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Prediction of biomarkers' trajectory in Huntington's disease: application to precise clinical trial design

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1. Introduction

Patient inclusion is a crucial step in the setting of clinical trials, especially in rare diseases like Huntington's disease. The current selection process relies mostly on baseline measurements and cofactor values. This coarse estimate of the patient's profile leads to heterogeneous cohorts in clinical trials, which leads to uncertain therapeutic approaches. To this end, we developed a method that can position any patient on a common reference timeline of HD progression. From it, patients can be selected based on their future temporal profile.

2. Methods

2.1 Dataset & Features

We used data from two multicentric cohorts, namely Track-HD, which follows pre-manifest and manifest HD mutation carriers, and Track-ON, that includes follow-ups of Track-HD individuals as well as newly added pre-manifest pathogenic expansion carriers. We selected 7 clinical features (UHDRS-TMS, Stroop word reading test, SDMT, UHDRS-TFC, Direct and Indirect Circle Tracing, PBA-Apathy) and 8 imaging variables (striatum, globus pallidus, putamen, ventricular system, caudate nucleus, white matter, grey matter and total brain). As we consider patients with at least two visits to build the longitudinal model, it results in 299 patients representing 1,333 visits.

2.2 Statistical spatiotemporal model

The patients are used to estimate a long-term model of biomarkers' changes through all disease stages. The estimation of the model is based on a statistical learning approach which re-aligns and recombines individual short-term observations of patients seen at various disease stages [1, 2]. The resulting model of HD progression may be personalized to patients' data by automatically adjusting several mutually-exclusive parameters: age at onset, global pace of progression, and the timing of one biomarker trajectory relatively to the other ones. These individual parameters describe the heterogeneity of disease progression across cohorts.

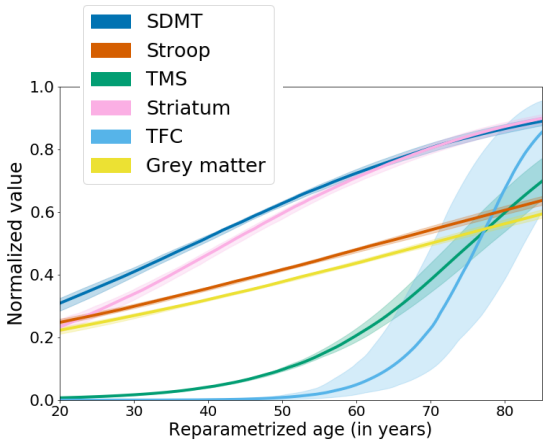

Figure 1: Typical progression of 6 imaging and clinical variables over time over the course of HD (variable renormalization for comparison purposes).

2.3 Clinical trial design

The personalization of the progression model to baseline data of any new individual allows his positioning onto the disease timeline and the prediction of imaging and clinical biomarker values at any future time-points. We simulate an clinical trial inclusion procedure where patients are selected if their predicted data meet a predefined criterion. We evaluate a posteriori how many patients have truly met the endpoints at the targeted date.

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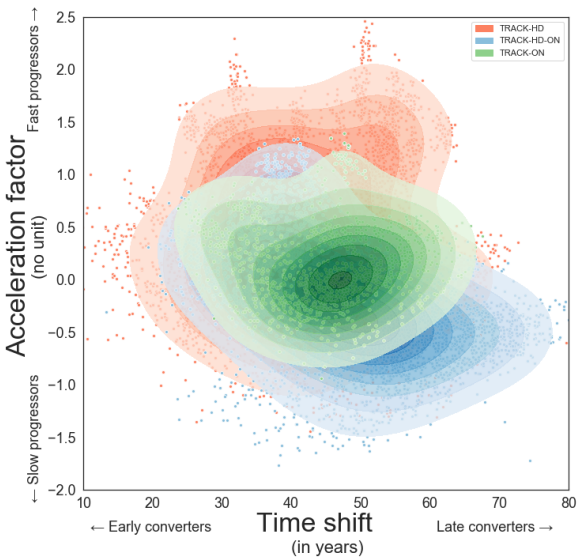

Figure 2: Distribution of time-shift and acceleration factor. Each point represents one patient from Track-HD only (red), Track-ON only (blue) or followed from Track-HD to Track-ON (green).

3. Results and discussion

3.1 HD progression

Figure 1. shows the typical long-term HD progression. Its personalization to all the Track patients allows to explore the heterogeneity of individual progressions thanks to the individual parameters. Figure 2 exhibits fast and slow progressors, early and late onset individuals. This summary is independent from the stage at which the patients are included and followed. It shows that among the fast progressors (top part) included in Track-HD, none were followed-up in Track-ON. Similarly, all the late and slow progressors (right bottom part) of Track-HD were followed in Track-ON.

3.2 Design of clinical trials

The model is used to predict the future biomarkers values of new patient by personalizing the model to his/her baseline data. It yields a mean relative error of prediction ranging from 3.1% at one year up to no more than 4.2% at four years. We simulate the inclusion in a clinical trial based on such simulations. Patients included based on the predictions (rather than baseline values only) better target a particular disease stage. For instance, as shown on Figure 3, from patients with a TMS < 5 at baseline, only 20% will have their TMS > 10 and a pathological caudate volume 3 years after inclusion. This percentage grows above 40%, even up to 80% (at the cost of less selected patients), thanks to prediction-based criteria.

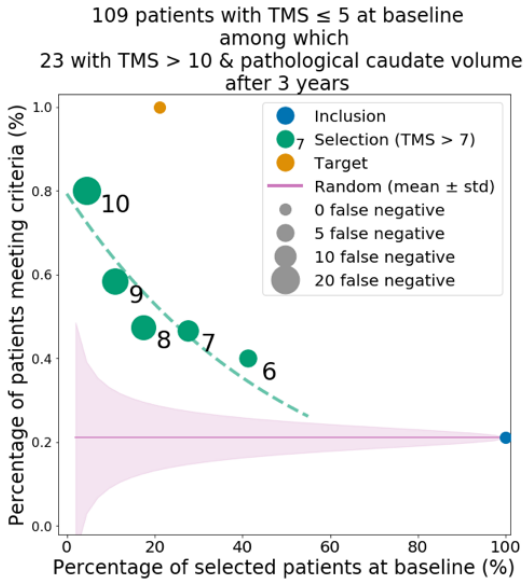

Figure 3: Performance of a prediction-based inclusion protocol. Methods: classical inclusion criteria (blue), random pick among the corresponding patients (pink), our method for different values of the TMS to be crossed at 3years (green) and the perfect method (orange) that selects only the desired patients.

4. Conclusion

We developed a digital brain twin which, that given only the baseline data of a new patient, is able to position him/her on the disease progression timeline and predict the value of his/her imaging and cognitive markers up to four years in time. This allows us to decrease the number of patients to be included for testing disease modifying therapeutic approaches by targeting the right individuals at the right time.

References.

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[2] Simulating Alzheimer's disease progression with personalized digital brain models. *Koval et al.* Preprint. 2019.