Score test for random changepoint in a mixed model

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October 6, 2017

BORDEAUX POPULATION HEALTH Research Center - U1219 | Biostatistics

Alzheimer's Disease (AD)

- A major public health issue today and tomorrow
- A very long pre-diagnostic phase
- Heterogeneous and non-linear decline trajectories

Different profiles?

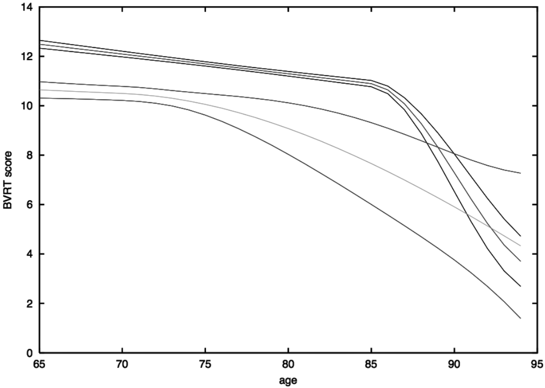


Figure: Estimated mean BVRT score according to age for 2 subjects demented at 90 with low or high educational level (Jacqmin-Gadda et al., 2006)

Objective

Propose a test for the existence of a random changepoint in a mixed model for longitudinal data.

The mixed model with random changepoint

$$Y(t_{ij}) = Y_{ij} = \beta_{0i} + \beta_{1i} t_{ij} + \beta_2 \sqrt{(t_{ij} - \tau_i)^2 + \gamma} + \varepsilon_{ij} \qquad (1)$$

with

$\beta_{ki} = \beta_k^T X_{ki} + \alpha_{ki}$ for $k = 0, 1$,

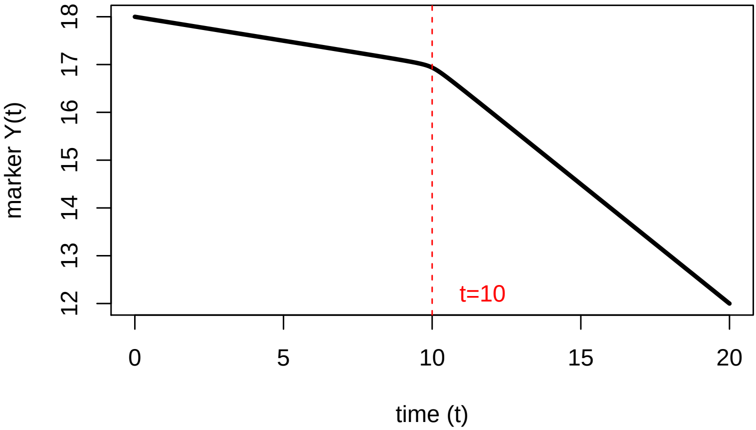
$\alpha_i = (\alpha_{0i}, \alpha_{1i})^T \sim \mathcal{N}(0, B)$,

$\tau_i = \mu_\tau + \sigma_\tau \tilde{\tau}_i$ with α_i independent from $\tilde{\tau}_i$ and $\tilde{\tau}_i \sim \mathcal{N}(0, 1)$,

$\gamma = 0.1$ a fixed smoothness parameter.

β_{1i} is the mean slope and β_2 half the difference of the slopes.

The mixed model with random changepoint



Estimation

- Model estimated by MLE and integral computed by gaussian quadrature (15 nodes)

$$\ell_n(Y;\theta) = \sum_{i=1}^{n} \log \iint \prod_{j=1}^{n_i} f(Y_{ij}|\alpha_i, \tilde{\tau}_i) f(\alpha_i) f(\tilde{\tau}_i) \mathrm{d}\alpha_i \mathrm{d}\tilde{\tau}_i.$$

- No known methods to test the existence of a *random* CP

Classic score test

- $(H_0) : \beta_2 = \beta_2^0$ vs. $(H_1) : \beta_2 \neq \beta_2^0$
- test statistic:

$$S_n = \frac{U_n(\beta_2^0, \hat{\theta}_0)^2}{Var(U_n(\beta_2^0, \hat{\theta}_0)^2)} \text{ with } U_n(\beta_2^0, \hat{\theta}_0) = \left. \frac{\partial \ell_n(Y; \beta_2, \hat{\theta}_0)}{\partial \beta_2} \right|_{\beta_2 = \beta_2^0}$$

  with $\hat{\theta}_0$ the MLE of nuisance parameters under the null
- null distribution: $\chi^2(1)$

Identifiability issue

$$Y_{ij} = \beta_{0i} + \beta_{1i} t_{ij} + \beta_2 \sqrt{(t_{ij} - \mu_\tau - \sigma_\tau \tilde{\tau}_i)^2 + \gamma} + \varepsilon_{ij}$$

Hypotheses:

$$(H_0) : \beta_2 = 0 \text{ vs. } (H_1) : \beta_2 \neq 0$$

- nuisance parameters : $\beta_0, \beta_1, \sigma, \sigma_0, \sigma_1, \sigma_{01}, \mu_\tau, \sigma_\tau$
- μ_τ and σ_τ unidentifiable under the null: we can't use the classic score test statistic S_n which depends on them.

The score under the null ($\beta_2 = 0$)

$$U_n(0;\theta) = \sum_{i=1}^{N} \left[\int f(\tilde{\tau}_i) \int f(\alpha_i) \prod_{j=1}^{n_i} \frac{1}{\sqrt{2\pi}\sigma} \exp\left\{ -\frac{1}{2\sigma^2}(Y_{ij} - \beta_{0i} - \beta_{1i}t_{ij})^2 \right\} \mathrm{d}\alpha_i \mathrm{d}\tilde{\tau}_i \right]^{-1}$$

$$\times \iint f(\alpha_i) f(\tilde{\tau}_i)(\sqrt{2\pi}\sigma)^{-n_i} \sum_{j=1}^{n_i} \left[\frac{1}{\sigma^2} \exp\left\{ -\frac{1}{2\sigma^2}(Y_{ij} - \beta_{0i} - \beta_{1i}t_{ij})^2 \right\} \right.$$

$$\left. (Y_{ij} - \beta_{0i} - \beta_{1i}t_{ij}) \times \sqrt{(t_{ij} - \mu_\tau - \sigma_\tau \tilde{\tau}_i)^2 + \gamma} \prod_{k \neq j} \exp\left\{ -\frac{1}{2\sigma^2}(Y_{ik} - \beta_{0i} - \beta_{1i}t_{ik})^2 \right\} \right] \mathrm{d}\alpha_i \mathrm{d}\tilde{\tau}_i$$

How to circumvent this problem?

Score test with identifiability issue

Classic problem when testing homogeneity on mixture models.
Two main approaches :

- replace μ_τ and σ_τ by the MLE under the alternative (Conniffe, 2001)
- consider the supremum in (μ_τ, σ_τ) of the score test statistic (Hansen, 1996)

The sup score test

- $(H_0) : \beta_2 = 0$ vs. $(H_1) : \beta_2 \neq 0$
- test statistic:

$$T_n = \sup_{(\mu_\tau, \sigma_\tau)} S_n(0; \mu_\tau, \sigma_\tau, \hat{\theta}_0)$$

with

$$S_n(0; \mu_\tau, \sigma_\tau, \hat{\theta}_0) = \frac{U_n(0; \mu_\tau, \sigma_\tau, \hat{\theta}_0)^2}{Var(U_n(0; \mu_\tau, \sigma_\tau, \hat{\theta}_0))}$$

with $\hat{\theta}_0$ the MLE of identifiable nuisance parameters under the null

- null distribution: approached by MC perturbation algorithm or multiplier bootstrap (van der Vaart and Wellner, 1996).

The complete procedure

1. estimation of the null model (linear mixed model) using `nlme`
2. computing the observed test statistic (optimization via quasi-Newton and integral via pseudo-adaptive gaussian quadrature)

$$T_n^{obs} = \sup_{(\mu_\tau, \sigma_\tau)} \frac{U_n(0; \mu_\tau, \sigma_\tau, \hat{\theta}_0)^2}{\hat{Var}(U_n(0; \mu_\tau, \sigma_\tau, \hat{\theta}_0))}$$

where $U_n(0; \mu_\tau, \sigma_\tau, \hat{\theta}_0) = \sum_{i=1}^n u_i(0; \mu_\tau, \sigma_\tau, \hat{\theta}_0)$ and the variance is estimated by

$$\sum_{i=1}^n u_i(0; \mu_\tau, \sigma_\tau, \hat{\theta}_0)^2.$$

The complete procedure

4. perturbation algorithm: for $k = 1, \ldots, K = 500$
   - generate n r.v. $\xi_i^{(k)} \sim \mathcal{N}(0,1)$
   - compute

$$T_n^{(k)} = \sup_{(\mu_\tau, \sigma_\tau)} \frac{\left(\sum_{i=1}^n u_i(0; \mu_\tau, \sigma_\tau, \hat{\theta}_0) \xi_i^{(k)}\right)^2}{\sum_{i=1}^n u_i(0; \mu_\tau, \sigma_\tau, \hat{\theta}_0)^2}$$

5. compute the empirical $p-$value

$$p_K = \frac{1}{K} \sum_{k=1}^{K} \mathbf{1}_{T_n^{(k)} > T_n^{(obs)}}$$

Tests for the variability of β_2

If we reject the null hypothesis, we can test if there is a

1. random effect for the difference of slope:

$$\beta_{2i} = \beta_2 + \alpha_{2i} \text{ with } \alpha_i = (\alpha_{0i}, \alpha_{1i}, \alpha_{2i}) \sim \mathcal{N}(0, B)$$

$\Rightarrow$ corrected LR test for variance component (Stram and Lee, 1994)

2. dependance on covariates:

$$\beta_{2i} = \beta_{20} + \beta_{21} X_{2i}$$

$\Rightarrow$ Wald test

Simulation scenarios

$$Y_{ij} = \beta_{0i} + \beta_{1i} t_{ij} + \beta_2 \sqrt{(t_{ij} - \tau_i)^2 + \gamma} + \varepsilon_{ij}$$

with

$\beta_{0i} = 20 + \alpha_{0i}$ and $\beta_{1i} = -0.3 + \alpha_{1i}$

$\alpha_i = (\alpha_{0i}, \alpha_{1i})^T \sim \mathcal{N}\left(\begin{pmatrix} 0 \\ 0 \end{pmatrix}, \begin{pmatrix} 1 & 0.1 \\ 0.1 & 0.2 \end{pmatrix}\right),$

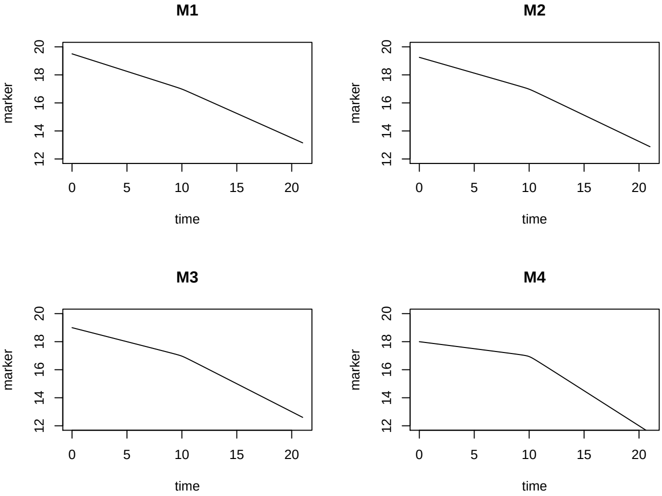
$\tau_i = 10 + 2\tilde{\tau}_i$ with α_i independant from $\tilde{\tau}_i$ and $\tilde{\tau}_i \sim \mathcal{N}(0,1)$,

$\gamma = 0.1, \sigma_\varepsilon = 1, t_{ij} = 0, 3, 6, 9, 12, 15, 18, 21$ for all i,

$\beta_2 = 0, -0.05, -0.075, -0.1, -0.2,$

Probability of drop-out at each visit: $0.1 \Rightarrow$ around 50% of the sample remaining at $t = 21$.

Simulation Scenarios



Results

N		100		200	
drop-out		no	yes	no	yes
size	M_0	0.029	0.042	0.034	0.039
power	M_1	0.397	0.054	-	-
	M_2	0.749	0.067	-	-
	M_3	0.949	0.093	-	-
	M_4	1	0.206	-	0.425

Table: Size and power of the test computed on 1000 replicates of each scenarios with $K = 500$ perturbations.

The PAQUID cohort

- 3777 subjects older than 65 from the french departments of Gironde and Dordogne, 25 years follow-up
- Marker : Isaac 15s score
- sample selection: incident case of dementia between year 1 and 25
- High education sample
  - 522 subjects with at least 1 measure
  - 1 to 12 measures by subject (mean = 5.8)
- Low education sample
  - 358 subjects with at least 1 measure
  - 1 to 12 measures by subject (mean = 4.6)
- model (1) with $\beta_{ki} = \beta_k + \alpha_{ki}$ for $k = 0, 1$ (no covariate)

Score test results

	obs. statistic test*	p-value
High education	14.059	0.001
Low education	1.388	0.443

Table: Score test results with $K = 1000$

For the high education subjects, we clearly reject the null hypothesis of no random changepoint.

Estimation (nq = 15)

	PAQUID demented sample			
	High education		Low education	
N	522		358	
Log-lik	-8845.889		-4685.284	
	Est	sd	Est	sd
β_0	23.087	0.219	20.477	0.342
β_1	-0.838	0.026	-0.531	0.039
β_2	-0.559	0.022	-0.354	0.033
μ_τ	-4.101	0.375	-5.512	0.694
σ	3.476	0.045	3.358	0.074
σ_0	4.195	0.134	3.873	0.172
σ_1	0.213	0.017	0.209	0.024
σ_τ	2.925	0.016	1.776	0.026
σ_{01}	0.275	0.343	0.178	0.675
slope 1/2	-0.279 / -1.397		-0.177 / -0.885	

Estimation of the mixed model with random CP

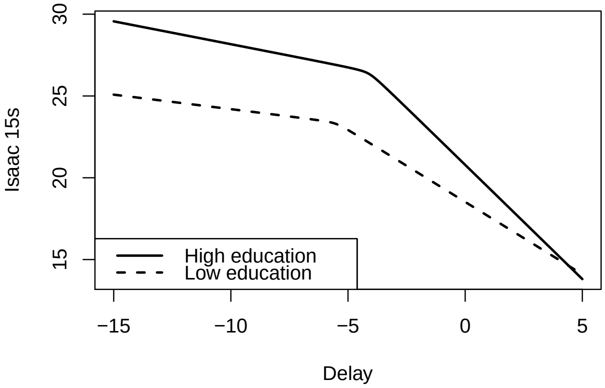


Figure: Mean estimation trajectory of the mixed model with random changepoint on the two educational level subsamples.

Variability of β_2: random effect ?

On high education subsample

$$(H_0) : \sigma_2 = 0 \text{ vs. } (H_1) : \sigma_2 \neq 0$$

where $\beta_{2i} = \beta_2 + \alpha_{2i}$ with $\alpha_{2i} \sim \mathcal{N}(0, \sigma_2^2)$.
LRS = -137.2 $\Rightarrow p < 0.001$
$\Rightarrow$ We need to add a random effect on β_2

Next steps

- simulations with varying σ_τ
- extension to :
  - joint models
  - joint multi-state models for interval censored data
  - models for multiple markers
  - etc.

References

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Thank you for
your attention!