



Mayday Pathway Viewer HowTo

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1 Pathway Viewers in Mayday

Mayday features two viewers for metabolic pathways. Those are the KEGG viewer and the BioPax viewer. They are used for different purposes. KEGG (<http://www.genome.jp/kegg/>) features comprehensive maps of metabolic path-



ways for a multitude of organisms. KEGG pathways maps are carefully designed and are well-known among a wide range of researchers.

Further pathways and other biochemical information is available in the BioPax format from various sources including Meta/Bio/Eco/Human-Cyc, Pathway Commons and Reactome. These pathways have a slightly different focus than the KEGG pathways, as they are much more diverse and / or detailed.

2 General Features of the Pathway Viewers

2.1 Pathway Components

Each Pathway is displayed as a number of components layouted on the window (sometimes called the canvas). Each component:

- can be interacted with in several ways (see section 2.2).
- can be connected with one ore other components by one more directed edges (see section 2.3).
- can be rendered in different ways (see section 2.4).

Depending on the viewer, specific context menus or other properties are available. For details see the documentation of the respective viewer.

2.2 Component Interactions

Visibility: Hiding Components Components can be hidden to allow the user to focus on certain aspects of the plot. Hiding a component is possible in different ways: Using the component context menu (entry "Hide"), the canvas context menu (see section 2.5).

Moving Components Left-click on the component, and drag the component to the desired location. When multiple components are selected, all selected components more relatively to their original positions.

Zooming Components Middle-click on the component. A small Window will appear that displays an enlarged view of the component and some additional information about it.

Resizing Components Use the mouse wheel to resize a component (keeps the aspect ratio). Use shift-mouse wheel to resize the component vertically and control-mouse wheel to resize it horizontally.



Selecting Components To select a component, left-click on it. The selection is communicated to other open plot views in Mayday. Selections can also be made using a selection rectangle, which appears when on left-click on the plot background. The selection is cleared when the user clears it by menu or when a left-click on the plot background occurs.

Context Menu The component context menu offers the following options:

- **Component Name:** no function is associated with this entry.
- **Select:** Selects the component.
- **Hide:** Hides the component.
- **Size:** This sub menu allows to set the component's size to the minimum, maximum or to its original size.
- **Renderer:** Sets the renderer of the individual component. This entry is not available for all types of components.

The component context menu contains additional entries in different viewers.

2.3 Component Renderers

Several different types of component renderers are available (see figure 2):

Renderer Name	What does it draw?	Number of values
Default Renderer	Name and type of object	0
Box	A small box	1 value (Color)
Diamond	A small diamond	1 value (Color)
Circle	A small circle	1 value (Color)
Gradient	Large box	1 value (Color)
Heat Stream	Array of colored bars	1 Probe (Color)
Heat Map	small heatmap	multiple Probes (Color)
Profile Plot	Set of lines	multiple Probes (Height)

“1 value” means that exactly one value can be visualized with the renderer.

“1 Probe” means that the expression profile of a single probe is displayed.

“multiple probes” means that the expression profiles of one or more probes are displayed.

For the renderers, several additional settings are available: The Renderer Settings allow to control these features:

- **Probe Indices:** Add small tickmarks indicating where different probes are rendered. Only applies when using a HeatMap Renderer.
- **Experiment Indices:** Add small tickmarks indicating where different experiments are rendered.



- **Use Class Labels:** Experiments can belong to different classes. These class mapping can be displayed by a small color bar below the expression value plots. The button next to class selection allows allows to define these class partition.
- **MI Group (Color Bar):** Sometimes it is useful to display a meta information (annotation, test statistic, p-value, etc) in addition to the expression values. To do so, select a meta information group (Button "Select") and check the button "Display MI Group (Color bar)". The gradient used can also be adjusted by clicking on the gradients preview image.
- **MI Group (Transparency)** To display yet more information on one object, a relevance statistic can be used to shade the overall appearance of the object. Relevant objects are unshaded, irrelevant objects are hidden. The MI Group ("Source MI Group"), the Mapping function ("Mapping"), if the relevance mapping should be reserved ("Invert relevance") and how missing values should be treated ("Missing Values") can be adjusted. The color used for shading can be adjusted by clicking on the colored box next to "Shading color".

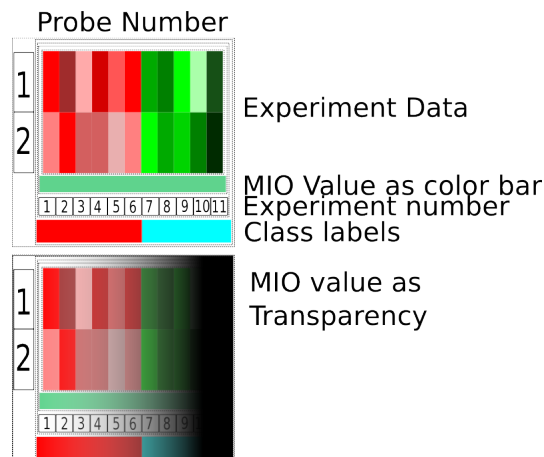


Figure 1: General schema of a component renderer. Any part except the Experiment Data is optional.

2.4 Edges

Edges are routed directly from source to target node. The edges can be drawn in different styles, which globally apply to all edges in one plot. To select new edge style, right-click on the plot background, and select a new edge style from the menu "Edges". The following styles are available:

- **Simple edges:** A straight line is drawn between the two components.
- **Bezier Edges Type 1:** A bezier curve resembling a straight line with a bended end is used

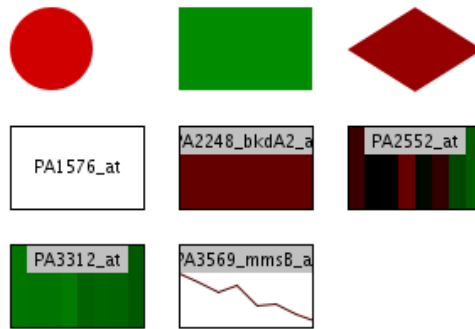


Figure 2: Different rendering styles available in Mayday. From left to right, top to bottom: circle, box, diamond, default, gradient, heatmap, profile plot

- **Bezier Edges Type 2:** Edges are drawn as bezier curves in an overhand style.
- **Bezier Edges Type 3:** Edges are drawn as bezier curves in an underhand style.
- **Smart Edges:** Edge style is dynamically chosen to reduce edge crossings.

For examples, see figure 3

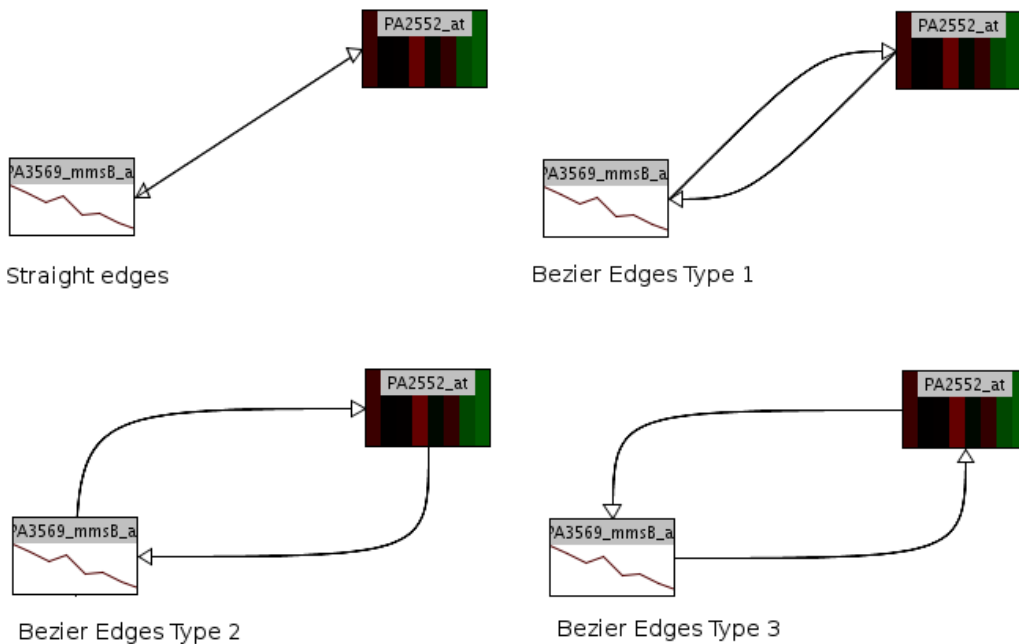


Figure 3: Different edge styles available in the Mayday Pathway Viewers

2.5 Canvas Options

Most canvas options can be set via the canvas context menu:



- **Select All:** Select all components in the plot
- **Clear Selection:** Unselects all selected components.
- **Show only selected components:** Hides all components, except the ones that are selected.
- **Hide selected components:** Hides all currently selected components. All other visible components remain visible.
- **Zoom:** Allows to zoom the plot to predefined zoom levels or fitting the width or the whole frame.
- **Component Inspector:** Open the Component Inspector.
- **Edges:** Allows to set the edge style. See section 2.4 for details.

2.6 Component Inspector

The component inspector (see figure 4 shows a list of all components, along with their position in the plot and their visibility status. Clicking on a row scrolls the plot if necessary to ensure the component is visible. Right-clicking on a row brings up the components context menu. The visibility of a component can be changed using the check box in the visibility column.

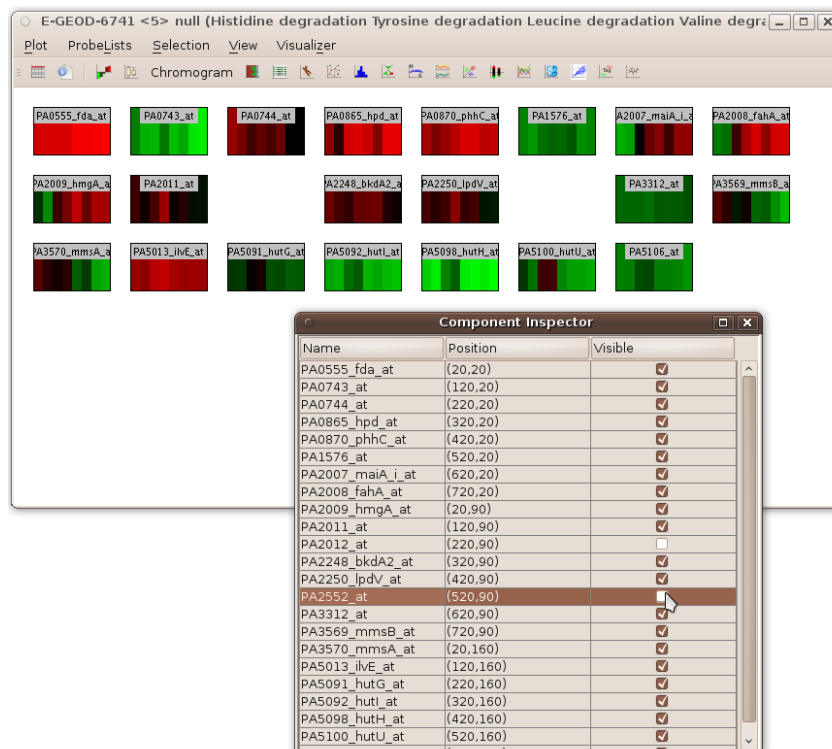


Figure 4: Component inspector with the plot it works on



3 Using the KEGG Pathway Viewer

3.1 Prerequisites

The KEGG Pathway Viewer has the following prerequisites:

- A folder where pathways and annotation files can be stored
- Optimally, a copy of the following files available from KEGG are available:
 - The KEGG Ontology file called “ko”.
 - The KEGG Compound database called “compound”.
 - The List of Pathways available from KEGG called “map_title.tab”.
 - Any number of Pathway files in KGML format (extension: .xml).

The files are available from `ftp://ftp.genome.jp/pub/kegg/`. They can be automatically downloaded when required.

- A mapping of probes to KEGG identifiers. This mapping may be in three different forms:
 - The probe names or
 - The probe display names or
 - Any MIO Group containing String MIOs can be used.

These mappings must be available in Mayday when the viewer is used.

The user is queried for this mapping when the viewer starts.

3.2 Display Options

The KEGG Pathway viewer is a Mayday Visualization plugin and fully integrated in the visualization framework, which means that all standard visualization features are available.

When starting the KEGG Pathway viewer, a dialog shows up that queries some necessary information. From top to bottom, the “KEGG Pathway Settings”-dialog has several fields. The following fields are concerned with data acquisition, storing and mapping. These settings must be adapted to the individual work environment, organism and analysis platform used.

- **Taxon** This field uses a KEGG taxon identifier and influences the Pathways and Gene names used. Choose a valid identifier. A list is available from KEGG. Common names are:



Organism	Identifier
<i>Homo sapiens</i>	hsa
<i>Mus musculus</i>	mmu
<i>Rattus norvegicus</i>	rno
<i>Caenorhabditis elegans</i>	cel
<i>Zea mays</i>	zma
<i>Arabidopsis thaliana</i>	ath
<i>Escherichia coli K12</i>	eco
<i>Bacillus subtilis</i>	bsu
<i>Pseudomonas fluorescens Pf-5</i>	pfl

A list of such names is available at www.genome.jp/dbget-bin/get_htext?br08601.keg
Note that for some organisms, different strains have individual identifiers.

- **KEGG Data directory:** The data directory where annotation files and pathway files are stored.
- **Pathway File:** Here a KGML file can be selected to be viewed. It must not be necessarily stored in the KEGG Data directory.
- **Default Pathway:** The ID of the pathway the is initially displayed in the viewer. Default is 00010, which references to the Glycolysis / Gluconeogenesis pathway.
- **ID Mapping:** Here, the user can choose if the probe names, probe display names or any MIO group containing strings should be used to map KEGG identifiers to probe identifiers. For example, if the probe identifiers are Affymetrix probe set ids, these can not be directly mapped to KEGG identifiers. However, a MIO group containing Gene symbols (“il18r”, “gapdh”, “akt3”) can be used. Usable identifiers depend on the organism. For example, for *Pseudomonas aeruginosa*, names following the PAXxxx- naming convention are optimal.

The next settings are concerned with the appearance of the pathways. These settings affect how stuff is drawn. Default values will be good for most situations:

- **Reaction Settings:** Sets in what color the reaction edges is painted (Reaction Color) and what stroke (solid, dashed, dotted) (Reaction stroke)
- **Relation Settings:** The same settings for relation edges as available for reaction edges.
- **Display Settings:** “Display neighbor pathways” controls if (checked) or not (unchecked) the connections of objects to neighboring pathways should be displayed. These pathway links are connected to enzymes and metabolites with relation edges called maplinks. Whether these should be painted can be controlled using “Display Maplinks”.



The last box controls how expression data is rendered on the pathway components. Several different renderers with some additional options are available:

- **Renderer:** The default renderer for each enzyme and metabolite (called objects) can be selected here. See section 2.3 for details on the renderers.

3.3 Working with KEGG Pathways

A typical view of a pathway can be seen in figure 5

3.3.1 Pathway Objects

Three different Kinds of objects are visible in a typical KEGG pathway:

- **Metabolites:** Drawn as boxes and marked by a small Erlenmeyer flask.
- **Enzymes:** Drawn as boxes and marked by the white letter “E” in a red circle.
- **Pathway Links** Drawn as rounded boxes and marked with a stylized pathway image. Double-clicking these boxes automatically loads the pathway it links to.

Generally, the names are taken from the KEGG pathway file. The name label disappears when the mouse pointer enters the bounds of the component to allow an unobstructed view of the component.

Context Menu

- **Component Name:** no function is associated with this entry.
- **bf Select:** Selects the component.
- **bfHide:** Hides the component.
- **bfSize:** This sub menu allows to set the component’s size to the minimum, maximum or to its original size.
- **bfRenderer:** Sets the renderer of the individual component. Only available for Enzymes and Metabolites.
- **bfLook up in KEGG:** Opens the KEGG website that contains information about the selected component. Only available for Enzymes and Metabolites.
- **bfLoad pathway...** Loads this pathway. Only available for Pathway Links

3.3.2 Menus

Most functions of the KEGG Pathway Viewer are available from the main menu of the window. It contains three menus in addition to the basic Mayday Visualization menus.

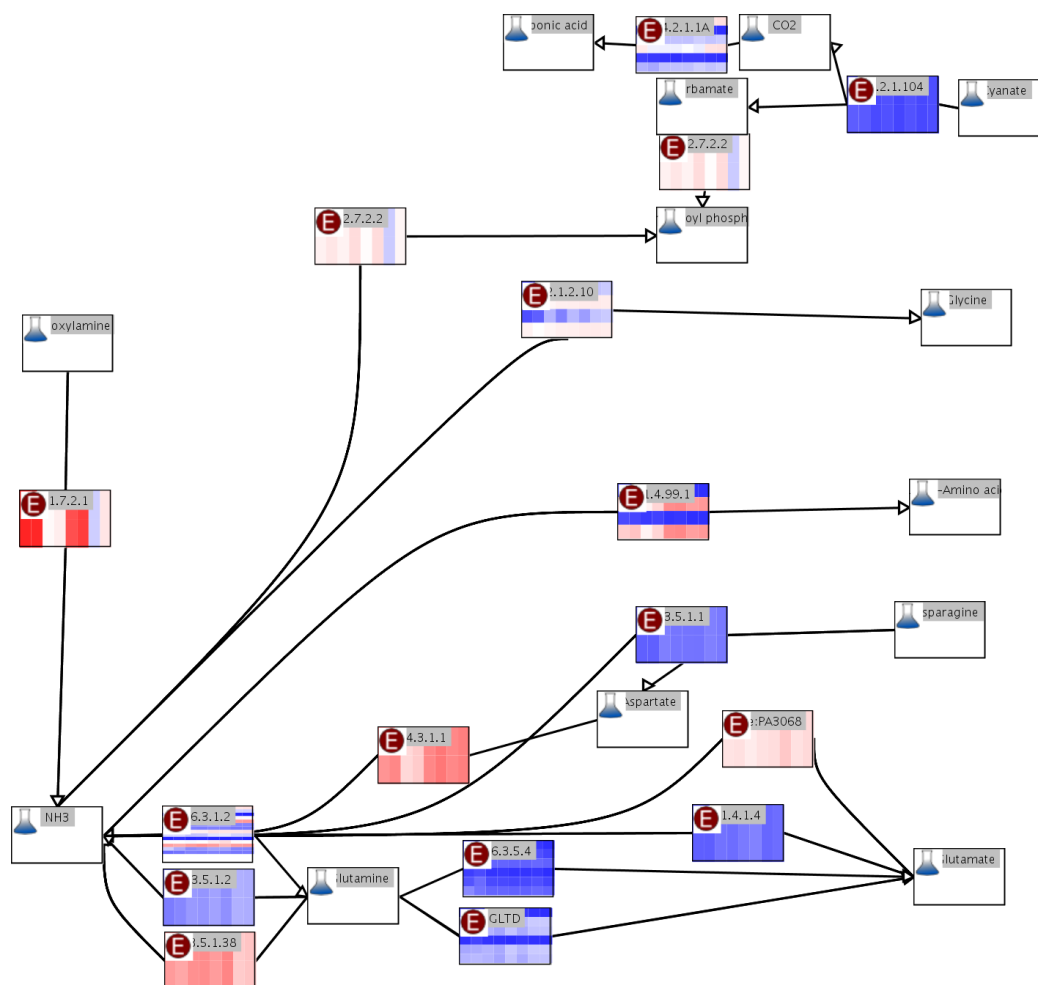


Figure 5: Typical view of KEGG Pathway showing enzymes and metabolites.

View The view Menu contains each setting adjustable at the startup of the viewer. See section 3.2 for details. Click on “Detach Menu” to bring up a window containing all options.

Pathway The “Pathway” menu contains the following options:

- **bfSelect Pathway:** Allows to choose a new pathway. Brings up a list of all KEGG Pathways. To select a pathway, double-click on the respective row. Pathways highlighted in gray are not locally available and must be downloaded from KEGG or are not available for the selected species.
- **bfDetails:** Allows to hide components depending on their connection degree. “All Nodes” shows each node, “Backbone” hides all nodes that have less than two edges, “Hubs” only retains nodes with three or more edges.
- **bfPathway License:** Shows license terms applying to the KEGG pathways.



Components The “Components”-Menu contains the following options:

- bfComponent Inspector: Brings up the component inspector.
- bfSelect All: Selects all components.
- bfClear Selection: Unselects all selected components.
- bfShow all: Un-hides all hidden components

3.3.3 Changing the Way Things look like

There are several ways to change the appearance of the plot:

- Renderers can be adjusted globally (menu View / Renderer Settings) or for a component individually (component context menu)
- Components can be freely moved, single or in groups
- Edges can be adjusted (menu View / Reaction settings, Relation settings).
- Color gradients can be adjusted to highlight different expression profiles or meta information (menu View / Coloring)
- Pathway links can be shown or hidden, relations to them can be shown or hidden (menu View / Display settings)
- Components can be hidden (component context menu, background menu, Component Inspector).
- The depth of details of the pathway can be adjusted (menu Pathway/Details).

3.3.4 Switching between Pathways

There are two ways to switch between pathways:

- Double click on a Pathway Link, or use the “Load Pathway...” function from its context menu.
- Choose “Select Pathway form the “Pathway” menu and choose the correct pathway from the list.

3.4 Additional KEGG Tools

Two additional tools for working with KEGG pathways are available in Mayday. They can be found in the category “Pathway” in the Probe List menu. Initially, the dialog described above queries the necessary information. All display settings, however are unused.



3.4.1 KEGG Pathway Overview

The plugin displays a list of all pathways for which genes could be found in the selected probe lists, among with the percentage of genes found (of the total number of genes in the pathway). The results are presented in a table view.

3.4.2 KEGG Pathways to ProbeList

This plugin creates one probe list for each pathway, containing all genes from the original probe list that are available in this pathway.

4 Using the SBGN Pathway Viewer

4.1 Data Prerequisites

The SBGN Pathway Viewer has the following prerequisites:

- A BioPax OWL file containing one or more metabolic pathways.
- A mapping of probes to identifiers used in the selected BioPax file. This mapping may be in three different forms:
 - The probe names or
 - The probe display names or
 - Any MIO Group containing String MIOs can be used.

These mappings must be available in Mayday when the viewer is used.

The user is queried for this mapping when the viewer starts.

4.2 Running the SBGN Pathway viewer

Run the SBGN Pathway Viewer from the Probe List Menu. It can be found in the Visualization sub menu. On start, a settings panel will show up. In this panel, some settings must be made in order to make the viewer work correctly.

- bfPathway File: Select a BioPax OWL file. These files are available from several sources, including any *Cyc-Database, Pathway Commons, KEGG and others. This setting is required.
- bfID Mapping: Here, the user can choose if the probe names, probe display names or any MIO group containing strings should be used to map BioPax identifiers to probe identifiers. For example, if the probe identifiers are Affymetrix probe set ids, these may not be directly mapped to the identifiers from the file. However, a MIO group containing Gene symbols (“il18r”, “gapdh”, “akt3”) can be used. Usable identifiers depend on the organism. For example, for *Pseudomonas aeruginosa*, names following the PAXxxx- naming convention are optimal. This setting is required.



- **bfRenderer Settings:** Here, the renderer can be set. See section 2.3 for details. The checkbox “Display SBGN” controls whether components associated with one or more probes should be rendered as SBGN or if the expression profile should be rendered using the selected renderer.
- **Layouter Settings:** Controls how the pathway should be layouted. There are several options for doing so:
 - **bfUse Pathway Layouter:** Sets if a recursive layouting scheme that uses several layouters for different types of pathways should be used (Recommended)
 - **bfLinear Layouter, bfCircular Layouter, bfBranched Layouter, bfComplex Layouter:** The layouters for the different kinds of pathway topologies. Good choices are Linear: Snake Layout, Circular: Circular Layout, Branched Layouter: Hierarchical Layout, Complex Layouter: Force Based.
 - **bfLayout Side Components:** Heuristically layout the side components, i.e. enzymes, substrates around the reaction nodes.
 - **bfLayouter:** The layouter used if “Use Pathway Layouter” is not selected.
- **bfDisplay Settings:** Controls several display options:
 - **bfDisplay Side Nodes:** Hide enzymes and substrates that are connected with less than two reactions.
 - **bfSummarize reactions:** If checked, a summary of the reaction activity is displayed at the reaction nodes. The Summary Settings control the way this summary is calculated. In general, the activity profiles of all adjacent components is used.
 - * **bfSummary method:** How the summary is calculated: Options include: Mean, Median, Minimum, Maximum,
 - * **bfWeight method:** There are different methods for weighting the incoming and outgoing edges of the reaction: All positive, and any possible combination of positive, negative and zero weights for incoming and outgoing edges.

4.3 Selecting a pathway

To select a pathway, choose one from the list in the dialog “Select Pathway”. The name, number of reactions and additional names are displayed for each pathways. The text field on the top of the dialog allows to search the list. It supports regular expressions.



4.4 Working with SBGN Pathways

In this viewer, pathway components are displayed as SBGN glyphs. A reference for SBGN can be found at <http://sbgn.org>. The most common glyphs are a circle, which represents a small chemical, a small box, which represents a reaction, and a rounded box, which represents a macromolecule, usually an enzyme.

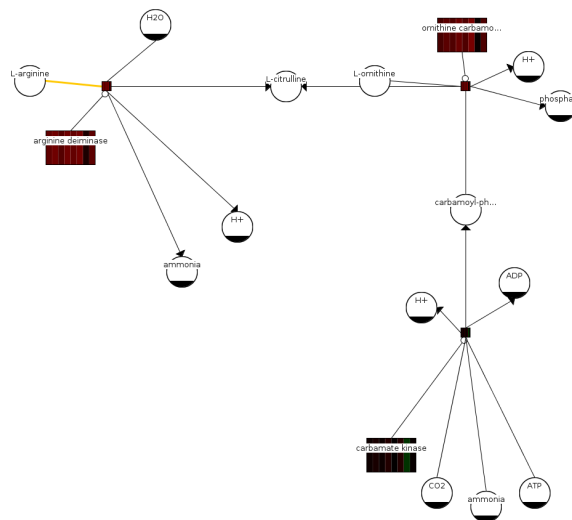


Figure 6: SBGN viewer plot of a simple pathway.

4.4.1 Menu View

The menu "View", located in the main menu bar, contains all options explained above in section 4.2. Additionally, "Show Controls" invokes the control panel and "Enhance/ Select Pathway" allows to select a new pathway.

4.4.2 Component Context Menu

In addition to the options described in section 2.2, this menu has the following options:

- **bfCreate Probe List from this Node:** A new probe list is created containing all probes associated with this component.
- **bfDisplay:** Decides what to display at this node. If more than one probe is associated with one component, the user can decide which one should be displayed. Also, the mean and median of the probes can be displayed. Applies not if heat map or profile plot renderers are used.
- **bfAnnotations:** Shows the annotations extracted from the BioPax file .



4.4.3 Viewer Control

The viewer control allows a more user friendly control of the SBGN pathway viewer properties than the menus. It also provides a list of components in the current plot.

Tool Bar From left to right, the options are:

- Show Side nodes
- Hide Side nodes
- Show SBGN
- Hide SBGN (i.e. show expression profiles)
- Show reaction summary profile
- Hide reaction summary profile

For details, see 4.2.

Pathway Entities The viewer controls shows a list of all entities, i.e. Reactions, Small Chemicals, Proteins and Enzymes and Complexes present in the current pathway. It features the name, the plotted image, the position and the visibility status of the components. Right-click on a row opens the components context menu, left-click scrolls the main plot to ensure the component is visible and marks the component with a red ellipse.

Reactions A small plot is shown that shows how the reactions are connected.

This Mayday How-To was written and edited by Stephan Symons. If you have comments or questions please contact the author via email, symons@informatik.uni-tuebingen.de. The latest version of this document can be found at <http://www.zbit.uni-tuebingen.de/pas/mayday>.
