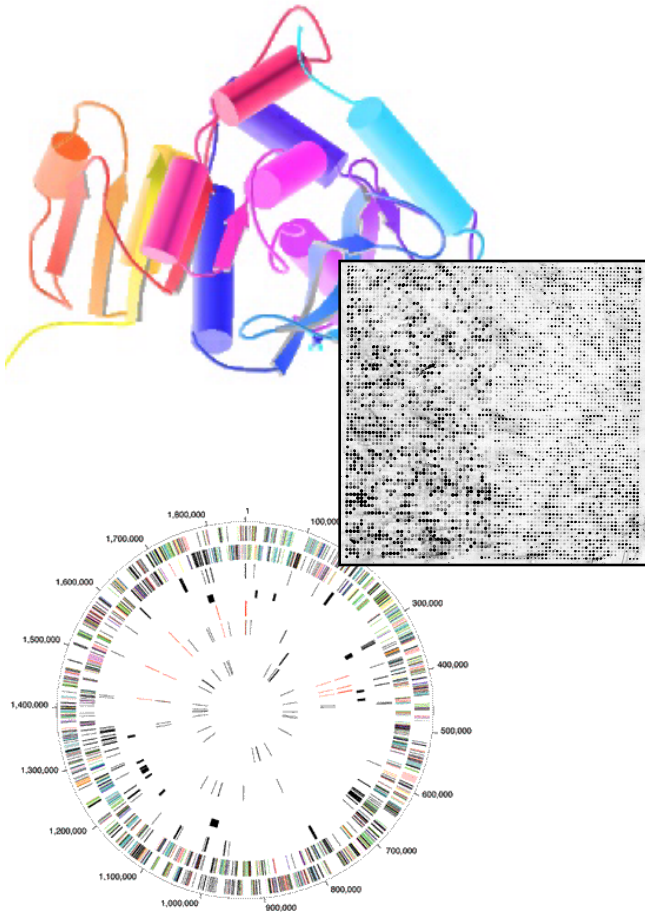


Bioinformatics: Analysis of Network Topology

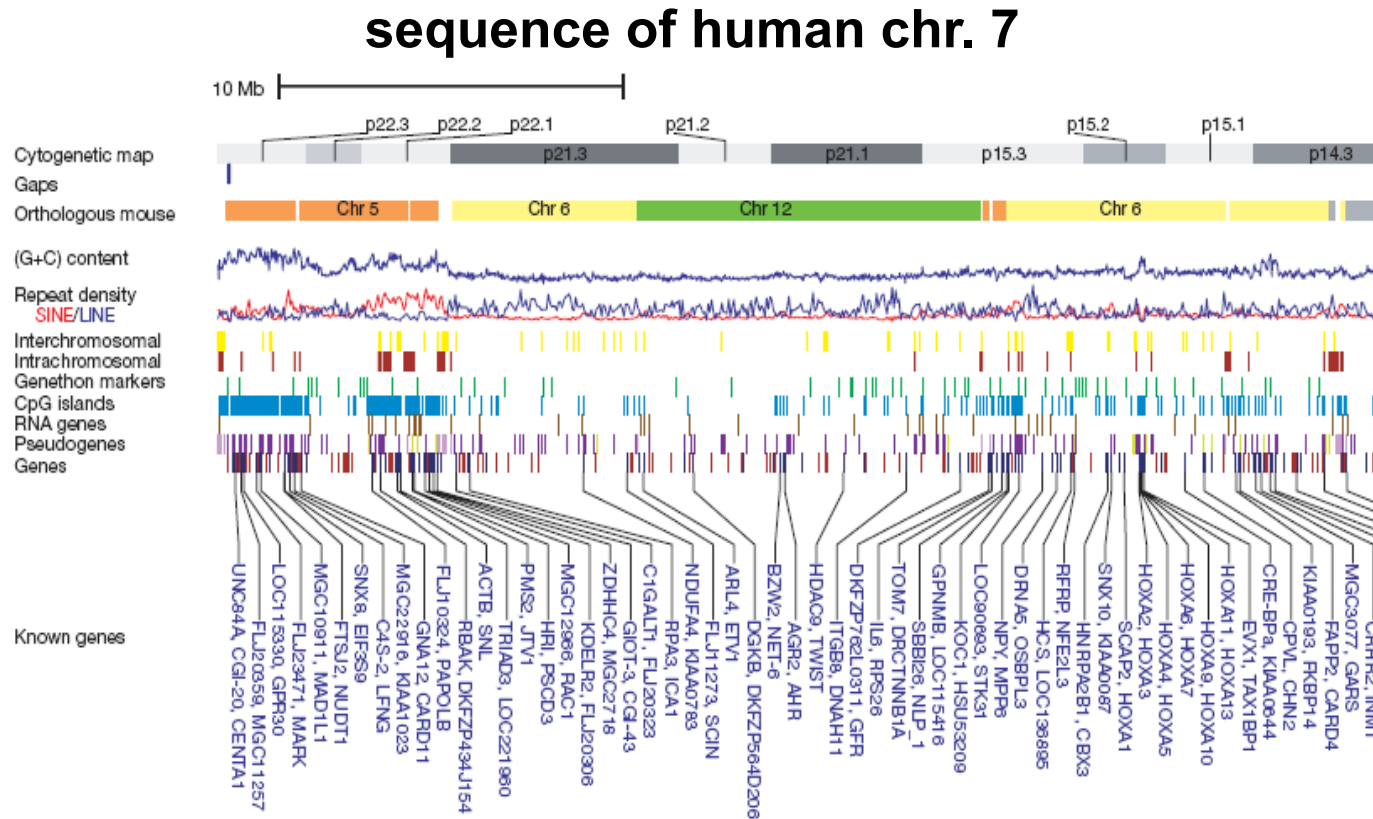


Mark Gerstein, Yale University
gersteinlab.org/courses/452
(last edit in spring '16)

Reasons for Networks

- (1) Provide a scalable, systematic way to definite "function"

The problem: Grappling with Function on a Genome Scale?



~1,200 protein-coding genes
(~950 pseudogenes)

Traditional single molecule way to integrate evidence & describe function

EF2_YEAST

Descriptive Name:
Elongation Factor 2

Lots of references
to papers

Summary sentence describing function:
This protein promotes the GTP-dependent translocation of the nascent protein chain from the A-site to the P-site of the ribosome.

UniProt
the universal protein knowledgebase

Home > Database > UniProt Protein Viewer

Text Search UniProt Knowledgebase

Home About UniProt Getting Started Searches/Tools Databases Support/Documentation

General information about the UniProt/Swiss-Prot entry	
Entry name	EF2_YEAST
Primary accession number	P32324
Entered in Swiss-Prot	Release 27, 01-OCT-1993
Sequence was last modified	Release 27, 01-OCT-1993
Annotations were last modified	Release 47, 01-MAY-2005

Protein description	
Protein name	Elongation factor 2
Synonyms	EF-2

References

[1] NUCLEOTIDE SEQUENCE (EFT1 AND EFT2). MEDLINE=92112760; PubMed=1730643; [NCBI, ExPASy, EBI, Israel, Japan] Perentesis J.P., Phan L.D., Laporte D.C., Livingston D.M., Bodley J.W.; "Saccharomyces cerevisiae elongation factor 2. Genetic cloning, characterization of expression, and G-domain modeling."

Comments	
FUNCTION	This protein promotes the GTP-dependent translocation of the nascent protein chain from the A-site to the P-site of the ribosome.
SUBCELLULAR LOCATION	Cytoplasmic.

U20073, H460421.1, HEMERY, GenBank, EMBL, TrEMBL, UniProt

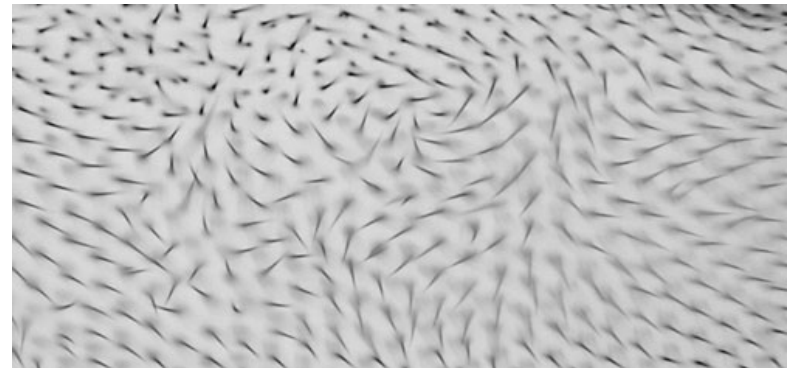
DIR Δ41778- Δ41778

Some obvious issues in scaling single molecule definition to a genomic scale

- Fundamental complexities
 - Role Conflation:
molecular, cellular, phenotypic
 - Often >2 proteins/function
 - Also Multi-functionality:
2 functions/protein
 - phenotypically – e.g. Pleiotropic effects such as human PKU being involved in retardation & eczema
 - cellular role – e.g. Depending on the molecule it interacts with HSP70 is involved with protein folding, translocation of proteins into mitochondria, biogenesis of certain subunits..

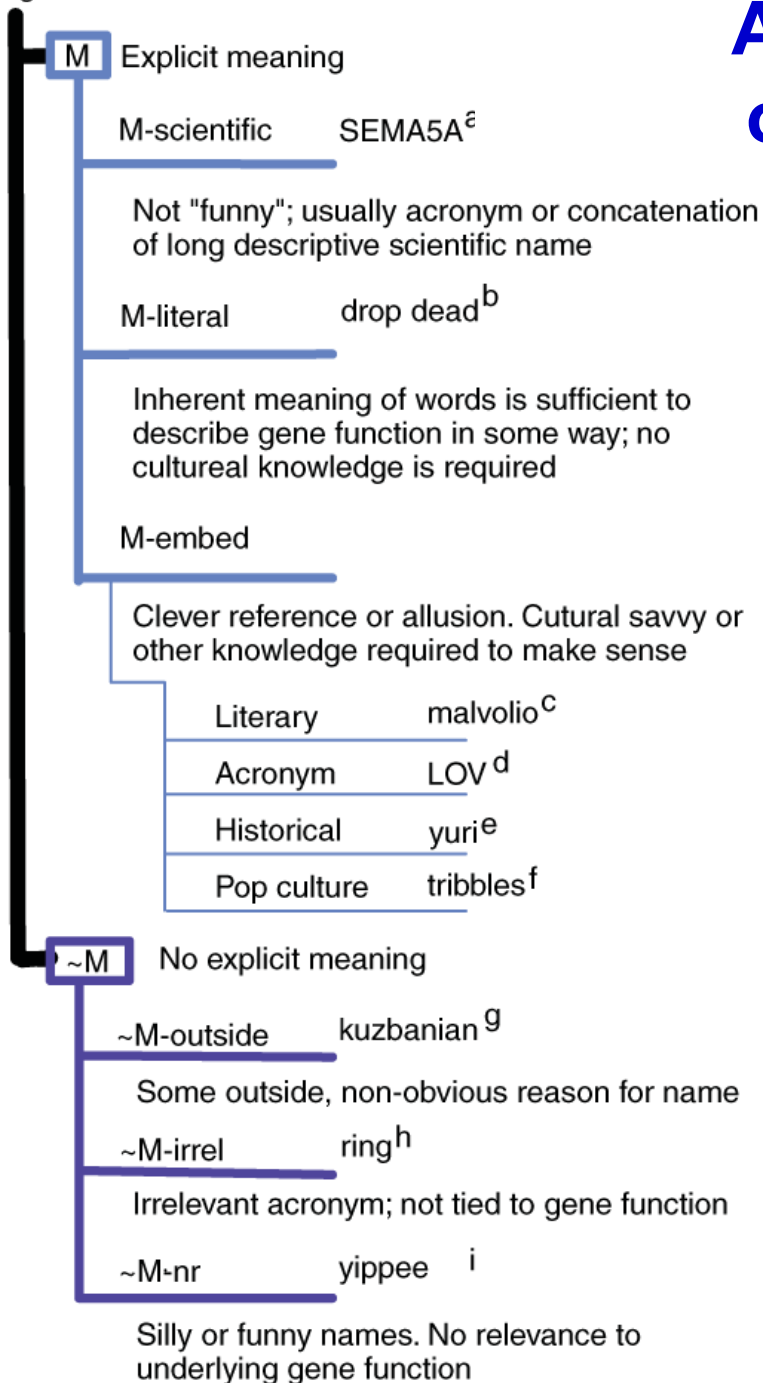
Some obvious issues in scaling single molecule definition to a genomic scale

- Fundamental complexities
 - Role Conflation: molecular, cellular, phenotypic
 - Often >2 proteins/function
 - Also Multi-functionality: 2 functions/protein
 - phenotypically – e.g. Pleiotropic effects such as human PKU being involved in retardation & eczema
 - cellular role – e.g. Depending on the molecule it interacts with HSP70 is involved with protein folding, translocation of proteins into mitochondria, biogenesis of certain subunits..
- Fun terms... but do they scale?....
 - **Starry night** (P Adler, '94)

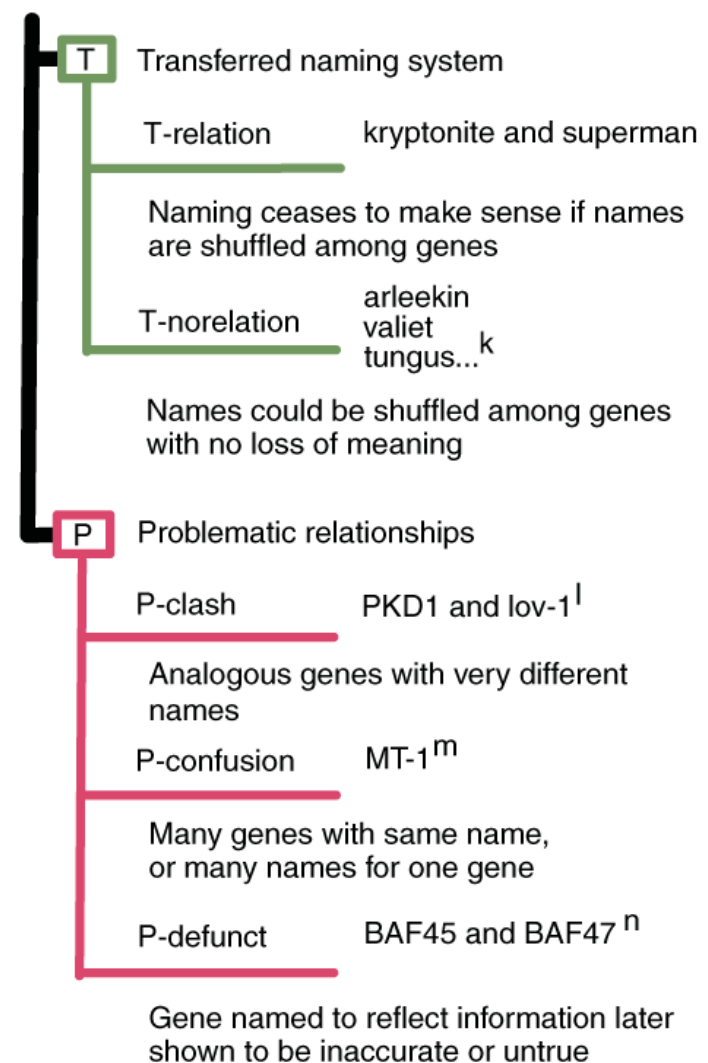


An Aside: An Ontology of Naming Pathologies

Single

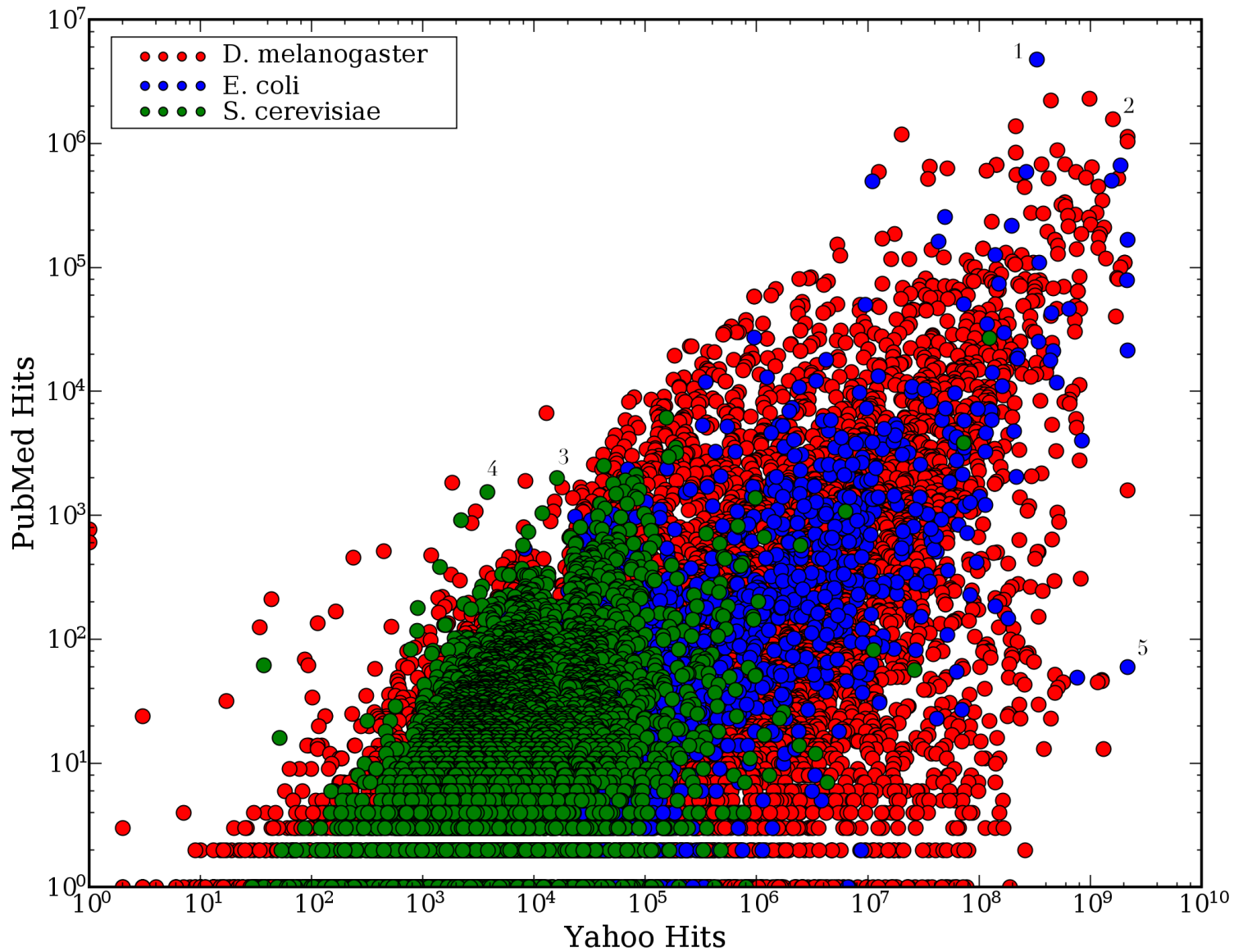


Multi



[Sringhaus et al. GenomeBiology (2008)]

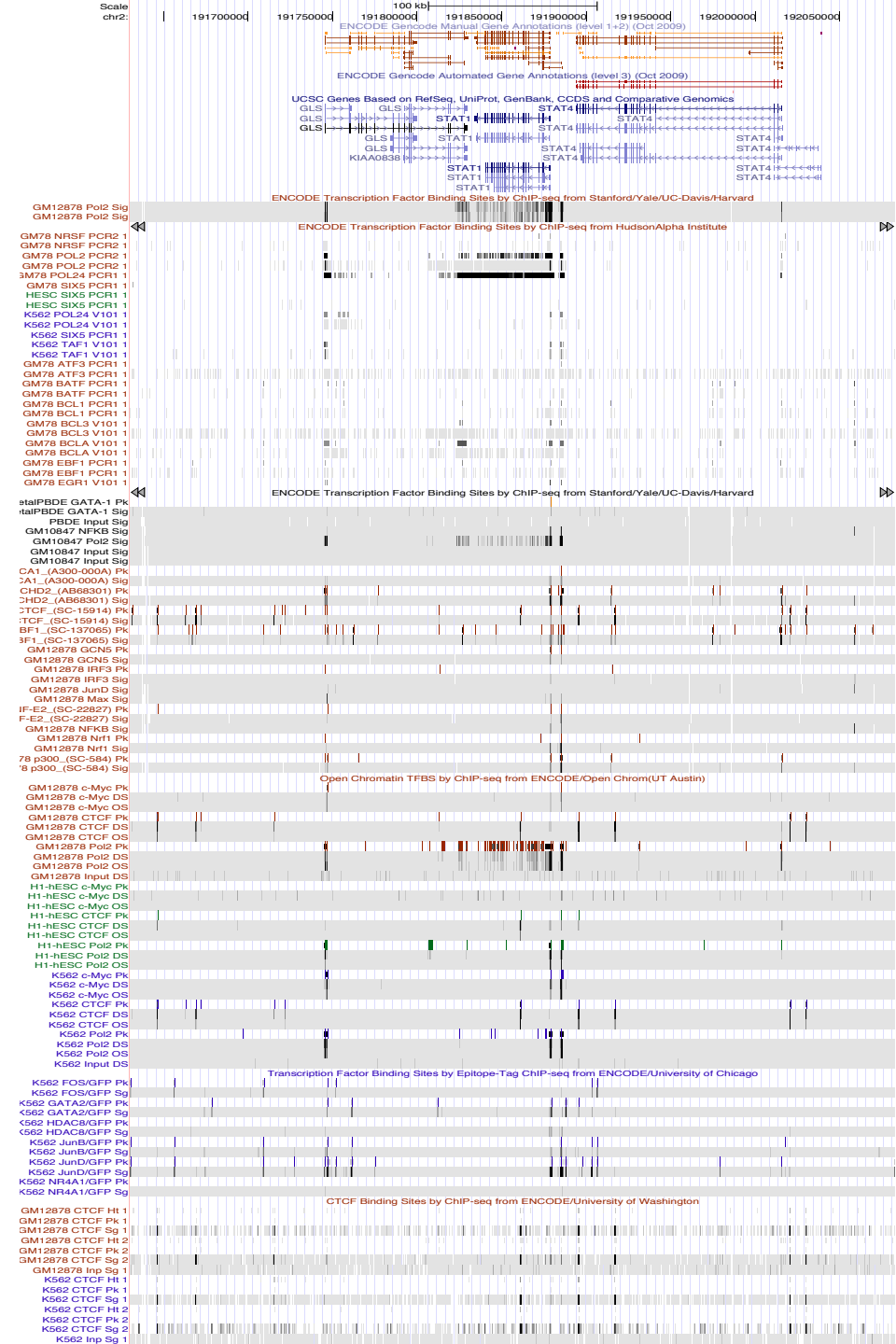
Gene Name Skew



[Seringhaus et al. GenomeBiology (2008)]

Reasons for Networks

(2) Overcome shortcomings
of linear genome annotation

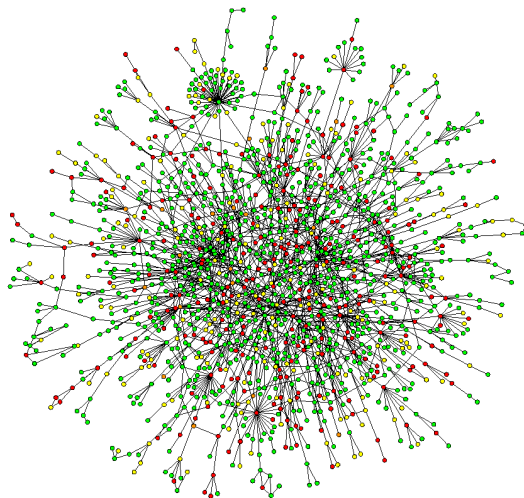
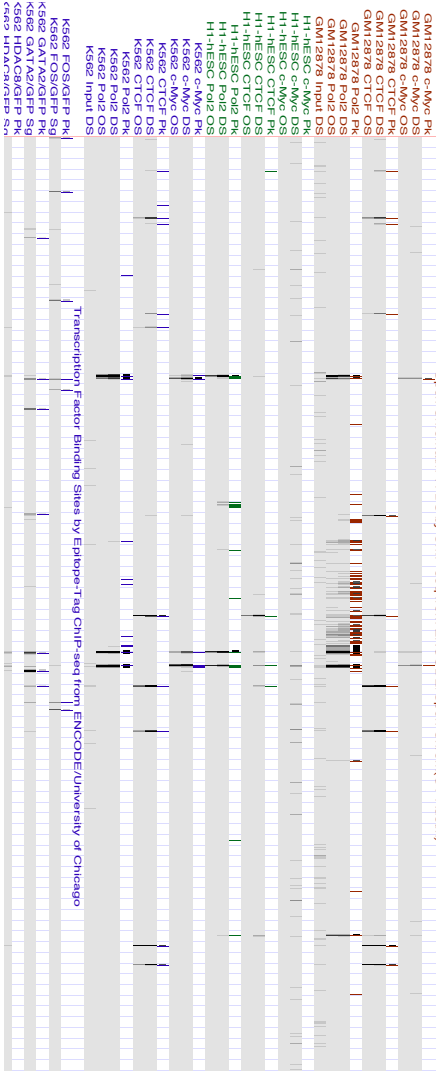


Current Annotation: 1D Browser Tracks

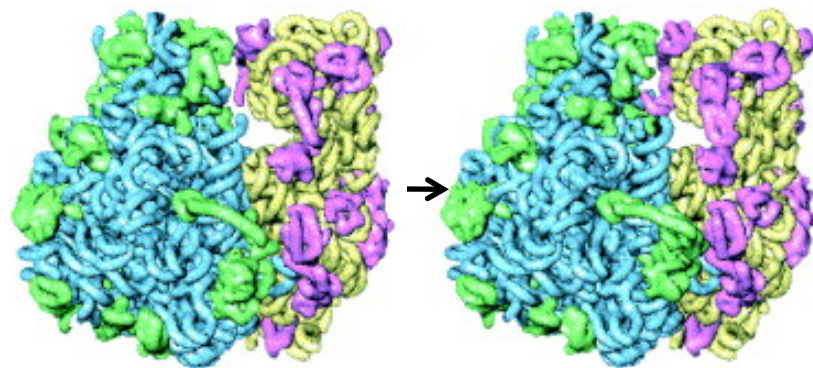
Will this scale to 1000+ tracks? What will next-gen annotation look like?...

Systems from Parts

Networks occupy a midway point in terms of level of understanding



~2D: Network Wiring Diagram of a Molecular System



3D & 4D: Detailed structural understanding of cellular machinery (e.g. ribosome in different functional states)

[UCSC genome browser]

[Jeong et al. Nature, 41:411]

[Chiu et al. Trends in Cell Biol, 16:144]

1D: Complete Partslist ("Elements" in genomic tracks)

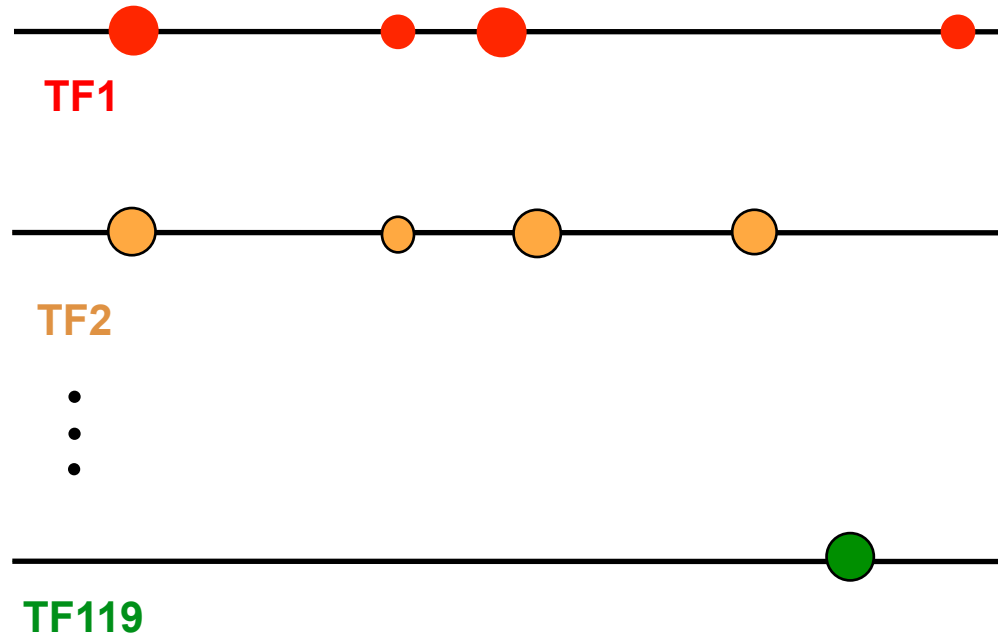
Data Flow: Chip-seq expts. to co-associating peaks

119 TFs from 458 ChIP-Seq experiments (2 Tb tot.)

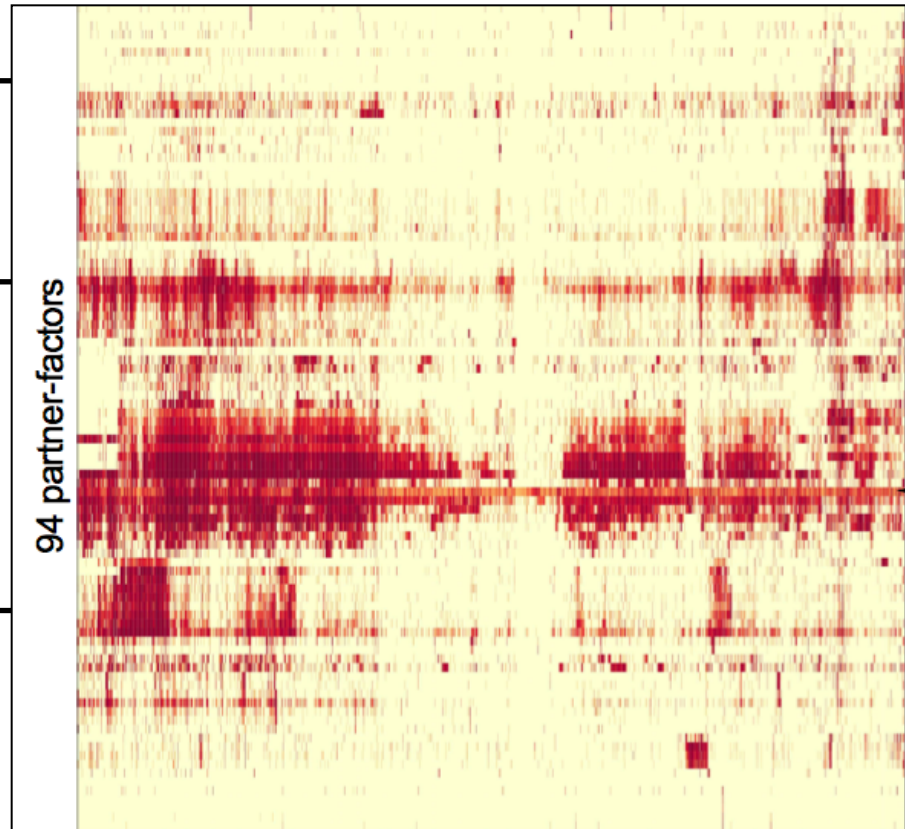
↓
Signal Tracks



↓
7M Peaks from Uniform Peak Calling



- Mostly in Tier 1 cell lines
 - K562, GM12878, H1h-ESC...
- Matching RNA-Seq data in all cell-lines
- SPP & PeakSeq
- thresholding w. IDR (replicas)



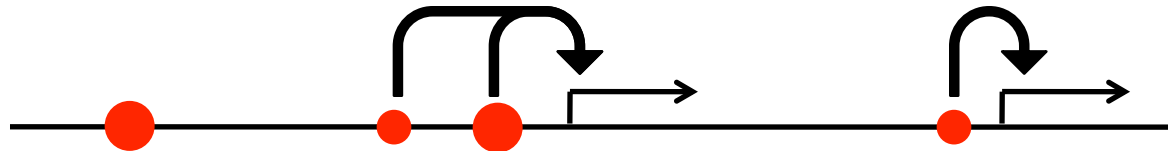
Data Flow: peaks to proximal & distal networks

[Cheng et al., *Bioinfo.* ('11);
Gerstein et al. *Nature* (in press, '12) ;
Yip et al., *GenomeBiology* (in press, '12)]

Peak Calling

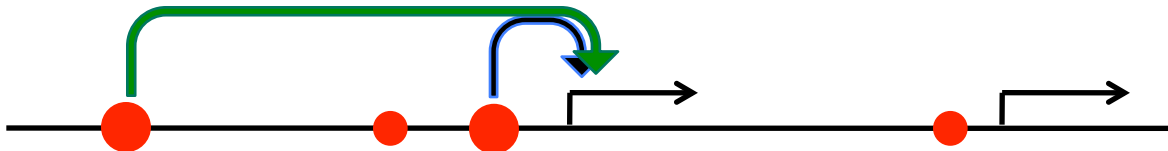


Assigning TF binding sites to targets

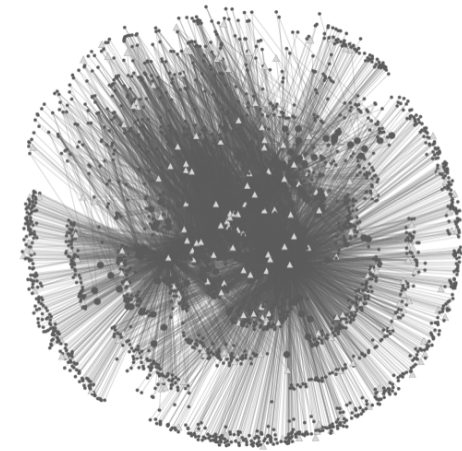


Filtering high confidence edges & distal regulation

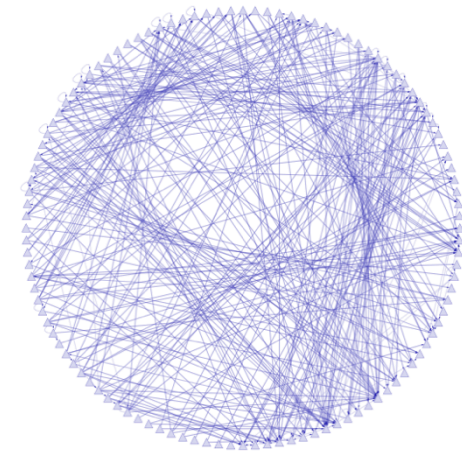
Based on stat. model combining
signal strength & location relative to typical binding



~500K
Edges

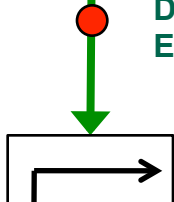


~26K
Edges



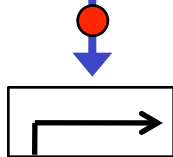
TF

Potential
Distal
Edge



TF

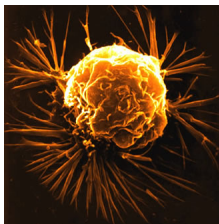
Strong
Proximal
Edge



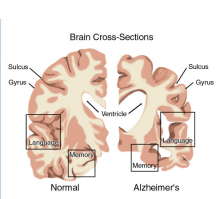
Reasons for Networks

(3) Useful way of thinking about disease

Network pathology & pharmacology



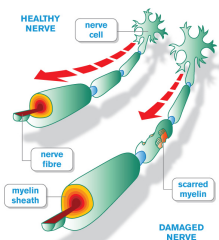
Breast Cancer



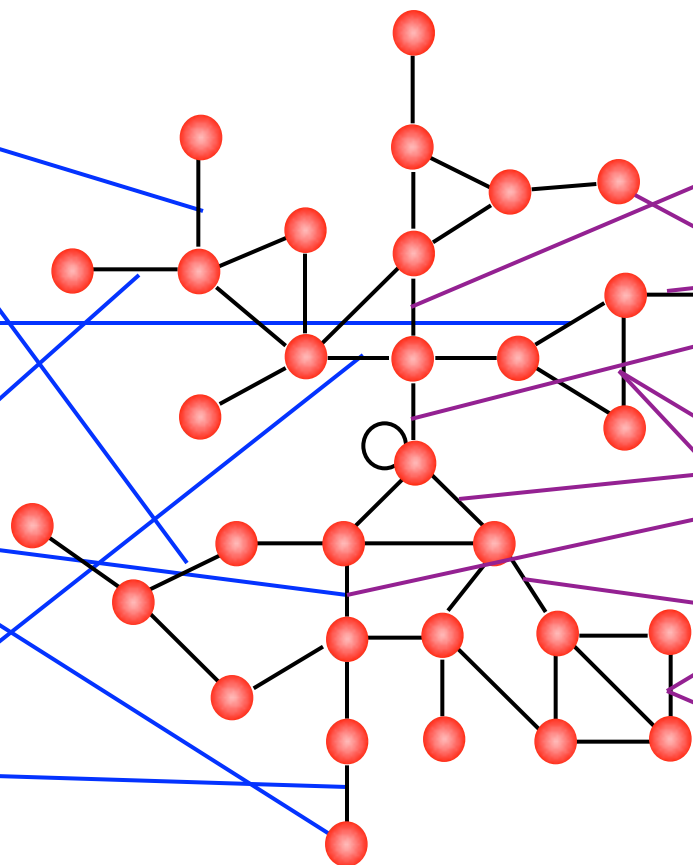
Alzheimer's Disease



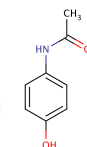
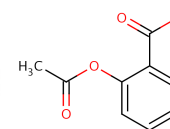
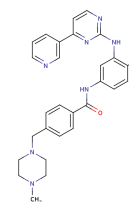
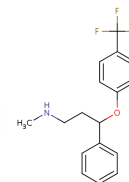
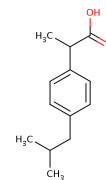
Parkinson's Disease



Multiple Sclerosis



Interactome networks



Interactome Networks and Human Disease

Vol 455 | 23 October 2008 | doi:10.1038/nature07385 nature

ARTICLES

Comprehensive genomic characterization defines human glioblastoma genes and core pathways

The Cancer Genome Atlas Research Network*

Phenotypes

Mendelian disorders

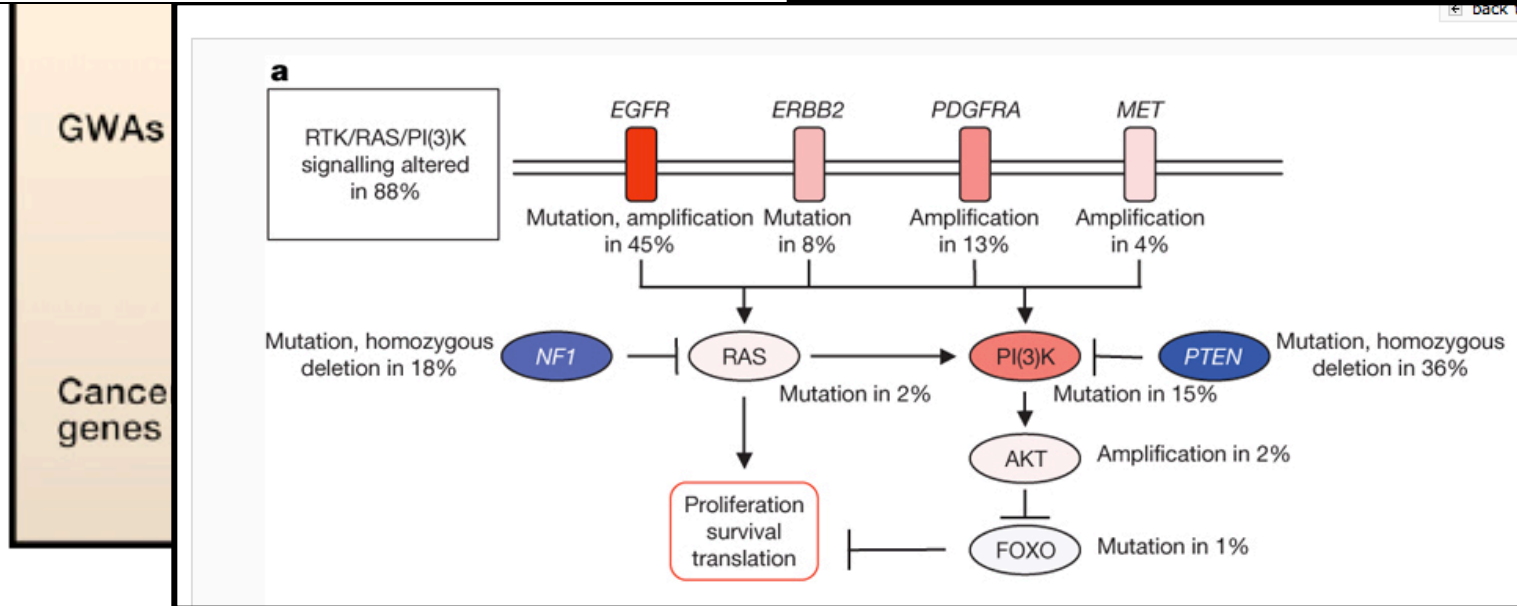
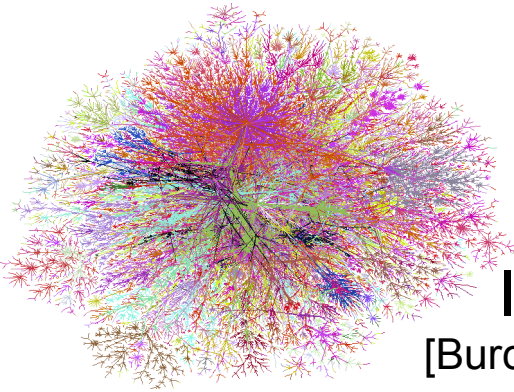


Figure 1. Perturbations in Biological Systems and Cellular Networks May Underlie Genotype-Phenotype Relationships

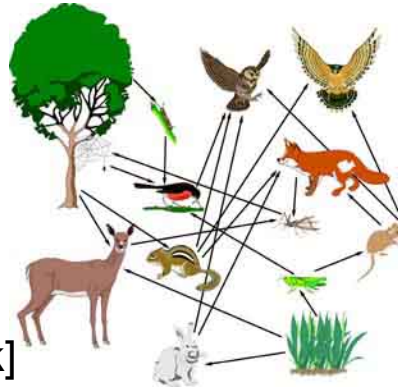
Reasons for Networks

(4) Comprehensive representation, capable of representing many types of biological & non-biological data & bridging between disciplines

Networks as a universal language



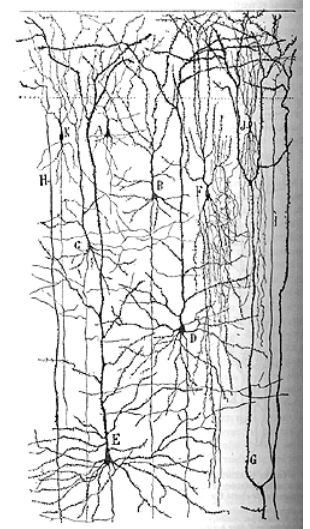
Internet
[Burch & Cheswick]



Food Web



Electronic
Circuit



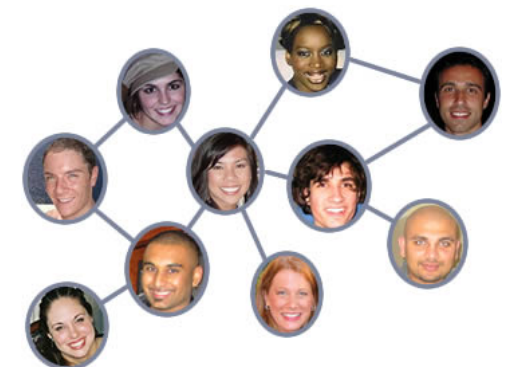
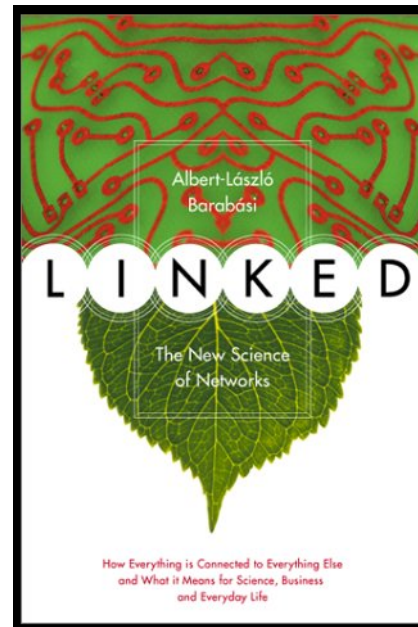
Neural Network
[Cajal]



Disease
Spread
[Krebs]



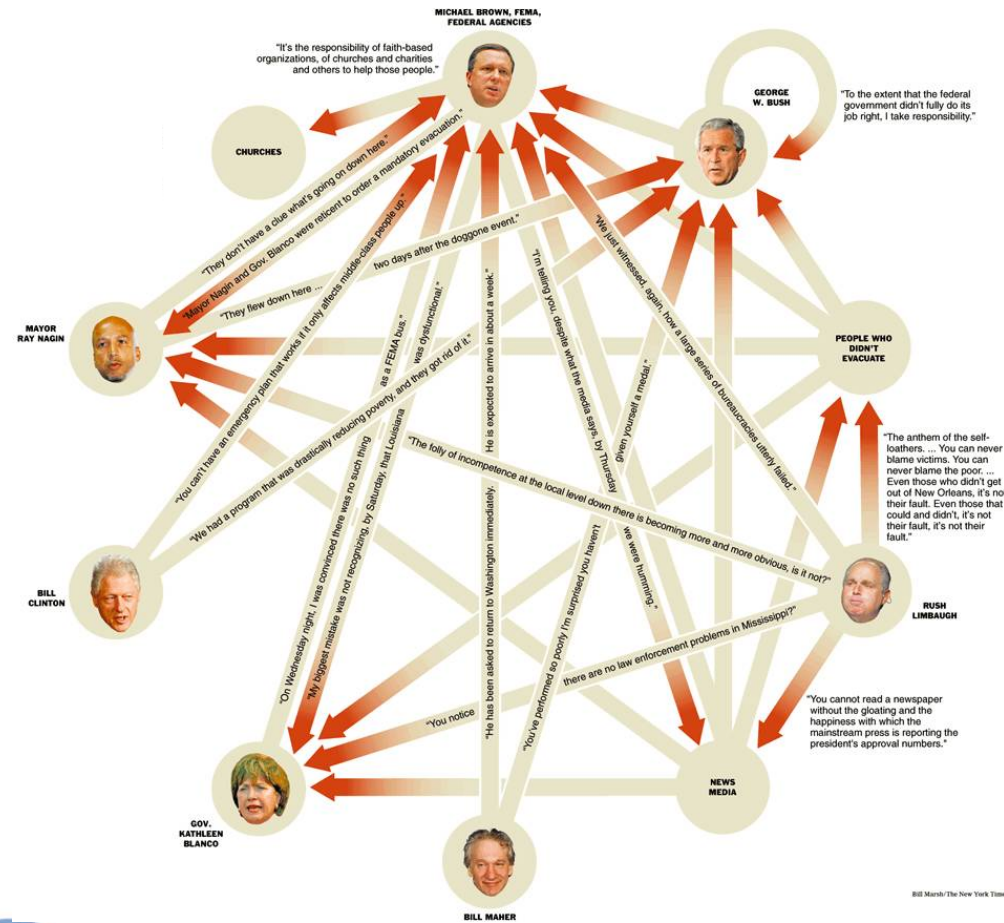
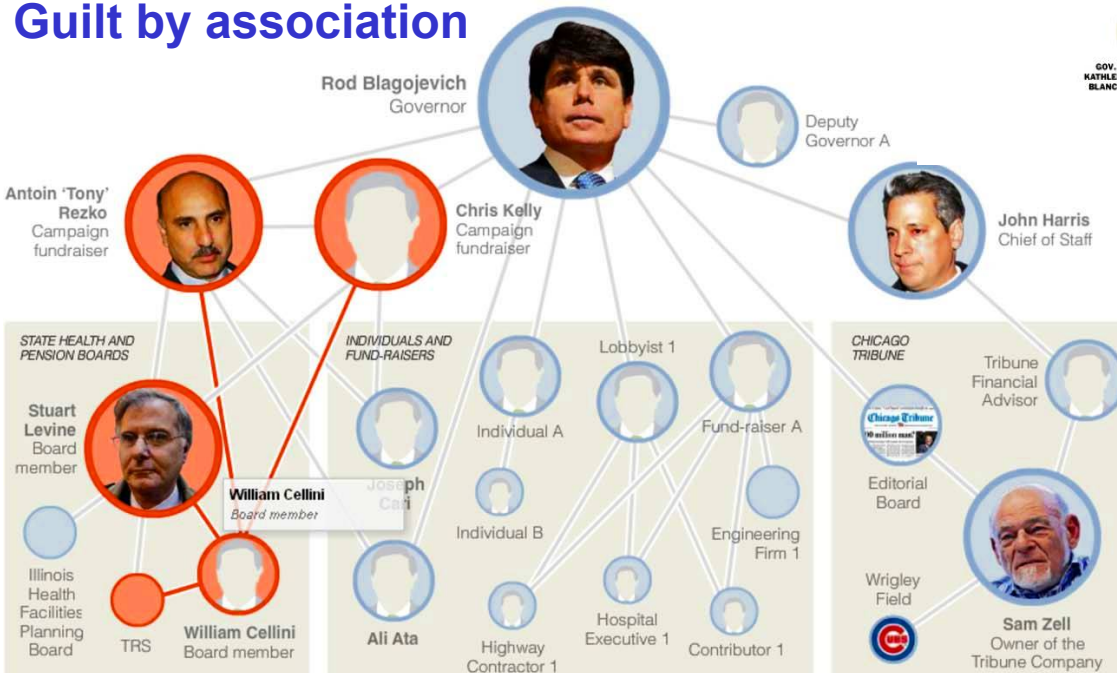
Protein
Interactions
[Barabasi]



Social Network

Using the position in networks to describe function

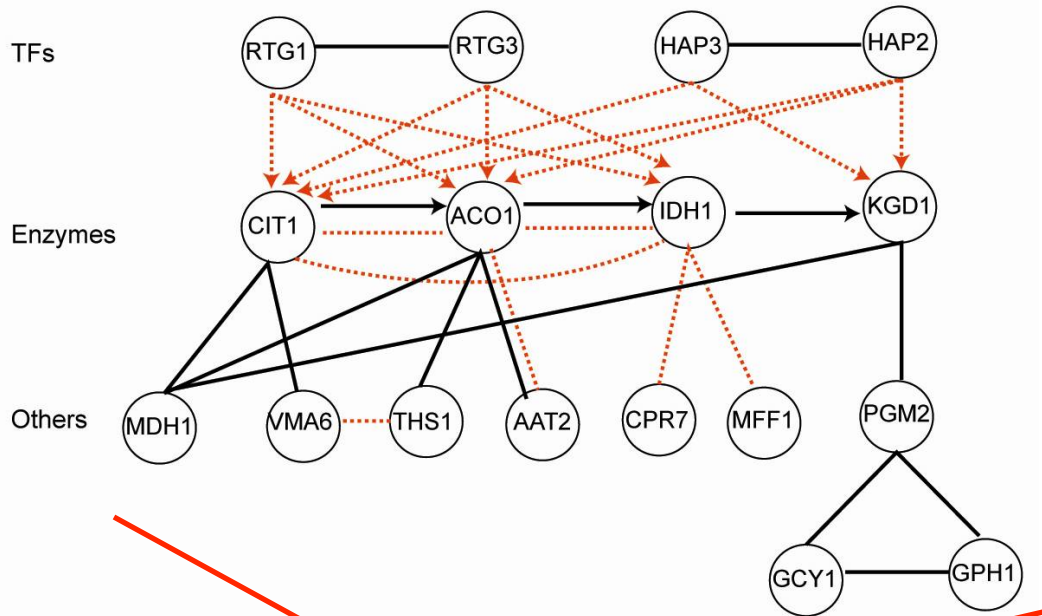
Guilt by association



Finding the causal regulator (the "Blame Game")

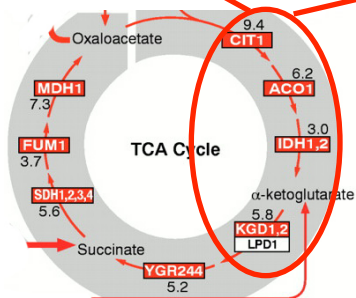
[NY Times, 2-Oct-05, 9-Dec-08]

Combining networks forms an ideal way of integrating diverse information



- **Metabolic pathway**
- **Transcriptional regulatory network**
- **Physical protein-protein Interaction**
- **Co-expression Relationship**

Genetic interaction (synthetic lethal)
Signaling pathways

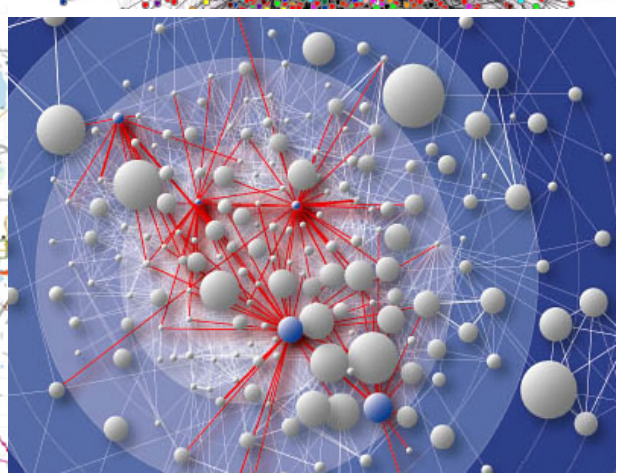
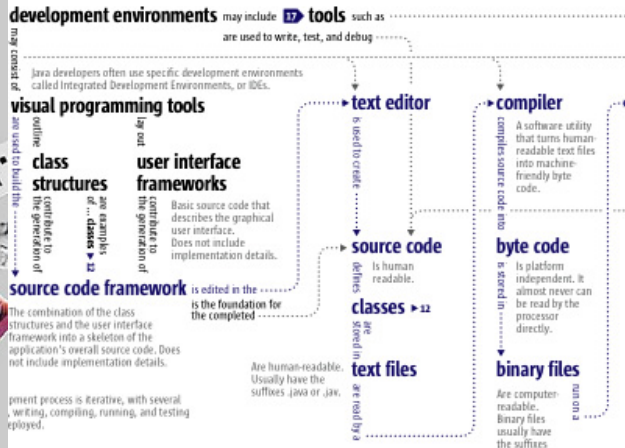


Part of the TCA cycle

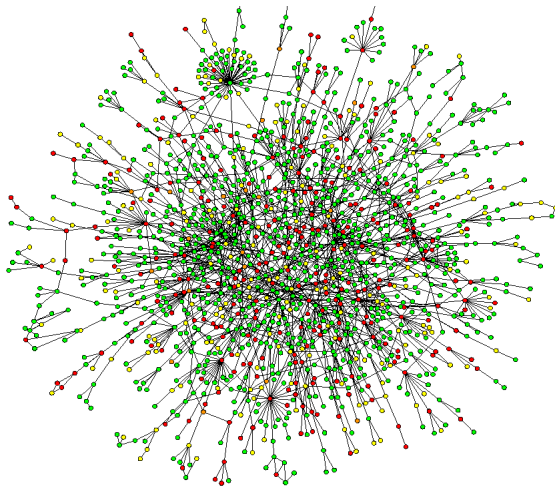
Richness of the Visual Representation of Networks

Some structure (connectivity) but some flexibility (e.g. edge colors, node positions and shapes) that can be used to encode additional information

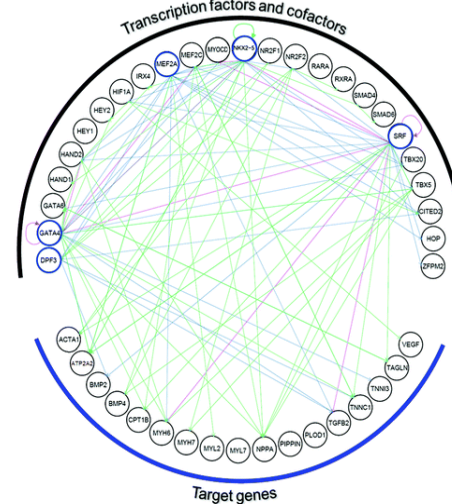
VisualComplexity.com



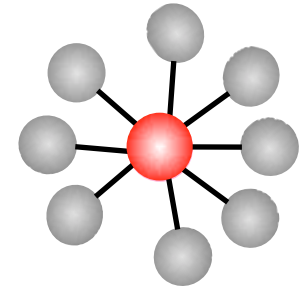
Different Types of Molecular Networks



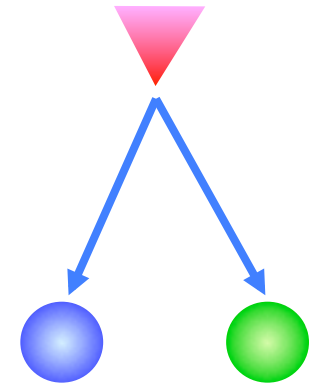
Protein-protein Interaction networks



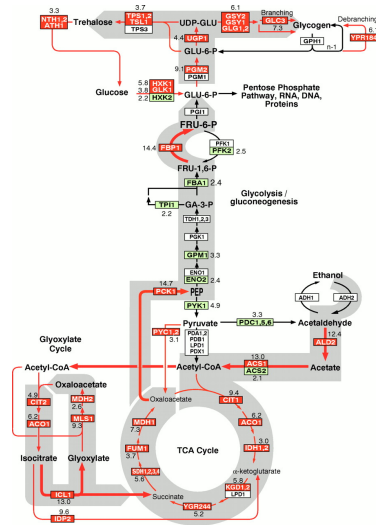
TF-target-gene Regulatory networks



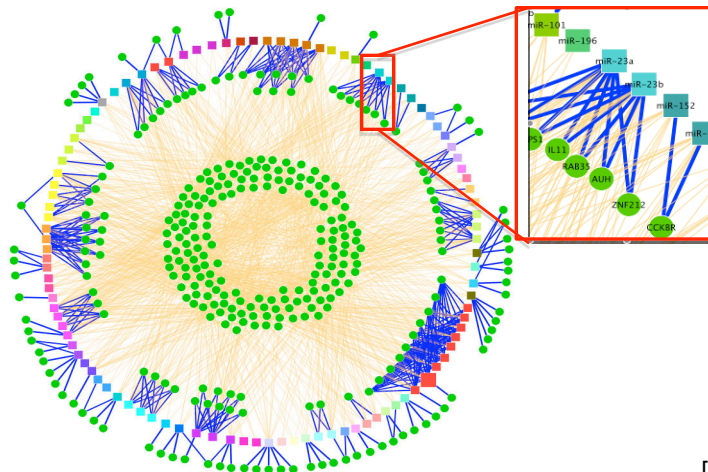
Undirected



Directed



Metabolic pathway networks

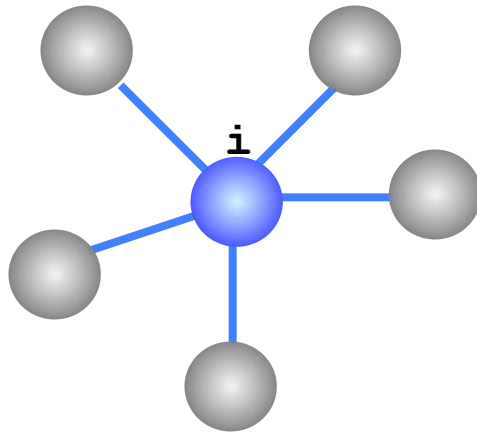


miRNA-target networks

[Toenjes, *et al*, *Mol. BioSyst.* (2008);
Jeong *et al*, *Nature* (2001); [Horak, *et al*,
Genes & Development, 16:3017-3033;
DeRisi, Iyer, and Brown, *Science*,
278:680-686]

Networks:
What are the Main
Quantities that Can be
Calculated from
Network Topology?

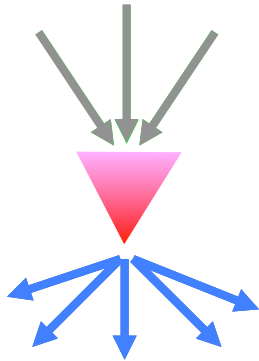
- **Degree of a node:** the number of edges incident on the node



Degree of node $i = 5$

Network parameters

Number of incoming and outgoing connections



Connectivity

Incoming connections = 2.2

→ each gene is regulated by ~ 2 TFs

In-degree

Outgoing connections = 20.2

→ each TF regulates ~ 20 genes

Out-degree

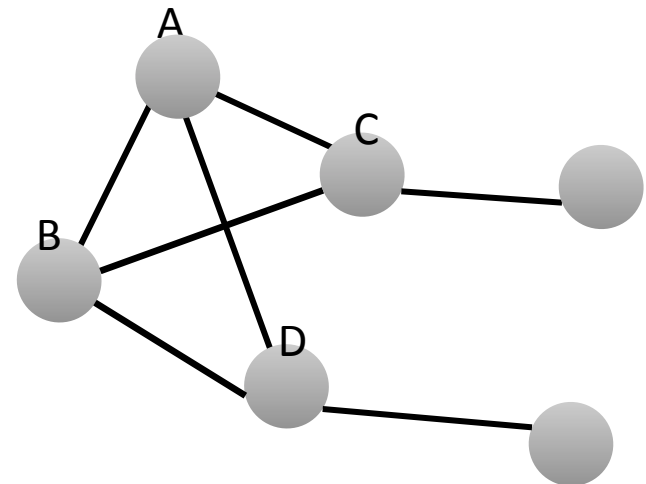
Clustering coefficient

- Average Coefficient:
 - Average of clustering coefficients of all nodes n

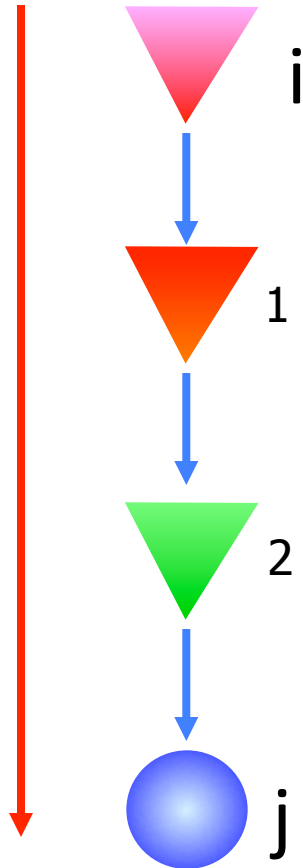
$$\bar{C} = \frac{1}{n} \sum_{i=1}^n C_i$$

- Measure of inter-connectedness of the network
 - Global property

- Example:
 - Clustering coefficient:
 $C_A=2/3$ $C_B=2/3$
 $C_C=1/3$ $C_D=1/3$
 - Average coefficient =
 $1/4(2/3+2/3+1/3+1/3)= 0.5$



Path length

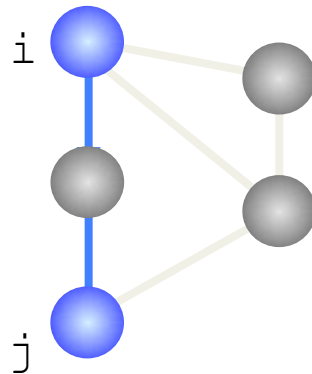


- Number of edges along a path
- Path length = 3
- Meaning:
 - Number of intermediate TFs to reach final target
 - Indication of how immediate a response is

Path length

- Shortest path length:

- $L_{(i,j)}$ is the minimum number of edges that must be traversed to travel from a vertex i to another vertex j of a graph G



$$L_{(i,j)} = 2$$

Graph Theory Terminology (Batten, pp. 92-105)

- Characteristic path length (Average path length)

- The characteristic path length L of a graph is the average of the $L_{(i,j)}$ for every possible pair (i,j)

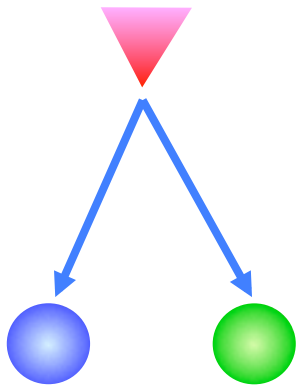
$$L = \frac{1}{n(n-1)} \sum_{i,j} L_{(i,j)}$$

- Networks with small values of L are said to have the “small world property”

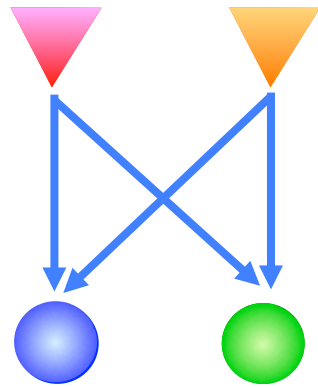
http://en.wikipedia.org/wiki/Average_path_length

Network motifs

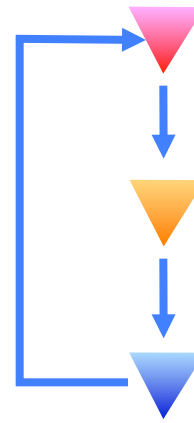
Regulatory modules within the network



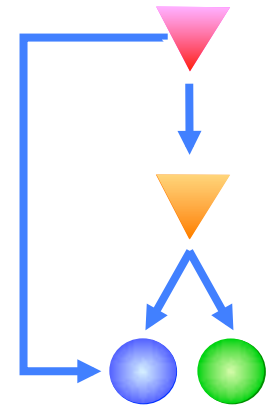
SIM



MIM

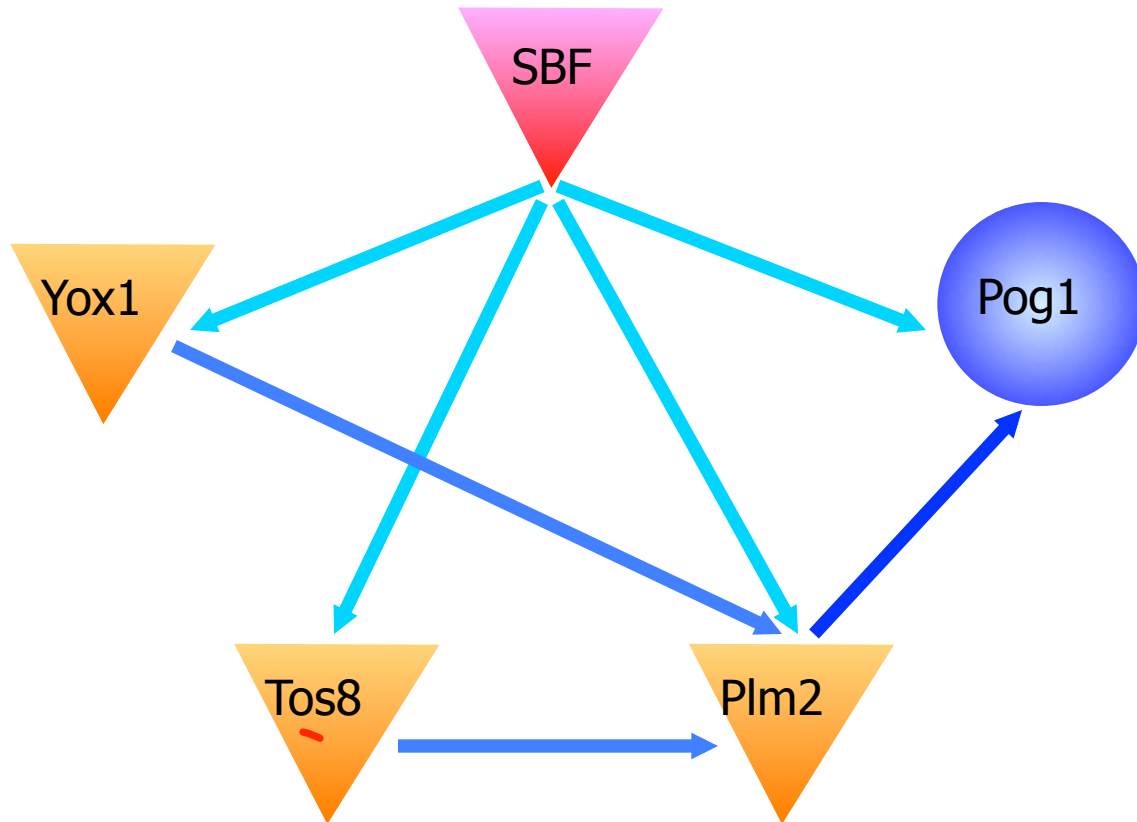
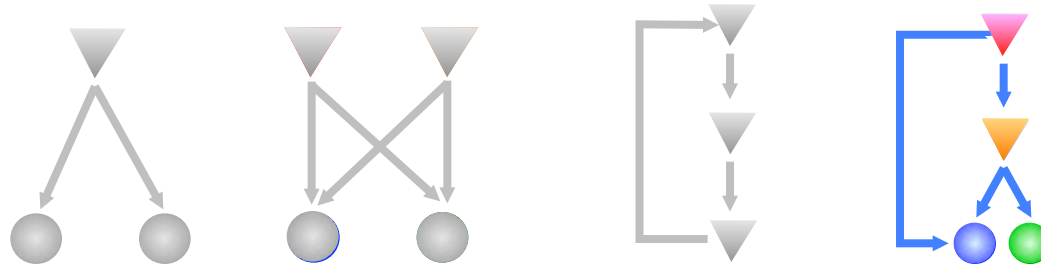


FBL



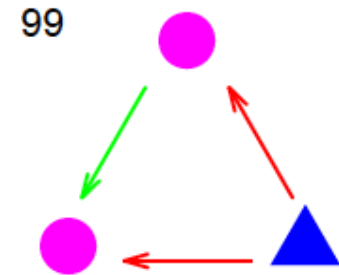
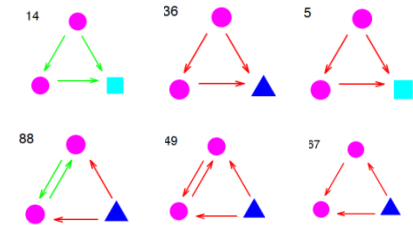
FFL

FFL = Feed-forward loops

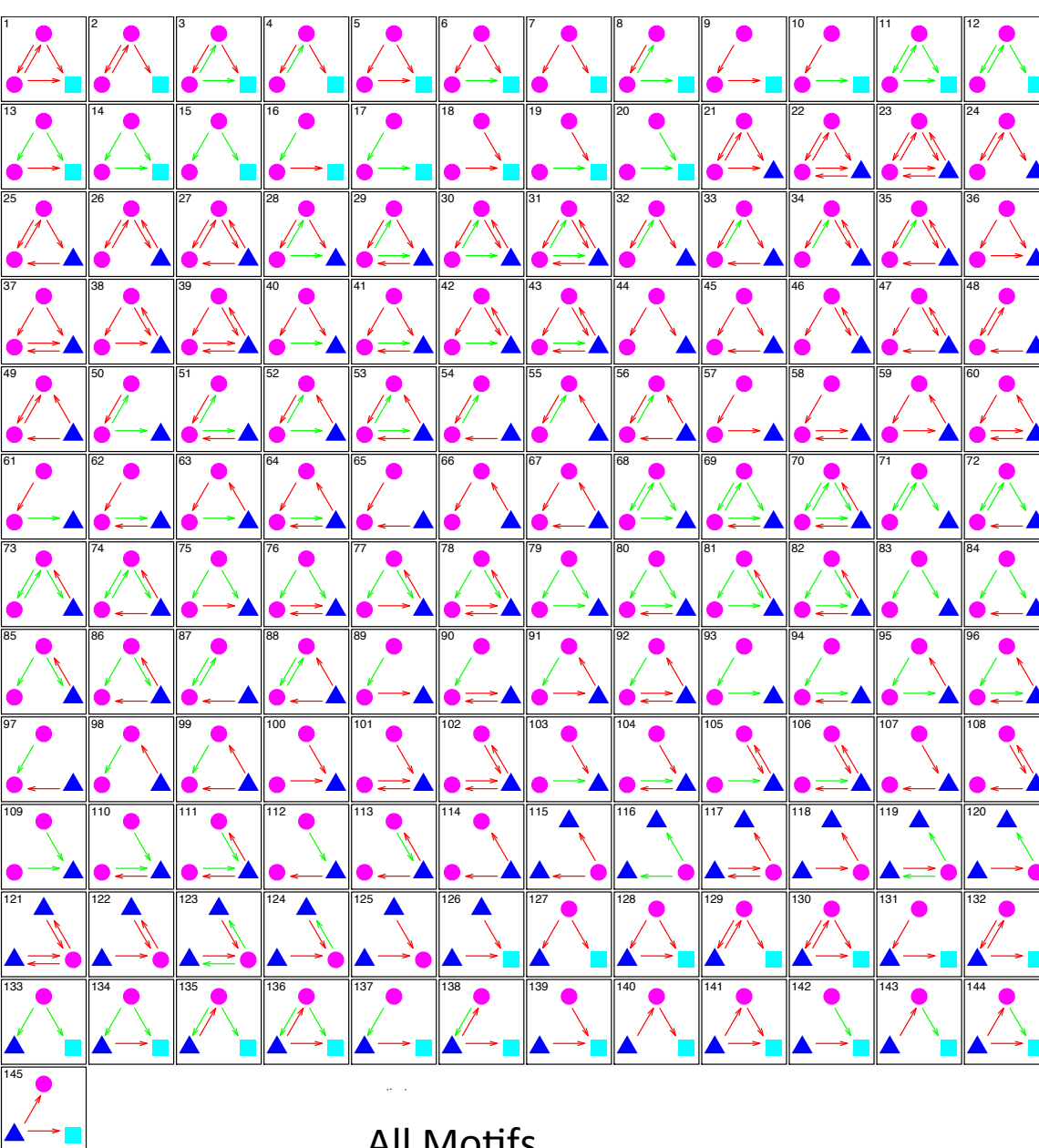


Network Motifs

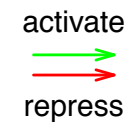
7 Motifs
Over-represented



FFL involving
miRNA & 2 TFs



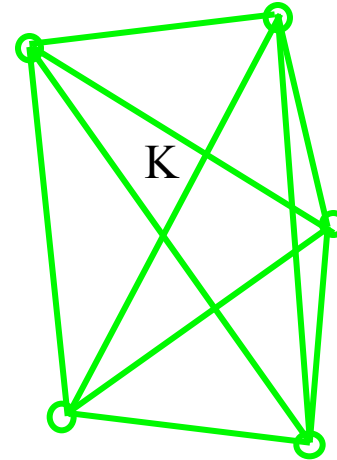
All Motifs



Cliques

- Fully connected sub-components
- Related measures
k-cores : For all vertices in a graph G have degree at least k

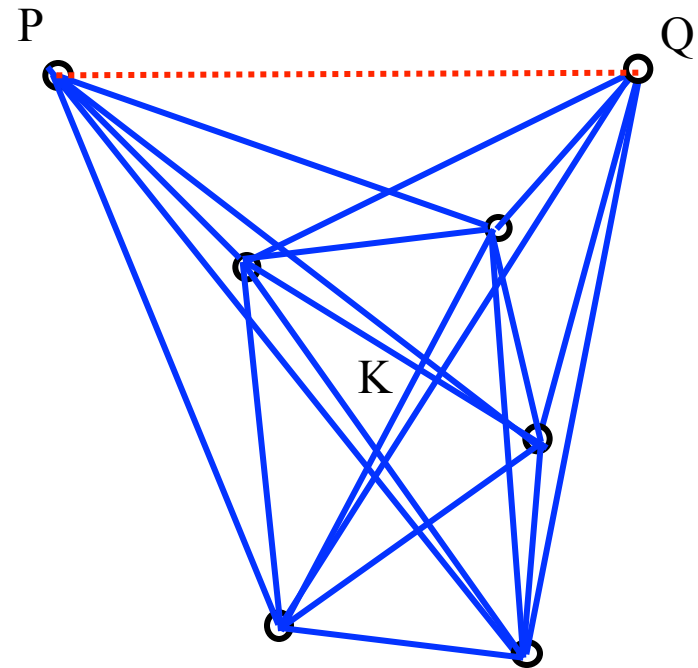
[Hogue et al, BMC BIOINFORMATICS, 2003]



Problem: High-throughput experiments are prone to missing interactions

One solution—defective cliques

- If proteins P and Q interact with a clique K of proteins which all interact with each other, then P and Q are more likely to interact with each other
- P, Q, and K form a **defective clique**

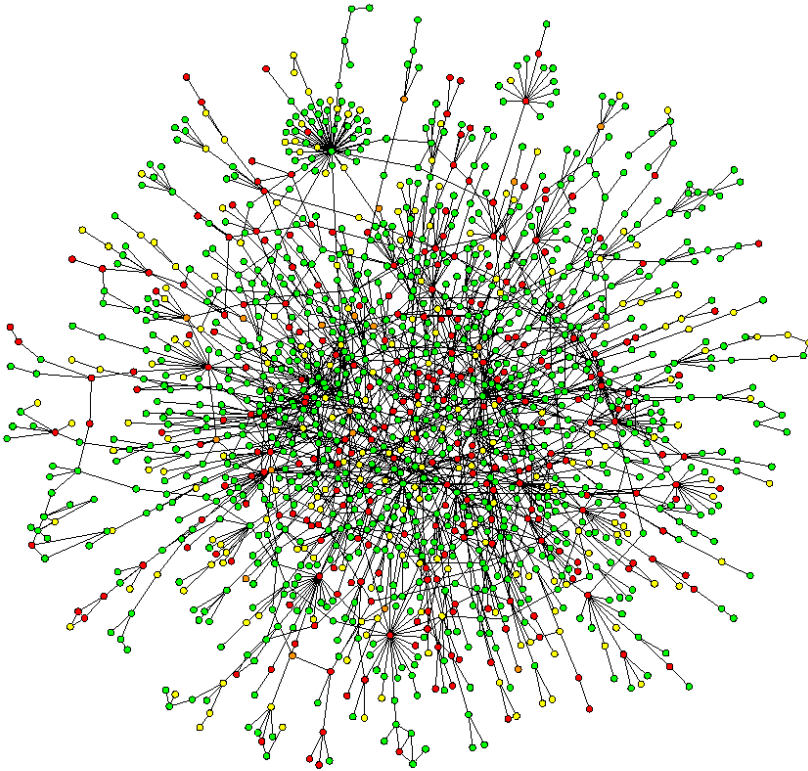


Predicting protein interactions by completing defective cliques

Networks: Simple
Mathematical Models
for Interpreting
Complex Topology

Scale Free Networks & Hubs

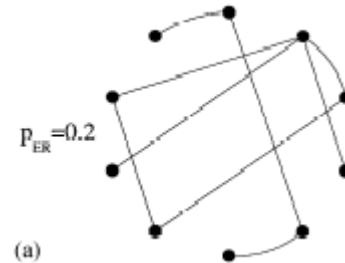
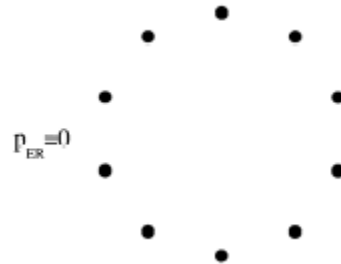
Models for networks of complex topology



- Erdos-Renyi (1960)
- Watts-Strogatz (1998)
- Barabasi-Albert (1999)

**A Barabási & R Albert
"Emergence of scaling in
random networks,"
Science 286, 509-512 (1999).**

The Erdős-Rényi [ER] model (1960)

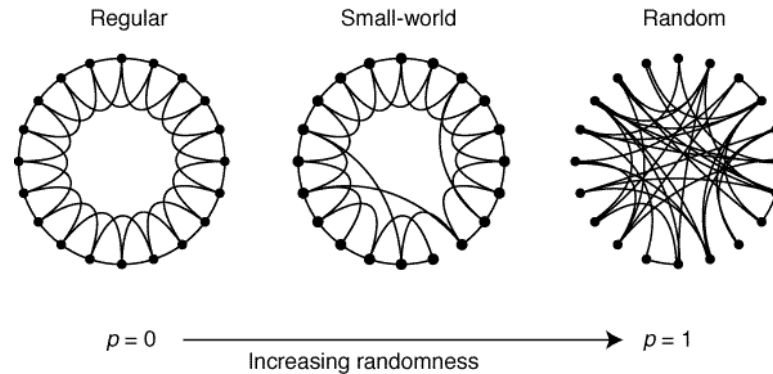


- Start with N vertices and no edges
- Connect each pair of vertices with probability P_{ER}

Important result: many properties in these graphs appear quite suddenly, at a threshold value of $P_{ER}(N)$

- If $P_{ER} \sim c/N$ with $c < 1$, then almost all vertices belong to isolated trees
- Cycles of all orders appear at $P_{ER} \sim 1/N$

The Watts-Strogatz [WS] model (1998)



- Start with a regular network with N vertices
- Rewire each edge with probability p

For $p=0$ (Regular Networks):

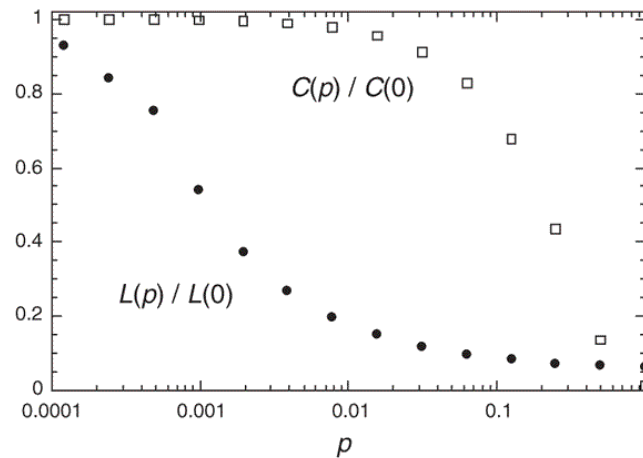
- high clustering coefficient
- high characteristic path length

For $p=1$ (Random Networks):

- low clustering coefficient
- low characteristic path length

QUESTION: What happens for intermediate values of p ?

1) There is a broad interval of p for which L is small but C remains large



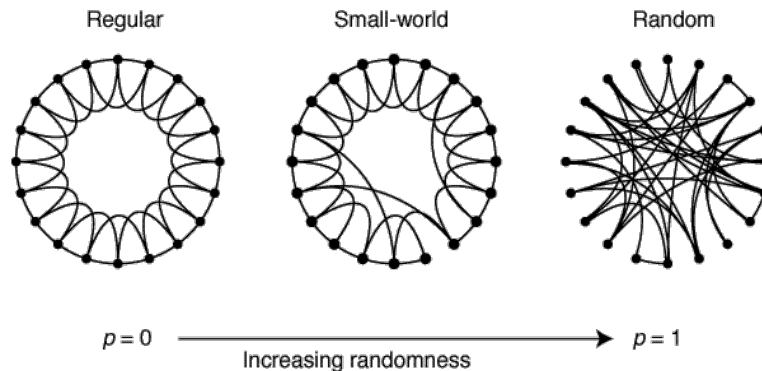
2) Small world networks are common :

Table 1 Empirical examples of small-world networks

	L_{actual}	L_{random}	C_{actual}	C_{random}
Film actors	3.65	2.99	0.79	0.00027
Power grid	18.7	12.4	0.080	0.005
<i>C. elegans</i>	2.65	2.25	0.28	0.05

Small world network

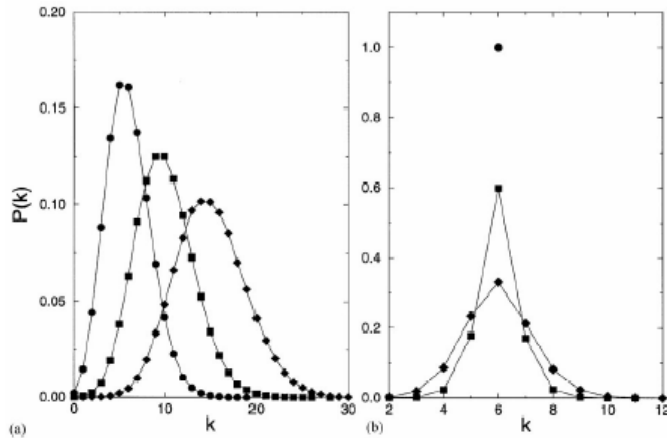
- A simple connected graph G exhibiting two properties:
 - **Large Clustering Coefficient:** Each vertex of G is linked to a relatively well-connected set of neighboring vertices, resulting in a large value for the clustering coefficient $C(G)$;
 - **Small Characteristic Path Length:** The presence of short-cut connections between some vertices results in a small characteristic path length $L(G)$.



- local connectivity and global reach

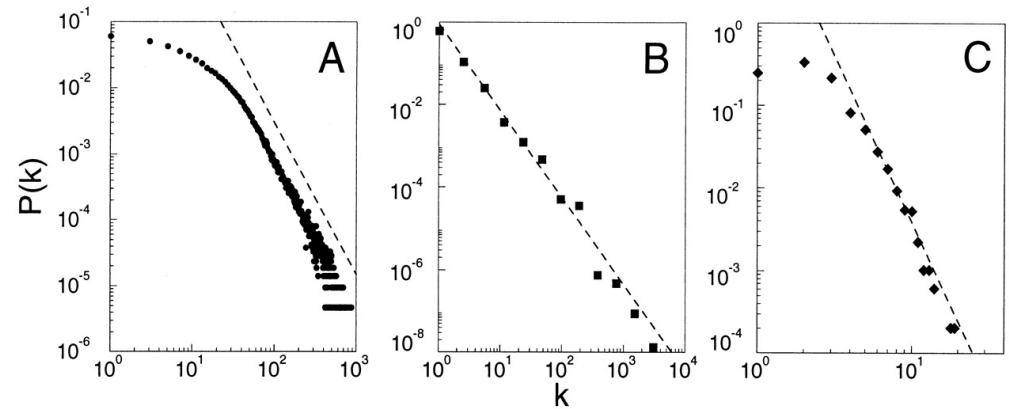
The Barabási-Albert [BA] model (1999)

Look at the distribution of degrees



ER Model

WS Model



actors

power grid

www

The probability of finding a highly connected node decreases exponentially with k

$$P(K) \sim K^{-\gamma}$$

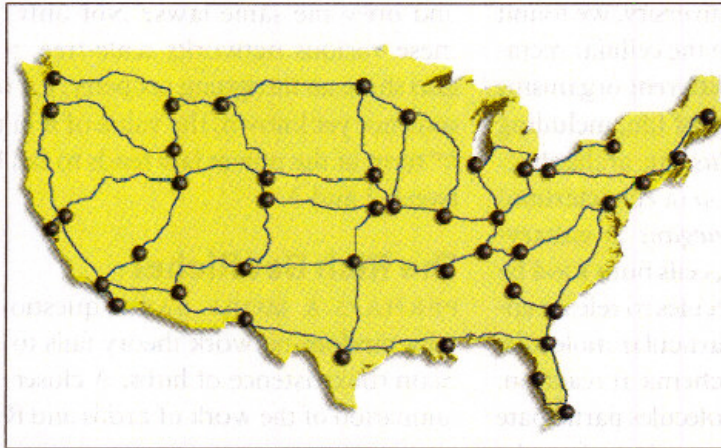
Random v Scale-free Networks

RANDOM NETWORKS, which resemble the U.S. highway system (*simplified in left map*), consist of nodes with randomly placed connections. In such systems, a plot of the distribution of node linkages will follow a bell-shaped curve (*left graph*), with most nodes having approximately the same number of links.

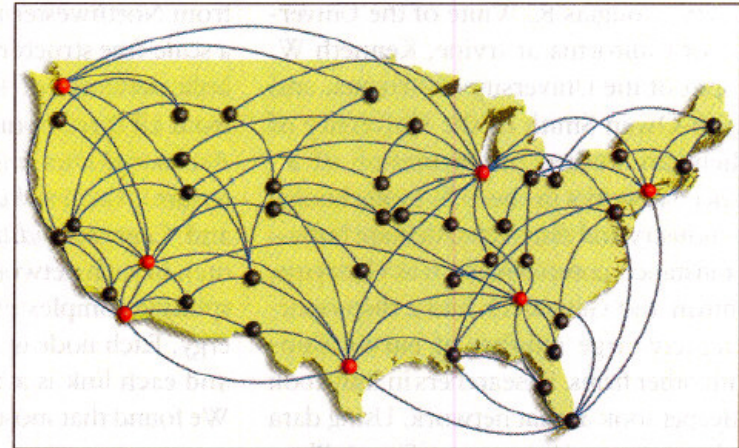
In contrast, scale-free networks, which resemble the U.S. airline system (*simplified in right map*), contain hubs (*red*)—

nodes with a very high number of links. In such networks, the distribution of node linkages follows a power law (*center graph*) in that most nodes have just a few connections and some have a tremendous number of links. In that sense, the system has no “scale.” The defining characteristic of such networks is that the distribution of links, if plotted on a double-logarithmic scale (*right graph*), results in a straight line.

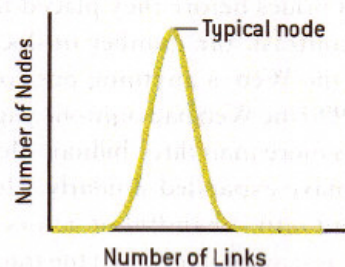
Random Network



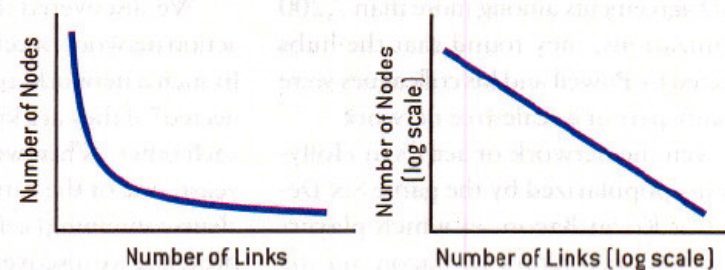
Scale-Free Network



Bell Curve Distribution of Node Linkages

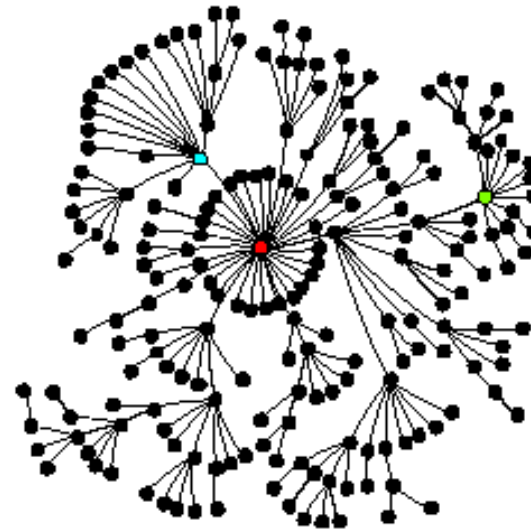
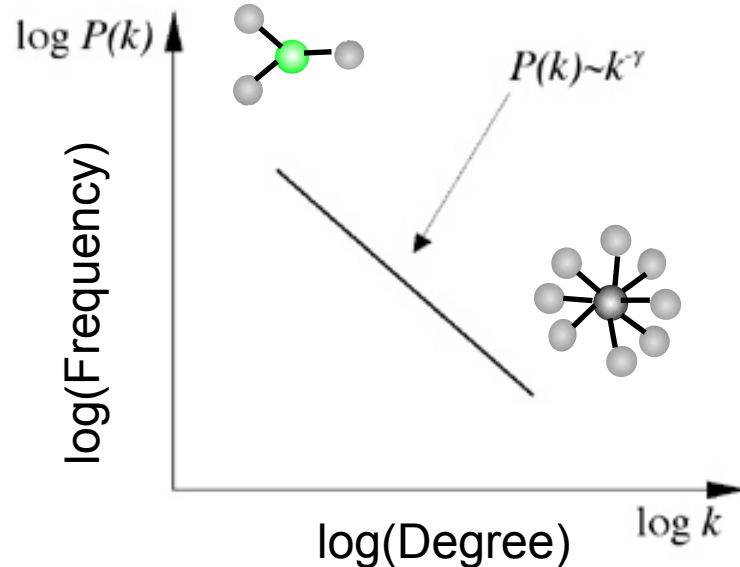


Power Law Distribution of Node Linkages



Scale-free networks in Biology

Power-law distribution



Hubs dictate the structure of the network

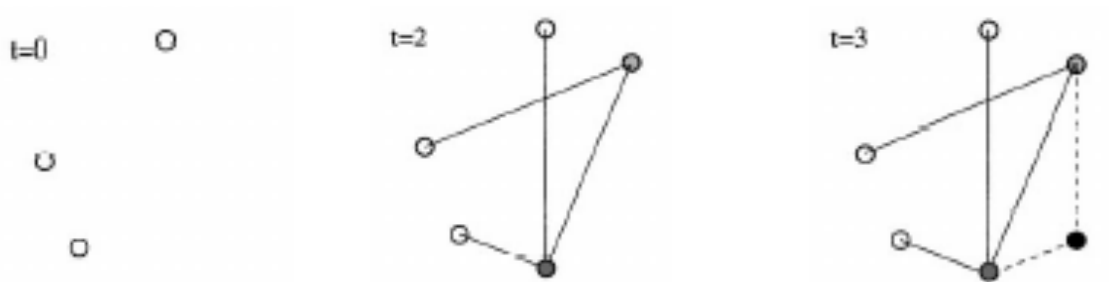
[Barabasi]

- two problems with the previous models:
 1. N does not vary
 2. the probability that two vertices are connected is uniform

- GROWTH: starting with a small number of vertices m_0 at every timestep add a new vertex with $m \leq m_0$

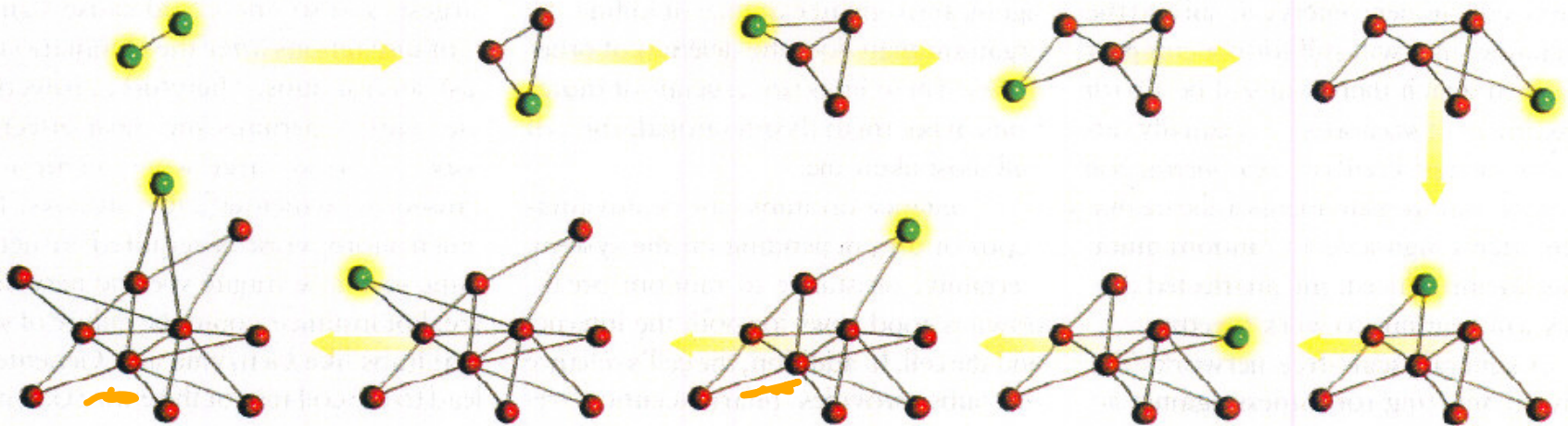
- PREFERENTIAL ATTACHMENT: the probability Π that a new vertex will be connected to vertex i depends on the connectivity of that vertex:

$$\Pi(k_i) = \frac{k_i}{\sum_j k_j}$$



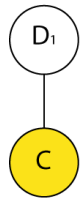
Birth of Scale-Free Network

A SCALE-FREE NETWORK grows incrementally from two to 11 nodes in this example. When deciding where to establish a link, a new node [green] prefers to attach to an existing node [red] that already has many other connections. These two basic mechanisms—growth and preferential attachment—will eventually lead to the system's being dominated by hubs, nodes having an enormous number of links.

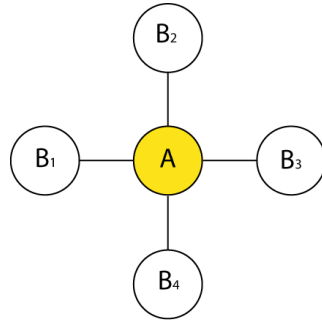


SCALE FREENESS GENERALLY EVOLVES THROUGH PREFERENTIAL ATTACHMENT (THE RICH GET RICHER)

The Duplication Mutation Model



Gene duplication



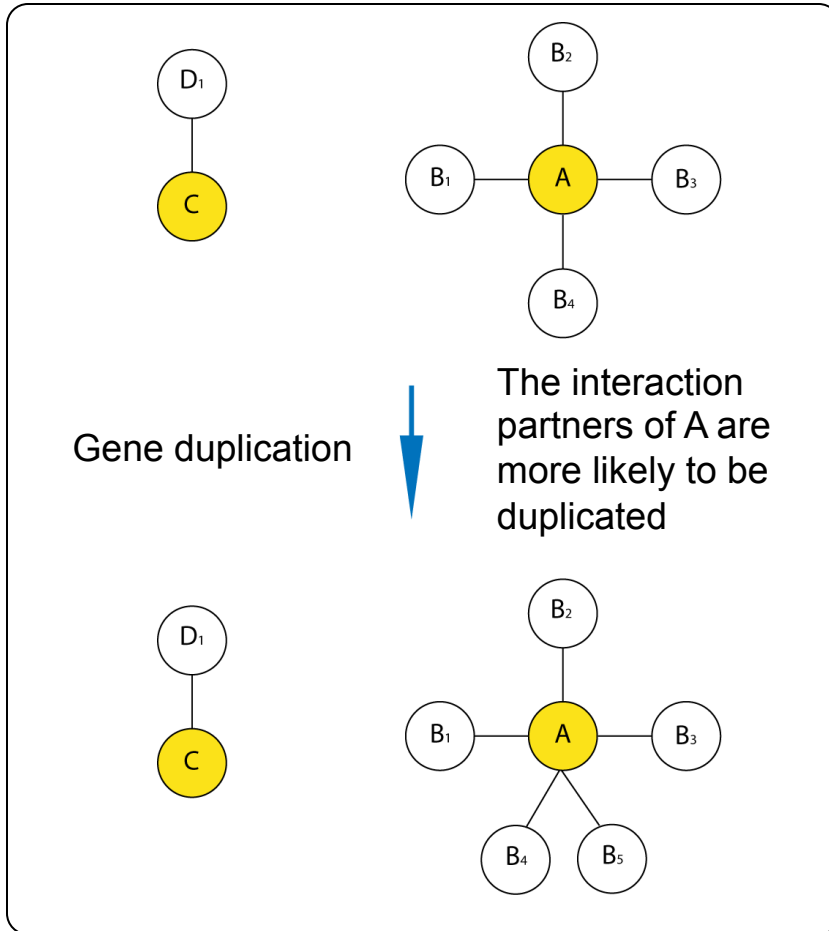
The interaction partners of A are more likely to be duplicated

Description

- Theoretical work shows that a mechanism of preferential attachment leads to a scale-free topology (“The rich get richer”)
- In interaction network, gene duplication followed by mutation of the duplicated gene is generally thought to lead to preferential attachment
- Simple reasoning: The partners of a hub are more likely to be duplicated than the partners of a non-hub

SCALE FREENESS GENERALLY EVOLVES THROUGH PREFERENTIAL ATTACHMENT (THE RICH GET RICHER)

The Duplication Mutation Model

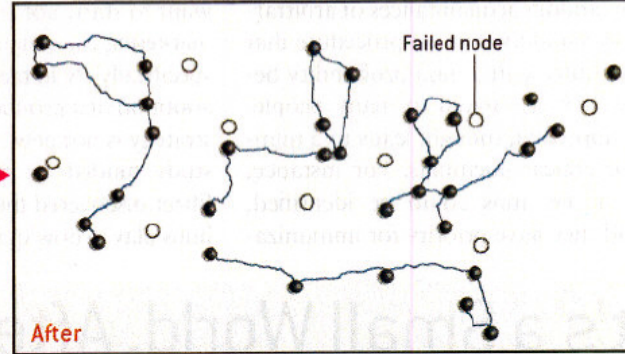
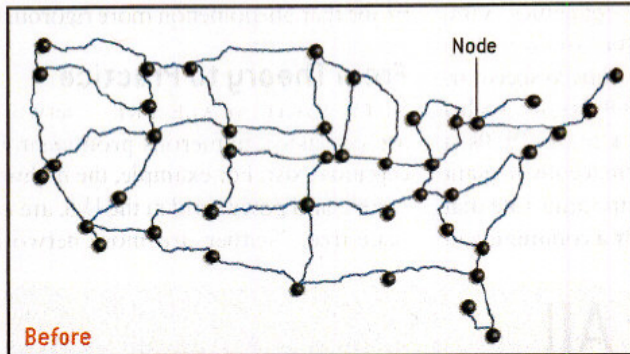


Description

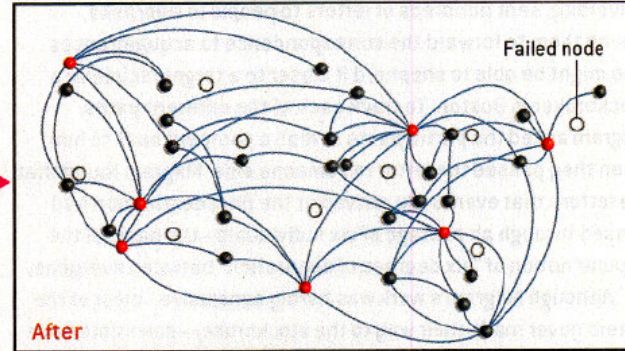
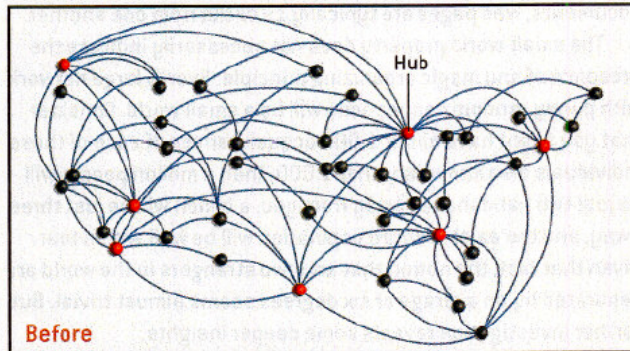
- Theoretical work shows that a mechanism of preferential attachment leads to a scale-free topology (“The rich get richer”)
- In interaction network, gene duplication followed by mutation of the duplicated gene is generally thought to lead to preferential attachment
- Simple reasoning: The partners of a hub are more likely to be duplicated than the partners of a non-hub

Knocking Out Nodes in Scale-free and Random Networks

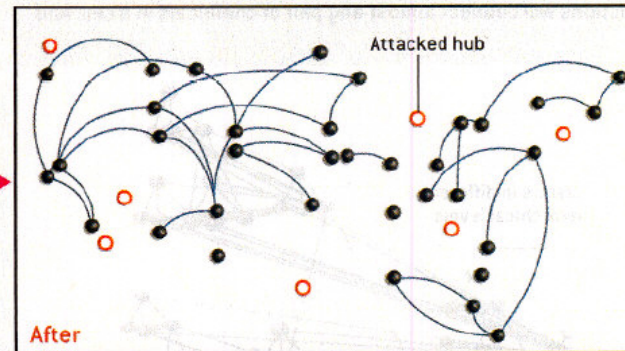
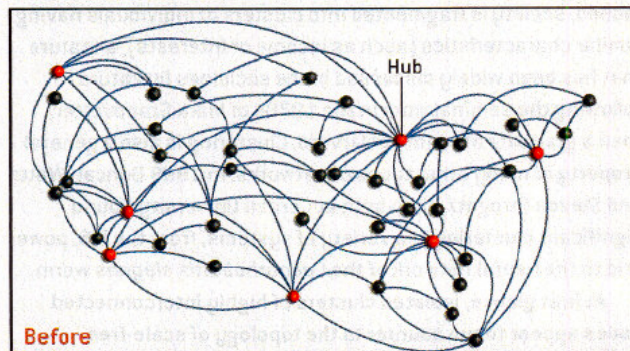
Random Network, Accidental Node Failure



Scale-Free Network, Accidental Node Failure



Scale-Free Network, Attack on Hubs



[From Barabasi & Bonabeau, *Sci. Am.*, May '03]

Hubs tend to be Essential

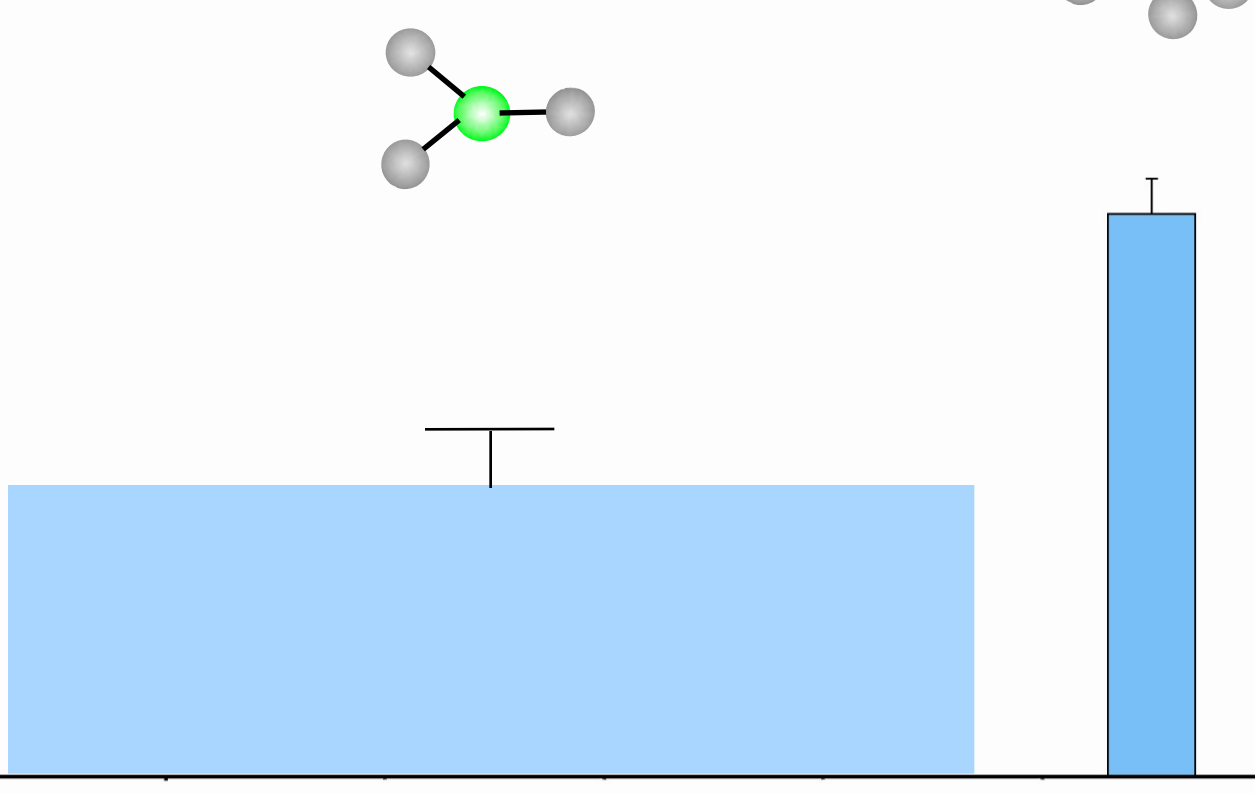
Integrate gene essentiality data with protein interaction network. Perhaps hubs represent vulnerable points?

[Lauffenburger, Barabasi]

"hubbiness"

Average degree (K)

25
20
15
10
5
0

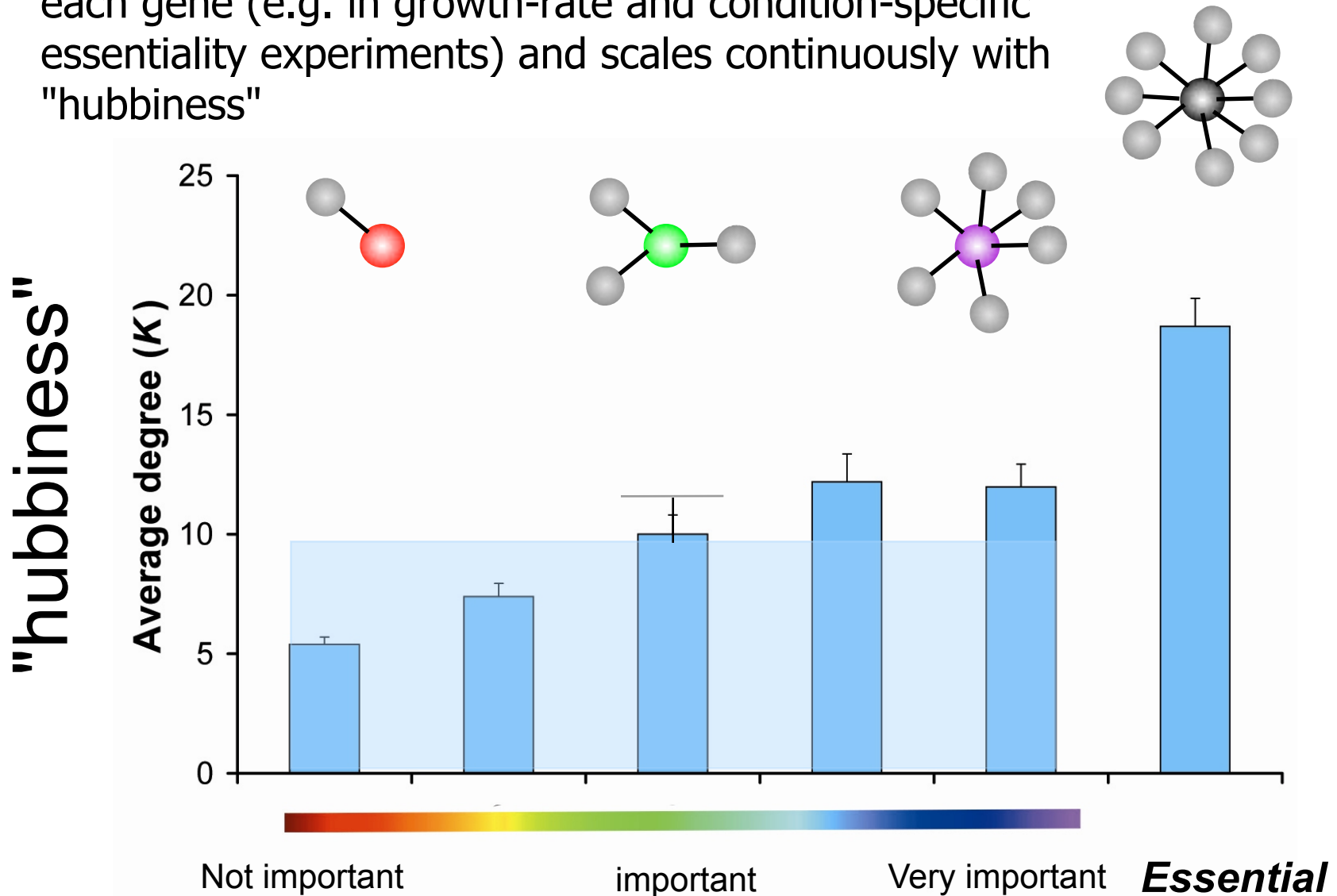


Non-Essential

Essential

Relationships extends to "Marginal Essentiality"

Marginal essentiality measures relative importance of each gene (e.g. in growth-rate and condition-specific essentiality experiments) and scales continuously with "hubbiness"



Networks & Variation

**Which parts of the network vary most in sequence?
Which are under selection, either positive or negative?**

Notably, the most highly conserved proteins were highly connected in *E.coli* protein interaction network. (*E.coli*)

- Butland et al. 2004, Nature

Connectivity of well-conserved proteins in network is negatively correlated with their rate of evolution. (*Saccharomyces cerevisiae*)

- Fraser et al. 2002, Science

- Fraser et al. BMC Evol. Biol. (2003)

Proteins that have a more central position evolve more slowly and are more likely to be essential for survival. (*Saccharomyces cerevisiae*; *C. elegans*; *Drosophila*)

- Hahn et al. 2005, Mol Biol Evol

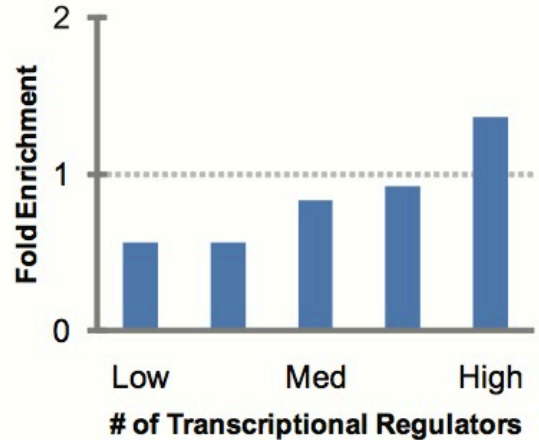
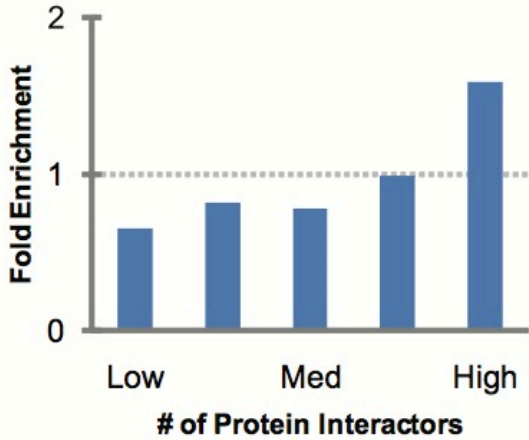
More miRNA regulation of a target gene associated with lower dN/dS ($r = -.21$) (*M. musculus*)

- Cheng et al. 2009, BMC Genomics

Slowly evolving proteins tend to have more interaction partners. (*Saccharomyces cerevisiae*)

- Xia et al. 2009, Plos Comput Biol

**More Connectivity,
More Constraint :
A theme borne out
in many studies**



Fold Enrichment of slowly evolved proteins - Xia et al.

Rapid Evolution in the interaction network takes place at the periphery

- **Pos. sel. v. deg. centrality:**

$\rho = -.06$, $P < 1.2e-6$

- Effect is independent of any bias due to gene expression differences
- Update w. 1000G Phase I SNP dens. v. centrality:
 $\rho = -.1$, $p < 2.2e-16$

- **Nonsyn / synonymous SNPs v. deg. centrality:**

$\rho = -.1$, $P < 4.0e-4$

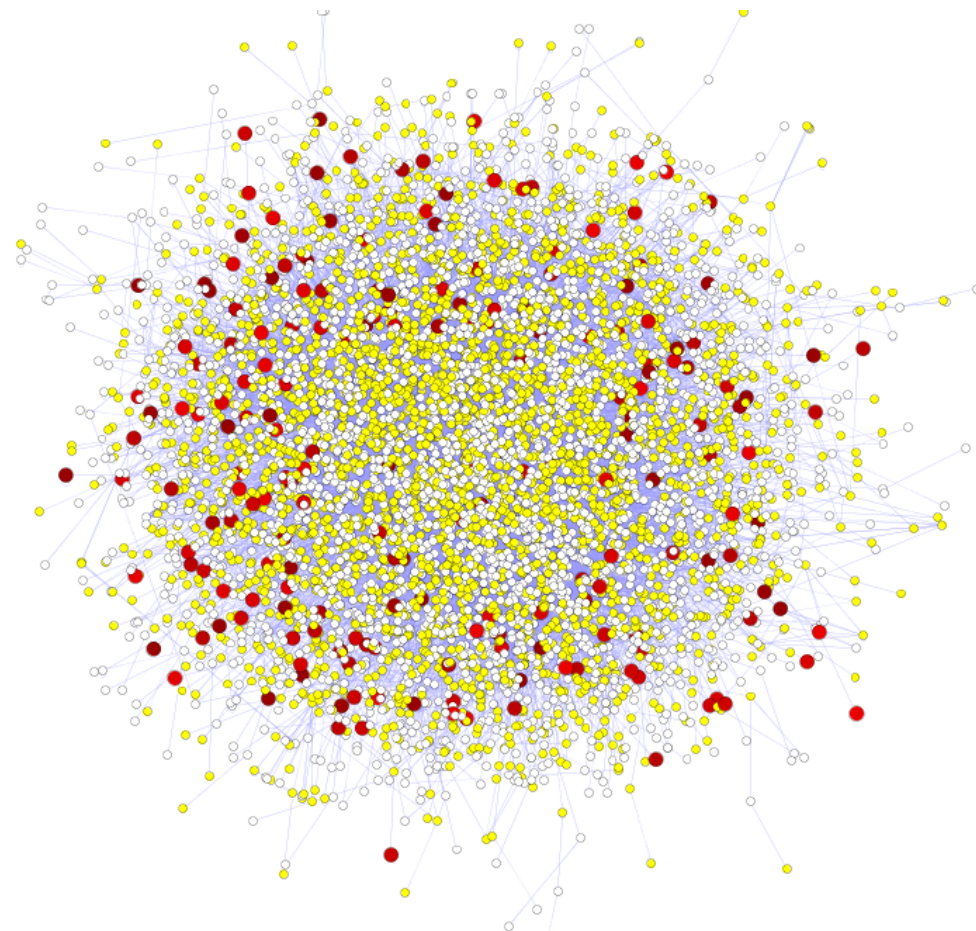
$\rho = -.3$, $P < 2.2.0e-16$ (updated to 1000G phase I)

- **# overlapping SDs of each gene v. betweenness centrality :**

$\rho = -.04$, $P < 3.3e-3$

- **# CNVs intersecting a gene v. network centrality:**

$\rho = -.03$, $P < 0.002$



- **High likelihood of positive selection**
- **Lower likelihood of positive selection**
- **Not under positive selection**
- **No data about positive selection**

Source: Nielsen et al. *PLoS Biol.* (2005), HPRD, and Kim et al. *PNAS* (2007)

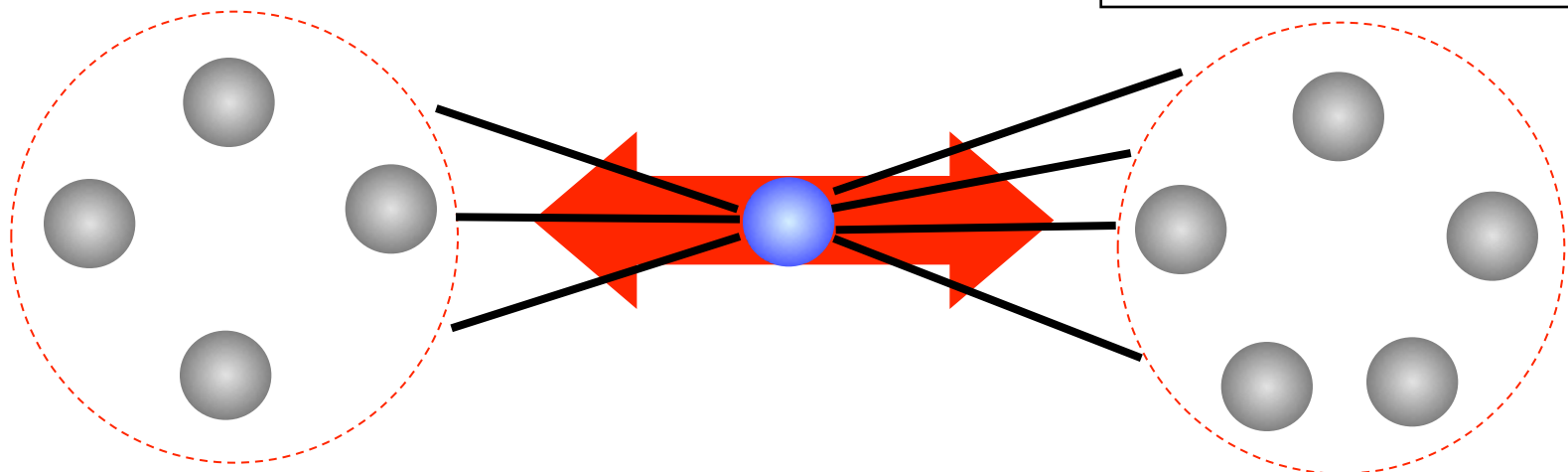
Other Measures of Centrality besides Hubs: Bottlenecks & their Calculation

Another measure of Centrality: Betweenness centrality

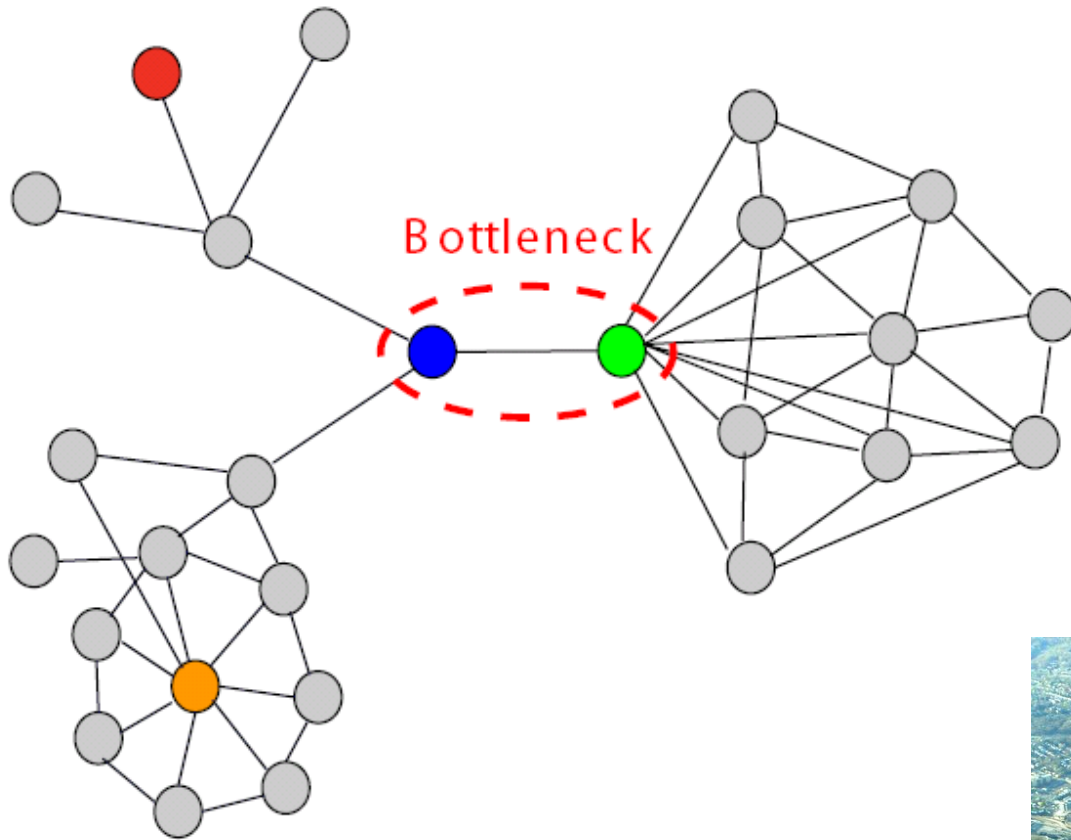
Betweenness of a node is the number of shortest paths of pairs of vertices that run through it -- a measure of information flow.





Freeman LC (1977) Set of measures of centrality based on betweenness. *Sociometry* 40: 35–41.

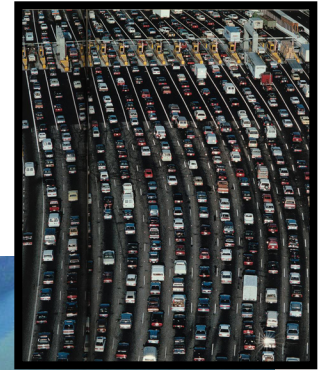
Girvan & Newman (2002) *PNAS* 99: 7821.



Bottlenecks & Hubs

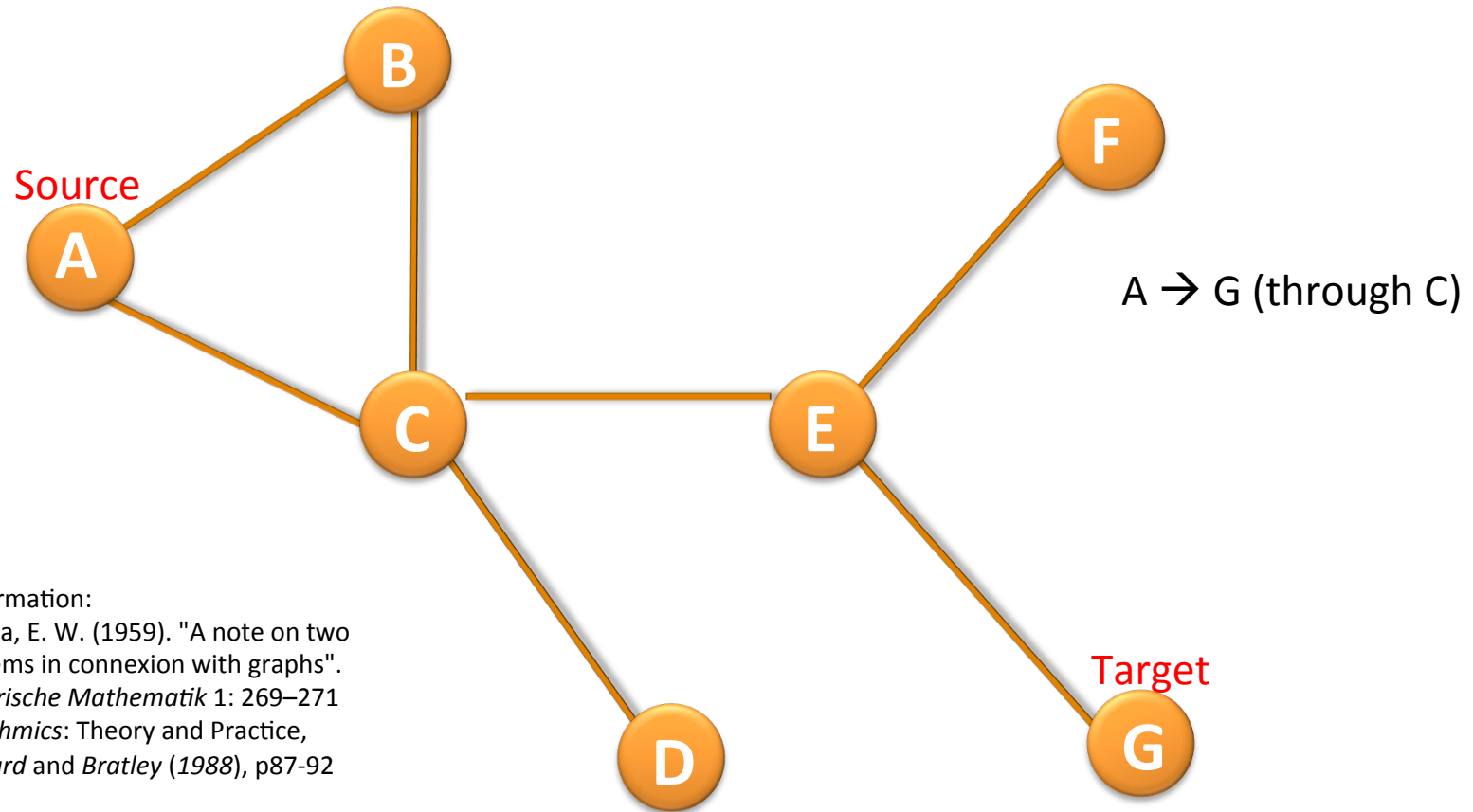


-  Hub-bottleneck **node**
-  Non-hub-bottleneck **node**
-  Hub-non-bottleneck **node**
-  Non-hub-non-bottleneck **node**



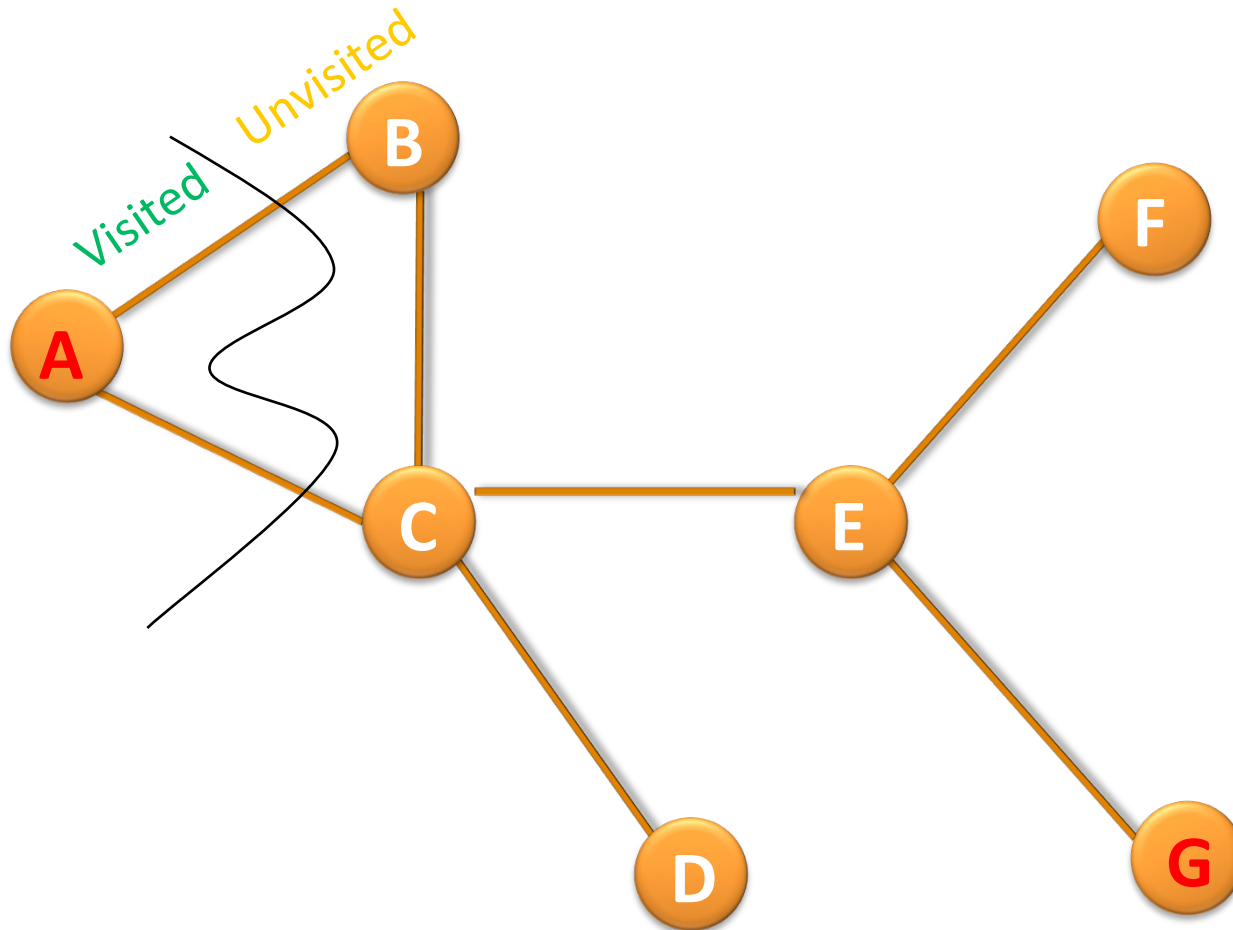
[Yu et al., PLOS CB (2007)]

Shortest Paths: The Dijkstra Algorithm

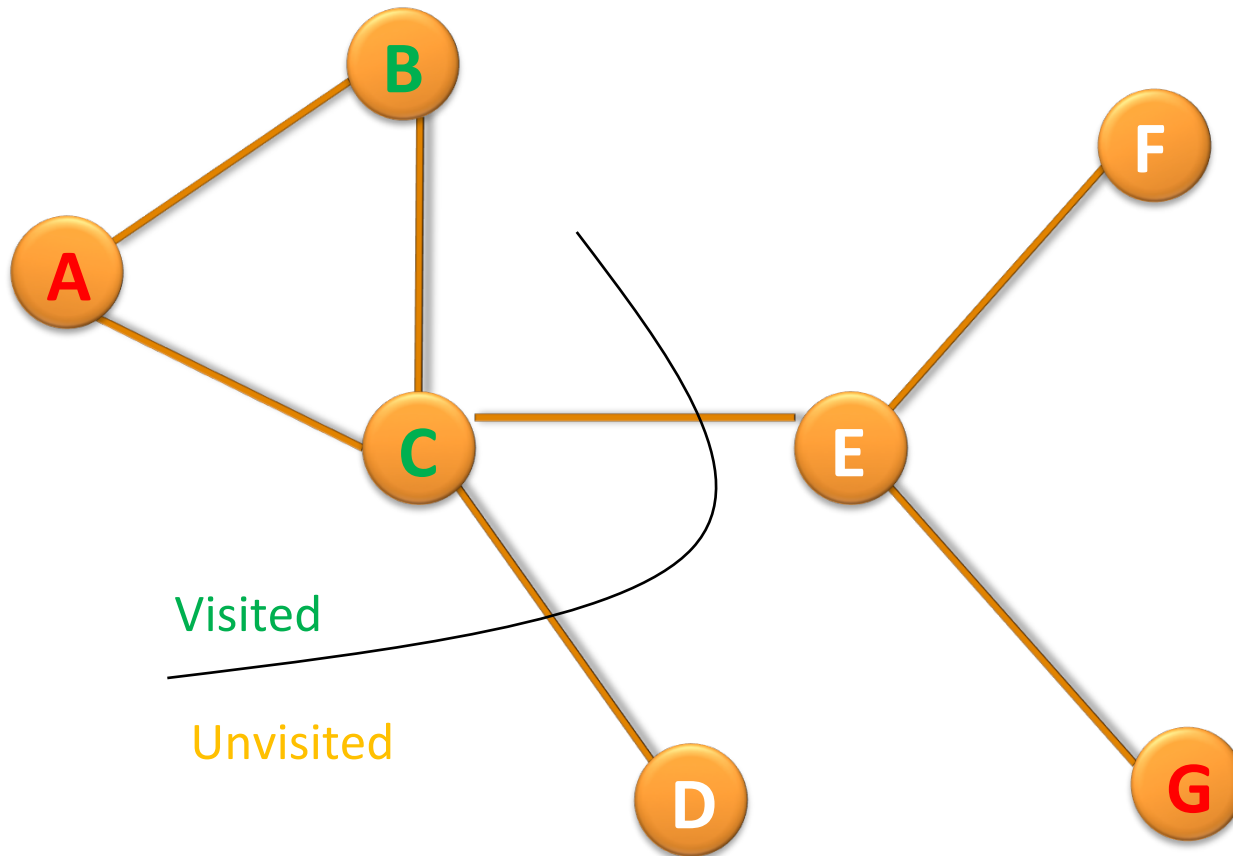


More information:

1. Dijkstra, E. W. (1959). "A note on two problems in connexion with graphs". *Numerische Mathematik* 1: 269–271
2. *Algorithmics: Theory and Practice*, Brassard and Bratley (1988), p87-92

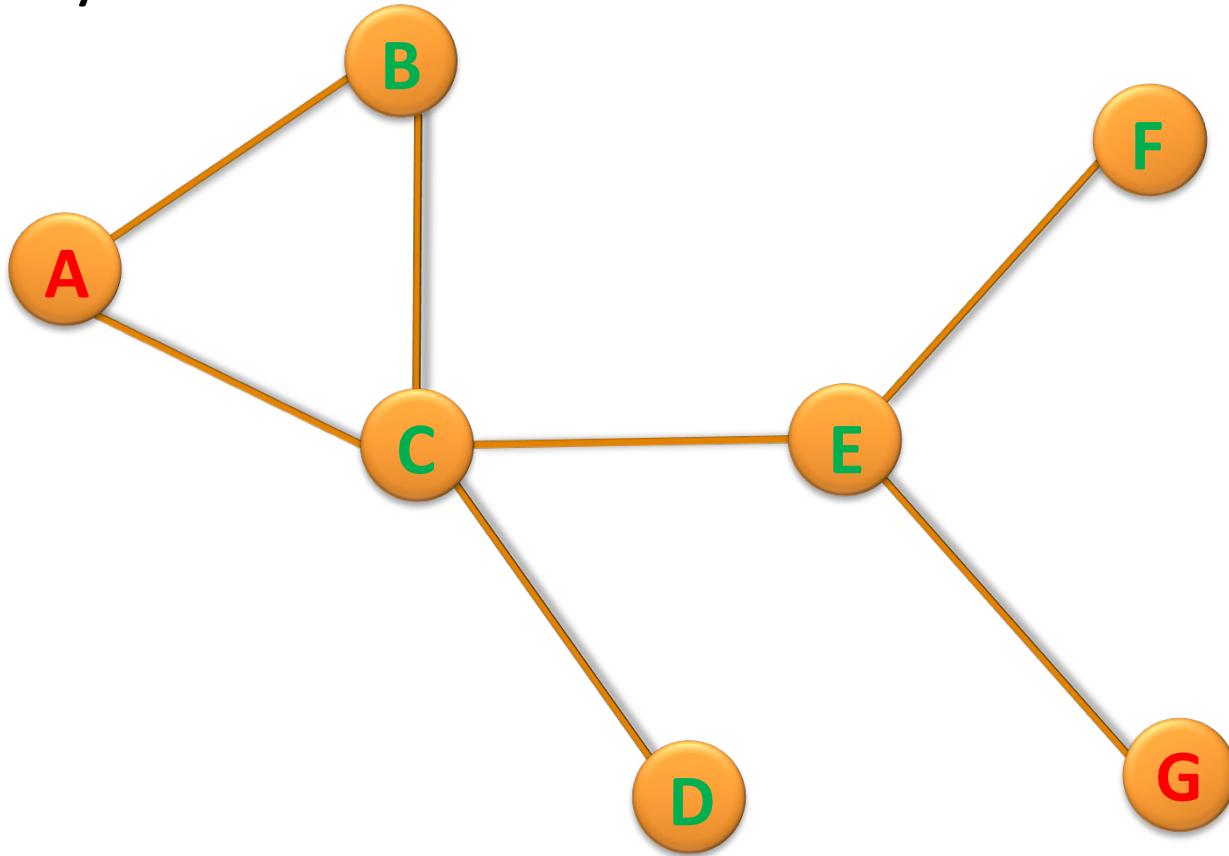


	B	C	D	E	F	G
Distance	∞	∞	∞	∞	∞	∞
Previous						



	B	C	D	E	F	G
Distance	1	1	∞	∞	∞	∞
<i>Previous</i>	A	A				

...Finally



	B	C	D	E	F	G
Distance	1	1	2	2	3	3
<i>Previous</i>	A	A	C	C	E	E

Traceback- dynamic programming

- Use the previous array, track back from G to E, then C, and finally A.

	B	C	D	E	F	G
Distance	1	1	2	2	3	3
<i>Previous</i>	A	A	C	C	E	E

Target

Source

Betweenness of C

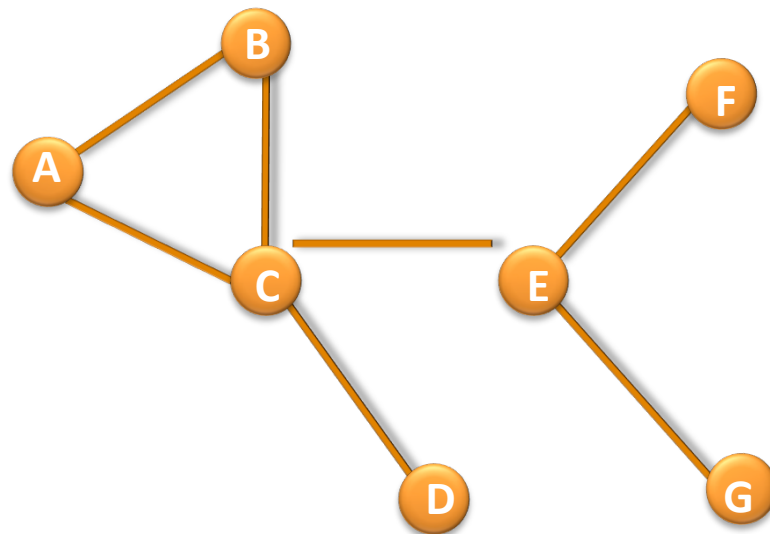
Pair of nodes

Source	Target
A	B
A	C
A	D
A	E
A	F
A	G
B	C
B	D
B	E
B	F
B	G
C	D
C	E
C	F
C	G
D	E
D	F
D	G
E	F
E	G
F	G

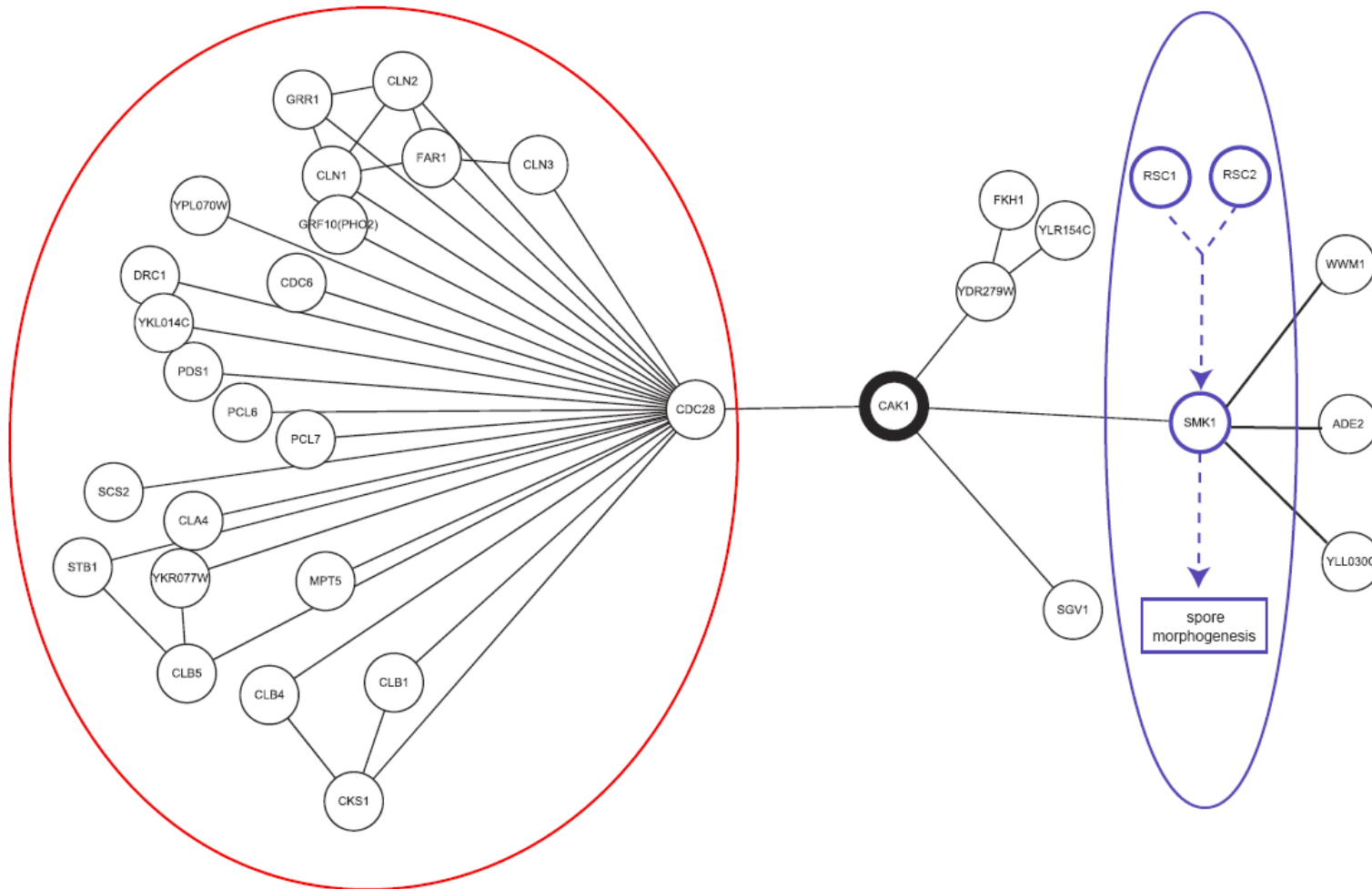
$$\textit{Betweenness}(v) = \sum_{s \neq v \neq t} (\sigma_{st}(v) / \sigma_{st})$$

where σ_{st} is the total number of shortest paths from source s to target t and $\sigma_{st}(v)$ is the number of those paths that pass through v .

11 shortest paths going through C



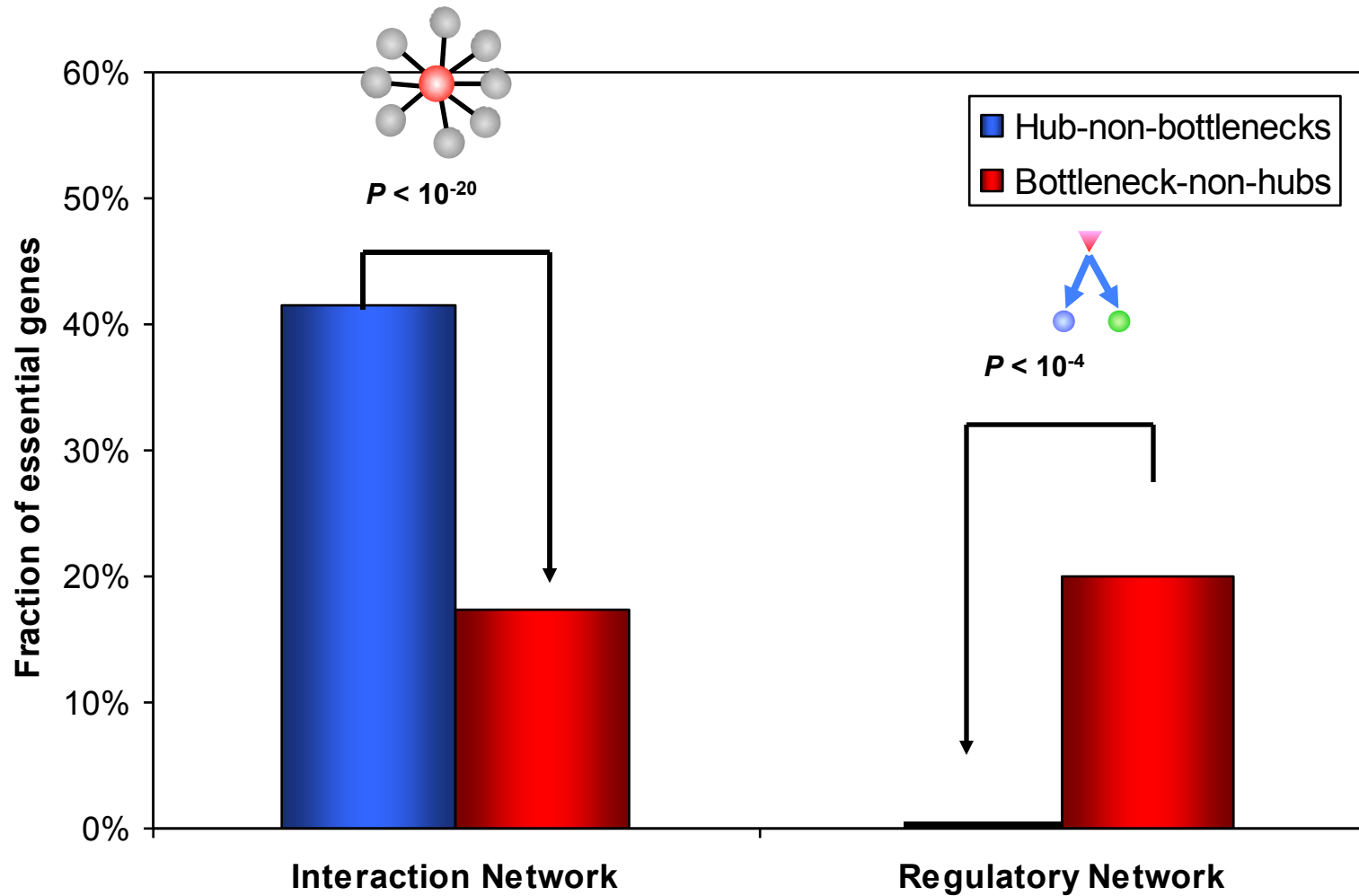
Bottleneck bridging between processes



Regulation of mitotic cell cycle

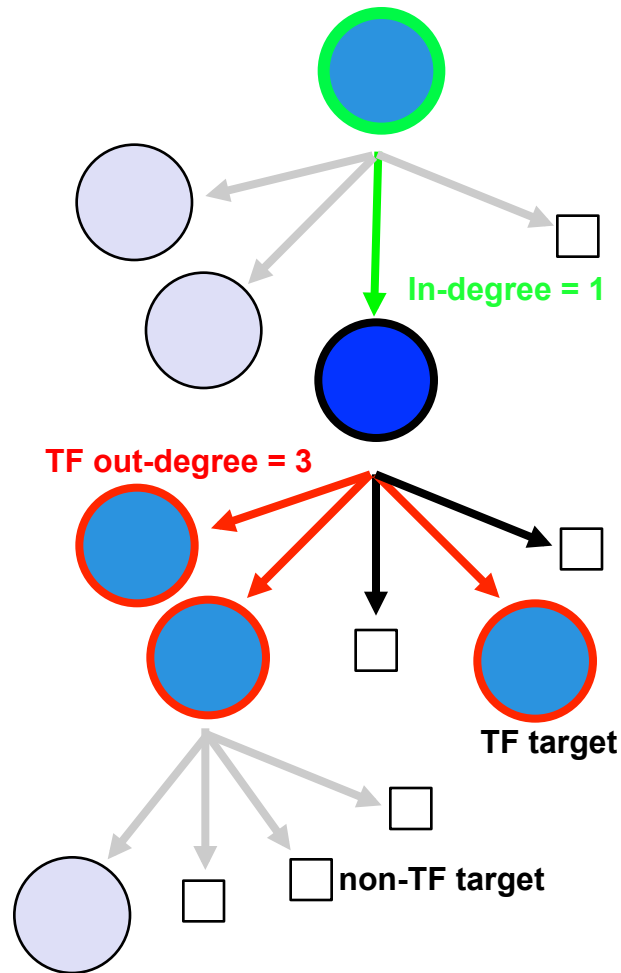
MAP Kinase pathway
regulating spore morphogenesis

Bottlenecks are what matters in regulatory networks



Other Measures of Centrality besides Hubs: Heirarchy

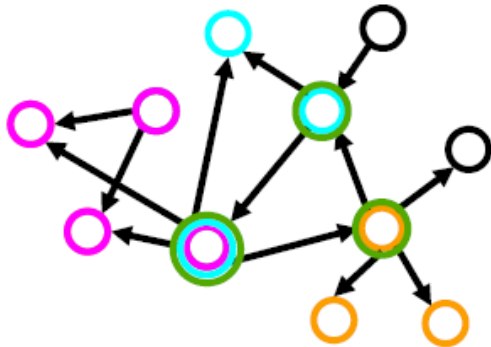
Network Stats to Identify Hierarchy



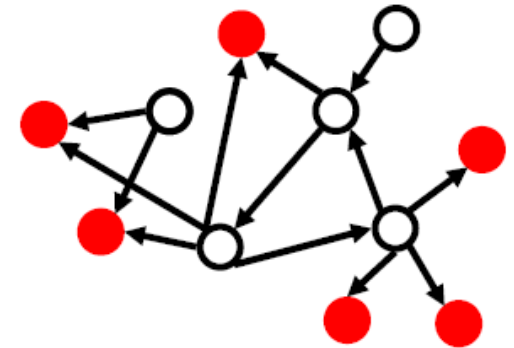
**Hierarchy Height Statistic =
(normalized TF Out deg. – In deg.)**

Determination of "Level" in Regulatory Network Hierarchy with Breadth-first Search

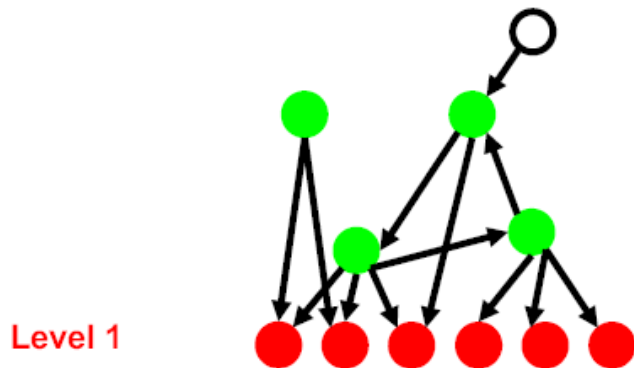
I. Example network with all 4 motifs



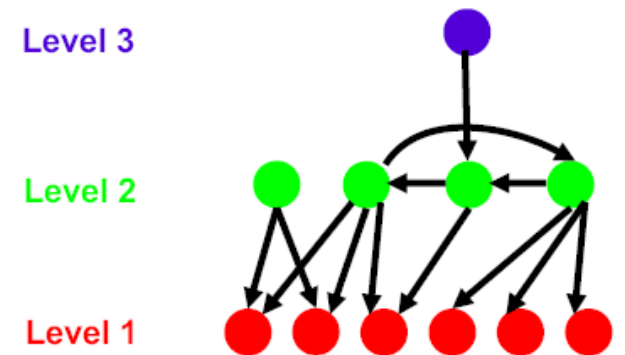
II. Finding terminal nodes (Red)



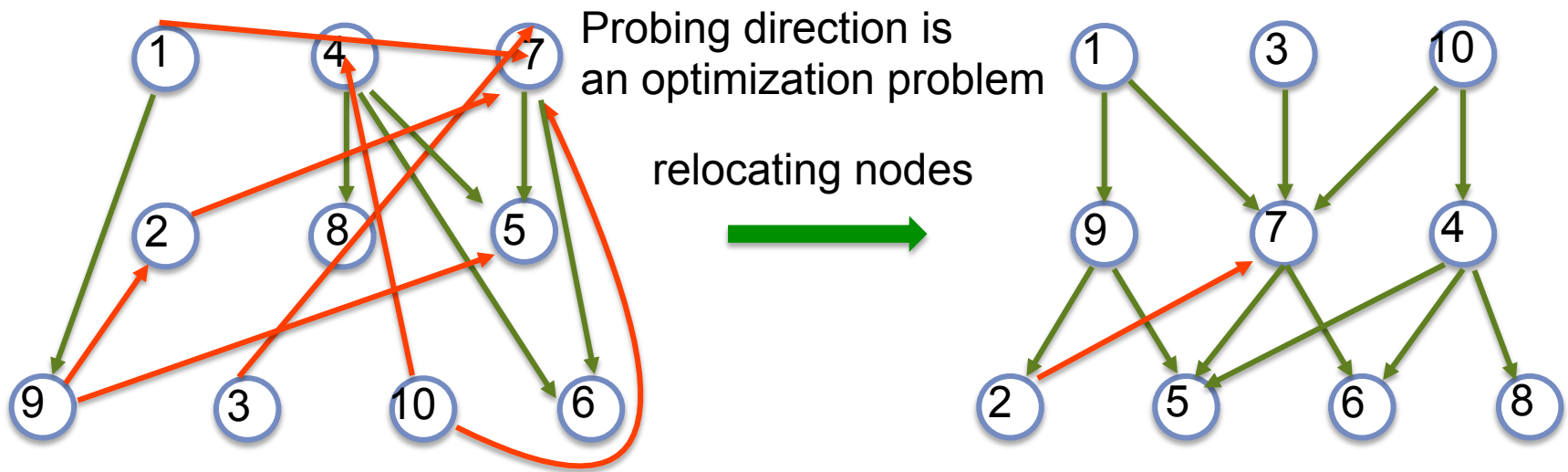
III. Finding mid-level nodes (Green)



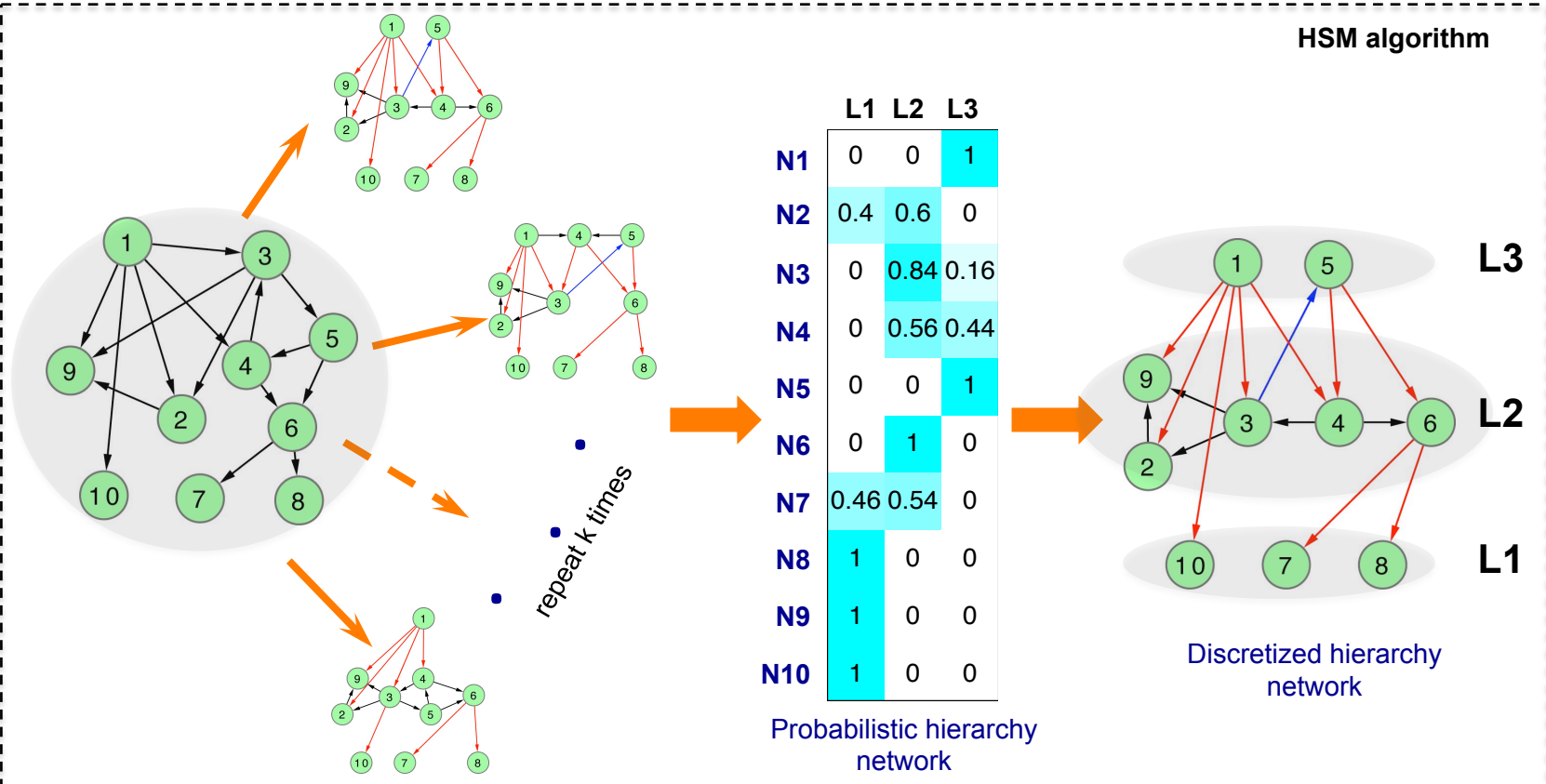
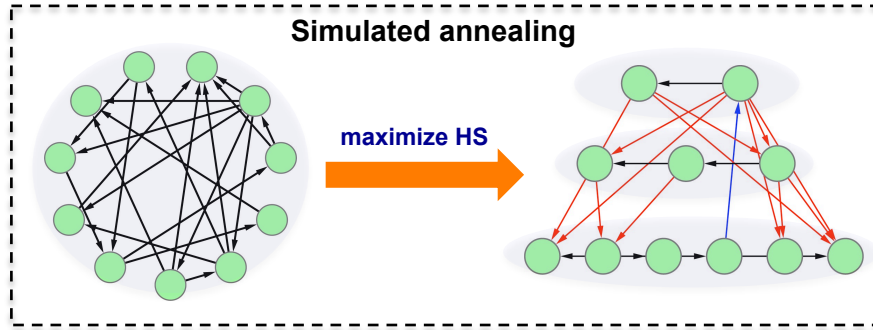
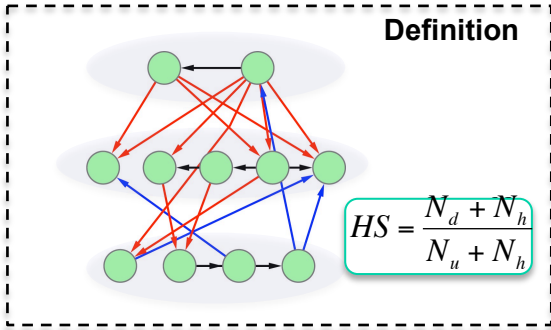
IV. Finding top-most nodes (Blue)



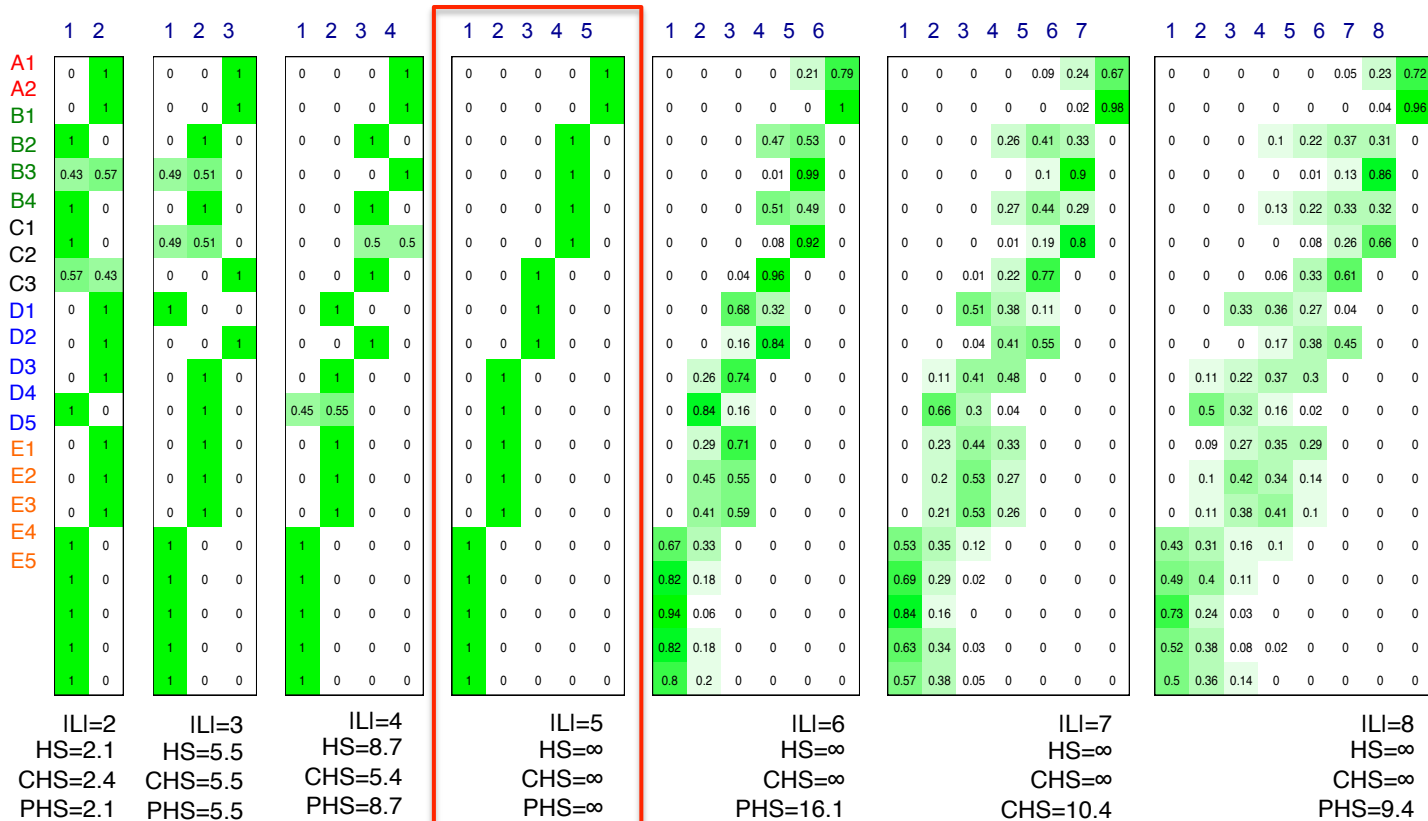
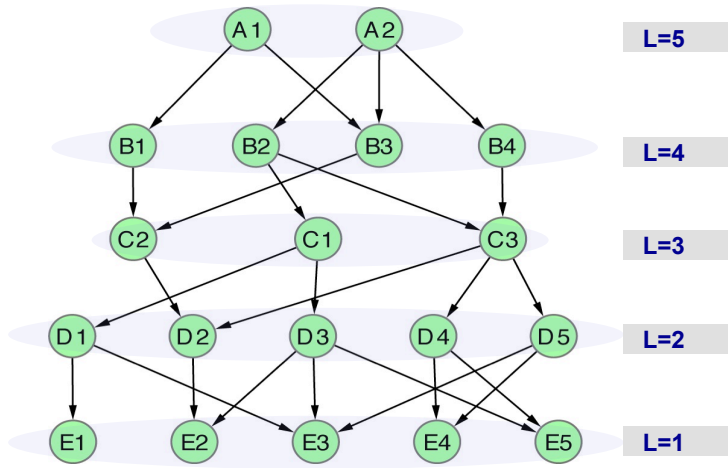
Using Simulated Annealing to Globally Minimize the Number of Upward Pointing Edges



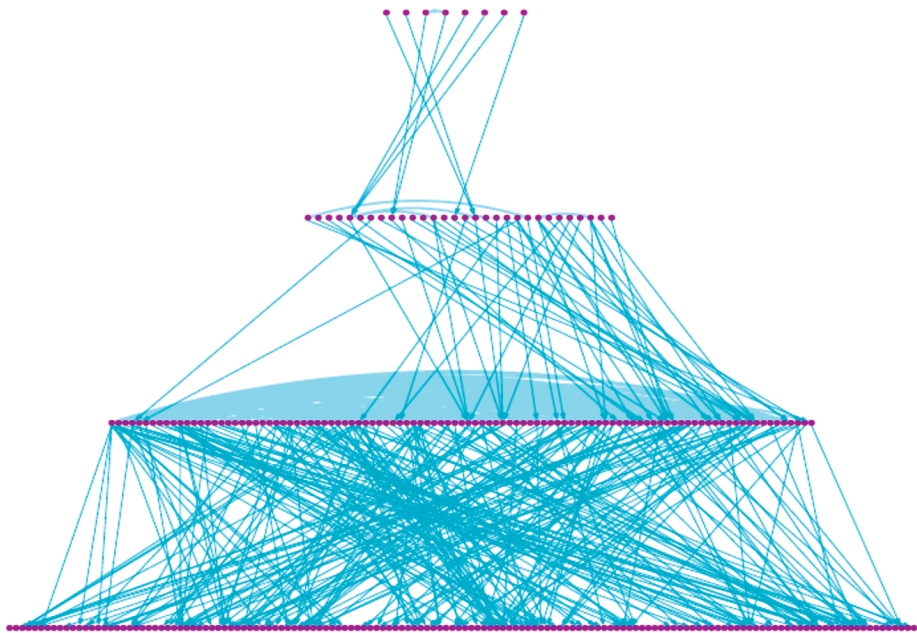
Hierarchy Score Maximization Algorithm



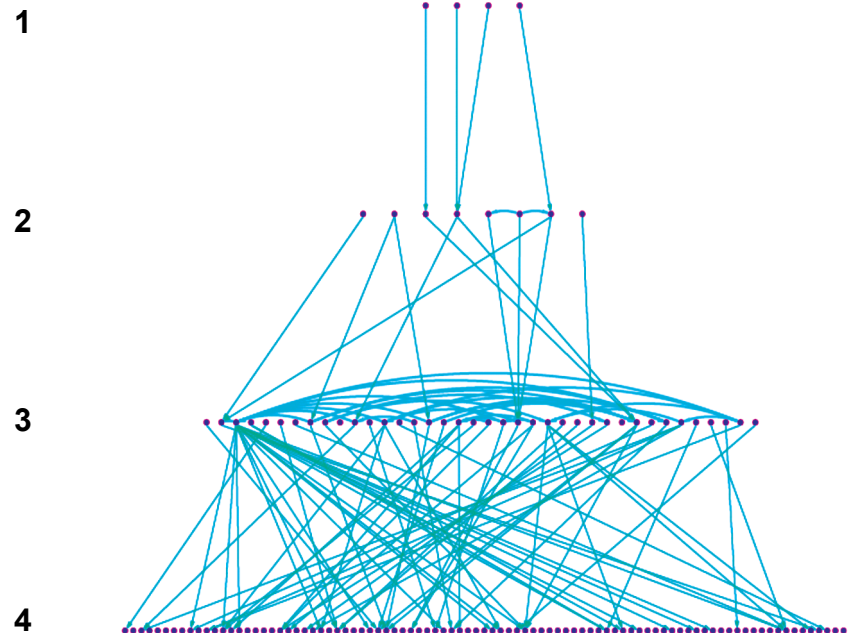
Apply HSM to a toy example



Regulatory Networks have similar hierarchical structures

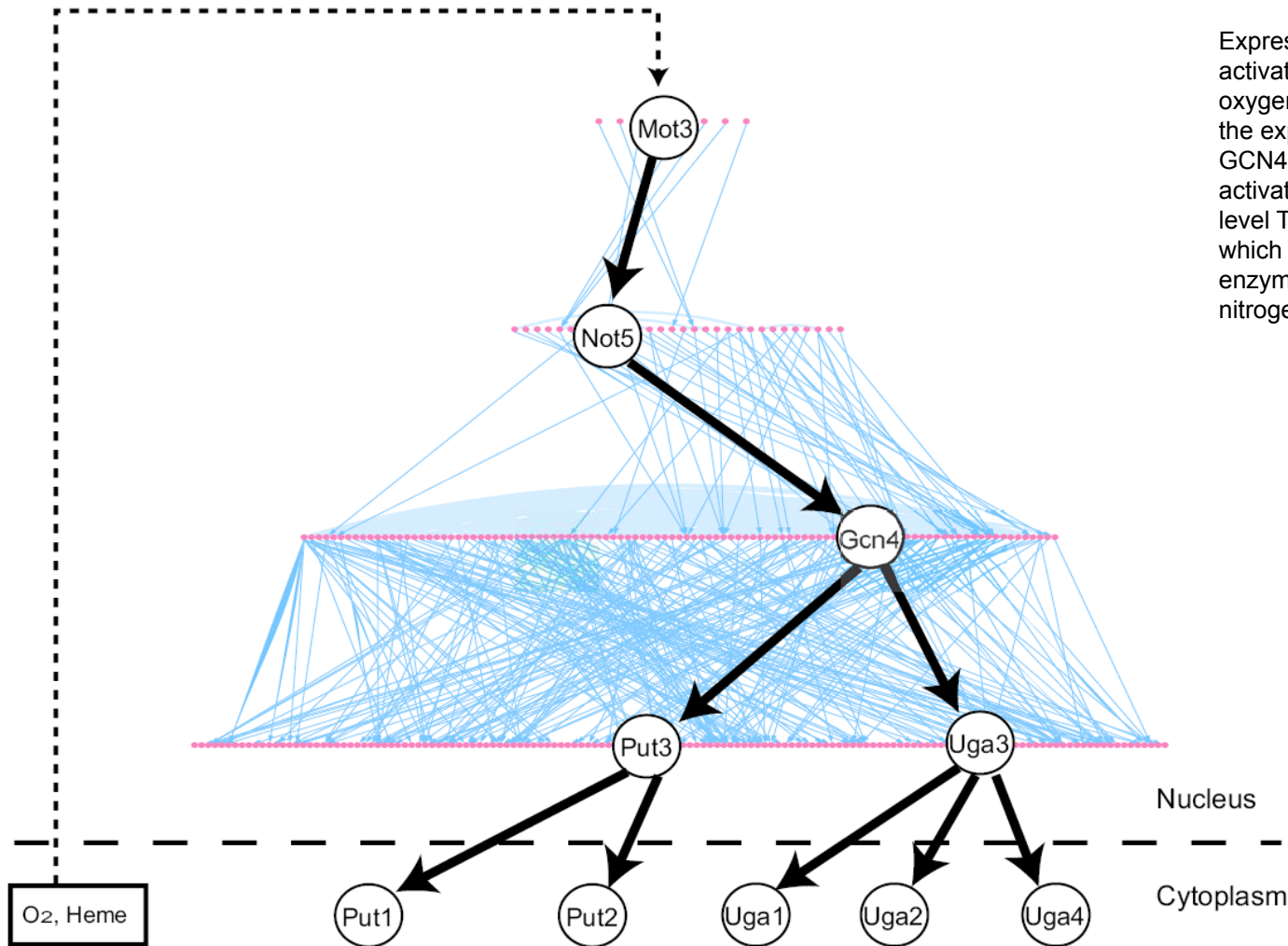


S. cerevisiae

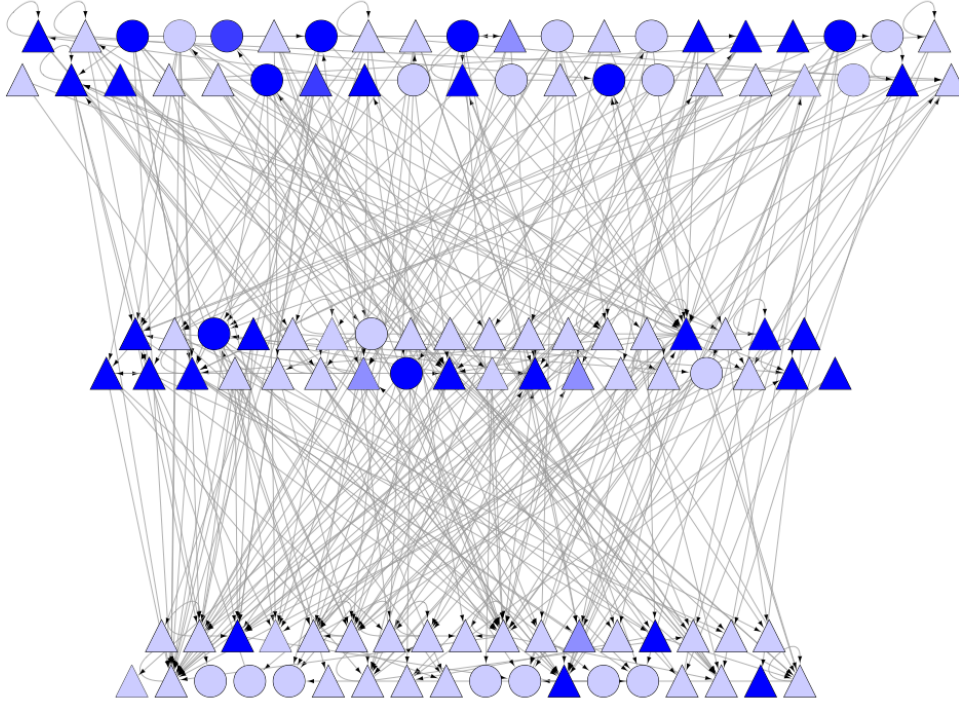


E. coli

Example of Path Through Regulatory Network



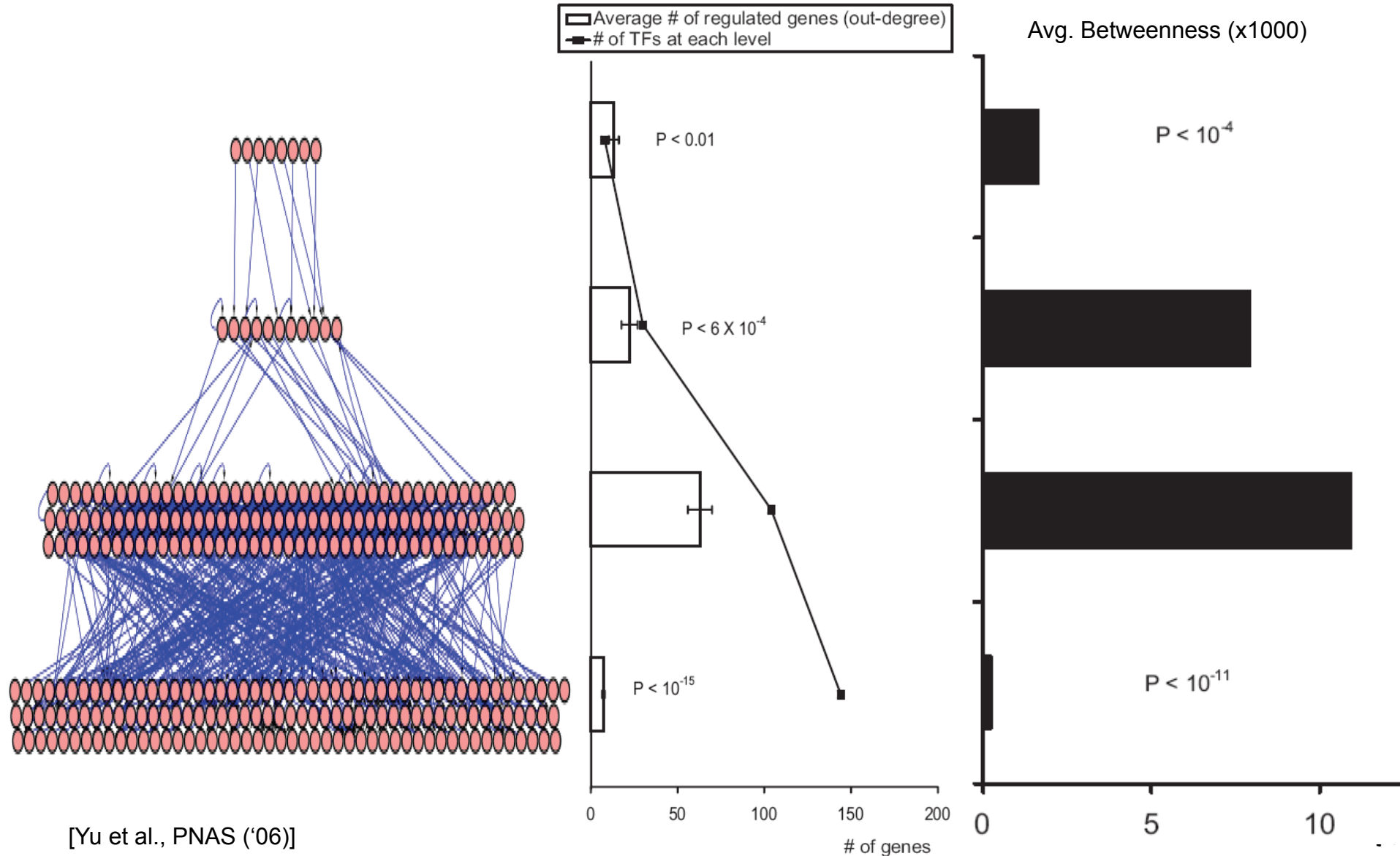
Expression of MOT3 is activated by heme and oxygen. Mot3 in turn activates the expression of NOT5 and GCN4, mid-level hubs. GCN4 activates two specific bottom-level TFs, Put3 and Uga3, which trigger the expression of enzymes in proline and nitrogen utilization.

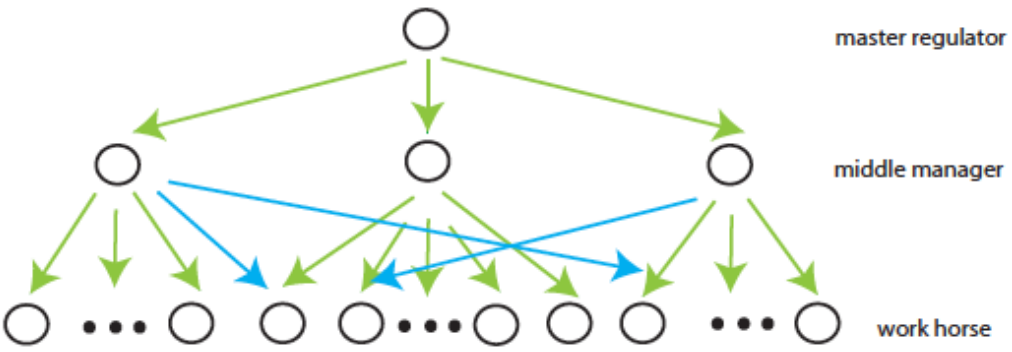
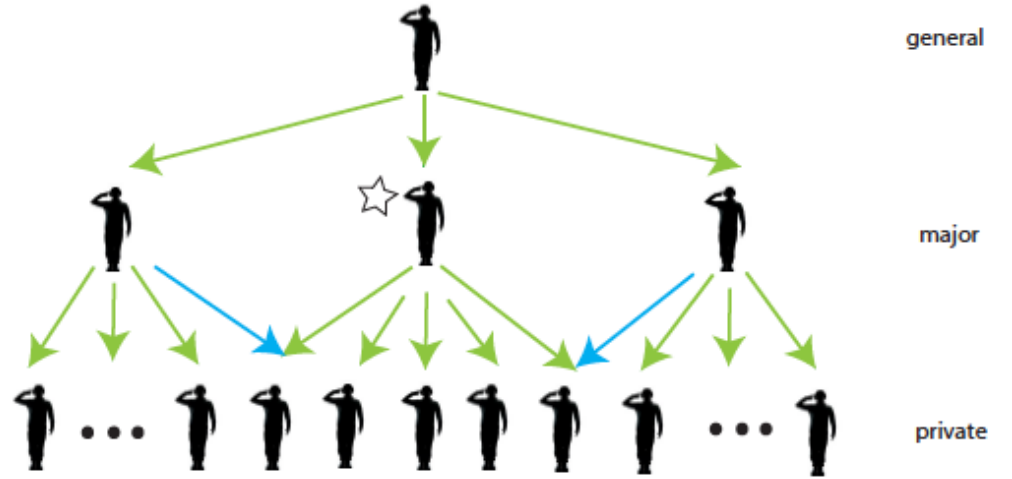
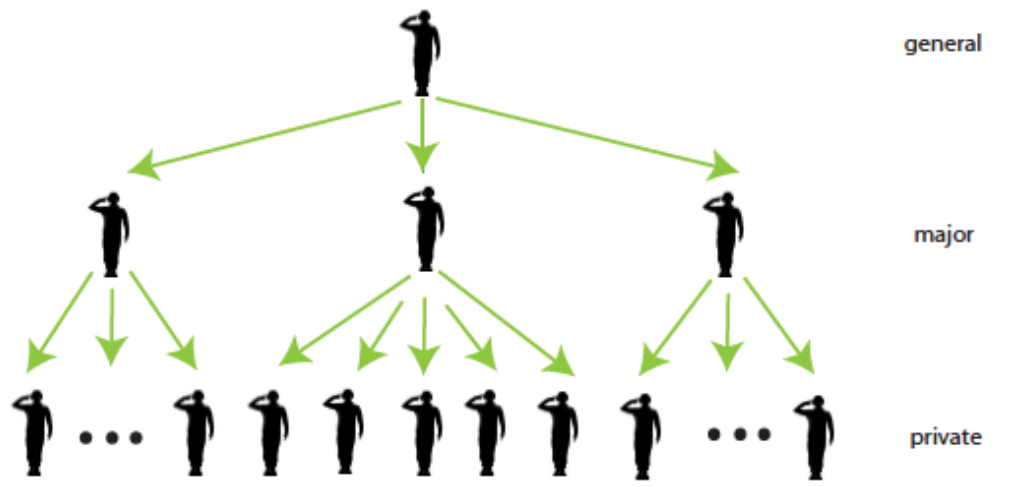


Avg. #
of PPI for
each TF

**Integration of TF hierarchy
with other 'omic information :
more connected TFs on the top**

Yeast Regulatory Hierarchy: Middle-managers Rule

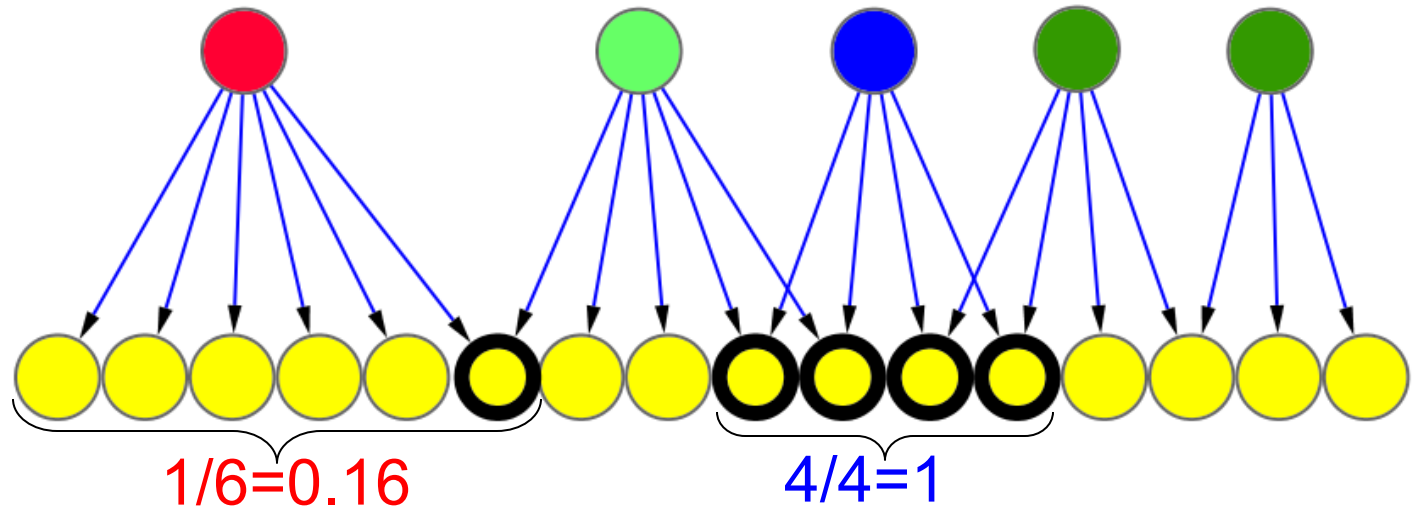




Collaborative Nature of the Nodes

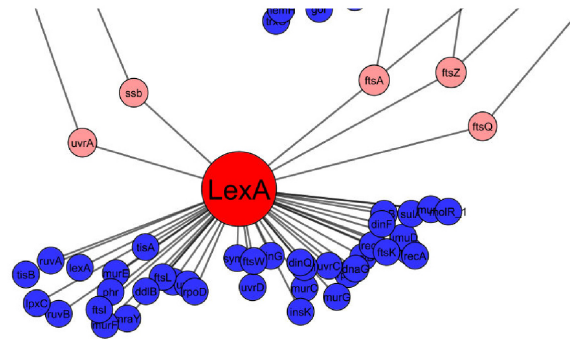
Autonomous

Collaborative

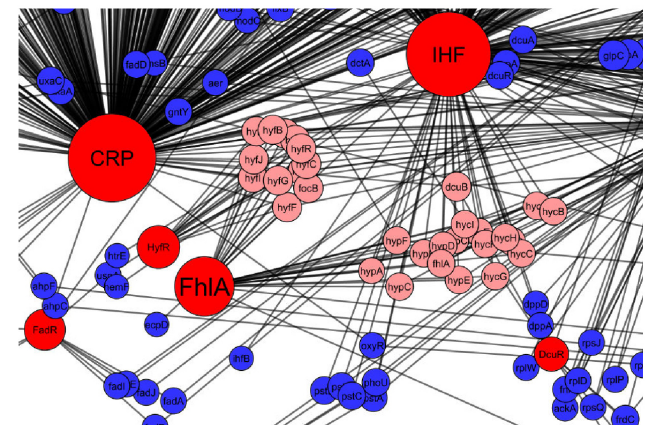


More Collaborative:
Democratic
More Autonomous:
Autocratic

Autonomous



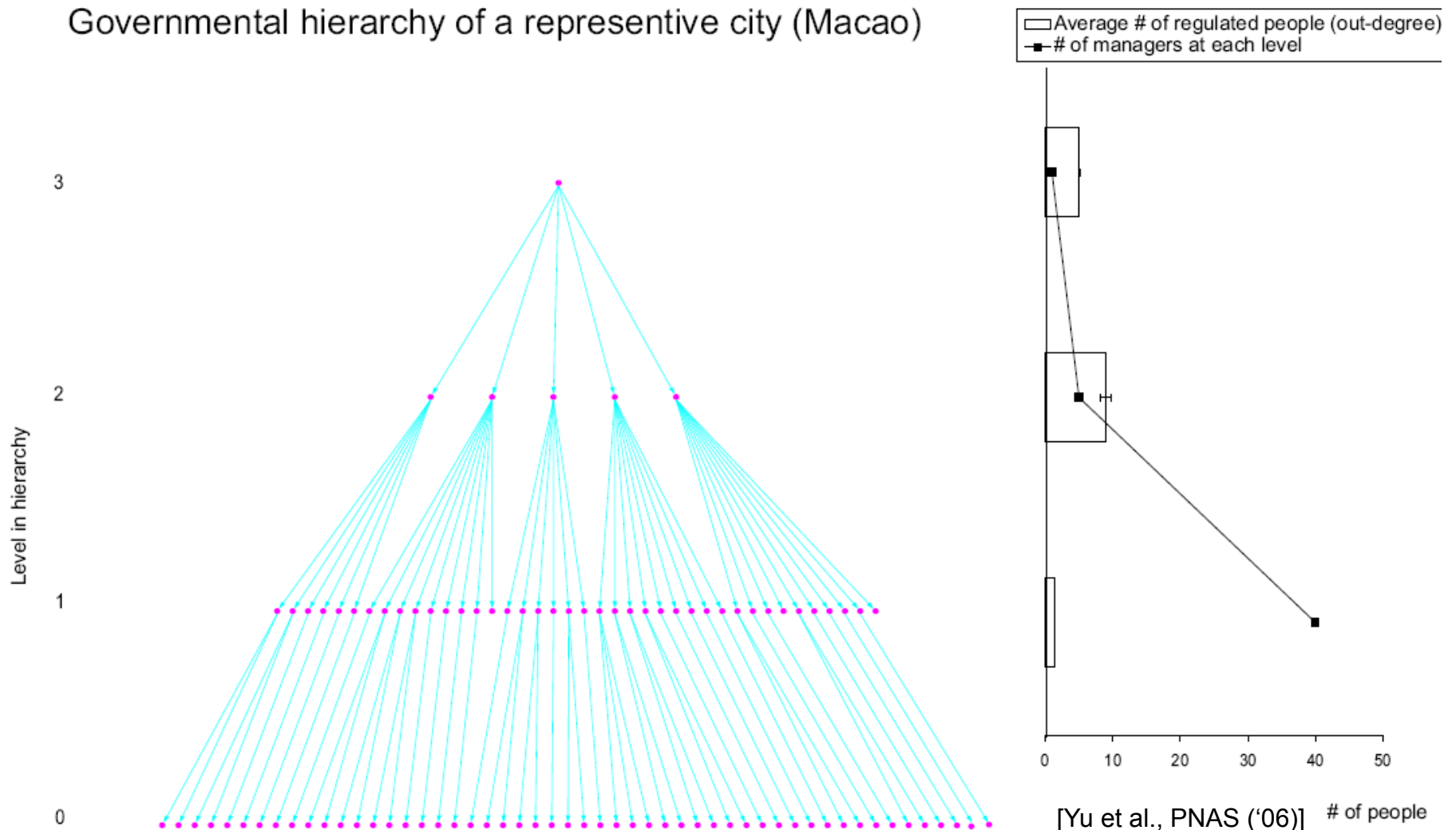
Collaborative



[Bhardwaj et al., PNAS (2010)]

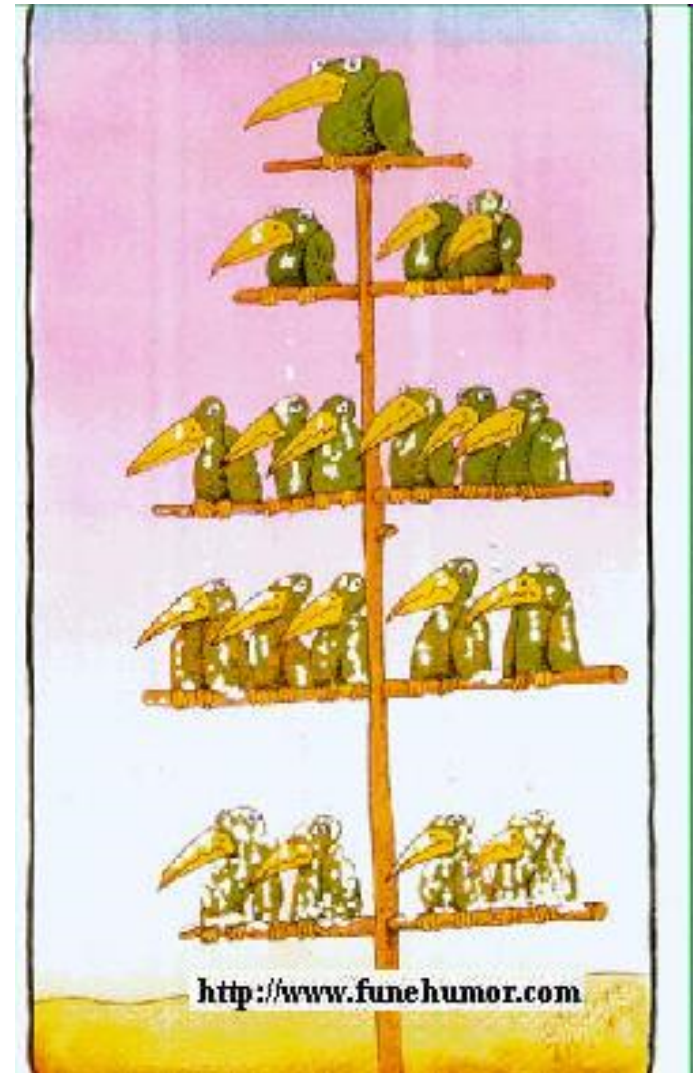
Yeast Network Similar in Structure to Government Hierarchy with Respect to Middle-managers

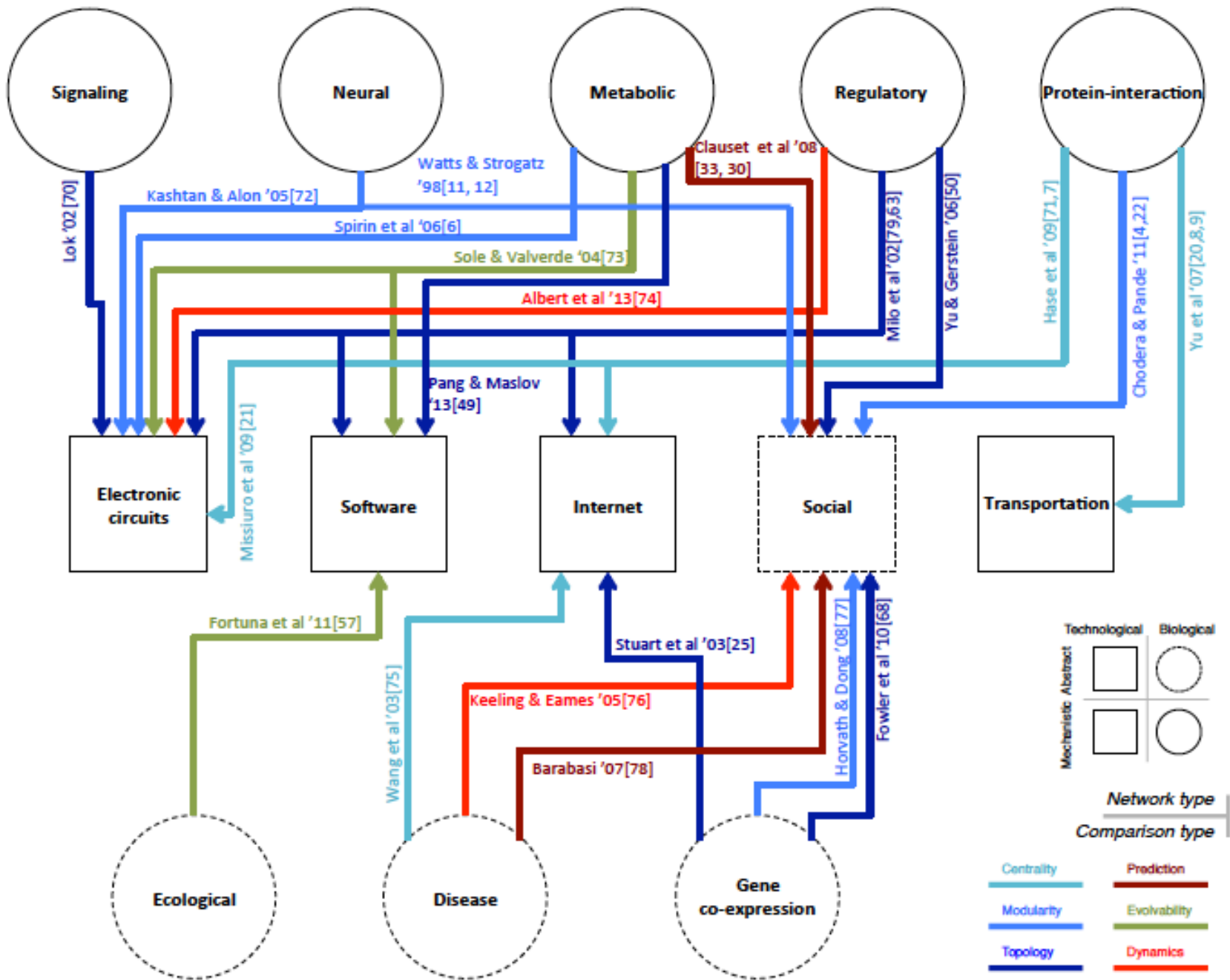
Governmental hierarchy of a representative city (Macao)



Middle Managers Interact the Most in Efficient Corporate Settings

- Floyd, S. W. et al (1992)
Middle management involvement in strategy and its association with strategic type
Strategic Management Journal 13, 153-167.
- Woodward, J. (1982) *Industrial Organization: Theory and Practice* (Oxford University Press, Oxford).
- Floyd, S. W. et al (1993)
**Dinosaurs or Dynamos?
Recognizing Middle Management's Strategic Role**
The Academy of Management Executive 8, 47-57.
- Floyd, S. W. et al (1997)
Middle management's strategic influence and organizational performance
Journal of Management Studies 34, 465-485.





[Yan et al., Cell Systems ('16)]