Network Biology: Understanding the Cell's Functional Organization

Albert-László Barabási & Zoltán N. Oltvai

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presented by

William Joseph Allen

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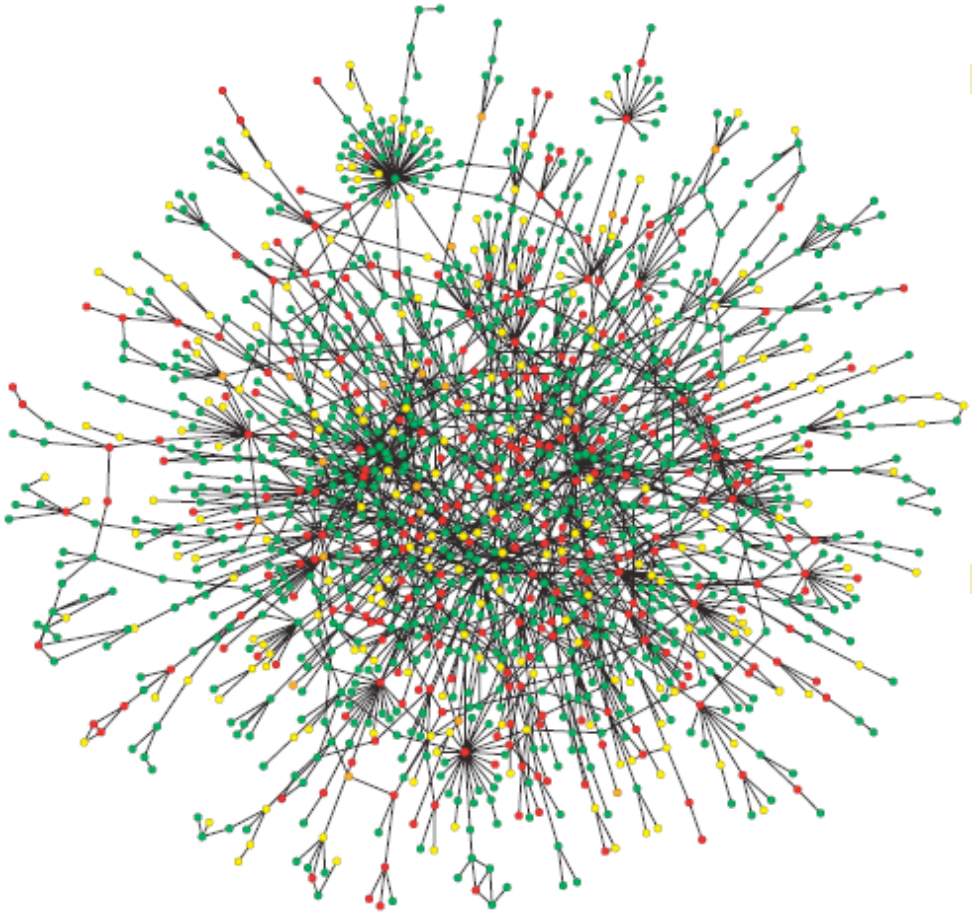
Shifting views in biology

- Reductionism to network (systems) biology
  - A network can not be described by just the sum of its parts
- Ultimately, a higher conceptual framework could revolutionize views in biology and pathology

A "network of networks"



PPI network in *S. cerevisiae*

- Individual networks
  - PPI, gene expression, metabolic, transcription regulatory
- Cellular networks
  - How do they connect?

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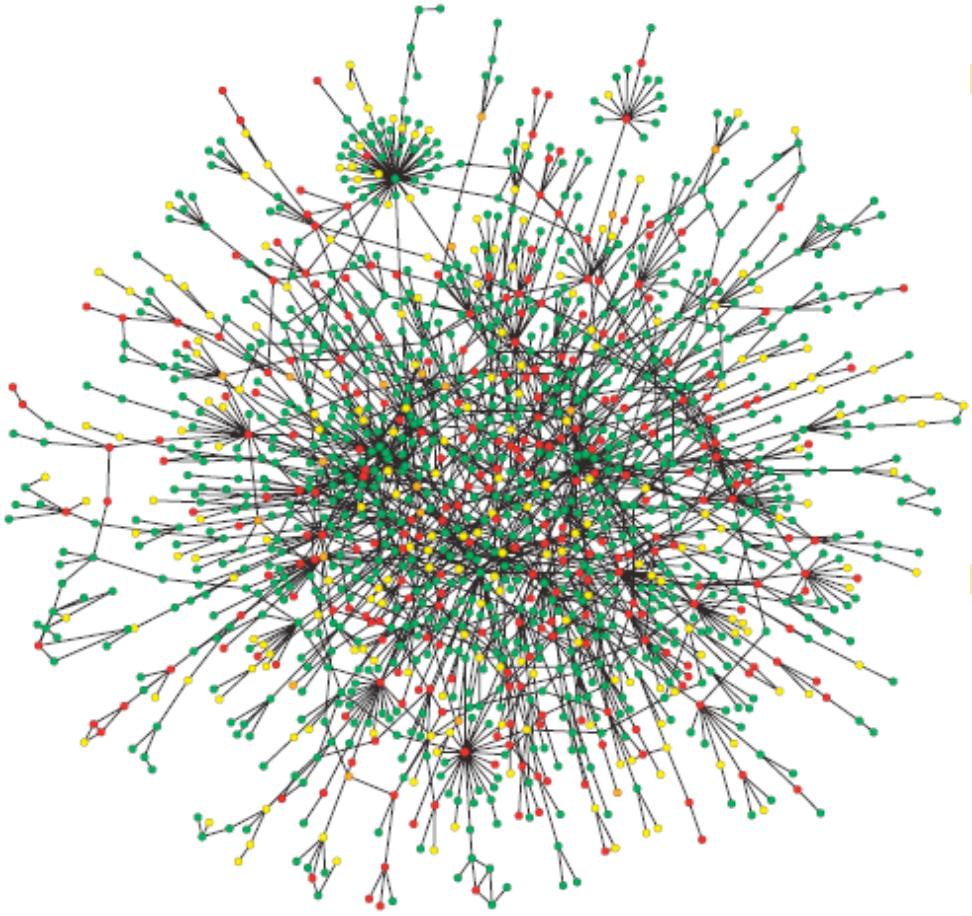

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The author's message

- Challenge: figure out how to integrate, map out, model, and understand the topological & dynamical properties of cellular networks

- While: keeping it relevant to experimental biologists / pathologists

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Outline

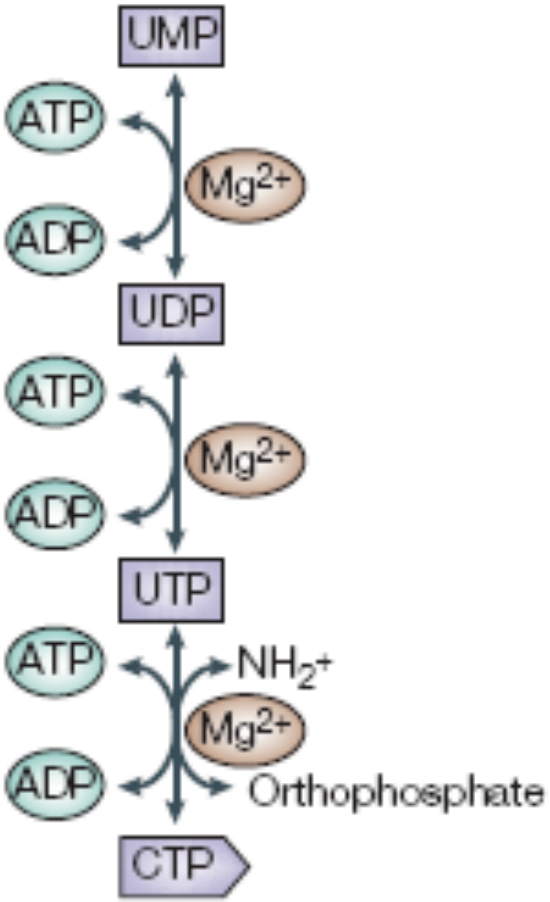
- Basic network nomenclature

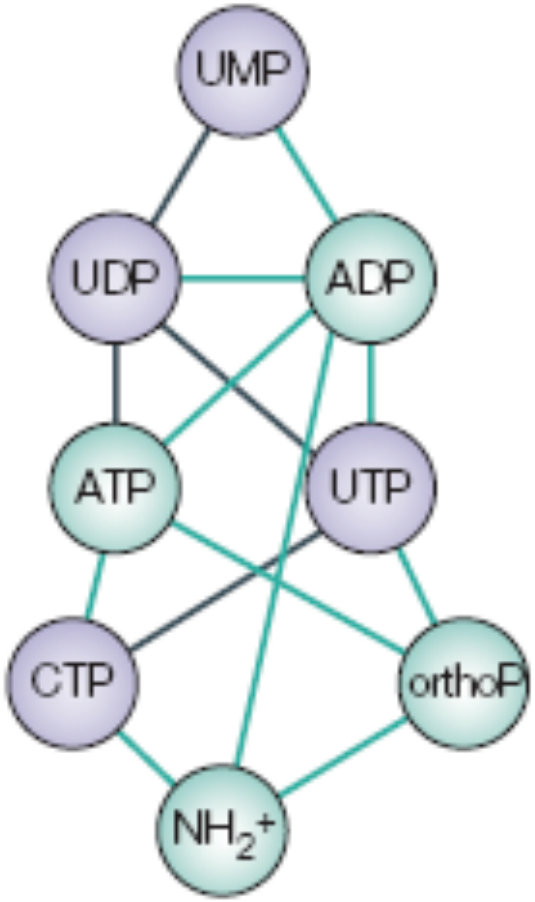
- Architectural features of cellular networks
- Modules and motifs
- Network robustness
- Characterizing the links

- Future directions and concluding thoughts

Basic network nomenclature

- Nodes + edges = networks





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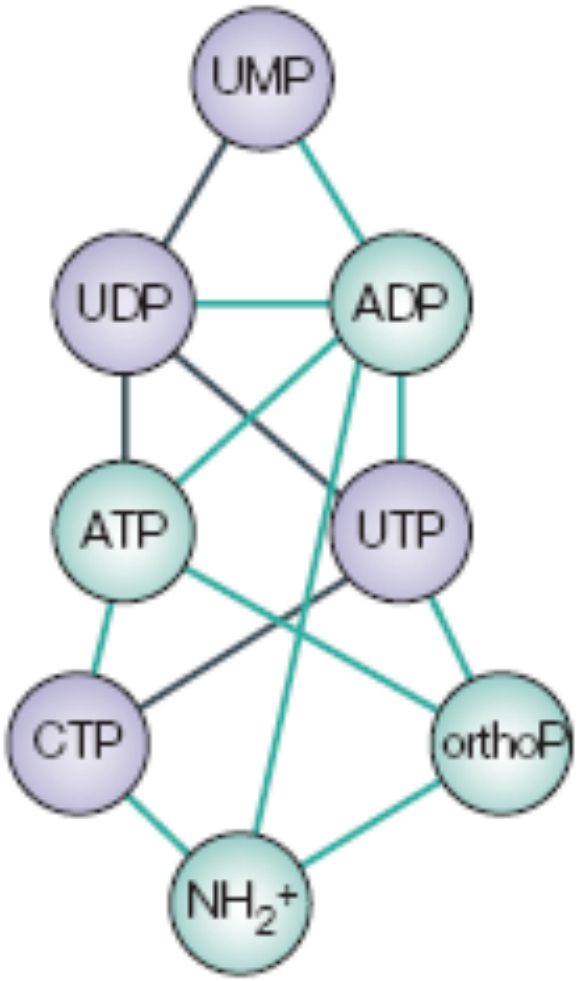
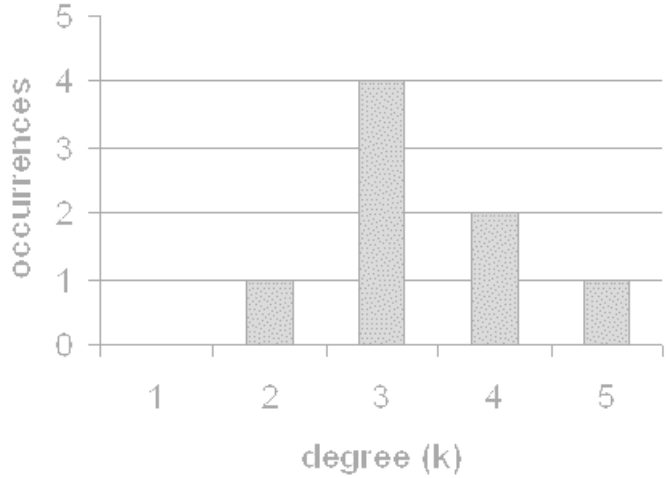


- Degree (connectivity) – k
  - High k is a hub
- Degree distribution – P(k)



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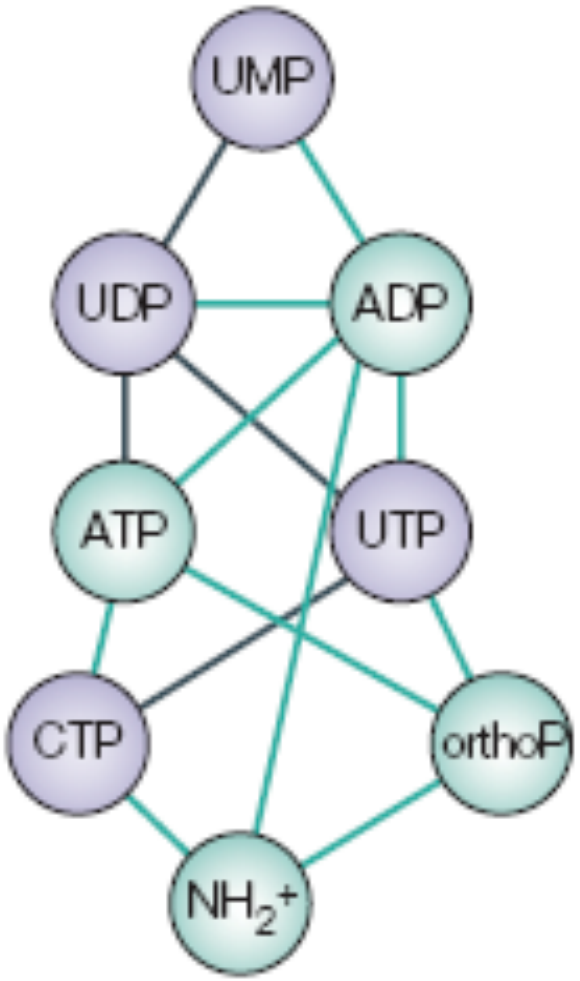

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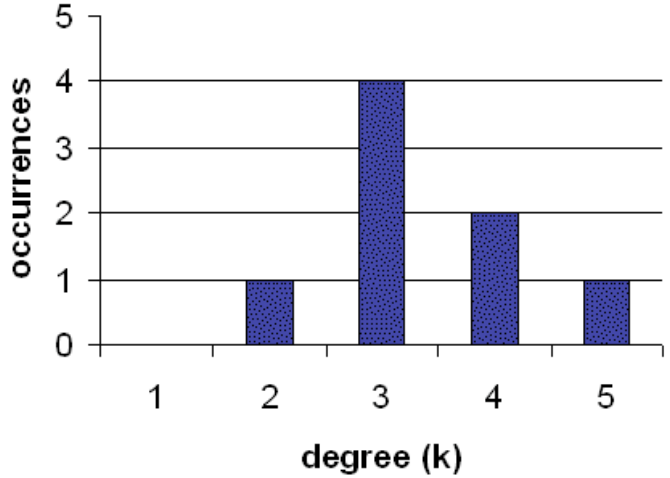

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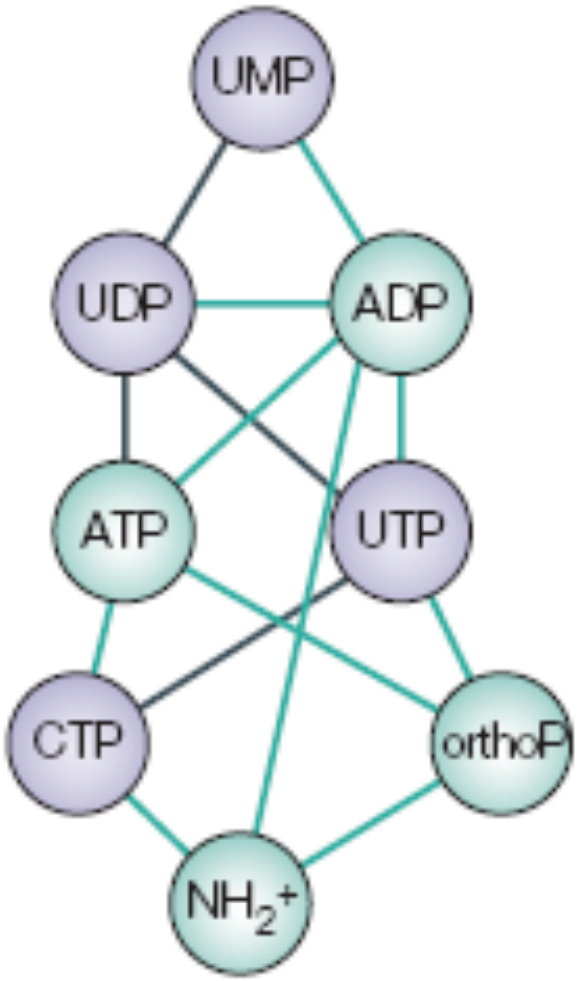

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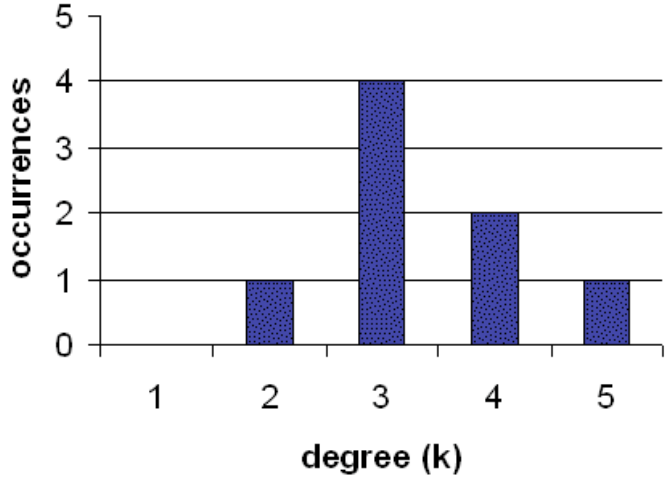

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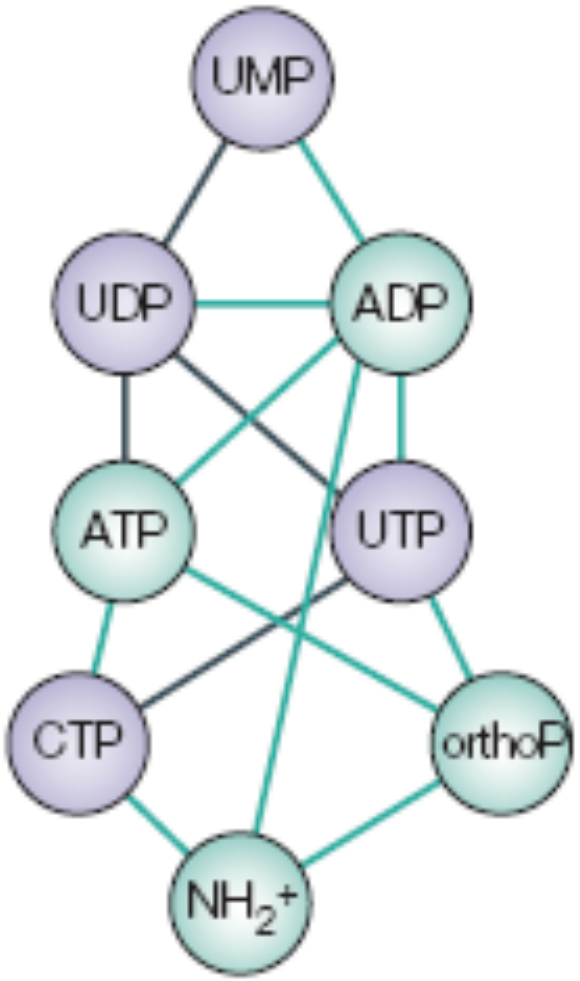

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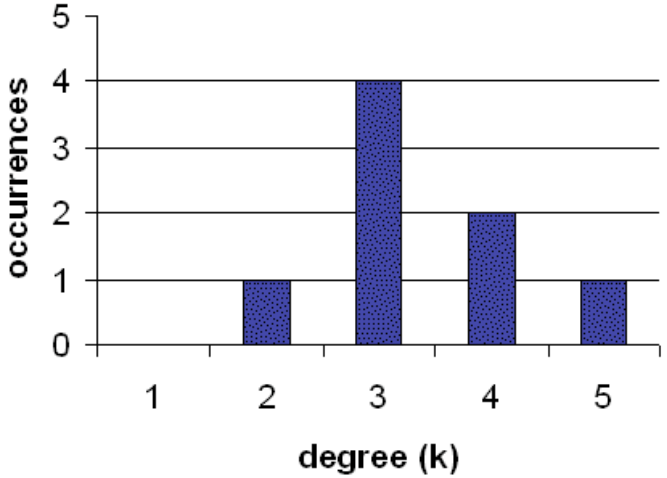

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Architectural features of cellular networks

- Three kinds of networks:
  - Random – nodes randomly connected with edges
  - Scale-free – lack of any typical node to compare the others
  - Hierarchical – similar to scale-free, but forms unique modules (clusters)

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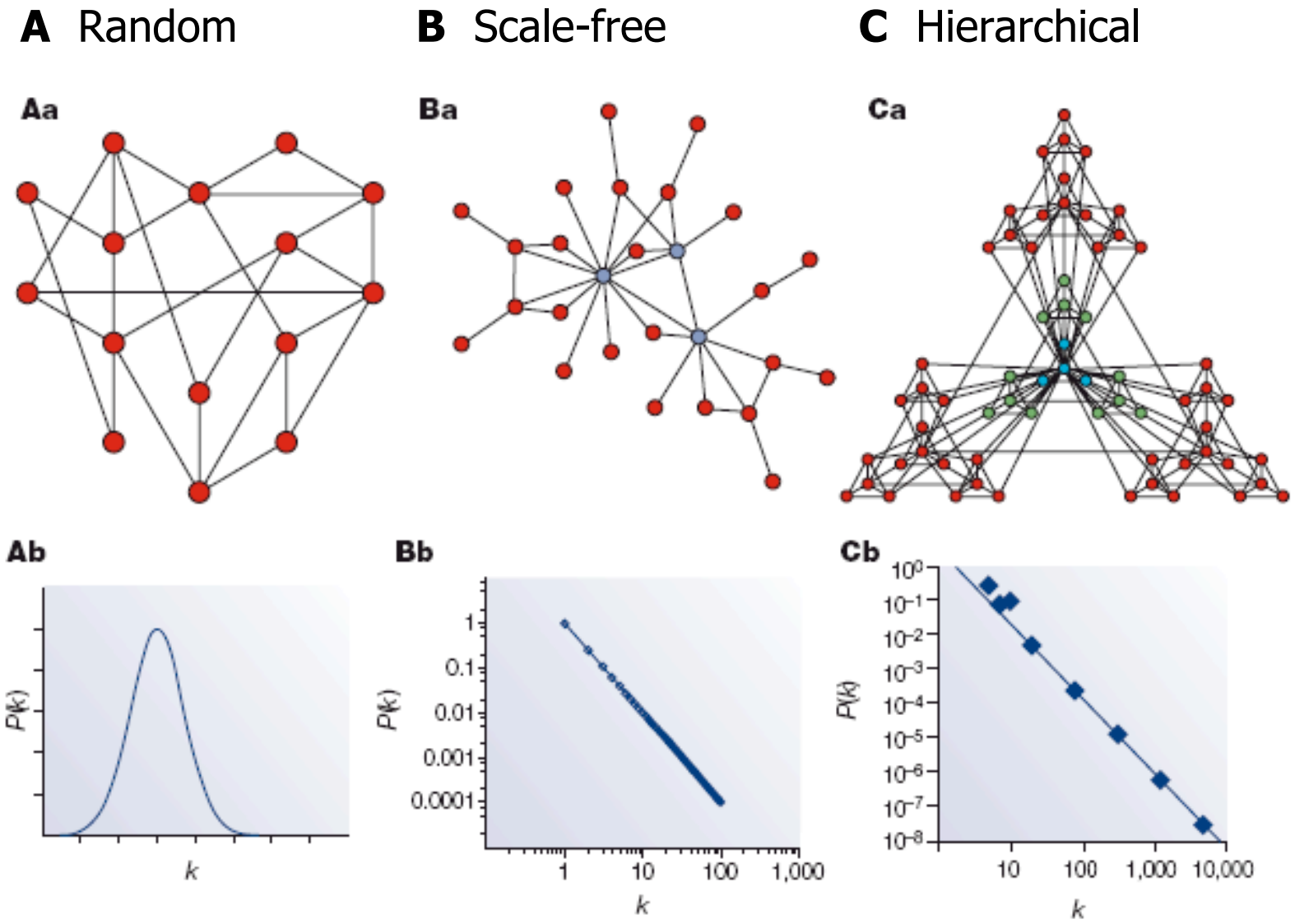
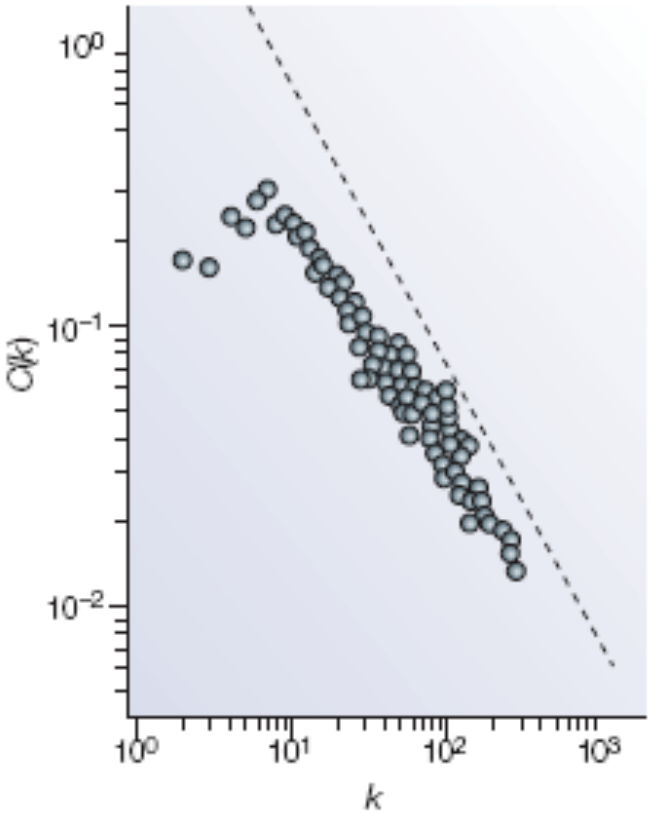
- **Cellular networks are scale-free**
  - Comparable to some human engineered networks
  - Computer chips, internet, social networks (to a degree)

Different types of networks



Scale-free topology

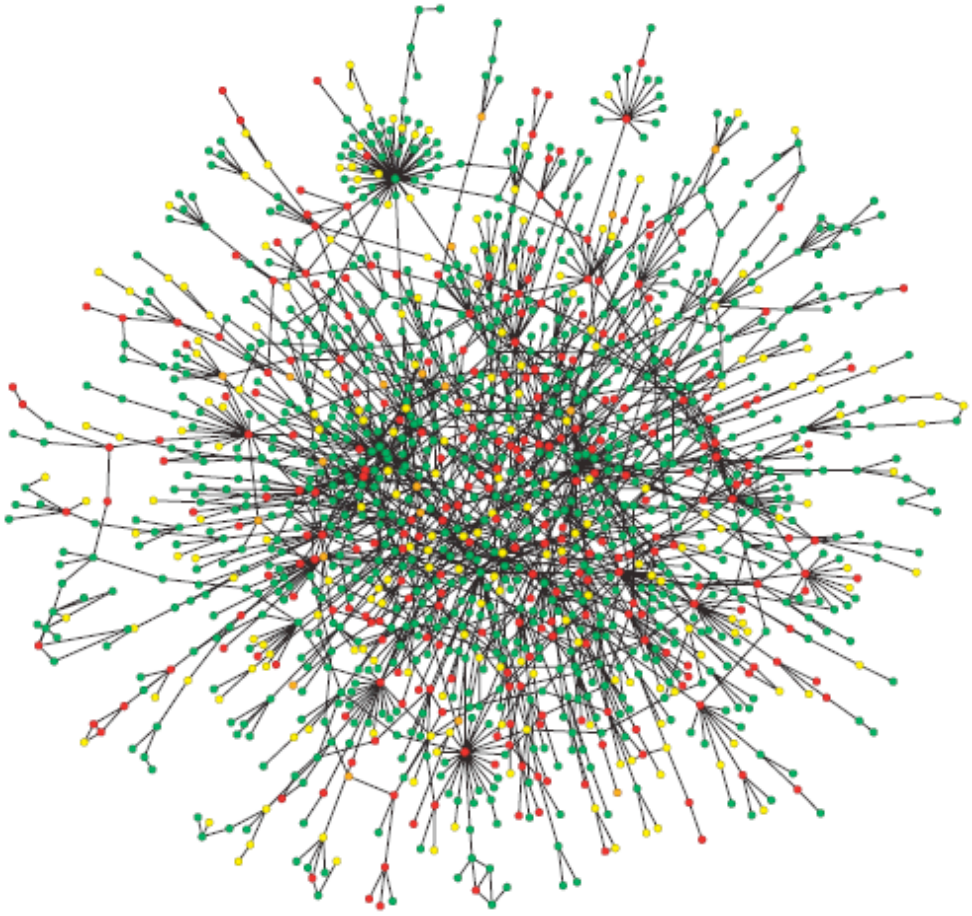


- First evidence seen in metabolic network
- More evidence in PPI network maps, transcription regulatory networks, and more
- A key feature of scale-free networks is the presence of hubs

$P(k) \sim k^{-\gamma}$; γ = degree exponent

-smaller γ means more important hubs

The importance of the hubs



PPI network in *S. cerevisiae*

- The small-world effect
- The ultra-small-world effect
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- But why do hubs avoid linking directly to each other?
  - Remains unexplained

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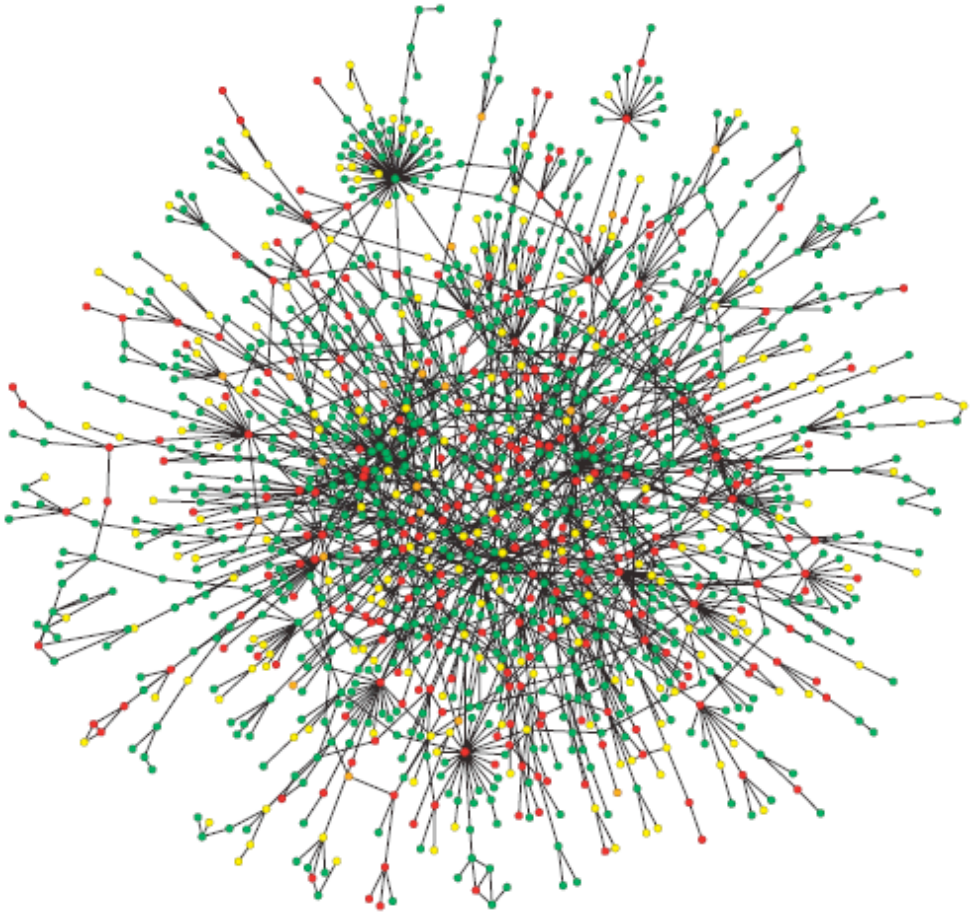

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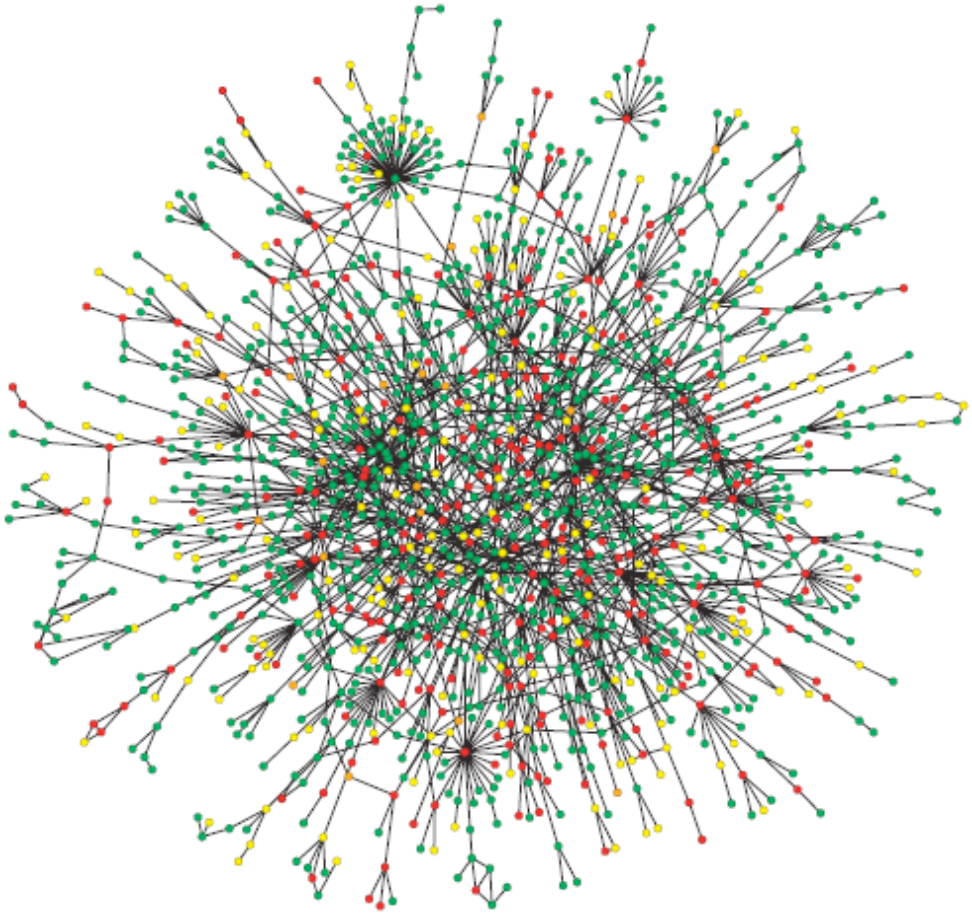

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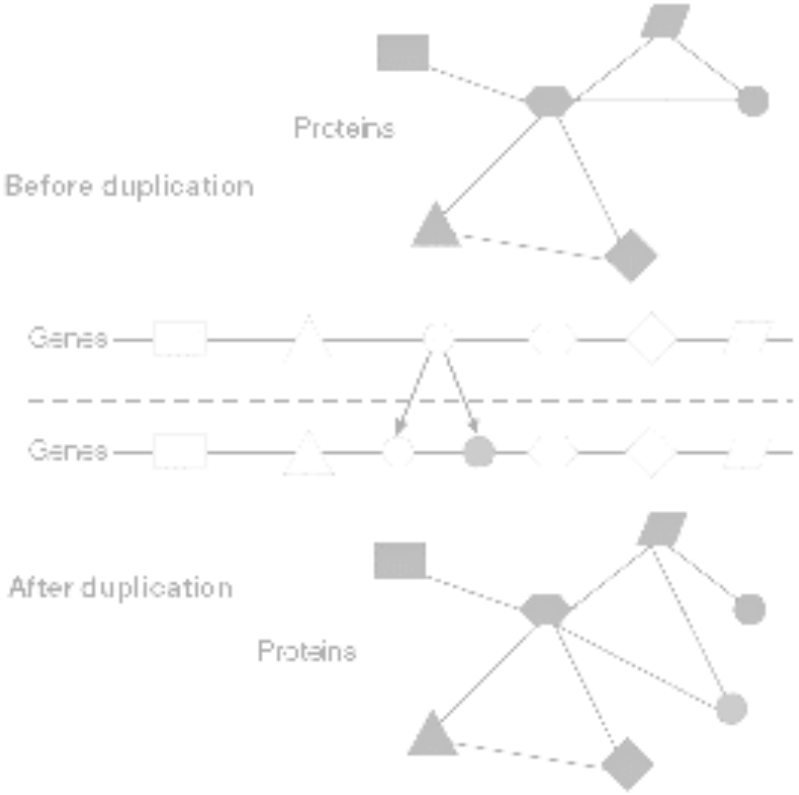
How did networks evolve this way?

- Growth and preferential attachment
  - "…[new] nodes prefer to connect to nodes that already have many links…"



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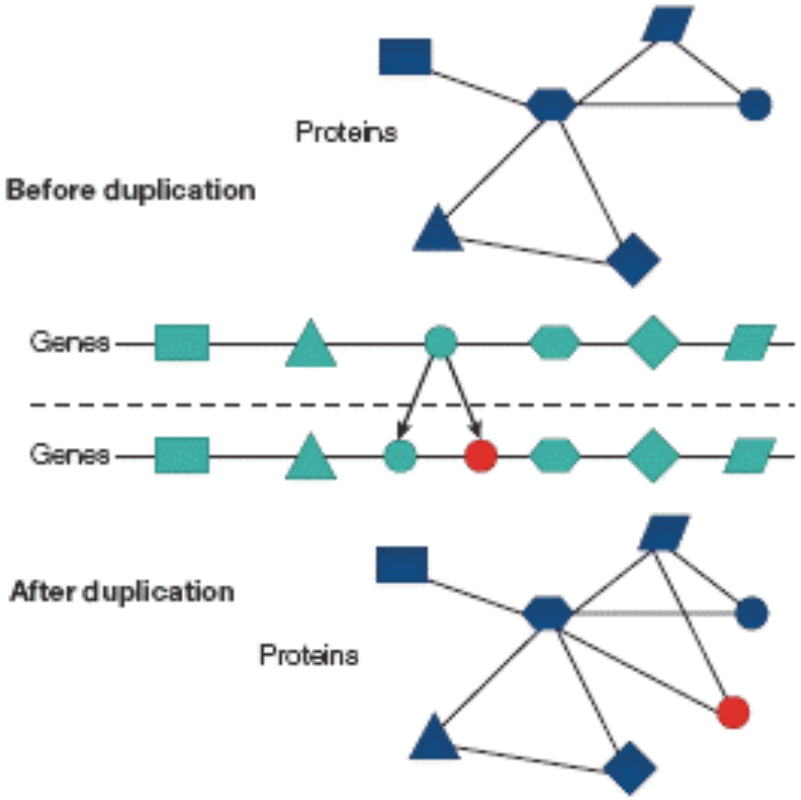

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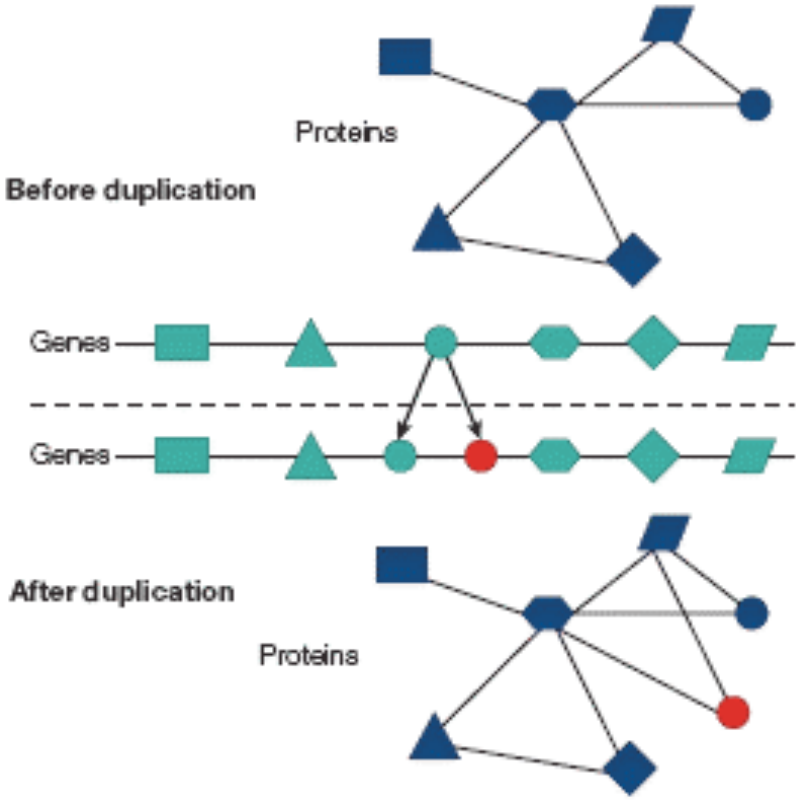

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Cellular function is modular

- High modularity is an inherent part of cellular networks
- Modules and their relationships need to be explicitly identified

- Modules (clusters) and motifs
  - What role they play in cellular networks

Clustering in cellular networks

$$C_I = 2n_I / k(k-1)$$

- High clustering coefficients (C) are typical in most real networks
- PPI networks, metabolic networks, protein domain networks all have a high <C>

- Random networks have much lower C values

The role of motifs

- Examples of motifs:

- Some motifs occur more often in cellular networks than in random networks
- Evidence that specific motifs in *S. cervisiae* are conserved in evolution
- Aggregation of motifs in to motif clusters needs to be studied

Hierarchical modularity

- As the number of nodes increases, the number of modules increases exponentially
- Creating hierarchies by a common function is a convenient way to study them
- Networks with few nodes have a high C, and those with many nodes have a low C

$$C(k) \sim k^{-1}$$

- This holds true for cellular networks and has been conserved evolutionarily
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Network robustness

- The ability to respond to changes in the external conditions or internal organization while maintaining relatively normal behavior
- How does the topology of the network create robustness?

Resistance to network disintegration

- Unlike random networks, scale-free networks can remain highly connected after random node deletions
- If 80% of nodes fail, the remaining 20% can still form a compact cluster

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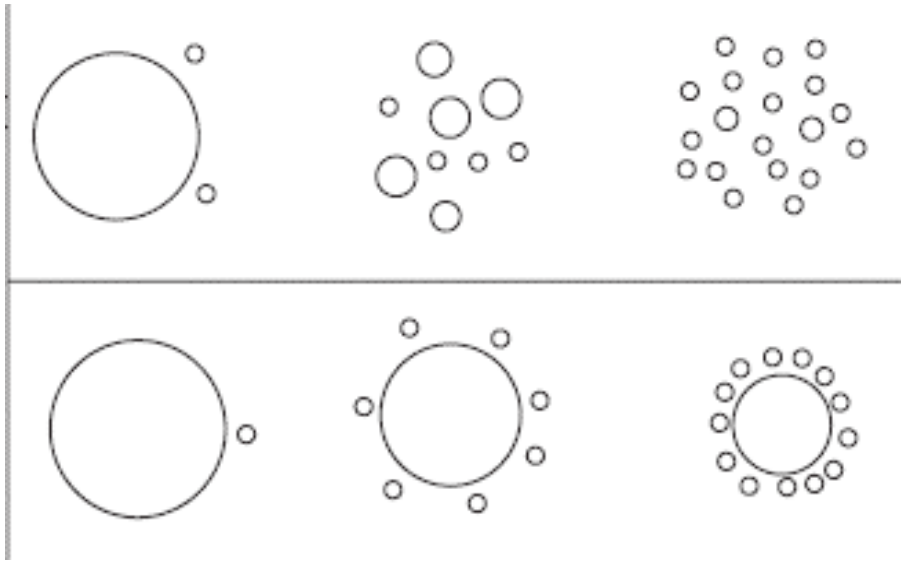

Albert, et al;
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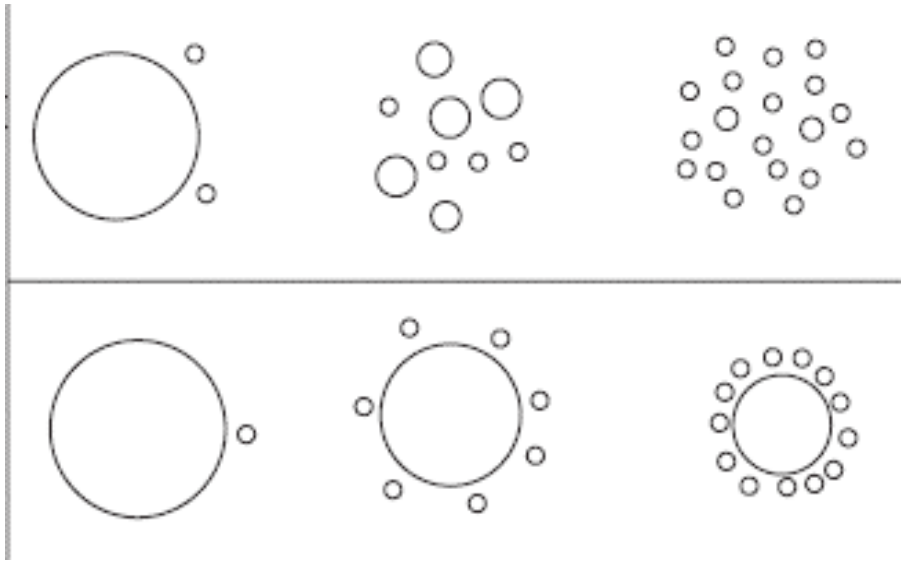


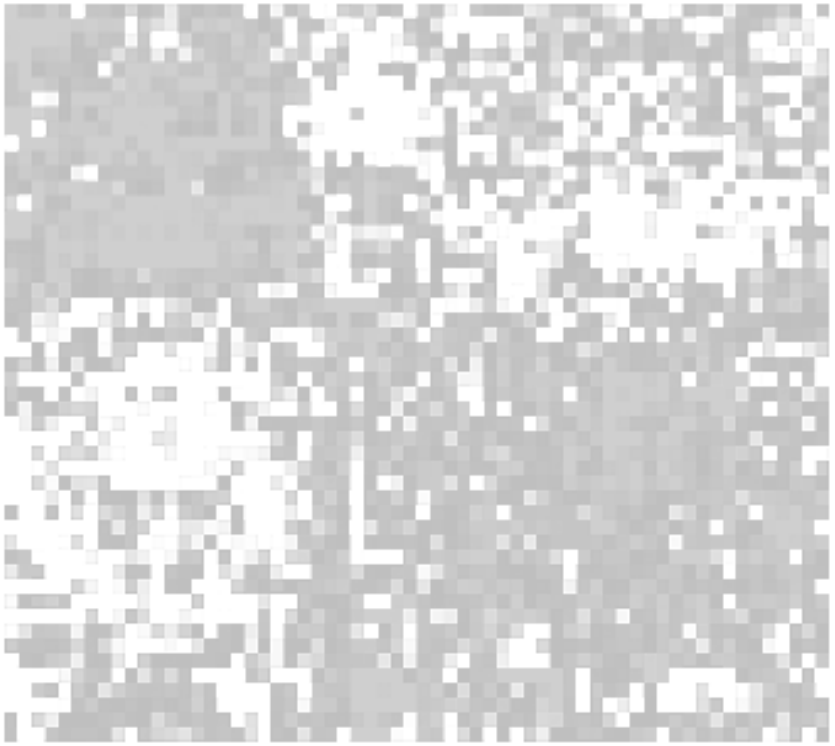
Albert, et al; *Nature*, 2000

- Hubs are very vulnerable to attacks
  - The more connections a node has, the more necessary that node is to the network

Functional and dynamical robustness

- Consider an external perturbation:
  - The function of many nodes may not change at all
  - The function of some nodes will change completely
- This is another inherent network property
- Although robustness helps the cell, it still has vulnerabilities

Characterizing linkages



- How do you help complete the full picture of a cellular network?
  - Intensity (strength) and temporal aspects must be considered
- Gene co-expression is measured by microarray
  - Amount of co-expression is proportional to intensity
- In metabolic networks, flux is measured
  - Flux is time dependent

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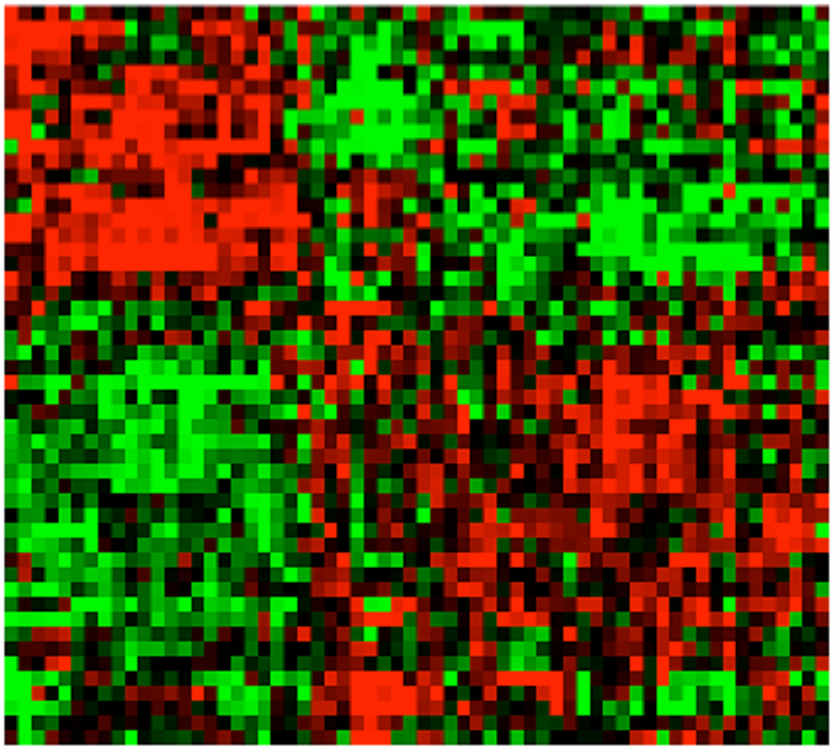

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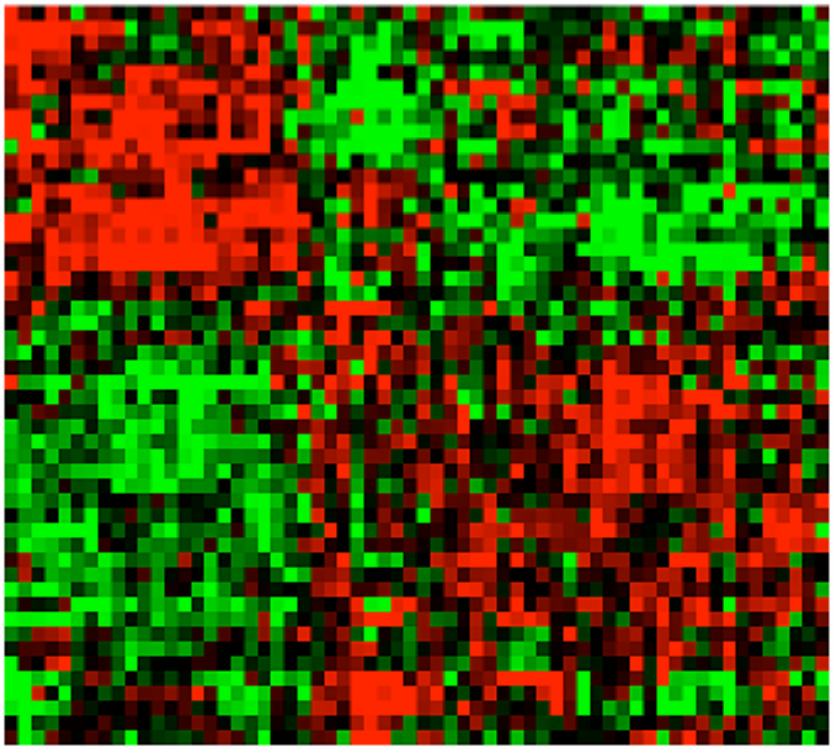

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Review

- Cellular networks are scale-free
  - Hubs are important
  - Small mean path length (ultra-small-world effect)
- Cellular networks are modular
  - High clustering coefficients (C)
  - Motifs occur more than random
  - Functional hierarchies are key
- Cellular networks are robust
  - Topological and dynamical
- Cellular networks are dependent on linkages
  - Intensity- and time-dependent

Future directions

- Develop new methods to characterize networks
- Dynamics of motif clusters and biological function

- "This will require the development of highly sensitive tools for identifying and quantifying the concentrations, fluxes and interactions of various types of molecules at high resolution both in space and time."

- Focus even higher than the various subsets of cellular networks
  - Obtain a complete picture of all interactions at all strengths for an entire cell at any given time
  - Computational power?

Concluding thoughts

- Network and systems biology are still in their infancy, but have come a long way
- Structure, topology, network usage, robustness, and function are all connected
- Will eventually have important implications for the study of disease and the practice of medicine

Thank you for your attention

- Questions?