Learning transition times in event sequences: the Temporal Event-Based Model of disease progression

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Connecting ideas from event-based and hidden Markov modelling to derive a new interpretable model of disease progression

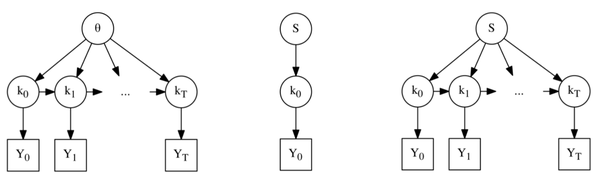
Progressive diseases such as Alzheimer's disease (AD) are characterised by monotonic deterioration in functional, cognitive and physical abilities over a period of years to decades. Data-driven models of disease progression can be used to learn hidden information, such as individual-level stage, from observed data. Here we address the problem of how to learn transition times in event sequences of disease progression, by introducing a new generative Temporal Event-Based Model (TEBM) of disease progression. The main novelties of our work are as follows.

- We generalise a formerly cross-sectional model (the EBM: event-based model Fonteijn et al. 2012), allowing it to account for longitudinal data.
- We define a Bayesian 'event-based' framework to inject prior information into structured inference from longitudinal data.
- We use our model to learn a new clinically interpretable sequence and timing of events in AD and to predict individual-level trajectories.

Methods

The Temporal Event-Based Model

To formulate TEBM, we make three assumptions, namely i) monotonic feature changes; ii) a consistent event sequence, S, across the whole sample; and iii) Markov (memoryless) stage transitions.



(a) CTHMM (b) EBM (c) TEBM

Assuming independence between observed features i=1,...,I, if a patient j=1,...,J is at latent state $k_{j,t}$= 0,...,N at time t=1,...,T_j in the progression model, the likelihood of their data $Y_{j,t}$ is given by:

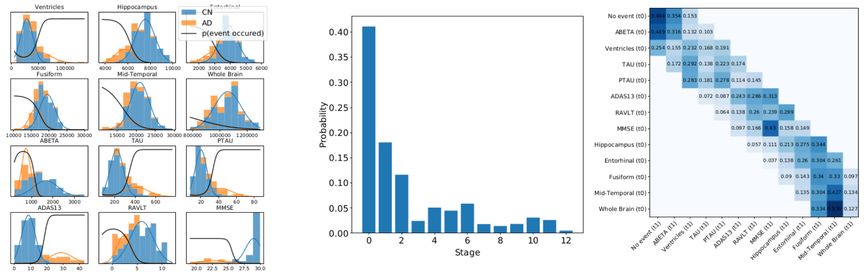
$$P(Y|\theta,S) = \prod_{j=1}^{J}\left[\sum_{k=0}^{N} P(k_{j,t=0}) \prod_{t=1}^{T_j} P(k_{j,t}|k_{j,t-1}) \prod_{t=0}^{T_j}\prod_{i=1}^{k_{j,t}} P(Y_{i,j,t}|k_{j,t},\theta_i^p,S) \prod_{i=k_{j,t}+1}^{I} P(Y_{i,j,t}|k_{j,t},\theta_i^c,S)\right]$$

Here θ^p_i= [μ^p_i,σ^p_i,w^p_i] and θ^c_i=[μ^c_i,σ^c_i,w^c_i] are the mean, μ, standard deviation, σ, and mixture weights, w, for the patient and control mixture model distributions, which define the event-based model. For a full derivation see Wijeratne & Alexander, 2021.

Results

Inferring the timeline of feature changes in Alzheimer's disease

We use data from the ADNI study, a longitudinal multi-centre observational study of AD. We select 468 participants (119 CN: cognitively normal; 297 MCI: mild cognitive impairment; 29 AD: manifest AD; 23 NA: not available), and three time-points per participant (baseline and follow-ups at 12 and 24 months). Individuals were allowed to have missing data at any time-point.



(a) Biomarker distributions and mixture models (b) Initial probability density (c) Event-based transition matrix

Figure 1: TEBM parameters inferred from ADNI. (a) Gaussian mixture model fits to distributions of CN and manifest AD groups. (b) Initial probability density inferred by TEBM. (c) Event-based transition matrix inferred by TEBM. Events are ordered by the maximum likelihood sequence, S.

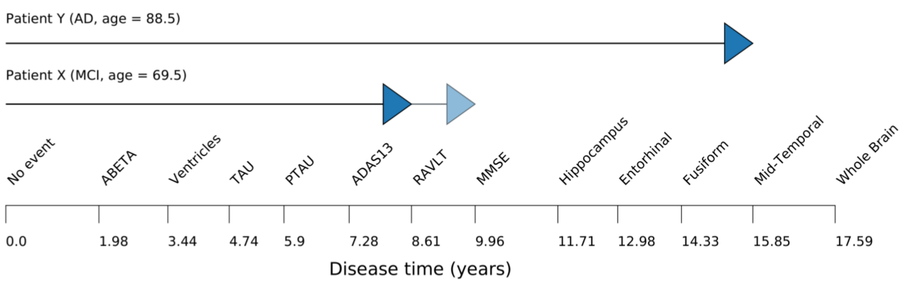


Figure 2: AD timeline inferred by TEBM. The order of events on the horizontal axis is given by the maximum likelihood sequence S, and the time between events is calculated from A. Baseline stage (solid arrow) and predicted next stage (shaded arrow) estimated by TEBM for two example patients are shown, chosen from the MCI and AD sub-groups.

Model	AU-ROC
TEBM (Dataset 1)	0.755 ± 0.12
TEBM (Dataset 2)	0.717 ± 0.15
CTHMM (Dataset 2)	0.489 ± 0.22

Table 1: TEBM improves predictive utility over a standard continuous time hidden Markov model (CTHMM). Performance for the task of predicting conversion, using either the full data (including individuals with missing data) or subset data (only individuals with complete data).

% missing	AU-ROC
25%	0.756 ± 0.12
33%	0.729 ± 0.13
50%	0.723 ± 0.17

Table 2: TEBM maintains performance with missing data. Performance for the task of predicting conversion with % missing data.

Discussion

A new interpretable model of disease progression

A key corollary benefit of TEBM's formulation is that it can infer probabilistic estimates of group- and individual-level progression from datasets with missing data, both in terms of observed features and time-points. This gives TEBM high utility in clinical applications where resources are scarce and/or it is too expensive to observe a patient multiple times, making TEBM an ideal tool for advancing on the objective of accessible healthcare. Future work with TEBM will be focused on relaxing its assumptions, in particular allowing for non-monotonic trajectories and multiple event sequences (subtypes).

References

Fonteijn et al. (2011). "An event-based disease progression model and its application to familial Alzheimer's disease." In: Information Processing in Medical Imaging (IPMI) 2011, 6801:748–759

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