Inference on random changepoint models: application to pre-dementia cognitive decline

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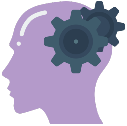
Context: pre-dementia cognitive decline



- Very long and progressive pre-diagnosis phase
- Heterogeneous and non-linear decline trajectories
- Subject-specific acceleration of cognitive decline

Context: pre-dementia cognitive decline trajectories

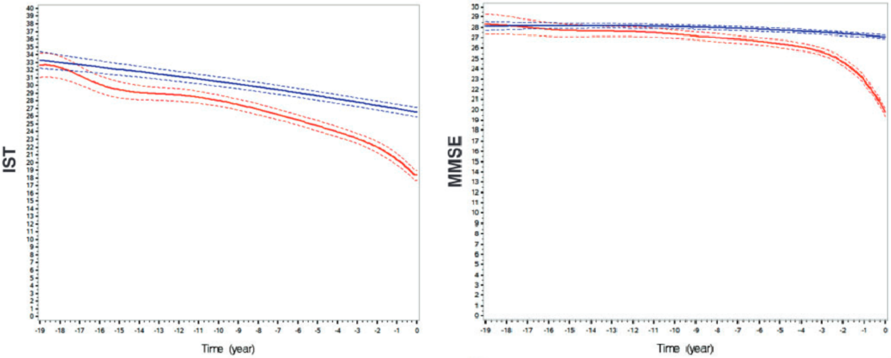


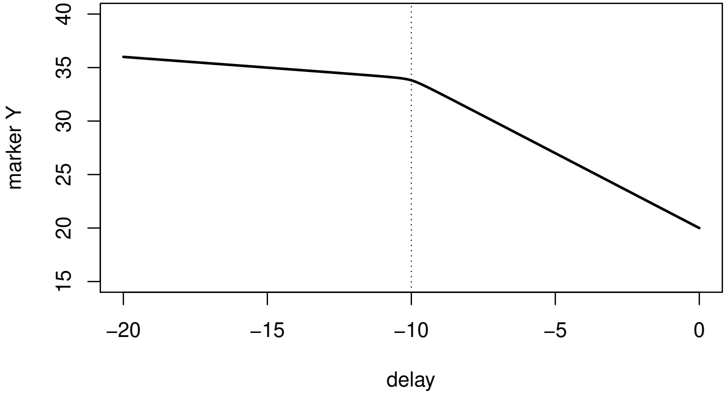
Figure: Estimated cognitive trajectories for cases (red) and matched controls (blue) for high educational subjects from French cohort PAQUID (Amieva et al., 2014).

Project 1

Objective: Testing the existence of a random changepoint in a mixed model

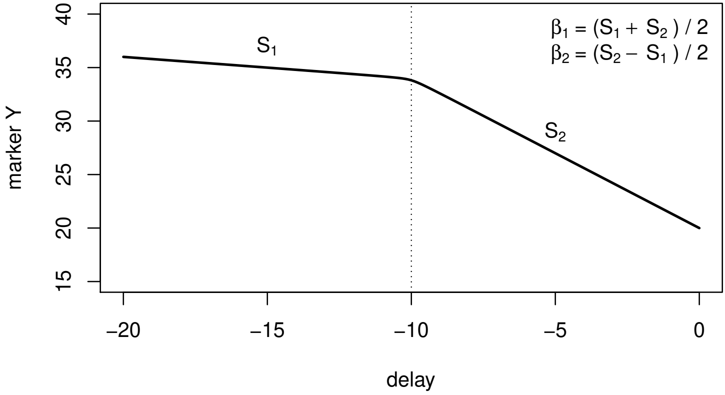
Segalas C, Amieva H, Jacqmin-Gadda H. A hypothesis testing procedure for random changepoint mixed models. *Statistics in Medicine*, 2019.
https://doi.org/10.1002/sim.8195

The random changepoint mixed model



The random changepoint mixed model

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



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- $\beta_{ki} = \beta_k + b_{ki}$ for $k = 0, 1$ with $b_i = (b_{0i}, b_{1i}) \sim \mathcal{N}(0, B)$
- $\tau_i = \mu_\tau + \sigma_\tau \tilde{\tau}_i$ with $\tilde{\tau}_i \sim \mathcal{N}(0, 1)$ and $\tilde{\tau}_i \perp b_i$
- $\sqrt{. + \gamma}$ a smooth transition function
- $\varepsilon_{ij} \sim \mathcal{N}(0, \sigma)$ residual error $\perp$ of the random effects

At this stage β_2 is assumed non random

A score test approach

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

- Objective: H_0: $\beta_2 = 0$ vs. H_1: $\beta_2 \neq 0$

A score test approach

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

- Objective: H_0: $\beta_2 = 0$ vs. H_1: $\beta_2 \neq 0$
- Nuisance parameters: $\underbrace{\beta_0, \beta_1, \sigma, \sigma_0, \sigma_1, \sigma_{01}}_{\theta}, \mu_\tau, \sigma_\tau$
- Classic score test statistics depends upon $\hat{\mu}_{\tau 0}, \hat{\sigma}_{\tau 0}$

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

with

$$U_n(0, \mu_\tau, \sigma_\tau, \theta) = \left. \frac{\partial \ell_n(Y; \beta_2, \mu_\tau, \sigma_\tau, \theta)}{\partial \beta_2} \right|_{\beta_2 = 0} \text{ and } U_n = \sum_{i=1}^{n} u_i$$

The supremum score test (Hansen, 1996)

- Test statistic:

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

with $\hat{\theta}_0$ MLE of identifiable nuisance parameters under H_0

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- Empirical distribution of T_n under H_0: perturbation algorithm (van der Vaart et al., 1996). For $k = 1, \dots, K$, we generate n r.v. $\xi_i^{(k)} \sim \mathcal{N}(0,1)$ and compute

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

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

Additional tests for heterogeneity

Heterogeneity in β_2?

- Is β_2 subject specific (i.e. random)?

  $$H_0\colon\ B = \begin{pmatrix} \sigma_0^2 & \sigma_{01} & 0 \\ \sigma_{01} & \sigma_1^2 & 0 \\ 0 & 0 & 0 \end{pmatrix}, \text{ vs. } H_1\colon\ B \text{ unstructured}$$

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

- Does β_2 depend on covariate?
  $\Rightarrow$ Wald test

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

- Does β_2 depend on covariate?
  $\Rightarrow$ Wald test

Heterogeneity in τ_i?

- Does τ_i depend on covariate?
  $\Rightarrow$ Wald test

Application: the PAQUID cohort

- cohort of 3777 elderly subjects ($\geq$ 65yo) from the French departments of Gironde and Dordogne, 25 years follow-up
- 901 incident cases of dementia between year 1 and 25
- Isaac 15s score (verbal fluency)
- Stratified analysis on the educational level

Application: results

	obs. statistic test	$p-$value
High education	143.7	<0.001
Low education	56.9	<0.001

Table: Score test results with $K = 500$

$\Rightarrow$ We clearly reject H_0: $\beta_2 = 0$ for both group

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Table: Score test results with $K = 500$

$\Rightarrow$ We clearly reject H_0: $\beta_2 = 0$ for both group

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

$$(H_0) : \mathrm{B} = \begin{pmatrix} \sigma_0^2 & \sigma_{01} & 0 \\ \sigma_{01} & \sigma_1^2 & 0 \\ 0 & 0 & 0 \end{pmatrix}, \text{ vs. } (H_1) : B \text{ unstructured}$$

$\Rightarrow$ We reject H_0: $\sigma_2 = 0$ for both group ($p < 0.001$)

Discussion

- Valid test with good power
- `testRCPM` function in `rcpm` package
- Assumption of a fixed β_2 (test with random β_{2i} robust)
- Relaxing the assumption of a Gaussian distribution for $\tilde{\tau}_i$

Project 2

Objective: Compare mean CP date between markers

Segalas C, Helmer C, Jacqmin-Gadda H. A curvilinear bivariate random changepoint model to assess temporal order of markers. *Statistical Methods in Medical Research*, 2020.
https://doi.org/10.1177/0962280219898719

The bivariate random changepoint mixed model

$$Y^\ell(t_{ij}^\ell) = \beta_{0i}^\ell + \beta_{1i}^\ell(t_{ij}^\ell - \tau_i^\ell) + \beta_{2i}^\ell\sqrt{(t_{ij}^\ell - \tau_i^\ell)^2 + \gamma} + \varepsilon_{ij}^\ell \quad \ell = 1, 2$$

- $\beta_{ki}^\ell = \beta_k^\ell + b_{ki}^\ell$ with $b_i^\ell = (b_{0i}^\ell, b_{1i}^\ell, b_{2i}^\ell) \sim \mathcal{N}(0, B^\ell)$
- $\tau_i^\ell = \mu_\tau^\ell + \sigma_\tau^\ell \tilde{\tau}_i^\ell$ with $\tilde{\tau}_i^\ell \sim \mathcal{N}(0,1)$ and $\tilde{\tau}_i^\ell \perp b_i$
- $\sqrt{. + \gamma}$ a smooth transition function
- $\varepsilon_{ij}^\ell \sim \mathcal{N}(0, \sigma^\ell)$ residual error $\perp$ of the random effects

$+$ $corr(b_i^1, b_i^2) = B^{12}$ and $corr(\tilde{\tau}_i^1, \tilde{\tau}_i^2) = \rho_\tau^{12} \Rightarrow$ bivariate model

Curvilinearity

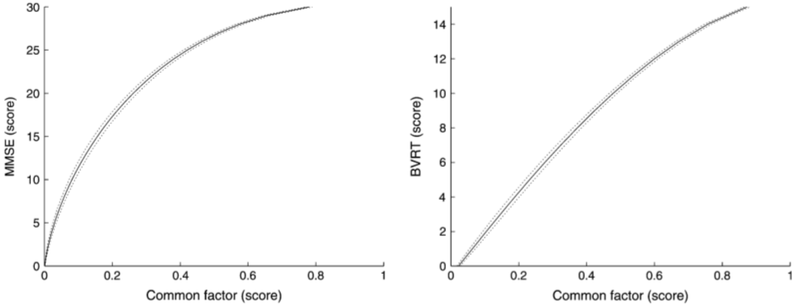

Figure: Estimated link function between crude score and the underlying latent process (Proust Lima et., 2006)

Curvilinearity

I-spline transformation of both crude markers Y^ℓ:

$$\tilde{Y}_{ij}^\ell = g^\ell(Y_{ij}^\ell, \eta^\ell) = \eta_0^\ell + \sum_{k=1}^{5} \eta_k^{\ell 2} I_k^\ell(Y_{ij}^\ell) \quad \ell = 1, 2$$

- I-splines of degree 2 with 2 internal knots at the quantiles
- $\tilde{Y} = (\tilde{Y}^1, \tilde{Y}^2)$ follows bivariate random changepoint model
- Identifiability constraints on the model: $\beta_0^\ell = 0$ and $\sigma_\epsilon^\ell = 1$

Inference

- Log-likelihood $\tilde{\tau}_i = (\tilde{\tau}_i{}^1, \tilde{\tau}_i{}^2)$:

$$\ell(\theta) = \sum_{i=1}^{n} \log \int f(\tilde{Y}_i|\tilde{\tau}_i) f(\tilde{\tau}_i) \mathrm{d}\tilde{\tau}_i + n \log |J_g^1||J_g^2|$$

where $\tilde{Y}_i|\tilde{\tau}_i$ is a multivariate Gaussian.

- Optimization: Levenberg-Marquardt algorithm and pseudo adaptive Gaussian quadrature
- Test: H_0: $\mu_\tau^1 - \mu_\tau^2 = 0$ vs. H_1: $\mu_\tau^1 - \mu_\tau^2 \neq 0$: a Wald test

Application: the Three City (3C) cohort

- cohort of 2104 elderly subjects ($\geq$ 65yo)
- 401 incident cases from Bordeaux center
- Grober and Bushke (GB) immediate vs. free recall

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Table: Results of the preliminary tests on the 3C sample.

	$\beta_2 = 0$ vs. $\beta_2 \neq 0$	$\sigma_2 = 0$ vs. $\sigma_2 \neq 0$
GB immediate recall	< 0.001	< 0.001
GB free recall	< 0.001	< 0.001

Application: results

Table: Results of the bivariate estimation on the 3C sample.

	GB immediate recall		GB free recall		Wald test	
	$\hat{\beta}$	$\widehat{se}(\hat{\beta})$	$\hat{\beta}$	$\widehat{se}(\hat{\beta})$	stat.	$p-$value
β_1	-0.286	0.023	-0.262	0.037	0.589	0.443
β_2	-0.230	0.022	-0.229	0.029	0.024	0.877
μ_τ	-3.177	0.347	-5.820	0.579	3.937	0.047

se: standard error

$\Rightarrow$ difference between GB immediate and free recall

Application: marginal estimation

$$E(\tilde{Y}^{\ell}(t), \hat{\theta}^{\ell}) = \int E(\tilde{Y}^{\ell}(t)|\tau_i^{\ell}, \hat{\theta}^{\ell}) f(\tau_i^{\ell}|\hat{\theta}^{\ell}) \mathrm{d}\tau_i^{\ell}$$

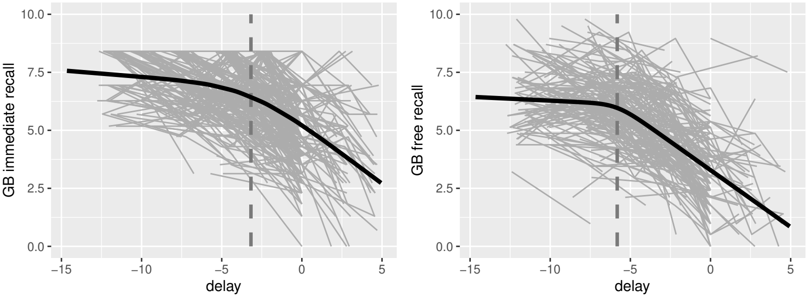


Figure: All individual GB immediate and free recall trajectories on the transformed scale compared to the estimated marginal trajectory $E(\tilde{Y}^{\ell}(t))$

Application: fit of the model

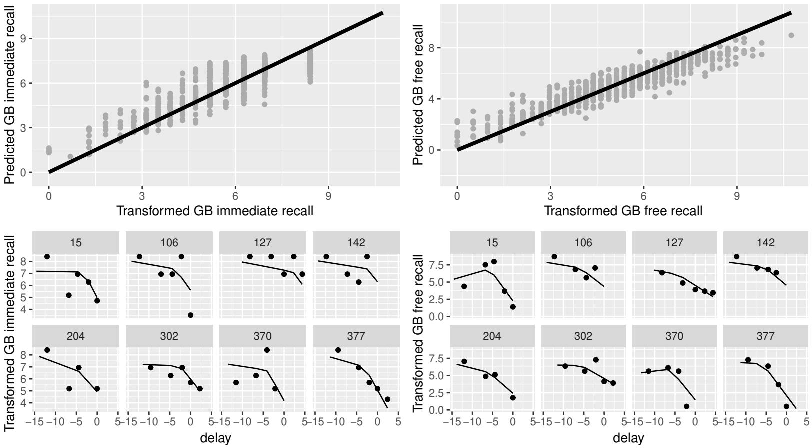


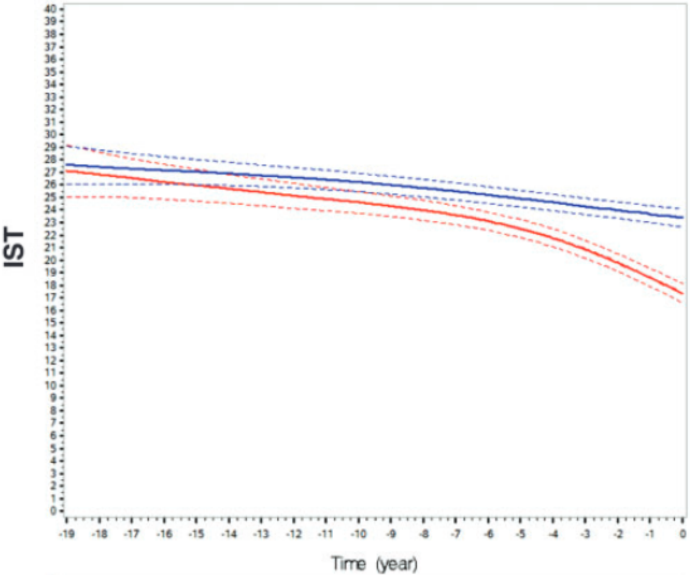
Figure: Upper panes: true transformed observation vs. predicted observations; Lower panes: individual observations (dots) vs. their predicted trajectories (solid line).

Discussion

- Valid estimation procedure and valid test
- `bircpme` function in `rcpm` package
- Identification of a late acceleration of cognitive decline
  $\Rightarrow$ modelling cases and controls together?

Perspectives & discussion

Time of differenciation versus late accelerated decline



A semi-latent class random changepoint model

$$Y(t_{ij}) = \beta_{0i} + \beta_{1i} t_{ij} + c_i \beta_{2i} f(t_{ij} - \tau_i, \eta) + \varepsilon_{ij}$$

A semi-latent class random changepoint model

$$Y(t_{ij}) = \beta_{0i} + \beta_{1i} t_{ij} + c_i \beta_{2i} f(t_{ij} - \tau_i, \eta) + \varepsilon_{ij}$$

- with a class membership model

$$\pi_i = \mathbb{P}(c_i = 1 | X_i, \delta_i) = \left(\frac{\exp(\eta^\top X_i)}{1 + \exp(\eta^\top X_i)} \right)^{1-\delta_i}$$

- δ_i case indicator (1 for cases, 0 for controls)

⇒ all cases have a changepoint
⇒ some controls have a changepoint

Discussion

- Selection bias: a joint model approach
  - the longitudinal marker $Y(t_{ij}) = \tilde{Y}(t_{ij}) + \varepsilon_{ij}$
  - the time to dementia: $\lambda(t_{ij}) = \lambda_0(t_{ij}) \exp(\nu^\top Z_i + \gamma \tilde{Y}(t_{ij}))$

$\Rightarrow$ possible to test for the existence of the random CP

- The timescale issue: age or delay?

- Random changepoint model vs. flexible nonlinear model

Thank you for your attention!

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https://github.com/crsgls