Joint modelling of multivariate longitudinal mixed outcomes and a time-to-event: a latent variable approach

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University of Vienna, Austria - January 21, 2013

Joint modelling in cohort studies

Multiple outcomes collected simultaneously :

- repeated measures of one or several longitudinal markers
- time to one or several events of interest

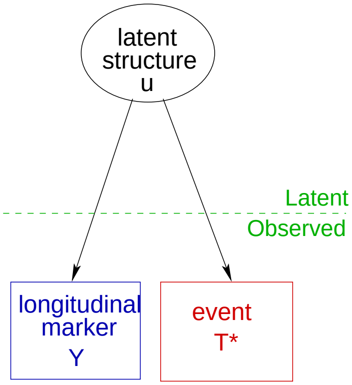
Interest in :

- Describing the markers trajectories avoiding biases (natural history of a disease)
- Predicting the risk of event based on a longitudinal marker
- Understanding the link between multiple processes

$\rightarrow$ use of joint models

Principle of joint models (Henderson, Biostat 2000)

Simultaneous modelling of multiple correlated outcomes



$\rightarrow$ latent structure u :

- individual marker characteristics (random-effects, individual deviation)
  $\rightarrow$ *shared random-effect models*
- homogeneous subgroups of subjects (latent classes)
  $\rightarrow$ *joint latent class models*

$\rightarrow$ most developments for :

- a single longitudinal marker
- a Gaussian longitudinal marker

Special case of psychological & QoL scales

Bounded quantitative or ordinal longitudinal outcomes

ex : pain scale, quality-of-life (QoL) scale (patient reported outcomes)

ex : cognitive test, disability evaluation (indirect outcomes)

→ ceiling /floor effects

→ varying sensitivity to change ("curvilinearity")

→ *linear mixed model not adapted* *(risk of spurious associations - see Proust-Lima, AJE 2011)*

Multiple outcomes measuring the same latent process

ex : different items of quality of life

ex : psychometric tests battery for cognitive functioning

→ Specific interest in the dynamics of the underlying latent process ("construct", "latent trait")

→ *multivariate extensions of the mixed models and joint models*

Outline of the talk

- A latent process mixed model for :
  - one or multivariate longitudinal markers
  - quantitative (not necessarily Gaussian), bounded quantitative & ordinal outcomes
- Joint latent class model :
  - multivariate & mixed longitudinal outcomes + associated time-to-event
  - dynamic predictive tool

Motivating application : cognitive ageing & dementia

Dementia characterised by a progressive and continuous decline of cognitive functions

→ interest in cognitive change & risk factors of cognitive change
captures the dynamics of the disease progression

→ profiles of cognitive change associated with onset of dementia
natural history of the disease & prediction of dementia

Cognition= latent process defined in continuous time

Outcomes = Psychometric tests

→ collected in discrete times

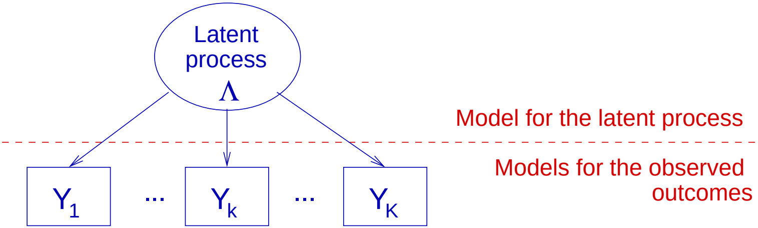
→ noisy measures of cognitive functions

→ ceiling/floor effects, curvilinearity, ...

Latent process model

Latent process model : the principle

Latent variable framework extended to longitudinal setting (Dunson, SMMR 2007)



- Structural equations : latent process described according to covariates, time, etc
- Measurement models : link between the latent process and the outcomes

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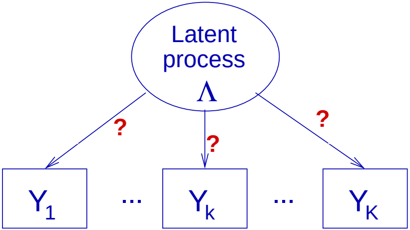
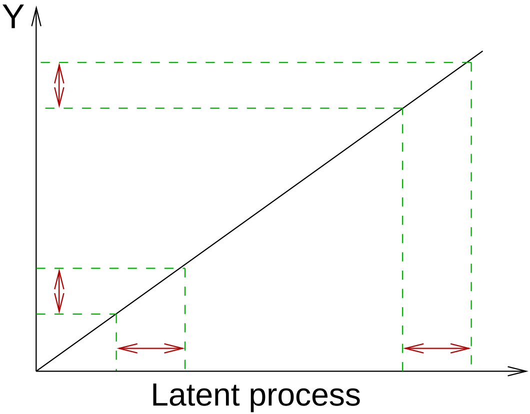


- Structural equations : latent process described according to covariates, time, etc
- Measurement models : link between the latent process and the outcomes

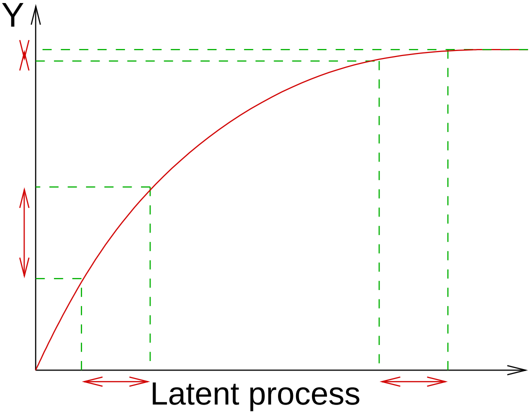
What is the link between the latent process & the outcomes ?

Linear transformation (Roy, Bcs 2000)



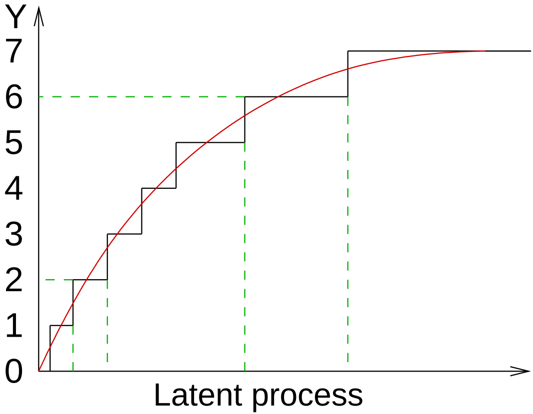
→ *same sensitivity in the whole range Y*

Nonlinear transformation (Proust, Bcs 2006 ; Proust-Lima, 2012)



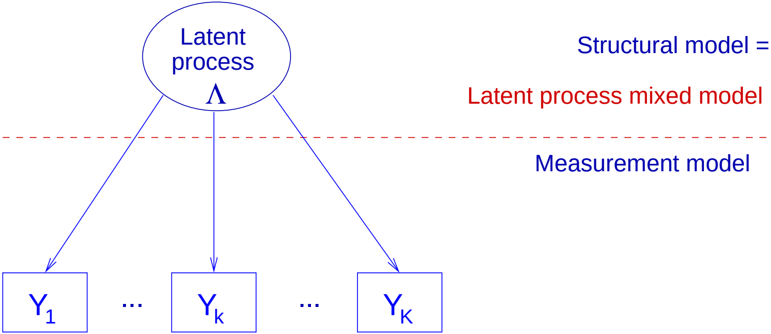
→ *ceiling /floor effects + varying sensitivity i.e. curvilinearity*

Threshold transformation (Liu, Bcs 2006 ; Proust-Lima, 2012)



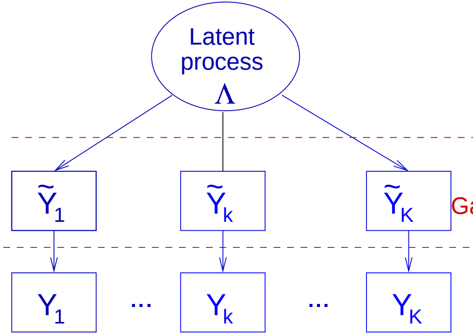
→ *Interval of Λ values for a given level of Y*

Multivariate general latent process mixed model



for clarity, time is omitted here

Multivariate general latent process mixed model



Structural model =

Latent process mixed model

Measurement model =

Gaussian intermediate variable

+

Outcome transformation H_K

for clarity, time is omitted here

Specification of the general latent process mixed model

For outcome k $(k = 1, ..., K)$, subject i $(i = 1, ..., N)$ & occasion j $(j = 1, ..., n_{ik})$:

- Structural model for the latent process :

$$\Lambda_i(t) = \mathbf{X_{1i}}(t)^T \boldsymbol{\beta} + \mathbf{Z_i}(t)^T \mathbf{u_i} + w_i(t), t \in \mathbb{R}$$

with $u_i \sim MVN(\mu, D)$, $w_i(t)$ Brownian motion
& $u_{i0} \sim N(0, 1)$ for identifiability

- Measurement models for the observed outcomes

$$H_k(Y_{ijk}; \eta_k) = \tilde{Y}_{ijk} = \Lambda_i(t_{ijk}) + \mathbf{X_{2i}}(t)^T \boldsymbol{\gamma}_k + \alpha_{ik} + \epsilon_{ijk}$$

with $\alpha_{ik} \sim \mathcal{N}(0, \sigma^2_{\alpha_k})$, $\epsilon_{ijk} \sim \mathcal{N}(0, \sigma^2_{\epsilon_k})$
with H_k = parameterised transformation with parameters η_k

Families of parameterised transformations

Quantitative outcome (general case) :

$$H_k(;\eta) = \text{family of increasing monotonic functions}$$

→ Linear combination (Gaussian assumption) *[2 parameters]*

i.e. standard linear mixed model

→ Standardised Beta CDF *[4 parameters]*

→ Quadratic I-splines *[m+2 parameters for m nodes]*

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Bounded quantitative outcome *[same number of parameters]* :

→ Same definition in (min,max) & probability of observing min/max

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Bounded quantitative outcome *[same number of parameters]* :

→ Same definition in (min,max) & probability of observing min/max

Ordinal outcome with M_k levels *[M_k-1 parameters]* :

$$Y_{ijk} = m \Leftrightarrow \eta_m \leq \tilde{Y}_{ijk} < \eta_{(m+1)} \text{ with } m \in \{0, M_k - 1\}$$

$$\& \ \eta_0 = -\infty \ \& \ \eta_{M_k} = +\infty$$

i.e. cumulated probit model

Maximum likelihood estimators

Individual contribution **without ($l_i^{(1)}$)** ordinal or bounded outcomes :

$$l_i^{(1)} = f(Y_i) = f(\tilde{Y}_i) \times \prod_{k=1}^{K} \prod_{j=1}^{n_{ik}} J(H_k(Y_{ijk}))$$

with $Y_i = (Y_{i1}, ..., Y_{iK})$ & $\tilde{Y}_i = (\tilde{Y}_{i1}, ..., \tilde{Y}_{iK})$

& J Jacobian of the transformation & $f(\tilde{Y}_i)$ Multivariate Gaussian

Iterative (Marquardt) algorithm

Maximum likelihood estimators

Individual contribution **without** ($l_i^{(1)}$) or **with** ($l_i^{(2)}$) ordinal or bounded outcomes :

$$l_i^{(1)} = f(Y_i) = f(\tilde{Y}_i) \times \prod_{k=1}^{K} \prod_{j=1}^{n_{ik}} J(H_k(Y_{ijk}))$$

$$l_i^{(2)} = f(Y_i) = \int_{u_i} \prod_{k=1}^{K} \int_{\alpha_{ik}} \prod_{j=1}^{n_{ik}} f_y(Y_{ijk}|u_i, \alpha_{ik}) f_\alpha(\alpha_{ik}) d\alpha_{ik} f_u(u_i) du_i$$

with $Y_i = (Y_{i1}, ..., Y_{iK})$ & $\tilde{Y}_i = (\tilde{Y}_{i1}, ..., \tilde{Y}_{iK})$

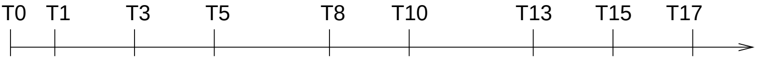
& J Jacobian of the transformation & $f(\tilde{Y}_i)$ Multivariate Gaussian

$\rightarrow$ *in $l_i^{(2)}$: numerical integrations by Gauss-Hermite (no Brownian motion)*

Iterative (Marquardt) algorithm

Dataset : PAQUID cohort

3,777 subjects of 65 years and older followed up over 17 years



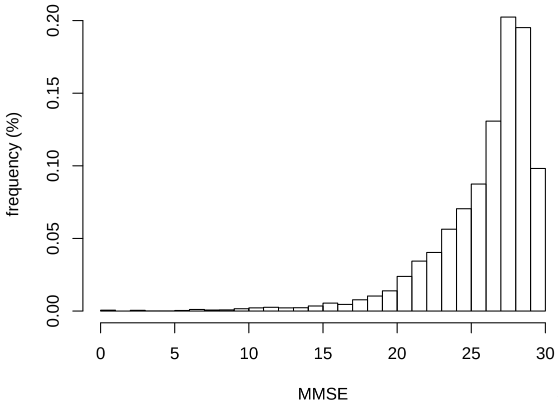
At each follow-up :

- Two phase diagnosis of dementia
- Battery of psychometric tests (global functioning, memory, fluency, etc)
- Risk factors (behaviour, health, occupation, etc)

Application 1 : Curvilinearity of MMSE (Proust-Lima, BJMSP 2012)

Investigate the curvilinearity of the MMSE using the repeated measures collected over 17 years in PAQUID

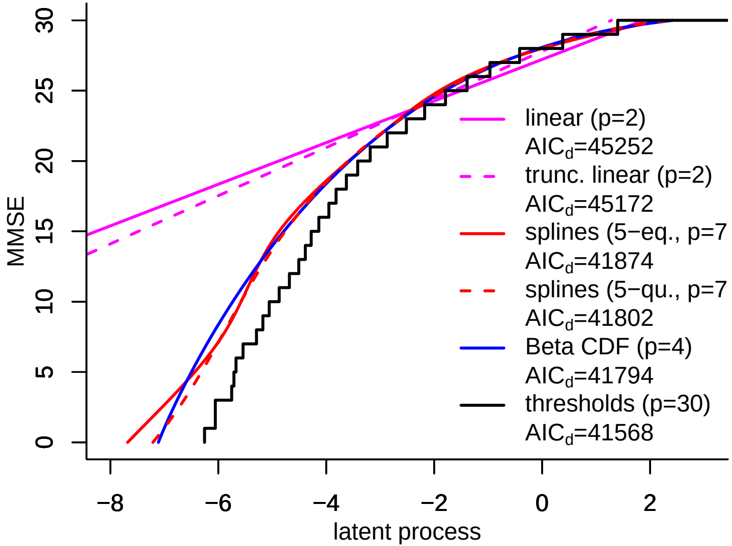
MMSE= Mini Mental State Examination :
→ a 30-point scale evaluating global cognitive functioning



→ Linear mixed model for the underlying latent process *(with age & age^2)*

→ Comparison of different estimated transformations H

Estimated transformations



Summary

Comparison of models via AIC_d : ”discretized” AIC

- different measures (Lebesgues and counting)
- computes posterior likelihood from continuous models according to the counting measure

  → large differences in goodness-of-fit for MMSE

  → favours nonlinear transformations

Curvilinearity (varying sensitivity to change) = intrinsic property

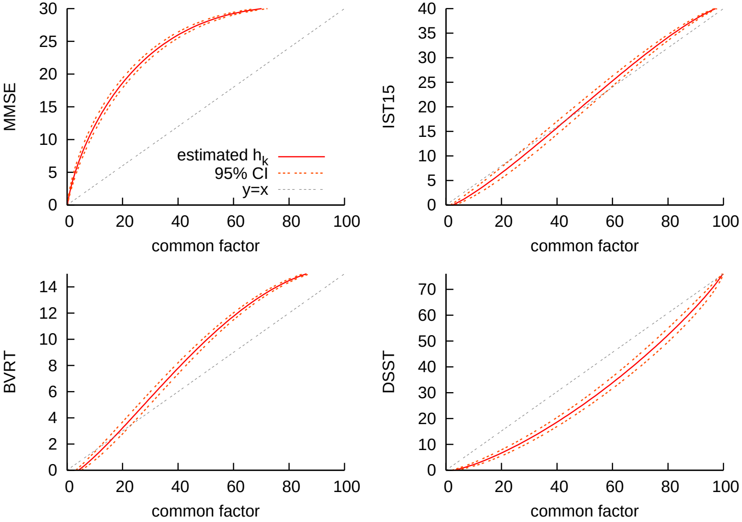
- independent of covariate relationships, population (Philipps, 2013)
- can exist with any measurement scale

Not accounting for it in LMM potentially induces spurious associations

→ type I error inflated up to 93% for MMSE (Proust-Lima, AJE 2011)

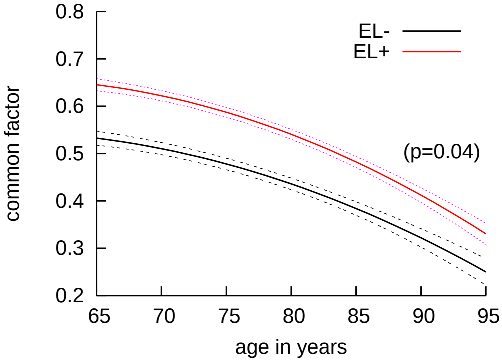
Application 2 : Metrological properties of 4 psychometric tests

(Proust-Lima et al., AJE, 2007)



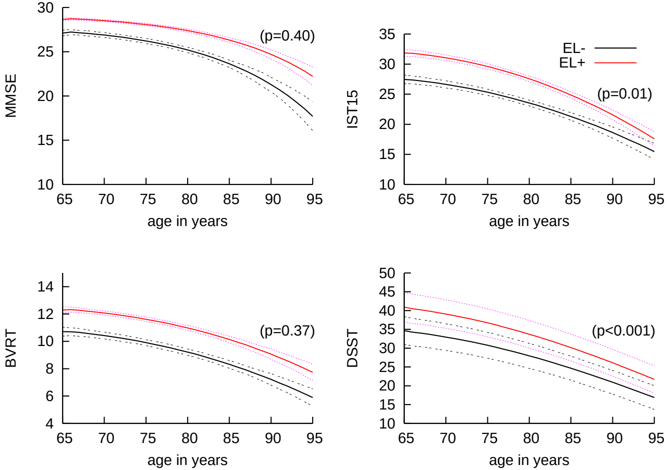
Application 3 : Education and cognitive decline (Proust-Lima, P&A, 2008)

Distinction between education effect on the common factor of 4 psychometric tests ...



Application 3 : Education and cognitive decline (cont'd)

... and its contrasts (differential effects) on the 4 psychometric tests



Concluding remarks

Handles outcomes of different natures :

→ accounts for metrological properties of scales (curvilinearity)

→ provides correct inference

→ computationally easy with Beta CDF or I-splines

implemented in lcmm R package (univariate case online, multivariate case on request)

In the multivariate setting :

→ comparison of outcomes (sensitivity/ covariates)

→ increased power/information used

→ includes IRT models for longitudinal data as a specific case

Limits :

→ single latent process (unidimensionality of the outcomes)

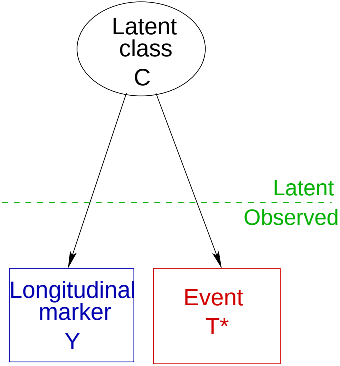
→ missing at random data

→ homogeneous population

Joint latent class model

Joint latent class model (JLCM) (Lin, JASA 2002, Proust-Lima, SMMR 2012)

With a single outcome,



Subject i (i=1...,N)
Class g (g=1,...,G)
Occasion j (j=1...,ni)

- Latent classes of subjects :

  → latent class membership :

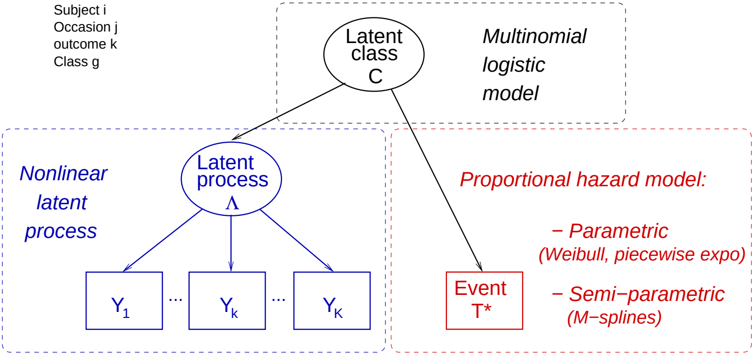
$$\pi_{ig} = P(c_i = g | X_{1i}) = \frac{e^{\xi_{0g} + X_{1i}{}^T \xi_{1g}}}{\sum_{l=1}^{G} e^{\xi_{0l} + X_{1i}{}^T \xi_{1l}}}$$

- Given class g,

  → specific marker evolution (linear mixed model)

  → specific risk of event (prop. hazard model)

Extended joint latent class model for multivariate outcomes (Proust-Lima, CSDA 2009)



$\Lambda_i(t) \mid_{c_i=g} = \mathbf{X_{1i}}(t)^T \boldsymbol{\beta_g} + \mathbf{Z_i}(t)^T \mathbf{u_{ig}}$ ← heterogeneous mixed model

← constraints : $u_{0i1} \sim N(0,1)$

$Y_{ijk} \mid \Lambda_i(t_{ijk}), c_i = g$ ← outcome-specific observation equation

Maximum likelihood estimators

Estimation for a fixed number of latent classes G (parameters θ_G)

Individual contribution to the likelihood :

→ *conditional independence given the latent classes*

$$l_i(\theta_G) = \sum_{g=1}^{G} \pi_{ig} f(Y_i \mid c_i = g; \theta_G) \lambda(T_i \mid c_i = g; \theta_G)^{E_i} S_i(T_i \mid c_i = g, \theta_G)$$

with $S_i(t \mid c_i = g, \theta_G)$ the class-specific survival function
and $f(Y_i \mid c_i = g; \theta_G)$ computed as in the initial latent process model

Iterative (Marquardt) algorithm

Optimal number of latent classes chosen using the BIC, ICL, CI test, ... (Hawkins, CSDA 2001 ; Han, SiM 2007, Jacqmin-Gadda, Bcs 2010)

implemented in lcmm R package (univariate case for the moment) + HETMIXSURV.f90 program

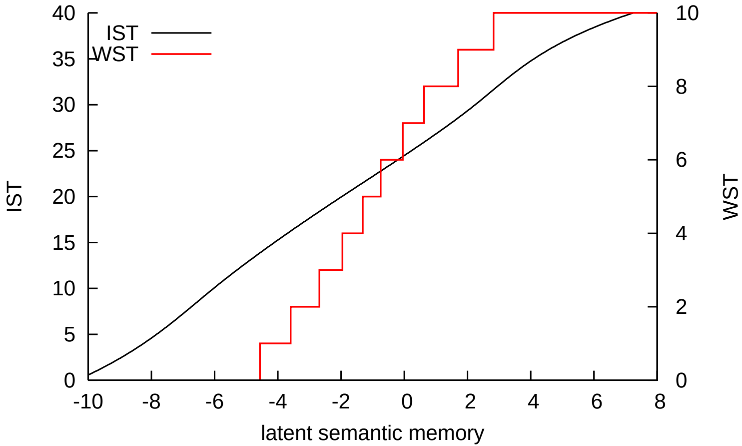
Application 4 : profiles of semantic memory

Profiles of semantic memory decline associated with onset of Alzheimer's disease in the elderly

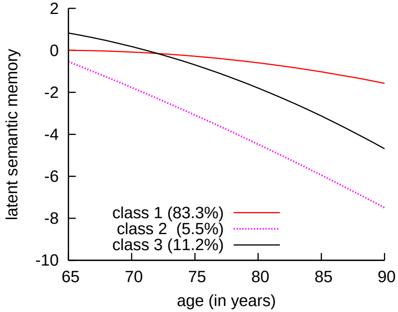
- 2 longitudinal measures of semantic memory :
  - $\rightarrow$ Wechsler similarities test (WST) (ordinal in $\{$0-10$\}$)
  - $\rightarrow$ Isaacs Set Test (IST15) (discrete quantitative in $\{$0-40$\}$)
- Age at onset of Alzheimer's disease (AD) :
  - $\rightarrow$ right censored and left truncated data
- Binary covariates : education, gender

Subsample of 2484 subjects (417 incident AD -16.8%) from PAQUID

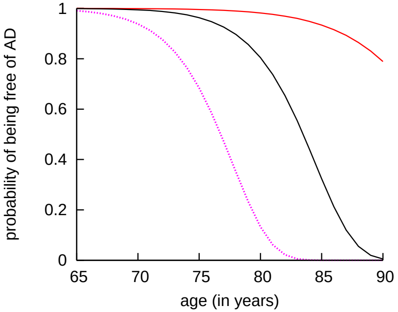
Predicted transformations of the markers



Predicted trajectories of semantic memory & probability of being free of dementia with age

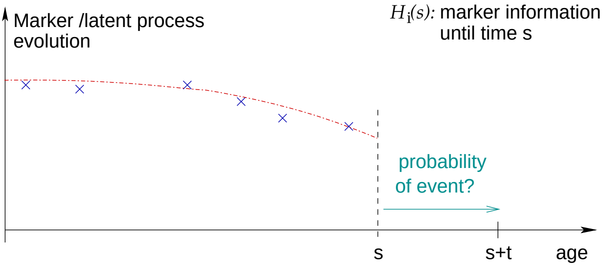


Predicted mean evolution of the latent process in each class



Predicted probability of being free of AD in each class

Prognostic/early detection tools derived from joint models (Proust-Lima, Biostat 2009, Rizopoulos, Bcs 2011, Proust-Lima, SMMR 2012)



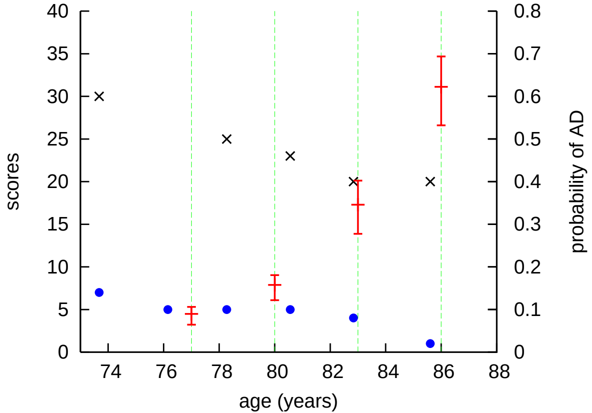
Predicted probability of event in (s,s+t) in the JLCM :

$$P(T_i \leq s+t \mid T_i > s, \mathcal{H}_i(s), X_i; \hat{\theta}) =$$

$$= \sum_{g=1}^{G} P(T_i \leq s+t \mid c_i = g, T_i > s, X_i; \hat{\theta}) \times \underbrace{P(c_i = g \mid \mathcal{H}_i(s), X_i, T_i > s; \hat{\theta})}_{\hat{\pi}_{ig}^{ys}}$$

Dynamic predictive tool of AD

Probability of dementia in 5 years updated every 3 years



Diagnosed
at 87 years old

x IST
● WST + Prediction
with 95%CI

Concluding remarks

JLCM, alternative to the shared random-effect approach

$\rightarrow$ *different assumptions ...*

- heterogeneous population
- no identified shared marker characteristic
- multiple covariate evaluations

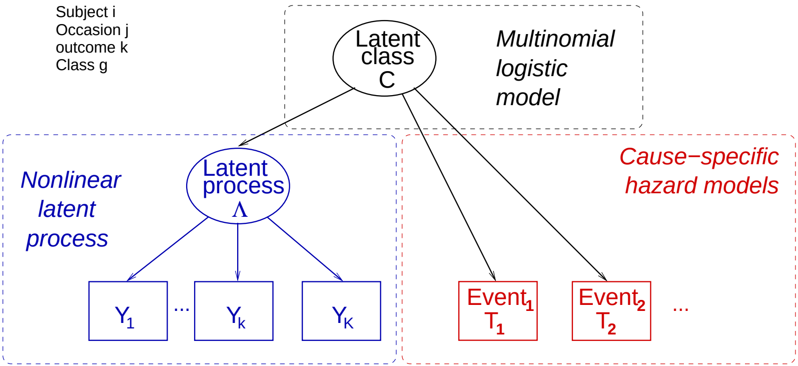
Straightforward extension to multivariate mixed longitudinal outcomes

- particularly adapted to QoL & psychological scales
- dynamic predictive tools from any longitudinal information

From this ...

- evaluation of the predictive accuracy (Error of prediction, EPOCE, etc)
- extension to multiple times-to-event (dementia & death)

Extension to multiple times-to-event



Biostatistics Team

http://biostat.isped.u-bordeaux2.fr

References

Latent variable mixed models :

- Dunson (2007). *SMMR*, **16**, 399-415
- Liu & Hedecker (2006). *Biometrics*, **62**, 261-8
- Proust, Jacqmin-Gadda, Taylor et al. (2006). *Biometrics*, **62**, 1014-24
- Proust-Lima, Amieva et al. (2007). *Am J Epidemiol*, **165**, 344-50
- Proust-Lima, Amieva et al. (2008). *Psychol & Aging*, , **23(3)**, 608-20
- Proust-Lima, Dartigues & Jacqmin-Gadda (2011). *Am J Epidemiol*, **174(9)**, 1077-88
- Proust-Lima, Amieva & Jacqmin-Gadda (2012). *British J Math Stat Psychol*
- Roy & Lin (2000). *Biometrics*, **56**, 1047-54

Joint models and dynamic predictions :

- Han, Slate & Pena (2007). *Stat Med*, **26(29)**, 5285-302
- Henderson, Diggle & Dobson (2000). *Biostatistics*, **1(4)**, 465-80
- Jacqmin-Gadda, Proust-Lima, Taylor & Commenges (2010). *Biometrics*, **66**, 11-19
- Lin, Turnbull, McCulloch & Slate (2002). *JASA*, **97**, 53-65
- Proust-Lima, Letenneur & Jacqmin-Gadda (2007). *Stat Med*, **26**, 2229-45
- Proust-Lima, Joly & Jacqmin-Gadda (2009). *CSDA*, **53**, 1142-54
- Proust-Lima & Taylor (2009). *Biostatistics*, **10**, 535-49
- Proust-Lima, Sène, Taylor & Jacqmin-Gadda. (2012). *SMMR - early view*
- Rizopoulos (2011). *Biometrics*, **67**, 819-29