Review Article **Allied Science**

International Journal of Pharma and Bio Sciences **ISSN 0975-6299**

AN OVERVIEW OF BIOLOGICAL NETWORKS: MECHANISMS, METHODOLOGIES AND APPLICATIONS

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ABSTRACT

In this new epoch, one of the major problems addressed by the system biologist is the process of understanding gene regulation in different segments of biological environments. In a given cell, many genes expressed themselves and they work together to achieve the cell's fitness, function, and survival. In order to ensure that they achieve the desired outcomes, the genes must express themselves in proper amounts and time. This being an important factor should be taken into major consideration. Gene Regulatory Networks (GRNs) aims at realizing the kinetics of the networks and mechanisms of the diseases that come due to dysregulation in cellular processes. The aim of this paper is to discuss various types of biological networks and to throw some light on the mechanism of gene regulatory networks and methodologies applied for the structure of gene regulatory networks. Though it is quite difficult to state which technique is more suitable as it varies from one domain to other but Bayesian networks are usually more suitable as they work with the concept of probability.

KEYWORDS: **Gene Expression; Biological Networks; Gene Regulatory Networks; Boolean Network; Bayesian Network; Dynamic Bayesian Networks**

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INTRODUCTION

System biology is an emerging field that basically represents a new generalized way of thinking about biology with an impact over the way research is performed. One of the greatest difficulties that any natural scientist confronts in this post genomic time is that of using data created by numerous advances like transcriptomics, proteomics, metabolomics etc.[1] A real leap forward in the field of molecular biology is the advancement of a computation branch famously called as *Bioinformatics*. It contains two significant fields: molecular biology and information technology.[2] Bioinformatics in the field of biology is where we develop methods and software tools to understand the biological data. With the recent advancement and extensive use of high throughput technology measuring gene expression data for identification and classification in variety of areas has quite been successful.[3] These high throughput expression experiments produces large amount of data that can develop our understanding of disease processes. Most cellular processes involve many different molecules and the cell metabolism involves many interlinked reactions and the products of one reaction will be an extract of the next, hence forming the metabolic network.[4] The basic units of heredity are the *genes* in the living organisms that play an important role in the control of cell processes.[5] Some of the crucial cellular pathways and molecular processes are usually based on the interactions of the genes. In the living cells, they regulate each other to control the production of gene products.[6] However, the gene dataset includes only few samples but with thousands or even tens of thousands of genes. Such a limited availability of high dimensional samples is quite problematic. Discovering relationships and interactions over genes is an important advancement in the field of bioinformatics.[7-8] Several types of models have been proposed for representing such interactions and some of them are mostly used in the gene regulatory networks (GRNs).[9] The GRNs have been utilized to depict and model the regulatory interactions among the genes and thus have picked up an impressive imperativeness and exactness in demonstrating the regulatory process.[10]Gene selection is one of the foremost technique that can be used for the construction of GRNs. Instead of considering the whole dataset, if small subset of useful genes can be extracted then constructing the network would be far more easier and less time consuming. The objective of this paper is to study diverse sorts of biological networks and from it the most important network that is GRNs that have picked up a ton of ubiquity and has been an enthusiasm for part of analyst. This paper also describes various approaches or techniques used for construction of GRNs like Boolean networks, Bayesian Networks, Dynamic Bayesian networks etc.[1-12]Section II introduces the biological networks and its types, section III focuses on different techniques used in gene regulatory network. Lastly section IV, summarizes our work and provides some of the future directions and scopes for carrying out further work in this field.

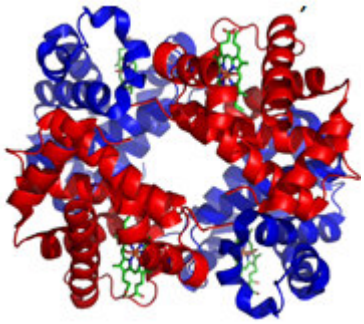
BIOLOGICAL NETWORKS

The biological organisms are complex and it involves role between various factors like proteins, small molecules and nucleic acids. These complex systems can be represented as different computable networks and hence a network that applies to biological systems is called as biological networks.[13] Inference of biological networks has always remained as a major challenge in systems biology. Some of them are: *Protein-Protein Interaction* (*PPI*); *Gene Regulatory Networks* (*GRN*) or *DNA- Protein Interaction*; *Metabolic Networks*; *Signaling Networks*.[14]

(i) Protein -Protein Interaction Networks

PPI usually refers to a physical interactions or binding between proteins.[15] Proteins being an important molecule of living cells can interact with another protein to build or activate a protein complex.[16] They are very important for structure and function of a cell and participate in signal induction and play a major role in many diseases like cancer. Figure 1 portrays a form of quaternary protein structure where a set of proteins bind to do a peculiar part.[15]

Figure 1
Quaternary Protein Structure



Definition: It is directed graph, G= (V, E, δ) and a rooted tree, T where, V is the set of proteins, E is the set of direct interactions and δ: E→T defines the type of each edge.[17] There are various biological and computational approaches available for detecting PPIs.[18] Two most significant methods are: Co-immunoprecipitation and Yeast two hybrid screening.

(ii) Gene Regulatory Networks

It is also called as DNA-protein interaction network. Here, the activities of the genes are regulated by transcription factors, proteins that usually bind to the DNA.[19] In GRNs genes can be viewed as nodes and the links are regulatory influences or relationships between genes. These usually control most of the cellular process where sometimes unwanted behavior leads to diseases. In other words, GRN models the complex regulatory process that controls the activity of various genes in a living cell and provides a clear representation of the entire gene regulation.[20] The inference of the regulator is the major element in translating the actual regulatory conditions and it supplies a mechanism to build a relationship between target genes and regulator genes.[21] A crucial input to the GRN is the gene expression data which serve as a raw input data that supplies information like gene-gene interaction for constructing a GRN.[22] Biological researcher is taking a keen interest in constructing and inferring GRNs for extracting useful information that can be used for drug designing or other related fields. *Definition*: It is a mixed graph $G=(V, U, D)$ over a set of nodes V, corresponding to gene activities with unordered pairs U, the undirected edges and ordered pairs D, the directed edges.[23] From V_i to V_j, a directed edge d_{ij} is present *iff* a causal effect runs from node V_i to V_j and there exist no nodes or subsets of nodes in V that are intermediating the causal influences. Between nodes V_i and V_j, undirected edge U_{ij} is present *iff* gene activities V_i and V_j are associated by other means than direct causal influence and there exist no node or subsets of nodes in V that explains the association. Figure 2, describes a generalized model of GRN and figure 3 presents a genetic network for part of the phase λ decision circuit.[24-25] This network includes the gene CI and CII.

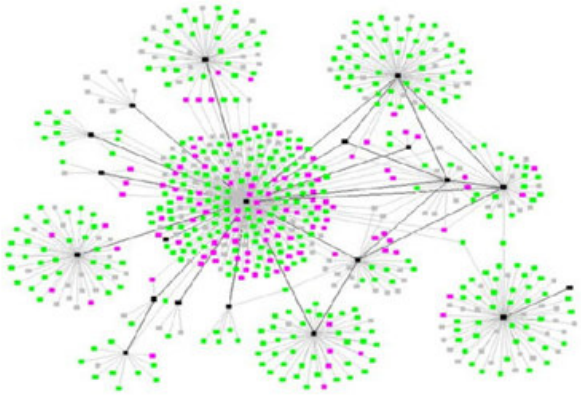


Figure 2
An example of complex gene regulatory network with key regulatory genes or 'hubs' indicated by black squares [24]

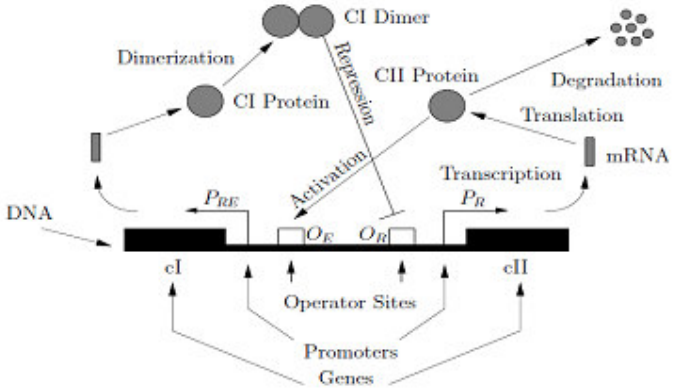


Figure 3
A portion of the genetic network for the phage λ decision circuit[24]

In order to build a GRN model many complex and simplified models are available like Boolean networks, Bayesian networks etc.[26] These techniques are explained in section III.

(iii) Metabolic Networks

These networks are applied for studying and modeling metabolism that is a set of chemical reactions that occur in living organisms which allows an organism to grow, reproduce, respond and sustain its structure.[27] This reaction is catalyzed by enzymes that are proteins which regulate chemical reactions. This answers in a metabolic product that is to be used or stored in the cell or it initiates another metabolic pathway.[28] A number of reactions occur at whatever time in living cells and product of one reaction is ordinarily employed by another reaction. Thus, metabolic reactions are extremely interconnected and form metabolic pathways and networks.[29] These reactions are reversible and

occur in both commissions. The metabolic pathways of a cell forming a metabolic network. Directed edges are drawn between proteins that catalyze chemical reactions (enzymes) and substrates (molecules that act upon by an enzyme). Enzymes and substrates correspond to nodes and directed edges to metabolic reaction in a metabolic network.[30] In other words, metabolic pathway is a hyper graph (it can be represented by bipartite graph) where nodes represent the substances and the edges represent the reactions.[31] Figure 4 below shows a graphical representation of a metabolic pathway for affymmetric Arabidopsis ATH1 genome array (Arabidopsis thaliana).[31]

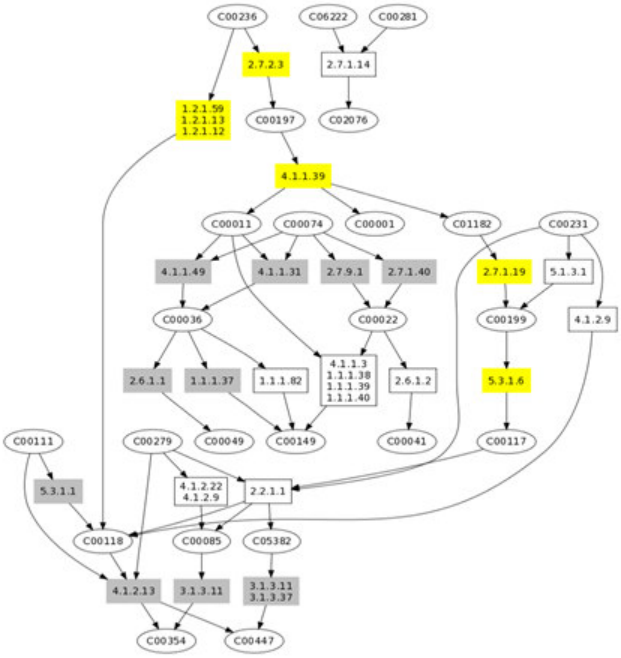


Figure 4
Carbon fixation-Affymetrix Arabidopsis ATH1 genome array (Arabidopsis thaliana)[31]

(iv) Signaling Networks

On a huge scale, cellular interaction networks are formed by the genes with their regulation interaction where most of them have been carefully examined and studied to get an insight about the association between genes and diseases. Cell signaling is taken as a complex arrangement of communication that usually governs basic cellular activities like repair, immunity, development and so on the cell converts one kind of signal to another and the errors in signaling causes serious diseases like cancer, diabetes etc.[32-33] Such biological networks are essentially derived from vast, generic knowledge compiled from several cell types.[34] These networks consist of signaling pathways that are some biochemical reaction sequences ordered in a cell and the changes are induced by the receptor activation. In such types of network, nodes represent the protein and edges between them are directed.[35] It is one of the most extensively studied areas in the context of human diseases and signaling between cells of a single organism (unicellular). Nevertheless, between cells of two different organism's cell signaling do occur (multicellular organism cell signaling). Figure 5 describes a signaling network of humans.[36]

Figure 5
Human signaling networks. Light gray lines represent the physical interactions, dark black lines represent the inhibited interactions, and pink lines represent the activated interactions. The dark red nodes are cancer-related genes[36]

TECHNIQUES FOR GENE REGULATORY NETWORK CONSTRUCTION

This section discusses three basic fundamental techniques that are mostly used for the construction of gene regulatory networks, to represent the gene-gene interaction. There are many gene regulatory network construction techniques like neural network, differential equations and many more. Apart from these, there are many hybridized gene network construction methods developed using optimization techniques. These are Boolean networks, Bayesian networks and dynamic Bayesian networks.[11-12]

(i) Boolean Network (BN)

Boolean logic networks are very simple yet powerful and qualitative approach for modeling of GRN that has become quite popular in the last few years.[37,38] This network is easy to simulate and can capture the dynamical behavior of the gene regulatory networks and the interactions of genes. BNs are based on the assumption of binary on/off switches that can be used to describe various gene regulation aspects.[39] These networks can be defined as the *n*-tuple of 0s and 1s that describes which genes in the network are expressed and which are not expressed at the particular moment.[40] In other words, a *boolean function* has at least one input variable that is valued (0 or 1) which determines the value of the output function regardless of other variables.[41,42] It is a function of boolean variables connected by logic operators.On a formal note, we can define a BNs as a directed graph *G* (*V*, *E*), where $v_i \in V$, the nodes are the Boolean variables and to each node, v_i there is a *Boolean function*, $f_{i1} = (v_{i1}, v_{i2}, \ldots . v_{il})$ associated,where l≤ *n*, $v_{ij} \in V$. All the arguments are only the parent nodes of v_i in *G*. At any given time, the states or values of all the nodes represent the state of the network that is given as the vector in equation (1),

$$N(t) = (v_1(t), v_2(t), \ldots \ldots . v_n(t)) \qquad (1)$$

In any given gene networks, the variables of the node denotes the levels of gene expression that is categorized as either up or down (regulated). Figure 6 indicates a BN for 10 nodes.[43]

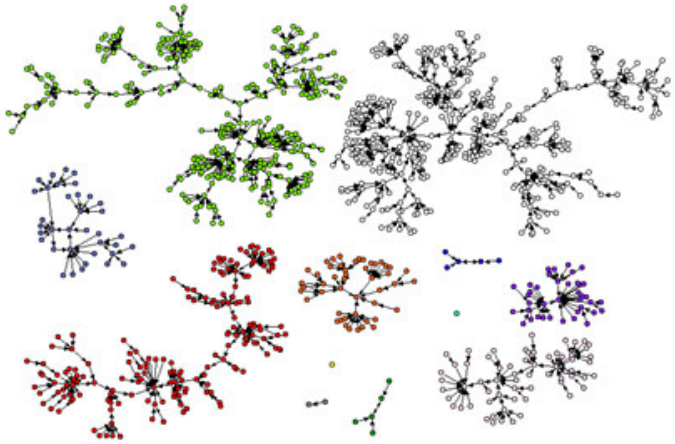


Figure 6
***The entire state space of an RBN with 10 nodes. Note: Self connections do not appear so a period-1 attractor appears to have no outputs although each network state must have exactly one output.*[43]**

Applications of Boolean Networks

Politano *et al*., discussed how miRNAs and post-transcriptional regulatory interactions can be modeled resorting to BN.[44] They proposed BN based post-transcriptional model that was implemented and simulated a BN to compute the *attractors* of the network taking into account post-transcriptional activities. They also discussed the set of *attractors* of two biologically confirmed networks, focusing on the regulatory role of miR-7. The attractors were compared with networks in which the miRNA was removed. The central role of the miRNA is for increasing the network stability, which was highlighted in both the networks, confirming the cooperative stabilizing role of miR-7.Chueh *et al*., proposed an innovative approach to reconstruct time delay BN as a means for exploring biological pathways.[45] They generalized the BN model for coping up with the dependencies that had two kinds of relationships: similarity and prerequisite. They also proposed an approach for reconstruction of genetic network inference from gene expression data that relied on the assumption that the expression of a gene is likely to be controlled by a relatively small number, *n* of genes. Kim *et al*., introduced a variable selection method based on Chi-Square Test (CST) called as CST-BN that reduces Boolean Network computation time and also obtains optimal network constructions by using chi-square statistics for examining the independence in contingency tables.[46] The proposed CST- based BN adopts the *Best-Fit Extension* problem, to effectively regulate all possible *Boolean functions*. The CST-based BN method was about 6.9 times quicker than the original BN method. If the network had a larger number of nodes, and then the difference between the computing times of the two algorithms would be significantly higher. Silvescu *et al*., presented a generalization of the BN model to address dependencies among genes that span for more than one unit of time.[47] The model, called the *Temporal Boolean Network* allowed the expression of each gene to be controlled by a Boolean function of the expression levels of at most k genes at times. They also staged a

popular machine learning algorithm for decision tree induction for infers of the *Temporal Boolean Network* from gene expression data. The detailed description is shown in Table 1:

Table 1
Detailed study for Boolean Networks

Authors/Reference	Input	Description
Politano *et al.*[44]	Probe set and state constraint set for two Gene Regulatory Networks for *Drosophilia*	Both the networks were tested and the role of miR-7 in *Drosophilia* was analyzed by computing the exhaustive set of attractors and trajectories. Likewise, the solutions obtained from the network analysis were subsequently compared with some of the previous findings that hypothesized a stabilizing role of miR-7 against perturbations that change the cell fate in terms of growth.
Chueh *et al.*[45]	Pairs of genes	The time delay BN that is proposed generalizes the BN model in order to cope up with the dependencies that hold two kinds of relationships: similarity and prerequisite
Kim *et al.*[46]	Yeast cell cycle data	It successfully handled the dynamic behavior of the yeast cell and proposed a variable selection method that improves the computing time of the BNs.
Silvescu *et al.*[47]	Artificially generated genetic network created from multiple time series data	*Temporal Boolean Network* inference problem was reduced to the problem of inferring a lot of decision trees, where the effectiveness of a simple and fast decision tree learning algorithm was established.

(ii) Bayesian Network

Bayesian Networks (BYNs) is produced by combing two basic fundamental areas of math that is probability and graph theory. In other words, BYNs are probability distribution based graph models that capture properties of conditional independence between variables.[48] The networks use directed acyclic graph for representation where the vertices corresponds to the genes and the edges represent the relationship between the genes. BYNs have become a highly computationally popular method for GRNs from expression data as these are rather easy to interpret by the researchers or biologists. Here, the expression levels of genes are represented by nodes and influences by directing edges.[49] A BYN is a tuple (*X*, *Y*), where *X*=<*V*, *E*> having directed acyclic graph nodes that represents the variables in *V* and the edges are represented the probabilistic dependencies between them. The joint probability distribution in *V* is represented by *Y*. The BN structure has a set of conditional assumptions where each node is conditionally independent of all its non-descendants in *X*.[50] With this assumption the joint probability distribution can be stated as in equation (2):

$$P(v_1, v_2, \ldots . v_n) = \prod_{i=1}^{n} P(x_i \mid Pa(x_i)) \qquad (2)$$

where, $v_i \in V$ are variables, $Pa(x_i)$ is the set of parents for each node and ($P(x_i|Pa(x_i))$ is the conditional probability distribution.

Modeling of BYN usually involves model selection and parameter learning as two of its basic steps. In model selection the network structure is created and in parameter learning probability values are estimated with each network node. For network creation a Bayesian scoring metric is used for evaluation, where the score is the log of the chance that the model correctly defines.

Applications on Bayesian Network

Liu *et al*., proposed two-stage structure learning algorithm that integrates immune evolution algorithm for constructing a Bayesian network.[51] The answers showed that the suggested algorithm is able to determine many of the known real regulatory relationships and anticipate the unknown with a high validity and accuracy. The algorithm optimizes the network parameters by utilizing the *immune evolutionary algorithm* and it simplifies the traditional three-point algorithm.Adabor *et al*., presented a search method that is a hybridized version of *Simulated Annealing with a Greedy Algorithm* (SAGA).[52] It searches the search space by undergoing a two-phase search: first with a *Simulated Annealing* search and then with a *Greedy search*. The method evolved to offer a near optimal solution within a fixed time without degrading the quality of the true regulatory network achieved. But here prior domain knowledge is required to direct SAGA so that the results have biological meaning and utility. Likewise, it does not limit the number of nodes for effective structure learning, thus giving equal chances to any given variable to refer to other variables.Heijden *et al*., developed an algorithm to learn temporal probabilistic models from the clinical time series data having missing values.[53] They have also projected a variety of a learning algorithm which is based on naïve Bayes networks having attractive properties of reduced computational complexity, good prediction performance. These proposed methods were also applied to construct predictive models of *Chronic Obstructive Pulmonary Disease* patient's health status and the models can manage both the dynamic nature and uncertainty inherent in the disease progression.Wang *et al*., suggested a hybrid constraint-based scored-searching method for discovering gene networks from DNA microarray data.[54] An algorithm was utilized to generate a BY N based on dependency analysis and the resulting construction was used to search a scoring metric. The detailed description is shown in Table 2:

Table 2
Detailed study for Bayesian Networks

Authors/Reference	Input	Description
Liu *et al*.[51]	Yeast Cell Cycle data	Implementation of two stage algorithm on the yeast cell cycle showed that the method has higher efficiency and effectiveness. It can find the known gene regulatory relationships by anticipating the unknown ones with improved accuracy.
Adabor *et al*.[52]	Breast cancer data Human Airway Smooth Muscle Mouse whole brain	Here, varying rate of performance for the algorithms that were proposed with respect to each dataset. That is, for datasets where the numbers of variables are large, SAGA capable to infer models with high rates of recovered relationships when used to infer BYNs over longer periods with larger prior relationships.
Heijden *et al*.[53]	Data from Chronic Obstructive Pulmonary Disease patients	An algorithm for learning temporal probabilistic models were introduced and a model was constructed to predict the occurrence of events
Wang *et al*.[54]	*Saccharomyces cerevisiae*	The proposed method achieves more precise answers than any other existing methods and also the running time complexity is quite less for the algorithm.

(iii) Dynamic Bayesian Network

Dynamic refers to modeling a dynamic organization, and not the graph structure that varies over time.[55] Dynamic Bayesian networks (DBNs), or dynamic probabilistic networks, are simple model class, capable of representing complex temporal stochastic processes.[56] These are quite recognized for being capable enough to capture the active behavior of the gene regulation and to capture several other modeling frameworks, like Hidden Markov Models and Kalman Filter models, as its special cases. BYNs are really efficient for analyzing microarray data, but they apply only when there are no cyclic dependencies. DBNs usually overcome this problem. In DBNs, time is seen as a series of intervals called time slices.[57] For each time slice, the state of the modeled system at the time is represented by a sub model or simply network is constructed to represent gene regulation.

Applications of Dynamic Bayesian Network

Labatut *et al*., aimed at the understanding of how large-scale network activation is extracted from cerebral information processing mechanisms that only explains apparently conflicting activation data.[58] Here, a formal technique based on Dynamic Bayesian Network (DBN) was introduced that integrates the biological plausibility in the framework.Kim *et al*., extended the BYN and the DBN model, which can construct cyclic regulations for time series data.[59,60] They optimized the structure of the network, which makes the best possible kind of representation in the gene interactions described by the data with noise. There model was capable of considering time information into account and can analyze the microarray data as the continuous data without the extra data treatments such as discretization. Even the model is capable of extracting the nonlinear relations.Chen *et al*., proposed a Bayesian approach for detection of longitudinal morphological changes in the human brain.[61] The technique employs a DBN for representing inter-regional dependencies. Here, dynamic Bayesian network modeling represents complicated interactions among temporal processes and they validated the approach by analyzing a simulated atrophy study. Later it was found that this approach requires only a small number of samples to detect the ground-truth temporal model. Pen˜a *et al*., examined the cross validation method for scoring criterion and also studied the Bayesian scoring criterion for learning DBN model.[62,63] They experimentally proved that cross-validation leads to model and generalize range of sample sizes than BYN model. The detailed description is shown in Table 3:

Table 3
Detailed study for Dynamic Bayesian Networks

Authors/Reference	Input	Description
Labatut *et al*.[58]	Two phonetically close syllables: /pa/ and /ta/	The DBNS modeled the brain as a dynamic causal probabilistic network with nonlinear relationships that interprets neuro-imaging data concerning various cognitive or sensor tasks.
Kim *et al*.[59]	*Saccharomyces cerevisiae*	The BYNs and nonparametric regression model usually tend to estimate many false positives in the cyclic regulation, but the proposed method can bring down the number of false positives and estimate gene regulations effectively
Chen *et al*.[60]	Brain images	It model dynamic systems, and is suited for analyzing discrete time-series data and can model arbitrary multivariate inter-regional associations between categorical variables, whether linear or nonlinear. This technique can correctly identify the structure of the underlying dynamic system
Pen˜a *et al*.[61]	*Saccharomyces cerevisiae*	The model involves 30 transcription factors and 56 interactions between them. For each sample size, the same performance measures were recorded.

SUMMARY AND FUTURE WORK

In this theme, we presented the types of biological networks, available as well as we threw a clear insight about GRNs. We also brought in various modeling methods applied to infer GRNs and described their applications in the context of biology. Various computational methods have also been developed for the construction of network from expression data. Most of the GRN models do share similar principles and ideas, but they have been improving performances over iterations. But some computational issues mostly remain in the area of network modeling and one such issue is scalability. If the number of genes and interactions in regulatory networks increases, the number of network parameter also increases rapidly. In this setting, we encounter many chances to develop sound techniques for the approximation of parameters and to find answers for various multi-dimensional problems. Hence, it is significant to examine the active attributes of the network parameter and to pay more care towards other issues like robustness of the network and reliability.

CONFLICT OF INTEREST

I on behalf of all authors would like to state that the no case of animal study conduction has been done in accordance of the relevant ethical committee.

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