Modelling the Neuroanatomical Progression of Alzheimers Disease and Posterior Cortical Atrophy

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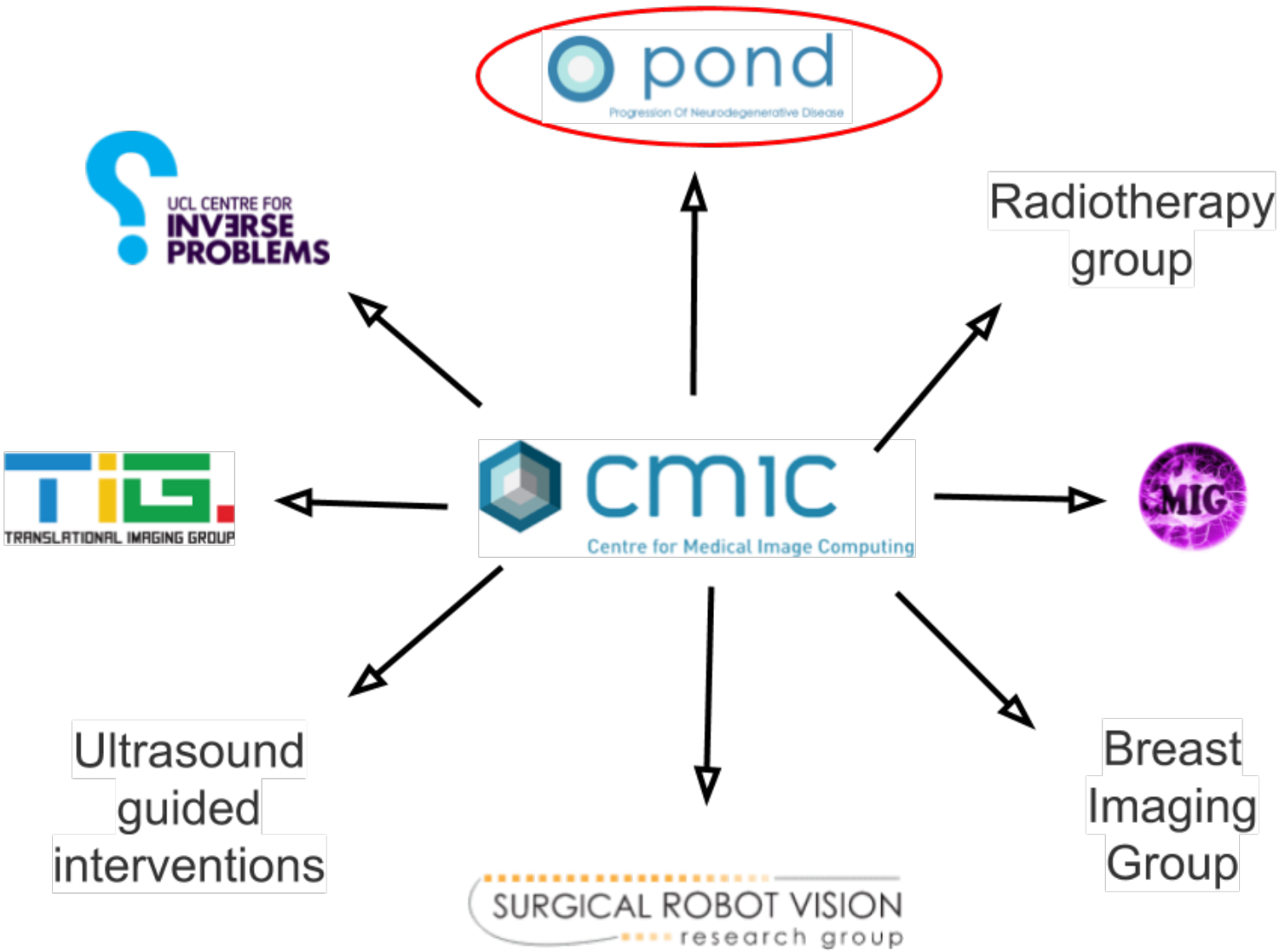
Medical Vision Group, Massachusetts Institute of Technology

About me

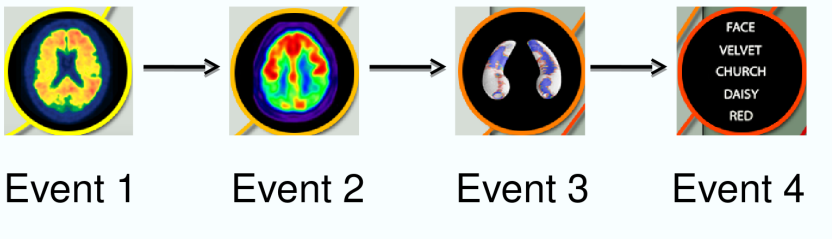
- Grew up in Pitesti, Romania
- 2010-2014: Studied a 4-year MEng in Computer Science at Imperial College London
- 2014-2019: PhD in Medical Imaging at UCL (with Daniel Alexander)
- 2019: Postdoc at MIT with Pollina Golland (working on image analysis of stroke)

Progression of Neurodegenerative Diseases (POND)

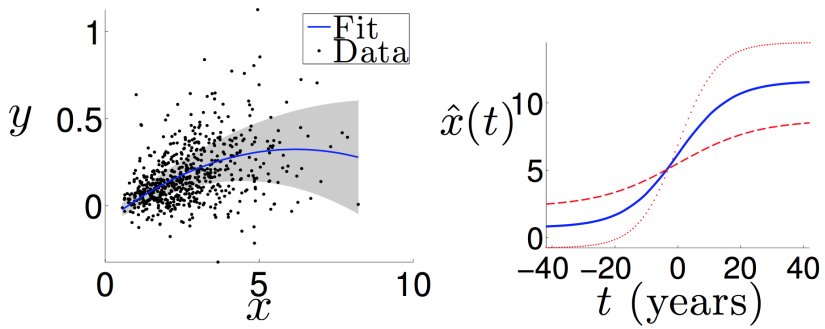


POND Aim: Develop Computational Models for Disease Progression

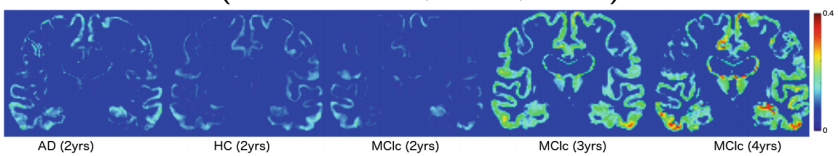
Event-Based Model
(Fontejin et al., Neuroimage, 2012)



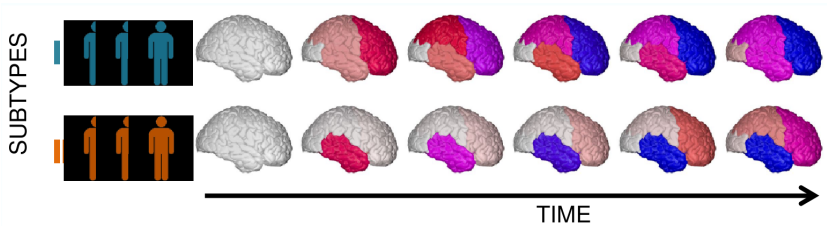
Differential Equation Model
(Oxtoby et al., submitted, 2017)



Gaussian-Process Regression
(Lorenzi et al., IPMI, 2015)

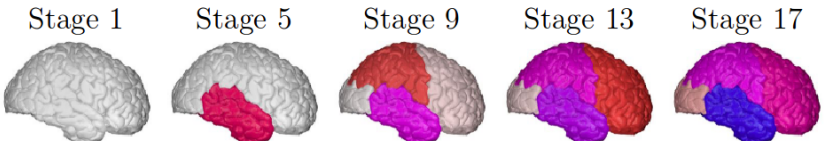


Subtype and Stage Inference
(Young et al., submitted, 2017)

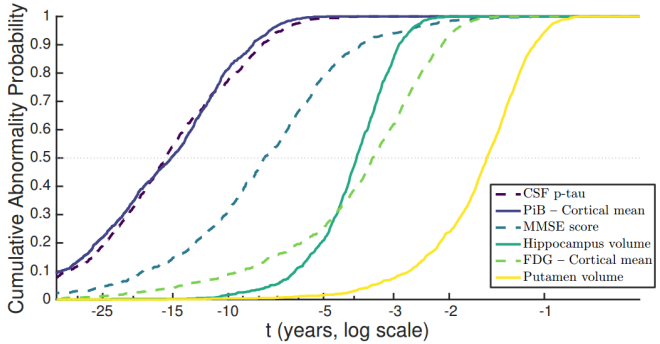


POND Aim 2: Apply the Models to Distinct Neurodegenerative Diseases

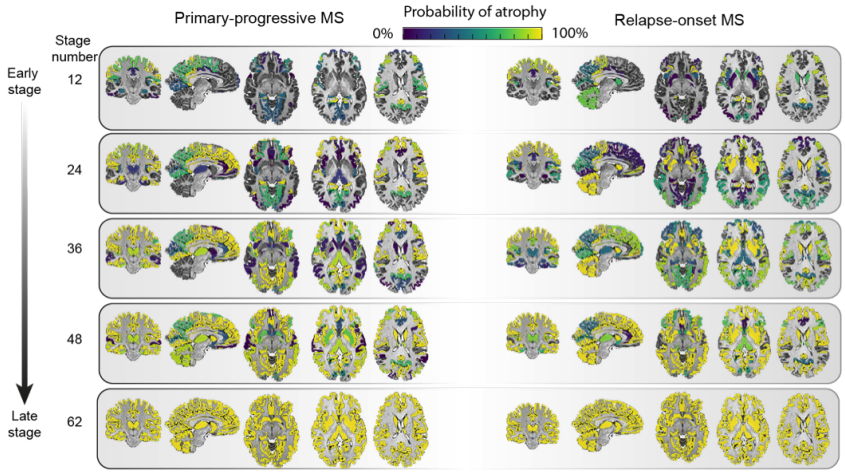
typical AD
(Young et al., Nature Comms., 2018)



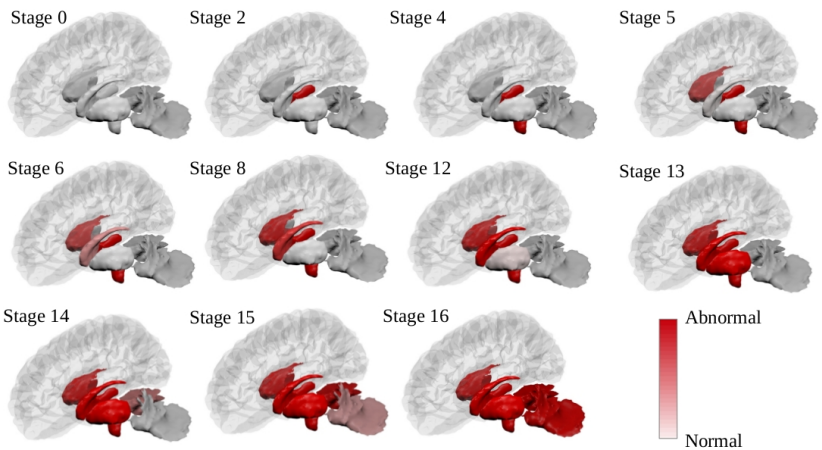
Familial AD
(Oxtoby et al., Brain, 2018)



Multiple sclerosis
(Eshaghi et al., Brain, 2017)

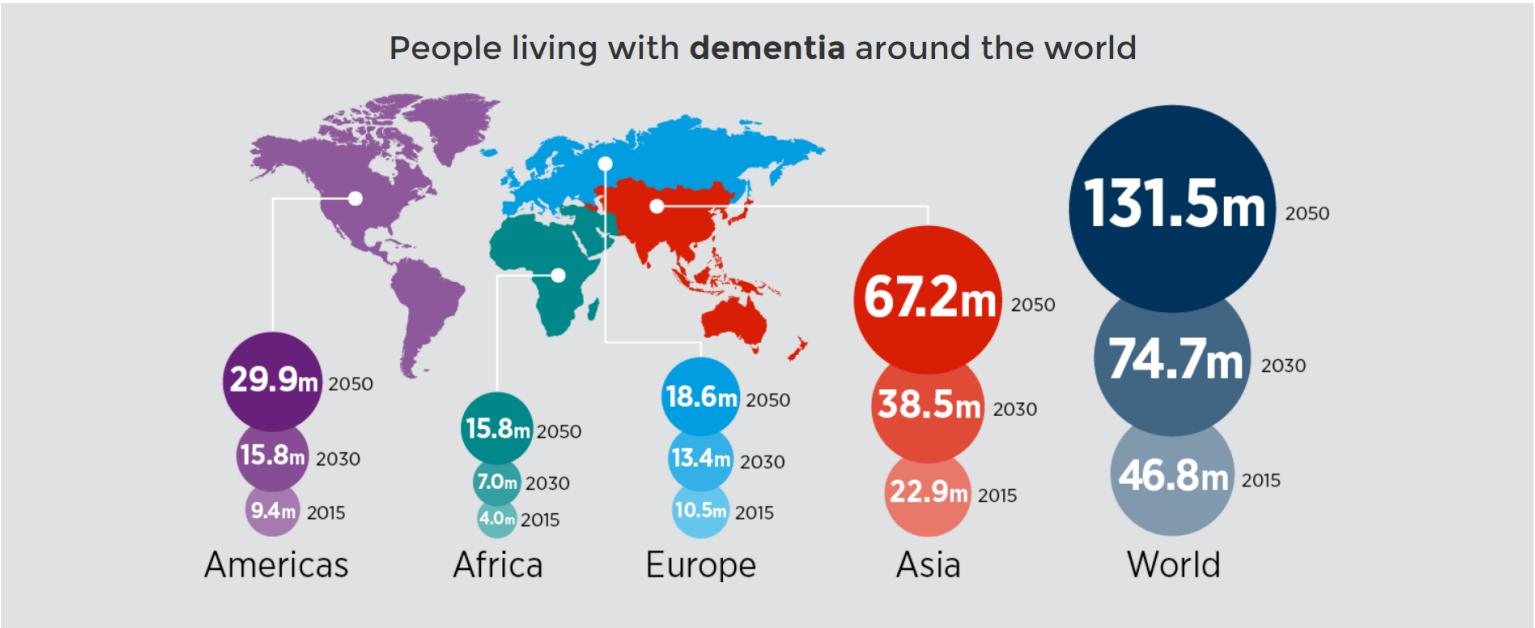


Huntington's disease
(Wijeratne et al., Ann. Clin. Neurol;, 2018)



Alzheimer's Disease is a Devastating Disease

- 46 million people affected worldwide



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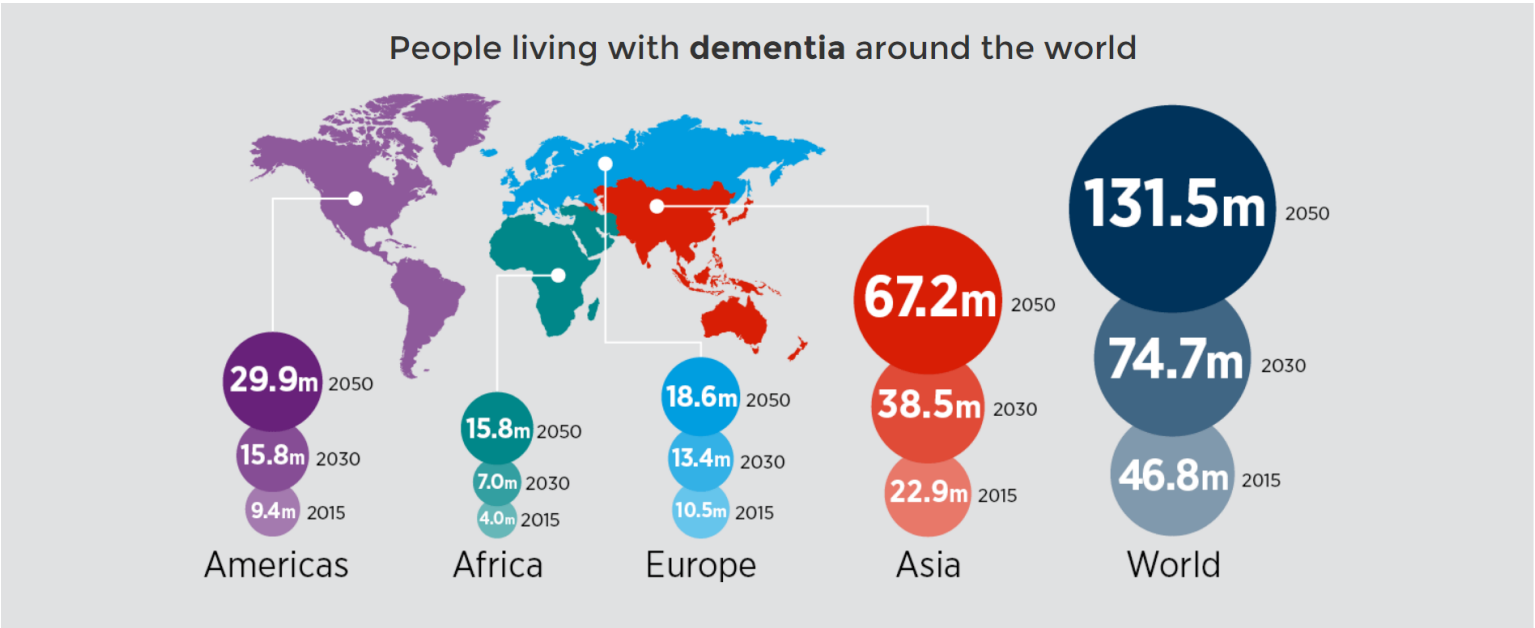

- No treatments available that stop or slow down cognitive decline
- Q: Why did clinical trials fail? A: Treatments were not administered early enough

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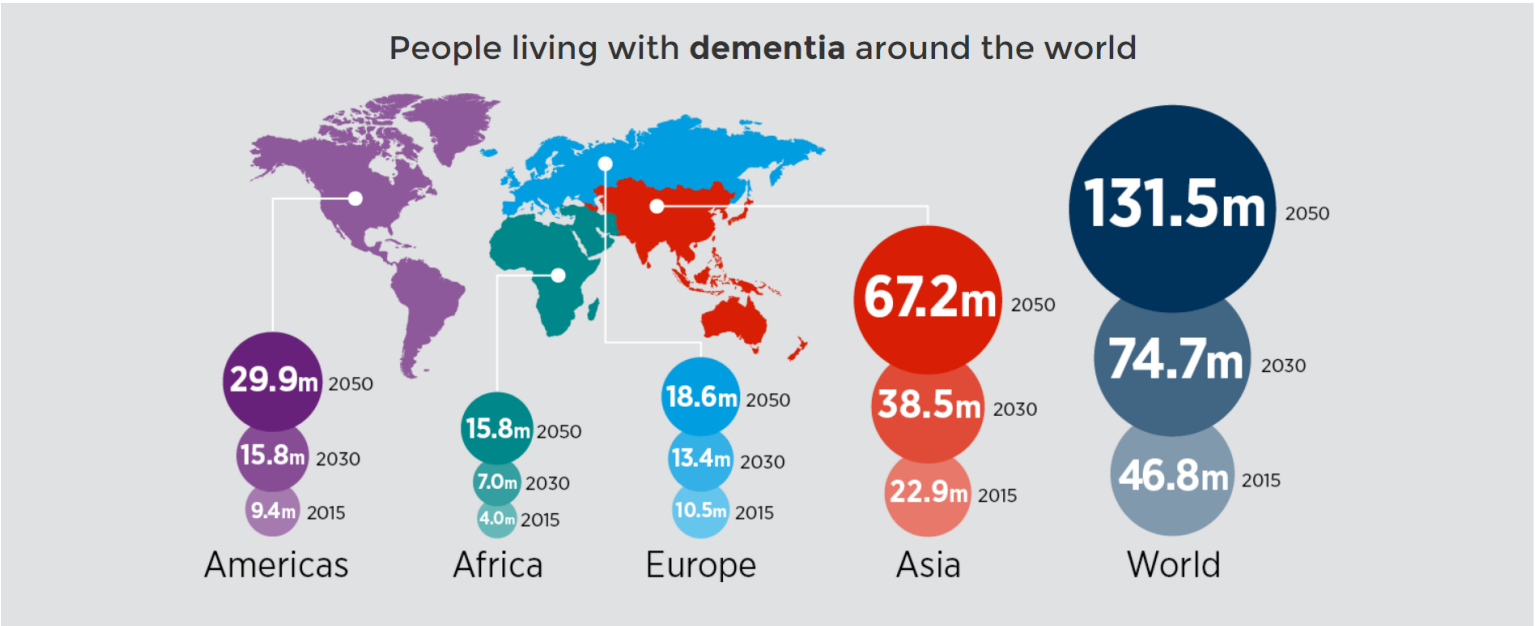
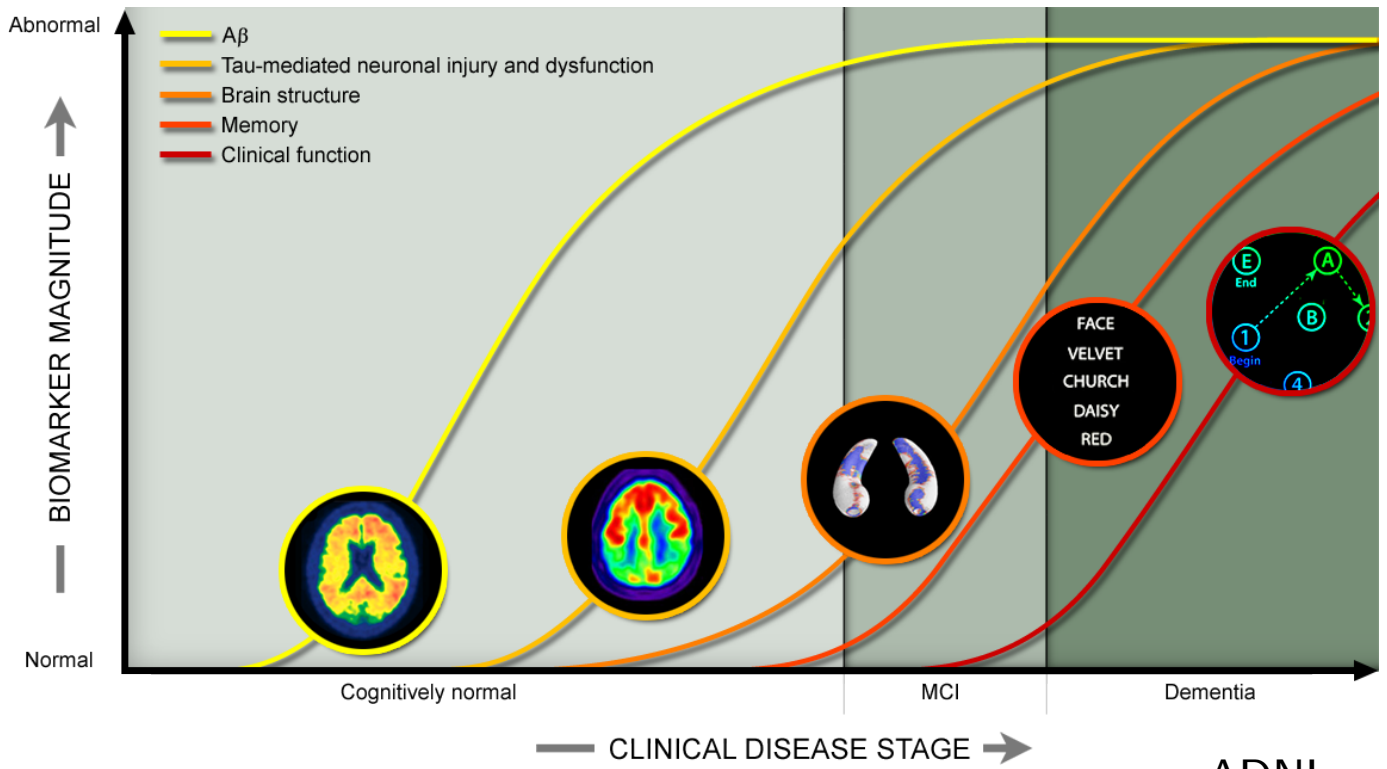


- No treatments available that stop or slow down cognitive decline
- Q: Why did clinical trials fail? A: Treatments were not administered early enough

- Q: How can we then identify subjects **early** in order to administer treatments?
- A: Biomarkers ...

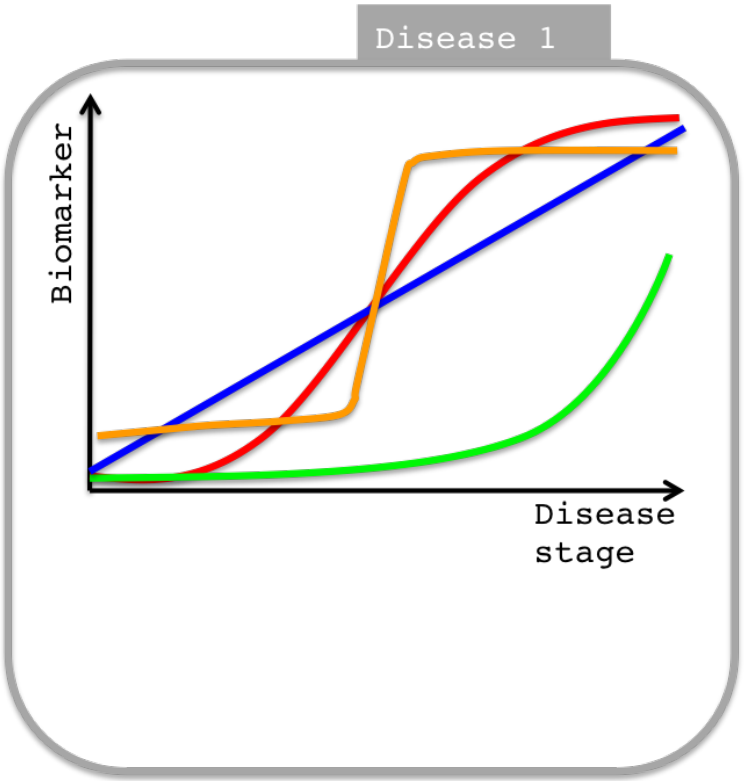
Biomarker Evolution creates a Unique Disease Signature that can be used for Staging Individuals in Clinical Trials



ADNI website

- Accurate disease staging $\rightarrow$ better patient stratification
- Problem: This is a "hypothetical" (i.e. qualitative) disease progression model
- Why construct a quantitative model?

Benefits of Quantitative Disease Progression Models



- Basic biological insight

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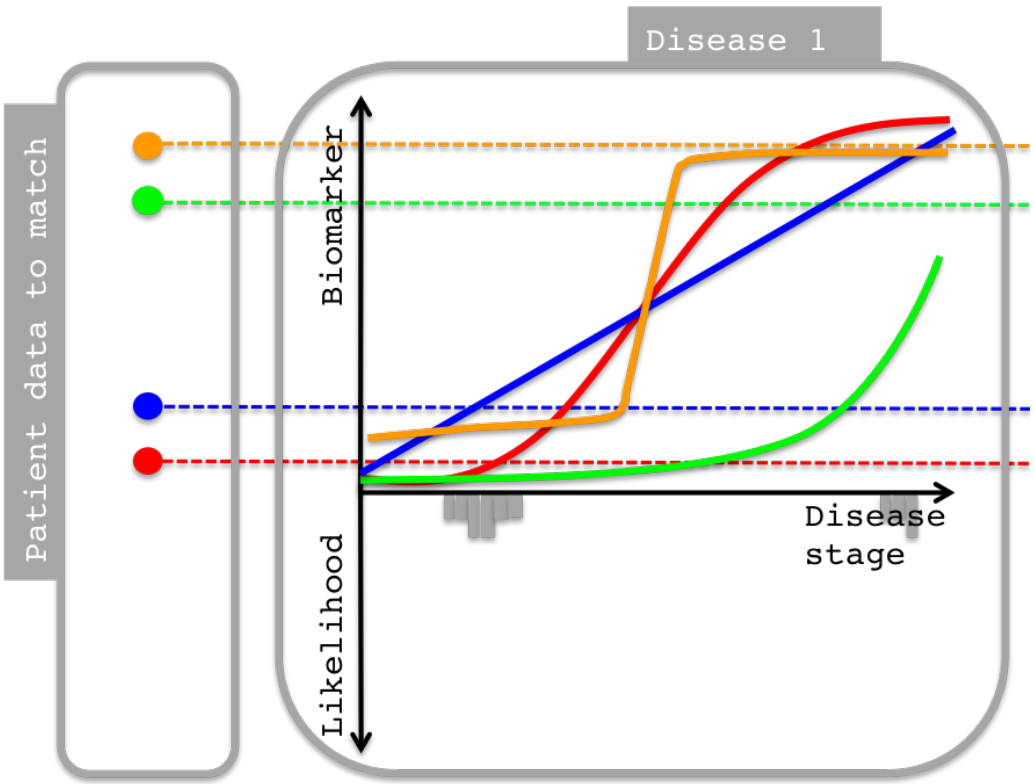

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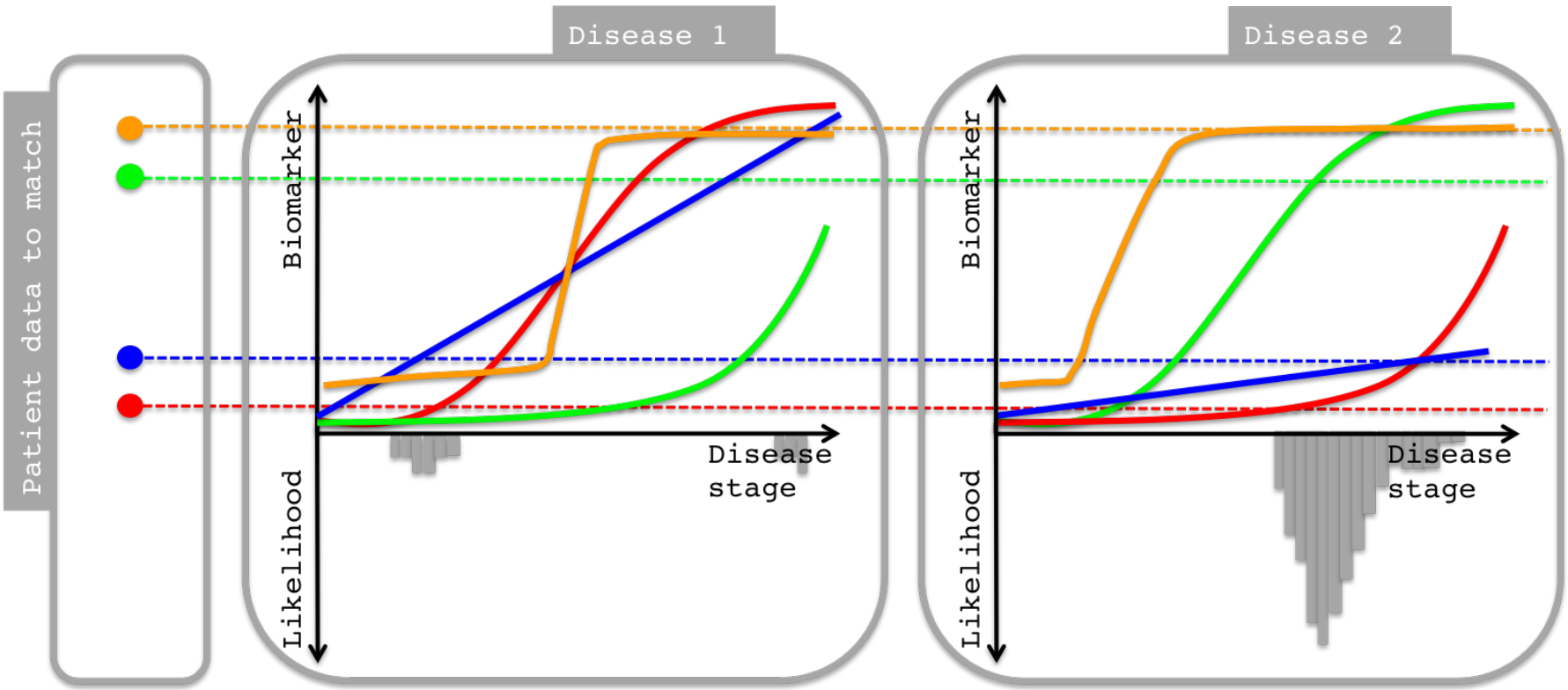

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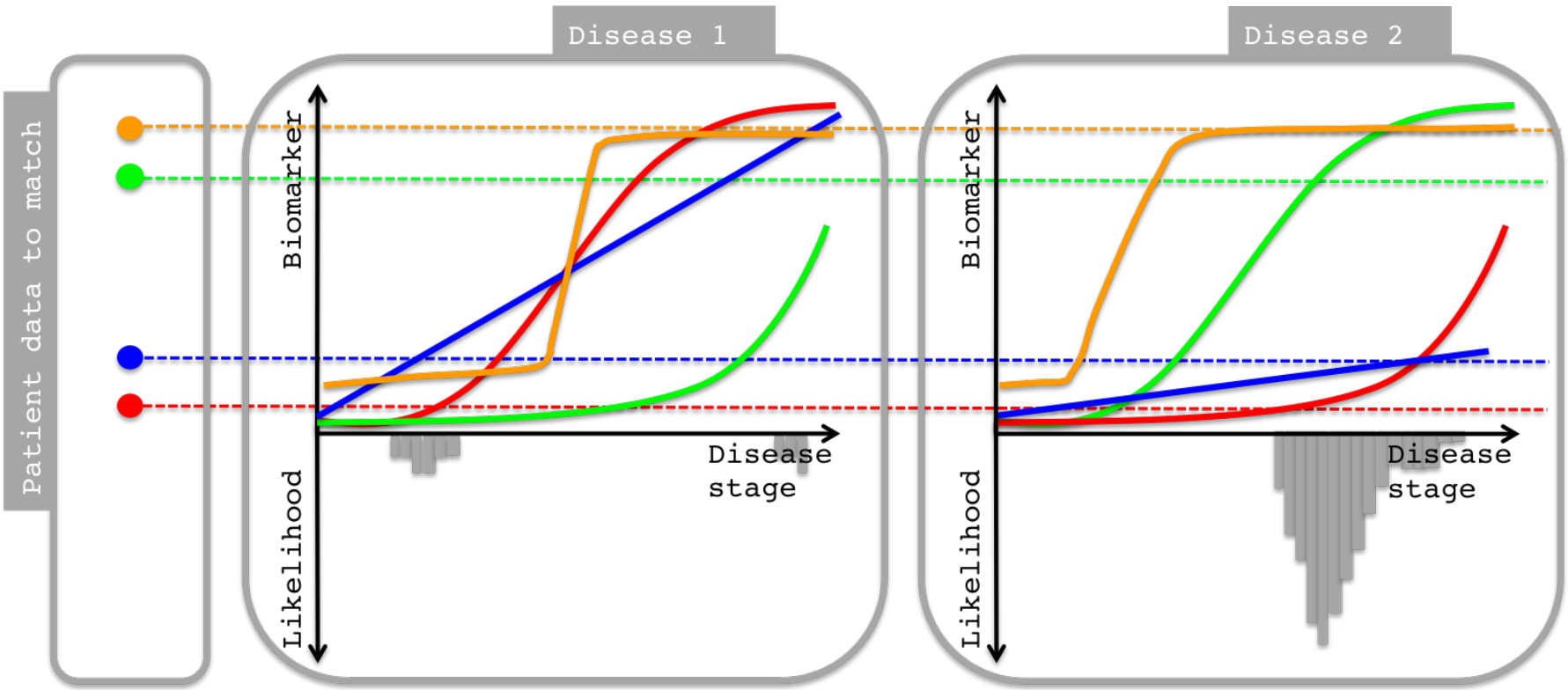

- Basic biological insight
- Staging can help stratification in clinical trials
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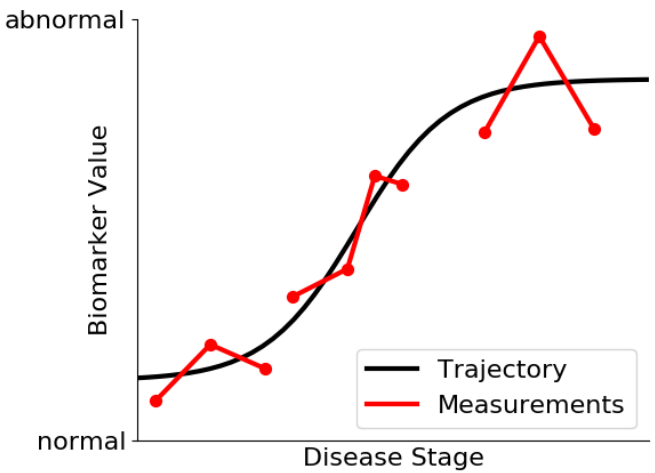
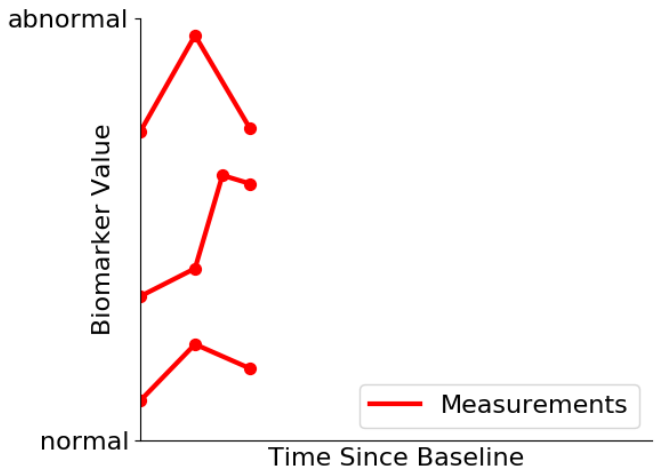
How can we build such a disease progression model?

Building a Quantitative Disease Progression Model is difficult



Building a Quantitative Disease Progression Model is difficult

what we have



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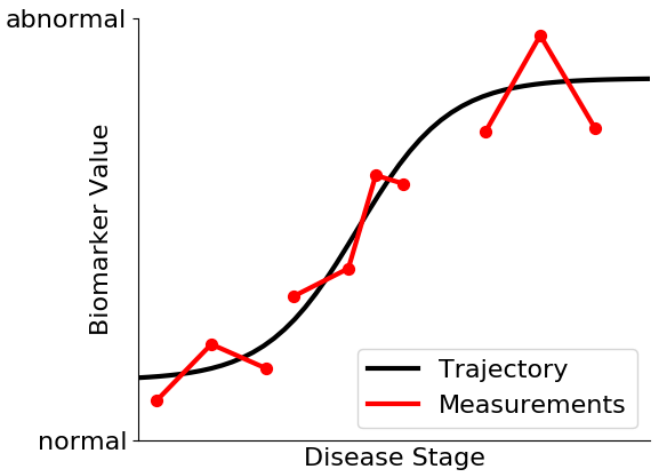

Challenges:

- Patients are at unknown disease stages

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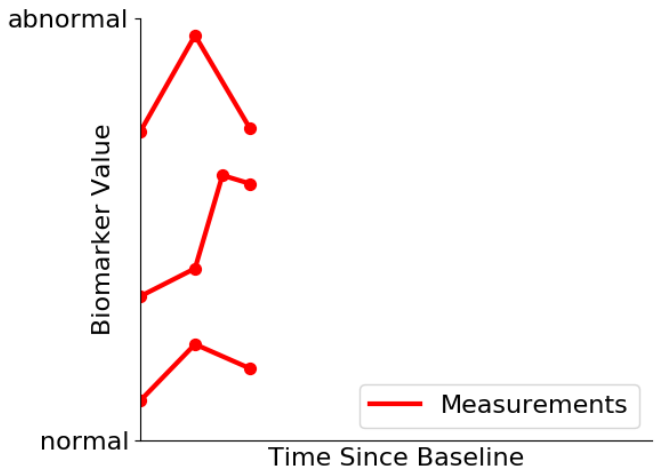

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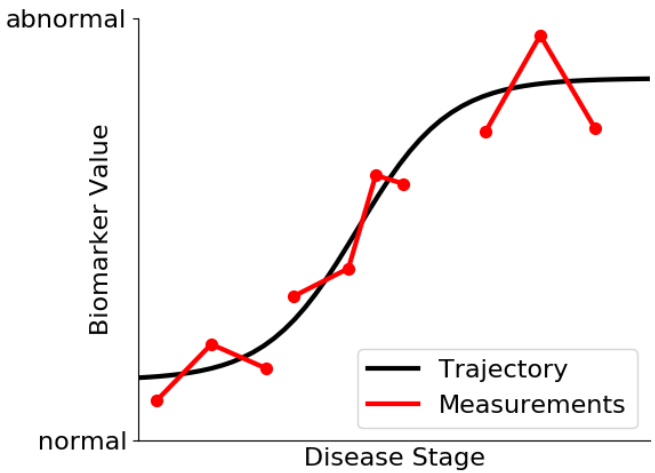

Challenges:

- Patients are at unknown disease stages
- X-axis are not the same (need to construct the disease stage axis)

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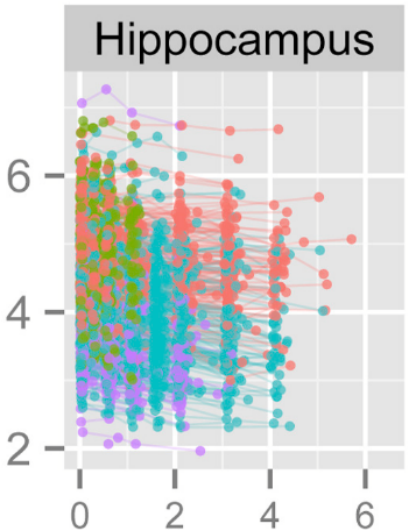

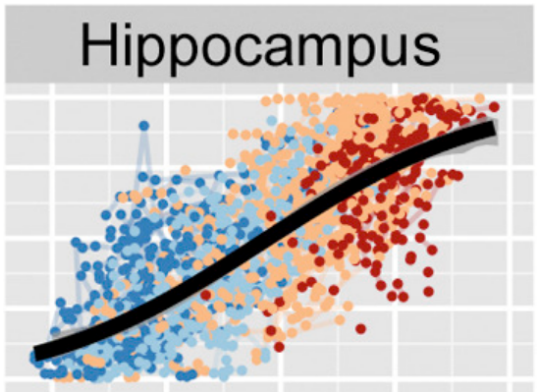

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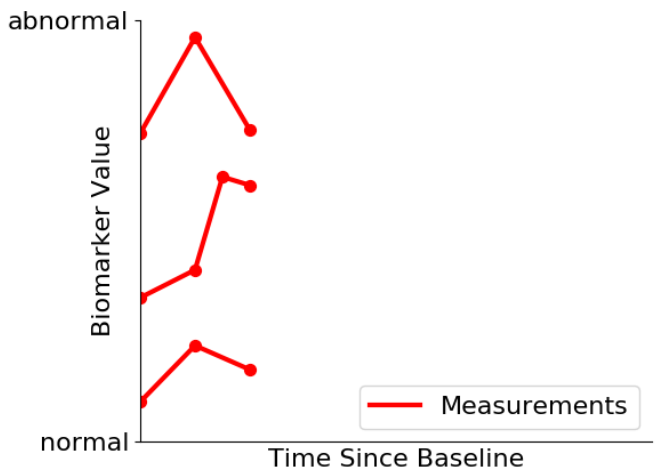

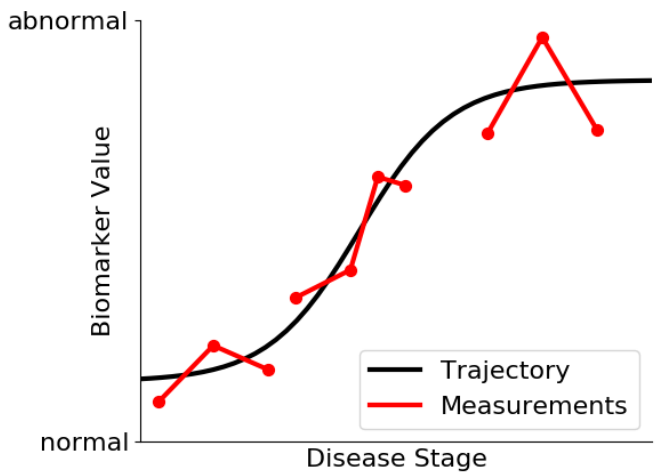

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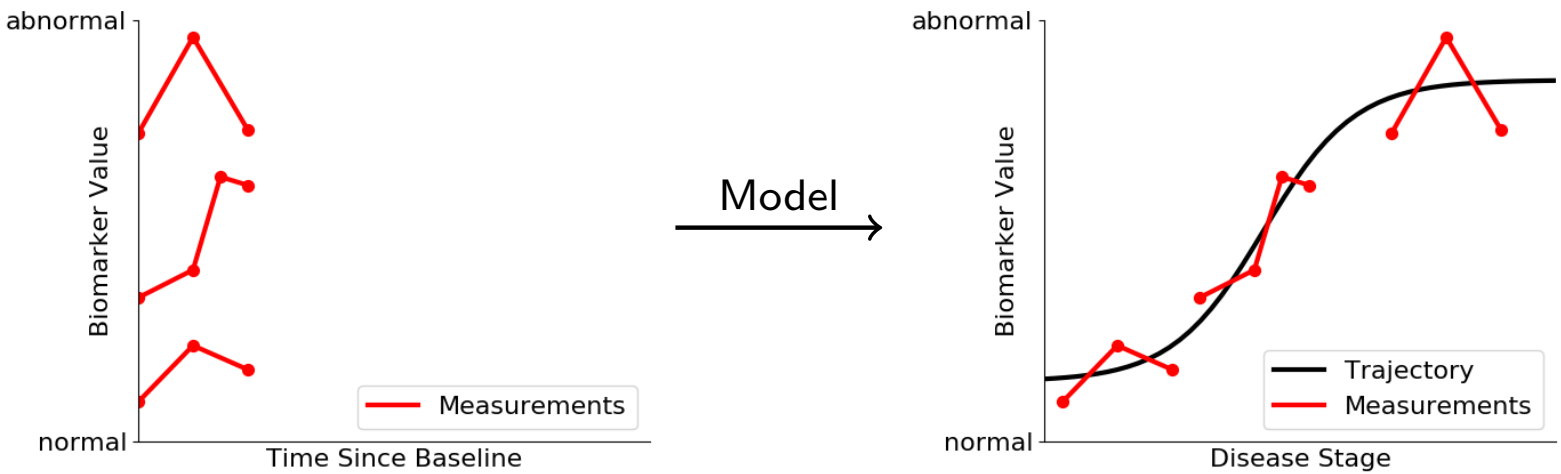

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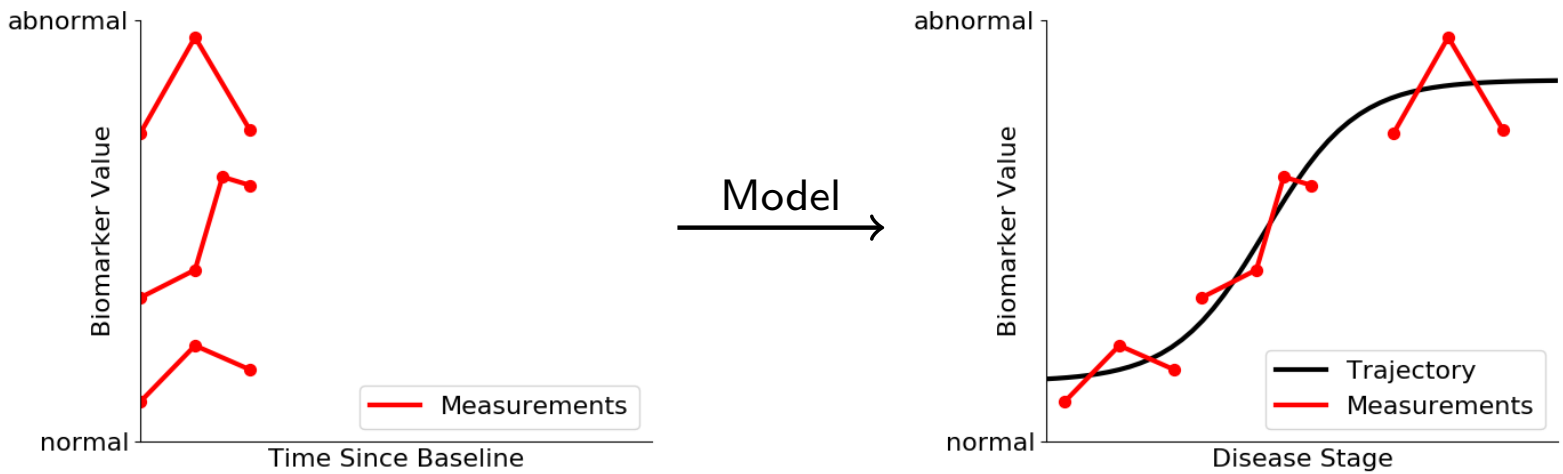
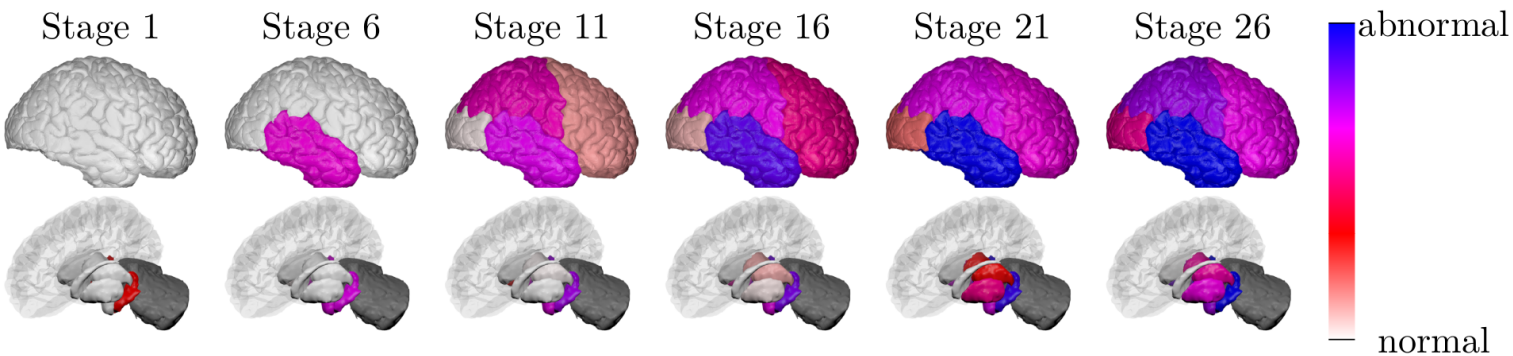


Challenges:

- Patients are at unknown disease stages
- X-axis are not the same (need to construct the disease stage axis)
- Biomarkers have different trajectory shapes
- Cohort is heterogenous
- Control population not well defined

My PhD Aim

1. Study the progression of atrophy in two diseases (using existing models):
   - typical Alzheimer's Disease (tAD)
   - Posterior Cortical Atrophy (PCA)

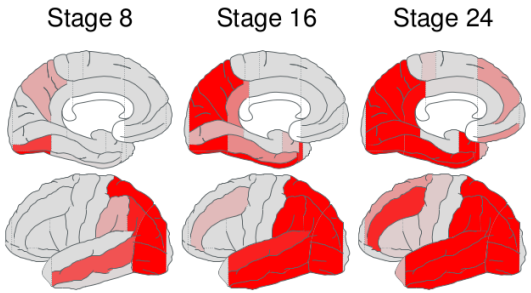


2. Develop novel disease progression models (DPMs)

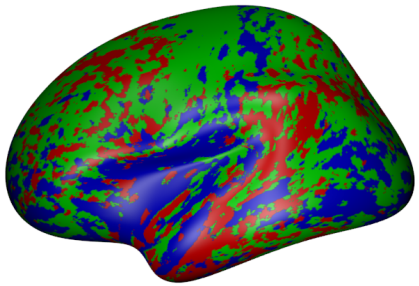
$$p(X|S) = \prod_{j=1}^{J} \left[\sum_{k=0}^{N} p(k) \left(\prod_{i=1}^{k} p\left(x_{s(i),j}|E_{s(i)}\right) \prod_{i=k+1}^{N} p\left(x_{s(i),j}|\neg E_{s(i)}\right) \right) \right] \quad (1)$$

My PhD Contributions

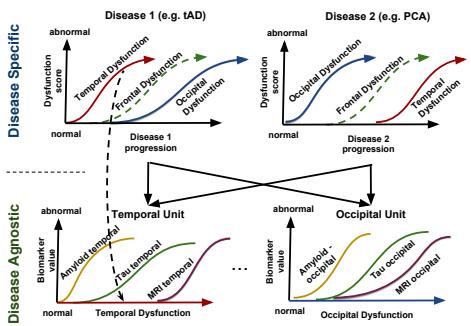
1. Modelled progression of PCA and tAD



2. Spatio-temporal Progression Modelling



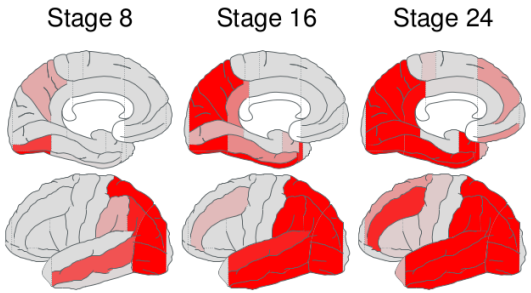
3. Disease Knowledge Transfer across Neurodegenerative Diseases



4. TADPOLE Competition

Overview

1. Modelled progression of PCA and tAD



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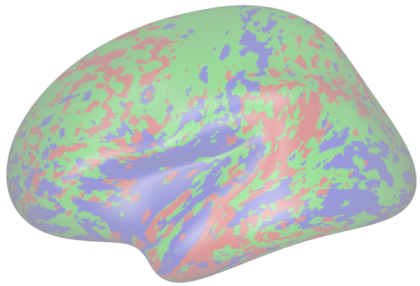

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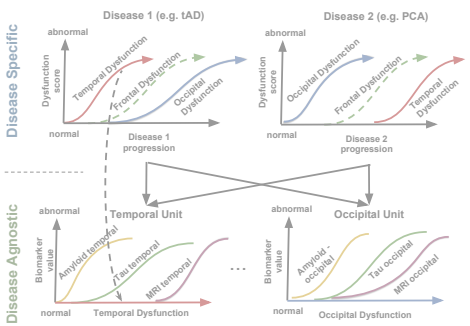

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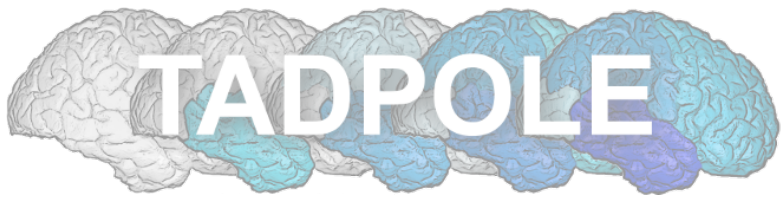

Clinical question: Find the order in which GM regions become atrophied

- in PCA
- in tAD

Why? No previous studies modelled disease progression in PCA

Demographics:

- cohort from the Dementia Research Centre with uniquely large PCA population (70)

	# Subjects	Gender M/F	Age at baseline (years)	Years from onset (years)
Controls	89	33/56	60.5 $\pm$ 11	-
PCA	70	27/43	63.0 $\pm$ 7	4.4 $\pm$ 2.8
AD	65	34/31	66.3 $\pm$ 8	4.8 $\pm$ 2.6

Data: Structural MRI scans

Impact: the first major investigation of PCA disease progression

How? The Event-Based Model ...

Key Idea: The Event-Based Model Estimates an Atrophy Sequence from Informative Patient Snapshots

- Event-Based Model (EBM): Fontejin et al., Neroimage, 2012.
- Aim: Region 1 $\rightarrow$ Region 2 vs Region 2 $\rightarrow$ Region 1

	Patient 1	Patient 2	Patient 3
Region 1	1.1	0.9	0.1
Region 2	0.95	0.0	0.05

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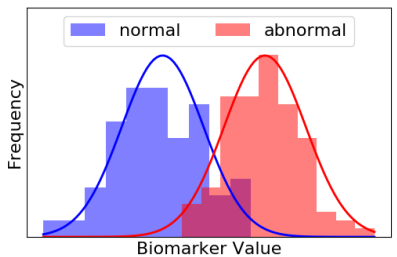
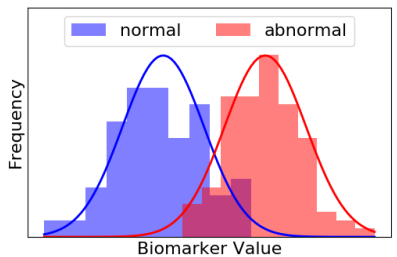


Region 2



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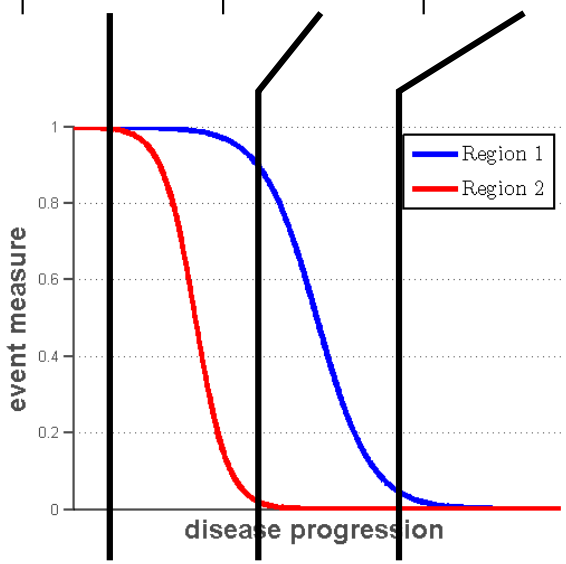


Estimated Sequence: Region 2 $\rightarrow$ Region 1

The EBM assumes a subject at stage k has first k biomarkers "abnormal" and the last $N - k$ biomarkers "normal"

- Evaluate data likelihood under normal and abnormal distributions:
  - normal - $p\left(x_{s(i),j}|\neg E_{s(i)}\right)$
  - abnormal - $p\left(x_{s(i),j}|E_{s(i)}\right)$
- Compute likelihood of one subject j being at stage k given sequence S:

$$p(X_j|S,k) = \prod_{i=1}^{k} p\left(x_{s(i),j}|E_{s(i)}\right) \prod_{i=k+1}^{N} p\left(x_{s(i),j}|\neg E_{s(i)}\right)$$

- Marginalise stage k:

$$p(X_j|S) = \sum_{k=0}^{N} p(k) \left(\prod_{i=1}^{k} p\left(x_{s(i),j}|E_{s(i)}\right) \prod_{i=k+1}^{N} p\left(x_{s(i),j}|\neg E_{s(i)}\right) \right)$$

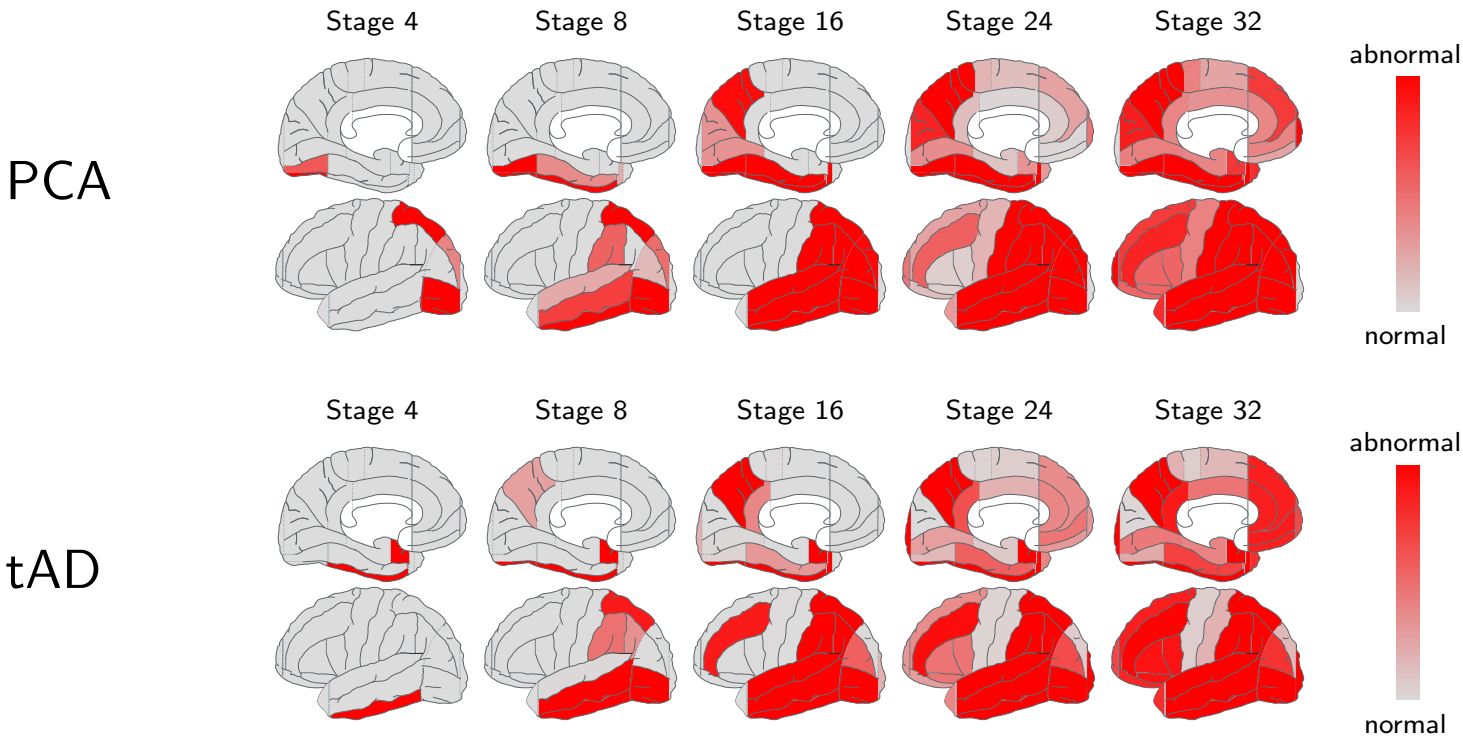
- Extend to all subjects:

$$p(X|S) = \prod_{j=1}^{J} \left[\sum_{k=0}^{N} p(k) \left(\prod_{i=1}^{k} p\left(x_{s(i),j}|E_{s(i)}\right) \prod_{i=k+1}^{N} p\left(x_{s(i),j}|\neg E_{s(i)}\right) \right) \right]$$

- Sequence and uncertainty estimated with MCMC sampling

The EBM finds a Distinct Atrophy Sequence in PCA compared to tAD

- PCA $\rightarrow$ early occipital and superior parietal atrophy
- tAD $\rightarrow$ early hippocampal and inferior temporal atrophy

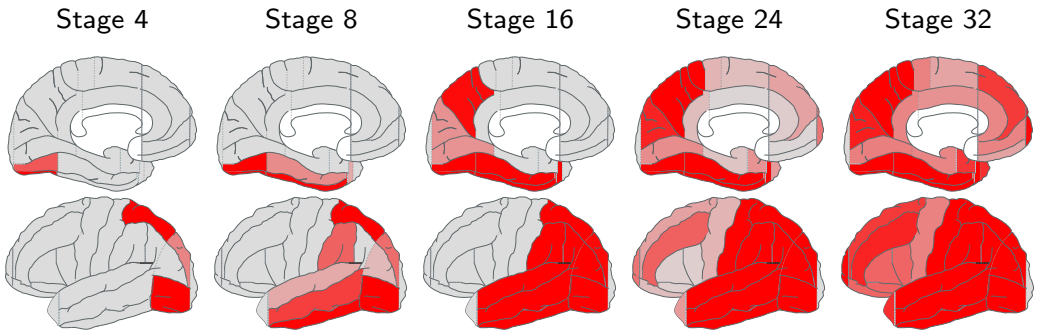


Firth, Marinescu and Primativo, in first revision (Brain)

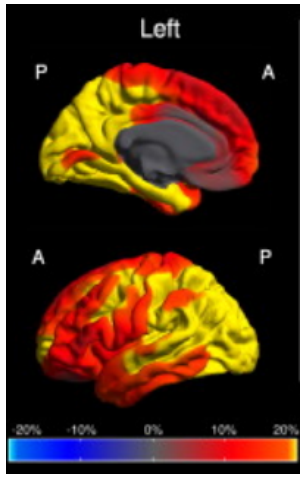
Atrophy Patterns Resemble Previous Studies from the Literature

- PCA → early occipital and superior parietal atrophy
- tAD → early hippocampal and inferior temporal atrophy

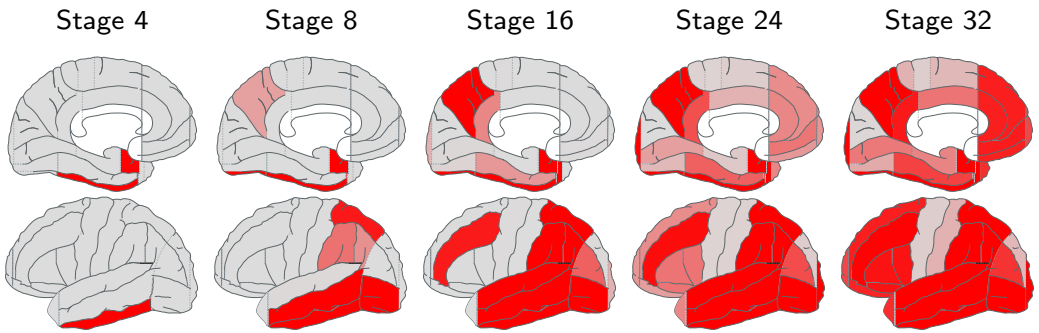
PCA



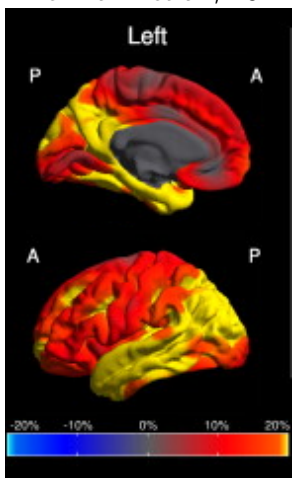
Lehmann et al., 2012



tAD



Lehmann et al., 2012



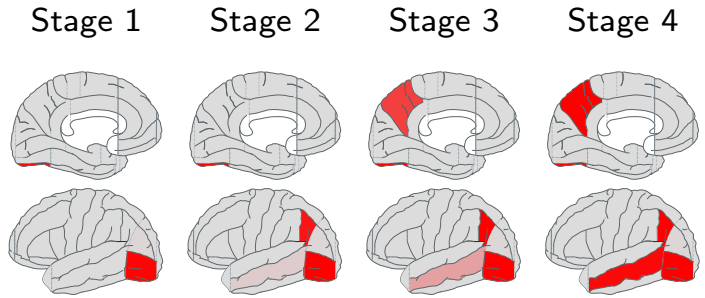
Firth, Marinescu and Primativo, in first revision (Brain)

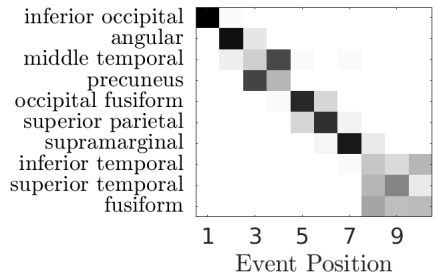
PCA Subtypes show Different Atrophy Progressions, providing Evidence for Heterogeneity within PCA

Initial hypotheses

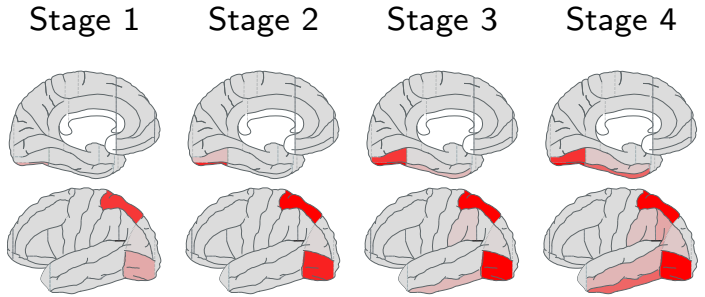
1. Basic visual impairment → early atrophy in occipital lobe
2. Space perception impairment → early atrophy in superior parietal lobe
3. Visuoperceptual impairment → early atrophy in inferior temporal lobe

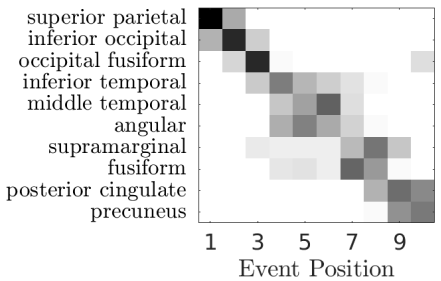
1. Basic visual impairment (n=21)



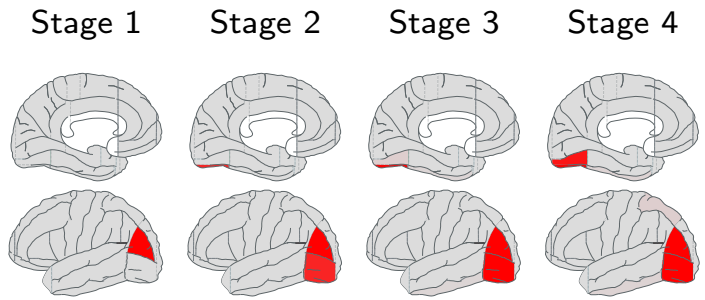


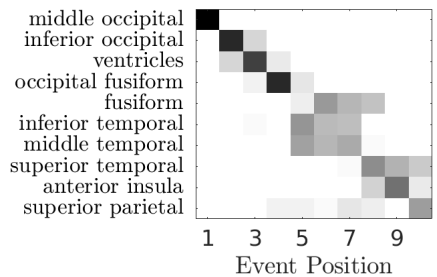
2. Space perception impairment (n=21)





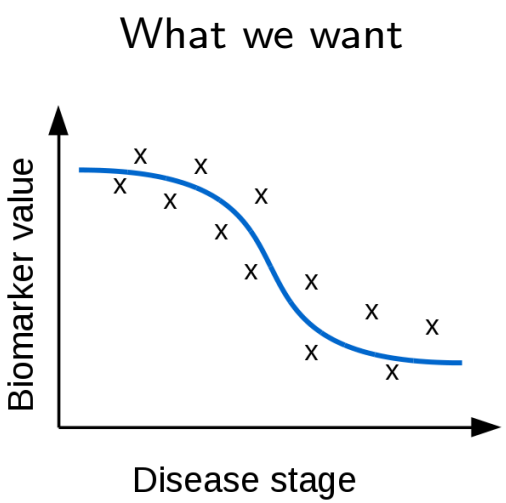
3. Visuo-perceptual impairment (n=22)

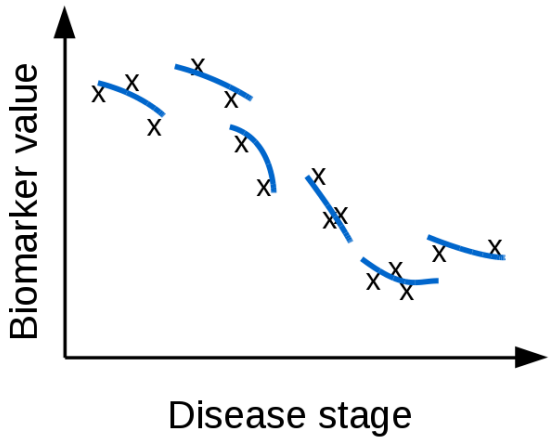


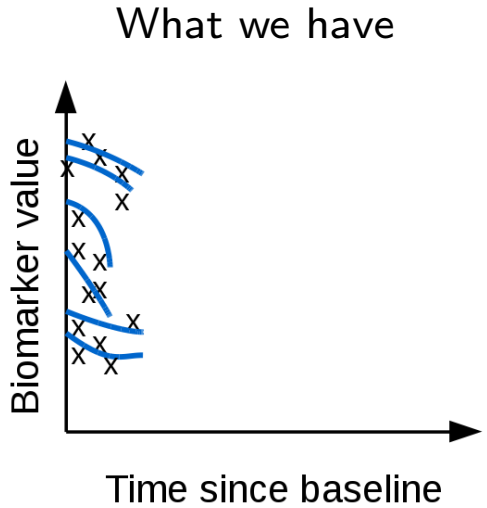


Firth, Marinescu and Primativo, in first revision (Brain)

The Differential Equation Model reconstructs Biomarker Trajectories from Short-term Longitudinal Measurements



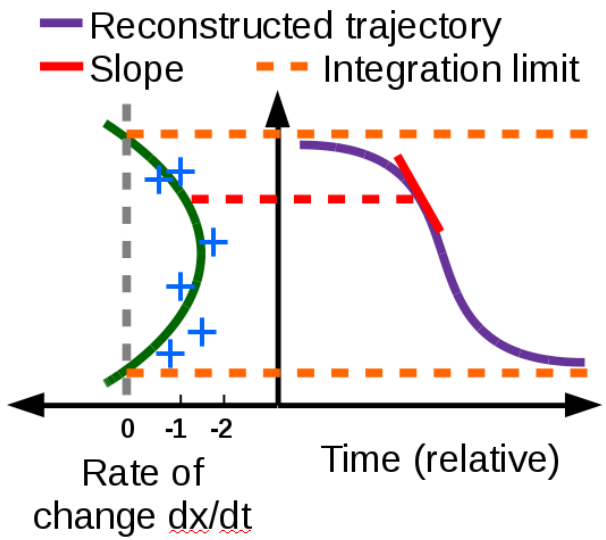


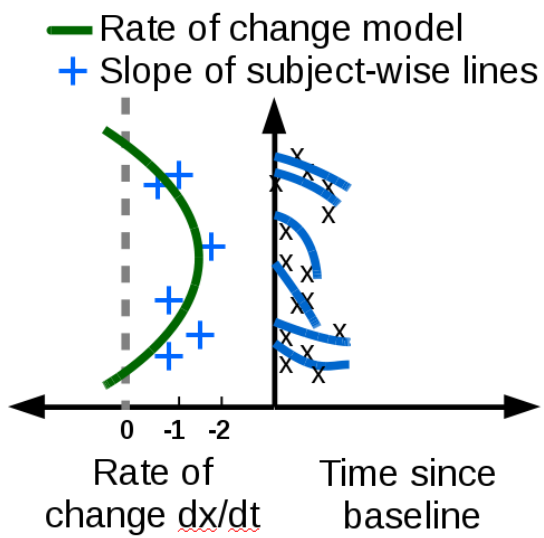


$$lim_{\Delta t \to 0} \frac{\Delta x}{\Delta t} = \frac{\delta x}{\delta t} = f(x)$$

Solve for x using the Euler method:

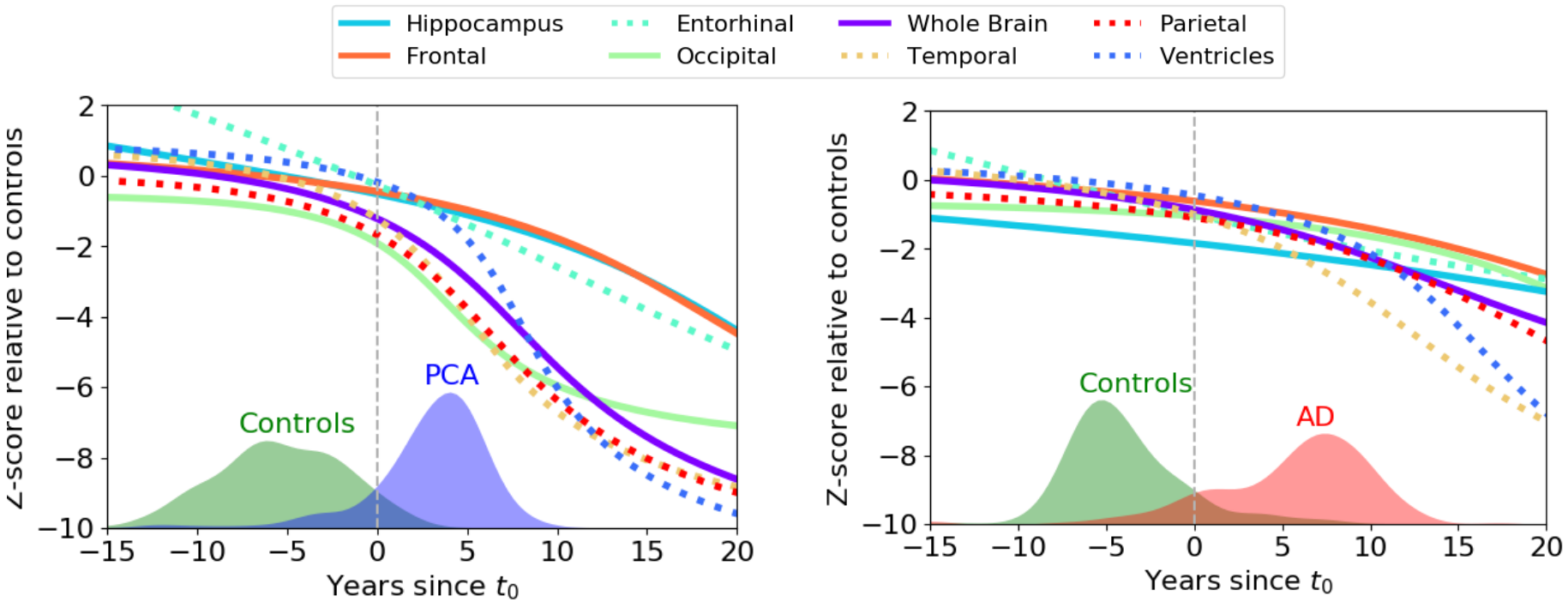
$$t_1 = t_0 + \delta t$$
$$x_1 = x_0 + f(x_0)\delta t$$





Model Recapitulates Differences in PCA vs tAD Atrophy Progression

- PCA: rapid and extensive atrophy in occipital and parietal regions
- tAD: global atrophy pattern, with early hippocampal involvement



(a) PCA

(b) tAD

Firth, Marinescu and Primativo, in first revision (Brain)