

# Title: Interpreting Cis-regulatory Mechanisms from Genomic Deep Learning with Kolmogorov-Arnold Networks

Xitian(Tina) Yu

Abstract:

Non-coding DNA encodes complex cis-regulatory mechanisms that regulate gene expression by orchestrating transcription factor binding within specific sequence contexts. Although deep learning has advanced our understanding of these mechanisms, the black box nature makes it difficult to understand what drives their decision-making process. Thus, interpreting deep learning models remains a key challenge for translating their strong predictive performance into actionable biological insights. Here we explore whether Kolmogorov-Arnold Networks (KAN) offer improved interpretability over existing post hoc explainable AI methods. A key feature of KANs is their learnable edge functions that provide direct relationships among input features, enabling the visualization of feature interactions. This approach offers mechanistic interpretability as well as symbolic function discovery to provide an analytical explanation of how KANs make their predictions. To assess the utility of KANs in studying gene regulation, we applied them to a previously published Drosophila enhancer activity dataset measured via cSTARR-seq. Our analysis demonstrates that KANs achieve predictive performance comparable to SQUID (Surrogate Quantitative Interpretability for Deepnets), a state-of-the-art method for interpreting sequence-based deep learning models, and In Silico Mutagenesis, a widely used baseline. Importantly, KANs effectively capture regulatory patterns across various configurations, offering complementary insights to current methods, including a symbolic function as a novel form of interpretation. While further validation is necessary to confirm the components of these symbolic functions, our findings highlight the potential of KANs to advance scientific discovery in regulatory genomics. By bridging predictive performance and interpretability, KANs open new avenues for understanding and modeling complex cis-regulatory mechanisms.