

# Networks

Paris

Who am I?

1992 1999



*Student (Msc, PhD)*  
Nicotinic receptors:  
Bioinformatics,  
Neuroanatomy  
Behaviour

2001 2003



*CNRS Researcher*  
Nicotinic receptors:  
Bioinformatics

***“A tale of  
two cities”***

2014



*Chief data officer*

1999 2001



*EMBO post-doc*  
Bacterial chemotaxis:  
Bioinformatics,  
Mathematical Modelling

2003 2012



*Group leader*  
Systems Biology  
Synaptic signalling:  
Modelling, knowledge  
Representation, databases

2012



*Senior group leader*  
Signalling  
neurodegeneration  
epigenetics  
stem-cells

Cambridge

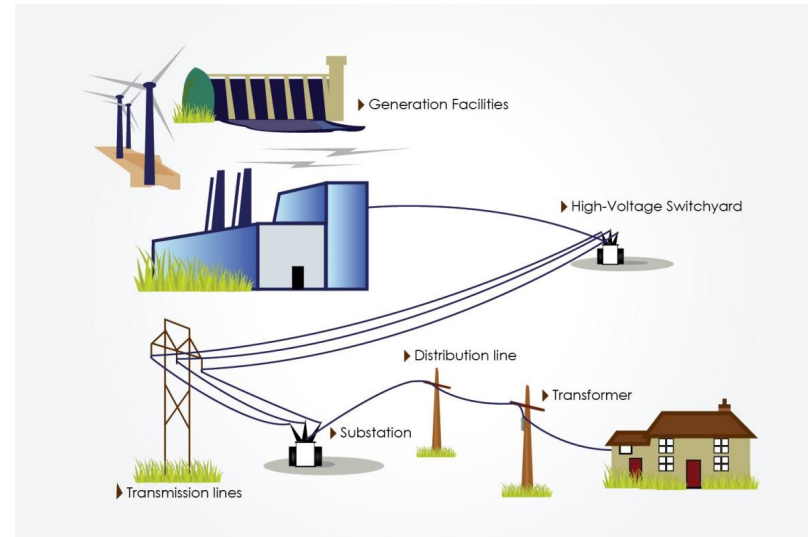


# What are we going to talk about?

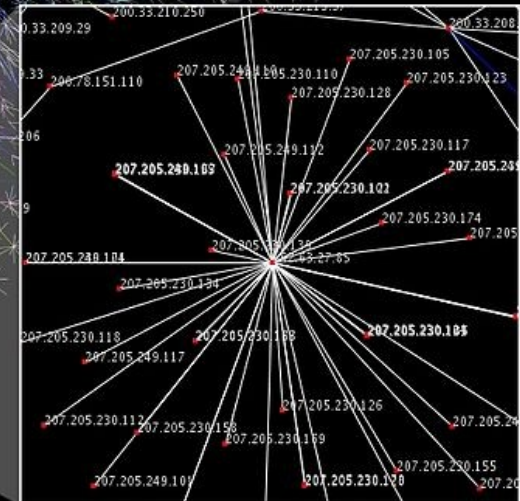
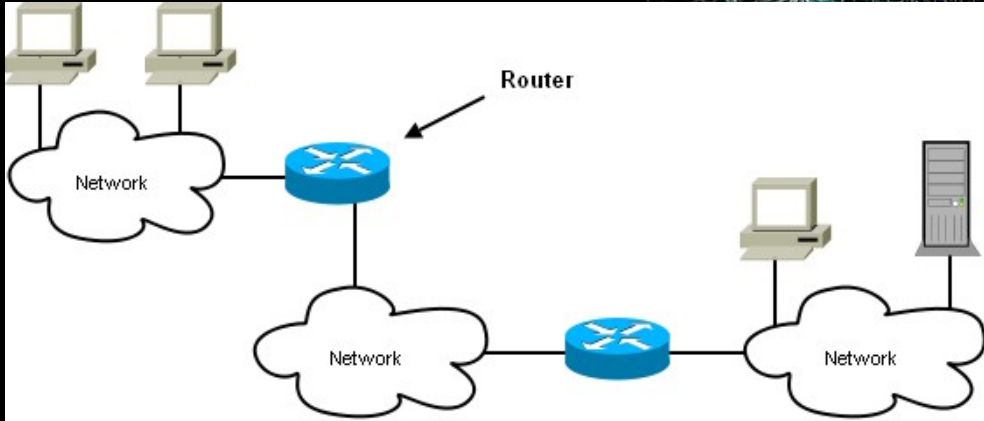
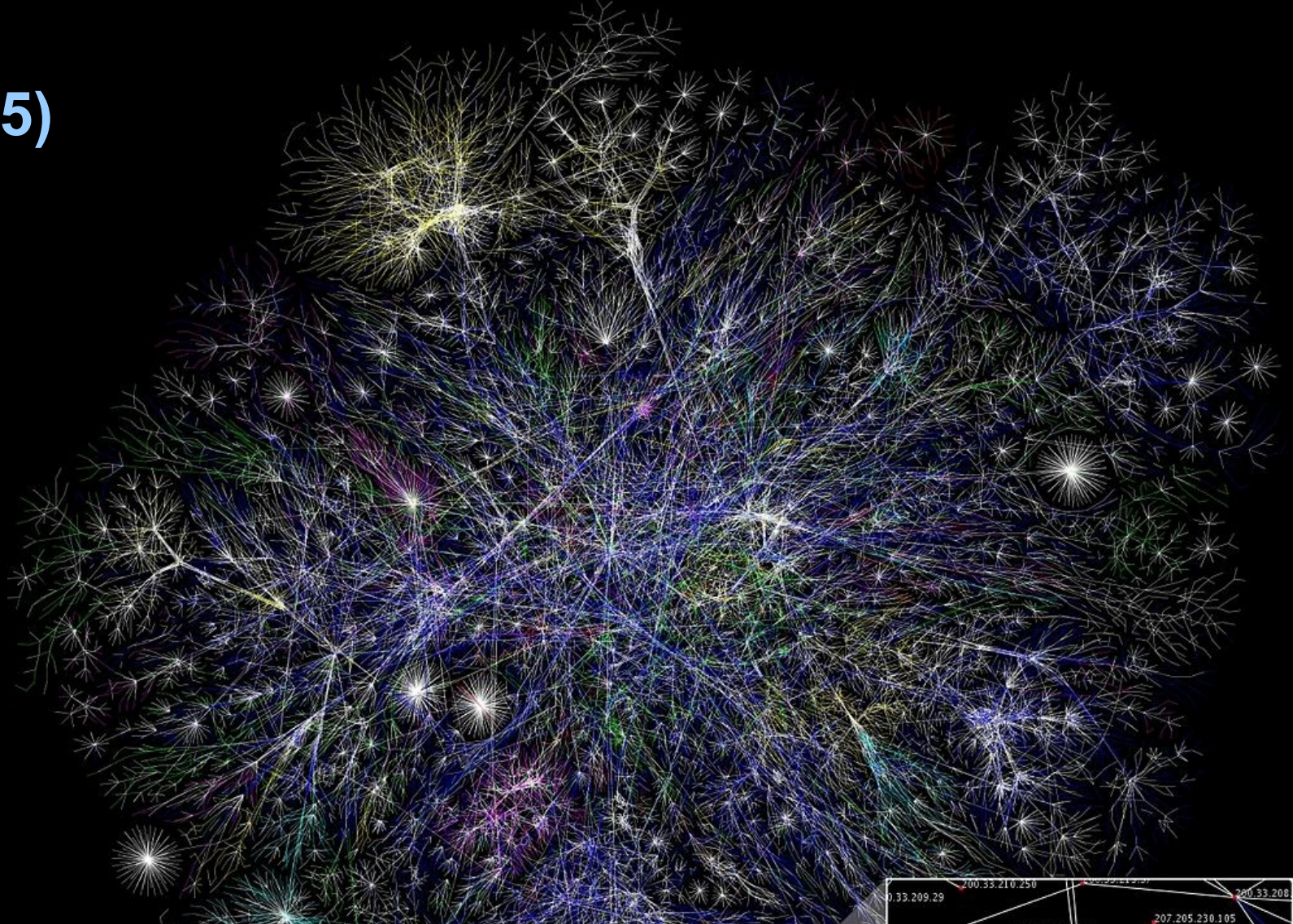
- Networks
- Analysing networks
- Reconstructing networks
- Biochemical networks
- Example of synthetic gene network

# Networks are everywhere

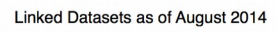
# Power grid (detail, US)

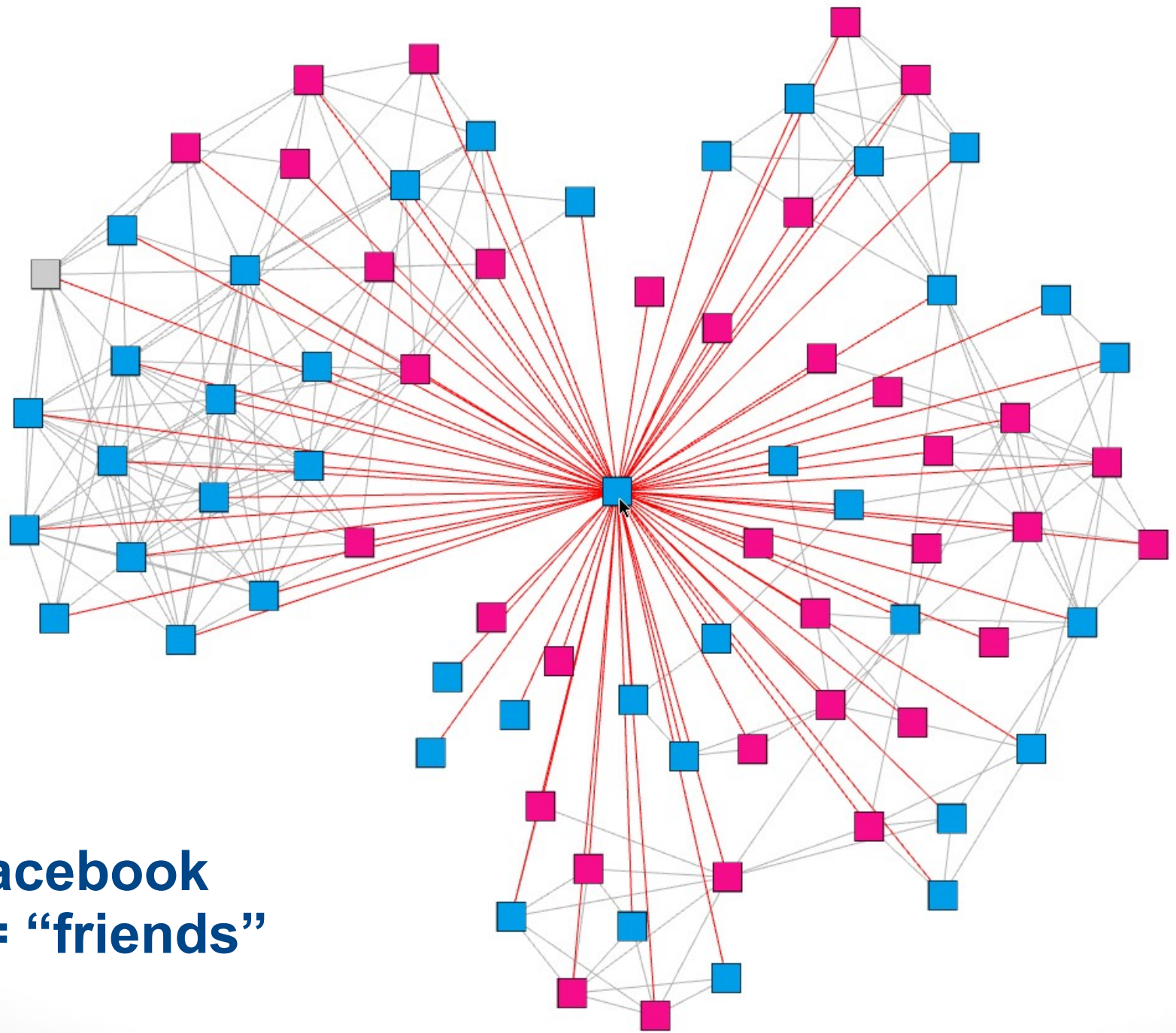


# Internet (portion, 2005)



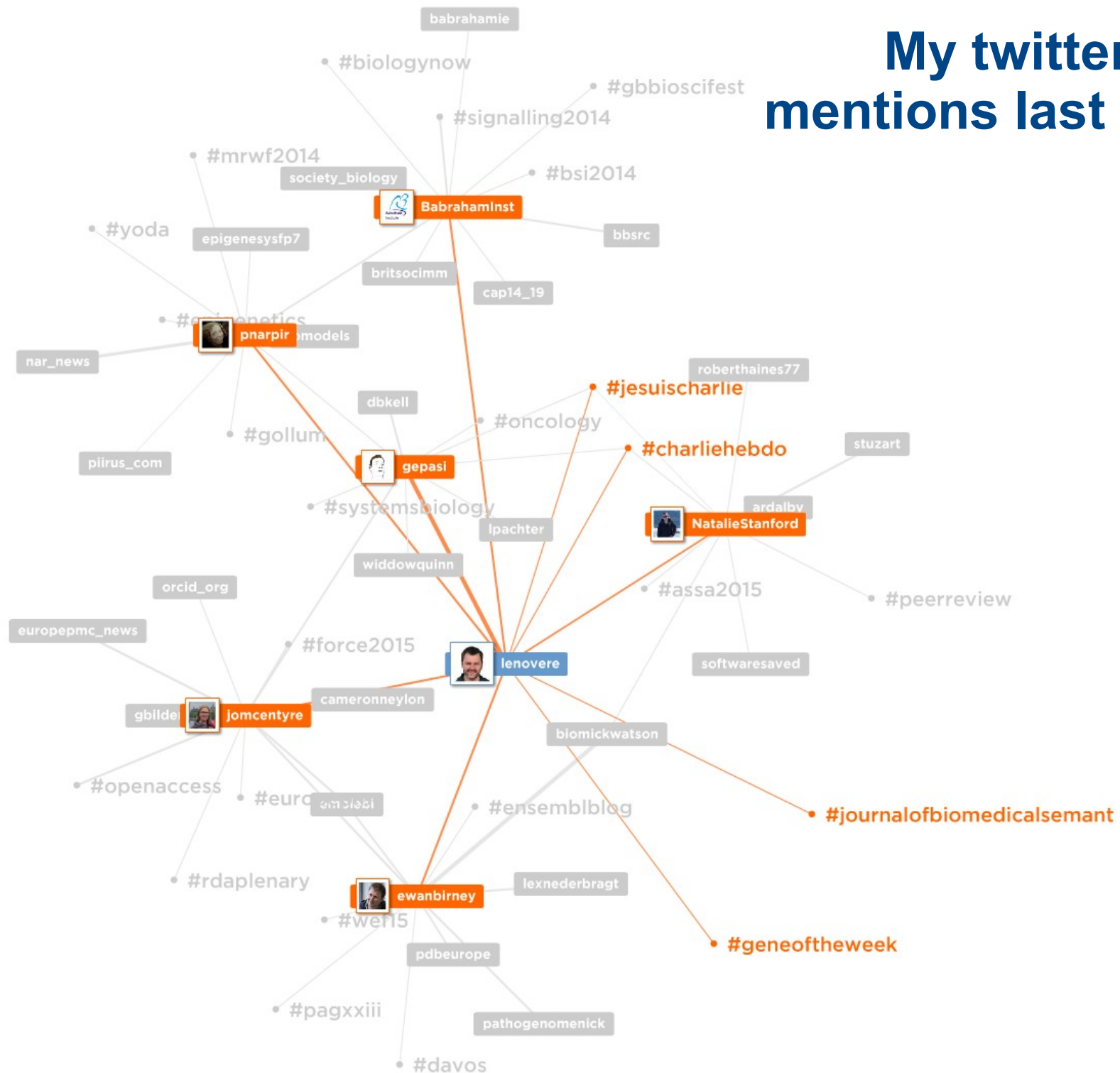
## UTC, 26 January 2015



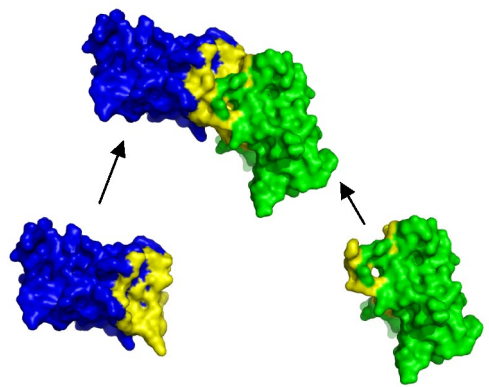
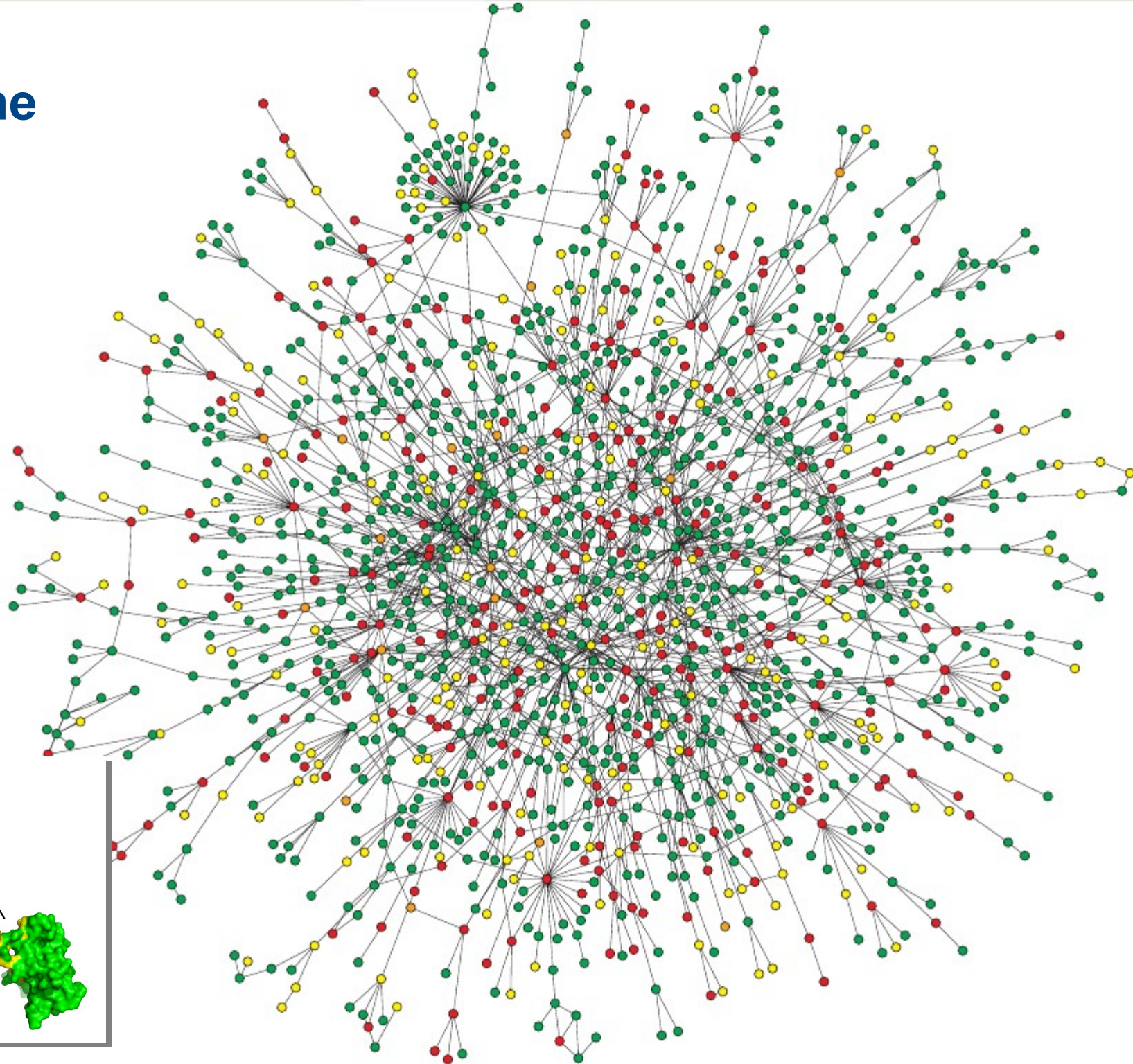


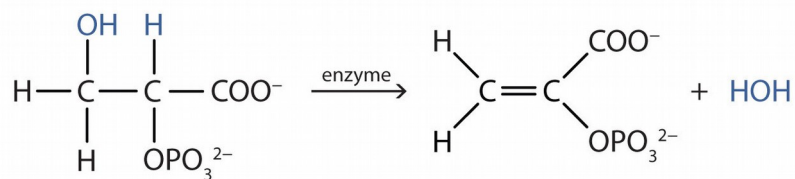
**My Facebook  
nodes = “friends”**

# My twitter mentions last week



# Protein interactome (yeast)

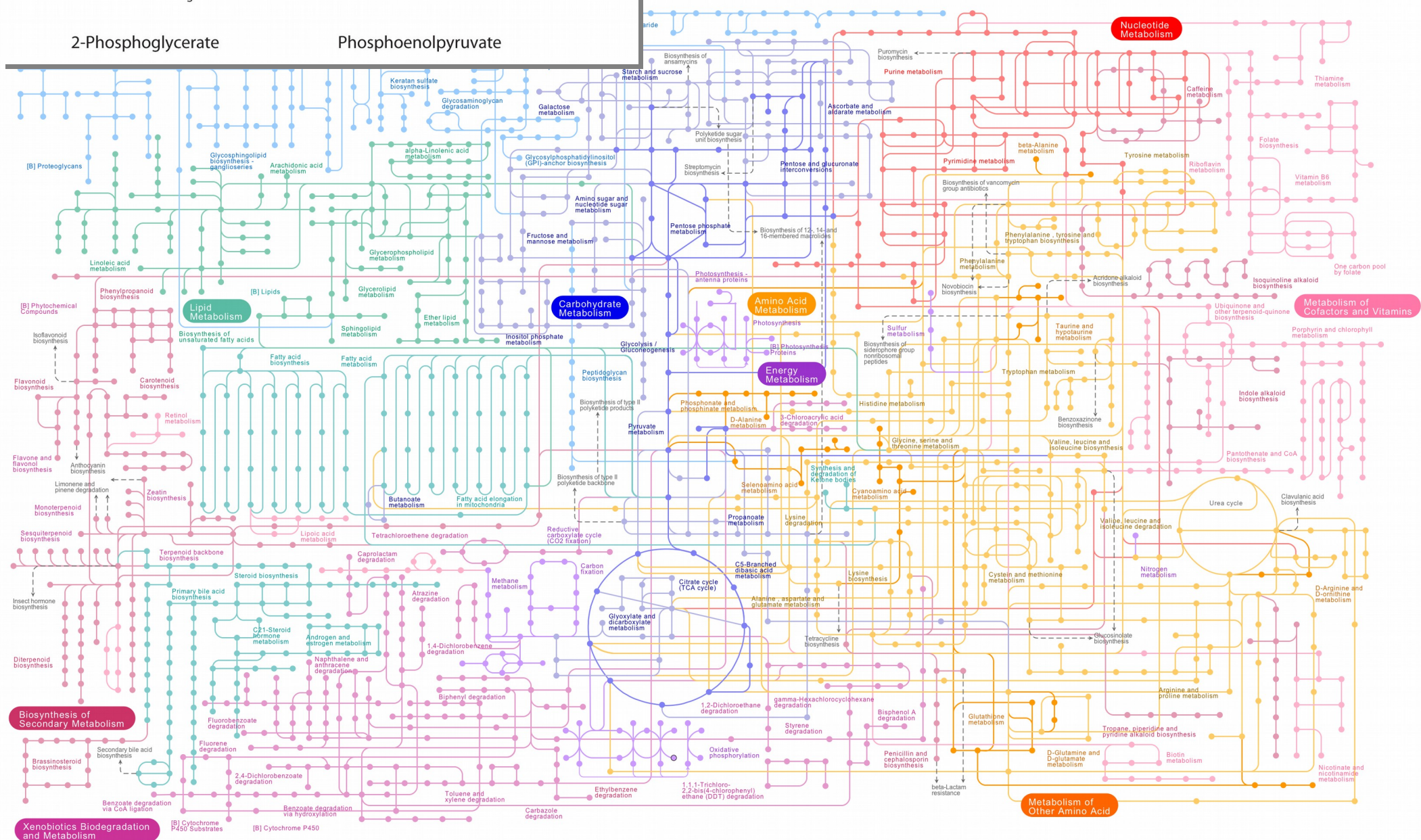




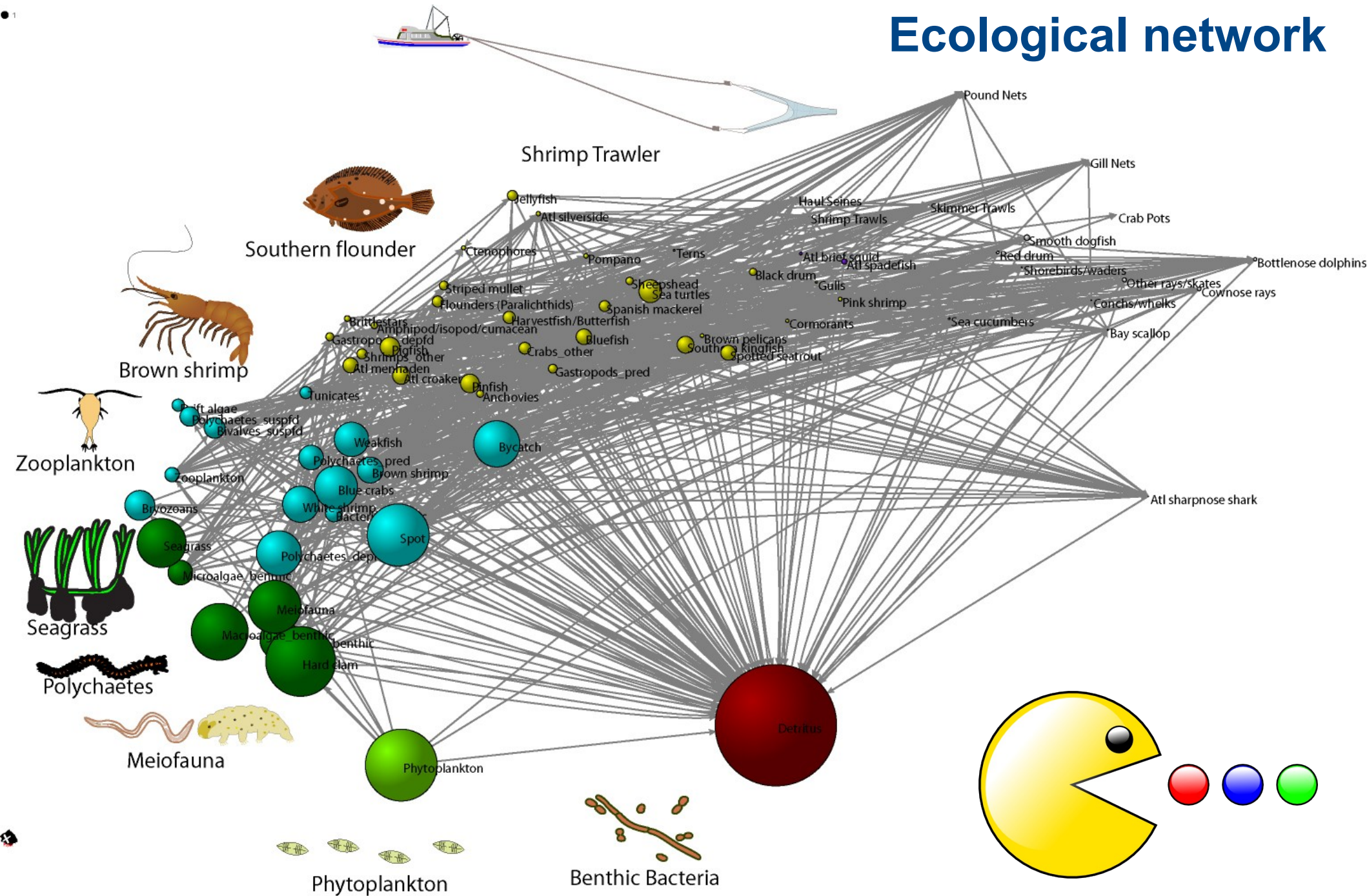
2-Phosphoglycerate

Phosphoenolpyruvate

# Metabolic network



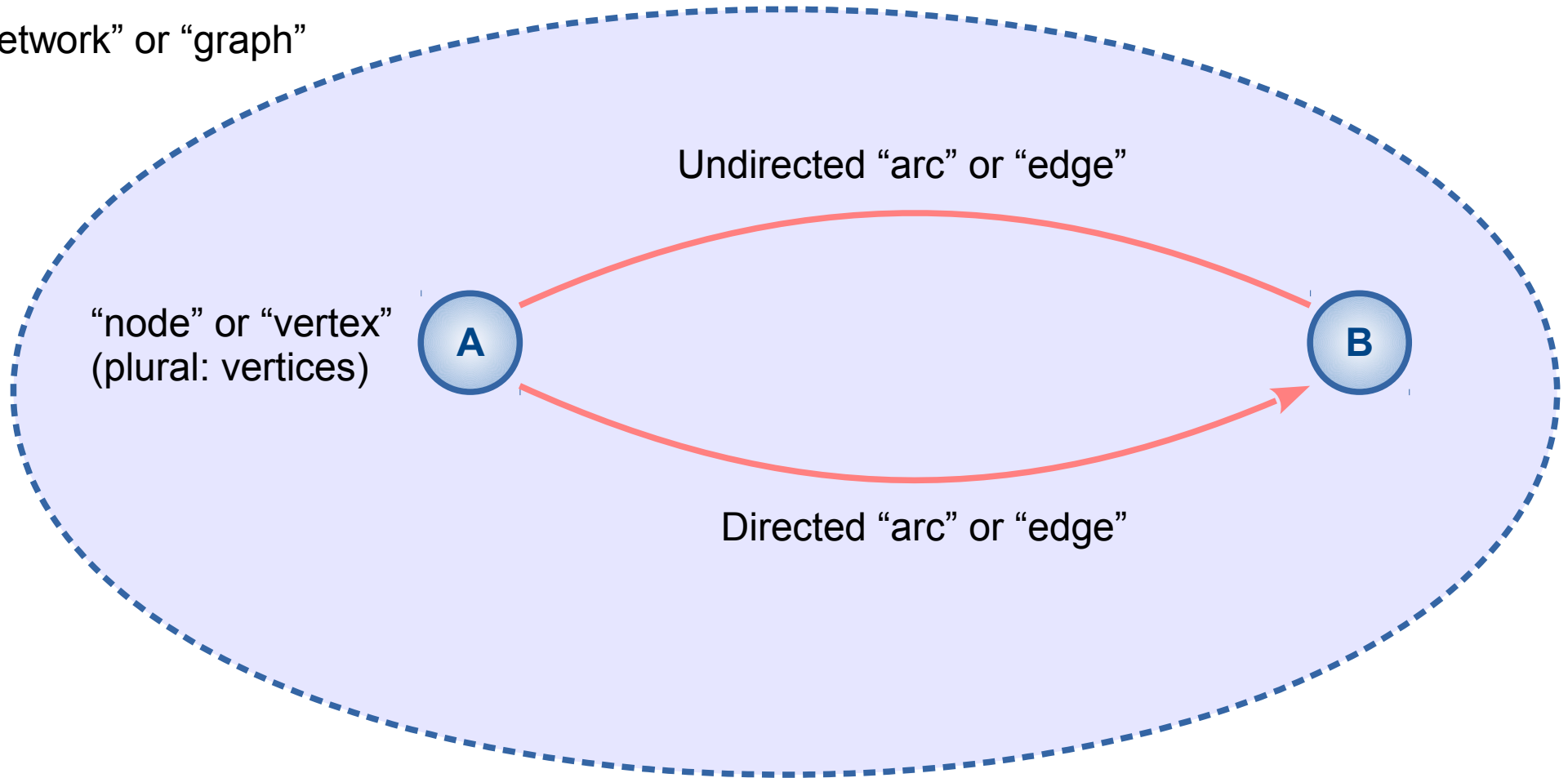
## Ecological network



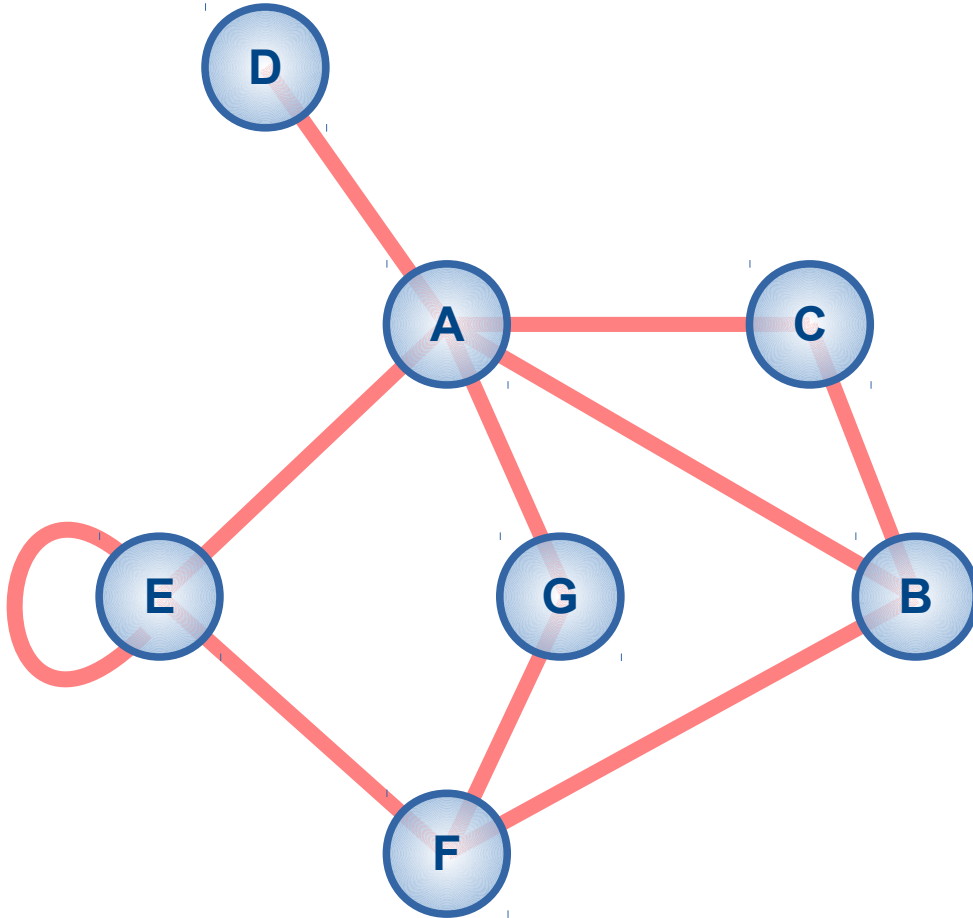
# Analysing Networks

# Definitions

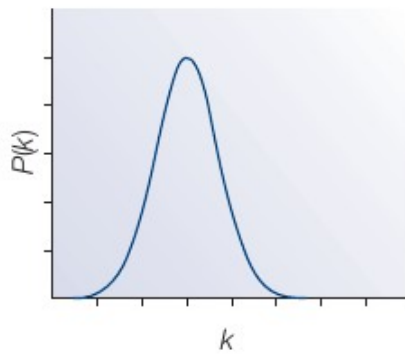
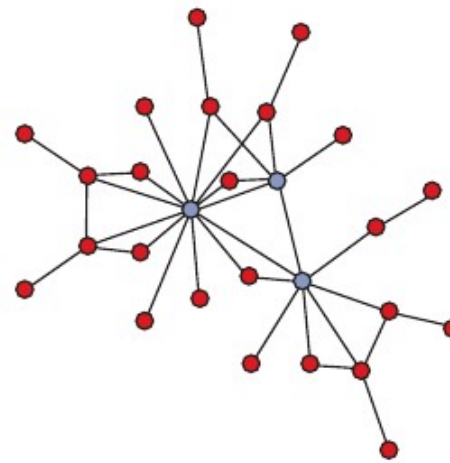
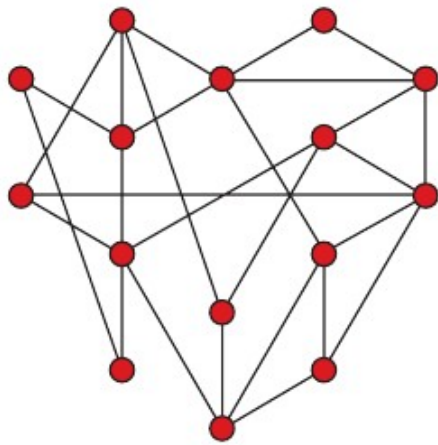
“network” or “graph”



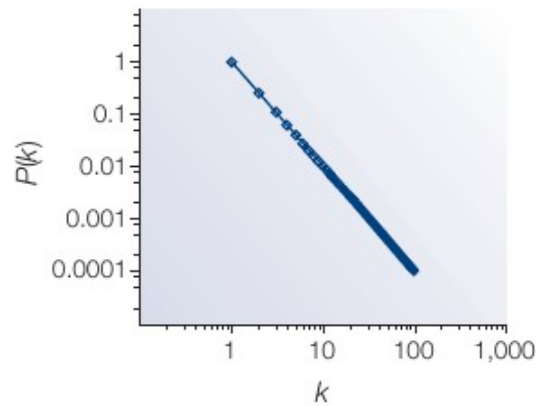
# Node degree (k): number of ending edges



| node | k |
|------|---|
| A    | 5 |
| B    | 3 |
| C    | 2 |
| D    | 1 |
| E    | 4 |
| F    | 3 |
| G    | 2 |

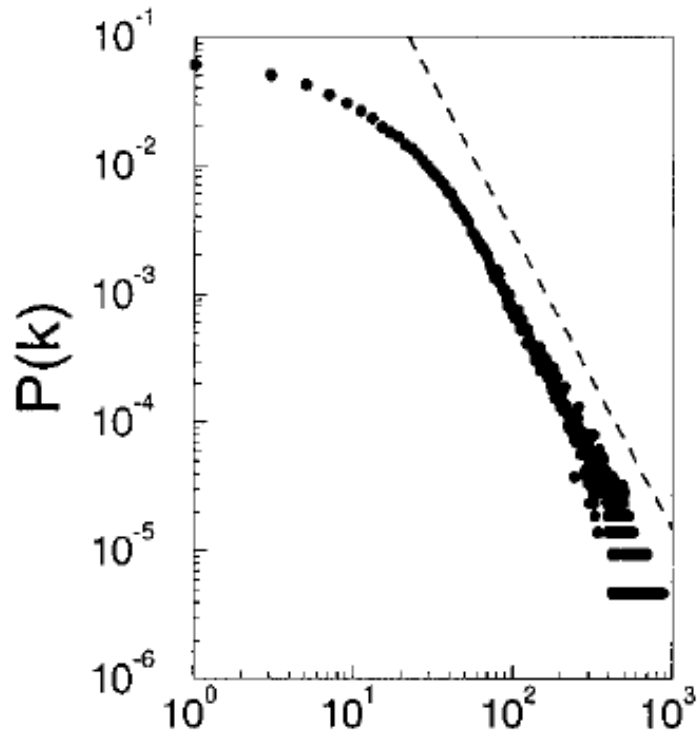


random  
networks  
(Erdős & Rényi)

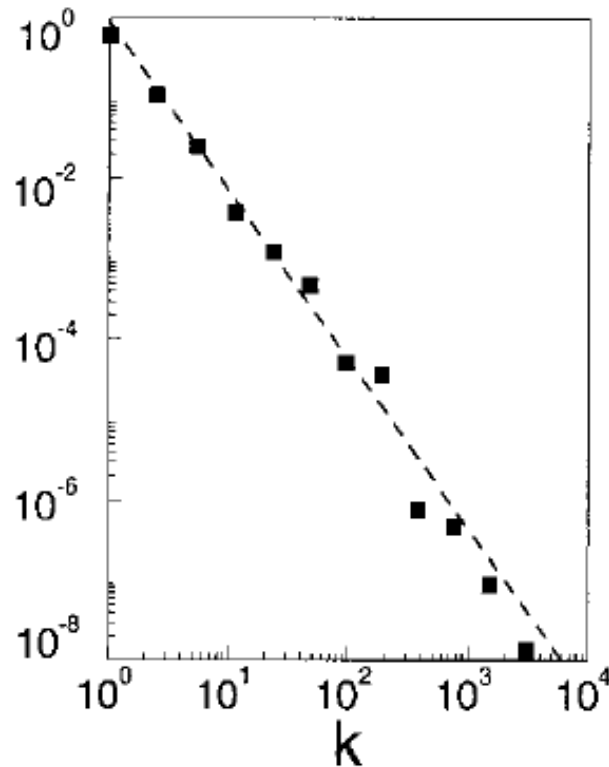


Power law  
networks  
(Barabási & Albert)

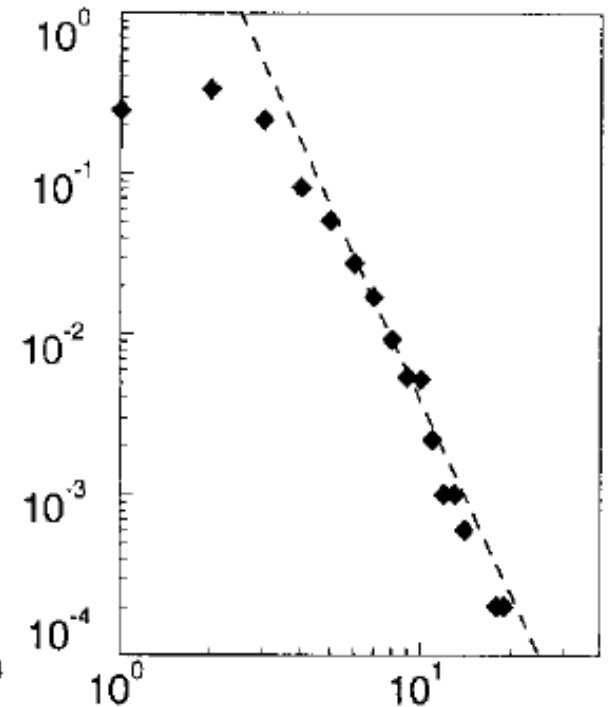
# Examples of power-law networks



Actor  
collaboration

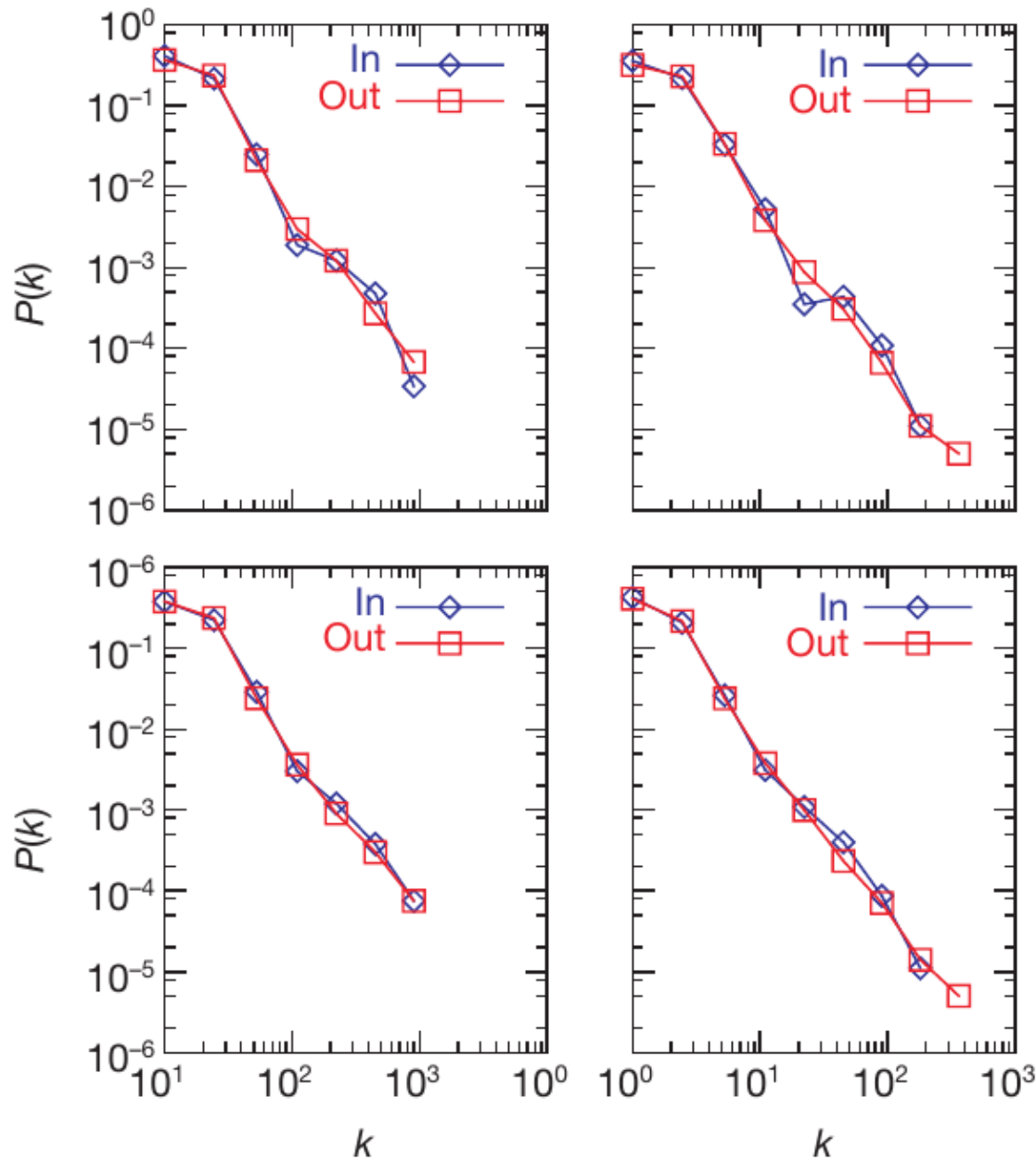


WWW



Power grid

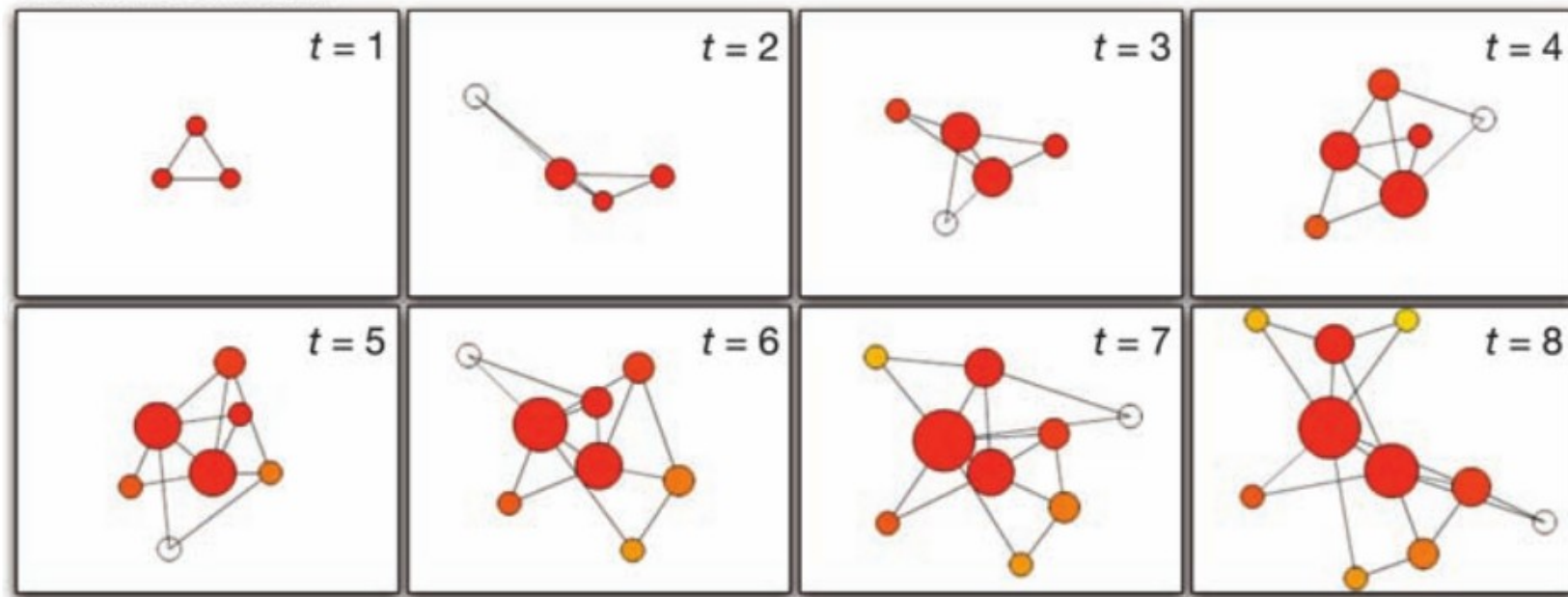
# Metabolic networks are power-law



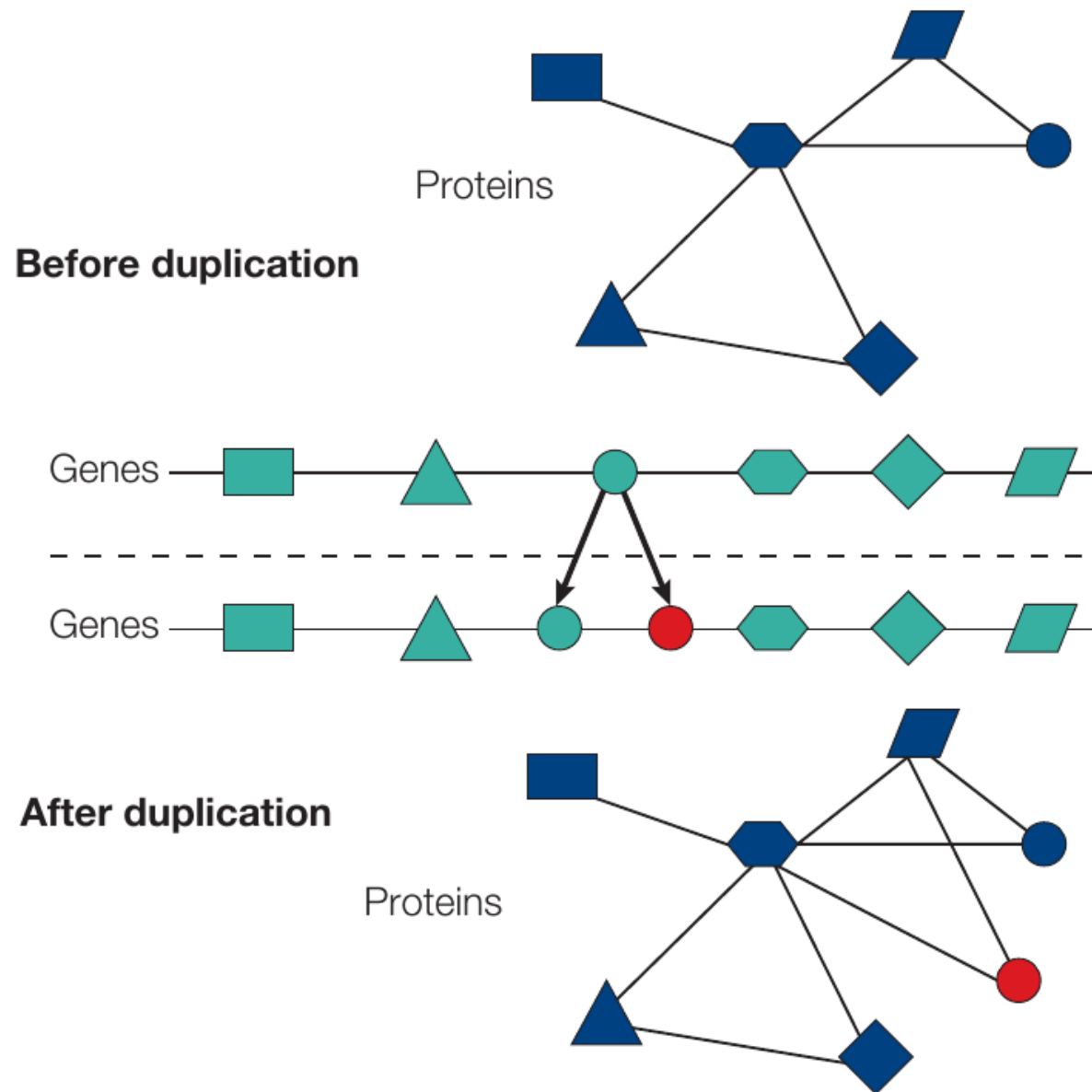
Metabolism of  
different organisms

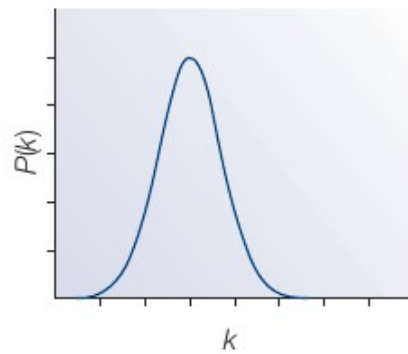
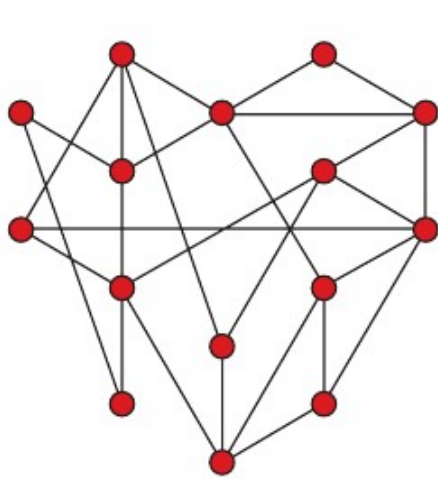
# Creation = random, Evolution = power-law

- Random creation at once:  
Do  $v$  times: pick a node among  $n$ , pick another among the same  
→ random network
- Evolution:  
Repeat until  $n$  nodes: add a new node, link it to existing nodes with a probability depending on their existing degree  
→ power-law network

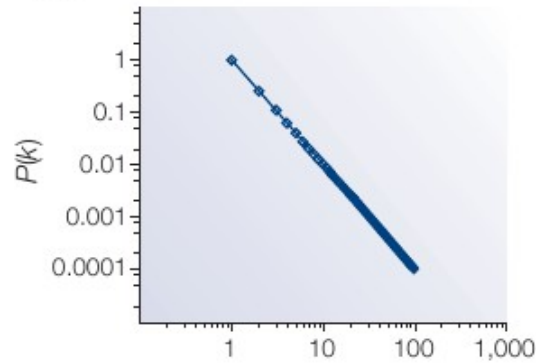
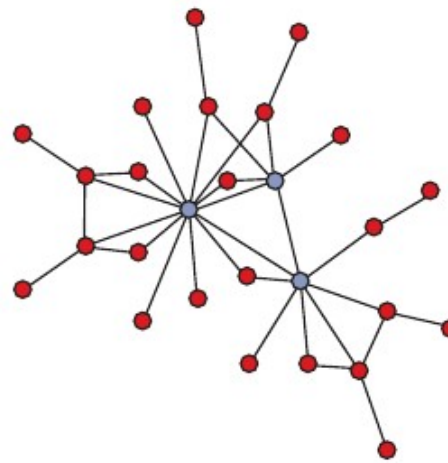


# Gene duplications and power-law interactomes

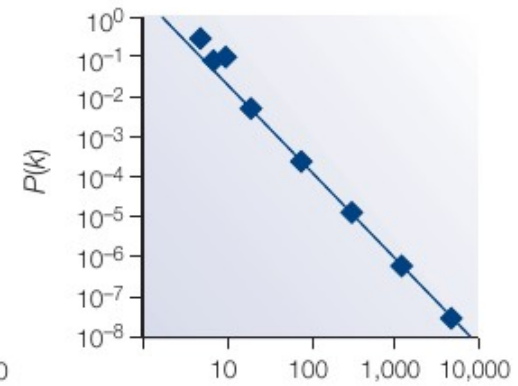
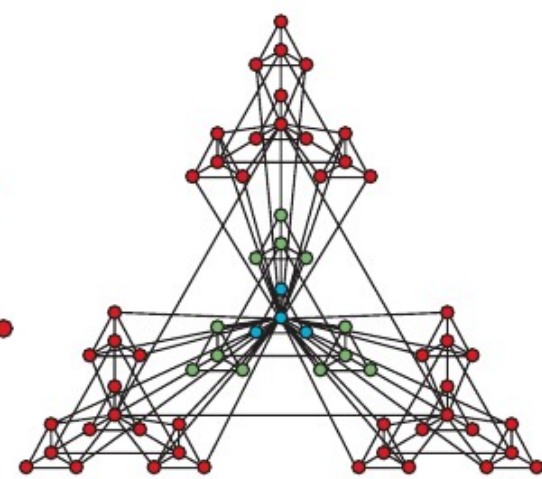




Random networks

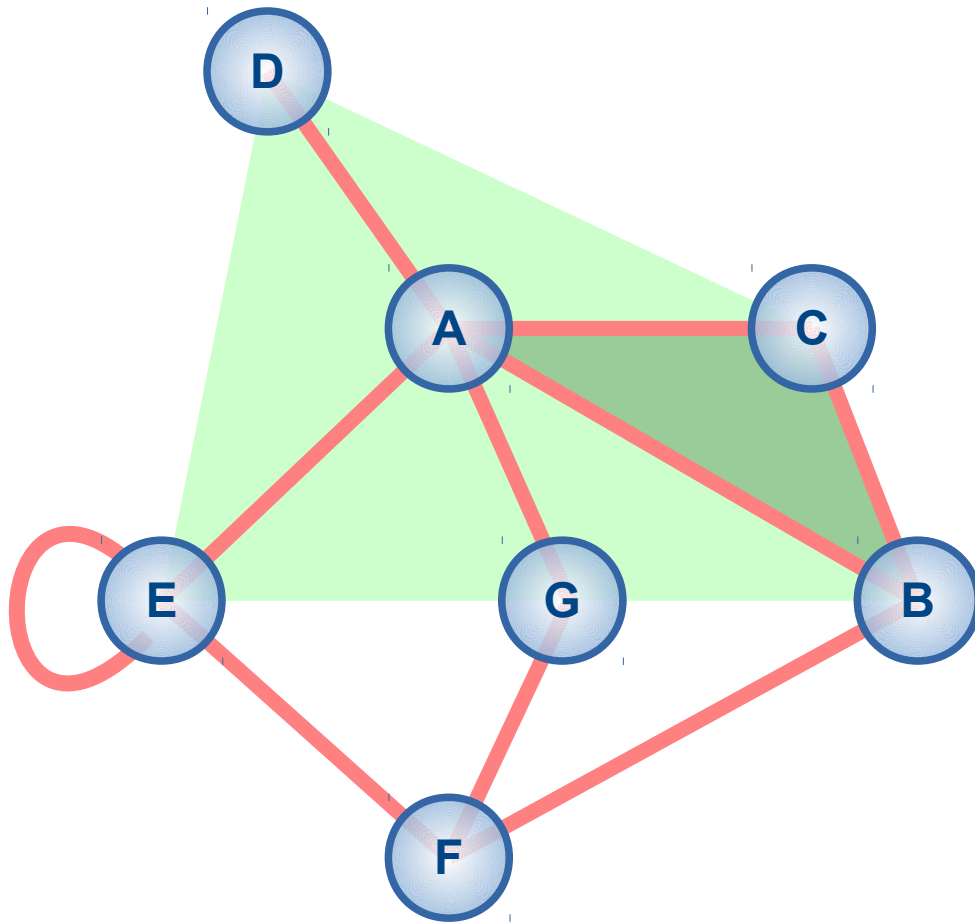


Power law networks

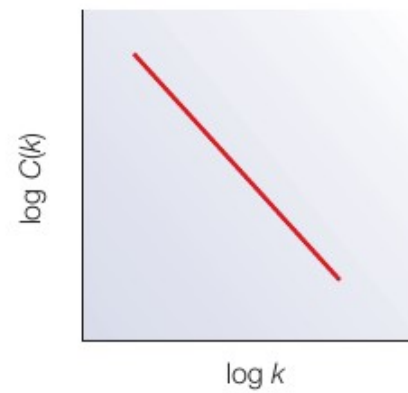
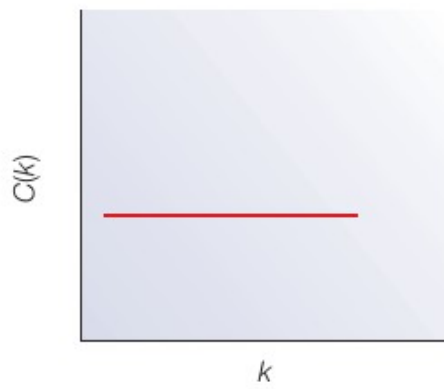
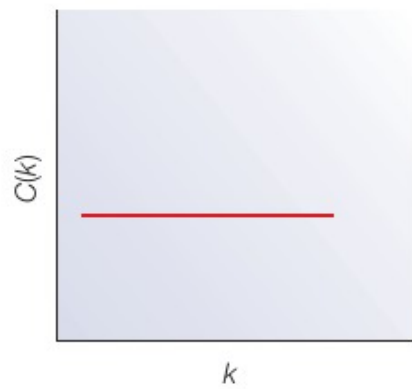
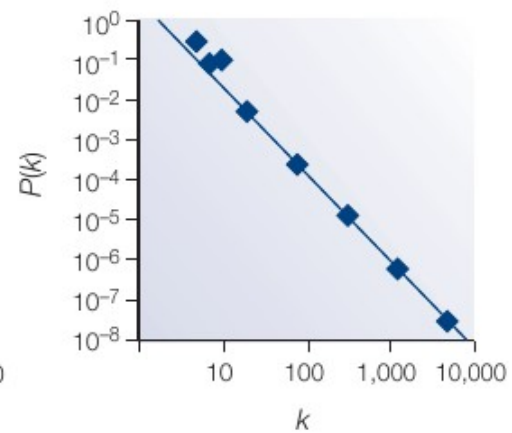
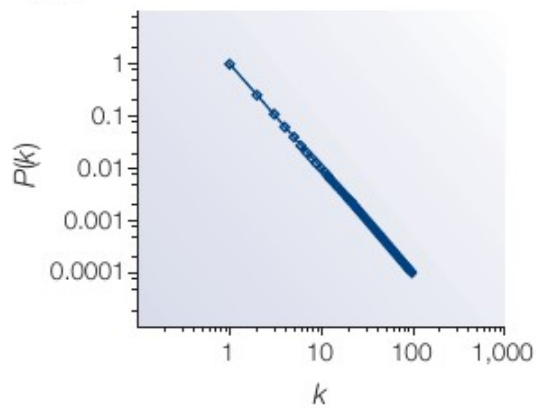
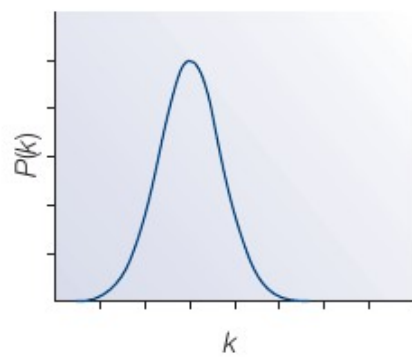
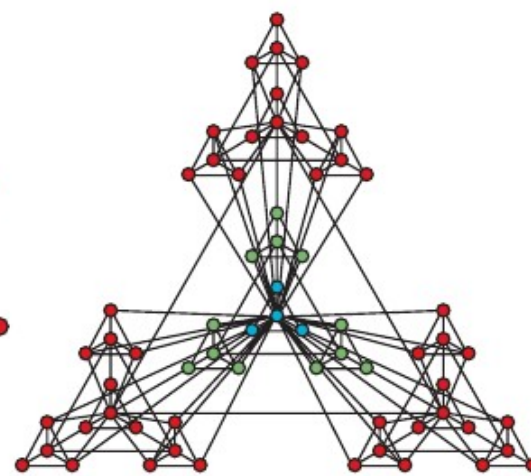
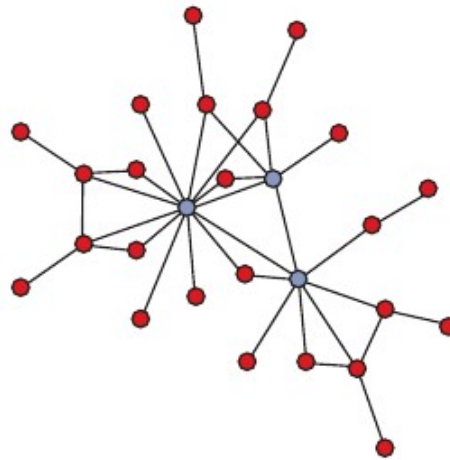
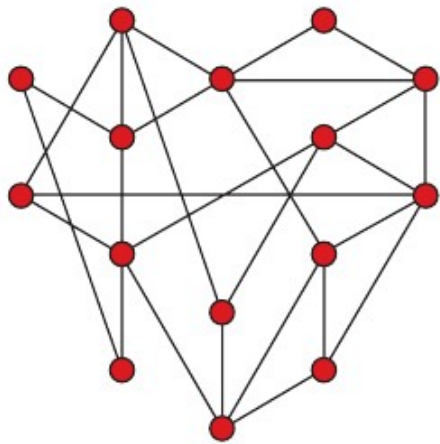


Hierarchical networks

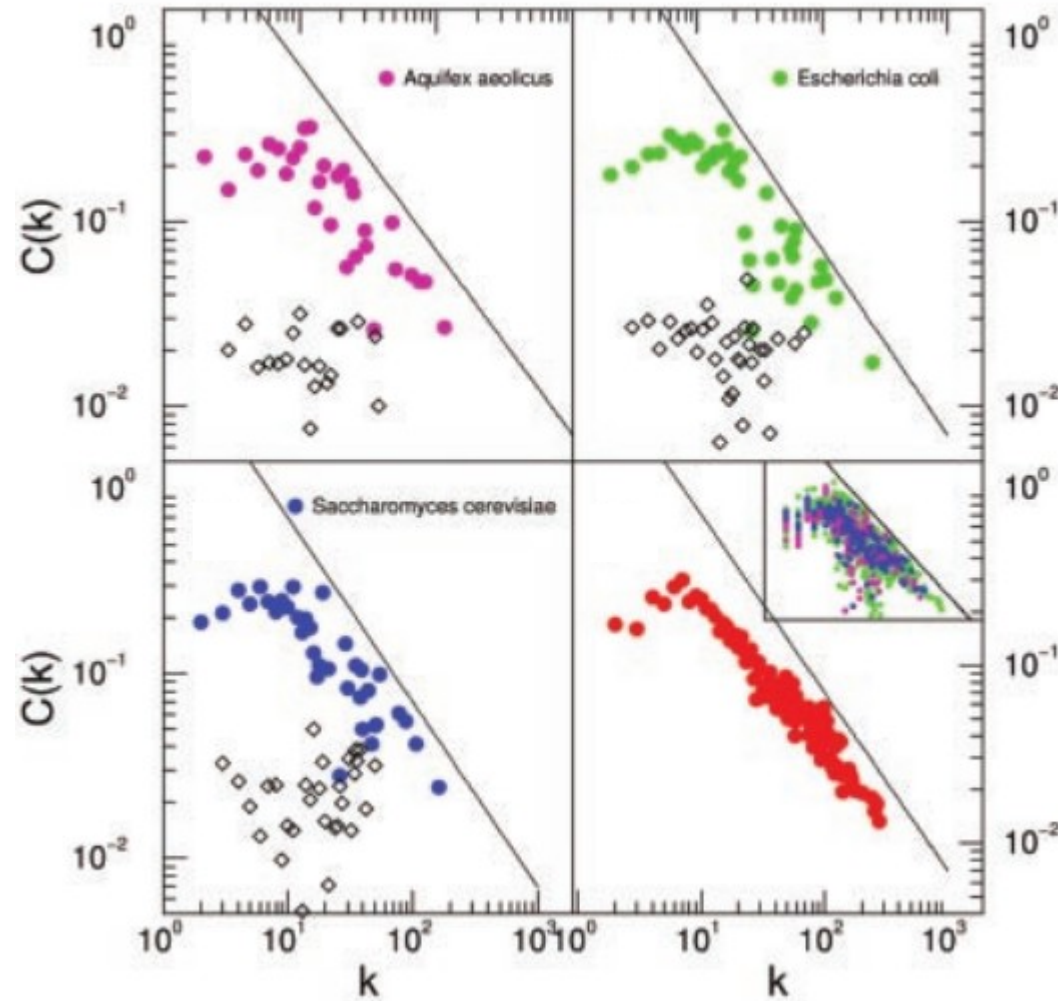
# Clustering (C): Proportion of possible cliques



| node | k | C    |
|------|---|------|
| A    | 5 | 0.1  |
| B    | 3 | 0.33 |
| C    | 2 | 1    |
| D    | 1 | 0    |
| E    | 4 | 0    |
| F    | 3 | 0    |
| G    | 2 | 0    |

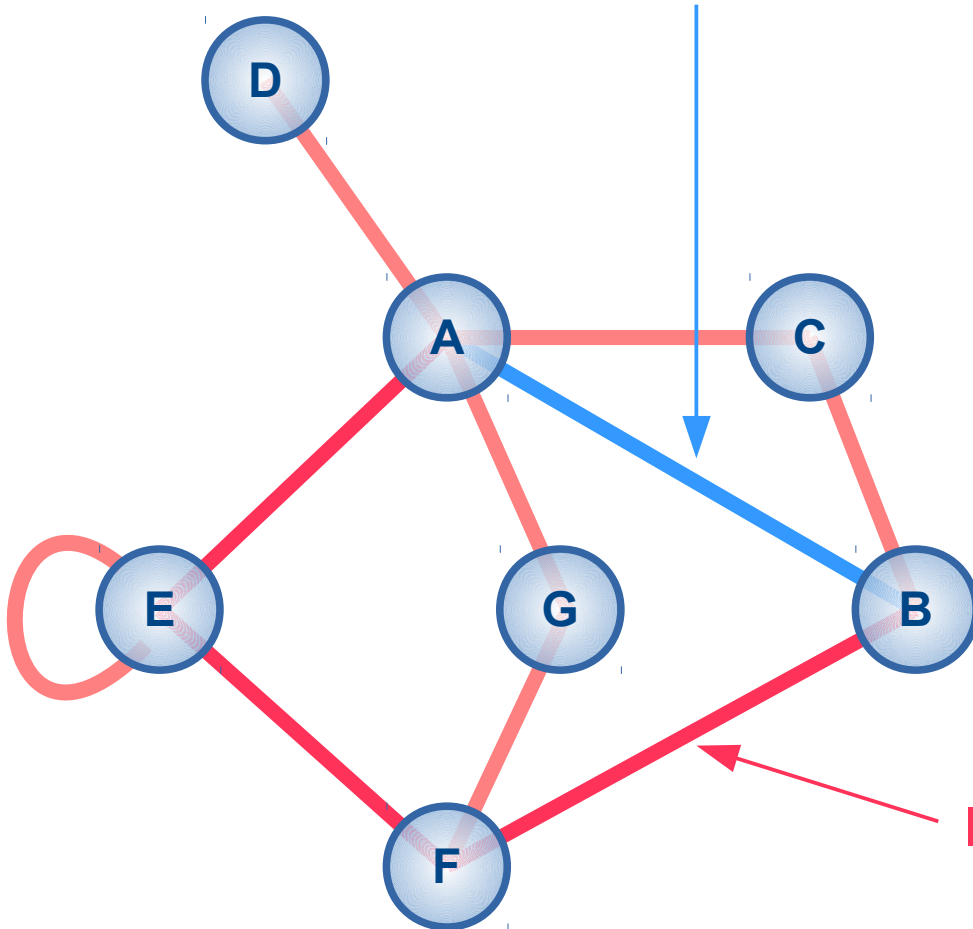


# Metabolic networks are hierarchical



# Shortest path (<SP>)

shortest path between A and B



| node | k | C    | <SP>  |
|------|---|------|-------|
| A    | 5 | 0.1  | 1.167 |
| B    | 3 | 0.33 | 1.5   |
| C    | 2 | 1    | 1.67  |
| D    | 1 | 0    | 2     |
| E    | 4 | 0    | 1.67  |
| F    | 3 | 0    | 1.67  |
| G    | 2 | 0    | 1.67  |

longest path between A and B

# Example of shortest path: Erdős number

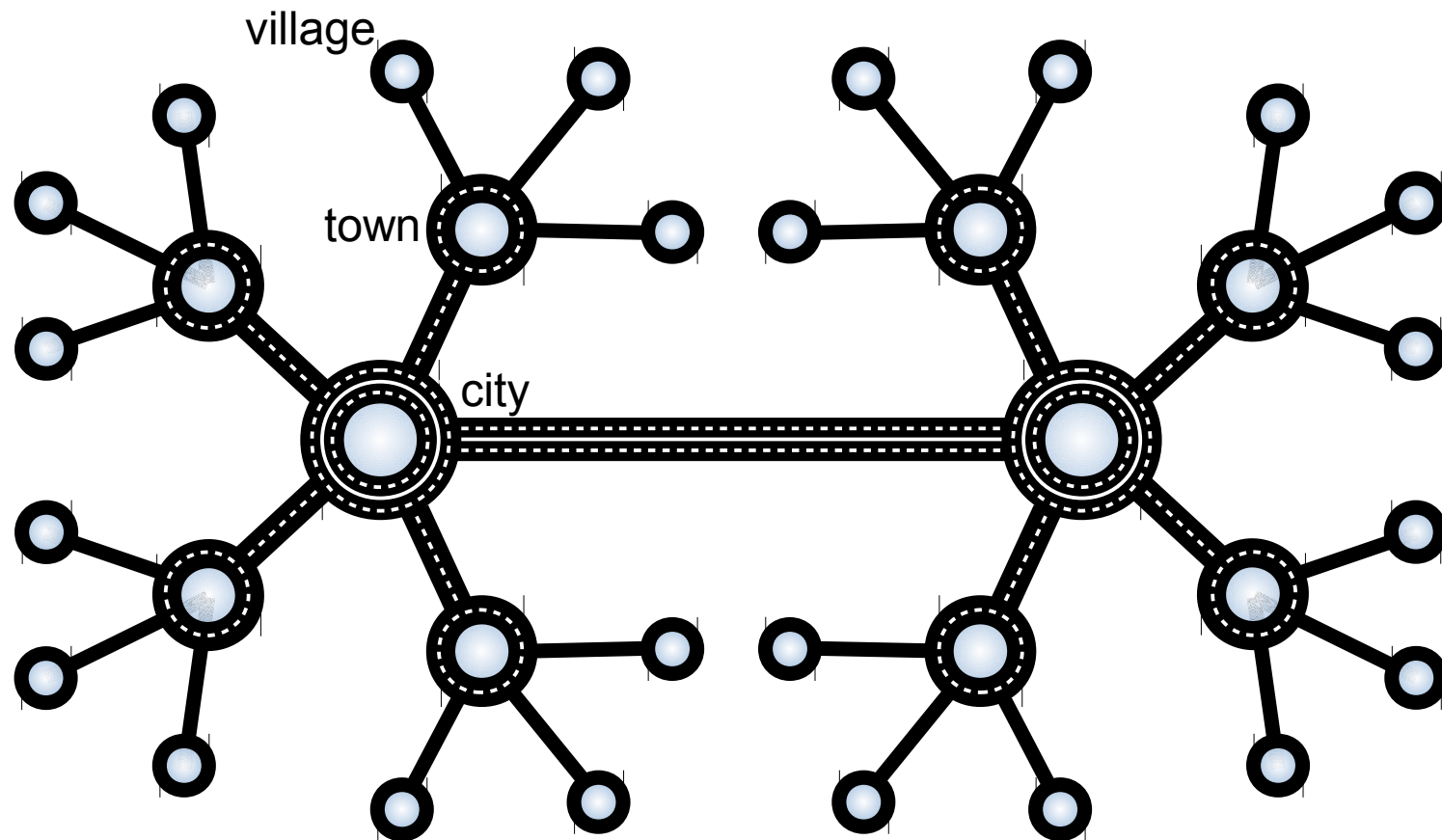


- 13 Field medals with  $E_n=2$
- 2 Nobel Physics with  $E_n=2$ , 14 with  $E_n=3$
- 4 Nobel Chemistry with  $E_n=3$
- 3 Nobel Medicine with  $E_n=3$
- 1 Nobel Economy with  $E_n=2$ . 8 with  $E_n=3$
- My Erdős number is 4

(Le Novère – Doyle – Boyd – Diaconis – Erdős  
Le Novère – Sauro – Nadim – Salamon - Erdős)

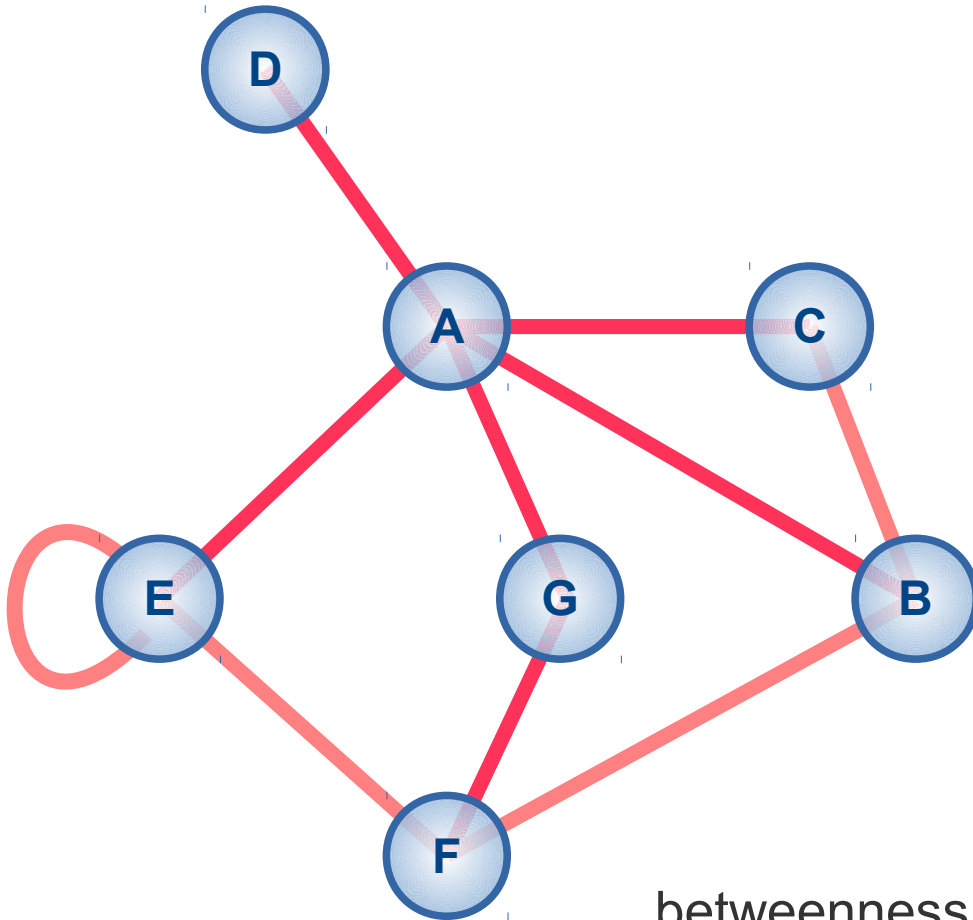


# Power law often = small-world



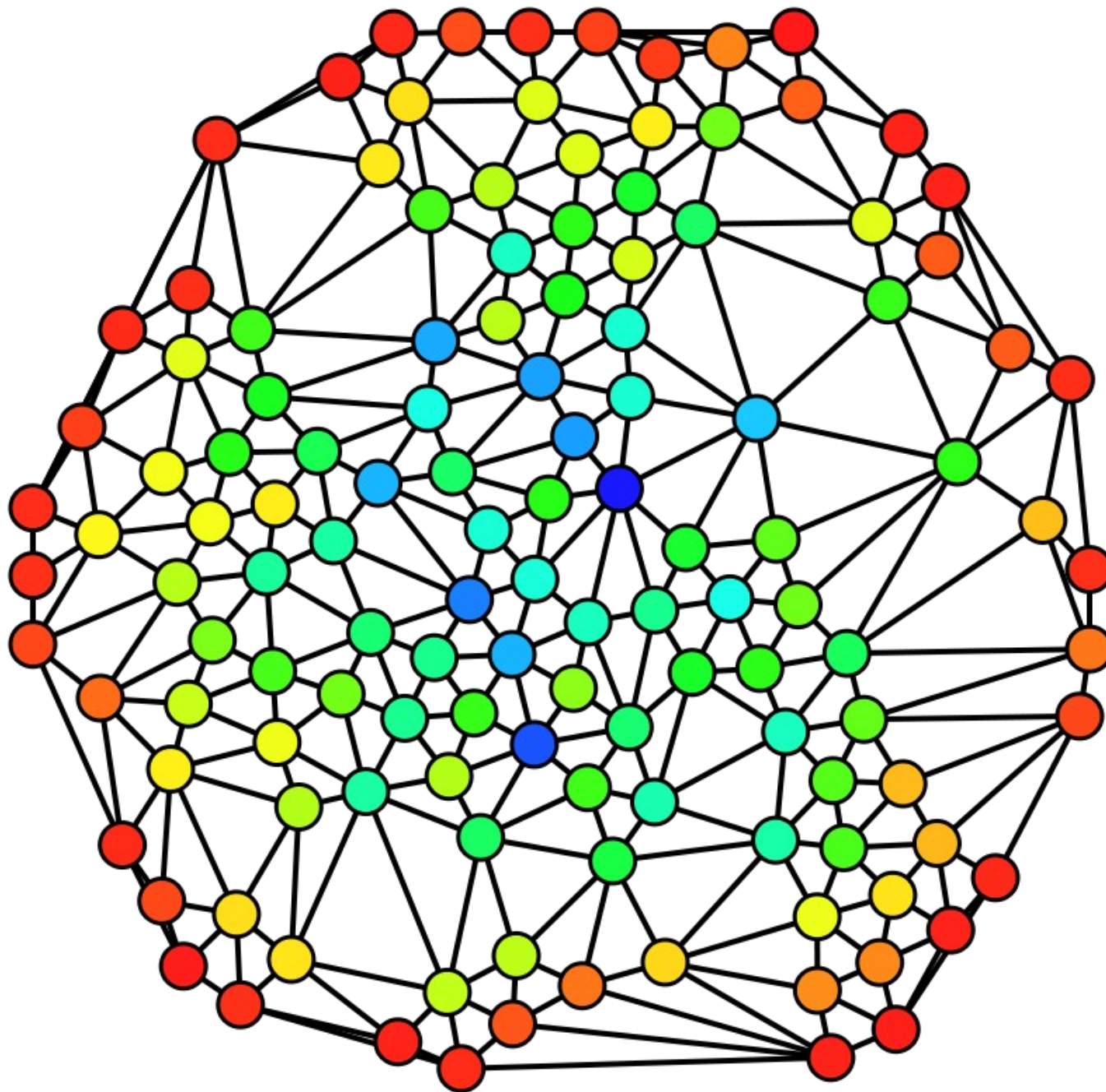
The perfect road system

# Betweenness centrality (Cb)

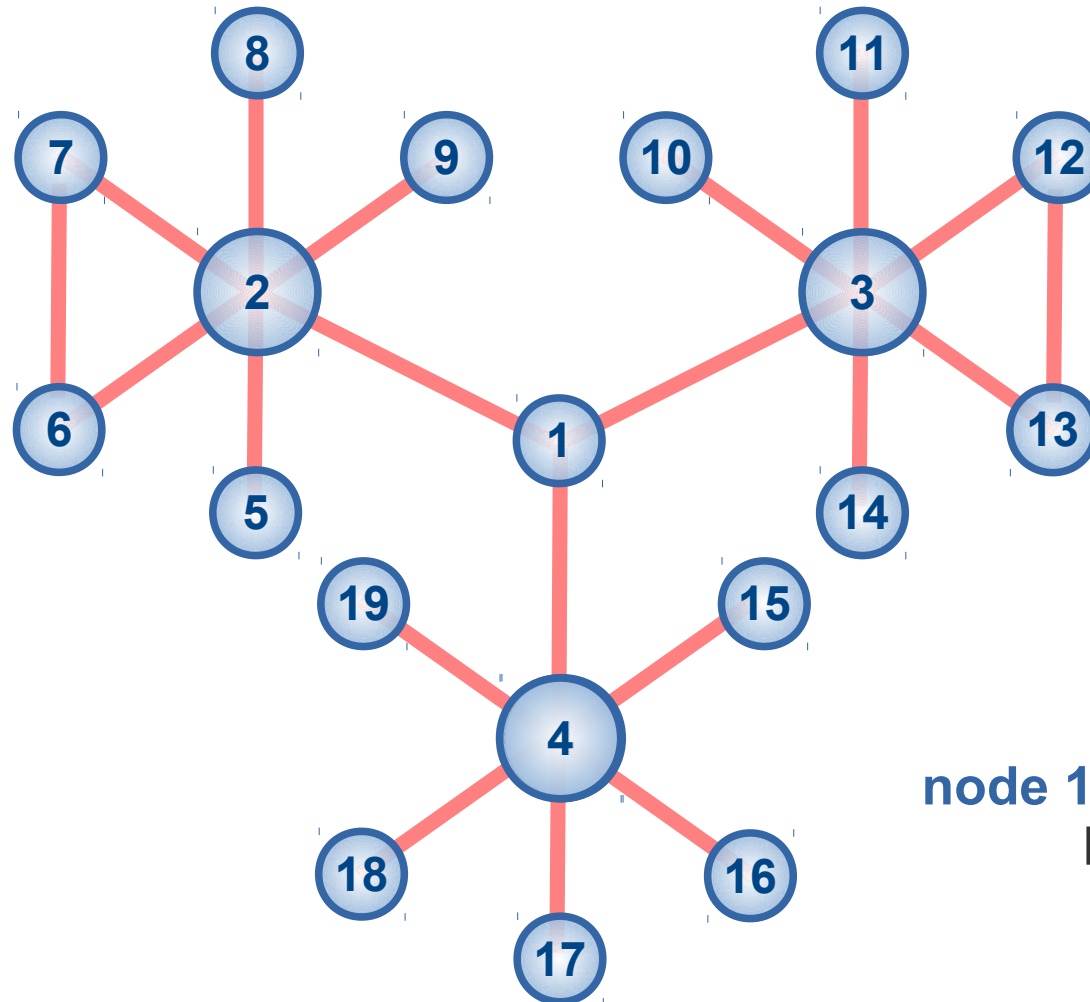


| node | k | C    | <SP>  | Cb    |
|------|---|------|-------|-------|
| A    | 5 | 0.1  | 1.167 | 0.567 |
| B    | 3 | 0.33 | 1.5   | 0.111 |
| C    | 2 | 1    | 1.67  | 0     |
| D    | 1 | 0    | 2     | 0     |
| E    | 4 | 0    | 1.67  | 0.044 |
| F    | 3 | 0    | 1.67  | 0.1   |
| G    | 2 | 0    | 1.67  | 0.044 |

betweenness = fraction of encountered shortest paths



# No need to be highly connected to be important



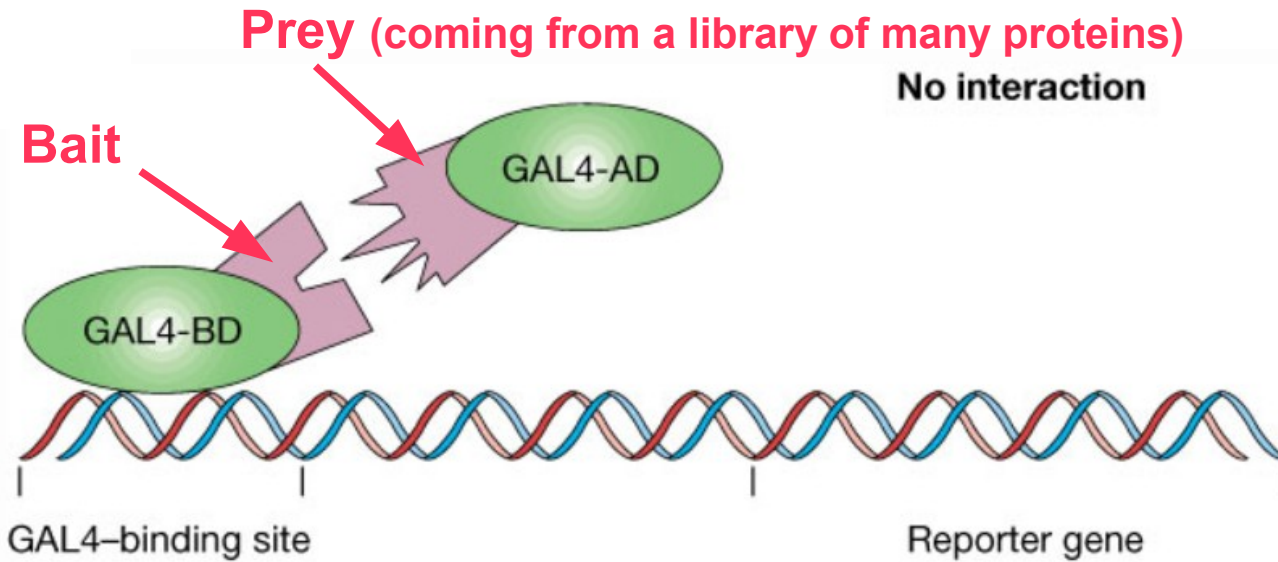
**node 1** has low degree, low clustering  
but largest betweenness

# Reconstructing networks

# Pre-existing knowledge



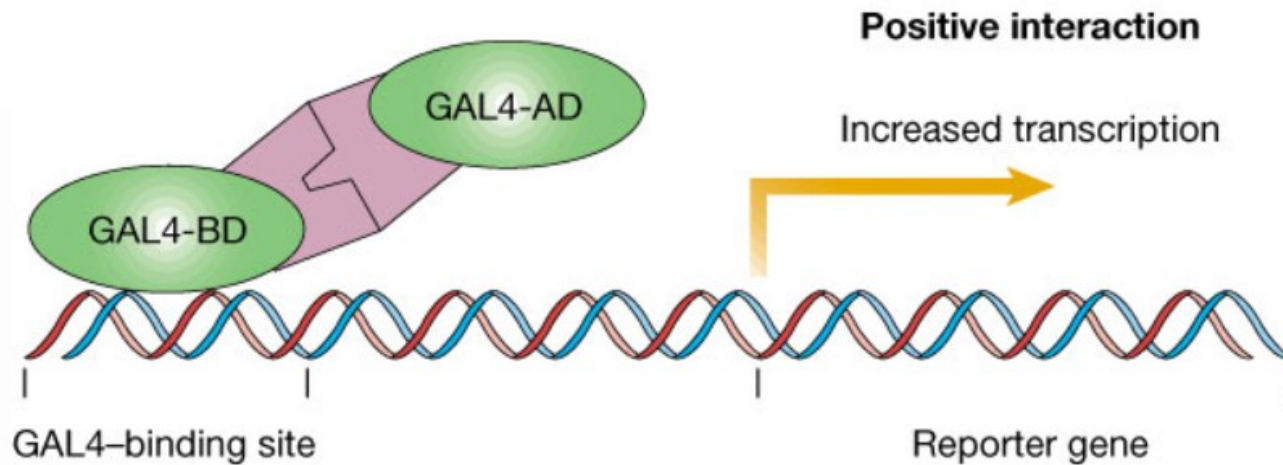
# observations: yeast two hybrid system



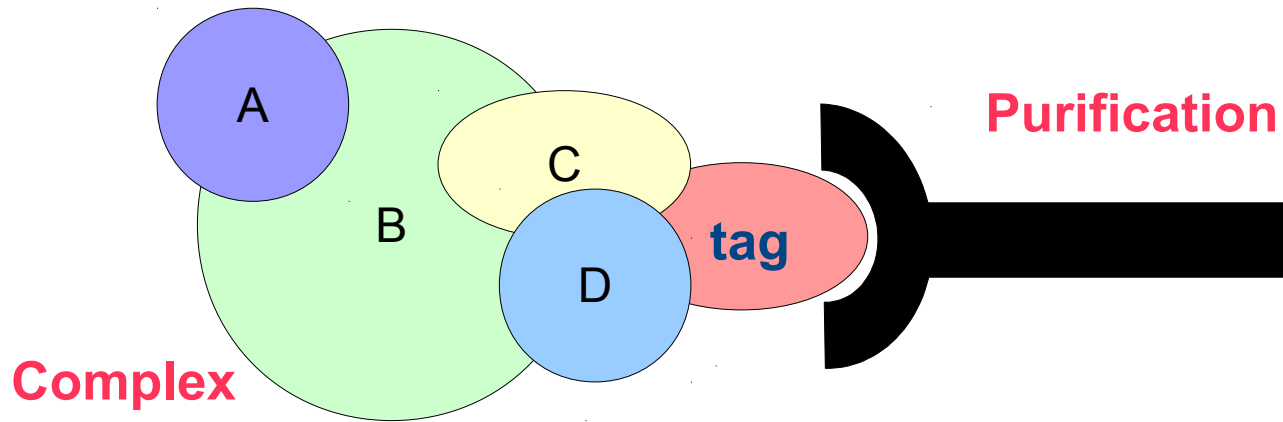
**Direct physical interactions**



**All possible interactions (may never actually occur)**

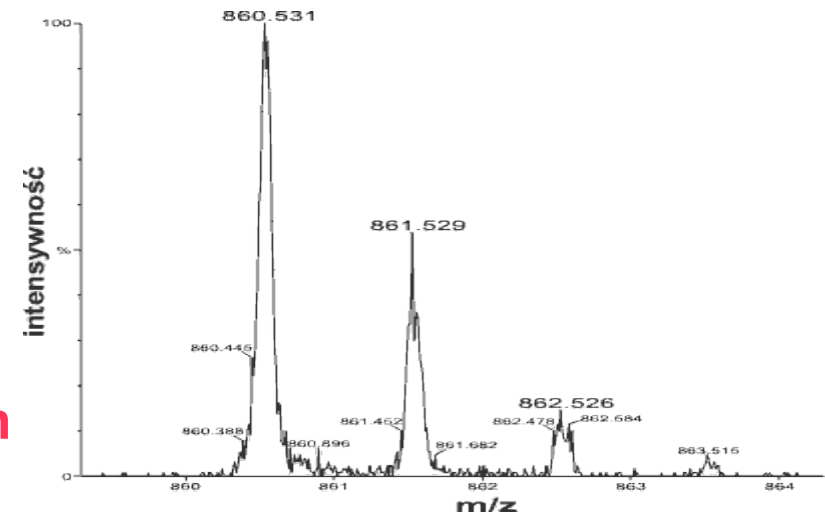
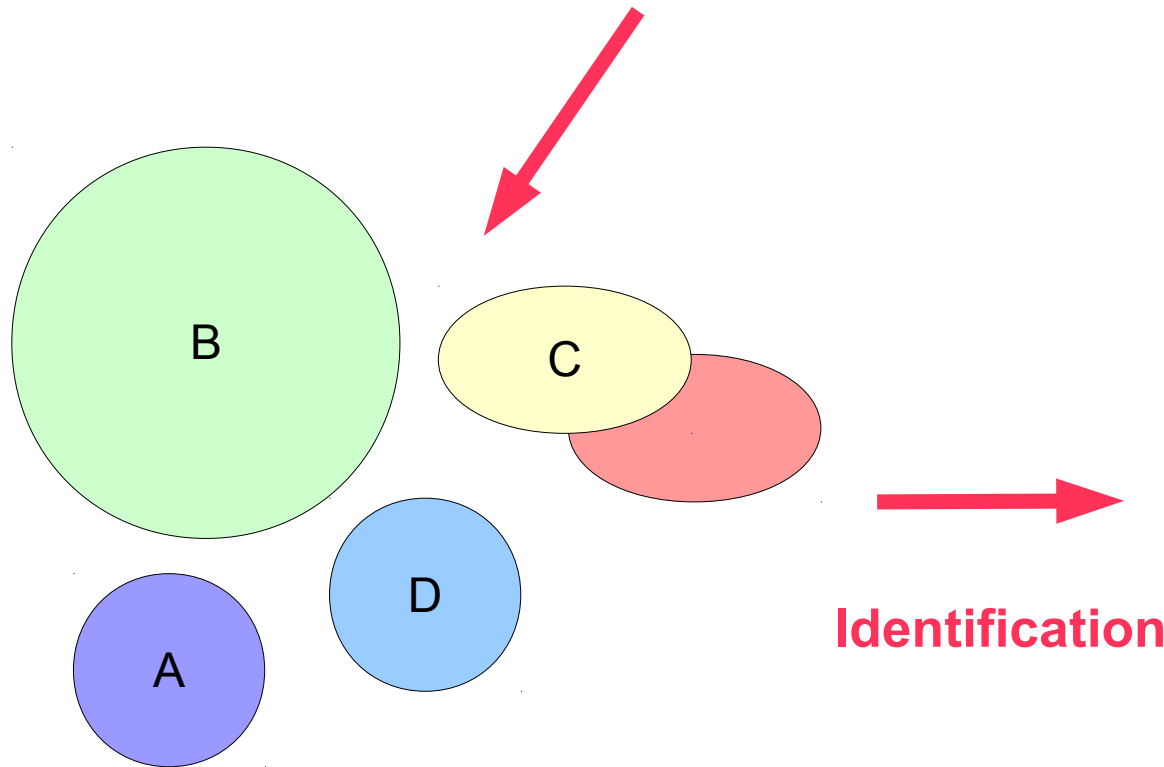


# observations: protein complex precipitation

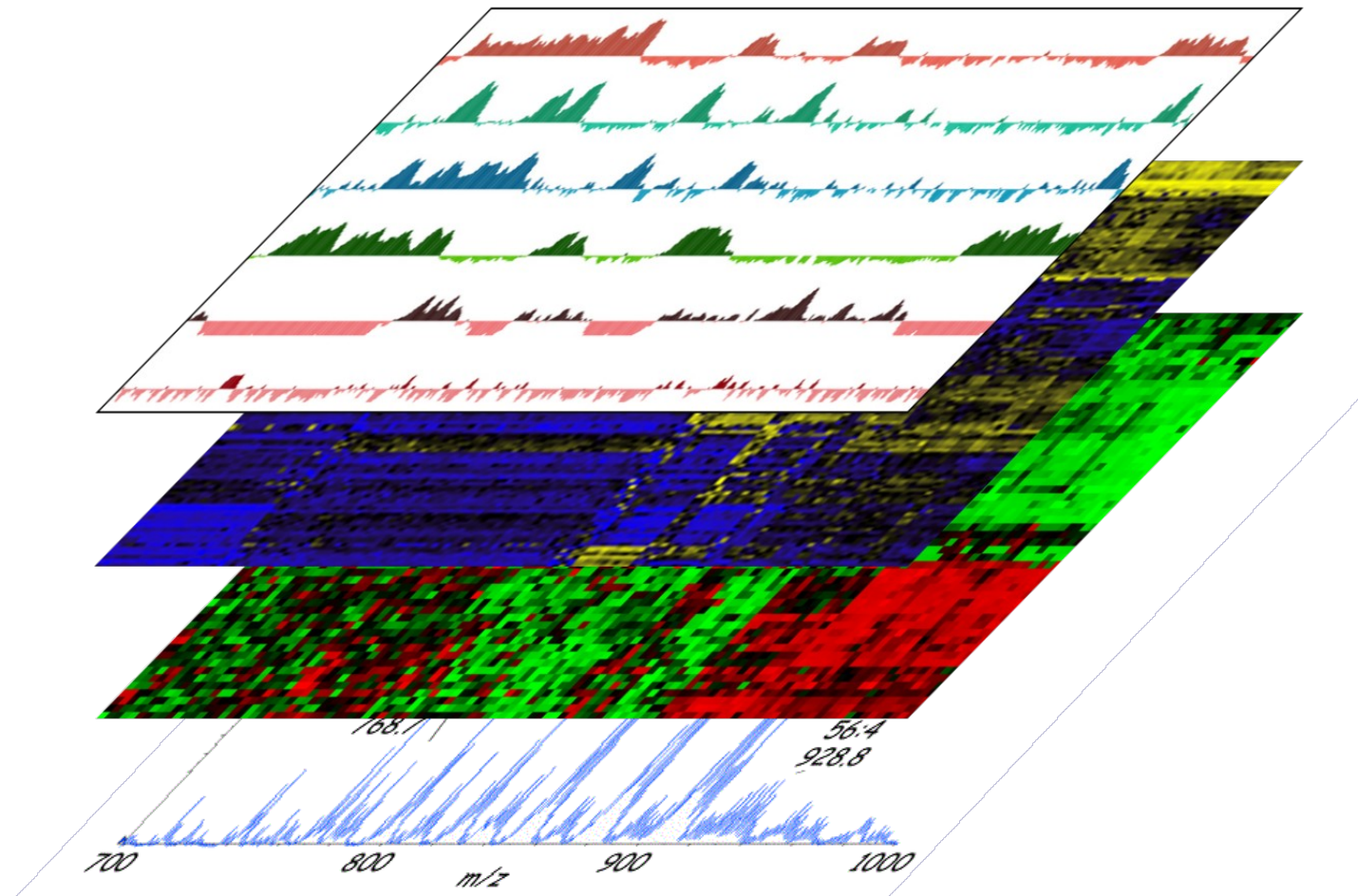


✓  
actual complex

✗  
not direct  
interactions  
(A-C and B-C  
wrongly predicted)

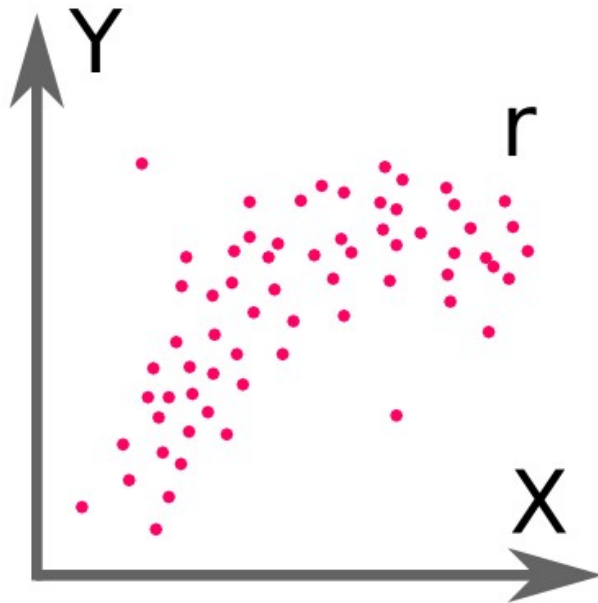


# network inference from data



# Network inference (1): correlation

e.g. **linear regression**



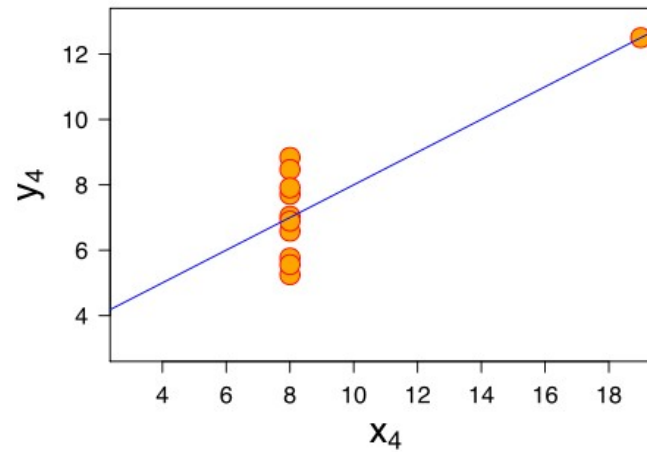
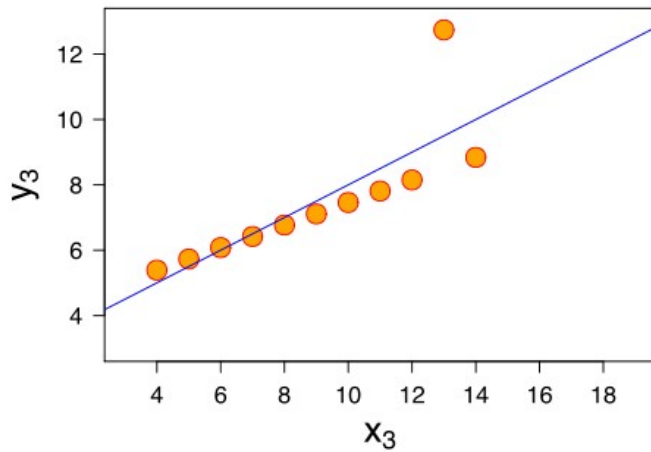
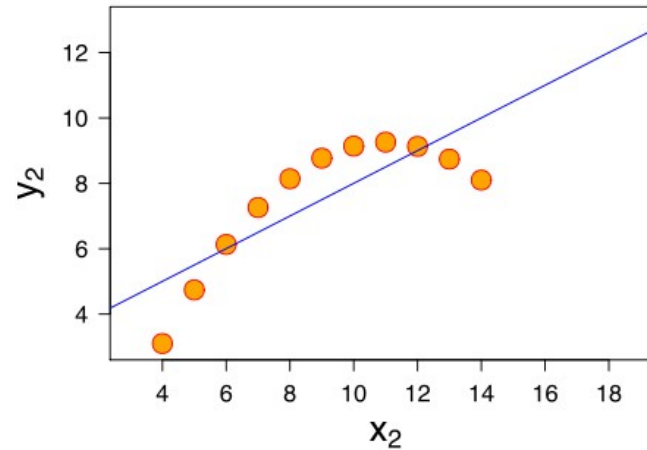
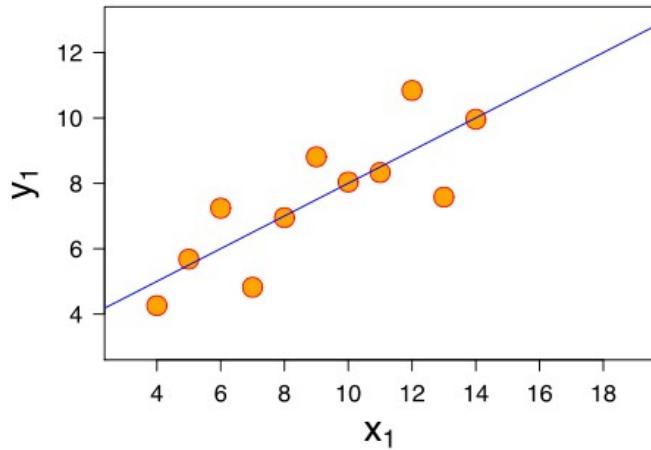
$1 > r > 0$  Values of X are somewhat positively related to values of Y

$-1 > r > 0$  Values of X are somewhat negatively related to values of Y

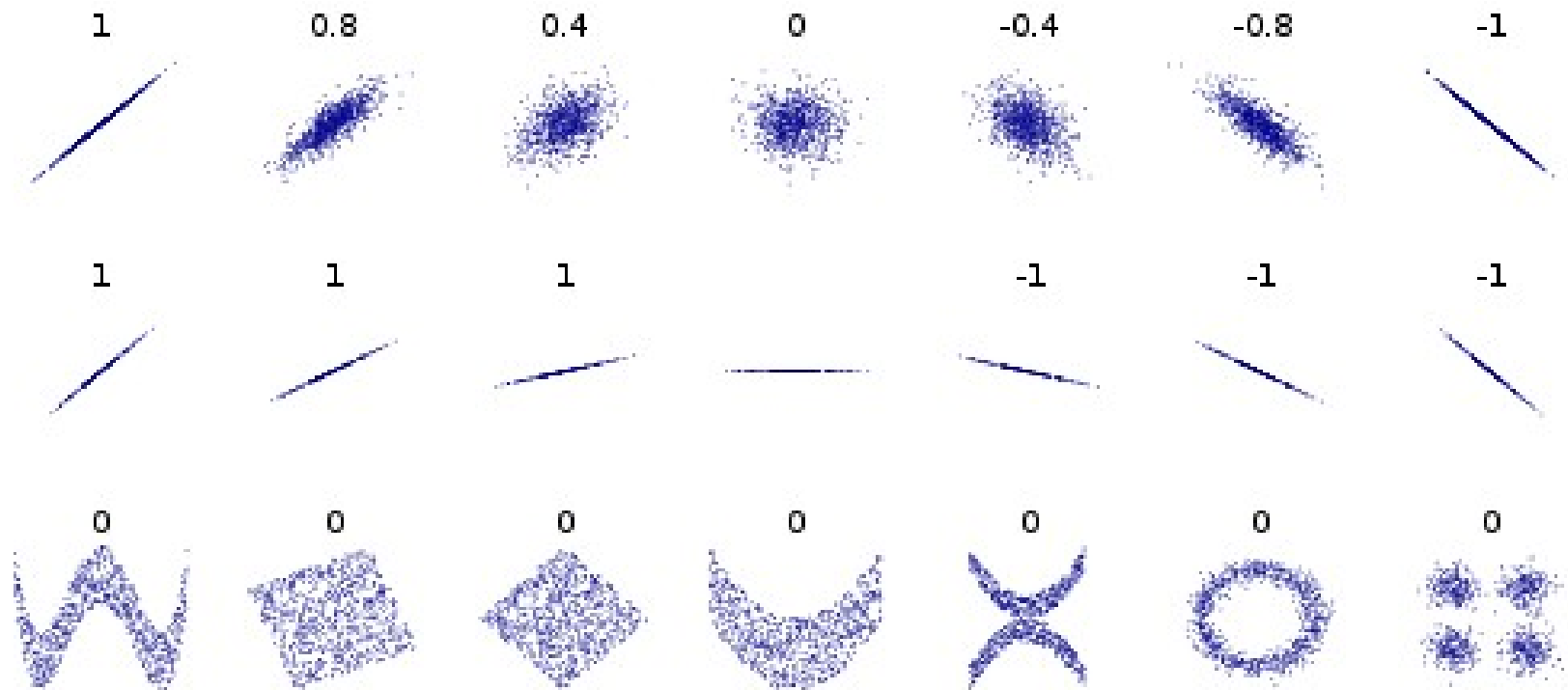
$r \approx 0$  Values of X are not related to values of Y

$$r = \frac{\sum_{i=1}^n (X_i - \bar{X})(Y_i - \bar{Y})}{\sqrt{\sum_{i=1}^n (X_i - \bar{X})^2} \sqrt{\sum_{i=1}^n (Y_i - \bar{Y})^2}}$$

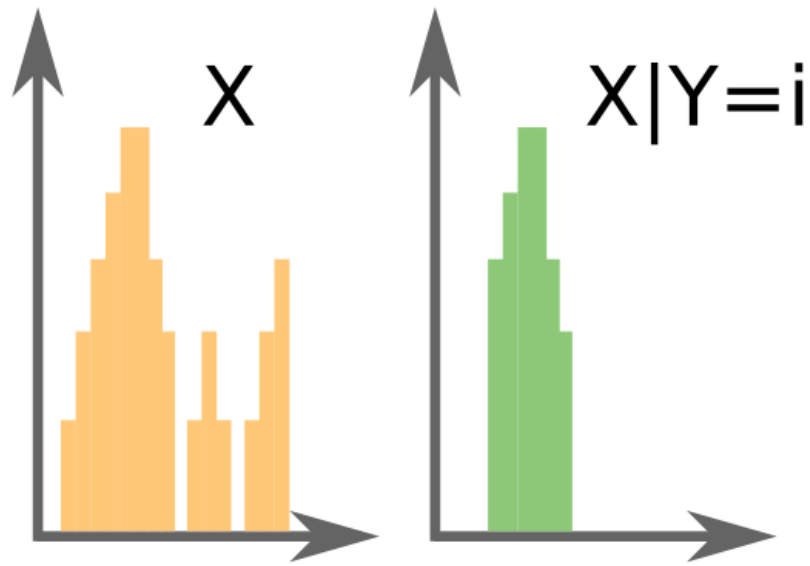
# Correlation does not tell nature or relation



# Correlations might not be linear



## Network inference (2): information theory



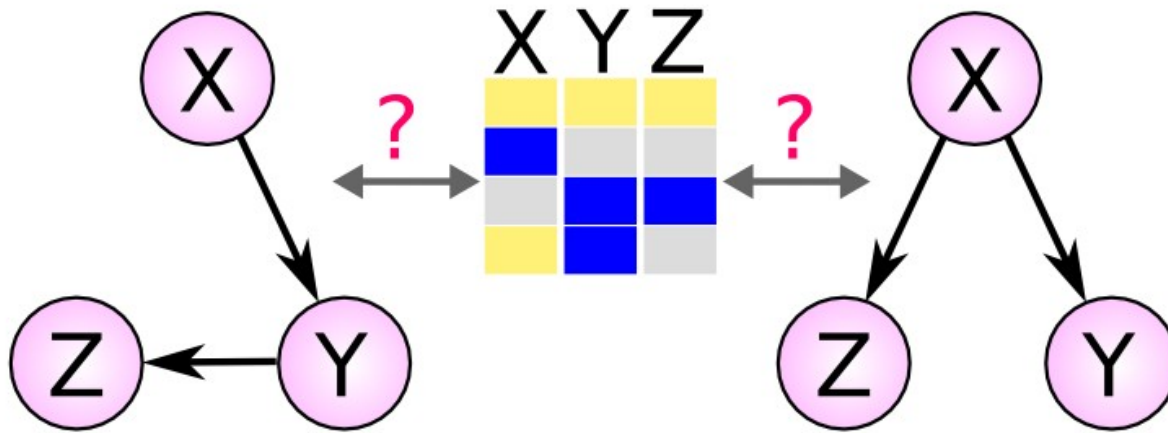
$$I(X, Y) = H(X) - H(X|Y)$$

e.g. **Mutual information**

Fix the value of  $Y$ . Look at the corresponding values of  $X$ . Does the knowledge of  $Y$  reduce the uncertainty on the values of  $X$ ?

If yes, then  $X$  and  $Y$  are linked

## Network inference (3): Bayes

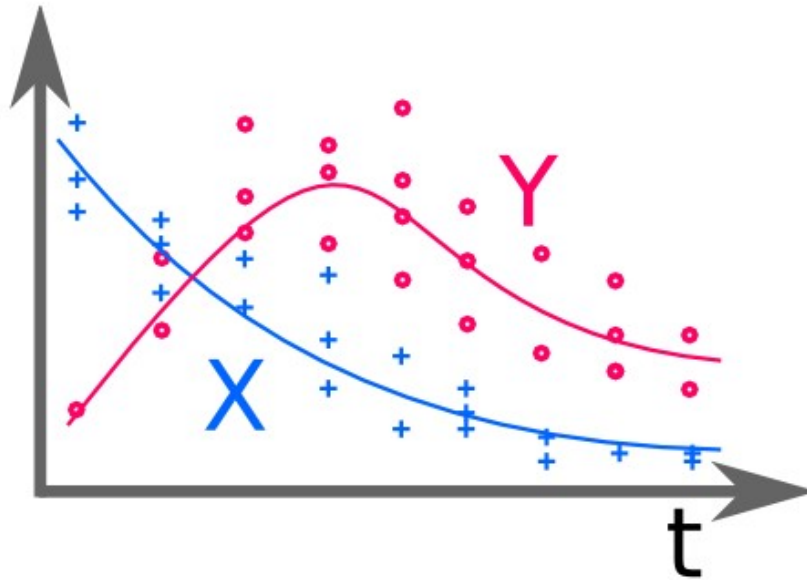


$$P(X|Y) = \frac{P(Y|X)P(X)}{P(Y)}$$

Bayesian inference

Which is the network that most probably generated this dataset.

# Network inference (4): temporal model



Ordinary Differential Equations

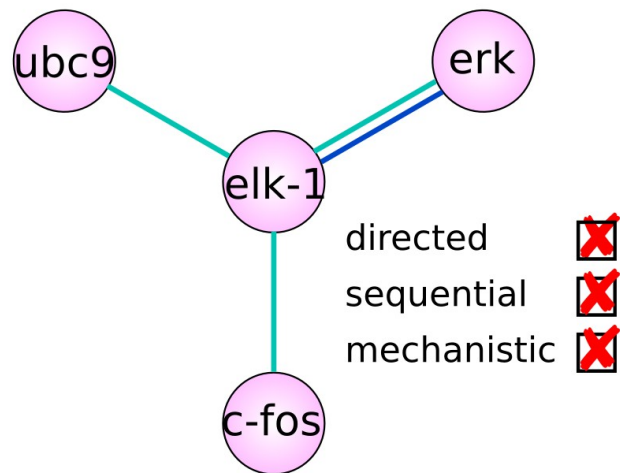
Equations best describing  
observed time courses

$$\frac{dx_i}{dt} = \sum_{j=1}^n a_{i,j} x_j$$

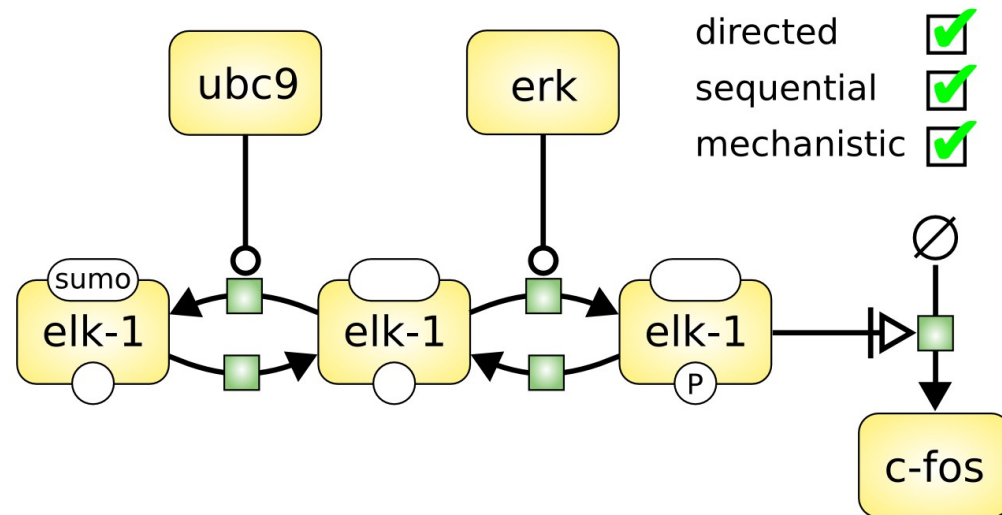
# Biochemical Networks

# Four types of (incompatible) networks

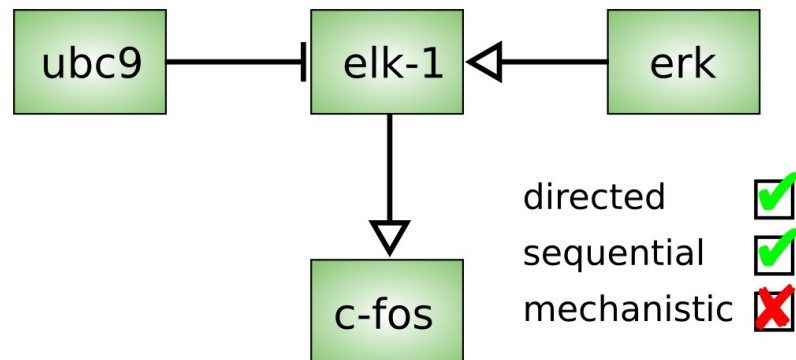
## interaction network



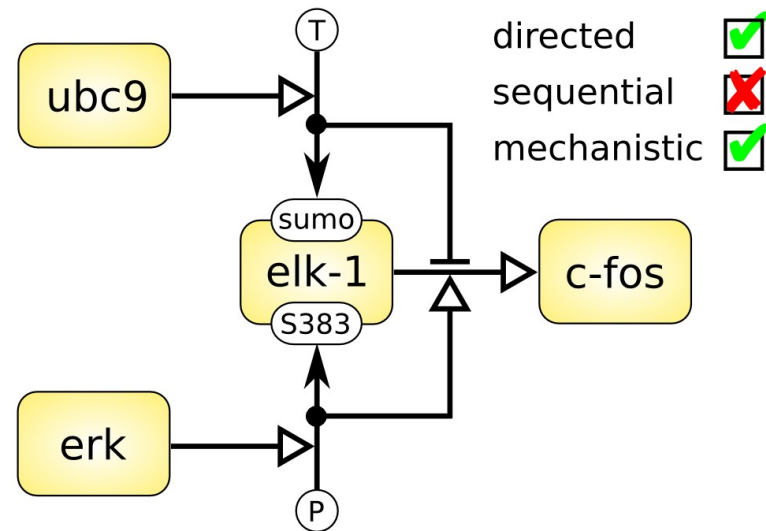
## process descriptions



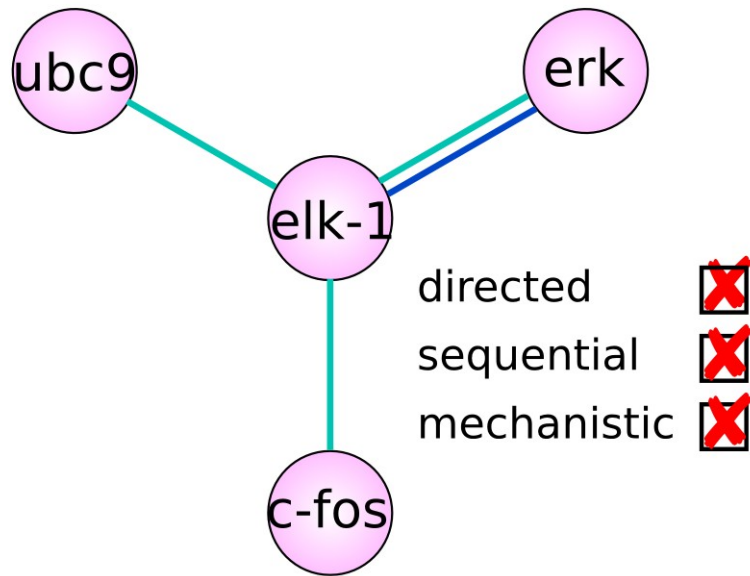
## activity flows



## entity relationships

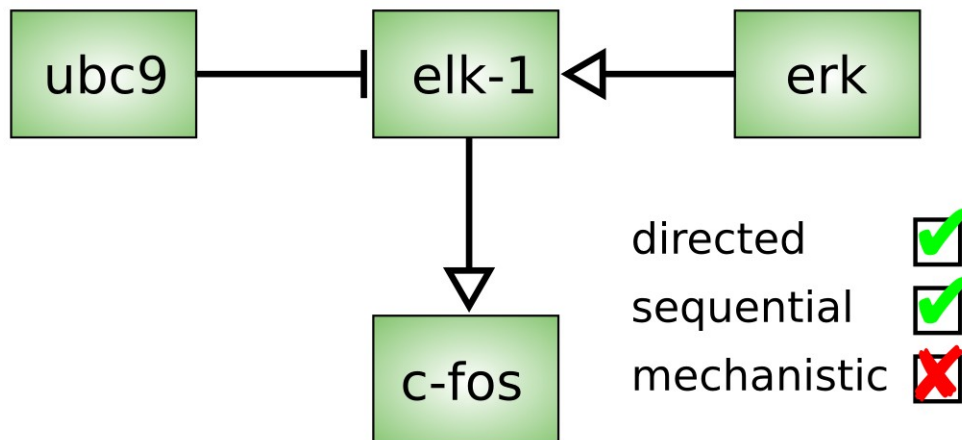


# Interaction networks



- Statistical modelling
- Functional genomics

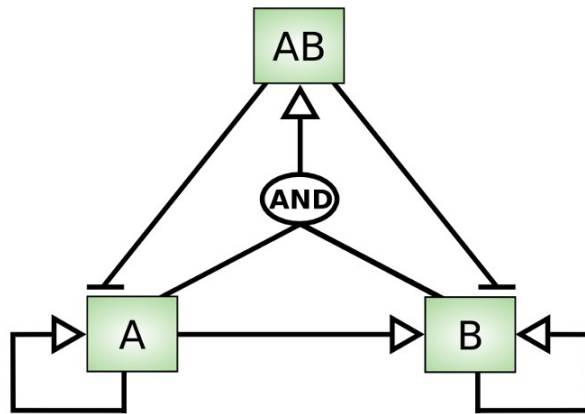
# Activity Flows



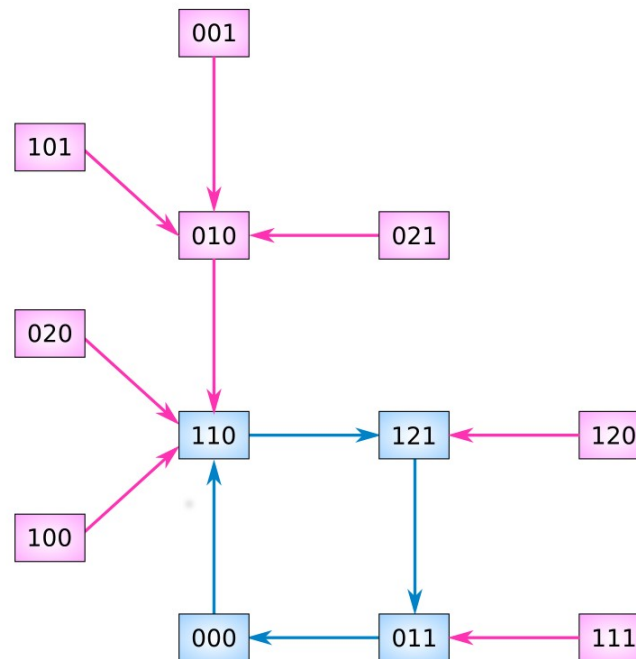
- Logical modelling
- Signalling pathways, gene regulatory networks

# Logic models

- Variables can take a discrete number of values, at least 2
- Transitions of output are expressed as logical combinations of input values
- Simulations can be:
  - synchronous: all the nodes are updated at once
  - asynchronous: nodes are updated one after the other
- One can add delays, inputs etc.

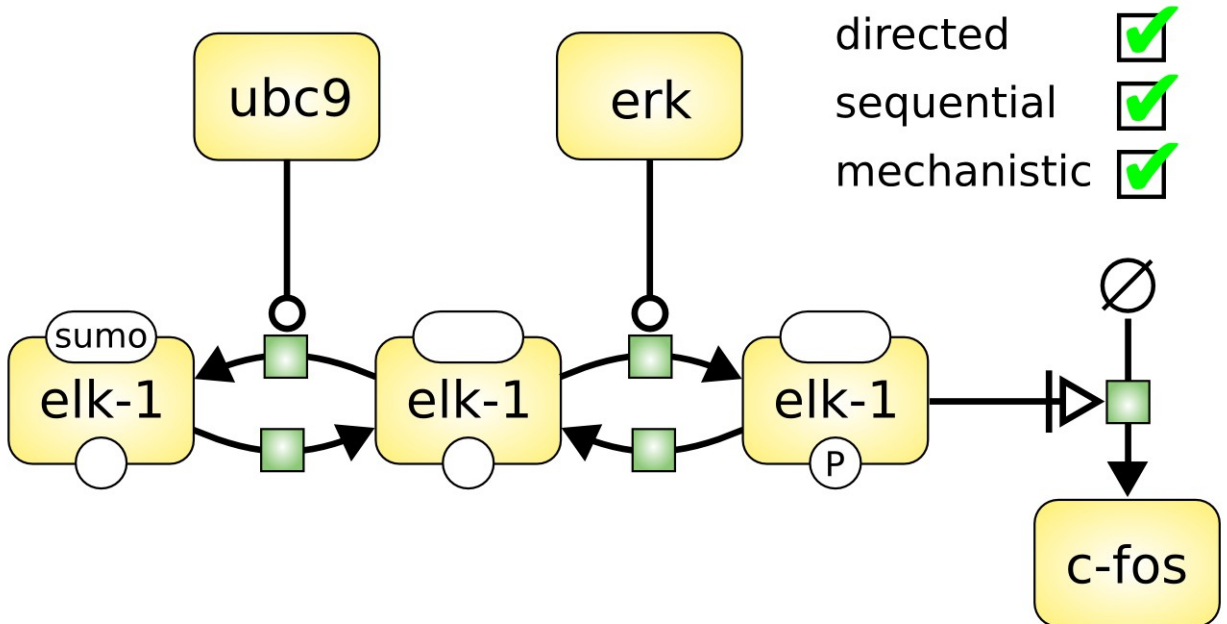


Influence diagram



state diagram

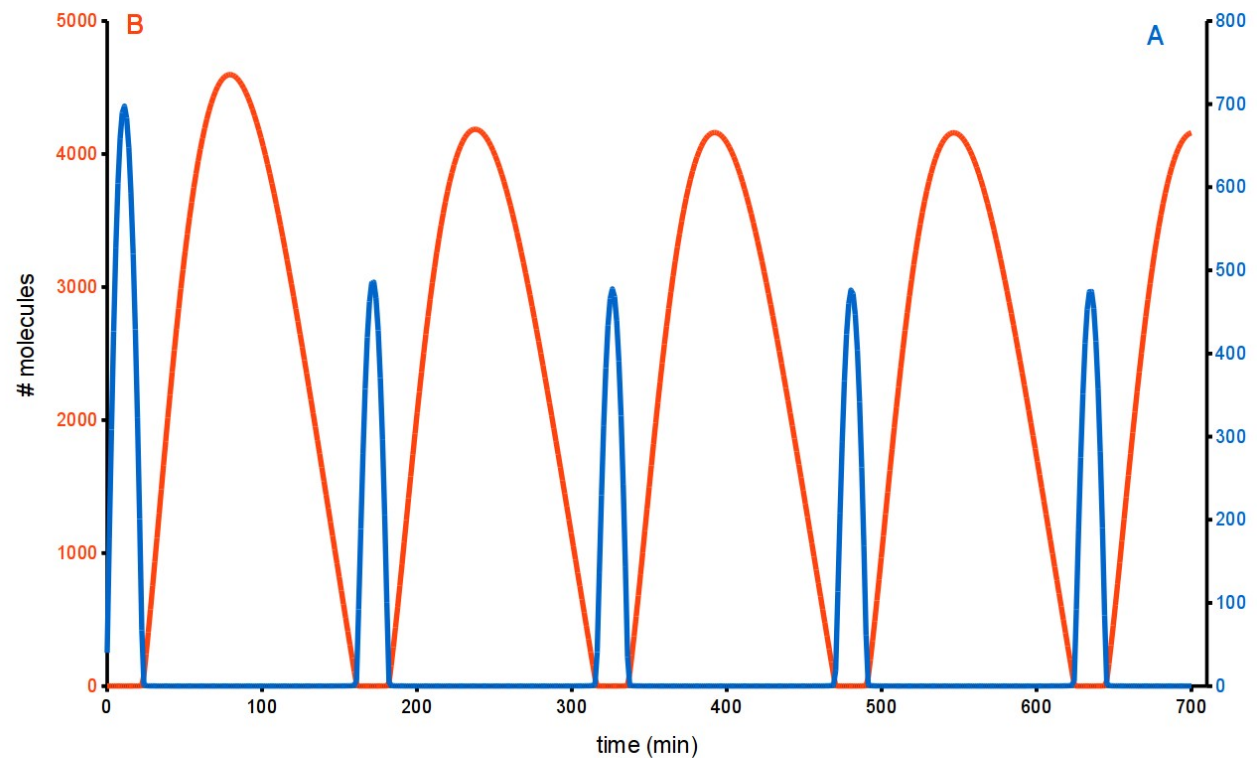
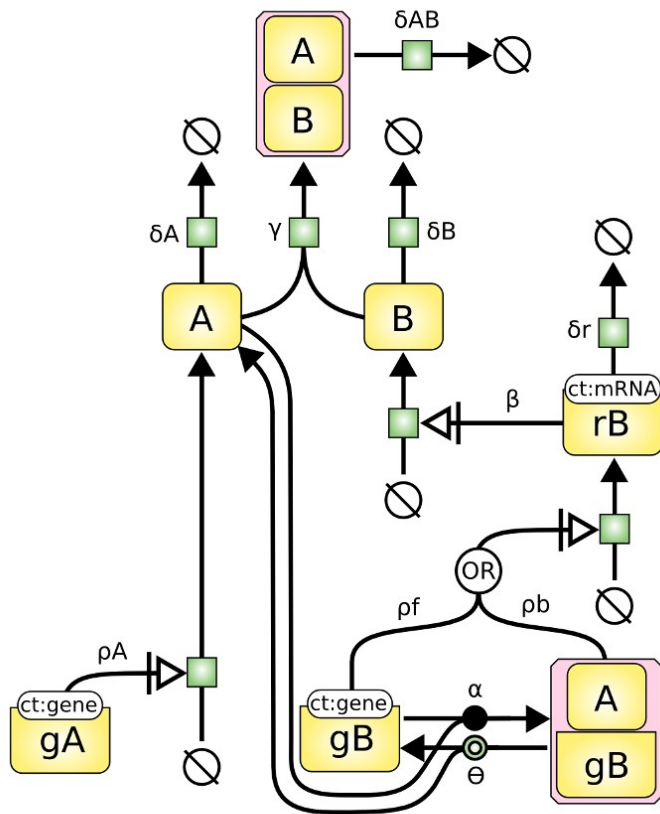
# Process Descriptions



- Process modelling
- Biochemistry, Metabolic networks
- Generally within “closed world”
- Subjected to combinatorial explosion

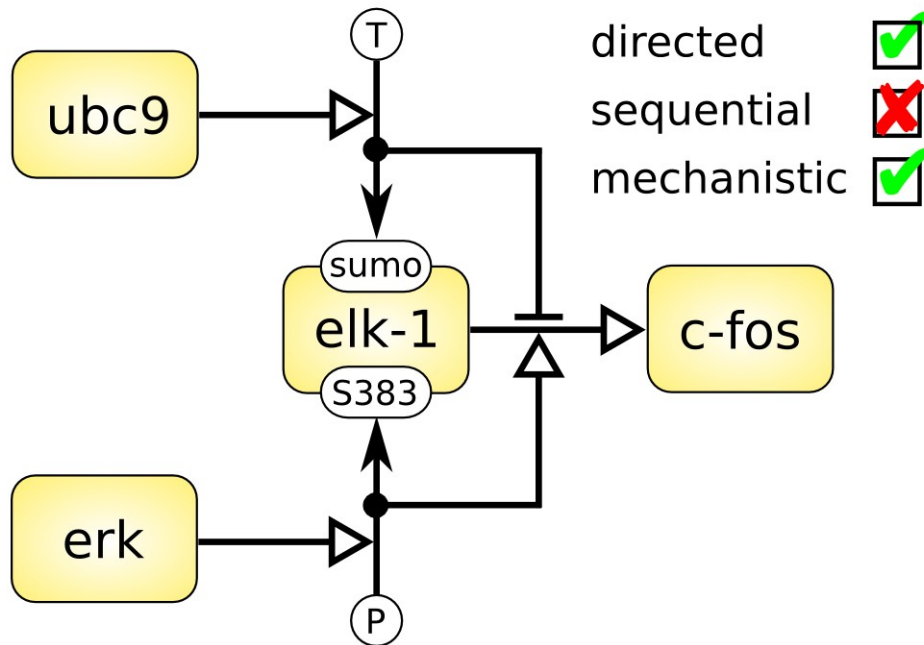
# Quantitative models

- Variables are concentrations or amounts
- Reactions rates are calculated based on quantitative values
- Simulations deterministic or stochastic

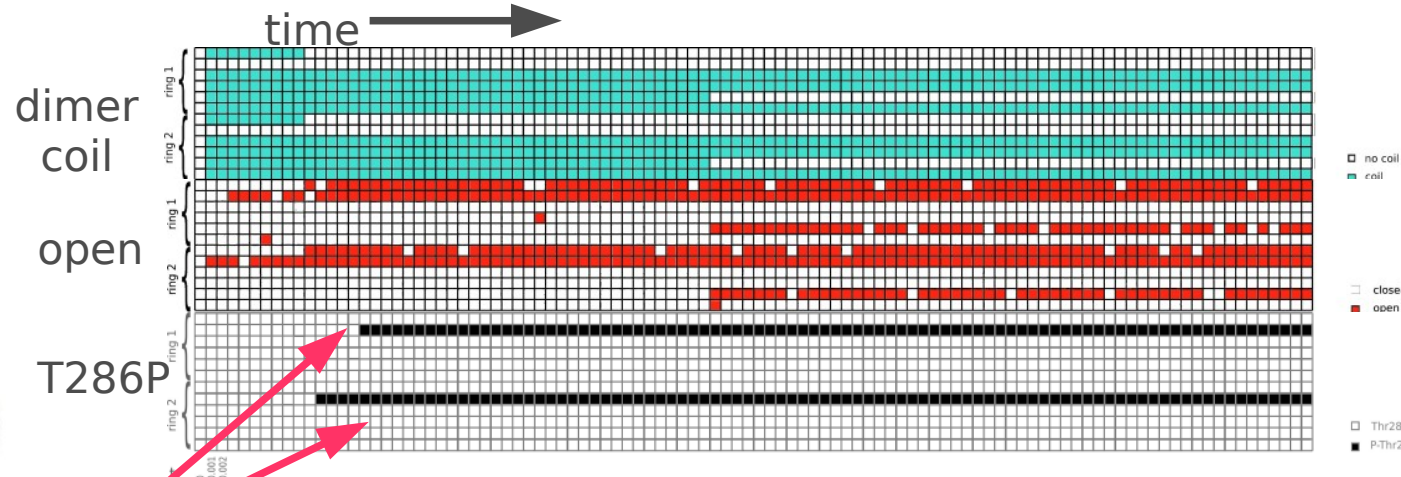
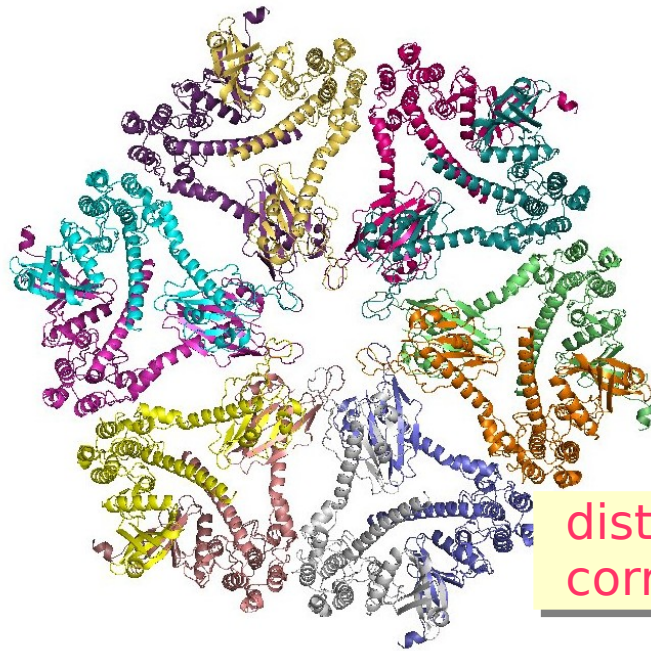


# Entity Relationships

- Rule-based modelling
- Molecular Biology
- “Open world”
- Independent rules: no explosion



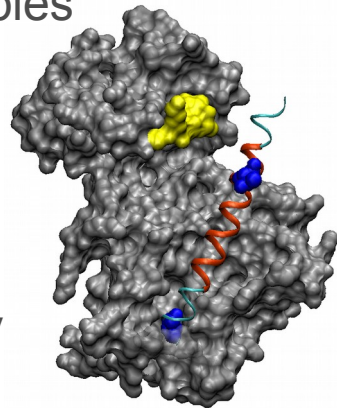
# Multi-agent simulation of CaMKII



distant correlations

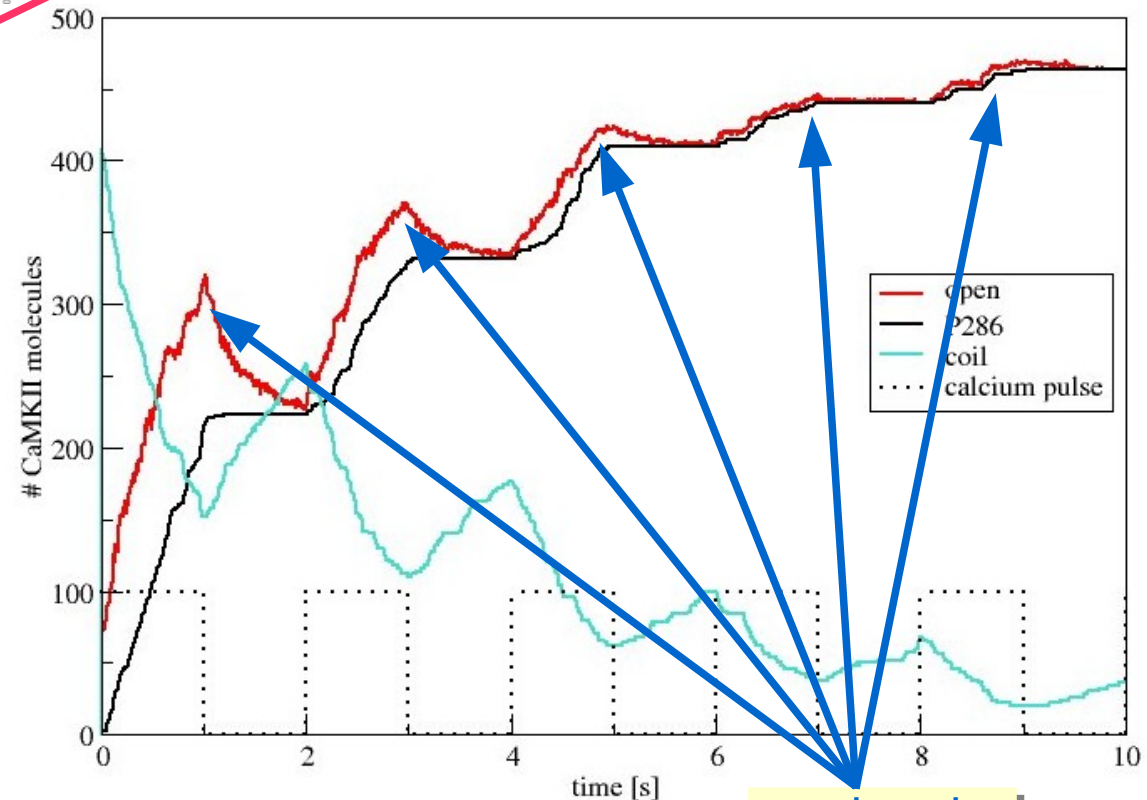
5 binary state variables

Open/Closed  
T286 P/nonP  
T306 P/nonP  
CaM on low affinity  
CaM on high affinity



$2^{60}$  states = 1 billions of billions

Le Novère 2001, Stefan *et al* 2015

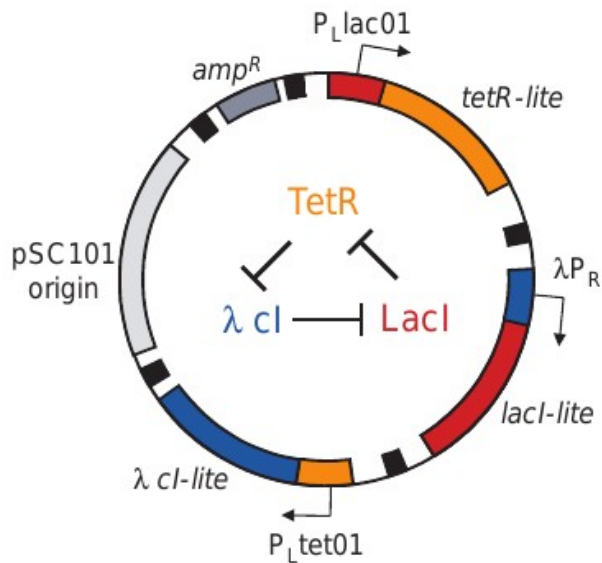


molecular memory

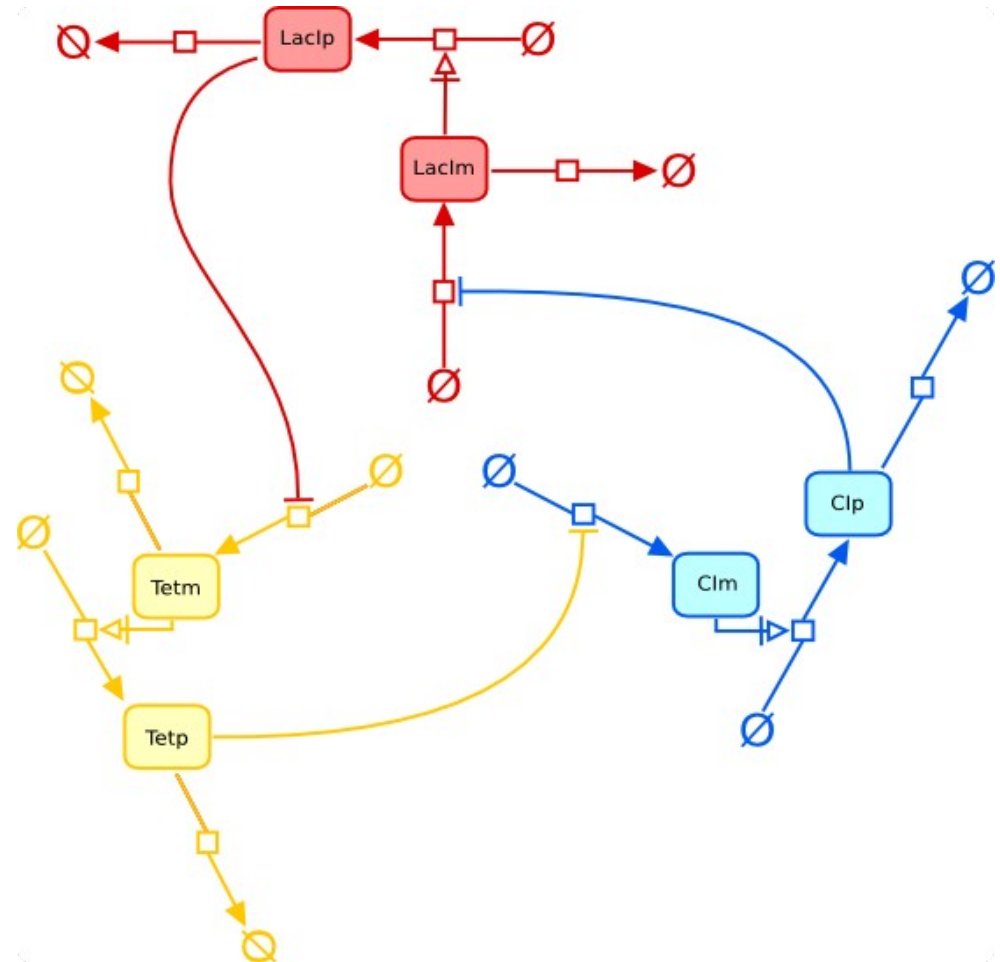
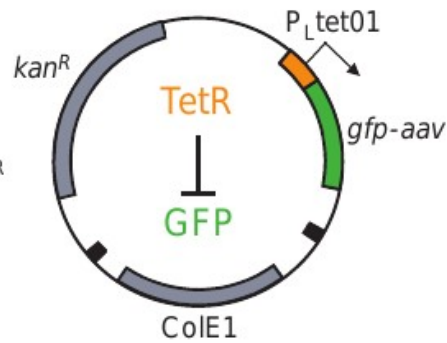
# An example of synthetic gene regulatory network

# The Repressilator -structure

Repressilator



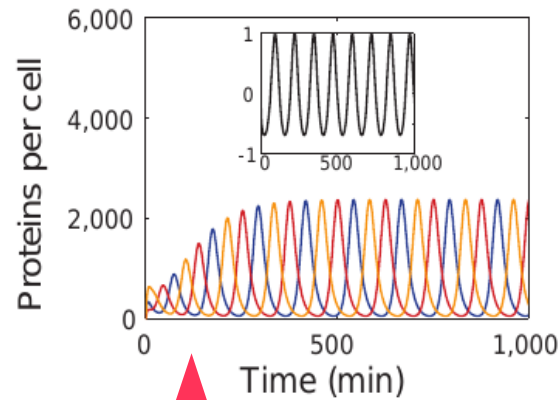
Reporter



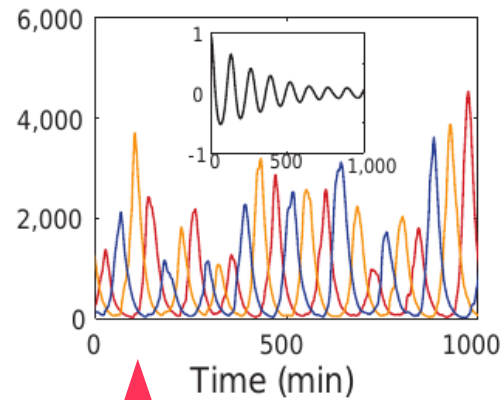
$$\frac{dm_i}{dt} = -m_i + \frac{\alpha}{(1 + p_j^n)} + \alpha_0 \quad \left( \begin{array}{l} i = lacI, tetR, cl \\ j = cl, lacI, tetR \end{array} \right)$$

$$\frac{dp_i}{dt} = -\beta(p_i - m_i)$$

# The Repressilator -function

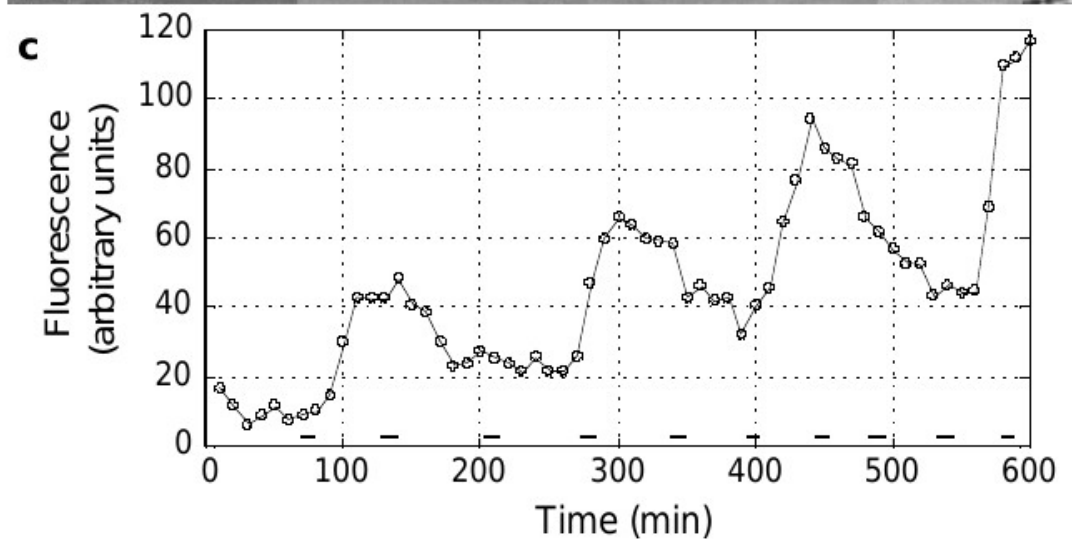
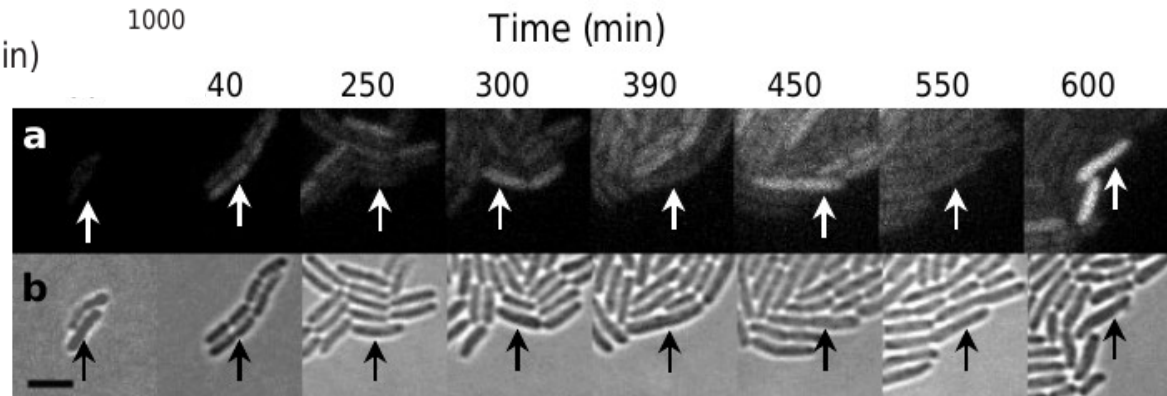


deterministic  
simulation



stochastic  
simulations

Fluorescence



# Demo?

Using COPASI (Complex Pathway Simulator, <http://www.copasi.org>)

Original article:

Elowitz, Leibler. A synthetic oscillatory network of transcriptional regulators.  
*Nature* (2000) **403**: 335-338

Repressilator model to import in COPASI:

<http://identifiers.org/biomodels.db/BIOMD0000000012>

Any question: [n.lenovere@gmail.com](mailto:n.lenovere@gmail.com)

Further information:

Barabási & Zoltán. Network biology: understanding the cell's functional organization. *Nature Reviews Genetics* (2004) **5**: 101-113

Le Novère. Quantitative and logic modelling of molecular and gene networks. *Nature Reviews Genetics* (2015) **16**: in the press

