A review about Petri Nets and Bioinformatics: representations of systems biology

Alex D. Camargo, Karina S. Machado

Abstract – With the exponential volume of data available, it has become clear that biologists need computational methods for data visualization and analysis. Petri Nets (PNs) incorporate a bipartite graphical representation with formal semantics, allowing exhaustive analysis to prove certain net properties. In Bioinformatics, PN tools enable users to verify system properties, system soundness and simulate the dynamic behavior of biological systems. This work review the effectiveness of PNs for the modelling, analysis and simulation on biological systems, serving as a starting point for the development of PNs in biological modeling.

Keywords – Petri Nets; Biological networks; Biological processes

I. INTRODUCTION

Petri Nets (PNs) incorporate an bipartite graphical representation with formal semantics, allowing exhaustive analysis to prove certain net properties [14]. PNs provide useful unique visualization techniques with possibilities for hierarchical modelling and animation. This aspect is very important for the dialog between experimentalists and theoreticians [15]. Many extensions to the simple PN model have been developed, include the following: Coloured Petri Nets, Stochastic Petri Nets and Hybrid Petri Nets [10].

PNs were mainly related to the modelling and analysis of man-made systems (manufacturing systems, communication networks, computational distributed systems, etc.), but, more recently, PN modelling appeared for 'natural' systems [1]. Biological networks are complex and may consist of hundreds of reactions that directly and indirectly affect each other [5].

Alex D. Camargo is graduated in Information Systems (URCAMP) and Computer Engineering Master's Degree candidate at FURG. (alexcamargo@furg.br)

Karina S. Machado is PhD in Computer Science (PUCRS) and Lecturer in Computer Engineering at C3 - FURG. (karina.machado@furg.br)

Most PNs have a visual representation that facilitates the comprehension. In Bioinformatics, PN tools enable users to verify system properties, system soundness and simulate the dynamic behavior [9].

This paper is organized as follows: Important features of PNs are described in Section 2. Qualitative and quantitative modelling are detailed in Section 3 and Section 4, respectively. Section 5 introduces the relation between PNs and Bioinformatics. Related works are apresented in Section 6. Examples of applications are described in Section 7. Finally, the discussion and conclusion is given in Section 8.

II. PETRI NETS

The most basic PN is a bipartite graph in which nodes are either places or transitions. Places represent Boolean conditions (e.g., parasite in the bloodstream) and transitions represent activities (e.g., invasion of a host cell) [9]. In this context, there are two types place nodes (represented as circles) and transition nodes (represented as boxes). The arcs may be characterized by an integer that the weight of some transation, if the arc is unlabelled we can assume to have a weight equal to 1 [10]. Tokens are places that define the state of the PN (marking) resides. This condition represents true values [8].

PNs and their various elements have a standardized graphical representation as shown in Figure 1: places p1, p2 and p3 are circles, transition t1 is a full rectangle, individual tokens are full dots and arcs are drawn as arrows where a positive integer indicates their weight (for instance the arc from p1 to t1 has the weight of 1, from p2 to t1, weight 3 and so on) [4]. The number of tokens in each place is associated with variables, which are m1, m2 and m3.

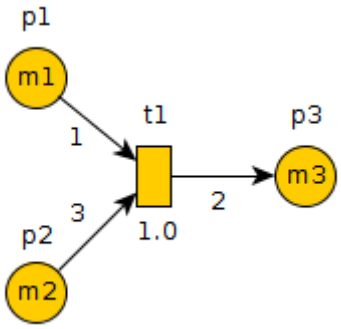

Fig 1. A simple example of Pns. Adapted from [4].

The main extensions of PNs are described in the following subsections. For each extension we present examples of applications on Biology.

A. Coloured Petri Nets

Coloured Petri Nets (CPNs) attach data values to the tokens by defining colour sets and expressions are assigned to the arcs [1]. They were created to diminish model size and so allow the models to manage more information without rendering its structure too complex [3]. The main goal of the CPNs has a formally modeling language for concurrent systems that would make it possible to formally analyze and validate concurrent systems and that, from a modeling perspective, scale to industrial systems [6].

B. Stochastic Petri Nets

Stochastic Petri Nets (SPNs) have provided powerful methods for the performance evaluation of both hardware and software architectures, more specifically, models based on Continuous Time Markov Chains (CTMCs) [7]. For example in Biology, in the SPN model of a system composed of molecular interactions, each place corresponds to a particular molecular species. Tokens represent molecules and transitions between places are chemical reactions involving reactants (input places) and products (output places) [4].

C. Hybrid Petri Nets

Hybrid Petri Nets (HPNs) allow the existence of both continuous and discrete processes [1]. Hybrid PNs can be used by quantitative models using continuous transitions whose rate is a differential equation that may depend on place markings [9].

The necessity to represent discrete and continuous quantities in the same model motivated the development of HPNs, this way many biological processes and systems have already been modeled and simulated [4].

III. Qualitative Modelling

In the context reviewed on this paper, qualitative models represent the fundamental compounds, their interaction, and the relationships between them while quantitative models describe, in addition, the time-related changes of the components [12].

In the derivation of the qualitative PN model of the biochemical network behavior under the steady state assumption each biochemical compound (metabolites, auxiliary compounds) is assigned to a place [11].

IV. Quantitative Modelling

PNs are good illustrations of the suitability of high-level quantitative analysis of complex biological systems. In the future, the researchers will prove that these representations are useful for bioinformaticians develop ever more integrated representations for biological networks [10]. The model aim at representing the system in a detailed way, producing quantitative results [1].

V. Petri nets & Bioinformatics

With the exponential volume of data available, it has become clear that biologists need computational methods for data organization and analysis [8]. Initially, Reddy et al. [13] suggested the use of PNs in biology systems, who qualitatively analyzed metabolic pathways. When a biological network is modeled, it is crucial to consider the relevant level of abstraction.

Modeling and simulation of metabolic networks becomes a promising field of bioinformatics in the post-genomic era and the PN theory exhibits a mathematical formalism to model [2]. Figure 2 illustrates the PN modelling of five types of reactions; places represent reactants, products or enzymes whereas transitions represent reactions, each modifying the amounts of its products and reactants [1].

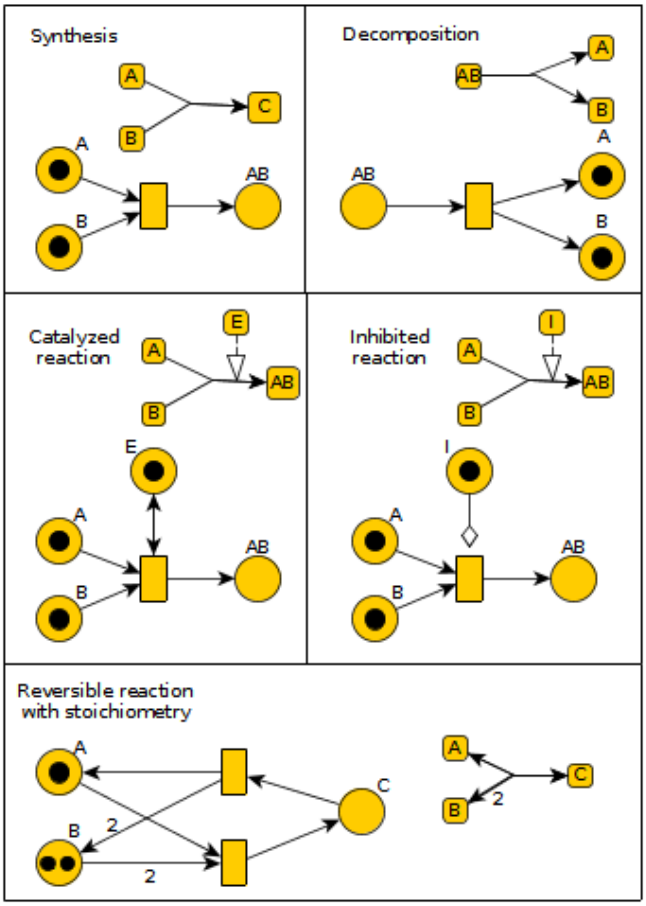

Fig 2. PN modelling of different basic reactions. Adapted from [1].

VI. Relevant Work

The extensions to PNs have special features that make them more suitable to represent and analyze biological features than regular PNs [9]. In [4], the modeling and simulation of biological process with stochastic, colored and hybrid PNs are presented and the characteristics of each approach are discussed. The similarities between modeling in molecular biology in silico (on computer) and PN theory are thoroughly discussed in [17].

VII. Petri nets frameworks for bioinformatics

The use of computational models with Pns allows bioinformaticians an in-depth view of the problems that need to be solved and points to new strategies and alternatives [5]. Recently, a large number of modelling frameworks have been applied for the analysis and simulation of biological networks [1]. Below are discussed two frameworks that have been developed for the use of PNs.

A. Framework: Biology Petri Net Markup Language (BioPNML)

The work of Chen *et al.* [2] proposes the creation of a framework based on XML (eXtensible Markup Language) called BioPNML. Figure 3 shows the model definition of the single biochemical reaction from L-arginine to L-ornithine catalyzed with the enzyme arginase.

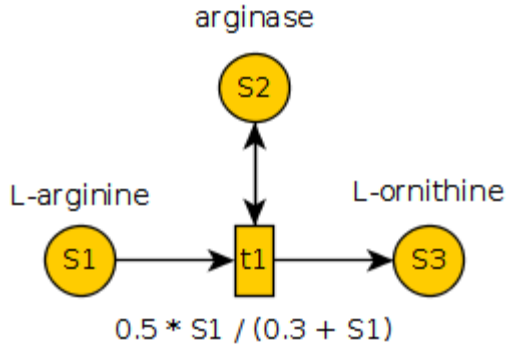

Fig 3. Biology PN model, where S1, S2 and S3 are variables for the concentrations of the substances involved. Adapted from [2].

The basics idea of BioPNML is shown in Figure 4. According to the authors, in real applications the XML part may contain many reactions.

```
<?xml version="1.0" encoding="UTF-8"?>
<!DOCTYPE net SYSTEM "BioPNML.dtd">
<BioPNML>
  <!--***BioPNML***-->
  <Bionet>
    <model name="Metabolic reaction">
      <listOfCompartments>
        <compartment name="Cytosol" volume="1"/>
      </listOfCompartments>
      <listOfSpecies>
        <specie id="s1" name="L-arginine" initialAmount="0.1"
        compartment="Cytosol" boundaryCondition="false"/>
        <specie id="s2" name="arginase" initialAmount="0.5"
        compartment="Cytosol" boundaryCondition="true"/>
        <specie id="s3" name="L-ornithine" initialAmount="0"
        compartment="Cytosol" boundaryCondition="false"/>
      </listOfSpecies>
```

Fig 4. BioPNML XML code. Adapted from [2].

B. Framework: Snoopy

Snoopy [14] is set up as unifying PN framework, comprising a family of related PN models. It is specialized by their kinetic information: qualitative (time-free) place/transition Petri nets (QPN) as well as quantitative (time-dependent) Petri nets such as stochastic Petri nets (SPN) and continuous Petri nets (CPN). Figure 5 shows the three paradigms integrated in Snoopy.

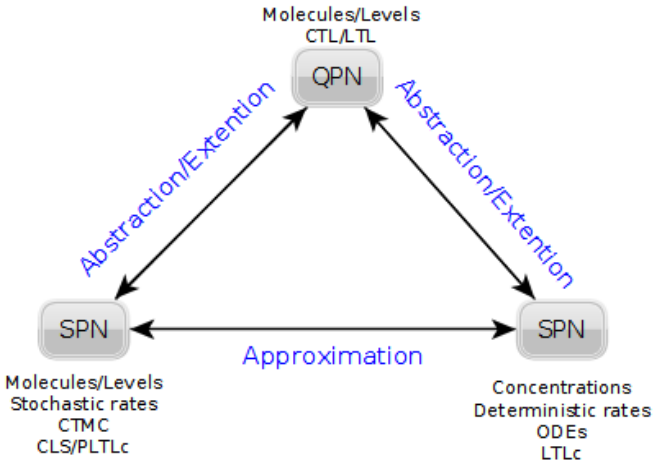

Fig 5. The three paradigms integrated in Snoopy's framework. Adapted from. [14]

VIII. Discussion and Conclusion

PNs are used to model a variety of biological networks, such as metabolic networks, gene regulatory networks and signal transduction networks [16]. The representation of hierarchical process knowledge in biology is therefore a major challenge for bioinformatics [8]. PN is a formalism with many advantages for bioinformaticians. It has analytical and simulation capabilities which provide means to test hypotheses and gather information that might help the elaboration of experiments [4]. This work emphasized the effectiveness of PNs for the modelling, analysis and simulation in biological systems, serving as a starting point for the development of PNs in biological modeling.

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