Towards cross-cohort estimation of cognitive decline in neurodegenerative diseases

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1. Introduction

Heterogeneity of cohorts, in terms of inclusion criteria, design of follow-up visits and batteries of cognitive assessments, hinders any thorough comparisons between them. For that reason, we build a cross-cohort model of cognitive decline that can be personalized to any patient, allowing to impute partially or totally missing scores. This enables to compare at an individual level disease progression of subjects from different cohorts, with a temporal realignment and regarding a broader set of biomarkers.

2. Methods

2.1 Model calibration

Based on a generic framework of disease progression that handles longitudinal data [1] and implemented in the *Leaspy* Python package, we first estimate a typical Alzheimer's disease (AD) progression scenario from the ADNI database where we pooled together cognitively normal (CN) progressors, mild cognitive impaired (MCI) subjects with stable diagnosis or converting to AD and stable AD. Using all glimpses of individual trajectories, the model estimates a group-average joint progression of a large set of biomarkers along a long-term disease timeline, from a normal to a pathological state.

** mean (± 1.96 SD)*	**ADNI**	**AIBL**	**PharmaCog**
Subjects	1454	282	142
Visits*	5.2 (±3.0)	1.9 (±1.3)	4.3 (±1.5)
Years followed*	3.5 (±3.0)	1.5 (±2.1)	1.7 (±0.7)
Age at baseline*	73.7 (±7.6)	74.5 (±7.3)	69.1 (±7.3)

Table 1 – Overview of data used

2.2 Individual-level personalization

This group-average continuous progression is then personalized to individual trajectories of patients from the PharmaCog and AIBL cohorts. In particular, every subject has his very own pace of progression and age at disease onset relatively to the group-average timeline. Besides this time reparameterization, the model accounts for others individual-specific patterns in the disease progression (cognitive troubles, as measured by the different biomarkers, may arise in slightly different orders for instance). An overview of data used for experiments is produced in table 1.

2.3 Imputation of missing scores

To assess how well our model performs and to what extent it generalizes, we start by imputing missing values of a given score, based on its past and future values together with the dynamics of concurrent features. We compare errors with other classical imputation strategies – constant predictions or univariate linear regressions, with imputation errors on training cohort and with data intrinsic level of noise – that can be evaluated from test-retest studies for each modality, as measured in [2] for mini-mental state examination (MMSE).

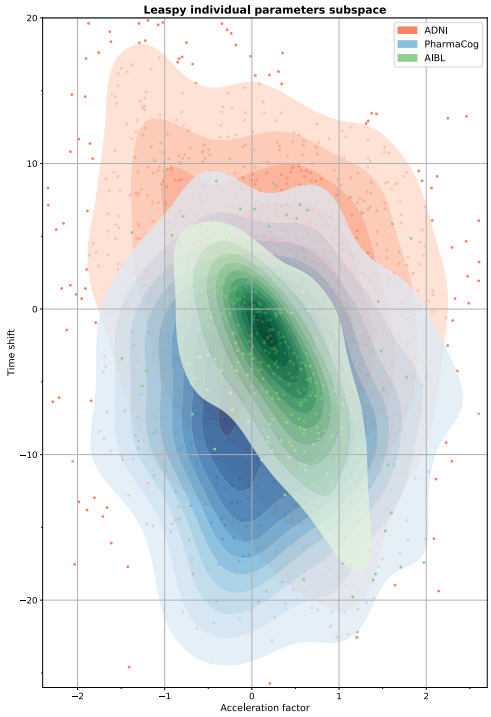

Figure 1 – Relative positioning of subjects of three different AD cohorts with our model

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2.4 Reconstruction of lacking features

We go further by simulating at an individual level purposely concealed scores, only taking advantage of the remaining features and the typical disease scenario learned before. By this way we mock the reconstruction of features that are entirely missing in a particular cohort. We look at different simulation setups depending on how many and which features we retain, down to only one particular cognitive assessment or neuro-imagery biomarker.

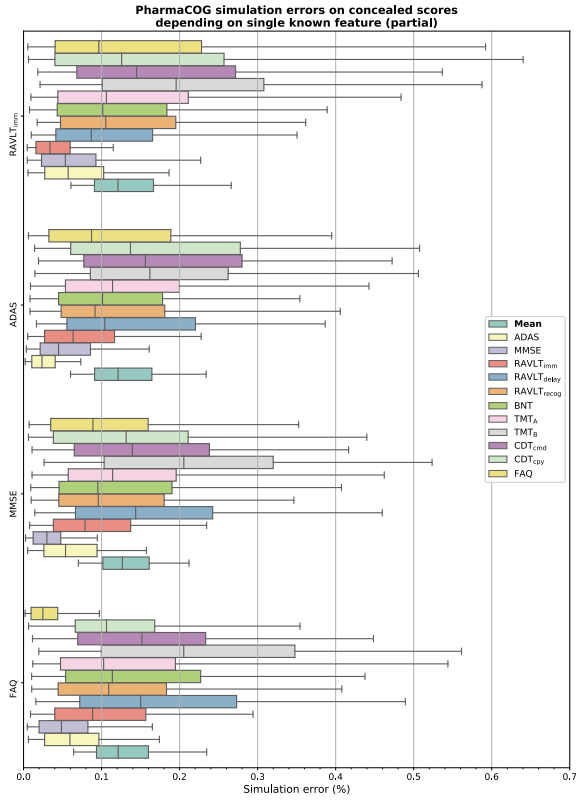

Figure 2 – Simulation errors on PharmaCog

3. Results and discussion

Figure 1 shows one possible[2] relative positioning of all subjects from the three cohorts based on their individual pace of progression (*acceleration factor*) and their age at disease onset (*time-shift*), together with a kernel density estimation of the underlying distributions. Such characterization enables to shed light on subtle differences between cohorts. We can notice that PharmaCog and ADNI cohorts share strong similarities in this respect (apart from earlier ages at disease onsets for PharmaCog, as hinted by patients' ages at baseline differences), while AIBL cohort seems to exhibit a different profile, spanning a tinier subspace of patients for whom ages at disease onset are correlated with paces of progression, unlike the two other cohorts.

Concerning missing values imputation, for most of available scores our model performs slightly better than other classical strategies – forward fill with last known value or linear interpolation – that are not specific to disease progression modelling and as such are not leveraging a multivariate group-average scenario of disease progression as we do. In particular, MMSE imputation errors we make on AIBL and PharmaCog are comparable to the intrinsic noise level of this score. Besides, our model exhibits strong generalization as imputation errors we make on not trained-on cohorts are not significantly different than the one we make on the discovery cohort (ADNI).

Finally, from the repeated measurements of a single score, the model is able to reconstruct the individual progression of several other features at the corresponding visits with a controlled error rate. Figure 3 illustrates the errors made in reconstructing all neurocognitive assessments available in PharmaCog only knowing the progression of one of them.

4. Conclusions

Our end-to-end model enables comparison of patients' trajectories from different cohorts and of cohorts themselves from an overall point of view. It permits to lessen imputation errors of most cognitive scores in not trained-on cohorts compared to other techniques and demonstrates a new way to simulate, at any individual visit, features that have not been measured in practice, which may be a way to overcome preclusion of composite scores computation for example.

5. References

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[2] Others positioning are possible leveraging others individual-specific parameters, capturing unique patterns of progression.