Biological Networks Analysis

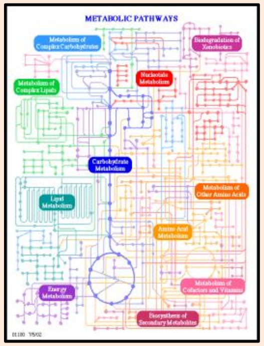
Degree Distribution and Network Motifs

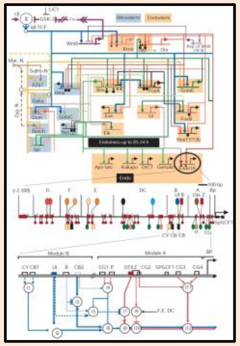
Genome 559: Introduction to Statistical and Computational Genomics

Elhanan Borenstein

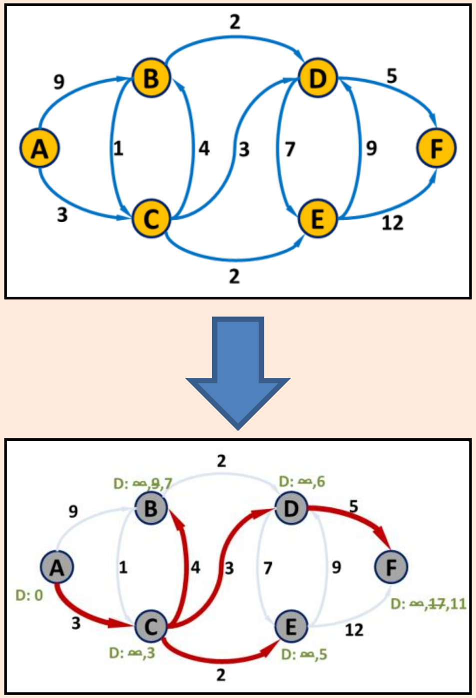
A quick review

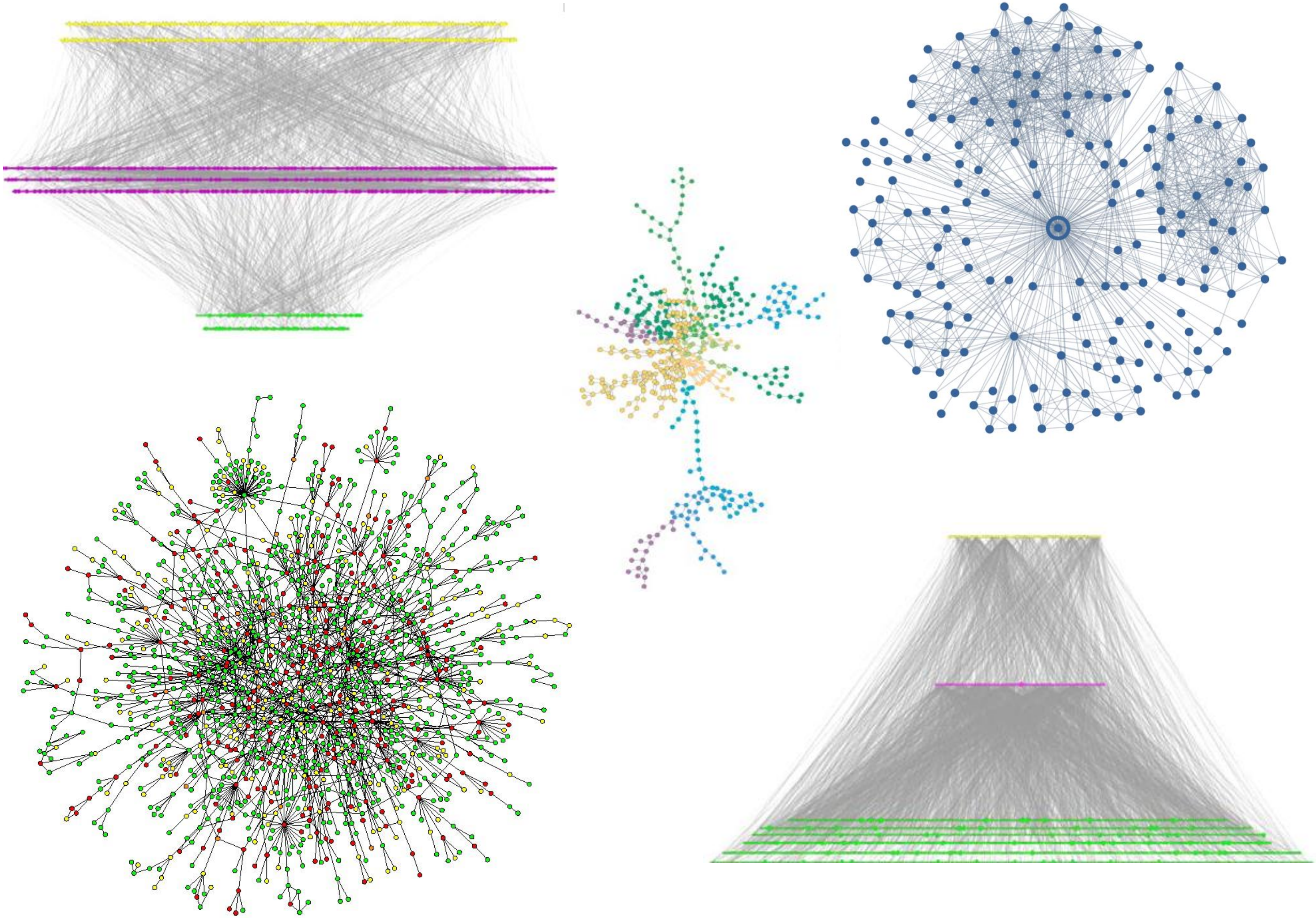
- Networks:
  - Networks vs. graphs
  - A collection of **nodes** and **links**
  - Directed/undirected; weighted/non-weighted, …
  - Networks as models vs. networks as tools





- Many types of biological networks
- The shortest path problem
- Dijkstra's algorithm
  1. **Initialize**: Assign a distance value, D, to each node. Set D=0 for *start* node and to infinity for all others.
  2. **For each unvisited neighbor of the current node:** Calculate tentative distance, D^t, through current node and if $D^t < D$: D← D^t. Mark node as visited.
  3. **Continue with the unvisited node with the smallest distance**





Comparing networks

- We want to find a way to “compare” networks.
  - “Similar” (not identical) **topology**
  - “Common” **design principles**

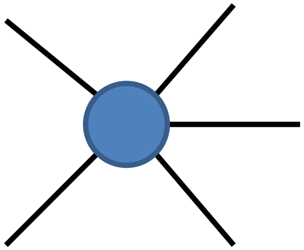
- We seek measures of network topology that are:
  - Simple
  - Capture **global** organization
  - Potentially “important”

Summary statistics

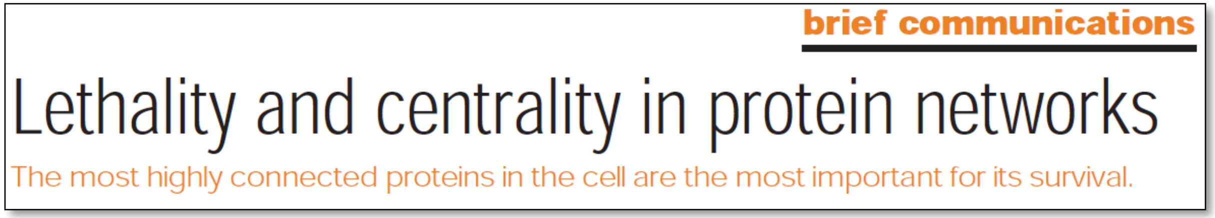
(equivalent to, for example, GC content for genomes)

Node degree / rank

- Degree = Number of neighbors



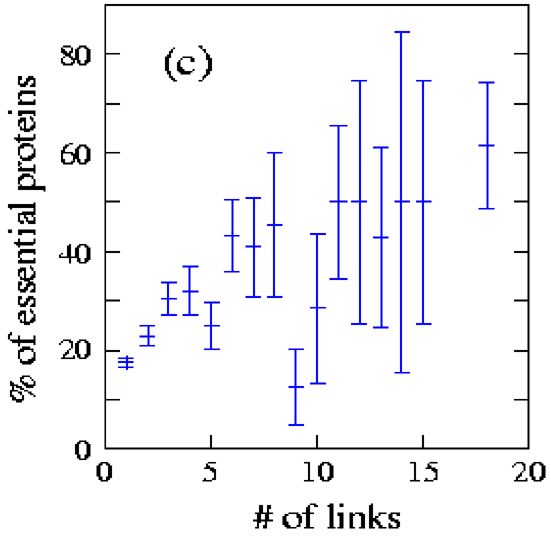
- Node degree in PPI networks correlates with:
  - Gene essentiality
  - Conservation rate
  - Likelihood to cause human disease



brief communications

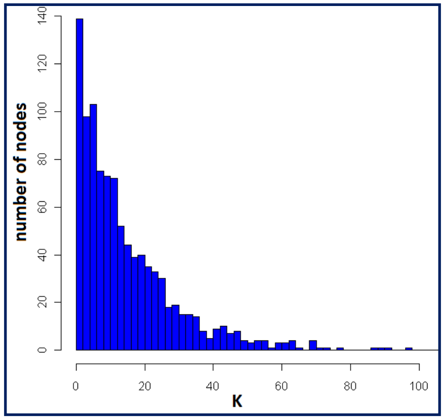
Lethality and centrality in protein networks

The most highly connected proteins in the cell are the most important for its survival.



Degree distribution

- P(k): probability that a node has a degree of exactly k



- Common distributions:

Poisson:

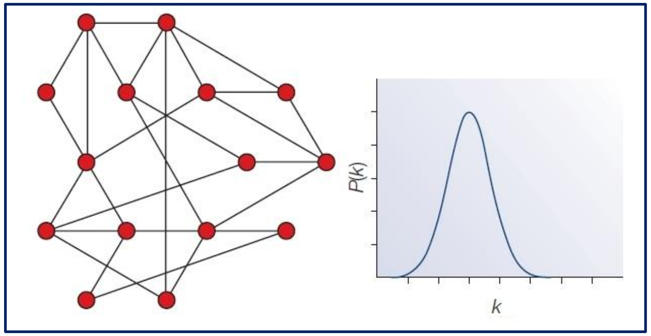
$$P(k) = \frac{e^{-d} d^k}{k!}$$

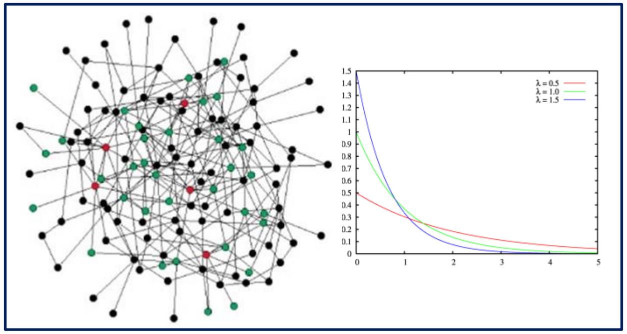
Exponential:

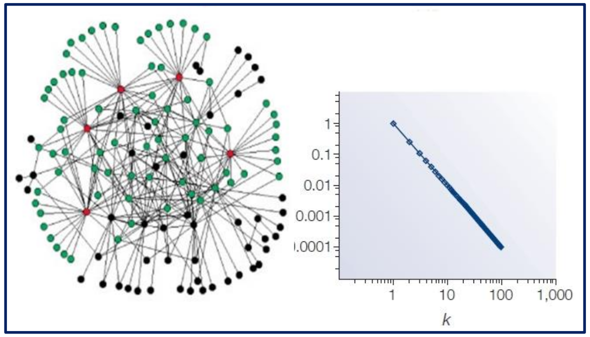
$$P(k) \propto e^{-k/d}$$

Power-law:

$$P(k) \propto k^{-c}, k \neq 0, c > 1$$

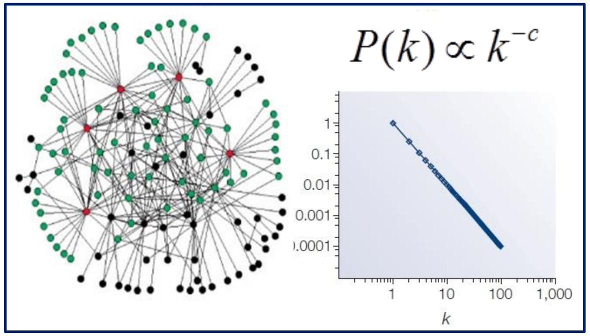






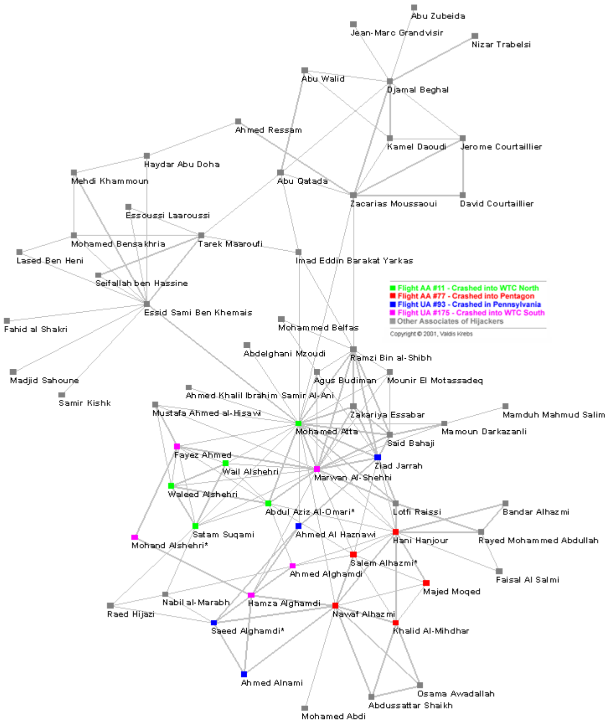
The power-law distribution

- **Power-law distribution has a “heavy” tail**!
  - Characterized by a small number of highly connected nodes, known as **hubs**
  - A.k.a. “scale-free” network



- **Hubs are crucial:**
  - Affect **error** and **attack** tolerance of complex networks (Albert et al. Nature, 2000)

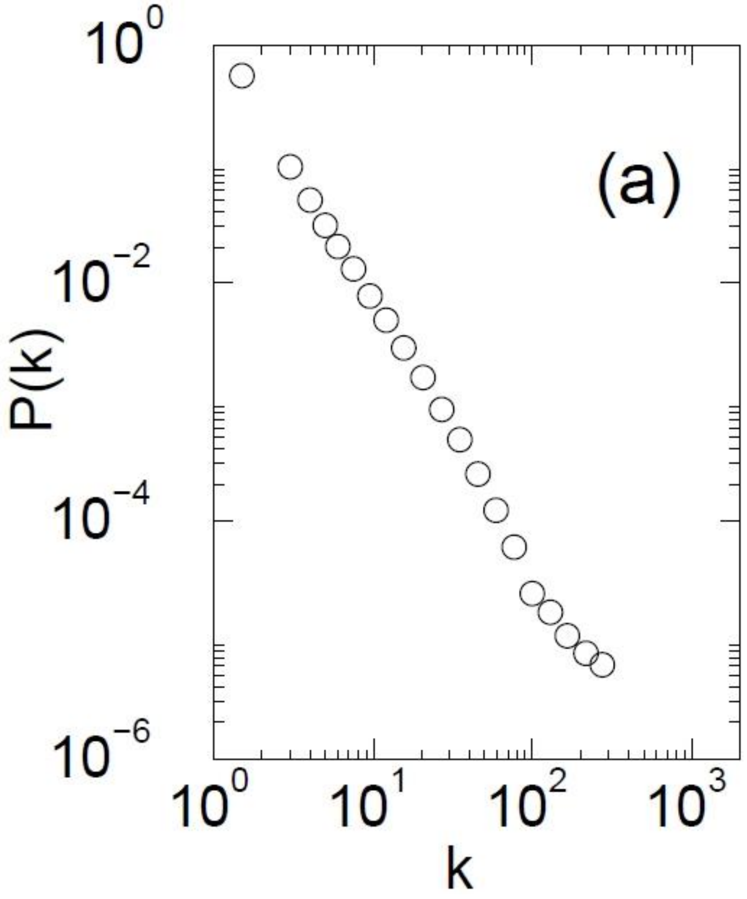
CANADA
MEXICO
Atlantic Ocean
Pacific Ocean
Gulf of Mexico
BAHAMAS



The Internet

- **Nodes** – 150,000 routers
- **Edges** – physical links

- P(k) ~ $k^{-2.3}$



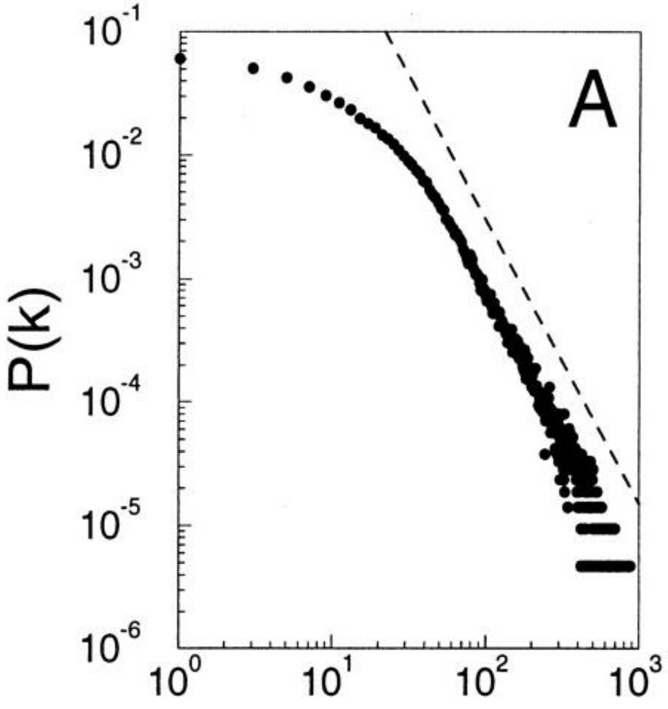
Govindan and Tangmunarunkit, 2000

Movie actor collaboration network

Tropic Thunder (2008)

- **Nodes** – 212,250 actors
- **Edges** – co-appearance in a movie

- P(k) ~ $k^{-2.3}$

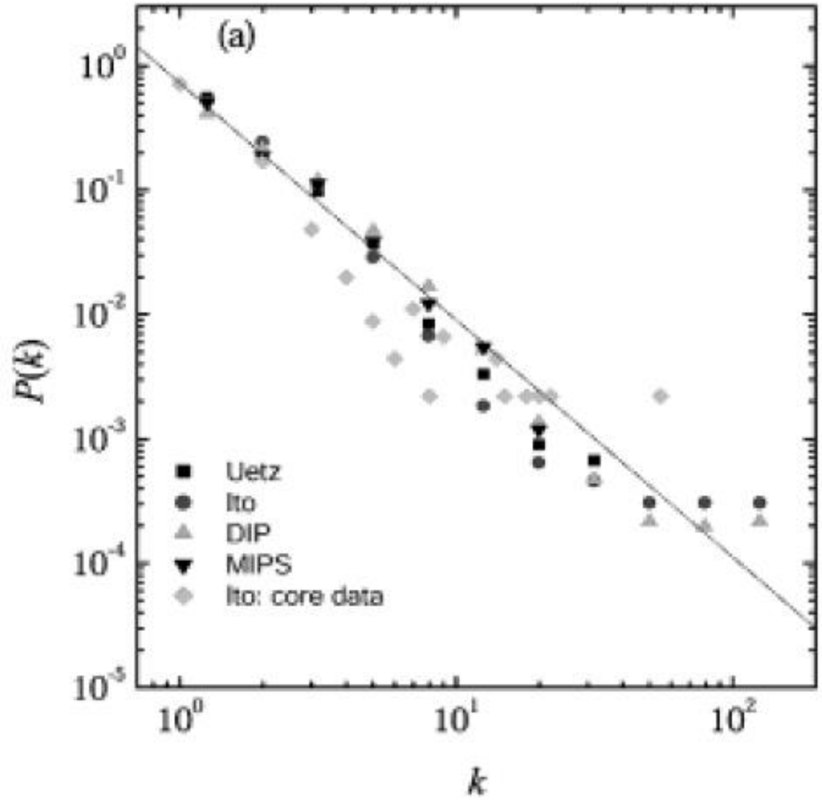


Barabasi and Albert, Science, 1999

Protein protein interaction networks

- **Nodes** – Proteins
- **Edges** – Interactions (yeast)

- P(k) ~ $k^{-2.5}$



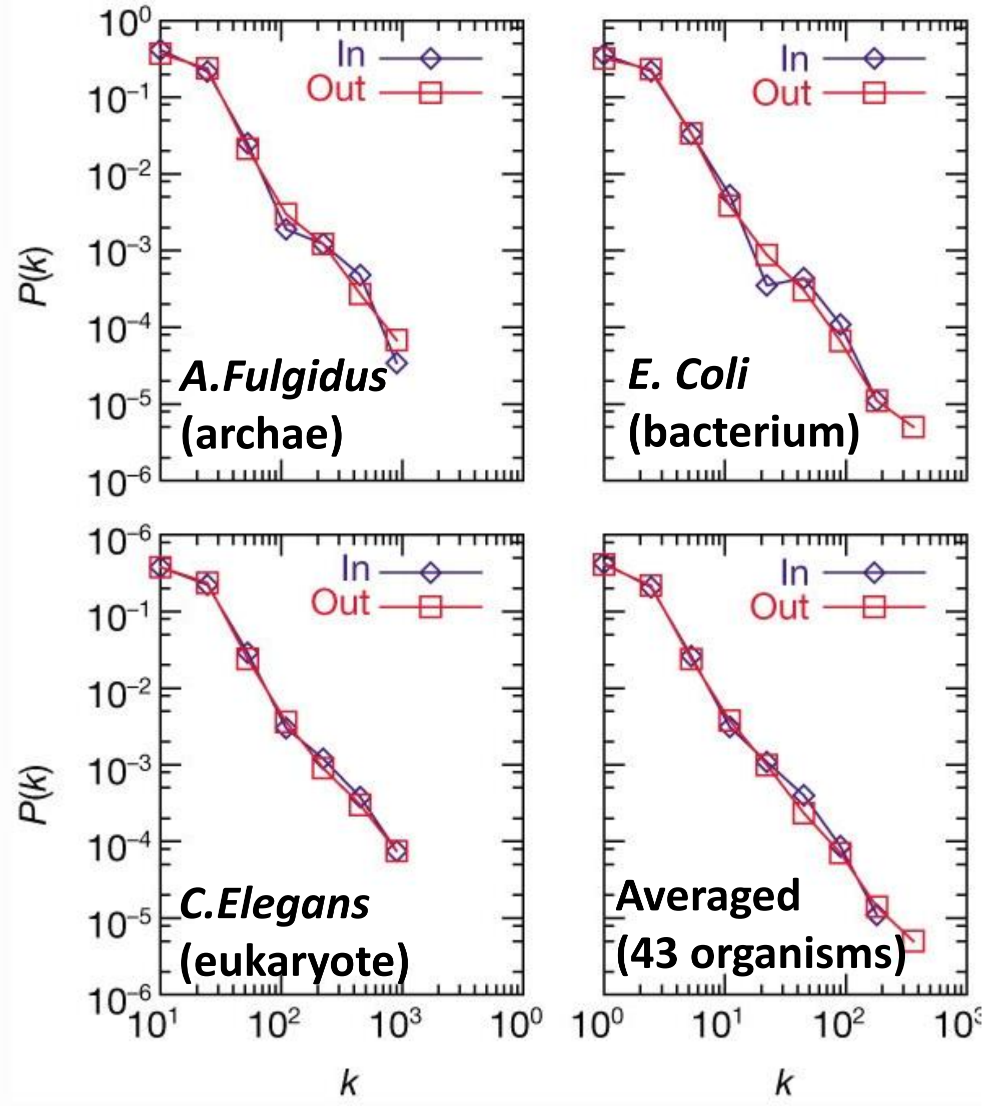
Yook et al, Proteomics, 2004

Metabolic networks

- **Nodes** – Metabolites
- **Edges** – Reactions

- P(k) ~ $k^{-2.2±2}$

Metabolic networks across all kingdoms of life are scale-free



Jeong et al., Nature, 2000

Why do so many real-life networks exhibit a power-law degree distribution?

- Is it “selected for”?
- Is it expected by chance?
- Does it have anything to do with the way networks evolve?
- Does it have functional implications?

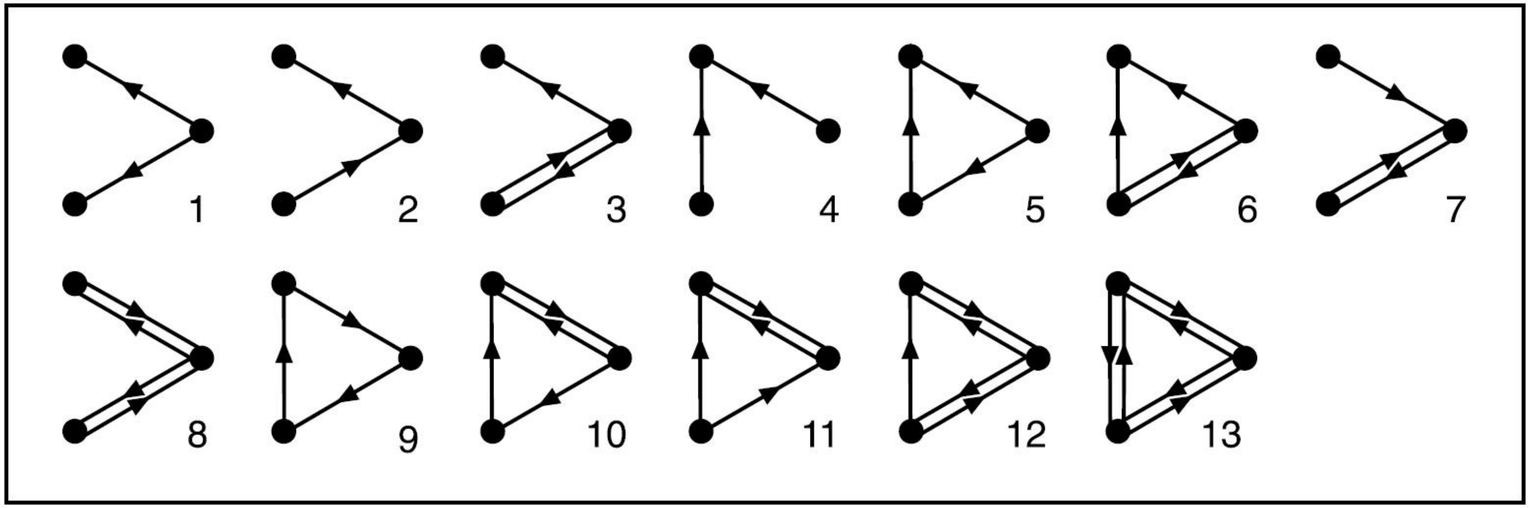
?

Network motifs

- Going beyond degree distribution …
- Generalization of sequence motifs
- Basic building blocks
- Evolutionary design principles?

What are network motifs?

- Recurring patterns of interaction (***sub-graphs***) that are significantly **overrepresented** (w.r.t. a background model)



13 possible 3-nodes sub-graphs
(199 possible 4-node sub-graphs)

R. Milo et al. Network motifs: simple building blocks of complex networks. Science, 2002

Finding motifs in the network

1a. Scan all n-node sub-graphs in the ***real*** network

1b. Record number of appearances of each sub-graph (*consider isomorphic architectures*)

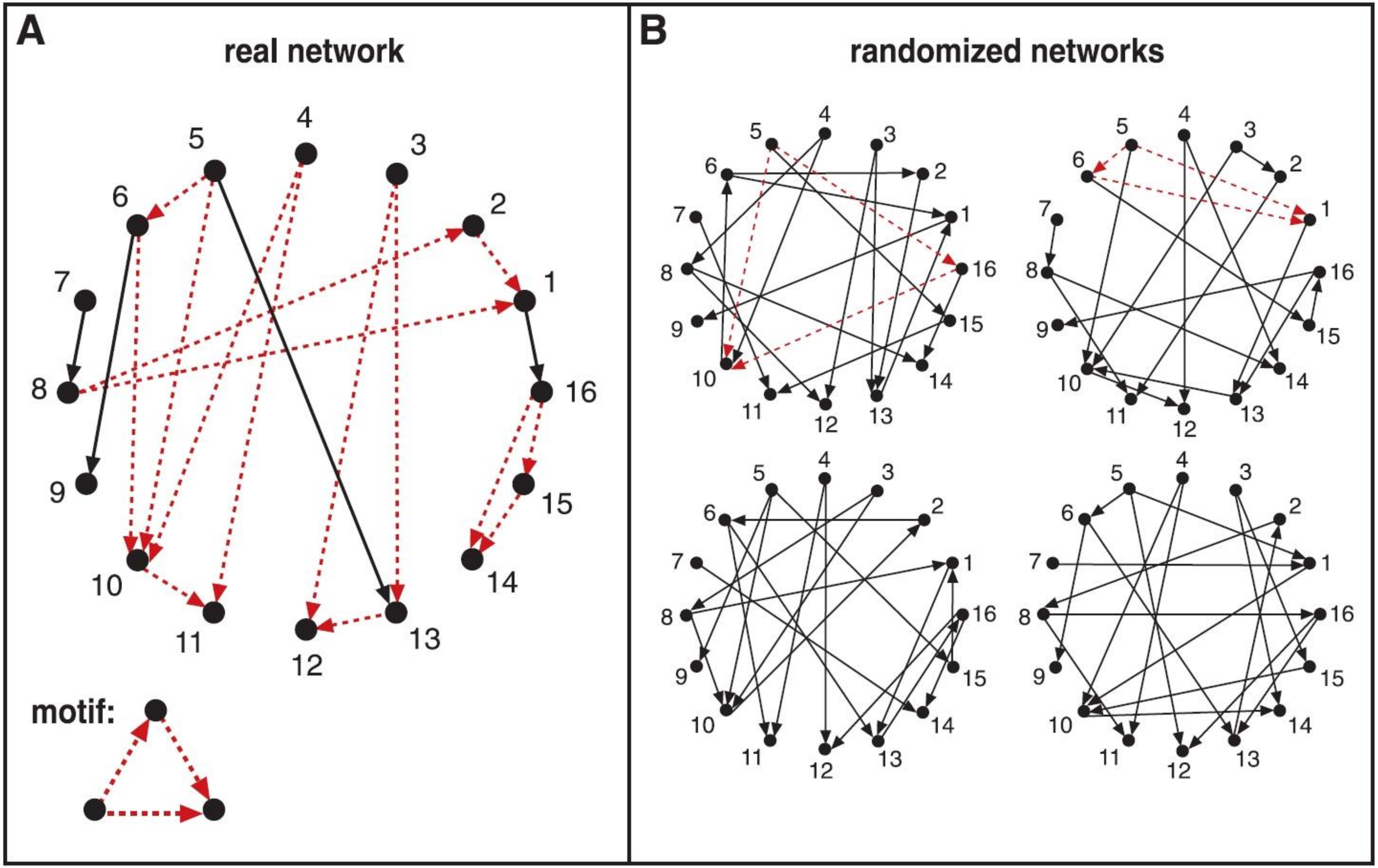
2. Generate a large set of random networks

3a. Scan for all n-node sub-graphs in **random** networks

3b. Record number of appearances of each sub-graph

4. Compare each sub-graph’s data and identify motifs

Finding motifs in the network



Network randomization

- How should the set of random networks be generated?
- Do we really want “completely random” networks?
- What constitutes a good null model?

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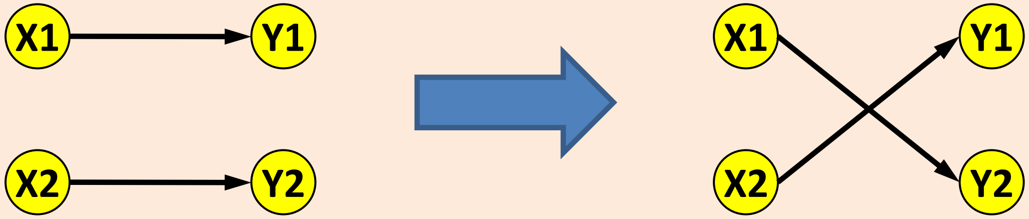
↓

Preserve in- and out-degree

Generation of randomized networks

Network randomization algorithm :

- Start with the real network and repeatedly swap randomly chosen pairs of connections
  (X1→Y1, X2→Y2 is replaced by X1→Y2, X2→Y1)

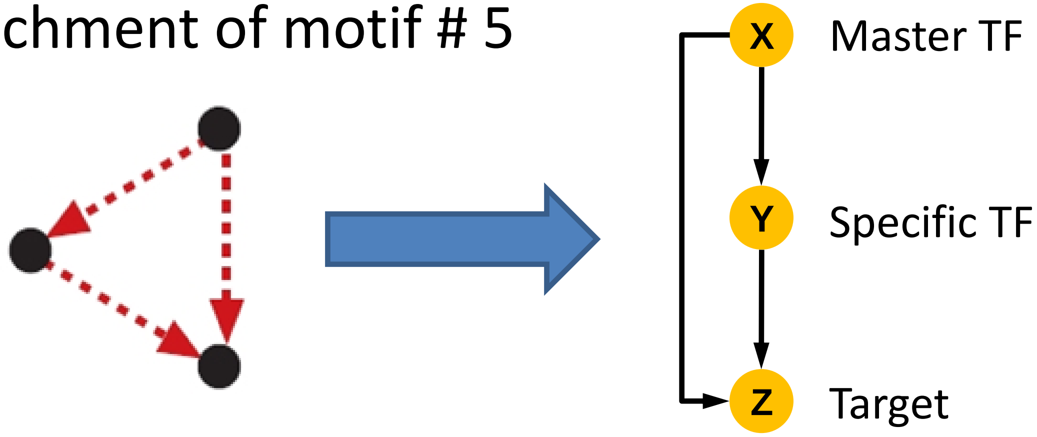


(Switching is prohibited if the either of the X1 →Y2 or X2 →Y1 already exist)

- Repeat until the network is “well randomized”

Motifs in transcriptional regulatory networks

- E. Coli network
  - 424 operons (116 TFs)
  - 577 interactions
  - Significant enrichment of motif # 5

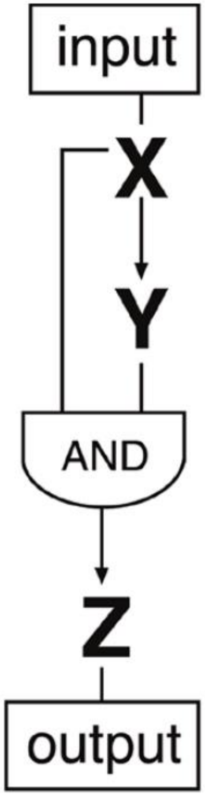


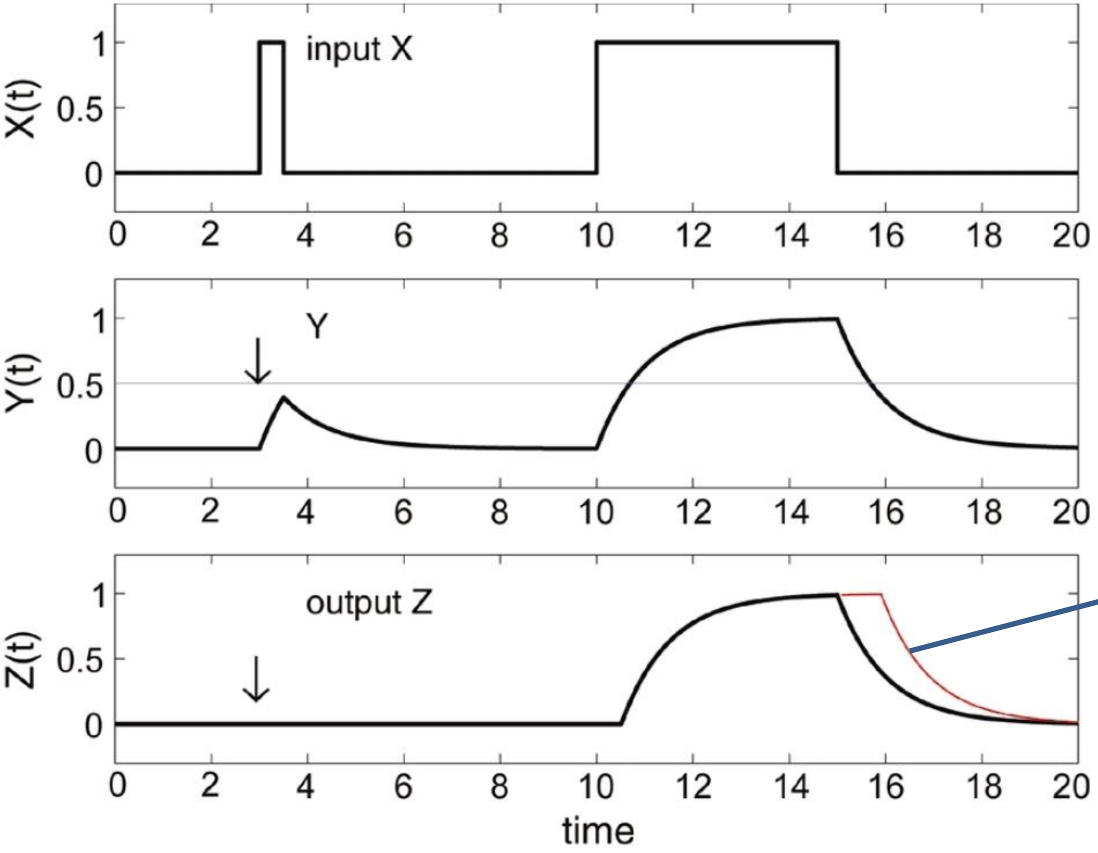
(40 instances vs. 7±3)

Feed-Forward Loop (FFL)

S. Shen-Orr et al. Nature Genetics 2002

What’s so interesting about FFLs





Boolean Kinetics

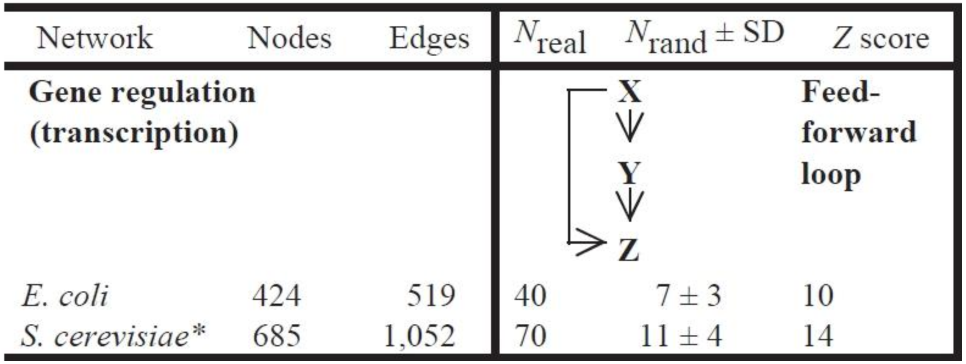
$$dY/dt = F(X,T_y) - aY$$

$$dZ/dt = F(X,T_y)F(Y,T_z) - aZ$$

A simple cascade has slower shutdown

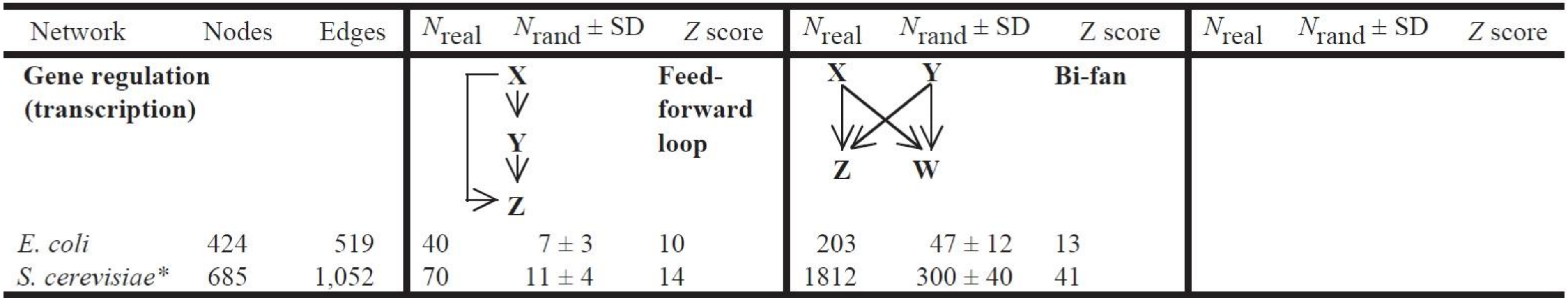
A coherent feed-forward loop can act as a circuit that rejects transient activation signals from the general transcription factor and responds only to persistent signals, while allowing for a rapid system shutdown.

Network motifs in biological networks



Network	Nodes	Edges	N_{real}	$N_{rand} \pm SD$	Z score
Gene regulation (transcription)				**X** **Y** **Z**	**Feed-forward loop**
E. coli	424	519	40	7 ± 3	10
*S. cerevisiae**	685	1,052	70	11 ± 4	14

Network motifs in biological networks



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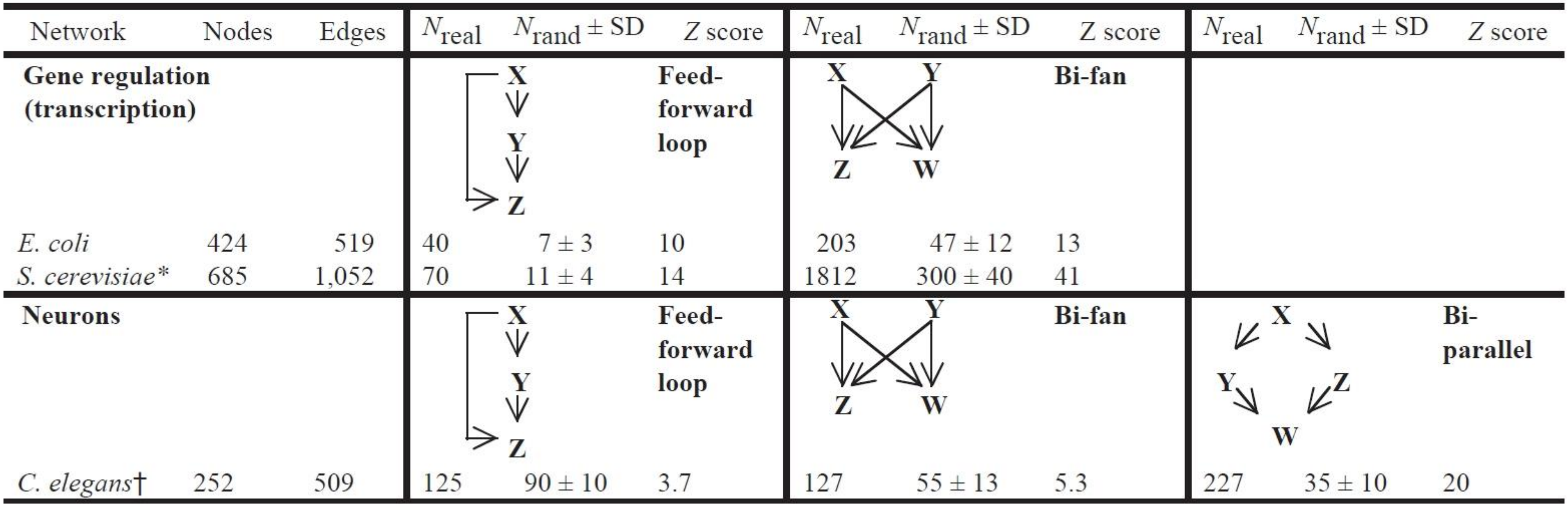

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Neurons					**Feed-forward loop**			**Bi-fan**			**Bi-parallel**
C. elegans†	252	509	125	90 ± 10	3.7	127	55 ± 13	5.3	227	35 ± 10	20

Network motifs in biological networks

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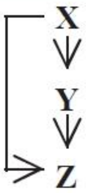
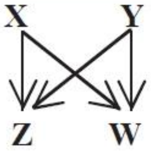
Gene regulation (transcription)					**Feed-forward loop**			**Bi-fan**			
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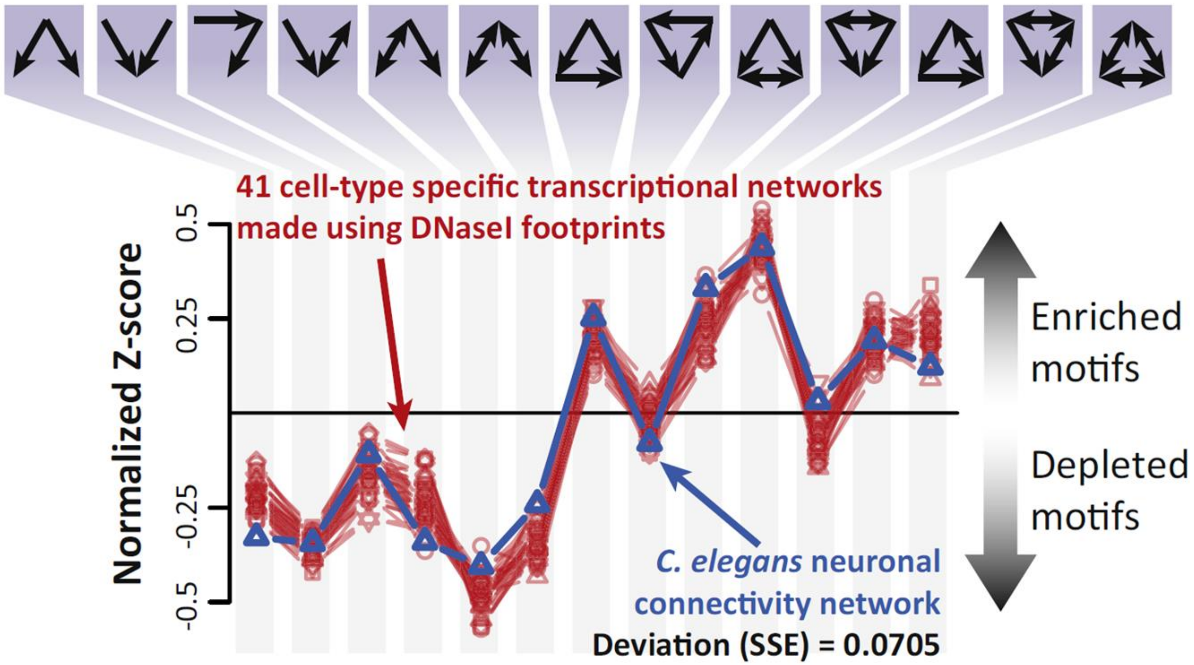
- Human cell-specific networks



41 cell-type specific transcriptional networks made using DNaseI footprints

Enriched motifs

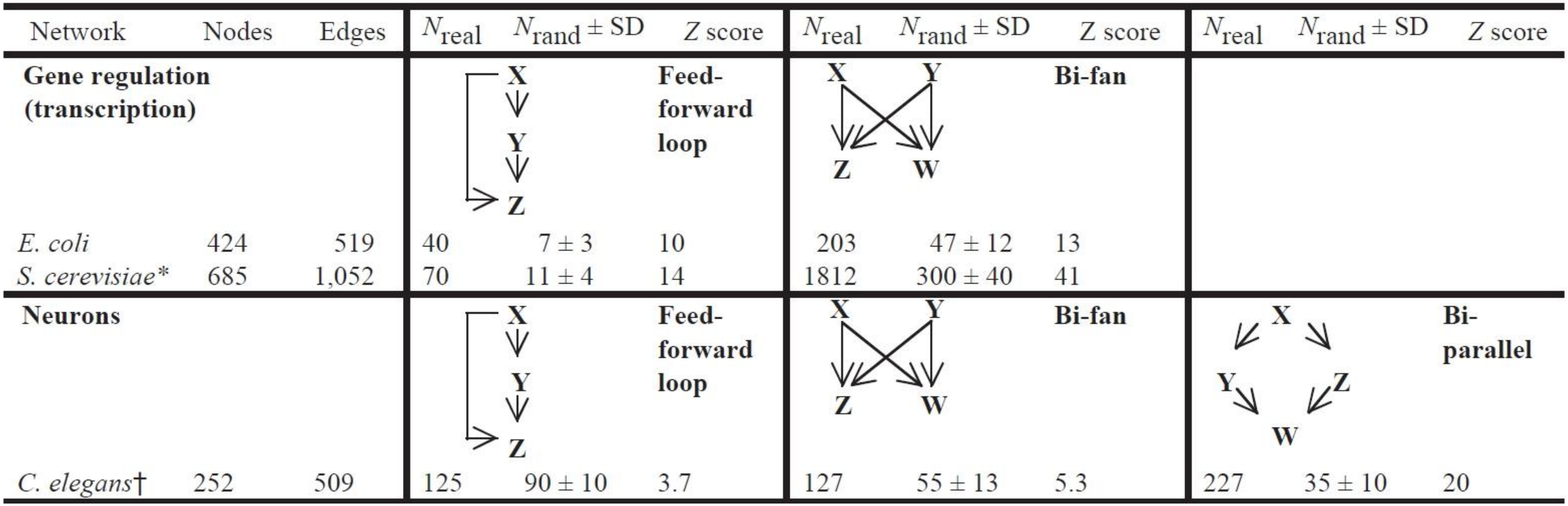
Depleted motifs

C. elegans neuronal connectivity network

Deviation (SSE) = 0.0705

Neph et al. Cell 2012

Network motifs in biological networks



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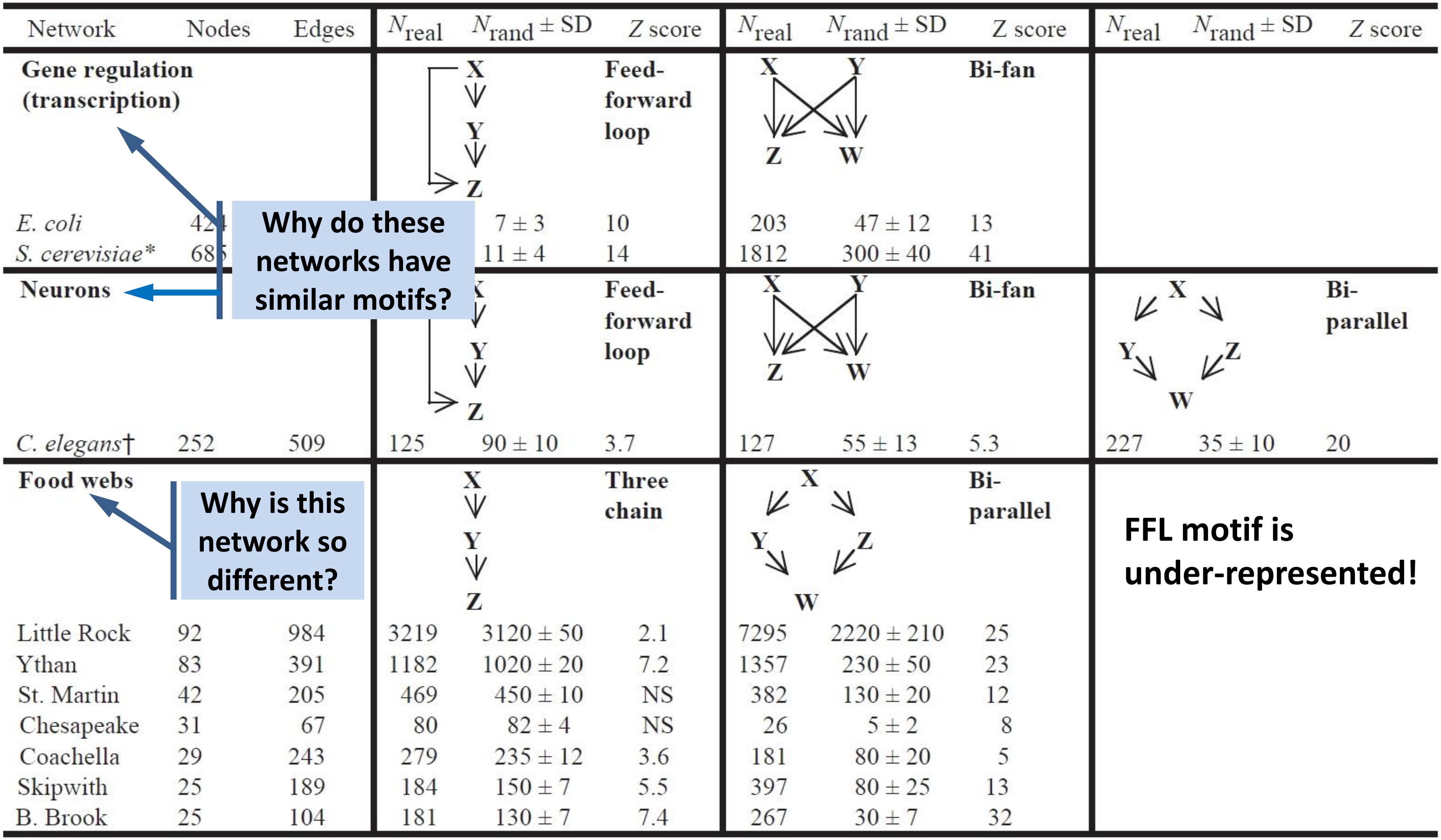
Network motifs in biological networks



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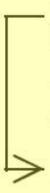
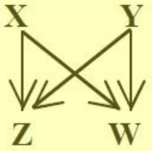
C. elegans†	252	509	125	90 ± 10	3.7	127	55 ± 13	5.3	227	35 ± 10	20
Food webs					**Three chain**			**Bi-parallel**			
Little Rock	92	984	3219	3120 ± 50	2.1	7295	2220 ± 210	25			
Ythan	83	391	1182	1020 ± 20	7.2	1357	230 ± 50	23			
St. Martin	42	205	469	450 ± 10	NS	382	130 ± 20	12			
Chesapeake	31	67	80	82 ± 4	NS	26	5 ± 2	8			
Coachella	29	243	279	235 ± 12	3.6	181	80 ± 20	5			
Skipwith	25	189	184	150 ± 7	5.5	397	80 ± 25	13			
B. Brook	25	104	181	130 ± 7	7.4	267	30 ± 7	32			

Why do these networks have similar motifs?

Why is this network so different?

FFL motif is under-represented!

Information Flow vs. Energy Flow

Network	Nodes	Edges	N_{real}	$N_{\text{rand}} \pm \text{SD}$	Z score	N_{real}	$N_{\text{rand}} \pm \text{SD}$	Z score	N_{real}	$N_{\text{rand}} \pm \text{SD}$	Z score
Gene regulation (transcription)					**Feed-forward loop**			**Bi-fan**			
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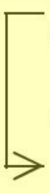
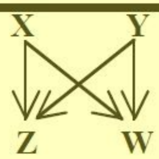
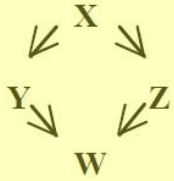
Neurons					**Feed-forward loop**			**Bi-fan**			**Bi-parallel**
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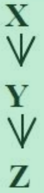
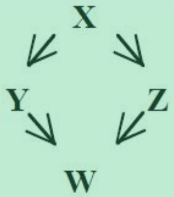
Food webs					**Three chain**			**Bi-parallel**	**FFL motif is under-represented!**		
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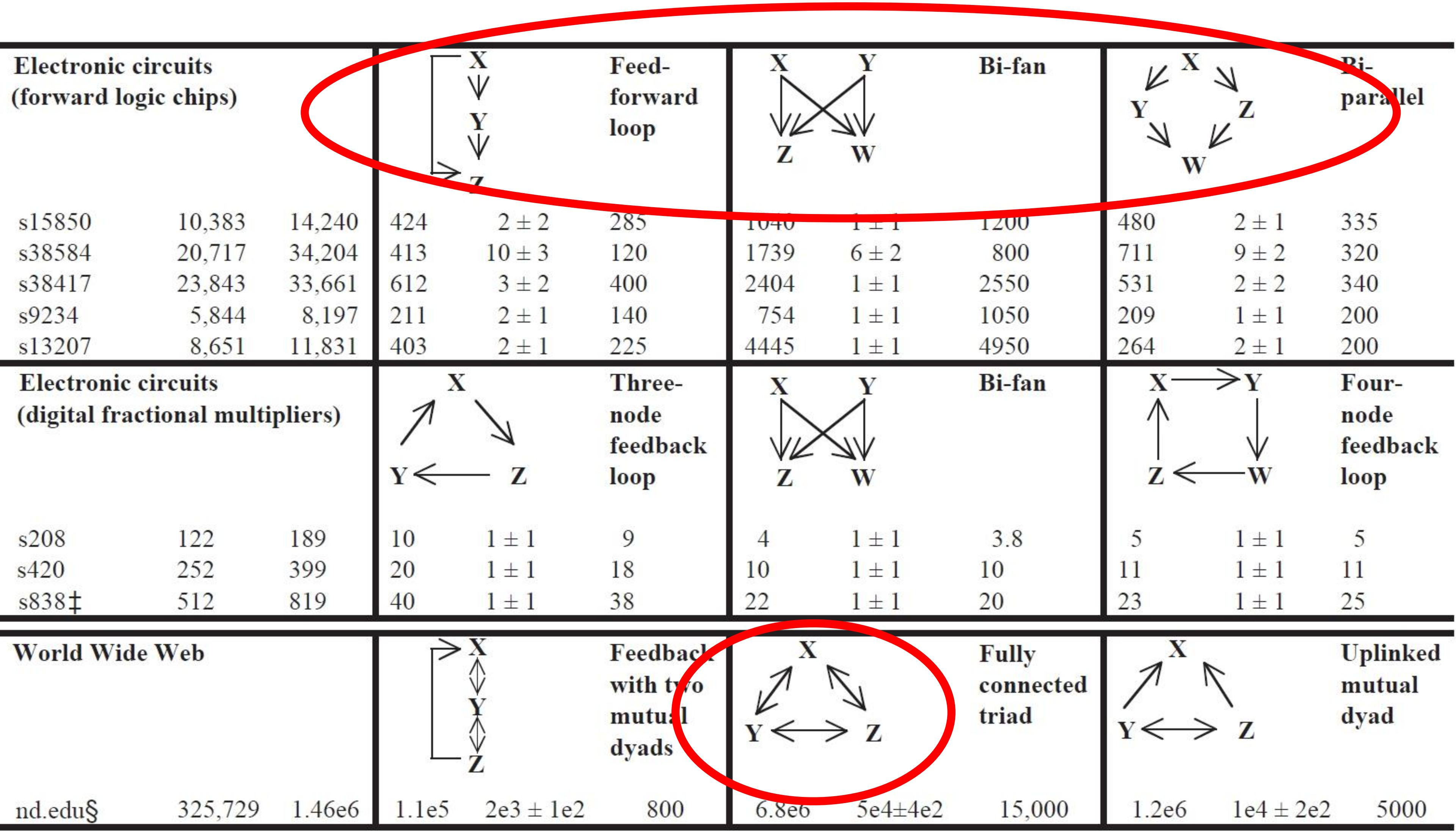
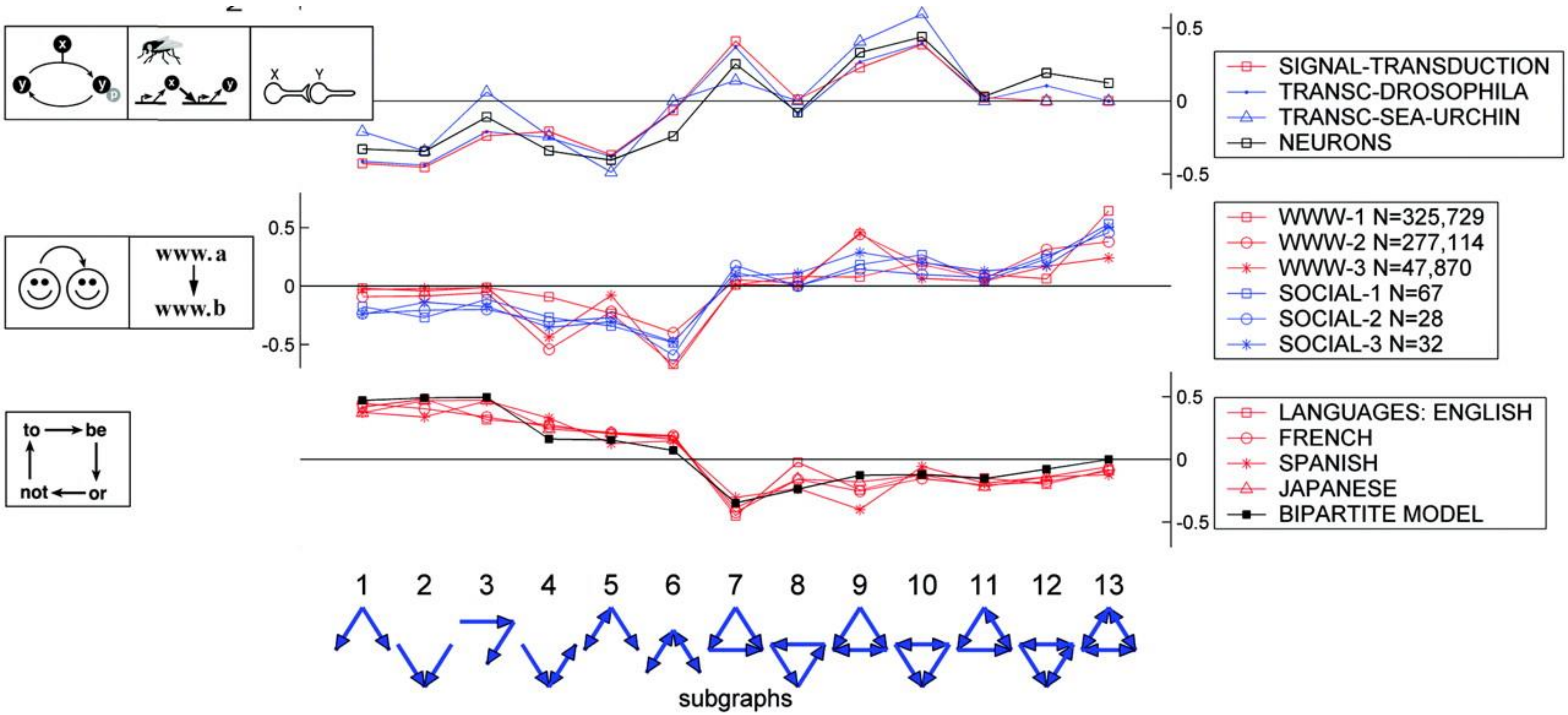
Network Motifs in Technological Networks



Electronic circuits (forward logic chips)					Feed-forward loop			Bi-fan			Bi-parallel
s15850	10,383	14,240	424	2 ± 2	285	1040	1 ± 1	1200	480	2 ± 1	335
s38584	20,717	34,204	413	10 ± 3	120	1739	6 ± 2	800	711	9 ± 2	320
s38417	23,843	33,661	612	3 ± 2	400	2404	1 ± 1	2550	531	2 ± 2	340
s9234	5,844	8,197	211	2 ± 1	140	754	1 ± 1	1050	209	1 ± 1	200
s13207	8,651	11,831	403	2 ± 1	225	4445	1 ± 1	4950	264	2 ± 1	200
Electronic circuits (digital fractional multipliers)					Three-node feedback loop			Bi-fan			Four-node feedback loop
s208	122	189	10	1 ± 1	9	4	1 ± 1	3.8	5	1 ± 1	5
s420	252	399	20	1 ± 1	18	10	1 ± 1	10	11	1 ± 1	11
s838‡	512	819	40	1 ± 1	38	22	1 ± 1	20	23	1 ± 1	25
World Wide Web					Feedback with two mutual dyads			Fully connected triad			Uplinked mutual dyad
nd.edu§	325,729	1.46e6	1.1e5	2e3 ± 1e2	800	6.8e6	5e4±4e2	15,000	1.2e6	1e4 ± 2e2	5000

Motif-based network super-families



R. Milo et al. Superfamilies of evolved and designed networks. Science, 2004