Soft Computing Approach for Modeling Genetic Regulatory Networks

Khalid Raza and Rafat Parveen

Department of Computer Science, Jamia Millia Islamia (Central University), New Delhi, India
kraza@jmi.ac.in, rafatparveen@yahoo.co.in

Abstract. Interactions among the cellular components determine the behaviour of the complex biological system. The major challenge of the post-genomic era is to understand how interactions among various molecules in a cell determine its form and function. Several computational techniques for modeling biological systems, particularly gene regulatory networks (GRNs), has been proposed in order to understand the complex biological interactions and behaviours. Gene regulatory models has been proved to be the most widely used mechanism to model, analyze and predict the behaviour of an organism. In this paper, we have reviewed the role of soft computing techniques, such as fuzzy logic, artificial neural networks, evolutionary algorithms and their hybridization, for modeling GRNs. In addition, recent developments in this area are introduced and various challenges and opportunities for future research are discussed.

1 Introduction

Networks play an important role in biological investigations and used to represent processes in biological systems. It captures the interactions and dependencies between molecular biological entities such as genes, transcripts, proteins and metabolites [22]. Systems biology is rapidly growing research area which aims at the system level understanding of biological systems [1]. Systems biology is one of the large application areas for network-centred analysis and visualization of biological entities. With the availability of complete genome sequences and high-throughput post-genomics experimental data, last decade have witnessed a viable interest in the study of networks of macromolecular interactions such as gene regulatory networks, metabolic networks, protein-protein interaction networks, or signal transduction networks. Today computational modeling of biological systems has become rather essential in order to understand the complex biological interactions and behaviour. Many theoretical models have been proposed to model, analyze and infer complex regulatory interactions and provide hypothesis for experimental verification.

A genetic regulatory network (GRN) is a network depicting interactions between genes and model causal relationship between gene activities. A GRN denotes the assembly of regulatory effects and gene interactions in a biological system. The GRN helps us understand the intricate interactions of multiple genes under various stimuli or environmental conditions [3]. Modeling GRNs enables us to decipher the gene interaction mechanism for a particular stimulation and further we can utilize this

N. Meghanathan et al. (Eds.): Advances in Computing & Inf. Technology, AISC 178, pp. 1–11.
springerlink.com

information to predict adverse effects of new drugs or to determine a new drug target [20]. Due to improved understanding of gene regulation processes modeling efforts are increasingly being used for generating the hypotheses that are then tested with experimental data. Generally, the process of GRNs modeling consists of a few main steps: (i) selection of an appropriate model (ii) inferring parameters from data (iii) validating the model and (iv) conducting simulation of GRNs, to predict its behaviour under various conditions [48]. Hence, there is a need for efficient computational tools for the qualitative modeling of GRNs so as to understand the experimental data in the context of the dynamical behavior of a cell and generates hypotheses with the assistance of computational tools [4, 5].

Some review papers on GRNs modeling exists in the literature [1, 2, 18, 19, 21, 48], but we have approached in a different way. We have done survey of soft computing based techniques for modeling GRNs. In addition, recent developments and future challenges in the area are discussed.

2 Basic Modeling Techniques

There are several techniques for modeling GRNs including Directed graph, Petri nets [16, 17], Boolean networks [6–8, 17], generalized Bayesian networks [9, 10], linear and non-linear ordinary differential equations (ODEs) [11–15], machine learning approach, etc. *Directed graph* is a straightforward and most simple way to model a GRN, where vertices represent genes and edges interactions among the genes. A directed edge is defined as a tuple (i, j, s), where i denotes the head, j the tail of the edge and s is equal to either + or – indicating whether i is activated or inhibited by j. The graphical representations of GRNs permit a number of operations that can be carried out to make prediction about biological processes [1]. Petri nets are an extension of graph models that represents a well-established technique for modeling regulatory systems. *Petri net* is a non-deterministic method which has successfully been applied for simulating GRN, allowing simple quantitative representation of dynamic processes. The limitation of Petri nets model is that it does not support hierarchical structuring, which makes them difficult to be use for large-scale networks. *Boolean networks* are deterministic method based on logical functions. The Boolean method assumes the expression level of each gene is either expressed (ON) of not expressed (OFF). In the network, each node's logical function is determined by finding the minimum set of nodes whose expression level can explain the observed changes in the state of a given node. The advantages of Boolean methods are its simplicity and finite state space. Boolean methods are also more computationally tractable. The algorithm, REVEAL (reverse engineering algorithm) [17] was first step towards modeling large-scale network using Boolean network. However, these models ignore the effect of genes at intermediate levels and impractically assume that transitions between states are synchronous.

Bayesian networks (BNs) uses a graphical representations of multivariate joint probability distribution, having two parts, a directed acyclic graph and a set of local joint probability distributions. These models can deal with the stochastic aspects of gene regulation and able to handle noisy and incomplete data which is prevalent in microarray technology. However, these models can not deal with dynamic aspects of

gene regulation. Dynamic Bayesian networks have been formulated to overcome the problem of dynamicity. *Ordinary differential equations* (ODEs) formalism have been mostly used method for modeling dynamic biochemical networks, particularly, GRNs. The ODEs approach is able to capture detailed information about the network's dynamics but it needs high-quality data on kinetic parameters and hence it is currently appropriate for a few systems only. A detailed discussion about various differential equation-based approaches can be found in [1] and [19].

3 Soft Computing Techniques

Prof. L. A. Zadeh coined the term "soft computing" (SC) in 1992 which is an evolving collection of methodologies, that aims to exploit tolerance for imprecision, uncertainty, and partial truth to achieve robustness, tractability, and low cost. Fuzzy logic (FL), neural networks (NN), and evolutionary computation (EC) are the core methodologies of SC. Each of these methodologies has their own strength, for example, FL is capable of representing knowledge via fuzzy rules, ANNs can be used for learning and adaptation and EAs for the optimization. However, FL, NN, and EC should not be viewed as rival of each other rather synergistic and complementary instead. Soft computing is causing a breakthrough in engineering and science fields since it can solve problems that have not been able to be solved by traditional hard-computing methods [25]. In Zadeh's own words, *"Soft computing is an emerging approach to computing which parallel the remarkable ability of the human mind to reason and learn in an environment of uncertainty and imprecision"* [23].

4 Role of Soft Computing in GRN Modeling

Soft computing is gradually opening up several opportunities in bioinformatics, especially by generating low-cost, low-precision (approximate) and good solutions. It provides us efficient solutions to the various challenging problems from bioinformatics such as protein structure prediction, microarray data analysis, gene sequence analysis, modeling genetic and biochemical networks [24]. Soft computing techniques, particularly, FL, ANNs, EAs and their hybridization have been successfully used for modeling GRNs.

Fuzzy Logic

The biological systems behave in a fuzzy manner. FL provides a mathematical framework for modeling and describing biological systems. Literature reports that FL has been successfully used for modeling GRNs due to its capability to represent non-linear systems, its friendly language to incorporate and edit domain knowledge in the form of fuzzy rules. Woolf and Wang [28] proposed a novel algorithm for analysing gene expression data using FL. The model was designed to find triplets (activators, repressors, targets) in yeast gene expression data set. The model was implemented using C-language and executed on an 8-processor SGI Origin 2000 system, which took ~200 hours to analyse the relationships between 1,898 genes. Later, Ressom, *et. al.* [39] has extended and improved the work of Woolf and Wang [28] in terms of

reducing computation time and generalizing the gene regulatory model to accommodate co-activator and co-repressors. Reduction in computation time is achieved by using clustering as a pre-processing step. The improved algorithm achieves a reduction of 50% computation time. Later on R. Ram, *et.al.* [33] has also improved the fuzzy logic model developed by Woolf and Wang [28] to predict changes in expression values and infer causal relationship between genes. They have improved the searching activator/repressor regulatory relationship between gene triplets in the microarray data. A pre-processing technique for the fuzzy model has also been proposed to remove redundant computations due to presence of similar expression profiles in the microarray data. The pre-processing technique groups the genes based on similarity in their expression profile variations and yeast expression data has been used to test the model but the limitation is that interactions extracted from the microarray data are not necessarily causative but are likely to be associated in a similar biological pathway.

Pan Du, *et.al.* [32] has applied fuzzy weights for modeling the interactions between genes in a GRN. The interaction in the network is modelled as fuzzy function that depends on the detail known about the network. The analysis and creation of GRNs involves first clustering of data using multi-scale fuzzy k-means clustering and then searching for weighted time correlation between the cluster centre time profiles. The link validity and strength is then evaluated using fuzzy metric based on evidence strength and co-occurrence of similar gene function within a cluster. Experimental results on the carbohydrate metabolism of the model plant *Arabidopsis thaliana* have been illustrated. GO database has been used to evaluate gene regulatory relationships from a biological viewpoint.

Y. Sun, *et.al.* [3] has applied dynamic fuzzy modeling approach by incorporating structural knowledge to model GRNs. This technique infers information on gene interactions in the form of fuzzy rules and considers the dynamic aspects of gene regulation. It is able to reveal more biological relationships among genes and their products. It has used two sets of data to validate the models, synthetic data from a numerical example and real *SOS DNA repair network* data with structural knowledge. The distinguishing feature of this model is that (a) prior structural knowledge on GRN can be incorporated for the purpose of faster convergence of the identification process and (b) non-linear dynamic property of the GRN can be well captured for the better prediction.

Artificial Neural Networks

An artificial neural network (ANN) is a computational model that is inspired by the structural and functional aspects of biological nervous systems. The capabilities of ANNs to learn from the data, approximate any multivariate nonlinear function and its robustness to noisy data make ANN a suitable candidate for modeling gene regulatory interactions from gene expression data. Several types of ANNs have been successfully applied for modeling gene regulatory interactions including perceptrons [40–42], self-organizing maps (SOM) [43, 44] and recurrent neural networks (RNNs) [30, 37].

Ed. Keedwell, *et.al.* [43] has successfully applied ANN in the purest sense for the reconstruction of GRNs from microarray data. The design of the neural network was quite simple when dealing with Boolean networks and standard feed-forward

backpropagation method has been applied. The modelled ANN was tested under various conditions and found that resulting networks were able to encode complex relationship between genes. Vohradsky [27] has also proposed an ANN based model assuming that the regulation effect on the gene expression of a particular gene can be expressed as a neural network. Each node in the network represents a particular gene and the wiring between the nodes represents regulatory interactions. Here each layer of the network represents the level of gene expression at time t and output of a node at time $t+\Delta t$ can be derived from the expression levels. The regulatory effect is transformed using a sigmoidal transfer function to the interval (0, 1). The main advantage of this model is that it is continuous, uses a transfer function to transform the inputs to a shape close to those observed in natural processes and does not use artificial elements. The drawback is that it consists of large number of parameters that must be computed from experimental data.

Stochastic neural network model in the framework of a coarse-grained approach was proposed by Tiam and Burrage [30] for better description of the GRNs. The model is able to represent both intermediate regulation as well as chance events in gene expression. Poisson random variables are applied to represent chance events. X. Hu *et.al.* [45] has proposed a general recurrent neural network (RNN) model for the reverse-engineering of GRNs and to learn their parameters. RNN has been deployed due to its capability to deal with complex temporal behaviour of genetic networks. The model was tested on *SOS DNA Repair* network of the *e.coli*. The model was able to discover complex regulatory relationships among genes in the SOS network.

Evolutionary Algorithms

Evolutionary algorithms (EAs) are basically optimization algorithm based on Darwin's theory of evolution. It is basically a search algorithm that is modeled on the mechanics of natural selection and survival for the fittest. It combines survival of the fittest among individuals with a structured yet randomized information exchange to form a search algorithm. In EAs optimization techniques searching from a population are done from a single point and for each iteration a competitive selection is done. The solutions with high "fitness" are recombined with other solutions. The solutions are then "mutated" by making a small change to a single element of the solution. The main purpose of recombination and mutation is to generate new solutions but it is biased towards regions of the space for which good solutions have already been identified. Generally, three evolutionary techniques are distinguished: genetic programming (GP), genetic algorithms (GA) and evolutionary programming (EP). The GP focuses on programs evolution, GA on optimizing general combinatorial problems and EP focuses on optimizing continuous functions without recombination. EAs belong to probabilistic algorithms and they differ from random algorithms in that they combine elements of directed and stochastic search. Due to this reason EAs are more robust than directed search methods. Another merit of EAs is that they maintain a population of potential solutions while other search techniques process a single point of the search space. The limitation of GP and GA-based modeling techniques are that they do not take care of the noise effect which is prevalent in microarray data.

Various constituents of EAs have been successfully applied for modeling GRNs. A combination of GP and Least Mean Square (LMS) method, called LMS-GP, has been applied by Ando *et.al.* [46] to identify a concise form of regulation between genes

from time series data. LMS is applied to determine the coefficients of the GPs, which decreases the Mean Squared Error (MSE) between the observed and model time series without complicating the GPs. This model has been tested on artificial as well as real-world data. The proposed LMS-GP model has average MSE of 4.21×10^{-3} over 10 runs, while standard GP averaged MSE is 6.704×10^{-3} over 10 runs. Wang *et.al.* [47] has proposed a joint GP and Kalman filtering (KF) approach to infer GRNs from time series data. Here nonlinear differential equation model is adopted and an iterative algorithm has been proposed to identify the model, where GP is employed to identify the structure of the model and KF is deployed to estimate the parameters in each iteration. The proposed model has been tested using synthetic as well as time-series gene-expression data of yeast protein synthesis. Due to noise in microarray data, the KF may not be appropriate for estimating parameters.

Noman and Iba [50] have applied decoupled S-system formalism for the inference of effective kinetic parameters from time series data and employed Trigonometric Differential Evolution (TDE) as the optimization engine for capturing the dynamics of gene expression data. The fitness function used here is a modified version of Kimaru *et.al.* [51] for reducing the number of false positive predictions. The spare network structure has been identified with the help of hill-climbing local search (HCLS) method within the framework of proposed EA. Experiments on well studied small scale artificial network in noise-free as well as noisy environment is done. The proposed model successfully identifies the network structure and its parameter values. Real-life data has also been used for reconstructing the *SOS DNA repair network* of *e.coli*. The proposed model correctly identified the regulations of gene *lexA* and some other known regulations. Chowdhury and Chetty [52] extended the work of Noman et.al. [50]. In this model, GA is applied for scoring the networks' several useful features for accurate inference of network, such as a Prediction Initialization (PI) algorithm to initialize the individuals, a Flip Operation (FO) for matching the values, and a restricted execution of HCLS over few individuals. A refinement algorithm for optimizing sensitivity and specificity of inferred networks was also proposed.

Hybridized Techniques

Each of the soft computing (SC) constituents has their own advantages. The learning and adaptation capability of ANN, knowledge representation via fuzzy rules through FLs and optimization capability of GAs when joined together, one can exploit the advantages of each in the hybridized model. The most common form of hybridizations are ANN+FL=Neuro-Fuzzy, ANN+GA=Neuro-Genetic and ANN+FL+GA=Neuro-Fuzzy-Genetic. Many hybridized forms of SC techniques has been reported in the literature for modeling GRNs [12, 26, 29, 31, 34-38, 54]. Table 1 summarizes the various types of hybridization used for modeling GRNs.

Neuro-fuzzy is one of the earliest and most widely used forms of hybridization. Liu *et.al.* [26] has proposed a neuro-fuzzy network models with biological knowledge to infer strong regulatory relationships and interrelated fuzzy rules. This model infers fuzzy rules automatically which describes the regulatory conditions in GRNs and explain the meaning of nodes and weight value in the neural network. Vineetha *et.al.* [35] presented a multilayered dynamic neuro-fuzzy network (DNFN) to extract gene regulatory relationship and reconstruct GRN for circulating plasma RNA data from

colon cancer patients. This hybridized model combines the features of connectionist and FL to encode the knowledge learned in the form of fuzzy rules and processes data by applying the principles of fuzzy reasoning. A neuro-fuzzy inference system (NFIS) was applied by Jung & Cho [37] for reconstruction of GRNs. Here gene expression profile is first transformed into a mapping form then the transformed data are mapped into the NFIS and resulting fuzzy rules are applied to infer the relationship. The mapping of gene expression profile to fuzzy rules provides NFIS noise filtering capability for noisy and uncertain gene expression profile. Datta *et.al.* [34] tried to model GRN by a combination of RNN and fuzzy membership distribution of weights. A cost function had been applied to match the neurons response with the gene expression data and a differential evolution algorithm applied to minimize the cost function. The model has been used to infer the GRN of *SOS DNA repair network* of *e. coli*.

Table 1. Hybridized techniques for Modeling GRNs

Modeling techniques	Results obtained	References
RNN + PSO + ACO	Reconstructed genetic interaction network of yeast as well as SOS response system of e. coli	K. Kentzoglanakis, 2012 [36]
Neuro-fuzzy	Reconstruction of partial GRN of yeast	Liu et.al., 2011 [26]
Neuro-fuzzy	Extract regulatory relationships & construct GRN	Vineetha et.al., 2010 [35]
RNN+Fuzzy	Extracted GRN from yeast	Maraziotis, et.al., 2010 [12]
RNN+Clustering+PSO	Inferred GRN	Zhang, et.al., 2009 [29]
RNN+Fuzzy	Determine regulatory interaction between genes	Datta et.al., 2009 [34]
RNN + GA	Extracted GRN modules	Chiang & Chao, 2007 [31]
Neuro-fuzzy	Reconstructed GRN from microarray data	Jung & Cho, 2007 [37]
RNN + PSO	Extracted GRN from gene expression profiles.	Xu Rui et.al. 2007 [38]

Maraziotis *et.al.* [12] proposed a multilayer evolutionary trained neuro-fuzzy recurrent network (ENFRN) that select potential regulators of target genes and their regulation type. The recurrent, self-organizing structure and evolutionary training of the network give rise to an optimized collection of gene regulatory relations and its fuzzy nature eliminates noise-related issues. The ENFRN was tested on several benchmark datasets of yeast and it successfully retrieve biologically valid regulatory relationships and provide better insights for understanding the dynamics of GRNs. Chiang & Chao [31] has introduced a GA-RNN hybrid approach for finding feed-forward regulated genes. This GA-RNN hybrid method constructs various kinds of regulatory modules. RNN controls the feed-forward and feed-backward loop in regulatory module and GA provide ability of global searching of common regulated genes. This method extricates new feed-forward connections in gene regulatory models by modified multi-layer RNN architectures.

Zhang *et.al.* [29] proposed a hybridized form of PSO (particle swarm optimization) and RNN, called PSO-RNN. The PSO is a computational method that tries to optimize a problem by iteratively improving a candidate solution with regard to a given measure of quality. In this method, they have tried to integrate gene expression data and gene functional category information for the inference of GRNs. The inference was based on module network model which consists of two parts. The first is module selection part which determines the optimal modules using fuzzy c-means (FCM) clustering technique and incorporate functional category information. The second is network inference part, which uses PSO-RNN, to infer the underlying network between modules. The model was tested on real data from development of rat central nervous system (CNS) and the yeast cell cycle process. Another RNN-PSO (particle swarm optimization) based approach was proposed by X. Rui *et.al.* [38]. In this approach [38], gene interaction is demonstrated through a connection weight matrix and PSO-based searching algorithm is presented to uncover genetic network constructions that best fit with the time series data and analyse possible genetic interactions. PSO is used to train the network and find out the network parameters. For the real data set, this framework provides a meaningful insight into gene interactions in the network. K. Kentzoglanakis [36] has hybridized PSO, ant colony optimization (ACO) and ANN for modeling dynamic behaviour of gene regulatory systems. The ACO is a probabilistic technique for solving computational problems which can be reduced to finding good paths through graphs. ACO has been used for searching the discrete space of network architecture, PSO for searching the corresponding continuous space of RNN model parameters. This framework has been tested for the reconstruction of small artificial network as well as real-world data set of SOS response system of the *e.coli*.

5 Conclusions and Discussions

The gene regulatory networks (GRNs) demonstrate the interactions between genes. Understanding GRNs is essential because (i) it provides a large-scale, coarse-grained view of an organism at the mRNA level (ii) gives valuable indications for the therapeutics of complex diseases (iii) explains how different phenotypes emanate and which groups of genes are responsible for them and (iv) helps in understanding evolution by comparing genetic networks of various genomes. When comparing various methods for modeling GRNs, Boolean networks methods are useful to capture simplified interactions but these methods suffers from the loss of information due to discretisation. Also, it impractically assumes that transitions between activation states of the genes are synchronous. However, despite such limitations, these methods can be applied where accuracy is not the main concern. On the other hand, Bayesian networks methods are capable to deal with the stochastic aspects of gene expression and can handle noisy and incomplete data. However, it cannot deal with the dynamic aspects of gene regulations. Dynamic Bayesian networks were devised to solve dynamicity problem. To overcome information loss due to discretisation, ODE-based approach can be applied. These approaches provide detailed information about the network's dynamics but it requires huge amount of high-quality experimental data. The results of these methods are highly affected by noisy data.

When above methods are compared with soft computing (SC) based approach, SC-based approach are more robust and tolerant to noisy and incomplete data. The

learning and adaptation capability of ANNs, knowledge representation through FLs and optimization capability of GAs when joined together, one can exploit the advantages of each of them. Also, different types of hybridization let us incorporate the generic and application-specific properties of these soft computing constituents. However, these SC-based methods require huge computation. The overall picture is that there is no any super model exists covering all aspects of cellular dynamics. We have observed that most of the techniques applied are hybridized forms of various SC techniques and clustering. Clustering is important because it allows preprocess of data and reduce data dimensionally so that computation time can be reduced.

We can improve our understanding of genetic interactions by (i) incorporating prior biological knowledge into the model (ii) integrating multiple biological data sources and (iii) decomposing the problem into smaller modules [29]. Modeling techniques can also be improved by (a) preprocessing gene expression data to reduce noises (b) incorporating clustering techniques to identify biologically meaningful modules which reduces the dimensionality of the data (c) applying soft computing method to capture nonlinear and dynamic relationships between genes.

Most of the proposed methods have various advantages and disadvantages; thus, we perceive a greater need for improving our understanding about the fundamental idea for each method and must consider available input data and constraints in choosing an appropriate modeling technique. Current research focuses on the modeling of GRNs from synthetic data, or on the simulation of small-scale regulatory networks with several genes or gene clusters. The modeling of large-scale genetic networks is yet to be done. Large number of genes, magnitude of the regulatory effect between the genes and speed of their regulatory response should also be incorporated in the model.

References

[1] de Jong, H.: Modeling and simulation of genetic regulatory systems: A literature review. J. Computational Biology 9, 67–103 (2002)

[2] Cho, K.-H., Choo, S.-M., et al.: Reverse engineering of gene regulatory networks. IET Syst. Biol. 1(3), 149–163 (2007)

[3] Sun, Y., Feng, G., Cao, J.: A new approach to dynamic fuzzy modeling of genetic regulatory networks. IEEE Transactions on Nanobioscience 9(4), 263–272 (2010)

[4] Naldi, A., Thieffry, D., Chaouiya, C.: Decision Diagrams for the Representation and Analysis of Logical Models of Genetic Networks. In: Calder, M., Gilmore, S. (eds.) CMSB 2007. LNCS (LNBI), vol. 4695, pp. 233–247. Springer, Heidelberg (2007)

[5] Remy, É., Ruet, P., Mendoza, L., Thieffry, D., Chaouiya, C.: From Logical Regulatory Graphs to Standard Petri Nets: Dynamical Roles and Functionality of Feedback Circuits. In: Priami, C., Ingólfsdóttir, A., Mishra, B., Riis Nielson, H. (eds.) Transactions on Computational Systems Biology VII. LNCS (LNBI), vol. 4230, pp. 56–72. Springer, Heidelberg (2006)

[6] Akutsu, T., Miyano, S., Kuhara, S.: Identification of genetic networks from a small number of gene expression patterns under the Boolean network model. In: Pac. Symp. Biocomput., pp. 17–28 (1999)

[7] Martin, S., Shang, Z., Martino, A., Faulon, J.-L.: Boolean dynamics of genetic regulatory networks inferred from microarray time series data. Bioinformatics 23, 866–874 (2007)

[8] Shmulevich, I., Dougherty, E.R., Kim, S., Zhang, W.: Probabilistic Boolean networks: A rule-based uncertainty model for gene regulatory networks. Bioinformatics 18, 261–274 (2002)

[9] Friedman, N., Linial, M., Nachman, I., Pe'er, D.: Using Bayesian networks to analyze expression data. J. Computational Biology 7, 601–620 (2000)
[10] Husmeier, D.: Sensitivity and specificity of inferring genetic regulatory interactions from microarray experiments with dynamic Bayesian networks. Bioinformatics 19, 2271–2282 (2003)
[11] Klipp, E.: Systems biology in practice: concepts, implementation and application. Wiley-VCH, Weinheim (2005)
[12] Maraziotis, I.A., Dragomir, A., Thanos, D.: Gene regulatory networks modeling using a dynamic evolutionary hybrid. BMC Bioinformatics 11, 140 (2010)
[13] de Jong, H., Page, M.: Search for steady states of piecewise-linear differential equation models of genetic regulatory networks. IEEE/ACM Trans. Computational Biology and Bioinformatics 5(2), 208–222 (2008)
[14] Chen, T., He, H.L., Churck, G.M.: Modeling gene expression with differential equations. In: Pac. Symp. Biocomput., pp. 29–40 (1999)
[15] Tyson, J.J., Csikasz-Nagy, A., Novak, B.: The dynamics of cell cycle regulation. Bioessays 24(12), 1095–1109 (2002)
[16] Koch, I., Schueler, M., Heiner, M.: STEPP – search tool for exploration of Petri net paths: a new tool for Petri net-based path analysis in biochemical networks. Silico Biol. 5, 129–137 (2005)
[17] Liang, S., Fuhrman, S., Somogyi, R.: REVEAL, a general reverse engineering algorithm for inference of genetic regulatory network architectures. In: Pacific Symposium on Biocomputing, vol. 3, pp. 18–29. World Scientific Publishing (1998)
[18] Mitra, S., Das, R., Hayashi, Y.: Genetic networks and soft computing. IEEE/ACM Trans. on Comp. Biology and Bioinformatics 8(1), 94–107 (2011)
[19] Karlebach, G., Shamir, R.: Modeling and analysis of gene regulatory networks. Nature Reviews Molecular Cell Biology 9, 770–780 (2008)
[20] Bower, J.M., Bolouri, H.: Computational modeling of genetic and biochemical networks, pp. 1–48. MIT Press, London (2001)
[21] Schlitt, T., Brazma, A.: Current approaches to gene regulatory network modeling. BMC Bioinformatics 8 (suppl. 6), S9 (2007)
[22] Schreiber, F., et al.: A generic algorithm for layout of biological networks. BMC Bioinformatics 10, 375 (2009)
[23] Zadeh, L.A.: Fuzzy logic, neural networks and soft computing. One-page course announcement of CS 294-4. University of California at Berkeley (1992)
[24] Mitra, S., Hayashi, Y.: Bioinformatics with soft computing. IEEE Trans. Systems, Man, and Cybernetics, Part C: Applications and Rev. 36(5), 616–635 (2006)
[25] Zadeh, L.A.: Fuzzy logic, neural networks, and soft computing. Comm. ACM 37, 77–84 (1994)
[26] Liu, G., et al.: Combination of neuro-fuzzy network models with biological knowledge for reconstructing gene regulatory networks. Journal of Bionic Engineering 8(1), 98–106 (2011)
[27] Vohradsky, J.: Neural network model of gene expression. FASEB J. 15, 846–854 (2001)
[28] Woolf, P.J., Wang, Y.: A fuzzy logic approach to analyzing gene expression data. Physiological Genomics 3, 9–15 (2000)
[29] Zhang, Y., et al.: Reverse engineering module networks by PSO-RNN hybrid modeling. BMC Genomics 10 (suppl. 1), S15 (2009)
[30] Tian, T., Burrage, K.: Stochastic neural network models for gene regulatory networks. In: IEEE Congress on Evolutionary Computation, pp. 162–169 (2003)
[31] Chiang, J.-H., Chao, S.-Y.: Modeling human cancer-related regulatory modules by GA-RNN hybrid algorithms. BMC Bioinformatics 8, 91 (2007)

[32] Du, P., et al.: Modeling gene expression networks using fuzzy logic. IEEE Transcation on Systems, Man and Cybernetic – Part B: Cybernetics 35(6), 1351–1359 (2005)
[33] Ram, R., Chetty, M., Dix Trevor, I.: Fuzzy model for gene regulatory network. In: Proc. of IEEE Congress on Evolutionary Computation, pp. 1450–1455 (2006)
[34] Datta, D., et al.: A recurrent fuzzy neural model of a gene regulatory network for knowledge extraction using differential equation. In: Proc. of IEEE Congress on Evolutionary Computation, pp. 2900–2906 (2009)
[35] Vineetha, S., Chandra, C., Bhat, S., Idicula, S.M.: Gene regulatory network from microarray data using dynamic neural fuzzy approach. In: Proceedings of the International Symposium on Biocomputing (ISB 2010). ACM, New York (2010)
[36] Kentzoglanakis, K.: A swarm intelligence framework for reconstructing gene networks: searching for biologically plausible architectures. IEEE/ACM Transactions on Computational Biology and Bioinformatics 9(2), 358–371 (2012)
[37] Jung, S.H., Cho, K.-H.: Reconstruction of gene regulatory networks by neuro-fuzzy inference system. In: Frontiers in the Convergence of Bioscience and Information Technologies, pp. 32–37 (2007)
[38] Rui, X., Wunsch, D.C., Frank, R.L.: Inference of genetic regulatory networks with recurrent neural network models using particle swarm optimization. IEEE/ACM Transactions on Comp. Biology and Bioinformatics 4(4), 681–692 (2007)
[39] Ressom, H., Wang, D., Varghese, R.S., Reynolds, R.: Fuzzy logic-based gene regulatory network. In: IEEE International Conference on Fuzzy Systems, vol. 2, pp. 1210–1215 (2003)
[40] Kim, S., et al.: Multivariate measurement of gene expression relationships. Genomics 67, 201–209 (2000)
[41] Huang, J., Shimizu, H., Shioya, S.: Clustering gene expression pattern and extracting relationship in gene network based on artificial neural networks. J. Bioscience and Bioeng. 96, 421–428 (2003)
[42] Zhou, X., et al.: A Bayesian connectivity-based approach to constructing probabilistic gene regulatory networks. Bioinformatics 20(17), 2918–2927 (2004)
[43] Keedwell, E., Narayanan, A., Savic, D.: Modeling gene regulatory data using artificial neural networks. In: Proc. of the 2002 IEEE/INNS/ENNS International Joint Conference on Neural Networks (IJCNN 2002), pp. 183–189 (2002)
[44] Weaver, D.C., Workman, C.T., Stormo, G.D.: Modeling regulatory networks with weight matrices. In: Proc. Pacific Symp. Biocomputing, pp. 112–123 (1999)
[45] Hu, X., Maglia, A., Wunsch II, D.C.: A general recurrent neural network approach to model genetic regulatory networks. In: Proc. of IEEE Engineering in Medicine and Biology Annual Conference, pp. 4735–4738
[46] Ando, S., Sakamoto, E., Iba, H.: Modeling genetic network by hybrid GP. In: Proc. of the Congress on Evolutionary Computation, CEC 2002, vol. 1, pp. 291–296 (2002)
[47] Wang, H., Qian, L., Dougherty, E.: Inference of gene regulatory networks using genetic programming and Kalman filter. In: IEEE GENSIPS, pp. 27–28 (2006)
[48] Sirbu, A., Ruskin, H.J., Crane, M.: Comparison of evolutionary algorithms in genetic regulatory network model. BMC Bioinformatics 11, 59 (2010)
[49] Maeshiro, T., et al.: An evolutionary system for prediction of gene regulatory networks in biological cells. In: SICE Annual Conference 2007, pp. 1577–1581 (2007)
[50] Noman, N., Iba, H.: Reverse engineering genetic networks using evolutionary computation. Genome Informatics 16(2), 205–214 (2005)
[51] Kimura, S., et al.: Inference of S-system models of genetic networks using cooperative coevolutionary algorithm. Bioinformatics 21(7), 1154–1163 (2005)
[52] Chowdhury, A.R., Chetty, M.: An improved method to infer gene regulatory network using S-System. In: IEEE Congress on Evolutionary Computation, pp. 1012–1019 (2011)