

Cytoscape 2.2



User Manual

Nov. 2005

The Cytoscape Collaboration

The **Cytoscape** project is an ongoing collaboration between:



University of California at San Diego

Institute for Systems Biology



Memorial Sloan-Kettering Cancer Center

Institut Pasteur



Funding for Cytoscape is provided by a federal grant from the U.S. National Institute of General Medical Sciences (NIGMS) of the National Institutes of Health (NIH) under award number GM070743-01. Corporate funding is provided through a contract from Unilever PLC.

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1. Introduction

Cytoscape is an open-source community software project for integrating biomolecular interaction networks with high-throughput expression data and other molecular states into a unified conceptual framework. Although applicable to any system of molecular components and interactions, Cytoscape is most powerful when used in conjunction with large databases of protein-protein, protein-DNA, and genetic interactions that are increasingly available for humans and model organisms. A software “Core” provides basic functionality to layout and query the network; to visually integrate the network with expression profiles, phenotypes, and other molecular states; and to link the network to databases of functional annotations. The Core is extensible through a straightforward plug-in architecture, allowing rapid development of additional computational analyses and features. **The central organizing metaphor of Cytoscape is a network graph, with genes, proteins, and molecules represented as nodes and interactions represented as links, i.e. edges, between nodes.**

Development

Cytoscape is a collaborative project between the Institute for Systems Biology (Dr. Leroy Hood), the University of California San Diego (Dr. Trey Ideker), Memorial Sloan-Kettering Cancer Center (Dr. Chris Sander) and the Institut Pasteur (Dr. Benno Schwikowski).

Visit <http://www.cytoscape.org> for more information.

License

Cytoscape is protected under the GNU LGPL (Lesser General Public License). The License is included as an appendix to this manual, but can also be found online:

<http://www.gnu.org/copyleft/lesser.txt> Cytoscape also includes a number of other open source libraries, which are detailed in Section 10, Acknowledgements below.

What's New in 2.2

Cytoscape version 2.2. contains several new features, plus improvements in the performance and usability of the software. These include:

- Enhanced support for node and edge attribute handling, including a powerful new attribute browser, for navigating, defining, and editing node and edge attributes. For plugin coders, this also includes a greatly improved API (`cytoscape.data.CyAttributes`).
- Support for dockable, tabbed panels (CytoPanels).
- A set of Cytoscape editors for building and modifying networks interactively by adding nodes and edges to a drawing canvas.
- Improved support for ontologies and other structured annotations.
- Simplified mechanism for saving Visual Styles in between sessions.
- A new GML visual style to manage to manage visual properties from GML files
- Many performance improvements and bug fixes.

2. Launching Cytoscape

Cytoscape is a Java application that runs on Linux, Windows, and Mac OS X. Although Cytoscape handles arbitrary types and sizes of interaction network, it is most powerful when used in conjunction with large interaction data sets such as are currently available for species such as *Saccharomyces cerevisiae* (budding yeast).

System requirements:

The system requirements for Cytoscape depend on the size of the networks the user wants to load, view and manipulate. We recommend a recent computer (1GHz CPU or higher) with a high-end graphics card and at least 512MB of free physical RAM. Cytoscape expects a minimum screen resolution of 1024x768.

There are a number of options for downloading and installing Cytoscape:

- For Windows and Linux platforms, one-step installation is available via *InstallAnywhere*. For one-step installation, go to <http://www.cytoscape.org>, click Download Cytoscape, and follow the on-screen instruction.
- For Mac OS X, we provide an alternative installation, available as a .dmg.zip file. When installed via this method, Cytoscape functions as a regular Mac application, and can be accessed via your Applications folder.
- Finally, you can download and install a compressed archive distribution. Instructions for this option are provided below.

(1) Download and unpack the distribution. Cytoscape is distributed as a compressed archive (tar.gz or zip) containing the following files and directories:

cytoscape.jar	Main Cytoscape application (Java archive)
cytoscape.props	User-configurable properties and preferences
vizmap.props	User-configurable visual mapping preferences
cytoscape.sh	Script to run Cytoscape from command line (Linux, Mac OS X)
cytoscape.bat	Script to run Cytoscape (Windows)
LICENSE.txt	Cytoscape GNU License
Cytoscape2_2Manual.pdf	Cytoscape 2.2 Manual (the document you are reading now)
sampleData/	
galFiltered.gml	Sample molecular interaction network file *
galFiltered.sif	Identical network in Simple Interaction Format *

galExpData.pvals	Sample gene expression matrix file *
BINDyeast.sif	Network of all yeast protein-protein interactions in the BIND database as of July, 2004 **
BINDhuman.sif	Network of all human protein-protein interactions in the BIND database as of July, 2004 **
yeastHighQuality.sif	Sample molecular interaction network file ***
annotation/	Directory containing Gene Ontology database entries (currently for yeast only). Info in this directory is used to associate gene names with synonyms as well as process, function, and cellular location data.
plugins/	Directory containing cytoscape PlugIns, in .jar format.

* From Ideker et al, Science 292:929 (2001)

** Obtained from data hosted at http://www.blueprint.org/bind/bind_downloads.html

*** From von Mering et al, Nature, 417:399 (2002) and Lee et al, Science 298:799 (2002)

(2) If necessary, install Java. If not already installed on your computer, download and install the Java 2 Runtime Environment, version 1.4.2 or higher. It can be found at:

<http://java.sun.com/j2se/1.4.2/download.html>

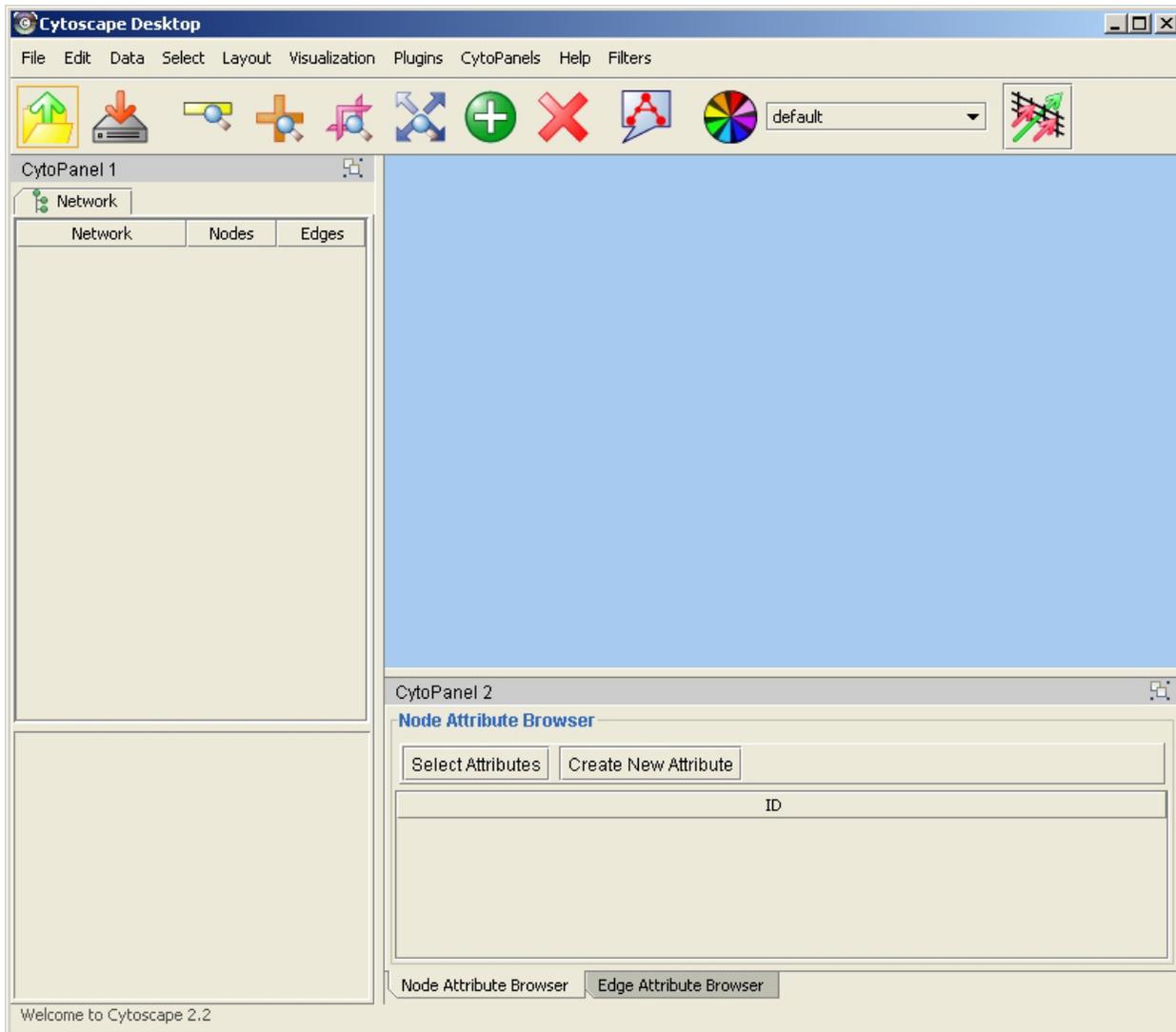
(3) Launch the application by running "cytoscape.sh" from the command line (Linux or Mac OS X) or double-clicking "cytoscape.bat" (Windows). Alternatively, you can pass the .jar file to Java directly using the command "java -jar cytoscape.jar". In Windows, it is also possible to directly double-click the .jar file to launch it. However, this does not allow specification of command-line arguments (such as the location of the annotation data directory, see the section on command line arguments for details). On **Mac OS X**, users who downloaded the Mac OS X version of Cytoscape, can double-click on the Cytoscape icon to start Cytoscape. Either double-clicking or dragging onto the Cytoscape application any .sif or .gml file will load that file into Cytoscape.

! Important Note:

For the application to work properly, ALL FILES MUST BE LEFT IN THE DIRECTORY IN WHICH THEY ARE UNPACKED. The core Cytoscape application assumes this directory structure when looking for certain files, such as cytoscape.props, vizmap.props, and the annotation/ database.

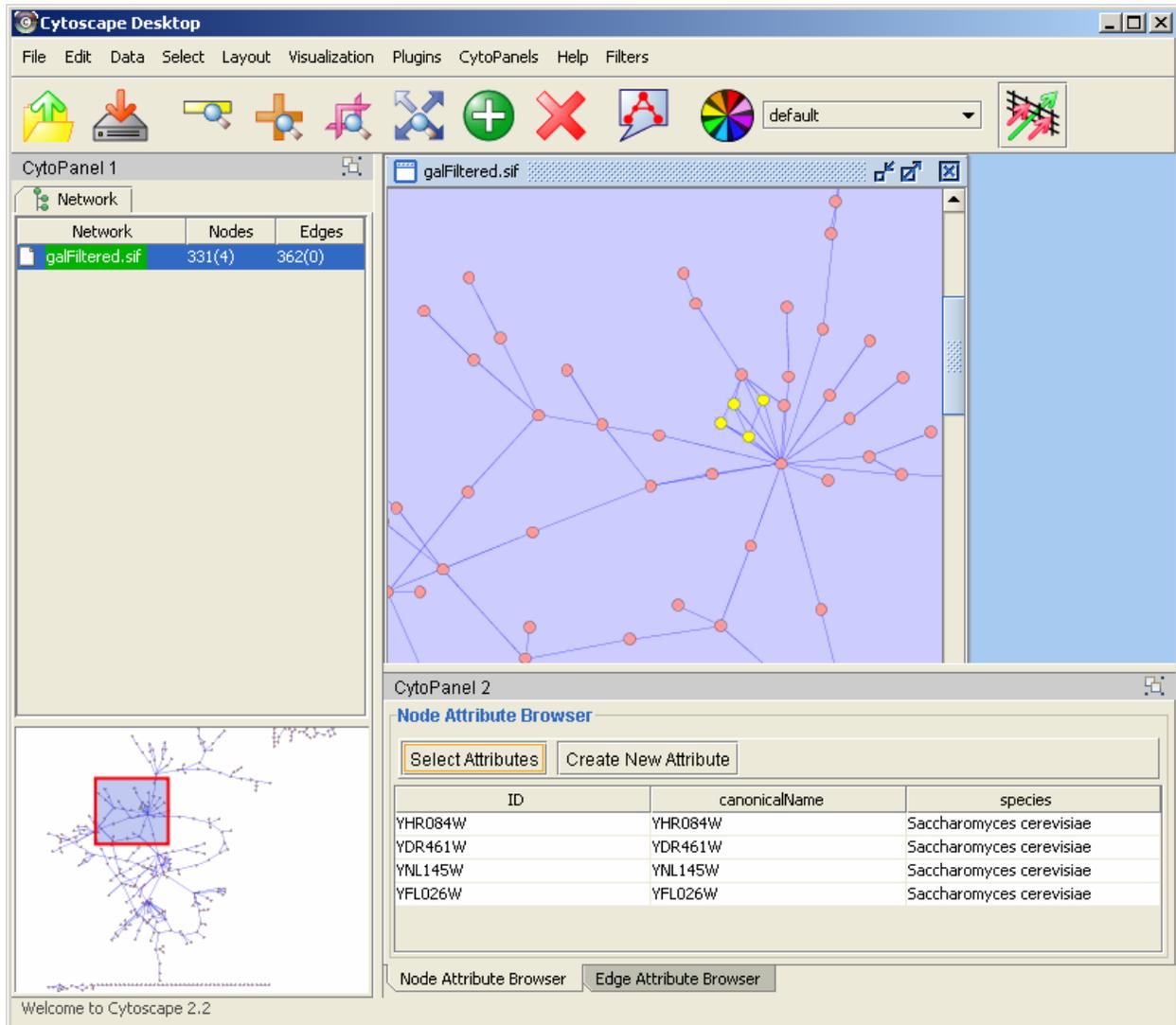
Cytoscape Window

When you succeed in launching Cytoscape, a window will appear that looks like this:



3. Quick Tour of Cytoscape

When a network is loaded, Cytoscape will look something like the image below:



The main window here has several components:

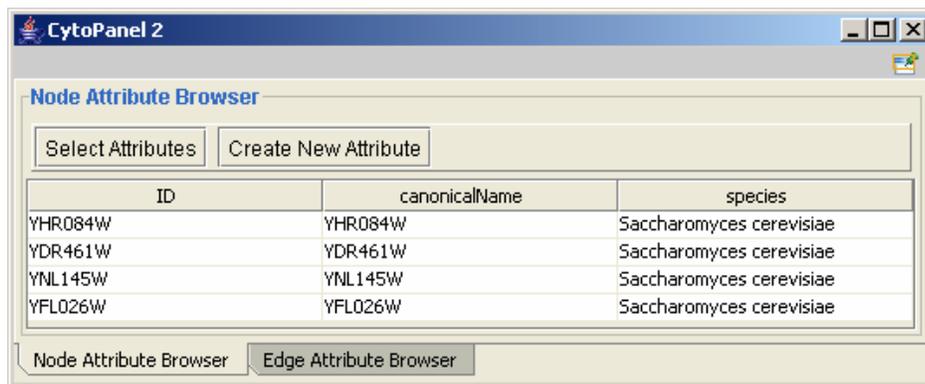
1. The menu bar at the top (See below for more information about each menu item).
2. The toolbar, which contains icons for commonly used functions. These functions are also available via the menus. Hover the mouse pointer over an icon and wait momentarily for a description to appear as a tooltip.
3. The network management panel (top-left). This contains an optional network overview pane (bottom-left overview of the network).
4. The main network view window, which displays the network.

5. The attribute browser panel (bottom panel), which displays attributes of selected nodes and edges and enables you to modify the values of attributes.

The network management and attribute browser panels are dockable tabbed panels known as CytoPanels. You can undock any of these panels by clicking on the Float Window control in the upper-right corner of the CytoPanel.



If you select this control, say on the attribute browser panel, you will now have two Cytoscape windows, the main window, and a new window labeled CytoPanel 2, similar to the one shown below.



Note that CytoPanel 2 now has a Dock Window control. If you select this control, the window will dock onto the main window.

Cytoscape also has a set of editors that enable you to build and modify networks interactively by dragging and dropping nodes and edges from a palette onto the main network view window. The editors can be invoked using the Set Editor command on the File menu. An example of a simple biomolecule editor, with the palette contained in CytoPanel 1, is shown below.

Cytoscape Desktop

File Edit Data Select Layout Visualization Plugins CytoPanels Help Filters

CytoPanel 1

Network Editor

Cytoscape Editor

To add a node to a network, drag and drop a shape from the palette onto the canvas.

To connect two nodes with an edge, drag and drop the arrow onto a node on the canvas, then move the cursor over a second node and click the mouse.

Directed Edge

Protein

Catalysis

Small Molecule

Biochemical Reaction

Net:0

Nodes: 5 (0 selected) Edges: 4 (0 selected)

CytoPanel 2

Node Attribute Browser

Select Attributes Create New Attribute

ID	canonicalName	species

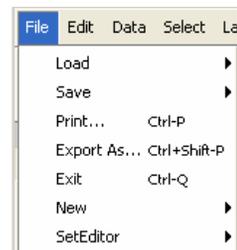
Node Attribute Browser Edge Attribute Browser

Welcome to Cytoscape 2.2

The Menus

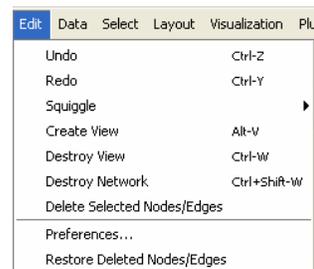
File

The File menu contains most basic file functionality: File / Load for loading a variety of file types; File / Save for saving. File/Help displays a credits screen. File / Print allows printing. File / Export As... allows you to export to a file in a number of graphics formats (such as postscript). File / Exit closes all windows of Cytoscape and exits the program. File/New opens up a New network for editing. This menu item is disabled until an editor is chosen using the File/SetEditor menu item.



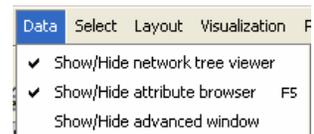
Edit

The Edit menu contains Undo and Redo menu items which undo and redo edits made in the Attribute Browser. The menu also contains a Squiggle feature that enables you to mark up your network. This can be particularly useful during live presentations. There are also options for creating and destroying views (graphical representations of a network) and networks (the network data – not yet visualized), as well as an option for deleting selected nodes and edges from the current network. All deleted nodes and edges can be restored to the network via the Edit/Restore Deleted Nodes/Edges menu item. The Edit Menu also supports Preferences editing for properties and plug-ins via a Preferences Dialog. Preferences editing operates on the cytoscape.props file associated with the user's instance of Cytoscape. See “Commands Line Arguments and Properties” for more information.



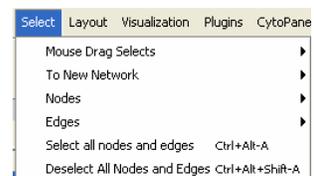
Data

The Data menu allows you to display or hide the network management panel (CytoPanel 1). It allows you to display or hide the attribute browser (CytoPanel 2), which lets you view and edit attributes assigned to both nodes and edges. (See section 7. *Node and Edge Attributes*) The Data menu allows you to display an advanced window (contents of CytoPanel 3).



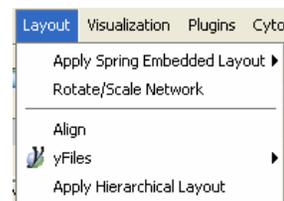
Select

The Select menu contains methods and operations for selecting nodes and edges, and using the current selection to create a new network and an associated view.



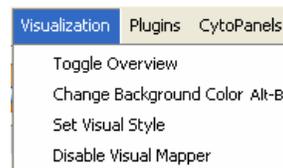
Layout

The Layout menu has an array of features for organizing the network visually according to one of several algorithms, aligning and rotating groups of nodes, and adjusting the size of the network. Most of these features are available from plugins that are packaged with Cytoscape 2.2



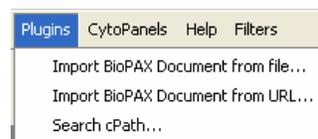
Visualization

The Visualization menu provides options for changing the mapping from biological data to a visual representation: colors of nodes, thickness of edges, etc. These features are explored in-depth in section on visual styles. This menu also provides an Overview (Bird's Eye view) of your entire network, which is helpful for navigating very large networks.



PlugIns

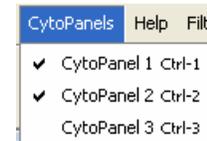
The PlugIns menu has menu entries or choices added by plugins that have been loaded, such as "Import BioPAX Document from file".



Note: A list of Cytoscape PlugIns with descriptions is available online at: <http://cytoscape.org/plugins2.php>

CytoPanels

CytoPanels are floatable / dockable panels which cut down on the number of pop-up windows within Cytoscape. The CytoPanels menu allows you to show or hide CytoPanel 1, CytoPanel 2, or CytoPanel 3 based on the menu item selected.



Note:

In order for these keyboard short-cuts to work, the Cytoscape Desktop Window needs to have the focus.

Help

The **Help** menu allows you to launch the online help viewer and browse the table of contents (Contents...), or view the help text associated with a context-sensitive selection (Context Sensitive...). By selecting Context Sensitive... menu item and then selecting a GUI component, the help related to the selected item is launched. The “About...” menu item displays information about the running version of Cytoscape.



Filters

This menu allows you to bring up a user interface for defining and running filters (see 10. *Filters*). Filters enable you to extract subnetworks based upon the values of node and edge attributes.

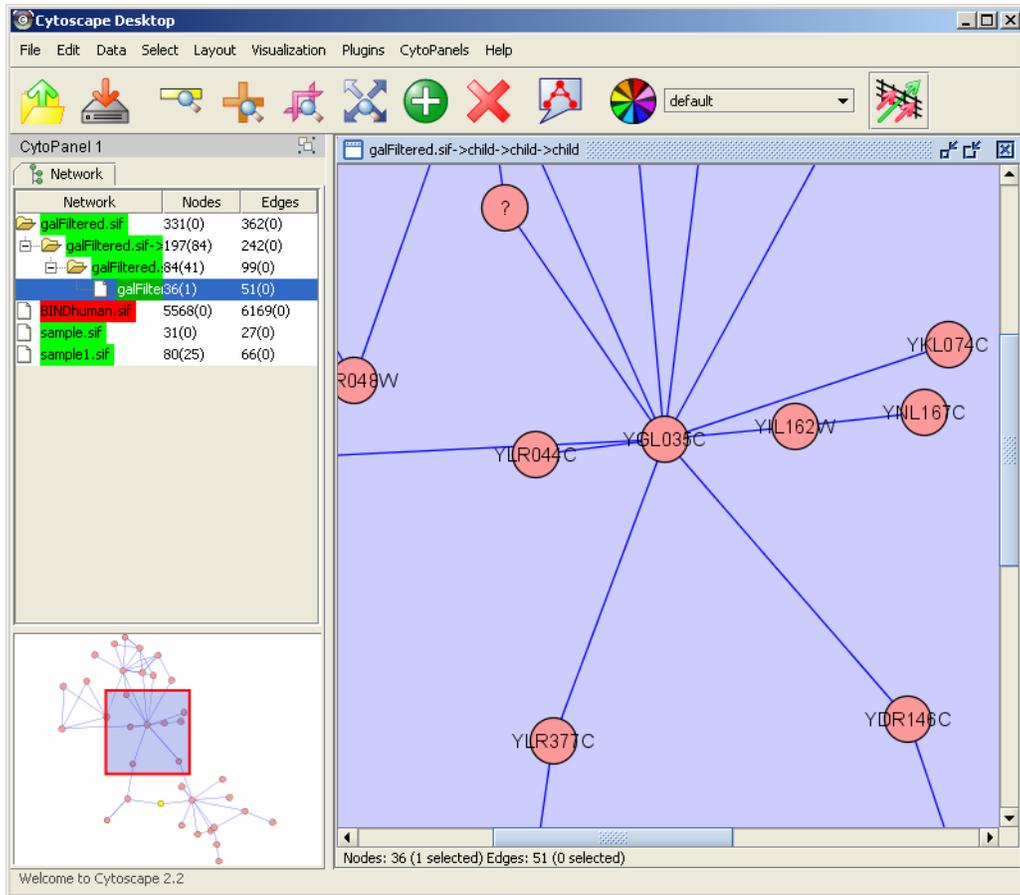


Additional menus may appear, depending on the set of PlugIns you have chosen to load.

Network Management

Cytoscape 2.2 allows multiple networks to be loaded at a time, either with or without a view. A network stores all the nodes and edges that are loaded by the user and a view displays them. You can have many views of the same network. Networks (and their optionally associated views) can be organized hierarchically.

An example where a number of networks have been loaded and arranged hierarchically is shown below:



The network manager (top-right tree view in CytoPanel 1) shows the networks that are loaded. Clicking on a network here will make that view active in the main window, if the view exists (green highlighted networks only). Each network has a name and size (number of nodes and edges), which are shown in the network manager. If a network is loaded from a file, the network name is the name of the file.

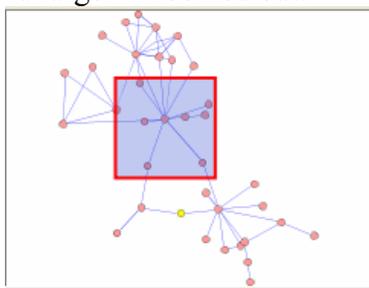
Some networks are very large (thousands of nodes and edges) and can take a long time to display. For this reason, a network in Cytoscape may not contain a 'view'. Networks that have a view are highlighted in green and networks that don't have a view are highlighted in red. You can create or destroy a view for a network by right-clicking the network name in the network manager or by choosing the appropriate option in the edit menu. You can also destroy previously loaded networks this way. In the picture above, seven networks are loaded, six green ones with views and one red ones without a view.

Certain operations in Cytoscape will create new networks. If a new network is created from an old network, for example by selecting a set of nodes in one network and copying these nodes to a new network (via the Select->To New Network option), it will be shown as a child of the network that it was derived from. In this way, the relationships between networks that are loaded in Cytoscape can be seen at a glance. Networks in the top part of the tree in the figure above were generated in this manner.

The available network views are also arranged as multiple, overlapping windows in the network view window. You can maximize, minimize, and destroy network views by using familiar window controls.

The Network Overview Window

The network overview window shows an overview (or ‘bird’s eye view’) of the network. It can be used to navigate around a large network view. This feature can be turned on or off via the Visualization menu. The red-outlined blue rectangle in the overview window shown below can be dragged with the mouse to navigate to a part of the network. The size of the navigation rectangle depends on the size of the active view and the zoom level of the view. The rectangle is smaller if the view is zoomed in and larger if zoomed out.



4. Command Line Arguments and Properties

Cytoscape recognizes a number of optional command line arguments, including run-time specification of network files and expression data:

- g | -graph** <GML network filename> (xxx.gml)
Loads a network file in GML format (see section on Building and Storing Interaction Networks)
- i | -interaction** <SIF interactions filename> (yyy.sif)
Loads a network file in SIF format (see section on Building and Storing Interaction Networks)
- b | -BDS | -bioDataServer** <bioData directory> (e.g. annotation/manifest)
Specifies which directory to use for the BioDataServer annotations
- e | -expression** <expression filename> (zzz.pvals)
Loads an expression data file (see section on Loading Gene Expression Data)
- n | -nodeAttributes** <nodeAttributes filename> (one or more)

- Loads node attributes files (see section on Node and Edge Attributes)
- j | -edgeAttributes** <edgeAttributes filename> (one or more)
Loads edge attributes files
(see section on Node and Edge Attributes)
-)
- s | -species** Set the default species name
- c | -noCanonicalization** Turn off default node name canonicalization
- h | -help | -help | --help** Help: display these command line arguments
- p | -plugin | --JLD | --JLW | --JLL** Specify a list of plugins (jar files), directories containing plugins, URLs (http://) to jar files, or URLs to manifest files listing jar files
- props** <properties file> specify and load a properties file (usually named cytoscape.props)
- vprops | -vp | -vizprops** <properties file> specify and load a visual mapping properties file (usually names vizmap.props)
- noDialog | -suppressView** Do not popup informational dialog when express file is loaded
- vt | --VT** <view threshold> Specify the threshold # of nodes at which views will not automatically be created
- project** <project file> Specify the location of the project file
- script | --script** <script text...> **-end** Specify script text
- rp | -resourcePlugin** <resource plugins...>
Specify the list of resource plugins

Note that most data sets may also be loaded after Cytoscape is running.

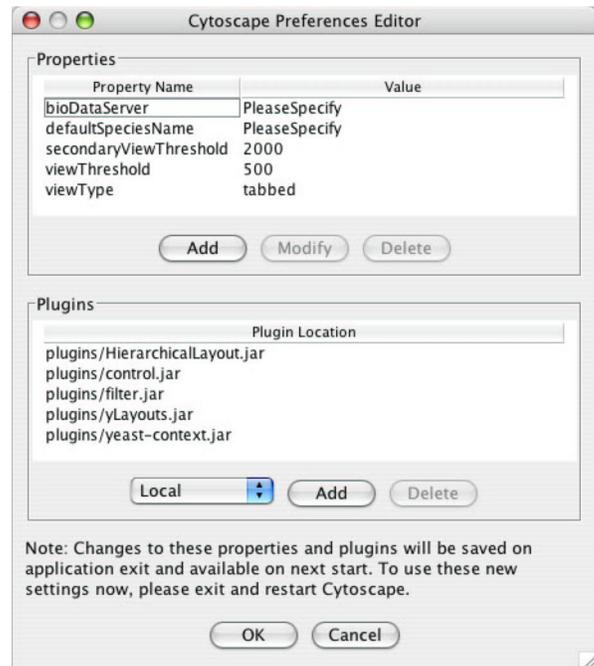
Additional command line arguments that are not recognized by the Cytoscape core are passed to the PlugIn modules. Please refer to the documentation for each specific PlugIn for more details.

Cytoscape Properties

The Cytoscape Preferences Dialog, accessed via Edit->Preferences..., has sections for general properties display/editing and plugins specification via the properties mechanism. Preferences in Cytoscape are stored in the form of Java properties specified in the cytoscape.props file located in the users' working directory, home directory or Cytoscape distribution directory (called ".cytoscape" and located in the users' home directory). This file is automatically loaded at startup time and written upon normal exit of the application.

Cytoscape properties are displayed in the Properties section of the dialog. These properties are configurable via Add, Modify and Delete operations.

The specification of plugins to be loaded into Cytoscape at startup time is also supported in cytoscape.props and accessible in this dialog under the Plugins section. In this special case, the plugins property specifies a comma-separated list of jar files or URLs to jar files containing plugins. This property is parsed into its constituents and presented and managed in the Plugins table, as at left.



Some common properties are described below.

Property name	Default value	Valid values	Related command line argument
defaultSpeciesName	PleaseSpecify	species names this value must match the name in the first line of the file specified in the bioDataServer's manifest for synonyms e.g., for yeast synonyms, specify <i>Saccharomyces cerevisiae</i>	-s -species
bioDataServer	PleaseSpecify	annotation/manifest, and other manifest file locations	-b -BDS
viewThreshold	500	integers > 0	-vt --VT
secondaryViewThreshold	2000	integers > 0	
viewType	tabbed	tabbed	
plugins		comma-separated list of jar files containing plugins, or URL's to jar files containing plugins (e.g.,	-p -plugin --JLD

Property name	Default value	Valid values	Related command line argument
		http://server/my-plugin.jar)	--JLW --JLL
defaultWebBrowser			

5. Building and Storing Interaction Networks

Cytoscape reads an interaction network in two ways: from a simple interaction file (SIF or .sif format) or from a standard format known as Graph Markup Language (GML or .gml format). SIF specifies nodes and interactions only, while GML stores additional information about network layout and allows network data exchange with a variety of other network display programs. Typically, SIF is used to import interactions when building a network for the first time, since it is easy to create in a text editor or spreadsheet. Once the interactions have been loaded and layout has been performed, the network may be saved to and subsequently reloaded from GML format in future Cytoscape sessions. Both SIF and GML are ASCII text files, and you can edit and view them in a regular text editor. Additionally, GML is supported by some other network visualization tools.

SIF FORMAT:

The simple interactions format is convenient for building a graph from a list of interactions. It also makes it easy to combine different interaction sets into a larger network, or add new interactions to an existing data set. The main disadvantage is that this format does not include any layout information, forcing Cytoscape to re-compute a new layout of the network each time it is loaded.

Lines in the SIF file specify a source node, a relationship type (or edge type), and one or more target nodes:

```
nodeA <relationship type> nodeB
nodeC <relationship type> nodeA
nodeD <relationship type> nodeE nodeF nodeB
nodeG
...
nodeY <relationship type> nodeZ
```

A more specific example is:

```
node1 typeA node2
node2 typeB node3 node4 node5
node0
```

The first line identifies two nodes, called `node1` and `node2`, and a single relationship between `node1` and `node2` of type `typeA`. The second line specifies three new nodes, `node3`, `node4`, and `node5`; here "node2" refers to the same node as in the first line. The second line also specifies three relationships, all of type `typeB` and with `node2` as the source, with `node3`, `node4`, and `node5` as the targets, respectively. This second form is simply shorthand for specifying multiple relationships of the same type with the same source node. The third line indicates how to specify a node that has no relationships with other nodes. This form is not needed for nodes that do have relationships, since the specification of the relationship implicitly identifies the nodes as well. Duplicate entries are allowed and indicate multiple edges between the same nodes. For example, the following specifies three edges between the same pair of nodes, two of type `pp` and one of type `pd`:

```
node1 pp node2
node1 pp node2
node1 pd node2
```

Edges connecting a node to itself (self-edges) are also allowed:

```
node1 pp node1
```

Every node and edge in Cytoscape has an identifying name, most commonly used with the node and edge data attribute structures. Node names must be unique as identically names nodes will be treated as identical nodes. The name of each node will be the name in this file by default (unless another string is mapped to display on the node using the visual mapper. This is discussed in the section on visual styles. The name of each edge will be formed from the name of the source and target nodes plus the interaction type: for example, `sourceName edgeType targetName`.

The tag `<interaction type>` should be one of:

```
pp ..... protein – protein interaction
pd ..... protein -> DNA
          (e.g. transcription factor binding upstream of a regulating gene.)
```

Any text string will work, but the above are the conventions that have been followed thus far.

Additional interaction types are also possible, but not widely used, e.g.:

```
pr ..... protein -> reaction
rc ..... reaction -> compound
cr ..... compound -> reaction
gl ..... genetic lethal relationship
pm ..... protein-metabolite interaction
mp ..... metabolite-protein interaction
```

Even whole words or concatenated words may be used to define other types of relationships e.g. `geneFusion`, `cogInference`, `pullsDown`, `activates`, `degrades`, `inactivates`, `inhibits`, `phosphorylates`, `upRegulates`

Delimiters. Whitespace (space or tab) is used to delimit the names in the simple interactions file format. However, in some cases spaces are desired in a node name or edge type. The standard is that, if the file contains any tab characters, then tabs are used to delimit the fields and spaces are considered part of the name. If the file contains no tabs, then any spaces are delimiters that separate names (and names cannot contain spaces).

If your network unexpectedly contains no edges and node names that look like edge names, it probably means your file contains a stray tab that's fooling the parser. On the other hand, if your network has nodes whose names are half of a full name, then you probably meant to use tabs to separate node names with spaces.

Networks in simple interactions format are often stored in files with a ".sif" extension, and Cytoscape recognizes this extension when browsing a directory for files of this type.

GML FORMAT:

In contrast to SIF, GML is a rich graph format language supported by many other network visualization packages. The GML file format specification is available at:

<http://www.infosun.fmi.uni-passau.de/Graphlet/GML/>

It is generally not necessary to modify the content of a GML file directly. Once a network is built in SIF format and then laid out, the layout is preserved by saving to and loading from GML. Visual attributes specified in a GML file will result in a new visual style named "*Filename.style*" when that GML file is loaded

COMMANDS:

Load and save network files using the File menu of Cytoscape. Network files may also be loaded directly from the command line using the `-i` (SIF format) or `-g` (GML format) options.

FOR EXAMPLE:

To load a sample molecular interaction network in SIF format, use the menu File / Load / Network. In the resulting file dialog box, select the file "sampleData/galFiltered.sif". After a few seconds, a small network of 331 nodes should appear in the main window. To load the same interaction network as a GML, use the menu: File / Load / Network again. In the resulting file dialog box, select the file "sampleData/galFiltered.gml". Node and edge attribute files as well as expression data and extra annotation can be loaded as well.

NODE NAMING ISSUES IN CYTOSCAPE:

Typically, genes are represented by nodes, and interactions (or other biological relationships) are represented by edges between nodes. For compactness, a gene also represents its corresponding protein. Nodes may also be used to represent compounds and reactions (or anything else) instead of genes.

If a network of genes or proteins is to be integrated with Gene Ontology (GO) annotation or gene expression data, the gene names must exactly match the systematic ORF names specified in the

other data files. We strongly encourage naming genes and proteins by their systematic ORF name or standard accession number; common names may be displayed on the screen for ease of interpretation, so long as these are available to the program in the annotation directory or in a node attribute file. Cytoscape ships with all yeast ORF-to-common name mappings in a synonym table within the annotation/ directory. Other organisms will be supported in the future.

Why do we recommend using standard gene names? All of the external data formats recognized by Cytoscape provide data associated with particular names of particular objects. For example, a network of protein-protein interactions would list the names of the proteins, and the attribute and expression data would likewise be indexed by the name of the object.

The problem is in connecting data from different data sources that don't necessarily use the same name for the same object. For example, genes are commonly referred to by different names, including a formal "location on the chromosome" identifier and one or more common names that are used by ordinary researchers when talking about that gene. Additionally, database identifiers from every database where the gene is stored may be used to refer to a gene (e.g. protein accession numbers from Swiss-Prot). If one data source uses the formal name while a different data source used a common name or identifier, then Cytoscape must figure out that these two different names really refer to the same biological entity.

Cytoscape has two strategies for dealing with this naming issue, one simple and one more complex. The simple strategy is to simply assume that every data source uses the same set of names for every object. If this is the case, then Cytoscape can easily connect all of the different data sources.

To handle data sources with different sets of names, as is usually the case when manually integrating gene information from different sources, Cytoscape needs a data server that provides synonym information (See *12. Annotation.*). A synonym table gives a canonical name for each object in a given organism and one or more recognized synonyms for that object. Note that the synonym table itself defines what set of names are the "canonical" names. For example, in budding yeast the ORF names are commonly used as the canonical names.

If a synonym server is available, then by default Cytoscape will convert every name that appears in a data file to the associated canonical name. Unrecognized names will be preserved. This conversion of names to a common set allows Cytoscape to connect the genes present in different data sources, even if they have different names – as long as those names are recognized by the synonym server.

For this to work, Cytoscape must also be provided with the species to which the objects belong, since the data server requires the species in order to uniquely identify the object referred to by a particular name. This is usually done in Cytoscape by specifying the species name on the command line with the `-s` option or by adding a line to the `cytoscape.props` file of the form:

```
defaultSpeciesName=Saccharomyces cerevisiae
```

The automatic canonicalization of names can be turned off with the `-c` command line argument (i.e. `java -jar cytoscape.jar -c`) or by not loading any annotation. This canonicalization of names

currently does not apply to expression data. Expression data should use the same names as the other data sources or use the canonical names as defined by the synonym table.

6. Loading Gene Expression Data

Interaction networks are certainly useful as stand-alone models. However, they are most powerful for answering scientific questions when integrated with further information about the biology associated with the network, such as gene or protein expression levels. Once loaded, expression ratios/levels may be visually superimposed on the network, used in a filter to select a subset of nodes, or used to identify active modules and subsystems (via plugin analysis tools). An expression data set can be loaded at any time, but are only relevant once a network has been loaded.

FORMAT:

Gene expression ratios are specified over one or more experiments using a text file. The file consists of a header and a number of space- or tab-delimited fields, one line per gene, with the following format:

```
GeneName [CommonName] ratio1 ratio2 ... ratioN [pval1 pval2 ... pvalN]
```

Brackets [] indicate fields that are optional. The first two fields are the systematic gene name followed by an optional common name. Expression ratios are provided for each experiment, optionally followed by a p-value per experiment or other measure of the significance of each ratio, i.e. whether the ratio represents a true change in expression (according to some statistical model.) Significance values are generated by a variety of software packages for analyzing expression data generated by DNA microarrays (for instance the VERA program, from the Institute of Systems Biology, <http://www.systemsbio.org/VERAandSAM>). A list of other microarray analysis packages is available at: <http://www.nslj-genetics.org/microarray/soft.html>

Example:

```
GENE DESCRIPT gal1RG.sig gal2RG.sig gal3RG.sig gal1RG.sig gal2RG.sig gal3RG.sig
YHR051W COX6 -0.034 -0.052 0.152 1.177 0.102 0.857
YHR124W NDT80 -0.090 -0.000 0.041 0.130 0.341 0.061
YKL181W PRS1 -0.167 -0.063 -0.230 -0.233 0.143 0.089
```

The first line is a header line giving the names of the experimental conditions. Note that each condition is duplicated; the first set of columns gives expression ratios and the second set gives significance values. The significance columns can be omitted if your data doesn't include significance measures. Every remaining row specifies the values for a gene, starting with the formal name of the gene, then a common name, then the ratios, then the significance values.

Some variations on this basic format are recognized: see the formal file format specification below for more information. Expression data files commonly have the file extensions ".mrna" or ".pvals", and these file extensions are recognized by Cytoscape when browsing for data files.

COMMANDS:

Load an expression data file using the File menu of Cytoscape, or by specifying the filename using the `-e` option at the command line. The `-x` command line option indicates that the expression data should not be loaded into node attributes. This is an advanced option, and is typically only used when the number of expression conditions is sufficiently large that it becomes unwieldy in the normal user interface.

FOR EXAMPLE:

Load a sample gene expression data set using the menu: File / Load / Expression Matrix File. In the resulting file dialog box, select the file “sampleData/galExpData.pvals”. As described in the following sections, Cytoscape is now ready to integrate these data with the underlying molecular interaction network.

Detailed file format (Advanced users)

In all expression data files, any whitespace (spaces and/or tabs) is considered a delimiter between adjacent fields. Every line of text is either the header line or contains all the measurements for a particular gene. No name conversion is applied to expression data files. .

The names given in the first column of the expression data file should match exactly the names used elsewhere (i.e. in SIF or GML files).

The first line is a header line with one of the following three formats:

```
<text> <text> cond1 cond2 ... cond1 cond2 ... [NumSigConds]
<text> <text> cond1 cond2 ...
<tab><tab>RATIOS<tab><tab>...LAMBDA5
```

The first format specifies that both expression ratios and significance values are included in the file. The first two text tokens contain names for each gene. The next token set specifies the names of the experimental conditions; these columns will contain ratio values. This list of condition names must then be duplicated exactly, each spelled the same way and in the same order. Optionally, a final column with the title `NumSigConds` may be present. If present, this column will contain integer values indicating the number of conditions in which each gene had a statistically significant change according to some threshold.

The second format is similar to the first except that the duplicate column names are omitted, and there is no `NumSigConds` fields. This format specifies data with ratios but no significance values.

The third format specifies an MTX header, which is a commonly used format. Two tab characters precede the `RATIOS` token. This token is followed by a number of tabs equal to the number of conditions, followed by the `LAMBDA5` token. This format specifies both ratios and significance values.

Each line after the first is a data line with the following format:

```
FormalGeneName CommonGeneName ratio1 ratio2 ... [lambda1 lambda2 ...] [numSigConds]
```

The first two tokens are gene names. The names in the first column are the keys used for node name lookup; these names should be the same as the names used elsewhere in Cytoscape (i.e. in the SIF or GML files). Traditionally in the gene expression microarray community, who defined these file formats, the first token is expected to be the formal name of the gene (in systems where there is a formal naming scheme for genes), while the second is expected to be a synonym for the gene commonly used by biologists, although Cytoscape does not make use of the common name column. The next columns contain floating point values for the ratios, followed by columns with the significance values if specified by the header line. The final column, if specified by the header line, should contain an integer giving the number of significant conditions for that gene. Missing values are not allowed and will confuse the parser. For example, using two consecutive tabs to indicate a missing value will not work; the parser will regard both tabs as a single delimiter and be unable to parse the line correctly.

Optionally, the last line of the file may be a special footer line with the following format:

```
NumSigGenes int1 int2 ...
```

This line specified the number of genes that were significantly differentially expressed in each condition. The first text token must be spelled exactly as shown; the rest of the line should contain one integer value for each experimental condition.

7. Node and Edge Attributes

Cytoscape allows the user to add arbitrary node and edge information to Cytoscape as node and edge **attributes**. Attributes could be, for example, annotation data on a gene or confidence values in a protein-protein interaction. These attributes can then be visualized in a custom user-defined way by setting up a mapping from data attributes to visual attributes (colors, shapes, etc.) See the section on visual styles for a discussion of this.

Node and edge attribute files are very simply formatted: A node attribute file begins with the name of the attribute on the first line, and on each following line, has the name of the node, followed by an equals sign, followed by the value of that attribute. Numbers and text strings are the most common attribute types. All values for a given attribute must have the same type. For example:

```
FunctionalCategory  
YAL001C = metabolism  
YAR002W = apoptosis  
YBL007C = ribosome
```

An edge attribute file has much the same structure, except that the name of the edge is the source node name, followed by the interaction type in parentheses, followed by the target node name. Directionality counts, so switching the source and target will refer to a different (or perhaps non-existent) edge. The following is an example edge attributes file:

```
InteractionStrength  
YAL001C (pp) YBR043W = 0.82
```

```
YMR022W (pd) YDL112C = 0.441
YDL112C (pd) YMR022W = 0.9013
```

Cytoscape treats edge attributes as directional, so note that the second and third edge attribute values refer to two different edges (source and target are reversed, though the nodes involved are the same).

Each attribute is stored in a separate file. Node and edge attribute files use the same format. Node attribute file names often use the suffix ".noa", while edge attribute file names use the suffix ".eda". Cytoscape recognizes these suffixes when browsing for attribute files.

Node and edge attributes may be loaded at the command line using the `-n` and `-j` options or via the File / Load menu.

When expression data is loaded using an expression matrix, it is automatically copied into the Node Attributes data structure unless explicitly specified not to.

Detailed file format (Advanced users)

Every attribute file has one header line that gives the name of the attribute, and optionally some additional meta-information about that attribute. The format is as follows:

```
attributeName (class=formal.class.of.value)
```

The first field is always the attribute name: it cannot contain spaces. If present, the class field defines the formal (package qualified) name of the class of the attribute values. For example, `java.lang.String` for Strings, `java.lang.Double` for floating point values, `java.lang.Integer` for integer values, etc. If the value is actually a list of values, the class should be the type of the objects in the list.

If no class is specified in the header line, Cytoscape will attempt to guess the type from the first value. If the first value contains numbers in a floating point format, Cytoscape will assume `java.lang.Double`; if the first value contains only numbers with no decimal point, Cytoscape will assume `java.lang.Integer`; otherwise Cytoscape will assume `java.lang.String`. Note that the first value can lead Cytoscape astray: for example,

```
floatingPointAttribute
firstName = 1
secondName = 2.5
```

In this case, the first value will make Cytoscape think the values should be integers, when in fact they should be floating point numbers. It's safest to explicitly specify the value type to prevent confusion.

Every line past the first line identifies the name of an object and the String representation of the attribute value. The delimiter is always an equals sign; whitespace (spaces and/or tabs) before and after the equals sign is ignored. This means that your names and values can contain whitespace, but object names cannot contain an equals sign and no guarantees are made concerning leading or trailing whitespace. Usually the object names should be the same as the

names in your graph file, unless name conversion is being used (see the section on name resolution in section).

Edge names are all of the form:

```
sourceName (edgeType) targetName
```

Note that this format is different from the specification of interactions in the SIF file format. To be explicit: in a SIF file, an interaction looks like

```
sourceName edgeType targetName
```

To set an attribute for the edge defined by this interaction, the matching line in an attributes file should look like

```
sourceName (edgeType) targetName = value
```

(Yes, this is confusing; we're planning on fixing this in the next file format update for Cytoscape).

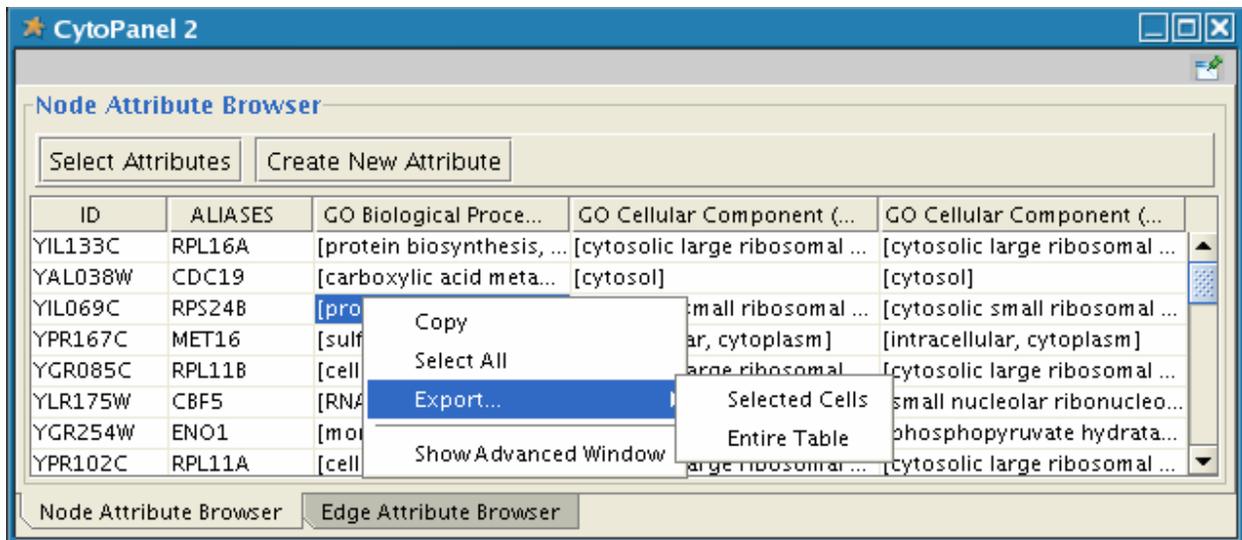
To specify lists of values, use the following syntax:

```
listAttributeName (class=java.lang.String)
firstObjectName = (firstValue::secondValue::thirdValue)
secondObjectName = (onlyOneValue)
```

This defines an attribute which is a list of Strings. The first object has three strings, and thus three elements in its list, while the second object has a list with only one member. In the case of a list every attribute value should be specified as a list, and every member of the list should be of the same class. Again, the class will be inferred if it is not specified in the header line. Lists are not supported by the visual mapper, so can't be mapped to visual attributes.

Attribute Browser

When Cytoscape is started, the Attribute Browser appears in the bottom Cytopanel. This browser can be hidden and restored using the F5 key. Like other Cytopanels, the browser can be undocked by pressing the little icon in the browser's top right corner.



To swap between displaying node attributes and edge attributes use the bottom tabs “Node Attribute Browser” and “Edge Attribute Browser”.

The attribute browser displays attributes belonging to selected nodes and/or edges. To populate the browser with rows (as pictured above), simply select nodes and/or edges in a loaded network. By default, only the “ID” of nodes and edges is shown. To display more than just the ID, click the “Select Attributes” button and choose the attributes that are to be displayed. Each attribute chosen there will result in one column in the attribute browser (in the screenshot above there are 5 columns total including the ID).

Most attribute values can be edited by double-clicking an attribute cell; list values cannot be edited, and neither can the ID.

Attribute rows in the browser can be sorted alphabetically by specific attribute by clicking on a column heading.

A new attribute can be created using the “Create New Attribute” button. Attributes created using the attribute browser must be one of four types – integer, string, floating point, or boolean.

The right-click menu on the Attribute Browser has several functions. This menu is useful for exporting attribute information to spreadsheet applications. For example, choose “Select All” and then “Copy” from the right-click and then paste into a spreadsheet application.

8. Navigation and Layout

BASIC FEATURES:

Use the zooming buttons located on the toolbar to zoom in / out of the interaction network shown in the current network display. Zoom icons are detailed below:



From Left to Right:

- Zoom Out
- Zoom In
- Zoom Selected Region
- Zoom out to Display all of Current Network

You can also zoom in/out by holding down the right mouse button and moving the mouse to the right (zoom in) or left (zoom out).

Use the left mouse button to select a node (hold down the Shift key to select more than one node). Use the right mouse button to launch a context sensitive menu with additional information about the node that was clicked on.

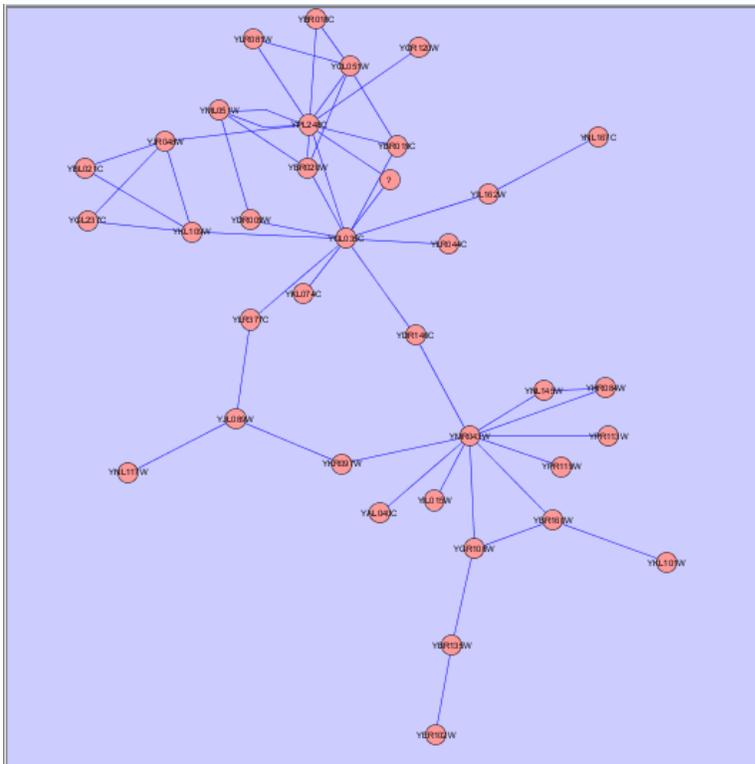
NETWORK LAYOUT:

The Layout menu has an array of features for organizing the network visually according to one of several algorithms, aligning and rotating groups of nodes, and adjusting the size of the network. Most of these features are available from plugins that are packaged with Cytoscape 2.2. Some of the layout algorithms provided with Cytoscape 2.2 are:

Spring-embedded Layout

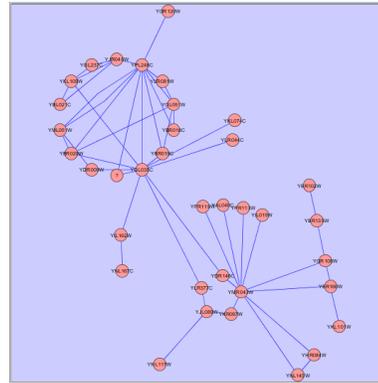
Spring-embedded layout is based on a “force-directed” paradigm. Network nodes are treated like physical objects that repel each other, such as electrons. The connections between nodes are treated like metal springs attached to the pair of nodes. These springs repel or attract their end points according to a force function. The layout algorithm sets the positions of the nodes in a way that minimizes the sum of forces in the network.

To lay out your network in Cytoscape using a Spring Embedded Layout, select Layout → Apply Spring Embedded Layout from the main menu. A sample screen shot is provided below:



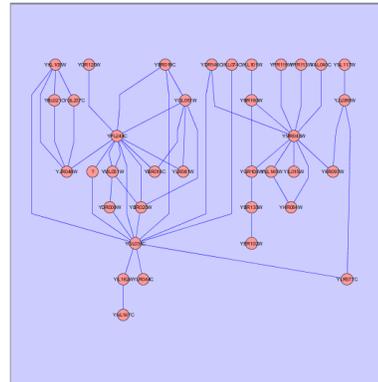
Circular Layout

This algorithm produces layouts that emphasize group and tree structures within a network. It partitions the network by analyzing the connectivity structure of the network, and arranges the partitions as separate circles. The circles themselves are arranged in a radial tree layout fashion.



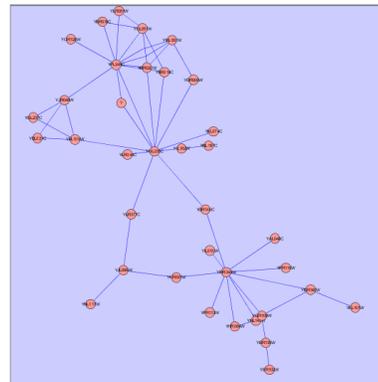
Hierarchical Layout

The hierarchical layout algorithm is good for representing main direction or *flow* within a network. Nodes are placed in hierarchically arranged layers and the ordering of the nodes within each layer is chosen in such a way that minimizes the number of edge crossings.



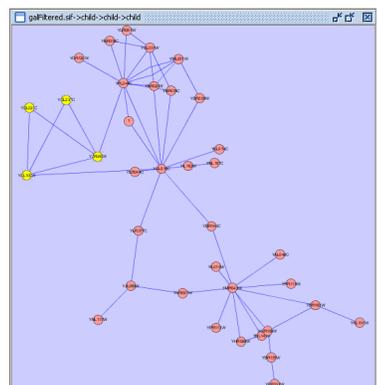
Organic Layout

The organic layout algorithm is a kind of spring-embedded algorithm that combines elements of the other algorithms to show the clustered structure of a graph.



Scaling and Rotation

Cytoscape provides operations for scaling and/or rotating networks or segments of networks. The figure at right shows the network view from the organic layout, with the selected nodes scaled by a factor of 1.5 and rotated by 90 degrees..



9. Visual Styles

With the Cytoscape Visual Style feature, you can easily customize the visual appearance of your network. For example, you can specify a default color and shape for all nodes, use specific line types to indicate different types of interactions, or visualize gene expression data using a color gradient. All these features are available by selecting Visualization → Set Visual Properties from the main menu or clicking on the color wheel in the main button bar menu.

Introduction to Visual Styles

The Cytoscape distribution you have downloaded automatically loads several predefined visual styles when you start Cytoscape by using one of “cytoscape.sh” or “cytoscape.bat” start-up scripts (see step 3 in section 2. *Launching Cytoscape*).

The Cytoscape distribution you have downloaded includes three predefined visual styles to get you started. The Cytoscape distribution you have downloaded automatically loads several predefined visual styles when you start Cytoscape by using one of the “cytoscape.sh” or “cytoscape.bat” scripts (see step 3 in section 2. *Launching Cytoscape*.) To demonstrate these styles, try out the following example:

- Load a sample network: From the main menu, select File → Load → Graph, and select sampleData/galFiltered.sif.
- Layout the network: select Layout->yFiles->Organic.
- Load a sample set of expression data: From the main menu, select File → Load → Expression Matrix File, and select sampleData/galExpData.pvals.

By default, the Visual Style labeled “default” will be automatically applied to your network. This default style has a blue background, circular pink nodes, and blue edges (see sample screenshot below).

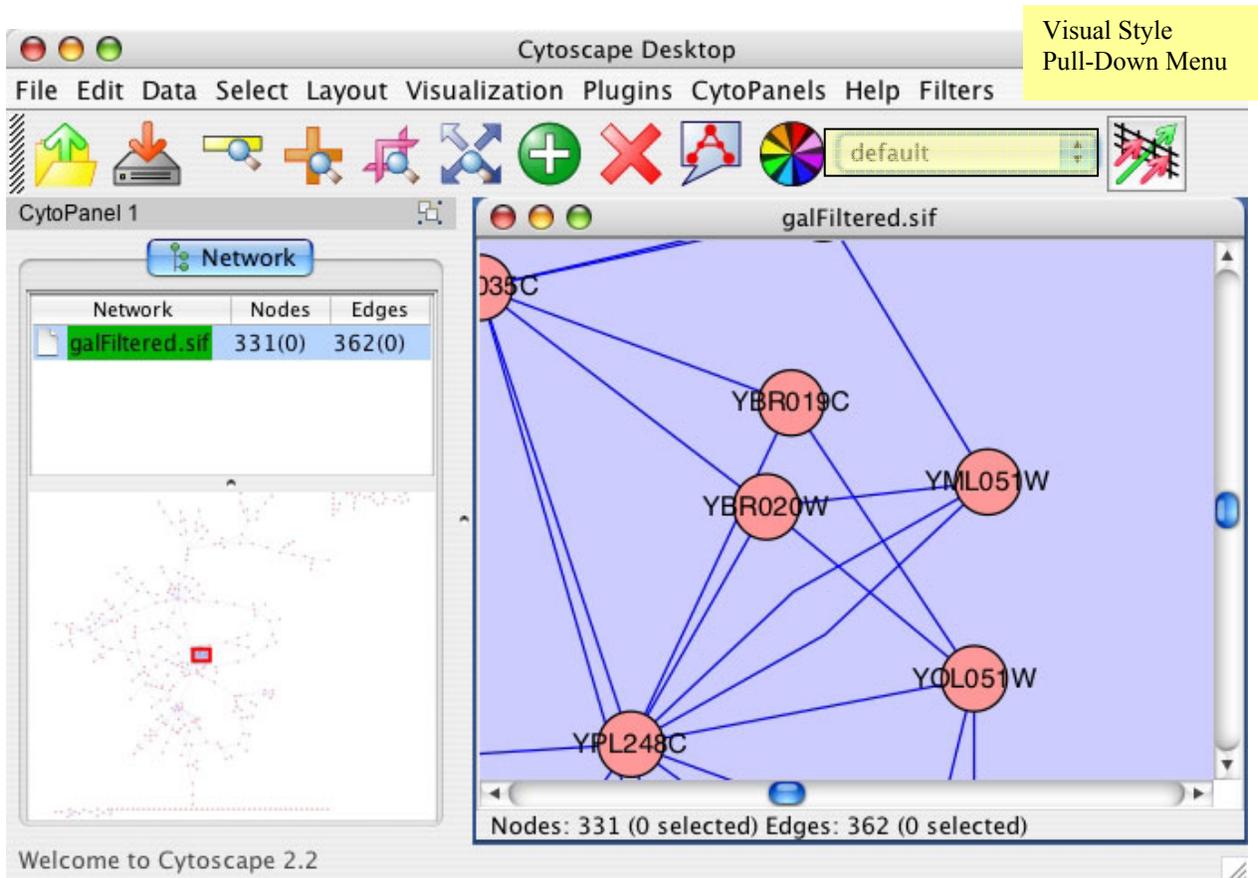


Figure: Using the default Visual Style.

The vizmap.props File: All Cytoscape Visual Style settings are automatically loaded from a file called vizmap.props. The location of this file can be specified from the command line (-vp). If it is not specified through the command line, then Cytoscape looks for this file in the Cytoscape distribution directory (“cytoscape”, located in the users’ home directory). If you start Cytoscape for the first time, and you do not start it using one of the start-up scripts (cytoscape.sh or cytoscape.bat), then, a very simple visual style will be automatically created. When you exit Cytoscape, any modifications you made to the visual styles, and any new visual styles you created, are automatically saved to the loaded vizmap.props file.

[!] If you are upgrading from Cytoscape 2.1: If you are upgrading from Cytoscape 2.1, you may want to use your vizmap.props file that is located in your home directory, since this file was used in 2.1 to store visual styles. To do this, you can either specify its location in the command line (edit cytoscape.sh or cytoscape.bat), or copy the file to the Cytoscape distribution directory (named “.cytoscape”) located in your home directory (on Windows XP, this is the “Documents and Settings” directory, on Linux or Mac this is your home directory, for example, /Users/iavila, or ~/).

You can flip through different visual styles by making a selection from the Visual Style pull down menu. For example, if you select “Sample1”, a new visual style will be applied to your network, and you will see a green background and round blue nodes. Additionally, if you zoom in closer, you can see that protein-DNA interactions (specified with the label: pd) are drawn with dashed edges, whereas protein-protein interactions (specified with the label: pp) are drawn with a light yellow color which is difficult to discern on the green background (see sample screenshot below). The background can be changed through the Visualization menu.

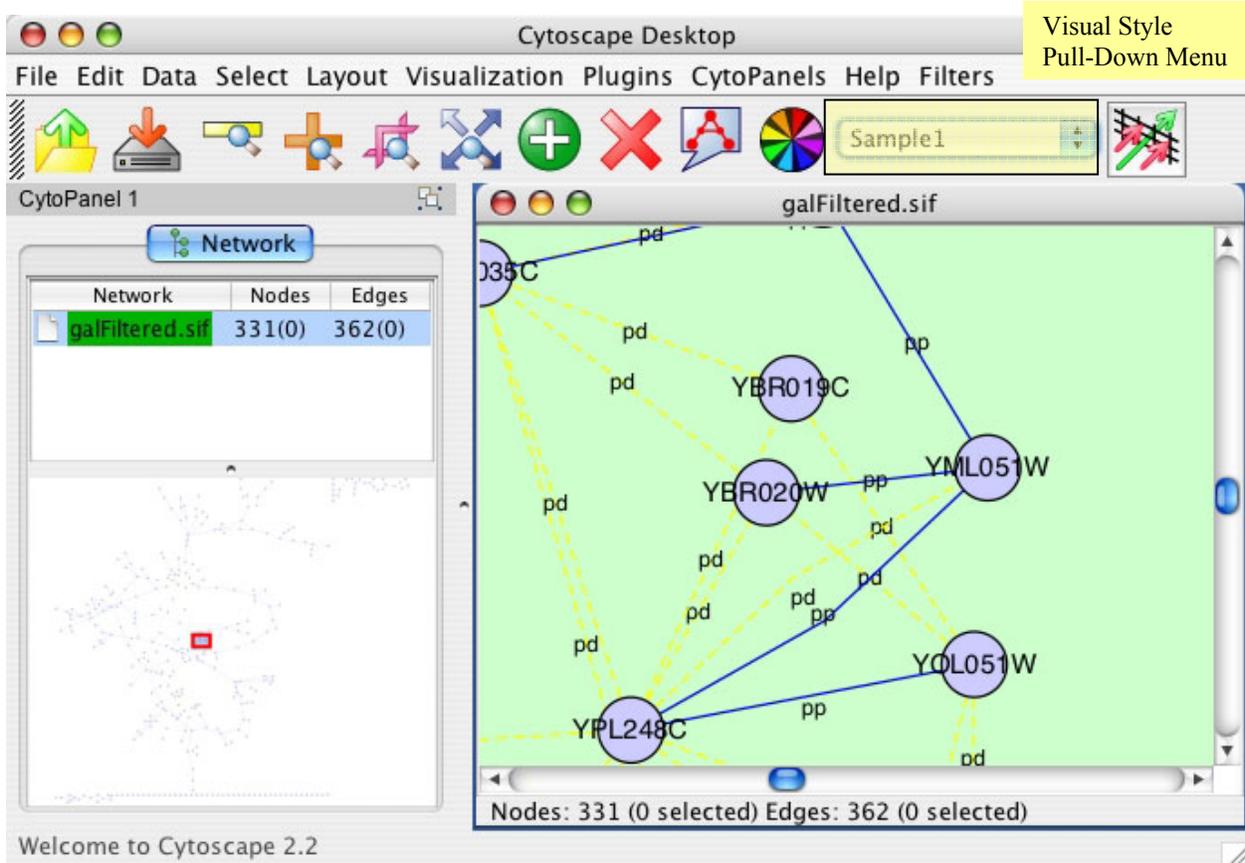


Figure: Using the Sample1 Visual Style. Protein-Protein interactions (solid lines) are now distinguishable from Protein-DNA interactions (dashed yellow lines).

Finally, if you select “Sample2”, gene expression values for each node will be colored along a color gradient between red and green (where red represents a low expression ratio, and green represents a high expression ratio - with thresholds set for the gal1RGexp experiment bundled with Cytoscape in the sampleData/galExpData.pvals file). See sample screenshot below:

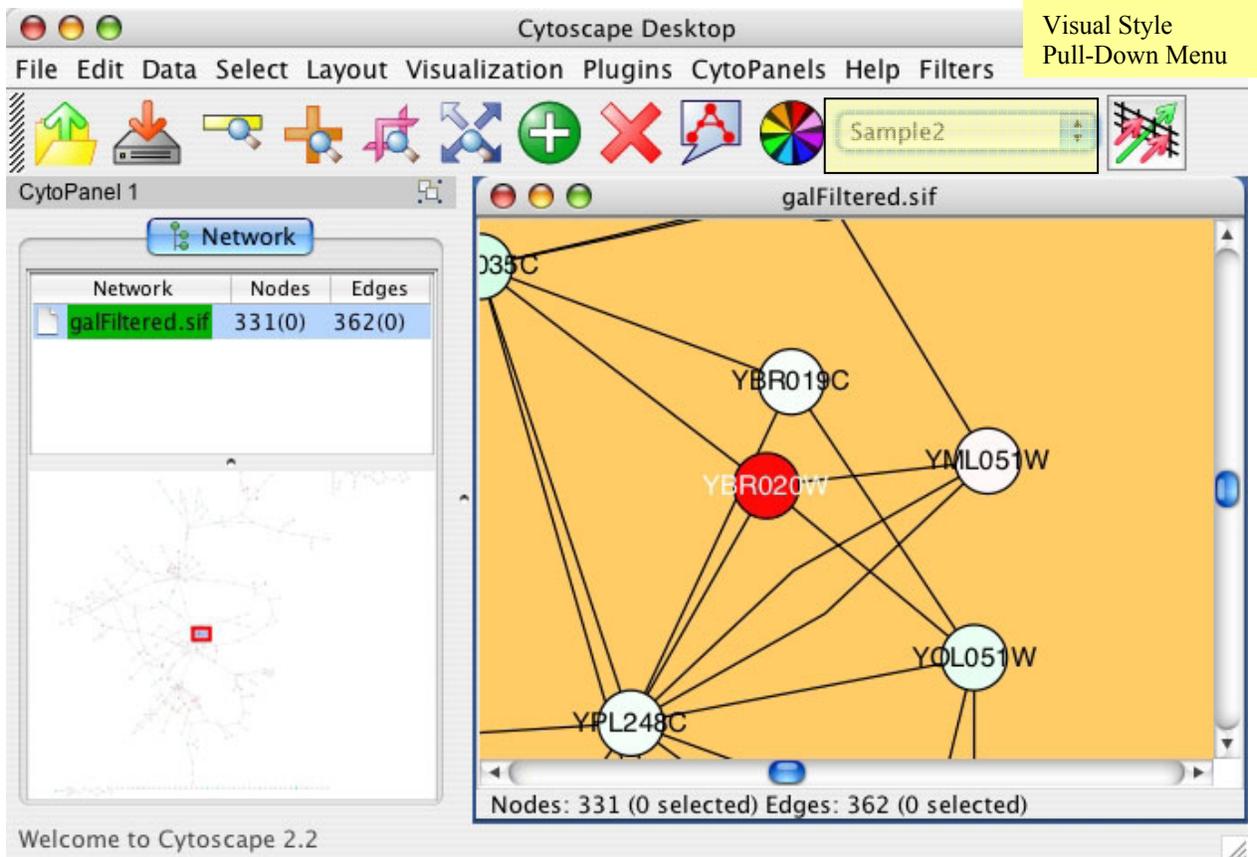


Figure: Using the Sample2 Visual Style. Gene expression values are now displayed along a red/green color gradient.

Visual Attributes, Graph Attributes and Visual Mappers

The Cytoscape Visual Mapper has three core components: *visual attributes*, *graph attributes* and *visual mappers*:

- A *visual attribute* is any visual setting that can be applied to your network. For example, you can change all nodes to squares by setting the node shape visual attribute.
- A *graph attribute* is any attribute associated with a node or an edge. For example, each edge in a network may be associated with a label, such as “pd” (protein-DNA interactions), or “pp” (protein-protein interactions).

- A *visual mapper* maps graph attributes to visual attributes. For example, a visual mapper can map all protein-DNA interactions to the color blue, and all protein-protein interactions to the color red.

Cytoscape includes a large number of visual attributes. These are summarized in the tables below.

Visual Attributes Associated with Nodes:
<ul style="list-style-type: none"> • Node Color • Node Border Color • Node Border Type. The following options are available:

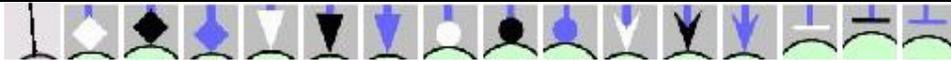
<ul style="list-style-type: none"> • Node Shape. The following options are available:

<ul style="list-style-type: none"> • Node Size: width and height of each node. • Node Label: the text label for each node. • Node Font: node font and size.

Visual Attributes Associated with Edges:
<ul style="list-style-type: none"> • Edge Color • Edge Line Type. The following options are available:

<ul style="list-style-type: none"> • Edge Source Arrow. The following options are available:

<ul style="list-style-type: none"> • Edge Target Arrow. The following options are available:



- Edge Label: the text label for each edge.
- Edge Font: edge font and size.

Global Visual Properties:

- Background Color

For each visual attribute, you can specify a default value or define a visual mapping. Cytoscape currently supports three different types of visual mappers:

- **Passthrough Mapper:** graph attributes are passed directly through to visual attributes. A passthrough mapper only works for node / edge labels. For example, a passthrough mapper can draw the common gene name on all nodes.
- **Discrete Mapper:** discrete graph attributes are mapped to discrete visual attributes. For example, a discrete mapper can map all protein-protein interactions to the color blue.
- **Continuous Mapper:** continuous graph attributes are mapped to visual attributes. Depending on the visual attribute, there are two types of continuous mappers:
 - **continuous to continuous mapper:** for example, you can map a continuous value (0..1) to a color gradient (red..green) or node/font size (10..100).
 - **continuous to discrete mapper:** for example, all values below 0 are mapped to square nodes, and all values above 0 are mapped to circular nodes. However, there is no way to smoothly morph between circular nodes and square nodes.

The matrix below shows visual mapper support for each visual property.

	Passthrough Mapper	Discrete Mapper	Continuous Mapper
Node Properties			
Node Color	⊘	●	●
Node Border Color	⊘	●	●
Node Border Type	⊘	●	◐
Node Shape	⊘	●	◐
Node Size	⊘	●	●
Node Label	●	●	◐
Node Font Family	⊘	●	◐
Node Font Size	⊘	●	●
Edge Properties			
Edge Color	⊘	●	●
Edge Line Type	⊘	●	◐
Edge Source Arrow	⊘	●	◐
Edge Target Arrow	⊘	●	◐
Edge Label	●	●	◐
Edge Font Family	⊘	●	◐
Edge Font Size	⊘	●	●

Legend	
⊘	Mapping is not supported for specified visual property.
●	Mapping is fully supported for specified visual property.
◐	Mapping is partially supported for specified visual property. Support for “continuous to continuous” mapping is not supported.

Tutorial: Creating a New Visual Style

To create a new visual style, select Visualization → Set Visual Properties from the main menu, or select the color wheel icon in the main button bar. You will now see a new Visual Styles dialog box (shown at right.)



Click the New button, and enter a name for your new visual style when prompted. Then click the Define button. You will now see the main Visual Styles Properties dialog box (shown at right.)

From this dialog box, you can flip between Node Attributes, Edge Attributes, and Global Defaults. You can also specify default values for any visual property, or define a new custom mapping.

For example, to set the default node shape to triangles, select Node Attributes → Node Shape. Then, click the “Change Default” button, and select the Triangle icon from the selection list.

Applying Changes to the Network

To apply your visual style to your network, hit the “Apply to Graph” button, available in the bottom of the dialog panel.

Saving a Visual Style

When you exit Cytoscape, new visual styles or newly modified visual styles will automatically be saved in the vizmap.props file. You can therefore create a new visual style and apply it to all future networks.

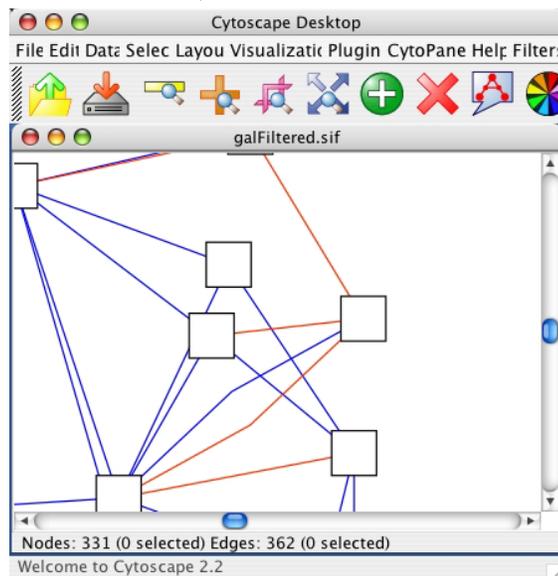
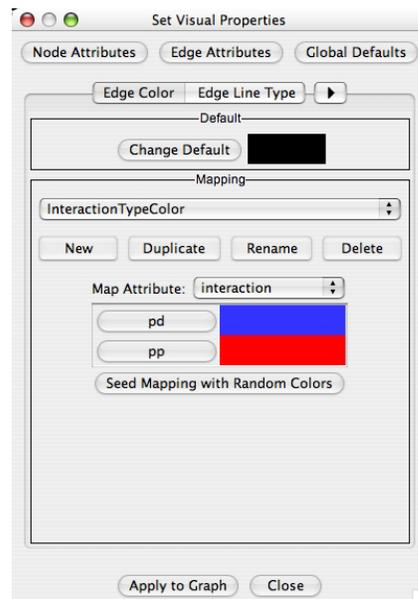


Tutorial: Creating a New Visual Style with a Discrete Mapper

The following tutorial demonstrates how to create a new visual style with a discrete mapper. The goal is to draw Protein-DNA interactions with blue edges, and Protein-Protein interactions with red edges.

- Load a sample network: From the main menu, select File → Load → Graph, and select sampleData/galFiltered.sif.
- Select Visualization → Set Visual Properties.
- Select “New” to create a new Visual Style. Name your new style: “Sample3”.
- Click the “Define” button to define the newly created Visual Style.
- In the “Set Visual Properties” Dialog box, select Edge Attributes → Edge Color.
- Click the New button in the mapping panel.
- You will be prompted to select a mapping type: passthrough mapper, discrete mapper or continuous mapper (for an overview of the differences between these mappers, please refer back to section 8.2.) Select “discrete mapper”, and enter a descriptive name. For example, enter: “InteractionTypeColor”.
- From the “Map Attribute” pull-down menu, select “interaction.” You should now see two buttons, one for pd (Protein-DNA interactions), and one for pp (Protein-Protein interactions).
- Click the “pd” button and select a blue color.
- Click the “pp” button and select a red color.
- Click the “Apply to Graph” button.

Your network should now show “pd” interactions in blue, and “pp” interactions in red. Sample screenshot is provided at right

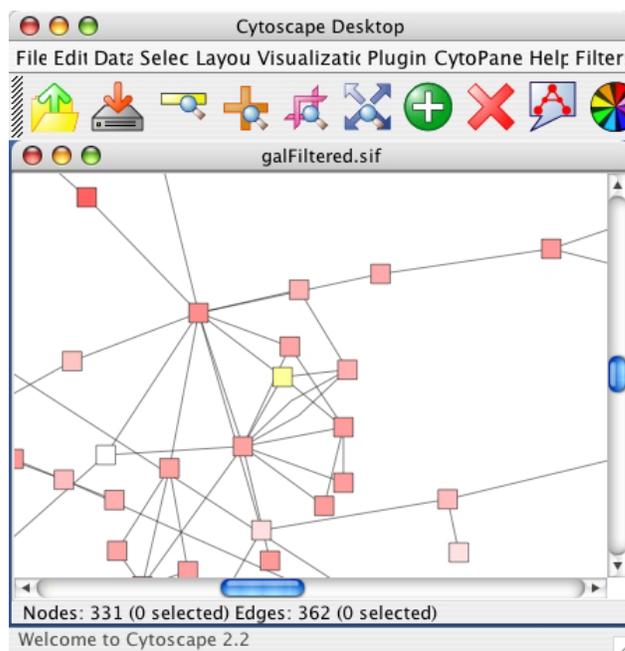
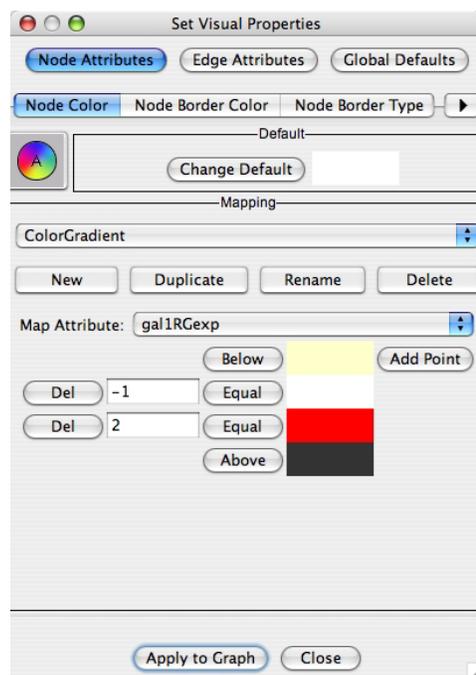


Tutorial: Visualizing Expression Data on a Network

The following tutorial demonstrates how to create a new continuous mapper. The goal is to superpose gene expression data onto a network, and to display gene expression values along a color gradient.

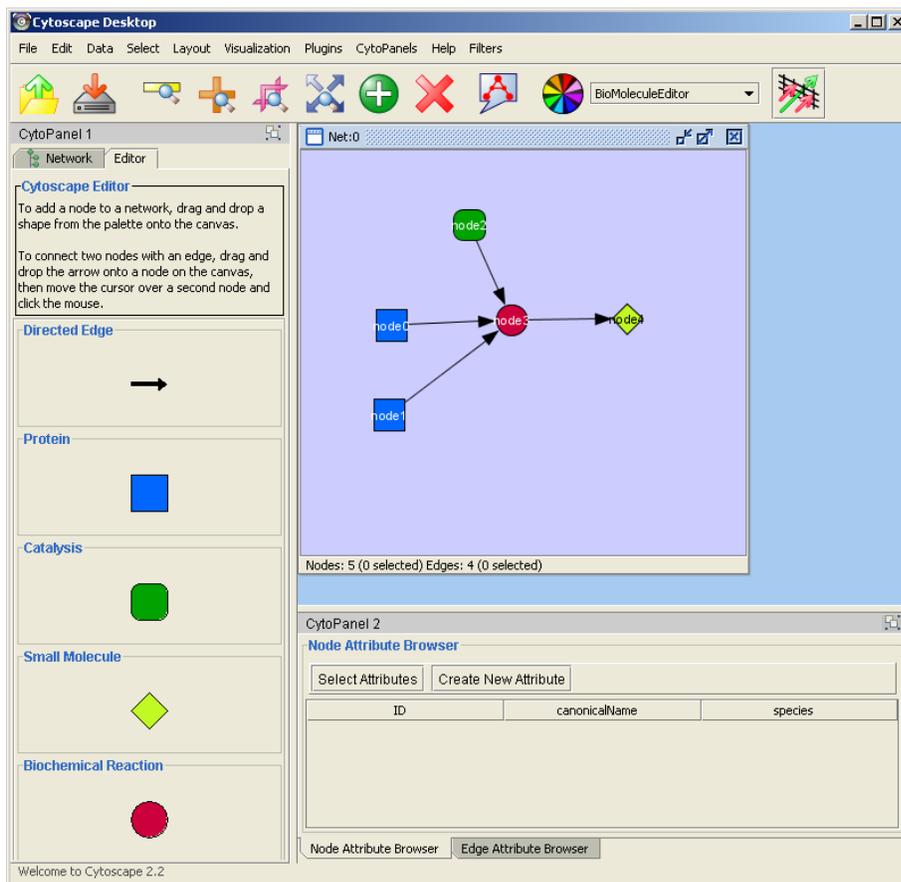
- Load a sample network: From the main menu, select File → Load → Network, and select sampleData/galFiltered.sif.
- Load a sample set of expression data: From the main menu, select File → Load → Expression Matrix File, and select sampleData/galExpData.pvals.
- Select Visualization → Set Visual Properties.
- Select “New” to create a new Visual Style. Name your new style: “Sample4”.
- Click the “Define” button to define the newly created Visual Style.
- In the “Set Visual Properties” Dialog box, select Node Attributes → Node Color.
- Click the New button in the mapping panel.
- You will be prompted to select a mapping type: passthrough mapper, discrete mapper or continuous mapper (for an overview of the differences between these mappers, please refer back to section 8.2.) Select “continuous mapper”, and enter a descriptive name. For example, enter: “ColorGradient”.
- From the “Map Attribute” pull-down menu, select “gal1RGexp.”
- Click the “Add Point” button twice to add two data points.
- Set the first point to “-1”, Below = Yellow, Equal = White.
- Set the second point to “2”, Equal = Red, Above = Black.
- Click the “Apply to Graph” button.

This visual mapper will set all nodes with a gal1RGexp value less than -1 to Yellow, and all nodes with a gal1RGexp value greater than 2 to Black. Additionally, all values between -1 and 2 will be painted with a white/red color gradient. Sample screenshot is shown at right.



10. Editing Networks

Cytoscape has a set of editors that enable you to build and modify networks interactively by dragging and dropping nodes and edges from a palette onto the main network view window. The palette contains a set of shapes (for nodes) and arrows (for edges). The shapes on the palette are defined by the current Visual Style, with Node Shape and Node Color mapping into the shape and color of a node, and Edge Target Arrow mapping into the target arrow of an edge. An example of an editor, with the palette contained in CytoPanel 1, is shown below.



To bring up an editor, use the **File->Set Editor** menu item. In this version of Cytoscape, you will be given a choice of three editors,

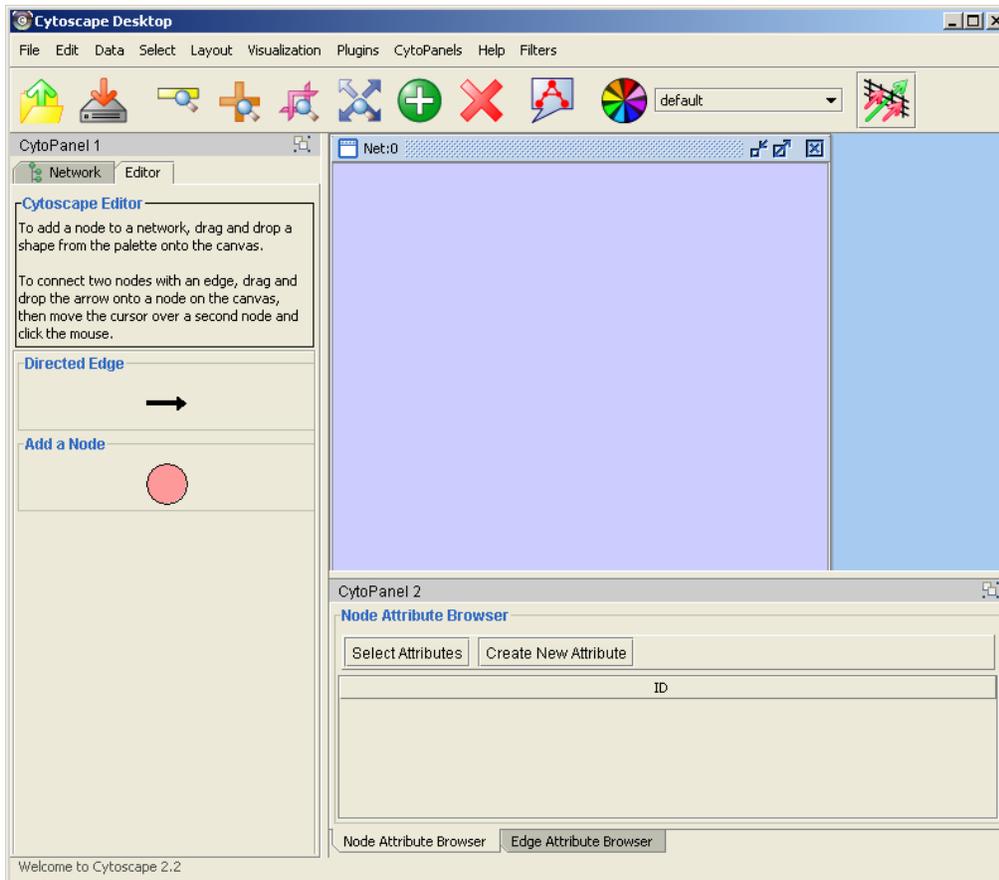
- a *DefaultCytoscapeEditor*, which contains one default node and one default edge on its palette. This editor will define the nodes and shapes on its palette using the current Visual Style.
- a *SimpleBioMoleculeEditor*, which defines the nodes and shapes on its palette using the SimpleBioMolecule Visual Style.
- a *SimpleBioPAX_Editor*, defines the nodes and shapes on its palette using a Visual Style that maps node shapes and colors according to the value of the

"BIOPAX_NODE_TYPE" attribute and maps edge target arrows according to the value of the "BIOPAX_EDGE_TYPE" attribute. Note that, in this version of Cytoscape, the *SimpleBioPAX_Editor* is **not** a fully functional BioPAX editor, but rather serves as an example. Moreover, there is no facility for output to BioPAX format in the current version of Cytoscape. A fully functional BioPAX editor, with output to BioPAX format, is planned for a future version of Cytoscape.

When you bring up an editor, the visual style for the current network view is set to the visual style that is associated with the editor. If there is no current view at the time you make the **File->Set Editor**, then a new network and view (and network) will be created automatically for you.

To start editing a new network, use the **File->New->Network** menu item.

The figure below shows shows the display for the *DefaultCytoscapeEditor*.



To add a node to a network, drag and drop a node shape from the palette onto the canvas.

To connect two nodes with an edge, drag and drop an arrow shape onto a node on the canvas. This node becomes the source node of the edge. Move the cursor and a rubber-banded line follows the cursor. As the cursor passes over another node, that node is highlighted and the

rubber-banded line will snap to a connection point on that second node. Click the mouse while over this node and the connection is established.

You can abort the drawing of the edge by clicking on an empty spot on the palette.

Note that if you change the Visual Style, the palette used by the current network view will also change to be consistent with the mappings in the new Visual Style.

There is also an **Edit => Connect Selected Nodes** menu item that, when chosen, creates a clique amongst the selected nodes.

The editor provides accelerators for adding nodes and edges. Control-clicking at a position on the canvas creates a node at that position. The `NODE_TYPE` attribute of the node will be the same as the `NODE_TYPE` of the node most recently added, defaulting to "DefaultNode" type. In this manner, you can use control-clicking as a kind of "stamp" to add multiple nodes of the same type to the network. Control-clicking on a node on the canvas starts an edge with source at that node. Move the cursor and a rubber-banded line follows the cursor. As the cursor passes over another node, that node is highlighted and the rubber-banded line will snap to a connection point on that second node. Control-click the mouse again and the connection is established. The `EDGE_TYPE` attribute of the edge will be the same as the `EDGE_TYPE` of the edge most recently added, defaulting to "DefaultEdge" type. You can abort the drawing of the edge by control-clicking on an empty spot on the palette.

You can delete nodes and edges by selecting a number of nodes and edges, then selecting the **Edit => Delete Selected Nodes and Edges** menu item. You can recover any nodes and edges deleted from a network by selecting the **Edit => Restore Deleted Nodes and Edges** menu item. Note that this will restore **all** nodes and edges that were previously deleted from the network, not just those deleted by the most recent delete operation.

11. CytoPanels

What are CytoPanels?

CytoPanels are floatable / dockable panels. CytoPanels were developed to cut down on the number of pop-up windows within Cytoscape and to create a more unified user experience. For example, in Cytoscape 2.1, the cPath PlugIn enables users to click on a node and immediately view node details in a pop-up window. Now with CytoPanels, we can now show these node details in an embedded CytoPanel and present a more integrated experience to the user. For example, the image below shows a screenshot of the latest BioPAX PlugIn. When you click on a node, the node details appear directly in the left CytoPanel.

Cytoscape Desktop

File Edit Data Select Layout Visualization Plugins CytoPanels Help

BioPAX v 0_2

CytoPanel 1

Network BioPax Plugin

Apoptosis.owl

Node Details

Type
Protein

Name
UniProt:Q9NR28-1
Diablo homolog,
mitochondrial precursor
(Second
mitochondria-derived
activator of caspase)
(Smac protein) (Direct
IAP binding protein with
low pI)

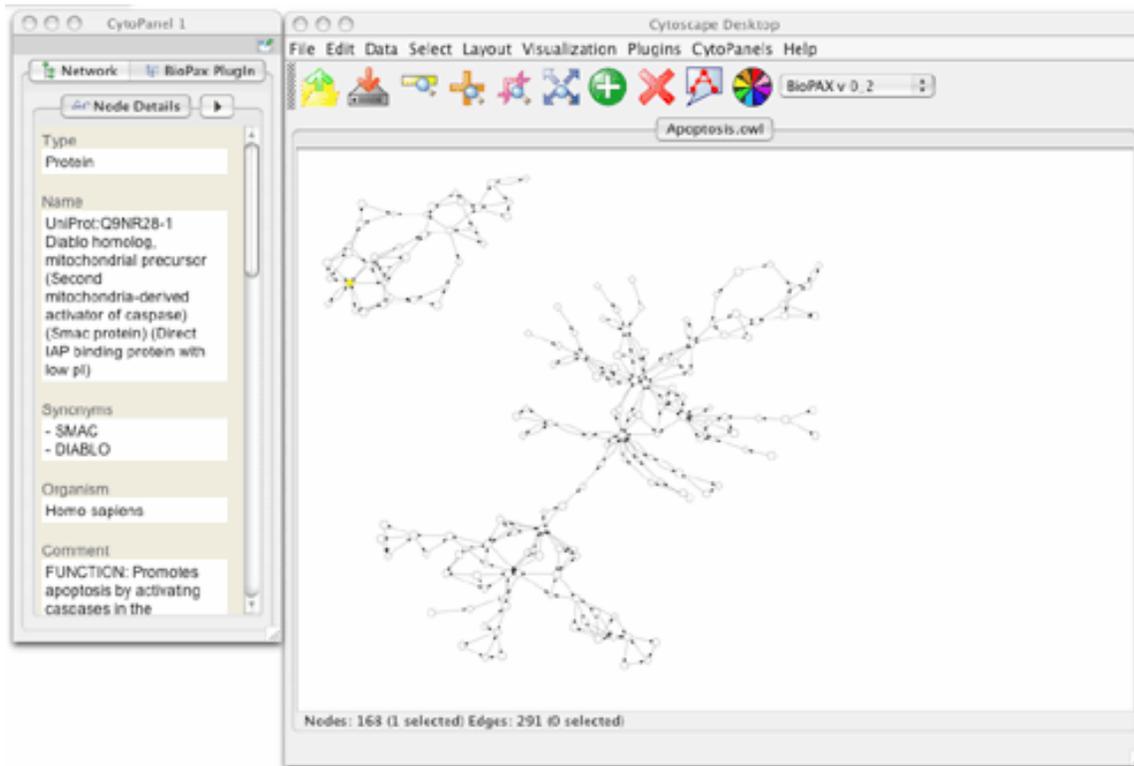
Synonyms
- SMAC
- DIABLO

Organism
Homo sapiens

Comment
FUNCTION: Promotes
apoptosis by activating
caspases in the
cytochrome

Nodes: 168 (1 selected) Edges: 291 (0 selected)

The user can then chose to resize, hide or float the left CytoPanel. For example, in the screenshot below, the user has chosen to float it:



Basic Usage

Cytoscape 2.2 now includes three CytoPanels: CytoPanel 1 (appears on the left), CytoPanel 2 (appears on the bottom), and CytoPanel 3 (appears on the right). By default, only CytoPanel 1 will appear, and it will automatically contain the network list and bird's eye view component. The other panels may appear depending on the mix of PlugIns currently installed in your Cytoscape distribution.

CytoPanels can be shown or hidden by selecting the desired menu item within the CytoPanels menu or by entering the proper keyboard accelerator short-cut (in order for the keyboard short-cuts to work, the Cytoscape Desktop must have the focus).



In addition, CytoPanels can be floated or docked by selected the icon at the top-right corner of each CytoPanel. The icon and tooltip will change based on the CytoPanel state. If the CytoPanel is docked, clicking on the icon will float the CytoPanel, as indicated by the "Float Window" tooltip. Alternatively, if the CytoPanel is floating, clicking on the icon will dock the CytoPanel, as indicated by the "Dock Window" tooltip.



12. Annotation

Annotations in Cytoscape are stored as a set of ontologies (e.g. the Gene Ontology). An ontology consists of a set of controlled vocabulary terms that annotate the genes for a given organism and a synonym table for gene names. For example, using the Gene Ontology, the *Saccharomyces Cerevisiae* **GAL4** gene's biological process is described as "regulation of transcription", to which GO has assigned the number 45449 (a GO ID). You can see below that "regulation of transcription" is a subcategory of "transcription", which is a subcategory of "nucleobase, nucleoside, nucleotide and nucleic acid metabolism", etc.

```
GO 8150 biological_process
  GO 7582 physiological processes
    GO 8152 metabolism
      GO 6139 nucleobase, nucleoside, nucleotide and nucleic acid metabolism
        GO 6350 transcription
          GO 45449 regulation of transcription
```

Cytoscape can use this 'hierarchical' ontology to annotate recognized genes if the user chooses a level of the hierarchy to use for a given set of annotations. The ontology provided to Cytoscape does not have to be hierarchical, but if it is not, there is no real advantage to storing annotations this way compared to just storing the annotation terms in a node attribute file.

The Gene Ontology Server (originally called the biodata server) is a Cytoscape feature which allows you to load, navigate, and assign annotation terms to nodes in a network.

In version 2.2, Cytoscape has a new feature called *Gene Ontology Server Wizard*, which enables users to select local ontology and annotation files from GUI. Although 2.2 has backward compatibility with the old file formats (manifest file, which includes list of *anno* and *onto* files), we strongly suggest to use the new file formats. See Appendix B for a description of how the old file formats can be created and used.

New Ontology and Annotation Files

The standard file formats used in this release are OBO and gene association. The GO website details these file formats:

- Ontologies and Definitions: <http://www.geneontology.org/GO.downloads.shtml#ont>
- Current Annotations: <http://www.geneontology.org/GO.current.annotations.shtml>

Cytoscape provides an outdated copy of the *Gene_ontology.obo* text file in the *annotation* directory for use with the software. An up-to-date *Gene_ontology.obo* file is maintained by the GO project and is updated every 30 minutes. Please download the latest version of this file (from

<http://www.geneontology.org>) if you intend to use it during analysis. In addition to the gene ontology file, we also provide gene association files for Yeast and Human (*gene_association.sgd* and *gene_association.goa_human*, both in the *annotations* directory). Other gene association files can be found at the gene ontology web site.

Sample Files

gene_ontology.obo:

```
format-version: 1.0
date: 11:08:2005 16:57
saved-by: midori
auto-generated-by: DAG-Edit 1.419 rev 3
default-namespace: gene_ontology
remark: cvs version: $Revision: 1.1 $
subsetdef: goslim_yeast "Yeast GO slim"
subsetdef: goslim_goa "GOA and proteome slim"
subsetdef: goslim_plant "Plant GO slim"
subsetdef: goslim_generic "Generic GO slim"
subsetdef: gosubset_prok "Prokaryotic GO subset"

[Term]
id: GO:0000001
name: mitochondrion inheritance
namespace: biological_process
def: "The distribution of mitochondria\, including the mitochondrial genome\, into daughter cells after mitosis or meiosis\, mediated by interactions between mitochondria and the cytoskeleton."
[PMID:10873824, PMID:11389764, SGD:mcc]
is_a: GO:0048308 ! organelle inheritance
is_a: GO:0048311 ! mitochondrion distribution

[Term]
id: GO:0000002
name: mitochondrial genome maintenance
namespace: biological_process
def: "The maintenance of the structure and integrity of the mitochondrial genome." [GO:ai]
is_a: GO:0007005 ! mitochondrion organization and biogenesis
```

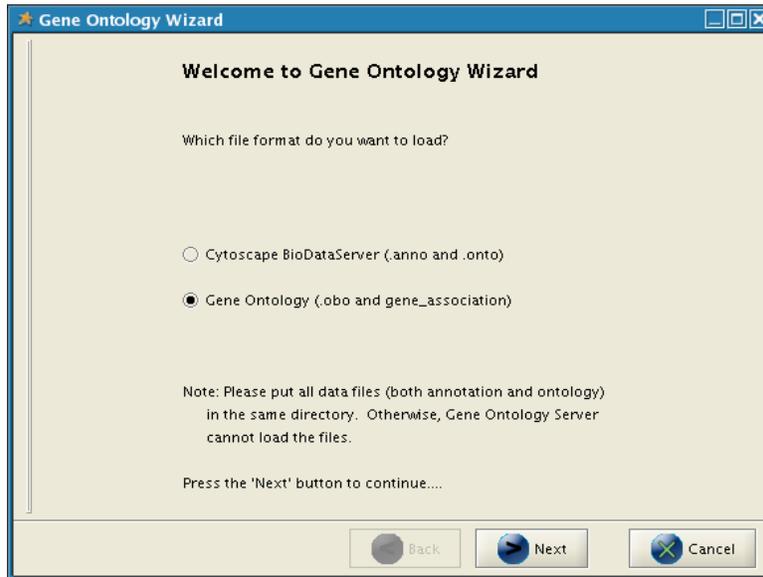
gene_association.sgd (annotation file for yeast):

```
SGD      S000003916      AAD10      GO:0006081      SGD_REF:S000042151|PMID:10572264
ISS      P      aryl-alcohol dehydrogenase (putative)      YJR155W gene      taxon:4932
20020902      SGD
SGD      S000005275      AAD14      GO:0008372      SGD_REF:S000069584      ND      C
aryl-alcohol dehydrogenase (putative)      YNL331C gene      taxon:4932      20010119      SGD
```

Gene Ontology Server Wizard

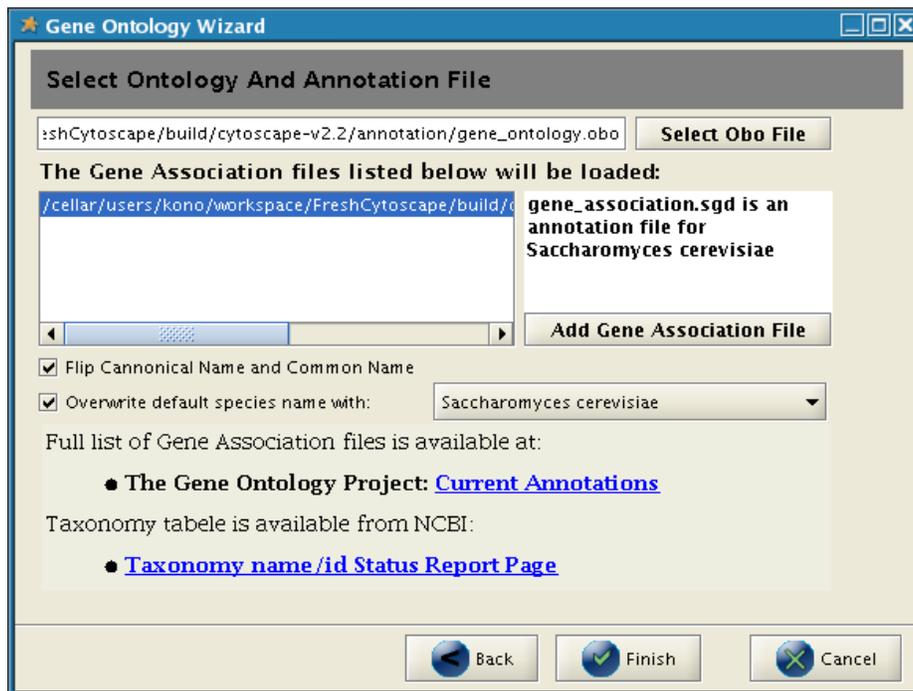
The Gene Ontology Server Wizard is a new graphical user interface used to select ontology and annotation files. By following the wizard, you do not have to write manifest files, which were used in older versions of Cytoscape to specify ontologies.

Step 1. Select Data Format



In this panel you can select two types of data formats: Cytoscape Bio Data Server or new Gene Ontology. Select *Gene Ontology* to use the new formats (obo and gene_association). If you want to use the old file formats, select *Cytoscape Bio DataServer*. A description of how the old formats can be created and used can be found in Appendix B.

Step 2. Select OBO and Gene Association Files



If you choose *Gene Ontology* in the first step, this panel appears. The basic function of this panel is selecting OBO file (ontology) and gene_association files. This panel has the following functions:

- *Select Obo File Button*
By pressing this button, you can choose an OBO file to be loaded.
- *Add Gene Association File Button*
You can add a gene_association file to the list by pressing this button. Once you select a file, the file name will be shown in the list in the left. If you click on the file name, the species name for the file will be shown. You can select multiple gene_association files.
- *Flip Canonical Name and Common Name Check box*
The following is an entry in the gene_association.sgd file (annotation file for yeast):

```
SGD      S000004660      AAC1          GO:0006839      SGD_REF:S000050955|PMID:2167309
IGI      SGD:S000000126 P  ADP/ATP translocator YMR056C gene  taxon:4932
20040226      SGD
```

The third element (*AAC1*, called *DB_Object_Symbol* in the gene_association format) will be used as a node identifier and canonical name for the gene. However, some network files (gal or sif) instead use the 11th element (*YMR056C*, the first entry in *Synonym*) as a node identifier. Since Cytoscape applies annotations based on these identifiers, the identifiers in the network file and in *DB_Object_Symbols* must match. This check box is used when you load network files that use the *Synonym* as the node identifier.

- *Overwrite default species name menu*
If not specified, species name for a network data will be overwritten by a property called defaultSpeciesName and Gene Ontology Server will use it to choose which annotations to be applied. You can change defaultSpeciesName from this list.
- *Links to related web sites*
You can navigate to GO's Current Annotation and NCBI's Taxonomy pages from the links. The links open the default web browser when clicked.

Once you have finished specifying the options, click on finish. The OBO file and gene_association files specified in this panel will be automatically loaded

Note 1: The OBO file and gene_association files MUST be in the same directory, and you must have write permission for the directory.

Note 2: Please make sure that your network file uses exact same ID's used in the gene association file. Otherwise, nothing will appear in the Annotation Panel.

13. Filters

The Cytoscape Filter plugin, which is packaged with the official Cytoscape 2.2 release and is active by default, allows for a wide variety of fine-tuned filtering on node and edge attributes loaded onto Cytoscape networks. For example, you can easily select all the nodes whose name contains a specific pattern that you define. Several types of filters are available. Basic filters allow the selection of multiple nodes or edges according to attribute data:

- **String** filters allow selection of nodes or edges with attributes matching specified patterns. These patterns may include the wildcards * and ?.
- **Numerical** filters allow selection of nodes or edges according to numerical attributes and the mathematical operators >, =, and <.

Compound filters allow selection based on the application of pre-existing filters:

- **Topology** filters allow selection of nodes with neighbors that match some pre-existing filter.
- **Boolean** filters allow the combination of multiple filters using the AND, OR and XOR operators.

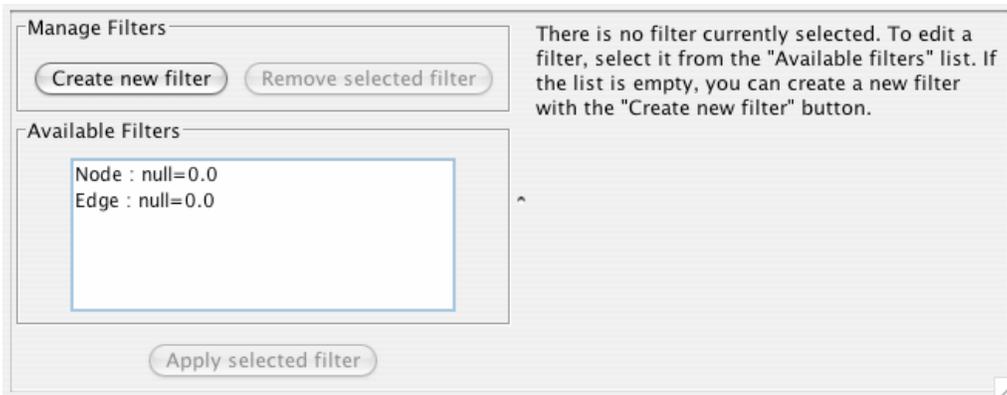
Example filters are shipped with the plugin to get started.

Using the Plugin

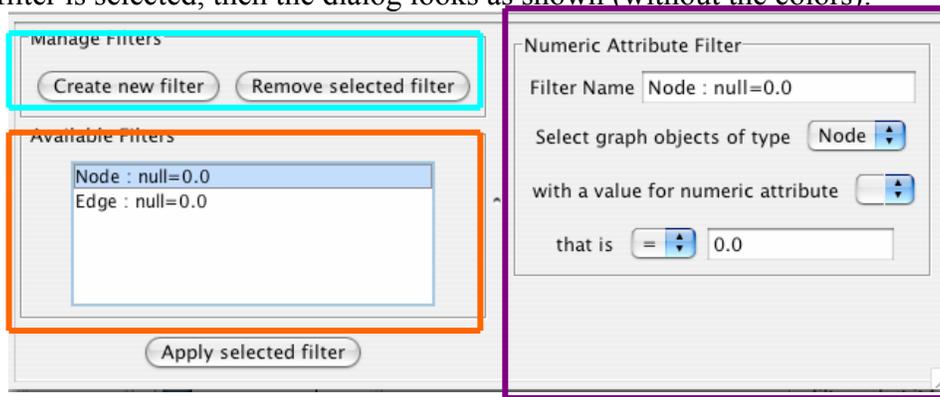
If the Filter plugin is loaded, then you should see a filter icon on the toolbar.



If you press the filter icon, you will see a filters dialog which looks initially like the following:



If the first filter is selected, then the dialog looks as shown (without the colors):



As for the colors:

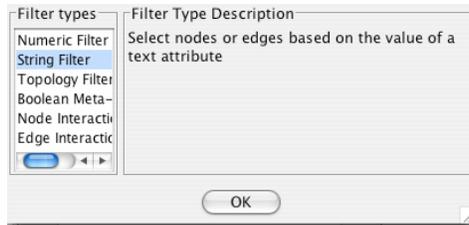
The Purple Box: An existing or newly created filter can be edited in this area. Each filter type has its own user interface for editing.

The Orange Box: All available filters are shown in this list. Initially, this list will contain sample filters, but as you create more, they will be added here.

The Cyan Box: Pressing “Create new filter” adds a filter to the “Available Filters” box, and “Remove selected filter” deletes the currently selected filter.

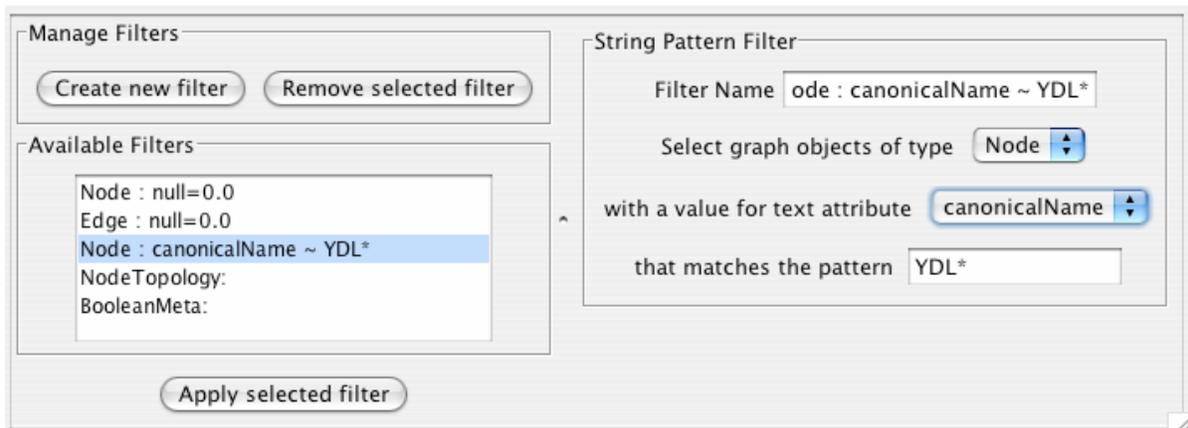
Creating Filters

The “Create new filter” button brings up the Filter creation dialog box, shown below.



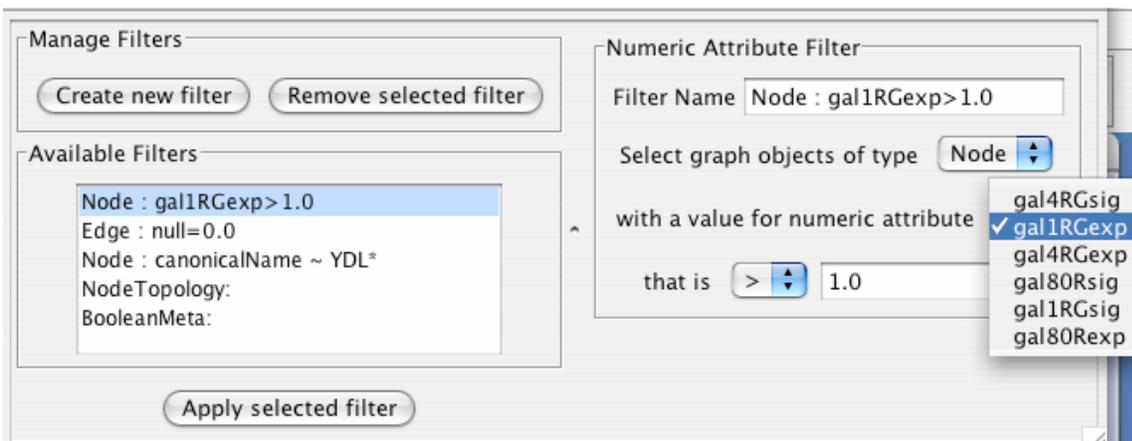
The important thing to realize when creating a filter is that the filter does not **do** anything by itself. Once created, the filter must be run.

String Filter:



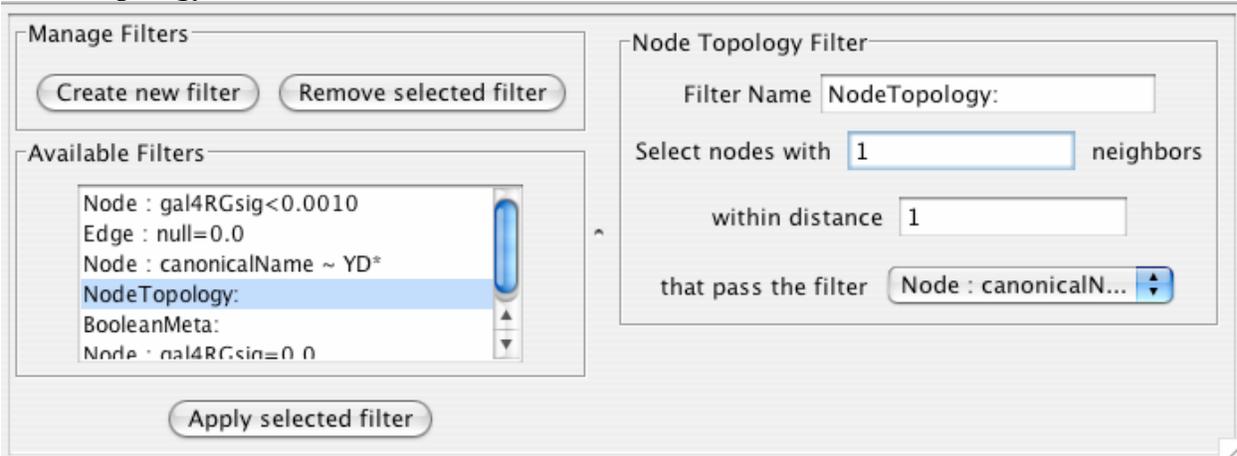
The String Filter allows you to filter Node or Edges, and gives you a list of available attributes to search for each (those attributes that are loaded on the network). Search terms are entered in the text box at the bottom. For example to match any Node whose canonicalName starts with “YDL” you would select “Node”, “canonicalName” and type “YDL*”. The * is important as it matches anything for any number of characters after YDL. If you want to be more specific and only select Nodes whose canonicalName starts with YDL00 followed by any other two characters, you would type “YDL00??”. The “?” denotes any single character, while the “*” represents zero or more characters. Full regular expression searching is supported, although is not covered here. Once the filter is defined, it will be assigned a default descriptive name.

Numerical Filter:



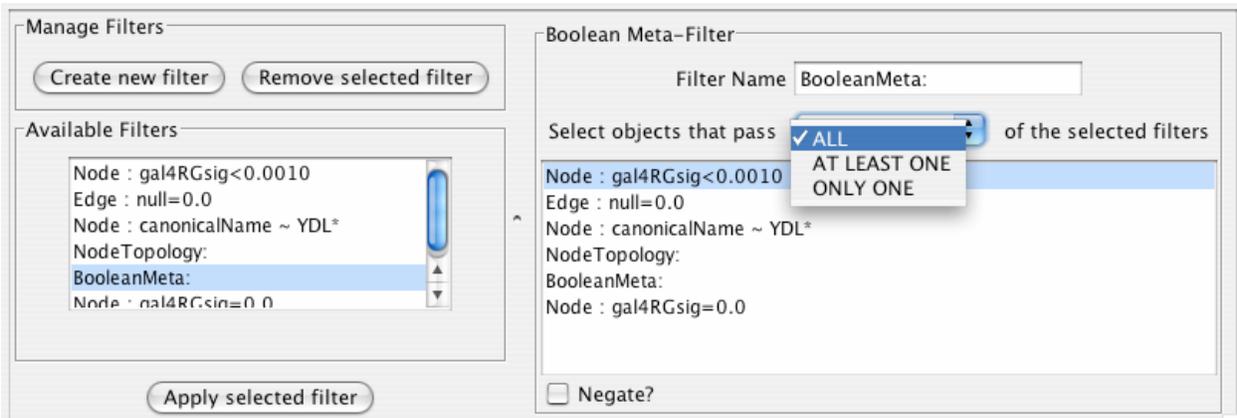
The Numerical Filter also allows you to filter Nodes or Edges, and presents you with a list of available attributes. This filter matches greater-than, less-than, or equal-to a number you type in the search box.

Node Topology Filter:



The node topology filter allows you to select nodes with at least n neighbors of distance m or less that pass some other selected filter. For instance, to select all the nodes adjacent to a node with the canonical name matching ‘YD*’, you would “select nodes with 1 neighbors”, “within distance 1”, “that pass the filter Node: canonicalName ~ YD*”.

Boolean Filter:



The Boolean filter allows you to define a new filter that is a logical combination of existing filters. Available filters are displayed. By selecting one or more filters, you can then choose whether Nodes or Edges pass “ALL” (AND), “AT LEAST ONE” (OR), or “ONLY ONE” (XOR) of the selected filters. Once created Boolean filters can then themselves be combined using the Boolean filter to create arbitrarily complex logical combinations of filters. Note that unlike the String and Numerical Filters, Boolean Filters will need to be assigned a name manually.

Once created, filters are saved for future sessions, as long as you exit Cytoscape normally via the exit command in the File menu (i.e. not via ctrl-c on Linux).

Running filters

Any available filter can be run by pressing the ‘Apply selected filter’ button. When a filter is applied and multiple nodes or edges are selected, all of the normal selection-related operations may be performed, such as Delete Selected Node/Edges, Copy To New Network, and Invert Selection.

14. Acknowledgements

Cytoscape is built with a number of open source 3rd party Java libraries. The Cytoscape team gratefully acknowledges the following libraries:

- The Colt Distribution: Open Source Libraries for High Performance Scientific and Technical Computing in Java. Information is available at: <http://hoschek.home.cern.ch/hoschek/colt/>.
- GNU Getopt in Java. Information is available at: <http://www.urbanophile.com/arenn/hacking/download.html>.
- Graph INterface librarY a.k.a. GINY. Information is available at: <http://csbi.sourceforge.net/>.
- JDOM. Information is available at: <http://www.jdom.org>.
- JUnit. Information is available at: <http://junit.org>.
- JGoodies Looks. Information is available at: <http://www.jgoodies.com/freeware/looks/index.html>.
- Piccolo. Information is available at: <http://www.cs.umd.edu/hcil/jazz/>.
- Type-Specific Collections Library, from Sosnoski Software Solutions, Inc. Information is available at: <http://www.sosnoski.com/opensource/tclib/>.
- Xerces Java XML parser. Information is available at: <http://xml.apache.org/xerces-j/>.

This product includes software developed by the Apache Software Foundation (<http://www.apache.org/>).

This product includes software developed by the JDOM Project (<http://www.jdom.org/>).

One-step Installation of the Cytoscape software is accomplished using the *InstallAnywhere* product from ZeroG Software, Inc. (<http://zerog.com>)

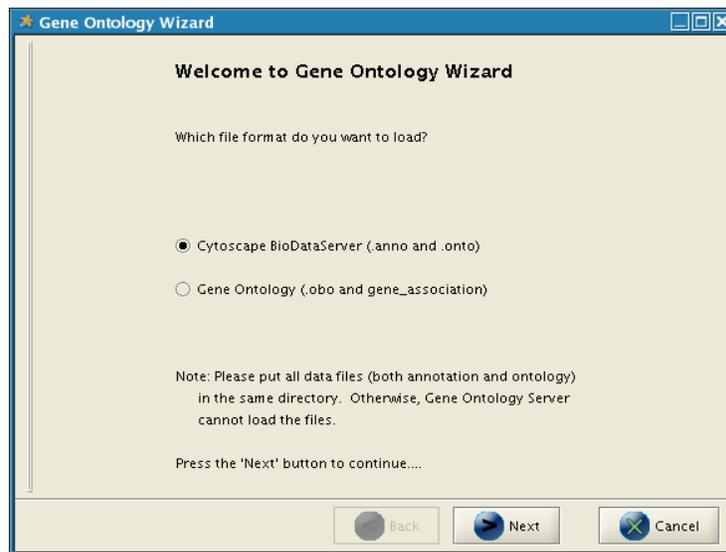
Appendix A: Old Annotation Server Format

The following section is still valid, however we *strongly* recommend using the new formats described in the previous section. See the introduction in Appendix A for a general discussion of Cytoscape annotation handling.

Gene Ontology Server Wizard

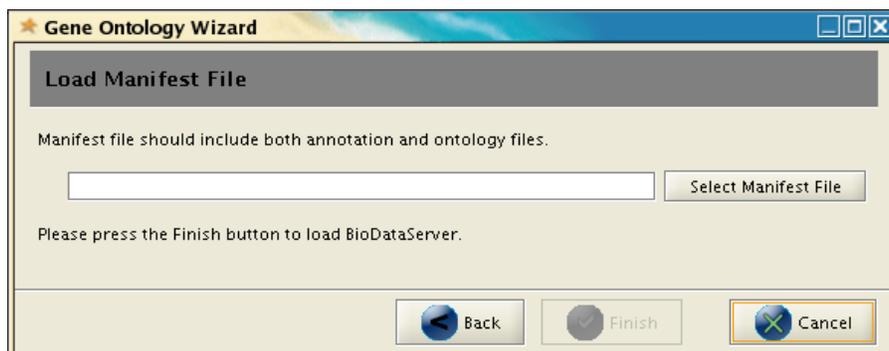
The Gene Ontology Server Wizard is a new graphical user interface used to select ontology and annotation files.

Step 1. Select Data Format



If you want to use old manifest file to load annotations, select *Cytoscape BioDataServer*. See Appendix A for a description of using the new file formats (*Gene Ontology*).

Step 2. Specify Manifest File



If you selected *Cytoscape BioDataServer* in the first step, you need to specify manifest file (list of ontology and annotation files). Then click on finish. All data files will be automatically loaded into Cytoscape. For more information about manifest file and how to create it, please read the section below.

Building your own annotation files

The annotation server requires that the gene annotations, and associated ontology on controlled vocabulary terms, follow a simple format. This simple format was chosen because it is efficient to parse and easy to use.

The flat file formats are explained below:

The Ontology Format

By example (the Gene Ontology - GO):

```
(curator=GO) (type=all)
0003673 = Gene_Ontology
0003674 = molecular_function [partof: 0003673 ]
0008435 = anticoagulant [isa: 0003674 ]
0016172 = antifreeze [isa: 0003674 ]
0016173 = ice nucleation inhibitor [isa: 0016172 ]
0016209 = antioxidant [isa: 0003674 ]
0045174 = glutathione dehydrogenase (ascorbate) [isa: 0009491 0015038 0016209 0016672 ]
0004362 = glutathione reductase (NADPH) [isa: 0015038 0015933 0016209 0016654 ]
0017019 = myosin phosphatase catalyst [partof: 0017018 ]
...
```

A second example (KEGG pathway ontology):

```
(curator=KEGG) (type=Metabolic Pathways)
90001 = Metabolism
80001 = Carbohydrate Metabolism [isa: 90001 ]
80003 = Lipid Metabolism [isa: 90001 ]
80002 = Energy Metabolism [isa: 90001 ]
80004 = Nucleotide Metabolism [isa: 90001 ]
80005 = Amino Acid Metabolism [isa: 90001 ]
80006 = Metabolism of Other Amino Acids [isa: 90001 ]
80007 = Metabolism of Complex Carbohydrates [isa: 90001 ]
...
```

The format has three required features:

1. The first line contains two parenthesized assignments, for *curator* and *type*. In the GO example above, the ontology file (which is created from the XML GO provides) nests all three specific ontologies (molecular function, biological process, cellular component) below the 'root' ontology, named 'Gene_Ontology'.

```
(type=all)
```

tells you that all three ontologies are included in that file.

2. Following the mandatory title line, there are one or more category lines, each with the form:

```
number0 = name [isa:|partof: number1 number2 ...]
```

'isa' and 'partof' are terms used in GO; they describe the relation between parent and child terms in the ontology hierarchy.

3. The trailing blank before each left square bracket is *not* required; it is an artifact of the python script that creates these files.

The Annotation Format

By example (from the GO biological process annotation file):

```
(species=Saccharomyces cerevisiae) (type=Biological Process) (curator=GO)
YMR056C = 0006854
YBR085W = 0006854
YJR155W = 0006081
...
```

and from KEGG:

```
(species=Mycobacterium tuberculosis) (type=Metabolic Pathways) (curator=KEGG)
RV0761C = 10
RV0761C = 71
RV0761C = 120
RV0761C = 350
RV0761C = 561
RV1862 = 10
...
```

The format has these required features:

1. The first line contains three parenthesized assignments, for *species*, *type* and *curator*. In the example just above, the annotation file (which we create for budding yeast from the flat text file maintained by SGD for the Gene Ontology project, and available both at their web site and at GO's) shows three yeast ORFs annotated for biological process, with respect to GO, described (further above).
2. Following the mandatory title line, there are one or more annotation lines, each with the form:

```
canonicalName = ontologyTermID
```

3. Once loaded, this annotation (along with accompanying ontology) can be assigned to nodes in a Cytoscape network. **For this to work, the species type of the node must agree exactly with the species named on the first line of the annotation file. The**

canonicalName of your node must exactly match the canonicalName present in the annotation file. If you don't see the expected results when using this feature of Cytoscape, check this again, as getting either of these wrong is a common mistake.

Load Data In-Process

The easiest way to make annotations available to Cytoscape is by loading annotations into an in-process annotation server. This is the default behavior for the official release of Cytoscape.

The Annotation Manifest

You must first create a text file to specify the files you want Cytoscape to load. Here is an example, from a file which (for convenience) we usually call “**manifest**”

```
ontology=goOntology.txt
annotation=yeastBiologicalProcess.txt
annotation=yeastMolecularFunction.txt
annotation=yeastCellularComponent.txt
```

Use the Cytoscape **-b** command line argument to specify the annotation manifest file to read (e.g. **-b manifest**). Please note that the **-s** switch, which sets the default species for your data is required to exactly match the species named in any annotation file you wish to use.

Getting and Reformatting GO Data

The Gene Ontology (GO) project is a valuable source of annotation for the genes of many organisms. In this section we will explain how to:

1. Obtain the GO ontology file
2. Reformat it into the simpler flat file Cytoscape uses
3. Obtain an annotation file (we illustrate with yeast and human annotation)
4. Reformat the annotation files into the simple Cytoscape format

Obtain the GO ontology file

Go to the GO XML FTP (<ftp://ftp.geneontology.org/pub/go/xml/>) page. Download the latest **go-YYYYMM-termdb.xml.gz** file.

Reformat GO XML ontology file into a flat file

```
gunzip go-YYYYMM-termdb.xml.gz
python parseGoTermsToFlatFile.py go-YYYYMM-termdb.xml > goOntology.txt
```

(See below for Python script listing)

Obtain the 'association' file for your organism

GO maintains a list of association files for many organisms; these files associate genes with GO terms. The next step is to get the file for the organism/s you are interested in, and parse it into the form Cytoscape needs. A list of files may be seen at <http://www.geneontology.org/GO.current.annotations.shtml>. The rightmost column contains

links to tab-delimited files of gene associations, by species. Choose the species you are interested in, and click 'Download'.

Let's use '**GO Annotations @ EBI Human**' as an example. After you have downloaded and saved the file, look at the first few lines:

```
SPTR    000115  DRN2_HUMAN          GO:0003677      PUBMED:9714827  TAS           F
Deoxyribonuclease II precursor IPI00010348    protein taxon:9606           SPTR
SPTR    000115  DRN2_HUMAN          GO:0004519      GOA:spkw        IEA           F
Deoxyribonuclease II precursor IPI00010348    protein taxon:9606           20020425     SPTR
SPTR    000115  DRN2_HUMAN          GO:0004531      PUBMED:9714827  TAS           F
Deoxyribonuclease II precursor IPI00010348    protein taxon:9606           SPTR
...
```

Note that line wrapping has occurred here, so each line of the actual file is wrapped to two lines.

The goal is to create from these lines the following lines:

```
(species=Homo sapiens) (type=Molecular Function) (curator=GO)
IPI00010348 = 0003677
IPI00010348 = 0004519
IPI00010348 = 0004531
...
or
(species=Homo sapiens) (type=Biological Process) (curator=GO)
NP_001366 = 0006259
NP_001366 = 0006915
NP_005289 = 0007186
NP_647593 = 0006899
...
```

The first sample contains molecular function annotation for proteins, and each protein is identified by its IPI number. IPI is the International Protein Index, which maintains cross references to the main databases for human, mouse and rat proteomes.

The second sample contains biological process annotation, and each protein is identified by its NP (RefSeq) number.

These two naming systems, IPI and RefSeq, are two of many that you can use for canonical names when you run Cytoscape. For budding yeast, it is much easier: the yeast community always uses standard ORF names, and so Cytoscape uses these as canonical names. For human proteins and genes, there is no such single simple standard. See section

5. Building and Storing Interaction Networks for more information.

The solution (for those working with human genes or proteins) is, once you have downloaded the annotations file, to:

1. Decide which naming system you want to use.

2. Download <ftp://ftp.ebi.ac.uk/pub/databases/GO/goa/HUMAN/xrefs.goa>. This cross-reference file, when used strategically, allows you to create Cytoscape-compatible annotation files in which the canonical name is the one most meaningful to you.
3. Examine *xrefs.goa* to figure out which column contains the names you wish to use.
4. Make a very slight modification to the python script described below, and then
5. Run that script, supplying both *xrefs.goa* and that annotation file as arguments.

Here are a few sample lines from *xrefs.goa*:

```
SP      000115  IPI00010348      ENSP00000222219;      NP_001366;
      BAA28623;AAC77366;AAC35751;AAC39852;BAB55598;AAB51172;AAH10419;      2960, DNASE2
      1777, DNASE2
SP      000116  IPI00010349      ENSP00000324567;ENSP00000264167;      NP_003650;
      CAA70591;      327,AGPS      8540,AGPS
SP      000124  IPI00010353      ENSP00000265616;ENSP00000322580;      NP_005662;
      BAA18958;BAA18959;AAH20694;      7993,D8S2298E
...
```

Note that line wrapping has occurred here – each line in this example starts with the letters SP.

See the README file for more information

(<ftp://ftp.ebi.ac.uk/pub/databases/GO/goa/HUMAN/README>)

Finally, run the script to create your three annotation files for human proteins:

- **bioproc.anno** (GO biological process annotation)
- **molfunc.anno** (GO molecular function annotation)
- **cellcomp.anno** (GO cellular component annotation)

using the supplied python script. It may be necessary to modify this script slightly if RefSeq identifiers are not used as canonical names.

```
python parseAssignmentsToFlatFileFromGoaProject.py gene_association.goa_human xrefs.goa
```

(See below for Python script listing)

Python script examples:

These scripts, described above require Python version 2.2 or later.

Script 1 - parseGoTermsToFlatFile.py

```
# parseGoTermToFlatFile.py: translate a GO XML ontology file into a simpler
# Cytoscape flat file
#-----
# RCS: $Revision: 1.3 $      $Date: 2003/05/18 00:38:43 $
#-----
import re, pre, sys
#-----
def flatFilePrint (id, name, isaIDs, partofIDs):
    isa = ''
    if (len (isaIDs) > 0):
        isa = '[isa: '
        for isaID in isaIDs:
            isa += isaID
            isa += ' '
        isa += ']'

    partof = ''
    if (len (partofIDs) > 0):
        partof = '[partof: '
        for partofID in partofIDs:
```

```

    partof += partofID
    partof += ' '
    partof += ']'

result = '%s = %s %s %s' % (id, name, isa, partof)
result = result.strip ()
if (result == 'isa = isa' or result == 'partof = partof'):
    print >> sys.stderr, 'meaningless term: %s' % result
else:
    print result
#-----
if (len (sys.argv) != 2):
    print 'usage: %s <someFile.xml>' % sys.argv [0]
    sys.exit ();

inputFilename = sys.argv [1];

print >> sys.stderr, 'reading %s...' % inputFilename
text = open (inputFilename).read ()
print >> sys.stderr, 'read %d characters' % len (text)

regex = '<go:term .*?>(.*?)</go:term>';
cregex = re.compile (regex, re.DOTALL) # . matches newlines

m = re.findall (cregex, text)
print >> sys.stderr, 'number of go terms: %d' % len (m)

regex2 = '<go:accession>GO:(.*?)</go:accession>.*?<go:name>(.*?)</go:name>';
cregex2 = re.compile (regex2, re.DOTALL)

regex3 = '<go:isa\s*rdf:resource="http://www.geneontology.org/go#GO:(.*?)"\s*/>';
cregex3 = re.compile (regex3, re.DOTALL)

regex4 = '<go:part-of\s*rdf:resource="http://www.geneontology.org/go#GO:(.*?)"\s*/>';
cregex4 = re.compile (regex4, re.DOTALL)

goodElements = 0
badElements = 0

print '(curator=GO) (type=all)'
for term in m:
    m2 = re.search (cregex2, term)
    if (m2):
        goodElements += 1;
        id = m2.group (1)
        name = m2.group (2)
        isaIDs = []
        m3 = re.findall (cregex3, term);
        for ref in m3:
            isaIDs.append (ref)
        m4 = re.findall (cregex4, term);
        partofIDs = []
        for ref in m4:
            partofIDs.append (ref)
        flatFilePrint (id, name, isaIDs, partofIDs)
    else:
        badElements += 1;
        print >> sys.stderr, 'no match to m2...'
        print >> sys.stderr, "-----\n%s\n-----" % term

print >> sys.stderr, 'goodElements %d' % goodElements
print >> sys.stderr, 'badElements %d' % badElements

#-----

```

Script 1 - parseAssignmentsToFlatFileFromGoaProject.py

```

#!/tools/bin/python
import sys

```

```

#-----
def fixCanonicalName (rawName):
# for instance, trim 'YBR085W|ANC3' to 'YBR085W'
    bar = rawName.find ('|')
    if (bar < 0):
        return rawName
    return rawName [:bar]

#-----
def fixGoID (rawID):

    bar = rawID.find (':') + 1
    return rawID [bar:]

#-----
def readGoaXrefFile (filename):

    lines = open (filename).read().split ('\n')
    result = {}
    for line in lines:
        if (len (line) < 10):
            continue
        tokens = line.split ('\t')
        ipi = tokens [2]
        np = tokens [5]
        semicolon = np.find (';')
        if (semicolon >= 0):
            np = np [:semicolon]
        if (len (ipi) > 0 and len (np) > 0):
            result [ipi] = np

    return result

#-----
if (len (sys.argv) != 3):
    print 'error! parse <gene_associations file from GO> <goa xrefs file> '
    sys.exit ()

associationFilename = sys.argv [1];
xrefsFilename = sys.argv [2]
species = 'Homo sapiens'

ipiToNPHash = readGoaXrefFile (xrefsFilename)
tester = 'IPI00099416'
print 'hash size: %d' % len (ipiToNPHash)
print 'test map: %s -> NP_054861: %s ' % (tester, ipiToNPHash [tester])

bioproc = open ('bioproc.txt', 'w')
molfunc = open ('molfunc.txt', 'w')
cellcomp = open ('cellcomp.txt', 'w')

bioproc.write ('(species=%s) (type=Biological Process) (curator=GO)\n' % species)
molfunc.write ('(species=%s) (type=Molecular Function) (curator=GO)\n' % species);
cellcomp.write ('(species=%s) (type=Cellular Component) (curator=GO)\n' % species);

lines=open(associationFilename).read().split('\n')
sys.stderr.write ('found %d lines\n' % len (lines))

for line in lines:
    if (line.find ('!') == 0 or len (line) < 2):
        continue
    tokens = line.split ('\t')
    goOntology = tokens [8]
    goIDraw = tokens [4]
    goID = goIDraw.split (':')[1]
    ipiName = fixCanonicalName (tokens [10])
    if (len (ipiName) < 1):
        continue

    if (not ipiToNPHash.has_key (ipiName)):

```

```
    continue
refseqName = ipiToNPHash [ipiName]
printName = refseqName
#printName = ipiName
if (ipiName == tester):
    print '%s (%s) has go term %s' % (tester, printName, goID)
if (goOntology == 'C'):
    cellcomp.write ('%s = %s\n' % (printName, goID))
elif (goOntology == 'P'):
    bioproc.write ('%s = %s\n' % (printName, goID))
elif (goOntology == 'F'):
    molfunc.write ('%s = %s\n' % (printName, goID))
#-----
```

Appendix B: GNU Lesser General Public License

GNU LESSER GENERAL PUBLIC LICENSE
Version 2.1, February 1999

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