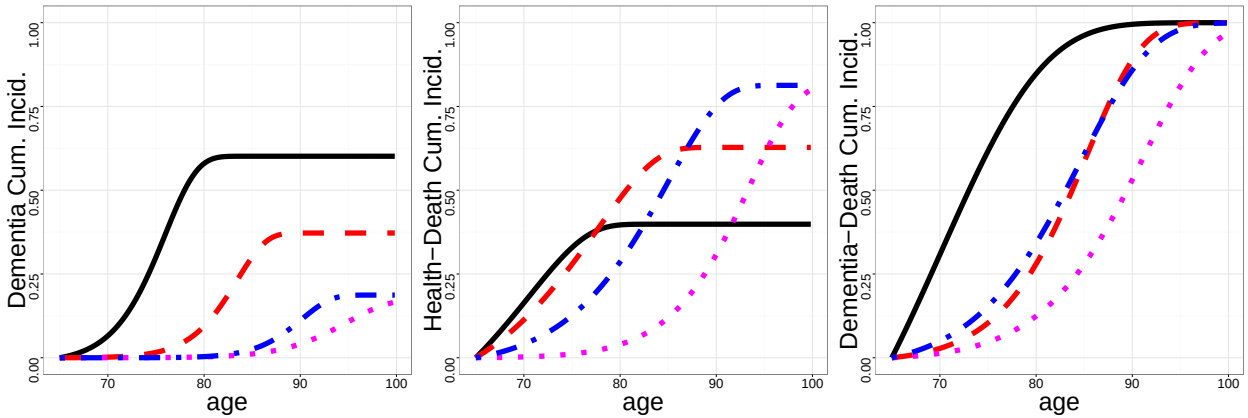
Model choice

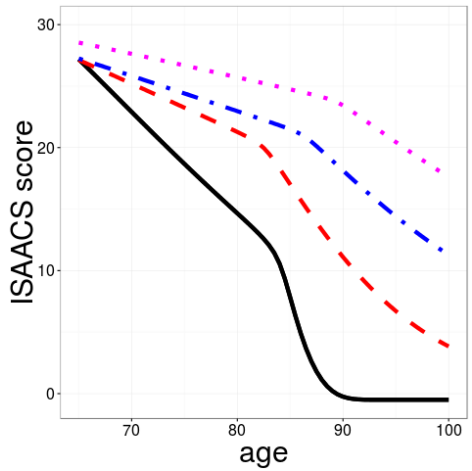
	BIC	
	Markovian	Semi-markovian
G=1	106901	107055
G=2	106270	106356
G=3	106081	106177
G=4	106005	106091
G=5	106027	106107

Mortality among subjects with dementia depends more on age than on the duration of dementia.

The minimum value of BIC with G = 4 classes.







	N	CEP=0	CEP=1	men	women
Class 1	11.12%	23.2	76.8	40.1	59.9
Class 2	32.91%	29.7	70.3	40.7	59.3
Class 3	9.73%	42.9	57.1	42.0	58.0
Class 4	46.24%	38.0	62.0	43.8	56.2

Discrimination of the posterior classification

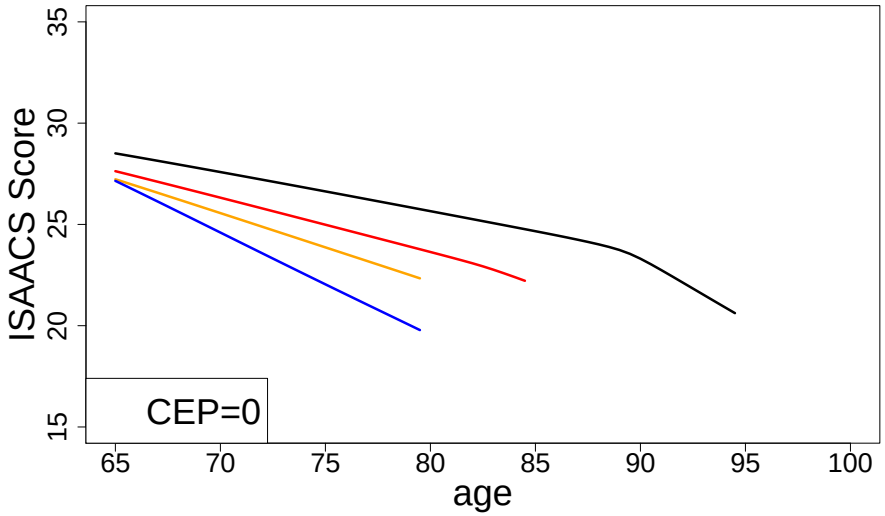
Classification according to:

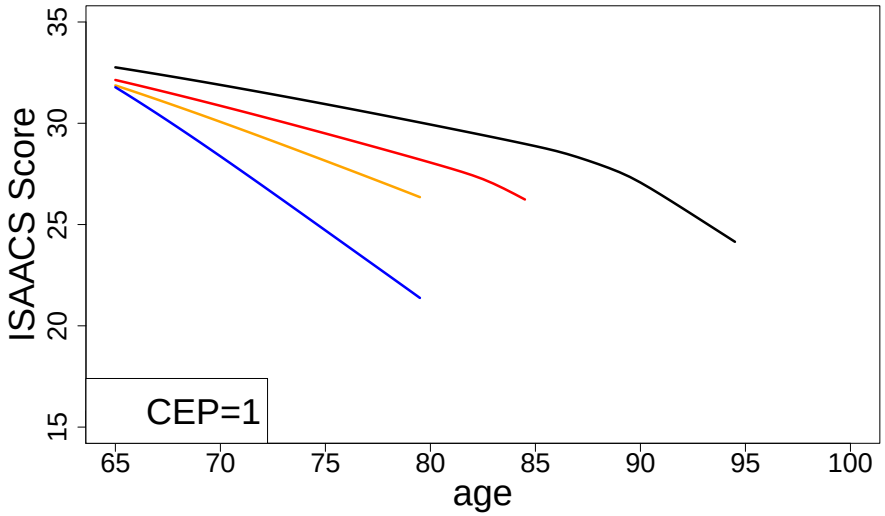
$$\hat{\pi}_{ig}^{Y,D} = P(c_i = g|Y_i, D_i, \hat{\theta}_G) = \frac{f(Y_i|c_i = g; \hat{\theta}_G)P(D_i|c_i = g; \hat{\theta}_G)\ P(c_i = g; \hat{\theta}_G)}{\sum_l^G f(Y_i|c_i = l; \hat{\theta}_G)P(D_i|c_i = l; \hat{\theta}_G)\ P(c_i = l; \hat{\theta}_G)}$$

Class	1	2	3	4
1	71.36	21.92	0.18	6.54
2	12.83	61.54	1.24	24.39
3	0.01	0.47	79.11	20.40
4	0.96	19.11	12.96	66.97

Table 1 – Mean probabilities to belong to each class according to the posterior classification.

Estimated trajectories according to dementia onset & death





Man with a low/high level of education
in 4 different cases:

man alive and dementia-free at 95
$E(Y(t)|T_i^A > 95, T_i^D > 95, \delta_i^A = 0, \delta_i^D = 0; \hat{\theta}_G)$

man alive and dementia-free at 85

man dead dementia-free at 80

man alive with dementia at 80

Discussion

- Joint models extended to several kinds of multivariate survival data
  - See Hickey G.L. et al. (2018) for a full state-of-the-art
- Ferrer et al. (2016) developed a joint multi-state model with shared random effects to
  - Model the disease evolution in its whole
  - Using an easy-to-use function implemented in R
- Rouanet et al. (2016) developed a joint latent class illness-death model accounting for
  - Heterogeneity in the data
  - Competing risk of death
  - Interval censoring
- Model diagnostics
  - Study of the residuals for validating the model assumptions
  - Graphical comparison of the observations and predictions of the model as goodness-of-fit tool

Discussion (cont'd)

- Goodness-of-fit assessment in joint multi-state models using a score test for the inclusion of a Gaussian frailty term
  - for shared random effect models
  - for joint latent class models
- Useful to validate the model assumptions and check its goodness-of-fit
  - Markovian assumption
  - Incomplete adjustment on covariates
  - Presence of non-linear covariate effect
  - ~~Violation of the proportional intensities assumption~~
- Available at `http://github.com/LoicFerrer/JMstateModel/` for shared random effect models
- Submitted for publication in a few days

References

[1.] Rizopoulos D. (2012). *Joint models for longitudinal and time-to-event data: With applications in R*. Chapman and Hall/CRC.

[2.] Proust-Lima C., Séne M., Taylor J.M. & Jacqmin-Gadda H. (2014). Joint latent class models for longitudinal and time-to-event data: A review. *Statistical Methods in Medical Research*, 23(1):74–90.

[3.] Hickey G.L., Philipson P., Jorgensen A. & Kolamunnage-Dona R. (2018). Joint models of longitudinal and time-to-event data with more than one event time outcome: a review. *The International Journal of Biostatistics*, 14(1).

[4.] Ferrer L., Rondeau V., Dignam J., Pickles T., Jacqmin-Gadda, H. & Proust-Lima C. (2016). Joint modelling of longitudinal and multi-state processes: application to clinical progressions in prostate cancer. *Statistics in Medicine*, 35(22):3933–3948.

[5.] Rouanet A., Joly P., Dartigues J-F., Proust-Lima C. & Jacqmin-Gadda H. (2016). Joint Latent Class Model for Longitudinal Data and Interval-Censored Semi-Competing Events: Application to Dementia. *Biometrics*, 72(4):1123–1135.

Numerical approximation of the integral over the random effects

- Likelihood function

$$L(\theta) = \prod_{i=1}^{N} \int_{\mathbb{R}^q} f_Y(Y_i|b_i;\theta)\ f_E(E_i|b_i;\theta)\ f_b(b_i;\theta)\,\mathrm{d}b_i$$

- Adaptive Gauss-Hermite rule $\rightarrow$ Centering and rescaling the integral around its modal value at each step of the optimisation algorithm

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- Adaptive Gauss-Hermite rule $\rightarrow$ Centering and rescaling the integral around its modal value at each step of the optimisation algorithm
  1. Pseudo-adaptive GH rule: based on the posterior distribution of the random effects from the LMM

$$\widetilde{b}_i = \arg\max_b \{\log f(Y_i, b; \widetilde{\theta}_Y)\}$$

  and their associated covariance matrix

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  2. Multi-step pseudo-adaptive GH rule: based on the posterior distribution of the random effects from the JM

$$\overset{\star}{b}_i = \arg\max_b \{\log f(E_i, Y_i, b; \overset{\star}{\theta})\}$$

     and their associated covariance matrix

Joint multi-state model – Implementation in R (1/4)

- Example of R code

$$\begin{cases} Y_{ij} &= Y_i^*(t_{ij}) + \epsilon_{ij} \\ &= (\beta_0 + \beta_{0,X} X_i + b_{i0}) + (\beta_1 + \beta_{1,X} X_i + b_{i1}) \times t_{ij} + \epsilon_{ij} \\ \lambda_{hk}^i(t|b_i) &= \lambda_{hk,0}(t) \exp\left(\gamma_{hk} X_i + \eta_{hk,\texttt{level}} Y_i^*(t) + \eta_{hk,\texttt{slope}} \partial Y_i^*(t)/\partial t\right) \end{cases}$$

where the multi-state process included three states ($(h,k) \in \{0,1,2\}^2$) and three transitions ($0 \to 1,\ 0 \to 2,\ 1 \to 2$),
the log-baseline intensities are a linear combination of cubic-splines

```
library(mstate)
library(JM)
source("JMstateModel.R")
load("data.RData")

# Initialisation of the longitudinal sub-part
lmeFit <- lme(fixed = Y ~ 1 + X + time + X:time,
              data = data_long,
              random = ~ (1 + time) | id,
              method = "REML",
              control = list(opt = "optim"))
```

Joint multi-state model – Implementation in R (2/4)

```
# Data peparation to the multi-state framework
tmat <- matrix(NA, 3, 3)
tmat[1, 2:3] <- 1:2
tmat[2, 3] <- 3
dimnames(tmat) <- list(from = c("State_0", "State_1", "State_2"),
                       to = c("State_0", "State_1", "State_2"))

covs <- "X"

data_mstate <-
  msprep(time = c(NA, "time_of_State_1", "time_of_State_2"),
         status = c(NA, "State_1", "State_2"),
         data = data_surv,
         trans = tmat,
         keep = covs,
         id = "id")

data_mstate <- expand.covs(data_mstate, covs,
                           append = TRUE, longnames = FALSE)
```

Joint multi-state model – Implementation in R (3/4)

```
# Initialisation of the multi-state sub-part
coxFit <- coxph(Surv(Tstart, Tstop, status) ~
                    X.1 + X.2 + X.3 + strata(trans),
                data = data_mstate,
                method = "breslow", x = TRUE, model = TRUE)
```

Joint multi-state model – Implementation in R (4/4)

```
dForm <- list(fixed = ~ 1 + X,
              indFixed = c(3, 4),
              random = ~ 1,
              indRandom = 2)

# Joint multi-state model
jointFit_both <-
  JMstateModel(lmeObject = lmeFit,
               survObject = coxFit,
               timeVar = "time",
               parameterization = "both",
               method = "spline-PH-aGH",
               interFact = list(value = ~ strata(trans) - 1,
                                slope = ~ strata(trans) - 1,
                                data = data_mstate),
               derivForm = dForm,
               Mstate = TRUE,
               data.Mstate = data_mstate,
               ID.Mstate = "id",
               control = list(GHk = 9, lng.in.kn = 3))
```

Joint multi-state model with an additional frailty

- Model formulation

$$\begin{cases} Y_{ij} &= X_i^L(t_{ij})^\top \beta + Z_i(t_{ij})^\top b_i + \epsilon_{ij} \\ \lambda_{hk}^i(t) &= \lambda_{hk,0}(t) \exp\left(X_{hk,i}^{E\top} \gamma_{hk} + W_{hk,i}(b_i, t)^\top \eta_{hk} + v_i\right), \quad \text{for } (h,k) \in S^2 \end{cases}$$

  - $v_i \sim \mathcal{N}(0, \sigma_v^2)$ the frailty term
  - $v_i \perp\!\!\!\perp b_i$, $v_i \perp\!\!\!\perp \epsilon_i$

- Likelihood function $L(\sigma_v^2, \theta)$

$$L(\sigma_v^2, \theta) = \prod_{i=1}^{N} \int_{\mathbb{R}^{q_b}} f_Y(Y_i|b_i;\theta) f_b(b_i;\theta) \int_{\mathbb{R}} f_E(E_i|b_i, v_i;\theta) f_v(v_i;\theta)\, \mathrm{d}v_i\, \mathrm{d}b_i$$

Score test: score statistic and its variance

$$H_0 : \sigma_v^2 = 0 \qquad \text{vs} \qquad H_1 : \sigma_v^2 > 0$$

- Score statistic $U(0,\theta) = U(\sigma_v^2 = 0, \theta)$

$$U(0,\theta) = \sum_{i=1}^{N} U_i(0,\theta) = \sum_{i=1}^{N} \frac{\partial \log L_i(\sigma_v^2, \theta)}{\partial \sigma_v^2} \Bigg|_{\sigma_v^2=0}$$

  - Analytic expression

- Asymptotic variance corrected for the estimation of the nuisance parameters

$$\text{Var}\left\{U(0,\theta)\right\} = \left(I_{\sigma_v^2\sigma_v^2} - I_{\sigma_v^2\theta} I_{\theta\theta}^{-1} I_{\theta\sigma_v^2}\right) \Big|_{\sigma_v^2=0}$$

  - Forward finite difference method

Score test: test statistic

- Test statistic

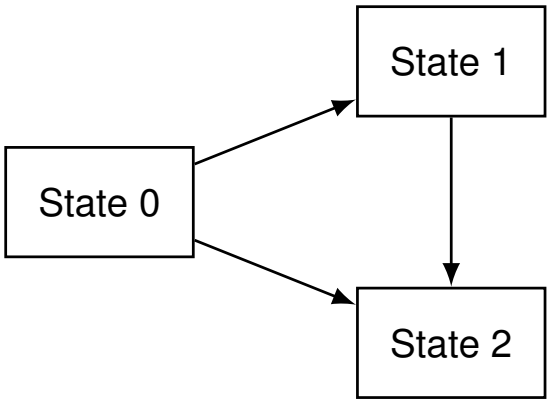
$$T = \begin{cases} 0 & \text{if} \quad U(0, \widehat{\theta}_0) \leq 0 \\ \dfrac{\left\{U(0, \widehat{\theta}_0)\right\}^2}{\text{Var}\left\{U(0, \widehat{\theta}_0)\right\}} & \text{if} \quad U(0, \widehat{\theta}_0) > 0 \end{cases}$$

  - $\widehat{\theta}_0$ the model parameters estimated under the null hypothesis
  - T follows asymptotically a mixture of chi-square distributions

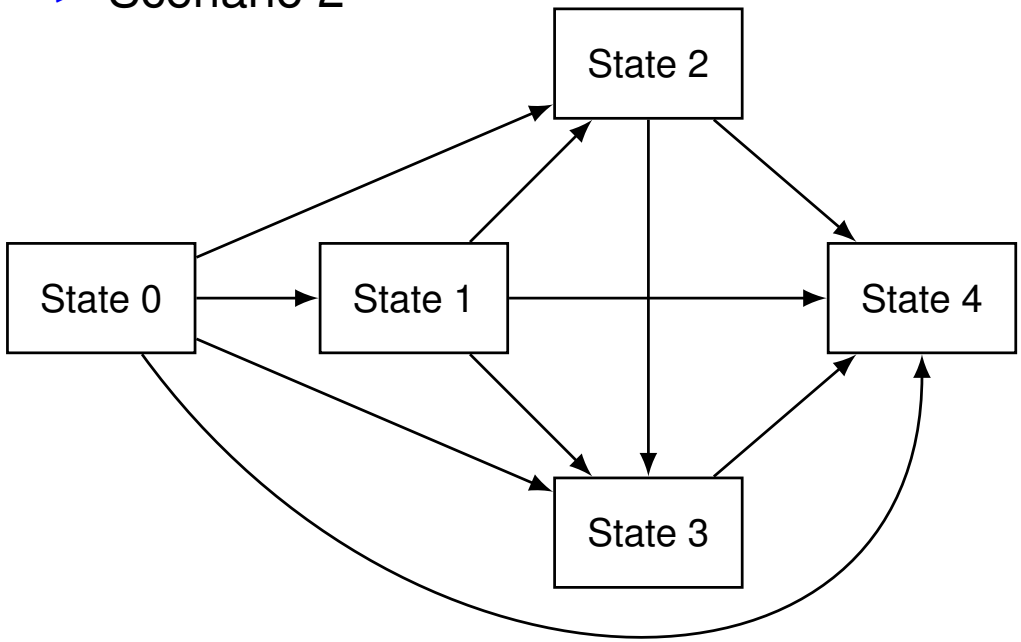
$$T \sim \frac{1}{2}\chi_0^2 + \frac{1}{2}\chi_1^2$$

Assessment by simulation study

- Scenario 1



- Scenario 2



- For each subject $i = 1, \ldots, N$ of the 500 replicates,

$$\begin{cases} Y_i(t) &= Y_i^*(t) + \epsilon_i(t) \\ &= (\beta_0 + \beta_{0,X} X_i + b_{i0}) + (\beta_1 + \beta_{1,X} X_i + b_{i1}) \times t + \epsilon_i(t) \\ \lambda_{hk}^i(t) &= \lambda_{hk,0}(t) \exp\left(\gamma_{hk} X_i + \eta_{hk,0} Y_i^*(t) + \eta_{hk,1} \partial Y_i^*(t)/\partial t + v_i\right) \end{cases}$$

Simulation study – results

- Empirical type-I error rate (nominal level of 5%)

	Scenario 1 (3 states) $\sigma_v^2 = 0$ $(\overline{M} = 0.70)$	Scenario 2 (5 states) $\sigma_v^2 = 0$ $(\overline{M} = 2.84)$
$N = 500$	0.008	0.028
$N = 1000$	0.010	0.054
$N = 1500$	0.020	0.060

- Empirical statistical power (nominal level of 5%)

	Scenario 1 (3 states)		Scenario 2 (5 states)	
	$\sigma_v^2 = 0.5$ $(\overline{M} = 0.74)$	$\sigma_v^2 = 1$ $(\overline{M} = 0.75)$	$\sigma_v^2 = 0.5$ $(\overline{M} = 2.73)$	$\sigma_v^2 = 1$ $(\overline{M} = 2.65)$
$N = 500$	0.278	0.438	0.884	0.990
$N = 1000$	0.568	0.850	0.998	1.000
$N = 1500$	0.846	0.970	1.000	1.000

$\overline{M}$: average number of observed direct transitions per subject

Score statistic

- Score statistic $U(0,\theta)$

$$U(0,\theta) = \sum_{i=1}^{N} \frac{1}{2L_i(0,\theta)} \times$$

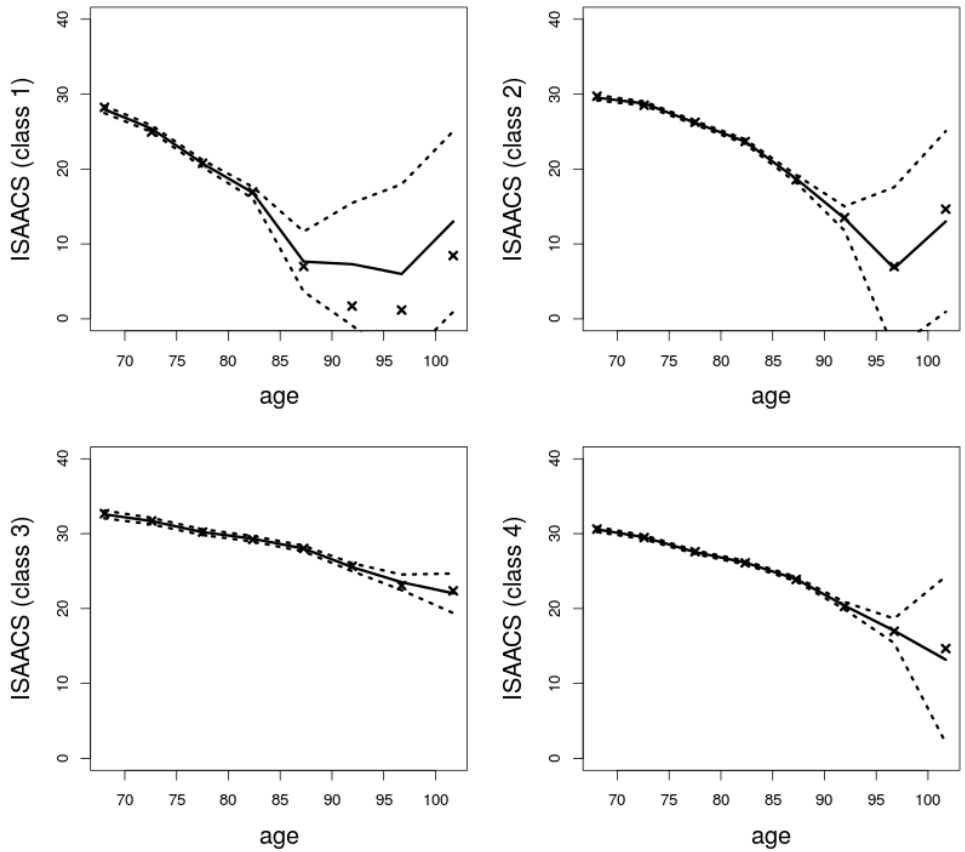
$$\int_{\mathbb{R}^{q_b}} f_Y(Y_i|b_i;\theta) f_E(E_i|b_i;0,\theta) f_b(b_i;\theta) \times$$

$$\left\{ \left[\sum_{r=0}^{m_i-1} \left(\delta_{i(r+1)} + \Lambda^i_{E_i(T_{ir}),E_i(T_{ir})} \left(T_{ir}, T_{i(r+1)}|b_i;0,\theta \right) \right) \right]^2 + \right.$$

$$\left. \sum_{r=0}^{m_i-1} \left(\Lambda^i_{E_i(T_{ir}),E_i(T_{ir})} \left(T_{ir}, T_{i(r+1)}|b_i;0,\theta \right) \right) \right\} \mathrm{d}b_i$$

$$= \sum_{i=1}^{N} \frac{1}{2} \int_{\mathbb{R}^{q_b}} f_b(b_i|Y_i,E_i;0,\theta) \{ \ldots \} dbi$$

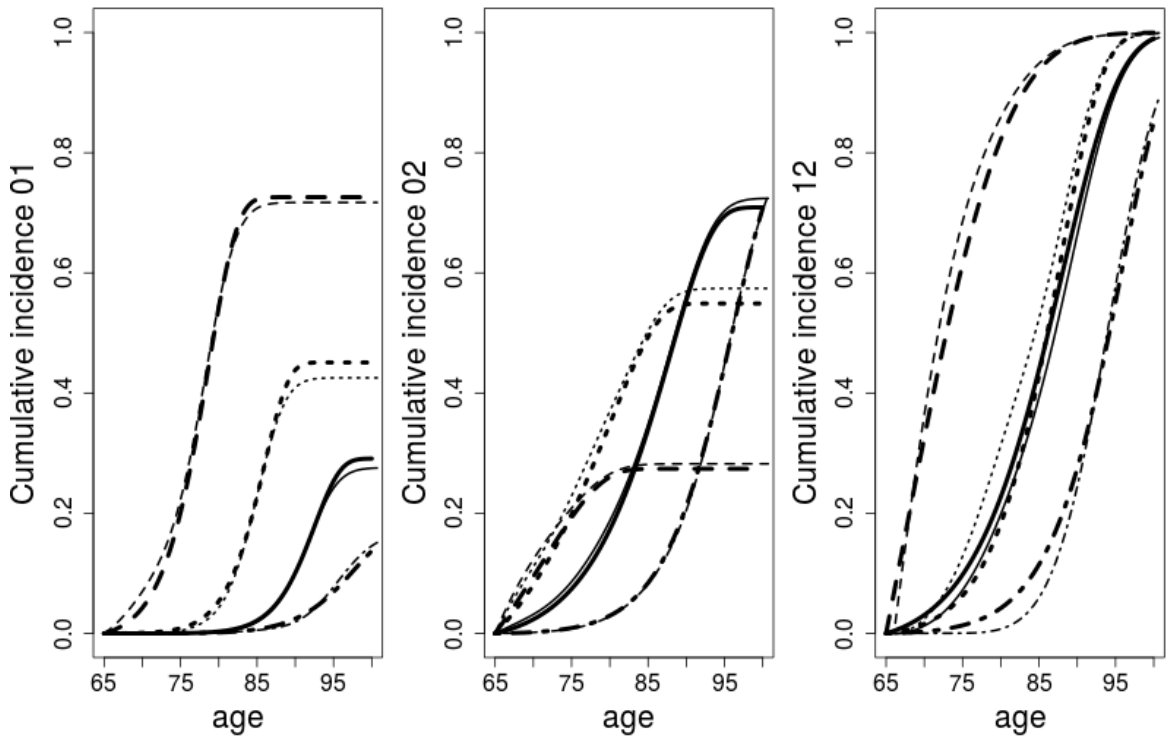
Goodness-of-fit of the longitudinal predictions



$$\hat{\mu}^{o}_{gl} = \frac{\sum_{(i,j)|\tau_l<t_{ij}<\tau_{l+1}} Y_{ij}\, P(c_i = g|Y_i, D_i; \hat{\theta}_G)}{\sum_{(i,j)|\tau_l<t_{ij}<\tau_{l+1}} P(c_i = g|Y_i, D_i; \hat{\theta}_G)}$$

$$\hat{\mu}^{u}_{gl} = \frac{\sum_{(i,j)|\tau_l<t_{ij}<\tau_{l+1}} E(Y_{ij}|c_i = g, \hat{u}_{ig}; \hat{\theta}_G)\, P(c_i = g|Y_i, D_i; \hat{\theta}_G)}{\sum_{(i,j)|\tau_l<t_{ij}<\tau_{l+1}} P(c_i = g|Y_i, D_i; \hat{\theta}_G)}, \text{ with } \hat{u}_{ig} = E(u_{ig}|Y_i, \hat{\theta}_G)$$

Goodness-of-fit of the illness-death predictions



Class-specific cumulative incidences, marginal on covariates:
Joint latent class illness-death model vs. Semi-parametric illness-death model with baseline transition intensities modeled by M-splines.