Modelling the Neuroanatomical Progression of Alzheimers Disease and Posterior Cortical Atrophy

Răzvan Valentin Marinescu

Supervisors: Prof. Daniel Alexander, Dr. Sebastian Crutch, Dr. Neil Oxtoby

Centre for Medical Image Computing, University College London, UK

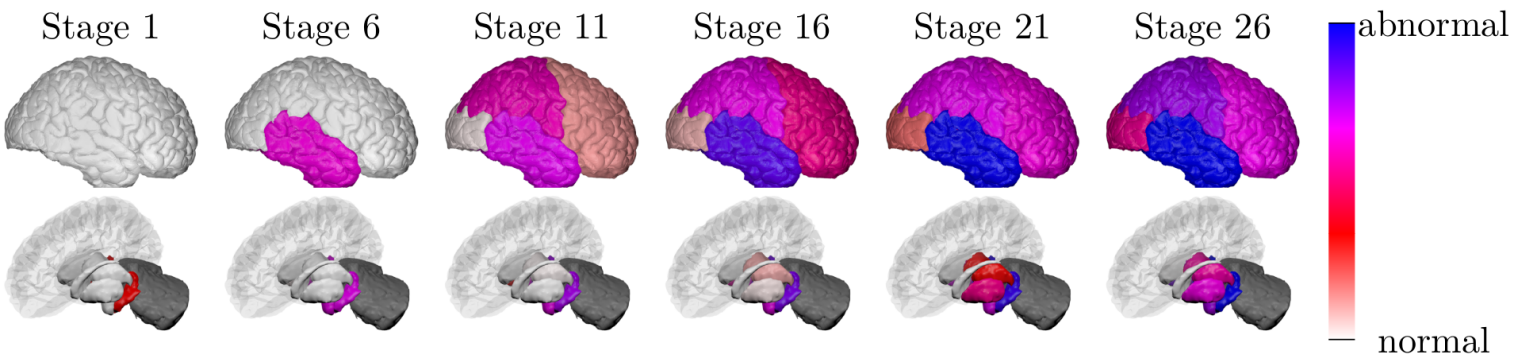
About me

- Grew up in Pitesti, Romania
- 2010-2014: Studied a 4-year MEng in Computer Science at Imperial College London

- 2014: Masters and PhD in Medical Imaging at UCL
- Working with Prof. Daniel Alexander on disease progression modelling

My PhD Aim

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

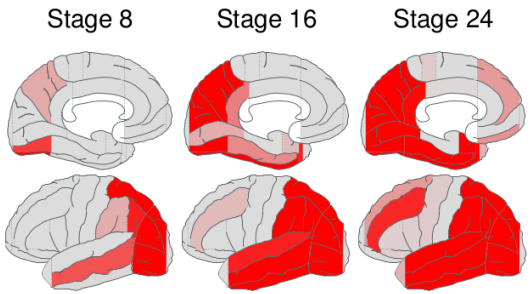


2. Develop novel disease progression models (DPMs)

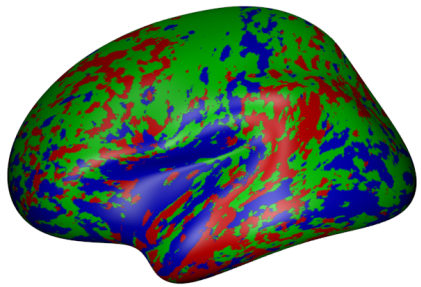
$$p(X|S) = \prod_{j=1}^{J} \left[\sum_{k=0}^{N} p(k) \left(\prod_{i=1}^{k} p\left(x_{s(i),j}|E_{s(i)}\right) \prod_{i=k+1}^{N} p\left(x_{s(i),j}|\neg E_{s(i)}\right) \right) \right] \quad (1)$$

My PhD Contributions

1. Modelling the Progression of PCA



2. DIVE Spatiotemporal Model



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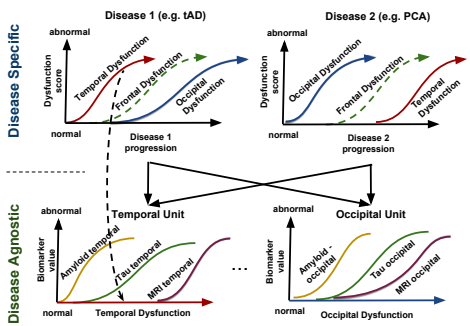

4. Novel Extensions of EBM and DEM

Model	Staging Consistency		Time-lapse	
	Hard	Soft	Hard	Soft
EBM - Standard	0.91 ± 0.16	0.71 ± 0.07	-	-
EBM - Sampling	0.96 ± 0.07	0.76 ± 0.10	-	-
EBM - EM	0.99 ± 0.01	0.72 ± 0.07	-	-
DEM - Standard	0.87 ± 0.10	0.88 ± 0.08	0.72 ± 0.91	0.67 ± 0.92
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5. TADPOLE Competition

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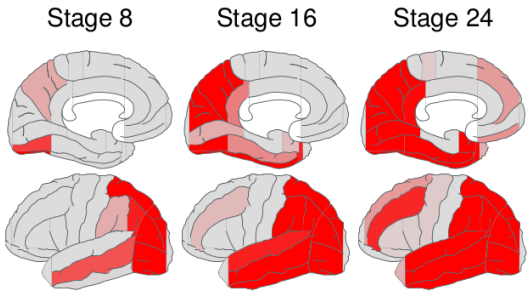

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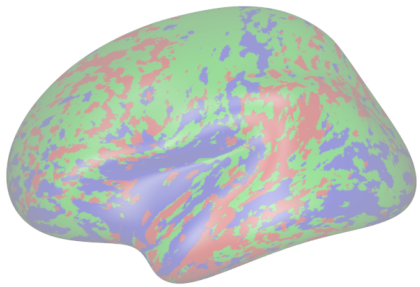

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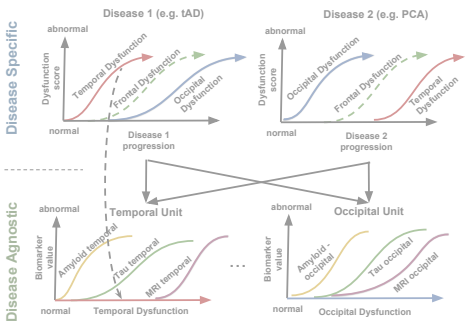

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5. TADPOLE Competition

Aim: Estimate the Progression of Atrophy in PCA

Why? No comprehensive studies modelled disease progression in PCA so far

Demographics:

- MRI Data 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

Impact: the first major investigation of PCA disease progression

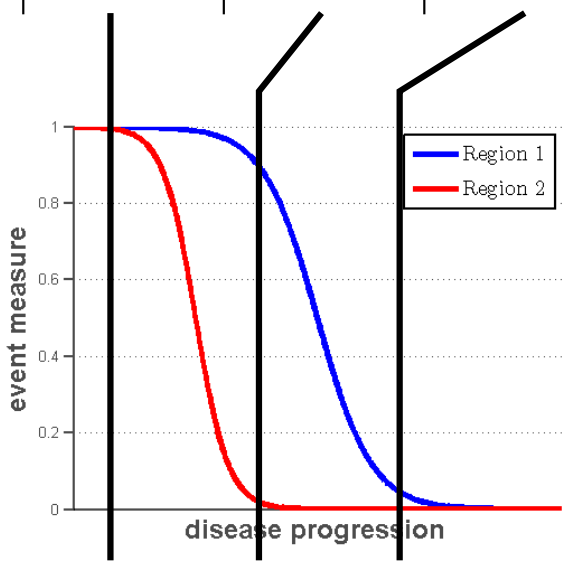
Key Idea: The Event-Based Model Estimates an Atrophy Sequence from Informative Patient Snapshots

- 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

$\longrightarrow$

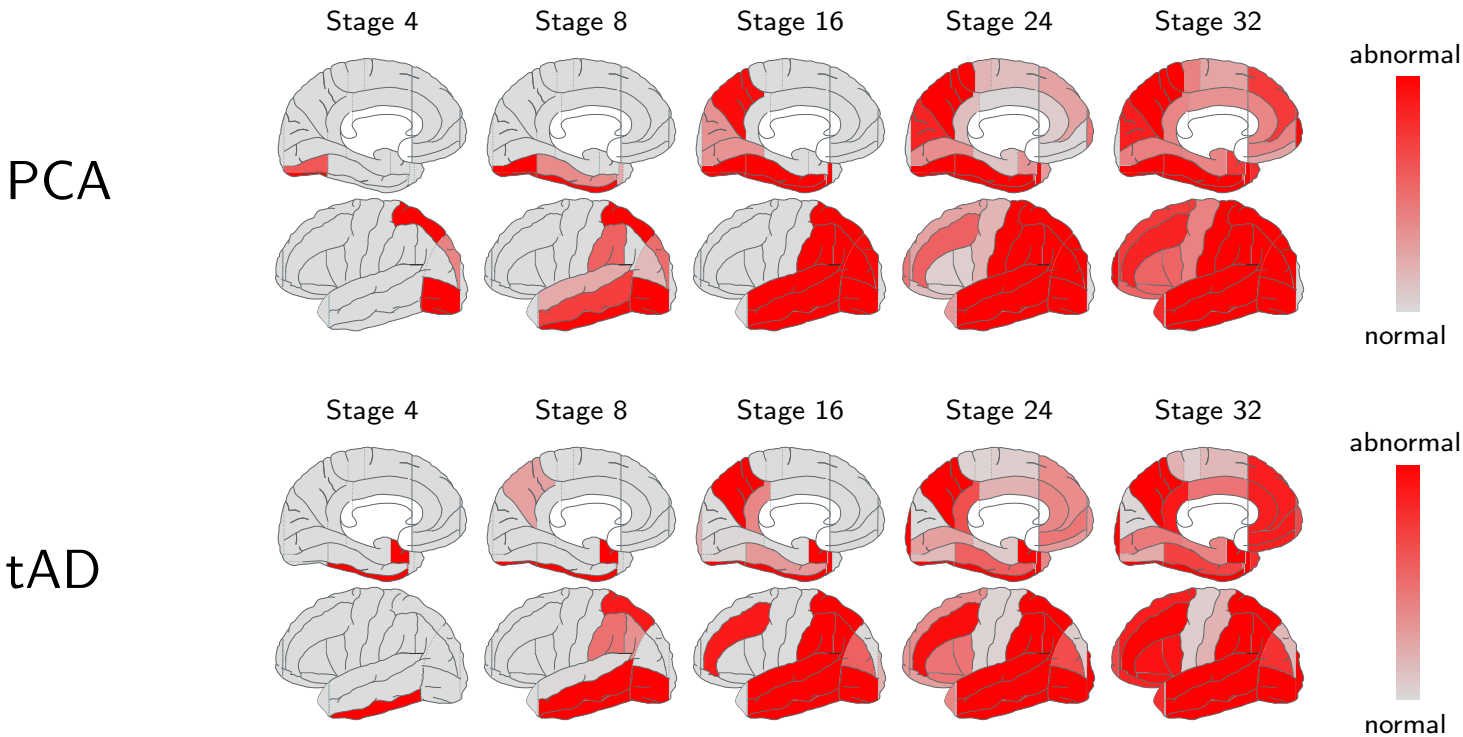
	Patient 1	Patient 2	Patient 3
Region 1	normal	normal	abnormal
Region 2	normal	abnormal	abnormal



Estimated Sequence: Region 2 $\rightarrow$ Region 1

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

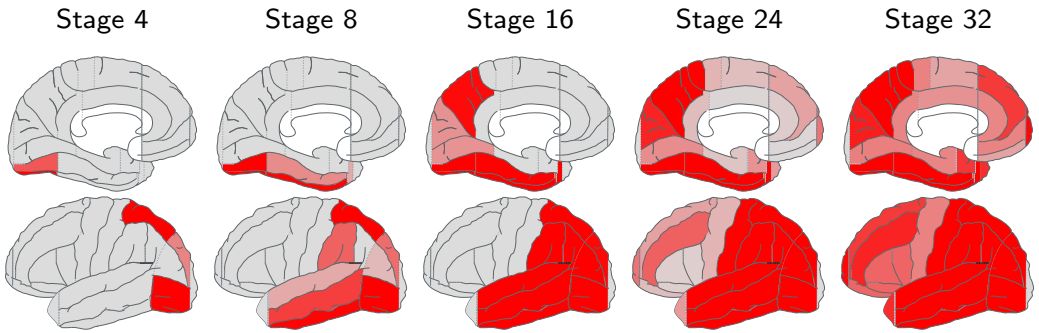


Firth, Marinescu and Primativo, in first revision (Brain)

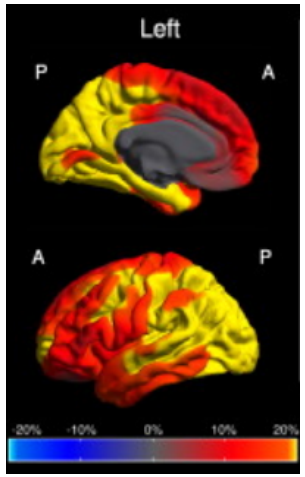
Atrophy Patterns Resemble Previous Studies from the Literature

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

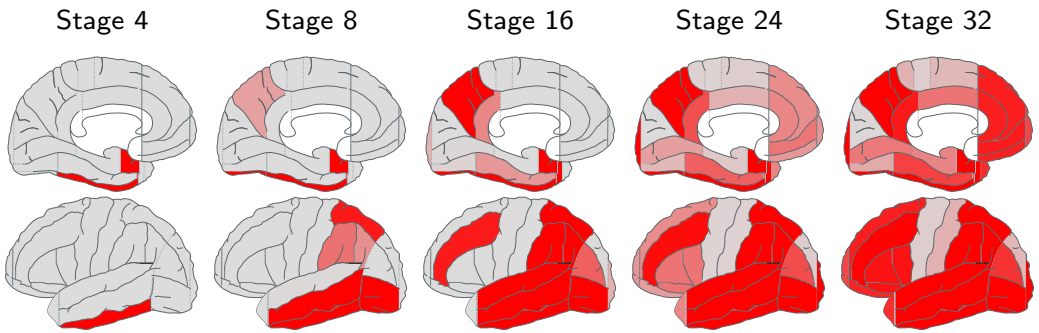
PCA



Lehmann et al., 2012



tAD



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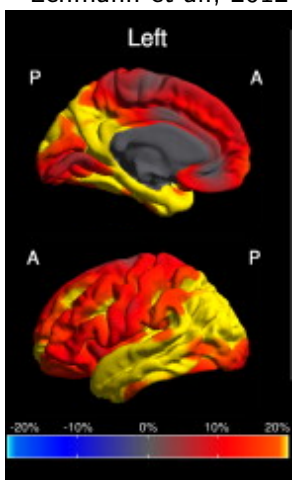

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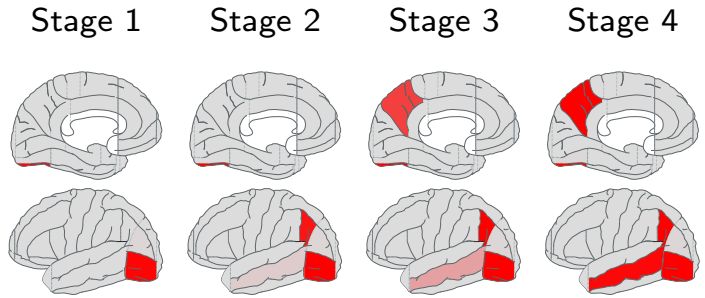
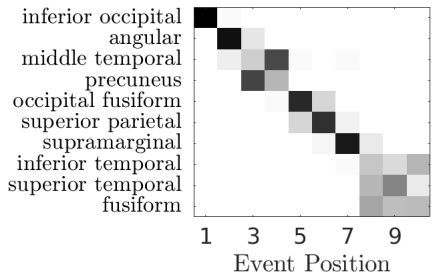
PCA Subtypes show Different Atrophy Progressions, providing Evidence for Heterogeneity within PCA

Initial hypotheses

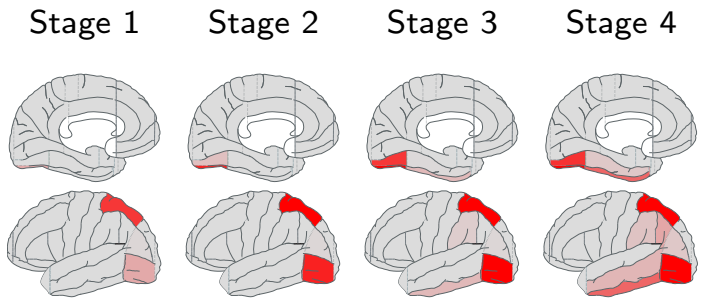
1. Basic visual impairment → early atrophy in occipital lobe
2. Space perception impairment → early atrophy in superior parietal lobe
3. Visuoperceptual impairment → early atrophy in inferior temporal lobe

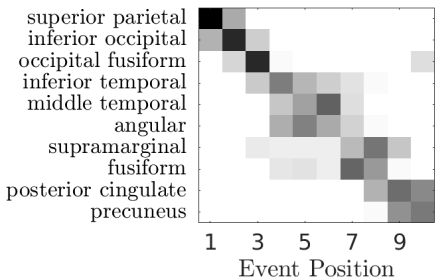
1. Basic visual impairment (n=21)



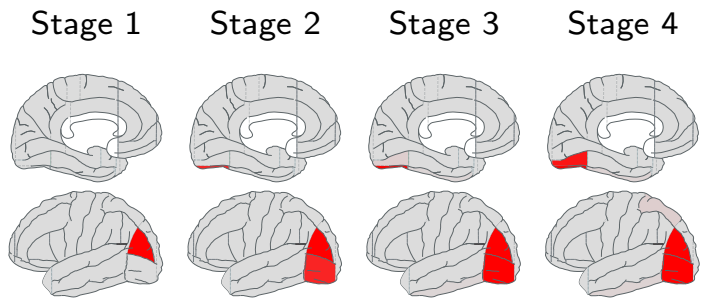


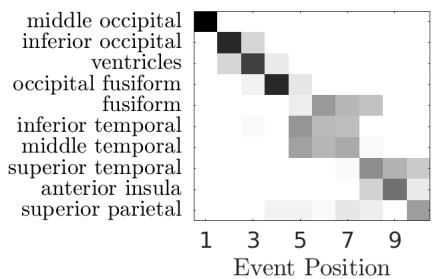
2. Space perception impairment (n=21)





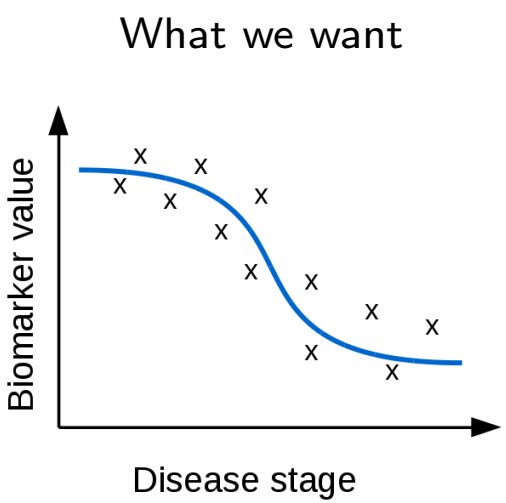
3. Visuo-perceptual impairment (n=22)

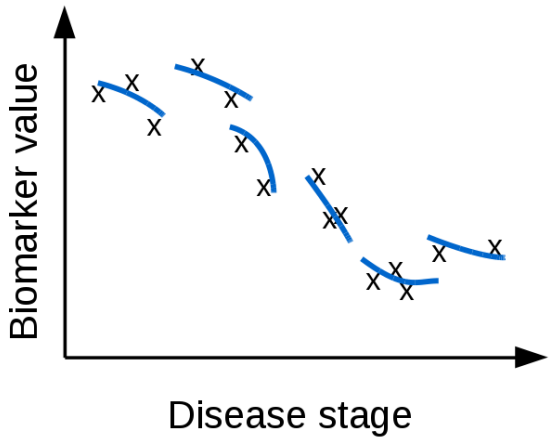


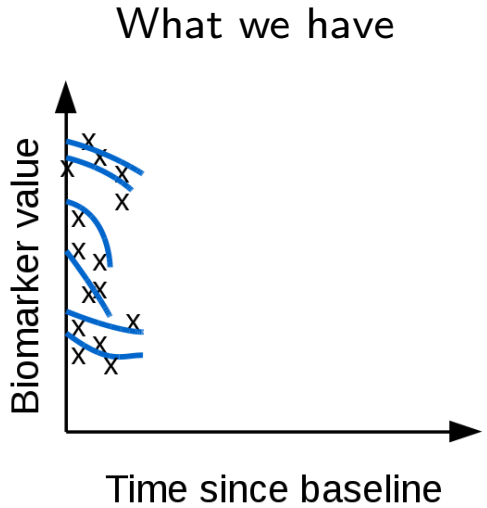


Firth, Marinescu and Primativo, in first revision (Brain)

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



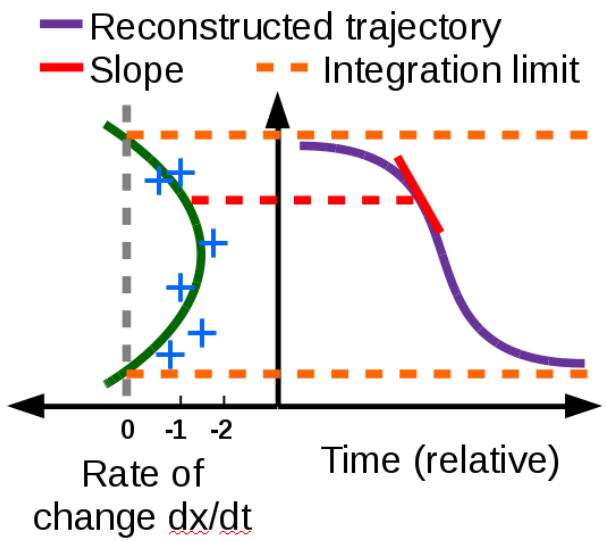


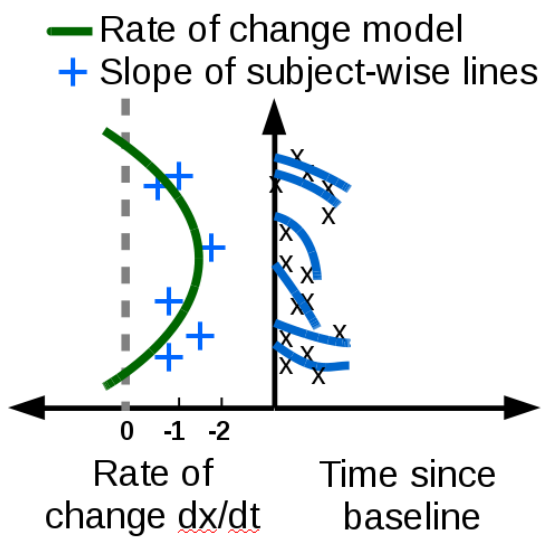


$$lim_{\Delta t \to 0} \frac{\Delta x}{\Delta t} = \frac{\delta x}{\delta t} = f(x)$$

Solve for x using the Euler method:

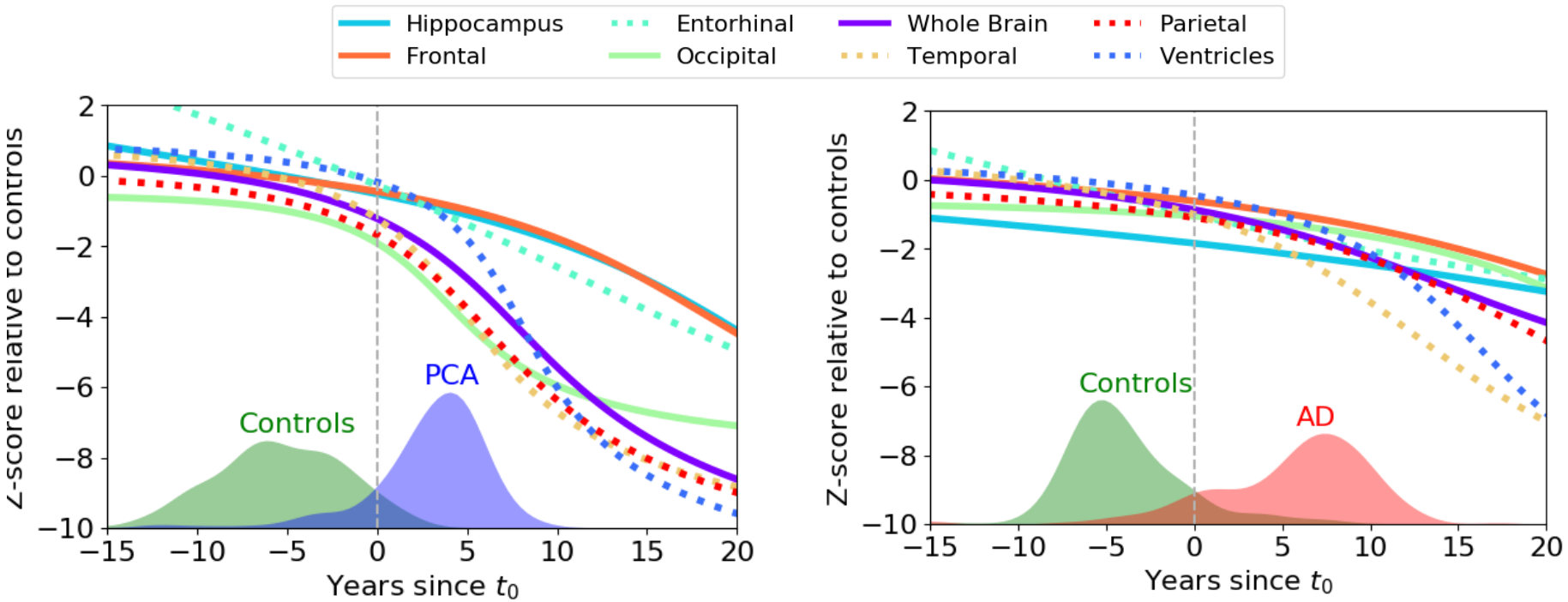
$$t_1 = t_0 + \delta t$$
$$x_1 = x_0 + f(x_0)\delta t$$





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)

My PhD Contributions

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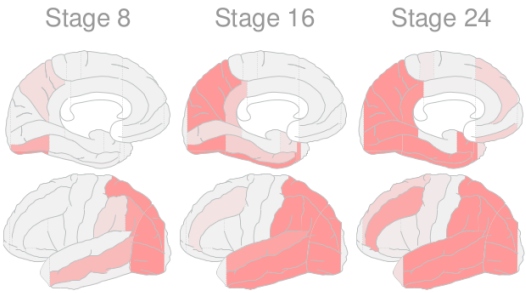

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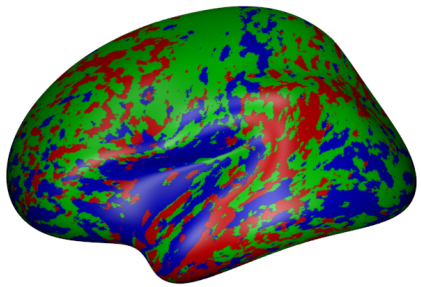

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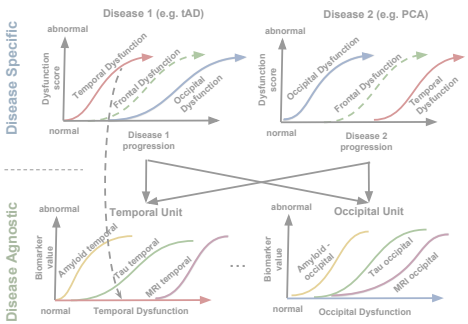

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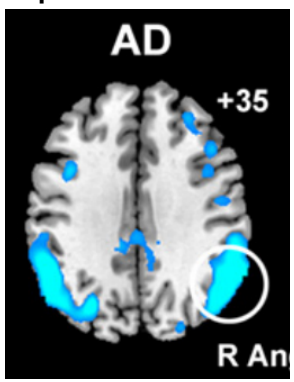
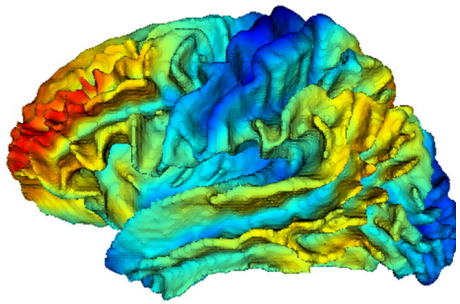
5. TADPOLE Competition

Aim: Build a Disease Progression Model of Pathology over the Brain that Avoids Limitations of Previous Models

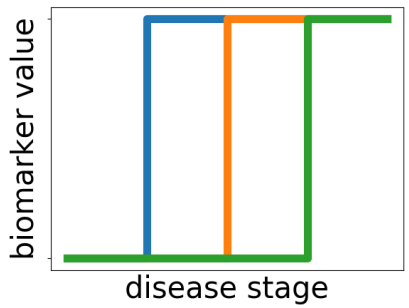
Avoids pre-defined ROI parcellation



Avoids simplistic spatial correlation structure



Avoids simplistic biomarker trajectories



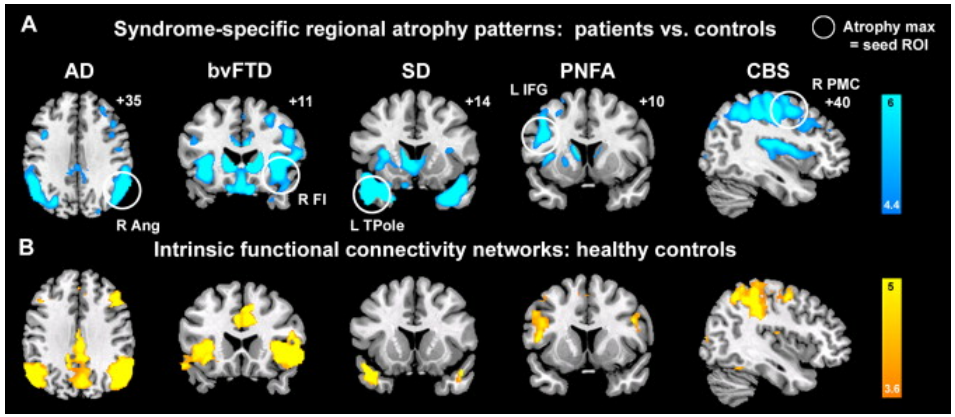
This leads to a technique that simultaneously:

- parcellates the brain into disconnected components that undergo similar progression
- estimates biomarker trajectories

Motivation

1. Atrophy correlates with functional networks, which are not spatially connected (Seeley et al., Neuron, 2009)

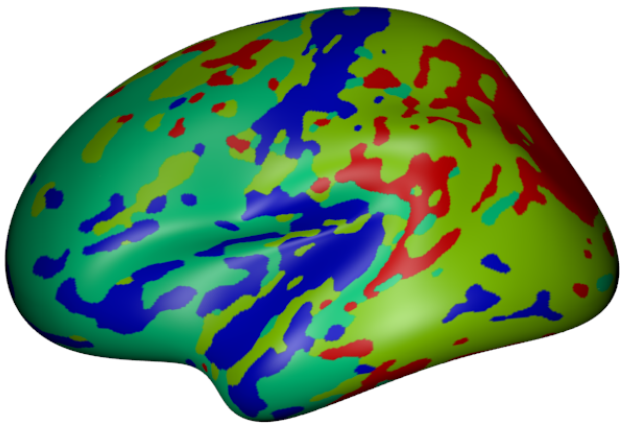
2. Better biomarker prediction and disease staging



(a) Seeley et al., Neuron, 2009

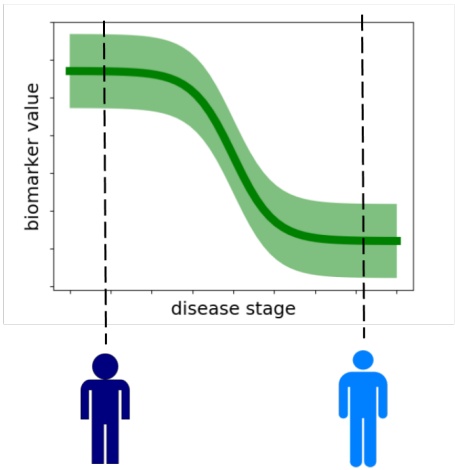
Method Idea - Combine Unsupervised Learning and Disease Progression Modelling

Only Unsupervised Learning (i.e. Clustering)



- Can identify disconnected atrophy patterns ✓
- No biomarker trajectories ✗
- No disease staging of subjects ✗

Only Disease Progression Modelling

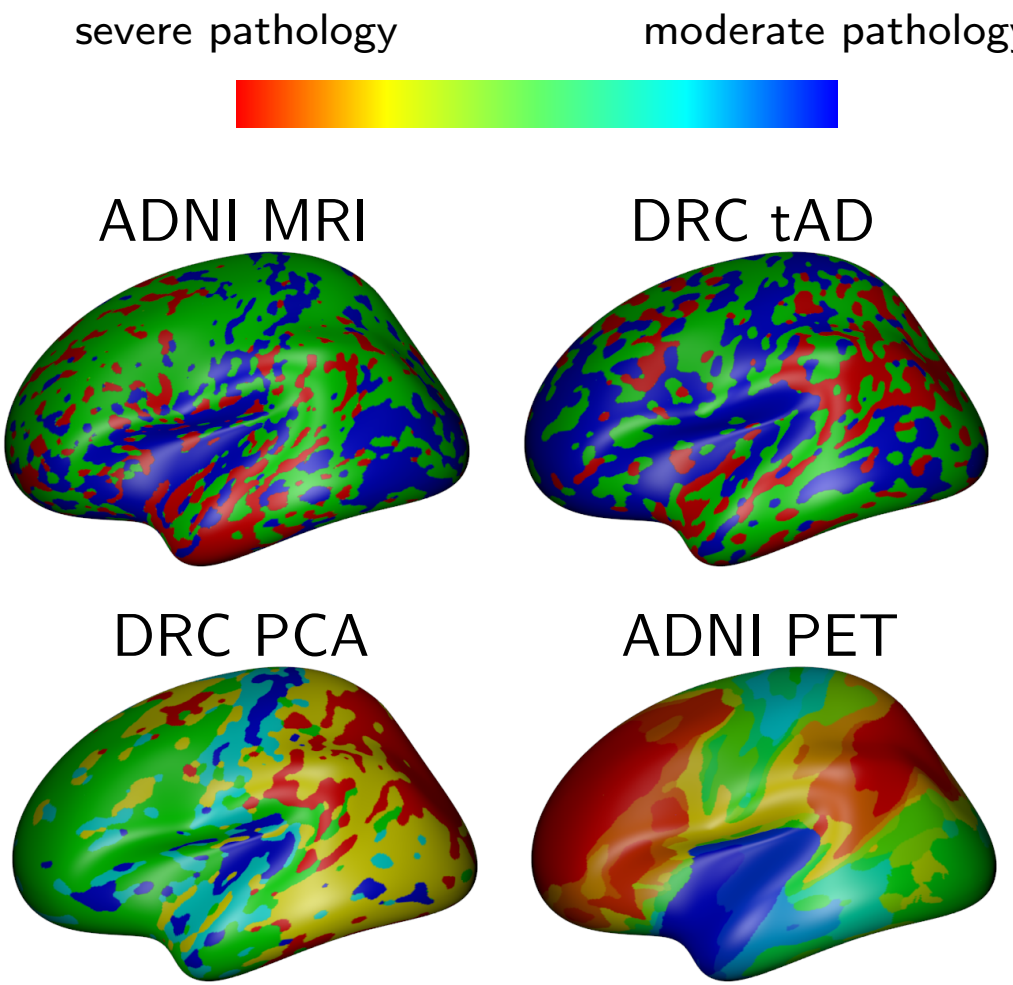


- Cannot identify disconnected atrophy patterns ✗
- Can estimate biomarker trajectories ✓
- Can estimate subjects disease stages ✓

- Estimate trajectories for each vertex on the cortical surface
- Vertex measures cortical thickness at that location

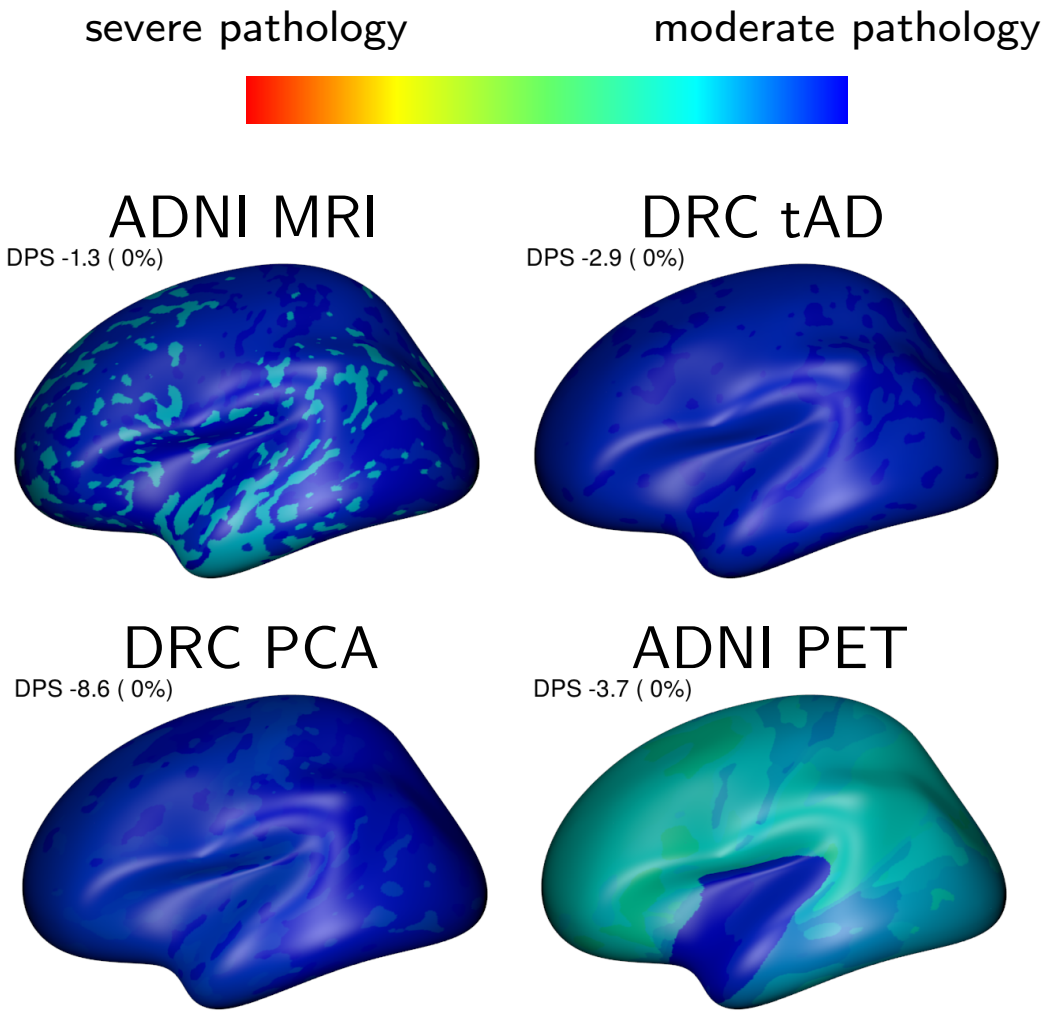
DIVE Finds Plausible Atrophy Patterns on Four Datasets

- Similar patterns of tAD atrophy in independent datasets: ADNI and UCL DRC
- Distinct patterns of atrophy in different diseases (tAD and PCA) and modalities (MRI vs PET)



Marinescu et al., NeuroImage, under second review

DIVE Estimates the Temporal Evolution of Pathology, Enabling Understanding of Disease Mechanisms



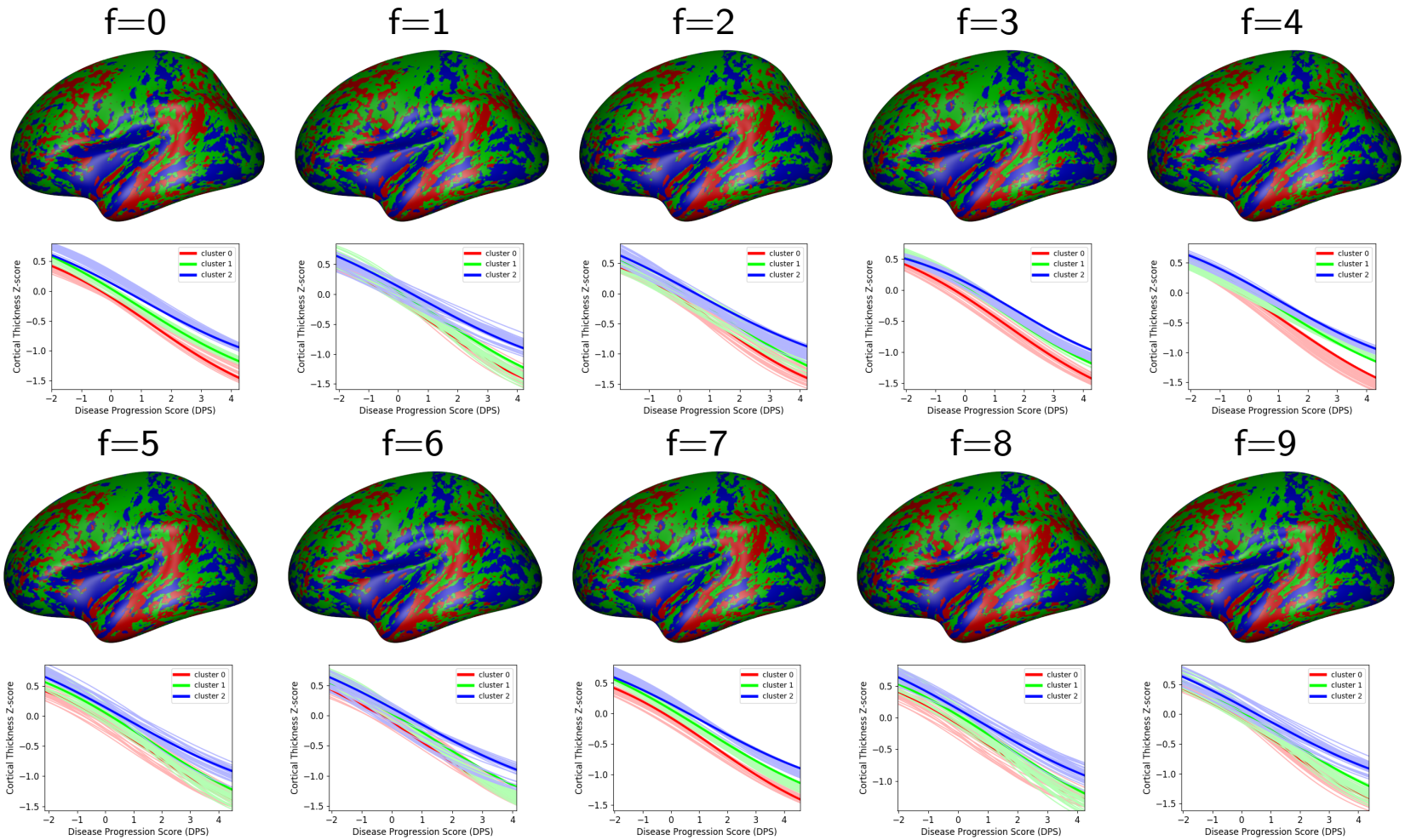
Marinescu et al., Neuroimage, under second review

- Open-source brain colouring/animation software to be published

Validation - Model Robustly Estimates Atrophy Patterns

Method: Tested the consistency of the spatial clustering in ADNI using 10-fold CV

Results: Good agreement in terms of spatial distribution (dice score 0.89)



Marinescu et al., Neuroimage, under second review

Estimated Subject Progression Scores are Clinically Relevant

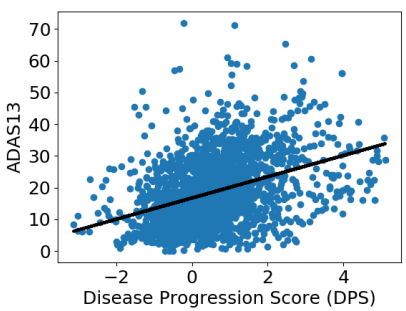
Hypothesis:

- Clinical relevance $\rightarrow$ DPS correlates with other markers of disease progression

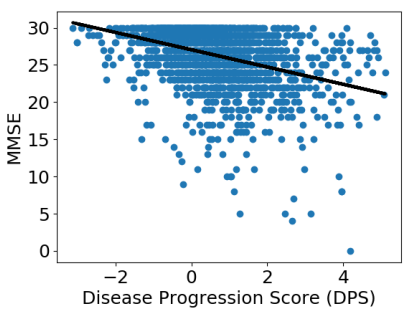
Method: Ran our model on ADNI using 10-fold cross-validation

Results: Progression scores correlate well with cognitive tests:

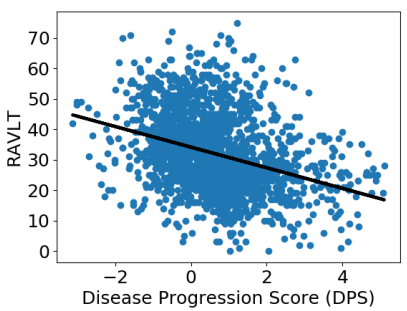
CDRSOB ($\rho = 0.41$, $p < 1e-66$)



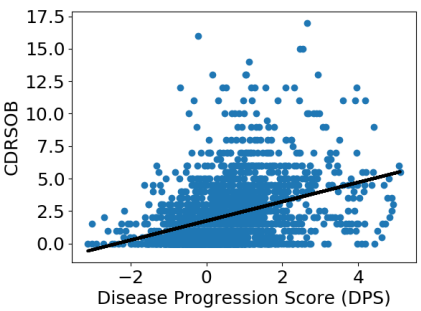
ADAS-COG ($\rho = -0.40$, $p < 1e-62$)



MMSE ($\rho = -0.39$, $p < 1e-58$)



RAVLT ($\rho = 0.39$, $p < 1e-58$)



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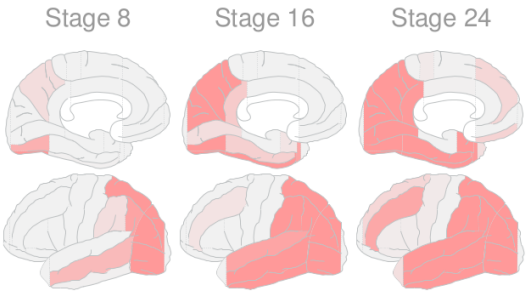

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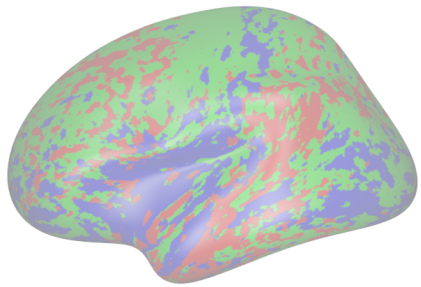

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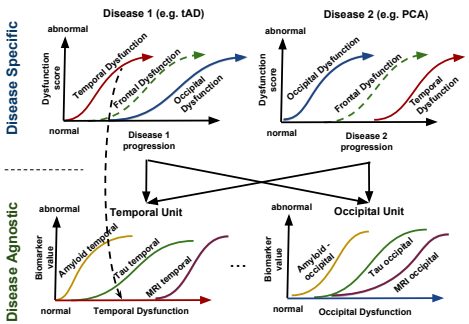


4. Novel Extensions of EBM and DEM

Model	Staging Consistency		Time-lapse	
	Hard	Soft	Hard	Soft
EBM - Standard	0.91 ± 0.16	0.71 ± 0.07	-	-
EBM - Sampling	0.96 ± 0.07	0.76 ± 0.10	-	-
EBM - EM	0.99 ± 0.01	0.72 ± 0.07	-	-
DEM - Standard	0.87 ± 0.10	0.88 ± 0.08	0.72 ± 0.91	0.67 ± 0.92
DEM - Optimised	0.87 ± 0.10	0.88 ± 0.08	0.74 ± 0.92	0.69 ± 0.92

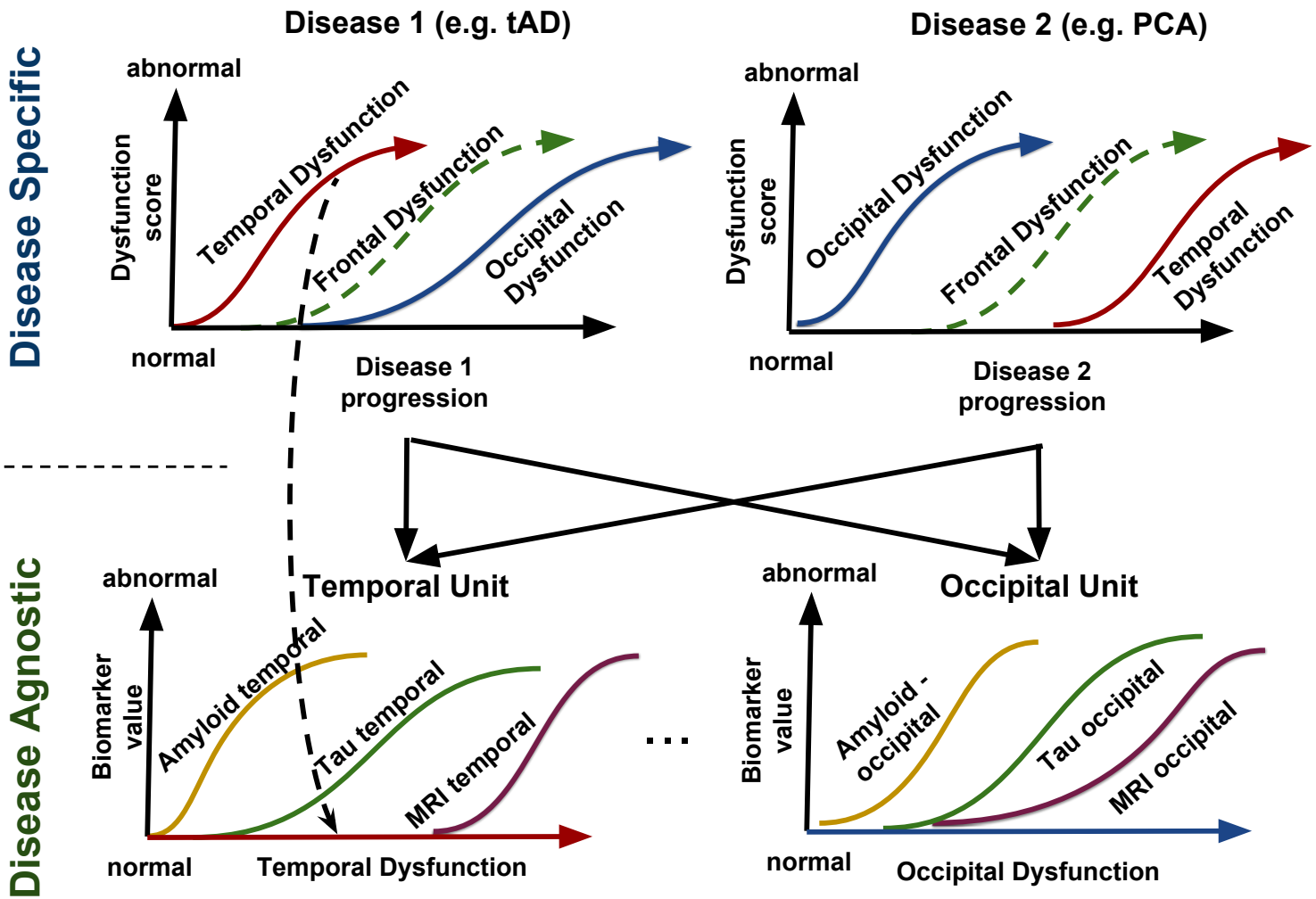
5. TADPOLE Competition

Aim: Estimate the *Longitudinal*, *Multimodal* Progression of Rare Neurodegenerative Diseases

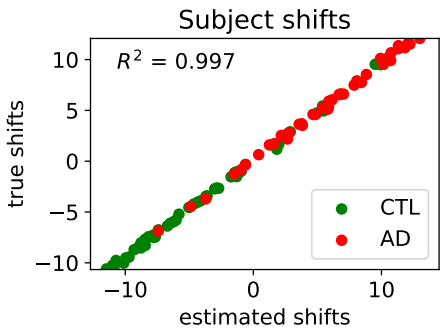
- Current disease progression models require large, multimodal datasets
- Applications to rare neurodegenerative diseases are challenging due to lack of data
- Deep transfer learning techniques exist, but are not interpretable

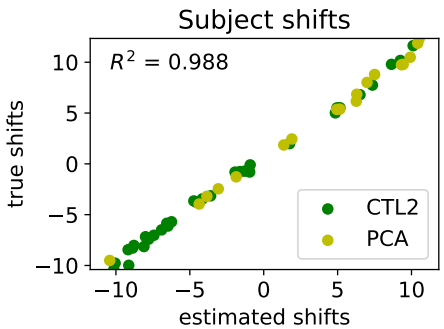
Typical Neurodegenerative Diseases	Rare Neurodegenerative Diseases
▶ Large datasets ✓	▶ Small datasets ✗
▶ Multimodal imaging ✓	▶ MRI only ✗
▶ Longitudinal ✓	▶ Cross-sectional only ✗

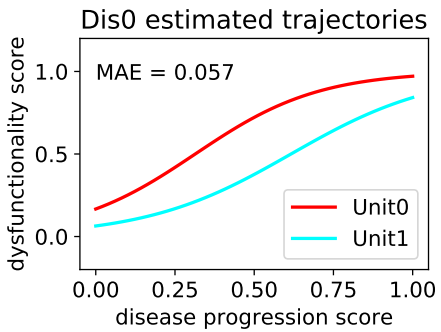
Disease Knowledge Transfer (DKT) can estimate multimodal trajectories in *rare diseases* by transferring information from *larger datasets* of typical diseases.

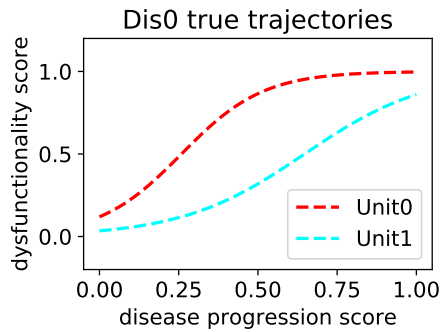


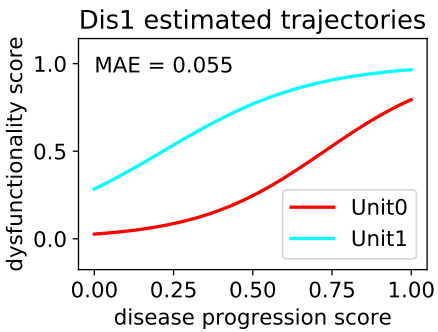
DKT Accurately Estimates Ground Truth Parameters on Synthetic Data

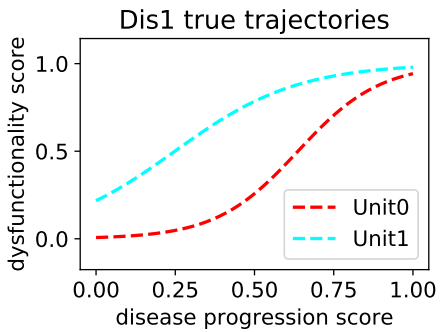


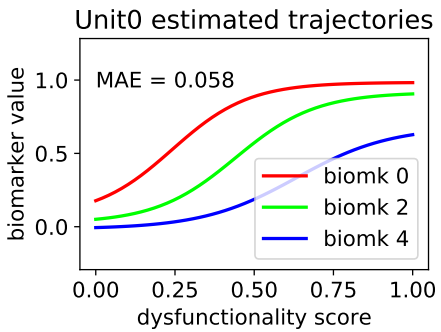


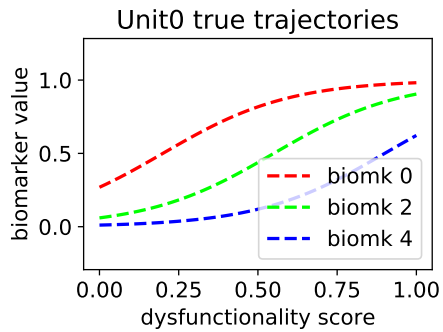


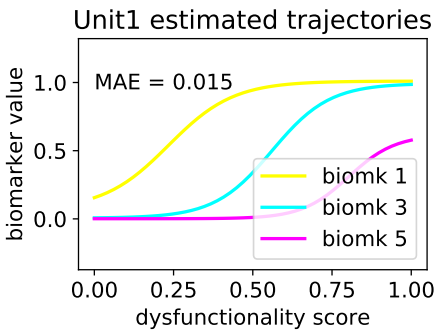


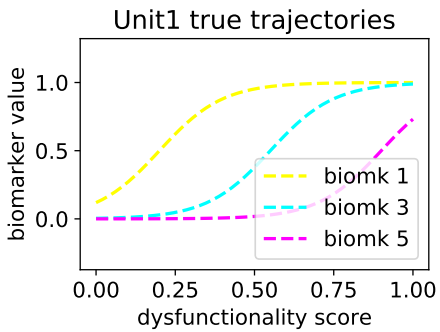






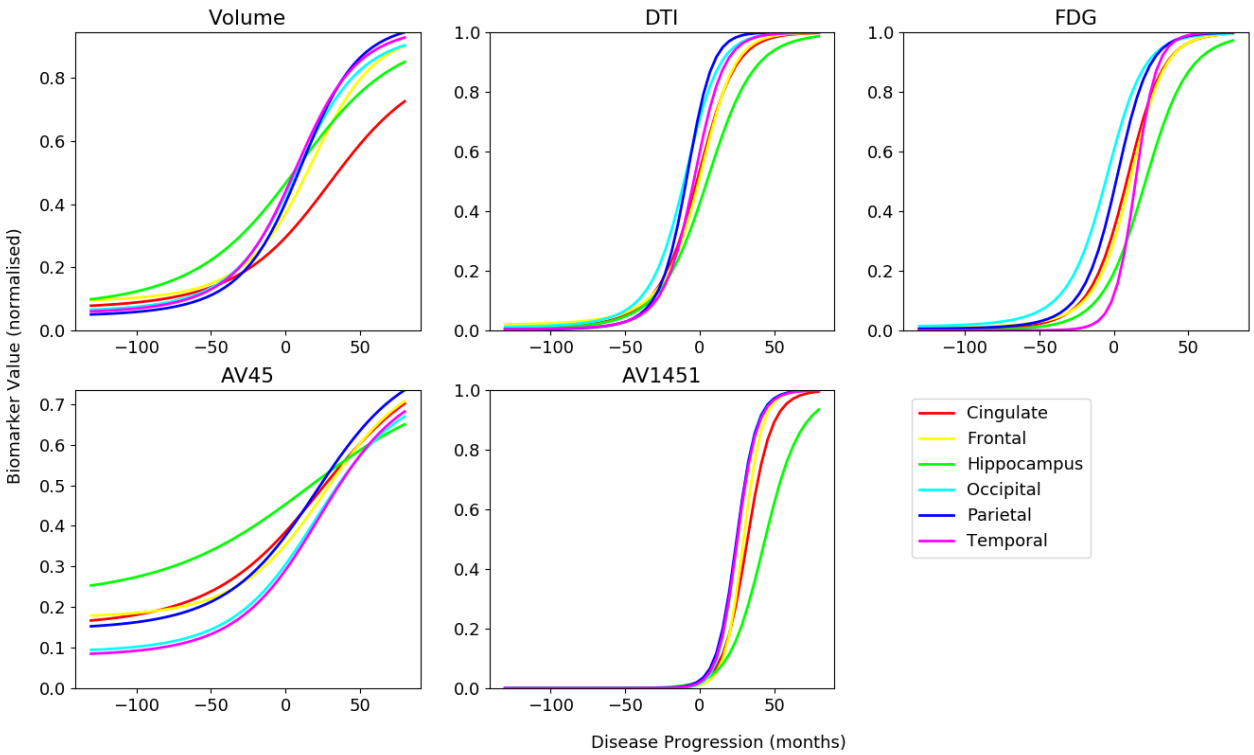






On Patient Data, DKT Estimates Plausible Multimodal PCA Trajectories

- only MRI data was available in PCA

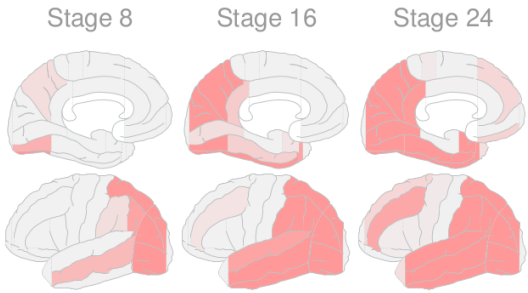


Validation: DKT has Favourable Performance Compared to Other Approaches

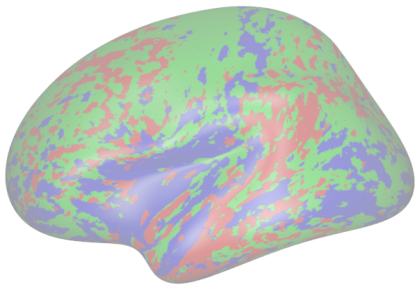
Model	Cingulate	Frontal	Hippocampus	Occipital	Parietal	Temporal
			Prediction Error (MSE)			
DKT	0.09±0.04	0.03±0.01	0.18±0.03	0.04±0.02	0.06±0.02	0.04±0.02
Latent stage model	0.09±0.04	0.03±0.01	0.17±0.03	0.04±0.02	0.06±0.02	0.04±0.02
Linear Model	0.05±0.02*	0.15±0.04*	0.09±0.03*	0.07±0.03*	0.07±0.02*	0.07±0.02*
			Rank Correlation (Spearman rho)			
DKT	0.76	0.48	0.76	0.55	0.55	0.33
Latent stage model	0.76	0.49	0.80*	0.56	0.51*	0.33
Linear Model	0.48*	0.31*	0.64*	0.61*	0.57*	0.27*

- Latent stage model: assumes PCA and tAD all follow the same progression
- Linear model: estimates DTI from MRI using ROI-wise linear model

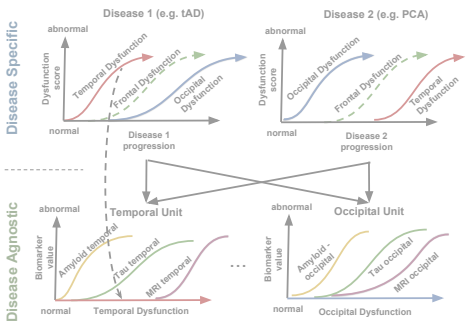
1. Modelling the Progression of PCA



2. DIVE Spatiotemporal Model



3. Disease Knowledge Transfer (DKT)



4. Novel Extensions of EBM and DEM

Model	Staging Consistency		Time-lapse	
	Hard	Soft	Hard	Soft
EBM - Standard	0.91 ± 0.16	0.71 ± 0.07	-	-
EBM - Sampling	0.96 ± 0.07	0.76 ± 0.10	-	-
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DEM - Optimised	0.87 ± 0.10	0.88 ± 0.08	0.74 ± 0.92	0.69 ± 0.92

5. TADPOLE Competition

Aim: Improve the Parameter Estimation in EBM and DEM Models

Why:

- EBM assumed parameter independence
- DEM trajectory alignment challenging due to measurement noise.
- Accurate parameters $\rightarrow$ better disease staging $\rightarrow$ better patient stratification

Secondary Aim:

- Develop performance criteria for evaluation of disease progression models

Why?

- Comparative performance of disease progression models currently unknown

Novel EBM and DEM Extensions Perform Better than Standard Implementations

- Novel extensions vs standard implementations

Model	Staging Consistency		Time-lapse	
	Hard	Soft	Hard	Soft
EBM - Standard	0.88 ± 0.12	0.66 ± 0.09	-	-
EBM - Sampling	0.96 ± 0.06	0.70 ± 0.06	-	-
EBM - EM	0.95 ± 0.10	0.68 ± 0.11	-	-
DEM - Standard	0.94 ± 0.06	0.95 ± 0.05	0.54 ± 0.31	0.52 ± 0.29
DEM - Optimised	0.95 ± 0.05	0.95 ± 0.04	0.56 ± 0.28	0.52 ± 0.27

Table 1: PCA - DRC cohort

Model	Staging Consistency		Time-lapse	
	Hard	Soft	Hard	Soft
EBM - Standard	0.91 ± 0.16	0.71 ± 0.07	-	-
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Table 2: tAD - DRC cohort

Novel Performance Criteria More Sensitive than Accuracy of Diagnostic Predictions

Model	Staging Consistency		Time-lapse	
	Hard	Soft	Hard	Soft
EBM - Standard	0.88 ± 0.12	0.66 ± 0.09	-	-
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Table 3: PCA - DRC cohort

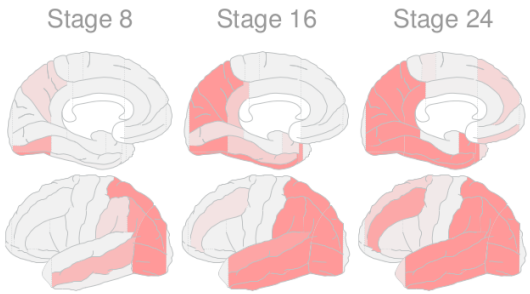
Model	PCA vs AD	Controls vs PCA	Controls vs AD
EBM - Standard	0.72 ± 0.13	0.95 ± 0.05	0.90 ± 0.06
EBM - Simultaneous Sampling	0.79 ± 0.09	0.94 ± 0.06	0.90 ± 0.05
EBM - EM	0.80 ± 0.07	0.95 ± 0.05	0.87 ± 0.05
DEM - Standard	0.81 ± 0.07	0.95 ± 0.05	0.90 ± 0.11
DEM - Trajectory Alignment	0.82 ± 0.09	0.93 ± 0.06	0.88 ± 0.14
Support Vector Machine	0.79 ± 0.14	0.91 ± 0.06	0.88 ± 0.07

Table 4: Accuracy of diagnosis prediction - DRC data

- Work still in progress

My PhD Contributions

1. Modelling the Progression of PCA



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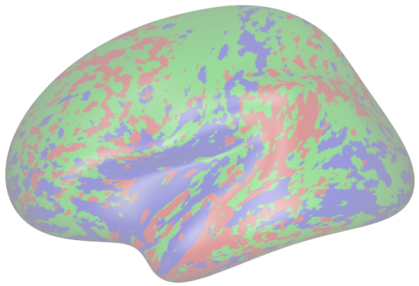

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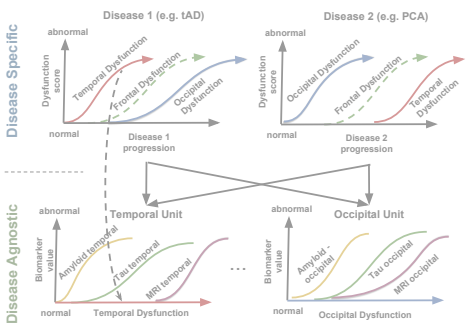

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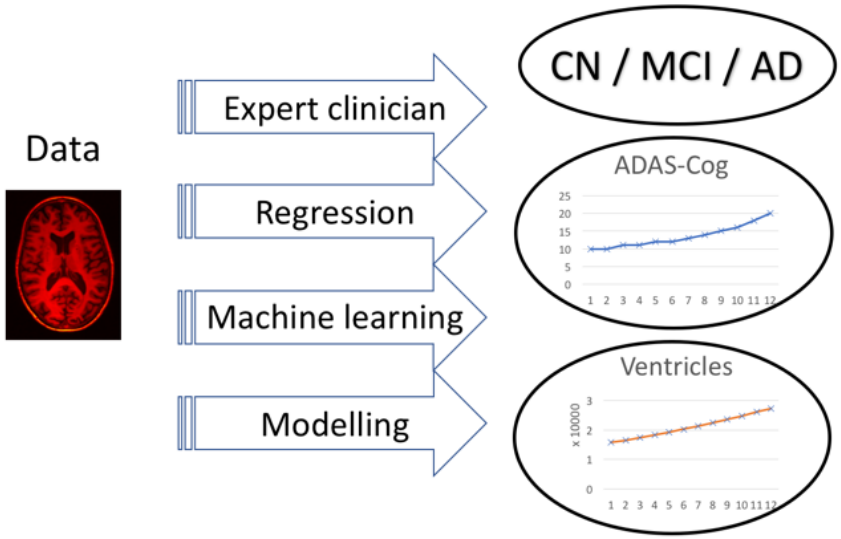
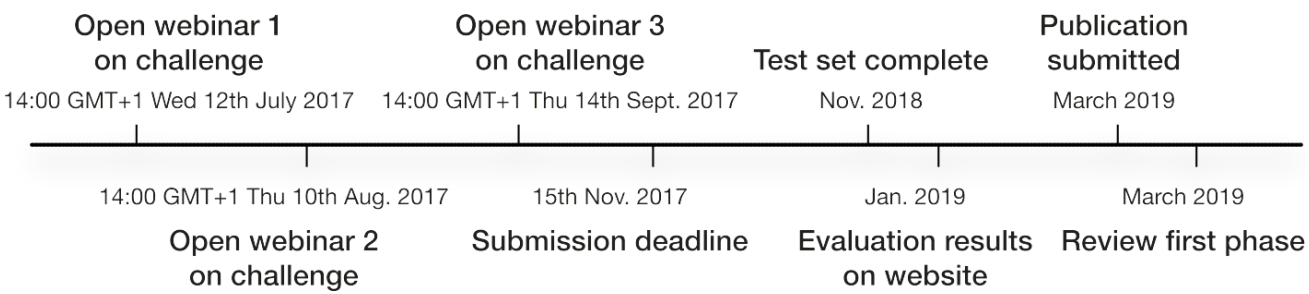
5. TADPOLE Competition

TADPOLE is a Challenge to Predict the Progression of Individuals at Risk of AD

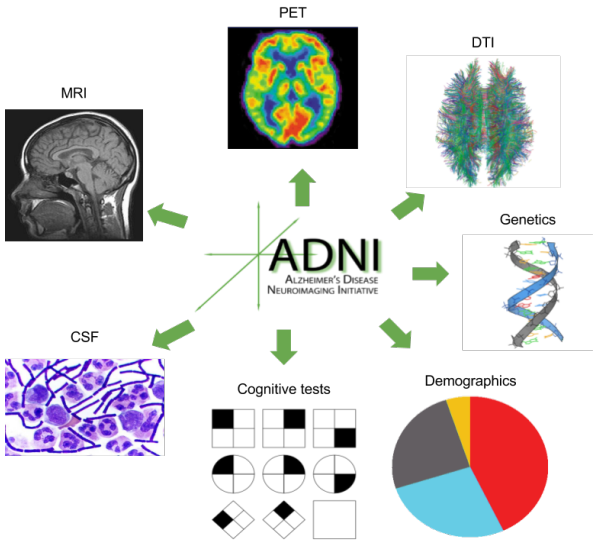


- Train on existing data from ADNI subjects, then predict future values over the next 5 years



My TADPOLE Contributions

- Assembled the training datasets from several ADNI spreadsheets
- Helped create the website
- Built an automated evaluation system and leaderboard
- Wrote the challenge design paper



RANK	TEAM NAME	MAUC	BCA	ADAS MAE	VENTS MAE	ADAS WES	VENTS WES	ADAS CPA	VENTS CPA	DATE
1	TeamAlgosForGood1	0.809	0.856	4.087	4.52e-03	4.087	3.81e-03	0.091	0.006	2017-09-18 09:34 (UTC+0)
2	FPC1	0.758	0.722	5.000	4.19e-03	4.976	4.19e-03	0.350	0.381	2017-09-18 09:34 (UTC+0)
3	FPC3	0.706	0.721	6.369	2.56e-03	6.736	2.56e-03	0.250	0.267	2017-09-12 22:51 (UTC+0)
4	FPC2	0.706	0.721	6.369	2.56e-03	6.711	2.56e-03	0.392	0.324	2017-09-18 09:34 (UTC+0)

Join the TADPOLE Challenge!

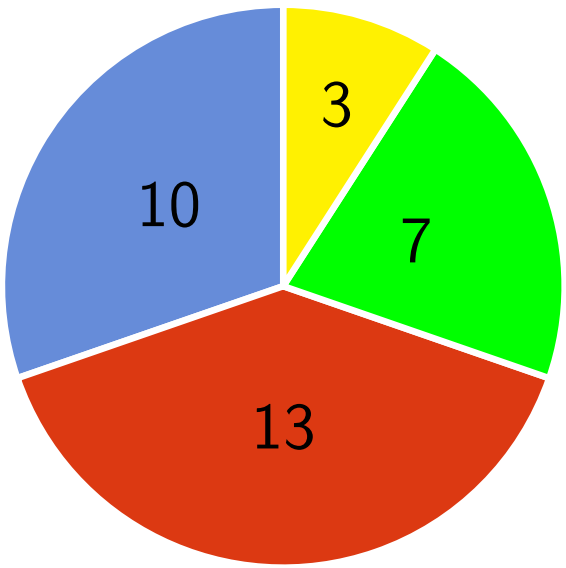
- URL: https://tadpole.grand-challenge.org/
- Deadline: 15 November 2017
- Prize fund: £30,000

Team Locations

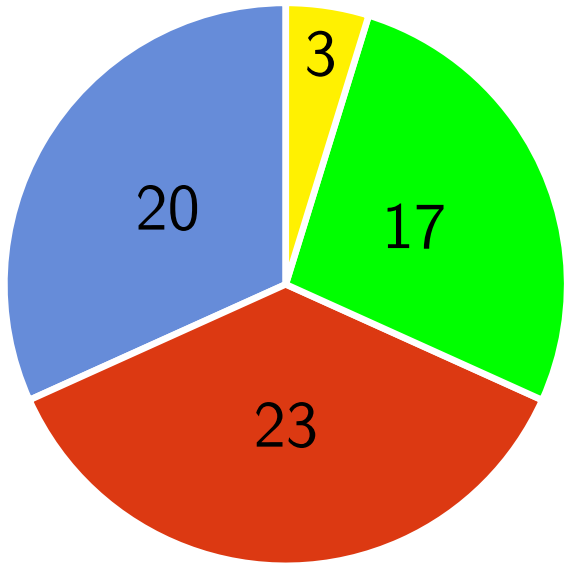
- USA 9
- UK 8
- France 4
- Denmark 2
- Netherlands 2
- Mexico 2
- Australia 1
- Romania 1
- Canada 1
- Israel 1
- Finland 1

Prediction Methods

Breakdown by number of teams



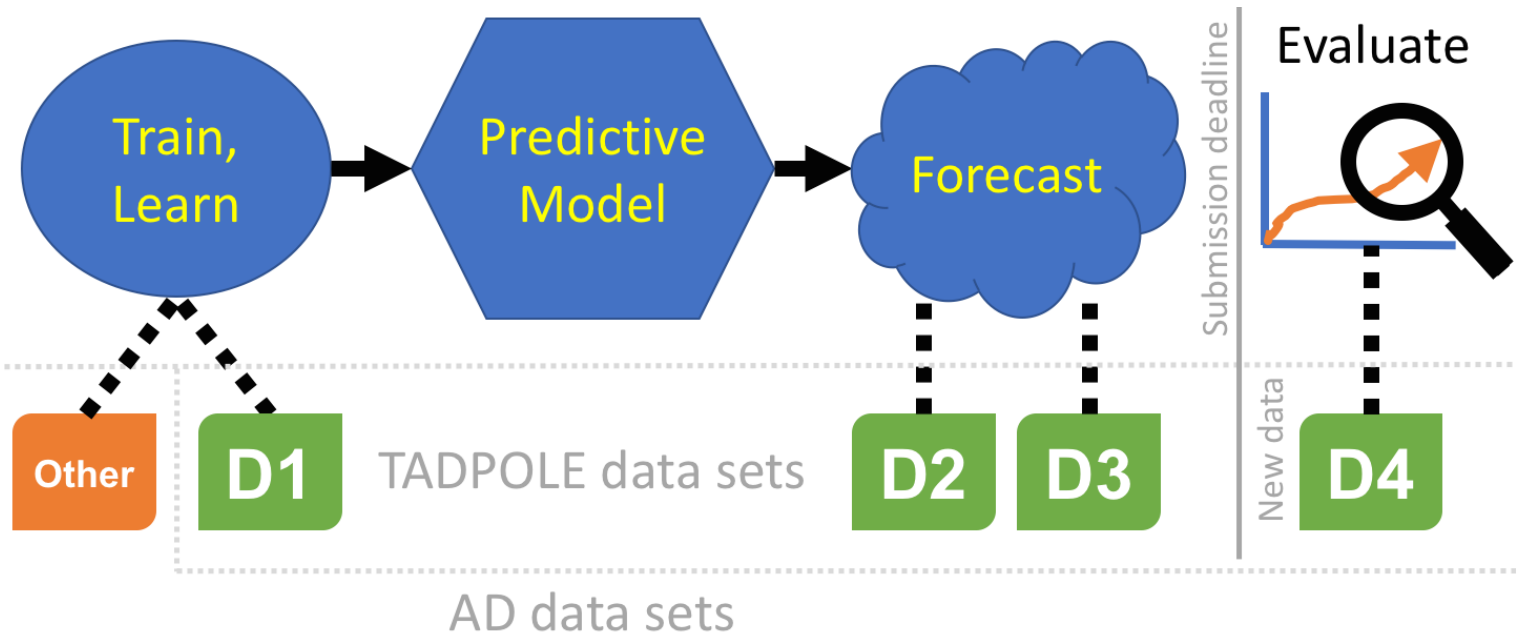
Breakdown by number of entries



- Regression
- Machine learning
- Disease Progression Model
- Other

Next steps

- Run final evaluation with ADNI data so far
- Submit publication with results



Acknowledgements

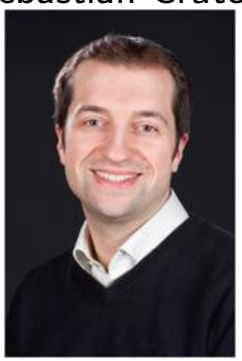
Collaborators

1. Leon Aksman
2. Maura Bellio
3. Arman Eshaghi
4. Nicholas Firth
5. Sara Garbarino
6. Kyriaki Mengoudi
7. Marco Lorenzi
8. Neil Oxtoby
9. Peter Wijeratne
10. Alexandra Young

Project supervisors

Daniel Alexander

Sebastian Crutch



Neil Oxtoby

Funders

UCL EPSRC CDT in Medical Imaging

EPSRC Pioneering research and skills