Data-Driven Disease Progression Modelling for Research (and Healthcare?)

Neil Oxtoby

UKRI Future Leaders Fellow
POND group: Progression Of Neurodegenerative Disease
My quest for supermodels and drugs

Neil Oxtoby
Today’s menu

Alzheimer’s Disease
Heterogeneity

Disease Progression Modelling
Pseudo-time

DPM & Clinical Trials
Enrichment
Alzheimer’s Disease

• Defined by post mortem histopathology

• Clinical syndrome: memory *etc.*

• *Loooooong* pre-symptomatic period: decades of pathology

• Heterogeneity in syndrome, onset, progression, and pathology!
Treatments for Alzheimer’s?

- Amyloid cascade hypothesis (Hardy/Higgins 1992; Selkoe/Hardy 2016)
  + Plenty of supporting evidence
  - Anti-amyloid therapies not proving efficacious in large clinical trials

- Why are clinical trials “failing”? (hundreds since 2003)
  - Wrong time? (too late: prevention vs cure)
  - Wrong people? (subgroups)
  - Insufficient duration?
  - Insensitive end-points? (biology/biomarkers vs clinical benefit)
  - Amyloid hypothesis “wrong”? (wrong biology / comorbidities / multitarget strategies)
    (Salloway, CTAD 2019; Aisen, CTAD 2019; + many at CTAD 2021/22)

O’Connor et al. Alz Res Ther 2020
Oxtoby et al. medRxiv 2021; Frontiers 2022
What have clinical trials done?

M. ten Kate et al., Alz. Res. Therapy (2018)

See also: D. Cash et al., Alz. Res. Therapy (2014)
What have clinical trials done?
**Sporadic AD, natural history: no time zero!**

![Graph](Image)

**Diagnosis**
- CN
- SMC
- EMCI
- LMCI
- AD

Credit: Mike Donohue, USC

Alzheimer’s Disease Neuroimaging Initiative (adni-info.org)
Data-driven Disease Progression Modelling

Lorenzi et al, NeuroImage 2017
Data-driven Disease Progression Modelling

Progression staging in ADNI Ab+ individuals (training data)

Lorenzi et al,
NeuroImage 2017
Data-driven Disease Progression Modelling

Lorenzi et al, NeuroImage 2017
Data-driven Disease Progression Modelling

Disease/Subtype 1

Disease/Subtype 2

Biomarker

Disease stage

Biomarker

Disease stage
Data-driven Disease Progression Modelling

Patient data to match

Disease/Subtype 1

Disease/Subtype 2

Biomarker

Disease stage

Disease stage
Data-driven Disease Progression Modelling

Disease/Subtype 1

Patient data to match

Disease/Subtype 2

Biomarker

Disease stage

Biomarker

Disease stage
Data-driven Disease Progression Modelling

Disease/Subtype 1

Biomarker

Disease/Subtype 2

Biomarker

Likelihood

Disease stage

Patient data to match
Data-driven Disease Progression Modelling

Lorenzi et al, NeuroImage 2017
Disease Progression Modelling + Clustering

• Discrete: Subtype and Stage Inference
  Young at al., Nature Communications 2018

• Continuous: LT-NLME + GMM
  Poulet & Durrleman, IPMI 2019
Event-based model

- Estimates the order of disease “events” from a cross-sectional (or short-term longitudinal) data set

Data-driven: no prior knowledge of disease stage
Event based model

- Cough
- Sneeze
Event based model

- Sneeze
- Cough

Graphs showing event measures for cough and sneeze with different colors for HC, AD: Cough, and AD: Sneeze.
Event based model of Alzheimer’s disease progression

Model Stages:
0
1-3  CSF
4-5  Rates of atrophy
6-8  Cognitive test scores
9-14 Brain volumes

Abeta
P-tau
T-tau
Hippo. Atrophy
Brain Atrophy
ADAS-Cog
RAVLT
Hippocampus
Entorhinal
MMSE
Mid Temporal
Brain
Fusiform
Ventricles

Young et al, Brain 2014
Event based model of Alzheimer’s disease progression

Model Stages:
0
1-3 CSF
4-5 Rates of atrophy
6-8 Cognitive test scores
9-14 Brain volumes

Young et al, Brain 2014
Event based model in Alzheimer’s disease progression: CSF vs PET

Janelidze et al, JAMA Neurol 2021

Associations of Plasma Phospho-Tau217 Levels With Tau Positron Emission Tomography in Early Alzheimer Disease

Shorena Janelidze, PhD; David Berron, PhD; Ruben Smith, MD, PhD; Olof Strandberg, PhD; Nicholas K. Proctor, BS; Jeffrey L. Dage, PhD; Erik Stomrud, MD, PhD; Sebastian Palmqvist, MD, PhD; Niklas Mattsson-Carlsgren, MD, PhD; Oskar Hansson, MD, PhD
Event based model in Alzheimer’s disease progression: CSF vs PET

Figure 3. Order of Change in Plasma Tau Phosphorylated at Threonine 217 (P-tau217), Cerebrospinal Fluid (CSF) P-tau217, and Tau-Positron Emission Tomography (PET) Abnormality

A | Predicted sequence of biomarker abnormality

Uncertainty

CSF P-tau217
Plasma P-tau217
Entorhinal ROI
Temporal meta-ROI
Neocortical meta-ROI

EBM stage

0 0.2 0.4 0.6 0.8 1.0

B | Biomarker changes across event-based modeling stages

Difference in biomarker abnormality, z-scored

CSF P-tau217
Plasma P-tau217
Entorhinal ROI
Temporal meta-ROI
Neocortical meta-ROI

EBM stage

C | Biomarker changes across global neocortical Aβ-PET SUVR

Outcome measures, scaled

[11C]flutemetamol composite, SUVR

Janelidze et al, JAMA Neurol 2021
Subtype and Stage Inference (DPM + clustering)

Young et al., Nat Commun 2018

(a) Underlying model
- Subtypes I
- Subtypes II
- Time

(b) Input data: heterogeneous patient snapshots

(c) Subtypes I

(d) Application: subtyping and staging new patients
- Probability
- Stage
- Subtype

Output: reconstruction of disease subtypes and stages

Young et al., Nat Commun 2018
Subtype and Stage Inference – Genetic FTD

Young et al, Nat Commun 2018
Subtype and Stage Inference – sporadic AD

Typical (CVS = 0.97, f = 0.35)
Stage 1  Stage 5  Stage 9  Stage 13  Stage 17  Stage 21  Stage 25

Cortical (CVS = 0.95, f = 0.38)
Stage 1  Stage 5  Stage 9  Stage 13  Stage 17  Stage 21  Stage 25

Subcortical (CVS = 0.92, f = 0.27)
Stage 1  Stage 5  Stage 9  Stage 13  Stage 17  Stage 21  Stage 25

SuStain subtype

SuStain stage

Young et al, Nat Commun 2018
Subtype and Stage Inference — sporadic AD

b

Typical (CVS = 0.97, f = 0.35)
Some individuals strongly identify with subtypes from early stages.
Some individuals strongly identify with subtypes from early stages.
Subtype and Stage Inference
– further reading

Four distinct trajectories of tau deposition identified in Alzheimer’s disease

Jacob W. Vogel, Alexandra L. Young, Neil P. Oxtoby, Ruben Smith, Rik Ossenkoppele, Olof T. Strandberg, Renaud La Joie, Leon M. Aksman, Michel J. Grothe, Yasser Iturria-Medina, the Alzheimer’s Disease Neuroimaging Initiative, Michael J. Pontecorvo, Michael D. Devous, Gil D. Rabinovici, Daniel C. Alexander, Chul Hyoung Lyoo, Alan C. Evans and Oskar Hansson

Identifying multiple sclerosis subtypes using unsupervised machine learning and MRI data


Uncovering the heterogeneity and temporal complexity of neurodegenerative diseases with Subtype and Stage Inference

Alexandra L Young et al.
Applications of DPM in Clinical trials in Alzheimer’s disease
Applications of DPM in Clinical trials in Alzheimer’s disease

SHOW ME THE DATA!

Jerry Maguire, Sony Pictures 1996
Applications of DPM in Clinical trials in Alzheimer’s disease

• Event-based model
  
  Oxtoby et al., Frontiers 2022

• Subtype and Stage Inference
  
  Shand et al., AD/PD 2022
MCI clinical trial of Donepezil (& vitamin E)

Experiments:
1. Build model (ADNI data)
2. Stage trial data (BL/SC)
3. Stratify
4. Analyse subgroups
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<table>
<thead>
<tr>
<th>Instrument</th>
<th>Treatment</th>
<th>6mo</th>
<th>12mo</th>
<th>18mo</th>
<th>24mo</th>
<th>30mo</th>
<th>36mo</th>
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<tbody>
<tr>
<td>SS &lt; 5</td>
<td>Donepezil</td>
<td>−0.14</td>
<td>−0.04</td>
<td>−0.11</td>
<td>−0.29</td>
<td>−0.60</td>
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<tr>
<td></td>
<td>Vitamin E</td>
<td>−0.56</td>
<td>−0.71</td>
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<td>0.68</td>
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<td>5 ≤ SS ≤ 10</td>
<td>Donepezil</td>
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<td>−0.77</td>
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<td>−1.05</td>
<td>1.10</td>
<td>0.33</td>
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<td></td>
<td>Vitamin E</td>
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<td>−1.83</td>
<td>−0.50</td>
<td>0.47</td>
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<tr>
<td>SS &gt; 10</td>
<td>Donepezil</td>
<td>1.92</td>
<td>3.71*</td>
<td>0.20</td>
<td>4.34</td>
<td>0.52</td>
<td>6.31*</td>
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<td>1.97</td>
<td>1.16</td>
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<tr>
<td>All</td>
<td>Donepezil</td>
<td>0.79</td>
<td>0.89</td>
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<td>0.42</td>
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<td>Vitamin E</td>
<td>−0.15</td>
<td>−0.64</td>
<td>−0.22</td>
<td>−0.56</td>
<td>−2.14</td>
<td>0.04</td>
</tr>
</tbody>
</table>

Table 1. Group differences (Placebo – Treatment) in ADAS-Cog 13 between treatment and placebo (two-sample t test).

* p < 0.05

Experiments:
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2. Stage trial data (BL/SC)
3. Stratify
4. Analyse subgroups
FYN trial of ADZ0530

Experiments:
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Figure 1: Positional variance diagrams showing disease progression event sequence (intensity indicates sequence positional density)
FYN trial of ADZ0530

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Figure 1: Positional variance diagrams showing disease progression event sequence (intensity indicates sequence positional density)

Figure 2: Disease stage histogram in ADNI (top) and FYN (bottom)
FYN trial of ADZ0530

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*Figure 1*: Positional variance diagrams showing disease progression event sequence (intensity indicates sequence positional density)

*Figure 2*: Disease stage histogram in ADNI (top) and FYN (bottom)
FYN trial of ADZ0530

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**Figure 3:** Change in ADAS-Cog 12 scores across 52-week period for whole cohort and two subtypes, separated by trial arm (greater point increase = greater cognitive decline)

**Figure 4:** Change in FDG-PET sROI across 52-week period for whole cohort and two subtypes, separated by trial arm (greater sROI decrease = greater neurodegeneration)
FYN trial of ADZ0530

Experiments:
1. Build model (ADNI data)
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Figure 5: Percentage change in regional volumes across 52-week period for whole cohort and two subtypes, separated by trial arm
Take home messages

• Alzheimer’s disease is a heterogeneous mystery

• Disease Progression Modelling can help to unravel the mystery

• DPM produces quantitative templates of AD progression that can enrich clinical trials to find *the right patients at the right time*
Healthcare?

- Local memory clinic in England
- T2w MRI used for routine care
- T1w MRI cropped!
My quest for supermodels and drugs

Neil Oxtoby

Thanks to all research participants, their families, and my colleagues, in particular those in POND developing supermodels.