Leveraging a Context-Aware Graph Neural Network for Drug Target Discovery in Alzheimer's Disease

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Alzheimer's disease (AD) is a complex, progressive neurodegenerative disorder characterized by extracellular Aß plaques, neurofibrillary tau tangles, and neuronal degeneration, involving multiple cell-types and pathways. Modeling protein function across these varied cellular and molecular contexts poses a significant algorithmic challenge. A context-aware model is needed to identify key drug targets in AD progression and enable targeted interventions. To address this, we developed ALZ-GNN, a context-aware graph neural network, using brain omics data spanning the aging-to-AD spectrum. ALZ-GNN was trained on 14,951 proteins and 206,850 protein interactions, and fine-tuned with AD risk genes. We constructed 48 cell-subtype specific protein networks using differentially expressed genes. ALZ-GNN uses neural message passing to update node embeddings across these graphs and leverages an attention bridge to align protein and cell-subtype representations, generating protein embeddings that capture the unique biological context of each cell-subtype. Investigating APOE, the largest genetic risk factor for AD, we found high embedding similarity in microglial, neuronal, and CD8 cells, suggesting similar roles across these cell-types. Additionally, pathway analysis of the vulnerable layer 2/3 excitatory neurons revealed potential molecular targets. ALZ-GNN outperformed state-of-the-art models with improvements of 70.83% in AP@5 and 72.92% in AUPRC, demonstrating its ability to rank AD risk genes and capture complex biological relationships. Our results demonstrate that ALZ-GNN provides a powerful computational framework for uncovering novel insights into AD neurobiology, with potential to revolutionize drug target discovery and accelerate the development of precision therapeutics.

Awards Won: