Top-down and bottom-up multimodal computational models of Alzheimer’s disease progression

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Why am I here?

Data-driven disease progression modelling

Fusing snippets of multimodal data into quantitative signatures of progression

- Top-down (phenomenology, *James Rowe: precision phenotype*)
- Bottom-up (mechanistic)

Young et al. Nature Comms. 2018
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Neuroimaging **lean**: Heidi Johansen-Berg’s talk

Clinical impact:

*Young et al. Nature Comms. 2018*
Understanding complex systems (brain diseases)

**Top-down approaches**
- ✓ Phenomenology: *in vivo* + clinical
- ✓ Amenable to data-driven…
  - × Mechanistic insight
- Reverse engineering

**Bottom-up approaches**
- × Requires postmortem
  - × Data-driven?
- ✓ Mechanistic insight
- Forward engineering
What do we know about Alzheimer’s?

- *Defined* by postmortem histopathology
  - Braak staging

- Clinical syndrome: memory *etc.*

- *Loooonng* pre-symptomatic period: decades of pathology
  - Rare familial/inherited forms
  - Risk factors: genetics, etc.

- Heterogeneity in syndrome, onset, progression, and pathology!
  - Can probe pathology *in vivo* (PET, MRI)
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: Craig Ritchie’s talk)
  • Too late? (wrong time: prevention vs cure)
  • Individual variability? (wrong people)
  • Insufficient duration?
  • Insensitive end-points? (biology/biomarkers vs clinical benefit: Craig Ritchie’s talk)
  • Amyloid hypothesis “wrong”? (wrong biology / comorbidities / multitarget strategies)
    (Salloway, CTAD 2019; Aisen, CTAD 2019)

• What has/can be done about it?

O’Connor et al. ART 2020
Oxtoby et al. medRxiv 2021
Top-down models
The Journey to
Data-driven disease progression modelling
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2002–2008 Traditional: stage == symptoms
The Journey to Data-driven disease progression modelling

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- Regression

Bethmann et al. PNAS 2002

- Parentage of symptom onset independently using ADSE test

Bateman et al. NEJM 2012

- Parentage of symptom onset independently using MMSE test
The Journey to Data-driven disease progression modelling

2002–2008 Traditional: stage == symptoms

- Regression
- Pattern recognition (supervised ML)

Classifying structural MRI in AD

Klöppel et al. Brain 2008

Disease State Fingerprint for AD

See also Zoe Kourtzi’s talk

Mattila et al. JAD 2011
The Journey to Data-driven disease progression modelling

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• Regression, Pattern recognition (supervised ML)

2004 Alzheimer’s Disease Neuroimaging Initiative
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2010 Hypothetical Models of Alzheimer’s progression

Jack et al. TLN 2010
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Sweeney et al. Nat Comms 2018

Laura Parkes’ talk
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• Pseudo-time methods:
  • discrete (EBM sequencing)

Fontein et al. NeuroImage 2012
Young et al. Brain 2014
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  - discrete (EBM sequencing)
  - continuous (latent-time: LTJMM, IRT, GPPM)

Li et al. Stat Meth Med Res 2017
Leoutsakos et al. JPAD 2016
Lorenzi et al. NIMG 2017
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Subtype & Stage Inference (SuStaIn)

Young et al. Nat. Comms 2018
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- \(\tau\) PET:
  - Vogel et al. medRxiv 2020

Subtype & Stage Inference (SuStaIn)

Young et al. Nat. Comms 2018
What about disease mechanisms?

Can we understand/explain
Top-down observations of pathology, using
Bottom-up models of mechanism?
Bottom-up models

2009–2012 Hypotheses of neurodegeneration due to pathogens

- Selective vulnerability / Wear-and-tear / Network / Use-it-or-lose-it
Bottom-up models

2009–2012 Hypotheses of neurodegeneration


2012– Protein (prion) Spreading Models

- 2012: Network diffusion model (heat eq)
- 2014: Epidemic Spreading Model

Raj et al. Neuron 2012
Iturria-Medina+ PLOS Comp. Biol. 2014
2009–2012 Hypotheses of neurodegeneration

- Seeley et al. Neuron 2009
- Zhou et al. 2012

2012– Protein (prion) Spreading Models

- 2012: Network diffusion model (heat eq)
- 2014: Epidemic Spreading Model
- 2018–19: Physics (Network Spreading + misfolding kinetics)
  - Fisher-Kolmogorov = reaction-diffusion eq. (no mechanistic insight)
  - Heterodimer = normal & abnormal proteins (+ clearance/production)
  - Smoluchowski = stat. physics workhorse (+ size of protein aggregates)

Weickenmeier et al. Phys Rev Lett 2018
Fornari et al. J.R.Soc. Interface 2019
Mouse models

- Network diffusion + selective vulnerability

Fig. 4: Network diffusion model based on anatomical connectivity explains pathological α-synuclein spread.

Henderson et al. Nature Neuroscience 2019
Recap

• Whirlwind tour of Data-Driven Disease Progression Modelling

Take Home (At Home?) Message:

Physics-based computational models are improving our understanding and clinical management of neurodegenerative diseases at multiple scales
Related work from the UCL POND group

- **Sara Garbarino** (former PDRA), w/ Marco Lorenzi
  - Topological progression profiles in Aging, AD, MS (*eLife* 2019 + IPMI)

- **Anna Schroder** (PhD student)
  - False positive/negative connections in tractography

- **Isaac Llorente** (PhD student), Marc Busche (UK DRI @ UCL)
  - Neuroscience-informed Physics-based models (across scales)
    - *Paul Matthews’ Conceptual Challenge 4 (mechanisms)*

- **Hanyi Chen** (senior PDRA), Andre Altmann
  - E-DADS project: early detection (with COMBINE lab at UCL)
    - *Paul Matthews’ Conceptual Challenge 1 (distinguish early)*

- **Neil Oxtoby** (UKRI Future Leaders Fellowship), Cameron Shand…
  - Individualised AI/ML/modelling for Medicine (Alzheimer’s; Clinical Trials; Mechanisms)
The Alzheimer’s Disease Progression Of Longitudinal Evolution Challenge

TADPOLE

Predictive modelling challenge for Alzheimer’s disease

tadpole.grand-challenge.org
TADPOLE SHARE: tadpole-share.github.io

Marinescu et al. arxiv:1805.03909
arxiv:2002.03419
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- E-DADS  e-dads.github.io

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