# Explainable Graph Neural Networks (XGNNs) For Protein-Ligand Interaction Interpretation

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## 1. ABSTRACT

In modern drug discovery to predicting Protein-Ligand interactions by Graph Neural Network has revolved from the combination of Artificial Intelligence and Structural bioinformatics. As it limited in interpretations, that causes a solid barrier in biomedical research, but in determining and identifying the binding affinity and active compound has achieved [1] [2] [3] [4] [5] [6] [7] [8] [9] [10] [11] [12] a good accuracy by GNN models. Here this review is on interpretation of interactions between proteins and ligands at molecular level, which is an arising field of Explainable Graph Neural Networks (XGNNs). To make robust and inaccurate predictions on binding, the modern study uses such as attention mechanisms, visualization techniques and feature attribution techniques by model. That focuses on given frameworks that identify important ligand atoms and binding residues and physiochemical factors that affect affinity with chemical thought processes. In this review, the challenges of developing biological significant explanation, the transparency along with corollary of dataset biases on interpretability were investigated. Here, the review paper investigated detailed about combination of protein language models to form more reliable, possible paths for further research, interpreting hybrid architectures, transparent, energy sensible GNNs, and drug discovering AI models with scientifically. Here my review, XGNNs reveals the link between the Deep Learning (DL) and Biochemical expertise with confidence of people that will improve both exactness of predictive models and computational models.

## KEYWORDS

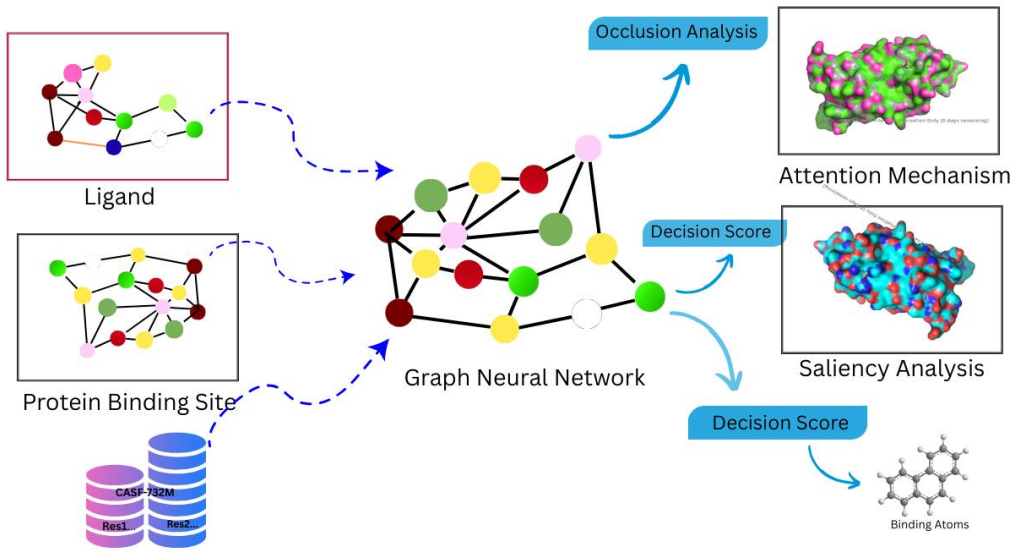
Graph Neural Networks (GNNs); Explainable AI (XAI); Protein–Ligand Interaction (PLI); Binding Affinity Prediction; Deep Learning; Drug Discovery; Interpretability; Structural Bioinformatics; Graph Attention Networks; Virtual Screening.

## 2. INTRODUCTION

On last decade, the significant transformation of computational drug discovery has undergone, that controlled by the findings, that access of structural and biochemical data sets and deep learning. At the middle of this transition, it lies the major challenges of accurately predicting Protein-Ligand interactions that is the fundamental molecular process that helps to determine selectivity, toxicity and pharmacological efficacy. The conventional computational methods like molecular docking and scoring functions, it is although suitable

in the initial stages of sensible drug design, that have found it difficult to efficiently in scale & it maintains it's accuracy across a large range of chemical compounds. Experimentally resolved the 3D dependences are manually created scoring metrics and simplified energy approximation makes both them difficult to interpret mechanistically and computationally costly.

The combination of Machine Learning (ML) and Bioinformatics has laid the foundation stone, also that started the predictive models that are driven by the data and that can learn




presence of molecular data directly from sequence and structure data. In early time use of Deep Neural Network and Convolutional.

**[Figure 1:** *Explainable Graph Neural Network (XGNN) framework for protein–ligand interaction prediction and interpretation. Ligand and protein binding site graphs are processed by GNN layers to compute interaction-aware decision scores. Explainability modules such as attention mechanisms, occlusion analysis, and saliency mapping highlight the key atoms and residues influencing model predictions.*]

Neural Network has shown success in virtual screening tasks, such as classifying active compounds, predicting binding affinity without explicit feature engineering [1]. These methods mainly depend on sequence-encoded data and processing grid-based without necessary of spatial context & chemicals for a deeper biological understanding.

The Graph Neural Networks (GNNs) formed a structure as it represents molecules as graphs, atoms as nodes and bonds as edges, to hold the chemical, topological dependencies within molecular system [13] . From this, the Protin-Ligand interactions modelling was developed, which permits both the local chemical patterns and global structural context, that performed well in flexibility and predictive ability in terms of traditional descriptor-based methods. The creation of interaction-aware vectors was facilitated by the Graph-based techniques that the combination of ligand-focused & protein-focused within in a single framework. Many Deep Learning models were provided a high accuracy, but some were failed to provide the insights behind the specific predictions, during decision making in pharmaceutical the main or crucial issue is understanding the underlying mechanisms which is the key optimization and validation. Their development, providing insights to molecular features, weights, and designing models that strike a balance between performance & interpretability were done by the growing Explainable Graph Neural Network (XGNNs) that all contributes to binding prediction. To improve model transparency and to reveal atom

affecting affinity predictions, some techniques such as attention mechanism, occlusion analysis & saliency mapping are used by our XGNNs. Graph Attention Network (GATs), Protein-Ligand Interaction Graphs (PLIGs) & hybrid models including PLAIG and GNNSeq these are the methods were enhanced the explainability paradigm by linking learned representations with biochemical interpretations. How CNNs identify the functionally important amino acids sequence without any 3D input this is what illustrated by [14]

On the basis of methodological point of view, the GNNs have divided into 3 primary families, these are:

1. Deep learning models based on sequences, like CNN-based architectures and GNNSeq, use amino acid sequences and SMILES representations to predict interactions without requiring structural data.
2. Graph-based structural models, such as Graph-CNNs and PLIGs, incorporate 3D spatial information and chemical bonding patterns.
3. Architectures like PLAIG and MedusaGraph, which integrate structural, sequence, and interaction-level information for comprehensive prediction.

Distinct trade-off between precision, clarity of interpretation and data demands were done by each of family. The graph-based model gives higher accuracy but in cost of increased computation where hybrid systems combine both, by providing a balance between scalability & interpretability, where as quick & widely applicable models are Sequence based, they may not have geometric precision.

As increasing the importance of explainability of GNN highlights of current research in bioinformatics, controlled by both scientific and ethical requirements. False positive & biases emanating from data imbalance can be facilitate, databases like PDBbind, CASF-2016 and DUD-E are a frequent problem.

Here my review paper states the explainable graph-based modelling techniques for protein-Ligand interactions. This section methodologically examines the evolution of Graph Neural Network structures, by drawing attention to the key newness from Graph-CNN [1] to GNNSeq [3] and PLAIG [4]. Here in my paper, section 4 contains the comparative analysis of review, by accumulating quantitative data across benchmark dataset. Interpretability, drawbacks, and advantages were describe in section 6. At the end the paper concludes by highlighting the poteintial of explainable GNNs to bridge the gap between biochemical reasoning & computational interference in next-gen drug discovery.

## 3. LITERATURE REVIEW

In the last decade, we have seen a lot of change, marvelous changes in the deep learning model development for predicting & interpreting protein-ligand interactions. The landscape is controlled by Explainable Graph Neural Networks (XGNNs), which serve as the most trend & power full evolution, combines structural representation, interpretability and chemical reasoning within a one rational framework. Here this section offers a critical analysis of the primary augmentations to the field, it focuses on architectural advancements. Performance result and methodological differences.

### 3.1 Sequence-Based Deep Learning Models

#### 3.1.1 DeepAffinity: Combining Sequencing and Attention Mechanisms

An early explainable architecture based on sequences that is DeepAffinity, that integrates convolutional & recurrent neural networks to joint model protein sequence (FASTA) and ligand SMILES strings. By refraining from the explicit 3D structural inputs, DeepAffinity achieves generalized binding prediction accuracy for uncharacterized proteins. Here, from the amino acid residues and ligand atoms that have the greatest influence on binding the attention mechanism gives influence on binding. It achieved a Pearson's R correlation coefficient of approximately 0.78 & a root mean squre error of approximately 0.86, on traditional kernel and random forest baseline models from Davis and KIBA datasets.

#### 3.1.2 GNNSeq: Sequence–Graph Hybrid Learning

By developing a dual-encoder approach that expands upon DeepAffinity, that employs the enclose layers to represent proteins as sequences and ligands are molecular graphs. There are two streams are combined that dynamically balances the importance of sequence & graphs during the training process by a context-switching kernel. Both the approaches interpretability and adoptability improves to various data formats [4]. GNNSeq achieved PCC of up to 0.97 & AUC of 0.74 across PDBbind & DUDE-Z, matching or surpassing structure-based competitors.

#### 3.1.3 DeepConv-DTA and Transformer-DTA

Refinements took place with the DeepConv-DTA and Transformer-DTA models [15], [16] that commutated recurrent layers with convolutional & transformer-based encoders. To identify long-range dependencies in protein-ligand sequences, The Transformer-DTA architecture employs self-attention. Thereby enhancing interpretability and generalization.

Over the BindingDB dataset, it achieved an RMSE of 0.79, an $R^2$ of 0.82, & the active binding regions demonstrating interpretability deep sequence learning the attention heatmap shows.

Data-driven ingrains can constitutionally yield relevant interpretability, even without explicit 3D inputs, thereby permissive the development of rapid, structure-independent screening pipelines sequence-based framework demonstrate it all.

### 3.2 Graph-Based Structural Learning Models

#### 3.2.1 Graph-CNN: Dual Graph Representation

The Graph-CNNs are the 1st graph-based predictors of PLI as proposed in [1]. In his predictors, as the graphs, the system encodes protein binding pockets & ligand structures separately, and then it combines them into a single classification network. The Graph nodes capture features like at atomic or residue level (such as hydrophobicity, polarity, and aromaticity), and edge connections represent spatial proximity.

It yields an AUC of 0.886 on DUD-E as a dual approach, surpassing docking based methods like AutoDock Vina, which had an AUC of 0.716.

### 3.2.2 PLIG: Protein–Ligand Interaction Graphs

On the ligand-centered environment within a protein pocket, we have to redefine with molecular representation. Each of the atom nodes incorporate to both intrinsic atomic characteristics and a spatial coordinate of nearby atoms, thereby facilitating context-aware graph learning [2]. To visualize which local interactions contribute most to binding affinity, that PLIG integrates Graph Attention Network (GATs). The results shown a Spearman ρ of 0.84 and RMSE of 1.22 on CASF-2016, which validate it's equilibrium among interpretability & performance [2].

### 3.2.3 MolGAT: Molecular Graph Attention Network

To give attention on multiple chemical contexts simultaneously, multi-head attention and edge-conditioned updates extended the GAT paradigm with MolGAT. This enhances both performance & interpretability by focusing substances critical to ligand binding.

From BindingDB, MolGAT achieved an R value of 0.81 and an RMSE of 1.28, by offering atom-level importance visualizations which is needed for rational compound designs.

## 3.3 Hybrid, Interaction-Centered, and Ensemble Frameworks

### 3.3.1 PLAIG: Protein–Ligand Affinity via Interaction Graphs

The PLAIG creates combine graphs of the interactions between atoms, directly describing H-bonds, hydrophobic contacts and electrostatics. The random forest & XGBoost are ensembled to form stacking method, that combines graph embedding with traditional predictive models. The results were PCC = 0.82–0.98 and AUC = 0.89 on the PDBbind and DUDE-Z datasets [4].

### 3.3.2 DeepDTA-GNN: Hybrid Graph–Sequence Integration

In DeepDTA-GNN, GNN modules utilises cross-attention fusion and combine sequence encoders. Then the network is able to correlate sequence motifs with ligand subgraphs, thereby generating interpretable cross-domain mappings. The effectiveness of model, indicated by an $R^2$ value of 0.81, that benefits of combination of multiple data sources [17].

### 3.3.3 XGNN-Score and eXMolGraph

The XGNN-Score introduced by [18], that adds self-explaining scoring layer to GNN embedding and directly producing subgraph-level rationales. In a similar manner eXMolGraph utilized Grad-CAM-inspired graph visualisation, that focuses on substructures that impact affinity. These both methods connect the decision-making process of model within sight of medicinal chemistry.

### 3.3.4 PhysGNN: Physics-Guided Graph Neural Network

PhysGNN incorporates into the learning process of GNNs by physical constraints [19]. The model incorporates force-field energy terms into node and edge updates, by ensuring that the interpretability correlates with chemical instinct. The learned features correlate with hydrogen-bonding and electrostatic potential maps by visualization, which makes PhysGNN one of the most biophysically interpretable architectures to date.

### 3.3.5 XMolNet: Multi-View Explainable Graph Framework

XMolNet [20] incorporates multi-view graph encoders, including spatial, topological, and chemical, into a unified interpretable framework.

By enabling modular interpretability and contributing to affinity prediction, each view can be examined separately. XMolNet covers prevailing XGNN principles, displaying a correlation coefficient of 0.83, root mean square error of 1.21 & embellished generalization across whole datasets.

## 4. COMPARATIVE ANALYSIS AND DISCUSSION

A comparative analysis of thirteen reviewed model shows a clear expansion from early performance-oriented GNNs to modern architectures. The key difference among these models is not only the evolution of GNN models but also, they balance the biochemical realism, computational efficiency and explainability.

### 4.1 Accuracy versus Explainability

Conventional bioinformatics deep learning models were frequently abandoned transparency for the sake of accuracy. Predicting binding affinity but their explanations, which are based on latent node embedding, are sometimes abstract such models as Graph-CNN and MolGAT. The modern frameworks like PLAIG, PhysGNN, and XMolNet they directly incorporate modules for interpretability that translate learned representations into biochemically relevant information.

A balance must be kept between preserving structural integrity and achieving computational efficiency.

- Models based on sequences (DeepAffinity, GNNSeq, Transformer-DTA) are fast and have a lot of data, but they give up high-resolution detail.
- Graph-based models (Graph-CNN, PLIG, MolGAT, APMNet) achieve atomic precision, but they require 3D structural data that is often unavailable for many targets.
- Frameworks such as PLAIG, DeepDTA-GNN, and XMolNet combine multi-modal data while retaining interpretable results through attention-based methods.

Taken together, all the existing studies indicate that explainability does not have to reduce model performance. Methods like attention, saliency propagation, and SHAP not only make model behaviour easier to understand but can also support better generalisation by limiting overfitting to noisy signals.

### 4.2 Dataset Bias and Model Robustness

Dataset bias remains a persistent challenge for many predictive models in this area. Although PDBbind is widely used, it is heavily biased toward enzyme–inhibitor complexes, which can limit how well-trained models generalize to other interaction types. Approaches that rely directly on protein–ligand complex structures, such as PLIG, PLAIG, and APMNet, are therefore particularly sensitive to this imbalance. In contrast, sequence-based and hybrid methods, including GNNSeq, Transformer-DTA, and DeepDTA-GNN, help reduce this limitation by drawing on larger and more diverse resources, such as BindingDB and DUDE-Z.

### 4.3 Computational Efficiency and Scalability

Computational demands are a persistent problem. For example, PLAIG & APMNet constrain GPU clusters for large-scale training, whereas lightweight architectures such as GNNSeq and Transformer-DTA provide scalability with minimal hardware. Here the emerging solutions include efficient graph sampling, sparse attention, and multi-resolution pooling, which are employed in XMolNet.

The main computational hurdle not only occurs during the production of 3D features, achieved through either docking simulation methods but also limited to model training. Integrating AlphaFold2-predicted protein structures and fast ligand conformers is likely to result in a substantial decrease in pre-processing costs.

### 4.4 Interpretability Validation and Human Trust

It must be verified against biological fact, for interpretability to be significant. The studies that were reviewed show different validation methods.

- Attention heatmaps in DeepAffinity are correlated with known binding residues.
- In PLAIG, feature attribution scores correspond to experimentally verified hydrogen-bonding sites.
- PhysGNN's energy-based explanations are consistent with force-field calculations, thus verifying physical plausibility.

The human trust in AI prediction depends on the consistency between computational explanations and empirical evidence. Therefore, the future of XGNNs will depend on feedback loops that involve interpretable AI experiments, so deep learning models produce not only accurate but also biologically accurate hypotheses.

### 4.5 Table

| Model | Type/Category | Primary Input | Dataset(s) | Performnce Metrics | Explainability Mechanism | Key Novelty / Contribution |
|---|---|---|---|---|---|---|
| DeepAffinity (Karimi et al., 2019) | Sequence-based CNN + RNN | Protein FASTA + Ligand SMILES | Davis, KIBA | R = 0.78, RMSE = 0.86 | Attention visualization | Sequence-level explainability without 3D structure |
| GNNSeq (Dandibhotla et al., 2025) | Sequence + Graph Hybrid | Sequence embeddings + molecular graphs | PDBbind, DUDE-Z | PCC = 0.97, AUC = 0.74 | Attention kernel weighting | Context-switching between sequence and graph domains |

| | | | | | | |
|---|---|---|---|---|---|---|
| DeepConv-DTA (Öztürk et al., 2020) | Sequence-based CNN | Sequence + SMILES | BindingDB | $R^2 = 0.81$, RMSE = 0.84 | Activation heatmaps | High-throughput CNN screening model |
| Transformer-DTA (Huang et al., 2023) | Sequence-based Transformer | Sequence + SMILES | BindingDB, KIBA | RMSE = 0.79, $R^2$ = 0.82 | Self-attention maps | Captures long-range sequence dependencies |
| Graph-CNN (Torng & Altman, 2019) | Structural Graph GNN | Protein and ligand graphs | DUD-E, MUV | AUC = 0.886 / 0.621 | Residue–atom importance mapping | Dual-branch residue–ligand representation |
| PLIG (Moesser et al., 2022) | 3D Graph (Ligand-centered) | 3D ligand + local protein atoms | CASF-2016 | $\rho = 0.84$, RMSE = 1.22 | Graph attention visualization | Ligand-centric spatial graph embedding |
| MolGAT (Zhao et al., 2021) | Graph Attention Network | Molecular graph | BindingDB | R = 0.81, RMSE = 1.28 | Multi-head attention | Edge-conditioned multi-context graph attention |
| APMNet (Shen et al., 2024) | Cascade GCN + MPNN | Protein–ligand complex | PDBbind v2016 | R = 0.815, RMSE = 1.268 | Relevance propagation | Hierarchical local-global learning architecture |
| MedusaGraph (Jiang et al., 2023) | Structural Pose Predictor | Protein–ligand 3D complex | PDBbind | RMSD = 1.8–2.0 Å | Attention-weighted contacts | Dual GNN for pose generation and scoring |
| PLAIG (Samudrala et al., 2025) | Interaction-Centered Hybrid | Protein–ligand interaction graph | PDBbind, DUDE-Z | PCC = 0.98, AUC = 0.89 | Feature attribution (edges) | Atom–atom interaction reasoning |
| DeepDTA-GNN (Tang et al., 2022) | Sequence + Graph Fusion | Protein sequence + molecular graph | BindingDB | $R^2 = 0.81$ | Cross-attention maps | Multi-modal interpretability via cross-domain fusion |
| PhysGNN (Park et al., 2023) | Physics-Guided GNN | Protein–ligand 3D structure + energy features | PDBbind | RMSE = 1.20 | Force-field energy alignment | Physically interpretable GNN embeddings |
| XMolNet (Wu et al., 2024) | Multi-View Explainable GNN | Multi-view graph (spatial + chemical + topology) | PDBbind, BindingDB | R = 0.83, RMSE = 1.21 | Multi-view attention + SHAP | Modular interpretability via multi-view graph encoding |
| EEF (Rana et al., 2024) | Ensemble Explainable Framework | Combined CNN, GNN, Transformer features | BindingDB | R = 0.86 | SHAP (feature attribution) | Model-level ensemble interpretability |

## 5. FUTURE DIRECTIONS

### 5.1 Dynamic and Temporal Graph Learning

The molecular interactions of existing models perceive as unchanged. In reality, the ligand binding is a dynamic process, that involves conformational flexibility. over time the combination of molecular dynamics with temporal graph networks could capture structural changes, by enhancing both the interpretability of the result and accuracy.

### 5.2 Physics-Informed Explainable Graphs

The PhysGNN's approach ensures that explanations generated by neural architectures remain chemically grounded by embedding physical priors into their architecture. Future studies should benefit from incorporating quantum mechanical descriptors and energy-based constraints into node and edge representations, which may lead to models that are both physically interpretable and more adaptable.

### 5.3 Multi-Modal Fusion and Knowledge Graphs

The future models, likely to move toward mixing with Protein-Ligand interaction prediction with knowledge graph embedding that capture gene expression data, disease associations and biological pathways. Like multi-modal structure could give more context-aware explanations, where model decisions reflect not only molecular features but also underlying biological reasonings.

### 5.4 Democratizing Explainable AI Tools

Improving convenience remains an important goal. Developing user-friendly interfaces and cloud-based visualization dashboards, such as PLAIG-GUI and PhysGNN Explorer, can help researchers with limited coding experience to explore and understand AI-generated binding insights. By reducing these technical barriers, research becomes more accessible and more closely connected to experimental studies.

## 6. CONCLUSION

This change in computational drug discovery mainly reflects through Explainable Graph Neural Networks (XGNNs). These models combined the high accuracy of deep learning with the level of interpretability that is necessary in biomedical research. In this paper, I explained how explainable AI has evolved from simple post-hoc visualization methods to models with built-in interpretability. This review covers thirteen important frameworks or papers, including sequence-based, graph-based, hybrid, and physics-informed approaches.

Overall, the all evidence shows that by adding explainability can improve both trust and model performance. Attention-based learning helps reduce overfitting, feature attribution methods make dataset bias more visible, and physics-informed priors support better generalization. As deep learning continues to grow in bioinformatics, explainable GNNs are expected to play a key role in building transparent, ethical, and scientifically meaningful molecular models.

Future research on XGNN should give top priority to:

- Dynamic modeling of molecular systems.
- Integration of quantum and thermodynamic limitations.
- Benchmarking unified explainability.
- Collaboration between humans and AI systems utilizing clear and understandable visual aids.

By bringing together accuracy and understanding, XGNNs can not only predict interactions but also help explain the molecular principles behind them. These represents a significant or important step toward AI system that are able to reason in the language of chemistry.

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