A mixed-effects model with time reparametrization for longitudinal univariate manifold-valued data

Schiratti J. B. et al.

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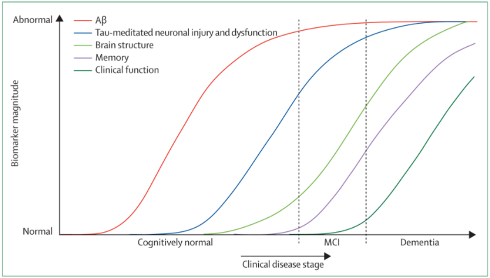
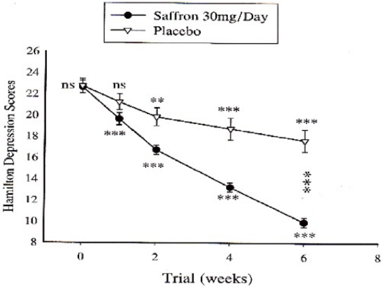
Overview - Disease Progression Models

Aims:

- understand the progression of the disease
- accurately stage subjects in clinical trials
- prognosis



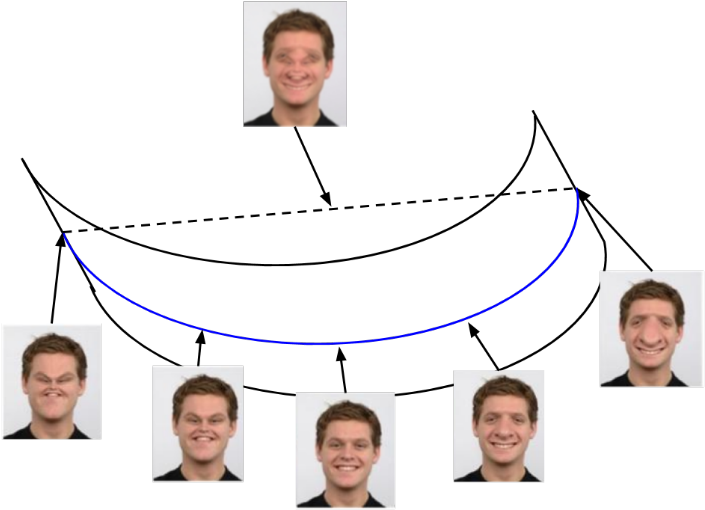


Timeline of disease progression models

Model	Trajectory shape	Subject staging	Main limitation
Comparison of symptomatic stages: mild, moderate, severe	not modelled	only to categories	biased categories
Event-based Model	step-functions	discreete stages	no notion of time
Differential Equation Model	non-parametric	disease onset and progr. speed	trajectories not aligned
Disease Progression Score	sigmoids	disease onset and progr. speed	sigmoidal assumption
Self-modelling regression	non-parametric	disease onset and progr. speed	assumes all subjects follow same progression
Manifold Model	sigmoids	disease onset and progr. speed	...

What is a manifold?

- An N-dimensional space that generalises the Euclidean space
- Equipped with an inner product and distance metric



The model

- The model is a non-linear mixed effects model placed in a Riemannian manifold setting
- Each subject i has an associated:
  - time shift τ_i
  - progression speed α_i
- Fixed effects are:
  - time shift t_0
  - progression speed v_0
  - observation point on the manifold p_0
- The biomarker trajectory γ_{p_0,t_0,v_0}

$$y_{i,j} = \gamma_{p_0,t_0,v_0}(\alpha_i v_0(t_{i,j} - t_0 - \tau_i)) + \epsilon_{i,j} \tag{1}$$

where

$$\begin{cases} \alpha_i = exp(\eta_i) \\ \eta_i \sim \bigotimes_{i=1}^{p} N(0, \sigma_\eta^2) \\ \tau_i \sim \bigotimes_{i=1}^{p} N(0, \sigma_\tau^2) \\ \epsilon_{i,j} \sim \bigotimes_{i,j} N(0, \sigma^2) \end{cases} \tag{2}$$

Data

ADNI:

- ADAS-COG from 1391 subjects - ADNI1, ADNIGO and ADNI2
- cortical thickness in 34 ROIs from 725 subjects - ADNI1
- follow-up: 18 months to 4 years

Results - time shifts

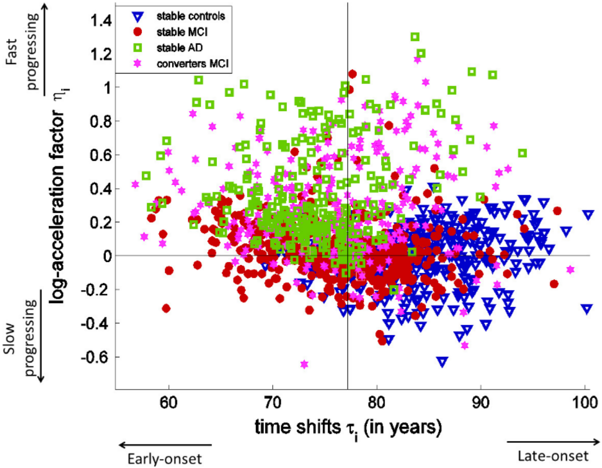


Fig. 1. Log-acceleration factors η_i plotted against the time shifts τ_i for the 1391 individuals with ADAS-Cog measurements. An horizontal line was plotted at the level $\eta_i = 0$ (no change in speed with respect to the average trajectory) and at $\tau_i = t_0 = 77.17$ (the estimated reference time t_0).

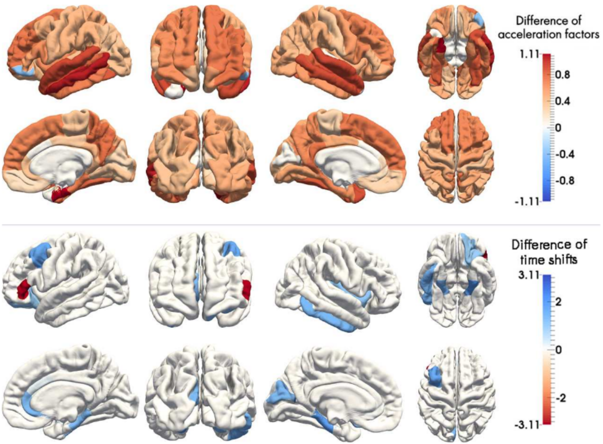


Fig. 2. At the top (respectively bottom) : the difference in averaged acceleration factors (respectively time shifts) between AD patients and stable controls is displayed on the cortex. Acceleration factors (and respectively time shifts) were averaged per regions of interest. Only regions where the difference was statistically significant ($p < 0.05$, corrected for multiple comparisons) were colored.

Results - MCI converters vs MCI stable

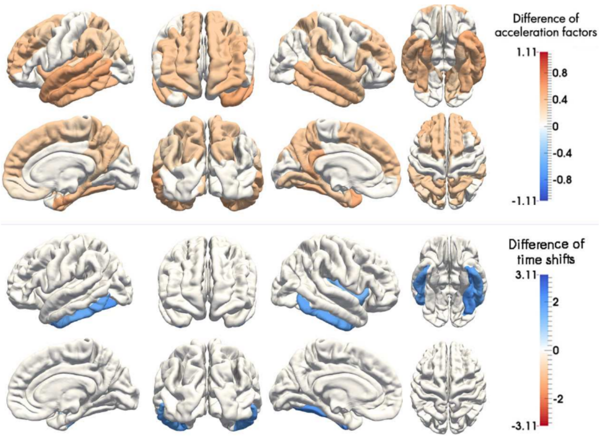


Fig. 3. At the top (respectively bottom) : the difference in averaged acceleration factors (respectively time shifts) between converters MCI and stable MCI is displayed on the cortex. Acceleration factors (and respectively time shifts) were averaged per regions of interest. Only regions where the difference was statistically significant ($p < 0.05$, corrected for multiple comparisons) were colored.

Learning spatiotemporal trajectories from manifold-valued longitudinal data

Jean-Baptiste Schiratti[2,1], **Stéphanie Allassonnière**[2], **Olivier Colliot**[1], **Stanley Durrleman**[1]
[1] ARAMIS Lab, INRIA Paris, Inserm U1127, CNRS UMR 7225, Sorbonne Universités, UPMC Univ Paris 06 UMR S 1127, Institut du Cerveau et de la Moelle épinière, ICM, F-75013, Paris, France
[2]CMAP, Ecole Polytechnique, Palaiseau, France
jean-baptiste.schiratti@cmap.polytechnique.fr,
stephanie.allassonniere@polytechnique.edu,
olivier.colliot@upmc.fr, stanley.durrleman@inria.fr

Abstract

We propose a Bayesian mixed-effects model to learn typical scenarios of changes from longitudinal manifold-valued data, namely repeated measurements of the same objects or individuals at several points in time. The model allows to estimate a group-average trajectory in the space of measurements. Random variations of this trajectory result from spatiotemporal transformations, which allow changes in the direction of the trajectory and in the pace at which trajectories are followed. The use of the tools of Riemannian geometry allows to derive a generic algorithm for any kind of data with smooth constraints, which lie therefore on a Riemannian manifold. Stochastic approximations of the Expectation-Maximization algorithm is used to estimate the model parameters in this highly non-linear setting. The method is used to estimate a data-driven model of the progressive impairments of

Model extension - NIPS paper

- Multivariate
- Each subject has its own unique trajectories
- Fitting is performed with Stochastic Approximation EM instead of Nelder-Mead

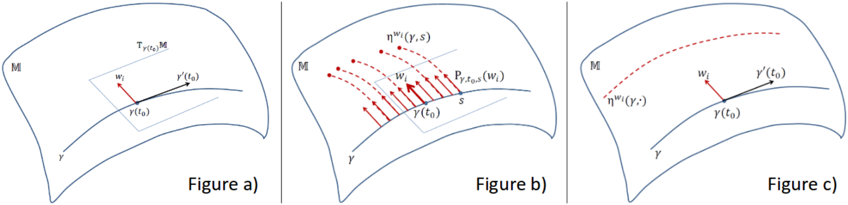


Figure 1: Model description on a schematic manifold. Figure a) (left) : a non-zero vector $\mathbf{w}_i$ is choosen in $\mathrm{T}_{\gamma(t_0)}\mathbb{M}$. Figure b) (middle) : the tangent vector $\mathbf{w}_i$ is transported along the geodesic γ and a point $\eta^{\mathbf{w}_i}(\gamma, s)$ is constructed at time s by use of the Riemannian exponential. Figure c) (right) : The curve $\eta^{\mathbf{w}_i}(\gamma, \cdot)$ is the parallel resulting from the construction.

Summary

Model strenghts:

- The Riemannian manifold framework enables many types of trajectory models
- For every subject it estimates:
  - unique biomarker trajectories (in NIPS extension)
  - disease onset
  - progression speed

Limitations:

- assumes a parametric shape of the biomarker trajectories