

Biological networks and their properties

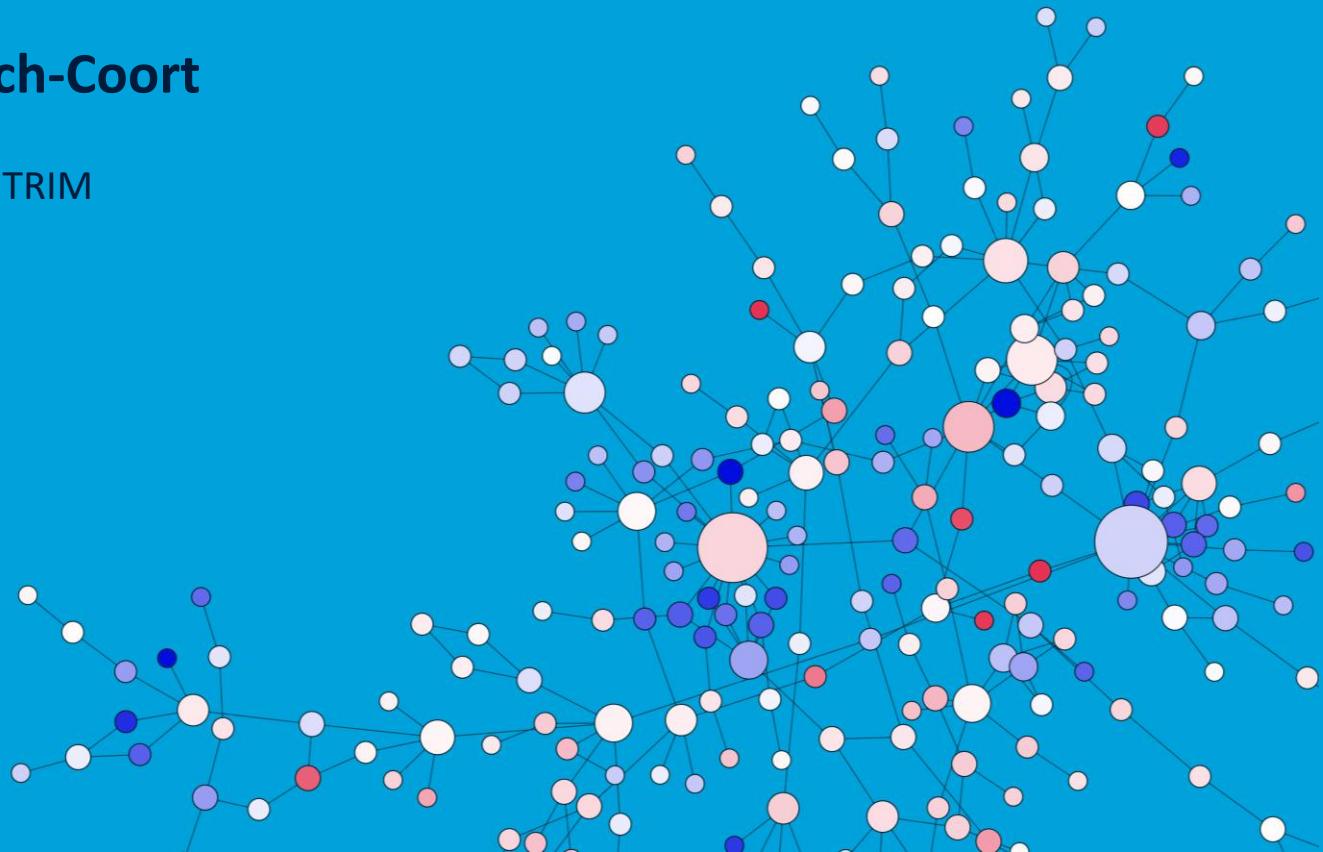
Dr. Susan Steinbusch-Coort

Associate Professor

Bioinformatics-BiGCaT, NUTRIM

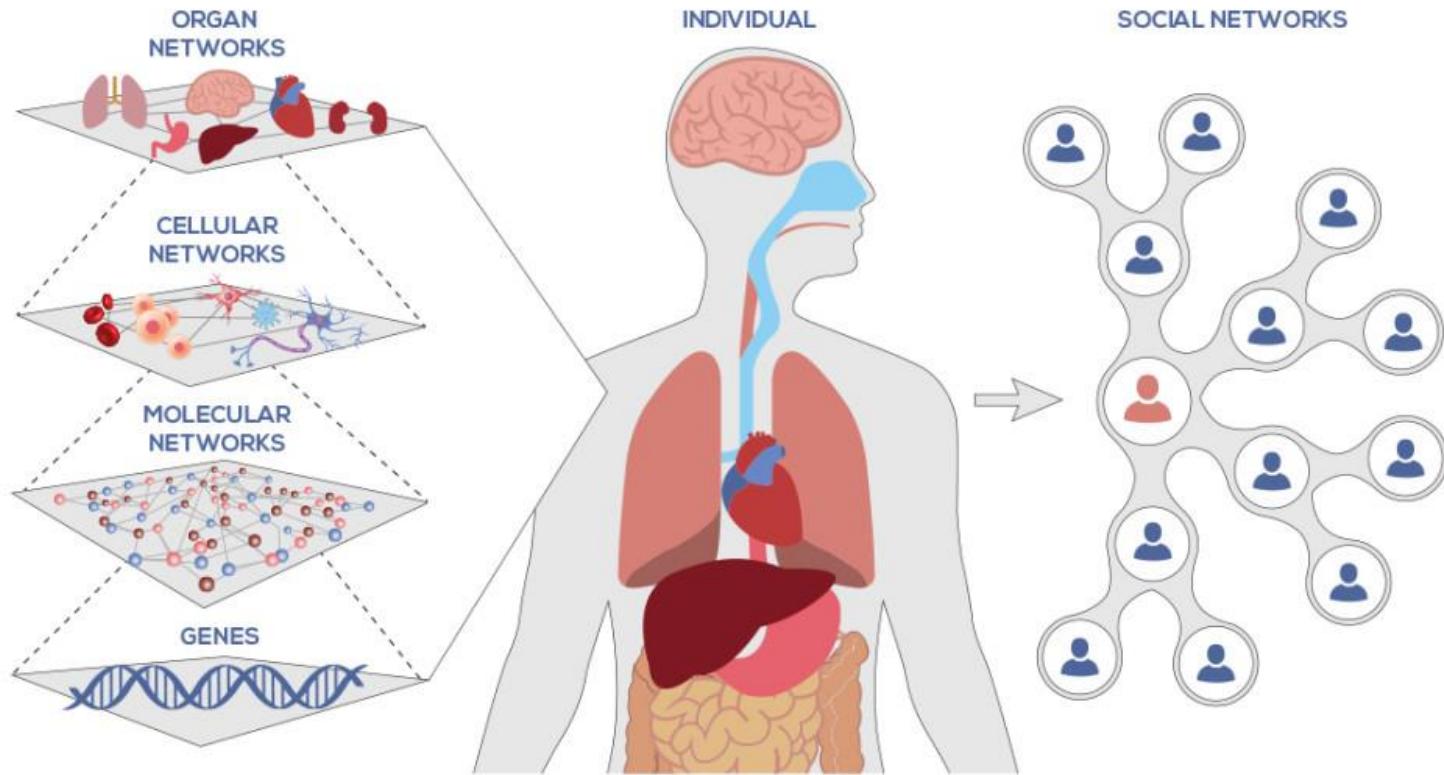
STREAMLINE

December 15th , 2023

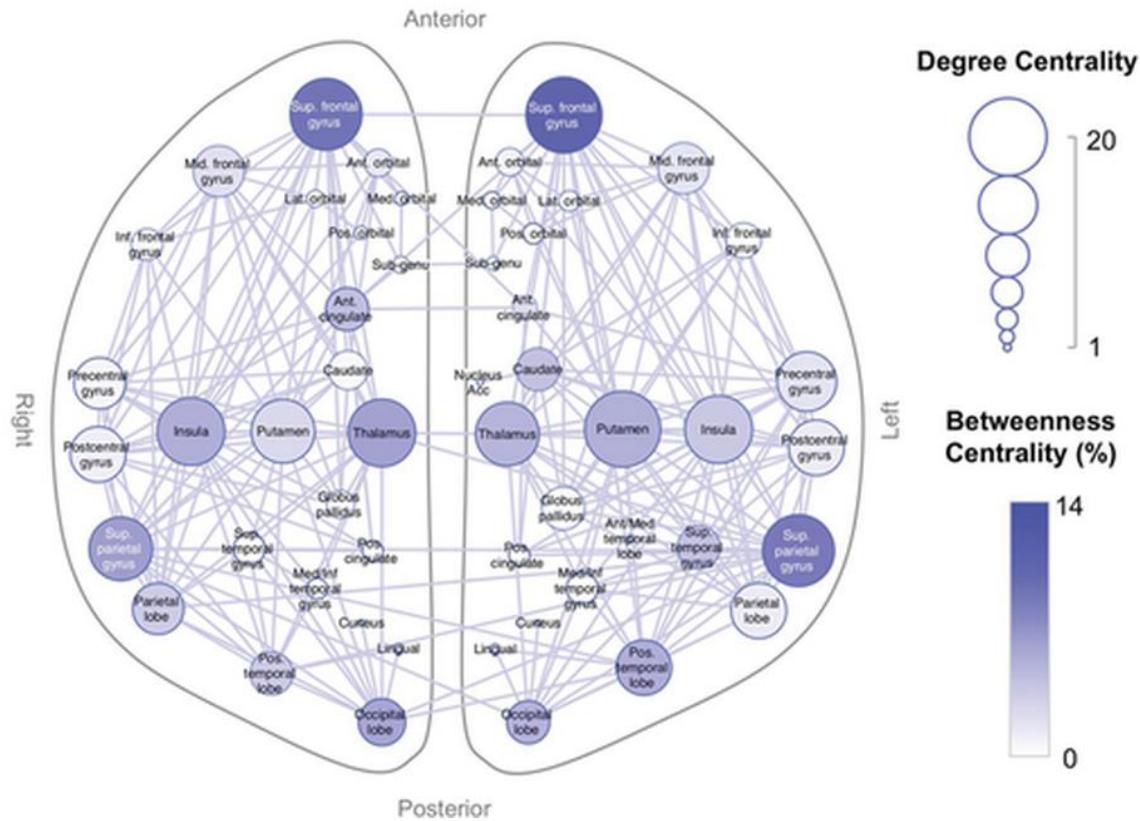


Maastricht University

Complexity of biological networks

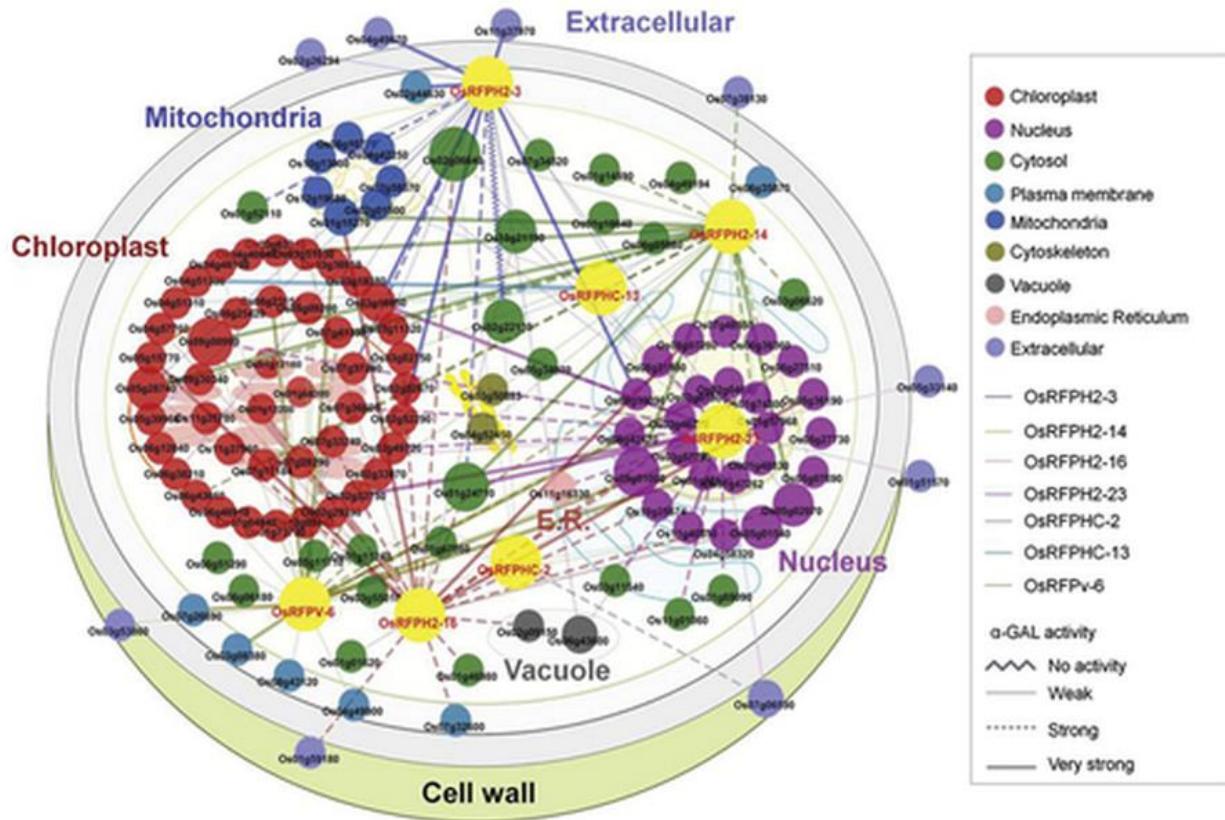


<http://cytoscape-publications.tumblr.com/archive>



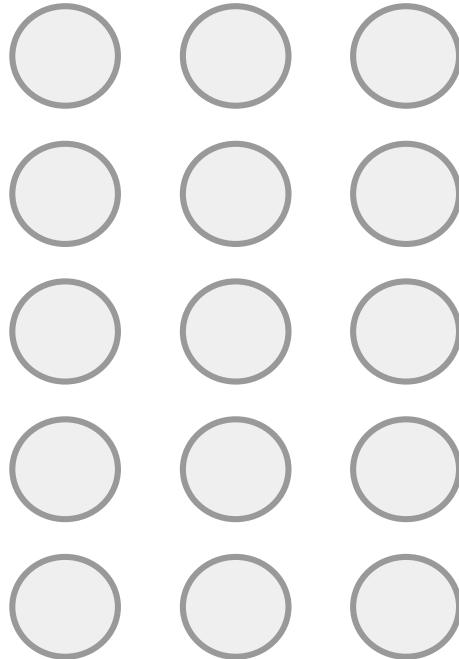
Whole-Brain Mapping of Structural Connectivity in Infants Reveals Altered Connection Strength Associated with Growth and Preterm Birth.
Pandit et al, Cereb Cortex. 2013 Mar 31.

<http://cytoscape-publications.tumblr.com/archive>



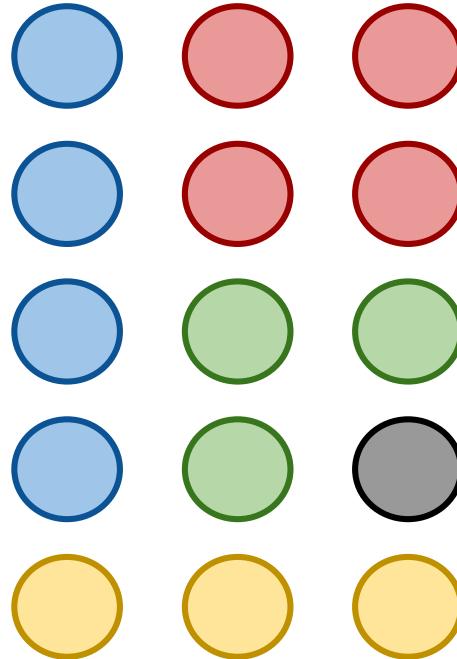
Comprehensive Analysis of the Rice RING E3 Ligase Family Reveals Their Functional Diversity in Response to Abiotic stress.
Lim et al, DNA Res. 2013 Apr 9.

Data



Quantitative measurements
Isolated data points

Conventional analysis



Comparative statistics

Isolated lists

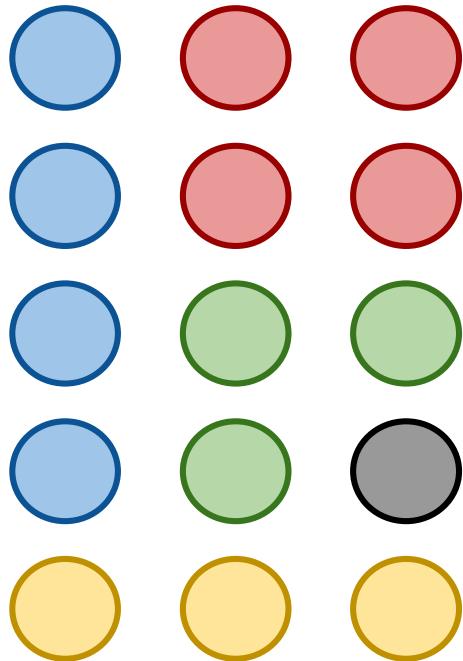
Clustering

Isolated groups

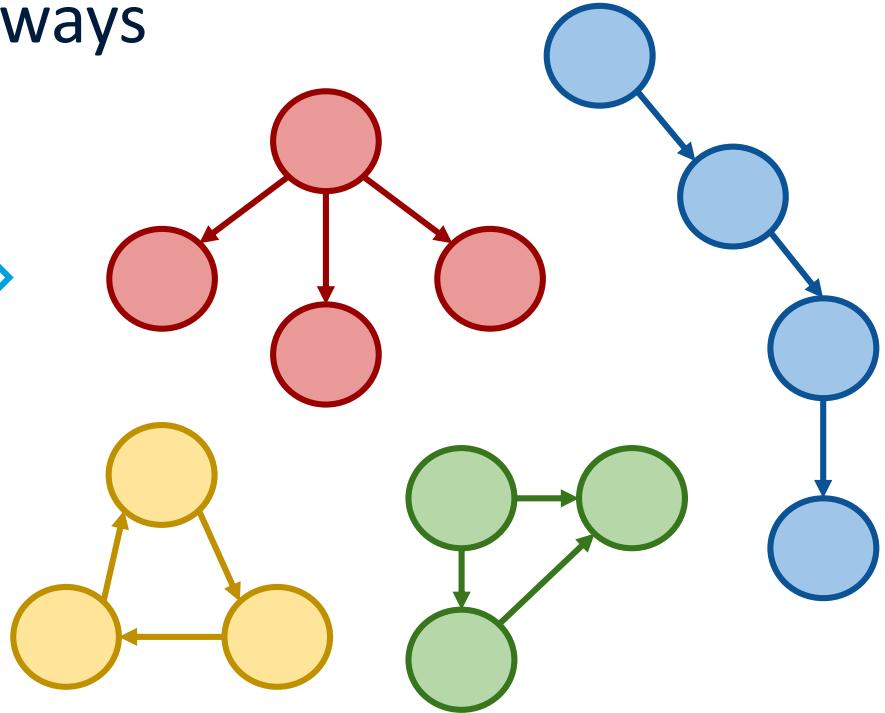
Gene sets

Functional groups

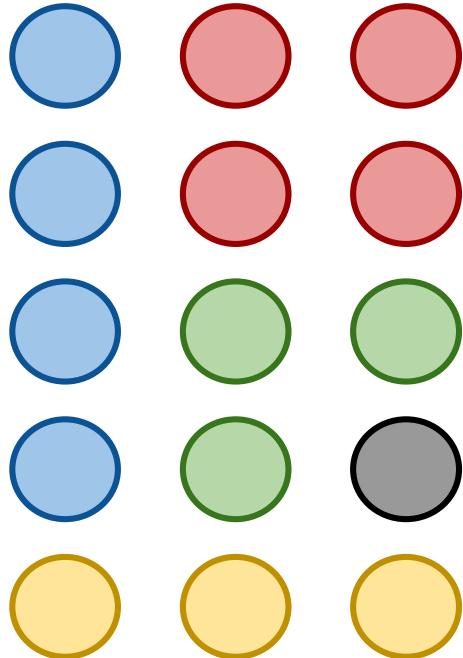
Pathway analysis



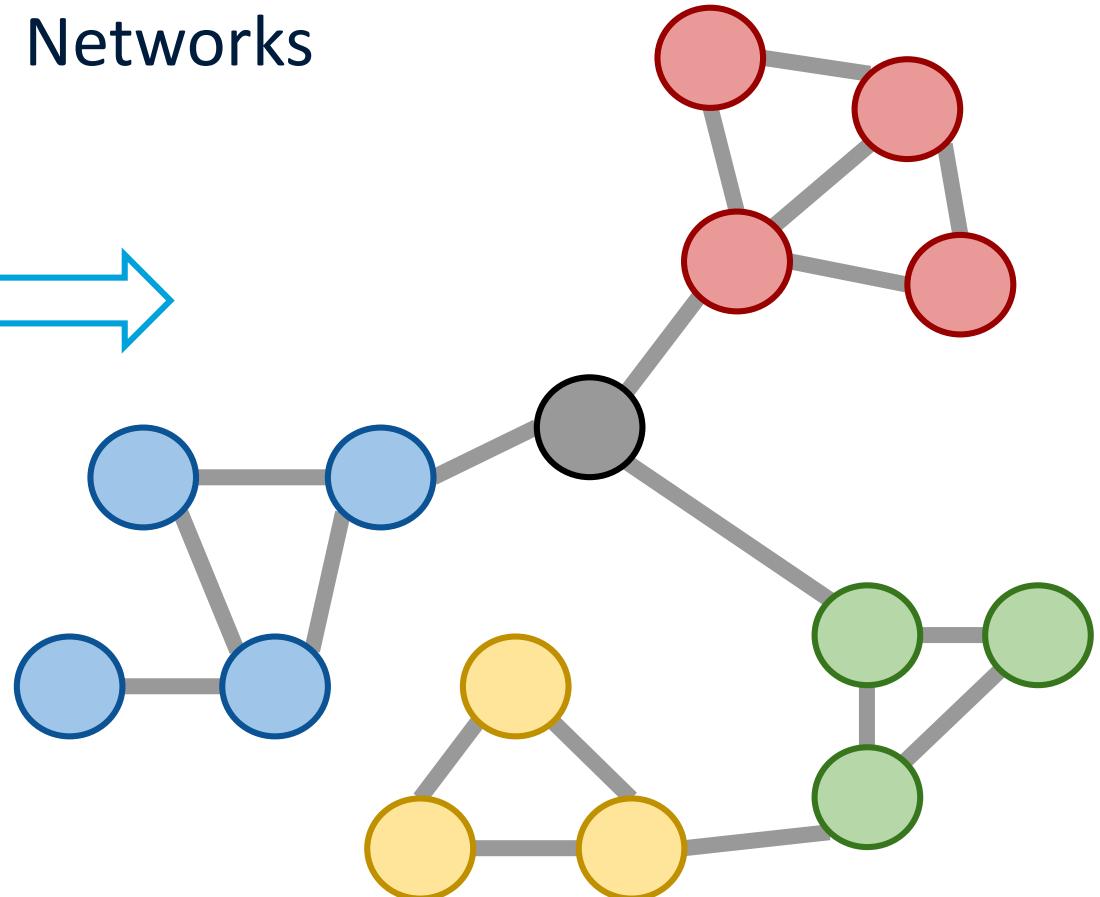
Functional organization
Pathways



Network analysis

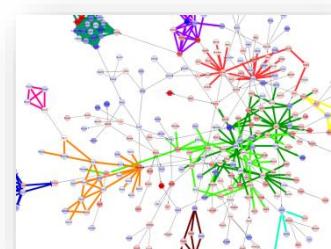
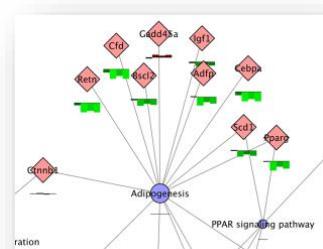
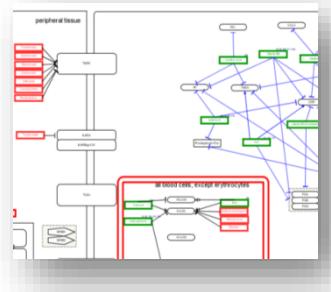
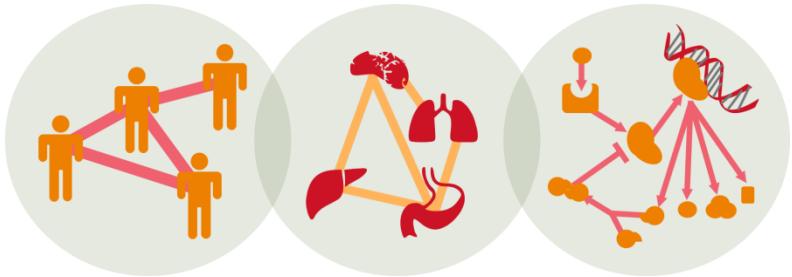


Systems organization
Networks



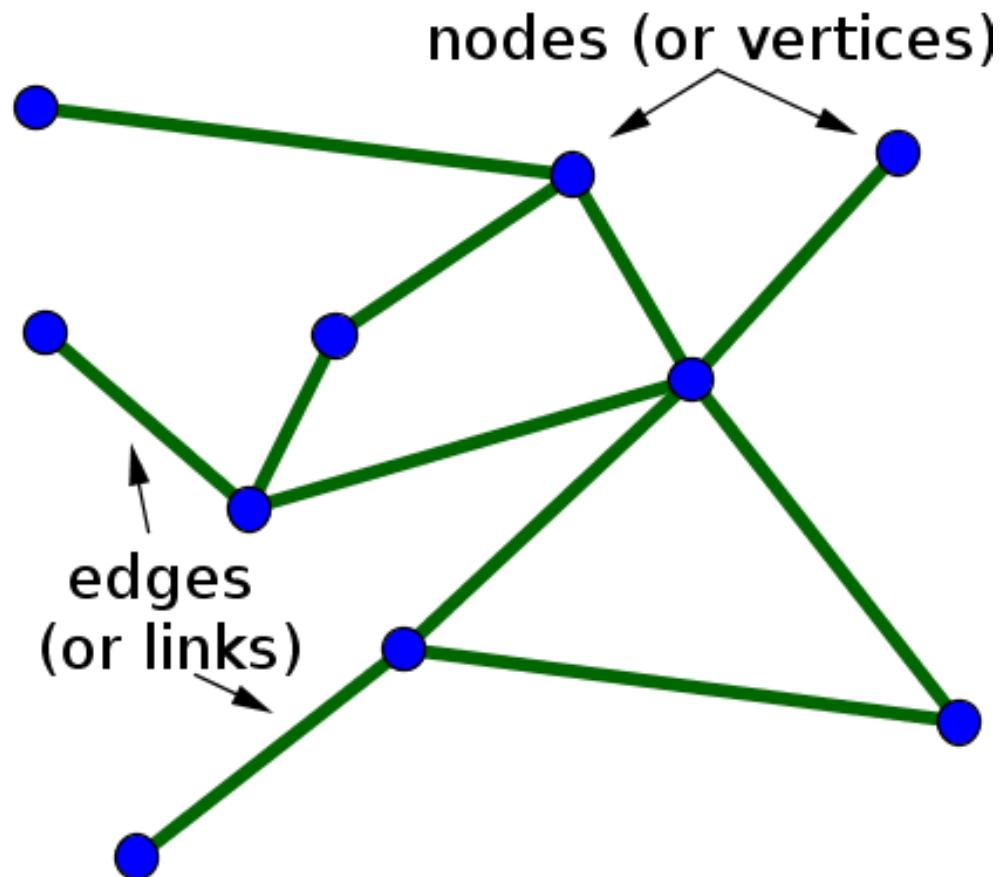
Understanding biological complexity at all levels

- **Integrate** diverse types of data
- Exploit **prior knowledge**
- **Visualize** complex data
- Find **relations & patterns**
- Identify key **pathways and drivers**
- Link to molecular data to **health benefit** readout
- Find functional signatures of **interventions**
- Find **perturbed paths**



Network properties

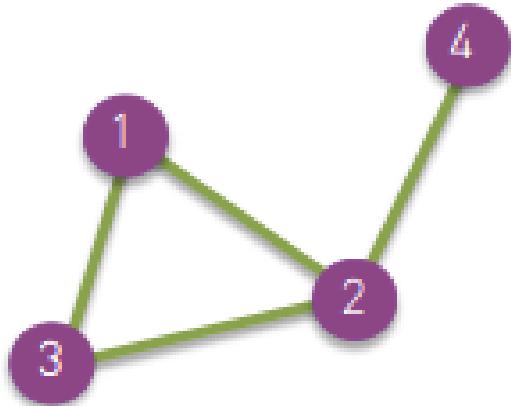
Elements in networks



Network properties

Undirected

Links: undirected (symmetrical)

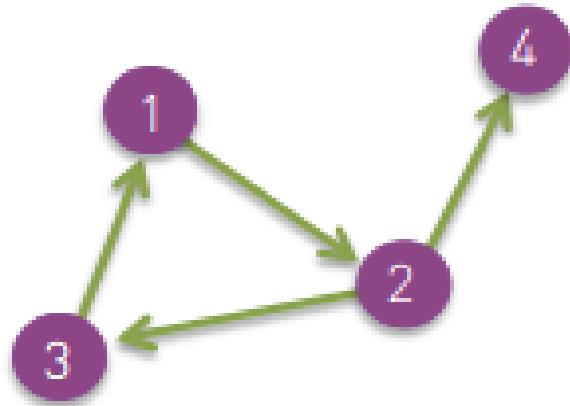


Examples:

Co-authorship, actor network, protein interactions

Directed

Links: directed (arcs)



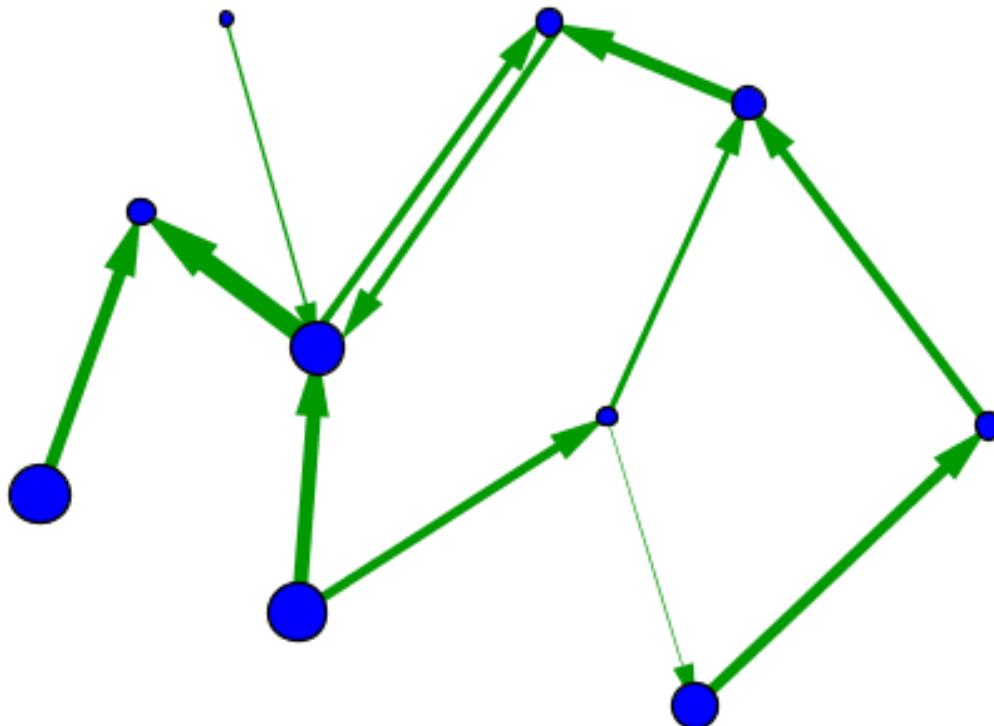
Examples:

URLs (internet), phone calls, metabolic reactions

Network properties

Weighted

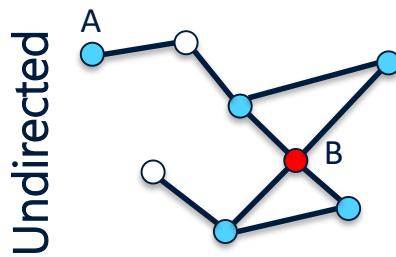
Links: weight, strength, flow



Network properties – degree and degree distribution

Degree

- k : Degree
 - number of links a node has to other nodes

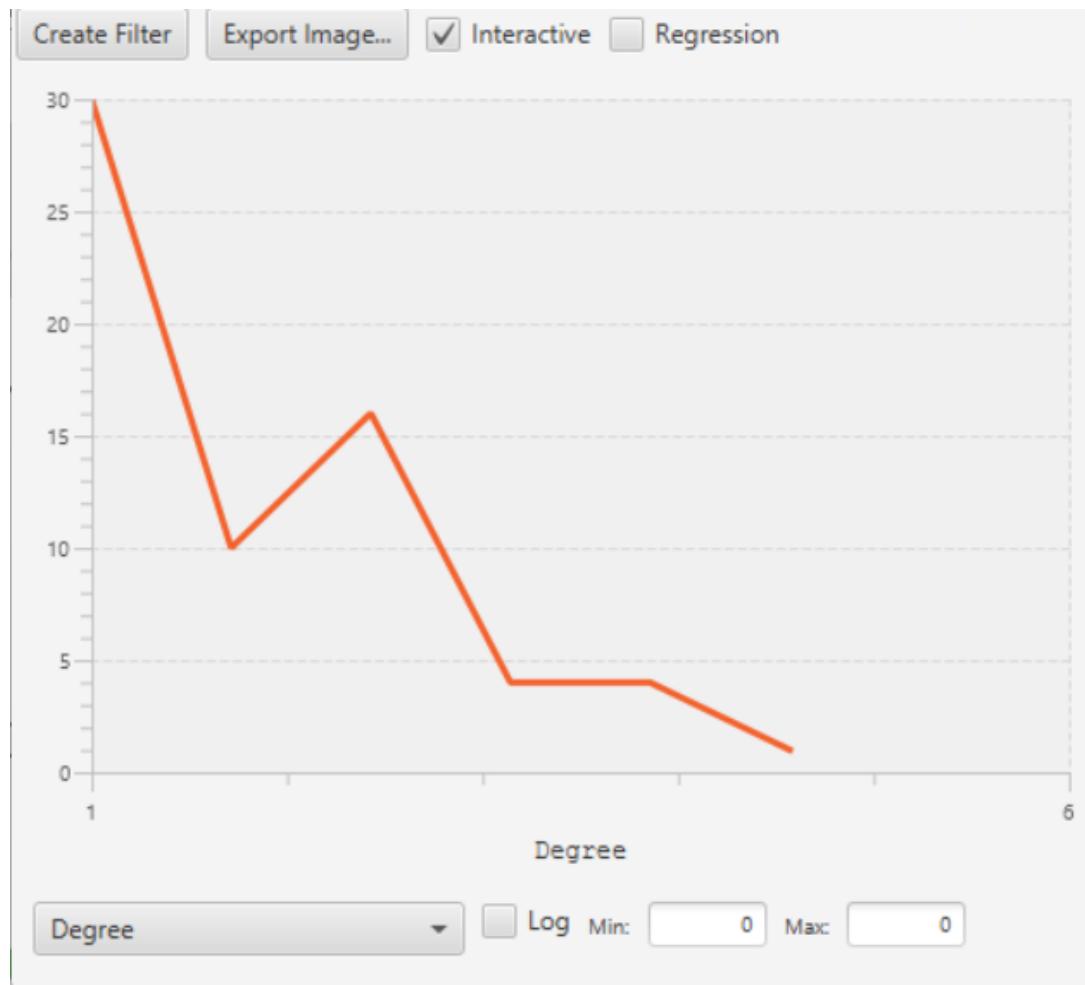


$$k_A = 1$$

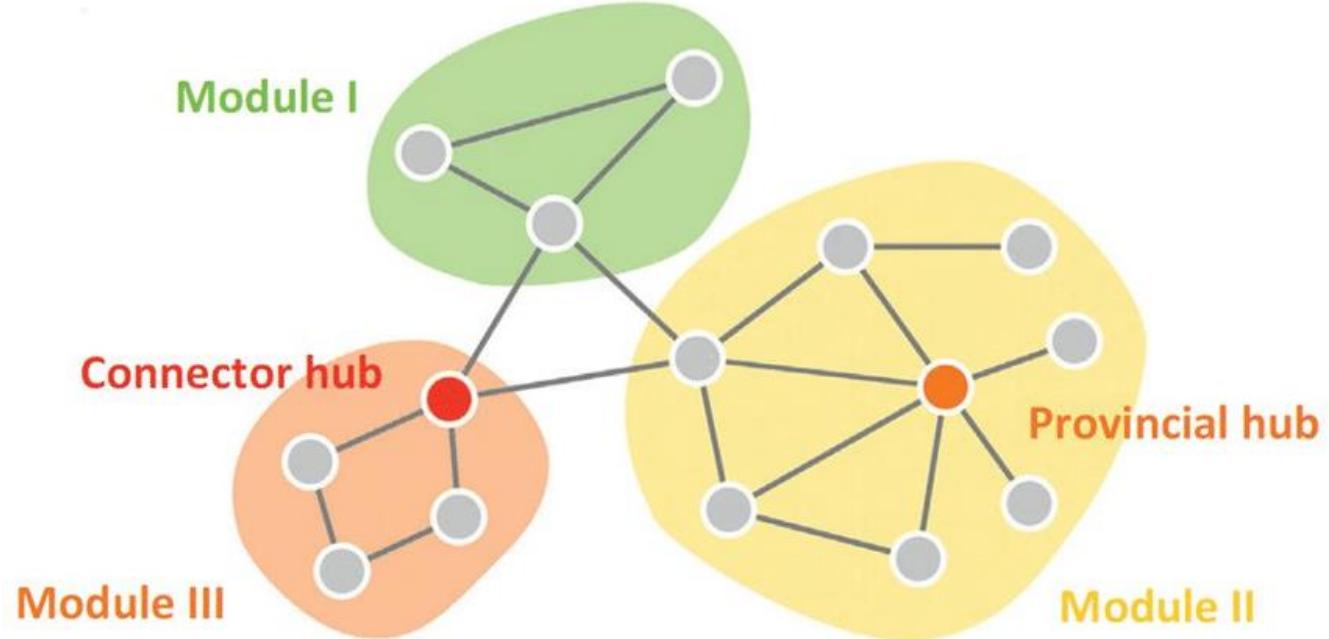
$$k_B = 4$$

$$L = \frac{1}{2} \sum_{i=1}^N k_i$$

Degree distribution



Hub nodes



Provincial hubs are high-degree nodes that primarily connect to nodes in the same module.

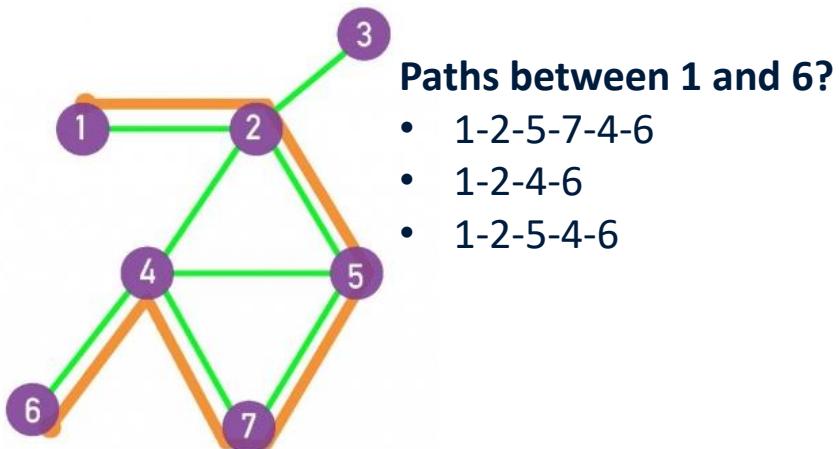
Connector hubs are high-degree nodes that show a diverse connectivity profile by connecting to several different modules within the network

Network properties – paths and distances

Paths

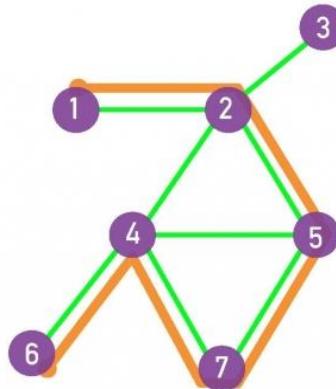
Definitions:

- A path is a route that runs along the links of the network.
- A path's length represents the number of links the path contains.



Shortest path

- Path with the fewest number of links – never loops or intersects itself!
- Shortest path is often called the distance between two nodes

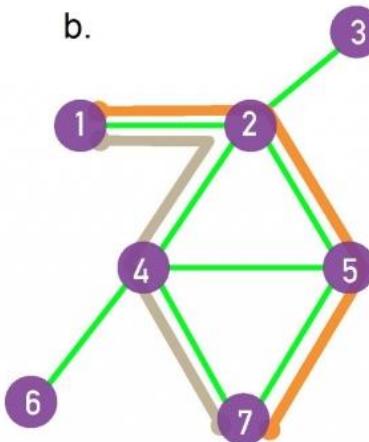


Paths between 1 and 6?

- 1-2-5-7-4-6 d=5
- **1-2-4-6** **d=3**
- 1-2-5-4-6 d=4

Shortest path

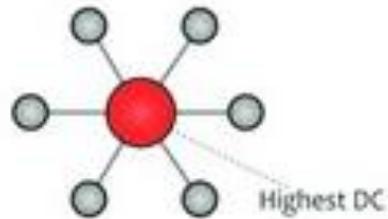
- Path with the fewest number of links – never loops or intersects itself!
- Shortest path is often called the distance between two nodes
- Multiple shortest paths of the same length d are possible
 - $d_{1,7} = 3$
 - Paths: 1-2-4-7 or 1-2-5-7



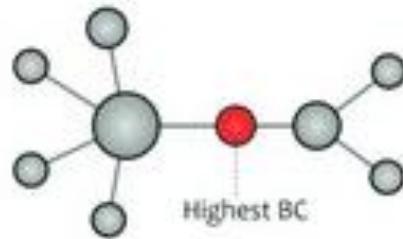
Betweenness centrality

It captures how much a given node is in-between others. This metric is measured with the number of shortest paths (between any couple of nodes in the graphs) that passes through the target node.

Degree centrality



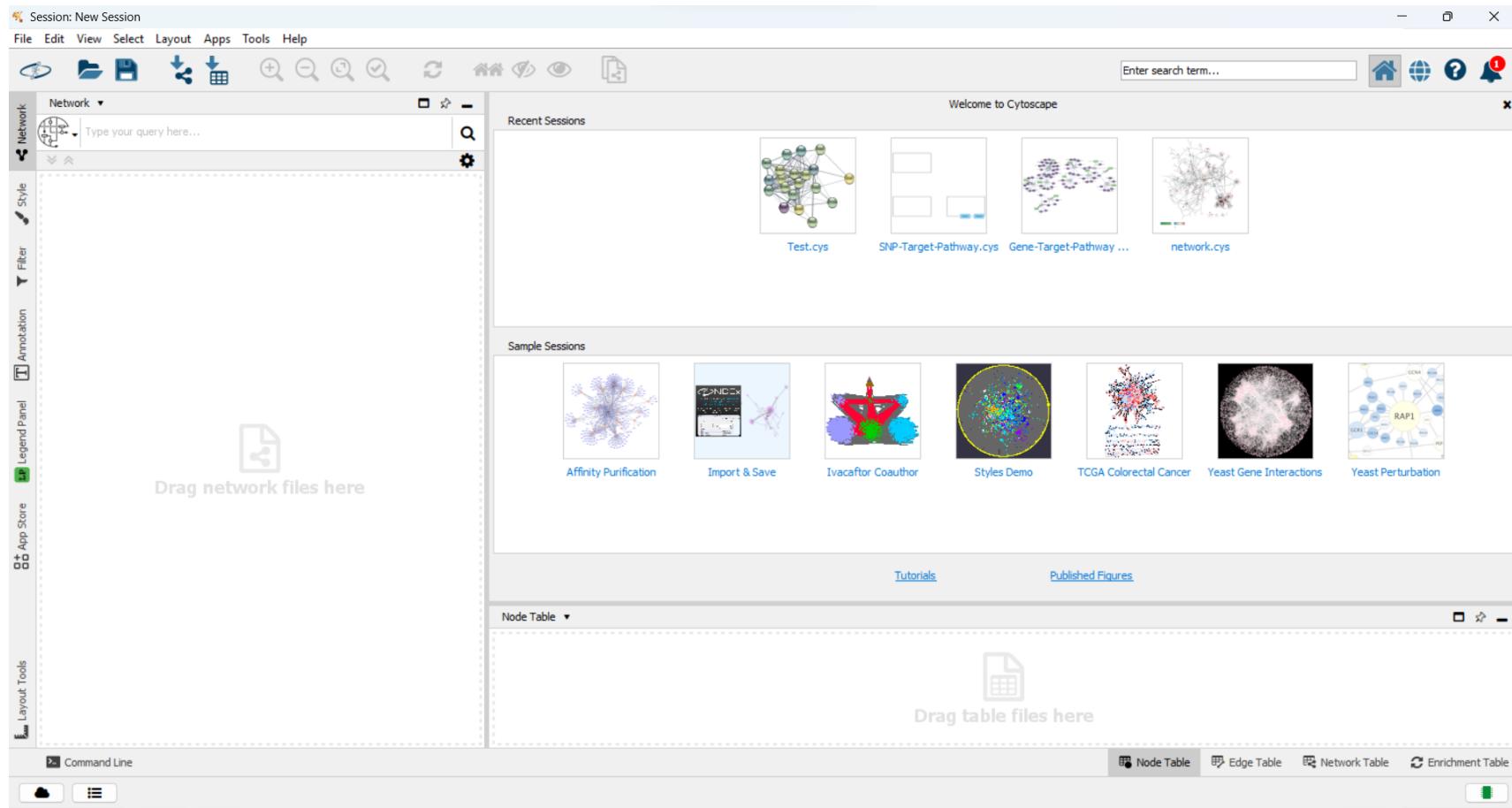
Betweenness centrality



Nodes with a high betweenness centrality are interesting because they lie on communication paths and can control information flow



Cytoscape (v3.10.1)



Cytoscape App store

The screenshot shows the Cytoscape App Store interface. At the top, there's a navigation bar with links to various tools like NRNB Tools, Galaxy Training!, Enrichr, gProfiler, RaMP, ENA Browser, DataHub Portal, Network analysis in..., and The European Bio... A search bar and sign-in options are also present.

All Apps

Categories

- collections
- data visualization
- network generation
- network analysis
- graph analysis
- online data import
- automation
- integrated analysis
- clustering
- systems biology
- utility
- enrichment analysis
- visualization
- data integration
- core app
- layout
- annotation
- pathway database
- ontology analysis
- import

[more »](#)

Newest Releases

[Get Started with the App Store »](#)

App	Description	Rating
CyEnGNet	CyEnGNet: Cytoscape Ensemble Gene Network	3.0+
stringApp	Import and augment Cytoscape networks from STRING	3.0+
Omics Visualizer	Import & Visualize several data for the same node	3.0+
Orthoscape	Orthoscape aimed to analyze evolutionary information in the	3.0+
BioGateway Cytoscape Plugin	An explorative network building plugin that works with the	3.0+
cyPlot	A utility to display data plots	3.0+

[more newest releases »](#)

Top Downloaded Apps

App	Description	Rating
ClueGO	Creates and visualizes a functionally grouped network of	3.0+
stringApp	Import and augment Cytoscape networks from STRING	3.0+
BINGO		3.0+
MCODE		3.0+

Types of Biological Network Data

1. Protein-protein interaction (PPI) networks

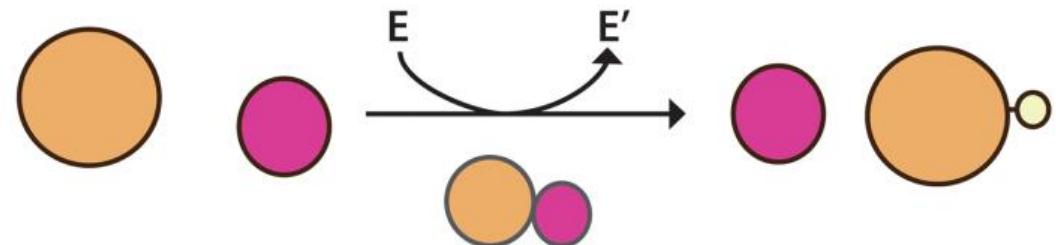
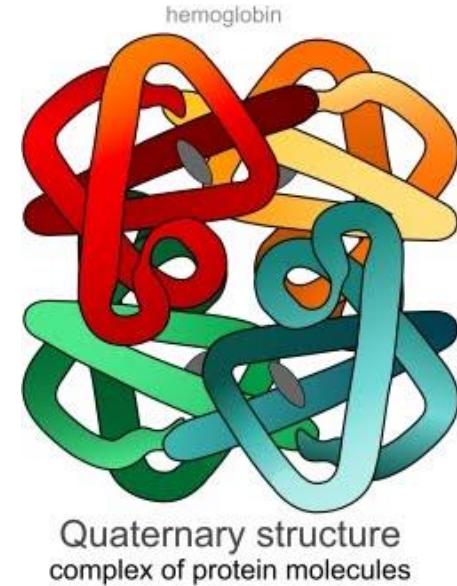
PPI: Physical contacts with molecular docking between proteins that occur in a cell or in a living organism *in vivo*

These contacts

- are specific;
- occur between defined binding regions in the proteins; and
- have a particular biological meaning (i.e., they serve a specific function).

Types of PPIs

- Stable interactions are formed in protein complexes (e.g. ribosome, haemoglobin).
- Transient interactions are brief interactions that modify or carry a protein, leading to further change (e.g. protein kinases, nuclear pore importins). They constitute the most dynamic part of the interactome.

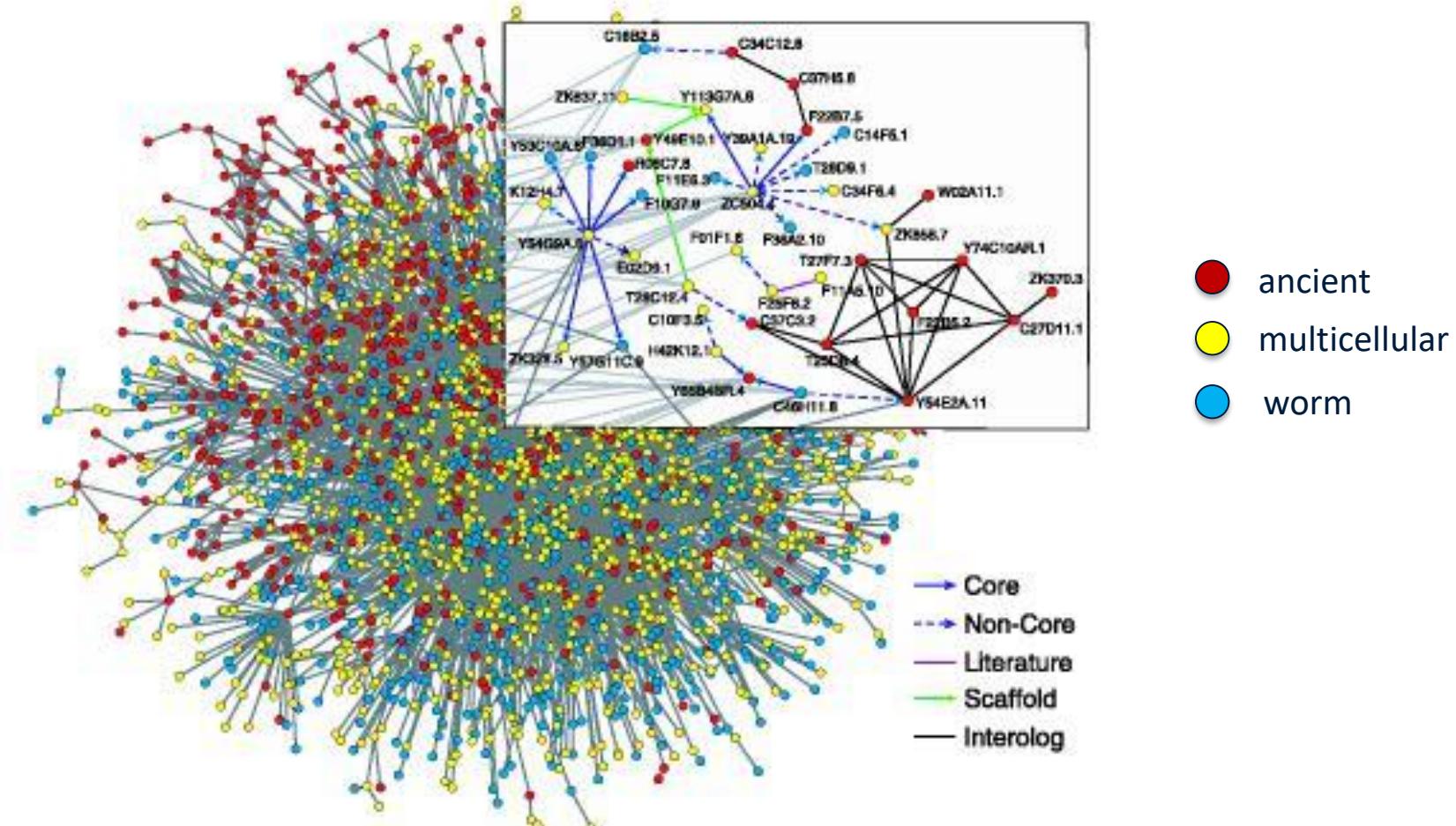


Interactome

The **interactome** is the totality of PPIs that happen in a cell, an organism or a specific biological context.

The development of large-scale PPI screening techniques, especially high-throughput affinity purification combined with mass-spectrometry and the yeast two-hybrid assay, has caused an explosion in the amount of PPI data and the construction of ever more complex and complete interactomes.

C. Elegans interaction network



Science 23 Jan 2004:
Vol. 303, Issue 5657, pp. 540-543
DOI: 10.1126/science.1091403

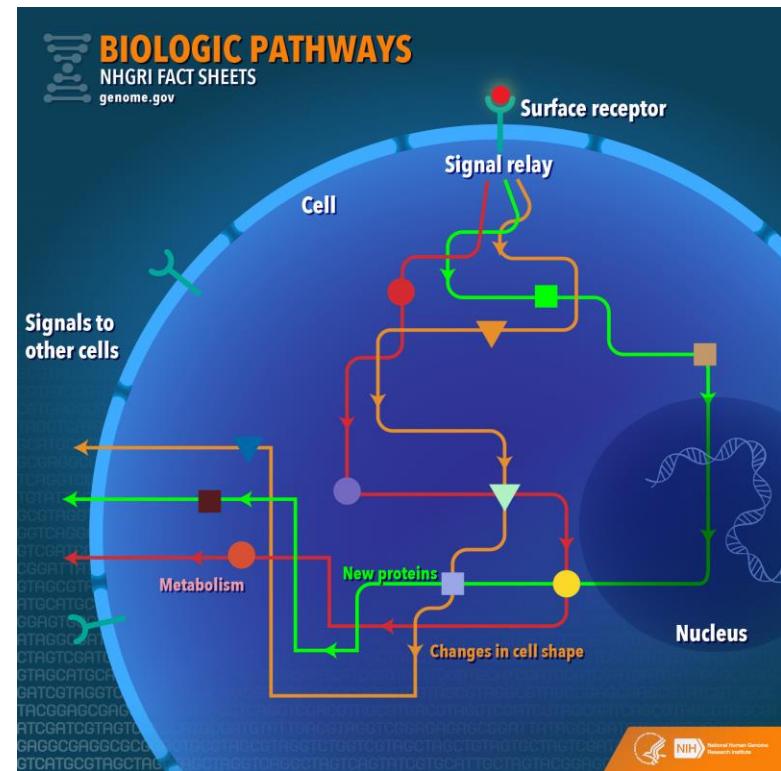
2. Biological pathways

Definition on Wikipedia:

“ A biological pathway is a series of **interactions** among **molecules** in a cell that leads to a certain product or a change in a cell.

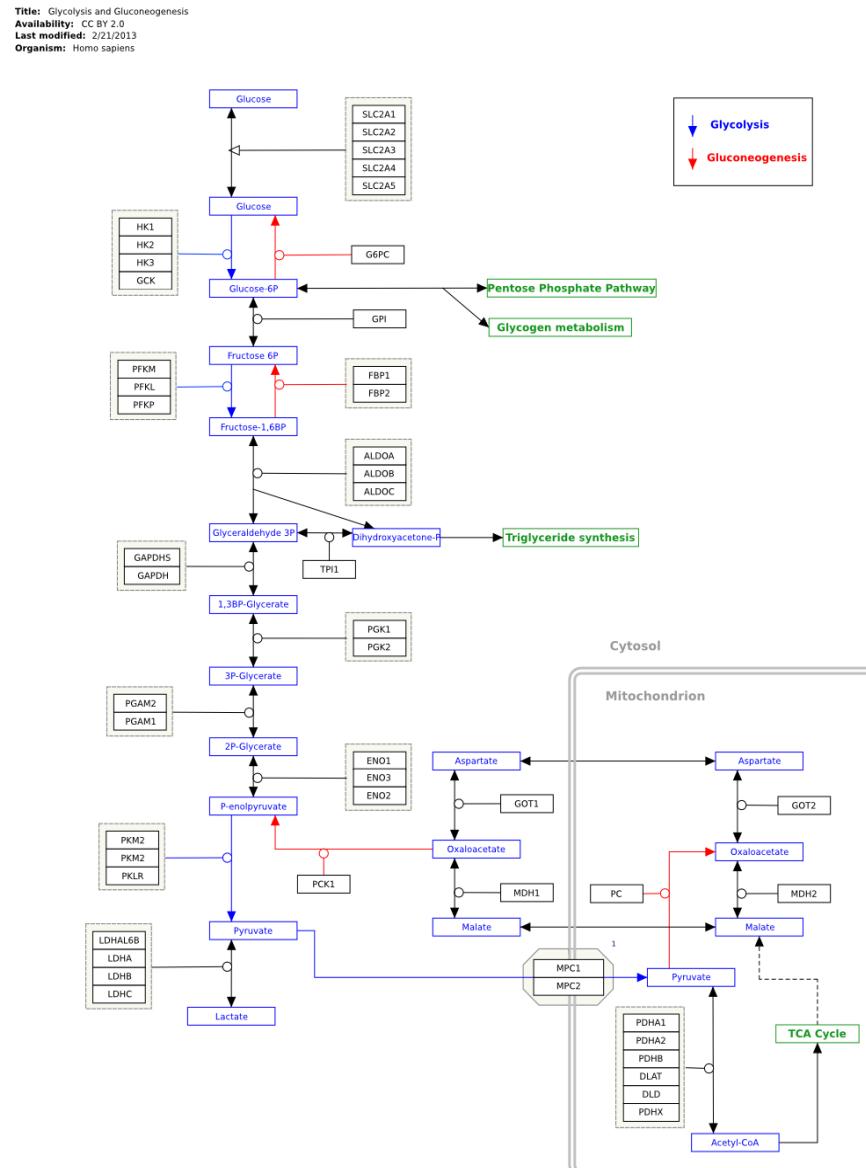
Types:

1. **Metabolic pathways**
2. **Gene regulation pathways**
3. **Signal transduction pathways**

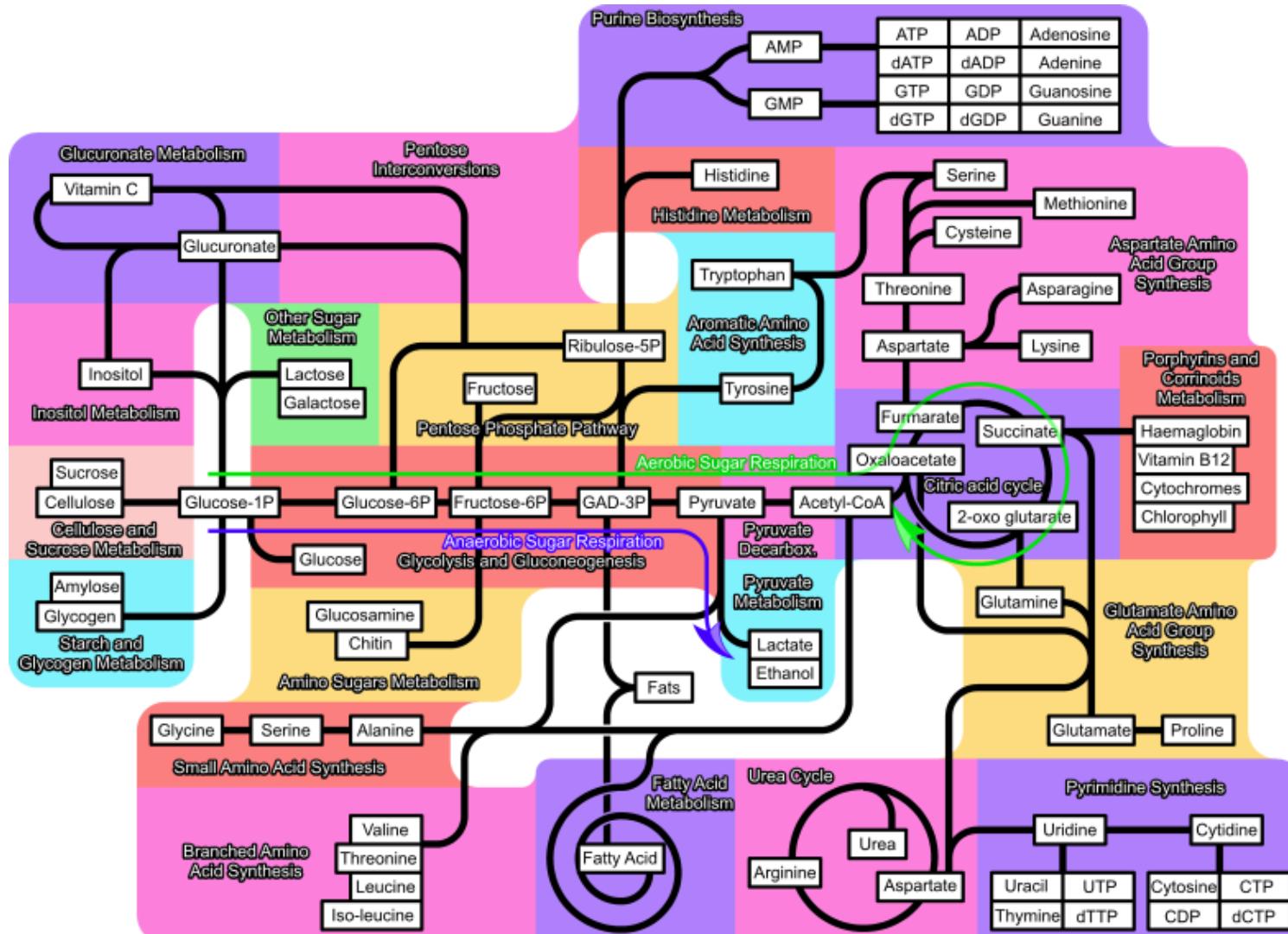


Metabolic pathways

- "... series of chemical reactions occurring within a cell."
- Enzymes catalyze these reactions.
- Example: Glycolysis

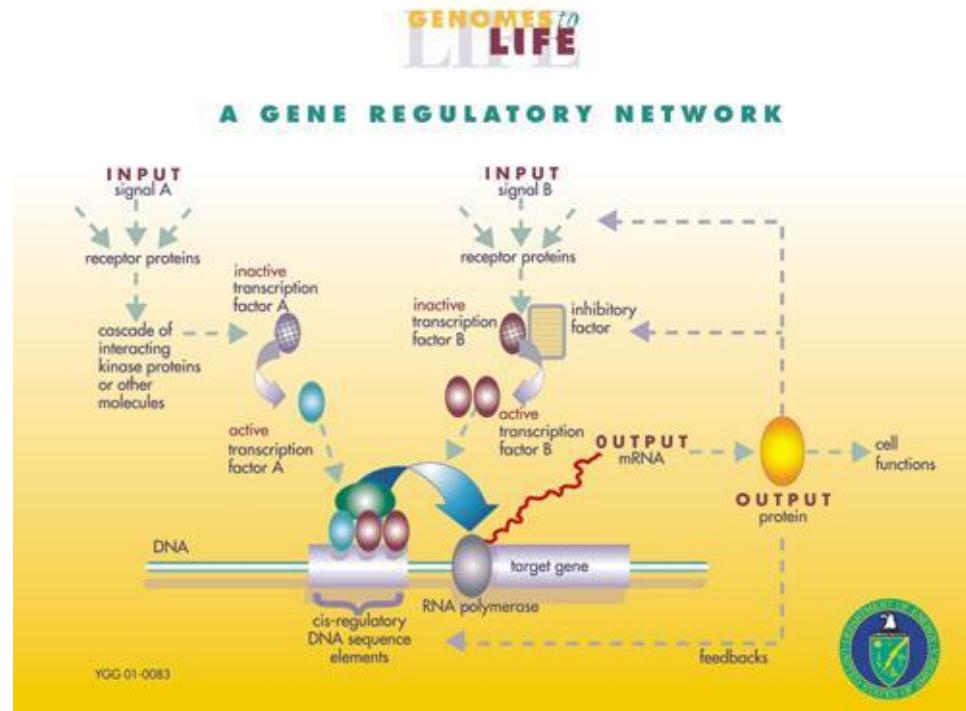


Metabolic pathways



Gene regulation pathways

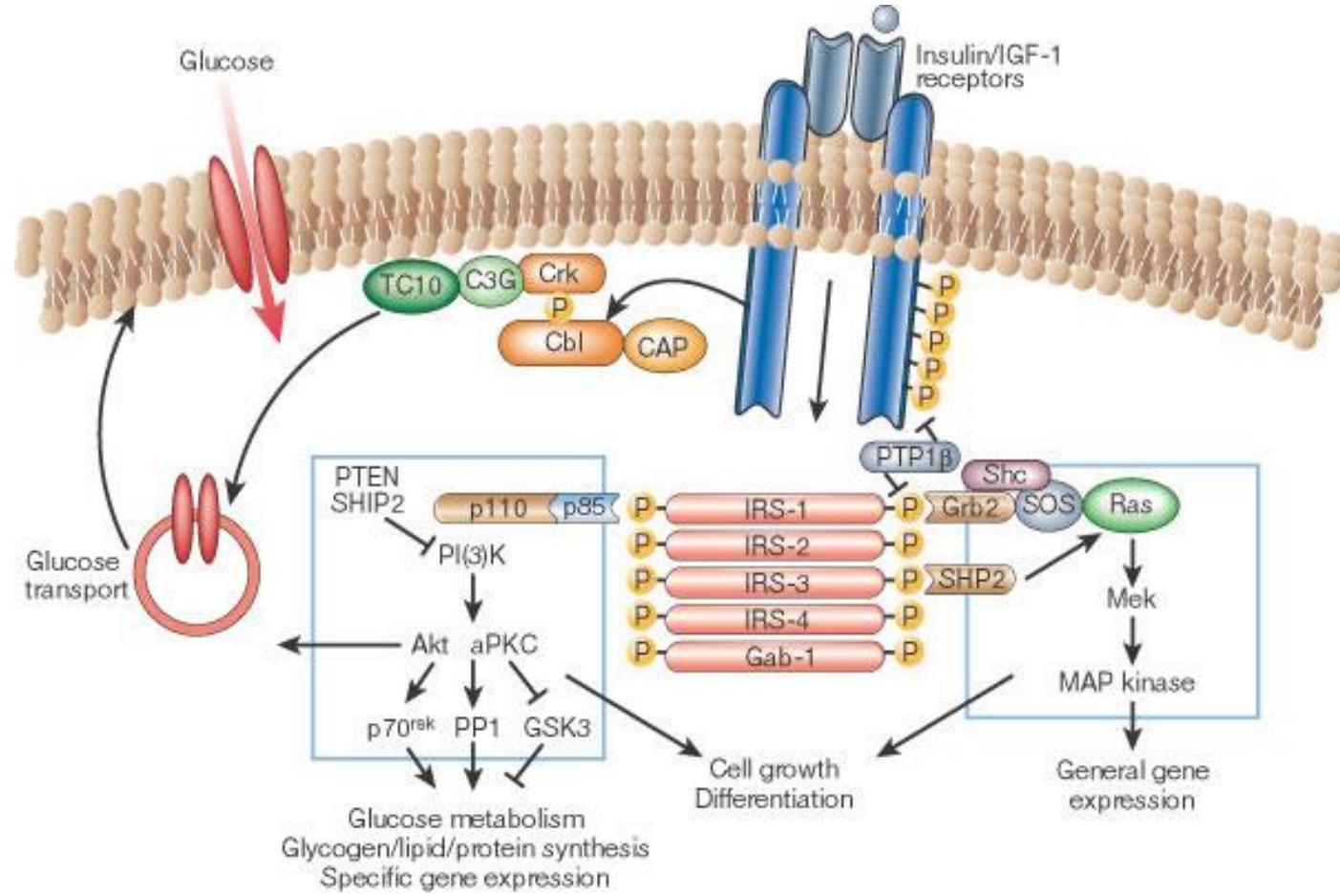
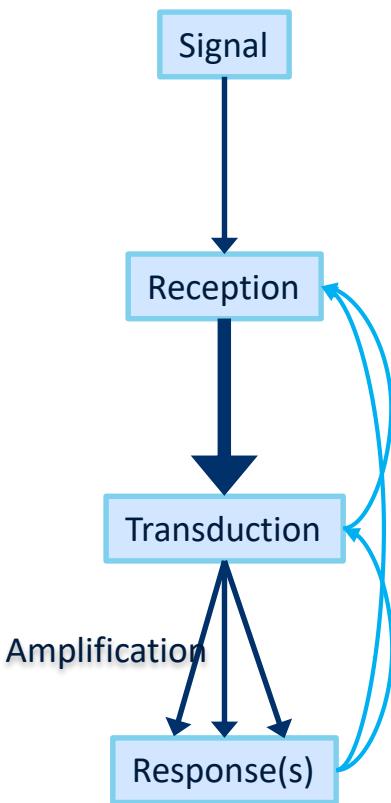
- Pathways that regulate the level of gene expression
- Often sub-pathway in a larger pathway
- Linked to gene regulatory networks



http://en.wikipedia.org/wiki/Gene_regulatory_network

Signal transduction pathways

PRINCIPLE



PathGuide (www.pathguide.org)

Interaction data (e.g. protein-protein interaction)

STRING, IntAct,

Pathway data

- WikiPathways, KEGG, Reactome, Panther, BioCarta
ConsensusPathDB, BioCyc, PathwayCommons, ...

The screenshot shows the PathGuide website interface. At the top right, there are links for Home, BioPAX, cBio, and MSKCC. The main header reads "Pathguide the pathway resource list". On the left, a navigation sidebar includes sections for Protein-Protein Interactions, Metabolic Pathways, Signaling Pathways, Pathway Diagrams, Transcription Factors / Gene Regulatory Networks, Protein-Compound Interactions, Genetic Interaction Networks, Protein Sequence Focused, and Other. Below these are search filters for Organisms (All), Availability (All), and Standards (All), with "Reset" and "Search" buttons. The central content area has three main sections: "Complete Listing of All Pathguide Resources", "Protein-Protein Interactions", and a "News" sidebar. The "Complete Listing" section contains a paragraph about the database's scope and a link to send feedback. The "Protein-Protein Interactions" section lists various databases with columns for Details, Availability (Free or X), and Standards (BioPAX). The "News" sidebar highlights major updates in September 2017 and August 2013, noting new resources.

Complete Listing of All Pathguide Resources

Pathguide contains information about 702 biological pathway related resources and molecular interaction related resources. Click on a link to go to the resource home page or 'Details' for a description page. Databases that are free and those supporting BioPAX, CellML, PSI-MI or SBML standards are respectively indicated.

If you know of a pathway resource that is not listed here, or have other questions or comments, please [send us an e-mail](#).

News

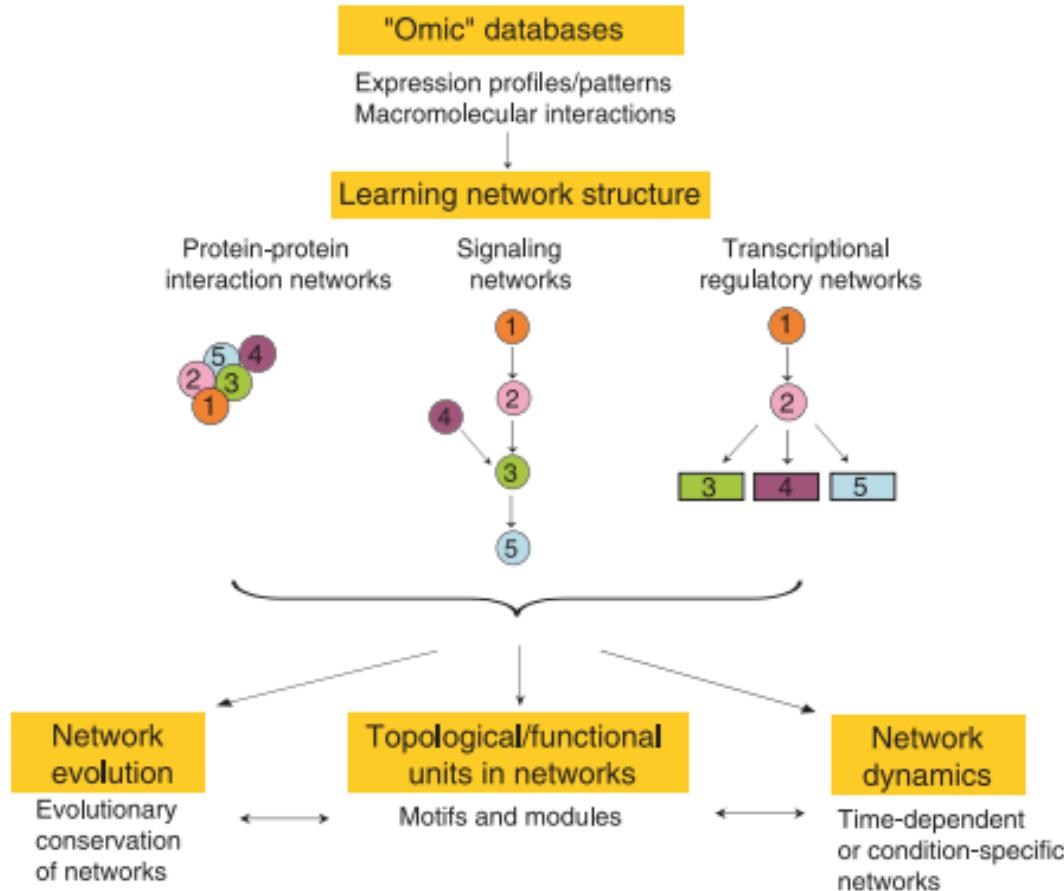
Major new update of Pathguide
September 2017
We now have information for over 690 resources!

Major new update of Pathguide
August 2013
We now have information about ~550 resources!

Protein-Protein Interactions

Database Name (Order: alphabetically by web popularity ⓘ)	Full Record	Availability	Standards
2P2Idb - The Protein-Protein Interaction Inhibition Database	Details	Free	
3D-Interologs - 3D-Interologs	Details	Free	
3DID - 3D interacting domains	Details	Free	
ACSN - Atlas of Cancer Signalling Network	Details	Free	BioPAX
ADAN - Prediction of protein-protein interaction of modular domains	Details	X	
AHD2.0 - Arabidopsis Hormone Database 2.0	Details	Free	
AllFuse - Functional Associations of Proteins in Complete Genomes	Details	X	
aMAZE - Protein Function and Biochemical Pathways Project	Details	X	
ANAP - Arabidopsis Network Analysis Pipeline	Details	Free	

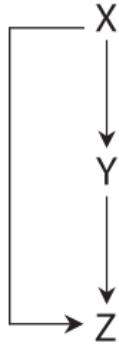
Biological Network analysis based on “Omics”data



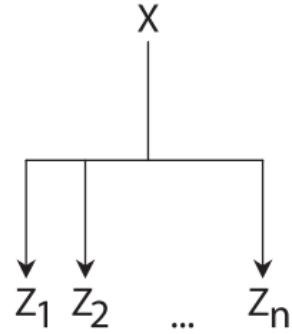
Modularity of biological networks

- Topological patterns that enable the functionality
- Find basic building blocks of biological networks

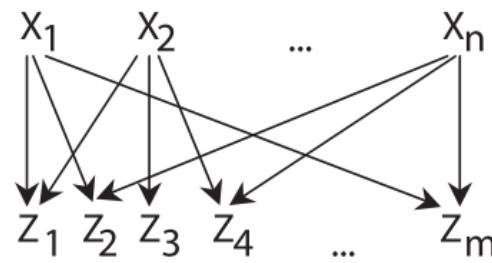
Feed-forward loop



Single input motif



Multiple input motif



- Exists in a variety of biological context, i.e., protein complexes, metabolic pathways, transcriptional regulation

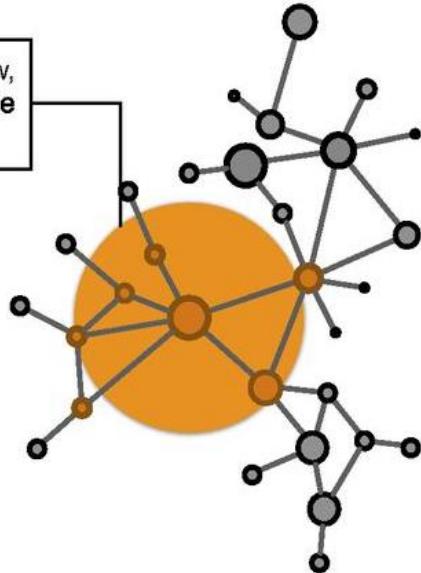
Dynamics of biological networks

- Gene activities and interactions exhibit temporal profiles and spatial compartmentalizations
- By integrating PPI networks with gene expression data, modules could be defined that are more active at specific times and locations.
- Network topologies reveal dynamic properties that contribute to cellular functions.
- Requirement of time-series of condition-specific data to look at cellular dynamics.
- Often mRNA expression -> single cell sequencing needed!

Influence patterns in biological networks

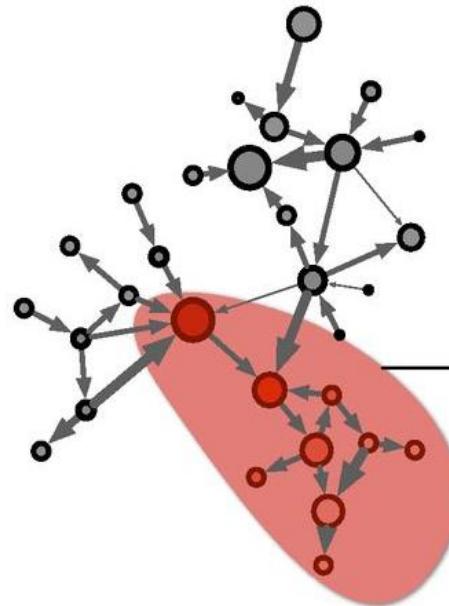
Topology

In a purely topological view, influence from a central node propagates along the links



Dynamics

Kinetic parameters and compartmentalization can create more complex propagation patterns, channelling the spread of perturbations in selected directions



Model complexity

Biochemical entities interact and form the subcellular network

PPI network resources – STRING and IntAct

Welcome to STRING

Protein-Protein Interaction Networks
Functional Enrichment Analysis

ORGANISMS

12535

PROTEINS

59.3 mio

INTERACTIONS

>20 bln

<https://string-db.org/>



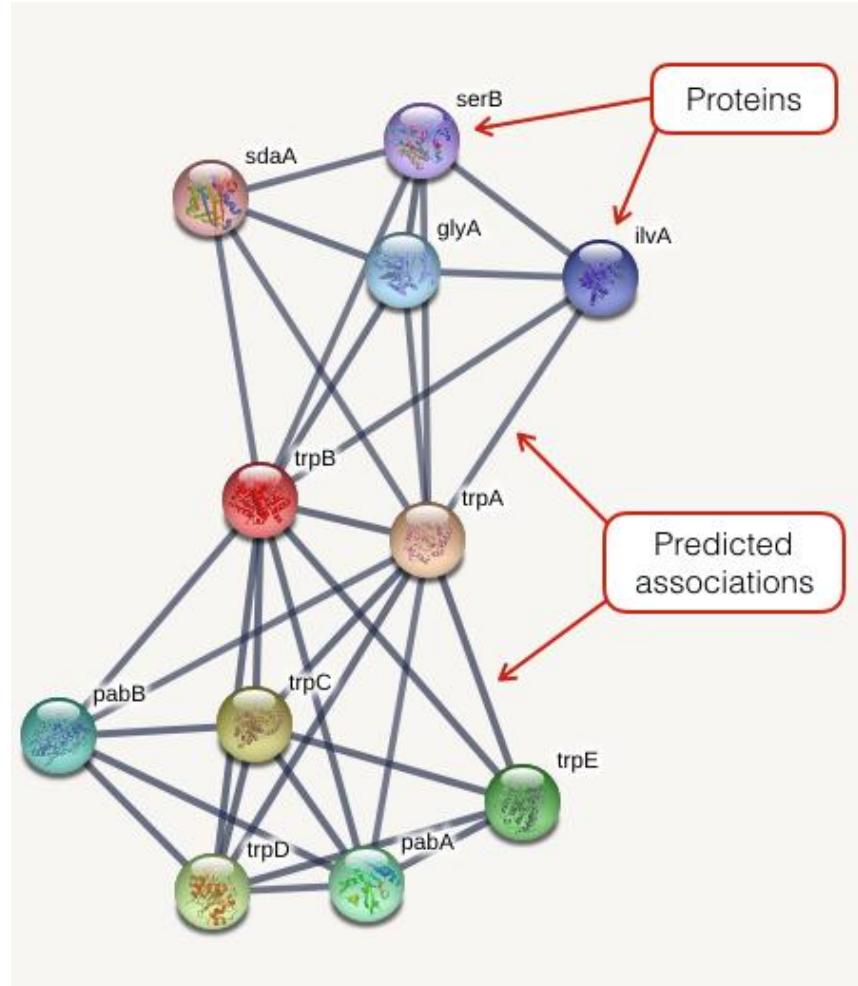
Maastricht University

STRING network

The network view summarizes the network of predicted associations for a particular group of proteins.

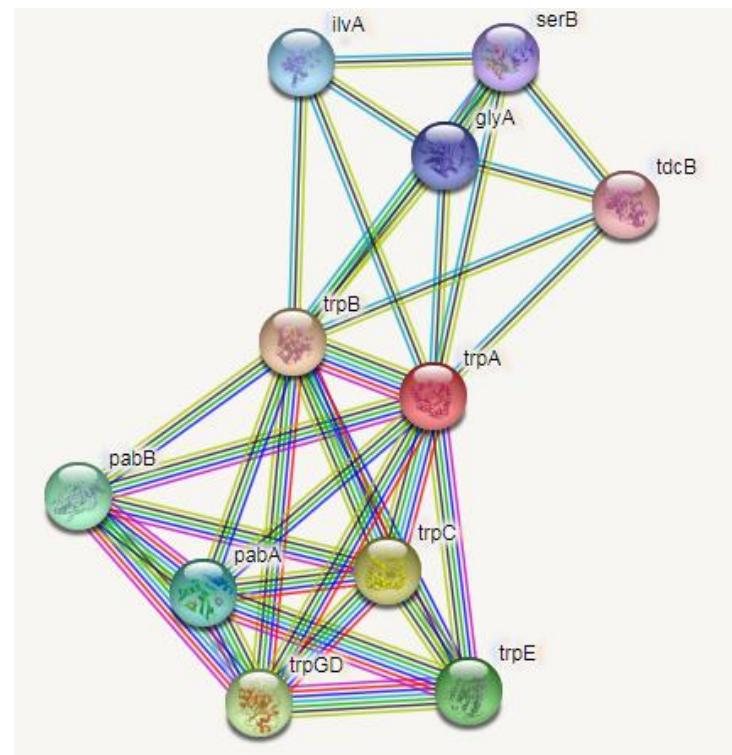
The network nodes are proteins.

The edges represent the predicted functional associations.



STRING – network (edges)

- In *evidence mode*, an edge may be drawn with up to 7 differently colored lines - these lines represent the existence of the seven types of evidence used in predicting the associations.
 - Red line - the presence of fusion evidence
 - Green line - neighborhood evidence
 - Blue line - cooccurrence evidence
 - Purple line - experimental evidence
 - Yellow line - textmining evidence
 - Light blue line - database evidence
 - Black line - coexpression evidence.

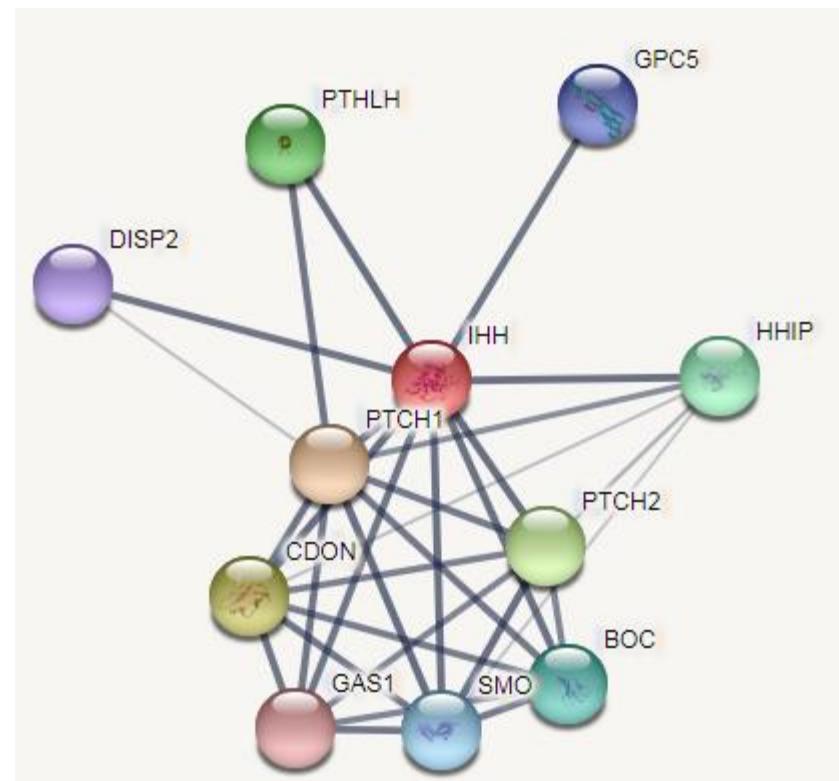


STRING – network (scoring)

Confidence, i.e. how likely STRING judges an interaction to be true, given the available evidence. All scores rank from 0 to 1, with 1 being the highest possible confidence.

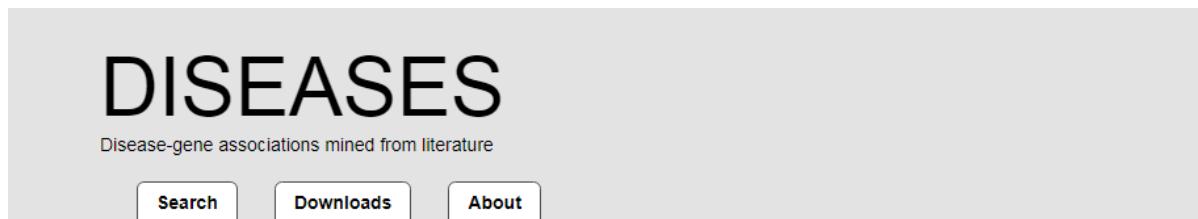
Confidence limits are as follows:

- low confidence - 0.15 (or better),
 - medium confidence - 0.4,
 - high confidence - 0.7,
 - highest confidence - 0.9.



Disease query in STRING

- Find the top-N human proteins linked to a disease
- Information comes from the DISEASES database
-> text mining and data integration of disease-gene associations



Search for a human gene or a disease: (examples: #1 #2)

Developed by [Sune Frankild](#), [Albert Pallejà](#), [Kalliopi Tsafou](#), and [Lars Juhl Jensen](#) from the [Novo Nordisk Foundation Center for Protein Research](#).

<https://diseases.jensenlab.org/>



IntAct Molecular Interaction Database

IntAct provides a freely available, open source database system and analysis tools for molecular interaction data. All interactions are derived from literature curation or direct user submissions and are freely available. The IntAct Team also produce the [Complex Portal](#).

Search in IntAct

[Search](#) [Search Tips](#)

Examples

- Gene, Protein, RNA or Chemical name: [BRCA2](#), [Stauroporine](#)
- UniProtKB or ChEBI AC: [Q06609](#), [CHEBI:15996](#)
- UniProtKB ID: [LCK_HUMAN](#)
- RNACentral ID: [URS00004C95F4_559292](#)
- PMID: [25416956](#)
- IMEx ID: [IM-23318](#)

Data Content

- Publications: [20319](#)
- Interactions: [859043](#)
- Interactors: [107811](#)

Submission

[Submit](#) your data to IntAct to increase its visibility and usability!

Citing IntAct

Training



Contributors

Manually curated content is added to IntAct by curators at the EMBL-EBI and the following organisations:

Featured Dataset

An orthogonal proteomic survey uncovers novel Zika virus host factors.

- Scaturro et al. [IntAct](#) [PSI-MI 2.5](#) [PSI-MI TAB](#)
- [Go to Archive](#)

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News



IntAct at EBI Retweeted

PRIDE at EBI
@pride_ebi

Out @nature "An orthogonal proteomic survey uncovers novel Zika virus host factors" go.nature.com/2LYBVFT Datasets #PXD009551, #PXD009557, #PXD009560 & #PXD009561. bit.ly/2oIF5Ey @pride_ebi @ProteomeXchange



An orthogonal proteomic s...
Integrative analyses identif...
[nature.com](#)

<https://www.ebi.ac.uk/intact/>

IntAct

The Molecular Interactions team produces the IntAct database of evidence for molecular interactions.

The team's primary goal is to help researchers make the most of public interaction data, and to facilitate the adoption of standards in this important area of molecular biology.



IntAct - Network

279 binary interactions found for search term *BRCA2*

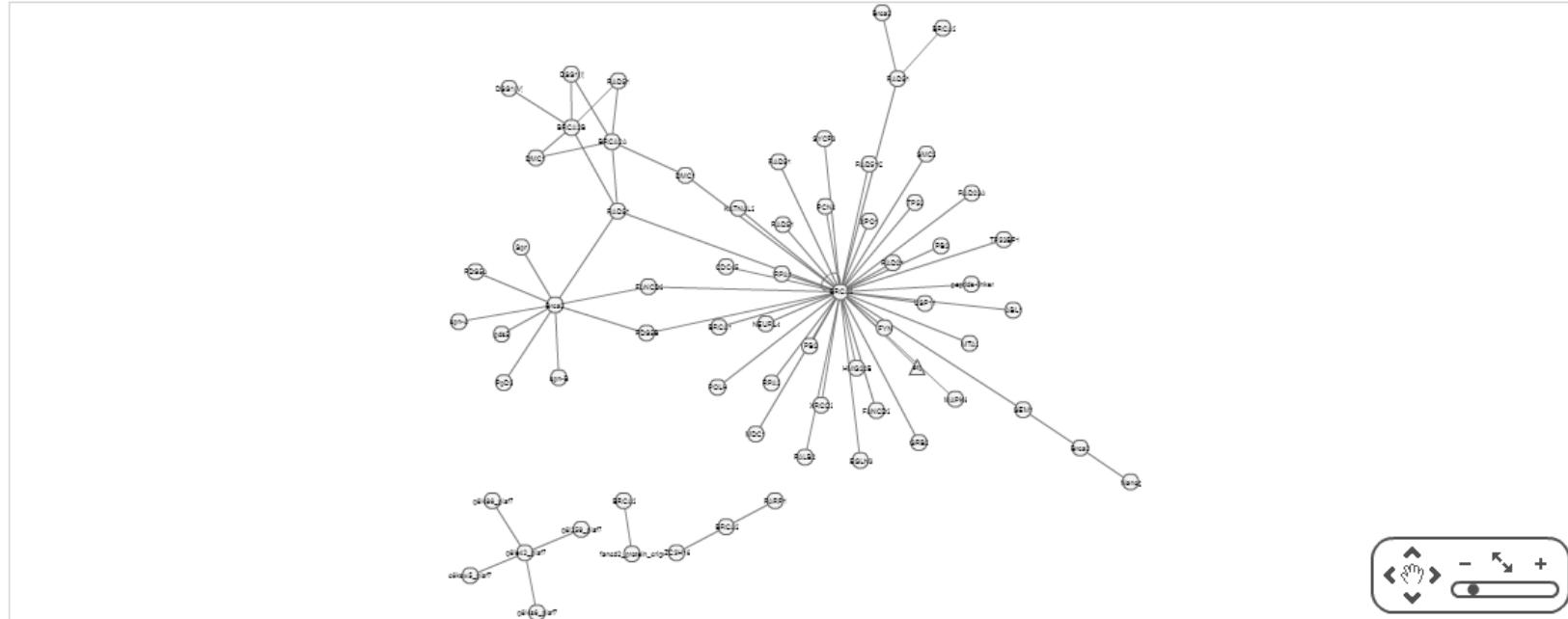
Interactions (279)

Interactors

Interaction Details

Graph

Network visualisation



IntAct – Network (interactors)

Proteins (66) Complexes (0) Compounds (1) Nucleic Acids (0) Genes (1)

Action for selection: [Search Interactions](#) | [Chromosome Location](#) | [mRNA Expression](#) | [Pathways](#) [What is this view](#)

		Names	Type	Interactions	Links	Species	Accession	Description
1	pds5b_human	protein	27		EBI-1175604	human (9606)	EBI-1175604	Sister chromatid cohesion protein PDS5 homolog B
2	palb2_human	protein	22		EBI-1222653	human (9606)	EBI-1222653	Partner and localizer of BRCA2
3	q06609-1	protein	12		EBI-15557721	human (9606)	EBI-15557721	DNA repair protein RAD51 homolog 1
4	q8r4x4_crigr	protein	5		EBI-1639762	crigr (10029)	EBI-1639762	
5	fancd2_protein_crigr	protein	5		EBI-1639774	crigr (10029)	EBI-1639774	Chinese hamster FANCD2 protein
6	brca2_drome	protein	9		EBI-178981	drome (7227)	EBI-178981	Breast cancer type 2 susceptibility protein homolog
7	ra51c_human	protein	5		EBI-2267048	human (9606)	EBI-2267048	DNA repair protein RAD51 homolog 3
8	polh_human	protein	6		EBI-2827270	human (9606)	EBI-2827270	DNA polymerase eta
9	rad51_human	protein	48		EBI-297202	human (9606)	EBI-297202	DNA repair protein RAD51 homolog 1
10	brc2a_arath	protein	13		EBI-307680	arath (3702)	EBI-307680	Protein BREAST CANCER SUSCEPTIBILITY 2 homolog A
11	rad51_arath	protein	10		EBI-307687	arath (3702)	EBI-307687	DNA repair protein RAD51 homolog 1
12	brc2b_arath	protein	16		EBI-307707	arath (3702)	EBI-307707	Protein BREAST CANCER SUSCEPTIBILITY 2 homolog B

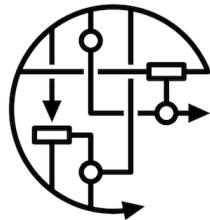
IntAct – Network (scoring)

The IntAct MI score is based on the manual annotation of every instance of a binary interaction (A-B) within the IntAct database.

1. Each entry is scored by the interaction detection method and by the interaction type.
2. The number of publications the interaction has appeared in is counted, up to a maximum of 8.

Interaction Detection Method	Weighting
Biochemical	3
Biophysical	3
Protein complementation Assay (PCA)	2
Imaging Techniques	0.6

Interaction Type	Weighting
Association	1
Physical Association	2
Direct Association (and child terms)	5
Colocalization	0.2



WikiPathways

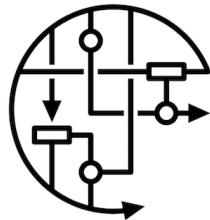
- Biological pathway database
www.wikipathways.org
- Founded in 2008 by Gladstone Institutes and the Department of Bioinformatics in Maastricht

- **WikiPathways - What is a wiki?**

“A wiki is an application, typically a web application, which allows collaborative modification, extension, or deletion of its content and structure.”



Definition Wikipedia 2017



WikiPathways

- A Wikipedia for pathways
 - Collection and curation of knowledge
 - Community curated
 - Everybody can contribute pathways
 - Everybody can edit and curate pathways
 - Everybody can use the pathway collections
 - Tools
 - Not just images but fully annotated models
 - Interactive pathway viewer
 - Full pathway editor and analysis software: PathVisio
 - New findings can be added immediately - fast!
 - Collaboration with Reactome

PPIs in Cytoscape



Maastricht University

stringApp

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stringApp

Import and augment Cytoscape networks from STRING



(13)

29032 downloads | posts | citations



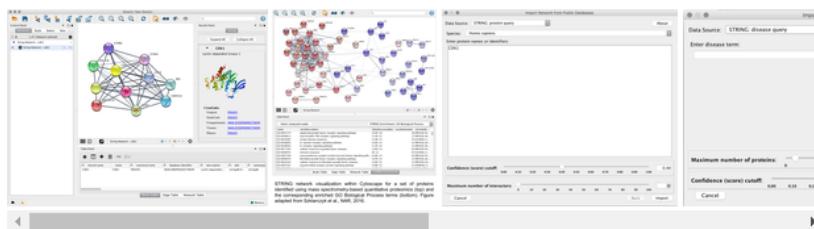
3.0+



Details

Release History

Categories: annotation, automation, data visualization, disease, enrichment analysis, gene-disease association, gene function prediction, import, interaction database, network generation, online data import, PPI-network, visualization



stringApp imports protein-protein and protein-chemical interaction data from [STRING](#),
uses [STRING](#), [STITCH](#), [DISEASES](#) and from PubMed text mining into Cytoscape. Users provide

CYTOSCAPE 3

Download

Version 1.4.0

Released 20 Jul 2018

Works with [Cytoscape 3.6](#)

[Download Stats](#) [Click here](#)

RESOURCES

Ask a question

Search posts

<http://apps.cytoscape.org/apps/stringapp>



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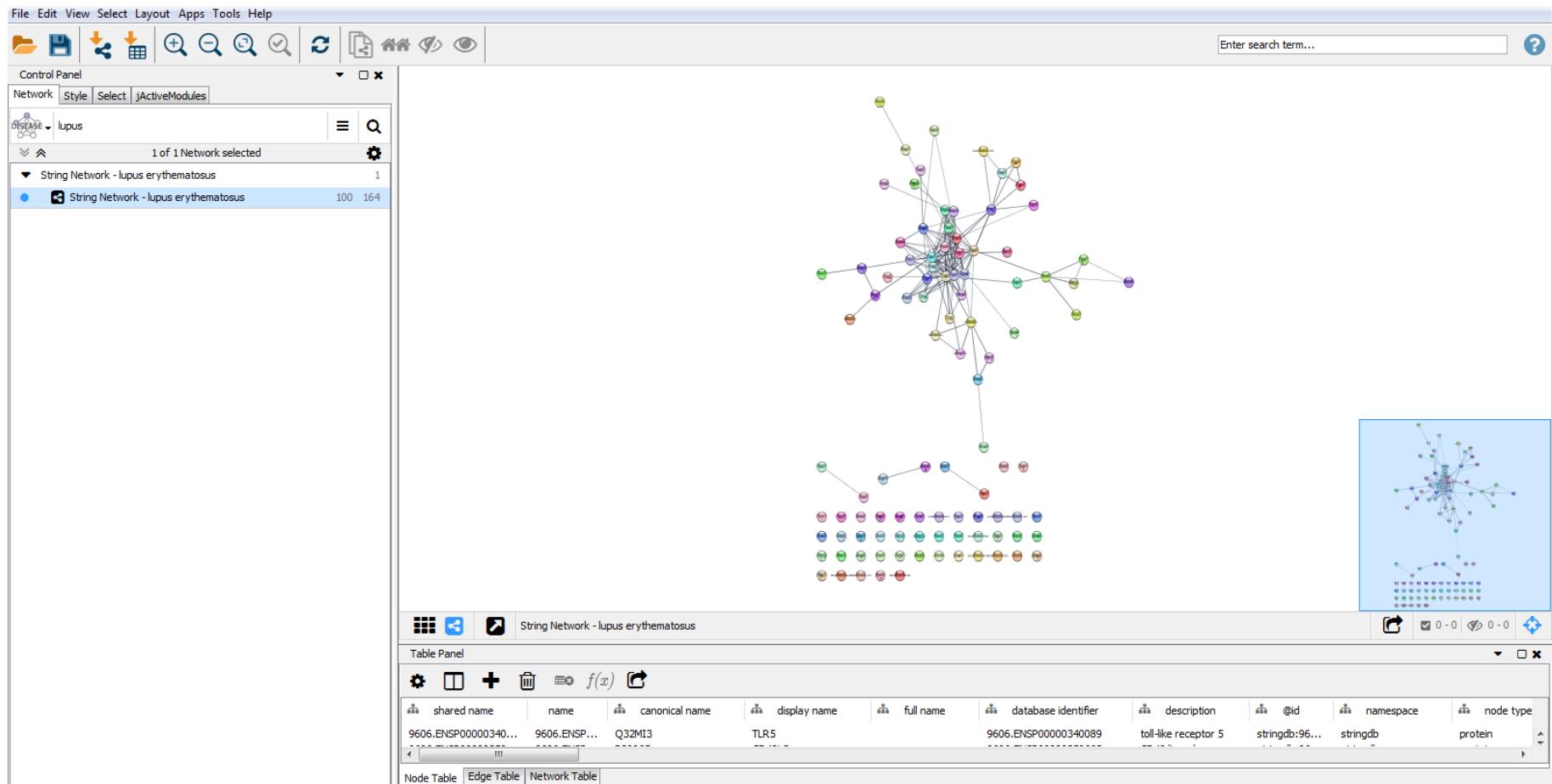
stringApp

- *stringApp* imports protein-protein and protein-chemical interaction data from [STRING](#), [Viruses.STRING](#), [STITCH](#), [DISEASES](#) and from PubMed text mining into Cytoscape. Users provide a list of one or more gene, protein, compound, disease, or PubMed queries, the species, and a confidence score and *stringApp* will query the database and return the matching network.

stringApp - Queries

- STRING: **Protein** query -- enter a list of protein names (e.g. gene symbols or UniProt identifiers/accession numbers) to obtain a STRING network for the proteins
- STRING: **PubMed** query -- enter a PubMed query and utilize text mining to get a STRING network for the top N proteins associated with the query
- STRING: **Disease** query -- enter a disease name to retrieve a STRING network of the top N proteins associated with the specified disease
- STITCH: **Protein/compound** query -- enter a list of protein or compound names to obtain a network for them from STITCH

STRING network - Lupus



Pathways as networks



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WikiPathways app

Cytoscape App Store

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Want an easier way to install apps? Click here to learn how! ×



WikiPathways

WikiPathways web service client and GPML file format importer

★★★★★ (11)

25964 downloads | posts | citations



Details

Release History

Categories: automation, local data import, network generation, online data import, pathway database



The WikiPathways App provides Cytoscape users with easy access to pathway content at WikiPathways.org. With the app installed, you can import GPML network files generated by WikiPathways or PathVisio. You can also query and import pathways via the

CYTOSCAPE 3

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Version 3.3.1

License [Click here](#)

Released 17 Nov 2017

Works with [Cytoscape 3.6](#)

Download Stats [Click here](#)

RESOURCES

Ask a question

Search posts

<http://apps.cytoscape.org/apps/wikipathways>

Kutmon M, Lotia S, Evelo CT and Pico AR.

WikiPathways App for Cytoscape: Making biological pathways amenable to network analysis and visualization

[version 2; referees: 2 approved]

F1000Research 2014, 3:152 (doi: [10.12688/f1000research.4254.2](https://doi.org/10.12688/f1000research.4254.2))



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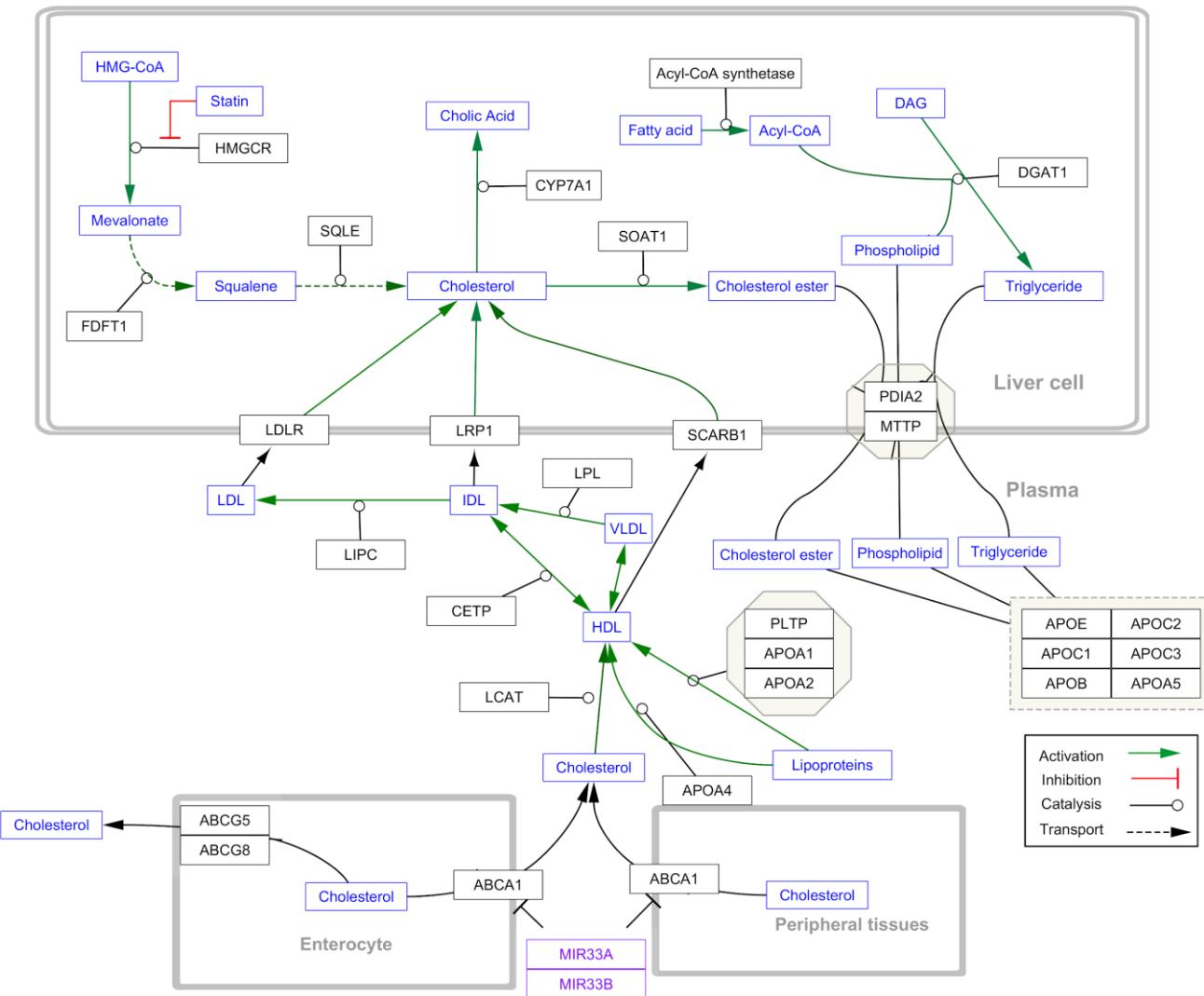
WikiPathways app for Cytoscape

- Pathway import
 - Online database search within Cytoscape (using the webservice)
 - Local GPML file
- App supports two views:
 - Pathway view
 - complete visual appearance
 - ideal for data visualization
 - Network view
 - simplified networks without any of the graphical elements of the original pathway diagram
 - ideal for topological analyses, network merging and automatic layout



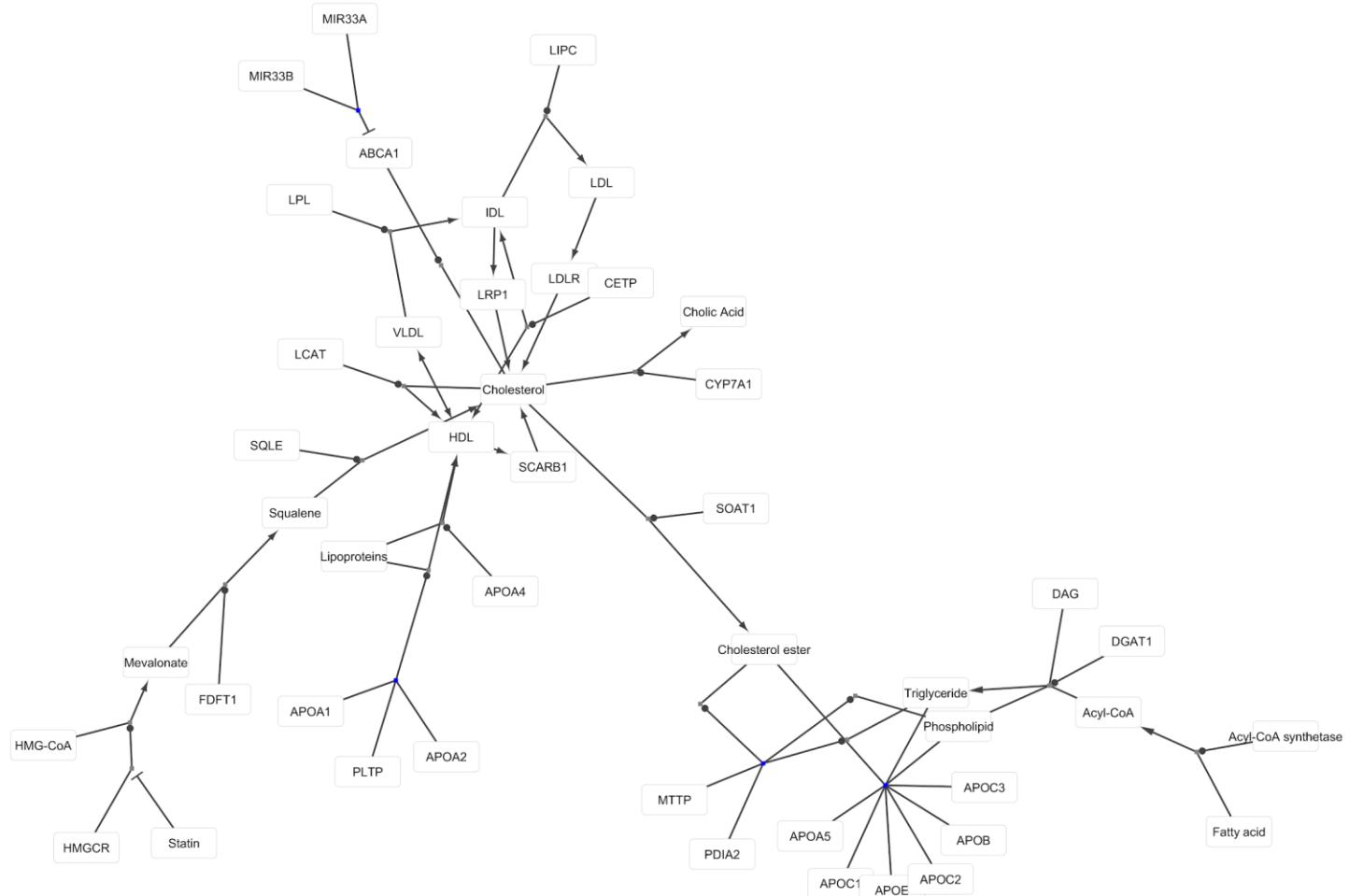


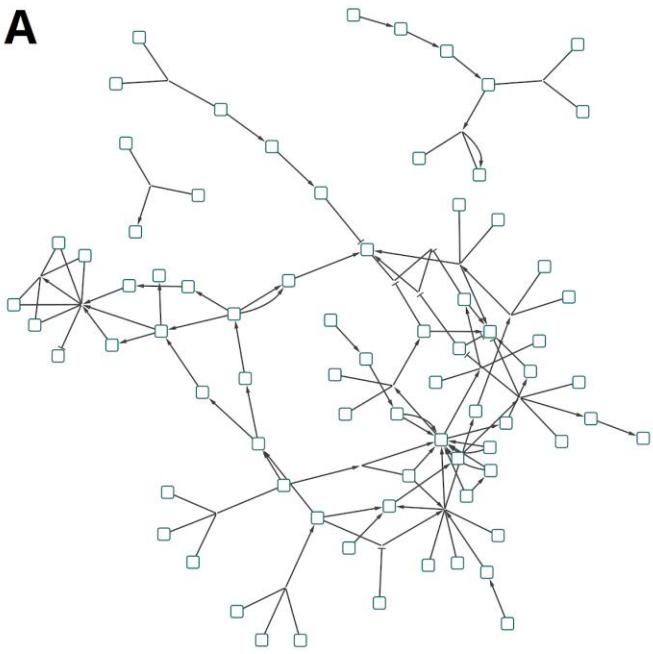
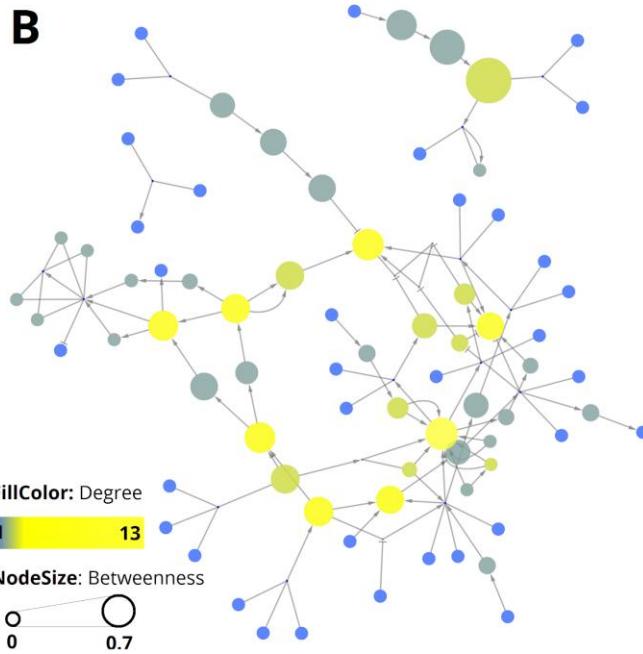
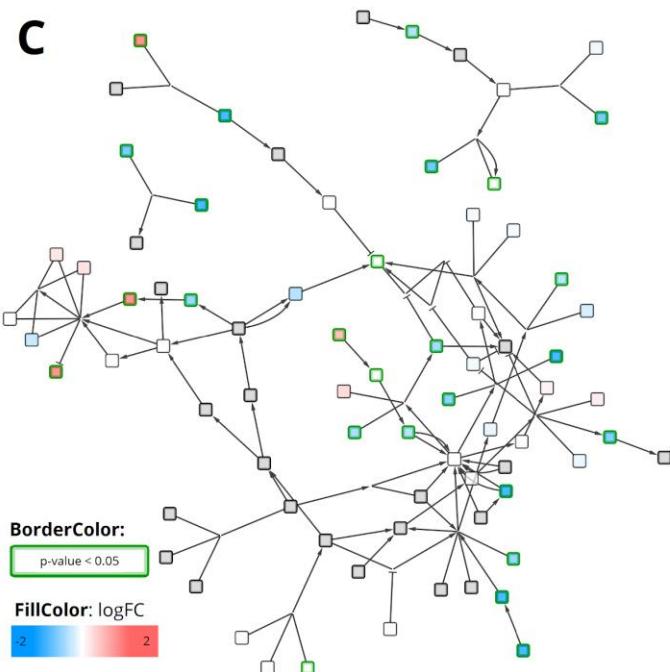
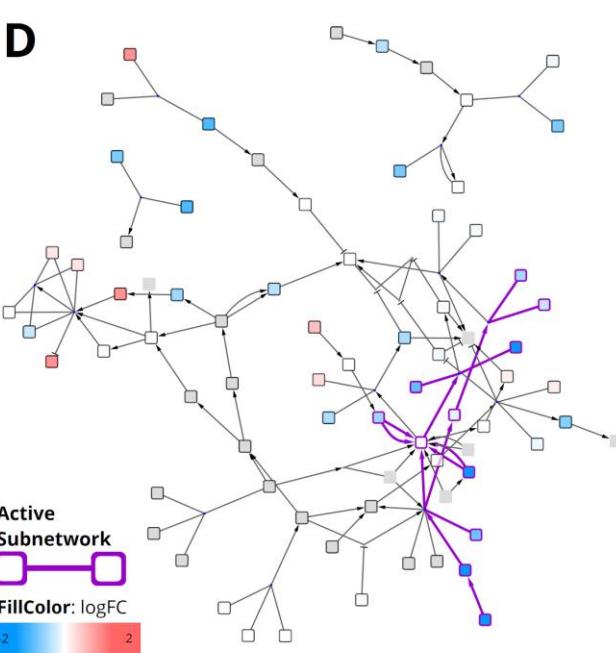
Pathway view





Network view



**A****B****C****D**

Sharing Biological Networks



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Sharing Biological Network Data



Welcome to the NDEx Public Server - v2.3.1

Search Examples ▾ Browse All ▾

Perform Search Term Expansion (Genes and Proteins only)

Featured Collections: [Pathway Interaction Database \(NCI-PID\)](#) [Signor DB](#) [The NDEx Butler](#) [The BioGRID](#) [NetPath](#)



Link between NDEx and Cytoscape

[← Go back to home](#)



CyNDEEx-2

Core App: CyNDEEx-2 is a user-friendly app for browsing, importing, and exporting networks to an NDEx server.



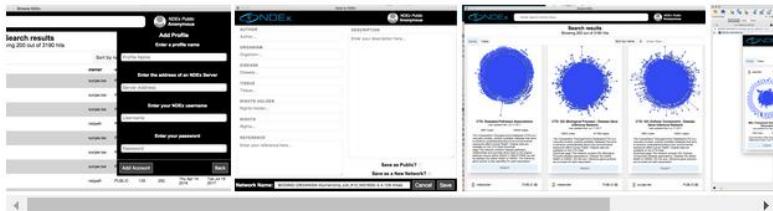
(4) 6197 downloads | helpdesk | discussions



Details

Release History

Categories: automation, core app, database, data integration, network repository, online data import, systems biology



Welcome to CyNDEEx-2!

The latest **CyNDEEx-2** build available here on the App Store (**v2.3.2**) is a recommended update and will be included in the upcoming Cytoscape 3.7.2 release. If you experience issues with CyNDEEx-2 with other versions of Cytoscape, please update to the latest build.

CYTOSCAPE 3

[Download](#)

Version 2.3.2

Released 4 Sep 2019

Works with [Cytoscape 3.7](#)

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[Automation Support](#)

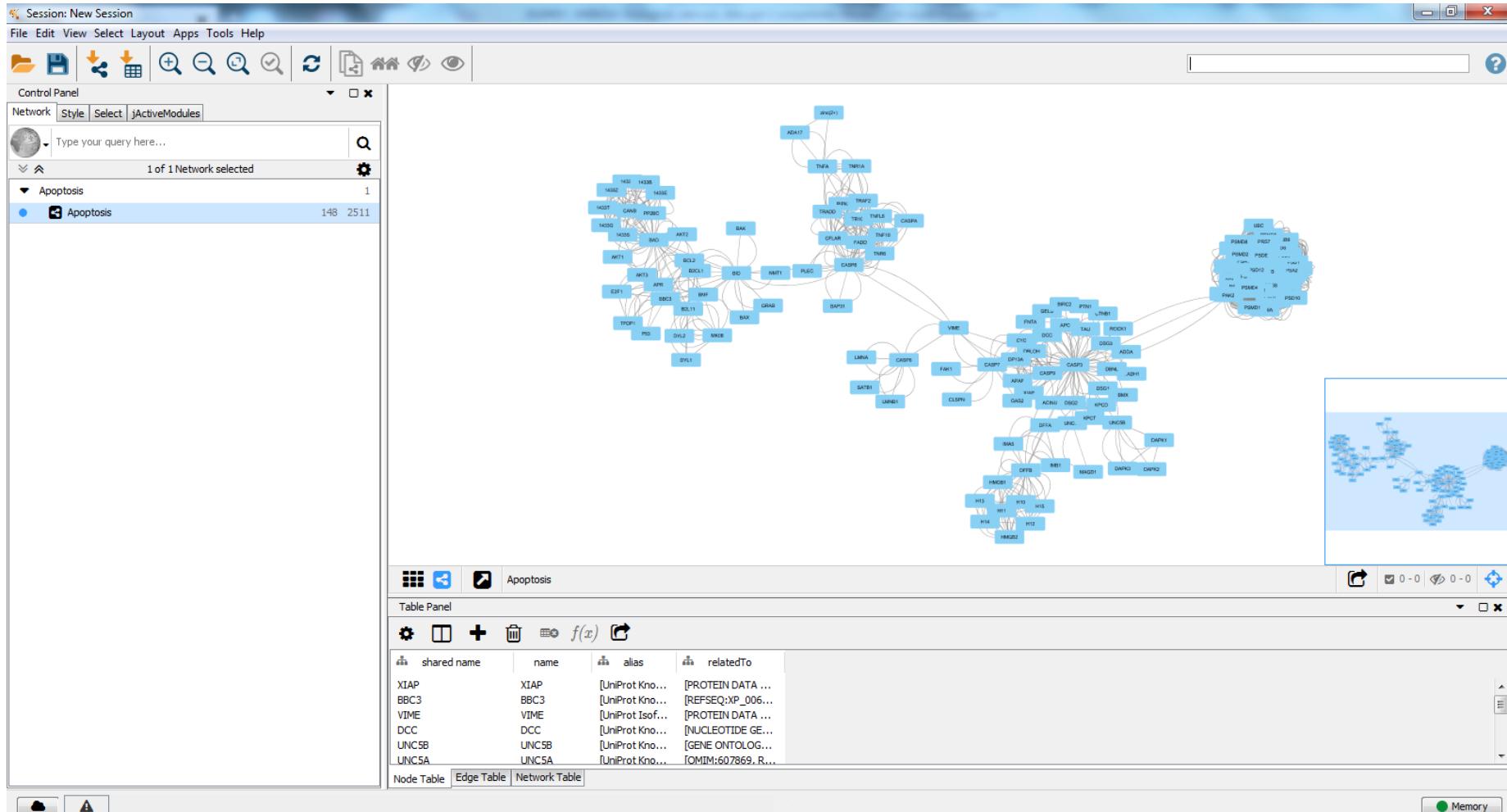
[E-mail](#)



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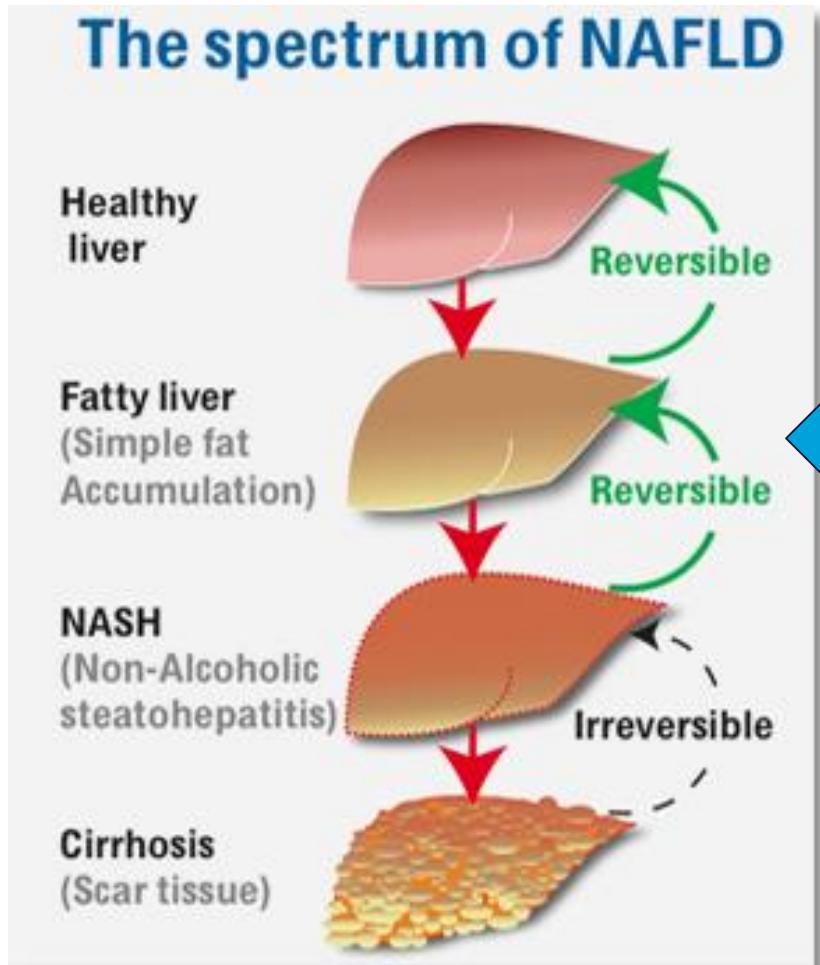
<http://apps.cytoscape.org/apps/cyndex2>

Example network from NDEx



Biological example

Non-alcoholic fatty liver disease (NAFLD)

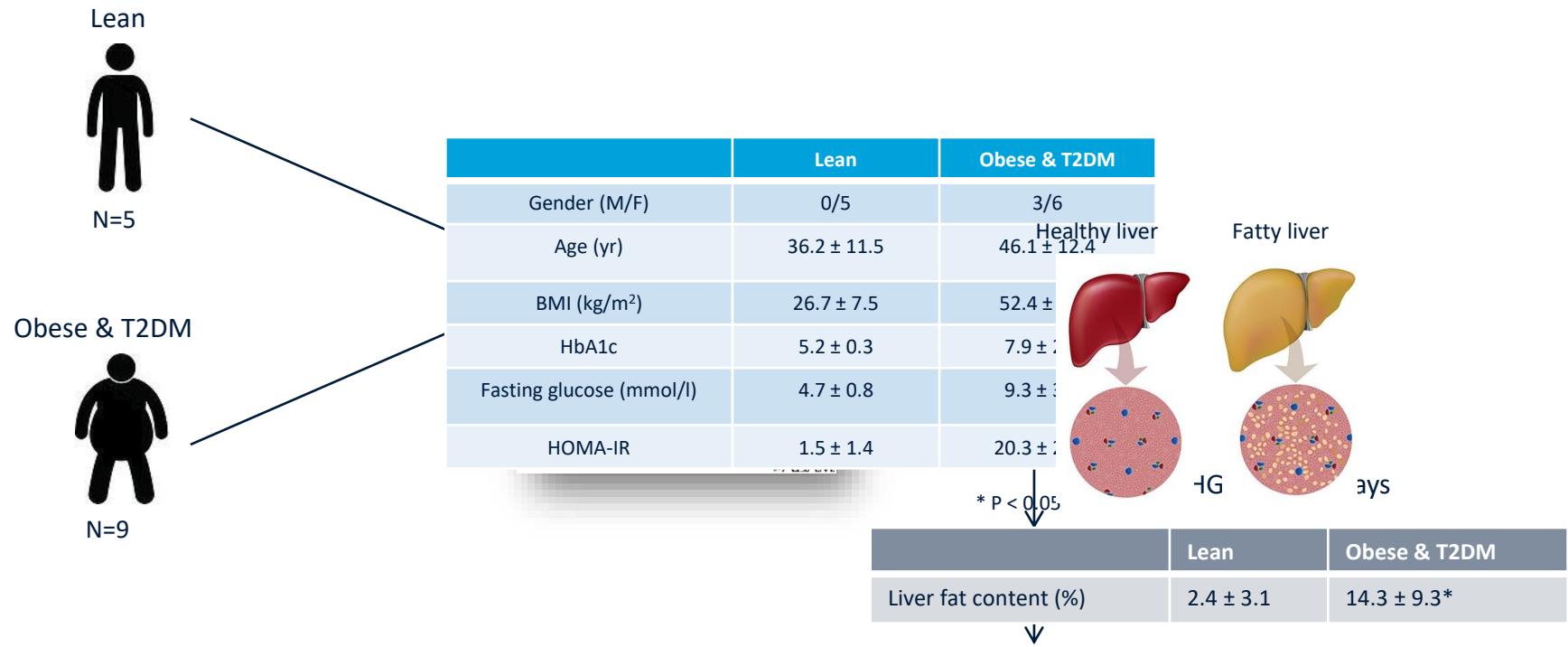


10-25% of the general population
70% of the diabetic and obese population

Aim

- To integrate differential **gene expression** in the human diabetic liver with **pathway** information by building a **network** of interconnected pathways.
- To extend the biological **network** with regulatory information (**transcription factor** – gene and **drug** – gene target interactions).

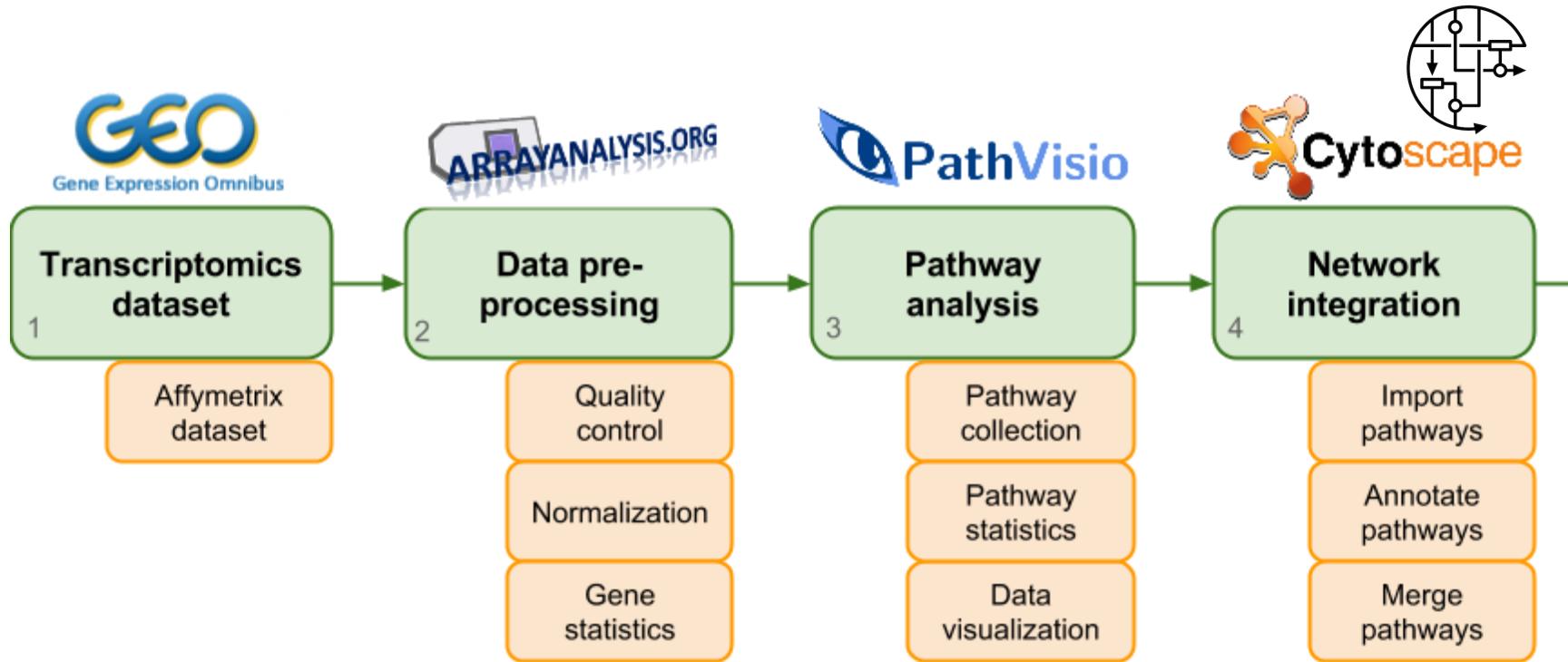
Transcriptomic data



Publicly available at Gene Expression Omnibus
(accession number GSE15653).

Pihlajamäki J et al. (2009) Thyroid hormone-related regulation of gene expression in human fatty liver. *J Clin Endocrinol Metab.* 94(9):3521-9. doi: 10.1210/jc.2009-0212.

Analysis workflow



Study published in BMC Genomics

Kutmon M, Evelo CT, Coort SL. (2014) A network biology workflow to study transcriptomics data of the diabetic liver. BMC Genomics. 15:971. doi: 10.1186/1471-2164-15-971.

Differential expression

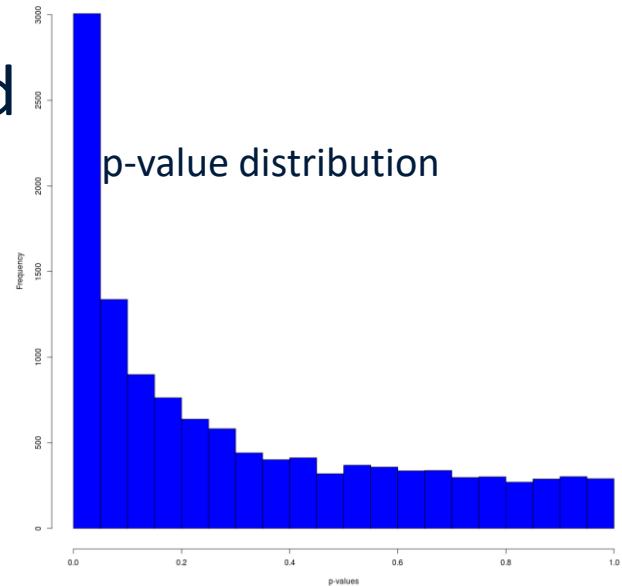
Differentially expressed genes comparing obese & T2DM versus lean.

- Absolute log₂ fold change > 1
- P-value < 0.05

11,878 genes measured and annotated

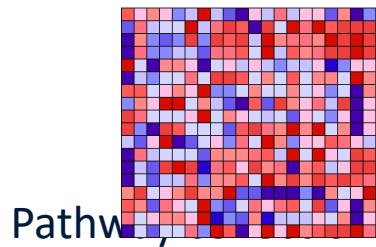
181 differentially expressed genes

↑ 118 genes
↓ 63 genes

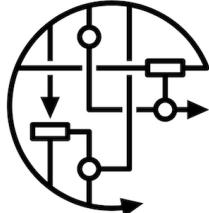


Over-representation analysis

Transcriptomics data

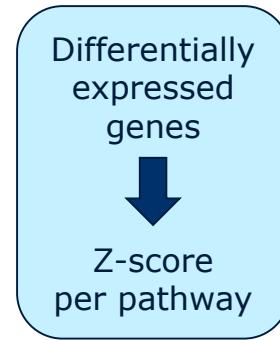


Pathways



Analysis collection from WikiPathways
(www.wikipathways.org)

Over-representation analysis



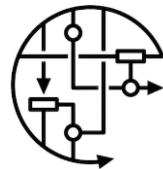
Ranking of pathways
based on z-score

[PathVisio 3: an extendable pathway analysis toolbox.](#)
Kutmon M, van Iersel MP, Bohler A, Kelder T, Nunes N, Pico AR, Evelo CT.
PLoS Comput Biol. 2015 Feb 23;11(2):e1004085

Seven pathways altered in diabetic liver

Pathway	Z-score	P-value	# genes	Differentially Expressed Genes
Triacylglyceride synthesis	3.78	0.001	3 (19)	↑ AGPAT2, GPD1, DGAT1
Proteasome degradation	3.32	0.006	5 (53)	↑ RPN1, PSMB3, HLA-B, HLA-E, HLA-J
Statin pathway	3.10	0.006	3 (25)	↑ DGAT1, APOA4, CYP7A1
Fluoropyrimidine activity	2.84	0.013	3 (28)	↑ SLC22A7 ↓ ABCG2, DPYD
Pathogenic E.coli infection	2.76	0.011	4 (46)	↑ ARPC1A, ARPC1B, ACTB ↓ ROCK1
Adipogenesis	2.41	0.016	7 (121)	↑ SREBF1, CDKN1A, NRIH3, PNPLA3, AGPAT2 ↓ CISD1, ZMPSTE24
AMPK signaling	2.38	0.029	4 (54)	↑ SREBF1, P21 ↓ LEPR, PFKFB3

Connecting pathways in Cytoscape



Import pathways with WikiPathways app¹



BridgeDb Annotate pathways with BridgeDb app²



Merge pathways with Cytoscape core functionalities



7 pathways in one interconnected network

1. Kutmon M et al. (2014) WikiPathways App for Cytoscape: Making biological pathways amenable to network analysis and visualization.

*F1000Res.*3:152. doi: 10.12688/f1000research.4254.2. eCollection 2014.

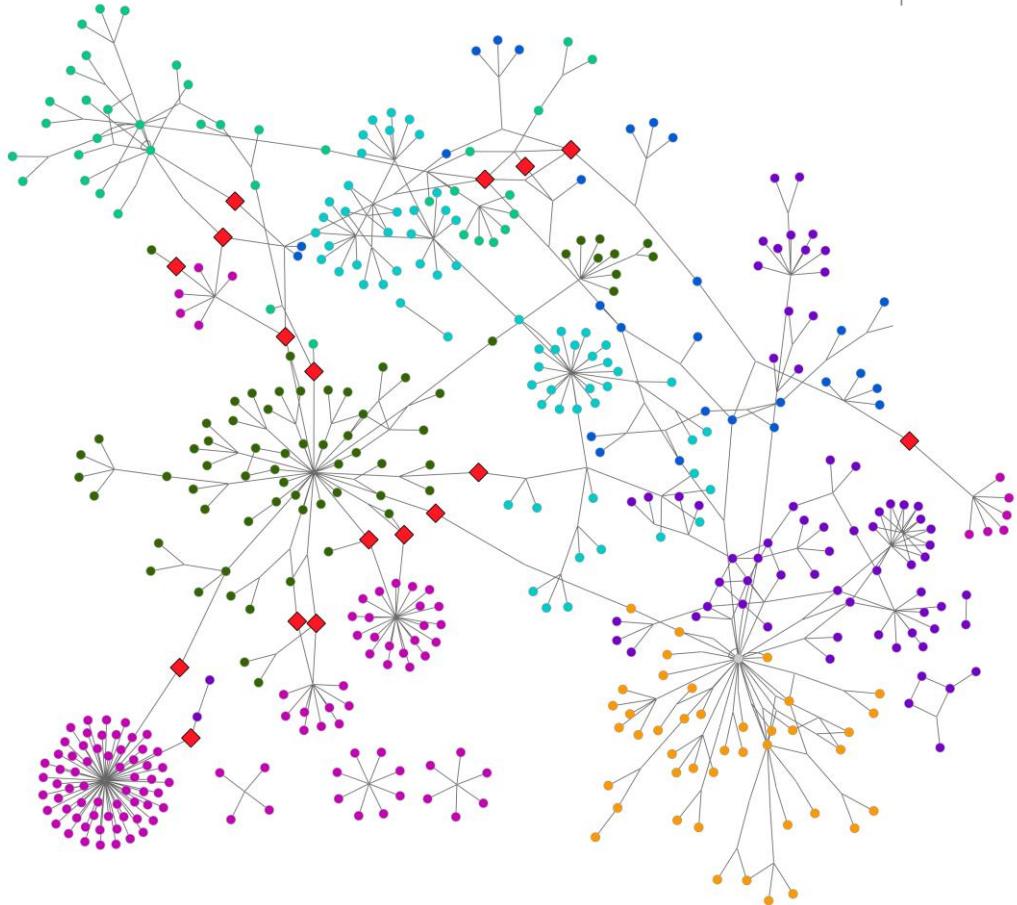
2. Gao J et al. (2014) "BridgeDb app: unifying identifier mapping services for Cytoscape." *F1000Research*.

Connecting pathways in



Legend

- ◆ Nodes linking two or more pathways
- Fluoropyrimidine Activity
- Adipogenesis
- Proteasome Degradation
- ▲ Triacylglyceride Synthesis
- Pathogenic Escherichia coli infection
- AMPK Signaling
- Statin Pathway



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Nodes linking the 7 pathways

Legend

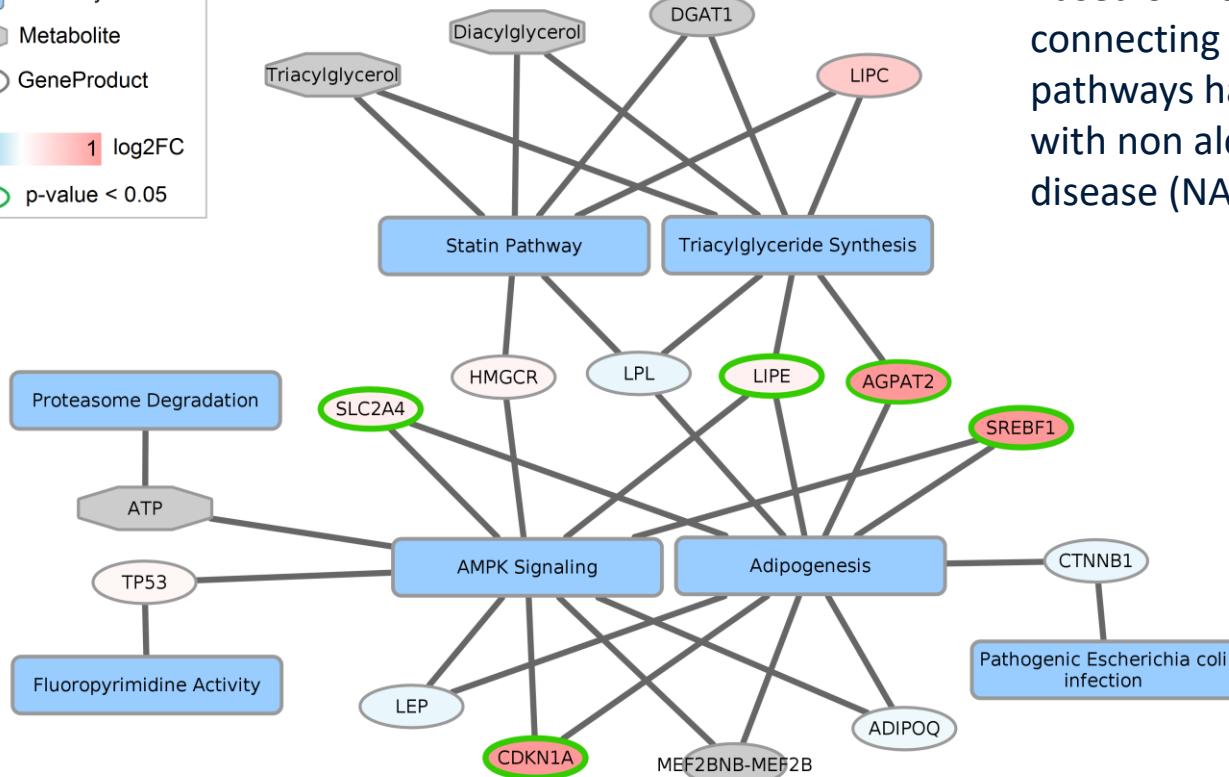
Pathway Node

Metabolite

GeneProduct

-1 1 log2FC

p-value < 0.05



Based on literature all genes connecting two or more pathways have a clear link with non alcoholic fatty liver disease (NAFLD)/T2DM



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