ARAMIS LAB
BRAIN DATA SCIENCE

# Personalised simulations of Alzheimer's Disease progression

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Apr 4th, 2019

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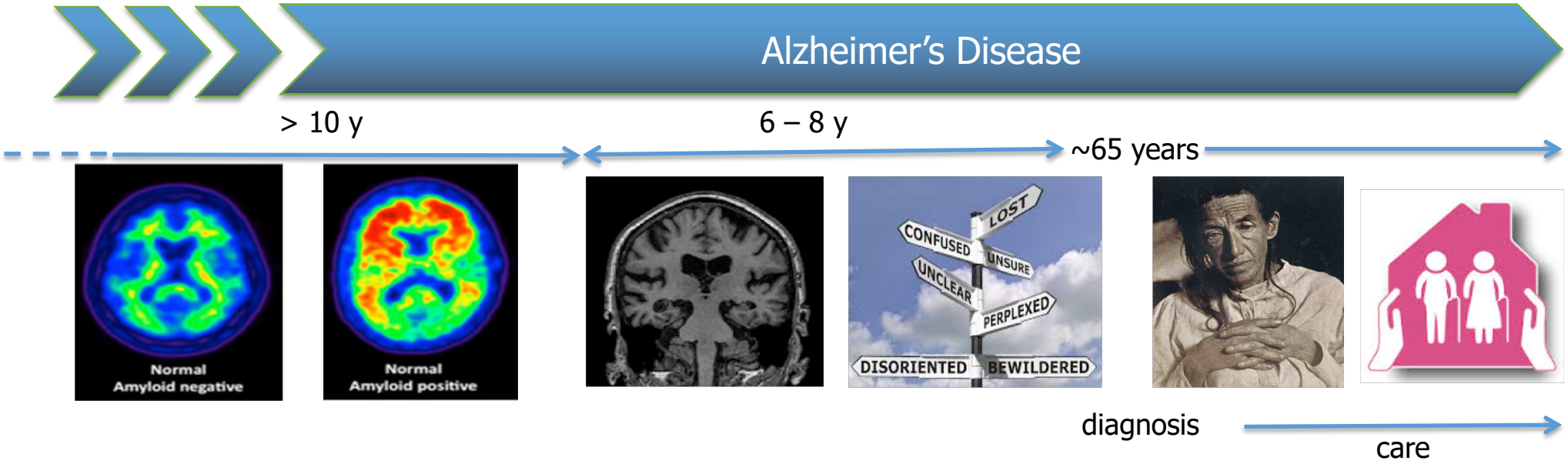
@SDurrleman

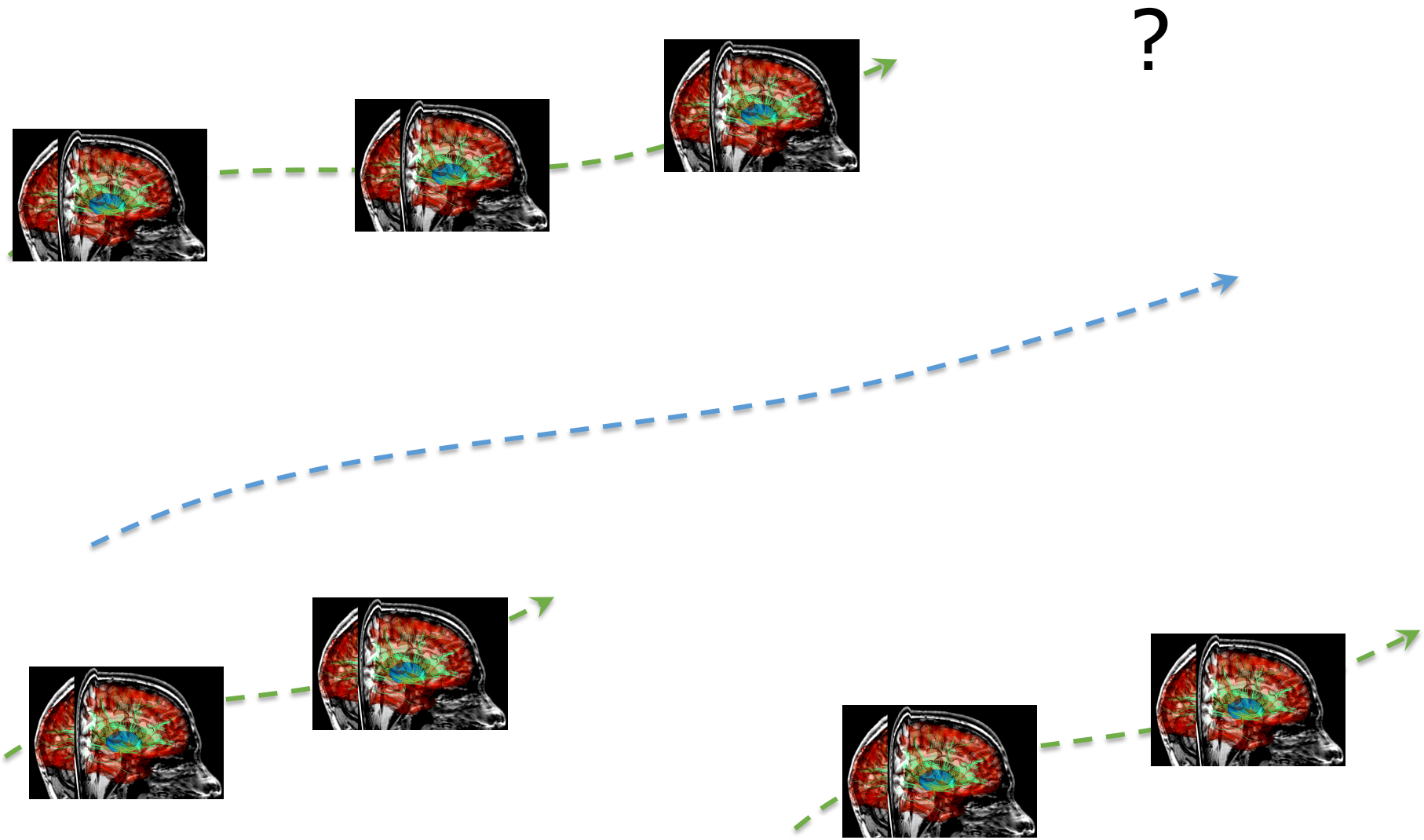



## Build digital model of brain aging

from clinical and imaging data

**Understand**
the heterogeneity of the effects of the disease on the brain

**Predict**
disease or symptoms onset



## Hierarchical model

Population level

Average trajectory :

$\gamma_0(\cdot) = \gamma_{p_0,t_0,v_0}(\cdot)$

→ Geodesic on a Riemannian manifold $\mathbb{M}$

Individual level $(1 \leq i \leq p)$

Individual trajectory $\gamma_i(\cdot) = \eta^{w_i}(\gamma_0, \psi_i(\cdot))$

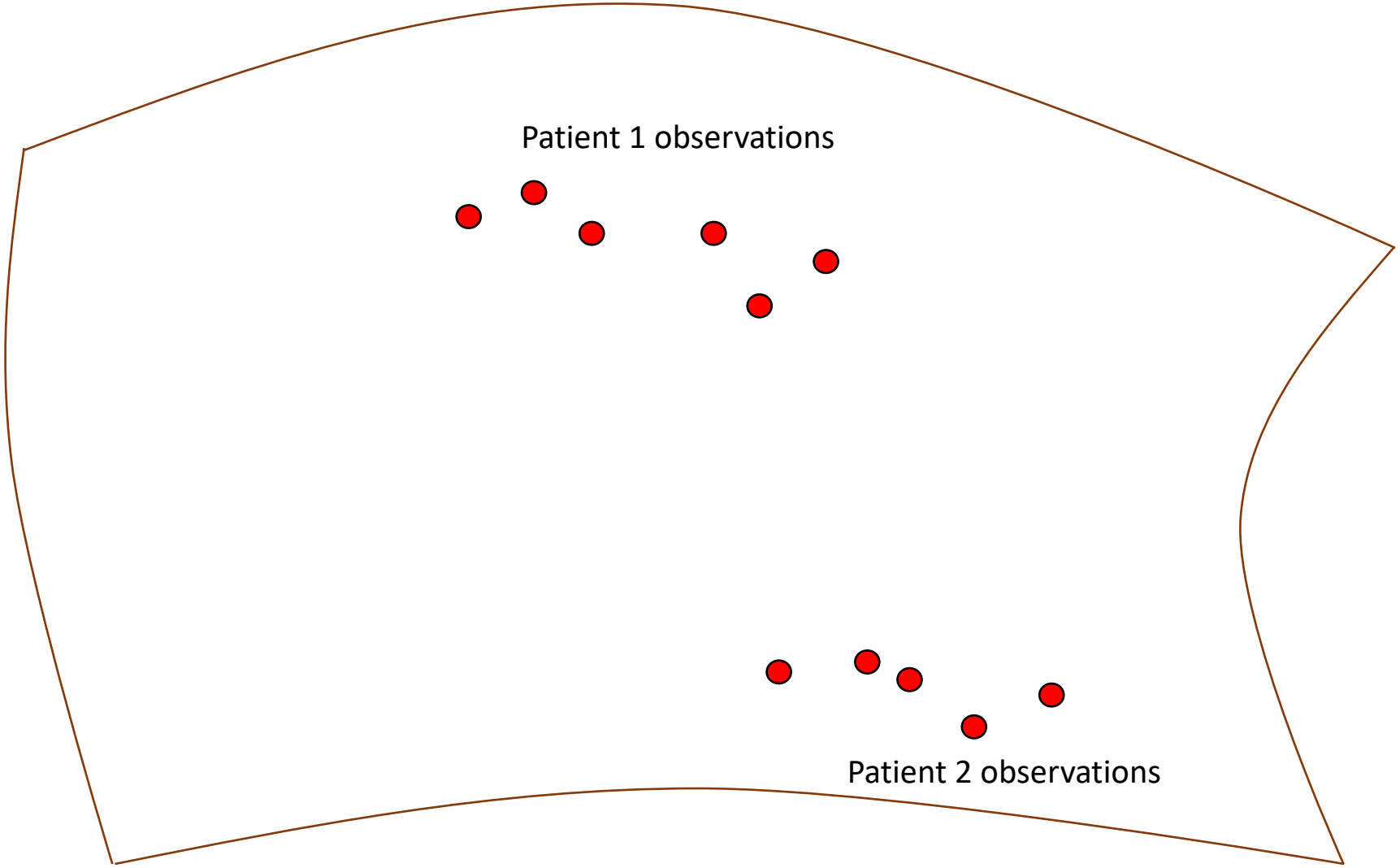
→ Spatiotemporal transform of trajectory

Observations

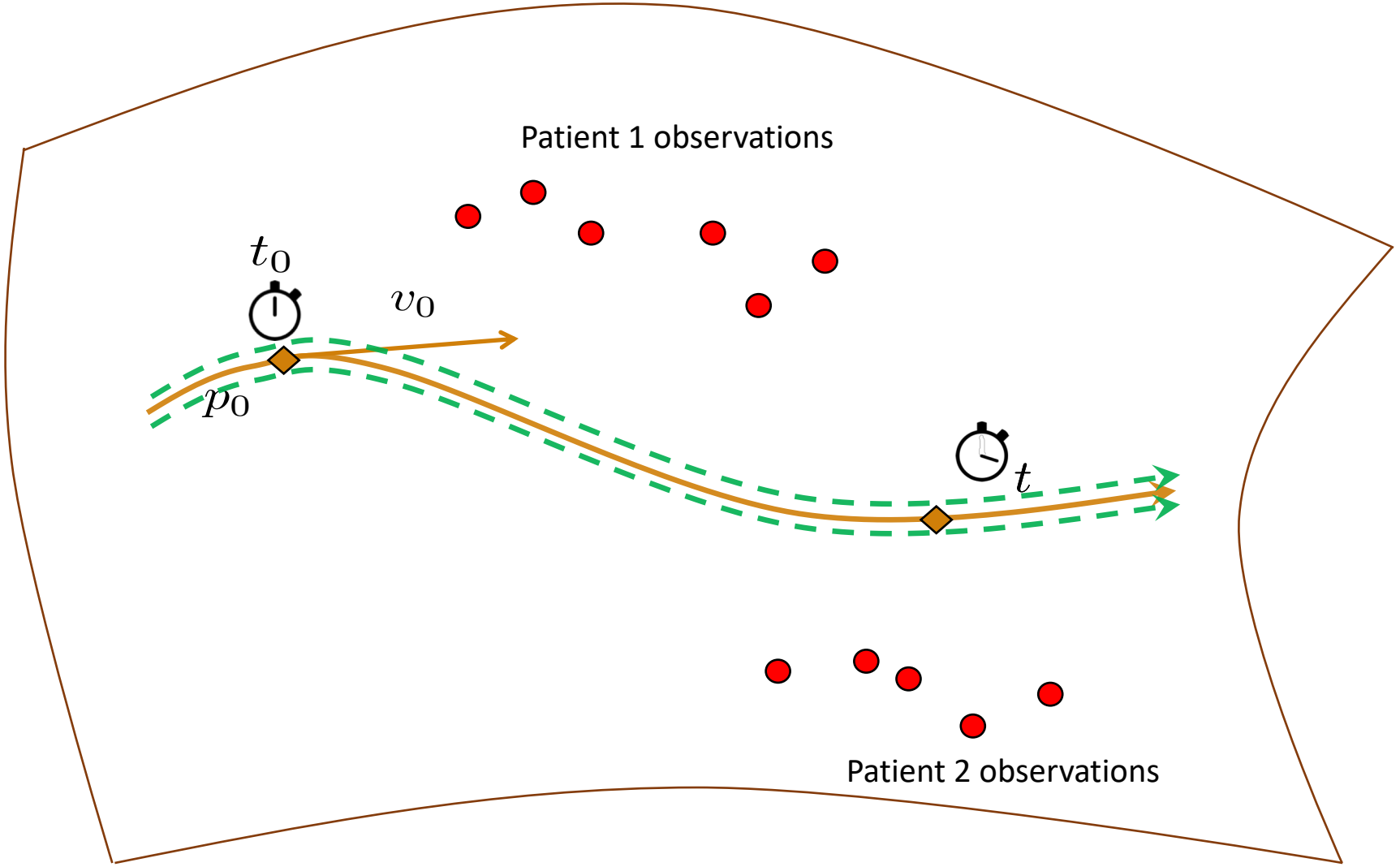
$y_{i,j} = \gamma_i(t_{i,j}) + \varepsilon_{i,j}$

→ data point lying on a sub-Riemannian manifold

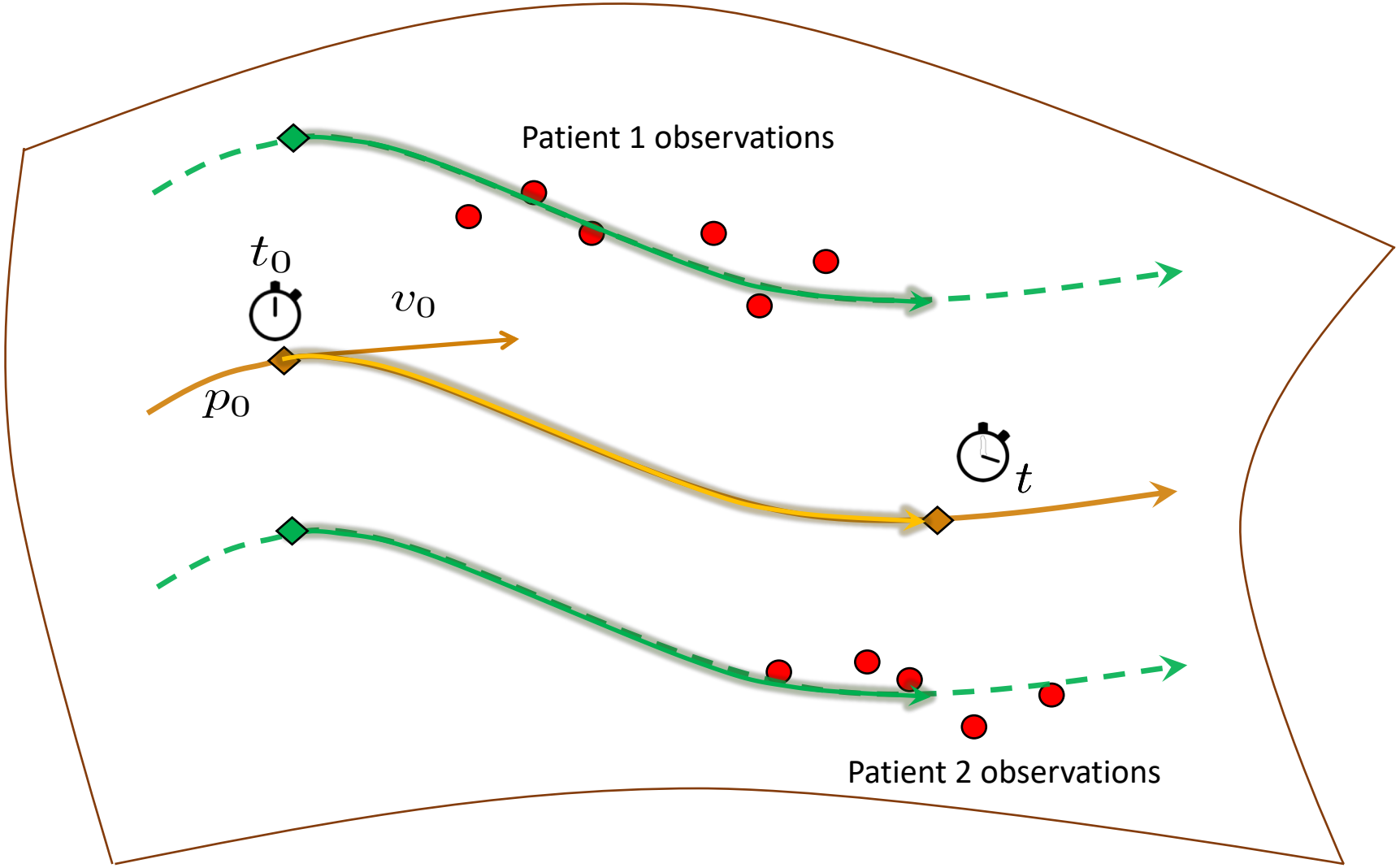
# Bayesian non-linear mixed-effect model



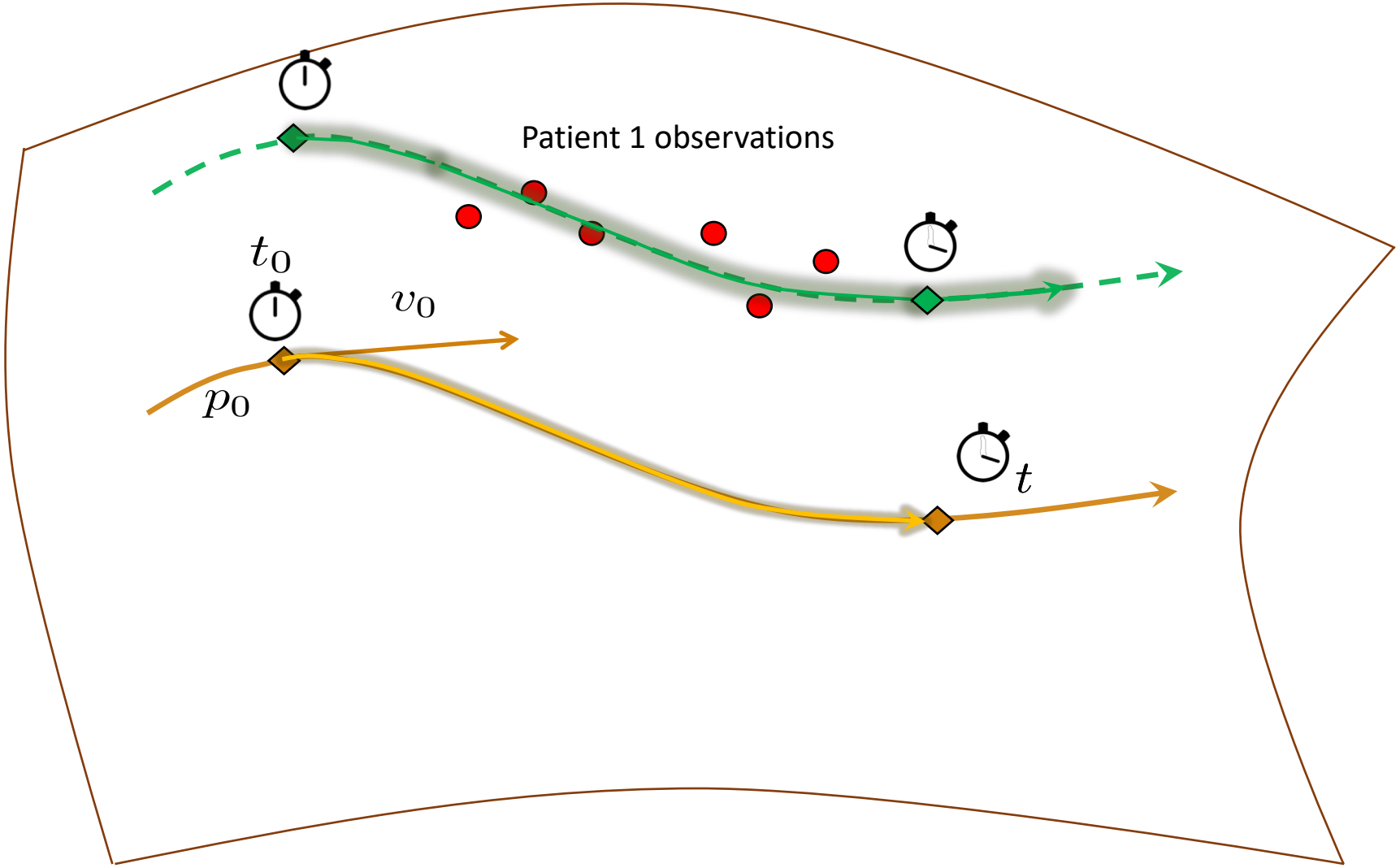
# Bayesian non-linear mixed-effect model



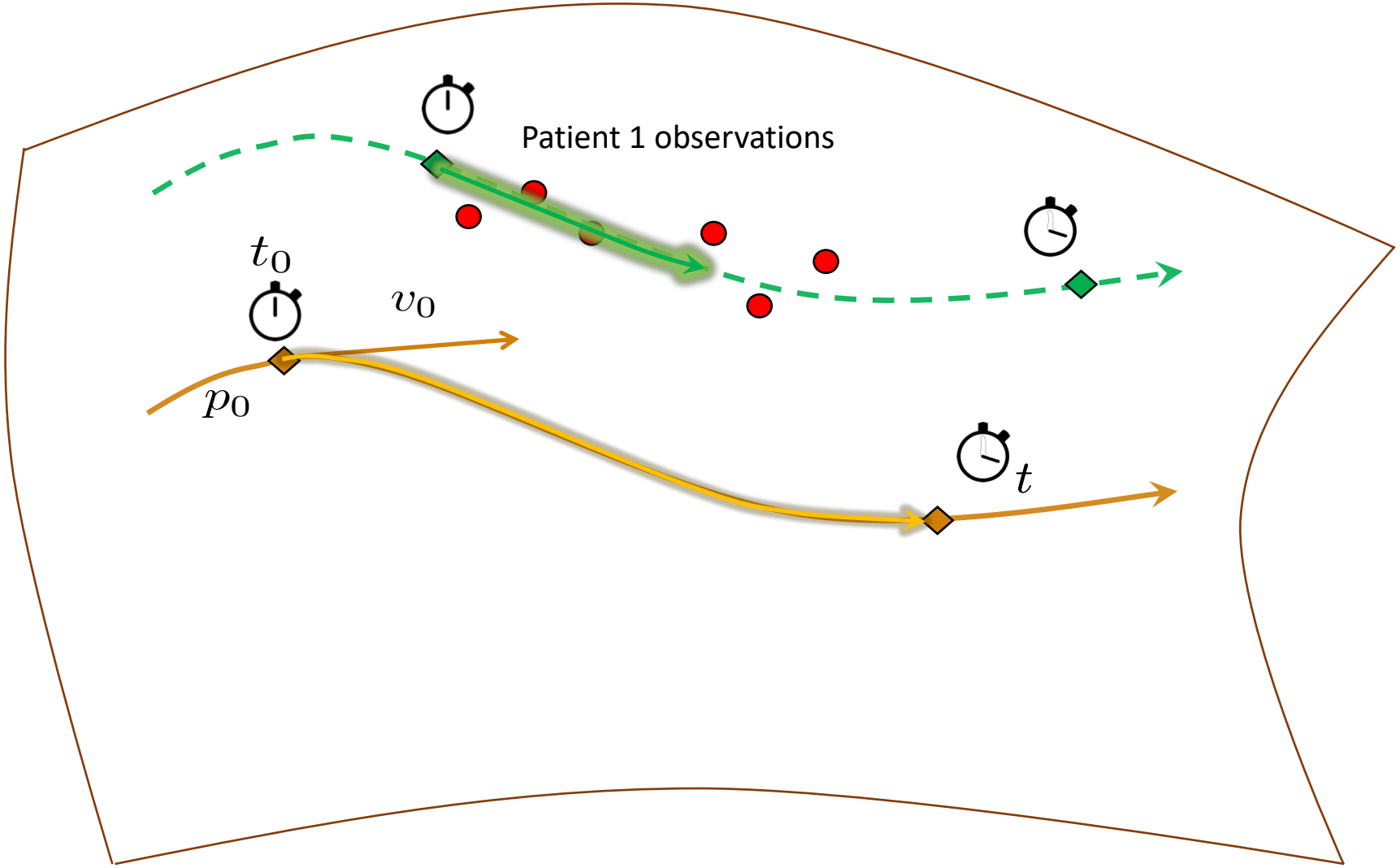
# Bayesian non-linear mixed-effect model



# Bayesian non-linear mixed-effect model



# Bayesian non-linear mixed-effect model



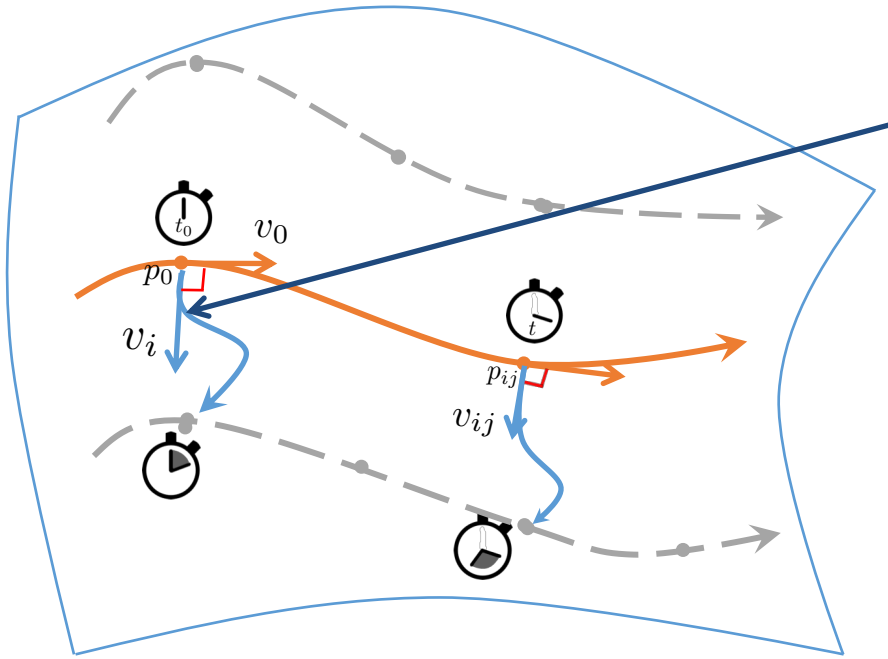
## Spatiotemporal hierarchical model

[Schiratti et al. IPMI'15, NIPS'15, PhD'17, JMLR'17]

Random effects: Space-shift Acceleration factor Time-shift

$$v_i = (A_1|\dots|A_K)\, s_i \qquad A_k \perp v_0$$

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




Parallel shift

Time-warp

$$y_{ij} = T_i[\gamma_0]\left(\psi_i(t_{ij})\right) + \varepsilon_{ij}$$

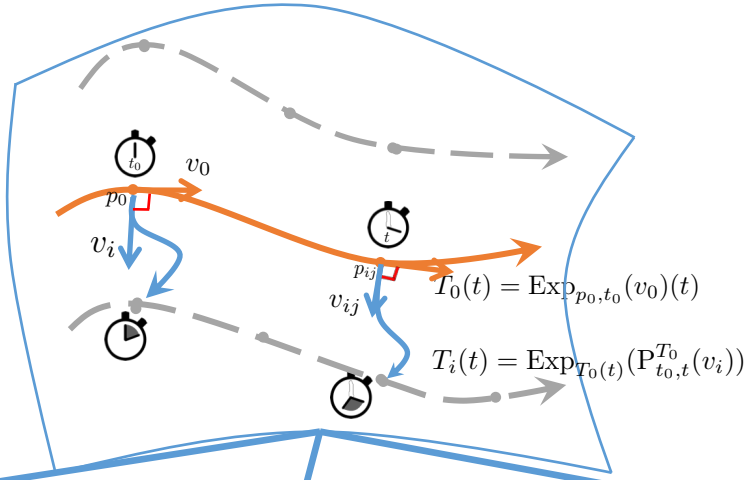
Average trajectory

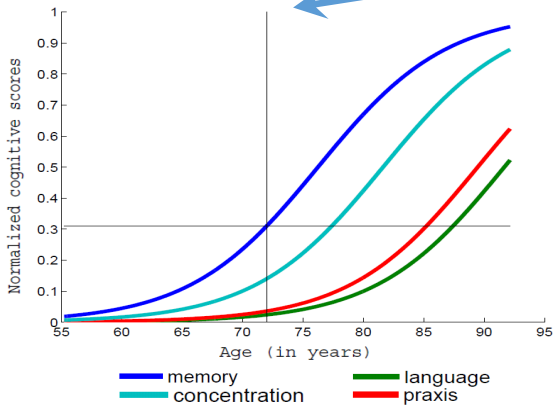
noise

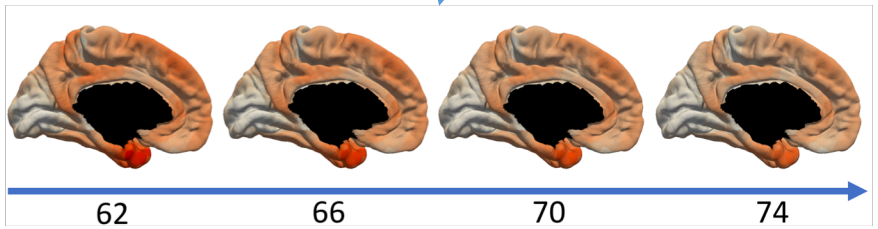
Fixed effects: $(p_0, t_0, v_0)$

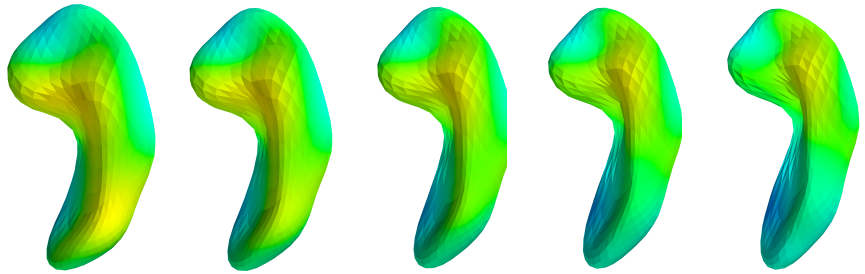
Fixed and random effects estimated by maximum likelihood optimation (MCMC-SAEM)

# Generic spatiotemporal model



Unstructured data

Image data

Shape data

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# Models of Alzheimer's disease progression

Jan 23th, 2019

S. Durrleman

# Reconstruct the natural history of AD: ADNI subjects with confirmed AD diagnosis

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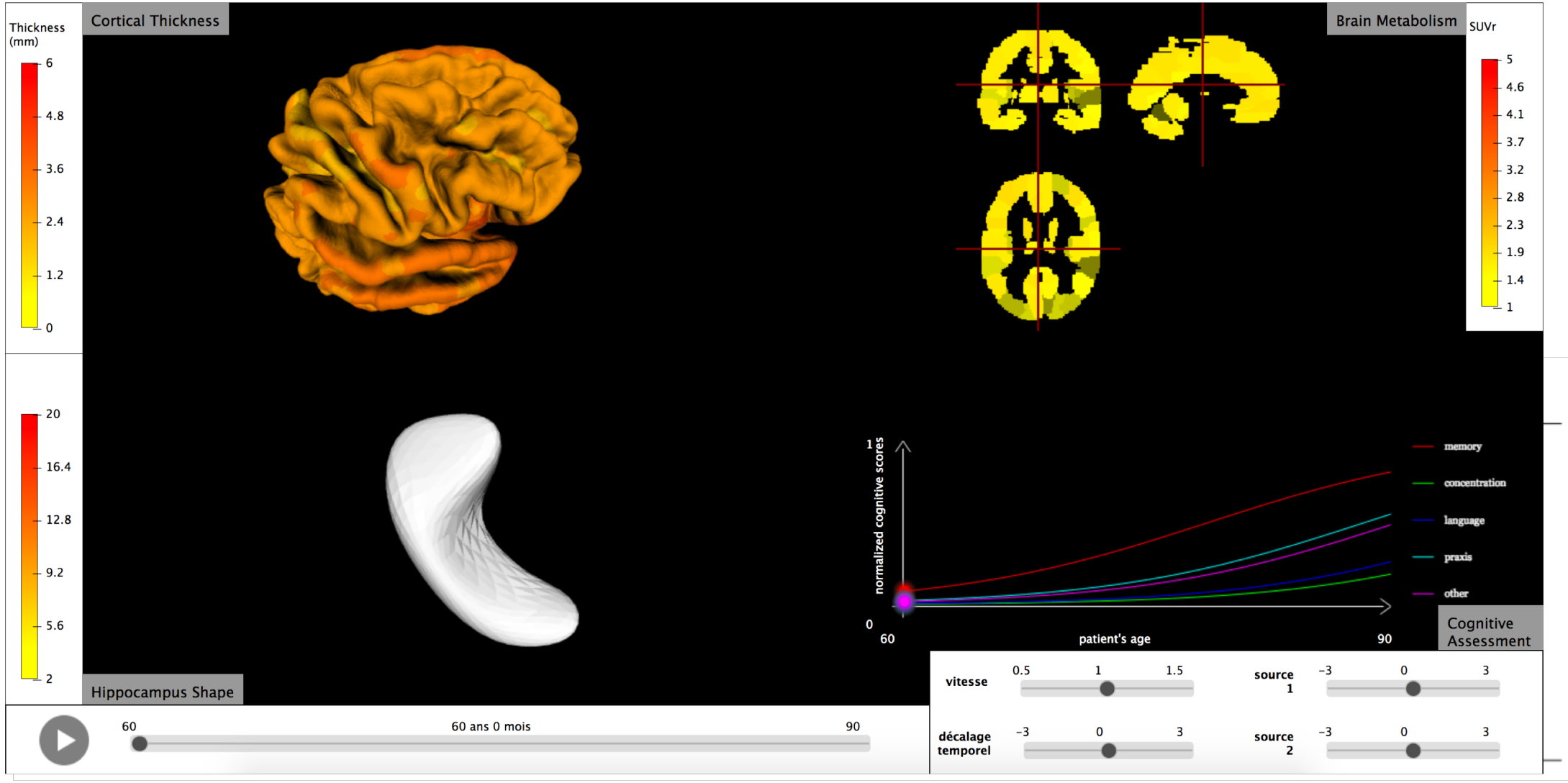
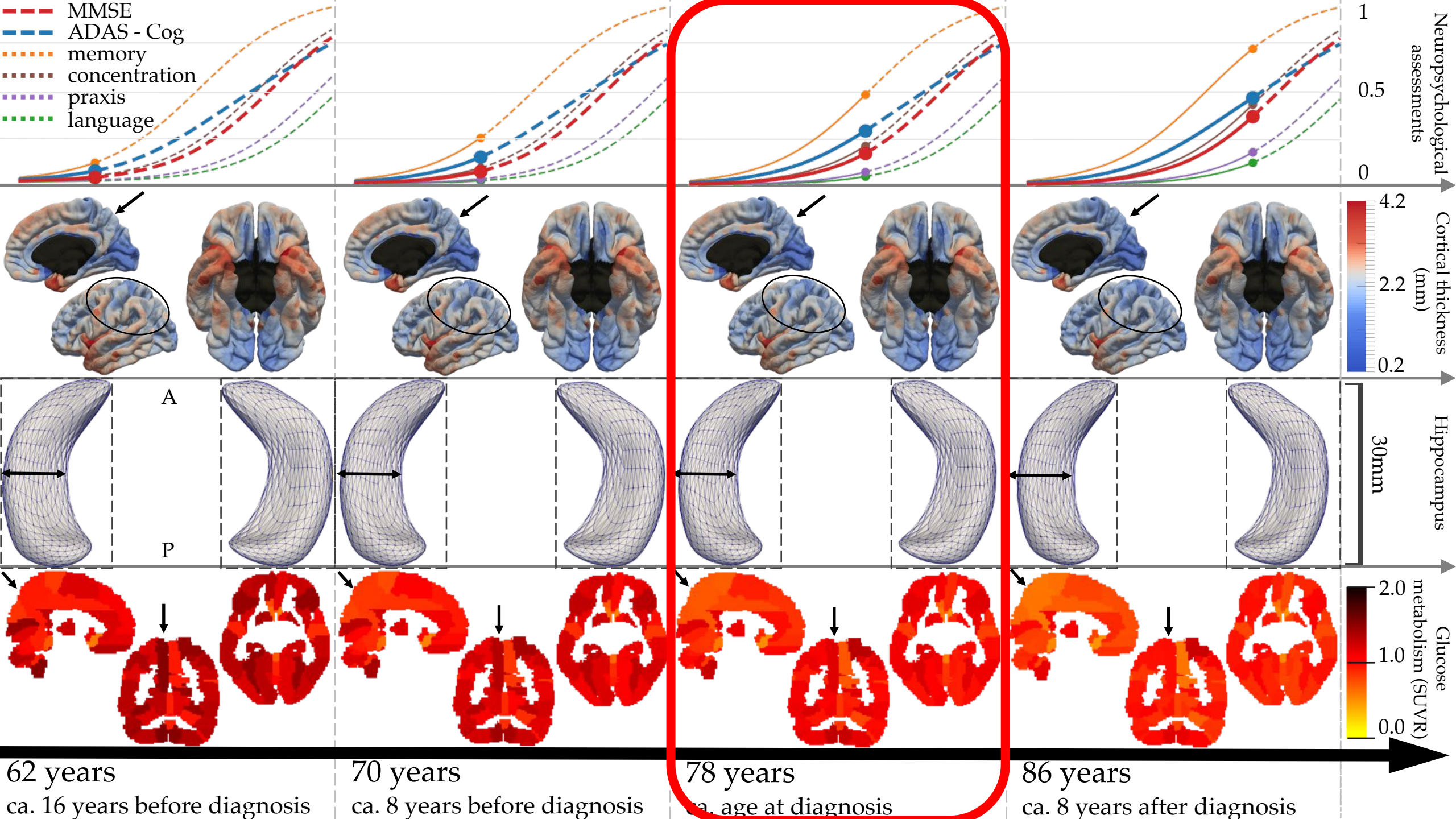
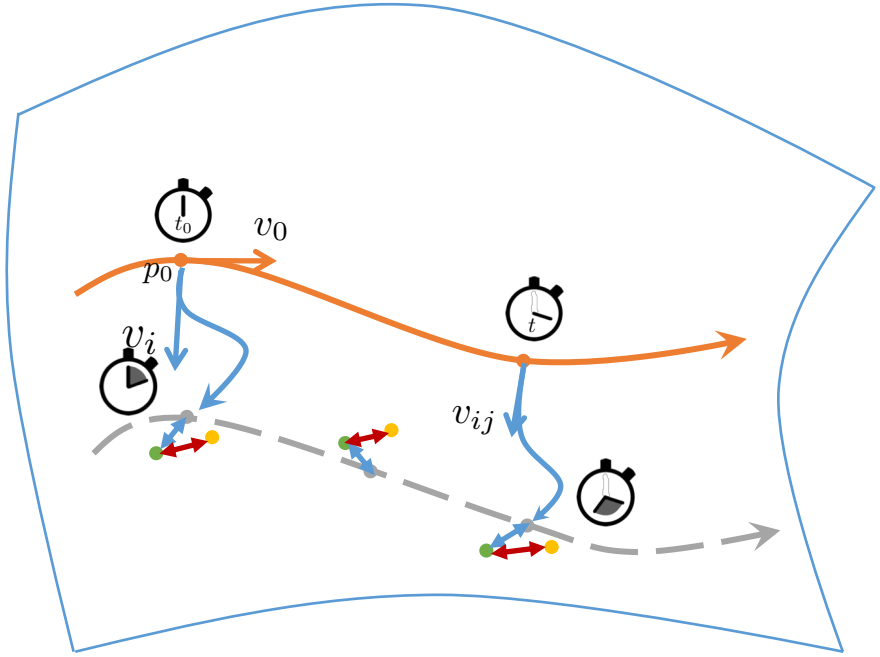
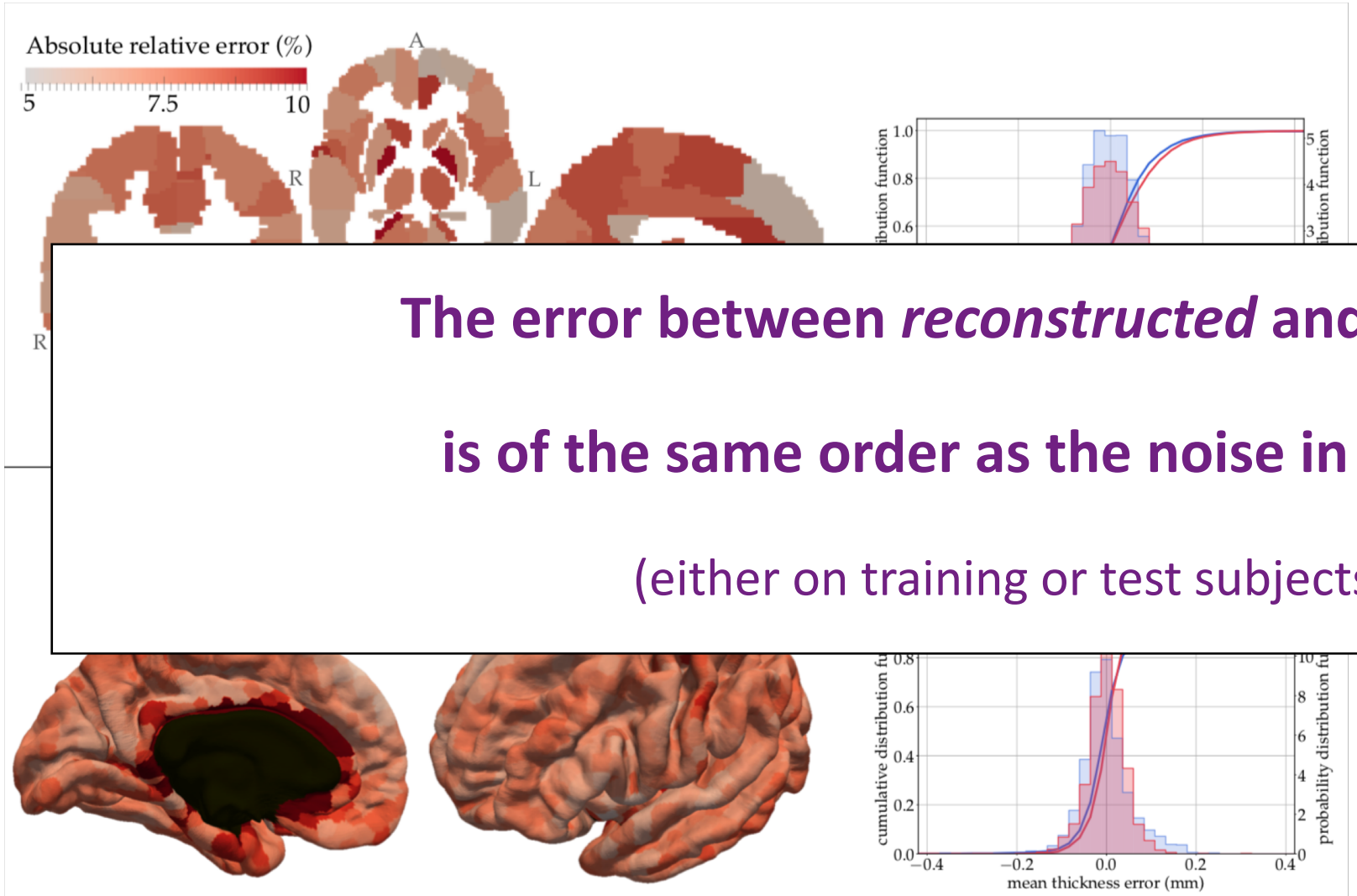



MMSE
ADAS - Cog
memory
concentration
praxis
language
1
0.5
0
Neuropsychological assessments
4.2
2.2
0.2
Cortical thickness (mm)
A
P
30mm
Hippocampus
2.0
1.0
0.0
Glucose metabolism (SUVR)
62 years
ca. 16 years before diagnosis
70 years
ca. 8 years before diagnosis
78 years
ca. age at diagnosis
86 years
ca. 8 years after diagnosis

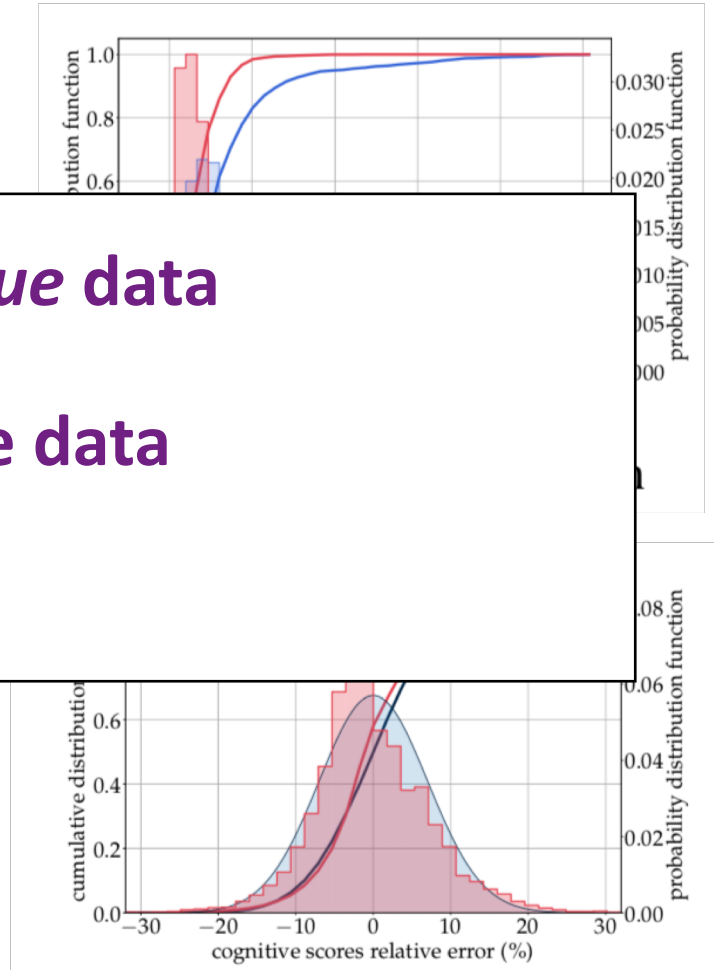



- **Personalize these models to individual subjects by optimizing:**
  - Time-shift
  - Acceleration factor
  - Space shifts
- **Reconstruction errors**
  - Goodness-of-fit (on training data)
  - Generalization to unseen data (CV)
- **Uncertainty on measurements**
  - MRI data: test / re-test images
  - PET data: consecutive images of cognitively normal subjects w/o amyloidosis
  - Cognitive assessments: literature review

## Blue: distribution of noise data  Red: distribution of reconstruction errors




(b) Cortical Thickness maps

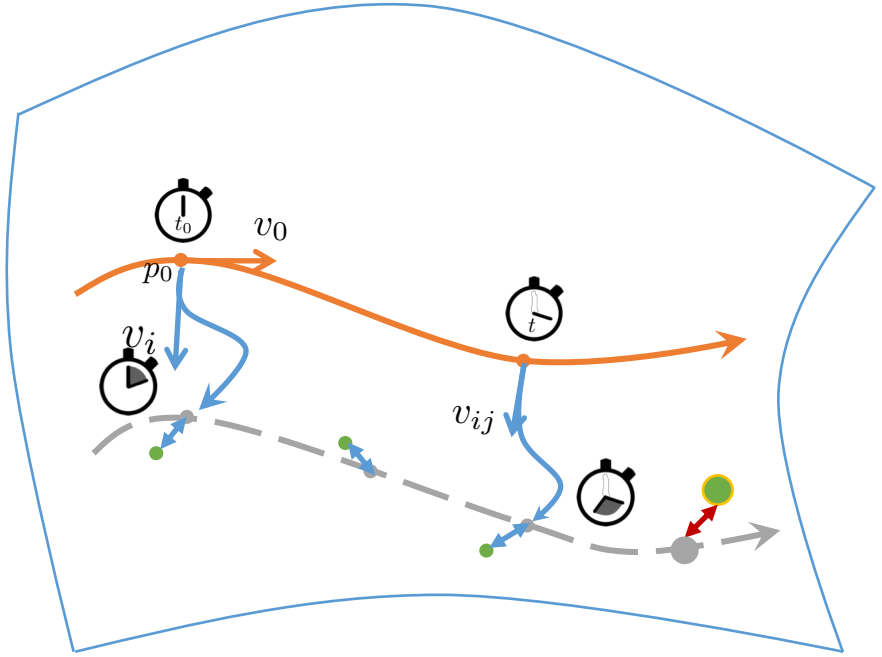



(e) Neuro-psychological assessments

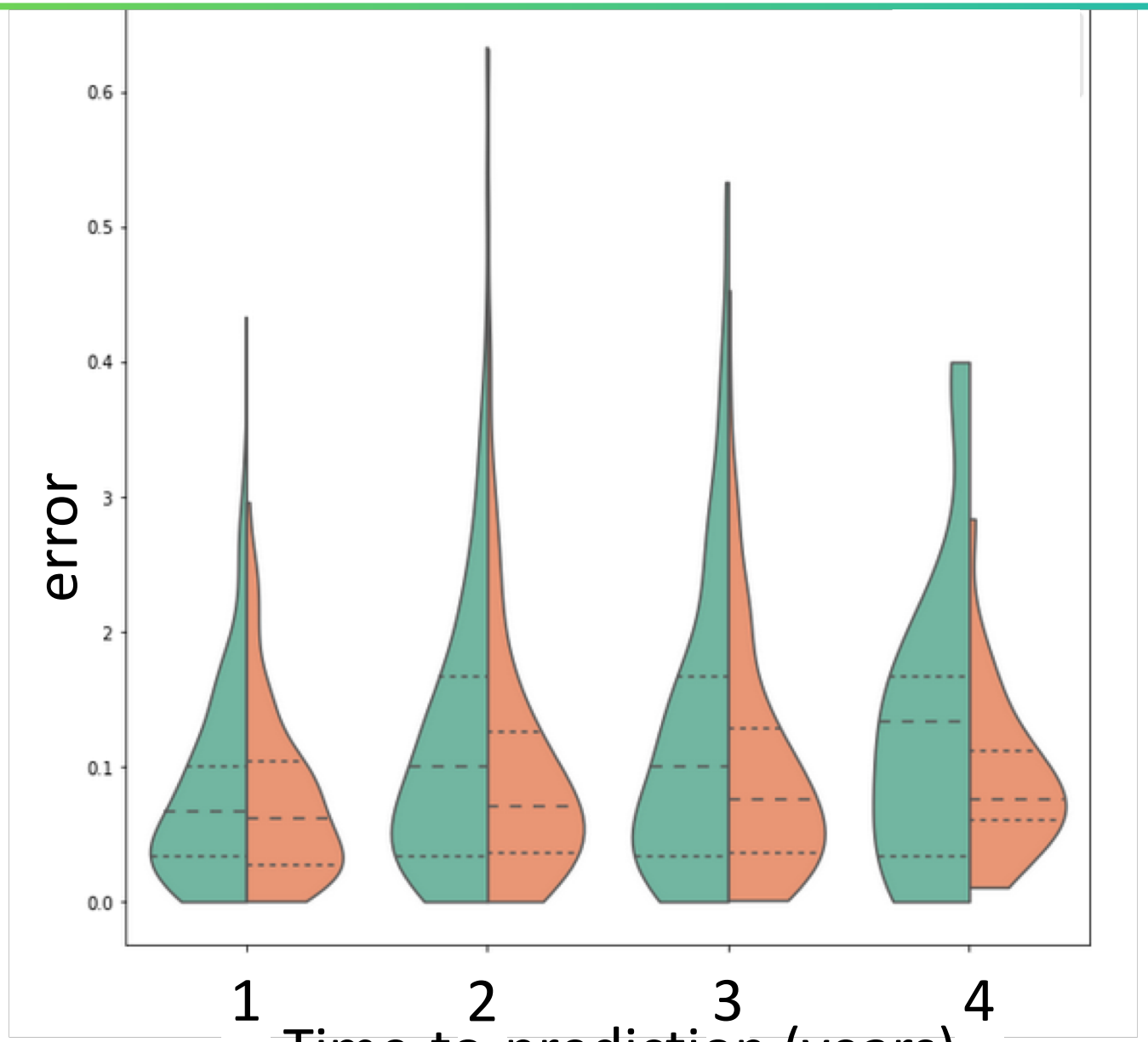
**The error between *reconstructed* and *true* data**

**is of the same order as the noise in the data**

(either on training or test subjects)

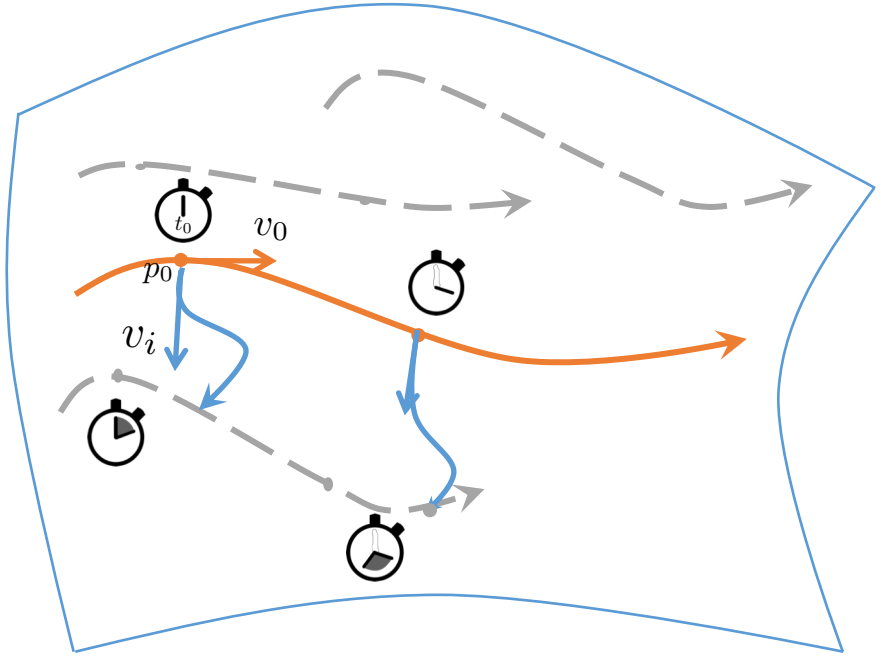



- **Simulate disease progression, and extrapolate in the future**
- **Measure prediction errors**




Constant progression

Personalized simulation




- **Simulate a cohort of virtual patients**
- **Sample virtual patients' trajectories**
- **Build a synthetic data set**

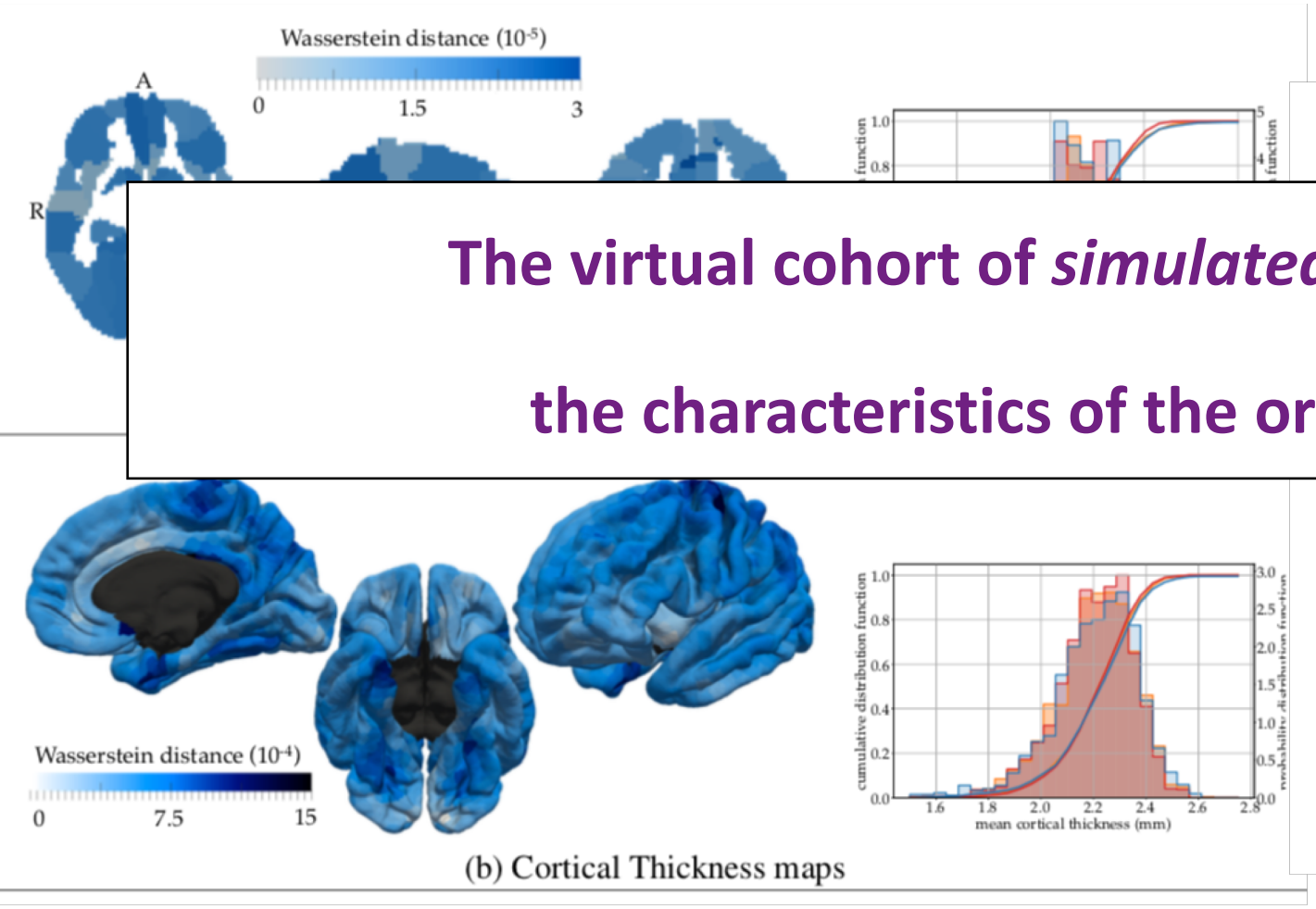
**For validation, we reproduce a virtual cohort with same characteristics as ADNI (sex ratio, number of subjects, distribution of time-points per subjects)**

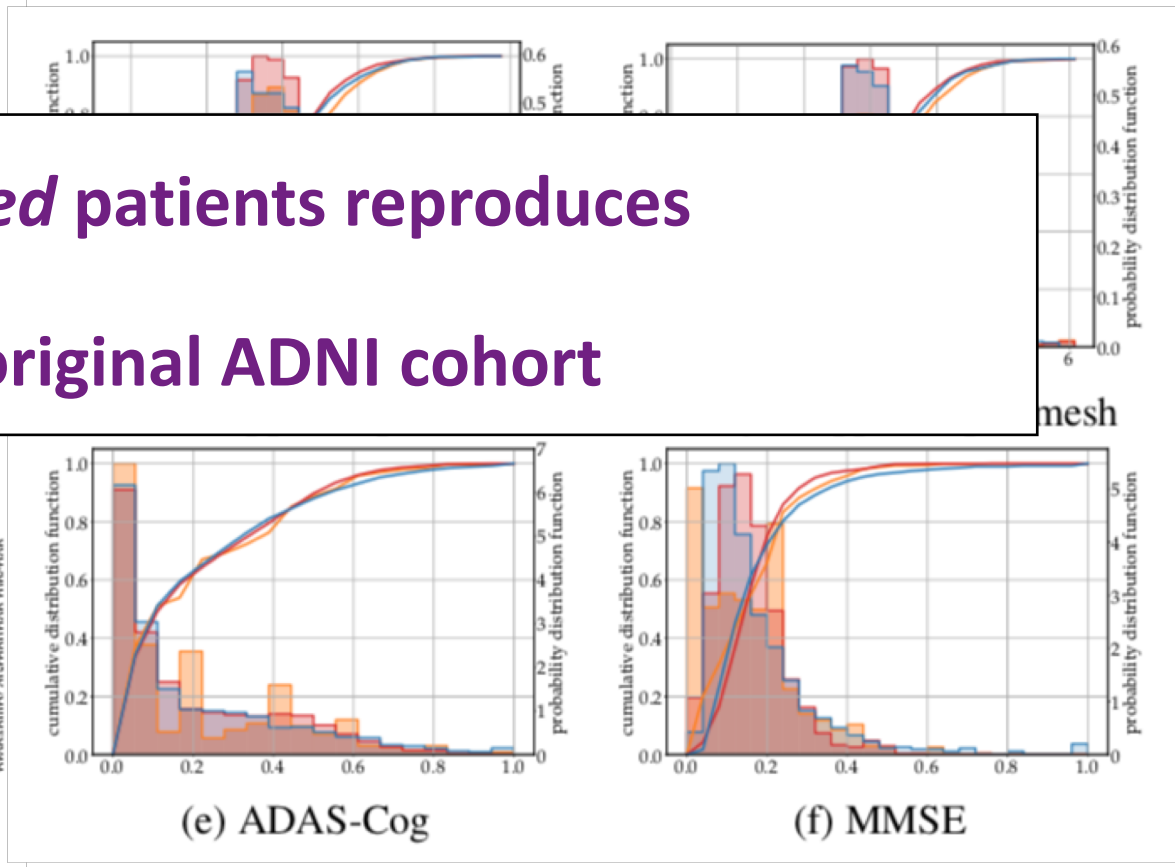
**Blue: characteristics of simulated data** **Red: characteristics of reconstructed data**

**Orange: characteristics of original data**

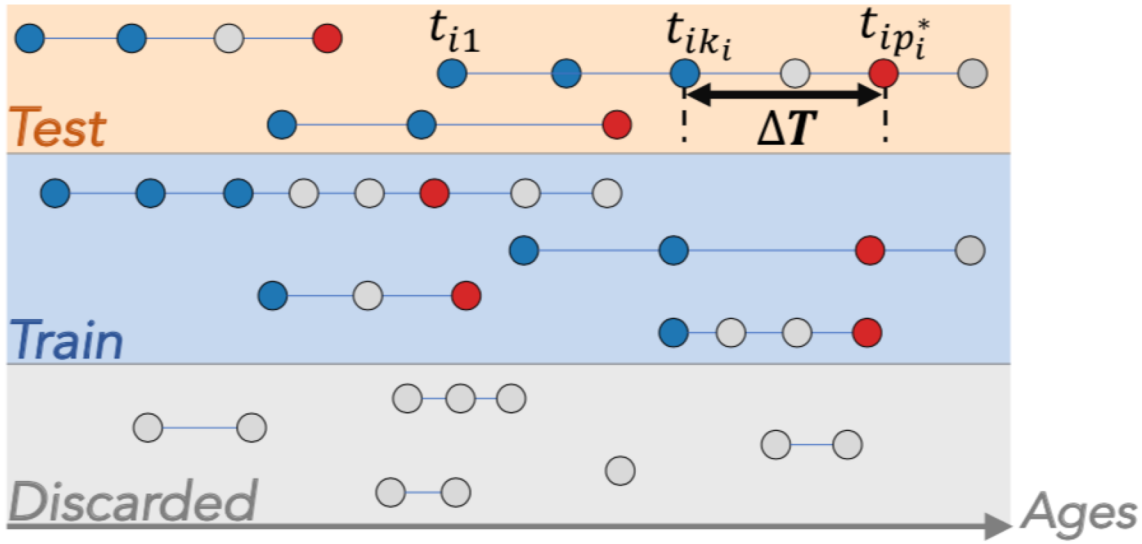
**The virtual cohort of *simulated* patients reproduces**

**the characteristics of the original ADNI cohort**



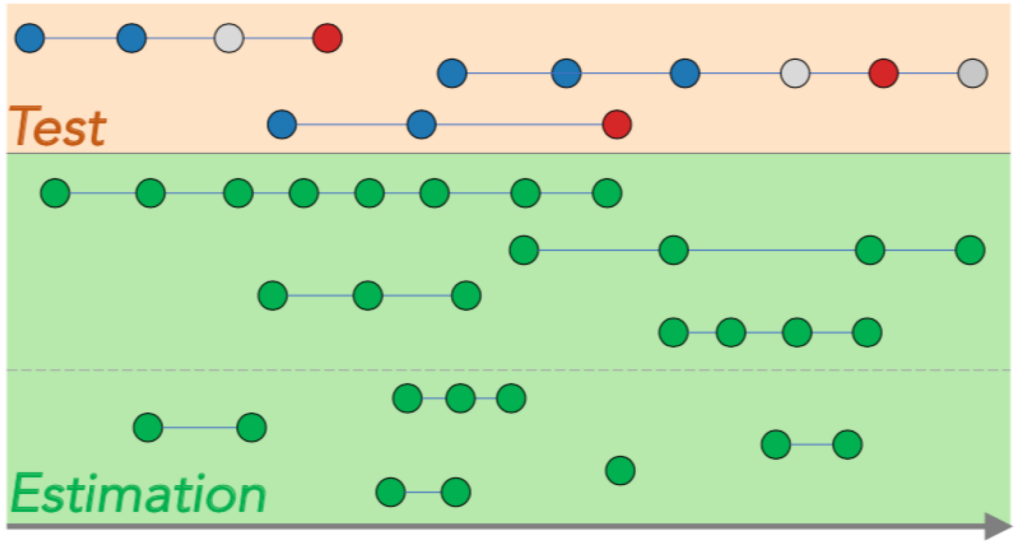



STANDARD PREDICTION SETTING

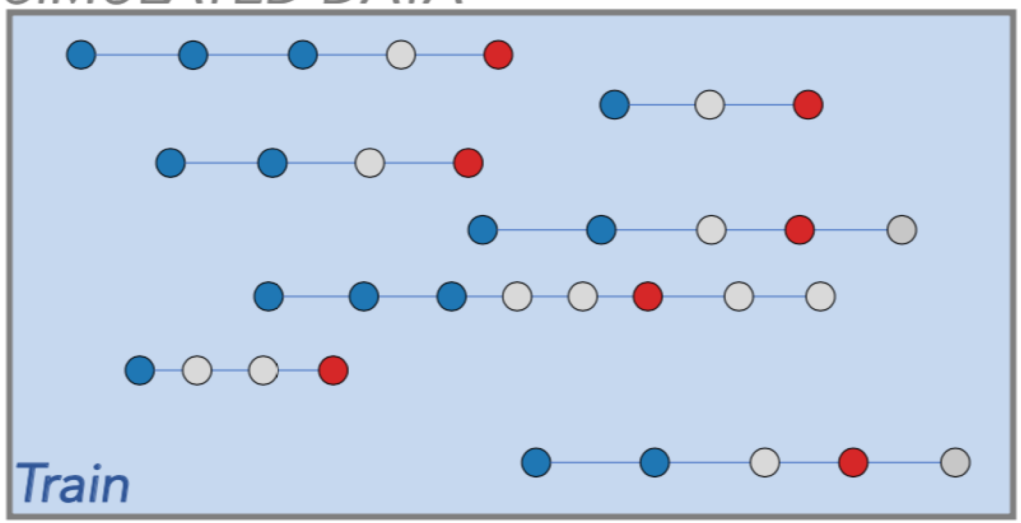


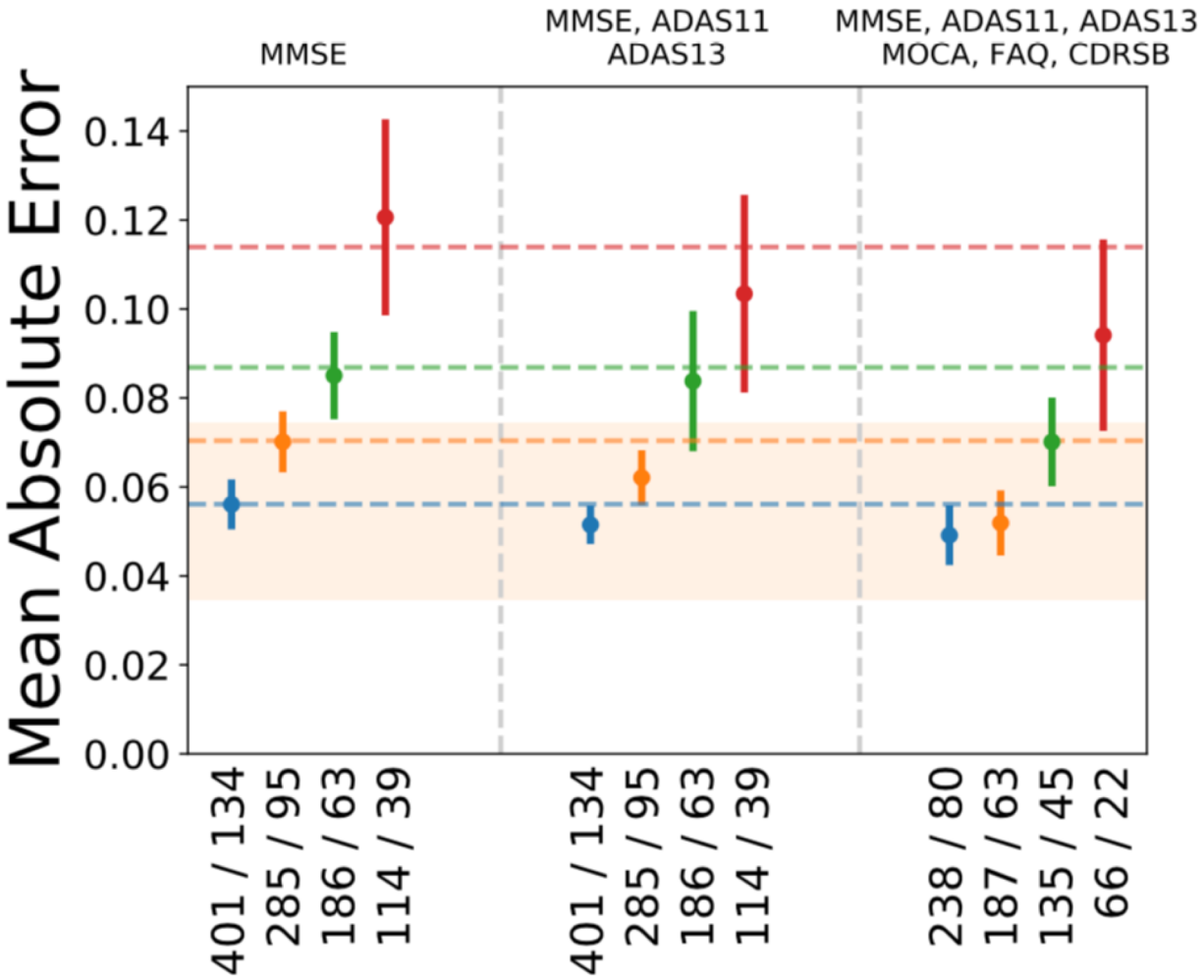

- Training observation
- Observation to predict
- Discarded observation
- Estimation observation

PREDICTION WITH SIMULATED DATA

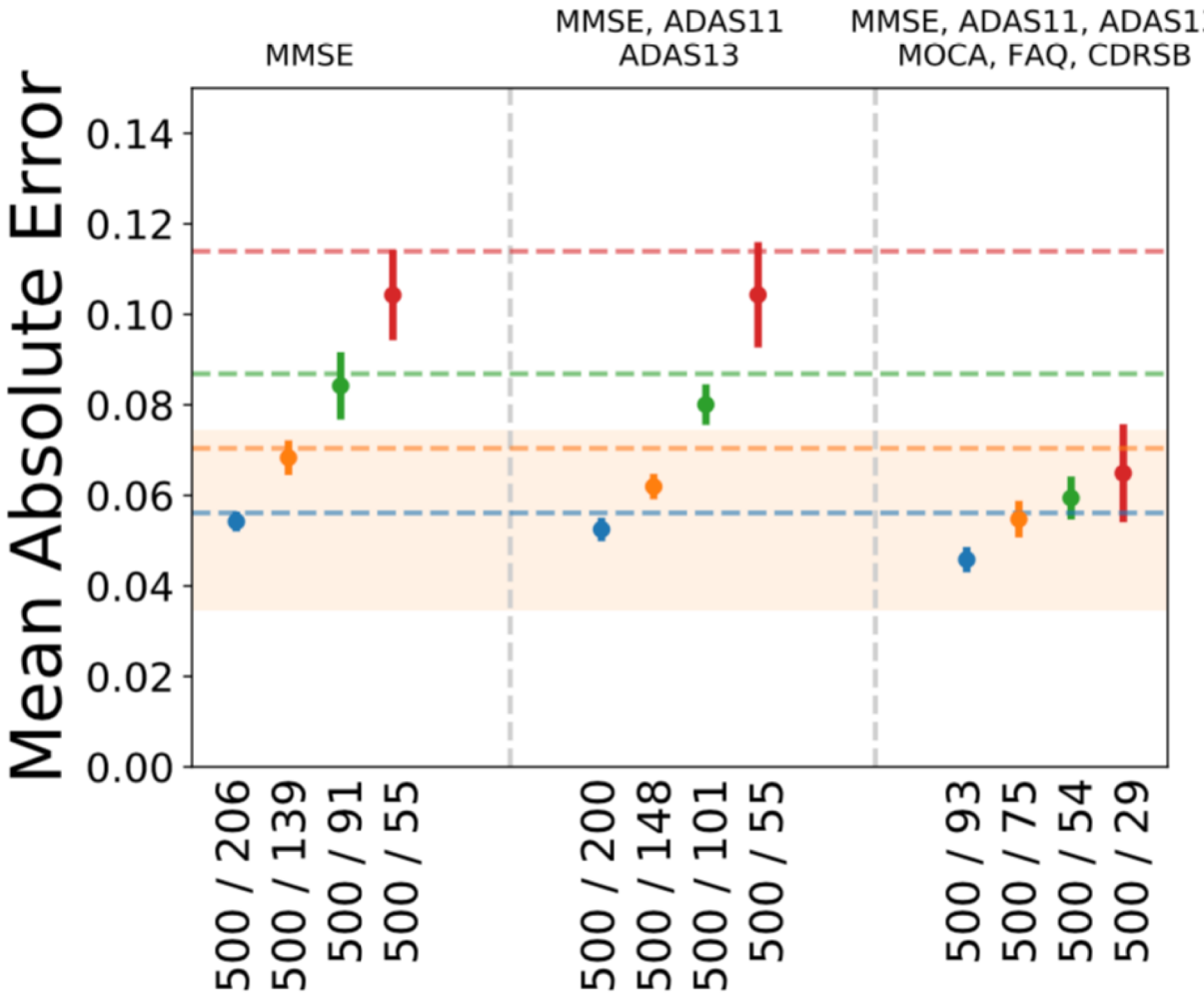



SIMULATED DATA



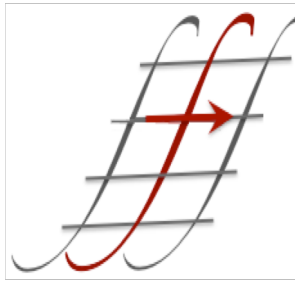



(a) Standard prediction




(b) Augmented data

- Multi-modal model of Alzheimer's disease progression
  - **Fits individual data with the same precision as the noise**
  - **Simulate and predict future disease progression at the individual level**
  - **Simulates synthetic data sets indistinguishable from the original ones (same statistics)**
    - Data augmentation & temporal resampling – soon a release of *ADNI-One Million*



Deformetrica

conda install -c aramislab deformetrica


To be released soon

www.digital-brain.org

Koval et al., Simulating AD progression with personalised brain models, preprint, 2018

| | | | hypo-metabolism (FDG-PET) | hippocampus atrophy (MRI) left hemisphere | | hippocampus atrophy (MRI) right hemisphere | | cortical thinning (MRI) | | cognitive decline (ADAS+MMSE) | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| genetic | gender female vs. male | speed factor | | $\times 1.27$ | CI=[1.11, 1.45] p=2.26e-3** | $\times 1.26$ | CI=[1.08, 1.45] p=6.15-3** | | | $\times 1.46$ | CI=[1.10, 1.92] p=8.42e-3 ** |
| | | time-shift | | $-33.6$ | CI=[-55.8, -11.6] p=3.71e-3** | $-29.0$ | CI=[-53.0, -4.91] p=2.31e-2* | | | $-36.8$ | CI=[-11.6, -62.0] p=4.48e-3 ** |
| | | space-shift | | $\pm 0.55$ | CI=[0.28, 0.82] p=4.00e-4*** | $\pm 0.60$ | CI=[0.34, 0.86] p=3.89e-5**** | $\pm 0.48$ | CI=[0.22, 0.75] p=2.24e-3 ** | | |
| | APOE-$\varepsilon$4 carrier vs. non-carrier | speed factor | | $\times 1.17$ | CI=[1.02, 1.33] p=2.77e-2* | | | $\times 1.42$ | CI=[1.12, 1.82] p=2.17e-2* | $\times 1.25$ | CI=[1.03, 1.51] 2.17e-2 * |
| | | time-shift | | $-45.0$ | CI=[-66.9, -23.2] p=1.57e-4*** | $-36.8$ | CI=[-60.5, -13.0] p=4.27e-3** | | | | |
| | | space-shift | | | | | | | | | |
| biological | amyloid positive vs. negative | speed factor | | $\times 1.18$ | CI=[1.06, 1.32] p=8.20e-3** | $\times 1.23$ | CI=[1.09, 1.39] p=4.03e-3** | | | | |
| | | time-shift | | | | | | | | $-21.9$ | CI=[-2.5,-41.2] p=2.70e-2 * |
| | | space-shift | | | | | | $\pm 0.28$ | CI=[0.05, 0.50] p=2.24e-3 ** | | |
| environmental | marital married vs. non-married | speed factor | | $\times 1.25$ | CI=[1.07, 1.48] p=1.08e-2* | | | | | | |
| | | time-shift | | $-59.5$ | CI=[-86.6, -32.5] p=1.06e-4*** | $-52.7$ | CI=[-82.2, -23.2] p=1.28e-3** | | | $-32.6$ | CI=[1.8, 63.3] p=3.78e-2* |
| | | space-shift | | | | | | | | | |
| | education nb. of years of education | speed factor | | | | | | | | | |
| | | time-shift | | $-6.04$ | CI=[-9.67, -2.42] p=1.95e-3** | $-7.60$ | CI=[-11.55, -3.64] p=9.53e-4*** | | | | |
| | | space-shift | | | | | | | | | |