Constructing multivariate Disease Trajectory Curves for Alzheimer's Disease

Timothy Cox | 1-December-2022

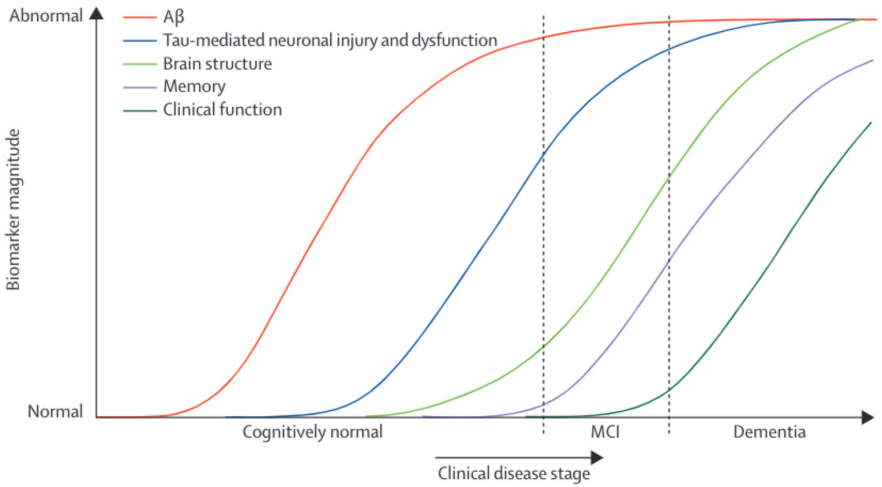
Alzheimer's disease.

Alzheimer's disease is the most common form of dementia, affecting around 70% of people with dementia. If we are to delay onset or prevent progression of the disease, new preventative and/or treatment strategies must be developed.

Treatment for Alzheimer's will only be successful if administered early. As such it is important to understand the the sequential order and timing of different biomarkers, to assist design and recruitment for clinical trials.

Disease trajectories

During progression of Alzheimer's biomarkers typically change in a well defined order. With biomarkers detected by imaging changing before memory and the results.
The age of onset varies person to person.



C.R. Jack *et. al.* Lancet Neurol. 2010, **9**, 119-128
Suggest disease curves.

Can we construct such curves from longitudinal data?

Example Longitudinal study.

- Study started 2006.
- Data collected every 18 months
- Multiple domains: **cognition, imaging**, lifestyle, …
- Participants over 60.
- Patients with Alzheimer's disease (AD), mild cognitive impairment (MCI) and healthy volunteers.
- Most participants in the study for less than a decade.
- All data is collected at two centres (40% subjects from Perth in Western Australia, 60% from Melbourne, Victoria).
- More than 2,000 participants.

aibl

The Australian Imaging, Biomarkers and Lifestyle Flagship Study of Ageing

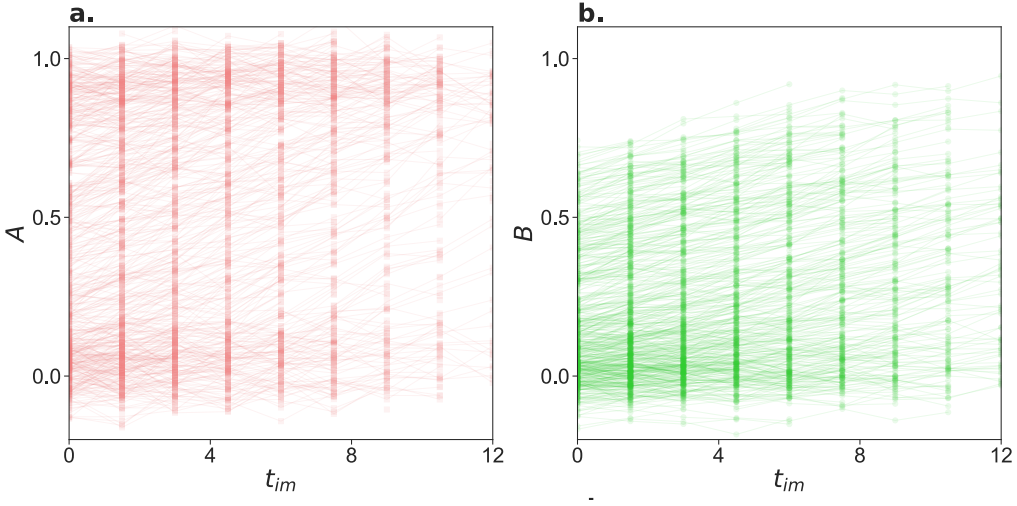
Collaborators

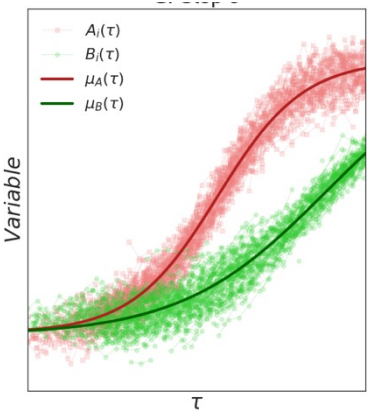
AIBL is a large collaborative study and a complete list of contributors can be found at www.aibl.csiro.au

Goal

Use longitudinal data to:

- Construct a multivariate set of disease trajectory curves depending on a single disease progression time.
- Obtain estimates for participants' disease progression that aligns them with these curves .

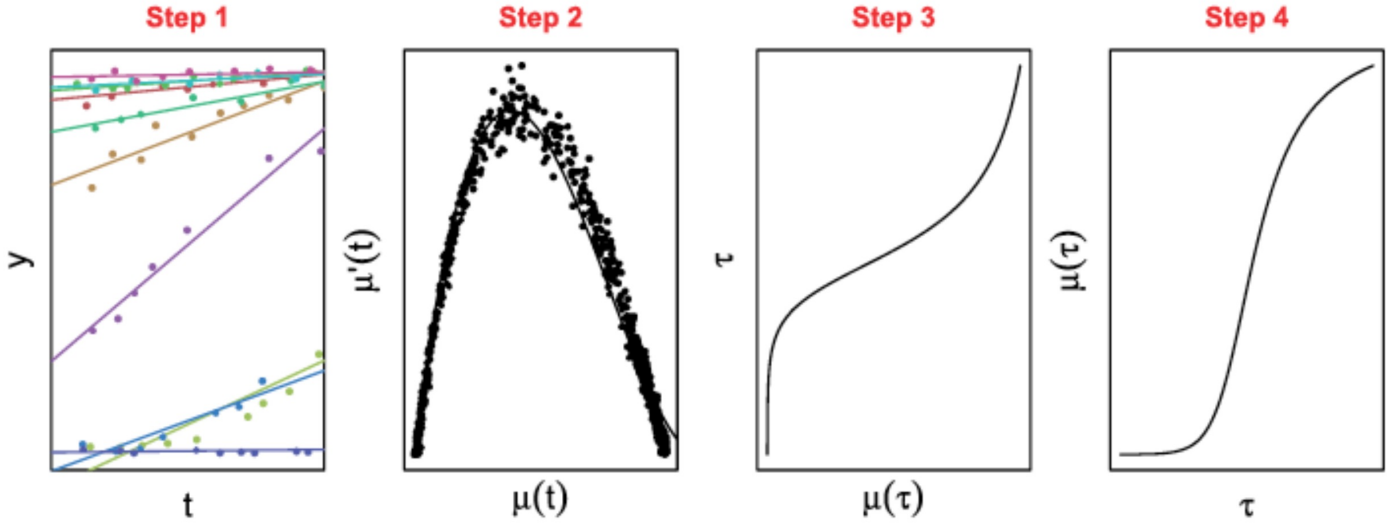




Phase-Plane method

V.L. Villemagne, *et. al.,* Lancet Neurol 2014, **12**,357-67
C. Budgeon, *et. al. Statistics in medicine 2017, **36,** 2720-2734*

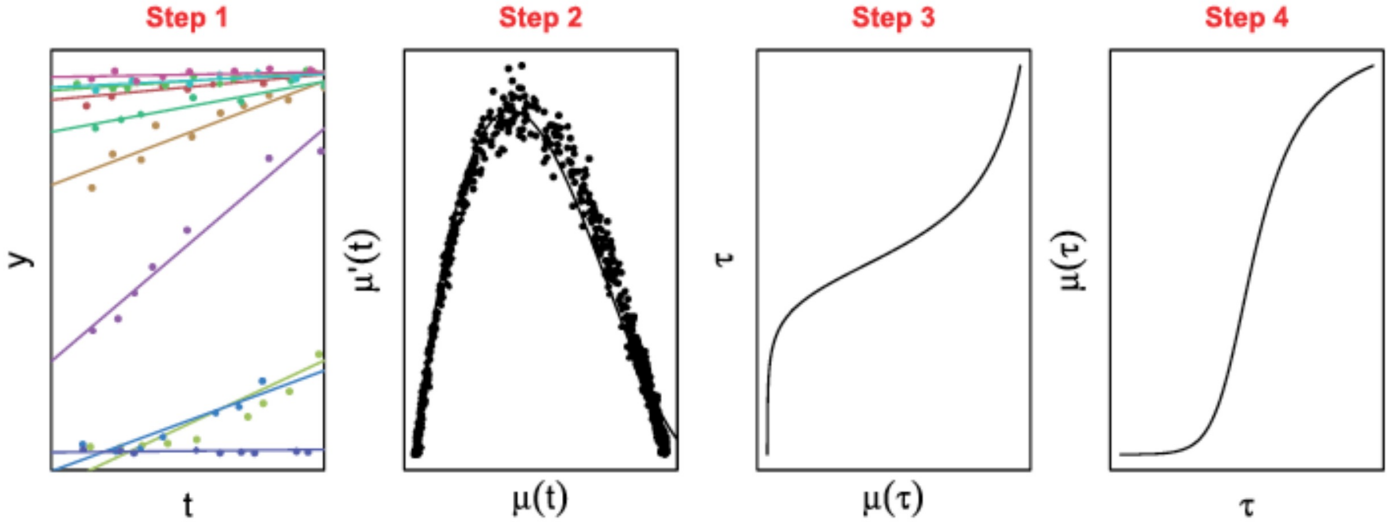
Method for constructing single variable trajectory $\mu_Q(\tau)$ for quantity Q



Phase-Plane method

1. Obtain for phase plane point $(\widehat{\dot{Q}_i(\bar{t}_p)}, \widehat{Q_i(\bar{t}_p)})$ for each participant.
2. Fit a function to approximate a relationship $\dot{Q} = f_Q(Q)$.
3. Integrate $\widehat{f_Q}(Q)$ to obtain $\tau(\mu) = \int_{\mu_0}^{\hat{\mu}_Q} f_Q(v)dv$
4. Invert this to obtain $\hat{\mu}_Q(\tau)$

Step 3 introduces an integration constant equivalent to the zero of time axis



Multi-Modal Phase-Plane method

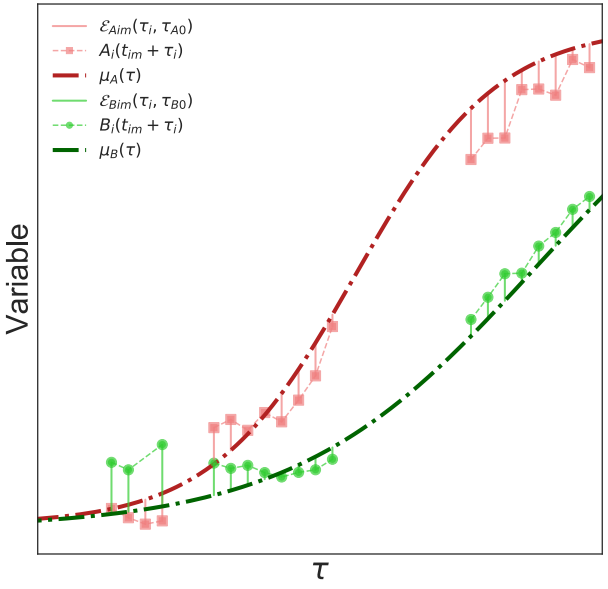
T. Cox, *et. al.*
Submitted

Generalise this to multiple quantities $Q \in \mathcal{Q}$:

- Preform steps 1-4 for each quantity to obtain single variable curve for each quantity $\widehat{\mu}_Q(\tau - \tau_{Q0})$. ($\tau_{Q0}$ integration constant for each quantity)

- Introduce anchor time τ_i for each participant *i* to define a disease time for each participant.

- Obtain values for the anchor times $\{\tau_i\}$ and integration constants $\{\tau_{Q0}\}$ by minimizing a weighted error in the fit using $\{\tau_i\}$ and $\{\tau_{Q0}\}$ as free parameters.



The weighted error

MS error per-datapoint for each quantity

$$\epsilon_Q^2\left(\{\tau_j\}_{j\le N}, \tau_{Q0}\right) = \frac{1}{n_Q}\sum_{i=1}^{N}\sum_{m=1}^{n_i}\left[Q^i(t_{im}) - \mu_Q^*\left(t_{im} + \tau_i - \tau_{Q0}\right)\right]^2$$

Weight for quantity Q determined by its per-point error

$$W_Q = \frac{1}{\epsilon_Q^2\left(\{\tau_j\}_{j\le N}, \tau_{Q0}\right)},$$

Weighted square error

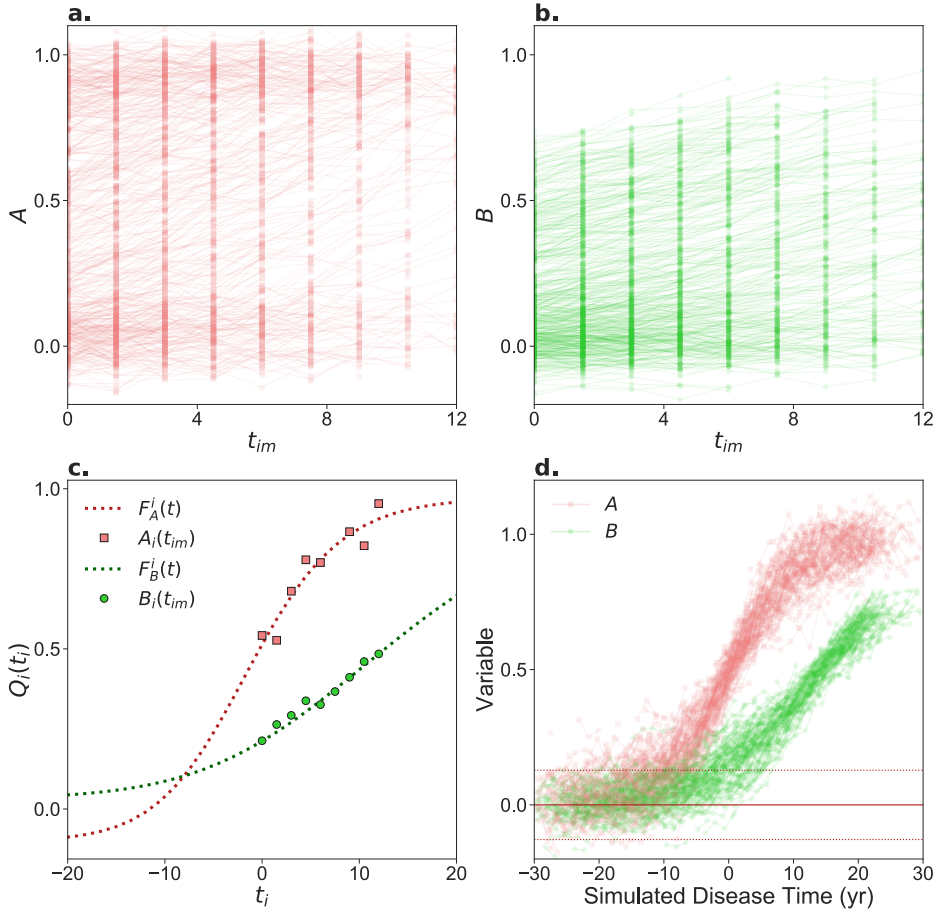
$$\mathcal{E}_W^2\left(\{\tau_j\}_{j\le N}, \{\tau_{Q0}\}_{Q\in\mathcal{Q}}\right) = \sum_{Q\in\mathcal{Q}} W_Q \sum_{i=1}^{N}\sum_{m=1}^{n_i}\left[Q^i(t_{im}) - \mu_Q^*\left(t_{im} + \tau_i - \tau_{Q0}\right)\right]^2$$

Testing with simulated data

Each simulated participants' data follows a five-parameter logistic functions with randomly distributed parameters with noise added to each timepoint.

This choice is inspired by hypothetical models of Amyloid-β protein in the brain and cognitive decline.

Data is constructed with a well defined simulated disease time.



Testing with simulated data

Each simulated participants' data follows a five-parameter logistic functions with randomly distributed parameters with noise added to each timepoint:

$$X_i(t_{im}) = \left(L_X^i + \left(R_X^i - L_X^i\right)\left[1 + e^{-a_X^i\left(t_{im} - \widetilde{b_X^i}\right)}\right]^{-g_X^i}\right) + \xi_X^{im}$$

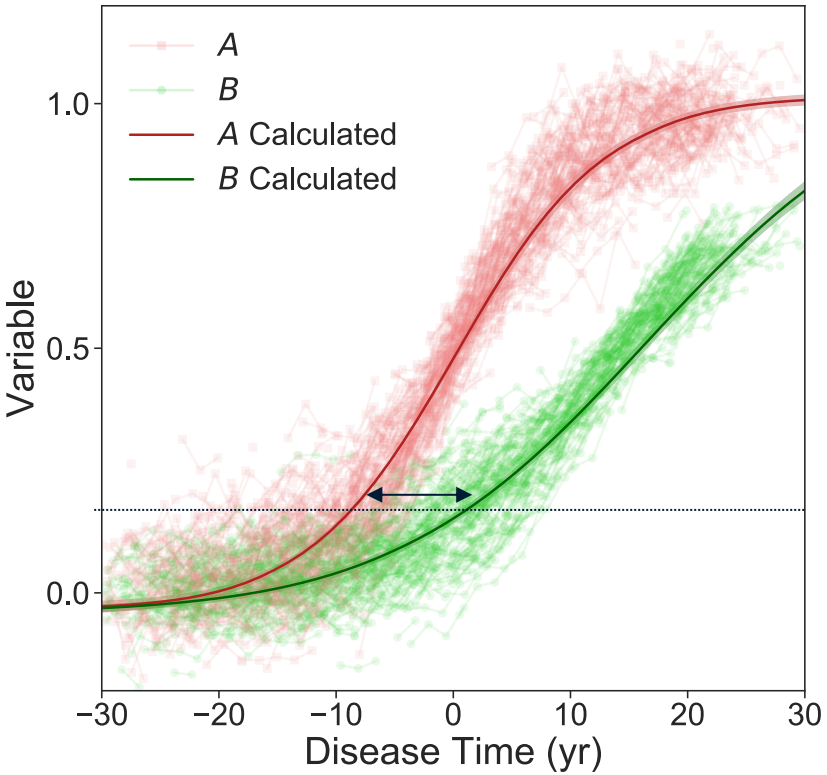
$$\widetilde{b_X^i} = b_X^i + \frac{1}{a_X^i}\log\left(2^{1/g_X^i} - 1\right)$$

a_A^i	$\sim$	$\mathcal{N}_-^+(0.2,0,\infty,0.05^2)$	a_B^i	$\sim$	$\mathcal{N}_-^+(0.1,0,\infty,0.025^2)$
b_A^i	$\sim$	$U(-20,30)$	b_B^i	$=$	$b_A^i + \Delta b^i$ with $\Delta b \sim \mathcal{N}(14,0.1^2)$
L_A^i	$\sim$	$\mathcal{N}(0,0.05^2)$	L_B^i	$\sim$	$\mathcal{N}(0,0.05^2)$
R_A^i	$\sim$	$\mathcal{N}(0.98,0.05^2)$	R_B^i	$\sim$	$\mathcal{N}(0.98,0.05^2)$
g_A^i	$\sim$	$\mathcal{N}(1,0.1^2)$	g_B^i	$\sim$	$\mathcal{N}(2,0.1^2)$
ξ_A^{im}	$\sim$	$\mathcal{N}(0,0.04^2)$	ξ_B^{im}	$\sim$	$\mathcal{N}(0,0.02^2)$

Can define a simulated disease time

$$\theta_{im} = t_{im} - b_A^i,$$

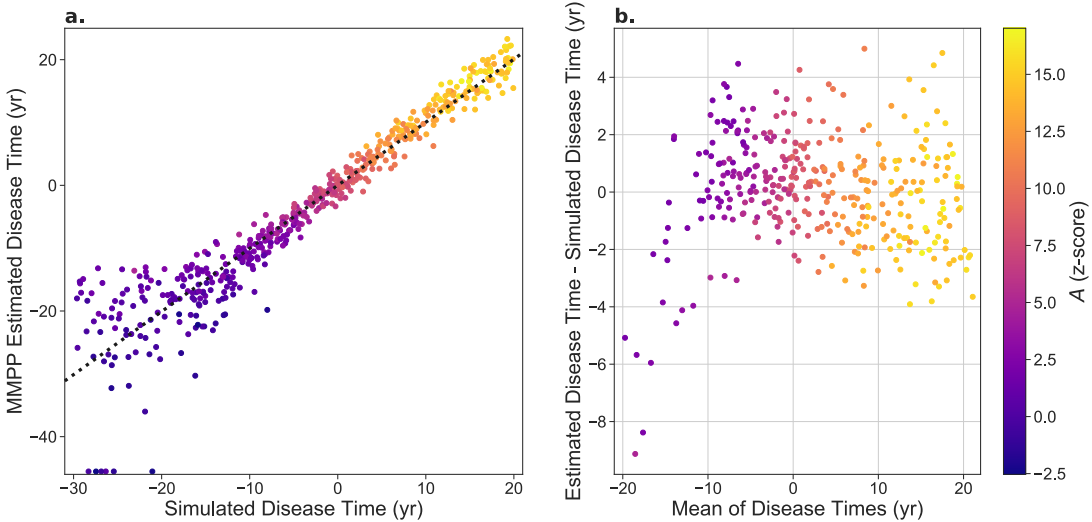
How well does this predict the disease curves?



Delay between detectible levels of A & B:

Estimated=15.3 ± 0.4 yr
Simulated distribution=14 ± 2 yr

How well does this individual progression?



So long as participants biomarkers are significantly different than “pre-disease levels” we can obtain an estimate of disease progression.

Conclusions:

We have:

- Developed a method for constructing multivariate disease curves, from longitudinal data.
- Showed that for simulated data the method can:
  - Reproduce disease trajectory curves.
  - The method can be used to estimate the progression for simulated participants who progress.

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