

## CySBML: a Cytoscape plugin for SBML

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### ABSTRACT

**Summary:** CySBML is a plugin designed to work with Systems Biology Markup Language (SBML) in Cytoscape having the following features: SBML import, support of the SBML layout and qualitative model packages, navigation in network layouts based on SBML structure, access to MIRIAM and SBO-based annotations and SBML validation. CySBML includes an importer for BioModels to load SBML from standard repositories.

**Availability and implementation:** Freely available for non-commercial purposes through the Cytoscape plugin manager or for download at <http://sourceforge.net/projects/cysbml/>.

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**Supplementary Information:** Tutorial, usage guide, installation instructions and additional figures are available for download at <http://www.charite.de/sysbio/people/koenig/software/cysbml/>.

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### 1 INTRODUCTION

The Systems Biology Markup Language (SBML) is a free and open interchange format for computer models of biological processes (Hucka *et al.*, 2003), which is currently supported by >230 software tools (June 2012). SBML is used to represent models for a wide range of cell biology, including cell signaling, metabolism and gene regulation. SBML provides a common standard of interoperability and exchange allowing several researchers to work with diverse tools on building, curation, annotation, simulation, analysis and visualization of the same model. Standard repositories of SBML models such as BioModels (Li *et al.*, 2010) have been established, providing annotated models on a molecular level for a wide range of biological questions with access to their resources through web services (Li *et al.*, 2010). However, preserving models without the semantic layer of information needed for an unambiguous identification and interpretation of model components is meaningless (Courtot *et al.*, 2011). To this end, SBML can be annotated based on Minimum Information Required for the Annotation of Models (MIRIAM; Laibe and Le Novère, 2007) and Systems Biology Ontology (SBO; Le Novère, 2006a, b), a set of controlled vocabularies in systems biology.

Cytoscape (Shannon *et al.*, 2003), a widely used open-source platform for complex network analysis and visualization, currently provides only rudimentary SBML capabilities; its application to SBML models is limited to a subset of SBML. The SBML document structure is inaccessible for visualization, validation of

SBML files is not possible and neither the information from SBO or MIRIAM annotation nor SBML packages for layout information or qualitative models are supported.

### 2 DESCRIPTION

We present CySBML, a Cytoscape SBML plugin based on JSBML (Dräger *et al.*, 2011), a free, open-source Java™ library for SBML. CySBML supports all versions and levels of SBML, handles models in SBML and the SBML Qualitative Model format, includes validation of imported SBML files and provides a navigation menu based on SBML structure and easy access to BioModels through web services. All functions of CySBML are available with one or two clicks through the Cytoscape menu bar. CySBML was successfully tested with all networks from the SBML Test Suite (version 2.0.2) and BioModels (release 21).

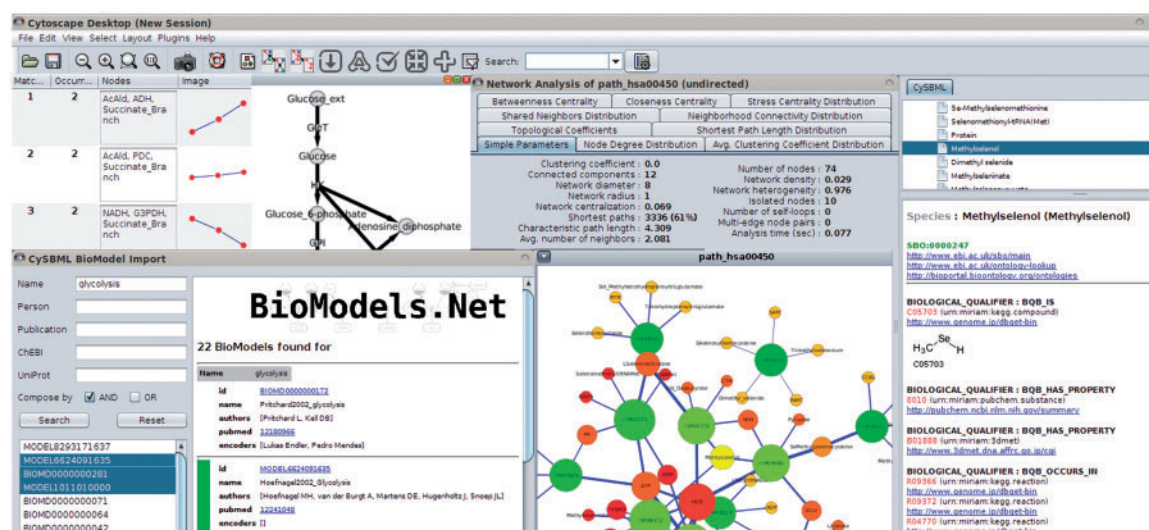
CySBML utilizes layout information encoded through the SBML layout extension (Gauges *et al.*, 2006) or alternatively applies standard layouts based on visual styles optimized for the bipartite species/reaction model underlying SBML. Species and reactions are assigned to different visualization classes with nodes being color coded according to their SBML compartment.

Special focus was put on making annotation information and the semantic layer accessible to the user and linking these data to additional web resources (see the methylselenol example in Fig. 1). CySBML reads RDF-based MIRIAM annotations of the SBML elements and provides access to the annotated resources within the network visualization. Clicking at links to online annotation resources and databases opens additional information in a browser window. In this way, information from a wide range of resources and databases can be integrated within the visualization. SBML files from BioModels can be imported either by their identifiers or searched through name, author, publication, ChEBI or UniProt (Fig. 1). Multiple models can be imported at once for comparative analysis.

Validation of the imported SBML is available through the menu bar. Validation results can be filtered with respect to the severity of the errors. SBML annotation, BioModel import and SBML validation are based on web services and therefore require an Internet connection.

CySBML integrates seamlessly with other plugins by making SBML information as Cytoscape node and edge attributes under names defined in `CySBMLConstants` accessible. A wide range of tools works out of the box with CySBML providing additional functionality for SBML models, such as analysis of topological parameters with NetworkAnalyzer (Assenov *et al.*, 2008), search of network motifs with NetMatch (Ferro *et al.*, 2007) or

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**Fig. 1.** CySBML interface and features. SBML models can be imported through the BioModels import dialog based on search criteria or BioModel identifiers. Multiple models can be loaded for comparative analysis and are accessible through the Cytoscape Control Panel. Visualizations for the imported models are generated in the central Cytoscape area based on information from the SBML layout extension or generic layout algorithms (middle, KEGG pathway MAP00450, seleno compound metabolism). SBML annotations for network nodes are accessible through the CySBML annotation window (right). After selection of nodes in the network or the SBML structure (top right), the respective MIRIAM and SBO resources are displayed. In the example, among others, methylselenol information from KEGG, PUBCHEM, 3DMET and SBO with the corresponding direct links to the web pages of the original resources. CySBML works out of the box with a multitude of other plugins including analysis of topological parameters with NetworkAnalyzer (results shown for MAP00450 with visual mapping of node degree to node size, closeness centrality to node color and edge betweenness to edge size), search for network motifs with NetMatch (top left, Human erythrocyte model glycolysis, linear chain of three nodes) or visualization of flux distributions (top center, Human erythrocyte model glycolysis, flux balance analysis (FBA) solution for glucose utilization for ATP synthesis)

visualization of fluxes with FluxViz (König and Holzthütter, 2010) (Fig. 1).

### 3 CONCLUSION

CySBML combines SBML, the standard format of models of biological processes, with Cytoscape, one of the standard platforms for the visualization of biological networks. Cytoscape has already been used in numerous applications for visualization and graphical network analyses, whereas the BioModels database collects and annotates structural and mathematical models in SBML format that provide insights into the dynamic behavior of biological networks. CySBML makes it possible to combine these two important system biological resources in a convenient and easy-to-use way with special focus on the semantic layer defining the models. This work opens the door for the development of further plugins facilitating the analysis of SBML models in Cytoscape.

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**Conflict of Interest:** none declared.

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