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Combination of Neuro-Fuzzy Network Models with Biological Knowledge for Reconstructing Gene Regulatory Networks

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Abstract

Inferring gene regulatory networks from large-scale expression data is an important topic in both cellular systems and computational biology. The inference of regulators might be the core factor for understanding actual regulatory conditions in gene regulatory networks, especially when strong regulators do work significantly. In this paper, we propose a novel approach based on combining neuro-fuzzy network models with biological knowledge to infer strong regulators and interrelated fuzzy rules. The hybrid neuro-fuzzy architecture can not only infer the fuzzy rules, which are suitable for describing the regulatory conditions in regulatory networks, but also explain the meaning of nodes and weight value in the neural network. It can get useful rules automatically without factitious judgments. At the same time, it does not add recursive layers to the model, and the model can also strengthen the relationships among genes and reduce calculation. We use the proposed approach to reconstruct a partial gene regulatory network of yeast. The results show that this approach can work effectively.

Keywords: neuro-fuzzy network, biological knowledge, regulators, gene regulatory networks

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1 Introduction

One of the hottest topics in genome science is the interaction between genes. The study of Gene Regulatory Network (GRN) is focused to understand metabolic pathways and bioprocesses. As a system, a GRN comprises of biomolecular components (genes, mRNA and proteins) which interact with each other. These interactions determine gene expression levels, that is, determine the rate of gene transcription to mRNA. In general, each mRNA molecule can be translated into a specific protein (or set of proteins). On one hand, some proteins serve only to activate other genes in nuclei, which are thought of the transcription factors that are the main players in regulatory networks. Transcription factors which transcribe genes into mRNAs, can be considered as input signals. When transcription factors bind to promoter regions adjacent to the regulated gene, they recruit RNA polymerase to perform transcription function. On the other hand, proteins that are translated from the mRNAs, can be considered as output signals. Some proteins act as transcription factors themselves to upregulate or downregulate gene expressions. These courses form feedback loops in the network, in which direct or indirect self-regulation happens[1–3]. With the rapid development in recent years, microarray data has become an important resource for bioinformatics research increasingly. Based on time series expression data obtained from DNA microarrays regulatory networks, we can identify the complicated regulatory relationships, uncover the regulatory patterns in the cell, and obtain a systematic view for biological process. GRN models can be used to identify genetic diseases and to estimate the effects of medications. One of the most challenging tasks is to reconstruct interactional structures and to confirm mechanisms in cellular systems from available experimental data. Due to the lack of the experimental data and prior knowledge, it is hard to verify regulatory relations, which are required to construct the regulatory network in traditional methods. Therefore, there is still a lot of work to do on gene networks construction[4,5].

Many computational approaches have been proposed to reconstruct GRNs based on large-scale

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microarray data which is retrieved from such biological experiments as Boolean networks[6], differential equations[7], linear combination and weighted model[8], Bayesian networks[9] and neural networks[10]. But all the existing regulatory network models have some inevitable drawbacks. For example, Boolean network models are used simply to determine the discrete model, but they are relatively rough, fixed, and have low accurate results. The differential equation model is a continuous network model, and it describes the relationships of gene impacts and changes. Although this model can reflect the genetic continuous dynamic relations better, it is difficult to establish differential equations in the right forms. It is thought that the linear combination and weighted model in the respect of establishing the relationship among genes is linear, but in fact, the relationship among genes is often very complex and nonlinear. While Bayesian network models are attractive due to dealing with stochastic aspects of gene expression and noisy measurements, but they also have the disadvantage of minimizing dynamic gene regulation. Recently, there have been some attempts to apply neural network models to investigate gene networks for better results.

In this paper, we apply a neuro-fuzzy network model and optimize weight values with genetic algorithm. By this approach we obtain strong regulators to regulate known genes, which include 7 genes whose regulators are indefinite, and get fuzzy rules during calculation. Finally we reconstruct a partial gene regulatory network using the obtained strong regulators and fuzzy rules, and satisfactory results are obtained from experiments.

2 Method

2.1 Model

It is very popular that neural network is used for inferring. For example, dynamic neuro-fuzzy network model, whose network structure and rules are constructed during on-line learning, is flexible[15]. But the determined rules are not necessarily accurate. Recurrent neuro-fuzzy network model is better in dealing with the series data than other neuro-fuzzy networks, but it is more complex in calculation[16].

The proposed model is a six-layer, two-input and single-output neuro-fuzzy network, which has the advantages of both neural networks and fuzzy systems. As a hybrid neuro-fuzzy architecture, it can not only infer the fuzzy rules, which are suitable for describing the regulatory conditions in regulatory networks, but also explain the meaning of nodes and weight value in the neural network. It can get useful rules automatically without factitious judgments[17,18]. At the same time, no recursive layers are added to the model, but the model can still strengthen the relationships among genes and reduce calculation. The proposed neuro-fuzzy network model is shown in Fig.1.

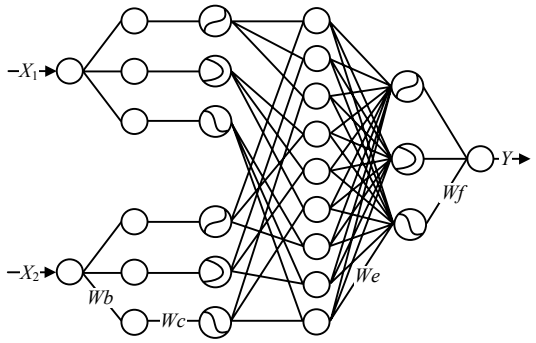

Fig. 1 The neuro-fuzzy network model.

We use O_i^j and I_i^j to respectively represent the output and input of the *i*-th node in the *j*-th layer.

In the first layer, each node represents an input linguistic variable (a linguistic input variable). There is no calculation taking place in this layer, and each node transfers the value of an input variable to the next layer.

$$O_i^1 = I_i^1 = X_i \ (i = 0,1), \tag{1}$$

where X_i represents gene.

We make input linguistic variable turn into fuzzy output in the second and third layers. Each node in the second layer needs to do a conversion as

$$O_i^2 = I_i^2 - Wb_i = X_i - Wb_i \ (i = 0,\ 1,\ \ldots\ ,5). \tag{2}$$

where Wb_i is the weight from I_i to O_i in the second layer.

In the third layer, input and output variables define three fuzzy sets (*big*, *mid*, *small*), which present large, medium and small respectively. The membership functions are represented as

$$\begin{aligned} big(x) &= \mathrm{sigmoid}(\alpha_1(x-\beta_1)) \\ &= 1/\left(1+\exp(-\alpha_1(x-\beta_1))\right), \end{aligned} \tag{3}$$

$$mid(x) = \exp(-(x-\beta_2)/\alpha_2), \tag{4}$$

$$\begin{aligned} small(x) &= 1-\mathrm{sigmoid}(\alpha_3(x-\beta_3)) \\ &= 1-1/\left(1+\exp(-\alpha_3(x-\beta_3))\right), \end{aligned} \tag{5}$$

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