BMC Bioinformatics

RESEARCH

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Association filtering and generative adversarial networks for predicting lncRNA-associated disease

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Abstract

Background: Long non-coding RNA (lncRNA) closely associates with numerous biological processes, and with many diseases. Therefore, lncRNA-disease association prediction helps obtain relevant biological information and understand pathogenesis, and thus better diagnose preventable diseases.

Results: Herein, we offer the LDAF_GAN method for predicting lncRNA-associated disease based on association filtering and generative adversarial networks. Experimentation used two types of data: lncRNA-disease associated data without lncRNA sequence features, and fused lncRNA sequence features. LDAF_GAN uses a generator and discriminator, and differs from the original GAN by the addition of a filtering operation and negative sampling. Filtering allows the generator output to filter out unassociated diseases before being fed into the discriminator. Thus, the results generated by the model focuses only on lncRNAs associated with disease. Negative sampling takes a portion of disease terms with 0 from the association matrix as negative samples, which are assumed to be unassociated with lncRNA. A regular term is added to the loss function to avoid producing a vector with all values of 1, which can fool the discriminator. Thus, the model requires that generated positive samples are close to 1, and negative samples are close to 0. The model achieved a superior fitting effect; LDAF_GAN had superior performance in predicting fivefold cross-validations on the two datasets with AUC values of 0.9265 and 0.9278, respectively. In the case study, LDAF_GAN predicted disease association for six lncRNAs-H19, MALAT1, XIST, ZFAS1, UCA1, and ZEB1-AS1-and with the top ten predictions of 100%, 80%, 90%, 90%, 100%, and 90%, respectively, which were reported by previous studies.

Conclusion: LDAF_GAN efficiently predicts the potential association of existing lncRNAs and the potential association of new lncRNAs with diseases. The results of fivefold cross-validation, tenfold cross-validation, and case studies suggest that the model has great predictive potential for lncRNA-disease association prediction.

Keywords: LncRNA-disease association prediction, Generative Adversarial networks, Filtering associations, Negative sampling

Introduction

Biologists first discovered the existence of long non-coding RNA [1] (lncRNA) in 1990s, which opened new doors for biomedical research. Long non-coding RNAs, which are more than 200 nucleotides in length, are involved in numerous biological processes, such as chromatin modification, cell proliferation, and transcriptional regulation [2]. A relationship exists between lncRNA and disease, such that mutations can lead to many diseases, such as lung cancer [3], cardiovascular diseases [4], and neurodegenerative diseases [5]. Therefore, the study of lncRNA-disease association can clarify the functions of lncRNA, and facilitate the prevention, diagnosis and treatment of human diseases. Unfortunately, biological experiments to prove the association between lncRNA and diseases are often costly, and this and time constitute major obstacles. Alternatively, computational methods can efficiently study the association of lncRNA with diseases. Current popular methods of research involve two categories: machine learning and predictive biological networks.

Recently, machine learning is a leading edge as exemplified by bioinformatics. Zhao et al. [6] developed a computational method based on a simple Bayesian classifier of lncRNA association data and a genome that achieved excellent results. However, their classifier requires on negative samples, which affects the model's performance. Lan et al. [7] integrated multiple data sources of lncRNA and diseases, and used multiple approaches to calculate lncRNA and disease similarity for different data sources. They used a SVM classifier and organized it into a web server LDAP, by feeding RNA sequences into LDAP to make predictions. Biswas et al. [8] offered a method that used a non-negative decomposition matrix and multiple association data and expression profile data. Their low-rank computational model well described the association between two-dimensional matrices. In addition, an idea has been adopted by many studies that diseases or lncRNAs with similar properties may have the same association object. Chen et al [9]. constructed a semi-supervised framework, LRLSLDA, based on lncRNA and disease similarity. Advantageous, the semi-supervised model did not entirely rely on data labels. Although the method discovered potential associations without negative samples, the model has many parameters, and the choice of parameters will inevitably affect the prediction results. Finally, Chen et al. [10] developed two semantic similarity-based models, LNCSIM1 and LNCSIM2, and organically combined them with the LRLSLDA [9] model, which significantly improved model performance.

Biological networks usually build various association or similarity networks. The most common methods are based on lncRNA disease-association, lncRNA similarity, and disease similarity networks. For example, RWRlncD [11] uses lncRNA functional similarity networks and random wandering (RWR) to make a prediction, but its biggest drawback is that it cannot be applied to disease prediction without known associations. Geng et al. [12] constructed a heterogeneous network of lncRNAs, miRNAs, and diseases to discover potential associations. The greatest advantage of the heterogeneous network is that features of multiple nodes can be fused to make predictions more accurate. Yao et al. [13] constructed a multilayer composite network (LncPriCNet) on multiple interactions data. They used a RWR method to mine potential associations, and LncPriCNet still maintained advantages in the face of insufficient information on lncRNAs due to the support of the multilayer composite network. lncRDNetFlow [14] integrated multiple source networks to predict lncRNA disease associations, and in the absence of known associations.

Both types of methods require lncRNA-disease association data. Because verified biological experimental association data are limited, researchers must use lncRNA expression profiles, tissue specificity, gene location, etc. to predict associations. Li et al. [15] used gene locations to predict the association of lncRNAs with vascular disease. The drawback of their method is that it is limited by gene location information, and because there is no guarantee that the lncRNAs have adjacent genes, even if there are adjacent genes, they are not necessarily associated. Liu et al. [16] proposed using disease and lncRNA expression profiles that can be independent of known lncRNA-disease relationships, but the few associated gene records limit its application.

Recent attention has focused Generative Adversarial Networks (GANs). GANs consist of a generator and a discriminator, which can be trained to generate samples extremely similar to the original data [17]. GANs have no dimensional requirement on the input of the generator, and only require a gradient back-propagation to train the model, avoiding the use of complex Markov chains. This iterative approach has spread to the natural language processing and recommendation system. GANs has the advantage of semi-supervised learning. Most of the data in the recommendation system yield only positive feedback, which is ideal for training with semi-supervised learning. Currently, many GAN recommendation models have emerged, such as IRGAN [18], GraphGAN [19], PSGAN [20], APL [21], and CFGAN [22]. Numerous studies have shown that these models obtain superior results in the recommendation domain compared to baseline models. In this paper, lncRNA-disease association data and user-item recommendation data have similar properties, i.e., prediction of unknown associations based on known association data. So it is reasonable to assume that for the same sparse lncRNA-disease association data, GAN-based association prediction algorithms have significant advantages over supervised learning. Notably, Du et al. [23] offered LDA-GAN for lncRNA-disease association prediction. It uses the Gumbel-SOFTMAX technique to construct separable processes to simulate discrete sampling.

Inspired by LDA-GAN and CFGAN. The application of LDA-GAN in lncRNA disease association prediction guided our study, but the inability to directly back-propagate gradients during model training also posed many inconveniences. In contrast, CFGAN with real-valued vector adversarial training achieves better prediction results, which provides a new idea for our research. Unlike CFGAN, our model needs to process lncRNA sequence data and obtain effective implicit feature information, so network structures that can extract sequence features need to be introduced in the design of generators and discriminators. Meanwhile, considering the sequence characteristics of lncRNA nucleotide sequences, this paper combined Doc2Vec and fully connected neural network to optimize the generator and discriminator, so that lncRNA sequence features is able to more accurately participate in the generation and determination of lncRNA-disease association. we offer LDAF_GAN, a method for lncRNA-associated disease prediction based on association filtering and GANs. The filtering involves a dot product of the generated results of the generator with real data (retaining the part of the association matrix that corresponds to 1 in real data). Thus LDAF_GAN only focuses on associated data. Negative sampling assumes that values of 0 in the association matrix have no association, and the remaining values have unknown associations. By adding a regular term to the loss function, the generator cannot generate all-1 vectors, which ultimately improves the generative power of LDAF_GAN. Experimental results reveal that LDAF_GAN has fivefold cross-validation AUC values over 91% and tenfold cross-validation AUC values over 92% on four trial datasets. Further, disease associations for six common lncRNAs predicted by LDAF_GAN reveal that accuracy can achieve 100%, 80%, 90%, 90%, 100%, and 90% for H19, MALAT1, XIST, ZFAS1, UCA1, and ZEB1-AS1, respectively.

Methods

Generative adversarial networks

GAN architecture [17] of the LDAF_GAN model, which was built to fit our data, was not based on a fixed structured model, but rather an adversarial framework. The structure of the sub-model depended on the type of data. Parameter definitions are listed in Table 1.

Generative network

LDAF_GAN mainly consisted of a generative and discriminative networks. The former was a multilayer, fully connected neural network denoted as $G(\theta)$. When LDAF_GAN was trained on dataset1, the input was represented as $G(\theta, z)$, where θ was the parameter of the generator and z the random noise. Next, the output of G was expressed as ld_r_g (i.e., represents the result of the random noise z input to the generator and then output by the softmax function), which had the same dimension as the noise dimension. When LDAF_GAN was trained on dataset2, the input was represented as $G(\theta, \{z, c\_seq\})$, where c_seq denoted the lncRNA sequence feature, “{}″ denoted the connection noise z, and the lncRNA sequence feature was c_seq, and the output of G was $ld\_seq\_r_g$.

Discriminative network

Discriminator network was also a multilayer fully connected neural network that had the same input dimensions, but the output dimension was 1. Accordingly, $D(\phi)$ was used to

Table 1 Parameter definitions for the LDAF_GAN model

θ	Parameters of the generator
ϕ	Parameters of the discriminator
z	Random noise
ld_r_g	LDAF_GAN generates data
c_seq	lncRNA sequence characteristics
$\{\}$	Connection symbols
$ld\_seq\_r_g$	LDAF_gan_seq generates data
ld_real	Real data
fua_real	Data for filtering operations
ld_r_g'	LDAF_gan filtered results
$ld\_seq\_r_g'$	LDAF_gan_seq filtered results
G	Generators
D	Discriminator
fua_real_sample	Filtered data after negative sampling
α	Adjustable parameters for regular terms
N_sample	Number of negative sampling samples

represent the discriminator, where ϕ was the parameter of the discriminator. In LDAF_GAN, every iteration of the discriminator required the input of real and generated data. The generated data were represented as either $ld\_r_g \odot fua\_real$ or $ld\_seq\_r_g \odot fua\_real$ (where operation “$\odot''$ was used for filtering and fua_real was consistent with the real data). Then, generated data were fed into the discriminator as either $D(\phi, G(\theta, z))$ or $D(\phi, G(\theta, \{z, c\_seq\}))$. Meanwhile, ld_real (ld_real represents the Boolean matrix composed of real association data) or $\{ld\_real, c\_seq\}$ was input to D. Finally, the model give feedback to G by calculating the gap between the generated data and the real data, and the gradient back propagation was adjusted to the G network to generate new data that were closer to the original data distribution.

LncRNA sequence feature extraction

The lncRNA sequence is composed of four nucleotides, “A”, “G”, “C” and “T”. The traditional k-mer method obtains the feature of sequences by counting the frequency of nucleotide occurrences. However, the k-mer ignores the order of nucleotides, thus we would like to take the nucleotide order into consideration in this study. Firstly, we adopt the idea of k-mer to divide the sequence into several sub-strings of length k; secondly, we adopt the Doc2vec model to obtain the vector expression of each string; finally, these strings are combined vertically into a matrix in order to obtain the features of the sequence. An example is shown in Fig. 1.

LDAF_gan

The sub-model LDAF_gan of LDAF_GAN was trained using associated data without lncRNA sequence features. Upon combining the generative and discriminative networks, we completed a generative adversarial network. We followed the common GAN [17] to construct the LDAF_GAN model. The main structure involved generator G and the discriminator D, but for the output of G we employed a simple filtering operation; the final model architecture is shown in Fig. 2.

Following the input of random noise, generator $G(\theta, z)$ yielded a matrix of lncRNA-disease association where θ was a hyperparameter of G and z denoted noise. The row vector of the matrix represents the likelihood that a particular lncRNA is associated with all diseases, and the column vector represents the likelihood that a disease is associated with all lncRNAs. Each value of matrix was interpreted as the association likelihood of a lncRNA with

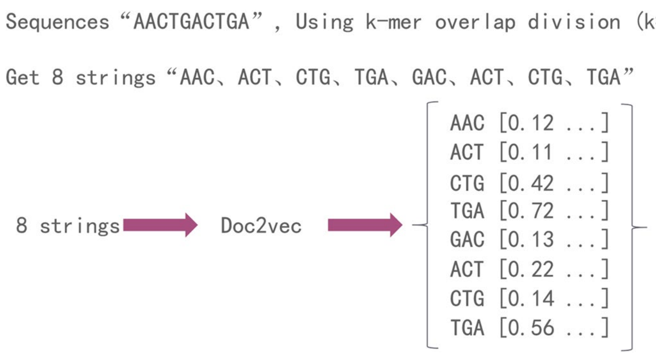


Fig. 1 lncRNA feature extraction

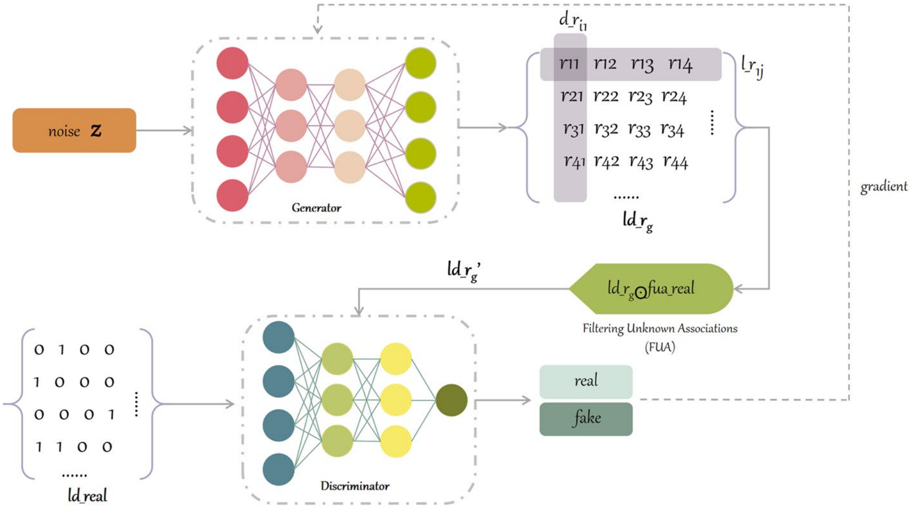


Fig. 2 Architecture of LDAF_gan

a predicted disease. Each value of vector was interpreted as the association of an lncRNA with a predicted disease. The softmax function normalized the association between (0,1) to get ld_r_g. Next, filtering (Filtering Unknown Associations, FUA) eliminated the effect of unknown associations on the generated results. The filtering operation is to dot product the output of the generator with the negative sampling matrix of real lncRNA-disease association, and the filtering will retain the values corresponding to the positive and negative samples in the generated results, which makes the discriminator feedback more accurate. After filtering, ld_rg' is obtained, which was denoted as $ld\_r_g \odot fua\_real$. Then, ld_r_g' was fed into the discriminator together with real data ld_real as $D(\phi, G(\theta, z))$ and $D(\phi, ld\_real)$, and the output value indicated the probability of accuracy. Finally, D was fed back to G, which made adjustments, where G minimized the probability of a false result; the loss function of G was expressed as Eq. (1).

$$J^G = \min_{\theta} E_{z \sim P_{noise(z)}} [log(1 - D(G(z)))] \tag{1}$$

where z denotes the noise vector that obeys the distribution of noisy data P_{noise}. Correspondingly, D improved discriminatory capabilities by maximizing the gap between the real data and the generated data. Thus, the loss function of D was expressed as Eq. (2).

$$J^D = \max_{\phi} E_{x \sim P_{real(x)}} [logD(x)] + E_{z \sim P_{noise(z)}} [log(1 - D(G(z)))] \tag{2}$$

where x denotes the vector of real data, following the real data P_{real} distribution. G and D were represent in Eq. (3).

$$\min_{G} \max_{D} V(G, D) = E_{x \sim P_{real(x)}} [logD(x)] + E_{z \sim P_{noise(z)}} [log(1 - D(G(z)))] \tag{3}$$

LDAF_gan_seq

Sub-model LDAF_gan_seq was trained with fused lncRNA sequence data. LDAF_gan_seq differed slightly from LDAF_gan via slightly adjusting *G* and *D* network dimensions of LDAF_gan. The overall model is shown in Fig. 3.

Features of lncRNA sequences, mainly composed of “A”, “G”, “C” and “T”, were extracted using the methods mentioned in above. It is worth noting that for lncRNA sequence features, our model specifically constructs a network module in the generator to extract the implicit features of lncRNA sequences, and the same network layer is set in the discriminator, which constitutes the overall model structure of sequence feature processing, lncRNA-disease association generation and discrimination. Random noise was then connected with sequence features as the input of *G*, which is represented by $G(\theta, \{z, c\_seq\})$ (Fig. 2), where “{}″ denotes connecting the noise z with the feature c_seq, and outputting the same dimension as the noise after passing *G*. Subsequently, the softmax function was used to normalize $ld\_seq\_r_g$, followed by the FUA operation $ld\_seq\_r_g \odot fua\_real$, filtering out the unknown association data to get $ld\_seq\_r'_g$. Real data ld_real and generated data $ld\_seq\_r'_g$ were fed into *D*, and the results are expressed as $D(\phi, ld\_real)$ and $D(\phi, G(\theta, \{z, c\_seq\}))$, where ϕ is the hyperparameter of *D*. The output was judged to be the probability of accuracy. The loss function of *G* in LDAF_GAN was expressed as Eq. (4).

$$J^G = \min_{\theta} E_{z \sim P_{noise(z)}}[log(1 - D(G(z, c\_seq)))] \tag{4}$$

Then, the loss function of D was shown in Eq. (5).

$$J^D = \max_{\phi} E_{x \sim P_{real(x)}}[logD(x, c\_seq)] + E_{z \sim P_{noise(z)}}[log(1 - D(G(z, c\_seq)))] \tag{5}$$

Negative sampling

Sections 1.2 and 1.3 introduce the GAN-based LDAF_GAN approach to prediction. The greatest drawback in our approach is the absence of negative samples for the association data. Values of 0 in the matrix do not differentiate between no association and

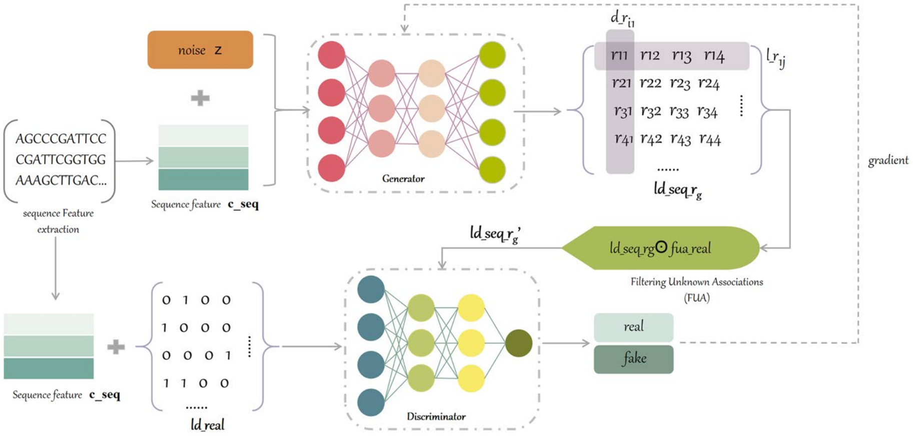


Fig. 3 Sub-model LDAF_gan_seq

an association waiting to be predicted. In LDAF_GAN, the generation of all-1 vectors, which is the same result as the original data after filtering, is meaningless, therein necessitating a negative sampling strategy. Partial negative sampling in the unknown association data (matrix value of 0) gives value to unknown associations, which are denoted as no association. To avoid generating all vectors with values of 1, a regular term is added to the loss function in the training of *G*. The loss function of *G* is changed slightly (taking the fused lncRNA sequence feature model as an example), and the loss of *G* after negative sampling is represented as follows:

$$\begin{aligned} J^G &= E_{z\sim P_{noise(z)}}\left[log(1-D(G(z,c\_seq)))+\alpha\sum_i\left(x_{li}-\hat{x}_{li}\right)^2\right] \\ &= \sum\nolimits_{lnc}\left[log\left(1-D\left(\left(ld\_seq\_r_g\cdot fua\_real\right)\mid c\_seq\right)\right)+\alpha\sum_i\left(x_{li}-\hat{x}_{li}\right)^2\right] \end{aligned} \tag{6}$$

where x_{li} denotes the negative sampling result on the original data and $\hat{x}_{li}$ is negative sampling result on *fua_real*. Considering the associated and unassociated terms in the training process of *D*, the negative sampling results must be as close to 0 as possible, while the true association is as close to 1 as possible to give feedback information to *G*. Accordingly, the loss function of *D* is adjusted as follows:

$$\begin{aligned} J^D &= \max_{\phi} E_{x\sim P_{real(x)}}[logD(x\mid c\_seq)] \\ &\quad + E_{z\sim P_{noise(z)}}\left[log\left(1-D\left(\left(ld\_seq\_r_g\cdot fua\_real\_sample\right)\mid c\_seq\right)\right)\right] \\ &= -\sum\nolimits_{lnc}[logD(x\mid c\_seq)] \\ &\quad + \left[log\left(1-D\left(\left(ld\_seq\_r_g\cdot fua\_real\_sample\right)\mid c\_seq\right)\right)\right] \end{aligned} \tag{7}$$

Model evaluation

To facilitate a comparison between LDAF_GAN and other models, we used fivefold and tenfold cross-validations. The former divides the samples into five uniformly disjoint parts, one as the test set and the remaining four as the training set. We then conducted five experiments in turn. The latter cross-validation divided the samples into ten uniformly disjoint parts, one part as the test set and the remaining nine as the training set, and we conducted ten experiments. The AUC was the area enclosed by the curves and axes in the coordinate system, with *FPR* as the horizontal coordinate and *TPR* as the vertical coordinate. This was used to evaluate the predictive performance of the model. The *AUPR* value was the area enclosed by the curve and the axis in the coordinate system, composed of recall as the horizontal coordinate and precision as the vertical coordinate. This evaluated the overall performance of the model, and was calculated as follows:

$$\begin{aligned} FPR &= \frac{FP}{TN+FP}, TPR=\frac{TP}{TP+FN} \\ recall &= \frac{TP}{TN+FN}, precision=\frac{TP}{TP+FP} \end{aligned}$$

where *TP* denoted the probability of positive samples being correctly predicted as positive samples, and *FN* denoted the probability of positive samples being incorrectly predicted as negative samples. *FP* denoted the probability of negative samples being incorrectly predicted as positive samples, and *TN* denoted the probability of negative sample being correctly predicted as negative samples.

Results

Comparison with other state-of-the-art methods

Experimental setting and datasets

This experiment was implemented on the PyTorch platform. To demonstrate the performance of the model, LDAF_GAN was applied to four datasets. First, fivefold cross-validation and tenfold cross-validation were performed on two publicly available datasets taken from BiGAN [24]: LncRNADisease 2.0 [25] and Lnc2Cancer v2.0 [26]. Further, lncRNADisease 2.0 [25] contained 19,166 lncRNAs and 529 diseases, then 205,959 lncRNA-disease association data were finally obtained; there were 9254 lncRNA-disease associations in the Lnc2Cancer dataset, which contained 2659 lncRNAs and 216 diseases. Second, cross-validation was performed on our constructed datasets dataset 1 and dataset 2, both of which contained 5213 associations with 1301 lncRNAs and 497 diseases, while there were 1301 corresponding lncRNA sequences in dataset 2 and none in dateset 1 (lncRNA sequence data from the database Refseq [25])).

LncRNADisease dataset comparison experiment

Firstly, we compared several methods, such as BiGAN [24], CNNLDA [26], NBCLDA [29], TILDA [27] and LDAP [7] on the LncRNADisease 2.0 [25] dataset, and the tenfold cross-validation ROC curves were shown in Fig. 4. Experimental results showed that the LDAF_GAN method on the LncRNADisease dataset was significantly more effective than several other methods, and the AUC value reached about 0.975. The results demonstrated that the semi-supervised learning of GAN is very effective for lncRNA-disease association prediction even when only positive samples were available.

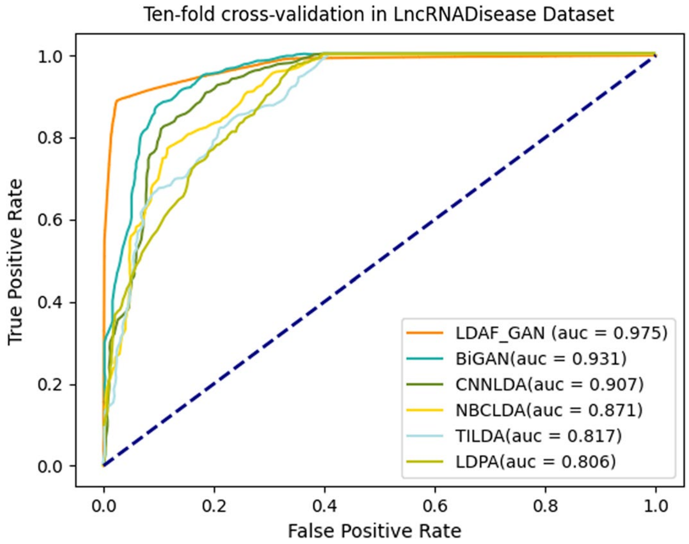


Fig. 4 Ten-fold cross-validation on LncRNADisease dataset (results except for LDAF_GAN taken from Yang et al. [24])

Lnc2Cancer dataset comparison experiments

LDAF_GAN was compared with BiGAN [24], CNNLDA [26], NBCLDA [29], TILDA [27] and LDAP [7] on the Lnc2Cancer v2.0 [26] dataset. The AUC value reached 0.915, and ROC curves under tenfold cross validation were shown in Fig. 5. LDAF _GAN achieved the best results among these models, and was second only to BiGAN [25]. However, our model did not utilize lncRNAs or a diseases similarity network, and relied on association data alone. For the prediction of a new lncRNA node, LDAF_GAN only required the lncRNA sequence features without calculating the similarity vector again.

Experiments on all data sets

Finally, LDAF_GAN was cross-validated on dataset 1 and dataset 2, and then divided into two sub-models: LDAF_gan and LDAF_gan_seq. The LDAF_gan model was constructed on dataset 1, while the LDAF_gan_seq model was constructed on dataset 2. The results of LDAF_GAN on both datasets showed that LDAF_GAN predicted well not only the association data without sequence features, but also the multimodal data with fused sequence features. Our fivefold cross-validation results were shown in Fig. 6, where Fig. 6a showed the results of LDAF_GAN on dataset 1; the average AUC value obtained was 0.926. Figure 6b showed the fivefold cross-validation results of LDAF_gan_seq on dataset 2, and the average AUC value was 0.928. Figure 6c showed the fivefold cross-validation results of LDAF_GAN on the LncRNADisease [25] dataset, and Fig. 6d the fivefold cross-validation results of LDAF_gan on the Lnc2Cancer [26] dataset. Finally, all results of the LDAF_GAN validation on three datasets without lncRNA sequence features were shown in Table 2, including the mean AUC values and mean AUPR values under five- and tenfold cross-validation. LncRNADisease [25] dataset reached an average AUPR value of 0.45, Lnc2Cancer [26] dataset an average AUPR value of 0.15, and our dataset an average AUPR value of 0.15. LDAF_GAN achieved excellent predictions

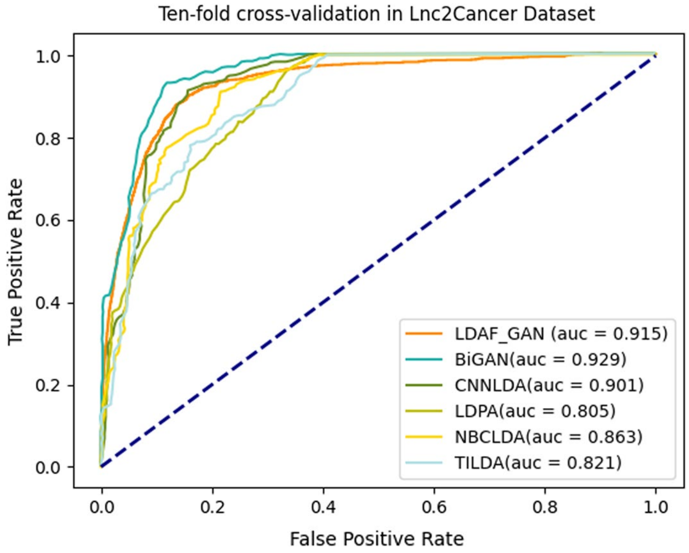
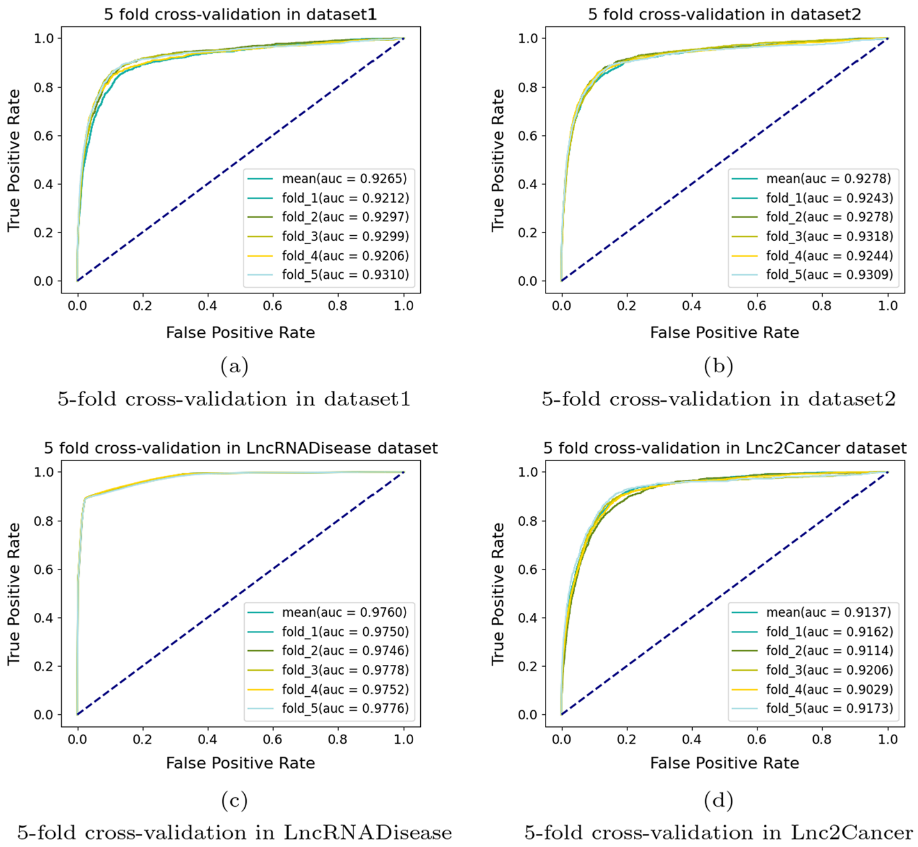


Fig. 5 Ten-fold cross-validation on Lnc2Cancer dataset (results except for LDAF_GAN taken from Yang et al. [24])



(a) 5-fold cross-validation in dataset1

(b) 5-fold cross-validation in dataset2

(c) 5-fold cross-validation in LncRNADisease

(d) 5-fold cross-validation in Lnc2Cancer

Fig. 6 Five-fold cross-validation results of LDAF_GAN on four datasets

Table 2 Experimental results of LDAF_GAN on different datasets (Note: dataset1 is a prediction without serial correlation data)

	AUC/AUPR	LncRNADisease	Lnc2Cancer	dataset1
10-fold cross-validation	AUC	0.9752	0.9145	0.9192
	AUPR	0.4502	0.1553	0.1457
5-fold cross-validation	AUC	0.9760	0.9137	0.9265
	AUPR	0.4861	0.1493	0.1876

on several datasets, which was initially designed for training on continuous values, and while still achieving excellent predictions on discrete values. The negative sampling strategy used by LDAF_GAN helped the model to selectively generate results close to 0 or 1, thus avoiding misclassification caused by generating all-1 vectors.

Case studies

We used lncRNAs H19, MALAT1, XIST, ZFAS1, UCA1, and ZEB1-AS1 to verify LDAF_GAN. The two sub-models based on LDAF_GAN have two prediction methods, both of which is able to predict the disease associated with a specific lncRNA. Based on LDAF_gan, the known association vector (i.e., the vector containing only 0 and 1) of lncRNA(e.g., H19) is fed into the generator, and after passing through the softmax

Table 3 The top 10 predicted H19 associated with diseases

LncRNA	Disease	Rank	Evidence
H19	Hepatocellular carcinoma	1	Lnc2Cancer
	Gastric cancer	2	Lnc2Cancer
	Breast cancer	3	Lnc2Cancer
	Colorectal cancer	4	Lnc2Cancer
	Esophageal squamous cell carcinoma	5	Lnc2Cancer
	Glioma	6	Lnc2Cancer
	Nasopharyngeal cancer	7	Lnc2Cancer
	Prostate cancer	8	Lnc2Cancer
	Ovarian cancer	9	Lnc2Cancer
	Lung cancer	10	Lnc2Cancer

Table 4 The top 10 predicted MALAT1 associated with diseases

LncRNA	Disease	Rank	Evidence
MALAT1	Hepatocellular carcinoma	1	Lnc2Cancer
	Gastric cancer	2	Lnc2Cancer
	Breast cancer	3	Unconfirmed
	Colorectal cancer	4	Lnc2Cancer
	Non small cell lung cancer	5	Lnc2Cancer
	Esophageal squamous cell carcinoma	6	Lnc2Cancer
	Glioma	7	Lnc2Cancer
	Lung adenocarcinoma	8	Lnc2Cancer
	Prostate cancer	9	Lnc2Cancer
	Cervical cancer	10	Unconfirmed

function, an association vector will be output, whose elements are between (0,1). Disregarding the known associated diseases among them, the top-ranked corresponding diseases in the predicted associations are selected as the final prediction results. Based on LDAF_gan_seq, a random noise is connected with the sequence features of a certain lncRNA (e.g., ZFAS1) and fed into the trained generator. Finally, an association vector also is output through softmax function, and the top-ranked diseases are selected as the final prediction result. The predicted disease association on H19, MALAT1, and XIST reached 100%, 80%, and 90%, respectively (based on experimental validations from the Lnc2Cancer [18] database) (Tables 3, 4, 5, respectively). We singled out lncRNA ZFAS1, UCA1, and ZEB1-AS1, which were not included in the training data, and used the lncRNA sequence features of ZFAS1, UCA1, and ZEB1-AS1 as the input of LDAF_GAN to generate the top 10 ranked diseases. The prediction accuracy value reached 90%, 100%, and 90%, respectively (Table 6, 7, 8, respectively).

Discussion

Our lncRNA-associated disease prediction model LDAF_GAN,which is based on association filtering and Generative Adversarial Networks, fuses lncRNA sequence features to achieve prediction. Compared with several other prediction models, LDAF_GAN is

Table 5 The top 10 predicted XIST associated with diseases

LncRNA	Disease	Rank	Evidence
XIST	Hepatocellular carcinoma	1	Lnc2Cancer
	Breast cancer	2	Lnc2Cancer
	Colorectal cancer	3	Lnc2Cancer
	Non small cell lung cancer	4	Lnc2Cancer
	Esophageal squamous cell carcinoma	5	Lnc2Cancer
	Nasopharyngeal cancer	6	Lnc2Cancer
	Glioma	7	Lnc2Cancer
	Lung adenocarcinoma	8	Lnc2Cancer
	Osteosarcoma	9	Lnc2Cancer
	Cervical cancer	10	Unconfirmed

Table 6 The top 10 predicted ZFAS1 associated with diseases

LncRNA	Disease	Rank	Evidence
ZFAS1	Colorectal cancer	1	dataset 1
	Hepatocellular carcinoma	2	dataset 1
	Breast cancer	3	dataset 1
	Non small cell lung cancer	4	dataset 1
	Prostate cancer	5	dataset 1
	Gastric cancer	6	dataset 1
	Astrocytoma	7	Unconfirmed
	Esophageal squamous cell carcinoma	8	dataset 1
	Glioma	9	dataset 1
	Ovarian cancer	10	dataset 1

Table 7 The top 10 predicted UCA1 associated with diseases

LncRNA	Disease	Rank	Evidence
UCA1	Breast cancer	1	dataset 1
	Hepatocellular carcinoma	2	dataset 1
	Non-small cell lung cancer	3	dataset 1
	Colorectal cancer	4	dataset 1
	Gastric cancer	5	dataset 1
	Cervical cancer	6	dataset 1
	Prostate cancer	7	dataset 1
	Astrocytoma	8	dataset 1
	Ovarian cancer	9	dataset 1
	Glioma	10	dataset 1

stable and achieves superior performance. As a semi-supervised learning GAN, LDAF_GAN achieves good results even when only positive samples are available. In particular, the prediction of new lncRNAs does not require associated data, and the data distribution captured by GAN during training can support the prediction of new nodes. Thus, the method can achieve superior results both on the prediction of the original nodes

Table 8 The top 10 predicted ZEB1-AS1 associated with diseases

LncRNA	Disease	Rank	Evidence
ZEB1-AS1	Breast cancer	1	dataset 1
	Hepatocellular carcinoma	2	dataset 1
	Colorectal cancer	3	dataset 1
	Gastric cancer	4	dataset 1
	Non-small cell lung cancer	5	dataset1
	Astrocytoma	6	dataset 1
	Prostate cancer	7	dataset 1
	Cervical cancer	8	Unconfirmed
	Glioma	9	dataset 1
	Stomach cancer	10	dataset 1

and the prediction of new nodes. Further, excellent prediction results derives from two key points: filtering and negative sampling. Filtering allows the model to focus only on the parts with known associations, while negative sampling avoids pattern collapse due to the generation of all-1 vectors, which are also crucial for training. Finally, case studies show that LDAF_GAN accurately predicts disease associations for lncRNAs with known associations and lncRNA nodes without known associations but with lncRNA sequences. Nevertheless, some future developments may enhance predictions. For example, we adopt a negative sampling strategy, yet there is no guarantee that the negative samples are unassociated, which affects judgment of the model. For diseases, the model performance will be improved once appropriate disease features are incorporated.

Conclusion

LncRNAs play an important role in biological life processes, and discovering potential associations between lncRNAs and diseases facilitates better diagnoses and prevention of diseases. To this end, we offer a method for lncRNA-associated disease prediction based on association filtering and Generating Adversarial Networks, called LDAF_GAN. Experiments use two types of datasets: association data, and association data with fused lncRNA sequence features. Sub-model LDAF_gan is useful for cases of only association data. Three association data validate this approach, and the results show that the fivefold cross-validation AUC values of LDAF_gan are 0.9760, 0.9137 and 0.9265. For data with sequence features, sub-model LDAF_gan_seq is applicable. It has an average fivefold cross-validation AUC value of 0.9278. Validation results from several datasets show that LDAF_GAN can achieve excellent results and high accuracy predictions. LDAF_gan_seq can make predictions in the absence of lncRNA-disease association, which is valuable in the absence of known associations; accurate predictions can be achieved using sequence features of lncRNAs as input. The validation results of LDAF_GAN on two publicly available and our own datasets verify credibility of the model. The correct prediction of most of the top 10 diseases by LDAF_GAN for six lncRNAs demonstrates its effectiveness.

Abbreviations

ld_r_g	LDAF_GAN generates data
c_seq	lncRNA sequence characteristics
$ld\_seq\_r_g$	LDAF_gan_seq generates data
ld_real	Real data
fua_real	Data for filtering operations
ld_r_g'	LDAF_gan filtered results
$ld\_seq\_r_g'$	LDAF_gan_seq filtered results
fua_real_sample	Filtered data after negative sampling
N_sample	Number of negative sampling samples

Acknowledgements

We would like to thank the the Advanced Computing Center of Yunnan University. Their constructive comments have led to an improved version of the paper.

Author contributions

LL and HZ conceived and designed the study. LT, SL and ZL contributed to the data collection and analysis. HZ wrote the manuscript. GL, JL and RM revised the manuscript.

Funding

This work was supported by the National Natural Science Foundation of China (grant no. 61862067, U1902201), Yunnan Provincial Science and Technology Department-Yunnan University Double First-Class Joint Fund Key Projects (grant no. 2019FY003027), the Applied Basic Research Project in Yunnan Province (grant no. 202201AT070042) and National Key R &D Program of China (grant no. 2022YFC2602500).

Availability of data and materials

The LDAF_GAN source code is available at https://github.com/ZhonghuaYNNU/LDAF_GAN LncRNADisease v2.0: http://www.rnanut.net/lncrnadisease/index.php/home/info/download. Lnc2Cancer: http://www.bio-bigdata.net/lnc2cancer/download.html. dataset1: http://www.cuilab.cn/lncrnadisease and http://www.bio-bigdata.net/lnc2cancer/download.html. dataset2: https://lncipedia.org/ and https://www.ncbi.nlm.nih.gov/refseq/.

Declarations

Ethics approval and consent to participate

Not applicable

Competing interest

The authors declare that they have no competing interests.

Consent for publication

Not applicable.

Received: 6 February 2023 Accepted: 29 May 2023
Published online: 05 June 2023

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