UCL Centre for Medical Image Computing

Image-based disease progression modelling of dementia and its application to Huntington's disease

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Motivation

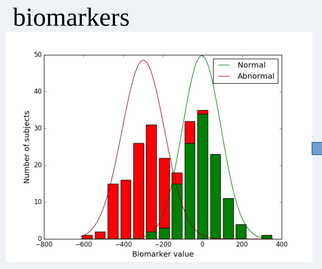
Measurements of brain atrophy using imaging data can provide powerful markers for clinical trials in neurodegenerative diseases. However, individual data can be confounded by inter-subject variability, measurement noise and individual disease stage. Disease progression modelling uses probabilistic methods 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

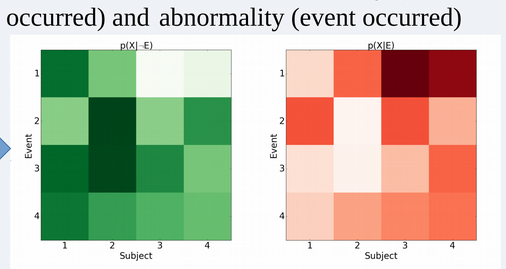
Method – Event-Based Model

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

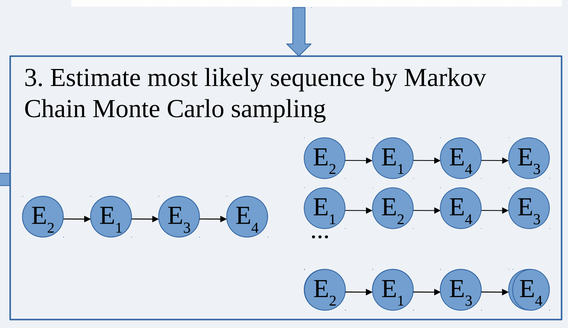
1. Fit mixture models to biomarkers

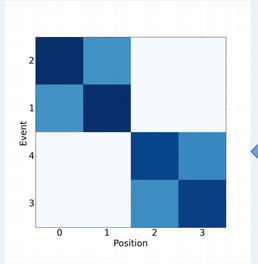


2. Calculate likelihoods of normality (event not occurred) and abnormality (event occurred)



3. Estimate most likely sequence by Markov Chain Monte Carlo sampling

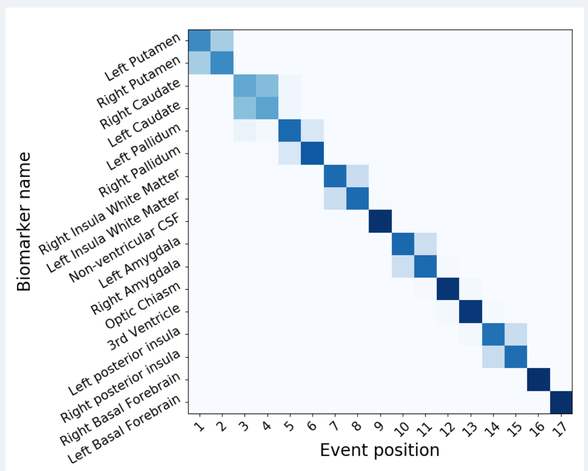


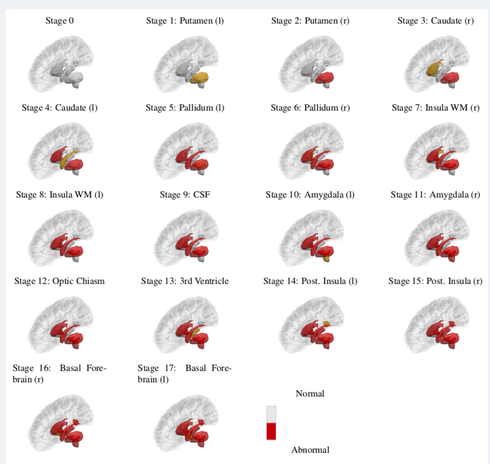


4. Sequence of events

Results – Event-Based Model

Figure 1 shows the inferred sequence of regional brain volume changes, with a central to peripheral spread. The model also estimates the most likely stage along the sequence for each individual, and successfully stages sub-groups by disease burden.





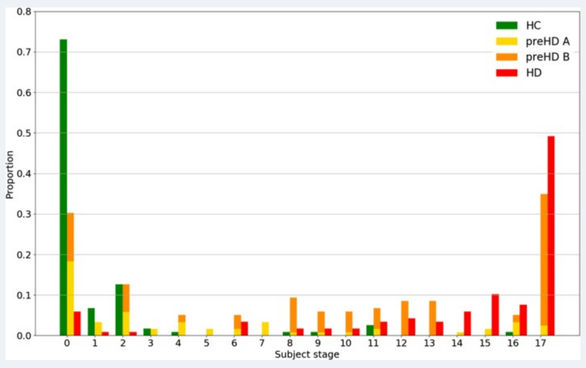
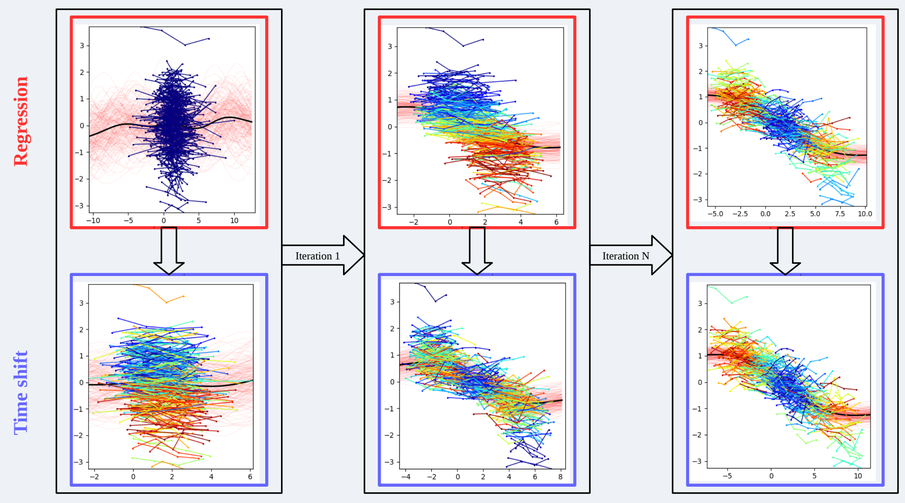


Figure 1: Clockwise from top left: i) Sequence of events inferred by the event-based model. Shading indicates possible event permutations with strength proportional to the off-diagonal components; ii) Graphic representation of the event sequence showing the corresponding regional brain volumes transitioning from an initially healthy (grey) state to an unhealthy (red) state; iii) Distribution of individual-level stages. Clinical labels (by increasing disease stage): Healthy control (HC), pre-manifest A (preHD A), pre-manifest B (preHD B), and manifest (HD).

Longitudinal data

Method – Gaussian Process Progression Model

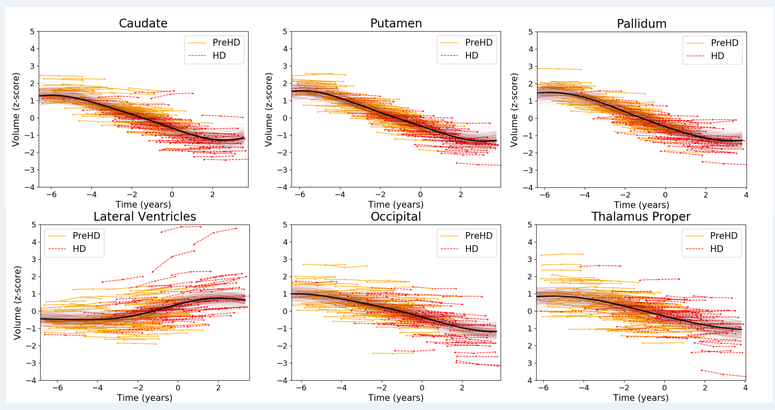
We use the **Gaussian Process Progression Model** to infer trajectories of regional brain volume changes from post-processed individual-level **longitudinal** structural MRI data from the TRACK-HD study [1,3].



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 separates sub-groups.



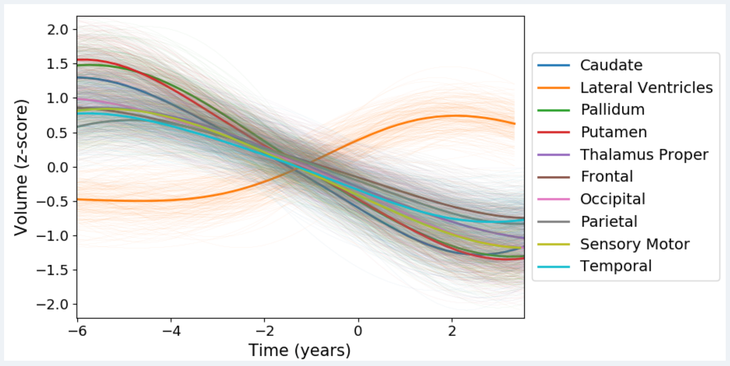


Figure 2: Top: Example group- and individual-level regional brain volume trajectories inferred from genotype positive (PreHD: pre-manifest, and HD: manifest HD) individuals. Standardised volumes (y-axis) are shown, and the time-scale (x-axis) is centred such that t=0 when the fitted trajectory (black line) is equal to the mean value of the HD group. Uncertainty in the fit is shown as light shading about the mean and was estimated using 200 samples from the posterior. Note that the model infers the position of individuals along the group-level disease trajectory (i.e., the time-shift). Bottom: group-level trajectories for ten regional volumes with uncertainty overlaid as shaded lines.

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. Ann Clin Transl Neurol. 2018; doi: 10.1002/acn3.558
[3] Wijeratne et al. ISMRM 2020, URL: https://www.ismrm.org/20/program_files/O10.htm