rBioNet 1.0
Manual

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May 24, 2011

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1 About

The rBioNet is a Matlab based GUI to create reconstruction models and manage internal databases. It is assumed for this manual that the user has basic knowledge of systems biology and is familiar with the COBRA Toolbox. It was created with a few rules in mind that can be used in describing it's usage:

- 2 databases, one with metabolites and another with reactions.
- Reactions can only contain metabolites from database.
- Reconstruction models can only use reactions from database.
- No duplicate entries can exist in database.

ReconstructionTool: is the tool used to interact with your local database. Metabolites and reactions in the database can be used in reconstructions. While populating the database variety of tests are done: balance checks, checks for duplicities, reaction similarities. For instance the quality control system makes it impossible to add the same reaction under two different abbreviation to the database.

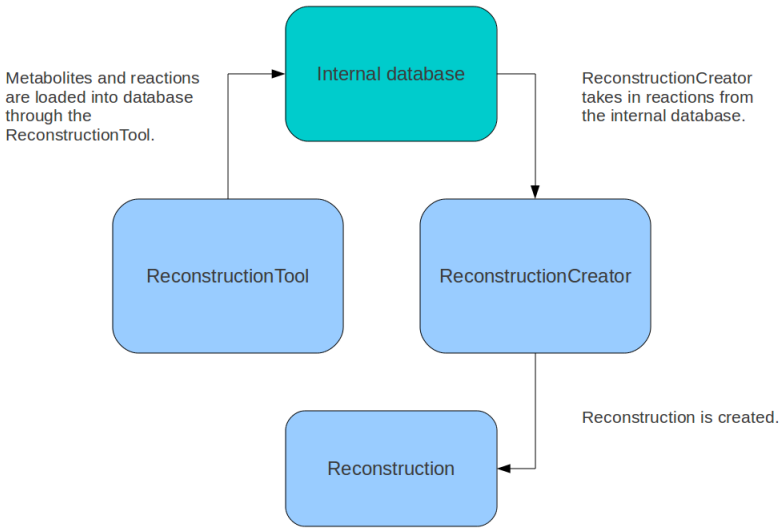

Figure 1: Diagram of the rBioNet

ReconstructionCreator: is the tool used to create COBRA based reconstructions. Here reactions are added to models, GPRs are created, description is set and reconstructions can be analyzed. Everything from Sparsity matrix of S to viewing all neighbor reactions.

Created by Dr. Ines Thiele and Stefan G. Thorleifsson.

2 Setup

Unzip your rBioNet with winzip, winrar or any other compatible program, it's recommended to put rBioNet in your COBRA Toolbox folder. Add to Matlab path /rBioNet and /rBioNet/inc. To do so go to the menu bar, select File - Set Path and click Set Path with Subfolders, find the rBioNet and click Ok. Another way is to use the command addpath, for more information

```
>>doc addpath
```

The next thing you need to do is set the directories of your databases. This is done with the rBioNetSettings file. Start the program.

```
>>rBioNetSettings
```

Possibly you will be promted for the Settings file. It's named rBioNetSettingsDB.mat and can be located in the /rBioNet folder. The standard database files are rxn.mat, metab.mat and compartments.mat and can be located in rBioNet/inc. Click Change and select these three files and you are ready to go, don't forget to initialize the COBRA Toolbox (>> initCobraToolbox).

>> means command is written in Matlab Command Window.

3 Basics

3.1 ReconstructionTool

The Reconstruction Tool is an interface to help users interact with the metabolite and reaction database. It's main function is to add new metabolites and reactions to database, there are three methods to populate the database:

- Create metabolites/reactions one-by-one in a simple manner, detailed description: How to create metabolites/reactions.
- Add multiple metabolites/reaction simultaneously, detailed description: How to use text files.
- Add a complete reconstruction model via text files, detailed description: Previous reconstructions.

All new items go through a series of tests before being saved into database:

- Similarity: User is notified if new items are similar (charge formula or reaction formula) to existing items in database.
- Abbreviation: User is notified if abbreviation already exists in database.
- Reactions go through a balance check.

Open the Reconstruction Tool by typing:

```
>>ReconstructionTool
```

in the Command Window. In the beginning you may notice three buttons

[Reaction View Table] [Metabolite View Table] [Metabolite/Reaction]

The first two change the View Table (upper table) between the reaction and metabolite databases. Click [Refresh / Show All] to view all metabolites or reactions. The third button mentioned changes between panels where metabolites and reactions are created. The reaction panel is set as default.

3.2 ReconstructionCreator

This is a tutorial that goes through the basics steps needed to create systems biology models. Don't be afraid to click around.

3.2.1 Saving and loading options

The Reconstruction Creator has two loading and saving options. The obvious option is to save it as an complete reconstruction or in other words as a model. The other option is saving as an mat file. This option is used when a reconstruction needs to be saved but is not ready to be saved as a model. This can happen e.g. when starting from a previous reconstruction which contains reactions or metabolites that are not present in the database. Now you could have guessed that the 2 loading options are a complete reconstruction (model) and mat file. Do not load mat files that where not created in the rBioNet. However, it is possible to load any model into the Reconstruction Creator as long as it was created with COBRA Toolbox.

Technically complete reconstructions are also mat files (saved under that format) but here we call incomplete models mat files and complete ones reconstruction models.

These options can be found under *File* → *Save* and *File* → *Open Reconstruction* in the menu bar.

3.2.2 Getting started

Start Matlab and start the Reconstruction Creator by typing

```
>>ReconstructionCreator
```

into the Command Window. Now you can see a big empty table, when reactions are added to models they fill up that table. It is worth mentioning that the first column called Enable makes it possible to disable certain reactions in models without removing them. They will be saved in reconstructions but not be active.

There are two panels under the table, Edit Reaction shows all the properties that can be changed before reaction is added to model and the Reaction Properties shows those that cannot. Reactions are loaded in via [Load Reaction], modified and then added to model by clicking [Add Reaction]. The two buttons on the upper right refer to the reconstruction table, remove a reaction or load it back in to the workspace to be altered.

At the bottom right there are two buttons, [Description] where you can add a detailed description to your reconstruction and [View Genes] where you can view all the genes in gene index and model and see what reactions they are connected to.

3.2.3 Adding reactions

Click [Load Reaction]. Search for a reaction that includes ATP by changing the search column from Abbreviation to Formula in the pop-up menu and type in ATP where it says *Search for* and click [Search], the search engine is not case sensitive. Select ACS or any reaction of your choosing, but make sure to only have one line selected and then click [Load Reaction]. Note: The popup window uses the uiwait command, that means that all commands Matlab recieves are put on hold until the window is closed.

Default UB (upper bound) value is 1000 for all reactions and LB (lower bound) is 0 for non reversible and -1000 for reversible reactions. All properties in the Edit Reaction panel can be changed, notice the More Properties button. To add this reaction to model click [Add Reaction].

Now let us add a GPR to our reaction, on detailed information on GPRs see How to create GPRs. Start by loading in a Gene Index, click File - Load Gene Index and select the sample file ExampleGeneIndex.txt in the Examples folder. Next click [Create GPR]. Select a few genes in the upper table and click Add Genes. The genes will appear in the lower table which is the work area. Select Genes in the work area and group them be clicking Group And or Group Or. Continue until only one line remains in work space then click Finish. Now select [Add Reaction] and overwrite the reaction in the model.

Hopefully this guide has given you some insight into the functionality of the rBioNet, however the best thing you can do is to play around with it. You could open the Ecoli model in the Examples folder. Remove, disable, edit and add reactions. Save it as an complete reconstruction and inspect the changes in the Reconstruction Analyzer.

4 FAQs

4.1 Previous reconstructions

When dealing with previous COBRA reconstructions the rBioNet is very agile. If all the reactions and metabolites are already in database you can load it directly into the ReconstructionCreator. If not however it is possible to go to the ReconstructionTool, File menu - Add reconstruction To Database, select the reconstruction and the rBioNet will automaticly load it into addmetabolites and addreactions scripts, used when adding text files. You reconstruction will need to have the compulsory data (see How to use text files).

4.2 SBML files

If you want to use SBML models in the rBioNet it must first be converted to .mat format. To do so you need to have the SBML Toolbox installed and use readCBModel.m from the COBRA Toolbox. Further information needs to be optained from their developers.

4.3 How to create reactions

A reaction can be created from scratch or by loading a reaction from database.

From scratch: Select a metabolite in the metabolite database (upper table), in the Metabolite panel below, set compartment, reaction side and coefficient, then click Add. It will appear in the lower table. Continue adding metabolites until the reaction is complete. To remove a metabolite from the new reaction, select it in the lower table and click Remove. Specify reaction abbreviation, description and other necessary properties. To finish click Save reaction.

Notice: Click More Properties in the Reaction panel to see reaction notes, references, EC number and KeggID.

Program tests for: Abbreviation duplicity, reactions charge/mass balance and similar reaction formula, in that order.

Load reaction: Select a reaction in the database and click Load Reaction. Edit metabolites until the reaction is complete. Specify reaction abbreviation, description and other necessary properties. To finish click Save reaction.

Program tests for: Abbreviation duplicity, reactions charge/mass balance and similar reaction formula, in that order.

4.4 How to create metabolites

Click [Metabolite/Reaction] to get the metabolite panel up. Fill out the metabolite properties. Properties marked with star (*) are compulsory. Click Save Metabolite to finish. To start from a metabolite in database select it in the upper table and click Load Metabolite. Note that all properties are imported.

Program tests for: Abbreviation duplicity and similar charge formula.

4.5 How to use text files

Multiple metabolites and reactions can be added to database simultaneously with text files. Data from Excel can be copied directly to Notepad/Gedit/TextEdit. Columns are divided by tabs and one metabolite (or reaction) per line. Properties are arranged in same order as in database. Time properties are added automatically. Inspect the example files before creating your own text files.

4.5.1 Metabolites:

Open the Reconstruction Tool and go to the menu bar and select

```
File -> Add text file -> With Metabolites.
```

Click Load text file and open your reaction text file. Properties must be in same order as in table. Metbolites can be edited in table. Remove metabolites by clicking Remove line. The fields marked with (*) need to be filled out: Abbreviation, Description, Charged Formula and Charge. Click Continue. You will get a notice of metabolites in database with the same charge formula as your metabolites and also if the abbreviation exist. If everything is acceptable just carry on.

Program tests for: Abbreviation duplicity, reactions charge/mass balance and similar reaction formula, in that order.

4.5.2 Reactions:

Open the Reconstruction Tool and go to the menu bar and select

```
File -> Add text file -> With Reactions.
```

Click Load text file and open your reaction text file. Properties must be in same order as in table. Reactions can be edited in table. Remove reaction by selecting it and then clicking [Remove Reaction]. Click Perform Check. Similarities are displayed in lower table. Click Finish if similarities are acceptable.

Program tests for: Abbreviation duplicity, reactions charge/mass balance and similar reaction formula, in that order.

Note: Program does not check for reaction formula uniqueness of the text file. For the time being authors are responsible for not having the same reaction formula under different abbreviations in their text file. Remember when adding reconstruction models to database it is done through the text file scripts, so this applies for that as well. This will be added in future updates.

4.6 How to create new compartments

Go to the menu bar and select

```
Edit - Compartment.
```

Remove: Select a compartment in the pop-up menu and click Remove.

Create new compartment: Write compartment name in edit window to the left, marked Name, specify abbreviation letter to the right, marked Abbreviation.

Note: Do not use space or brackets. Abbreviation can only have one character.

4.7 How to add and remove reactions

Add: Start by clicking Load Reaction. Find the correct reaction in the pop up window, select it and click Load Reaction. Edit the reaction in the Edit Reaction panel. Notice the More Properties button. To assign GPRs see: How to create GPRs. When reaction is ready, click Add.
Remove: Select a reaction in the Reconstruction table and click Remove Reaction.

4.8 How to create GPRs

GPRs are created from gene indexes. Gene indexes can be loaded in to the Reconstruction Creator along side loading complete reconstructions or separately through File - Load Gene Index. The Gene index is a text file with

information to help users create GPRs. One gene per line and columns are in the following order: Locus name, gene symbol, Chromosome, 5th coordinates, 3rd coordinates, gene type and putative function. Locus name is compulsory but everything else optional. Columns are divided by tabs. Please inspect the ExampleGeneIndex.txt before creating your own gene index file. Next click Create GPR. In the upper table select one or more genes and click Add Genes. Multiple genes can be selected by holding down Ctrl, Shift or by dragging with the mouse. Notice how the genes appear in the lower table. The lower table contains wanted genes. There they are grouped to form GPRs by using the following buttons:

- Group AND: Groups selected genes with and.
- Group OR: Groups selected genes with or.
- Remove Genes: Removes unwanted genes from lower table.
- Scatter: Breaks down GPRs to genes.

When done only one line is allowed to remain, click Finish. The GPR is automatically loaded into the edit box next to the Create GPR button.

5 Applications

5.1 External links to databases

Link to database: by selecting a metabolite or reaction you can right click and select reference database if item in question has reference in any of the database fields (EC number, KeggID, PubChemID, CheBlID or HMDB) then Matlab will automatically open the item on the selected database in the computers default web browser.

Note: to use this option the metabolites and reactions must include the database IDs when they are added to the rBioNet database.

5.2 Reconstruction Analyzer

Reconstruction Analyzer is a tool solely based on COBRA functions, to make it easier to study a reconstruction. The reconstruction must be compiled (Save as reconstruction model) or loaded (Open reconstruction model) in the ReconstructionCreator, then find the Reconstruction Analyzer in the menu bar. Applications available:

- Find and fix dead ends. Go through the list of dead end metabolites and see if there is a an exchange reaction available in the database. The Add button will be enabled if it exists.
- The binary stoichiometric matrix.
- Distribution of node connectivities (2nd tab). In the table Metabolite Connectivity the list can be viewed. Click Plot to plot the data and select the nodes (on the graph) to see their names. Press Esc or return to stop.

- Neighbor reactions (2nd tab): Brows reactions on the listbox on the left and see all there neighbor reactions. Metabolites that the neighbor reactions share are listed under 'Metabolites' in the table to the right. For large databases finding all neighbor reactions can take some time.