UNIVERSITY OF CAMBRIDGE

Clustering Trajectories of Neurodegenerative Disease

With Mixtures of State Space Models

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Outline

- Methods
  - Background & motivation
  - Our approach
- Results
  - Application to a research cohort
  - Transferring trained models from a research to a clinical setting
- Conclusions and future work

Motivation & approach

Motivation

- Alzheimer's disease (AD) is the most common cause of dementia
  - Age correlates strongly with disease
  - Prevalence expected to increase in the coming decades
- Drug trials have been largely unsuccessful
  - Potentially because interventions occur too late in disease progression
  - Effective widespread early detection could assist clinical trials
- Current gold-standard indicators of AD (mostly neuroimaging-based biomarkers) are invasive and expensive
  - Not practical for population-wide screening
- Cognitive tests / digital metrics can be obtained readily and cheaply
  - But may not be as predictive

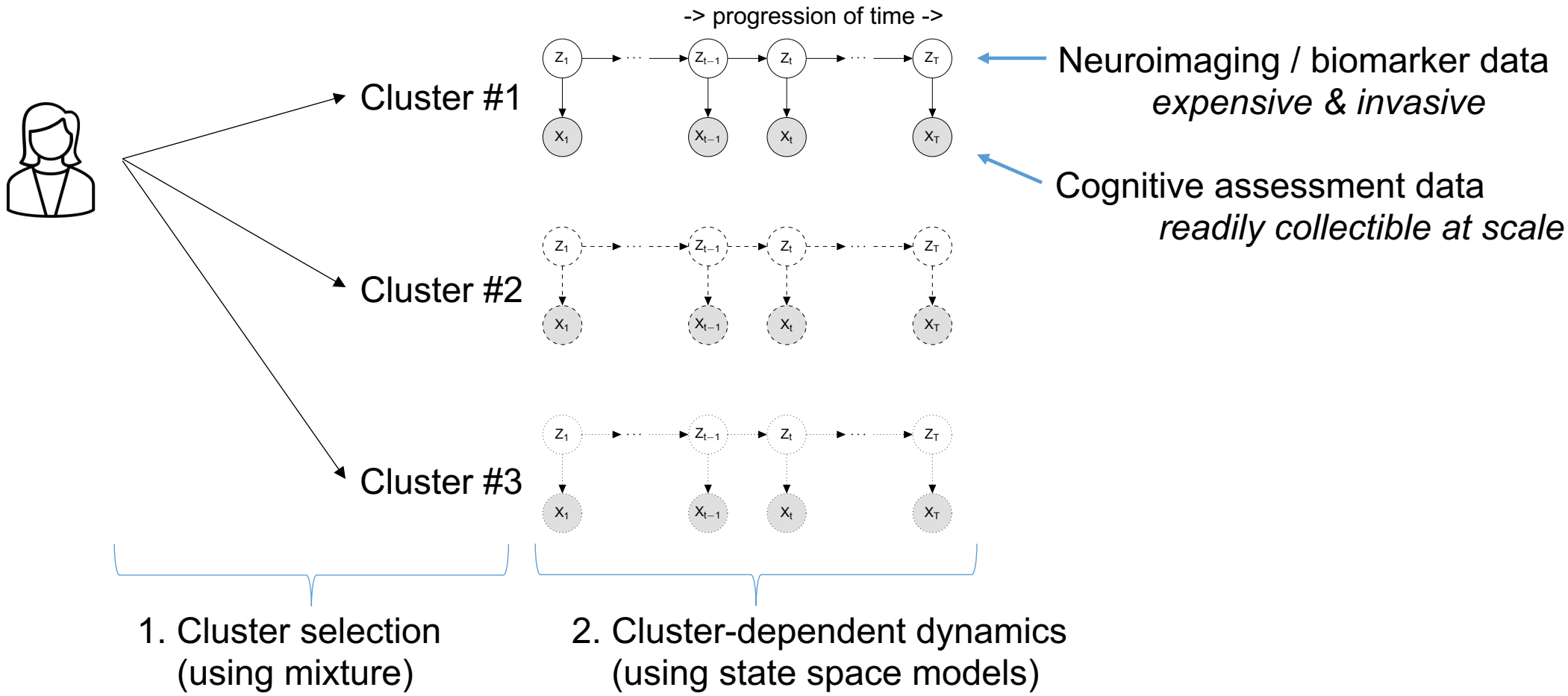
Can we combine longitudinal biomarker and cognitive data to cluster trajectories in a clinically meaningful way?

Why unsupervised?

- Misdiagnosis is common
  - Clinical labels are not 100% accurate
  - Common comorbidities, such as geriatric depression and stroke, also cause memory problems
  - Some clinicians view ‘Mild Cognitive Impairment’ (MCI) with skepticism
- Emphasis on earlier diagnosis
  - Changes in the brain begin years before symptoms
  - We want to be making predictions before labels are available
- Possible to discover subtypes and different patterns of disease progression
  - The disease may progress differently for different people

A model-based approach

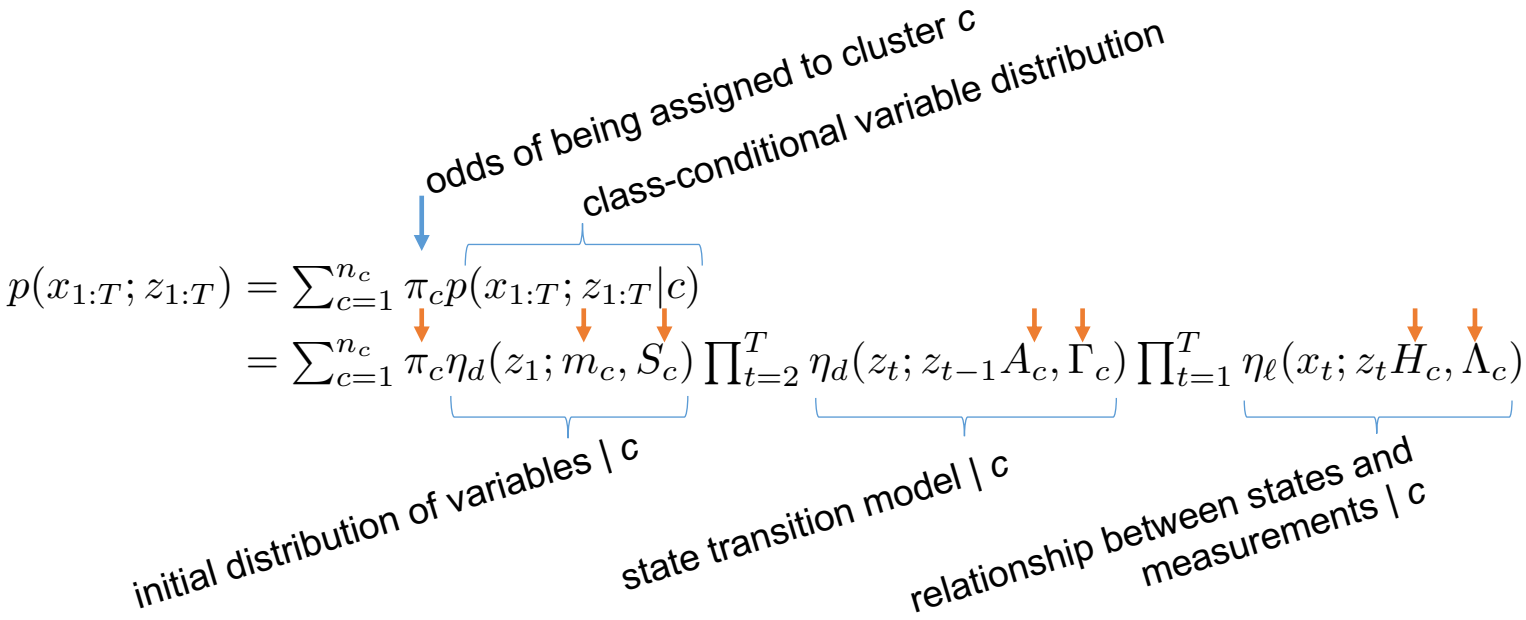
- We learn a mixture of state space models on the trajectory data:



Model specification

We specify a parameterized, generative distribution on the sequences of biomarkers and cognitive assessments

- start with linear Gaussian dynamics
  - same model underlying mixture Kalman filters
  - analytic marginalization for missing / hidden data
- training done using EM with hard assignment
  - makes moving to nonlinear specifications very straightforward



Results on ADNI research data

ADNI data description

We created trajectories at regular 2-year intervals using ADNI data:

- Biomarkers
  - Grey matter score
  - Amyloid burden
- Cognitive scores
  - ADNI-Mem
  - ADNI-EF
  - ADAS-13
  - MoCA
- We also collect MMSE to profile clusters

- After quality control, this gives us trajectories:

trajectory	CN	sMCI	pMCI	AD	total
length 2	142	122	13	60	**337**
length 3	72	93	6	23	**194**
length 4	20	9	0	11	**40**
total	**234**	**224**	**19**	**94**	**571**

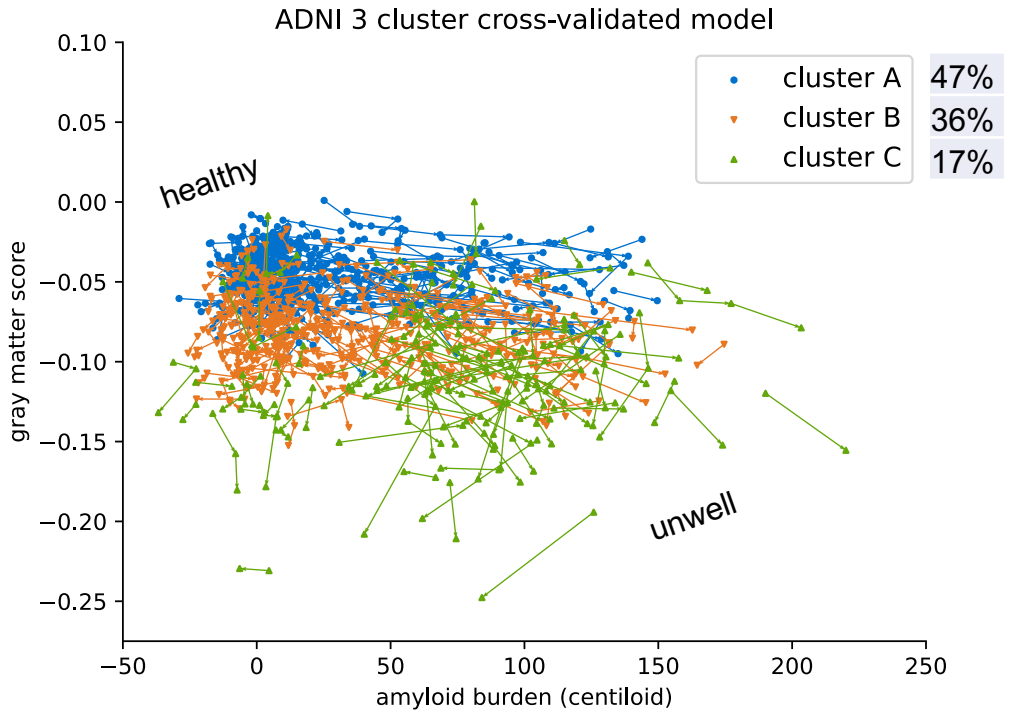
where clinical labels correspond to the final observation in each trajectory:

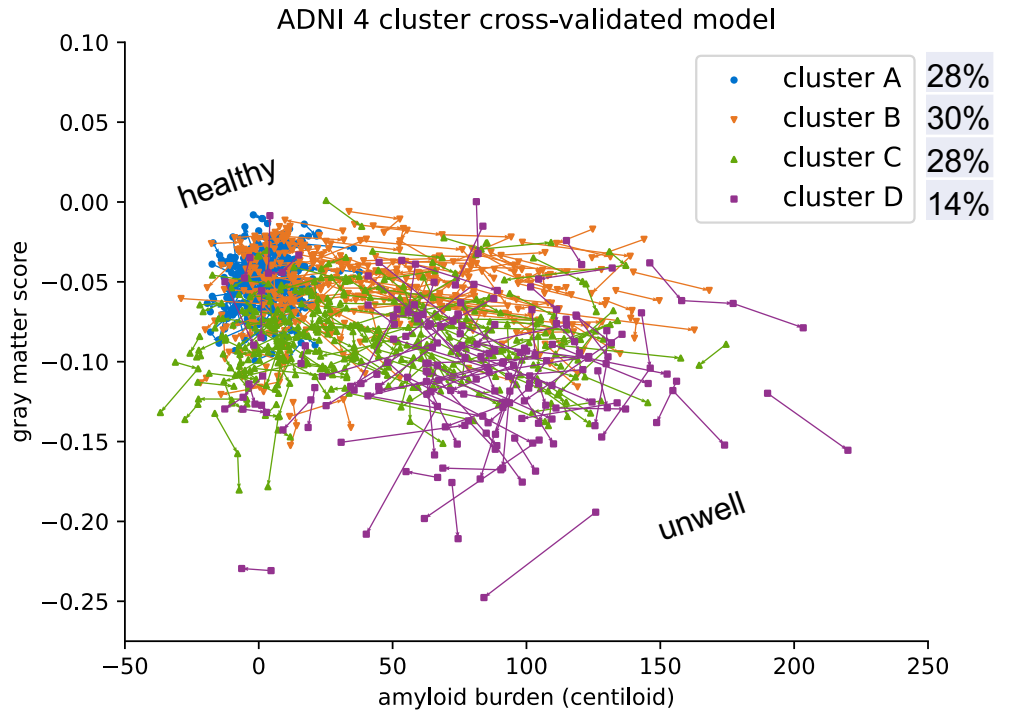
- CN = cognitively normal
- sMCI = stable Mild Cognitive Impairment
- pMCI = progressive MCI
- AD = Alzheimer's disease

** pMCI = MCI now + AD diagnosis within 3 years*

3- & 4-cluster plots coloured by cluster

- predictions using 10-fold cross-validation





Predicting without access to latent states

We can mask

- amyloid score, or
- both amyloid and gray matter

when making predicting model predictions

3 cluster model

- 93% of labels are maintained when missing amyloid alone
- 75% of labels maintained when missing both amyloid and gray matter
- of those that do switch, all switch by only one level (i.e. A->B and not A->C)

		no amyloid/GM		
		A	**B**	**C**
original	**A**	225	44	0
	B	64	138	4
	C	0	30	66

4 cluster model

- 76% of labels maintained when missing amyloid alone
- 58% of labels maintained when missing both
- of those that do switch, 74% move only one level

		no amyloid/GM			
		A	**B**	**C**	**D**
original	**A**	103	38	18	0
	B	50	84	33	2
	C	38	40	78	5
	D	0	6	12	64

Predicting without access to history

The model requires trajectory data for training

- however, once trained, we can predict cluster membership using snapshot measurements

3 cluster model

- 91% of labels are maintained when history is masked

		final snapshot		
		A	**B**	**C**
original	**A**	257	11	1
	B	12	175	19
	C	1	6	89

4 cluster model

- 85% of labels maintained when history is masked

		final snapshot			
		A	**B**	**C**	**D**
original	**A**	141	11	7	0
	B	15	138	14	2
	C	7	7	129	18
	D	1	2	3	76

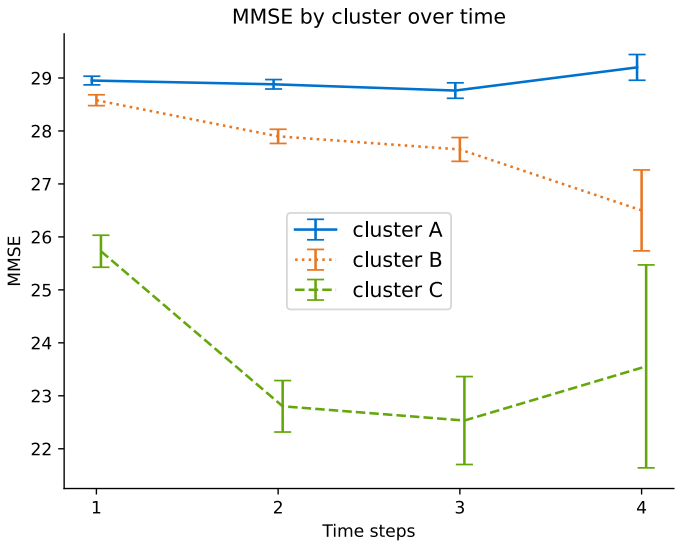
Profiling clusters by MMSE

The Mini-Mental State Exam (MMSE) is a 30-point test for detecting MCI

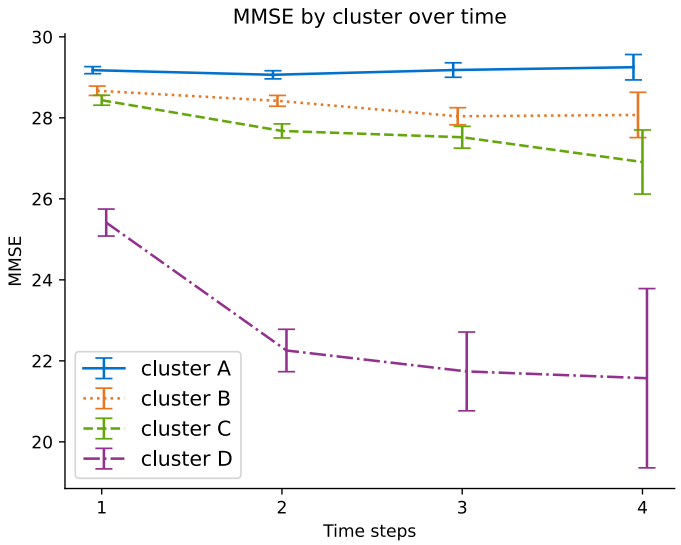
- not as sensitive as some of the other cognitive metrics
- very widely used in the clinical community
- held-out from the model

3 cluster model

- mean +/- std err.
- for time steps 3 & 4, taken over trajectories having 3rd and 4th observation



4 cluster model



Summary comparison of average outcomes versus labels

		ours				sustain	
cluster	**diagnosis**	**train**	**test**	**test (s.)**	**test (n.h.)**	**train**	**test**
A	CN	59%	58%	58%	63%	41%	47%
	sMCI	40%	40%	40%	36%	40%	34%
	pMCI	0%	1%	1%	0%	4%	3%
	AD	**1%**	**1%**	**1%**	**1%**	**15%**	**17%**
B	CN	35%	36%	38%	24%	42%	38%
	sMCI	47%	48%	49%	54%	39%	41%
	pMCI	6%	5%	4%	6%	3%	5%
	AD	**12%**	**11%**	**9%**	**16%**	**16%**	**16%**
C	CN	4%	3%	4%	1%	40%	36%
	sMCI	19%	19%	20%	9%	38%	45%
	pMCI	5%	7%	9%	7%	3%	3%
	AD	**72%**	**71%**	**67%**	**83%**	**18%**	**16%**

s. = test on snapshots
n.h. = test w/o hidden variables

		ours				sustain	
cluster	**diagnosis**	**train**	**test**	**test (s.)**	**test (n.h.)**	**train**	**test**
A	CN	64%	65%	63%	65%	48%	45%
	sMCI	36%	33%	36%	35%	39%	40%
	pMCI	0%	1%	1%	1%	4%	5%
	AD	**0%**	**1%**	**1%**	**0%**	**9%**	**10%**
B	CN	46%	46%	48%	46%	46%	48%
	sMCI	47%	47%	46%	47%	37%	36%
	pMCI	3%	2%	2%	3%	4%	3%
	AD	**4%**	**5%**	**5%**	**4%**	**13%**	**13%**
C	CN	32%	31%	34%	23%	40%	42%
	sMCI	46%	48%	48%	51%	40%	40%
	pMCI	7%	8%	7%	6%	2%	2%
	AD	**16%**	**13%**	**11%**	**21%**	**18%**	**16%**
D	CN	3%	2%	4%	0%	21%	13%
	sMCI	16%	17%	21%	10%	43%	46%
	pMCI	4%	4%	4%	7%	4%	6%
	AD	**77%**	**77%**	**71%**	**83%**	**32%**	**36%**

<<< declining health <<<

SuStaIn is another unsupervised method for clustering trajectories

NUS clinical data

Data description

- Transferring models to different populations (esp. from research to clinical cohorts) remains a challenging problem in the AD space
- We applied our model trained on ADNI to clinical data from NUS in Singapore

- 185 observations of
  - GM score
  - amyloid burden
  - MoCA score
- Missing: ADNI-Mem, ADNI-EF, ADAS-13
- We have MMSE for profiling
- Diagnostic outcomes as follows:

diagnosis	rate
normal	16%
CIND mild	30%
CIND moderate	24%
vascular dementia	11%
AD	20%

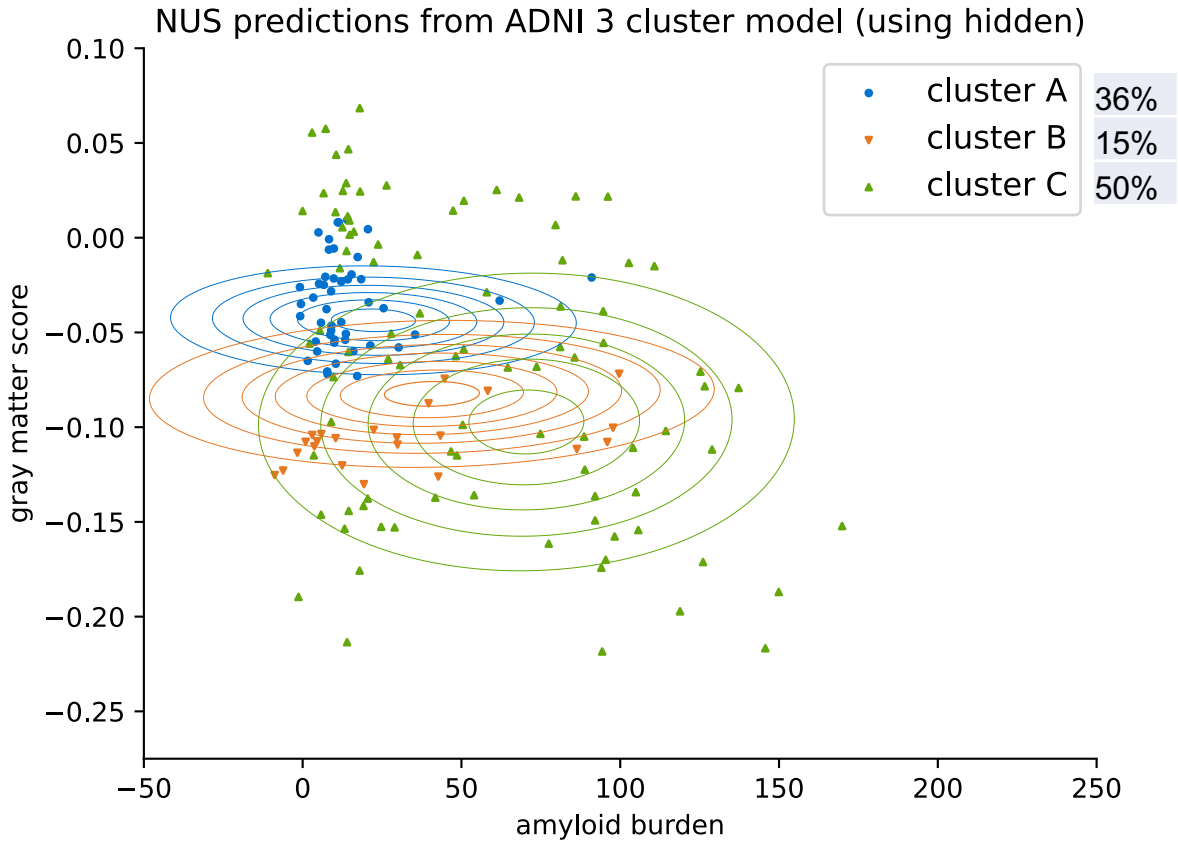
3 clusters

- Very similar breakdowns by clinical outcome for an entirely new cohort

cluster	NCI	CIND-mild	CIND-moderate	VAD	AD
A	32%	46%	17%	3%	3%
B	7%	41%	33%	11%	7%
C	7%	16%	26%	16%	35%

cluster	avg. MMSE
A	26.2
B	23.8
C	19.1

*** highly significant



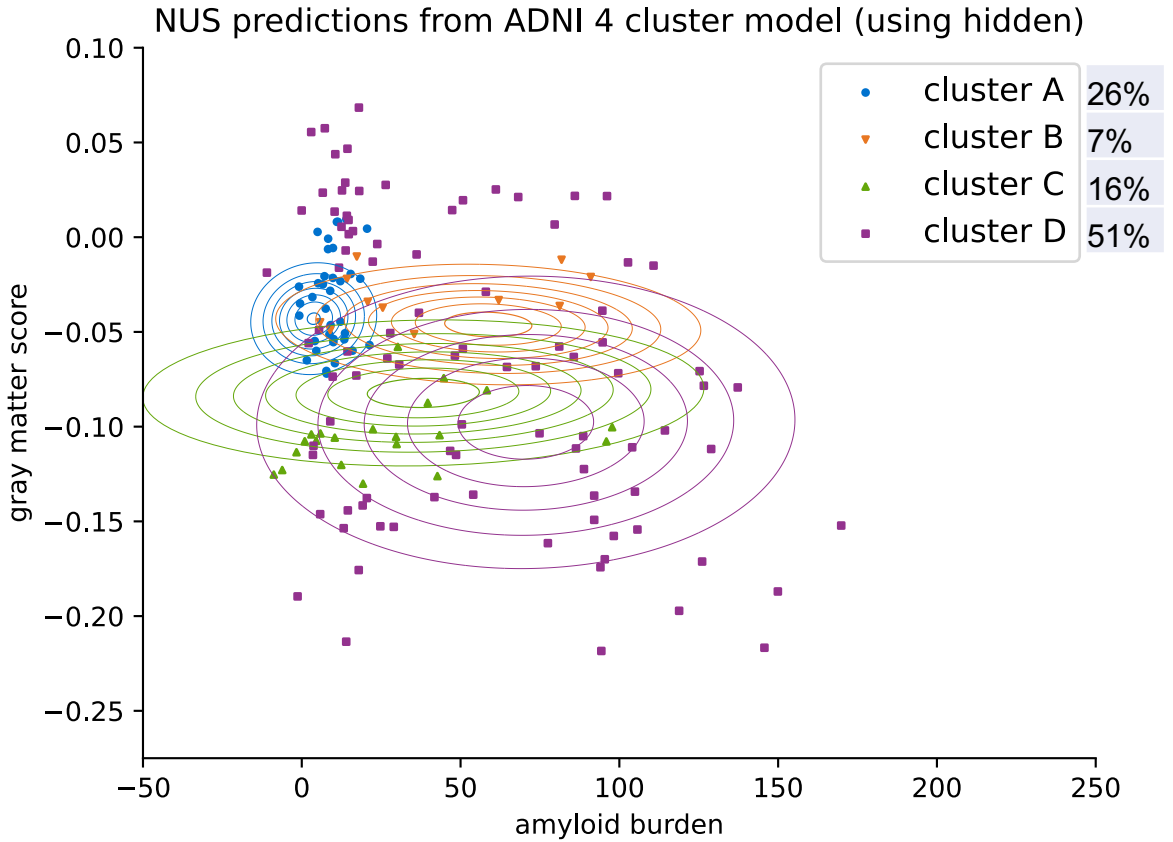
4 clusters

- Similar story with 4 clusters

cluster	NCI	CIND-mild	CIND-moderate	VAD	AD
A	31%	48%	17%	4%	0%
B	25%	50%	17%	0%	8%
C	17%	43%	30%	7%	3%
D	6%	15%	26%	17%	36%

cluster	avg. MMSE
A	26.7
B	24.1
C	24.4
D	19.3

*** highly significant



Next steps

Moving forward

- We've been experimenting with nonlinear / non-gaussian models for the trajectory components
  - No biological reason to assume that the relationship between cognitive assessments and underlying biomarker levels is linear
- We've been gathering larger datasets that will allow us to increase model complexity / the number of clusters considered
  - We're also gathering datasets of currently healthy people for earlier profiling
- We plan to develop more informative digital features that can be collected readily and inexpensively at scale
  - From Fitbits, EEG headbands, smartphone apps
  - As part of the EDoN Initiative (https://edon-initiative.org)

Thanks!

From all of us at the Adaptive Brain Lab

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