

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

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Abstract

Cy3sabiork is a Cytoscape 3 app for the visualization of kinetic records from SABIO-RK, a curated database storing comprehensive information about biochemical reactions and their kinetic properties.

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

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.

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 scientific literature contains a tremendous amount of kinetic data describing the dynamic behaviour of biochemical reactions over time. These data are needed for computational modelling to create models of biochemical reaction networks and to obtain a better understanding of the processes in living cells.” {Wittig2014}

“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. We have developed the SABIO-RK database for biochemical reaction kinetics.” {Wittig2014}

“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}

“In recent years, the number of available biological databases has grown, offering the advantage of providing unified structures. 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}

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

“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 (<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}

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>).

“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}

“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}

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. It adds a “cy3sabiork” tab with specific functionality to the Cytoscape “Results Panel”. Kinetic records are retrieved in SBML format either via the SABIO-RK web page export or the cy3sabiork web service queries. The data import functionality is implemented as a Cytoscape Task using the registered cy3sbml {Koenig2012} SBMLReaderTask via the Cytoscape LoadNetworkFileTaskFactory. The cy3sbml SBML reader was extended to support the SABIO-RK specific SBML annotations.

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

(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 the modeling of galactose metabolism of the human liver. In the following the workflow for retrieval of single kinetic records (**Figure**

Conclusion

cy3sabiork allows easy visual analysis of kinetic records from SABIO-RK kinetic records. Especially 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.

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

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Figures

TODO

Figure 0. Workflow diagram (overview over exchange)

Combine with Figure 2, to show the content of the information.

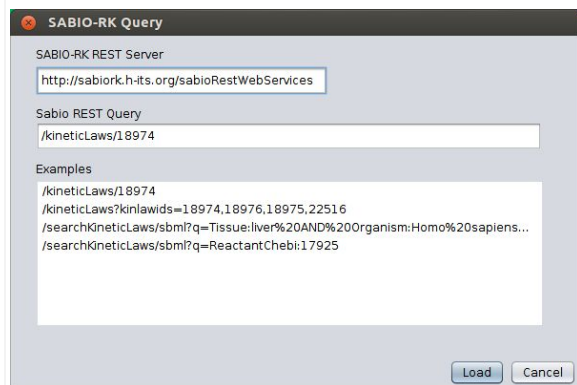
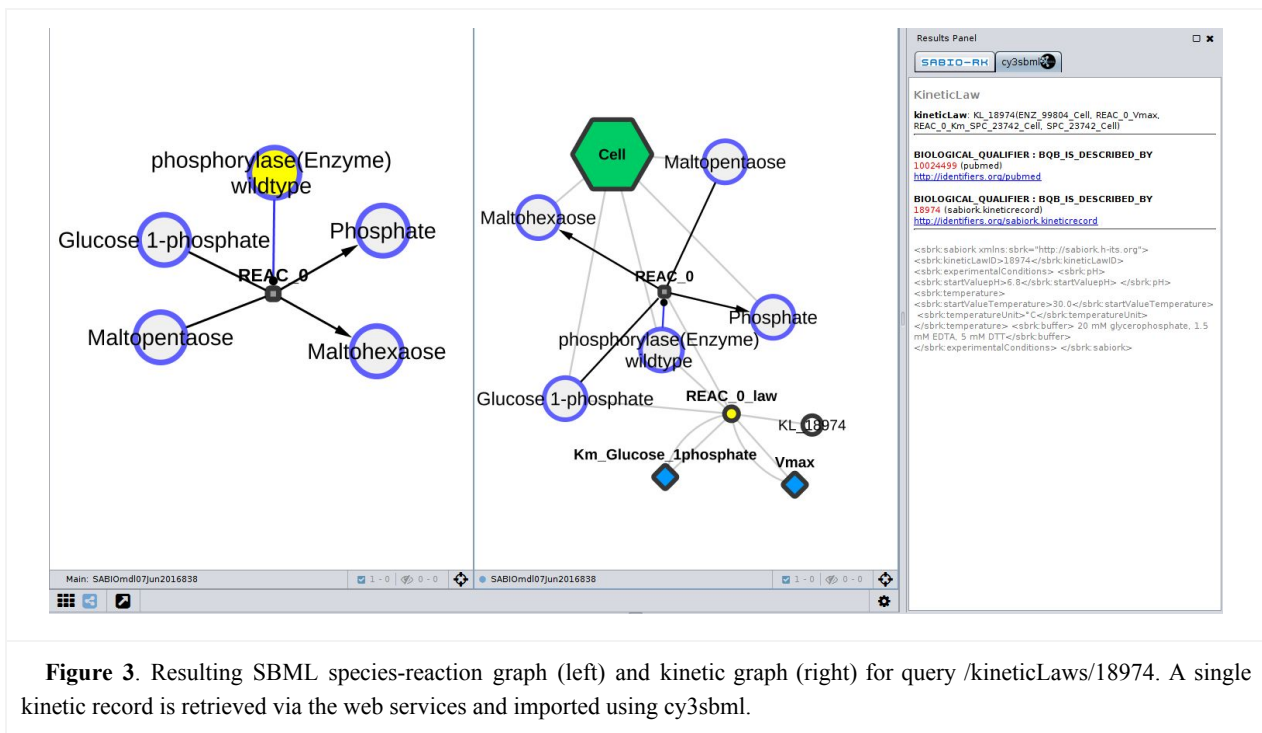


Figure 1. cy3sabiork GUI for web service queries. In the example the kinetic record 18974 is retrieved (<http://sabiork.h-its.org/sabioRestWebServices/kineticLaws/18974>). The web service returns the SABIO-RK information in SBML.

Kinetic data for SABIO kinetic law id 18974

General information							
Organism	Oryctolagus cuniculus						
Tissue	muscle ↗						
EC Class	2.4.1.1						
SABIO reaction id	10080						
Variant	wildtype						
Experiment Type	in vitro						
Event Description	-						
Substrates							
name	location	comment					
Maltopentapose	-	-					
Glucose 1-phosphate	-	-					
Products							
name	location	comment					
Phosphate	-	-					
Maltohexaose	-	-					
Modifiers							
name	location	effect	comment	protein complex			
phosphorylase(Enzyme)	-	Modifier-Catalyst	-	((P00489)*2)*2;			
Enzyme (protein data)							
	UniProtKB_AC	name	mol. weight (kDa)	deviation (kDa)			
subunit	P00489	-	-	-			
complex	-	-	-	-			
Kinetic Law							
type	formula	annotation					
-	-	-					
Parameter							
name	type	species	start val.	end val.	deviat.	unit	comment
A	concentration ↗	Glucose 1-phosphate	1.6	40.0	-	mM	
E	concentration ↗	Enzyme	10.0	-	-	µg/ml	
Km	Km ↗	Glucose 1-phosphate	8.0	-	-	mM	
Vmax	Vmax ↗		35.0	-	-	µM/(min*mg)	
Experimental conditions							
	start value	end value				unit	
pH		6.8				-	
temperature		30.0				-	°C
buffer	20 mM glycerophosphate, 1.5 mM EDTA, 5 mM DTT						
comment	-						
Reference							
title	author	year	journal	volume	pages	PubMed	
Synthesis and kinetic evaluation of 4-deoxymaltopentaose and 4-deoxymaltohexaose as inhibitors of muscle and potato alpha-glucan phosphorylases	Mosli R, Withers SG	1999	Biochem J	338	251-6	10024499	

Figure 2. Overview over SABIO-RK kinetic law entry <http://sabiork.h-its.org/kineticLawEntry.jsp?viewData=true&kinlawid=18974>



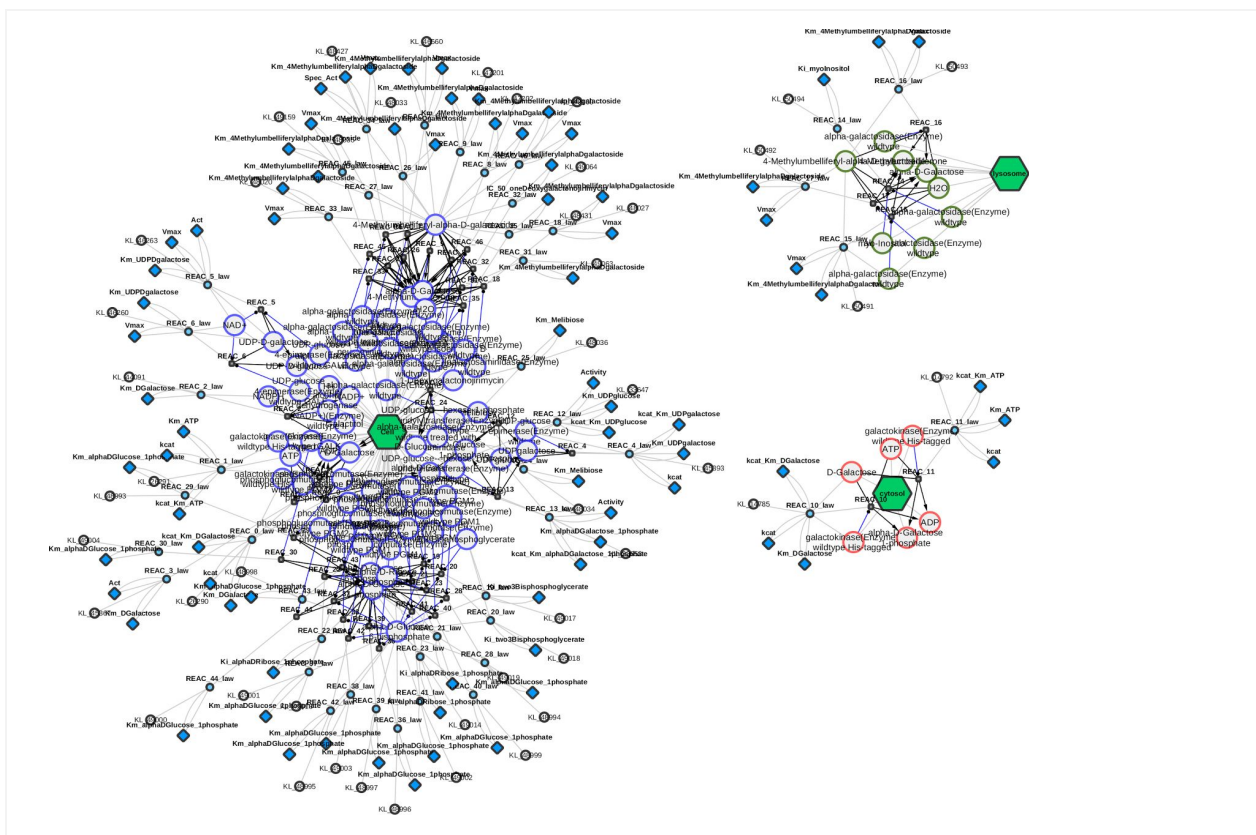


Figure 4. Graph of SABIO-RK kinetic records for the Human liver galactokinase, consisting of 47 entries (query 2016-06-08, Organism="homo sapiens" & Pathway="galactose metabolism" & wildtype=True, SBML and session file in supplement). Three clusters can be seen, depending on the localization of the reported protein. The lysosomal reactions are non-canonical reactions in the galactose pathway.