KAN-Fusion: Interpretable Multimodal Networks for Novel Neurodegenerative Disease Target Discovery

Prokofev, Daniil (School: Thomas Jefferson High School for Science and Technology)
Leetyn, Isaac (School: Thomas Jefferson High School for Science and Technology)

Neurodegenerative disease therapeutic development faces hurdles from multi-omic complexity and the poor interpretability of standard ML models (e.g., MLPs), limiting target discovery. We developed a novel multimodal Kolmogorov-Arnold Network (KAN) pipeline integrating genomics, proteomics, neuroimaging, and clinical data from harmonized ADNI/PPMI datasets. Rigorous preprocessing (imputation, batch correction, VAE imaging standardization) was applied. KAN architecture enables construction of fusible, optimized, metric-specific subnetworks, trained on diverse data combinations (SNPs, protein expression, structural MRI/PET, clinical assessments) to predict outcomes like MDS-UPDRS progression. We implemented a novel late-layer fusion strategy—combining techniques such as edge-wise modulation (genetics-proteomics), additive attention (proteomics-imaging), and multiplicative gating (imaging-clinical)—followed by unsupervised training refinement. The resulting fused model achieved 92% average accuracy across 14 distinct disease progression metrics. A key advantage: networks trained on full multimodal data, including expensive types, can perform inference (e.g., target identification) using only more accessible data types, leveraging comprehensive knowledge for higher performance than standard single-modality networks. KAN's inherent interpretability, combined with game-theoretic network stimulation (SHAP), identified 147 viable therapeutic targets, including 17 novel candidates, while confirming cross-modal biological associations. Extensive 5-fold cross-validation demonstrated our KAN-Fusion approach's superior accuracy and interpretability compared to standard models (Random Forest, SVM, Gradient Boosting, MLPs) across all external validation datasets.

Awards Won: