

The diagram illustrates a complex metabolic network. At the top left, citrate is converted to fumarate by citrate lyase, a reaction that consumes ATP and produces H₂. Fumarate is then converted to succinyl-CoA by succinyl-CoA synthetase, which produces ATP. Succinyl-CoA is further converted to succinate by succinyl-CoA lyase, which produces PPI. Succinate is then converted to fumarate by succinate dehydrogenase, which produces FAD. Fumarate is converted to malate by fumarate hydratase, and malate is converted to oxaloacetate by malate dehydrogenase. Oxaloacetate combines with acetyl-CoA to form citrate, completing the cycle. The diagram also shows the synthesis of heme from succinyl-CoA, involving the formation of δ-ALA, Porphobilinogen (PBG), and uroporphyrin III, which is then converted to heme. Other molecules shown include pyruvate, alanine, and various cofactors like CoA-SH, NADH, and FADH₂.

Hierarchical Modularity in Complex Networks

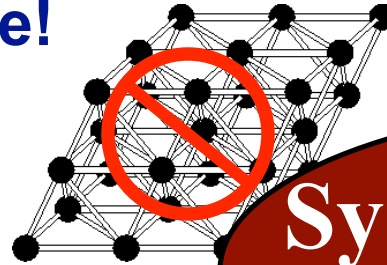
Erzsébet Ravasz

Center for Nonlinear Studies, Los Alamos National Laboratory

Networks?

The cell is not regular

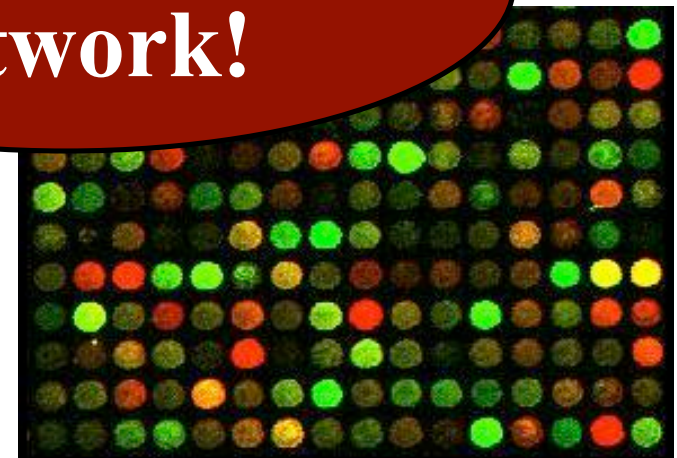
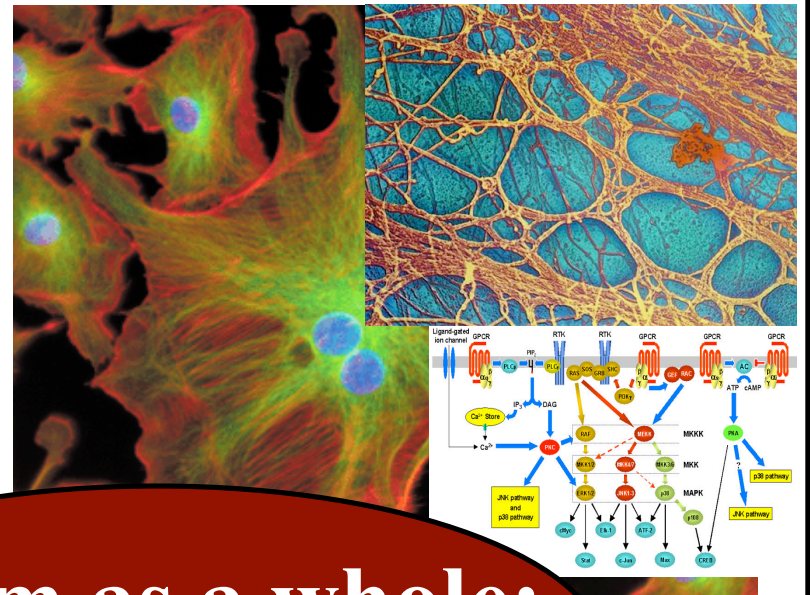
- Many different components
- A variety of interactions
- Not a lattice!



System as a whole:
network!

Systems Biology

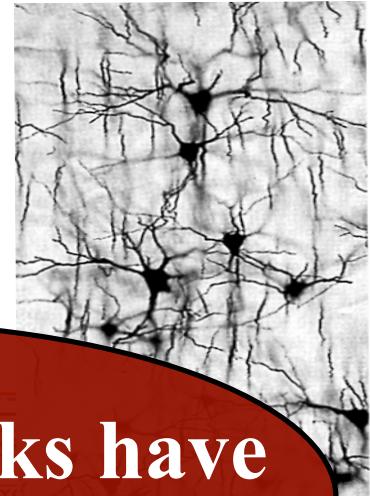
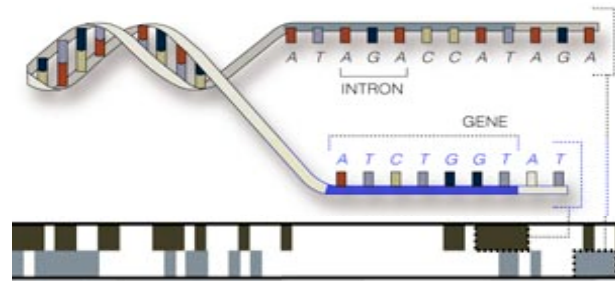
- Data on system level
- Methods and focus shift
- Asking for statistical physics



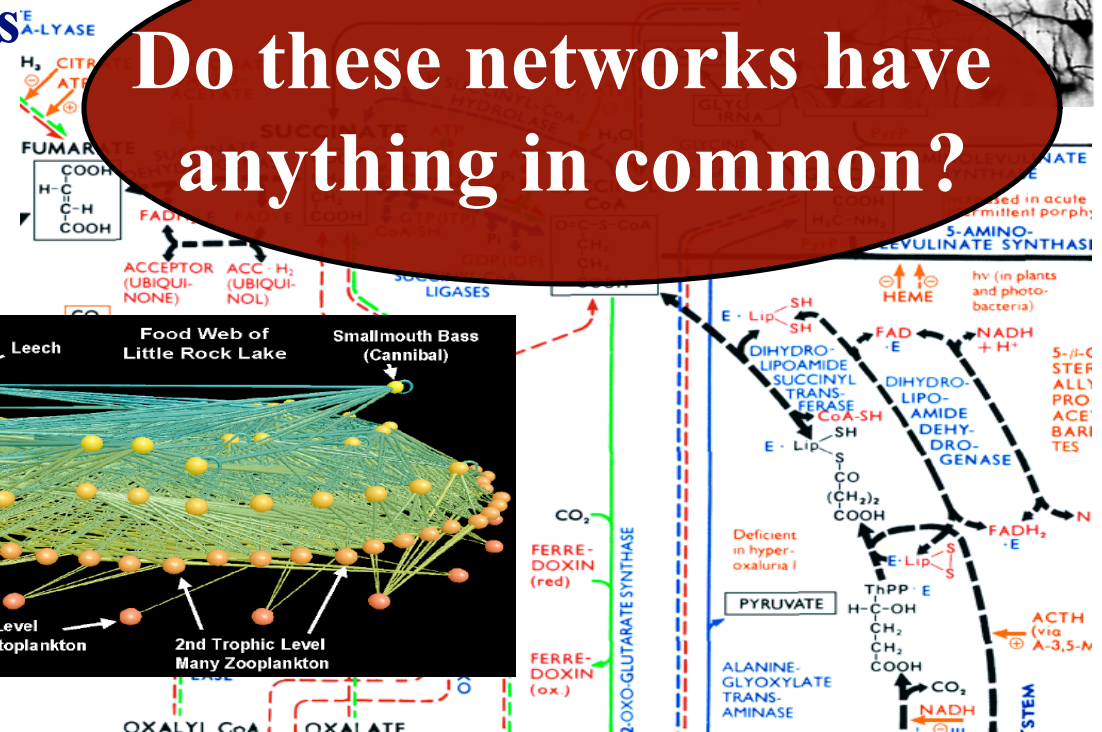
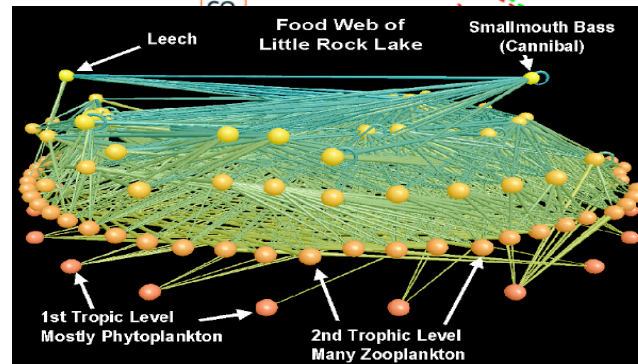
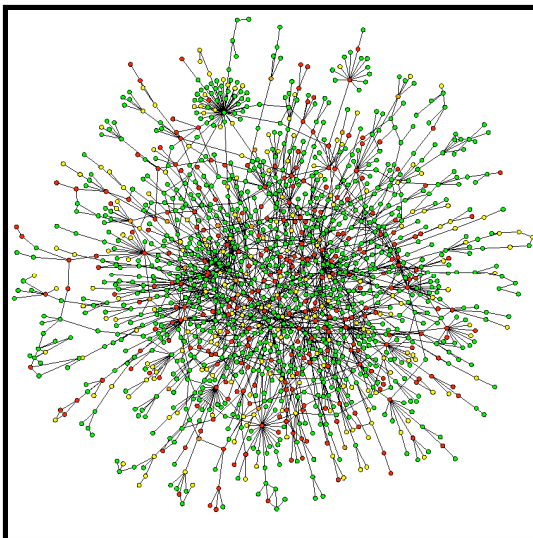
Networks in life

Biology

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

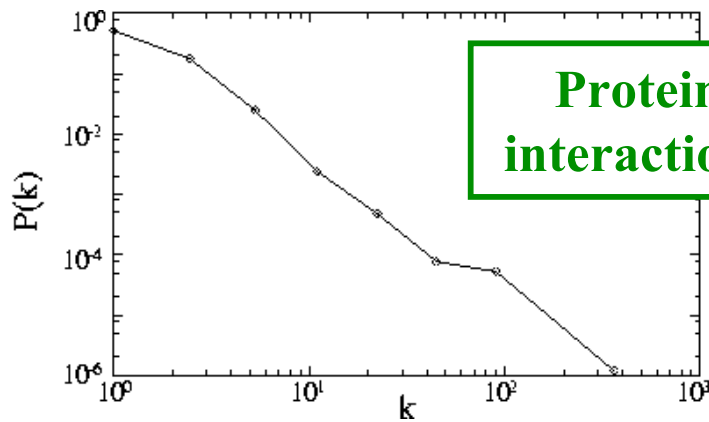


Do these networks have anything in common?



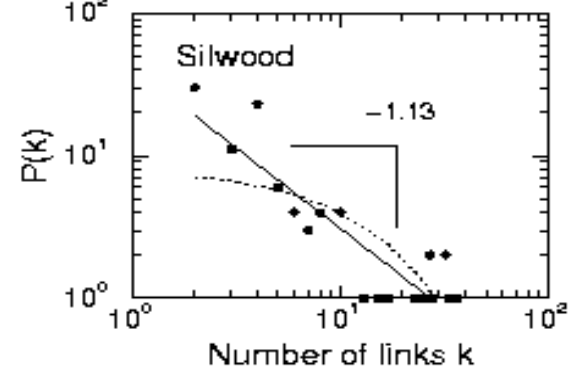
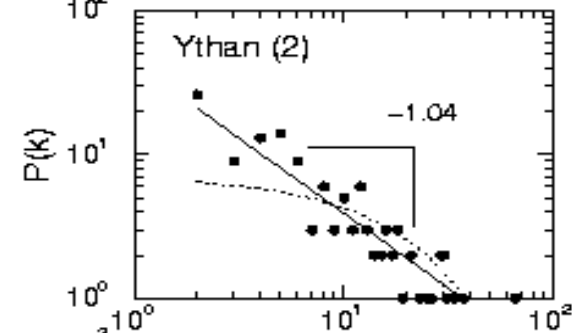
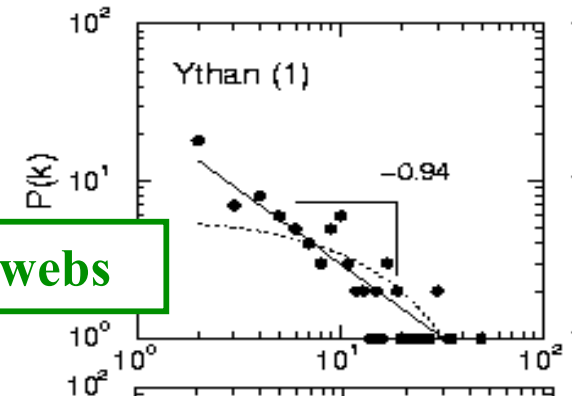
Degree distribution

Not random networks!

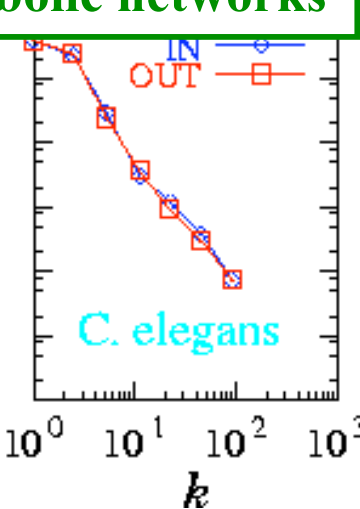
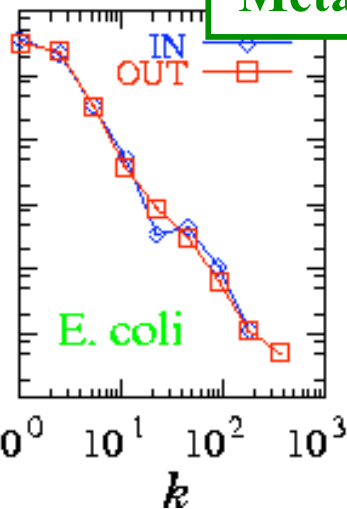
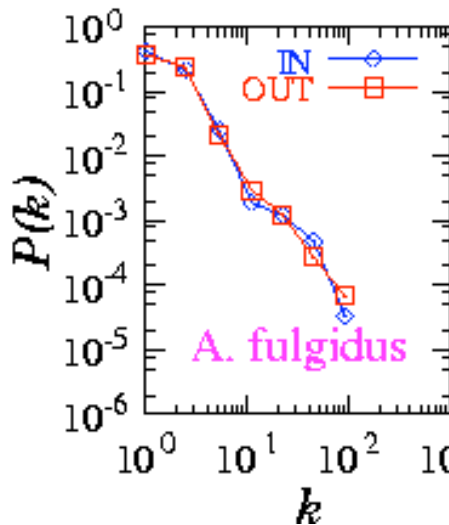


Protein interactions

Food webs



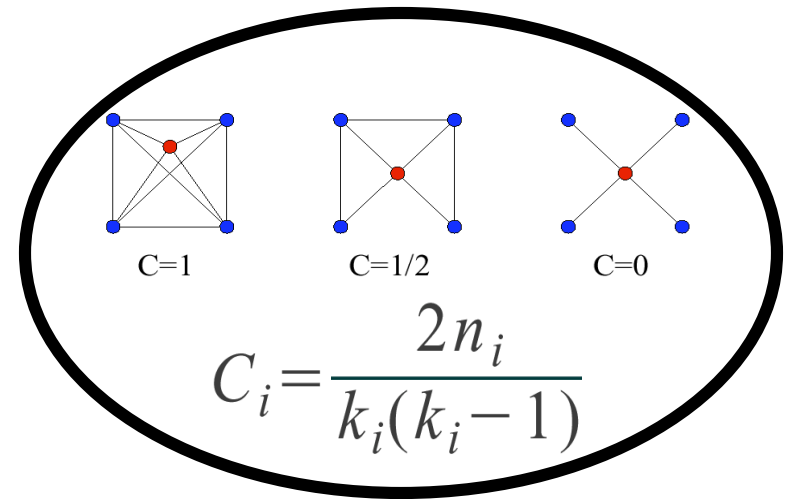
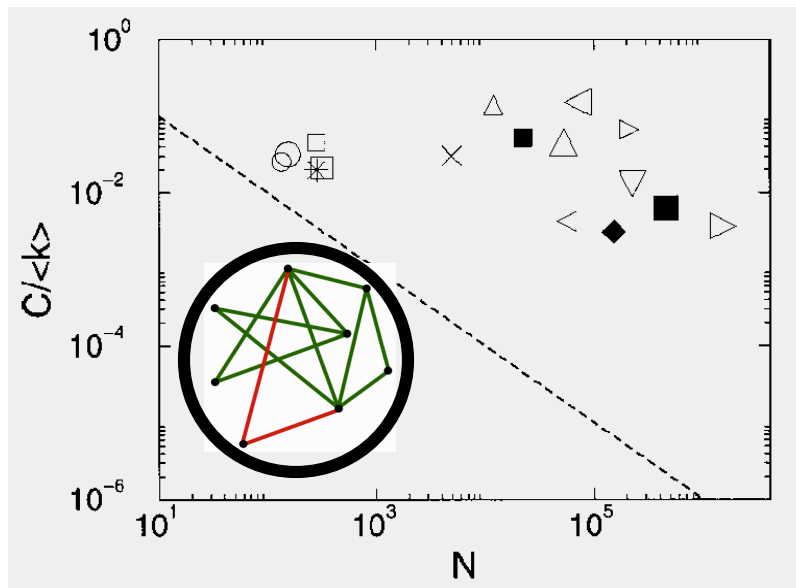
Metabolic networks



Clustering

Clustering coefficient

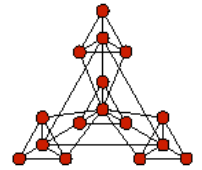
- High average in real networks
- Scale-free model: $C \sim (\ln N)^2/N$



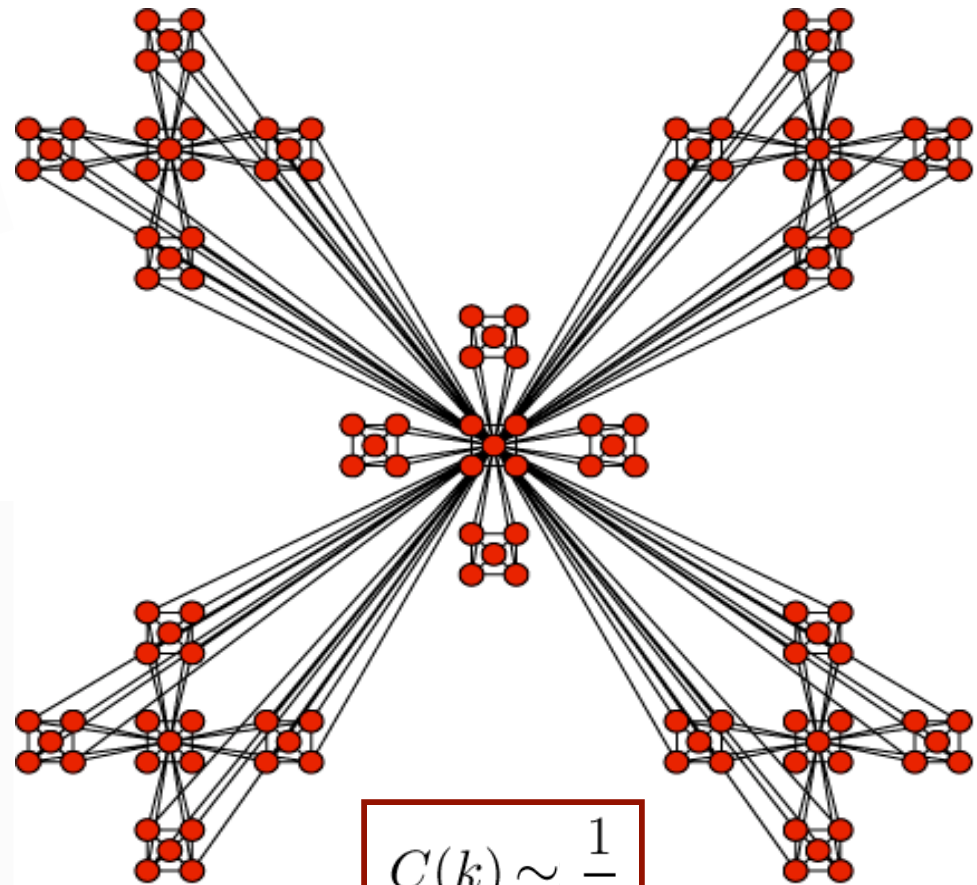
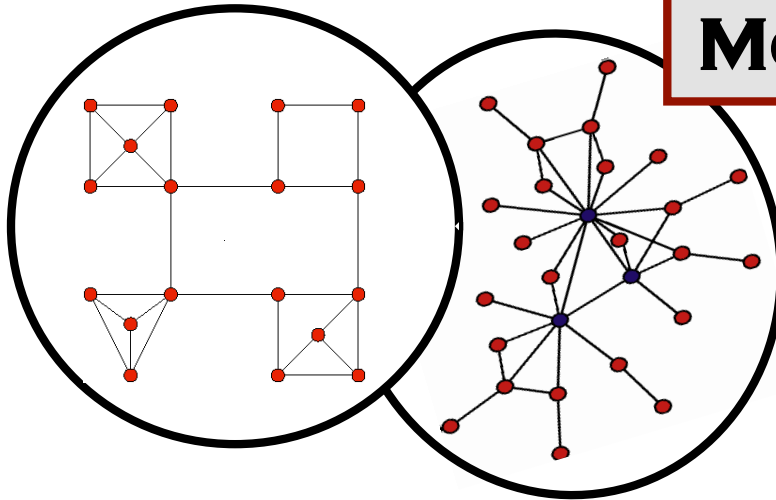
Modular organization

- protein complexes
- regulatory modules
- pathways

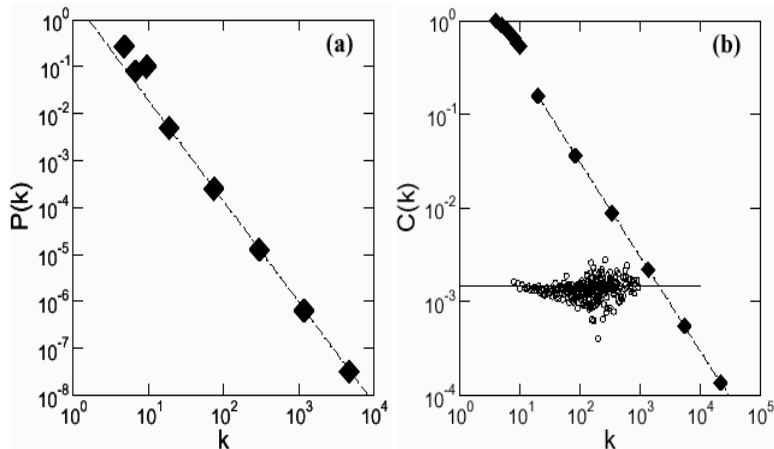
Module hierarchy



MODULAR AND SCALE-FREE?



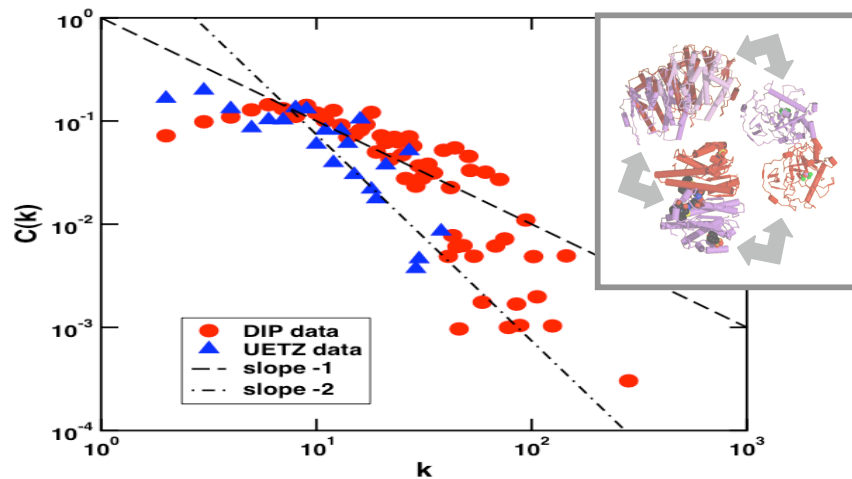
Hierarchical model



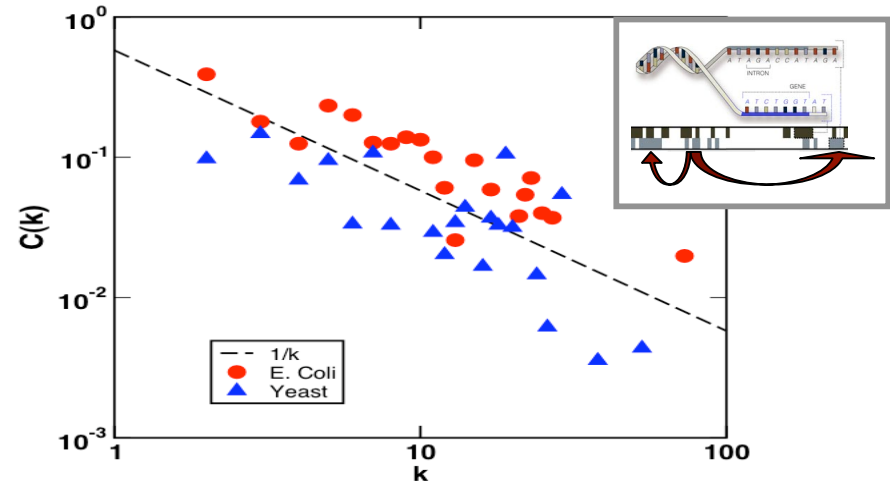
$$C(k) \sim \frac{1}{k}$$

Hierarchy in Biology

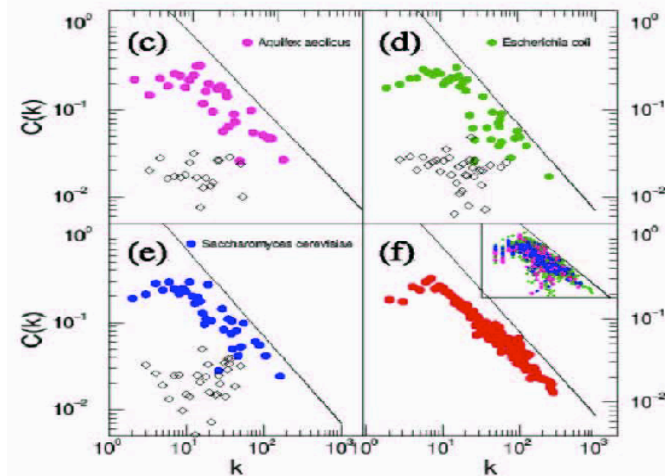
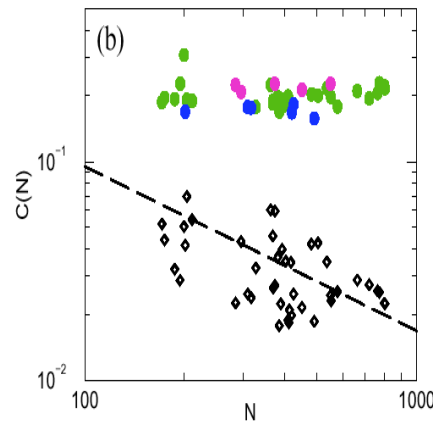
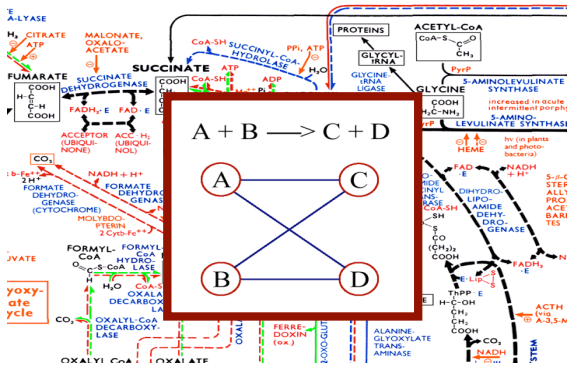
Protein-protein interaction



Regulatory networks

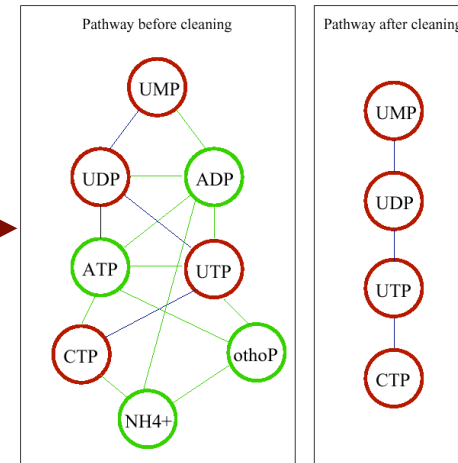
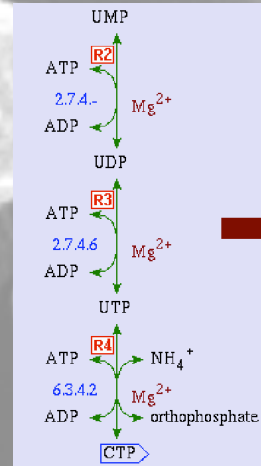
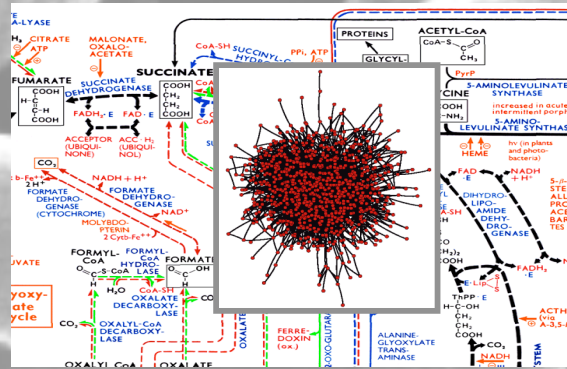


Metabolic networks

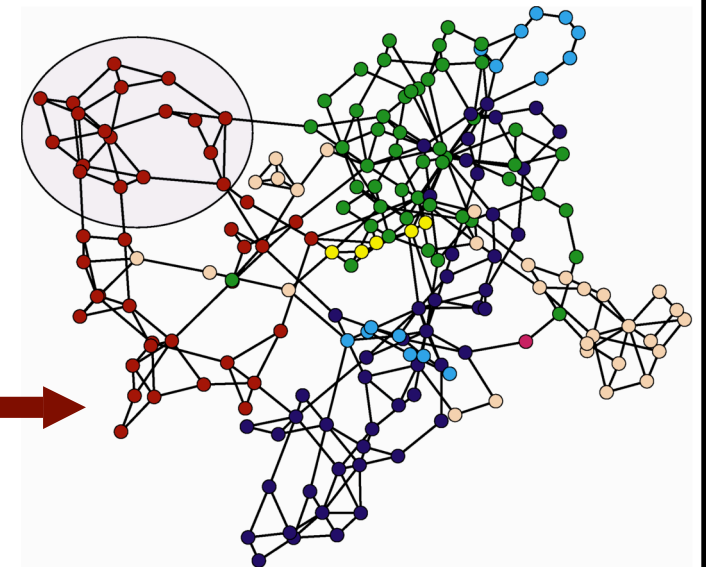
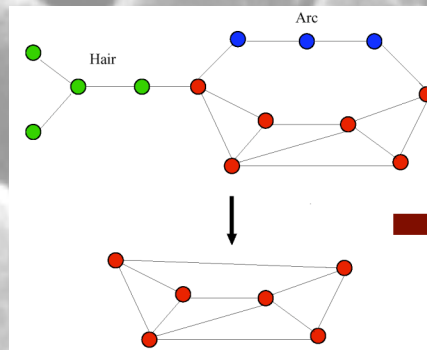
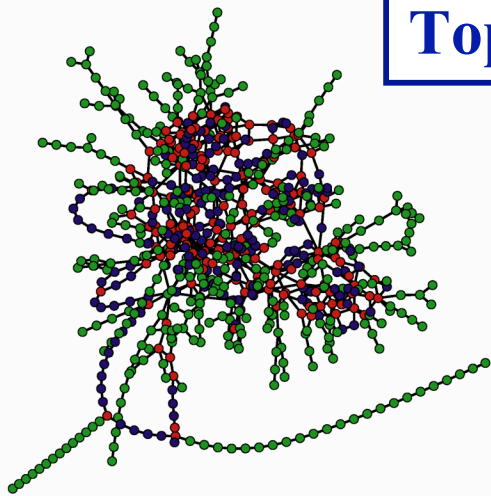


The metabolism of *E. Coli*

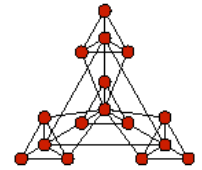
Biochemical reduction



Topological reduction

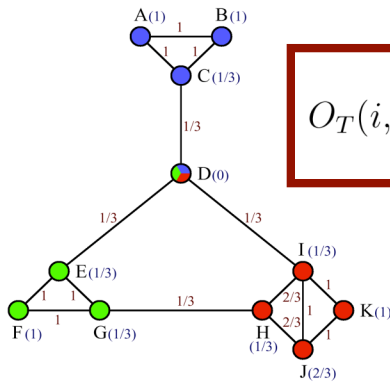


Finding the modules



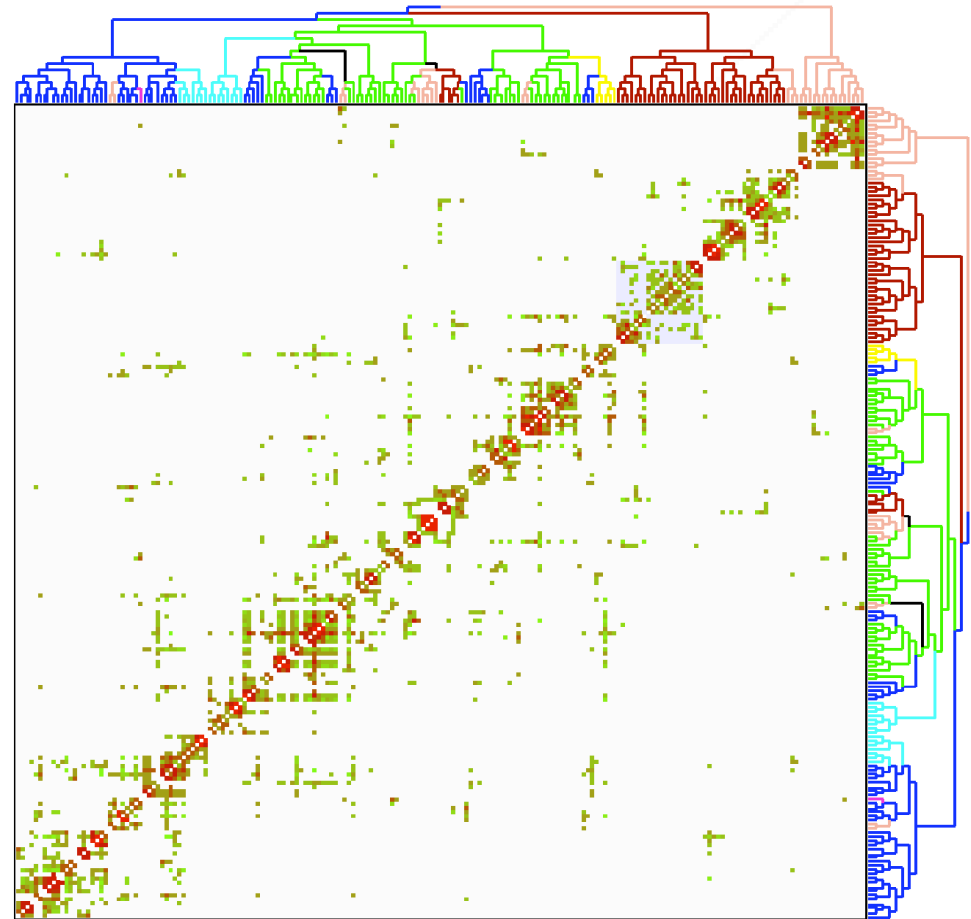
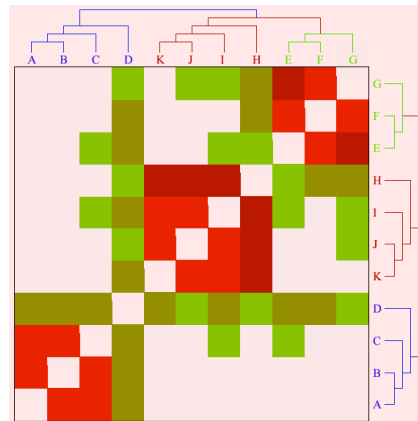
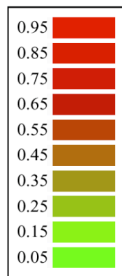
Hierarchical clustering

→ Similarity matrix



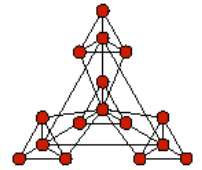
$$O_T(i, j) = \frac{\sum_{l=1}^N l_{i,l} \cdot l_{j,l} + l_{i,j}}{\min(k_i, k_j) + 1 - l_{i,j}}$$

→ Average linkage clustering (UPGMA)

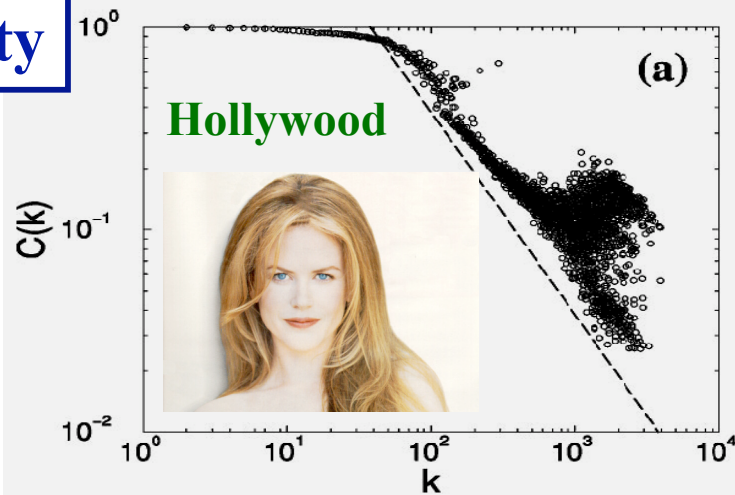


| Carbohydrates | | Lipids | | Amino acids | | | | | | | Nucleotides Nucleic Acids | | Coenz. Vit. | | | | | | | |
|---------------|-----------------|-----------------|-------------|---------------|----------|---------|----------|-------------------|----------|--------------|------------------------------|--------------|----------------|-----------|----------|------------------------------|------------|--------|------------------------|-----------|
| Disaccharides | Monosaccharides | Membrane Lipids | Fatty Acids | Organic Acids | Cysteine | Lactate | Pyruvate | Serine, Threonine | Tyrosine | Nicotinamide | Purine | Byosynthesis | Glycoxilate | Glutamate | Arginine | Metab. sugar etc. Formate | Pyrimidine | Purine | Sirohem Chorisinate | Vitamin K |

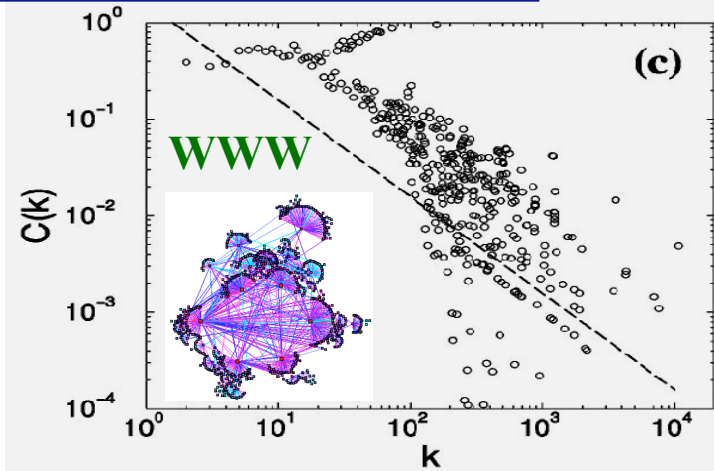
Hierarchical networks



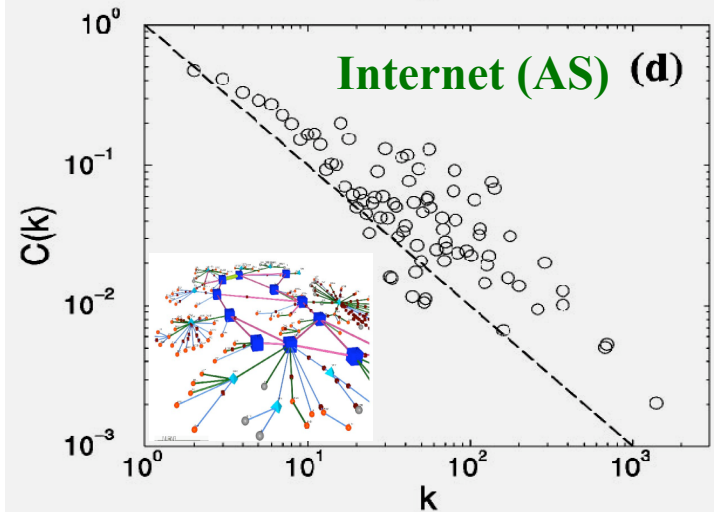
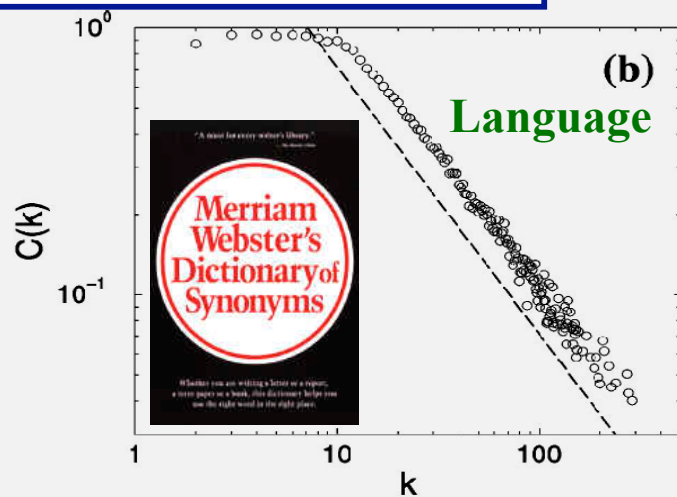
Society



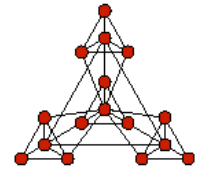
The electronic skin



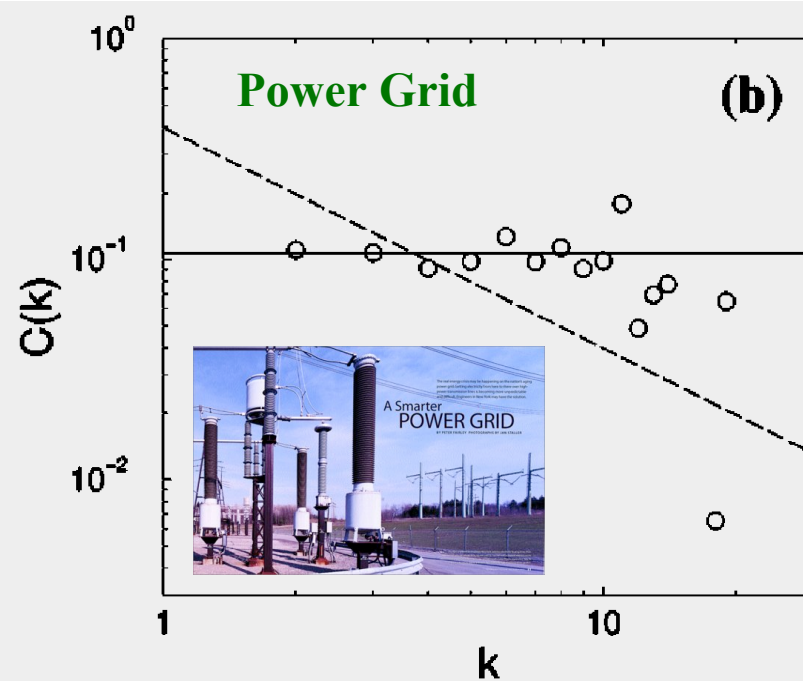
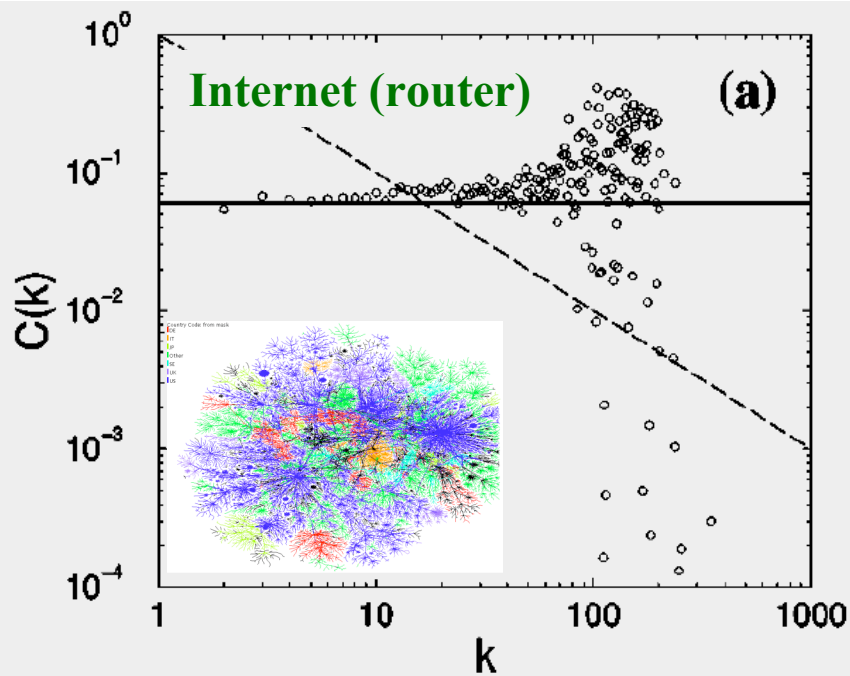
Human communication



Absence of hierarchy



Geographically localized networks



Economic pressure to minimize link lengths

Thank you!

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

Thanks to:

- Albert László Barabási
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