Inferring Gene Regulatory Networks from Multiple Time Course Gene Expression Datasets

Bo-Lin Chen
Division of Biomedical Engineering
University of Saskatchewan
Saskatoon, SK S7N 5A9, Canada
bolin.chen@usask.ca

Li-Zhi Liu
Department of Mechanical Engineering
University of Saskatchewan
Saskatoon, SK S7N 5A9, Canada
Lizhi.Liu@usask.ca

Fang-Xiang Wu
Division of Biomedical Engineering, Department of Mechanical Engineering University of Saskatchewan
Saskatoon, SK S7N 5A9, Canada
faw341@mail.usask.ca

***Abstract*—We proposed a scheme to infer gene regulatory networks from multiple time course gene expression datasets. As the scarcity of time course data, most current methods usually making the inferred gene regulatory network structure as an ill-posed one, and typically cannot handle multiple experimental datasets directly. On the other hand, gene expression data generated by different groups worldwide are increasingly accumulated. In this paper, we first formulate the inference of sparse and stable gene regulatory networks as a constraint optimization problem, which can be easily solved by a given single dataset. Then, two methods of network combination are proposed, which can combine structures inferred from various experimental datasets. After that, the parameters in gene regulatory network with that structure are estimated by solving another optimization problem. Finally, we test and validate our methods on synthetic datasets in a series of numerical experiments in terms of the structure accuracy and the model error.**

Keywords-gene regulatory network; network combination; sparsity; stability; constraint optimization; l1-norm

I. INTRODUCTION

With the rapid advancement of cDNA and oligonucleotide microarray technologies, mRNA expression levels are now possible being measured on a genome-wide scale, which provide various descriptions of gene activities [1-3]. Inferring gene regulatory networks from such time course gene expression data has become increasingly essential in investigating functions of genes and proteins, and then understanding the complex biological functions and processes.

A wide variety of methods have been proposed to reverse-engineer the gene networks, such as Boolean networks [4], Bayesian networks [5], genetic algorithms [6], neural networks [7], differential/difference equations [8, 9] and state space model [10]. Although these approaches are very useful in some specific areas, they usually restricted as the demand of a large amount of time course data.

However, real-life gene regulatory networks may consist of thousands of genes, while the relative experimental measurement data involve in only several dozens of time points (generally less than 50) [3]. Therefore, the scarcity of time course data or so called the dimensionality problem is one of the root causes of major challenges, and then usually making the inferring of gene regulatory network structure an ill-posed one [1-3]. Moreover, the single set of time course data are generated under specific experimental conditions, and hence often fail in using them to construct gene regulatory networks accurately.

To circumvent the problem of data scarcity, two strategies are typically adopted. One strategy is to add certain ad hoc assumptions to models. A common ad hoc assumption is that the connectivity of networks is less than a small fixed number (2 or 3) [4, 5, 8, 9]. With this assumption, parameters in models can be uniquely identified. Alternatively, some researchers have tried to exploit methods which can combine datasets under different experimental conditions. The gene experimental data generated by various groups worldwide become accumulated and can easily be accessed from public database or individual websites. Therefore, the latter strategy can greatly alleviate the difficulty of data deficiency and made the inferred gene regulatory networks more reasonable. It is worth to mention that multiple time course gene expression datasets cannot be simply arranged together, due to the normalization issues and the absence of temporal relationships.

It is generally believed that gene regulatory networks are sparse and stable [11]. In most existing methods, sparsity was abused as ad hoc assumptions to avoid densely connected gene regulatory relationships among components of a network, such as adding the assumption that one gene interacts with only a couple of genes [1, 3, 8, 12]. Although the inferred networks by using these methods are sparse, they might not be stable that as a result do not appear to make reasonable biological sense.

Generally, stability is used as a criterion to evaluate the qualification of the inferred gene networks [11], but rarely used as constraints to reverse engineering gene regulatory networks. Zalanos et al [13] proposed a method to infer sparse and stable gene regulatory network from perturbation data near the equilibrium states of the network. Wu et al [11] employed an optimization method to infer such networks from single set of time course data. The performances of their algorithms were investigated on synthetic datasets, and worked out with certain accuracy about the structure of networks.

In terms of using multiple datasets, Yong Wang et al [2] proposed a method called GNR (gene network reconstruction tool) which can combine variety microarray datasets from different experiments. The method is based on linear

978-1-4577-1666-9/11/$26.00 ©2011 IEEE

programming and a decomposition procedure, and is developed for inferring gene networks with the consideration of sparsity of connections.

In this paper we propose a scheme to infer sparse and stable gene regulatory networks from multiple datasets. Inferring gene regulatory networks consist of two issues: the structure identification and parameter estimation of the model. The remainder of the paper is organized as follows. Section II gives a brief introduction to gene regulatory networks, where the issue of inferring networks is formulated as a constraint optimization problem, which can be easily solved to generate a sparse and stable solution from each single set of data. Section III proposes two methods of network combination, which can combine structures that inferred from various multiple datasets. Once the structure is determined, the parameters of gene regulatory networks are estimated by solving another optimization problem in Section IV. To investigate the proposed method, in Section V, a sparse and stable gene regulatory network with five genes is tested by using synthetic data. In Section VI we draw some conclusions and briefly discuss about the future work along with this study.

II. GENE REGULATORY NETWORKS

Generally, a gene regulatory network consisting of *n* genes can be modeled as a dynamic system by a set of *n* differential equations with each gene expression level as variables

$$\begin{aligned} \dot{x}(t) &= C \cdot x(t) + S \cdot r \\ r &= f\left(x(t)\right) \end{aligned} \tag{1}$$

Here $x(t) = [x_1(t), x_2(t), \cdots x_n(t)]^T \in R^n$ is the concentration of mRNAs that reflect the expression levels of the genes. C is a diagonal matrix $C = diag[-c_1, -c_2, \cdots, -c_n] \in R^{n \times n}$, where c_i is a positive number representing the self-degradation rate of gene i. Vector $r = [r_1, r_2, \cdots r_n]^T \in R^n$ is the reaction rates, which is a function of the concentrations of mRNAs, and matrix $S \in R^{n \times n}$ represents the stoichiometric matrix of the biological network. For simplicity, assume that the reaction rate r is the linear combination of mRNAs concentrations

$$r = F \cdot x(t) \tag{2}$$

where $F \in R^{n \times n}$. Substituting (2) into (1) yields:

$$\dot{x}(t) = C \cdot x(t) + B \cdot x(t) \tag{3}$$

where $B = SF \in R^{n \times n}$. Matrix B describes the structure of gene regulatory network in the following meanings: $b_{ij}>0$ if gene j promotes gene i directly; $b_{ij}=0$ if gene j does not regulate gene i directly; and $b_{ij}<0$ if gene j represses gene i directly. Without loss of generality, assume that main diagonal elements of matrix B are zeros. To identify structure of gene regulatory network, we need to determine the sign of elements in matrix B.

As gene expression data are discrete, we need to discretize the continuous system (3). By pre-multiplying the matrix e^{-Ct}, the equation (3) becomes

$$e^{-Ct} \cdot \dot{x}(t) - e^{-Ct} \cdot C \cdot x(t) = e^{-Ct} \cdot B \cdot x(t) \tag{4}$$

According to the formula of matrix exponential, the equation can be written as

$$\frac{d}{dt}\left(e^{-Ct} \cdot x(t)\right) = e^{-Ct} \cdot B \cdot x(t) \tag{5}$$

Solving this differential equation, we can get the analytical solution of the continuous model, which is

$$x(t) = e^{Ct} \cdot x(0) + \int_o^t e^{C(t-\tau)} \cdot B \cdot x(\tau) d\tau \tag{6}$$

In order to discretize the expression of $x(t)$, let

$$x[k] = x(k \cdot \Delta t) \tag{7}$$

and substituting (6) into (7), we can get the discrete form of the model, that is

$$x[k+1] = A \cdot x[k] \tag{8}$$

where $A = e^{C\Delta t} + C^{-1}(e^{C\Delta t} - I)B$.

It is worth to mention that C is a diagonal matrix. Hence, both matrices $e^{C\Delta t}$ and $C^{-1}(e^{C\Delta t} - I)$ are diagonal as well. Furthermore, it is obvious that all diagonal elements of matrices $e^{C\Delta t}$ and $(e^{C\Delta t} - I)C^{-1}$ are positive numbers, hence all diagonal elements of matrix A are positive and all off diagonal elements have the same sign with the relative elements in matrix B. Therefore, inferring the structure of gene regulatory networks becomes the estimation of all elements of matrix A.

Let $X = [x_{ij}] \in R^{n \times m}$ denote a single set of time course gene expression data that comes from a specific gene regulatory network, where n is the number of genes and m is the number of time points at which gene expression levels are measured. Let $x[k]$ denote the k_{th} column of X, then we should have

$$x[k+1] = Ax[k] + \varepsilon_k \tag{9}$$

for $k = 1, 2, \ldots, m-1$, where $\varepsilon_k \in R^n$ is the model error and/or measurement error at time point k.

Let

$$X_1 = X(:, 1:m-1) \quad \text{and} \quad X_2 = X(:, 2:m)$$

which are the sub-matrices of the first and the last $m-1$ columns of X, respectively. Then (9) can be written as

$$X_2 = AX_1 + \varepsilon \tag{10}$$

where $\varepsilon = [\varepsilon_1, \varepsilon_2, \ldots, \varepsilon_{k-1}] \in R^{n \times (k-1)}$. Now the identification of gene regulatory network becomes determining an $n \times n$ matrix A such that the model errors is minimized, that is

$$\min_{A \in R^{n \times n}} \quad \left\| AX_1 - X_2 \right\|_2^2 \tag{11}$$

where $\|\cdot\|_2$ is the Euclidean norm.

To make the biological sense, matrix A should be sparse and stable. It is easy to understand the sparsity, but we would like to introduce more detail about what the "stable" means when terms to a matrix. In mathematics, a square matrix is said to be a stable matrix if and only if all its eigenvalue have negative real parts. In terms of a simply stable system, it can converge to nearby of an equilibrium point for all nearby initial conditions. Specifically, in the following system of linear differential equations

$$x'(t) = A \cdot x(t)$$

978-1-4577-1666-9/11/$26.00 ©2011 IEEE

It is obvious that the point $x(t)=0$ is an equilibrium point, and the trajectory $x(t)$ will converge to 0 for every initial value of $x(0)$ if and only if the matrix A is a stable matrix. We can further employing Gershgorin circle theorem, which suggests that matrix A is stable if $\sum_{j=1}^{n}|a_{ij}|\le 1$ is true for all $i=1,\ldots,n$.

Therefore, according to the optimization principle [14], *l_1-norm* approximation gives relatively large weight to small residuals, and then tends to produce sparse solutions of a problem. We adding an *l_1-regularization* to the objective function (11) and further attaching the sable constraints to the optimization problem, then the identification of gene regulatory networks becomes solving the following optimization problem

$$\begin{aligned} \min_{A\in R^{n\times n}} \quad & \|AX_1 - X_2\|_2^2 + \gamma\|A\|_1 \\ \text{s.t.} \quad & A \text{ is stable} \end{aligned} \tag{12}$$

where γ is a positive constant and $\|A\|_1=\sum|a_{ij}|$ is the *l_1-norm* of matrix A. Furthermore, in order to generate the specific expression of the model (12), we employ the Gershgorin circle theorem to express its stable constraint as follows:

$$\begin{aligned} \min_{A\in R^{n\times n}} \quad & \|AX_1 - X_2\|_2^2 + \gamma\|A\|_1 \\ \text{s.t.} \quad & \sum_{j=1}^{n}|a_{ij}|\le 1 \quad \text{for all } i=1,\ldots,n \end{aligned} \tag{13}$$

There are many optimization solvers that can solve the optimization problem (13). In this preliminary study, we will not focus on designing algorithms to solve it, but just employ some solvers to handle this problem, such as the standard MATLAB function *fmincon*, or the MATLAB routines of *L_1-MAGIC* which written by Emmanuel Candès and Justin Romberg [15]. Beside this, problem (13) can also be reduced to n small size optimization problems, for elements on each row of matrix A are mutually independent with each other, and therefore can be divided as

$$\begin{aligned} \min \quad & \|X_1^T a_i^T - X_{2,i}^T\|_2^2 + \gamma\|a_i^T\|_1 \\ \text{s.t.} \quad & \sum_{j=1}^{n}|a_{ij}|\le 1 \end{aligned} \tag{14}$$

where $a_i=[a_{i1},a_{i2},...,a_{in}]$ is the i_{th} row of matrix A, and $X_{2,i}=[x_{i,2},x_{i,3},...,x_{im}]$ is the i_{th} row of matrix X_2. The solution of problem (14) contributes a row to matrix A. Let A_e denote the matrix identified by solving either problem (13) or (14).

By using optimization solvers, we can get an identification of the gene regulatory network from a single set of time course gene expression data. The sign of matrix A_e indicates a specific structure of the gene regulatory network.

Before giving the idea of network combination, two issues about proposed method should be carefully addressed. First of all, the matrix A_e which identified by solving problem (13) usually has many elements whose values are not exactly zero, but very close to zero. Therefore, the first issue is to determine if an element in A_e is zero. One can design some complicated method to handle this issue. In this study, we consider an element is actually zero if its absolute value is less than 0.05 which is 5% of the sum of absolute values on each row of A_e.

The second issue is the choice of value of positive constant γ in problem (13). The large value of γ will result that a large number of elements in A_e are zeros while model residual is large, and vice versa. To our knowledge, there is no way to choose the optimal value for γ. In this study, we empirically choose the value of 0.02 for γ.

III. MULTIPLE NETWORK COMBINATION

The sign of elements in matrix A in equation (13) gives a group structure information of the gene regulatory network. Specifically, using 1, 0 and -1 represent the sign of each element, it is easy to get the adjacency matrix of the network, where $a_{ij}=1$, if gene j promotes gene i directly; $a_{ij}=0$ if gene j does not regulate gene i directly; and $a_{ij}=-1$ if gene j represses gene i directly. As we illustrated in Section II, let A_e denote the adjacency matrix identified from a single set of gene expression data by solving the problem (13). Since each single dataset can generate a specific structure of the gene network, but none of them can describe the real network exactly due to the scarcity of time point. Therefore, it becomes indispensable to infer a more reasonable gene network by using multiple datasets.

Given k groups of gene expression data, let $A_e^{(1)},A_e^{(2)},...,A_e^{(k)}$ denote each identified adjacency matrix (they are discrete, and further assume that each of them has the same number of gene and is arranged as the same order), then the following proposed network combination methods are aim to identify the maximum likelihood gene network from these candidacy adjacency matrix. For simplicity, we handle only one edge at a time, instead of taking the whole gene network into consideration. It is reasonable, because each edge in the network is independent, and makes the illustration of network combination method more clear.

For any given edge in the network, let $a_{eij}^{(1)},a_{eij}^{(2)},...,a_{eij}^{(k)}$ denote the identified results in matrices $A_e^{(1)},A_e^{(2)},...,A_e^{(k)}$, respectively. Assume that there is no further prior information about the system. The network combination methods are to combine these inferred edges, thereby generating the structure of the network.

Two methods of network combination are proposed here, using the statistic mean and mode of a given series, respectively. Either of methods can be used to infer gene regulatory networks, depending on the character of datasets.

Firstly, the mean of a given series present an average meaning of the group of data. Let

$$m_{ij}=\frac{1}{k}\sum_{p=1}^{k}a_{eij}^{(p)} \tag{15}$$

denote the value of mean. Then, given a positive value Δ, if $m_{ij}>\Delta$, let $a_{eij}=1$, if $-\Delta\le m_{ij}\le\Delta$, let $a_{eij}=0$ and if $m_{ij}<-\Delta$, let $a_{eij}=-1$. By doing these processes on all edges, a new topological structure of the network can be generated according to the differences of m_{ij}s, which actually

978-1-4577-1666-9/11/$26.00 ©2011 IEEE

combines the structures that inferred from multiple datasets. Here, the most important issue is to determine the value of Δ, which indicates a threshold of network combination. In this study, we empirically choose 0.3 as its value.

Secondly, another statistic "mode" means the value that occurs most often, and thus carries the information about the average of a group of data. Using the value of mode to represent the interactions between there two genes is the second way to do network combination. It is particularly useful when most of the identified edges between two genes are contrary and incompatible from different dataset.

As differences between the character of mean and mode, it seems that network combination which uses the value of mean as the criterion result in a sparser network, while that use mode result in more interactions between genes. This is due to the fact that the value of mean will trend to close to zero, while the value of mode will either equals to "1" or "-1", if most of the inferred edges are contrary. Furthermore, the increase number of datasets also contributes to more small value of mean. In practice, either of them can be used to infer the structure of networks, and it is better to pick the one that more reasonable, according to the character and the number of datasets and the prior information about systems.

IV. Parameter Estimation

The network combination methods can generate the structure of gene regulatory networks by combining information from multiple datasets, thereby increasing the accuracy of inferred topological structure. We will further illustrate how to estimate the parameter of a gene regulatory network after giving the information of such structure. Without confusing, we still use A_e to denote the inferred adjacency matrix after network combination, then the problem of parameters estimation in gene regulatory network can be formulated as determining matrix A that minimizes the model errors of

$$\begin{aligned} \min_{A\in R^{n\times n}} \quad & \left\| AX_1 - X_2 \right\|_2^2 \\ \text{s.t.} \quad & A \text{ has the same structure with } A_e \end{aligned} \tag{16}$$

where X_1 and X_2 are sub-matrices of X that illustrate in Section II. Then the parameters of this network base on X are the best character of network of this specific single dataset. In order to employ the MATLAB standard function *fmincon* to solve model (16), we need to divide this model into n optimization problem, each having n variables which are elements on a row of matrix A. Similarly to the problem (13), model (16) can be written as n optimization problem, that is,

$$\begin{aligned} \min \quad & \left\| X_1^T a_i^T - X_{2,i}^T \right\|_2^2 \\ \text{s.t.} \quad & 0< a_{ij} \le 1 \qquad \text{if } a_{eij} = 1 \\ & a_{ij} = 0 \qquad \text{if } a_{eij} = 0 \\ & -1 \le a_{ij} < 0 \qquad \text{if } a_{eij} = -1 \end{aligned} \tag{17}$$

Here the $a_{eij}s$ are elements in matrix A_e. In practice, it should be mentioned that the function *fmincon* only attempts to find a solution of the model that starting at an initial value. Therefore, it is sensitive to initial values and may only find the local optimal solution. To handle this problem, we randomly choose 100 initial values for problem (17), and the solutions that minimize the objective function are considered as the final optimal solution. Let $\hat{A}$ denote the inferred matrix that reflects the regulatory relationships in the gene network.

V. Evaluation and Computational Experiments

To test the performance of the methods described above, several computational experiments are performed on synthetic datasets, where the inferred structures and network parameters can be easily compared with the original system.

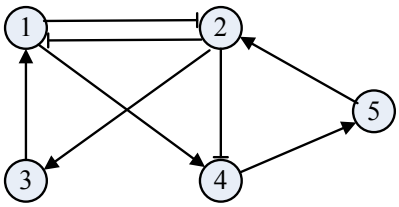

Figure 1. A gene regulatory network with five genes [11] (→: promotion, ⊣: repression)

To evaluate the accuracy of inferred structure of networks, we compare the sign of elements in A with the sign of those in A_e. Here A represents the real adjacency matrix of original system, and A_e characterize matrix that is inferred through network combination. Let r_1, r_2 and r_3 denote the number of correctly identified positives, zeros and negatives, respectively. Then the accuracy of identification can be defined as

$$accuracy = \frac{r_1 + r_2 + r_3}{n^2} \tag{18}$$

In terms of the estimation accuracy of parameters, similarly to the method suggested by Michal Ronen et al [16], we can measure the sum errors of inferred parameters, that is

$$E = \frac{1}{n^2} \sum_{i=1}^{n} \sum_{j=1}^{n} \left| a_{ij}^{measured} - a_{ij}^{predicted} \right| \tag{19}$$

where $a_{ij}^{measured}$ is the element in matrix A, and $a_{ij}^{predicted}$ is the element that in matrix $\hat{A}$.

In the following, we report on one group of numerical experiments that we have conducted to test our proposed methods. The experiments are performed on a simplified synthetic gene regulatory network, which consists of only five genes, used in [11]. The structure of the gene regulatory network is shown in Figure 1., and the adjacency matrix is

$$A_0 = \begin{bmatrix} 1 & -1 & 1 & 0 & 0 \\ -1 & 1 & 0 & 0 & 1 \\ 0 & 1 & 1 & 0 & 0 \\ 1 & -1 & 0 & 1 & 0 \\ 0 & 0 & 0 & 1 & 1 \end{bmatrix} \tag{20}$$

where positive "1" at (i, j)-entry means gene j promotes the expression of gene i; negative "-1" at (i, j)-entry means gene j represses the expression of gene i; and zero "0" at (i, j)-entry means gene j does not directly affect the expression of gene i. At each experiment, the values of nonzero regulatory

978-1-4577-1666-9/11/$26.00 ©2011 IEEE

parameters are assigned randomly, and the gene expression profiles are created by using model (8), with randomly chosen initial values x(0).

Firstly, we study changes of accuracy of the inferred structure about the gene regulatory network, by varying the number of time points and altering conditions of network combination. To be more precise, we test the results of gene expression profiles with the time points m=3, 4 and 5, respectively. For each given length of gene expression profiles, we randomly generate 10000 stable matrices A with the same template A_0 defined in (20), and then inferring the structure of gene networks by solving model (13) directly (which means using each single set of gene expression profiles without network combination), by using the above results and every five or ten solutions as a group to infer structures (which means using five or ten gene expression profiles datasets with network combination). The experiments results are shown in Figure 2, where m is the length of gene expression profiles, and N is the number of datasets that used to do network combination. Both results of network combination that using the statistic mean and mode are shown in this Figure. The more accurate results are given in Table 1.

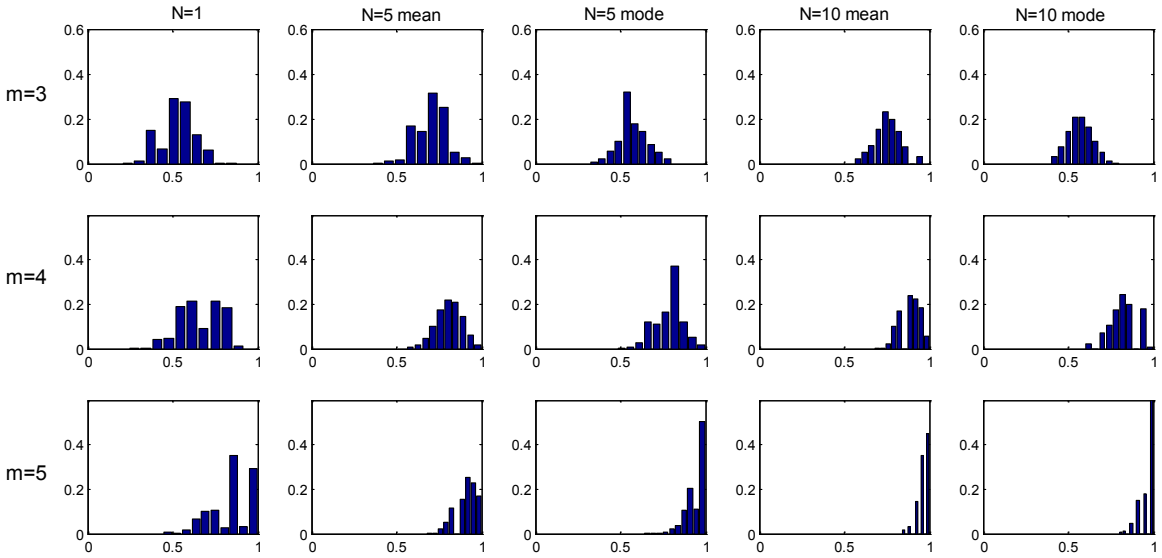

Figure 2. Histograms of accuracy for the different number of time points with two network combination methods

It can be clearly see from the table that both lengths of gene expression profiles and ways of network combination greatly influence the accuracy of inferred gene networks. However, the more significant conclusion indicates from the results is that network combination can dramatically increase the accuracy of the topological structure of gene network, not only largely better than that with same length of gene expression profiles, but even more accuracy than that with more time points.

Table 1. The variance of the average accuracy

	N = 1	N = 5		N = 10	
		mean	mode	mean	mode
m=3	0.5251	0.6974	0.5758	0.7720	0.5888
m=4	0.6601	0.8058	0.7850	0.8918	0.8358
m=5	0.8553	0.9167	0.9521	0.9674	0.9716

Secondly, we test the parameters error about the inferred gene regulatory networks. As illustrated in Section IV, we can estimate the parameters of networks with the specific inferred structures. In order to compare the average parameter errors of gene networks, we perform a group of numerical experiments on different length of gene expression profiles and different ways of network combination. The sum errors are measured at a specific condition by varying the number of datasets for network combination. Specifically, the length of gene expression profiles are three, four and five, respectively, while the ways of network combination changes between using statistic mean and mode. The numbers of datasets for network combination are one, five and ten respectively, and each of them is performed on 500 experiments. The test results are shown in Figure. 3, and we can clearly cluclude that the more accuracy structure of networks, the less errors of the regulatory parameters.

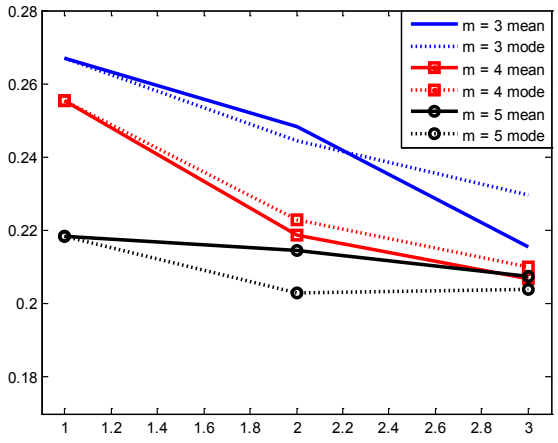

Figure 3. The comparision of parameters errors

978-1-4577-1666-9/11/$26.00 ©2011 IEEE

Finally, we study the influence of noise in gene expression profiles to the accuracy of structure identification, as gene expression levels are noise contaminated in practice. To be reality, we consider each gene expression profile with four time points which are less than the number of genes in the network. Nine levels of system noise are added into system (9), varying from 0% to 20%, respectively. At each noise level, 10000 groups of gene regulatory systems are produced from randomly created networks with template A_0 defined in (20), and the gene expression profiles are generated by randomly choosing initial values and associated noises. The average accuracies with respect to different noise levels are plotted in Figure 3. It is unsurprising that the accuracy decreases with the increase of noise level. However, it is worth nothing that the results with network combination can still maintain higher accuracies. Specifically, the average accuracy with network combination (mean) using ten groups of datasets could still maintains around 65%, even the noise level soars to 20%, while that without network combination only stays at about 45%.

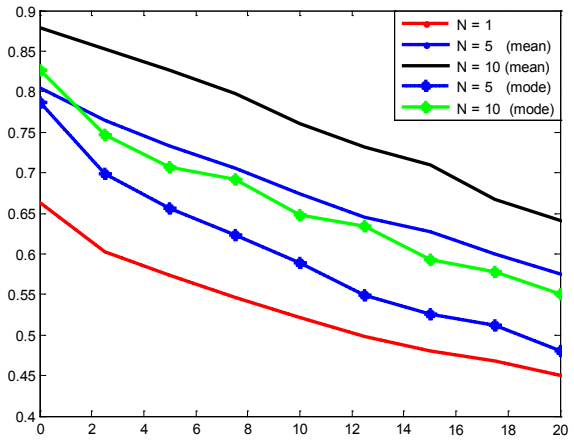

Figure 4. The average accuracy with different noise levels

It is well known that large amount of gene expression data can get a better identification about gene regulatory network. However, in reality, the number of time points in gene expression profile is far less than the number of genes, and it is also expensive to obtain. From the results of our numerical experiments, we can find that network combinations contribute another way to infer the accuracy networks, and it can generate the network with lower parameter errors.

VI. CONCLUSION

In this paper, we have proposed a method for inferring sparse and stable gene regulatory networks from multiple datasets of gene expression profiles. The results from our computational experiments have shown that the proposed methods can correctly find the majority connections and lower parameters errors in synthetic networks.

In this study, we empirically choose the values for γ in problem (13) and the cut-off value to determine if an element is zero. In the future, we should develop a more objective method to choose these two values. Furthermore, the accuracy we proposed need to know the real network structure, while it is of course unavailable for the real experimental datasets. We will investigate the more general evaluation methods to handle real experimental datasets.

ACKNOWLEDGMENT

This study was supported by Natural Science and Engineering Research Council of Canada (NSERC).

REFERENCES

[1] M. K. S. Yeung, J. Tegnér and J. J. Collins, “Reverse engineering gene networks using singular value decomposition and robust regression”, PNAS, 99(9), 6163-6168, 2002

[2] Y. Wang, T. Joshi, X. S. Zhang, D. Xu and L. Chen, “Inferring gene regulatory networks from multiple microarray datasets”, Bioinformatics, 22(19), 2413-2420, 2006

[3] R. Xu, D. C. Wunsch II and R. L. Frank, “Inference of Genetic Regulatory Networks with Recurrent Neural Network Models Using Particle Swarm Optimization”, IEEE/ACM Transactions on Computational Biology and Bioinformatics, 4(4), 681-692, 2007

[4] T. Akutsu, S. Miyano, and S. Kuhara, “Identification of genetic networks from a small number of gene expression patterns under the Boolean network model,” Pacific Symposium on Biocomputing 4, 17-28, 1999.

[5] A. J. Hartemink, D. Gifford, T. Jaakkola and R. Young, “Using graphical models and genomic expression data to statistically validate models of genetic regulatory networks”, Pac. Symp.Biocomput., 6, 422–433.

[6] J. Hertz, M. Wahde, "Coarse-grained reverse engineering of genetic regulatory networks", Biosystems, 55, 129-136, 2000

[7] P. D’Haeseleer, S. Liang and R. Somogyi, “Genetic network inference: from co-expression clustering to reverse engineering”, Bioinformatics, 16(8), 707-726, 2000

[8] T. Chen, H. L. He, and G. M. Church, “Modeling Gene Expression with Differential Equations,” Pacific Symposium on Biocomputing 4, 29-40, 1999.

[9] M. J. L. de Hoon, S. Imoto, K. Kobayashi, N. Ogasawara, and S. Miyano, “Inferring Gene Regulatory Networks from Time-Ordered Gene Expression Data of Bacillus Subtilis Using Differential Equations”, Pacific Symposium on Biocomputing 8, 17-28, 2003.

[10] F. X. Wu, W. J. Zhang, and A. J. Kusalik, “Modeling gene expression from microarray data with state space equations,” Pacific Symposium on Biocomputing 9: 581-592, 2004

[11] F. X. Wu, L. Z. Liu, and Z. H. Xia, “Identification of gene regulatory networks from time course gene expression data”, 32nd Annual International Conference of the IEEE EMBS, 795-798, 2010

[12] B. E. Perrin, L. Ralaivola, A. Mazurie, S. Bottani, J. Mallet and F. d’Alché-Buc, “Gene networks inference using dynamic Bayesian networks”, Bioinformatics, 19(Suppl.2), ii138-ii148, 2003

[13] M. M. Zalanos, A. A. Julius, S. P. Boyd and G. J. Papas, “Identification of stable genetic networks using convex programming”, Proceedings of 2008 American Control Conference, 2755-2760, 2008.

[14] S. Boyd and L. Vandenbergehe, “Convex Optimization” Cambridge: Cambridge University Press, 2004

[15] E. Candès and J. Romberg, “L1-MAGIC: Recovery of Sparse Signals via Convex Programming”, 2005 http://www.acm.caltech.edu/l1magic/

[16] M. Ronen, R. Rosenberg, B. I. Shraiman and U. Alon, “Assigning numbers to the arrows: Parameterizing a gene regulation network by using accurate expression kinetics”, PNAS, 99(16), 10555-10560, 2002