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MIRNA DISEASE ASSOCIATION PREDICTION USING HETEROGENEOUS DATA

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***Abstract*— MicroRNAs (miRNAs) are playing very important role in diagnosis and study of diseases. In recent years, many papers been published on MiRNA research. Association of MiRNA with Diseases is one of the interesting topics of the research for biologists. MiRNAs are one of the main regulators in causing diseases. We have many databases showing the associations between Diseases and MiRNAs. Lot of computational methods been developed for predicting Disease related MiRNAs. Still research in this domain is ongoing. We have not come across the computational method, which overcomes all the existing limitations in the previous methods. In our paper, we have taken into account Functional Similarity of MiRNAs, similarity between miRNAs based on Environmental factors, Similarity between miRNAs based on diseases, Disease Semantic Similarity, for the predictions. We have implemented heterogeneous graph inference for predicting disease related MiRNAs in which we have examined about 8 diseases and we were able to get good prediction results**

***Keywords*—** *MiRNA Functional Similarity, Disease Semantic similarity, Environmental Factors, heterogeneous graph*

1. INTRODUCTION

MiRNAs are one of the short non-coding RNAs of length 22 nt. Victor Ambrose [1] discovered them in the year 1960. They are involved in the regulation of gene expression at the post transcription level by degrading their target miRNAs or inhibiting their translation. They play a major role in post-transcriptional regulation of proteins. MiRNA called as multivalent as one MiRNA can target several MRNAs regulating the expression of proteins. It is been confirmed, that they act on several key processes such as cell differentiation, cell cycle progression, and apoptosis. In tumors, some of the MiRNAs act as oncogenes and some as tumor suppressors. MiRNA Disease association prediction is one of the most important topics of research for both biologists and Computer Scientists. We have several databases that are available containing the experimentally confirmed MiRNAs associated with particular diseases. Experimental approaches for finding the disease associations are expensive and time consuming in order to help the biologist many computational methods been developed. Computational methods will predict the potential miRNAs responsible for the diseases while reducing the cost and time of biologists. In the recent year lot of research, publications been published on this topic. Still, we are not able to get the 100% efficient method. In this paper, we have developed computational method for predicting Disease-related miRNAs, which integrates the heterogeneous data such as MiRNA Functional Similarity Data, MiRNA sequence similarity data, Disease Semantic Data, Disease Functional Similarity data and implemented the heterogeneous graph inference method. In which we can predict the MiRNAs for all the disease simultaneously and we can predict MiRNAs for the disease, which has no related MiRNAs.

2. Review of previous methods

Wang et al [11] have developed a method to calculate the functional similarity between the miRNAs based on the MiRNAs disease data and DAG. Many researchers for further predicting disease-related miRNAs have used this method. K Han et al. [27] developed a method called Dismipred, which based on the assumption that functionally related miRNAs related to common diseases. Nalluri et al. [25] developed a tool called DISMIRA using maximum weighted matching model and motif-based analysis determine and prioritize the set of diseases, which most certainly impacted upon the activation of a group of queried miRNAs, in a miRNA-disease network. Xing Chen et al [8] developed a semi-supervised

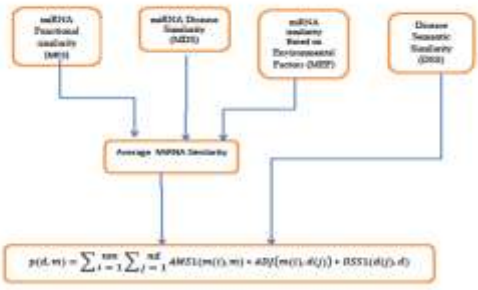
classifier-based method to predict novel disease-related between Environmental factors and MiRNAs. MiRefScan is useful bioinformatics resource to study the relationship among miRNAs, Diseases and Environmental Factors. Ping Xian et al [9] predicted miRNAs associated with diseases based on k most neighbours. In this paper to predict miRNA similarity, they have calculated the functional similarity by incorporating the information content of disease terms and phenotype similarity between diseases. Members of miRNA family or clusters assigned higher weight because it assumed that they are associated with similar diseases. They were able to achieve good performance. Jinan

Ha et al. [12] extracted disease- related miRNAs through propagation algorithm. In this paper, they have combined the functional similarity for miRNA, MiRNA similarity based on Environmental factors, MiRNA Similarity based on Disease. In this paper, it was not possible to predict disease related miRNAs for the diseases, which do not have the related miRNAs. Hong obo she et al [19] have developed the method of walking the interactive to identify human miRNA disease associations through the functional link between targets and disease genes. Chen et al [3] developed Random walk with a restart for predicting miRNA disease associations. In this paper, they made use of global network information. They only considered known miRNA disease association and Functional Similarity between miRNAs for predicting miRNAs associated with diseases. This was one of the drawbacks associated with this method. RWRMDA was unable to predict the miRNAs for the disease, which did not have any associated miRNA. Zhen Sheen et al [4] developed a collaborative matrix factorization method for predicting disease-related miRNAs. Several experimentally confirmed datasets been used in this paper including miRNA disease associations, miRNA functional similarity, and Disease semantic similarity. This method was able to predict the miRNAs for the diseases, which did not have any associated miRNAs. With this method, it was possible to predict the miRNAs for all the diseases simultaneously. This method causes bias to the miRNAs, which are associated with more diseases. Pang et al [7] developed an improved low-rank matrix recovery method for predicting miRNA associated with diseases. MiRNA –MiRNA similarity information, disease- disease similarity information and miRNA family information integrated in this method. Still, there is a possibility improving the performance for this method by reasonably constructing weight matrix. There are several methods, which considered machine learning. Chen et al developed RLSMDA model which is based on semi-supervised learning it calculated semantic similarity between different diseases. This method had trouble in finding appropriate parameters to combine the classifiers from miRNA space and disease space together [27]. Chen et al [16] developed another computational method called RBMMMDA which presented a restricted Boltzmann machine which is a two-layer undirected graphical model consisting of visible and hidden units.it was difficult to learn the complex parameters in this method.

Chen et al [18] developed a model HGIMDA for predicting miRNA disease associations, which integrated the miRNA functional data, Disease semantic data, and Gaussian kernel similarities for MiRNA and Disease. This method was able to predict miRNA for all the diseases simultaneously. There is a possibility of improving performance. Inspired by Chen et al we have implemented the heterogeneous graph inference algorithm by integrating the miRNA Functional Similarity, MiRNA Similarity based on Environmental factors , Similarity between miRNAs based on diseases, Disease Semantic Similarity for predicting the MiRNA disease prediction.

I

Work Flow



AMS1: Average miRNA Similarity(Normalized)
DSS1: Disease Semantic Similarity (Normalized)

3 MATERIALS AND METHOD

The source of various matrices, MFS [10], MEF[12] , MDS [12], DSS [10], ADJ used in the proposed method are as follows.

Disease Semantic Similarity (DSS)

We calculate MiRNA functional similarity according to MISIM (Wang et al., 2010)[10]. They have used the disease semantic similarity and the known associations between miRNAs and diseases. Here, MFS(i,j) is the functional similarity score between miRNAs mi and mj.

MiRNA disease adjacency matrix (ADJ)

We collected the 5430 MiRNA disease association from HMDD database [5]. We represented the MiRNA Disease association as adjacency matrix ADJ (i, j) where $1 \leq i \leq 642$ miRNAs and $1 \leq j \leq 383$ diseases. ADJ is a Boolean matrix with ADJ (i, j) =1 miRNA i is associated with disease j else ADJ (i, j) =0

MiRNA Functional Similarity Matrix(MFS)

The Wang et al's [11] miRNA–miRNA functional similarity scores are downloaded from http://cmbi.bjmu.edu.cn/misim. In this dataset, a functional similarity score for each miRNA pair is calculated based on the observation that genes with similar functions are often associated with similar diseases. MiRNA functional similarity matrix is defined as MFS, where the entity MFS(i,j) in row i, column j is the functional similarity score between miRNAs mi and mj.

MIRNA Disease Similarity(MDS)

The miRNA disease data is downloaded from Human MiRNA Disease Database (HMDD) [30]. The operation of merging the miRNAs of different copies that produce the same mature miRNA into one group, and unifying the name of different mature miRNAs as one miRNA gene has been done after which we get 5430 miRNA association. The disease names are curated based on standard MeSH disease terms [NCBI].

To calculate MiRNA Similarity matrix based on Environmental Factors(MEF)

Experimentally verified miRNA-EF association data from the MirEnvironment database [21] is also used in this work. This database contains more than 2500 entries, including 800 miRNAs, and 260 environmental factors, such as drugs, cigarettes, alcohol, viruses, stress, radiation etc. Inspired by J Ha et al [12], the MiRNA similarity based on EFs is also computed using the equation given here.

$$MEF(i,j) = \frac{MEF(i,j)}{\sqrt{T(i,i)}\sqrt{T(i,i)}} \rightarrow \text{I}$$

Entry MEF(i,j) is the (i, j) entry in the matrix MEF. This is nothing but the number of common EFs between miRNAs mi, mj. T(i,i) denote the sum of common EFs between mi and all other miRNAs. T(j, j) is similarly computed as the jth column sum of MEF

Similarly, disease association matrix MDS is also calculated from a similar equation as (I) using HMDD.

Average MiRNA Similarity matrix AMS is calculated using equation

$$AMS = \frac{MFS(i,j) + MEF(i,j) + MDS(i,j)}{3}$$

Matrices AMS, DSS are used to compute the probabilities of miRNA disease associations. Probabilities been computed, if such an association is reported (HMDD). We took DSS Disease semantic Similarity and Average MiRNA similarity(AMS) and implemented heterogeneous graph Algorithm for predicting MiRNA diseases. For a disease d and miRNA m, it is possible to define their potential association probability as follows if they do not have any known associations

$$p(d,m) = \sum_{i=1}^{nm} \sum_{j=1}^{nd} AMS(m(i),m) * ADJ(m(i),d(j)) * DSS(d(j),d) \rightarrow 2$$

With this equation, we can infer potential association between disease D and miRNA M by summarizing all paths of length equal to three. Iteration of above procedure is considered and equation represented as matrix multiplication. Iteration equation will be

$$P(i+1) = \alpha AMS1 * P(i) * DSS1 + (1-\alpha)A \rightarrow 2$$

Here α is a decay factor similar to that of in Random walk with restart. Its value ranges from 0.1 to 0.9.We have tested for all the values from 0.1 to 0.9. We were able to get the better values for $\alpha = 0.4$ .The association Probability matrix will

converge if AMS and DSS properly normalized according to the Equations 3 and 4

$$AMS1(m(i)m(j) = \frac{AMS(m(i),m(j))}{\sqrt{\sum_{i=1}^{nm} AMS(m(i),m(l)} \sqrt{\sum_{i=1}^{nm} AMS(m(j),m(l)}}$$

→3

$$DSS1(d(i),d(j)) = \frac{DSS(m(i),m(j))}{\sqrt{\sum_{i=1}^{nd} DSS(d(i),d(l)} \sqrt{\sum_{i=1}^{nd} DSS(d(j),d(l)}}$$

→4

After few steps the values will be stable the difference between P(i) and P(i+1) is measured by L1 Norm is less than given cut off we take it as 10-6.

4. RESULTS

With the proposed method we were able to predict the miRNAs for the diseases which did not have any related miRNAs. In the Table 1 we have mentioned the no of confirmed miRNAs out of 50 predicted miRNAs which have been confirmed by DbDEMC database and miRCancer database which contains the repository of experimentally verified miRNAs for diseases.

Table 1:

Disease Name	No of confirmed out of top 50 miRNAS
Breast Cancer	48
Pancreatic Cancer	50
Liver Cancer	49
Ovarian Cancer	48
Brain Cancer	44
Stomach Cancer	49
Thyroid Cancer	45

Top 50 predicted MiRNAs for 3 major diseases are shown in the below tables all the results are confirmed with DbDEMC[10] database and miRCancer[28] which contain the experimentally verified miRNA disease association.

Pancreatic Cancer

Table 2:

SlNo	MiRNA	Confirmed by
1	hsa-mir-296	DbDEMC,miRCancer,
2	hsa-mir-10b	DbDEMC,miRCancer,
3	hsa-mir-25	DbDEMC,miRCancer,
4	hsa-mir-27a	DbDEMC,miRCancer,
5	hsa-mir-34c	DbDEMC,miRCancer,
6	hsa-mir-18a	DbDEMC
7	hsa-mir-218	DbDEMC,miRCancer,
8	hsa-mir-125b	DbDEMC,miRCancer,
9	hsa-mir-17	DbDEMC,miRCancer,
10	hsa-mir-200c	DbDEMC,miRCancer,
11	hsa-mir-210	DbDEMC,
12	hsa-mir-214	DbDEMC,miRCancer,
13	hsa-let-7f	DbDEMC,miRCancer,
14	hsa-mir-126	DbDEMC,miRCancer,
15	hsa-mir-223	DbDEMC,miRCancer,
16	hsa-mir-107	DbDEMC,miRCancer,
17	hsa-mir-106a	DbDEMC,miRCancer,
18	hsa-mir-146b	DbDEMC,miRCancer,
19	hsa-let-7g	DbDEMC,miRCancer,
20	hsa-mir-182	DbDEMC,miRCancer,
21	hsa-mir-200a	DbDEMC,miRCancer,
22	hsa-let-7d	DbDEMC,miRCancer,
23	hsa-mir-200b	DbDEMC,miRCancer,
24	hsa-let-7e	DbDEMC,miRCancer,
25	hsa-mir-150	DbDEMC,miRCancer,
26	hsa-let-7c	DbDEMC,miRCancer,
27	hsa-mir-222	DbDEMC,miRCancer,
28	hsa-mir-199b	DbDEMC,miRCancer,
29	hsa-mir-145	,DbDEMC,miRCancer,
30	hsa-mir-34b	miRCancer,
31	hsa-mir-30c	DbDEMC,miRCancer,
32	hsa-let-7b	DbDEMC,miRCancer,
33	hsa-mir-486	DbDEMC,miRCancer,
34	hsa-mir-146a	miRCancer,
35	hsa-mir-143	DbDEMC,miRCancer,
36	hsa-let-7i	DbDEMC,miRCancer,
37	hsa-mir-181b	DbDEMC,miRCancer,
38	hsa-mir-133b	DbDEMC,miRCancer,
39	hsa-mir-199a	DbDEMC,miRCancer,
40	hsa-mir-204	DbDEMC,miRCancer,
41	hsa-mir-191	DbDEMC,miRCancer,
42	hsa-mir-148a	DbDEMC,miRCancer,
43	hsa-mir-34a	DbDEMC,miRCancer,
44	hsa-mir-212	DbDEMC,miRCancer,
45	hsa-mir-21	DbDEMC,miRCancer,
46	hsa-mir-135b	DbDEMC,miRCancer,
47	hsa-mir-186	DbDEMC,miRCancer,
48	hsa-mir-155	DbDEMC,miRCancer,
49	hsa-mir-197	DbDEMC,miRCancer,

50	hsa-mir-20a	DbDEMC,miRCancer,

Liver Cancer
Table 3:

Sl NO	MiRNA	Confirmed by
1	hsa-mir-10b	miRCancer
2	hsa-mir-34c	DbDEMC,miRCancer
3	hsa-mir-210	DbDEMC,miRCancer
4	hsa-mir-30a	DbDEMC,miRCancer
5	hsa-mir-223	DbDEMC,miRCancer
6	hsa-mir-200a	miRCancer
7	hsa-mir-372	miRCancer
8	hsa-mir-29a	DbDEMC,miRCancer
9	hsa-mir-486	DbDEMC,miRCancer
10	hsa-let-7b	DbDEMC,miRCancer
11	hsa-mir-133b	miRCancer
12	hsa-let-7i	DbDEMC,miRCancer
13	hsa-mir-21	DbDEMC,miRCancer
14	hsa-mir-629	miRCancer
15	hsa-mir-24	DbDEMC,miRCancer
16	hsa-mir-375	miRCancer
17	hsa-mir-122	DbDEMC,miRCancer
18	hsa-mir-296	DbDEMC
19	hsa-mir-125a	DbDEMC,miRCancer
20	hsa-mir-302c	DbDEMC
21	hsa-mir-302b	Unconfirmed
22	hsa-mir-25	DbDEMC,miRCancer
23	hsa-mir-30d	DbDEMC,miRCancer
24	hsa-mir-27a	DbDEMC,miRCancer
25	hsa-mir-18a	miRCancer
26	hsa-mir-218	DbDEMC,miRCancer
27	hsa-mir-125b	miRCancer
28	hsa-mir-17	DbDEMC,miRCancer
29	hsa-mir-205	miRCancer
30	hsa-mir-200c	miRCancer
31	hsa-mir-214	miRCancer
32	hsa-mir-373	miRCancer
33	hsa-let-7f	miRCancer
34	hsa-mir-107	DbDEMC,miRCancer
35	hsa-mir-126	DbDEMC,miRCancer
36	hsa-mir-106a	DbDEMC,miRCancer
37	hsa-mir-182	miRCancer
38	hsa-mir-93	DbDEMC,miRCancer
39	hsa-let-7g	DbDEMC,miRCancer
40	hsa-mir-98	DbDEMC,miRCancer
41	hsa-let-7d	DbDEMC,miRCancer
42	hsa-mir-130a	DbDEMC,miRCancer
43	hsa-mir-330	DbDEMC,miRCancer
44	hsa-mir-423	DbDEMC,miRCancer
45	hsa-mir-139	DbDEMC,miRCancer
46	hsa-let-7e	DbDEMC,miRCancer
47	hsa-mir-150	DbDEMC,miRCancer
48	hsa-let-7c	DbDEMC,miRCancer
49	hsa-mir-222	DbDEMC,miRCancer
50	hsa-mir-199b	DbDEMC,miRCancer

Stomach Cancer
Table 4:

Sl No	**MiRNA**	**Confirmed by**
1	hsa-mir-30d	DbDEMC
2	hsa-mir-205	DbDEMC
3	hsa-mir-210	DbDEMC
4	hsa-mir-30a	DbDEMC
5	hsa-mir-98	DbDEMC
6	hsa-let-7d	DbDEMC
7	hsa-mir-330	DbDEMC
8	hsa-mir-423	DbDEMC
9	hsa-let-7e	DbDEMC
10	hsa-let-7c	DbDEMC
11	hsa-mir-92b	DbDEMC
12	hsa-let-7b	DbDEMC
13	hsa-let-7i	DbDEMC
14	hsa-mir-526b	DbDEMC
15	hsa-mir-197	DbDEMC
16	hsa-mir-339	DbDEMC
17	hsa-mir-381	DbDEMC
18	hsa-mir-99b	DbDEMC
19	hsa-mir-324	DbDEMC
20	hsa-mir-96	DbDEMC
21	hsa-mir-203	DbDEMC
22	hsa-mir-215	DbDEMC
23	hsa-mir-452	DbDEMC
24	hsa-mir-338	DbDEMC
25	hsa-mir-23b	DbDEMC
26	hsa-mir-520b	DbDEMC
27	hsa-mir-518b	DbDEMC
28	hsa-mir-144	DbDEMC
29	hsa-mir-484	DbDEMC
30	hsa-mir-450b	DbDEMC
31	hsa-mir-320e	Unconfirmed
32	hsa-mir-10a	DbDEMC
33	hsa-mir-19b	DbDEMC
34	hsa-mir-345	DbDEMC
35	hsa-mir-367	DbDEMC
36	hsa-mir-193a	DbDEMC
37	hsa-mir-15b	DbDEMC
38	hsa-mir-432	DbDEMC
39	hsa-mir-202	DbDEMC
40	hsa-mir-15a	DbDEMC

41	hsa-mir-217	DbDEMC
42	hsa-mir-26a	DbDEMC
43	hsa-mir-219	DbDEMC
44	hsa-mir-99a	DbDEMC
45	hsa-mir-508	DbDEMC
46	hsa-mir-92a	DbDEMC
47	hsa-mir-181d	DbDEMC
48	hsa-mir-29b	DbDEMC
49	hsa-mir-30e	DbDEMC
50	hsa-mir-23a	DbDEMC

5. CONCLUSION

Our model is capable of predicting the miRNAs for the disease, which does not have any associations. We even implemented our algorithm by deleting all the associations for a given disease. We had tested our algorithm for Breast Cancer, Kidney Cancer and stomach cancer in each case we were able to predict 48,47,49 MiRNAs respectively out of top 50 predictions.

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