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| *Systems biology*  **cy3sbml: a Cytoscape app for SBML**  Matthias König1,\*, Nicolas Rodriguez2 and Andreas Dräger3  1Institute for Theoretical Biology, Humboldt University Berlin, Berlin, Germany  2  3Center for Bioinformatics Tuebingen (ZBIT), University of Tuebingen, Tübingen, Germany  Received on XXXXX; revised on XXXXX; accepted on XXXXX  Associate Editor: XXXXXXX |

**ABSTRACT**

**Summary:** cy3sbml is an app for the work with SBML in Cytoscape 3 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. cy3sbml includes an importer for BioModels to load SBML from standard repositories.

**Availability and implementation:** Freely available for non-commercial purposes via the Cytoscape app store <http://apps.cytoscape.org/apps/cy3sbml> or for download at <https://github.com/matthiaskoenig/cy3sbml/>.

**Contact:** [konigmatt@googlemail.com](mailto:konigmatt@googlemail.com)

**Supplementary information:** Source code, tutorial, usage guide, installation instructions and additional figures are available at <https://github.com/matthiaskoenig/cy3sbml/>.

# **INTRODUCTION**

The SBML (Systems Biology Markup Language) is a free and open interchange format for computer models of biological processes {Hucka2003} currently supported by over 280 software tools [July 2016]. 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 {Li2010} have been established, providing annotated models on a molecular level for a wide range of biological questions with access to their resources via web services {Li2010}. However, preserving models without the semantic layer of information needed for an unambiguous identification and interpretation of model components is meaningless {Courtot2011}. To this end, SBML can be annotated based on MIRIAM (Minimum Information Required for the Annotation of Models) {Laibe2007} and SBO (Systems Biology Ontology) {Novere2006}, a set of controlled vocabularies in systems biology.

Cytoscape {Shannon2003}, a widely used open-source platform for complex network analysis and visualization, currently only provides 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.

With the release of Cytoscape 3

* major update in infrastructure (OSGI, service model, maven)
* no backwards compatibility, new app architecture

Requirement of porting CySBML {Koenig2012} to Cytoscape 3: cy3sbml

# **DESCRIPTION**

We present cy3sbml, a Cytoscape 3 app for SBML based on JSBML {Draeger2011, Rodriguez2015}, a free, open-source Java™ library for SBML. cy3sbml ports all major features from Cytoscape 2 to Cytoscape 3, i.e. supports all versions and levels of SBML, handles models in SBML and the SBML Qualitative Model format, includes validation of imported SBML files, provides a navigation menu based on SBML structure and easy access to BioModels via web services.

cy3sbml utilizes layout information encoded via the SBML Layout extension {Gauges2006}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.

* now full kinetic graph with access to parameters, kinetic laws, function definitions, compartments, ...
* additional visual styles

Special focus was put on making annotation information and the semantic layer accessible to the user and linking these data to additional web resources (Figure 1).

cy3sbml reads RDF-based MIRIAM annotations of the SBML elements and provides access to the annotated resources within the network visualization (Figure 1). Clicking at links to online annotation resources and databases opens additional information in the browser. In this way, information from a wide range of resources and databases can be integrated within the visualization. Key information for the RDF annotations are retrieved via web services from ? {REF}, like terms and term definitions.

* redesign of GUI, additional REST information

cy3sbml was successfully tested with all networks from the SBML Test Suite [version 3.1.1], BioModels [release 30], and BiGG models [release v1.2] {King2016}.

Many additional features have been implemented: comp, groups and fbc v2 support, full kinetic networks providing access not only to species and reactions but to parameters and kinetics. A full set of examples is now included with cy3sbml directly accessible from the menu. Redesign and implementation of the information display based on JavaFX.

* Cofactor nodes

SBML files from BioModels can be imported either by their identifier or searched via name or authors. Multiple models can be imported at once for comparative analysis.

Validation of the imported and loaded SBML is available via the menu bar. Validation results can be filtered with respect to warnings and error types. SBML annotation, BioModel import and SBML validation are based on web services and therefore require an internet connection.

cy3sbml is now implemented as an OSGI bundle providing an API for other apps to consume (or via python/R and CyREST). This provides easy integration with additional functionality, like using it for the visualization of kinetic information from SABIO-RK {Wittig2012, Koenig2016}.

**Fig. 1.** CySBML interface. Example SBML for hepatic glucose metabolism of the Human liver from {Koenig2012}. SBML file is provided as supplementary file.

# CONCLUSION

cy3sbml combines SBML, the standard format of models of biological processes, with Cytoscape, one of the standard platforms for the visualization of biological networks. With this release all functionality from the original plugin {Koenig2012}, like support for SBML groups, fbc and comp model.

The provided API/OSGI allows ...

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*Conflict of Interest*: none declared

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