Biological network analysis

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Overview

1. **Introduction to network analysis**
2. Terminology
3. Network construction
4. Key network properties
5. Community analysis

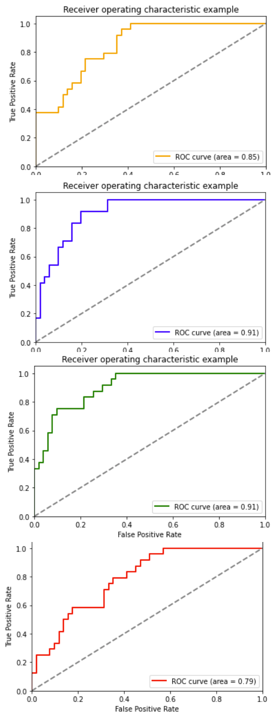
Introduction

raw data

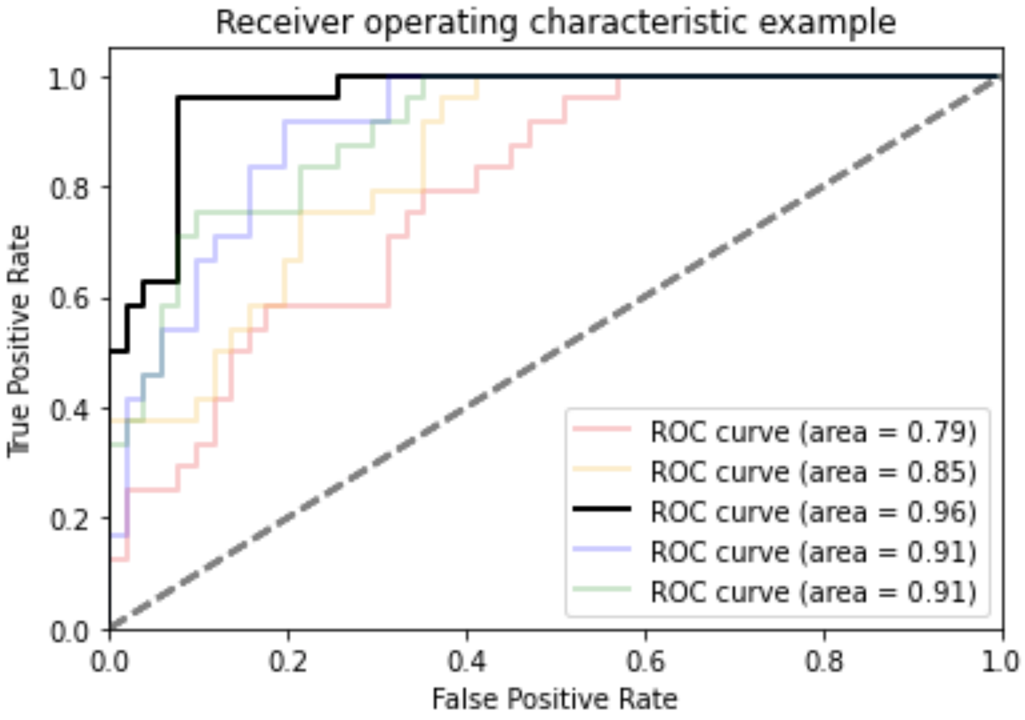
Individual performance

Integration

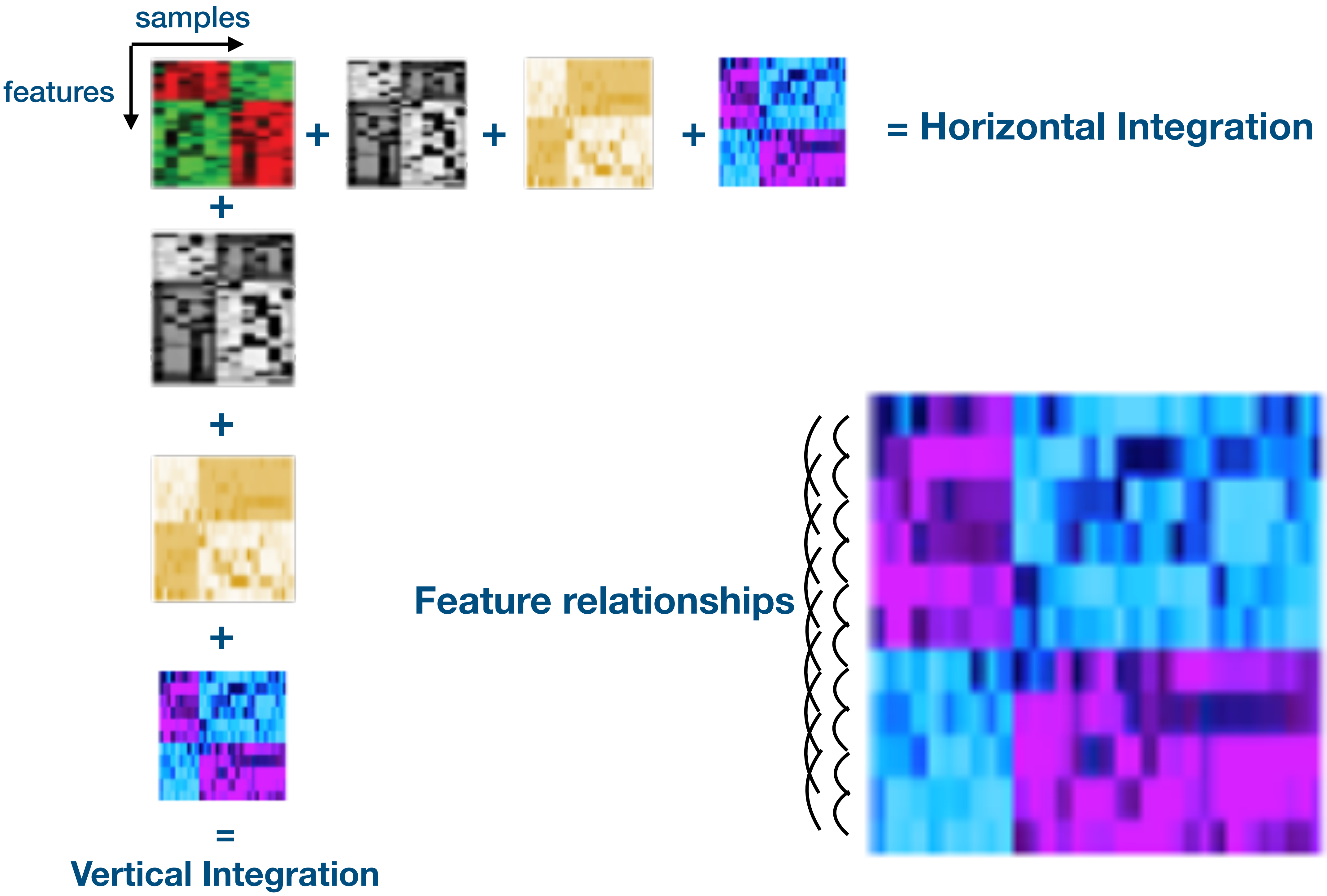
Joint performance



MOFA
Mixomics
DL
Graph



Introduction



samples

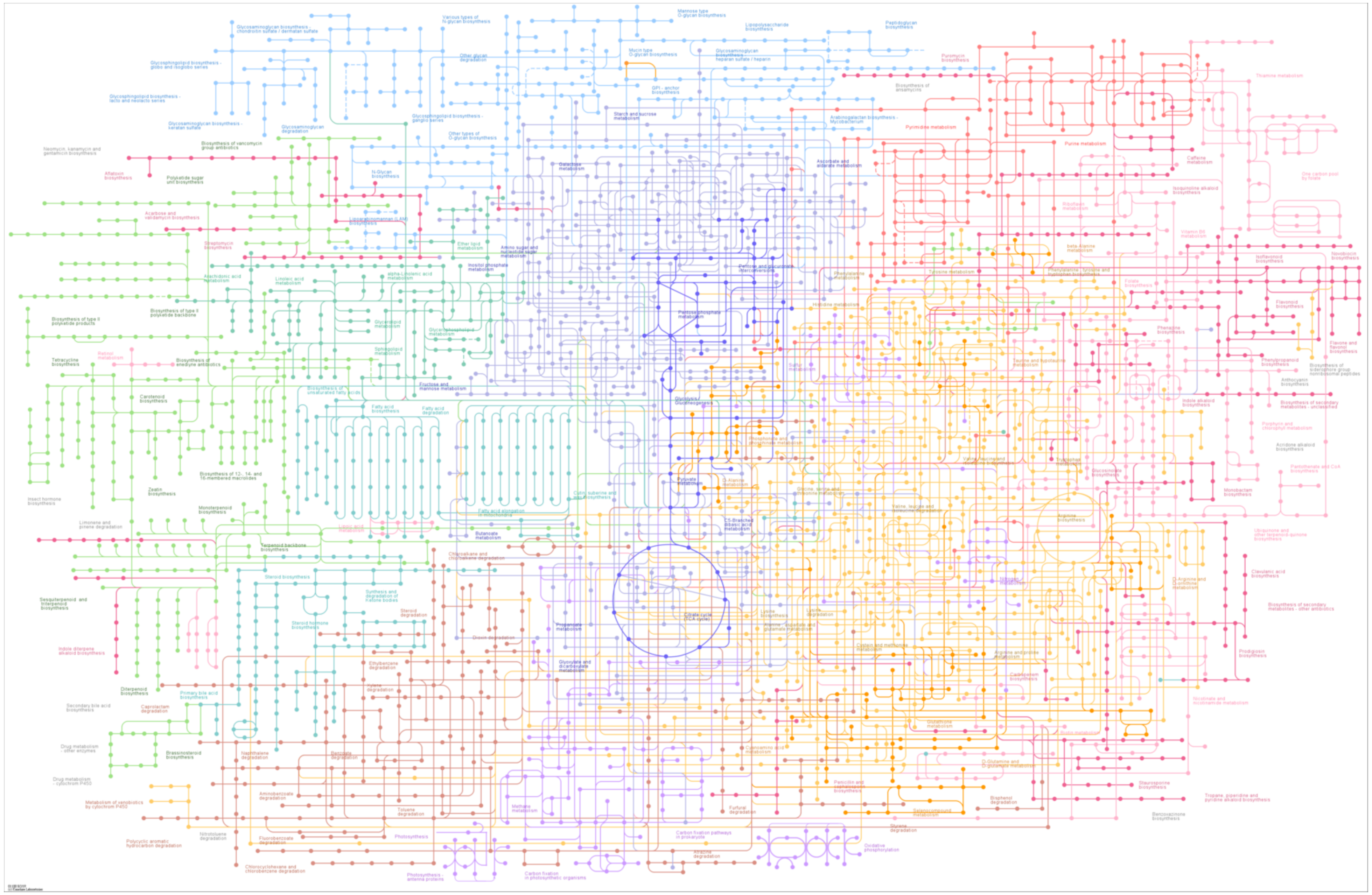
features

+ + + = **Horizontal Integration**

+ + + = **Vertical Integration**

Feature relationships

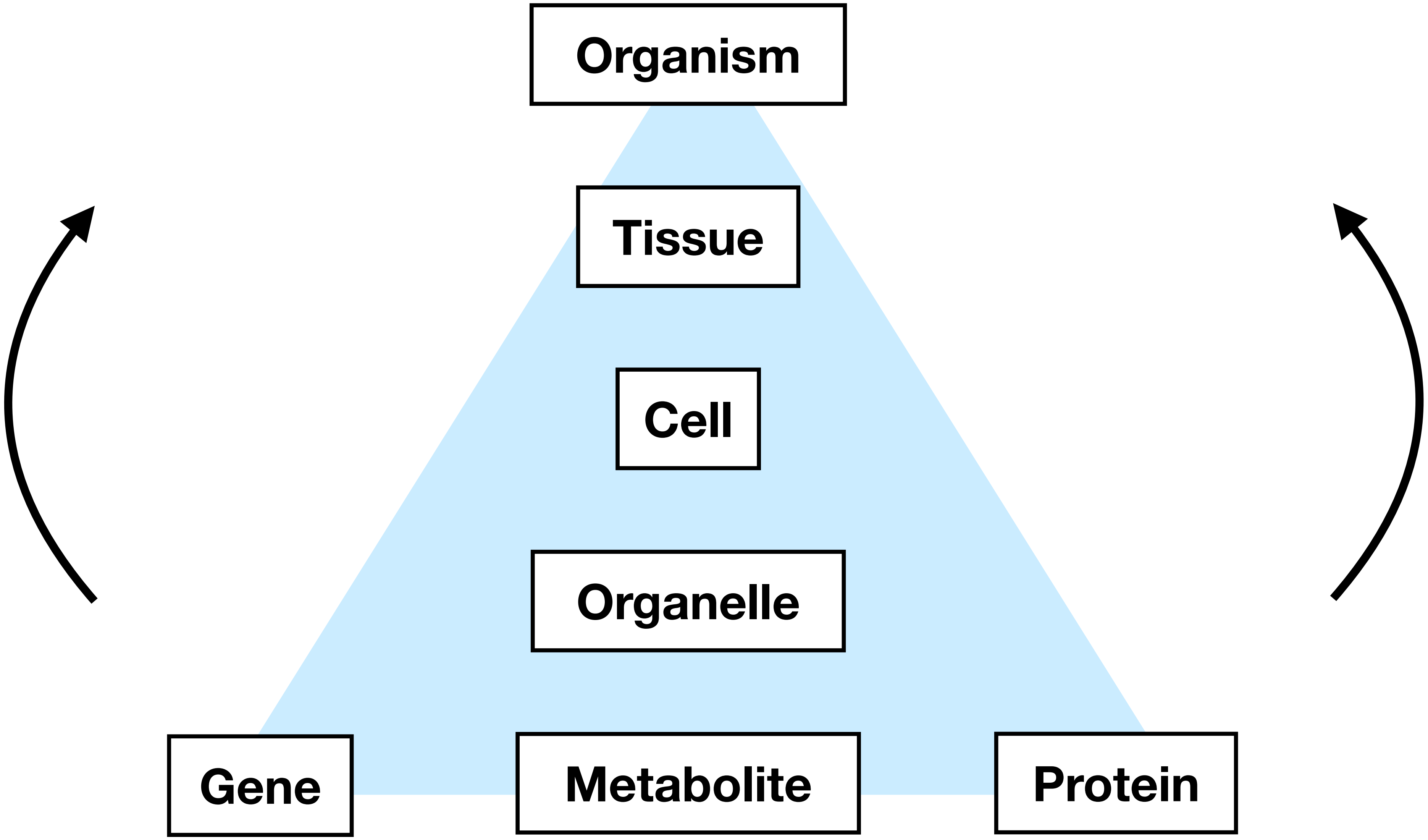
How to tackle biological complexity?



genome.jp/kegg/

How to tackle biological complexity?

Moving from reductionist approaches towards global characterisations



Organism

Tissue

Cell

Organelle

Gene

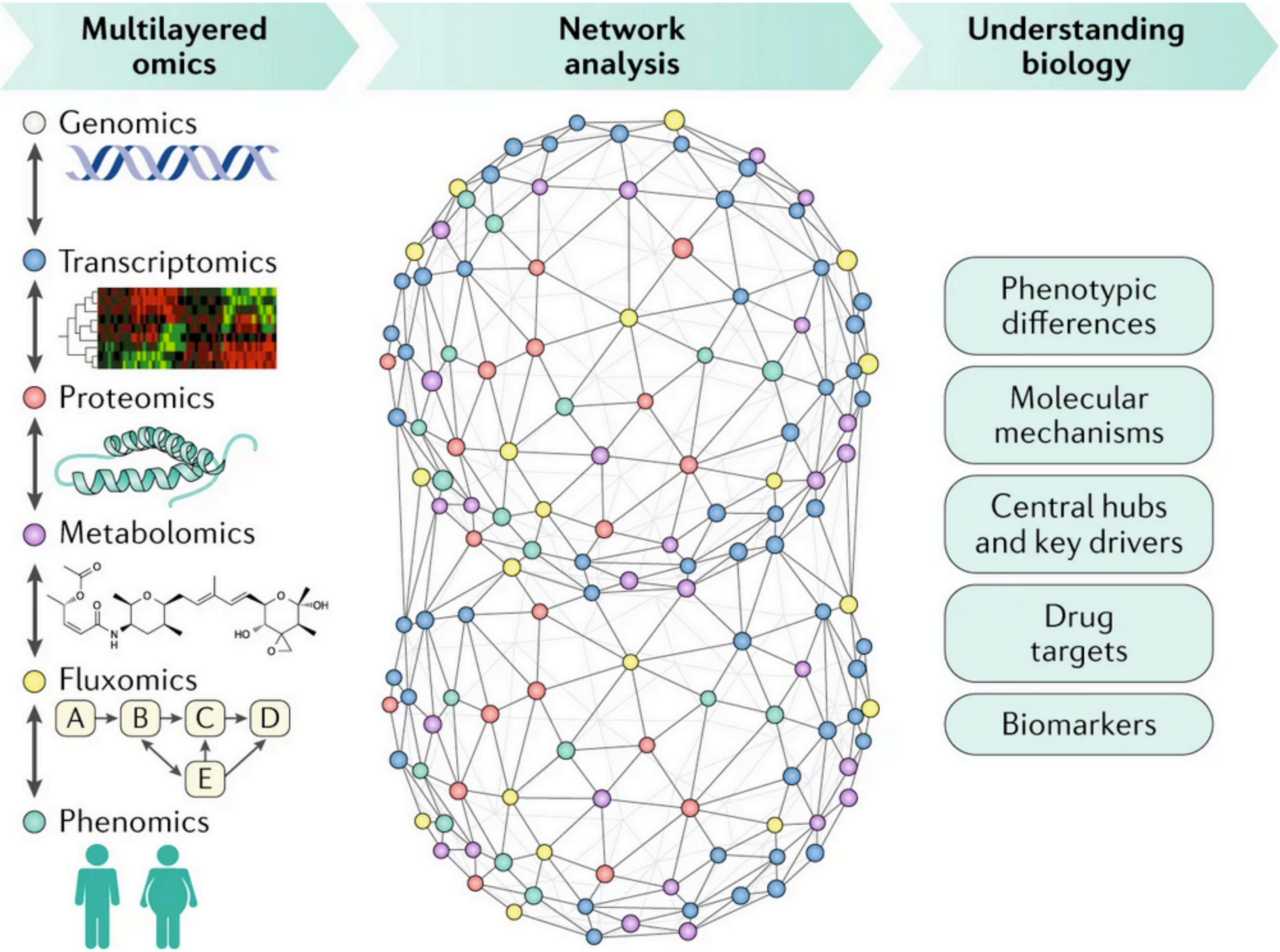
Metabolite

Protein

How to tackle biological complexity?

Integrative approaches, and global patterns

- Feature association
- Network analysis
- Modeling
  (Genome-scale metabolic modeling)



Mardinoglu 2018

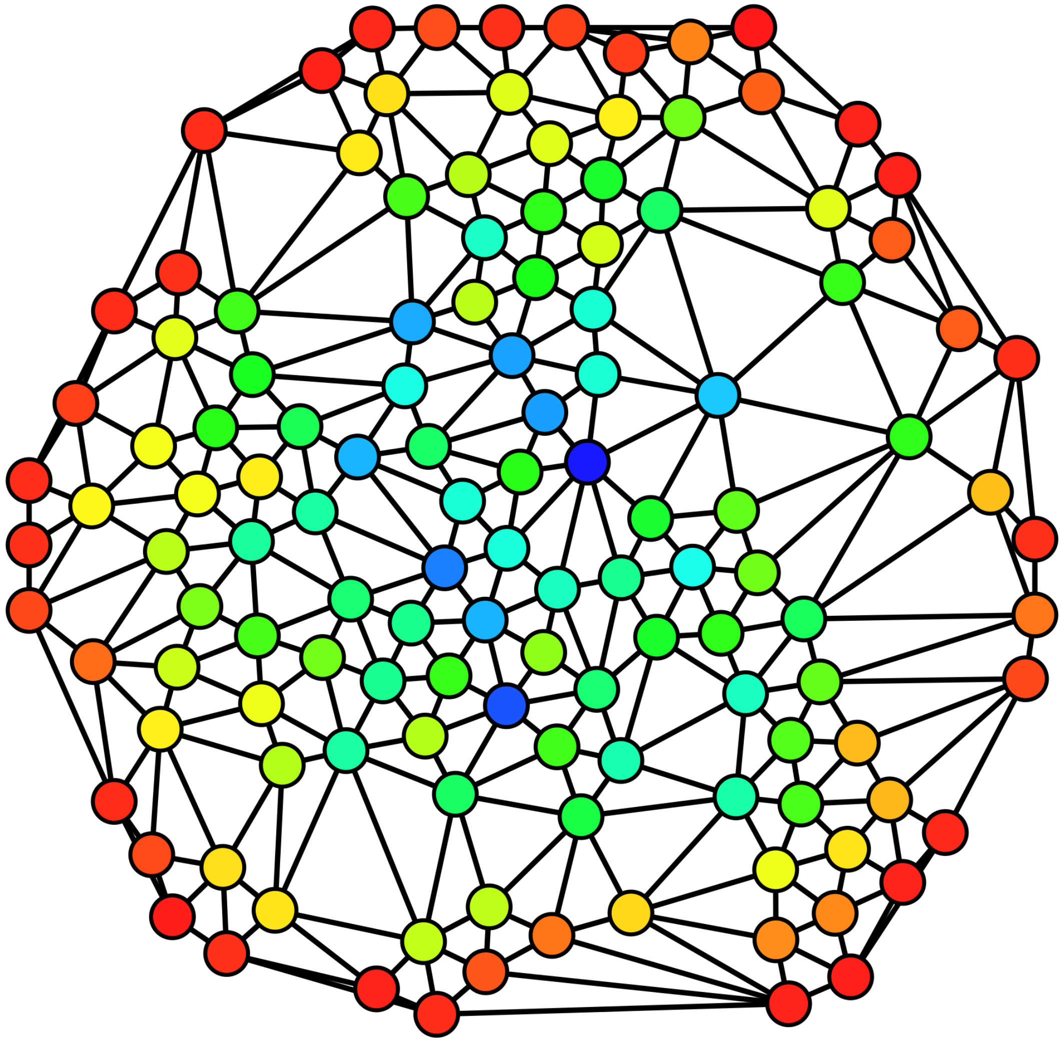
What are networks?

Networks are representations of complex systems

Permit defining and studying global properties of interacting components

Give us insight not easily achieved by other approaches:

- Comprehensive
- Coordinated



What are biological networks?

Protein - Protein interaction (PPI) networks

Transcription-factor regulatory networks

Gene - gene co-expression networks

Signal transduction networks

What are biological networks?

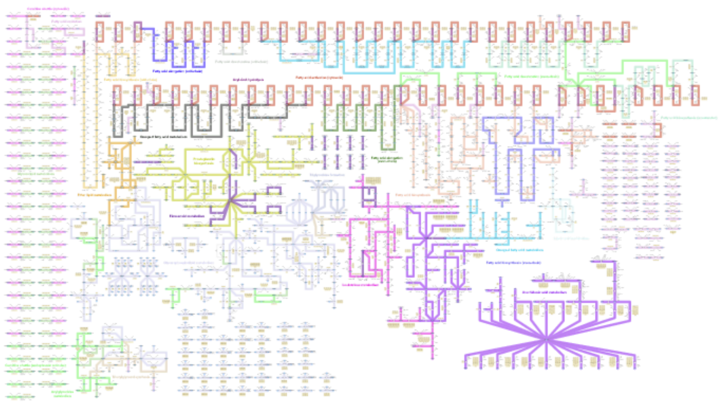
Metabolite - Enzyme - Signal - Genes (GEMs)

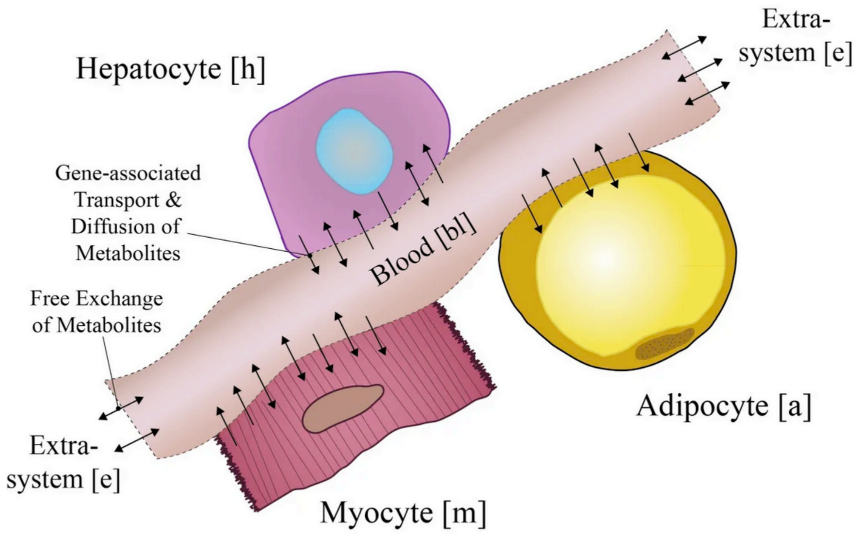
Multi-tissue networks

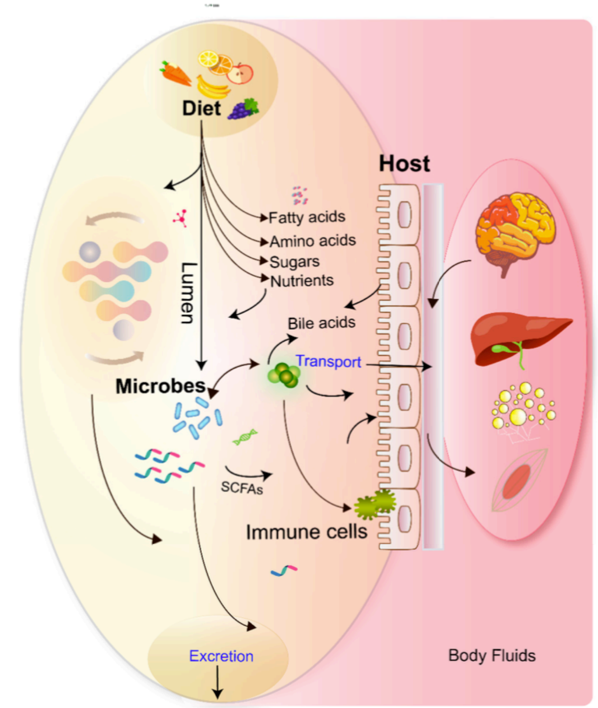
Multi-species networks

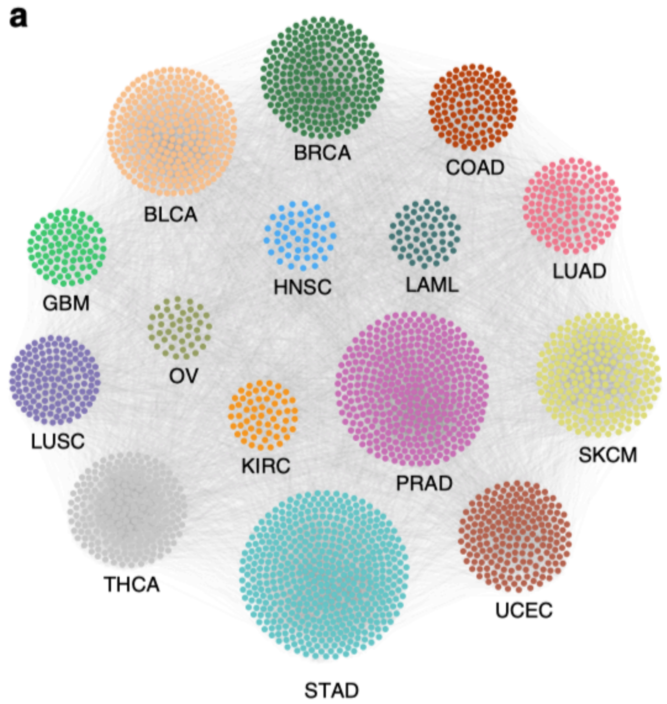
Disease networks

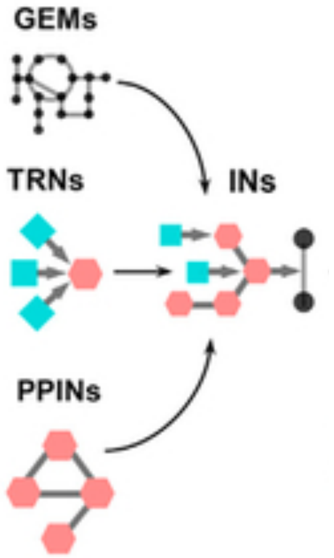
Integrated networks





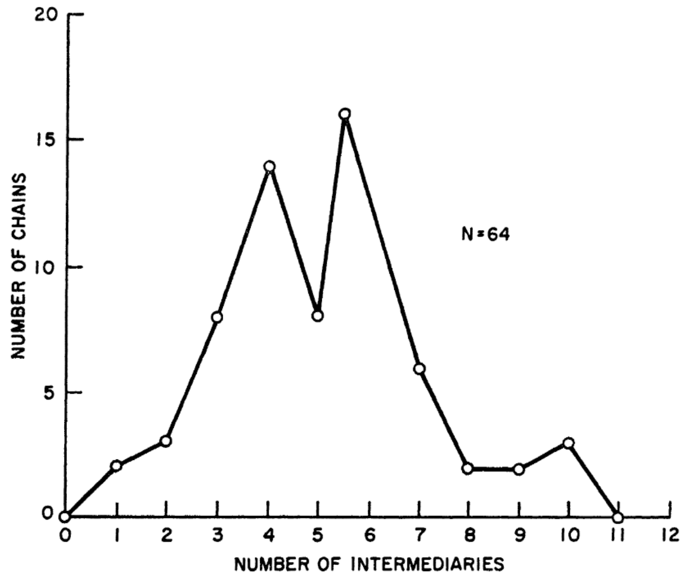






https://metabolicatlas.org/
Bordbar et al 2011
Sen & Oresic 2019
Cheng et al 2019
Lee et al 2016

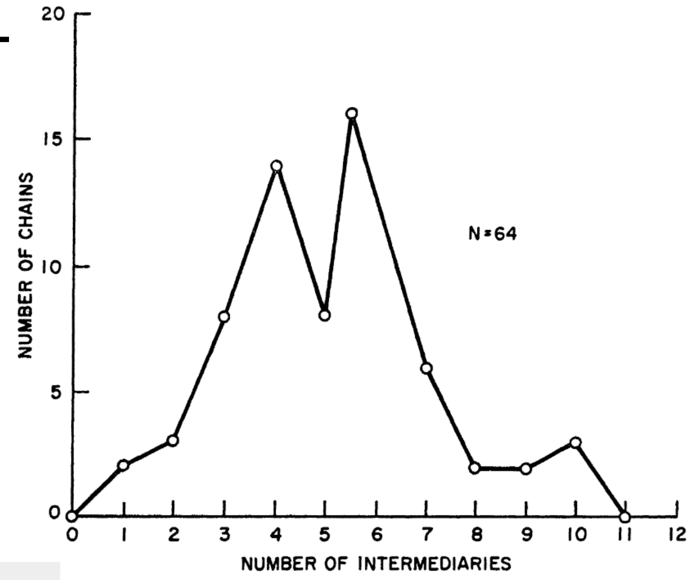
Small world



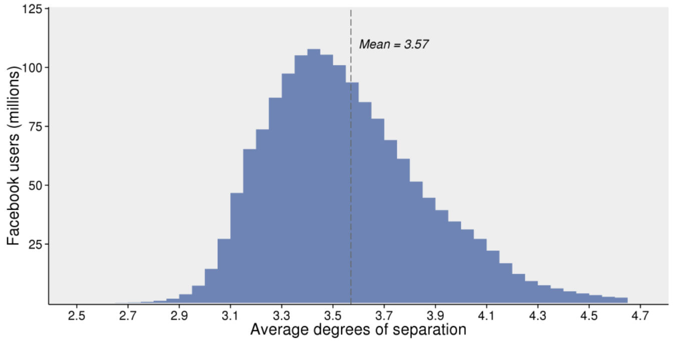
Stanley Milgram (1967) - 6 degrees

- 64 / 296 letters successful

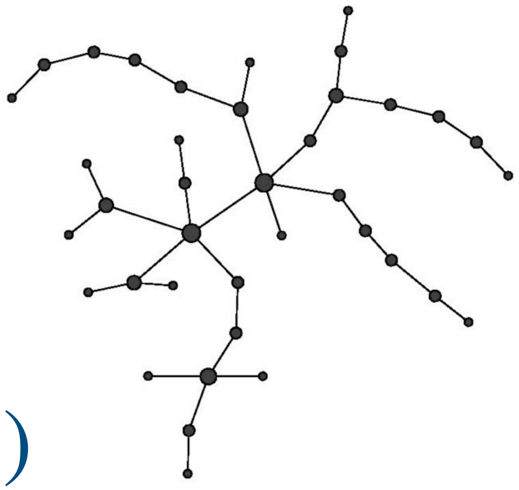
Small world



Stanley Milgram (1967): 6 degrees

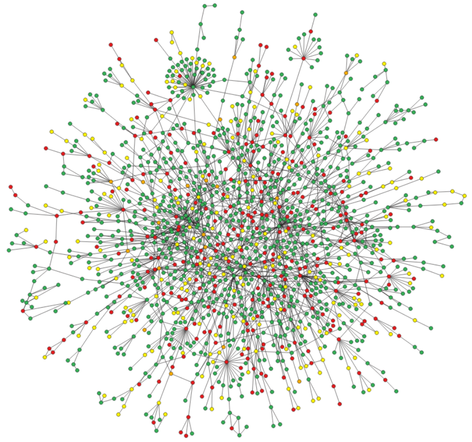


Backstrom et al. (2016): 3.6 degrees



Random networks: $l(G) \approx logN$ for network of size *N*

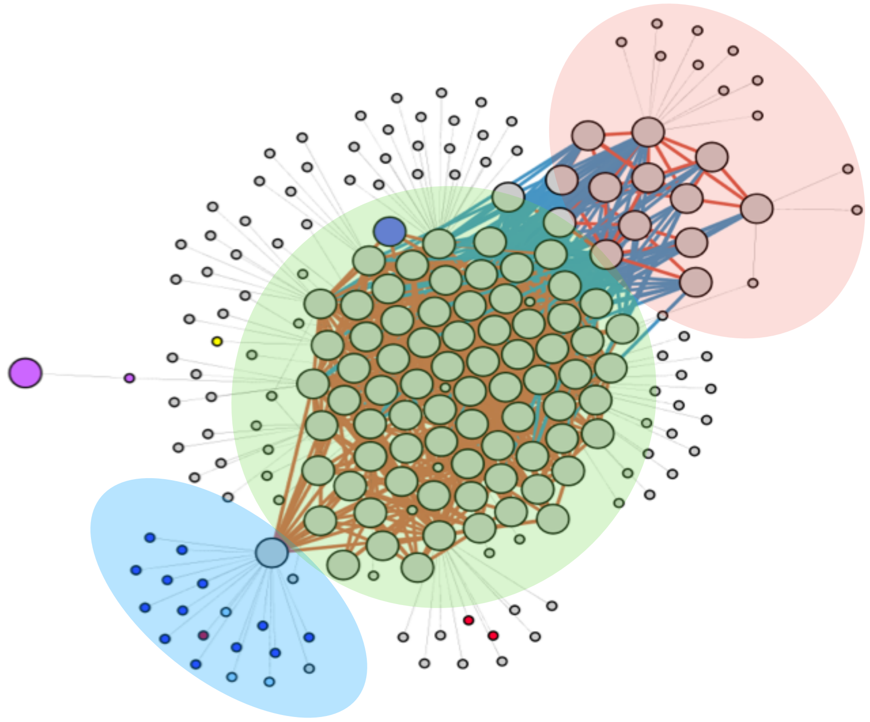
Biological Networks: **ultra-small world** $l(G) \approx log(logN)$



Why look at network topology?

Use networked systems to:

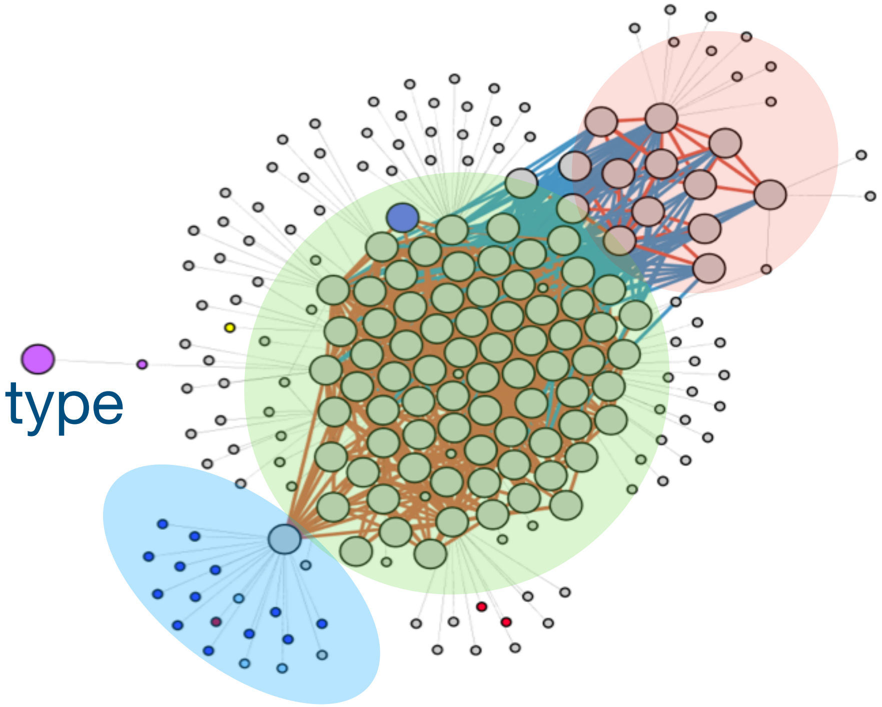
- Identify global / local patterns
- Identify functional properties
- Make predictions



Examples:

- How associated are the elements of my network?
- What are its first-hand associated elements?
- What are the groups of closely-associated elements in my network? What are their functional relationships?
- What are the “key” elements in my network?
- What are the "weakest" links in the network?

What is my biological network?



Any distance matrix may be translated to a network format

Many standard analyses may be employed regardless of data type

…but care must be taken in generating the network

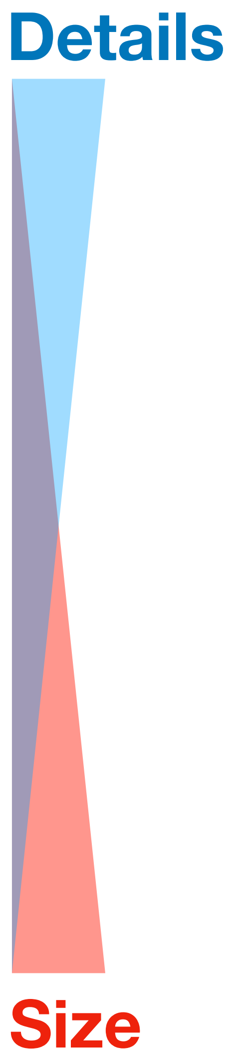
Limitations:

- Some of the functional analyses depend on annotation
- Sample size
- Effect size
- False discovery

Motivation

What modeling formalism suits your data and biological question?

	Pros	**Cons**
Kinetic models	Detailed Quantitative Dynamic / Steady state	Small Requires detailed parameterization
Stoichiometric **GEMs**	Large Semi-quantitative Steady state	Static
Topological **Graphs**	Large Only topological information	No dynamic properties



Adapted from Hartmann et al.

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4. Key network properties
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Original sources of images provided as reference and hyperlinks, where applicable.

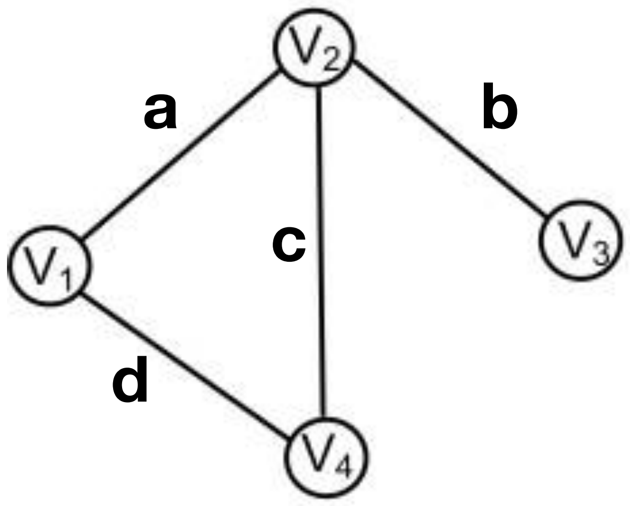
Graphs, nodes, edges

Graph *G* consists of a set of **nodes** (V) interconnected by **edges** (E)

$$G = (V, E)$$

$$V=\{v1,v2,v3,v4\}$$

$$E=\{a,b,c,d\}$$



Nodes sometimes called **vertices**

Two connected nodes are called **neighbours, adjacent,** or **end-nodes**

Simple vs multigraphs

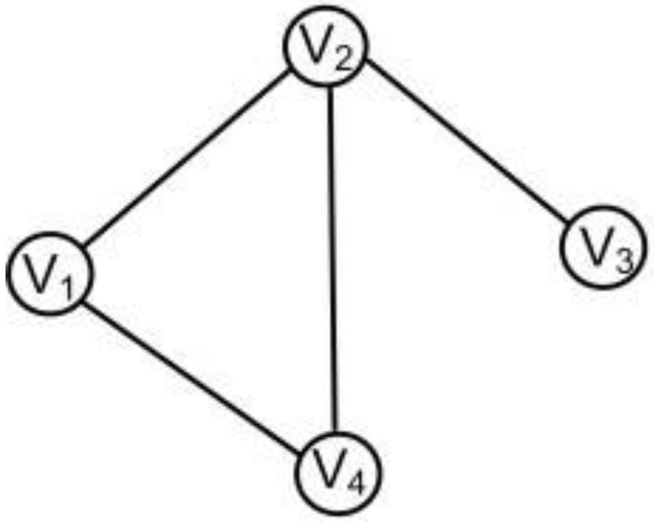
Multigraphs contain parallel edges

Multi-edged connections indicate different properties

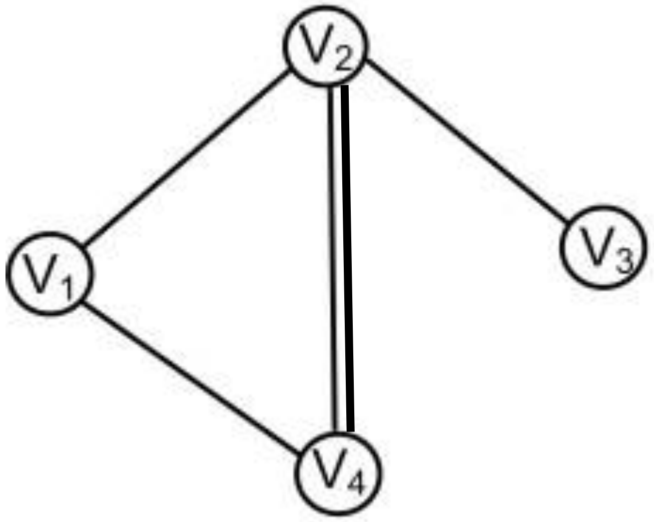
Example: PPI

- Physical evidence for interaction
- Co-expression

Simple

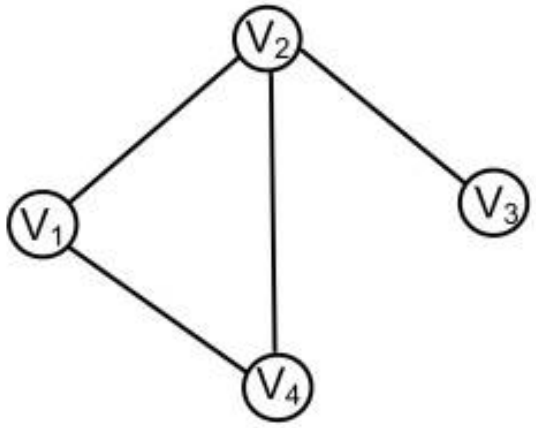


Multigraphs

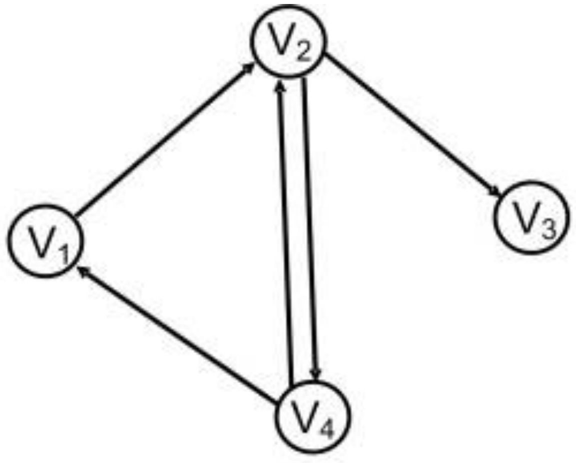


Directed vs undirected graphs

Undirected graphs:
co-expression networks

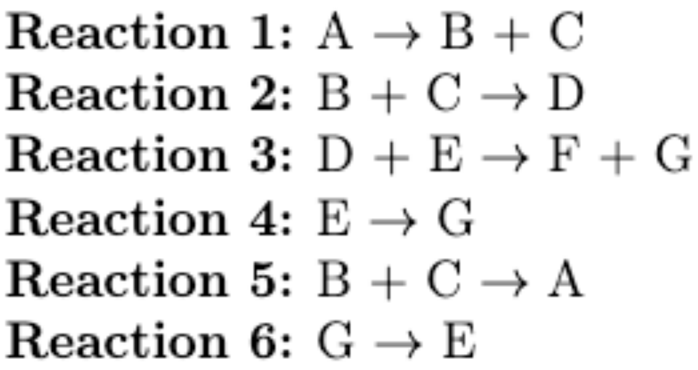


Directed graphs:
metabolic networks



Hypergraphs

Hypergraphs contain edges that connect any number of nodes



Reaction 1: $A \rightarrow B + C$

Reaction 2: $B + C \rightarrow D$

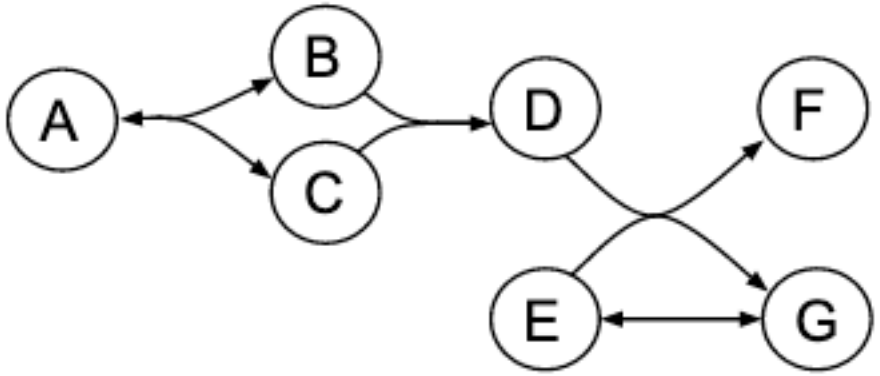
Reaction 3: $D + E \rightarrow F + G$

Reaction 4: $E \rightarrow G$

Reaction 5: $B + C \rightarrow A$

Reaction 6: $G \rightarrow E$

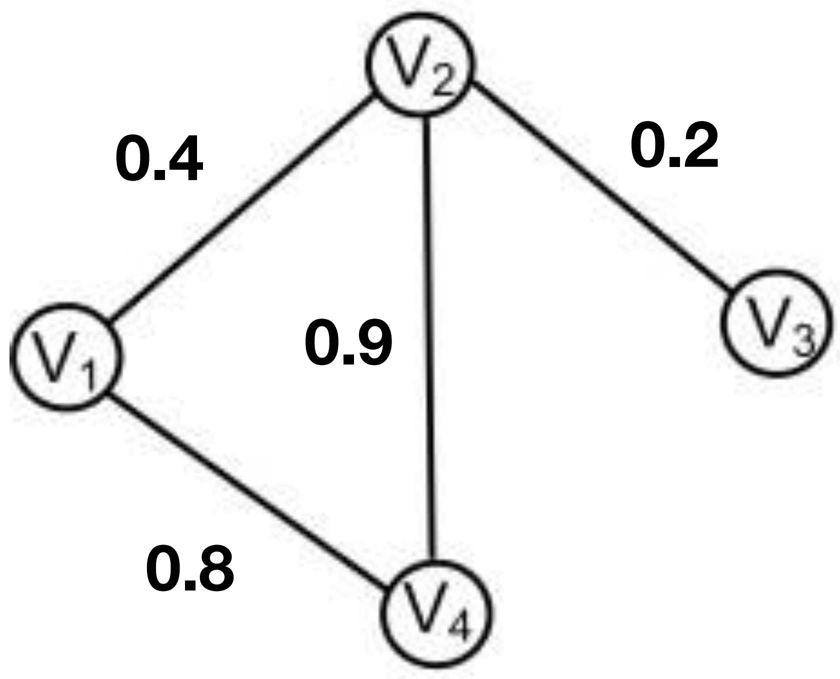
(a) Reaction network



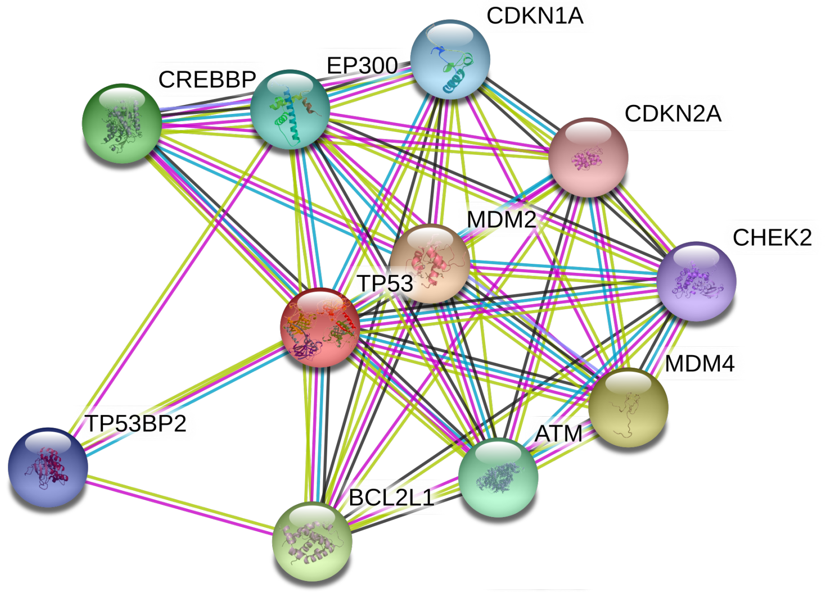
Weighted vs unweighted graphs

Weighted edges associate a value to an interaction between two nodes. Usually give the confidence in the interaction.

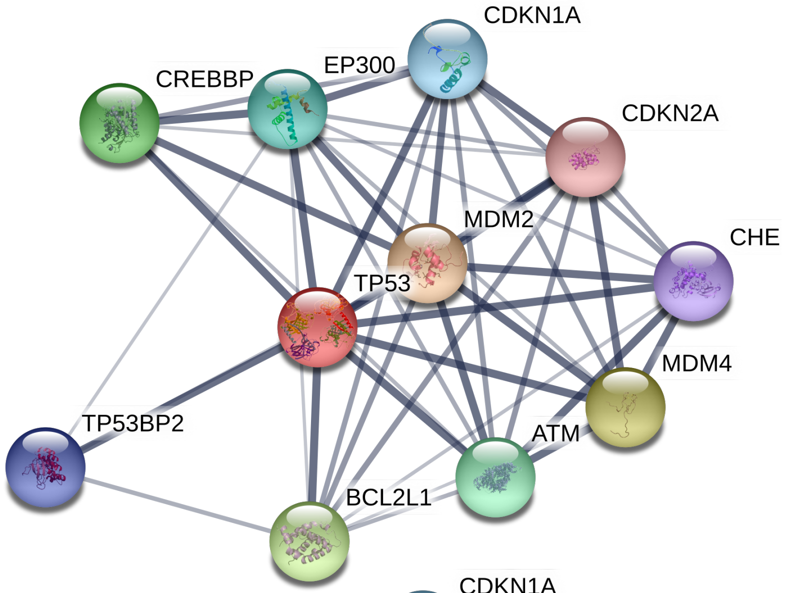
E.g. weighted co-expression networks



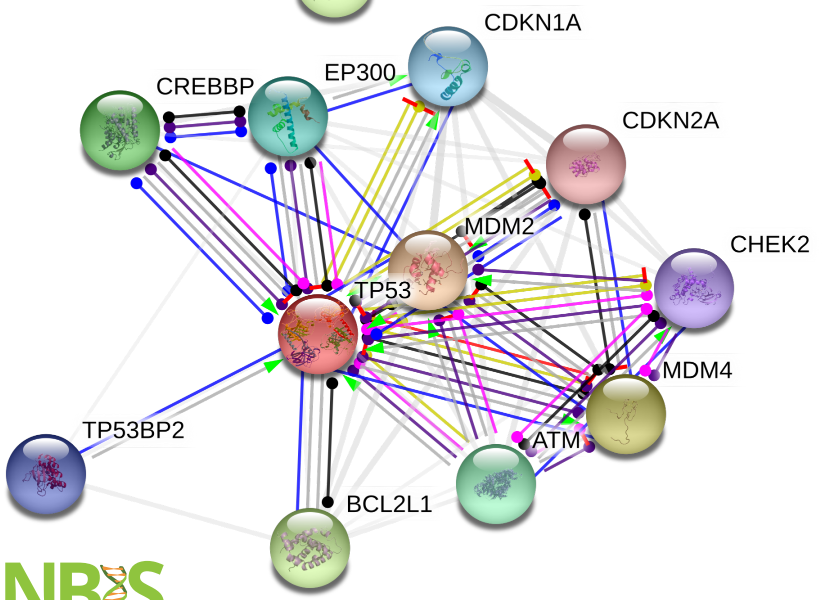
STRING-db.org: TP53



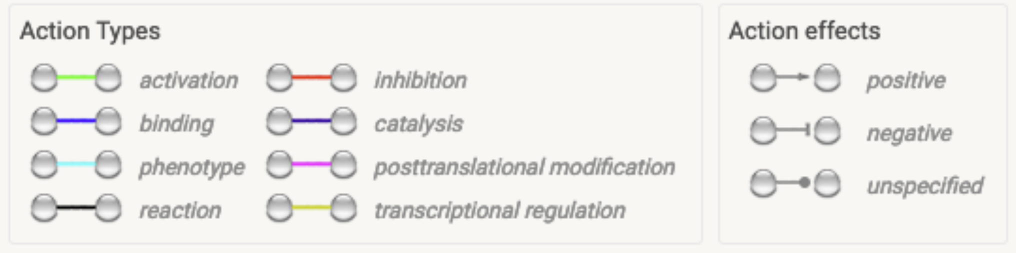
Multi-edged



Weighted multi-edged



Multi-edged directed



Bipartite graphs

A graph

$$G=(V,E)$$

Examples?

may be partitioned into two sets of nodes (V_1, V_2) such that

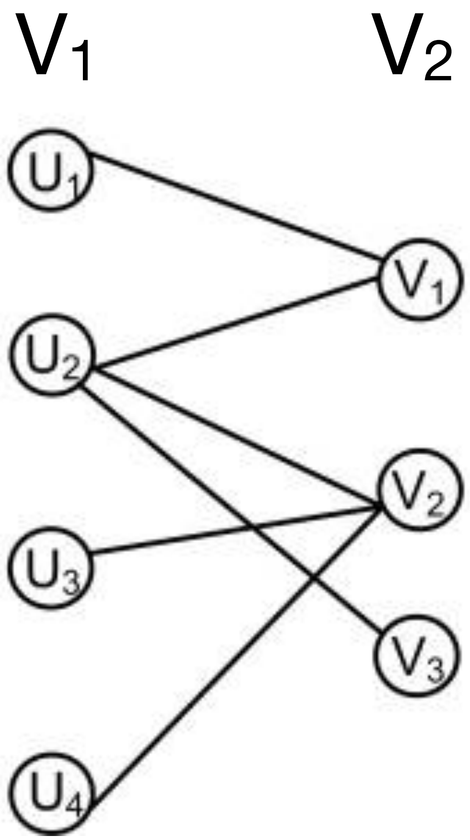
$$u \in V_1 \text{ and } v \in V_2$$

All e_i has end-nodes in V_1, V_2

A **subgraph** of G will thus be given by

$$G_1 = (V_1, E_1)$$

1



Bipartite and *k*-partite graphs

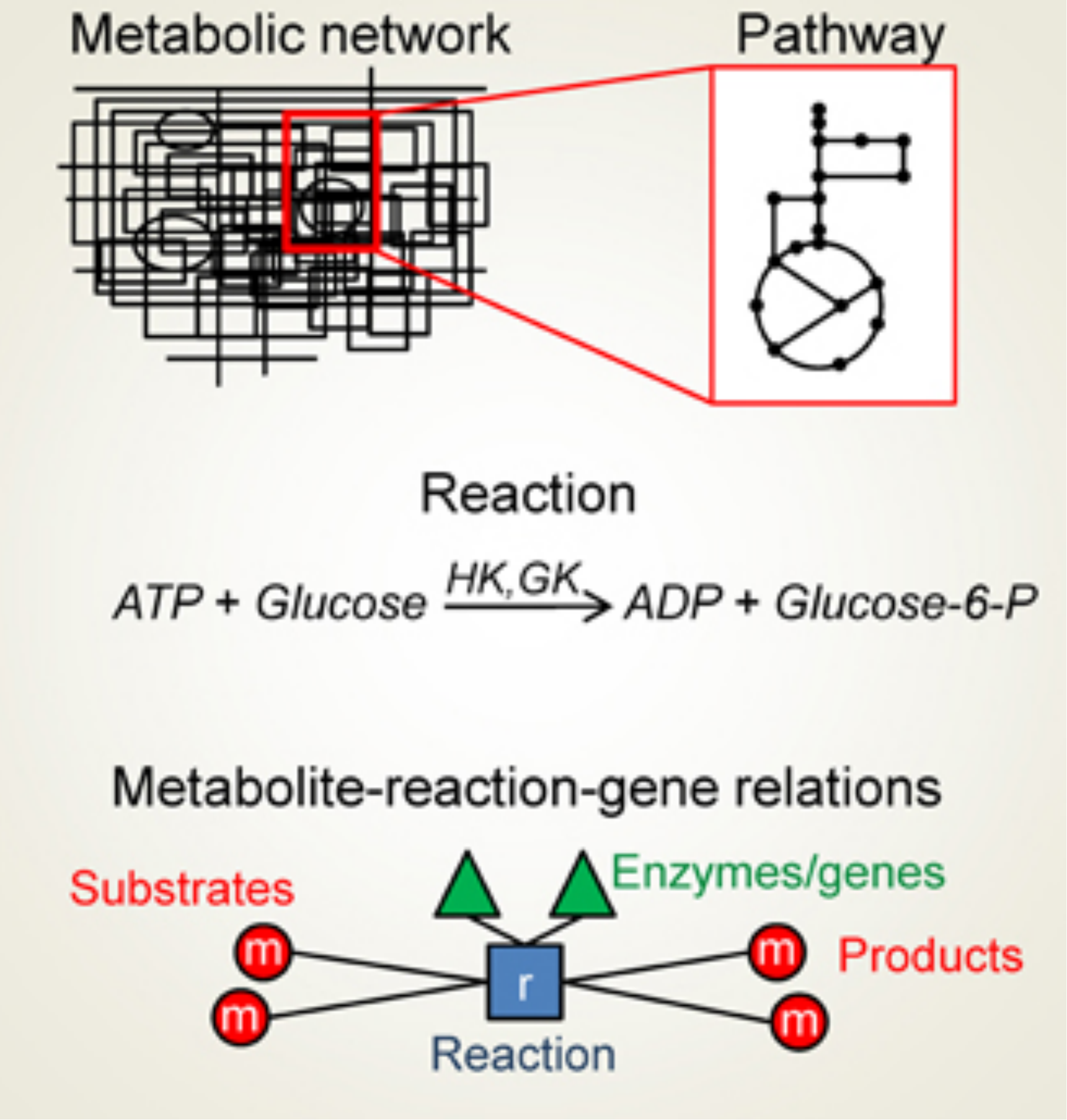
Bipartite graph:

- Gene - Reaction

Tripartite graph:

- Metabolite - reaction - enzyme

k-partite graphs display *k*-types of nodes



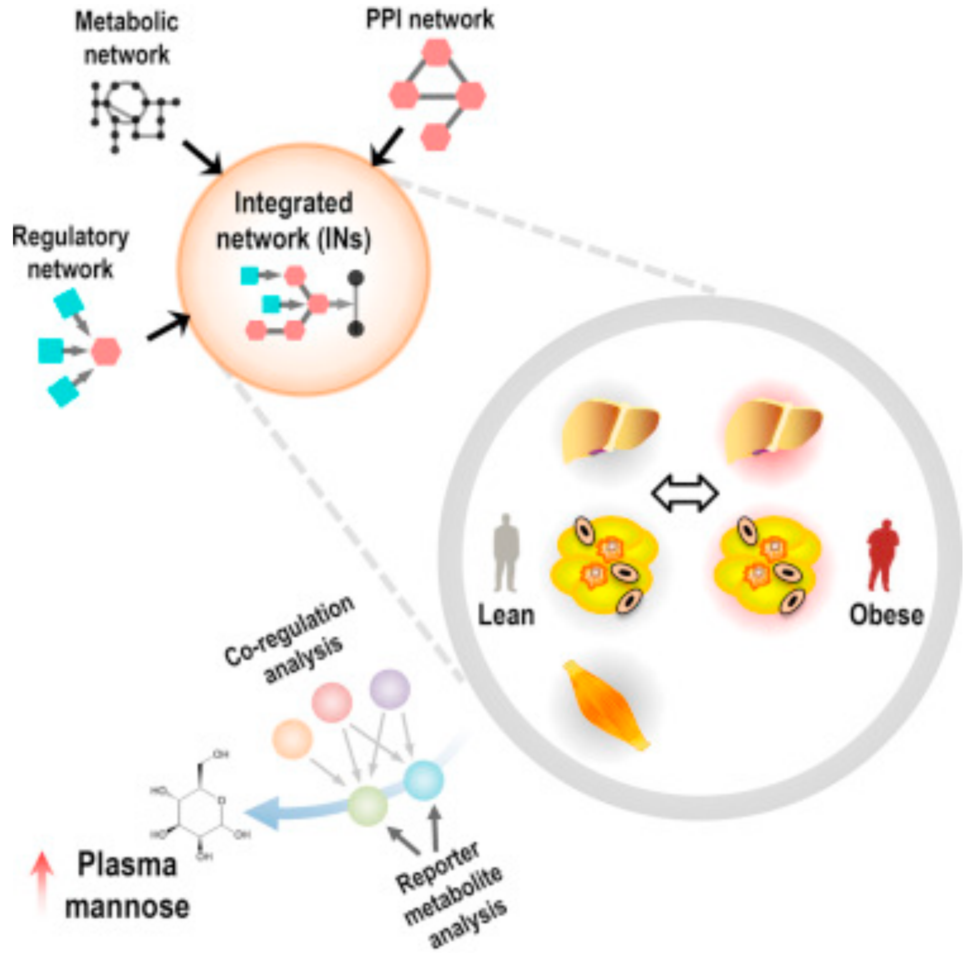
Väremo 2013

k-partite graphs

Multi-modal (*k*-partite) networks may be generated from different sources

- Transcription-factor - Gene (DNAseq)
- Gene-gene (Co-expression, PPI, GEMs)
- Gene-metabolite (GEM)
- Metabolite-metabolite (GEM)

Integrated Networks



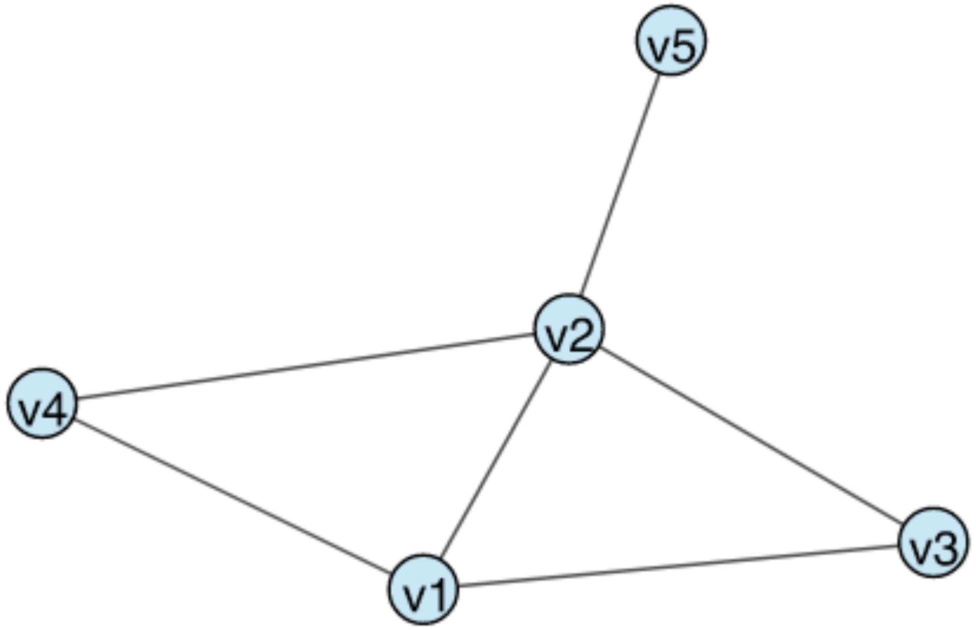
Lee 2016

Adjacency matrix (undirected graphs)

Vertex association

(undirected network)

n1	n2
v1	v2
v1	v4
v2	v4
v2	v3
v2	v5
v1	v3



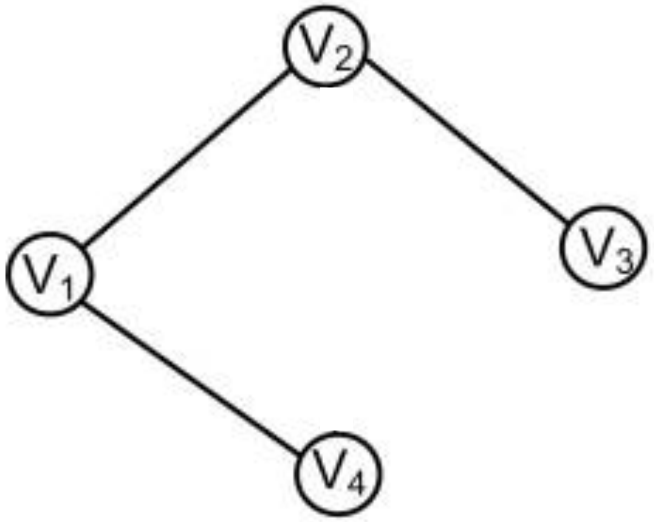
Adjacency matrix is symmetric

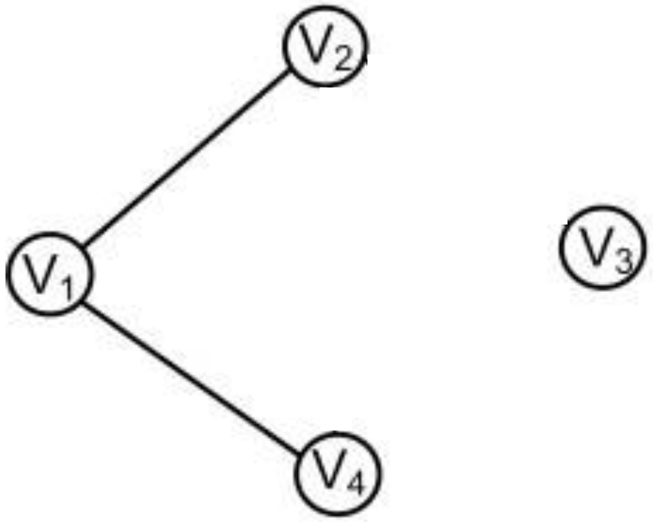
	v1	v2	v3	v4	v5
v1	0	1	1	1	0
v2	1	0	1	1	1
v3	1	1	0	0	0
v4	1	1	0	0	0
v5	0	1	0	0	0

Connected vs disconnected networks

Connected network: there is at least 1 path connecting all nodes in a network

Disconnected network: some of the nodes are unreachable

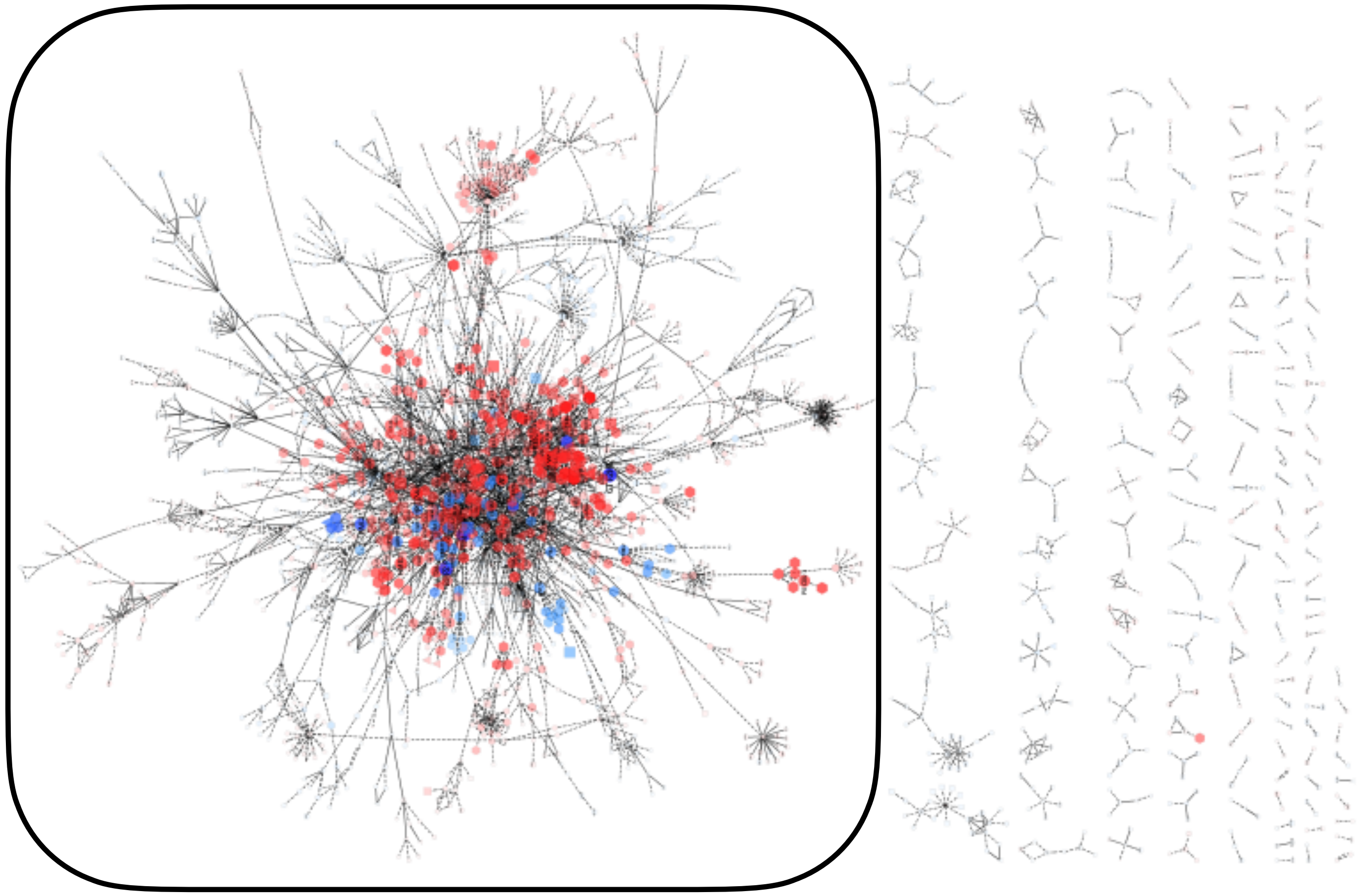




Connected components

Connected components are those where all nodes of each subgraph are connected.

In biological networks, often the most insightful properties come from the **largest connected component(s)**



Additional reading

- Network Science - Textbook on graph theory and network analysis.
- Communication dynamics in complex brain networks - Network topology applied to study the brain
- A Systematic Evaluation of Methods for Tailoring Genome-Scale Metabolic Models - Review and discussion on methods to use in genome-scale metabolic models.
- Analysis of Biological Networks - General introduction into biological networks, network notation, and analysis, including graph theory.
- Multi-omics approaches to disease - Introduction to how integrative approaches may be applied in disease

Additional references displayed as hyperlinks in each slide.