Bayesian monotone regression for quantifying Alzheimer disease progression

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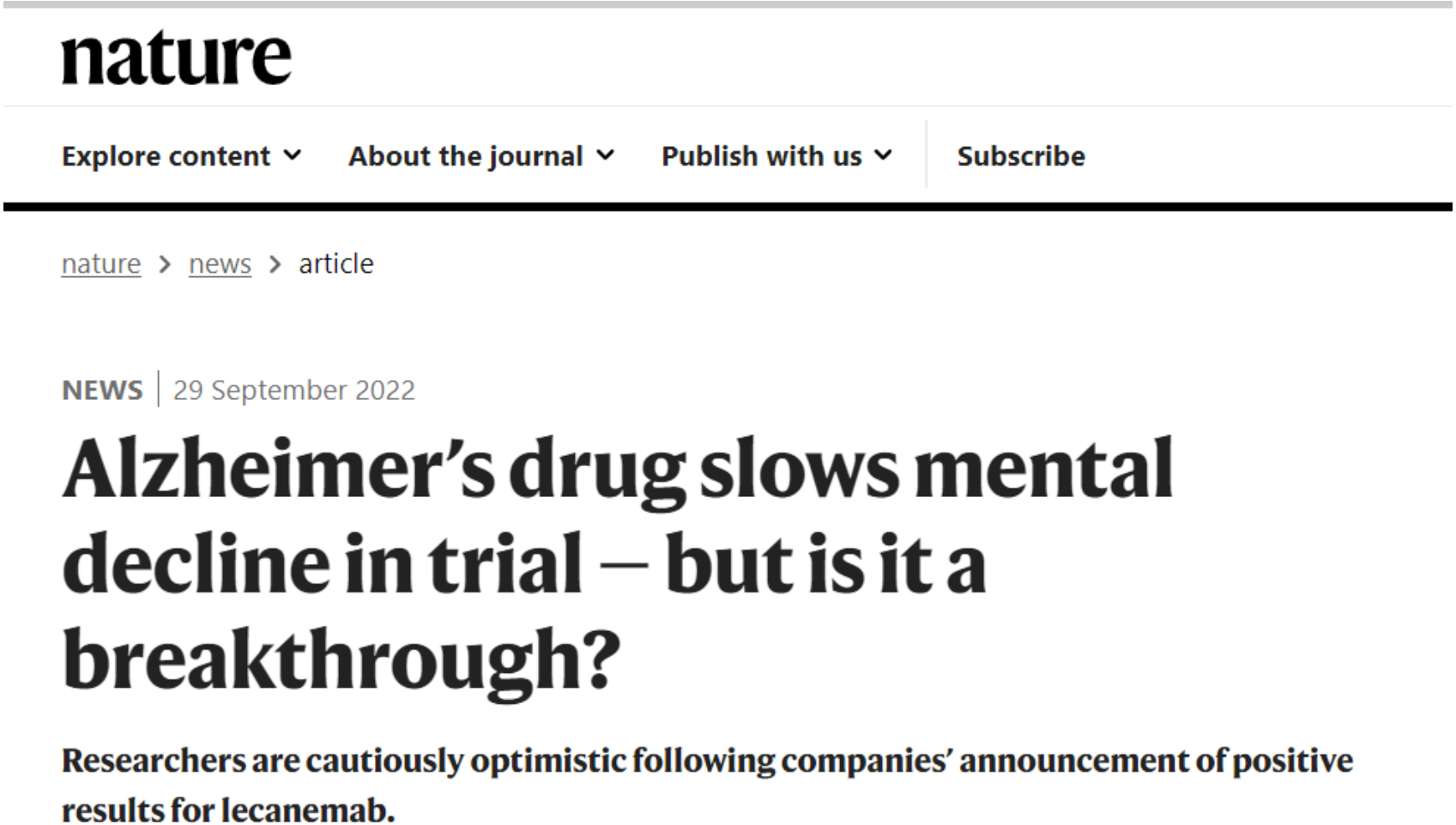
Alzheimer's Disease Remain a Challenge



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NEWS | 29 September 2022

Alzheimer's drug slows mental decline in trial – but is it a breakthrough?

Researchers are cautiously optimistic following companies' announcement of positive results for lecanemab.

Source: https://www.nature.com/articles/d41586-022-03081-0

Late Detection

Centers for Disease Control and Prevention
CDC 24/7: Saving Lives, Protecting People™

Alzheimer's Disease and Healthy Aging

What are the warning signs of Alzheimer's disease?

Alzheimer's disease is not a normal part of aging. Memory problems are typically one of the first warning signs of Alzheimer's disease and related dementias.

In addition to memory problems, someone with symptoms of Alzheimer's disease may experience one or more of the following:

- Memory loss that disrupts daily life, such as getting lost in a familiar place or repeating questions.
- Trouble handling money and paying bills.
- Difficulty completing familiar tasks at home, at work or at leisure.
- Decreased or poor judgment.
- Misplacing things and being unable to retrace steps to find them.
- Changes in mood, personality, or behavior.

Even if you or someone you know has several or even most of these signs, it doesn't mean it's Alzheimer's disease. Know the 10 warning signs (also available in Spanish).

Memory Loss Video

Watch this video "Memory Loss is Not a Normal Part of Aging"

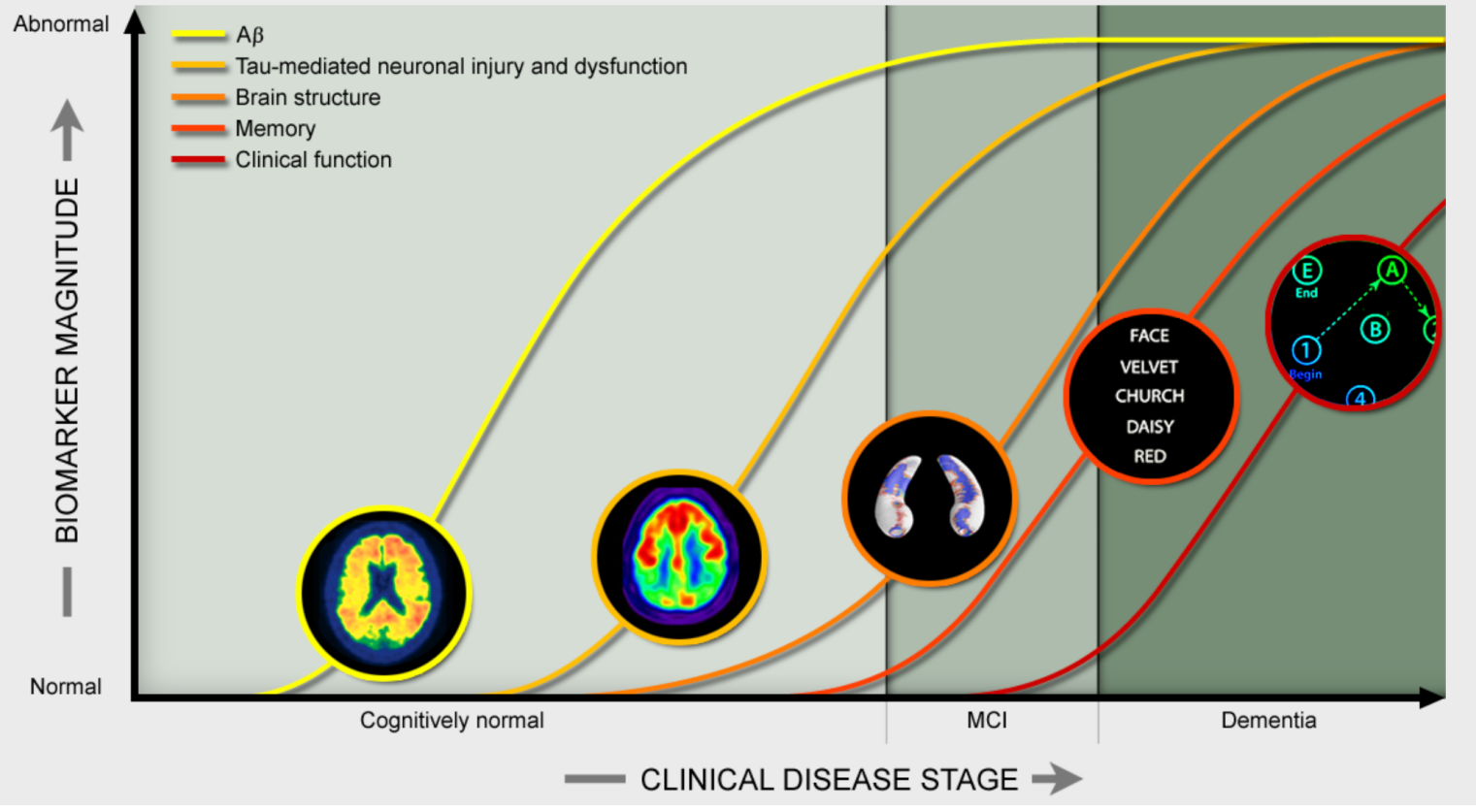
Source: https://www.cdc.gov/aging/aginginfo/alzheimers.htm

Modeling AD Biomarkers

Hypothesis on AD Biomarker Progression

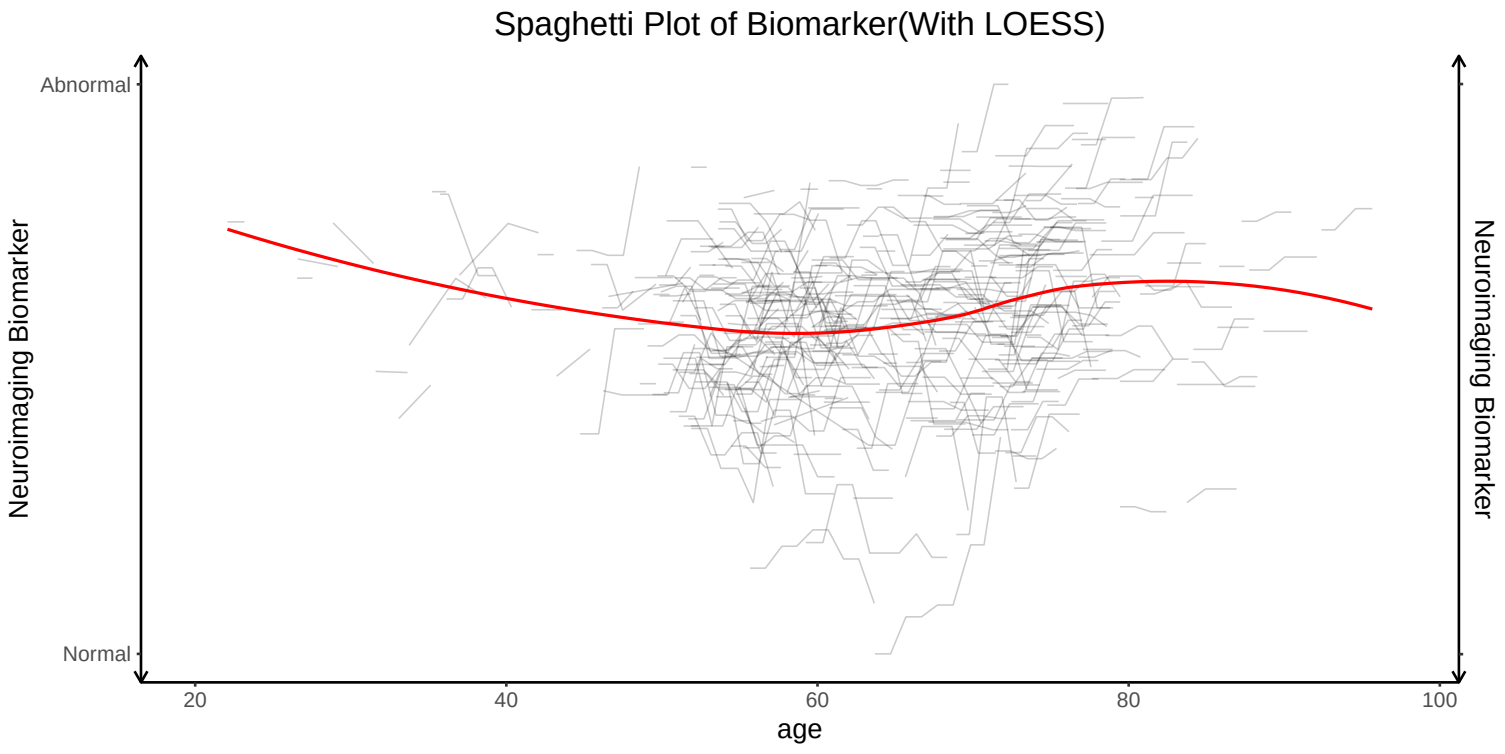
Temporal Ordering of Progression: Early detection and action

e.g. Protein level $\rightarrow$ Brain Structure$\rightarrow$ Cognitive Damage



Source: Jack et al, 2013, Lancet Neurology

The Problem Is...



Short follow-up duration + Individual variability

Biomarker Model

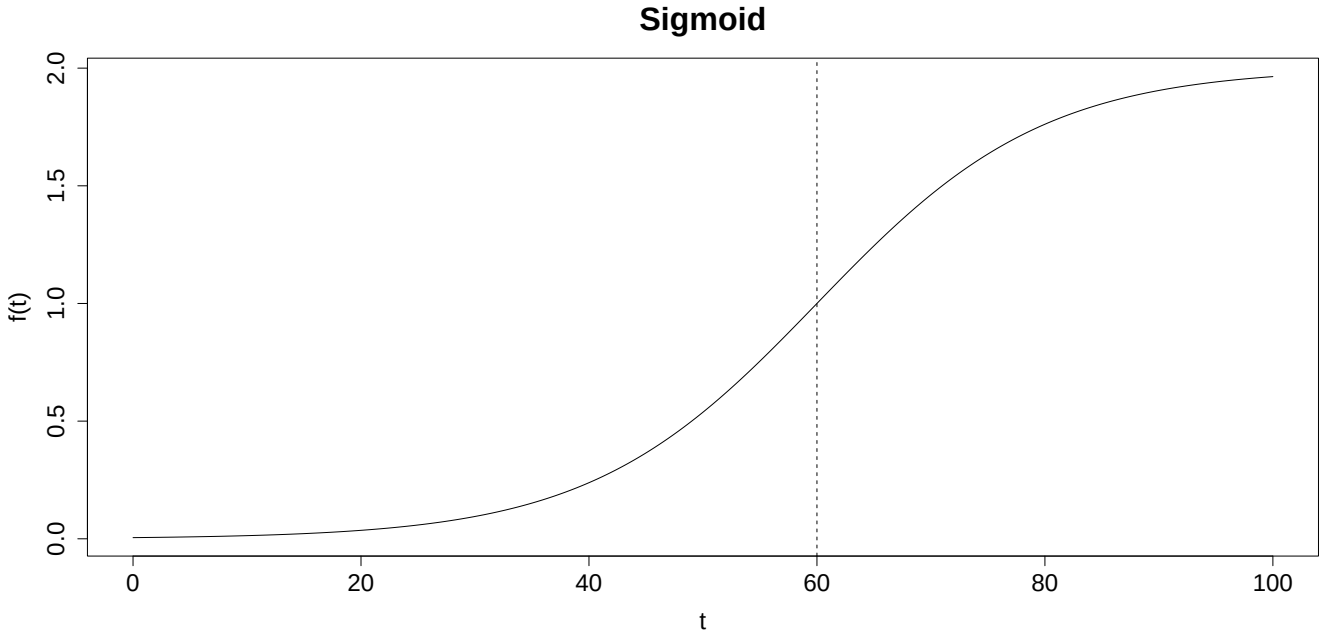
Our aim: Quantifying Alzheimer Disease Progression

$$\begin{aligned}\text{Biomarker level} \sim\ & \text{Baseline(Covariate-dependent)} \\ & + \textbf{Progression as function of age} \\ & + \text{Individual Heterogeneity}\end{aligned}$$

The key: regression where mean is an increasing function $f(t)$

Monotone Regression

The parametric way: Sigmoids $f(t) = \frac{\beta_1}{1+\exp(-\frac{t-\beta_2}{\beta_3})}$



However...

More Flexible Choices?

Models are good to have, but they are not true

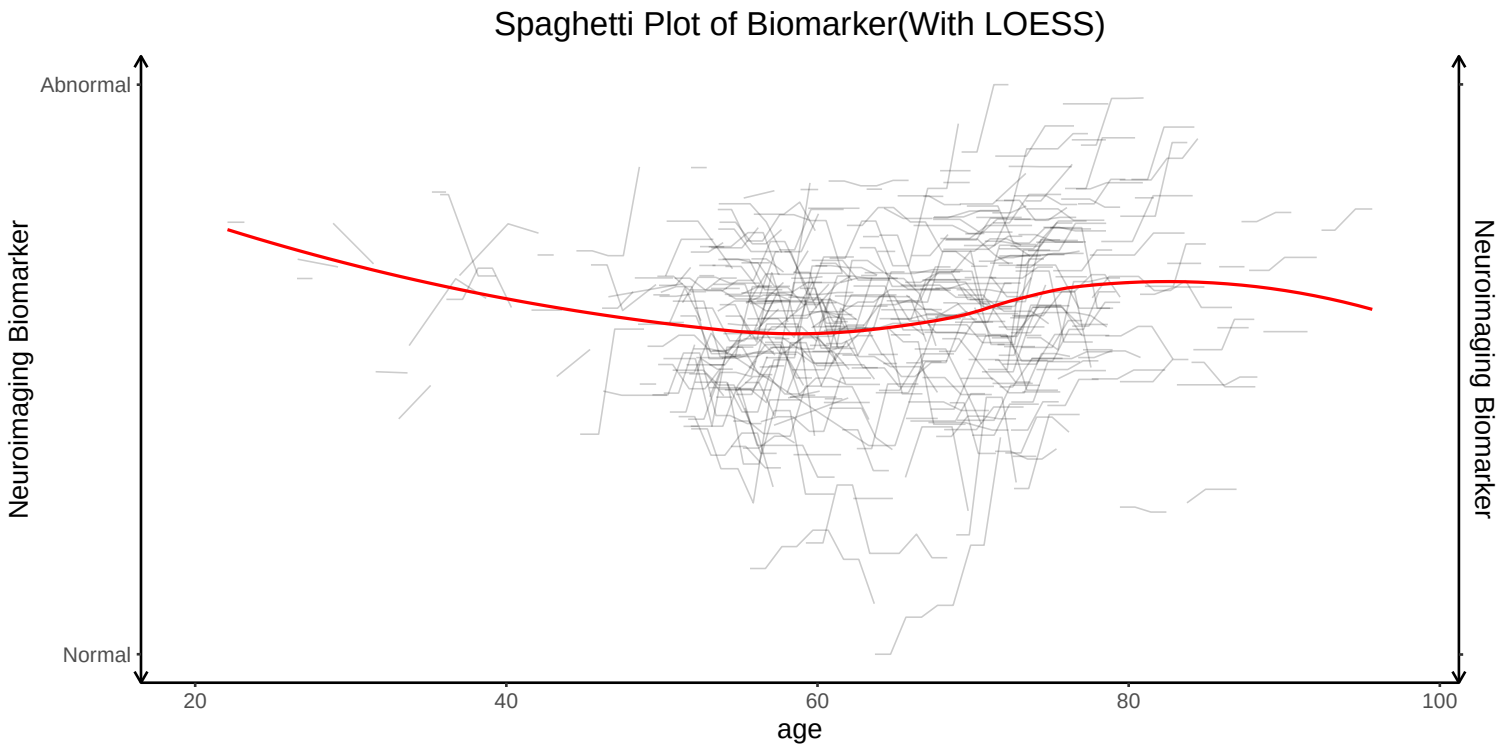
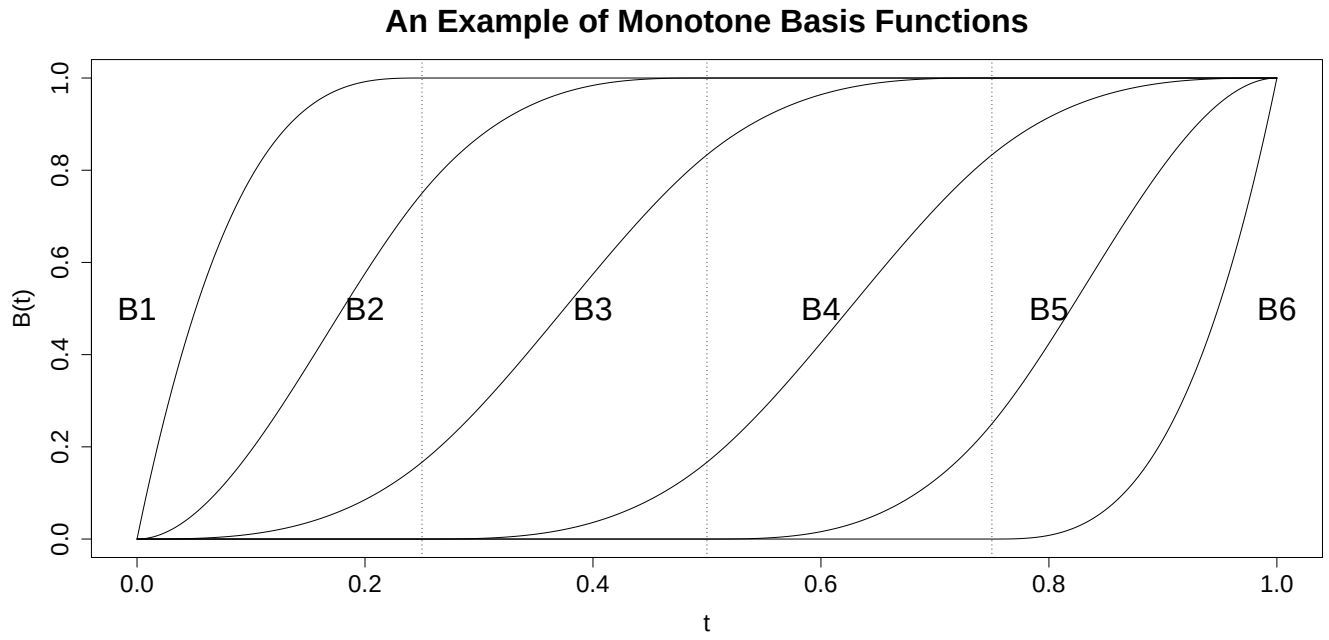


Figure: Visualization of MRI biomarker in BIOCARD data

Monotone Spline

Positive linear combinations of monotone basis functions:

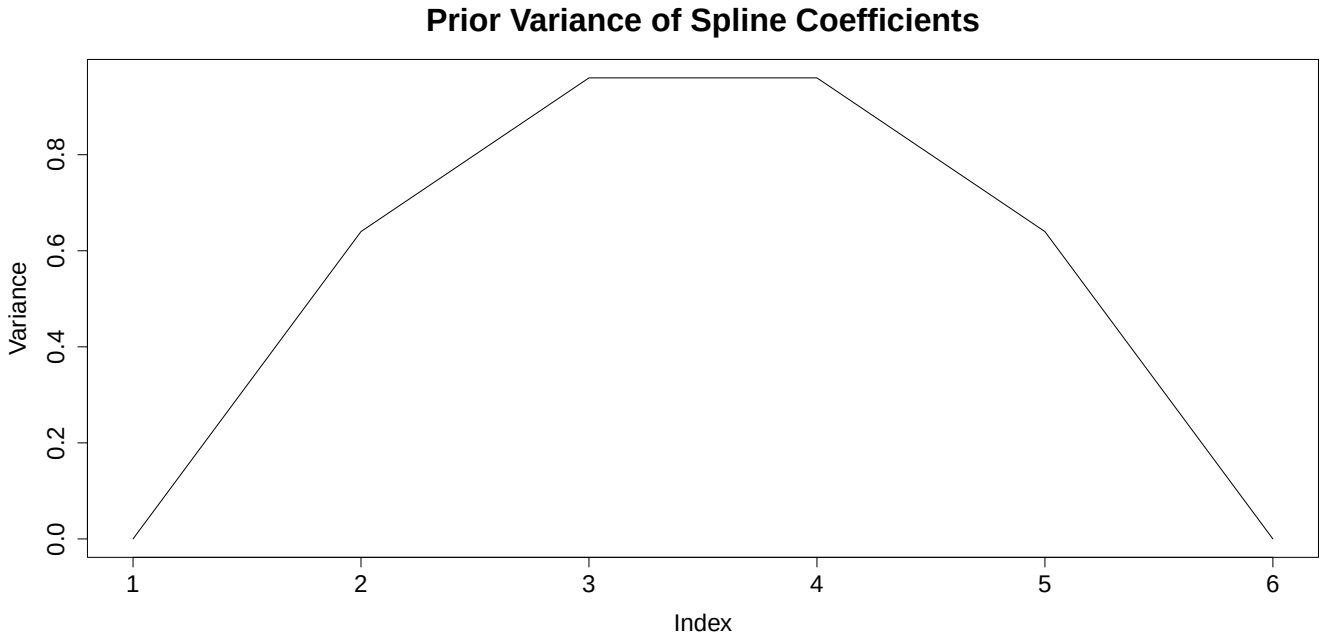
$$f(t;\gamma) = \sum_{j=1}^{L} \gamma_j B_j(t), \gamma_j \geq 0$$



Bayesian Penalized Spline

Purpose of prior: put more weight on "preferred" curves

- Flat near boundaries$\rightarrow$ Smaller coefficients at both ends



Bayesian Penalized Spline

Purpose of prior: put more weight on "preferred" curves

- Less wiggly curves$\rightarrow$ Adjacent coefficients being similar ($|\gamma_j - \gamma_{j-1}|$ being small)

Results

Current Results

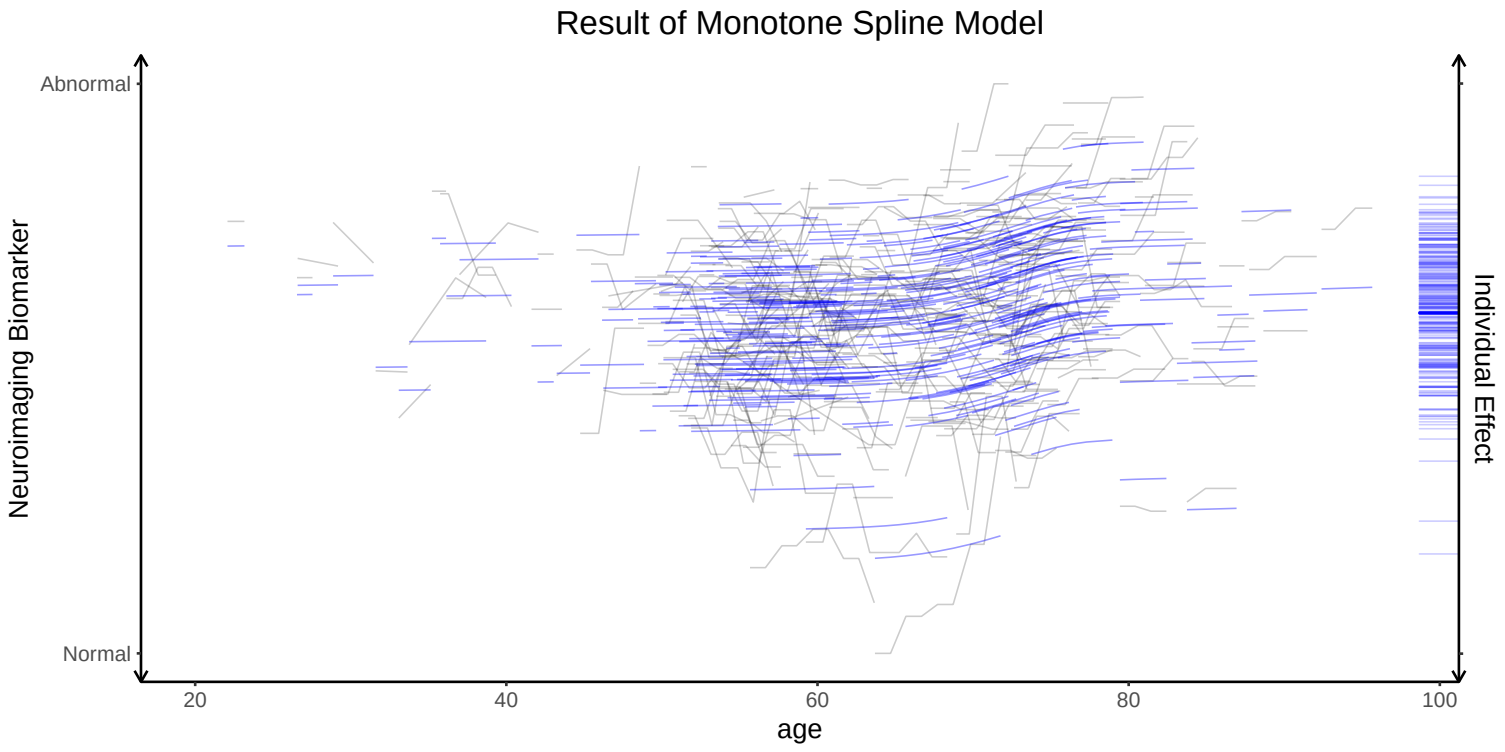


Figure: Model result on one MRI biomarker

Current Results

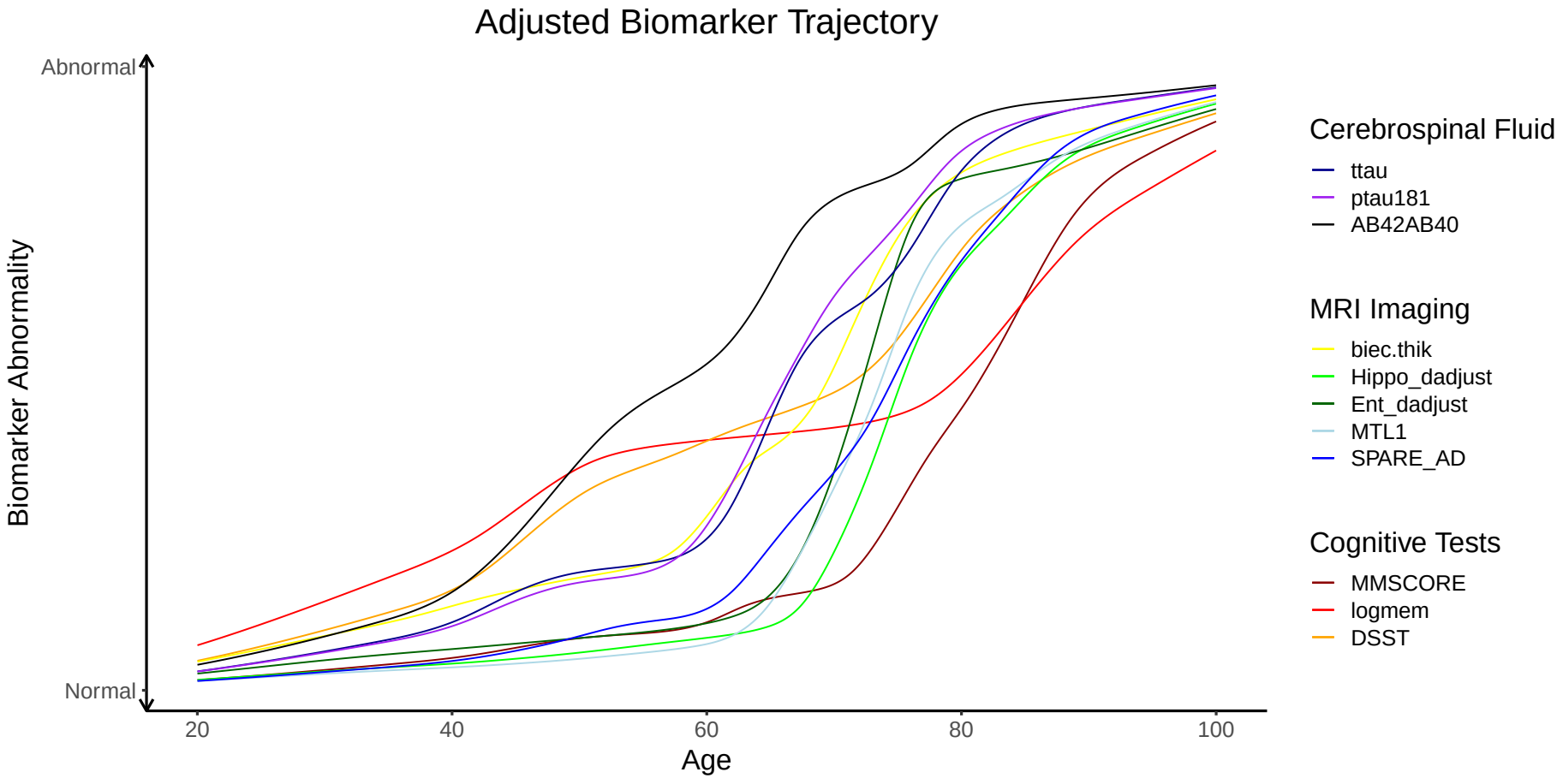


Figure: Combined graph of all 11 biomarkers

Discussions

What next?

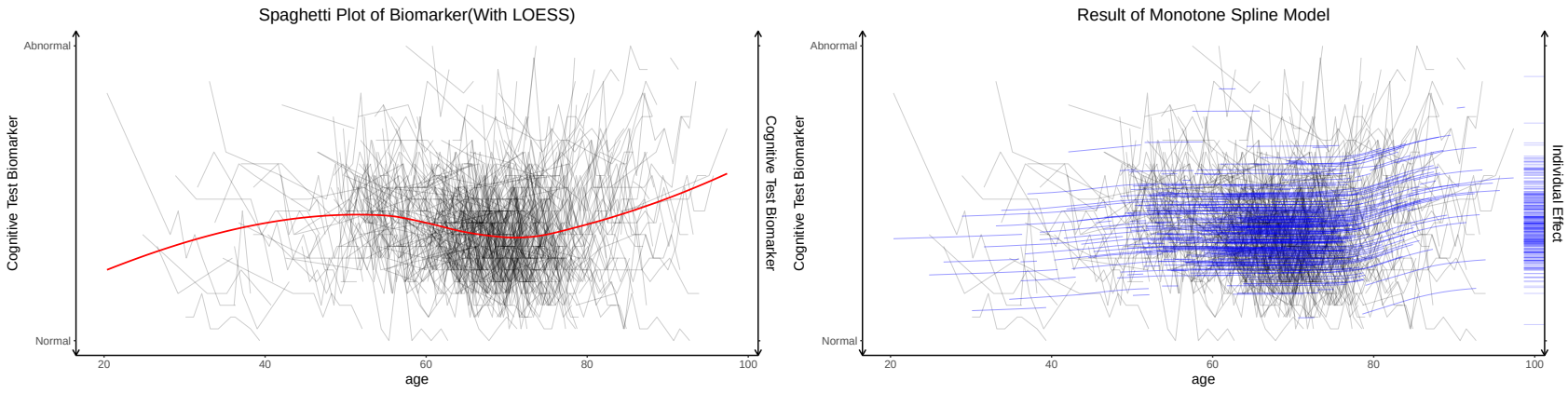


Figure 1: Visualization of Model results for Logical Memory Scores

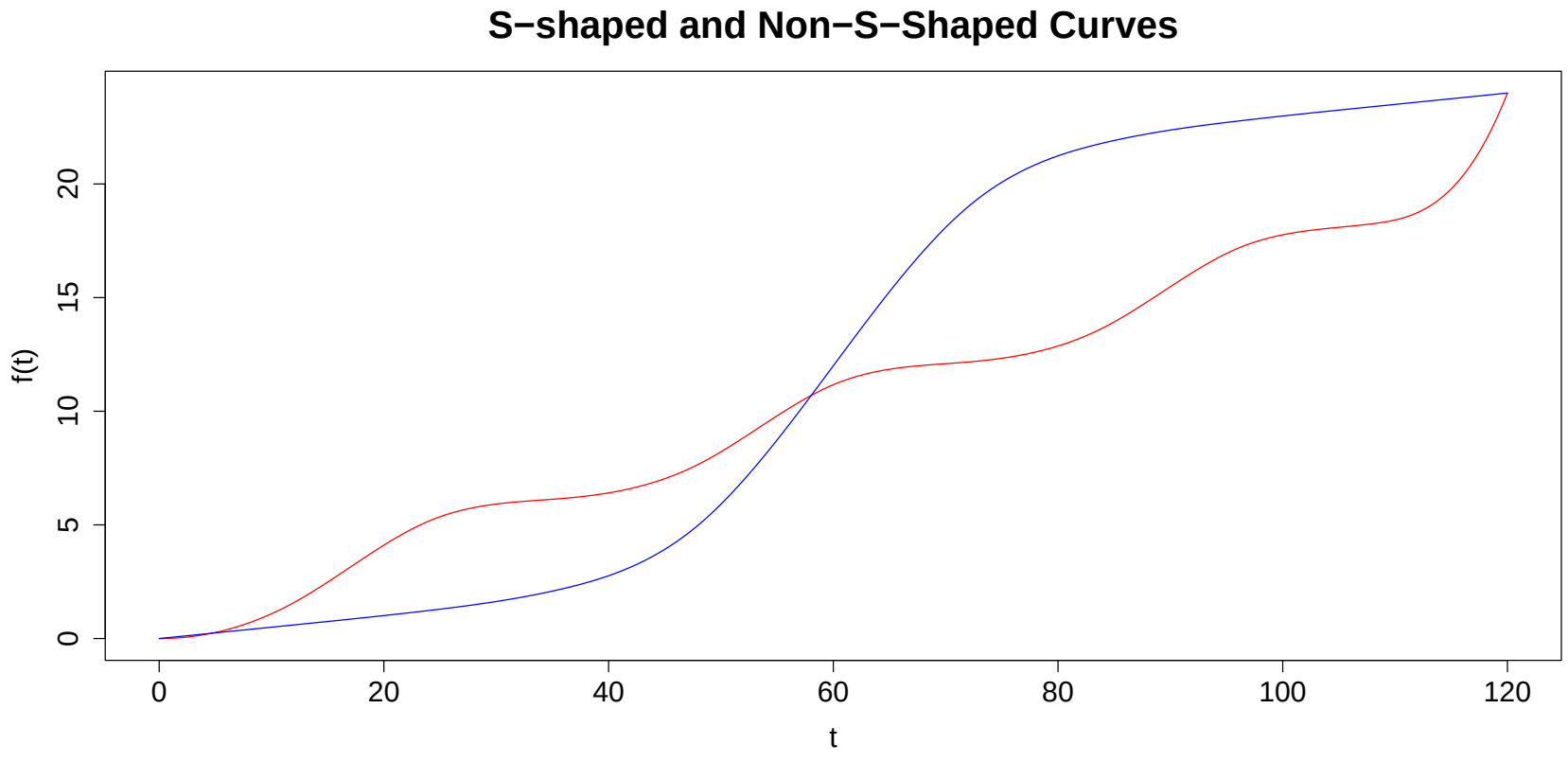
"Flatness" in the middle captures patterns from data.

Loss in interpretability

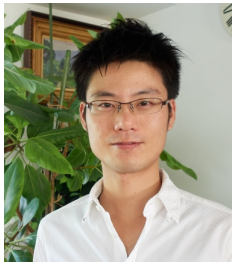
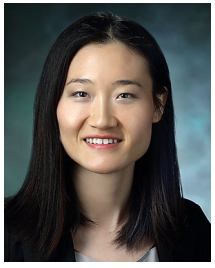
What next: Smoother fit & Less overfitting

Fit curves with at most one inflection point:

where the derivative reach maximum



Acknowledgement

Joint work with  and 

Reference

Work-in-progress Manuscript:

Bayesian penalized monotone regression for quantifying Alzheimer disease progression with biomarkers (2022+)

Relevant Work:

A computational neurodegenerative disease progression score: Method and results with the Alzheimer's disease neuroimaging initiative cohort(Bruno et al, 2012)

Monotone Regression Splines in Action(Ramsay, 1988)

Unimodal Regression Using Bernstein-Schoenberg Splines and Penalties(Köllman et al, 2014)