Effective drug–target interaction prediction with mutual interaction neural network

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Abstract

Motivation: Accurately predicting drug–target interaction (DTI) is a crucial step to drug discovery. Recently, deep learning techniques have been widely used for DTI prediction and achieved significant performance improvement. One challenge in building deep learning models for DTI prediction is how to appropriately represent drugs and targets. Target distance map and molecular graph are low dimensional and informative representations, which however have not been jointly used in DTI prediction. Another challenge is how to effectively model the mutual impact between drugs and targets. Though attention mechanism has been used to capture the one-way impact of targets on drugs or vice versa, the mutual impact between drugs and targets has not yet been explored, which is very important in predicting their interactions.

Results: Therefore, in this article we propose MINN-DTI, a new model for DTI prediction. MINN-DTI combines an interacting-transformer module (called Interformer) with an improved Communicative Message Passing Neural Network (CMPNN) (called Inter-CMPNN) to better capture the two-way impact between drugs and targets, which are represented by molecular graph and distance map, respectively. The proposed method obtains better performance than the state-of-the-art methods on three benchmark datasets: DUD-E, human and BindingDB. MINN-DTI also provides good interpretability by assigning larger weights to the amino acids and atoms that contribute more to the interactions between drugs and targets.

Availability and implementation: The data and code of this study are available at https://github.com/admislf/MINN-DTI.

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1 Introduction

In drug discovery and design, verifying whether a drug interacts with a certain target is a key step to prove the effectiveness of the drug. Since large-scale in vitro and in vivo experiments are high-cost and time consuming, computational methods for drug–target interaction (DTI in short) prediction have received increasing attention. However, traditional computational methods have obvious limitations. For example, the widely used molecular docking is inefficient and sometimes ineffective because of its huge amount of computation and inaccurate scoring function (Su et al., 2019). On the other hand, traditional machine learning models such as Random Forest (RF) and Support Vector Machine (SVM) have also been used for DTI prediction (Ballester and Mitchell, 2010; Bleakley and Yamanishi, 2009; Liu et al., 2015). These methods are generally simple and efficient, but the performance is far from satisfaction. Recently, the introduction of deep learning models to DTI prediction has greatly advanced this area (Bagherian et al., 2021; Tian et al., 2016). In deep learning-based works, DTI prediction can be characterized as a binary classification, a ranking task or a regression task for binding affinity. Usually, deep learning models for DTI prediction are composed of a target feature extraction module, a drug feature extraction module and a prediction module. These modules are carefully designed according to various practical factors including the input representations.

The most commonly used representations of drugs and targets are one-dimensional (1D) sequences such as Simplified Molecular Input Line Entry Specification (SMILES) strings for drugs and amino acid sequences for targets (Karimi et al., 2019; Liu et al., 2020; Peng et al., 2020; Tsubaki et al., 2019; Zheng et al., 2020). The models with 1D sequences as input generally use Convolutional Neural Network (CNN), Recurrent Neural Network (RNN), Long Short-Term Memory (LSTM) blocks or Gated Recurrent Unit (GRU) blocks to extract drug and target features. For instance, Ozturk et al. used CNN modules to extract hidden representations of amino acid sequences and SMILES strings, which were later combined and
input to a multi-layer perceptron to perform the prediction (Ozturk et al., 2018). Besides sequences, feature vectors representing physicochemical properties of targets/drugs and drug molecular fingerprints are also common forms of 1D input to DTI prediction models (Lee et al., 2019; Lenselink et al., 2017; Rifaioglu et al., 2021). Slightly different from the work of Ozturk et al., instead of SMILES strings, Lee et al. used molecular fingerprints with fully connected networks to extract drug features to predict DTI prediction (Lee et al., 2019). According to the research of Lenselink et al. (2017), with feature vectors composed of physicochemical properties of targets/drugs and molecular fingerprints as input, Deep Neural Network (DNN) models outperform Naive Bayes, RF, SVM, logistic regression models in DTI prediction. Two-dimensional (2D) paired feature map has also been used for DTI prediction, which uses a matrix of a specific property calculated for amino acid pairs in the corresponding protein sequence to represent a target (Rifaioglu et al., 2021; Zheng et al., 2020). For example, Rifaioglu et al. used multi-channel protein feature maps involving sequence, structural, evolutionary and physicochemical properties to represent proteins for proteochemometric protein-drug binding affinity prediction (Rifaioglu et al., 2021). 2D structural images are intuitive representations of drugs and have been used in DTI prediction (Rifaioglu et al., 2020; Wang et al., 2021). Wang et al. proposed an efficient DTI prediction system using only 2D images as input, which includes CNN-based models for 704 targets (Rifaioglu et al., 2020). Two-dimensional (2D) molecular graph is another effective representation of drugs, which has been widely used in Graph Neural Network (GNN)-based models for predicting molecular properties (Gilmer et al., 2017; Song et al., 2020; Xiong et al., 2020; Yang et al., 2019; Zhang et al., 2021). Recently, molecular graph has also been increasingly used in DTI prediction (Nguyen et al., 2021; Torng and Altman, 2019; Tsubaki et al., 2019). Tsubaki et al. used GNN to extract the information of a small molecule as a feature vector, which is then concatenated with the target feature vector extracted by CNN from amino acid sequence to make prediction (Tsubaki et al., 2019). Compared with SMILES-based models, graph-based models can readily exploit topological information of molecules, which show obvious advantages in the task of DTI prediction.

Although 1D and 2D-based DTI prediction models have made significant progress recently, as DTI is in essence three-dimensional (3D) physical interaction, it is natural and reasonable to predict DTI using three-dimensional structural information. Many studies directly use 3D Cartesian coordinates to represent the 3D structures of targets, but the limited samples cannot cover such a huge space, which leads to poor performance (Ragoza et al., 2017; Wallach et al., 2015; Zheng et al., 2019). Some models apply 3D voxel grids to represent targets and use 3D-CNN to extract target features, their accuracy is limited because the grid coordinates are not accurate enough to represent the spatial positions of targets’ atoms. On the other hand, 2D paired distance map represents 3D structure of each target by a matrix of internal pairwise distances between the amino acids of the target, which has been mainly used in protein structure prediction (Skolnick et al., 1997). Recently, Zheng et al. proposed an advanced model called drugVQA to predict DTI, where LSTM and dynamic 2D-CNN were used to extract features from SMILES strings and distance maps, respectively (Zheng et al., 2020), and achieved satisfactory performance. Though 2D paired distance map and molecular graph are promising representations of targets and drugs, respectively. However, they have not yet been jointly used for DTI prediction.

After extracting feature vectors from the drug and the target, respectively, the features are usually concatenated and input to a MLP to predict DTI. In most existing models, targets and drugs are represented and processed separately, they can hardly capture the interacting context between targets and drug molecules. The attention mechanism is often used to acquire the contributions of different components of a drug or target to the interaction (Karimi et al., 2019; Tsubaki et al., 2019; Zheng et al., 2020), which has been recently used to characterize the interactions between targets and drugs (Chen et al., 2020, 2021). The attention mechanism was found to be able to better capture the impact of targets on drugs and vice versa, so as to obtain better representations. However, these models pay attention only to the impact of one participant of a DTI on the counterpart, such as target on drug, but ignore the reverse impact. According to the induced-fit theory (Johnson, 2008), interacting drug molecules and targets are mutually impacted. Therefore, it is natural and reasonable to consider their mutual impacts when learning to represent the drugs and targets for DTI prediction.

In this article, to overcome the above-mentioned drawbacks of existing DTI prediction models, we propose a new model for DTI prediction. In this model, 2D paired distance maps of proteins and molecular graphs are served as inputs for targets and drugs, respectively. To capture the interactive impacts between targets and drugs, we design a mutual interaction neural network (MINN) by innovatively combining two interacting-transformers (Interformer in short) with an improved Communicative Message Passing Neural Network (CMPNN) (called Inter-CMPNN). In the experiments, our model achieves better performance than state-of-the-art methods on DUD-E, human and BindingDB benchmark datasets. Case studies show that individual contributions of residues in the target and atoms in the drug to the formation of DTI can be inferred from learned attention weights, which indicates that our proposed model is interpretable and can help to explain the drug action mechanism, and suggests the direction of drug optimization in the future.

2 Materials and methods

2.1 Overview

The architecture of our proposed model MINN-DTI is shown in Figure 1. It consists of three modules: a target preprocessing network (TPN), a MINN and an interaction prediction network (IPN). MINN is the core component of our model, which consists of an Interformer module and an Inter-CMPNN module. The Interformer module is constructed by two interacting transformer decoders, and the Inter-CMPNN module is a variant of CMPNN. With these two modules, we can extract the latent vectors of targets and drugs while considering their interacting contexts.

The 2D distance map and 2D molecular graph are served as the input representation of a given target and a molecule, respectively. The molecular graph is directly used, while the distance map is first preprocessed by the target preprocessing network (TPN). The latent feature vectors of both the target and the molecule are extracted by MINN. These latent feature vectors are then concatenated and fed to the interaction prediction network (IPN) to predict DTI. The details of these modules are presented in the following sections.

2.2 Target preprocessing network

Given a target, we calculate a 2D paired distance map (Skolnick et al., 1997), which is subsequently preprocessed by the target preprocessing network (TPN) into a fixed-size matrix following drugVQA (Zheng et al., 2020). TPN is implemented by a dynamic attentive CNN. As shown in Figure 2, the dynamic attentive CNN is composed of a Dynamic CNN (DyCNN) block and a Sequential Self-Attention (SSA) block. The DyCNN block contains a number of residual blocks and an average pooling layer as ResNet (He et al., 2016). To handle targets with different lengths, the pooling layers between the residual blocks are eliminated. Through the DyCNN, a 2D paired distance map \( P \in \mathbb{R}^{d \times d} \) is transformed into a feature map \( P^r \in \mathbb{R}^{d \times f} \), where \( f \) is the number of filters of the residual block. With the SSA block, a weight matrix \( A_r \in \mathbb{R}^{d \times d} \) is derived by a two-layer perceptron without bias from \( P^r \):

\[
A_r = \text{softmax}(W_p \tanh(W_q P^r))
\]

where \( W_p \) and \( W_q \) are learnable parameters. This multilayer perceptron (MLP) block can be regarded as a multi-head attention where the number of neurons \( r \) in the last layer is interpreted as the number of attentional heads. The attentional feature map \( A_r \in \mathbb{R}^{d \times d} \) is derived by multiplying \( A_r \) and \( P^r \), which indicates the relative importance of amino acid sites.
2.3 Mutual interaction neural network (MINN)

The goal of MINN is to learn the representations of targets and drugs while considering their interacting contexts. For this purpose, we design an Interformer module to interact the information extracted from targets and small molecules and an Inter-CMPNN module to support information interacting from the drug side. Thus, we can get more comprehensive representations of the targets and drugs, and consequently boost DTI prediction.

2.3.1 Interformer

Here, we use two interacting transformer decoders to extract feature vectors of targets and drugs, which is called Interformer in short. The structure of Interformer is shown in Figure 3. Each decoder of Interformer consists of one or more identical layers, similar to transformer (Vaswani et al., 2017). Each layer of Interformer consists of three sublayers: a multi-head self-attention layer, an interaction attention layer and a fully connected feed-forward network. The multi-head self-attention sublayer and the feed-forward sublayer are essentially consistent with transformer, except that the mask operation is eliminated to leverage complete drug and target information following the work of Chen et al. (2020).

The interaction attention layer in each decoder of Interformer adopts a multi-head scaled dot attention block to receive the external information from another decoder. The source of external information is the biggest difference between interaction attention layer of Interformer and encode-decoder layer of transformer, where the source of external information is the encoder. A scaled-dot attention block can be expressed as:

$$\text{Attention}(Q, K, V) = \text{softmax}\left(\frac{QK^T}{\sqrt{d_k}}\right)V$$

where $Q$ is the linearly transformed output of the multi head self-attention layer of the decoder, $K$ and $V$ are linearly transformed outputs of the last layer of another transformer decoder, and $d_k$ is the dimension of $K$ and $V$.

$$\text{head}_k = \text{Attention}(QW^Q, KW^K, VW^V)$$

$$\text{MultiHead}(Q, K, V) = \text{Concat}([\text{head}_1, \ldots, \text{head}_h])W^O$$

where $W^Q$, $W^K$, $W^V$ and $W^O$ are parameter matrices. With the Interformer, the representation of each small molecule/target is involved with the information of the corresponding interacted target/drug, which conforms to the real situation of DTI.

2.3.2 Inter-CMPNN

The Inter-CMPNN module is implemented by an improved CMPNN, which is a variant of message passing neural network based on directed graph (Song et al., 2020). CMPNN strengthens the message interaction between nodes and edges through three well designed modules (AGGREGATE, COMMUNICATE, UPDATE) for $L$ iterations:

$$m^k(v) = \text{AGGREGATE}(b^{k-1}(e))$$

$$b^k(v) = \text{COMMUNICATE}(m^k, b^{k-1}(v))$$

$$b^k(e) = \text{UPDATE}(b^k(v), b^k(e), b^{k-1}(e)), k = 1, 2, \ldots, L$$

where $m^k(v)$ is the message obtained by node $v$ in iteration $k$, $b^k(v)$ is the hidden representation of node $v$ in iteration $k$, $b^k(e)$ is the hidden representation of edge $e$ in iteration $k$. After $L$ iterations, one more iteration is executed to exchange information more thoroughly:

$$m = \text{AGGREGATE}(b^L(e))$$

$$b = \text{COMMUNICATE}(m, b^L(v), x)$$

where $x$ is the raw features of atoms. The AGGREGATE module incorporates a message booster, which processes the information of edges with a maximum pooling layer and calculates the

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**Fig. 1.** Architecture of MINN-DTI

**Fig. 2.** The structure of target preprocessing network

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3.1 Datasets

3.1.1 The DUD-E dataset

The DUD-E dataset consists of 22,886 active compounds against 102 targets. For each active compound, 50 decoys are generated, which have similar physico-chemical properties but dissimilar 2-D topologies to the active compound (Mysinger et al., 2012). We processed the DUD-E dataset following the works of Zheng et al. (2020) and Ragoza et al. (2017), we obtained 22,645 positive examples and 1,407,145 negative examples, which were split according to a three-fold cross-validation strategy. Ligands for the targets belonging to the same target family are put into the same fold. We randomly selected the same number of negative samples as the active samples in training to obtain a balanced model, but we used unbalanced data in model evaluation.

3.1.2 The human dataset

The human dataset contains highly credible positive and negative CPI samples extracted by a systematic screening framework according to a similarity rule (Liu et al., 2015). Following the works of Zheng et al. (2020) and Tsubaki et al. (2019), we used a dataset with equal number of positive and negative samples, forming 3,369 positive interactions between 1,052 unique compounds and 852 unique targets. Then, the dataset was randomly divided into a training set, a validation set and a test set according to the ratio of 8:1:1. To evaluate the generalization power of our model on different data, we redivided the human dataset according to molecular scaffold similarities between drugs. The scaffold-based split method implemented in the open source DeepChem package of MoleculeNet (Wu et al., 2018) was used to divide structurally different molecules into training/validation/test sets according to the ratio of 8:1:1.

3.1.3 The BindingDB dataset

The BindingDB dataset (Gao et al., 2018) was a customized subset of the Binding database (Gilton et al., 2016), which is publicly accessible database that mainly contains the interaction affinities between targets and drug-like small molecules. The BindingDB dataset contains 39,747 positive samples and 31,218 negative samples, which was divided into a large training set (50,155 samples), a validation set (5,607 samples) and a test set (5,508 samples). To evaluate the generalization power of our model on novel targets, the data of the test set were divided into two parts to check the model performance according to whether the targets appear in the training set.

3.2 Implementation details and experimental settings

We implemented MINN-DTI with Pytorch 1.7.1 (Paszke et al., 2019). The Adam optimizer was used in training and the learning rate was set to 0.0001 (Kingma and Ba, 2015). The number of residual blocks, the number of filters and the dimension of molecular graph features were set to 32. We explored hyperparameters on the human dataset, and the best parameters are listed in Table 1.
Following the work of Zheng et al. (2020), hyperparameter optimization was not performed for the DUD-E and BindingDB datasets. All experiments were conducted on NVIDIA RTX3090 GPUs.

### 3.3 Performance metrics

Here, different metrics were used on different datasets following previous works (Chen et al., 2020; Zheng et al., 2020). The area under the receiver operating characteristic curve (AUC) was used as the main metric to evaluate our model. Besides, the ROC enrichment metric (RE) that describes the ratio of the true positive rate (TPR) to the false positive rate (FPR) at a given FPR threshold was used for performance assessment on the DUD-E dataset, where FPR was set to 0.5%, 1%, 2% and 5%, respectively as the threshold. Moreover, recall and precision were used for performance evaluation on the human dataset, while the area under precision recall curve (PRC) was applied to performance evaluation on the BindingDB dataset. We repeated each experiment three times with different seeds to calculate the mean and the standard deviation as in the work of Zheng et al. (2020).

### 3.4 Results

#### 3.4.1 Performance on the DUD-E dataset

Here, we compared our model with different types of existing methods on DUD-E. These compared methods include two traditional machine learning-based methods NNscore (Durrant and Dodds on DUD-E. These compared methods include two traditional machine learning-based methods NNscore (Durrant and Dodds, 2006) and RF-score (Ballester and Mitchell, 2010), a docking-based method Vina (Trott and Olson, 2009) and three recent deep learning-based methods 3D-CNN (Ragoza et al., 2017), PocketGCN (Torng and Altman, 2019), and DrugVQA (Zheng et al., 2020). As shown in Table 2, MINN-DTI has significant advantage in terms of AUC and RE. The AUC of MINN-DTI is about 2.5% higher than that of the state-of-the-art method DrugVQA, and over 10% higher than that of the other methods. In terms of RE, MINN-DTI is at least twice as high as all the other methods. These results show that our method is more effective in drug screening, since the number of positive samples in DUD-E is much less than that of negative samples, which is close to the actual situation of virtual screening. In addition, deep learning-based methods are obviously superior to the descriptor-based traditional machine learning methods and the docking-based method in terms of AUC and RE, which suggests that deep learning-based methods are more effective in learning the representations of drugs and targets.

| Hyperparameter | Value |
|----------------|-------|
| Learning rate  | 0.0001|
| Number of residual blocks | 32    |
| Number of filters     | 32    |
| Graph feature size  | 32    |
| Attention heads       | 8     |
| Hidden size of Decoder | 32    |
| Iterations of message passing | 4     |
| Dropout              | 0.2   |

#### 3.4.2 Performance on the human dataset

Here, we compared our method with nine existing methods on the human dataset to further evaluate our model, including k-nearest neighbor (k-NN), random forest (RF), L2-logic (L2), support vector machine (SVM), graph neural network (GNN) (Tsubaki et al., 2019), graph convolution network (GCN), GraphDTA (Nguyen et al., 2021), TransformerCPI (Chen et al., 2020) and DrugVQA (Zheng et al., 2020). The results are presented in Table 3, from which we can see that our model is 0.2% better than the state-of-the-art method DrugVQA in AUC. However, in terms of recall and precision, SVM is the best. Actually, it is difficult to objectively and completely evaluate the performance of a model by using only recall and precision, as the performance of SVM is generally inferior to deep learning models according to many existing works. Given the reliability of AUC, we can still claim that our method is the best one. A newly constructed dataset with a scaffold-based split was also used to train and test the above-mentioned methods. As shown in Table 4, our model consistently exceeds all the competitors in AUC. Compared to the results on the random splitting human dataset, the performance of all models on the scaffold splitting human dataset degrades. However, our model has the slightest drop in AUC, i.e. 1.4%, about half of that of the second-place DrugVQA. These results suggest that more comprehensive extraction of DTI information could help enhance our model’s ability to identify novel interactions.

#### 3.4.3 Performance on the BindingDB dataset

We also compared our model with GCN, GNN (Tsubaki et al., 2017), GraphDTA (Nguyen et al., 2021), DrugVQA (Zheng et al., 2020) and TransformerCPI (Chen et al., 2020) on the BindingDB dataset. As shown in Table 5, our model achieves the highest AUC.

| Model         | AUC   | Recall | Precision |
|---------------|-------|--------|-----------|
| k-NN          | 0.860 | 0.927  | 0.798     |
| RF            | 0.940 | 0.897  | 0.861     |
| L2            | 0.911 | 0.913  | 0.861     |
| SVM           | 0.910 | 0.966  | 0.969     |
| GNN           | 0.970 | 0.918  | 0.923     |
| GCN           | 0.956 ± 0.004 | 0.862 ± 0.006 | 0.928 ± 0.010 |
| GraphDTA      | 0.960 ± 0.005 | 0.882 ± 0.040 | 0.912 ± 0.040 |
| TransformerCPI | 0.973 ± 0.002 | 0.916 ± 0.006 | 0.925 ± 0.006 |
| DrugVQA       | 0.979 ± 0.003 | 0.961 ± 0.002 | 0.954 ± 0.03  |
| MINN-DTI      | 0.981 ± 0.003 | 0.945 ± 0.030 | 0.902 ± 0.045 |

Note: The first row, the percentage before RE is the given threshold of FPR. Best results of the corresponding experiments were represented in bold.

### Table 2. Performance comparison between our model and existing methods on the DUD-E dataset

| Model         | 0.5% RE | 1.0% RE | 2.0% RE | 5.0% RE |
|---------------|---------|---------|---------|---------|
| NNscore       | 0.584   | 4.166   | 2.980   | 2.460   | 1.891 |
| RF-score      | 0.622   | 5.628   | 4.274   | 3.499   | 2.678 |
| Vina          | 0.716   | 9.139   | 7.321   | 5.811   | 4.444 |
| 3D-CNN        | 0.868   | 42.559  | 26.635  | 19.363  | 10.710 |
| PocketGCN     | 0.886   | 44.406  | 29.748  | 19.408  | 10.735 |
| DrugVQA       | 0.972 ± 0.003 | 88.17 ± 4.88 | 58.71 ± 2.74 | 35.06 ± 1.91 | 17.39 ± 0.94 |
| MINN-DTI      | 0.992 ± 0.007 | 175.89 ± 12.02 | 90.77 ± 5.81 | 46.49 ± 2.63 | 19.10 ± 0.71 |

*Means results obtained from the article (Zheng et al., 2020).

*Means results obtained from the article (Chen et al., 2020).

Best results of the corresponding experiments were represented in bold.

### Table 3. Performance comparison between our model and existing methods on the random splitting human dataset

| Model         | AUC   | Recall | Precision |
|---------------|-------|--------|-----------|
| k-NN          | 0.860 | 0.927  | 0.798     |
| RF            | 0.940 | 0.897  | 0.861     |
| TransformerCPI| 0.973 ± 0.002 | 0.916 ± 0.006 | 0.925 ± 0.006 |
| MINN-DTI      | 0.981 ± 0.003 | 0.945 ± 0.030 | 0.902 ± 0.045 |

*Means results obtained from the article (Zheng et al., 2020).
While for new targets, our model still maintains an AUC of the subset without the training targets, which means that the performance of the other models regardless of whether or not the tested targets are true on the DUD-E dataset. We speculate that the main reason for the different results may be due to the different data distribution of the two datasets: the test set of DUD-E has unbalanced positive and negative samples, while human dataset is balanced. The second and third models achieve significantly improved performance compared with the first model, which indicates that adopting transformer or Interformer to extract the interaction information between drug and target is helpful for DTI prediction. The second model is still much more effective than transformer in DTI prediction. As MINN-DTI shows considerable performance advantage over the third model, we believe that the iterative use of Interformer in Inter-CMPNN is beneficial to the extraction of drug and protein interaction information. The ablation results show that MINN-DTI combining Interformer with Inter-CMPNN can indeed improve the prediction performance to a considerable extent.

### 3.5 Ablation study

We conducted ablation studies on the DUD-E and human datasets to check the effectiveness of different configurations of MINN-DTI. All experiments were repeated three times on the divided datasets used above with different seeds to calculate the mean and the standard deviation. Models with different configurations and their performance are presented in Table 6. The first model concatenates the output vectors of DynCNN and CMPNN and uses MLP to predict DTI. The second model replaces Interformer in MINN-DTI with transformer. There are two possible settings: the encoder of transformer receives the information of protein, or vice versa. For mimicking and competing with Inter-CMPNN, the first setting was used to extract drug information during each round of message passing with the decoder in second model. For the third model, only an Interformer is deployed behind the whole CMPNN module instead of deploying an Interformer during each round of message passing using multiple Interformer as MINN-DTI. As shown in Table 6, MINN-DTI maintains the best performance on both datasets and the model without Interformer module (the first model) performs worst. The performance of the third model is close to the second model, with a difference of only 0.002/0.003 in AUC. However, the results are different on the two datasets. The second model is better than the third model on the human dataset, while the opposite is true on the DUD-E dataset. We speculate that the main reason for the different results may be due to the different data distribution of the two datasets: the test set of DUD-E has unbalanced positive and negative samples, while human dataset is balanced. The second and third models achieve significantly improved performance compared with the first model, which indicates that adopting transformer or Interformer to extract the interaction information between drug and target is helpful for DTI prediction. The second model is still much more effective than transformer in DTI prediction. As MINN-DTI shows considerable performance advantage over the third model, we believe that the iterative use of Interformer in Inter-CMPNN is beneficial to the extraction of drug and protein interaction information. The ablation results show that MINN-DTI combining Interformer with Inter-CMPNN can indeed improve the prediction performance to a considerable extent.

### 3.6 Interpretability and visualization

Two representative DTIs were selected to illustrate the interpretability of our model. By inputting the target distance map and the compound graph representations, the model generates multi-head attentions of the target and the compound, and the weights of each amino acid residue and each atom in the target and drug molecule are calculated to identify their importance in the prediction. Protein distance maps and attention bars representing attention weights of residues and atoms are shown in Figure 6. Here, we visualize the top-5 weighted residues of the example target as pink skeletons, and highlight the top-10 weighted atoms by red dots. We found that the significantly weighted residues and atoms are highly consistent with the actual interacting residues and atoms. In CXCR4 protein co-crystal complex 3DU, GLU288, ASP97 and CY5186 form hydrophobic interactions with the drug molecule. These residues and atoms that form the interactions have larger attention weights, which can also be seen in the target ALK5 with co-crystal 3HMM. Meanwhile, there are also residues or atoms with low

![Figure 5](image.png)

**Figure 5.** Performance comparisons on seen and unseen protein targets from the BindingDB dataset. Error bars indicate the standard deviations.
weight, which are considered to have low contribution to the formation of interactions. For example, in the drug attention bar of complex 3ODU, atoms 21–26 of ligand have small weights, and this group is actually exposed to the solvent without participating in the formation of interaction. The above exploration shows that our model can learn and highlight the important target amino acid residues and drug atoms. This helps us to understand DTIs more comprehensively, which is beneficial to the study on the structure-activity relationship and action mechanism of drugs.

4 Conclusion

In this article, we proposed a novel model MINN-DTI to boost DTI prediction by comprehensively mining the mutual impacts between the targets and drugs, which are represented by protein distance maps and molecular graphs, respectively. To this end, a MINN was designed by combining a newly designed Interformer with an improved CMPNN (called Inter-CMPNN) to capture the interacting context of drugs and targets. Compared with the existing models, MINN-DTI achieves the best performance on three public datasets, due to the fact that MINN-DTI can more effectively exploit the interacting information between targets and drugs. We believe that the Interformer and Inter-CMPNN-based MINN should be also effective in other related tasks, including target–target, target–peptide and drug–drug interaction prediction.

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