Identification of Novel Target Genes and ML-Based Drug Repurposing and Discovery for Alzheimer’s Disease in the Presence of Metabolic Comorbidities

Pai, Shriya (School: Jesuit High School)

Alzheimer's disease (AD) is a complex neurodegenerative disorder with no cure, despite decades of research. More than six million adults in America are living with Alzheimer’s and the number of deaths due to this disease has nearly doubled since 2000. AD is characterized by the deposition of amyloid-beta fibrils and tau proteins in the brain which results in cognitive decline and other debilitating symptoms. Despite numerous clinical trials, no effective anti-AD drug has been developed, and novel drug strategies continue to fail in clinical trials. Over 90% of people living with AD have additional co-existing conditions such as hypertension, hypercholesterolemia, or diabetes. In this project, I aimed to provide a multi-step solution to address the gaps in finding AD cures. First, I utilized Machine learning algorithms to determine existing drug combinations that provide effective results using longitudinal study datasets using ML models, which predicted the cognitive score at a maximum of 89% accuracy. Metformin, Atorvastatin, Donepezil, and Amlodipine used for the treatment of AD and related comorbidities were predicted, along with anti-inflammatory drugs, to reduce the rate of cognitive decline. Second, I found target genes by comparing AD and comorbidities' differential gene expressions. I found many common genes, like AKT1, CHUK, PPM1A, and STARD3NL, and validated them as being correlated directly to the AD pathway through literature studies and STRING/GO pathway analyses. Lastly, I conducted early de novo drug design using an autoencoder to analyze latent space with drug-like molecules that satisfy certain physicochemical properties with the SMILES datasets produced from target gene analysis.