*Ki*MoSys – a web-based repository of experimental data for KInetic MOdels of biological SYStems

User Guide

Version 2.0

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1. Introduction

Kinetic modeling of biological systems is a fundamental element of systems biology as a tool for performing experiments *in silico* with biotechnological and biomedical applications. It is mainly composed of three steps than can proceed iteratively i) model building, ii) simulation and iii) analysis. Specifically, for model building, it is usually required to add initial metabolite concentrations, and to assign the kinetic rate laws, as well as experimental data for parameter fitting.

Public access to experimental datasets and data standardization are requirements for the modeling of biochemical networks. However, experimentalists present only a summary of obtained results (i.e. without experimental data values) for publication. The complete data files remain private and difficult to access, since they are not usually submitted to any public repository. Furthermore, disadvantages are also the unavailability of a system to associate kinetic models with the experimental data. Hence, a web-based platform which offers researchers the access to experimental data files and associated models, and a view of metadata, as well as, support to the construction process of kinetic models would be of great help.

2. General Information

***Ki*MoSys** is a user-friendly platform that includes a **public data repository** of relevant published measurements, including **metabolite concentrations, flux data, and enzyme measurements**. It is designed to search, exchange and disseminate the experimental data (and associated kinetic models) for a wider systems biology community.

***Ki*MoSys** also integrates computational tools to **support and facilitate the kinetic model construction process** of large-scale metabolic networks, especially when the systems biologists perform computational research. Other tools for kinetic model editing, simulation and analysis will be added in upcoming versions.

User Guide

This document introduces new users to the basics of working with ***Ki*MoSys**. The platform can be accessed online using a web browser at http://*kimosys*.org. The description of the platform is fully described in the manuscript.

3. Header Section

The guest header is organized in two areas: the primary menu links (*Home, Repository, Tools, Documentation, Links* and *Contact Us*) and the user bar (see Figure 3.1). The primary menu provides the main navigation and the user bar allows users to *Register*, and *Login*.

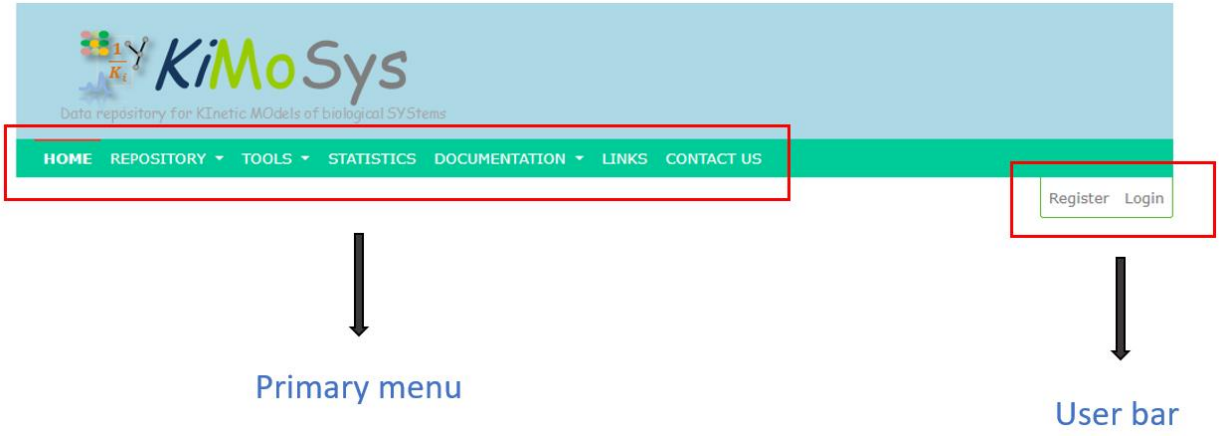


Figure 3.1: Guest layout of *Ki*MoSys: primary menu and user bar.

*Ki*MoSys has the following pages:

Home – return to the *Ki*MoSys home page.

Repository – contains the main table of the data available in the repository. Here the user can search and submit new data to the repository.

Tools – available tools to support kinetic models' construction.

Statistics – provides the database content**.**

Documentation – includes this User Guide and the source code.

Links – includes related external links for kinetic modeling.

Contact Us – launches the contact web form.

4. Registration and Login

Register to browse the *Repository* for search, view and download data and associated models, as well as access the *Tools* tab is not required. However, access to submit (via electronic data-submission) data and associated model files or update existing submission are restricted to the active session. To create a new account [(*)] the user need to click on the "*Register*" link positioned right beneath the header section. Registration for the user is free and simple, having to provide a first and last name, affiliation, research interests, homepage or ORCID iD (www.orcid.org), a valid email address and a password. Only the first, last name, affiliation, email and password are required fields.

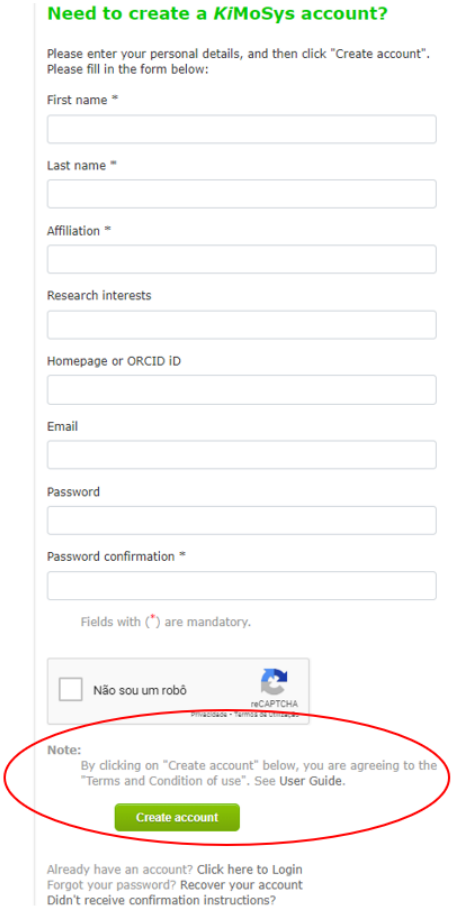
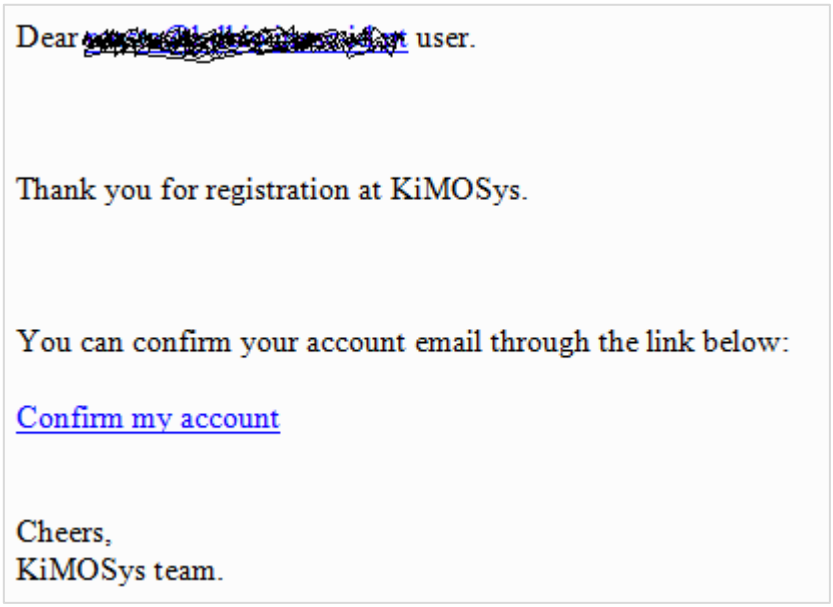


Figure 4.1: Register screen for *Ki*MoSys. First and last name, affiliation, email and password fields are mandatory.

[(*)] When the users register an account, we do not use the personal information that you provide for purposes other than operational communication and to support academic research into the use of *Ki*MoSys. First name and email that you provide to register an account will be made public to facilitate community interactions.

After filling and submitting this form (Figure 4.1), the user will be presented with an automated email to confirm that you have requested the ***Ki*MoSys** account (Figure 4.2). After clicking the included link "*Confirm my account*" to activate the account the user has all needed to have a ***Ki*MoSys** account.


Dear [redacted] user.

Thank you for registration at KiMOSys.

You can confirm your account email through the link below:

Confirm my account

Cheers,
KiMOSys team.

Figure 4.2: Example of an email information to verify the user account.

The system allows registered users to login for subsequent visits to the *repository*, by clicking on the *Login* link. This link is seen at the user menu at the bottom of the header (User bar). Enter your email and password and at last, click on *[Login]* button. To logout, click on the *Logout* link available after login at the top-right of your window (Figure 4.3). The user may also *Edit user* information and *Cancel* the account at any time.

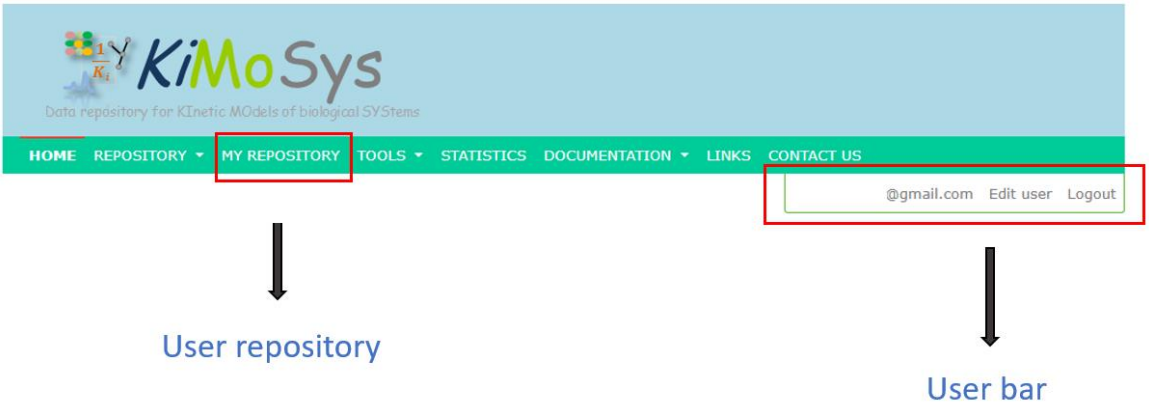


Figure 4.3: Register layout of *Ki*MoSys.

When registered and logged-in, the users can see their own repository area (*My Repository* tab) in the primary menu (see Figure 4.3).

5. Home WebPage

The homepage provides a summary description of the platform, news and an overview of the features included. The "*News*" panel connected to the social network *Twitter* displays information about main updates, and new data and associated model files submitted to the repository. Click the *[Follow]* button to follow ***Ki*MoSys** news.

Figure 5.1: *Ki*MoSys welcome front page.

6. Browsing, search and downloading

The ***Ki*MoSys** repository is a centralized place for storing, accessing and sharing experimental data and associated kinetic models.

The main table (quick view) displays which experimental data are stored in the *Repository*. The organism and strain use to generate the data are also shown. Moreover, it is possible to view for each visible *Data EntryID* that the data is public (or private) and if they have any associated kinetic models with the data (i.e. experimental data on which the model building, refining and/or validation process are based).

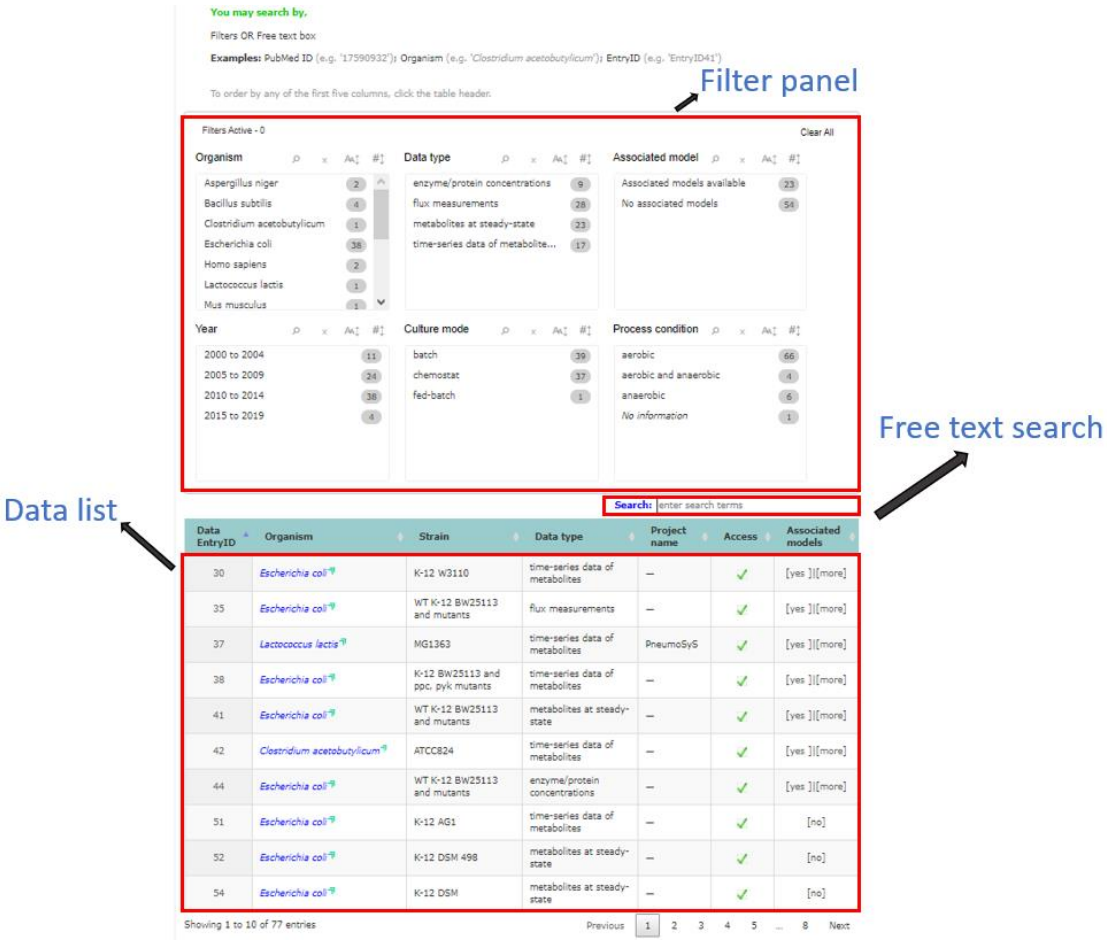


Figure 6.1: Page with the table of data list and basic information. The database can be queried using the filter panel and/or the search box.

In the filter panel you can select as many filters as you like. It is possible to choose filters from the same box as well, by clicking ***Ctrl + filter***. As Figure 6.2 shows, the panel refreshes after a selection of a filter: all the other filters are updated according to the first selection, indicating the number of items remaining, as well as the total number present in the database (the number between the "( )"). In addition, each box has the ability to sort items by amount or alphabetically, a search box, and a button to clear filters.

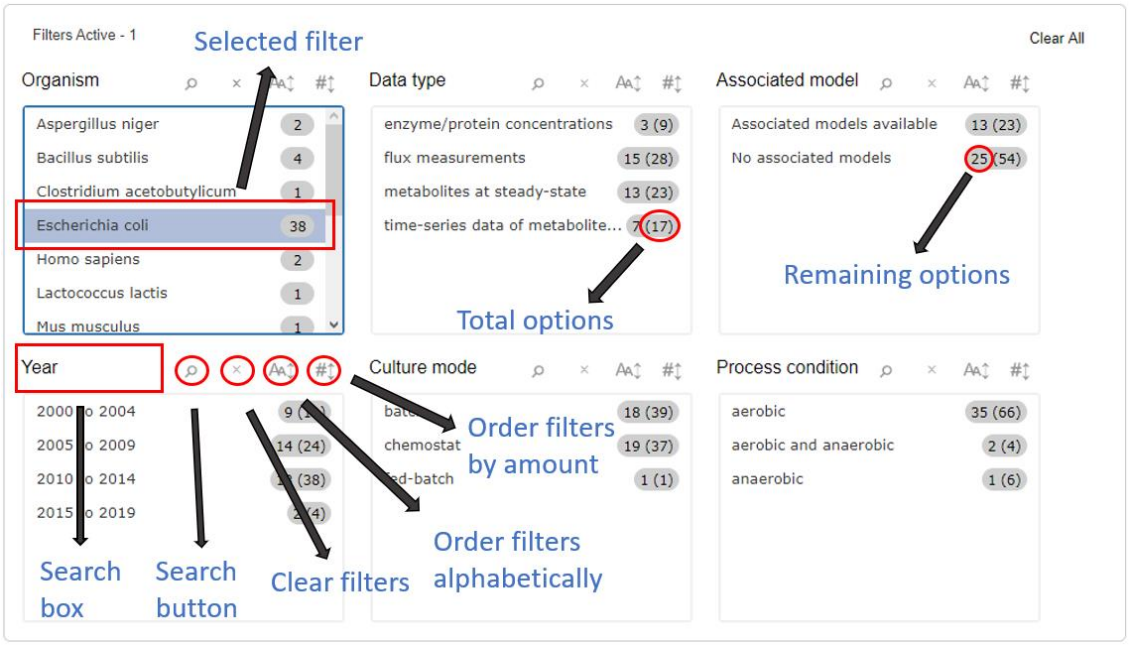


Figure 6.2: Search panel when a filter is clicked.

You can also use the simple search box to perform simple queries (quick search) on the *Repository* table using free text like Google (see Figure 6.1). Only entries containing the search word(s) and filters (if selected) will be displayed in the table output.

You may search by,

Examples:

• **Data EntryID** – internal data accession identifier (e.g. '41').

• **Organism** – name of the organism used to generate the dataset (e.g. '*Clostridium acetobutylicum*').

• **Data type** – experimental data type (metabolites at steady-state, time-series data of metabolites, fluxes or enzyme data).

In addition, the search facility provides the ability to search through the underlying fields (e.g. PubMed ID, original title that are stored in *Ki*MoSys, KEGG ID or ChEBI ID present in the datasets).

The output of any type of search is a summary table with all the experiments reporting when matched basic information about the data. The search result table has the following

main column headers: *Data EntryID*, *organism*, *strain*, *data type* and *project name*. By clicking on the table header it is possible to sort the table rows in ascending or descending order by any of the first five columns. To reverse the sort order, click the column header a second time.

As an example, the index was queried for the organism "*Saccharomyces cerevisiae*". The result hits are shown below:

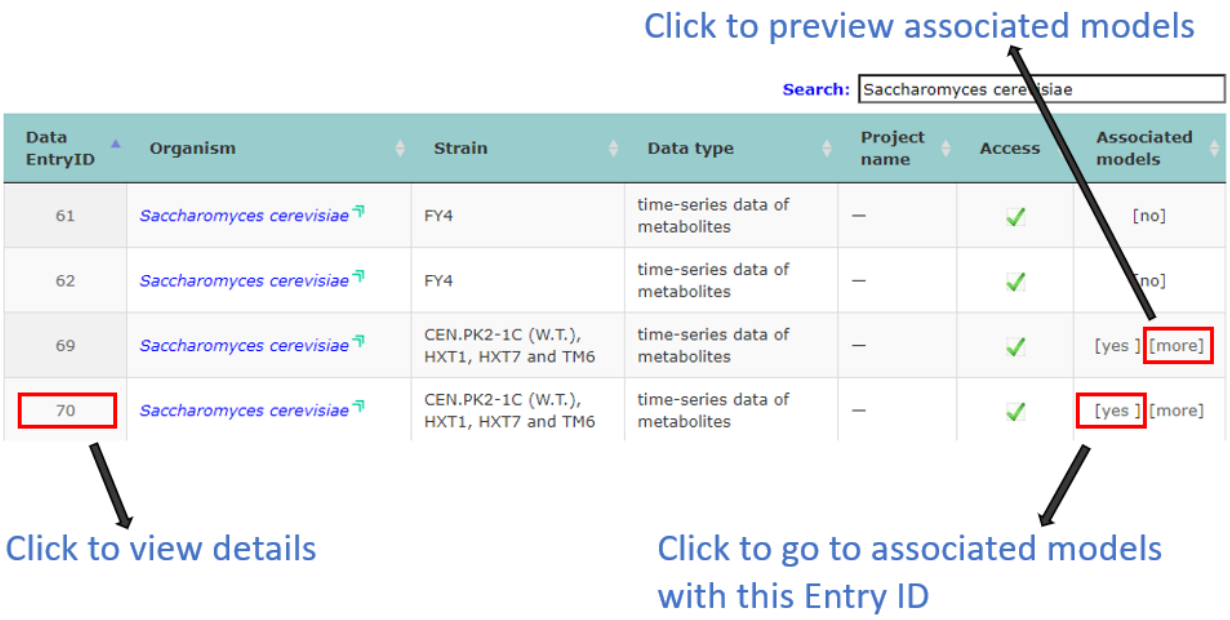


Figure 6.3: Web-interface screenshot of the query result (e.g. search for "*Saccharomyces cerevisiae*"). The output of search is a table containing only the experiments that where a match.

To go directly to the associated models table with a data *EntryID* click *[yes]* button or to display the associated models with a specific data *EntryID* click on the *[more]* button. If you wish to see more details about the data, click on the hyperlink on each *Data EntryID* number (e.g. *70*) and you will be directed to a detailed view page which contains a second table title "*Detail View – Data Access ID"* (see figure 6.3). This page is designed and divided into three different sections to provide full information of the corresponding *Data EntryID* and a summary view of associated models with the data. For the full information of the corresponding *Data EntryID* a section for (i) general metadata information, (ii) followed by a section for the experiment description and then (iii) a section for the data file(s) listening are presented:

(i) General Information

• **Manuscript title** – reference title of the manuscript where the data are described/published or a general title if not published yet.

• **PubMed ID** – ID number of the manuscript in PubMed. The hyperlink will take you to the PubMed abstract page for a particular reference. Link to the PubMed database enable the user to refer to the original publication (source reference) and gather further information.

• **Journal** – journal name of the manuscript.

• **Year** – year of publication.

• **Authors** – authors of the manuscript.

• **Affiliations** – affiliation(s) of the first author.

• **Keywords** – general keywords that characterize the data.

• **Full text article** – attached article .pdf file (only if open source) where the data are published.

• **Project name** - comprehensive name (acronym) of the project (if the data is part of a general project).

(ii) Experiment Description

• **Organism** – name of the organism used to generate the dataset.

• **Strain** – name of the strain used to generate the dataset.

• **Data type** – experimental data type to submit.

• **Data units** – units of the data.

• **Execution date** - start date of the experiment.

(iii) Experimental Details

• **Temperature** – temperature in (ºC) of the experimental condition measurements.

• **pH** – pH of the experimental condition measurements.

• **Carbone source** – carbon source used by the organism.

• **Culture mode** – how the culture growth in the experiment.

• **Process condition** – process condition of the experiment.

• **Dilution rate** – in (h^{-1}) of the experiment in chemostat culture.

• **Working volume** – in (L) used in the reactor/flasks.

• **Biomass concentration** – dry cell weight measurement in (gDW/L).

• **Medium composition** – detailed concentrations components used in the medium.

• **General protocol information** – short information about the protocol and instrument type.

• **Methods description - Notes** – a summary description (free text) of the overall experiment, main process steps that have been performed and any other pertinent information helpful for researches reading this file. Description taken and adapted from the original manuscript.

• **Data file** – structured Excel file containing the data and corresponding metadata that can be downloaded and previewed.

• **Alternative formats** – other data files formats (.csv and/or .txt) that can be added. These files contain the data for each worksheet of the Excel file. The .txt file(s) (metabolites at steady-state and flux data) are in the format that can be used as input for the "*Tools*" tab and the .csv file(s) are in the SBtab (http://www.sbtab.net) exchange format. Additionally, .csv files can be previewed.

• **Export metadata** – .txt, RDF and .xml files containing the metadata information.

• **Related data** – entities with the same PubMedID, organism or project.

Related data, submission and curation information to this *EntryID*, such as the submitter name, the date when the data was submitted, team member's name, the date of last modification, the version number (by default the latest version is visible, not older versions) and the number of views and downloads are also provided (see Figure 6.4). Moreover the "*status*" indicated whether the *EntryID* has been manually annotated from the original publication by the ***Ki*MoSys** curators (*"reviewed"* and date) or not ("*unreviewed*"). For logged-in users they can click on the "Entered by" name to contact the submitter.

To download and save the Excel data file (data and associated metadata), simply click on the *[Download Data]* button (Figure 6.3) and for the alternative files (.txt and/or .csv) click on the corresponding file name. All data are freely available for download in this variety of formats. Moreover, the *[Download all]* button allows to save the manuscript and the data

files in a unique .zip archive. File preview is also available for .csv and .xlsx files, with the later having also a plot of the data.

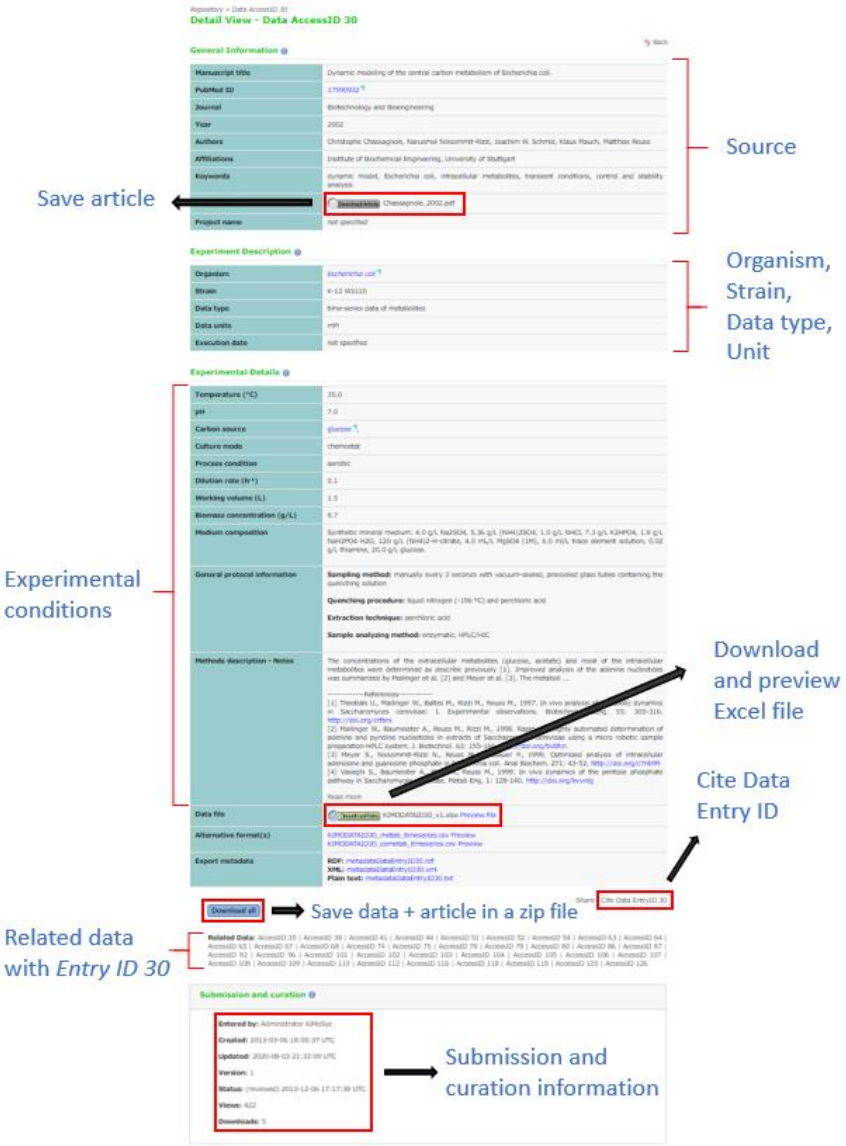


Figure 6.4: Web interface screenshot of a detail view from a single data entry (e.g *EntryID 70*) without log in.

In the same view page you can see the associated model(s) (scroll down the page) and associate new ones to the corresponding *Data EntryID* (see figure 6.5). You can use the simple search box to perform simple queries (quicksearch) on this table in a similar way as for the data table. The table provides an overview about the model information and has the following main column headers: *Model EntryID* (unique accession number), model name, category and model type. It is also possible to view for each visible *Model EntryID*

that the model is public (or private). The user can only submit new model files for existing *Data EntryID´s*.

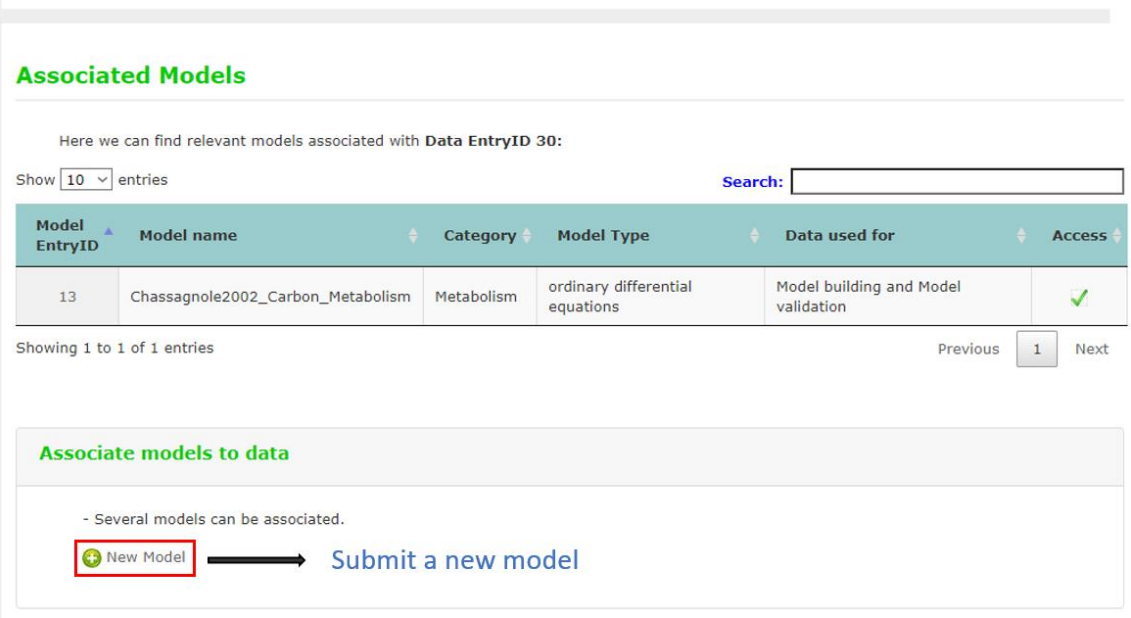


Figure 6.5: Table for associated models with the *Data EntryID* (e.g. *EntryID 70*).

If you wish to see more details about the model(s), click on the *Model EntryID* button and you will be directed to a detail view page which contains a table title *Detail View – Model Access ID* (see Figure 6.6). This page is designed to provide the model details. To save directly the model file(s), simply click on the *[Download Model]* button. Here you can view the model versions history (if available). The *[Download full archive]* button allows to save the manuscript, model and the data files in a unique .zip archive. Moreover, the *[Download COMBINE archive]* button (if available) allows to save the COMBINE archive (see specifications http://co.mbine.org/documents/archive). To open the COMBINE archive the user can download the latest Windows binary version from http://sourceforge.net/projects/sbw/files/modules/CombineArchive/.

Figure 6.6: Example of a detail view from an associated model (*Model EntryID 28*) with the *Data EntryID 70* for submitters logged-in.

The model details displayed all the following properties:

(i) General Information

• **Manuscript title** – reference title of the manuscript (or general title of not published) in which the model is described/published.

• **PubMed ID** – ID number of the manuscript in PubMed. Link to the PubMed database enable the user to refer to the original publication (source reference) and gather further information.

• **Journal** – journal name of the manuscript.

• **Year** – year of publication.

• **Authors** – authors of the manuscript.

• **Affiliation** – affiliation(s) of the first author.

• **Keywords** – general keywords that characterize the model.

• **Full text article** – article file (.pdf) where the model is described.

• **Project name** – comprehensive name (acronym) of the project (if the model is part of a general project).

• **Data used for** – information if the data where used for model building, validation and/or refining.

ii) Model Information

• **Model name** – generic name of the model.

• **Organism** – name of the organism to which the model corresponds.

• **Model Type** – type of the model uploaded.

• **Category** – category of the model (e.g. enzymology, metabolism, etc.).

• **Number of reactions** – number of reactions in the model.

• **Number of species** – number of the species in the model.

• **Number of regulators** – number of regulators in the model.

• **Number of parameters** – number of parameters in the model.

• **Number of compartments** – number of compartments in the model.

• **Dilution rate** – dilution rate in (h^{-1}) used to simulate the model.

• **Model file(s) and history** – the attached model file(s). Provides all versions (if available) so that all the model files history can be accessed. For each version the timestamp (timepoint of change) and creator (user performing modifications) are shown. Moreover, store information on the model revision history to understand the relationship between them including the current final version model (LATEST version). For each version (if available) a comment with the differences are shown. It is possible to simulate (see section 9.5 for more information) and preview each file. The preview shows the .xml code, as well as the species and reactions from the model, with the available equations, parameters and initial concentrations.

• **Notes** – provide model source and any other pertinent model information helpful for researchers.

• **Software** – provide web address and name of the tool used to build/validate and simulate the model.

• **BioModels or JWS Online ID** – ID of the model in the BioModels or JWS online database (if the original model is obtained from these databases). Link to the BioModels [1] and JWS online database [2], where models can be simulated.

• **Export metadata** – txt, RDF and xml files containing the model metadata.

• **Related model(s)** – entities with the same PubMedID, organism or project.

The *[My Repository]* tab (login is required) contains a summary table that displays information about the data and models that you have submitted as well as where the user name has required permissions (Figure 6.7).

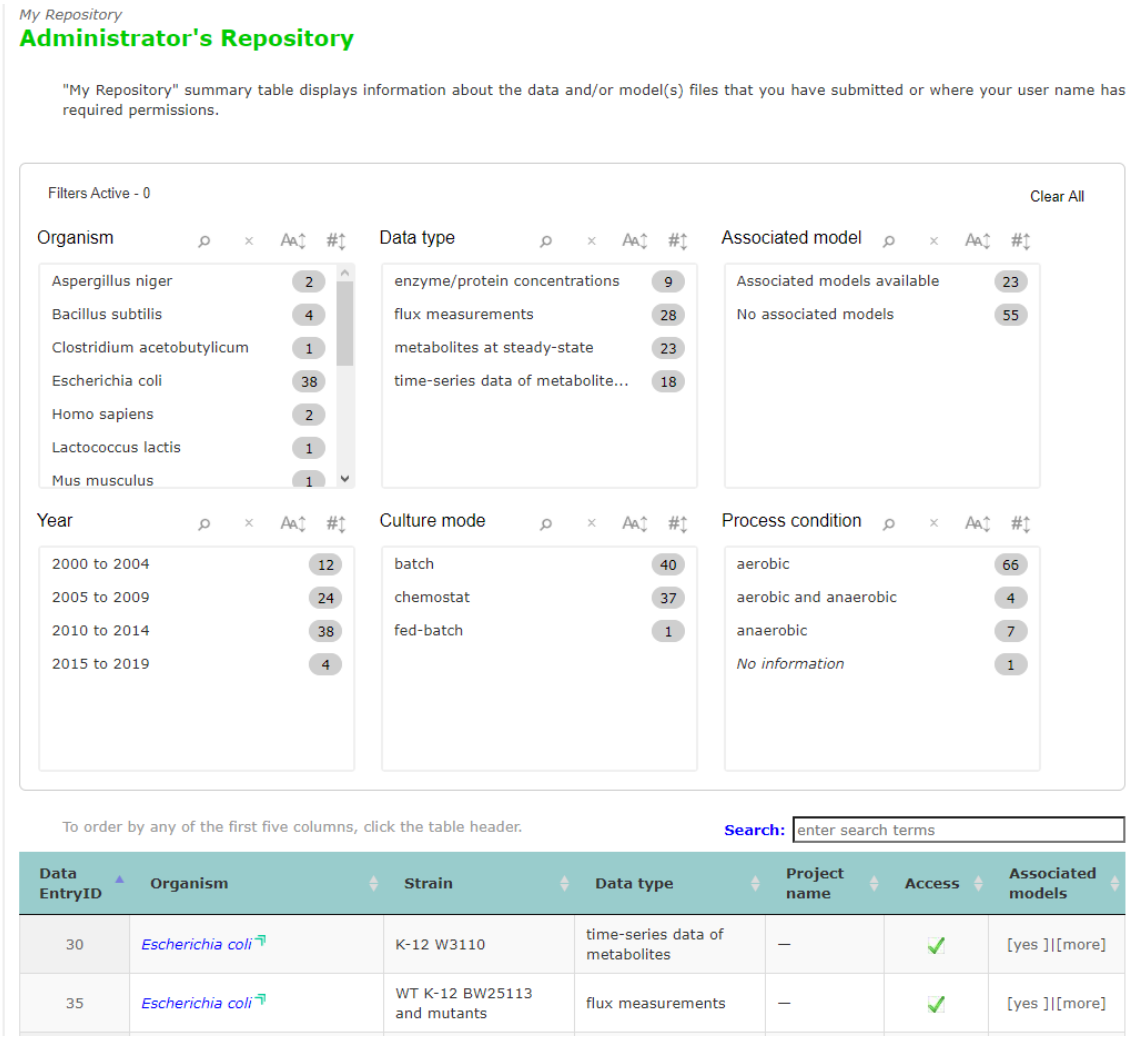


Figure 6.7: Example of a "*My Repository*" summary table for a specific *Ki*MoSys user.

7. User Access

Submitter *EntryID* records in ***Ki*MoSys** can be marked as public or remain private (visible or invisible) until the data and model files are published (see Figure 7.1). Unregistered users (not require an account) are able to browse, search, as well as download the existing public data and associated model files. However, only registered users (upon authorized Login) are able to submit new data and/or associated models via online submission form.

Submitters per *EntryID* entity are able to:

- share *public* data and models in visible mode to all users.
- share *private* data and models in invisible mode (hidden from view) to all users.
- share *private* data and models in visible mode for specific users (e.g. *invite* scientific project collaborators or reviewers).

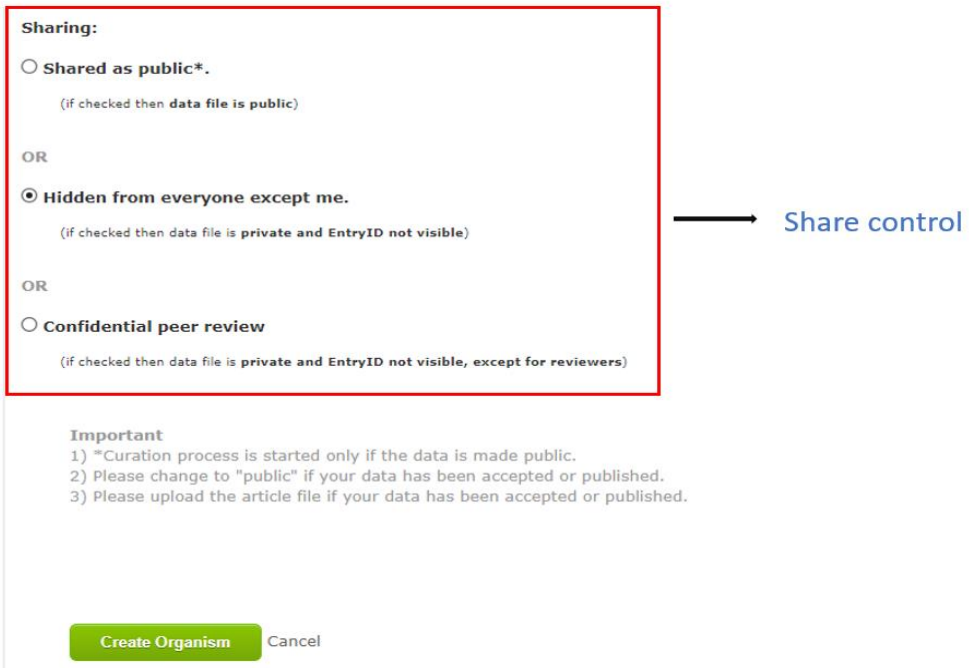


Figure 7.1: Example of the share control option on the direct electronic data-submission form.

All of the data and model files per *EntryID* are private and visible by default, i.e. the users are able to see a description of the metadata, but are not able to download it.

8. Submit data and Link Kinetic Models

Users can contribute and submit data to the database using the manually-assisted "*web platform submission*" form or the "*paper form submission*" (Figure 8.1) using an Excel template file. The user can download the Excel file to see instructions how to prepare the data to submit. The users use the Excel file to adjust your own data to the predefined structure (see examples on the template file for each different data type). **Experimental data accepted by this database inlude metabolite concentrations (steady-state and time-series), flux data and enzyme measurements that support an article or study.** Journal publication is not a requirement for data submission to *Ki*MoSys.

Note that **submitters are responsible for the description of the data and their associated models**, **as well as for any content that is you uploaded and submited. *Ki*MoSys** team will take every care to preserve private data and models stored in the repository but **we will not be liable for loss of data.** Note that for operational purposes **we may make a backup copy of them**.

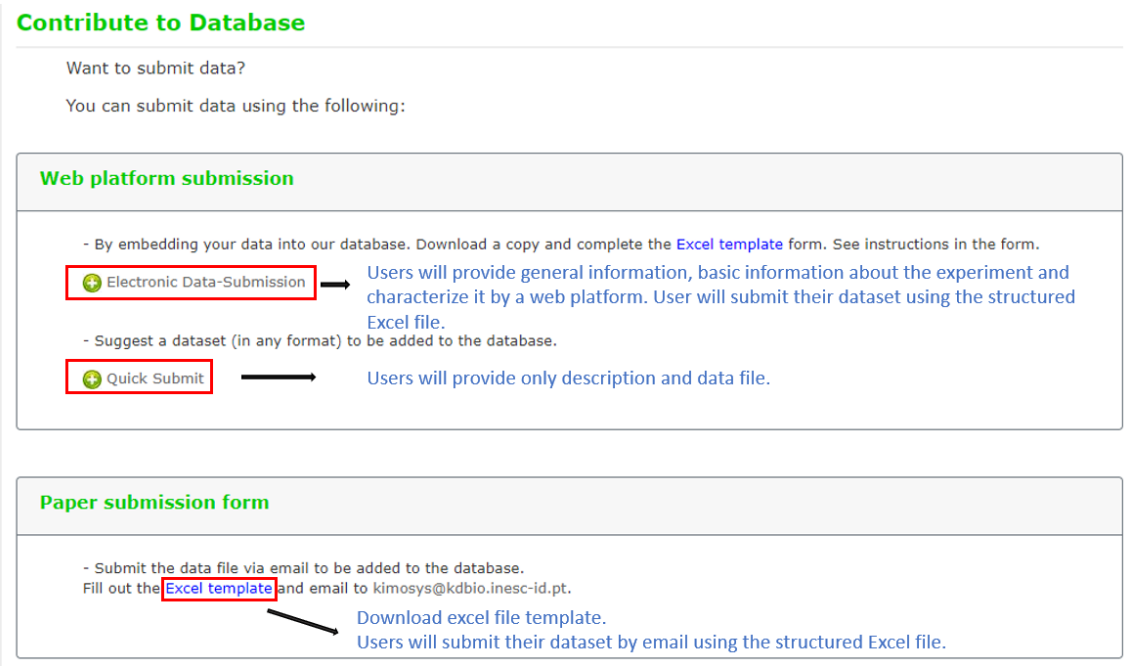


Figure 8.1: Submit a new data in the database. Three options are available: web platform submission (automatic submission and quick submit) and paper form submission.

8.1 Web-submission form

Users can submit data directly into the database by clicking on the green plus sign (see Fig. 8.2). The *electronic data-submission* form (online-guided submission) is **based on a structured template** to encourage the deposition of available metadata and the use of standards.

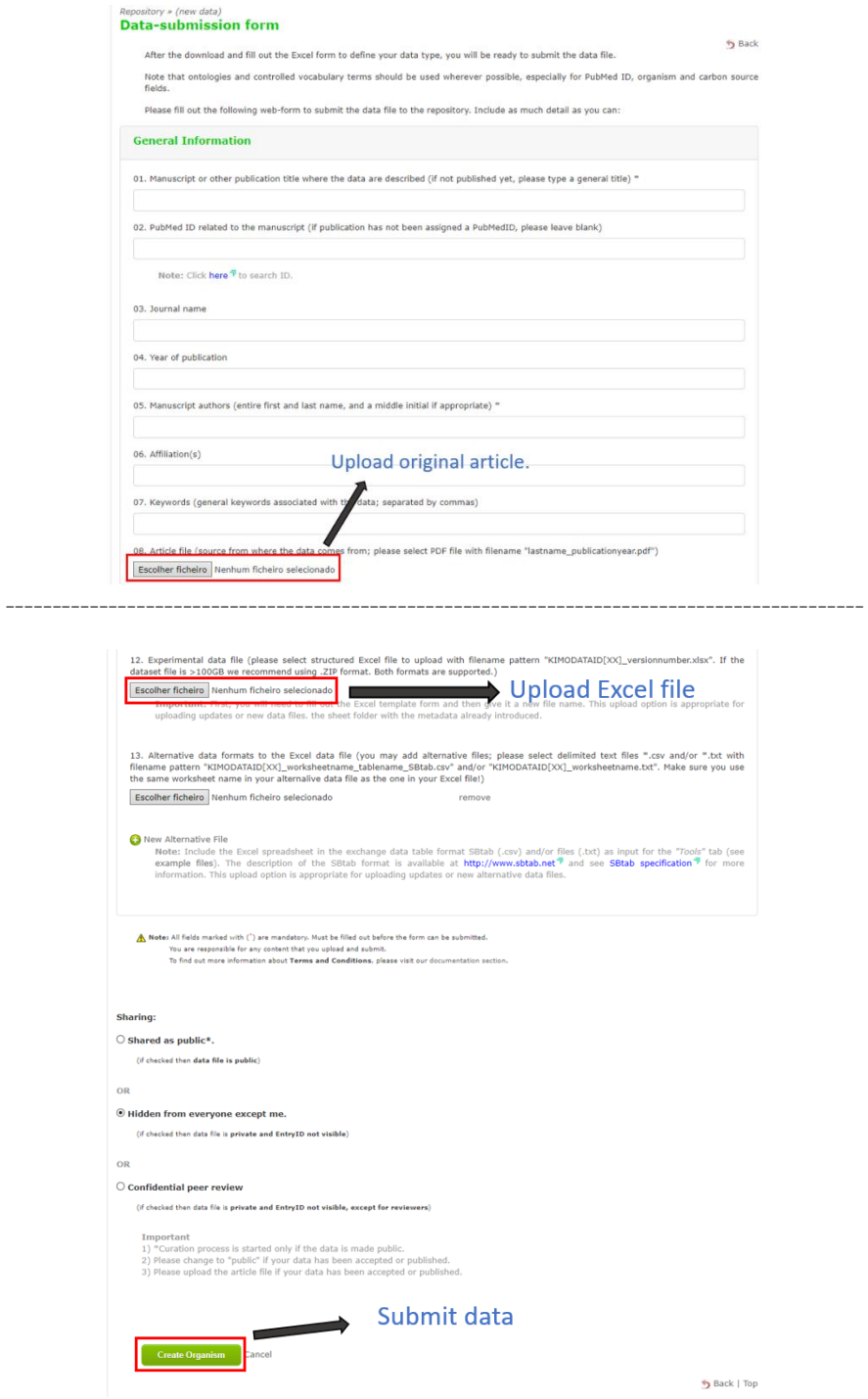


Figure 8.2: Submitting data page in the electronic web platform.

The Excel worksheets are in a format to allocate metadata and the data in a predefined template (see example Figure 8.4). The Excel file name will be saved with file name pattern "*KIMODATAID[XX]_versionnumber.xlsx*". After fill out the Excel form (including experimental data, information about the experiment, and corresponding metadata with annotations links to other databases and ontologies) to define the data, the user will be ready to submit the data file. Biological ontologies and external databases used in ***Ki*MoSys** are ChEBI [3], KEGG [4], UniProt [5] and NCBI organism taxonomy [6]. The user need fill out all mandatory fields (see section 4) marked with a red asterisk before submit the data, upload the complete Excel data file and click the *[Send Data]* button**.** Additionally, the user may upload alternative file formats with the following extensions .csv and .txt. For this, the structured Excel file will be modified to conform to the SBtab (http://www.sbtab.net) exchange format (.csv) and as .txt input file of the "*Tools"* tab (only for the metabolites at steady-state and flux data). SBtab format is a proposal to establish an easy-to-use format that is flexible and clearly structured. It comprise defined tables for different kinds of data, database identifiers used for annotation, syntax rules and standardised formulae for reaction stoichiometries. Please check the SBtab documentation (http://www.sbtab.net/documents/SBtab_Specification.pdf) for more details

After submitting the data, users have also the option of selecting which collaborators (if any) may have access to the data while it is still private. Note that, **only after the data shared in public mode the curation process is started**. The database curators read the publication to review whether correct information has been captured and adjust the data file to ***Ki*MoSys** standards to avoid inconsitencies (with the help of the submitter). Care is taken to ensure that the files are in appropriate format and the metadata are correctly linked. Every change on the Excel data file upload on the *[Edit]* page is saved as a new version with the database showing the current version by default. Subsequently, the curators change the status of the *Data EntryID* from "*unreviewed*" to "*reviewed*". After this the ***Ki*MoSys** curator emails the submitter to inform that the *Data EntryID* is reviewed. When the submission is approved, the users can cite the data accession number.

Note that only register users can submit data via *electronic data-submission form*. If you do not already have a ***Ki*MoSys** acount, create one (see section 4).

In summary, to deposit new data to ***Ki*MoSys** via **electronic web platform** the user need follow these steps:

1. **Create a user account or Login.**
2. **Select "*Electronic Data-Submission*".**
3. **Download an "*Excel template*" copy.**
4. **Choose appropriated data type template.**
5. **Complete the Excel spreadsheet template (metadata + data).**
6. **Fill out the web-form and upload the data file.**
7. **Submit the data.**
8. **Needs to be confirmed by a curator.**
9. **After the curation process the *Data EntryID* are marked "*reviewed*" and a DOI is assigned.**
10. **Curator emails the submitter to inform that the *Data EntryID* is reviewed.**

A **quick submitting** form is also available to alert us to publications (datasets and/or associated kinetic models) that we might have missed. In this case you don´t need a ***Ki*MoSys** account. Fill out all mandatory fields (see Figure 8.3) marked with a red asterisk (description of the data, data file in any format and email) and click the *[Submit]* button. After a curation step (verification of results and maybe discussions with the submitters to ensure there is no information ambiguity) the data will then be submitted by the administrator to the ***Ki*MoSys** repository.

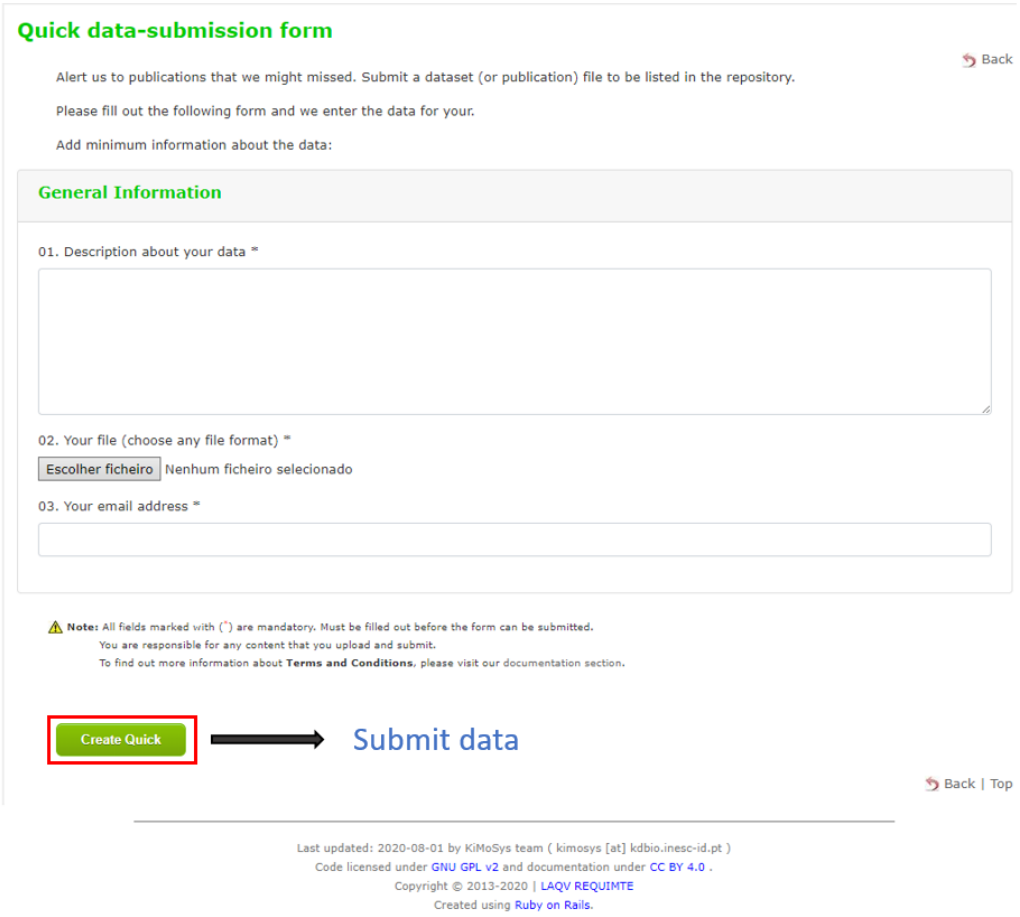


Figure 8.3: Quick submitting page.

8.2 Paper submission form

The user can also submit their data by simply send the Excel file by email to kimosys@kdbio.inesc-id.pt. The structured Excel file template (e.g. for metabolites at steady-state, Figure 8.4) can be downloaded by clicking on the "*Excel template*" link. The Excel file includes two worksheets (metadata + data), which the user needs to fill out. After a manual curation process the data file and related experiment information will then be added by the ***Ki*MoSys** team to the database.

Note that **for the paper form submission** for data not published the user needs to **fill a term of agreement and responsibility** before the data can make public.

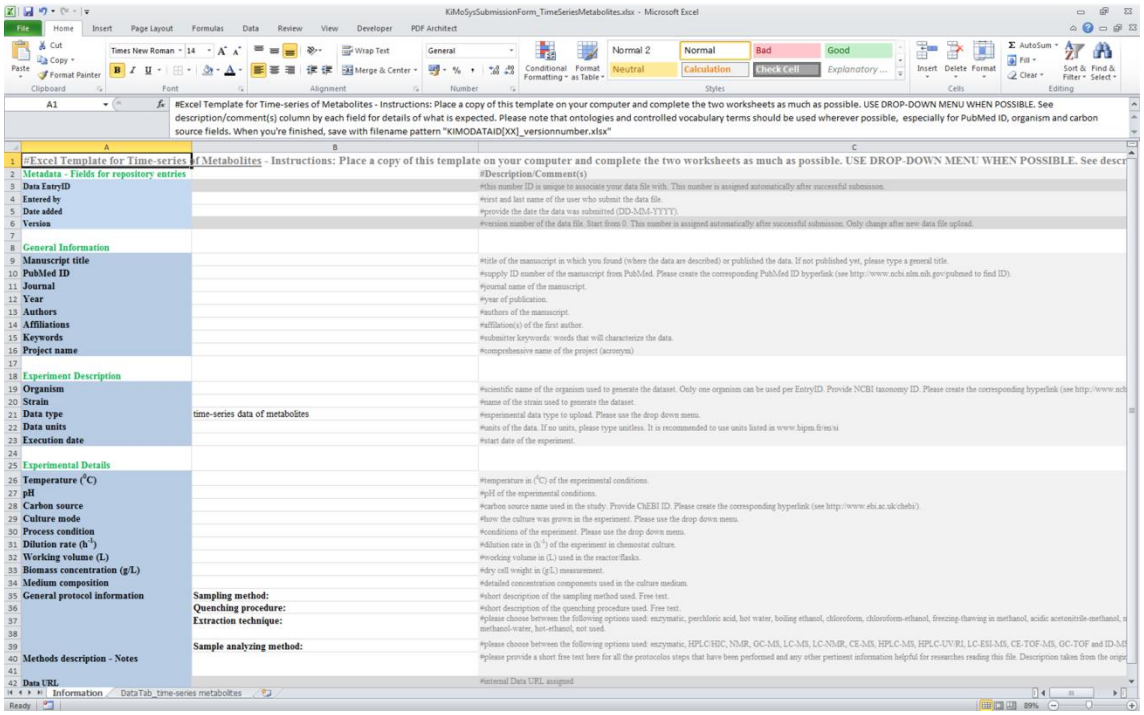


Figure 8.4: Example of the structured Microsoft Excel template file for time-series of metabolites. In the first worksheet users will provide general and basic information about the experiment and characterize it (metadata). In the following worksheets users will provide the experimental datasets (including names, units, unique ChEBI identifiers for annotation) and a short description of the data.

In summary, to deposit new data to ***Ki*MoSys** via **paper form** the user need follow these steps:

1. **Download an "*Excel template*" copy.**
2. **Choose appropriated data type template.**
3. **Complete the Excel spreadsheet template (metadata + data).**
4. **Submit the data file via email to kimosys@kdbio.inesc-id.pt.**
5. **Fill a term of agreement and responsibility.**
6. **We curate, assign *accession number* and add data to the database.**

These options encourage the community to submit their own experimental data files to be included in the repository and to expand the database to cover many more data in the future. **It is possible to submit your own data and also from older articles by any community member whether or not the user is a co-author of the paper.**

8.3 Associated models with data

For each *Data Entry ID*, the user can associate several models by clicking on the *[New Model]* button (see figure 6.4). **Note that registered users can only associate kinetic model to existing data (*Data Entry ID*)**. Journal publication is not a requirement for model submission to ***Ki*MoSys**.

The minimum fields to submit models are more or less the same as they are for data. Here the user can also upload several intermediate files of the final kinetic model by providing a simple history of changes. Note that only SBML, CellML, Matlab-ZIP and CopasiML model formats can be uploaded. The model file name will be saved with file name pattern "*KIMOMODELID[XX].extension*". If the model file is obtained from BioModels [1], JWS online [2] or Physiome model database, original model file name must be maintained (e.g. BIOMD0000000051.xml). Since ***Ki*MoSys** can refers to the original source of kinetic models these are linked back to the original source. Fill out all mandatory fields (marked with a red asterisk) and click the *[Send Model]* button. After that, the database annotators read the publication to validate the model submission and to avoid inconsistencies. Note that, **only after the model shared in public mode the curation process is started**. Similar to the data submission process, every change on the model file upload (*[Edit]* page) is saved as a new version with the database showing the current version by default. After the curation process, the ***Ki*MoSys** curators change the status of the *Model EntryID* from "*unreviewed*" to "*reviewed*". After this the ***Ki*MoSys** curator emails the submitter to inform that the *Model EntryID* is reviewed. When the submission is approved, the users can cite the model accession number.

Administrators and submitters are notified in real time via email (see example Figure 8.5) when data and/or associated kinetic models are submitted to the repository. In addition, the project collaborators are notified when they are invited to a specific data or model *EntryID*.

From: kimosys@kdbio.inesc-id.pt
To: Kimosys user
Cc:
Subject: [KiMoSys] New information

Confirmation

The following experimental data was successful submitted to the repository

Data EntryID: 79

Organism: Escherichia coli

Access: Public

Type of Data: time-series data of metabolites

Dataset file name: KIMODATAID79_v0.xlsx

User: kimosys@kdbio.inesc-id.pt

Data URL

Thank you for supporting KiMoSys repository!!

KiMoSys team.

Figure 8.5: Example of an email confirmation after a new data submission.

In summary, to submit a new model the user need follow these steps:

1. **Create a user account or Login.**
2. **Fill out the web-form and upload the model file(s).**
3. **Submit the model.**
4. **After the curation process the *Model EntryID* are marked "*reviewed*" and a DOI is assigned.**

8.4 Submitter rights

Note that the submitters determine the access level, so some *EntryID´s* may only be viewed by team member(s). The submitter of the *EntryID* item can update and/or *edit* **your existing data and associated model records (*EntryID* fields) at any time**, *invite* users , and remove the *EntryID* (see Figure 6.6). **Note that submitters are not permitted to remove your *EntryID* made public.** Submitter can also remove invited members by clicking the [(×)] button in the "submission and curation" section. Invited users with permission (team members, editors or reviewers) per *EntryID* can access the private data and/or model submissions, and update their related fields at any time. Fields can be

changed by clicking on the *edit* icon  . However, team members cannot invite other users to this *EntryID*.

Administrators are editors who have access to all data and associated models information for all *EntryID´s*. They are able to add, edit and delete entries. However, we not make data and models public available without submitter consent (see Section 8 for more details).

8.5 How the users delete your data and models?

The submitter can just use the delete button  when they are displayed (i.e. for data and model *EntryID* that have been made private). After a data and/or model is publicly deposited in ***Ki*MoSys**, it is permanently stored and can never be deleted only modified.

9. Tools

***Ki*MoSys** provides a number of operations to the first metabolic kinetic modeling steps, including semi-automated kinetic rate equations generation and model network reduction. Furthermore, it allows for adding automatically all metabolite and flux values in the rate reaction. The tools available appear after the user clicks the "*Tools*" tab and their goal is to go from metabolic networks to kinetic models.

9.1 Model reduction

The use of the "*Model reduction" tool* requires tree input files:

1. Select and load an SBML model file (metabolic network) OR upload directly a SBML file stored in the ***Ki*MoSys** repository.
2. Load the flux distribution (e.g. obtained from FBA) text file (first column contains the flux/reaction names and the second column the flux distribution values) for the SBML model.
3. Define the metabolite names to remove.

Note that the metabolites names to remove and flux/reaction names in the text files must coincide with the names included in the SBML.

To use this tool click on "*Reduction*".

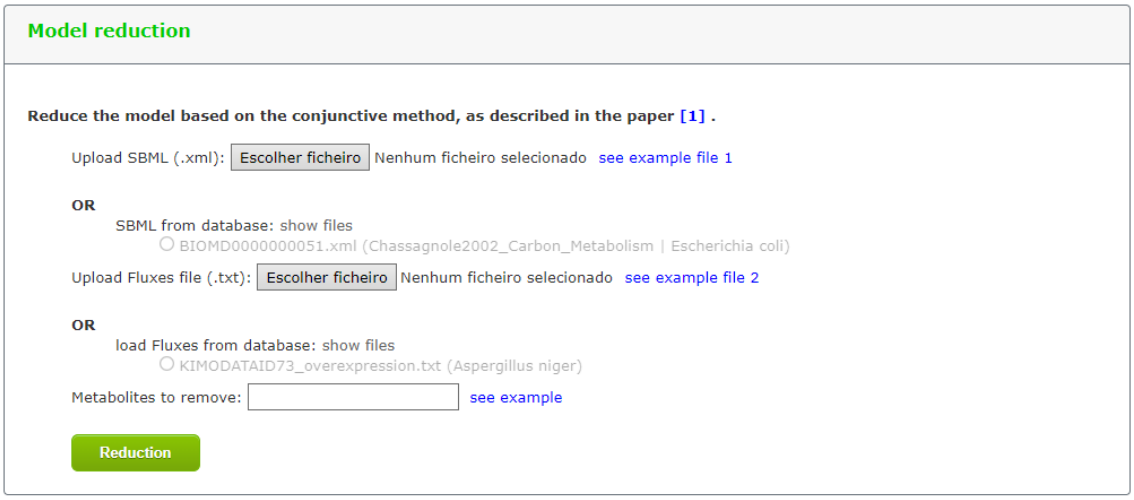


Figure 9.1: Model reduction tool as described in [7].

Output files:

1. Reduced SBML model file ("reduced_model.xml").
2. New flux distribution of the reduced model ("new_fluxes.txt").

Save the .zip file that includes the two files.

9.2 Add metabolites

The use of the *Add metabolites* tool requires two input files:

1. Load the SBML model file OR upload directly a SBML file stored in the ***Ki*MoSys**.
2. A text file with known reference metabolite names (as defined in SBML file) and their associated values to set in the model is needed as an input (first column contains the metabolite names and the second column the metabolite values). Load a text file OR upload directly a metabolites (at steady-state) text file stored in the ***Ki*MoSys** repository. Note that the metabolites names must coincide with the names included in the SBML.

To use this tool, click on "*Set*".

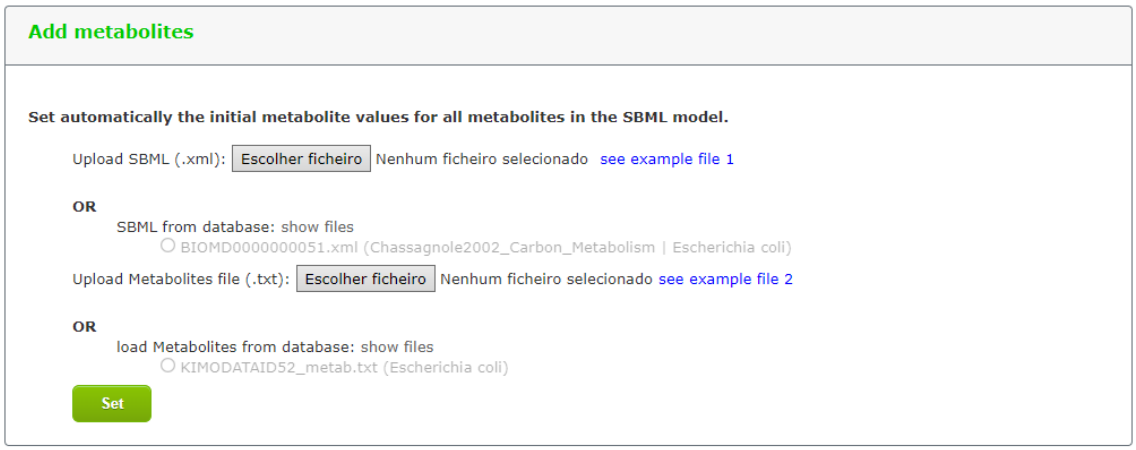


Figure 9.2: Setting automatically the initial metabolite concentration values into rate equations according to each reaction.

Output file:

The SBML output file gives the model with the reference values for metabolites (output_file.xml). Save the file.

9.3 Translate kinetic equations

The use of the *Translate kinetic equations* tool requires two input files:

1. Select the file to load SBML model input OR upload directly a SBML file stored in the ***Ki*MoSys** repository.
2. Select the kinetic type from the list. The user can specify between the convenience [8], linlog [9] and mass action [10] kinetics.

To use this tool click on *Convert* button to generate all kinetic equations.

Figure 9.3: Generate automatically approximated rate equations based on the stoichiometric matrix of the network.

Output file:

The standard SBML output file is produced automatically (kinetic_model.xml). Save the file. It gives the rate equations for all the reactions in the model. All the kinetic parameter values in the corresponding kinetic rate law are initiated with 1 by default.

9.4 Add fluxes

The use of the *Add fluxes* tool requires two input files:

1. Load the SBML model OR upload directly a SBML file stored in the ***Ki*MoSys** repository.
2. A text file with the reference flux/reaction names (as defined in SBML file) and their associated values to set in the model (first column contains the flux/reaction names and the second column the flux distribution values). Load a file OR upload directly a flux text file stored in the ***Ki*MoSys** repository. Note that the flux/reaction names must coincide with the names included in the SBML.

To use this tool click the "*Set*" button.

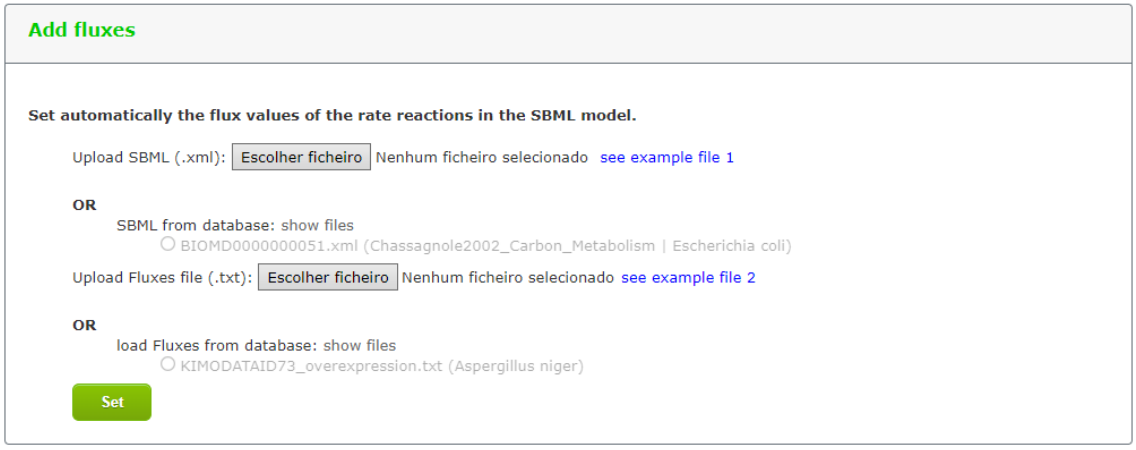


Figure 9.4: Setting automatically the flux distribution values into rate equations according to each reaction.

Output file:

The SBML output file gives the reduced kinetic model with the reference flux values (output_file.xml). Save the file.

The final created kinetic model (SBML file) can then be open, and further parameterized and/or analyzed by various free external software tools (see examples at the Links tab).

9.5 Model simulation

By clicking on “simulation”, the dynamic simulation interface will appear. There are three simulations available:

- Time-course simulation for metabolites
- Time-course simulation for reaction fluxes
- Steady-state

It is possible to simulate the SBML kinetic models present in the repository, or an uploaded SBML model. For the time course simulations, you can select the initial time, duration and number of steps, as well as download the .CSV file of the simulation results. You can also select/deselect all the elements present in the plot.

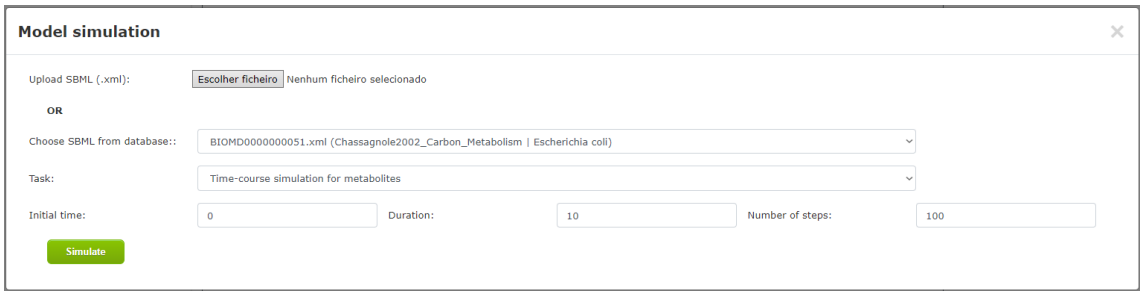


Figure 9.5: Kinetic model simulating interface.

10. Links

Helpful external links to tools for dynamic modelling, including available simulation software packages and other databases can be obtained on the *[Links]* tab.

11. License Information

11.1 Terms and condition of use

***Ki*MoSys** platform is copyrighted by the team developing the resource under license GNU GPL *v2* (http://www.gnu.org/licenses/gpl-2.0.html). The source code is all available (see *Documentation* page). However, each individual data and model file retains the copyright assigned by the biologists that measures the data and the creators of the kinetic model, as well as the author(s) of the reference publication. **Moreover, when the data (and/or model) files are shared by the submitter as public, they understand that public data**

(and/or model) is freely available by any other user and for any purpose under the term of the Creative Commons Attribution License (http://creativecommons.org/licenses/by/4.0/). ***Ki*MoSys** team not assumes responsibility for any purpose for which they are used and for copyrighted material. ***Ki*MoSys assumes that the submitter has received any necessary consent authorizations required prior to submitting the data and/or model.**

All users accept the risk and responsibility for the accuracy, completeness, or lack thereof, of any submitted information. In addition, any contribution to ***Ki*MoSys** repository must be appropriate for sharing with the systems biology community. Access to the ***Ki*MoSys** web site is granted free of charge for academic purposes. Users for commercial purpose please contact the ***Ki*MoSys** team.

For any questions regarding our privacy or data usage policies feel free to contact ***Ki*MoSys** team through our web form (see *Contact Us* tab).

11.2 How to cite data and models?

Any publication created through usage the source of a specific data or model should **cite the original paper reference**, and also cite the data and/or associated model using a format similar to the following examples:

1) Example to reference a specific data

"The data was downloaded from KiMoSys repository http://kimosys.org [1] (KiMoSys (https://kimosys.org). (2020, August 4). Data EntryID 30 (Escherichia coli). https://doi.org/10.34619/7pa6-va85)" (e.g. using APA citation style).

2) Example to reference a specific associated model

"The model was downloaded from KiMoSys repository http://kimosys.org [1] (KiMoSys (https://kimosys.org). "Model EntryID 13 (Escherichia coli)." 2020, https://doi.org/10.34619/3y5p-9947)" (e.g. using MLA citation style).

On the other hand, for **referencing a submitted data and/or associated model** we recommend adding the following to the manuscript:

"The data (or model) have been deposited to the KiMoSys repository (http://kimosys.org) [1] with the dataset identifier Data EntryID XX (or model identifier Model EntryID xx). Doi:XXX"

12. Acknowledgements

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13. References

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