

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

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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.

We applied cy3sabiork within the computational modelling of galactose metabolism in the Human liver.

Keywords

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

Introduction

One of the main challenges for the modeling of biochemical systems is the availability of reliable information on the individual reaction steps and their kinetics from the literature. This information includes kinetic parameters with their rate equations as well as detailed descriptions of how these were determined {Wittig2014}.

SABIO-RK is a manually curated database storing comprehensive information about biochemical reactions and their kinetic properties, with data manually extracted from the literature and directly submitted from lab experiments {Wittig2012, Wittig2014}. Available information comprises kinetic parameters with their corresponding rate equations, kinetic law and parameter types and experimental conditions under which the kinetic data were determined. In addition, information about the biochemical reactions and pathways including their reaction participants, cellular location and the catalyzing enzyme are recorded {Wittig2012}.

The information in SABIO-RK is structured in datasets, so called database entries, which can be accessed either through the web-based user interface (<http://sabio.h-its.org/>) or via web services (<http://sabiork.h-its.org/sabioRestWebServices>). Both interfaces support the export of the data in the Systems Biology Markup Language (SBML), a free and open interchange format for computer models of biological processes {Hucka2003}.

Database entries are annotated with controlled ontologies and vocabularies based on Minimum Information Required for the Annotation of Models (MIRIAM; {Laibe2007}), e.g. reaction participants (e.g. small chemical compounds and proteins), as well as kinetic rate laws, and parameters. The annotation information is encoded as RDF-based MIRIAM annotations, and additional XML based SABIO-RK specific annotations, e.g. for experimental conditions. Hereby, the kinetic information is integrated with external resources like ChEBI {deMatos2010}, UniProtKB {UniProtConsortium2011}, Pubmed, or KEGG {Kanehisa2010}.

Despite the importance of kinetic information for computational modelling there has been no simple solution to visualize the database entries from SABIO-RK, and provide access to the rich information encoded in the annotations. An intuitive visualization is hereby the species-reaction graph extended with kinetic information, reflecting the reaction-centered approach of SABIO-RK.

In this work, we developed the Cytoscape app cy3sabiork for the visualization of graphs of kinetic entries from SABIO-RK, based on data either from the web interface or the web services. Cy3sabiork provides access to the kinetic information via a combination of graph structure and annotations of nodes, i.e. to: (I) reaction details, enzyme and organism; (II) Kinetic law, formula, parameters; (III) Experimental conditions; (IV) Publication (V) annotations. Cy3sabiork 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.

Methods

Implementation

Cy3sabiork was written in Java as an OSGi bundle for Cytoscape 3. The bundle activator adds the cy3sabiork tab to the Cytoscape “Results Panel”, providing the interface to the SABIO-RK web service. SABIO-RK entries are retrieved via the web interface or programmatically using HTTP requests to the REST web services. The created SBML 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.

RDF based annotations are read with JSBML {Draeger2011} and hyperlinks to the respective resources are created by parsing the resources.

Operation

(I) Searching kinetic entries

Kinetic entries can either be searched via the web services in the cy3sabiork panel (**Figure 1**) or via the web interface (<http://sabio.h-its.org/>).

“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}

“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}

“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}” {Wittig2012} After finalizing the search the selected kinetic entries are exported as SBML.

The web interface supports the same query options, which can be added in the REST query GUI, but allows a direct import of the SBML without the requirement for search in the web interface and export and subsequent import of the SBML. Example queries are provided in Figure 1 and Figure 3.

(II) Loading kinetic entries

In case of web interface searches the SBML is imported as file in cy3sbml, in case of the web service queries the SBML is loaded automatically without the need for additional file operations.

(III) Display information

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

Hyperlinks to annotated online resources are provided, i.e. via SABIO-RK internal identifiers and identifiers from external databases. The annotation information and semantic layer accessible to the user and linking these data to additional web resources.

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 metabolism 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

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Supplementary material

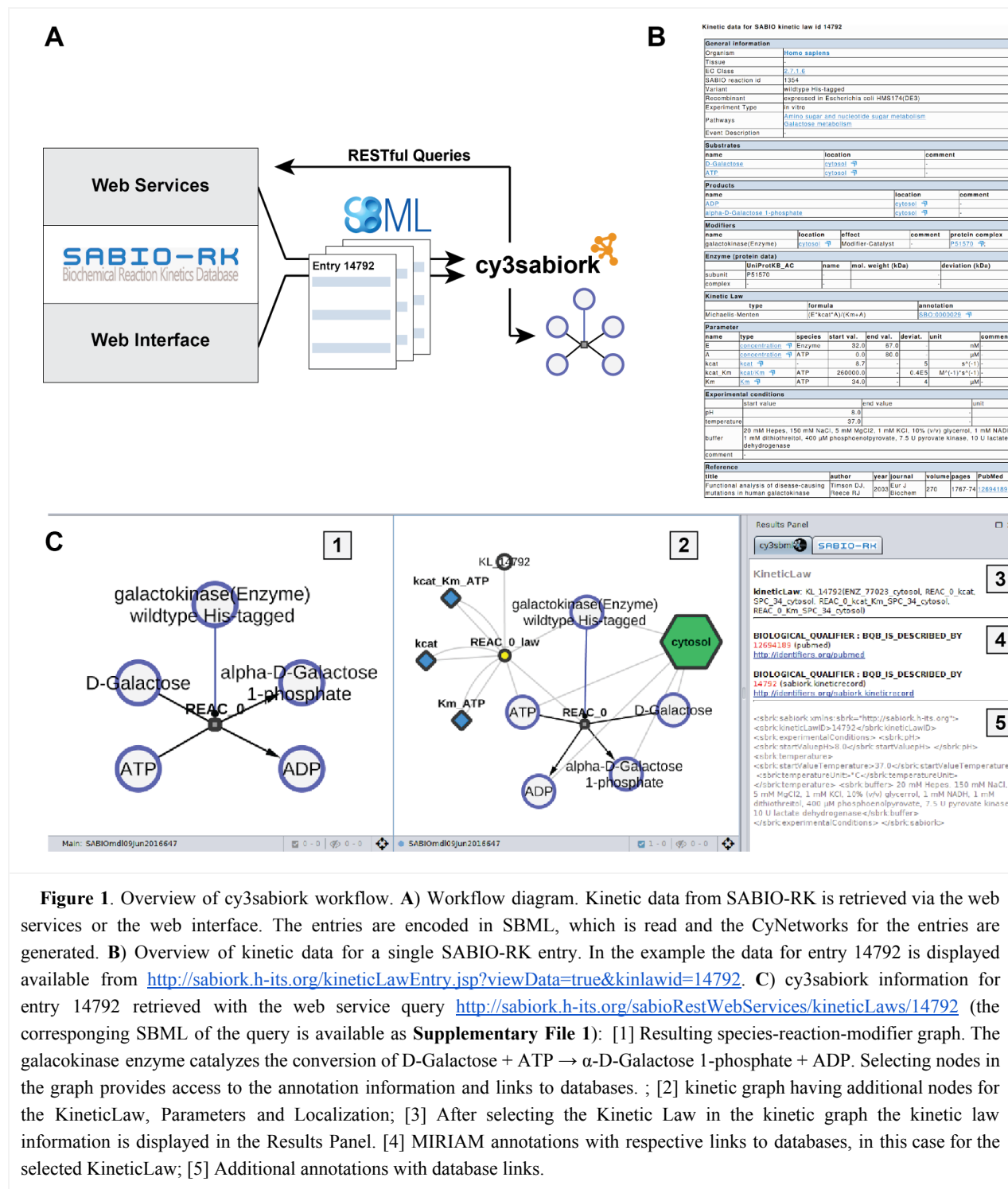
Supplementary File S1: SBML for query <http://sabiork.h-its.org/sabioRestWebServices/kineticLaws/14792> (see Figure 1)

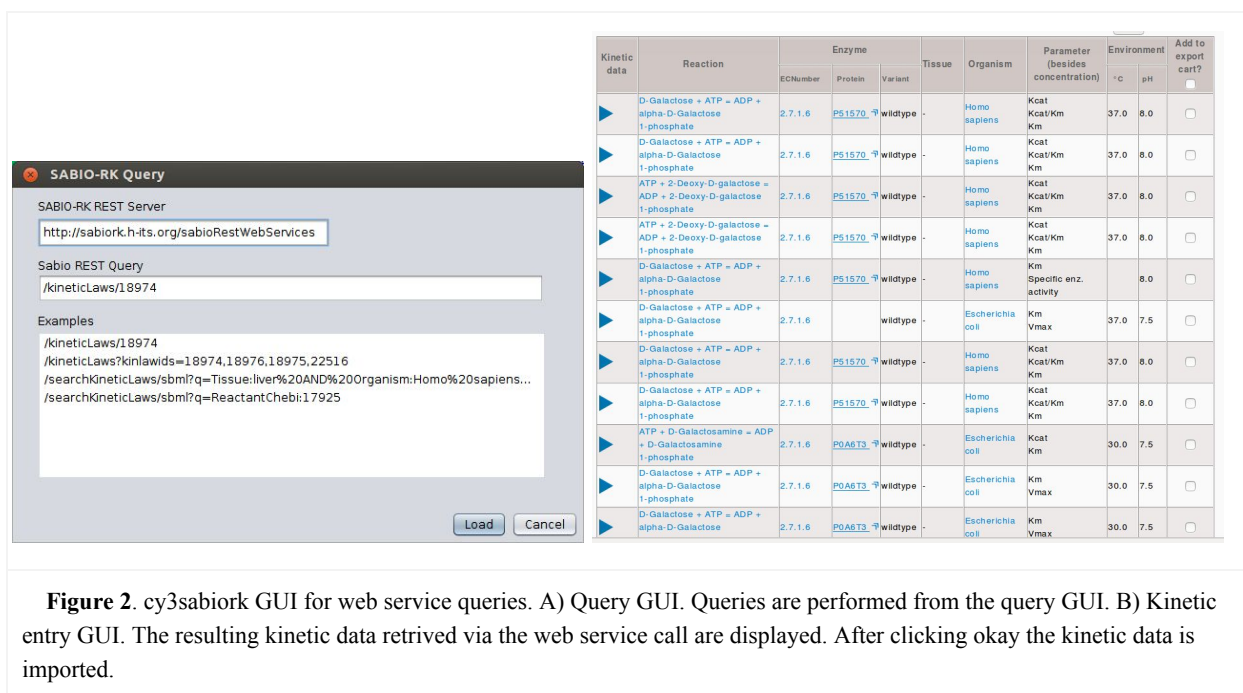
Supplementary File S2: SBML for query <http://sabiork.h-its.org/kineticLawEntry.jsp?viewData=true&kinlawid=14792> (see Figure 2 and Figure 3)

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Figures





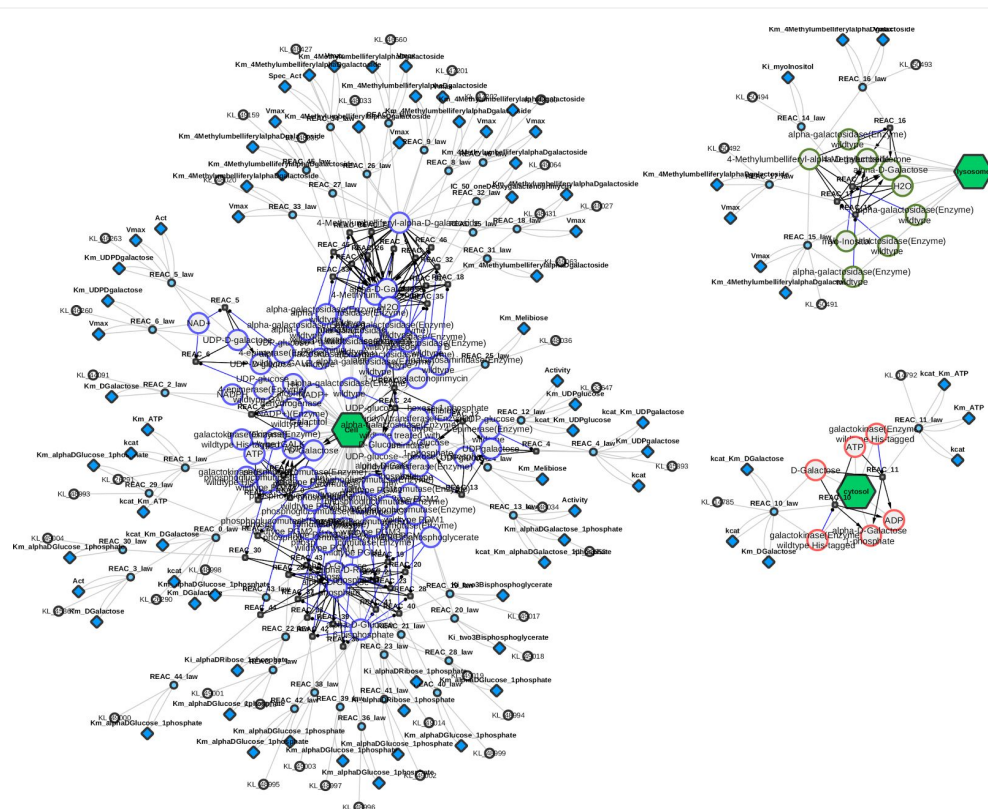


Figure 3. Graph of SABIO-RK kinetic records for the Human galactose metabolism, consisting of 47 entries (query 2016-06-08, Organism="homo sapiens" & Pathway="galactose metabolism" & wildtype=True, SBML for query available as **Supplement S2**). Three clusters can be seen, depending on the localization of the reported protein. The lysosomal reactions are non-canonical reactions in the galactose pathway.

sabiork.h-its.org/sabioRestWebServices/searchKineticLaws/sbml?q=Pathway:"galactose metabolism" AND Organism:"homo sapiens"