

# Inference of gene regulatory network with regulation type based on signed graph convolutional network from time-series data

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**Abstract.** Currently, most existing methods for GRN reconstruction ignore the information about the regulation types. Additionally, most methods employ the same approach to process the time-series expression values of different samples, without considering the differences in gene expression values among them. To this end, this work proposes the SGCGRNT model (Signed Graph Convolutional neural network for GRN Inference from Time-series data), which utilizes a signed graph convolutional network to infer GRNs with both the direction and regulatory type from time-series data. Meanwhile, we define Spearman's Rank Correlation Mutual Information to enable SGCGRNT to adapt to various types of gene expression data. In order to save time and resources in inferring large-scale datasets, we combine the idea of GraphSAGE to aggregate neighboring nodes. Experimental results demonstrate SGCGRNT can accurately predict GRNs with both direction and regulation types.

**Keywords:** Gene regulatory network, Signed graph convolutional network, Link prediction, Regulation type

## 1 Introduction

Gene regulatory network (GRN) is Gene regulatory network (GRN) is a complex directed network established by regulating RNA or proteins between genes, revealing the hierarchical structure and mechanism of gene expression regulation [1]. Inferring GRN will help us gain a deeper understanding of the molecular mechanisms of organisms, thereby revealing the essential laws of numerous biological processes within the organism. GRN can be used for various tasks, such as guiding the design of biological experiments, and developing personalized drugs [2].

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If relying solely on artificial biological experiments to verify all regulatory relationships in GRN one by one, it will consume a lot of manpower and material resources. Therefore, various researchers have proposed many mathematical calculation methods for inferring GRN [3,4,5,6]. Existing GRN inference methods can be divided into correlation methods, Boolean network methods, Bayesian network methods, differential equation methods and neural network methods, etc. [7,8,9,10].

In recent years, with the development of deep neural networks, an increasing number of methods based on neural networks have been proposed. CNNC [11] uses convolutional neural network (CNN) to reconstruct GRN from single-cell RNA sequencing data. It is worth noting that CNNC converts gene expression data into histogram images, so that CNN can better extract features. However, CNNC can only be applied to static gene expression data, and TDL [12] makes the model applicable to time series gene expression data by introducing 3D-CNN and LSTM. DGRNS [13] uses a sliding window to capture correlation information between genes and infers regulatory relationships between genes through CNN and Recurrent Neural Network (RNN).

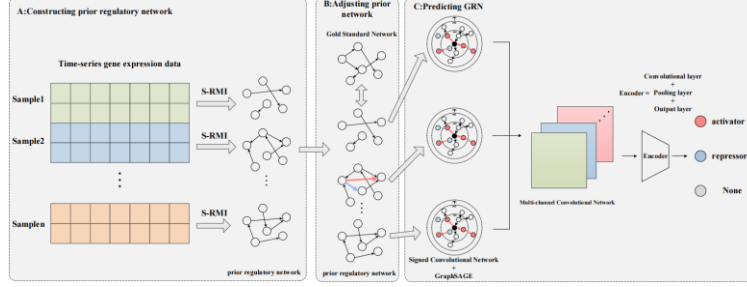
With the advancement of biological experimental technology, more data containing specific types of gene regulation have emerged, such as activation, inhibition, etc. How to efficiently process this type of data is currently a major research topic in the field of GRN inference.

Therefore, in this work, we propose a method, SGCGRNT, for inferring GRN based on signed graph convolutional neural network. In order to fully utilize the characteristics of time-series data, we construct prior regulatory networks based on Spearman's Rank Correlation Mutual Information (S-RMI) for time-series gene expression data of different samples. Afterwards, by comparing the differences between the gold standard network and various prior regulatory networks, some regulatory relationships in the prior regulatory network are adjusted to enhance the training efficiency of the model and improve predictive performance. In order to identify the regulatory relationship between regulatory factors and target genes, namely activation regulation, inhibition regulation and non-regulation, this study models GRN as a signed and directed graph, and used the signed graph neural network [14] to implement the link prediction problem. To ensure the characteristics of different sample time-series data, we adopt a batch learning method to input the adjusted prior regulatory network into a model based on the signed graph convolutional network for prediction [15]. Then, the output of the neural network is obtained through a multi-channel convolutional network to obtain the prediction results [18]. In addition, we conduct experiments to demonstrate the prediction performance of SGCGRNT model in prediction GRN with both direction and regulation type.

## 2 Method

SGCGRNT consists of three modules: A) Constructing prior regulatory networks. In this step, Spearman's Rank Correlation Mutual Information is used to construct prior regulatory network. B) Adjusting the prior regulatory networks by comparing the gold standard network. C) Predicting gene regulatory networks through signed

convolutional and multi-channel convolutional network. The flowchart of SGCGRNT is shown as **Fig. 1**.



**Fig. 1.** The flowchart of SGCGRNT model

## 2.1 Constructing prior regulatory networks

Many existing correlation coefficients are already applicable to calculate the correlations among genes, however, there are still have rooms for improvement, especially for data related to gene regulatory networks. For example, the Spearman correlation coefficient can handle linear and nonlinear data and has some robustness to noisy data, but lacks adaptability to discrete data [16]. Mutual information emphasizes the shared information between two variables, but is sensitive to noisy data [17]. In this study, in order to adapt to types of data such as discrete and continuous, handle data of different scales, and have a certain degree of robustness to noisy data, we propose a new method called Spearman's Rank Correlation Mutual Information (S-RMI) by combining the Spearman correlation coefficient with bivariate-Mutual information.

Let  $X$  and  $Y$  be two variables, represented as  $(X_1, X_2, \dots, X_n)$  and  $(Y_1, Y_2, \dots, Y_n)$ , respectively,

(1) Calculate the rank of variables, denoted as  $R_X$  and  $R_Y$ , respectively.

(2) Calculate the Spearman rank correlation coefficient:  $r_s = 1 - \frac{6 \sum_{i=1}^n d_i^2}{n(n^2-1)}$ , where  $d_i$  is the difference in rank between  $X_i$  and  $Y_i$ , and  $n$  is the number of samples.

(3) Calculate the mutual information between the rank sequences of  $X$  and  $Y$ :  $(rank(X); rank(Y)) = \sum_{x \in X} \sum_{y \in Y} P(x, y) \log \left( \frac{P(x, y)}{P(x)P(y)} \right)$ , where  $P(x, y)$  is rank,  $P(x)$  and  $P(y)$  are marginal probability distributions, respectively.

(4) The calculation of S-RMI needs to be combined with specific research content and data analysis. This work adopts a weighted synthesis method:  $S - RMI(X, Y) = \alpha \cdot r_s + \beta \cdot I(rank(X); rank(Y))$ . It can be flexibly adapted to the characteristics of different data and tasks by adjusting weight parameters  $\alpha$  and  $\beta$ .

Since time series gene expression values are obtained from samples in different experimental settings. This will result in certain differences in gene expression values between different samples. Therefore, this work used batch learning methods [15,15] to process the expression data of different samples separately. In order to improve the prediction accuracy of the model, this work constructed a prior regulatory network for the data of different samples using S-RMI. Because the correlation coefficient ranges

from -1 to 1, it is divided into positive and negative correlation based on the positive and negative values. Based on the three-classification task of SGGRNT, this work sets the regulatory relationship between positively correlated genes as positive links, i.e. activation regulation relationship, and vice versa as a negative link, i.e. inhibition regulation relationship. The regulatory direction is from regulatory factors to target genes. A prior gene regulatory network is constructed according to the above rules.

## 2.2 Prior regulatory network adjustment rules

The Golden Standard Network is a regulatory relationship that has been proven to exist through relevant biological experimental techniques. Correlation coefficients among genes can indicate the possibility of regulatory relationships. If there is a regulatory relationship between two genes based on their coefficients, but there is no information about this regulatory relationship in the gold standard network, we assume that there is a high possibility that this regulatory relationship is an undiscovered regulatory relationship between genes. Based on the above assumptions, we adjust the prior network using the conditions and rules in Table 1.

**Table 1.** Prior regulatory network adjustment rules

The conditions for prior network adjustment	Specific rules for prior network adjustment
Half or more of the prior networks of all samples have a certain regulatory relationship	Regulatory relationships should be added to all prior networks, as shown in Module B of <b>Fig. 1.</b> , the regulatory relationship with the red link in the prior regulatory network.
Half or more of the prior networks of all samples do not have any regulatory relationship	If this regulatory relationship exists in the gold standard network, it should be added to the prior network, as shown in Module B of <b>Fig. 1.</b> , the regulatory relationship with the blue link in the prior regulatory network. If the regulatory relationship does not exist in the gold standard network, it should be deleted from the prior network.

After adjustment, the prior regulatory networks constructed for each sample are closer to the complete gene regulatory network, allowing for more accurate prediction of whether there is a regulatory relationship between genes.

## 2.3 Signed Graph Convolutional Network

This work considers the activated regulatory relationship as a positive link and the suppressed regulatory relationship as a negative link, which is more in line with the definition of signed graph convolutional network and can also use signed graph network to better handle three types of tasks.

The main purpose of this study is to further infer whether the regulatory relationship is activation or inhibition based on predicting the direction of gene regulation. Because these two regulatory relationships are different, and in some cases even completely opposite, it is necessary to consider them separately and input them into the neural network for calculation when inferring the type of relationship. Previous work on graph

convolutional networks has primarily focused on unsigned networks, which consist solely of positive links. However, with the increasing prevalence of social media, signed networks (graph structures with both positive and negative links) have become common [19].

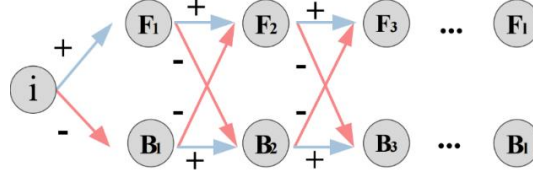


Fig. 2. Balance path diagram

The main problem in designing a Signed Graph Convolutional Network (SGCN) is how to handle negative links and how to combine the processing of positive and negative links into a unified model. Although there are significant differences in the properties and semantics of the two types of links, they are not isolated and independent of each other in the network structure. Therefore, the balance theory of signed social theory can be used to construct a relationship between two types of links [20,24,25].

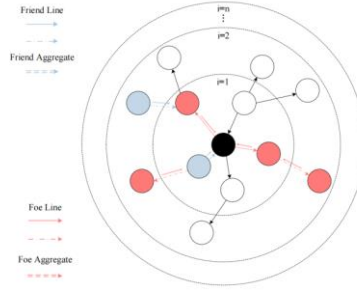


Fig. 3. Signed graph convolutional network feature aggregation process

Firstly, not all neighbors are the same in a signed network, because there are two different types of links in the network. Nodes connected through positive (or negative) links are defined as “friend” nodes (or “foe” nodes). Therefore, signed graph convolution stores “friend” nodes (or “foe” nodes) in a balanced node set (or imbalanced node set) through balance theory. As shown in Fig. 2, node  $F_l$  is a neighboring node of node  $i$ 's  $l$ -hop. If there are even positive (negative) links between the paths of two nodes, then the path is a balanced path, and node  $F_l$  is a balanced node. It is stored in the set of  $l$ -hop balanced nodes  $F_i(l)$  of node  $i$ ; Similarly, if there are an odd number of positive (negative) links between node  $B_l$  and node  $i$  in the path, then the path is an unbalanced path. Node  $B_l$  is stored in the  $l$ -hop unbalanced node set  $B_i(l)$  of node  $i$ .

After defining the balanced node set and the unbalanced node set, the aggregation of feature information can begin, as shown in Fig. 3.

In the process of aggregating first-order neighborhood information, the neighborhood information of negative and positive links is directly aggregated using the following formula:

$$h_i^{F(1)} = \sigma \left( W^{F(1)} \left[ \sum_{j \in N_i^+} \frac{h_j^{(0)}}{|N_i^+|}, h_i^{(0)} \right] \right) \quad (1)$$

$$h_i^{B(1)} = \sigma \left( W^{B(1)} \left[ \sum_{k \in N_i^-} \frac{h_k^{(0)}}{|N_i^-|}, h_i^{(0)} \right] \right) \quad (2)$$

Among them,  $W^{F(1)}$  and  $W^{B(1)}$  are “friend” and “foe” nodes from the first layer of balanced node set  $F_i(1)$  and unbalanced node set  $B_i(1)$ ,  $\sigma$  is activation function.

Starting from layer  $l (l > 1)$ , due to the balance theory, taking “friend” nodes as an example, it is necessary to aggregate the “friend” nodes of layer  $l - 1$  “friend” nodes and the “foe” nodes of layer  $l - 1$  “foe” nodes, that is, to aggregate node information from the set of balance nodes in layer  $l$  through formula (3); Similarly, aggregate node information from the non-equilibrium node set in layer  $l$  through formula (4):

$$h_i^{F(l)} = \sigma \left( W^{F(l)} \left[ \sum_{j \in N_i^+} \frac{h_j^{F(l-1)}}{|N_i^+|}, \sum_{k \in N_i^-} \frac{h_k^{B(l-1)}}{|N_i^-|}, h_i^{F(l-1)} \right] \right) \quad (3)$$

$$h_i^{B(l)} = \sigma \left( W^{B(l)} \left[ \sum_{j \in N_i^+} \frac{h_j^{B(l-1)}}{|N_i^+|}, \sum_{k \in N_i^-} \frac{h_k^{F(l-1)}}{|N_i^-|}, h_i^{B(l-1)} \right] \right) \quad (4)$$

Similar to the aggregation formula in the first layer,  $W^{F(l)}$  and  $W^{B(l)}$  are nodes in the balanced node set  $F_i(l)$  and the unbalanced node set  $B_i(l)$  in the first layer.

To enable the model to handle large-sample data, a GraphSAGE-like aggregation method is employed during the process of aggregating neighbor nodes' features in the graph convolutional network. In order to more accurately select neighboring nodes that may have moderating relationships for aggregation. SGCGRNT selects nodes with higher S-RMI values for aggregation. This approach allows aggregation of more useful node information, thereby enhancing the predictive performance of the model.

## 3 Experiment

### 3.1 Datasets

The primary objective of this work is to infer the types of regulatory relationships between genes. Therefore, the existing binary-classification datasets, which only distinguish between regulatory relationships (labeled as 1) and no regulatory relationships (labeled as 0), are not suitable for SGCGRNT, as it functions as a three-classification model. Consequently, a three-classification dataset containing regulatory types is required [29]. The three-classification data were obtained from the RegulonDB database [21], which encompasses 6060 regulatory associations among 2571 genes in E.coli. Additionally, the temporal gene expression values of 4400 genes of E.coli were retrieved from the GEO database [22]. After matching the same genes between the two databases, 4329 directed regulatory associations with regulation type between 2205 genes were obtained. Unknown association types were eliminated, resulting in 4104 regulatory associations between 2205 genes, including 2070 activation associations and

2034 inhibition associations. The specifics of the experimental data are illustrated in Table 2.

**Table 2.** Three-classification data situation

Datasets	Gene	Sample	Time points	Known regulatory interaction	activation	repression
Cold Stress	2205	3	8	4104	2070	2034
Heat Stress	2205	3	8	4104	2070	2034
Lactose	2205	3	4	4104	2070	2034
Oxidative Stress	2205	3	11	4104	2070	2034

Each datasets conducted three independent repeated experiments, including Cold Stress, Heat Stress, Lactose, and Oxidative Stress. The Cold and Heat networks detected expression values at 8 time points in each group of experiments, while the Lactose network detected expression values at 4 time points in each group of experiments. Similarly, the Oxidative network detected expression values at 11 time points in each group of experiments.

### 3.2 Performance metrics

In order to evaluate the performance of our model, we use 10 times of 5-fold cross-validation and calculate the average Area Under the ROC curve (AUROC) as our final performance metrics, where AUROC is the area under the ROC curve drawn with the false positive rate (FPR) as the abscissa and the true positive rate (TPR) as the ordinate.

$$TPR = \frac{TP}{TP+FN} \quad (5)$$

$$FPR = \frac{FP}{FP+TN} \quad (6)$$

$$ACC = \frac{TP+TN}{TP+FP+TN+FN} \quad (7)$$

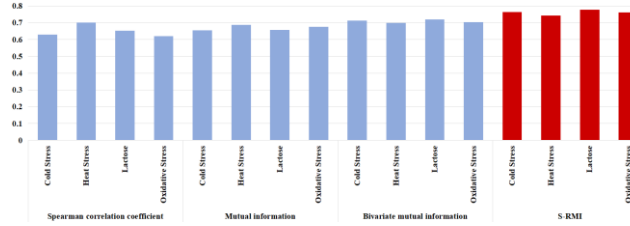
where TP refers to the number of links correctly identified, TN refers to the number of false links correctly identified, FP refers to the number of links incorrectly identified, and FN refers to the number of false links incorrectly identified.

### 3.3 Ablation study

In order to verify the effectiveness of the S-RMI designed in this work, it is necessary to conduct comparative experiments with the results obtained from other correlation coefficients. There are two places where S-RMI is used in SGCRNT: (1) constructing a prior network; (2) Neighbor node sampling method. Next, separate experiments need to be conducted on these two parts to demonstrate the effectiveness of S-RMI.

Firstly, the part of constructing a prior network was compared with Spearman correlation coefficient, Mutual information, and Bivariate-Mutual information. In this section, 10 times of five-fold cross-validation experiments were conducted, and the average AUC value is shown in **Fig. 4**. It can be observed from **Fig. 4** that using S-RMI to

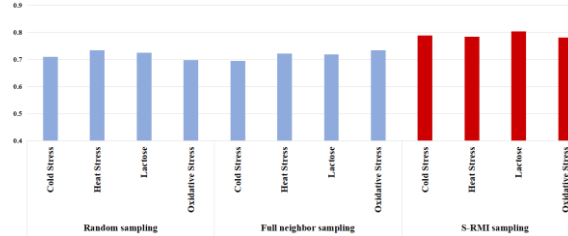
construct a prior network has the best predictive performance. This is because S-RMI weighted the Spearman correlation coefficient and mutual information, combining the advantages of the two correlation coefficients. It has strong robustness against noisy data and can be applied to large and small sample sizes, as well as linear and nonlinear data. Therefore, when using S-RMI to construct a prior regulatory network, the model can better infer the regulatory relationships between genes from time-series gene expression data.



**Fig. 4.** Comparison of a priori network parameter analysis experiments

Following that, this work needs to conduct experiments on the sampling methods of neighboring nodes. Generally, the sampling method is the default random sampling of GraphSAGE. In addition, this work also uses full neighbor sampling (the same as GCN) for comparison. Similarly, by comparing the evaluation AUC values of different sampling methods in 10 times of five-fold cross validation in four networks, the experimental results are shown in **Fig. 5**.

To validate the effectiveness of batch learning in handling time-series data and multi-channel convolutional networks in processing neural network outputs in this study, a series of ablation experiments were designed to compare the model prediction results. The experimental findings are presented in Table 3.



**Fig. 5.** Experimental comparison of neighbor node sampling methods

Because the output layer, which comprises of multi-channel convolutional networks, is tailored for various neural network outputs, if batch learning is not employed to proc-

**Table 3.** Ablation experiments to verify the effectiveness of each module in the model

	Experimental results			
	Cold Stress	Heat Stress	Lactose	Oxidative Stress
E.1	0.694	0.685	0.648	0.701
E.2	0.755	0.764	0.771	0.766
E.3	0.782	0.789	0.807	0.782



ess time-series data into multiple prior regulatory networks, only one output layer consisting of a convolutional network is required. Consequently, a total of three sets of ablation experiments were designed:

E.1: Instead of constructing different prior regulatory network based on different samples using time-series data, a prior regulatory network was constructed using all the data. If the prior network does not have a regulatory relationship that exists in the gold standard network, the regulatory relationship is added to the prior network.

E.2: Time-series data is constructed into different prior regulatory network based on different samples. However, in the final output layer, the results obtained from multiple neural networks are averaged and fused to obtain an output matrix, which is ultimately output through a convolutional neural network.

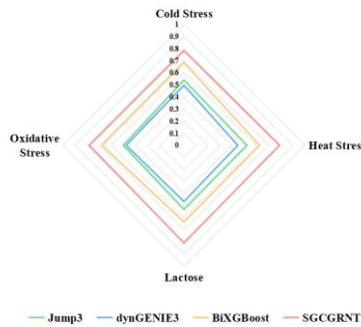
E.3: Conduct the experiment using the normal process of the SGCCRNT model.

By comparing the results of E.1 and E.2, it can be seen that when batch learning is used to process different samples of time-series data separately, the prediction results are significantly improved, that is, the effectiveness of module A of SGCCRNT is more significant.

By comparing the results of E.2 and E.3, it can be seen that using multi-channel convolutional neural networks to process the output of signed graph networks for different prior networks can retain the differences in information between samples to a certain extent, thereby improving the prediction results to a certain extent.

### 3.4 Comparing with other methods

Because previous deep learning-based models were binary-classification models, they only focused on whether there were regulatory relationships between genes and ignored the types of regulatory relationships. SGCCRNT is a three-classification model that uses data from three labels. Although this work can directly modify the output layers of other models to achieve the effect of three classes, it will result in the output values not accurately representing the probability distribution of the three categories. This will cause errors in the training and prediction stages of the model, as the interpretation of the output values does not match the actual target of the model. So, this work converts the results of SGCCRNT into binary-classification and compares them with the results of other models.



**Fig. 6.** Comparison with the results of existing binary-classification methods

Without modifying the SGCRNT model, it is necessary to calculate the binary-classification results based on the predicted scores and known labels. Therefore, this work adds up the predicted scores of the activation and inhibition relationships, treating them as the predicted regulatory relationships in the binary-classification. When other binary-classification models utilize three-classification data, they treat activation and inhibition as regulatory gene pairs labeled as 1, while the labels of the remaining gene pairs are set to 0. The experimental results are shown in **Fig. 6**.

From the results in **Fig. 6**, it can be seen that the prediction results of SGCRNT are superior to other existing methods [26,27,28]. Although purely from the perspective of predictive indicators, the performance improvement of SGCRNT is limited, from the perspective of research significance, SGCRNT not only infers whether there is a regulatory relationship between genes, but also can infer the types of activation or inhibition regulation, which is more important in practical research.

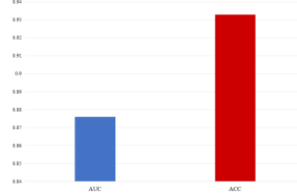
### 3.5 Independent dataset testing

The generalization performance of a model refers to its ability to predict unknown data. Therefore, in order to verify the generalization performance of the model, this work used independent datasets to test the trained model. The training data is the Cold network on the E. coli dataset, and then the independent test data set is used for testing. The independent dataset used is the three-classification dataset of DREAM5 competition network one [23], and the specific situation of the dataset is shown in Table 4.

**Table 4.** Independent dataset

Dataset	Network	Gene	Expression data	Known activation type	Known repression type
DREAM5	Network1	1643	805	2236	1776

By observing the AUC and ACC values of SGCRNT on independent datasets in **Fig. 7**, it can be seen that the model in this work has good generalization performance and strong predictive ability for unknown data.



**Fig. 7.** Independent dataset prediction results

## 4 Summary

This work proposes a method named SGCRNT for reconstructing gene regulatory networks (GRNs) with regulatory types, which makes significant contributions in the

following aspects. Firstly, this study models GRNs with regulatory types as signed directed graphs and employs signed graph convolutional neural networks (SGCNNs) for feature extraction. Ultimately, GRNs with regulatory types are inferred from gene expression data, laying a foundation for further exploration of the regulatory mechanisms of gene expression. Secondly, the adoption of signed graph convolutional neural networks in this work enables the extraction of diverse features, including gene expression features, network topological features, and regulatory type features, providing novel insights into computational methods for GRN inference. Finally, this paper introduces S-RMI, which effectively combines the robustness of Spearman's correlation coefficient to noisy data with the advantages of bivariate mutual information in handling various types of data.

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