

Biological networks (BIO 390, 09.11.2021)



University of
Zurich^{UZH}

Session 1 (45 min): Examples of biological networks

Session 2 (45 min): Properties of networks



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<https://github.com/dasmeh>



@PouriaDasmeh

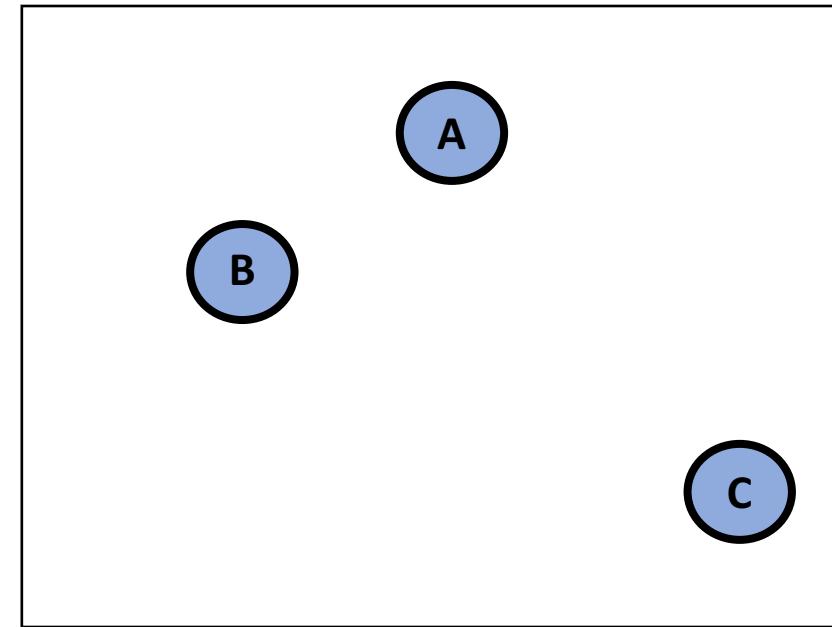
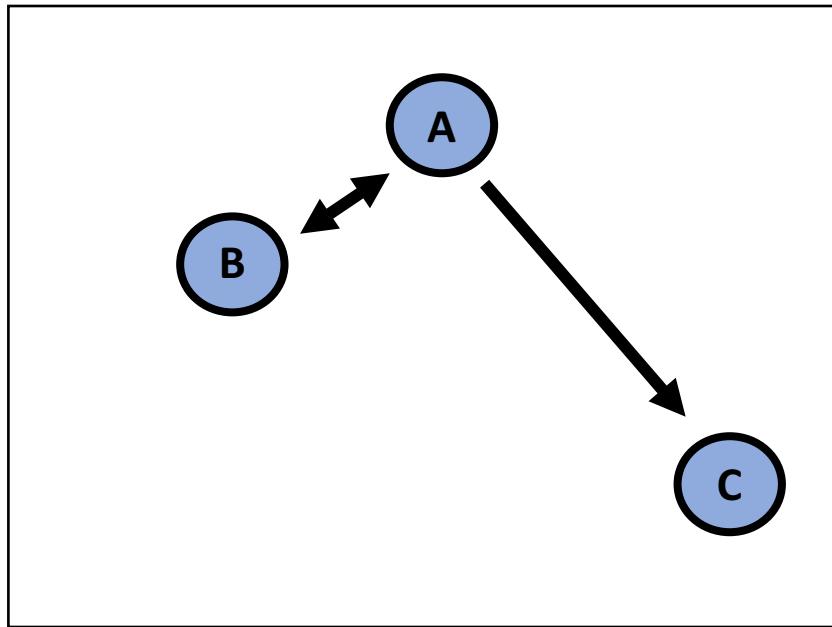
Pouria.dasmeh@uzh.ch

Session 1

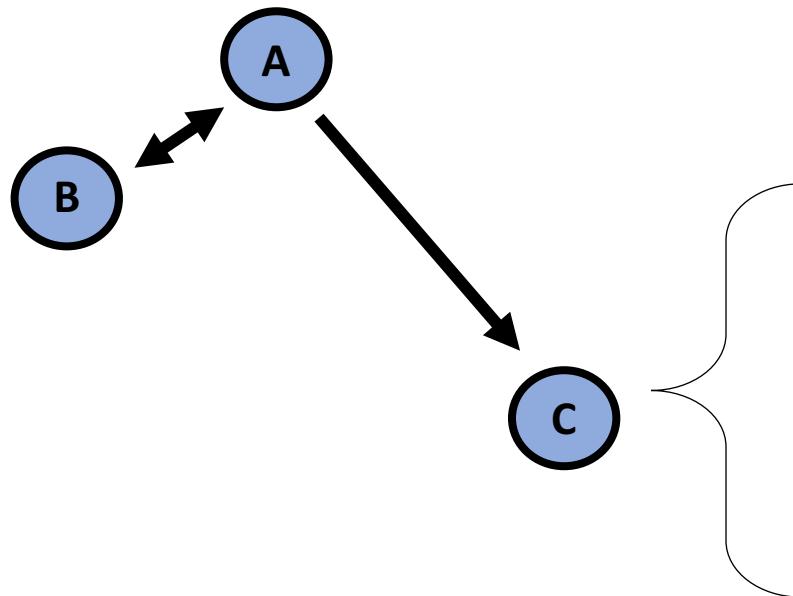
Examples of biological networks

What is a network?

Two or more components that can “interact” with each other



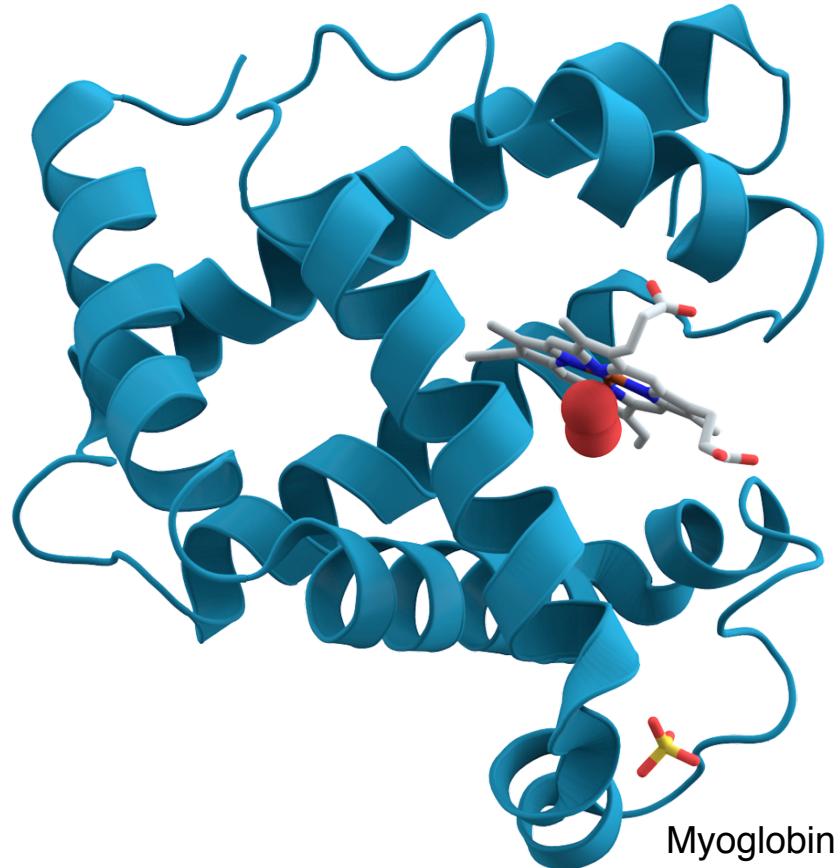
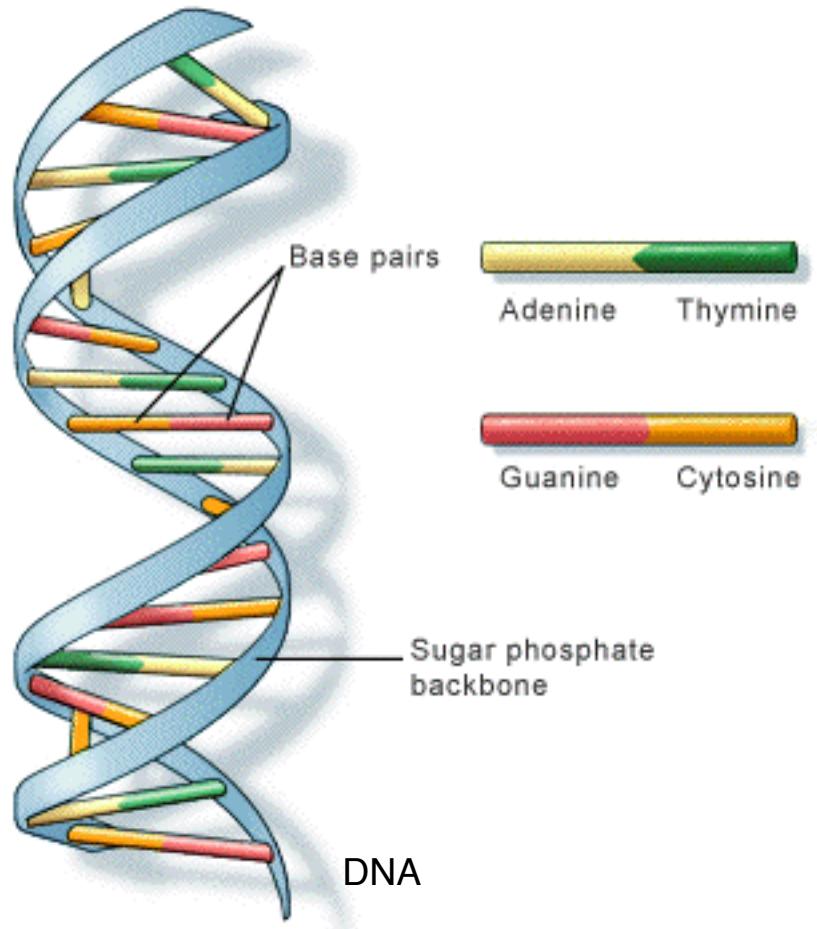
Biological networks



Networks that apply to biological systems:

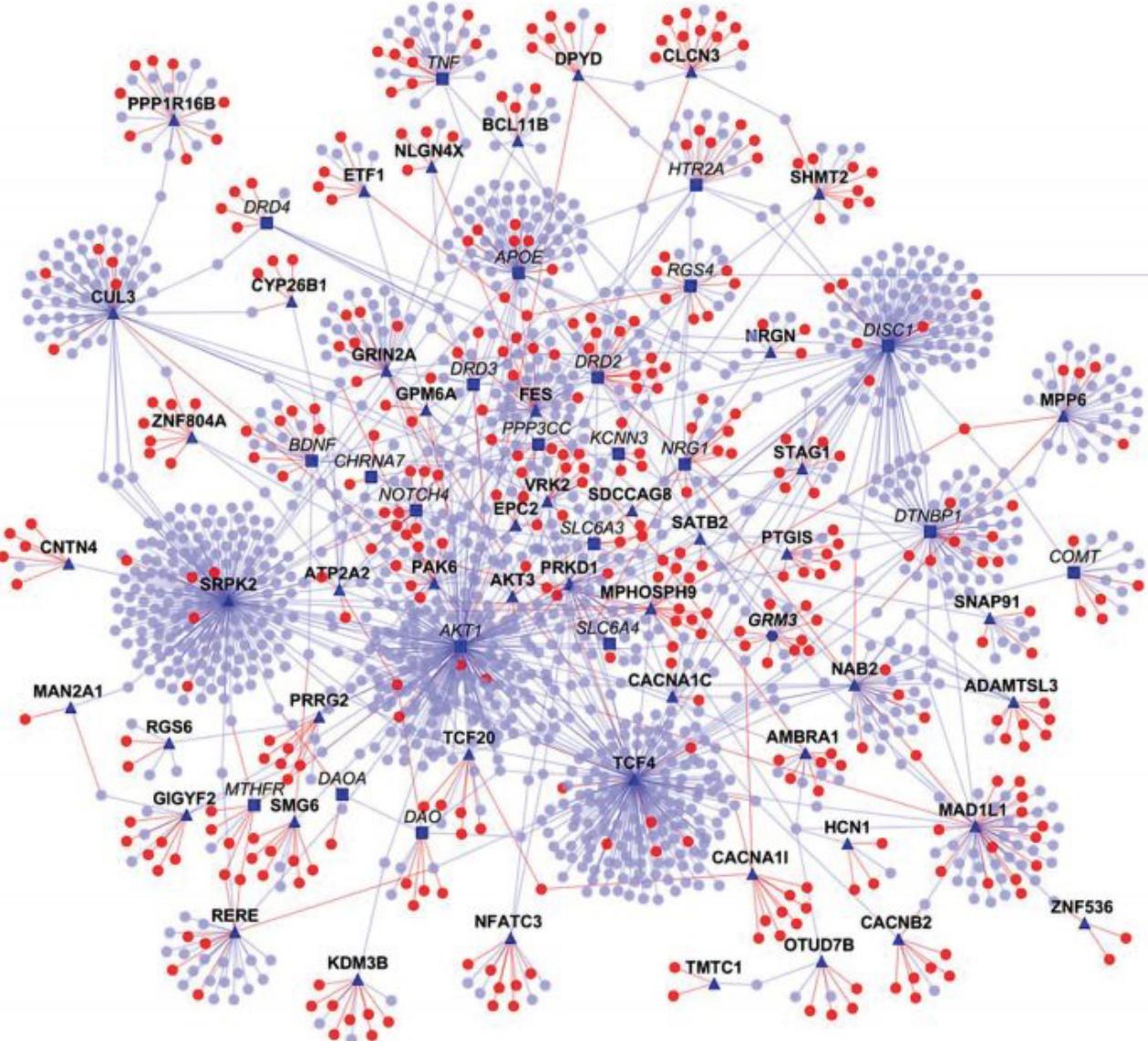
- 1) DNA
- 2) Protein
- 3) Cell
- 4) Organisms
- 5)

DNA and Proteins

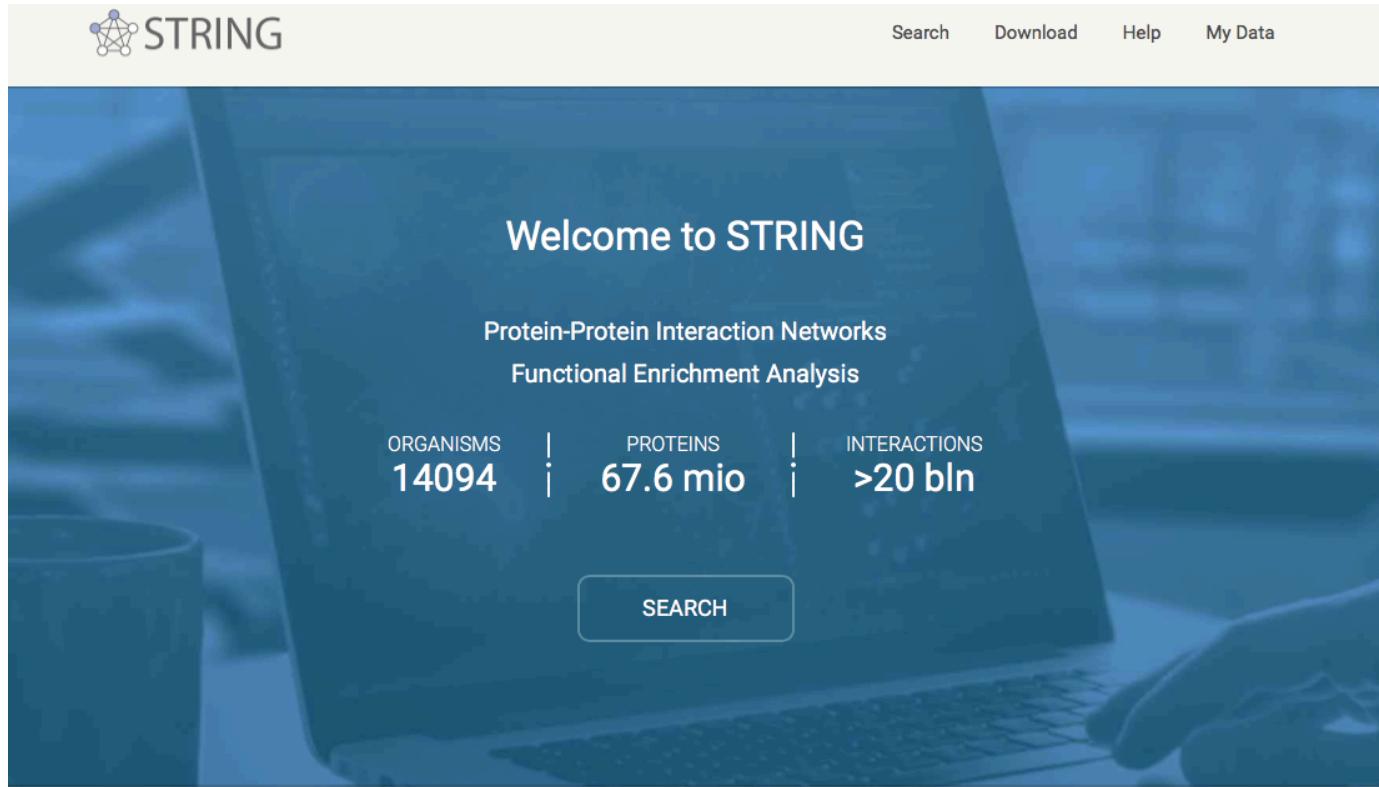


Chemical structures (networks)

Protein-protein interaction network



Protein-protein interaction network



The screenshot shows the STRING homepage. At the top, there is a navigation bar with links for "Search", "Download", "Help", and "My Data". The main header "STRING" is accompanied by a logo of a molecular structure. Below the header, a large banner features the text "Welcome to STRING" and "Protein-Protein Interaction Networks Functional Enrichment Analysis". It also displays statistics: "ORGANISMS 14094", "PROTEINS 67.6 mio", and "INTERACTIONS >20 bln". A prominent "SEARCH" button is located below these stats. The background of the banner is a blue-toned image of a computer keyboard and screen. At the bottom of the page, there is a footer with copyright information ("© STRING CONSORTIUM 2021") and links to various partners: SIB - Swiss Institute of Bioinformatics, CPR - Novo Nordisk Foundation Center Protein Research, and EMBL - European Molecular Biology Laboratory. The footer also includes links for "ABOUT", "INFO", "ACCESS", and "CREDITS", each leading to sub-sections like "Content", "Scores", "Versions", "Funding", etc.

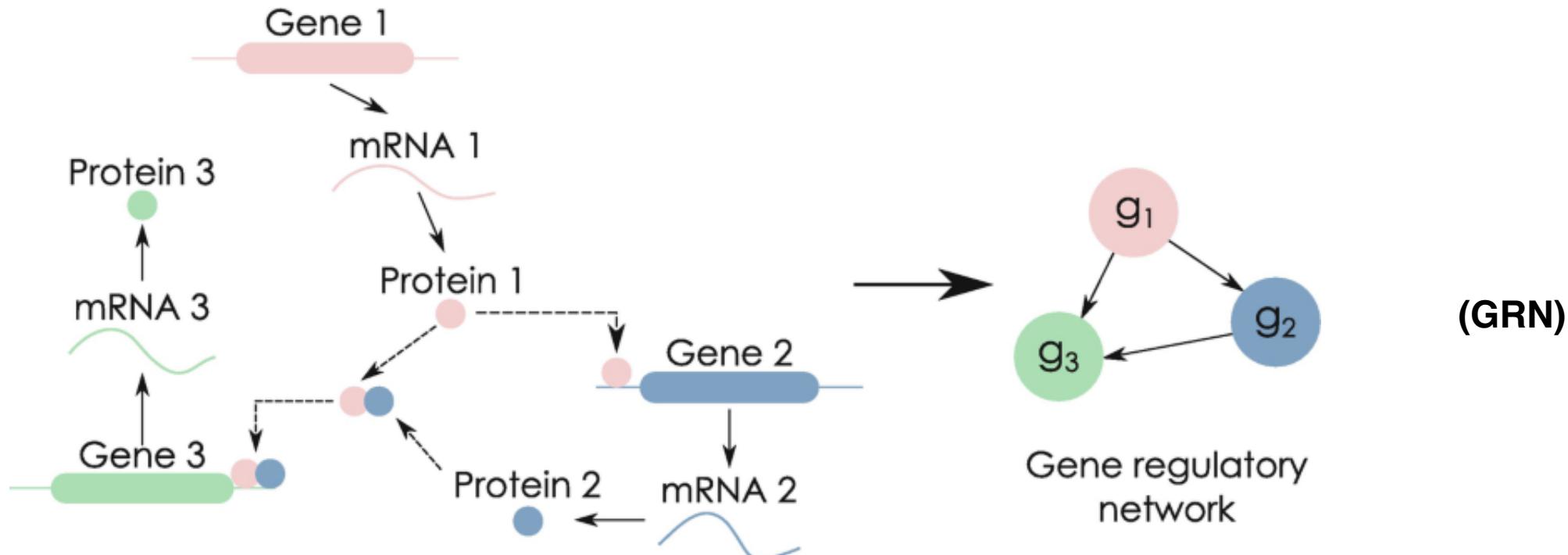
Compare the interaction networks of two proteins in human:

- Myoglobin (Mb)
- DNA-directed RNA polymerase II (RPB1)

Why do we have different tissues
and cell types if we have only one DNA
molecule?



Gene regulatory networks (DNA-protein interaction networks)

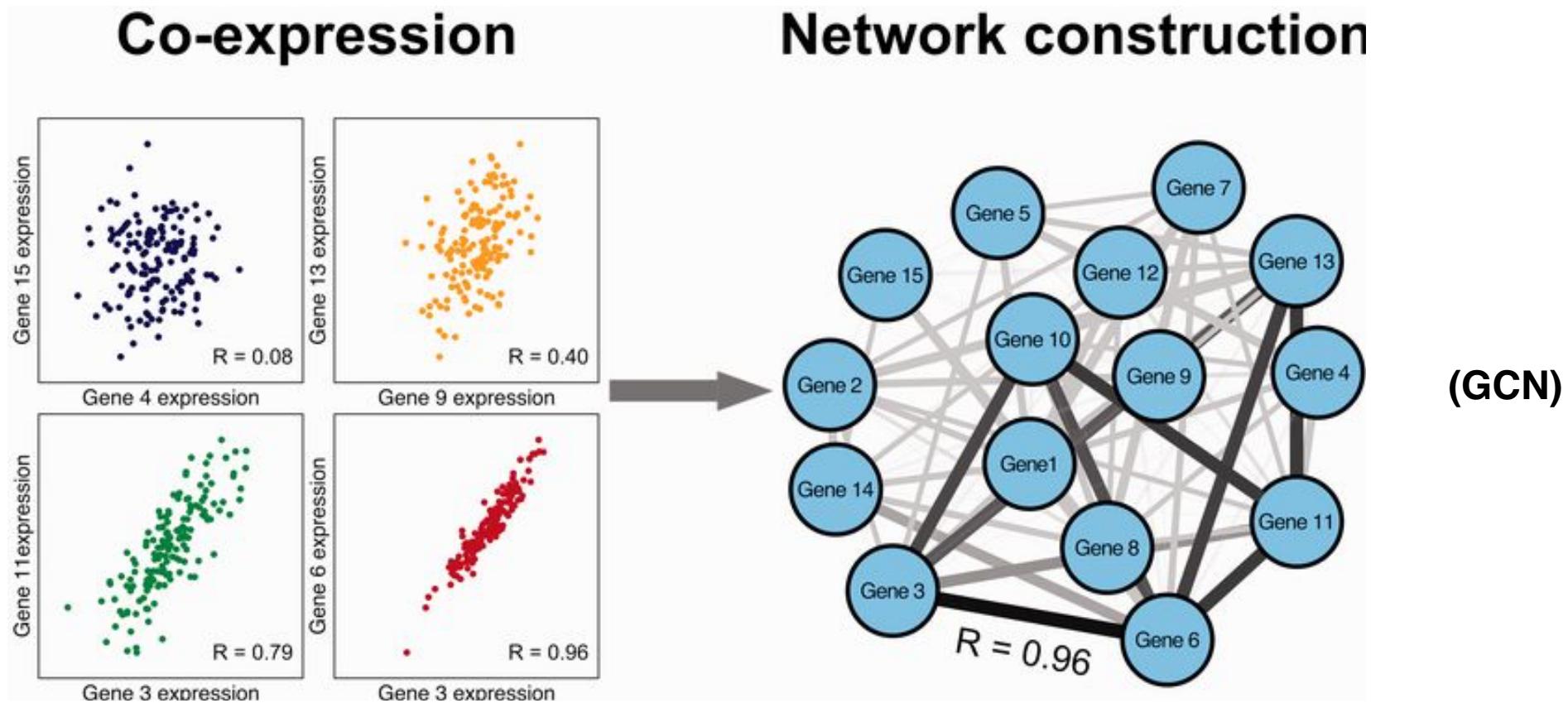


A set of molecular **regulators** that interact with each other to govern the **gene expression** levels of mRNA and proteins >> the **function** of the **cell**.

Responses to stress often involve co-expression of many genes. How do cells achieve this coordinated response?



Gene co-expression network



A gene co-expression network can be built by finding pairs of genes which show a similar expression pattern across samples,

Gene co-expression network

RNA-seq
or
Microarray
experiments



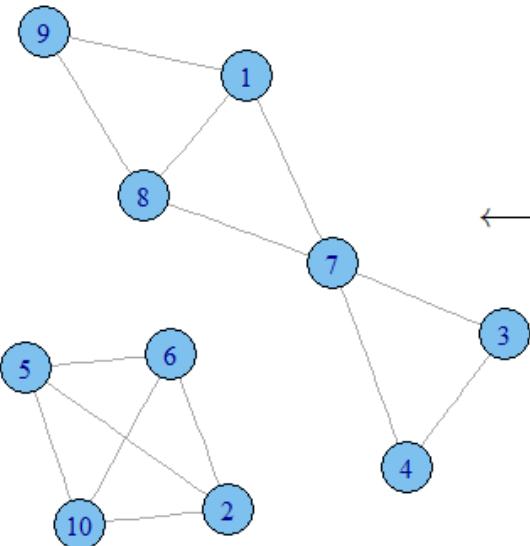
	S_1	S_2	S_3
G_1	43.26	40.89	5.05
G_2	166.6	41.87	136.65
G_3	12.53	39.55	42.09
G_4	28.77	191.92	236.56
G_5	114.7	79.7	99.76
G_6	119.1	80.57	114.59
G_7	118.9	156.69	186.95
G_8	3.76	2.48	136.78
G_9	32.73	11.99	118.8
G_{10}	17.46	56.11	21.41

Gene expression values

$|r(G_i, G_j)|$
 Pearson
 correlation

	G_1	G_2	G_3	G_4	G_5	G_6	G_7	G_8	G_9	G_{10}
G_1	1.00	0.23	0.61	0.71	0.03	0.35	0.86	1.00	0.97	0.37
G_2	0.23	1.00	0.63	0.52	0.98	0.99	0.29	0.30	0.46	0.99
G_3	0.61	0.63	1.00	0.99	0.77	0.53	0.93	0.56	0.41	0.51
G_4	0.71	0.52	0.99	1.00	0.69	0.41	0.97	0.66	0.52	0.40
G_5	0.03	0.98	0.77	0.69	1.00	0.95	0.48	0.09	0.27	0.94
G_6	0.35	0.99	0.53	0.41	0.95	1.00	0.17	0.41	0.57	1.00
G_7	0.86	0.29	0.93	0.97	0.48	0.17	1.00	0.83	0.72	0.16
G_8	1.00	0.30	0.56	0.66	0.09	0.41	0.83	1.00	0.98	0.42
G_9	0.97	0.46	0.41	0.52	0.27	0.57	0.72	0.98	1.00	0.58
G_{10}	0.37	0.99	0.51	0.40	0.94	1.00	0.16	0.42	0.58	1.00

Similarity (Co-expression) score



	G_1	G_2	G_3	G_4	G_5	G_6	G_7	G_8	G_9	G_{10}
G_1	0	0	0	0	0	0	1	1	1	0
G_2	0	0	0	0	1	1	0	0	0	1
G_3	0	0	0	1	0	0	1	0	0	0
G_4	0	0	1	0	0	0	1	0	0	0
G_5	0	1	0	0	0	1	0	0	0	1
G_6	0	1	0	0	1	0	0	0	0	1
G_7	1	0	1	1	0	0	0	1	0	0
G_8	1	0	0	0	0	0	1	0	1	0
G_9	1	0	0	0	0	0	0	1	0	0
G_{10}	0	1	0	0	1	1	0	0	0	0

$|r(G_i, G_j)| \geq 0.8$
 Significance threshold

Network adjacency matrix

Metabolic networks

A metabolic network is a set of chemical reactions that produces

energy

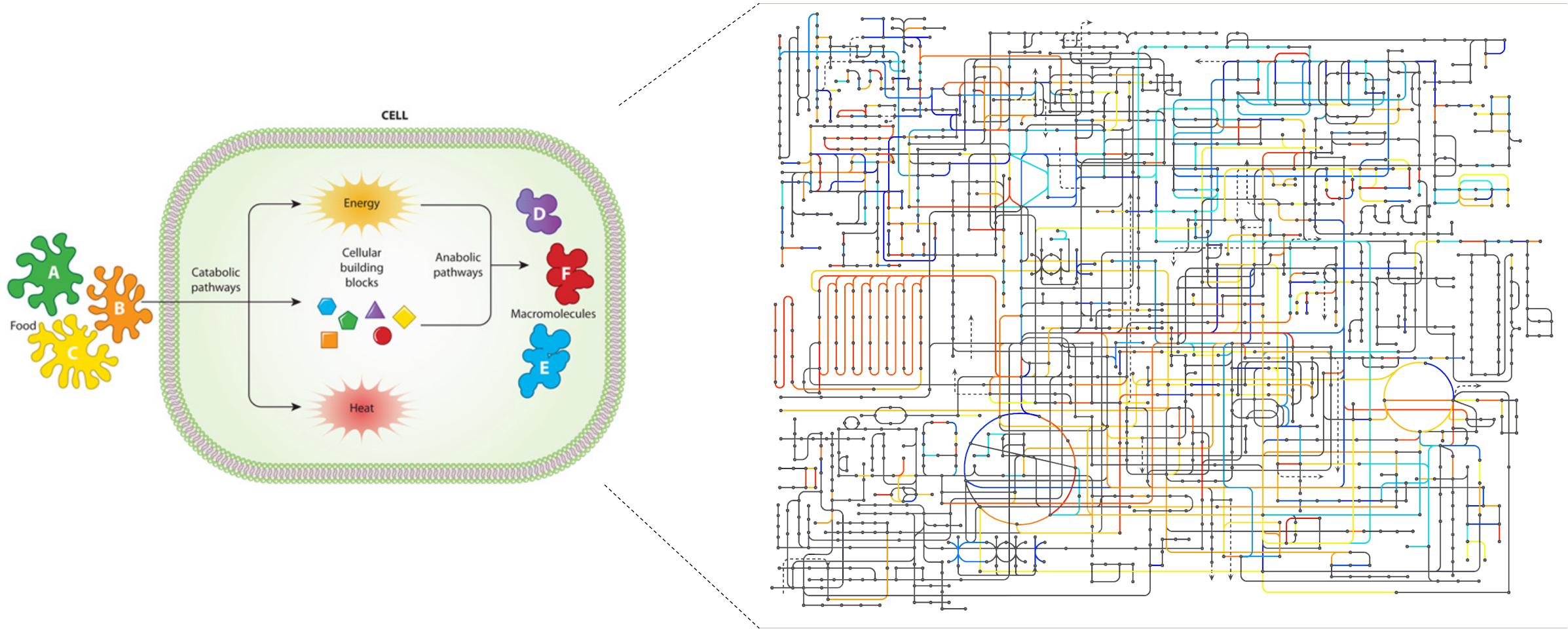
(for maintenance of cell functions and for biosyntheses)

molecular building blocks for biosyntheses

These reactions are catalyzed by enzymes that are encoded by genes.

In free-living heterotrophic organisms, several hundred such enzymatic reactions are necessary to fulfill these functions.

Metabolic networks



Metabolic networks



KEGG PATHWAY Database
Wiring diagrams of molecular interactions, reactions and relations

KEGG2 PATHWAY BRITE MODULE KO GENES COMPOUND DISEASE DRUG

Select prefix Enter keywords Go Help

[New pathway maps | Update history]

Pathway Maps

KEGG PATHWAY is a collection of manually drawn pathway maps representing our knowledge of the molecular interaction, reaction and relation networks for:

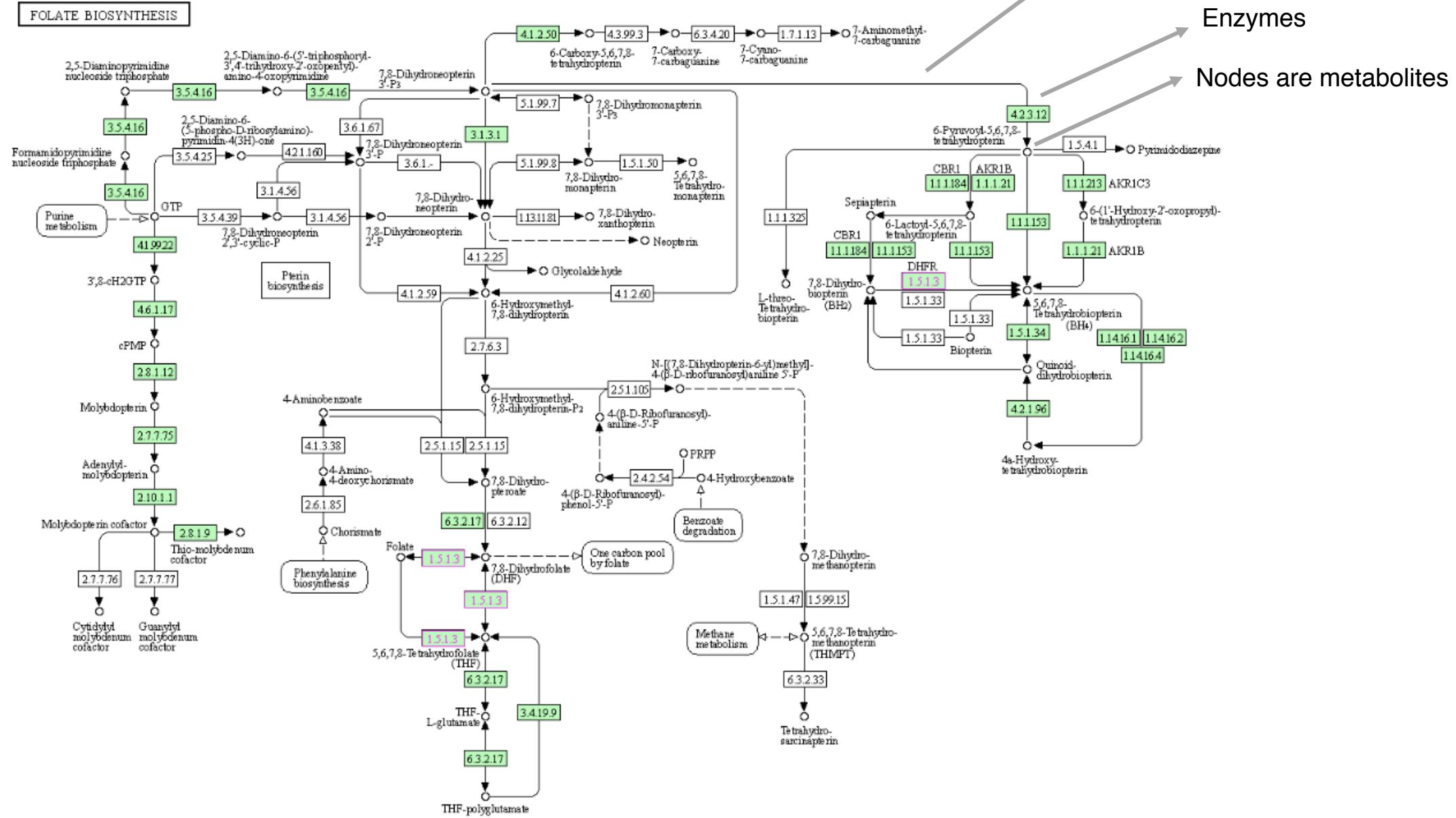
- 1. Metabolism**
Global/overview Carbohydrate Energy Lipid Nucleotide Amino acid Other amino Glycan Cofactor/vitamin Terpenoid/PK Other secondary metabolite Xenobiotics Chemical structure
- 2. Genetic Information Processing**
- 3. Environmental Information Processing**
- 4. Cellular Processes**
- 5. Organismal Systems**
- 6. Human Diseases**
- 7. Drug Development**

KEGG PATHWAY is the reference database for pathway mapping in **KEGG Mapper**.

Find the folate biosynthetic pathway
in Human and *E.coli*

Database 2: KEGG

Folate pathway

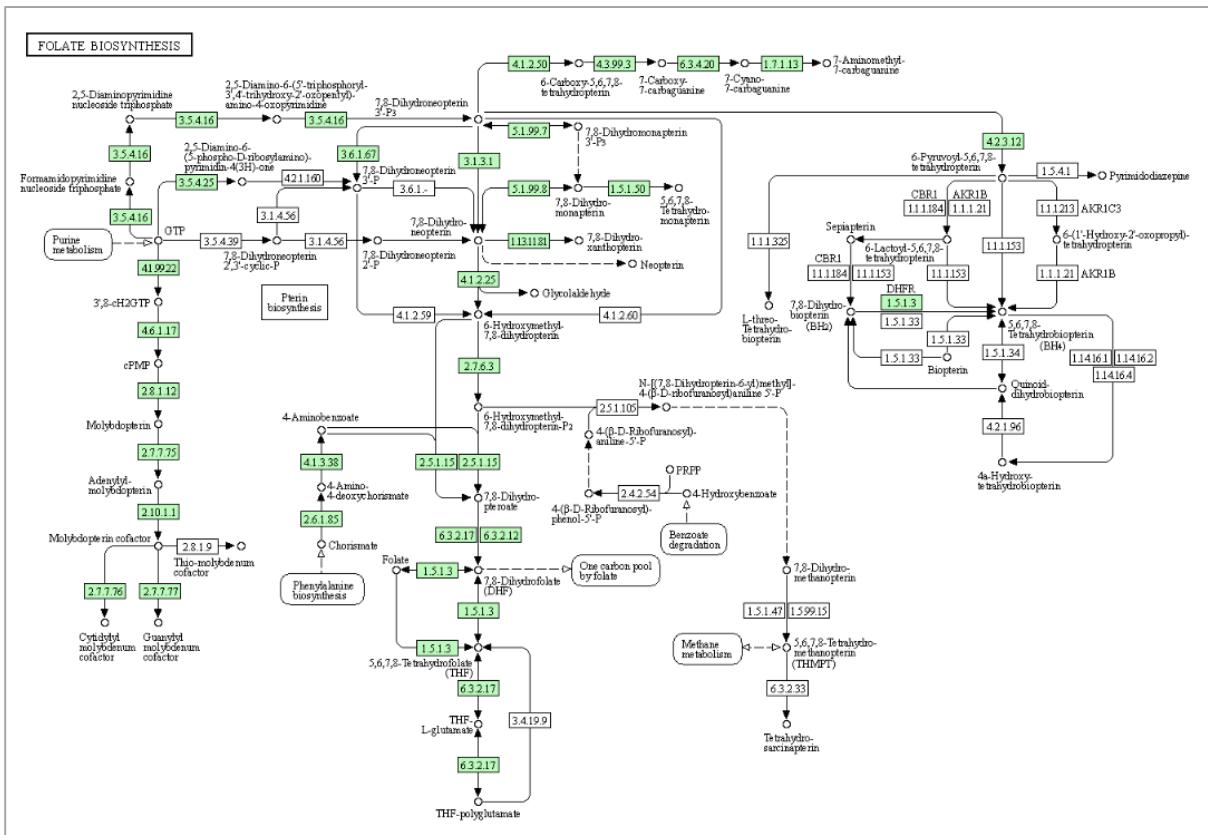


Arrows are reactions

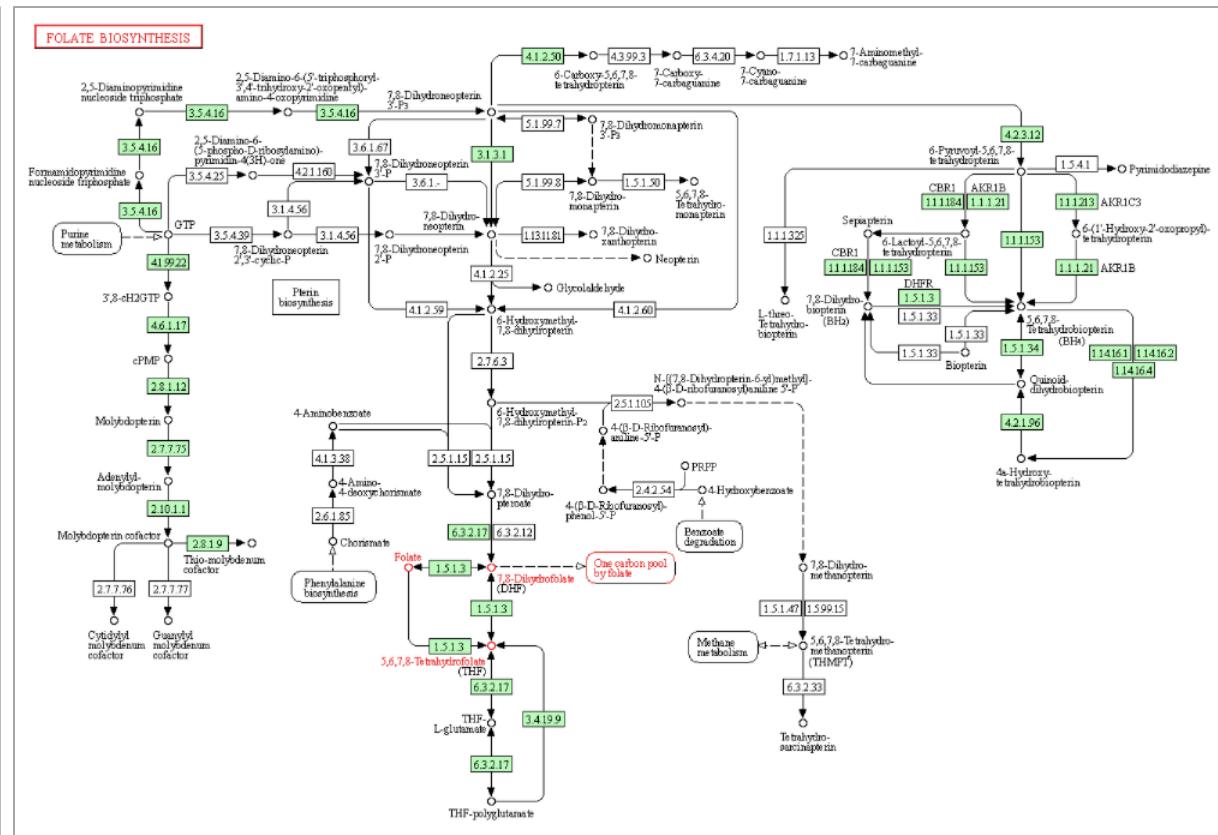
Enzymes

Nodes are metabolites

Folate pathway in E.coli and Human

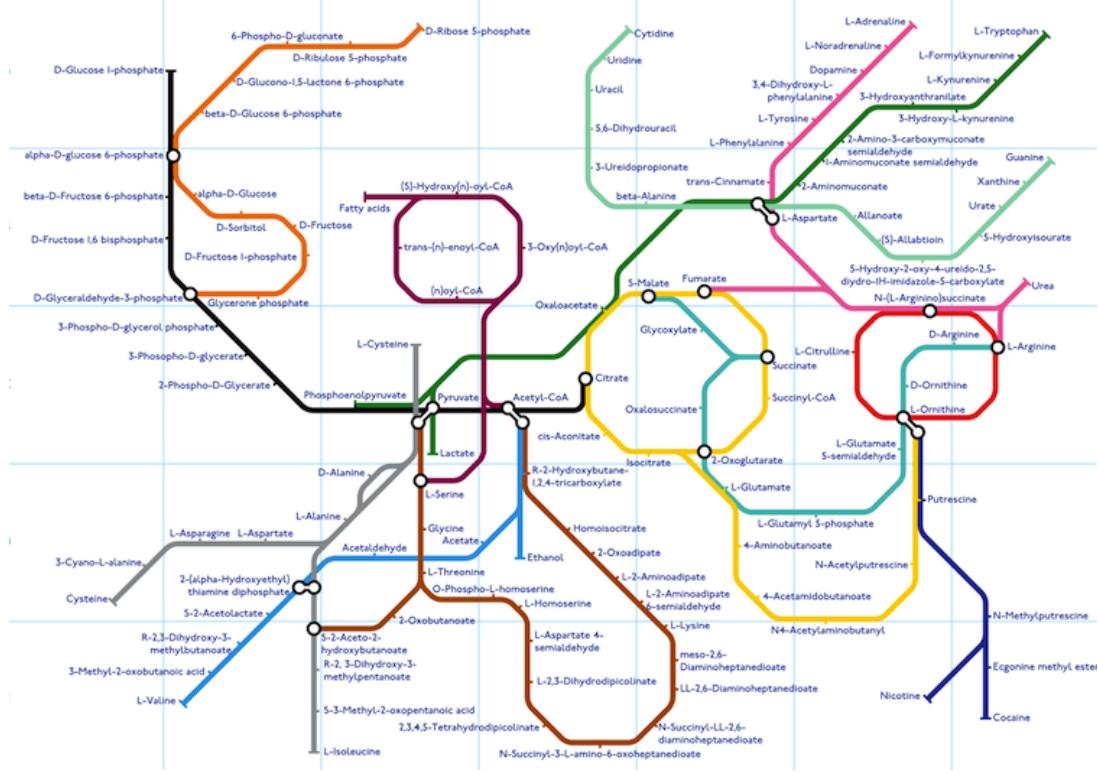


E.coli



Human

Biological and other complex networks may have similar structures



Metabolic map

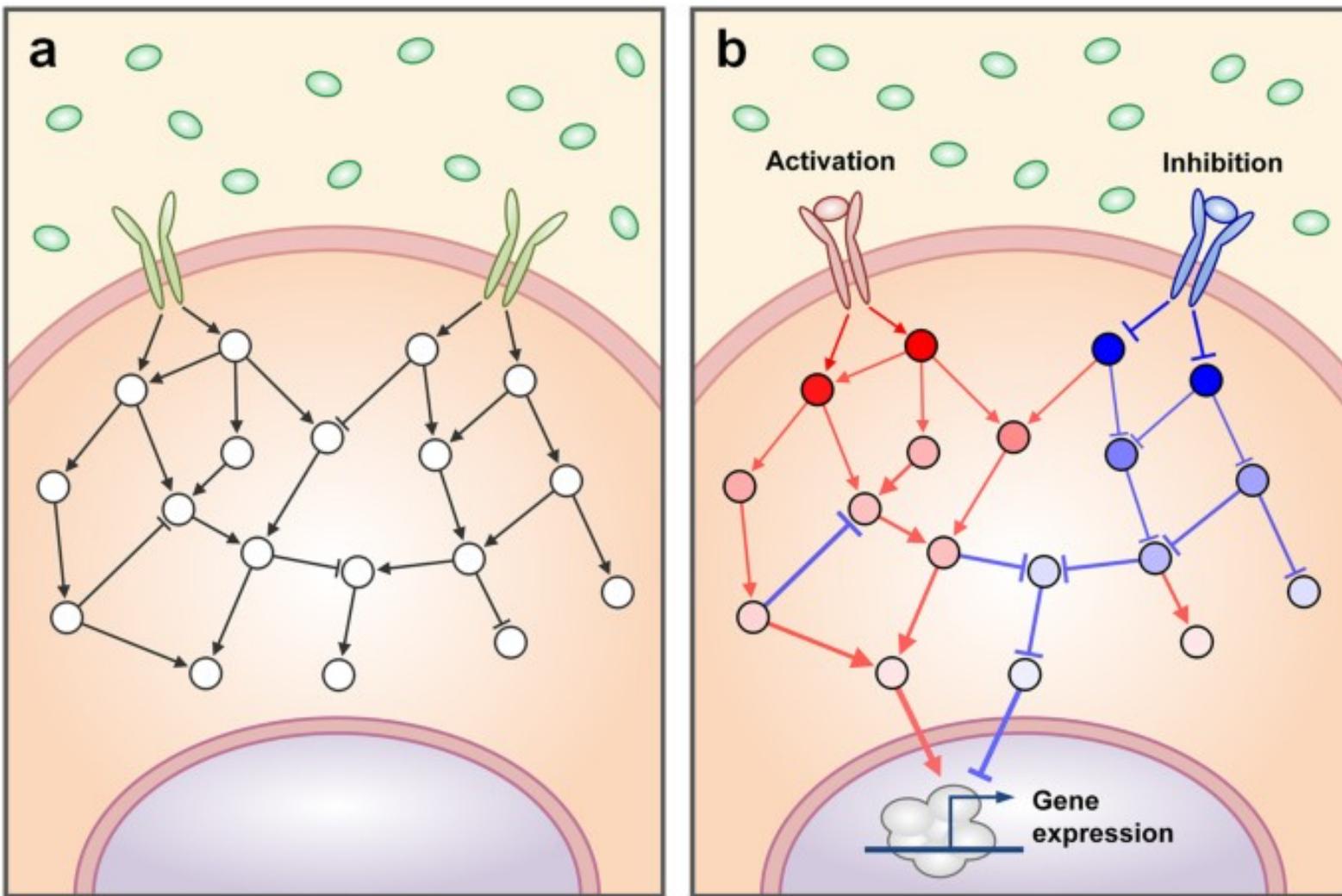


New York subway map

(Obviously!) cells should communicate.
How do they achieve this?



Signaling networks

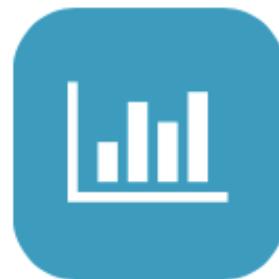


Find Reactions, Proteins and Pathways

e.g. O95631, NTN1, signaling by EGFR, glucose

Go!**Pathway Browser**

Visualize and interact with Reactome biological pathways

**Analysis Tools**

Merges pathway identifier mapping, over-representation, and expression analysis

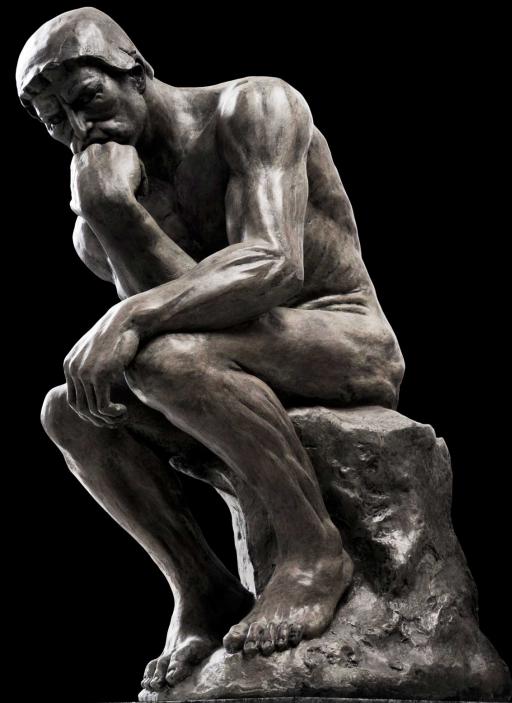
**ReactomeFIViz**

Designed to find pathways and network patterns related to cancer and other types of diseases

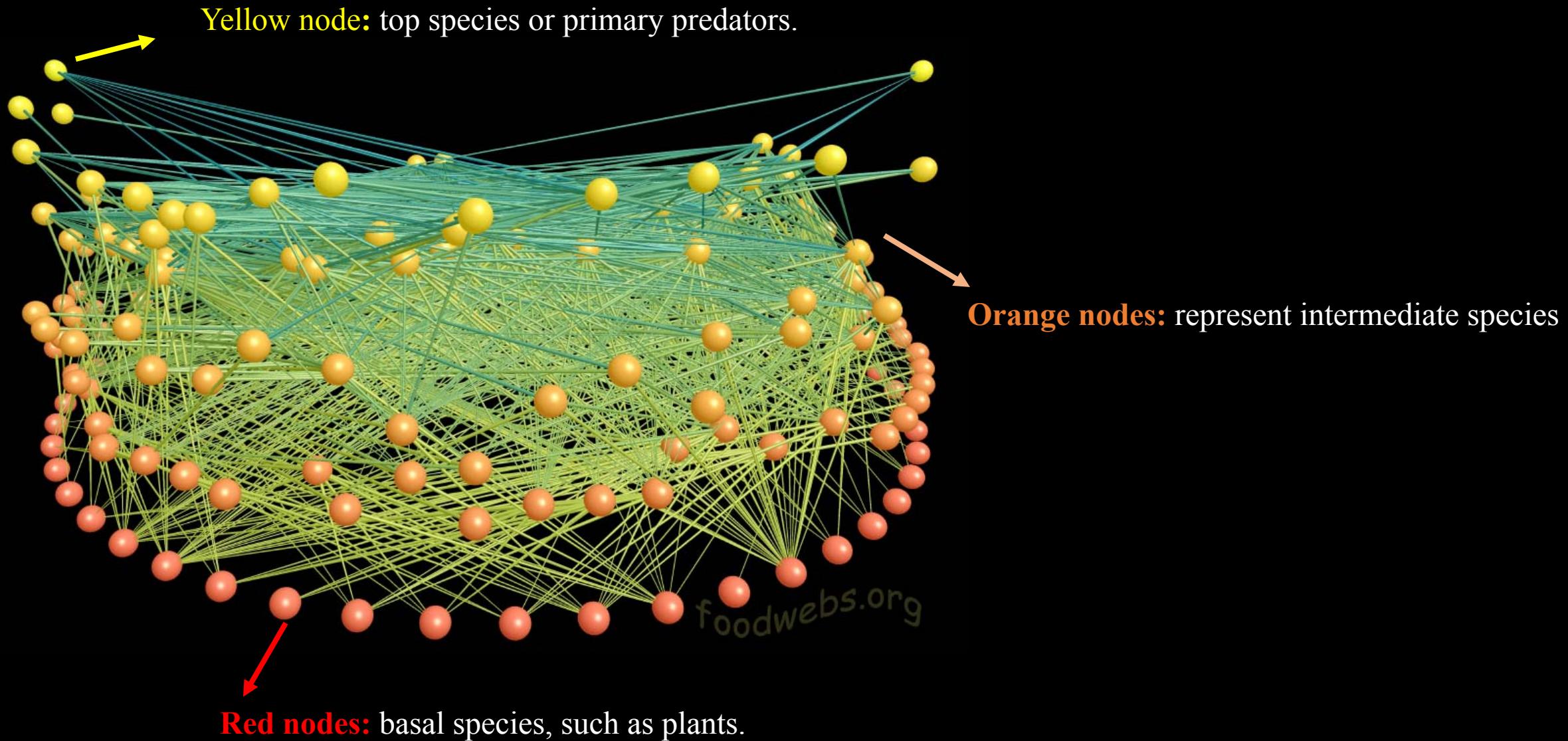
**Documentation**

Information to browse the database and use its principal tools for data analysis

Any higher-level network to talk about?



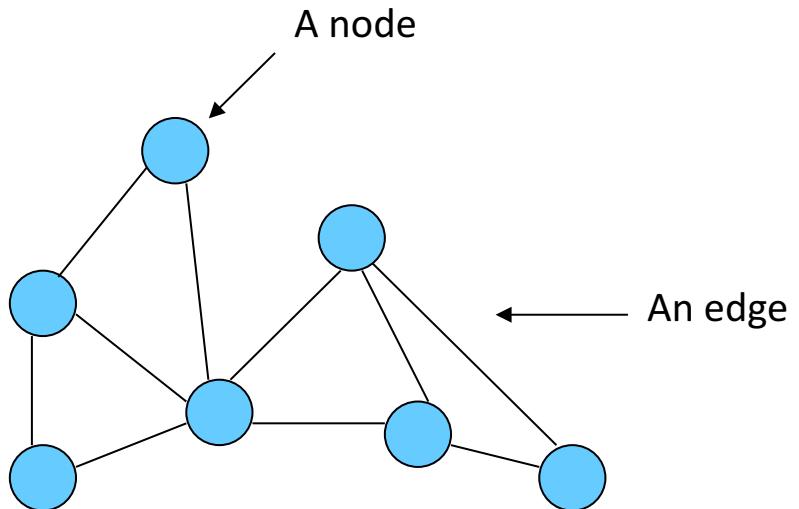
Food web



Session 2

Properties of networks

Graphs

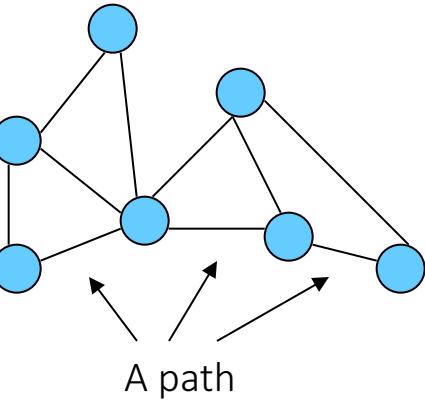


A graph $G=(V,E)$ comprises
a set V of nodes (vertices)
a set E of edges

$$V = \{V_1, \dots, V_n\}$$
$$E = \{(V_i, V_j), \dots, (V_k, V_l)\}$$

Protein interaction networks are undirected graphs
(Individual node pairs in E are unordered.)

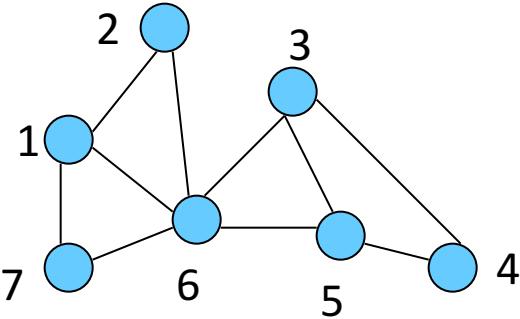
Graphs



A path is a sequence of alternating nodes and edges in which no node is visited more than once

A geodesic is the shortest path between two nodes.

Graphs can be represented by matrices



Adjacency matrix $A=(a_{ij})$

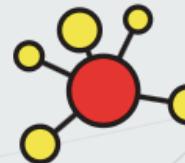
$$\begin{array}{ll} a_{ij}=1 & (V_i, V_j) \in E \\ a_{ij}=0 & \text{otherwise} \end{array}$$

$$A = \begin{pmatrix} 0 & 1 & 0 & 0 & 0 & 1 & 1 \\ 1 & 0 & 0 & 0 & 0 & 1 & 0 \\ 0 & 0 & 0 & 1 & 1 & 1 & 0 \\ 0 & 0 & 1 & 0 & 1 & 0 & 0 \\ 0 & 0 & 1 & 1 & 0 & 1 & 0 \\ 1 & 1 & 1 & 0 & 1 & 0 & 1 \\ 1 & 0 & 0 & 0 & 0 & 1 & 0 \end{pmatrix}$$

Class activity:

Determine the degree distribution of your network of friends ($n=5$)





igraph – The network analysis package

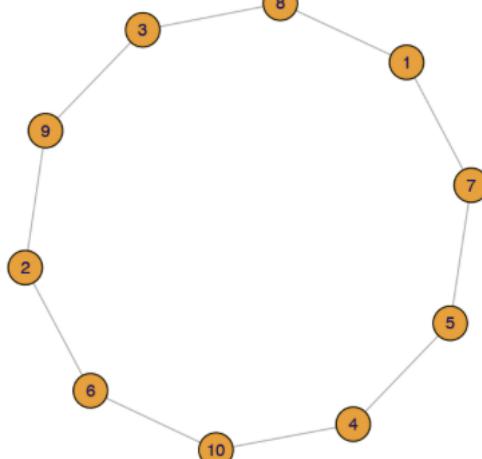
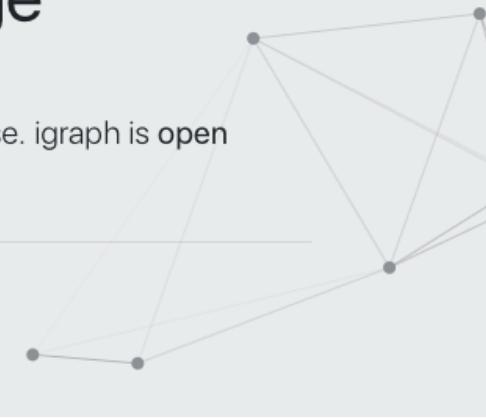
igraph is a collection of network analysis tools with the emphasis on efficiency, portability and ease of use. igraph is open source and free. igraph can be programmed in R, Python, Mathematica and C/C++.

igraph R package

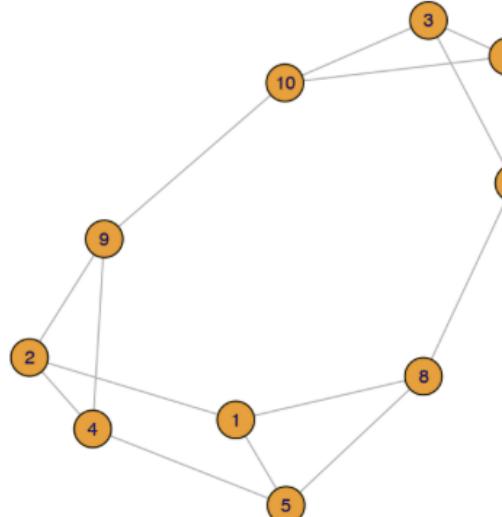
python-igraph

IGraph/M

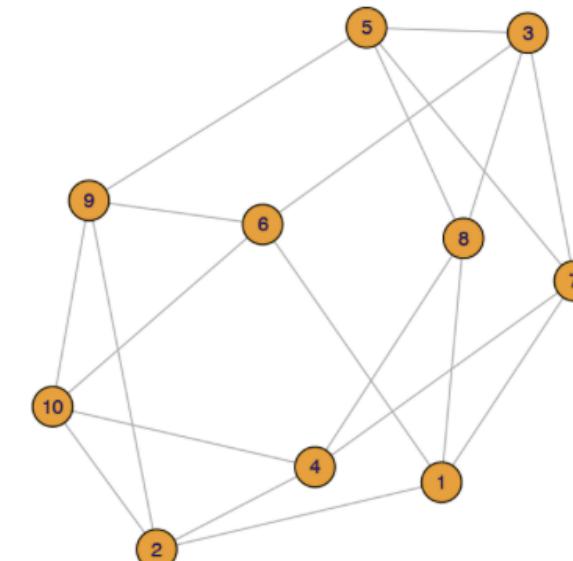
igraph C library



`plot(sample_k_regular(10, 2))`

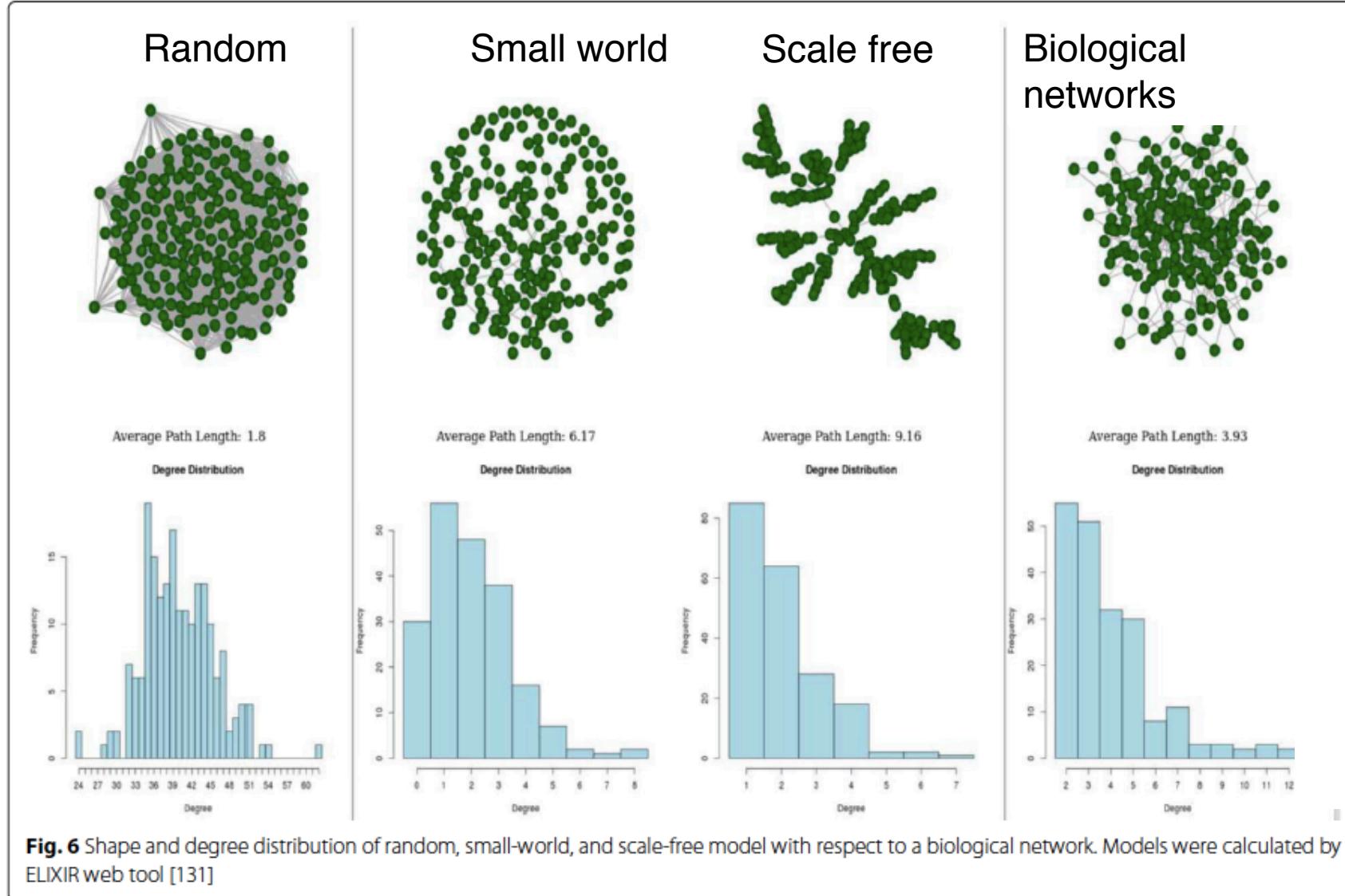


`plot(sample_k_regular(10, 3))`



`plot(sample_k_regular(10, 4))`

Degree distribution can help us determine the type of networks



EURASIP Journal on
Bioinformatics and Systems
Biology 2017.1 (2017): 1-16.

Class activity:

How do you build a random graph?

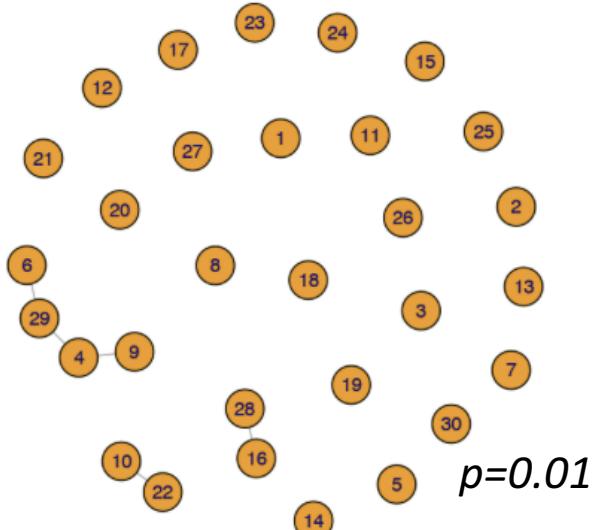


The random graph

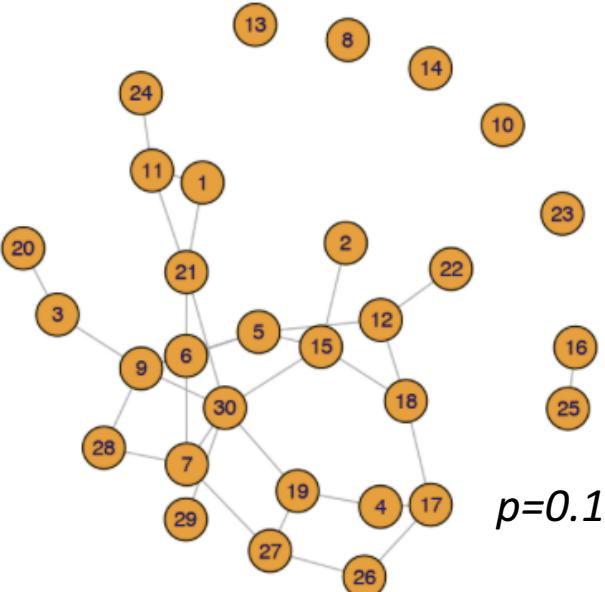
Erdős–Rényi model

$$P(k) = \binom{n-1}{k} p^k (1-p)^{n-1-k}$$

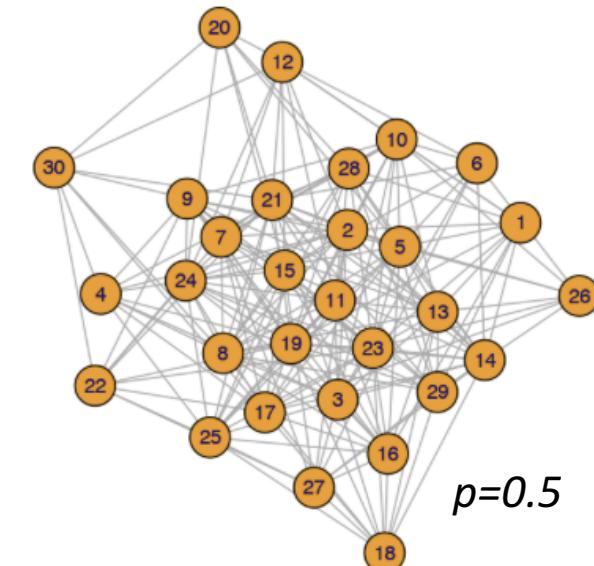
$$P(k) = e^{-(np)} \frac{(np)^k}{k!}$$



```
plot(sample_gnp(30, 0.01))
```

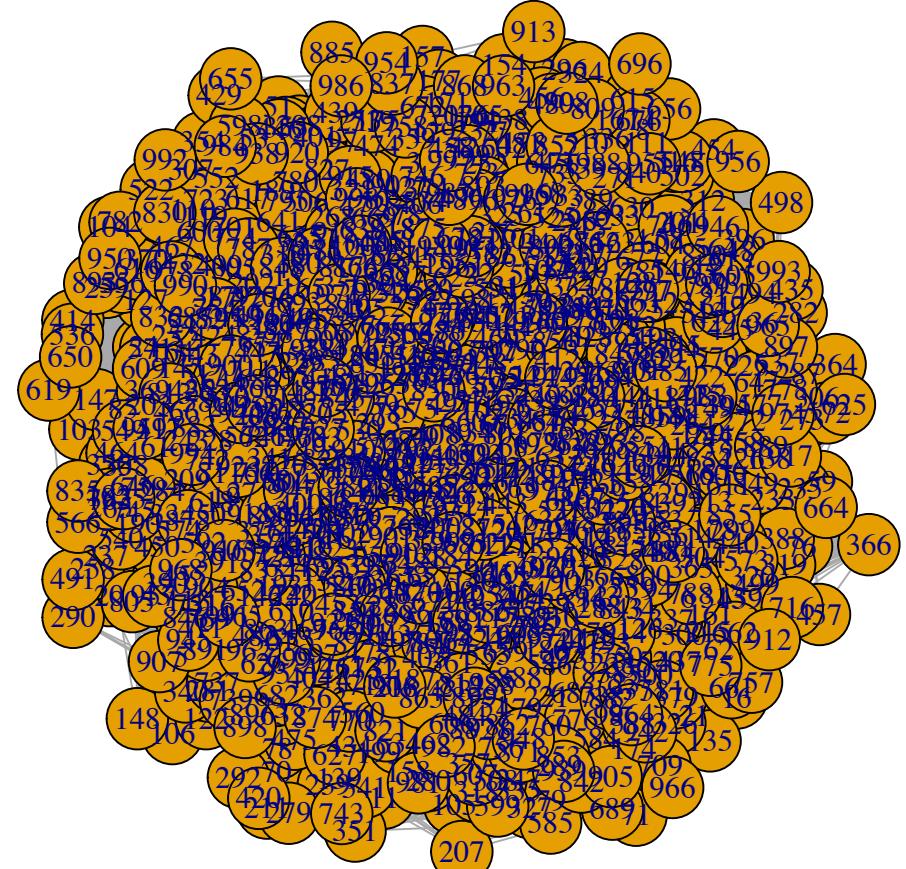
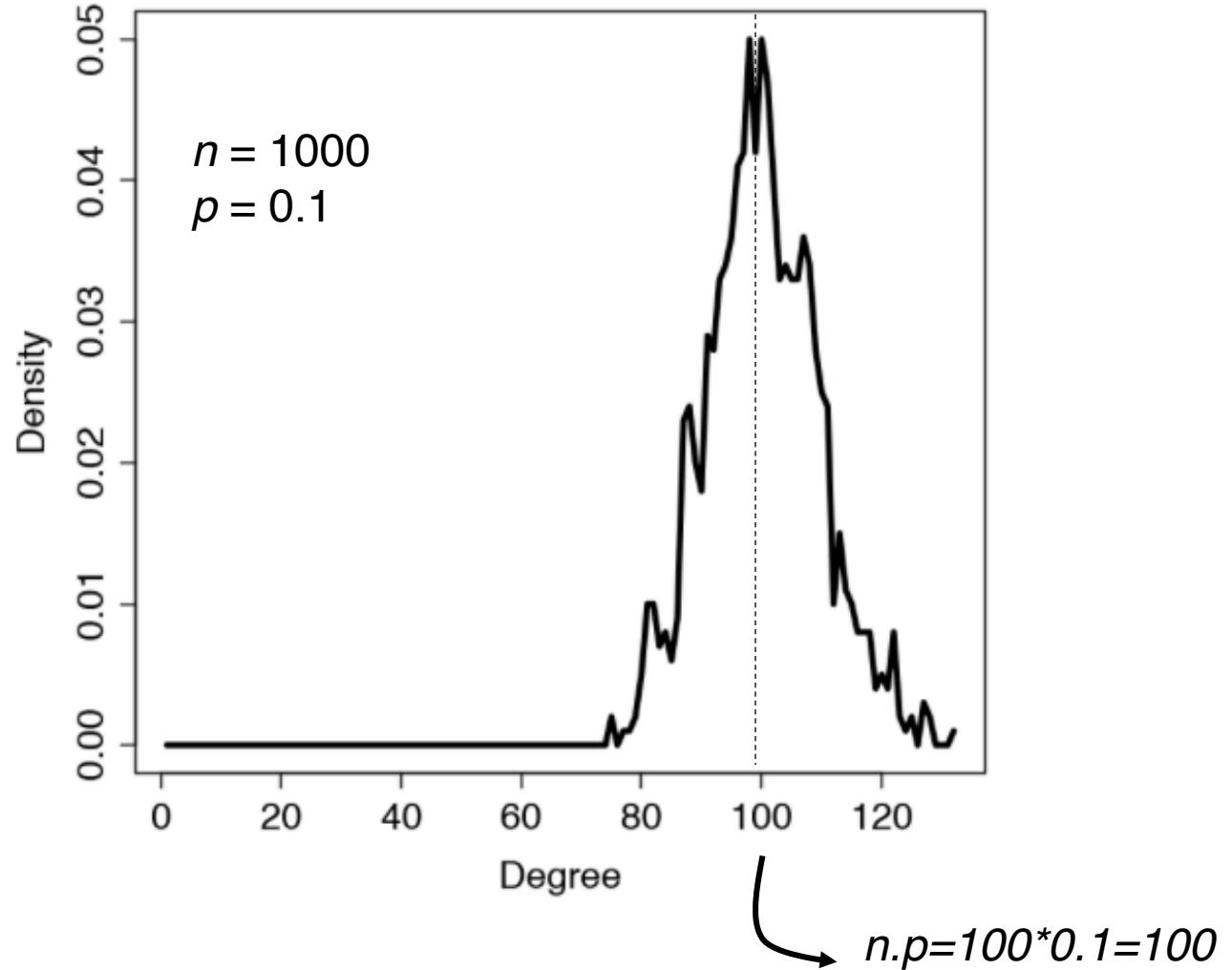


```
plot(sample_gnp(30, 0.1))
```

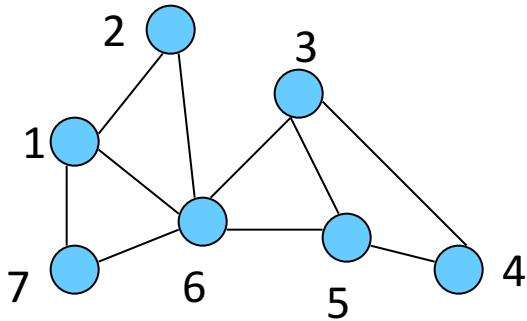


```
plot(sample_gnp(30, 0.5))
```

The random graph



Degree distribution of graphs

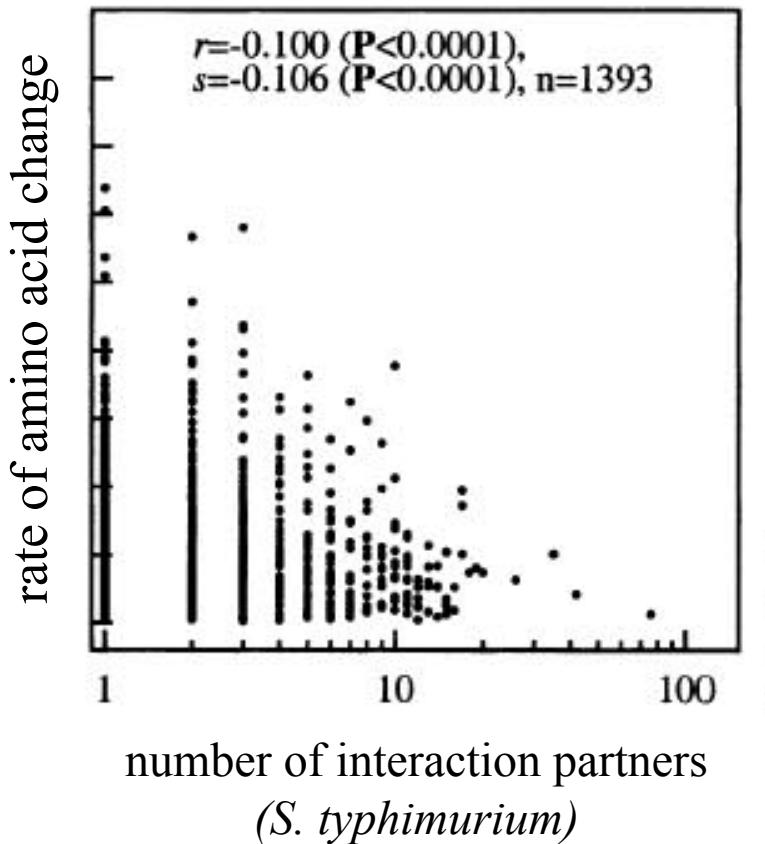


The degree (connectivity) k_i of a node V_i is the number of edges incident with the node (e.g., $k_1=3$, $k_6=5$).

$$k_i = \sum_j a_{ij}$$

Graphs can be characterized according to their degree distribution $P(k)$, the fraction of nodes having degree k .

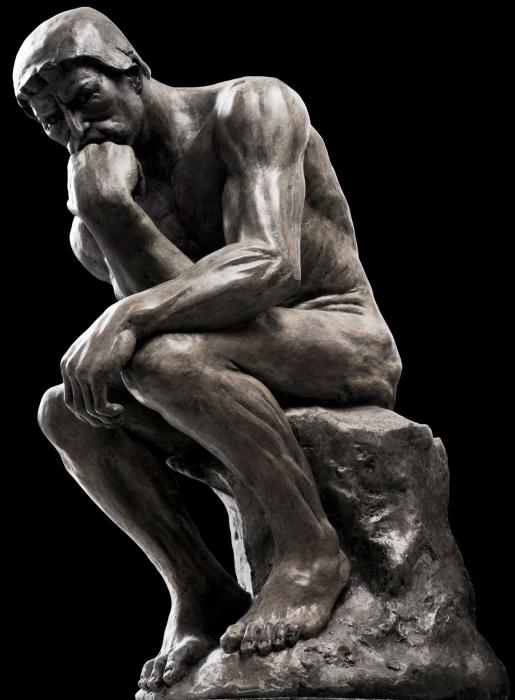
Connectivity can affect the evolution of proteins!



Highly connected proteins tolerate fewer amino acid substitutions in their evolution

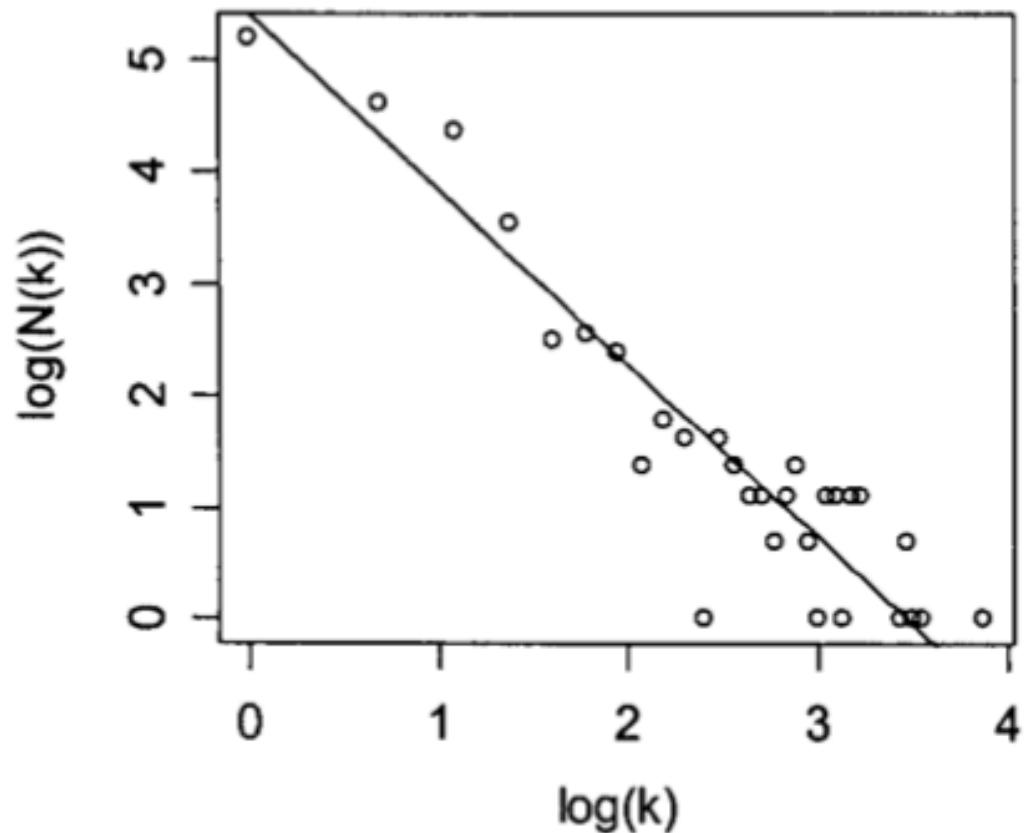
Hahn et al. Journal of Molecular Evolution 2004

Are biological networks random?



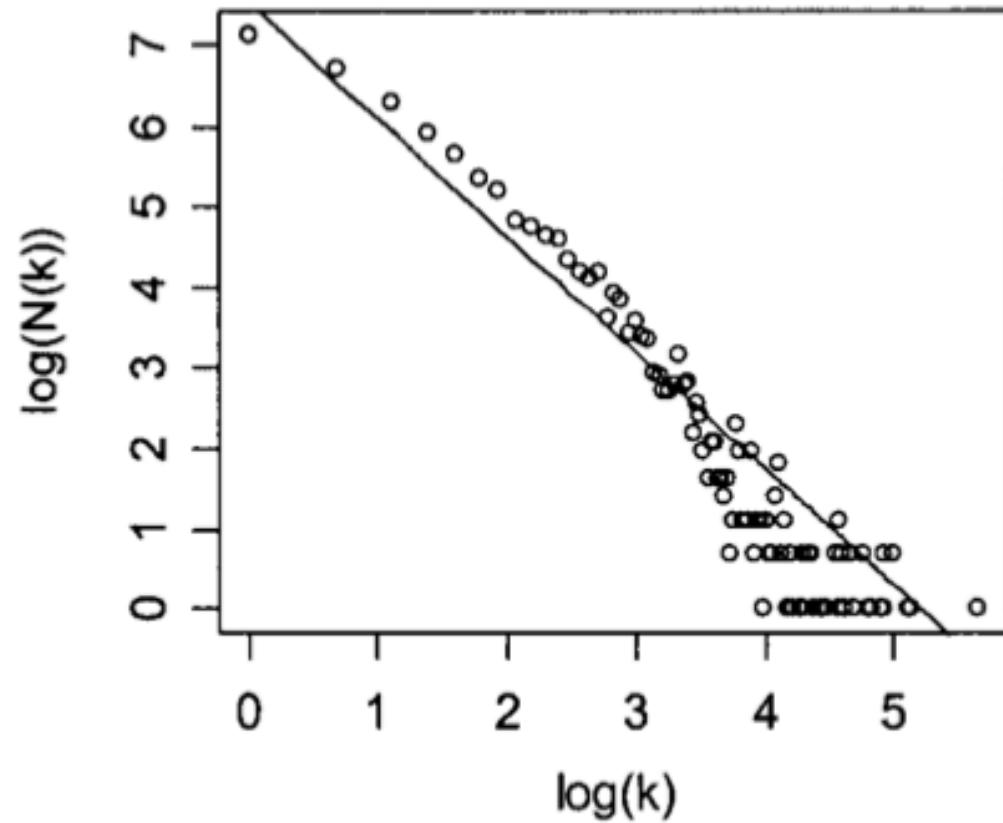
Biological network are non-random

Guelzim *et al.*, 2002



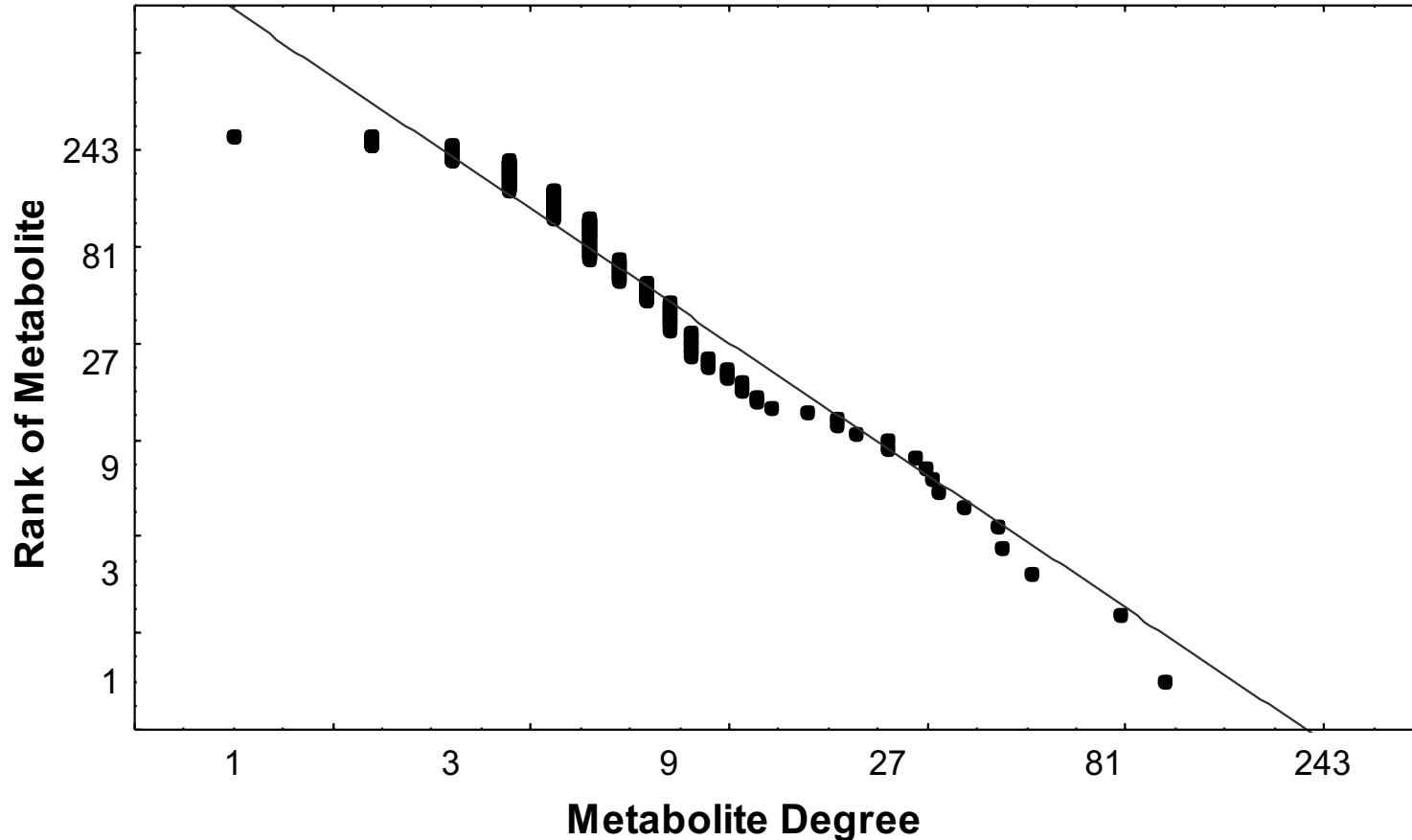
Transcriptional
regulatory network

Tong *et al.*, 2004



Genetic interaction
network

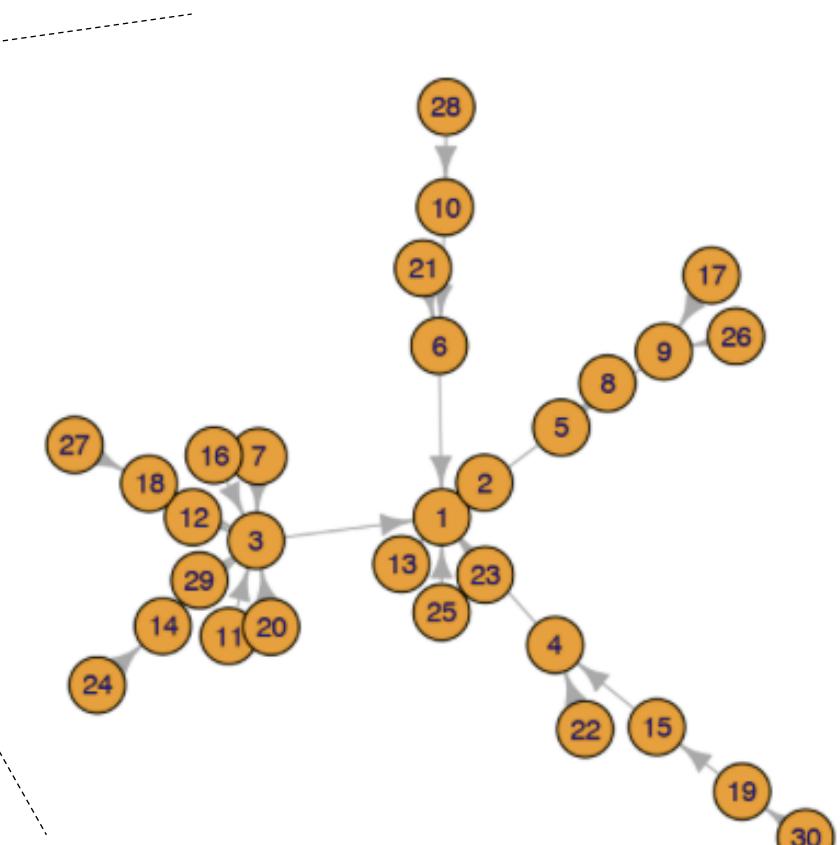
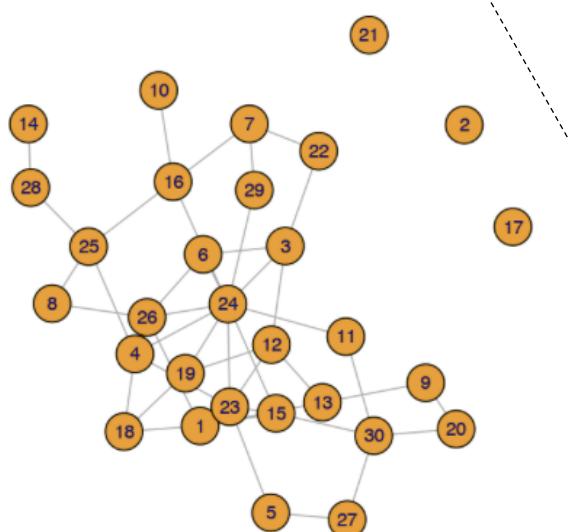
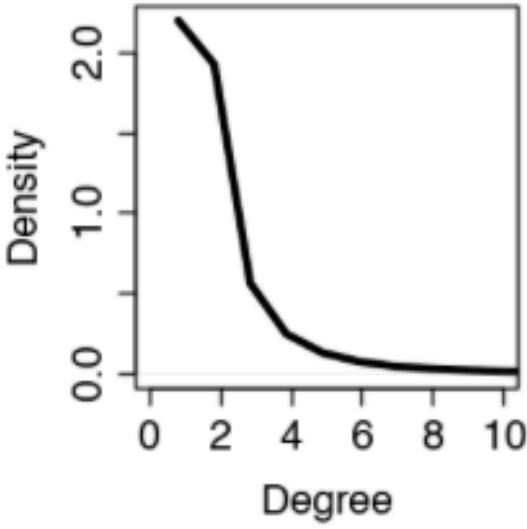
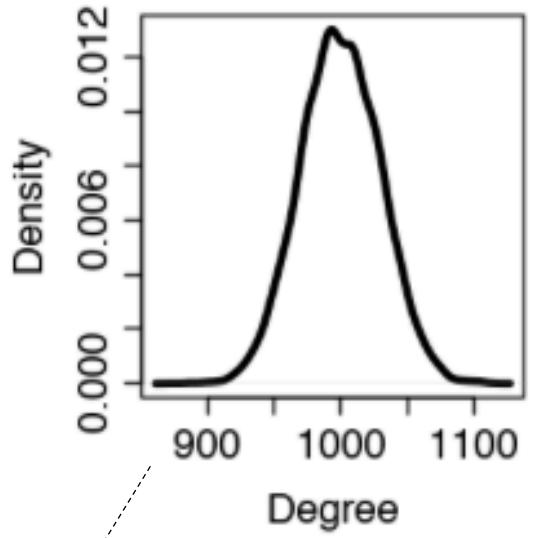
Metabolic networks have a broad-tailed degree distribution



Substrate network of *E. coli*

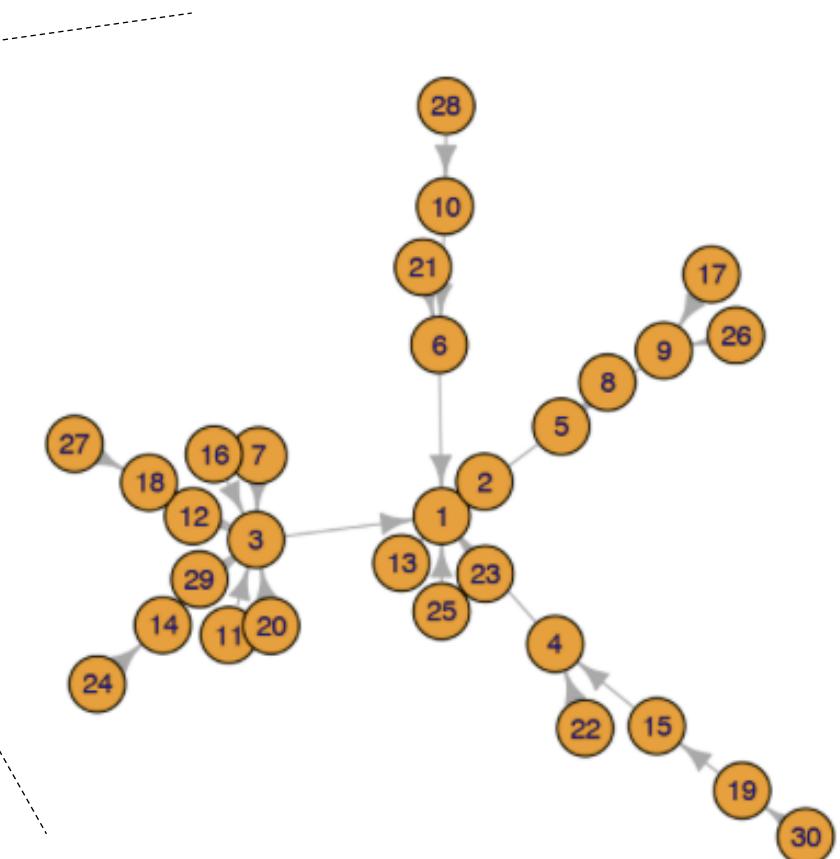
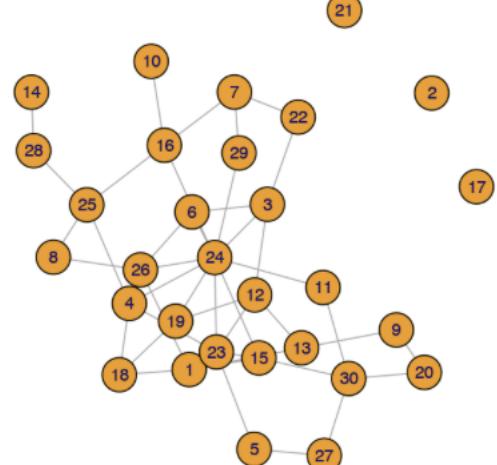
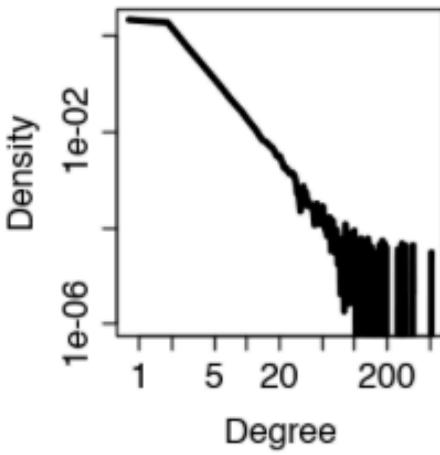
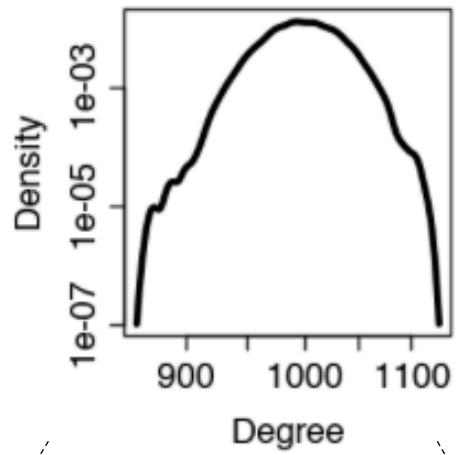
Wagner and Fell, Proc. Roy. Soc. London B 2001

The random graph vs. scale-free graph



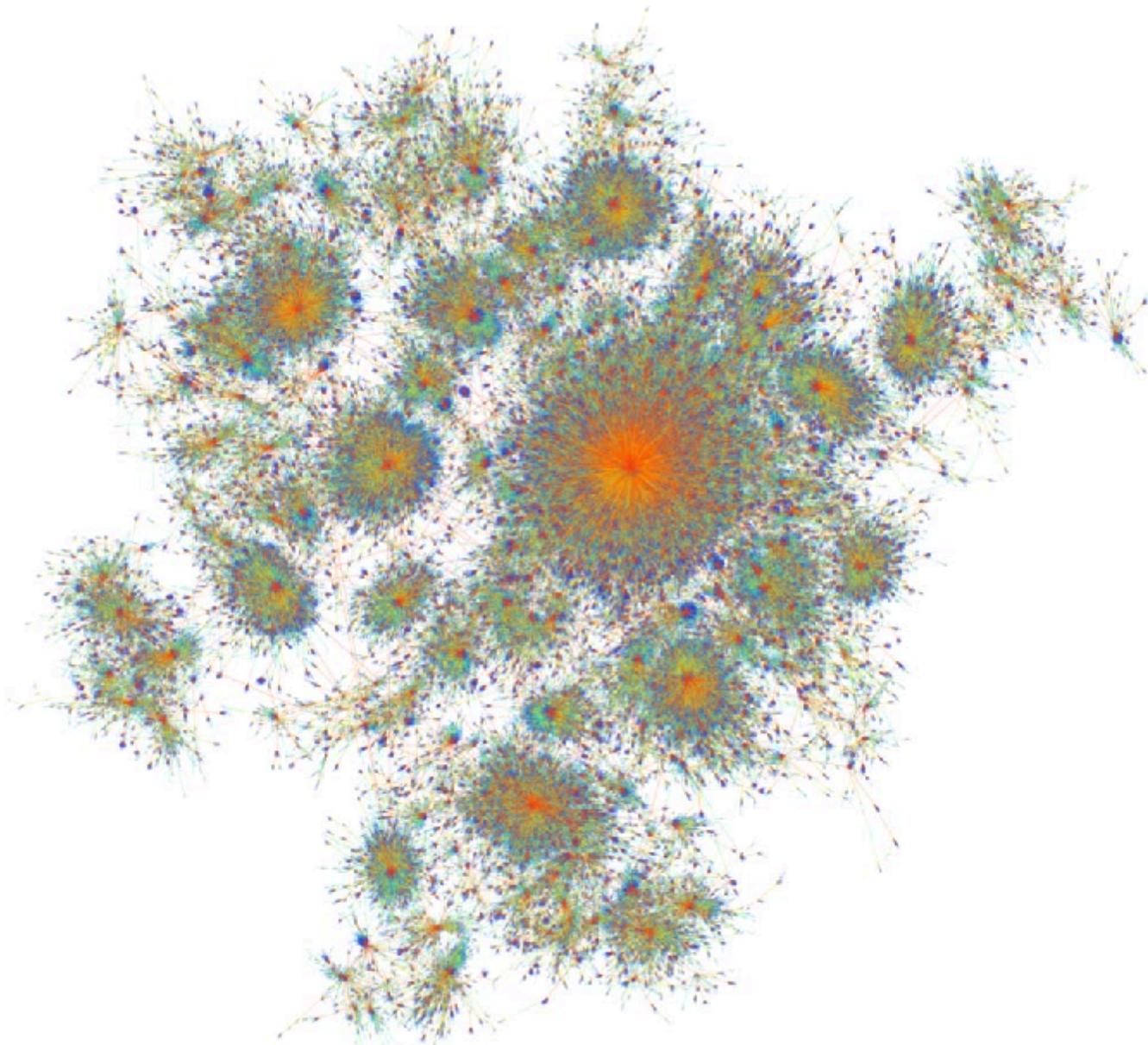
Linear-linear scale

The random graph vs. scale-free graph



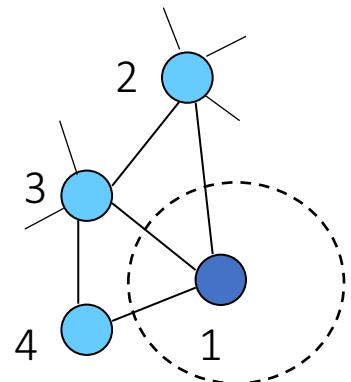
Log-log scale

What is so special about scale-free networks?



Nearest-neighbor degree of nodes

Average nearest neighbor degree of a node



$$k_1=3$$

$$k_2=5$$

$$k_3=5$$

$$k_4=2$$

$$k_{nn,1} = (1/3)(5+5+2) = 4$$

$$k_{nn,i} = \frac{1}{k_i} \sum_{j, \text{ nearest neighbors of } i} k_j$$

Assortative vs. Disassortative networks

Average nearest neighbor degree of all nodes with degree k

$$k_{nn,i} = \frac{1}{k_i} \sum_{j, \text{ nearest neighbors of } i} k_j$$

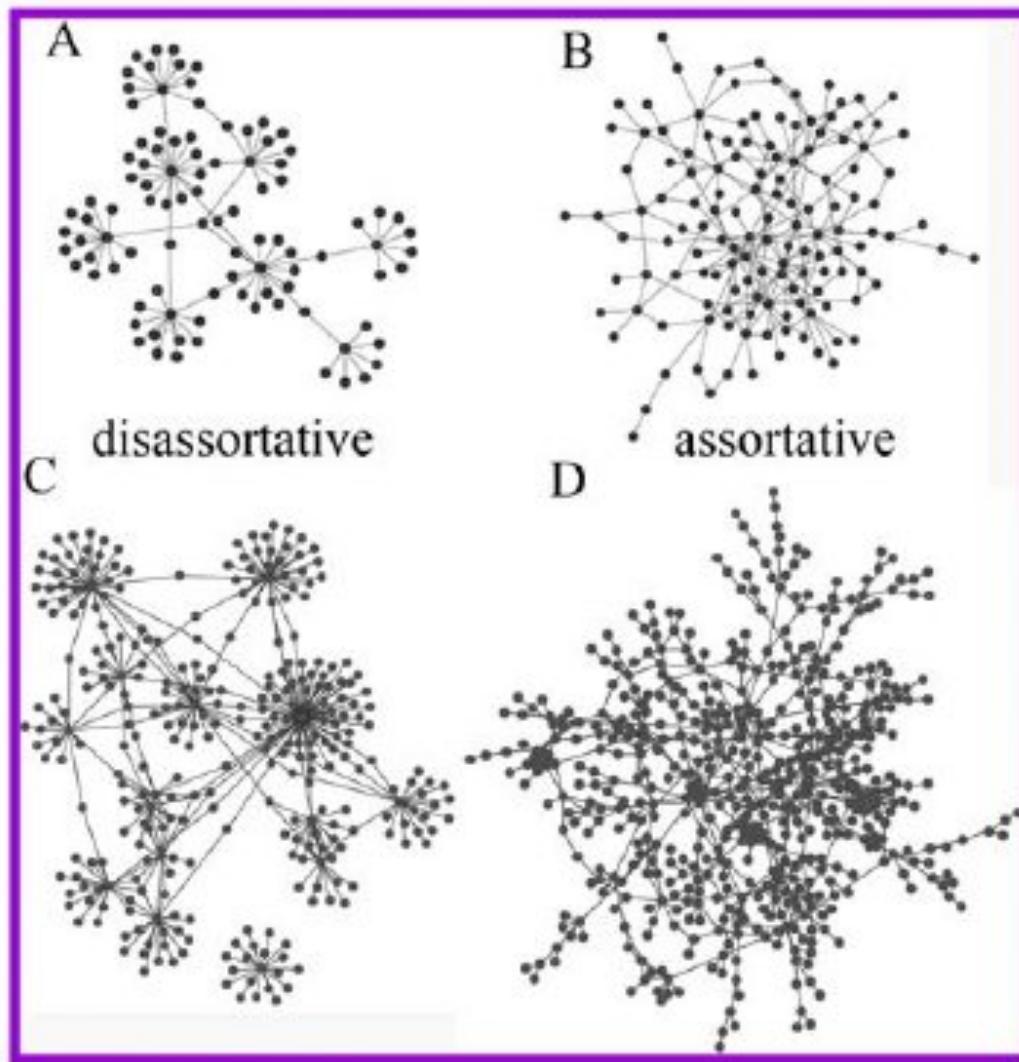
N_k ...number of nodes with degree k

$$k_{nn}(k) = \frac{1}{N_k} \left(\sum_{\text{nodes with degree } k} k_{nn,k} \right)$$

A graph is assortative if $k_{nn}(k)$ increases with k
nodes connect to nodes of similar connectivity

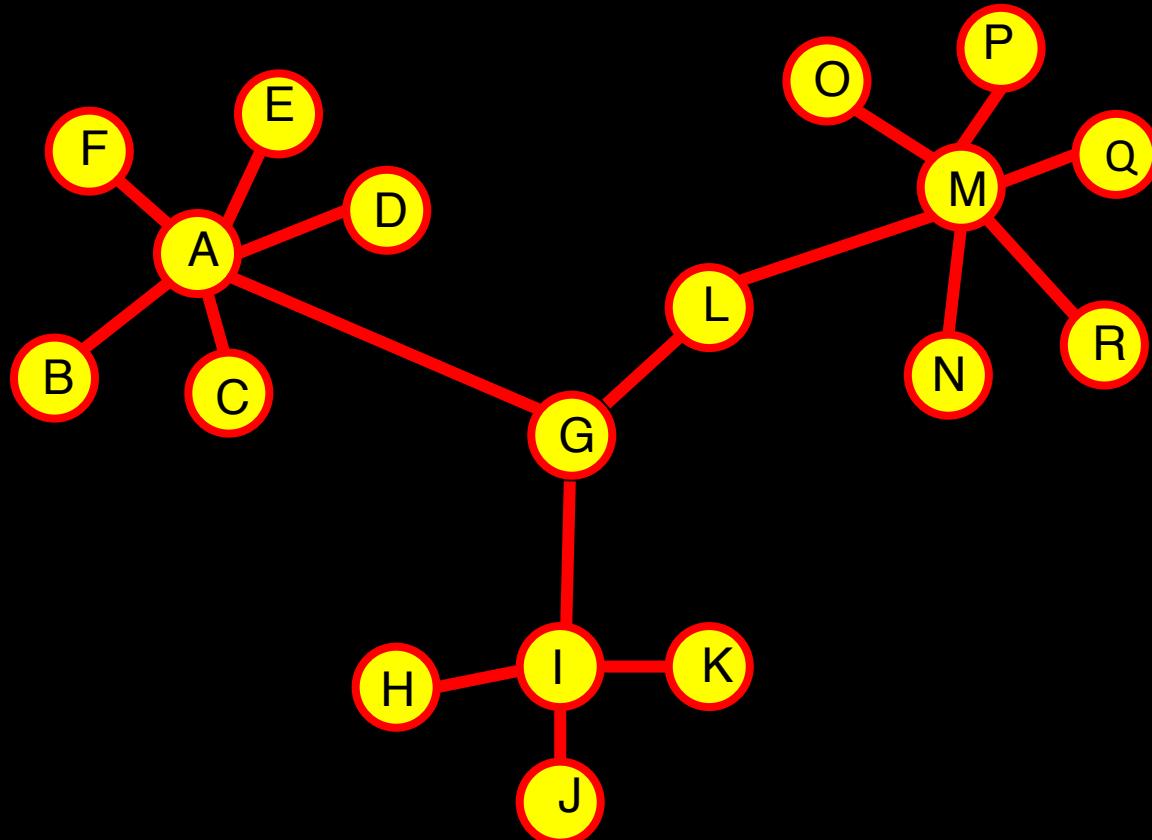
A graph is disassortive if $k_{nn}(k)$ decreases with k

Assortative vs. Disassortative networks

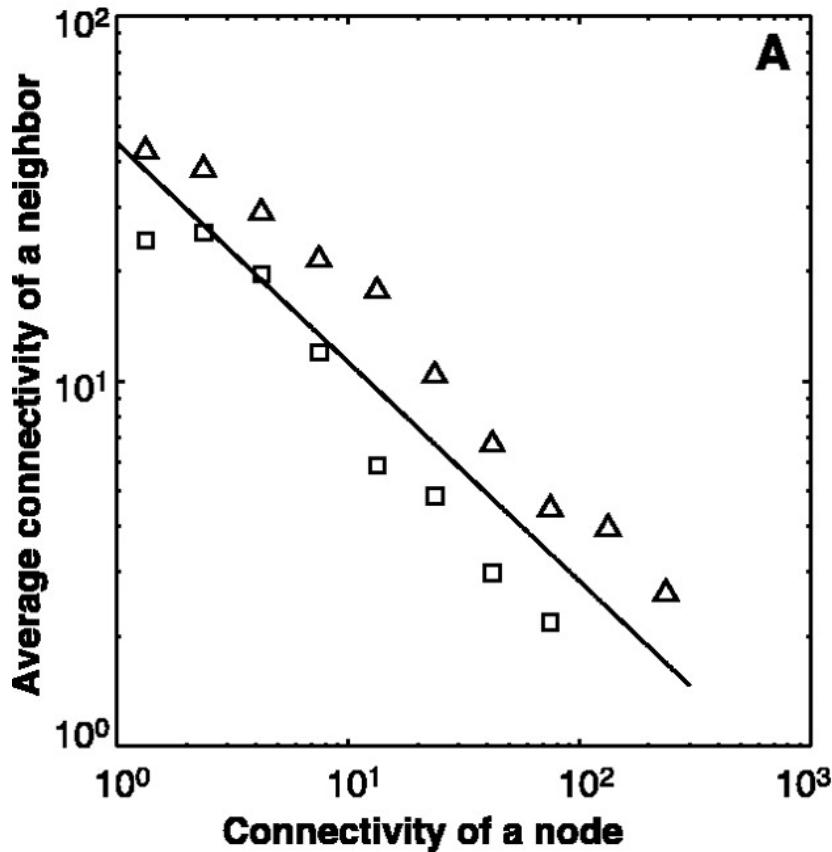


Class activity:

With only three choices, how would you i) preserve and ii) decrease the disassortative nature of the graph.



Protein interaction networks are disassortative

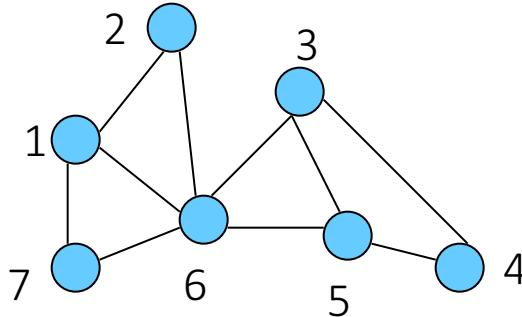


Plot of $P_{nn}(k)$ against k for the yeast protein interaction network (triangles) and the transcriptional regulation network (squares)

Few interactions between hubs
Many interactions between hubs and neighbors with low degree

Maslov and Sneppen, Science 2002

Measures of graph compactness: path length and diameter



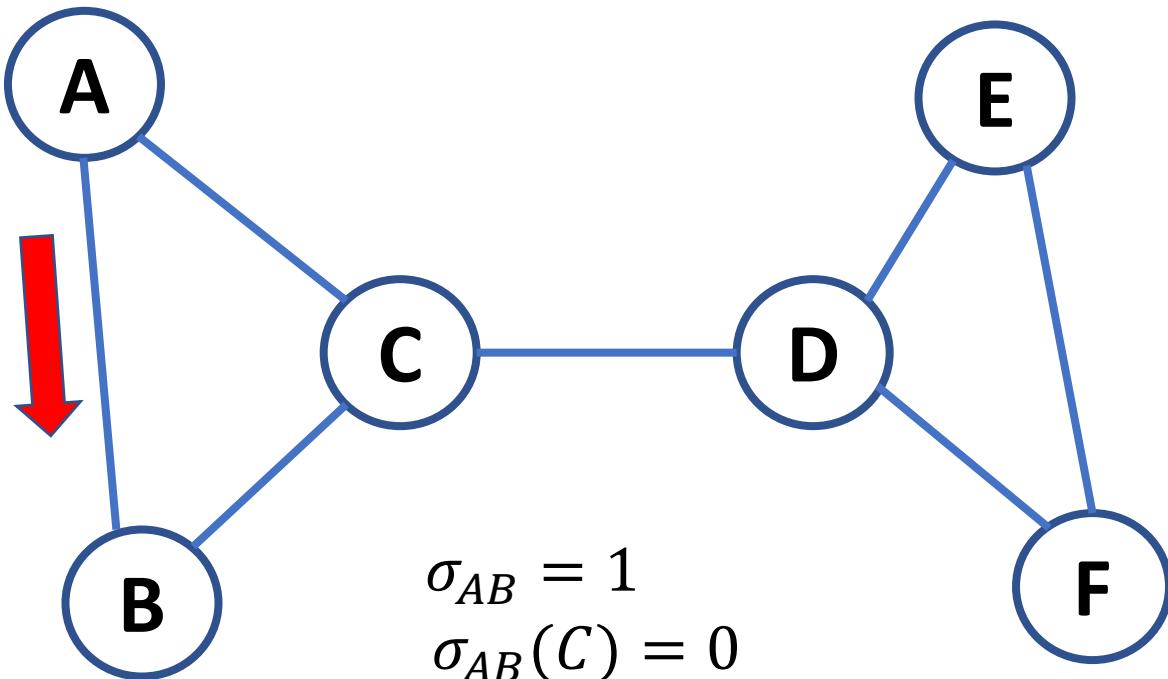
Matrix of shortest paths $D=(d_{ij})$

$$D = \begin{pmatrix} 0 & 1 & 2 & 3 & 2 & 1 & 1 \\ 1 & 0 & 2 & 3 & 2 & 1 & 2 \\ 2 & 2 & 0 & 1 & 1 & 1 & 2 \\ 3 & 3 & 1 & 0 & 1 & 2 & 3 \\ 2 & 2 & 1 & 1 & 0 & 1 & 2 \\ 1 & 1 & 1 & 2 & 1 & 0 & 1 \\ 1 & 2 & 2 & 3 & 2 & 1 & 0 \end{pmatrix}$$

Connected graph: $d_{ij} < \infty$ for all i, j

Betweenness centrality

Measure of centrality in a graph based on shortest path



$$\sigma_{uw}$$

of shortest path between nodes u and w

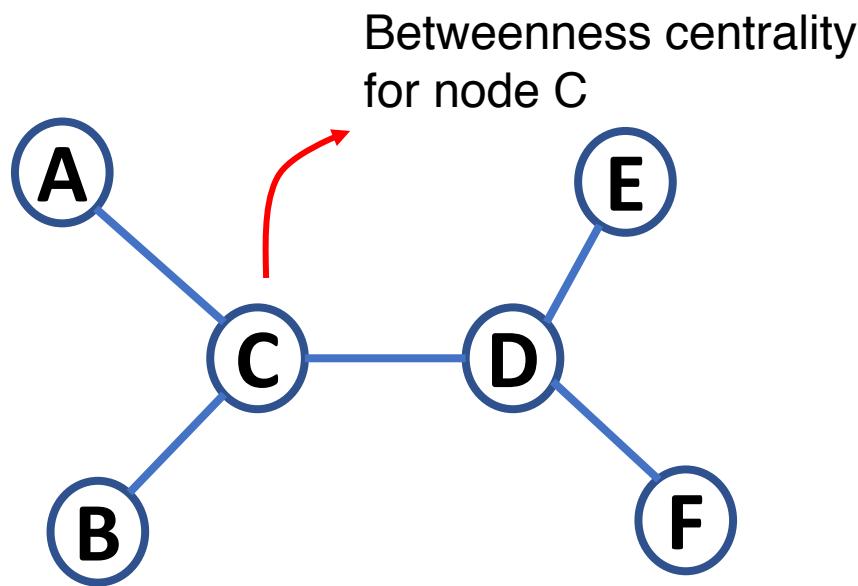
$$\sigma_{uw}(v)$$

of shortest path between nodes u and w that involve v

Betweenness centrality

$$= \frac{\sigma_{uw}(v)}{\sigma_{uw}}$$

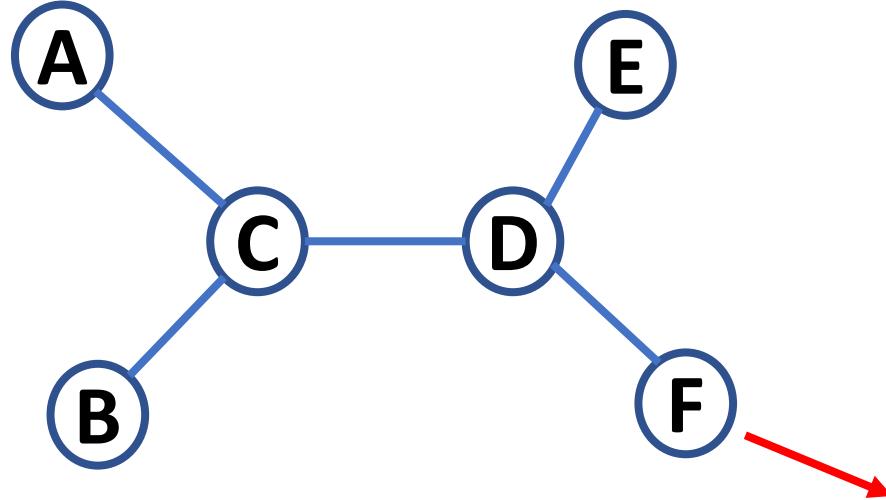
Betweenness centrality



	σ_{uw}	$\sigma_{uw}(v)$	$\sigma_{uw}(v)/\sigma_{uw}$
(A,B)	1	0	0
(A,D)	1	1	1
(A,E)	1	1	1
(A,F)	1	1	1
(B,D)	1	1	1
(B,E)	1	1	1
(B,F)	1	1	1
(D,E)	1	0	0
(D,F)	1	0	0
(E,F)	1	0	0

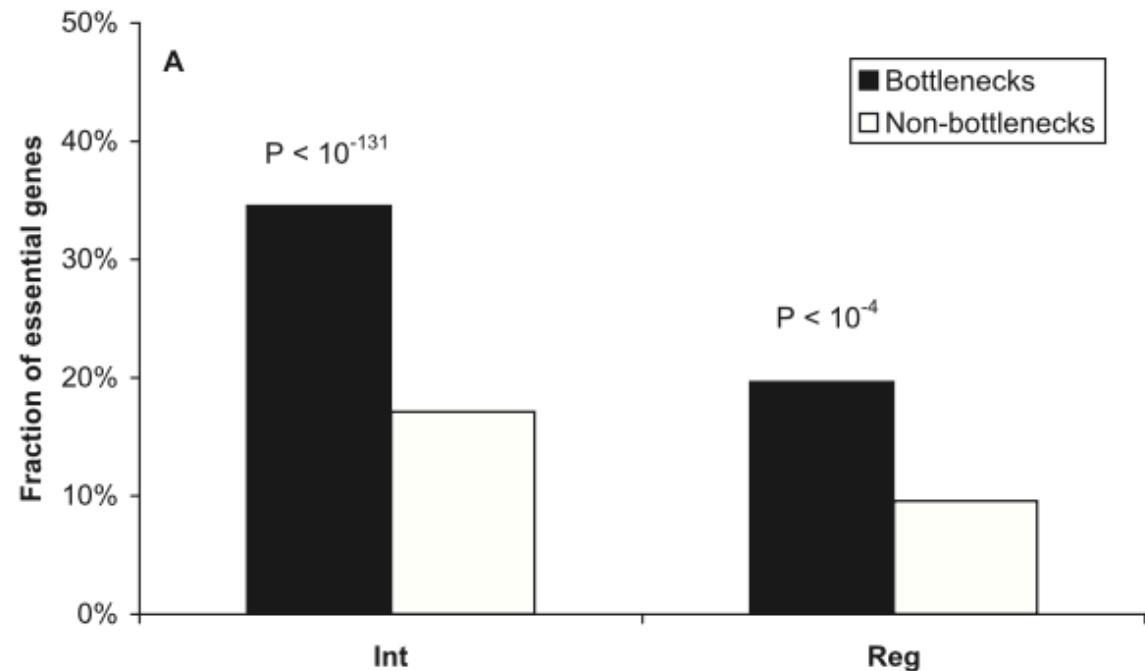
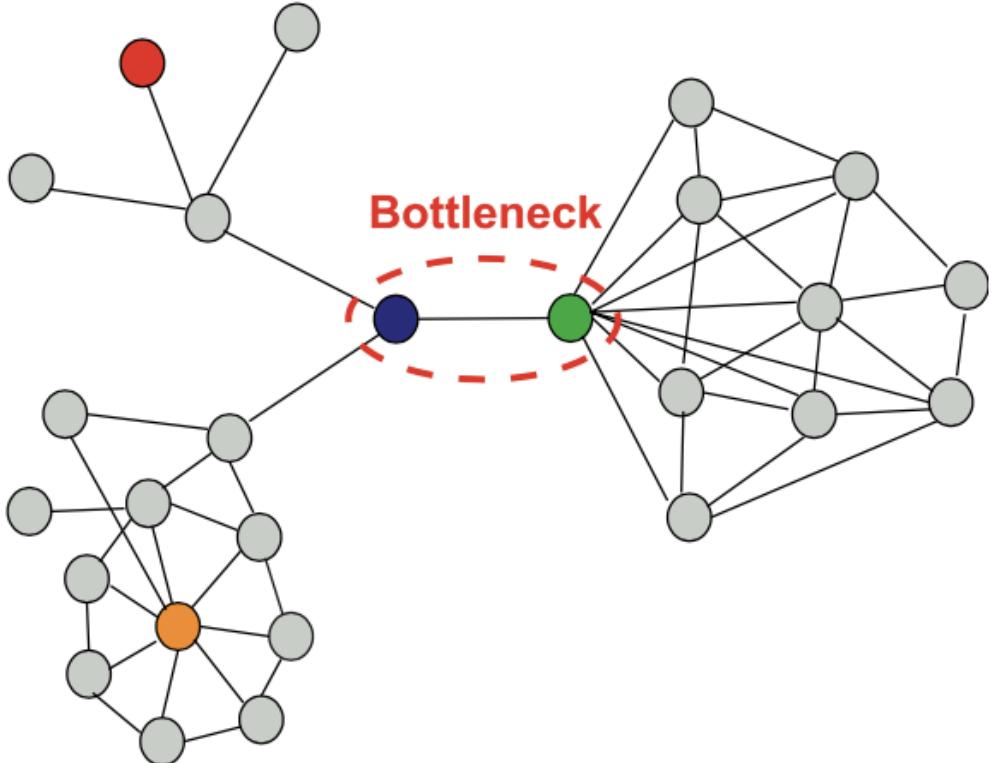
Sum=6

Betweenness centrality



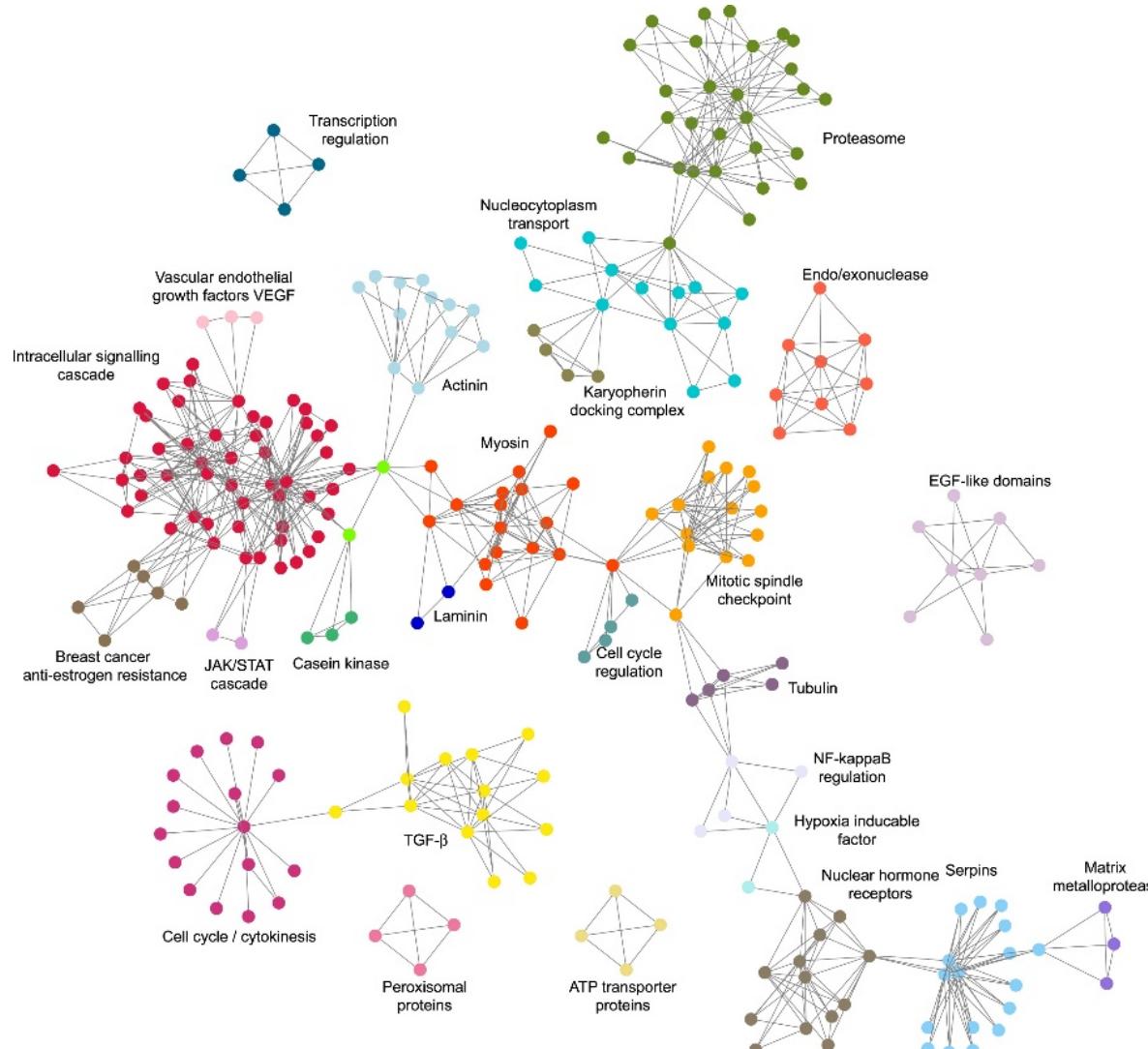
What is the betweenness centrality of the node F ?

Bottlenecks have high betweenness centrality scores



Proteins with high betweenness scores
tend to be more essential

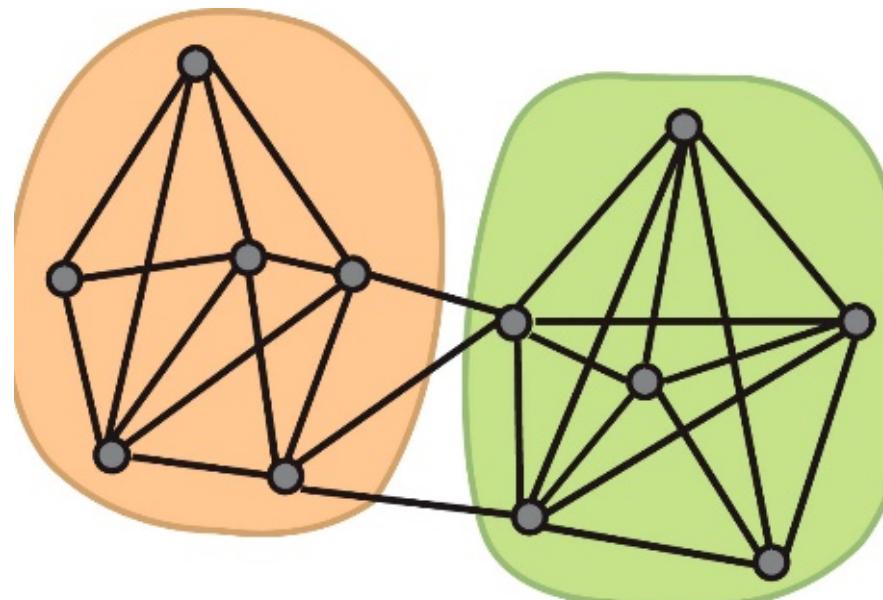
Advanced topics: Graphs can be subdivided into “communities”



Community structure of a rat protein interaction network

Advanced topics: Graphs can be subdivided into “communities”

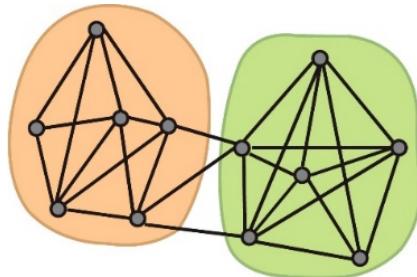
In a graph that can be subdivided into communities (clusters, modules) nodes fall into groups that share more edges with each other than with nodes outside the community



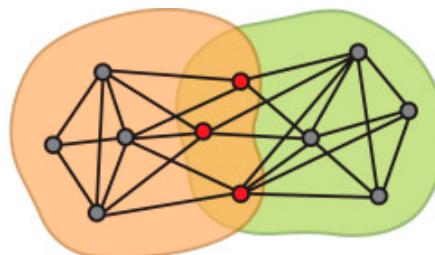
Advanced topics: Graphs can be subdivided into “communities”

Some require information about the total number of communities (easier), others don't (more difficult).

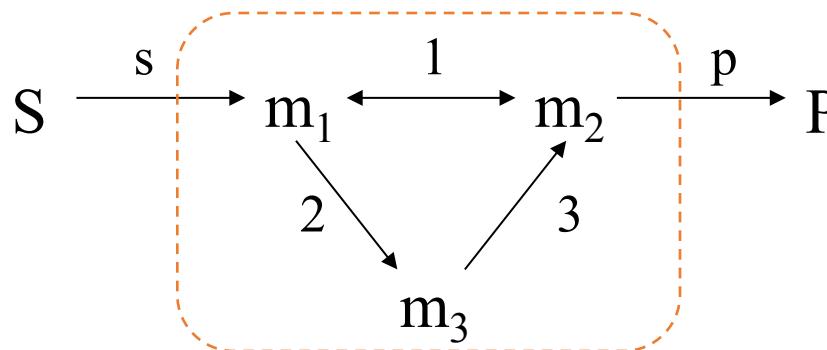
Hard-clustering methods generate non-overlapping communities (easier)



Soft-clustering methods allow overlapping communities (more difficult)



Advanced topics: We can do calculations with graphs



A chemical reaction network

Metabolite concentrations m_i change according to the equations

$$\frac{dm_1}{dt} = v_s - v_1 - v_2$$

$$\frac{dm_2}{dt} = v_1 + v_3 - v_p$$

$$\frac{dm_3}{dt} = v_2 - v_3$$

$$\frac{d\vec{m}}{dt} = \mathbf{S}\vec{v}$$

$$\mathbf{S} = \begin{pmatrix} 1 & -1 & -1 & 0 & 0 \\ 0 & 1 & 0 & 1 & -1 \\ 0 & 0 & 1 & -1 & 0 \end{pmatrix}$$

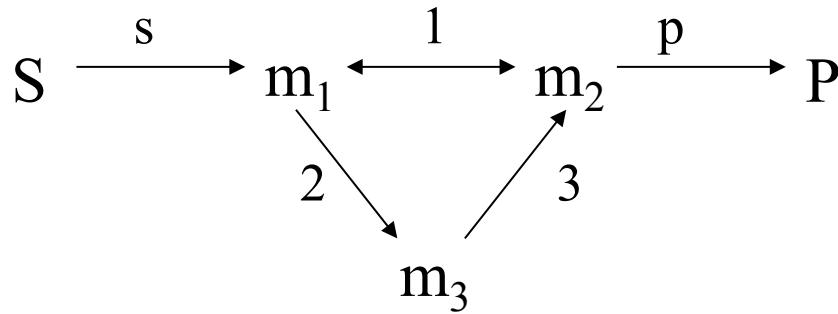
Stoichiometry matrix

v_i metabolic flux through reaction i

$$\vec{v} = (v_s, v_1, v_2, v_3, v_p)^\top$$

Rows: metabolites
Columns: reactions

Advanced topics: We can do calculations with graphs



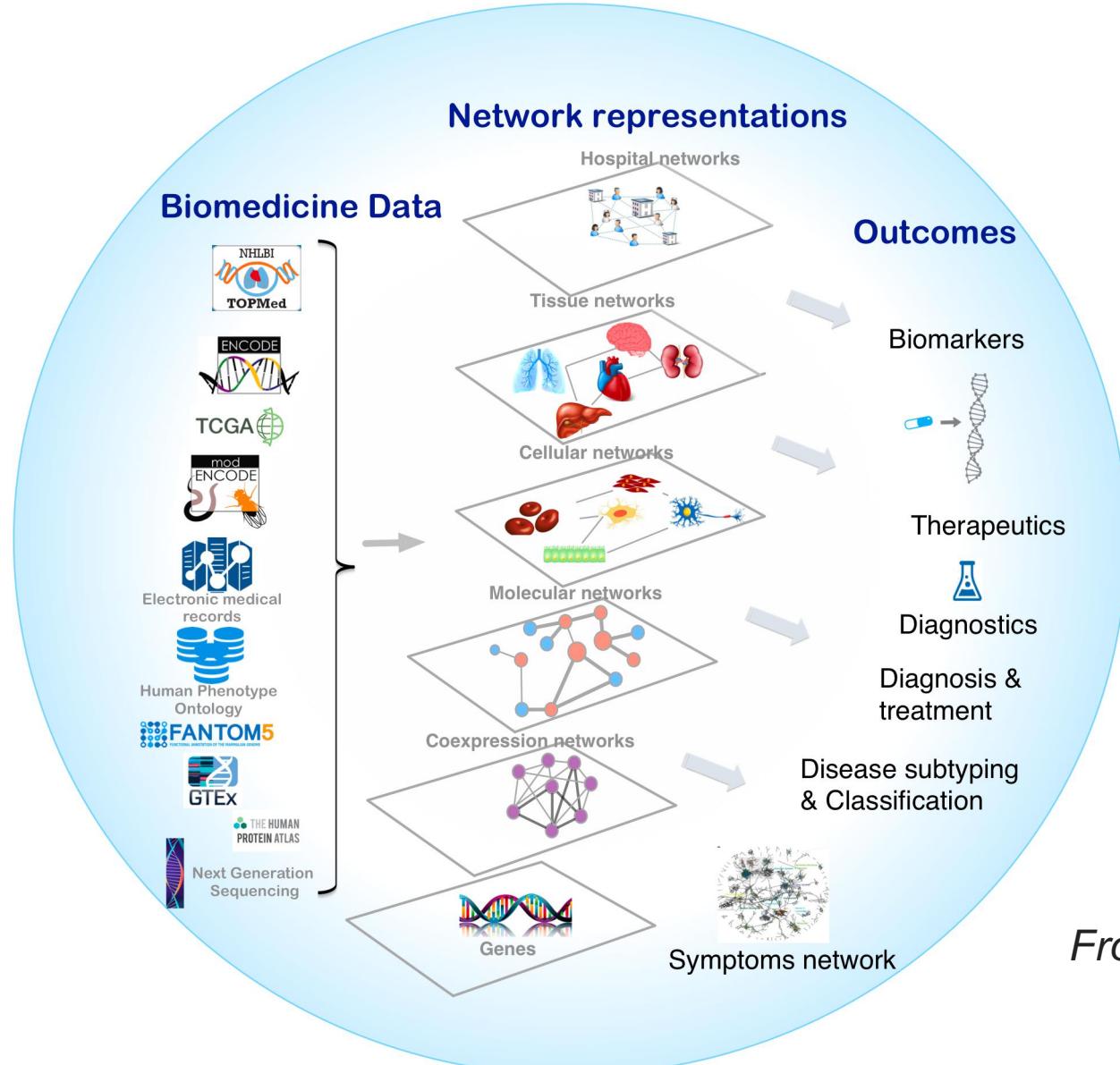
FBA assumes that metabolism is in a steady state where the concentrations of metabolites no longer change

$$\frac{d\vec{m}}{dt} = 0$$

$$\mathbf{S}\vec{v} = 0$$

The solutions of these equations are the allowable metabolic fluxes. They form the so-called null space of S

Advanced topics: Network medicine



Frontiers in Genetics 10 (2019): 294.

Concluding remarks

- Networks are everywhere! Biological systems also behave as interconnected networks.
- Several mathematical approaches and disciplines such as graph theory help us model networks.
- We don't just visualize networks. We also use networks for:
 - Quantitative analyses
 - Predictions (Bayesian graph networks)
- Don't overlook the experimental approaches to build networks!
- Network theory can be used for diagnosis (Network medicine)

Further reading

Complex networks in general

Newman, MEJ. The structure and function of complex networks. *SIAM Review* **45**, 167-256, 2003.

Fortunato, S., Hric, D. Community detection in networks: A user guide. *Physics Reports* **659**, 1-44. 2016.

Protein interaction networks

Xia et al. Analyzing cellular biochemistry in terms of molecular networks. *Annu. Rev. Biochem.* **73**:1051–87, 2004

Rajagopala et a., The binary protein-protein interaction landscape of *Escherichia coli*. *Nature Biotechnology* **32**, 285-290, 2014

Metabolic networks

Price et al. *Nature Reviews Microbiology* **2**, 886-897, 2004

Exam questions

