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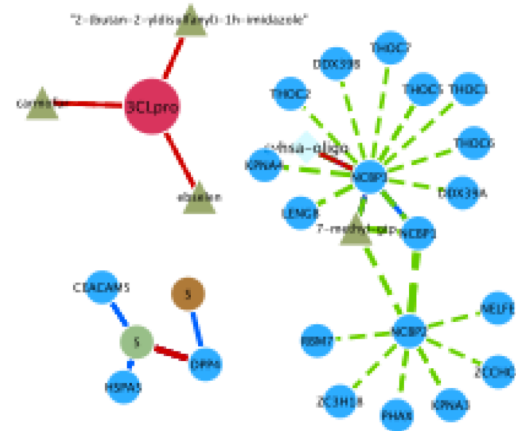
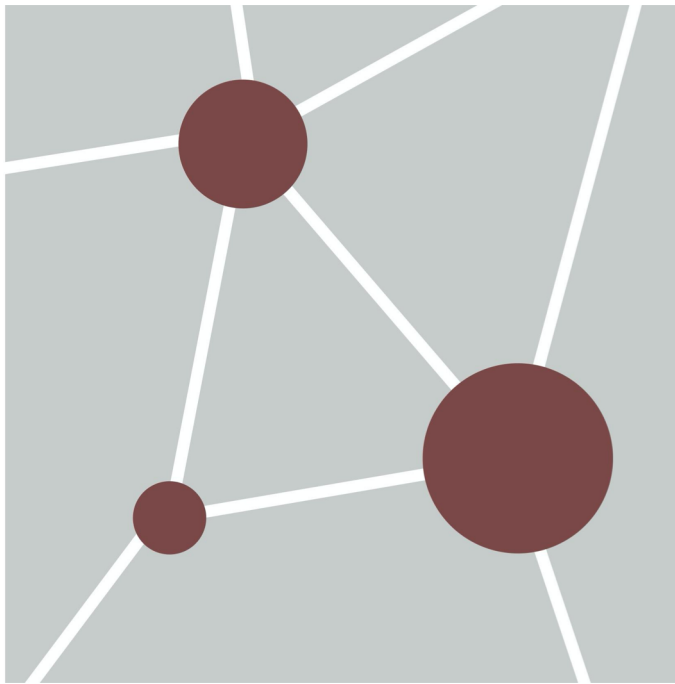
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# Module 3 Network Visualization and analysis with Cytoscape

Ruth Isserlin

Pathway and Network Analysis of -omics Data

May, 10-12, 2021



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# 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

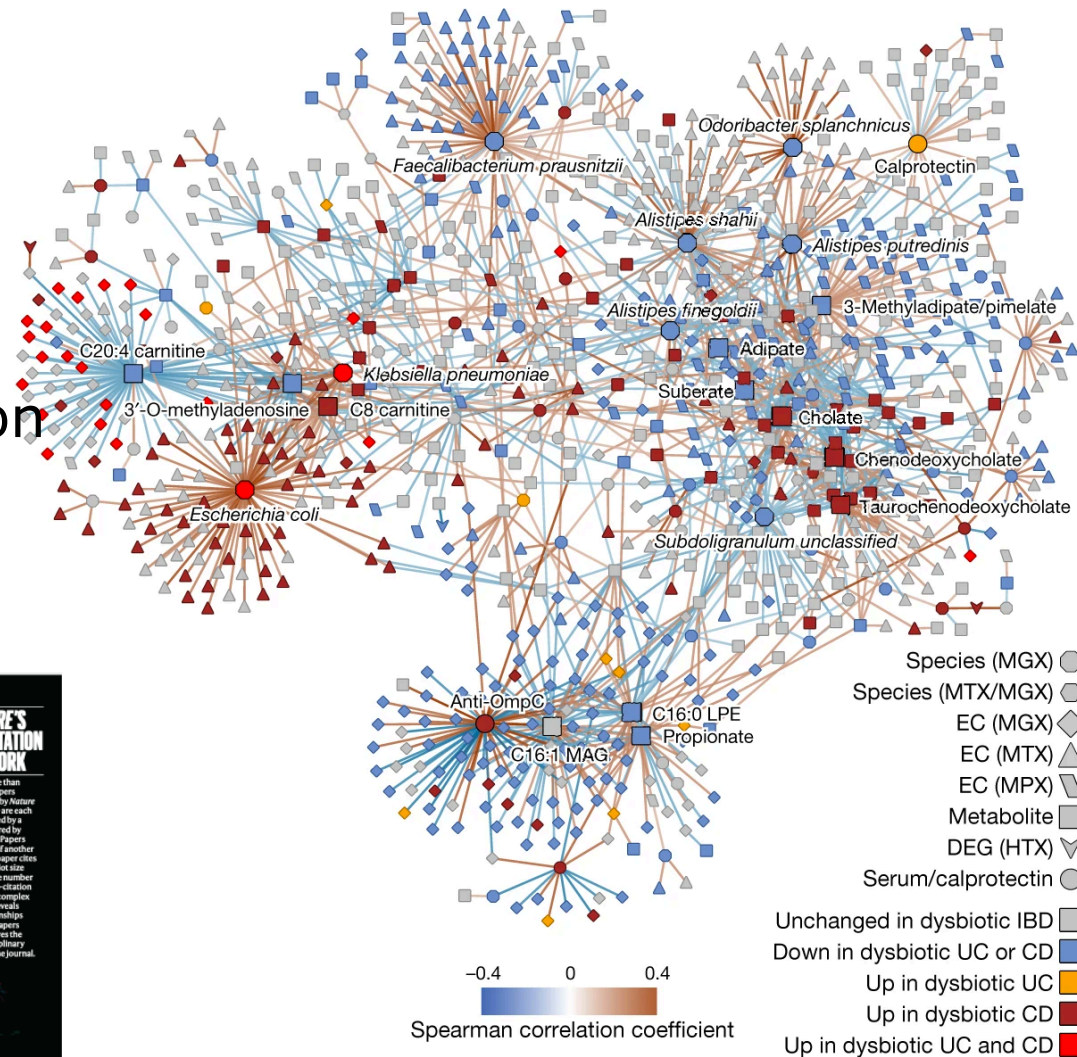
# Six Degrees of Separation

- Everyone in the world is connected by at most six links.
- Originally demonstrated by Stanley 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

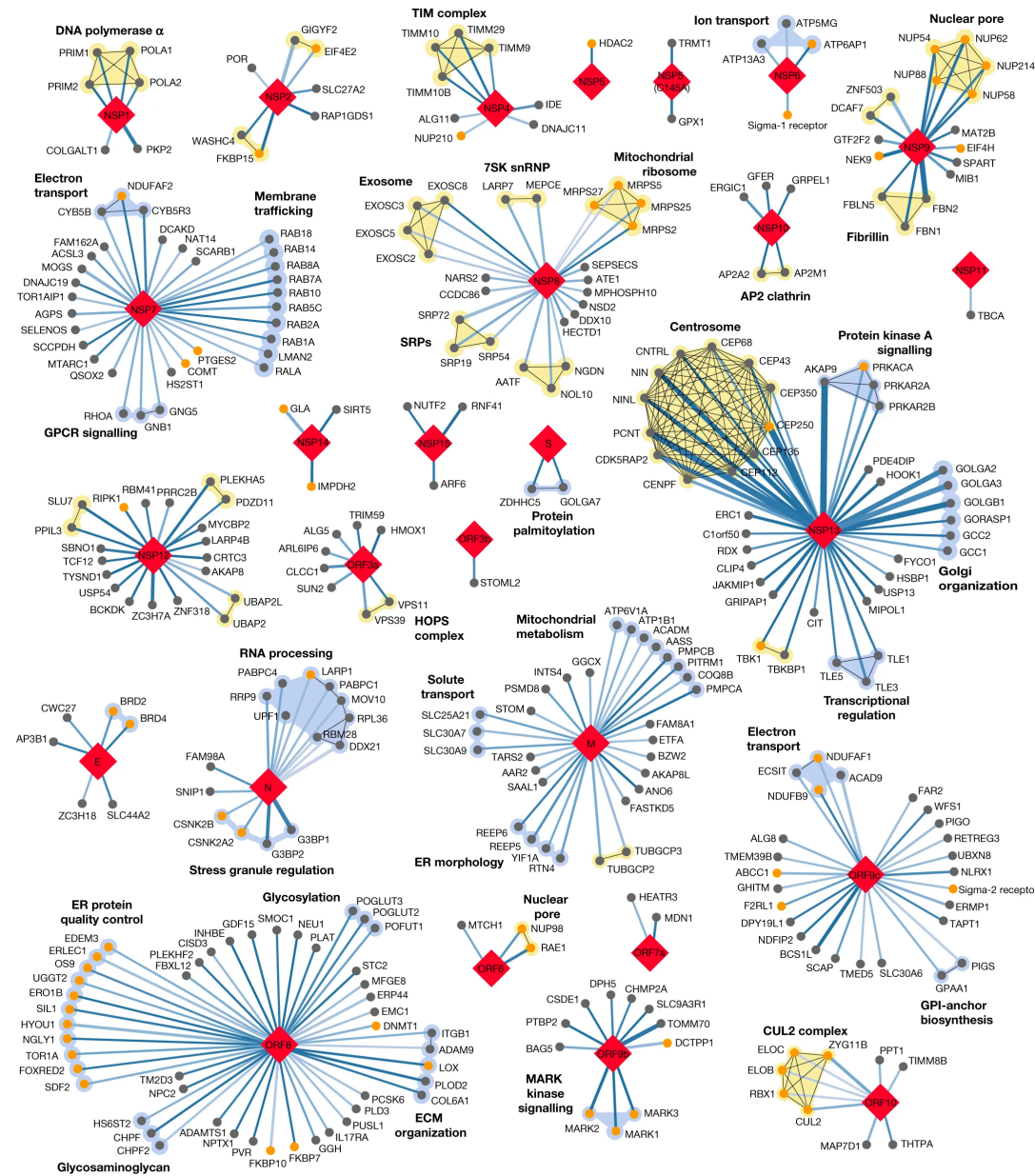


Lloyd-Price, J., Arze, C., Ananthakrishnan, A.N. *et al.* Multi-omics of the gut microbial ecosystem in inflammatory bowel diseases. *Nature* **569**, 655–662 (2019)

# 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  
 0.7 ▬  
 181 ▬ Spectral count  
 2 ▬  
● Protein complex  
● Biological process

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).



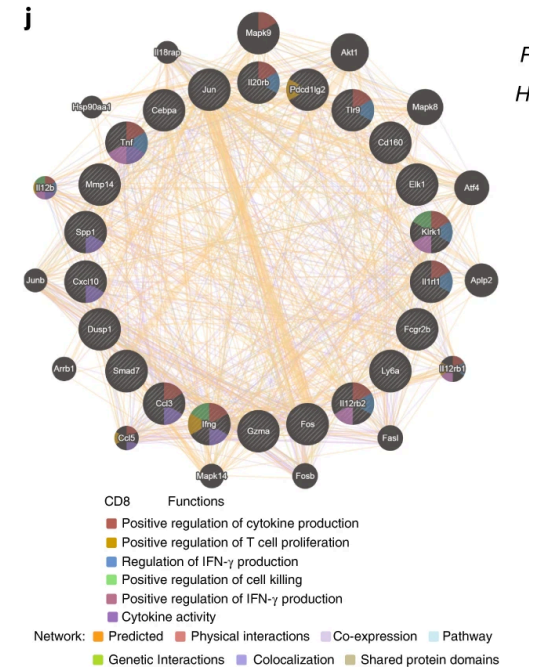
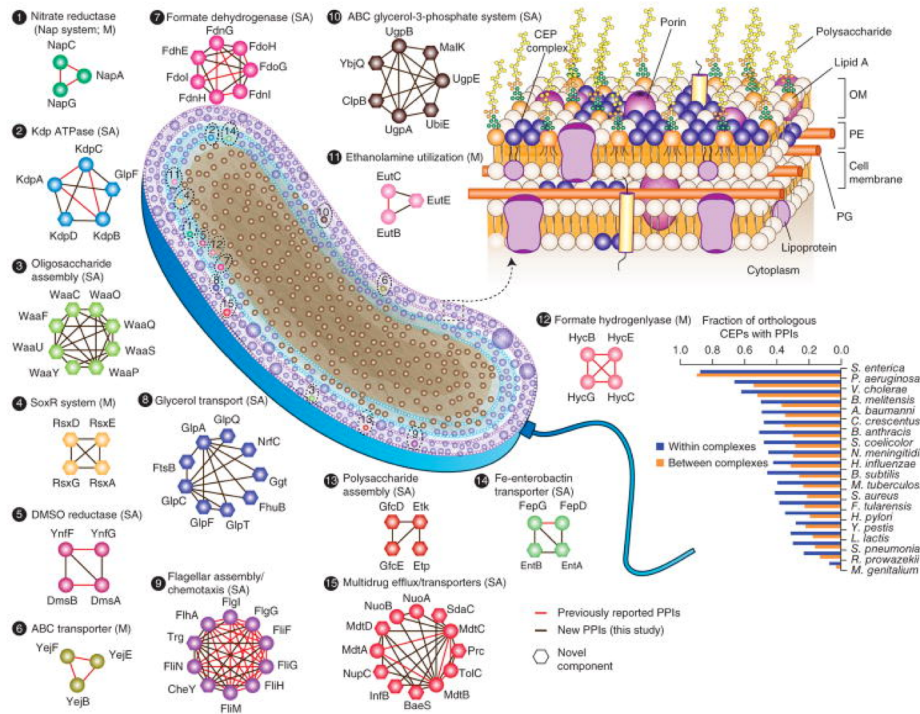
# Why Would We Use Network Visualization for Biological Data?

- 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.

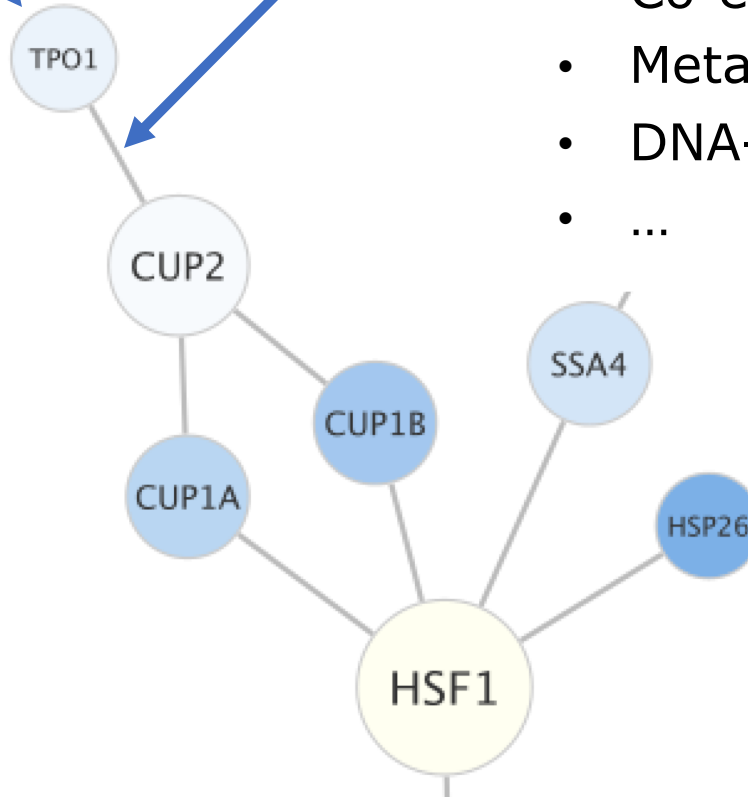
# Network Basics

## Node (molecule/entity)

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

## Edge (interaction/relationship)

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



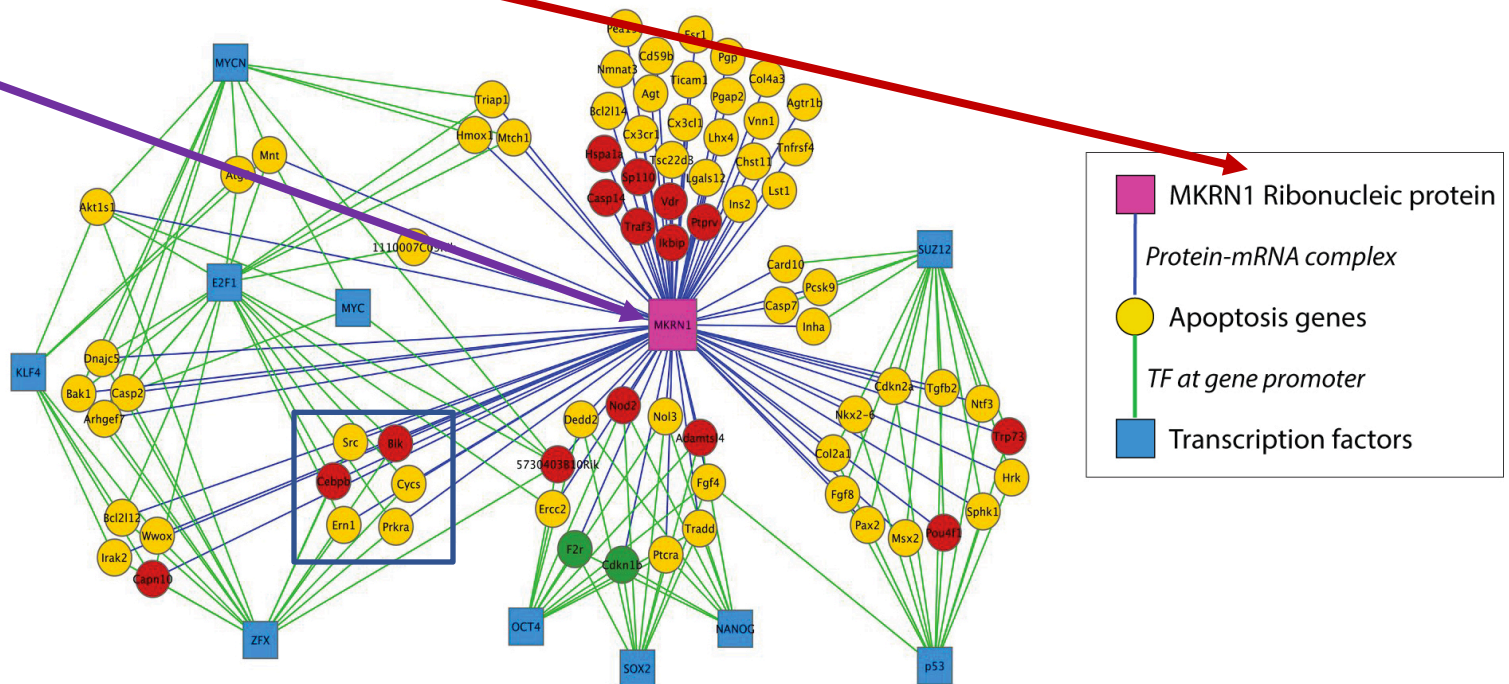


# Networks as Tools

## 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

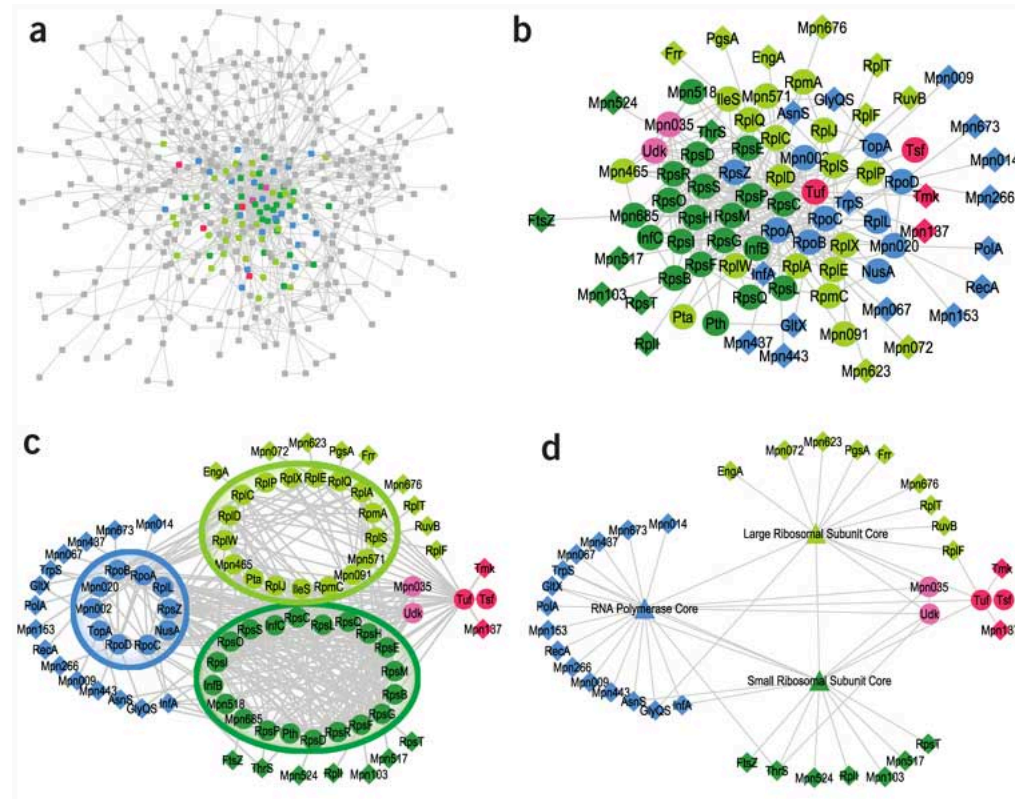


# Networks as Tools

## 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

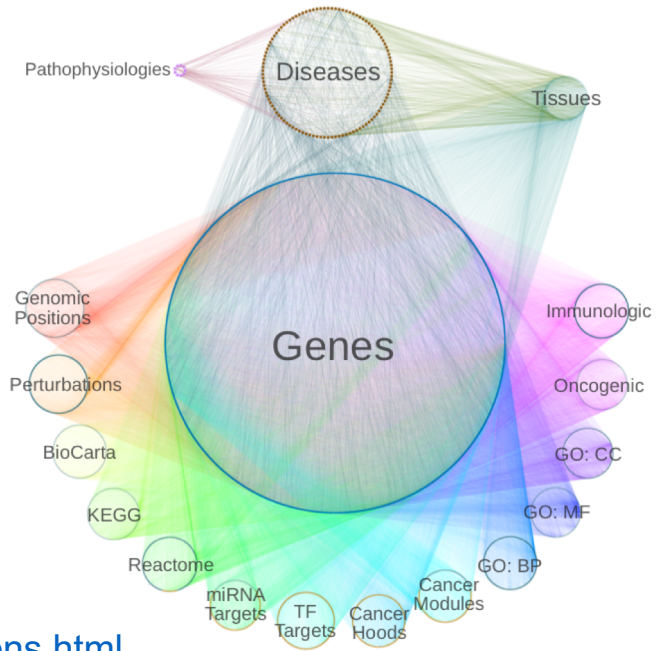
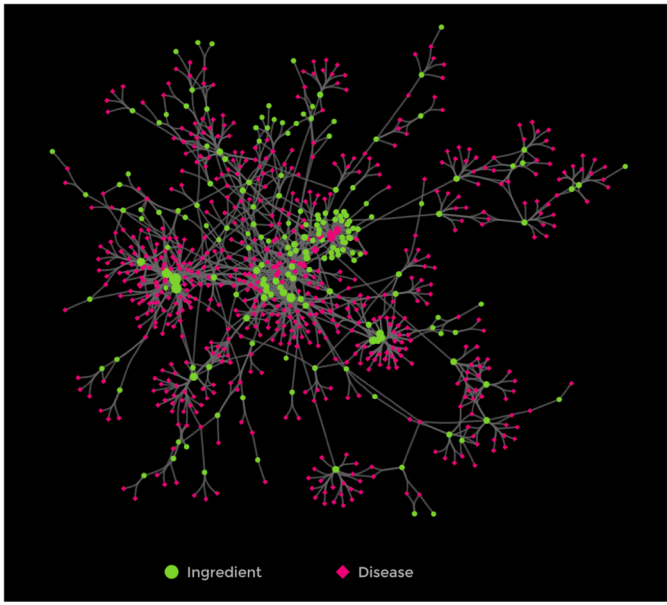
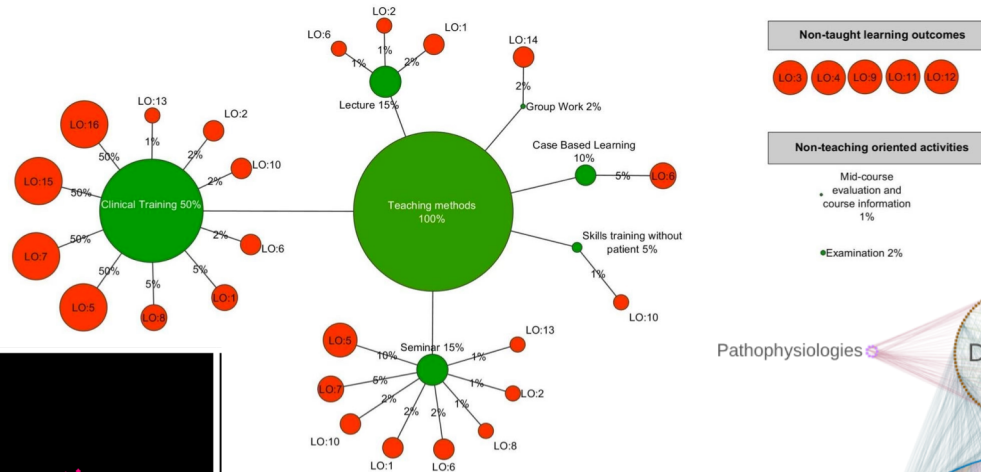
# Network Visualization and Analysis using Cytoscape

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

# Cytoscape (cytoscape.org)



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



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

# Cytoscape (cytoscape.org)



## Partners and Collaborators

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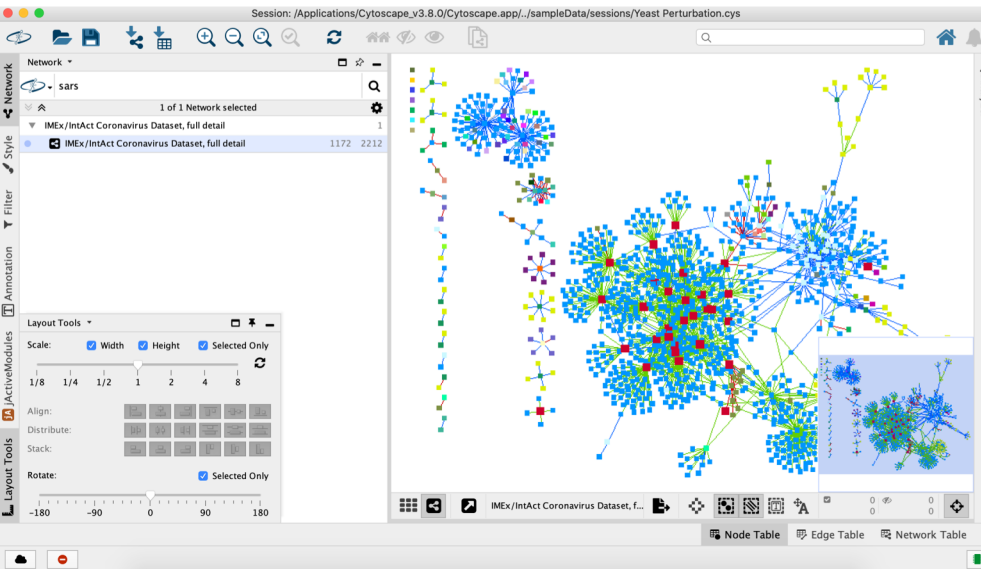
 **GENEONTOLOGY**  
Unifying Biology



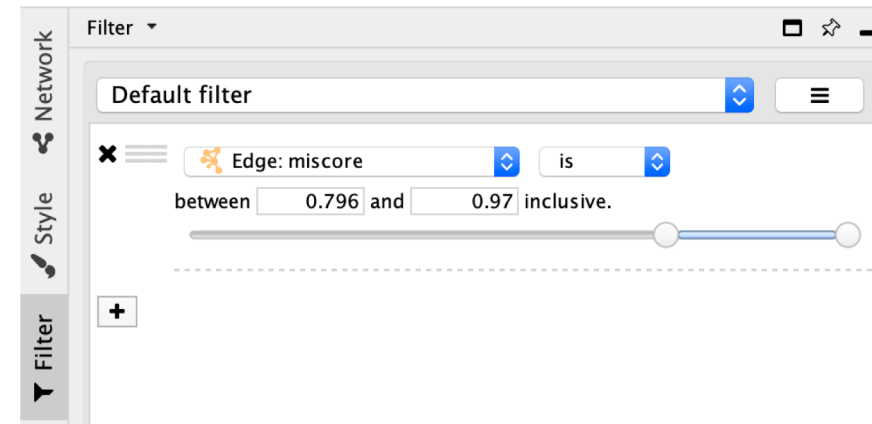




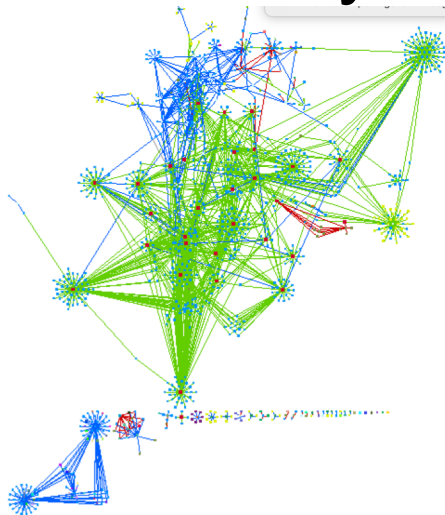
# Manipulate Networks



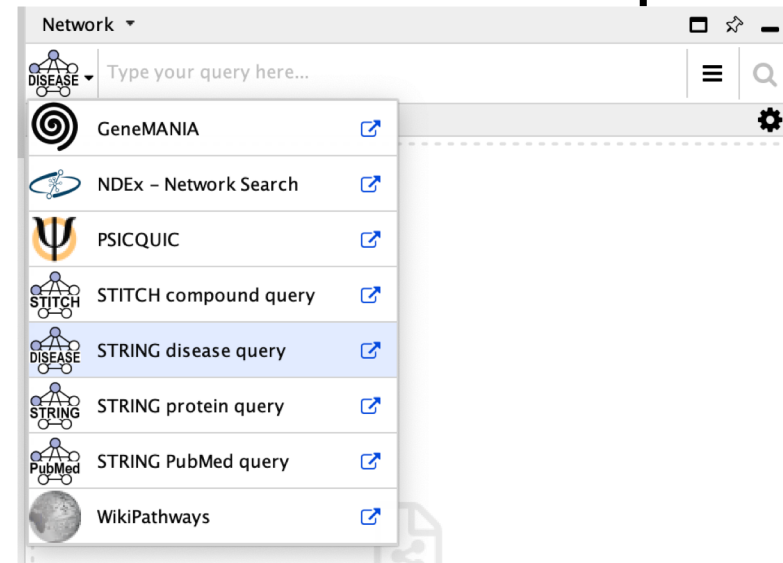
# Filter/Query



# Automatic Layout



# Network Import





# The Cytoscape App Store

Cytoscape App Store

Submit an App

Search the App Store

Sign In

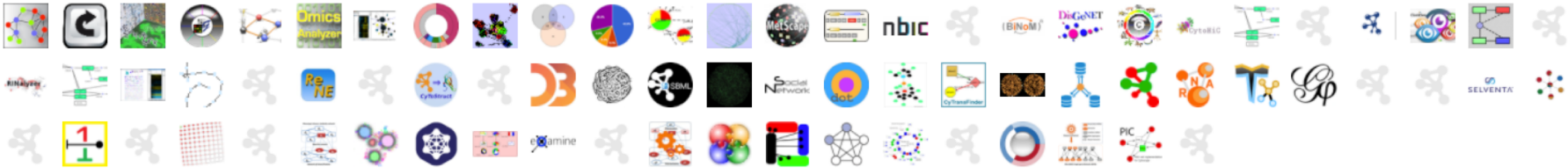
<http://apps.cytoscape.org>

Wall of Apps 361 total

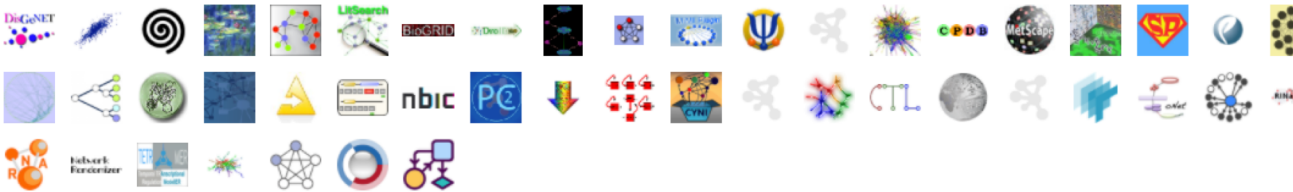
collections



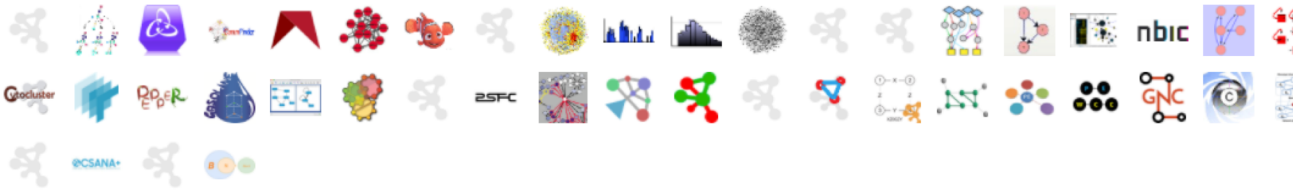
data visualization



network generation



graph analysis



network analysis



- 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

# Cytoscape Demo

Version 3.8.0

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

# Interface Overview

Results Panel

Session: /Applications/Cytoscape\_v3.8.0/Cytoscape.app/./sampleData/sessions/Yeast Perturbation.cys

Network manager

Network overview

Canvas

Table Panel

Control Panel

shared name	name	alias	taxid	species	m.type	m.type.mi	mutated
Q06093	Q06093	U47	10370	hhv6u	protein	MI:0326	
P27228	P27228	E6	10587	Human papillo...	protein	MI:0326	
P24835	P24835	E6	10588	Human papillo...	protein	MI:0326	
P50804	P50804	E6	39457	Human papillo...	protein	MI:0326	
Q8NHY3	Q8NHY3	GAS2L2	9606	human	protein	MI:0326	
Q9BY21	Q9BY21	GPR87	9606	human	protein	MI:0326	

# Basic Navigation

Open or save network to NDex

Open a session

Save your session

Zoom in/out

Apply preferred layout

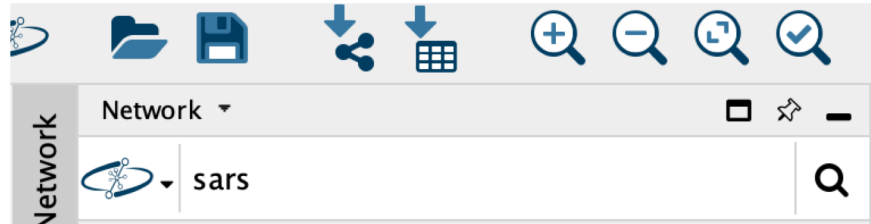
Hide selected nodes and edges

Import Network/table from file

Select first neighbours of selected nodes

The screenshot shows the jActiveModules software interface. The top toolbar contains several icons: a network icon, a folder icon, a save icon, a share icon, a zoom in/out icon, a refresh icon, a home icon, a hide icon, and a document icon. Red arrows point from these icons to text labels: 'Open or save network to NDex' points to the network icon, 'Open a session' points to the folder icon, 'Save your session' points to the save icon, 'Zoom in/out' points to the zoom icons, 'Apply preferred layout' points to the refresh icon, 'Hide selected nodes and edges' points to the hide icon, 'Import Network/table from file' points to the share icon, and 'Select first neighbours of selected nodes' points to the home icon. The interface also shows a sidebar with 'jActiveModules' and 'Style' sections, and a main window displaying a network graph with blue nodes and green edges.

# Load a Network



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

The 'Find Networks' dialog box from NDEX is shown. The search bar contains 'sars'. A red arrow points from the text 'Click on download arrow to load network into Cytoscape' to a red-bordered download icon in the first row of the results table. The table lists various network datasets with columns for name, owner, visibility, nodes, edges, and modified date.

	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.

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

Close Dialog



# About the network

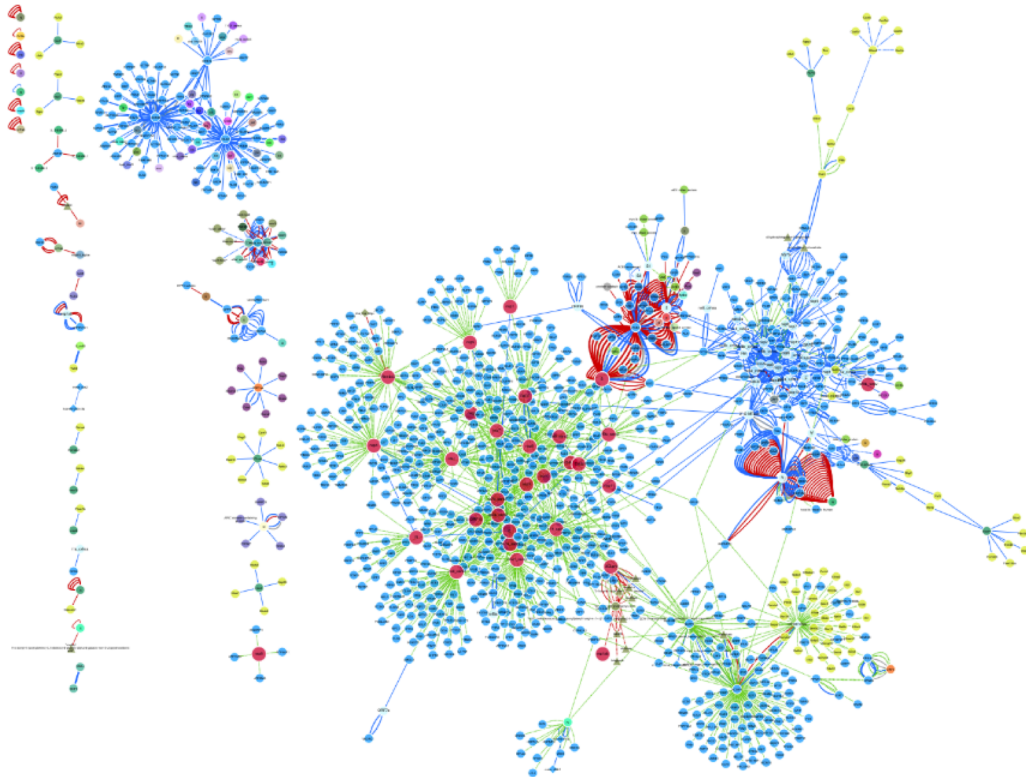
<http://ndexbio.org/#/network/3e13a4de-a4d7-11ea-aaef-0ac135e8bacf>



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Network Info Nodes/Edges

## IMEx/IntAct Coronavirus Dataset, full detail

DOI: 10.18119/N9RC8F

**Nodes:** 1172    **Edges:** 2212  
**PUBLIC** Q  
**@context:** [view namespaces](#)

<b>Owner</b>	Pablo Porras Millan
<b>Created</b>	Jun 2, 2020 9:44:55 AM
<b>Last Modified</b>	Jun 15, 2020 5:40:49 AM
<b>UUID</b>	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:

<b>author</b>	IMEx Consortium Curators & Pablo Porras
<b>disease</b>	COVID19, SARS
<b>organism</b>	SARS-CoV-2, SARS, Coronaviridae, human, mouse, mammal

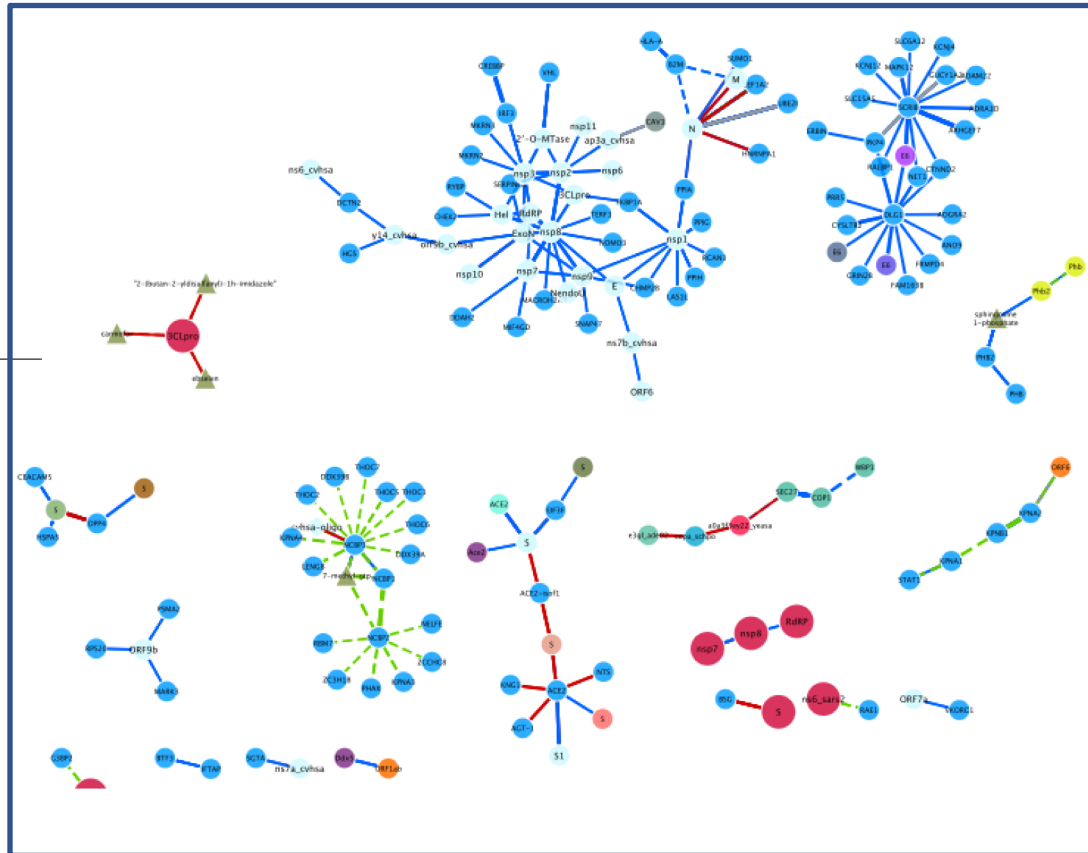
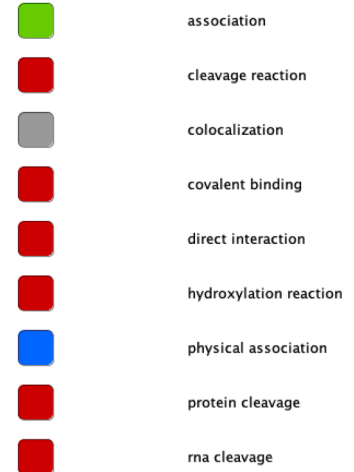


# Visual Styles

## Edge Stroke Color (Unselected) Mapping

### Edge Stroke Color (Unselected)

### int.type

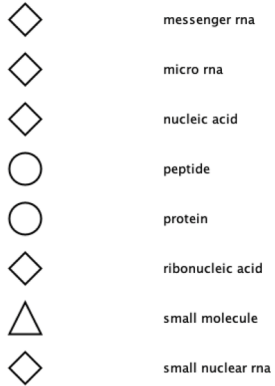


## Node Properties

### Node Shape Mapping

#### Node Shape

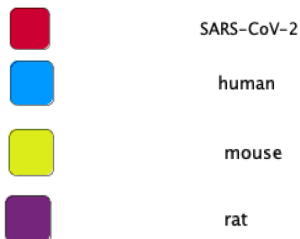
#### m.type



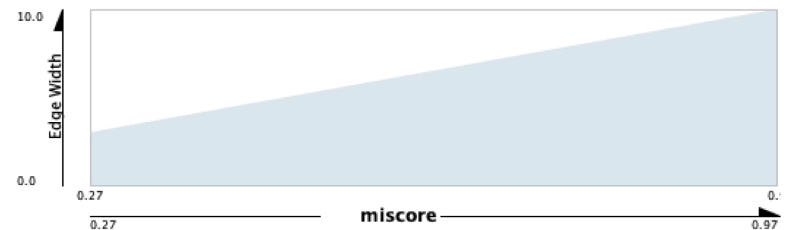
### Node Fill Color Mapping

#### Node Fill Color

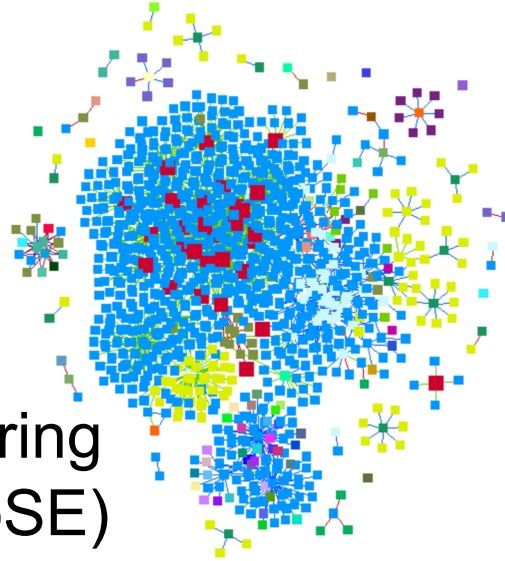
#### species



### Edge Width Mapping

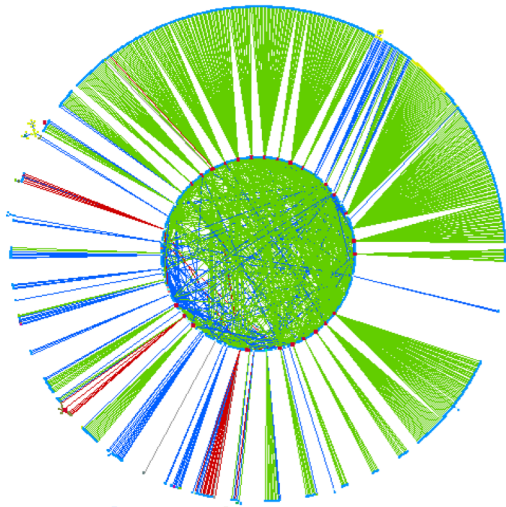
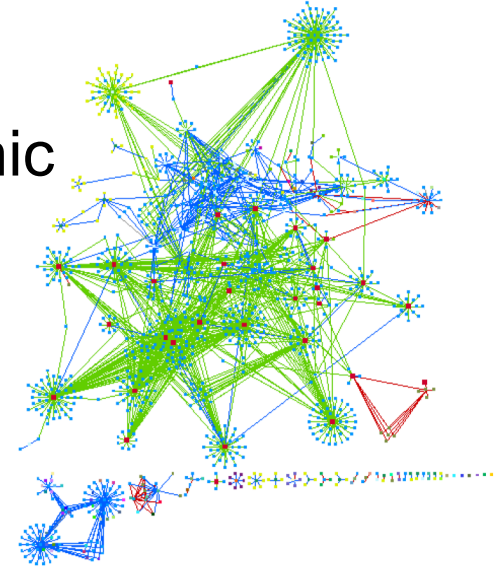


# Experiment with different layouts

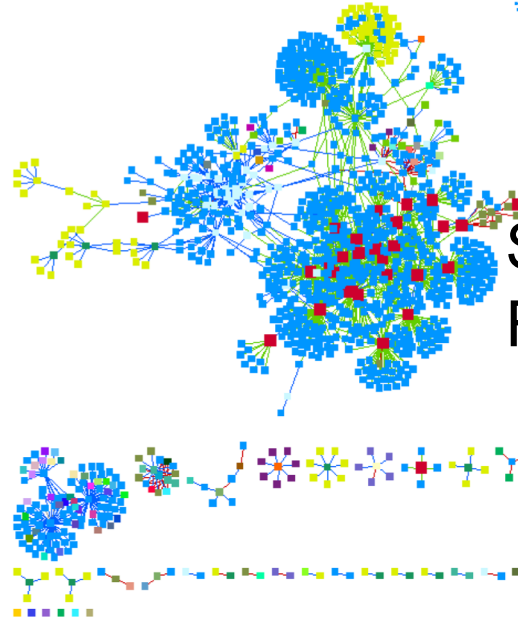


Compound Spring Embedder (CoSE)

yfiles organic

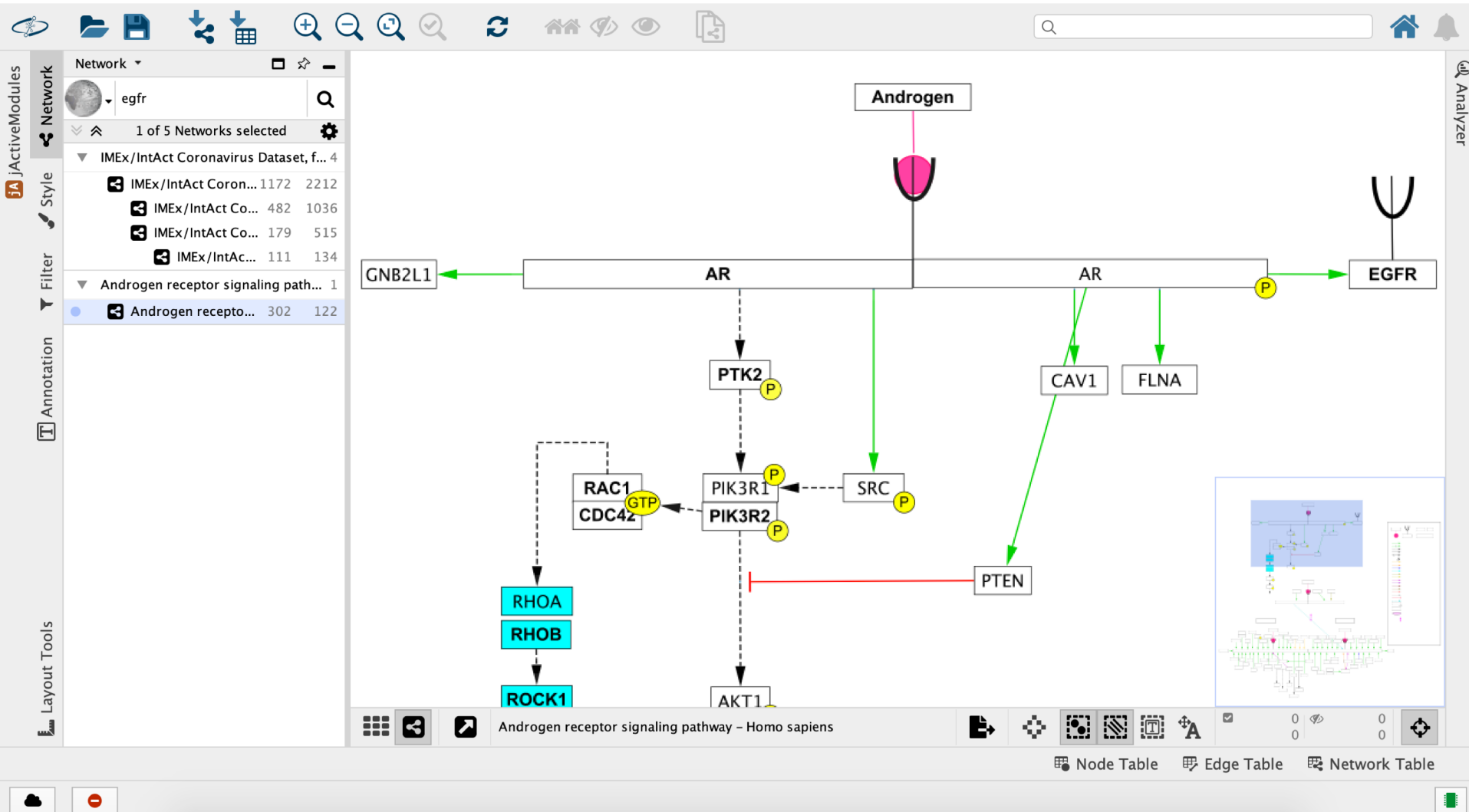


Circular Layout



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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Canadian Centre for  
Computational  
Genomics



HPC4Health



**MiC:M** McGill initiative in  
Computational Medicine