

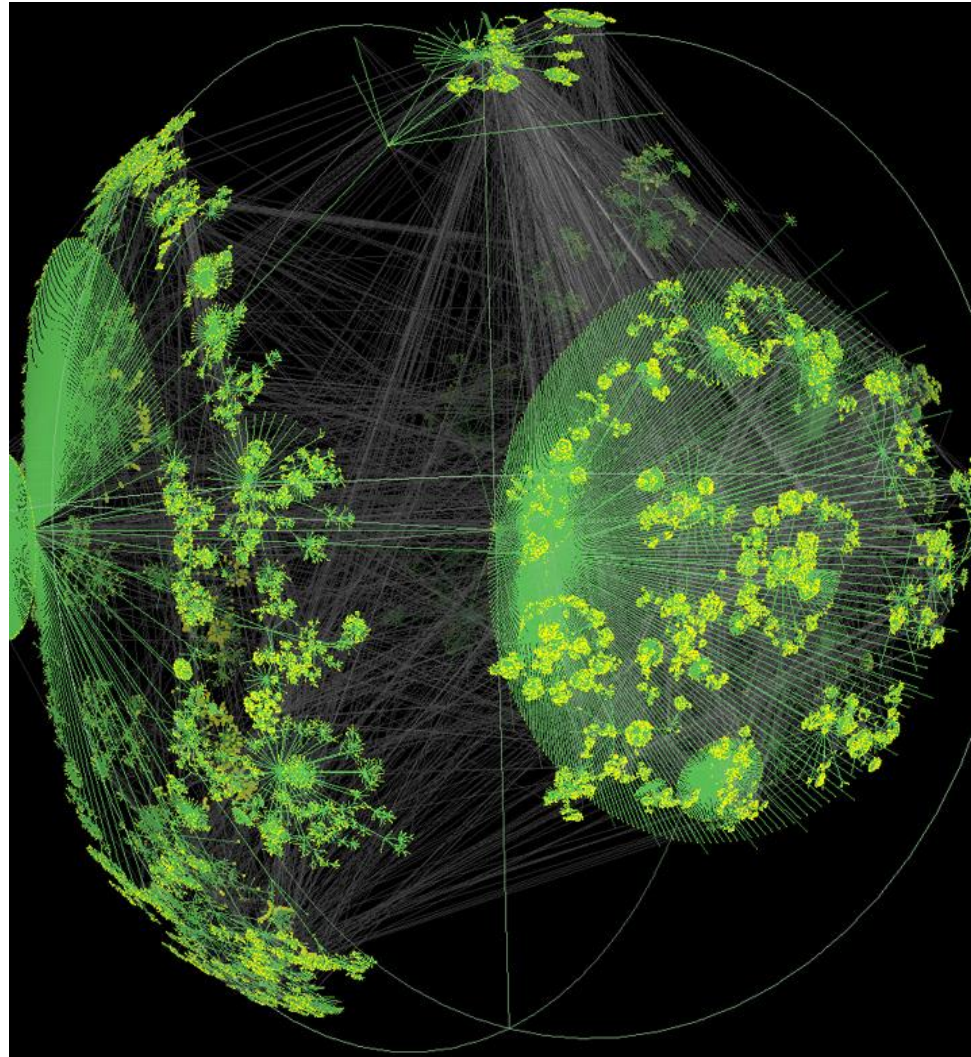
# Ch3 Biological Network

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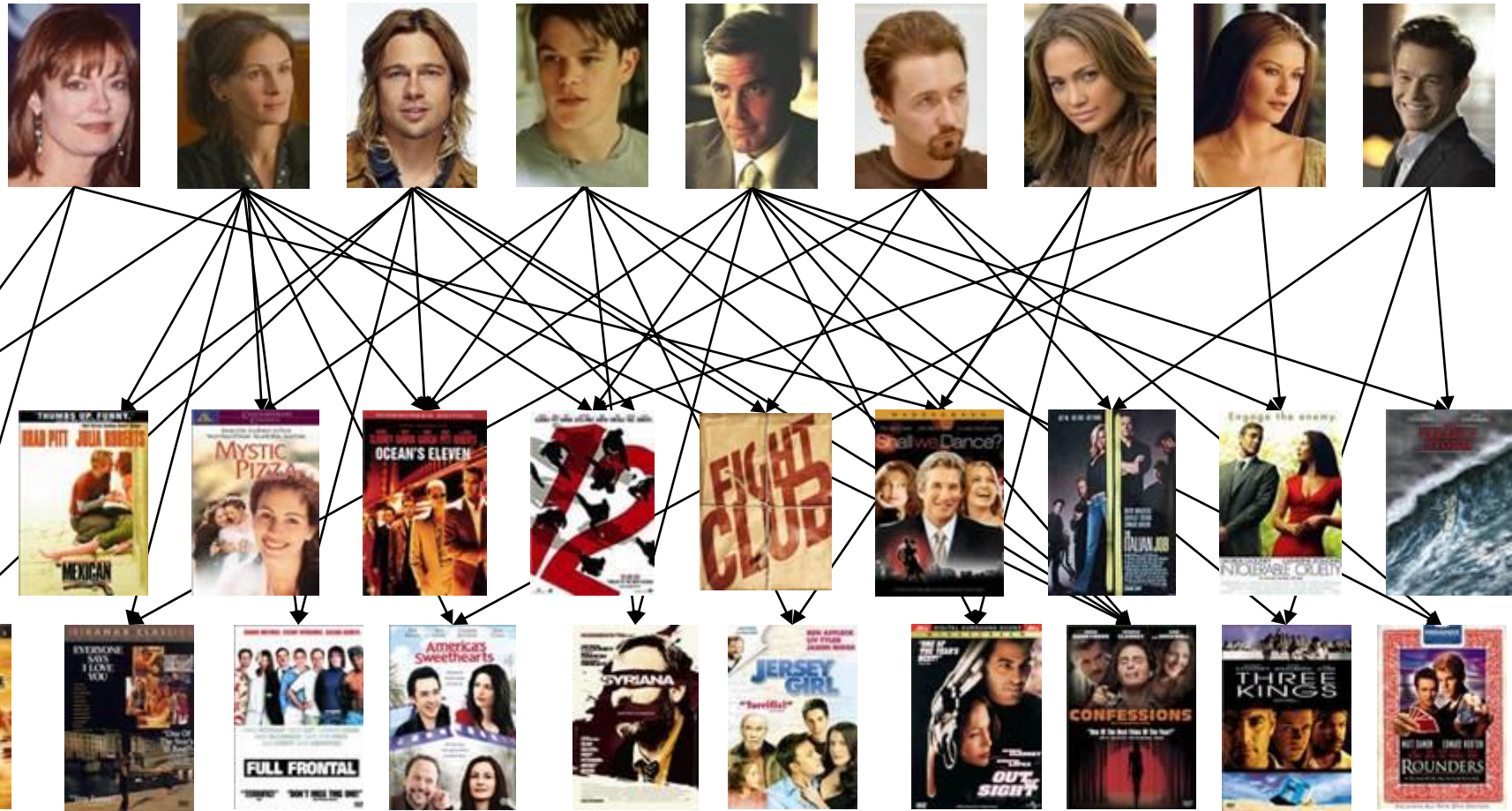
# Biological networks

- Introduction
- Biological Networks
  - Protein-Protein Interaction Network
  - Signaling Transduction Network
  - Metabolic Pathway Network
  - Gene Regulatory Network
  - Expression Network
  - .....
- Discussion

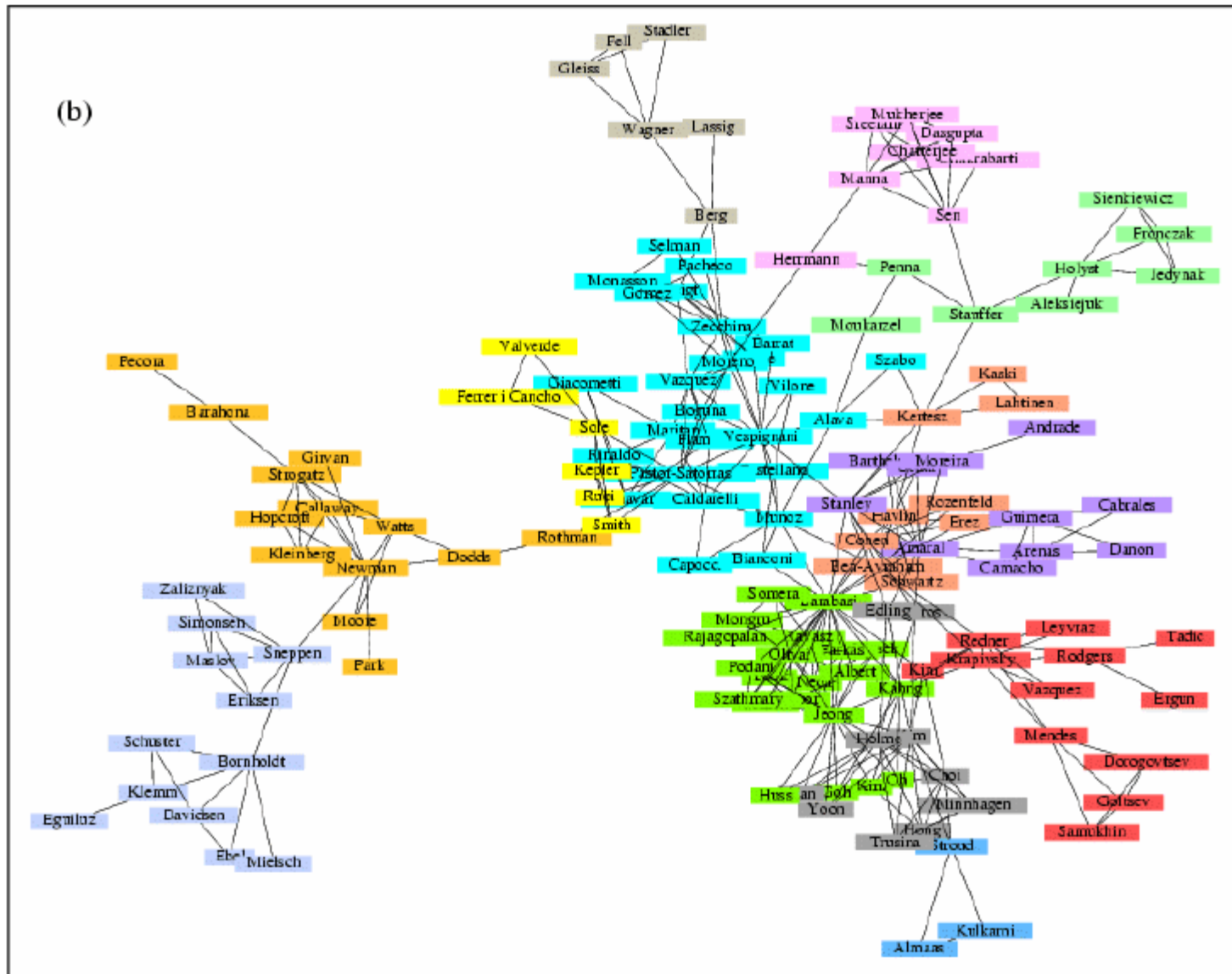
# Network Example - The Internet



# Network of actor co-starring in movies



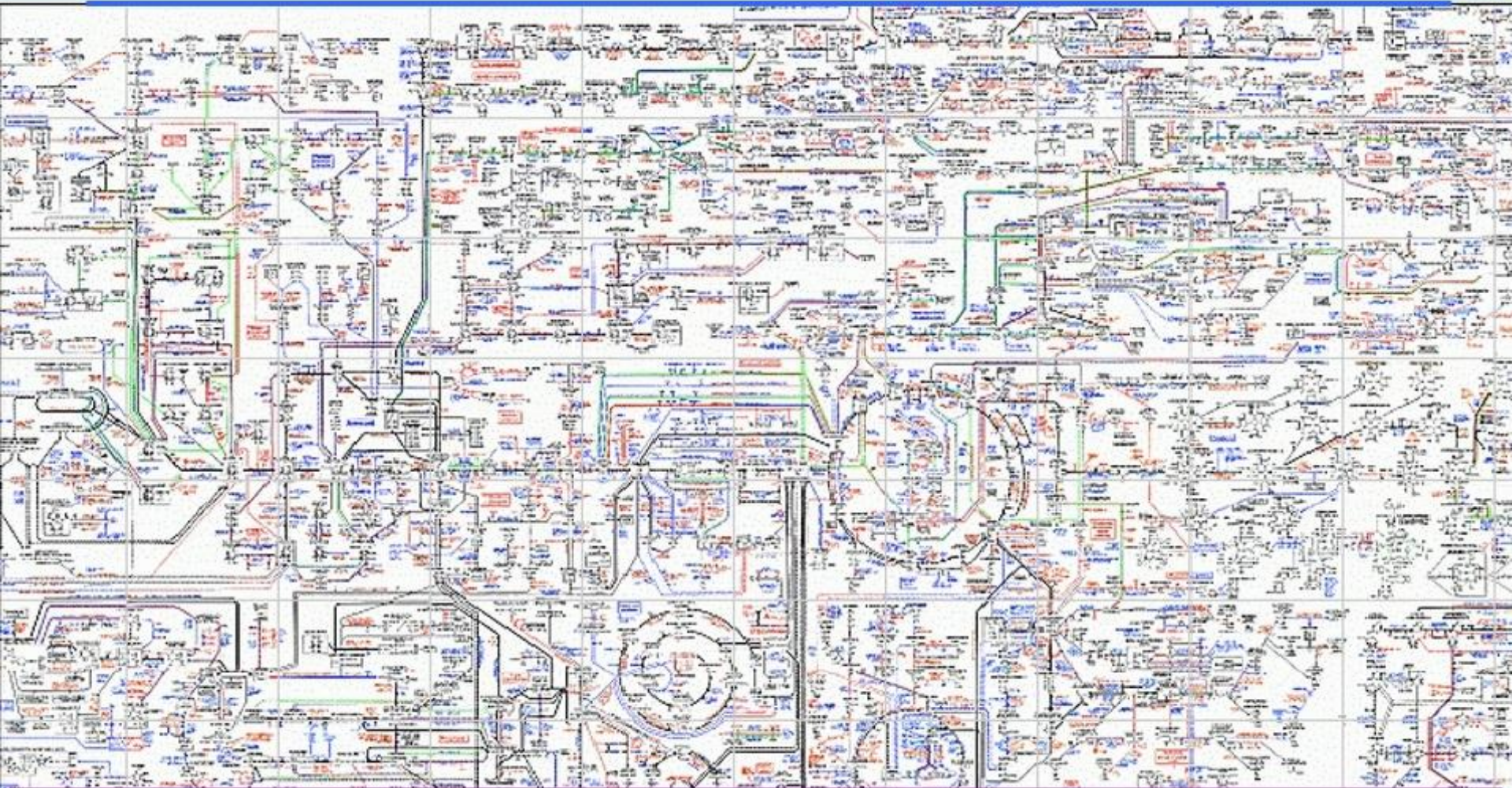
# Networks of scientists' co-authorship of papers



# transportation networks: airlines

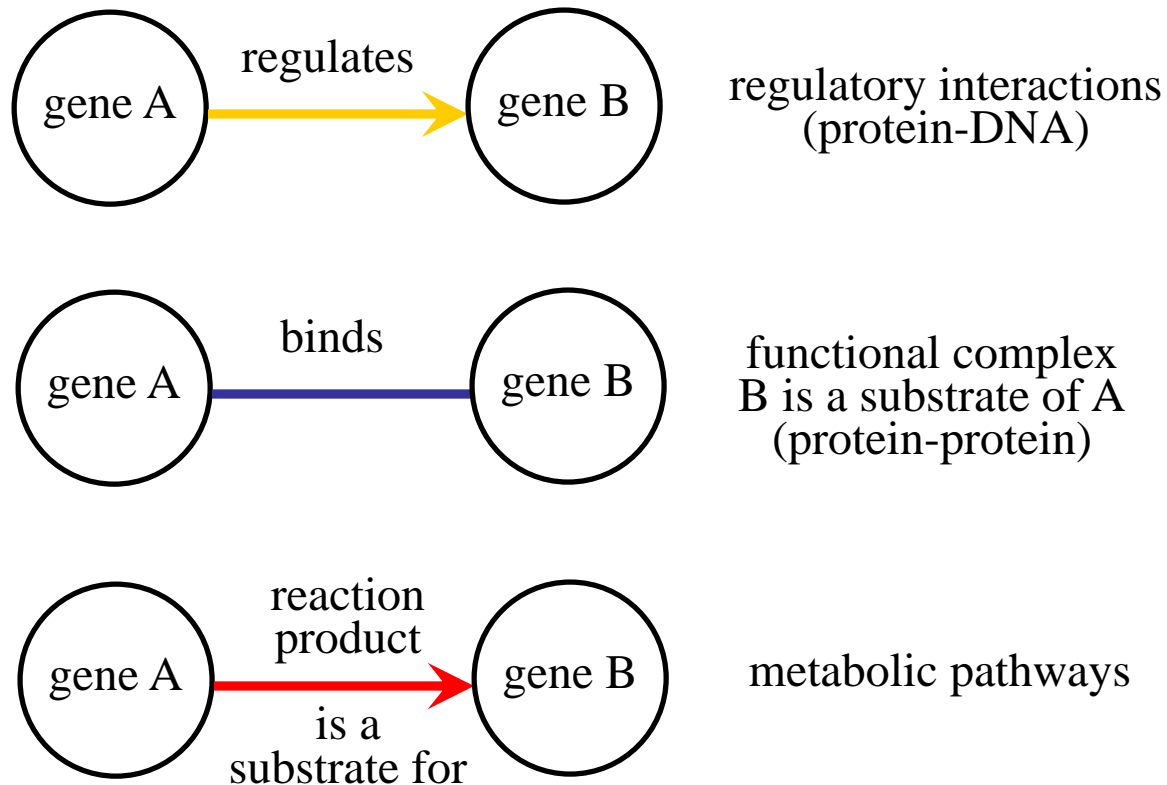


# Traits and Phenotypes are Controlled by Molecular Networks



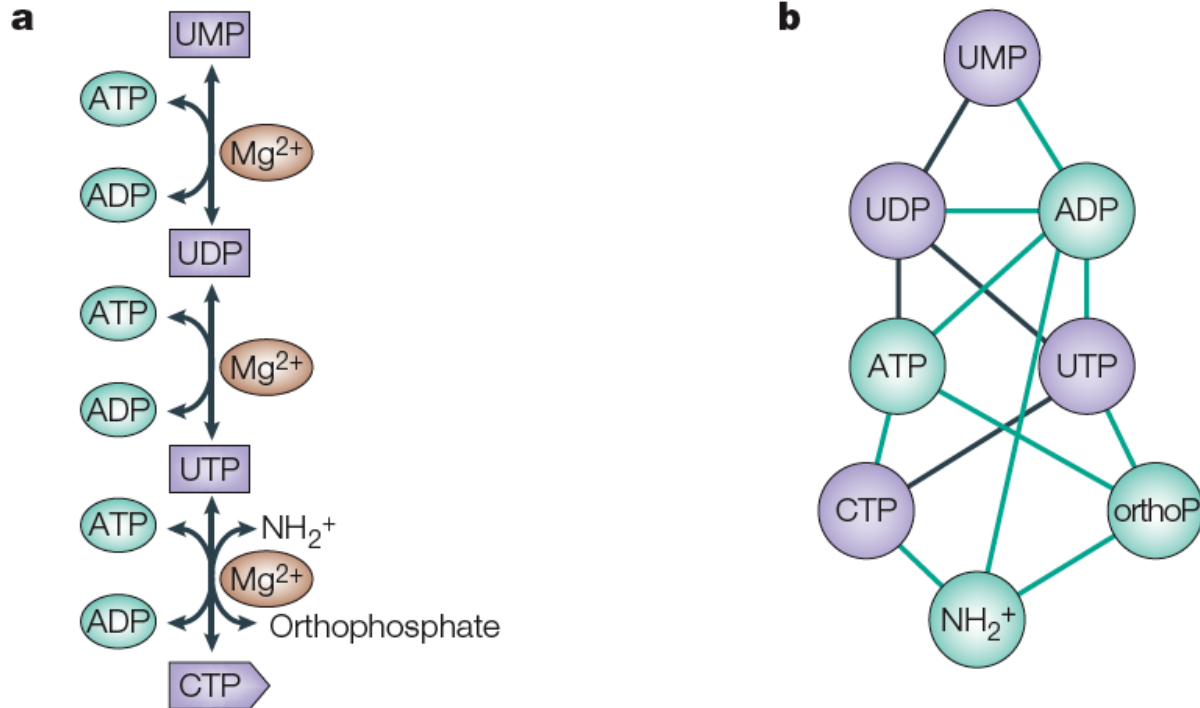
Trying to understand life without knowledge of biochemical network would be like trying to understand Shakespeare without knowledge of English grammar.

# Network Representation





# Representation of Metabolic Reactions



Networks are found in biological systems of varying scales:

1. Evolutionary tree of life
  2. Ecological networks
  3. Expression networks
  4. Regulatory networks
    - genetic control networks of organisms
  5. The protein interaction network in cells
  6. The metabolic network in cells
- ... more biological networks

# Why Study Networks?

- It is increasingly recognized that complex systems cannot be described in a reductionist view.
- Understanding the behavior of such systems starts with understanding the topology of the corresponding network.
- Topological information is fundamental in constructing realistic models for the function of the network.

# Biological Network Model

- Network

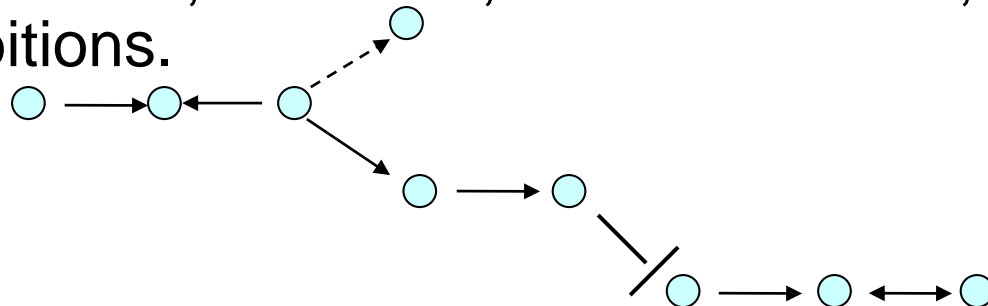
- A linked list of interconnected nodes.

- Node

- Protein, peptide, or non-protein biomolecules.

- Edges

- Biological relationships, etc., interactions, regulations, reactions, transformations, activation, inhibitions.



# Proteins in a cell

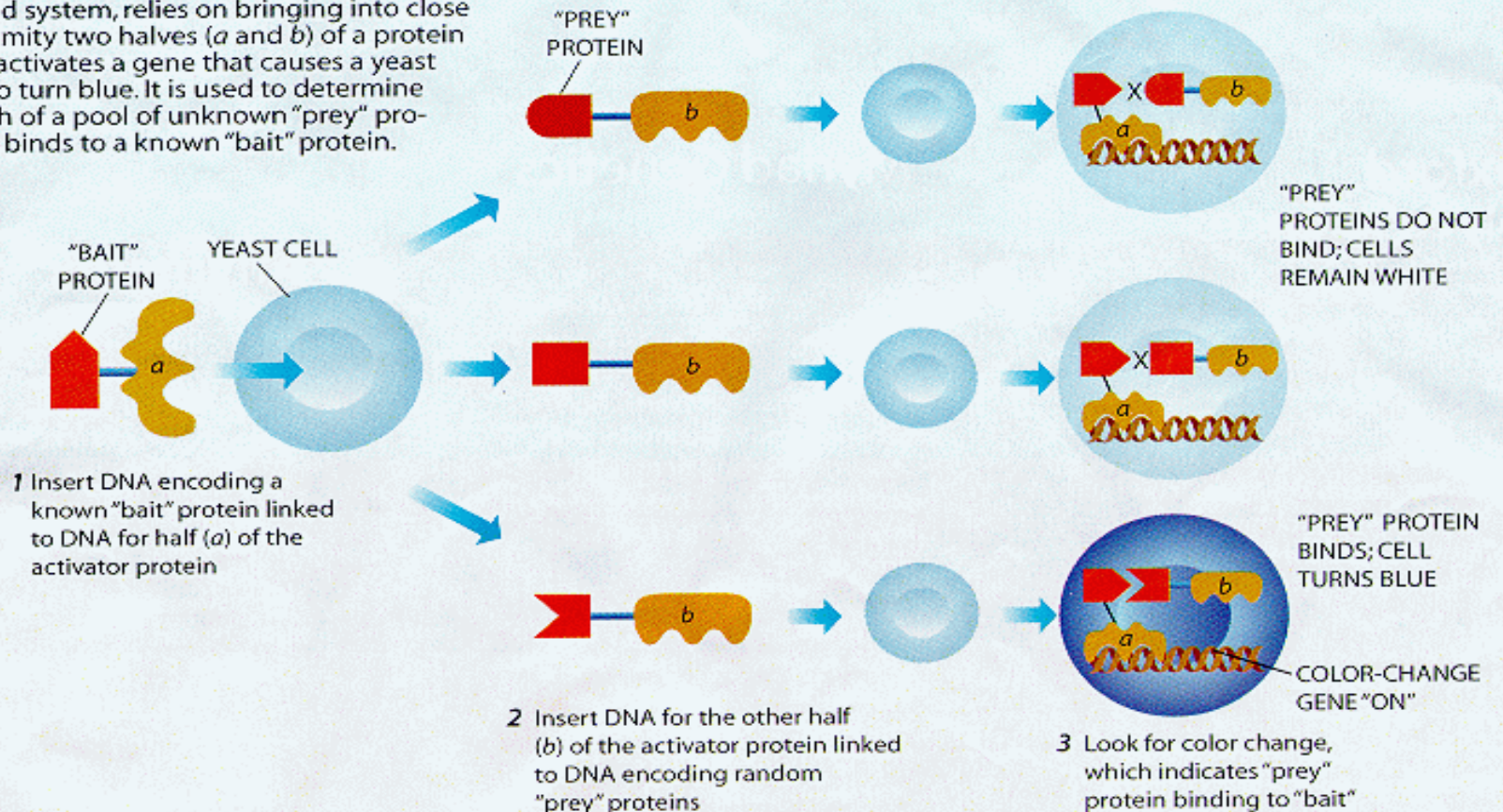
- There are thousands of different active proteins in a cell acting as:
  - enzymes, catalysors to chemical reactions of the metabolism
  - components of cellular machinery (e.g. ribosomes)
  - regulators of gene expression
  - Certain proteins play specific roles in special cellular compartments.
  - Others move from one compartment to another as “signals”.

# Protein Interactions

- Proteins perform a function as a complex rather than as a single protein.
- Knowing whether two proteins interact can help us discover unknown proteins' functions:
  - If the function of one protein is known, the function of its binding partners are likely to be related- “guilt by association”.
  - Thus, having a good method for detecting interactions can allow us to use a small number of proteins with known function to characterize new proteins.

# Finding Proteins That Interact

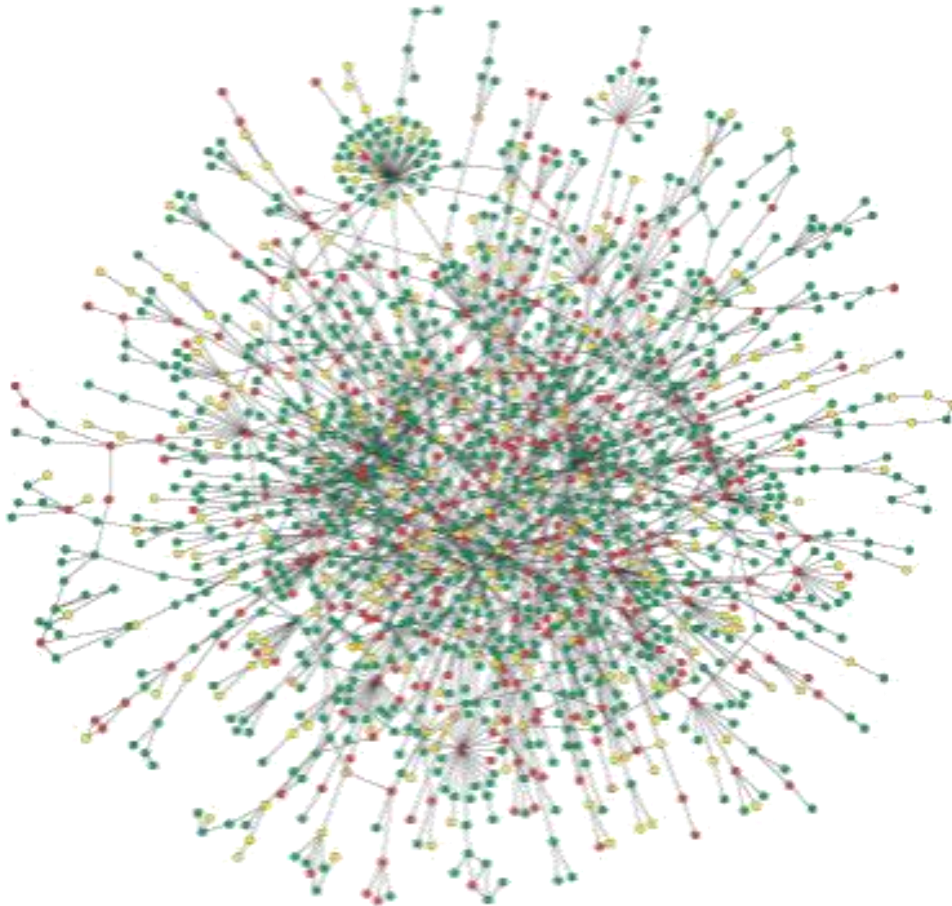
One technique, called the yeast two-hybrid system, relies on bringing into close proximity two halves (*a* and *b*) of a protein that activates a gene that causes a yeast cell to turn blue. It is used to determine which of a pool of unknown "prey" proteins binds to a known "bait" protein.



## Yeast Two Hybrid

P. Uetz, et al. **Nature**, 2000; Ito et al., **PNAS**, 2001; ...

# Yeast Protein Interaction Network



**Nodes**: proteins

**Links**: physical interactions (binding)



# Database for protein interaction

– HPRD

<http://www.hprd.org/>

– BioGRID (physic and genetic interaction)

<http://www.thebiogrid.org/>

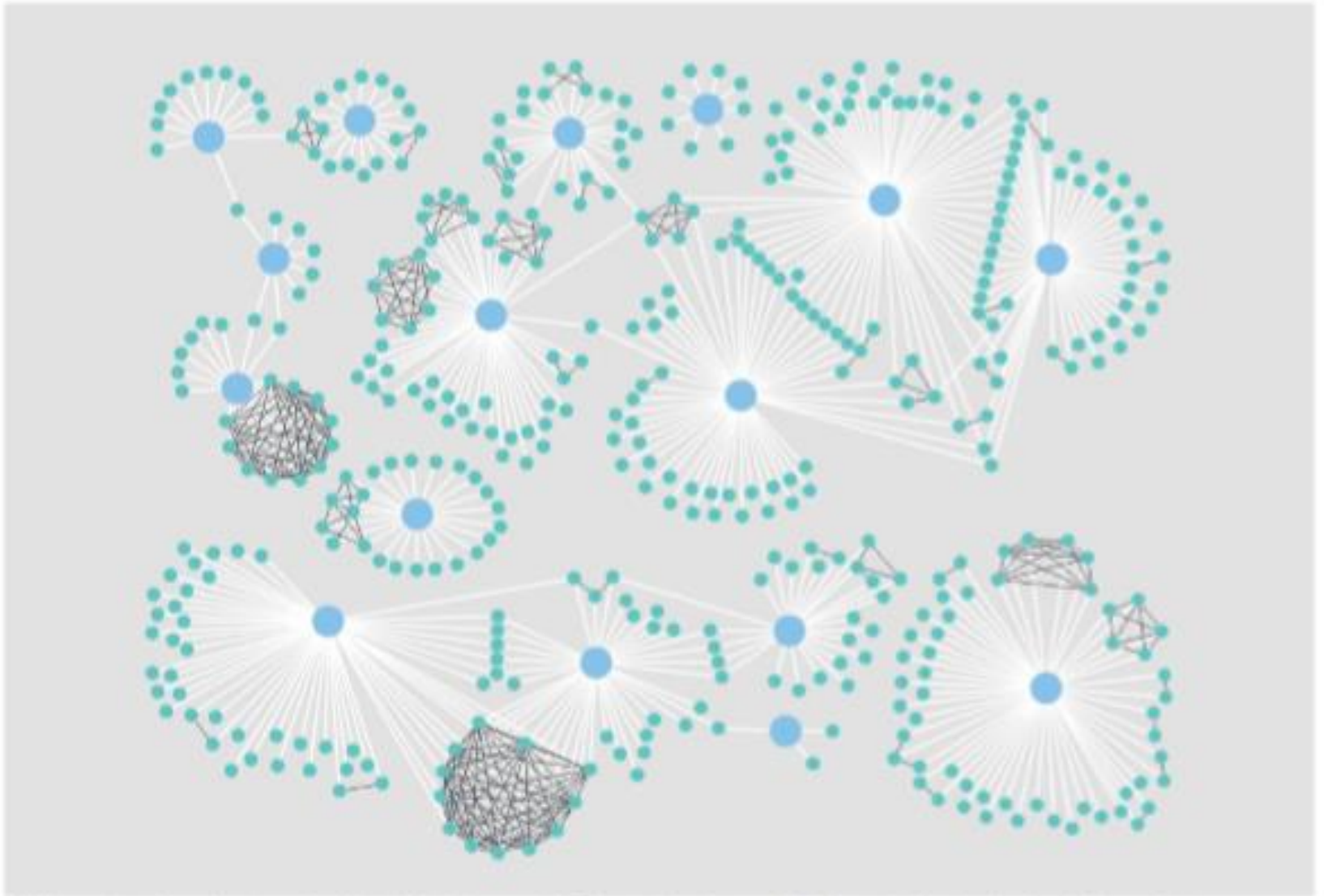
– DIP (experimentally determined)

<http://dip.doe-mbi.ucla.edu/dip/Main.cgi>

-- STRING

<https://string-db.org/>

# HIV病毒蛋白与人体蛋白的互作网络



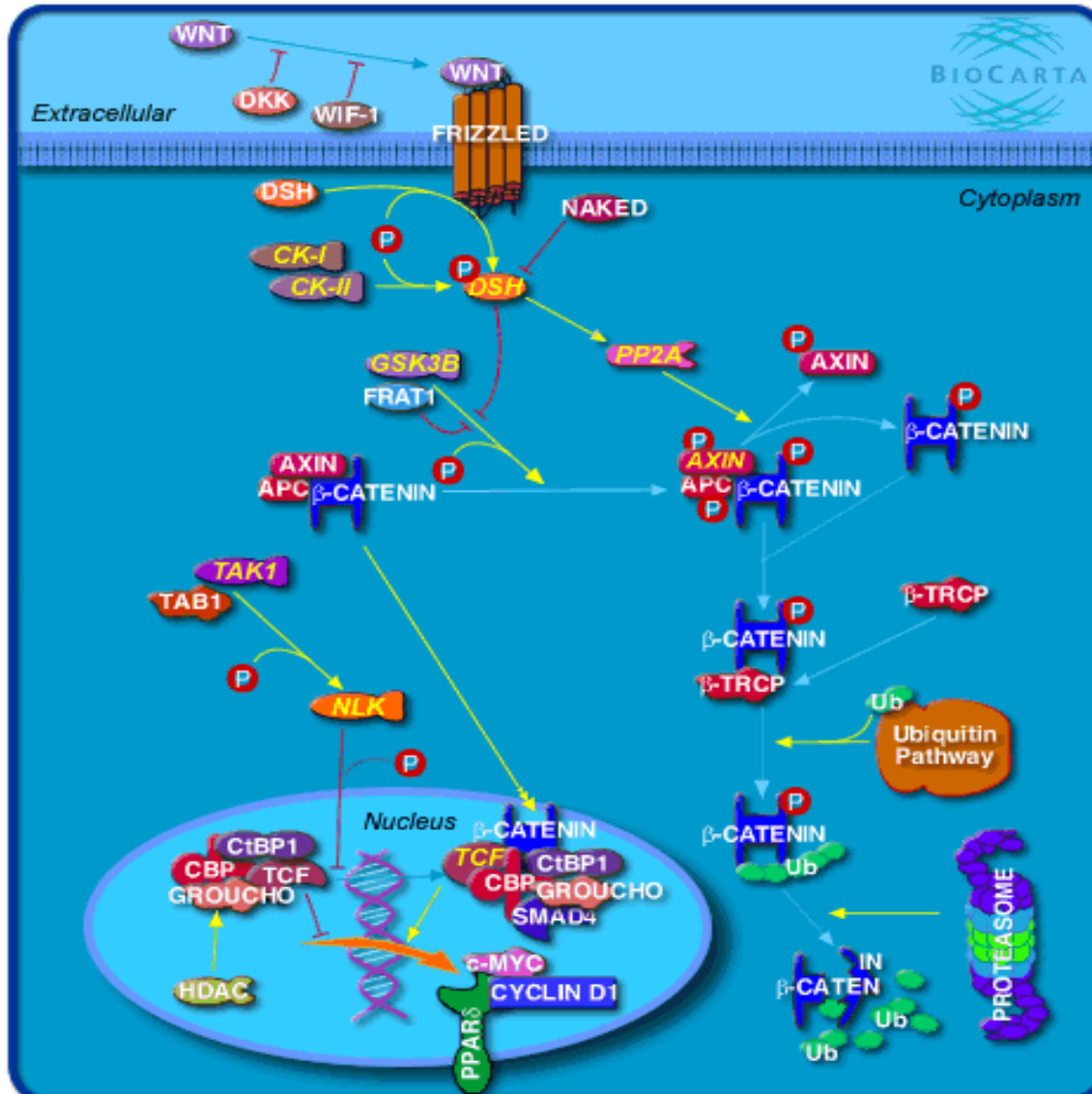
Multiple replicated experiments and sophisticated statistics reveal 497 interactions between 16 HIV proteins (blue) and hundreds of human factors.

Nature (2012), 484: 271.

# Signaling Transduction Network

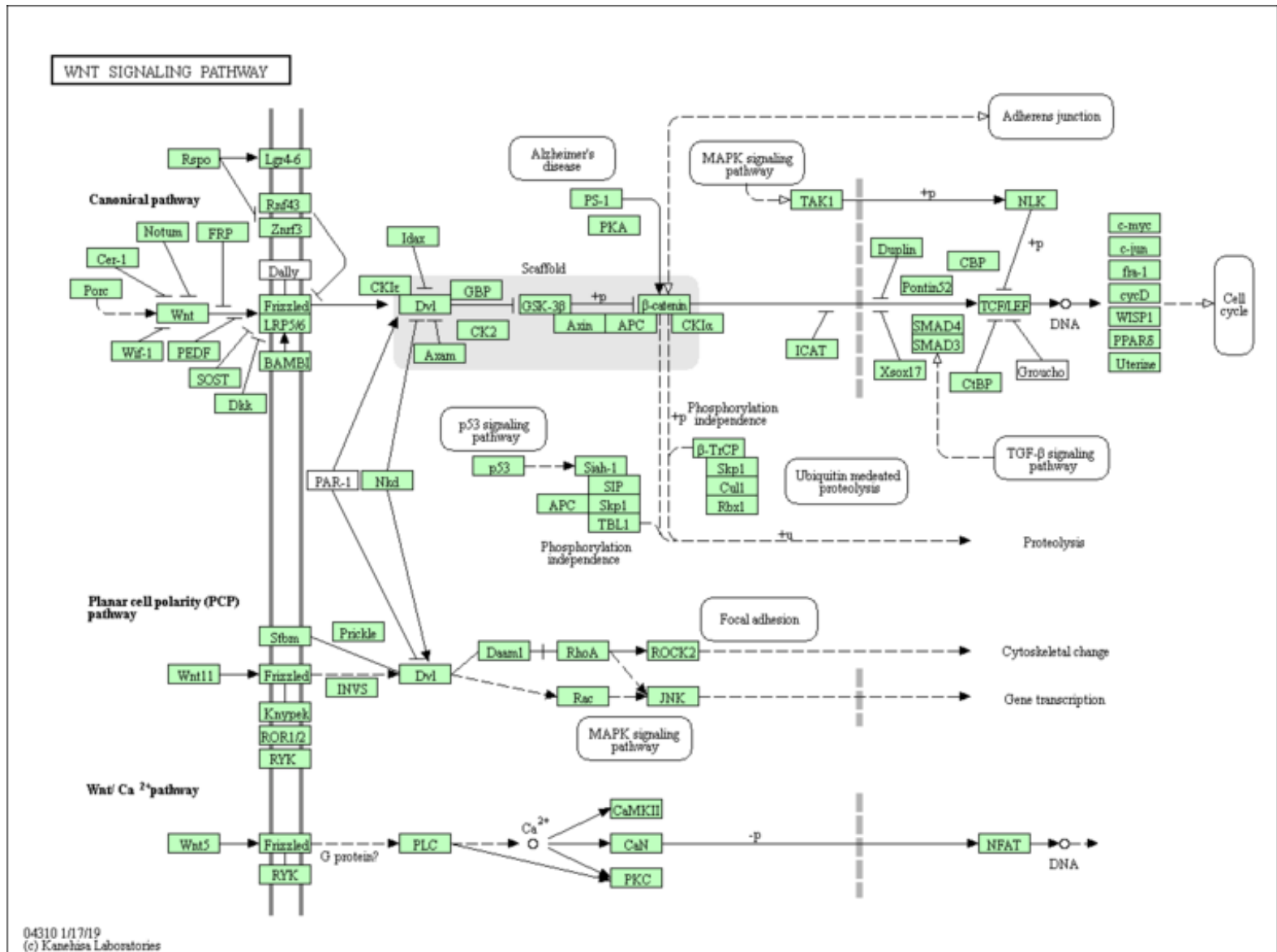
- In biology a **signal** or **biopotential** is **an electric quantity** (voltage or current or field strength), caused by chemical reactions of charged ions.
- refer to any process by which a cell converts one kind of signal or stimulus into another.
- Another use of the term lies in describing the **transfer of information between and within cells**, as in signal transduction.

# Signaling transduction network



Biocarta  
KEGG  
STKE

# Wnt Signaling pathway in KEGG

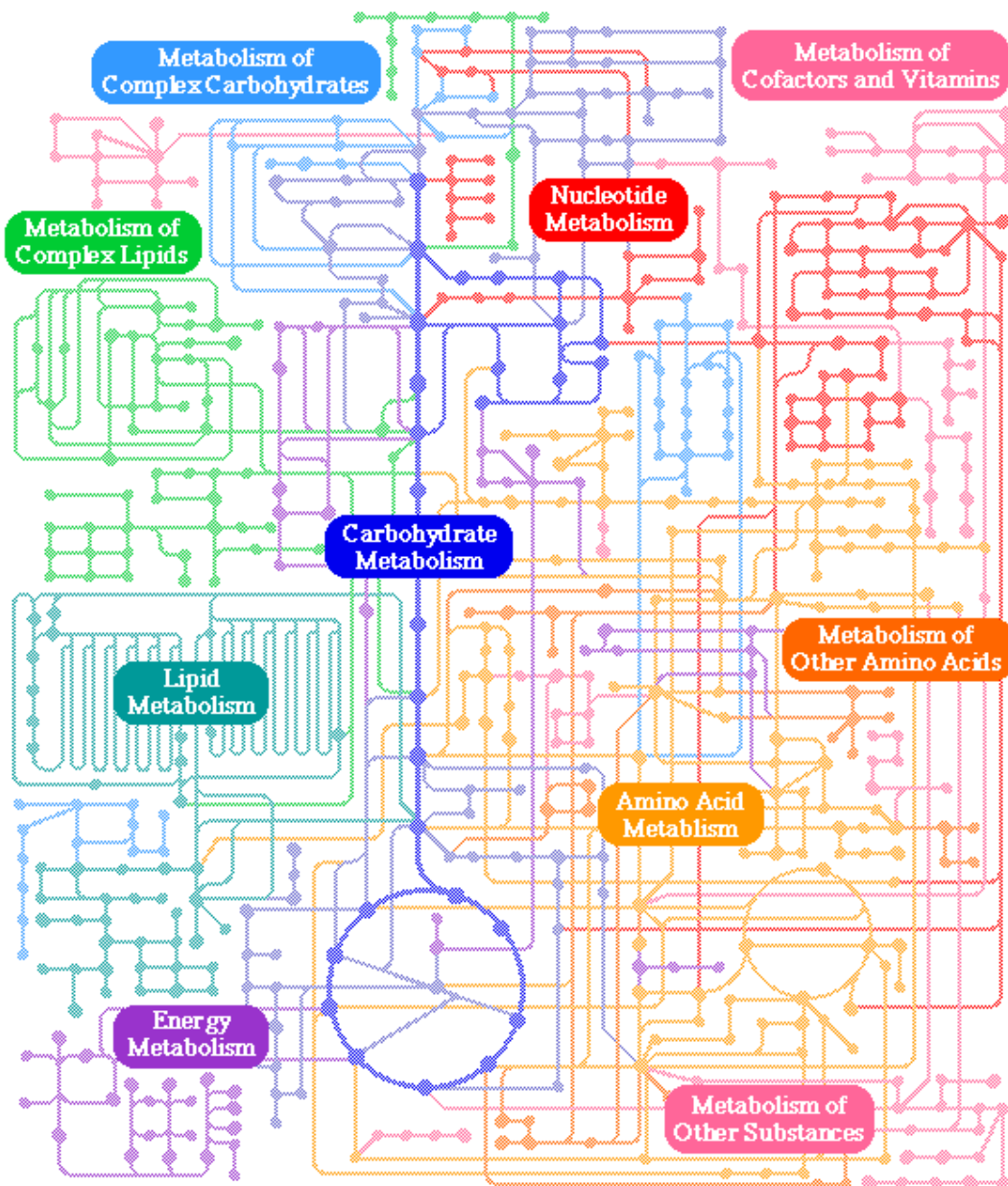


# Metabolic Network

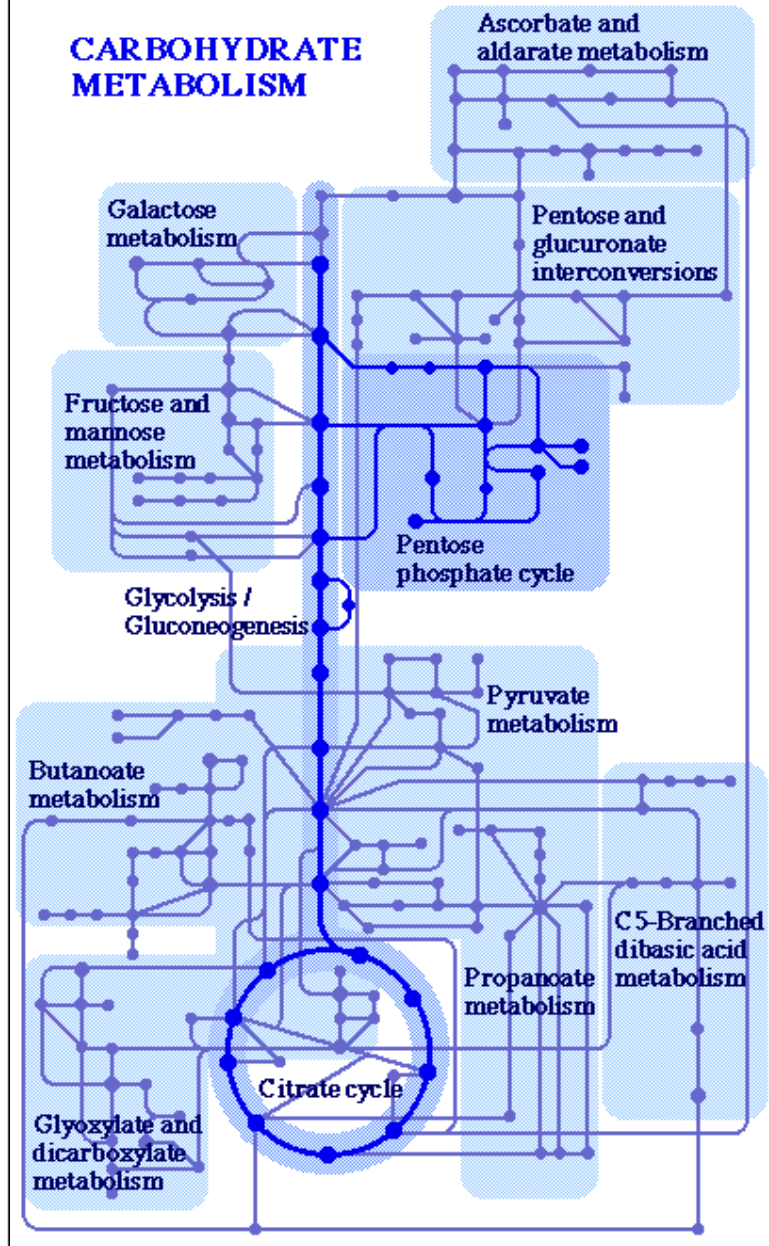
- A series of chemical reactions occurring within a cell, catalyzed by enzymes, resulting in either the formation of a metabolic product to be used or stored by the cell, or the initiation of another metabolic pathway

# KEGG Metabolic Pathway

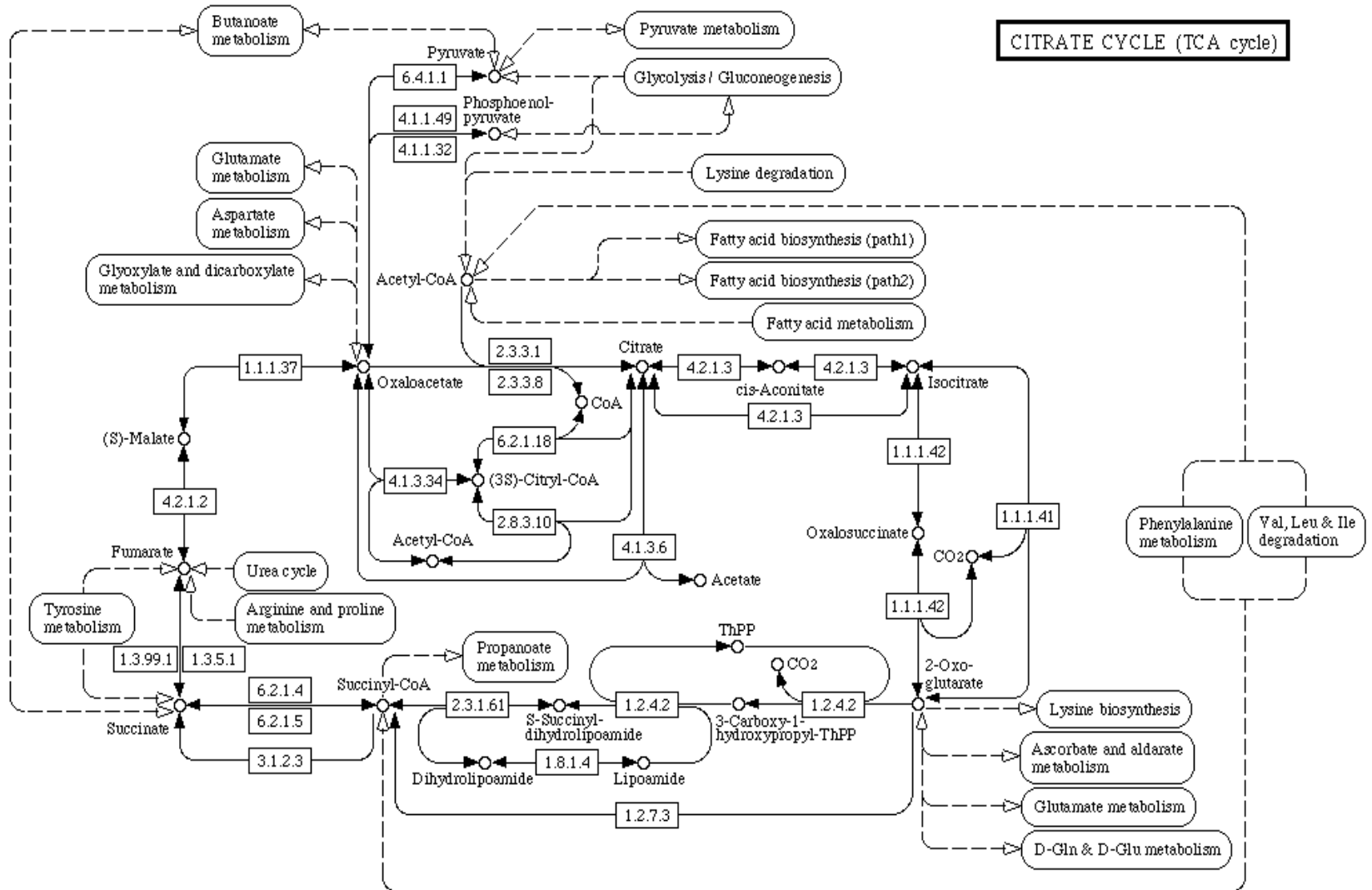
## METABOLIC PATHWAYS



## CARBOHYDRATE METABOLISM



# Metabolic Pathway Example





# Database for metabolic pathway



KEGG

<http://www.genome.jp/kegg/>



BioCyc

<http://biocyc.org/>



PlantCyc

<http://www.plantcyc.org/>



BRENDA

<http://www.brenda-enzymes.org/>



Reactome

<http://www.reactome.org/>



BIGG

<http://bigg.ucsd.edu/>

# Regulatory Network

- A collection of DNA segments (genes) in a cell which interact with each other and with other substances in the cell, thereby governing the rates at which genes in the network are transcribed into mRNA.



# Regulatory Network Resource

RegulonDB <http://regulondb.ccg.unam.mx/>

The screenshot shows the RegulonDB website in a web browser. The browser's address bar displays <http://regulondb.ccg.unam.mx/>. The website's header features the RegulonDB logo and a navigation menu with the following items: Home, Features, Integrated Views & Tools, Downloads, and Doc & Help. The main content area is divided into several sections:

- Search by type of object:** A search box with a magnifying glass icon, a dropdown menu set to "Gene", and a red "Search" button. Below the search box, an example is provided: "Example: 'araC in Regulon'".
- Downloads:** A section with a red download icon and the title "Downloads". It contains two sub-sections:
  - Experimental Datasets:** Described as "Data files of manually curated biological objects with experimental evidence (confirmed, strong or weak)." with a red right-pointing arrow icon.
  - Computational Predictions Datasets:** Described as "Data files of genome-wide computationally predicted biological objects." with a red right-pointing arrow icon.
- Escherichia coli K-12 Transcriptional Regulatory Network:** A section with a blue title and a text box stating: "Currently the major electronically-encoded regulatory network of any free-living organism."
- RegulonDB Features:** A section with a blue title and a list of features:
  - RegulonDB is the primary database on transcriptional regulation in *Escherichia coli* K-12 containing knowledge manually curated from original scientific publications, complemented with high throughput datasets and comprehensive computational predictions.
  - Graphic and text-integrated environment with friendly navigation where regulatory information is always at hand.
  - We strive for facilitating integrated views for users to understand

# YeastRACT <http://www.yeastRACT.com/>

http://www.yeastRACT.com/formregassociations.php

王健林注资马克

Zimbra: 收件箱 (42) | RegulonDB Database | YEASTRACT

**YeastRACT** **TÈCNICO LISBOA**

Home > Search Regulatory Associations [Contact Us](#) [Tutorial](#) [Help](#)

Quick search... [GO](#)

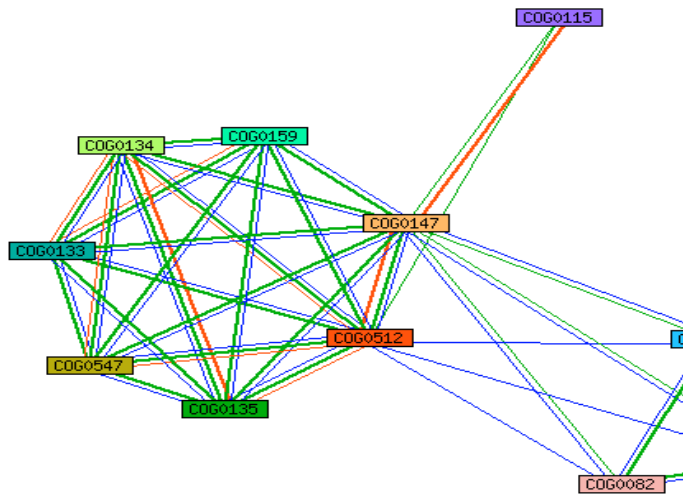
### Search Regulatory Associations

Filter Regulations by	Transcription factors	Target ORF/Genes
<b>Documented</b> <ul style="list-style-type: none"><li><input type="radio"/> Only DNA binding evidence</li><li><input type="radio"/> Only Expression evidence<ul style="list-style-type: none"><li><input checked="" type="checkbox"/> TF acting as activator</li><li><input checked="" type="checkbox"/> TF acting as inhibitor</li></ul></li><li><input checked="" type="radio"/> DNA binding <b>plus</b> expression evidence</li><li><input type="radio"/> DNA binding <b>and</b> expression evidence</li></ul>		
<b>Potential</b> <ul style="list-style-type: none"><li><input type="checkbox"/> Consider PBM/MITOMI-based motifs</li></ul>		
<b>Filter Documented Regulations by environmental condition:</b> Group: ---- Subgroup: ----		
<b>While searching for regulations, consider:</b> <ul style="list-style-type: none"><li><input checked="" type="radio"/> User TF list against User target gene list</li><li><input type="radio"/> YeastRACT TF list against User target gene list</li><li><input type="radio"/> User TF list against YeastRACT target gene list</li></ul>		
<b>Search regulations between:</b> <ul style="list-style-type: none"><li><input checked="" type="radio"/> Each Transcription Factor to Any Gene</li><li><input type="radio"/> Every Transcription Factor to Any Gene</li></ul>		

Back to top

# Expression Network

- A network representation of genomic data.
- Inferred from genomic data, i.e. microarray.



Similarity of gene expression

Your Input:

- COG0512 - Anthranilate/para-aminobenzoate synthases component II

Predicted Functional Associations:

	Score
COG0147 - Anthranilate/para-aminobenzoate synthases component I	0.998
COG0547 - Anthranilate phosphoribosyltransferase	0.958
COG0134 - Indole-3-glycerol phosphate synthase	0.930
COG0135 - Phosphoribosylanthranilate isomerase	0.863
COG0159 - Tryptophan synthase alpha chain	0.843
COG0133 - Tryptophan synthase beta chain	0.791
COG0128 - 5-enolpyruvylshikimate-3-phosphate synthase	0.707
COG0169 - Shikimate 5-dehydrogenase	0.707
COG0115 - Branched-chain amino acid aminotransferase/4-amino-4-deoxychorismate 1 [...]	0.555
COG0082 - Chorismate synthase	0.454

# Discussion

- **Problems**
  - Network Inference
    - Micro Array, Protein Chips, other high throughput assay methods
  - Function prediction
    - The function of 40-50% of the new proteins is unknown
    - Understanding biological function is important for:
      - Study of fundamental biological processes
      - Drug design
      - Genetic engineering
  - Functional module detection
    - Cluster analysis
  - Topological Analysis
    - Descriptive and Structural
    - Locality Analysis
    - Essential Component Analysis
  - Dynamics Analysis
    - Signal Flow Analysis
    - Metabolic Flux Analysis
    - Steady State, Response, Fluctuation Analysis
  - Evolution Analysis
- Biological Networks are very rich networks with very limited, noisy, and incomplete information.
- Discovering underlying principles is very challenging.