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CytoModeler: a tool for bridging large-scale network analysis and dynamic quantitative modeling

Tian Xia[1,*], John Van Hemert[1] and Julie A. Dickerson[1,2,*]

[1]Program of Bioinformatics and Computational Biology and [2]Department of Electrical and Computer Engineering, Iowa State University, Ames, IA 50011, USA

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ABSTRACT

Summary: CytoModeler is an open-source Java application based on the Cytoscape platform. It integrates large-scale network analysis and quantitative modeling by combining omics analysis on the Cytoscape platform, access to deterministic and stochastic simulators, and static and dynamic network context visualizations of simulation results.

Availability: Implemented in Java, CytoModeler runs with Cytoscape 2.6 and 2.7. Binaries, documentation and video walkthroughs are freely available at http://vrac.iastate.edu/~jlv/cytomodeler/.

Contact: julied@iastate.edu; netscape@iastate.edu

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1 INTRODUCTION

Large-scale network analysis and quantitative modeling have emerged as key methods for interpreting biological datasets. Large-scale network analysis uses networks to model large-scale omics data produced by high-throughput screening, where nodes represent biological species and edges between nodes stand for interactions between the species. Quantitative mathematical modeling of biological systems has a much longer history than large-scale network analysis. In this method, researchers build mathematical equations for biological systems and simulate, predict and test behaviors of the systems *in silico*.

Significant progress has been made in the development of software that focuses on large-scale network and quantitative modeling over the past 10 years such as Cytoscape (Shannon *et al*., 2003), a popular open-source software platform for large-scale network visualization and for viewing and editing data, along with a highly flexible and extensible plug-in mechanism, Systems Biology Toolbox (SBT; Schmidt and Jirstrand, 2006) and Systems Biology Workbench (SBW; Sauro *et al*., 2003) for quantitative modeling.

While the number of active software tools which implement these two types of methods singly is growing fast, linkages between them are missing. Knowledge inferred from large-scale network analysis can be quantitatively modeled for examining the dynamics of smaller subsystems with respect to various physiological conditions or time courses. CytoModeler is a software tool dedicated to bridging large-scale network analysis and quantitative modeling by providing the following features: (i) access to a wide range of functionality for large-scale network analysis by being a plug-in tool on Cytoscape platform, (ii) a built-in compact quantitative model editor which enables model creating, importing and exporting with several formats including SBML levels 1 and 2, (iii) a model exchanger which allows users to transfer modeling information between Cytoscape and quantitative modeling tools such as the SBT on MATLAB and SBW and (iv) advanced visualization for quantitative simulation results in a network context. This functionality enables biologists to integrate large-scale network analysis and quantitative modeling into an analytical workflow of systems biology.

2 FUNCTIONALITY AND IMPLEMENTATION

The architecture of CytoModeler is categorized into three functional components. The first component, the CytoModeler Model Editor, is a built-in equation editor. It offers concise model editing function by using CyNodes, CyNetworks and HyperEdges (CyNode, CyNetwork: basic elements in Cytoscape to represent node and biological network; HyperEdge, a special type of edge which is able to represent biochemical reaction.) of the Cytoscape platform. It also provides a model transformer which enables communication with other Cytoscape function plug-ins. Furthermore, it allows users to import and export the edited model into several formats such as SBML. The second component, the CytoModeler Simulation Interface gives users multiple choices for simulating the model. It is based on an improved version of ISBJava (Ramsey *et al*., 2005), including new simulator interface, enhanced visualization for simulation results and support for exporting and importing SBML level 2 version 1 file. This simulator offers many numerical solvers including deterministic and stochastic algorithms. If a user needs more sophisticated systems analysis such as bifurcation analysis, the CytoModeler Simulation Interface can connect with the modeling information with other dedicated analytical tools such as SBT on MATLAB, SBW and COPASI to facilitate the further system analysis using Java interface and SBML standard file format. The extensible architecture allows it to be integrated with other third party systems biology tools. The third component, CytoModeler Visualizer, provides advanced visualization for simulation results. The visualization modes include both static and dynamic points of view. In static visualization mode, the user can individually plot X–Y charts showing simulation result of each species in its corresponding CyNode view or plot the $X-Y$ chart in the Cytoscape data panel. When the user clicks any of the time series for a biochemical species

*To whom correspondence should be addressed.

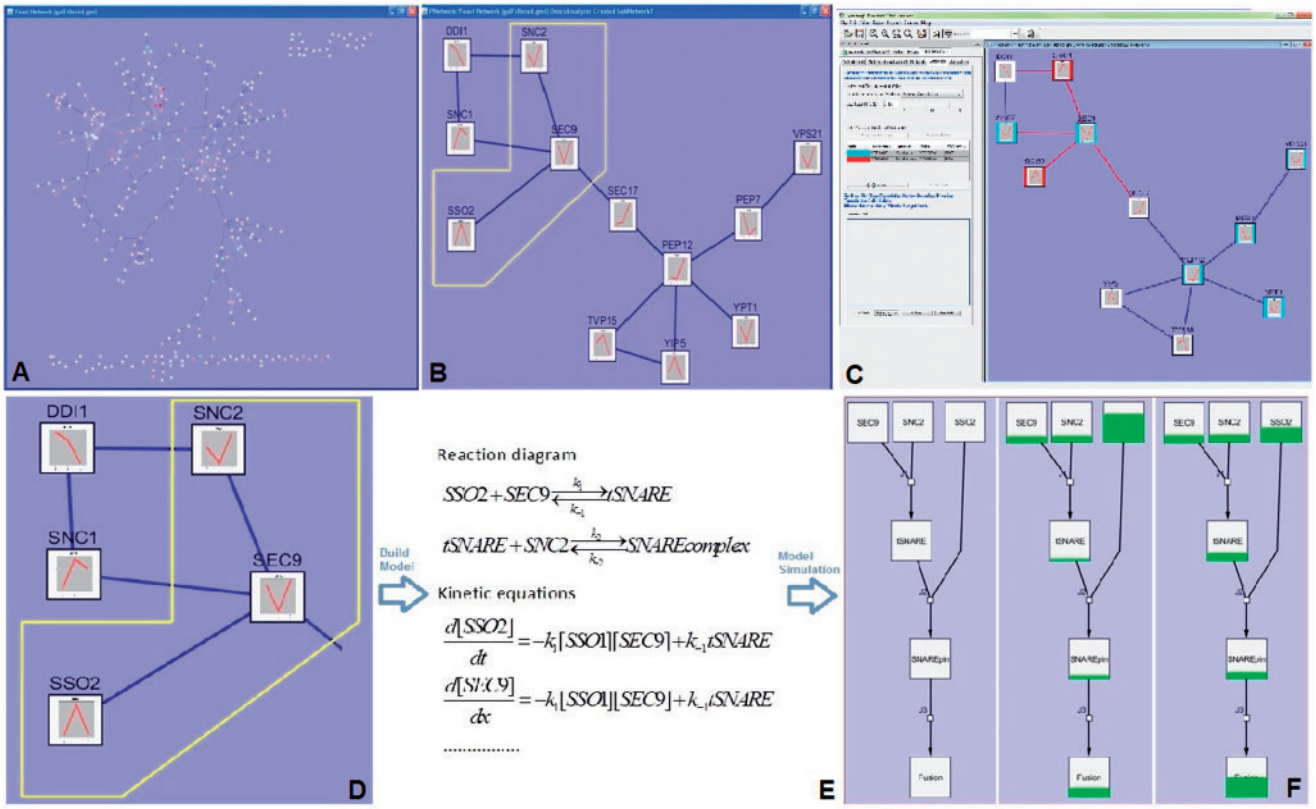

Fig. 1. (**A**) GAL network is constructed and imported in Cytoscape network panel. (**B**) The subnetwork community in the GAL network responsible for vesicular fusion is created by SubgraphCreator in a new network panel. Microarray data are imported and visualized in network context by OmicsAnalyzer. (**C**) A statistical correlation cluster calculation (Pearson's) was performed by OmicsAnalyzer according to the imported omics data. Two clusters were found and highlighted in cyan and red colors. (**D**) Original SEC9-SNC2-SSO2 network motif. (**E**) The motif was transformed into kinetic model by CytoModeler. (**F**) The original system is shown on the left. The middle graph shows the effect of a smaller initial concentration of tSNARE protein. The right side shows the effect of a large initial concentration of tSNARE protein which induces a high rate of fusion.

in the $X-Y$ chart, both the plot and the node representing the species in the network are highlighted. In the dynamic visualization mode, the CytoModeler Visualizer uses animation to dynamically visualize simulation results in network element views including cascading and shaking animations.

3 USAGE EXAMPLE

Figure 1 shows how to perform the integrated analysis (from omics analysis to dynamics modeling) to a specific functional module of the network by using Cytoscape functional plug-in OmicsAnalyzer (Xia *et al*., 2010), SubgraphCreator and CytoModeler. As a proof of concept, we focused on a network motif Sec9-Snc1/2-Sso2 of the vesicular transport community of the Yeast galactose utilization (GAL) network (Ideker *et al.*, 2001) (given in the Cytoscape sample data folder as 'galFiltered.gml') because the motif actually identifies protein interactions between SNARE (soluble N-ethylmaleimide-sensitive factor attachment protein receptor) proteins which are crucial players in vesicle transportation and exocytosis (Jahn and Scheller, 2006). First, by using SubgraphCreator, another Cytoscape plug-in developed by our group, we created a subnetwork for the vesicular transport community from the GAL network in Cytoscape. Secondly, OmicsAnalyzer was used to map omics data (given in the Cytoscape sample data folder as 'galExpData.pvals' file format) to the Sec9-Snc1/2-Sso2 network motif of the community network. Then, OmicsAnalyzer visualizes the imported data in a network context and examines the statistical correlation of the SNARE gene expressions. Finally, we connected omics analysis with dynamical modeling of the Sec9-Snc2-Sso2 motif using CytoModeler. We transformed the motif to a CytoModeler network by clicking 'Create Model from Current Network' button and adding the reaction equations through the reaction palette in the CytoModeler Model Editor. After adding in sample protein and reaction constant with parameters, we built a simulation-ready model for the network. Using the CytoModeler simulation interface with the built-in ODE solver, a fifth-order adaptive Runge-Kutta method, the *in silico* experiments successfully produced the previous observations (Scott *et al*., 2004), which shows how different initial concentrations of these SNARE proteins have large effects on the progression of membrane fusion.

The supplementary data provides the models for the example given in Figure 1.

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Conflict of Interest: none declared.

REFERENCES

Ideker,T. *et al.* (2001) Integrated genomic and proteomic analyses of a systematically perturbed metabolic network. *Science*, **292**, 929–934.

Jahn,R. and Scheller,R.H. (2006) SNAREs–engines for membrane fusion. *Nat. Rev.*, **7**, 631–643.

Ramsey,S. *et al.* (2005) Dizzy: stochastic simulation of large-scale genetic regulatory networks (supplementary material). *J. Bioinform. Comput. Biol.*, **3**, 437–454.

Sauro,H.M. *et al.* (2003) Next generation simulation tools: the Systems Biology Workbench and BioSPICE integration. *Omics*, **7**, 355–372.

Schmidt,H. and Jirstrand,M. (2006) Systems Biology Toolbox for MATLAB: a computational platform for research in systems biology. *Bioinformatics*, **22**, 514–515.

Scott,B.L. *et al.* (2004) Sec1p directly stimulates SNARE-mediated membrane fusion in vitro. *J. Cell Biol.*, **167**, 75–85.

Shannon,P. *et al.* (2003) Cytoscape: a software environment for integrated models of biomolecular interaction networks. *Genome Res.*, **13**, 2498–2504.

Xia,T. *et al*. (2010) OmicsAnalyzer: a Cytoscape plug-in suite for modeling omics data. *Bioinformatics*, **26**, 2995–2996.