

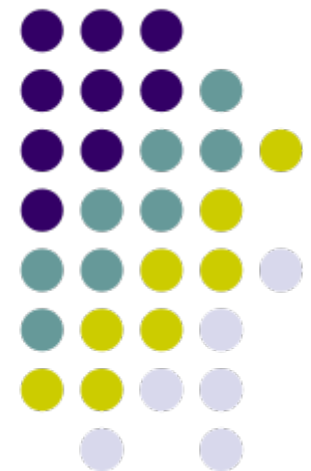
# Network Visualization and Analysis

Gary Bader (University of Toronto)

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Gary Bader  
Prash Suravajhala  
<http://wiki.bioinformatics.org/prash>



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Euskara Suomi français français (CA) Galego עברית hrvatski Magyar Italiano 日本語 한국어 Macedonian Malayu  
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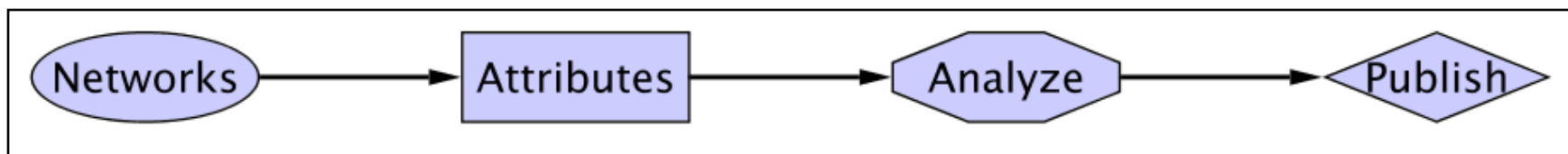
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Daniele Merico  
Canadian Bioinformatics Workshops

# Network Analysis Workflow

- Load Networks e.g. PPI data
  - Import network data into Cytoscape
- Load Attributes e.g. gene expression data
  - Get data about networks into Cytoscape
- Analyze and Visualize Networks
- Prepare for Publication
- A specific example of this workflow:
  - Cline, et al. “Integration of biological networks and gene expression data using Cytoscape”, Nature Protocols, 2, 2366-2382 (2007).



# Network Visualization and Analysis Outline

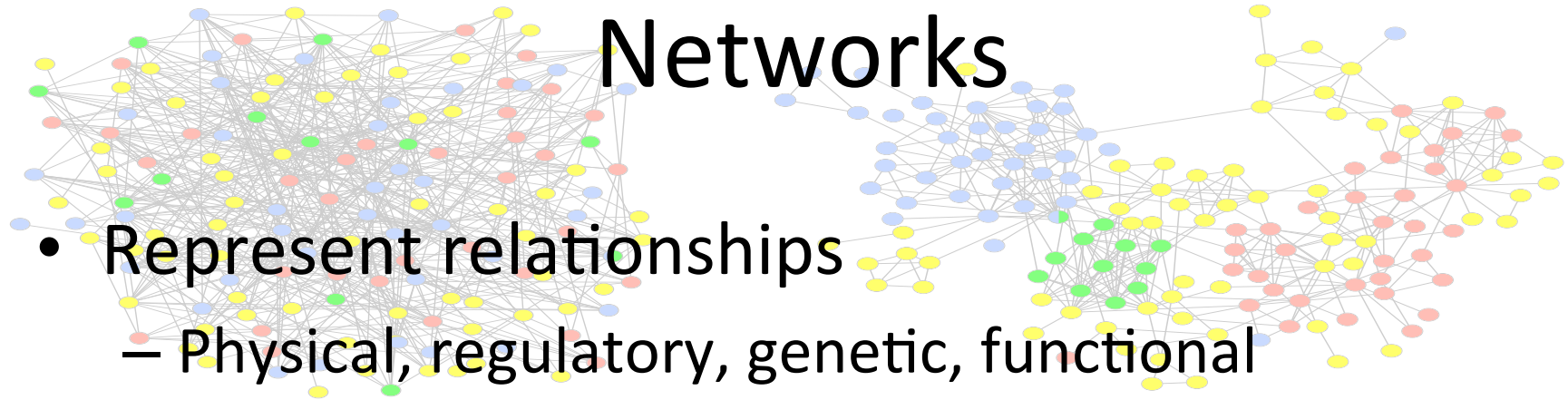
- Network introduction
- Network visualization
- Cytoscape software tool for network visualization and analysis
- Network analysis



Before layout

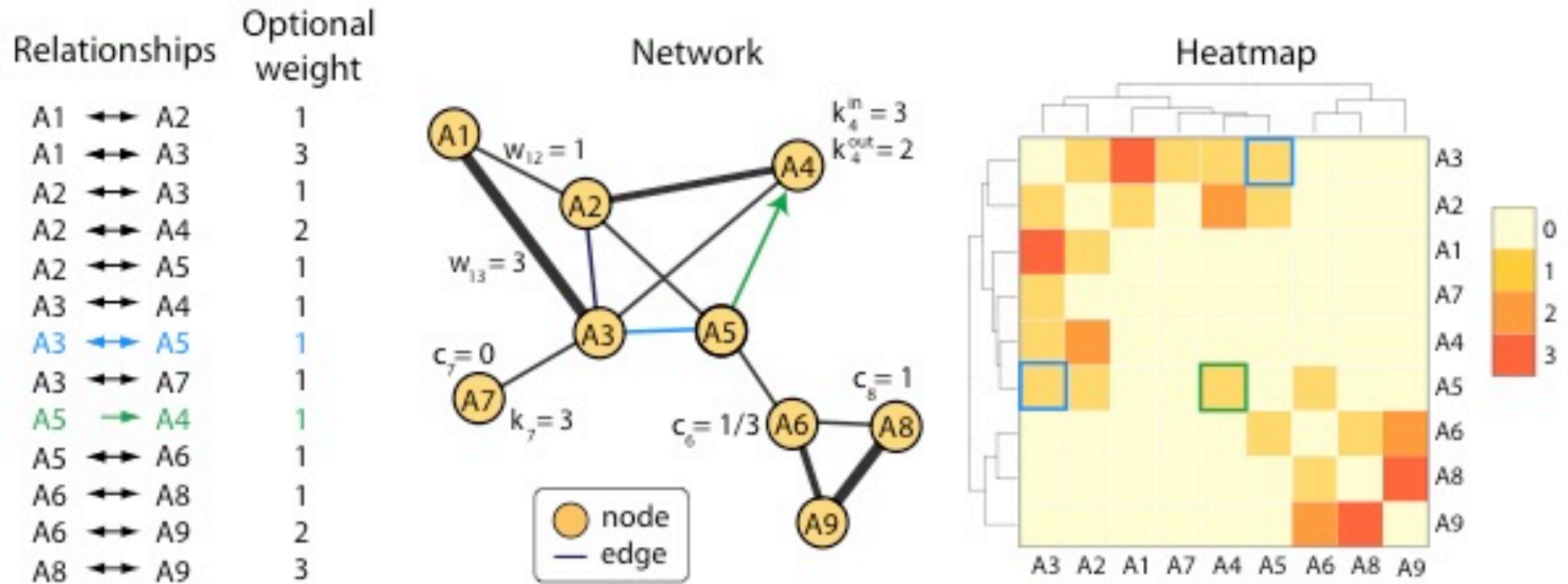
After layout

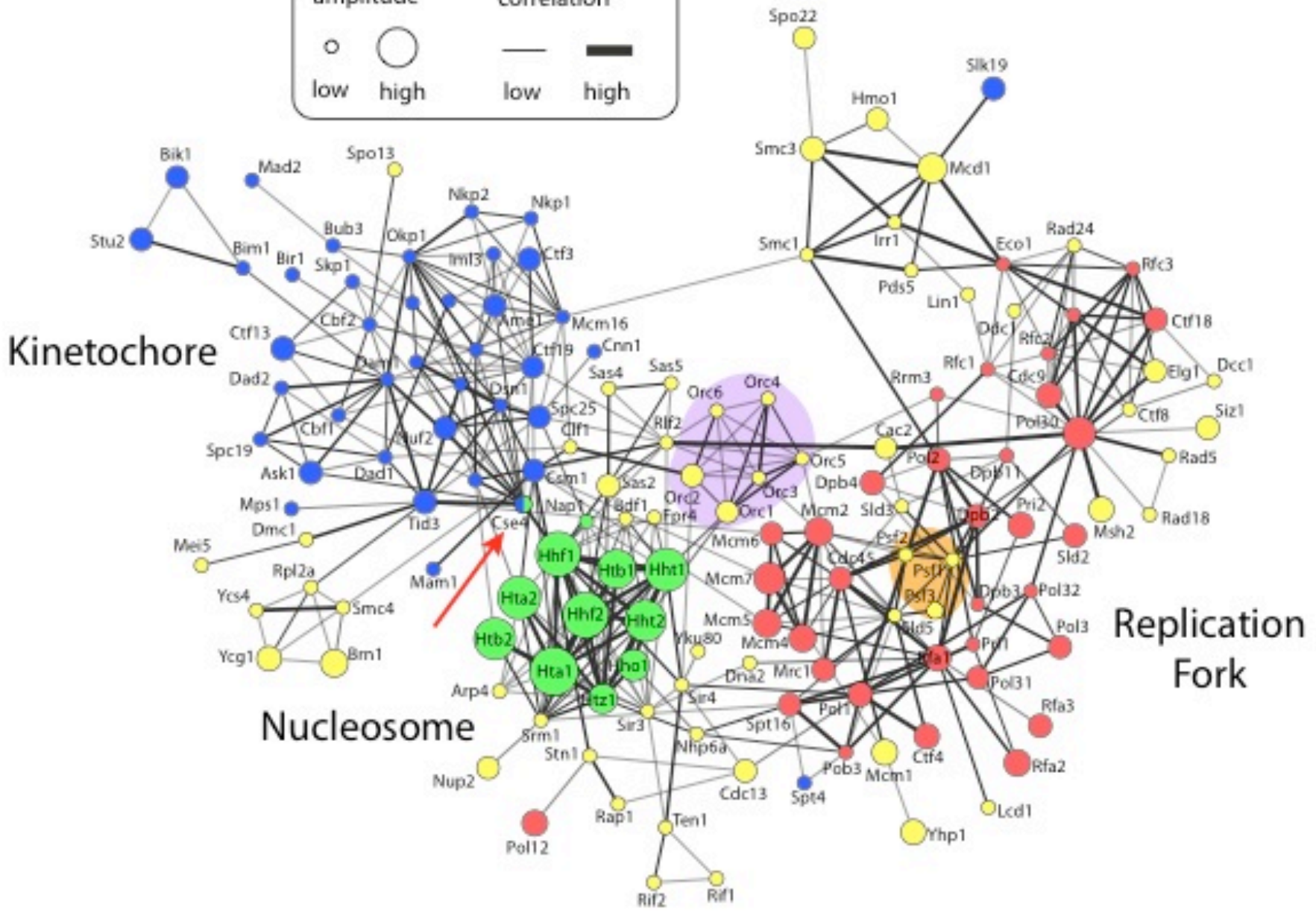
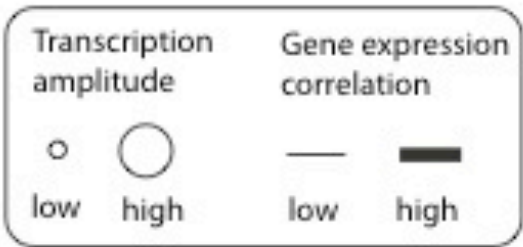
# Networks



- Represent relationships
  - Physical, regulatory, genetic, functional interactions
- Useful for discovering relationships in large data sets
  - Better than tables in Excel
- Visualize multiple data types together
  - See interesting patterns

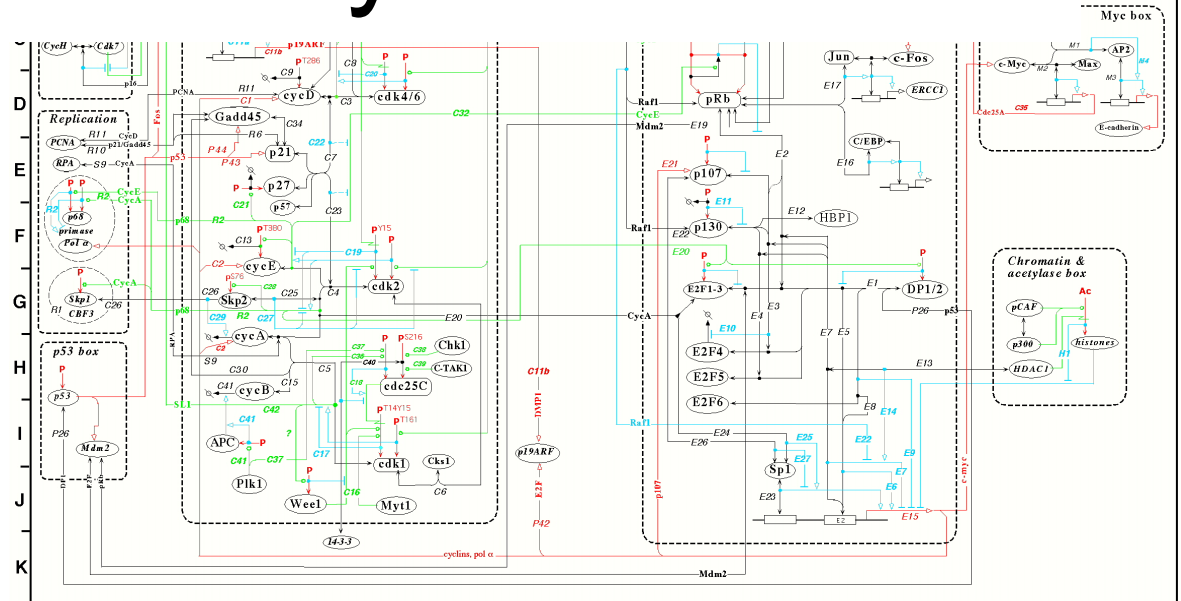
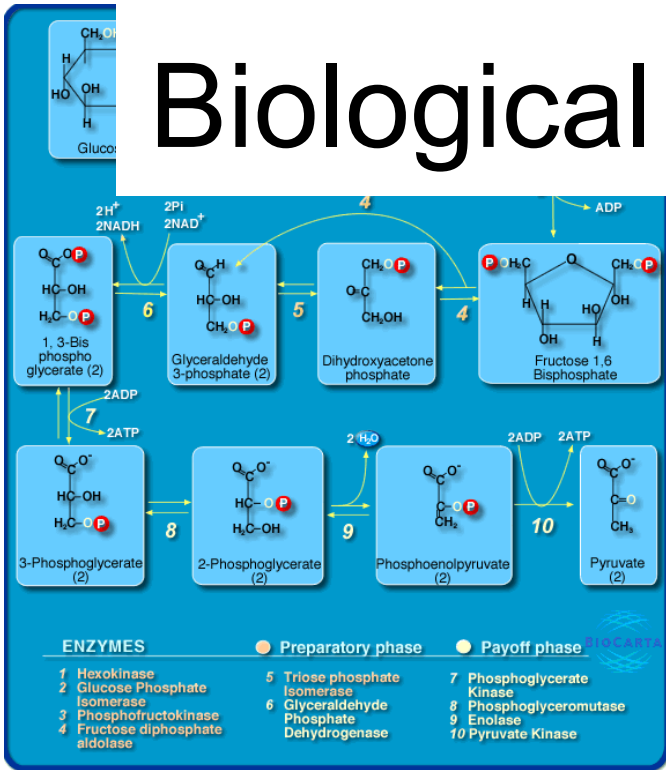
# Network Representations





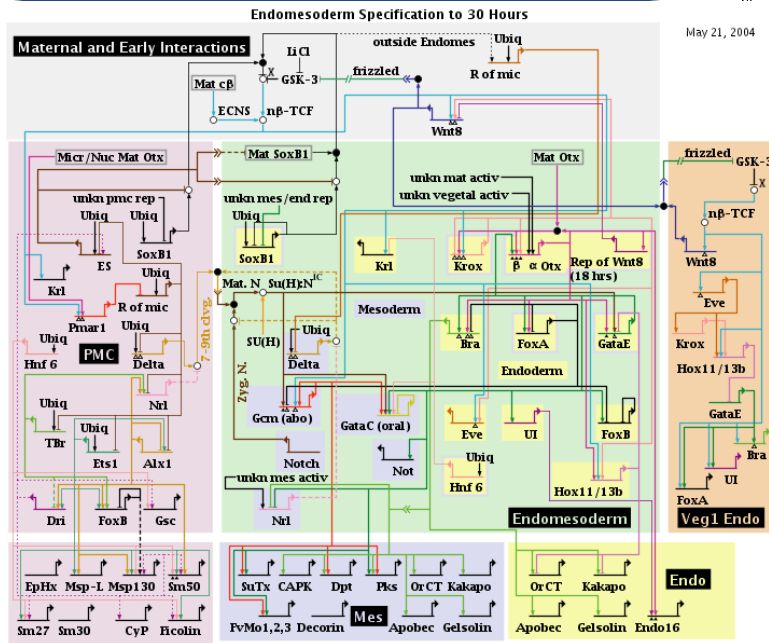
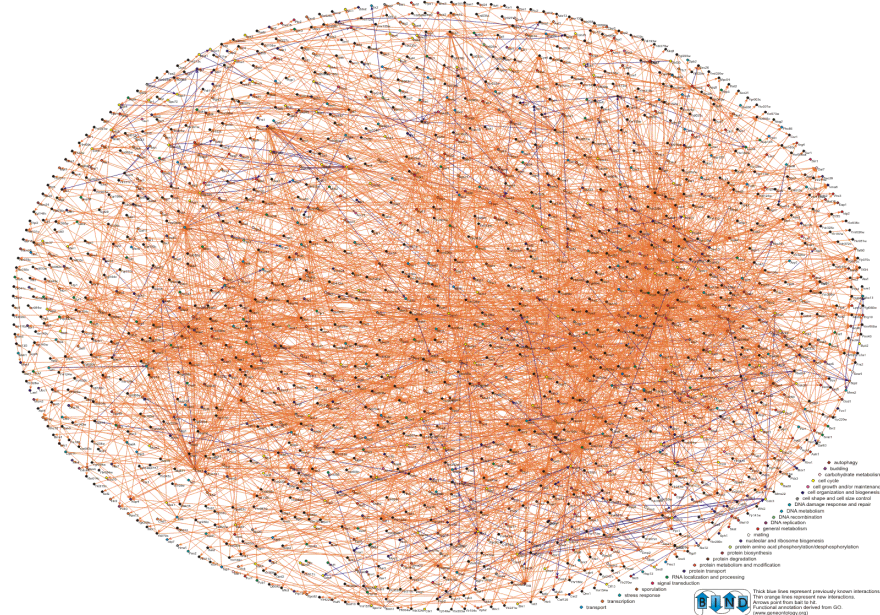


# Biological Pathways/Networks?



5A: The Cyclin - E2F cell cycle control system (version 3a - June 8, 1999)

Systematic identification of protein complexes in *Saccharomyces cerevisiae* by mass spectrometry

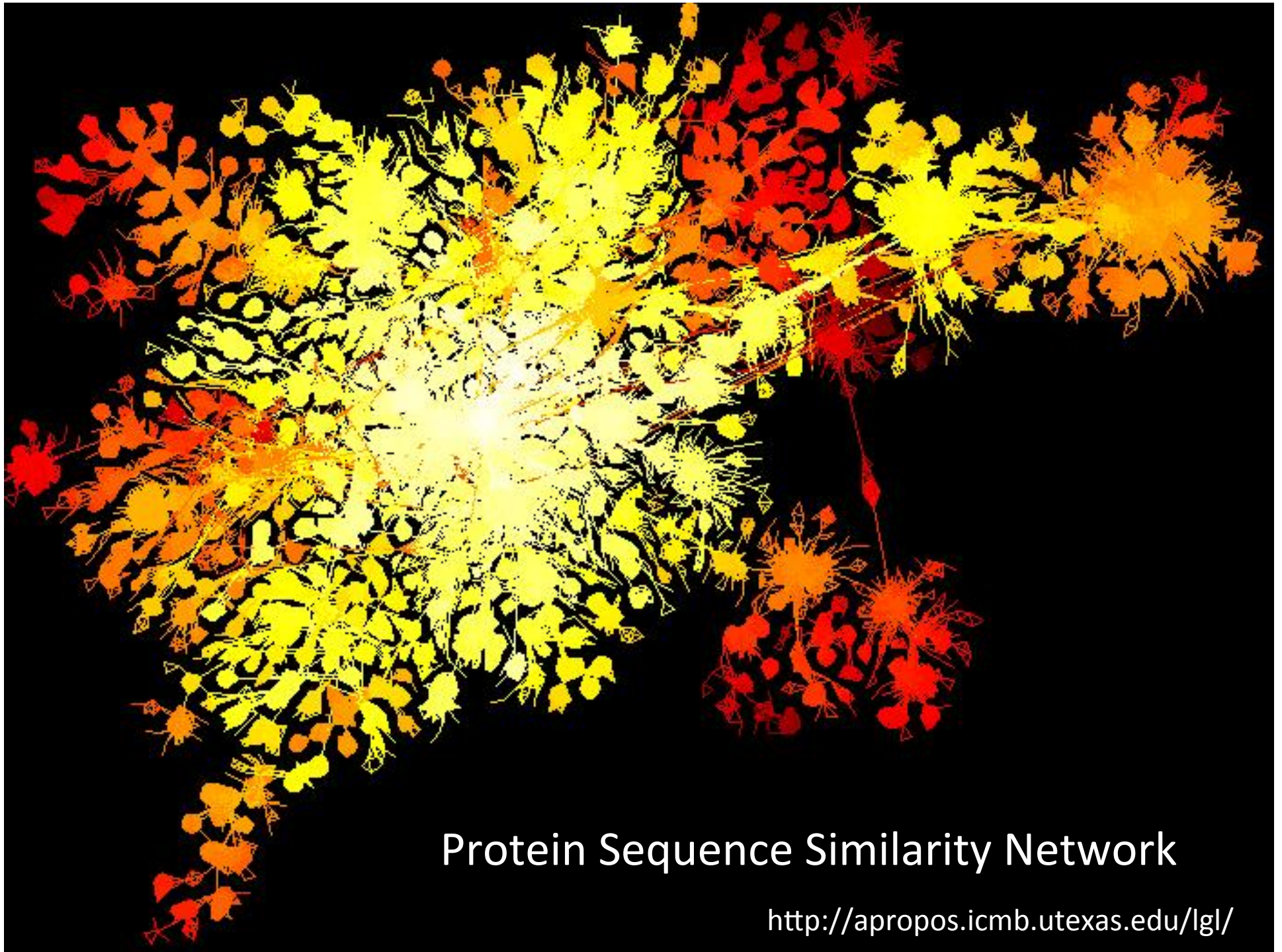


Copyright © 2001-2004 Hamid Bolouri and Eric Davidson

# Mapping Biology to a Network

- A simple mapping
  - one compound/node, one interaction/edge
- A more realistic mapping
  - Cell localization, cell cycle, cell type, taxonomy
  - Only represent physiologically relevant interaction networks
- Edges can represent other relationships
- **Critical:** understand what nodes and edges mean





## Protein Sequence Similarity Network

<http://apropos.icmb.utexas.edu/lgl/>

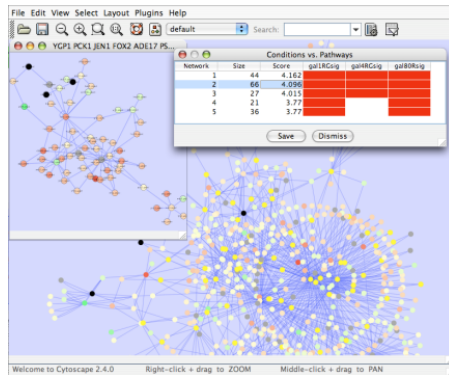
# Six Degrees of Separation

- Everyone in the world is connected by at most six links
- Which path should we take?
- Shortest path by breadth first search
  - If two nodes are connected, will find the shortest path between them
- Are two proteins connected? If so, how?
- Biologically relevant?

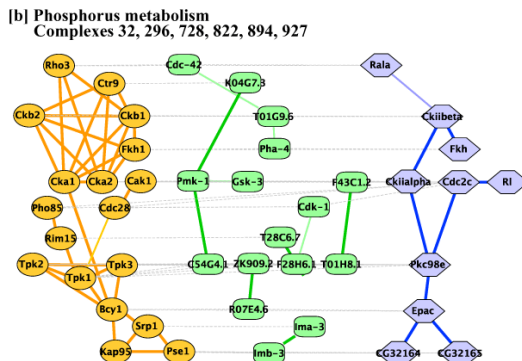


<http://www.time.com/time/techttime/200406/community.html>

# Applications of Network Biology



jActiveModules, UCSD

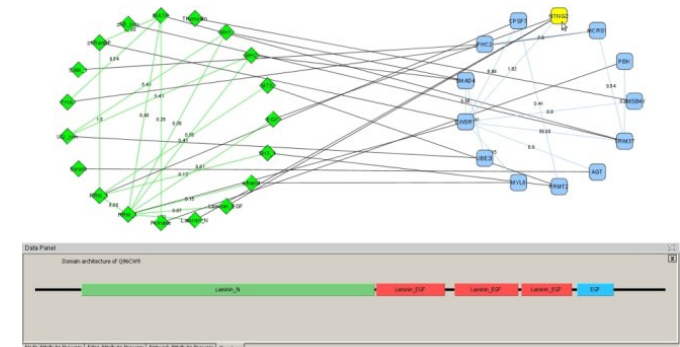


PathBlast, UCSD

- **Gene Function Prediction** – shows connections to sets of genes/proteins involved in same biological process
- **Detection of protein complexes/ other modular structures** – discover modularity & higher order organization (motifs, feedback loops)
- **Network evolution** – biological process(es) conservation across species
- **Prediction of new interactions and functional associations** – Statistically significant domain-domain correlations in protein interaction network to predict protein-protein or genetic interaction



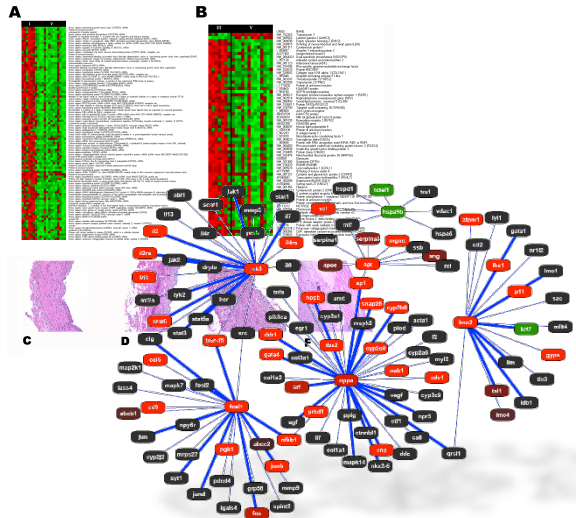
MCODE, University of Toronto



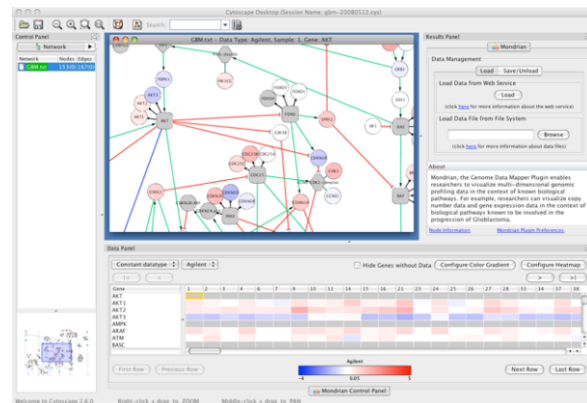
DomainGraph, Max Planck Institute



# Applications of Network Informatics in Disease

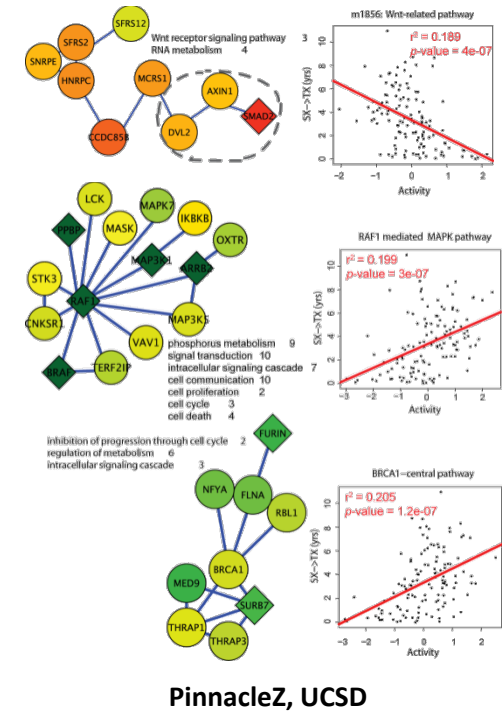


Agilent Literature Search



Mondrian, MSKCC

- **Identification of disease subnetworks** – identification of disease network subnetworks that are transcriptionally active in disease.
- **Subnetwork-based diagnosis** – source of biomarkers for disease classification, identify interconnected genes whose aggregate expression levels are predictive of disease state
- **Subnetwork-based gene association** – map common pathway mechanisms affected by collection of genotypes



PinnacleZ, UCSD

# What's Missing?

- Dynamics
  - Pathways/networks represented as static processes
    - Difficult to represent a calcium wave or a feedback loop
  - More detailed mathematical representations exist that handle these e.g. Stoichiometric modeling, Kinetic modeling (VirtualCell, E-cell, ...)
    - Need to accumulate or estimate comprehensive kinetic information
- Detail – atomic structures
- Context – cell type, developmental stage

# What Have We Learned?

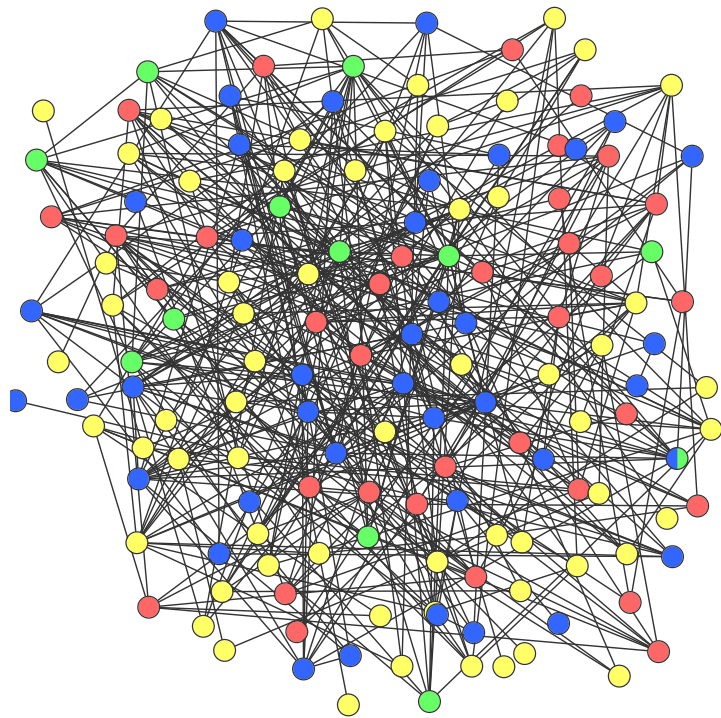
- Networks are useful for seeing relationships in large data sets
- Important to understand what the nodes and edges mean
- Important to define the biological question - know what you want to do with your gene list or network
- Many methods available for gene list and network analysis
  - Good to determine your question and search for a solution
  - Or get to know many methods and see how they can be applied to your data

# Network Visualization Outline

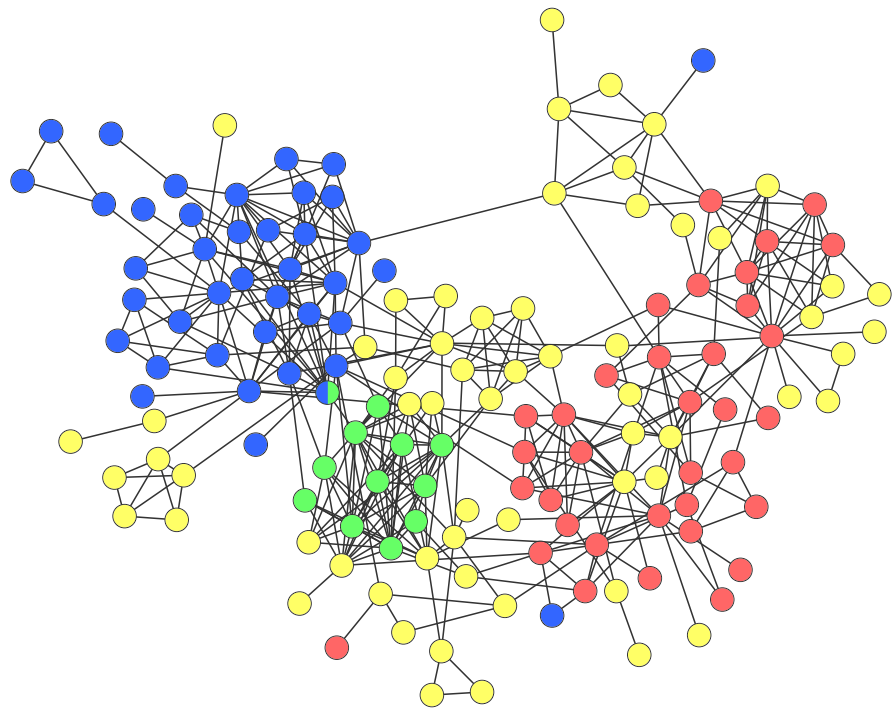
- Automatic network layout
- Visual features
- Visually interpreting a network

# Automatic network layout

Before layout



After layout

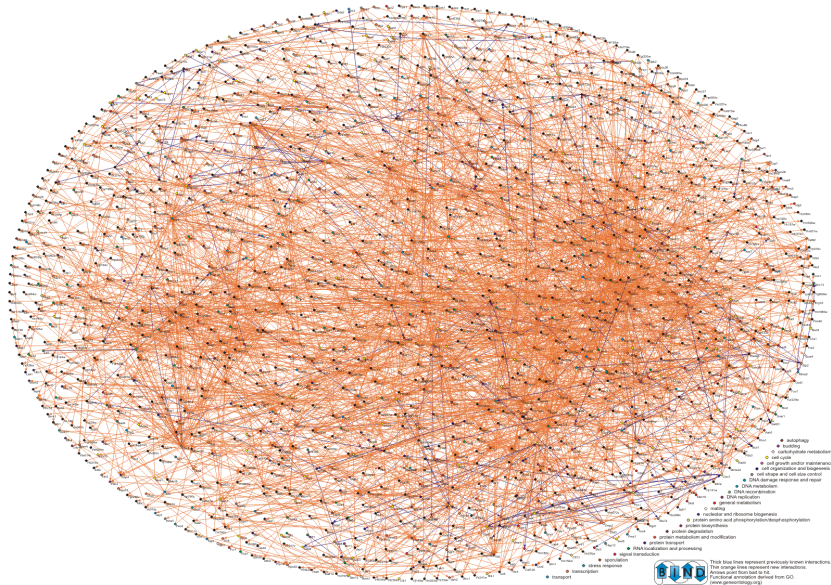


# Automatic network layout

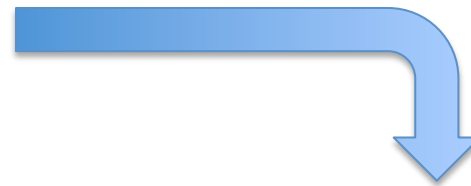
- Force-directed: nodes repel and edges pull
- Good for up to 500 nodes
  - Bigger networks give hairballs - Reduce number of edges
- Advice: try force directed first, or hierarchical for tree-like networks
- Tips for better looking networks
  - Manually adjust layout
  - Load network into a drawing program (e.g. Illustrator) and adjust labels

# Overview

Systematic identification of protein complexes in *Saccharomyces cerevisiae* by mass spectrometry

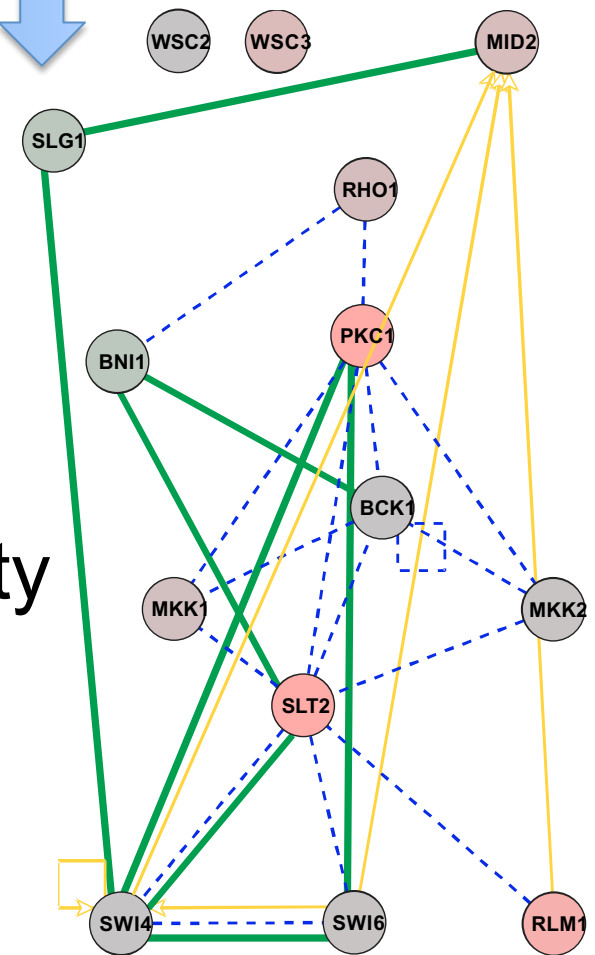


## Zoom



## Focus

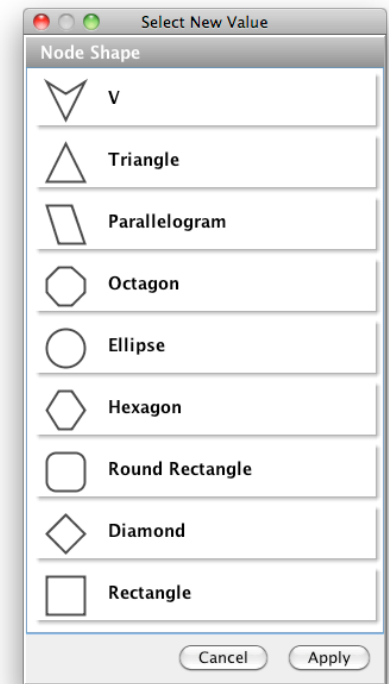
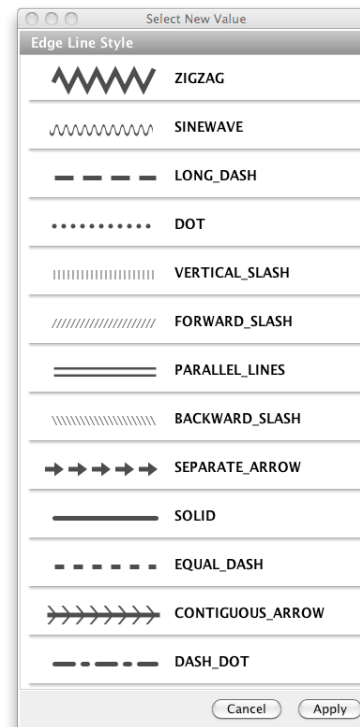
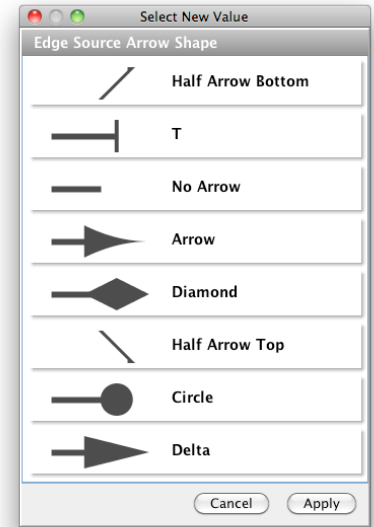
### PKC Cell Wall Integrity



-  Synthetic Lethal
-  Transcription Factor Regulation
-  Protein-Protein Interaction
-  Up Regulated Gene Expression
-  Down Regulated Gene Expression

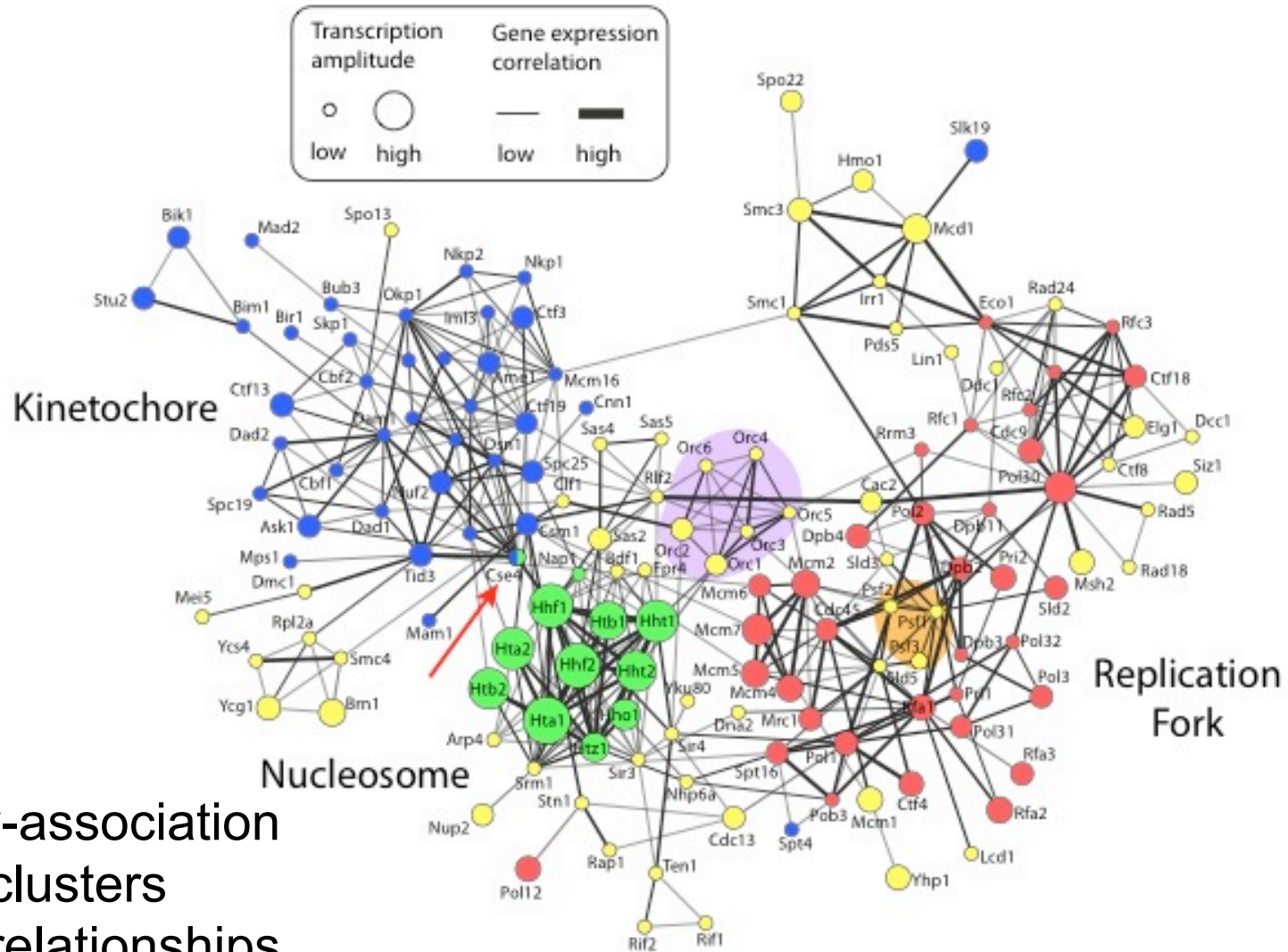
# Visual Features

- Node and edge attributes
  - String, integer, float, Boolean, list
  - E.g. represent gene, interaction attributes
- Visual attributes
  - Node, edge visual properties
  - Colour, shape, size, borders, opacity...





# Visually Interpreting a Network



Guilt-by-association  
Dense clusters  
Global relationships

# What Have We Learned?

- Automatic layout is required to visualize networks
- Networks help you visualize interesting relationships in your data
- Avoid hairballs by focusing analysis
- Visual attributes enable multiple types of data to be shown at once – useful to see their relationships

# Network Visualization and Analysis using Cytoscape

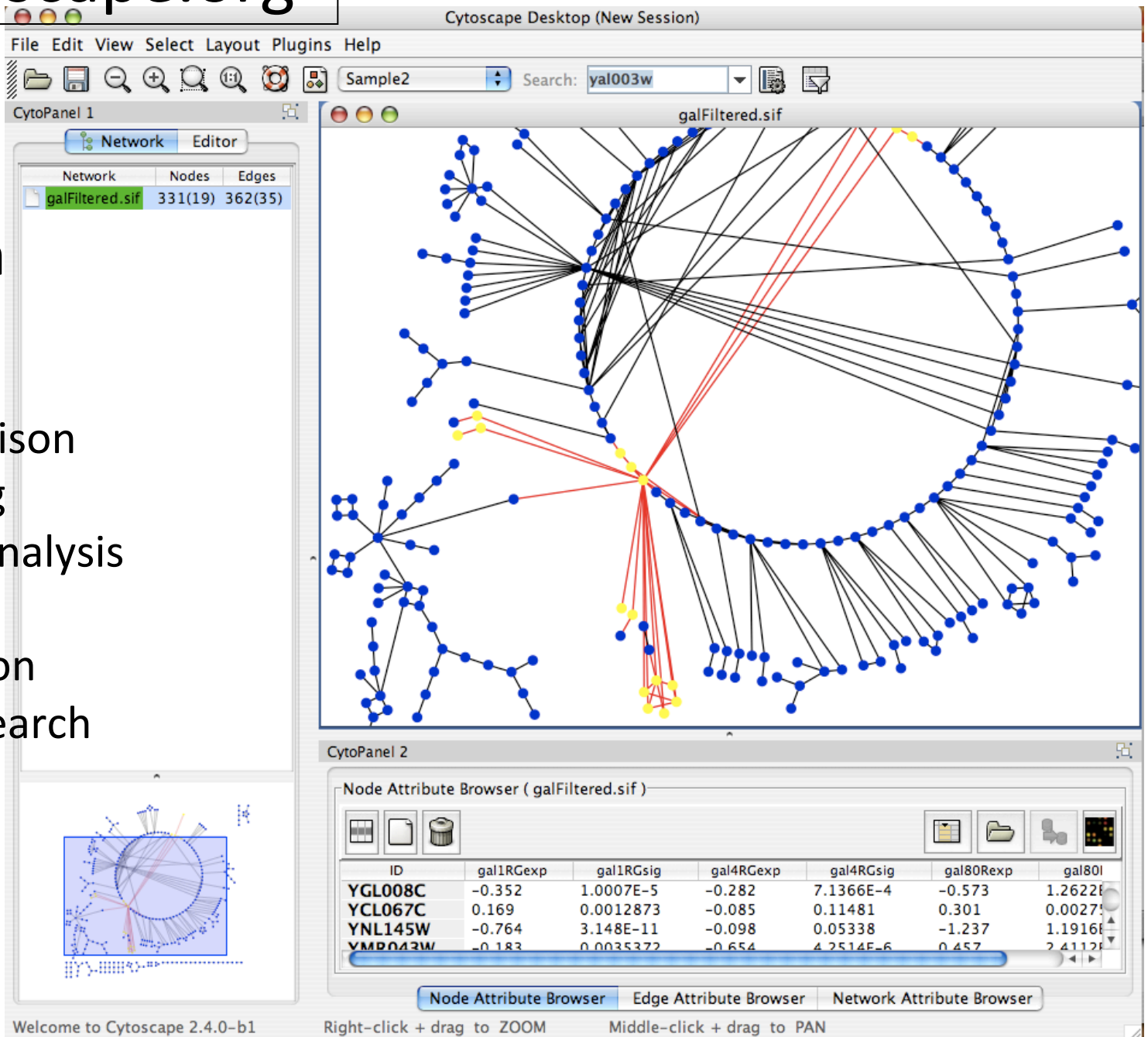
- Network visualization and analysis using Cytoscape software
- Cytoscape basics
- Cytoscape network analysis examples

<http://cytoscape.org>

# Network visualization and analysis

Pathway comparison  
Literature mining  
Gene Ontology analysis  
Active modules  
Complex detection  
Network motif search

UCSD, ISB, Agilent,  
MSKCC, Pasteur, UCSF,  
Unilever, UToronto, U  
Texas

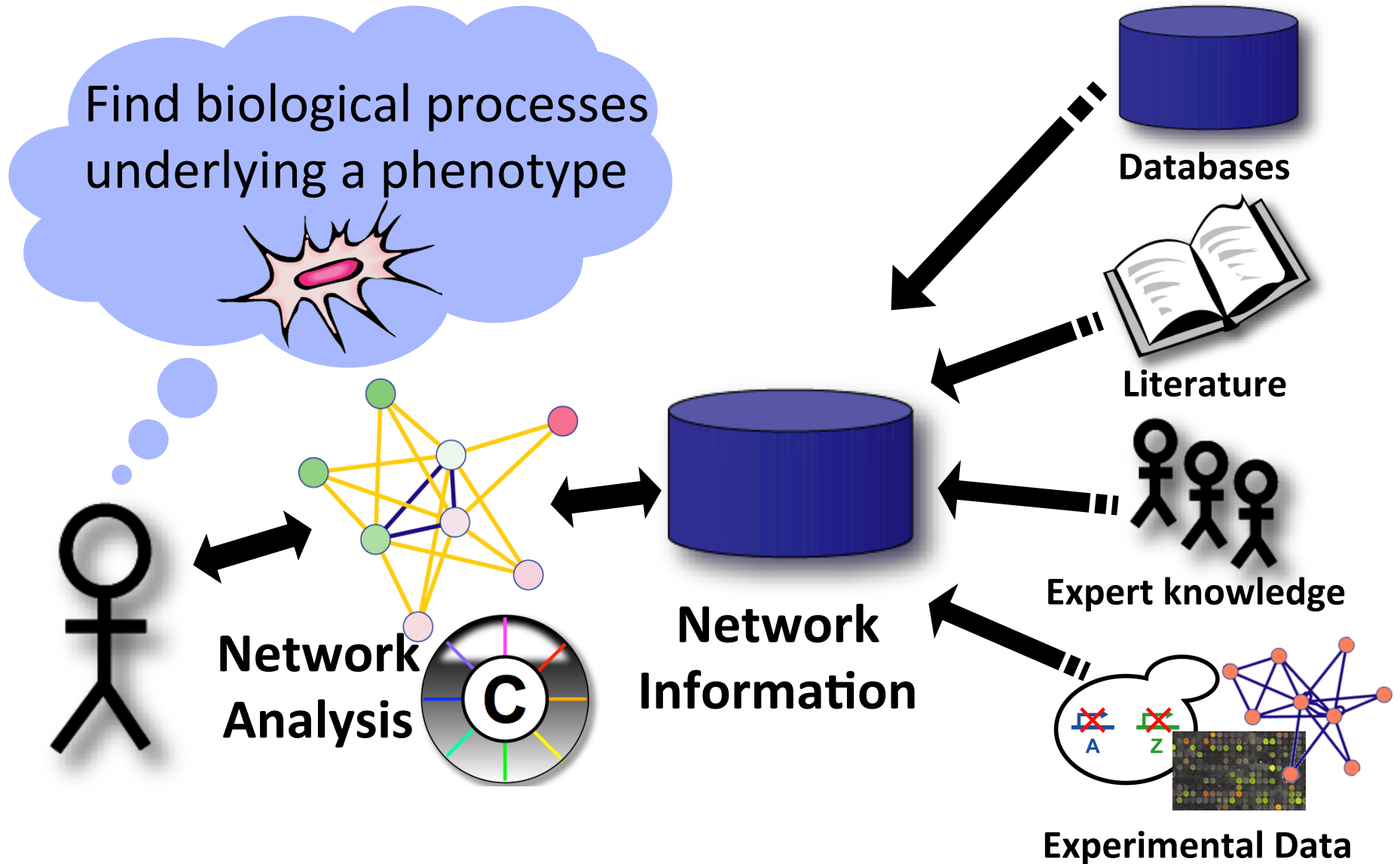


Welcome to Cytoscape 2.4.0-b1

Right-click + drag to ZOOM

Middle-click + drag to PAN

# Network Analysis using Cytoscape



# Active Community

<http://www.cytoscape.org>

- Help

- Tutorials, case studies
- Mailing lists for discussion
- Documentation, data sets

Cline MS et al. Integration of biological networks and gene expression data using Cytoscape  
Nat Protoc. 2007;2(10):2366-82

- Annual Conference: San Diego, May 18-21, 2011
- 10,000s users, 2500 downloads/month
- >100 Plugins Extend Functionality
  - Build your own, requires programming





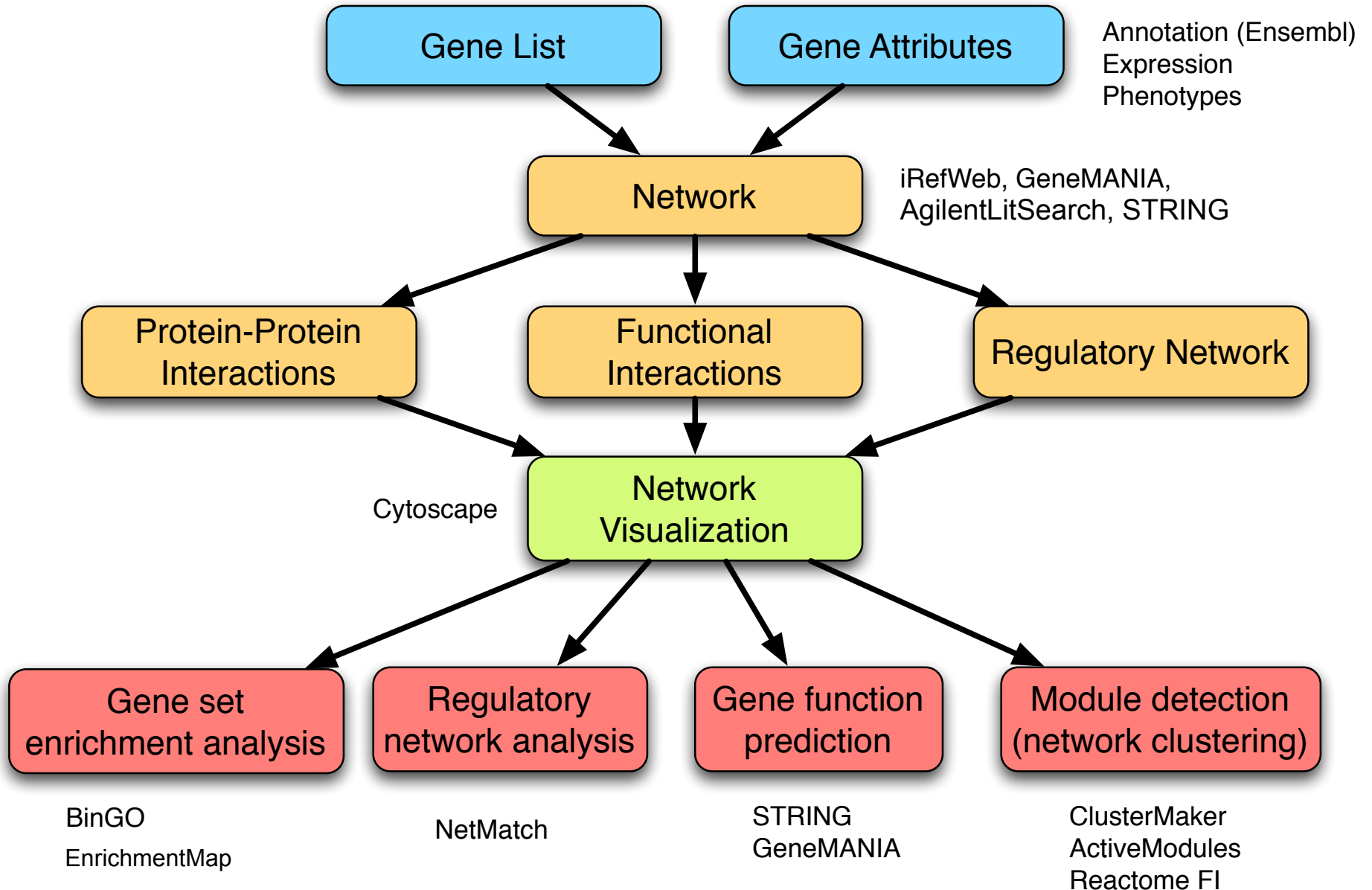
# Cytoscape Demo

Version 2.8.0

[www.cytoscape.org](http://www.cytoscape.org)



# Gene List and Network Analysis Overview



Find genes in

related to

Go

Showing 20 related genes

Show advanced options

File

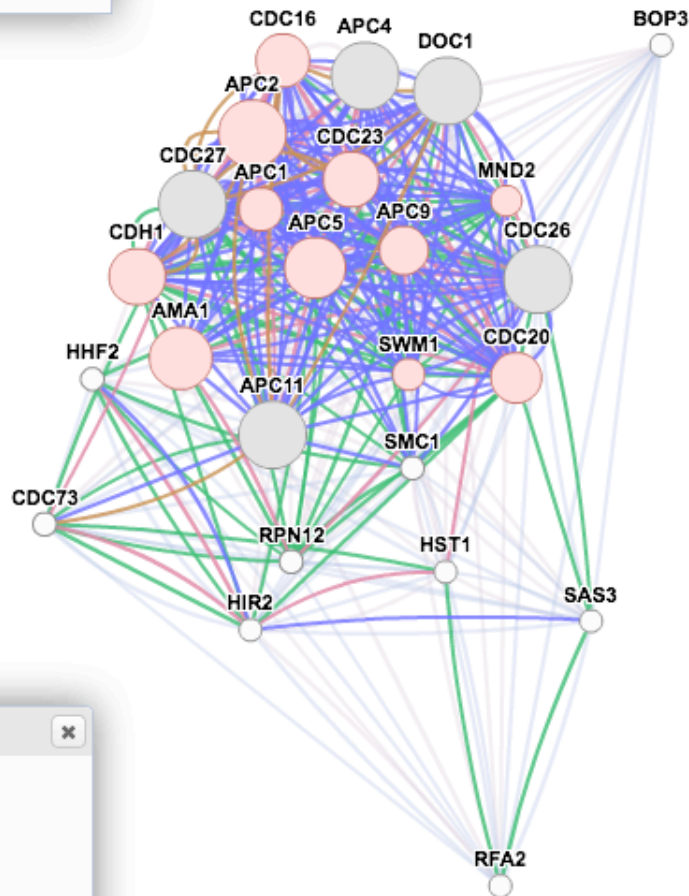
Actions

Networks legend

Functions legend

Functions legend

- query genes
- anaphase-promoting complex



Networks legend

- Co-expression
- Co-localization
- Genetic interactions
- Other
- Physical interactions
- Predicted

Networks

Genes

Functions

Help

Sort by: [name](#), [score](#)

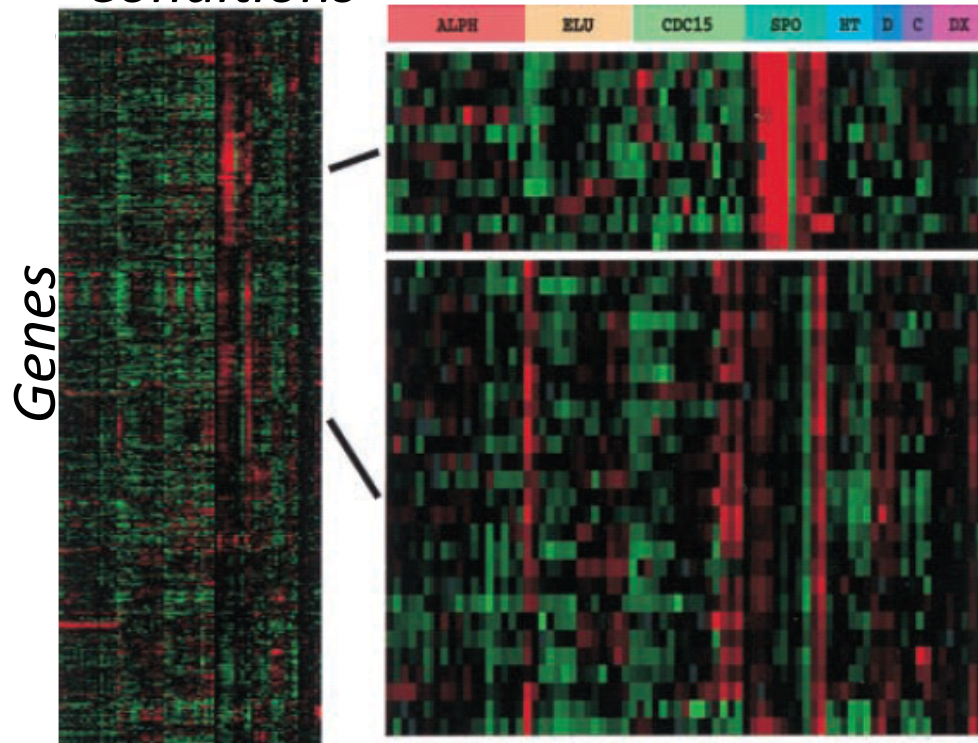
Expand: [all](#), [none](#)

- ▶ **DOC1** Processivity factor required for the ubiquitination activity of th
- ▶ **APC4** Subunit of the Anaphase-Promoting Complex/Cyclosome (AI
- ▶ **APC11** Catalytic core subunit of the Anaphase-Promoting Complex
- ▶ **CDC26** Subunit of the Anaphase-Promoting Complex/Cyclosome (
- ▶ **CDC27** Subunit of the Anaphase-Promoting Complex/Cyclosome (
- ▶ **APC2** Subunit of the Anaphase-Promoting Complex/Cyclo: 0.81
- ▶ **AMA1** Activator of meiotic anaphase promoting complex (A 0.75
- ▶ **APC5** Subunit of the Anaphase-Promoting Complex/Cyclo: 0.73
- ▶ **CDH1** Cell-cycle regulated activator of the anaphase-promc 0.67
- ▶ **CDC23** Subunit of the Anaphase-Promoting Complex/Cycl 0.66
- ▶ **CDC16** Subunit of the anaphase-promoting complex/cyclc 0.64
- ▶ **CDC20** Cell-cycle regulated activator of anaphase-promotir 0.60
- ▶ **APC9** Subunit of the Anaphase-Promoting Complex/Cyclo: 0.58
- ▶ **APC1** Largest subunit of the Anaphase-Promoting Comple 0.52
- ▶ **MND2** Subunit of the anaphase-promoting complex (APC); 0.37
- ▶ **SWM1** Subunit of the anaphase-promoting complex, whic 0.37
- ▶ **RPN12** Subunit of the 19S regulatory particle of the 26S pr 0.28
- ▶ **CDC73** Component of the Paf1p complex that binds to an 0.28
- ▶ **HHF2** Histone H4, core histone protein required for chroms 0.27
- ▶ **HIR2** Subunit of the HIR complex, a nucleosome assembly 0.27
- ▶ **HST1** NAD(+)-dependent histone deacetylase; essential sut 0.27
- ▶ **BOP3** Protein of unknown function, potential Cdc28p sub: 0.27
- ▶ **RFA2** Subunit of heterotrimeric Replication Protein A (RPA), 0.27
- ▶ **SAS3** Histone acetyltransferase catalytic subunit of NuA3 c 0.27
- ▶ **SMC1** Subunit of the multiprotein cohesin complex, essen 0.27



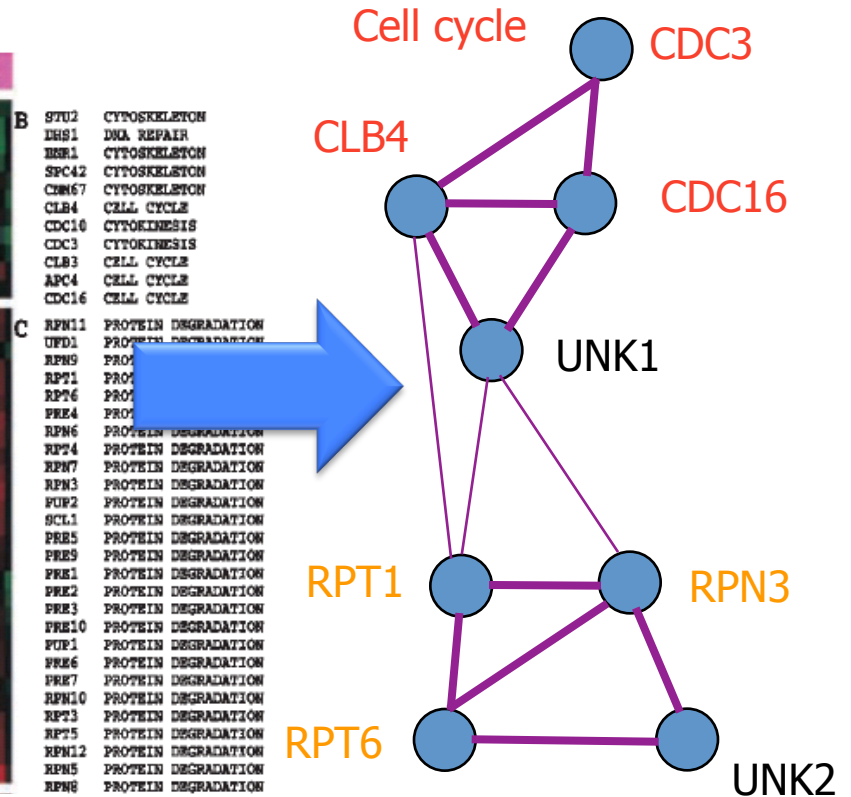
# Guilt-by-association principle

Microarray expression data  
Conditions



Eisen et al (PNAS 1998)

Co-expression network



Fraser AG, Marcotte EM - A probabilistic view of gene function - Nat Genet. 2004 Jun;36(6):559-64

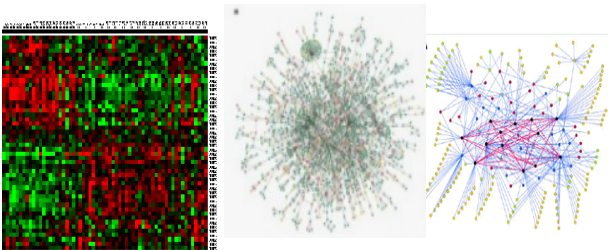
# Two types of functional prediction

- **“Give me more genes like these”**,
  - e.g. find more genes in the Wnt signaling pathway, find more kinases, find more members of a protein complex
  
- **“What does my gene do?”**
  - Goal: determine a gene’s function based on who it interacts with: “guilt-by-association”.

# “Give me more genes like these”

## Input

Network and profile data



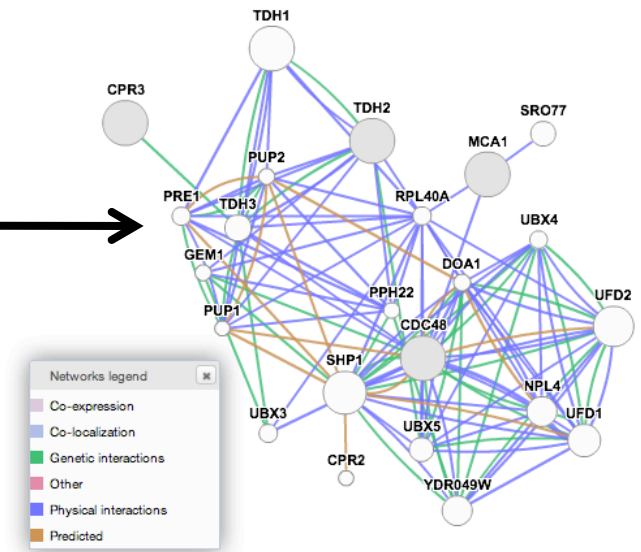
Query list

CDC48  
CPR3  
MCA1  
TDH2

Gene  
recommender  
system

## Output

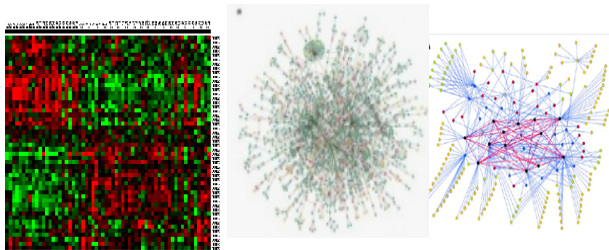
from GeneMANIA



# “What does my gene do?”

## Input

Network and profile data

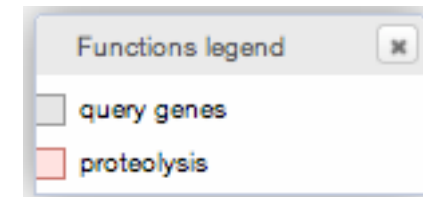
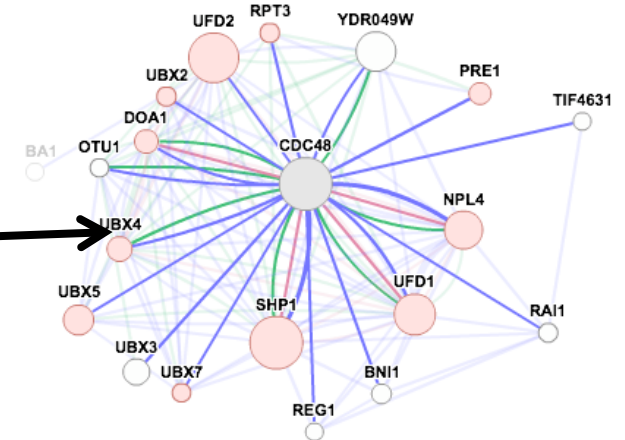


Query list

CDC48

Gene recommender system, then enrichment analysis

## Output

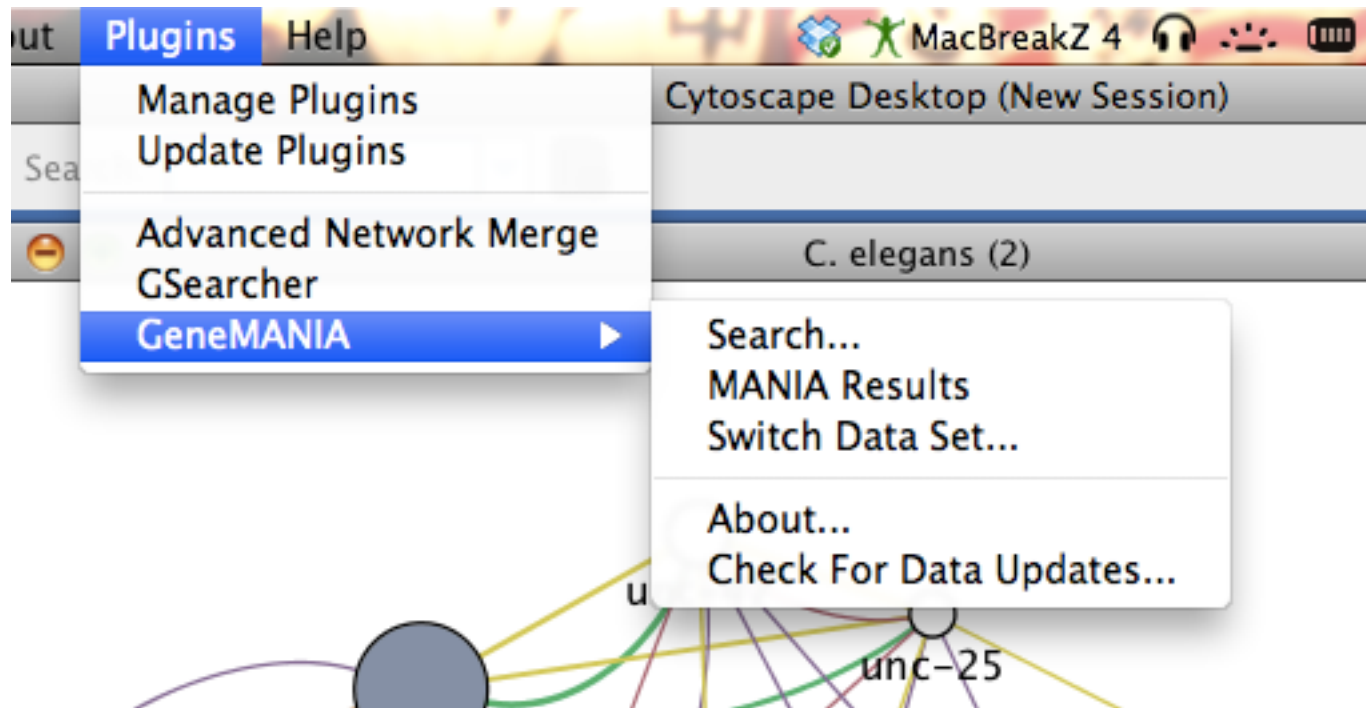


# Three parts of GeneMANIA:

- A large, automatically updated collection of interactions networks.
- A query algorithm to find genes and networks that are functionally associated to your query gene list.
- An interactive, client-side network browser with extensive link-outs



# Cytoscape plugin



<http://www.genemania.org/plugin/>



**GeneMANIA**

---

**Available Data**

Organisms	Networks	Genes	Interactions	Version	Manage Data
1	76	20247	9394174	2010-04-28	

---

**Choose Query Genes**

Organism: C. elegans (worm)

Name	Description
unc-18 (UNC18_CAEEL)	unc-18 encodes the C. elegans ortholog of Saccharomyces cerevisiae SEC1 and mammalian Munc18 proteins. U
unc-30 (UNC30_CAEEL)	unc-30 encodes a homeodomain-containing protein that is orthologous to the Pitx family of homeodomain tra
unc-4 (UNC4_CAEEL)	The unc-4 gene encodes a paired-class homeodomain protein with homologs in Drosophila and vertebrates. I
unc-5 (UNC5_CAEEL)	unc-5 encodes a netrin receptor. unc-5 activity is required cell autonomously for dorsalward cell and pioneer

Remove
Remove All

---

**Choose Interaction Networks**

Select: [all](#), [none](#), [default](#).

<input checked="" type="checkbox"/> Co-expression (3/10)	<input type="checkbox"/> Baugh-Hunter-2005	
<input checked="" type="checkbox"/> Co-localization (1/1)	<input type="checkbox"/> Fox-Miller-2007 A	
<input checked="" type="checkbox"/> Genetic interactions (2/4)	<input type="checkbox"/> Fox-Miller-2007 B	
<input type="checkbox"/> Other (0/1)	<input type="checkbox"/> Kirienko-Fay-2007	
<input checked="" type="checkbox"/> Physical interactions (4/8)	<input type="checkbox"/> Lee-Marcotte-2008 Co-expressi	
<input type="checkbox"/> Predicted (0/50)	<input checked="" type="checkbox"/> Lewis-Jackson-2009	
<input type="checkbox"/> Shared protein domains (0/2)	<input type="checkbox"/> McElwee-Gems-2004	
	<input type="checkbox"/> Stuart-Kim-2003	
	<input checked="" type="checkbox"/> Troemel-Kim-2006	

Start

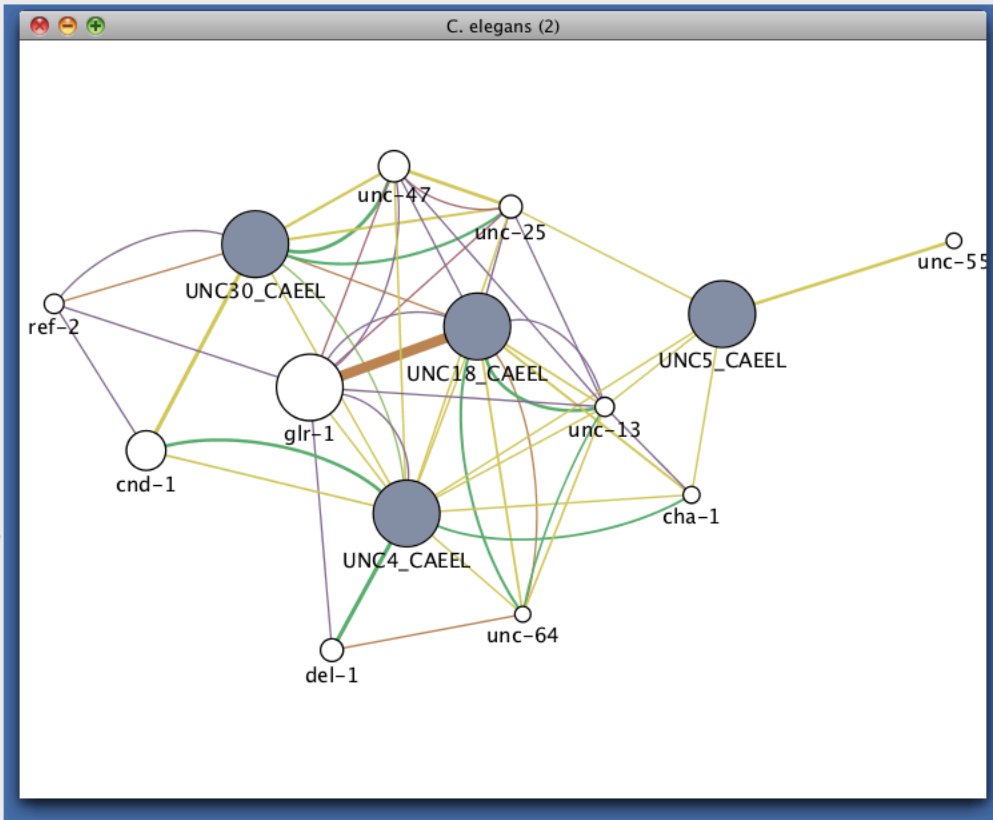
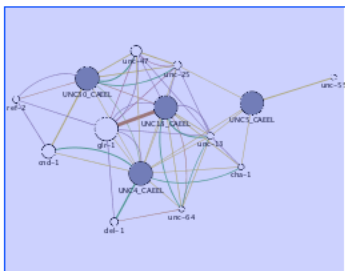
---

Find the top 10 related genes using automatic weighting.

Control Panel

Network VizMapper™

Network	Nodes	Edges
C. elegans (1)	14(0)	18(0)
C. elegans (2)	14(0)	53(0)



Results Panel

MANIA Results

Organism: C. elegans

Networks Genes

Sort by: [name](#), [per cent weight](#)

Expand: [all](#), [top-level](#), [none](#)

Enable: [all](#), [none](#)

- Predicted 84.
- Other 4.
- Genetic interactions 3.
- Co-expression 3.
- Shared protein domains 2.
- Physical interactions 0.
- Co-localization 0.

Export results...

Hide results

Data Panel

ID

ID
----

Node Attribute Browser Edge Attribute Browser Network Attribute Browser

Cytoscape Desktop (New Session)

**Control Panel**

Network VizMapper™

Network	Nodes	Edges
C. elegans (1)	14(0)	18(0)
C. elegans (2)	14(0)	53(0)

C. elegans (2)

+ QueryRunner

**Results Panel**

MANIA Results

Organism: C. elegans

Networks Genes

Sort by: [name](#), [per cent weight](#)

Expand: [all](#), [top-level](#), [none](#)

Enable: [all](#), [none](#)

- ▶  Predicted 84.
- ▶  Other 4.
- ▶  Genetic interactions 3.
- ▶  Co-expression 3.
- ▶  Shared protein domains 2.
- ▶  Physical interactions 0.
- ▶  Co-localization 0.

Export results...  
Hide results

**Data Panel**

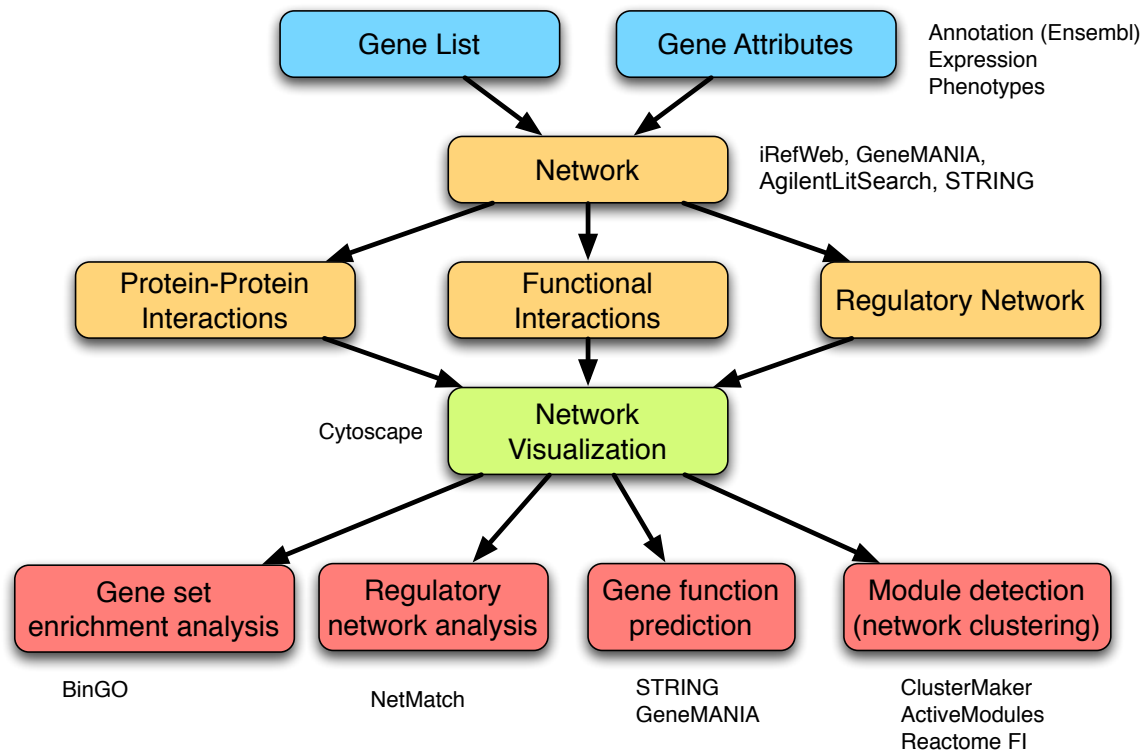
ID

Node Attribute Browser
Edge Attribute Browser
Network Attribute Browser

Welcome to Cytoscape 2.7.0    Right-click + drag to ZOOM    Middle-click + drag to PAN

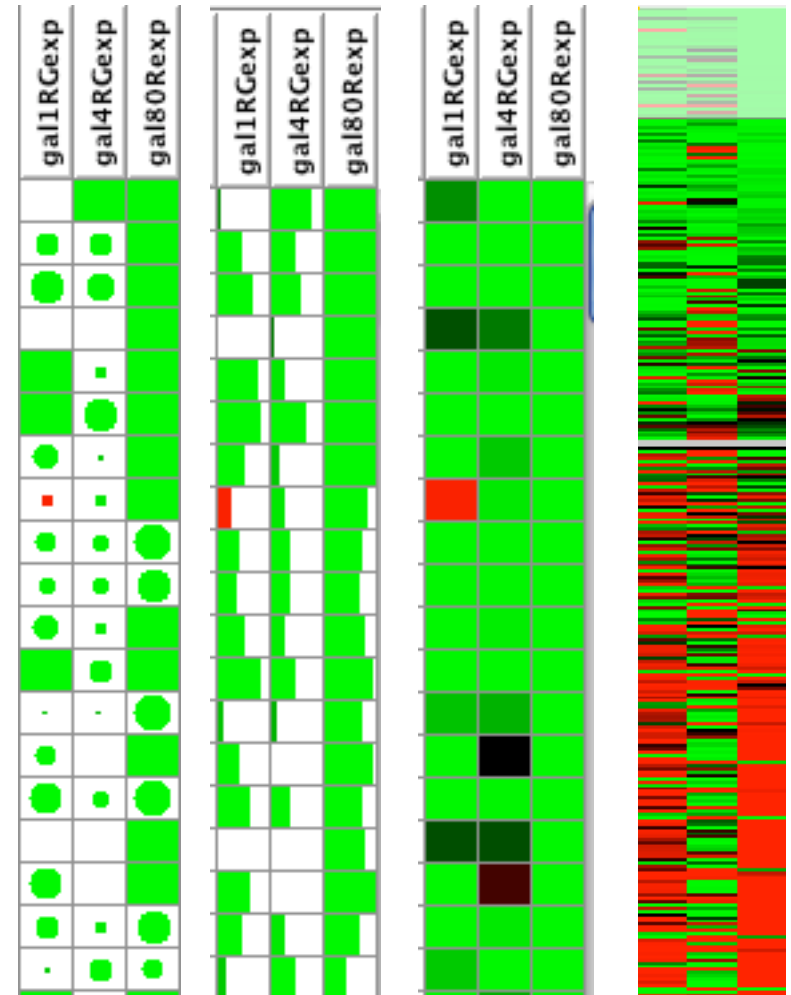
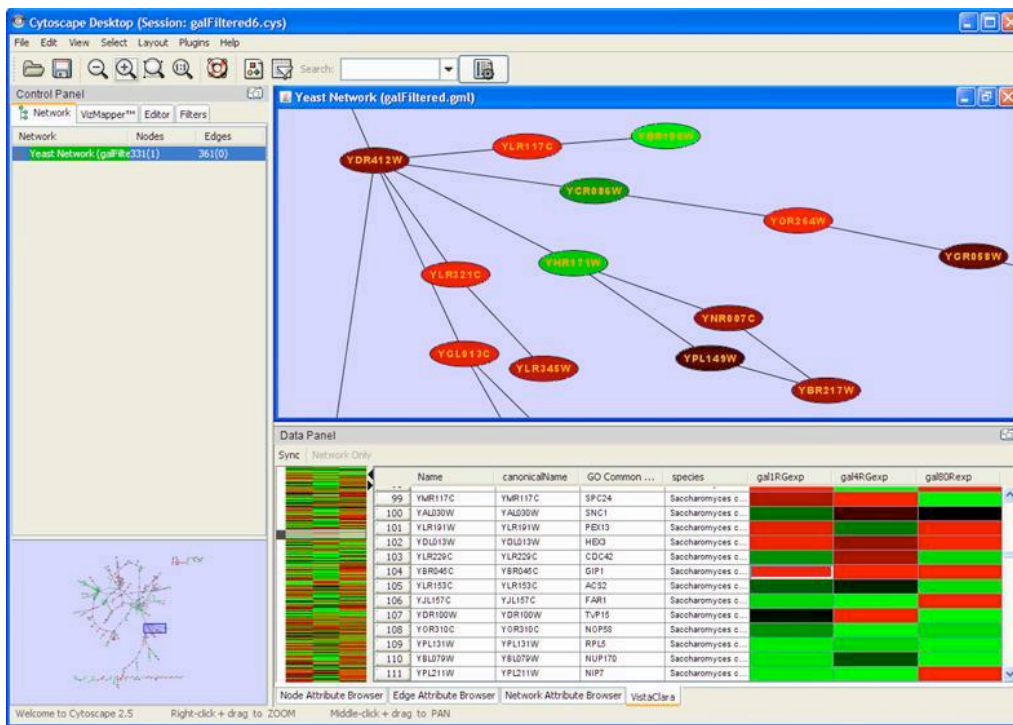
# More detail on specific network analysis tasks using Cytoscape

## Gene List and Network Analysis Overview



# VistaClara

- Visualization for gene expression data
- Heat maps, sorting, animation



# Cytoscape Lab

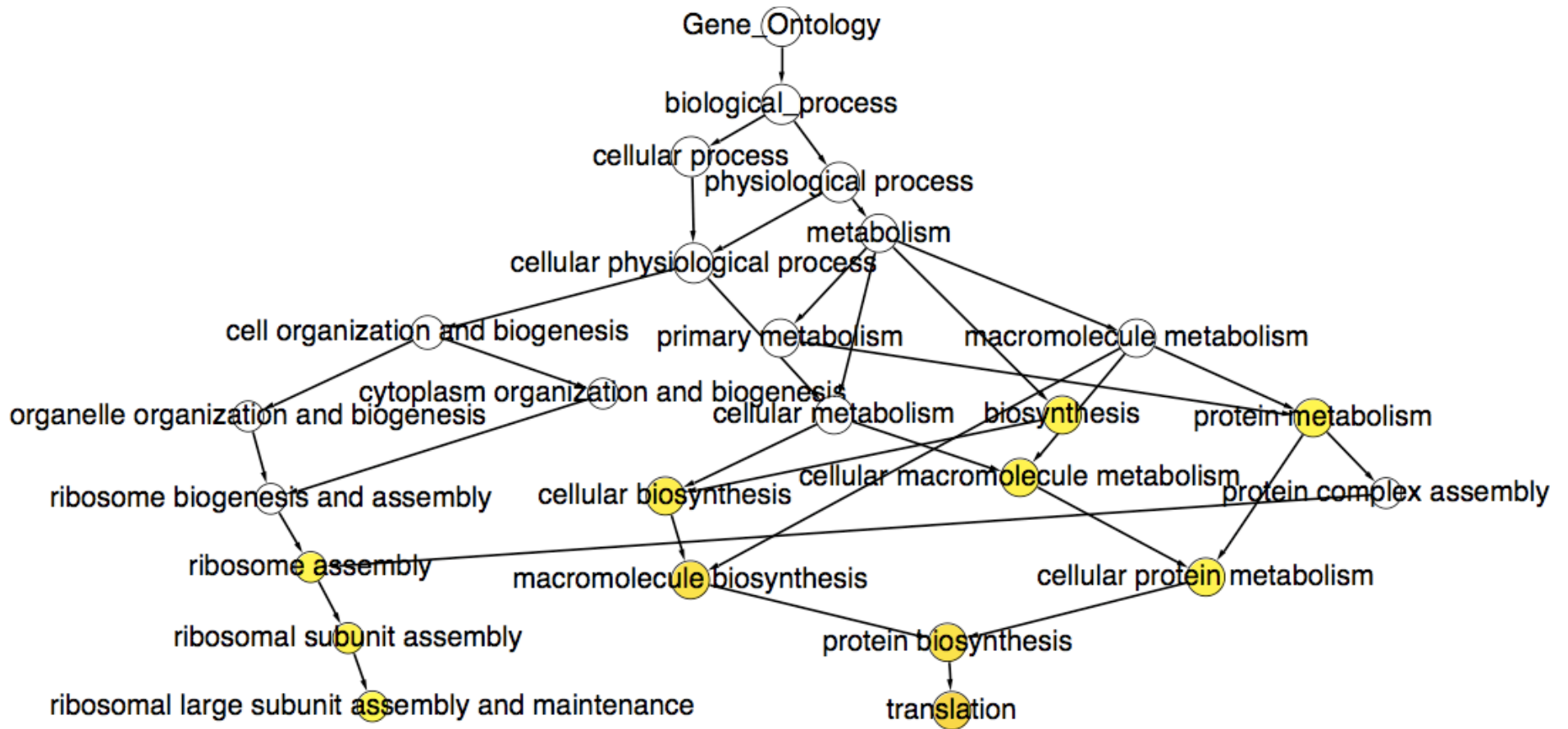
- Cytoscape – expression data visualization
  - Load the sample network file: galFiltered.sif
  - Lay it out – try different layouts
  - Load expression data - galExpData.pvals
    - Use File->Import->Attribute from Table
  - Examine node attributes
  - Visualize gene expression data using the Visual Mapper
  - Install the VistaClara plugin from the plugin manager
  - Play the expression data as a movie

# BiNGO plugin

- Calculates over-representation of a subset of genes with respect to a background set in a specific GO category
- Input: subnetwork, or list
  - Background set by user
- Output: tree with nodes color reflecting overrepresentation; also as lists
- Caveats: Gene identifiers must match; low GO term coverage, GO bias, Background determining

# BiNGO

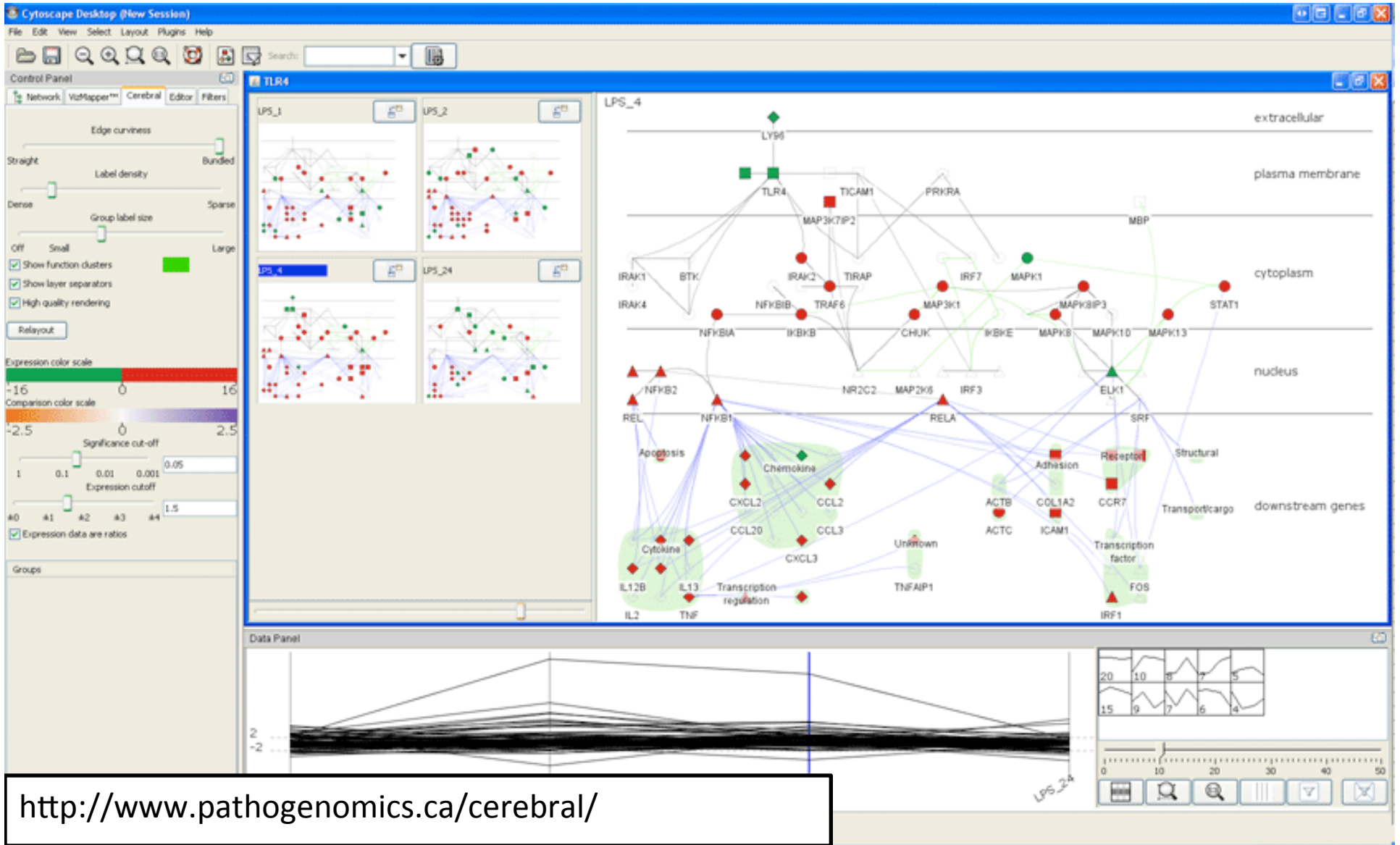
Hypergeometric p-value  
Multiple testing correction  
(Benjamini-Hochberg FDR)



Maere, S., Heymans, K. and Kuiper, M  
Bioinformatics 21, 3448-3449, 2005



# Cerebral



# Find Active Subnetworks

- Active modules
  - Input: network + p-values for gene expression values e.g. from GCRMA
  - Output: significantly differentially expressed subgraphs
- Method
  - Calculate z-score/node,  $Z_A$  score/subgraph, correct vs. random expression data sampling
  - Score over multiple experimental conditions
  - Simulated annealing used to find high scoring networks

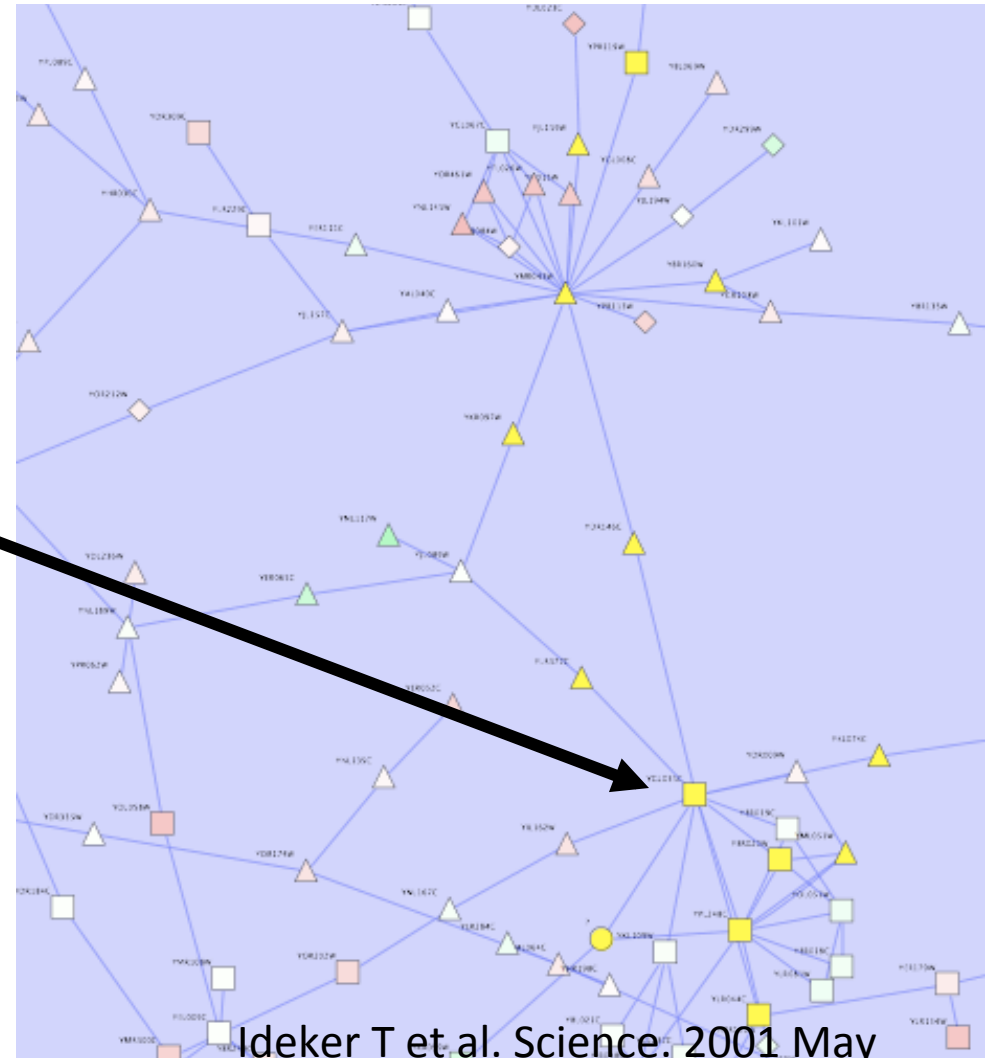
# Active Module Results

Network: yeast protein-protein and protein-DNA network

Expression data: 3 gene knock out conditions (enzyme, TF activator, TF repressor)

Network	Size	Score	gal1RGsig	gal4RGsig	gal80Rsig
1	14	3.78			
2	26	3.584			
3	10	2.994			
4	7	2.934			
5	4	2.636			

Save Dismiss



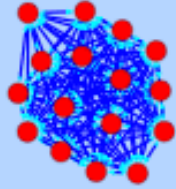
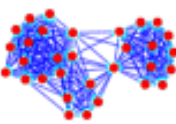
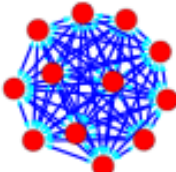
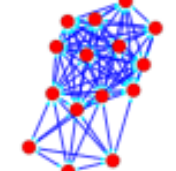
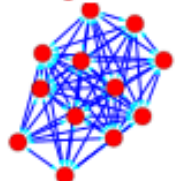
Note: non-deterministic, multiple runs required for confidence of result robustness

Ideker T et al. Science. 2001 May 4;292(5518):929-34.

# Network Clustering

- Clusters in a protein-protein interaction network have been shown to represent protein complexes and parts of pathways
- Clusters in a protein similarity network represent protein families
- Network clustering is available through the ClusterMaker Cytoscape plugin

MCODE Results Summary

Rank	Score	Size	Names	Complex
1	7.25	16,116	YGR232W, YDL007W, YKL145W, YFR052W, YFR004W, YLR421C, YOR261C, YDL147W, YDR427W, YHR200W, YER021W, YOR117W, YDL097C, YOR259C, YPR108W, YDR394W	
2	6.387	31,198	YPL093W, YBL004W, YOR272W, YNL110C, YKL009W, YFL002C, YOL077C, YPL126W, YIL035C, YLR409C, YLR129W, YOR061W, YKR060W, YCR057C, YDR449C, YOR039W, YJL109C, YPL012W, YGR103W, YLR449W, YOR206W, YKL014C, YLL008W, YKL172W, YNL002C, YLR002C, YGL111W, YOL041C, YGL019W, YOR145C, YPR016C	
3	5.417	12,65	YGL011C, YOL038W, YPR103W, YMR314W, YBL041W, YOR362C, YER012W, YJL001W, YML092C, YGR253C, YER094C, YGR135W	
4	5	15,75	YPL043W, YMR290C, YER006W, YKR081C, YDR496C, YDL031W, YNL061W, YNL132W, YLR222C, YLR197W, YMR049C, YHR052W, YJL069C, YKL099C, YDL014W	
5	5	12,60	YPR187W, YPR010C, YPR110C, YNL248C, YOR341W, YNR003C, YKL144C, YOR207C, YPR190C, YNL113W, YOR116C, YBR154C	

Create a new child network.

Save

Done

# Text Mining

- Computationally extract gene relationships from text, usually PubMed abstracts
- Useful if network is not in a database
  - Literature search tool
- BUT not perfect
  - Problems recognizing gene names
  - Natural language processing is difficult
- Agilent Literature Search Cytoscape plugin
- iHOP ([www.ihop-net.org/UniPub/iHOP/](http://www.ihop-net.org/UniPub/iHOP/))

**Agilent Literature Search 1.0.4**

Edit View Help

**Terms**  
 CSF2RB  
 EDN1  
 EGFR  
 LMNA  
 PDK2  
 TRAF1  
 WBSR14

**Context**  
 atherosclerosis

**Match Controls**  
 Max Engine Matches: 10 Organism: Homo sapiens

**Query Controls**  
 Use Aliases:  Use Context:

**Extraction Controls**  
 Interaction Lexicon: limited

**Query Editor**  
 (((csf2rb OR if5rb OR cd131 OR cdw131 OR if3rb)) AND atherosclerosis  
 ((edn1 OR et1)) AND atherosclerosis  
 ((egfr OR mena OR erbb OR erbb1)) AND atherosclerosis  
 ((lmna OR lmnc OR cmt2b1 OR fpl OR ifp OR hgps OR emd2 OR ldp1 OR lmn1 OR fpld)) AND atherosclerosis  
 (PDK2) AND atherosclerosis  
 ((traf1 OR mgc:10353 OR ebi6)) AND atherosclerosis  
 ((wbscr14 OR ws-bhlh OR chreb OR mondob OR mio)) AND atherosclerosis

**Query Matches**



**Cytoscape Desktop**

File Edit Data Select Layout Visualization Plugins Help Filters

Network Nodes Edges  
 1 46(0) 77(0)

Nodes: 46 (0 selected) Edges: 77 (0 selected)



Use Aliases:  Use Context:  Interaction Lexicon: limited

**Query Editor**  
 (((csf2rb OR if5rb OR cd131 OR cdw131 OR if3rb)) AND atherosclerosis  
 (CRKL) AND atherosclerosis  
 (((csf2rb OR if5rb OR cd131 OR cdw131 OR if3rb)) AND atherosclerosis  
 ((edn1 OR et1)) AND atherosclerosis  
 ((egfr OR mena OR erbb OR erbb1)) AND atherosclerosis  
 ((lmna OR lmnc OR cmt2b1 OR fpl OR ifp OR hgps OR emd2 OR ldp1 OR lmn1 OR fpld)) AND atherosclerosis  
 (PDK2) AND atherosclerosis  
 ((traf1 OR mgc:10353 OR ebi6)) AND atherosclerosis  
 ((wbscr14 OR ws-bhlh OR chreb OR mondob OR mio)) AND atherosclerosis

**Query Matches**

**Results**

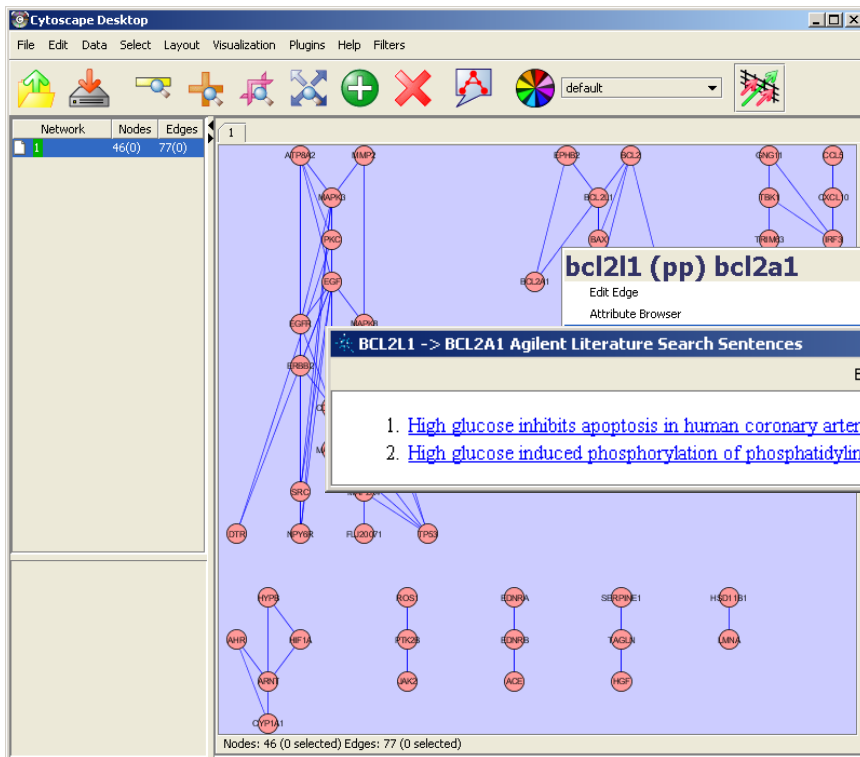
- [Association between the eNOS \(Glu298Asp\) and the RAS genes polymorphisms and premature coronary artery disease in a Turkish population \(by Berdeli A, Sekuri C, Sirri Can F, Ercan E, Sagcan A, Tengiz I, Eser E, Akim M\).](#)  
 BACKGROUND: The renin-angiotensin system (RAS) and endothelial nitric oxide (NO) affect the pathogen...  
 Source:  
 [PubMed]http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list\_uids=15563875

# Agilent Literature Search

# Cytoscape Network produced by Literature Search.

## Abstract from the scientific literature

## Sentences for an edge



Abstract from the scientific literature

Search results for the edge BCL2L1 -> BCL2A1.

BCL2L1 -> BCL2A1 Agilent Literature Search Sentences

1. [High glucose inhibits apoptosis in human coronary artery smooth muscle cells by increasing bcl-xL and bfl-1/A1.](#)
2. [High glucose induced phosphorylation of phosphatidylinositol 3-kinase \(PI 3-K\) and extracellular signal-regulated kinase \(ERK\)1/2 along with bcl-xL and bfl-1/A1 upregulation.](#)

Abstract from the scientific literature

High glucose inhibits apoptosis in human coronary artery smooth muscle cells by increasing bcl-xL and bfl-1/A1.

Author: Moto M, Okumura M, Kojima T, Maruyama T, Yasuda K.

Journal: *Journal of Internal Medicine*, Gifu University School of Medicine, Gifu 500-8705, Japan.

Cardiovascular disease is a serious complication in diabetic patients. To elucidate the precise mechanisms of atherosclerosis in diabetic patients, the effects of high glucose concentration (25 mM) on apoptosis regulation and bcl-2 family protein expression in human coronary artery smooth muscle cells (CASMC) were examined. Treatment with a high level of glucose (25 mM) caused a significant decrease in apoptosis in CASMC compared with the same cells treated with a physiologically normal glucose concentration (5.5 mM) (23.9 +/- 2.4% vs. 16.5 +/- 1.8%, P < 0.01). With respect to apoptosis regulation, treatment of CASMC with high glucose concentration markedly increased mRNA expressions of bcl-xL and bfl-1/A1 compared with cells treated with normal glucose. High glucose induced phosphorylation of phosphatidylinositol 3-kinase (PI 3-K) and extracellular signal-regulated kinase (ERK)1/2 along with bcl-xL and bfl-1/A1 upregulation. These results suggest that high glucose suppresses apoptosis via upregulation of bcl-xL and bfl-1/A1 levels through PI 3-K and ERK 1/2 pathways in CASMC. High glucose-induced increase in the expression of antiapoptotic proteins may be important in the development of atherosclerosis in diabetic patients.

PMID: 12107051 [PubMed - indexed for MEDLINE]

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Mar 29 2005 17:30:14



# Analysis Lab

## Find Network Motifs - Netmatch plugin

- Network motif is a sub-network that occurs significantly more often than by chance alone
- Input: query and target networks, optional node/edge labels
- Output: topological query matches as subgraphs of target network
- Supports: subgraph matching, node/edge labels, label wildcards, approximate paths
- <http://alpha.dmi.unict.it/~ctnyu/netmatch.html>

# Finding specific biological relevant TF-PPI sub-networks

The screenshot displays the NetMatch V1.0.1 software interface, divided into two main windows: the Query Editor and the Results window.

**Query Editor (Left Window):** Titled "NetMatch Query Editor - new query\*", it features a "Query Edit" toolbar with icons for file operations and help. Below the toolbar is a "Palette" and "Motifs" section. A "Feed Forward Loop" motif is highlighted in the palette, showing a diagram of three nodes where one node points to two others, which both point to a third. The main workspace shows a query graph with three nodes (represented by red circles with question marks) and three directed edges. A "Query" label is placed over the graph. At the bottom, a status bar indicates "Nodes: 6 Edges: 6 Paths: 0 Loops: 0".

**Results Window (Right Window):** Titled "NetMatch V1.0.1", it contains a "File Query Wizard Help" menu. The "Graph Properties" section has "Labeled" and "Directed" checked. The "Query Properties" section shows the query as "QE-FFL". The "Network Properties" section shows the network as "1-galFiltered.sif". The "Network Node Attributes" is set to "annotation.GO BIOLOGIC..." and "Network Edge Attributes" is "TextSourceInfo". The "Options" section includes "Acquire Data", "Go", and "Reset" buttons. The main results area contains a table with the following data:

Match Number	Nodes	Image
1	YMR309C, YOR361C, YPR041W	
2	YOR310C, YDL014W, YLR197W	
3	YDR100W, YGL161C, YOR036W	
4	YIL015W, YMR043W, YCL067C	

Below the table, there is a "Create a new child network." checkbox and a "Save" button. At the bottom, a text area displays the following results:

```

1 matches YBR020W
2 matches YGL035C
***** Match 21
0 matches YPL248C
1 matches YML051W
2 matches YPR020W
*****
0 matches Y
1 matches Y
2 matches Y
*****

```

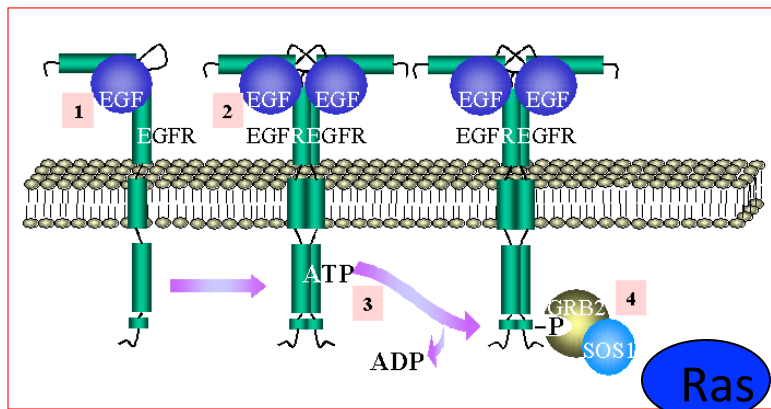
A "Results" label is placed over the bottom part of the results window.

# Find Signaling Pathways

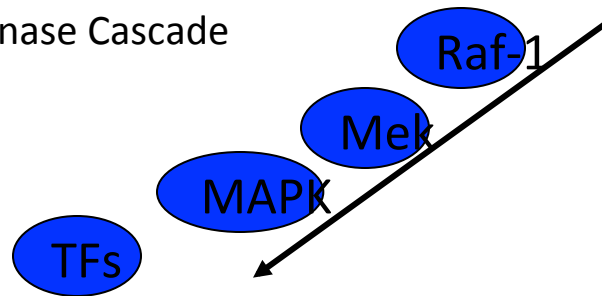
- Potential signaling pathways from plasma membrane to nucleus via cytoplasm

NetMatch Results

Signaling pathway example

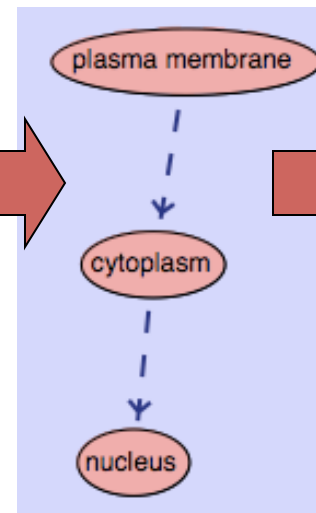


MAP Kinase Cascade



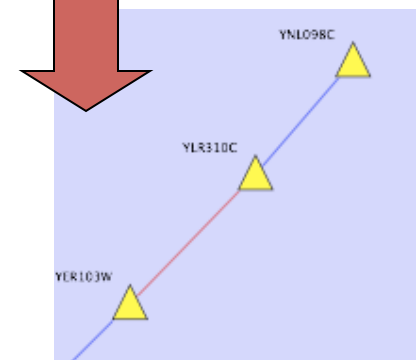
Nucleus - Growth Control  
Mitogenesis

NetMatch query



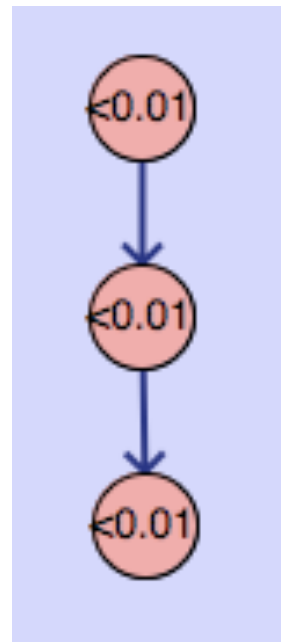
Shortest path between subgraph matches

Match Number	Nodes	Image
	YGL008C	
4	YJL157C, YMR043W, YLR229C	
5	YJL157C, YAL040C, YLR229C	
6	YLR310C, YER103W, YNL098C	

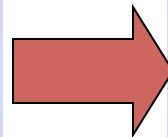


# Find Expressed Motifs

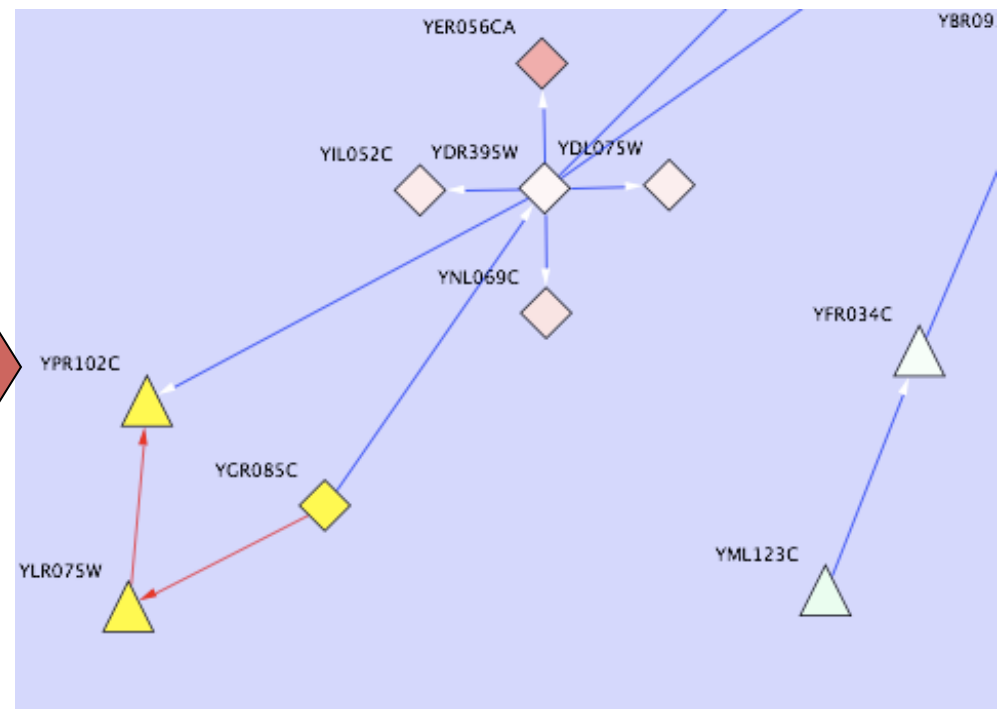
NetMatch query



Find specific subgraphs where certain nodes are significantly differentially expressed



NetMatch Results



Protein  
YLR075W  
YGR085C  
YPR102C

Differential Expression Significance  
1.7255E-4  
2.639E-4  
3.7183E-4

# Cytoscape Tips & Tricks

- “Root graph”
  - “There is one graph to rule them all....”
  - The networks in Cytoscape are all “views” on a single graph.
  - Changing the attribute for a node in one network *will* also change that attribute for a node with the same ID in all other loaded networks
  - There is no way to “copy” a node and keep the same ID
  - Make a copy of the session

# Cytoscape Tips & Tricks

- Network views
  - When you open a large network, you will not get a view by default
  - To improve interactive performance, Cytoscape has the concept of “Levels of Detail”
    - Some visual attributes will only be apparent when you zoom in
    - The level of detail for various attributes can be changed in the preferences
    - To see what things will look like at full detail:
      - View → Show Graphics Details

# Cytoscape Tips & Tricks

- Sessions
  - Sessions save pretty much everything:
    - Networks
    - Properties
    - Visual styles
    - Screen sizes
  - Saving a session on a large screen may require some resizing when opened on your laptop



# Cytoscape Tips & Tricks

- Logging
  - By default, Cytoscape writes it's logs to the Error Dialog: Help→Error Dialog
  - Can change a preference to write it to the console
    - Edit→Preferences→Properties...
    - Set `logger.console` to true
    - Don't forget to save your preferences
    - Restart Cytoscape
  - (can also turn on debugging: `cytoscape.debug`, but I don't recommend it)

# Cytoscape Tips & Tricks

- Memory
  - Cytoscape uses lots of it
  - Doesn't like to let go of it
  - An occasional restart when working with large networks is a good thing
  - Destroy views when you don't need them
  - Java doesn't give us a good way to get the memory right at start time
    - Since version 2.7, Cytoscape does a much better job at “guessing” good default memory sizes than previous versions

# Cytoscape Tips & Tricks

- `.cytoscape` directory
  - Your defaults and any plugins downloaded from the plugin manager will go here
  - Sometimes, if things get really messed up, deleting (or renaming) this directory can give you a “clean slate”
- Plugin manager
  - “Outdated” doesn’t necessarily mean “won’t work”
  - Plugin authors don’t always update their plugins immediately after new releases