Cytoscape User Manual

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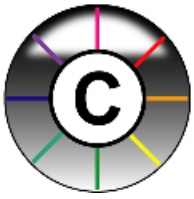

Cytoscape 2.4.0-b1 User Manual

[attachment:cyto-logo-smaller.gif]

Authors: The Cytoscape Collaboration

The Cytoscape project is an ongoing collaboration between:

Table 1.

University of California at San Diego	[attachment:ucsd-logo.gif]
Institute for Systems Biology	[attachment:isb-logo.gif]
Memorial Sloan-Kettering Cancer Center	[attachment:msk-logo.gif]
Institut Pasteur	[attachment:pasteur-logo.gif]
Agilent Technologies	[attachment:agilent-logo.gif]

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Introduction

Cytoscape is an open-source community software project for integrating biomolecular interaction networks with high-throughput expression data and other molecular state information for visualization and analysis. 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 state information; and to link the network to databases of functional annotations. The Core is extensible through a 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 Acknowledgements below.

What's New in 2.3

Cytoscape version 2.3. contains several new features, plus improvements to the performance and usability of the software. These include:

- A much faster rendering engine. Cytoscape can now render at interactive speed graphs with over 100,000 nodes and edges.
- The ability to save a session. You can now save all of your work in Cytoscape to a single file. When re-opened, this file will return Cytoscape to the state in which you left it including all networks, attributes, and properties.
- A node grouping plugin. This will allow one node to contain and display subnetworks.
- Enhanced Undo/Redo support.
- An enhanced attribute browser.
- An enhanced Ontology Server Wizard.
- An improved command line interface.
- The ability to rename networks.
- The GraphMerge plugin included by default.
- Enhanced context or pop-up menus for nodes.
- Many performance improvements and bug fixes.
- A rewritten "bird's eye view" of the network that is enabled by default.
- The ability to load expression data according to node attribute (such as a commercial probeset identifier) instead of ndoe ID.

Are you an experienced Cytoscape user? If so, you should definitely read the following sections because important parts of Cytoscape have changed and what used to work, may no longer work as you expect!!!

- Properties (cytoscape.props and vizmap.props) handling.
- Rendering Engine.
- Command line arguments.
- The menu system.
- Network Panel Navigation.

Launching Cytoscape

Cytoscape is a Java application that runs on Linux, Windows, and Mac OS X.

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 instructions.

- 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 LGPL License
Cytoscape2_3Manual.pdf  Cytoscape 2.3 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 *
  galFiltered.cys       Sample session file created from datasets above *
  BINDyeast.sif Network of all yeast protein-protein interactions in the
                          BIND database as of Nov, 2005 **
  BINDhuman.sif Network of all human protein-protein interactions in the
                          BIND database as of Nov, 2005 **
  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 -Xmx512M -jar cytoscape.jar -p plugins". The *-Xmx512M* flag tells java to allocate more memory for Cytoscape and the *-p plugins* option tells cytoscape to load all of the plugins in the plugins directory. Loading the plugins is important because many key features like layouts, filters and the attribute browser are included with Cytoscape as plugins in the *plugins* directory. See the Command Line chapter for more detail. 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 plugin directory). 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 icon any .sif or .gml file will load that file into Cytoscape.

Table 2.

Important Note: For the application to work properly, all files should be left in the directory in which they were unpacked. The core Cytoscape application assumes this directory structure when looking for the various libraries needed to run the application. If you are adventurous, you can get creative with the $CLASSPATH and/or the cytoscape.jar manifest file and run Cytoscape from any location you want.

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

[attachment:cytoscape_startup.png]

Quick Tour of Cytoscape

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

[attachment:cytoscape_startup_network.png]

The main window here has several components:

1. The menu bar at the top (See below for more information about each menu).
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.

[attachment:image015.gif] If you select this control, e.g. 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.

[attachment:attribute_browser_nodes.png] 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 an editor that enables you to build and modify networks interactively by dragging and dropping nodes and edges from a palette onto the main network view window. The Node shapes and Edge arrows on the palette are defined by the currently used Visual Style. To edit a network, just select the Editor tab on CytoPanel 1. An example of an editor, with the palette contained in CytoPanel 1 and defined by the BioMoleculeEditor Visual Style, is shown below.

[attachment:image018.png]

The Menus

File The File menu contains most basic file functionality: File → Open for opening a Cytoscape session file, File → Save for saving a session file, File → Import for importing data such as networks and attributes, File → Export for exporting data and images. File → Print allows printing. File → Quit closes all windows of Cytoscape and exits the program. File → New creates a new network, either blank for editing, or from an existing network.

[attachment:menu_file.png]

Edit The Edit menu contains Undo and Redo menu items which undo and redo edits made in the Attribute Browser and the Network Editor.

- 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 → Undo menu item. The Edit Menu also supports Preferences editing for properties and plug-ins via a Preferences Dialog.

[attachment:menu_edit.png]

View The View menu allows you to display or hide the network management panel (CytoPanel 1), the attribute browser (CytoPanel 2), the Network Overview (in CytoPanel 1), and the Advanced window. The View menu also allows you to open the VizMapper and lock the VizMapper. The View → Desktop provide futher control over the various CytoPanels.

[attachment:menu_view.png]

Select The Select menu contains different options selecting nodes and edges. It also contains the Select → Use Filters option which allows filters to be created which can be used to automatically select portions of a network whose node or edge attributes meet a filtering criterion.

[attachment:menu_select.png]

Layout The Layout menu has an array of features for organizing the network visually. The top of the menu contains tools for manipulating sections of networks. These tools include scale, rotate, distribute, and align. The bottom section of the menu lists a variety of layout algorithms which automatically lay a network out.

[attachment:menu_layout.png]

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

[attachment:menu_plugins.png]

Table 3.

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

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.

[attachment:menu_help.png]

Network Management

Cytoscape 2.3 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:

[attachment:cytoscape_network_heirarchy.png]

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 one 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 File → 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 the normal window controls for your operating system.

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 View → Show/Hide Network Overview menu. The 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.

[attachment:network_overview.png]

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Command Line Arguments

Table 4.

Important! The command line arguments have changed in version 2.3, so please read this section carefully.

Cytoscape recognizes a number of optional command line arguments, including run-time specification of network files, attribute files, and session files. This is the output generated when the cytoscape is executed with the "-h" or "--help" flag.

```
usage: java -Xmx512M -jar cytoscape.jar [OPTIONS]
 -h,--help                      Print this message.
 -v,--version                 Print the version number.
 -s,--session <file>        Load a cytoscape session (.cys) file.
 -N,--network <file>     Load a network file (any format).
 -e,--edge-attrs <file>    Load an edge attributes file (edge attribute format).
 -n,--node-attrs <file>   Load a node attributes file (node attribute format).
 -m,--matrix <file>        Load a node attribute matrix file (table).
 -p,--plugin <file>         Load a plugin jar file, directory of jar files,
                                    plugin class name, or plugin jar URL.
 -P,--props <file>         Load cytoscape properties file (Java properties
```

```
                                format) or individual property: -P name=value.
 -V,--vizmap <file>      Load vizmap properties file (Java properties format).
```

Any file specified for an option may be specified as either a path or as a URL. For example you can specify a network as a file (assuming that myNet.sif exists in the curret working directory): `cytoscape.sh -N myNet.sif`. Or you can specify a network as a URL: `cytoscape.sh -N http://example.com/myNet.sif`.

Table 5.

Argument	Description
-h,--help	This flag generates the help output you see above and exits.
-v,--version	This flag prints the version number of cytoscape and exits.
-s,--session <file>	This option specifies a session file to be loaded. Since only one session file can be loaded at a given time, this option may only specified once on a given command line. The option expects a **.cys** cytoscape session file. It is customary, although not necessary, for session file names to contain the **.cys** extension.
-N,--network <file>	This option is used to load all types of network files. SIF, GML, and XGMML files can all be loaded using the -N option. You can specify as many networks as desired on a single command line.
-e,--edge-attrs <file>	This option specifies an edge attributes file. You may specify as many edge attribute files as desired on a single command line.
-n,--node-attrs <file>	This option specifies a node attributes file. You may specify as many node attribute files as desired on a single command line.
-m,--matrix <file>	This option specifies a data matrix file. In a biological context, the data matrix consists of expression data. All data matrix files are read into node attributes. You may specify as many data matrix files as desired on a single command line.
-p,--plugin <file>	This option specifies a cytoscape plugin (.jar) file to be loaded by cytoscape. This option also subsumes the previous "resource plugin option". You may specify a class name that identifies your plugin and the plugin will be loaded if the plugin is in Cytoscape's CLASSPATH. For example, assuming that the class MyPlugin can be found in the CLASSPATH, you could specify the plugin like: `cytoscape.sh -p MyPlugin.class`. A final means of specifying plugins is to specify a file name who's contents contain a list of plugin jar files.
-P,--props <file>	This option specifies cytoscape properties. Properties can be specified either as a properties file (in Java's standard properties format), or as individual properties. To specify individual properties, you must specify the property name followed by the property value where the name and value are separated by the '=' sign. For example to specify the defaultSpeciesName: `cytoscape.sh -P defaultSpeciesName=Human`. If you would like to include spaces in your property, simply enclose the name and value in quotation marks: `cytoscape.sh -P "defaultSpeciesName=Homo Sapiens"`. The property option subsumes previous options -noCanonicalization, -species, and -bioDataServer. Now it would look like: `cytoscape.sh -P defaultSpeciesName=Human -P noCanonicalization=true -P bioDataServer=myServer`.
-V,--vizmap <file>	This option specifies a visual properties file.

Aside from plugins, all options described above can be loaded from the GUI once 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.

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Cytoscape Properties

Table 6.

Important! If you have used previous versions of Cytoscape, you will notice that handling of properties has changed. The most important change is that properties are no longer saved by default to the current directory or to your home .cytoscape directory. Properties are stored by default in Cytoscape Session files. The cytoscape.props file still exists in the .cytoscape directory but is only written to when the user explicitly requests that the current settings be made the defaults for all future sessions of Cytoscape. *Unless you have something important in your .cytoscape/cytoscape.props file, your best bet will be to delete the file and use the defaults.*

The Cytoscape Preferences Dialog, accessed via Edit → Preferences…, has sections for general properties display/editing and plugins specification via the properties mechanism. Preferences are now stored in Cytoscape session files. Any changes made to properties while running Cytoscape will be saved to the current session when you save the session. If you do not save the session, export the properties (File → Export), or set them as defaults (see below), the properties will be lost and the next time Cytoscape starts, defaults will be used.

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

[attachment:preferences_editor.png]

Some common properties are described below.

Table 7.

Property name	Default value	Valid values
defaultSpeciesName	PleaseSpecify	Species name. 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 Saccharomyces cerevisiae
bioDataServer	PleaseSpecify	annotation/manifest, and other manifest file locations
viewThreshold	10000	integer > 0
secondaryViewThreshold	30000	integer > 0
viewType	tabbed	tabbed
plugins		comma-separated list of jar files containing plugins, or URL's to jar files containing plugins (e.g., http://server/my-plugin.jar)
defaultWebBrowser		A path to the web browser on your system. This only needs to be specified if Cytoscape can't find the web browser on your system.

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 and presented and managed in the Plugins table, as at left.

Setting Default Properties It is possible to alter the default properties for Cytoscape. In the Cytoscape Preferences Dialog, accessed via Edit → Preferences…, edit any preferences, then click the "Make Current Cytoscape Properties Default" checkbox in the "Default Cytoscape Properties" section of the dialog. This

will save any properties to the .cytoscape directory contained in your home directory. You should only do this if you want specific properties to apply to all of your Cytoscape sessions. You can rely on the Cytoscape session file to maintain the properties used for that particular session, so making certain properties default is not necessary to save the properties.

Building and Storing Interaction Networks

Cytoscape reads an interaction network in three ways: a simple interaction file (SIF or .sif format), a standard format known as Graph Markup Language (GML or .gml format), and an XML standard called XGMML (extensible graph markup and modelling language). SIF specifies nodes and interactions only, while GML and XGMML store 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 or XGMML format in future Cytoscape sessions. SIF, GML, and XGMML are text files and you can edit and view them in a regular text editor. Additionally, GML and XGMML are supported by some other network visualization tools.

SIF FORMAT:

The simple interaction 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 named 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 interaction 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.

XGMML FORMAT:

XGMML is the XML evolution of GML and is based on the GML definition. The XGMML file format specification is available at:

http://www.cs.rpi.edu/~puninj/XGMML/

XGMML is now preferred to GML because it offers the flexibility associated with all XML document types. If you're unsure about which to use, choose XGMML.

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 –N option (works for SIF, GML, and XGMML).

FOR EXAMPLE:

To load a sample molecular interaction network in SIF format, use the menu File → Import → 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 → Import → 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 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 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 not be changed. 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 –P option (`cytoscape.sh -P "defaultSpeciesName=Saccharomyces cerevisiae"`) or by editing the properties in the Preferences Dialog (Edit → Preference...).

The automatic canonicalization of names can be turned off using the -P option (`cytoscape.sh -P canonicalizeName=false"`) or by editing the properties in the Preferences Dialog (Edit → Preferences...). 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.

Loading Gene Expression (Attribute Matrix) Data

Interaction networks are useful as stand-alone models. However, they are most powerful for answering scientific questions when integrated with additional biological information, 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 or values are specified over one or more experiments using a text file. Ratios result from a comparison of two expression measurements (experiment vs. control). Some expression platforms, such as Affymetrix, directly measure expression values, without a comparison. The file consists of a header and a number of space- or tab-delimited fields, one line per gene, with the following format:

```
Identifier [CommonName] value1 value2 ... valueN [pval1 pval2 ... pvalN]
```

Brackets [ ] indicate fields that are optional.

The first field identifies which Cytoscape node the data refers to. In the simplest case, this is the gene name - exactly as it appears on the Cytoscape canvas (case sensitive!). Alternatively, this can be some node attribute that identifies the node uniquely, such as a probeset identifier for commercial microarrays.

The next field is an optional common name. It is not used by Cytoscape, and is provided strictly for the user's convenience. With this common name field, the input format is the same as for commonly-used expression data anaysis packages such as SAM (http://www-stat.stanford.edu/~tibs/SAM/).

The next set of columns represent expression values, one per experiment. These can be either absolute expression values or fold change ratios. Each experiment is identified by its experiment name, given in the first line.

Optionally, significance measures such as P values may be provided. These values, generated by many microarray data analysis packages, indicate where the level of gene expression or the fold change appears to be greater than random chance. If you are using significance measures, then your expression file should contain them in a second set of columns after the expression values. The column names for the expression significance measures should match those of the expression values *exactly*.

For example, here is an excerpt from the file galExpData.pvals in the Cytoscape sampleData directory::

```
GENE COMMON gal1RG gal4RG gal80R gal1RG gal4RG gal80R
YHR051W COX6 -0.034 0.111 -0.304 3.75720e-01 1.56240e-02 7.91340e-06
```

```
YHR124W NDT80 -0.090 0.007 -0.348 2.71460e-01 9.64330e-01 3.44760e-01
YKL181W PRS1 -0.167 -0.233 0.112 6.27120e-03 7.89400e-04 1.44060e-01
YGR072W UPF3 0.245 -0.471 0.787 4.10450e-04 7.51780e-04 1.37130e-05
```

This indicates that there is data for three experiments: gal1RG, gal4RG, and gal80R. These names appear two times: the first time gives the expression values, and the second gives the significance measures. For instance, the second line tells us that in Experiment gal1RG, the gene YHR051W has an expression value of -0.034 with significance measure 3.75720e-01.

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 attribute matrix file using the Cytoscape menu options File → Import → Attribute/Expression Matrix to bring up the import dialog box, or by specifying the filename using the -m option at the command line. If you use the command line input, you must enter your expression data by node ID. If you use the dialog box, then you can either load expression data by node ID (the default option), or can optionally select a node attribute to use in assigning your expression data to your Cytoscape nodes. If you do use a node attribute, then (1) the attribute should already be loaded, and (2) the node attribute value must match the first column in your matrix file.

FOR EXAMPLE:

For the sample network file **sampleData/galFiltered.sif**:

1. Load a sample gene expression data set using the menu: File → Import → Attribute/Expression Matrix. In the resulting file dialog box, in the field labeled "Please select an attribute or expression matrix file...", select **sampleData/galExpData.pvals**. The identifiers used in this file are the same ones used in the network file **sampleData/galFiltered.sif**, so you do not need to touch the field labeled "Assign values to nodes using...". A few lines of this file are shown below:

```
GENE COMMON gal1RG gal4RG gal80R gal1RG gal4RG gal80R
YHR051W COX6 -0.034 0.111 -0.304 3.75720e-01 1.56240e-02 7.91340e-06
YHR124W NDT80 -0.090 0.007 -0.348 2.71460e-01 9.64330e-01 3.44760e-01
YKL181W PRS1 -0.167 -0.233 0.112 6.27120e-03 7.89400e-04 1.44060e-01
```

- or -

2a. After loading the network, load the node attribute file **sampleData/gal.probeset.na**, using the menu options File → Import → Node attributes.... This file is shown in part below:

```
Probeset
YHR051W = probeset2
YHR124W = probeset3
YKL181W = probeset4
```

2b. After loading the node attribute file, select the expression data file **sampleData.galExpPvals.probeset.pvals**, shown in part below:

```
GENE COMMON gal1RG gal4RG gal80R gal1RG gal4RG gal80R
probeset2 COX6 -0.034 0.111 -0.304 3.75720e-01 1.56240e-02 7.91340e-06
probeset3 NDT80 -0.090 0.007 -0.348 2.71460e-01 9.64330e-01 3.44760e-01
probeset4 PRS1 -0.167 -0.233 0.112 6.27120e-03 7.89400e-04 1.44060e-01
```

After selecting this file, in the field labeled **Assign values to nodes using...**, select **Probeset**. You will see that this loads exactly the same expression data as in Case 1, but provides extra flexibility in case the node name cannot be used as an identifier.

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>...LAMBDAS
```

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 LAMBDAS 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, GML, or XGMML 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.

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 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 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 –e options or via the File → Import 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.

Node and edge attributes are attached to nodes and edges, NOT to networks. If two different networks have the same nodes, then those nodes will have the same attributes. Even if a network is loaded after attributes have been loaded, if the nodes or edges found in the new network already exist, then any existing attributes will be applied to those nodes.

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 or the View → Show/Hide attribute browser menu option. Like other Cytopanels, the browser can be undocked by pressing the little icon in the browser's top right corner.

[attachment:attribute_browser_nodes.png] To swap between displaying node, edge, and network attributes use the tabs on the bottom of the panel: "Node Attribute Browser", "Edge Attribute Browser", and "Network Attribute Browser". The attribute browser displays attributes belonging to selected nodes and/or edges and the currently selected network. 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" [attachment:attributes_select_icon.png] button and choose the attributes that are to be displayed. Each attribute chosen 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" [attachment:attributes_new_icon.png] button. Attributes created using the attribute browser must be one of four types – integer, string, real number (floating point), or boolean. Attributes can be deleted using the "Delete Attributes..." [attachment:attributes_delete_icon.png] button. NOTE: Deleting attributes removes them from Cytoscape, not just the attribute browser! To remove attributes only from the browser simply unselect the attribute using the "Select Attributes" [attachment:attributes_select_icon.png] button. 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. Each attribute browser panel has a button for importing new attributes: [attachment:attributes_import_icon.png] .

The Node Attribute Browser panel has additional buttons for loading Gene Expression attribute matrices ([attachment:attributes_gene_expr_icon.png]) and for selecting Gene Ontology (GO) terms ([attachment:attributes_go_icon.png]) as node attributes. The Ontology selection button is only available if an

Ontology Server has been imported. You can import an Ontology server through the File → Import → Ontology → Ontology Server menu option.

Navigation and Layout

Navigation

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:

[attachment:image049.jpg]

From Left to Right:

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

Zoom 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).

Pan You can pan the network image by holding down the middle mouse button and moving the mouse. You can also pan the image by holding down the left mouse button over the blue box in the Network Overview panel in the lower left hand of the Cytoscape desktop.

Select Click the left mouse button on a node or edge to select that object. You can hold down the Shift key to select more than one node/edge or you can hold down the left mouse button and drag the mouse to select groups of nodes/edges.

Context Click the right mouse button on a node/edge to launch a context sensitive menu with additional information about the node/edge.

Automatic Layout Algorithms

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 2.3. Some of the layout algorithms provided with Cytoscape 2.3 are:

Cytoscape 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. This algorithm is available from the Layout → Cytoscape Layouts → Spring Embedded menu item. A sample screen shot is provided below:

[attachment:image051.png] **yFiles Circular Layout**

This algorithm produces layouts that emphasize group and tree structures within a network. It partitions the network by analyzing its connectivity structure, and arranges the partitions as separate circles. The circles themselves are arranged in a radial tree layout fashion. This algorithm is available from the Layout → yFiles → Circular menu item.

[attachment:image053.png] **yFiles 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. This algorithm is available from the Layout → yFiles → Heirarchical menu item.

[attachment:image055.png] **yFiles 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. This algorithm is available from the Layout → yFiles → Organic menu item.

[attachment:image057.png] Several other alignment algorithms, including a selection from the JGraph project (http://jgraph.sourceforge.net), are also available under the Layout menu.

Manual Layout

The simplest method to manually layout a network is to click on a node and drag the node. If you select multiple nodes, all of the selected nodes will be moved together.

Edge Handles

A little known feature! If you select an edge and then Ctrl-left-click on the edge, an edge "handle" will appear. This handle can be used to change the shape of the line. To remove a handle, simply Ctrl-left-click on the handle again.

[attachment:edge_handles.png]

The Select → Edges menu has two menu items that provide further control: "Smooth Selected Edges" turns an edge consisting of line segments into a smoothed bezier curve, and "Straighen Selected Edges" turns a curved edge back into line segments.

[attachment:menu_select_edges.png]

Rotate

[attachment:rotate_dialog.png]

The Layout → Rotate menu opens the Rotate dialog. Rotate will either rotate the entire network or a selected portion of the network. The image below shows a network with selected nodes rotated.

[attachment:rotate_network.png]

Scale

[attachment:scale_dialog.png]

The Layout → Scale menu opens the Scale dialog. Scale will scale the position of the entire network or of the selected portion of the network. Note that only the position of the nodes scale, not the node sizes. Node size can be adjusted using the VizMapper. The image below shows selected nodes scaled.

[attachment:scale_network.png]

Align/Distribute

[attachment:align_distribute_dialog.png]

The Layout → Align/Distribute menu opens the Align/Distribute dialog. The Align buttons of the dialog provides different options for either vertically or horizontally aligning selected nodes against a line. The differences are in what part of the node gets aligned, e.g. the center of the node, the top of the node, the left side of the node. The Distribute buttons evenly distribute selected nodes between the two most distant nodes along either the vertical or horizontal axis. The differences are again a function what part of the node is used as a reference point for the distribution. The table below provides a mapping from button to name to result.

Starting position for all aligned examples.

[attachment:align_begin.png]

Table 8.

Button	Description	Result
[attachment:V_ALIGN_TOP.gif]	Vertical Align Top - The tops of the selected nodes are aligned with the top-most node.	[attachment:align_vertical_top.png]
[attachment:V_ALIGN_CENTER.gif]	Vertical Align Center - The centers of selected nodes are aligned along a line defined by the midpoint between the top and bottom-most nodes.	[attachment:align_vertical_center.png]
[attachment:V_ALIGN_BOTTOM.gif]	Vertical Align Bottom - The bottoms of the nodes are aligned with the bottom-most node.	[attachment:align_vertical_bottom.png]
[attachment:H_ALIGN_LEFT.gif]	Horizontal Align Left - The left hand sides of the selected nodes are aligned with the left-most node.	[attachment:align_horizontal_left.png]
[attachment:H_ALIGN_CENTER.gif]	Horizontal Align Center - The centers of selected nodes are aligned along a line defined by the midpoint between the left and right-most nodes.	[attachment:align_horizontal_center.png]
[attachment:H_ALIGN_RIGHT.gif]	Horizontal Align Right - The right hand sides of the selected nodes are aligned with the right-most node.	[attachment:align_horizontal_right.png]

Starting position for all vertically distributed examples.

[attachment:distribute_begin_vertical.png]

Table 9.

Button	Description	Result
[attachment:V_DIST_TOP.gif]	Vertical Distribute Top - The tops of the selected nodes are distributed evenly between the top-most and bottom-most nodes, which should stay stationary.	[attachment:distribute_vertical_top.png]
[attachment:V_DIST_CENTER.gif]	Vertical Distribute Center - The centers of the selected nodes are distributed evenly between the top-most and bottom-most nodes, which should stay stationary.	[attachment:distribute_vertical_center.png]
[attachment:V_DIST_BOTTOM.gif]	Vertical Distribute Bottom - The bottoms of the selected nodes are distributed evenly between the top-most and bottom-most nodes, which should stay stationary.	[attachment:distribute_vertical_bottom.png]

Starting position for all horizontally distributed examples.

[attachment:distribute_begin_horizontal.png]

Table 10.

Button	Description	Result
[attachment:H_DIST_LEFT.gif]	Horizontal Distribute Left - The left hand sides of the selected nodes are distributed evenly between the left-most and rigth-most nodes, which should stay stationary.	[attachment:distribute_horizontal_left.png]
[attachment:H_DIST_CENTER.gif]	Horizontal Distribute Center - The centers of the selected nodes are distributed evenly between the left-most and rigth-most nodes, which should stay stationary.	[attachment:distribute_horizontal_center.png]
[attachment:H_DIST_RIGHT.gif]	Horizontal Distribute Right - The right hand sides of the selected nodes are distributed evenly between the left-most and rigth-most nodes, which should stay stationary.	[attachment:distribute_horizontal_right.png]

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 along a color gradient.

All these features are available by selecting the View → Open Viz Mapper menu item or clicking on the color wheel [attachment:vizmap_color_wheel.gif] button on the main button bar.

Introduction to Visual Styles

The Cytoscape distribution includes several predefined visual styles to get you started. To demonstrate these styles, try out the following example:

- Load a sample network: From the main menu, select File → Import → Network, 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 → Import → Attribute Matrix 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).

[attachment:default_viz_mapper.png] **Figure: Using the default Visual Style.**

You can flip through different visual styles by making a selection from the Visual Style pull down menu (available directly to the right of the color wheel).

For example, if you select "Sample1", a new visual style will be applied to your network, and you will see a white 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 red edges, whereas protein-protein interactions (specified with the label: pp) are drawn with a light blue color (see sample screenshot below).

[attachment:sample1_vizmap.png] **Figure: Using the Sample1 Visual Style. Protein-Protein interactions (solid blue lines) are now distinguishable from Protein-DNA interactions (dashed red 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:

[attachment:sample2_vizmap.png] **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, network 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 *network 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 network 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.

Table 11.

Visual Attributes Associated with Nodes:
Node Color
Node Border Color
Node Border Type. The following options are available: [attachment:image070.jpg]
Node Shape. The following options are available: [attachment:image072.jpg]
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:
Edge Color
Edge Line Type. The following options are available: [attachment:image070.jpg]
Edge Source Arrow. The following options are available: [attachment:image075.jpg]
Edge Target Arrow. The following options are available: [attachment:image075.jpg]
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:** network 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 network 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 continuous 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.

Table 12.

Node Properties	**Passthrough Mapper**	**Discrete Mapper**	**Continuous Mapper**
Node Color	-	X	X
Node Border Color	-	X	X
Node Border Type	-	X	o
Node Shape	-	X	o
Node Size	-	X	X
Node Label	X	X	o
Node Font Family	-	X	o
Node Font Size	-	X	X
Edge Properties	**Passthrough Mapper**	**Discrete Mapper**	**Continuous Mapper**
Edge Color	-	X	X
Edge Line Type	-	X	o
Edge Source Arrow	-	X	o
Edge Target Arrow	-	X	o
Edge Label	X	X	o
Edge Font Family	-	X	o
Edge Font Size	-	X	X

Legend

Table 13.

Symbol	*Description*
-	Mapping is not supported for specified visual property.
X	Mapping is fully supported for specified visual property.
o	Mapping is partially supported for specified visual property. Support for “continuous to continuous” mapping is not supported.

Visual Styles Tutorials

Tutorial 1: Creating a Basic Visual Style

To create a new visual style, select the View → Open Viz Mapper menu item, or select the color wheel icon in the main button bar. You will now see a new Visual Styles dialog box (shown below.)

[attachment:image078.jpg]

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 below.)

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.

[attachment:image080.jpg] To apply your visual style to your network, hit the **Apply to Network** button, available in the bottom of the dialog panel.

Tutorial 2: 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 → Import → Network, and select sampleData/galFiltered.sif.
- Click the color wheel [attachment:vizmap_color_wheel.gif] button on the tool bar.
- 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 to the text above) Select “discrete mapper”, and enter a descriptive name. For example, enter: Interaction_Type_Color.
- 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 Network" button.

You network should now show “pd” interactions in blue, and “pp” interactions in red. Sample screenshot is below

[attachment:image090.png]

Tutorial 3: Visualizing Expression Data on a Network

The following tutorial demonstrates how to create a new continuous mapper. The goal is to superimpose 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 → Import → Network, and select sampleData/galFiltered.sif.
- Load a sample set of expression data: From the main menu, select File → Import → Attribute Matrix and select sampleData/galExpData.pvals.
- Click the color wheel [attachment:vizmap_color_wheel.gif] button on the tool bar.
- 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 to the section above) Select “continuous mapper”, and enter a descriptive name. For example, enter: Color_Gradient.
- 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 Network" 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 below.

[attachment:image094.png]

Managing Visual Styles

All Cytoscape Visual Style settings are initially loaded from a a default file called vizmap.props that cannot be altered by users. When users make changes to the visual properties, a vizmap.props file is saved in the session file. This means that assuming you save your session, you will not lose your visual properties. No other vizmap.props files are saved during normal operation.

Saving Visual Styles

Visual styles are automatically saved with the session they were created in. Before Cytoscape exits, you will be prompted to make sure you save the session before quitting. It is also possible to save your visual styles in a file separate from the session file. To do this, navigate to the File → Export → Vizmap property file... menu and choose the file the properties should be saved to. This feature can be used to share visual styles with other users.

Importing Visual Styles

To import existing visual styles navigate to the File → Import → Vizmap Property File menu option and select a vizmap.props file. Imported properties will supplement existing properties or override existing properties if the properties have the same name. You can also specify a visual properties file using the -V command line option (cytoscape.sh -V myVizmap.props). Visual properties loaded from the command line will override any default properties.

Default Visual Styles

It is possible to change the default visual properties for all sessions of cytoscape. To do this, navigate to the Edit → Preferences... menu, check the "Make Current Visual Styles Default" box in the "Default Visual Styles" section, and click "Ok". This will save the current visual styles as a vizmap.props file to your .cytoscape directory (found in your home directory). These visual styles will be loaded each time Cytoscape is started.

Editing Networks

Using Cytoscape's Editor, you can 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.

[attachment:image096.gif] To edit an existing network, just select the Editor tab in CytoPanel 1. To start editing a new network, use the File → New → Network menu item.

The figure below shows the editor with palette defined by "Default" visual style.

[attachment:image097.gif] 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.

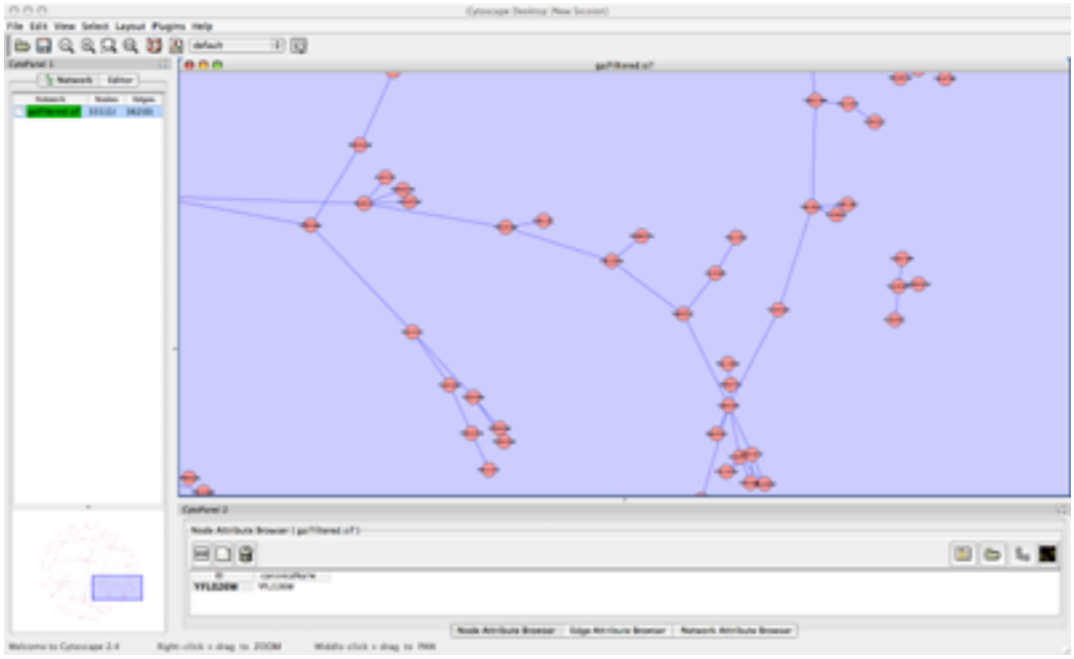
You can delete nodes and edges by selecting a number of nodes and edges, then selecting the Edit → Delete Selected Nodes and Edges menu item. You can recover any nodes and edges deleted from a network by selecting the Edit → Undo menu item. Note that this will restore **all** nodes and edges that were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

CytoPanels

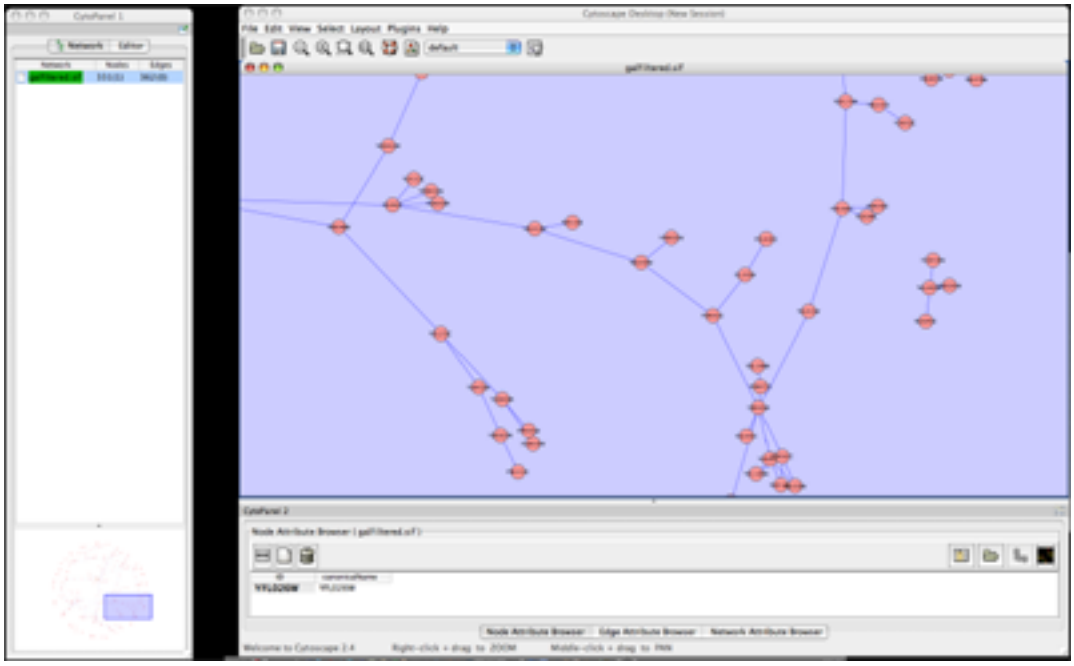
What are CytoPanels?

CytoPanels are floatable / dockable panels designed to cut down on the number of pop-up windows within Cytoscape and to create a more unified user experience. The following screenshot shows the galFiltered.sif file loaded into Cytoscape. In CytoPanel 1, the CytoPanel on the left-hand side of the screen, the Network

Manager, Network Overview, and Cytoscape Editor have been loaded. In addition, in CytoPanel 2, the Node Attribute Browser has been loaded.



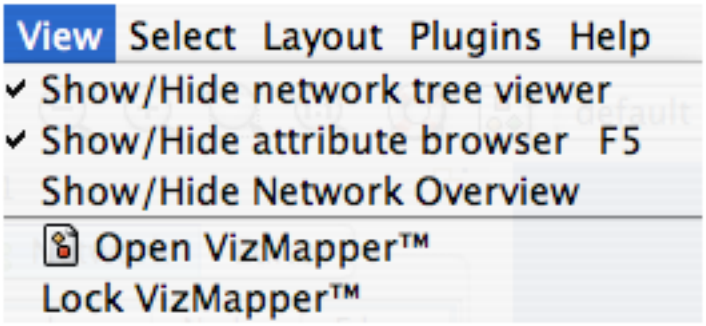
The user can then chose to resize, hide or float the left CytoPanel. For example, in the screenshot below, the user has chosen to float CytoPanel 1:



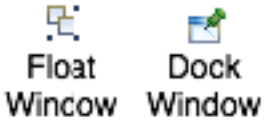
Basic Usage

Cytoscape 2.2 includes three CytoPanels: CytoPanel 1 (appears on the left), CytoPanel 2 (appears on the bottom), and CytoPanel 3 (appears on the right). By default, CytoPanel 1 and CytoPanel 2 will appear. CytoPanel 3 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.



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.



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Rendering Engine

In Cytoscape 2.3 a new network rendering engine is being introduced. The goal of the rendering engine is to be able to display large networks (>10,000 nodes) yet retain interactive speed. To accomplish this goal a technique involving *level of detail* is being used. Based on the count of objects (nodes and edges) being rendered, an appropriate *level of detail* is chosen. For example, by default, node labels (if present) are only rendered when less than 100 nodes are visible because drawing text is a relatively expensive operation. This can create some unusual behavior. If the screen currently contains 98 nodes, node labels will be displayed. If you pan the screen, such that now 101 nodes are displayed, the node labels will disappear. As another example, if the sum of rendered edges and rendered nodes is greater than or equal to a default value of 2000, a very coarse level of detail is chosen, where edges are always straight lines, nodes are always rectangles, and no antialiasing is done. The default values used to determine these thresholds can be changed by setting properties in the Edit → Preferences menu. **Beware!** The greater these thresholds become, the slower performance will become. If you work with small networks (a few hundred nodes), this shouldn't be a problem, but for large networks it will produce noticeable slowing. The various thresholds are described below.

Table 14.

render.coarseDetail-Threshold	If the sum of *rendered* nodes and *rendered* edges equals to or exceeds this number, a very coarse level of detail will be chosen and all other detail parameters will be ignored; this value defaults to 2000.
render.nodeBorder-Threshold	If the number of *rendered* nodes equals to or exceeds this number, node borders will not be rendered; this value defaults to 200.
render.nodeLabelThreshold	If the number of *rendered* nodes equals to or exceeds this number, node labels will not be rendered; this value defaults to 100.
render.edgeArrow-Threshold	If the number of *rendered* edges equals to or exceeds this number, edge arrows will not be rendered; this value defaults to 300.
render.edgeLabelThreshold	If the number of *rendered* edges equals to or exceeds this number, edge labels will not be rendered; this value defaults to 150.

When printing networks or exporting to formats such as PostScript, the highest level of detail is always chosen regardless of what is currently being displayed on the screen.

Annotation

Annotations in Cytoscape are stored as a set of ontologies (e.g. the Gene Ontology - GO). 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 2.3, Cytoscape has enhanced the *Gene Ontology Server Wizard*, which enables users to select a local ontology and annotation files from the user interface. Although 2.3 remains backwards compatible with the old file formats (the manifest file, which includes a list of *anno (annotation)* and *onto (ontology)* files), we strongly suggest using 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 a 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 (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." [PM
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
SGD     S000005275      AAD14           GO:0008372      SGD_REF:S000069584      ND              C       aryl-alcohol dehydrogenase (putative)        YNL331C gene    taxon:4932      20010119
```

Gene Ontology Server Wizard

The Gene Ontology Server Wizard is a 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 the file location of the ontology and gene annotation files.

Step 1. Select Data Format

- [attachment:ontology_wizard_begin.png]

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

Step 2. Select OBO File

[attachment:ontology_wizard_obo.png] If you choose *Gene Ontology* in the first step, this panel appears to help you first select an OBO (ontology) file. The wizard displays the header information of the OBO file loaded. Once an OBO file is loaded, the *Next* button becomes enabled. Click the *Next* button to proceed.

Step 3. Select Gene Association File

[attachment:ontology_wizard_goa.png]

You can add a gene_association file to the list by pressing *Add* 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 header information will be displayed in the center window. You can select multiple gene_association files.

The "Transfer GO Species Name to Nodes" can be used to apply the species name (taxon) found in the selected Gene Association file to the nodes of the currently selected network. This may be an important feature if the nodes of your network do not have a species attribute set. You can can see the current network's nodes and species attribute for the nodes in the left hand window. You can see the GO symbols, terms, aspects, synonyms, and taxons (species), in the bottom window. For nodes in your network to map to GO terms, either a symbol or synonym of a term must match the node ID.

Step 4.

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. This will then open up the Ontology Mapper dialog.

[attachment:ontology_mapper.png]

The Ontology Mapper is used to reduce the number of node attributes created from the gene ontology. Selecting a term in the left hand column and clicking the >> button will select that term to create an attribute for. You can unselect a term using the << button. The ***Apply All*** button will select all terms for attribute creation. In most cases, ***Apply All*** should be used to import all GO Terms for the network. Otherwise, only subset of GO Terms in the tree is imported. Once the desired terms have been selected, click the **OK** button. This will create node attributes for all selected GO terms. If you select some GO Terms in the right-side window, nodes with the GO Terms will be shown in the Node AttributeBrowser. By right-clicking on a GO Term in the ***GO Data as Attributes*** window, you can search the GO Term in AmiGO (this function requires internet connection and a web browser). The GO terms will now be visibile in the Node Attribute Browser by clicking on the Select button ([attachment:attributes_select_icon.png]).

If you would like to choose deifferent GO terms from the same gene association file, you do not need to re-import the files. Instead, you can click the GO button ([attachment:attributes_go_icon.png]) in the Attribute Browser panel or on the File → Import → Ontology → Ontology Mapper menu and the Ontology Mapper dialog will open.

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 (Symbol or Synonym column). Otherwise, the annotations will not appear in the Annotation Panel.

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 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.

[attachment:image110.gif] If you press the filter icon, you will see a filters dialog which looks initially like the following:

[attachment:image111.png] If the first filter is selected, then the dialog looks as shown:

[attachment:image124.png] 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.

[attachment:image127.png] 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:

[attachment:image129.png] The String Filter allows you to filter nodes or edges by a given string node or edge attribute. Attributes that are loaded on the network are available for filtering against. 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 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:

[attachment:image131.png] 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:

[attachment:image133.png] 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:

[attachment:image135.png] The Boolean Meta-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.

Linkout

The LinkOut plugin provides a mechanism to link nodes to external web resources within Cytoscape. Right-clicking on a node item in Cytoscape view opens a popup menu with a list of web links.

The external links are specified in the `linkout.props` file, which includes a number of default links such as Entrez, SGD, iHOP, Google, as well as a number of species-specific links. In addition to the default links, users can customize the LinkOut menu by adding (or removing) links without the need to restart Cytoscape or reload the network.

External links are listed as *‘key’-‘value’* pairs in the `linkout.props` file where *key* specifies the name of the link and *value* is the search URL. The LinkOut menus are organized in a hierarchical structure that is specified in the key. All key terms start with the keyword `linkouturl`.

For example, the following entry: `linkouturl.yeast.SGD=http://db.yeastgenome.org/cgi-bin/locus.pl?locus\=%ID%`

places the SGD link under the yeast submenu. This link will appear in Cytoscape as:

[attachment:Figure1_linkout.png]

In a similar fashion one can added new submenus.

The **`%ID%`** string in the URL is a place-holder for the node label. When the popup menu is generated this marker is substituted with the node label. In the above example the generated SGD link for YIM protein is: `http://db.yeastgenome.org/cgi-bin/locus.pl?locus\=YIM1`

Currently there is no mechanism to check whether the constructed URL query is correct and if the node label is meaningful. Similarly there is no ID mapping between various identifiers. For example, a link to NCBI Entrez from a network that uses ensembl gene identifiers as node label will produce a link to Entrez using ensembl ID, which results in an incorrect link. It is the users responsibility to ensure that the node label that is used as the search term in the URL link will result in a meaningful link.

Adding or Removing links The default links are defined in a `linkout.props` file contained in the linkout.jar. These links are normal java properties and can be editited while running in the Edit → Preferences menu. New links can be defined this way as well. New links can be defined at startup in a separate file and loaded from the command line, either by specifying a file containing the links `cytoscape.sh -P new_linout.props` or as individual properties `cytoscape.sh -P linkouturl.yeast.SGD=http://db.yeastgenome.org/cgi-bin/locus.pl?locus\=%ID%`. Any links defined on the command line will supersede the default links.

To remove a link from the menu simply delete the property from the Edit → Preferences menu.

•

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/.
- 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/opensrc/tclib/.
- Xerces Java XML parser. Information is available at: http://xml.apache.org/xerces-j/.
- CLI command line parser. Information is available at: http://jakarta.apache.org/commons/cli/.
- FreeHEP library. Information is available at: http://java.freehep.org.

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, since they are easier to download directly from the Gene Ontology project and use directly.

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

[attachment:image137.png] If you want to use the old manifest file to load annotations, select *Cytoscape BioDataServer*.

Step 2. Specify Manifest File

[attachment:image139.png] If you selected *Cytoscape BioDataServer* in the first step, you need to specify manifest file (which lists ontology and annotation files to load). Then click on finish. All data files will be 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.

1. 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.

1. 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
```

1. Once loaded, this annotation (along with the accompanying ontology) can be assigned to nodes in a Cytoscape network. **For this to work, the species type of the node must exactly match 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 into Cytoscape

The easiest way to make annotations available to Cytoscape is by loading annotations into the Cytoscape 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    O00115  DRN2_HUMAN              GO:0003677      PUBMED:9714827  TAS             F       Deoxyribonuclease II precursor  IPI00010348     protein taxon:9606              SPTR
SPTR    O00115  DRN2_HUMAN              GO:0004519      GOA:spkw        IEA             F       Deoxyribonuclease II precursor  IPI00010348     protein taxon:9606      20020425        SPTR
SPTR    O00115  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      O00115  IPI00010348             ENSP00000222219;        NP_001366;              BAA28623;AAC77366;AAC35751;AAC39852;BAB55598;AAB51172;AAH10419; 2960,DNASE2     1777,DNASE2
SP      O00116  IPI00010349             ENSP00000324567;ENSP00000264167;        NP_003650;              CAA70591;       327,AGPS        8540,AGPS
SP      O00124  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 or if you are using a more recent version of Python.

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

```
  sys.exit ();
inputFilename = sys.argv [1];
print >> sys.stderr,  'reading ~np~%~/np~s...' ~np~%~/np~ inputFilename
text = open (inputFilename).read ()
print >> sys.stderr,  'read ~np~%~/np~d characters' ~np~%~/np~ len (text)
regex = '<go:term .*?>(.*?)</go:term>';
cregex = pre.compile (regex, re.DOTALL)   # . matches newlines
m = pre.findall (cregex, text)
print >> sys.stderr, 'number of go terms: ~np~%~/np~d' ~np~%~/np~ 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~np~%~/np~s\n------------------" ~np~%~/np~ term
print >> sys.stderr,  'goodElements ~np~%~/np~d' ~np~%~/np~ goodElements
print >> sys.stderr, 'badElements ~np~%~/np~d' ~np~%~/np~ badElements
#-------------------------------------
```

Script 1 - parseAssignmentsToFlatFileFromGoaProject.py

```
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: ~np~%~/np~d' ~np~%~/np~ len (ipiToNPHash)
print 'test map: ~np~%~/np~s -> NP_054861: ~np~%~/np~s ' ~np~%~/np~ (tester, ipiToNPHash [tester])
bioproc = open ('bioproc.txt', 'w')
molfunc = open ('molfunc.txt', 'w')
cellcomp = open ('cellcomp.txt', 'w')
bioproc.write ('(species=~np~%~/np~s) (type=Biological Process) (curator=GO)\n' ~np~%~/np~ species)
molfunc.write ('(species=~np~%~/np~s) (type=Molecular Function) (curator=GO)\n' ~np~%~/np~ species);
```

```
cellcomp.write ('(species=~np~%~/np~s) (type=Cellular Component) (curator=GO)\n' ~np~%~/np~ species);
lines=open(associationFilename).read().split('\n')
sys.stderr.write ('found ~np~%~/np~d lines\n' ~np~%~/np~ 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 '~np~%~/np~s (~np~%~/np~s) has go term ~np~%~/np~s' ~np~%~/np~ (tester, printName, goID)
  if (goOntology == 'C'):
    cellcomp.write ('~np~%~/np~s = ~np~%~/np~s\n' ~np~%~/np~ (printName, goID))
  elif (goOntology == 'P'):
    bioproc.write ('~np~%~/np~s = ~np~%~/np~s\n' ~np~%~/np~ (printName, goID))
  elif (goOntology == 'F'):
    molfunc.write ('~np~%~/np~s = ~np~%~/np~s\n' ~np~%~/np~ (printName, goID))
#-------------------------------------------------------------------------------
```

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When a "work that uses the Library" uses material from a header file that is part of the Library, the object code for the work may be a derivative work of the Library even though the source code is not. Whether this is true is especially significant if the work can be linked without the Library, or if the work is itself a library. The threshold for this to be true is not precisely defined by law.

If such an object file uses only numerical parameters, data structure layouts and accessors, and small macros and small inline functions (ten lines or less in length), then the use of the object file is unrestricted, regardless of whether it is legally a derivative work. (Executables containing this object code plus portions of the Library will still fall under Section 6.)

Otherwise, if the work is a derivative of the Library, you may distribute the object code for the work under the terms of Section 6. Any executables containing that work also fall under Section 6, whether or not they are linked directly with the Library itself.

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b) Use a suitable shared library mechanism for linking with the Library. A suitable mechanism is one that (1) uses at run time a copy of the library already present on the user's computer system, rather than copying library functions into the executable, and (2) will operate properly with a modified version of the library, if the user installs one, as long as the modified version is interface-compatible with the version that the work was made with.

c) Accompany the work with a written offer, valid for at least three years, to give the same user the materials specified in Subsection 6a, above, for a charge no more than the cost of performing this distribution.

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