

Biological network analysis

Rui Benfeitas

NBIS - National Bioinformatics Infrastructure Sweden
Science for Life Laboratory, Stockholm
Stockholm University

rui.benfeitas@scilifelab.se



SciLifeLab



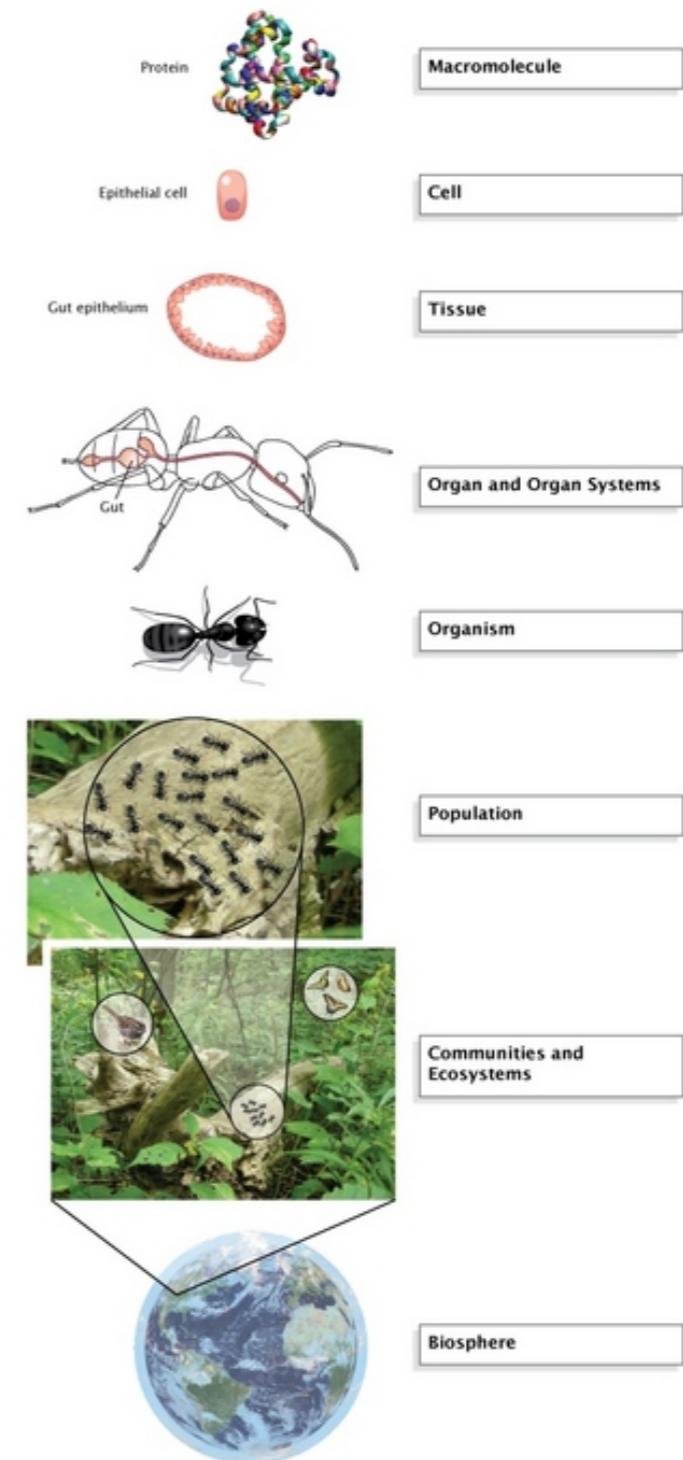
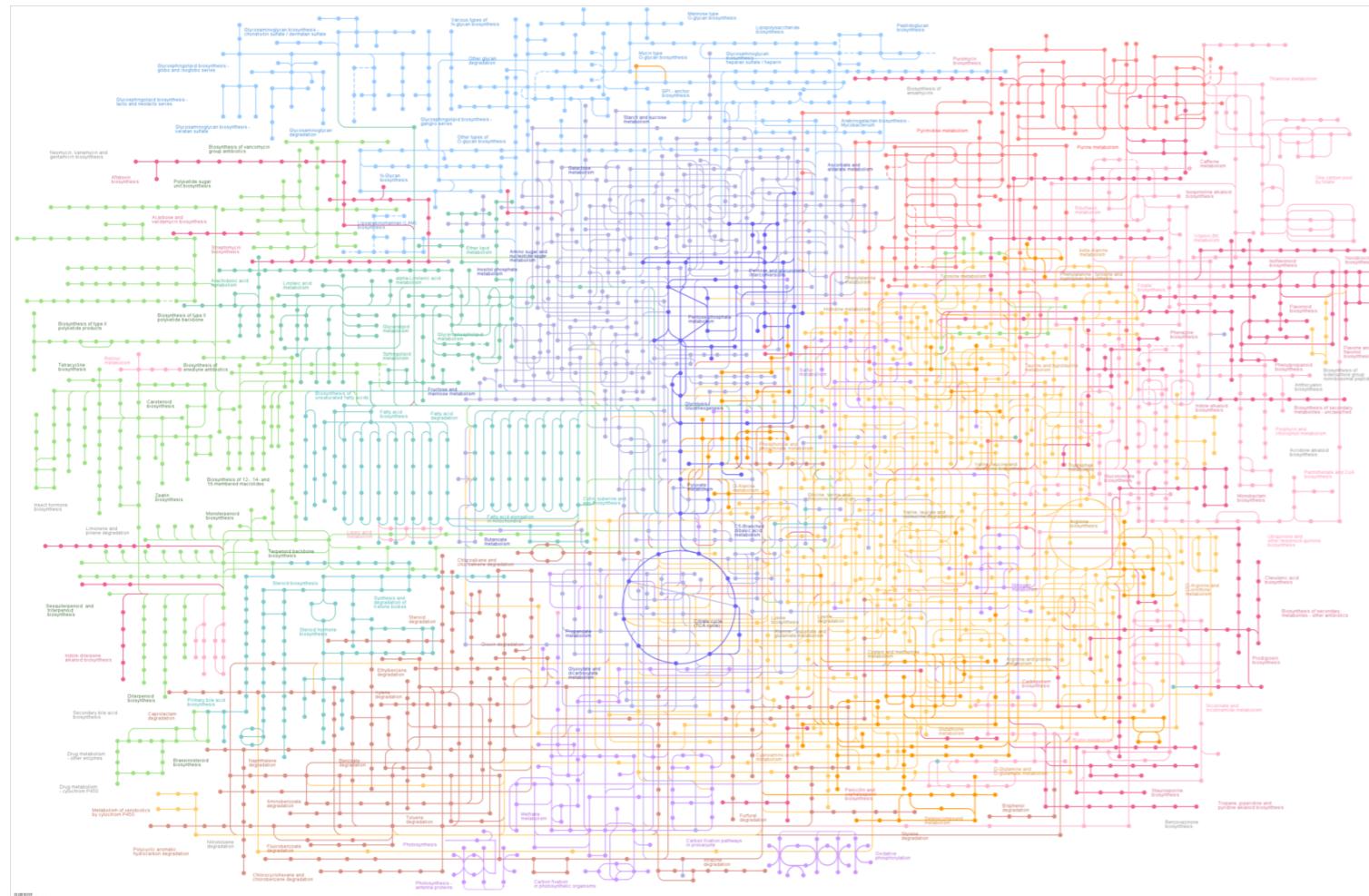
Overview

1. Introduction to network analysis
2. Terminology
3. Network construction
4. Key network properties
5. Community analysis
6. Visualization
7. Workshop

Introduction

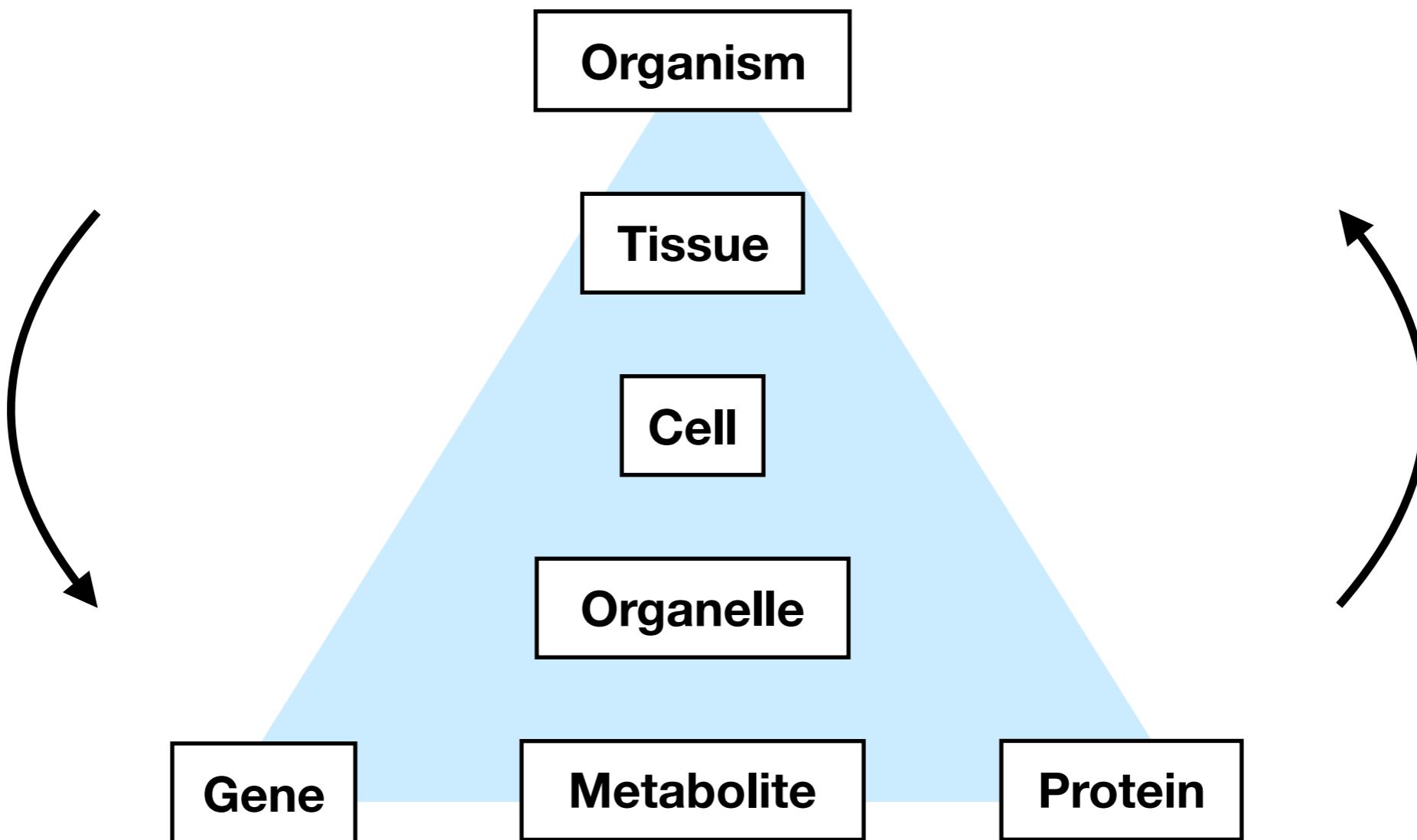
- [**1. Introduction**](#)
- [**2. Terminology**](#)
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Biological complexity under attack



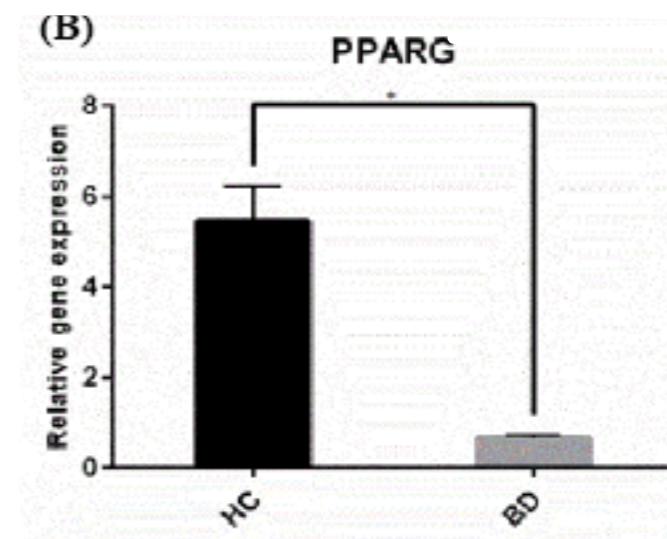
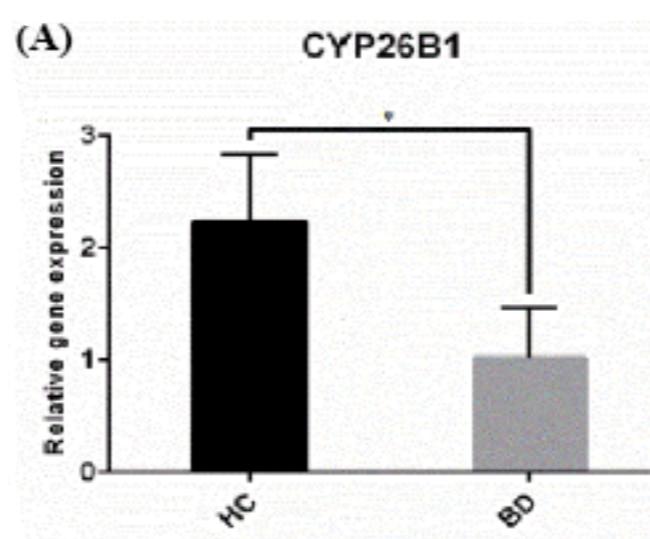
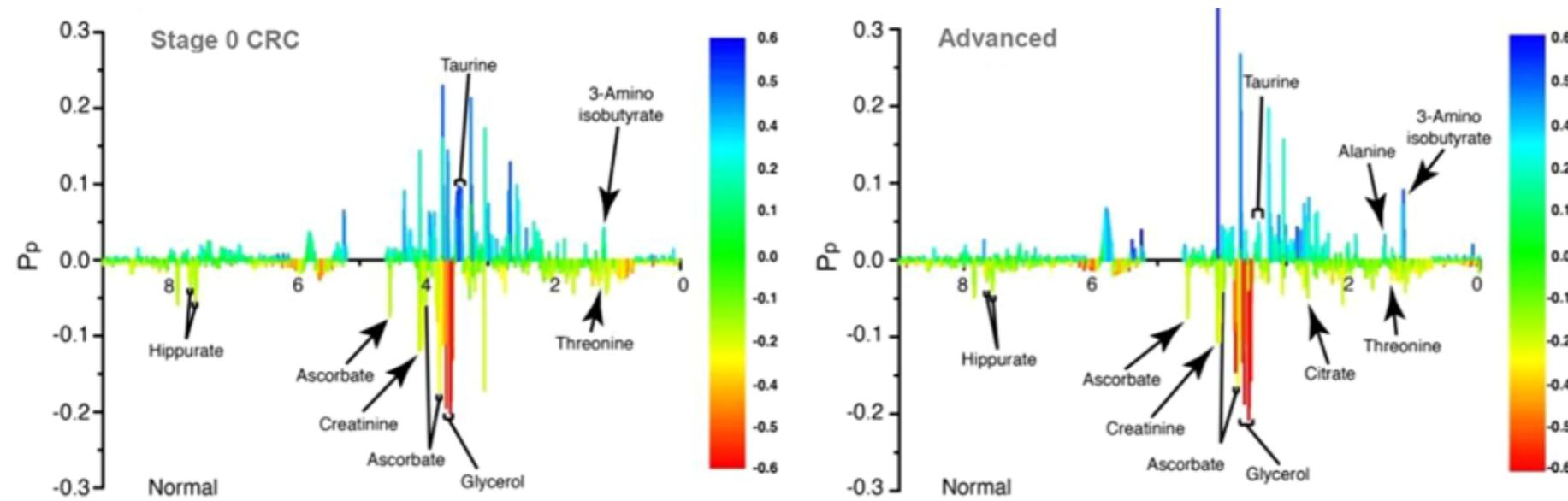
How to tackle biological complexity?

Moving from reductionist approaches towards global characterisations



How to tackle biological complexity?

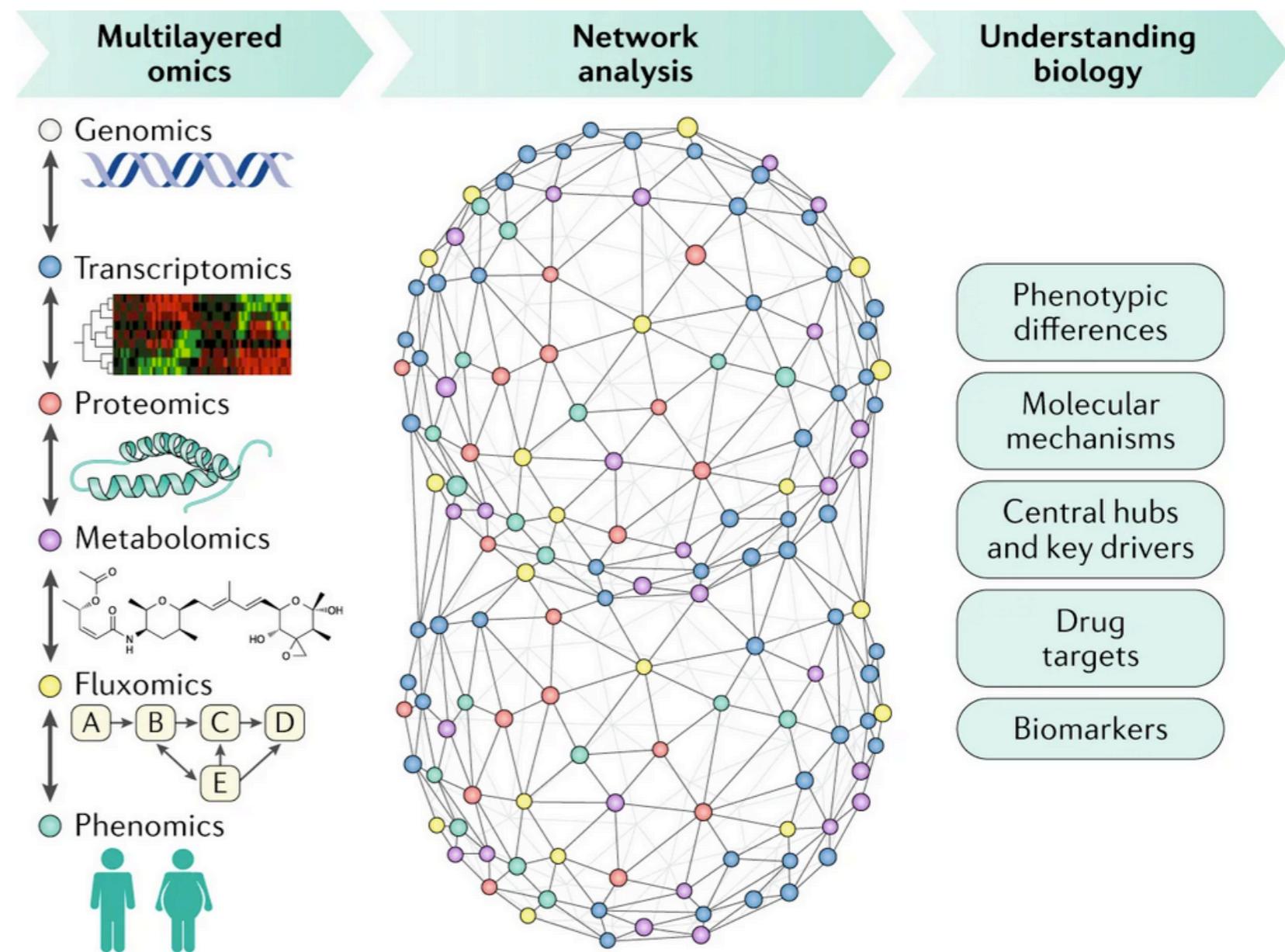
Moving beyond reductionist approaches



How to tackle biological complexity?

Integrative approaches, and global patterns

- Feature association
- Modeling
- Network analysis



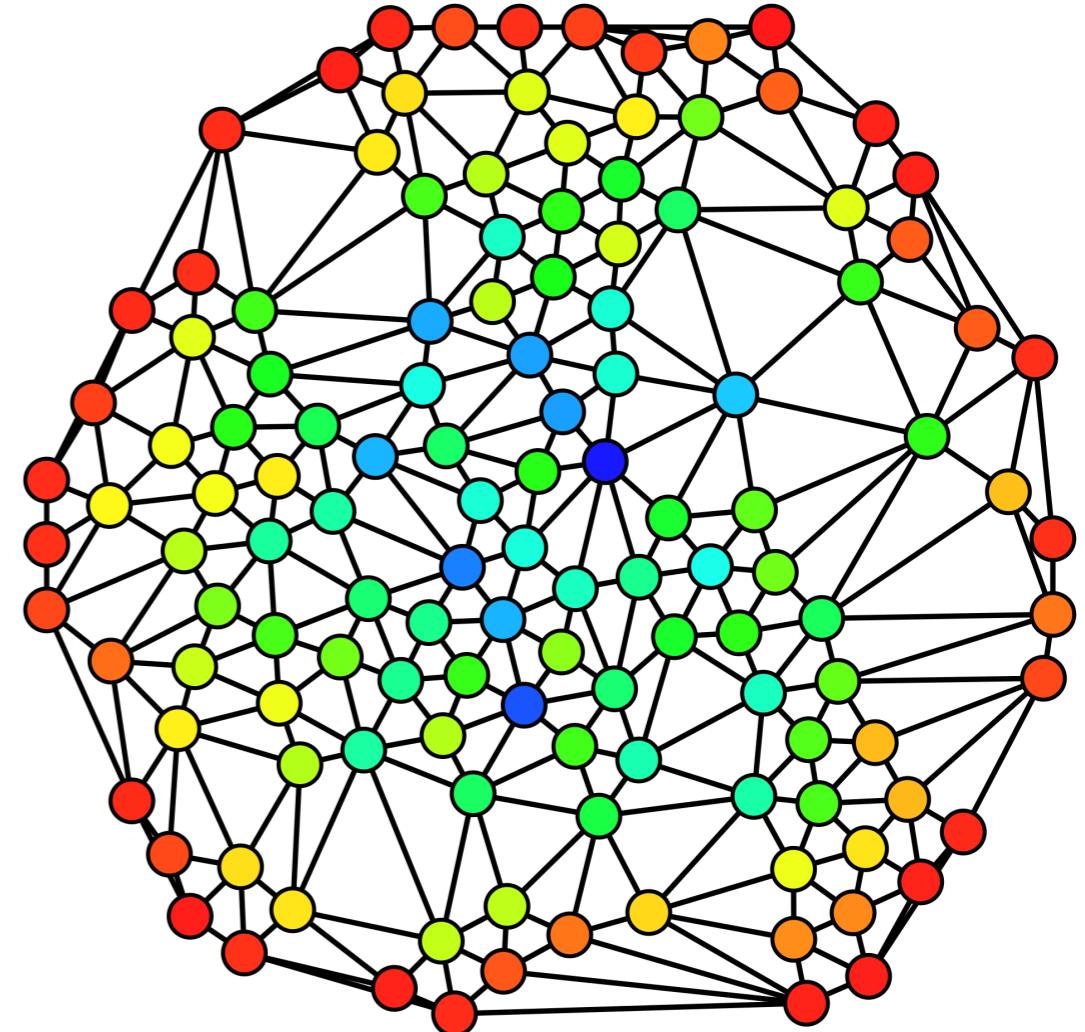
What are networks?

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



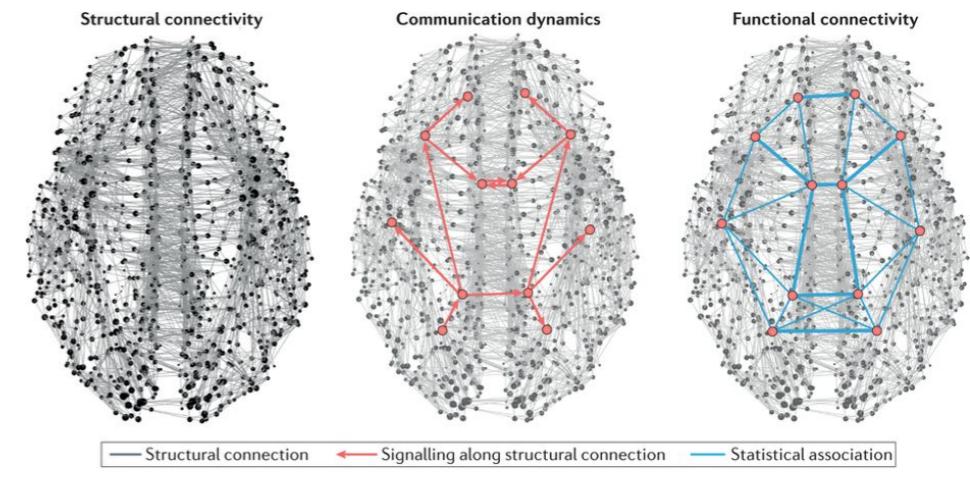
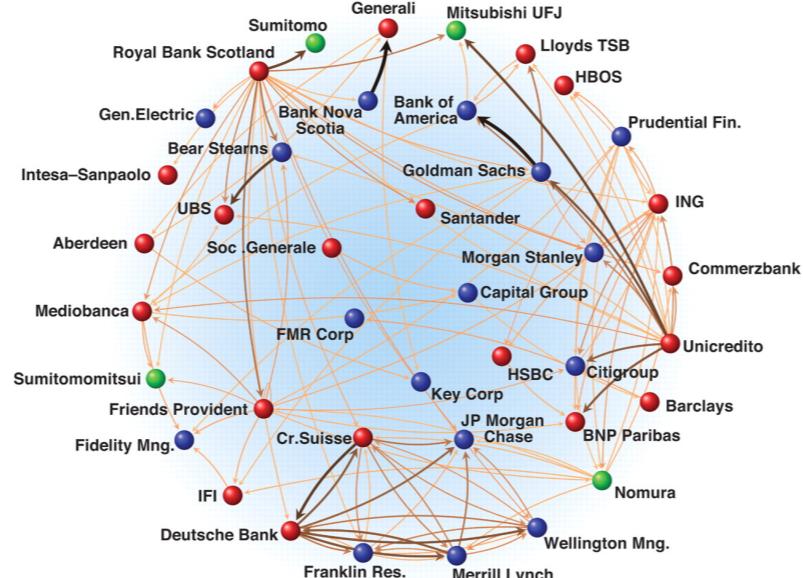
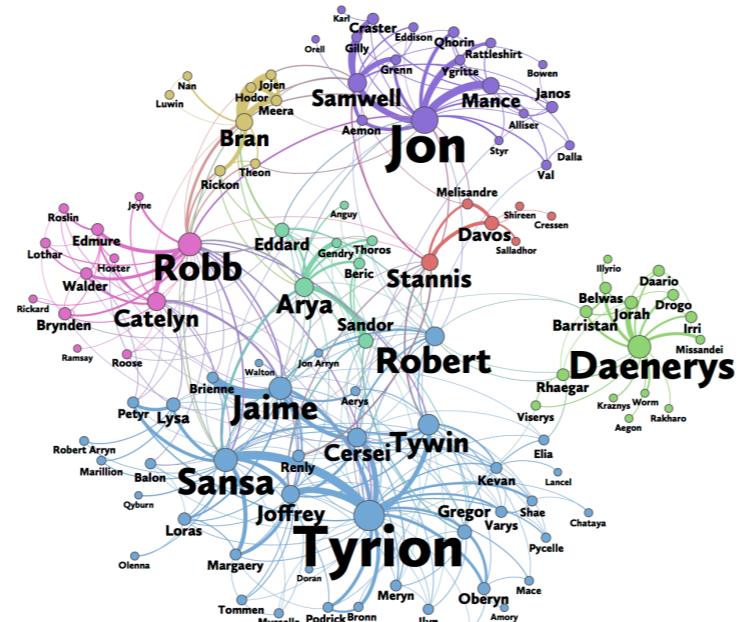
What are networks?

Social

Economic

Communication

Neuronal



Nature Reviews | Neuroscience

What are biological networks?

Protein - Protein interaction (PPI) networks

Transcription-factor regulatory networks

Gene - gene co-expression networks

Signal transduction networks

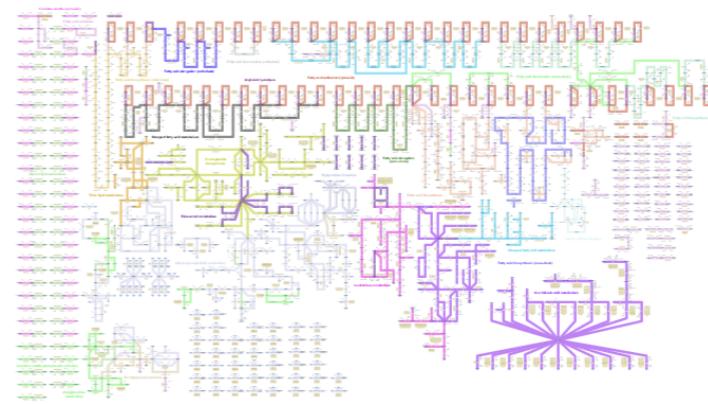
Transcription-Factor Regulatory networks

Drug-disease association networks

Aim
Functional characterisations

What are biological networks?

Metabolite - Enzyme - Signal - Genes (GEMs)

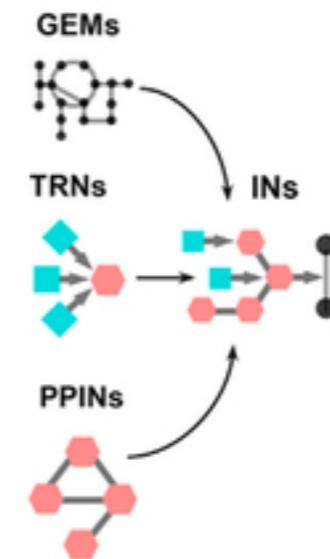
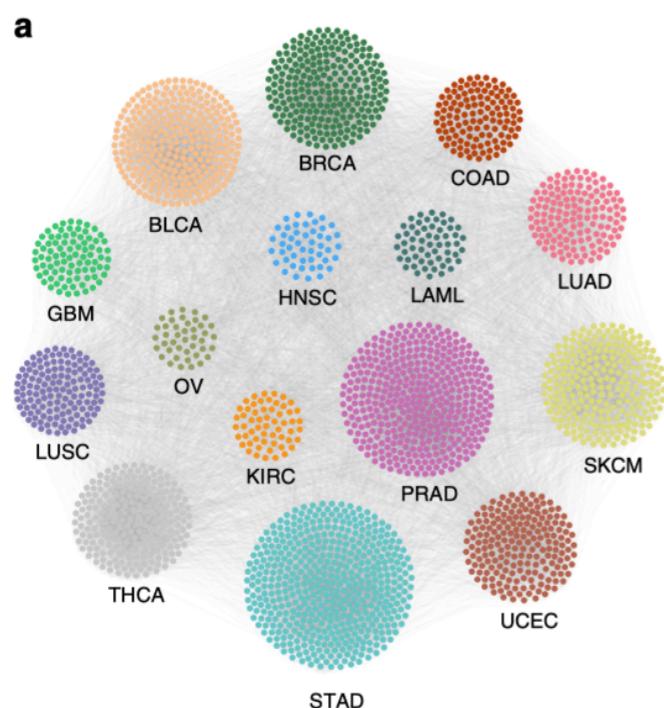
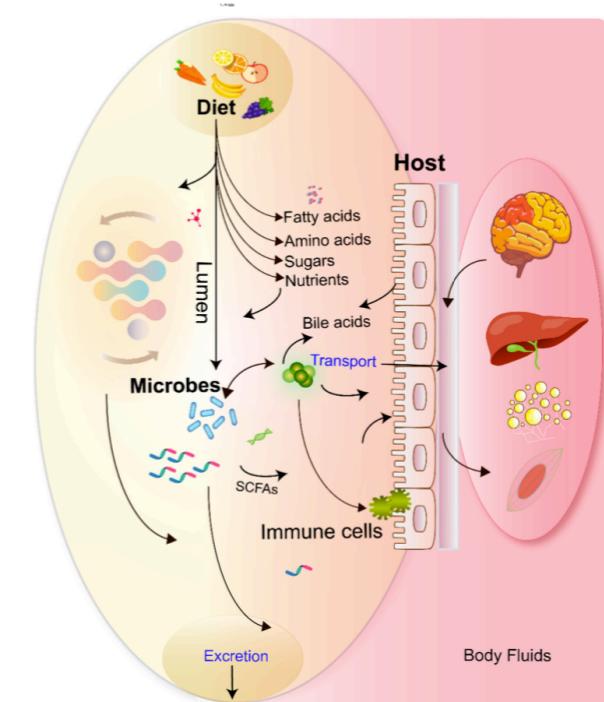
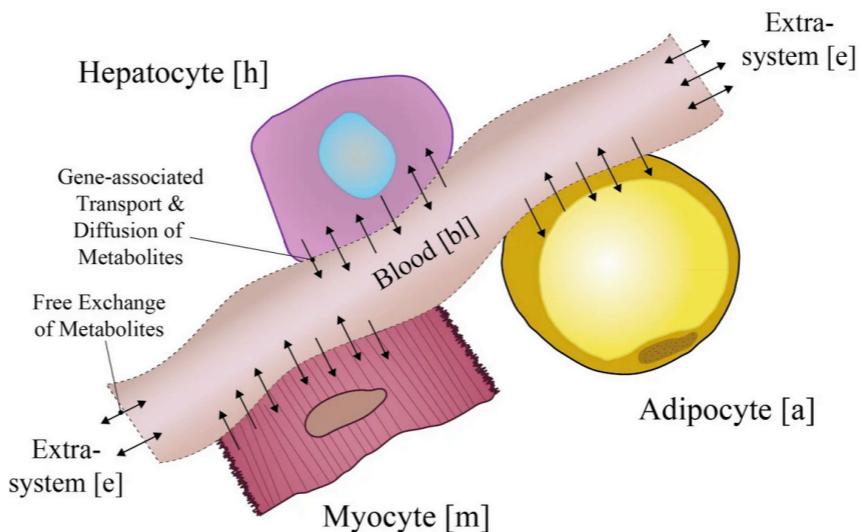


Multi-tissue networks

Multi-species networks

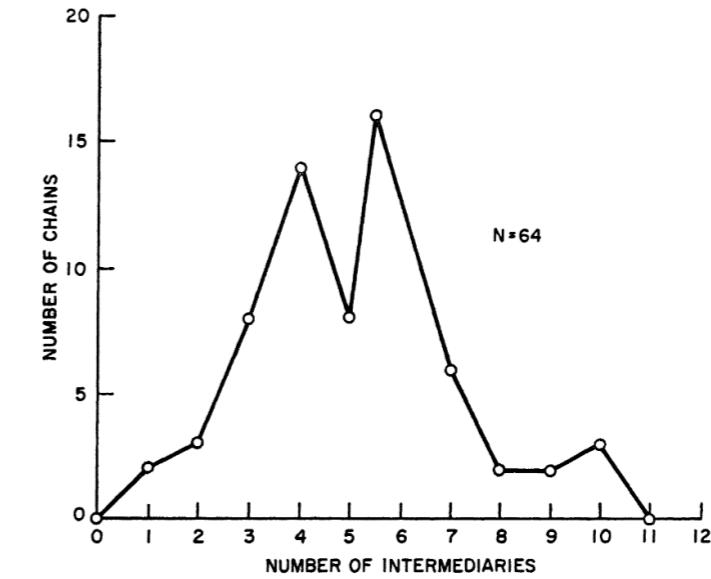
Cancer-disease networks

Integrated networks

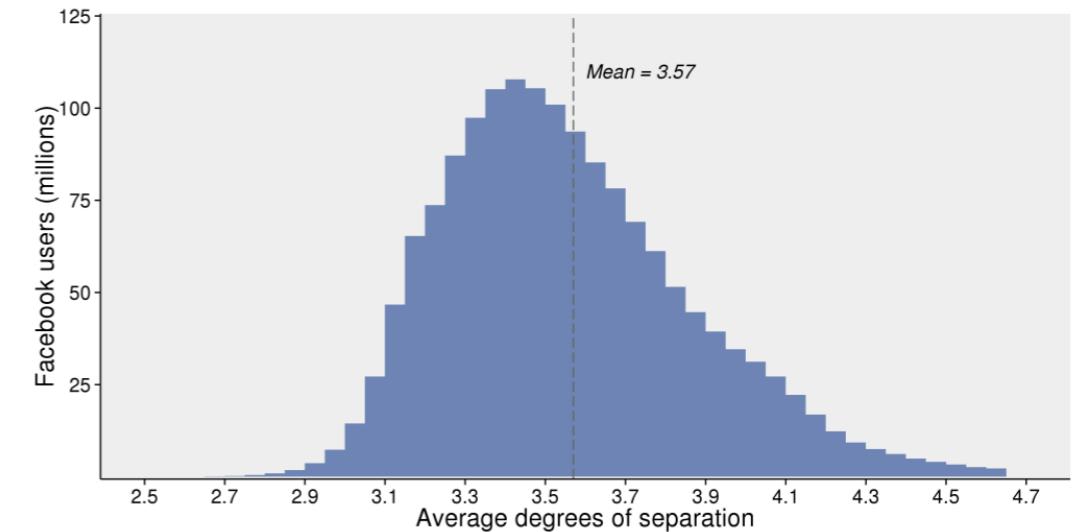


Small world

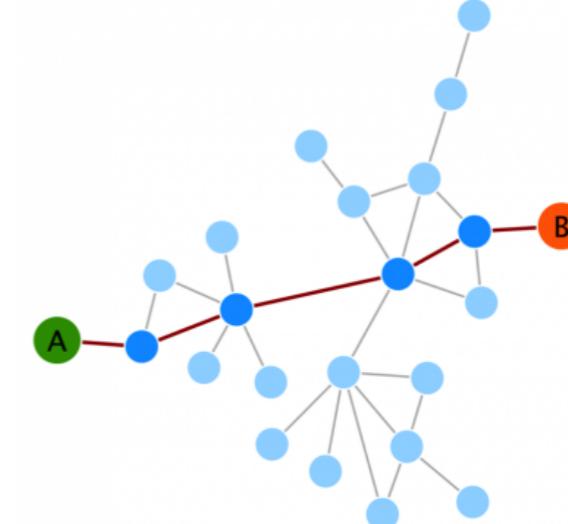
Stanley Milgram (1967) - 6 degrees



Backstrom et al. (2016) - 3.6 degrees



Biological Networks



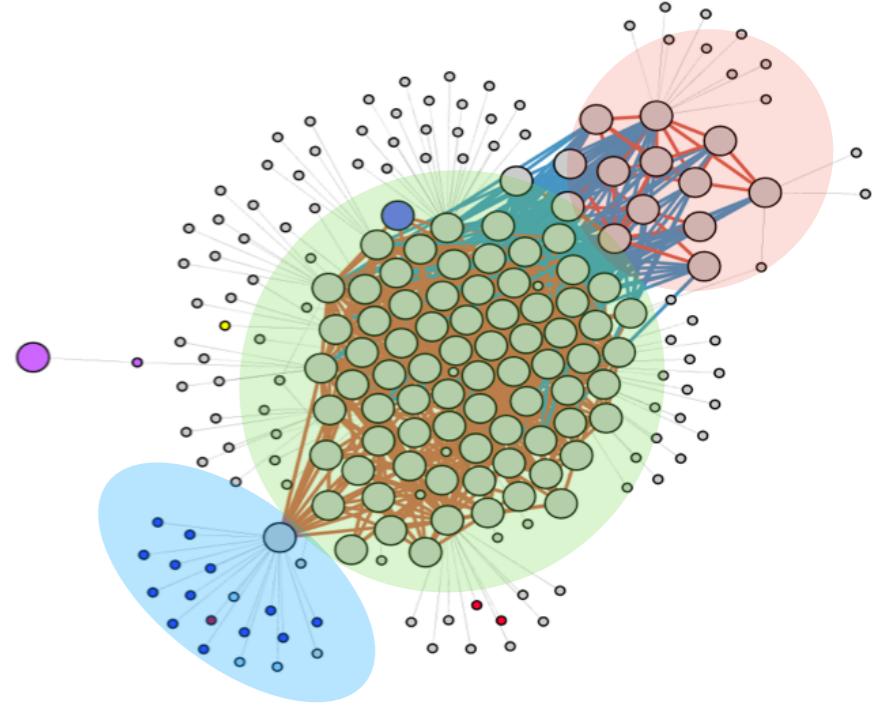
Why look at network topology?

Use networked systems to identify:

- 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 "weakest" links in the network?



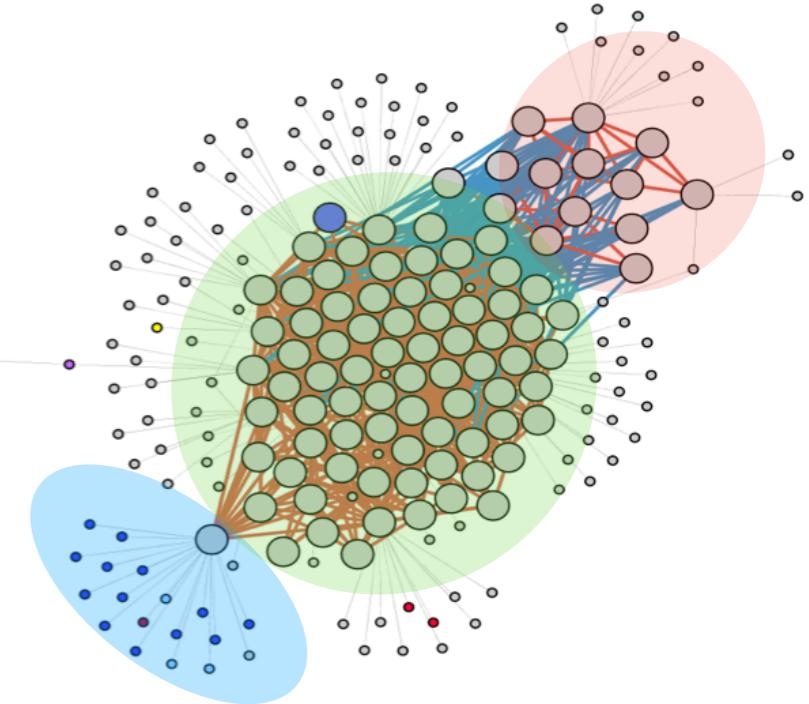
What is my biological network?

Any association 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

Some of the functional analyses depend on annotation



Limitations

Sample size

False discovery

~requires high throughput

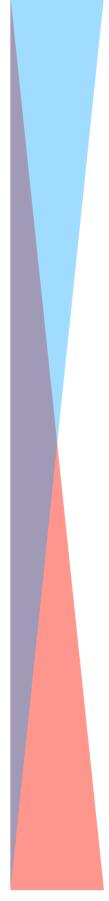
(further discussed in following lectures)

Terminology and initial properties in graph analysis

1. Introduction
- 2. Terminology**
3. Network construction
4. Key properties
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Motivation

What modeling formalism suits your data and biological question?

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

Graphs, nodes, edges

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

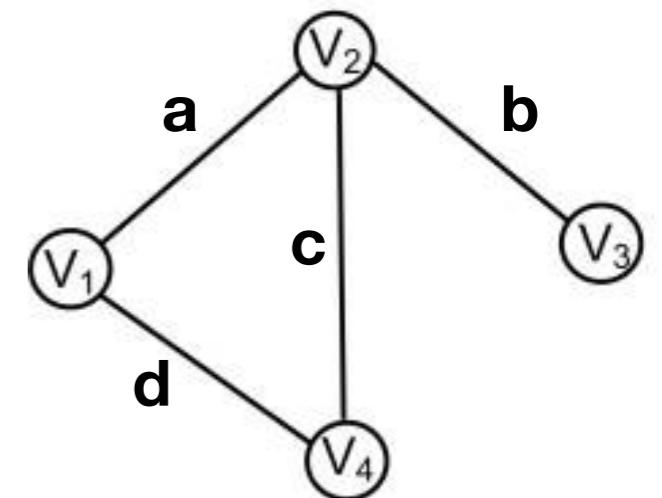
$$G = (V, E)$$

$$V=\{v_1, v_2, v_3, v_4\}$$

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

Nodes sometimes called **vertices**

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



Simple vs multigraphs

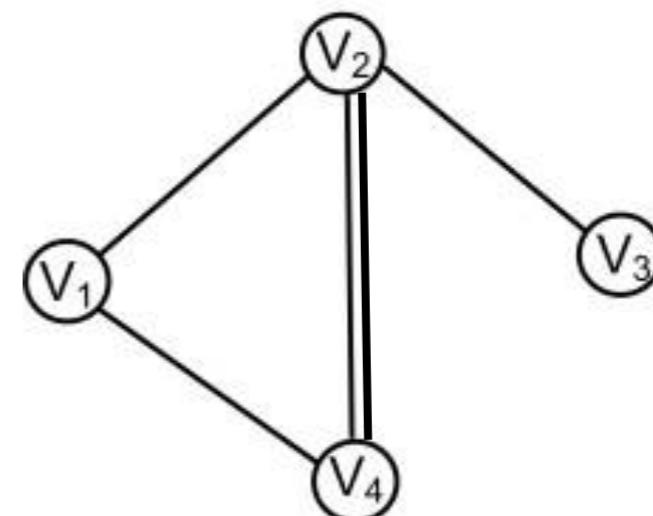
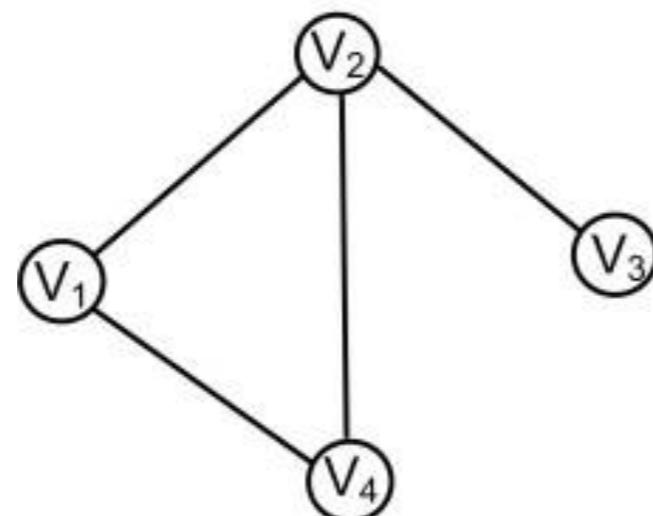
Multigraphs contain parallel edges

Multi-edged connections indicate different properties

Multigraphs vs **simple** graphs

Example: PPI

- Experimental evidence for interaction
- Co-expression



Hypergraphs

Hypergraphs contain edges that connect any number of nodes

Reaction 1: $A \rightarrow B + C$

Reaction 2: $B + C \rightarrow D$

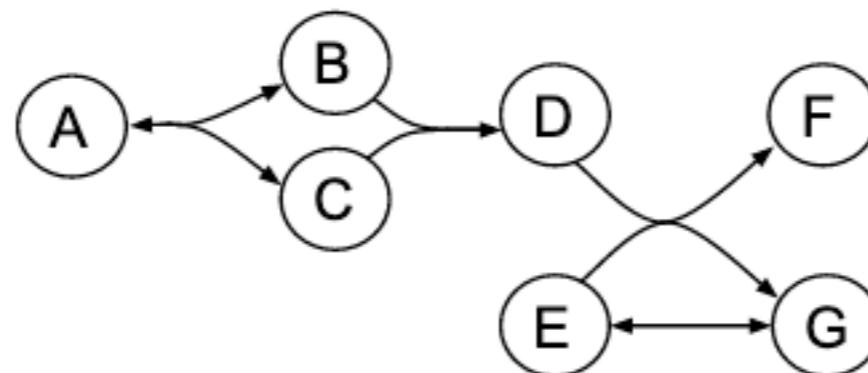
Reaction 3: $D + E \rightarrow F + G$

Reaction 4: $E \rightarrow G$

Reaction 5: $B + C \rightarrow A$

Reaction 6: $G \rightarrow E$

(a) Reaction network



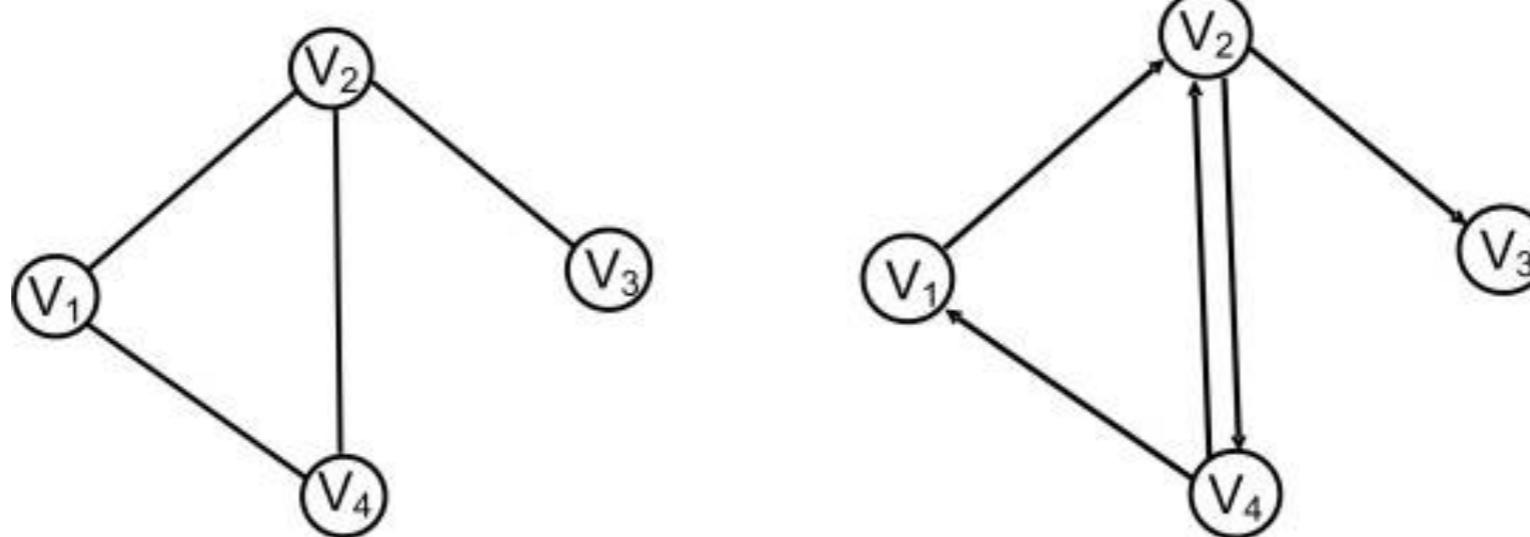
Directed vs undirected graphs

Directed graphs is given by an ordered triple

$$G = (V, E, f)$$

f : function mapping an element in **E** to the ordered pair of vertices in **V**

$$E = \{ (v_1, v_2), (v_2, v_3), (v_2, v_4), (v_4, v_1), (v_4, v_2) \}$$



Directed vs undirected graphs

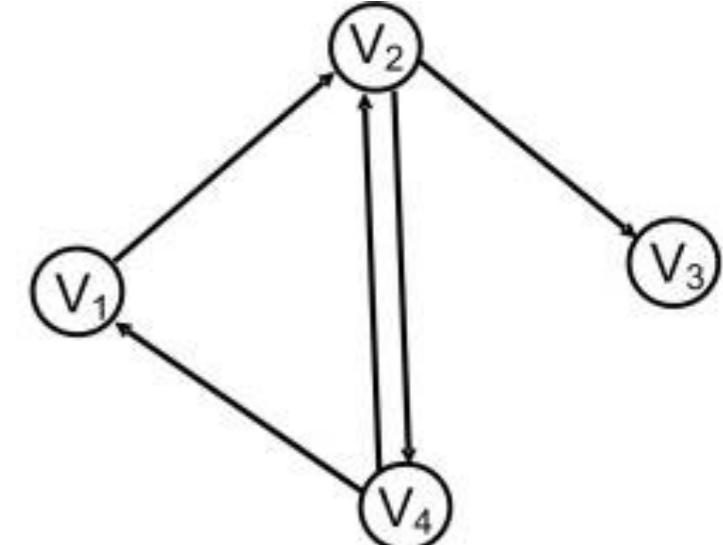
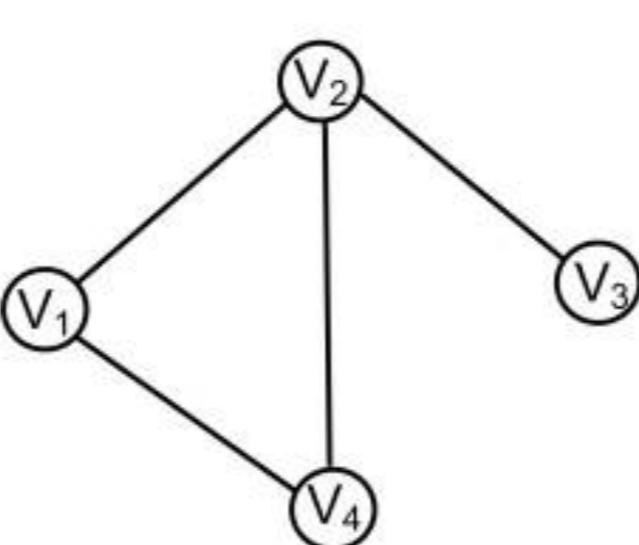
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Examples:

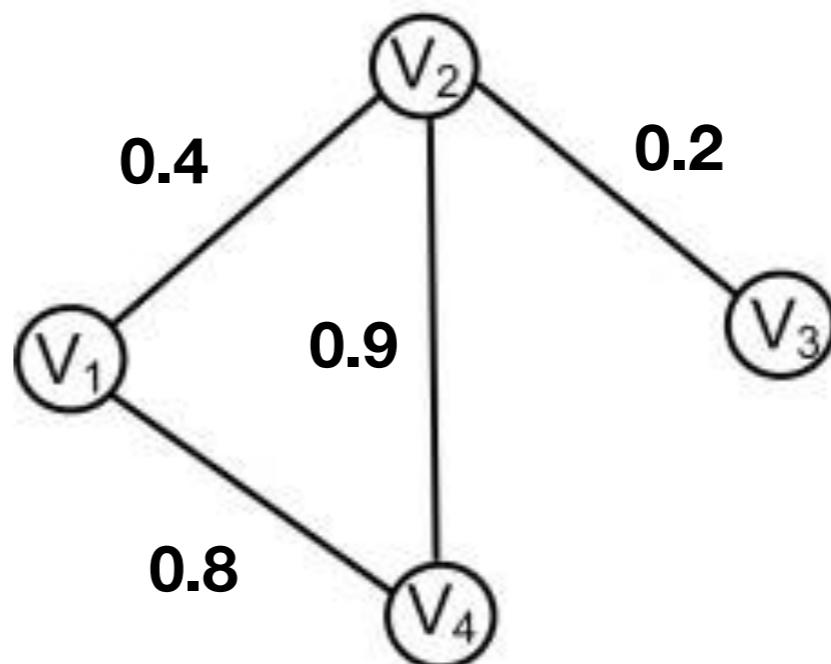
- **Undirected graphs:** co-expression networks
- **Directed graphs:** metabolic networks



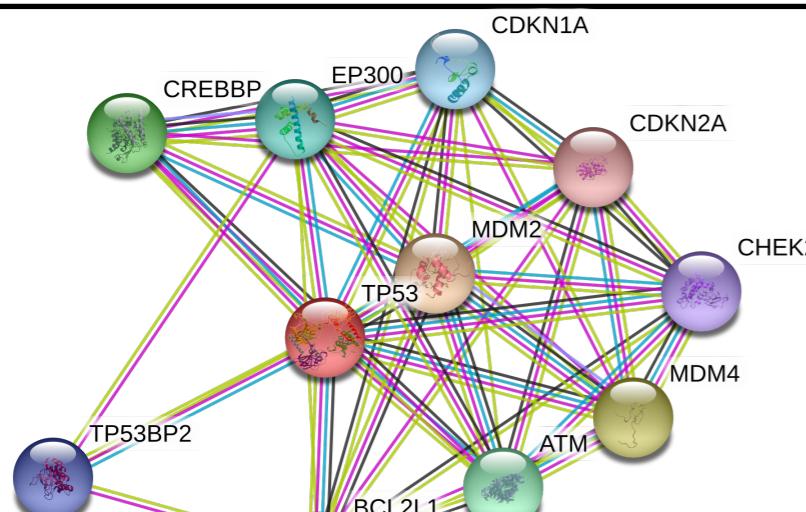
Weighted vs unweighted graphs

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

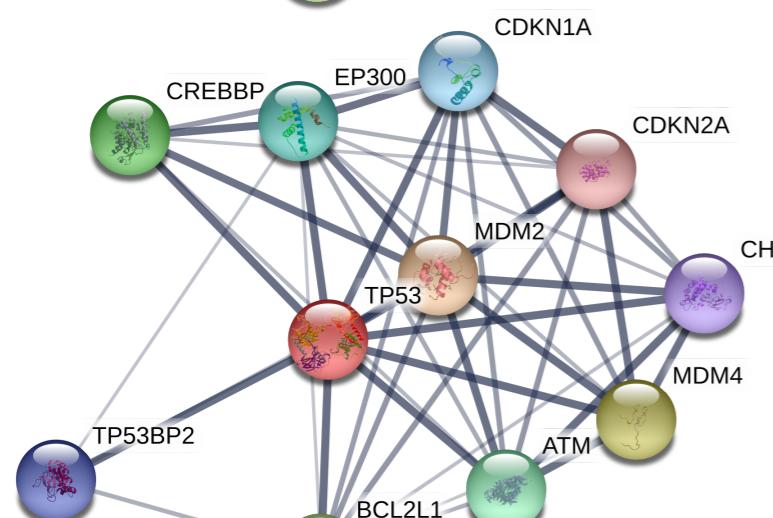
E.g. weighted co-expression networks



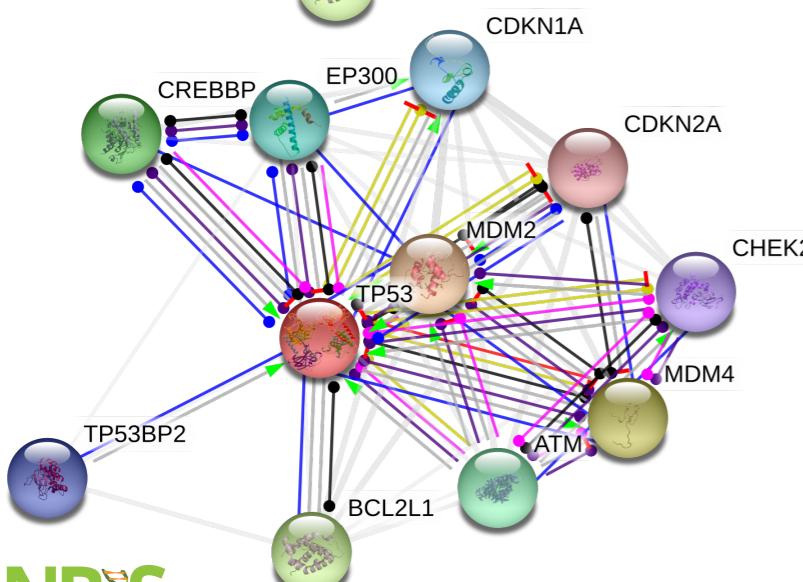
STRING-db.org: TP53



Multi-edged



Weighted multi-edged



Multi-edged directed



Bipartite graphs

A graph

$$G=(V,E)$$

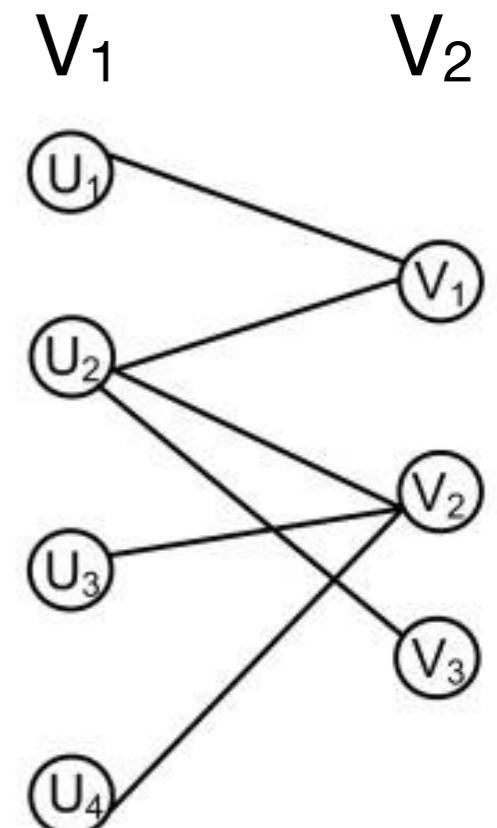
may be partitioned into two sets of nodes (V_1, V_2)
such that

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

or

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

All e_i has end-nodes in V_1, V_2



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

$$G_1 = (V_1, E_1)$$

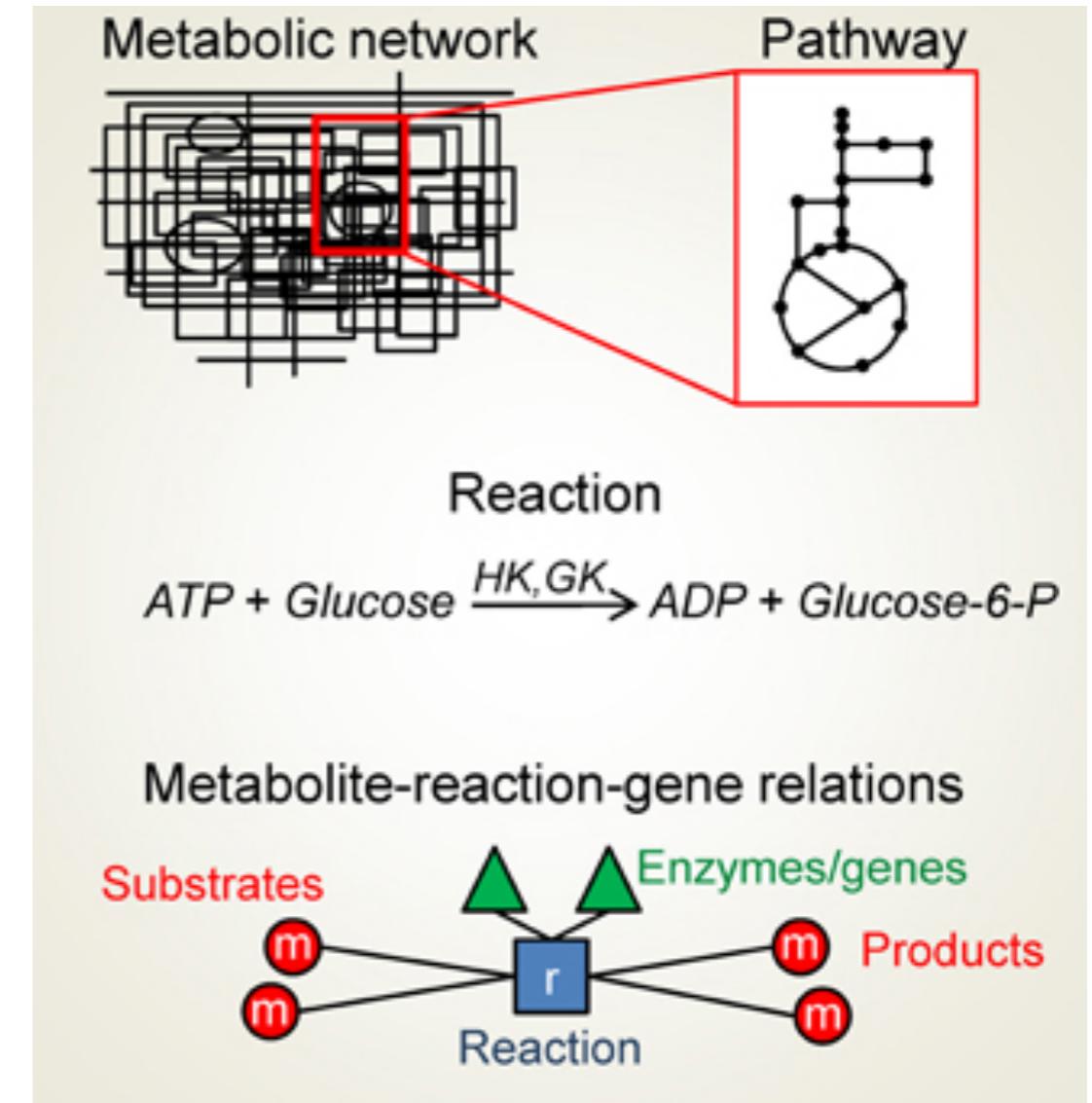
Bipartite and k -partite graphs

Example of bipartite graph:

Enzyme - Reaction

Metabolite - reaction - enzyme

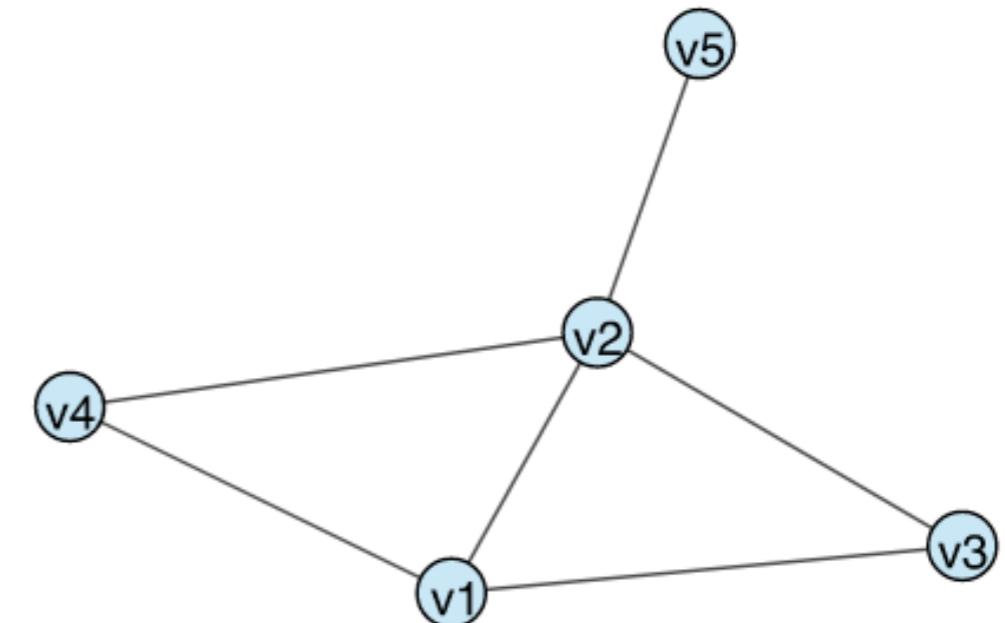
k -partite graphs display k -types of nodes



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

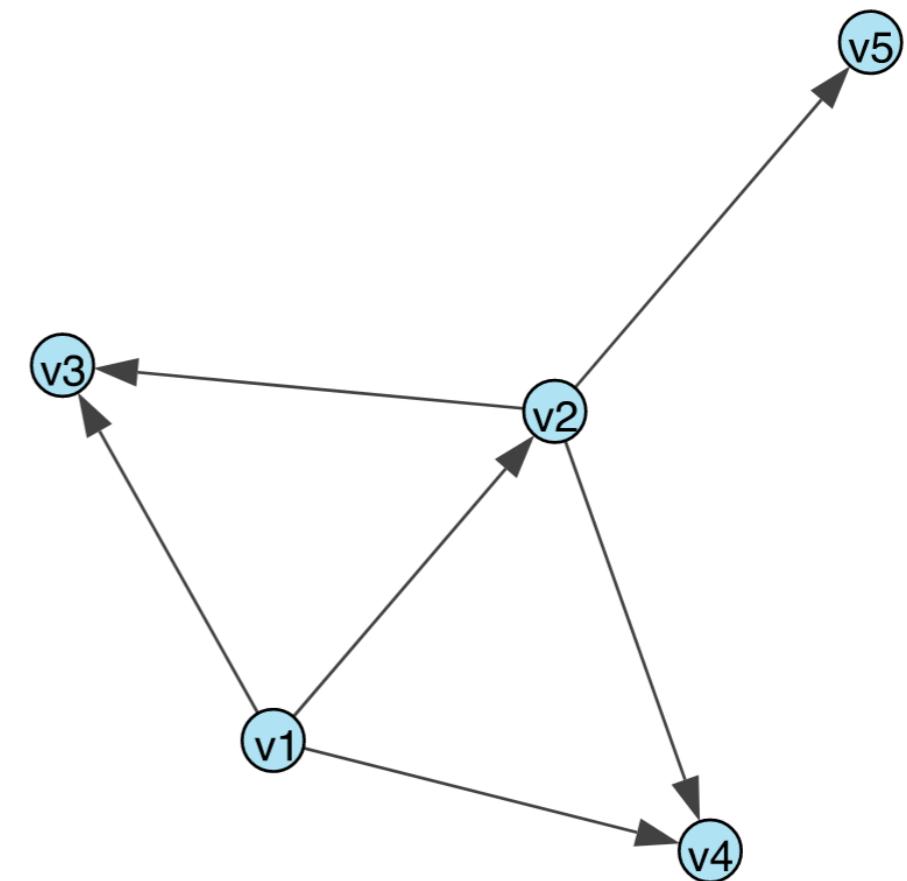
Upper triangular

Lower triangular

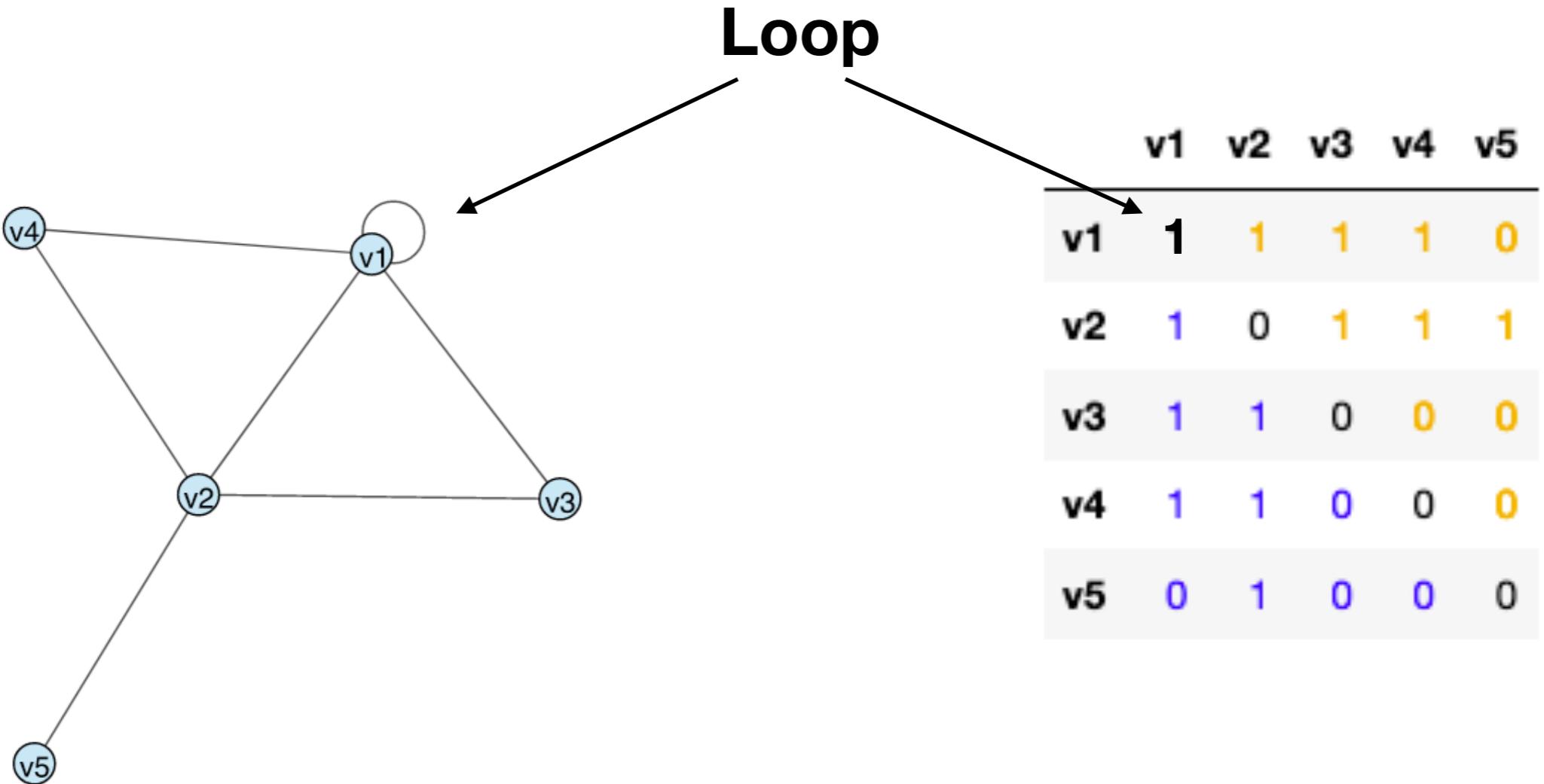
Diagonal

Adjacency matrix (directed graphs)

		Target				
		v1	v2	v3	v4	v5
Source		v1	v2	v3	v4	v5
v1	0	1	1	1	0	
v2	0	0	1	1	1	
v3	0	0	0	0	0	
v4	0	0	0	0	0	
v5	0	0	0	0	0	



Graphs may contain self-loops

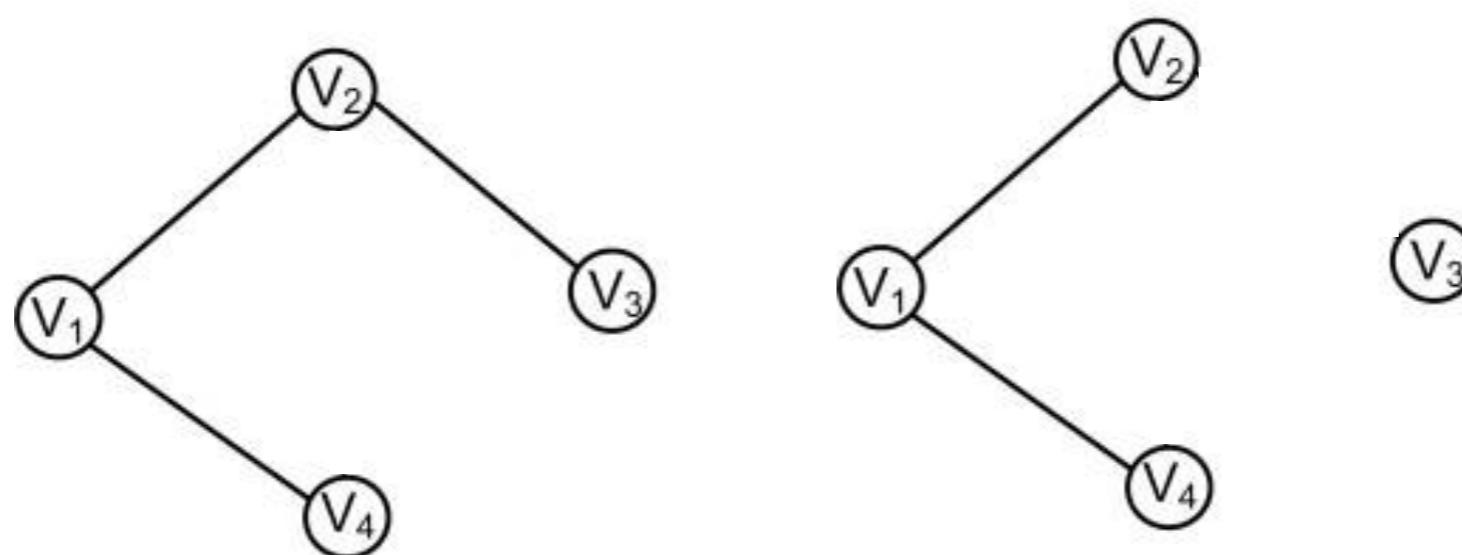


Examples of **self-loops** are auto-regulatory mechanisms in Transcription Factor regulatory networks

Connected vs disconnected networks

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

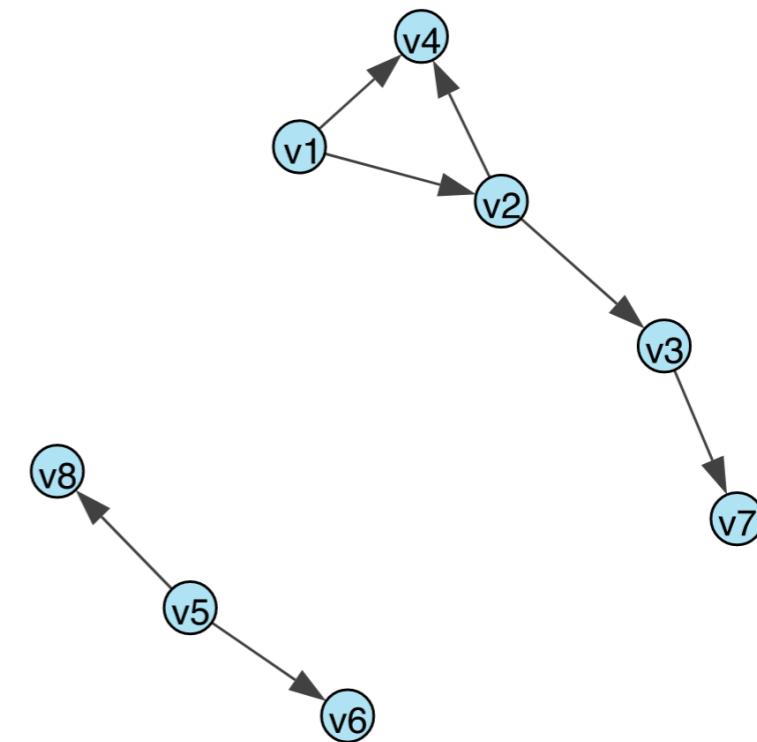
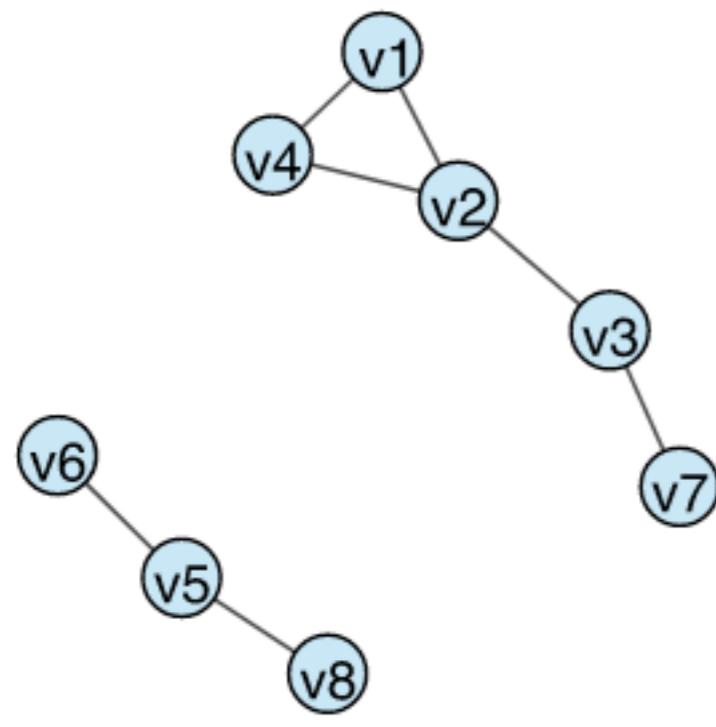
Disconnected network: some of the nodes are unreachable



Connected components

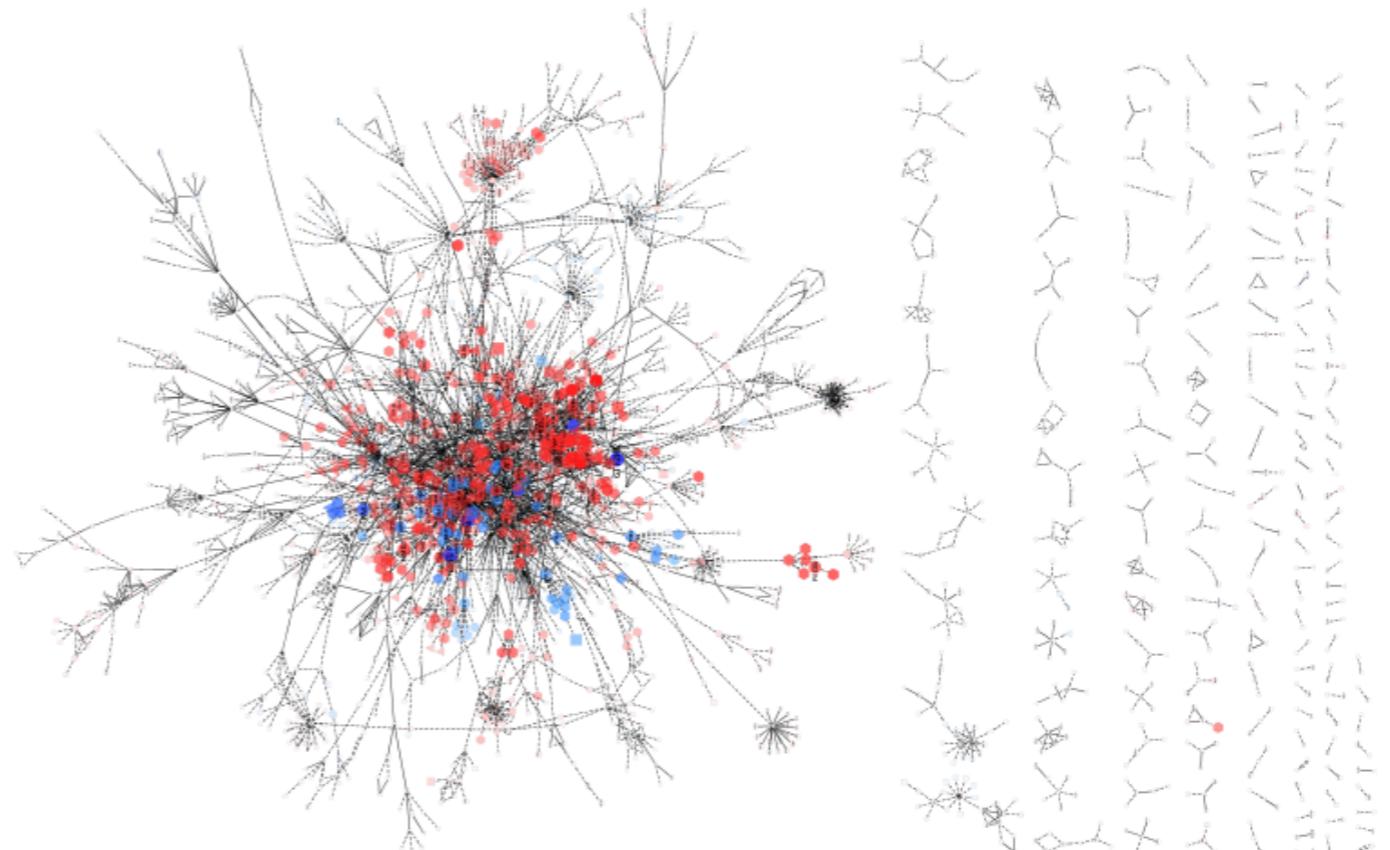
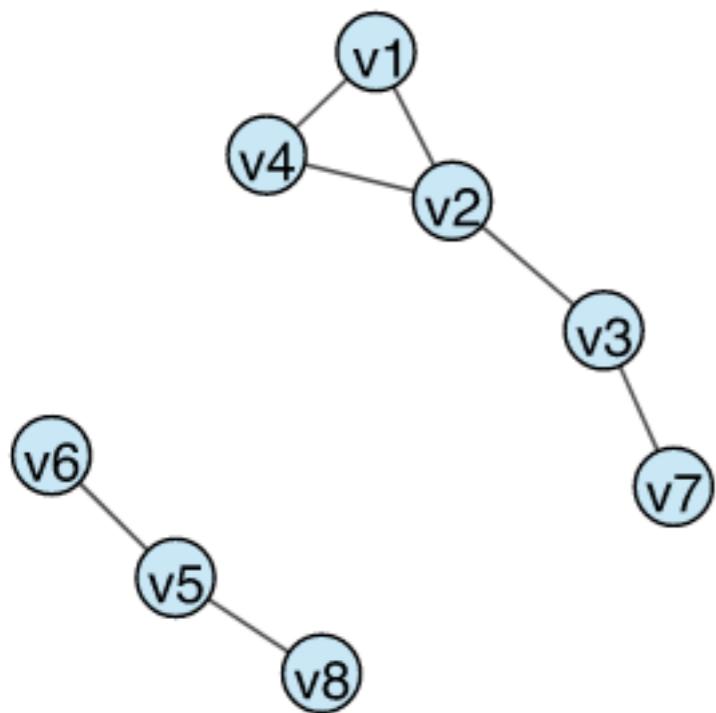
Connected components are those where all nodes of each subgraph are connected.

Weak vs strong components



Connected components

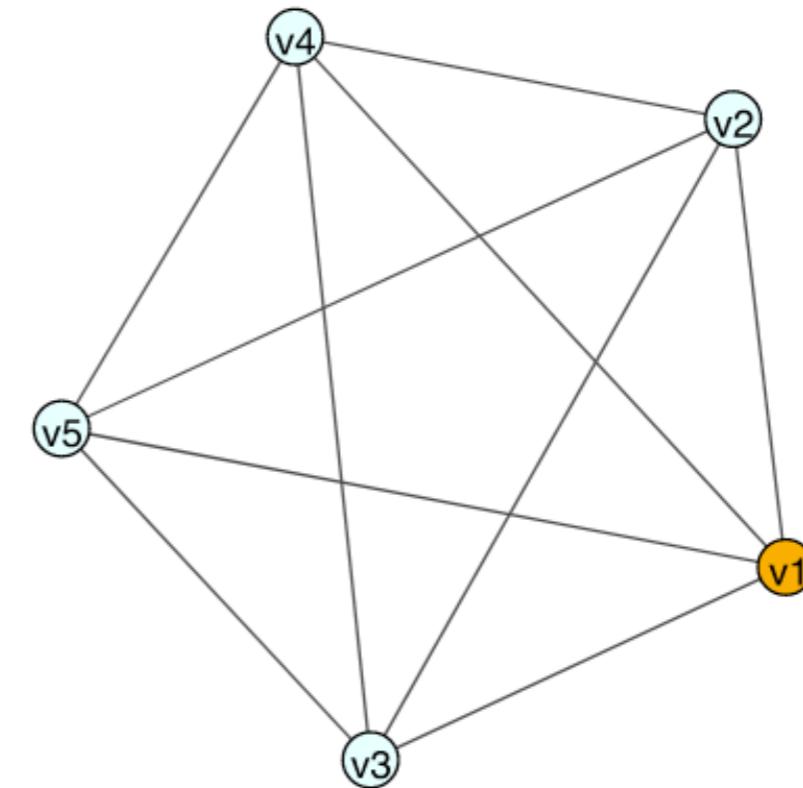
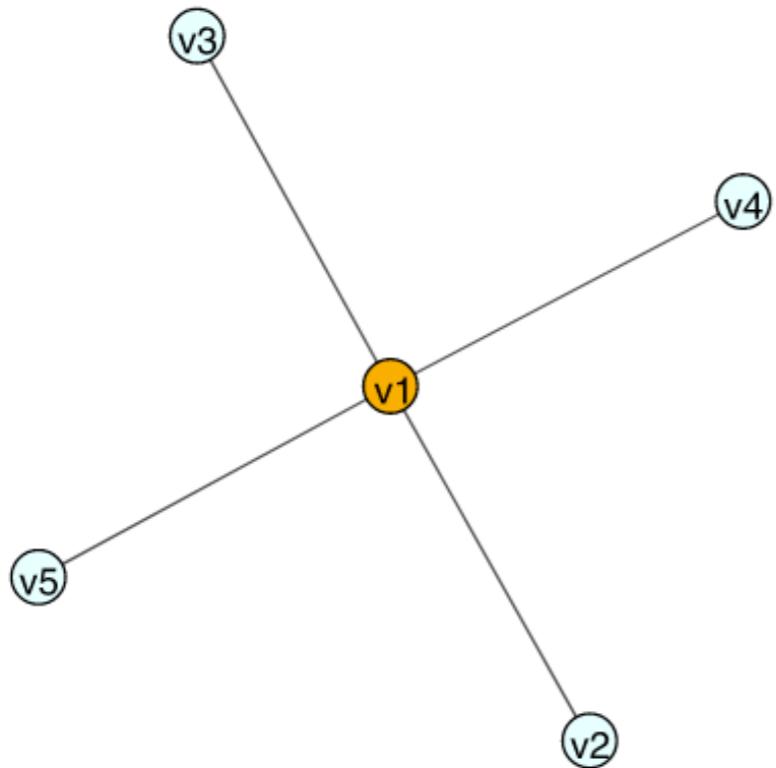
In biological networks, often the most insightful properties come from the **largest connected component**



Stars vs cliques

A star forms a **complete bipartite subgraph**

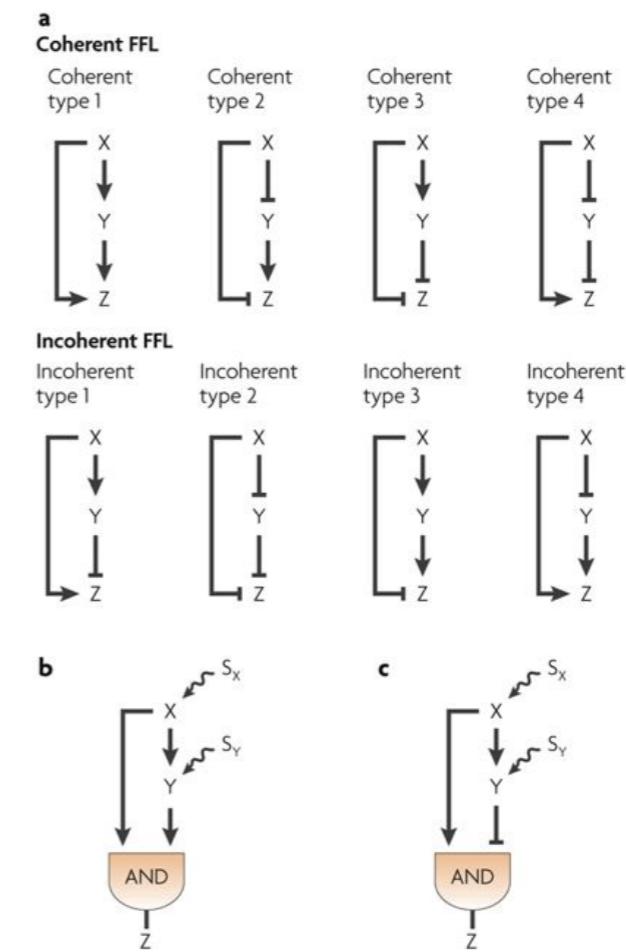
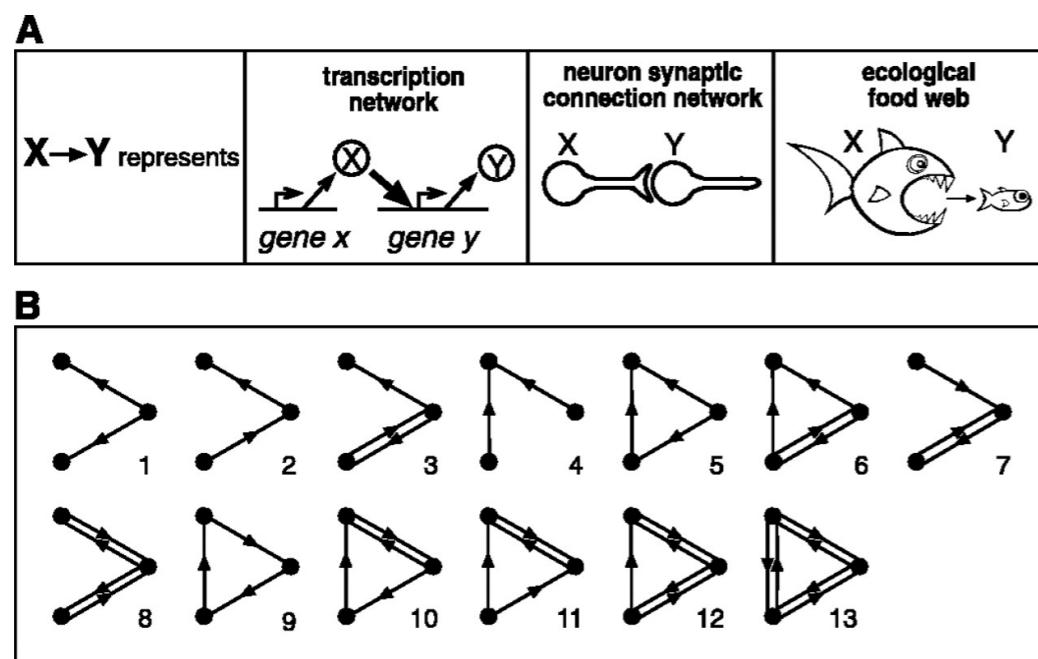
A **clique** is a subgraph where all nodes are adjacent



Motifs

Subgraphs are characterised by different motifs

Exploring prevalent motifs may allow us to understand the evolutionary advantage of a given architecture



Milo 2002
Alon 2007

Additional reading

- [Network Science](#) - A fascinating textbook on graph theory and network analysis.
- [Communication dynamics in complex brain networks](#) - Interesting discussion about whether and how network topology may be applied to study the brain networks.
- [A Systematic Evaluation of Methods for Tailoring Genome-Scale Metabolic Models](#) - General 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.