Modeling Signal Transduction of Neural System by Hybrid Petri Net Representation

Shih Chi Peng[1], Hsu-Ming Chang[1], D. Frank Hsu[2], Chuan Yi Tang[1]

[1] Dept. of Computer Science, National Tsing Hua University, Hsinchu 300, Taiwan, ROC
shihchi@url.com.tw; hmchang@life.nthu.edu.tw; cytang@cs.nthu.edu.tw

[2] Dept. of Computer and Information Science, Fordham University, New York, NY 10023, USA
hsu@cis.fordham.edu

Abstract

Biological neural system can be considered as a series of biochemical reactions and signal transmission. It is important to provide an intuitive representation of the neural system to biologists while keeping its computational consistency. In this paper, we propose a method to exploit Hybrid Petri Net (HPN) for intuitive representation and quantitative modeling. The HPN is an extension of Petri Nets and represented by a directed, bipartite graph in which nodes are either discrete/continuous places (such as ion channels) or discrete/continuous transitions (such as phosphorylation), where places represent conditions and transitions represent activities. It can easily model the interactions among receptors, ionic flows (such as calcium), G-proteins, protein kinases and transcription factors that are very complicate in terms of the dynamics of all participants and their correlations. We demonstrate that, in the biological neural system, it is possible to translate and map these complex phenomena into HPNs in a natural manner. In our model, the dynamic properties of the neural signal processing can be examined, especially the interactions among neural modulators and signal transduction pathways. With such a mechanism model in hand, our ability to collaborate with neural scientists is greatly enhanced so as to simulate and examine the robustness of the neural transmission under the local biochemical perturbations.

1. Introduction

Signal transduction is a major mechanism that a cell uses to convert an external stimulation into a series of biochemical reaction. Many molecules can be viewed as triggers or effectors at different stages of the highly complicated transduction activities. We hope to use a computational model to help understanding the mechanism of signal transduction in a neuron when we analyze experimental data and conduct simulations. Nevertheless, as a first step, we need a representation of the complex system with relevant information.

With proper representations, every component in a network can be analytically coupled and evaluated. Representations of bio-system can be loosely classified into four main groups [1]: ontologies, database models, structural network models and quantitative analysis models. Theses traditional models are based on systems of ordinary differential equations (ODEs) such as Michaelis-Menten equations [2], graph theory model [3], and discrete event technique [4]. In recent years some Hybrid Petri Net (HPN) models have been proposed for gene regulatory networks and metabolic networks [2] [5]. HPNs are well suited for describing and analyzing the structure and function of dynamic systems. In bio-system, HPN's enable us to maintain various characteristics of the biological process such as DNA or protein concentration using continuous value. HPN's also allow us to model and visualize system concurrency.

The cellular signal to trigger the whole transduction network can be as simple as a small ionic current passing through channels on the cell membrane, after ligands binding to receptors. Some kinases are activated there after. Eventually, various kinases cause side chains of some peptides such as tyrosine (tyrosine kinase) or serine/threonine (serine or threonine kinase) to be phosphorylated. The conformation of the protein is altered and its activity changed.

In this paper, we focus on modeling signal transduction process of the neural system using Hybrid Petri Net representation. In Section 2, we review and define the modeling concept of a Hybrid Petri Net in the context of a neuron system. In Section 3, we use the HPN to model the signal transduction pathways in a neuron. An example is given to illustrate our framework. Section 4 discusses issues for future work.

2. Hybrid Petri Net

Petri Net was developed in the 1960's by Carl Adam Petri [6]. It is a mathematical and graphical modeling tool used in various applications domain including communication protocols, production systems and flexible manufacturing systems. Traditional Petri Net can only be used in a model with discrete events and not suited for continuous system like fluid mechanics.

Hybrid Petri Net (HPN) is an extension of a Petri Net that handles continuous events by real number. There are two kinds of places and transitions in HPN, dis-