Inferential methods for random change-point models

Corentin Segalas, Hélène Jacqmin-Gadda
INSERM U1219, Biostatistics team, Bordeaux

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Biostatistics

Context: dementia

- Alzheimer's Disease (AD) main cause of dementia
- Major public health issue today and tomorrow
- Very long and progressive pre-diagnosis phase
- Heterogeneous and non-linear decline trajectories

Objectives

1. Testing the existence of a random changepoint (CP)
    - for a given marker
    - for a giver subpopulation

2. If so, compare mean changepoint time between markers (order of degradation)

The random changepoint mixed model

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

with

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

β_{0i} is the value at the CP, β_{1i} is the mean slope and β_{2i} half the difference of the slopes.

Objective 1 : Testing the existence of a random changepoint in a mixed model

How ? Using a two step procedure based on score test with a new parametrization

Segalas C, Amieva H, Jacqmin-Gadda H. A hypothesis testing procedure for random changepoint mixed models. Statistics in Medicine. 2019;1–13. https://doi.org/10.1002/sim.8195

A score test approach

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

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

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

with

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

The supremum score test

- 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

- Empirical distribution of T_n under H_0 approached by multiplier bootstrap. For $k = 1, \ldots, K$, we generate n r.v. $\xi_i^{(k)} \sim \mathcal{N}(0,1)$ and compute

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

- 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?

- Does β_2 depend on covariate?
  $\Rightarrow$ Wald test
- Is β_2 subject specific (i.e. random)?
  $\Rightarrow$ corrected test for variance components (Stram and Lee, 1994)

Heterogeneity in τ_i?

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

Objective 2 : Compare mean CP date between markers

How ? Developing a bivariate random changepoint model

Segalas C, Helmer C, Jacqmin-Gadda H. A curvilinear bivariate random changepoint model to assess temporal order of markers. Submitted.

Bivariate curvilinear random CP model

$$Y_{ij}^{l} = \beta_{0i}^{l} + \beta_{1i}^{l}(t_{ij}^{l} - \tau_{i}^{l}) + \beta_{2i}^{l}\sqrt{(t_{ij}^{l} - \tau_{i}^{l})^2 + \gamma} + \varepsilon_{ij}^{l} \quad l = 1, 2$$

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

Bivariate curvilinear random CP model

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

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

$$\tilde{Y}_{ij}^{l} = g^l(Y_{ij}^{l}, \eta^l) = \eta_0^l + \sum_{k=1}^{5} \eta_k^{l2} I_k^l(Y_{ij}^{l}) \quad l = 1, 2$$

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 simple Wald test

Three City (3C) cohort

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

Results

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

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

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

	GB immediate recall		GB free recall		Wald test	
	$\hat{\beta}$	se($\hat{\beta}$)	$\hat{\beta}$	se($\hat{\beta}$)	stat.	pvalue
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 free and immediate recall

Fit of the model for GB free and immediate recall

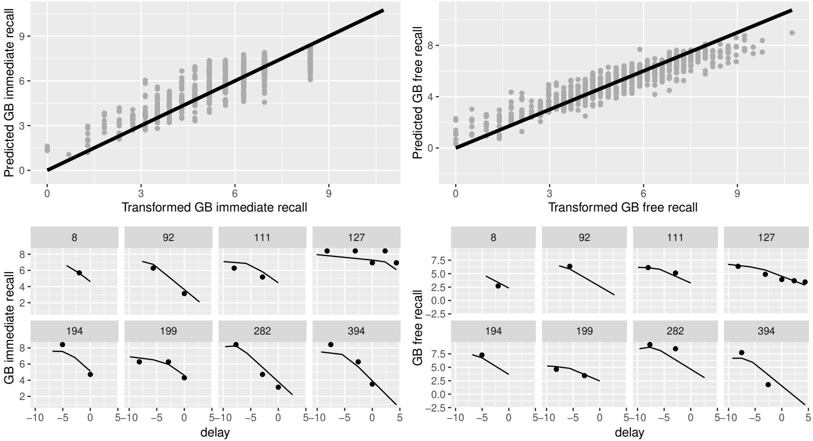

Figure: Upper panes: true transformed observation vs. predicted observations; Lower panes: individual observations (dots) vs. their predicted trajectories (solid line).

Discussion

- First: test for the existence of a random CP
- Second: bivariate random CP model for easy comparison of mean CP

- R package `rcpm` available on Github
- Improve code (speed and options)
- Extend to joint modeling
- Extend to a mixture model

Thank you for your attention!

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corentin.segalas@u-bordeaux.fr

https://github.com/crsgls