

# Protein-Protein Interactions

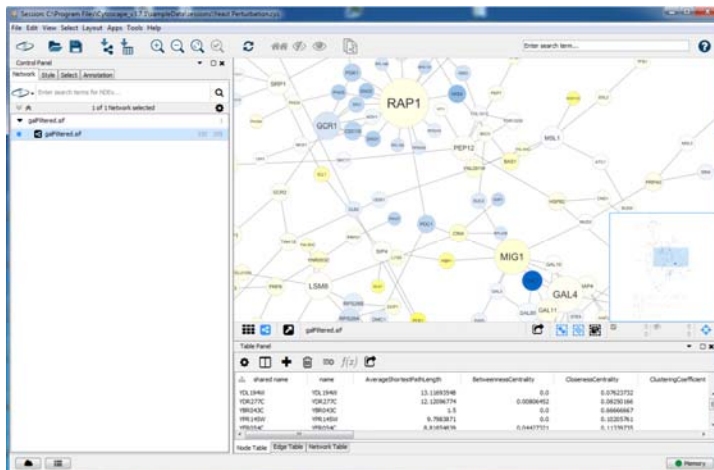
## *Introduction to Cytoscape*

May 2019

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 Boyer Hall 205

## Cytoscape

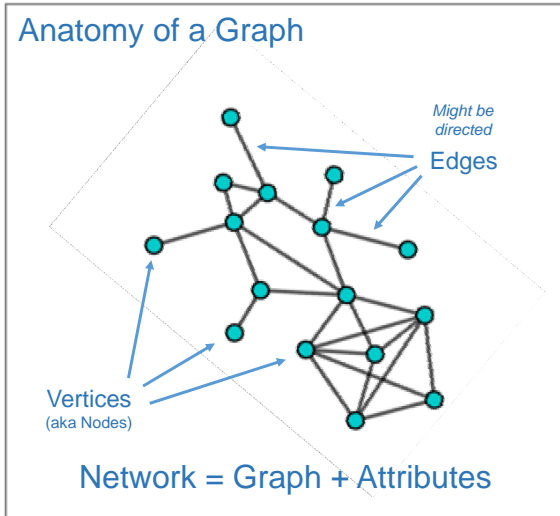
<https://cytoscape.org/>



## Topics

- Graph/network models
- Cytoscape GUI overview
- Data sources
- Data integration
- Apps overview

## Cytoscape: Data model



### Graph Theory

Béla Bollobás. *Modern Graph Theory*.  
Springer. ISBN 978-0-387-98488-9 (<https://link.springer.com>)

Richard J. Trudeau. *Introduction to Graph Theory*.  
Dover. ISBN: 978-0-486-67870-2

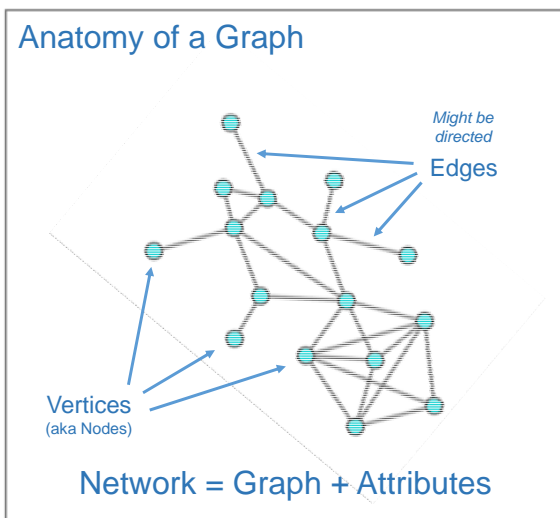
Gary Chartrand. *Introductory Graph Theory*.  
Dover. ISBN: 978-0-486-24775-5

Béla Bollobás. *Random Graphs*.  
Cambridge University Press. ISBN: 978-0-521-80920-7

### Popular Science

Albert-László Barabási. *Linked: The New Science of Networks*.  
Perseus Books Group. ISBN 978-0-738-20667-7.

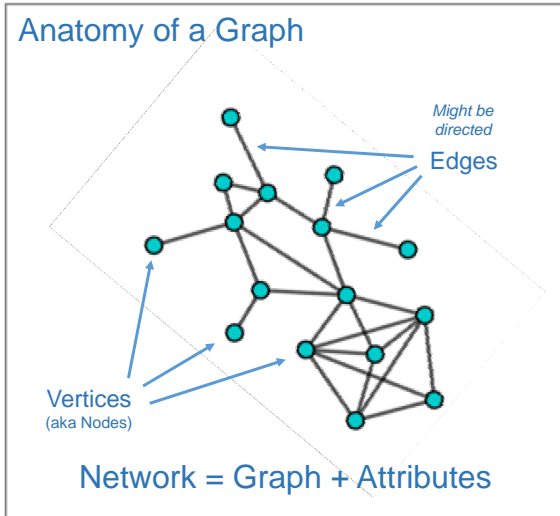
## Cytoscape: Data model



### Interaction Networks

- Graph is just a model...
  - All interactions are binary
  - No time dependence
  - No spatial information
- Vertices/Nodes represent genes or molecules with varying level of detail
  - ☐ One node – one gene
  - ☐ One node – one protein
  - ☐ One node – one protein state
  - ☐ One node – one protein domain
- Edges represent interactions
  - ☐ Molecular interactions
  - ☐ Genetic interactions
  - ☐ Functional relationships

# Cytoscape: Data model

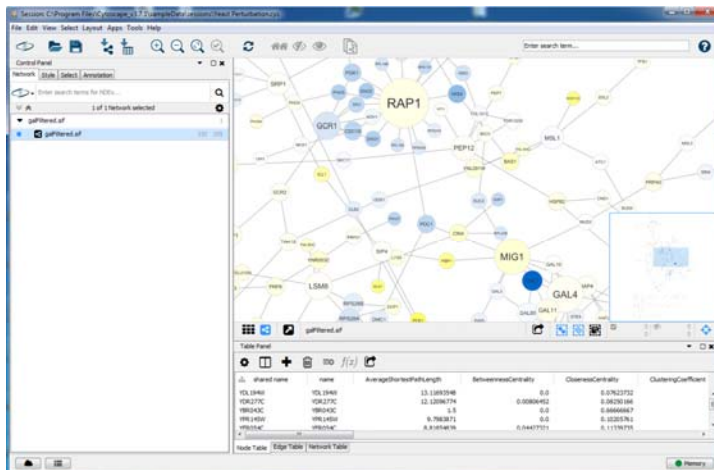


## Interaction Networks

- Common node attributes
  - ☐ Graph theory-based properties (node degree, centrality, etc)
  - ☐ Gene/protein name
  - ☐ UniprotKB/RefSeq/GeneBank identifier
  - ☐ GO annotation
  - ☐ Cellular localization
  - ☐ Expression/methylation/phosphorylation level
  - ☐ Enzymatic activity
  - ☐ ...
- Common edge attributes
  - ☐ Graph theory-based properties (
  - ☐ Interaction type
  - ☐ Experimental method
  - ☐ Number of supporting experiments
  - ☐ Expression level correlation
  - ☐ Quality score
  - ☐ ....

# Cytoscape

<https://cytoscape.org/>

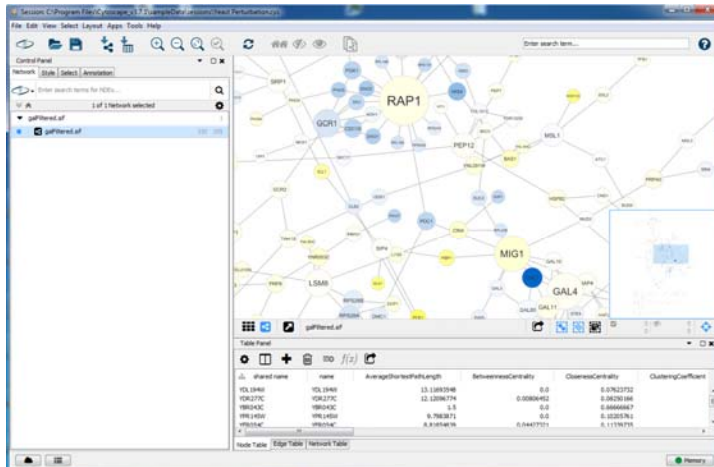


## Key features

- Open source
- Windows/Mac/Linux
- Network visualization
- Data integration
- Expandable through Apps (aka plugins)
- Scripting interface

# Cytoscape

<https://cytoscape.org/>



## Topics

- Graph/network models
- Cytoscape GUI overview
- Data sources
- Data integration
- Apps overview

## Cytoscape: GUI

### GUI Anatomy

#### Control Panel

- Select network view
- Select/edit network view style
- Annotate network view
- Filter network

Zoom In/Out

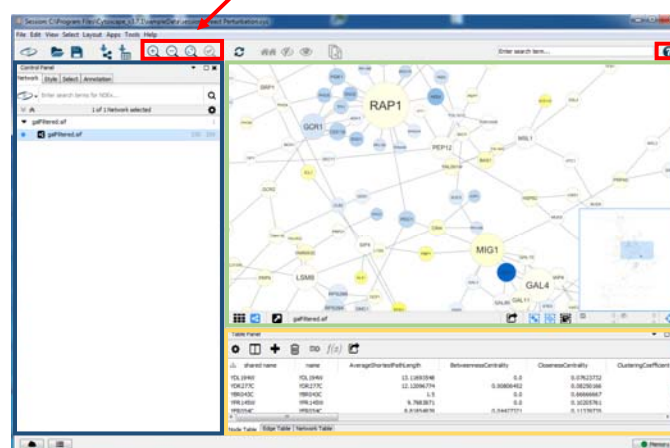
Online Help

#### Network Panel

- View/edit current view of the network
- Switch between different views of the network

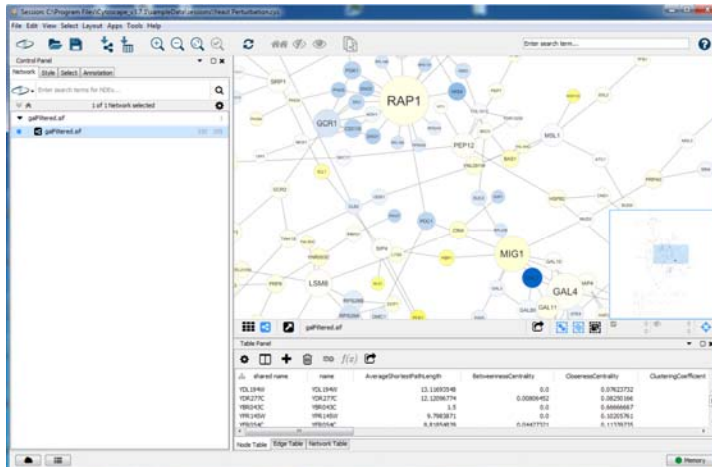
#### Table Panel

- View/edit node and edge attributes
- View network table



# Cytoscape: GUI

## Layout modifications



### Individual nodes

- Select (LBM) and drag

### Groups of nodes

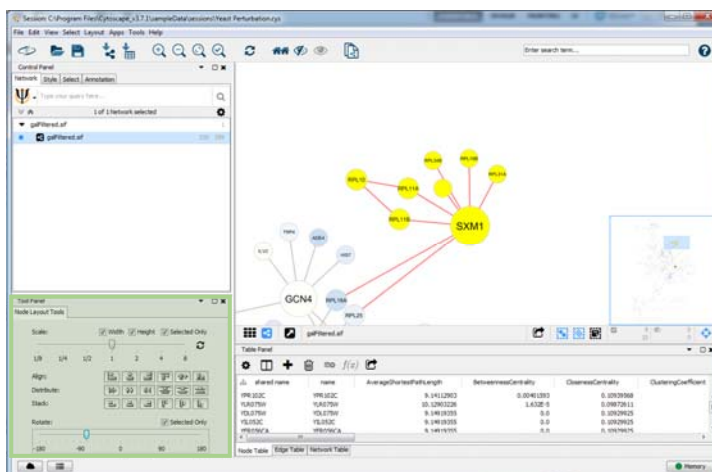
- Select (shift-LBM)
- Drag (LBM) to translate
- Use Tool Panel to translate and scale

### Entire network

- Use layout menu
- Some algorithms work on node selections

# Cytoscape: GUI

## Layout modifications



### Individual nodes

- Select (LBM) and drag

### Groups of nodes

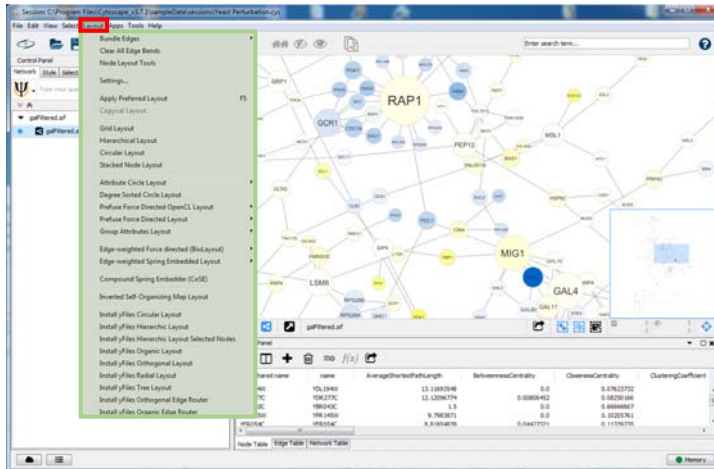
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# Cytoscape: GUI

## Layout modifications



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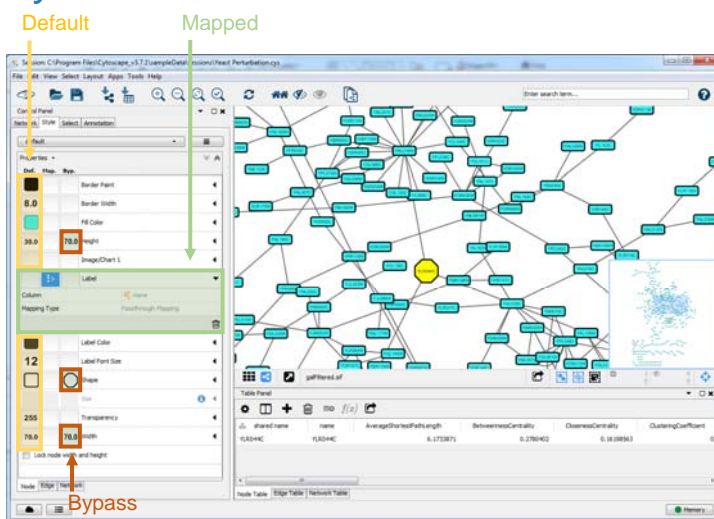
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### Entire network

- Use layout menu
- Some algorithms work on node selections

# Cytoscape: GUI

## Style modifications



### Passthrough Mappers

- Directly uses column values (e.g. name column values shown as node labels)

### Continuous Mappers

- Scales column values (numbers)
- Converts column values (numbers) into color scale

### Discrete Mappers

- Converts discrete values (numbers or text) into numbers
- Converts discrete values (text or numbers) into colors

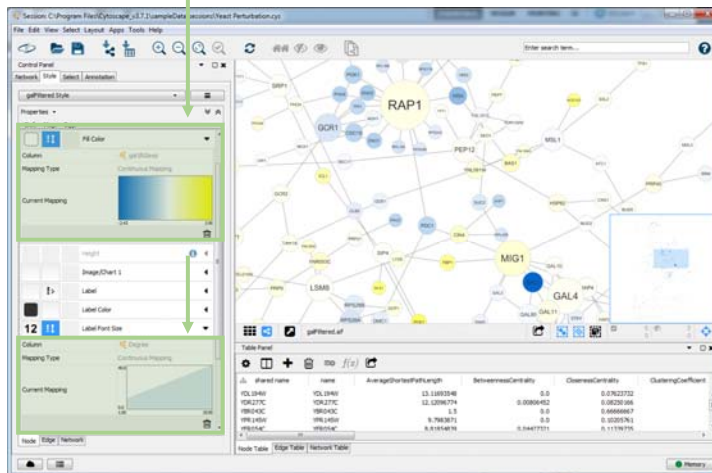
### Bypass

- Custom style for a specific node/edge

# Cytoscape: GUI

## Style modifications

Mapped



## Passthrough Mappers

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## Continuous Mappers

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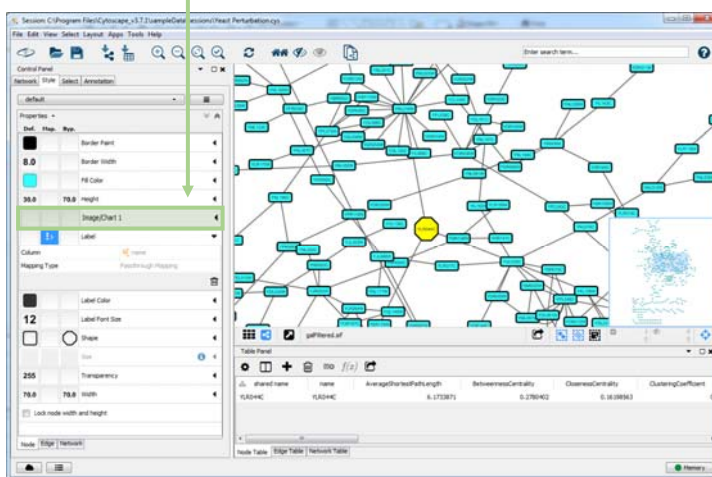
## Bypass

- Custom style for a specific node/edge

# Cytoscape: GUI

## Style modifications

Image/Chart



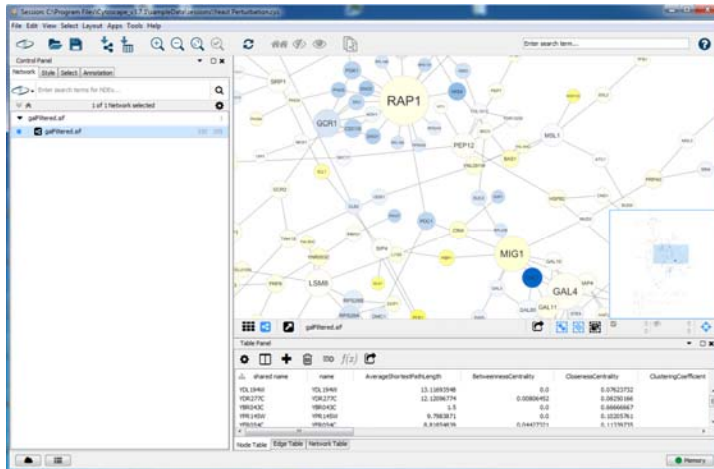
## Node Paint

- Display node as an image
- Display node as a chart



# Cytoscape

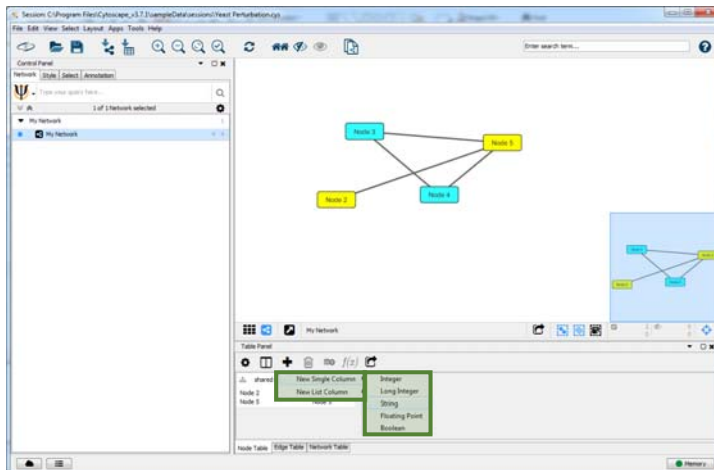
<https://cytoscape.org/>



## Topics

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- Cytoscape GUI overview
- Data sources
- Data integration
- Apps overview

# Cytoscape: Data Sources

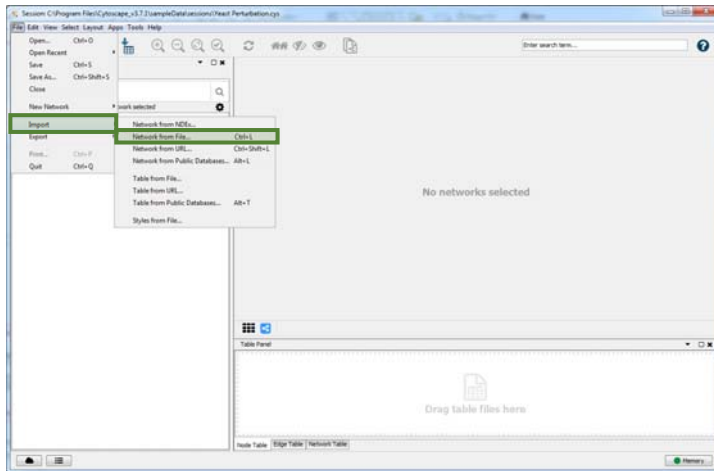


## Data entry modes

- By hand
- File import
- Built-in Web services
- Apps



# Cytoscape: Data Sources

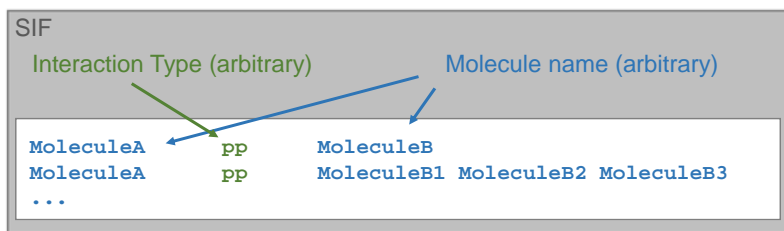


## Data entry modes

- By hand
- File import
  - Simple interaction file (SIF)
  - Delimited text
  - Excel Workbook
  - PSI-MI Level 1 and 2.5
  - Graph Markup Language (GML)
  - XGMML
  - GraphML
  - SBML
  - BioPAX
  - Nested network format (NNF)
  - Cytoscape.js JSON
  - Cytoscape CX

# Cytoscape: Data Sources

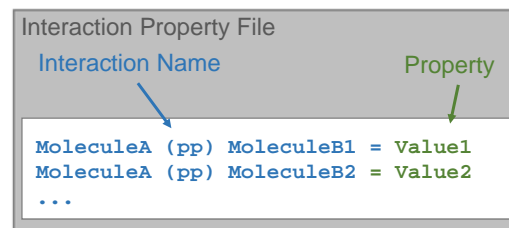
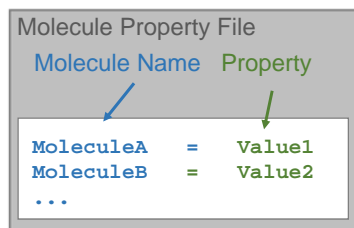
## SIF format



### Common Edge Types

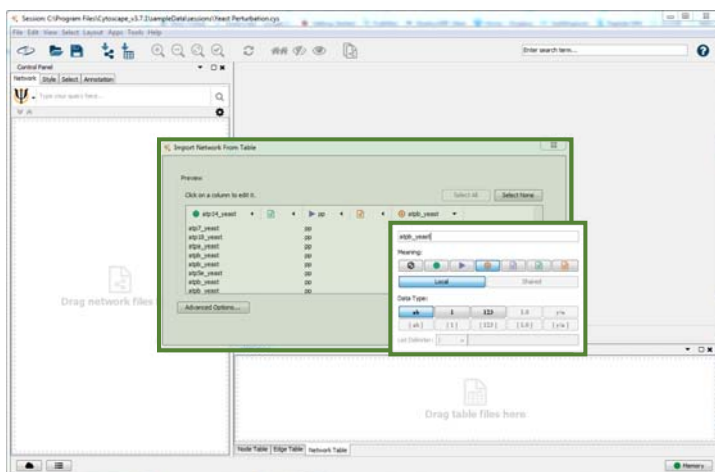
-----

pp .. protein - protein  
 pd .. protein - DNA  
 gl .. genetic lethal  
 pm .. protein-metabolite  
 mp .. metabolite-protein



## Cytoscape: Data Sources

Tabular data



### File types

- Text files (arbitrary delimiter)
- Excel files (.xls, .xlsx)

Network  
and/or  
Annotation

## Cytoscape: Data Sources

PSI-MI XML (MIF) Files

```

<?xml version="1.0" encoding="UTF-8" standalone="yes"?>
<experimentList><experimentList>
  <experiment id="2877059">
    <name>
      <shortLabel>Bmi-1</shortLabel>
    </name>
    <type>
      <experimentType>
        <name>
          <shortLabel>Bmi-1</shortLabel>
        </name>
      </experimentType>
    </type>
    <interactionList>
      <interaction id="2877059">
        <name>
          <shortLabel>Bmi-1</shortLabel>
        </name>
        <type>
          <interactionType>
            <name>
              <shortLabel>Bmi-1</shortLabel>
            </name>
          </interactionType>
        </type>
        <featureList>
          <feature id="2877062">
            <name>
              <shortLabel>Bmi-1</shortLabel>
            </name>
            <type>
              <featureType>
                <name>
                  <shortLabel>Bmi-1</shortLabel>
                </name>
              </featureType>
            </type>
          </feature>
        </featureList>
      </interaction>
    </interactionList>
  </experiment>
</experimentList>
</experimentList>
  
```



### Interaction Record

#### Interaction Experiment

Interaction Detection Method:	Pull down (MI:0096)
Experiment Host/Cell Line:	in vitro
Interaction Type:	Direct (MI:0407)

#### Participant List

Molecule Type:	Protein (MI:0326)
Molecule Name:	Cellular tumor antigen p53
Molecule Symbol:	p53
Species of Origin:	Human (Taxid:9606)
Cross-reference(s):	P04637-1 (UniProtKB), NP_00537, (RefSeq), ...

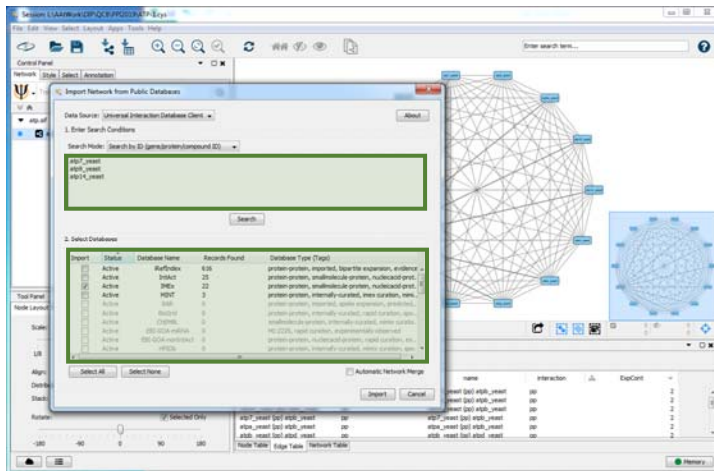
Experimental Role:	Bait (MI:0496)
Experimental Source:	E. coli K12 (Taxid: 83333)
Identification method(s):	Predetermined (MI:0396)

Features:	
Feature Type:	Sufficient binding region (MI:0442)
Feature Range:	1-73
Identification Method:	Deletion analysis (MI:0033)

1 2 ... N

1 2 ... M

## Cytoscape: Data Sources



### Data entry modes

- By hand
- File import
- Universal DB Client (PSICQUIC)

## Interaction Data Sources

Registry: <https://www.ebi.ac.uk/Tools/webservices/psicquic/registry/registry?action=STATUS>

Name	Status	Interactions	Version	URL	Description	Restricted	Type
BioRxiv	Active	2,338,337	1.3.14	SOAP: <a href="http://refindex.ebi.ac.uk/webservices/psicquic">http://refindex.ebi.ac.uk/webservices/psicquic</a> REST: <a href="http://refindex.ebi.ac.uk/webservices/current/search/">http://refindex.ebi.ac.uk/webservices/current/search/</a>	protein-protein, reported, biophysical expression, evidence	NO	protein-protein, reported, biophysical expression, evidence
BioGrid	Active	1,513,281	1.3.14	SOAP: <a href="http://www.ebi.ac.uk/Tools/webservices/psicquic">http://www.ebi.ac.uk/Tools/webservices/psicquic</a> REST: <a href="http://www.ebi.ac.uk/Tools/webservices/current/search/">http://www.ebi.ac.uk/Tools/webservices/current/search/</a>	protein-protein, internally curated, evidence, biophysical expression, evidence	NO	protein-protein, internally curated, evidence, biophysical expression, evidence
BindingDB	Active	1,011,029	v1.3	SOAP: <a href="http://bindingdb.org/psicquic">http://bindingdb.org/psicquic</a> REST: <a href="http://bindingdb.org/psicquic/webservices/current/search/">http://bindingdb.org/psicquic/webservices/current/search/</a>	small molecule, protein, internally curated, evidence, biophysical expression, evidence	NO	small molecule, protein, internally curated, evidence, biophysical expression, evidence
EMBL	Active	817,913	1.1.6	SOAP: <a href="http://www.ebi.ac.uk/Tools/webservices/psicquic">http://www.ebi.ac.uk/Tools/webservices/psicquic</a> REST: <a href="http://www.ebi.ac.uk/Tools/webservices/current/search/">http://www.ebi.ac.uk/Tools/webservices/current/search/</a>	protein-protein, internally curated, evidence	NO	protein-protein, internally curated, evidence
EMBL	Active	717,696	1.3.14	SOAP: <a href="http://www.ebi.ac.uk/Tools/webservices/psicquic">http://www.ebi.ac.uk/Tools/webservices/psicquic</a> REST: <a href="http://www.ebi.ac.uk/Tools/webservices/current/search/">http://www.ebi.ac.uk/Tools/webservices/current/search/</a>	EMBL contains experimentally verified protein interaction reports annotated by members of the EMBL Consortium	NO	protein-protein, experimentally verified, evidence, biophysical expression, evidence

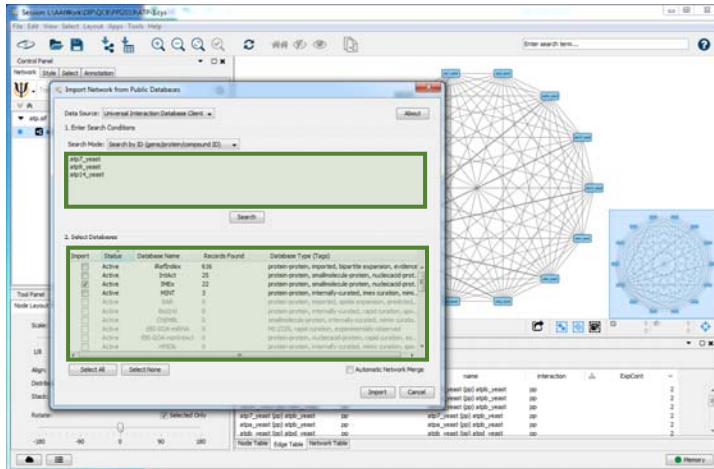
### Programmatic access to interaction data

- SOAP & REST APIs
- Results returned as PSI-MI, MITAB, etc
- MIQL Queries  
(brca1 or brca2) and species:human  
(atpa\_yeast or atpb\_yeast) and type:"physical association"

### References

- <https://psicquic.github.io/MiqlDefinition.html>
- Aranda *et al.* PSICQUIC and PSISCORE: accessing and scoring molecular interactions. Nat Methods. 8:528-9 (2011) PMID:21716279
- Nucleic Acids Res. del-Toro *et al.* A new reference implementation of the PSICQUIC web service. NAR 41:W601-606 (2013) PMID:2367134

## Cytoscape: Data Sources



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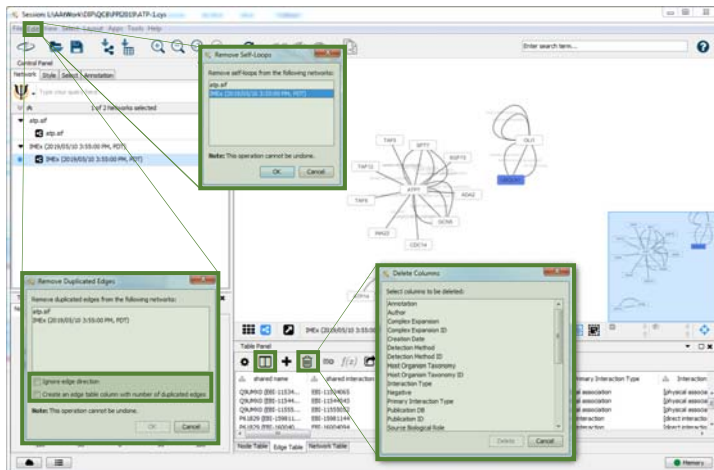
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- File import
- Universal DB Client (PSICQUIC)

### Caveats

- Different providers might use different protein identifiers
- One edge per experiment
- Directed edges
- Possible cross-species interactions
- A lot of attributes

**Often requires cleanup !!!**

## Cytoscape: Data Sources



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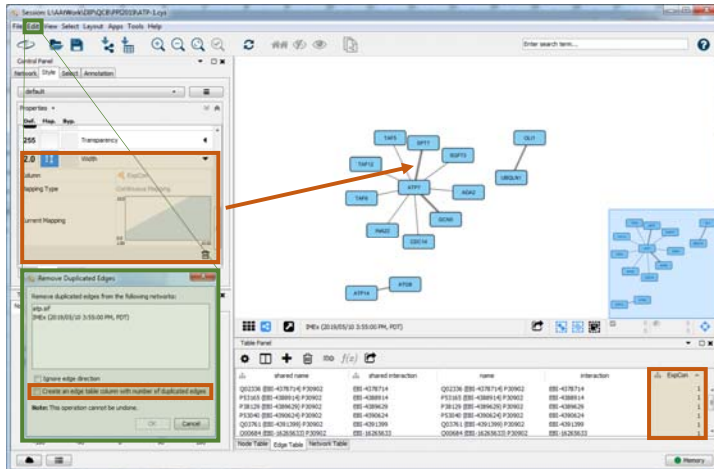
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