LncRNA–disease association prediction through combining linear and non-linear features with matrix factorization and deep learning techniques

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***Abstract*—Long non-coding RNAs (lncRNAs) are the foundation for understanding mechanisms of many human diseases. Considering the limited number of known experimentally verified associations between lncRNAs and diseases, it is appealing to develop accurate and effective computational methods to identify lncRNA-disease associations. Conventional matrix factorization-based methods cannot model complicated associations between lncRNAs and diseases. In this study, we propose a novel computational framework, through combining linear and non-linear features, which is used for lncRNA–disease association prediction. In our model, a conventional matrix factorization method is applied to extract linear features between lncRNAs and diseases. Deep learning techniques (fully connected layers) are applied to extract non-linear features between lncRNAs and diseases. Finally, linear and non-linear features are fused to improve predictive performance. Compared to previous studies, our model can take advantages of the combination of linear and non-linear features between lncRNAs and diseases, and thus can effectively identify potential lncRNA-disease associations. The results show that our method achieves state-of-the-art performance in the leave-one-out cross-validation. The source codes of our method can be found at https://github.com/CSUBioGroup/DMFLDA2.**

Keywords—deep learning, matrix factorization, singular value decomposition, lncRNA-disease associations

I. INTRODUCTION

Long non-coding RNAs (lncRNAs) are a type of non-coding RNAs (ncRNAs) with more than 200 nucleotides in length [1-3]. LncRNAs function in various biological processes including regulation of gene expression, alternative splicing, nuclear organization, and genomic imprinting [4]. Thus lncRNAs play crucial roles in many human diseases. For example, lncRNA "PCGEM1" can regulate cell growth in prostate tumors [5]. lncRNA "MALAT1" is upregulated in early-stage non-small cell lung cancer [6]. Identifying potential lncRNA–disease associations can enhance the study of human complex diseases. Conventional wet-lab experiments are expensive, time-consuming and laborious, which leads to only a small portion of lncRNA–disease associations have been experimentally verified. Thus it is appealing to develop accurate and effective computational methods to identify lncRNA-disease associations.

In recent years, a lot of computational methods for predicting potential lncRNA–disease associations have been proposed [7-17]. Matrix factorization based methods are the most popular methods. Traditional matrix factorization based methods only capture linear features between lncRNAs and diseases. But the associations between lncRNAs and diseases are too complicated, which cannot model such complicated associations by linear models. To tackle this problem, we want to extract non-linear features between lncRNAs and diseases to enhance the representation ability of traditional matrix factorization based methods. Recently, deep learning techniques have been successfully applied in various research fields, such as computer vision, natural language processing and bioinformatics [18-24]. Deep learning techniques are powerful representation learning techniques and are ideal for extracting features in the recommendation problem [25, 26]. Inspired by their success, we use deep learning techniques to extract non-linear features of lncRNAs and diseases. We believe that the complicated relationship between lncRNAs and diseases is hard to capture by pure linear or non-linear features only. Thus if we can use a combination of linear and non-linear linear features, so that they can reinforce each other to better model the complicated associations between lncRNAs and diseases, the performance will be improved. To integrate the advantages of conventional matrix factorization methods and deep learning techniques, we design a deep learning framework to enhance traditional matrix factorization based methods for predicting lncRNA-disease associations. The main idea of our model is to treat the prediction of potential lncRNA-disease associations as a recommendation problem. We use conventional matrix factorization method to obtain linear features of lncRNAs and diseases. In the meanwhile, we use two fully connected layers to learn non-linear features of lncRNAs and diseases. Then the linear and non-linear features of lncRNAs and diseases are fused to a vector, respectively. Last, the hybrid linear and non-linear representation of lncRNAs and diseases are concatenated to estimate new interaction values. There are two advantages of introducing

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deep learning techniques to a conventional matrix factorization model. First, deep learning techniques are good at learning the features of lncRNAs and diseases. Compared with conventional matrix factorization methods, deep learning framework can learn non-linear, more complex features of lncRNAs and diseases. Second, the learned non-linear features can be used as a complement to linear features to better predict lncRNA–disease associations.

To evaluate the performance of our model, we compare our model with four existing competing methods including SIMCLDA [11], MFLDA [10], TPGLDA [27] and LDAP [9]. We carry out a leave-one-out cross-validation on verified lncRNA–disease associations; the results show that the AUC obtained by our model is higher than other methods, which indicates that our method outperforms other competing methods.

II. MATERIALS AND METHODS

In this study, we propose a deep learning framework to enhance traditional matrix factorization methods for predicting lncRNA-disease associations by integrating linear and non-linear features. We first give the problem formulation of lncRNA–disease association prediction. Next, we give the technical details about singular value decomposition, deep learning network, and their combination.

A. Problem formulation

As our previous study [11], we formulate lncRNA–disease association prediction as a recommendation problem. Given M lncRNAs R = {r1, r2, r3,…, rm}, N diseases D = {d1, d2, d3,…, dn}. We construct lncRNA–disease interaction matrix $R \in R^{m \times n}$ based on known lncRNA–disease associations in different datasets. The values in the interaction matrix R are defined as follows:

$$R_{ij} = \begin{cases} 1, & \text{if lncRNA i is linked to disease j} \\ 0, & \text{if the relationship is unknown} \end{cases} \quad (1)$$

The purpose of lncRNA–disease association prediction is to use known and unknown lncRNA–disease associations to predict new associations between lncRNAs and diseases. It's worth noting that in the problem of lncRNA–disease association prediction, the unobserved values (0 in the interaction matrix R) do not mean that there is no relationship between lncRNAs and diseases.

B. Extracting linear features with singular value decomposition (SVD)

Matrix factorization techniques have been proven very useful in recommendation problem. The SVD-based model is one of the earliest models of matrix factorization for recommendation [28]. Thus we use SVD technique to obtain the linear latent representation of lncRNAs and diseases. Below, we describe the details of SVD.

Let M be a real matrix (m×n), the SVD of matrix M is a factorization of three matrices (U, $\sum$, and V^T).

$$M = U \sum V^T \quad (2)$$

where U is a real matrix (m×m), $\sum$ is a diagonal matrix (m×n) with non-negative square roots of the eigenvalues of the product M^TM on the diagonal, and V is a real matrix (n×n). The diagonal elements σ_i are called singular values of matrix M. Note that:

$$\sigma_1 >= \sigma_2 >= ... >= \sigma_n >= 0 \quad (3)$$

If we keep the k largest singular values, we can get an approximation representation of matrix M.

$$M \approx U_k \sum_k (V_k)^T \quad (4)$$

where U is a real matrix (m×k), $\sum$ is a diagonal matrix (k×k), and V is a real matrix (k×n).

C. Extracting non-linear features with deep learning networks

Recently, deep learning techniques have been successfully applied in various fields [29-31]. It is straightforward to apply deep learning techniques to matrix factorization model. Inspired by their work [25, 26], we design a deep learning framework to enhance traditional matrix factorization based methods for predicting lncRNA-disease associations.

In our deep learning framework, the input is the raw interaction matrix R; each row of the interaction matrix R is considered as the raw representation of the corresponding lncRNA, each column of the interaction matrix R is considered as the raw representation of the corresponding disease. Thus the input layer of our deep learning framework consists of two raw feature vectors, i.e. lncRNA and disease feature vectors. The output is the label of a pair of corresponding lncRNA and disease, i.e. the intersection of a row and a column. Then the two feature vectors are fed into two fully connected layers with non-linear activation function to obtain non-linear feature vectors of lncRNAs and diseases. Formally, we denote x and y as the lncRNA and disease raw feature vectors, respectively.

After the first fully connected layer, the outputs O_{x1} and O_{y1} are:

$$O_{x1} = \sigma(W_{x1}x + b_{x1}) \quad (5)$$

$$O_{y1} = \sigma(W_{y1}y + b_{y1}) \quad (6)$$

where σ is the activation function, W_{x1} and W_{y1} are weight matrices, b_{x1} and b_{y1} are bias term.

After the second fully connected layer, the outputs O_{x2} and O_{y2} are considered as the non-linear features of lncRNAs and diseases:

$$O_{x2} = \sigma(W_{x2}O_{x1} + b_{x2}) \quad (7)$$

$$O_{y2} = \sigma(W_{y2}O_{y1} + b_{y2}) \quad (8)$$

where σ is the activation function, W_{x2} and W_{y2} are weight matrices, b_{x2} and b_{y2} are bias term.

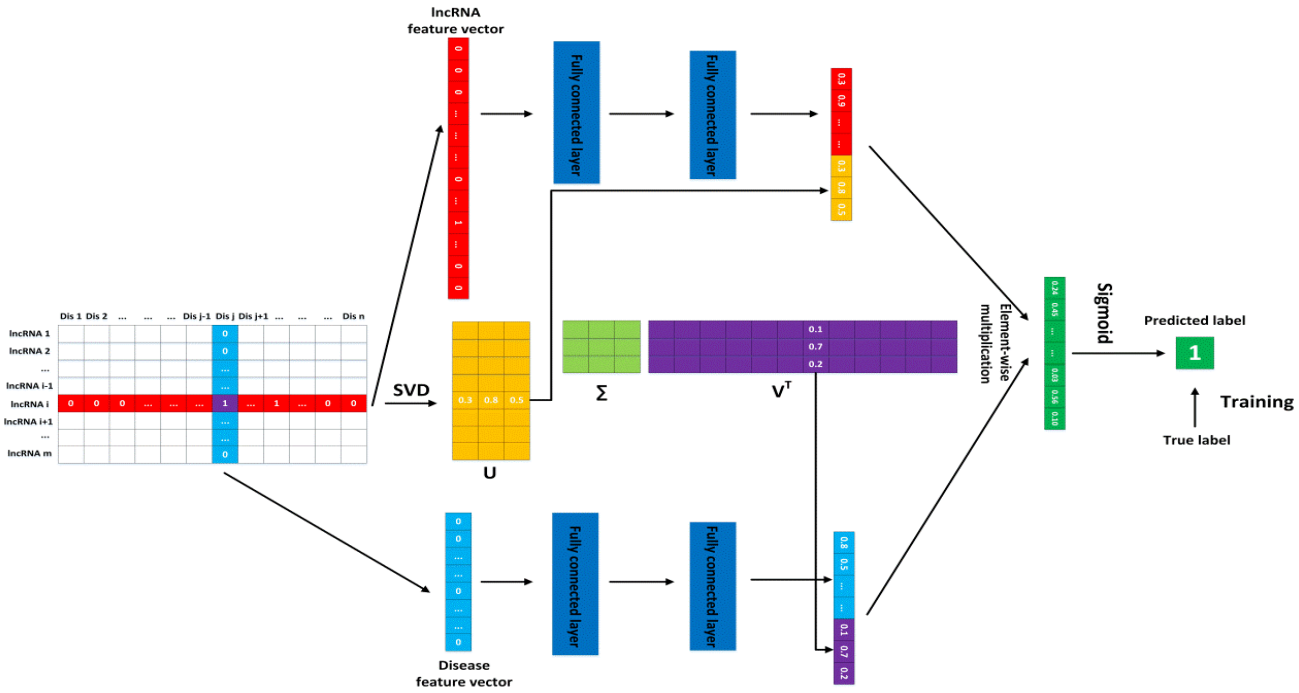

Figure 1. Illustration of fusion of SVD technique and deep learning network for prediction of lncRNA–disease associations. The framework consists of two parts: SVD and deep learning part. The raw interaction matrix is decomposed into three matrices by using the SVD technique. The raw of U matrix and the column of V^T represent linear features of lncRNAs and diseases, respectively. The red vector in the interaction matrix is considered as the raw representation of the corresponding lncRNA. The blue vector in the interaction matrix is considered as the raw representation of the corresponding disease. The two vectors are fed into two fully connected layers to extract non-linear features.

The ReLU activation function is used as the activation function in each fully connected layer, it is defined as follows:

$$\mathrm{ReLU}(x) = \max(0, x) \tag{9}$$

D. *Fusion of SVD technique and deep learning networks*

So far we have obtained two kinds of feature vectors of lncRNAs and diseases. The question then arises: how can we fuse linear and non-linear features in a computational framework. A straightforward idea is to combine them to perform our task. Specifically, the linear and non-linear features of a lncRNA and disease are concatenated to a new feature vector, respectively. Then we use element-wise multiplication to fuse the two new feature vectors into a new vector. Last, the new feature vector is fed into a fully connected layer with a sigmoid activation function to predict potential lncRNA-disease associations. Figure 1 gives a schematic view of the fusion of SVD technique and deep learning network. The process can be formulated as:

$$\mathrm{Lnc}_{\mathrm{new\_feature}} = \begin{bmatrix} U_i \\ O_{x2} \end{bmatrix} \tag{10}$$

$$\mathrm{Dis}_{\mathrm{new\_feature}} = \begin{bmatrix} V_j^T \\ O_{y2} \end{bmatrix} \tag{11}$$

where [ ] is concatenation operation.

$$\mathrm{vec}_{\mathrm{new}} = \mathrm{E} - \mathrm{w\ mul}\ (\mathrm{Lnc}_{\mathrm{new\_feature}}, \mathrm{Dis}_{\mathrm{new\_feature}}) \tag{12}$$

where $\mathrm{E} - \mathrm{w\ mul}$ is element-wise multiplication.

$$\mathrm{sigmoid}(x) = \frac{1}{1+\exp(-x)} \tag{13}$$

$$\mathrm{R}_{\mathrm{pred}} = \mathrm{sigmoid}(\mathrm{vec}_{\mathrm{new}}) \tag{14}$$

We use a binary cross-entropy loss function as loss function, which is the most popular loss function in the classification task. It is defined as follows:

$$\mathrm{Loss} = \sum [\mathrm{R}\log(\mathrm{R}_{\mathrm{pred}}) + (1-\mathrm{R})\log(1-\mathrm{R}_{\mathrm{pred}})] + \lambda(|\theta|\hat{}2) \tag{15}$$

where θ is the weight vector of our deep learning framework, λ is a weight to balance the empirical risk and regularized term.

III. Results

A. *Data sources*

The known lncRNA-disease associations were retrieved from LncRNADisease [32], GeneRIF [33] and Lnc2Cancer [34]. We remove all repeating records and all entries of other organisms by checking names of lncRNAs (according to Lncipedia, lncrnadb, HGNC, and NCBI) and diseases (according to Mesh, UMLS, and NCBI). There are 1583 associations between 577 lncRNAs and 272 diseases; the

density of associations is about 1%. It is very hard to predict potential associations precisely from such a sparse dataset.

B. Evaluation metrics

To evaluate the performance of our model, leave-one-out cross-validation (LOOCV) is applied to our study. In LOOCV method, in each turn, each known lncRNA–disease association is regarded as the test sample while the other lncRNA–disease associations are regarded as the training samples. Then we calculate the true positive rate (TPR) and false positive rate (FPR):

$$\mathrm{TPR} = \frac{\mathrm{TP}}{\mathrm{TP+FN}} \tag{16}$$

$$\mathrm{FPR} = \frac{\mathrm{FP}}{\mathrm{FP+TN}} \tag{17}$$

where TP represents the number of positive samples correctly identified as positive, FP represents the number of negative samples incorrectly identified as positive, TN represents the number of negative samples correctly identified as negative, FN represents the number of positive samples incorrectly identified as negative.

In addition, the receiver operating characteristic (ROC) curve is used to evaluate the performance of our model and other competing methods. ROC curve plots the TPR against the FPR at various threshold settings. AUC is the area under the ROC curve. A large AUC indicates good prediction performance.

C. Implementation details

The SVD is implemented by Scipy library; the deep learning framework is implemented by Tensorflow which is a popular deep learning library developed by Google [35]. We use a 64-dimensional vector to represent linear features of lncRNAs and diseases, and use two fully connected layers to extract non-linear features of lncRNAs and diseases. The neuron numbers of the first and second connected layer are 48 and 32, respectively. The non-linear activation function in the two fully connected layers is the ReLU function. To avoid overfitting, the dropout rate is set to 0.05. The regularization parameter λ is set to 0.001. The batch size is set to 32. The Adam optimizer is used as an optimizer to train our deep learning framework; the initial learning rate is set to 0.001.

D. Comparison with other competing methods

To evaluate the performance of our model, four competing methods (SIMCLDA, MFLDA, TPGLDA and LDAP) are compared. The four competing methods are machine learning-based methods. The details of competing methods are given as follows: SIMCLDA: it integrates prior knowledge of lncRNAs and diseases to estimate the lncRNA–disease association matrix based on inductive matrix completion. MFLDA: it decomposes matrices of heterogeneous data into low-rank matrices based on matrix tri-factorization technique which can exploit intrinsic and shared structure of heterogeneous data. TPGLDA: it uses an allocation algorithm to predict potential lncRNA-disease associations by integrating gene-disease associations with lncRNA-disease associations. LDAP: it uses a bagging SVM to predict potential lncRNA-disease associations by fusing lncRNA similarity and disease similarity data.

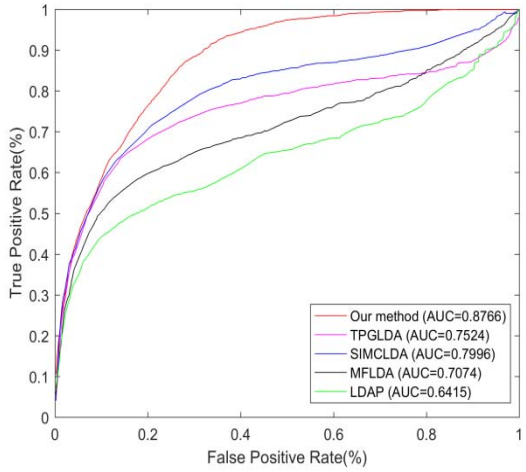

Figure 2. The ROC curves of our method and other competing methods.

Figure 2 plots the ROC curves of our method and other competing methods. Our method, SIMCLDA, TPGLDA, MFLDA and LDAP obtain AUCs of 0.8766, 0.7996, 0.7524, 0.7074 and 0.6415, respectively. Furthermore, we evaluate the numbers of correctly retrieved lncRNA–disease associations. Specifically, each predicted association has a responding rank, if the rank higher than a specified rank threshold k, and then we regard it as a correctly retrieved association. Figure 3 shows the results. In the top 10, 20, 50, and 100, our method can find more correct associations than other competing methods. Therefore, in comparison with the other competing methods, we conclude that our method has made advance in improving the performance of lncRNA-disease association prediction.

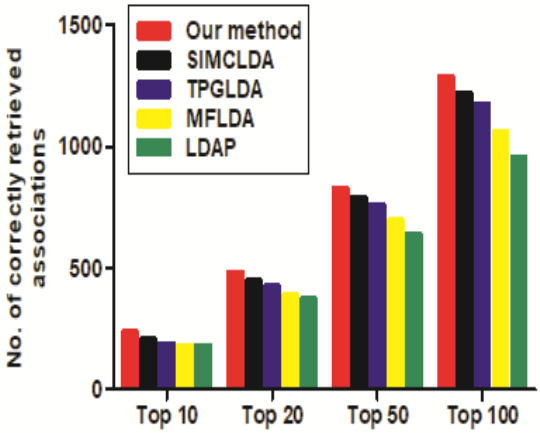

Figure 3. The number of correctly retrieved known lncRNA–disease associations for specified rank thresholds.

IV. Conclusions

Identifying potential disease-related lncRNAs could provide new insights into the role of lncRNA for understanding the mechanisms of diseases at the lncRNA level. Consequently, a lot of computational methods have been proposed to predict lncRNA-disease associations. In this study, we design a deep learning framework to enhance traditional matrix factorization based methods. The conventional matrix factorization method is used to obtain linear features of lncRNAs and diseases. The designed deep learning network is used to learn non-linear features of lncRNAs and diseases. We fuse the linear and non-linear features into new vectors and use them to perform prediction task. In order to evaluate the performance of our method, we compare our method with four competing methods. The LOOCV results show that our method outperforms other competing methods.

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