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Abstract. Complex interactions between biology entities (drugs, diseases, side-effects, etc.), have posed difficulties for drug discovery and treatment. Despite the significant efforts that have been invested in drug-target interaction prediction, existing methods are still afflicted by the highly sparse datasets for drug-target interaction prediction and ignore the impact of interactions between different types of biological entities when constructing heterogeneous biology networks. To address the issue, we develop a framework based on the mixed expert model, named MEDTI, which captures the intra-type relationships of interactions between the same type of biological entities and inter-type relationships of interactions among different biological entities for drug-target interaction prediction. The MEDTI consists of three main components: the edge representation extractor, the type-prior information extractor, and the mixed expert discriminator. The edge representation extractor is responsible for constructing a heterogeneous biology network from numerous types of biology networks, such as drug-drug interaction, drug-target interaction, drug-disease association, and drug-side-effect association networks. Then the edge representation extractor maps the representation of different types of networks into their type spaces. The type-prior information extractor exploits prior information of different types of networks by using a type gate to aggregate information of each type spaces in heterogeneous biology networks. Cooperating with the type-prior information extractor, the mixed expert discriminator resists the implications of different types of biology entities and predicts the unobserved drug-target interaction. Experiments on real-world heterogeneous biology network datasets show that the MEDTI can outperform the state-of-the-art methods and predict different drug-target interactions accurately.

Keywords: mixed expert model, drug-target interaction prediction, type gate

1 Introduction

Recently, drug-target interaction prediction has played a vital role in the drug discovery process. Specifically, in the drug discovery process, the problem can be described as the existence prediction of drug-target interactions in the basis of existing drug-target interactions in the heterogeneous biology network dataset. To figure out existence relationships among drugs and targets, numerous targets have been tested in recent decades for discovering safe and effective drugs. However, it is troublesome to figure out the specific types of interactions between different types of biological entities. There may be various existent but unobserved interactions between them. Therefore, there is a great need for a drug-target interaction prediction method to eliminate the interference between different drug interactions and correctly identify drug-target interactions.

Thus far, various drug-target interaction prediction methods, including traditional machine learning-based models [1,2,3] and deep learning-based models [4,5,6], have been exploited to identify drug-targeted actions. In the context of adequate validation of different drug-relative actions (e.g., drug-drug, drug-disease, etc.), existing deep learning-based models have achieved better performance than traditional machine learning-based models due to their superior biological network feature extraction capabilities. Many of them have incorporated multiple data sources which include different interactions, such as drug-drug, protein-protein, drug-protein interactions into a framework for drug-target interaction prediction. Some methods have tried to apply supervised or unsupervised models to learn dimensional feature representation of drugs and target proteins from heterogeneous biology network datasets and predict drug-target interactions. There are also knowledge graph-based methods utilizing knowledge graph embedding of different biological entities to learn the vector representations of drugs and target proteins. However, they still cannot handle the unique challenges of drug target prediction. The lack of

appropriate type-prior information about interactions between different types is challenging to obtain promptly, which leads to the unsatisfactory performance of existing models. Actually, existing models tend to construct heterogeneous networks[7,8,9,10] to capture specific features of different biology interactions, which cannot be used as they are in predicting drug-target interactions and require some processing.

For this reason, we consider constructing specific representations of different types of interactions in heterogeneous networks to extract their features. Therefore, the goal of this work is to construct a framework based on the mixed expert model for drug-target interaction prediction by constructing heterogeneous biology networks containing different types of interactions. To predict drug-target interaction, the first step is to identify the drug-target interaction correctly. For different types of drug interactions, they all have their own unique or specific representations that are not shareable. Such representations of different types of interactions can be identified by learned representations. Thus, identifying drug-target interaction is equivalent to measuring the difference between other representations of interactions and drug-target interaction on heterogeneous biology networks. However, this is a technically challenging problem. First, since representations of different types of interactions are high-dimensional, simple metrics like squared error may not be able to estimate the difference between such complex representations. Second, the representations remain changeable during the training process. This requires the proposed measurement mechanism to capture the changes in the representations and provide accurate measurements continuously. Although it is very challenging, effective estimation of the differences between the learned features of different drug relationships is a prerequisite for correctly predicting drug-target interactions. Therefore, how to effectively estimate dissimilarity under such conditions is a challenge that we must address.

To address the above challenges, we propose a novel framework called mixed expert model (MEDTI), which captures the intra-type and inter-type relations of different edges for drug-target interaction prediction. MEDTI exploit the powerful representation ability of deep learning to represent biological entities for drug-target interaction prediction. Inspired by domain gates [11,12] and expert models [11,13], we incorporate the type-prior information extractor and the mixed expert discriminator in the training phase to fuse the prediction results of multiple experts on drug-target interaction prediction. The proposed MEDTI model consists of three main components: an edge representation extractor, a type-prior information extractor, and a mixed expert discriminator. The type-prior information extractor and the mixed expert discriminator are built on the basis of the edge representation extractor to perform the main task of drug target prediction. Experimental results on two large-scale real-world heterogeneous biology network datasets show that the proposed MEDTI outperforms the state-of-the-art approaches. The main contributions of this paper can be summarized as follows:

- To better describe relationships between drugs and targets, we construct a heterogeneous biology network with multiple types of biology interactions and networks and propose a mixed expert model for drug-target prediction (MEDTI), which captures the intra-type and inter-type relations of different biology interactions for drug-target interaction prediction.
- We use R-GCN to extract the feature representations of biological entities in the heterogeneous biology network, and utilize the mixed expert discriminator and the type prior information extractor to explore potential and deeper drug-target interactions to improve the prediction performance of drug-target interactions.
- The experimental results on two real-world datasets show that the MEDTI outperforms the state-of-the-art methods and predicts drug-target interactions accurately.

2 Related Work

The drug-target interaction prediction is significant for drug discovery [14] and repositioning [15,16]. Specifically, in the drug discovery process, a large number of chemical and biological entities have been tested in recent decades for discovering safe and effective drugs. Two biological-based experimental methods have been applied to solve the problem of drug-target interaction prediction: protein microarrays [17] and affinity chromatography [18. Nevertheless, drug development based on experiments is a time-consuming and expensive process. To expedite drug development, it is essential to develop validated combinatorial methods to drug-target interaction prediction [2,5,6,19,20]. Existing computational-based methods for drug-target interaction prediction can be divided into three categories: text mining-based methods, feature engineering-based methods, and network-based methods.

Text mining-based approaches extract features from context literature for drug-target interaction prediction by treating descriptions of drugs and targets as their features [21]. A semantic similarity-based

model using SVM and Random Forest and methods has been proposed to drug-target interaction prediction [22]. On the basis of chemical and biological spaces, the model builds a semantic network and utilize it to extract features. Unfortunately, text mining-based approaches can be influenced by variances of semantic representations and obfuscation among different literatures.

The main idea of feature engineering-based methods is to extract biometric features of drugs and targets. For example, an SVM-based approach named BLM (binary local model) [23], which treated the drug-target interaction prediction problem as a binary classification problem by using chemical and genomic data to consider similarities of drug-target, drug-drug and target-target interactions. A computational framework called BLMNII, which is based on the BLM, was proposed by Mei et.al [24]. BLMNII combines the neighbor-based interaction spectrum inference (NII) approach with BLM. Wang et al. proposed a stacked autoencoder-based model [25] to learn PSSM-based features. The model then uses Random Forest for drug-target interaction prediction. However, these methods still do not deeply explore drug-drug or protein-protein interactions.

In network-based approaches, networks can represent complex interactions between different types of biological entities (i.e., drugs, proteins, diseases, side-effect). Several network-based methods have been developed for drug-target interaction prediction [16,26,27,28,29,30]. Cheng et al. proposed a network-based inference model called NBI to predict new drug-target interactions [19]. NBI only utilized drug-target bipartite network topology similarity to score the similarity between a drug and a target. Integrating other types of networks can improve the performance of the network approach. Chen et al. [20] used a heterogeneous network which consists of protein-protein and drug-drug similarities networks, and the known drug-target interaction network to propose an effective model called NRWRH [32]. Compared with only one network, it has achieved significant performance improvement. In addition, many machine learning methods have been applied to predict drug-target interaction while the size of experimental data increases. Establishing a classification model is a commonly used machine learning method. It uses the drug -target pair (DTP) as input, and whether there is an interaction between the drug -target to (DTP) as the output. The most applied machine learning model is a binary classifier, such as Random Forests and SVM. Zhao et al. [33] proposed a network-based method combining graph convolutional neural network and deep neural network for drug-target interaction prediction. In detail, this method builds a drug–protein pair (DPP) network through the drug-drug interaction network, protein-protein interaction network and drug-protein interaction network. A node in the DPP network represents a drug-target pair, and the edge represents the link strength between these pairs. Then, the problem of drug-target interaction prediction is converted into an edge classification problem.

These three categories of methods usually extract features based on different types of interactions and features are concatenated together by extraction networks. Those methods do model the heterogeneous information in a multiple-types heterogeneous network. Therefore, they cannot fully consider the associations among multiple types of biological entities, such as drug, disease, protein, side-effect, etc. Distinguished from the three categories of methods above, methods on the basis of constructing heterogeneous graph representation have obtained great achievements in many tasks such as item recommendation [34,35] and polypharmacy side-effects prediction [36]. Compared with three categories of methods, method based on heterogeneous graphs can model multiple types of biological entities and complex interactions in a single heterogeneous network. In this research, we propose a mixed expert model for drug-target interaction prediction (MEDTI), which captures the intra-type and inter-type relations of different biology interactions for drug-target interaction prediction.

3 Problem Definition

To facilitate the presentation in this study, Table 1 summarizes frequently used symbols. A heterogeneous biology network is a network with multiple types of nodes and edges. Given a heterogeneous biology network, it can be represented as $G = (V, E, \mathcal{R})$, where $v_i \in V$ represents the node in the heterogeneous biology network, and $e = (v_i, v_j) \in E$ represents the edge and $r \in \mathcal{R}$ represents the edge type of each e in the heterogeneous biology network. Specifically, in the heterogeneous biology network, there are numerous types of nodes(v_i) (i.e., drug, protein, disease, side-effect).

Formally, we define the problem of this research as follows. Given V, E, and $\mathcal{R}$, we need construct a heterogeneous biology network $G = (V, E, \mathcal{R})$ for predicting drug-target interaction in E, where each edge in E is assigned with a type e to predict its existence.

Table 1. The frequently used symbols

Symbol	Meaning	Symbol	Meaning
G	Heterogeneous biology network.	S	The edge representation.
V	Nodes that denote different types of biological entities.	r	The edge type in the heterogeneous biology network.
E	Edges which represent interactions between different types of biological entities.	D	The type representation.
$\mathcal{R}$	Types of interactions between different types of biological entities.	P_i	The conclusion of the single expert network
h_i	The hidden state of each node	E_i^r	The degree of the node i
W_r^{l+1}	The weight matrix under relation r	δ	The set of weight representing the importance of different experts

4 Methods

We detail the proposed MEDTI in this section. A general overview of the MEDTI is presented in Section 4.1. Section 4.2 explains the extraction process of edges representation in heterogeneous biology networks. Section 4.3 details how the type gate exploits the type-prior information of different types in heterogeneous biology network. Section 4.4 introduces the mixed expert discriminator to produce a type representation to represent its type-prior information. In Section 4.5, based on the three components of the proposed MEDTI, the integration of the MEDTI to predict drug-target interaction in the heterogeneous drug-target graph networks is detailed.

4.1 Overview

The goal of the proposed novel framework MEDTI is to predict drug-target interaction in the heterogeneous biology networks. As is shown in Fig.1, in order to achieve this goal, the proposed MEDTI integrates the edge representation extractor, the type gate and the type expert network. We firstly construct the heterogeneous network by combining several types of biology networks through the edge representation extractor. Both the type gate and the type expert network are built on top of the edge representation extractor. The type gate extracts type representations of each specific biology network. Finally, the mixed expert discriminator evaluates different biology interactions by different experts and predicts the presence of it.

4.2 Edge Representation Extractor

In this section, we build a heterogeneous biology network to obtain edge representation. Then the heterogeneous drug-target graph G is fed into the R-GCN layer to obtain the edge representation set $S = \{s^e, e \in E\}$.

For the detailed procedures, the R-GCN layer is a graph-to-graph layer that adopts a set of node representations and the topological structure of the graph as inputs and generates a novel collection of representations for nodes. In a heterogeneous biology graph $G = (V, E, \mathcal{R})$, V is a set of nodes while the $(v_i, v_j) \in E$ is a set of tuples indicating existence of undirected edges. The hidden state of each node v_i is represented as h_i, where h_i is a d-dimensional vector. Every node v_i aggregates neighbors' information h_j in it as described in Eq (1).

$$h_i^{l+1} = \psi\left(\sum_{r\in R}\sum_{j\in E_i^r}\frac{1}{c_{i,r}}W_r^l\, h_j^l + W_0^l h_i^l\right), \forall v_i \in V \quad (1)$$

where ψ denotes an activation function, $c_{i,r}$ represents a normalization weight, W_r^l and W_0^l denote the relation specie transformations used by the RGCN during the training, respectively.

Intuitively, Eq (1) accumulates transformed representations of neighboring nodes through a normalized sum [28]. Different from regular GCNs, we introduce relation-specific transformations, i.e., depending on the type and direction of an edge in the heterogeneous network. To ensure that the

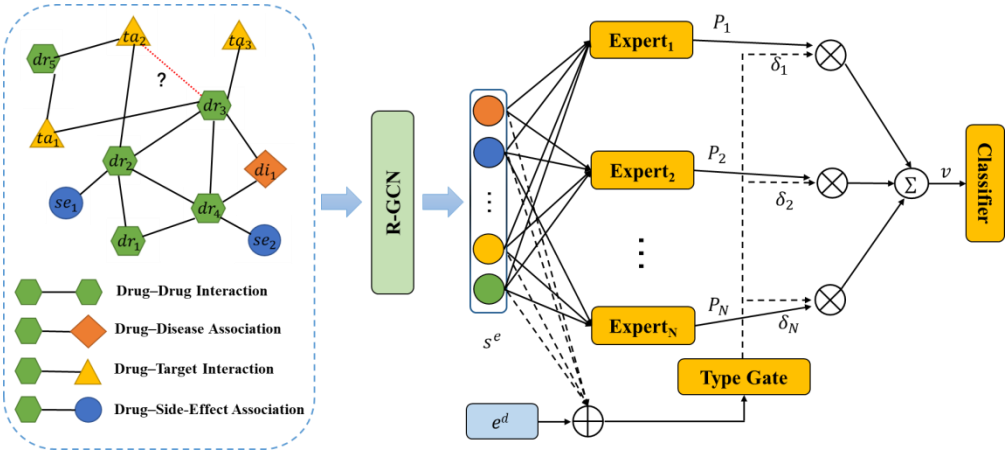


Fig.1 The framework of the MEDTI. The input of the MEDTI is the heterogeneous biology network dataset which includes different types of interactions among different biological entities such as drug, target, side-effect, and disease. Then through the R-GCN layer, the MEDTI obtains the edge representation of various interactions and the type representation of each biological entity. The expert model and type gate mechanism, which are specific to be the mixed expert discriminator and the type-prior information extractor in the MEDTI respectively, are responsible for exploring accurate feature representation of various interactions. The output of our method is the result of drug-target interaction prediction.

representation of a node at layer $l+1$ can also be informed by the corresponding representation at layer l, we add a single self-connection of a special relation type to each node in the network dataset. Note that instead of simple linear message transformations, one could select more flexible functions such as multi-layer neural networks (at the expense of computational efficiency). A neural network layer update consists of evaluating Eq (1) in parallel for every node in the graph. In practice, Eq (1) can be implemented efficiently by using sparse matrix multiplications to avoid explicit summation over neighborhoods. Multiple layers can be stacked to allow for dependencies across several relational steps. We refer to this graph encoder model as a relational graph convolutional network (R-GCN).

The edge representation is established on the basis of the node representation. The edge representation s^e is represented as follow.

$$s^e = h_i^{l+1} \times h_j^{l+1} \tag{2}$$

The output of the R-GCN layer is edge representation $s^e \in S$, which is denoted as the input of mixed expert discriminator.

4.3 Type-prior information extractor

To figure out the potential information among different types of interactions, we introduce type-prior information extractor based on type gate to produce a type representation to represent its type prior information. The type prior information can explore relations of edge representation in one type edges.

To achieve this purpose, we set a learnable type representation $e^d \in D$, which can help personalize the representation extraction for each edge type. Note that different type gates specialize in different types, and they are good at exploiting different type information. For the proposed MEDTI, we use an adaptive type gate to explore the type representation. The purpose of adopting a type-prior information extractor is to generate high-quality representations of different types of edges. Nevertheless, if the representations of all experts are simply averaged as the final representation, this approach does not achieve high-quality drug-target interactions. Since simple averaging removes information about specific types of interactions. Each type gate is good at dealing with a specific type representation, and if the type gate can be adaptively selected, then the best use can be achieved. Following this idea, this paper proposes an edge type gate, where the edge representations and type representations are used as inputs to guide the selection process of the mixed expert model. The edge type gate can be expressed as $T(;\phi)$, where ϕ is the parameter of the edge type gate, then it can be expressed by Eq (3).

$$\delta_i = softmax\big(T(e^d \oplus s^e;\phi)\big) \tag{3}$$

where the type gate $T(;\phi)$ is a feed-forward network. e^d and s^e are the type representation and edge representation, respectively. The output of $T(;\phi)$ is normalized using a softmax network, and $\delta_i \in \delta$ is a weight representing the importance of different experts and δ is the set of weight.

4.4 Mixed Expert Discriminator

Although the different experts for predicting their specific type of edge, their conclusions for the other types of edges are still beneficial. To further explore unobserved edges in the heterogeneous biology network, the mixed expert discriminator obtains different discriminable conclusions for one type edge. We obtain different feature representations of specific types through different type experts and capture the correlations between different biological edge representations by analyzing the relationships among different experts.

The expert network is denoted by $\Phi_i(s^e;\theta)(1 \le i \le N)$, where $s^e \in S$ represents the edge representation as the input to the expert network, θ represents the parameters and N is a hyperparameter that indicates the number of expert network. P_i represents the conclusion of the single expert network as follow.

$$P_i = \Phi_i(s^e;\theta) \tag{4}$$

Cooperating with the type gate, the final representation of the edge is obtained as follow.

$$v = \sum_{i=1}^{N} \delta_i P_i \tag{5}$$

where v denotes the final representations of different types of edges. v is the input of a prediction network utilizing multi-layer perception (MLP) network with a softmax output layer, which is designed for the detection of the existence of drug-target interactions as follow.

$$\hat{y} = softmax(MLP(v)) \tag{6}$$

The goal of the mixed expert discriminator is to determine the existence or absence of drug-target interactions. We use y^i for the actual label and $\hat{y}^i$ for the predicted label. The loss function uses a binary cross-entropy loss (BCELoss) for classification as follow.

$$L = -\sum_{i=1}^{N}(y^i log\hat{y}^i + (1-y^i)\log(1-\hat{y}^i)) \tag{7}$$

4.5 Model integration

Based on the edge representation extractor, the type-prior information extractor, and the mixed expert discriminator, the proposed MEDTI captures the intra-type and inter-type relations of different biology interaction for drug-target interaction prediction. At each iteration, $S = \{s^e, e \in E\}$ represents the set of edge representation, and the corresponding label sets of S is denoted as $Y(S) = \{y(s^e), e \in E\}$.

The integration process of the MEDTI is as follows. First, we feed the node set V into R-GCN model to calculate the set of edge representation $S = \{s^e, e \in E\}$. For each s^e, we set a learnable type representation $e^d \in D$ to learn the type-prior information. Then, a type gate is used to integrate the s^e and e^d, and learn the importance of different experts $\delta_i \in \delta$. Second, mixed experts evaluate s^e with different conclusions P_i. Cooperating with the type gate, we obtain the final representation of the edge v. Finally, the proposed MEDTI predict the final representations of edges v existence or not. The procedures of the MEDTI are summarized as follows.

MODEL: MEDTI	
INPUT:	V— Nodes set.
	E— Edges set.
	R— Edges type set.
OUTPUT:	U— Set of unobserved edges.
Step 1:	$U = \emptyset$.
Step 2:	For each training iterations do
Step 3:	Feed $v \in V$ to obtain the edge representation s^e by Eq (1).
Step 4:	For each edge $s^e \in S$ do
Step 5:	Different experts evaluates the edge as follows:
Step 6:	$P_i = \Phi_i(s^e;\theta)$
Step 7:	Exploiting type representation e^d by integrating prior information of its type.
Step 8:	Guide selection process of the mixed experts:
Step 9:	$\delta_i = softmax\big(T_i(e^d \oplus s^e;\phi)\big)$
Step 10:	The final representation of the edge is obtained as follow.
Step 11:	$v = \sum_{i=1}^{N} \delta_i P_i$
	End for
Step 12:	Predict unobserved edge u for each type by Eq (6).
Step 13:	$U = U + \{u\}$

End for
Step 14: return U

5 Experiments

In this section, we firstly introduce the drug-target dataset in our experiment, then present commonly used drug-target interaction prediction methods and analyze the performance of the MEDTI.

5.1 Dataset

To evaluate the performance of the MEDTI on drug-target interaction prediction, we have tested it on two datasets, namely Luo et al. dataset [16] and Zhang et al. [37] dataset. These two datasets have been widely used to evaluate the drug-target interaction prediction algorithms in pervious researches.

The Luo et al. dataset is Drug Target Prediction benchmark, which is used for predicting drug target interactions, including four drug or protein related networks: drug-drug interaction network[Drug Bank (Version 3.0)] [38], drug-protein interaction network [Drug Bank (Version3.0)] [38], drug-disease association network (Comparative Toxicogenomic Database) [39] and drug-side-effect association network [sider database (version 2)] [40].

The Zhang et al. integrates bioinformatics and chemical informatics resources to provide detailed drug data, including drug chemical substructures, target, enzyme, pathways and drug-drug interactions. This dataset is adopted with multiple drug features obtained from the DrugBank database released in April 2018 (version 5.1.0). The details of our datasets are listed in Table 1 as follow.

Table 2. The detailed description of our datasets.

Dataset	Data Type	Database	Description
Luo et al. dataset	Drug	DrugBank	708 drug types
	Target	DrugBank	1512 target types
	Disease	Comparative Toxicogenomic	5603 disease types
	Side-effect	Sider	4192 side-effect types
Zhang et al. dataset	Drug	DrugBank	841 drug types
	Target	DrugBank	1333 target types
	Enzyme	DrugBank	214 enzyme types
	Pathway	KEGG	307 pathway types
	Substructure	PubChem	619 substructure types

5.2 Comparison Methods

To validate the effectiveness of the proposed MEDTI, we choose baselines from the following four state-of-the-art algorithms, including DTINet [16], BLMNII [41], NetLapRLS [42] and CMF [43].

DTINet: DTINet consolidates the multiple types of networks and learns low-rank knowledgeable features for drug and protein feature representation. The low-dimensional feature vectors that are learned by DTINET acquire contextual knowledge of each network, as well as topological characteristics of nodes in multiple networks. On the basis of these low-rank features, DTINet discovers an optimal representation of the target space from the drug space that predicts the new drug-target interactions based on the geometric approximation of the vectors that are mapped in the unified space.

BLMNII: BLMNII focuses on finding targets for new drug candidate compounds and identifying target drugs for new candidate target proteins. It is based on the bipartite local models (BLM) which transforms the drug-target interaction prediction into a binary classification problem. BLMNII combines neighbor-based interaction profile inferring (NII) method with BLM to handle the new candidate problem. The interaction profile is viewed as label information and is used for model to learn new candidates, which is significant for finding targets for new drug-target compounds and identifying targeting drugs for new target-candidate proteins.

NetLapRLS: NetLapRLS is a semi-supervised method which incorporates a new kernel built from a known drug-protein interaction network into the standard LapPLS. It trains two classifiers in the drug and protein types individually and then combines them together to provide the final prediction. NetLapRLS takes the interactions between drugs and targets into consideration and simultaneously focuses on similarities of drug-drug interactions and target-target interaction.
CMF: CMF presents a multiple similarity collaborative matrix decomposition (MSCMF), which maps drug and target into a common low-rank feature space. The matrices of drug and target is further aligned with the weighted similarity matrices of the drug and the target. The weights of these two low-rank matrices and the similarity matrix are estimated by alternating least squares. CMF can collaboratively predict drug-target interactions from the two low-rank matrices.

5.3 Experiment Setting

We split each dataset into the training set and testing set in a ratio of 8:2, where the training set is used to optimize the parameters of the MEDTI and the testing set is used to evaluate its performance. In the edge representation extractor, we set k = 100 for dimensions of graph embedding. The expert network on the mixed expert discriminator consists of two fully connected layers: the first layer has a hidden size of 64 and the second layer has a hidden size of 32. The type gate also includes two fully connected layers: the first layer has a hidden size of 200 and the second layer has a hidden size of 320. The prediction network on the mixed expert discriminator has a hidden size of 320. For all benchmarks and proposed models, we use the same batch size for training epochs of 100. The settings of the parameters of DTINet, BLMNII, NetLapRLS and CMF are as [16, 41, 42, 43].

5.4 Performance Comparison

The drug-target interaction prediction can be viewed as a binary classification problem. We utilize Area Under the Receiver Operating Characteristic Curve (AUROC), Area Under the Precision Recall Curve (AUPR), Accuracy (Acc) and F1-score (F1) for evaluating models. For comparison, we use BLMNII, NetLapRLS, CMF, and DTINet, which are all mainstream algorithms. Based on Luo et al. dataset and Zhang et al. dataset, Table 2 shows experimental results of baselines and the proposed MEDTI. The proposed MEDTI are much more accurate than the baselines in terms of AUROC, AUPR, Acc and F1 metrics.

With the help of R-GCN, a powerful tool for extracting useful features, we can capture the features of different drug relationships. Compared with other types of feature representations, the features extracted by R-GCN are more expressive of the characteristics among various relationships. For NetLapRLS, although two types of classifiers, drug and target, are trained separately, its poor recognition of other biological entities (e.g., diseases and side-effect) contributes to its fewer effective results than the MEDTI. For CMF, it maps drugs and targets into a common low-rank feature space, and the matrices of drugs and targets are further aligned with the weighted similarity matrix of drugs and targets. This approach allows the CMF to predict drug-target interactions synergistically from two low-rank matrices, improving prediction efficiency and accuracy, with the disadvantage that the same lack of attention to other biological entities makes its prediction slightly inferior to our proposed MEDTI. DTINet integrates multiple types of networks and learns low-rank knowledge features of drug and protein feature representations, which confirms the superiority of integrating multiple types of networks for drug target prediction tasks. Based on such a basic idea, the MEDTI sufficiently extracts features of various types of entities and relationships by constructing heterogeneous biology networks that represent various biological entities and interactions and associations among these entities to better polish up drug-target interaction prediction in a specific mapping space.

Specifically, the MEDTI improved AUROC and AUPR by 1.48% and 3.43%, respectively, and Acc and F1 scores by 1.45% and 2.22%, respectively, compared with the optimal baseline.

5.5 The effects of different types of edges in the heterogeneous network

The edge representation extractor is the significant construction process of heterogeneous biology networks in the MEDTI, which is evaluated in the section. To assess the affection of different types of edges and their interactions in heterogeneous biology networks, we conduct ablation experiments on Luo et al. dataset with AUROC and AUPR metrics. We design three variants of the proposed MEDTI

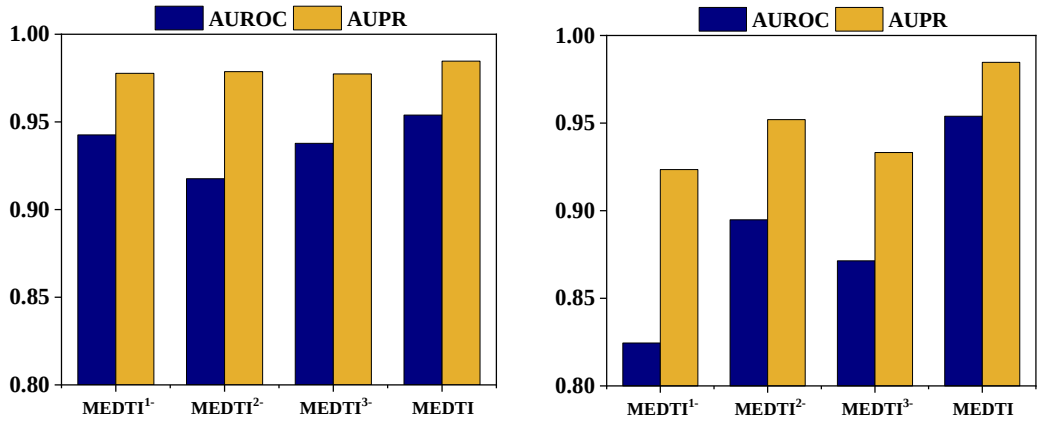
Table 3. Performance comparison of methods in datasets

Dataset and Metrics		DTINet	BLMNII	CMF	NetLapRLS	MEDTI
Luo et al dataset	AUROC	0.9308	0.6595	0.9222	0.9391	0.9539
	AUPR	0.9504	0.6382	0.9413	0.9476	0.9847
	Acc	0.9441	0.6854	0.9375	0.9452	0.9597
	F1	0.9118	0.7031	0.8989	0.9223	0.9445
Zhang et al dataset	AUROC	0.8867	0.7852	0.7936	0.8339	0.9496
	AUPR	0.8695	0.8298	0.8251	0.8557	0.9208
	Acc	0.9062	0.8025	0.8134	0.8884	0.9601
	F1	0.8995	0.8117	0.8555	0.8723	0.9096

for comparison, including MEDTI^{1-}, MEDTI^{2-} and MEDTI^{3-}. The MEDTI^{1-}, MEDTI^{2-}, MEDTI^{3-} remove edges of drug-disease interactions, edges of drug-drug interactions, edges of drug-side-effect interactions, respectively.

Table 3 shows that MEDTI has advantages when all networks are used. When edges of drug-side-effects are removed, AUROC and AUPR decrease slightly, but when edges of drug-disease interactions are removed, AUROC and AUPR highly decrease. A reasonable explanation for this phenomenon is that side-effects are only associated with drugs, but diseases are associated with both drugs and targets in the heterogeneous biology network. Therefore, we speculate that adding disease nodes and related edges can improve drug-target recognition on drug-target interaction prediction problem.

By comparing the variants with the MEDTI, we can figure out that other types of edges also contribute to the drug-target interaction prediction, such as drug-disease and drug-side-effect. These types can bring accuracy improvement to the drug-target interaction prediction.



(a) Luo et al. dataset (b) Zhang et al. dataset

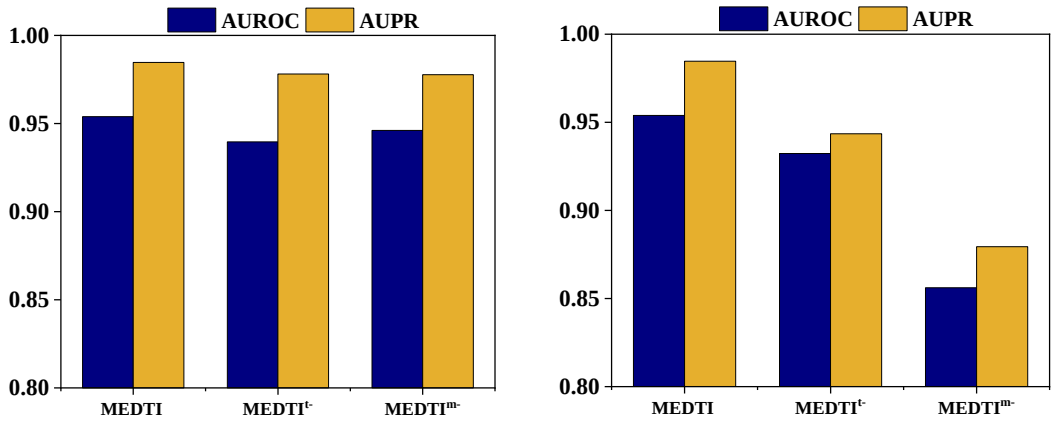
Fig. 3 Performance comparison of the MEDTI, MEDTI^{1-}, MEDTI^{2-} and MEDTI^{3-} on the two datasets.

5.6 Ablation Study

5.6.1 Importance of the type-prior information extractor

One of important attributes of the proposed MEDTI is to use a type gate to aggregating type-prior information in heterogeneous biology networks. In the MEDTI, the type-prior information extractor aggregates each type-prior information of different interactions and enhance the representation of each edge representation. We design a variant of the our model, named MEDTI^{t-}, to confirm the significance of the type-prior information extractor. The only difference between MEDTI and MEDTI^{t-} is that MEDTI^{t-} does not contain the type-prior information extractor. To describe the performance change of the two models, we used the AUROC and AUPR values. The performance comparisons between MEDTI and MEDTI^{t-} is shown in Fig. 4.

The MEDTI achieves better performances than MEDTI^{t-} both in the AUROC and AUPR in Fig.4. In



(a) Luo et al. dataset (b) Zhang et al. dataset

Fig. 4 Performance comparison of the MEDTI, MEDTI^{t-} and MEDTI^{m-}.

process of constructing type-prior information, different type edges have distinguishable representation, and distinguishable representation of edges can be an indicator for the drug-target interaction prediction. The combination of representation of edges and types can provide an additional dimension to train classifier and improve performance of drug-target interaction prediction. Accordingly, this ablation study shows that type-prior information extractor offers a useful manner for the MEDTI, which contain the type-prior information extractor, to have better performance.

5.6.2 Importance of the type-prior information extractor

To analyze the importance of the mixed expert discriminator in drug-target interaction prediction, we design a variant of the proposed MEDTI, named MEDTI^{m-} for comparison. Thus, the MEDTI^{m-} only used a single expert model. The performance comparison of MEDTI and MEDTI^{m-} is presented in Fig. 5.

Fig.4 shows that the MEDTI achieves significant performance improvements. Compared with the MEDTI^{m-}, which only used a single expert model, the MEDTI can better exploit the contribution of several expert models which corresponding to other types of interactions and associations to drug-target interaction prediction. This substantial improvement can be attributed to the mixed expert discriminator, which uses multiple mixed expert from the edges of different types of edges for drug-target interaction prediction. The MEDTI, which contains the type-prior information extractor, automatically exploits structural and biological features of different types of interactions and associations in drug-target interaction prediction. Therefore, the MEDTI obtains better drug-target interaction prediction performance.

6 Conclusion

This study demonstrates that heterogeneous network-based node representation method can model multiple types of entities and complex interactions between different types of entities in a single heterogeneous network which can provide additional information in drug-target interaction prediction. The MEDTI exhibited the AUPR curve of 98.47% and outperformed the BLMNII and CMF methods on this task. The MEDTI also showed close performance to the NetLapRLS and DTINet methods. Further investigations of this method such as exploiting the common and individual features in different types of networks may result in training more distinguished type representations, which can promote the detection performance. Additionally, the MEDTI will be applied on other domain datasets such as cancer and neurodegenerative disease to evaluate the performance.

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