CySBGN Tutorial

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Introduction

CySBGN allows Cytoscape users to import, validate and export the layout of SBGN diagrams stored in SBGN-ML format. This plug-in extends Cytoscape features to SBGN diagrams as shown in the last section of this tutorial.

CySBGN dependencies are:

- **LibSBGN** allows CySBGN to read, query, save and validate SBGN-ML files.

- **CySBML** is necessary for the automated conversion of SBML into SBGN, where CySBML is used to import SBML models into Cytoscape.

- **SBFC** stands for Systems Biology Format Converter and is also vital for the automated generation of SBGN diagram form a SBML model. SBFC is responsible to convert the SBML model file into a SBGN-ML file.

CySBGN is developed in Java and it is available under GNU GPL v3 license. Further information is available on plug-in's webpage www.ebi.ac.uk/saezrodriguez/cysbgn/

How to download and install CySBGN

CySBGN can be downloaded and installed from its webpage or directly within Cytoscape using Plugins Manager.

Cytoscape recommended version: **Cytoscape v2.8.3**

From the webpage

1. Download CySBGN from http://www.ebi.ac.uk/saezrodriguez/cysbgn/

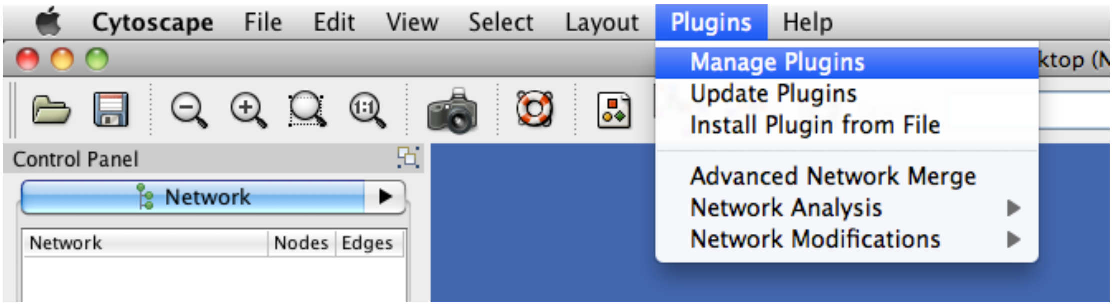
2. Save the ***CySBGN-vX.X.jar*** in Cytoscape plugins folder. By default is:
    a. **Windows**: “C:\Program Files\Cytoscape-v2.x.x\plugins\”
    b. **Mac OS**: “/Applications/Cytoscape-v2.x.x/plugins/

3. Restart Cytoscape.

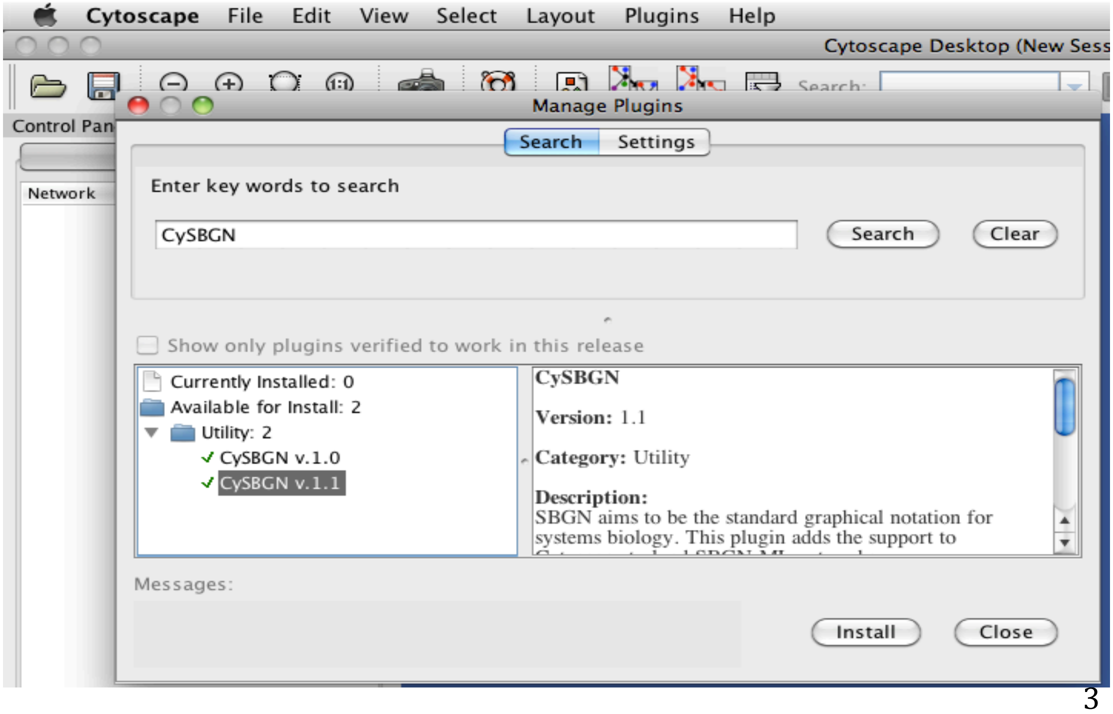
From Cytoscape

Within Cytoscape:

1. Go to Plugins Manager



2. Search for CySBGN and click **Install** button



Enter key words to search

CySBGN

☐ Show only plugins verified to work in this release

CySBGN

Version: 1.1

Category: Utility

Description:
SBGN aims to be the standard graphical notation for systems biology. This plugin adds the support to

Installing CySBGN dependencies

The last step in **CySBGN** installation is to install its dependencies. **CySBGN** requires **CySBML** to allow the automated conversion of **SBML** files into **SBGN** diagrams.

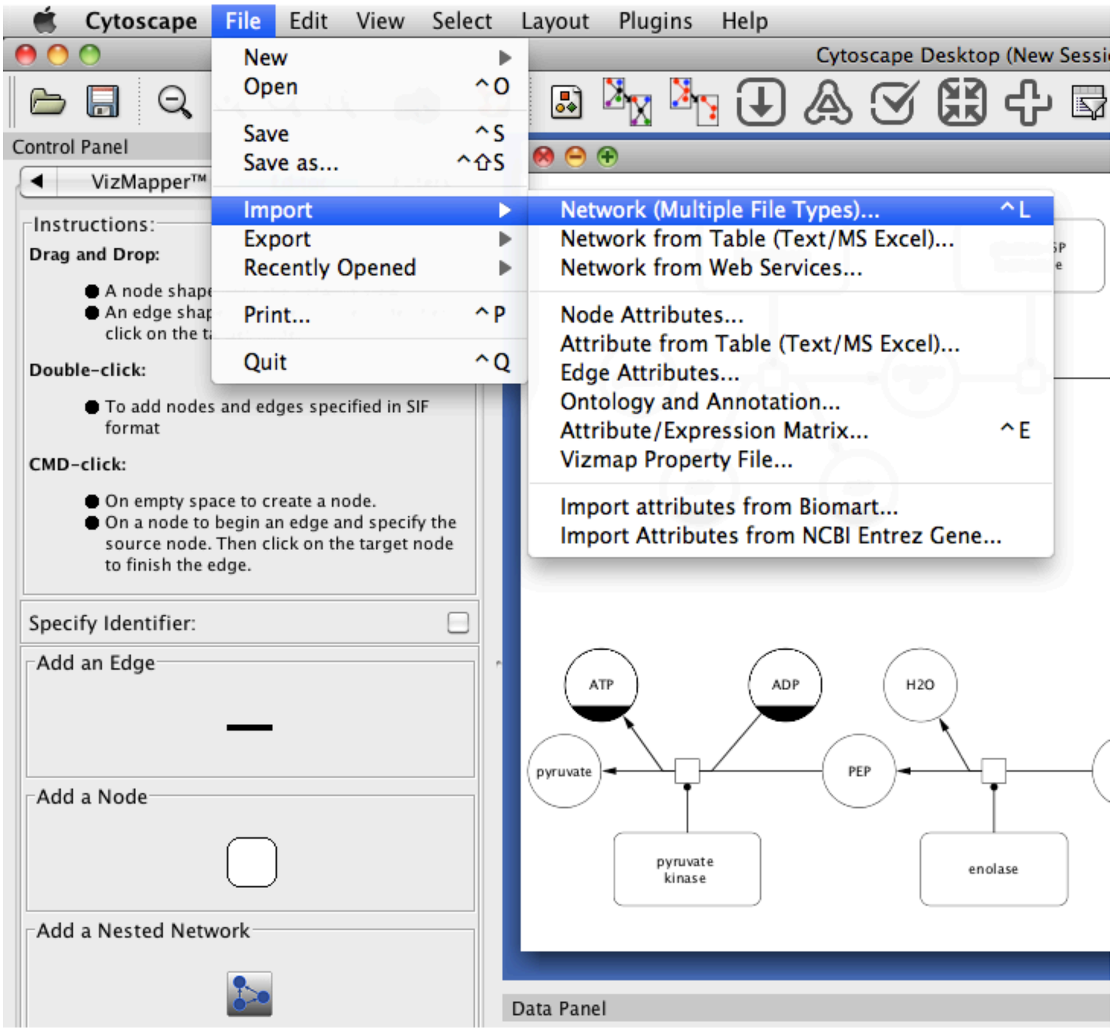
1. The fully supported version of CySBML can be **downloaded** in CySBGN webpage (http://www.ebi.ac.uk/saezrodriguez/cysbgn/) in Download section.

2. **Save** the ***CySBML-vX.X.jar*** in Cytoscape plugins folder. By default is:
    a. **Windows**: "C:\Program Files\Cytoscape-v2.x.x\plugins\"
    b. **Mac OS**: "/Applications/Cytoscape-v2.x.x/plugins/

3. Remove ***sbml-reader-2.8.X-jar-with-dependencies.jar*** file in Cytoscape plugins folder

How to import a SBGN diagram

After CySBGN is installed the user can import a SBGN diagram by clicking in ***File -> Import -> Network (Multiple File Types)*** and then select the respective SBGN-ML file.



- A node shape
- An edge shap click on the t

- To add nodes and edges specified in SIF format

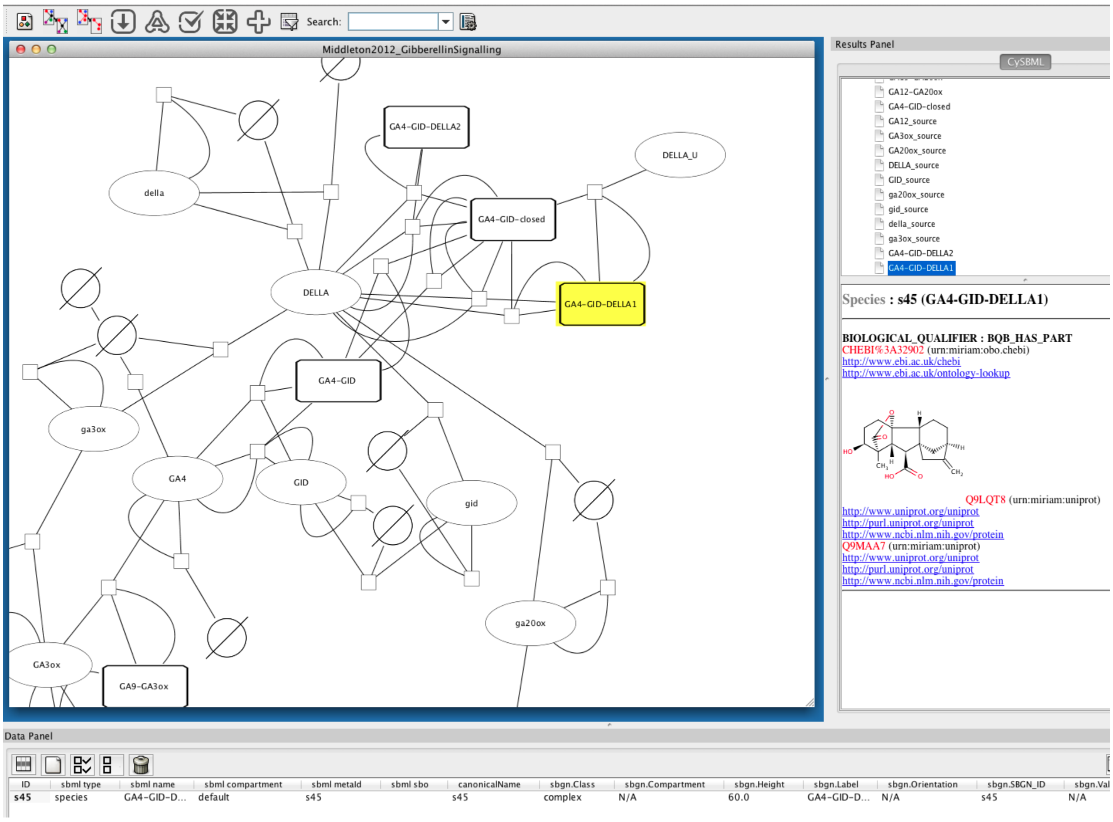
- On empty space to create a node.
- On a node to begin an edge and specify the source node. Then click on the target node to finish the edge.

Note: Example SBGN-ML files can be found and downloaded in the following link: http://sourceforge.net/projects/cysbgn/files/SBGN-ML_Example_Files/

How to generate a SBGN diagram from a SBML file

CySBGN allows to automatically generate SBGN diagrams from SBML models by making use of CySBML plug-in and SBFC converter.

Once CySBGN is fully installed (CySBGN and CySBML) the user can select a SBML model, then CySBGN uses SBFC to convert the selected SBML file into a SBGN-ML file.



Species : s45 (GA4-GID-DELLA1)

BIOLOGICAL_QUALIFIER : BQB_HAS_PART
CHEBI%3A32902 (urn:miriam:obo.chebi)
http://www.ebi.ac.uk/chebi
http://www.ebi.ac.uk/ontology-lookup

Q9LQT8 (urn:miriam:uniprot)
http://www.uniprot.org/uniprot
http://purl.uniprot.org/uniprot
http://www.ncbi.nlm.nih.gov/protein
Q9MAA7 (urn:miriam:uniprot)
http://www.uniprot.org/uniprot
http://purl.uniprot.org/uniprot
http://www.ncbi.nlm.nih.gov/protein

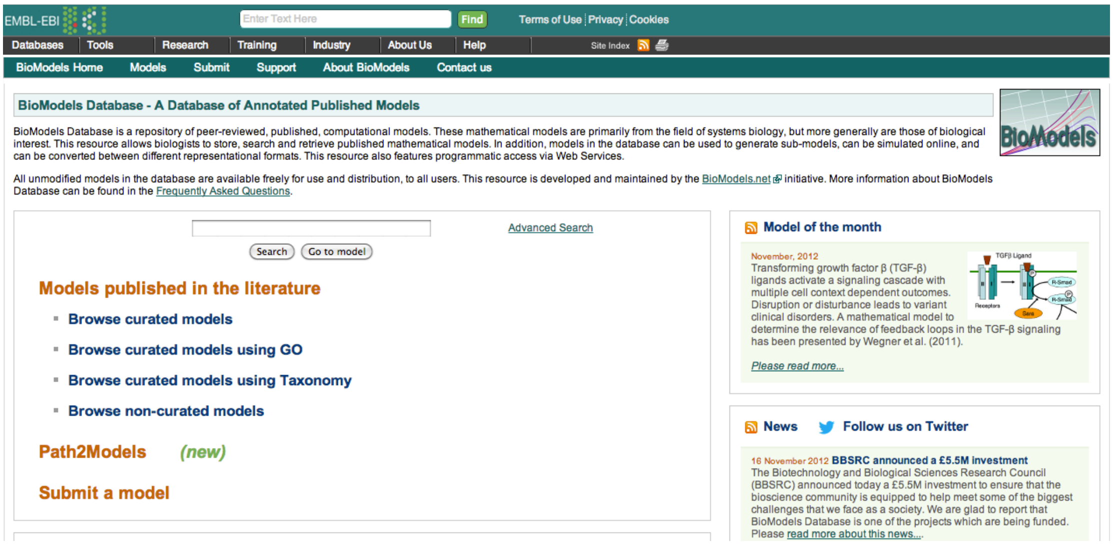
ID	sbml type	sbml name	sbml compartment	sbml metaId	sbml sbo	canonicalName	sbgn.Class	sbgn.Compartment	sbgn.Height	sbgn.Label	sbgn.Orientation	sbgn.SBGN_ID	sbgn.Val
s45	species	GA4-GID-D...	default	s45		s45	complex	N/A	60.0	GA4-GID-D...	N/A	s45	N/A

Note: The conversion process may take a while

After the conversion the SBGN diagram visualization is integrated with the information made available by CySBML plug-in (e.g. information contained in web databases about the selected specie is displayed in a right side panel by CySBML plug-in).

BioModels Database

The user can also take advantage of BioModels database as a resource of SBML models.



BioModels Database - A Database of Annotated Published Models

BioModels Database is a repository of peer-reviewed, published, computational models. These mathematical models are primarily from the field of systems biology, but more generally are those of biological interest. This resource allows biologists to store, search and retrieve published mathematical models. In addition, models in the database can be used to generate sub-models, can be simulated online, and can be converted between different representational formats. This resource also features programmatic access via Web Services.

All unmodified models in the database are available freely for use and distribution, to all users. This resource is developed and maintained by the BioModels.net initiative. More information about BioModels Database can be found in the Frequently Asked Questions.

Models published in the literature

Model of the month

November, 2012
Transforming growth factor β (TGF-β) ligands activate a signaling cascade with multiple cell context dependent outcomes. Disruption or disturbance leads to variant clinical disorders. A mathematical model to determine the relevance of feedback loops in the TGF-β signaling has been presented by Wegner et al. (2011).

Please read more...

News

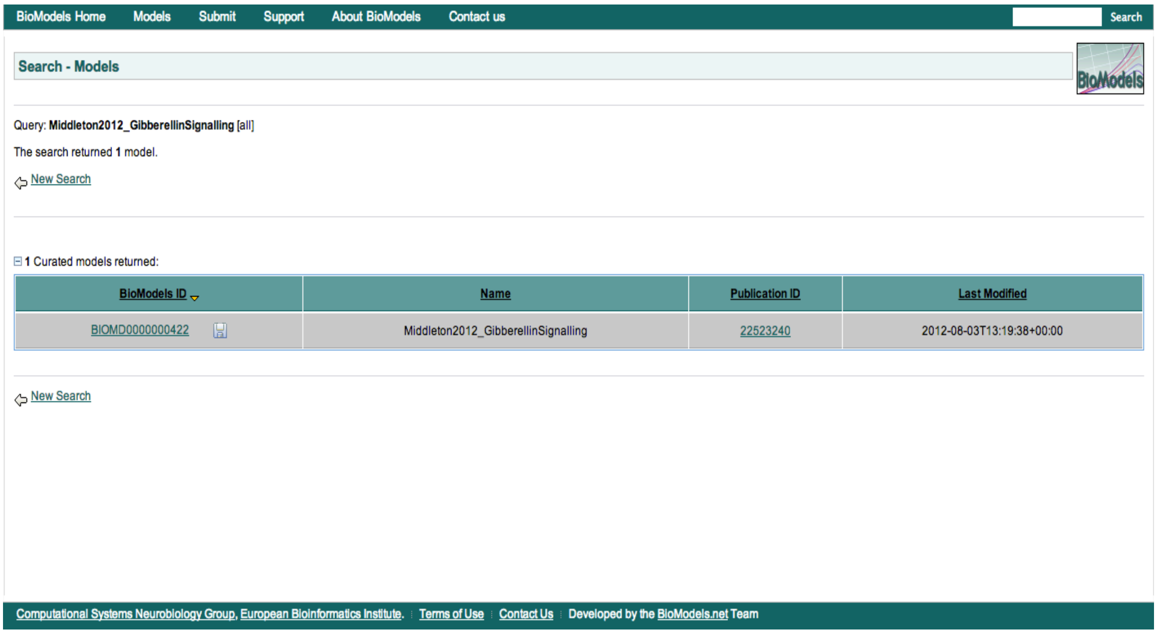
16 November 2012 **BBSRC announced a £5.5M investment**
The Biotechnology and Biological Sciences Research Council (BBSRC) announced today a £5.5M investment to ensure that the bioscience community is equipped to help meet some of the biggest challenges that we face as a society. We are glad to report that BioModels Database is one of the projects which are being funded. Please read more about this news....

URL: http://www.ebi.ac.uk/biomodels-main/

How to download SBML models from BioModels Database

1. From BioModels main webpage (the one above) type the desired model's name and hit *Search* button
    a. e.g. *Middleton2012_GibberellinSignalling*

2. The list with the matching models is presented. To select the model click on the model's ID



Search - Models

Query: **Middleton2012_GibberellinSignalling** [all]

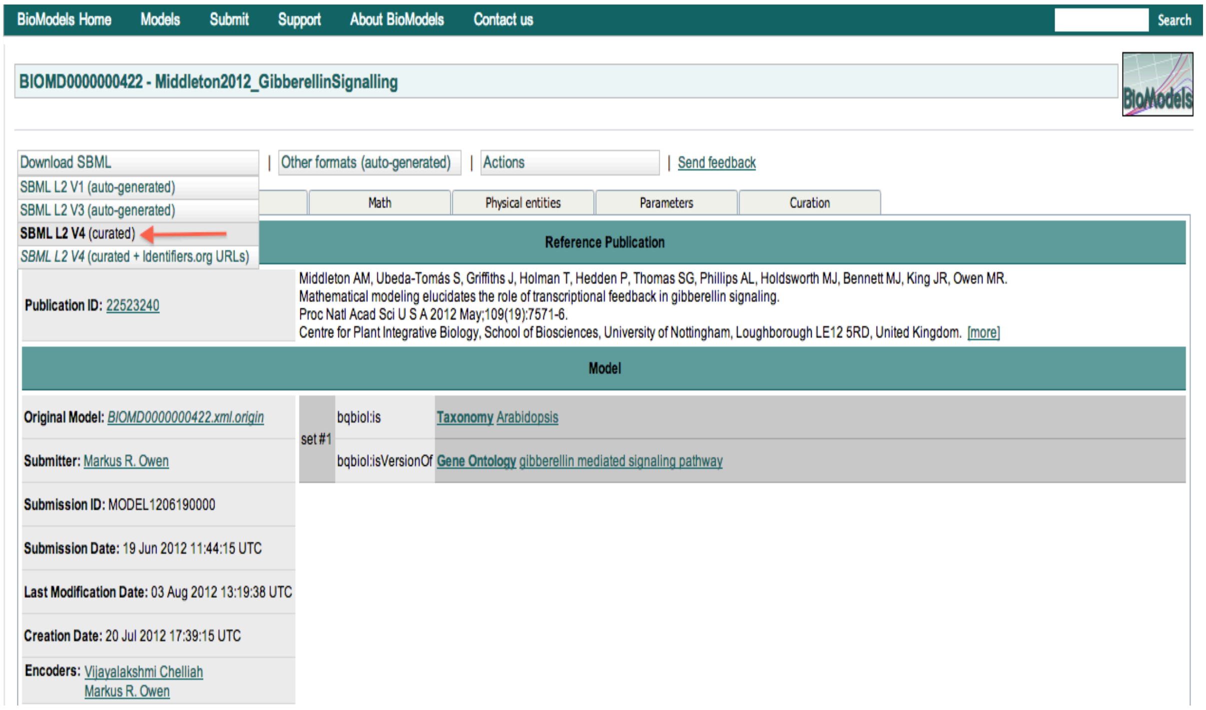
The search returned **1** model.

⊟ **1** Curated models returned:

BioModels ID	Name	Publication ID	Last Modified
BIOMD0000000422	Middleton2012_GibberellinSignalling	22523240	2012-08-03T13:19:38+00:00

Note: Obtained model list for *Middleton2012_GibberellinSignalling* search

3. The user can then visualise detailed information about the model or download it in SBML format.
    a. For full support of SBFC and CySBGN we recommend, whenever possible, to download the SBML version **without identifiers**



BIOMD0000000422 - Middleton2012_GibberellinSignalling

Reference Publication

Publication ID: 22523240

Middleton AM, Ubeda-Tomás S, Griffiths J, Holman T, Hedden P, Thomas SG, Phillips AL, Holdsworth MJ, Bennett MJ, King JR, Owen MR.
Mathematical modeling elucidates the role of transcriptional feedback in gibberellin signaling.
Proc Natl Acad Sci U S A 2012 May;109(19):7571-6.
Centre for Plant Integrative Biology, School of Biosciences, University of Nottingham, Loughborough LE12 5RD, United Kingdom. [more]

Model

Original Model: BIOMD0000000422.xml.origin

Submitter: Markus R. Owen

Submission ID: MODEL1206190000

Submission Date: 19 Jun 2012 11:44:15 UTC

Last Modification Date: 03 Aug 2012 13:19:38 UTC

Creation Date: 20 Jul 2012 17:39:15 UTC

Encoders: Vijayalakshmi Chelliah
Markus R. Owen

set #1	bqbiol:is	**Taxonomy** Arabidopsis
	bqbiol:isVersionOf	**Gene Ontology** gibberellin mediated signaling pathway

URL: http://www.ebi.ac.uk/biomodels-main/BIOMD0000000422

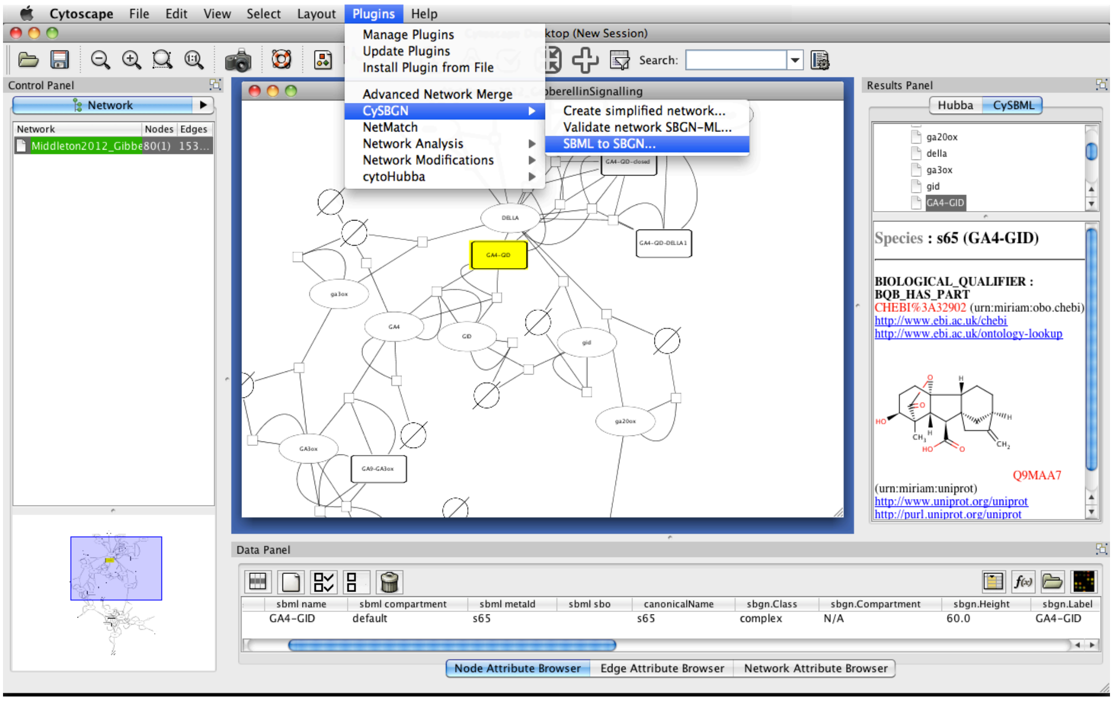
4. As shown in the picture above, to get the SBML model click **Download SBML** and select the appropriate version of the SBML file.

5. Save the file.

How to generate SBGN diagrams from SBML models

After installing CySBGN and CySBML plug-ins correctly (check ***How to download and install CySBGN*** section for detailed instructions) the user can complement SBML model visualisation with an automated generated SBGN diagram of the model.

1. Through ***Plugins -> CySBGN -> SBML to SBGN...*** the user can select a SBML model and generate the respective SBGN diagram.
    a. The conversion process may take awhile



Species : s65 (GA4-GID)

BIOLOGICAL_QUALIFIER :
BQB_HAS_PART
CHEBI%3A32902 (urn:miriam:obo.chebi)
http://www.ebi.ac.uk/chebi
http://www.ebi.ac.uk/ontology-lookup

Q9MAA7
(urn:miriam:uniprot)
http://www.uniprot.org/uniprot
http://purl.uniprot.org/uniprot

sbml name	sbml compartment	sbml metaId	sbml sbo	canonicalName	sbgn.Class	sbgn.Compartment	sbgn.Height	sbgn.Label
GA4-GID	default	s65		s65	complex	N/A	60.0	GA4-GID

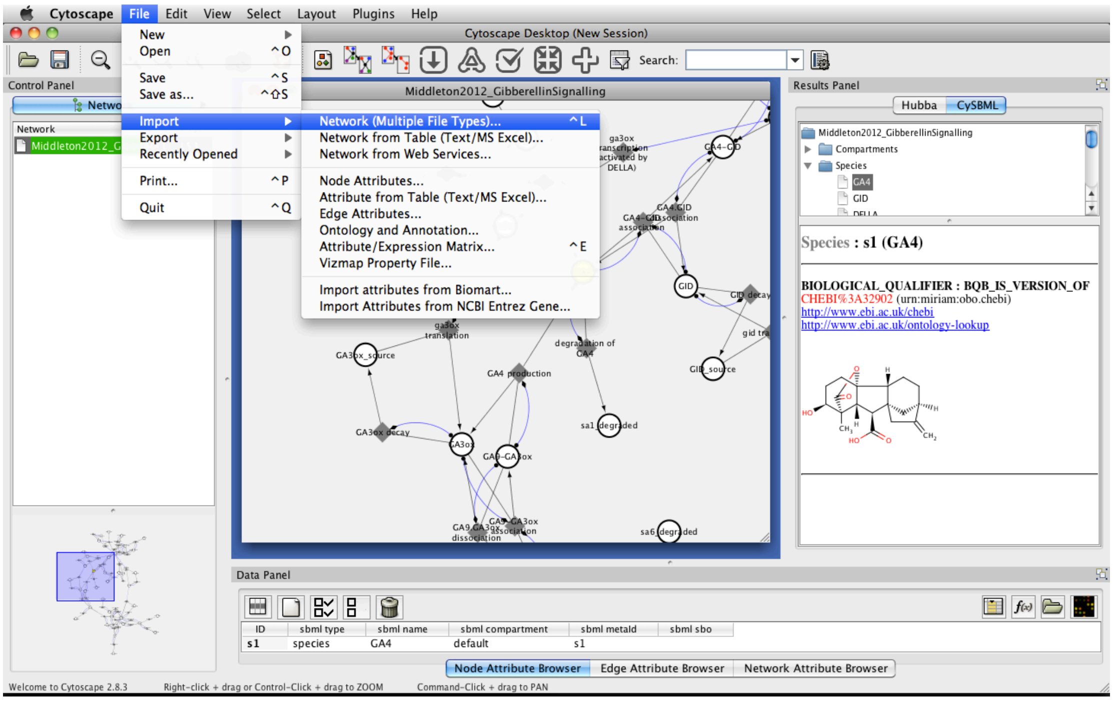
Note: Since we are dealing with automated generation of diagrams the layout may need some manual correction. Here the overlapping nodes were moved to be completely visible. SBML model link: http://www.ebi.ac.uk/saezrodriguez/cysbgn/files/BIOMD0000000422.xml

2. Selected node information is visible in the Results Panel (right side panel) in CySBML tab, also Data Panel (bottom panel) shows SBML and SBGN node's attributes.
    a. Some attributes may be hidden. Click **Select All Attributes** (☑) button to visualise all the attributes

How to import the SBML models into Cytoscape

Before importing the SBML model in Cytoscape, check if CySBML plug-in is correctly installed (check ***How to download and install CySBGN*** section for detailed instructions in process is analogous).

1. After CySBML is installed the user can import a SBML model by clicking in ***File -> Import -> Network (Multiple File Types)*** and then select the respective SBML file.



Species : s1 (GA4)

BIOLOGICAL_QUALIFIER : BQB_IS_VERSION_OF
CHEBI%3A32902 (urn:miriam:obo.chebi)
http://www.ebi.ac.uk/chebi
http://www.ebi.ac.uk/ontology-lookup

ID	sbml type	sbml name	sbml compartment	sbml metaId	sbml sbo
s1	species	GA4	default	s1	

Note: This is how Cytoscape should look like when importing the selected model in the previous steps using CySBML. SBML model link: http://www.ebi.ac.uk/saezrodriguez/cysbgn/files/BIOMD0000000422.xml

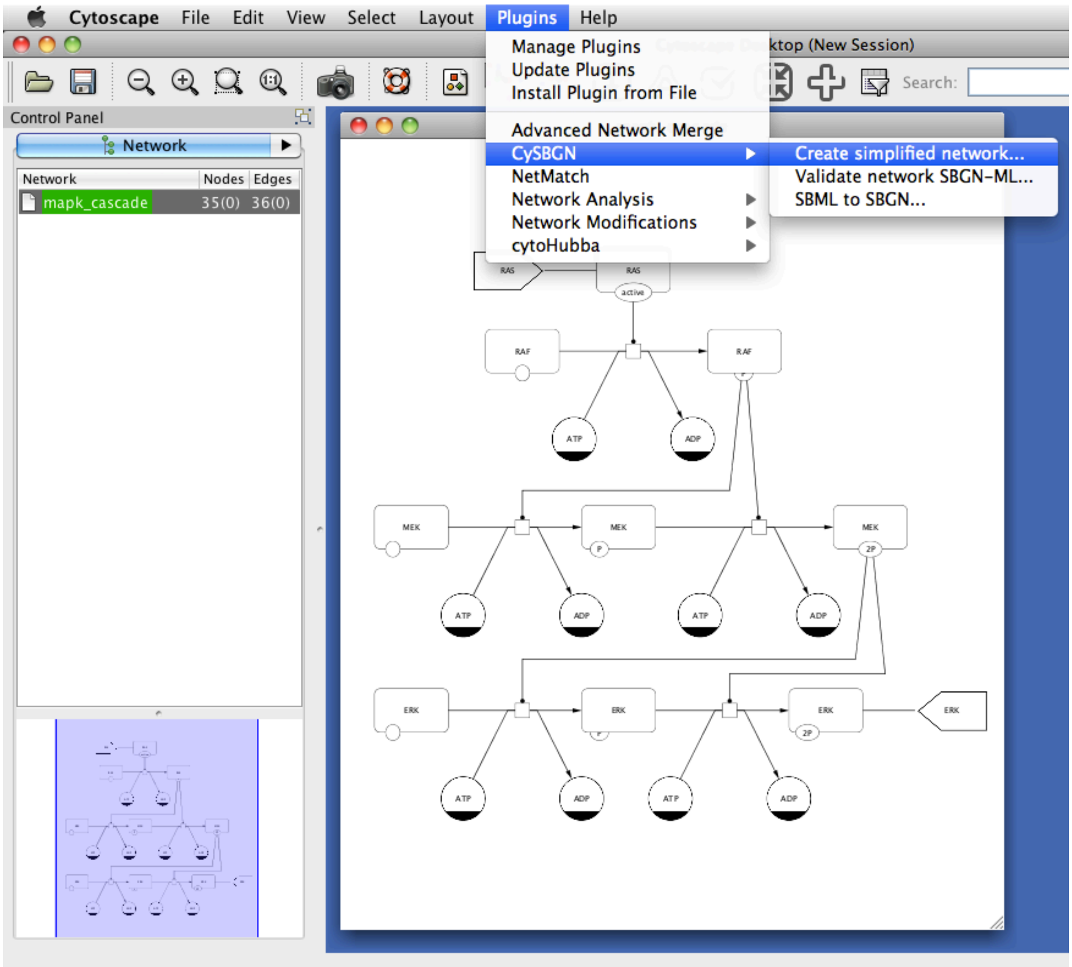
How to simplify a SBGN diagram

To render the diagrams as close as possible to the original, CySBGN creates some auxiliary nodes and edges to overlap the Cytoscape rendering restrictions (e.g. invisible ports to allow a edge to connect with another edge). Although, this auxiliary shapes represent some limitations to the correct operability of Cytoscape analysis or display methods (e.g. in a shortest path algorithm the auxiliary nodes are considered as one step as well).

To overcome this a simplification method was available allowing to remove displaying auxiliary shapes, SBGN complex or compartments entities. The image below shows how a user can preform the simplification of a previously imported SBGN diagram.

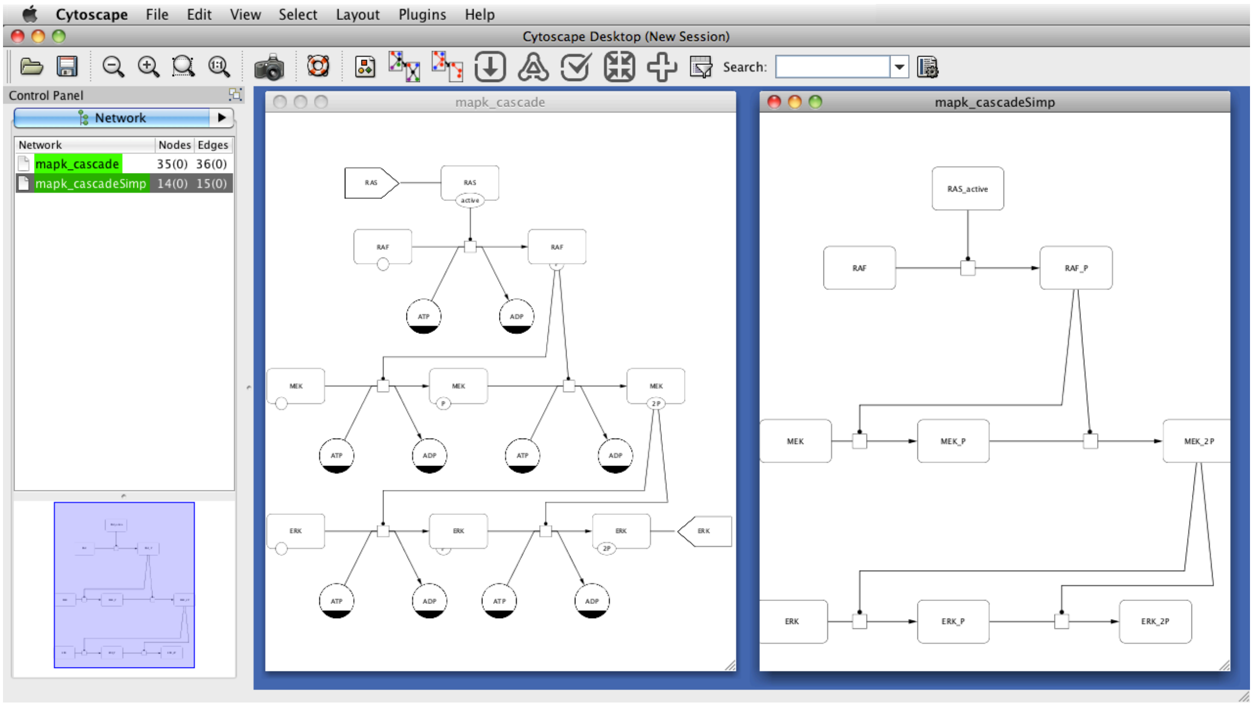
1. Import a SBGN diagram.
    a. Example map kinase cascade diagram (image below)

2. The user can then automatically generate a simplified version of the diagram. ***Plugins -> CySBGN -> Create simplified network…***



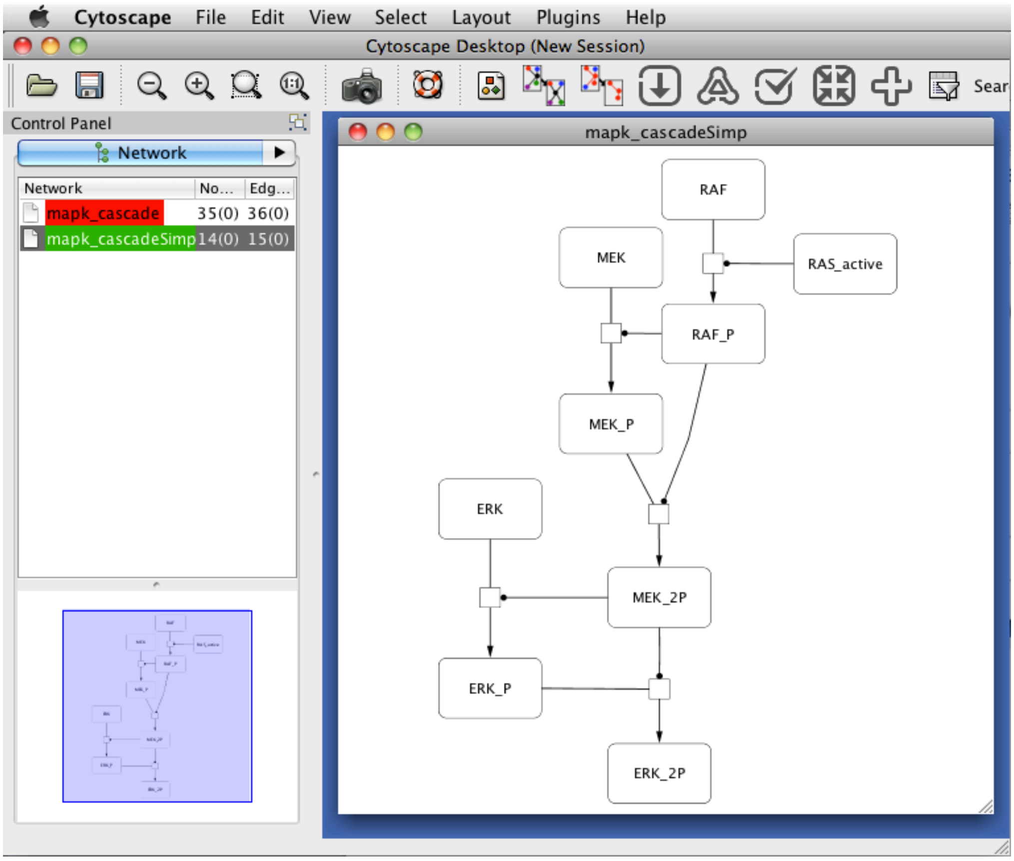
Note: Link for the SBGN-ML file http://sourceforge.net/projects/cysbgn/files/SBGN-ML_Example_Files/mapk_cascade.sbgn/download

3. After the simplification process the simplified network can be seen side-by-side with the original SBGN diagram.



Network	Nodes	Edges
mapk_cascade	35(0)	36(0)
mapk_cascadeSimp	14(0)	15(0)

4. Analysis methods or layout algorithms can be applied to the simplified network.



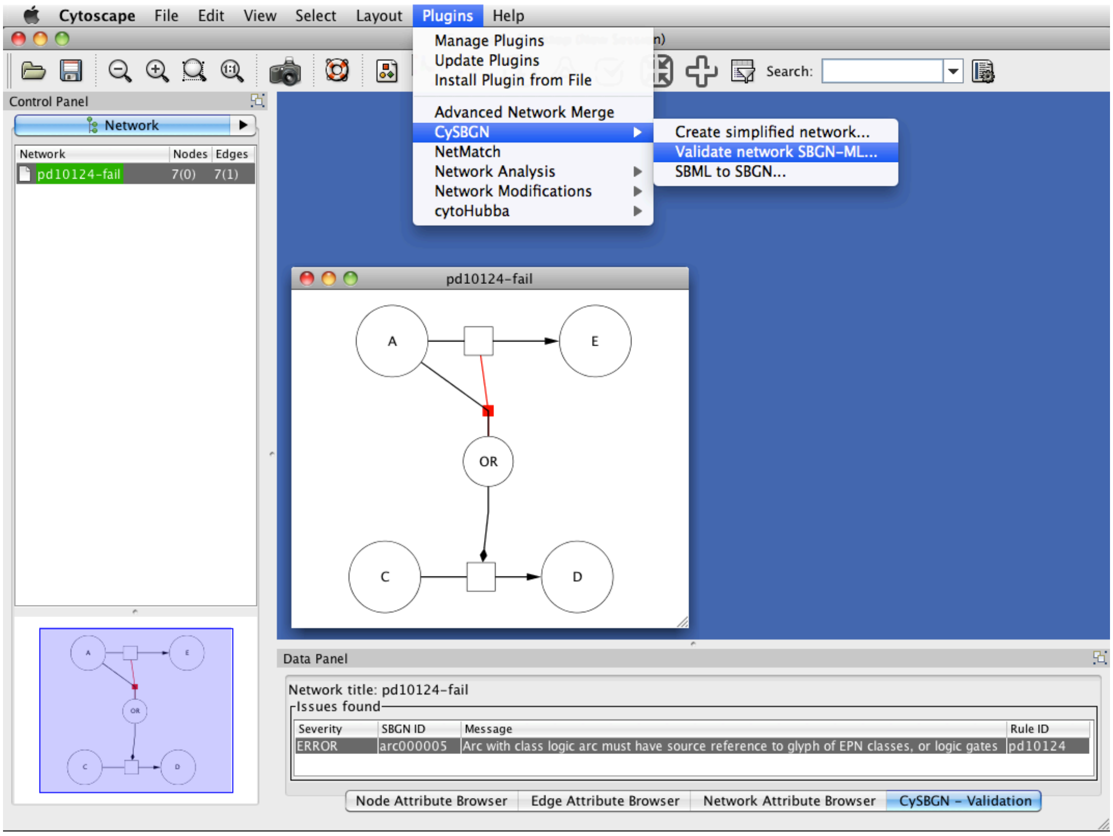
Network	No…	Edg…
mapk_cascade	35(0)	36(0)
mapk_cascadeSimp	14(0)	15(0)

Note: After applying the yFiles hierarchical layout manual modifications were done of obtain a better visualisation.

How to validate a SBGN-ML file

CySBGN allows users to perform a syntactic validation of SBGN-ML documents using libSBGN. The validation function is accessible under the CySBGN menu in the Plugins menu and runs a syntax validation of the SBGN-ML file used to import currently selected SBGN-ML diagram.

1. The user can select the SBGN-ML to validate through ***Plugins -> CySBGN -> Validate Network SBGN-ML …***



Network title: pd10124-fail

Issues found

Severity	SBGN ID	Message	Rule ID
ERROR	arc000005	Arc with class logic arc must have source reference to glyph of EPN classes, or logic gates	pd10124

2. Any issue found with the SBGN-ML file is listed in the Data Panel (bottom panel) in the CySBGN-Validation tab. Selecting the issue from the list will highlight the correspondent arc or node.

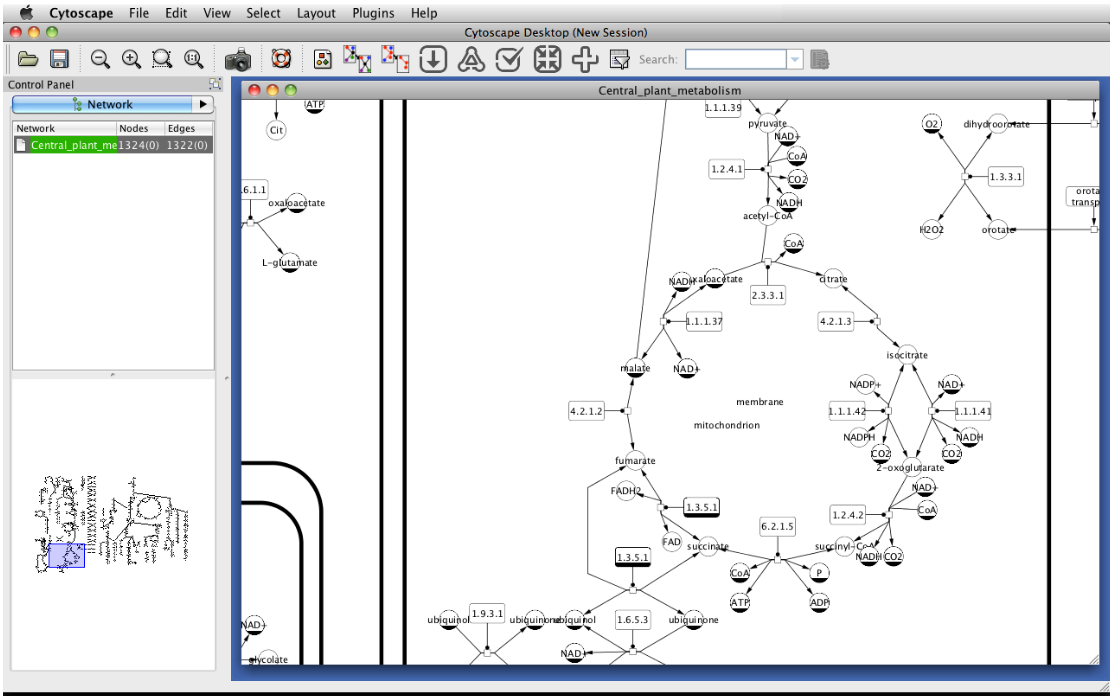
CySBGN extending Cytoscape features to SBGN diagrams

Shortest path in a metabolic pathway

A simple example of the interaction of CySBGN with other Cytoscape plug-ins is for instance the use CytoHubba plug-in to detect the shortest path between two metabolites in a metabolic network.

1. Install CytoHubba plug-in through Cytoscape Plugins Manger
    a. Check **How to download and install CySBGN** for more details

2. Import a SBGN metabolic network
    a. e.g. Central plant metabolism

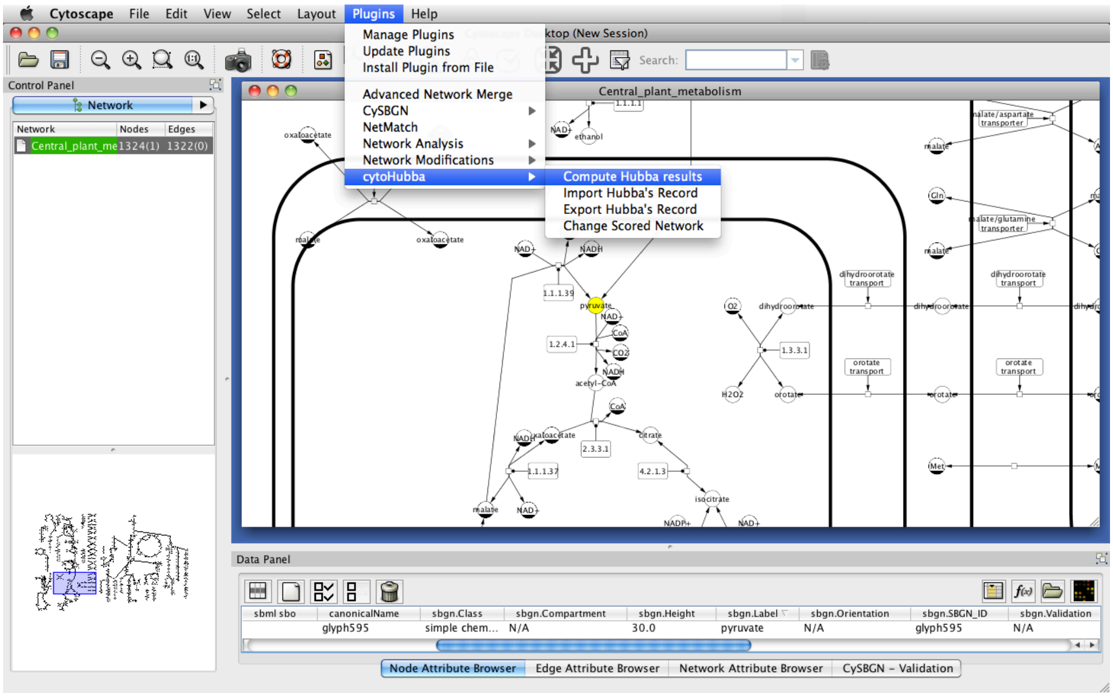


Network	Nodes	Edges
Central_plant_me	1324(0)	1322(0)

Note: Link for the SBGN-ML file
http://sourceforge.net/projects/cysbgn/files/SBGN-ML_Example_Files/central_plant_metabolism.sbgn/download

3. In this example we want to find the shortest path between Pyruvate and Succinate
    a. After checking the network attributes (Data Panel) we know that Pyruvate node ID is ***glyph595*** and Succinate node ID is ***glyph387***

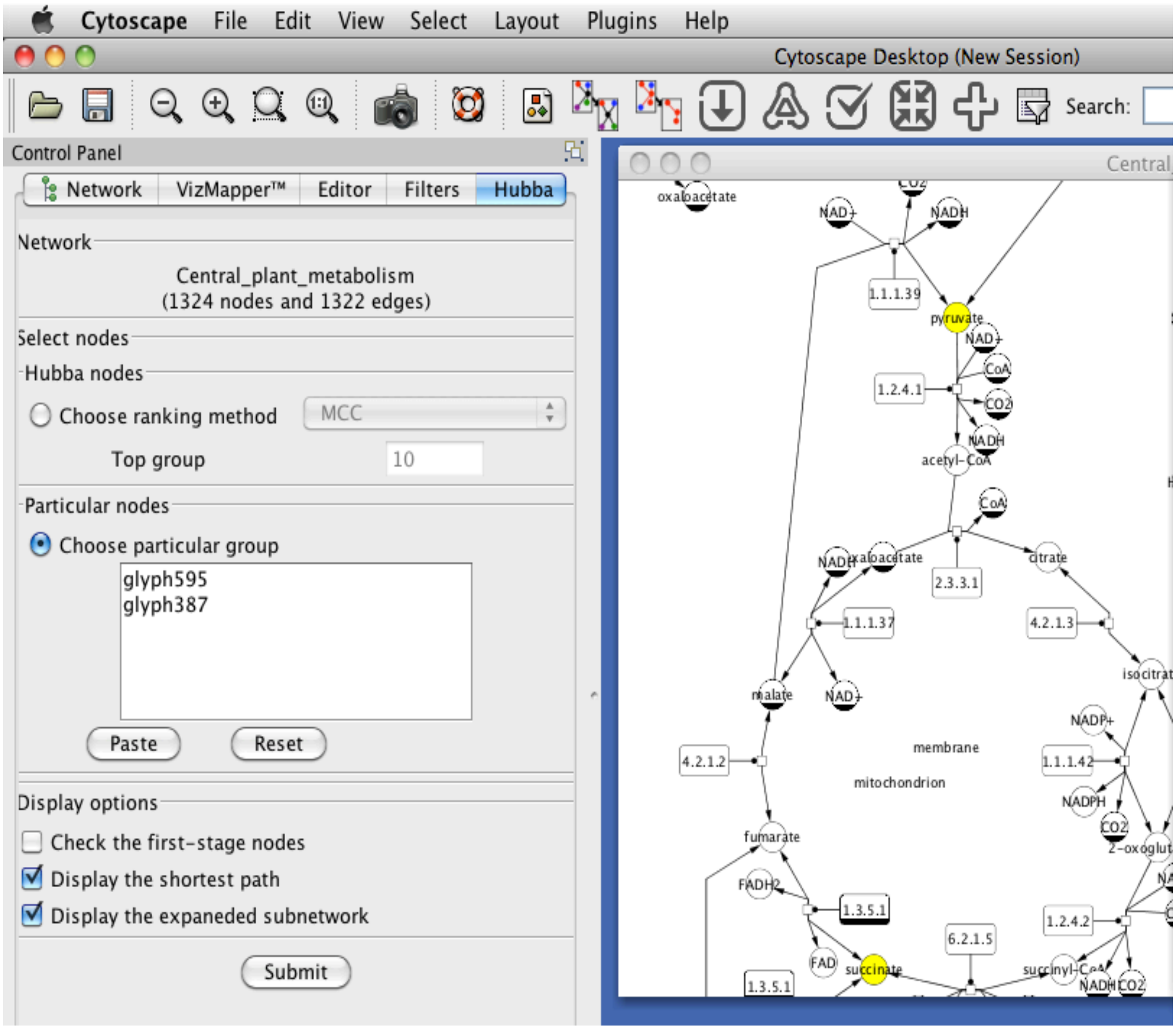
4. Before running the shortest path algorithm we need first to compute Hubba results for each node of the network. ***Plugins -> cytoHubba -> Compute Hubba results***



sbml sbo	canonicalName	sbgn.Class	sbgn.Compartment	sbgn.Height	sbgn.Label	sbgn.Orientation	sbgn.SBGN_ID	sbgn.Validation
	glyph595	simple chem...	N/A	30.0	pyruvate	N/A	glyph595	N/A

5. CytoHubba will then ask the user to select the desired network and the attribute name to store the computed results.
   a. Network: Central_plant_metabolism
   b. Attribute Name: example

6. After the scores are computed we can now define the start and end nodes in Hubba tab in the control panel as shown below.
    a. Path from **Pyruvate (glyph595)** to **Succinate (glyph387)**



Control Panel

Network

Central_plant_metabolism
(1324 nodes and 1322 edges)

Select nodes

Hubba nodes

○ Choose ranking method MCC

Top group 10

Particular nodes

● Choose particular group

glyph595
glyph387

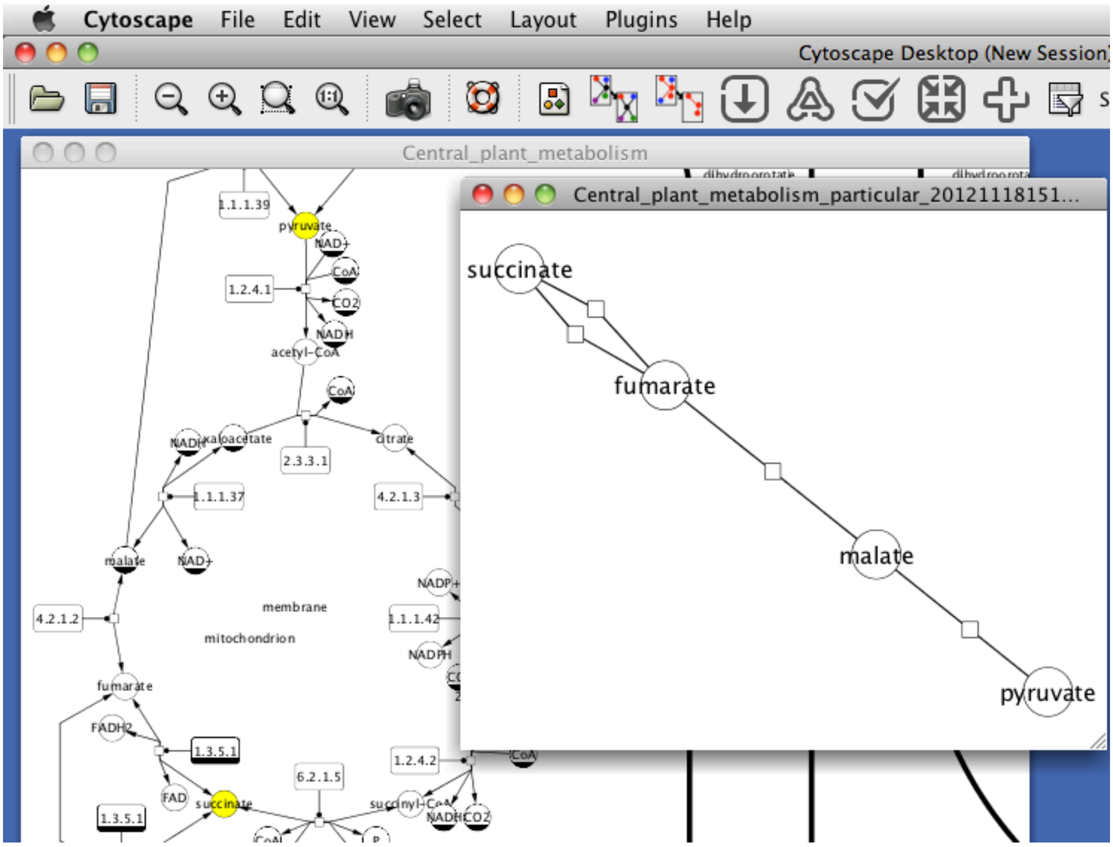
Display options

☐ Check the first-stage nodes

☑ Display the shortest path

☑ Display the expaneded subnetwork

7. After adding the configurations click submit button to run the algorithm. The expected result is shown below.



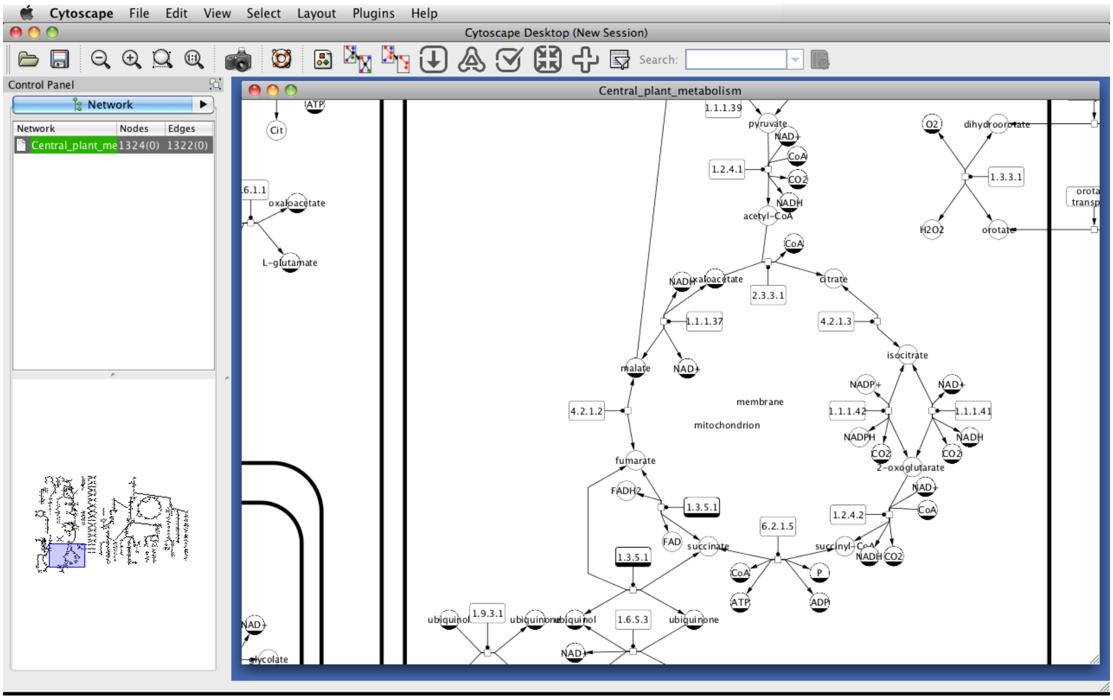
Note: The SBGN layout may not be selected by default in the shortest path network. Set SBGN visual style in VizMapper tab in the Control Panel (left side panel).

Network motifs discovery

Another example of CySBGN interoperability with other plug-ins is for instance the discovery of network motifs using NetMatch Cytoscape plug-in.

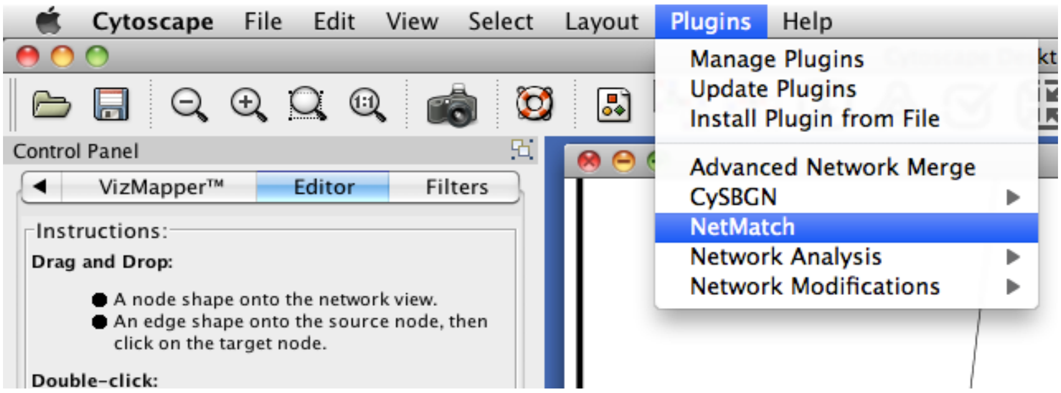
1. Install ***NetMatch*** plug-in through Cytoscape Plugins Manger
    a. Check **How to download and install CySBGN** for more details.
    b. ***NetMatch*** is not verified to work with the latest versions of Cytoscape, although it operates correctly.

2. Import a SBGN metabolic network
    a. e.g. Central plant metabolism



Note: Link for the SBGN-ML file http://sourceforge.net/projects/cysbgn/files/SBGN-ML_Example_Files/central_plant_metabolism.sbgn/download

3. Start ***NetMatch*** by clicking in NetMatch menu under Plugins. See image below.



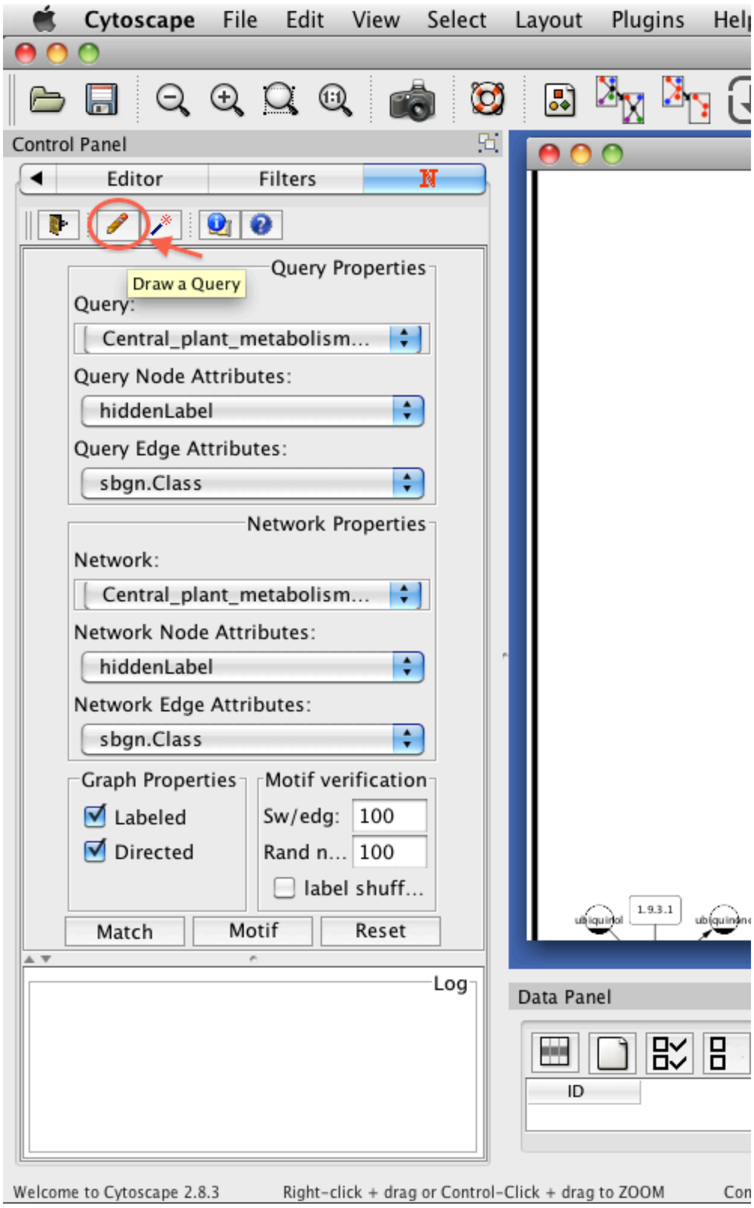
Instructions:

Drag and Drop:

- A node shape onto the network view.
- An edge shape onto the source node, then click on the target node.

Double-click:

4. Now ***NetMatch*** tab should be visible in Control Panel (left side panel). Click Draw a Query (pencil icon) to draw the desired motif to search in the network.



Query Properties

Query: Central_plant_metabolism...

Query Node Attributes: hiddenLabel

Query Edge Attributes: sbgn.Class

Network Properties

Network: Central_plant_metabolism...

Network Node Attributes: hiddenLabel

Network Edge Attributes: sbgn.Class

Graph Properties

☑ Labeled

☑ Directed

Motif verification

Sw/edg: 100

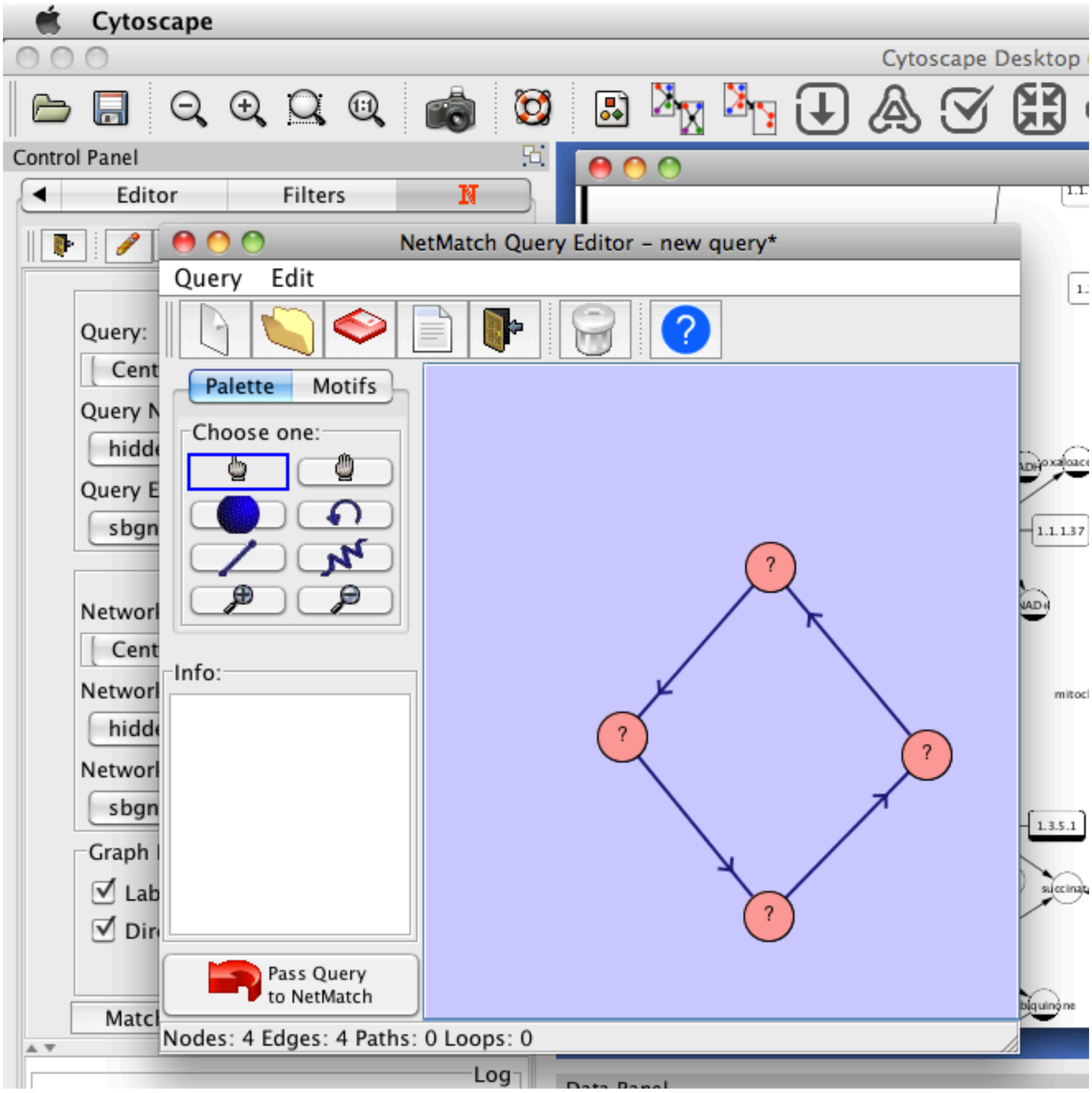
Rand n... 100

☐ label shuff...

Welcome to Cytoscape 2.8.3

Right-click + drag or Control-Click + drag to ZOOM

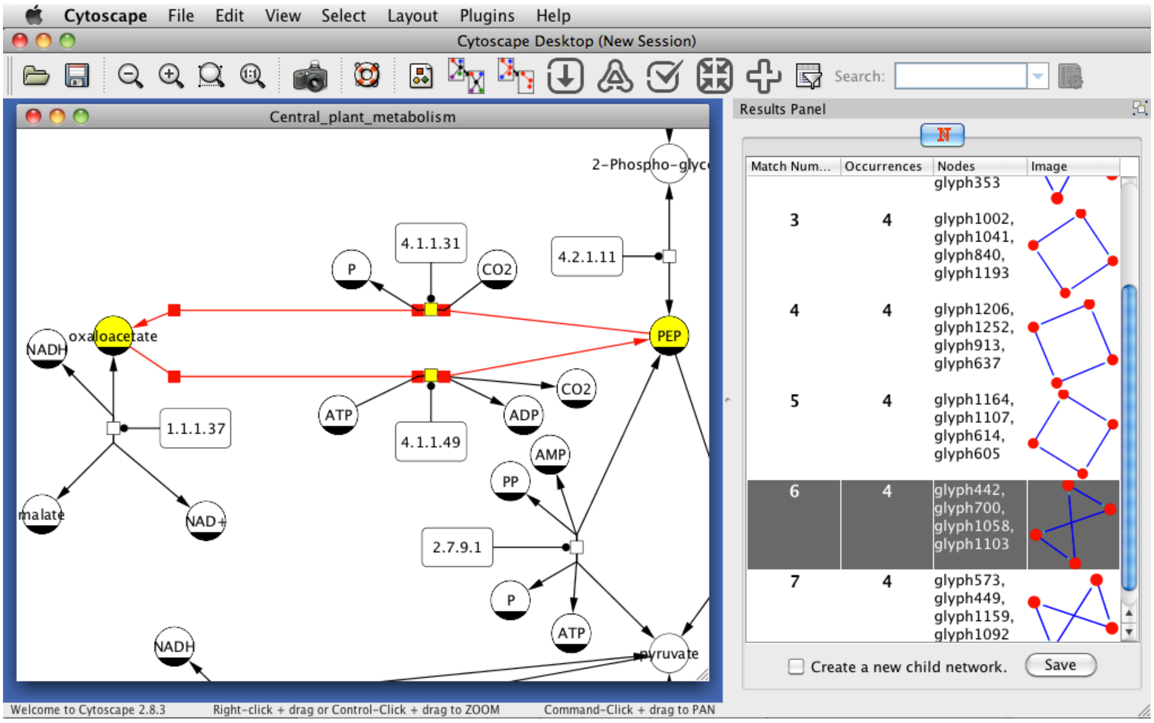
5. In this case (image below) we are looking for a motif that represents a metabolite that can be converted into another using one enzyme, and the other way around by another different enzyme. After defining the motif click **Pass Query to NetMatch** button.



Nodes: 4 Edges: 4 Paths: 0 Loops: 0

6. Click **Match** button in the bottom part of **NetMatch** tab in Control Panel.

7. At this point **NetMatch** should have found some matches to the motif defined before. The matching motifs are listed in the **Result Panel** (right side of the window).



Match Num...	Occurrences	Nodes	Image
		glyph353	
3	4	glyph1002, glyph1041, glyph840, glyph1193	
4	4	glyph1206, glyph1252, glyph913, glyph637	
5	4	glyph1164, glyph1107, glyph614, glyph605	
6	4	glyph442, glyph700, glyph1058, glyph1103	
7	4	glyph573, glyph449, glyph1159, glyph1092	

☐ Create a new child network. Save

Note: Here is highlighted the reversible transformation of oxaloacetate to PEP using different enzymes.