Wired for Survival: Modeling Gene Networks to Identify Resilience and Neuron Subtypes in ALS via Graphical Optimization

Kalbhavi, Shripriya (School: Lynbrook High School)

Can neuron resilience be predicted as topological failure of cellular identity? Amyotrophic lateral sclerosis (ALS) is a fatal neurodegenerative disease marked by TDP-43 aggregation and motor neuron (MN) death. While current research emphasizes degeneration, mechanisms of neuronal resilience and their potential as therapeutic targets remain unclear. This study engineered a topologically-aware graph neural network via protein-protein interactions to model ALS resilience through network stability. The model distinguished ALS with 85% accuracy and identified a 20-gene resilience hub enriched in chromatin remodeling (p=7.61e-04). This hub serves as a biomarker of early disease state determination and a scaffold for epigenetic therapy. scRNA-seq data (GSE226482) revealed MN subtypes exist on a state-specific spectrum as immature neurons show resilience, while mature, vulnerable MNs display end-stage markers. Type 7, expressing MNX1, is unique in being highly resilient despite a mature state. Spatial expression of these subtypes was confirmed via spinal cord tissue imaging. These neuron subtypes, identified as prognostic biomarkers, were validated in patient data: Type 7 was enriched in long-surviving samples (p=1.93e-03), and high resilience correlated with increased survival (p=0.044). Mathematical modeling using path-finding algorithms defined a “differentiation tax,” the cost to neuron identity under stress, and identified low-cost efficient resilience networks. By redefining ALS as topological failure, this research uncovers an epigenetic gene hub for resilient neuronal subtypes. This scalable, clinically-relevant framework identifies therapeutic targets to preserve neuron identity, providing hope for ALS patients via active neuroprotection.

Awards Won:

The Consortium for Mathematics and its Applications: Outstanding In-kind

The Consortium for Mathematics and its Applications: Outstanding