Modelling the Neuroanatomical Progression of Alzheimer’s Disease and Posterior Cortical Atrophy

Răzvan V. Marinescu

Supervisors: Polina Golland (current), Daniel C. Alexander (previous)

Medical Vision Group, Massachusetts Institute of Technology
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
▶ 2014-2019: 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., Brain, 2018)

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

**Subtype and Stage Inference**
(Young et al., Nature Comms., 2018)
POND Aim 2: Apply the Models to Distinct Neurodegenerative Diseases

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

![Brain images showing stages 1, 5, 9, 13, and 17 of typical AD progression.]

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

![Graph showing cumulative abnormality probability over time for different biomarkers.]

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

![Brain images showing progression from early to late stage of multiple sclerosis with stages 12 to 62.]

**Huntington’s disease**

![Brain images showing stages 0 to 16 of Huntington’s disease progression.]

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Introduction
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)

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

(1)
Alzheimer’s Disease is a Devastating Disease

- 46 million people affected worldwide
Alzheimer’s Disease is a Devastating Disease

- 46 million people affected worldwide

![Map of people living with dementia around the world with data for 2015, 2030, and 2050.](image)

- No treatments available that stop or slow down cognitive decline
- Q: Why did clinical trials fail? A: Treatments were not administered early enough
Alzheimer’s Disease is a Devastating Disease

- 46 million people affected worldwide

![Map showing dementia distribution worldwide](image)

- 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

Accurate disease staging → 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

How can we build such a disease progression model?

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Disease Progression Modelling
Benefits of Quantitative Disease Progression Models

- Basic biological insight
- Staging can help stratification in clinical trials
Benefits of Quantitative Disease Progression Models

- Basic biological insight
- Staging can help stratification in clinical trials
- Differential diagnosis and prognosis
Benefits of Quantitative Disease Progression Models

- Basic biological insight
- Staging can help stratification in clinical trials
- Differential diagnosis and prognosis

How can we build such a disease progression model?
Building a Quantitative Disease Progression Model is difficult

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
Building a Quantitative Disease Progression Model is difficult

what we have

<table>
<thead>
<tr>
<th>Biomarker Value</th>
<th>Time Since Baseline</th>
</tr>
</thead>
<tbody>
<tr>
<td>abnormal</td>
<td>Measurements</td>
</tr>
<tr>
<td>normal</td>
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</table>

what we want

<table>
<thead>
<tr>
<th>Biomarker Value</th>
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<tbody>
<tr>
<td>abnormal</td>
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Challenges:

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**what we have**

- Biomarker Value vs Time Since Baseline

**what we want**

- Biomarker Value vs Disease Stage

**Challenges:**

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My PhD Contributions

1. Modelled progression of PCA and tAD (using existing methods)

2. Developed Novel Spatio-temporal Model (DIVE)

3. Developed Novel Transfer Learning method (DKT)

4. Organised TADPOLE Competition

5. Created BrainPainter software
Overview

1. Modelled progression of PCA and tAD (using existing methods)

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5. Created BrainPainter software
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)

<table>
<thead>
<tr>
<th></th>
<th># Subjects</th>
<th>Gender M/F</th>
<th>Age at baseline (years)</th>
<th>Years from onset (years)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Controls</td>
<td>89</td>
<td>33/56</td>
<td>60.5 ± 11</td>
<td>-</td>
</tr>
<tr>
<td>PCA</td>
<td>70</td>
<td>27/43</td>
<td>63.0 ± 7</td>
<td>4.4 ± 2.8</td>
</tr>
<tr>
<td>AD</td>
<td>65</td>
<td>34/31</td>
<td>66.3 ± 8</td>
<td>4.8 ± 2.6</td>
</tr>
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Data: Structural MRI scans

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

- Aim: Region 1 $\rightarrow$ Region 2 vs Region 2 $\rightarrow$ Region 1

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Estimated Sequence: Region 2 $\rightarrow$ Region 1
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Estimated Sequence: Region 2 \(\rightarrow\) Region 1

![Frequency distribution for Region 1 and Region 2](image)
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Estimated Sequence: Region 2 $\rightarrow$ Region 1

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Cross-sectional Modelling
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* et al., Brain (recently accepted), 2019
Atrophy Patterns Resemble Previous Studies from the Literature

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

---

Firth*, Marinescu* and Primativo* et al., Brain, 2019
PCA Subtypes show Different Atrophy Progressions, providing Evidence for Heterogeneity within PCA

**Initial hypotheses**

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

![Brain images with atrophy progression stages](image-url)
The Differential Equation Model reconstructs Biomarker Trajectories from Short-term Longitudinal Measurements

What we want

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

What we have

Solve for \( x \) using the Euler method:

\[
t_1 = t_0 + \delta t
\]
\[
x_1 = x_0 + f(x_0)\delta t
\]
PCA: rapid and extensive atrophy in occipital and parietal regions

tAD: global atrophy pattern, with early hippocampal involvement

Firth*, Marinescu* and Primativo* et al., Brain, 2019
My PhD Contributions

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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: Correlate with brain networks + better prediction/staging

▶ **Aim:** Move from ROI-based analysis to voxelwise/vertexwise

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 ✗

- Estimate trajectories for each vertex on the cortical surface
- Vertex measures pathology (e.g. thickness, amyloid) at that location

Only Disease Progression Modelling

- Cannot identify disconnected atrophy patterns ✗
- Can estimate biomarker trajectories ✓
- Can estimate subjects disease stages ✓
DIVE clusters vertices/voxels with similar trajectories of pathology

A

Subject 1, visit 2 Subject 2, visit 2

B

extract vertexwise/voxelwise measures (cortical thickness, PET, DTI)

C

group vertices into clusters based on trajectory dynamics

D

iterate until convergence

E

estimate average trajectory for each cluster

estimate disease progression scores

Vertex measure

Disease Progression score

Vertex 1 measure

Disease Progression score
Each subject $i$ at visit $j$ has an associated disease progression score (DPS) $s_{ij}$:

$$s_{ij} = \alpha_i t_{ij} + \beta_i$$

where:

- $s_{ij}$ - disease progression score of subject $i$ at timepoint $j$
- $t_{ij}$ - age of subject $i$ at timepoint $j$
- $\alpha_i$ - progression speed of subject $i$
- $\beta_i$ - time shift of subject $i$
Step 2 - Model Evolution of Pathology at Specific Location in the Brain

▶ Each biomarker measurement $V_{ij}^l$ follows a sigmoidal curve $f(\cdot; \theta)$ along the disease progression:

$$V_{ij}^l \approx f(s_{ij}; \theta_k) = \frac{a_k}{1 + \exp(-b_k(s - c_k))} + d_k$$

where

▶ $V_{ij}^l$ - biomarker (e.g. thickness, amyloid) at location $l$ for subject $i$, timepoint $j$
▶ $\theta_k = [a_k, b_k, c_k, d_k]$ - parameters of $k$-th sigmoid curve

▶ We assume Gaussian noise along the $k$-th trajectory:

$$p(V_{ij}^l | \alpha_i, \beta_i, \theta_k, \sigma_k) \sim N(f(\alpha_i t_{ij} + \beta_i; \theta_k), \sigma_k)$$

where:
▶ $N$ - pdf of the Gaussian distribution
▶ $\sigma_k$ - noise level
Our Model So Far

1. Model disease progression score for one subject $i$ at visit $j$:
   \[ s_{ij} = \alpha_i t_{ij} + \beta_i \]

2. Model biomarker trajectory of one vertex (point) on the brain:
   \[ p(V_{ij} | \alpha_i, \beta_i, \theta_k, \sigma_k) \sim N(f(\alpha_i t_{ij} + \beta_i; \theta_k), \sigma_k) \]
Step 3: Group Vertices with Similar Progression Dynamics into Clusters

Define $Z_l$ as the cluster that generated vertex $l$:

$$p(V_l^{ij} | \alpha_i, \beta_i, \theta_{Z_l}, \sigma_{Z_l}) \sim N(f(\alpha_i t_{ij} + \beta_i; \theta_{Z_l}), \sigma_{Z_l})$$

where

- $Z_l$ - discrete latent variable allocating vertex $l$ to a cluster $k \in [1 \ldots K]$.

Extend to all subjects and vertices:

$$p(V, Z | \alpha, \beta, \theta, \sigma) = \prod_{l} \prod_{(i,j) \in I} N(V_l^{ij} | f(\alpha_i t_{ij} + \beta_i; \theta_{Z_l}), \sigma_{Z_l})$$

where

- $L$ - the total number of vertices on the cortical surface
- $I = (i, j)$ - set of available timepoints for each subject $i$ and timepoint $j$
- we assume independence across subjects and voxels in different clusters
1. Model disease progression score for one subject $i$ at visit $j$:

\[ s_{ij} = \alpha_i t_{ij} + \beta_i \]

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$$p(V, Z | \alpha, \beta, \theta, \sigma) = \prod_{l} \prod_{(i,j) \in I} N(V^T_{ij} | f(\alpha_i t_{ij} + \beta_i; \theta_Z), \sigma_Z)$$

4. Marginalise over the hidden variables $Z_l$ (cluster assignments):

$$p(V | \alpha, \beta, \theta, \sigma) = \prod_{l} \sum_{k} \ p(Z_l = k) \prod_{(i,j) \in I} N(V^T_{ij} | f(\alpha_i t_{ij} + \beta_i; \theta_k), \sigma_k)$$
Step 5: Modelling Spatial Correlation using Markov Random Fields

Motivation

- measurements from neighbouring vertices are inherently correlated
- can "fill-in holes", eliminate noisy cluster assignments due to noise

\[
p(V, Z | \alpha, \beta, \theta, \sigma) = \prod_l \prod_{(i,j) \in I} N(V^l_{ij} | f(\alpha_i t_{ij} + \beta_i | \theta, Z_l), \sigma Z_l) \prod_{l_1 \sim l_2} \psi(Z_{l_1}, Z_{l_2})
\]

where

- \( \psi(Z_{l_1} = k_1, Z_{l_2} = k_2) = \begin{cases} \exp(\lambda) & \text{if } k_1 = k_2 \\ \exp(-\lambda) & \text{otherwise} \end{cases} \)

- \( \lambda \) - MRF parameter

(a) Without MRF (b) With MRF, \( \alpha = 5 \).
Model Fitting with Expectation-Maximisation (EM)

▶ **E-step:**
  - Estimate vertex assignment to clusters $z_{lk}^{(u)} = \zeta_{lk}(\lambda^{(u)})$:
  
  $$
  \lambda^{(u)} = \arg\max_{\lambda} \sum_{l=1}^{L} \sum_{k=1}^{K} \zeta_{lk}(\lambda) \left[ D_{lk} + \lambda \sum_{l_2 \in N_l} \zeta_{l_2 k}(\lambda) - \lambda^2 \sum_{l_2 \in N_l} (1 - \zeta_{l_2 k}(\lambda)) \right]
  $$

  $$
  \zeta_{lk}(\lambda) \approx \exp \left( D_{lk} + \sum_{l_2 \in N_l} \log \left[ \exp(-\lambda^2) + z_{l_2 k}^{(u-1)}(\exp(\lambda) - \exp(-\lambda^2)) \right] \right)
  $$

  where:

  $$
  D_{lk} = -\frac{1}{2} \log (2\pi (\sigma_k^{(u)})^2) |I| - \frac{1}{2} \left( \sigma_k^{(u)} \right)^2 \sum_{i,j \in I} (V_{ij}^{(u)} - f(\alpha_i t_{ij} + \beta_i | \theta_k^{(u)}))^2
  $$

▶ **M-step:**
  - Update trajectories:

  $$
  \theta_k = \arg\min_{\theta_k} \left[ \sum_{l=1}^{L} z_{lk} \sum_{(i,j) \in I} (V_{ij}^{(u)} - f(\alpha_i t_{ij} + \beta_i | \theta_k))^2 \right] - \log p(\theta_k)
  $$

  (2)

  - Update subject progression scores:

  $$
  \alpha_i, \beta_i = \arg\min_{\alpha_i, \beta_i} \left[ \sum_{l=1}^{L} \sum_{k=1}^{K} z_{lk} \frac{1}{2\sigma_k^2} \sum_{j \in I_i} (V_{ij}^{(u)} - f(\alpha_i t_{ij} + \beta_i | \theta_k))^2 \right] - \log p(\alpha_i, \beta_i)
  $$

  (3)
Numerical optimisation

- E- and M-steps have no analytical solution
- Perform numerical optimisation with Nelder-Mead
  - robust and fast convergence
- EM still converges with partial E- and M-steps

Initialisation

- We set $\alpha_i = 1$ and $\beta_i = 0$, $\forall i$
- We initialise $z_{lk} = p(Z_l = k|V_l, \Theta^{old})$ using k-means clustering
  - feature vector for vertex $I$: $[V_{ij}|(i,j) \in I]$ (measurements for all subjects at that location)
- Estimate the optimal number of clusters with the Bayesian Information Criterion (BIC)
  - Number of parameters: $5K + 2S$
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, 2019
source code: https://github.com/mrazvan22/dive
DIVE Estimates the Temporal Evolution of Pathology, Enabling Understanding of Disease Mechanisms

Marinescu et al., Neuroimage, 2019
source code: https://github.com/mrazvan22/dive

Animations generated using BrainPainter: https://github.com/mrazvan22/brain-coloring
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, 2019

source code: https://github.com/mrazvan22/dive
Estimated Subject Progression Scores are Clinically Relevant

Hypothesis:
▶ Clinical relevance → 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** ($\rho = 0.41, p < 1 e^{-66}$)
- **ADAS-COG** ($\rho = -0.40, p < 1 e^{-62}$)
- **MMSE** ($\rho = -0.39, p < 1 e^{-58}$)
- **RAVLT** ($\rho = 0.39, p < 1 e^{-58}$)
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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

### Typical Neurodegenerative Diseases
- Large datasets ✓
- Multimodal imaging ✓
- Longitudinal ✓

### Rare Neurodegenerative Diseases
- Small datasets ✗
- MRI only ✗
- Cross-sectional only ✗
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
- Transfer learning methods exist, but
  - cannot estimate continuous signatures
  - are not interpretable

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- MRI only ✗
- Cross-sectional only ✗
Disease Knowledge Transfer (DKT) can estimate multimodal trajectories in rare diseases by transferring information from larger datasets of typical diseases.
Assume subject $i$ at visit $j$ has dysfunctionality score $\gamma_{ij}^l$ representing multimodal pathology in brain region $l$:

$$\gamma_{ij}^l = f(\beta_i + m_{ij}; \lambda_{d_i}^l)$$ (4)

- $m_{ij}$ - months since baseline
- $\beta_i$ - time shift of subject $i$
- $f(\cdot; \lambda_{d_i}^l)$ - parametric trajectory for unit $l$ in disease $d_i$

Assume measurement $y_{ijk}$ of biomarker $k$ follows trajectory $g(\cdot; \theta_k)$

$$p(y_{ijk}|\theta_k, \lambda_{d_i}^{\psi(k)}, \beta_i, \epsilon_k) = \mathcal{N}(y_{ijk}|g(\gamma_{ij}^{\psi(k)}; \theta_k), \epsilon_k)$$ (5)

Extend the model to all subjects, visits and biomarkers:

$$p(y|\theta, \lambda, \beta, \epsilon) = \prod_{(i,j,k)\in\Omega} p(y_{ijk}|\theta_k, \lambda_{d_i}^{\psi(k)}, \beta_i)$$ (6)
DKT Accurately Estimates Ground Truth Parameters on Synthetic Data

Marinescu et al, 2019, arXiv (submitted to MICCAI)

source code: https://github.com/mrazvan22/dkt
On Patient Data, DKT Estimates Plausible Multimodal PCA Trajectories

- Only MRI data was available in PCA
- Posterior regions are generally affected in late stages
- First time non-MRI biomarker trajectories are quantitatively inferred in PCA

Marinescu et al, 2019, arXiv (submitted to MICCAI)
source code: https://github.com/mrazvan22/dkt
Validation: DKT has Favourable Performance Compared to Other Approaches

Task: Predict missing DTI markers in two datasets: ADNI and PCA

<table>
<thead>
<tr>
<th>Model</th>
<th>Cingulate</th>
<th>Frontal</th>
<th>Hippocam.</th>
<th>Occipital</th>
<th>Parietal</th>
<th>Temporal</th>
</tr>
</thead>
<tbody>
<tr>
<td>DKT (ours)</td>
<td>0.56 ± 0.23</td>
<td>0.35 ± 0.17</td>
<td>0.58 ± 0.14</td>
<td>-0.10 ± 0.29</td>
<td>0.71 ± 0.11</td>
<td>0.34 ± 0.26</td>
</tr>
<tr>
<td>Latent stage</td>
<td>0.44 ± 0.25</td>
<td>0.34 ± 0.21</td>
<td>0.34 ± 0.24*</td>
<td>-0.07 ± 0.22</td>
<td>0.64 ± 0.16</td>
<td>0.08 ± 0.24*</td>
</tr>
<tr>
<td>Multivariate</td>
<td><strong>0.60 ± 0.18</strong></td>
<td>0.11 ± 0.22*</td>
<td>0.12 ± 0.29*</td>
<td>-0.22 ± 0.22</td>
<td>-0.44 ± 0.14*</td>
<td>-0.32 ± 0.29*</td>
</tr>
<tr>
<td>Spline</td>
<td>-0.24 ± 0.25*</td>
<td>-0.06 ± 0.27*</td>
<td>0.58 ± 0.17</td>
<td>-0.16 ± 0.27</td>
<td>0.23 ± 0.25*</td>
<td>0.10 ± 0.25*</td>
</tr>
<tr>
<td>Linear</td>
<td>-0.24 ± 0.25*</td>
<td>0.20 ± 0.25*</td>
<td>0.58 ± 0.17</td>
<td>-0.16 ± 0.27</td>
<td>0.23 ± 0.25*</td>
<td>0.13 ± 0.23*</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>ADNI subgroups: Hippocampal subgroup to Cortical subgroup</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Latent stage model: assumes PCA and tAD all follow the same progression</td>
</tr>
<tr>
<td></td>
<td>Multivariate: estimates DTI markers from all MRI markers using Gaussian Process (RBF kernel)</td>
</tr>
<tr>
<td></td>
<td>Univariate: estimate DTI marker from MRI marker corresponding to the same region (cubic spline)</td>
</tr>
<tr>
<td></td>
<td>Linear model: same as above but linear.</td>
</tr>
</tbody>
</table>

Marinescu et al, 2019, arXiv (submitted to MICCAI)
source code: https://github.com/mrazvan22/dkt
My PhD Contributions

1. Modelled progression of PCA and tAD (using existing methods)

2. Developed Novel Spatio-temporal Model (DIVE)

3. Developed Novel Transfer Learning method (DKT)

4. Organised TADPOLE Competition

5. Created BrainPainter software
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

- Prize fund: £30,000
My TADPOLE Contributions

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

Marinescu et al., TADPOLE Challenge: Prediction of Longitudinal Evolution in Alzheimer's Disease, arXiv, 2018
33 teams from diverse locations participated

- USA 9
- UK 8
- France 4
- Denmark 2
- Netherlands 2
- Mexico 2
- Australia 1
- Romania 1
- Canada 1
- Israel 1
- Finland 1
Various prediction methods were used

Breakdown by number of teams

- Regression: 10
- Machine learning: 13
- Disease Progression Model: 7
- Other: 3

Breakdown by number of entries

- Regression: 20
- Machine learning: 23
- Disease Progression Model: 17
- Other: 3
Next steps

- Running final evaluation with ADNI data so far
- Results to be published at end of May: https://tadpole.grand-challenge.org/
- Submit publication with results
My PhD Contributions

1. Modelled progression of PCA and tAD (using existing methods)

2. Developed Novel Spatio-temporal Model (DIVE)

3. Developed Novel Transfer Learning method (DKT)

4. Organised TADPOLE Competition

5. Created BrainPainter software
BrainPainter generates drawings of cortical and subcortical regions

**Input**: .csv file with numbers between (0-1)

<table>
<thead>
<tr>
<th></th>
<th>hippocampus</th>
<th>inferior temporal</th>
<th>superior parietal</th>
<th>...</th>
</tr>
</thead>
<tbody>
<tr>
<td>Image 1</td>
<td>0.6</td>
<td>0.8</td>
<td>1</td>
<td>...</td>
</tr>
<tr>
<td>Image 2</td>
<td>0.8</td>
<td>0.3</td>
<td>1</td>
<td>...</td>
</tr>
<tr>
<td>Image 3</td>
<td>0.2</td>
<td>1</td>
<td>0.2</td>
<td>...</td>
</tr>
<tr>
<td>Image 4</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>...</td>
</tr>
</tbody>
</table>

**Output**:

- Cortical - front
- Cortical - back
- Subcortical

- No installation required (with docker container)
- [https://github.com/mrazvan22/brain-coloring](https://github.com/mrazvan22/brain-coloring)
BrainPainter Example Use: Progression of ADNI Sub-populations

Young et al., Nature Comms, 2018
BrainPainter Example Use: Subcortical Progression of Huntington’s

Future research directions

Modelling:
- Incorporate biological mechanisms (Raj et al., 2012, Georgiadis et al., 2018)
- Incorporate other sources of data: e.g. genetics (Sclesi et al, Brain, 2018)
- Account for heterogeneity (e.g. Young et al., Nature Comm., 2018)

Simulations:
- Use disease progression models to simulate cohorts (Koval et al., arXiv, 2019)

Applications:
- Other NDs: Multiple Sclerosis, Huntington’s, Parkinson’s
- Other pathologies: e.g. tumours, lesions
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Collaborators

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4. Nicholas Firth
5. Sara Garbarino
6. Marco Lorenzi
7. Kyriaki Mengoudi
8. Neil Oxtoby
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