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Introduction

PathArt is a dynamic pathway articulator, which builds molecular interaction networks from curated databases. The articulator maps the pathways based on a logical set of molecular interactions. It also features a user interface to annotate functionality of genes. PathArt is a step towards giving a biological interpretation to voluminous data generated by microarray experiments. Moreover, PathArt also provides a useful means to identify the responsive genes in a physiology or a pathway with their regulatory information and mode of interaction there by allowing design of microarray experiments. PathArt is a platform for target identification and prioritizing.

Key Features

- All participant molecules in the pathway are logically linked and are represented as a pathway map.
- Curated information on the biomolecules and their regulatory effects is displayed along with the graph.
- The nature of interactions between two molecules (i.e. direct, indirect) is made obvious in the display.
- The user can easily navigate using tabs to view information related to mutation, knock out, localization etc.
- Appropriate references and links to Pubmed citations are tagged with the information.
- Expression profiles of the responsive genes are displayed.

The Database

The information in the database is collated through manual curation from research articles. The database consists of more than 400 pathways spanning across diverse physiologies such as Inflammation, Apoptosis etc and disease pathways for 9 high priority diseases. The database mainly focuses on information related to molecular interactions that constitutes a pathway with a coverage on knock out and mutation studies. Information is tagged with appropriate references and linked to respective Pubmed citations. PathArt consists of pathways for Homo sapiens and Mus musculus. In addition to this PathArt also provides data from 11 public domain databases.

- Covers physiologies such as Inflammation, Apoptosis, Cell adhesion, Cell cycle, Development and Myogenesis.
- Coverage of 9 high priority diseases which includes Asthma, Diabetes type2, Atherosclerosis, Chronic myeloid leukemia, Breast cancer, Colon cancer, Prostate cancer, Lung cancer and Parkinson's disease

Microarray Data Analysis Component

Using our proprietary methods, information on genes is summarized from over eleven public domain databases and presented through this component. Provision to use various statistical analysis methods is available through filters. This tool helps in understanding the microarray data in the context of physiology and function by quickly identifying the gene expression information provided in the data set and mapping it on the pathway. It is also compatible with all commonly used microarray data analysis software packages.

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System Configuration

This section provides information about system requirements, procedures on configuring the system for using PathArt 1.0 software, and some tips on improving efficiency and performance when using PathArt. Below are the requirements and recommendations for systems on which you intend to run PathArt. Requirements are the basic suggested system components necessary to run PathArt; recommendations are the optimum suggested system components. If you're using Windows 2000, Jubilant Biosys recommends that you log in as a user with administrative privileges before you install the suggested system components. If you do not have administrative privileges, contact your system administrator for assistance.

Java Runtime Environment (JRE) 1.4

JRE 1.4 is available for the following operating systems:

- Microsoft Windows® XP, Windows 98SE, Windows NT® 4.0 with Service Pack 5 or 6, Windows 2000 with Service Pack 3, or Windows Millennium Edition
- Linux
- Solaris™ SPARCTM 32-bit
- Solaris™ SPARCTM 64-bit
- Solaris x86 (Solaris 7, Solaris 8)

For JRE 1.4 installation instructions please go to <http://java.sun.com/j2se/1.4.1/jre/install.html>.

Web Browser

One of the following or compliant Web Browsers with appropriate JRE 1.4 plug-in installed.

- Microsoft Internet Explorer 5.0 or later
- Netscape Navigator 4.5 or later

User Interface

The workspace window is split into four regions viz., **Pathway Hierarchy** window, **Pathway Schematic** window, **Curated Data** window and the **Gene Name/Unigene Identifiers** window.

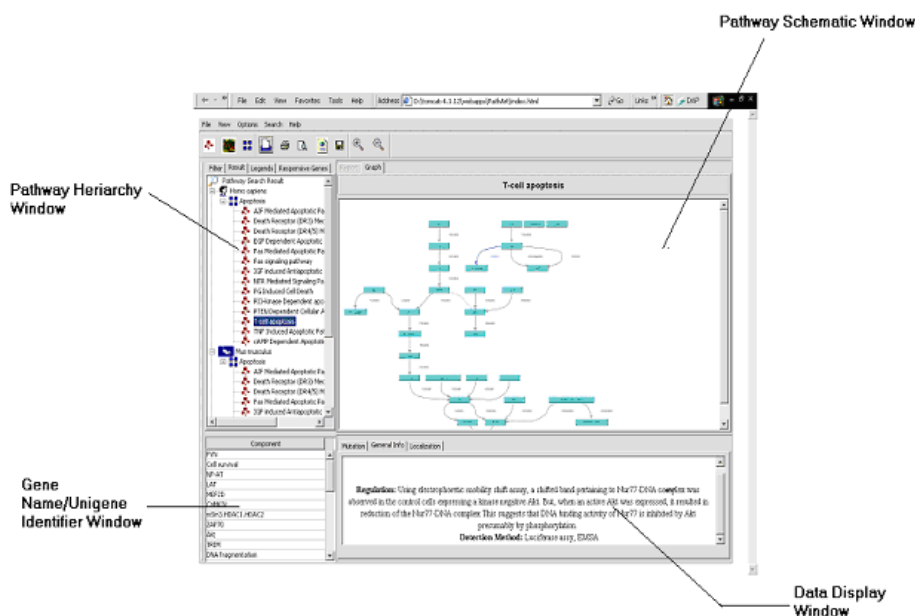


Fig 1. PathArt Workspace

The Pathway Hierarchy window lists the physiologies and the corresponding pathways in a tree grouped by Organism, Physiology or Disease, and Pathway. All the physiologies/ diseases and the pathways that are retrieved by the query are displayed hierarchically. The Pathway schematic window displays the pathway. The molecules are represented as solid rectangles, cross talking pathways and effects are represented as ellipses. Selecting a physiology node in the Pathway Hierarchy window, displays the entire pathway for the selected physiology comprising of merged pathways of all the pathways listed in it. A right click on pathway name in the Pathway Hierarchy window highlights the pathway. Selection of a pathway under a physiology/disease displays the pathway. Selecting any molecule/arrow between molecules displays the curated information from database in the Curated Data window.

PathArt provides a platform to interpret microarray data. The user can query the pathways based on unigene ids and expression ratios from microarray experiments. The molecules in the displayed pathway are differentially color-coded based on their level of expression. Color-coding of the molecules is based on expression ratios, i.e. genes with expression ratio above 2 fold (upregulated) are colored red. The genes exhibiting an expression ratio in the range of 1 and 0 (downregulated) are colored green. The genes with expression ratio in the range 1 to 2 (unchanged) are colored yellow. The unigene ids of the genes displayed in the pathway are depicted in the Unigene Identifiers window on the left bottom pane. Selection of unigene ids in Unigene Identifiers window highlights the corresponding molecule in the pathway. Inter-molecular interactions are displayed as either dotted or solid lines with mode or regulation written on it. A click on these lines, displays regulatory information.

Using PathArt

This section takes you through a step by step guide, explaining how PathArt can be used in a research environment.

Using Pathway Search

Click Pathway Search icon from the toolbar. Pathway Search Form box appears. Pathway Search Form consists of a list of alphabetically sorted curated pathways in the left pane and all the physiologies covered in the right pane. The lists in the bottom window give the enlisted diseases and the organisms covered.

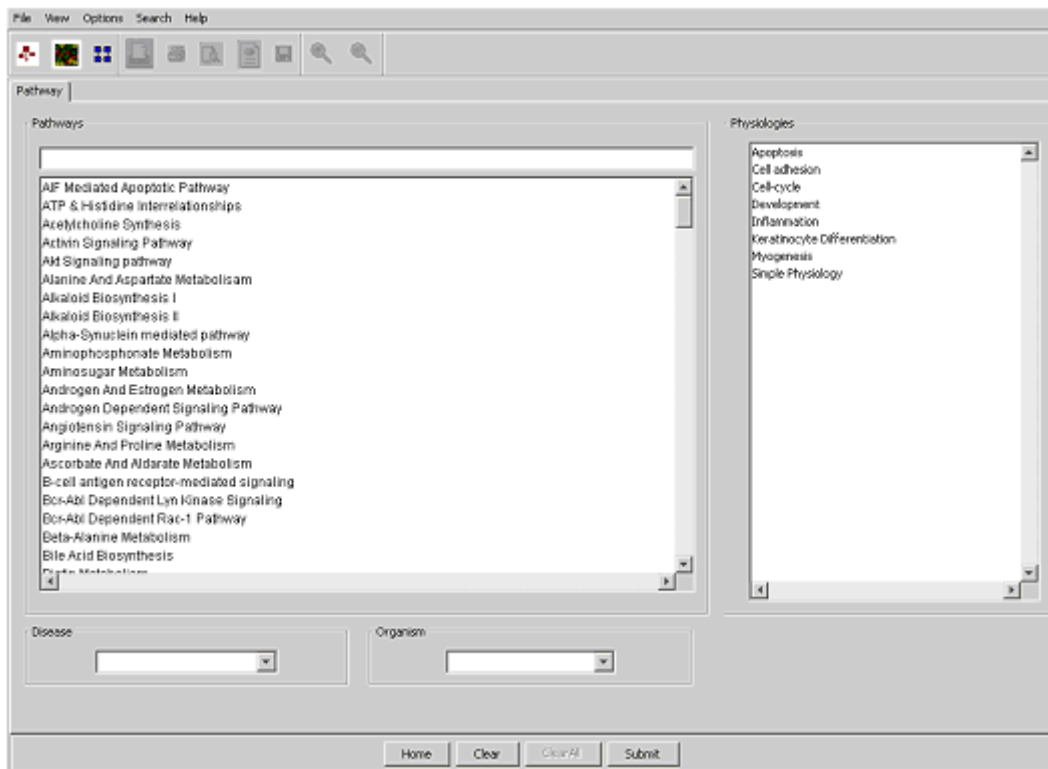


Fig 2 The Pathway Search Window

Viewing Pathways

- Browse through the pathway list pathway using the scroll bar
- Choose the appropriate pathway by clicking on the pathway name
- Click Submit

PathArt results page appears with the Pathway hierarchy

Viewing Physiology

- Choose the appropriate physiology by clicking on the physiology name
- Click Submit

PathArt results page appears with the Pathway hierarchy

Viewing Diseases

- Choose the appropriate disease from the pull down
- Click Submit

PathArt results page appears with the Pathway hierarchy

To query by Organisms

- Choose the appropriate organism from the pull down
- Click Submit

PathArt results page appears with the Pathway hierarchy

To use the Microarray search

Choose Microarray Search icon from the main menu bar. A browser to upload the micro array data file will appear. Upload the file on to the Db. The uploaded file appears on to the window. Choose the file type by using the drop downs in the File and the delimiters using the radio button. The data file can have tab, semicolon, comma, or space as a delimiter.

The ID types can be Unigene, Locus link ID, or Affymetrix Probe set ID. The file formats can be Gene, Expression ratio; Gene, Cy3, Cy5; Gene, Cy3, Cy5, Expression ratio; or Gene, Ratio1, Ratio2, Ratio3, etc., for time series analysis.

To submit-Click on the 'OK' button

Microarray Data

Gene ID	Expression Ratio	Value
Hs.108441	1.0	4.5
Hs.2899	1.4	1.5
Hs.10071	1.0	4.5
Hs.11806	1.6	0.54
Hs.415877	1.7	0.5
Hs.28914	1.20	0.5
Hs.1200	1.08	0.5
Hs.73809	1.02	0.5

*Only first few lines of data has been shown

File

ID Type:

Format:

Delimiter

☐ Comma ☐ Tab

☐ Colon ☐ SemiColon

☐ Other

Ok Cancel

The uploaded set of genes are displayed in a table.

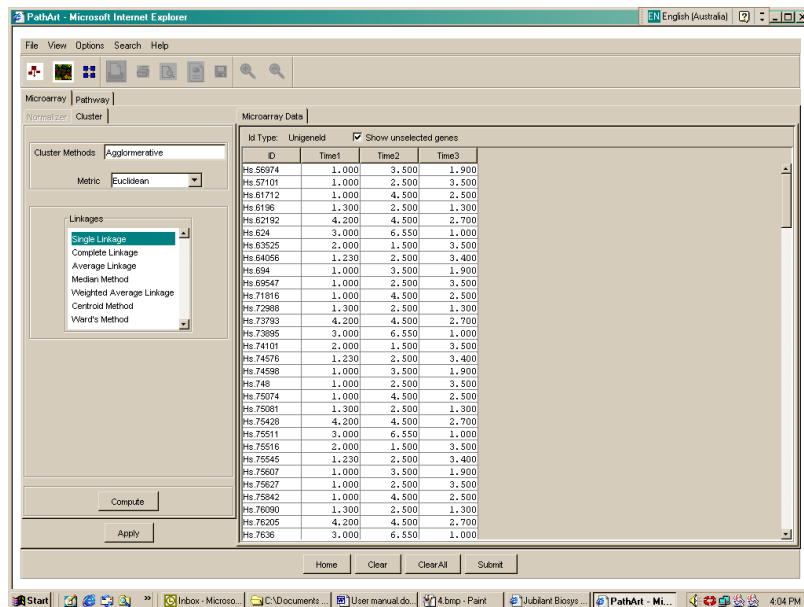
Analysis of microarray data

To cluster the genes

The uploaded gene set can be clustered using various metrics and linkages

Click on the Cluster tab in the left hand corner pane

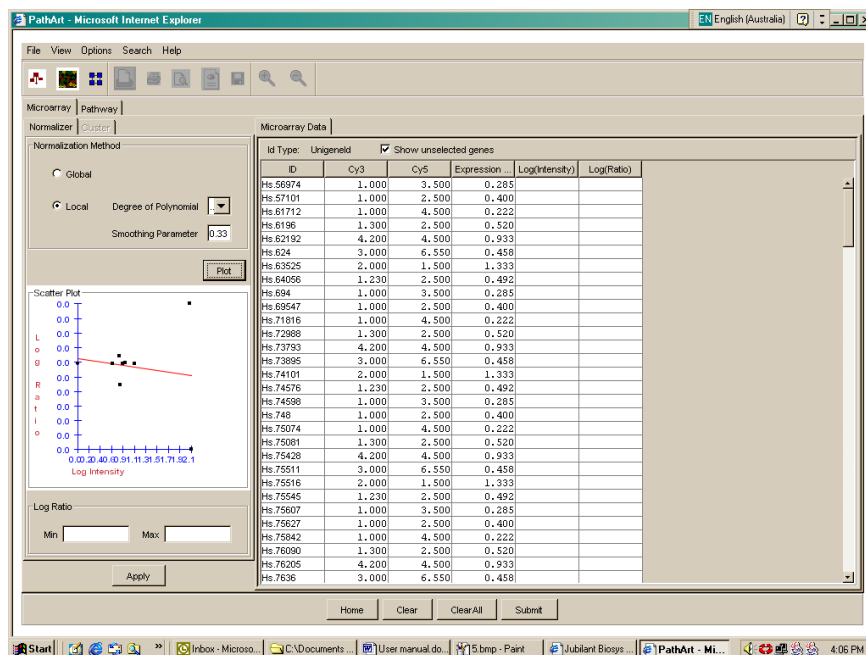
- Choose the relevant metric from the pull down menu
- Select the appropriate linkage method
- Click Compute
- Clusters appear on the right hand corner screen
- Check for the required clusters to be overlaid onto the pathways
- Click submit
- The queried set of genes are differentially highlighted on the pathway



PathArt results page appears with the Pathway hierarchy

To normalize the microarray data

This is for a raw microarray data which has Cy3 and Cy5 values for a set of Gene ID's for single time point or condition.

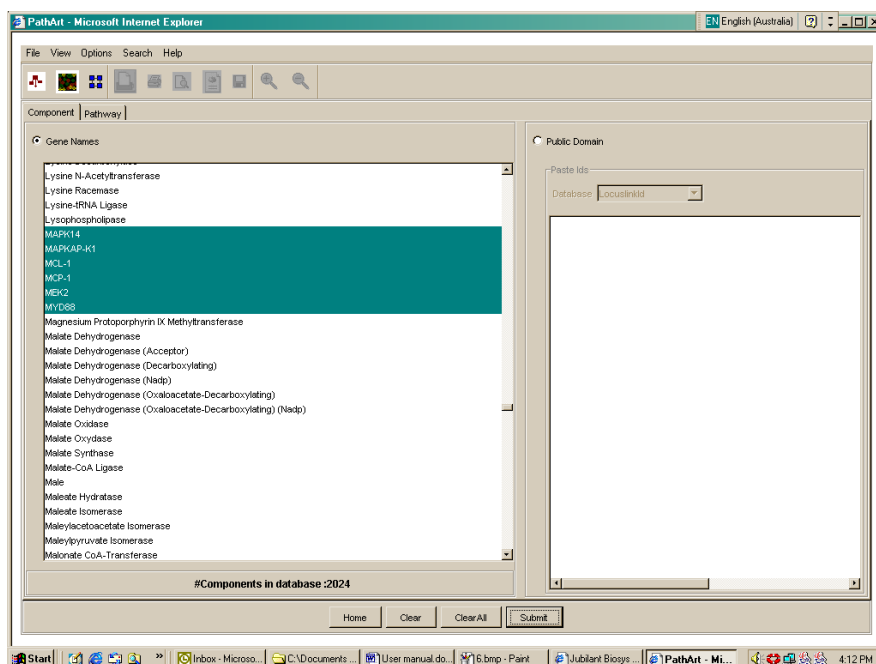


- Click on the Normalizer tab in the left hand corner pane
- Choose global or local normalization radio button
- To carry out local normalization choose the Degree of polynomial and the Smoothing parameter
- Click Plot to obtain the scatter plot
- Enter the min. and max. ratio to refine the data set
- Click Apply
- Click Submit to map the genes on to the pathway

PathArt results page appears with the Pathway hierarchy

To Use the component search option

Choose Component Search icon from the main menu bar. The component search dialog box appears. The component Search window consists of the Gene names on the left pane and a search by Public domain Ids on the right pane.



To query by Gene names existing in the database

- Select the radio button for the Gene names
- Choose single or multiple gene name holding the Ctrl or Shift key
- Click Submit

PathArt results page appears with the Pathway hierarchy

To query by public domain information Gene Ids

- Select the radio button for public domain
- Select the appropriate Id's to be uploaded from the database pull down
- Paste either of Locuslink, Unigene, Affymetrix identifiers
- Click Submit

The Pathway Result Page

The workspace window is split into four regions viz,

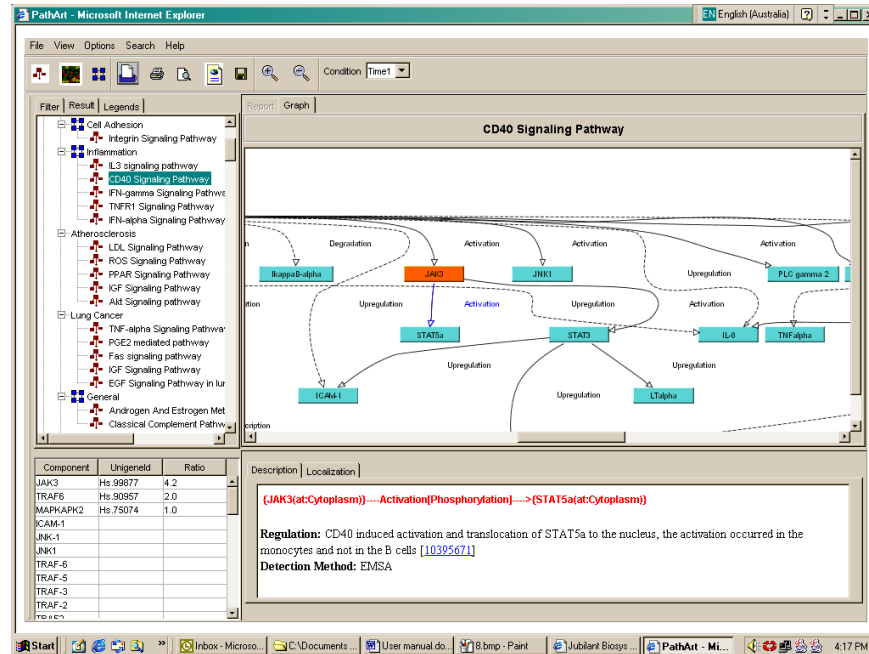
Pathway Hierarchy window, Pathway Schematic window, Data window and the Gene name/Unigene Identifiers window.

The Pathway Hierarchy window lists the physiologies and the corresponding pathways in a tree grouped by Organism, Physiology or Disease and Pathway. All the physiologies and the pathways that are retrieved by the query are displayed hierarchically.

To obtain pathway schematic for a pathway

- Select the pathway from the pathway hierarchy tree
- The pathway schematic window displays the representative pathway
- To view the entire pathway uncheck the tool bars from the view menu

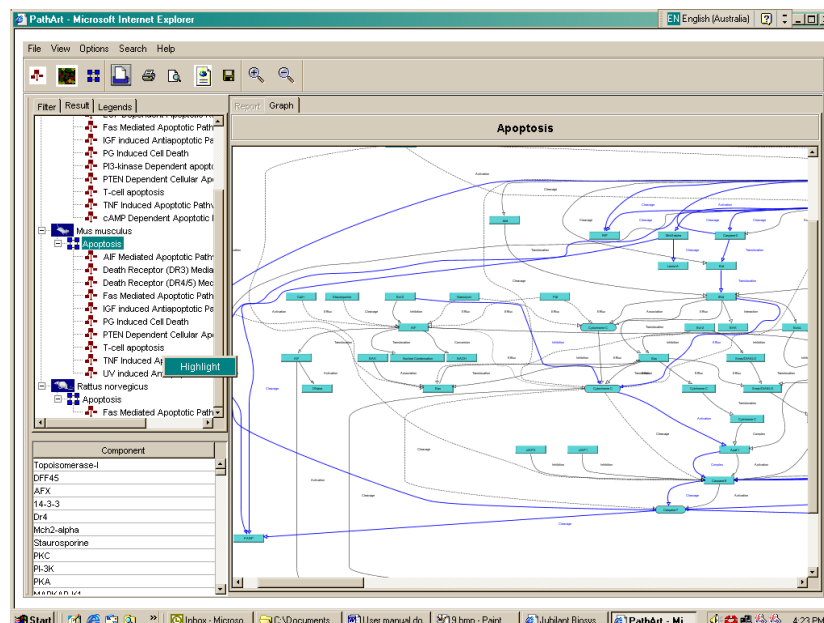
- The pathways could be navigated using the Gene name/ unigene Identifiers window.
- Clicking on any gene in the Gene name/ unigene Identifiers window highlights the selected components on the pathway.
- Click on the component to view the information regarding the curated function and public domain report
- Click on the arrows to view the regulation information, experimental protocol, cell line used



To view the physiology or disease pathway

Click on the disease or the pathway node in the tree hierarchy

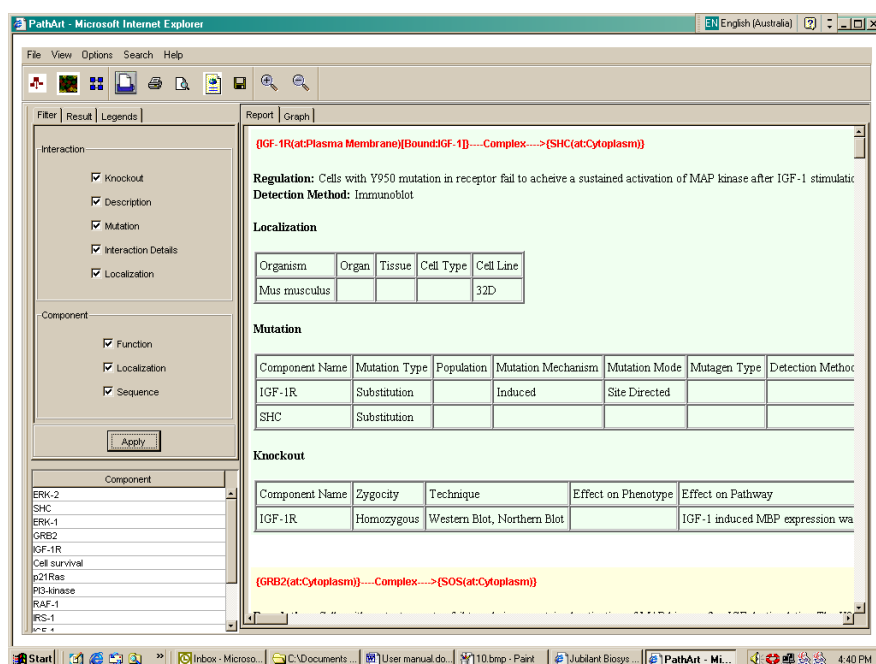
To highlight a pathway in a merged physiology/disease pathway



- Right click on the pathway of interest in the hierarchy tree window
- Select highlight
- The selected pathway is highlighted in the disease or physiology

To obtain the detailed pathway report

PathArt's aids in annotation of genes obtained from microarray experiments. It is a repository of data compiled across six public domain databases namely, UniGene, Locus Link, OMIM, BodyMap, Homologene, and KEGG. Hence providing a unified platform to compile, process and analyze microarray data in a meaningful manner. The results are represented in both graphical and tabular formats to enable the user to derive biological inference out of the microarray data. The annotator currently holds information for 2,23,354 Unigene Ids and 528 KEGG pathway compiled for human and mouse. The annotator facilitates query based on Unigene IDs and expression ratios for the genes obtained from microarray analysis.

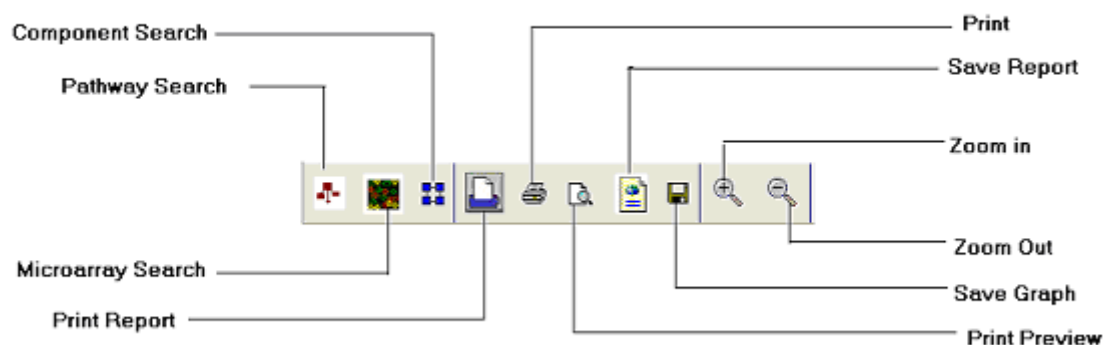


- Click on the filter tab on the left corner widow
- Check for the required information
- Click Apply

Reference Guide

This section has short description of all the MENUS in PathArt.

Toolbar:



File Menu: File menu has various options related to file operations

File	
Print	Report...
Print Preview	Graph...
Save	
Import	

Print: Prints the pathway diagram and text report

File	
Print	
Print Preview	Image...
Save	
Import	

Print preview: Previews how the document will print

File	
Print	
Print Preview	
Save	Report...
Import	Graph...

Save: Saves the pathway diagram and text report

File	
Print	
Print Preview	
Save	
Import	Microarray

Import:

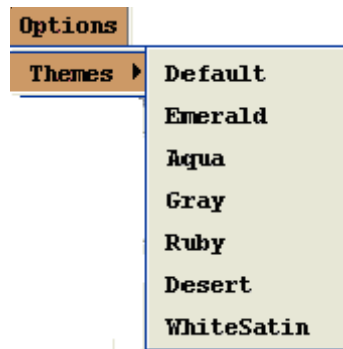
Imports the microarray data file

View	
<input type="checkbox"/> ToolBars	Ctrl-F11

View Menu: Uncheck the toolbar to have full screen view of the pathway








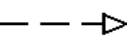
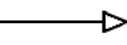
Search	
Pathway	
Component	

Search Menu: Search by component or pathway



Appendix A : Legends

Icons

Icons	Representation
	Represents a Search Result. The search criteria is displayed, in text, with this icon.
	Indicates that the organism is <i>Homo sapiens</i> .
	Indicates that the pathway is not specific to an organism, it is a Reference Pathway.
	Represents "Physiology" under which other pathways would be classified in the tree. Clicking on this icon displays all pathways involved in this physiology.
	Represents a pathway. Clicking on this icon displays the pathway.
	The molecules are represented in rectangular shapes and the abbreviated names of the molecule appears as text on this box.
	Indicates an effect or cross-talking physiology.
	Represents indirect relationship between two molecules. There may be an involvement of other intermediary molecules, whose identity is not clearly established.
	Represents direct and proven interactions between molecules.