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

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Abstract: 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 Express3D, 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 Express3D. 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.

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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 Express3D, a powerful tool for the visualization and analysis of network graphs (Freeman et al., 2007). Within BioLayout Express3D, 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 Express3D. 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 Express3D by conversion of graphs from...
Both sets of sample files have been imported into BioLayout Express3D 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 Express3D. 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).

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REFERENCES


