Meta-Analysis on Gene Regulatory Networks Discovered by Pairwise Granger Causality

Gary Hak Fui Tam and Yeung Sam Hung
Department of Electrical and Electronic Engineering
The University of Hong Kong
Hong Kong, China
hftam@eee.hku.hk, yshung@eee.hku.hk

Chunqi Chang
School of Electronic and Information Engineering
Soochow University
Suzhou, Jiangsu Province, China
cqchang@suda.edu.cn

***Abstract*—Identifying regulatory genes partaking in disease development is important to medical advances. Since gene expression data of multiple experiments exist, combining results from multiple gene regulatory network discoveries offers higher sensitivity and specificity. However, data for multiple experiments on the same problem may not possess the same set of genes, and hence many existing combining methods are not applicable. In this paper, we approach this problem using a number of meta-analysis methods and compare their performances. Simulation results show that vote counting is outperformed by methods belonging to the Fisher's chi-square (FCS) family, of which FCS test is the best. Applying FCS test to the real human HeLa cell-cycle dataset, degree distributions of the combined network is obtained and compared with previous works. Consulting the BioGRID database reveals the biological relevance of gene regulatory networks discovered using the proposed method.**

Keywords—gene regulatory network; meta-analysis; multiple experiments; pairwise Granger causality; Fisher's chi-square test

I. INTRODUCTION

Gene regulatory network (GRN) discovery detected gene-gene interactions from gene expression data [1]–[11]. Genes identified to play roles in disease development are potential targets of future drugs [2]–[4]. Since DNA microarray technology has been extensively applied to various medical problems, data of multiple experiments (datasets) concerning the same problem often exist. Combining results from multiple experiments offers higher statistical power and the discovered network is more reliable, but it is not a trivial task [1]. Particularly, data for multiple experiments may not contain the same set of genes. For example, in the widely studied human HeLa cell-cycle dataset [12], out of a total of 1134 periodic genes, the number of genes contained in experiments 1–3 are only 828, 828 and 1099, respectively [11]. (Although experiments 1 and 2 both have "828" genes, they correspond to slightly different gene subsets.) Therefore, many combining methods (e.g. [1], [8]) assuming the same gene set are not applicable. Meta-analysis (MA) provides a direct solution to the problem of how these experiments may be combined.

Previously, MA on gene expression data focused on detection of differentially expressed genes, e.g. see [13], [14]; while applications to GRN discovery are relatively fewer. Nevertheless, recent studies [15]–[17] demonstrate that MA is a powerful tool for combining multiple results for GRN discovery. However, to our knowledge, we have not seen a paper comparing MA methods in the usual situation that multiple experiments do not have the same set of genes. In this paper, we apply several most commonly adopted MA methods to this problem and compare their performance. First, the selected MA methods are evaluated by synthetic data. Then, the best performing MA method is applied to the HeLa dataset.

II. PAIRWISE GRANGER CAUSALITY

Granger causality (GC) [18] has a number of merits over other time-series analysis methods [19], and hence is adopted here for GRN discovery. Consider two time series X and Y, if Y can help predict the future of X, then Y "Granger-causes" X. Suppose the time series of these two variables have data length T, denoting their values at time t by X_t and Y_t (t=1,2,…,T), respectively, they can be modelled by a bivariate autoregressive (AR) model:

$$\begin{aligned} X_t &= \sum_{l=1}^{p}\left(a_{11,l}X_{t-l} + a_{12,l}Y_{t-l}\right) + \varepsilon_t \\ Y_t &= \sum_{l=1}^{p}\left(a_{21,l}X_{t-l} + a_{22,l}Y_{t-l}\right) + \xi_t \end{aligned} \tag{1}$$

where p is the model order, $a_{ij,l}$ (i,j=1,2) are coefficients of the model, and ε_t and ξ_t represent residuals. The coefficients can be estimated by ordinary least squares, and the GCs between X and Y can be detected by F tests [10], [11].

For a system with n variables, the above modelling can be applied to each pair of variables, which is referred to as pairwise GC (PGC). An n-variable network has a total of $M = n(n-1)$ possible directed edges, and each edge will be assigned a p-value by PGC. However, not all p-values are valid, since some bivariate models may not fit to data well and they may give rise to false discoveries easily. These badly fitted models are excluded by model validation, hence performance of PGC can be increased [10]. The valid p-values then undergo Benjamini-Hochberg false discovery rate (FDR) controlling procedure [20], where we need to provide a FDR level q to be controlled, and the procedure will return a threshold on p-value.

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Those edges with p-values ≤ the threshold are taken as detected GCs that constitute the discovered network. Further details can be found in [10] and [11].

III. META-ANALYSIS METHODS

In GRN discovery, a gene is referred to as a variable, so "gene" and "variable" may be used interchangeably in literature. We formulate the problem as follows. Suppose we have data of k experiments on a total of n genes. Each experiment E_i (i=1,2,…,k) contains n_i genes, which is a subset of the n genes. After applying PGC, each experiment gives a discovered network G_i of n_i genes, where every edge in G_i is associated with a p-value. We want to combine these k networks into one network G_{MA} of n genes. In the following, we consider methods belonging to two families of commonly adopted MA methods [14]–[17]: vote counting and Fisher's chi-square methods.

A. Vote Counting

G_{MA} has $M = n(n-1)$ possible edges. In vote counting (VC), for each of these possible edges, we count the number of times (votes) this edge is included in some G_i. Those edges with votes ≥ a certain threshold constitute G_{MA}. If we only require the number of votes ≥ 1, then G_{MA} includes all edges in G_i. We refer to this network as VC1. Similarly, the G_{MA} composed of edges with votes ≥ 2 is referred to as VC2, etc.

B. Fisher's Chi-Square Methods

According to [21], given p-values p_i (i=1,2,…,κ) from κ independent studies, the Fisher's chi-square (FCS) test statistic can be computed as:

$$\chi_{\text{F}}^2 = -2\sum_{i=1}^{\kappa} \ln p_i \,. \tag{2}$$

Regarding our GRN discovery problem, if an edge (say, from gene Y to gene X) has κ p-values from G_i ($\kappa \le k$), its χ_{F}^2 can be computed by (2). Under the null hypothesis that gene Y does not Granger-cause X, this χ_{F}^2 has a chi-square distribution with 2κ degrees of freedom. Hence, a new p-value p_{F} for combining κ studies can be obtained. After computing p_{F} for all potential edges, again we apply Benjamini-Hochberg FDR control (often at another FDR level q_{F}) to fix a p-value threshold and edges with p_{F} below the threshold will constitute G_{MA}. We term this method as FCS test (FCST).

Alternatively, χ_{F}^2 can also be used to rank the potential edges, e.g. as in [15]. We term this approach as FCS Ranking (FCSR). To compare with FCST, suppose the G_{MA} obtained by FCST consists of H_{F} edges, we also take H_{F} edges with largest χ_{F}^2 to be another G_{MA}, which is referred to as FCSR1. To compare with VC2, we take the same number of edges as VC2 from the FCSR to be a G_{MA} – denoted as FCSR2.

Since the FCSR approach does not have a natural threshold, we derive one as follows. Suppose G_i has H_i edges (remark: H_i comes from Benjamini-Hochberg FDR control at level q), we scale up H_i by the ratio of all possible edges (the search space in GRN discovery) between G_i and G_{MA}:

$$H' = \frac{1}{k}\sum_{i=1}^{k} \frac{n(n-1)}{n_i(n_i-1)} H_i \,. \tag{3}$$

H' is then rounded to nearest integer, which is the number of edges to be taken. The resulted G_{MA} is denoted as FCSR3.

It should be remarked that FCS methods are not restricted to PGC. They can also be applied to other GRN discovery methods, as long as every discovered edge has a p-value. VC does not even require a p-value.

IV. SIMULATIONS

A. Synthetic Data

To generate synthetic data, we adopt an 8-variable AR model (i.e. n=8), which is composed of two smaller models of 5 and 3 variables [22], [23]:

$$\begin{aligned}
x_1(t) &= 0.95\sqrt{2}x_1(t-1) - 0.9025x_1(t-2) + w_1(t)\\
x_2(t) &= 0.5x_1(t-2) + w_2(t)\\
x_3(t) &= -0.4x_1(t-3) + w_3(t)\\
x_4(t) &= -0.5x_1(t-2) + 0.25\sqrt{2}x_4(t-1) + 0.25\sqrt{2}x_5(t-1) + w_4(t)\\
x_5(t) &= -0.25\sqrt{2}x_4(t-1) + 0.25\sqrt{2}x_5(t-1) + w_5(t)\\
x_6(t) &= 0.8x_6(t-1) - 0.5x_6(t-2) + 0.4x_8(t-1) + w_6(t)\\
x_7(t) &= 0.9x_7(t-1) - 0.8x_7(t-2) + w_7(t)\\
x_8(t) &= 0.5x_8(t-1) - 0.2x_8(t-2) + 0.5x_7(t-1) + w_8(t).
\end{aligned} \tag{4}$$

The corresponding regulatory network is shown in Fig. 1. w_j and initial values of x_j (j=1,2,…,8) are independent Gaussian noises of zero mean and unit variance. This 8-variable model has order p=3. Starting with some initial values, we iterate (4) to get long time series of length 140×3. For each of the 140-long segments, the first 100 time points (transient) are dropped and the subsequent 40 time points are taken as experimental data (i.e. T=40). Hence, data of 3 experiments are obtained (k=3).

To simulate the situation that multiple experiments may not contain the same set of genes, we purposely exclude data of a

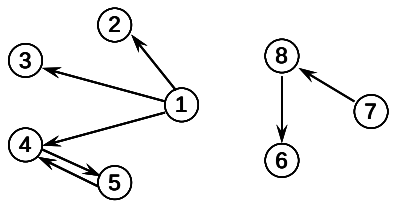

Fig. 1. Regulatory network of model (4).

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few variables in each experiment, where 0–3 variables may be excluded randomly. Since the average exclusion is 1.5 variables, on average each experiment contains n_i=6.5 variables. We also require that the union of variables in these 3 experiments should be 8, i.e. the 3 experiments together should contain all the 8 variables in (4).

B. Performance Measures

Here we describe some performance measures for a discovered network if ground truth is known. Suppose a discovered network has H edges, e of them are true positives (TPs), then precision $P = e/H$. Denote the number of edges of the ground truth network by L, then recall $R = e/L$. The mean compromising P and R is $F_1 = 2PR/(P+R)$. P, R and F_1 all range from 0 to 1, and they are different if $H \neq L$. In extreme cases, a 1-edge discovered network can have $P = 1$ (if this edge is a TP) but a low R; a discovered network consists of all M possible edges can have $R = 1$ but a low P. But $F_1 = 1$ requires the discovered network matches the ground truth exactly. Thus in the following, we focus more on F_1.

C. Results and Discussion

Using the synthetic data as generated above, we apply PGC with model validation to each experiment E_i separately to obtain discovered network G_i (i=1,2,3). We assume ground truth is unknown, so the model order of each PGC application is estimated by Akaike information criterion (AIC) [11], [24]. For the Benjamini-Hochberg FDR control, q is fixed at 0.05.

When the 3 G_i's are ready, MA methods are applied to them. Each MA method gives a G_{MA}, and its performance measures can be calculated by comparing with the ground truth network in Fig. 1. Since combining 3 experiments offers a much higher statistical power, the new p-values p_F in FCST are much smaller than those in G_i. Hence, q_F=0.001 is used for Benjamini-Hochberg FDR control in FCST.

The above exercise is repeated 30 times with different initial values for x_j. Results of these 30 runs are shown in Table I. Besides the MA methods, we also show the results of G_i in the first row – labelled by "1-Expt", because each G_i only comes from a single experiment. It turns out that ≈ 6.6 (±1.1) variables are included in each experiment. The model order estimated by AIC ≈ 3.3 (±1.1). The average number of edges in G_i is 5.0, and G_i's have average F_1 of 0.50.

From Table I(a), MA methods generally give higher F_1 than 1-Expt. VC1 contains too many edges (H=10.6 is substantially larger than L=7), so R is high, but P is even lower than 1-Expt case. VC2 has high P. But it is already a bit too strict that H is substantially smaller than L, so results in low R, making that F_1 is lower than VC1's. VC3 is really strict that very few edges can pass this criterion – in average H=0.7 only. However, it is amazing that all edges passing this criterion are correct (P=1)! Yet, since H is too small, VC3 is not useful in practice.

FCST and FCSR1 give the same and the highest (best) F_1=0.69 in these 30 runs. Discovered edges by FCST generally have p-values < 0.0006. FCSR2 should be compared with VC2: though H are the same, FCSR2 gives higher measures for {TP, P, R, F_1}, meaning that the ranking ordered by χ^2_F (through p-values from single experiment) is better than simple vote counting. FCSR3 turns out also to give high F_1.

Although FCST and FCSR1 give exactly the same results in the 30 runs, they are conceptually different. The same results here can be understood as follows. H of VC1, VC2 and FCST are 10.6, 3.7 and 6.2, respectively. That means the thresholding of FCST usually lies in VC=1 region, i.e. κ=1. With the same κ, the two criteria FCST and FCSR1 are the same. Nevertheless, we have repeated similar exercise as above 100 times with larger number of experiments k=10, then F_1 of FCST is a bit higher than FCSR1's, where the difference is 0.006. Their discovered networks differ in 9 out of 100 runs, where FCST is better in 7 runs and worse in 2 runs. It means that FCST and FCSR1 give the same discovered network most of the time. However, there are still some situations that they give different discovered networks, and FCST often works better in such cases. This reveals that the degrees of freedom in the chi-square test also count. Since χ^2_F is only a test statistic, and FCST rigorously returns a p-value, FCST is preferred conceptually. Moreover, there is lack of guidance for setting a threshold for FCSR. Therefore, among the MA methods listed in Table I, we conclude that FCST is the best. FCST will be applied to real data in next section.

TABLE I. SIMULATION RESULTS OF SINGLE EXPERIMENT AND META-ANALYSIS METHODS

(a) Mean					
	H	**TP**	***P***	***R***	***F*$_1$**
1-Expt	5.0	3.3	0.65	0.46	0.50
VC1	10.6	5.4	0.55	0.78	0.63
VC2	3.7	3.3	0.84	0.47	0.58
VC3	0.7	1.8	**1.00**	0.25	0.39
FCST	6.2	4.6	0.79	0.65	**0.69**
FCSR1	6.2	4.6	0.79	0.65	0.69
FCSR2	3.7	3.5	0.89	0.50	0.61
FCSR3	7.3	4.8	0.69	0.69	0.67

(b) Standard Deviation					
	H	**TP**	***P***	***R***	***F*$_1$**
1-Expt	3.1	1.7	0.27	0.24	0.20
VC1	3.4	1.0	0.16	0.14	0.11
VC2	2.1	1.4	0.18	0.19	0.17
VC3	1.0	0.8	0.00	0.11	0.14
FCST	2.2	1.0	0.17	0.15	0.11
FCSR1	2.2	1.0	0.17	0.15	0.11
FCSR2	2.1	1.3	0.15	0.19	0.15
FCSR3	2.3	1.0	0.15	0.14	0.10

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We have also repeated the simulation of 3 experiments using different data lengths $T = 20$, 30 and 40 in E_1, E_2 and E_3, respectively. This exercise leads to the same conclusion as before: FCST remains the best.

V. META-ANALYSIS ON REAL HELA DATA

The human HeLa dataset [12] contains time-series gene expression data from cell division cycle experiments using cDNA microarrays. Most GRN discovery studies on this dataset (e.g. [5]–[7]) concentrated on analyzing the 1134 periodic genes using data of experiments 1–3. In a previous work [11], for the sake of comparison, we have applied PGC with model validation also to the 1134 periodic genes in experiments 1–3. Discovered networks (G_i) consisting thousand of edges are obtained. A brief summary is given in Table II. E_3 yields substantially more edges than E_1 and E_2 because E_3 contains more genes and longer series which offer higher statistical power for GC detection.

Now, we apply FCST to the 3 G_i's. Since p-values from PGC are generally larger in HeLa real data (one order of magnitude higher than those in synthetic data), we relax q_F to 0.01 such that the number of discovered edges in G_{MA} is more reasonable and not too small. The resulted G_{MA} contains a total of 29146 edges, with p-values (p_F) ranging from 0.0066 to 6.0×10^{-11}, and their geometric mean is 9.3×10^{-4}. It turns out that these 29146 edges include all edges with VC≥2. E_1, E_2 and E_3 contribute 2301, 3878 and 24001 edges, respectively, and they have some overlaps.

TABLE II. SUMMARY OF ADOPTED HELA DATA AND DISCOVERED NETWORKS FROM PGC

	n_i	T^a	H_i
E_1	828	11	3691
E_2	828	26	7685
E_3	1099	47	33601

[a] Effective data length [11]

Since the ground truth network is unknown for this real dataset and hence previous measures {TP, P, R, F_1} cannot be computed, we compute degree distributions instead [25], which also provides insight to the structure of large networks [11], [26]. The discovered network G_{MA} involves 1101 genes, where 1088 have in-degree > 0 and 1007 have out-degree > 0. The (in-/out-) degree distributions of the 1101 genes are plotted in Fig. 2, which shows similar power-law decay as in [5] and [7]. Denoting degree by d, the degree distribution in Fig. 2(c) has a decay approximately as d^{-2}. The degree exponent 2 is consistent with our previous work [11], but it is smaller than 2.7 in [5] which used E_1 only.

Table III shows the top 10 genes with maximum (in-/out-) degrees. Network hubs (genes with high degrees) shown in Table III(c) generally have higher out-degrees than in-degrees, meaning that they act as sources rather than recipients in interactions. This agrees with our previous works [10], [11]. Genes 3.UBE2C, 5.CDC2, 10.FLJ10468, 16.TOP2A, 23.KNSL5, 26.CDC2, 42.DJ616B8.3, 87.USF1 were also found to have high degrees in [6].

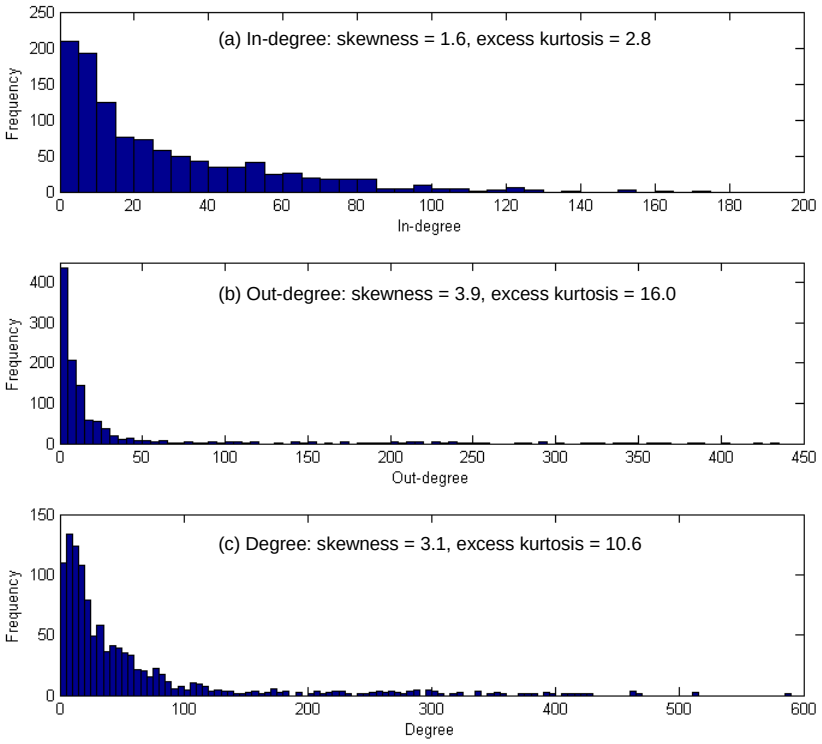

Fig. 2. Degree distributions of the 1101 genes involved in discovered network by FCST for HeLa dataset. Excess kurtosis = kurtosis – 3. So, skewness and excess kurtosis are both zero for Gaussian distribution.

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TABLE III. TOP 10 GENES WITH MAXIMUM (IN-/OUT-) DEGREES

(a) In-degree	
Gene name	*In-degree*
333.MCM6	172
257.ESTs	163
5.CDC2	154
190.MDS025	151
73.TTK	136
6.TOP2A	126
83.ESTs	125
66.CKAP2	123
86.FLJ23311	123
25.CCNA2	122

(b) Out-degree	
Gene name	*Out-degree*
5.CDC2	431
3.UBE2C	423
10.FLJ10468	400
16.TOP2A	389
6.TOP2A	388
47.KPNA2	384
42.DJ616B8.3	368
87.USF1	363
11.CCNF	361
26.CDC2	357

(c) Degree	
Gene name	*Degree*
5.CDC2	585
3.UBE2C	514
6.TOP2A	514
10.FLJ10468	467
23.KNSL5	464
16.TOP2A	462
26.CDC2	462
47.KPNA2	426
42.DJ616B8.3	423
11.CCNF	418

The numeric label preceding each gene name is the row number in the data file dataPlusScores_all5.txt that can be downloaded from the web link shown in the abstract of [12]. More information and discussion can be found in [12], and Sections 1.3.1 and 2.8 in [27].

From Table III(c), 5.CDC2 is the network hub with highest degree. 484 genes are connected to it in our discovered network G_{MA}. CDC2 is known as cyclin-dependent kinase 1, with official symbol CDK1. According to the Entrez Gene record on CDC2 [28], "the protein encoded by this gene is a member of the Ser/Thr protein kinase family". This protein is "essential for G1/S and G2/M phase transitions of eukaryotic cell cycle". In our discovered network, many interactions with CDC2 are documented in the BioGRID database [29]. For example, using low-throughput experiment, Qi *et al*. [30] found that BUB1 activity was enhanced by CDK1-mediated phosphorylation. This is consistent with the discovered edge "5.CDC2 → 15.BUB1". The interaction "5.CDC2 ↔ 17.CKS2" is confirmed by 2 papers [31], [32], where [32] mentioned that mammalian CKS2 bound CDK1 and participated in cell-cycle control. Kong *et al*. [33] found that "Cyclin F (CCNF) regulates the nuclear localization of cyclin B1 (CCNB1) through a cyclin-cyclin interaction", which involved "a complex composed of CDC2 and a B-type cyclin". This agrees well with our discovered edges involving these 3 genes, as drawn in Fig. 3.

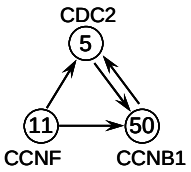

Fig. 3. Discovered edges involving genes 5.CDC2, 11.CCNF and 50.CCNB1.

VI. CONCLUSION AND DISCUSSION

We have applied MA methods to combine GRN discoveries (by PGC) from data of multiple experiments that may not have the same set of genes. Simulation results show that vote counting is outperformed by FCS methods, among which FCST is the best. Applying FCST to the HeLa dataset, degree distributions of the combined network is obtained and compared with previous works. The gene CDC2, which plays important roles in cell-cycle regulation, is found to be the network hub with highest degree. Many of our discovered edges are documented in the BioGRID database. It should be remarked that FCST can also be applied to networks obtained by GRN discovery methods besides PGC, as long as *p*-values of all discovered edges are available.

A potential improvement to the above scheme is to consider network inference under a single model which optimizes the network structure by consulting data of all multiple experiments simultaneously, such as the two methods in [1] and [8]. However, these methods need to be modified for the present situation that multiple experiments do not possess the same set of genes. This is a non-trivial task and demands further efforts.

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