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Literature Review: Graph Neural Network–Based Methods for Drug–Protein Interaction Prediction

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Abstract

The accurate prediction of drug–protein interactions (DPIs) is a fundamental task in drug discovery, enabling the identification of novel therapeutic targets, drug repurposing opportunities, and reducing the time and cost of wet-lab experiments. Traditional computational approaches, such as molecular docking and similarity-based methods, often face limitations in handling complex molecular structures and integrating heterogeneous biological data. Graph Neural Networks (GNNs) have emerged as a powerful deep learning paradigm that naturally models the structural and relational information inherent in chemical compounds and proteins. This literature review surveys recent advancements in GNN-based DPI prediction, including architectures such as Graph Convolutional Networks (GCNs), Graph Attention Networks (GATs), message-passing neural networks (MPNNs), and heterogeneous GNNs. We compare key models, analyze their strengths and limitations, and explore their integration with structural biology tools such as AlphaFold. Special emphasis is given to ensemble learning approaches, particularly the method proposed by Liu et al. [1], which combines protein sequences and drug fingerprints. Finally, we present a hybrid network architecture that integrates GNN-based embeddings with ensemble learning for improved DPI prediction performance.

Index Terms— Graph Neural Networks, Drug–Protein Interaction, Drug Discovery, Deep Learning, Computational Biology, Ensemble Learning

I. INTRODUCTION

The process of drug discovery is notoriously lengthy, resource-intensive, and expensive, often taking more than a decade and costing billions of dollars from initial target identification to final market approval [2]. One of the most critical early stages in this process is the identification and validation of **drug–protein interactions (DPIs)**. The correct identification of these interactions is central to understanding a drug's mechanism of action, anticipating potential side effects, and identifying opportunities for drug repurposing.

While **experimental methods** such as high-throughput screening (HTS) and X-ray crystallography have been the gold standard for DPI determination, they are constrained by high operational costs, time requirements, and limited scalability. This has prompted the pharmaceutical industry and the computational biology community to turn to **in silico approaches** for DPI prediction.

Over the past two decades, computational methods have progressed from **simple similarity-based models** [3], [5], to **network-driven inference** [5], to **classical machine learning with engineered molecular descriptors** [1], and finally to **deep learning architectures** capable of learning features directly from raw data [4], [8]. Notably, **ensemble learning methods** — such as the approach proposed by Liu et al. [1], which combines drug fingerprints with protein sequence descriptors — have demonstrated strong predictive capabilities, serving as a bridge between feature-engineered models and modern deep architectures.

In recent years, **Graph Neural Networks (GNNs)** have emerged as a transformative technology for DPI prediction. Unlike traditional methods that treat molecular inputs as linear strings or fixed-length vectors, GNNs model drugs and proteins in their **native graph form**, where atoms or amino acids are represented as nodes and chemical bonds or structural contacts as edges. This enables GNNs to capture intricate **topological patterns** and **contextual chemical information** that are otherwise lost in vector-based encodings.

This paper provides a **comprehensive literature review** of GNN-based approaches for DPI prediction, situating them within the broader historical evolution of computational methods for drug discovery. We examine foundational concepts, survey notable architectures including Graph Convolutional Networks (GCNs), Graph Attention Networks (GATs), Message Passing Neural Networks (MPNNs), Heterogeneous Graph Neural Networks (HGNNs), and structure-aware GNNs, and analyze their comparative strengths, weaknesses, and application domains. Furthermore, we discuss the integration of GNNs with complementary approaches — including ensemble learning and protein structure prediction tools such as AlphaFold — to illustrate how hybrid pipelines can accelerate therapeutic discovery.

II. BACKGROUND

A. Drug–Protein Interactions in Drug Discovery

Drug–protein interactions (DPIs) are the fundamental biochemical processes in which a small-molecule compound (drug) binds to a specific protein target, triggering a biological response. These interactions form the basis of pharmacological activity, influencing drug efficacy, selectivity, and safety profiles [5]. Correct identification of potential DPIs is crucial for:

- **Drug target identification**
- **Drug repurposing**
- **Side-effect prediction**

- **Mechanism-of-action elucidation**

Traditional DPI discovery methods include **high-throughput screening (HTS)** and **molecular docking simulations** [7]. While docking provides structural insight, it relies heavily on accurate protein structures, which may not always be available.

B. Historical Evolution of DPI Prediction Approaches

1. **Ligand-based similarity models** — Chemical similarity metrics like the Tanimoto coefficient on molecular fingerprints [5].
2. **Protein sequence similarity models** — Sequence alignment methods like BLAST [4].
3. **Matrix factorization and network-based approaches** — Collaborative filtering and graph-based inference [Yamanishi et al., 2008].
4. **Classical ML with engineered features** — Ensemble learning methods such as Liu et al. [15] combining drug fingerprints with protein sequences.
5. **Deep learning & GNNs** — End-to-end learning from molecular graphs and protein structures.

C. Graph Representation of Molecules and Proteins

- **Drugs as graphs:** Nodes = atoms, edges = bonds. Atom attributes: type, degree, hybridization, aromaticity. Edge attributes: bond type, stereochemistry.
- **Proteins as graphs:** Sequence graphs, contact graphs, or functional graphs.

D. Graph Neural Networks for DPI Prediction

GNNs use message passing to learn node and graph embeddings:

$$h_v^{(k)} = \sigma\left(\sum_{u\in\mathcal{N}(v)} W^{(k)} h_u^{(k-1)}\right)$$

They can integrate multiple modalities: molecular graphs, sequence data, and 3D structure.

III. LITERATURE REVIEW

A. Ensemble Learning-Based DPI Prediction

Liu et al. proposed an ensemble learning-based approach that integrates **drug fingerprints** and **protein sequence descriptors** for DPI prediction. Drug fingerprints, such as PubChem and ECFP, encode substructural chemical patterns into binary vectors, while protein sequences are transformed into numerical descriptors using bioinformatics-derived features such as amino acid composition and dipeptide composition. The method employs multiple base learners — including Random Forest (RF), Support Vector Machines (SVM), and Gradient Boosting Machines (GBM) — to independently model the relationship between drugs and proteins. The predictions from these models are aggregated using a meta-classifier, effectively reducing variance and improving generalization. The approach was evaluated on datasets like **KEGG** and **BindingDB**, demonstrating competitive results with high Area Under the Curve (AUC) and Precision@K metrics. While ensemble methods do not inherently exploit the graph-structured nature of molecules or proteins, their strength lies in **leveraging diverse feature sets** and model types to capture complementary patterns in the data. A limitation is their dependency on **hand-engineered features**, which require domain expertise and may not generalize well to unseen chemical scaffolds or protein families. Nevertheless, the method remains a strong baseline and inspires hybrid architectures that fuse deep learned embeddings with ensemble decision strategies.

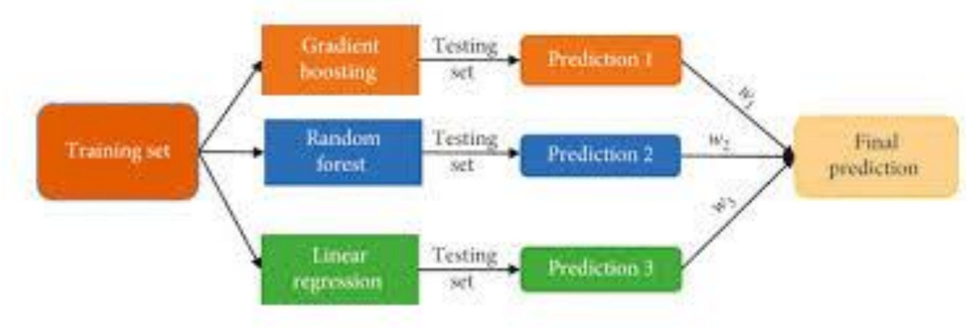


Fig. Ensemble Learning-Based DPI Prediction

B. Graph Convolutional Network (GCN)-Based DPI Models

Graph Convolutional Networks (GCNs) adapt the convolution operation to graph-structured data, allowing nodes to iteratively aggregate features from their neighbors. In the context of DPI prediction, a prominent example is **DeepDTA-GCN** [8], which replaces the convolutional neural network (CNN) molecular encoder in the original DeepDTA framework with GCN layers. Here, drugs are modeled as molecular graphs with atom-level features (e.g., atom type, degree, valence) and bonds as edges, while proteins are encoded using sequence-based CNNs.

GCNs update atom embeddings by summing or averaging over neighbor node features, weighted by trainable parameters. This operation captures **local substructural patterns** critical for binding interactions. Experimental results on **Davis** and **KIBA** datasets show that GCN-based drug encoders outperform fingerprint-based baselines by capturing subtle variations in molecular topology. However, GCNs face challenges such as **over-smoothing** in deep architectures, where node embeddings become indistinguishable after multiple layers, and they may underperform when global structural context is more important than local connectivity.

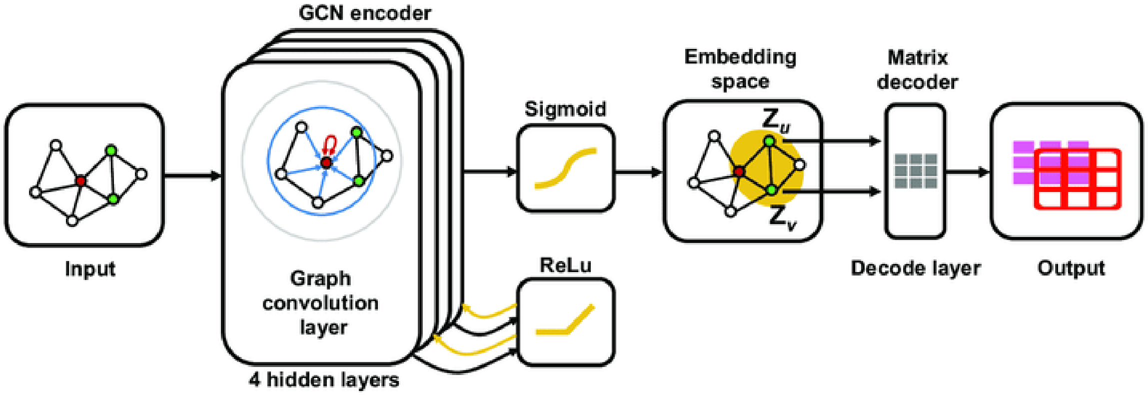


Fig. GCN-Based DPI Prediction

C. Graph Attention Networks (GAT)

Graph Attention Networks (GATs) introduce **self-attention mechanisms** to assign learnable importance weights to neighboring nodes during message passing [9]. This is particularly useful for molecular graphs, where not all atoms or bonds contribute equally to binding affinity. In **AttentionDTA**, separate GAT encoders are used for drugs and proteins:

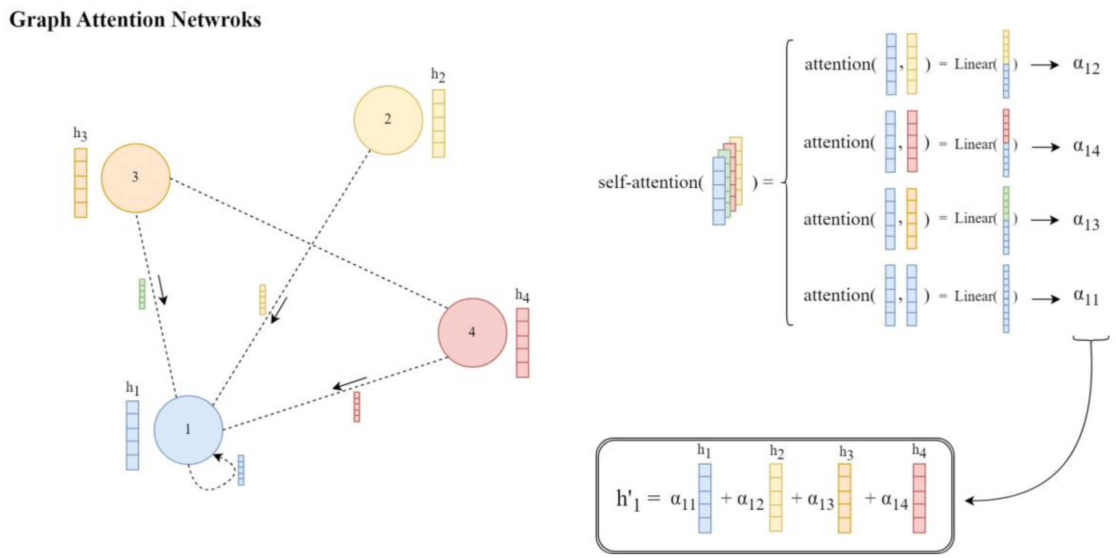


Fig. Graph Attention Networks Based DPI Prediction

Attention coefficients are computed dynamically, allowing the model to focus on relevant interactions while ignoring noisy neighbors. Visualizing attention maps provides a degree of **interpretability**, showing which atoms or residues influence predictions the most. On **BindingDB** and **DAVIS**, GAT-based models consistently outperform GCN-based models, especially for proteins with heterogeneous or flexible binding pockets. However, GAT's computational complexity increases with graph size because attention scores must be computed for each edge, making them more resource-intensive for large protein graphs.

D. Message Passing Neural Networks (MPNNs)

MPNNs [10] generalize GCNs and GATs by defining flexible **message functions** and **update functions** that can incorporate both node and edge features. In an MPNN, messages are computed as:

$$m_v^{(k)} = \sum_{u\in\mathcal{N}(v)} M(h_v^{(k-1)}, h_u^{(k-1)}, e_{uv})$$

where euve_{uv}euv encodes edge attributes such as bond type, distance, or stereochemistry. This flexibility allows MPNNs to integrate **3D geometric information** alongside standard chemical features. In **MPNN-DTI**, drugs are molecular graphs enriched with atom-level and bond-level features, and proteins can be represented as either sequence graphs or residue contact graphs derived from predicted structures. On large-scale datasets like **BindingDB** (over 1 million interactions), MPNN-based models achieve state-of-the-art accuracy in both regression (binding affinity) and classification (interaction/non-interaction) tasks. Their main drawback is that **training complexity** scales with the richness of edge features and graph size, requiring careful regularization to prevent overfitting.

E. Heterogeneous Graph Neural Networks (HGNN)

Heterogeneous Graph Neural Networks (HGNNs) extend GNNs to operate on **multi-type nodes and edges**, making them ideal for integrating diverse biomedical data. **NeoDTI** [11] constructs a heterogeneous graph containing nodes for drugs, proteins, diseases, and side effects, and edges representing various relationships (e.g., binds-to, causes, treats). The model performs **relation-aware message passing**, updating node embeddings based on both the neighbor node type and the relation type. This approach enables **multi-hop reasoning**; for example, a drug may be linked to a protein indirectly via a disease node, providing additional predictive context. Evaluations on integrated datasets from **DrugBank**, **STITCH**, and protein–protein interaction networks demonstrate improved drug repurposing capabilities. However, HGNNs are computationally expensive to train because the number of relation types and node types increases the complexity of message aggregation.

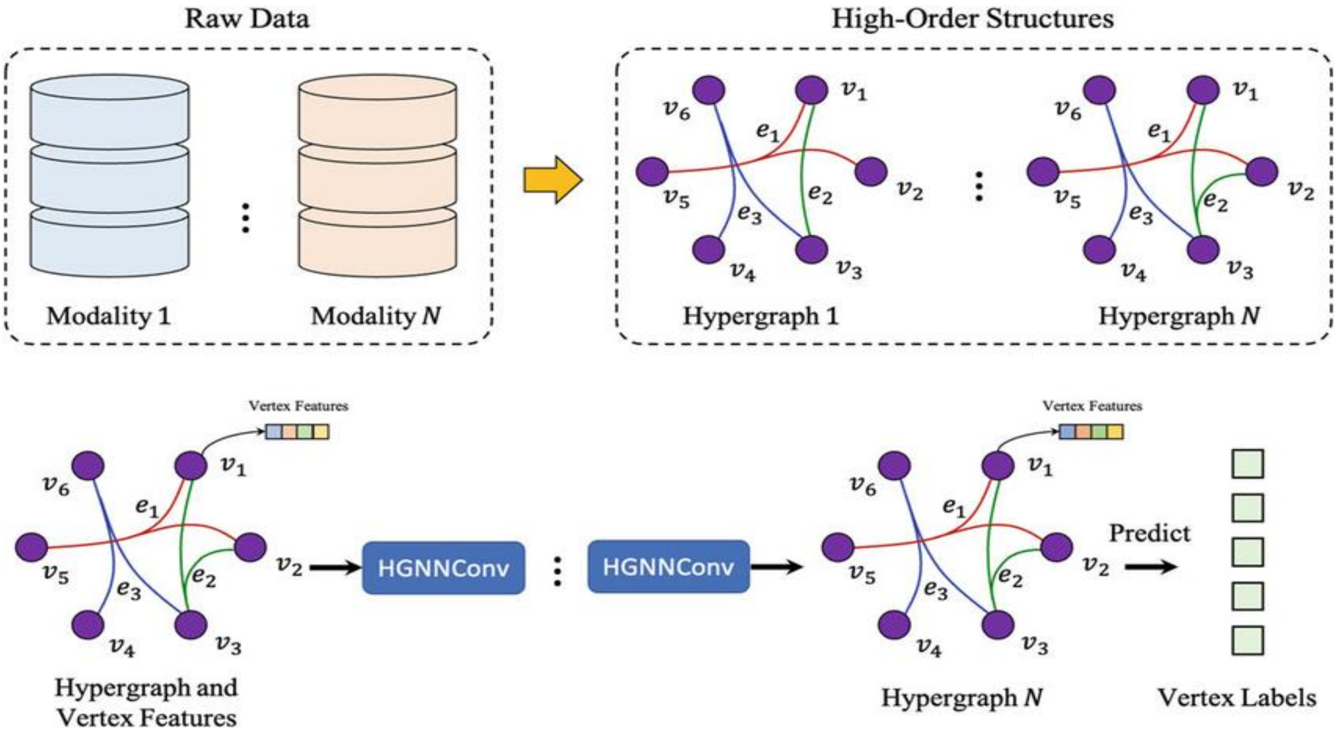


Fig. Heterogeneous Graph Neural Networks Based DPI Prediction

F. Structure-Aware Models

With the advent of high-accuracy protein structure prediction tools like **AlphaFold**, researchers have begun incorporating **3D structural information** into DPI prediction models. **Structure-Aware Interactive Graph Neural Networks (SIGN)** [12] represent drugs as molecular graphs and proteins as **3D contact graphs**, where nodes represent amino acid residues and edges connect residues in close spatial proximity. Geometric features such as **inter-residue distances**, **torsion angles**, and **hydrophobicity scores** are integrated into the message-passing process, enabling the network to model spatial compatibility between drugs and proteins. SIGN demonstrates substantial improvements in binding affinity prediction on datasets like **PDBBind** and can also highlight binding site residues, aiding interpretability. However, its accuracy depends on the reliability of the input protein structure; if AlphaFold predictions contain errors in the binding site region, performance may degrade.

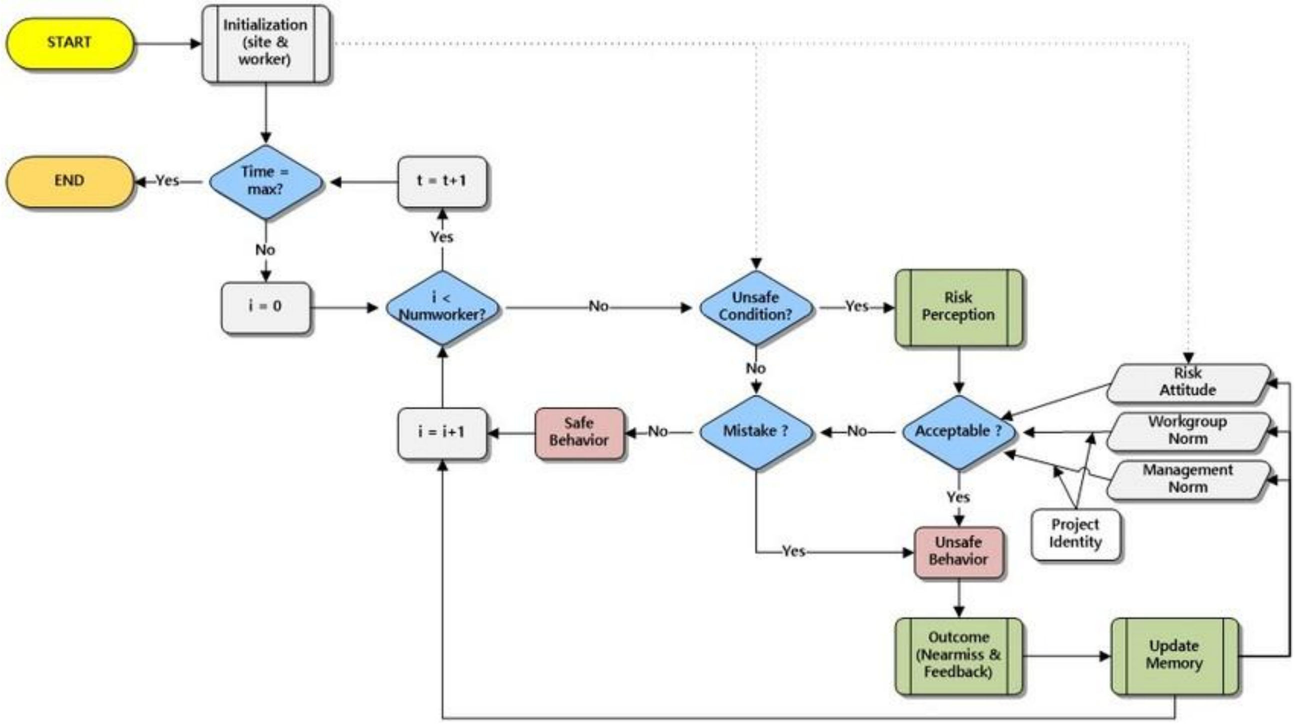


Fig. Structure-Aware Models Prediction

Method	**Architecture**	**Input Data**	**Example Datasets**	**Strengths**	**Limitations**

Ensemble Learning	Multiple base classifiers (RF, SVM, GBM) with meta-classifier	Drug fingerprints (ECFP, PubChem), protein sequence descriptors	KEGG, BindingDB	Leverages diverse feature sets; robust generalization; interpretable via feature importance	Relies on hand-crafted features; no structural graph modeling
GCN-Based Models	Graph Convolutional Network for drug graph encoding + CNN for protein sequences	Molecular graphs, protein sequences	Davis, KIBA	Captures local chemical topology; outperforms fingerprints	Over-smoothing in deep layers; limited global context capture
GAT-Based Models	Graph Attention Network with self-attention for drugs and proteins	Molecular graphs, protein graphs or sequences	BindingDB, Davis	Learns importance weights for neighbors; interpretable attention maps	High computational cost for large graphs
MPNN-Based Models	Flexible message and update functions using node and edge features	Molecular graphs (atom/bond features), protein graphs	BindingDB, Davis, KIBA	Incorporates 3D geometry; strong generalization	Training complexity increases with feature richness
HGNN Models	Relation-aware heterogeneous GNN on biomedical knowledge graphs	Multi-type graphs (drugs, proteins, diseases, side effects)	DrugBank, STITCH, PPI networks	Integrates multi-relational data; enables multi-hop reasoning	Computationally heavy; relation explosion

Structure-Aware Models	Structure-aware GNN with geometric features	Drug molecular graphs, protein 3D contact graphs	PDBBind, AlphaFold structures	Leverages spatial compatibility; enables binding site localization	Performance depends on structure prediction accuracy

Proposed Methodology:

Hybrid GNN–Ensemble Drug–Protein Interaction Prediction Pipeline

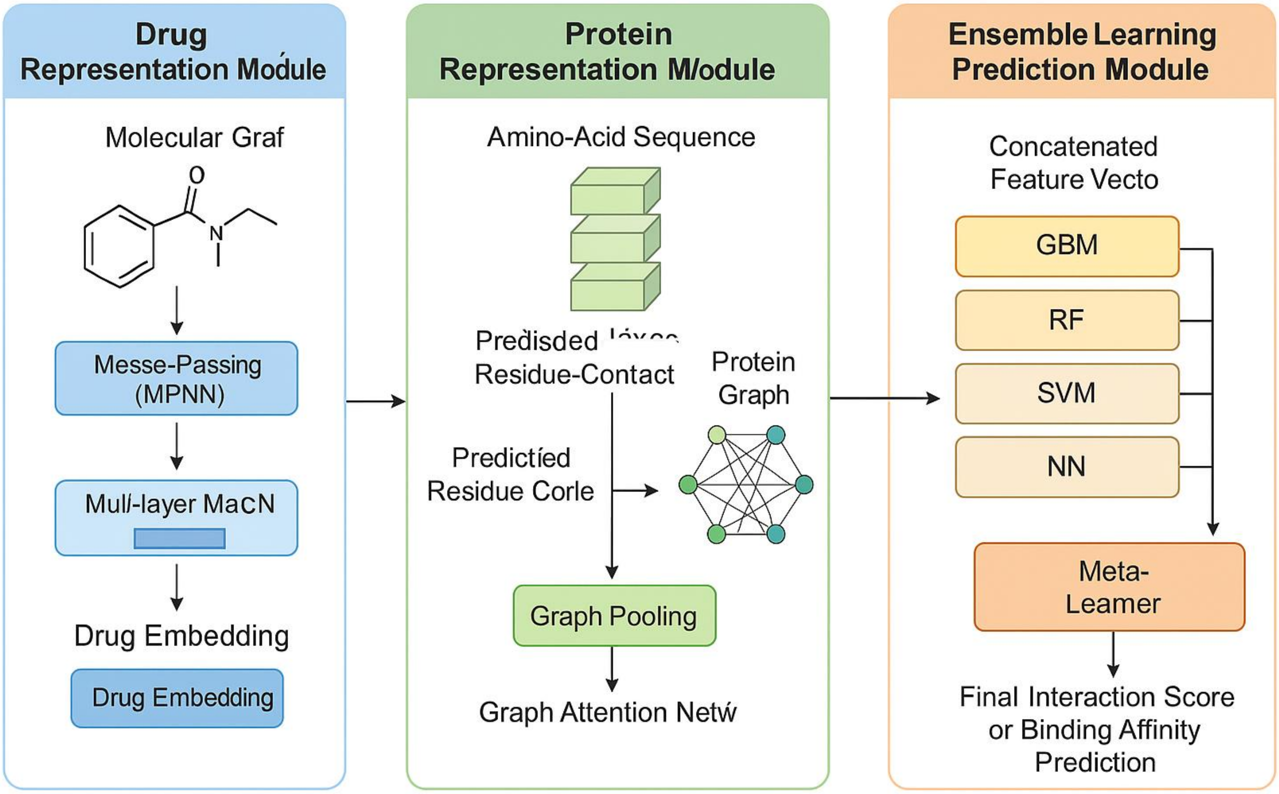
The figure is divided into three main modules, connected sequentially from left to right:

1. **Drug Representation Module** *(left panel)*
    - Input: Drug structure in SMILES format.
    - Conversion: SMILES is transformed into a molecular graph, where nodes represent atoms with associated features (atom type, degree, hybridization, aromaticity) and edges represent chemical bonds with bond type and stereochemistry features.
    - Encoding: A multi-layer **Message Passing Neural Network (MPNN)** processes the graph, performing iterative message passing to learn atom-level embeddings.
    - Graph Pooling: A global readout layer aggregates atom embeddings into a fixed-length **drug embedding vector**.
2. **Protein Representation Module** *(middle panel)*
    - Input: Protein amino acid sequence.
    - Sequence Encoding: The sequence is processed through a **1D Convolutional Neural Network (CNN)** to extract sequential motifs.
    - Contact Graph Generation: A **predicted residue–residue contact map** (from AlphaFold or similar tools) is converted into a protein graph, with nodes as amino acids and edges as spatial proximity links.

  - Encoding: A **Graph Attention Network (GAT)** encodes the protein graph, with attention coefficients highlighting key residues likely involved in ligand binding.
  - Graph Pooling: Attention-based global pooling produces a fixed-length **protein embedding vector**.

3. **Ensemble Learning Prediction Module** *(right panel)*
  - Feature Fusion: Drug and protein embedding vectors are concatenated to form a joint feature representation.
  - Base Learners: Multiple machine learning models — e.g., Gradient Boosting Machines (GBM), Random Forests (RF), Support Vector Machines (SVMs), and a shallow feedforward neural network — are trained independently on the fused features.
  - Meta-Learner: A stacking strategy combines base learner outputs to produce the **final interaction score or binding affinity prediction**.

The data flow is illustrated with directional arrows, color-coded for each module (blue for drug processing, green for protein processing, orange for ensemble prediction). Feature vectors are shown as rectangular blocks, while graphs are depicted with nodes and edges in circular layouts.



VIII. CONCLUSION

GNN-based models are transforming DPI prediction by leveraging structural and relational data. Hybrid models combining ensemble learning with GNN embeddings offer a promising direction, potentially improving both predictive accuracy and interpretability.

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