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Representing network reconstruction solutions with colored Petri nets

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ABSTRACT

The reconstruction of biological networks from experimental time series data is one of the challenges in systems biology. Currently, most network reconstruction approaches usually yield one solution. In contrast, the (automatic) network reconstruction method proposed by Marwan et al. generates all possible minimal solutions fitting the given set of data, and thus reveals all alternative mechanisms to explain the biological phenomena under study. Although this is interesting and helpful, the generated solutions are usually too many and thus difficult to manage. In this paper, we propose the use of colored Petri nets to represent all possible solutions for a network reconstruction problem by encoding each solution as a color. Specifically, we present two folding (coloring) approaches for generating colored Petri net models for a given set of Petri net networks (solutions). To do this, we not only offer a compact representation of all solutions in one colored model for a given network reconstruction problem, but also facilitate the analysis of each solution by choosing its corresponding color. We also give an application of our coloring approaches by taking the phosphate regulatory network in enteric bacteria as example.

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1. Introduction

Systems Biology [1] aims to study the behavior of a biological system at the system level by investigating the behavior and interactions of all of the components in the system. One of the most important challenges in systems biology is to build mathematical models of biological systems from experimental observations, that is, to reconstruct biological (e.g., regulatory or signaling) networks from experimental data [2,3]. Specifically, a (biological) network reconstruction problem aims to find possible networks (solutions) for a given set of experimental observations. At present, most network reconstruction approaches only yield one solution [4,5]. In contrast, the (automatic) network reconstruction method proposed by Marwan et al. [2,3,6] generates all possible minimal solutions fitting the given set of data, thus revealing all alternative mechanisms to explain the biological phenomena under study. Although this is interesting and helpful, the generated solutions are usually too many and thus difficult to manage.

To alleviate modeling issues of large scale systems, colored Petri nets [7,8] have been proposed, which substantially reduce the size of large models compared with standard Petri nets. Likewise, in this paper we propose the use of colored Petri nets in order to obtain compact representations for a number of network reconstruction solutions (Petri net models) produced by the algorithms given in [2,3,6].

Colored Petri nets [7,8] are a colored extension of standard Petri nets [9]. In a colored Petri net, groups of similar objects are represented as a colored place, each of which is defined as and thus distinguished by a color. Therefore, colored Petri nets provide the means for parameterized and compact representations of complex systems, while they do not lose the analysis capabilities of standard Petri nets. Using colored Petri nets, we can represent each possible (and similar) network (solution) for a given network reconstruction problem as a color. As a result, we can use the structure of only one network and the defined colors to compactly represent all network solutions of a network reconstruction problem. This works always, independently of the similarity degree of the individual networks.

The construction of a colored Petri net model for all solutions of a given network reconstruction problem is a folding (coloring) problem. Folding aims at obtaining a colored Petri net for a given standard Petri net, which is often a challenge. Just like folding a paper, two halves of this paper become overlaid, thus the size decreases to 1/2. Generally speaking, folding a Petri net means

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grouping several similar subnets and then overlaying them, which we also call colorizing [10]. Folding can be realized manually or automatically. Although automatic folding is usually attractive, to find similar subnets from a net for a given subnet (pattern) involves a subgraph isomorphism problem, which is NP-complete [11]. In the network reconstruction problem, we can skip the step of searching similar subnets which makes automatic folding a realistic task.

We have developed a colored Petri net tool, Snoopy, to support the modeling of (large scale) biological systems [12], which has been illustrated by a couple of case studies [13–16]. These applications demonstrate that colored Petri nets have become a powerful tool for modeling and analyzing large scale biological systems. In this paper, we will explore the application of colored Petri nets to the network reconstruction problem.

The main contributions of this paper are as follows. We present two approaches to generate a colored Petri net model by folding a set of (Petri net) solutions for a network reconstruction problem. This combines all the alternative solutions for a network reconstruction problem into one colored Petri net model, which not only offers a compact representation of all solutions, but also facilitates the analysis of each individual solution.

This paper is structured as follows. Section 2 describes related work on the application of colored Petri nets to systems biology, and Section 3 gives a brief introduction to Petri nets and colored Petri nets. After that, Section 4 presents two approaches for generating a colored Petri net model for the given solutions of a network reconstruction problem, followed by a case study and the conclusions in Sections 5 and 6, respectively.

2. Related work

In this section, we will briefly review related work on both biological network reconstruction and the application of colored Petri nets for the modeling of biological systems.

Biological network reconstruction: Network reconstruction is a key topic of systems biology and much effort has been devoted to reconstruct biological networks using a variety of methods [4,5]. For example, Hoon et al. [17] applied differential equations to reconstructing gene regulatory networks from time course gene expression data of Bacillus subtilis. Zou et al. [18] proposed a dynamic Bayesian network method for identifying gene regulatory networks from time course microarray data by limiting potential regulator, demonstrated using time series expression data of the yeast cell cycle. Marwan et al. [2,6] developed a set of Petri nets-based network reconstruction algorithms and demonstrated their power in some case studies, e.g., reconstructing the regulatory network of Physarum Polycephalum. Besides, process mining provides another technique of extracting information about processes and then constructing process models such as Petri net models [19]; see [20] for a more complete overview of process mining and its application.

Most existing network reconstruction approaches yield one possible best-fitting network for a given set of experimental data, while the approach by Marwan et al. [2,6] reconstructs all possible minimal networks that fit the given experimental data.

Colored Petri nets for the modeling of biological systems: Generally speaking, there is a lot of work reporting on the application of different classes of standard Petri nets to a variety of biochemical networks, see [21] for a recent review. However there is only little work which takes advantage of the additional power and ease of modeling comfort offered by colored Petri nets. To the best of our knowledge, the early applications of colored Petri nets in systems biology can be summarized as follows.

Refs. [22,23] deploy colored Petri nets to encode the concentration of species as colored tokens in order to implement continuous simulation for Design/CPN and CPN tools in the net annotation language ML. Colored Petri nets have been used for qualitative modeling and analysis in [24] to predict pathological phenotypes based on genetic mutations, and in [25] to model signal transduction networks. Here, colors encode mutations of the modeled molecules or distinguish between different molecules via their identifiers (colors). Colors have also been used to discriminate metabolites which follow different T-invariants (elementary flux modes) [26–28]. The use of colored Petri nets in a stochastic setting was first demonstrated in [29] using a very simple epidemic model. The host population is divided into at-risk classes, which are modeled as places, and color is used to encode the serological state of individuals (e.g., susceptible, infected, removed). From this summary of related work, we note that existing studies usually resort to Design/CPN [30] or its successor CPN tools [31] in order to model and analyze biological systems. However, neither tool was specifically designed with the requirements of systems biology in mind. Thus, they are not suitable in many aspects, e.g., they do not directly support stochastic or continuous modeling, nor the simulative analysis of the models by stochastic or deterministic simulation.

In order to overcome this inconvenience and to strengthen the modeling capabilities of existing tools for modeling biological systems, we have implemented colored Petri nets in the Petri net tool Snoopy, and extensively explored the applications of colored Petri nets for the modeling of biological systems. For example, in [32] we used colored stochastic Petri nets for modeling and analyzing stochastic membrane systems, where each compartment is encoded as a color. In [33], we described multiscale modeling of coupled Ca^{2+} channels using colored Petri nets by considering two levels (scales): Ca^{2+} release sites and Ca^{2+} channels. By encoding each level as a color set, we can uniquely represent a channel in a release site as a compound product color. In [14], colored stochastic and continuous Petri nets are used for multiscale modeling and analysis of Planar Cell Polarity in the Drosophila wing, and the model built consists of more than 800 cells in a two-level hierarchy of different geometries. In the higher inter-cellular level, cells are located in a rectangular honeycomb grid, representing the epithelium tissue, and the lower level is the intra-cellular organization represented by virtual compartments within one cell in a circular grid. In [34], a case study of Phase Variation in Bacterial Colony Growth is given, in which cells are distributed on a two-dimensional grid represented by both the Cartesian and polar coordinate systems. The issues highlighted in this application include multiple scales (from individual level to colony level), mutation with cell division, mobility of cells, and 2D pattern formation. In [16], colored Petri nets have been deployed to model reaction–diffusion systems, illustrated by the Brusselator model to generate Turing patterns.

We have shown that colored Petri nets are a very powerful modeling and analysis tool for large scale biological systems. In this paper, we will continue to explore a new application of colored Petri nets – the deployment of colored Petri nets for a concise representation of the solution set of a given network reconstruction problem.

3. Colored Petri nets

3.1. Petri nets

Petri nets [9] are weighted, directed, bipartite multigraphs, consisting of places, transitions and arcs that connect places with transitions or vice versa. Places usually represent species or any

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