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

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Joint analysis in longitudinal studies (Henderson, Biostat 2000)

Multiple outcomes collected simultaneously:
- repeated measures of one or several longitudinal markers
- time to one or several events of interest

Principle of the joint modelling:

→ latent structure $u$:
  - individual marker characteristics (random-effects, individual deviation)
  - homogeneous subgroups of subjects (latent classes)

→ 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 (subjective outcomes)
    → ceiling / floor effects
    → varying sensitivity to change (“curvilinearity”)
    → *linear mixed model not adapted* (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*
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, ...
Outline of the talk

- A latent process mixed model for:
  - one or multivariate longitudinal markers
  - quantitative (not necessarily Gaussian), bounded quantitative & ordinal outcomes
  → *illustration to the longitudinal analysis of a well-known psychometric test*

- Joint latent class model:
  - multivariate & mixed longitudinal outcomes + associated time-to-event
  - dynamic predictive tool
  → *application to profiles of semantic memory & Alzheimer’s disease*
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
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

What is the link between the latent process & the outcomes?
Linear transformation \((\text{Roy, Bcs 2000})\)

\[ \text{Y} \]

→ *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
General latent process mixed model

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

- **Structural model** for the latent process:

  \[ \Lambda_i(t) = \mathbf{X}_{1i}(t)^{T} \mathbf{\beta} + \mathbf{Z}_{i}(t)^{T} \mathbf{u}_i + \mathbf{w}_i(t), t \in \mathbb{R} \]

  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

  \[ H_k(Y_{ijk}; \eta_k) = \tilde{Y}_{ijk} = \Lambda_i(t_{ijk}) + \mathbf{X}_{2i}(t)^{T} \mathbf{\gamma}_k + \mathbf{\alpha}_i + \mathbf{\epsilon}_{ijk} \]

  with $\mathbf{\alpha}_i \sim \mathcal{N}(0, \sigma^2_{\alpha_k})$, $\mathbf{\epsilon}_{ijk} \sim \mathcal{N}(0, \sigma^2_{\epsilon_k})$

  with $H_k =$ parameterised transformation with parameters $\eta_k$
Families of parameterised transformations

Quantitative outcome (general case):

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

\[ \rightarrow \text{Linear combination (Gaussian assumption) [2 parameters]} \]
\[ \quad \text{i.e. standard linear mixed model} \]

\[ \rightarrow \text{Standardised Beta CDF [4 parameters]} \]

\[ \rightarrow \text{Quadratic I-splines [}m+2\text{ parameters for }m\text{ nodes]} \]

Bounded quantitative outcome [same number of parameters]:

\[ \rightarrow \text{Same definition in (min,max) & probability of observing min/max} \]

Ordinal outcome with \( M_k \) levels [\( M_k-1 \) parameters]:

\[ Y_{ijk} = m \iff \eta_m \leq \tilde{Y}_{ijk} < \eta_{(m+1)} \quad \text{with } m \in \{0, M_k - 1\} \]
\[ \text{& } \eta_0 = -\infty \text{ & } \eta_{M_k} = +\infty \]

i.e. cumulated probit model
Maximum likelihood estimators

Individual contribution without \( l^{(1)}_i \) or with \( l^{(2)}_i \) ordinal or bounded outcomes:

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

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

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

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

\( \rightarrow \) in \( l^{(2)}_i \): numerical integrations by Gauss-Hermite (no Brownian motion)

Iterative (Marquardt) algorithm
Illustration with MMSE (PAQUID ageing study, N=2897)

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

**Comparison** of several estimated transformations

![Graph showing various estimated transformations](image)

- **Linear mixed model** for the latent process *(with age & age²)*
- **Large differences** in goodness-of-fit *in favour of nonlinear transformations*
Concluding remarks

Handles outcomes of different natures:

→ accounts for metrological properties of scales
→ computationally easy with Beta CDF or I-splines

implemented in \texttt{l cmm} R package \textit{(univariate case for the moment)}

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 \textit{(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,

- 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)

\[ \Lambda_i(t) | c_i = g = X_{li}(t)^T \beta_g + Z_{i}(t)^T u_{ig} \leftarrow \text{heterogeneous mixed model} \]

\[ Y_{ijk} | \Lambda_i(t_{ijk}, c_i = g), \leftarrow \text{outcome-specific observation equation} \]
Maximum likelihood estimators

Estimation for a fixed number of latent classes $G$ (parameters $\theta_G$)

Individual contribution to the likelihood:

$\rightarrow$ 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: 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:
  → Wechsler similarities test (WST) (ordinal in \{0-10\})
  → Isaacs Set Test (IST15) (discrete quantitative in \{0-40\})

- Age at onset of Alzheimer’s disease (AD):
  → right censored and left truncated data

- Binary covariates: education, gender

Subsample of 2484 subjects (417 incident AD -16.8%) from a French cohort PAQUID
Predicted transformations of the markers

![Graph showing predicted transformations of IST and WST markers over latent semantic memory.](graph.png)
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

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

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

\[
= \sum_{g=1}^{G} P(T_i \leq s + t \mid c_i = g, T_i > s, X_i; \hat{\theta}) \times P(c_i = g \mid \mathcal{H}_i(s), X_i, T_i > s; \hat{\theta})
\]
Dynamic predictive tool of AD

Probability of dementia in 5 years updated every 3 years

- Score values range from 0 to 40.
- Probability of AD values range from 0% to 80%.
- Age values range from 74 to 88 years.

- Diagnosed at 87 years old.
- IST
- WST
- Prediction with 95% CI
Concluding remarks

JLCM, alternative to the shared random-effect approach

→ *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

Perspectives

  - multiple time-to-events (dementia & death)
  - predictive accuracy assessment (Brier score, EPOCE, etc)
References

Latent variable mixed models :

Joint models and dynamic predictions :