

A detailed metabolic map showing various biochemical pathways. Key features include: Citrate cycle (top left) with Citrate, Fumarate, and Malonate/Oxaloacetate; Succinyl-CoA and Succinate pathways (center); Heme synthesis (right) involving Uroporphyrinogen and Heme; and various other intermediates like Pyruvate, Alanine, and Glutamate. Enzymes and cofactors like ATP, NADH, FAD, and various lipids are also indicated. The map is color-coded with red, green, and blue lines and arrows.

Hierarchical Modularity in Metabolic Networks

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Networks?

The cell is not regular

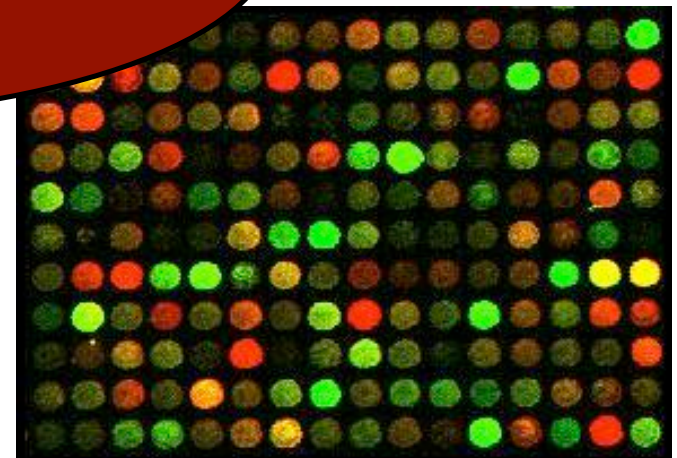
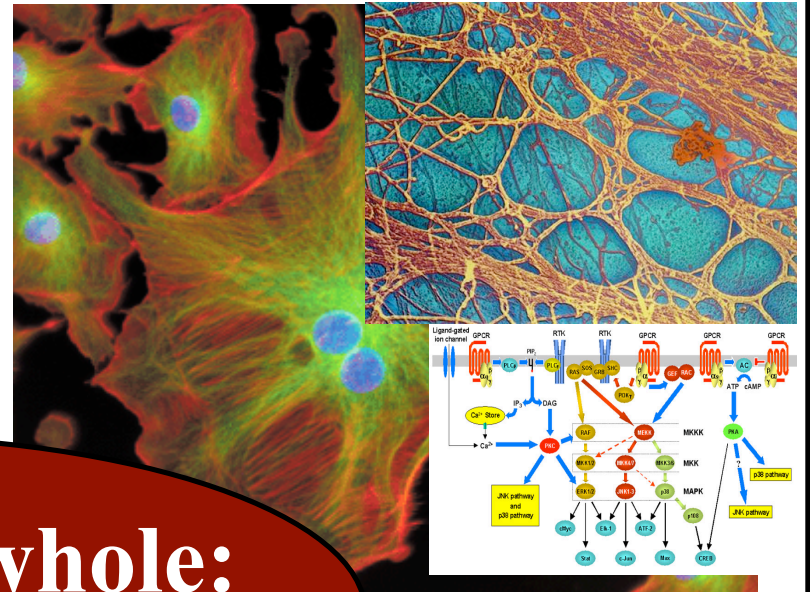
- Many different components
- A variety of interactions
- Not a lattice!



System as a whole:
network!

Systems Biology

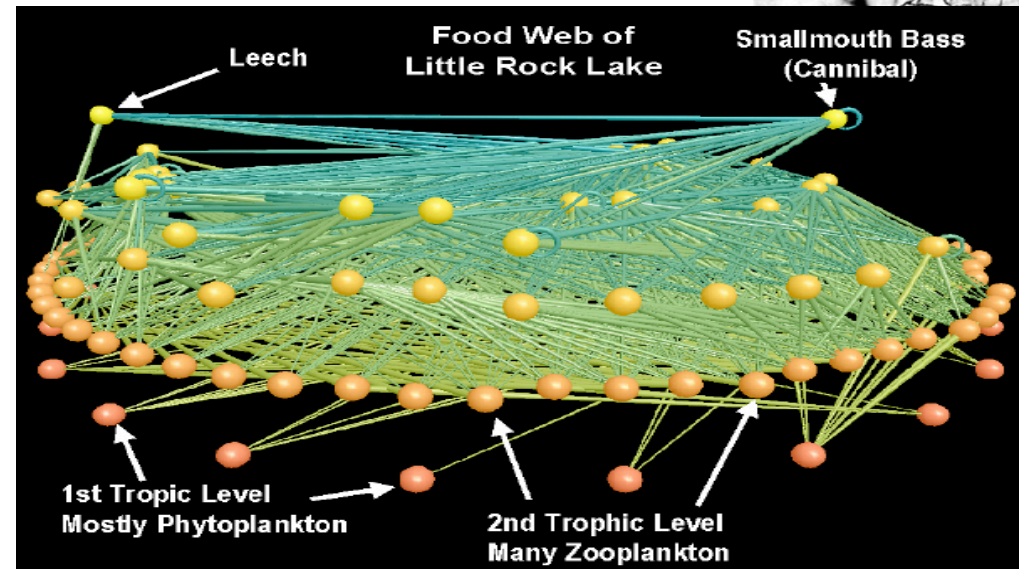
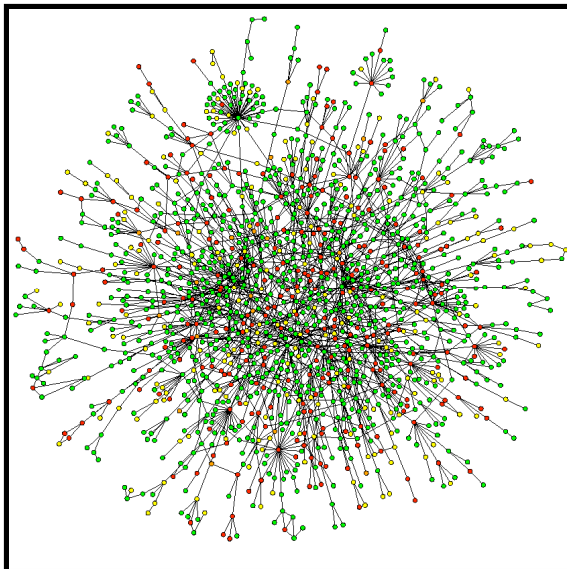
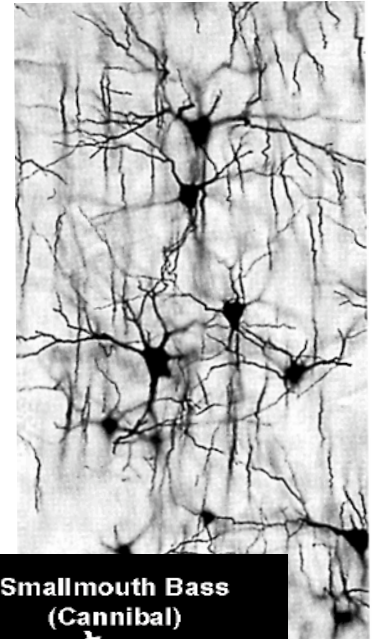
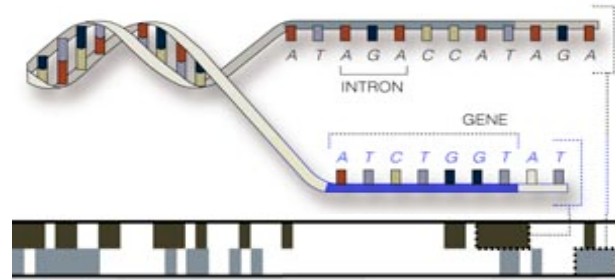
- Data on system level
- Methods and focus shift
- Asking for statistical physics



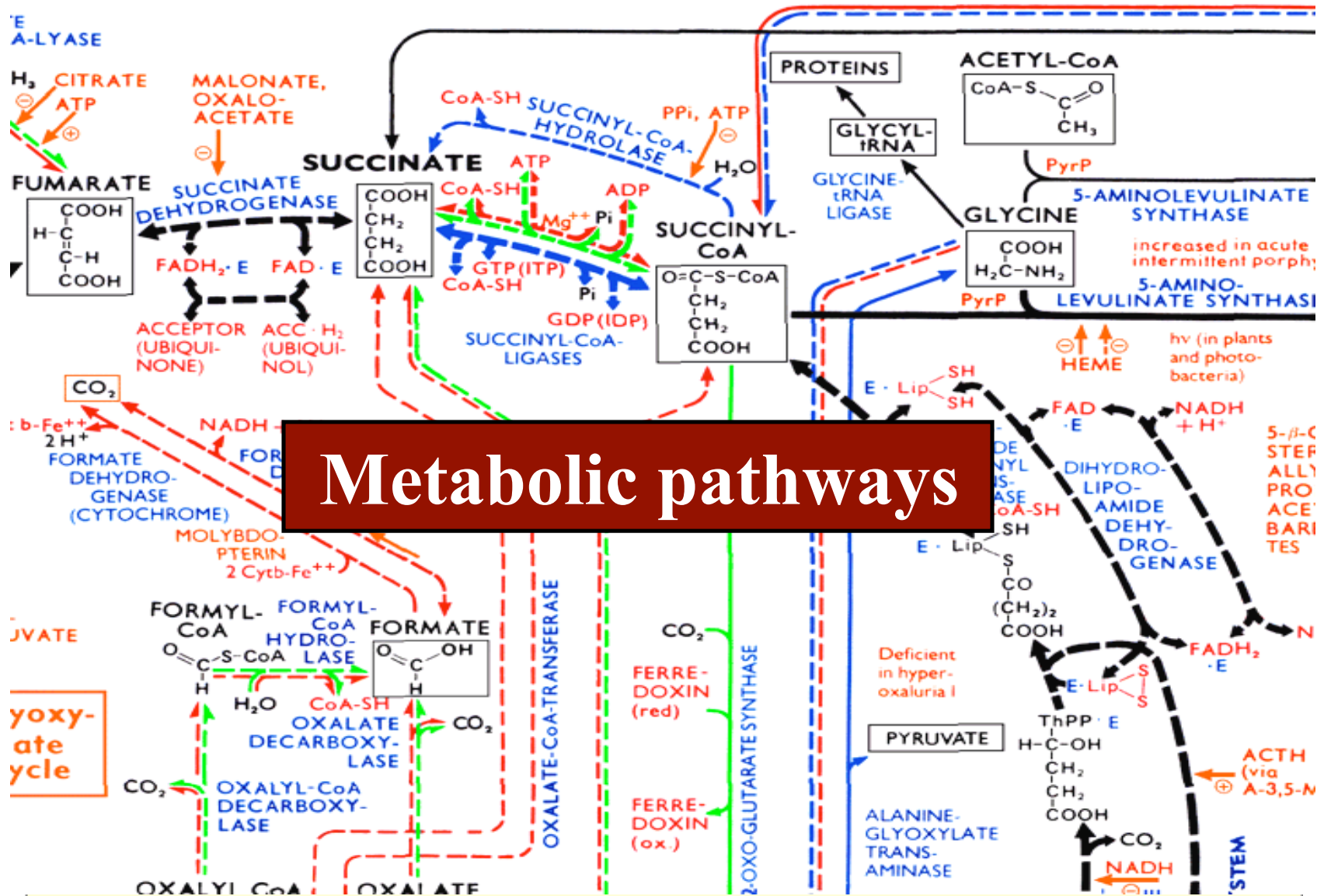
Networks in life

Biology

- Genetic regulation
- Protein-protein interactions
- Food webs
- Neuron networks

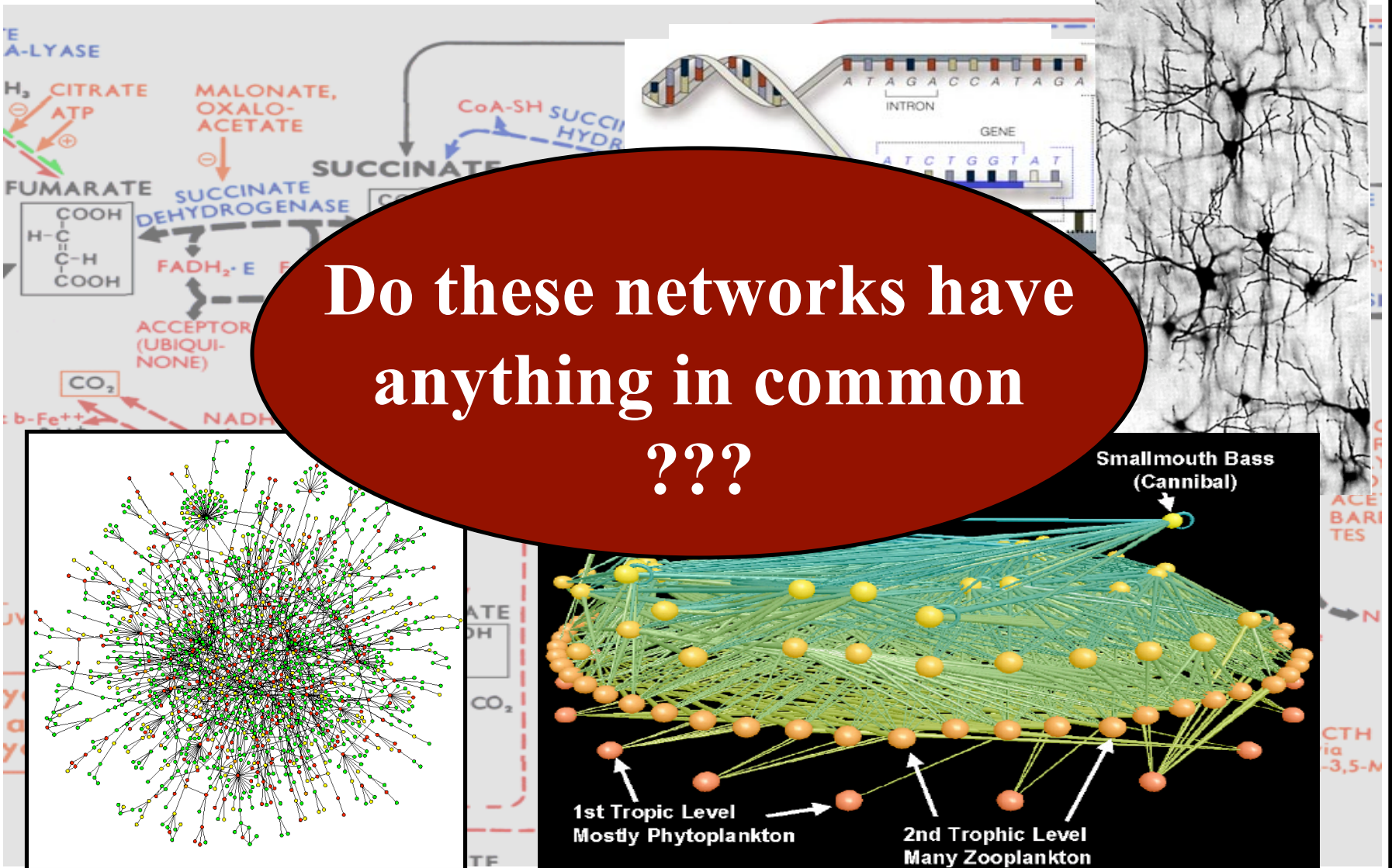
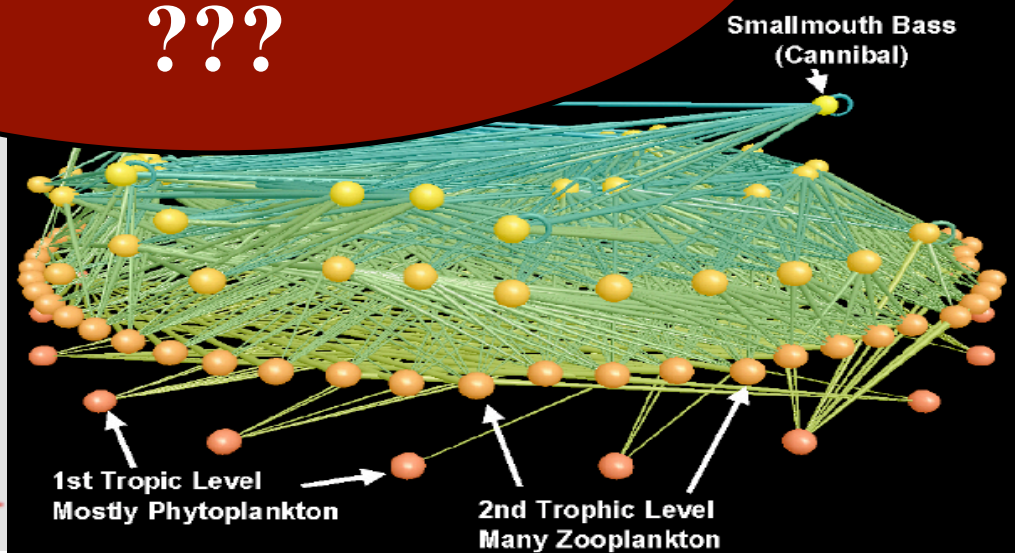
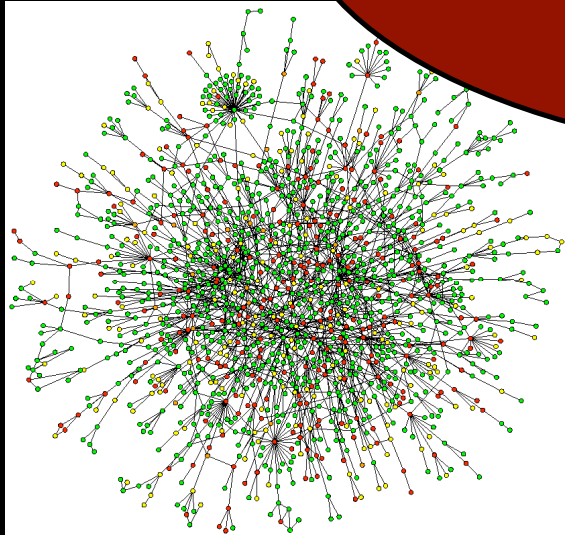


Networks in life



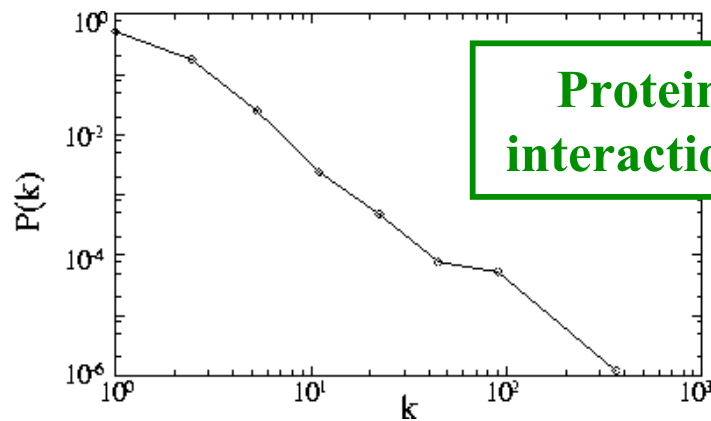
Networks in life

Do these networks have
anything in common
???



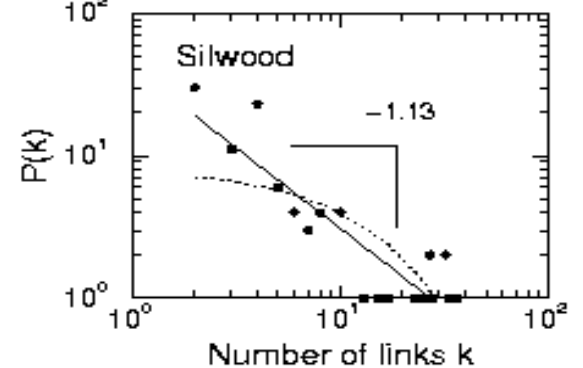
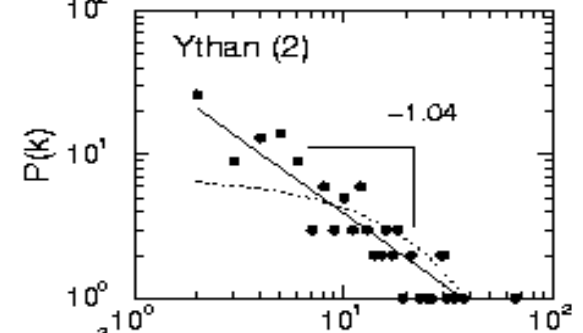
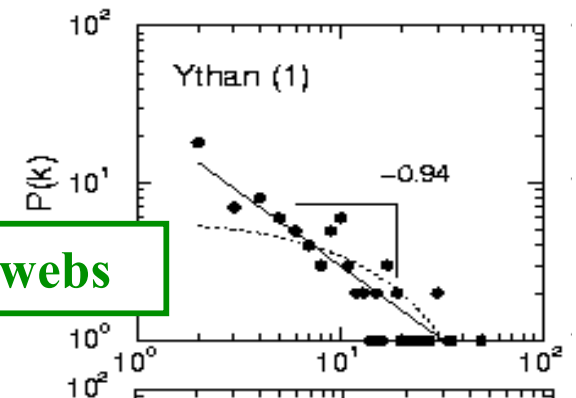
Degree distribution

Not random networks!

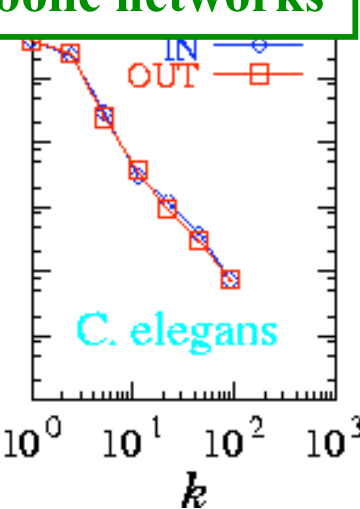
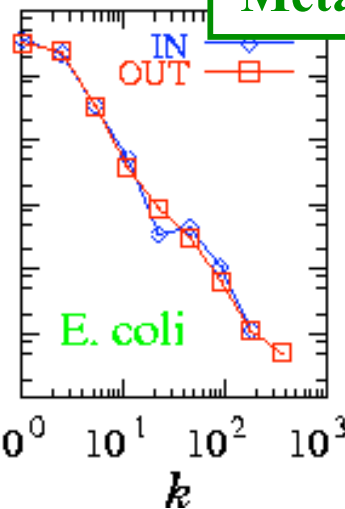
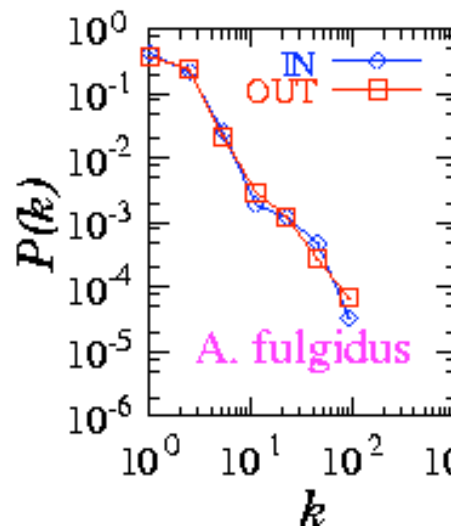


Protein interactions

Food webs



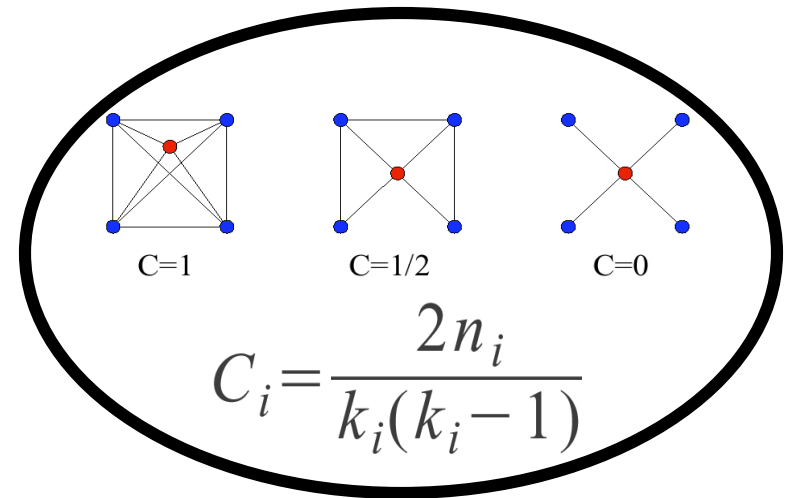
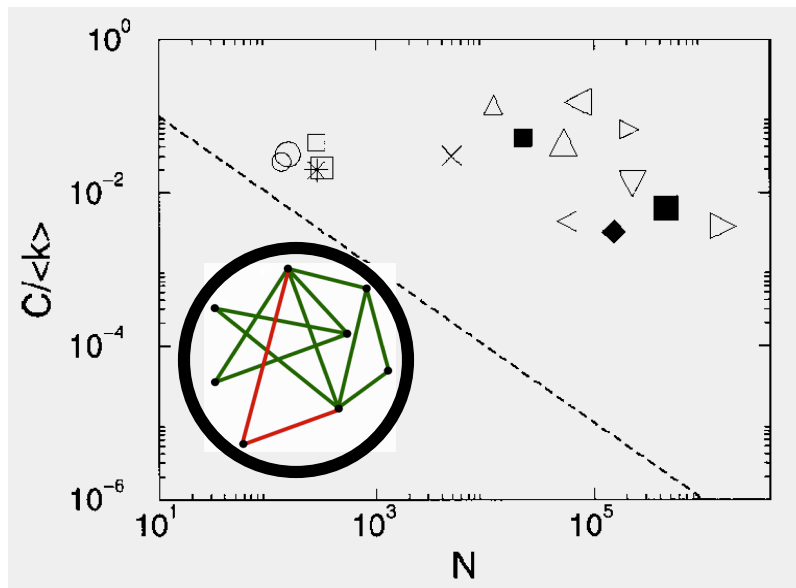
Metabolic networks



Clustering

Clustering coefficient

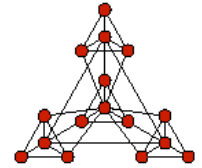
- High average in real networks
- Scale-free model: $C \sim (\ln N)^2 / N$



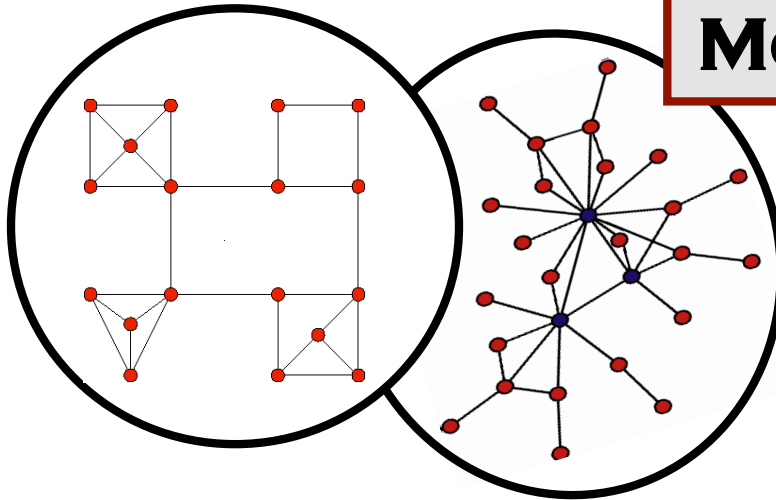
Modular organization

- protein complexes
- regulatory modules
- pathways

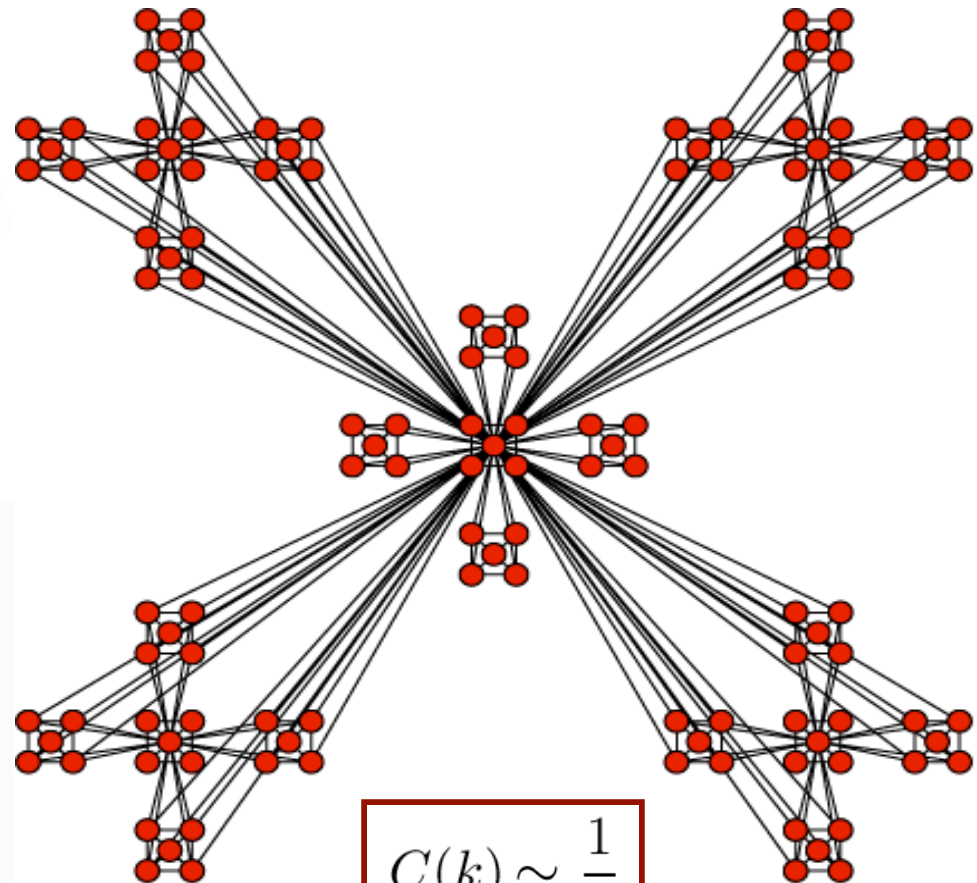
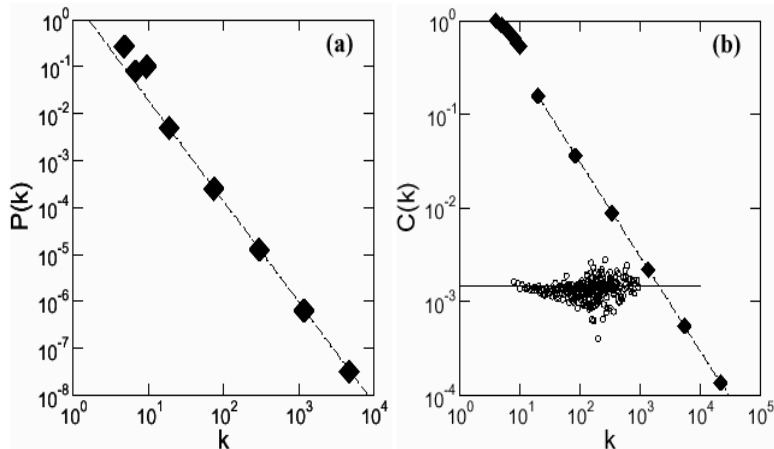
Module hierarchy



MODULAR AND SCALE-FREE?



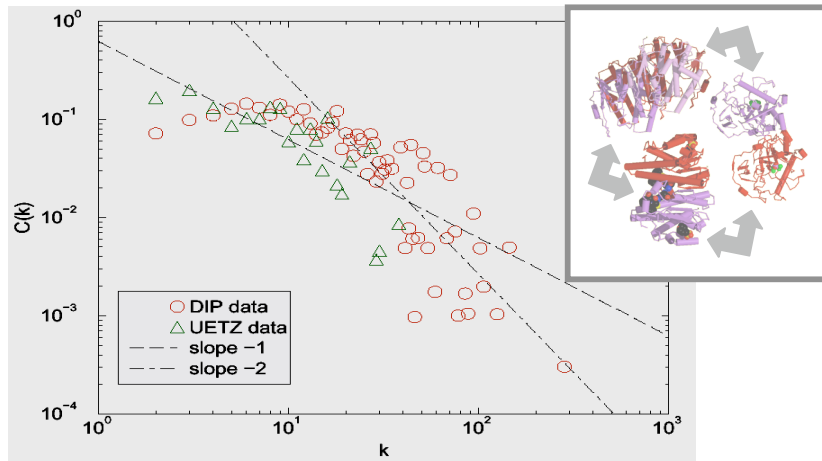
Hierarchical model



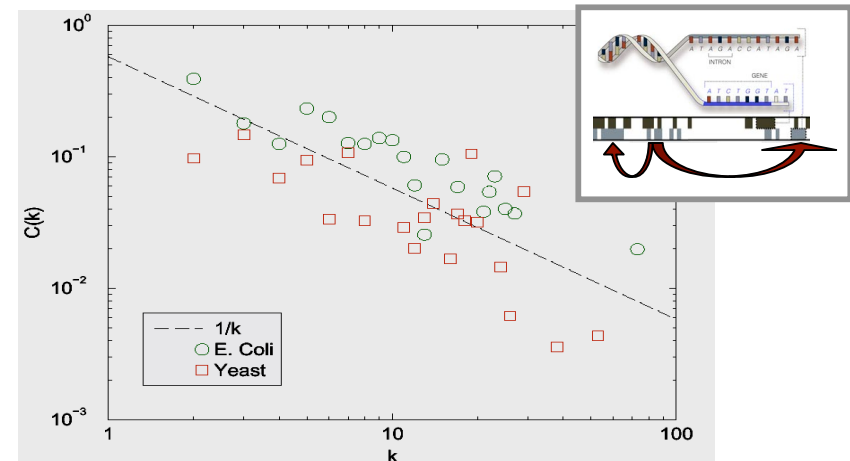
$$C(k) \sim \frac{1}{k}$$

Hierarchy in Biology

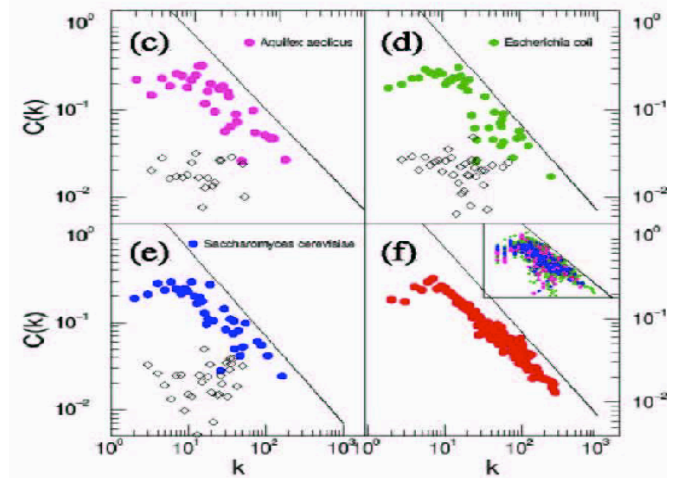
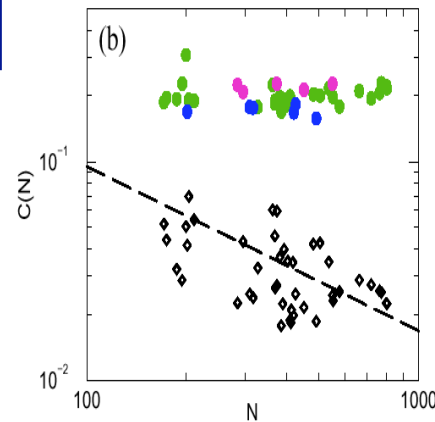
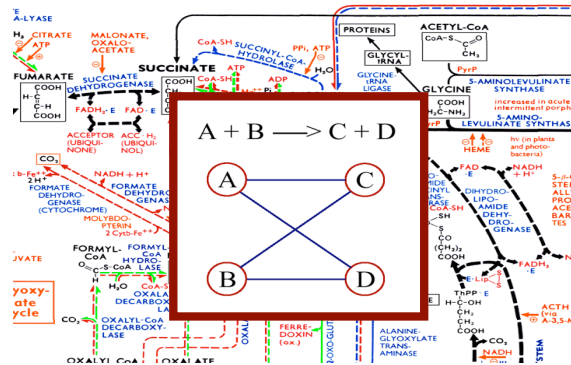
Protein-protein interaction



Regulatory networks

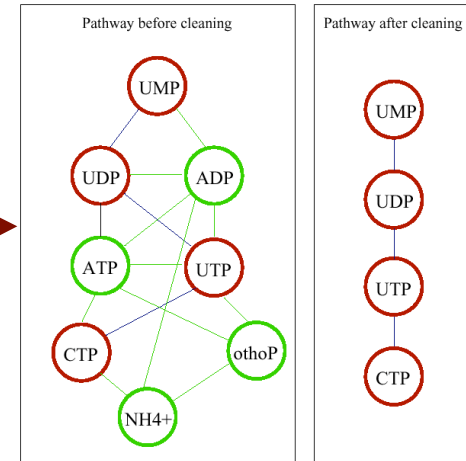
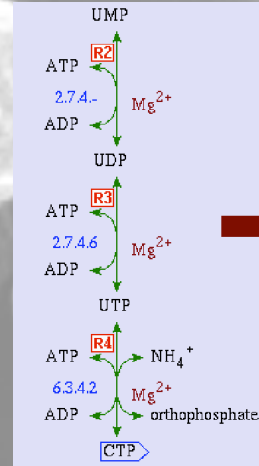
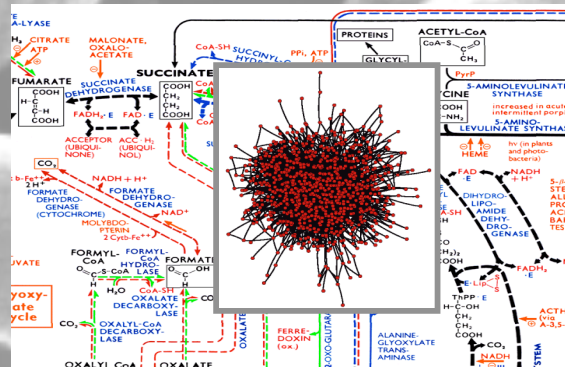


Metabolic networks

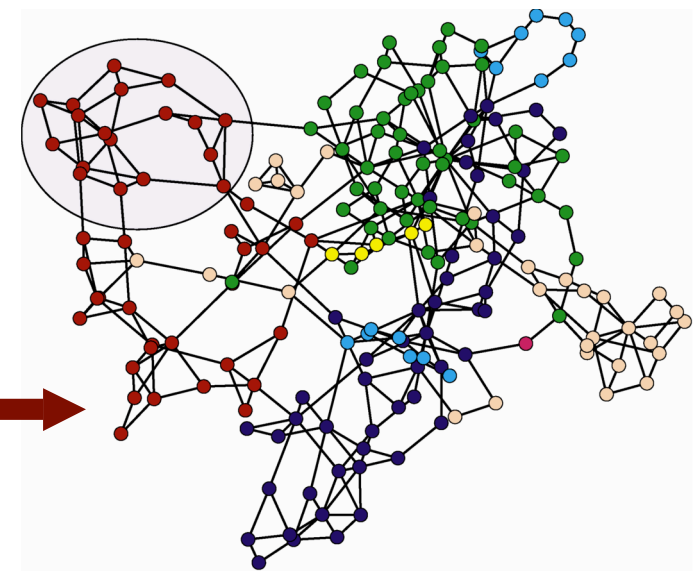
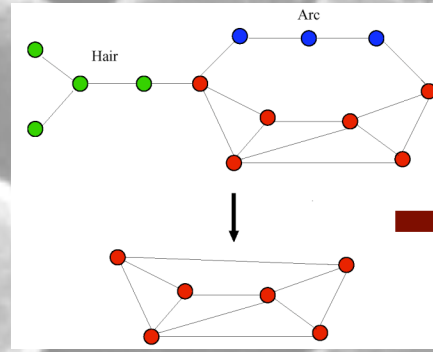
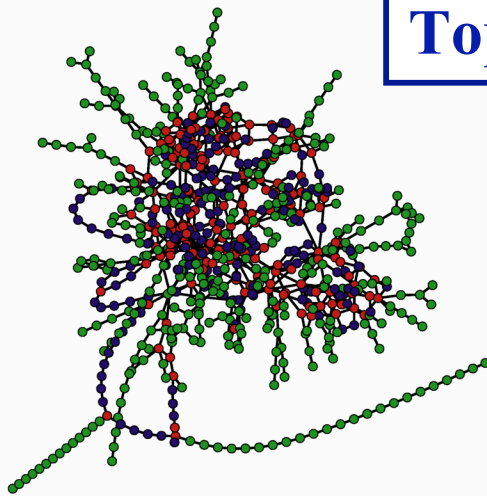


The metabolism of *E. Coli*

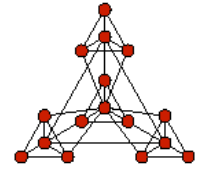
Biochemical reduction



Topological reduction

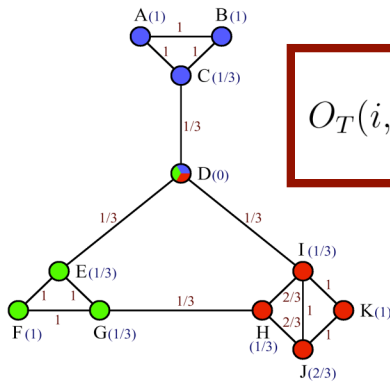


Finding the modules



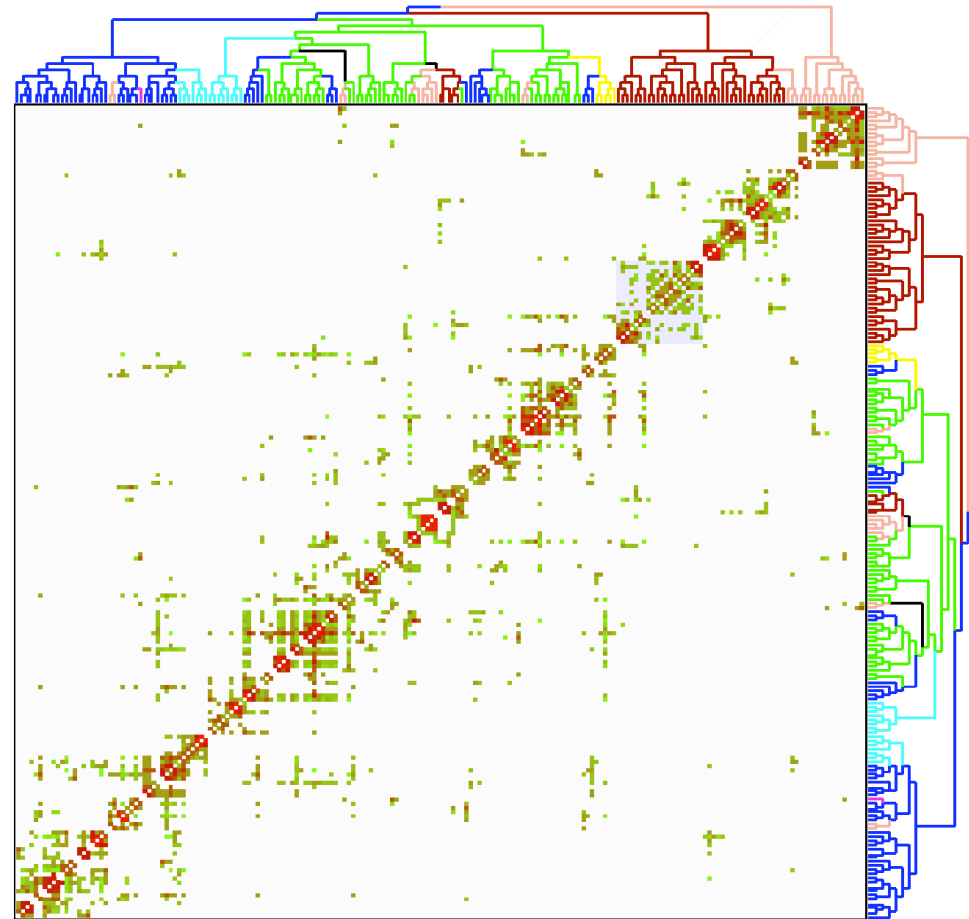
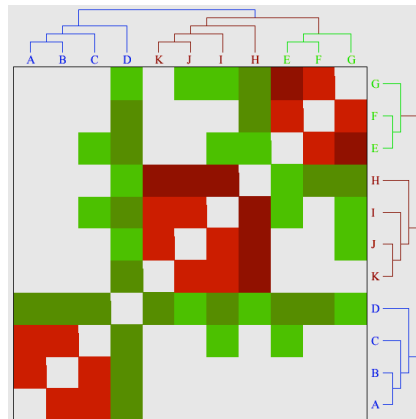
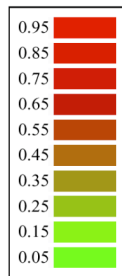
Hierarchical clustering

→ Similarity matrix



$$O_T(i, j) = \frac{\sum_{l=1}^N l_{i,l} \cdot l_{j,l} + l_{i,j}}{\min(k_i, k_j) + 1 - l_{i,j}}$$

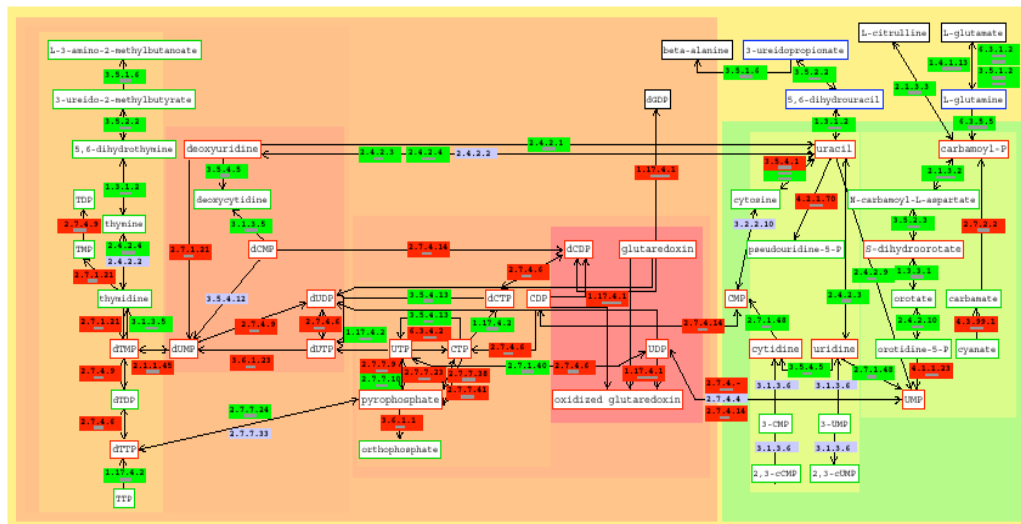
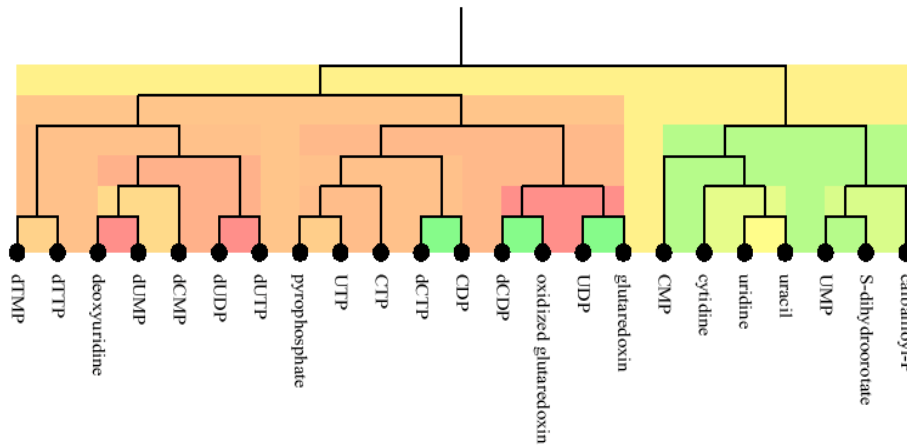
→ Average linkage clustering (UPGMA)



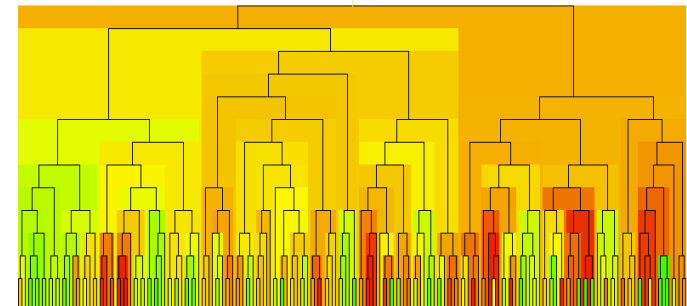
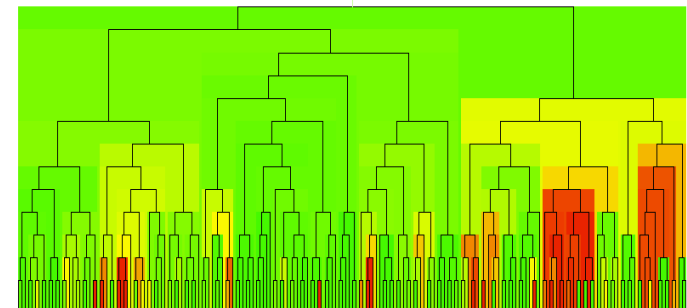
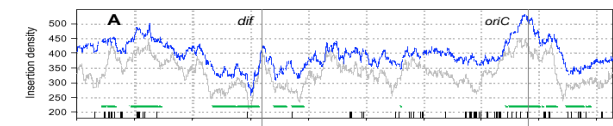
Carbohydrates		Lipids	Amino acids											Nucleotides Nucleic Acids		Coenz. Vit.														
Disaccharides		Membrane Lipids		Cysteine		Pyruvate		Serine, Threonine		Tyrosine		Nicotinamide		Purine Nucleosynthesis		Glyoxylate		Glutamate		Arginine		Metab. sugar alc. Formate		Pyrimidine		Purine		Sirohem Chorismate		Vitamin K
Monosaccharides		Fatty Acids		Lactate																										

Module lethality

Pyrimidine metabolism



Genome-wide lethality measurement



Carbohydrates			Aminoacids, Proteins, Peptides			Nucleotides, Nucleic acids		Coenzymes, Vitamins Lipids	<div><div></div><div>0.10</div></div> <div><div></div><div>0.00</div></div> <div><div></div><div>0.80</div></div> <div><div></div><div>0.70</div></div> <div><div></div><div>0.60</div></div> <div><div></div><div>0.50</div></div> <div><div></div><div>0.40</div></div> <div><div></div><div>0.30</div></div> <div><div></div><div>0.20</div></div> <div><div></div><div>0.10</div></div> <div><div></div><div>0.00</div></div>
Monosacch.	Disacch.	Polysacch.	Aminoacids	Aminoacids Organic Acids	Aminoacids	Purines	Pyrimidines		
Monosacch.	Monosacch.	Monosacch.	Monosacch.	Monosacch.	Monosacch.	Monosacch.	Monosacch.	Monosacch.	
Disacch.	Disacch.	Disacch.	Disacch.	Disacch.	Disacch.	Disacch.	Disacch.	Disacch.	
Polysacch.	Polysacch.	Polysacch.	Polysacch.	Polysacch.	Polysacch.	Polysacch.	Polysacch.	Polysacch.	
Met. Sugar/Alc.	Met. Sugar/Alc.	Met. Sugar/Alc.	Met. Sugar/Alc.	Met. Sugar/Alc.	Met. Sugar/Alc.	Met. Sugar/Alc.	Met. Sugar/Alc.	Met. Sugar/Alc.	
Monosacch.	Monosacch.	Monosacch.	Monosacch.	Monosacch.	Monosacch.	Monosacch.	Monosacch.	Monosacch.	

Thank you!

<http://www.nd.edu/~networks>

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