UCL Centre for Medical Image Computing

Modelling Huntington's disease progression: interpretation, staging and prognosis

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Motivation

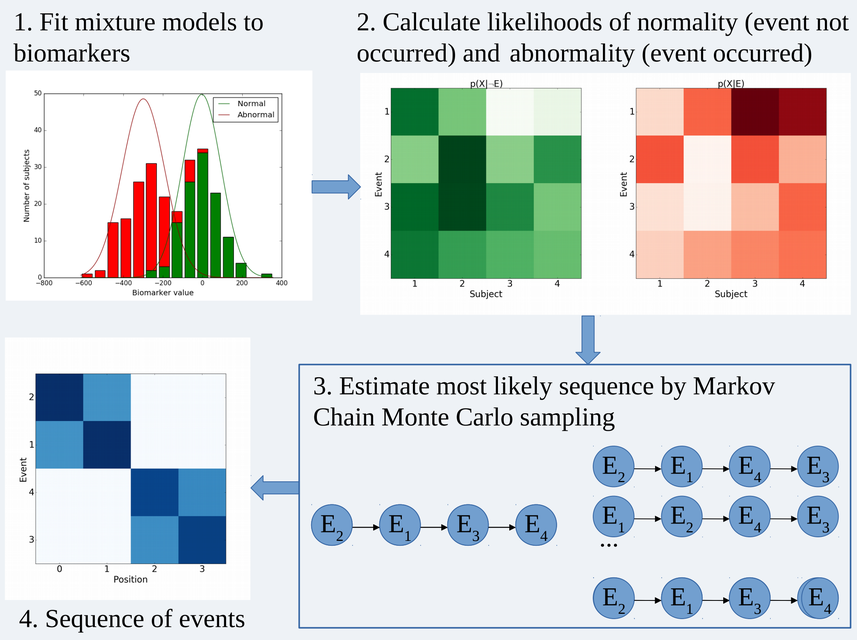
Measurements of brain atrophy using imaging data can provide powerful markers for clinical trials in neurodegenerative diseases. However, individual data can be confounded by inter-subject variability, measurement noise and individual disease stage. Disease progression modelling uses probabilistic methods to untangle confounding effects and hence learn patterns of disease-related changes directly from data. Here we apply recent developments in disease progression modelling to i) uncover insights into Huntington's disease, and ii) provide new staging and prognosis utility for clinical applications.

Cross-sectional data

Method – Event-Based Model

We use the **Event-Based Model** to infer the sequence of regional brain volume and clinical test score abnormality appearance from post-processed individual-level **cross-sectional** structural MRI data from the PREDICT-HD, TRACK-HD, and IMAGE-HD studies [1,2].

1. Fit mixture models to biomarkers
2. Calculate likelihoods of normality (event not occurred) and abnormality (event occurred)
3. Estimate most likely sequence by Markov Chain Monte Carlo sampling
4. Sequence of events



Results – Event-Based Model

Figure 1 shows the inferred sequence of regional brain volume and clinical test score changes across the three studies, which is remarkably consistent. The model also estimates the most likely stage along the sequence for each individual, and successfully stages sub-groups.

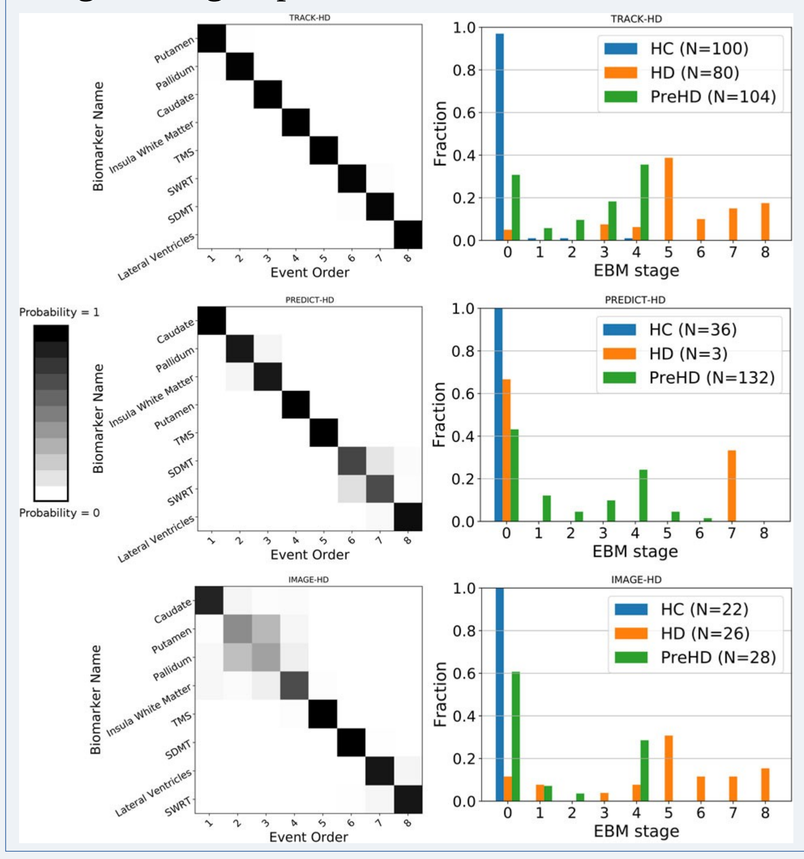
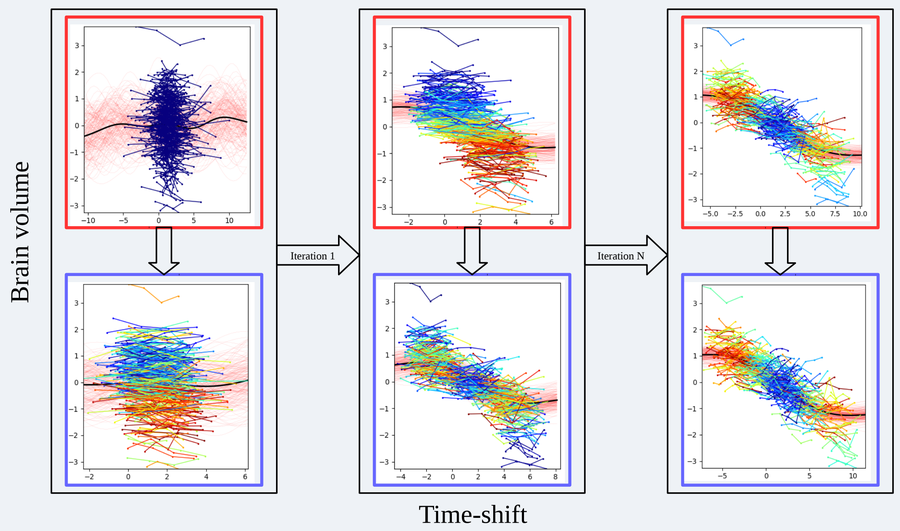


Figure 1: Left column: positional variance diagrams showing the estimated order of regional brain volume and clinical marker abnormality events in PreHD and manifest HD patients at baseline, from the TRACK-HD, PREDICT-HD and IMAGE-HD cohorts separately. The heatmaps indicate the magnitude of the probability of the ordering; dark diagonal boxes indicate strong event ordering, and lighter indicate possible event permutations with strength proportional to the off-diagonal boxes. Right column: individual-level disease stage for each group in each cohort, predicted by the EBM sequence fit to each cohort separately.

Longitudinal data

Method – Gaussian Process Progression Model

We use the **Gaussian Process Progression Model** to infer trajectories of regional brain volume changes from post-processed individual-level **longitudinal** structural MRI data from the TRACK-HD study [1,3].



1. Define Gaussian Process regression model with individual-level time-shift
2. Define a cost function: sum of model likelihood + regularisation term
3. Monotonicity constraint: enforced by requiring first derivative of fixed-effects > 0
4. Sequentially fit regression parameters and individual time-shift (shown above)

Results – Gaussian Process Progression Model

Figure 2 shows the inferred group level trajectories of regional brain volume changes, with the earliest changes in the sub-cortex (~2 years before canonical abnormality) followed by cortical changes over a period of ~11 years. The model also estimates individual-level trajectories along the disease timeline, and predicts progression.

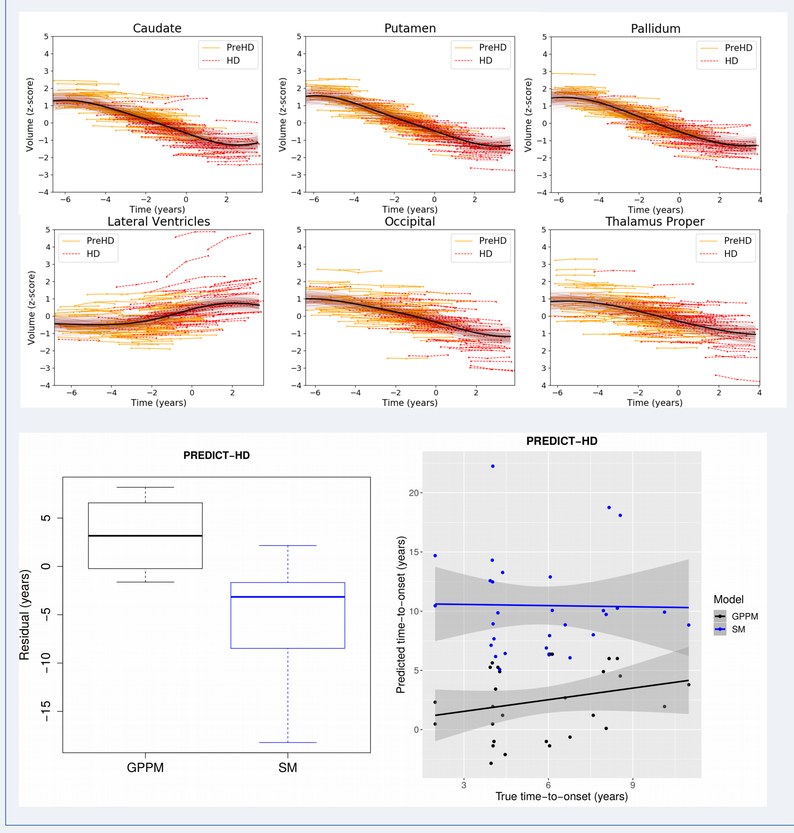


Figure 2: Top: Example group- and individual-level regional brain volume trajectories inferred from genotype positive (PreHD: pre-manifest, and HD: manifest HD) individuals. Standardised volumes (y-axis) are shown, and the time-scale (x-axis) is centred such that t=0 when the fitted trajectory (black line) is equal to the mean value of the HD group. Bottom: (Left) Difference (residual) between actual and predicted time-to-onset for GPPM and SM, for PreHD individuals from PREDICT-HD. Boxplots show the median, first and third quartiles, and outliers. (Right) Predicted and true time-to-onset for each model. Fits are from fixed effect linear models. GPPM: Gaussian Process Progression Model; SM: survival model.

Conclusions

Here we have shown the application of two disease progression models to extract useful group and individual-level information from cross-sectional and longitudinal datasets. These methods are complimentary and can reveal otherwise hidden information, such as individual-level disease stage, and support the use of disease progression modelling to enhance the ability of structural MRI markers to track Huntington's disease progression. Furthermore, our models can be applied to other neurological diseases to provide data-driven insights into disease progression, and utility in clinical staging and prognosis.

References
[1] Wijeratne et al. Ann Neurol. 2020; doi: 10.1002/ana.25709
[2] Wijeratne et al. Front. Big Data 2021; doi: 10.3389/fdata.2021.662200
[3] Wijeratne et al. Neurology Genetics 2021; doi: 10.1212/NXG.0000000000000617