Examples of joint models for multivariate longitudinal and multistate processes in chronic diseases

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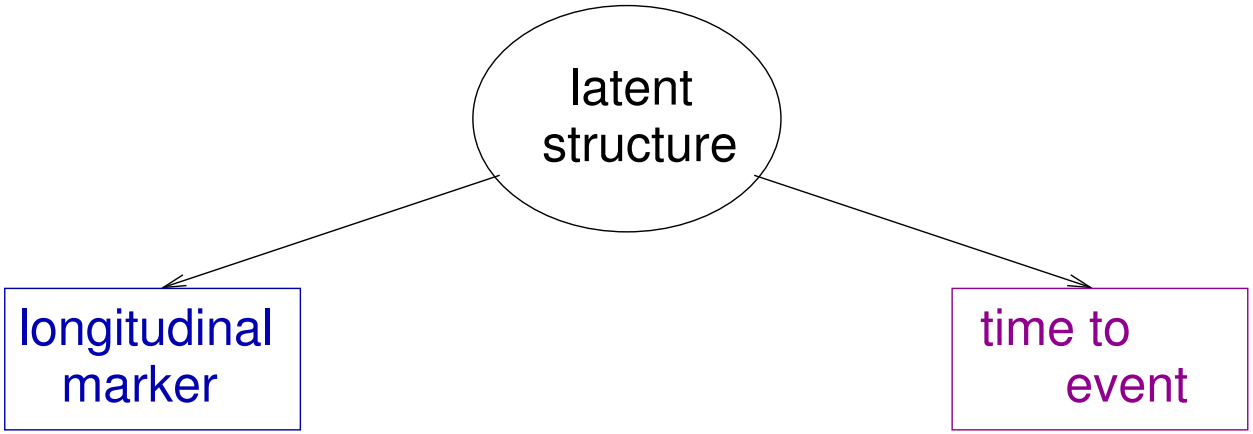
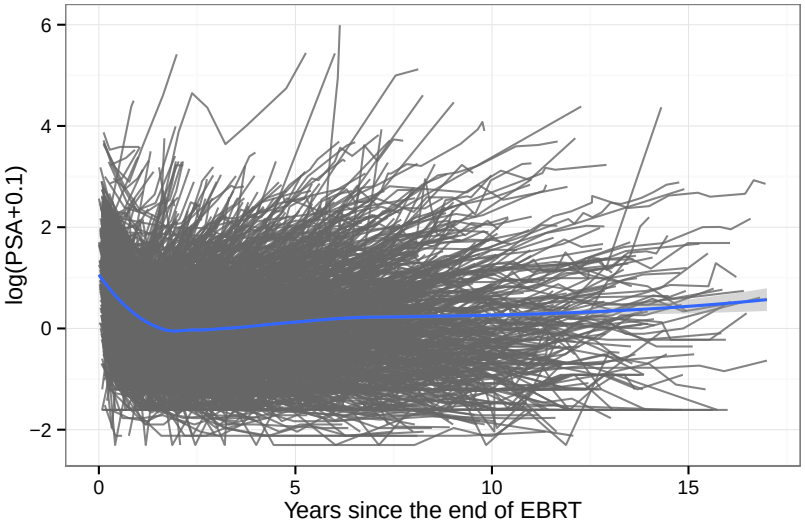
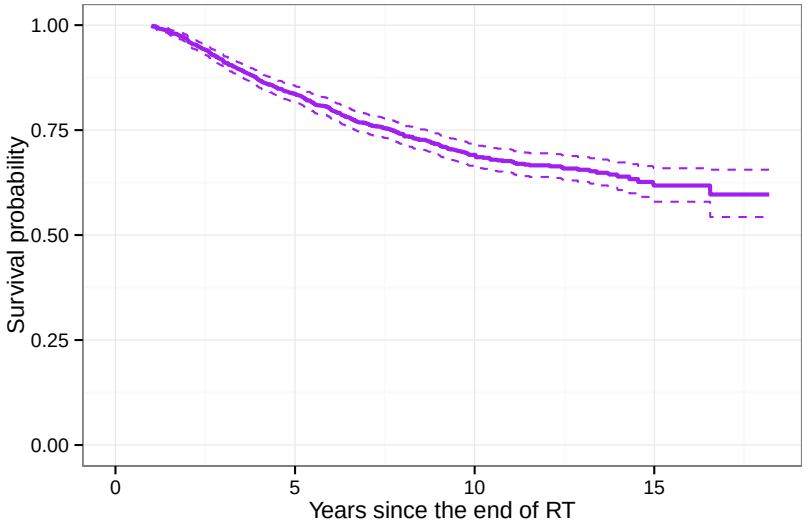
Workshop on Flexible Models for Longitudinal and Survival Data with Applications in Biostatistics

Joint modelling principle

Simultaneous modelling of correlated longitudinal and survival data







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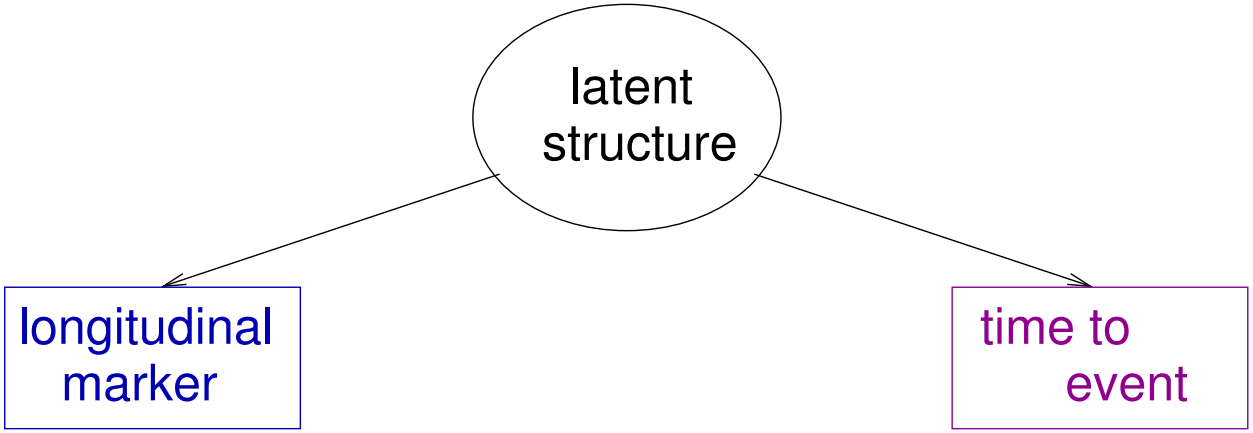
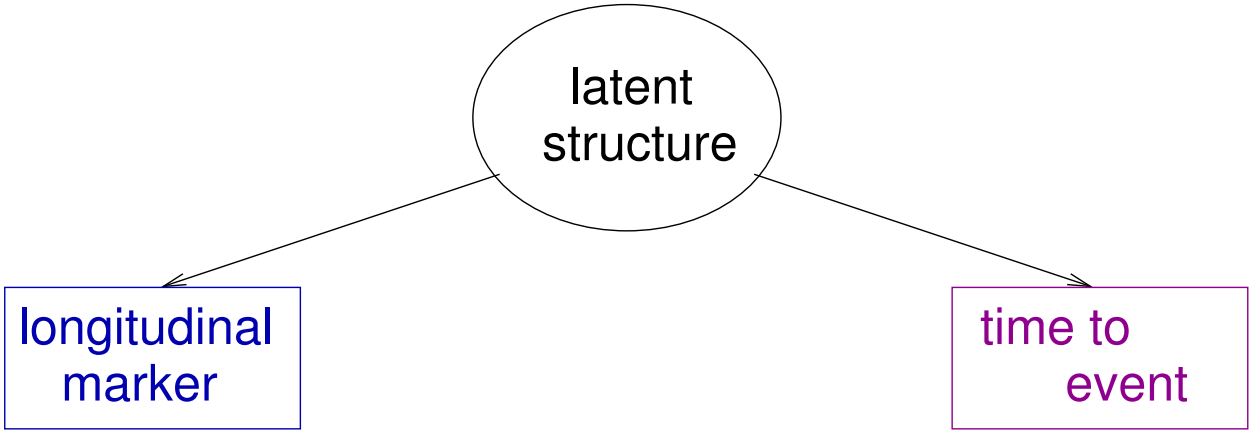


Objectives :

- describe the longitudinal process stopped by the event
- predict the risk of event ajusted for the longitudinal process
- explore the association between the two processes

2 main families of joint models



Mixed model
(usually linear)

Survival model
(usually proportional hazards)

Link with the latent structure :

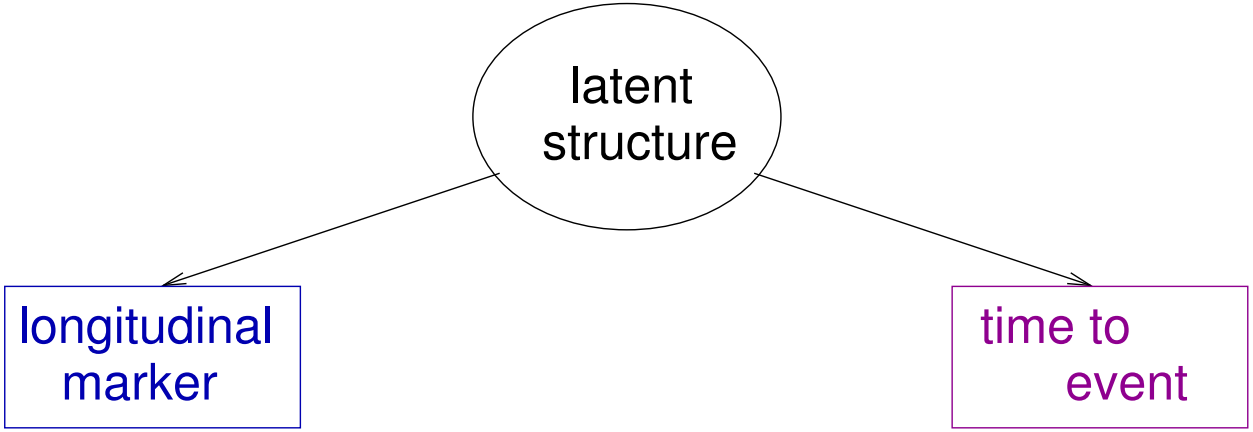
- random effects from the mixed model

  (shared random effect models)

- latent class structure

  (joint latent class models)

Shared random-effect model (SREM) (Rizopoulos, 2012)



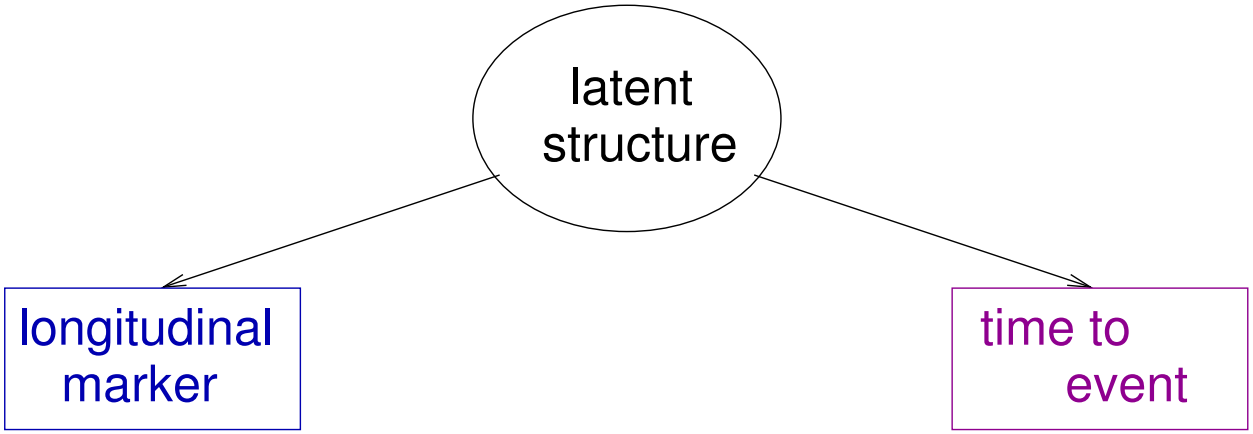
- Shared random-effects distribution : $b_i \sim \mathcal{N}(\mu, B)$
- Linear mixed model for the biomarker trajectory :

  $Y_i(t_{ij}) = Y_i(t_{ij})^* + \epsilon_{ij} = Z_i(t_{ij})^T b_i + X_{Li}(t_{ij})^T \beta + \epsilon_{ij}$ with $\epsilon_{ij} \sim \mathcal{N}(0, \sigma_\epsilon^2)$
- Proportional hazard model including marker trajectory characteristics :

  $\lambda(t \mid b_i) = \lambda_0(t) e^{X_{Si}(t)^T \delta + W_i(b_i, \beta, t)^T \eta}$

$\rightarrow$ JM, JMBayes in R, stjm in Stata, JMFit in SAS

Joint latent class model (JLCM) (Proust-Lima et al., 2014)



- Shared latent class (c_i) membership :

$$\pi_{ig} = P(c_i = g|X_{pi}) = \frac{e^{\xi_{0g}+X_{Ci}{}^{\top}\xi_{1g}}}{\sum_{l=1}^{G} e^{\xi_{0l}+X_{Ci}/top\xi_{1l}}} \text{ with } \xi_{0G} = 0 \text{ \& } \xi_{\mathbf{1G}} = \mathbf{0}$$

- Class-specific linear mixed model for the biomarker trajectory :

$$Y_i(t_{ij}) \mid_{c_i=g} = Z_i(t_{ij})^T b_{ig} + X_{Li}(t_{ij})^{\top}\beta_g + \epsilon_{ij} \text{ with } b_{ig} \sim \mathcal{N}(\mu_g, B_g),\ \epsilon_{ij} \sim \mathcal{N}(0, \sigma_\epsilon^2)$$

- Class-specific proportional hazard model :

$$\lambda(t \mid c_i = g) = \lambda_{0g}(t)e^{X_{Ti}(t)\delta_g}$$

$\rightarrow$ lcmm in R

Remarks (Proust-Lima et al., 2014)

Shared random effect models :

- extension of the standard time-to-event models
- assessment of specific associations (surrogacy)
- quantification of the association

Joint latent class models :

- heterogeneous population
- no assumption on the association
- useful for predictive tools

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In any case, most developments for :

- a Gaussian longitudinal marker
- a right-censored time to event

→ but more complex data in most cohort studies on chronic diseases

In chronic diseases

- Longitudinal part :
  - multiple markers of progression
  - markers of different nature
  - Gaussian, binary, poisson
  - ordinal
  - continuous but non Gaussian
- Survival part :
  - competing risks
  - recurrent events
  - multiple events
  - succession of different events

In chronic diseases

- Longitudinal part :
  - **multiple markers of progression**
  - markers of different nature
  - Gaussian, binary, poisson
  - **ordinal**
  - **continuous but non Gaussian**

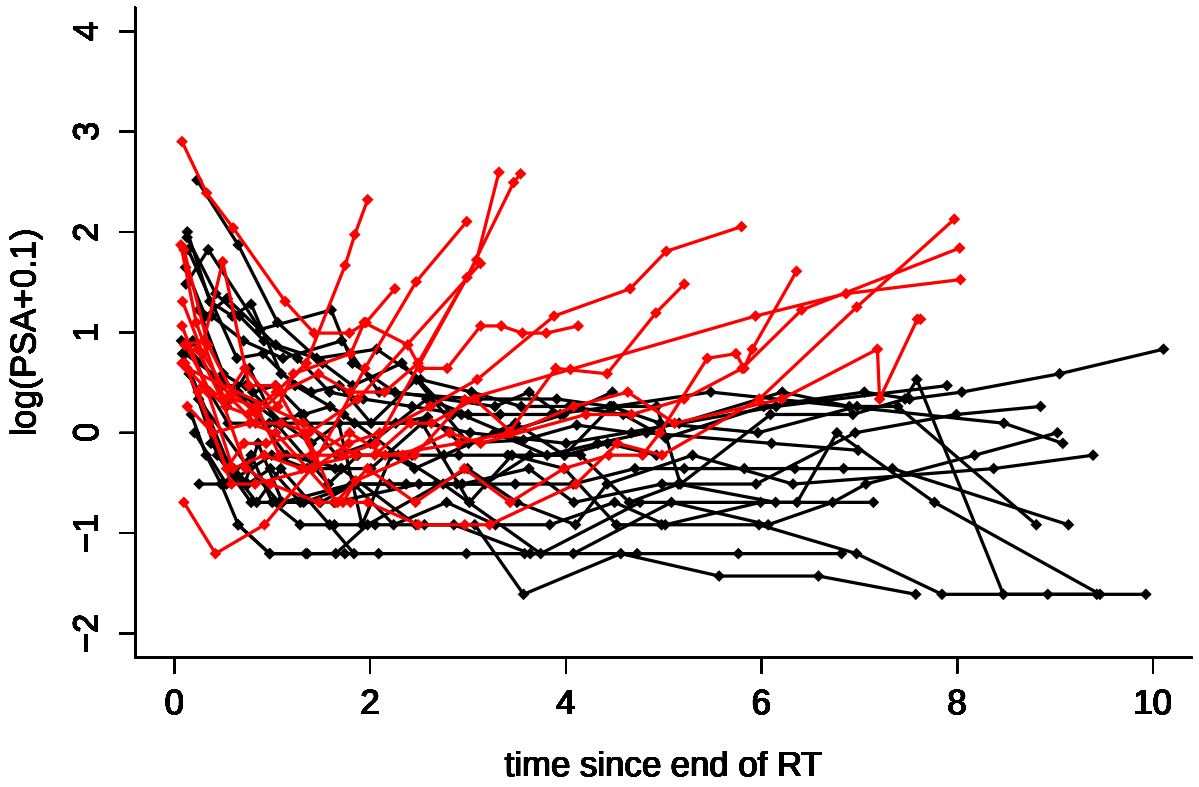
- Survival part :
  - **competing risks**
  - recurrent events
  - multiple events
  - **succession of different events**

3 examples of developments through the study of
  - progression of localized Prostate cancer after treatment
  - natural history of Alzheimer's disease

Progression of localized Prostate Cancer after a treatment by radiation therapy

Localized prostate cancer

- Monitoring of patients after radiation therapy for a localized Prostate cancer :
  - prognostic factors at diagnosis (T-stage, Gleason, dose of RT, ...)
  - repeated measures of PSA (prostate specific antigen) collected in routine

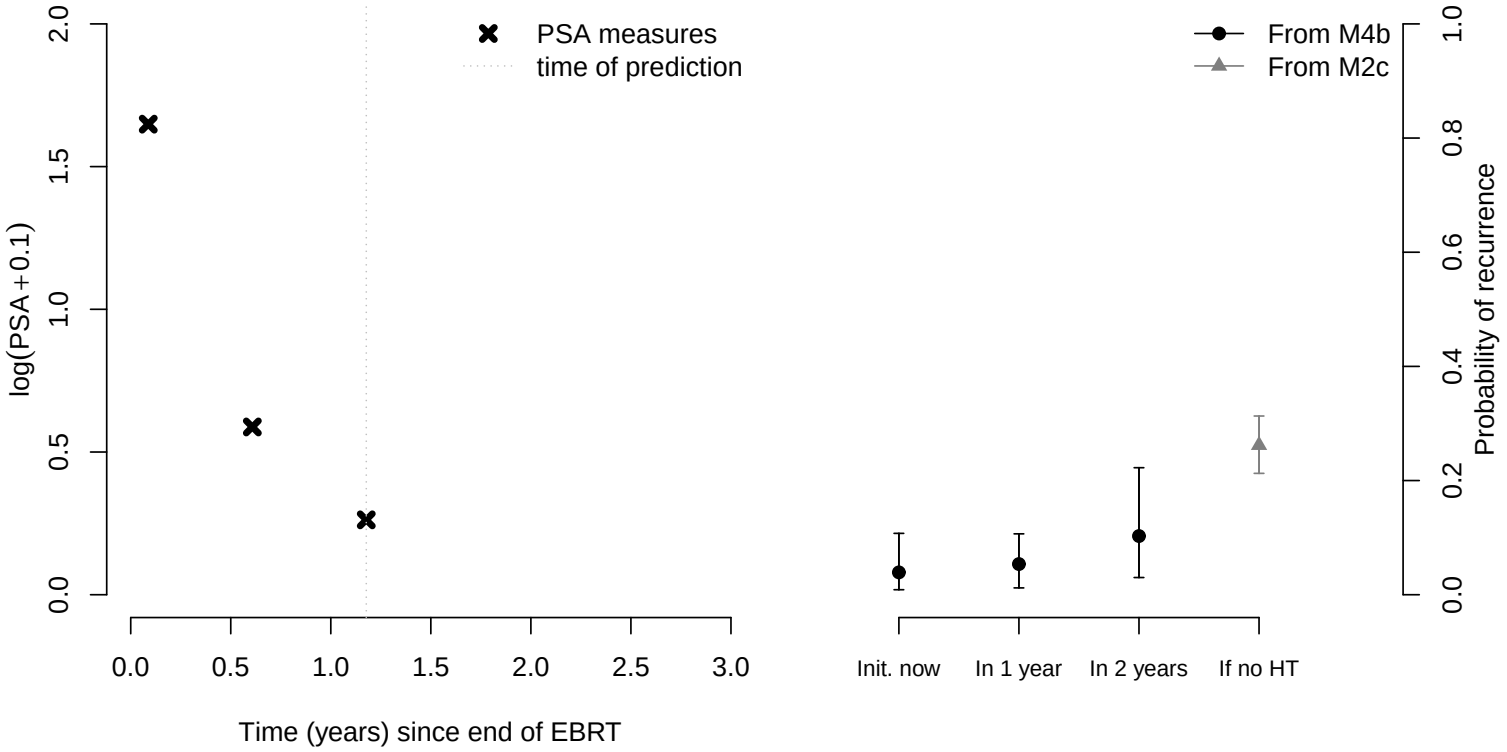


- Interest in predicting the risk of progression
  - multiple types : local recurrence, distant recurrence, death
  - problem of initiation of new treatment : hormonal treatment

Dynamic prediction of clinical recurrence of any type

(Sène et al., SMMR 2014) :

- Individualized probability of clinical recurrence :
  - in the next three years
  - for a man naive of HT
  - according to hypothetical times of initiation of HT (time-dependent covariate)



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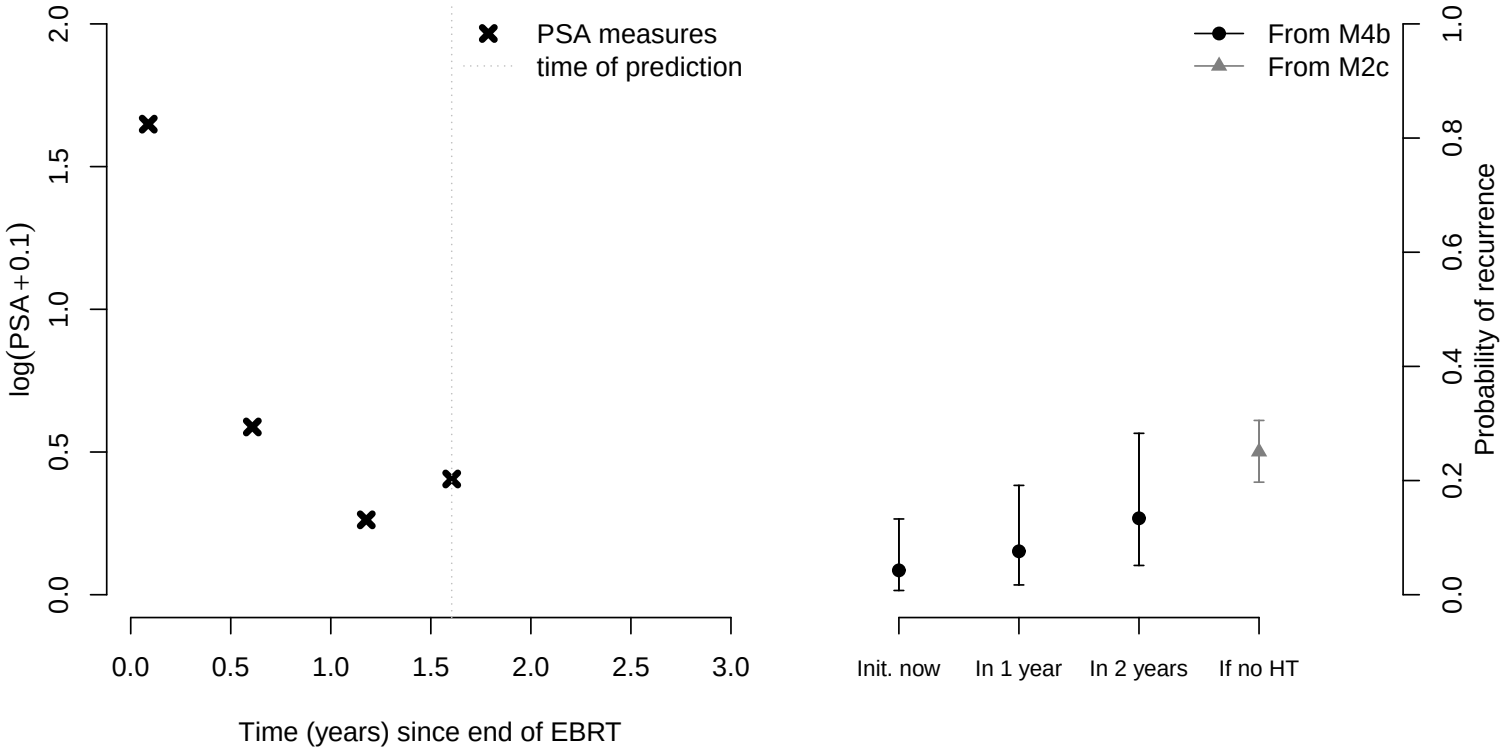

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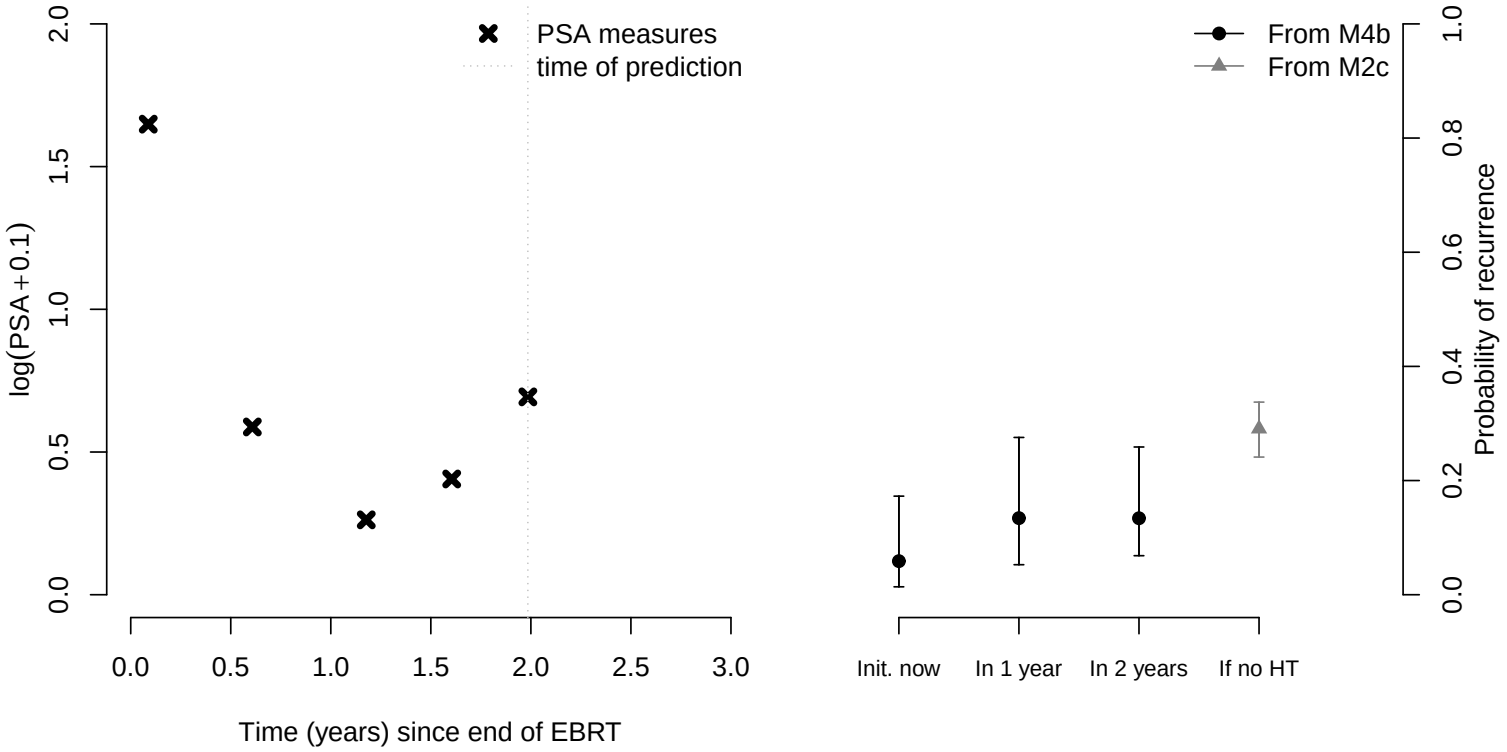
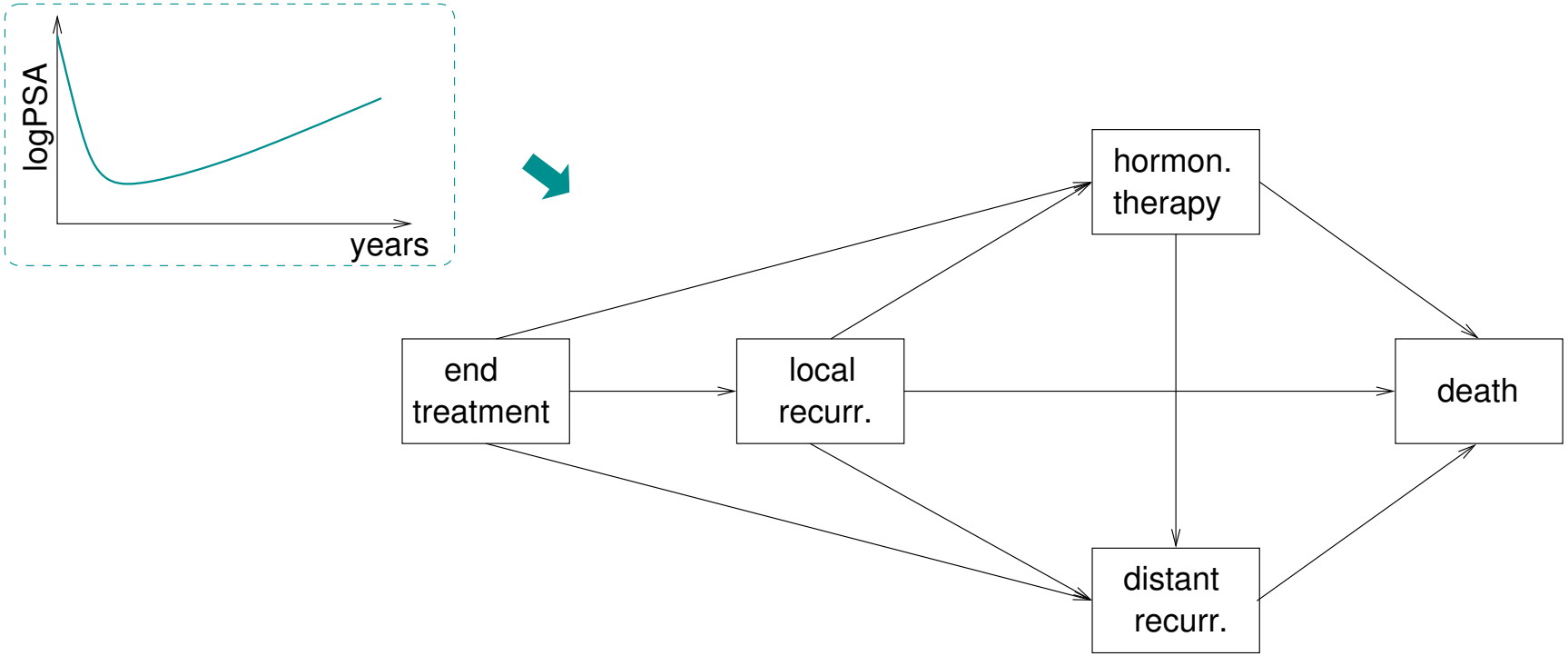


Multiple types of progression

- Clinical progression is a multistate process :



- Importance of distinguishing the different types to :
  - clarify the impact of PSA dynamics and other prognostic factors on each transition
  - predict type-specific progressions

The joint longitudinal and multistate model (Ferrer et al., arXiv 2015)

Notations :

- multi-state process
  - $E_i = \{E_i(t), T_{i0} \leq t \leq C_i\}$ is a non-homogeneous Markov process
    - $E_i(t)$ takes values in the finite state space $S = \{0, 1, \ldots, M\}$
    - T_{i0} the left truncation time, C_i the right censoring time
  - $T_i = (T_{i1}, \ldots, T_{im_i})^\top$ the m_i observed times with $T_{ir} < T_{i(r+1)}, \forall r \in S$
  - $\delta_i = (\delta_{i1}, \ldots, \delta_{im_i})^\top$ the vector of observed transition indicators
- longitudinal process
  - $Y_i = (Y_{i1}, \ldots, Y_{in_i})^\top$ the n_i measures of the marker collected at times $t_{i1}, \ldots, t_{in_i}$, with $t_{in_i} \leq T_{i1}$

The joint longitudinal and multistate model (Ferrer et al., arXiv 2015) (cont'd)

- Longitudinal part : mixed model

$$\begin{aligned} Y_{ij} &= Y_i^*(t_{ij}) + \epsilon_{ij} \\ &= X_{Li}(t_{ij})^\top \beta + Z_i(t_{ij})^\top b_i + \epsilon_{ij} \end{aligned}$$

  - $b_i \sim \mathcal{N}(0, D)$, $\epsilon_i = (\epsilon_{i1}, \ldots, \epsilon_{in_i})^\top \sim \mathcal{N}(0, \sigma^2 \mathrm{I}_{n_i})$, $b_i \perp\!\!\!\perp \epsilon_i$

- Survival part : multistate model

$$\begin{aligned} \lambda_{hk}^i(t|b_i) &= \lim_{\mathrm{d}t \to 0} \frac{\Pr(E_i(t+\mathrm{d}t) = k | E_i(t) = h; b_i)}{\mathrm{d}t} \\ &= \lambda_{hk,0}(t) \exp(X_{Thk,i}^\top \gamma_{hk} + W_{hk,i}(b_i, t)^\top \eta_{hk}), \quad \text{for } h, k \in S, \end{aligned}$$

  - $\lambda_{hk,0}(t)$ parametric baseline intensity, $X_{Thk,i}$ prognostic factors
  - $W_{hk,i}(b_i, t)$ the dependence structure (Sène et al., J sfds 2014)
    - ★ $W_{hk,i}(b_i, t) = Y_i^*(t)$ $\longrightarrow$ (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)
    - ★ ...

Maximum Likelihood Estimation

- Likelihood function using $Y_i \perp\!\!\!\perp_{b_i} T_i$,

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

with :

- Random effects part : $b_i \sim \mathcal{N}_q(0, D)$
- Longitudinal part : $Y_{i\ |b_i} \sim \mathcal{N}_{n_i}(X_{Li}^\top \beta + Z_i^\top b_i, \sigma^2 \mathrm{I}_{n_i})$
- Multi-state part :

$$f_T(T_i,\delta_i|b_i;\theta) = \prod_{r=0}^{m_i-1} \Big[P^i_{E_i(T_{ir}),E_i(T_{ir})}(T_{ir}, T_{i(r+1)}|b_i) \times \lambda^i_{E_i(T_{ir}),E_i(T_{i(r+1)})}(T_{i(r+1)}|b_i)^{\delta_{i(r+1)}} \Big]$$

with $P_{hh}(s,t) = \exp\left(\int_s^t \lambda_{hh}(u)\,\mathrm{d}u\right) = \exp\left(-\sum_{k\neq h}\int_s^t \lambda_{hk}(u)\,\mathrm{d}u\right)$

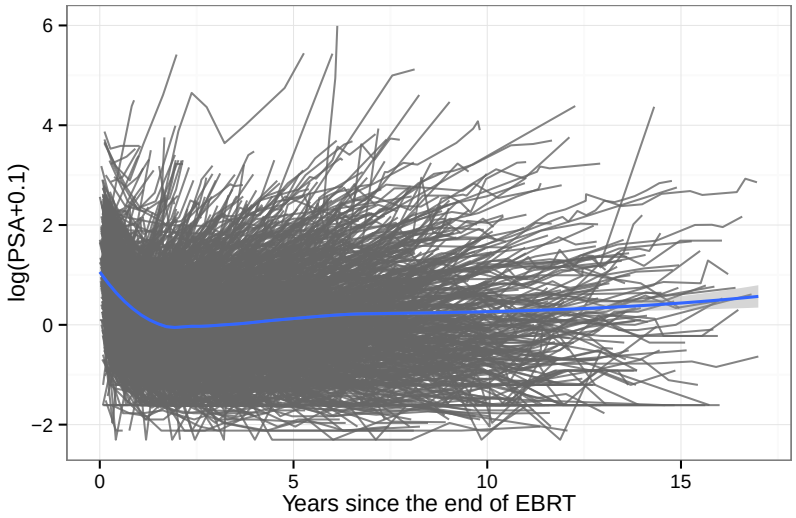
Implementation under R

- Relies on `JM` package
- Implementation procedure decomposed into four steps :
  1. `lme()` function (`nlme` package) to initialise the parameters in the longitudinal sub-model ;
  2. `mstate` package to adapt the data to the multi-state framework ;
  3. `coxph()` function (`survival` package) to initialise the parameters in the multi-state sub-model ;
  4. `JMstateModel()` function (extension of `jointModel()`) to estimate all the parameters of the joint multi-state model.
- Likelihood computed and optimised using :
  - numerical integration algorithms (Gaussian quadratures)
  - optimisation algorithms (EM + quasi-Newton)

Application

- 2 cohorts of men with localized prostate cancer treated by radiotherapy (N=1474)

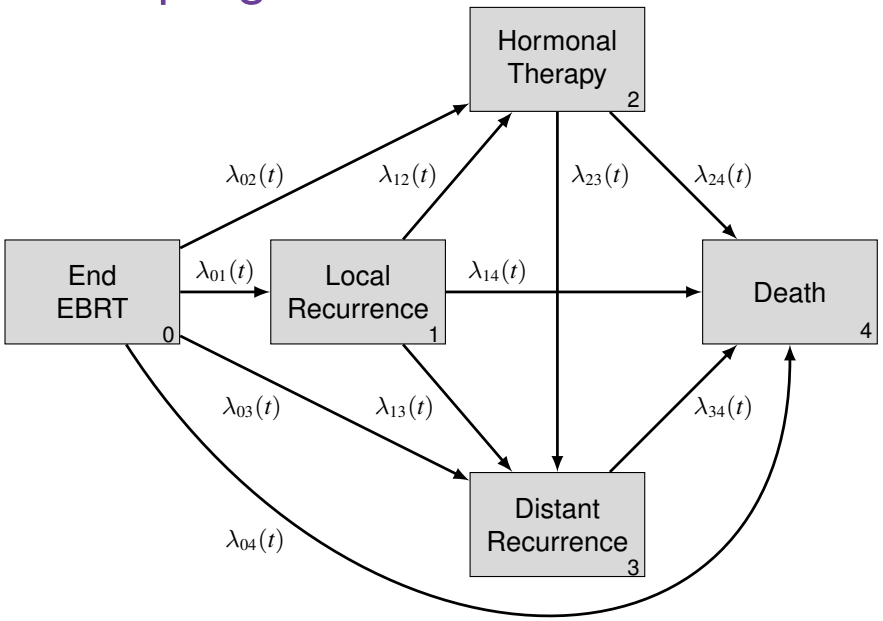
- Repeated measures of PSA



10 (3, 21) measurements per patient

(50th, (5th, 95th) %iles)

- Multi-state representation of the clinical progressions



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

matrix of direct transitions

Specification of the joint model (1/2)

- Longitudinal sub-model specification

$$
\begin{aligned}
Y_{ij} &= Y_i^*(t_{ij}) + \epsilon_{ij} \\
&= \left(\beta_0 + X_{L0i}^\top \beta_{0,\mathrm{cov}} + b_{i0}\right) + \\
&\quad \left(\beta_1 + X_{L1i}^\top \beta_{1,\mathrm{cov}} + b_{i1}\right) \times f_1(t_{ij}) + \\
&\quad \left(\beta_2 + X_{L2i}^\top \beta_{2,\mathrm{cov}} + b_{i2}\right) \times f_2(t_{ij}) + \epsilon_{ij}
\end{aligned}
$$

  - $f_1(t) = (1+t)^{-1.2} - 1$ and $f_2(t) = t$
  - $b_i = (b_{i0}, b_{i1}, b_{i2})^\top \sim \mathcal{N}(0, D)$, D unstructured, $\epsilon_i \sim \mathcal{N}(0, \sigma^2 I_{n_i})$
  - X_{L0i}, X_{L1i} and X_{L2i} were obtained using a backward stepwise procedure.

Specification of the joint model (2/2)

- Multi-state sub-model specification

$$\lambda_{hk}^{i}(t|b_i) = \lambda_{hk,0}(t)\exp\left(X_{T,hk,i}^{\top}\gamma_{hk} + \begin{pmatrix} Y_i^*(t) \\ \partial Y_i^*(t)/\partial t \end{pmatrix}^{\top} \begin{pmatrix} \eta_{hk,\texttt{level}} \\ \eta_{hk,\texttt{slope}} \end{pmatrix}\right)$$

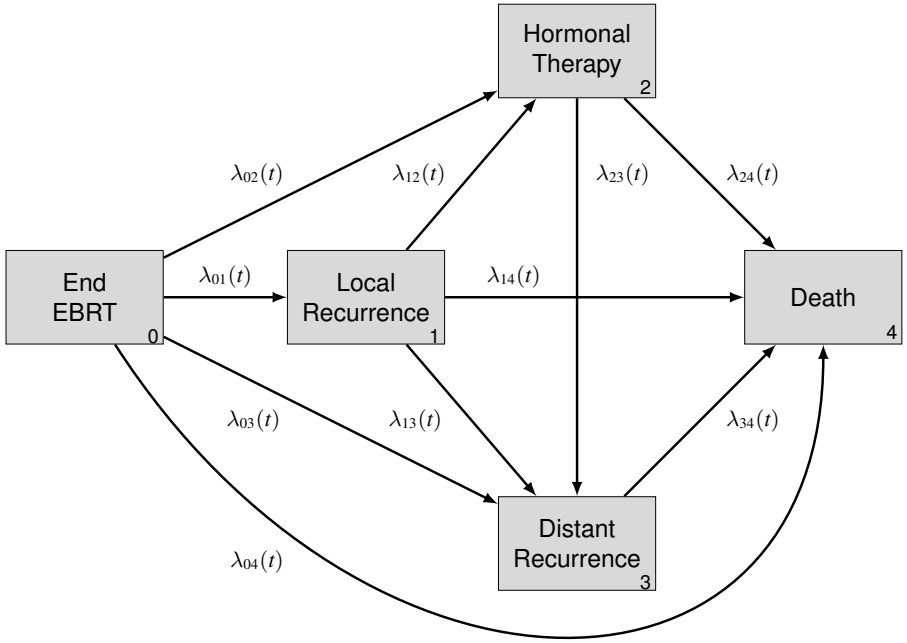
  - Log-baseline intensities approximated by B-splines
  - Proportionality assumptions between several baseline intensities
  - Backward stepwise procedure to select the prognostic factors
  - Dependence function chosen by Wald tests

Results

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

	Value	StdErr	p-value
Level : 01	0.37	0.09	< 0.001
Level : 02	0.51	0.07	< 0.001
Level : 03	0.45	0.11	< 0.001
Level : 04	-0.17	0.05	0.001
Level : 12	-0.16	0.10	0.110
Level : 13	-0.41	0.20	0.042
Level : 14	0.10	0.14	0.487
Level : 23	-0.15	0.09	0.120
Level : 24	0.00	0.05	0.412
Level : 34	0.04	0.08	0.609
	.....		
Slope : 01	2.54	0.31	< 0.001
Slope : 02	3.04	0.25	< 0.001
Slope : 03	2.43	0.49	< 0.001
Slope : 04	1.03	0.32	0.001
Slope : 12	2.01	0.61	0.001
Slope : 13	3.18	0.80	< 0.001
Slope : 14	-0.20	1.27	0.873
Slope : 23	0.97	0.67	0.150
Slope : 24	0.29	0.52	0.583
Slope : 34	-0.79	0.78	0.313

Multi-state process



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

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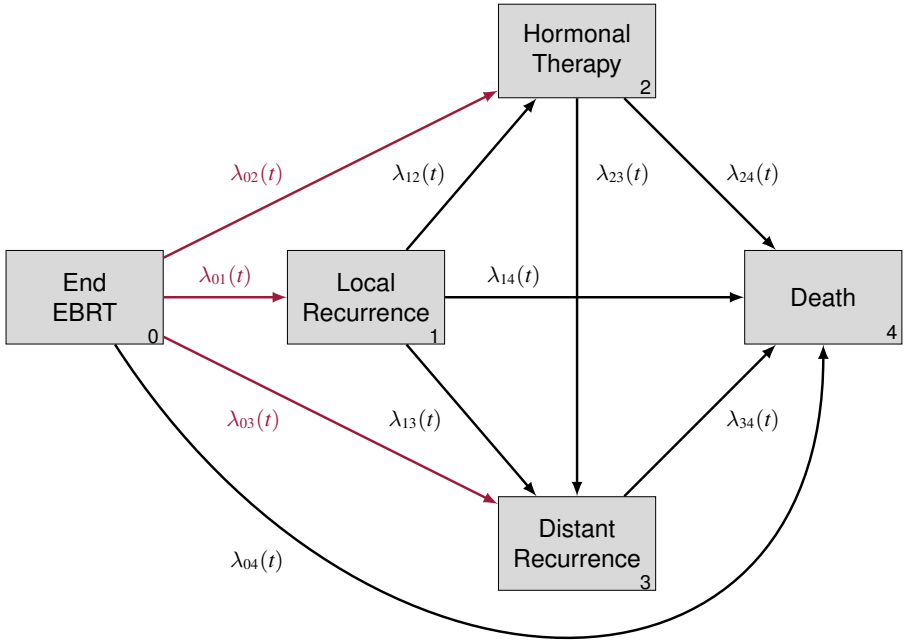

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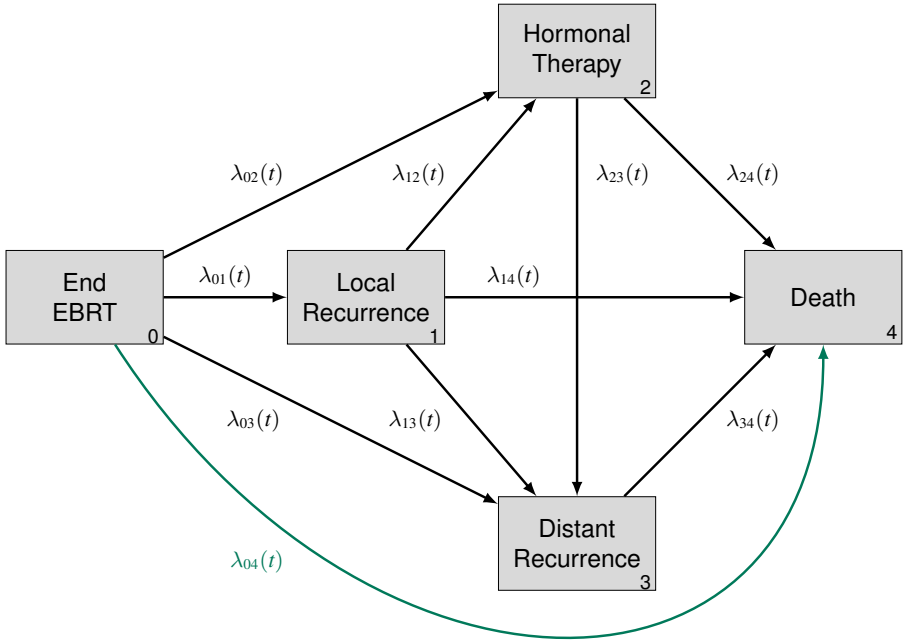

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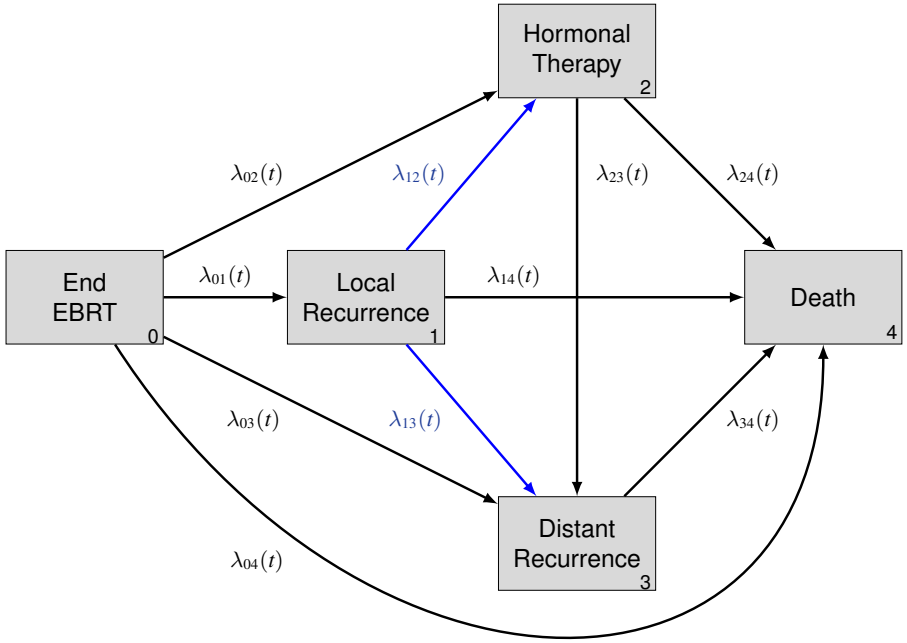
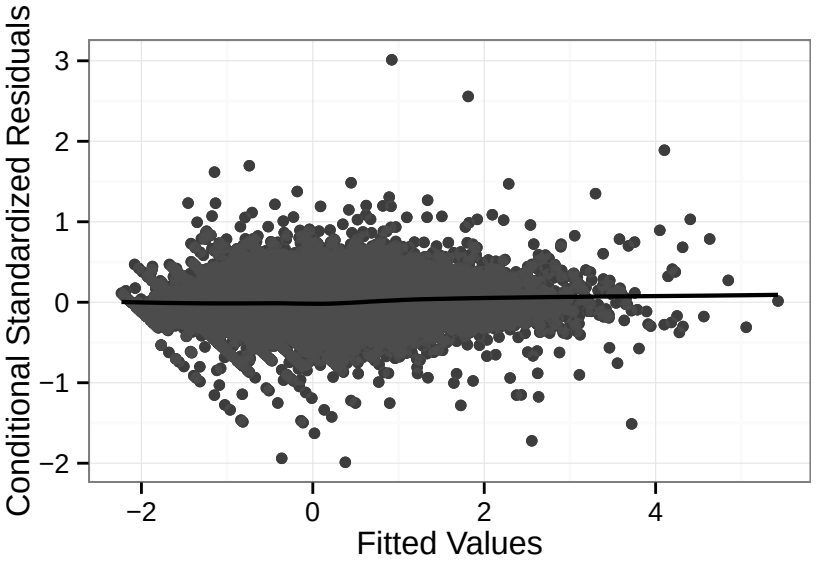
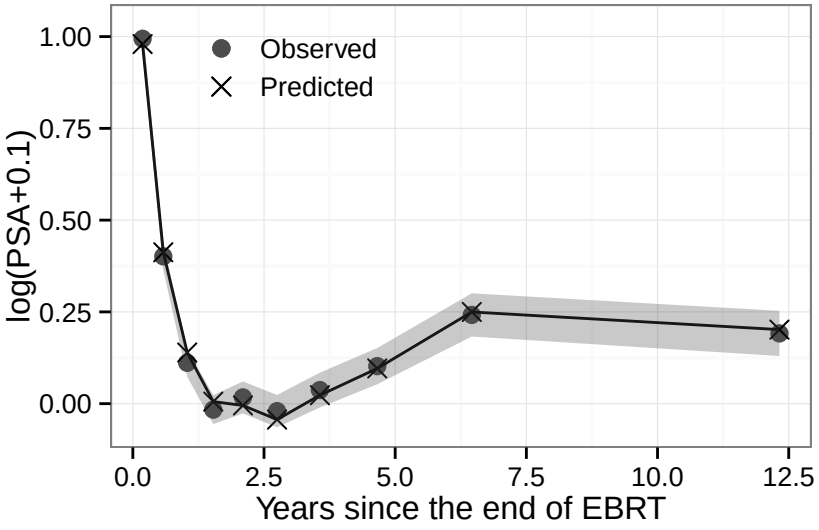


Prognostic factors : advanced initial stage not always associated with intensities of transitions between health states after adjustment on PSA

Diagnostics for the parametric assumptions

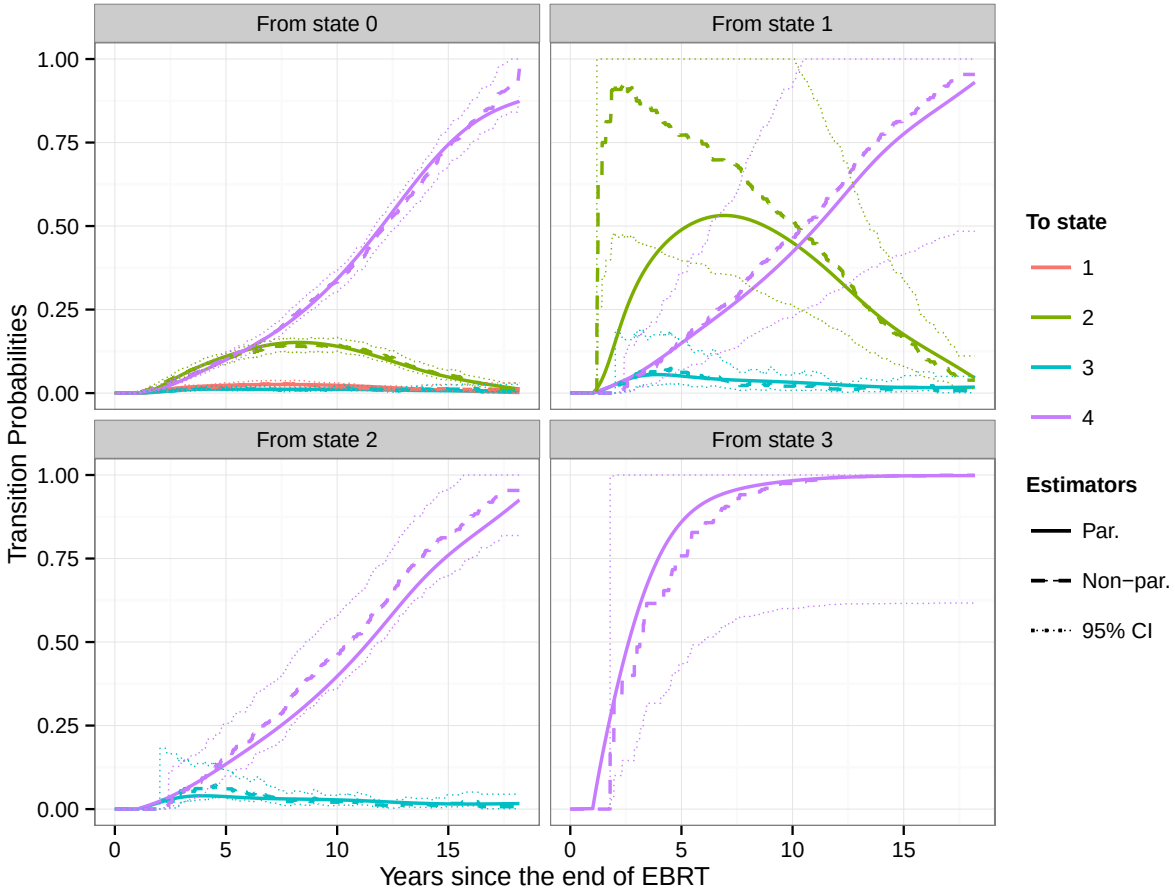
- Goodness-of-fit plots for the longitudinal process
  - Conditional standardized residuals versus fitted values
  - Observed and predicted values of the biomarker





Diagnostics for the parametric assumptions

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



Natural history of Alzheimer's disease, dementias and cognitive aging

Cognitive aging and dementia

- Dementia (e.g. Alzheimer's disease) characterized by a progressive decline of cognition
- Most interest in
  - the natural history of dementia
  - risk factors of cognitive decline and dementia
  - dynamic individual prediction of dementia

Cognitive aging and dementia

- Dementia (e.g. Alzheimer's disease) characterized by a progressive decline of cognition
- Most interest in
  - the natural history of dementia
  - risk factors of cognitive decline and dementia
  - dynamic individual prediction of dementia

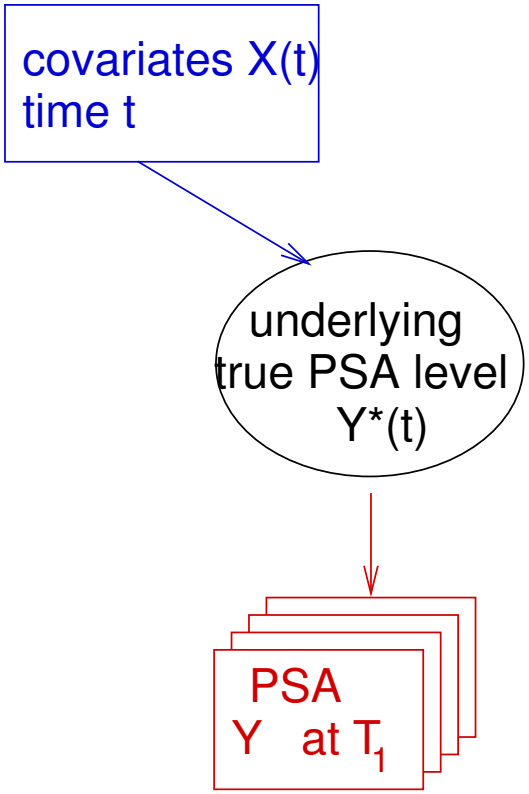
→ 1st complexity : elderly pathology

- delayed entry
- dementia in competition with death
- diagnosis at pre-established visit times

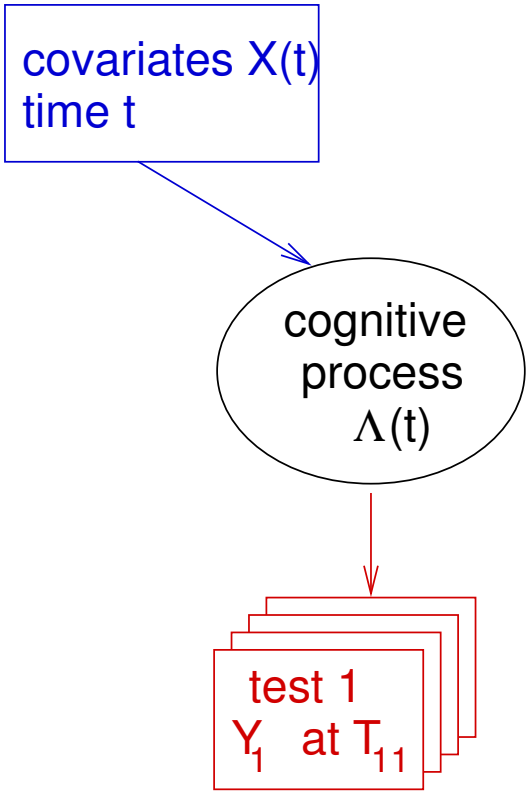
→ 2nd complexity : cognition is not directly observed

- cognitive process (trait) defined in continuous time
- repeated psychometric tests measured in discrete times
  - ★ multiple cognitive functions (langage, memory, attention,...)
  - ★ noisy measures of overall cognition
  - ★ limited statistical properties

Latent process mixed model



Latent process mixed model



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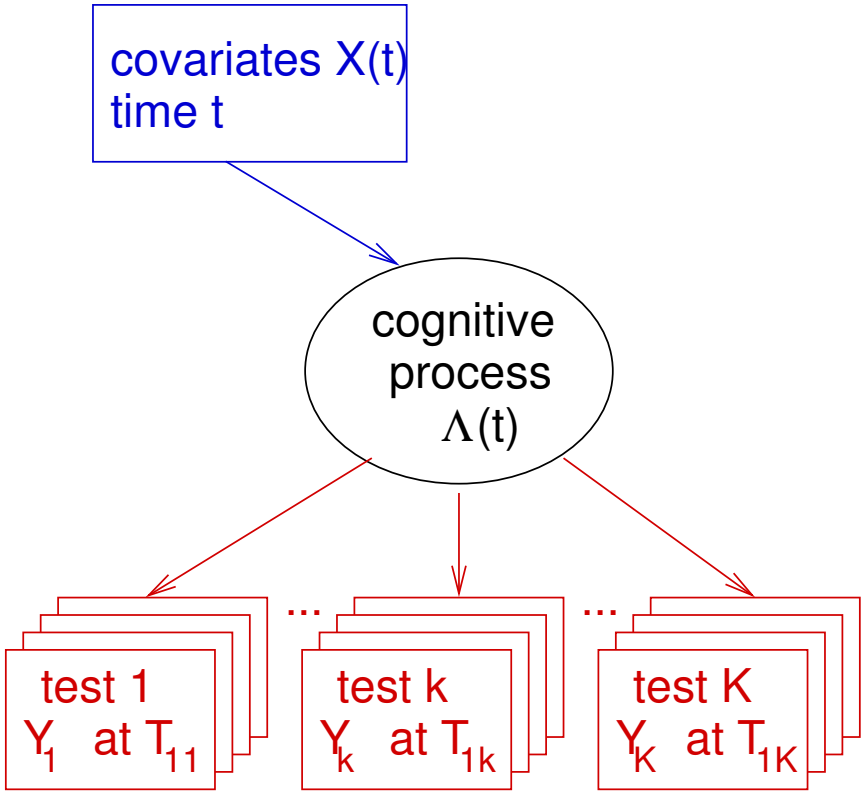

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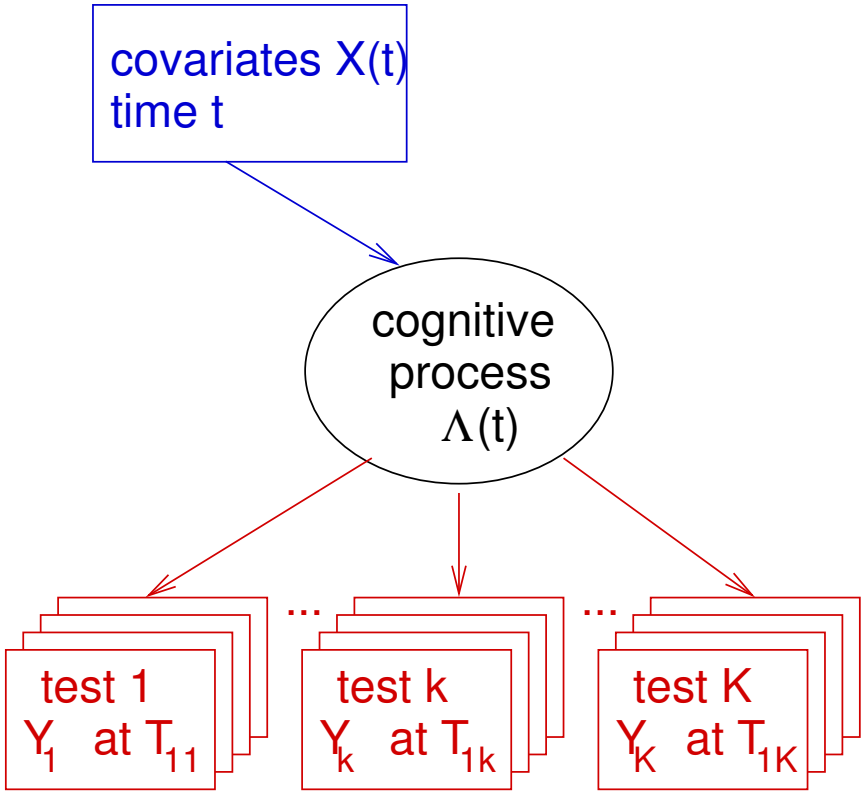
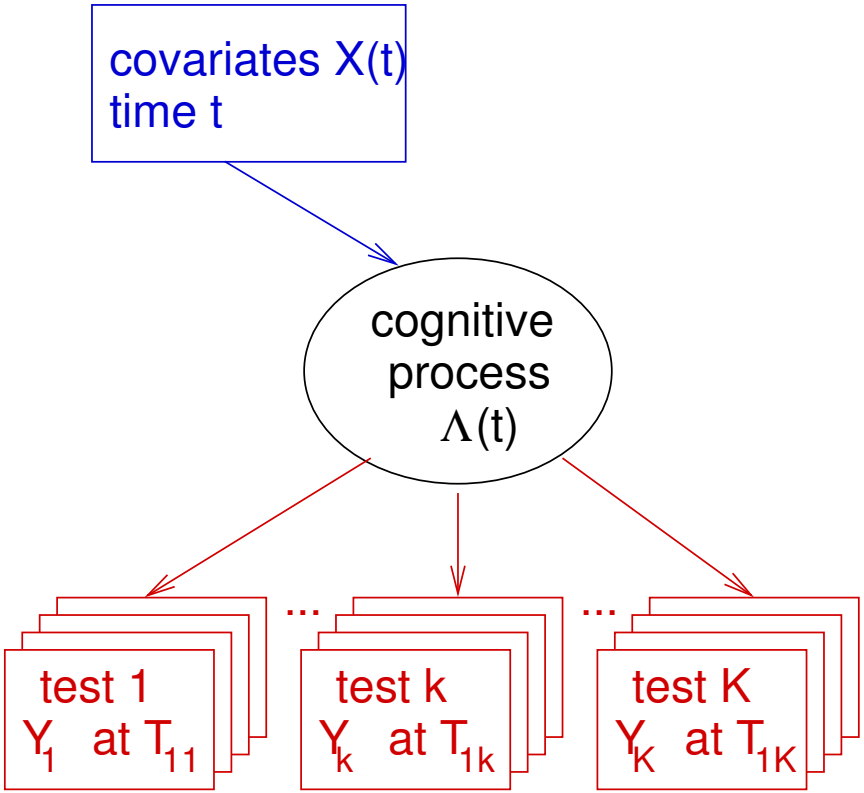


$$\leftarrow \quad \Lambda_i(t) = \mathbf{X_{L1i}}(t)^\top \boldsymbol{\beta} + \mathbf{Z_i}(t)^\top \mathbf{b_i} + w_i(t)$$

- $b_i \sim MVN(\mu, B)$
- $w_i(t)$ autocorrelated process
- $b_{i0} \sim N(0,1)$ for identifiability

Latent process mixed model



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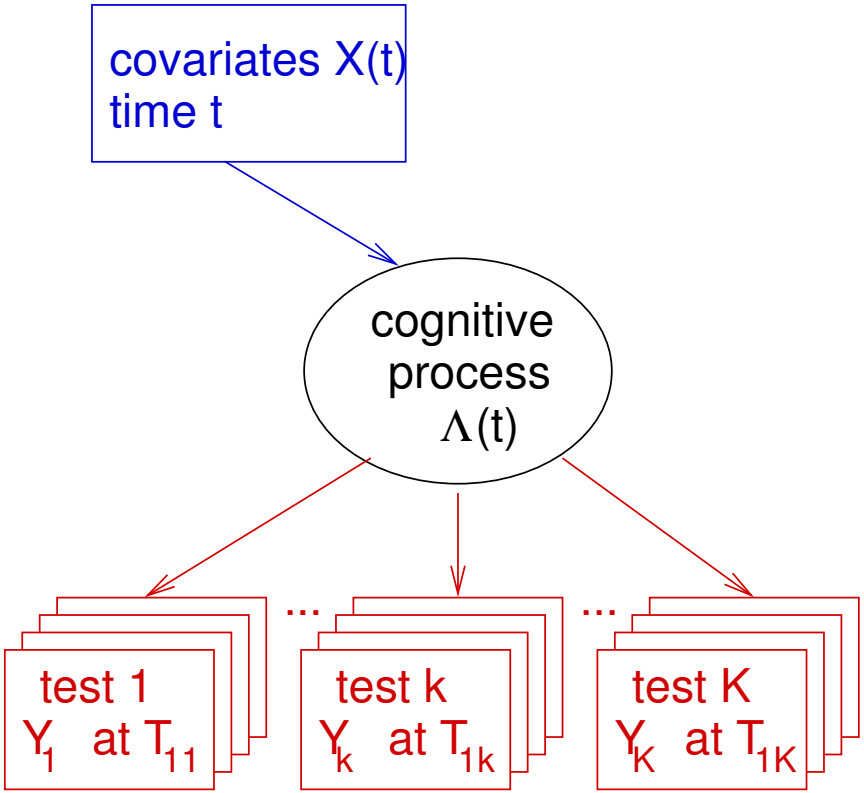
$\leftarrow \quad Y_{kij} = \zeta_{1k} + \zeta_{2k}\tilde{Y}_{kij}$

$\tilde{Y}_{kij} = \Lambda_i(t_{ijk}) + \epsilon_{kij}$

- $\epsilon_{kij} \sim \mathcal{N}(0, \sigma^2_{\epsilon_k})$

Latent process mixed model



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- $\alpha_{ki} \sim \mathcal{N}(0, \sigma^2_{\alpha_k})$
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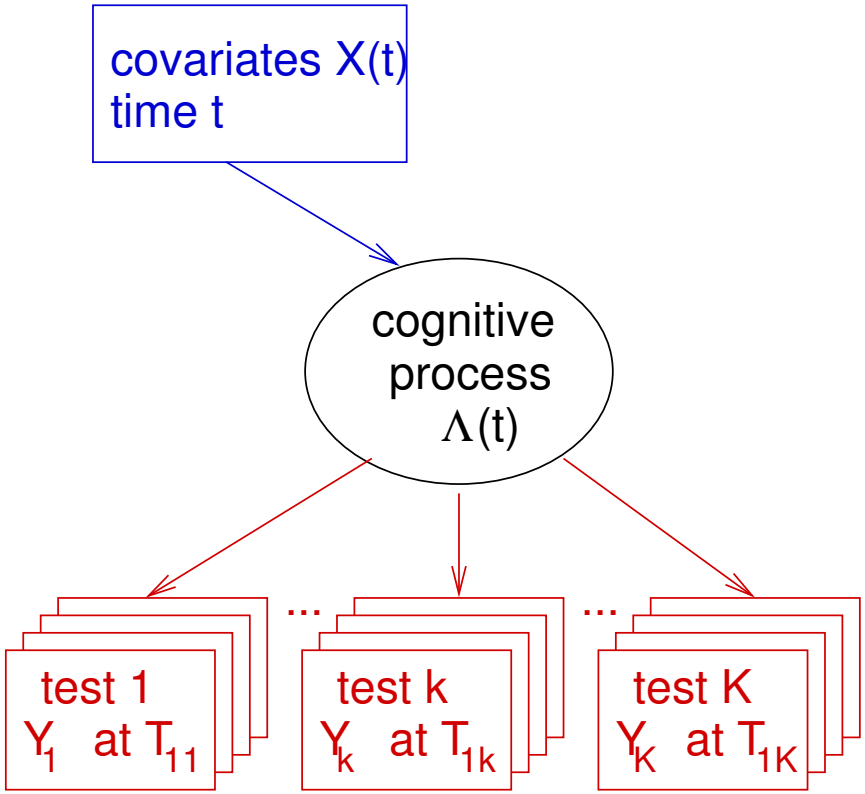
Latent process mixed model



$\leftarrow$ $\Lambda_i(t) = \mathbf{X_{L1i}}(t)^\top \boldsymbol{\beta} + \mathbf{Z_i}(t)^\top \mathbf{b_i} + w_i(t)$

- $b_i \sim MVN(\mu, B)$
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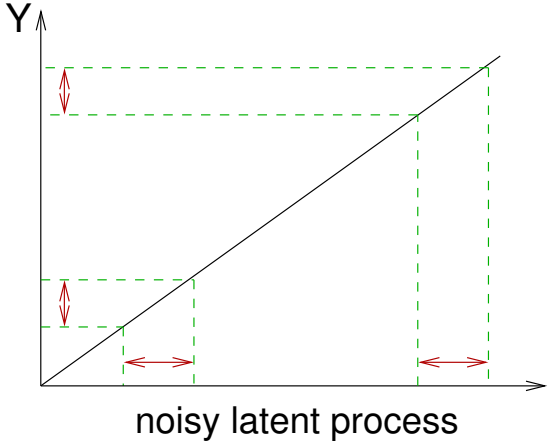
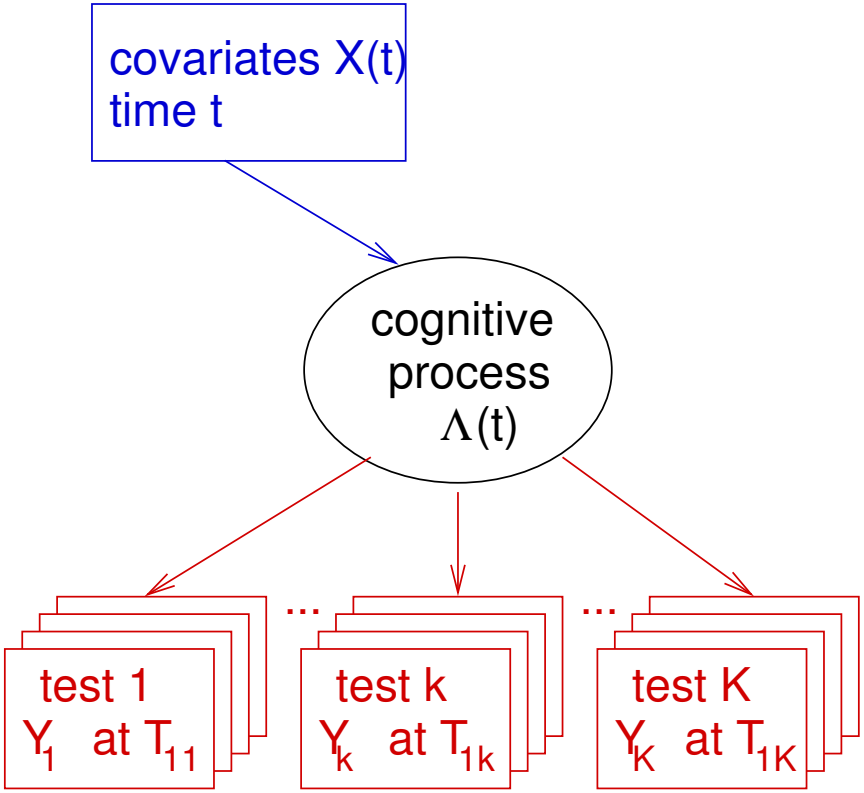
$\leftarrow$ linear link function



Latent process mixed model involving nonlinear link functions (Proust-Lima et al., 2015)



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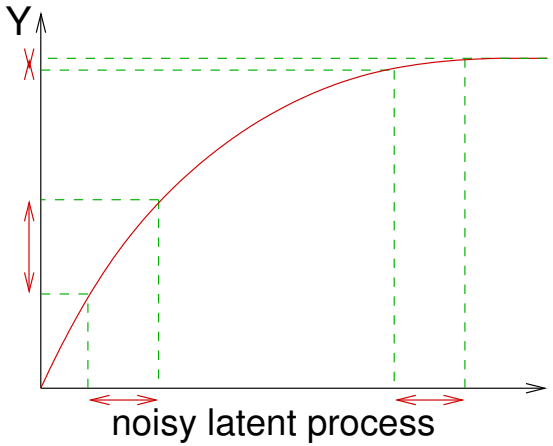

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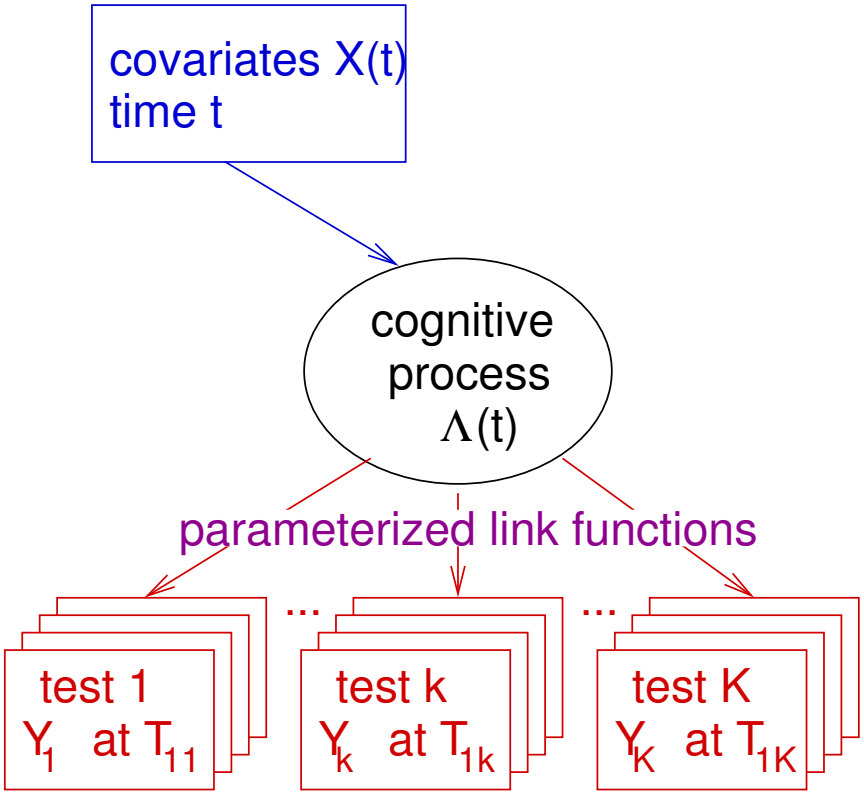

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- $b_{i0} \sim N(0,1)$ for identifiability

$\leftarrow \quad Y_{kij} = \boldsymbol{H_k}(\ \tilde{Y}_{kij}\ ; \zeta_k)$

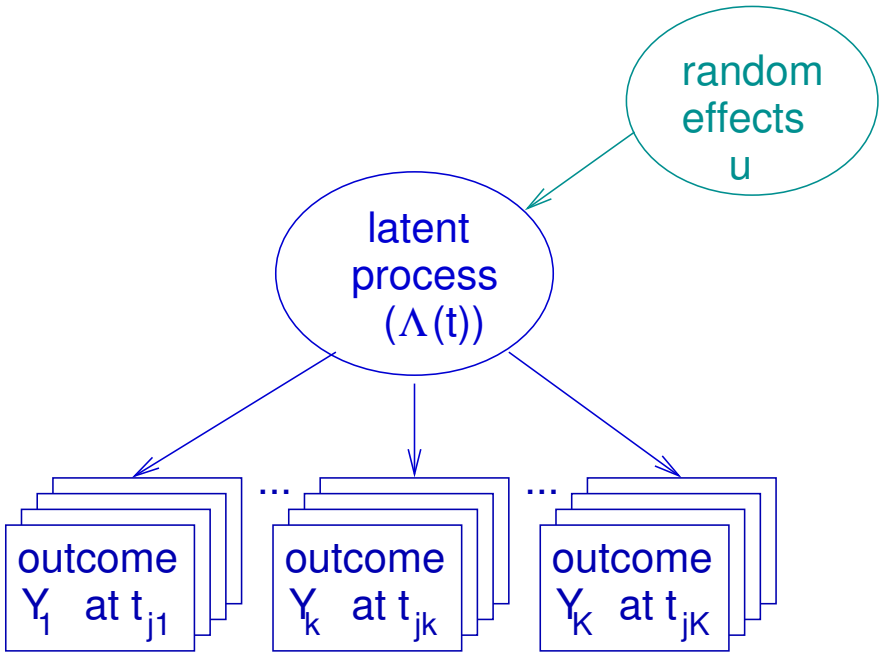
$\tilde{Y}_{kij} = \Lambda_i(t_{ijk}) + \mathbf{X_{L2i}}(t)^\top \gamma_k + \alpha_{ki} + \epsilon_{kij}$

- $\alpha_{ki} \sim \mathcal{N}(0, \sigma^2_{\alpha_k})$
- $\epsilon_{kij} \sim \mathcal{N}(0, \sigma^2_{\epsilon_k})$

H_k = flexible parameterized transformation for outcome k

$\rightarrow$ *linear, standardised Beta CDF, quadratic I-splines, thresholds, ...*

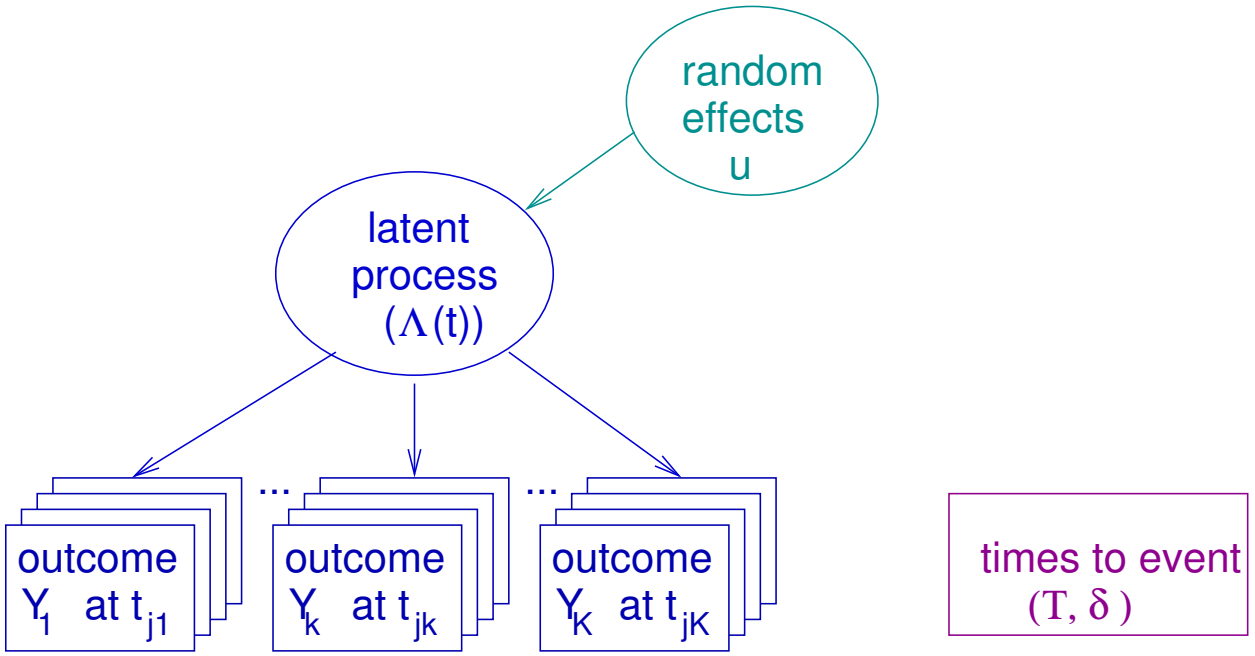
Joint model for multivariate cognitive measures, dementia and death



cognitive measures :

- latent process mixed model

Joint model for multivariate cognitive measures, dementia and death



cognitive measures :

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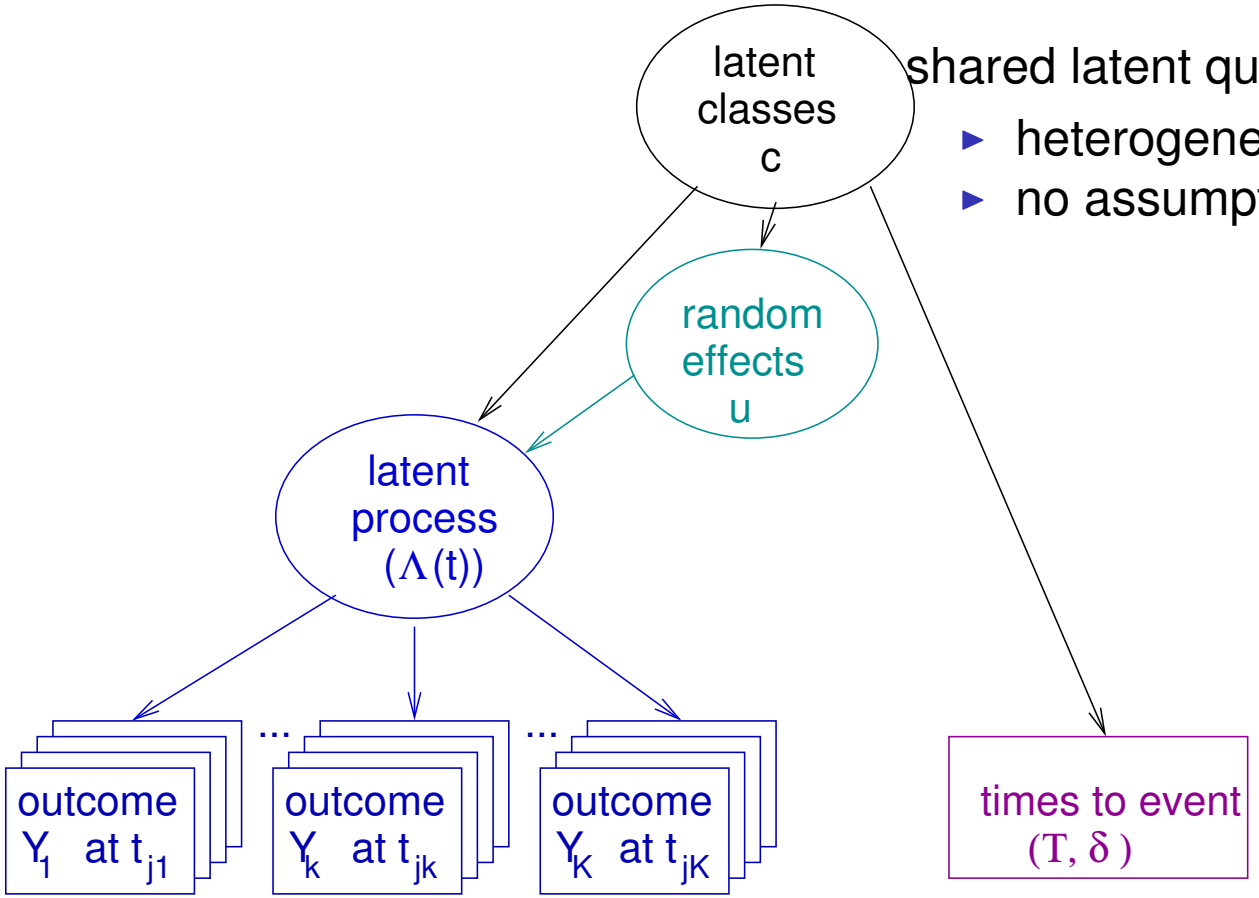
dementia and death ?

- option 1 : first event in competing setting
- option 2 : multistate model

Joint model for multivariate cognitive measures, dementia and death



shared latent quantity = latent classes

- heterogeneous trajectories
- no assumption on the association

cognitive measures :

- latent process mixed model

dementia and death ?

- option 1 : first event in competing setting
- option 2 : multistate model

Option 1 : competing setting (Proust-Lima et al., ArXiv 2014)

- Times to events = Time to P competing events
  - $T_i = \min($censoring $\tilde{T}_i$, and cause-spec. times $T^*_{i1}, ..., T^*_{iP})$,
  - $\delta_i = 0$ for censored, $\delta_i = p$ otherwise

- class-specific cause-specific proportional hazard models

$$\lambda_p(t)|_{c_i=g} = \lambda_{0p}(t; \nu_{pg}) \exp(X_{Ti}^\top \zeta_{pg})$$

  - λ_{0p} parametric (splines, Gompertz, Weibull,...)

Maximum Likelihood Estimation

- Likelihood function using $Y_i \perp\!\!\!\perp_{c_i} T_i$,

$$L(\theta) = \prod_{i=1}^{N} \sum_{g=1}^{G} f_Y(Y_i|X_{Li}, Z_i, c_i = g; \theta)\ f_T(T_i, \delta_i|X_{Ti}, c_i = g; \theta)\ P(c_i = g|X_{Ci}; \theta)$$

with :

  - $f_Y(Y_i|X_{Li}, Z_i, c_i = g; \theta)$ from the latent process mixed model
    - ★ closed form if only continuous markers :
      = multivariate normal $\times$ Jacobian of $(H_k)_{k=1,\ldots,K}$
    - ★ by numerical integration otherwise ...

  - $f_T(T_i, \delta_i|X_{Ti}, c_i = g; \theta)$ from the cause-specific model
      = overall survival S_{ig} $\times$ instantaneous risk for cause p in g if $\delta_i = p$

  - $P(c_i = g|X_{Ci}; \theta)$ from a multinomial logistic model

- Left truncation (entry at T_{0i}) : $l^{T_0}(\theta) = \log\left(\dfrac{L(\theta)}{\prod_{i=1}^{N} S_i(T_{0i}; \theta)}\right)$

Implementation, model selection and evaluation

- Iterative (Marquardt) algorithm for a given G
  - implemented in HETMIXSURV_V2 parallel Fortran90 program
  - validated in simulation studies (with for instance splines and threshold link functions)
  - implemented in Jointlcmm (R) for 1 marker

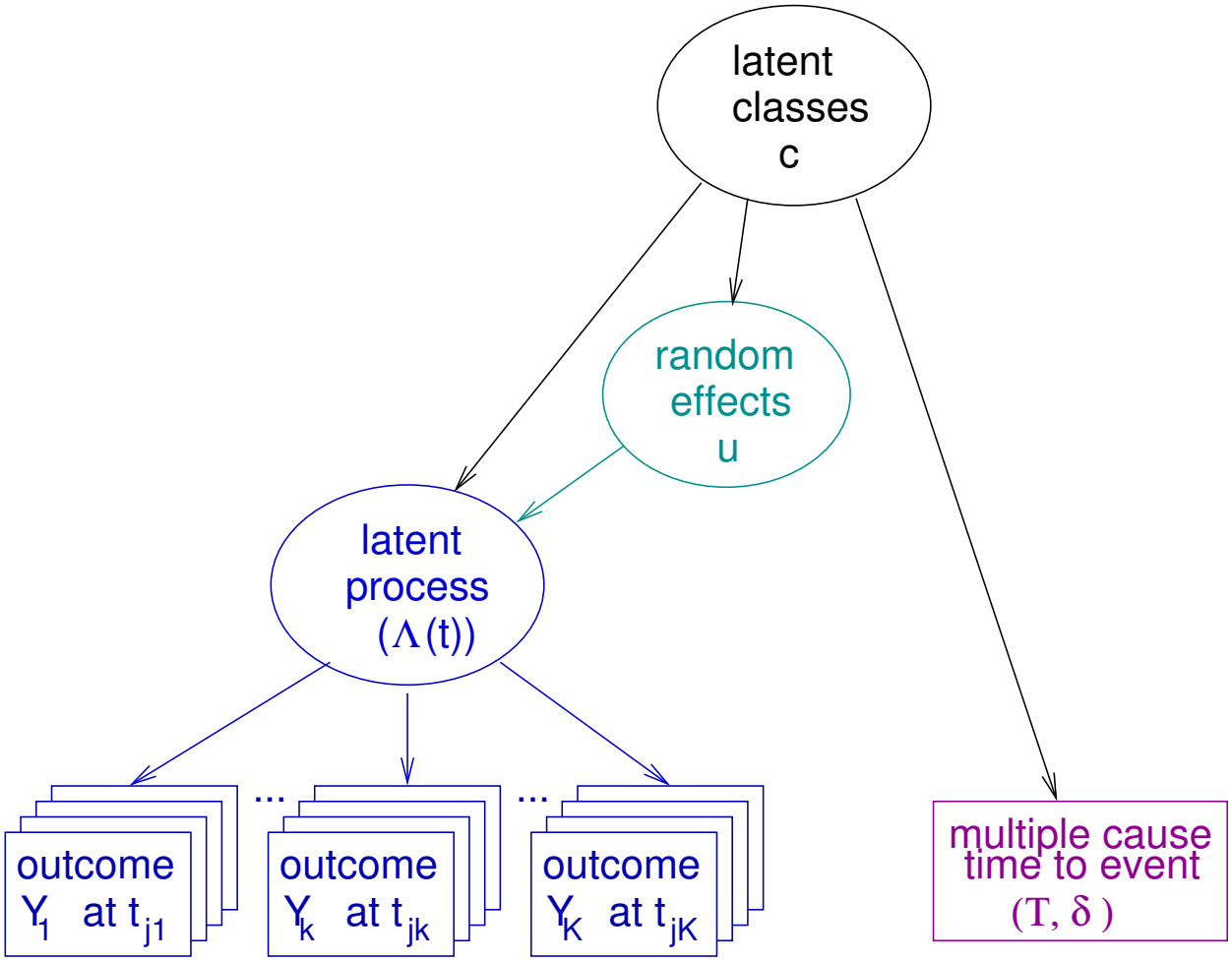
- Posterior selection of the optimal number G of latent classes
  - Information measures : AIC, **BIC**
  - Score Test for conditional independence assumption :
    $\rightarrow$ longitudinal and survival parts are independent conditionally on the latent classes

- Further evaluation of the model using :
  - Posterior classification
    stemmed from $P(c_i = g|X_i, Y_i, (T_i, \delta_i); \hat{\theta})$
  - Longitudinal/Survival predictions *versus* observations
    $\rightarrow$ posterior-probability-weighted means over time intervals

Conditional independence assumption :

Class-specific cause-specific proportional hazard model

$$\lambda_p(t) \quad = \lambda_{0p}(t;\nu_{pg})\exp(X_{Ti}^{\top}\zeta_{pg})$$

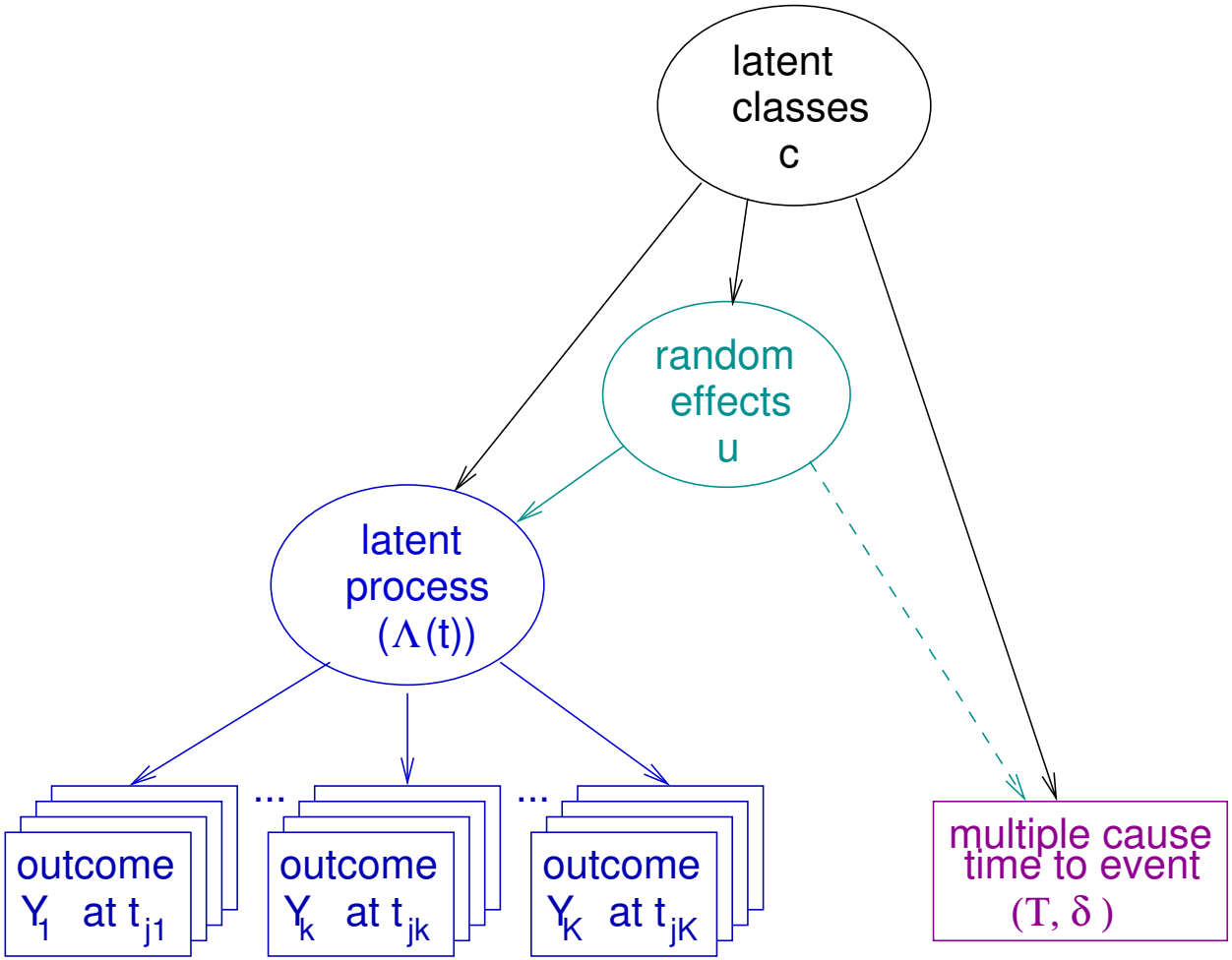


Conditional independence assumption : alternative

Class-specific cause-specific proportional hazard model

$\lambda_p(t)^{\mathcal{H}_1} = \lambda_{0p}(t;\nu_{pg})\exp(X_{Ti}^\top \zeta_{pg} \ + u_{ig}\kappa_p)$

→ Score test for $\mathcal{H}_0 : \kappa_p = 0$ and $\mathcal{H}_0 : \kappa = (\kappa_1^\top, ..., \kappa_P^\top)^\top = 0$



Application : Semantic memory decline in the elderly

- Clinical background
  - semantic memory (verbal fluency, ...) affected long before dementia diagnosis
  - could play a role for early prediction of dementia
- Objective
  - describe profiles of semantic memory decline in association with dementia and death
  - predict the risk of dementia from semantic memory history
- PAQUID cohort data :
  - population-based cohort on cerebral aging
  - 65 years and older
  - 22 years of follow-up every 2 or 3 years
  - subpopulation with genetic information : ApoE4

$\rightarrow$ 588 subjects

Dynamics of semantic memory

- 2 longitudinal measures :
  - Isaacs Set Test (`IST15`) (discrete quantitative in {0-40})
  - Wechsler similarities test (`WST`) (ordinal in {0-10})
- Trajectory according to age (natural history)
  - age at entry (`ageT0`), sex (`sex`), education (`EL`), apoE4 (`E4`)
- In each latent class g :

$$\begin{aligned}\Lambda(\textbf{age})|_{c_i=g} = b_{0ig} + \beta_1 \texttt{sex} + \beta_2 \texttt{EL} + \beta_3 \texttt{E4} + \beta_4 \texttt{ageT0} + \\ (b_{1ig} + \beta_5 \texttt{sex} + \beta_6 \texttt{EL} + \beta_7 \texttt{E4}) \times \textbf{age} \\ (b_{2ig} + \beta_8 \texttt{sex} + \beta_9 \texttt{EL} + \beta_{10} \texttt{E4}) \times \textbf{age}^2 + w_i(\textbf{age})\end{aligned}$$

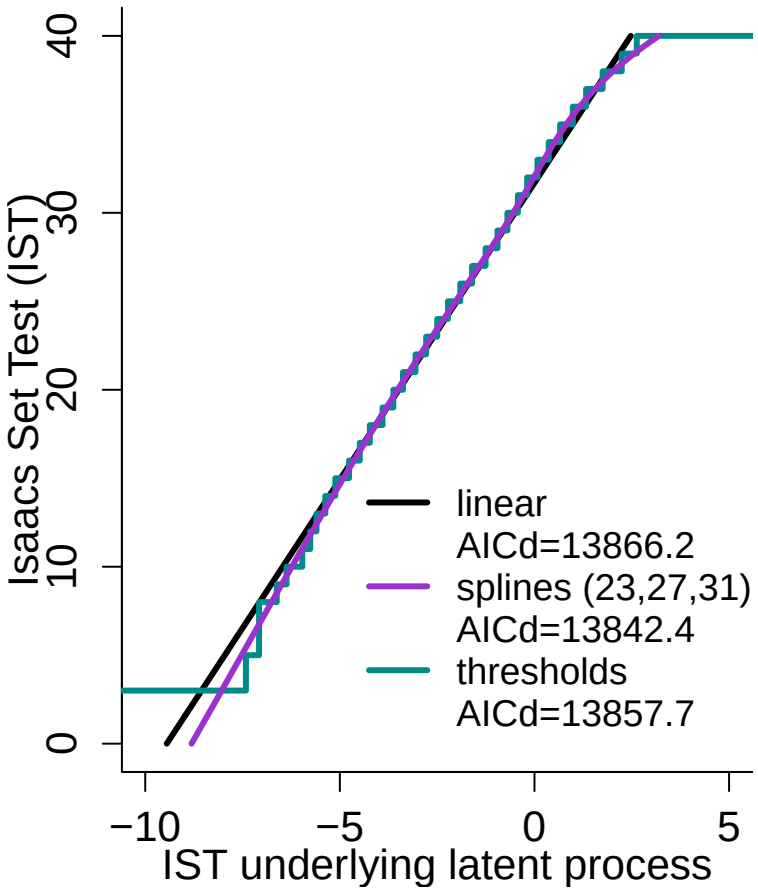
$$\begin{aligned}\texttt{IST15}_{ij} &= \boldsymbol{H_1}(\ \Lambda(\texttt{age}_{1ij}) + \alpha_{1i} + \epsilon_{1ij}\ ;\boldsymbol{\eta_1}) \\ \texttt{WST}_{ij} &= \boldsymbol{H_2}(\ \Lambda(\texttt{age}_{2ij}) + \alpha_{2i} + \epsilon_{2ij}\ ;\boldsymbol{\eta_2})\end{aligned}$$

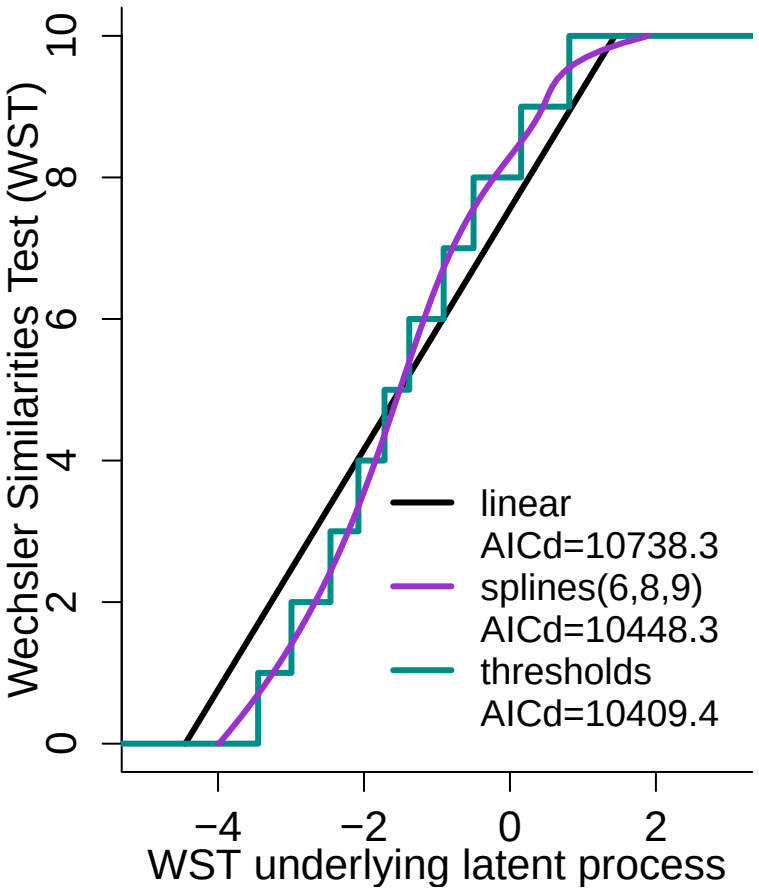
with $b_{ig} \sim \mathcal{N}(\mu_g, B)$, $w_i \sim$ Brownian motion
$\alpha_{2i} \sim \mathcal{N}(0, \sigma_\alpha^2)$, $\epsilon_{ki} \sim \mathcal{N}(0, {\sigma_k}^2)$, $k = 1, 2$

Preliminary analysis : link functions H_1 and H_2

In separated analyses, Splines with 3 internal knots =

good balance between estimation difficulty and goodness-of-fit





Risk of dementia in presence of death

2-cause censored time-to-event with delayed entry :

age at entry in the cohort

age at dementia (in between a negative and positive diagnosis)

age at death **in the two years after a negative dementia diagnosis**

In each latent class g :

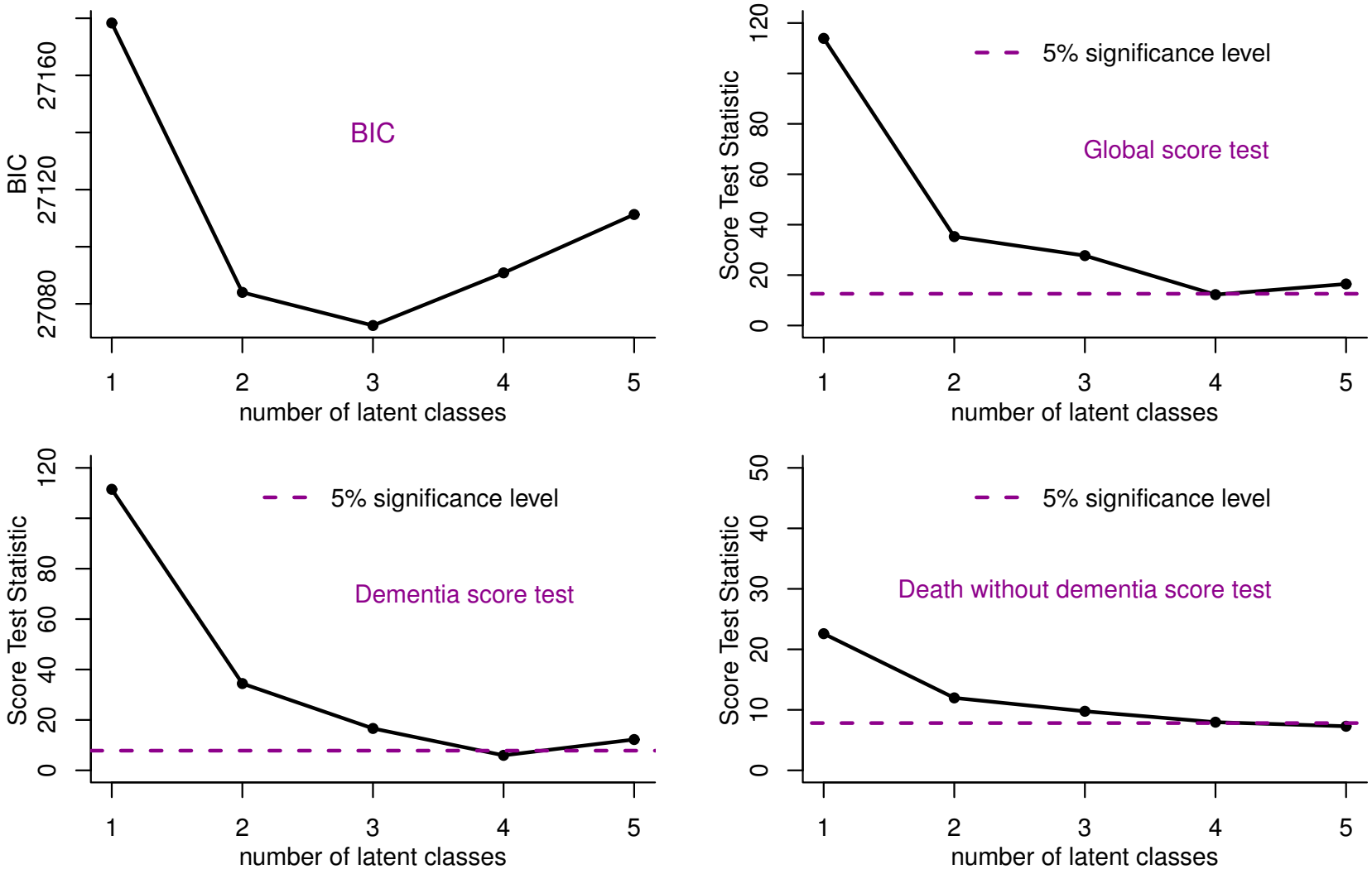
$$\lambda_p(t)|_{c_i=g} = \lambda_{0pg}(t;)e^{\zeta_{1p}\texttt{sex}+\zeta_{2p}\texttt{EL}+\zeta_{3p}\texttt{E4}}, \qquad p = 1, 2$$

$\lambda_{0pg}(t;)$ parametric hazards among Gompertz, Weibull, M-splines (5 knots) and piecewise constant (5 knots)

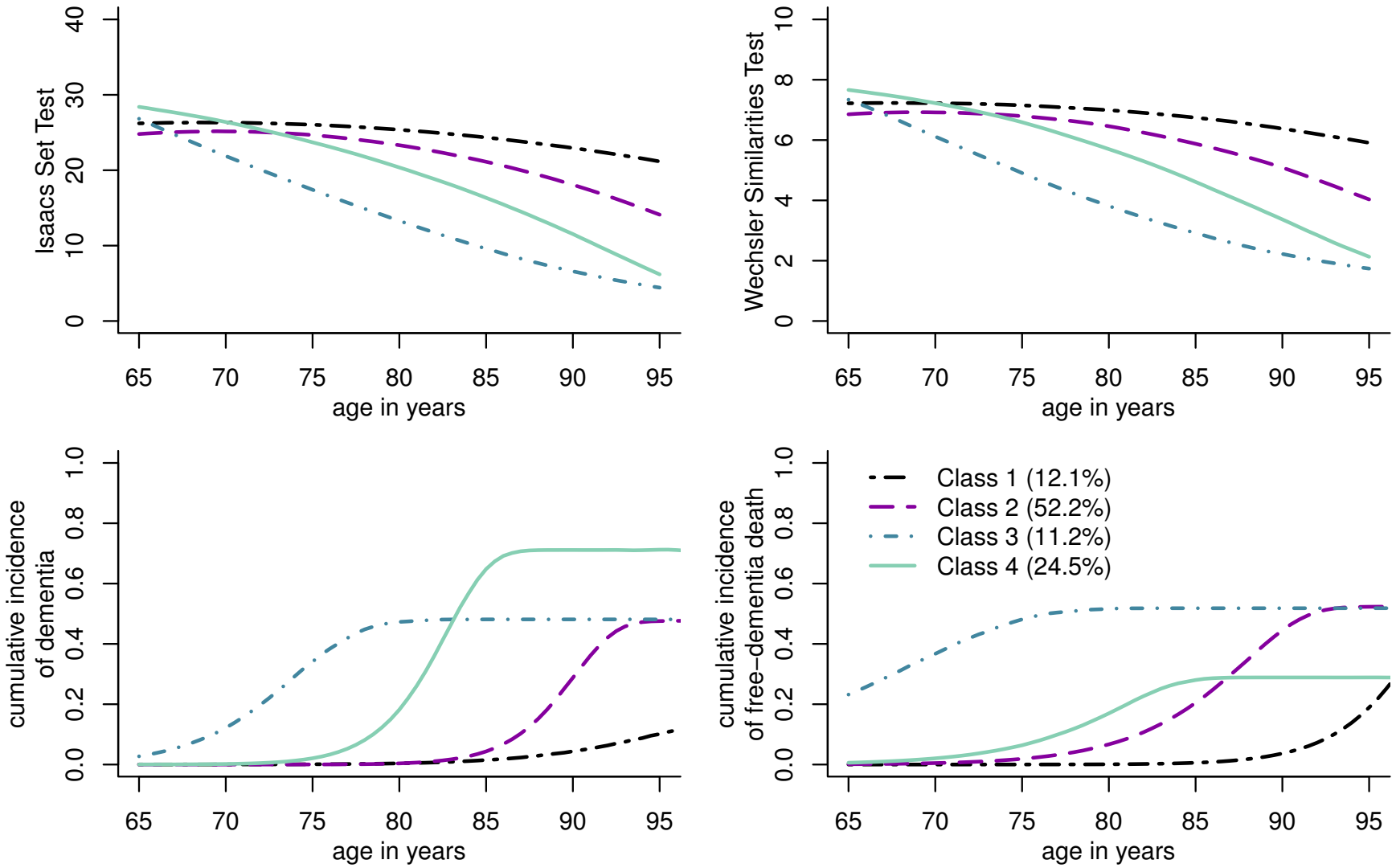
In separated analyses, Weibull hazards =

good balance between estimation difficulty and goodness-of-fit

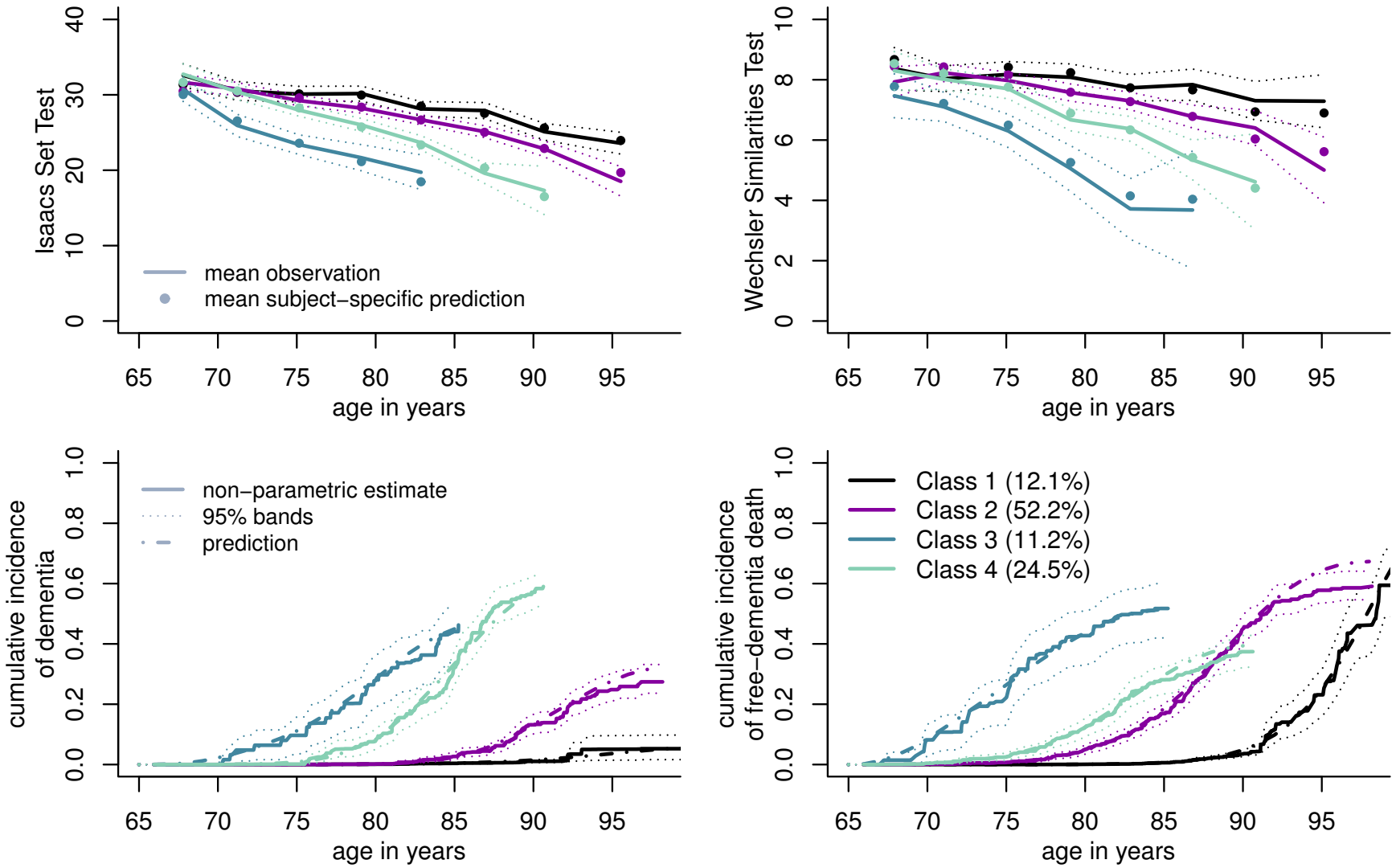
Selection of the number of classes in the joint model



4 profiles of semantic decline, dementia & death



Weighted predictions *versus* weighted observations



Individual dynamic prediction : the principle

- From a landmark age s
  - history of the markers $Y_i^{(s)} = \{Y_{kij}$ such as $t_{kij} \leq s\}$
  - history of the covariates $X_i^{(s)} = \{X_{L1i}(t_{kij}), Z_i(t_{kij}), X_{L2i}(t_{kij})$ such as $t_{kij} \leq s\}$
  - other time-independent covariates X_i

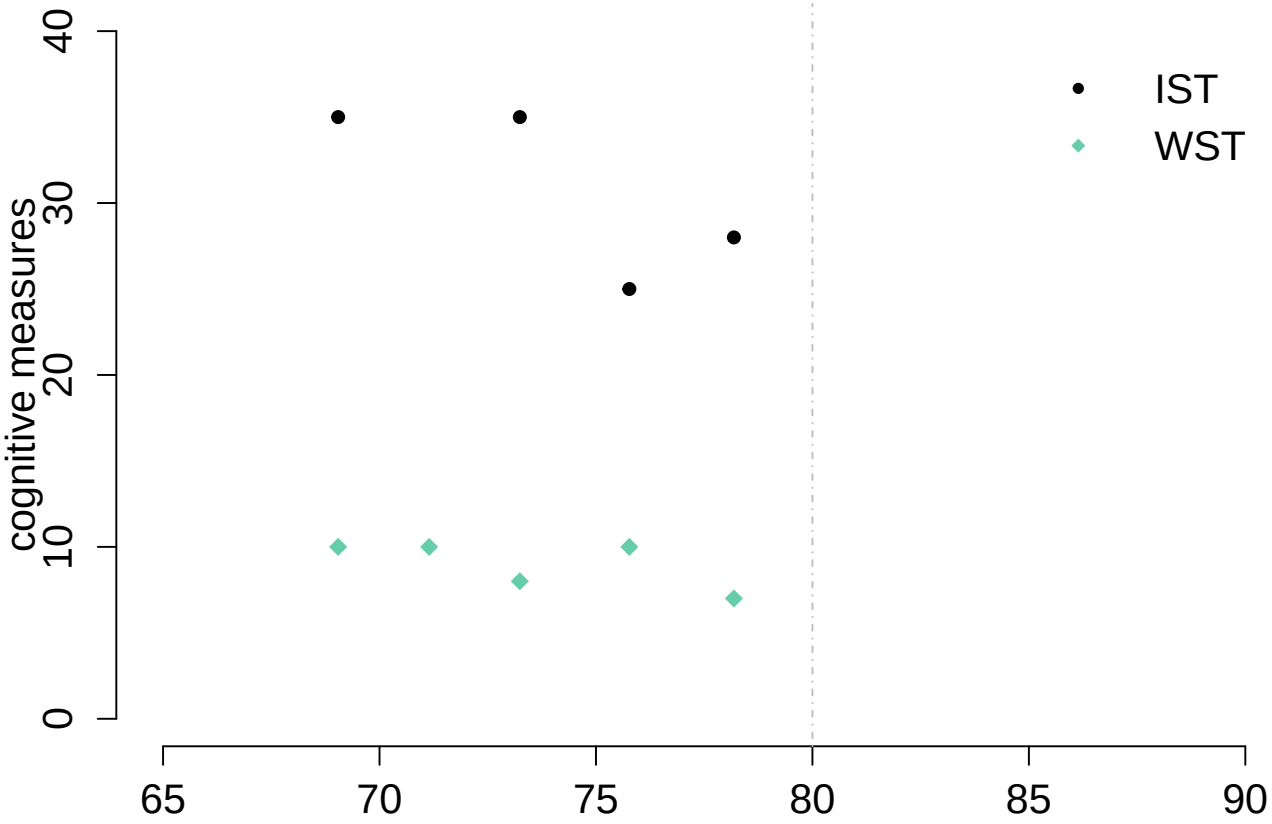
- Cumulative incidence for cause p at an horizon of t years

$$P_{pi}(s,t) = P(T_i \leq s+t, \delta_i = p | T_i > s, Y_i^{(s)}, X_i^{(s)}, X_{Ti}, X_{ci}; \theta) \quad (1)$$

  - computed using the Bayes theorem
    and the conditional independence assumption
  - with class-specific and cause-specific cumulative incidence
    approximated by Gauss-Legendre

- Monte-Carlo approximation of the posterior distribution of $P_{pi}(s,t)$

Example of individual dynamic prediction



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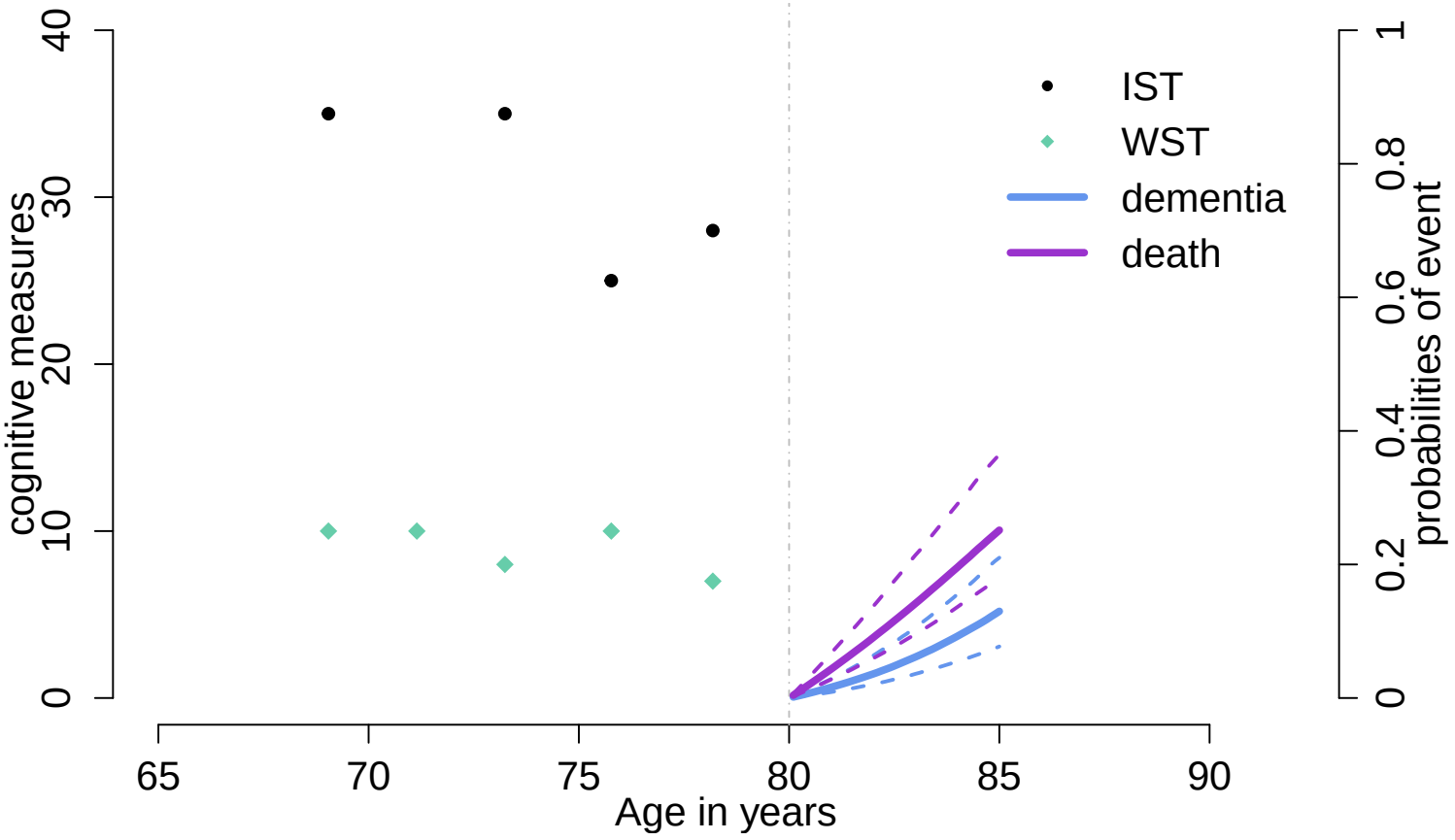
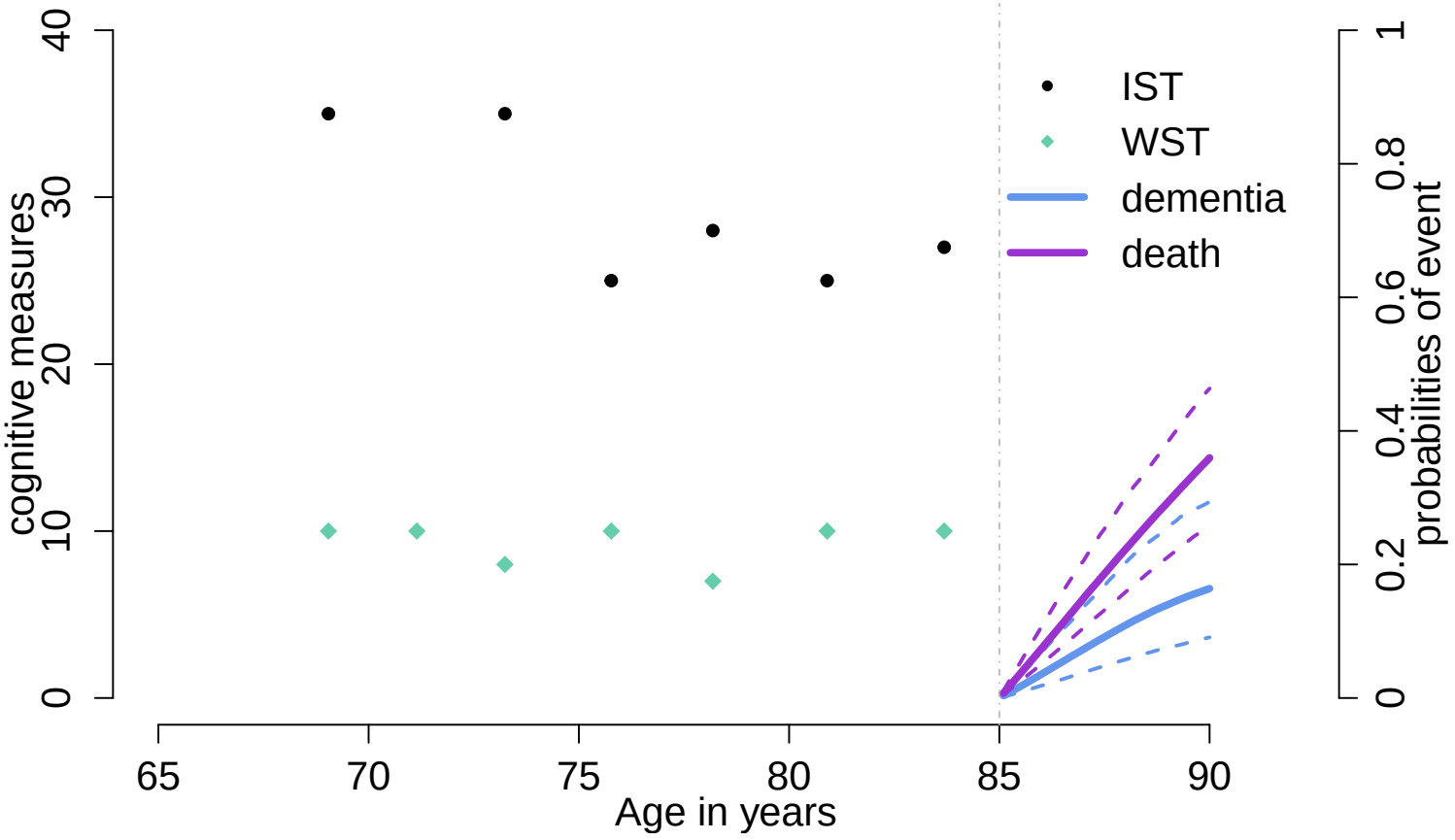


	at 80 years old
5-year probability of dementia (%) :	13.0 [7.7,21.0]
5-year probability of death (%) :	25.1 [18.1,36.5]

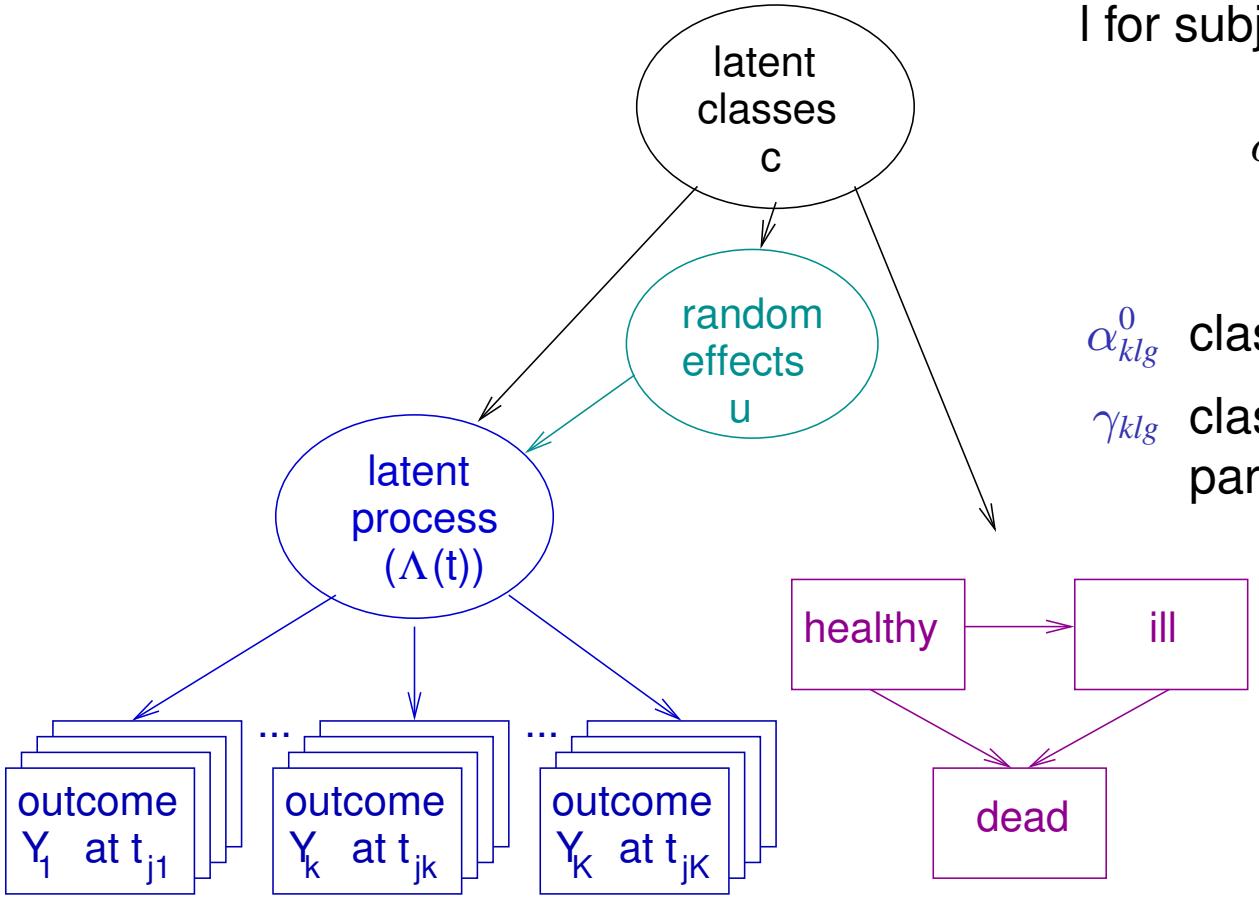
Example of individual dynamic prediction



	at 80 years old	at 85 years old
5-year probability of dementia (%) :	13.0 [7.7,21.0]	16.4 [9.1,29.4]
5-year probability of death (%) :	25.1 [18.1,36.5]	36.0 [25.9,46.3]

Option2 : multistate model with interval censoring

(Rouanet et al., ArXiv 2015)



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

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

α^0_{klg} class-specific baseline intensity

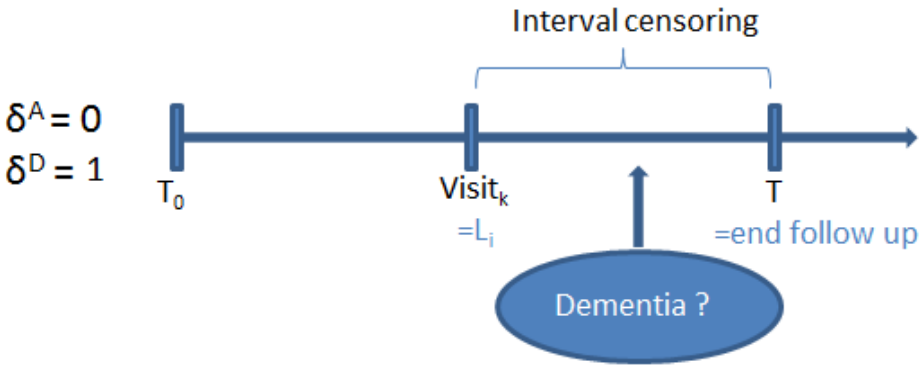
γ_{klg} class-specific regression parameters

Maximum Likelihood Estimation

- Likelihood function using $Y_i \perp\!\!\!\perp_{c_i} T_i$,

$$L(\theta) = \prod_{i=1}^{N} \sum_{g=1}^{G} f_Y(Y_i|c_i = g;\theta)\ f_D(D_i, \delta_i|c_i = g;\theta)\ P(c_i = g|X_i;\theta)$$

  - $P(c_i = g|X_i;\theta)$ from a multinomial logistic model
  - $f_Y(Y_i|c_i = g;\theta)$ from the latent process mixed model
  - $f_D(D_i, \delta_i|c_i = g;\theta)$ from the multistate model with interval censoring



$D_i^\top = (T_{0i}, L_i, R_i, \delta_i^A, T_i, \delta_i^D)$
with $R_i = +\infty$ if $\delta_i^A = 0$.

$$= \mathrm{e}^{-A_{01_g}(T)-A_{02_g}(T)}\ \alpha_{02_g}(T) + \int_{L_i}^{\top} \mathrm{e}^{-A_{01_g}(u)-A_{02_g}(u)}\ \alpha_{01_g}(u)\ \mathrm{e}^{-(A_{12_g}(T)-A_{12_g}(u))}\ \alpha_{12_g}(T)\mathrm{d}u$$

Application

- From PAQUID study (N=3777)
  - Change over time of Isaacs set test (verbal fluency)
  - in association with dementia and death

- Mixed model :

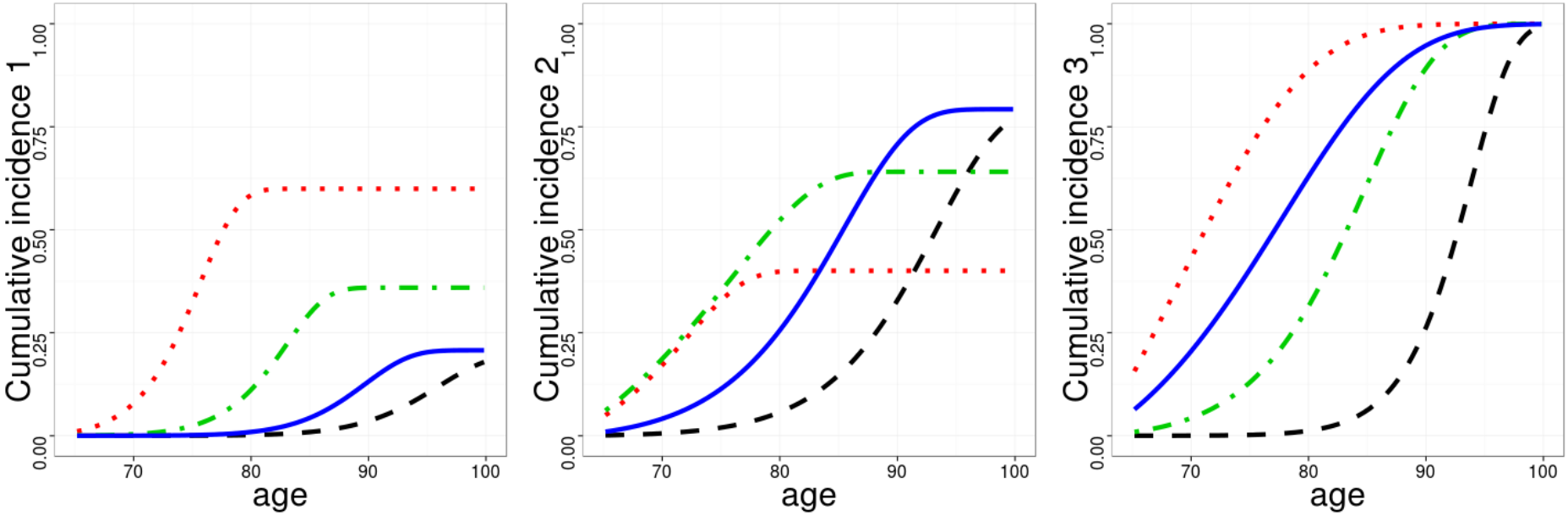
$$\Lambda(\mathbf{t})|_{c_i=g} = b_{0ig} + \beta_{1g}\texttt{sex} + \beta_{2g}\texttt{EL} + (b_{1ig} + \beta_{3g}\texttt{EL}) \times \mathbf{t} + (b_{2ig} + \beta_{4g}\texttt{EL}) \times \mathbf{t}^2$$

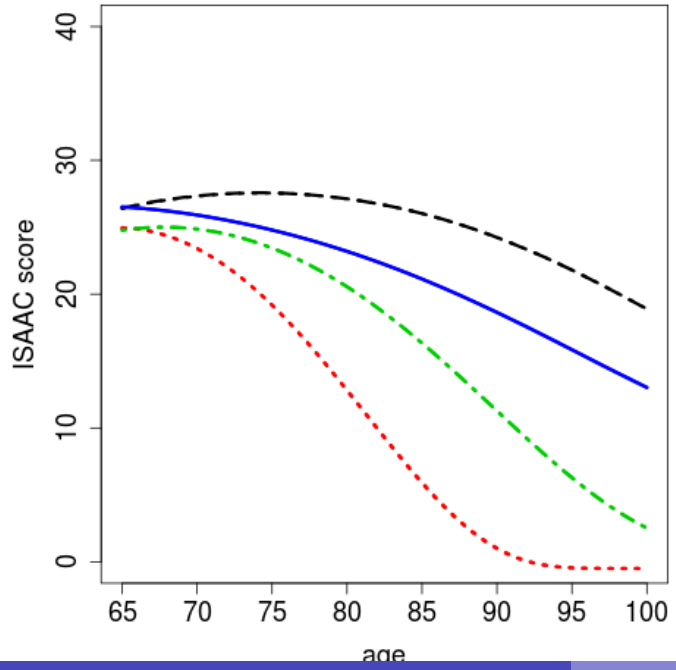
$$Y_{ij} = \Lambda_i(t_{ij}) + \epsilon_{ij} \quad \text{with} \quad b_{ig} \sim \mathcal{N}(\mu_g, B) \& \epsilon_i \sim \mathcal{N}(0, \sigma^2)$$

- Proportional transition intensities of the illness-death model :

$$\alpha_{klig}(t) = \alpha^0_{klg}(t)\ \mathrm{e}^{\gamma_{kls}\ \texttt{sex}_i + \gamma_{kle}\ \texttt{EL}_i}$$

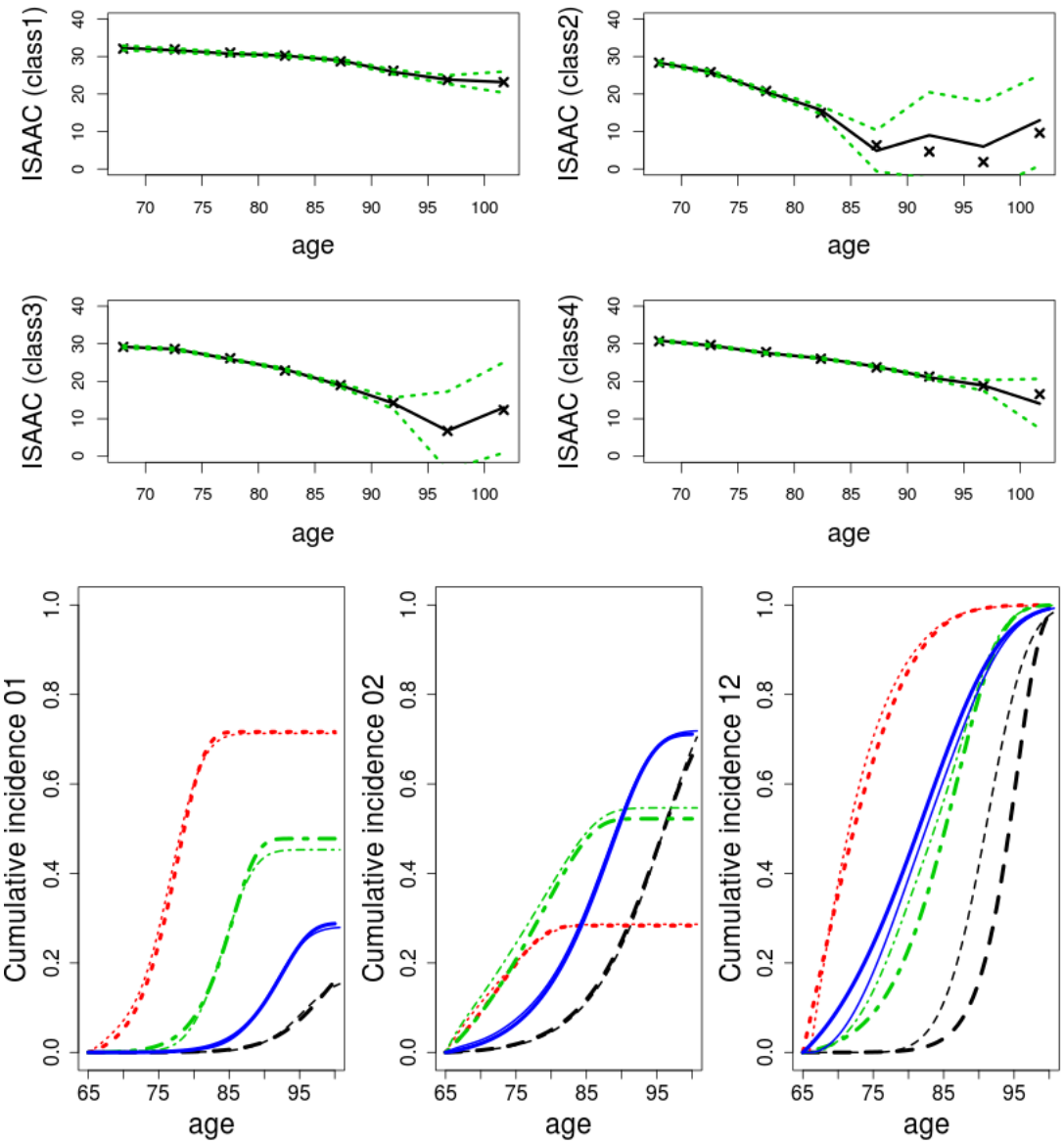
Four-class Markovian model : poorly educated men





	N	EL=0	EL=1	men	women
Class 1	7.3%	42.4	57.6	42.8	57.2
Class 2	8.3%	25.0	75.0	43.1	56.9
Class 3	34.2%	29.3	70.7	39.4	60.6
Class 4	50.5%	37.6	62.4	43.9	56.1

Goodness-of-fit assessment



Class-specific weighted predicted trajectories vs. observed

predicted class-specific cumulative incidences vs. semi-parametric estimator

Concluding remarks

- Joint model methodology
  - extended to multivariate longitudinal markers
  - extended to multistate process for events

→ useful for different purposes in chronic diseases

- Different assumptions for the shared quantity
  - depends on the data
  - depends on the objective

- Parametric assumptions
  - flexible and/or selected distributions according to the data
  - progressive construction of the models, goodness-of-fit (graphs, measures, tests) :
  - ... score tests for conditional independence assumptions (between events and marker, **between events**)

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Further details in :

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