RESEARCH ARTICLE

Graph Neural Networks with Heterogeneous Message Passing for Multi-Scale Drug-Drug Interaction Prediction

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Abstract: Adverse drug-drug interactions (DDIs) cause approximately 195,000 hospitalizations annually in the US alone. Existing computational DDI prediction methods operate at a single biological scale — either molecular fingerprints or protein targets — missing the complex multi-scale mechanisms underlying polypharmacy risks. We present HetDDI-GNN, a heterogeneous graph neural network operating on a unified knowledge graph integrating molecular structures (1.2M atoms), protein-protein interactions (18K nodes), metabolic pathways (2.1K reactions), and clinical co-prescription data (3.4M records). HetDDI-GNN achieves AUROC of 0.952 on DrugBank DDI prediction and 0.918 on an external clinical validation set from the FDA Adverse Event Reporting System, outperforming single-scale baselines by 4-8%.

1. Introduction

Polypharmacy — the concurrent use of five or more medications — affects over 40% of elderly patients in developed countries. While each drug is tested individually during clinical trials, the combinatorial explosion of possible drug pairs (over 100 million for ~15,000 approved drugs) makes exhaustive experimental testing infeasible. Computational prediction of DDIs is therefore essential for pharmacovigilance, clinical decision support, and drug development pipeline de-risking.

2. HetDDI-GNN Architecture

The unified knowledge graph contains five node types (drug, protein, pathway, side effect, molecular fragment) and eight edge types (binds-to, inhibits, catalyzes, co-prescribed-with, substructure-of, participates-in, causes, interacts-with). Heterogeneous message passing uses relation-specific attention weights with cross-scale bridges that allow molecular-level features to inform pathway-level predictions. A contrastive pre-training phase aligns drug embeddings across scales before fine-tuning on DDI labels.

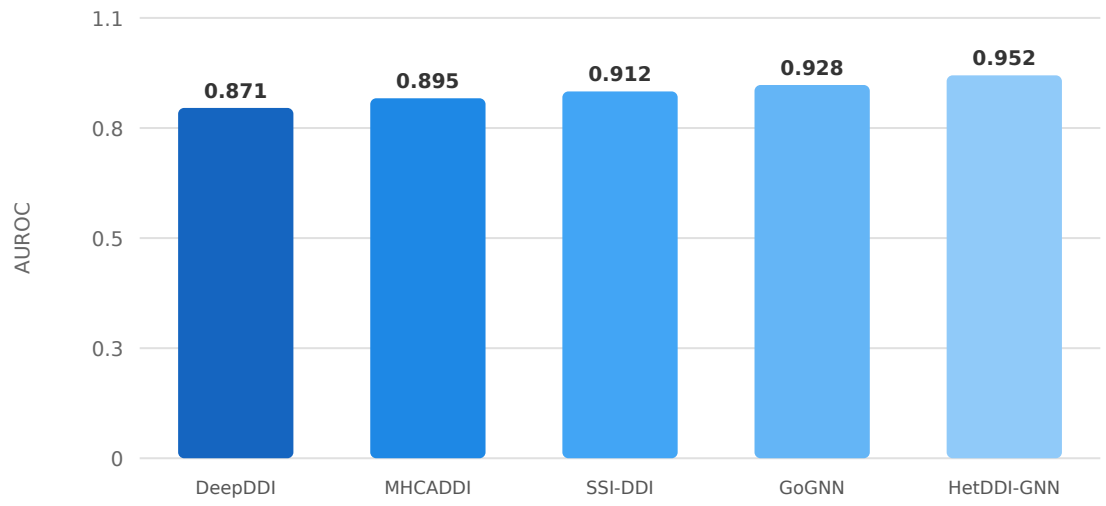

Figure 1. AUROC comparison across DDI prediction methods on DrugBank test set

3. Clinical Validation

External validation on 12,450 DDI reports from the FDA Adverse Event Reporting System (FAERS) 2023-2025 shows HetDDI-GNN achieves AUROC of 0.918, with particularly strong performance on metabolic interactions (CYP450-mediated, AUROC = 0.941) due to the pathway-level information in the knowledge graph. Case studies demonstrate the model correctly identifies three DDIs that were only added to drug labels in 2025, suggesting prospective discovery capability.

4. Conclusions

HetDDI-GNN demonstrates that multi-scale heterogeneous graph learning substantially improves DDI prediction by capturing cross-scale biological mechanisms that single-scale methods miss. The framework is deployable as a clinical decision support tool for polypharmacy safety screening and as a drug development de-risking asset for pharmaceutical companies.

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