

Joint model with latent classes for time-to-event and longitudinal data

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Joint models for time-to-event and longitudinal data

- **Data** : Simultaneous collection of
 - repeated measures of a quantitative variable (a marker)
 - and the time to an event.
- **Examples** :
 - Neuropsychological tests and time to dementia
 - Prostate Specific Antigen and time to prostate cancer recurrence
 - CD4 or HIV RNA and time to AIDS (or death or other clinical events)

Joint models for time-to-event and longitudinal data (2)

- Objective of joint modelling :
 - ⇒ Study the **association** between marker change and risk of event.
 - ⇒ Describe **natural history** of chronic disease
 - ⇒ Develop **prognostic tools** for the event based on repeated measures of the marker.

Overview I

Introduction

Joint latent class model

Evaluating conditional independence

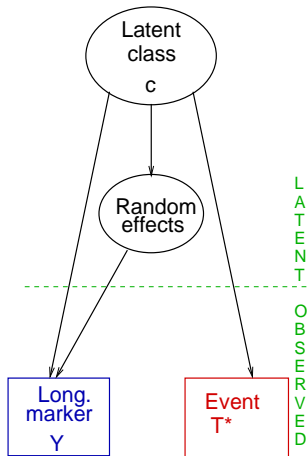
Application

Conclusion

Joint latent class model

- Class membership probability

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



Joint latent class model(2)

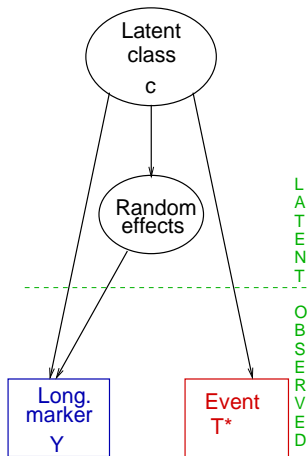
- Class membership probability

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

- Linear mixed model

$$Y_i |_{c_i=g} = Z_i(\mu_g + b_{ig}) + X_{2i}\beta_g + \epsilon_i$$

with $\epsilon_i \sim \mathcal{N}(0, \Sigma_i)$, $b_{ig} \sim \mathcal{N}(0, \omega_g^2 B)$.



Joint latent class model (3)

- Class membership probability

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

- Linear mixed model

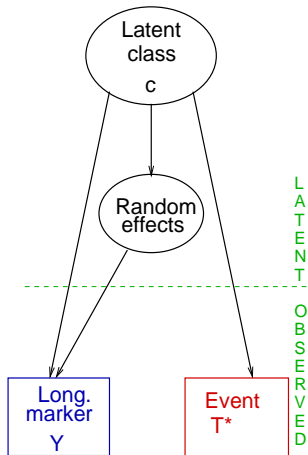
$$Y_i | c_i = g = Z_i(\mu_g + b_{ig}) + X_{2i} \beta_g + \epsilon_i$$

with $\epsilon_i \sim \mathcal{N}(0, \Sigma_i)$, $b_{ig} \sim \mathcal{N}(0, \omega_g^2 B)$.

- Survival model

$T_i = \min(T_i^*, C_i)$ and $\delta_i = 1_{T_i^* \leq C_i}$.

$$\lambda(t | c_i = g) = \lambda_0(t; \zeta_g) e^{X_{3i}^T \gamma_g}$$



Likelihood of the joint LCM

We denote θ the vector of parameters of the joint LCM. Thanks to the **conditional independence assumption** between Y_i and T_i given the latent class c_i , **for a fixed number of latent classes G** , the likelihood for subject i is :

$$L_i(\theta) = \sum_{g=1}^G \pi_{ig} f(y_i | c_i = g; \theta) \lambda(t_i | c_i = g; \theta)^{\delta_i} S(t_i | c_i = g; \theta)$$

with $S(t_i | c_i = g; \theta)$ the survival function.

G is selected by BIC.

Posterior classification

2 *posterior* class-membership probabilities :

$$\hat{\pi}_{ig}^{y,T} = P(c_i = g \mid y_i, (T_i, \delta_i), \mathbf{x}_i; \hat{\theta})$$

→ *used to assess the goodness-of-fit*

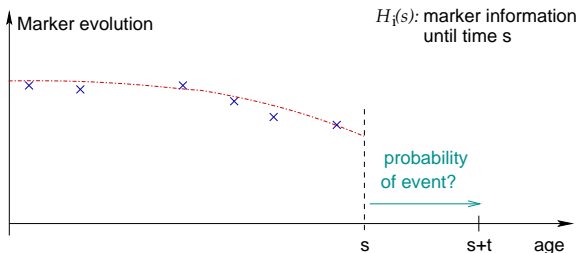
$$\hat{\pi}_{ig}^y = P(c_i = g \mid y_i, \mathbf{x}_i; \hat{\theta}) = \frac{P(c_i = g \mid \mathbf{x}_i; \hat{\theta})f(y_i \mid c_i = g, \mathbf{x}_i; \hat{\theta})}{\sum_{l=1}^G P(c_i = l \mid \mathbf{x}_i; \hat{\theta})f(y_i \mid c_i = l, \mathbf{x}_i; \hat{\theta})}$$

→ *used for prognostic tools*

Posterior classification :

$$\tilde{c}_i = g \text{ if } g = \operatorname{argmax}(\hat{\pi}_{ig}^{y,T}) \text{ or } g = \operatorname{argmax}(\hat{\pi}_{ig}^y)$$

Prognostic tool from JCLM



Prognostic marker : $P(s, t) = P(T \leq t + s | T > s, \mathcal{H}(s), X)$

Proust-Lima and Taylor, Biostatistics 2009

Prognostic tool from JCLM

$$\begin{aligned}P(s, t) &= P(T \leq t + s | T > s, \mathcal{H}(s), \mathbf{X}) \\&= 1 - P(T > t + s | T > s, \mathcal{H}(s), \mathbf{X}) \\&= 1 - \frac{S(t + s | \mathcal{H}(s), \mathbf{X})}{S(s | \mathcal{H}(s), \mathbf{X})}\end{aligned}$$

$$S(t + s | \mathcal{H}(s), \mathbf{X}) = \sum_{g=1}^G P(T > t + s | c = g, \mathbf{X}) P(c = g | \mathcal{H}(s), \mathbf{X})$$

Test of CI adjusting for posterior classes

Procedure :

- 1 Compute $\hat{\pi}_{ig}^{y,T}$
- 2 Assign subject i to class g ($\tilde{c}_i^N = g$) with probabilities $\hat{\pi}_{ig}^{y,T}$
- 3 Assess independence between Y_i and (T_i, δ_i) adjusting for \tilde{c}_i^N

Theoretical result : $\lim_{N \rightarrow \infty} [Y_i, T_i, \delta_i | \tilde{c}_i^N] = [Y_i, T_i, \delta_i | c_i]$

Bandein-Roche et al, JASA, 1997 ; Lin et al JASA 2002 ; Roy, Biometrics 2003 ; Lin et al, Biometrics 2004

Test of CI adjusting for posterior classes (2)

Test of independence

- Linear mixed model for Y_i with $f(T_i, \delta_i)$ as covariate

$$Y_i | \tilde{c}_i = g = Z_i(\mu_g + b_{ig}) + X_{2i}\beta_g + \eta f(T_i, \delta_i) + \epsilon_i \quad (1)$$

- Survival analysis with $f(Y_i)$ as covariate

$$\lambda(t | \tilde{c}_i = g) = \lambda_{0g}(t; \zeta_g) e^{X_{3i}^T \gamma_g + \eta f(Y_i(t))} \quad (2)$$

→ Problem : Choice of $f(T_i, \delta_i)$ or $f(Y_i)$

- $f(T_i, \delta_i)$: δ_i or δ_i/T_i
- $f(Y_i(t))$: nearest past or future observed value
- $f(Y_i(t)) = E(Y_i(t) | \hat{\theta})$

Score test for conditional independence

- Alternative hypothesis :

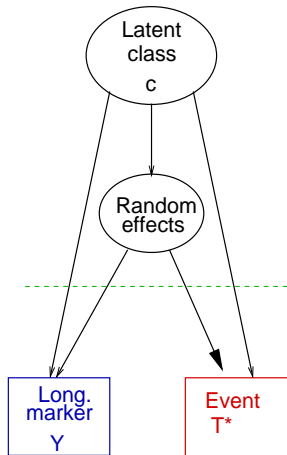
Joint LCM with shared random-effects :

$$\lambda_a(t|c_i = g, b_{ig}) = \lambda_{0g}(t; \zeta_g) e^{X_{3i}\gamma_g + b_{ig}^T \boldsymbol{\eta}}$$

- Score statistic for $H_0 : \boldsymbol{\eta} = 0$ versus $H_1 : \boldsymbol{\eta} \neq 0$:

$$U = \sum_{i=1}^N \sum_{g=1}^G Pr(c_i = g | Y_i, T_i, \delta_i)$$

$$[\delta_i - \Lambda_g(T_i)] E(b_{ig} | c_i = g, y_i)$$



Jacqmin-Gadda et al, Biometrics, 2010

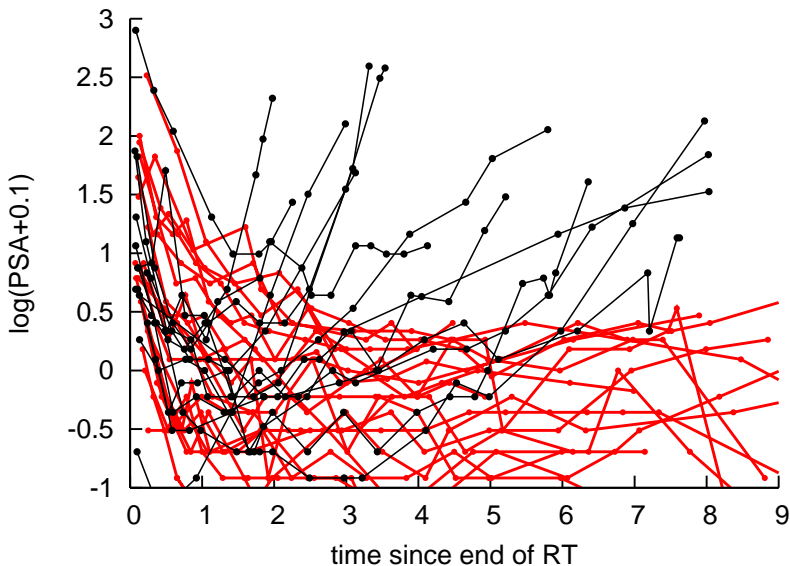
Application : Objective and Data

Objective : To distinguish profiles of change of post-treatment Prostate Specific Antigen (PSA) associated with different risks of prostate cancer recurrence.

Data :

- 459 patients treated by radiation therapy (1988-2004, Univ. of Michigan).
- Median of 8 PSA measures (IQR=[5 ;12]).
- Median follow-up of 5.16 years (IQR=[2.68 ;7.69]).
- 74 recurrences (16.1%), median time = 2.8 years .

PSA trajectories after radiation therapy



Application : Model

- **Mixed model** : $Y_{ij} = \ln(\text{PSA}_i(t_{ij}) + 0.1)$

$$Y_{ij} | c_i=g = (\mu_{0g} + b_{0ig}) + (\mu_{1g} + b_{1ig}) \frac{1}{(1+t)^{-1.5}} + (\mu_{2g} + b_{2ig})t + \epsilon_{ij}$$

with $\epsilon_i \sim \mathcal{N}(0, \sigma^2 I_{n_i})$ and

$$b_{ig} = (b_{0ig}, b_{1ig}, b_{2ig})^T \sim \mathcal{N}(0, \omega_g^2 B).$$

- **Time-to-event model** :

$$\lambda(t | c_i = g) = \lambda_0(t; \zeta_g) e^{X_{3i}^T \gamma}$$

with λ_{0g} =weibull

X_{3i} : pre-treatment PSA, clinical T-stage and Gleason score.

Application : Results

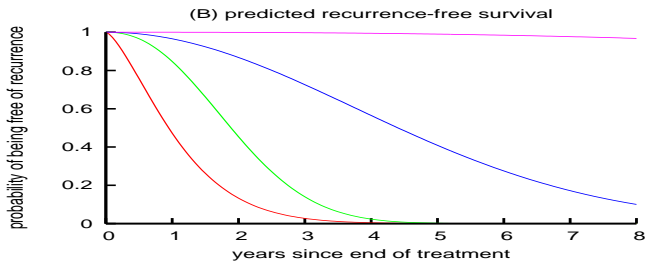
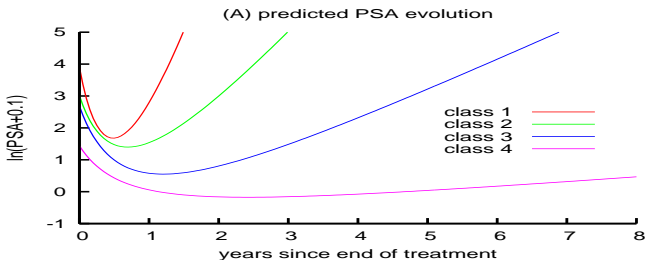
Joint LCM estimated with 1 to 5 latent classes

# clas.	Loglik.	BIC	Score test*	WMM**
1	-2877.2	5852.5	170.4 ($p < 0.001$)	7.9 ($p < 0.001$)
2	-2595.1	5331.2	30.7 ($p < 0.001$)	3.1 ($p < 0.01$)
3	-2529.6	5243.1	12.1 ($p < 0.01$)	1.34 ($p = 0.18$)
4	-2502.4	5231.5	5.6 ($p = 0.2$)	1.47 ($p = 0.14$)
5	-2490.9	5251.5	4.4 ($p = 0.3$)	1.92 ($p = 0.06$)

* Trivariate score test (with asymptotic variance)

** Wald test for dependence on δ_i in a weighted linear mixed model adjusted for posterior classes.

Application : Results



$$\pi_1 = 1.78\%$$

$$\pi_2 = 4.4\%$$

$$\pi_3 = 11.1\%$$

$$\pi_4 = 82.6\%$$

Discussion

- Link profiles of marker change and risk of event
→ Posterior classification
- Compared to shared random-effect joint models :
 - Handle heterogeneous population
 - Closed form likelihood
 - Easier interpretation (profiles)
- Other post-fit analyses useful :
 - Table of mean posterior probabilities/posterior class
 - Estimated mean evolution vs observed (Marginal or by class or separately for cases and censored subjects)