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RESEARCH ARTICLE

Identifying miRNA-disease association based on integrating miRNA topological similarity and functional similarity

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Background: **MicroRNAs (miRNAs) are a significant type of non-coding RNAs, which usually were encoded by endogenous genes with about ~22 nt nucleotides. Accumulating biological experiments have shown that miRNAs have close associations with various human diseases. Although traditional experimental methods achieve great successes in miRNA-disease interaction identification, these methods also have some limitations. Therefore, it is necessary to develop computational method to predict miRNA-disease interactions.**

Methods**: Here, we propose a computational framework (MDVSI) to predict interactions between miRNAs and diseases by integrating miRNA topological similarity and functional similarity. Firstly, the CosRA index is utilized to measure miRNA similarity based on network topological feature. Then, in order to enhance the reliability of miRNA similarity, the functional similarity and CosRA similarity are integrated based on linear weight method. Further, the potential miRNA-disease associations are predicted by using recommendation method. In addition, in order to overcome limitation of recommendation method, for new disease, a new strategy is proposed to predict potential interactions between miRNAs and new disease based on disease functional similarity.**

Results: **To evaluate the performance of different methods, we conduct ten-fold cross validation and *de novo* test in experiment and compare MDVSI with two the-state-of-art methods. The experimental result shows that MDVSI achieves an AUC of 0.91, which is at least 0.012 higher than other compared methods.**

Conclusions: **In summary, we propose a computational framework (MDSVI) for miRNA-disease interaction prediction. The experiment results demonstrate that it outperforms other the-state-of-the-art methods. Case study shows that it can effectively identify potential miRNA-disease interactions.**

Keywords: miRNA-disease association; CosRA index; miRNA functional similarity; recommendation method

Author summary: Rapidly increasing evidences show that miRNAs have close relationships with many diseases. Therefore, identifying miRNA-disease interactions may contribute to understand the pathogenesis of diseases. In this paper, we propose a computational framework to predict miRNA-disease interactions based on recommendation method. The experiment results show that our method outperforms other the-state-of-the-art methods.

INTRODUCTION

MiRNAs are a class of non-coding small RNAs with 20 to 25 nucleotides in length, which play important roles in various biological processes such as cell proliferation, cell differentiation, cell aging, cell development [1]. The

biogenesis of miRNA is like that: firstly, the primary miRNA (pri-miRNA) is generally transcribed from introns (or host gene) by RNA polymerase II. Then, the pri-miRNA will be processed into the precursor miRNA (pre-miRNA) with about 60 nucleotides in length by Drosha nuclease [2]. Further, the pre-miRNA is transported to the cytoplasm by Exportin-5. Finally, the mature miRNA, which can target the mRNA to regulate the expression of gene, is formed from pre-miRNA with RNase III enzyme. During the past decades, increasing studies have shown that miRNAs have close relationships with various human diseases such as breast cancer [3], liver cancer [4], and gastric carcinoma [5]. Therefore, identifying associations between miRNAs and diseases may contribute to uncover the pathogenesis of human diseases.

Since the first discovery of miRNA (lin-4) about 30 years ago, many miRNAs have been identified based on experimental methods [6]. However, these methods are time consuming and expensive. In order to overcome these limitations, some computational methods have been proposed to predict miRNA-disease associations [7–11]. Jiang *et al.* [12] proposed a computational model based on hypergeometric distribution to predict miRNA-disease association by integrating the miRNA functional similarity, disease phenotype similarity network and known miRNA-disease associations. Xuan *et al*. [13] presented a computational method named HDMP, to discover the relationships of miRNAs and diseases based on weighted k most similar neighbors. This method calculated the functional similarity by integrating the similarity of information content of disease terms and phenotype similarity between diseases. Mørk *et al*. [14] developed an approach called miRPD to predict disease-related miRNAs. Chen *et al.* [15] introduced regularized least squares to discover the potential relationships between miRNAs and diseases. Peng *et al*. [16] presented a new method to predict miRNA-disease association by integrating microRNA, disease, gene and environment factor networks. Yan *et al*. [17] proposed a computational approach based on logistic matrix factorization to identify interactions between miRNAs and diseases. Luo *et al.* [18] developed a computational approach based on unbalanced bi-random walk for predicting microRNA-disease associations. Lan *et al*. [19] utilized kernelized Bayesian matrix factorization method to infer potential miRNA-disease associations by computing sequence and functional similarity of miRNA, semantic similarity of disease. Liu *et al.* [20] presented a computational method to predict miRNA-disease interactions based on random walk. Zou *et al*. [21] proposed two methods, KATZ and CATAPULT, to identify potential miRNA-disease associations based on known similarity network analysis. Although all these existing methods have achieved great successes, the predicting accuracy still needs to be improved.

In this paper, we propose a computational framework to predict associations between miRNAs and diseases based on recommendation method. Firstly, the miRNA-miRNA similarity is calculated based on miRNA-disease topological feature and miRNA functional information. The disease-disease similarity is calculated based on disease-gene association. Then, the miRNA similarities are integrated to improve the reliability of miRNA similarity. Further, the potential miRNA-disease associations are predicted by using recommendation method. In addition, to over the limitation of existing recommendation method, a method is proposed for identifying interactions between miRNAs and new disease. In order to evaluate the performance of our method, the ten-fold cross validation and *de novo* test are implemented in experiment. We compare our method with other two the-state-of-the-art methods in term of AUC. The experimental results demonstrate that our method outperform other methods in prediction performance. The case study shows that our method can effectively identify potential miRNA-disease associations.

RESULTS

Evaluation

In this paper, ten-fold cross-validation and *de novo* test are utilized to evaluate the performance of our method. In the ten-fold cross-validation, all known miRNA-disease interactions are randomly divided into ten folds. For each cross validation round, one subset is treated as test samples and the rest nine subsets are regarded as training samples. After completing the test, predicted scores are generated. Then, we rank test samples and unknown miRNA-disease interactions. The corresponding predicted result of test samples is considered as true positive (TP) when the predicted relevance score is greater than the threshold. Otherwise, considered as false negative (FN). Similar, for the unknown miRNA-disease interactions, the corresponding predicted result consider as false positive (FP) when the predicted relevance score is greater than the threshold. Otherwise, considered as true negative (TN). Then, FPR (false positive rates) and TPR (true positive rates) are calculated as follow:

$$TPR = \frac{TP}{TP + FN}, \tag{1}$$

$$FPR = \frac{TN}{TN + FP}. \tag{2}$$

Finally, the receiver operating characteristic (ROC) curve is drew and the area under the ROC curve (AUC) is

calculated to evaluate the performance of method. The higher AUC value is, the better performance is.

Comparison with different predicted methods using ten-fold cross validation

We compare MDVSI with two the-state-of-the-art algorithms (LRLSLDA [15] and BRWH [18]). The result is shown in Figure 1. It can be observed from Figure 1 that MDVSI, LRLSLDA and BRWH achieve AUC of 0.9346, 0.9069 and 0.8393, respectively. It demonstrates that MDVSI outperforms other two methods in the prediction performance.

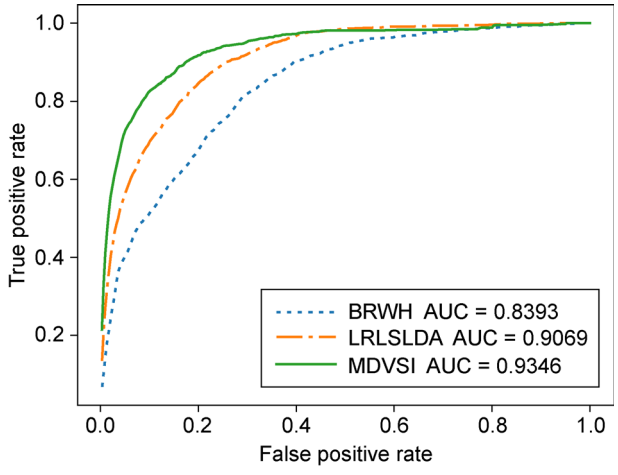

Figure 1. Comparison between MDVSI, LRLSLDA and BRWH by using ten-fold cross validation.

Comparison with different predicted methods using *de novo* test

To evaluate the ability of MDVSI in predicting interactions between miRNAs and new diseases, we conduct the *de novo* test here. In the *de novo* test, all the known miRNA-disease associations of one disease are removed. Then, the interactions are predicted by prediction method. It can be found in Figure 2 that MDVSI achieves AUC of 0.7468 which is 0.003 and 0.01 higher than LRLSLDA and BRWH, respectively. It demonstrates that MDVSI is an effective method for predicting interactions between new disease and miRNAs.

The effect of parameter β

We also test the effect of parameter β, which is used to balance the miRNA topological similarity and miRNA functional similarity in miRNA similarity integration process. The result is shown in the Table 1. It is easy to find that the MDVSI achieves the best performance in experimental result when $\beta = 0.5$.

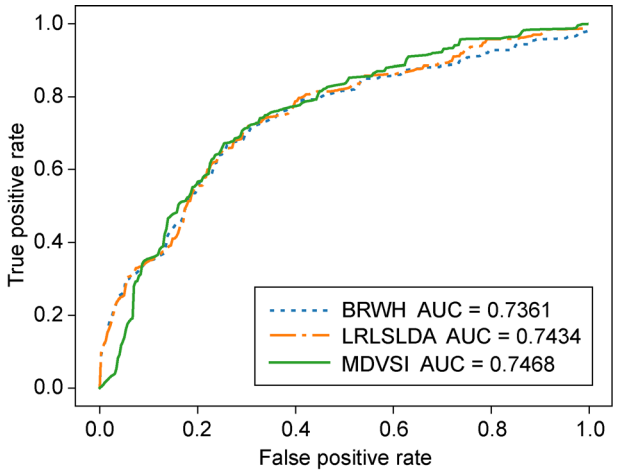

Figure 2. Comparison between MDVSI, LRLSLDA and BRWH by using *de novo* test.

Table 1 Effect of parameters on performance of MDVSI

Parameter	AUC
0	0.9311
0.1	0.9340
0.2	0.9312
0.3	0.9333
0.4	0.9331
0.5	0.9346
0.6	0.9332
0.7	0.9341
0.8	0.9332
0.9	0.9332

The effect of parameter k

In order to test the effect of parameter k, which is used to selecte the predicted interactions between miRNAs and new disease. The result is shown in the Table 2. It can be concluded that our method achieves the best performance when k ranges from 17 to 19.

Case studies

In order to validate the reliability of miRNAs predicted by our MDVSI, we select two important human cancers (lung cancer and breast cancer) as two case studies. We choose the top 50 predicted miRNAs of breast cancer and lung cancer, respectively. Then, we confirm these miRNAs by consulting databases and recent literatures.

Table 2 Effect of parameters *k* on performance

k	AUC
10	0.7195
11	0.7312
12	0.7331
13	0.7376
14	0.7373
15	0.7369
16	0.7451
17	0.7467
18	0.7467
19	0.7467
20	0.7466

Lung cancer is a kind of high death rate cancer for human. It has been proved that miRNAs have important roles in lung cancer. For example, the expression of miRNAs (has-miR-205, has-miR-19a, has-miR-19b, has-miR-30b and has-miR-20a) decreased strikingly after lung SCC surgery [22]. The top-50 predicted miRNAs related with lung cancer are shown in Table 3. It can be approved that 46 out of top 50 on the list are verified in recent literatures. We also discover some interesting miRNAs, such as hsa-mir-127, hsa-mir-9 and hsa-mir-146b. It demonstrates that our algorithm can not only effectively predict known relationships, but also can predict the potential relationships between diseases and miRNAs.

Breast cancer accounts for three percent of human malignancies and the mortality rate continues to increase over the past years. It is the most common malignancies in women all over the world. Accumulating researches have shown that miRNAs play key roles in breast cancer. For example, some studies have found that the higher expression of mature miRNAs (hsa-miR-103, hsa-miR-21-5p, hsa-miR-141, hsa-miR-25, hsa-miR-30b, hsa-miR-30c, and hsa-let-7i) contribute to breast cancer survival [23]. As shown in Table 4, 43 out of top 50 are verified by consulting published literatures. The results demonstrate that MDVSI is a useful tool for identifying the potential disease-associated miRNAs.

CONCLUSIONS

Increasing experimental studies have indicated that

Table 3 The top 50 potential lung cancer related miRNAs predicted by MDVSI

Rank	MiRNA	Evidence	Rank	MiRNA	Evidence
1	hsa-let-7d	PMID: 30675288	26	hsa-mir-218	PMID: 28830450
2	hsa-let-7f	PMID: 24130905	27	hsa-mir-126	PMID: 22009180
3	hsa-let-7e	PMID: 24130905	28	hsa-mir-30d	PMID: 25342220
4	hsa-let-7c	PMID: 23464461	29	hsa-mir-34c	PMID: 30142158
5	hsa-let-7a	PMID: 25214829	30	hsa-mir-9	Unknown
6	hsa-let-7b	PMID: 29849986	31	hsa-mir-29a	PMID: 26676674
7	hsa-let-7i	Unknown	32	hsa-mir-30b	PMID: 25344866
8	hsa-mir-19b	PMID:24130905	33	hsa-mir-214	PMID: 28396596
9	hsa-mir-145	PMID: 28927412	34	hsa-mir-223	PMID: 29163821
10	hsa-mir-132	PMID: 28321148	35	hsa-mir-128b	PMID: 28514100
11	hsa-mir-17	PMID:27735039	36	hsa-mir-192	PMID: 21511813
12	hsa-mir-18a	PMID: 28790336	37	hsa-mir-196a	PMID: 18521189
13	hsa-mir-199a	PMID: 30233883	38	hsa-mir-92a	PMID: 26893365
14	hsa-mir-191	PMID: 20169152	39	hsa-mir-146b	Unknown
15	hsa-mir-30c	PMID: 25344866	40	hsa-mir-155	PMID: 29065541
16	hsa-mir-34a	PMID: 23805317	41	hsa-mir-32	PMID: 25755781
17	hsa-mir-125a	PMID: 20569443	42	hsa-mir-24	PMID: 29850625
18	hsa-let-7g	PMID: 26316738	43	hsa-mir-200b	PMID: 25279705
19	hsa-mir-29b	PMID: 24130905	44	hsa-mir-106a	PMID: 24130905
20	hsa-mir-34b	PMID: 28869603	45	hsa-mir-106b	PMID: 27477696
21	hsa-mir-19a	PMID: 22303398	46	hsa-mir-429	PMID: 24523873
22	hsa-mir-101	PMID: 25210796	47	hsa-mir-219	PMID: 28790336
23	hsa-mir-20a	PMID: 26672767	48	hsa-mir-25	PMID: 29568911
24	hsa-mir-30e	PMID: 28178679	49	hsa-mir-127	Unknown
25	hsa-mir-205	PMID: 22303398	50	hsa-mir-210	PMID: 27557519

Table 4 The top 50 potential breast cancer related miRNAs predicted by MDVSI

Rank	MiRNA	Evidence	Rank	MiRNA	Evidence
1	hsa-mir-429	PMID: 30594253	26	hsa-mir-127	PMID: 27983524
2	hsa-mir-25	PMID: 27959953	27	hsa-mir-9	PMID: 30502282
3	hsa-mir-218	PMID: 29378184	28	hsa-mir-18a	PMID: 30817902
4	hsa-mir-367	PMID: 21810988	29	hsa-mir-219	PMID: 23813567
5	hsa-mir-93	PMID: 28765915	30	hsa-mir-339	PMID: 30683807
6	hsa-let-7d	Unknown	31	hsa-mir-30c	PMID: 25120384
7	hsa-mir-320	PMID:29538612	32	hsa-mir-153	PMID: 28101798
8	hsa-let-7f	PMID: 18812439	33	hsa-mir-194	Unknown
9	hsa-let-7a	PMID:29963109	34	hsa-mir-17	PMID: 28875846
10	hsa-mir-302c	Unknown	35	hsa-mir-296	PMID: 24527800
11	hsa-mir-215	PMID:30194145	36	hsa-mir-145	PMID: 30704524
12	hsa-mir-199a	PMID: 30001527	37	hsa-let-7e	Unknown
13	hsa-mir-302b	PMID: 26842910	38	hsa-mir-214	PMID: 27422604
14	hsa-mir-200a	PMID: 30786836	39	hsa-mir-19a	Unknown
15	hsa-mir-19b	PMID: 30343695	40	hsa-mir-34a	Unknown
16	hsa-mir-302a	PMID: 29435003	41	hsa-let-7b	PMID: 29849944
17	hsa-mir-106b	PMID: 30348127	42	hsa-mir-10b	PMID: 30250531
18	hsa-mir-302d	PMID: 26644266	43	hsa-mir-34b	PMID: 27557899
19	hsa-mir-30d	PMID: 29923255	44	hsa-mir-103	PMID: 28320108
20	hsa-mir-200b	PMID: 30847025	45	hsa-mir-141	PMID: 28440475
21	hsa-mir-125a	PMID: 30670152	46	hsa-mir-20a	PMID: 30092355
22	hsa-mir-30b	PMID: 30154547	47	hsa-mir-383	Unknown
23	hsa-mir-151	PMID: 27930738	48	hsa-mir-338	PMID: 26252944
24	hsa-mir-488	PMID: 27609814	49	hsa-let-7i	PMID: 24699530
25	hsa-mir-135b	PMID: 30665445	50	hsa-let-7c	PMID: 24866763

miRNAs play an important role in various biological processes [24,25]. Therefore, it is important to effectively identify the relationship between miRNA and disease [26,27]. While existing experimental methods for miRNA-disease interaction identification are generally time-consuming and unable to apply to large scale datasets. Therefore, it is demanded to develop computational method for predicting miRNA-disease associations. In the paper, we propose a novel method (MDVSI) to infer relationships between miRNAs and diseases. Firstly, we utilize disease-gene interaction downloaded from HumanNet to calculate disease-disease functional similarity. Then, the miRNA topological similarity is calculated based on miRNA-disease network topological feature. Further, the miRNA functional similarity and miRNA topological similarity are integrated to improve the accuracy of prediction by using recommendation method. In addition, in order to overcome the limitation of recommendation method in predicting interaction of new disease, we propose a new method to predict interactions between miRNAs and new disease based on disease similarity. To evaluate the prediction performance, we compare our method with other two algorithms via using ten-fold cross-validation and *de novo* test. Experimental results show that our model has superior performance than other compared methods for predicting miRNA-disease associations.

MATERIALS AND METHODS

Datasets

The miRNA-disease association is downloaded from HMDD [28]. In the final, we select 271 miRNAs, 137 diseases and 1,395 miRNA-disease associations as gold dataset. The adjacency matrix A is constructed to represent the relationships between miRNAs and diseases, where $A(i, j) = 1$ if miRNA i is associated with disease j, otherwise $A(i, j) = 0$.

We extract disease functional similarity from HumanNet dataset [29], which contains 16,243 genes and 476,399 interactions. The assigned score for paired genes in HumanNet represent the gene functional similarity.

The miRNA functional similarity is downloaded from misim [30]. Then, the miRNA-miRNA functional

similarity network is described as *FM* matrix based on the calculated score. The element of matrix *FM*(*i*,*j*) denotes the similarity score between miRNAs *i* and *j*.

Methods

We propose a computational framework, MDVSI, for miRNA-disease association identification. In the first step, we calculate disease functional similarity based on disease-gene interaction. Then, the miRNA functional similarity and miRNA topological similarity are calculated based on HumanNet and miRNA-disease network topological feature, respectively. Further, the miRNA functional similarity and miRNA topological similarity are integrated to enhance the reliability of miRNA similarity. Finally, the potential miRNA-disease associations are predicted by using recommendation method. In addition, to overcome the limitation of recommendation method for predicting interaction of new disease, we predict associations between new disease and miRNAs based on disease functional similarity. The flowchart of MDVSI is shown in Figure 3.

The disease-disease similarity

It has been proved that human disease has close relationships with gene. Therefore, based on the disease-gene association, we calculate the functional similarity of diseases. For the two genes g_i and g_j, the similarity between g_i and g_j is defined as follow:

$$ew(g_i,\ g_j) = \begin{cases} 1 & \text{if } g_i = g_j \\ cc(g_i,\ g_j) & \text{if } g_i \neq g_j,\ \ g_i \text{ and } g_j \text{ connected} \\ 0 & \text{if } g_i \neq g_j,\ \ g_i \text{ and } g_j \text{ not connected} \end{cases}, \tag{3}$$

where $ew(g_i,\ g_j)$ denotes the similarity between g_i and g_j. $cc(g_i,\ g_j)$ denotes log likelihood score between g_i and g_j which is calculated in HumanNet.

Given two gene sets $G_1 = \{g_{11},\ g_{12},\ \ldots,\ g_{1m}\}$ and $G_2 = \{g_{21},\ g_{22},\ \ldots,\ g_{2n}\}$ associated with disease d_1 and disease d_2, respectively. Then, the score between gene g_{2j} and disease d_1 is defined as follow:

$$GF_{d_1}(g_{2j}) = \max \sum_{i=1}^{m} (ew(g_{1i},\ g_{2j})),\ g_{1i} \in G_1, \tag{4}$$

$$GF_{d2}(g_{1i}) = \max \sum_{j=1}^{n} (ew(g_{1i},\ g_{2j})),\ g_{2j} \in G_2, \tag{5}$$

In the same way, the $GF_{d2}(g_{1i})$ can also be calculated.

Finally, the similarity of diseases d_1 and d_2 is defined as follow:

$$SD(d_1,\ d_2) = \frac{\sum_{j=1}^{n} GF_{d_1}(g_{2j}) + \sum_{i=1}^{m} GF_{d_2}(g_{1i})}{m+n}. \tag{6}$$

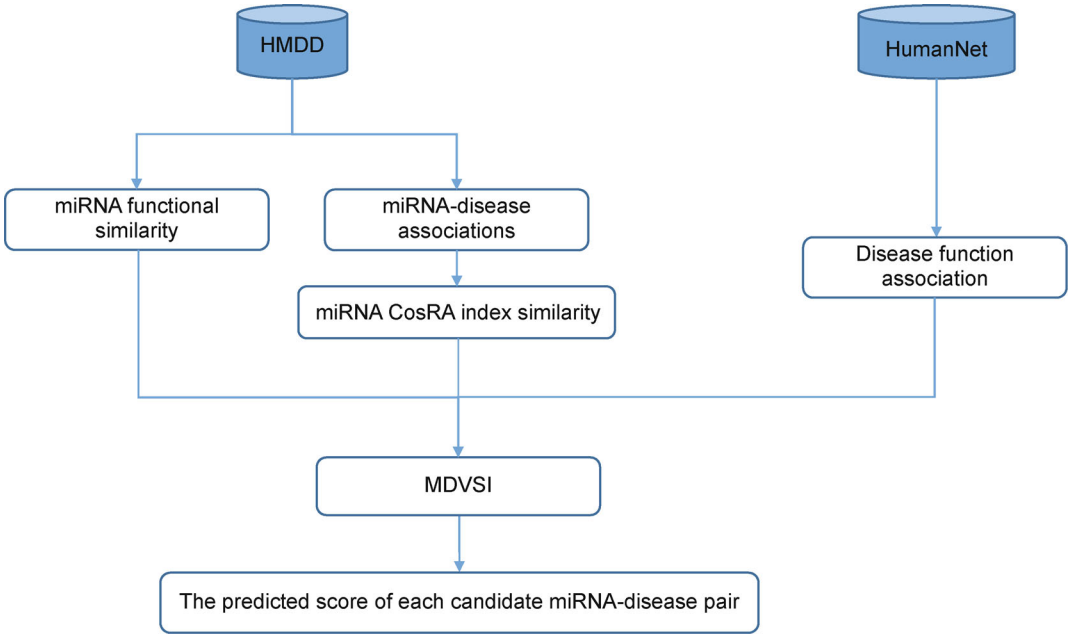

Figure 3. The flow chart for miRNA-disease interactions identification by using MDVSI.

The miRNA-miRNA topological similarity

Considering that miRNA-disease interaction may reflect topological feature, miRNA topological similarity is calculated by using CosRA index [31]. The miRNA topological similarity between miRNA i and j is defined as follows:

$$TM^{\mathrm{Cos}RA}(i, j) = \frac{1}{\sqrt{k_i k_j}} \sum_{x=1}^{p} \frac{a_{ix} a_{jx}}{k_x}, \quad (7)$$

where k_i and k_j denote the degree of miRNA i and j, respectively. k_x denotes the degree of disease x. a_{ix} represents the interaction between miRNA i and disease x ($a_{ix} = 1$ if miRNA i is related with disease x, otherwise $a_{ix} = 0$). a_{jx} denotes the interaction between miRNA j and disease x ($a_{jx} = 1$ if miRNA j is related with disease x, otherwise $a_{jx} = 0$). p is the sum number of diseases.

Integrate miRNA similarities

In order to improve the reliability of miRNA similarity, we integrate miRNA functional similarity and miRNA topological similarity as follows:

$$SM = \beta * TM^{\mathrm{Cos}RA} + (1 - \beta) * FM, \quad (8)$$

where FM denotes the functional similarity of miRNA. β is the parameter to balance two similarities in fusion process.

Predict potential miRNA-disease association

We predict potential miRNA-disease association based on recommendation method [32], which is used to calculate the miRNA-target prediction. According to the known relationships between miRNA and disease, the predicted score of potential relationships between miRNA i and disease j is calculated as follows:

$$\mathrm{Score}(i, j) = SM(i, *) \times A(*, j), \quad (9)$$

where SM denotes the miRNA similarity matrix. A denotes the miRNA-disease association matrix. The higher score is, the closer relationship between miRNA i and disease j is.

Predict interaction between miRNA and new disease

It is well known that the recommendation method is unable to predict new entity (*i.e.*, cold start problem). In order to overcome this limitation, we propose a new strategy for predicting potential interactions between miRNAs and new disease i. For new disease i, the top k most similarity diseases are selected based on disease functional similarity. And then it is considered to be associated with miRNA j if over two similar diseases have relationship with the miRNA j. We use these associations as known knowledge and predict the potential relationships between new disease i and miRNAs by using recommendation method.

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COMPLIANCE WITH ETHICS GUIDELINES

The authors Qingfeng Chen, Zhao Zhe, Wei Lan, Ruchang Zhang, Zhiqiang Wang, Cheng Luo and Yi-Ping Pheobe Chen declare that they have no conflict of interests.

This article does not contain any studies with human or animal subjects performed by any of the authors.

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