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DeepRNA-DTI: A Deep Learning Approach for RNA-Compound Interaction Prediction with Binding Site Interpretability

Haelee Bae[1], Hojung Nam[1,2,3*]

[1]*AI Graduate School, Gwangju Institute of Science and Technology (GIST)*
[2]*Department of Electrical Engineering and Computer Science, Gwangju Institute of Science and Technology (GIST)*
[3]*Center for AI-Applied High Efficiency Drug Discovery (AHEDD), Gwangju Institute of Science and Technology (GIST),*
**Corresponding author: hjnam@gist.ac.kr*

RNA-targeted therapeutics represent a promising frontier for expanding the druggable genome beyond conventional protein targets. However, computational prediction of RNA-compound interactions remains challenging due to limited experimental data and the inherent complexity of RNA structures. Here, we present DeepRNA-DTI, a novel sequence-based deep learning approach for RNA-compound interaction prediction with binding site interpretability. Our model leverages transfer learning from pretrained embeddings, RNA-FM for RNA sequences and Mole-BERT for compounds, and employs a multitask learning framework that simultaneously predicts both presence of interactions and nucleotide-level binding sites. This dual prediction strategy provides mechanistic insights into RNA-compound recognition patterns. Trained on a comprehensive dataset integrating resources from the Protein Data Bank and literature sources, DeepRNA-DTI demonstrates superior performance compared to existing methods. The model shows consistent effectiveness across diverse RNA subtypes, highlighting its robust generalization capabilities. Application to high-throughput virtual screening of over 48 million compounds against oncogenic pre-miR-21 successfully identified known binders and novel chemical scaffolds with RNA-specific physicochemical properties. By combining sequence-based predictions with binding site interpretability, DeepRNA-DTI advances our ability to identify promising RNA-targeting compounds and offers new opportunities for RNA-directed drug discovery.