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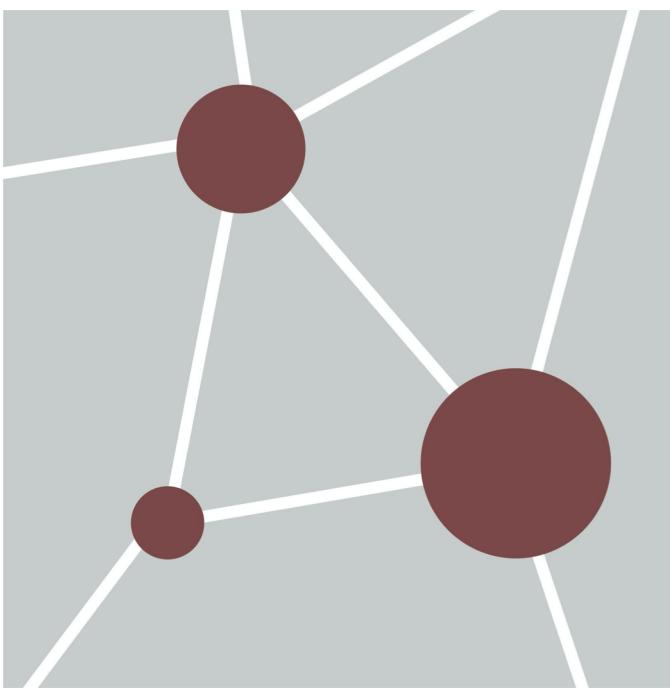
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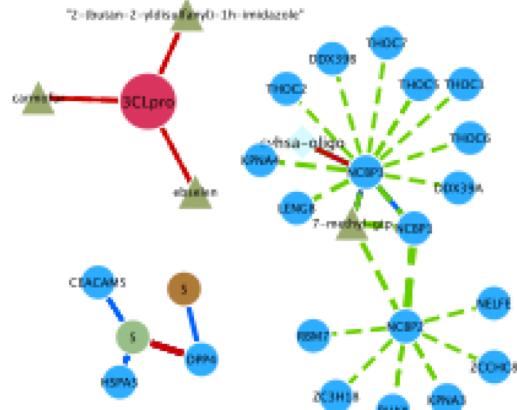
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Module 3

Network Visualization and analysis with Cytoscape



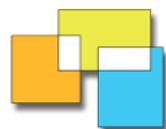
Ruth Isserlin
Pathway and Network Analysis of -omics Data
July 27-29, 2020



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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

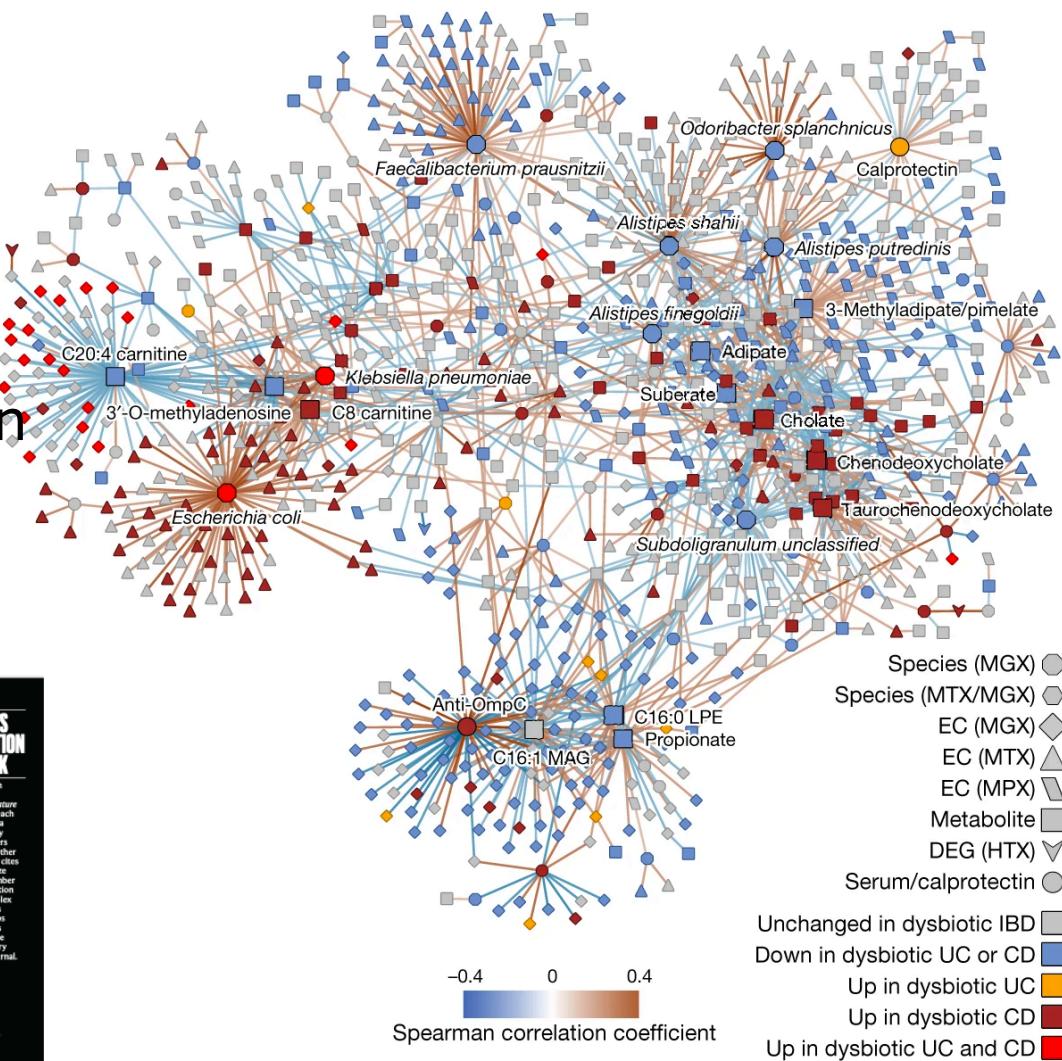
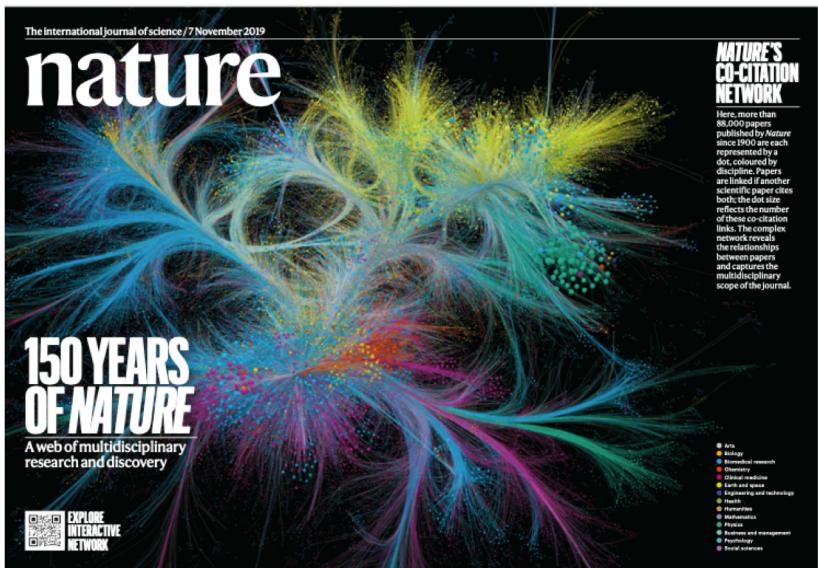
Six Degrees of Separation

- 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

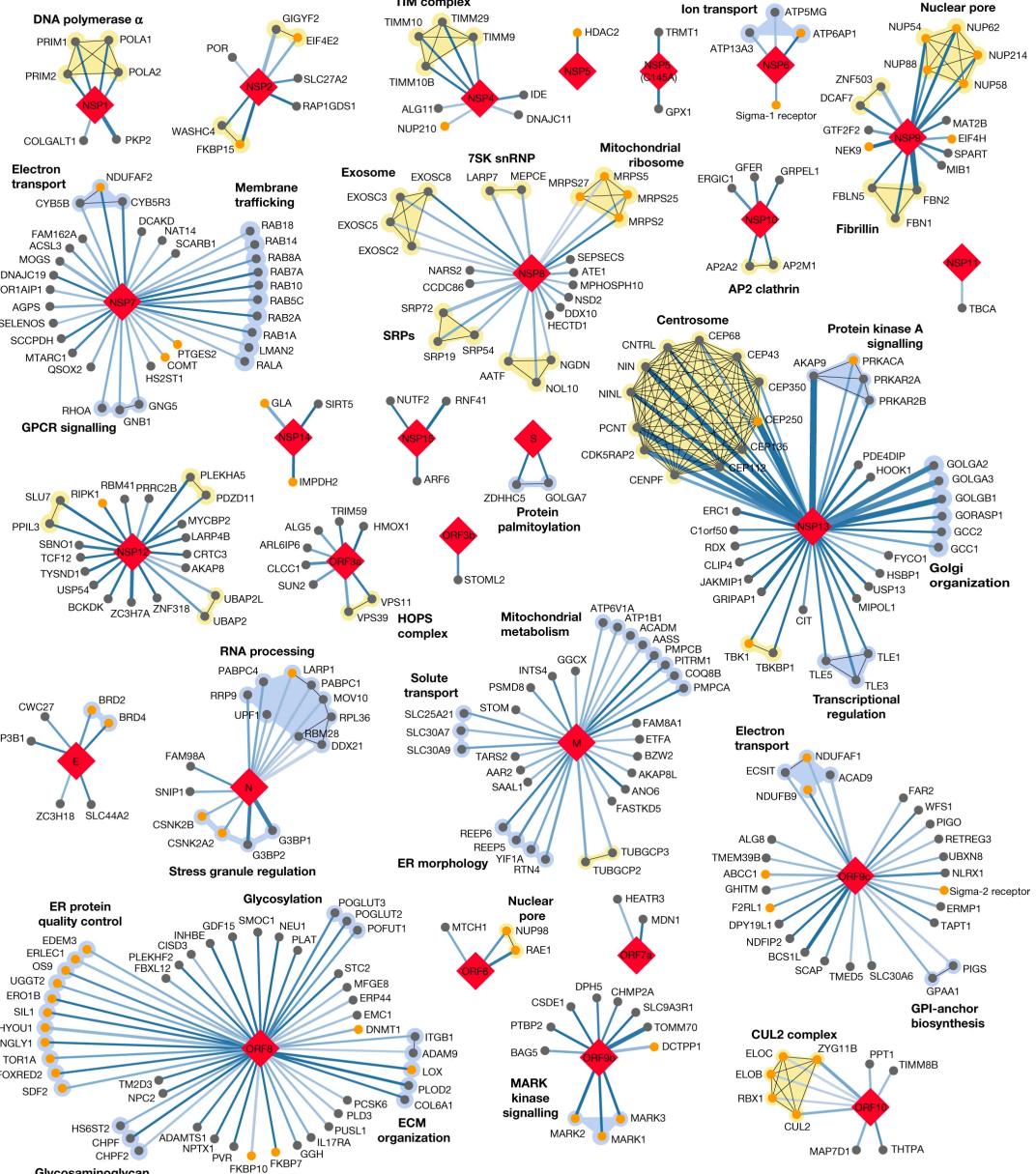
1.0 MIST score

 Protein complex

181 Spectral count
2

 Biological process

SARS-CoV-2 protein-protein interaction Network



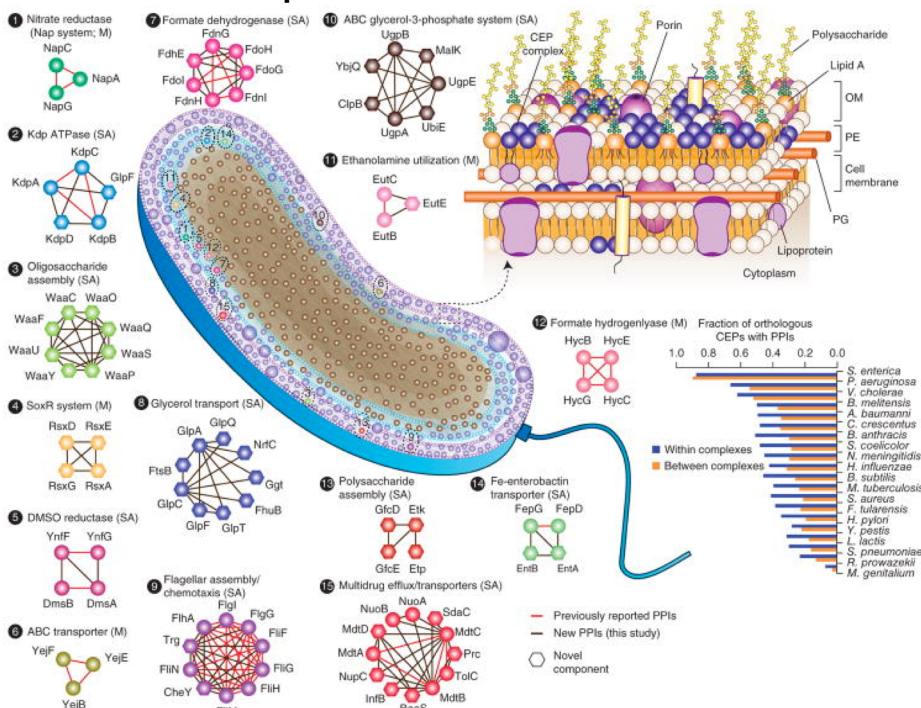
Gordon, D.E., Jang, G.M., Bouhaddou, M. et al. A SARS-CoV-2 protein interaction map reveals targets for drug repurposing. *Nature* **583**, 459–468 (2020).

Why Would We Use Network Visualization for Biological Data?

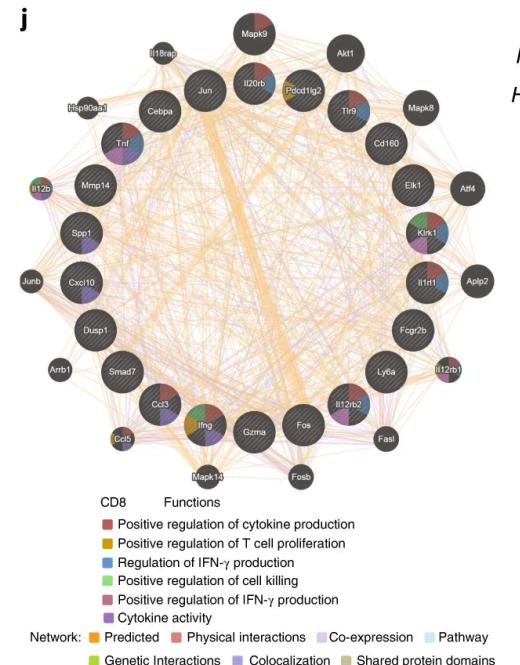
- Represent relationships of biological molecules
 - Physical, regulatory, genetic, functional interactions
- Useful for discovering relationships in large data sets
 - Better than tables in Excel
- Visualize multiple data types together
 - Discover interesting patterns
- Network analysis
 - Finding 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

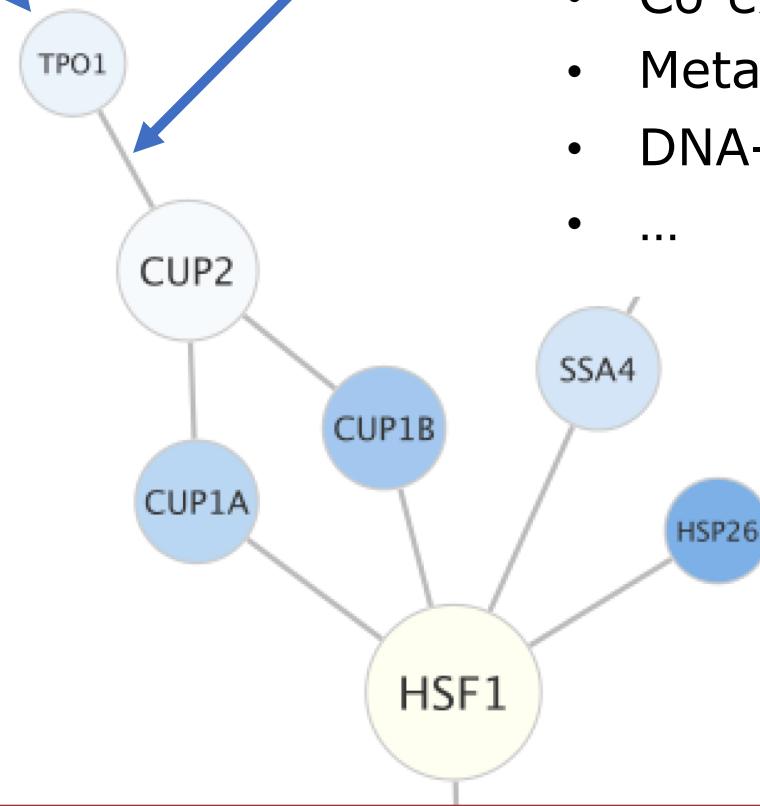
Motif analysis – discover higher order organization such motifs, feedback loops (small network patterns that are over-represented when compared to a randomized version of the same network)

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

Network Basics

Node (molecule/entity)

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



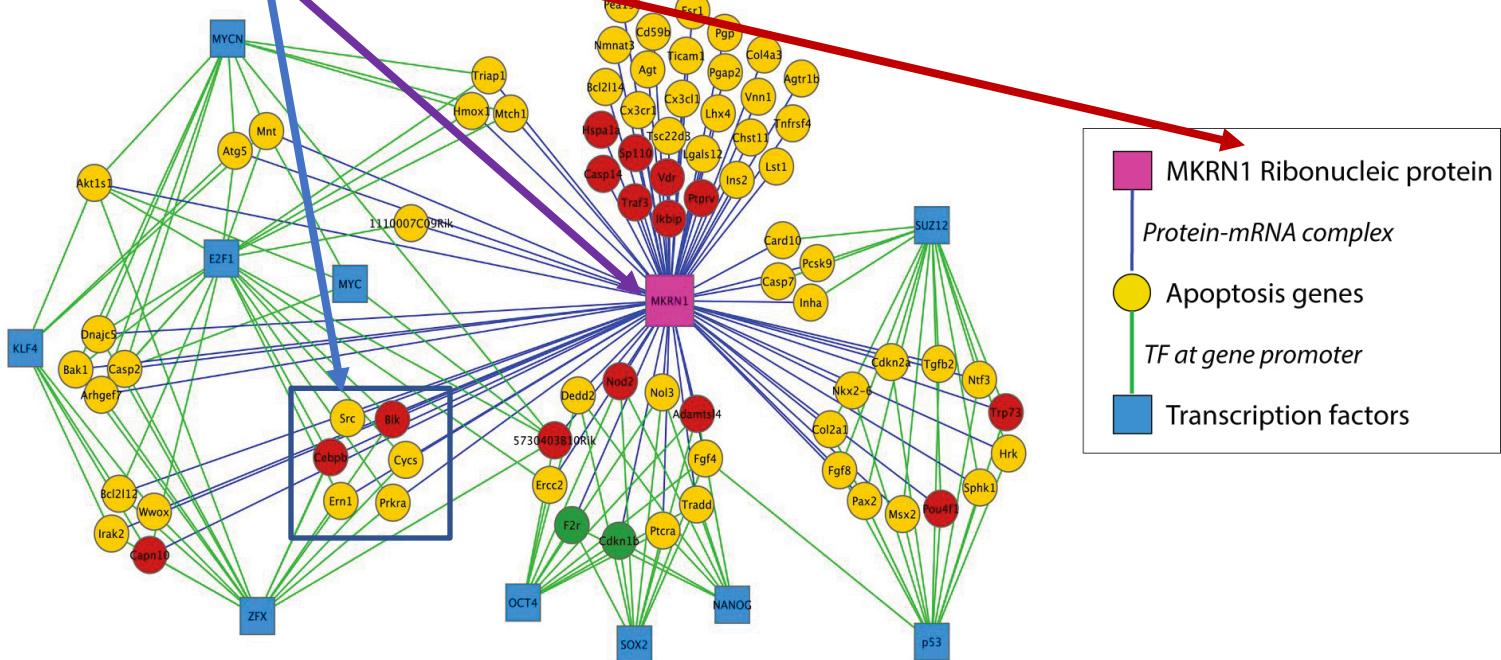
Edge (interaction/relationship)

- 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

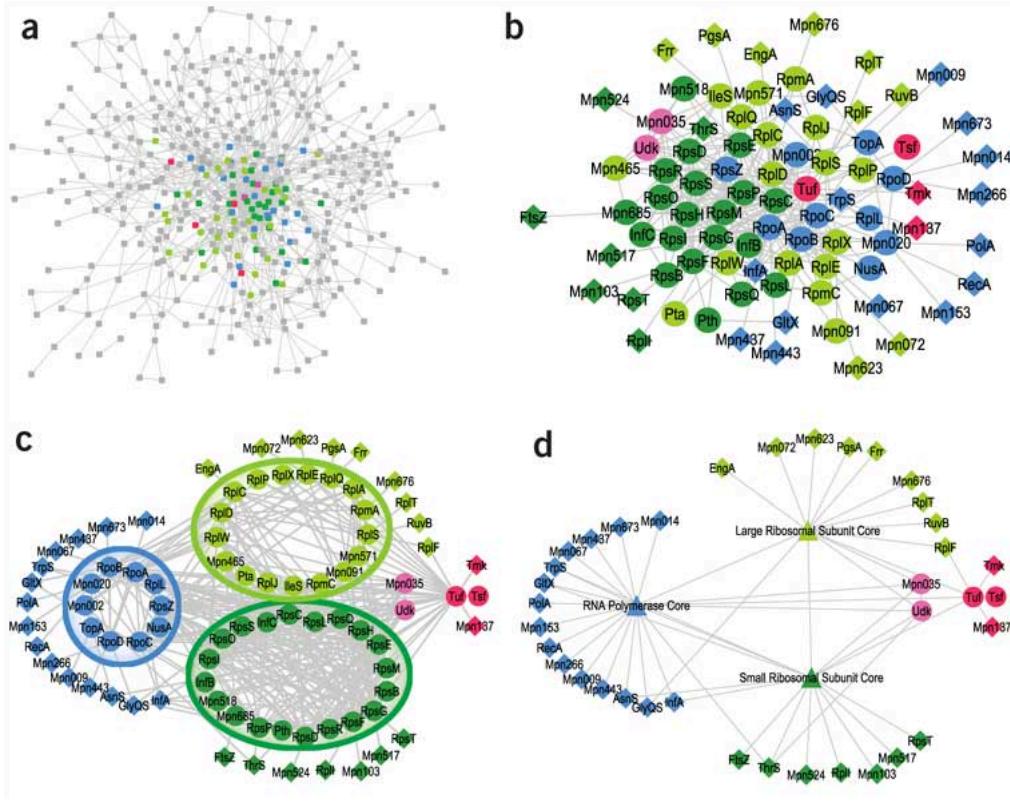


Networks as Tools

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

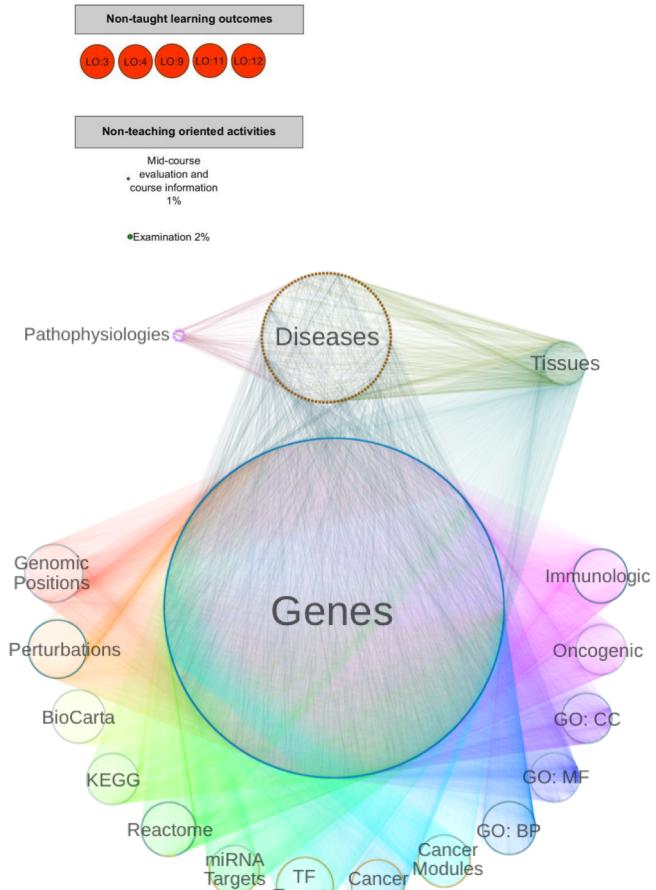
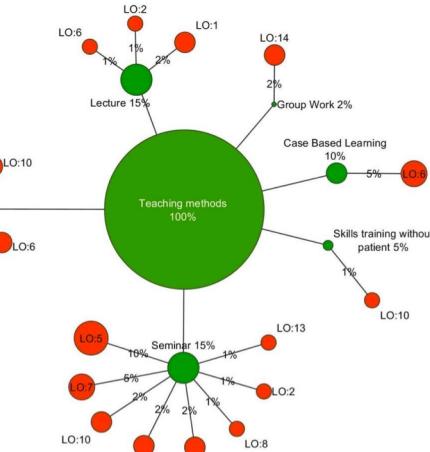
Network Visualization and Analysis using Cytoscape

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



Cytoscape (cytoscape.org)

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



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

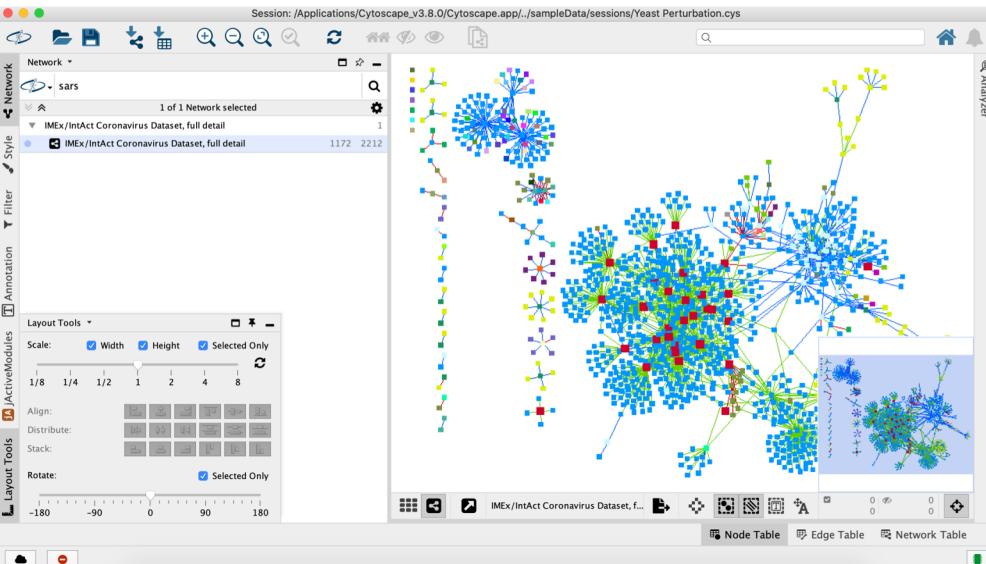
Cytoscape (cytoscape.org)



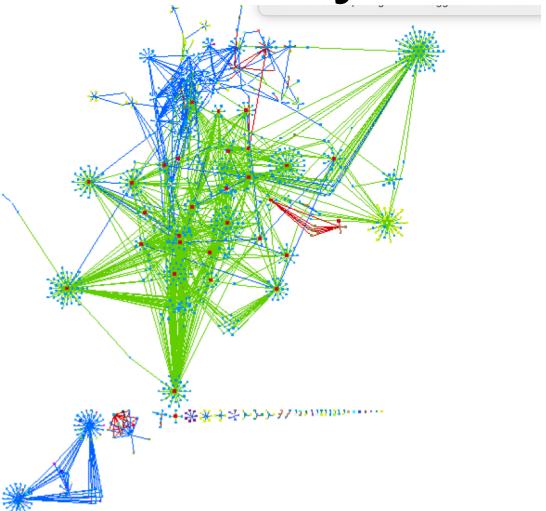
Partners and Collaborators



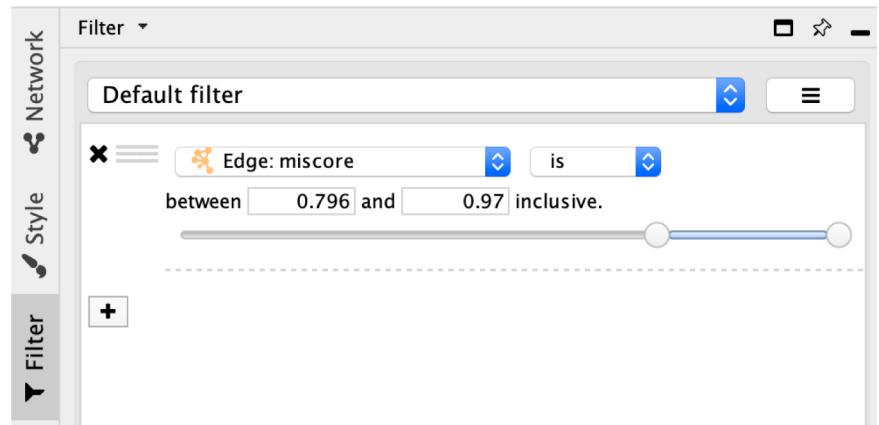
Manipulate Networks



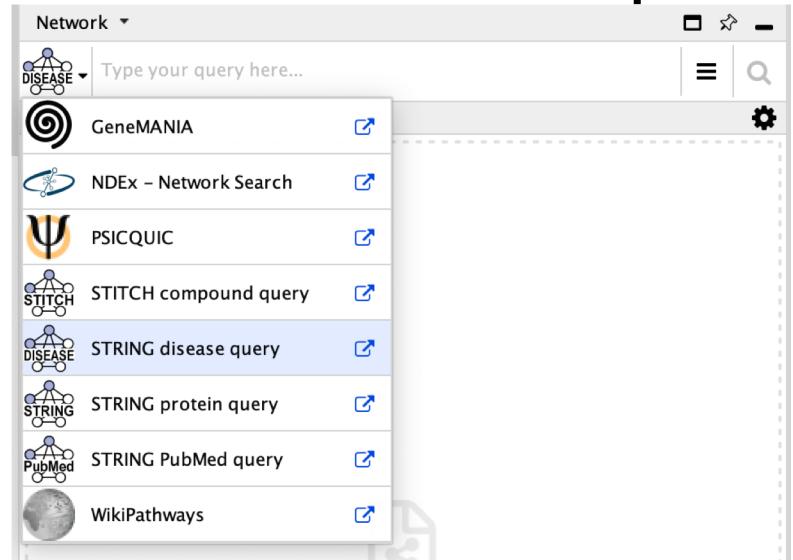
Automatic Layout



Filter/Query



Network Import



The Cytoscape App Store

Cytoscape App Store

Submit an App

Search the App Store

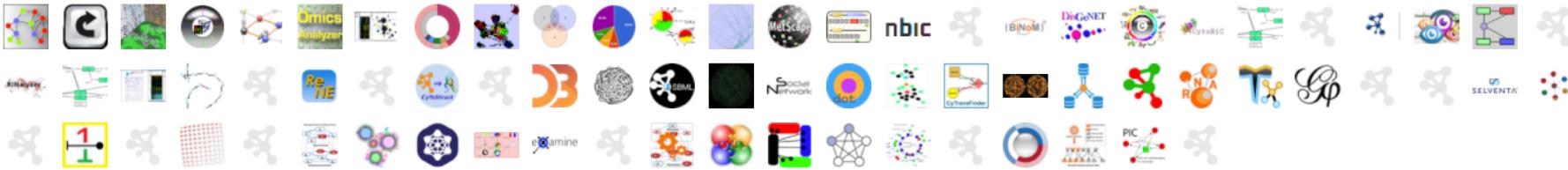
Sign In

Wall of Apps 361 total

collections



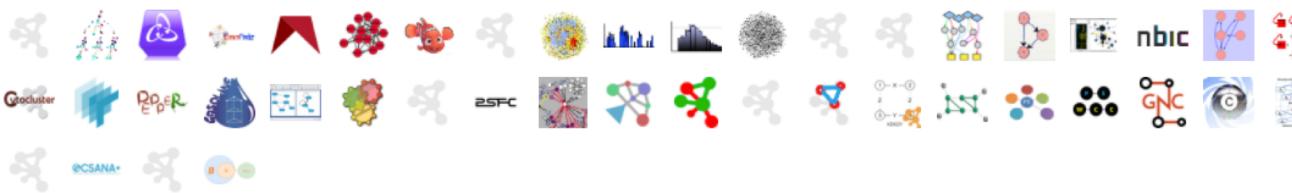
data visualization



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



bioinformatics.ca

Cytoscape Demo

Version 3.8.0

www.cytoscape.org

Interface Overview

Results Panel

The screenshot displays the Cytoscape application interface. On the left, the **Control Panel** contains various icons and buttons. The main workspace is divided into several panels: the **Network manager** on the far left, the **Canvas** in the center showing a complex network graph with green and blue nodes and edges, the **Table Panel** below the canvas displaying a table of node data, and the **Results Panel** at the top right. A black arrow points from the **Results Panel** label towards the top right corner of the interface.

Network manager

Canvas

Control Panel

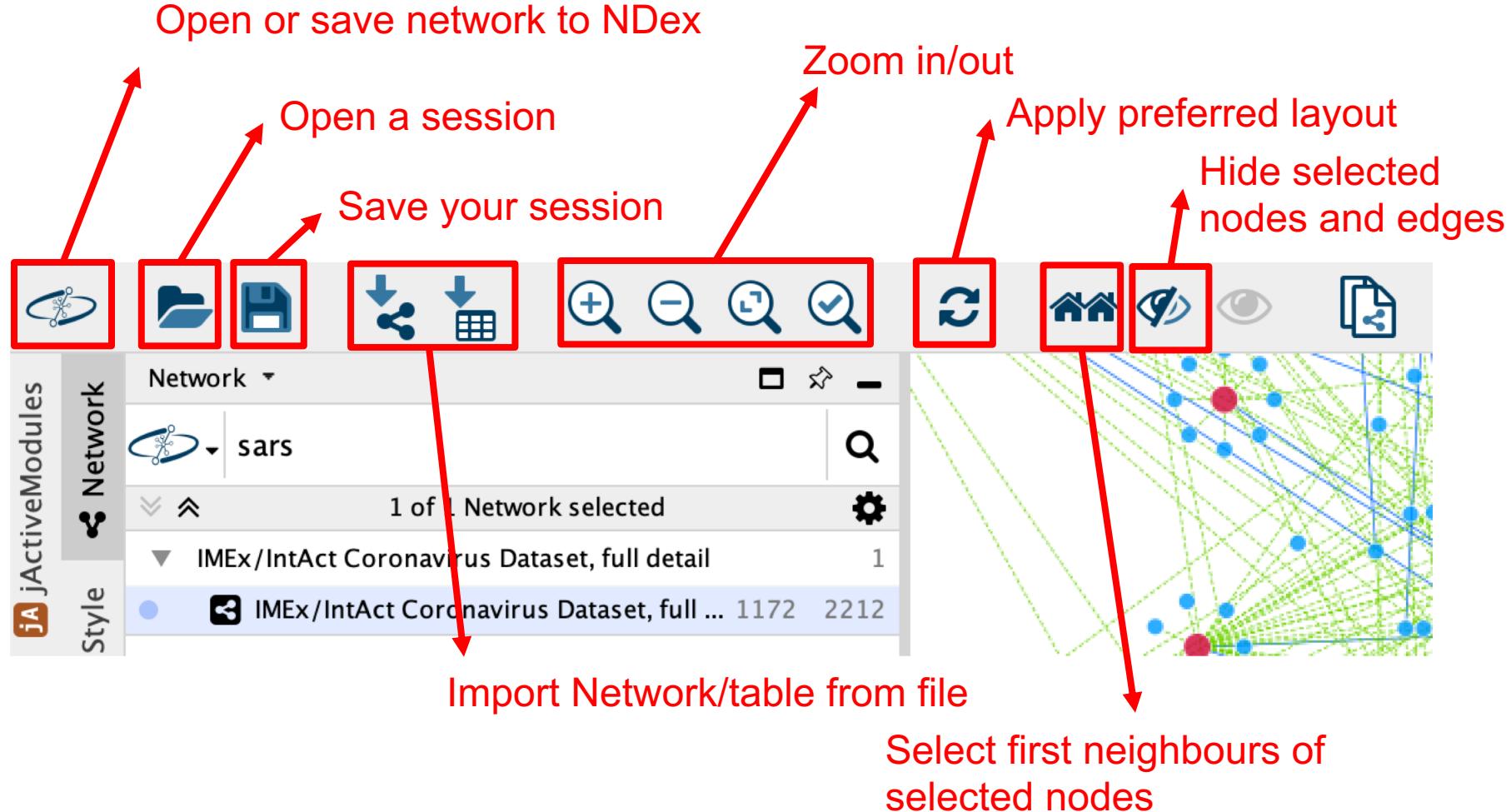
Table Panel

Network overview

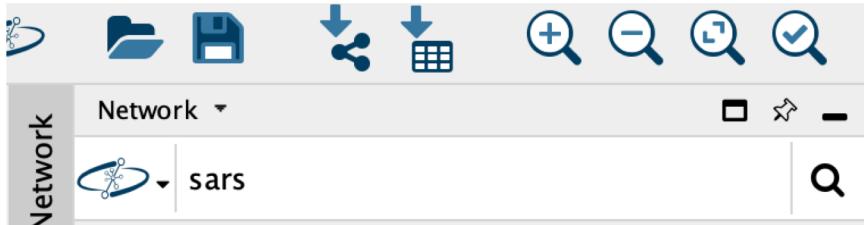
| shared name | name | alias | taxid | species | m.type | m.type.mi |
|-------------|--------|--------|-------|------------------|---------|-----------|
| Q06093 | Q06093 | U47 | 10370 | hhv6u | protein | MI:0326 |
| P27228 | P27228 | E6 | 10587 | Human papillo... | protein | MI:0326 |
| P24835 | P24835 | 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 |

Node Table **Edge Table** **Network Table**

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 |
|--|--|--------------|------------|-------|-------|------------------------|
| | 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

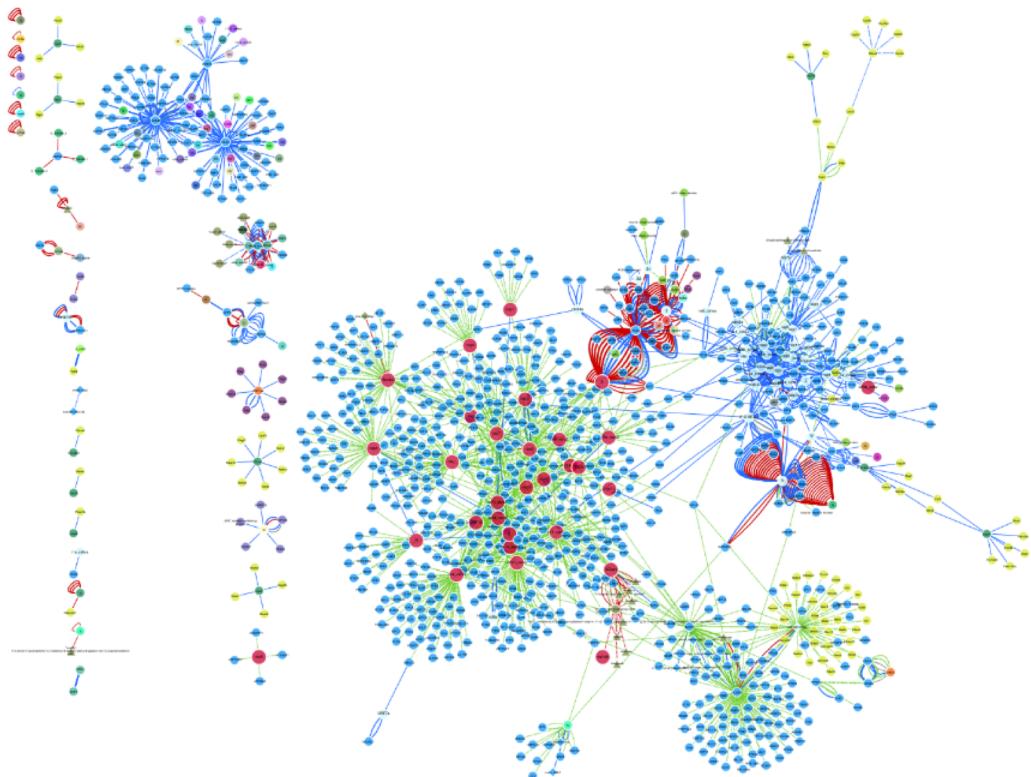
<http://ndexbio.org/#/network/3e13a4de-a4d7-11ea-aaef-0ac135e8bacf>



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

Edge Stroke Color (Unselected) Mapping

| Edge Stroke Color (Unselected) | int.type |
|--------------------------------|------------------------|
| green | association |
| red | cleavage reaction |
| grey | colocalization |
| dark red | covalent binding |
| dark red | direct interaction |
| dark red | hydroxylation reaction |
| blue | physical association |
| dark red | protein cleavage |
| dark red | rna cleavage |

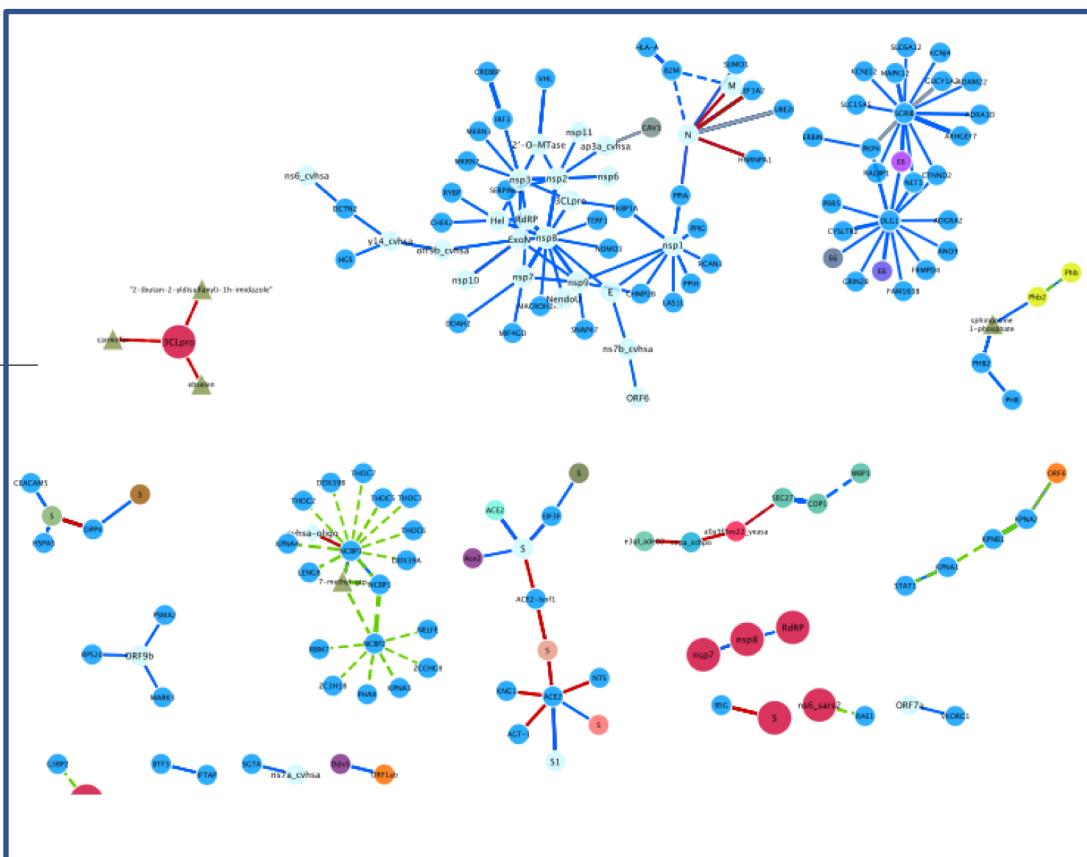
Node Properties

Node Shape Mapping

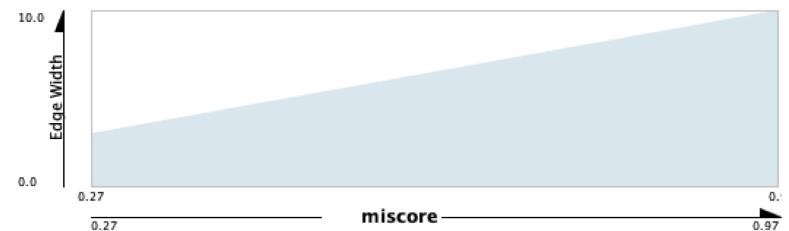
| Node Shape | m.type |
|------------|-------------------|
| diamond | messenger rna |
| diamond | micro rna |
| diamond | nucleic acid |
| circle | peptide |
| circle | protein |
| diamond | ribonucleic acid |
| triangle | small molecule |
| diamond | small nuclear rna |

Node Fill Color Mapping

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

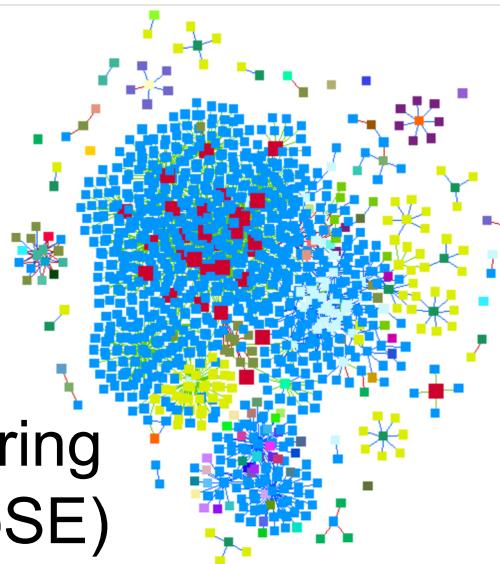


Edge Width Mapping

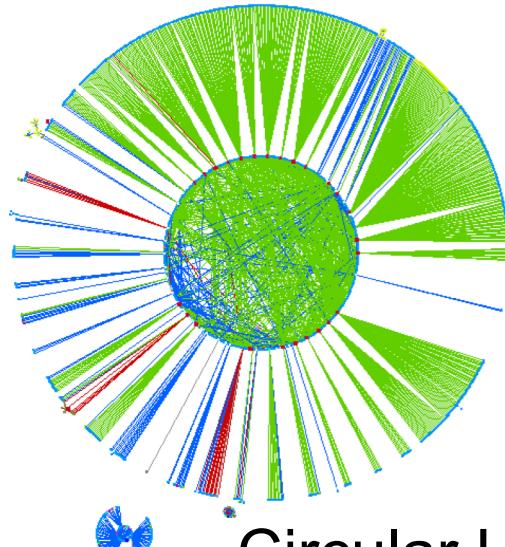
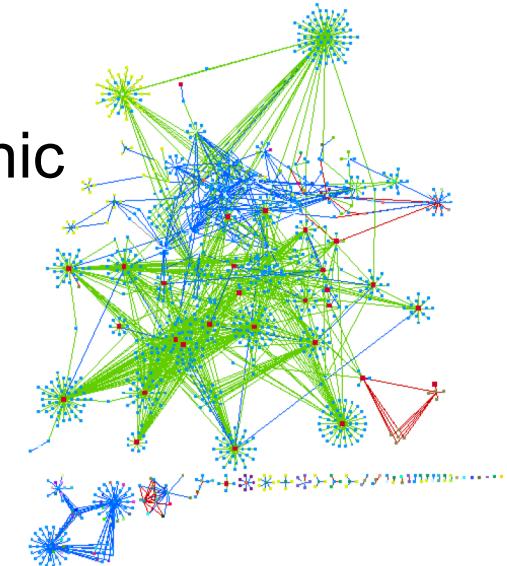


Experiment with different layouts

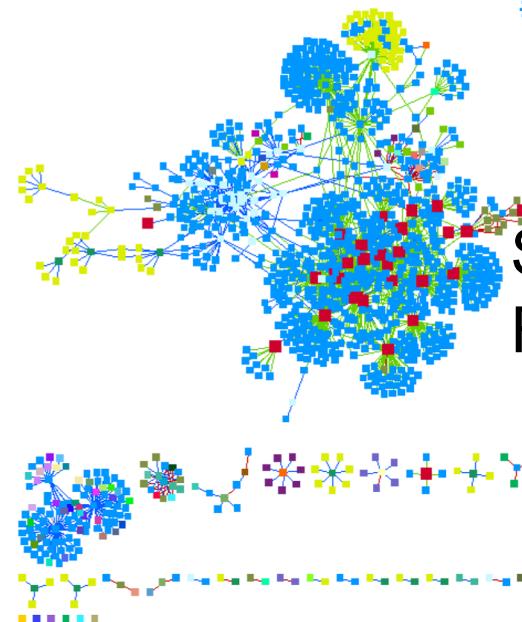
Compound Spring
Embedder (CoSE)



yfiles organic

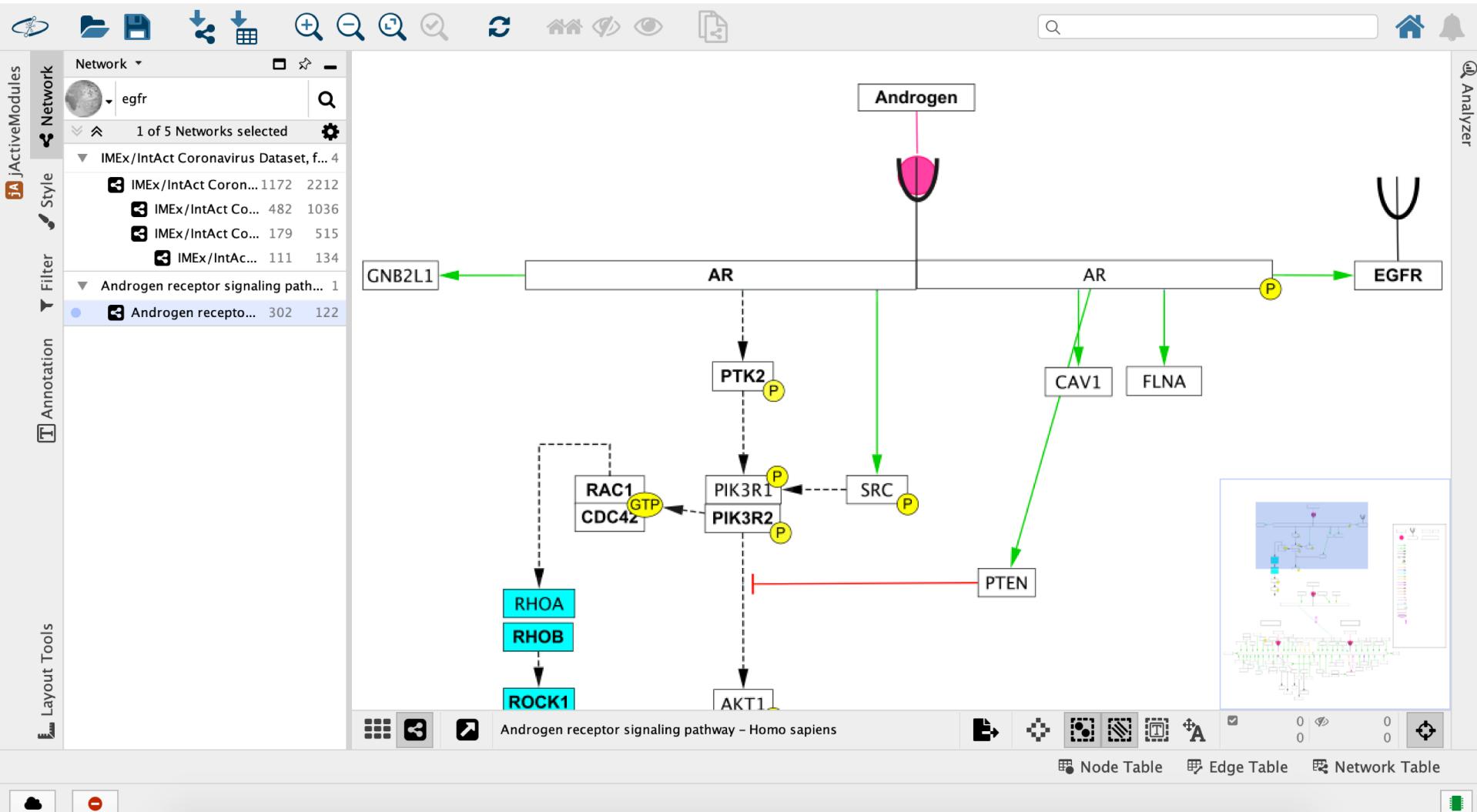


Circular Layout



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

compute | calcul
canada | canada



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