Interpretable Machine Learning for Biomarker Discovery in Alzheimer's Disease through Integrative Multi-Omics Analysis

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Abstract:

Alzheimer's disease (AD) is a complex, multifactorial neurodegenerative disorder with no definitive cure, highlighting an urgent need for innovative diagnostic and therapeutic strategies. This study leverages an interpretable machine learning framework to integrate multi-omics data—genomics and transcriptomics—from three cohorts of AD patients. By analyzing brain region-specific samples and whole genome sequencing data, we identify robust biomarkers and develop personalized therapeutic strategies.

Our robust Random Forest model employs leave-one-patient-out cross-validation, SHAP interpretability analysis, and unsupervised clustering to unveil distinct molecular signatures in different brain sub-tissues, linking these signatures to both genetic and transcriptomic markers. This approach allows us to categorize sub-tissue-specific variations and construct precise gene-gene interaction networks for each sub-tissue. The networks reveal critical hub genes, suggesting potential drug targets that are biologically relevant and could lead to targeted AD therapies. Moreover, functional enrichment analyses of these hub genes underscore their involvement in key biological processes implicated in AD pathogenesis, such as glucose metabolism, oxidative stress, and membrane integrity.

This integrative approach not only advances our understanding of the molecular diversity and systemic complexities of AD but also demonstrates the potential of using interpretable machine learning to enhance precision medicine [1]. By pinpointing actionable biomarkers and connecting them with potential therapeutic interventions, this study paves the way for clinical trials that could transform these findings into effective treatments for Alzheimer's disease.

[1] Winchester LM, Harshfield EL, Shi L, et al. Artificial intelligence for biomarker discovery in Alzheimer's disease and dementia. Alzheimer's Dement. 2023; 19: 5860-5871.