Using DeepNLME to identify promising biomarkers with an application to disease pro modelling of Alzheimer's disease

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INTRODUCTION

Disease modeling (DM) offers a quantitative framework to characterize and predict disease progression in Alzheimer's disease, supporting treatment evaluation and clinical trial design. A widely used method for tracking disease progression is by modeling the longitudinal trajectory of the Clinical Dementia Rating (CDRSB) Scale. DeepNLME [1] is a novel framework using neural networks to both discover the structural model and define the links between covariates and model parameters. In a previous work [2], the DeepNLME disease progression models of CDRSB were presented demonstrating their precision and accuracy.

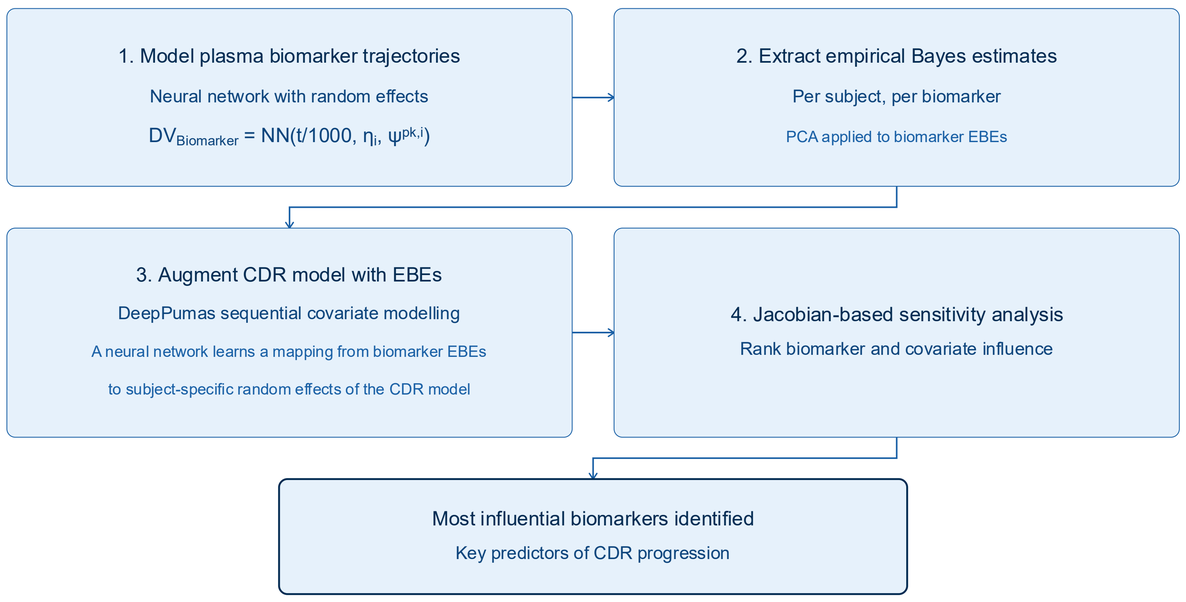
OBJECTIVES

In this work, we leverage a novel DeepNLME-based modeling approach to

- Model the progression of Clinical Dementia Rating (CDRSB) sum of boxes scores and several longitudinal biomarkers with and without drug.
- Identify promising biomarkers and baseline covariates with a high predictive power of CDRSB.

METHODS

The dataset used in this study was derived from the Gantenerumab trials [3] and comprised 326 subjects in the training set and 352 in the test set- both active and placebo groups. Longitudinal biomarker data were available for plasma, along with baseline demographic, physiological, and cognitive assessments. After modeling CDRSB scores using neural ODES –as shown in [2]- the analysis proceeded in the following steps:



where in the biomarker models, η_i are NN-specific random effects for individualization and ψ are the pk-related parameters.

RESULTS

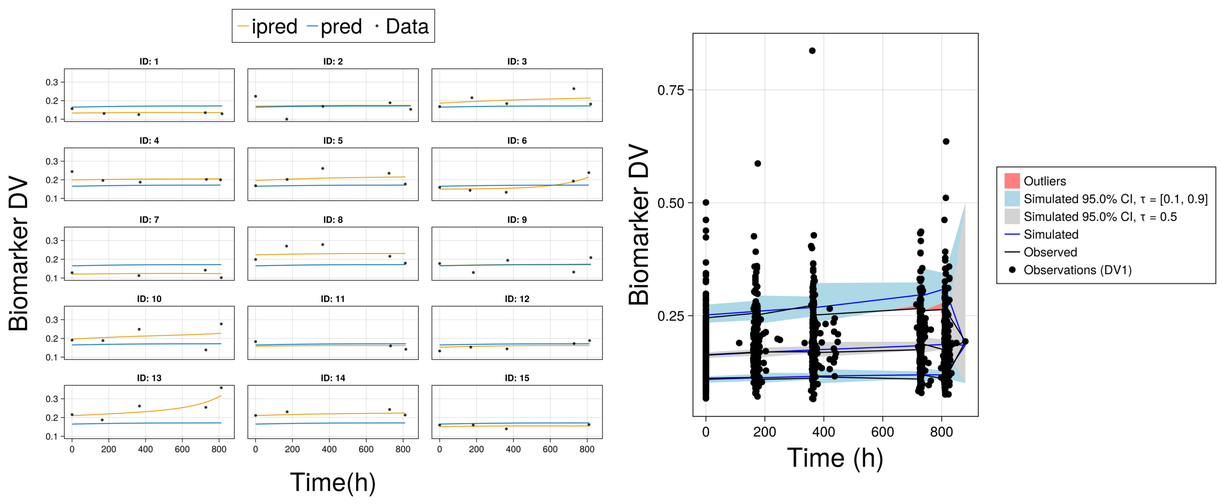


Figure 1. Left: Predictions for a subset of test population data of the placebo group for plasma *p-tau181. Right: VPC.*

The individual biomarker models fit both the relatively flat placebo profiles and the more complex PK-group trajectories well. Results for an indicative biomarker (plasma *p-tau181*) on the test set of the placebo group are shown in (1).

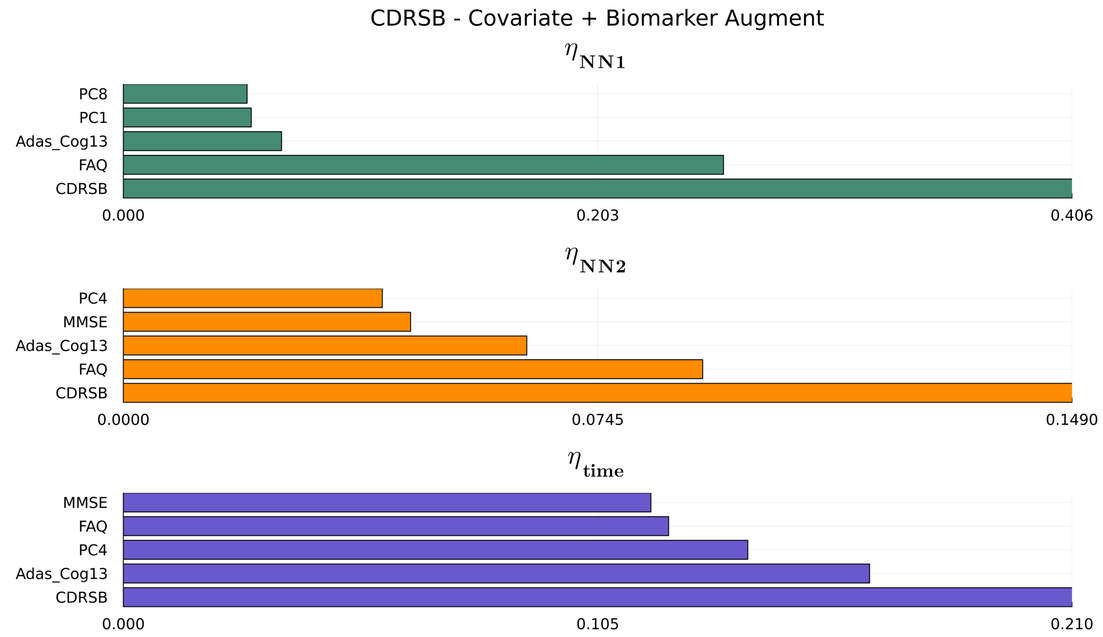


Figure 2. Sensitivity Analysis for the principal components of the biomarker EBEs and baseline cognitive scores for the placebo population. η_{NN} are NN-specific random effects for individualization and η_{time} captures the between-subject variability in the effect of time on the rate of change of CDRSB.

Sensitivity analysis on the principal components (PC) of the biomarker EBEs and the other baseline cognitive scores - Functional Activities Questionnaire (FAQ), Mini-Mental State Examination (MMSE), Alzheimer's Disease Assessment Scale Cognitive subscale (Adas-Cog) and the CDRSB itself- showed that baseline scores were the dominant contributors to improvements in CDRSB prediction. Adding EBE PCs to the CDRSB predictions improved log-likelihood but adding baseline cognitive scores on top yielded further gains — indicating these scores carry more substantial complementary information for CDRSB modeling. Results of the sensitivity analysis on the placebo population are shown in (2) while CDRSB prediction improvement is shown in the Log-Likelihood table below.

Population	Split	Base model CDR only	EBE-augmented + biomarker EBEs	Full model + cognitive scores
Placebo	Test	2014	2124	2459
	Train	1932	2032	2450
PK	Test	2688	2719	3090
	Train	2753	2835	3238

Log-likelihood values (higher is better); held-out test set vs. training set

Table of Log-Likelihoods for all scenarios tested.

CONCLUSIONS

We propose a novel approach for identifying potential associations between biomarker dynamics and clinical endpoints, such as CDRSB scores, used to characterize Alzheimer's disease progression. Using biomarker EBEs improves predictions but compromises temporal causality, serving mainly for hypothesis generation. Future steps are using joint modeling to robustly leverage longitudinal trajectories

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