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Research Article

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Clono–Hybrid Algorithm for the Reconstruction of Gene Regulatory Network using S-System

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ABSTRACT

Identification of relations in genes for a particular biological condition is a relevant problem in the area of bioinformatics. These relations can be represented as a network of genes. This paper presents a novel hybrid-optimization algorithm, called Clono-Hybrid algorithm, for the reconstruction of gene regulatory network. The proposed approach combines the effect of a global method called clonal selection based algorithm and a local search algorithm called BFGS quasi newton method. The famous S-system model parameters are optimized using the Clono-hybrid algorithm and constructing the gene regulatory network from microarray data set. The proposed approach tested on the five-dimensional artificial microarray data set and a real world SOS DNA repair system. The tested results are compared with the existing approaches. The proposed approach found to be superior in computational efficiency and accuracy.

***Keyword**: Clonal selection based search, Optimization technique, Gene regulatory network, DNA microarray, S-system model.*

INTRODUCTION

In this modern era, mining relevant information from the given data is well applicable in different problem domains. In bioinformatics identification of various patterns in biological data leads to better assessments about life. Identification of patterns in genes during a biological process is a well-known problem in the area of bioinformatics. Gene patterns can be modeled as a network of genes called gene regulatory network (GRN). Gene network is used to identify a particular gene or a set of genes that performs major role in the biological process. Gene network also helps to identify how these genes are related in a particular biological condition.

Prediction of gene regulatory network using DNA microarray is a network mapping between genes. The accuracy of the gene regulatory network depends on various aspects such as noise in the data, mathematical models and the optimization processes employed. DNA microarray is a technology that provides expression of genes in a regular interval of time for a biological process.

Mathematical modeling is a fundamental step in the reconstruction of gene regulatory network. Optimization of the parameters of mathematical model requires special attention for the efficient prediction of gene regulatory network.

Identifying the parameters of the model is a computationally complex process. There are infinitely many solutions for the problem. From these different solutions, one has to identify the optimal solution. Optimization algorithms are powerful tool for solving such problems. This paper proposes a *Clono-hybrid* optimization algorithm, which is an improvement over the clonal based algorithm proposed by Castro and Zuben[1]. The performance of the proposed algorithm is also compared with other standard algorithms to demonstrate its applicability for the gene regulatory network reconstruction problem.

The rest of the paper is structured as follows. In Section 2, a brief literature review is given. Section 3 provides the detailed description of the proposed approach. Section 4 deals with the experimentations and results, and finally, the work is concluded in Section 5.

Literature Survey

There are several approaches such as Boolean[2, 3, 4, 5], Bayesian[6,7,8,9,10,11,12,13], artificial neural methods[14,15,16] and association networks[17,18,19] for the reconstruction of the gene regulatory network. These approaches work on either continuous or discrete aspects[20] . In gene regulatory network system, both continuous and discrete aspects are present. Approaches that use only one aspect may lead to low accuracy. Hybrid approaches that combine the mathematical modeling and evolutionary algorithms are commonly used for achieving better accuracy. The most well accepted mathematical model for the gene network model is the S-system model proposed by Savageau[21].

There are several hybrid approaches based on evolutionary algorithms such as genetic algorithm[22,23,24,25,26,27], genetic programming[28,29], particle swarm algorithms[30.31], artificial bee colony algorithms[32,33]and Cuckoo search algorithms[34,35].

Genetic algorithm is an evolutionary algorithm based on mutation and cross over. There are wide variety of combinations such as genetic algorithm and Kalman filtering[22], genetic algorithm and fuzzy clustering[23], distributed genetic algorithm[24], Genetic algorithm using divide and conquer method (iTEA)[25] and Genetic algorithm with domain knowledge[26]. One of the well-known hybrid algorithms that combine genetic algorithm and evolutionary strategy is the memetic algorithm[27] . Memetic programing is an improvement over the genetic algorithm. One of the famous proposals based on genetic programming was that by Anto *et al.*[28] which is a hybrid algorithm that makes use of the genetic programming and least mean square approach for solving S-system model. Another important proposal was[29] that use a combination of genetic programming and Kalman filtering. Particle Swarm Optimization (PSO) algorithms, based on the randomness properties of particle in nature, are another important class of algorithms. Important works based on PSO algorithms are those by Rui *et al.*[30] and Shailendra[31]. Rui *et al.*[30] proposed a new method that uses PSO for training Recurrent Neural Network (RNN) to model gene network. The work in[31] proposed an algorithm, which is a combination of PSO and GA. This method is computationally very complex. Another class of algorithms, called the Bee colony algorithms, is inspired from the searching nature of food by bees. Based on this, Forghany *et al.*[32] employed an improved artificial bee colony algorithm (ABC) for the reconstruction of gene network. Another approach is that by Yeh *et.al*[33] in which ABC is used for the training and learning purposes for the neural network model. In[34] cuckoo search is employed for the gene regulatory network reconstruction. Cuckoo search is a global evolutionary algorithm, which is inspired from the process of survival of cuckoo birds for the next generation. Later, based on the paper in[34], a modified cuckoo search technique[35] is proposed for achieving further improvements in performance.

The present work introduces a new algorithm called *Clono-Hybrid* Algorithm (CHA) for the reconstruction of gene network. *Clono-Hybrid* algorithm is an improvement of Clonal selection based algorithm proposed by Castro and Zuben[1] . This approach is an improvement over the work[36,37] and makes use of a global-local optimization method.

PROPOSED METHODS

Network model

Gene network system is a nonlinear system that consists of genes and its relationships. Such nonlinear system can be modeled using differential equation modeling. This type of modeling provides the rate of change of gene expression of a particular gene as function of other genes. Mathematically, the model can be defined as, $\frac{dx_i}{dt} = f(x_1, x_2, \dots, x_n)$, where x_i is the concentration of the i^{th}gene expressed. Most popular differential equation model is the S-system model, which is a well-accepted nonlinear differential equation modeling proposed by Savageau[21] . In the S-system, the rate of change of concentration of gene x_i is defined as in equation 1.

$$\frac{dx_i}{dt} = \alpha_i \prod_{j=1}^{N} x_j(t)^{G_{i,j}} - \beta_i \prod_{j=1}^{N} x_j(t)^{H_{i,j}} \qquad (1)$$

Where $G_{i,j}$ and $H_{i,j}$ are excitatory and inhibitory components, respectively. $\boldsymbol{\alpha}_i \geq 0$, and $\boldsymbol{\beta}_i \geq 0$ are rate constants.

S-system is a power law formalism, which is inspired from the chemical reaction processes. Gene regulation interaction is a bio chemical process that takes place in a living organism. This model clearly demonstrates the chemical reaction that happens between genes. The number of parameters used in the S-system is $2N+2N^2$, where N is the number of genes in the reaction.

Clono–Hybrid Algorithm

Clono-Hybrid algorithm is a hybrid algorithm which combines the effect of Clonal selection based algorithm and BFGS Quasi-Newton method. This is a global-local optimization algorithm. The S-system model parameters are optimized using the *Clono-Hybrid* algorithm given in Algorithm 1. Flow/ block diagram representation of the approach is given as Figure 1.

Clonal selection algorithm is an optimization algorithm inspired from the immune system of living organisms. Whenever an antigen gets into a living organism, immune system will identify the foreigner and starts developing a neutralizing antibody. The antibody will combine with the antigen and the effect of antigen is nullified. This process of generating antibody is an optimization process in a biological body. Each time when an antigen comes to body the immune system will learn and train itself trying to produce optimal antibody. Castro and Zuben proposed a Clonal selection based algorithm based on this concept.

In the proposed algorithm, a set of randomly generated individuals are chosen as initial population. This population is evaluated using fitness function. In the next step, groups of selected individuals from the current population undergo cloning process. *Cloning* is a process of generating multiple copies of an individual. In the next step, each cloned individual undergoes BFGS Quasi-Newton weight updating process for '*n*' times. BFGS Quasi-newton method[39] is a local search algorithm proposed by Broyden, Fletcher, Goldfarb and Shanno (BFGS) and is given as algorithm 2. After multiple times of weight updating process, the matured individuals flow to gene pool. Similarly, '*E*' number of top fitness valued individuals flow to gene pool. For increasing the randomness property of the algorithm, '*R*' number of randomly generated individuals also merges with the gene pool. Finally, from the gene pool, 'P_{size}' numbers of best individuals are selected for the next generation. These global iterations continue until the algorithm converges to provide the best fitness value.

Algorithm 1 : *Clono-Hybrid* Algorithm

```
Randomly initialize parameters and population in first generation.
for each generation do
    for each individual do
        Generate gene network structure using S-system.
        Evaluate fitness value.
    end for
    Create a new population of size $P_{size}$, where top $E$ number of individual exists.
    Clone selected individuals from the population.
    Maturate cloned individuals using BFGS Quasi-Newton weight updating method for n times.
    Randomly generate R number of individuals.
    Generate new gene pool that combines maturated individuals, randomly generated individuals and the population individuals
end for
Find optimal gene network
```

Algorithm 2 : BFGS Quasi-Newton weight updating Algorithm

```
Initialize initial solution $x_o$ as the cloned individual.
for each iteration kdo
    Direction, $d_k = -G_k g_k$  /* $G_k$ is an approximate hessian matrix and $g_k$ is gradient vector*/
    Updated solution, $x_{k+1}=x_k + \alpha_k d_k$    /* $\alpha_k$ is the step size*/
    Find $G_{k+1}$ using the BFGS Quasi-Newton formula given as equation 2
end for
return local optimal gene network
```

BFGS Quasi-Newton formula

$$G_{k+1} = G_k + (r_k r_k^T / r_k^T \delta_k) - (G_k \delta_k \delta_k^T G_k / \delta_k^T G_k \delta_k) \tag{2}$$

Where G_k is an approximate hessian matrix,

$$r_k = G_{k+1} \delta_k \tag{3}$$

$$\delta_k = B_{k+1} r_k \tag{4}$$

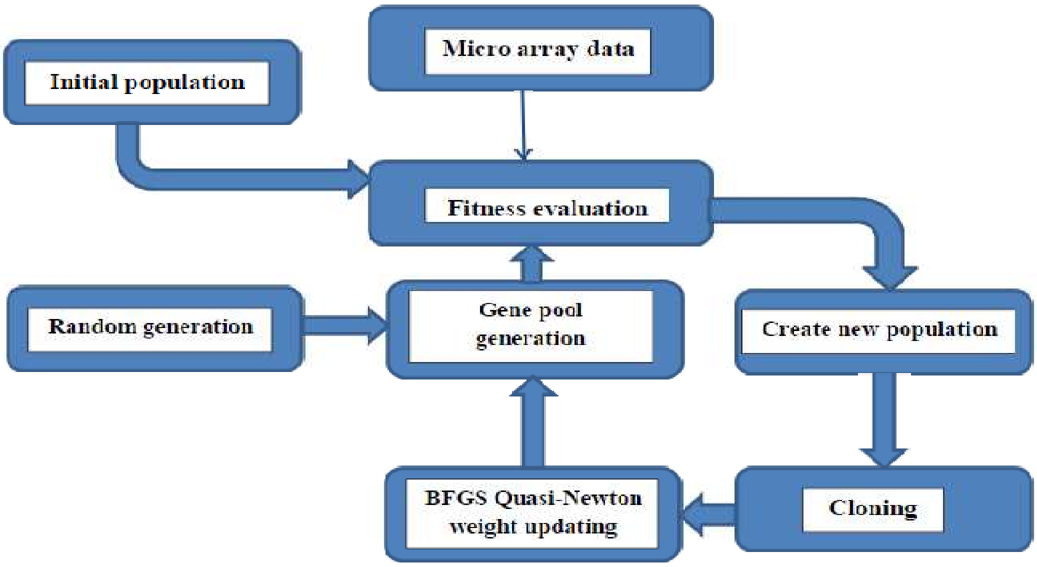
$$B_{k+1} = (H_{k+1})^{-1} \text{ (5)}$$

Fitness function: For the proposed approach, we have used Fitness function introduced by Tominaga *et al.*[38] for the evaluation. This fitness evaluation function is based on *Calculated* $(x_{i,t})$ and *Microarray*$(x_{i,t})$. *Calculated* $(x_{i,t})$ are the values obtained as a result of parameter estimation, and *Microarray*$(x_{i,t})$ are the experimental data obtained from microarray.

$$f = \sum_{i=1}^{N} \sum_{t=1}^{T} ((\mathit{Calculated}(x_{i,t}) - \mathit{Microarray}(x_{i,t}))/\mathit{Microarray}(x_{i,t}))^2 \tag{6}$$

Where N is number of genes and T is time-periods.

Fig.1: Flow/ Block diagram of the proposed approach

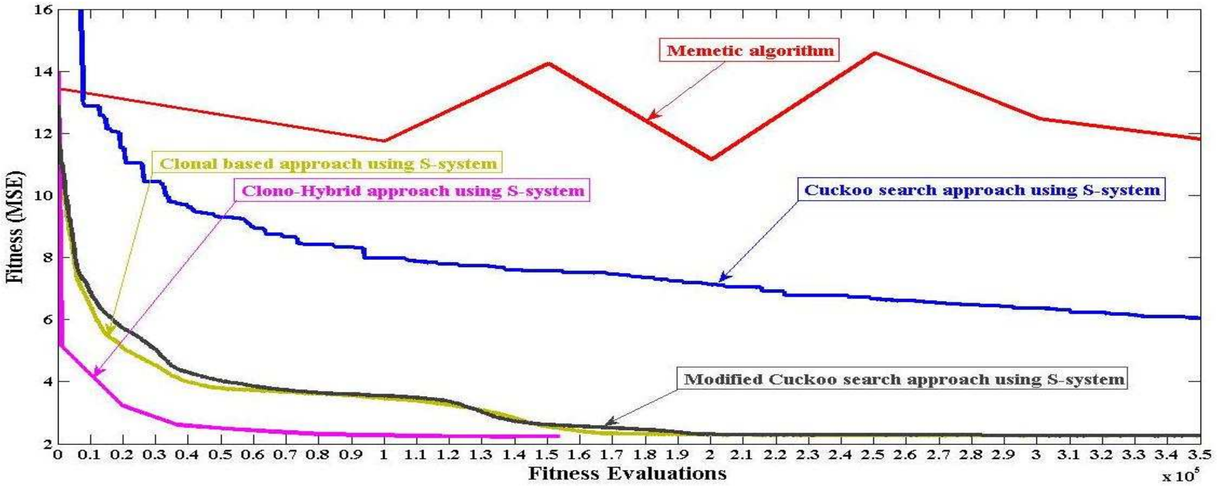


Experiments and result

The expression data used for the evaluation of proposed model are artificial gene expression data generated with the parameters proposed by the Hlavacek *et al.*[40] and SOSDNA repair system of *E.coli.* [40]. Artificial gene expression data contains five genes and is well-accepted data set for the evaluation purpose. The proposed method and already existing methods[27, 34, 35, 36] are implemented for the artificial data set, and the proposal is found to be superior to existing methods.

Figure 2 gives the performance comparison of the artificial data set. The graphical representation of performances in Figure 2 clearly demonstrates that the proposed method converges faster with better accuracy than the other methods. The *Clono-hybrid* based approach using S-system converged after 1.4 $*10^5$ fitness evaluations.

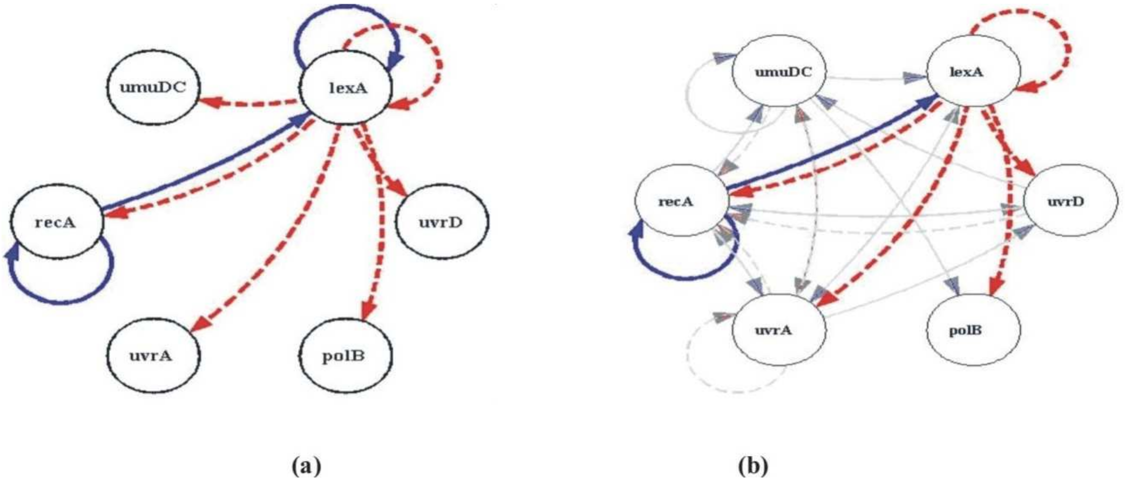
Fig. 2: Performance of Convergence



Comparison of average errors (MSE) obtained for memetic algorithm, Cuckoo search using S-system, Modified Cuckoo search using S-system , Clonal based approach using S-system model, and *Clono-Hybrid* approach using S-system

SOSDNA repair system of E.coli is a real life data set obtained from the experimentation by Uri Alon lab of Weizmann Institute of science from website http://wws.weizmann.ac.il/mcb/UriAlon/download/downloadable-data. This data contains eight genes out of which six genes are important for the SOS DNA repair system. The graphical representation of the SOS DNA repair system is shown in figure 3(a). According to this system, LexA acts as a suppressor for other genes. Due to suppression of other genes, the system will be in a stable condition. Due to any biological circumstances, when DNA damage happens, the concentration of LexA will be reduced. This will activate other genes and will start the repairing. After repairing, LexA will be retained, all other genes will be suppressed, and the system will again be in stable state. Figure 3(b) shows the gene network of SOS DNA repair system obtained by the proposed method. The comparison of the proposed method and other already existing methods are provided as Table 1. According to this, there are mainly nine relations identified by the biologists out of which seven are successfully identified by the proposed method. Compared to other methods reviewed, the proposed method is powerful and can predict relations more accurately.

Fig 3: (a) SOS DNA repair system of E.coli. (b) SOS DNA repair system of E.coli. Identified *Clono-hybrid* based approach using S-system model (Dotted line indicates the inhibition and solid line indicates the activation)



(a) **(b)**

Table1: Comparison of number of relations identified by the proposed approaches with other approaches in the literature for SOS DNA repair system of E.coli

Gene Relations	**[41]**	**[42]**	**[12]**	**[43]**	**[44]**	**[45]**	**[30]**	**Cuckoo -Ssys**	**Clonal-Ssys**	**[46]**	**Modified Cuckoo-Ssys**	***Clono-hybrid-Ssys***
LexA -|RecA	**no**	**yes**	**yes**	**yes**	**yes**	**yes**	**yes**	**yes**	**yes**	**yes**	**yes**	**yes**
LexA -|LexA	**yes**	**yes**	**yes**	**yes**	**yes**	**yes**	**no**	**yes**	**yes**	**yes**	**yes**	**yes**
LexA ->LexA	**no**	**no**	**no**	**no**	**no**	**no**	**no**	**yes**	**no**	**no**	**yes**	**no**
LexA -|umuDc	**no**	**no**	**no**	**yes**	**yes**	**yes**	**yes**	**no**	**no**	**yes**	**yes**	**no**
LexA -| uvrA	**yes**	**yes**	**yes**	**no**	**yes**	**no**	**yes**	**yes**	**yes**	**yes**	**yes**	**yes**
LexA -| uvrD	**yes**	**yes**	**no**	**yes**	**no**	**yes**	**yes**	**no**	**yes**	**yes**	**no**	**yes**
LexA -| polB	**no**	**no**	**no**	**yes**	**no**	**yes**	**yes**	**yes**	**yes**	**yes**	**no**	**yes**
RecA ->LexA	**no**	**no**	**yes**	**no**	**yes**	**no**	**no**	**yes**	**no**	**no**	**yes**	**yes**
RecA -> RecA	**no**	**no**	**no**	**no**	**no**	**no**	**no**	**no**	**yes**	**no**	**yes**	**yes**
No of relations Identified correctly	**3**	**4**	**4**	**5**	**5**	**5**	**5**	**6**	**6**	**6**	**7**	**7**
Sensitivity %	**33**	**44**	**44**	**56**	**56**	**56**	**56**	**67**	**67**	**67**	**67**	**78**
Specificity %	**69**	**64**	**72**	**61**	**69**	**81**	**47**	**52**	**15**	**48**	**61**	**55**

CONCLUSION

Biological systems behave different in different conditions. In order to model such systems we need a dynamical modeling. A nonlinear differential equation modeling for the dynamic biological systems is a common approach. This paper proposed an evolutionary global-local hybrid algorithm for the optimization of gene regulatory network modeling. An algorithm called clonal selection based optimization algorithm is combined with the BFGS Quasi-newton search method and developed a *Clono-hybrid* algorithm. The power law formalism modeling, called S-system, is used for the modeling of gene regulatory network reconstruction. The randomness property and local weight updating property are the key factors for the diversity in results. The proposed approach predicted gene network for artificial data set and SOS DNA repair system successfully. The convergence speed and accuracy compared with the existing approaches are found to be superior. The work concludes that a combination of nonlinear differential modeling and hybrid optimization method can provide better reconstruction of gene network.

REFERENCES

1. De Castro, L. Von Zuben, F., Learning and optimization using the Clonal selection principle. Evolutionary Computation, IEEE Transactions on, 6(3), 239–251 (2002)
2. Akutsu, T. Miyano, S. Kuhara, S. *et al*., Identification of genetic networks from a small number of gene expression patterns under the boolean network model., in Pacific Symposium on Biocomputing, **4**: pp. 17–28 (1999)
3. Sanchez, L. Thieffry, D., A logical analysis of the drosophila gap-gene system, Journal of theoretical Biology, **211(2)**: pp. 115–141 (2001)
4. Yuh, C.H. Bolouri, H. Davidson, E.H., Cis-regulatory logic in the endo16 gene: switching from a specification to a differentiation mode of control, Development, **128(5)**: pp. 617–629 (2001)

5. Albert, R. Othmer, H.G., The topology of the regulatory interactions predicts the expression pattern of the segment polarity genes in drosophila melanogaster, *Journal of theoretical biology*, **223(1)**: pp. 1–18 (2003)
6. Friedman, N. Murphy, K. Russell, S., Learning the structure of dynamic probabilistic networks, in Proceedings of the Fourteenth conference on Uncertainty in artificial intelligence, 1998; pp. 139–147, Morgan Kaufmann Publishers Inc.
7. Murphy, K. Mian, S. *et al.*, Modelling gene expression data using dynamic bayesian networks, tech. rep., Technical report, Computer Science Division, University of California, Berkeley, CA, 1999.
8. Friedman, N. Linial, M. Nachman, I. Pe'er, D., Using bayesian networks to analyze expression data, *Journal of computational biology*, **7(3-4)**: pp. 601–620 (2000)
9. Hartemink, A.J. Gifford, D.K. Jaakkola, T. Young, R.A., Using graphical models and genomic expression data to statistically validate models of genetic regulatory networks., in Pacific symposium on biocomputing, **6**: p. 266 (2001)
10. Imoto, S. Goto, T. Miyano, S. *et al.*, Estimation of genetic networks and functional structures between genes by using bayesian networks and nonparametric regression., in Pacific Symposium on Biocomputing, 2002; **7**: pp. 175–186, World Scientific.
11. Kim, S.Y. Imoto, S. Miyano, S., Inferring gene networks from time series microarray data using dynamic bayesian networks, Briefings in bioinformatics, **4(3)**: pp. 228–235 (2003)
12. Perrin, B.E. Ralaivola, L. Mazurie, A. Bottani, S. Mallet, J. dAlche Buc, F., Gene networks inference using dynamic bayesian networks, Bioinformatics, **19(2)**: pp. ii138–ii148. (2003)
13. Zou, M. Conzen, S.D., A new dynamic bayesian network (dbn) approach for identifying gene regulatory networks from time course microarray data, Bioinformatics, **21(1)**: pp. 71–79 (2005)
14. Khan, J. Wei, J.S. Ringner, M. Saal, L.H. Ladanyi, M. Westermann, F. Berthold, F. Schwab, M. Antonescu, C.R. Peterson, C. *et al*. Classification and diagnostic prediction of cancers using gene expression profiling and artificial neural networks. Nature medicine, **7(6)**: 673–679 (2001)
15. Vohradsky, J., Neural network model of gene expression. *The FASEB Journal,* **15(3)**:846–854 (2001)
16. Narayanan, A. Keedwell, E. Gamalielsson, J. Tatineni, S., Single-layer artificial neural networks for gene expression analysis. Neurocomputing, **61**: 217–240 (2004)
17. Butte, A.J. Kohane, I.S., Mutual information relevance networks: functional genomic clustering using pairwise entropy measurements. Pac Symp Biocomput, 2000; pages 418-429.
18. Katia Basso, Adam A Margolin, Gustavo Stolovitzky, Ulf Klein, Riccardo Dalla-Favera, and Andrea Califano. Reverse engineering of regulatory networks in human B cells. Nat Genet, **37(4)**: 382-390 (2005)
19. Jeremiah, J.F. Boris, H. Joshua, T.T. Ilaria, M. Jamey, W. Guillaume, C. Simon, K. James, J.C. Timothy, S.G., Large-scale mapping and validation of Escherichia coli transcriptional regulation from a compendium of expression profiles. *PLoS Biol,* **5(1)**: e8. (2007)
20. Vijesh, N. Chakrabarti, S.K. Sreekumar, J., Modeling of gene regulatory networks: A review. *Journal of Biomedical Science and Engineering,* **6**: 223 (2013)
21. Savageau, M.A. (20). years of s-systems. Canonical Nonlinear Modeling. S-systems Approach to Understand Complexity, pages 1–44.
22. Chan, Z.S. Kasabov, N. Collins, L., A two-stage methodology for gene regulatory network extraction from time–course gene expression data, Expert Systems with Applications. **30(1)**: 59–63 (2006)
23. Sehgal, M. Gondal, I. Dooley, L. Coppel, R., Afegrn: Adaptive fuzzy evolutionary gene regulatory network re-construction framework, In: Fuzzy Systems, 2006 IEEE International Conference on. pp. 1737–1741.
24. Daisuke, T. Horton, P., Inference of scale-free networks from gene expression time series, *Journal of bioinformatics and computational biology*. **4(02)**: 503–514 (2006)
25. Ho SY, Hsieh CH, Yu FC, Huang HL, An intelligent two-stage evolutionary algorithm for dynamic pathway identification from gene expression profiles, Computational Biology and Bioinformatics, IEEE/ACM Transactions on. 2007;4(4), 648–704.

26. Shu, L.S. Huang, H.L. Ho, S.J. Ho, S.Y., Establishing large-scale gene regulatory networks using a gene-knowledge-embedded evolutionary computation method. In: Computer Science and Automation Engineering (CSAE), 2011 IEEE International Conference on. vol. 4, pp. 272–276.
27. Spieth, C. Streichert, F. Speer, N. Zell, A., A memetic inference method for gene regulatory networks based on s-systems, Evolutionary Computation, CEC2004, Congress, IEEE, **1**:152-157 (2004)
28. Ando, S. Sakamoto, E. Iba, H., Modeling genetic network by hybrid gp, In: Evolutionary Computation, 2002. CEC'02. Proceedings of the 2002 Congress on, IEEE. vol. 1, pp. 291–296.
29. Wang, H. Qian, L. Dougherty, E., Inference of gene regulatory networks using genetic programming and kalman filter, In: Genomic Signal Processing and Statistics, 2006. GENSIPS' 06. IEEE International Workshop on, IEEE. pp. 27–28.
30. Xu, R. Donald, WII, Ronald, F., Inference of genetic regulatory networks with recurrent neural network models using particle swarm optimization." IEEE/ACM Transactions on Computational Biology and Bioinformatics (TCBB) 4.4 (2007): 681-692.
31. Singh, S., A Gene Regulatory Network Prediction Method using Particle Swarm Optimization and Genetic Algorithm. *International Journal of Computer Applications*, 83. (2013)
32. Forghany, Z. Mohsen, D. Ewa, B.S., "Gene regulatory network model identification using artificial bee colony and swarm intelligence." Evolutionary Computation (CEC), 2012 IEEE Congress on. IEEE, 2012.
33. Yeh, W.C. Tsung-Jung, H., Artificial bee colony algorithm-neural networks for S-system models of biochemical networks approximation. Neural Computing and Applications **21(2)**: 365-375 (2012)
34. Jereesh, A.S. Govindan, V.K., Gene regulatory network modelling using cuckoo search and s-system. International *Journal of Advanced Research in Computer Science and Software Engineering,* **3(9)**: 1231–1237 (2013)
35. Jereesh, A.S. Govindan, V.K., An effective reverse engineering methodology for the reconstruction of gene regulatory network using gene expression profile. *International Journal of Universal Pharmacy and Bio Sciences,* **2(6)**: 32–42 (2013)
36. Jereesh, A.S. Govindan, V.K., A clonal based algorithm for the reconstruction of genetic network using s system. International Journal of Research in Engineering and Technology (IJRET),2013; 2:44–50.
37. Jereesh, A.S. Govindan, V.K., Two weight matrix model based GNET reconstruction using clonal selection algorithm, *J. Advanced Bioinformatics Appli. & research*. **3(5)**: 121-133 (2014)
38. Tominaga, D. Koga, N. Okamoto, N., Efficient numerical optimization algorithm based on genetic algorithm for inverse problem. In Proceedings of the Genetic and Evolutionary Computation Conference, 251–258 (2007)
39. Wikipedia: Quasi-Newton method, http://en.wikipedia.org/ wiki/Quasi-Newton_method, (2014)
40. Hlavacek, W.S. Michael, A.S., Rules for coupled expression of regulator and effector genes in inducible circuits. *Journal of molecular biology,* **255**: 1 121-139 (1996)
41. Sutton, M.D. Smith, B.T. Godoy, V.G. Walker, G.C., The sos response: recent insights into umudc-dependent mutagenesis and dna damage tolerance, Annual review of genetics. **34 (1)**: 479-497 (2000)
42. Hsiao, Y.T. Lee, W.P., Inferring robust gene networks from expression data by a sensitivity-based incremental evolution method, BMC bioinformatics 2012;13 (Suppl 7) (2012) S8.
43. Mondal, B.S. Sarkar, A.K. Hasan, M.M. Noman, N., Reconstruction of gene regulatory networks using differential evolution, in: Computer and Information Technology (ICCIT), 2010 13th International Conferenceon, IEEE, 2010, pp. 440-445.
44. Kabir, M. Noman, N. Iba, H., Reverse engineering gene regulatory network from microarray data using linear time-variant model, BMC bioinformatics 11 (Suppl 1) (2010) S56.
45. Noman, N. Iba, H., Reverse engineering genetic networks using evolutionary computation, Genome Informatics Series **16(2)**: 205-214 (2005)
46. Kimura, S. Sonoda, K. Yamane, S. Maeda, H. Matsumura, K. Hatakeyama, M., Function approximation approach to the inference of reduced ngnet models of genetic networks, BMC bioinformatics, **9(1)**: 23 (2008)