Fuzzy Petri Nets for Modeling and Simulation of Genetic Regulatory Network

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Abstract

Genetic Regulatory Network (GRN) is the model that represents the interaction of genome and the external stimulus. Modeling Genetic Regulatory Network can be an excellent methodology to simulate the genetic interaction pattern. This helps to predict and analyze the cellular process. Since the Genetic Regulatory Mechanism is complex and understanding the whole process is time consuming, it is not possible to build an absolute mathematical model. The advancement of cDNA micro array technology ensures the possibility of understanding the gene regulation mechanism. Human expertise can be used to predict and explain the gene regulation mechanism based on cDNA micro array data. This human knowledge and expertise can be modeled using fuzzy GRN Petrinet computational technique. Based on the above implement methods, the present paper stressed the theory, methods of execution for the development of a software tool to simulate a genetic regulatory network.

Introduction

The advancement in cDNA array technology makes it possible to study the gene and protein expression levels for a well defined and known input stimulus (Xiang and Chen, 2000). Gene network modeling uses gene expression profiling data to describe the phenotypic behavior of a system under study (Lee and Tzou, 2009). This gene or protein expression time series data is useful to build the system model of GRN using system identification techniques (Segal et al., 2003). This model mimics the effect of input stimulus on the genome and its resultant expression levels as the output of gene regulation mechanism. The time series data can be analyzed using the human knowledge and reasoning by experts (Wichert et al., 2003). The measurement error and the uncertainties of the deduced model make modeling challenging (Panse and Kshirsagar, 2013). The uncertainties can be due to the effective variables which are uncontrollable during the experiments. Hence the model is essentially stochastic with deterministic and uncertainty components (Wilkinson, 2009). Hence the statistical information of the mRNA expression values is used to determine the global topological properties of the gene regulatory network (Karlebach and Shamir, 2008). Hence a statistical model can be used as a mathematical tool for the modeling and simulation of the observed phenomenon of GRN (Jong, 2002).

It is observed that the domain expert can heuristically predict the behavior of the GRN with reasonable accuracy. The fuzzy logic is one of the techniques listed under soft computing to model such type of systems (Sugeno and Yasukawa, 1993). Also the computational complexity of the fuzzy logic systems are lesser when compared to other soft computation techniques like genetic algorithm, spider web algorithm, evolutionary computing, artificial neural networks, swarm intelligence and bacteria forage algorithm (Deshmukh and Gupta, 2014). Fuzzy systems provide viable computational tools for inferring GRNs from gene expression data, thus contributing to the discovery of gene interactions responsible for specific diseases and/or ad hoc correcting therapies (Qazlan et al., 2014).

The real life model of the biological systems can be implemented using the Petri net (Peleg et al., 2002). This is due to the fact that the Petri net model is the ideal model to simulate the concurrent and networked processing elements (Barad, 2003). Hidden Fuzzy Transition is a methodology for the implementation of Fuzzy Petri net. It encapsulates the truth level calculation of linguistic variables from crisp values. The number of...
Table-1: Fuzzy Rule base

<table>
<thead>
<tr>
<th>Linguistic Variables</th>
<th>Low</th>
<th>C.F</th>
<th>Medium</th>
<th>C.F</th>
<th>High</th>
<th>C.F</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low</td>
<td>Target Medium</td>
<td>0.8</td>
<td>Target Low</td>
<td>0.6</td>
<td>Target Low</td>
<td>0.8</td>
</tr>
<tr>
<td>Medium</td>
<td>Target High</td>
<td>0.7</td>
<td>Target Medium</td>
<td>0.9</td>
<td>Target Low</td>
<td>0.95</td>
</tr>
<tr>
<td>High</td>
<td>Target High</td>
<td>0.8</td>
<td>Target High</td>
<td>0.99</td>
<td>Target Medium</td>
<td>0.9</td>
</tr>
</tbody>
</table>

Figure-1: Components of fuzzy inference Petri net

Figure-2: Input Membership Function (Hamed et al., 2010)

Figure-3: Output Membership Function (Hamed et al., 2010)
Figure-4: Output of Classical Fuzzy Logic

Figure-5: Output of HFT
Figure-6: Comparison of HFT and Classical Fuzzy Logic

Figure-7: Model of Fuzzy Petrinet GRN Tool
input and output places is restricted (i.e. one input and three outputs). Therefore the models of fuzzy Petri nets become more effective. Hence the combination of the two, called fuzzy Petri net (FPN) technique has been adopted (Aziz et al., 2010). Incorporating the fuzzy logic with fuzzy Petri nets (FPNs) has been widely used to deal with fuzzy knowledge representation and reasoning (Hamed et al., 2010). The present paper stressed the theory, methods of execution for the development of a software tool to simulate a genetic regulatory network.

Theory and Methodology

The necessary data such as generalized Genetic Regulatory Network, Fuzzy Inference System (FIS), Fuzzy reasoning system, Hidden fuzzy transition can be integrated to form the framework for implementation of fuzzy GRN model.

Generalized Fuzzy GRN Model

The GRN system is replaced by FIS (Hamed et al., 2010). Since the GRN is a network, the computational FIS model can be implemented using Petri Net framework. The components and component attributes of GRN fuzzy petrinet are assigned. The Petri net framework is extended to implement various components of FIS as shown in the figure-1.

Software

The Petri net tool can be developed using any programming language. Software architecture can be built in layers. The base layer can implement the generalized Petrinet software components. Abstract components called place, transition, token and arc are included in the base layer. The token management and the firing sequences pertaining to the Petrinet model can also be implemented in the base layer and can be specialized in the further layers.

The specialization layer implements the fuzzy Petrinet layer components which specializes the component defined in the Petrinet layer. Fuzzy arc, fuzzy complementary arc, value holder, Hidden fuzzy transition (HFT), DeFuzzification transition (DFT), normalization transition, denormalization transition, rule transition, input linguistic variable and output linguistic variable can be included in this layer. This layer can also contain the network management related components called network, network input and network output.

Analysis

In order to validate the software tool developed, an ideal piece of Genetic Regulatory Network defined by the relationship in Model Rule base, input and output membership functions (as per Hamed et al., 2010) was computed manually and the results were compared. The rule base is presented (Table-1) with the corresponding Confidence Factors (CF). The input (Figure-2) and output (Figure-3) membership functions are also presented.

Analysis of HFT

Hidden Fuzzy Transition is a new methodology for the implementation of the Fuzzy Petrinet. The Hidden Fuzzy transition enables the user to work with minimal Input Linguistic variables (Low, Medium and High). Thus the set of input variables are restricted to three. Hence the sufficiency of the three linguistic variables is to be ensured. The Hidden Fuzzy Transition truth values are compared with the Classical Fuzzy logic truth values for the same membership function. The HFT enables the designer to avoid manual feeding of the truth values of the Input linguistic variables. Thus the Fuzzy Petrinet...


