BIOINFORMATICS APPLICATIONS NOTE Vol. 29 no. 19 2013, pages 2507–2508
doi:10.1093/bioinformatics/btt421

Systems biology

Advance Access publication August 1, 2013

SPNConverter: a new link between static and dynamic complex network analysis

Jennifer E. Dent[1,2,†], Xinyi Yang[1,†] and Christine Nardini[1,*]

[1]Group of Clinical Genomic Networks, Key Laboratory of Computational Biology, CAS-MPG Partner Institute for Computational Biology, Shanghai Institutes for Biological Sciences, Shanghai, PR China and [2]Division of Community Health Sciences, St. George's University of London, Cranmer Terrace, London, SW17 0RE, UK

Associate Editor: Igor Jurisica

ABSTRACT

Summary: The signaling Petri net (SPN) simulator, designed to provide insights into the trends of molecules' activity levels in response to an external stimulus, contributes to the systems biology necessity of analyzing the dynamics of large-scale cellular networks. Implemented into the freely available software, BioLayout *Express*^{3D}, the simulator is publicly available and easy to use, provided the input files are prepared in the GraphML format, typically using the network editing software, yEd, and standards specific to the software. However, analysis of complex networks represented using other systems biology formatting languages (on which popular software, such as CellDesigner and Cytoscape, are based) requires manual manipulation, a step that is prone to error and limits the use of the SPN simulator in BioLayout *Express*^{3D}. To overcome this, we present a Cytoscape plug-in that enables users to automatically convert networks for analysis with the SPN simulator from the standard systems biology markup language. The automation of this step opens the SPN simulator to a far larger user group than has previously been possible.

Availability and implementation: Distributed under the *GNU General Public License Version 3 at* http://apps.cytoscape.org/apps/spnconverter.

Contact: christine@picb.ac.cn

Received on March 28, 2013; revised on June 10, 2013; accepted on July 15, 2013

1 INTRODUCTION

There are typically two approaches with respect to the analysis of biological networks: the first is to analyze the network in its static form, determining key features of the network; the second concerns analysis of the network dynamics which, due to the computationally heavy process involved in quantifying kinetic parameters, is typically restricted to small-scale networks. However, Petri nets (PNs) (Petri and Reisig, 2008) allow for the study of dynamics without the need to have detailed information on the kinetics. In this direction, the signaling Petri net (SPN) simulator, first described in Ruths *et al.* (2008), overcomes the aforementioned problem by adapting PNs to biological simulations, characterizing the dynamics of signal flow through a signaling network, using token distribution and sampling. SPNs allow one to analyze the dynamics of large-scale networks by providing insights into the trends of molecules' activity levels in response to an external stimulus. By representing a complex network as a PN, the SPN method models signal flow as the pattern of token accumulation at places (proteins), over time. Transitions in the network represent directed protein interactions, where each transition models the effect of a source protein on a target protein. By allowing tokens to pass through transition gates, the number of tokens assigned to the target, called *token-count*, varies, thus modeling the way that signals propagate through protein interactions in cellular signaling networks (Ruths *et al.*, 2008).

The described SPN simulator has since been adopted, and adapted, for use in BioLayout *Express*^{3D}, a powerful tool for the visualization and analysis of network graphs (Freeman *et al.,* 2007). Within BioLayout *Express*^{3D}, the user has the option to run the SPN simulator over biological networks, strictly input in .graphML format (Brandes *et al.*, 2002) and drawn as bipartite graphs comprising places, transitions and edges. Currently, the network editing software, 'yEd' (http://www.yworks.com), is one of the few that recognizes graphs in standard formats (.xml/.xls, .gml and .xgml), compatible with 'SBML-friendly' (Hucka *et al.*, 2003) software such as Cytoscape (Shannon *et al.*, 2003) and thus CellDesigner (Funahashi *et al.*, 2003). However, this preparation stage requires manual insertion of transition gates between molecules, a step that, particularly for the large maps that SPN is designed to run on, is both cumbersome and prone to error. To overcome this limitation, we have developed SPNConverter, a new application for Cytoscape, which prepares molecular networks for analysis in the SPN simulator in BioLayout *Express*^{3D}. As the Cytoscape plug-in BiNoM (Zinovyev *et al.*, 2008) transforms CellDesigner networks into Cytoscape ones, SPNConverter can be efficiently used on both widespread standards, filling in the missing link between analysis of complex networks in their static form and analysis of the dynamics of large-scale networks.

2 IMPLEMENTATION

SPNConverter is a platform-independent Java application for Cytoscape, an open source software platform for visualizing and analyzing complex networks. Available at www.picb.ac.cn/ClinicalGenomicNTW/SPNConverter.html, SPNConverter allows users to prepare complex networks for the SPN simulator in BioLayout *Express*^{3D} by conversion of graphs from

*To whom correspondence should be addressed.
†The authors wish it to be known that, in their opinion, the first two authors should be regarded as joint First Authors.

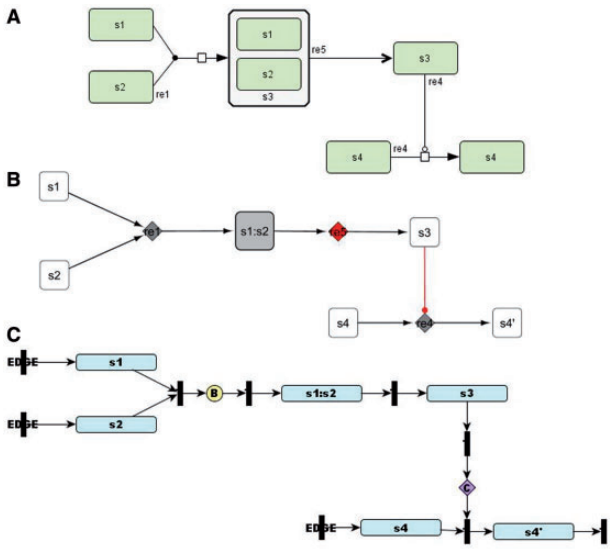

Fig. 1. Graphical representation of a simple network converted from (**A**) CellDesigner to (**B**) Cytoscape and (**C**) .graphML. Transition gates are added to graph C by SPNConverter and tokens allocated to 'edge' nodes

(Cytoscape and) CellDesigner, which follows already well-designed and established nodes, reactions and edge types.

After installation of SPNConverter as a plug-in in Cytoscape, and on importing a complex network from CellDesigner into Cytoscape (see also BiNoM), the user is able to export the selected network as a PN. First, the user must define the attributes to which the network has been built. A network will be associated with three attribute files, describing the characteristics of the nodes, reactions and edges. Although users can define the attribute files themselves, it is highly recommended that the default attribute files created by BiNoM during importation from CellDesigner are used. To refine the simulation, the user can change the default number of tokens that are assigned to edge nodes (during the export process or independently, see Readme file, section 3). Here, it is assumed that edge nodes are input nodes of pathways in the network, labeled 'EDGE' in Figure 1C.

Alternatively, the user can specify input nodes to allow one to investigate the effect of an external stimulus on up to 20 specific, user-defined, points in the network. Should the network be completely closed (i.e. there are no edge nodes), the user is requested to define a stimulation target, thus defining a set of target molecules in the SPN simulation that the biological stimulus would activate. The plug-in, implemented in Java, adds transition gates to the network and converts the network from systems biology markup language (SBML) into modified Edinburgh Pathway Notation, the formatting language used by BioLayout *Express*^{3D}. The network is then saved as a .graphML file, making it immediately recognizable by BioLayout *Express*^{3D} as an SPN simulation input network.

With the plug-in, we provide samples of simple reactions to demonstrate how SPNConverter converts reactions from the SBML format used in CellDesigner into SPN input graphs, as well as a larger example to demonstrate the ability of the plug-in to work efficiently on complex networks that are already in the public domain. The simple reactions are arbitrary, whereas the larger example is a published network of rheumatoid arthritis (Wu *et al.*, 2010).

Both sets of sample files have been imported into BioLayout *Express*^{3D} and the SPN simulator has been run. For the simple interactions, the 'expression profiles' were validated against sample networks provided by the authors of BioLayout *Express*^{3D}. The SPN simulator was also run on the complex network example, and output data were successfully compared with the results published in Dent and Nardini (2013), where the conversion was manual.

3 CONCLUSION

The ability to simulate the effects of a biological stimulus in the absence of detailed information on the kinetics of each reaction can be overcome in the PN frame. However, key to being able to fully benefit from the SPN is the ability for easy and safe conversion of biological networks from the most powerful visualization software into powerful analysis software. Until now, it has not been possible to link the former with the latter, without manual manipulation of networks, greatly restricting the availability of the SPN simulator to researchers. This missing link has been filled by SPNConverter, allowing researchers to investigate the effect of a drug, e.g. on a network *in silico* and with great ease. The results of previous work (with manual conversion) have led to recommendations on unsuitable interactions for rheumatoid arthritis drugs tested in clinical trials (Dent and Nardini, 2013), highlighting the power of the SPN simulator in complex network analysis and the importance of making it more widely accessible with SPNConverter. Future versions may be improved with the use of other standard such as Systems Biology Ontology (Courtot *et al.*, 2011).

Funding: This work was supported by the European Commission FP7-PEOPLE-2011-IRSES program 31028760, project ID 294935.
Conflict of Interest: none declared.

REFERENCES

Brandes,U. *et al.* (2002) GraphML progress report: structural layer proposal. In: *Graph Drawing*. Springer, Berlin, Heidelberg, pp. 501–512.
Courtot,M. *et al.* (2011) Controlled vocabularies and semantics in systems biology. *Mol. Syst. Biol.*, **7**, 543.
Dent,J.E. and Nardini,C. (2013) From desk to bed: computational simulations provide indication for rheumatoid arthritis clinical trials. *BMC Syst. Biol.*, **7**, 10.
Freeman,T.C. *et al.* (2007) Construction, visualisation, and clustering of transcription networks from microarray expression data. *PLoS Comput. Biol.*, **3**, 2032–2042.
Funahashi,A. *et al.* (2003) CellDesigner: a process diagram editor for gene-regulatory and biochemical networks. *BIOSILICO*, **1**, 159–162.
Hucka,M. *et al.* (2003) The Systems Biology Markup Language (SBML): a medium for representation and exchange of biochemical network models. *Bioinformatics*, **19**, 524–531.
Petri,C.A. and Reisig,W. (2008) Petri net. *Scholarpedia*, **3**, 6477.
Ruths,D. *et al.* (2008) The signalling petri net-based simulator: a non-parametric strategy for characterizing the dynamics of cell-specific signaling network. *PLoS Comput. Biol.*, **4**, e1000005.
Shannon,P. *et al.* (2003) Cytoscape: a software environment for integrated models of biomolecular interaction networks. *Genome Res.*, **13**, 2498–2504.
Wu,G. *et al.* (2010) A comprehensive molecular interaction map for rheumatoid arthritis. *PLoS One*, **5**, e10137.
Zinovyev,A. *et al.* (2008) BiNoM: a Cytoscape plugin for manipulating and analyzing biological networks. *Bioinformatics*, **24**, 876–877.