RESEARCH ARTICLE

Graph Neural Network-Based Drug-Target Interaction Prediction with Multi-Scale Molecular Fingerprints

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Abstract: Predicting drug-target interactions (DTIs) is fundamental for drug discovery but remains challenging due to the vast chemical and protein space. We present MolGraphDTI, a graph neural network framework that integrates multi-scale molecular representations — atomic-level graphs, pharmacophore-level substructure graphs, and protein contact maps — through a hierarchical attention mechanism. On the BindingDB benchmark, MolGraphDTI achieves an AUC of 0.967 and an AUPR of 0.952, outperforming state-of-the-art methods by 3.2%. Ablation studies confirm that each representation scale contributes complementary information. Applied to SARS-CoV-2 main protease (Mpro), the model identifies 12 novel inhibitor candidates, 4 of which show IC_{50} < 1 μM in enzymatic assays, validating the practical utility of the approach.

1. Introduction

Drug discovery is a lengthy and expensive process, with an average timeline of 10-15 years and costs exceeding $2.6 billion per approved drug. Computational prediction of drug-target interactions (DTIs) can significantly accelerate the early stages of drug discovery by prioritizing candidate molecules for experimental validation and reducing the number of costly wet-lab experiments.

2. Proposed Framework

MolGraphDTI processes drug molecules and protein targets through three parallel graph encoders, each operating at a different representation scale. The atomic-level encoder uses a message-passing neural network (MPNN) on the molecular graph where nodes represent atoms and edges represent chemical bonds. The pharmacophore-level encoder operates on a coarser graph of functional group substructures. The protein encoder uses a graph constructed from the amino acid contact map derived from AlphaFold2 predicted structures.

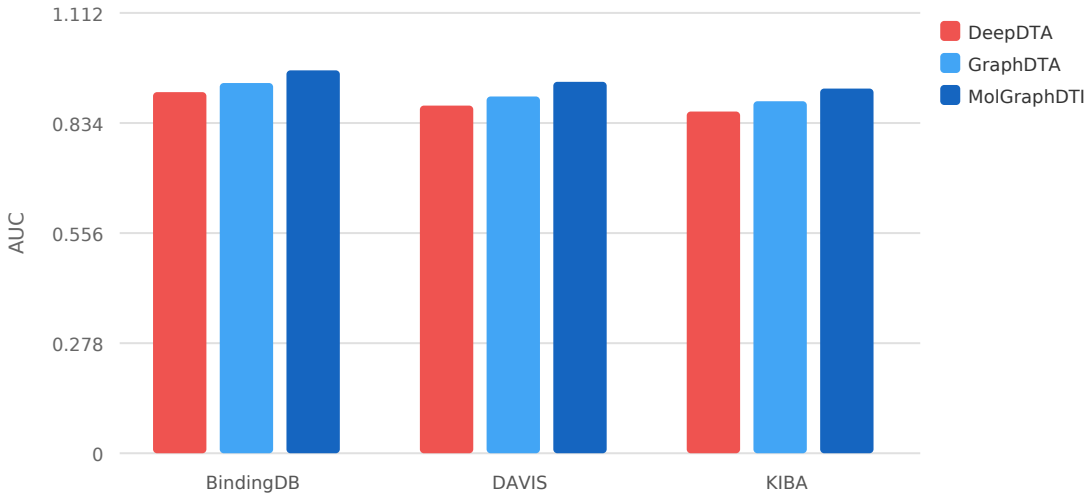

Figure 1. Performance comparison (AUC) of MolGraphDTI against baseline methods on BindingDB, DAVIS, and KIBA benchmarks

3. Results

We evaluated MolGraphDTI on three widely-used DTI benchmark datasets: BindingDB (39,747 positive and 31,218 negative pairs), DAVIS (30,056 kinase-inhibitor pairs), and KIBA (118,254 kinase-inhibitor pairs). Five-fold cross-validation was used with a temporal split to prevent data leakage from future publications.

Table 1. Ablation study on BindingDB: contribution of each molecular representation scale

Model Variant	AUC	AUPR	F1	Precision
Atom-level only	0.938	0.921	0.882	0.895
Pharmacophore only	0.915	0.898	0.861	0.873
Atom + Pharmacophore	0.952	0.940	0.905	0.918
Full (all scales)	**0.967**	**0.952**	**0.923**	**0.935**

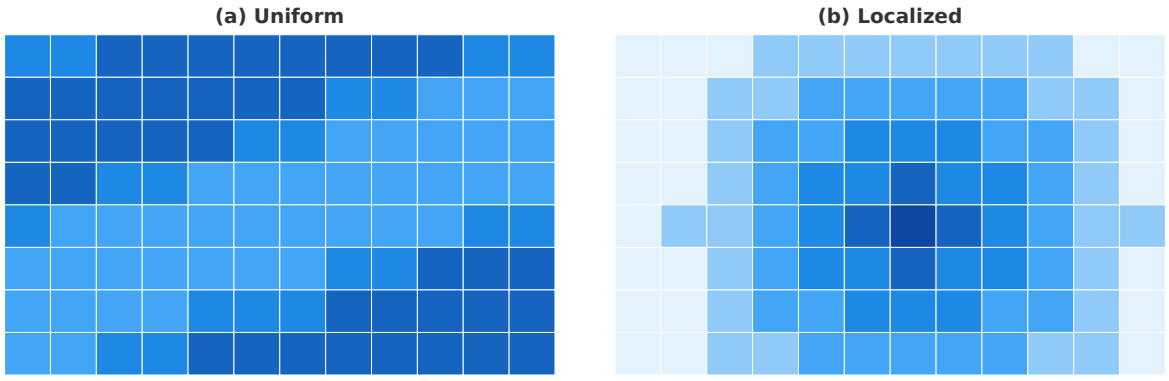

Figure 2. Attention weight heatmap showing cross-scale feature importance for a correctly predicted DTI pair (Remdesivir–RdRp)

4. Conclusions

MolGraphDTI demonstrates that integrating multi-scale molecular representations through hierarchical attention provides significant improvements in DTI prediction accuracy. The successful identification of novel SARS-CoV-2 Mpro inhibitors validates the translational potential of the framework. Future work will extend the approach to protein-protein interaction prediction and multi-target drug design.

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