PetriScape
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A plugin for discrete Petri net simulations in Cytoscape

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Summary

Systems biology plays a central role for biological network analysis in the post-genomic era. Cytoscape is the standard bioinformatics tool offering the community an extensible platform for computational analysis of the emerging cellular network together with experimental omics data sets. However, only few apps/plugins/tools are available for simulating network dynamics in Cytoscape 3. Many approaches of varying complexity exist but none of them have been integrated into Cytoscape as app/plugin yet. Here, we introduce PetriScape, the first Petri net simulator for Cytoscape. Although discrete Petri nets are quite simplistic models, they are capable of modeling global network properties and simulating their behaviour. In addition, they are easily understood and well visualizable. PetriScape comes with the following main functionalities: (1) import of biological networks in SBML format, (2) conversion into a Petri net, (3) visualization as Petri net, and (4) simulation and visualization of the token flow in Cytoscape. PetriScape is the first Cytoscape plugin for Petri nets. It allows a straightforward Petri net model creation, simulation and visualization with Cytoscape, providing clues about the activity of key components in biological networks.

1   Introduction

Unraveling and modeling the behavior of biochemical interactions between biological entities (genes, metabolites, proteins, RNAs, etc.) is crucial for our understanding of cell behavior inference and one of the main objectives in modern systems biology. We nowadays have millions of such interactions publicly available for computational analysis (the PSICQUIC protein-protein interaction querying service may serve as one example here; it offers >16 million interactions [1]). Such data can be visualized and analyzed with computational systems biology tools.

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The most popular one is Cytoscape [2]. It offers a set of standard functions for network visualization and an app store for bioinformatics data analysis tools, which cover thousands of different software solutions in various categories for combining networks with different kinds of omics data types [3]. While many apps for static network analysis exist, only few concentrate on modeling network dynamics, biochemical information or regulation flow through the network. This is important for our understanding of biology but may also result in potential medical and biotechnological applications [4, 5].

One useful methodology in biological network simulation are Petri nets (PNs). PNs can be applied to different classes of biological networks such as metabolic networks [6], gene regulatory networks [7], or signal transduction networks [8]. PNs were introduced by Adam Petri in 1966 [9] for studying concurrent systems. Their flexibility allows utilizing them for modeling the dynamics of biological networks of various kinds [6, 10]. PNs are bi-partite graphs consisting of two sets of nodes called *places* or *transitions*, and a set of edges called *arcs*. In a biological context, a *place* represents molecular unit (such as proteins, metabolites, genes). *Arcs* connect *places* via *transitions*, which represent a biochemical reaction. *Places* receive and lose tokens representing the state/behavior/activity of a certain *place* (e.g. molecular concentration, expression level). PNs can be modeled continuous, stochastic, or discrete; or in a hybrid way [11]. One big advantage of PNs is their intuitive interpretability and the possibility to dynamically visualize them. In the light of Cytoscape, this allows for a conversion of existing metabolic networks into Petri nets along with the visual analysis and simulation of the underlying biochemical reactions on a global systems view [8].

PNs proved useful in simulating and validating biological network models. Corresponding software, like Cell Illustrator [12], SNOOPY [13] and MoVisPP [14], have been established. Some example applications: Koch *et al.* simulated a discrete PN modeling sucrose metabolism in potato tuber and validated its' results with sucrose breakdown data, using invariant analysis [6]. In the same way, Grunwald *et al.* make use of a combination of invariant analysis and clustering for studying the regulatory process of the Duchenne muscular dystrophy [7]. Sackmann *et al.* demonstrate how qualitative Petri nets can be used for simulating the flow of biochemical signals through signal transduction networks, and how this can be applied to predict wet lab targets for future knockout experiments [8].

Bioinformatics Petri net analysis tools were used for all these analysis, but the standard bioinformatics tool for systems biology data processing and biological network analysis, Cytoscape, was not used, as no Petri net app/plugin was available. We account for this gap and introduce PetriScape, the first computational tool for creating and analyzing Petri nets in Cytoscape. Our app allows the user to create networks from SBML files, visualize them in Cytoscape, and to simulate and visualize the token flow through this network inside Cytoscape. In the additional material, we provide examples files (additional files 2-5) and technical details, as well as step-by-step instructions on how to install and utilize PetriScape, and on how to apply it to four example networks (additional file 1).

2 Methods

2.1 Implementation

With PetriScape, we introduce an easy way to perform discrete network flow simulations with Petri net models directly inside Cytoscape. The well-defined Petri net graphic formalism integrated with the Cytoscape network editor allows the creation of simple models. It also allows network editing (insertion or deletion of *places*, *transitions*, or *arcs*, and token editing on *places*) on the fly during the simulation. Petri nets can be created in two ways aided by PetriScape. (1) Manually: Petri nets can be created from scratch by using the Cytoscape editor and subsequent editing the network. Thereby node labels will be set to classify nodes as *places* or *transition* and to assign them an initial token distribution. See additional file 1 for technical details. (2) SBML import: PetriScape comes with a SBML file to Petri net converter. In the supplement, we gives details and example workflow including screenshots exemplarily for four networks (three from Biomodels Database [15], IDś: 1308080002, 1403120000 and 1403040000, as well as the glucose metabolism from Reactome [16, 17]).

2.2 *Transition* Dynamics

We have adopted the discrete Petri net modeling approach [18]. The tokens and *arc* weights are assigned integer values based on the user input. *Transitions* fire in parallel. Conflicting *transitions* fire in the order of a user-given priority (or in a random order if cases of no given or an equal priority). *Transitions* lacking input-*places* always fire, also known as *interfaces*. The firing rules take into account the number of tokens on the input *places* and the incoming *arc* weight. Every *transition*, if firing, consumes a number of tokens from all input *places* that is equivalent to the *arc*'s edge weight that connects the two. A *transition* fires only if enough tokens have accumulated on the input *places*. After all active transitions have consumed their input tokens, tokens are emitted to the output *places* in accordance to the outgoing *arc*'s edge weights and a corresponding number of tokens will be added to the target *places*.

2.3 SBML Data Conversion

PetriScape can convert SBML files into Petri nets and visualize them in Cytoscape as graphs. Reactions are converted to *transitions* and reactants or products to *places*. *Arc* weights are set up according to *stoichiometry* values (as given, for instance, by the Biomodels Database). Here, the initial token distribution is created according to the *species initial amount* tag value from the SBML file. PetriScape uses the JBSML API [19] for XML file parsing.

2.4 Visualization

PetriScape creates a Petri net visual style. *Places* are represented with circles, *transitions* by squares, and *arcs* by directed arrows. The token concentration on *places* and the activity of
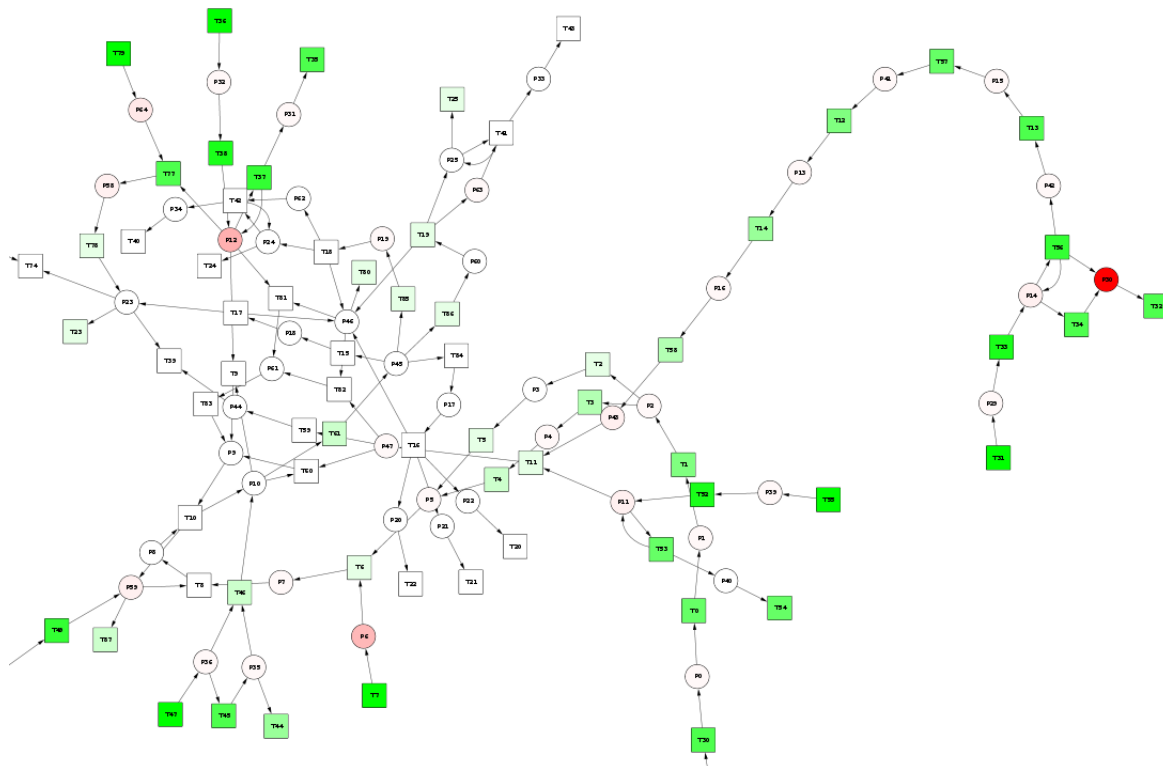
Figure 1: Screen shot of PetriScape plugin after simulating ten steps of the gene regulatory network modeling Duchenne muscular distrophy (previously used by Grunwald *et al.*, taken from Biomodels Database ID: 1403120000. Transitions were colorized in a green range according to the times that they were fired. Places were colorized in red in accordance to their relative token amount

transitions (over a user-given number of rounds) are represented by a color gradient (red and green, respectively). Figure 1 shows how PetriScape looks like after simulating ten rounds of the gene regulatory network model used by Grunwald and colleagues to study the Duchenne muscular distrophy [7], taken from Biomodels Database ID: 1403120000.

3   Conclusion

PetriScape is the first plugin for Petri net simulations in Cytoscape 3. It allows the user to create a Petri net model and visualize it with Cytoscape. It further allows to simulate the discrete Petri nets and to visualize this process. PetriScape provides an intuitive user interface. It will help to generate hypothesis regarding the activity of key components in biological process. Thus, it has the potential to motivate more biologists to apply Petri net models for quantitative analyses of biochemical networks, such as gene regulatory networks [20, 21], for instance.

The software is available at: `http://apps.cytoscape.org/apps/petriscape`

4   Author contributions

Diogo M. Almeida designed the software. Vasco Azevedo and Artur Silva provided the test data and help analyzing it. Jan Baumbach supervised the project and contributed to writing and result evaluation. All authors equally contributed to writing the manuscript.

5   Competing interests

The authors declare that they have no competing interests.

6   Grant information

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