TripletMultiDTI: Multimodal Representation Learning in Drug-Target Interaction Prediction

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Abstract

Background

In drug discovery, drug-target interaction (DTI) plays a crucial role. Identifying DTI in a wet-lab experiment is time-consuming, labor-intensive, and costly. Using reliable computational methods to predict DTI mitigates the enormous costs and time of drug discovery. Deep learning-based methods for predicting DTI have recently gained more attention.

Results

In this paper, a new multimodal approach to DTI is proposed. It is shown that a discriminative feature representation of the drug-target pair plays the main role in multimodal DTI prediction. To achieve this goal, we propose a new multimodal approach that utilizes triplet loss jointly with the prediction loss. The proposed approach is abbreviately called TripletMultiDTI. The proposed approach has two main contributions: a new architecture that fuses the multimodal knowledge to predict interaction affinity labels and a new loss function that utilizes the triplet loss. Triplet loss encourages clustering of feature space such that similar drug-target pairs have the same feature space and dissimilar drug-target pairs have different feature space.

Conclusions

As a result of our experiments, we were able to improve prediction performance. To this end, the proposed approach is evaluated on a well-known dataset and compared with state-of-the-art multimodal approaches. According to the obtained results, we can perform better than comparable approaches.

Introduction

Drug-target interaction (DTI) in drug discovery and development plays a crucial role [1-4]. Also, DTI is helpful for the exploration of potential new therapeutic effects of existing drugs and understanding their side effects [5-7]. In DTI, a drug activates or inhibits a biological process [8, 9]. Numerous FDA-approved drugs exist, and drugs within the late stage of clinical trials have not identified potential targets [10]. Despite the persisting efforts made by the researchers, the experimental identification of DTIs on a large scale is still costly and time-consuming [11, 12]. Hence, artificial intelligence and computational-based approaches were extensively utilized in drug discovery, especially in DTI prediction [11, 13].

Recent advances in deep learning techniques [9, 14] have led to the development of models with higher predictive abilities in various drug discovery settings [15]. Also, deep learning in handling multimodal data has emerged as a strong model [16]. The concept of "Modality" refers to a specific mechanism of encoding information [17]. In DTI, drug-related and target-related data come in various modalities, making it necessary to analyze them using an appropriate model [18]. Compared to classic machine learning, where all data comes from a single modality [19], deep-learning-based multimodal learning combines the

existing information across several modalities, which has many advantages [16, 20]. Integrating data from heterogeneous information sources in DTI prediction has contributed to performance improvement [21].

Recently, multimodal learning has been applied in related research areas in drug discovery. A method based on multimodal deep autoencoders (MDA) has been proposed by Wang et al. [6] to predict drug-target interactions based on a combination of various topological similarity measures. They showed great improvement in DTI predictive performance. Hooshmand et al. [20] introduced an unsupervised stochastic neural network approach based on multimodal learning named MM-RBM, which identifies drug clusters through information obtained from the chemical structure of small molecules and differentially expressed genes as two diverse modalities. Deng et al. [22] proposed a multimodal deep neural network framework for predicting drug-drug interactions (DDIs), combining various drug features to predict DDI-associated events. Based on the results of the model, it was determined that combining the features results in a significant improvement over using them individually.

Monteiro et al. [4] proposed an approach to the prediction of drug-target binding affinity (DTBA), which uses self-attention layers to capture the biological and chemical contexts of drugs and targets. They also have used cross-attention layers to exchange information and capture the pharmacological contexts of DTIs. Tanoori et al. [23] proposed a method that simultaneously uses five protein-protein similarity measures and five drug-drug similarity measures to predict the binding affinity value of a drug-protein interaction. The proposed method uses a k-nearest neighbor algorithm to identify *k* drug-protein pairs that are most similar to the input interaction, using each pair of drug-drug and protein-protein similarity measures. Mahdaddi et al. [24] proposed a CNN-AbiLSTM model that combines a CNN with attention-based biLSTM to predict drug-target binding affinity. In addition, building a powerful hybrid CNN-AbiLSTM model can be highly complicated and requires careful selection of the hyperparameters.

Zhou et al. [10] proposed a multimodal DTI prediction model based on a joint learning framework that uses heterogeneous networks. By combining the interaction or association information of the heterogeneous network with the drug/target sequence information, it maps the drugs, targets, side effects, and diseases in the heterogeneous network into a common space. In their study [25], Zhang et al. proposed a method that captures molecular structure data for the prediction of DTI using deep learning. They have used a transformer network integrating multilayer graph information; the approach captures the molecular features of a drug's structure to study the interactions between molecules. The WkNNIR method is proposed by Liu et al. [22]. It is based on Weighted k-Nearest Neighbor with Interaction Recovery (WkNNIR). WkNNIR can not only estimate interactions of new drugs and/or targets without retraining but can also recover missed interactions (false negatives). In addition, WkNNIR exploits local imbalance to enhance the influence of more reliable similarities on the interaction recovery and prediction processes. To improve performance, they have proposed a series of ensemble methods that employ various sampling strategies that can be paired with WkNNIR or any other DTI prediction method.

The main step in DTI is to learn a discriminative representation for each drug-target pair. This paper aims to learn a multimodal approach that maximizes the gap between the distribution of samples with different class labels. In order to achieve this, we have designed a new approach that optimizes prediction and triplet loss. In triplet loss, for each input sample (called anchor sample), we should select a sample that has the same label as the anchor sample (called positive sample) and a sample that has a different class label from the anchor sample (called negative sample). Then, we learn a representation for the input sample such that its representation is similar to the positive sample and completely dissimilar from the negative sample. In triplet loss, the way of determining negative samples is important. In this paper, semi-hard negative samples are used. The main contributions of the proposed approaches are as follows:

- The model's input is the drug-drug network, protein-protein network, drug molecule, and target protein sequence.
- Drug-drug and protein-protein networks are fed into two node2vec models to provide a representation for drug and target based on the structure of connection in the network.
- The Triplet loss function is used as an auxiliary loss to learn a better representation.

To be consistent with the literature, throughout this paper, we refer target-target network as the protein-protein network. This paper is organized as follows. At first, the problem formulation is given, and the proposed approach is explained in detail. Then experiments are demonstrated, and the results are analyzed. Finally, the discussion is given.

Methods

The proposed approach is explained in this section. The problem formulation is given first, then each step is explained in detail.

Problem Formulation

Given $\{\left(c^{(i)}, p^{(i)}\right), a^{(i)}\}_{i=1}^{N}$ where $c^{(i)}$ is the i^{th} SMILES format of drug, $p^{(i)}$ is the i^{th} protein sequence and $a^{(i)}$ denotes the corresponding affinity value. Our approach uses the protein-protein interaction (PPI) and drug-drug interaction (DDI) networks as auxiliary knowledge. The main goal is to design a model which takes drug, protein, DDI network, and PPI network as input and then predicts the affinity value of the input drug pair as output.

In our approach, to learn a better model, we could encourage the model to produce the same feature space for similar drug-protein pairs and different feature space for dissimilar drug-protein pairs. In this paper, to consider this issue, we have utilized triplet loss which encourages clustering of feature space and similarity between samples. The overall schematic of the proposed approach is given in Fig. 1. In the following, more details of the proposed approach are given.

Node2Vec

This paper uses the DDI and PPI networks as auxiliary knowledge. To describe this knowledge, Node2vec is utilized. Node2vec provides a framework to learn a representation for each node from highly structured objects like the graph. In other words, it gets a graph as input and then maps each node of a graph to an embedding space such that the representation reflects the local structure of the node with its neighborhood.

In the proposed approach, the PPI network is shown as a graph in which each node is a protein, and the edge between two proteins exists if there is an interaction between corresponding proteins. This network shown by G_{PP} is fed into the Node2vec as input. Nod2vec learns a feature representation for each protein based on its network neighborhood. The output of Node2vec for the PPI network is shown by $O_P^G \in \mathrm{R}^{n_p \times d_p}$ where n_p shows the number of unique proteins in the dataset and d_p shows the dimension of feature representation of each protein. A similar computation is done for the DDI network. The DDI network shown by G_{CC} is fed into the Node2vec as input. The output of Node2vec for the DDI network is shown by $O_C^G \in \mathrm{R}^{n_c \times d_c}$ where n_c shows the number of unique drugs in the dataset and d_c shows the dimension of feature representation of each drug.

Feature Descriptor

This section explains the feature descriptor networks for drug and protein sequences. We use 1D CNN architecture as a feature descriptor for both drug and protein sequences. The detailed architecture of the network is given in Fig. 1. CNN includes convolutional layers and pooling layers. 1D convolutional layer takes 1D sequence as input and then learns multiple filters (i.e., patterns, features) through one direction of the input (common horizontal stride). Pooling layer down-sample its input by reducing the resolution of the feature map, which leads to enlarging the receptive field. Assume that a protein sequence is shown by p into the 1D CNN. The output of CNN for input protein sequence is shown by $o_p^I \in \mathrm{R}^{1 \times d_p}$ where d_p shows the dimension of feature representation of each protein. Similarly, the output of feature descriptor (i.e., 1D CNN) for input drug molecule is shown by $o_c^I \in \mathrm{R}^{1 \times d_c}$ where d_c shows the dimension of feature representation of each drug.

The final feature descriptor for the input protein sequence is obtained by concatenating o_p^I and $O_P^G(p)$:

$$o_p = cocate(o_p^I, O_P^G(p))$$

1

The final feature descriptor for the input drug sequence is obtained in a similar way by concatenating o_c^I and $O_C^G(c)$:

$$o_c = cocate(o_c^I, O_C^G(c))$$

2

Finally, the feature descriptor of the paired drug and protein is computed as follows:

$$o_{d_p, d_c} = cocate(o_p, o_c)$$

3

Triplet Loss Function

The training step in this study incorporates both similar and dissimilar drug-target pairs. It causes the model to learn better feature space representation with margin maximizations. In the training step, one similar pair and one dissimilar pair are retrieved for each drug-protein pair. Therefore, three pairs are fed into the method: an anchor pair (input pair), a positive pair (similar pair), and a negative pair (dissimilar pair). In this case, the triplet loss is also considered in addition to the main loss function (prediction loss error).

The triplet loss is defined as follows:

$$L_{triplet} = \sum \max(dist\left(o_{d_a, t_a}, F_{d_p, t_p}\right) - dist\left(o_{d_a, t_a}, F_{d_n, t_n}\right) + margin, 0)$$

4

where (d_a, t_a), (d_p, t_p) and (d_n, t_n) denote the anchor pair, the negative pair, and the positive pair, respectively. Also, $dist(.,.)$ indicates a distance function which is defined as l_2 function.

Triplet loss encourages the anchor and positive sample representations to be similar together while the anchor and negative sample representations to be away from each other. The overall schematic of the triplet loss function is in Fig. 2. In the triplet loss, there is a $margin$ which enforces different points at a distance greater than the margin do not contribute to the loss function. In the triplet loss function, the way of selecting negative samples is important. In our approach, the semi-hard negative sample technique is utilized. In this case, for each input pair, the following computation is done between each input pair and all other pairs in the batch:

$$dist\left(o_{d_a, t_a}, o_{d_p, t_p}\right) - dist\left(o_{d_a, t_a}, o_{d_n, t_n}\right) - margin$$

5

Then, the *k* top ones with maximum value are chosen as negative samples, and k triplet inputs are provided. Positive samples are selected randomly based on their labels. It should be noted that triplet loss optimization is done in the training step hence utilizing the label of samples is unrestricted.

The prediction loss for the classification task is a categorical cross-entropy. The final descriptor of the paired input is fed into the prediction network shown by N_{pred} to produce the final label of the input sample. The prediction network is a multilayer perceptron that maps the input feature into interaction class labels. The prediction loss is defined as follows:

$$L_1 = \sum_k N_{pred}\left(o_{d_i, p_i}\right)_k \log\left(a_i^k\right)$$

6

At first, the proposed network is optimized using the task prediction function (i.e., categorical cross-entropy loss), and then it is tuned using the triplet loss function and task prediction loss. Iteratively, the process is repeated until convergence is achieved.

Experiments

In this section, the experimental results are given. The proposed approach is evaluated using the dataset provided by Wang et al. [25]. Their data have gathered six heterogeneous networks, including drug-drug interaction network, protein-protein interaction network, drug-protein interaction network, drug-disease association network, protein-disease association network, and drug side-effect association network. Drug-drug and protein-protein interaction networks are extracted from Drugbank Version 3.0 [26] and HPRD database Release 9 [27]. These networks include 708 unique drug nodes and 1512 unique protein nodes. Drug-drug and protein-protein interaction networks include 10036 and 7363 edges. Drug-target interaction network is extracted from Drugbank Version 3.0 [26] with 1923 edges. The drug-disease and protein-disease association networks are extracted from [28] with 199214 and 1596745 edges, respectively. The drug-side effect association network is also extracted from [29] with 80164 edges. All of these networks only provide binary edge weights.

In this paper, to evaluate the model, we have used a wide variety of performance measures, including accuracy, precision, recall, F1 score, the area under the receiver operating characteristic curve (AUC), and the area under the precision-recall curve (AUPRC). Since the applied dataset is imbalanced, utilizing measures like F1 score and AUPRC is essential. The imbalanced ratio of the dataset is high, and hence we need to use a technique to learn a more reliable model with more generalization ability. To handle this issue, similar to Wan et al.[30], the positive samples are oversampled ten times, and the negative samples are under-sampled by randomly selecting the samples such that they have the same size as the positive samples. Also, 10-fold cross-validation is used as an evaluation technique to have a fair comparison with the state-of-the-approaches.

In the proposed approach, hyper-parameter optimization is done using grid search. This optimization is done for the number of filters in drug and protein feature encoder networks search over [16, 32, 64, 128, 256], the size of filters for drug feature encoder network search over [4, 8, 12], and size of filters for protein

feature encoder search over [8, 12, 16], learning rate search over [0.0001, 0.001, 0.01, 0.1]. Also, semi-hard samples are used for batch definition in triplet loss minimization. First, each input's distance from all the samples in the subset is calculated to select semi-hard negative samples. Next, we select k samples with a larger distance from the anchor than the positive but still produce a positive loss. The hyper-parameter optimization for k is done over [3, 5, 7].

In order to evaluate the contribution of each component of the proposed approach, an ablation study is performed. In this case, two variants of the proposed approach are created. The first version of the multimodal knowledge that includes protein-protein and drug-drug interaction networks is not considered. This version is shortly called TripletDTI-uni-modal. In the second version, the triplet loss is not considered during the optimization, which is called DTI multimodal. The obtained results of these two versions and the full proposed approach are given in Table 1.

Table 1
The obtained results on the dataset and its comparison with the state-of-the-art approaches

Algorithms	Precision	Recall	Accuracy	F1-score	AU-PR	AU-ROC
DTI-multi-modal	0.802	0.971	0.865	0.878	0.927	0.940
TripletDTI-uni-modal	0.854	0.931	0.923	0.891	0.954	0.918
TripletMultiDTI	**0.931**	**0.950**	**0.942**	**0.940**	**0.994**	**0.993**

We compare our approach to four state-of-the-art approaches: NeoDTI [30], DTINet [31], HNM [25], and MultiDTI [10]. All of these approaches utilize heterogeneous networks to learn a more effective model for DTI prediction. Table 2 compares the proposed approach with state-of-the-art approaches, and its results are given. As it is shown, the proposed approach gets higher performance in four measures, including AU-PR, AU-ROC, F1-score, and Recall. Most improvement in performance is achieved in the F1-score, which is 0.072 over the MultiDTI and NeoDTI.

Table 2
The obtained results on the dataset and its comparison with the state-of-the-art approaches

Algorithms	Precision	Recall	Accuracy	F1-score	AU-PR	AU-ROC
NeoDTI	0.928	0.716	**0.969**	0.868	0.961	0.947
DTINet	**1.0**	0.048	0.524	0.090	0.914	0.932
HNM	NA	NA	NA	NA	0.572	0.890
MultiDTI	0.876	0.882	0.873	0.868	0.947	0.961
Our Approach	0.931	**0.950**	0.942	**0.940**	**0.994**	**0.993**

Discussion

This paper proposes a new approach to DTI, and its main goal is to learn an effective representation of drug-target pairs. This goal seeks to address the importance of the discriminative representation of drug-target pairs in affinity interaction prediction. This goal is achieved by using a new architecture and loss function. The proposed loss function is the sum of the prediction loss and the triplet loss. The triplet loss encourages the model to learn a representation for the input pair such that this representation is close to the similar ones and becomes far away from dissimilar ones.

A well-known dataset provided by Wang et al. is used to evaluate the proposed approach. The proposed approach performs better than other comparable approaches in experiments. Also, an ablation study is done to show the effectiveness of each proposed module in the approach. Each module performed well according to the results obtained. In this paper, the proposed approach is applied to the classification task, while it simply could be applied to the regression task.

One of the main other advantages of the proposed approach is that it utilizes multimodal knowledge. In this case, the drug molecule and protein sequence are fed as input to the approach, and the protein-protein and drug-drug networks are also fed as auxiliary input. In the proposed approach, the fusion of different modalities is done using a simple concatenate operator. In future work, the way of knowledge fusion could be further explored.

In future work, to determine triplet samples (anchor, positive and negative samples), we are going to do it based on a specific protein or drug. In this case, for the anchor sample with a specific protein (drug), positive and negative samples with different drugs (proteins) are selected. This leads the approach to learn the features in common for drugs (proteins) that interact with a specific protein (drug).

Abbreviations

DTI	Drug-Target Interaction
DDI	Drug-Drug Interactions
MDA	Multimodal Deep Autoencoder
DTBA	Drug-Target Binding Affinity
PPI	Protein-Protein Interaction
AUC	Area Under the Receiver Operating Characteristic Curve
AUPRC	Area Under the Precision-Recall Curve
CNN	Convolutional Neural Network

Declarations

Availability of Data and Materials

The code and sample data for TripletMultiDTI can be found on the GitHub repository: https://github.com/dehghan1401/TripletMultiDTI

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Authors' contributions

AD: conceptualization, data curation, result analysis, methodology, writing, review & editing. KA: formal analysis, writing original draft, programming, visualization & result analysis. SGH&PR: conceptualization, supervision, project administration, review & editing.

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Conflict of Interest

None declared.

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

References

1. Chu Y, Kaushik AC, Wang X, Wang W, Zhang Y, Shan X, Salahub DR, Xiong Y, Wei DQ: **DTI-CDF: a cascade deep forest model towards the prediction of drug-target interactions based on hybrid features**. Brief Bioinform 2021, **22**(1):451–462.
2. Sajadi SZ, Zare Chahooki MA, Gharaghani S, Abbasi K: **AutoDTI++: deep unsupervised learning for DTI prediction by autoencoders**. BMC bioinformatics 2021, **22**(1):1–19.
3. Lin X, Xu S, Liu X, Zhang X, Hu J: **Detecting Drug–Target Interactions with Feature Similarity Fusion and Molecular Graphs**. Biology 2022, **11**(7):967.

4. Monteiro NR, Oliveira JL, Arrais JP: **DTITR: End-to-end drug-target binding affinity prediction with transformers**. Computers in Biology and Medicine 2022:105772.
5. Chen C, Shi H, Jiang Z, Salhi A, Chen R, Cui X, Yu B: **DNN-DTIs: Improved drug-target interactions prediction using XGBoost feature selection and deep neural network**. Computers in Biology and Medicine 2021, **136**:104676.
6. Wang H, Wang J, Dong C, Lian Y, Liu D, Yan Z: **A Novel Approach for Drug-Target Interactions Prediction Based on Multimodal Deep Autoencoder**. Front Pharmacol 2020, **10**:1592–1592.
7. Yazdani-Jahromi M, Yousefi N, Tayebi A, Kolanthai E, Neal CJ, Seal S, Garibay OO: **AttentionSiteDTI: an interpretable graph-based model for drug-target interaction prediction using NLP sentence-level relation classification**. Briefings in Bioinformatics 2022, **23**(4):bbac272.
8. Lee I, Keum J, Nam H: **DeepConv-DTI: Prediction of drug-target interactions via deep learning with convolution on protein sequences**. PLoS Comput Biol 2019, **15**(6):e1007129.
9. Cheng Z, Zhao Q, Li Y, Wang J: **IIFDTI: predicting drug-target interactions through interactive and independent features based on attention mechanism**. Bioinformatics 2022.
10. Zhou D, Xu Z, Li W, Xie X, Peng S: **MultiDTI: drug–target interaction prediction based on multi-modal representation learning to bridge the gap between new chemical entities and known heterogeneous network**. Bioinformatics 2021, **37**(23):4485–4492.
11. Li Y, Huang YA, You ZH, Li LP, Wang Z: **Drug-Target Interaction Prediction Based on Drug Fingerprint Information and Protein Sequence**. Molecules 2019, **24**(16).
12. Abbasi K, Razzaghi P, Poso A, Amanlou M, Ghasemi JB, Masoudi-Nejad A: **DeepCDA: deep cross-domain compound–protein affinity prediction through LSTM and convolutional neural networks**. Bioinformatics 2020, **36**(17):4633–4642.
13. Ye Y, Wen Y, Zhang Z, He S, Bo X: **Drug-Target Interaction Prediction Based on Adversarial Bayesian Personalized Ranking**. BioMed Research International 2021, **2021**:6690154.
14. Dargan S, Kumar M, Ayyagari MR, Kumar G: **A Survey of Deep Learning and Its Applications: A New Paradigm to Machine Learning**. Archives of Computational Methods in Engineering 2020, **27**(4):1071–1092.
15. Wan F, Hong L, Xiao A, Jiang T, Zeng J: **NeoDTI: neural integration of neighbor information from a heterogeneous network for discovering new drug–target interactions**. Bioinformatics 2018, **35**(1):104–111.
16. Ramachandram D, Taylor GW: **Deep Multimodal Learning: A Survey on Recent Advances and Trends**. IEEE Signal Processing Magazine 2017, **34**(6):96–108.
17. Guo W, Wang J, Wang S: **Deep Multimodal Representation Learning: A Survey**. IEEE Access 2019, **7**:63373–63394.
18. Kim J, Park S, Min D, Kim W: **Comprehensive Survey of Recent Drug Discovery Using Deep Learning**. Int J Mol Sci 2021, **22**(18).

19. Razzaghi P, Abbasi K, Shirazi M, Shabani N: **Modality adaptation in multimodal data**. Expert Systems with Applications 2021, **179**:115126.
20. Hooshmand SA, Zarei Ghobadi M, Hooshmand SE, Azimzadeh Jamalkandi S, Alavi SM, Masoudi-Nejad A: **A multimodal deep learning-based drug repurposing approach for treatment of COVID-19**. Mol Divers 2021, **25**(3):1717–1730.
21. Luo Y, Zhao X, Zhou J, Yang J, Zhang Y, Kuang W, Peng J, Chen L, Zeng J: **A network integration approach for drug-target interaction prediction and computational drug repositioning from heterogeneous information**. Nature Communications 2017, **8**(1):573.
22. Deng Y, Xu X, Qiu Y, Xia J, Zhang W, Liu S: **A multimodal deep learning framework for predicting drug-drug interaction events**. Bioinformatics 2020, **36**(15):4316–4322.
23. Tanoori B, Jahromi MZ, Mansoori EG: **Drug-target continuous binding affinity prediction using multiple sources of information**. Expert Systems with Applications 2021, **186**:115810.
24. Mahdaddi A, Meshoul S, Belguidoum M: **EA-based hyperparameter optimization of hybrid deep learning models for effective drug-target interactions prediction**. Expert Systems with Applications 2021, **185**:115525.
25. Wang W, Yang S, Zhang X, Li J: **Drug repositioning by integrating target information through a heterogeneous network model**. Bioinformatics 2014, **30**(20):2923–2930.
26. Knox C, Law V, Jewison T, Liu P, Ly S, Frolkis A, Pon A, Banco K, Mak C, Neveu V *et al*: **DrugBank 3.0: a comprehensive resource for 'omics' research on drugs**. *Nucleic acids research* 2010, **39**:D1035-D1041.
27. Keshava Prasad TS, Goel R, Kandasamy K, Keerthikumar S, Kumar S, Mathivanan S, Telikicherla D, Raju R, Shafreen B, Venugopal A *et al*: **Human protein reference database–2009 update**. Nucleic acids research 2009, **37**:D767-D772.
28. Davis AP, Murphy CG, Johnson R, Lay JM, Lennon-Hopkins K, Saraceni-Richards C, Sciaky D, King BL, Rosenstein MC, Wiegers TC *et al*: **The comparative toxicogenomics database: update 2013**. Nucleic acids research 2013, **41**(D1):D1104-D1114.
29. Kuhn M, Campillos M, Letunic I, Jensen LJ, Bork P: **A side effect resource to capture phenotypic effects of drugs**. Molecular systems biology 2010, **6**(1):343.
30. Wan F, Hong L, Xiao A, Jiang T, Zeng J: **NeoDTI: neural integration of neighbor information from a heterogeneous network for discovering new drug-target interactions**. Bioinformatics 2019, **35**(1):104–111.
31. Luo Y, Zhao X, Zhou J, Yang J, Zhang Y, Kuang W, Peng J, Chen L, Zeng J: **A network integration approach for drug-target interaction prediction and computational drug repositioning from heterogeneous information**. Nature communications 2017, **8**(1):1–13.

Figures

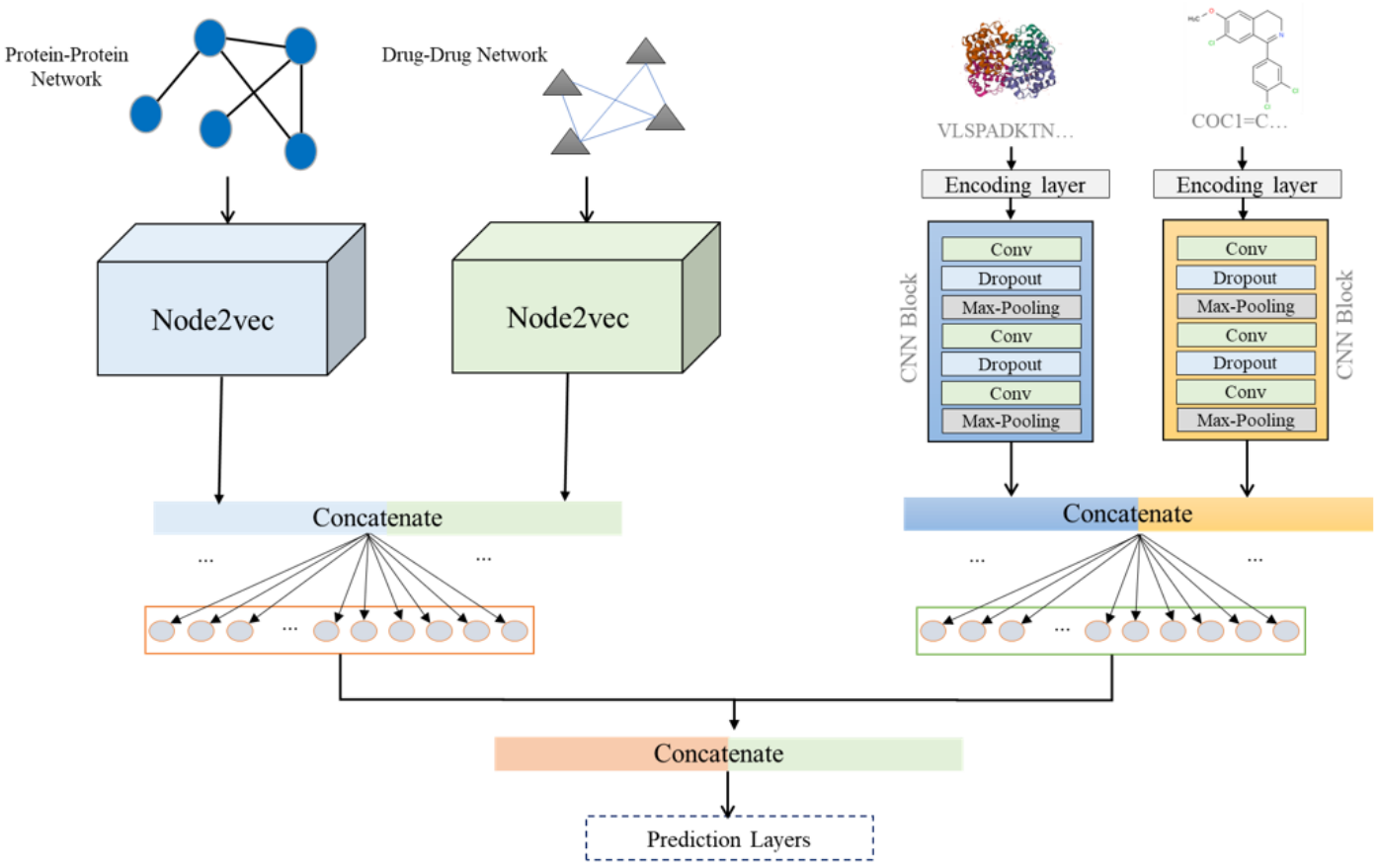

Figure 1

The overall schematic of the proposed approach.

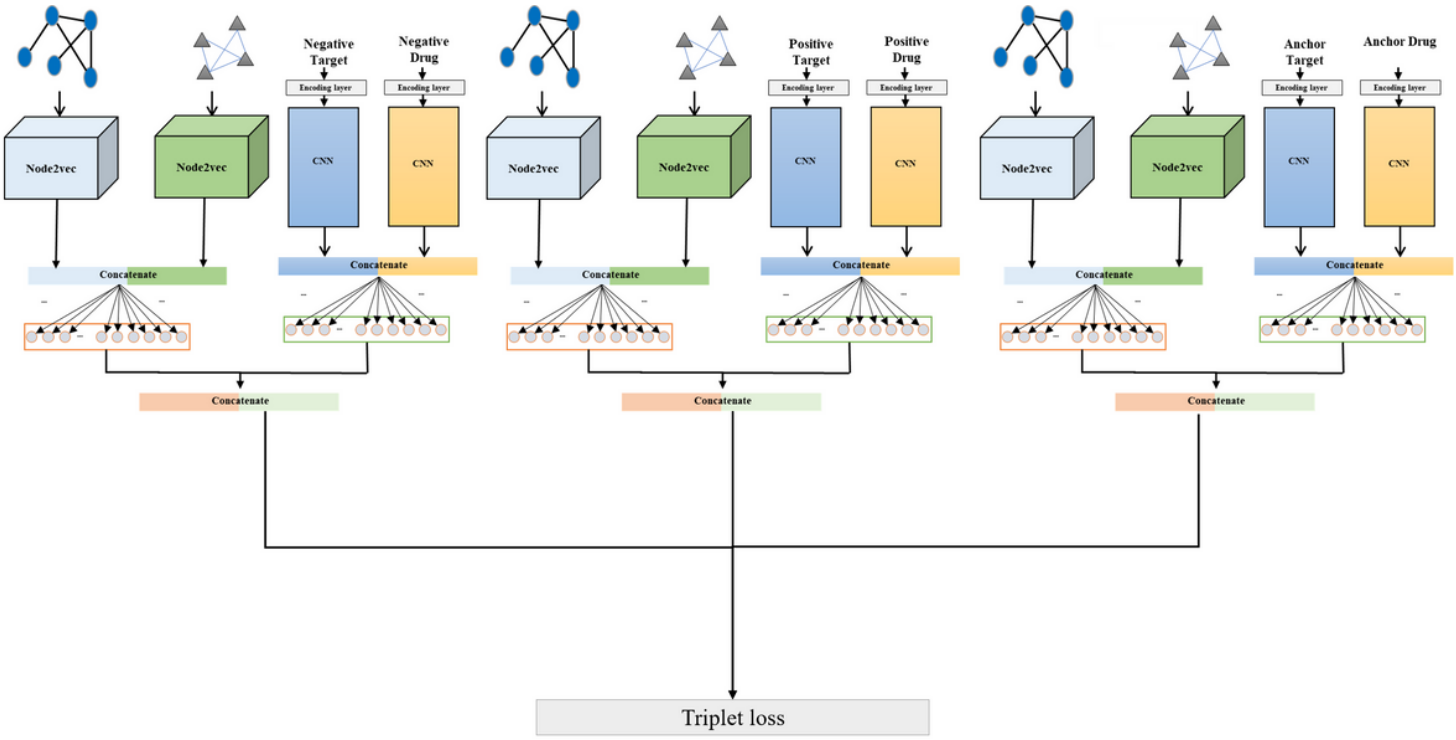

Figure 2

The overall schematic of the triplet loss function.