The inference method of the gene regulatory network with a majority rule

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Abstract: The regulatory interactions among genes are summarized by the gene regulatory network. Recently, the gene regulatory network that is described by the differential equations is widely used, and a lot of inference methods using time course data of the gene expression levels have been proposed. One of the successful inference methods of the gene regulatory network is the method using the neural network. In this study, as a method to improve a performance of the gene regulatory network inference using the neural networks, we propose the method to apply a kind of majority rule to the conventional method. Our proposed method infers the regulatory interactions in the gene network based on the results of a lot of trials of the inference using neural networks. In the simulations, we evaluate our proposed method using artificially defined gene regulatory networks. The results show the validity of the proposed method. The results also suggest that the strategy of the proposed method is applicable to various methods using the heuristic solver.

Key Words: gene regulatory network, neural network, function approximation

1. Introduction

The regulatory interactions among genes are the basic mechanism of the biological systems and they are described by the gene regulatory network. The gene regulatory network is known as an effective tool for the biological experiments and various studies in the field of biology or biochemistry. The inference of the gene regulatory network is one of the significant issues of the system biology.

For the representation and the inference of the gene regulatory network, a lot of models and methods have been proposed [1–3]. In general, the inference method requires massive computational resources. For example, some practical solutions are given by the systems based on the high performance computing [4]. Therefore, the development of the inference method of the gene regulatory network is still the significant issue in the system biology.

The boolean network is the basic well-known model to represent the gene regulatory network [5, 6]. It consists of a set of nodes and a list of boolean functions. The nodes represent the genes and the gene expression level is represented by the binary value. Several inference methods had been proposed for the boolean network models, for example, the method using state transition tables or empirical ways to identify a boolean network.
The model using the Bayesian network is also the successful model of the gene regulatory network [7]. It introduces a probabilistic framework to the model of the gene regulatory network. Some of the ordinary learning algorithms for the Bayesian network are able to be applied to the inference of the gene regulatory network and the model can show rich expression of biological structures compared to the boolean models. However, it is known that the model using the Bayesian network cannot represent the time evolution of the states in the gene regulatory network. Therefore, the method using the dynamic Bayesian network had been proposed and it shows rich and precise expression of the gene regulatory network [8].

Recently, the models based on the coupled ordinary differential equations have been developed. The differential equation models describe the dynamical characteristics of gene expressions based on the information of correlations among genes. The differential equation models are considered as one of the most outstanding tools to describe a mechanism of mutual interactions of genes, metabolism and so on [9–18].

In the differential equation models, the derivative of the gene expression level \( X_i \) is formulated as follows.

\[
\frac{dX_i}{dt} = G_i(X_1, X_2, \ldots, X_N),
\]

where \( G_i(X_1, X_2, \ldots, X_N) \) is an arbitrary unknown function and we assume that the target gene regulatory network consists \( N \) genes, i.e., \( i = 1, 2, \ldots, N \).

Recently, massive time course gene expression data are able to be obtained, because the experimental technologies such as DNA microarrays have been developed. The inference method of the differential equation model is based on an approximation of the arbitrary unknown functions \( G_1, G_2, \ldots, G_N \) using the experimental time course data. A lot of inference methods have been proposed and the most of them use the fixed form of the polynomial expressions for the unknown function \( G_i \).

On the other hand, the heuristic method is considered as one of the effective methods for the function approximation and some conventional studies use it for the inference of the gene regulatory network that is defined by the differential equations [12, 13]. In these heuristic methods, the method using the neural networks [13] is one of the successful methods, where the neural network is known as an outstanding solver for the function approximation. It can approximate unknown functions using the learning algorithm such as the error back propagation. That is, the method using the neural networks does not require the particular fixed form of the differential equations. Also, it had been reported that the method can reduce the computational time [13].

However, the result of the function approximation using the neural networks depends on the initial set of the parameters that are randomly initialized for every trial. That is, the conventional method has an uncertainty depending on the result of the function approximation. In addition, especially in practical use, the over-fitting in the function approximation decrease the relevance of the function approximation for the inference, because the experimental data from the DNA microarray will have much error. Therefore, in order to obtain the proper result of the inference of the gene regulatory network, the learning algorithm of the neural network must be developed to increase a relevance of the function approximation in the scheme of conventional studies.

In this study, we propose a new inference method of the gene regulatory network that is given by the coupled differential equations using neural networks. In our proposed method, a large number of trials of the inference by conventional method using the neural networks are performed and the inferred frequencies of the regulatory interactions among genes are used for the final decision of the gene network inference. That is, the proposed method takes a majority rule for the inference. Here, we assumed that the valid regulatory interactions would be inferred frequently through a lot of trials.

As we mentioned above, the relevance of the function approximation is the significant requirement in the conventional method. However the improvement of the relevance of the function approximation is still a difficult problem. On the other hand, our proposed method tolerates the uncertainty of the function approximation.

In the next section, we applied our proposed method to the inference of 4-gene network to show the
characteristics and the validity of the proposed method. Also, in the simulation results, our proposed method is applied to the artificially defined 10-gene and 30-gene networks to show the validity of the method.

2. The model and the conventional method

The gene regulatory network model used in this study is given by the coupled differential equations. In this model, the derivative of the gene expression level $X_i$ of gene $i$ is formulated by Eq. (1) in the previous section. The objective of the gene regulatory network inference is to determine the regulatory interactions among genes in the network. Kimura et al. had proposed the inference method using the neural networks [13]. In this study, we use this conventional method as a basic method of our proposed method. We summarize the conventional method in the following.

The first step of the inference of the gene regulatory network is to approximate the unknown functions $G_i(X_1, X_2, \ldots, X_N)$ in Eq. (1). Here, it is assumed that the three-layer feedforward neural networks are used for the function approximation. Inputs of the neural networks are the gene expression levels, $X_1, X_2, \ldots, X_N$, and the output is the transition of the gene expression level $X_i$, i.e., $\frac{dX_i}{dt}$, where the data set of the gene expression levels is assumed to be obtained from the experiments. Therefore, $N$ neural networks are used for the $N$-gene network in the conventional method.

In conventional studies, the GLSDC (genetic local search with distance independent diversity control) [19] is used as a learning algorithm of the neural networks. The GLSDC is one of the improved algorithms for the accurate function approximation by using the neural network.

The second step is to derive the regulatory interactions among genes from a set of approximated functions $G_i$. To derive the regulatory interactions, the sensitivity coefficient $S_i(j)$ had been proposed in the conventional study [13]. The sensitivity coefficient is defined as follows.

$$S_i(j) = \frac{\partial}{\partial X_j} \left( \frac{dX_i}{dt} \right) = \frac{\partial G_i(X_1, \ldots, X_N)}{\partial X_j}.$$ (2)

The sensitivity coefficient $S_i(j)$ represents an impact of the gene expression of the gene $j$ to that of the gene $i$. However, we usually cannot obtain the static regulatory interactions among genes from this sensitivity coefficient directly, because the sensitivity coefficients are time varying. Then, in the conventional method, the positive and the negative sensitivity coefficients, $S^p_i(j)$ and $S^n_i(j)$, are calculated as follows. These are considered as time-averaged values of the positive and the negative sensitivity coefficients.

$$S^p_i(j) = \frac{1}{T} \sum_{k=1}^{T} p \left( \frac{\partial G_i}{\partial X_j} \bigg|_{t_k} \right),$$ (3)

$$S^n_i(j) = \frac{1}{T} \sum_{k=1}^{T} n \left( \frac{\partial G_i}{\partial X_j} \bigg|_{t_k} \right),$$ (4)

where,

$$p(x) = \begin{cases} x & \text{if } x > 0 \\ 0 & \text{otherwise} \end{cases},$$ (5)

$$n(x) = \begin{cases} x & \text{if } x < 0 \\ 0 & \text{otherwise} \end{cases},$$ (6)

where, $T$ is a number of the sampling points of the time course data and $t_k$ is the time that the $k$th data was sampled. The sensitivity coefficient, $\frac{\partial G_i}{\partial X_j} \bigg|_{t_k}$, is calculated using the parameters in the learned neural network that approximate the function $G_i$.

According to the $S^p_i(j)$ and $S^n_i(j)$, it is decided that the regulatory interaction of the gene $j$ to gene $i$ is TRUE or FALSE. In the case that the regulatory interaction is decided as TRUE, it is also decided that the regulatory interaction is either the positive or the negative. These decisions are based on some user defined criteria. The details of the algorithm to decide the regulatory interactions are
described in the conventional study [13]. In this study, we use the criteria shown in the conventional study.

The results of the inference are evaluated using the sensitivity $S_n$ and the specificity $S_p$. These are defined as follows.

$$S_n = \frac{TP}{TP + FN},$$

$$S_p = \frac{TN}{FP + TN},$$

where, TP, FN, TN and FP are the numbers of regulatory interactions that are true-positive, false-negative, true-negative, and false positive, respectively. Here, the sensitivity shows a degree of correctly inferred regulatory interactions, and it does not depend on the incorrectly inferred regulatory interactions. On the other hand, the specificity shows how few the incorrect regulatory interactions are in the inferred network, and it does not depend on the number of the regulatory interactions that are not inferred incorrectly. For example, if the result of the inference shows that all the possible regulatory interactions are TRUE, the sensitivity and the specificity would become 1 and 0, respectively. On the contrary, in the case that no regulatory interactions are inferred, they would become 0 and 1, respectively.

3. The gene regulatory network inference with a majority rule

3.1 An example of the conventional method

In the following, we show an example of the results using the conventional method. In this example, we use the artificial data of the gene expression levels from the S-system [9] as the substitutes for the experimental time course data. The S-system is one of the gene regulatory network models, that is described by the coupled differential equations.

Here, we assume that the 4-gene network shown in the Fig. 1 is the target network and the network is described by the S-system, that is given by,

$$\frac{dX_i}{dt} = \alpha_i \prod_{j=1}^{N} X_j^{g_i,j} - \beta_i \prod_{j=1}^{N} X_j^{h_i,j} \quad (i = 1, 2, \ldots, N),$$

where the number of genes $N$ is 4, and the parameters in the S-system, i.e., $\alpha_i$, $g_i,j$, $\beta_i$ and $h_i,j$ are summarized in Table I. To obtain the artificial data, we sampled the value of $X_i$ from the results of the numerical calculation of the coupled differential equations given by Eq. (9).

Figure 2 shows examples of the inference results by the conventional method using the artificial gene expression data. As shown in the figures, the result of the inference is varied depending on the initial values of the parameters in neural networks.

The result shown in the Fig. 2(a) is one of the valid results in 100 trials of the inference. Here, we assumed that the initial conditions of the neural networks are randomly initialized for every trial.
Table I. Parameters of the S-system (4-gene network shown in Fig. 1).

<table>
<thead>
<tr>
<th>$\alpha_1$ = 10.0</th>
<th>$\alpha_2$ = 8.0</th>
<th>$\alpha_3$ = 5.0</th>
<th>$\alpha_4$ = 10.0</th>
<th>$\beta_1$ = 10.0</th>
<th>$\beta_2$ = 10.0</th>
<th>$\beta_3$ = 10.0</th>
<th>$\beta_4$ = 10.0</th>
</tr>
</thead>
<tbody>
<tr>
<td>$g_{11}$ = 0.0</td>
<td>$g_{21}$ = 2.0</td>
<td>$g_{31}$ = 0.0</td>
<td>$g_{41}$ = 0.0</td>
<td>$h_{11}$ = 2.0</td>
<td>$h_{21}$ = 0.0</td>
<td>$h_{31}$ = 0.0</td>
<td>$h_{41}$ = 0.0</td>
</tr>
<tr>
<td>$g_{12}$ = 0.0</td>
<td>$g_{22}$ = 0.0</td>
<td>$g_{32}$ = −1.0</td>
<td>$g_{42}$ = 0.0</td>
<td>$h_{12}$ = 0.0</td>
<td>$h_{22}$ = 2.0</td>
<td>$h_{32}$ = 0.0</td>
<td>$h_{42}$ = 0.0</td>
</tr>
<tr>
<td>$g_{13}$ = 1.0</td>
<td>$g_{23}$ = 0.0</td>
<td>$g_{33}$ = 0.0</td>
<td>$g_{43}$ = 1.0</td>
<td>$h_{13}$ = 0.0</td>
<td>$h_{23}$ = 0.0</td>
<td>$h_{33}$ = 2.0</td>
<td>$h_{43}$ = 0.0</td>
</tr>
<tr>
<td>$g_{14}$ = −1.0</td>
<td>$g_{24}$ = 0.0</td>
<td>$g_{34}$ = 2.0</td>
<td>$g_{44}$ = 0.0</td>
<td>$h_{14}$ = 0.0</td>
<td>$h_{24}$ = 0.0</td>
<td>$h_{34}$ = 0.0</td>
<td>$h_{44}$ = 2.0</td>
</tr>
</tbody>
</table>

Fig. 2. Examples of inferred gene regulatory network of the conventional method using the neural networks. The results of the inference are varied depending on the initial conditions of the learning. The sensitivity and the specificity are (a) $S_n = 0.90, S_p = 0.91$ and (b) $S_n = 0.70, S_p = 0.77$, respectively.

sensitivity and the specificity of this result are $S_n = 0.90$ and $S_p = 0.91$, respectively. Also, another result from the 100 trials is shown in Fig. 2(b). The sensitivity and the specificity of the result are $S_n = 0.70$ and $S_p = 0.77$, respectively. From these results, it is obviously observed that the inference result depends on the initial conditions of the neural networks.

These differences of the inference results depend on the results of the function approximation by the neural network. Although some procedures are given to increase a relevance of the function approximation in conventional study [13], it is still difficult to obtain optimum and repeatable results. Moreover, especially in practical use, the overfitting in function approximation should be avoided, because the experimental data will include a measurement error.

Also, in the practical problem, the inferred network cannot be evaluated using the sensitivity and the specificity, because the target network is unknown. This means that there is no method to verify the inferred network, and it is impossible to decide which one is the proper result among the results from the conventional method. Therefore, improvement of the relevance and the repeatability of function approximation and the experimental technique to obtain the accurate gene expression levels are significant requirements of the scheme of the conventional studies. However, these requirements are considered as the difficult problems at present.

3.2 The proposed method

As we mentioned in the previous section, the improvement of the function approximation and the measurement of the gene expression levels are still difficult problems. Therefore, we positively take into account these uncertainties in the conventional studies.

In this study, we propose the inference method of the gene regulatory network using the neural networks with a majority rule. In our proposed method, a large number of trials of the gene regulatory network inference using neural networks are performed, and the inferred frequency of each regulatory interaction is used to decide the gene network. In this study, we assumed that the frequently inferred regulatory interaction is the plausible regulatory interaction.

In the proposed method, the conventional method using neural networks [13] is used for each trial
of the inference, and the initial conditions of the neural networks are randomly initialized for every trial. The procedure of our proposed method is summarized as follows.

1. Approximate the unknown functions of the coupled differential equation model given by Eq. (1) using neural networks with the measured time course data.

2. Infer the gene regulatory network using the sensitivity coefficients $S_i(j)$ calculated from the approximated functions.

3. Repeat the procedures of 1–2 in sufficient number of trials.

4. For every possible regulatory interaction, count the frequency of the regulatory interaction that is inferred as TRUE through all trials.

5. The regulatory interaction that is inferred more than the threshold is assumed to be a proper regulatory interaction.

Comparing to the conventional method [13], our proposed method requires more computational resources. For example, in the case that the trial number is 100, it takes 100 times of the calculation. However, this increase of the computational time does not depend on the size of the problem i.e., a number of the genes in the network.

4. Simulation results

Our proposed method was applied to the problem to infer the 4-gene, 10-gene, and 30-gene target networks to evaluate its performance. These target networks are artificially defined by the S-system model, and the gene expression data from the S-system model is used instead of the experimental data.

First, we show the results of 4-gene network. The regulatory interactions in 4-gene target network were defined as Fig. 1 in the previous section. The S-system model that corresponds to the target network is given by Eq. (9), and the parameters were defined as shown in Table I.

The histograms in Fig. 3 summarize the inferred frequency of each of the regulatory interaction. For example, Fig. 3(a) shows a frequency of the inferred regulatory interactions to the gene #1 from the other genes in the network. Here the number of the trials is assumed to be 100. According to
Fig. 4. Gene regulatory networks inferred by the proposed method (4-gene network). (a) In the case that the threshold of the inferred frequency is 70% of the total number of the trials. The sensitivity and the specificity of the result are $S_n = 0.90$ and $S_p = 0.91$, respectively. (b) the threshold is 30%. The sensitivity and the specificity of the result are $S_n = 0.90$ and $S_p = 0.82$, respectively.

Fig. 5. The characteristics of the sensitivity and the specificity as a function of the threshold of the inferred frequency. The target network is the 4-gene network shown in Fig. 1. The inferred frequency is shown by a percentage of the total number of trials.

The results shown in Fig. 3, the gene regulatory network shown in Fig. 4 was inferred by the proposed method. Each Figs. 4(a) and (b) shows the inferred network in the case that the threshold of the inferred frequency is 70% and 30% of the total number of the trials, respectively. The sensitivity and the specificity of these results are $S_n = 0.90$, $S_p = 0.91$ and $S_n = 0.90$, $S_p = 0.82$ for the results shown in Figs. 4(a) and (b), respectively. Compared to the results in conventional method shown in the previous section, the proposed method also inferred the same valid result when the threshold of the inferred frequency is decided appropriately.

The results in Fig. 4 show that the sensitivity and the specificity of the inferred network depend on the threshold. Therefore, we show the characteristics of the sensitivity and the specificity as a function of the threshold of the inferred frequency in Fig. 5. From the results, the sensitivity and the specificity of the inferred network show the monotonic increasing/decreasing characteristics. These characteristics suggest that the limited range of the appropriate threshold will give a good plausibility of the inferred network.

We also show the results of 10-gene and 30-gene networks. The regulatory interactions in these target networks are defined as shown in Fig. 6. The parameters of the S-system models correspond to these target networks are shown in Tables II and III. The 30-gene network is the model used in the conventional study [13] and 10-gene network is the modified model based on the 30-gene network. The topology of these networks is artificially generated. However, these models have some typical structures that are observed in biochemical networks, e.g., cyclic regulatory interactions and feedback regulatory interactions. Then we consider that these models are valid to use for the test of the
Fig. 6. The target gene regulatory network (10-gene and 30-gene network). The data for the simulation is generated by the S-system defined by Eq. (9). The parameters of the S-system for these target networks are summarized in Tables II and III.

Table II. The parameters for the 10-gene network.

| \( \alpha_i \) | 1.0 |
| \( \beta_i \) | 1.0 |
| \( g_{i,j} \) | \( g_{3,1} = -0.4, \ g_{4,1} = 0.3, \ g_{5,2} = -0.3, \ g_{6,3} = 0.7, \ g_{10,4} = 0.6, \ g_{7,5} = 0.4, \ g_{9,6} = 0.5, \ g_{10,7} = -0.4, \ g_{7,8} = 0.3, \) other \( g_{i,j} = 0 \) |
| \( h_{i,j} \) | \( g_{6,4} = -1.0, \) other 1.0 if \( i=j, \) 0.0 otherwise. |

Table III. The parameters for the 30-gene network.

| \( \alpha_i \) | 1.0 |
| \( \beta_i \) | 1.0 |
| \( g_{i,j} \) | \( g_{1,14} = -0.1, \ g_{5,1} = 1.0, \ g_{6,1} = 1.0, \ g_{7,2} = 0.5, \ g_{7,3} = 0.4, \ g_{8,4} = 0.2, \ g_{8,17} = -0.2, \ g_{9,5} = 1.0, \ g_{9,6} = -0.1, \ g_{10,7} = 0.3, \ g_{11,4} = 0.4, \ g_{11,7} = -0.2, \ g_{11,22} = 0.4, \ g_{12,23} = 0.1, \ g_{13,8} = 0.6, \ g_{14,9} = 1.0, \ g_{15,10} = 0.2, \ g_{16,11} = 0.5, \ g_{16,12} = -0.2, \ g_{17,13} = 0.5, \ g_{19,14} = 0.1, \ g_{20,15} = 0.7, \ g_{20,26} = 0.3, \ g_{21,16} = 0.6, \ g_{22,16} = 0.5, \ g_{23,17} = 0.2, \ g_{24,15} = -0.2, \ g_{24,18} = -0.1, \ g_{24,19} = 0.3, \ g_{25,20} = 0.4, \ g_{26,21} = -0.2, \ g_{26,28} = 0.1, \ g_{27,24} = 0.6, \ g_{27,25} = 0.3, \ g_{27,30} = -0.2, \ g_{28,25} = 0.5, \ g_{29,26} = 0.4, \ g_{30,27} = 0.6, \) other \( g_{i,j} = 0 \) |
| \( h_{i,j} \) | 1.0 if \( i=j, \) 0.0 otherwise. |


Figure 7 shows the characteristics of the sensitivity and the specificity as a function of the threshold of the inferred frequency. Similarly to the case of the 4-gene network, the sensitivity and the specificity of the inferred network show the monotonic increase/decrease characteristics. These results also suggest that the limited range of the appropriate threshold will give a good plausibility of the inferred network.

The merit of the proposed method is that the result of the inference is uniquely specified when the threshold of the inferred frequency is decided. This also means that the result of the inference depends on the threshold, however, the specificity and the sensitivity show the monotonic increasing/decreasing characteristics as shown in Figs. 5 and 7. In this respect, it is also the merit of our proposed method.
that the method is able to generate various results depending on the threshold, and we can roughly estimate the characteristics of inferred network concerning the sensitivity and the specificity. These merits are unique to the proposed method and they cannot be realized in the conventional method.

The efficiency of our proposed method is caused by an uncertainty of the inference results based on the function approximation using neural networks. Here we had assumed that the valid regulatory interactions would be frequently inferred through a lot of trials. Because the valid results are obtained under this assumption as shown in the simulation results, it is considered that our assumption is appropriate. These results also suggest that the strategy of our proposed method is applicable to various methods using heuristic solver that shows the uncertainty similar to the neural networks.

However, related to the issue mentioned above, the decision of the threshold of the inferred frequency is a significant issue of our proposed method. In the next section, we will describe the method to decide the threshold.

5. The method to decide the threshold of the inferred frequency

The simulation results in the previous section showed the validity of our proposed method. However, the results also showed that the effect of our method is limited, that is, our proposed method is effective under the assumption that the appropriate threshold of the inferred frequency is decided. Therefore, in this section, we propose the method to decide the threshold automatically as a supplemental technique of our proposed method.

In the following example, we use the results of 10-gene network, and the number of the trials of the inference is 100. Figure 8 shows the histogram of the number of regulatory interactions for each inferred frequency. In the Fig. 8, the histogram is smoothed by simple moving average to emphasize the characteristics of this histogram. As shown in Fig. 8, the inferred frequency shows clustered distribution. A lot of regulatory interactions are clustered in the range of low inferred frequency and a few regulatory interactions are clustered in the range of high frequency. In Fig. 8, the result of the fitting with a quadratic polynomial curve is also shown. To decide the threshold automatically, we assumed that the threshold is set to the minimum of the fitting curve.

From the result of our proposed method, in the case of the 10-gene network, the threshold of the inferred frequency is decided as 63%, where the sensitivity is 0.810 and the specificity is 0.978. These values of the sensitivity and the specificity are almost the same as the relevant values that empirically decided from the results shown in the Fig. 7.

Also, we applied our proposed method to the 30-gene network. The threshold decided by our method is 60%, where the sensitivity is 0.971 and the specificity is 0.999. These are also close enough to the relevant values from the results in the Fig. 7. Therefore, it is considered that the threshold decided by our method can give a reasonable result of the inference. This supplemental technique for
the decision of the threshold ensures the validity of our proposed method.

6. Conclusions
In this study, we proposed the inference method of the gene regulatory network with a majority rule. The proposed method infers the valid regulatory interactions among genes through a lot of trials of the inference using the neural networks. In our method, the majority rule is applied to select the valid regulatory interactions. We showed some simulation results using the artificially defined gene regulatory networks as the target networks. The simulation results show that the unique and reasonable inference result can be obtained by our proposed method. Our proposed method positively takes the uncertainty of the function approximation by the neural networks. We consider that the results in this study suggest the validity of the application of the majority rule to various methods using heuristic solver.

In practical use of the inference method of gene regulatory network, it is assumed that the experimental data that includes measurement errors are used. However, in this study, we used the data from the artificial gene network that is defined by S-system and we did not consider the errors in the data of gene expression levels. Therefore, we would like to verify our proposed method in the case that the data from the target network include errors similar to the experimental data from DNA microarrays in the future work.

References


