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MODELING AND SIMULATION OF BIOLOGICAL PROCESSES USING PETRI NET THEORY

(ABSTRACT)

Biological processes are complex. They exhibit dynamics with a huge range of time scales: microseconds to years. Gene regulatory networks, signal transduction cascades, and metabolic pathways are considered important basic biological processes for systemic understanding. Modeling and simulation of gene regulatory networks (GRNs) becomes a promising field of bioinformatics in the post-genomic era. The focus of this work is on GRNs.

Petri nets are a graphical and mathematical modeling tool applicable to many systems, and are used here for the modeling and simulation of GRNs.

This work sets the foundation for formal models by using hybrid functional Petri nets to model and simulate the genetic networks in *Escherichia coli* as an example. The proposed models exhibit the main processes in gene expression, which are transcription, translation and degradation processes, together with the concentration of a protein, mRNA, complex of proteins, metabolites is an essential factor in expressing gene regulation. In this thesis the simulation of genetic regulatory networks using genomic object net tool with hybrid functional Petri nets has been presented.

Next, we focus our attention to the development of computational tools construct and validate biological networks. To have new tools and to develop new integrative approaches, we used a fuzzy Petri net (FPN) for GRNs. With the success stories of PNs and FPNs in various applications, no research has been done in the past on the use of fuzzy Petri nets for genetic regulatory networks. This inspired the research goal of this thesis. This goal is to design computational methods for the analysis of the data of models of GRNs that can reveal their systemic behavior.

We first present a FPN model approach for predicting target gene expression level. We also have successfully presented a FPN model to design the genetic regulatory Network. With the mathematical foundation of FPN, we construct the reasoning steps for FPN reasoning. We have built the FPN model and classified the input data in terms of time point and obtained the output data, so the system can be viewed as the two-input and one output system. In order to do so the concept of hidden fuzzy transition (HFT), an extension of the traditional concept of transition, has been suggested.

We introduce a FPN approach that allows a new interpretation of microarray data set and to infer GRNs. We validate our framework with an experimental study using microarray data sets. The results reported on GRN demonstrate the applicability and effectiveness of the proposed approach. We introduce a new algorithm for modeling and analyzing generic regulatory networks using fuzzy reasoning Boolean Petri nets (FRBPN). Using FRBPN algorithm, we can transform Boolean network into qualitative descriptors that can be evaluated by using a set of fuzzy rules. By recognizing the fundamental links between Boolean network (two-valued) and fuzzy Petri net (multi-valued), effective structural fuzzy rules is achieved through the use of well-established methods of Petri net. The proposed technique has been tested using real bacterium *E. coli* which under the nutritional stress response.

Understanding any cellular process is incomplete without knowledge of the activity of DNA. We introduce FPN models, determining confidence values for bases called in DNA sequencing. The FPN components and functions are mapped from the different type of fuzzy operators of If-parts and Then-parts in fuzzy rules. To illustrate the proposed algorithm the system has been applied to the part of a DNA sequence that involves some bases and a satisfactory result was confirmed. We have shown that the FPN model is appropriate and can reach the same accuracy performance of available tools.