Chapter 25

Petri Nets and GRN Models

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ABSTRACT

In this chapter, modeling of GRNs using Petri net theory is considered. It aims at providing a conceptual understanding of Petri nets to enable the reader to explore GRNs applying Petri net modeling and analysis techniques. Starting with an overview on modeling biochemical networks using Petri nets, the state-of-the-art with focus on GRNs is described. Other modeling techniques, for example, hybrid Petri nets are discussed. Basic concepts of Petri net theory are introduced involving special analysis techniques for modeling biochemical systems, for example, MCT-sets, T-clusters, and Mauritius maps. To illustrate these Petri net concepts, a more complex case study–the gene regulation in Duchenne Muscular Dystrophy–is explained in detail, considering the biological background and the interpretation of analysis results. Considering both, advantages and disadvantages, the chapter demonstrates the usefulness of Petri net modeling, in particular for GRNs.

INTRODUCTION

In the last years, modern high-throughput technologies enabled scientists to get a huge amount of qualitative and quantitative data on biological processes in the cell. Nearly complete metabolic networks of several organisms are available (Edwards, 2000), (Schilling, 2002). At present, the amount of qualitative data increases much faster than of quantitative data. In particular for GRNs, gene expression at mRNA level can be determined by various experimental high-throughput technologies. Due to experimental limits, the measurement of quantitative data in vitro as well as in vivo is often infeasible. In many cases, qualitative data is the only source for getting information about the system behavior. With the changing

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relation of available qualitative and quantitative data of biochemical systems as one important reason for applying discrete methods, different approaches for qualitative modeling have been developed. These methods range from Boolean methods to stoichiometry based approaches such as elementary mode analysis (Schuster, 1993), extreme pathway analysis (Schilling, 2000), flux coupling analysis (Larhlimi, 2006), and T-invariant analysis (Heiner, 2004).

The inconsistency and incompleteness of data, evoked by difficult and different measuring conditions, desire for modeling approaches which allow for combination of data at different abstraction levels in one model. In particular for biochemical networks, this property plays a crucial role, because, for example, gene regulatory processes are linked to signal transduction processes and/or metabolic processes. To investigate the interactions and dependencies of these different processes as they occur in the cell, we need to model these interactions in a unique description language.

Petri net (PN) theory offers the possibility to model systems at different abstraction levels within one model. Moreover, freely available PN tools often provide an intuitive graphic representation of the system with easily operating editors. This facilitates the communication between experimentally and theoretically working scientists, what is particularly useful in strong interdisciplinary fields like systems biology.

First PN models of biochemical processes have been developed by Reddy et al. (Reddy, 1994; Reddy et al., 1993 and 19961996), modeling the metabolic systems of the fructose metabolism in liver and the combined glycolysis and pentose phosphate pathway in erythrocytes.

In the past 15 years, many different applications of PNs to biochemical systems have been published. Modeling of metabolic networks as PNs is described in (Hofestädt, 1994), (Genrich, 2001), (Voss, 2003), (Oliveira, 2003), and (Koch, 2005). The analysis of signal transduction networks using PNs was introduced by (Lee, 2004), (Takai-Igarashi, 2005), and (Sackmann et al. 2006). For these network types, mostly qualitative discrete simulation and analysis techniques have been applied. The foundations of quantitative PN modeling are described in (Hofestädt & Thelen, 1998) and (Koch & Heiner, 2008).

The transition from Boolean networks to PNs for analyzing gene regulation is developed in (Steggles et al., 2006) and extended in Steggles et al., 2007). Marwan et al. (Marwan et al., 2005) reconstructed a regulatory network, controlling commitment and sporulation in a bacterium.

For modeling gene regulation, often various biochemical systems using different PN types were considered. For example, Goss & Peccaud (Goss & Peccaud, 1998), (Goss & Peccaud, 1999) investigated the genetic network controlling ColE1 plasmid regulation using stochastic PNs. Also hybrid PNs that comprise qualitative as well as quantitative properties into one model have been applied to different biochemical systems (Matsuno et al., 2000) (Chen, 2003), (Hardy, 2004; Matsuno et al., 2003), (Hardy, 2004), (Saito, 2006). The emphasis of these approaches is the analysis via simulation of gene regulation.

Besides investigations focused on these three biological network types, there are publications that combine different abstraction levels into one PN. For example, Simão et al. (Simão et al., 2005) combine gene regulation and metabolic processes focusing on the simulation. The approach considers the qualitative modeling of the biosynthesis of tryptophan in *E.coli*.

Nutsch et al. (Nutsch, 2005) modeled the kinetic mechanism of flagellar motor switching and its sensory control using first a qualitative PN model, which was then refined to give a quantitative one.

Kielbassa et al. (Kielbassa, 2008) developed a PN model which describes the U1 snRNP (uridine rich small nuclear ribonucleoprotein) assembly pathway in alternative splicing in human cells, considering signaling processes, transport processes, and gene expression.

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