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Reconstruction of Gene Regulatory Network from Gene Perturbation Data, Current Methods and Problems

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***Abstract*—The inference of regulators is the core factor in interpreting the actual regulatory conditions in gene regulatory networks (GRNs). Various methods have been developed to reconstruct GRNs with the motivation of improving the accuracy and scalability of network inference. Thus, this study will brief the structure of GRNs, discuss current methods of GRNs reconstruction and problems when dealing with gene perturbation data. Most of the information gathered from bioinformatics and system biology literature. At the end of the study several of GRNs reconstruction methods will be reviewed and identified their problem when dealing with gene perturbation data. This study is useful as a reference to develop more accurate GRNs inference methods particular for gene perturbation data.**

***Keywords*— gene regulatory network, reconstruction of gene regulatory networks (GRNs), gene expression data, gene perturbation, machine learning methods**

I. Introduction

Reconstruction of gene regulatory networks (GRNs) is the core factor in interpreting the actual regulatory conditions in GRNs [1]. It helps us to understand the working mechanisms of the cell in pathophysiological conditions [2]. GRNs describe control at the gene expression level and could be inferred from microRNAs (miRNAs), regulatory motifs, gene expression profiles and interactions between regulatory targets [3]. This provides a clearer blueprint on the relationship between the genes that affect the expression of other genes and adequately describing these effects [4]. The importance of gene interaction research studies has provided several useful applications such as the identification and discovery of potential targets for therapeutic intervention in diseases such as cancer [5]. Thus, a number of techniques have been proposed for GRNs reconstruction. Here we will first brief the structure of GRN, discuss the current methods for GRNs reconstruction, and present some problems when dealing with gene perturbation data.

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II. Structure of Gene Regulation Network (GRN)

GRN is a model in which nodes corresponding to gene-activities and can be represented in mixed graph, $G = (V, U, D)$ over a set V of nodes, with ordered pairs D, the directed edges and unordered pairs U, the indirected edges. A directed edge d_{ij} from v_i to v_j is present if a causal effect run from node v_i to v_j and there exist no nodes or subsets of nodes in V that are intermediating the causal influence (it may be mediated by hidden variables, i.e. variables not in V). An indirected edges u_{ij} between nodes v_i to v_j is present if gene-activities v_i and v_j are associated due to confounding, and there exist no nodes or subsets of nodes in V that explain that association (it is caused by a variable hidden to V).

The nodes in GRNs structure representing the genes, proteins, metabolites, their complexes or even modules while the edges represent direct or indirect interactions between nodes. Proteins and metabolites appear as hidden variables and GRNs are inferred only from gene expression data as observable variables. These hidden variables can model unobserved effects that cannot be measured. Fig. 1 presents the projection of interactions from the space of metabolites and proteins in genes space. Dashed lines represent gene interactions and the full lines represent the interactions among genes, proteins, metabolites and their complexes [6], [7].

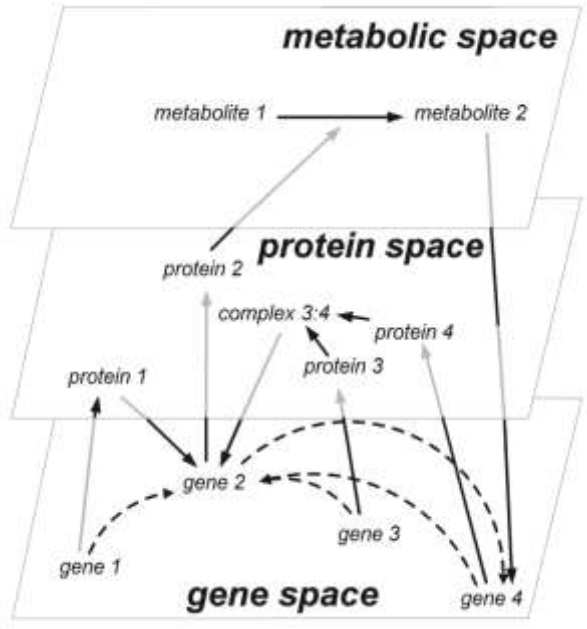

Figure 1. Projection of GRN in different spaces [7].

A gene may directly influence the activity of other target gene or gene product. Influence may be indirect by coding a transcription factor (TF) that in turn regulates another gene. A possible causal relationship in GRN is shown in Fig. 2. Apparently, four different types of causal relationship may be possible in a living cell. Based on the above figure we can derive the following causal relationship [8], [9].

- A gene can enhance the activity of more than one gene (relationship between A, B, C, and D).
- A gene's activity may be influenced by more than one gene (relationship between B, D, and F). Often F is referred as Collider [9], [10].
- Gene can also influence the activity of itself (node B).
- A gene may inhibit the activity of another gene (D inhibits E). Inhibition or negative regulation may also follow above three relationships, i.e., many to one, one-to-many, and self.

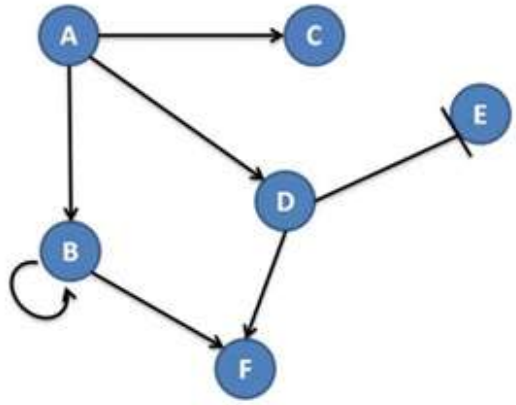

Figure 2. Possible causal dependency in GRN graph [9].

III. Algorithms for Reconstruction of GRN

Recently, various methods have been developed to reconstruct GRNs by producing hypotheses about the presence or absence of interactions among genes, hypotheses that can later be tested by laboratory experiments [4], [11]. In general, these GRNs reconstruction methods fall into two categories, namely model-based methods and machine learning-based methods [12], [13]. For model-based methods, chemical reaction of transcription and translation, as well as other cellular processes are described as linear or nonlinear differential equations, in which the parameters represent the regulation strengths of the regulators. Among the algorithms in this category include multiple linear regression [14], singular value decomposition method [12], [15]–[18], network component analysis [19], structural equation model (SEM) [20], sparse vector autoregressive [19] and linear programming. Adding to the list of methods is hybrid method [21]–[24], in which researchers have developed a novel method by incorporating more than one method.

Regression analysis widely used for prediction and forecasting, where its use has substantial overlap with the field of machine learning [25]. Multiple regression analysis is a very advanced statistical tool and it is extremely powerful when you are trying to develop a "model" for predicting a wide variety of outcomes [26]. Since the nature of GRNs that consists of simultaneous observation and analysis of more than one outcome variable [13], multiple regression analysis wise choice to reconstruct GRNs. There are a number of methods in this category, such as Multiple Linear Regression [27], Principle Component Regression [28], Partial Least Squares [29], Least Absolute Shrinkage [1] and Selection Operator (LASSO) [30] and Canonical Correlation Analysis [31]. While the linear regression model consists of a deterministic part and a random part, generally defined as

$$y = \beta_0 + \beta_1 x + \epsilon \quad (1)$$

The deterministic portion of the model,

$$\beta_0 + \beta_1 x \quad (2)$$

defines as, for any value of the independent variable, x, the population mean of the dependent or response variable, y, is described by the straight-line function $\beta_0 + \beta_1 x$. The linear regression-based method developed by [20] performs better in terms of power of detection, but requires a future work as the false discovery rate decrease in high-noise context, and apply new strategies to handle large-size gene networks.

Structural equation model (SEM) also produces results comparable to the results from any that regression techniques. For the reason, SEM has been applied frequently in the reconstruction of GRNs [13], [32]–[35]. Among the favoured position of using SEMs are allowing feedback loops, differentiating direct relations from indirect relations [13], able to correct for measurement error and falsifiable (able to be proved if the SEM model is wrong) . Maximum Likelihood (ML) is the method to estimate the parameters in SEM. It works iteratively to find the best solution by searching through solutions and testing them until it finds the best one as applied in [36].

For the machine learning-based methods, the network is inferred by measuring the dependencies or causalities between transcriptional factors (TFs) and target genes. Among methods fall in this category include the partial correlation coefficient (PCC) [37], Bayesian network [38], dynamic Bayesian network [39], Boolean network [40], probabilistic Boolean network [41], Ordinary differential Equations [42], mutual information (MI) [43], graph theory [44] and neural network [45]. Besides that, numerous methods for GRNs reconstruction are proposed, such as Collateral-Fuzzy Gene Regulatory Network Reconstruction (CF-GeNe) [46]. The detail descriptions including the advantages and disadvantages of each method reviewed in [6], [47].

Neural network was inspired by animals' central nervous systems. It is a flexible statistical method capable of recognizing input patterns, and modelling any functional relationships and data structure [47], [48]. For the reason, this method among the most popular used in GRNs reconstruction, especially the recurrent neural network (RNN) [17], [49], [50]. It is consists of feedback connections and dynamic memory units [17], [49], [51], [52]. The basic concept RNN, each node of the GRN represents a particular gene, and the wiring between the nodes defines as regulatory interactions. However, RNN is sometimes restricted in performance by the limited number

of samples (or time points) in DNA microarray experiments; their number generally being smaller than the number of attributes (or the parameters) to be estimated [53].

Another the most popular used method in GRNs reconstruction is the correlation based approaches such as Mutual Information (MI). MI proposed to extract genetic networks [54] by computing MI for all gene pairs in a microarray dataset and infer that two genes are biologically related if their MI is above a certain threshold [55]. The MI of discrete random variables X and Y is defined as

$$I(X < Y) = \sum_{x \epsilon X, y \epsilon Y} P(x,y) \log \frac{P(x,y)}{P_X(x) P_Y(y)} \quad (3)$$

where P_X, P_Y are the marginal probability mass functions of X and Y, respectively, and P is the joint probability mass function of (X, Y). Methods such as ARACNE [55], CLR [56], MRNET [57] and PCA-CMI [58] have succeeded in inferring the GRNs using MI-based methods [59]. Even though MI works well with co-expressed or positively regulated patterns, it fails in handling gene profile with negative and mixed patterns [54]. Moreover, MI is incapable of detecting edges directionality [59], therefore it unable to identify the relationships accurately [54] particularly when applied to a limited number of samples [20]. Despite of the limitations, MI is further improved by using Conditional Mutual Information (CMI) which measures conditional dependency between two variables (genes) given other gene(s) [58]. Although the CMI is able to identify the direct regulations, it generally underestimates the regulation strength. To overcome the problems, a novel concept, namely conditional mutual inclusive information (CMI2) proposed by [31], to describe the regulations between genes.

Despite the advantages of CMI2, there is still room to improve it. Firstly, similar to PCA-CMI, CMI2 cannot directly infer edge directionality, which is also a general problem of many other methods, especially for those not working on time series data [55], [31]. Secondly, it is still a challenge task to select the conditional genes in an optimization way. Recently a method incorporated Gaussian Noise Model and Pearson Correlation Coefficient has been proposed by [13]. This method has demonstrated the ability to (1) predict the presence of regulatory interactions between genes, (2) their directionality and (3) their states (activation or suppression). However, this prediction method generated high false positive values because the indirect regulations have been wrongly predicted as true relationships. The list of GRN inference methods can be seen in Table 1.

TABLE 1. LIST OF ALGORITHM FOR GRNs RECONSTRUCTION

Categories	Methods	References
1. Model-based	Multiple linear regression	[14]
	Singular value decomposition	[15]–[18]
	Network component analysis	[19]
	Structural equation model (SEM)	[20]
	Sparse autoregressive vector	[19]
	Linear programming	[60]
	Hybrid method	[21]–[24]
2. Machine Learning-based	Partial correlation coefficient (PCC)	[37]
	Bayesian network	[38]
	Dynamic Bayesian network	[39]
	Boolean network	[40]
	Probabilistic Boolean network	[41]
	Ordinary differential Equations	[42]
	Mutual information (MI)	[43]
	Graph theory	[44]
	Neural network	[45]
	Collateral-Fuzzy Gene Regulatory Network Reconstruction (CF-GeNe)	[46]

IV. Gene Perturbation Data for Reconstruction of GRN

Gene expression data are crucial for GRN construction. Gene expression data allow biologists to observe the expression level of genes on a large scale [61]. There are two types of gene expression data used for GRN construction: time series and gene perturbation experiments. Time series expression data enable biologists to investigate the temporal pattern in biological networks. While, data obtained from experiments that gene perturbation by knockouts or RNA interference contain useful information for addressing the GRN reconstruction problem [33] because it provides information on interactions direction.

However, several factors have impeded the accuracy GRNs reconstruction using gene perturbation data. First, it is needed to identify the two important parameters that are affected by noise: (1) the unaffected genes and (2) the wild-type strain values, which are more difficult to identify when a larger number of genes are involved. Second, though past research has been conducted in reconstructing GRN, only a few researchers applied their methods to real experimental GRN datasets, as an addition to synthetic data. Third, most previous research only focuses on GRN prediction, only a few attentions given to determining the directionality of the genes. Finally, many high false positive (FP) values are generated using the current GRNs reconstruction methods because the indirect regulations have been incorrectly predicted as true relationships.

V. Conclusion

This study discusses several of GRNs reconstruction methods and identified their problem when dealing with gene perturbation data. Since the main motivation of developing GRNs reconstruction methods to improve its accuracy and scalability, this study useful as a reference to develop more accurate GRNs reconstruction methods particular when dealing with gene perturbation data. In future work we are going to develop a method of GRNs reconstruction by attentions given to determining the directionality of the genes and reduce the high false positive (FP) values are generated using real gene perturbation experimental datasets. The experiments that assess the stated features of our method will be covered in our future research studies.

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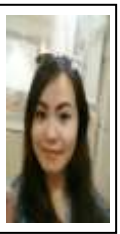

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