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# SABIO-RK (System for the Analysis of Biochemical Pathways-Reaction Kinetics)

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## Abstract

SABIO-RK is a database designed to store and offer access to information about biochemical reactions and their kinetics in a comprehensive and standardized manner. It integrates information from several sources to form a backbone of information necessary to include information about the kinetics of biochemical reactions. The kinetic data itself is primarily extracted from literature along with descriptions of the experimental conditions under which they were determined. This process is supported by the use of a web-based user interface which complies with most of the recommendations of the STRENDA committee for reporting on the results of enzyme/reaction kinetics. In this paper we describe the main characteristics of the SABIO-RK and its search and input interfaces.
Availability: http://sabio.villa-bosch.de/sabiork

## Introduction

The simulation of biochemical reaction networks depends on the combination of experimental data with modelling methods. A simulation requires information about the kinetics of the biochemical reactions participating in the network, such as the kinetic laws describing the dynamics of the reactions with their respective parameters determined under certain experimental conditions. These data are widely scattered through various publications and

described in many different formats. Moreover, each special field uses its own vocabulary and concepts. Thus, the process of integrating the kinetic data to simulate a biochemical network would be enormously facilitated by the definition and use of standards for reporting and exchanging the data obtained, both from experimentalist to modellers and for the feedback from modellers to experimentalists.

In order to compare kinetic data and integrate them into models of biochemical networks, kinetic parameters need to be consistently described and related to the kinetic mechanisms, the equations representing the kinetic laws and the environmental conditions. The known mechanisms of biochemical reactions should be reflected in mathematical formulas, which have to be linked to the corresponding parameters, such as kinetic constants and concentrations of each reaction participant. As kinetic constants highly depend on environmental conditions, they can only be specified completely by describing these conditions used for determination. Data sets based on experiments assayed under similar experimental conditions should be associated to each other to facilitate the comparison.

There is currently a small number of databases containing kinetic data of biochemical reactions. BRENDA [1] is a comprehensive database on information about enzymes. The enzyme entries also contain information about the reactions catalysed by the enzyme including data describing their reaction kinetics and in some cases information about the mechanism associated with the reaction's kinetics. Swiss-Prot [2] started to include experimental data like pH- and temperature dependence and kinetic parameters as comments related to biophysicochemical properties. The BioModels database [3] rather stores published mathematical simulation models of biological interest that are annotated and linked to relevant data resources (e. g. publications or databases), than experimental kinetic data of single reactions. The models include kinetic law equations and their parameters represented in SBML (Systems Biology Mark-up Language) format [4] and can be used for simulations of biochemical reactions or networks.

SABIO-RK, extends and supplements the information content of these databases by storing highly interrelated information about biochemical reactions and their kinetics, this last mainly experimentally obtained. It includes reactants and modifying compounds (i. e. inhibitors or activators) of reactions, information about the catalysing enzymes, and the kinetic laws governing the reactions, the latter with their parameters and information about experimental conditions under which they were determined. Data about biochemical reactions and their rate equations and parameters can be exported in SBML file format.

Most of the above mentioned databases manually obtain their information from publications. Data is typically loaded using in-house software, which has been designed on the basis of the structure of the underlying database. However, the ideal case would be that experimentalists or modellers could use a standard format to report their findings and that this format could be used by the databases to import kinetics data. Systems biologists use SBML format [4] to exchange models of biochemical reactions. However, it does not offer support to describe much of the information that documents the conditions and constraints of a given model or single experiment, unless this information is included in an unstruc-

tured open format as a comment or a description of the model. Information such as: under which experimental conditions does the model hold, or for which organism the data is reported, are not supported by SBML. It is planned however that this will change in the near future. In order to facilitate the integration of information the SBML community has incorporated and recommends the annotation of SBML files with references to controlled vocabularies and ontologies (see [5]). The STRENDA [6] (**St**andards for **R**eporting **En**zymology **Da**ta) commission is working on the definition of a standard for reporting on enzyme activity. The standard should contain the minimum amount of information that should accompany any published enzyme activity data. The use of references to controlled vocabularies and ontologies is also of great importance for the implementation of the STRENDA guidelines.

In this paper, we will report on SABIO-RK and the input interface used to load and store information about reactions and enzyme kinetics, and how this interface matches in most points with the current definition of the STRENDA standards especially with respect to the kinetics of enzymes and reactions. This interface would enable scientists to enter the results and conditions of their experiments into the database and to export these using a (to be defined) STRENDA format that can then be used to exchange the data.

## SABIO-RK (System for the Analysis of Biochemical Pathways-Reaction Kinetics)

SABIO-RK is an extension of the SABIO (System for the Analysis of Biochemical Pathways) biochemical pathway database, also developed at EML Research [7]. SABIO stores the fundamental information about biochemical pathways, like reactions and their participants (enzymes, compounds, etc.). It also offers support for the storage of information about proteins, protein complexes and genes, all this linked to organism (including strains) and to biochemical reactions (in the case of enzymes). SABIO integrates data from different sources, to establish a broad information basis. Most of the reactions, their associations with biochemical pathways, and their enzymatic classifications (enzyme classifications of the International Union of Biochemistry and Molecular Biology [8]) are extracted from the KEGG database (Kyoto Encyclopaedia of Genes and Genomes) [9].

SABIO-RK combines the data about biochemical reactions stored in SABIO with information about their kinetic properties. The kinetic data is mainly manually extracted from published scientific articles and then verified by curators. A kinetic law – if available in the article – is associated with a biochemical reaction (defined in terms of its substrates, products and modifiers) and its catalysing enzyme (typically defined by an Enzyme Classification number and a description of the enzyme variant, e. g. isoenzyme or mutant). A reaction can have multiple kinetic laws defined within one or multiple publications. This may depend on environmental and experimental conditions, enzyme variants, and the absence or presence of modifiers. As we will see in the next section, a kinetic law entry will contain data about the organism, tissue, and cellular location where the reaction takes

place, as well as the type of the kinetic law and the reaction's rate equation. The latter is shown with its parameters and the experimental conditions (e. g. pH, temperature, buffer) under which the parameters were determined or for which the parameters hold.

The SABIO-RK database has been conceived to serve the Systems Biology community as its main user. However it also contains useful information for experimentalist or researchers interested in information about biochemical reactions and their kinetics. It aims to support modellers with high quality data in setting up *in-silico* models describing biochemical reaction networks.

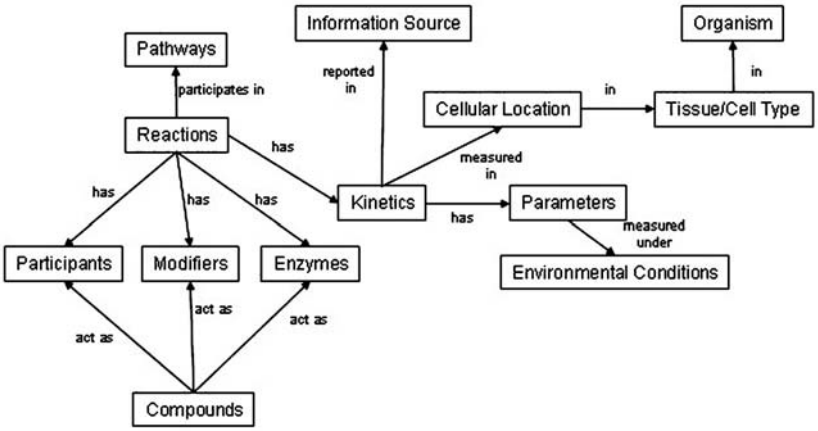



**Figure 1:** General concepts contained in the SABIO-RK database. (We have included plural definitions to facilitate reading.)

Figure 1 shows a general concepts contained in the database (not corresponding to tables in the database) and their relations. The current version the SABIO-RK web interface allows users to perform searches for reactions by specifying characteristics (one or many) of the reactions of interest (Fig. 2). For example the user can specify the pathway to which the reactions searched should belong to, e. g. Glycolysis; or he or she can specify one or more reaction participants (reactants or enzymes), organisms, tissues, or cell types in which the reaction is reported to occur. Additional search terms include cellular locations, environmental conditions (pH and temperature), or publications in which kinetic data are reported. The next version of the interface will also enable the user to search for networks or paths of reactions between two compounds or enzymes.

The system retrieves all entries satisfying the given criteria and indicates whether there is kinetic information available. A three colour-code is used to indicate this. Green means that for the associated reaction there are kinetic data available matching all search criteria. For a search like “find all reactions within the Glycolysis pathway for *Homo sapiens* which take place in liver”, this would mean that there is kinetic data reported on the respective reaction

in human liver. Yellow means there are kinetic data available, but not matching all search criteria. For example, the kinetic data were not determined for *Homo sapiens* but for *Rattus sp,* or not in liver but in heart. Red indicates that there are no kinetic data stored for the reaction reported.


**Figure 2:** Search facilities in SABIO-RK. Currently the system only offers the possibility of searching for reactions and their kinetics, but we plan to expand the search facilities to search for enzymes, specific parameters, and for compounds.

Apart from showing the availability of kinetic data for the specified reactions, the system will also indicate whether there is kinetic data available for the enzymes catalysing each of these reactions (see Fig. 3). We took this approach to offer complementary or alternative information about kinetic data for related reactions catalysed by the same enzyme. The availability of kinetic data for the enzyme is shown using the same three- colour code as used for the reactions. By clicking on a reaction, further information about it is displayed: Reactants, pathways in which it participates and enzymes catalysing this reaction that are reported with kinetic data in the database for a specific organism. Additional information about the enzyme (name, synonyms, classification and reactions it catalyses) can similarly be obtained by clicking on the EC number.

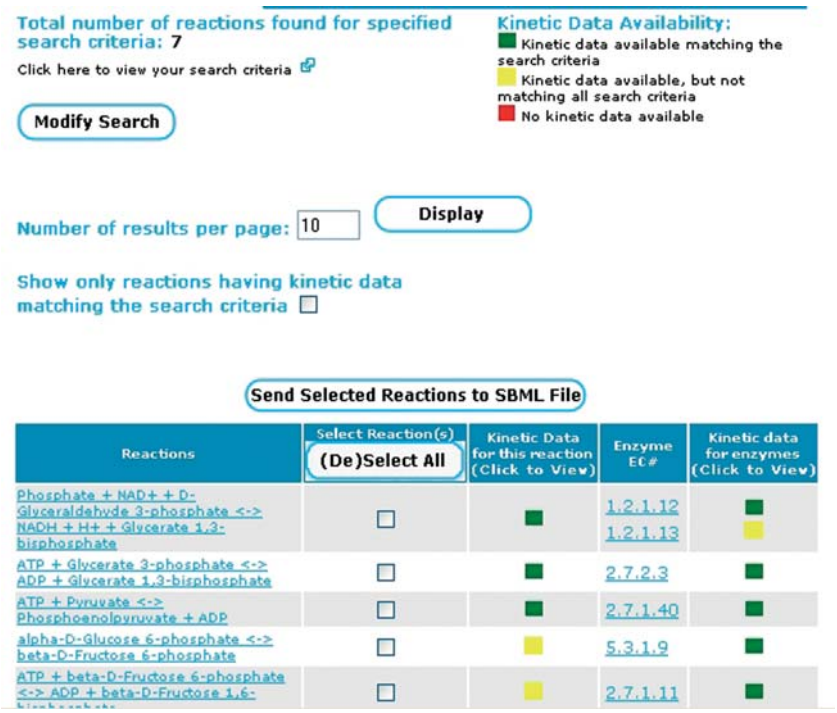
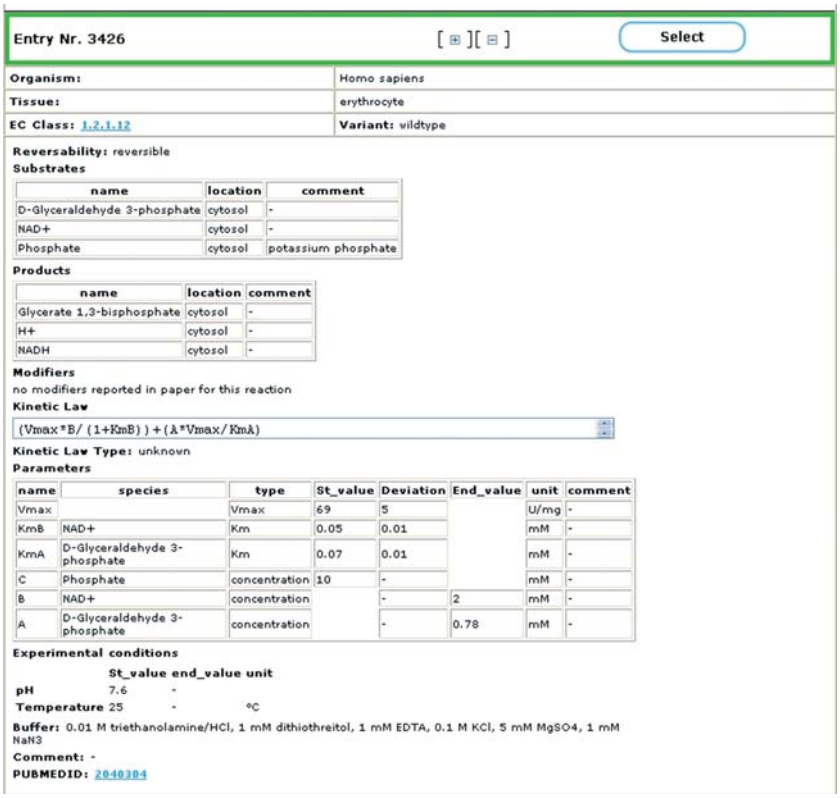



**Figure 3:** Results screen, showing the entries found for the given criteria (Glycolysis in *Homo sapiens*) and for each of these the availability of kinetic data.

From the result screen listing the specified reactions, the user can view the kinetic data belonging to each reaction, or all kinetic data available for the enzymes catalysing this reaction. In a new window the entries containing kinetic data for one reaction or one enzyme are listed. The user is presented with an overview showing for each entry the data on organism, tissue, enzyme classification and the variant of the enzyme. The expanded version of an entry shows all the kinetic data and additional information extracted from a publication, like environmental conditions. The information source of each database entry is indicated and linked to the PubMed database [10] in order to allow the user to refer to the original publication (Fig. 4).

The results on reactions and their corresponding kinetic laws and parameters can be stored and exported in a SBML (Systems Biology Mark-Up Language) formatted file. This format has been established as a standard exchange format between different tools including modelling and simulation software. The export is facilitated by using the libSBML API [4]. Not only single reactions, but also reaction clusters can be exported. The SBML file lists all the compounds (named species in SBML) belonging to the reactions as participants or modifiers. If a compound is present in more than one reaction, it will only be defined once in the file and will be referred to in the corresponding reactions. Thus, the reactions are coupled by the overlapping compounds.



Entry Nr. 3426 [ ⊞ ][ ⊟ ] Select

| | |
|---|---|
| **Organism:** | Homo sapiens |
| **Tissue:** | erythrocyte |
| **EC Class:** 1.2.1.12 | **Variant:** wildtype |

**Reversability:** reversible

**Substrates**

| name | location | comment |
|---|---|---|
| D-Glyceraldehyde 3-phosphate | cytosol | - |
| NAD+ | cytosol | - |
| Phosphate | cytosol | potassium phosphate |

**Products**

| name | location | comment |
|---|---|---|
| Glycerate 1,3-bisphosphate | cytosol | - |
| H+ | cytosol | - |
| NADH | cytosol | - |

**Modifiers**

no modifiers reported in paper for this reaction

**Kinetic Law**

(Vmax*B/(1+KmB))+(A*Vmax/KmA)

**Kinetic Law Type:** unknown

**Parameters**

| name | species | type | St_value | Deviation | End_value | unit | comment |
|---|---|---|---|---|---|---|---|
| Vmax | | Vmax | 69 | 5 | | U/mg | - |
| KmB | NAD+ | Km | 0.05 | 0.01 | | mM | - |
| KmA | D-Glyceraldehyde 3-phosphate | Km | 0.07 | 0.01 | | mM | - |
| C | Phosphate | concentration | 10 | - | | mM | - |
| B | NAD+ | concentration | | - | 2 | mM | - |
| A | D-Glyceraldehyde 3-phosphate | concentration | | - | 0.78 | mM | - |

**Experimental conditions**

| | St_value | end_value | unit |
|---|---|---|---|
| **pH** | 7.6 | - | |
| **Temperature** | 25 | - | °C |

**Buffer:** 0.01 M triethanolamine/HCl, 1 mM dithiothreitol, 1 mM EDTA, 0.1 M KCl, 5 mM MgSO4, 1 mM NaN3

**Comment:** -

**PUBMEDID:** 2040384

**Figure 4:** Kinetic data entry.

Due to the limitations of the SBML file format, the data exported requires some simplifications. For example no information about the experimental conditions, under which the parameters were determined, can be exported yet, although we plan to incorporate this information as annotations in the SBML file. Because parameter values can only be single values but no ranges, we include as parameter value the mean of the parameter range (if given). Also, the standard deviations of the parameters stored in the database, cannot be exported. Another restriction of the SBML format is the limitation to one kinetic law for each reaction. Thus, multiple kinetic laws (e. g. pseudo-first order kinetics) for one and the same reaction cannot be exported in one file.

As of June 2006, data of over 520 publications were inserted into the SABIO-RK database, corresponding to over 5100 database entries for 1100 different biochemical reactions and 325 distinct EC classes in 194 organisms. The stored parameters mainly describe steady-state kinetics for metabolic reactions. Around 40 % of all entries have a rate equation. The database entries describe around 4600 enzyme activities (like rate constants, $k_{cat}$ or $V_{max}$), 4600 $K_{\mathrm{m}}$ and 1000 $K_i$ (inhibitor constant) values.

## Data Input

The information about the kinetics of biochemical reactions is mainly extracted from text in a manual process carried out by student helpers. They use a web-based interface (Fig. 5) to enter the data into a temporary database. The main objective of this user interface is to supply a uniform format that the students and curators can employ to include the data found in the publications. The interface supports the students by pre-processing the data introduced and by offering the possibility to choose terms from predefined thesauri (here of course also allowing the introduction of new terms); this helps to avoid redundancies just because of aberrant notations or typing errors. The system will verify amongst other things if the parameters defined in a kinetic law are all defined as parameters, even if they do not have values associated with them.

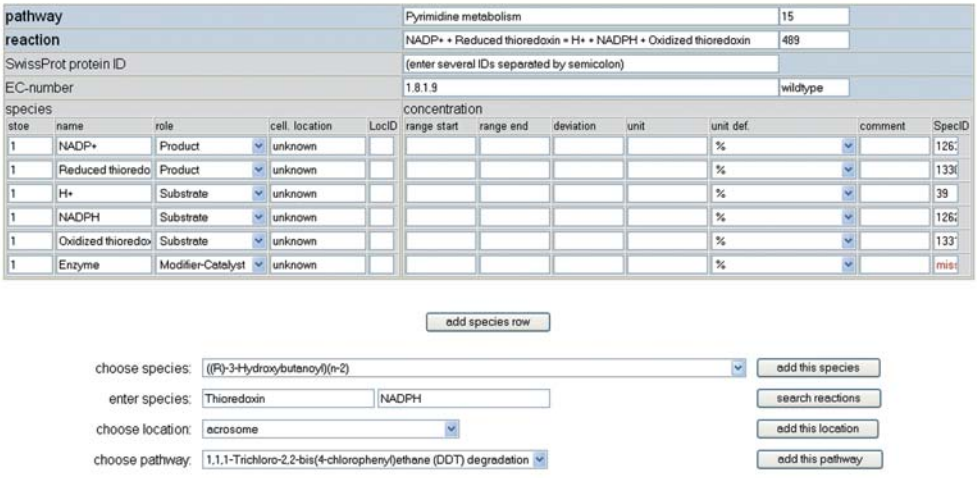



**Figure 5:** Input of the reaction data (substrates, products and modifiers) together with information about the pathway (optional) and about the enzyme.

Ideally students extract the following information for each reaction reported within a publication:

- Reaction defined by substrates and products
- Modifiers of the reaction (activators, inhibitors, catalysts, cofactors)
- Cellular location of compounds
- Enzyme classification number
- Swiss-Prot accession number(s) (of the enzyme)
- Variant of the enzyme (wild type or a certain isoenzyme or mutant)
- Kinetic law type (e. g. Michaelis–Menten, Ping–Pong Bi–Bi)

- Kinetic law formula
- Kinetic parameters (e. g. $K_m$, $k_{cat}$, $V_{max}$)
- Concentrations used for reactants, enzymes and modifiers
- Experimental conditions (e. g. temperature, pH, buffer composition)
- Biological source (e. g. cell type, tissue, organism, strain)
- Information source (reference)

For most of this information, comment lines are available to add information, for example about synthetic, labelled derivatives of physiological compounds or host organism for a recombinant enzyme.

In order to provide a better understanding of the interface, let us now go over the support offered by the system in the introduction of the fields mentioned above.

***Input of reactions' data***
To begin with, the student may enter some of the names of the reactants (substrates and products; we will also refer to these as species), followed by a database search which in turn displays all reactions stored in the database in which the reactants are involved. By choosing the appropriate reaction, all relevant information is automatically extracted from the database and displayed in the corresponding fields such as: species name, species stoichiometry and species role (substrate, product). However, it might be that the reaction is not found; in this case the user may enter all information manually. After the introduction of the substrates and products (in which ever way), the species can be associated to a location; this is also supported by offering a list of locations. Determining whether a reaction or a compound is already included in SABIO, is not a trivial issue, given that the search by name may not suffice to determine synonymic expressions. If a new reaction is given curators have to verify (as much as possible) whether this reaction is really new or if it is already in the database with a different notation. To support the curators, we are working on the development of linguistic methods to obtain compound structures from names and compare compounds at the level of their chemical structure [11].

Apart from the reactants the user should specify information about the enzyme (if applicable) like enzyme classification of the reaction plus Swiss-Prot identifier(s) of the protein or protein complex. The information of the pathway in which the reaction participates is optional; for reactions in the database this information is already present.

***Addition of kinetic laws*** **(Figure 6a)**
By the addition of the kinetic law information, the user is supported by providing a list of possible kinetic law types. Originally the system automatically offered a default formula for each type, which could be used by users as a basis; however this feature has been taken out by petition of the users, who manifested the preference in directly introducing the mathematical formula as specified in the paper. The user can define parameters and variables for the kinetic law. In order to avoid the proliferation of unit definitions, the user is

supplied with a list of units. New units can be added, but this is not encouraged unless completely necessary (no equivalent found in the list). Additionally, the user is supported by some verification procedures: all parameters and species referred to in the kinetic law formula must be defined in the parameter and species lists, respectively; the brackets in the kinetic law formula must be mathematically correct; naming of parameters must be consistent with SBML rules (e. g. no special characters allowed); parameter types can only be chosen from a given list of predefined terms (e. g. $V_{max}$, $K_m$, $K_i$); in case of a parameter–species relationship (e. g. for $K_m$ or concentration value)only predefined species from the reaction list can be entered. In addition to this, a browser plug-in has been implemented to allow the visualization of the kinetic law formula as a mathematical formula and not just as text, helping to verify its correctness.

***Experimental conditions*** **(Figure 6b)**

In this section the user should introduce the experimental conditions under which the kinetics were determined. Currently we consider the pH, temperature and the specification of the buffer, but the system allows the introduction of other conditions.

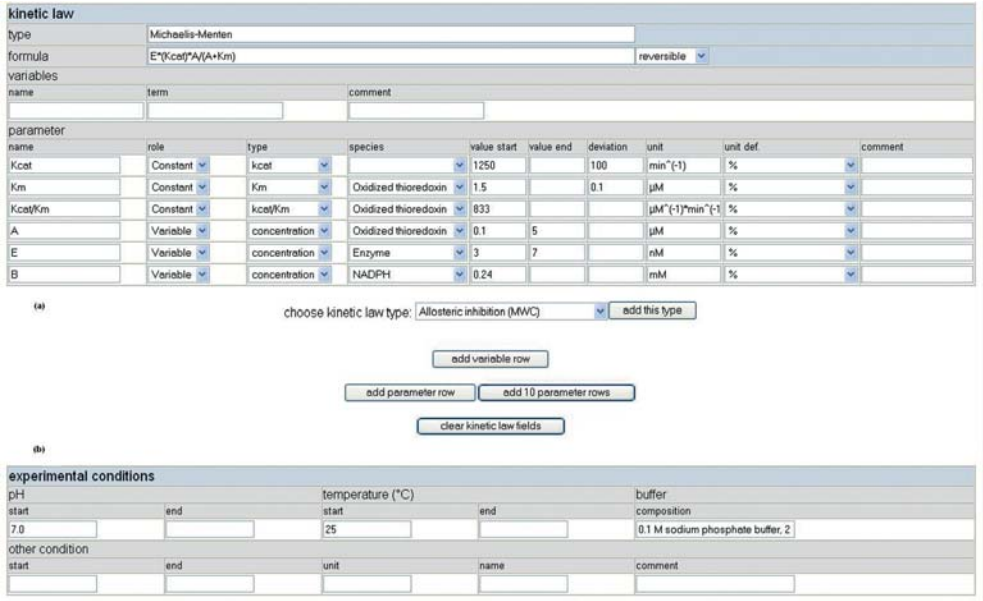



**Figure 6:** Input of the kinetic data (a) along with the information about the environmental conditions under which these were determined (b).

***General Information*** **(Figure 7)**

In this section of the entry form the user is asked to give information about the organism and tissue (if known) for which the kinetics were determined. Here again the user is supported by lists of names. Although these fields should belong to the experimental description, they have been put here due to the fact that typically a publication will report on the kinetics for multiple reactions under multiple experimental conditions, however the

organism and tissue are commonly constant within a publication. All data in the general section can be kept for its use for several kinetic data entries. The information source should also be given in this section, this is a compulsory field (there cannot be any entry without information source). The user can select from the list of publications in the database (using a search function) or introduce a new source. Also included in here is the possibility to add comments (general to the entry) and currently we have a field to indicate whether or not the paper provides detail information about the reactions mechanism; this information will be used when the system supports a detailed description of the reactions' mechanisms (see future plans).

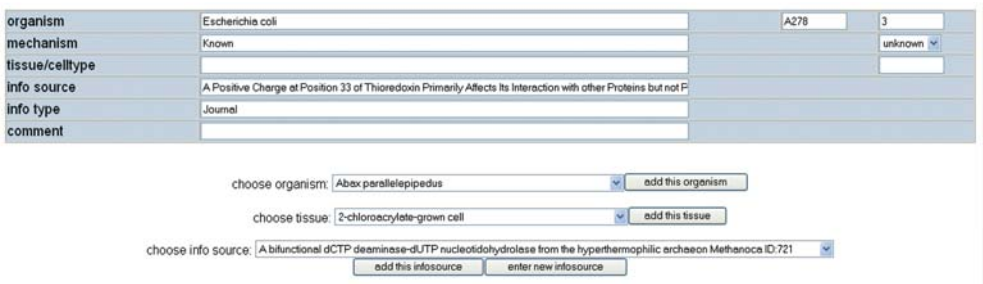



**Figure 7:** Input of complementary information to the entry, which very often is shared amongst many entries within the same publication.

Before the data is finally transferred to SABIO-RK, it is approved, complemented, and verified by a team of biological experts so as to detect possible errors and inconsistencies. The curators are faced with problems like synonymic or aberrant notations of compounds and enzymes, multiplicity of parameter units and missing information about assay procedures and experimental conditions. Frequently, the methods used are described fragmentarily or by a simple reference to another publication, which in turn refers to a third publication. Hence, it is sometimes almost impossible to get the complete description. Moreover, the description of a buffer can be very complex, containing for example information about coupled enzyme reactions or synthetic derivatives of physiological compounds. Chemical compounds and enzymes often have various alternative names, organisms can be described by their common or systematic name, and units of kinetic parameters and concentrations can be written in different ways or can be based on different unit systems. Furthermore, we are often faced by the problem of missing or partial information in the literature. For example, a reaction definition can be incomplete, which means that only substrates of reactions are named without a definition of the reaction products. If the chemical mechanism of the enzymatic reaction is known, the reaction equation can be completed, but in most cases this work is very time-consuming, and the result may also be imprecise.

During the curation process, the data is unified and structured consistently in order to facilitate the comparison of the kinetic data extracted from different sources, since it was usually obtained under different experimental conditions or from different organisms,

tissues etc. Furthermore, structured data enable the user to conclude general rules concerning the dependence of a biochemical reaction or an enzyme on environmental changes like for example increase of temperature or pH variations.

The interface is also used by the curators to check and complete the entries, and supports them in the administrational work (assignment of papers, statistics etc.). The publications to be revised have been obtained from PubMed [9], by using several queries leading to papers, which very likely contain information about biochemical reaction kinetics.

The information supported by this input interface covers most of the fields present in the STRENDA commissions' recommendations for the reports about reaction kinetics. Currently the input interface is being used only internally by the development team on SABIO-RK, however we hope that in the future experimental partners can directly introduce their data into the database and make it thus available through the SABIO-RK database interface.

## Future Directions

The SABIO-RK project started at the beginning of 2005. Currently the database contains mainly data about metabolic reactions. However, since cellular signal transduction is a fast-growing emerging field, one of our main objectives is to incorporate more kinetic information about signalling reactions. This includes the representation of molecules in different activation states, for instance modifications of signalling molecules like phosphorylation or acetylation of proteins. Another very important objective is the incorporation of detailed information about reactions' mechanisms. This will allow the user to obtain information about the kinetic properties of sub-reactions or binding mechanisms of enzymes and substrates. As mentioned in the data input section, we are keeping track of the publications having this information to facilitate the process of returning to the adequate literature. An extension of the data model to store reactions' mechanisms and the corresponding kinetic data has already been developed and will soon be implemented together with adaptations of the user interface.

In order to allow the users to refer to additional information about reactions, pathways, chemical compounds and enzymes, we are working on the cross-linking and annotation of the database content to other database resources. In addition, we will apply and annotate controlled vocabularies and ontologies such as those specified in the Open Biomedical Ontologies (OBO) [12] to enhance the standardization and comparability of the data stored in SABIO-RK. With these goals, we will adopt the proposed set of rules for the annotation of biochemical models described in MIRIAM (Minimum information requested in the annotation of biochemical models) [5]. The annotations will not only be used for cross-linking our database to other resources, but also can be exported in the SBML files.

The information describing environmental conditions under which the parameters were determined, as well as the literature source from which the data was extracted, cannot be completely exported in a structured and defined format in SBML. For this reason, we plan to define new XML based export schemas, in order to facilitate the exchange of detailed kinetic information together with their constraints.

On the side of the user interface of SABIO-RK we are working on the extension of search facilities, less reaction oriented, to permit searches for parameters and kinetic laws, e. g. search for all reactions that follow a certain kinetic law type or for all enzymes of the pathway glycolysis for which $K_m$ values are known. Also planned in the near future is to enable the user to search for networks or paths of reactions between two compounds or enzymes. Visual display of the reactions found as well as of the kinetic parameter values is also scheduled.

One of our biggest aims is to convince scientists to use the input interface to enter data directly into the database. As a result, all the needed information can be given by the experimenters and no information is lost. In doing so, users would be able to directly compare their own experimental results in SABIO-RK with similar kinetic data extracted from literature or entered by other users.

## Summary

SABIO-RK is a database storing highly interrelated information about biochemical reactions and their kinetics, within the context of cellular locations, tissues and organisms. The database has a web-based user interface that enables the user to search for biochemical reactions and their kinetics, based on the characteristics of the reactions and on the environmental conditions under which its kinetics were obtained. Although the main motivation of SABIO-RK was to act as a resource for modellers of biochemical networks to assemble information about reactions and their kinetics, the database is also aimed at experimenters wanting to obtain information about reactions kinetics and compare their own results with similar published data. The kinetics data is mainly extracted from literature sources by students and then revised and supplemented by a group of curators. The students employ a web-based interface to introduce the data in a standardized format. We hope that in the future both, experimentalists and modellers will be able to use this interface to directly introduce kinetic study results of their respective experiments or simulations into the database.

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