



# Canadian Bioinformatics Workshops

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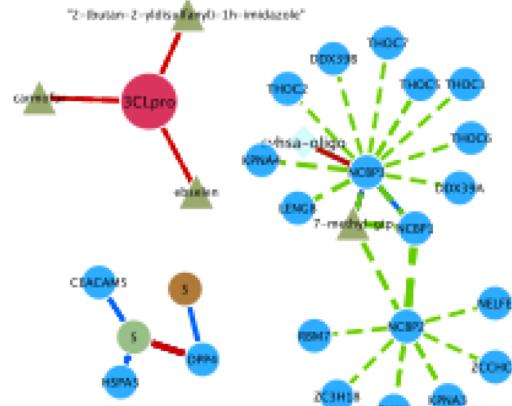
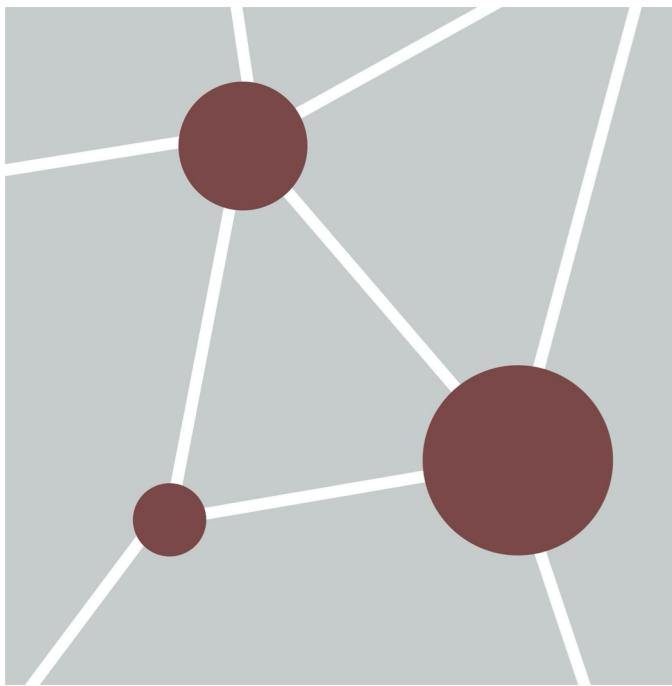
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# Module 3

# Network Visualization and analysis with Cytoscape



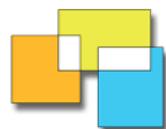
Ruth Isserlin  
Pathway and Network Analysis of -omics Data  
May, 10-12, 2021



**BADER**  
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Cellular & Biomolecular Research  
UNIVERSITY OF TORONTO

# Learning Objectives

- By the end of this lecture, you will:
  - Understand the advantages of network visualization.
  - Understand how to choose and install Cytoscape Apps
  - Be able to use basic Cytoscape features
  - Be able to create and optimize a network in Cytoscape

# Network Visualization and Analysis Outline

- Introduction
  - Network Basics
  - Network Visualization
  - Network Analysis
- 
- Demo: Cytoscape software tool for Network visualization and analysis

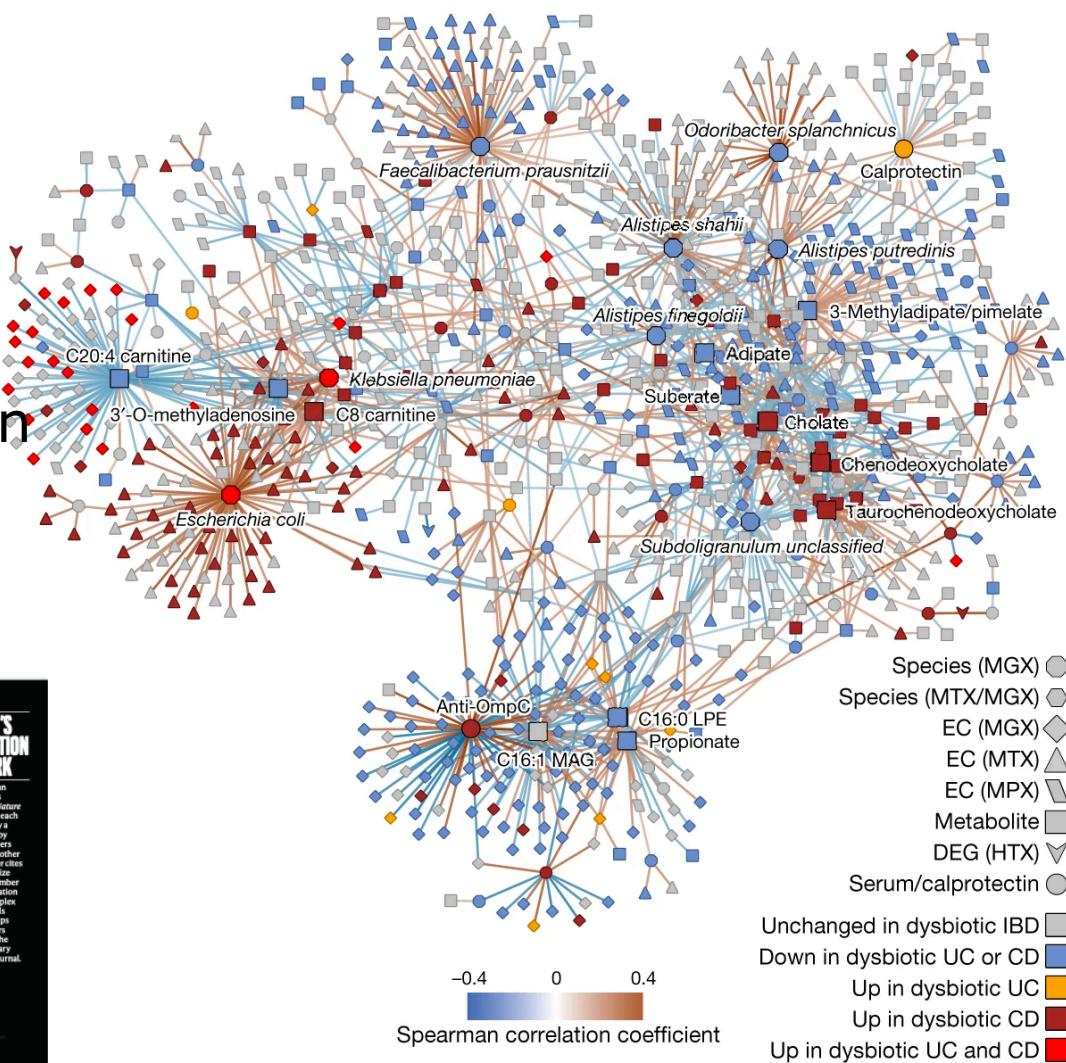
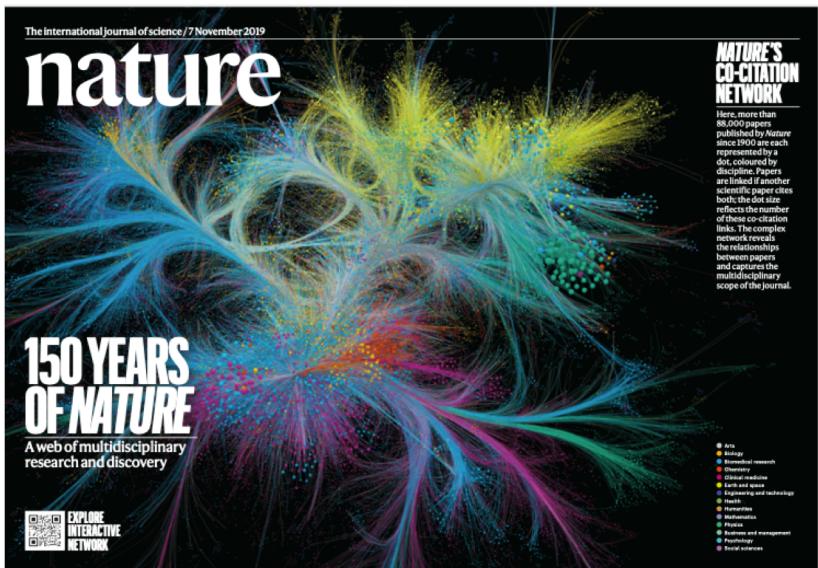
# Six Degrees of Separation

- Everyone in the world is connected by at most six links.
- Originally demonstrated by Stanely Milgram at Harvard in 1960s in an experiment to find how many random acquaintances it would take to connect two people.... sometimes defined as the the **social distance** between two people.
- Popularized in the 1990s with six degrees of Kevin Bacon.
- Demonstrated the interconnectivity of our social structures.
- Networks exists everywhere – power grids, cell tower networks, Fed ex delivery networks, supply chain networks ....
- Is this Biologically relevant?

# Why Networks?

Networks are everywhere....

- Molecular networks
- Cell-Cell Communication
- Nervous systems
- Social Networks



Lloyd-Price, J., Arze, C., Ananthakrishnan, A.N. et al. Multi-omics of the gut microbial ecosystem in inflammatory bowel diseases. *Nature* **569**, 655–662 (2019)

# Why Networks?

Networks are powerful tools....

- Reduce complexity
- More efficient than tables
- Great for data integration
- Intuitive visualization

 SARS-CoV-2 viral protein (26)

 Human protein (332)

 Drug target (62/332)

— Human–human PPI

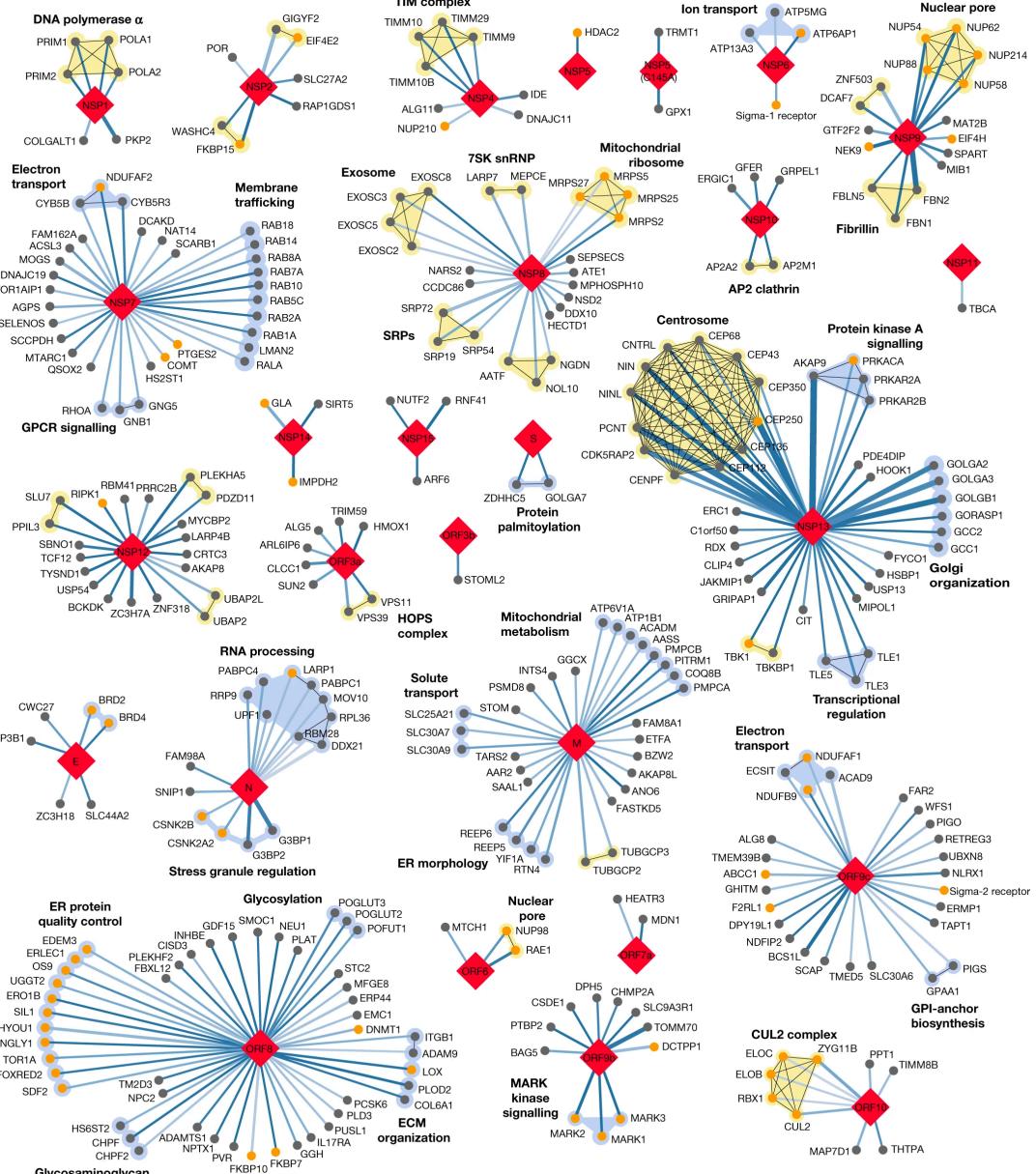
1.0 MIST score

 Protein complex

181 Spectral count

 Biological process

## SARS-CoV-2 protein-protein interaction Network



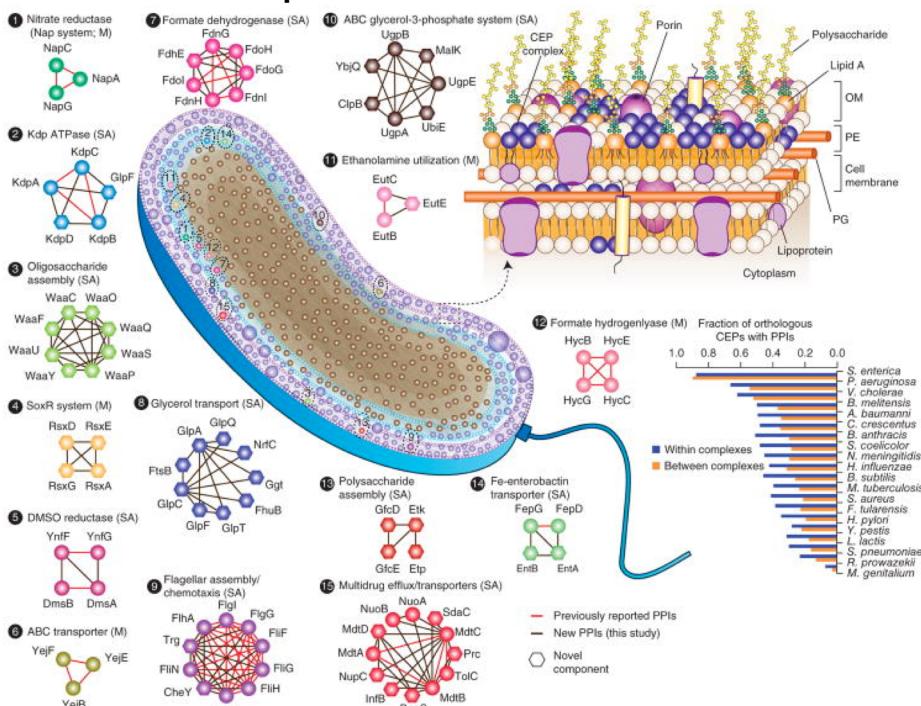
Gordon, D.E., Jang, G.M., Bouhaddou, M. et al. A SARS-CoV-2 protein interaction map reveals targets for drug repurposing. *Nature* **583**, 459–468 (2020).

# Why Would We Use Network Visualization for Biological Data?

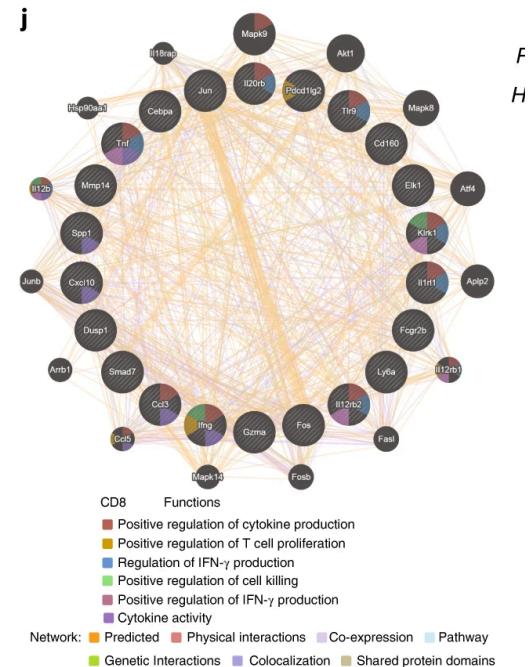
- Represent relationships of biological molecules
  - Physical, regulatory, genetic, functional interactions
- Useful for discovering relationships in large data sets
  - Better than tables in Excel
- Visualize multiple data types together
  - Discover interesting patterns
- Network analysis
  - Finding sub-networks with certain properties (densely connected, co-expressed, frequently mutated, clinical characteristics)
  - Finding paths between nodes (or other network “motifs”)
  - Finding central nodes in network topology (“hub” genes)

# Applications of Network Biology

**Detection of protein complexes/other modular structures** – identification of subnetworks of interconnected nodes that might work together to perform a specific function, i.e. molecular complexes.



**Gene Function Prediction** – associate novel gene to existing function or pathway



Wang, Z., Aguilar, E.G., Luna, J.I. et al. Paradoxical effects of obesity on T cell function during tumor progression and PD-1 checkpoint blockade. *Nat Med* **25**, 141–151 (2019)

Babu M, Bundalovic-Torma C, Calmettes C, et al. Global landscape of cell envelope protein complexes in *Escherichia coli*. *Nat Biotechnol*. 2018;36(1):103-112

# Applications of Network Biology

## **Subnetwork based diagnosis –**

biomarker or biomarker panel.

Identification of subnetworks activated in disease

## **Network Alignment and comparison –**

analyze evolution of networks between different species to identify similarities and evolutionary relationships

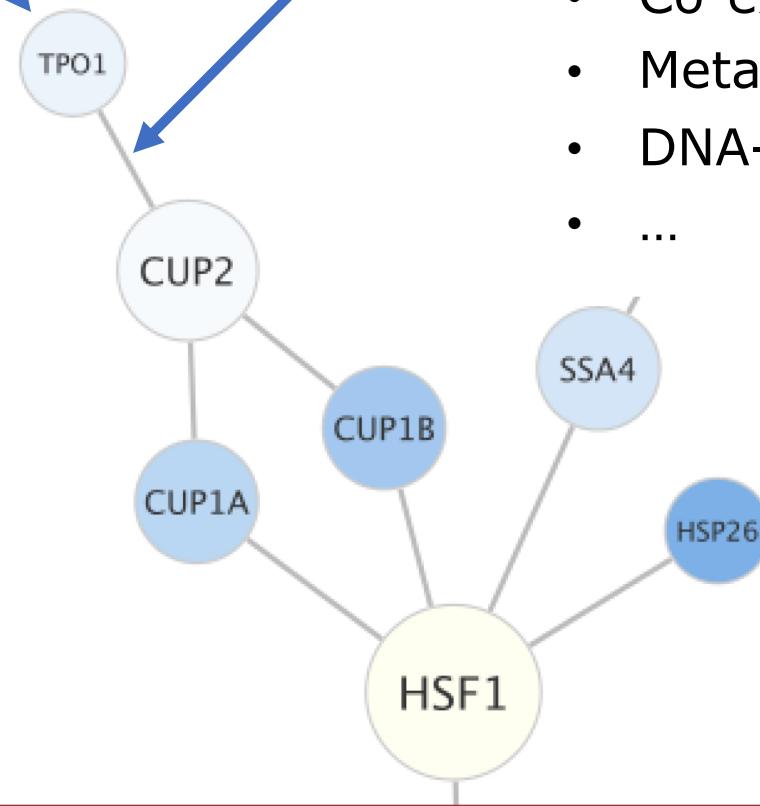
**Motif analysis –** discover higher order organization such motifs, feedback loops (small network patterns that are over-represented when compared to a randomized version of the same network)

**Pathway based gene association –** uncovering common pathways disturbed during disease.

# Network Basics

## **Node (molecule/entity)**

- Gene
- Protein
- Transcript
- Drug
- MicroRNA
- ...



## **Edge (interaction/relationship)**

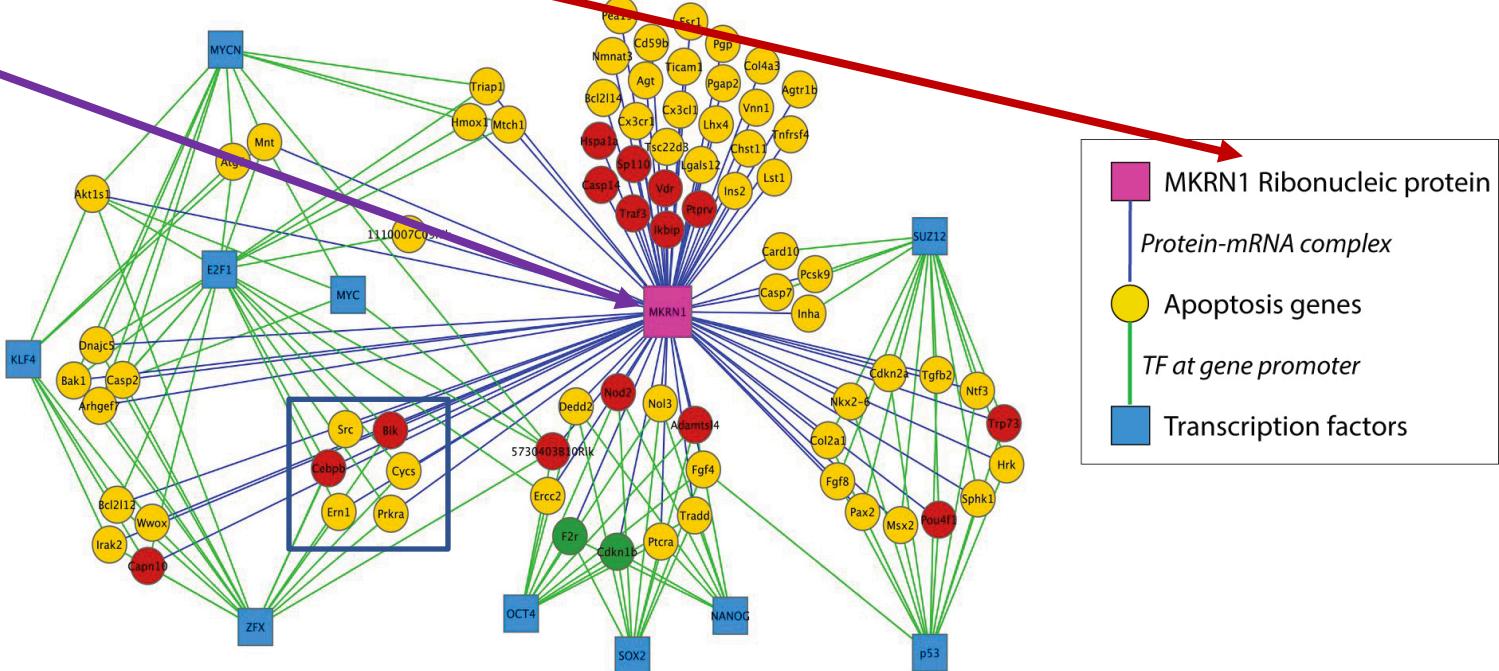
- Genetic interaction
- Physical protein interaction
- Co-expression
- Metabolic reaction
- DNA-binding
- ...

# Networks as Tools

## Analysis

- Topological properties
  - Hubs and subnetworks
  - Classify, cluster, diffuse and over-representation
  - Data integration

→ **Topological properties:**  
Number of nodes and edges  
Node degree  
Degree distribution  
Clustering coefficients

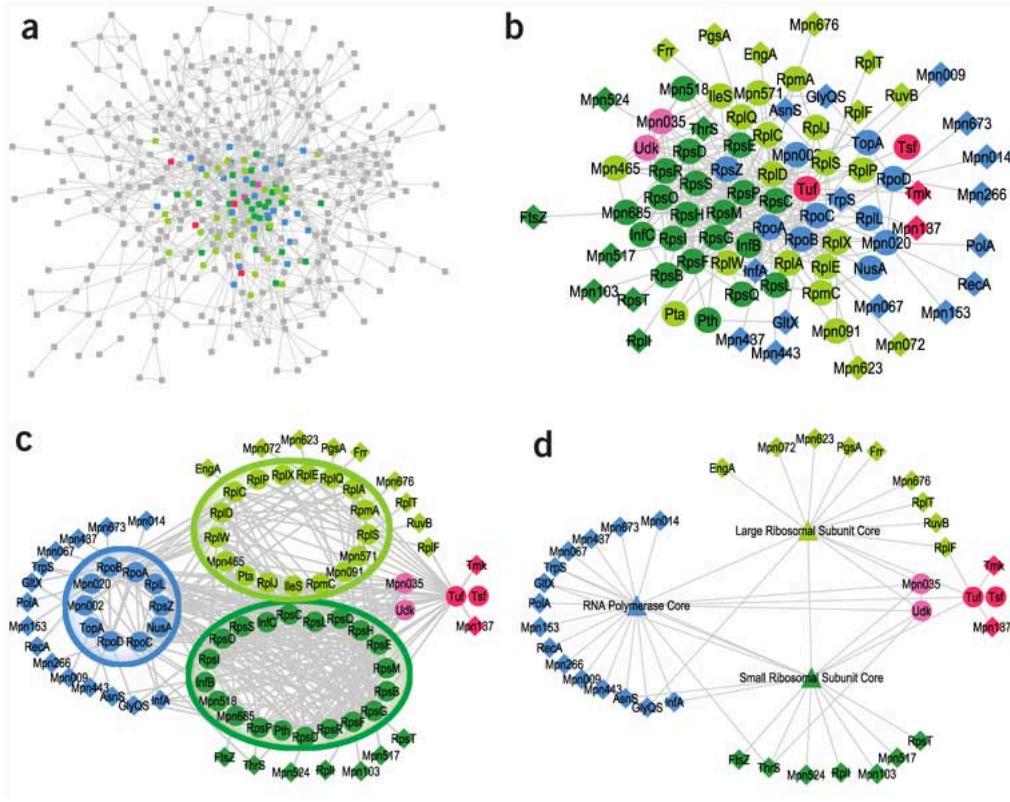


# Networks as Tools

## Visualization

- Data overlays – integrate multiple data types
- Layouts
- Exploratory analysis
- Context and interpretation

- (a) Mass spectrometry analysis: 400 PPI in pneumonia microbe.
- (b) Subnetwork with functional annotations
- (c) Same network as (b) with added knowledge of complexes
- (d) Same network as (c) with complexes collapsed to group nodes to reduce complexity



Gehlenborg N, O'Donoghue SI, Baliga NS, et al. Visualization of omics data for systems biology. *Nat Methods*. 2010;7(3 Suppl):S56-S68

# 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

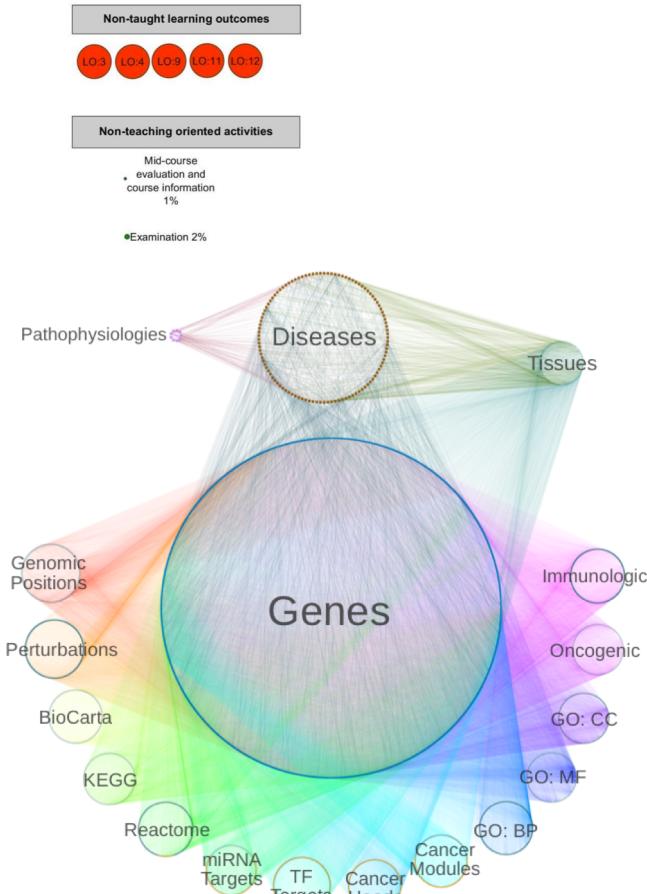
# Network Visualization and Analysis using Cytoscape

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



# Cytoscape ([cytoscape.org](http://cytoscape.org))

- An open source software platform for visualizing and analyzing complex networks.



<https://nrnb.org/competitions.html>

# Cytoscape ([cytoscape.org](http://cytoscape.org))

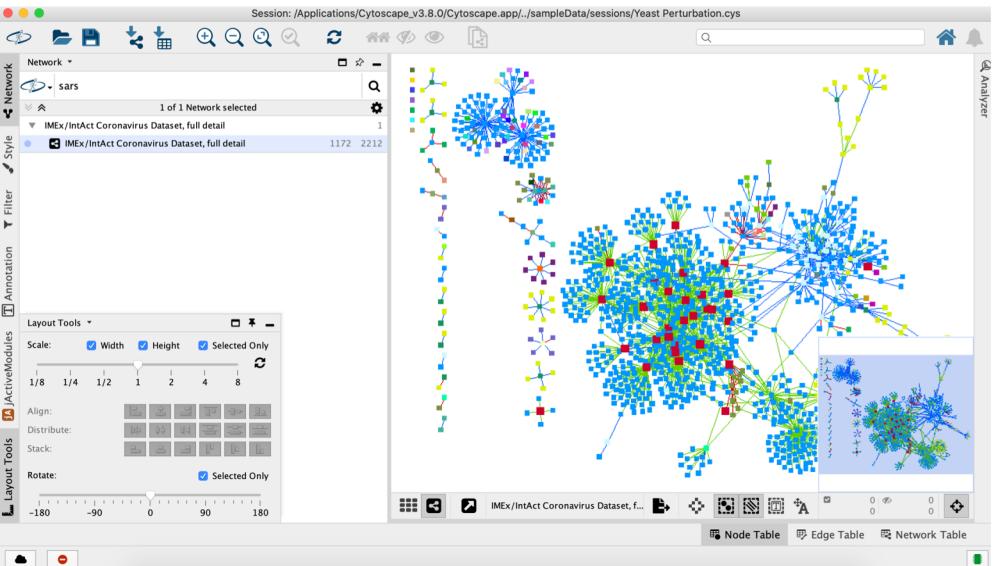


Partners and Collaborators

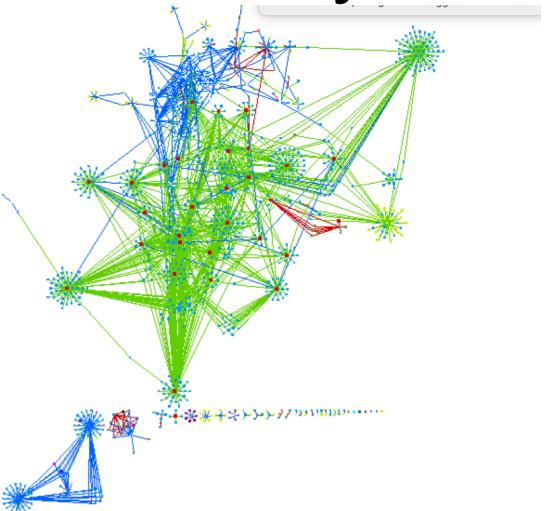
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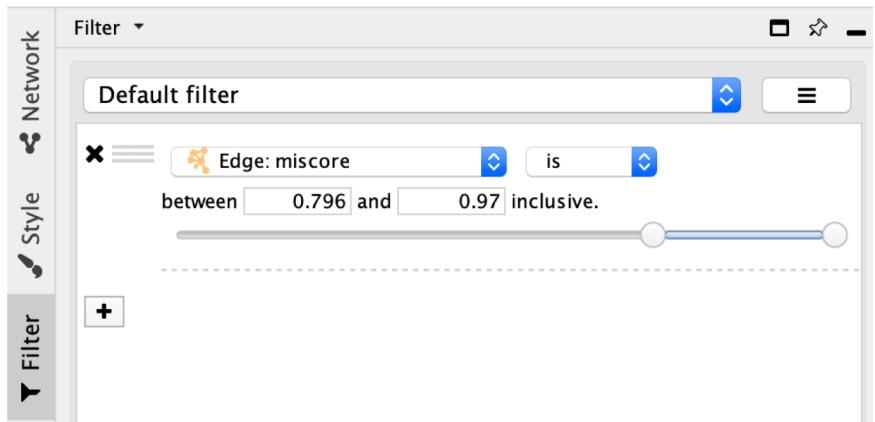
# Manipulate Networks



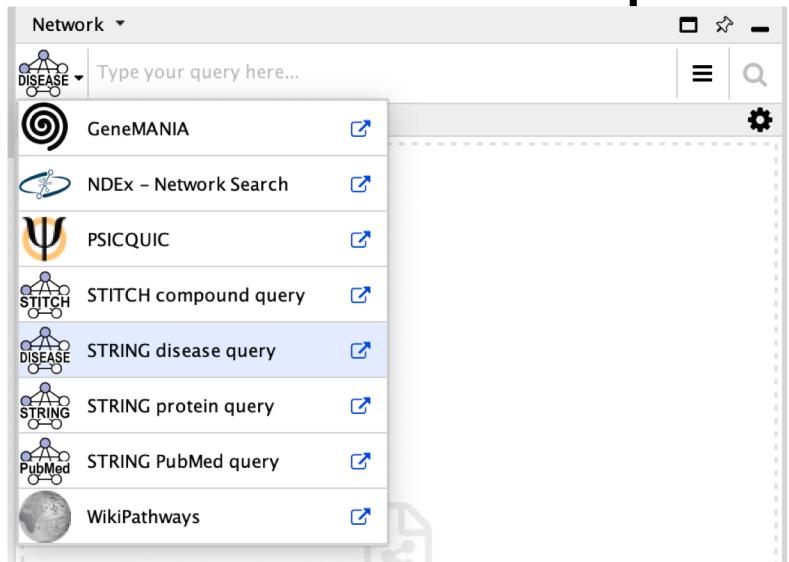
## Automatic Layout



# Filter/Query



## Network Import



# The Cytoscape App Store

Cytoscape App Store

Submit an App

Search the App Store

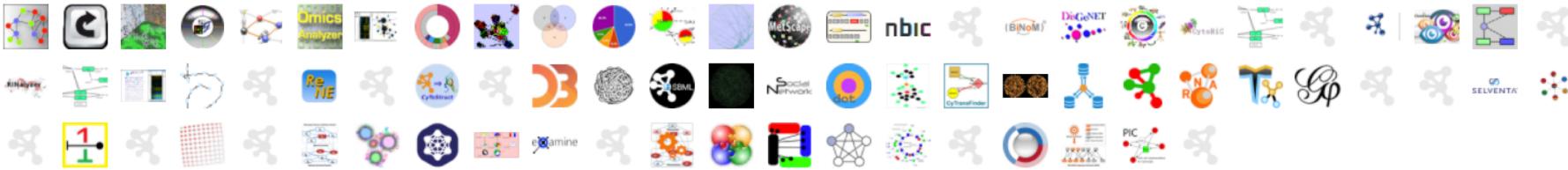
Sign In

Wall of Apps 361 total

collections



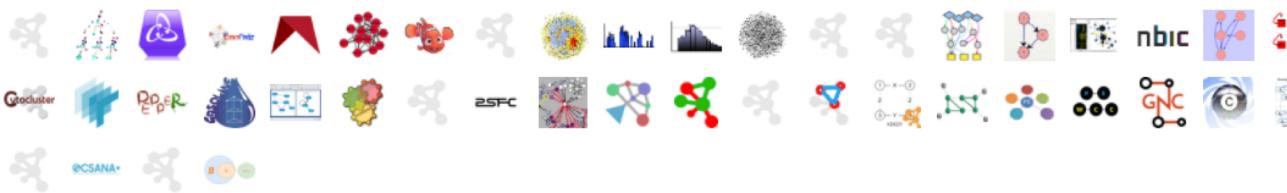
data visualization



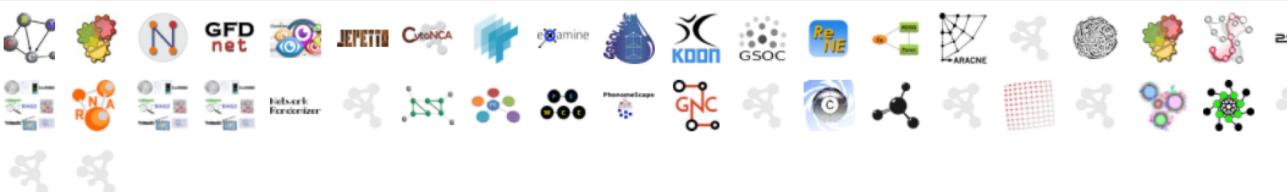
network generation



graph analysis



network analysis



<http://apps.cytoscape.org>

**Categories:**  
Data visualization  
Network generation  
Graph analysis  
Network analysis  
Online data import  
Automation  
Clustering  
Integrated analysis  
Utility  
Enrichment analysis  
Layout  
Network Comparison

# Active Community

<http://www.cytoscape.org>

- 10,000s users, >17,600 downloads/month (May 2018)
- Help
  - Documentation, data sets
  - Mailing lists
  - <http://tutorials.cytoscape.org>
- Automatable through R or python using cyrest
- Cited 2121 (google scholar), 1,437 (ISI web of Science)
- >361 Apps Extend Functionality (July 2020)
  - Build your own, requires programming

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

# What Have We Learned?

- Cytoscape is a useful, free software tool for network visualization and analysis
- Provides basic network manipulation features
- Apps are available to extend the functionality



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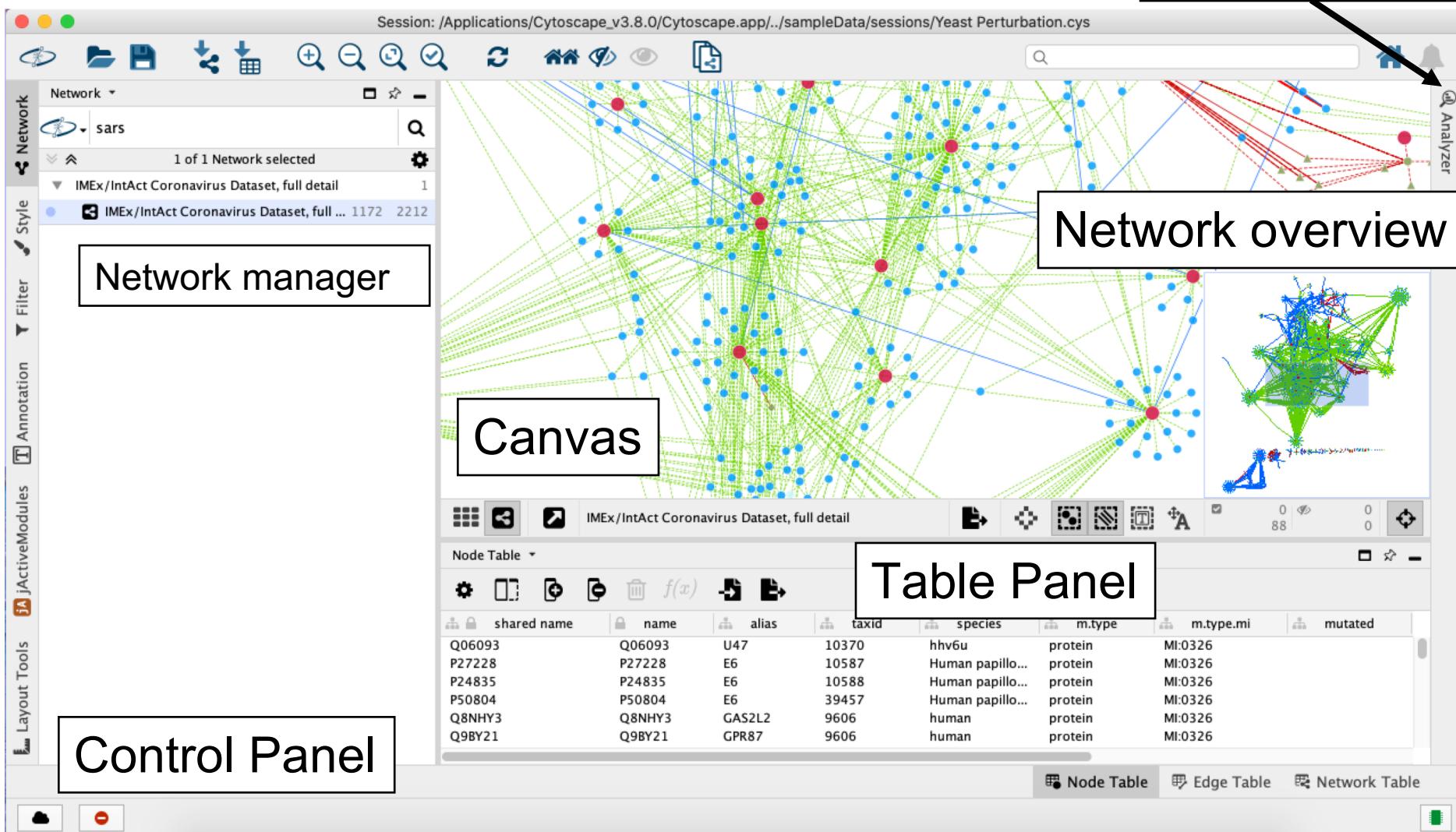
# Cytoscape Demo

Version 3.8.0

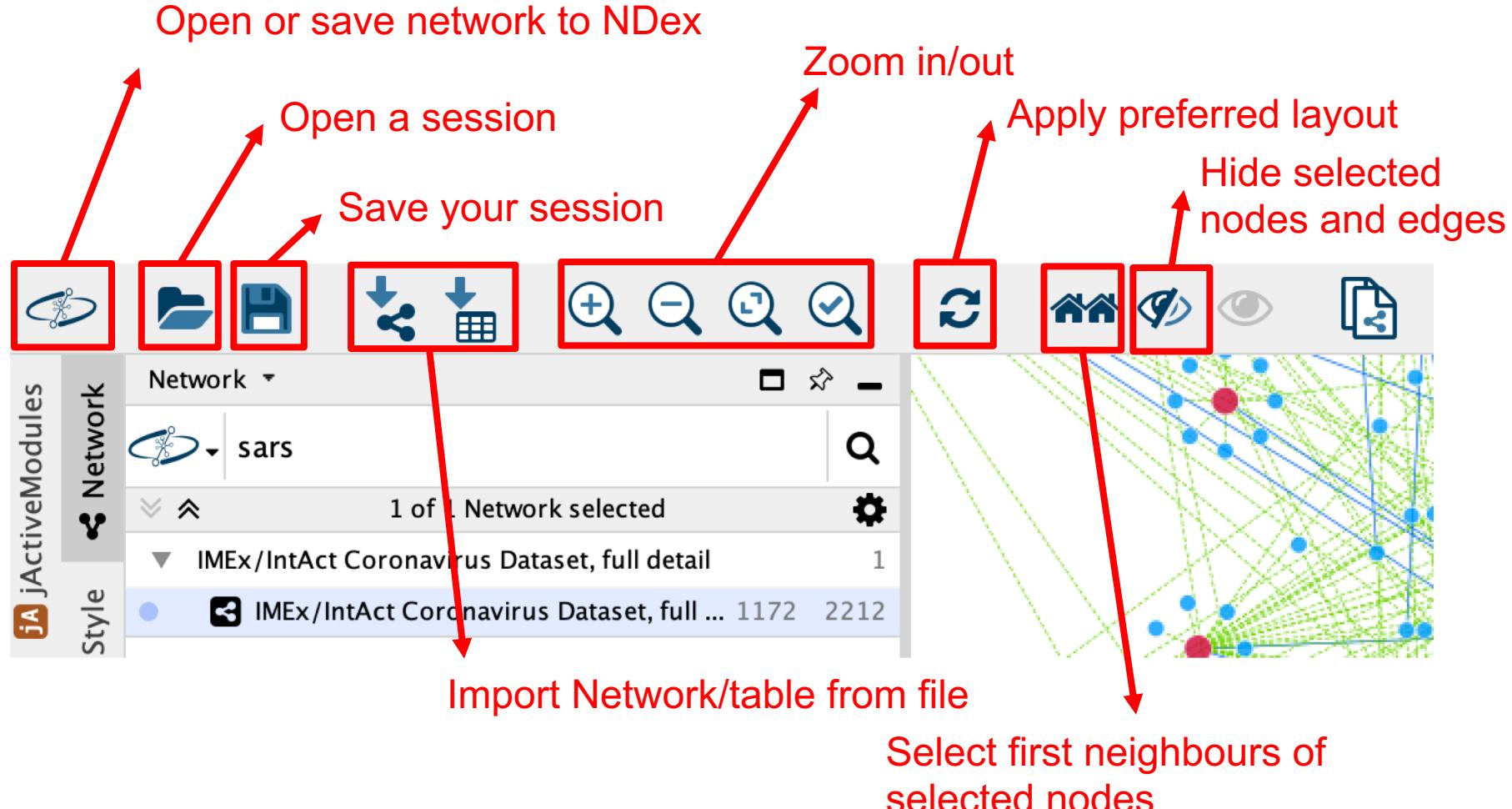
[www.cytoscape.org](http://www.cytoscape.org)

# Interface Overview

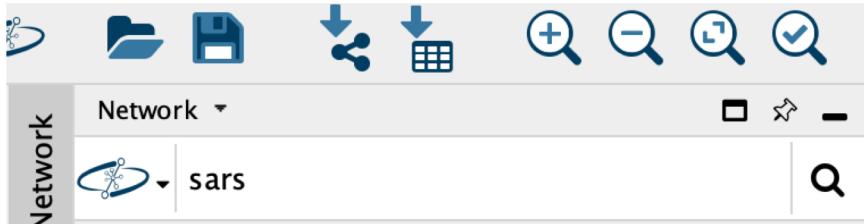
## Results Panel



# Basic Navigation



# Load a Network



Enter a search term into Network search bar. I am using Ndex-  
(<https://home.ndexbio.org/index/>)

Find Networks

NDEx

Sign in

sars

Results

name owner visibility nodes edges modified

name	owner	visibility	nodes	edges	modified
BioGRID: Protein-Protein Interactions (HIV-1)	biogrid	PUBLIC	1146	1338	2020-06-20, 12:40 p.m.
BioGRID: Protein-Protein Interactions (X. laevis)	biogrid	PUBLIC	1153	1259	2020-06-20, 12:13 p.m.
IMEx / IntAct Coronavirus Dataset, collapsed e...	pporras	PUBLIC	1172	1778	2020-06-15, 5:41 a.m.
IMEx/IntAct Coronavirus Dataset, full detail	pporras	PUBLIC	1172	2212	2020-06-15, 5:40 a.m.
IMEx/IntAct Coronavirus Dataset, binding regi...	pporras	PUBLIC	1172	2212	2020-06-15, 5:40 a.m.
IMEx/IntAct Coronavirus Dataset, mutations de...	pporras	PUBLIC	1172	2212	2020-06-15, 5:40 a.m.
WP3888 – VEGFA-VEGFR2 Signaling – Homo sa...	wikipathways	PUBLIC	1186	509	2019-12-16, 4:24 p.m.
Bandyopadhyay et al., NATURE METHODS (201...	rudipillich	PUBLIC	1346	2272	2018-02-07, 3:37 p.m.
SMPDB: Protein-Pathway Associations	ndexbutler	PUBLIC	1753	14187	2019-09-19, 9:19 p.m.
ProteomeHD – Top 0.5% Co-Regulated Proteins...	proteomehd	PUBLIC	2718	63290	2019-09-20, 2:23 p.m.
BioGRID: Protein-Protein Interactions (R. norve...	biogrid	PUBLIC	4148	7186	2020-06-20, 12:38 p.m.
Drugbank Database – v4.3	drugbank	PUBLIC	4606	9652	2016-05-03, 3:40 p.m.

Click on download arrow to load network into Cytoscape

WARNING: In some cases, not all network information stored in NDEx will be available within Cytoscape after loading.

Close Dialog

# About the network

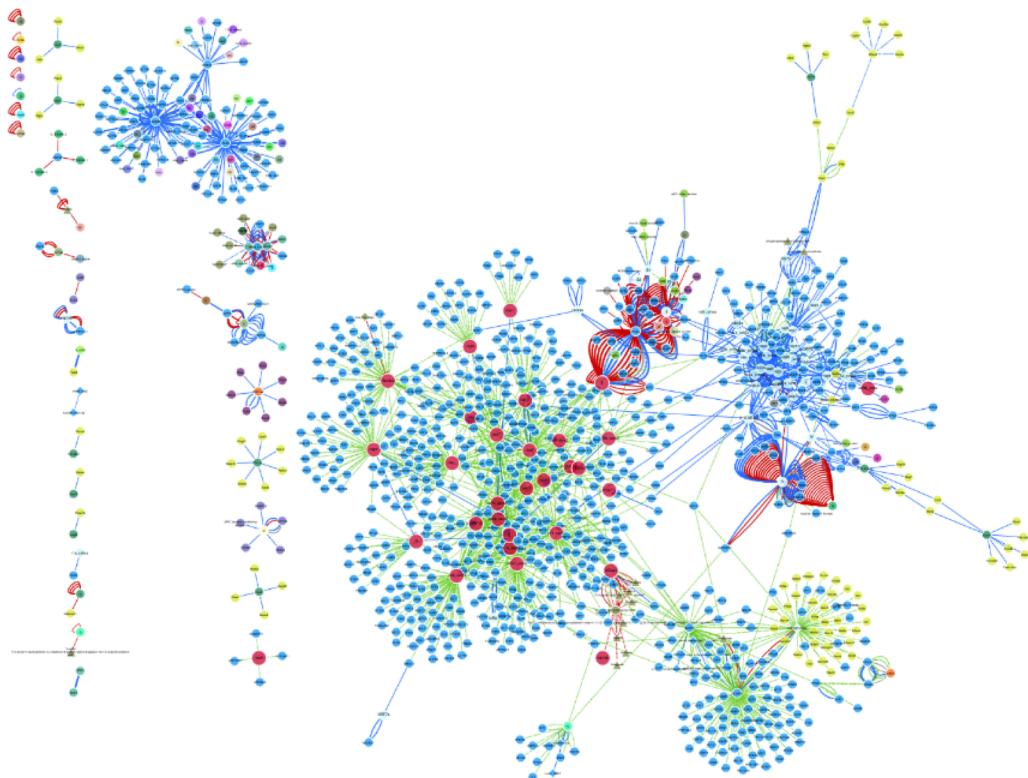
<http://ndexbio.org/#/network/3e13a4de-a4d7-11ea-aaef-0ac135e8bacf>



About Docs Report Bug Contact Us FAQ



Login/Register



Network Info Nodes/Edges

## IMEx/IntAct Coronavirus Dataset, full detail

DOI: 10.18119/N9RC8F

Nodes: 1172 Edges: 2212

PUBLIC @context: [view namespaces](#)

Owner Pablo Porras Millan

Created Jun 2, 2020 9:44:55 AM

Last Modified Jun 15, 2020 5:40:49 AM

UUID 3e13a4de-a4d7-11ea-aaef-0ac135e8bacf

### Description:

Full Coronavirus dataset as extracted from IntAct on May 2020. Each edge represents a separate piece of evidence for an interaction, with edge colour representing different interaction types. Dashed lines represent spoke-expanded interactions. Node colour represents different species origin and node shape different molecule types. SARS-CoV-2 and SARS proteins are represented as larger nodes for ease of identification. A short description of the dataset can be found here: <https://www.ebi.ac.uk/intact/resources/datasets>. Browse and download detailed interaction data on the IntAct website at: <https://www.ebi.ac.uk/intact/query/annot%22dataset:coronavirus%22>

Rights Holder: IMEx Consortium

Rights: Attribution 4.0 International (CC BY 4.0)

Version: 1.0

### Properties:

author IMEx Consortium Curators & Pablo Porras

disease COVID19, SARS

organism SARS-CoV-2, SARS, Coronaviridae, human, mouse, mammal

# Visual Styles

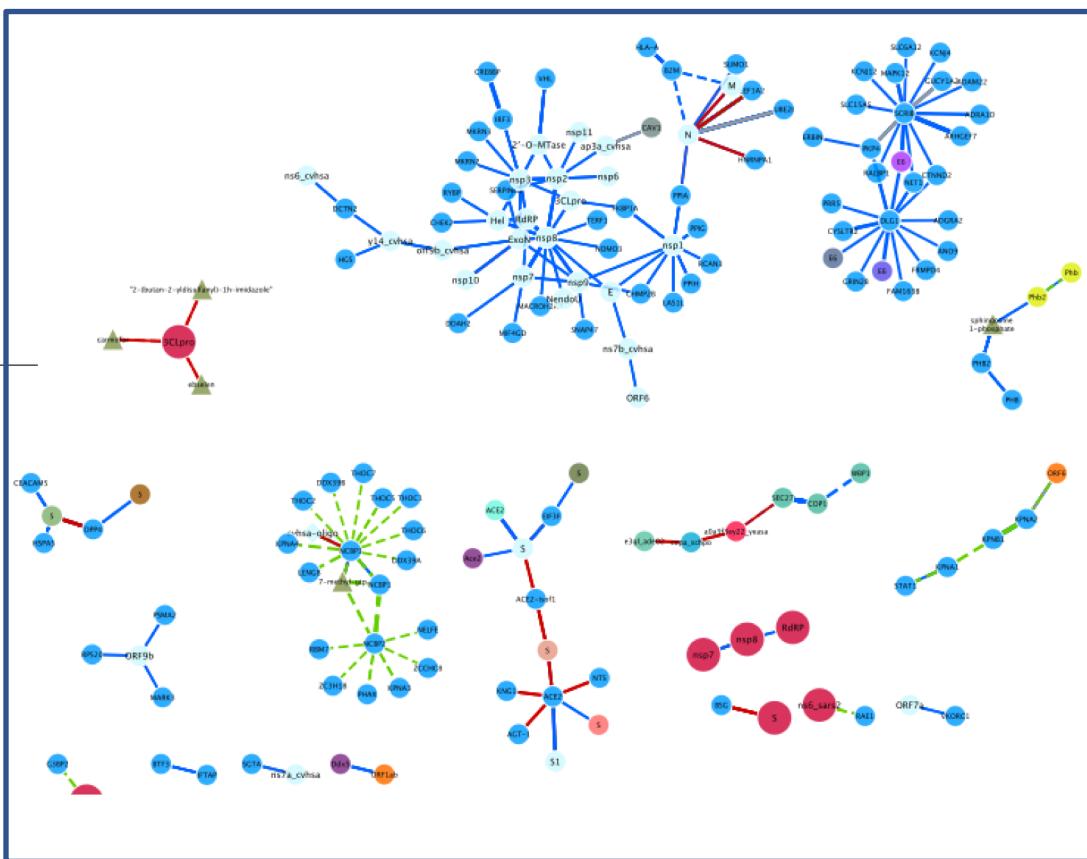
## Node Properties

### Node Shape Mapping

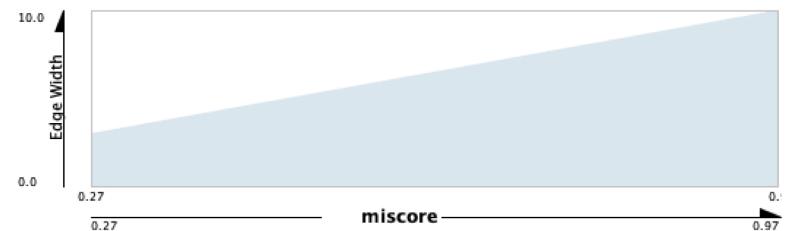
Node Shape	m.type
◊	messenger rna
◊	micro rna
◊	nucleic acid
○	peptide
○	protein
◊	ribonucleic acid
△	small molecule
◊	small nuclear rna

### Node Fill Color Mapping

Node Fill Color	species
red	SARS-CoV-2
blue	human
yellow	mouse
purple	rat

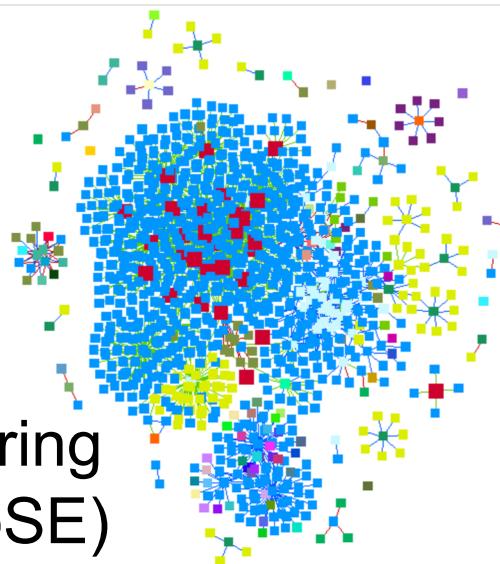


### Edge Width Mapping

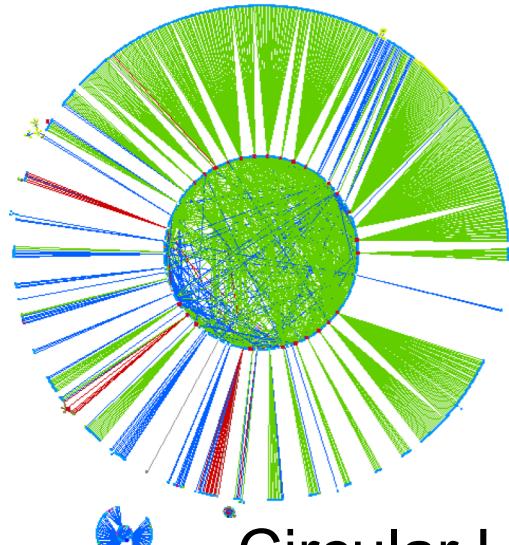
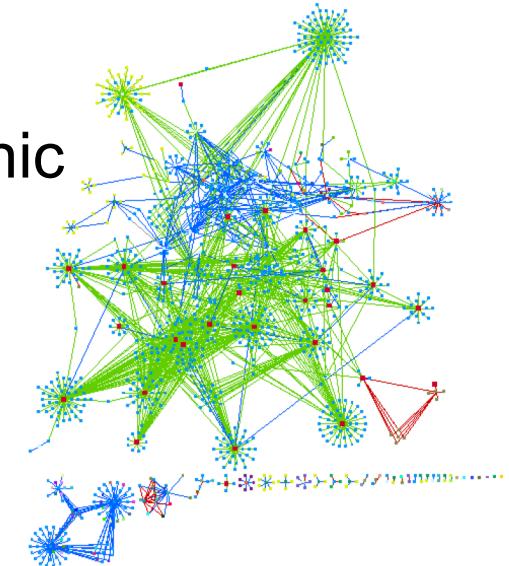


# Experiment with different layouts

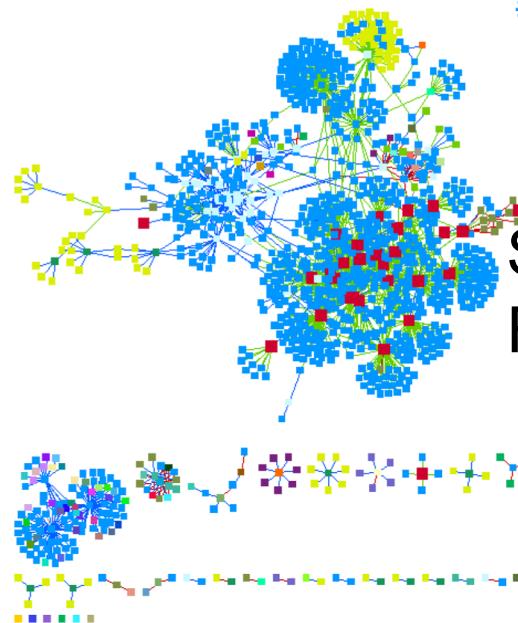
Compound Spring  
Embedder (CoSE)



yfiles organic

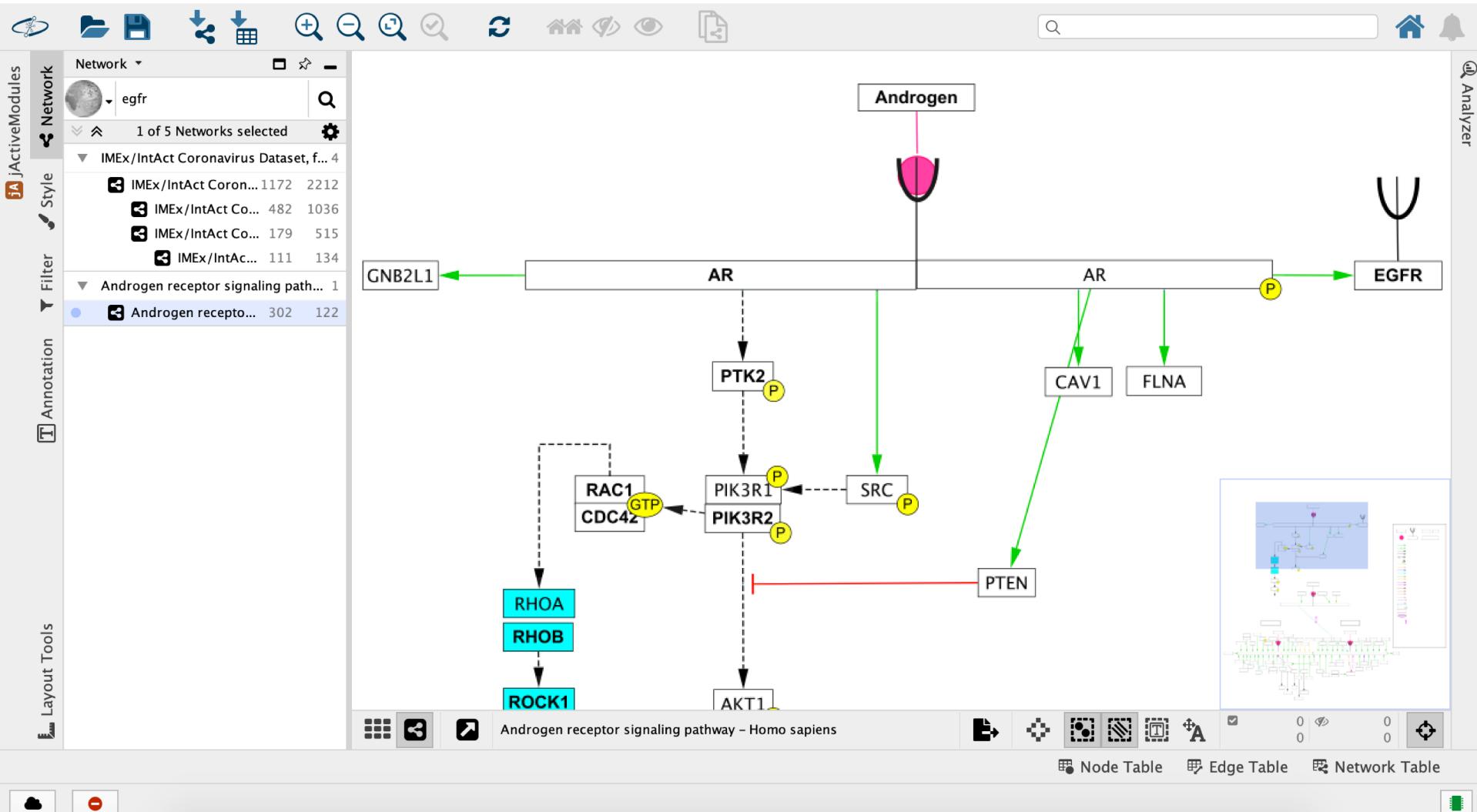


Circular Layout



Spring embedded  
Force directed

# Load different types of networks



Androgen Receptor Pathway from WikiPathways (WP138) –  
<https://www.wikipathways.org/index.php/Pathway:WP138>

# We are on a Coffee Break & Networking Session

Workshop Sponsors:

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