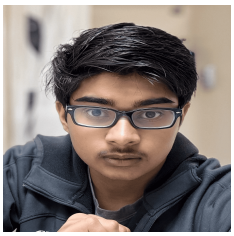
ALS-GNN: A graph neural framework for simulating neural degeneration and therapeutic adaptation

Naga Sriharsha Mudda*
Illinois Mathematics and Science Academy
naga.m2595@gmail.com



Sonit Sahoo*
Illinois Mathematics and Science Academy
vracto@icloud.com

*These authors contributed equally to this work.

Abstract

Studies on amyotrophic lateral sclerosis (ALS) have consistently faced a challenge in understanding the coexistence of progressive degeneration of motor neurons with transient compensatory plasticity, which involves a paradoxical dynamic of "growing while dying" that standard models fail to explain. To address this requirement, we developed a real-time virtual brain platform integrating multiscale computational models – Hodgkin-Huxley spiking neural networks with stochastic ion channels for simulating single-neuron degeneration, graph neural networks (GNNs) for dynamic small-world cortical connectivity mapping, and spike-timing-dependent plasticity (STDP) algorithms for synaptic adaptive rewiring modeling – with probabilistic neurodegeneration modules trained against clinical MRI/EMG datasets for region-specific motor neuron loss modeling (1.8% per month). The platform incorporates closed-loop pharmacokinetic-pharmacodynamic (PK-PD) interfaces, optogenetic-inspired stimulation, and integration of calcium imaging to monitor real-time activity in the setting of simulated therapeutic interventions. Our model predicted a 7% rise in pathological cortical connectivity and a critical neuron depletion threshold of around 43% in the early stages of ALS development, and validation against longitudinal MRI/EMG datasets of patients corroborated these predictions, with the measured hyperconnectivity rises of 6–8% and concomitant breakdown in function close to the predicted threshold. Real-time perturbation experiments demonstrated that neuroprotective drugs like riluzole, delay degeneration by 38% when administered pre-collapse, but exacerbate hyperexcitability post-collapse, while optogenetic circuit mapping revealed vulnerable hubs where targeted synaptic reinforcement prolongs network coherence. By incorporating multiscale modeling, mean-field-Bayesian inference for plasticity prediction, and patient-specific PK-PD simulations, this platform is capable of monitoring bidirectional neurodegeneration-compensation dynamics in real time. Its open-source platform enables screening of therapeutic strategies, compressing neurodegeneration pathways, and provides a precision medicine platform to stratify patients by plasticity-degeneration ratios, predict personalized therapeutic windows, and guide synaptic stabilization therapies in pre-symptomatic ALS; this research drives mechanistic insight and clinical translation in parallel, rendering computational modeling a keystone for curative ALS development.

Keywords: ALS, GNN, neurodegeneration, therapeutic adaptation, PK-PD, optogenetics, STDP, plasticity

Biography

`Naga Sriharsha Mudda`, a student researcher at the Illinois Mathematics and Science Academy, investigates the gut-brain axis's biological mechanisms in the progression of ALS, focusing on neuroinflammation, microbial metabolites, and neurodegeneration. Their research interests center on molecular neuroscience and translational medicine.

`Sonit Sahoo` is a student researcher at the Illinois Mathematics and Science Academy, pursuing computer science. They served as the programmer for the ALS-GNN project, focusing on the development of the graph neural network framework and its integration with multiscale computational models. Their interests include machine learning, quantum computing, neuroscience, and other interdisciplinary fields.