Mixed effect model for the spatiotemporal analysis of longitudinal manifold value data

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Computational Anatomy

- Represent and analyse **geometrical** elements upon which **deformations** can **act**
- Describe the observed objects as **geometrical variations** of one or several representative elements
- **Quantify** this variability inside a population

Deformable template model from Grenander

- How does the deformation act?
- What is a representative element?
- How to quantify the geometrical variability ?

Computational Anatomy

Important issues in atlas estimation:

- Register any new data in the « coordinates » of the reference shape:
  - Transport the available information from the representative element
  - *« Registration » penalised as a function of its « normality »*

- Quantify anatomical structure variability in different sub-groups

Targetted applications:

- Pathology effects
- Classification of new patients
- Early diagnostic

Computational Anatomy

One solution:

- Quantify the distance between images using deformations
- Provide a **statistical model** to approximate the generation of the observed population from the atlas
- Propose a **statistical learning algorithm**
- Optimise the numerical estimation

Bayesian Mixed Effect model

- First model :
  - **One observation per subject**
  - **Image or shape (viewed as currents)**
  - **Deformations either linearized or diffeomorphic**
  - **Homogeneous or heterogeneous populations (mixture models)**

Bayesian Mixed Effect model

Template

Deformation

Observations

$$\begin{cases} y_i \sim \mathcal{N}(I_0 \circ \phi_i^{-1}, \sigma^2 Id) \\ \phi_i = f(\beta_i) \\ \beta_i \sim \mathcal{N}(0, \Gamma_g) \end{cases}$$

deterministic parametrisation

Normal distribution with full covariance matrix

For $1 \leqslant i \leqslant n$ subjects,

Bayesian Mixed Effect model

Observations
- T1
- DWIs
- fMRI
- T1+fMRI

Template
- Grey level images
- Probability maps

Deformation
- Linearised
- Diffeomorphic

$$\begin{cases} y_i \sim \mathcal{N}(I_0 \circ \phi_i^{-1}, \sigma^2 Id) \\ \phi_i = f(\beta_i) \\ \beta_i \sim \mathcal{N}(0, \Gamma_g) \end{cases}$$

deterministic parametrisation

Normal distribution with full covariance matrix

Mixtures of all these models

For $1 \leqslant i \leqslant n$ subjects,

Bayesian Mixed Effect model

- First model :
  - **One observation per subject**
  - **Image or shape (viewed as currents)**
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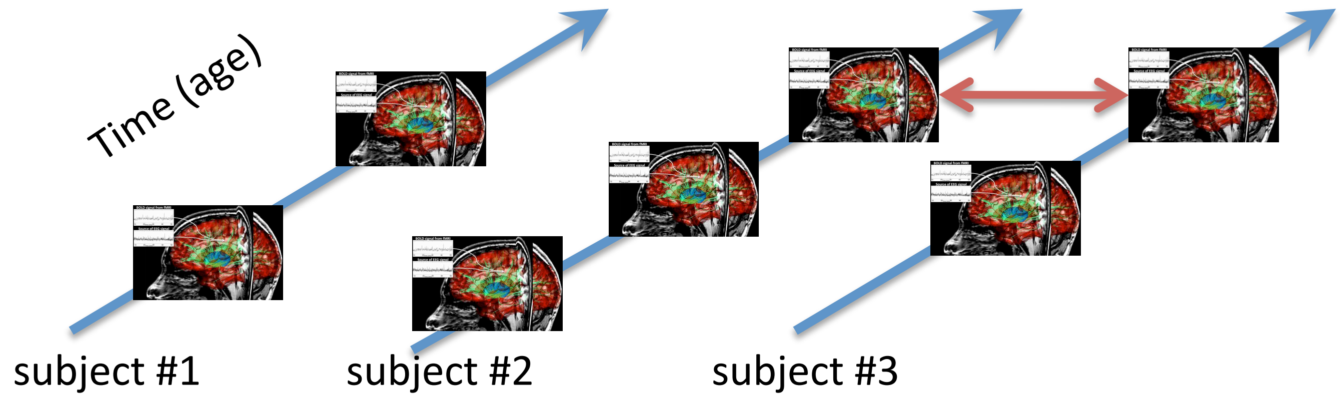
➢ **Limitations**

- **One observation per subject**
- **Corresponding acquistion time**

Longitudinal Data Analysis

- Longitudinal model :
  - **Several observation per subject**
  - **Image, shape, etc**
  - **Atlas = representative trajectory and population variability**

Longitudinal Data Analysis



How to learn representative trajectories of data changes from longitudinal data?

Temporal marker of progression
(e.g. time since drug injection, seeding, birth, etc..)

Regression
(e.g. compare measurements at same time-point)

Linear mixed-effects models
[Laird&Ware'82, Diggle et al., Fitzmaurice et al.]

Vector-valued data

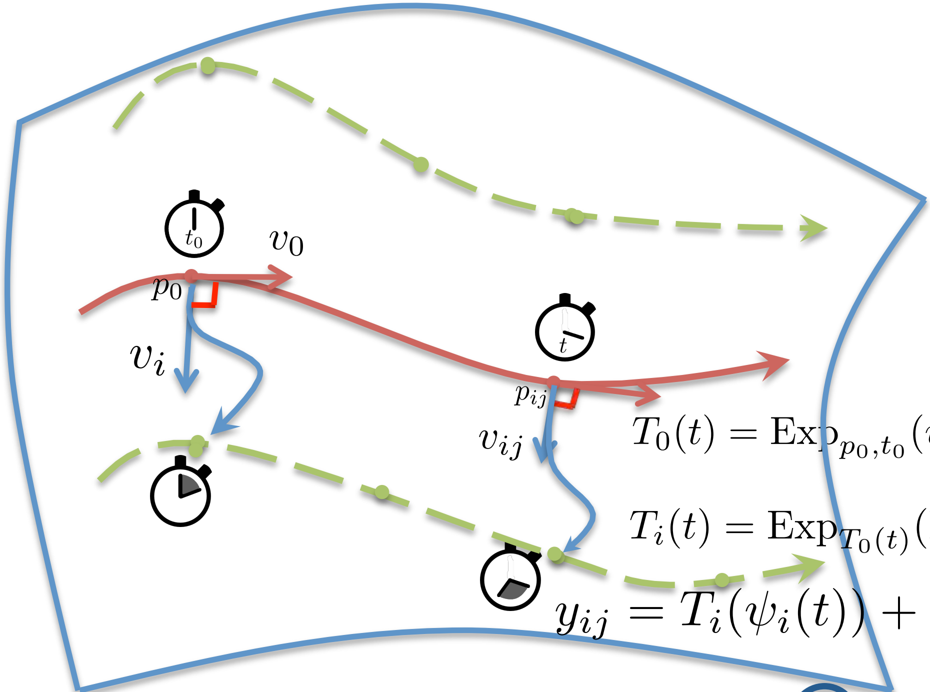
No temporal marker of progression
(e.g. in aging, neurodegenerative diseases, etc..)

Learning **spatiotemporal distribution** of trajectories
- *Find temporal correspondences*
- *Compare data at corresponding stages of progression*

Needs to disentangle differences in:
- Measurements
- *Dynamics of measurement changes*

manifold-valued data
(normalized data, positive matrices, shapes, etc.)

Spatiotemporal Statistical Model



$T_0(t) = \mathrm{Exp}_{p_0,t_0}(v_0)(t)$

$T_i(t) = \mathrm{Exp}_{T_0(t)}(\mathrm{P}^{T_0}_{t_0,t}(v_i))$

$y_{ij} = T_i(\psi_i(t)) + \varepsilon_{ij}$

$\psi_i(t) = t_0 + \alpha_i(t - t_0 - \tau_i)$

- Statistical model inclinding:
  - a **representative trajectory** of data changes
  - **spatiotemporal variations** in:
    - measurement values
    - pace of measurement changes
- Orthogonality condition ensures identifiability (unique space/time decomposition)
- Time is not a covariate but a random variable

	Acceleration factor	Time-shift	Space-shift
Random effects:	$\alpha_i \sim log\,\mathcal{N}(0, \sigma_\alpha^2)$	$\tau_i \sim \mathcal{N}(0, \sigma_\tau^2)$	$v_i = (A_1 \vert \ldots \vert A_K)\, s_i$ $A_k \perp v_0$

Fixed effects: (p_0, t_0, v_0) and $(\sigma_\alpha^2, \sigma_\tau^2, A_1, \ldots A_K)$

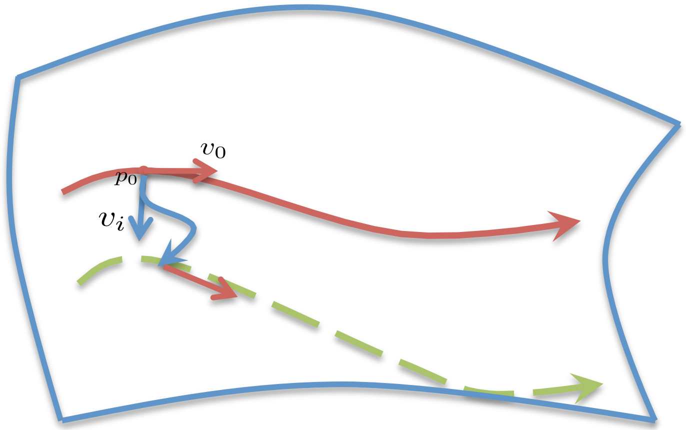
[Schiratti et al. IPMI'15, NIPS'15]

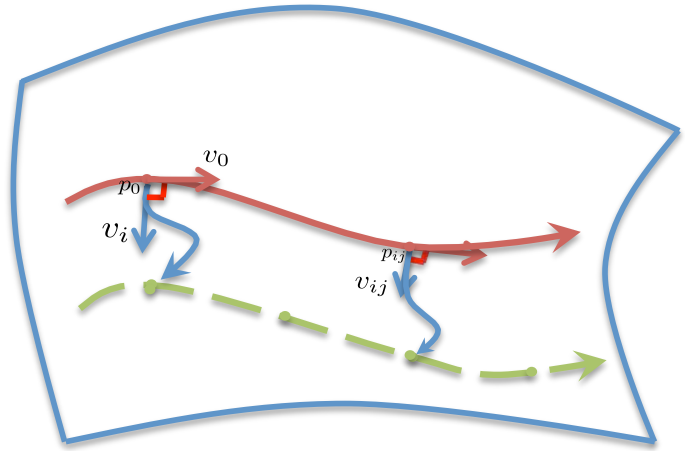
Spatiotemporal Statistical Model

$y_{ij} = T_i(\psi_i(t)) + \varepsilon_{ij}$	Submanifold value observations
$T_i(t) = \mathrm{Exp}_{T_0(t)}(\mathrm{P}_{t_0,t}^{T_0}(v_i))$	Parallel curve
$T_0(t) = \mathrm{Exp}_{p_0,t_0}(v_0)(t)$	Representative trajectory
$\psi_i(t) = t_0 + \alpha_i(t - t_0 - \tau_i)$	Linear time reparametrization
$\alpha_i \sim log\, \mathcal{N}(0, \sigma_\alpha^2)$ $\tau_i \sim \mathcal{N}(0, \sigma_\tau^2)$ $v_i = (A_1 \vert \ldots \vert A_K)\, s_i$ $A_k \perp v_0$	**Hidden random variables:** Acceleration factor Time shift Space shift
(p_0, t_0, v_0) $(\sigma_\alpha^2, \sigma_\tau^2, A_1, \ldots A_K)$	**Parameters:** Mean trajectory parametrization and prior parameter

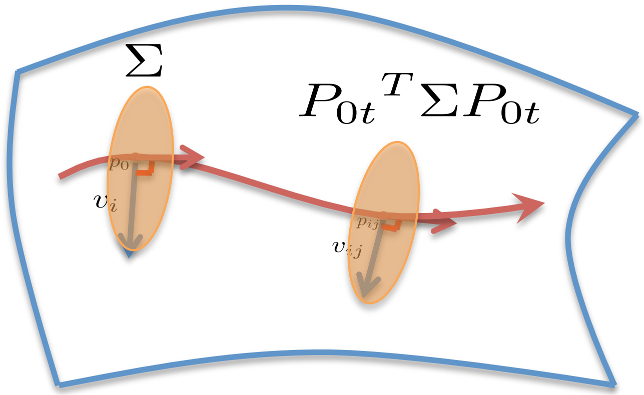
Spatiotemporal Statistical Model

Comparison with previous work:



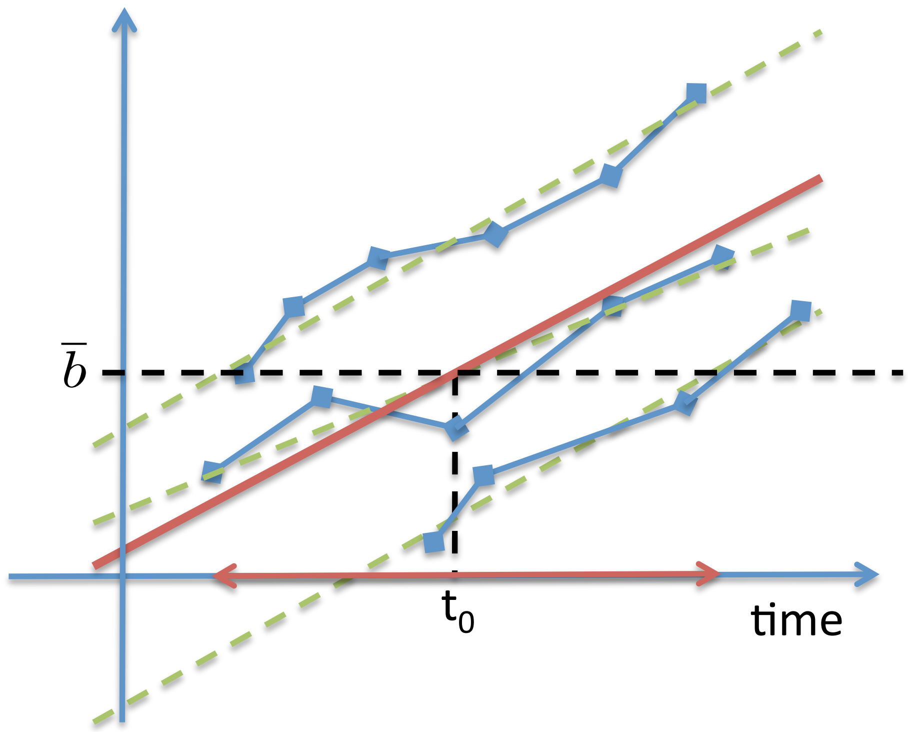


Interest: Parallel transport keep invariant the structure of the distribution, but updated it in time



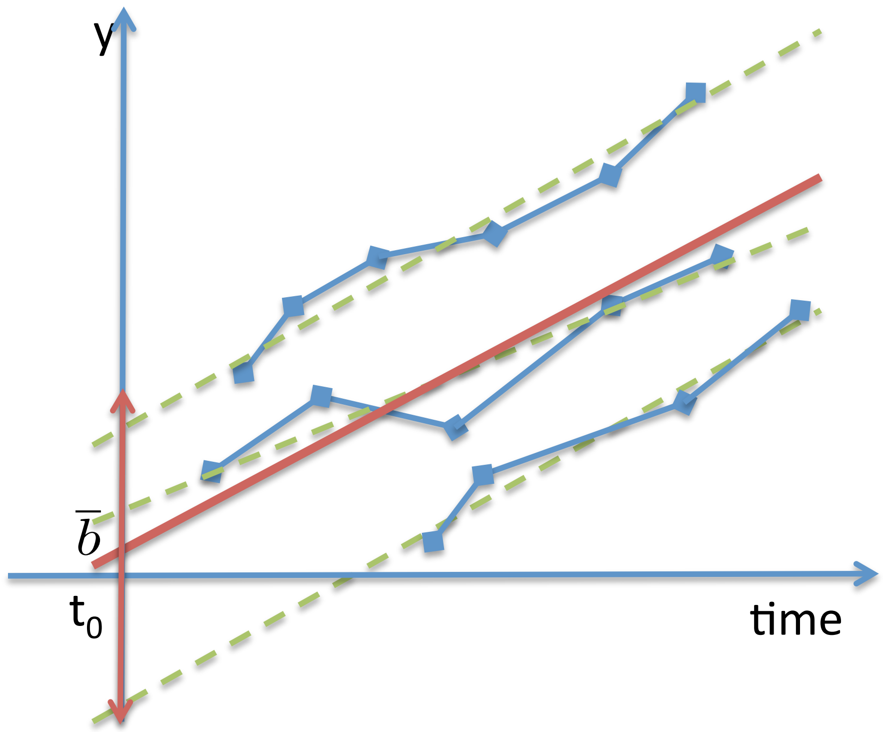
Spatiotemporal Statistical Model

- The straight line model $\mathbb{M} = \mathbb{R}$



$$y_{ij} = (\bar{a} * a_i)(t_{i,j} \underbrace{- t_0 - \tau_i}) + \bar{b} + \varepsilon_{i,j}$$

Time at which measurement of the i^{th} subject reaches $\bar{b}$



$$y_{ij} = (\bar{a} * a_i)(t_{i,j} - t_0) + \underbrace{\bar{b} + b_i} + \varepsilon_{i,j}$$

Measurement of the i^{th} subject at time t_0

Schiratti et al. (2015)

Laird & Ware (1982)

Spatiotemporal Statistical Model

- The logistic curve model $\mathbb{M} =]0,1[, \quad g(p)(u,v) = \frac{uv}{p^2(1-p)^2}$

  - Geodesic are logistic curves

$$\gamma_0(t) = 1 + \frac{(1-p_0)/p_0}{\exp\left(-\frac{v_0}{p_0(1-p_0)}(t-t_0)\right)} \qquad y_{ij} = \gamma_0\Big(t_0 + \alpha_i(t - t_0 - \tau_i)\Big) + \varepsilon_{ij}$$

  - It is *not* equivalent to a linear model on the logit of the observations (i.e. the Riemannian log at $p_0 = 0.5$), since p_0 is estimated

  - If we fix $p_0 = 0.5$ in our model → end up with our previous linear case (different from Laird&Ware)

Spatiotemporal Statistical Model

- The propagation model $\mathbb{M} =]0,1[^N,\ g(p)(u,v) = \sum_{k=1}^{N} \frac{u_k v_k}{p_k^2(1-p_k)^2}$

  - Geodesics are logistic curves in each coordinate

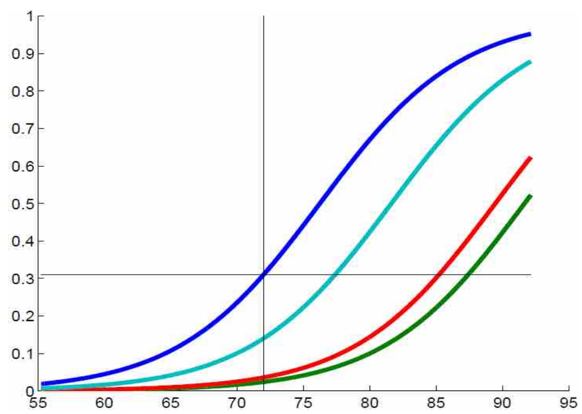
  - Parametric family of geodesics seen as a model of propagation of an effect

$$\gamma_\delta(t) = \Big(\gamma_0(t), \gamma_0(t-\delta_1), \ldots, \gamma_0(t-\delta_{N-1})\Big)$$

  - The parallel curve in the direction of the space-shift v_i writes

$$\left(\gamma_0\left(t + \frac{v_{i,1}}{v_0}\right), \gamma_0\left(t - \delta_1 + \frac{v_{i,2}}{v_0}\right), \ldots, \gamma_0\left(t - \delta_{N-1} + \frac{v_{i,N}}{v_0}\right)\right)$$

→ The parallel changes the *relative timing* of the effect onset across coordinates



Parameter Estimation

$$y = (y_1, ..., y_N),\ \ z = (z_1, ... z_N),\ \ \theta = (\sigma_z^2, \sigma_\varepsilon^2, A_1, ..., A_K, p_0, t_0, v_0)$$

- Maximum Likelihood:

$$max_\theta\, p(y|\theta) = \int p(y, z|\theta) dz$$

- EM: $\theta_{k+1} = argmax_\theta \sum_{i=1}^{N} \int \log \Big(\underbrace{p(y_i, z_i|\theta)}_{p(y_i|z_i,\theta)p(z_i|\theta)} \Big) p(z_i|y_i, \theta_k) dz_i$

- Distribution from the **curved exponential family**

$$\log p(y_i, z_i|\theta) = \phi(\theta)^T S(y_i, z_i) - log(C(\theta))$$

$$\theta_{k+1} = argmax_\theta \left\{ \phi(\theta)^T \sum_{i=1}^{N} \int S(y_i, z_i) p(z_i|y_i, \theta_k) dz_i - N \log(C(\theta)) \right\}$$

Parameter Estimation: stochastic algorithm

- **SA-EM**: replaces integration by one simulation of the hidden variable:

  sample $z_{i,k+1}$ from $p(z_i|y_i,\theta_k)$,

  and a stochastic approximation of the sufficient statistics

  $$\overline{S}_{k+1} = (1-\Delta_k)\overline{S}_k + \Delta_k \left(\frac{1}{N} \sum_{i=1}^{N} S(y_i, z_{i,k+1}) \right)$$

  Maximization step (unchanged)

  $$\theta_{k+1} = argmax_\theta \left\{ \phi(\theta)^T \overline{S}_{k+1} - \log(C(\theta)) \right\}$$

- **MCMC**-SAEM: replaces sampling by a single Markov Chain step
  - For each coordinate *p* (Gibbs sampler) sample $\tilde{z}_i^p \sim p(z_i^p | z_i^{q\neq p}, \theta)$
  - Set $z_{i,k+1}^p = \tilde{z}_i^p$ with probability $1 \wedge \frac{p(y_i|\tilde{z}_i,\theta)}{p(y_i|z_i,\theta)}$
  - $z_{i,k+1}^p = z_{i,k}^p$ otherwise

[Delyon, Lavielle, Moulines.'99]
[Allassonnière et al.'10]

Parameter Estimation: stochastic algorithm

- **Theoretical properties of the sampler**:

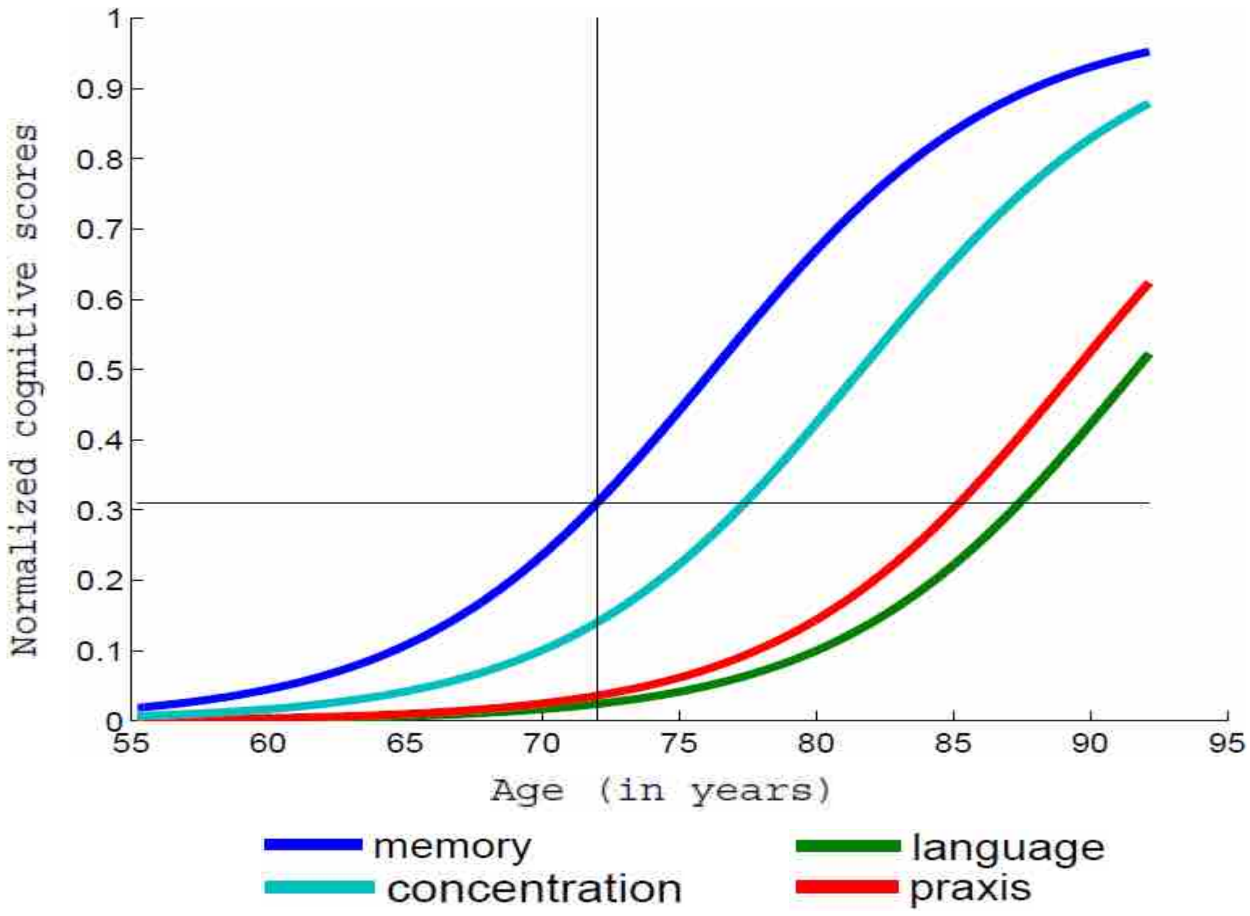
  Under mild conditions:
  - Drift property
  - Small set
  - **Geometric ergodicity uniformly on any compact set** of the parameters

- **Theoretical properties of the estimation algorithm**:
  - **a.s. convergence** towards the MAP estimator
  - **Normal asymptotic behaviour**: speed $1/\sqrt{\Delta_k}$
  - Normal asymptotoc behaviour with optimal speed with averaging sequences $1/\sqrt{k}$

Model of Alzheimer's disease progression

- Neuropsychological tests ADAS-Gog from ADNI
- 248 subjects who converted from MCI to AD
- 6 time-points per subjects on average (min 3, max 11)
- Data points $y_{ij} \in]0,1[^4$ with propagation logistic model

The average trajectory of data changes



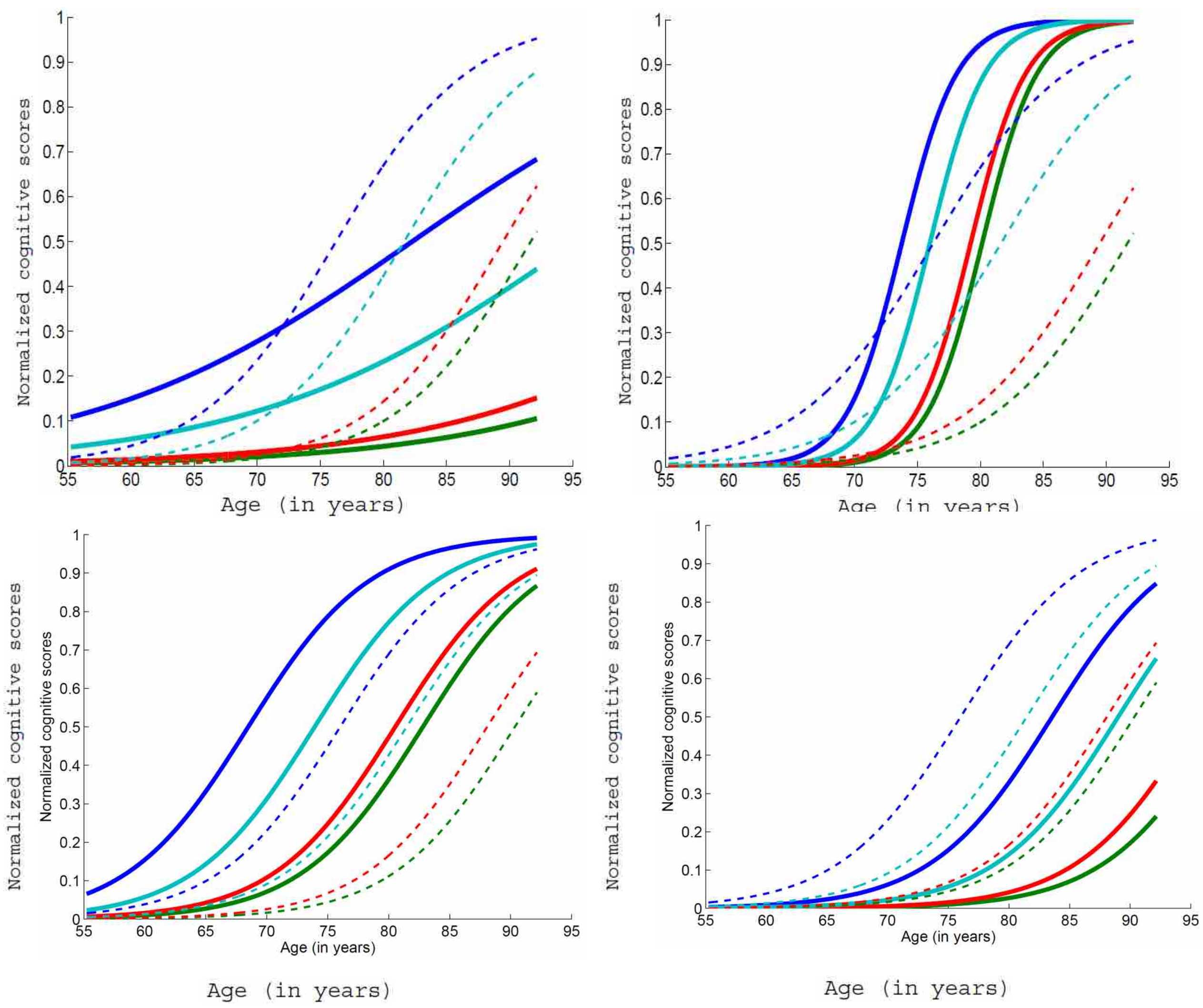
[Schiratti et al. IPMI'15, NIPS'15]

Model of Alzheimer's disease progression

-1σ $+1\sigma$

Acceleration factor α_i

Time-shift

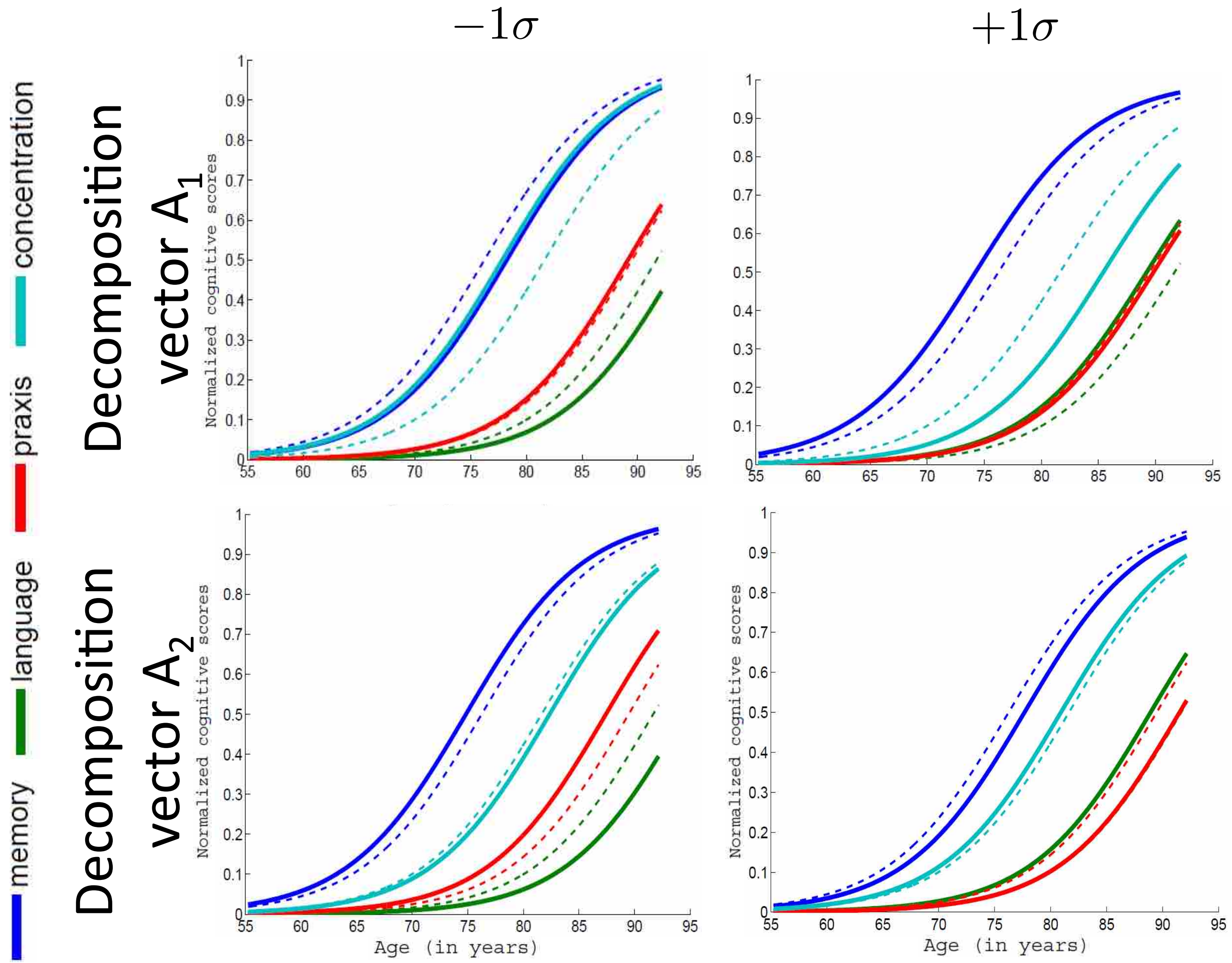


Distinguish **fast** vs. **slow** progressers

Distinguish **early** vs. **late** onset individuals

[Schiratti et al. IPMI'15, NIPS'15]

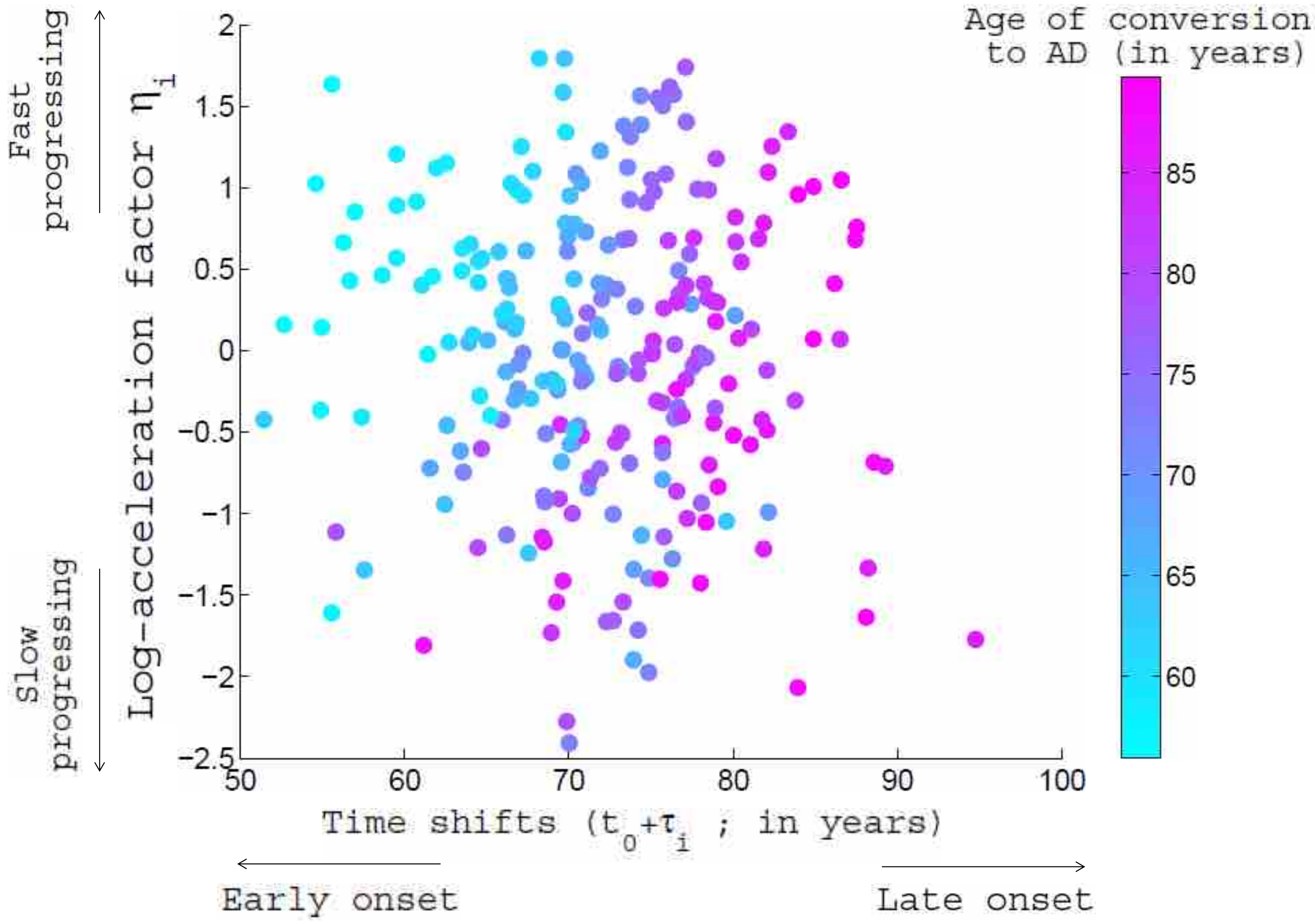
Model of Alzheimer's disease progression



Variability in the **relative timing** and **ordering** of the events

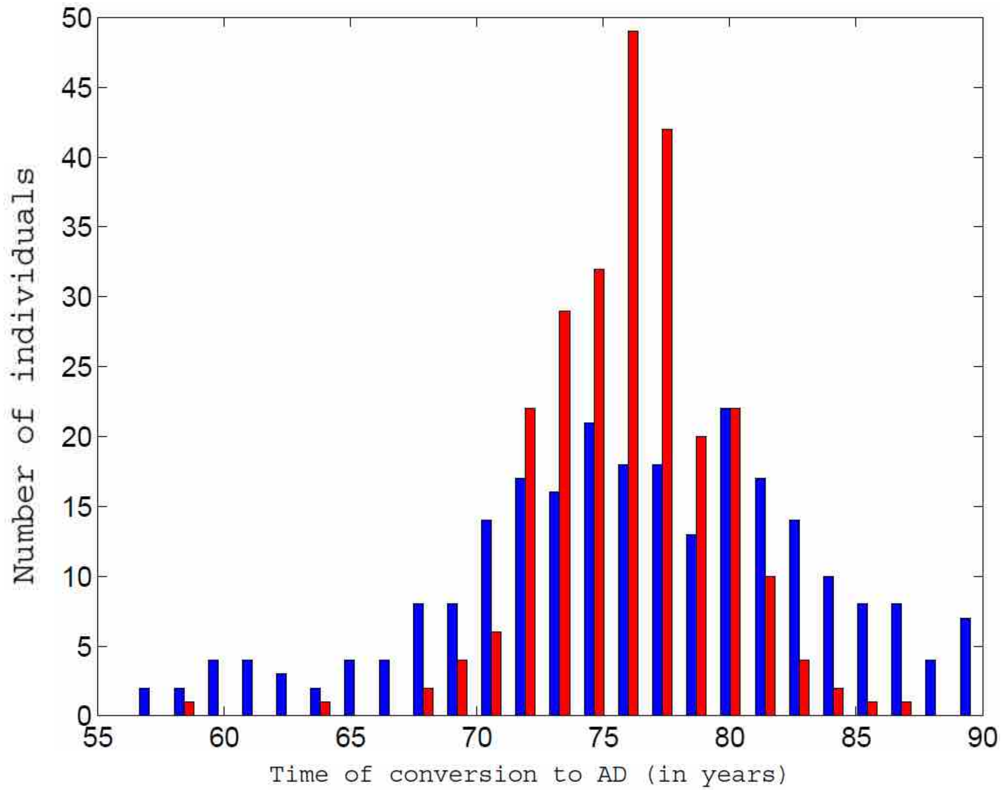
[Schiratti et al. IPMI'15, NIPS'15]

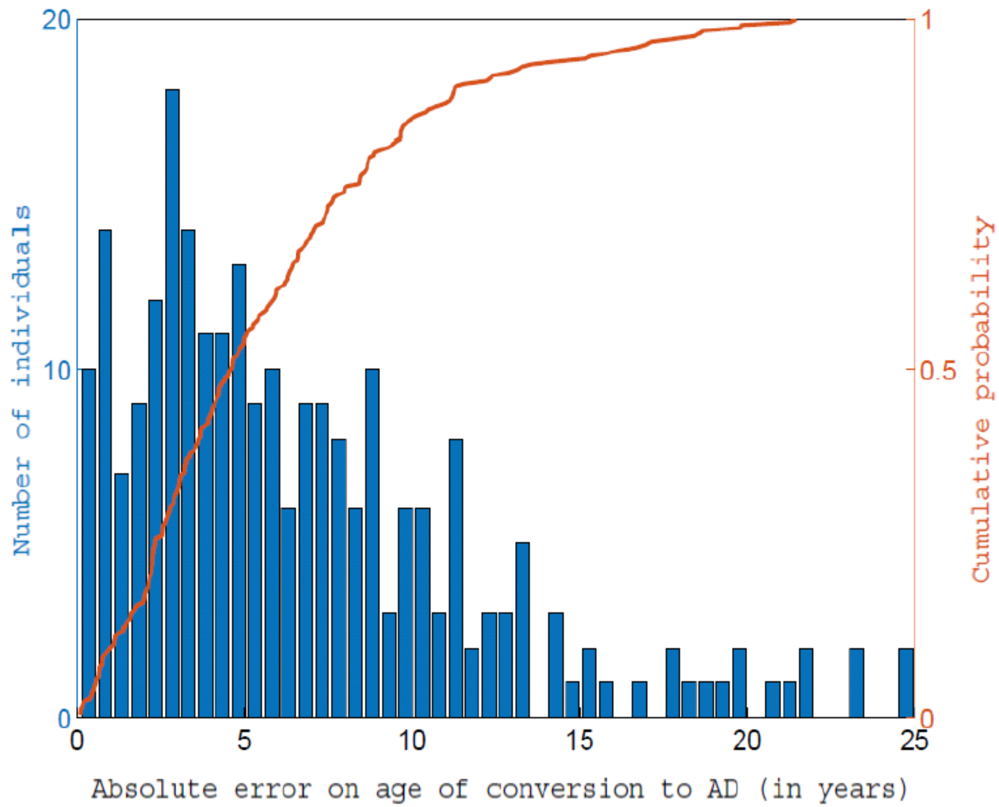
Model of Alzheimer's disease progression



[Schiratti et al. IPMI'15, NIPS'15]

Model of Alzheimer's disease progression

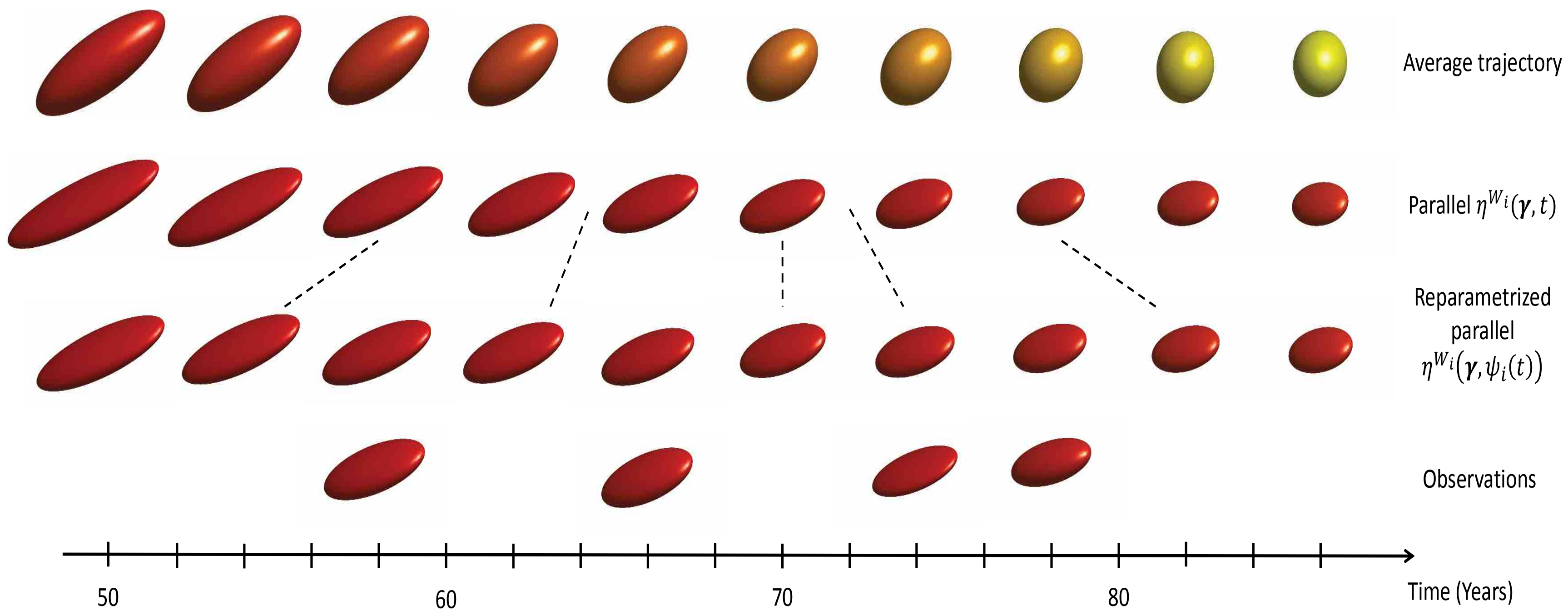




[Schiratti et al. IPMI'15, NIPS'15]

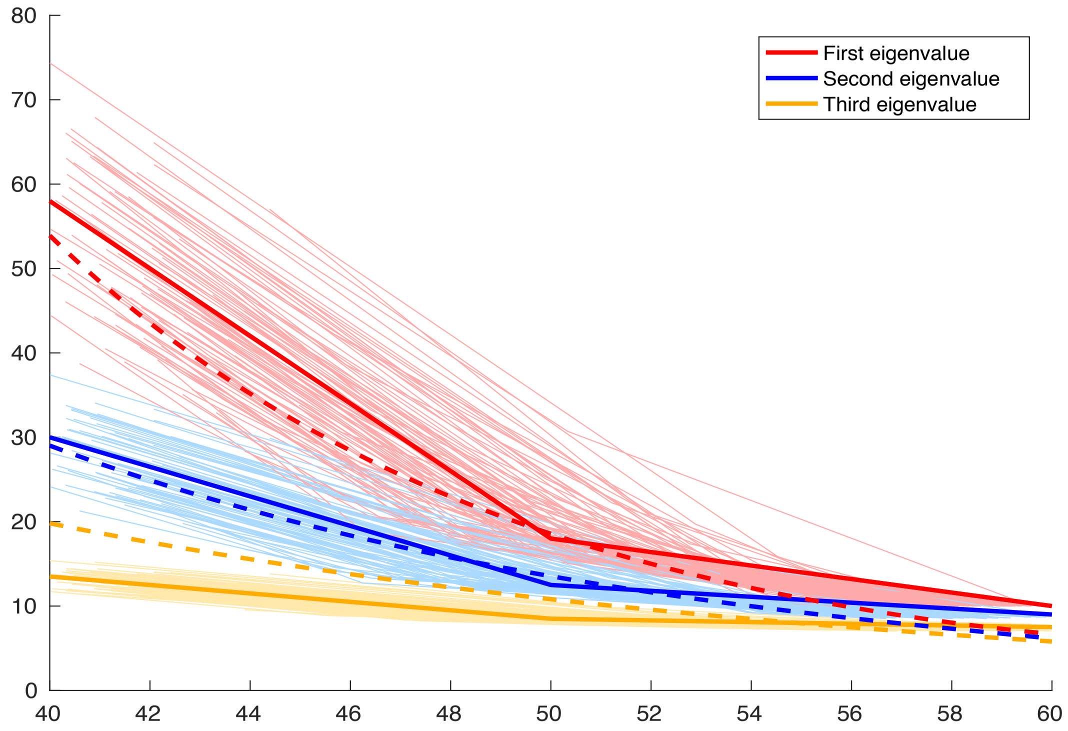
Model of diffusion tensors

- Geodesic in the Riemannian manifold of positive definite matrices
- Parallel transport the tensors
- Reprearamtrize in time
- Sample this curse



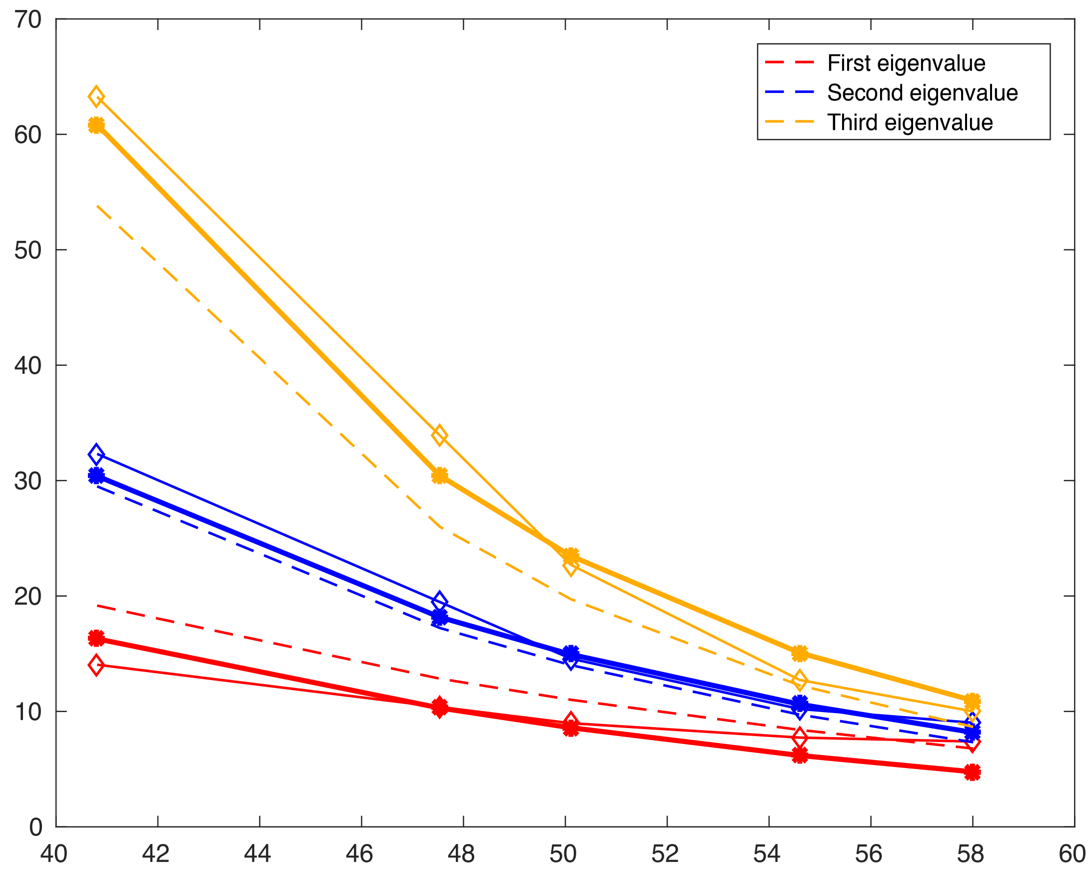
Model of diffusion tensors

- Synthetic data not generated from the model but imitating a non smooth evolution
- 100 subjects
- 5 time points in average



Model of diffusion tensors

- Fitting the model to a new patient



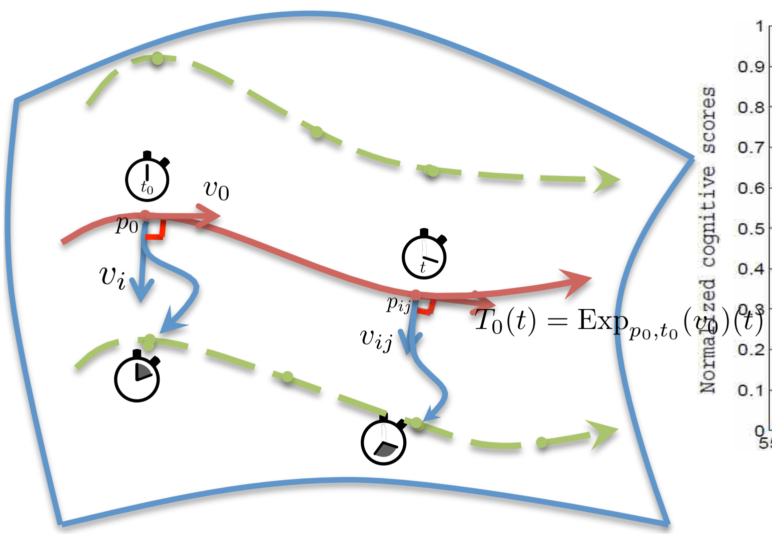
Conclusion

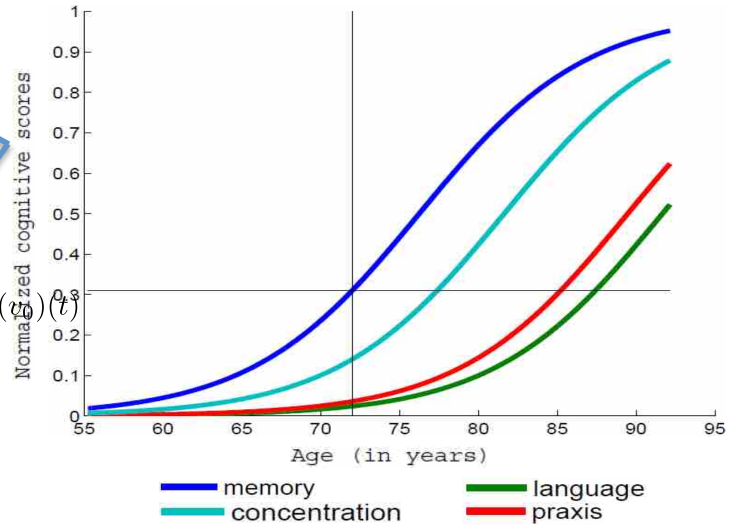
- Generic statistical model to learn **spatiotemporal distribution of trajectories** on manifolds:
  - Calibrated on **longitudinal** data sets using MCMC-SAEM
  - Automatically finds **temporal correspondences** among similar events that may happen at different age/time
  - Estimates the **variability** of the data at the corresponding events

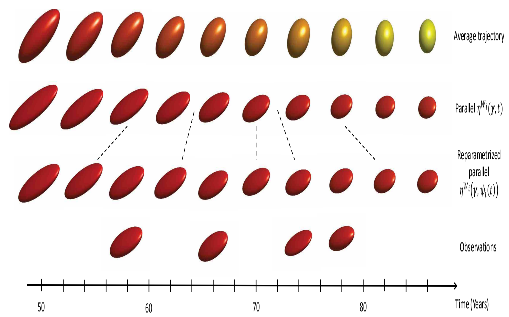
- It allows us to position disease progression within the life and history of the patient

- **Future work:**
  - Derive instances of the model for more complex manifold-valued data *(e.g. spatially distributed data, shape data, etc..)*

Thank you!


t_0
v_0
p_0
v_i
t
p_{ij}
v_{ij}
$T_0(t) = \mathrm{Exp}_{p_0,t_0}(v_0)(t)$


Normalized cognitive scores
Age (in years)
memory
concentration
language
praxis


Average trajectory
Observations
Time (Years)