Simulation and analysis of metabolic networks by time-dependent Petri nets

I. Koch*, S. Schuster
Max-Delbrück-Center for Molecular Medicine,
Dept. of Bioinformatics
Robert-Rössle-Str. 10,
13092 Berlin-Buch, Germany

M. Heiner
Brandenburg University of Technology at Cottbus,
Computer Science Institute
Postbox 10 13 44,
03013 Cottbus, Germany

* e-mail: ikoch@mdc-berlin.de
e-mail: schuster@bp.biologie.hu-berlin.de
phone: (++49 30) 9406-2831
phone: (++49 30) 9406-2834
fax: (++49 30) 9406-2832

Metabolic pathways are complex networks combining a large volume of diverse biological, chemical, and physical data. Because data is often incomplete the development of correct models is a challenge to theoretical biology. Computational methods are needed to model the complex biological processes in order to analyze and understand them.

Traditional mathematical models are focussed on the construction of kinetic models by solving algebraic equations for steady states and systems of differential equations for time-dependent states (for a review see Heinrich & Schuster [4]).

Petri net theory exhibits a mathematical formalism to model, analyze, and simulate discrete event systems with inherent concurrency (Peterson [7], Starke [9]). There are many applications in the field of modeling and control of discrete systems and in the field of concurrent software development (Heiner [3]).

The first application of Petri nets to modeling of metabolic pathways was published by Reddy et al. [8]. In recent years Petri net theory was applied to model metabolic pathways in relation to genetic and cell communication (Hofestädtt & Theilen[6]), to investigate quantitative properties of biochemical networks (Hofestädtt [5]), and to model stochastic systems using stochastic Petri nets (Goss & Peccoud [1]), which succeeded in analyzing the stabilizing effect of the protein Rom on the genetic network controlling ColE1 plasmid replication (Goss & Peccoud [2]).
A helpful tool in Petri net theory is the determination of minimal T-invariants (STARKE [9]), which are related to the elementary modes in metabolic networks (SCHUSTER et al. [10]).

Our poster describes the modeling, analysis, and simulation of the combined glycolytic and pentose phosphate pathway using time-dependent Petri nets. The places represent biological compounds (metabolites) and the transitions chemical reactions between metabolites which are usually catalyzed by a certain enzyme. We extend the model proposed by REDDY et al. [8] by taking also into account the reversible reactions and time dependencies.

STRYER [11] suggests four main modes of the pentose phosphate pathway. We want to focus on the first mode for a detailed analysis. In this mode more ribose 5-phosphate is required than NADPH, because rapidly dividing cells need ribose 5-phosphate for the synthesis of nucleotide precursors of DNA. Following the glycolytic pathway most of the glucose 6-phosphate is converted into fructose 6-phosphate and glyceraldehyde 3-phosphate phosphate, which are then converted by transaldolase and transketolase into ribose 5-phosphate.

We use a hierarchical Petri net for modeling this mode. The net was edited using the Petri net EDitor PED (TIEDEMANN, available via http://www-dssz.informatik.tu-cottbus.de/~wwwdssz/), which supports basically the construction of hierarchical place/transition nets with the specification of different types of places, transitions, and arcs, including their marking. The simulations of the nets were done using PEDVisor, which is not yet published. For the analysis of our model net we apply the program INA - Integrated Net Analyzer (STARKE & ROCH, available via http://www.informatik.hu-berlin.de/~starke/ina.html).

The used time dependencies are artificial. We assign to each transition a time interval to simulate a reaction rate. The first non-negative number is the earliest firing time eft and the second the latest firing time lft. If the transition yields at time \( \tau \) the concession to fire it can fire at the earliest at \( \tau + eft \), and it must fire at the latest at \( \tau + lft \). The time interval \([0,0]\) means that the transition will fire immediately.

The resulting Petri net is structurally bounded and covered by semi-positive \( P \)-invariants. That means that there exists a vector describing a special marking, which always results in a constant by the scalar multiplication with any reachable state of the net.

The net can reach 49 states. The minimal time is 21 units. The reachability graph is strongly connected and therefore the net is reversible. The
net exhibits no time deadlocks and no dynamic conflicts. The net is live.

Time-dependent Petri nets exhibit a useful method for modeling and verification of metabolic pathways, for their time-dependent and time-independent analysis, and simulation of metabolic networks with and without disturbances. We think that our work is an initial step in this direction.

References


