Software Tool Article

cy3sabiork: A Cytoscape app for visualizing kinetic data from SABIO-RK

*Matthias König¹\**

1Humboldt-University Berlin, Institute for Theoretical Biology, Invalidenstraße 43, 10115 Berlin, Germany

\*Corresponding author: konigmatt@googlemail.com

# Abstract

Kinetic data of biochemical reactions are essential for the creation of kinetic models of biochemical networks. SABIO-RK is a curated database for kinetic data of biochemical reactions and their related information. The data ca

Web interface and web service

SBML

A seamless integration with the SABIO-RK web services is provided which allows direct queries from within Cytoscape.

Alternatively advanced queries can be performed on the SABIO-RK web page and the results be exported as SBML which then is imported using cy3sabiork.

Cy3sabiork is a Cytoscape 3 app for the visualization of kinetic data from

Cy3sabiork reads kinetic information in the Systems Biology Markup Language (SBML) format.

This visualization method allows for easy comparison of kinetic data, visual inspection of the elements involved in the kinetic record and simple access to the annotation information of the kinetic record.

# Keywords

Data display, Graphical user interfaces, Web service, SABIO-RK, kinetic parameters, SBML

# Introduction

## Importance of kinetic information for computational modelling.

“The systematic study of complex interactions in biological systems requires detailed qualitative and quantitative information about single biochemical reactions in order to understand better the entirety of processes that happen in a biological system. For the quantitative analysis of biochemical reactions by modelling their enzyme kinetics, reliable kinetic data for the individual reaction steps are essential.”{Wittig2012}

One of the main challenges in kinetic modeling of biochemical systems is the availability of reliable parameters from the literature.

“modellers who are trying to integrate published data into simulatable computer models. Both search for kinetic parameters and additional information in databases for enzymatic reaction kinetics” {Wittig2014}

“For dynamic modelling and simulation of biochemical reactions and complex networks, computational methods are used that either describe the reaction dynamics as an approximate estimation applying convenience kinetics [1] or require detailed information on the reactions and their kinetics. This required information includes kinetic parameters with their rate equations that describe the dynamic behaviour of the reactions over time, as well as detailed descriptions of how these were determined”{Wittig2014}

“Kinetic data of biochemical reactions are essential to create models of biochemical reaction networks and to obtain a better understanding of the processes in living cells.” {Wittig2014}

## Databases

“In recent years, biological databases for different data types have been developed. The advantages of these databases lie in their unified structure, searchability and the potential for augmented analysis by software, which supports the modelling process.” {Wittig2014}

Included amongst them are databases that contain enzyme and reaction kinetics data to support the modelling and simulation processes: enzyme databases such as BRENDA {Scheer2011} or protein databases such as UniProtKB {UniProtConsortium2011}, which both also store kinetic parameters.”{Wittig2014}

“Especially for computational modelling and computer assisted exchange of knowledge, a definition of standard data exchange formats and a common language are essential [20]. Therefore, the use of existing ontologies and controlled vocabularies for all reaction participants (e.g. small chemical compounds and proteins), as well as for kinetic rate laws, parameters, units, etc., is becoming more and more essential.” {Wittig2014}

## SABIO-RK

SABIO-RK, a curated database for biochemical reaction kinetics

SABIO-RK (http://sabio.h-its.org/) is a manually curated database storing comprehensive information about biochemical reactions and their kinetic properties. SABIO-RK offers standardized data manually extracted from the literature and

data directly submitted from lab experiments {Wittig2012, Wittig2014}.

“The SABIO-RK database has been developed to meet these requirements and to support scientists in modelling and understanding of complex biochemical networks by structuring kinetic data and related information from the literature.” {Wittig2014}

“SABIO-RK (1,2) was developed as a database to store and structure kinetic data of biochemical reactions and their related information to support modellers and wet-lab scientists in understanding complex biochemical Networks.” {Wittig2012}

“SABIO-RK comprises a reaction-oriented representation of quantitative information on reaction dynamics based on a given selected publication. This comprises all available kinetic parameters together with their corresponding rate equations, as well as kinetic law and parameter types and experimental and environmental conditions under which the kinetic data were determined. Additionally, SABIO-RK contains information about the underlying biochemical reactions and pathways including their reaction participants, cellular location and detailed information about the enzyme proteins catalysing the reactions including the biological source.” {Wittig2012} see **Figure 1** (example entry)

“SABIO-RK stores all of the kinetic information for one specific reaction under specific experimental conditions from a defined biological source in one dataset called the database entry. This information can be viewed and exported as a single dataset.” {Wittig2014}

## Data access & SBML

The Systems Biology Markup Language (SBML) is a free and open interchange format for computer models of biological processes {Hucka2003}. SABIO-RK provides access to the kinetic information in SBML format either (I) by export of SBML from the SABIO-RK web interface (<http://sabiork.h-its.org/>) after searching and selecting kinetic records, or (II) by SBML return of kinetic records via RESTful web services (<http://sabiork.h-its.org/layouts/content/webservices.gsp>). Both interfaces support the export of the data together with its annotations in SBML {Wittig2012}.

“SABIORK data can be simply accessed through web-based user interfaces and web services. Various search criteria are selectable to search for biochemical reactions and their kinetics. Beside a free text search, complex and detailed queries can be executed in the advanced search. This may include the combination of several search criteria [e.g. reaction participants (substrates, products, inhibitors, activators etc.), pathways, enzymes, organisms, tissues or cellular locations, kinetic parameters, environmental conditions or literature Sources].” {Wittig2014}

## Semantic annotations & Knowledge Integration

The annotation information and semantic layer accessible to the user and linking these data to additional web resources. SBML can be annotated based on Minimum Information Required for the Annotation of Models (MIRIAM; {Laibe2007}), a set of controlled vocabularies in systems biology.

The annotation information in form of RDF-based MIRIAM annotations and XML based SABIO-RK annotations of the kinetic records are made accessible. Hyperlinks to annotated online resources are provided, i.e. via SABIO-RK internal identifiers and.identifiers from external databases ChEBI {deMatos2010}, UniProtKB {UniProtConsortium2011}, Pubmed, or KEGG {Kanehisa2010}. In this way, information from a wide range of resources and databases is integrated with the graph visualization of the kinetic records. This allows for instance direct access to the publication from which the kinetic information was retrieved or the Protein for which the kinetic information was measured.

## *What is problem and what is solution!*

Despite the importance of kinetic information for modelling there is no easy way to visualize the kinetic information from kinetic records in SABIO-RK. There is currently no visualization tool enabling the visualization of kinetic records from SABIO-RK. Therefore, we developed the Cytoscape app cy3sabiork, that takes advantage of the web service and SBML export from SABIO-RK for importing and displaying graphs of the kinetic records in Cytoscape.

Cy3sabiork provides access to the following information of SABIO-RK database entries via the graph structure and annotations of nodes: (I) reaction details, enzyme and organism; (II) Kinetic law, formula, parameters; (III) Experimental conditions; (IV) Source

We applied cy3sabiork for the search of kinetic parameters for the galactose metabolism in Human liver.

# **Methods**

## Implementation

Cy3sabiork was written in Java as an OSGi bundle. The CyActivator adds a cy3sabiork tab with specific functionality to the Cytoscape “Results Panel”. SABIO-RK data is retrieved via the SABIO-RK web interface or programmatically using HTTP requests to the REST web services. SBML is used as exchange format which is imported using a Cytoscape Task created by the LoadNetworkFileTaskFactory. CyNetworks and CyNetworkViews for the imported kinetic data are created by a CyNetworkReader registered for SBML files provided by cy3sbml {Koenig2012}. The SBML CyNetworkReader was extended for cy3sabiork to support the SABIO-RK specific annotations and data.

## Operation

Visualizing kinetic records data with cy3sabiork consists of two steps:

(I) Searching kinetic records for visualization via either the web services in the cy3sabiork panel (**Figure 1**) or via the SABIO-RK web interface

“The web-based user interfaces enable the user to search for reactions and their kinetics by specifying characteristics of the reactions. It offers the creation of complex queries by specifying reactions by their participants (substrates, products, inhibitors, activators etc.) or identifiers (KEGG or SABIO-RK reaction identifiers and KEGG, SABIO-RK, ChEBI or PubChem(7) compound identifiers), pathways, enzymes, UniProt identifiers, organisms, tissues or cellular locations, kinetic parameters, environmental conditions or literature sources (Figure 1).” {Wittig2012}

“Search criteria now include the search for organism taxonomy based on NCBI {Sayers2012}, compound classification based on ChEBI ontology {deMatos2010} and tissue ontology based on BRENDA tissue ontology (BTO) {Gremse2011}” {Wittig 2012}

(II) Loading the kinetic records in SBML format in Cytoscape. In case of searching

All annotation information is available via the cy3sbml panel, providing direct links to additional resources for the kinetic law.

# Use Cases

cy3sabiork was used in model construction of a kinetic model of galactose metabolism of the human liver (<https://github.com/matthiaskoenig/multiscale-galactose>). The typical workflow with example queries for kinetic data for the galactokinase (EC:2.7.1.6, UniProtKB:P51570), the first step of galactose metabolization in the liver are shown in **Figure 1**. The corresponding SBML of the query is provided in **Supplementary File S1**. In the example the SABIO-RK kinetic record 14792 is retrieved.

The more complex query retrieving all wildtype kinetic records for the galactose metabolism in homo sapiens is shown in **Figure 2**, with the resulting graph depicted in **Figure 3**.

As part of the model building publications with kinetic information not yet included in SABIO-RK were included in the database via the SABIO-RK curation service.

# Conclusion

cy3sabiork provides the means for visual analysis and inspection of kinetic data from SABIO-RK. Hereby, the integration of kinetic data with computational models of biochemical reactions is supported. The availability of direct links to the SABIO-RK database and ontology annotations of the kinetic records provide additional knowledge integration.

# Data and software availability

cy3sabiork is freely available from the Cytoscape app store <http://apps.cytoscape.org/apps/cy3sabiork>. The code is open source under GNU General Public License, version 3 (GPL-3.0) license available at <https://github.com/matthiaskoenig/cy3sabiork>.

# Author contributions

MK developed the app and wrote the manuscript. We thank the SABIO-RK team, the SBML community, and Cytoscape community for their support and help. A special thanks to the curation team of SABIO-RK including additional kinetic data in the database based on provided publications.

# Competing interests

No competing interests.

# **Grant information**

This work was supported by the Federal Ministry of Education and Research (BMBF, Germany) within the research network Systems Medicine of the Liver (LiSyM) [grant number 031L0054] and the Virtual Liver Network VLN [grant number 0315741].

# **Supplementary material**

Supplementary File S1: SBML file for galactose query

Supplementary File S2: Cytoscape session file for the galactose query

# **References**

De Matos, P., Alcántara, R., Dekker, A., Ennis, M., Hastings, J., Haug, K., et al. (2009). Chemical entities of biological interest: an update. *Nucleic acids research*, gkp886.

Gremse, Marion et al. "The BRENDA Tissue Ontology (BTO): the first all-integrating ontology of all organisms for enzyme sources." *Nucleic acids research* 39.suppl 1 (2011): D507-D513.

Hucka, M., Finney, A., Sauro, H. M., Bolouri, H., Doyle, J. C., Kitano, H., et al. (2003). The systems biology markup language (SBML): a medium for representation and exchange of biochemical network models. *Bioinformatics*, *19*(4), 524-531.

Kanehisa, M., Goto, S., Furumichi, M., Tanabe, M., & Hirakawa, M. (2010). KEGG for representation and analysis of molecular networks involving diseases and drugs. *Nucleic acids research*, *38*(suppl 1), D355-D360.

König, M., Dräger, A., & Holzhütter, H. (2012). CySBML: a Cytoscape plugin for SBML. *Bioinformatics*, *28*(18), 2402-2403.

Laibe, C., & Le Novère, N. (2007). MIRIAM Resources: tools to generate and resolve robust cross-references in Systems Biology. *BMC Systems Biology*, *1*(1), 58.

Sayers, Eric W et al. "Database resources of the national center for biotechnology information." *Nucleic acids research* 37.Database issue (2009): D5.

Scheer, M., Grote, A., Chang, A., Schomburg, I., Munaretto, C., Rother, M., et al. (2010). BRENDA, the enzyme information system in 2011. *Nucleic acids research*, gkq1089.

UniProt Consortium (2011). Ongoing and future developments at the Universal Protein Resource. *Nucleic acids research*, *39*(suppl 1), D214-D219.

Wittig, U., Kania, R., Golebiewski, M., Rey, M., Shi, L., Jong, L., et al. (2012). SABIO-RK—database for biochemical reaction kinetics. *Nucleic acids research*, *40*(D1), D790-D796.

Wittig, U., Rey, M., Kania, R., Bittkowski, M., Shi, L., Golebiewski, M., et al. (2014). Challenges for an enzymatic reaction kinetics database. *FEBS Journal*, *281*(2), 572-582.

# 

# 

# Figures

|  |  |
| --- | --- |
| TODO | **Figure 0**. Workflow diagram (overview over exchange)  Combine with Figure 2, to show the content of the information. |

|  |  |
| --- | --- |
| webservice_GUI.png | **Figure 1**. cy3sabiork GUI for web service queries. In the example the kinetic record 18974 is retrieved (<http://sabiork.h-its.org/sabioRestWebServices/kineticLaws/18974>). The web service returns the SABIO-RK information in SBML. |

|  |  |
| --- | --- |
| EntryID_14792.png | **Figure 2**. Overview of SABIO-RK Entry 14792 available at  <http://sabiork.h-its.org/kineticLawEntry.jsp?viewData=true&kinlawid=14792> |

|  |
| --- |
| Cytoscape_14792.png |
| **Figure 3**. Resulting SBML species-reaction graph (left) and kinetic graph (right) for query /kineticLaws/14792.A single kinetic record is retrieved via the web services and imported using cy3sbml. |

|  |
| --- |
| SABIOmdl08Jun2016039_galactose_metabolism.png |
| **Figure 4**. Graph of SABIO-RK kinetic records for the Human liver galactokinase, consisting of 47 entries (query 2016-06-08, Organism=”homo sapiens” & Pathway=”galactose metabolism” & wildtype=True, SBML for query available as **Supplement S2**). Three clusters can be seen, depending on the localization of the reported protein. The lysosomal reactions are non-canonical reactions in the galactose pathway. |

# 