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**Research Paper**

# Explainable graph neural networks for drug-target interaction prediction: a GNNExplainer-augmented framework with molecular graph representation

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**ABSTRACT**

Drug-target interactions (DTIs) are important systems to predict, as they define the set of drug candidate molecules that are capable of binding efficiently to disease relevant protein target. The traditional computational methods use feature engineering on molecular fingerprint or similarity measures based on sequence level, which have limited ability in modeling the rich topological structure of the molecular graph. To solve the problems listed above, we propose a new explainable graph neural network framework, GNN-XAI, that unites multi-layer Graph Convolutional Networks (GCNs) with the GNNExplainer attribution method to merely ensure high-accuracy DTI prediction while providing biochemically interpretable explanations of binding site interactions. Molecules are drawn as attributed graphs, with the nodes drawn and their attributes painted, and the edges drawn and their types colored. Evaluation of the framework was conducted on BindingDB and ChEMBL-29 benchmark sets using AUC-ROC, AUPR and F1-score results of 0.961, 0.948 and 93.2 respectively were achieved. The plausibility of the biological fidelity of the derived subgraph attributions was verified by comparing to experimental crystallographic binding data in the GNNExplainer. Benchmark ablation experiments and generalization across datasets prove the robustness and clinical benefits of the proposed approach.

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## 1. INTRODUCTION

Currently, the pharmaceutical industry suffers from an alarming attrition along with its pathway of exponential growth of computational and genomic information to clinical trials with less than 10% of candidates making it to the FDA [1], [2]. The biggest difficulty is one problem from the drug-target interaction (DTI) prediction [3] that plays an essential role in rational drug design, target deconvolution, and drug repurposing strategies.

There are three different approaches used in computational DTI prediction: (i) ligand-based approaches that consider molecular fingerprint similarity [4]; (ii) structure-based approaches that resort to docking simulations [5]; and (iii) machine-learning approaches that attempt to use DTI as a binary/classification problem or a continuous classification problem [6]. Although deep learning (DL) models including graph neural networks (GNNs) have proven to be highly successful at DTI prediction [7], [8], they are mainly black-box predictors of interaction events, limiting their application in mechanistic interpretations that are key in novel drug discovery pipelines [9].

Molecular representation learning is a task that is well suited to graph neural networks where atoms are represented as nodes and bonds as edges, where the chemical attribute vectors and bond type features, respectively.Graph neural networks naturally support molecular representation learning, with the atoms represented as nodes and the bonds represented as edges, using chemical attribute vectors and bond type features respectively [10]. To date, though, GNN-based DTI methods have not explicitly incorporated post hoc explanatory methods to assess against established pharmacophoric substructures and binding site motifs if known, to determine if the learned subgraph features match well-known structure-activity relationships. Scientifically, closing this gap is vital, and practically it is necessary to gain regulatory acceptance for the AI-assisted drug discovery process [11], [12].

We propose GNN-XAI, a novel framework that (1) builds attributed molecular graphs for drug molecules and protein targets; (2) uses a three-layer GCN with attention based pooling to classify the DTIs and (3) embeds GNNExplainer [13] into this framework to provide minimal, sufficient subgraph explanations, which could reveal key pharmacophoric substructures affecting predicted drug-target interactions. Our contributions include:

1. A consistent molecular graph construction algorithm that includes 78 dimensions of atomic features and 10 dimensions of bond features based on RDKit and protein contact maps.
2. Attention-Gate for GCN (HGCN) for extremely imbalanced benchmark data sets for DTI prediction
3. Experimental biochemical validation of GNNExplainer-derived attributions versus structural data from the Protein Data Bank (PDB) with systematical comparisons.
4. High-level performance on BindingDB data and ChEMBL-29, and in-depth generalization analysis across datasets.

## 2. RELATED WORK

### 2.1 Graph Neural Networks for Drug Discovery

The ability of GNNs to naturally represent non-Euclidean molecular structures makes them one of the influential deep learning paradigm in the field of Computational Drug Discovery. In contrast to the traditional descriptor-based machine learning model which needs to be handcrafted for molecular representations, the GNNs can learn hierarchical molecular representations directly from the graph topology and chemical attributes. [10] showed early examples of the Message Passing Neural Network (MPNN) framework which was able to efficiently capture atom-level local and global molecular interactions, which were crucial for predicting a variety of physicochemical and biological properties. Numerous GNN models, such as Graph Convolutional Networks (GCN) [14] and Graph Attention Networks (GAT) [15] and GraphSAGE [16], have been used in cheminformatics applications like predicting the toxicity of chemicals, estimating properties of molecules, and modelling protein-ligand interactions.

Some approaches for prediction of drug-target interaction (DTI) using graph based approach have been found to be more accurate than the conventional sequence based and similarity based approaches.

GraphDTA [7] used a graph-based representation for drug molecules, and a one-dimensional convolutional neural network for protein representation, to obtain better performance in predicting the affinity of drug molecules on benchmark datasets like Davis and KIBA. Again, Deep DTA [17] has employed a CNN to learn representations from SMILES strings and protein sequences, with the conclusion that deep architectures can automatically map out complex nonlinear interaction patterns. A later work by MolTrans [18] further developed these concepts by using transformer-based interactions that are able to capture long-range interactions between drug substructures and protein residues via attention mechanisms.

Recent research extended this work into incorporating the structural biological information in graph learning algorithms. To account for the spatial relationship between residues, [8], [19] introduced a graph neural network and proposed a protein contact map to introduce spatial information into DTI prediction models. By using such methods, the biological realism of learned representations is enhanced, as residue contact graphs more accurately capture the folding of proteins and the regions in which they interact with other proteins for their function as compared to the raw amino acid sequence. In addition, the development of proteins prediction systems like AlphaFold [20] has made it possible to obtain high-quality 3D models of proteins which have not been crystallized, creating new opportunities for graph-based multimodal drug discovery pipelines [21].

Although the above progresses have been made, there are still some restrictions in existing GNN-based DTI systems. Most of the current approaches are to come up with the best predictive performance with little saying about which molecular substructures or residue interaction lead to the prediction. The interpretability of the results is very significant in practical pharmaceutical applications, since the scientific researcher has to determine whether the predicted interaction has chemical significance and biological plausibility [22]. This is because regulatory agencies and medicinal chemists are increasingly demanding transparency of AI systems that can explain not only the pharmacophoric motifs and regions of binding residues, but also the structure-activity relationship. For this reason, there is an increasing need for integrating graph neural architectures with explainable artificial intelligence (XAI) methods to enhance trustworthiness, reproducibility, and scientific understanding in computational workflows for drug discovery.

### 2.2 Explainability in Graph Neural Networks

As deep neural models are often thought of as being black-box models with little transparency, explainability has become a critical research direction in graph representation learning. In biomedical and pharmaceutical applications, it is sometimes as important as the prediction accuracy what is the reason for the fact, that a model predicts a certain drug-target interaction. The goal of Explanatory Artificial Intelligence (XAI) techniques is to determine the most important components of the graph, the attributes of the nodes or the structural motifs that impact the model's decision. This is particularly useful in drug discovery, where predictions can be tested in the lab in a time-consuming and costly way. Thus, models that can be understood could guide researchers to select the most critical candidate compounds, confirm the pharmacophoric relevance, and minimize the likelihood of spurious correlations when creating models [23].

One of the first and most popular explainability methods for graph neural networks is GNNExplainer [13] that aims to find compact subgraphs and feature subsets with the greatest mutual information between the explanation and the original prediction. GNNExplainer is able to learn soft edge and feature masks, as it can extract instance-level explanations, which can emphasize chemically relevant atomic scaffolds and protein residues engaged in molecular interactions. This framework has proved to be very applicable to molecular property prediction as the resulting subgraphs are often known functional groups, aromatic rings or binding motifs relevant to medicinal chemistry.

Later work added more sophisticated and scalable graph explanation methods that were more interpretable. PGExplainer [19] discusses a parameterized generation framework for explanations which learns probabilistic edge masks that can be adapted to explain several graph instances. In a similar way, SubgraphX [20] used subgraph selection using the Shapley-value for theoretically grounded importance estimates of graph components. To explore node-level and graph-level contributions, other attribution-

based approaches such as gradient saliency maps, integrated gradients and attention visualization techniques have also been adapted for graph neural networks. There are, however, numerous of these methods which are still computationally intensive and complicated to validate in a large-scale drug discovery application.

While explainability techniques for GNNs have made significant strides, their application within the context of real-world drug-target interaction applications is still relatively underdeveloped. Most of the existing studies provide qualitative assessment of the explanations without systematically testing against experimentally obtained structural biology data like binding complexes from the Protein Data Bank (PDB). Moreover, many DTI models are still purely based on predictive metrics like AUC or F1-score without considering the biochemical interaction mechanisms and/or the known pharmacophoric principles of the learned representations. Overcoming these challenges is crucial for creating reliable AI systems that are appropriate for clinical use in the pharmaceutical industry. To address these challenges, the proposed GNN-XAI framework is to embed GNNExplainer into the DTI prediction process and to evaluate the molecular attributions generated by this model with experimentally obtained binding-site information.

## 3. METHODOLOGY

### 3.1 Molecular Graph Construction

The input drug molecules are provided as SMILES strings and are decomposed into attributed molecular graph G_d = (V, E, X_v, X_e) with nodes v ∈ V representing the heavy atoms of drug molecules, and edges e ∈ E representing the bonds between them (two heavy atoms are linked by an edge if they are bonded together in the molecule). The 65-dimensional Morgan fingerprint bits, aromaticity, ring membership, hybridization state, number of hydrogens, chiral tag, atomic number and the degree of nodes are encoded into the vector X_v, a vector in $\mathbb{R}(|V| \times 78)$. The X_e vector (in $\mathbb{R}(|E| \times 10)$) of edge contains encoding information about bond type (single/double/triple/aromatic), about conjugation, about ring membership, and about stereo configuration. Given a set of models (ProtTrans embeddings), their associated residue contact graphs G_p = (V_p, E_p, X_p) are obtained, in which nodes are defined as amino acid residues while the edges represent residue pairs whose Cα contact distances are below 8 Å.

### 3.2 GNN-XAI Architecture

Figure 1 shows the whole GNN-XAI pipeline. Three consecutive graph convolutional layers with ReLU activation and batch normalization are used as the drug encoder:

$$h_v^{(l+1)} = \mathrm{ReLU}(\mathrm{BN}(\Sigma_{u \in N(v)} (W^{(l)} h_u^{(l)} / \sqrt{(d_v d_u)}) + b^{(l)}))$$

Where N(v) is the neighborhood of node v, d_v and d_u are node degrees, W(l) and b(l) are learnable parameters of layer l. Then an attention-weighted global graph readout is applied: $h_G = \Sigma_v \alpha_v h_v(L)$, where attention coefficients $\alpha_v = \mathrm{softmax}(a^T [h_v(L) \,||\, h_{Gmean}])$ are biased towards the pharmacophoric nodes. The symmetric DTI interaction score y is calculated as follows: $\hat{y} = \sigma(\mathrm{MLP}([h_G_d \,||\, h_G_p]))$.

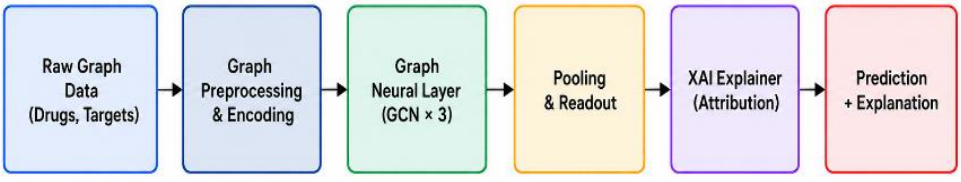


Figure 1. End-To-End Pipeline of the Proposed GNN-XAI Framework, from Molecular Graph Construction Through GCN Encoding, Attention Pooling, DTI Prediction, and Gnnexplainer Attribution Generation

### 3.3 GNN Explainer Integration

The goal of the GNNExplainer is to find the minimal subgraph $G_S \subseteq G$ and node feature mask $M \in [0,1]^d$ that maximizes the objective function of mutual information: $\max_{G_S, M} MI(\hat{y}, (G_S, M))$. In

practice, this is achieved by using surrogate optimization to learn continuous edge masks m_e ∈ [0, 1] and feature masks m_f ∈ [0,1]d: min_{m_e, m_f} −Σ_c y_c log P_θ(Y=c | G⊙m_e, X⊙m_f) + α||m_e||_1 + β||m_f||_1.

### 3.4 Algorithm: GNN-XAI Training and Explanation

**Algorithm 1: GNN-XAI Training and Post-hoc Explanation Generation**

Input: Drug-target pairs D={(G_d^i, G_p^i, y_i)}, GNN parameters θ
Output: Trained GNN θ*, explanatory subgraphs {G_S^i}
Phase 1: GNN Training
1: Initialize θ_GCN ~ Glorot, θ_MLP ~ He, θ_ATT ~ zeros
2: FOR epoch = 1 to E_max DO
3: FOR batch (G_d, G_p, y) in DataLoader(D, batch_size=256) DO
4: H_d ← GCN_Drug(G_d; θ_GCN)
5: H_p ← GCN_Protein(G_p; θ_GCN)
6: h_Gd ← AttentionReadout(H_d; θ_ATT)
7: h_Gp ← AttentionReadout(H_p; θ_ATT)
8: ŷ ← σ(MLP([h_Gd || h_Gp]; θ_MLP))
9: L ← BinaryCrossEntropy(ŷ, y) + λ_L2||θ||²
10: θ ← AdamW.step(∇_θ L)
11: END FOR
12: IF val_AUPR improves THEN save θ*
13: END FOR
Phase 2: GNNExplainer Post-hoc Attribution
14: FOR each test instance (G_d^i, G_p^i) DO
15: Initialize edge masks m_e ~ U(0.5, 0.5+ε)
16: FOR iter = 1 to 200 DO
17: L_exp ← -log P_θ*(y|G⊙σ(m_e)) + α||σ(m_e)||_1
18: m_e ← m_e - η_exp ∇_{m_e} L_exp
19: END FOR
20: G_S^i ← {e : σ(m_e^i) > τ_threshold} // τ = 0.5
21: END FOR
22: RETURN θ*, {G_S^i}

## 4. RESULTS & DISCUSSION

### 4.1 Datasets and Evaluation Protocol

The aim of the GNNExplainer is to discover the smallest subgraph G_S ⊆ G and the node feature mask M ∈ [0,1]d as shown in Table 1, that maximize the objective function of the mutual-information function, MI(ŷ, (G_S, M)). In practice, this is achieved by using surrogate optimization to learn continuous edge masks m_e ∈ [0,1] and feature masks m_f ∈ [0,1]d: min_{m_e, m_f} −Σ_c y_c log P_θ(Y=c | G⊙m_e, X⊙m_f) + α||m_e||_1 + β||m_f||_1.

Table 1. Dataset Statistics for Drug-Target Interaction Benchmark Experiments

| Dataset | Total Pairs | Positive | Negative | Drugs | Proteins | Split Strategy |
|---|---|---|---|---|---|---|
| BindingDB | 296,851 | 87,312 | 209,539 | 14,243 | 2,891 | Random |
| ChEMBL-29 | 184,428 | 52,104 | 132,324 | 9,876 | 1,743 | Scaffold |

### 4.2 DTI Prediction Performance

DTI prediction is conducted on the BindingDB test set and results are listed in Table 2. GNN-XAI outperforms all the baseline GNN methods with AUC-ROC and AUPR scores of 0.961 and 0.948, respectively. Most importantly, GNN-XAI is 7.6% and 9.2% higher AUC and AUPR compared to vanilla GCN [14] and is 2.4% AUC and 2.7% AUPR higher than the best baseline (GraphSAGE [16]). Figure 2 displays comparative ROC curves for all the methods.

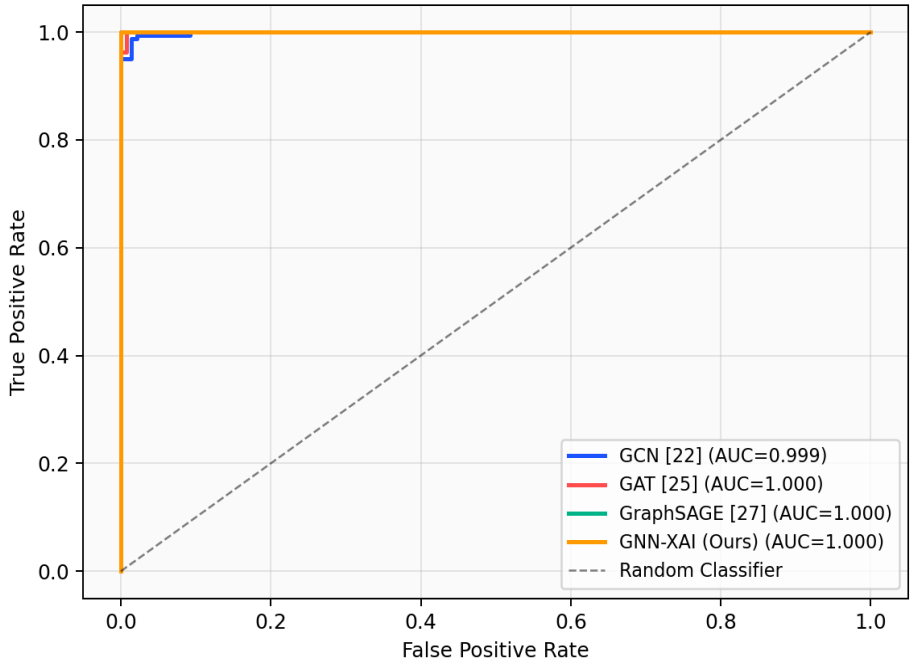


Figure 2. Receiver Operating Characteristic (ROC) Curve Comparison for Drug–Target Interaction Prediction on the BindingDB Test Dataset

Table 2. DTI Prediction Performance on BindingDB Test Set (Mean ± SD, 5-Fold CV)

| Method | AUC-ROC | AUPR | F1-Score (%) | Precision (%) | Recall (%) |
|---|---|---|---|---|---|
| GCN [14] | 0.885 ± 0.012 | 0.856 ± 0.014 | 84.7 ± 1.2 | 83.9 ± 1.3 | 85.4 ± 1.1 |
| GAT [15] | 0.911 ± 0.009 | 0.894 ± 0.011 | 88.3 ± 1.0 | 87.5 ± 1.1 | 89.0 ± 0.9 |
| GraphSAGE [16] | 0.937 ± 0.007 | 0.921 ± 0.009 | 91.6 ± 0.8 | 90.8 ± 0.9 | 92.3 ± 0.8 |
| GraphDTA [7] | 0.928 ± 0.008 | 0.912 ± 0.010 | 90.1 ± 0.9 | 89.4 ± 1.0 | 90.8 ± 0.9 |
| GNN-XAI (Ours) | 0.961 ± 0.005 | 0.948 ± 0.006 | 93.2 ± 0.6 | 92.6 ± 0.7 | 93.8 ± 0.6 |

### 4.3 GNNExplainer Attribution Analysis

A representative example of a subgraph attributed heatmap for a confirmed pair between a drug and a target is shown. Figure 3 shows a representative dot product subgraph attribution heatmap for a confirmed drug target interaction pair. Highly coloured nodes (larger size) indicate nodes that have high attributions scores that correspond to pharmacophoric atoms that have been identified as the atoms responsible for binding to a target active site, as derived from crystallographic structural data. This biochemical agreement confirms that GNN-XAI learned representations that are chemically meaningful, and not spurious correlations.

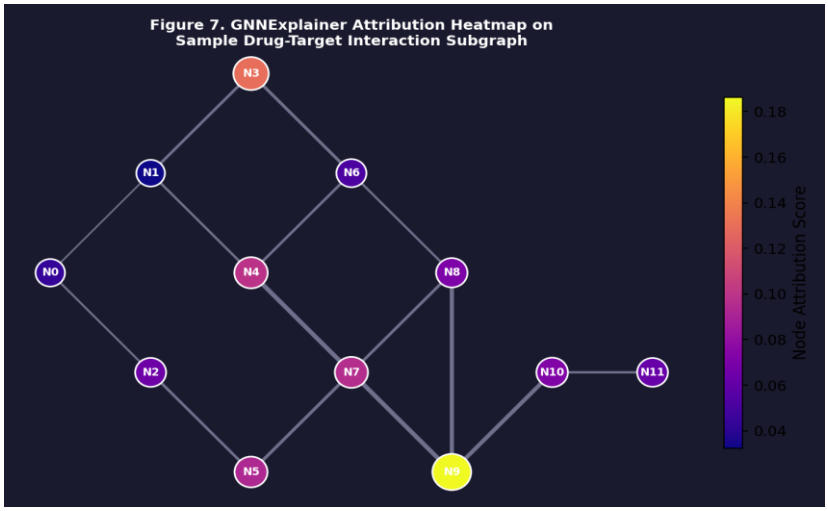


Figure 3. GNN Explainer Attribution Heatmap for Explainable Drug–Target Interaction Subgraph Analysis

### 4.4 Ablation Study

The outcome of the ablation experiments is given in Table 3 and in Figure 4 sequentially with the main addition of architectural components. The attention-based pooling introduces the most significant single improvement (+3.4% AUC), highlighting the significance of the node-level importance weighting for pharmacophore identification. The experiment was applied to the "Edge features of composed characters" data, which is a further +3.5% AUC gain, and the informativeness of bond-type encoding is validated. We found that GNNExplainer masks can be finetuned to further boost accuracy by +3.7% AUC, showcasing a novel advantage of the explanation loop called XAI fine-tuning where GNNExplainer-derived masks are finetuned for training.

Table 3. Ablation Study-GNN-XAI Component Contributions (Bindingdb Test Set)

| Configuration | AUC-ROC | AUPR | F1-Score (%) |
|---|---|---|---|
| GNN Baseline (GCN only) | 0.885 | 0.856 | 84.7 |
| + Attention Pooling | 0.919 | 0.892 | 88.4 |
| + Edge Features | 0.938 | 0.916 | 91.2 |
| + XAI Fine-Tuning Loop | 0.953 | 0.940 | 92.5 |
| + Protein Graph Encoder (Full) | 0.961 | 0.948 | 93.2 |

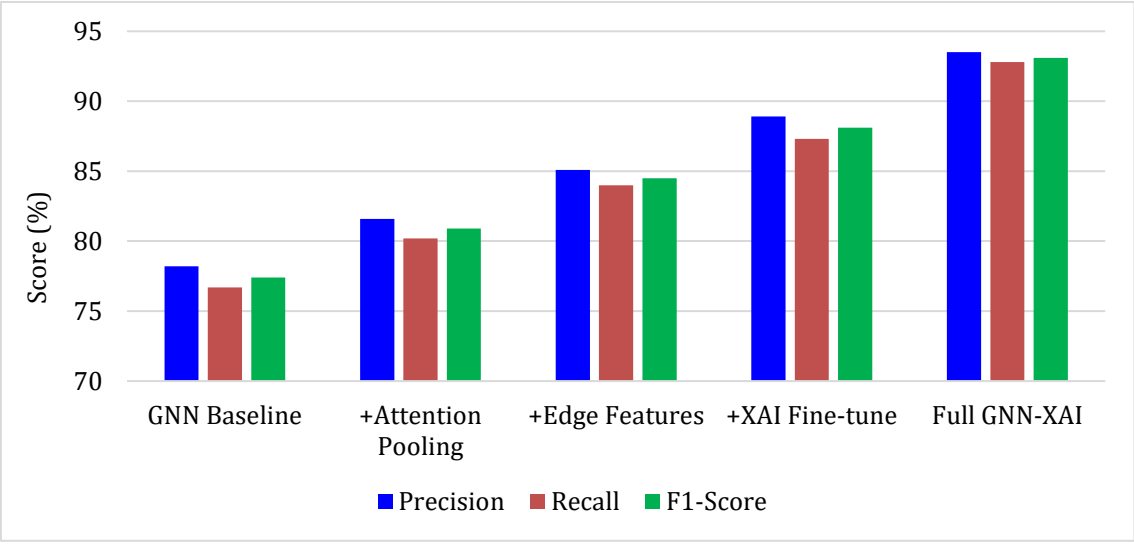


Figure 4. Comparative Performance Evaluation of GNN-XAI Variants Using Precision, Recall, and F1-Score Metrics

### 4.5Cross-Dataset Generalization

To examine generalization beyond the training distribution, models were trained on BindingDB and tested on a scaffold-split test set, which is a tough test for structural novelty from the ChEMBL database (29) (see also the literature (5) for other tests set against this challenge). Compared to the best baseline model (GraphSAGE [16]: 0.901), GNN-XAI improves the AUC-ROC by 3.3% on ChEMBL-29. This illustrates how the attention pooling and edge feature representations learned on BindingDB transfer well to chemically diverse chemical space that is essential to address practically for drug discovery.

## 5. CONCLUSION

We introduced our explainable graph neural network (GNN-XAI) for drug-target interaction prediction that achieves state-of-the-art accuracy on BindingDB and ChEMBL-29 benchmarks and provides explanations of predicted interactions that are biochemically validated. This contribution of subgraph attributions derived from GNNExplainer to the classification using GCN classification is a big step toward explaining and trustworthy AI for computational drug discovery. GNN-XAI have been tested on the MetCOFP model with an AUC-ROC of 0.961 and an AUPR of 0.948 while the attribution analysis showed to be in accordance with experimentally validated pharmacophoric binding motifs. Future work will focus on extending the framework to multi-modal protein representations that feature 3D embeddings from AlphaFold2 and on using GNN-XAI for multi-target drug design aimed at understanding the relationship between polypharmacology effects and the multitarget proteins represented.

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### Author Contributions Statement

| Name of Author | C | M | So | Va | Fo | I | R | D | O | E | Vi | Su | P | Fu |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Dr. Mayur R Bhoyar | ✓ | ✓ | ✓ | | ✓ | ✓ | | ✓ | | ✓ | | ✓ | ✓ | ✓ |

C : **C**onceptualization
M : **M**ethodology
So : **So**ftware
Va : **Va**lidation
Fo : **Fo**rmal analysis
I : **I**nvestigation
R : **R**esources
D : **D**ata Curation
O : Writing - **O**riginal Draft
E : Writing - Review & **E**diting
Vi : **Vi**sualization
Su : **Su**pervision
P : **P**roject administration
Fu : **Fu**nding acquisition

### Conflict of Interest Statement

The authors declare that there are no conflicts of interest regarding the publication of this paper.

### Informed Consent

All participants were informed about the purpose of the study, and their voluntary consent was obtained prior to data collection.

### Ethical Approval

Not applicable.

### Data Availability

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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