In-silico probabilistic modelling and prediction of the natural history of Alzheimer's disease based on serial measurements of clinical and imaging data

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The ability of tracking and quantifying the temporal and spatial dynamics of Alzheimer's disease (AD) across the entire history of the pathology would provide a unique opportunity for i) discovering disease specific tracking markers of neurodegeneration, ii) facilitating the discovery of modulators of the progression, and iii) improving diagnosis and treatment in clinical trials. To this end we introduce here novel probabilistic non-parametric tools for disease progression modeling and automatic diagnosis in AD, based on the estimation of the natural evolution of the pathology (spanning decades) from collections of short-term time series (up to 5 years follow-up time) of clinical measurements and multimodal brain images.

The proposed methodology is based on high-dimensional Gaussian process regression of multimodal time series where the individual measurements are i) interpolated in time in order to estimate longitudinal trajectories of individual changes; and ii) spatio-temporally normalized in a common reference frame, to define a group-wise model of spatio-temporal signal changes for the different modalities. Thanks to the proposed probabilistic setting, the framework also allows probabilistic prediction and uncertainty quantification of disease severity in testing individuals.

The proposed model is applied to clinical measurements and longitudinal T1 MR, FDG and AV45 PET images for a cohort of 431 amyloid positive individuals of the Alzheimer's Disease Neuroimaging Initiative (ADNI). The estimated disease progression spans roughly 20 years (Figure 1). The progression is characterized by initial amyloid deposition in parietal and temporal regions reaching a plateau configuration at year 10. Posterior hypometabolism appears at year 5 and further evolves to parietal and temporal regions. Hippocampal and temporal atrophy appear later, roughly 10 years after the initial amyloid deposition. At the latest stages the model finally shows the stereotypical pattern of posterior/temporal and parietal hypometabolim and amyloid deposition, along with an atrophy pattern spread across temporal cortical/subcortical areas.

The automatic staging provided by the model on testing individuals provides high face validity with respect to the clinical diagnosis (Figure 2), while using follow-up measurements largely reduce the prediction uncertainties.

The proposed formulation of disease progression modeling provides a statistical reference for the accurate probabilistic assessment of the pathological stage of de-novo individuals, and represents a valuable instrument for quantifying the variability and the

diagnostic value of biomarkers across disease stages. Moreover, this work allows for the first time the development of an image-based in-silico model of the multimodal relationship between brain atrophy, hypometabolism and amyloid deposition in AD. The model highlights spatio-temporal neurodegeneration patterns compatible with previous imaging findings and with classical hypothetical models of AD progression. The model thus provides a unique reference for the quantification of the severity of the disease in clinical trials of disease modifying drugs.

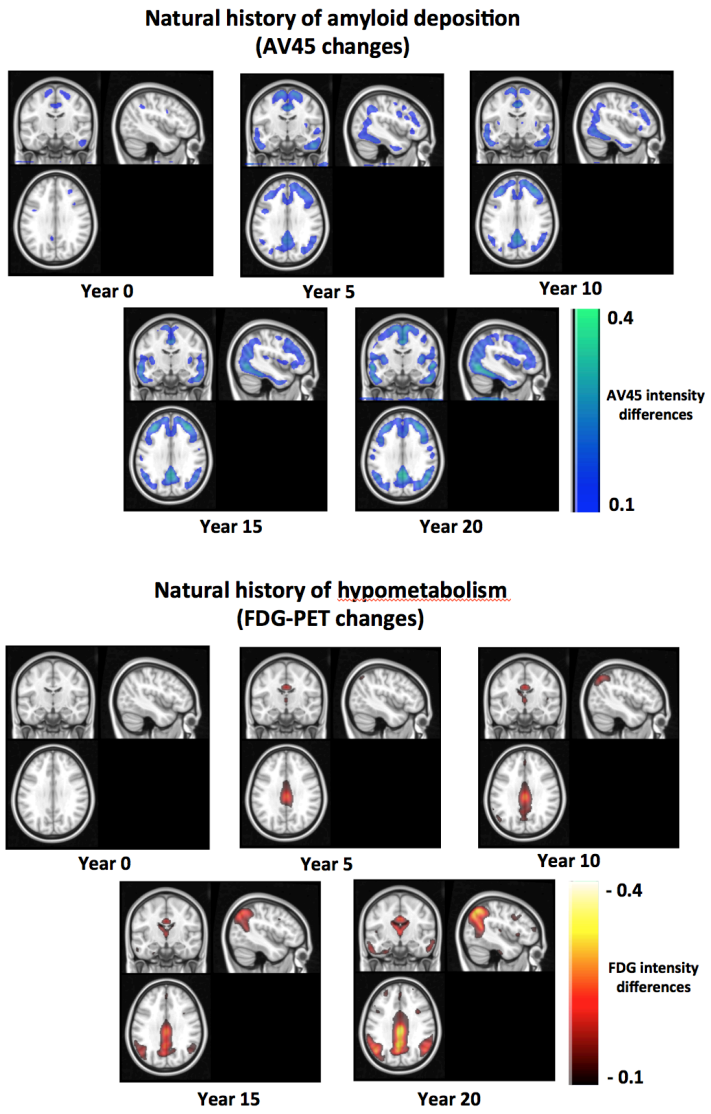

Figure 1. Spatio-temporal in-silico model of the natural history of AD, based on the joint analysis of short-term time-series of clinical and multimodal brain images. The AD progression is characterized by initial amyloid deposition in parietal and temporal regions reaching a plateau configuration at year 10. Posterior hypometabolism appears at year 5 and further evolves to parietal and temporal regions. Hippocampal and temporal atrophy appear later, roughly 10 years after initial amyloid deposition.

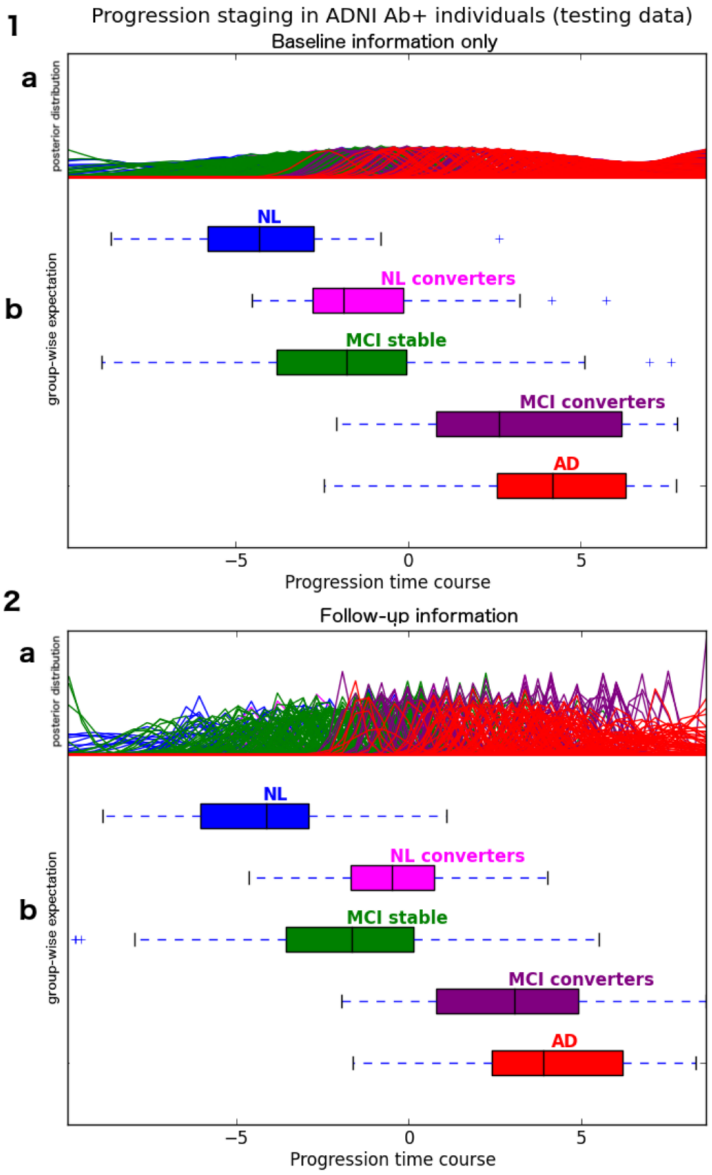

Figure 2. Posterior prediction for the individual disease staging in testing individuals by using i) only the baseline information (1a-b), and ii) the baseline + follow-up information available for each testing subject (2a-b). Healthy individuals are generally displaced at the early stages of the pathology, while the predictions for MCI and AD patients are associated with respectively intermediate and late progression stages. The results are similar for both scenarios, although by adding the follow-up information we largely reduce the uncertainty in the prediction of the individual's pathological stage (subfigure 1a vs 2a). NL: normal individuals; MCI: mild cognitive impairment; AD: Alzheimer's patients; Converters: converted to dementia during the clinical study.