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Inference of Gene Regulatory Network using Fuzzy Logic – A Review

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Abstract-Cellular processes like metabolism, responses to the actions or surroundings and reproduction of cells are controlled by proteins. Genesare responsible for thesynthesisof a protein. Some genes synthesize proteins which control the rate at which other genes synthesize protein and form the network of interactions between the genes named as Gene Regulatory Networks (GRNs). GRNs are the control systems which represents the causal relationships between genes, protein-protein interactions, etc. They provide a very useful contribution to cellular biology, mechanics of various harmful diseases like cancer, help in drug discovery and impact of those drugs on the individuals.Large amount of microarray gene expression datasetsare available that can be used to analyse the relationships between the genes. These datasets are imprecise and uncertain because of the noisy and missing values in gene expression datasets. Fuzzy logic based models are capable of handling uncertainty of data which provide the valuable contribution in the inference of GRNs. To address this most challenging area of cellular biology, this paper reviews various fuzzy logic based techniques to infer GRNs from microarray gene expression datasets.The main objective of this review paper is to present, analyse and compare contributions given by researchers in this field**.**

Keywords – Fuzzy Logic, Genetic Regulatory Networks, Microarray gene expression data, Clustering, GRN Inference.

I. Introduction

The activities of all living organisms and various cellular processes present in themare controlled by regulation processes. Regulation of genes takes place inside the cell which represents different biological processes. In these biological processes, cell determines when to express the gene and up to which level of expression[1].Genes are the most fundamental unit that act as the set ofinstructions which are helpful in the production of molecules called proteins such as haemoglobin, etc. Different biological processes like reproduction or division of cells, digestion, metabolism, activities at the molecular leveland gene expression are all controlled by proteins. In the gene regulation, genes are expressed when the DNA is transcribed into messenger RNA i.e. mRNA (named as transcription process) and then further translated into the proteins (named as translation process). Genes help in the formation of proteins. These formed proteins along with other genes control the rate of formation of further proteins. Some proteins increase the transcriptional activity of other genes i.e. rate of formation of proteins. This process is known asactivation. Some proteins suppress the transcriptional activity of genes known as inhibition.Hence, genes regulate other genes directly or indirectly and lead to the formation of complex network of interactions between the genes. This complex network is known as Genetic Regulatory Network (GRN) which shows the need to develop techniques that helps to construct, analyse and understand these complex biological networks. The research study of these complex networks provides various useful applications such as new drug discovery, adverse effect of a drug, help in tracking the development of cancer, providing disease specific cure, and personalized health care solutions [2].

With the advancement in experimental technologies for example, microarray from online database like NCBIand the next generation sequencing techniques, a huge amount of biological data is available.To analyse and get the meaningful information from this microarray datasets, very efficient computational techniques are needed that help us in the inference of the interactions between the genes [3]. Different mathematical modelshave been designed so far to analyse this data to infer the GRNs. This inference of GRNs from the microarray datasets is also named as 'Reverse Engineering' of the GRNs.

But these models are suffering from various problems such as dimensionality problem i.e. number of samples is very less as compared to number of genes in microarray gene expression datasets which shows the need to developtechniques that are computationally complex to eliminate the estimation error due to the presence of small number of samples and high dimensionality. Thousands of expression levels of genes in microarray dataset are subjected to noise. The noise should be removed for proper and accurate analysis.The inference of GRN is computational complex and has low accuracy due to incomplete and imprecise data. In literature, related works suggest to utilize domain knowledge while addressing these challenges. On the other hand, effort should be carried out to make the input precise and efficient so that computational methods can work flawlessly[4].

Several models that are computationally very complex are applied for the inference of GRNs like Boolean Networks, Bayesian Networks, Probabilistic Boolean Networks, Dynamic Bayesian Networks, Artificial Neural Network based models, Differential Equations, and Fuzzy Logic Based Models.

Boolean Networks[5-9]are the most simplestmodels that shows the synchronous relationships between the genes of the network. It is basically a directed graph that isused in the modelling of GRNs where each node of graph represents the state of network that can have two values either 1 which means active i.e. expressed and another one is 0 which means inactive state i.e. unexpressed. The interactions or casual relationships between the nodes i.e. genes are represented with the help of Boolean functions. But only two states are not enough to accommodate large number of genes in network and they are deterministic in nature.

Probabilistic Boolean network(PBN) [10-12] uses two or more boolean functions for the transitions between the states and during these state transitions, when Boolean network moves from one state to another with some certain probabilities. PBNs are the advanced version of Boolean Networks by accommodating more than one possible function for each node. These are capable of overcoming the deterministic nature of Boolean networks. It is stochastic in nature. But state space of these networks is very discrete.

Bayesian Networks (BN) shows the qualitative properties of GRNs. Itcombines two mathematical areas i.e. probability and graph theory. Bayesian Networks[13-15] represent the independent relationships between genes with the help of directed acyclic graphs (DAG). They are very effective in dealing with stochastic behaviour of genes and noise present in microarray gene expression datasetsbut these networks do not consider the dynamic forms of gene or transcriptional regulation.Dynamic Bayesian Networks[16-17] consider the dynamic nature of gene regulation but with the increase in number of genes in network, cost of computation also increases.Therefore, they can be implemented to only small datasets.

The Artificial Neural Network (ANN)[19-22] is similar to other regulatory network models such as Boolean model but ANN uses a weight matrix which further presents intermediate regulations between different nodes. A wiring between two genes means a non-zero weight in weight matrix. These are used with other methods to overcome their limitations. Ordinary Differential Equations[23-26] based models are continuous models and showthe gene relationships with the help of differential equations. They explicitly model the changes in concentration of molecules with time. As a result, they are suitable of describing continuous detailed descriptions of network dynamics. But it involves many parameters which make it very complex. Some hybrid models are also present [27-29] that take care of both continuous and discrete nature of gene regulation, but they are very expensive models[30].

Although Biological Networks are fuzzy in nature, but all above defined models are based on the crisp values.Due to the imprecision and uncertainty in biological data, fuzzy logic is one of the best method to infer GRNs from microarray datasets which is capable of dealing with the imprecision and uncertainty of biological experiments [31].

This paper is organised as follows. Section II constitutes Background that elaborates Microarray Datasets, Fuzzy Logic and GRNs. Section III discusses different fuzzy logic based methods for the inference of GRN. Section IV describes the comparison of discussed fuzzy logic based techniques with each other. Section V concludes the paper.

II. Background

A. Microarray Datasets

Different techniques are available to calculate the expression level of gene for example, Differential Display, Northern Analysis, Serial Analysis of Gene Expression (SAGE), Rapid Analysis of Gene Expression (RAGE), RT-PCR (real time-PCR), Reporter Genes, cDNA (complementary DNA) Technologies, DNA microarray. The DNA microarray [32] is a high-throughput method to analyze the gene expression (mRNA) used in molecular biology and plays a major role in functional genomics. This new technology made possible to calculate the gene expression levels of thousands of genes parallel in a singleexperiment[33]. Gene expression level is a numerical value that indicates the magnitude of gene at certain point of time.Microarray tool is a glass slide or a small membrane that contains samples of many genes to measure the expressions of those genes. Microarray values arecollected over a time course, allowing the study of thedynamic behaviour of gene expression.

B.Fuzzy Logic

Fuzzy logic is a fundamental approach of computing which is based on the degrees of truth rather than crisp values i.e. true or false (0 or 1) used by Boolean logic. It uses 0 and 1 for the extreme cases. Tagaki-Sugeno and Mamdaniare two well-known fuzzy logic inference techniques.These models work on natural language based if- then fuzzy rules. Fuzzy logic has various unique features like very robust as it does not require exact inputs or noise free inputs, it can be modified easily in order to improve the performance, itcan even produces the smooth output with wide range of inputs. The limitations of using fuzzy logic are that it requires high computational costs and optimizations [34].

C.Gene Regulatory Networks

Gene Regulatory Networks can be defined as a collection of genes, or their products, that interact with each other to control different cell functions, their fitness, and survival in living being. The proper working of GRNs will be maintained if each gene in network is expressed at the proper time and in the proper amounts to ensure the correct functional outcome. GRN can be shown with the help of a graph composed of nodes thatindicate genes and links which represents regulatory relationships. Graph can be directed or undirected. Undirected graph just shows the associations between the genes and directed graph shows the associations and tells whether the particular gene is activating or suppressing other genes. Derivation of GRNs from thehuge amount of available biological data is called GRN modelling. GRNs can also be represented using the wiring diagrams[35]. This is the convenient method of representation for finding the transitions between the states.

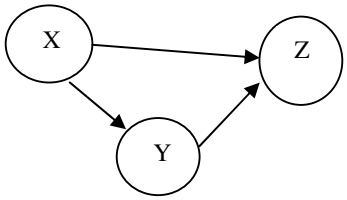

Figure-1 Representation of GRN

III. Different Fuzzy logic Based methods for the inference of GRN

Fuzzy logic based techniques are introduced for the inference of GRNs. Various Fuzzy logic based models are discussed below:

A.Wolf and Wang Fuzzy Logic based Model

Wolf and Wang [36] used the yeast data from the Sacchhromycescervisaecell cycle expression to present the fuzzy logic based technique to infer GRN. This is the simple technique consisting of network triplets i.e. activators, repressors and target genes. First step is to select the appropriate subset of genes to analyse on the basis of set minimum expression and differential thresholds that are further used in the algorithm. The differential threshold only accepts genes whose expression changes by a factor of at least 3i.e. the ratio between the gene's lowest and highest expression level value should be at least 3.

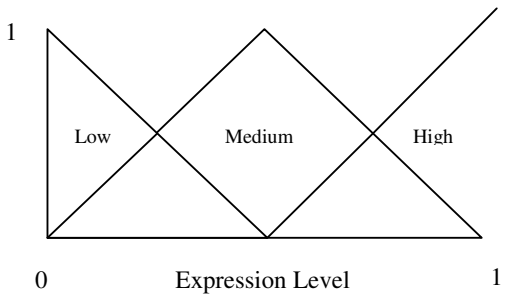

Figure-2 Fuzzy input membership functions

Once genes get selected, the expression values of genes get normalized on the scale of 0 to 1 by subtracting value of gene expression from minimum value of gene expression and then dividing the result of subtraction by range. Here, 1 indicates the highest gene expression level and 0 indicates the lowest gene expression level (same as the Boolean states ‘on’ and ‘off’). Then normalized values of genes are fuzzified into three fuzzy qualifiers, "High", "Medium", and "Low". Figure 2 shows the membership values

After the fuzzification of values, the target gene expression level is estimated for every pair of activator and repressor gene on the basis ofdecision matrix. The decision matrix provides with fuzzy rules i.e. IF-THEN clauses to determine target gene expression profile from input activator and repressor expression profiles. Figure 3 shows the decision matrix consisting of fuzzy rules.

The resulting target gene level is further converted back into predicted gene value i.e. from 0 to 1 through the process of defuzzification like centre of mass.

The predicted target gene level for every combination of N(N-1) activator and repressor gene is calculated, here N represents the total number of genes. For every gene pair, N-2 are the remaining target genes and the estimated target gene level value of a pair is compared with the actual expression levels of remaining genes. To decide which gene triplets best fit GRN, each repressor, activator and target gene triplet is evaluated on the basis of composite score i.e. formed with the combination of residual and variance score. The residual score tells how efficiently activator and repressor gene pair calculates the target gene expression level. The residual score is calculated on basis of the Mean Squared Error between the estimated target output and the actual Gene expression levels of target output. The variancedetermines the variation in configurations of activator and repressor genes with the time. Low variances shows that all fuzzy rules are fired nearly equal in number. The composite score is formed after multiplying residual and variance scores. Finally, the Network with lower scores has higher rank as they are better because they indicate low error and low variance [37].

All possible gene triplets repressor, activator and target gene are examined using the same steps. This program records the error and variance of each triplet. To save computation time and memory, error and variance limits can be set. If a triplet has a higher error than the specified limit, it will not berecorded in the results. If a particular activator and repressor combination has a varianceabove the specified limit, no other triplets with those genes in the activator and repressor positions will be examined.

If Activator \ If Repressor	Low	Medium	High
Low	Low Target	Low Target	Medium Target
Medium	Low Target	Medium Target	High Target
High	Medium Target	High Target	High Target

Figure 3 Decision Matrix

B. Fuzzy Model for predicting change in expression levels

Ram and Shetty [38] have proposed the improved version of fuzzy logic based method to infer GRN. This model predicts the change in the expression values and tries to infer the causal relationships between the genes. They have used the input as the drivers. Drivers are basically activators and repressors, provide positive and negative inputsthat reflects in the regulatory output and in the resulting gene expression levels. The drivers withlower expression levels are insignificant as they are not going toaffect the output expression level.

Target at t_n \ Target at t_{n+1}	Low	Medium	High
Low	Shift I	Shift MI	Shift HI
Medium	Shift MD	Shift I	Shift MI
High	Shift HD	Shift MD	Shift I

Figure-4 Fuzzy Decision Matrix

The pair of genes, activator and repressor, and their expression values are applied to the fuzzy model at time t_n and the output is generated on the basis of fuzzy rules which is classified into five states (increase, medium increase, insignificant, decreaseand medium decrease MD). The predicted changes of the gene expression profiles for all intervals are compared with actual change in the remaining gene expression levels.For example, at time t_n, the input is taken, then the predicted change is analyzed with the actual changein the time interval between$t_n$and t_{n+1}. Figure 4 shows the decision matrix i.e. fuzzy rules for calculatingactual change. The gene pairs with predicted changes in the expression levels forms an existing pattern among the genes (except the input pair) fit the repressor and activator regulatory relationship model.

In addition, they have introduced pre-processing techniqueto remove the unnecessary computations performed by Wolf and Wang model because of the presence of similar expression levels of genes. In pre-processing step, they form the groups of genes depending on the similarity between the changes in expression levels. Genes with the same expression levels that compose the same changes in them over all intervals will produce the same output from this model and results in the redundancy of computations. Replacing the groupof genes with a matching reference expression level will help in reducing the excess of computation cost. In comparison to various other clustering techniques like k-means, c-means, this method of grouping does not require any specific cluster number and any otherinformation of the datasets. Since these results send back to the model, there is no additional amount of cost involved in this pre-processing step.
In this paper, the dataset used contains all genes in Saccharomyces cerevisiae(yeast).

C.Clustering based Fuzzy Logic model

The basic Wolf and Wang fuzzy logic based model takes a huge amount of time to run the algorithm and to find the relationships between the genes because for every combination of repressor, activator, and target gene, the complexity of the algorithm is O(N^3), where N is the gene number. So, it will become very difficult to extend this algorithm to next level of complexity. A model that contains co-activators and co-repressors have the algorithmic complexity O(N^5). It means algorithm took days to finish the execution. Hence, in this paper [39], the authors proposed the technique that will lead to the creation of generalized gene interaction model which can work with any gene number. They proposed the preprocessing step i.e. clustering to decrease the computational time of algorithm and provide the generalized version of Wolf and Wang model to accommodate any number of gene combinations.

The clustering technique used in this paper is self-organising maps (SOM). SOM is the neural network which provides the mapping from the multidimensional data to one or two dimensional space. This technique is very flexible, scalable, robust and fast.SOMtrained for every dataset with varying number of clusters. Clustering is done to find the genes with almost same expression levelsand further these gene clusters can be used as metadata for gene dataset.Clusters of data are formed such that gene expression levels lie close to the centre of cluster and the difference in the Mean Squared Error should be very less. Therefore, if any combination of cluster centres does not fit the model, genes close to those cluster centres willalso not fit the model properly. So, combinations of genes whose nearest cluster centres do not fit the model properly can be removed. Hence, tremendous computation time can be saved.

This algorithm runs for the centre of clusters for triplets. Everytriplet of cluster centres is ranked according to the error i.e. lower error means higher rank.If any gene triplet of cluster lies below the specified threshold, then it will not beconsidered and the algorithm moves to next one triplet. The number of gene triplets considered (or ignored), the gene triplets that pass the error and variance cut offs and the execution time of process are stored.

In this paper, the dataset used is rat **.**CNSdata, yeast data and yeast elutriation.

D. Quantitative fuzzy logic modelling approach

Quantitative fuzzy logic based [40] modelling technique is introduced in order to handle the kinetics of biological experiments and to deal with incomplete and the missing values of microarray datasets. The above described fuzzy logic based methods are unable to handle the quantitative response of the system. Technique introduced in this paper works mainly to produce quantitative results and able to handle the partial data. Fuzzy logic approach produced the same results as produced by other quantitative approaches like Ordinary Differential Equations (ODEs) when kinetic data is known. But, if the kinetic data is uncertain and some values are missing from the datasets, then this fuzzy logic basedapproach produces better results and describes the quantitative behaviour of biological networks. This proposed model is used along with existing modelling techniques like ODEs to produce better outputs. Inputs given to the model are the current concentrations of species represented using x = (x_1,x_2,..., x_n). Outputs of the model are the change in concentrations given by

$$\frac{dx_i}{dt} = \sum_{j=1}^{m} f_{i,j}(x) \text{ for } i = 1,2,...,.n$$

In this equation, each function describes the process i.e transcription, translation, etc. In fuzzy logic, the author changed the function which is partially known because of incomplete or missing values.

$$\frac{dx_i}{dt} = FL_k(x) + \sum_{j=1}^{m} f_{i,j}(x) \text{ for } i = 1,2,...,n \text{ and } k \neq j$$

where$FL_k(x)$ is the fuzzy logic model of process.

E. Collateral Fuzzy Gene Regulatory Network Reconstruction

Microarray gene expression datasets contain 90 percent of the erroneous data due to experimental conditions like glass membrane scratches, hybridization errors, and other environmental problems. Collateral Fuzzy Gene Regulatory Network Reconstruction (CF-GeNe)technique uses the Collateral Missing Value Estimation (CMVE) algorithm to determine the missing values in microarray gene expression datasets. Firstly, they perform pre-processing step in order to take care of the noisy data, negative values of the gene expression level in datasets and the outliers affect. After that, CMVE based imputation strategy is applied to get the resulting imputation value. The number of clusters is calculated and fuzzy c-means clustering algorithm is applied in order to reduce the unnecessary computations. Genes, that show large inter class variations and small intra class variations, are selected to model the GRN. CF-GeNe can also model GRN even if all of the genes are selected. Finally, GRN is constructed on the basis of Spearman Rank Correlation which is calculated between each gene that is selected in the previous step. This model is applied and tested on three different breast cancer mutation datasets, for various ranges of randomly introduced missing values[41].

F. Exhaustive Search Fuzzy based Technique

The fuzzy based method for inferring GRN is tested by exhaustive search for different network models considering cycl in[42] (class of proteins that keep check on the growth of cells through the activation of cyclin-dependent kinase i.e. CDk enzymes)relationships between the genes in yeast cell cycle data. They further want to enhance this method in combination with experiments performed on bacterial regulatory networks. They also use three fuzzy sets High**,** Medium**,** and Low to represent the gene expression level. The input is normalized on the scale of -1 to +1.For defuzzification, the centroid method is used. In this paper, they are mainly focussed on the cyclin relationships between the proteins.

IV. Comparison Table of fuzzy Logic based Techniques

Name of Technique	Datasets Used	Pre-processing Technique	Advantages	Disadvantages
Wolf and Wang Fuzzy Logic based Model [36, 37]	Sacchhromycescervisae	None	Most simplest technique	Time complexity is very high O(N^3) as no pre-processing technique is applied to decrease it
Fuzzy Model for predicting change in expression levels [38]	Saccharomyces cerevisiae(yeast)	Form groupsof genes based on the almost same change in gene expression levels	Pre processing technique used does not require additional computational cost and results in small computation time. The output is classified into 5 states which improves the prediction accuracy for analysing gene relationships	The interactions determined from the microarray datasets are not always causative but they may involve in a similar biological pathway
Clustering based Fuzzy Logic model [39]	rat .CNS data, yeast data, and yeast elutriation	Self Organised Maps	It is the generalised techniques that can work with any number of genes. Therefore, it also includes co-activator and co-repressor relationships	No appropriate way for selecting the number of clusters and the percentage of cluster combinations
Quantitative fuzzy logic modelling approach [40]	Model of three-gene repressilator	None	Handle the quantitative response of system,the kinetics of biological data and works efficiently on the partial datasets	Computationally complex method for the inference of GRNs
Collateral Fuzzy Gene Regulatory Network Reconstruction (CF-GeNe) [41]	Breast cancer mutation datasets	Fuzzy C-means	Handles the missing values of microarray gene expression datasets. It can infer most co-regulated relationships even if large number of values is missing	Complex Technique
Exhaustive Search Fuzzy based Technique [42]	Yeast Cell Cycle	Clustering	Greater resolution and do not require the exact values of parameter	Computational complexity because of exhaustive search

V. CONCLUSION

Gene Regulatory Networks are the complex control systems which represents interactions between genes. GRNs provide a very useful contribution to cellular biology i.e. increase the understanding of various cellular functions like cell growth, cell division, protein synthesis and metabolism. Different models have been developed for the inference of GRNs using the microarray gene expression datasets. These datasets are imprecise and uncertain data due to noise and missing values. Fuzzy logic based models are capable of handling uncertainty of data which provide the valuable contribution in the inference of GRNs. In this paper, fuzzy logic based techniques are discussed to the inference of GRNs. Fuzzy logic techniques are robust and capable of dealing with noise but have high time complexity. The technique proposed by Wolf and Wang is the most basic technique with high time complexity. Therefore, with the time more techniques such as Clustering based technique, CF-GeNe and Exhaustive Search based technique, etc, have been introduced with some modifications like introduction of pre processing steps and different number of states to reduce the time complexity and increase the system performance. Further research work can include the ranking of the defined methods in terms of suitability and other filtering techniques along with fuzzy logic can help in providing better results.

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