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TA-PGL: Topology augmentation-based PU-aware graph learning framework for drug-target interaction prediction

Zixuan Ye, Chaolei Wu*

College of Information Engineering, Hubei University of Chinese Medicine, Wuhan 430065, P. R. China

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Abstract:
Drug-target interaction is a crucial task in drug discovery and repositioning. However, existing graph-based methods often suffer from two limitations: The sparsity of known drug-target interaction networks and the false-negative problem, i.e., the unlabeled drug-protein pairs are incorrectly assumed to be non-interacting. To address these challenges, this study proposes a topology augmentation-based PU-aware graph learning framework for drug-target interaction prediction, termed TA-PGL. TA-PGL enhances the conventional drug-target interaction graph with similarity-based edges for drugs and proteins, which can alleviate graph sparsity and make information propagate between functionally related nodes. It also formulates drug-target interaction prediction under a positive-unlabeled setting. Targeted hard negative sampling is combined with a hybrid loss that integrates binary cross-entropy loss and a non-negative PU loss. This design mitigates the false-negative problem. Experiments on DrugBank show that TA-PGL achieves an AUROC of 0.9391 and an AUPRC of 0.9408, outperforming the strongest baseline GeNNius by 0.9% and 1.0%, respectively. TA-PGL also exhibits significantly reduced variance across runs, suggesting better robustness. These results suggest that the joint augmentation of graph topology and unlabeled data is a promising direction for drug-target interaction prediction.

1. Introduction

Drug-target interaction (DTI) prediction is a computational method for identifying potential interactions between therapeutic compounds and biological targets. It is an important strategy for drug discovery and repurposing, accelerating the prioritization of candidate pairs for experimental validation. Therefore, with the rapid accumulation of chemical, biological, and pharmacological data, various machine learning and deep learning approaches have been developed to learn the complex relationships between drugs and protein targets[1, 2].

Recently, graph neural networks (GNNs) have attracted considerable attention in DTI prediction because drugs, proteins, and their interactions can be represented as nodes and edges in graph-structured biological networks. Compared with conventional feature-based approaches, GNNs can propagate information through graph neighborhoods and learn node representations that jointly encode node attributes and relational topology. Several studies have incorporated molecular structure, similarity networks, and heterogeneous biological relationships into graph-based DTI models, demonstrating the effectiveness of topology-aware representation learning for interaction prediction[3–5]. iNGNN-DTI employs a nested graph neural network together with pretrained molecular representations to improve the interpretability and discriminative ability of drug and target embeddings[3]. MIDTI integrates multiple drug and target similarity networks and introduces a deep interactive attention mechanism to model the interaction between learned drug and target representations[4]. These studies indicate that enhancing the graph structure and improving the interaction modeling process are both important for reliable DTI prediction. However, most existing models still face

*Corresponding author.
E-mail address: komorebi0618@stmail.hbucm.edu.cn (Z. Ye); charley5@stmail.hbucm.edu.cn (C. Wu).

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two key challenges: The sparsity of the DTI graph and the false-negative problem caused by treating unlabeled pairs as negatives.

To address these challenges, this study proposes a topology augmentation-based PU-aware graph learning framework for drug-target interaction prediction (TA-PGL). We enhance the DTI graph with drug-drug and protein-protein similarity-based edges, where drug similarities are computed from Morgan fingerprints and protein similarities from amino acid composition vectors. This augmentation solves graph sparsity and provides richer topological context for message passing. In addition, we conducted DTI prediction under the positive-unlabeled setting, in which unlabeled pairs are not treated as definite negatives. To reduce false negatives, we design a PU-aware hard negative sampling strategy that combines "same-drug-different-protein" and "same-protein-different-drug" negatives with a portion of random negatives. Finally, we train the model with a hybrid loss that combines binary cross-entropy (BCE) loss with a non-negative PU (nnPU) loss.

Overall, the contributions of the TA-PGL are summarized as follows:

1) We propose a topology augmentation strategy that augments the DTI graph by constructing a heterogeneous graph with drug-protein, reverse drug-protein, drug-drug similarity-based edges, and protein-protein similarity-based edges. This augmentation provides a richer topological context for message passing.
2) We design a PU-aware graph learning framework to address the false-negative problem in DTI prediction, where unlabeled pairs are often incorrectly treated as negatives. By combining hard negative sampling with BCE loss and nnPU loss, the model learns more robustly from labeled positives and unlabeled data.

The subsequent sections are organized as follows: Section 2 provides related work on DTI prediction. Section 3 gives the methods and architecture of the TA-PGL model. Section 4 describes the experimental design, dataset, ablation studies, parameter-sensitive tests, comparative experiments, and result analyses. Section 5 presents the conclusions and future work.

2. Related work

This section presents graph neural networks for DTI prediction, multimodal and attention-based DTI prediction, and positive-unlabeled learning and negative sampling.

2.1 Graph neural networks for DTI prediction

Graph neural networks (GNNs) are widely used for DTI prediction, where drugs and proteins are represented as nodes and known interactions as edges. They usually learn node representations that encode both feature and topological information. TAGIN-DTI shifts the prediction paradigm from a conventional node-level view to a subnetwork-level perspective, aggregating topological association features from drug-drug and protein-protein interaction networks via a dual-path Transformer encoder[6]. MAGNETIC models DTI as a multilayer attributed heterogeneous graph and trains separate adaptive graph diffusion networks per layer to preserve layer-specific topology, incorporating meta-path-derived similarity relations[7]. DCHG-DTI extracts local features from one-dimensional sequences and two-dimensional graphs of drugs and proteins while incorporating disease and side-effect information to construct heterogeneous graphs[8]. However, these methods primarily focus on architectural innovation and do not address the sparsity of the DTI graph through systematic topology augmentation.

2.2 Multimodal and attention-based DTI prediction

Recent advances have explored multimodal and attention-based approaches to enrich molecular representations and capture cross-modal interactions. LDM-DTI integrates pretrained language models with a three-layer graph convolutional network and an equivariant GNN to capture two-dimensional topological and three-dimensional geometric characteristics, fused via a dynamic interactive attention module[9]. MMF-DTI employs pretrained large language models to extract generalized representations and proposes a cross-modal attention module that facilitates interaction between sequence-based and structural features[10]. HADLGL-DTI introduces a hierarchical attention-driven multimodal fusion module that uses self-attention to fuse inter-modal features and dynamically learns modality-specific weights for local-to-global feature integration[11]. DBCA-DTI employs a dual-branch collaborative multimodal fusion framework with bidirectional adaptive gated cross-attention, combining large language model-enhanced semantic features with physicochemical property features[12]. MMTF-DTI designs a dual-path encoder with Transformers and GNNs, incorporating a dynamic multimodal fusion module with learnable attention weights and a domain adversarial neural network for cross-domain generalization[13]. Despite their strong predictive performance, these methods often require large pretrained models and extensive computational resources, and they rarely address the false-negative problem inherent in DTI data.

2.3 Positive-unlabeled learning and negative sampling

In DTI prediction, unlabeled drug-protein pairs are often incorrectly treated as negatives. This false-negative problem has attracted increasing attention. MKPUL-BLM combines multi-kernel and positive-unlabeled learning approaches to manage the lack of confirmed negative samples, using a positive-unlabeled learning approach to produce potential negative samples[14]. GRL-PUL screens reliable negative samples by applying weighted matrix factorization and the PU-bagging strategy on the microbe-drug bipartite network, then combines multi-model attributes with a graph attention autoencoder[15]. In the knowledge graph domain, ConDNS proposes a conditional diffusion-based negative sampling method that achieves dynamic difficulty modulation of synthetic negatives through global entity-relation information utilization[16]. However, these methods typically operate on bipartite or homogeneous networks and do not integrate topology augmentation with PU-

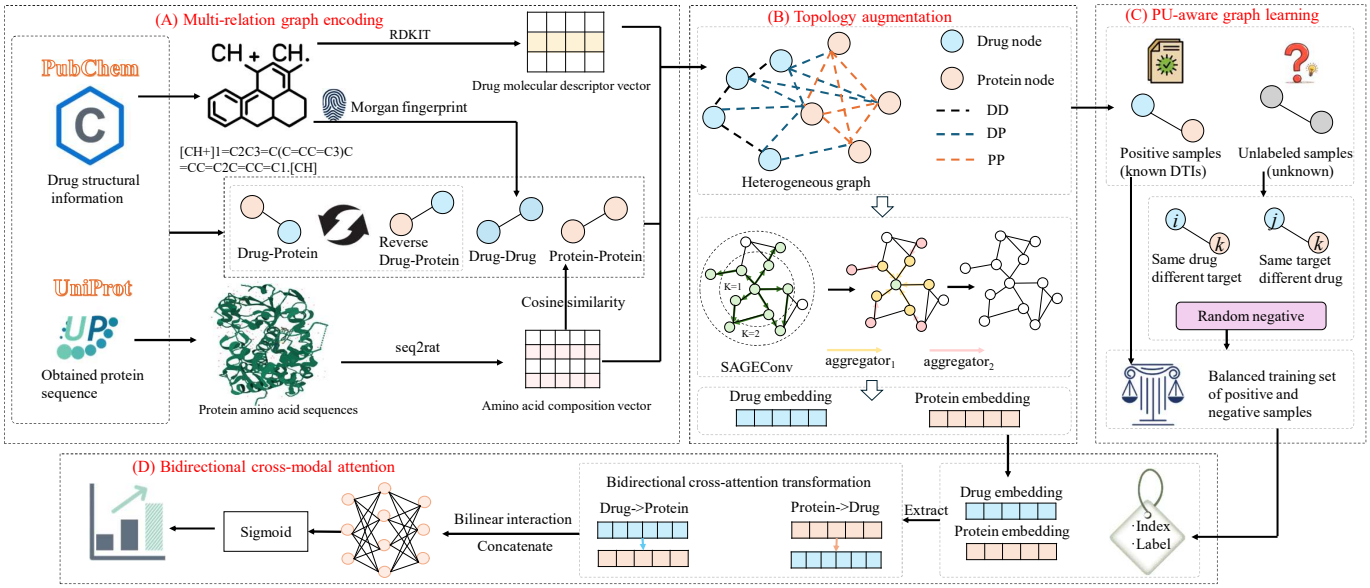

Fig. 1. The architecture of TA-PGL.

learning in a unified heterogeneous graph framework.

To summarize, current GNN-based methods are mostly concerned with architectural design and seldom enrich the graph topology to alleviate the sparsity. Multimodal and attention-based approaches enrich representations but often depend on large pre-trained models and rarely deal with false negatives. PU learning approaches allow false negatives, but they are generally bipartite or homogeneous graph-based. None of them simultaneously tackle the graph sparsity and false negatives in a unified heterogeneous graph framework, which is our proposed TA-PGL.

3. Methodology

This study proposes TA-PGL, a topology augmentation-based PU-aware graph learning framework for drug-protein interaction prediction. In TA-PGL, the DTI network is modeled as a heterogeneous graph with nodes of drugs and proteins and edges of multiple associations, including Drug-Protein (DP), reverse Drug-Protein (rev-DP), Drug-Drug (DD), and Protein-Protein (PP) relationships. The model enhances the original sparse drug-protein graph through similarity-based topology augmentation and learns robust node representations via a relation-aware heterogeneous graph encoder. A PU-aware learning strategy with hard negative sampling and hybrid loss is proposed to solve the false-negative problem in unlabeled data. As shown in Fig. 1, the model comprises four main modules: (A) Multi-relation graph encoding, (B) topology augmentation, (C) PU-aware graph learning, and (D) bidirectional cross-modal attention.

3.1 Multi-relation graph encoding

3.1.1 Drug representation

For each drug d, we retrieve its structural information from PubChem and take the SMILES string s_d as the entry. The topological and physicochemical descriptors are computed with RDKit and concatenated into a descriptor vector, denoted as $\mathbf{f}_d^{\text{RDKit}}$. This vector serves as the initial feature $\mathbf{x}_d$ of the drug node d:

$$\mathbf{x}_d = \mathbf{f}_d^{\text{RDKit}} \in \mathbb{R}^{d_1} \tag{1}$$

where d_1 is the descriptor vector dimension. The SMILES string is also used to generate a Morgan fingerprint, which is used for constructing DD similarity edges.

3.1.2 Protein representation

For each protein p, we obtain its amino-acid sequence from UniProt and encode it with seq2rat. The seq2rat converts the sequence into an amino-acid composition vector by computing the frequency of each amino-acid type in the sequence:

$$\mathbf{t}_p = \left[\frac{n_1}{L}, \frac{n_k}{L}, \ldots, \frac{n_{d_p}}{L}\right]^\top \tag{2}$$

where L is the sequence length, d_p is the number of standard amoni-acid types, and n_k is the number of occurrences of the k-th amoni-acid type. The resulting vector $\mathbf{t}_p \in \mathbb{R}^{d_p}$ is a compact and length-invariant description of the protein, which allows proteins of different sequence lengths to be compared in a common space.

3.1.3 Heterogeneous graph construction

We construct a heterogeneous graph $G = \{V, E, R\}$, where the node set V consists of nodes V_d and protein nodes V_p, and the edge set E is partitioned into four relation types $R = \{\text{DP}, \text{rev-DP}, \text{DD}, \text{PP}\}$. The relation DP contains directed edges from drugs to proteins, derived from DP interactions. We present the relation rev-DP, which contains the corresponding directed edges from proteins to drugs. The E_{DP} and E_{rev-DP} edges are both directed edges. The relation DD connects drugs with similar molecular representations. For each drug i, j $(i \neq j)$, we select its k_d nearest neighbors based on cosine similarity of Morgan fingerprints, subject to a similarity

threshold τ_d:

$$E_{\mathrm{DD}} = \{(i,\ j) | j \in \text{top-}k_d(i),\ \cos(\mathbf{f}_i^{\mathrm{Morgan}},\ \mathbf{f}_j^{\mathrm{Morgan}}) \geq \tau_d\} \quad (3)$$

where $\mathbf{f}_i^{\mathrm{Morgan}}$ and $\mathbf{f}_j^{\mathrm{Morgan}}$ are the Morgan fingerprints of drug i and j, $\cos(\cdot)$ is the cosine similarity, and top-k_d is the number of nearest neighbors retained for each drug. PP edges E_{PP} are defined on the amino-acid composition vectors:

$$E_{\mathrm{PP}} = \{(i,\ j) | j \in \text{top-}k_p(i), \cos(\mathbf{t}_i,\ \mathbf{t}_j) \geq \tau_p\} \quad (4)$$

where $\mathbf{t}_i$ and $\mathbf{t}_j$ are the amino-acid composition vector of proteins i and j, top-k_p is the number of nearest neighbors retained for each protein.

3.2 Topology augmentation

The heterogeneous graph is reconstructed by adding similarity-based edges. Then, the augmented graph is encoded by a stack of SAGE convolutional layers. For each node v with a feature vector $\mathbf{h}_v^{(l)}$ at layer l, the first layer aggregates the features of its neighbors under each relation and then fuses the aggregated message with the node's own representation:

$$h_{N(v)}^{(l)} = \sum_{r \in R} \sum_{u \in N_r(v)} W_r^{(l)} h_u^{(l)} \quad (5)$$

$$\tilde{\mathbf{h}}_v^{(l+1)} = \mathbf{h}_v^{(l)} + \mathbf{h}_{N(v)}^{(l)} \quad (6)$$

$$\mathbf{h}_v^{(l+1)} = \mathrm{Dropout}\Big(\mathrm{Tanh}\big(\mathrm{LayerNorm}\big(\tilde{\mathbf{h}}_v^{(l+1)}\big)\big)\Big) \quad (7)$$

where $N_r(v)$ is the set of neighbors of v connected via relation r, and $W_r^{(l)}$ are relation-specific trainable parameters. The intermediate representation after the residual connection is denoted as $\tilde{\mathbf{h}}_v^{(l+1)}$, where the residual connection is applied when the input and output dimensions match. The final layer generates the drug embedding $\mathbf{h}_d \in \mathbb{R}^d$ and the protein embedding $\mathbf{h}_p \in \mathbb{R}^d$, where d is the hidden dimension.

3.3 PU-aware graph learning

From the constructed heterogeneous graph, we define the positive set as the known drug-protein interactions and the unlabeled set as all remaining drug-protein pairs, following a positive-unlabeled (PU) assumption. The positive set is defined as P, and the remaining drug-protein pairs form the unlabeled set U. Our model uses three negative sampling strategies: The first one is random negatives N_{rand}, extracted uniformly from U. The second one is "same-drug-different-target" negatives N_{sd}, for each positive pair (d, p), we pair the same drug d with a different protein p' $(p' \neq p)$. The third one is "same-target-different-drug" negatives N_{st}. For each positive pair (d, p), we pair the same protein p with a different drug d' $(d' \neq d)$. These three subsets are combined into an integrated negative set:

$$N = N_{rand} \cup N_{sd} \cup N_{st} \quad (8)$$

it also balances against P to form set S used for training:

$$S = P \cup N \quad (9)$$

each pair in S haves an index label $y \in \{0, 1\}$, where $y = 0$ represents a sampled negative and $y = 1$ denotes a known positive interaction.

3.4 Bidirectional cross-attention interaction

The graph encoder generates the drug embedding $\mathbf{h}_d$ and the protein embedding $\mathbf{h}_p$. These two embeddings are fed into the interaction module, which computes the probability that the drug-protein pair interacts. The drug and protein embeddings are projected into query, key, and value spaces with $\mathbf{W}_Q, \mathbf{W}_K, \mathbf{W}_V$, respectively. The drug-to-protein attention is computed as:

$$g_{d \to p} = \sigma\left(\frac{(\mathbf{h}_d \mathbf{W}_Q)(\mathbf{h}_p \mathbf{W}_K)^\top}{\sqrt{d}}\right) \quad (10)$$

$$\mathbf{C}_{d \to p} = g_{d \to p} \cdot (\mathbf{h}_p \mathbf{W}_V) \quad (11)$$

and the protein-to-drug direction is defined as:

$$g_{p \to d} = \sigma\left(\frac{(\mathbf{h}_p \mathbf{W}_Q)(\mathbf{h}_d \mathbf{W}_K)^\top}{\sqrt{d}}\right) \quad (12)$$

$$\mathbf{C}_{p \to d} = g_{p \to d} \cdot (\mathbf{h}_d \mathbf{W}_V) \quad (13)$$

where $g_{d \to p}$ and $g_{p \to d}$ are the scalar attention weights for the drug-to-protein and protein-to-drug directions,respectively. And $\mathbf{C}_{d \to p}$ and $\mathbf{C}_{p \to d}$ denote the corresponding context representations. $\sigma(\cdot)$ is the sigmoid function. The two directional representations are concatenated with the original embeddings:

$$\mathbf{c} = \left[\mathbf{C}_{d \to p} \,\|\, \mathbf{C}_{p \to d} \,\|\, \mathbf{h}_d \,\|\, \mathbf{h}_p\right] \quad (14)$$

a bilinear interaction term is computed by:

$$z = \mathbf{h}_d^\top \mathbf{W}_b \mathbf{h}_p \quad (15)$$

where $\mathbf{W}_b$ is a learnable interaction matrix. The bilinear term captures the interactions between the drug and protein embeddings, while the concatenated representation $\mathbf{c}$ preserves additive information. The concatenated representation $\mathbf{c}$ and bilinear interaction term z are fused and passed to a multilayer perceptron:

$$\hat{y} = \sigma(\mathrm{MLP}([\mathbf{c} \,\|\, z])), \hat{y} \in [0, 1] \quad (16)$$

where $\hat{y}$ is the predicted probability that the candidate drug-protein pair interacts. The BCE loss is defined as:

$$L_{BCE} = -\frac{1}{|S|} \sum_{(d,p) \in S} \left[y_{dp} \log \hat{y}_{dp} + (1 - y_{dp}) \log(1 - \hat{y}_{dp})\right] \quad (17)$$

and the nnPU loss is defined as:

$$L_{nnPU} = \pi R_P^+ + \max(0, R_U^- - \pi R_P^-) \quad (18)$$

where π is the prior; R_P^+, R_U^-, and R_P^- are the empirical risks of positive, unlabeled, and negative samples, respectively. The model is trained on the set S with a hybrid loss L that consists of BCE loss and nnPU loss:

$$L = \alpha L_{BCE} + (1 - \alpha) L_{nnPU} + \lambda \|\Theta\|_2^2 \quad (19)$$

where Θ denotes all trainable parameters, and λ controls the strength of L_2 regularization.

4. Experiments

We compared TA-PGL with three models on the DrugBank dataset. Evaluation metrics include area under the receiver ope-

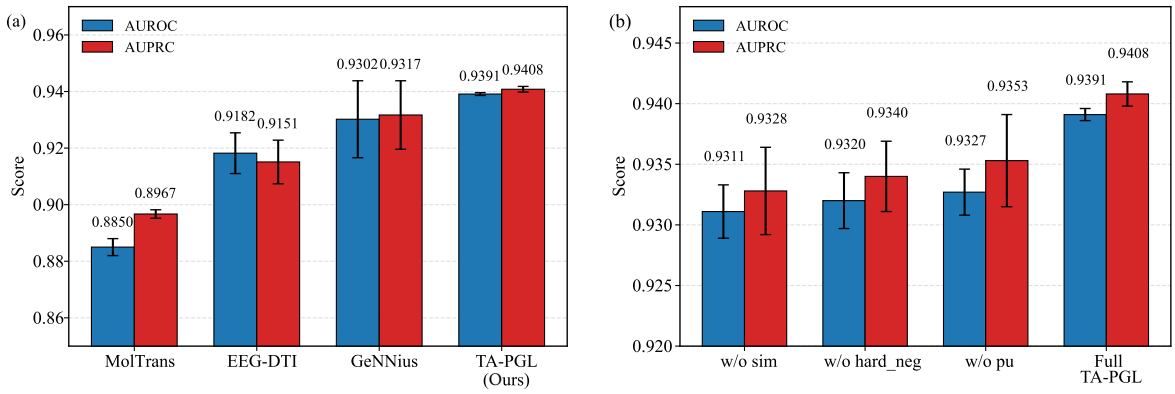

Fig. 2. The results of comparison experiments and ablation results of the TA-PGL. (a) Comparison experiment results, and (b) ablation results

Table 1. Hyperparameter settings.

Hyperparameter	Value	Hyperparameter	Value
Hidden dimension	17	Morgan fingerprint radius	2
Morgan fingerprint bits	1,024	Drug top-k	3
Drug similarity threshold	0.5	Protein top-k	3
Drug similarity threshold	0.5	Hard negative ratio	0.3
Hybrid loss weight	0.8	nnPU prior	0.5
Dropout	0.2	Learning rate	0.01
Weight decay	1e-4	Batch size	32
Early stopping patience	15	Minimum improvement	1e-4

rating characteristic curve (AUROC) and area under the precision-recall curve (AUPRC). Ablation studies were conducted to assess the contribution of each component, and parameter sensitivity tests were performed to evaluate the impact of key hyperparameters. The details of the hyperparameters are summarized in Table 1. All experiments were conducted on a system with 16.0 GB of RAM and a 3.60 GHz Intel Core i7-9700K CPU.

4.1 Datasets

We evaluated the TA-PGL and baselines on DrugBank, a representative public dataset. The dataset contains 6,489 drugs, 4,520 proteins, and 22,807 known drug-protein interactions. Following the standard protocol, we randomly split the interactions into 70% for training, 10% for validation, and 20% for test. For each positive pair, we sample an equal number of negative pairs to maintain a $1:1$ positive-to-negative ratio.

4.2 Baselines

We compared the proposed model TA-PGL with three representative models in DTI prediction, which are described as follows:

- GeNNius represents the DTI network as a drug-protein bipartite graph and employs SAGEConv layers to generate node embeddings. Drug and protein features are extracted from molecular descriptors and amino acid composition, respectively. The drug and protein embeddings are concatenated and fed into a multilayer perceptron classifier to predict interaction probabilities[1].
- MolTrans obtains substructure embeddings from drug SMILES and protein sequences through byte pair encoding and a Transformer encoder. It then uses a convolutional neural network to calculate and optimize the pairwise interactions between drug and target substructures, and finally predicts the interaction probability through a fully connected layer[17].
- EEG-DTI constructs an end-to-end heterogeneous graph with multiple node types and multiple edge types. It employs three graph convolutional network layers to generate low-dimensional embeddings for drugs and proteins, concatenates the embeddings from different layers, and computes the inner product to obtain the protein-drug interaction score for DTI prediction[18].

4.3 Experimental results and analyses

In this section, we conducted a series of experiments, including comparison experiments, ablation studies, and parameter-sensitive tests to evaluate the effectiveness of the proposed TA-PGL.

4.3.1 Comparison experiments

As shown in Fig. 2(a) and Table 2, TA-PGL achieves the best performance with an AUROC of 0.9391 ± 0.0005 and an AUPRC of 0.9408 ± 0.0010, outperforming all baselines. Specifically, compared to GeNNius, TA-PGL improves AUROC by 0.9% and AUPRC by 1.0%. EEG-DTI and MolTrans obtain lower scores, respectively. Notably, TA-PGL also exhibits the smallest standard deviation across runs, indicating superior robustness and stability.

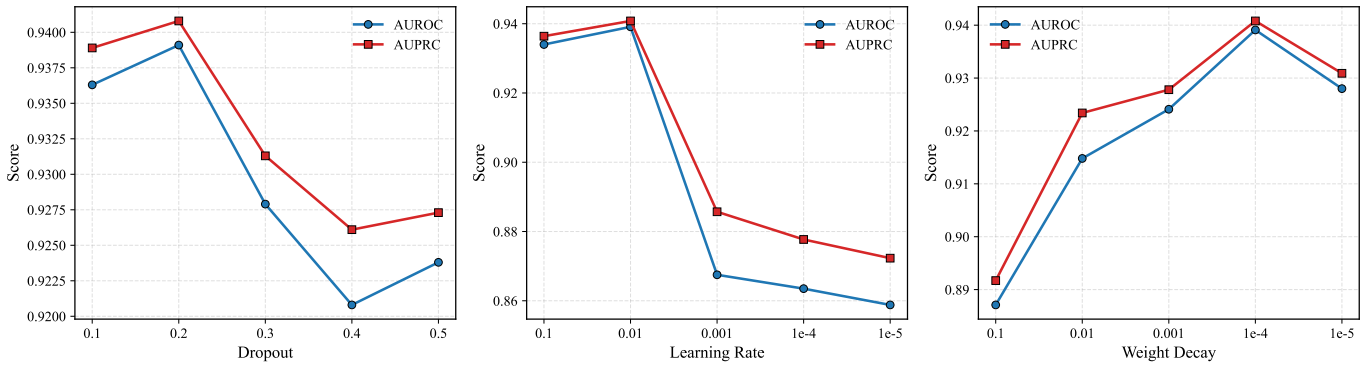

Fig. 3. The parameter sensitivity test results.

Table 2. The results of comparison experiments.

Model	AUROC	AUPRC
TA-PGL (Ours)	$\mathbf{0.9391 \pm 0.0005}$	$\mathbf{0.9408 \pm 0.0010}$
GeNNius	0.9302 ± 0.0136	0.9317 ± 0.0121
EEG-DTI	0.9182 ± 0.0072	0.9151 ± 0.0077
MolTrans	0.8850 ± 0.0030	0.8967 ± 0.0015

Table 3. The results of the ablation study.

Model variant	AUROC	AUPRC
w/o sim	0.9311 ± 0.0022	0.9328 ± 0.0036
w/o hard_neg	0.9320 ± 0.0023	0.9340 ± 0.0029
w/o nnPU	0.9327 ± 0.0019	0.9353 ± 0.0038
Full TA-PGL	$\mathbf{0.9391 \pm 0.0005}$	$\mathbf{0.9408 \pm 0.0010}$

4.3.2 Ablation study

To verify the contribution of each component in TA-PGL, we conduct ablation experiments by removing similarity-based topology augmentation, PU-aware hard negative sampling, and the nnPU loss. As shown in Fig. 2(b) and Table 3, the full model outperforms all ablated variants. Removing similarity edges leads to the largest drop. The score of AUROC decreases by 0.80%, confirming that topology augmentation is the most critical component. Removing hard negative sampling or the nnPU loss also results in noticeable degradation, demonstrating that both components contribute to mitigating the false-negative issue. These results validate the effectiveness of each proposed module.

4.3.3 Parameter sensitivity test

As shown in Fig. 3, we further analyze the sensitivity of TA-PGL to three key hyperparameters: Dropout rate, learning rate, and weight decay.

A larger dropout or a smaller learning rate causes significant performance degradation, while larger weight decay also makes the results worse. These findings indicate that TA-PGL is relatively robust within a reasonable range but requires appropriate regularization to avoid underfitting or overfitting.

Overall, the experimental results demonstrate that TA-PGL consistently outperforms baselines on the DrugBank dataset. The ablation study confirms that similarity-based topology augmentation is the most impactful component, followed by PU-aware hard negative sampling and the nnPU loss. The parameter sensitivity test results show that the default hyperparameters are near-optimal and that the model is stable across a reasonable range. These results validate the effectiveness of jointly addressing graph sparsity and false negatives in DTI prediction.

5. Conclusion

We proposed a topology augmentation-based PU-aware graph learning framework for drug-target interaction prediction, termed TA-PGL. It represents drugs and proteins as nodes in a directed heterogeneous graph with four relation types: DP, rev-DP, DD similarity edges, and PP similarity edges. Node features consist of RDKit descriptors and amino acid composition vectors. A relation-aware graph encoder generates node embeddings, which are used to estimate interaction probabilities. The training set is constructed on a PU assumption by combining random, "same-drug-different-target", and "same-target-different-drug" negatives, and is optimized with a hybrid loss of BCE loss and nnPU loss.

Experiments on the DrugBank dataset demonstrated that TA-PGL outperforms the other three methods. The model also had the lowest variance across independent runs. The ablation studies show that the biggest performance gain is from the similarity-based topology augmentation, followed by hard negative sampling and the nnPU loss. Our results demonstrate that topology augmentation and PU-aware graph learning are essential for DTI interaction.

In the future, we'll further evaluate our model on more datasets and cross-dataset settings, explore adaptive similarity thresholds, and integrate multimodal features such as protein structures and molecular graphs.

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Conflicts of interest

The authors declare no competing interests.

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References

[1] Veleiro, U., de la Fuente, J., Serrano, G., et al. GeNNius: An ultrafast drug-target interaction inference method based on graph neural networks. Bioinformatics, 2024, 40(1): btad774.

[2] Lu, Z., Song, G., Zhu, H., et al. DTIAM: A unified framework for predicting drug-target interactions, binding affinities and drug mechanisms. Nature Communications, 2025, 16(1): 2548.

[3] Sun, Y., Li, Y., Leung, C., et al. iNGNN-DTI: Prediction of drug-target interaction with interpretable nested graph neural network and pretrained molecule models. Bioinformatics, 2024, 40(3): btae135.

[4] Song, W., Xu, L., Han, C., et al. Drug-target interaction predictions with multi-view similarity network fusion strategy and deep interactive attention mechanism. Bioinformatics, 2024, 40(6): btae346.

[5] E, Z., Qiao, G., Wang, G., et al. GSL-DTI: Graph structure learning network for drug-target interaction prediction. Methods, 2024, 223: 136-145.

[6] Li, W., Gao, A., Ma, W., et al. TAGIN-DTI topology aggregation enhanced graph interaction network: Drug-target interaction prediction. Paper Presented at International Conference on Bioinformatics and Biomedicine (BIBM), Wuhan, China, 15-18 December, 2025.

[7] Papadopoulos, D., Liu, B., Malliaros, F., et al. Magnetic: Multilayer attention and graph neural network diffusion for effective drug-target interaction prediction. IEEE Journal of Biomedical and Health Informatics, 2026, https://doi.org/10.1109/JBHI.2026.3720334. (in Press)

[8] Tang, H., Fan, C., Yang, S., et al. Prediction of drug-target interactions based on dual-channel heterogeneous graph neural network. Paper Presented at International Conference on Natural Language Processing (ICNLP), Macau, China, 3-5 November, 2026.

[9] Ji, Y., Chen, Z., Liu, Z., et al. Ldm-dti: A multimodal framework integrating pretrained language models and geometric graph networks for interpretable drug-target interaction prediction. Expert Systems with Applications, 2026, 313: 131485.

[10] Fan, R., Dong, Z., Tian, Z., et al. Drug-target interaction prediction with pretrained llm feature learning and cross-modal fusion strategy. Paper Presented at International Conference on Bioinformatics and Biomedicine (BIBM), Wuhan, China, 15-18 December, 2025.

[11] Chen, H., Jin, M., Nunes, M. B., et al. Hierarchical attention-driven multimodal local to global learning framework for enhanced drug-target interaction prediction. Expert Systems with Applications, 2025, 299: 130076.

[12] Peng, J., Liu, X., Zhou, X., et al. Dbca-dti: A dual-branch multimodal framework based on bidirectional adaptive gated cross-attention mechanism for drug-target interaction prediction. Knowledge-Based Systems, 2026, 338: 115463.

[13] Zeng, P., Li, Z., Tang, X., et al. Mmtf-dti: Drug-target interaction prediction via multimodal feature extraction and dynamic fusion. Journal of Biomedical Informatics, 2026, 180: 105069.

[14] Keyvanpour, M. R., Mehrmolaei, S., Haddadi, F. An enhanced computational approach using multi-kernel positive unlabeled learning for predicting drug-target interactions. Current Computer-Aided Drug Design, 2025, 21(6): 766-792.

[15] Liang, J., Sun, Y., Ling, J. Grl-pul: Predicting microbe-drug association based on graph representation learning and positive unlabeled learning. Molecular Omics, 2025, 21(1): 38-50.

[16] Wang, Z., Li, N., Chen, K., et al. Condns: A novel conditional diffusion-based negative sampling method for knowledge graph embedding. Neurocomputing, 2025, 659: 131751.

[17] Huang, K., Xiao, C., Glass, L. M., et al. Moltrans: Molecular interaction transformer for drug-target interaction prediction. Bioinformatics, 2021, 37(6): 830-836.

[18] Peng, J., Wang, Y., Guan, J., et al. An end-to-end heterogeneous graph representation learning-based framework for drug-target interaction prediction. Briefings in Bioinformatics, 2021, 22(5): bbaa430.