

Protein-Protein Interactions

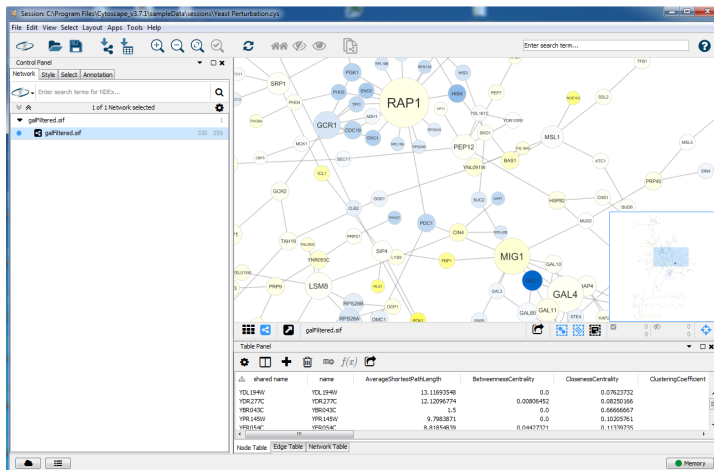
Introduction to Cytoscape

May 2019

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 Boyer Hall 205

Cytoscape

<https://cytoscape.org/>

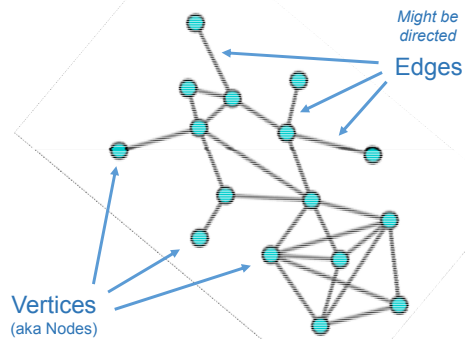


Topics

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

Cytoscape: Data model

Anatomy of a Graph



Network = Graph + Attributes

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

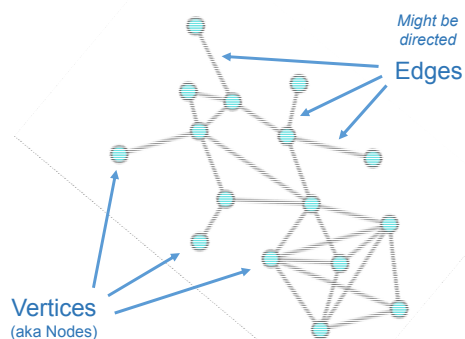
Béla Bollobás. *Random Graphs*.
Cambridge University Press. ISBN: 978-0-521-80920-7

Popular Science

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

Cytoscape: Data model

Anatomy of a Graph

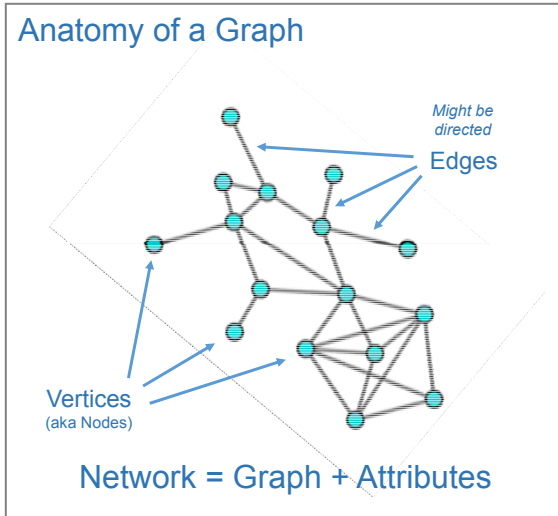


Network = Graph + Attributes

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

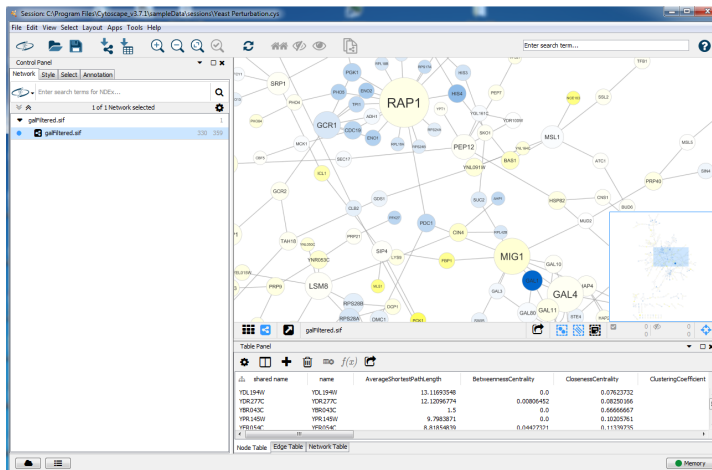


Interaction Networks

- 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/>

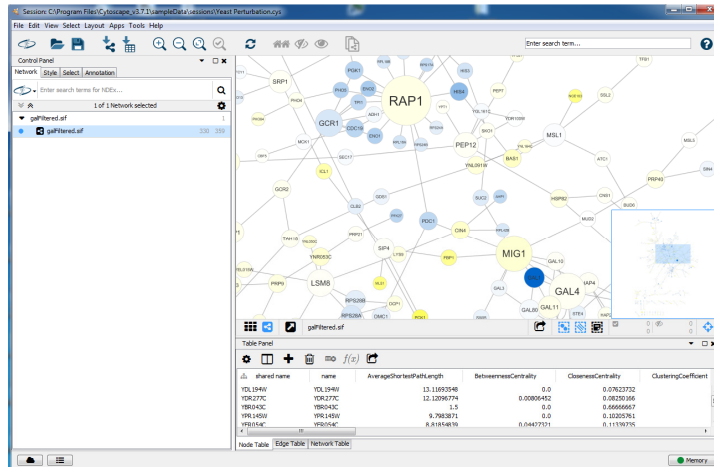


Key features

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

Cytoscape: GUI

Layout modifications



Individual nodes

- Select (LBM) and drag

Groups of nodes

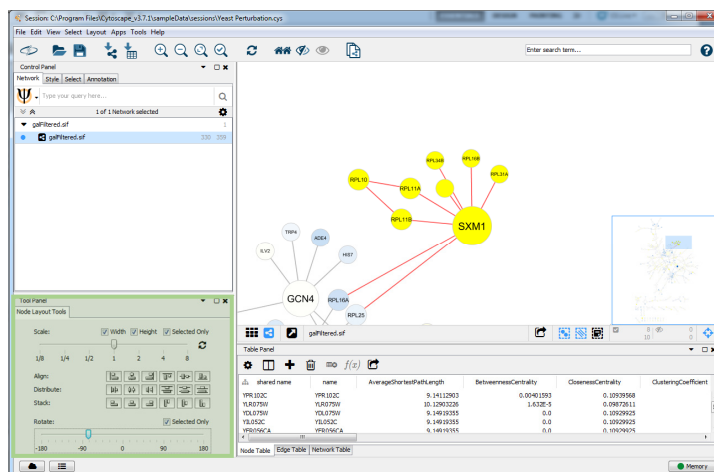
- Select (shift-LBM)
- Drag (LBM) to translate
- Use Tool Panel to translate and scale

Entire network

- Use layout menu
- Some algorithms work on node selections

Cytoscape: GUI

Layout modifications



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Groups of nodes

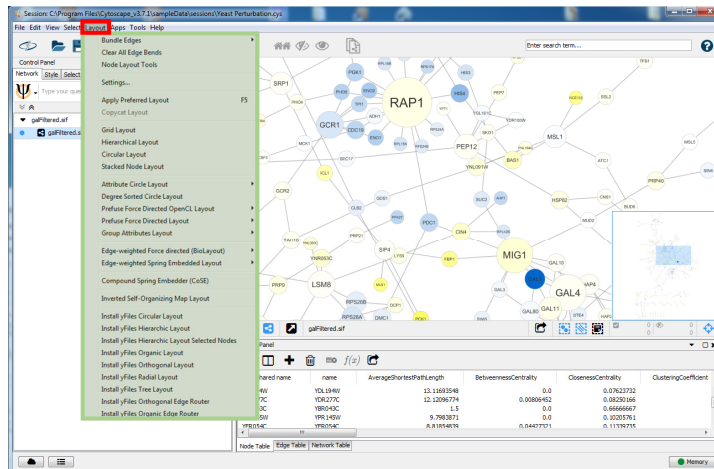
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Cytoscape: GUI

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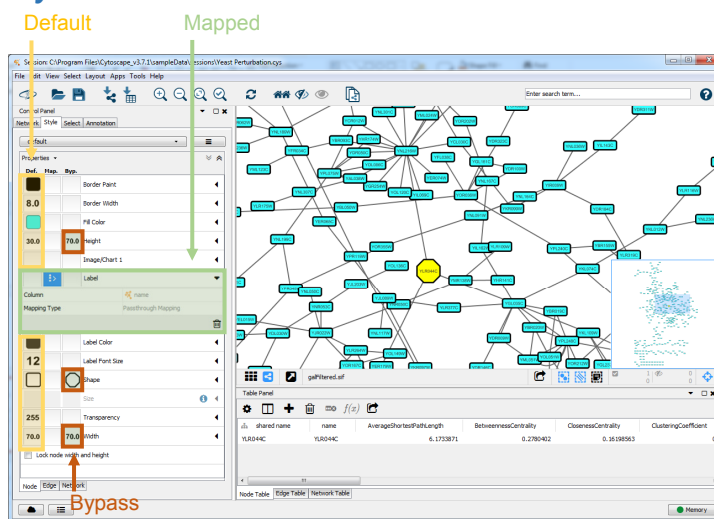
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Cytoscape: GUI

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

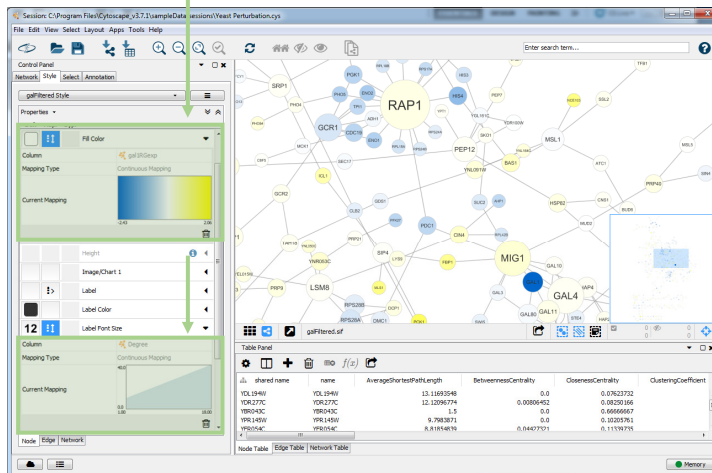
Bypass

- Custom style for a specific node/edge

Cytoscape: GUI

Style modifications

Mapped



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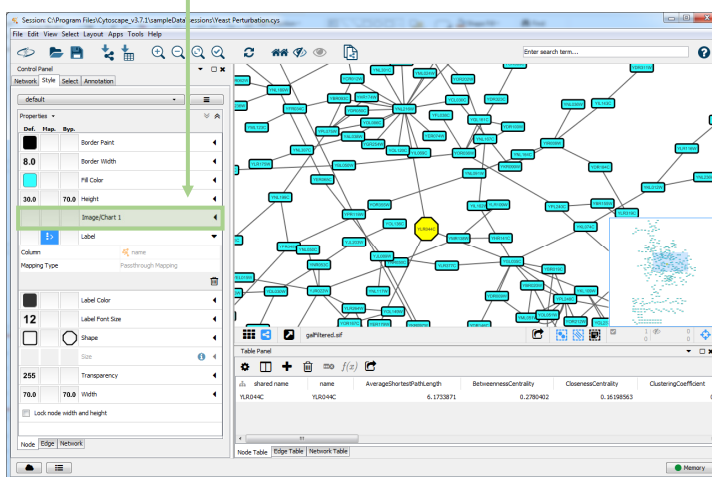
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Cytoscape: GUI

Style modifications

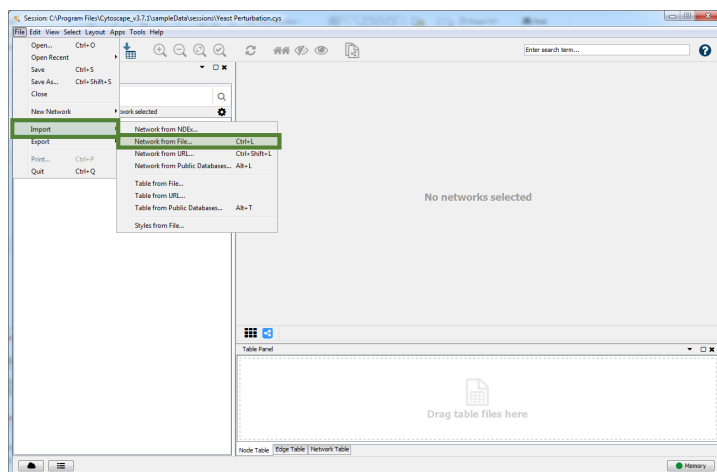
Image/Chart



Node Paint

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

Cytoscape: Data Sources

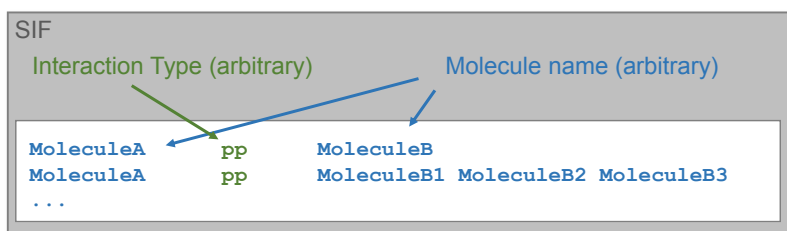


Data entry modes

- 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

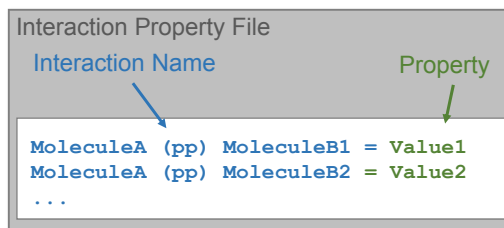
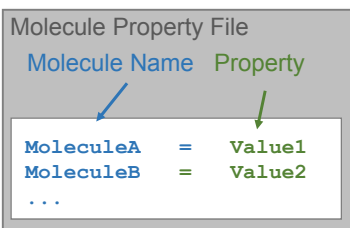
SIF format



Common Edge Types

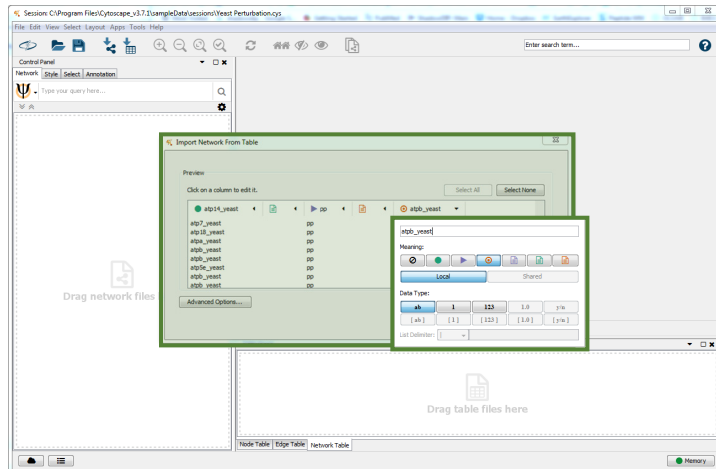
```

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"?>
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    <name>
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      <shortLabel>bem1-cla1-1</shortLabel>
    </description>
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      </name>
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      </description>
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  <experiment id="287071"></experiment>
  <experiment id="287078"></experiment>
  <experiment id="287084"></experiment>
</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)

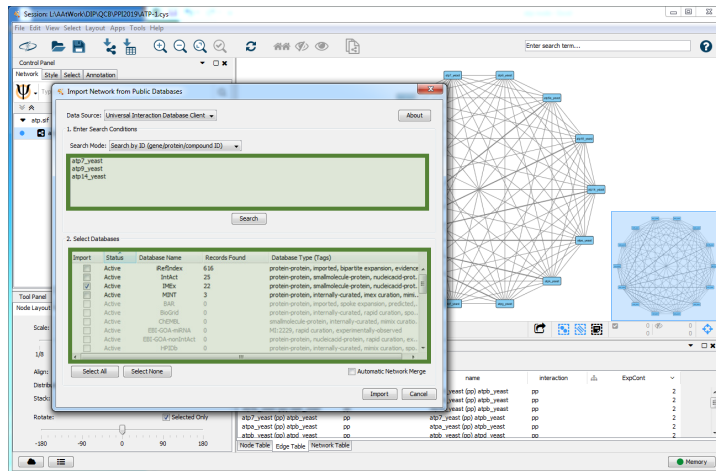
Features

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	URLs	Description	Restricted	Tags
RefIndex	●	2,338,337	1.3.14	SOAP: http://refindex.ebi.ac.uk/webservices/psicquic REST: http://refindex.ebi.ac.uk/webservices/current/search/		NO	protein:protein imported biogenic expansion evidence
BioGRID	●	1,513,281	1.3.14	SOAP: http://www.ebi.ac.uk/Tools/webservices/psicquic REST: http://www.ebi.ac.uk/Tools/webservices/psicquic		NO	protein:protein internally curated rapid curation spouse expansion evidence
BindingDB	●	1,011,029	v1.3	SOAP: http://bindingdb.org/psicquic-we REST: http://bindingdb.org/psicquic-we/webservices/psicquic		NO	smallmolecule: protein internally curated evidence spouse expansion experimentally observed
I2D	●	617,915	1.1.6	SOAP: http://ophid.utoronto.ca/psicquic-we/webservices REST: http://ophid.utoronto.ca/psicquic-we/webservices/current/search/		NO	protein:protein internally curated evidence
IMEx	●	717,696	1.3.14	SOAP: http://www.ebi.ac.uk/Tools/webservices/psicquic REST: http://www.ebi.ac.uk/Tools/webservices/psicquic	IMEx contains experimentally verified protein interaction records annotated by members of the IMEx Consortium	NO	protein:protein smallmolecule: protein nucleotide:protein internally curated

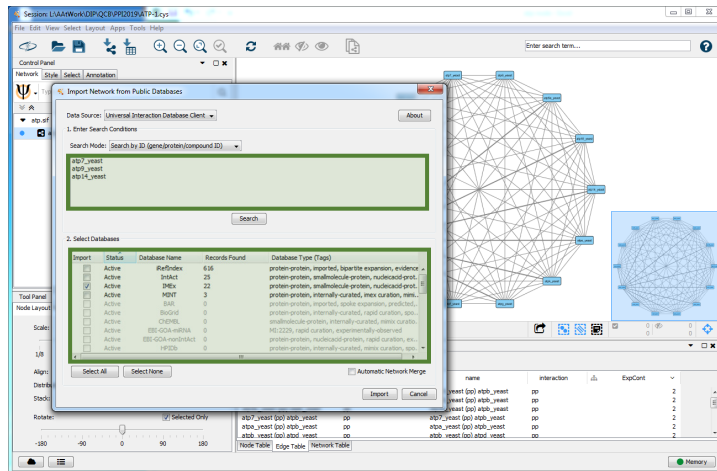
Programmatic access to interaction data

- 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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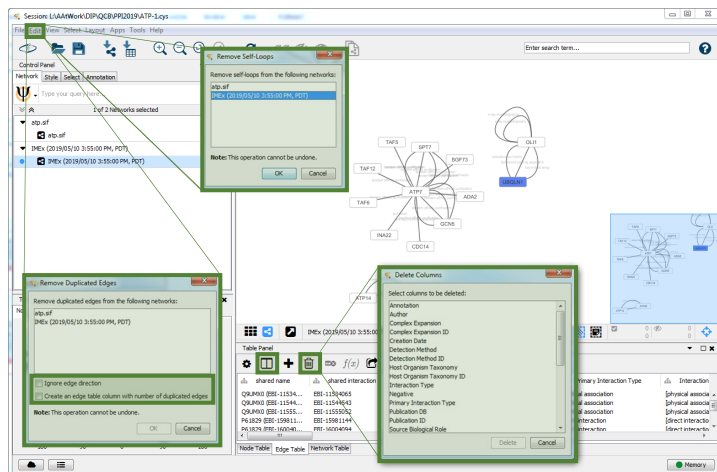
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Caveats

- 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



Data entry modes

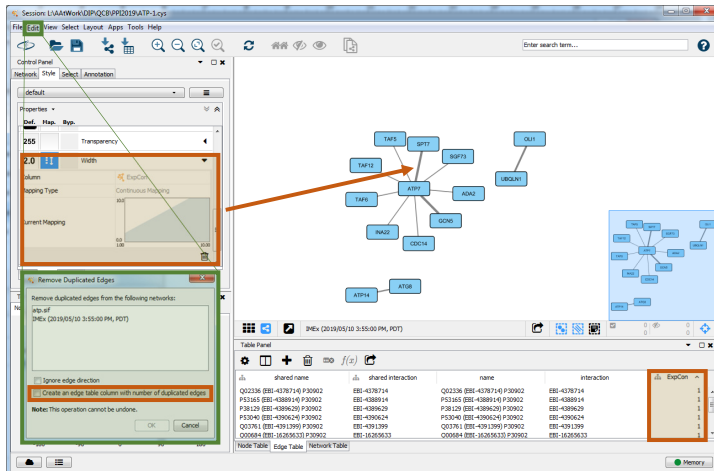
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