MiRNA-Disease Associations Prediction Based on Graph Neural Networks

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Abstract

MicroRNAs (miRNAs) are a class of non-coding RNAs that play key roles in various biological processes. Numerous studies have indicated that miRNAs are closely associated with the occurrence, development, and diagnosis of human diseases. Traditional biological experiments are costly and time-consuming. Therefore, effective computational models are increasingly popular for predicting associations between miRNAs and diseases, which can significantly facilitate the diagnosis and prevention of human diseases. However, existing computational methods often overlook the pivotal intermediary role of genes, limiting their focus to miRNAs and diseases, and the issue of data sparsity remains. To address these limitations, we plan to employ a multi-task learning framework that integrates multi-dimensional information such as miRNAs, diseases, and genes for feature extraction and fusion, enhancing the capability to identify miRNAdisease associations for downstream tasks of miRNA-disease association prediction. To evaluate the performance of our model, we compare it with competitive baseline models on a real-world dataset of experimentally supported miRNAdisease associations.

Introduction

MicroRNAs (miRNAs) are a class of non-coding RNA molecules that play a key role in gene regulation in animal species. Discovered more than two decades ago, these small but powerful entities have been implicated in a variety of biological processes and a variety of serious diseases, including cancer and, most recently, the COVID-19 pandemic. Computational methods to study the relationship between miRNAs and diseases are mainly based on network or machine learning, and have made great progress in predicting potential miRNA-disease associations. However, they face challenges due to the sparsity of known associations and the limitations of relying solely on disease or miRNA similarity for model predictions.

To address these challenges, this paper introduces a novel multi-task learning framework that exploits the relationships between miRNA-disease pairs to construct comprehensive disease-gene networks. The contributions of this study are manifold. We propose a multi-task learning model for predicting potential miRNA-disease associations that is innovative in architecture and efficient in application. This model integrates miRNAs, genes, and diseases into a multi-task learning framework, providing a more nuanced understanding of their interrelationships. Empirical validation on established datasets confirms that our model outperforms existing state-of-the-art methods, highlighting its potential to accurately predict miRNA-disease relationships and its utility in advancing the field of bioinformatics.

Related Work

Our research intersects with two primary areas of research in predicting miRNA-disease associations: network-based methods and machine learning-based methods.

Network-based Methods

Network-based approaches largely depend on the computation of various similarities, operating under the hypothesis that functionally similar miRNAs are likely to be associated with similar diseases, and vice versa. This hypothesis was initially put forward by Lu(Lu et al. 2008), laying the theoretical groundwork for studying miRNA-disease associations. Chen (Chen, Liu, and Yan 2012) introduced a global network similarity measure and employed random walks with restart to identify miRNA-disease associations, although this method has limitations when direct connections between miRNAs and diseases are absent. Xuan (Xuan et al. 2015) developed a miRNA network based on functional similarity and addressed the shortcomings of previous methods that neglected local topology information.

Chen (Chen et al. 2016) proposed the WBSMDA model, integrating disease and miRNA similarities to predict associations for diseases without known miRNAs. Li (Li et al. 2018) introduced a label propagation model with linear neighborhood similarity, transforming disease and miRNA similarity into a linear domain. Wang (Wang et al. 2021) developed the HFHLMDA model, employing high-dimensional features and hypergraph learning.

In advancing network-based methods, Alaimo (Alaimo, Giugno, and Pulvirenti 2014) proposed the ncPred method based on a triple network, and Yu (Yu et al. 2020) introduced a threelayer heterogeneous network combined with an unbalanced random walk. However, these methods tend

to overlook the rich structural information within the network.

Machine Learning-based Methods

Machine learning has also been extensively applied to predict miRNA-disease associations. Xu (Xu et al. 2011) used a support vector machine (SVM) to rank prostate cancer miRNAs. Chen (Chen et al. 2015) proposed a model for predicting potential miRNA-disease combinations and inferring their types. Chen (Chen et al. 2018) developed the RFMDA model, a random forest-based approach for predicting unknown associations. Liu (Liu et al. 2021) developed the SMALF framework, integrating network node features with XGBoost for prediction.

Recent studies have explored graph representation learning to capture high-order relationships. Li (Li et al. 2020) proposed the NIMCGCN model, and inspired by the GraphSAGE algorithm, and Li (Li et al. 2021) developed the GAEMDA model. Yan (Yan et al. 2022) proposed the PDMDA approach, utilizing GNNs to extract disease feature representations, while Lou (Lou et al. 2022) presented the MINIMDA method, learning embeddings from multimodal networks integrating multiple biological information.

Despite these advancements, most models do not fully address the sparsity of identified miRNA-disease relationships, which can lead to inaccuracies. To overcome this, we propose a multi-task learning framework, integrating multidimensional information such as miRNAs, diseases, and genes for feature extraction and fusion, aimed at effectively predicting potential miRNA-disease relationships.

Materials and Methods

Our model consists of two sub-networks, miRNA-disease and gene-disease, and the Gaussian similarity method is used to construct the sub-networks.

Human miRNA-disease associations

In our study, the miRNA-disease association is based on HMDD v2.0(Li et al. 2014), an authoritative dataset containing experimentally validated associations between $\mathrm{n_d}$(383) diseases and $\mathrm{n_m}$(495) miRNAs. In this dataset, 5430 miRNA-disease associations have been confirmed. In the experiment, we used a matrix MD with $\mathrm{n_d}$ columns and $\mathrm{n_m}$ rows to represent the relationship between the identified disease and the miRNA. If the corresponding disease is associated with the corresponding miRNA, then the element value in the matrix is 1, otherwise it is 0 (indicating that the relationship is unknown). The matrix MD is represented as follows:

$$\mathrm{MD}(i,j) = \begin{cases} 1, & \text{if } m_i \text{ is associated with } d_j \\ 0, & \text{otherwise} \end{cases} \tag{1}$$

where $\mathrm{m_i}$ represents the i-th miRNA (i-th row in MD) and $\mathrm{d_j}$ represents the j-th disease (j-th column in MD).

Human genes-disease associations

In our study, the original gene-disease relationship was derived from DisGeNet (Piñero et al. 2015). The same disease and related genes as the corresponding miRNA-disease subnetwork are selected to form the gene-disease sub-network, which contains associations between 9286 $\mathrm{n_d}$ (383) disease and $\mathrm{n_g}$ (4395) genes. We create a matrix GD with $\mathrm{n_g}$ rows and $\mathrm{n_d}$ columns. If the disease is related to a gene, the corresponding input value is 1, otherwise it is 0. Similarly, 9286 known disease-related associations are taken as positive samples for the gene-disease subnetwork, and then negative samples were randomly selected from entries with a median GD of 0 0. The matrix GD is represented as follows:

$$\mathrm{GD}(i,j) = \begin{cases} 1, & \text{if } g_i \text{ is associated with } d_j \\ 0, & \text{otherwise} \end{cases} \tag{2}$$

where $\mathrm{g_i}$ represents the i-th gene (i-th row in GD), and $\mathrm{d_j}$ represents the j-th disease (j-th column in GD).

Gaussian interaction profile kernel similarity for miRNAs and diseases in miRNA–disease subnetwork

Since similar diseases are often associated with functionally similar miRNAs (Wang et al. 2010), we use the Gaussian interaction nuclear similarity to simulate the similarity between miRNAs and diseases in the miRNA-disease subnetwork, which is calculated by the information of known mirna-disease associations. The binary vector $\mathrm{Y_m}$ is used to represent the rows in the matrix MD, i.e., the association between a particular miRNA and various diseases in the miRNA-disease subnetwork. The specific definitions are as follows:

$$K_{GIP,m}\left(m_i, m_j\right) = \exp\left(-r_m \left\|Y_{m_i} - Y_{m_j}\right\|^2\right) \tag{3}$$

where $\mathrm{r_m}$ represents the bandwidth of the kernel, which can be calculated by:

$$r_m = r'_m / \left(\frac{1}{n_m}\sum_{i=1}^{n_m}\left\|Y_{m_i}\right\|^2\right) \tag{4}$$

where $\mathrm{n_m}$ is the total number of miRNAs and $\mathrm{r'_m}$ is the normalization constant, which is set to 1.

Similarly, we can obtain the Gaussian interaction profile kernel similarity of the diseases according to the following formula:

$$K_{GIP,d}\left(d_i, d_j\right) = \exp\left(-r_d \left\|Y_{d_i} - Y_{d_j}\right\|^2\right) \tag{5}$$

$$r_d = r'_d / \left(\frac{1}{n_d}\sum_{i=1}^{n_d}\left\|Y_{d_i}\right\|^2\right) \tag{6}$$

where $\mathrm{Y_d}$ is the binary column vector of the matrix MD, which represents the association between the mirna and each

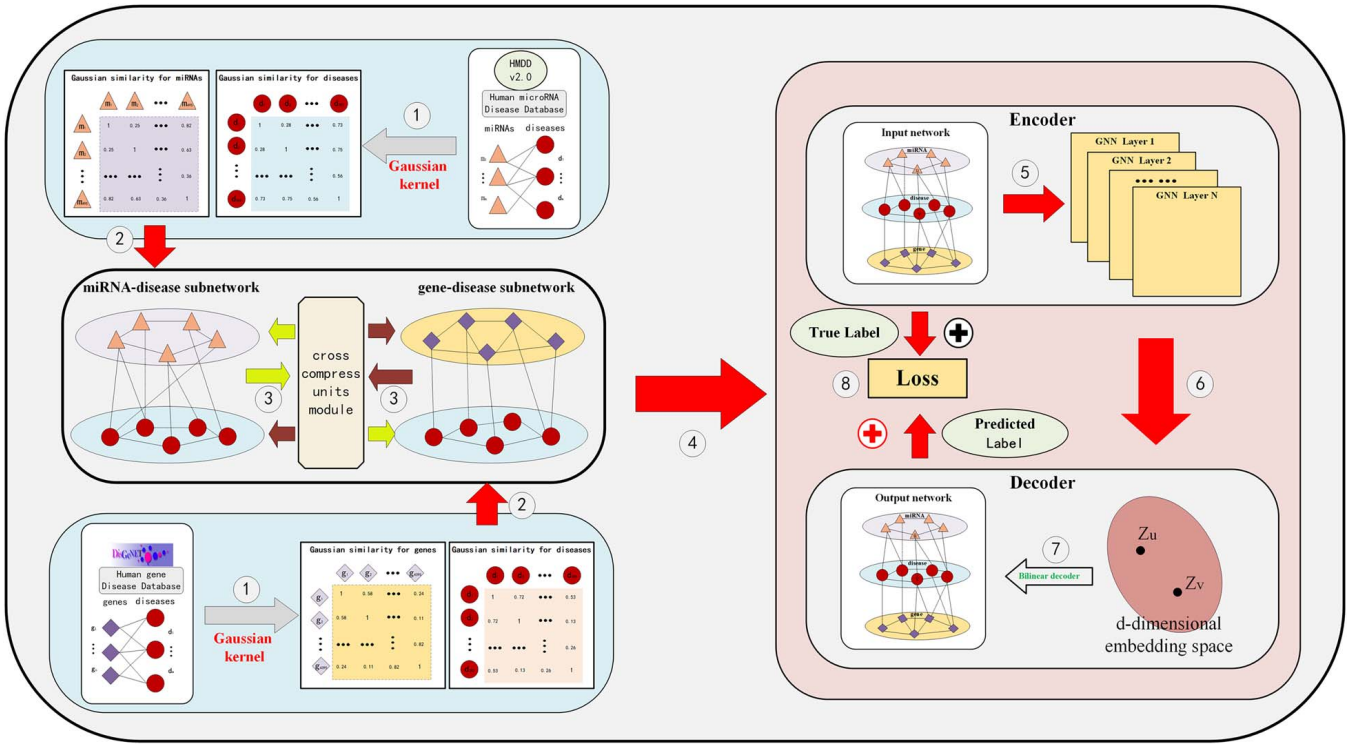


Figure 1: The overall framework of our model.

disease, and n_d is the total number of diseases, and the normalization constant r'_d is set to 1 following previous studies (Van Laarhoven, Nabuurs, and Marchiori 2011).

We used the Gaussian similarities obtained for disease and miRNA as initial node features for disease and miRNA in the miRNA-disease subnetwork, respectively.

Gaussian interaction profile kernel similarity for genes and diseases in the gene–disease sub-network

Previous studies have shown that there is a higher likelihood of physical interactions between gene products of genes associated with similar diseases (Goh et al. 2007). Therefore, we also use the Gaussian interaction profile kernel similarity method to calculate the similarity between genes and between diseases based on the gene-disease subnetwork GD. These two similarities are used as primitive features of disease and gene nodes in the gene-disease subnetwork, respectively.

Model framework

Our model consists of two sub-networks (i.e., miRNA-disease network and gene-disease network), a graph convolutional network encoder, and a bilinear decoder, as shown in Figure 1. Specifically, the entire model can be described in the following six steps:

Step I Following previous studies (Li et al. 2022), we randomly select miRNA–disease pairs from all the unknown miRNA–disease associations as negative samples, and we mine the associated gene–disease pairs in terms of diseases in miRNA–disease sub-network from the DisGeNet database. Taking the miRNA–disease sub-network as an example, the node feature of the i-th miRNA, M(i) and the node feature of i-th disease, $D_1(i)$, can be expressed as follows:

$$M(i) = (x^1_{i,1}, x^1_{i,2}, \cdots, x^1_{i,n_m}) \tag{7}$$

$$D_1(i) = (z^1_{i,1}, z^1_{i,2}, \cdots, z^1_{i,n_d}) \tag{8}$$

where $x^1_{i,j}$ represents the Gaussian similarity between miRNA m_i and miRNA m_j in the miRNA–disease sub-network, $z_{i,j}$ represents the Gaussian similarity between disease d_i and disease d_j.

Step II We designed a projection module to map the features of disease and miRNA nodes into a unified 1024-dimensional space through a transformation matrix. The process of the projection module is as follows(take the miRNA–disease sub-network as an example):

$$H_m(i) = M(i) \cdot W_m \tag{9}$$

$$H_{d1}(i) = D_1(i) \cdot W_d \tag{10}$$

where $H_m(i) \in \mathbb{R}^{1024}$ and $H_{d1}(i) \in \mathbb{R}^{1024}$ are projection features of miRNA node m_i and disease node d_i in miRNA–disease network. The learnable weight matrices $W_m \in \mathbb{R}^{495\times1024}$ and $W_d \in \mathbb{R}^{383\times1024}$ are automatically generated by calling the torch package, according to the size requirements of our designed space vector.

Step III We connect the two sub-networks by cross-compression unit modules and extract auxiliary information from both sub-networks by analyzing the MD and GD matrices.

$$H_{aux-m}(i) = MD \cdot W_{aux-m} \tag{11}$$

$$H_{aux-d1}(i) = GD^T \cdot W_{aux-d1} \tag{12}$$

where $\mathrm{H_{aux-m}} \in \mathbb{R}^{383\times1024}$ and $\mathrm{H_{aux-d1}} \in \mathbb{R}^{383\times1024}$ respectively represent the miRNA and disease nodes in the miRNA-disease network, $\mathrm{W_{aux-m}} \in \mathbb{R}^{383\times1024}$ and $\mathrm{W_{aux-d1}} \in \mathbb{R}^{383\times1024}$, are the weight matrices.

Ultimately, we concatenate the initial features of the nodes with the auxiliary features to form the new features of the nodes, which can be summarized as follows(take the miRNA–disease network as an example):

$$H_M = cat(H_m \cdot H_{aux-m}) \tag{13}$$

$$H_{D1} = cat(H_{d1} \cdot H_{aux-d1}) \tag{14}$$

where $\mathrm{H_M} \in \mathbb{R}^{495\times2048}$ and $\mathrm{H_{D1}} \in \mathbb{R}^{383\times2048}$ represent the integrated feature representations of nodes in the miRNA–disease network.

Step IV We use the Graph Convolutional Network (GCN) encoder to obtain the representation of the nodes of the two sub-networks based on the information of the direct neighbors in the two sub-networks. Here, we have chosen the Chebyshev filter-based method (ChebConv) as the encoder in view of its great expressive power(Defferrard, Bresson, and Vandergheynst 2016).

Step V We use a linear decoder to reconstruct the connection of the heterogeneous graphs in the two sub-networks.

$$\widehat{y}_{md} = Sigmoid(F_{m(i)})^T Q_1 F_{d1(j)} \tag{15}$$

where $\mathrm{\hat{y}_{md}}$ represents the predicted association probability of miRNA node m(i) and disease node d(j) in the miRNA–disease sub-network, $\mathrm{F_m}$ and $\mathrm{F_{d1}}$ represent the final miRNA and disease node embedding representations obtained through the encoder respectively in the miRNA–disease sub-network, and $\mathrm{Q_1}$ denotes a trainable parameter matrix, which is 64×64 dimensions.

Step VI In the following, we will elaborate the six steps in great details. We choose the cross-entropy loss function to measure the error between the true value y and the predicted probability value $\hat{y}$ for each association in the subnetwork.

$$LOSS_{m-d} = -\sum y_{ij} \log \widehat{y}_{ij} + (1-y_{ij}) \log(1-\widehat{y}_{ij}) \tag{16}$$

where $\mathrm{LOSS_{m-d}}$ represents the functional loss in the miRNA-disease sub-network, $\mathrm{\hat{y}_{ij}}$ represents the predicted link probability between disease and miRNA nodes, while $\mathrm{y_{ij}}$ represents the true label of the link.

$$Loss = LOSS_{g-d} + LOSS_{m-d} \tag{17}$$

Then, we use the Loss function in Eq.17 to train the whole model via the back propagation algorithm with an end-to-end manner.

Experiments

In this section, we show the comparison results under different experimental conditions and different models on HMDD v2.0 dataset to demonstrate the effectiveness of our model.

Implementation settings

Our model is implemented in the pytorch(v1.10.2) framework based on the DGL(v0.6.1) platform (Wang 2019).During the model training process, the model parameters are randomly initialized and optimized with the Adam optimizer. We use the grid search method to find the optimal hyperparameters and the learning rate is set to 0.0001 and the weight decay is set to 3×10^{-4}. We chose different dropout rates during training, from 0.1 to 0.9. The entire model was trained for 800 cycles, and the results of the test set were output every 10 cycles. We used a 5-fold cross-validation method to evaluate the performance of the model.

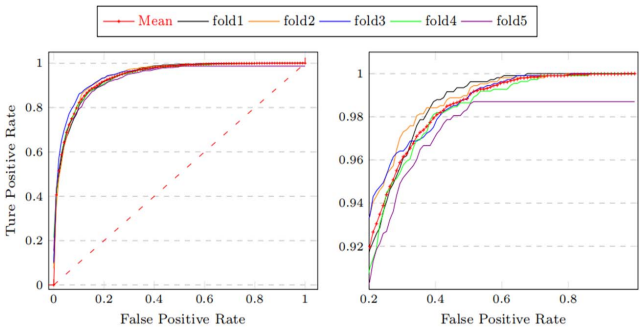
Evaluation metrics

We choose Precision (Prec.), Accuracy (Acc.), Recall, F1 score, AUC, and precision-recall (P–R) curve as the evaluation criteria. The abscissa of the P–R curve represents the recall of the model and the ordinate represents the precision. The larger area in the P–R curve represents better model performance. Table 1 describes the values of various evaluation indicators of our model using 5-fold cross-validation in detail.

Test set	Precision	Accuracy	Recall	F1-score
1	0.8730	0.8656	0.8831	0.8670
2	0.8762	0.8743	0.8745	0.8733
3	0.8520	0.8780	0.8537	0.8751
4	0.8903	0.8660	0.8756	0.8697
5	0.8899	0.8600	0.8630	0.8598
Mean	**87.63%**	**86.88%**	**87.74%**	**86.93%**
	±0.0046	**±0.0065**	**±0.0104**	**±0.0054**

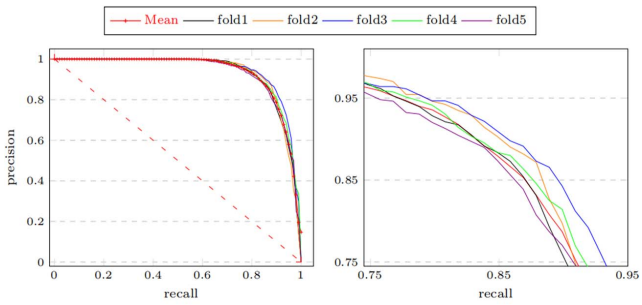
Table 1: 5-fold cross-validation results performed.

Our results show that our model achieves 86.88%, 87.63%, 87.74%, and 86.93% in terms of average accuracy, precision, recall, and F1 score, respectively. In addition, Figure 2 shows the AUC values of the ROC curve of our model under 5-fold cross-validation of 94.03%, 94.67%, 93.75%, 94.62%, and 93.79%, respectively, with a mean of 94.17% ± 0.0040. At the same time, Figure 3 shows the AUC values of the P–R curves of the model under 5-fold cross-validation of 93.27%, 93.53%, 94.55%, 94.10%, and 93.31%, respectively, with a mean value of 93.75% ± 0.0050. To further demonstrate the value of adding gene-disease information to our model, we conducted an experiment in which the miRNA-disease network was kept unchanged while randomly disrupting the gene-disease network to break the original association between genes and disease. The verification results are shown in Table 2. The two networks may still exhibit similar structures within the vector space of disease nodes in the initial non-specific task of multi-task learning



(A) ROC curve (B) Enlarged version of partial ROC curve

Figure 2: ROC curves of our model in 5-fold cross validation.



(A) P-R ROC curve (B) Enlarged version of partial P-R curve

Figure 3: P–R curves of our model in 5-fold cross validation.

(Long et al. 2017). Therefore, we verified that the perturbed gene-disease network can still provide important auxiliary information to the miRNA-disease network.

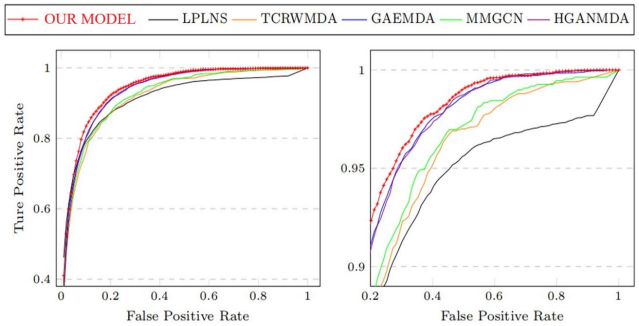
Comparison with other latest methods

We use the AUC values based on the ROC curve to compare the performance of our model with the other state-of-the-art models in a 5-fold cross-validation manner. We have selected the latest and most representative models in this field, which are "Predicting microRNA–disease associations using label propagation based on linear neighborhood similarity" (LPLNS) (Li et al. 2018), "Tree-layer heterogeneous network combined with unbalanced random walk for miRNA–disease association prediction" (TCRWMDA)(Yu et al. 2020), "A graph auto-encoder model for miRNA–disease associations prediction" (GAEMDA) (Li et al. 2021), "Multi-view multichannel attention graph convolutional network for miRN–disease association prediction" (MMGCN) (Tang et al. 2021) and "Hierarchical graph attention network for miRNA–disease association prediction" (HGANMDA) (Li et al. 2022). In order to be a fair experiment, we conducted a 5-fold cross-validation experiment on all five comparison algorithms on the HMDD v2.0 dataset. Figure 4 illustrates the ROC curves of our model compared to the other five algorithms.

Compared to other models, our model fully takes into account the relatively sparse relationships between miRNAs and diseases on the database and utilizes multi-task learning

Test set	Precision	Accuracy	Recall	F1-score	AUC
1	0.8561	0.8487	0.8249	0.8350	0.9275
2	0.8552	0.8565	0.8377	0.8565	0.9362
3	0.8496	0.8620	0.8528	0.8512	0.9265
4	0.8639	0.8638	0.8765	0.8562	0.9340
5	0.8427	0.8500	0.8379	0.8403	0.9284
Mean	**84.81%** **±0.0074**	**85.62%** **±0.0061**	**84.60%** **±0.0176**	**84.58%** **±0.0076**	**93.05%** **±0.0039**

Table 2: 5-fold cross-validation performed (random shuffle gene–disease associations).



(A) Overall performance (B) Partially enlarged version

Figure 4: Comparison of ROC curves in 5-fold cross validation based on HMDD v2.0.

to effectively explore the sparse relationships. Moreover, our model uses the information of gene–disease network to assist the prediction of miRNA–disease improving the overall performance of the model. Therefore, our model achieves excellent results.

Conclusion

A variety of malignant diseases in humans are formed by miRNAs regulating gene expression, and the abnormal expression of miRNAs is a key factor in human diseases. Therefore, accurately predicting the relationship between diseases and miRNAs can promote the development of human health. In this paper, we propose a multitasking learning model for predicting potential miRNA-disease associations, which is an end-to-end trainable graph neural network model using GCN-based autoencoders and decoders. We select the same disease and related genes from DisGeNet as the corresponding miRNA-disease subnetwork to construct a gene-disease subnetwork to assist in the prediction of miRNA-disease relationships. Compared with the five latest classical benchmark models, our proposed model achieves a higher AUC, which verifies the accuracy and reliability of our model in the prediction process.

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