# New Mixed-Effects and Time-Varying Coefficients Models for Fitting Genetic and Longitudinal Data with Applications to Alzheimer's Disease

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## ABSTRACT

Alzheimer's disease (AD) is known to be influenced by genetic factors, including Single Nucleotide Polymorphisms (SNPs) and genes. Cognitive assessments play a crucial role in diagnosing AD, and these assessments are often collected over time to track disease progression. This dissertation aims to investigate whether the effects of SNPs, genes, and pathways on longitudinal cognitive assessments exhibit time-varying patterns.

This dissertation research is motivated by the Alzheimer's Disease Neuroimaging Initiative (ADNI) data, comprising MRI and PET images, genetics, cognitive tests, Cerebrospinal Fluid (CSF), and blood biomarkers used as predictors of the disease. To work with the large ADNI genetic data of size 57.4GB with 620,901 SNPs, we adopt a sequential approach by partitioning the original data into manageable segments to find useful and important SNPs for subsequent analyses and model construction.

Due to the longitudinal nature of cognitive assessment measures, as AD status

changes over time, in this dissertation, we propose disease state-specific shared-parameter cross-state forward-regressive mixed-effects and disease state-specific time-varying coefficients models to accommodate patient-specific random trajectories and time-varying genetic effects. The proposed models are attractive and flexible as they capture the cross-state dependence of longitudinal measures and the non-parametric forms of time-varying coefficients and also allow us to fit SNPs or aggregate gene-level summary measures of SNPs.

Shrinkage priors are taken to address sparsity arising from a large number of B-spline parameters. The covariance matrices of random effects are re-parameterized to facilitate more flexible specification of the priors and convenient implementation of Markov chain Monte Carlo sampling. Variations of the Deviance Information Criterion are constructed for model comparisons and the Pearson-type residuals are also developed for checking model adequacy. An in-depth analysis of the ADNI data is carried out to demonstrate the usefulness of the proposed methodology.

The findings from this dissertation will shed light on the dynamic interactions between genetic factors and AD cognitive assessments over time. Understanding these time-varying effects is highly significant as it helps us to combat Alzheimer's disease more effectively.