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RESEARCH ARTICLE

BioNetSim: a Petri net-based modeling tool for simulations of biochemical processes

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ABSTRACT

BioNetSim, a Petri net-based software for modeling and simulating biochemistry processes, is developed, whose design and implement are presented in this paper, including logic construction, real-time access to KEGG (Kyoto Encyclopedia of Genes and Genomes), and BioModel database. Furthermore, glycolysis is simulated as an example of its application. BioNetSim is a helpful tool for researchers to download data, model biological network, and simulate complicated biochemistry processes. Gene regulatory networks, metabolic pathways, signaling pathways, and kinetics of cell interaction are all available in BioNetSim, which makes modeling more efficient and effective. Similar to other Petri net-based softwares, BioNetSim does well in graphic application and mathematic construction. Moreover, it shows several powerful predominances. (1) It creates models in database. (2) It realizes the real-time access to KEGG and BioModel and transfers data to Petri net. (3) It provides qualitative analysis, such as computation of constants. (4) It generates graphs for tracing the concentration of every molecule during the simulation processes.

KEYWORDS biochemical processes, simulation software, Petri net, Gillespie

INTRODUCTION

A huge amount of biological data are produced by the development of sequencing, which gives rise to a real challenge in understanding the complex interaction networks in the cell. Computational approaches such as metabolic control analysis (Fell, 1992), flux balance analysis (Orth et al., 2010), and elementary mode analysis (Trinh et al., 2009) have been employed. However, due to the limitation of time-consuming and knowledge-based process, these methods fail to deal with large scale production bioprocesses.

In recent years, quantitative approaches are helpfully complemented by qualitative approaches, which are more suitable to induce dynamical properties of complex systems, in particular when few data are accessible. Many quantitative models have been established to build and simulate a biological system, such as Fuzzy logic system (FLS), ordinary differential equations (ODE) and Petri nets (PNs). ODEs are typically derived from the Michaelis-Menten equation, which builds models by differential equations to generate realistic representation biochemically. Based on ODEs, Goryanin et al. analyzed cellular metabolism and regulation, Yang et al. simulated the arachidonic acid metabolic network, and Orton et al. modeled receptor-tyrosine-kinase-activated mitogen-activated protein kinase (MAPK) pathways (Goryanin et al., 1999; Orton et al., 2005; Yang et al., 2007). However, ODEs are hard to be applied when the network is complicated, because ODEs need to be estimated in terms of lots of free parameters to construct models.

In this paper, we developed a software named BioNetSim to model and simulate biochemical processes based on PNs. PNs, first introduced and formally defined by Prof. Carl Adam Petri in the 1960s (Reddy et al., 1996; Pinney et al., 2003), proposed a graphical and mathematical formalism suitable for the modeling and the analysis distributed systems (Murata, 1989; Jeng, 1997; Fanni and Giua, 1998). With their various extensions, PNs allow the definition of both qualitative and

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quantitative models and become a robust method of qualitative analysis of biochemical pathways (Aderem, 2005). This technique incorporates the use of a discrete event methodology for the representation and analysis of biochemical reaction networks. Applying Petri net theory and properties, reactions and other biological processes are modeled as discrete events and analyzed (Egri-Nagy and Nehaniv, 2008). Petri net is widely used in bioinformatics for its advantage on graphic application and mathematic theory. Furthermore, many extensions of Petri net were put forward, such as hybird PN, time PN, stochastic PN, hierarchical PN and colored PN, which makes Petri net be a powerful modeling tool. Typically, there are three categories of biological pathways: gene regulatory networks, metabolic pathways and signaling pathways. The model presented here, which describes biological system, successfully combined all the three networks by Petri nets.

RESULTS

Gillespie algorithm combined to Petri net

Differential functions do not perform well in biochemical processes simulation, because reactions in cells are numerous and the number of reagents typically numbers in the tens of molecules (or less), which makes differential functions quite complicated. In BioSimNet, we chose Gillespie algorithm, an algorithm popularized by Dan Gillespie in 1977, to simulate chemical or biochemical systems of reactions efficiently and accurately using limited computational power. The key step of the method is generating two random numbers to determine the next reaction to occur as well as the time interval. In our work, the random numbers decide which transition will take place and the time interval of next transition.

Logic structure of BioNetSim

BioNetSim, with a structure of C/S, is made up of application program and network database (as shown in Fig. 1). Application program includes simulation environment and tools. To create the simulation environment, we developed PN component, which compiled with COM and employed Gillespie (Angeli et al., 2007; Chaouiya, 2007) algorithm. And we adopted Dmath of VCL (Visual Component Library) (Wang and Huang, 2002) to be the tools for qualitative analysis, such as matrix operation of S-constant (Odd Bringslida, 2007). Data conversion tools for KEGG (Kanehisa et al., 2002) and BioModel (Li et al., 2010) are run as SOA clients, which are separately connected to the server by WebService. Furthermore, using ODBC, applications are accessed to MySQL database (Kiesling, 2003).

Database construction and connection

In BioNetSim, database is divided into four sub-ones for saving the constructed models. (1) Model sub-database is used to put all the models. (2) Node sub-database saves discrete and continuous nodes (place). (3) Edge sub-database saves the active and repressive edges (transitions). (4) Instance sub-database consists of examples of modeling and simulation.

BioNetSim connects to databases by ODBC. Firstly, we installed ODBC 5.0 for MySQL and set up the data source in control panel. And then we put Delphi's ADOConnection component into the project and configured the property of ConnectionString to point to the data source.

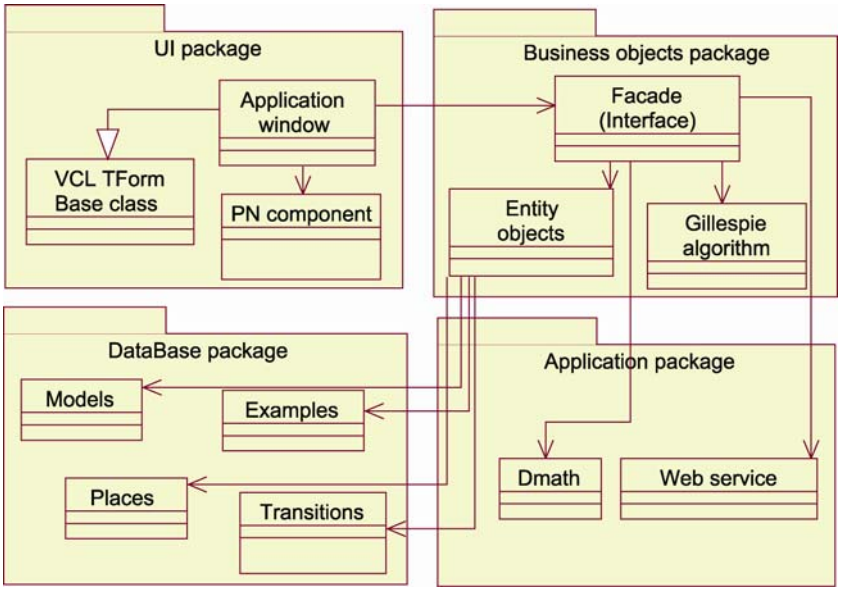


Figure 1. The logic structure of BioNetSim.

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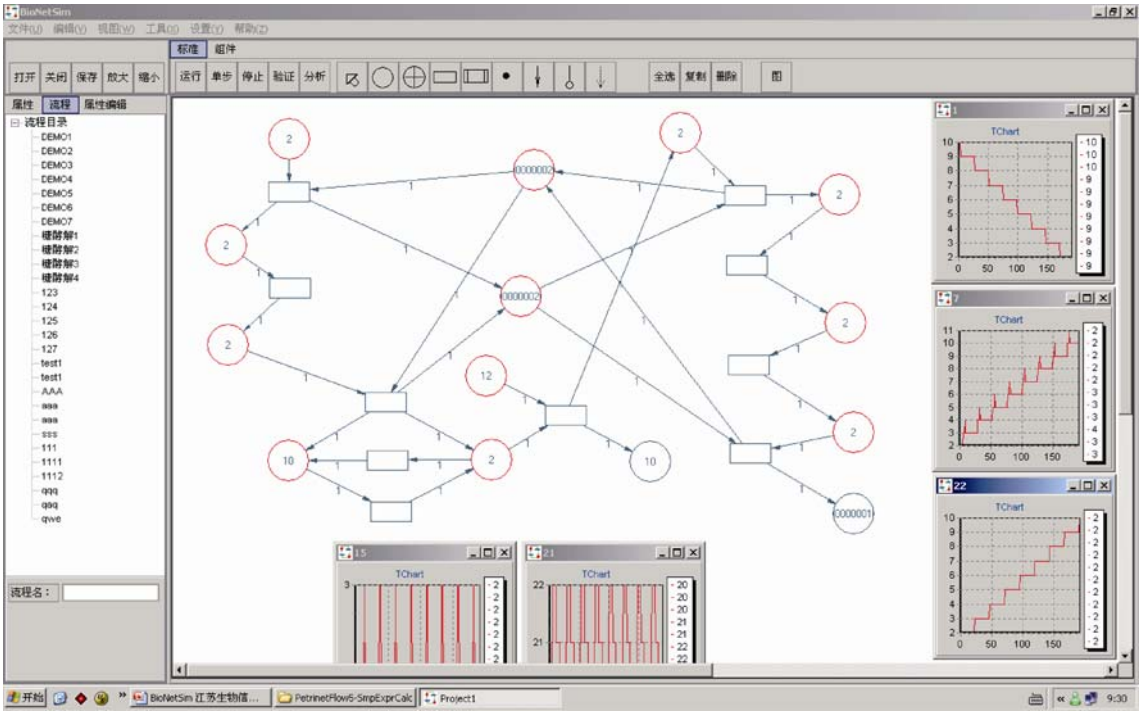


Figure 2. The interface of BioNetSim and the glycolysis simulation.

Glycolysis simulation in BioNetSim

The main interface of BioNetSim is divided into three areas (as shown in Fig. 2). The top section includes menu and shortcut button, left section is the model list displayed with tree component and in the right it is the modeling and simulation area. The model list provides all the models in the database, which brings convenience to user for choosing and maintaining. Users can modify, add and delete the models to meet their needs.

During the glycolysis simulation, we first selected the 'discrete/continuous place' in shortcut button section and put them into modeling area. Then, we used the 'discrete/continuous transition' to link all the places to create a PetriNet network which is connected with the reactions related to glycolysis.

Parameters of places and transitions were set to make the rough network concrete. For example, we initiated density of molecule (places), displayed the density of some molecule dynamically, etc. After finishing the setting of parameters, click the 'run' shortcut button to start the simulation. Every molecular has a separated window with dynamic density-time curve to show the density change during the simulation.

According to the case above, Petri network successfully combined the intuitive graphs and advanced math analysis tools, which any other modeling software cannot achieve. The comparison of biology modeling tools also shows the advantage of Petri network (as shown in Table 1).

DISCUSSION

BioNetSim is a powerful software for researchers to download existing network, create new network and simulate complicated biochemistry processes. It has overwhelming

Table 1 The comparison of biology modeling tools

Method		Graphical expression	Model validation techniques	Network topology analysis	Invariant analysis	Stochastic modeling	Continuous modeling
Mathematical methods	Differential equations	/	/	/	/	/	+
	Stochastic differential equation	/	/	/	/	+	/
Formal methods	Petri net	+	+	+	+	+	+
	Process algebra	/	/	/	/	+	/
	Cellular automata	+	/	/	/	+	/
	Other graph theory	—	/	+	/	/	/

'+'means it has this ability, '—'means it has restricted ability, and '/' means it does not have this ability.

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advantages over other softwares. The modeling in BioNetSim includes metabolism network, signal transduction network, gene regulation network and reaction kinetics. And BioNetSim successfully saves models in database, realizes the real-time access to KEGG and BioModel and transfers data to Petri net. Besides, it provides qualitative analysis and gives graphs for tracing the concentration of every molecule during simulation process. BioNetSim makes it more feasible and efficient for researchers to get models and do further study.

MATERIALS AND METHODS

Petri nets

A Petri net consists of places, transitions, and arcs. Specifically, Petri net is a triple N = (P, T, F) where: P is a set of states, called places; T is a set of transitions; F where $F \subset (P \times T) \cup (T \times P)$ is a set of flow relations called "arcs" between places and transitions (and between transitions and places).

Graphically, places in a Petri net may contain a discrete number of marks called tokens. Arcs run from a place to a transition or *vice versa*, never between places or between transitions. The places from which an arc runs to a transition are called the input places of the transition; the places to which arcs run from a transition are called the output places of the transition.

In the simulation of biochemistry process, “places” are the substances and products in metabolism, “transitions” are enzyme-mediated reaction, “arcs” are parameters of actions, “tokens” are the number of reactants, and a Petri net is the state of the biological system at a certain time (Reddy et al., 1996; Pinney et al., 2003; Zevedei-Oancea and Schuster, 2011).

Database sources

BioNetSim acquires data from KEGG and BioModel, then converse to Petri net. KEGG is a collection of online databases dealing with genomes, enzymatic pathways, and biological chemicals. The PATHWAY database records networks of molecular interactions in the cells, and other functional information, including homologous sub-pathway as well as biochemistry processes in cells, such as metabolism, translocation across membrane, signal transduction and cell cycle. BioModels Database is an online resource for storing and serving quantitative models of biomedical interest. All the models in the curated section of BioModels Database have been described in the peer-reviewed scientific literature. Both KEGG and BioModel open their models based on well-developed WebServise technology and introduce usage of each API in their developing documents.

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ABBREVIATIONS

FLS, Fuzzy logic system; ODE, ordinary differential equations; PNs, Petri nets

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