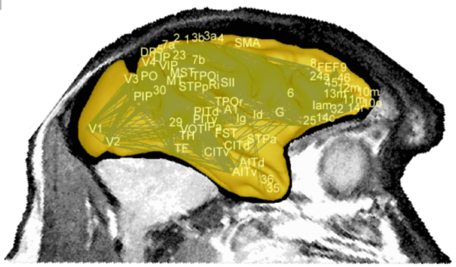

A Tutorial in Connectome Analysis (III): Topological and Spatial Features of Brain Networks

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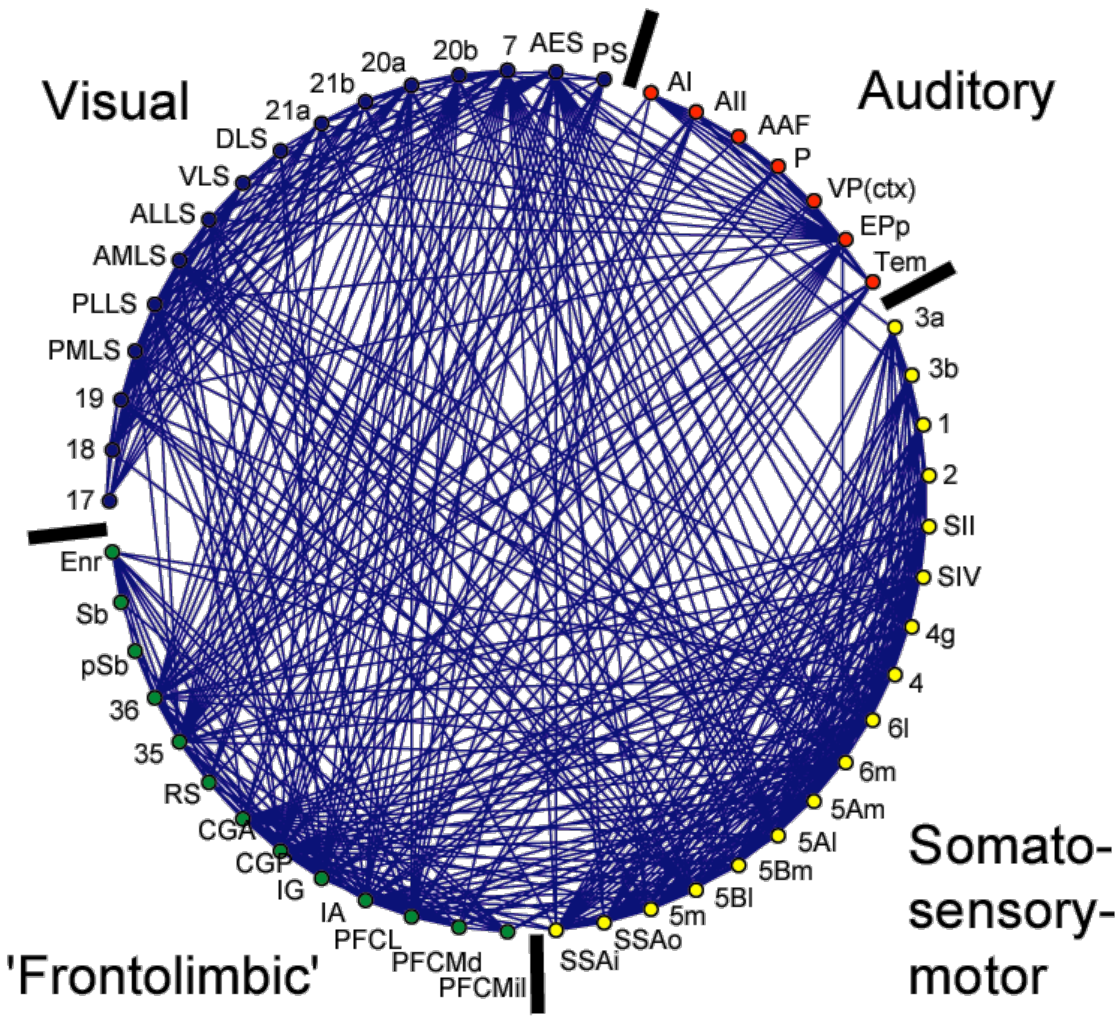
http://bcs.snu.ac.kr/

http://www.biological-networks.org

Brain connectivity



Hilgetag & Kaiser (2004) *Neuroinformatics* **2**: 353

<u>Types of Brain Connectivity</u>
Structural, functional, effective

<u>Small-world</u>
Neighborhood clustering
Shortest path length

<u>Spatial</u>
preference for short connections but more long-distance connections than expected

<u>Structure->Function</u>
Network changes lead to cognitive deficits (Alzheimer's disease, IQ)

Outline

Microscale (one component)

- Centrality measures

Mesoscale (several components)

- Motifs
- Clusters

Macroscale (all components)

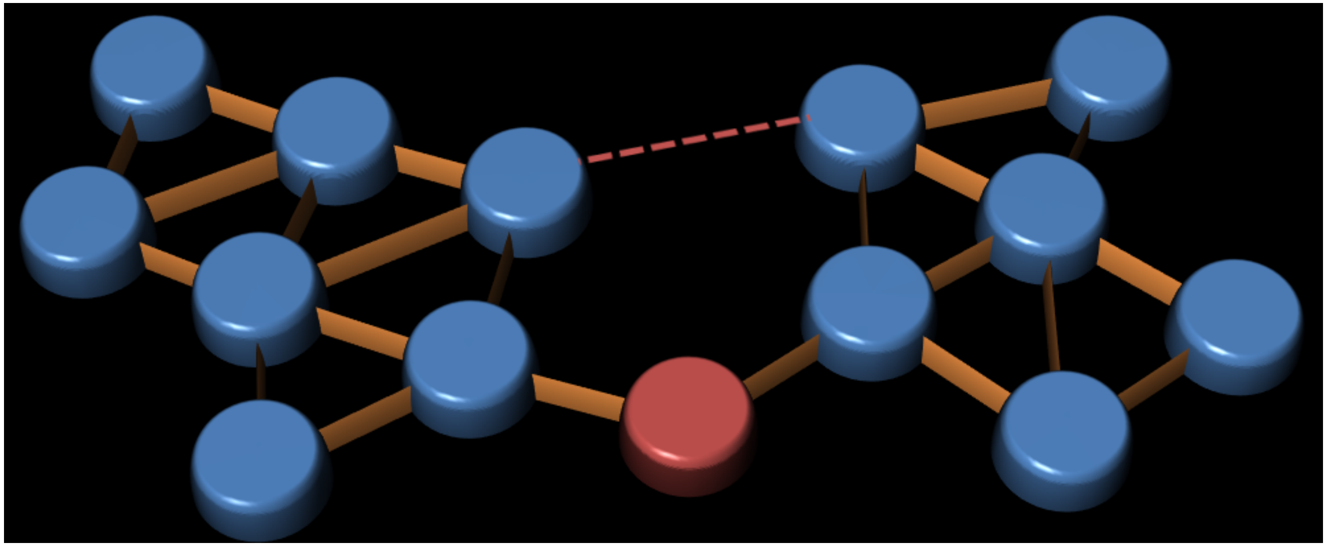
- Degree distributions:
  Random and Scale-free networks

Studying network robustness

Centrality measures

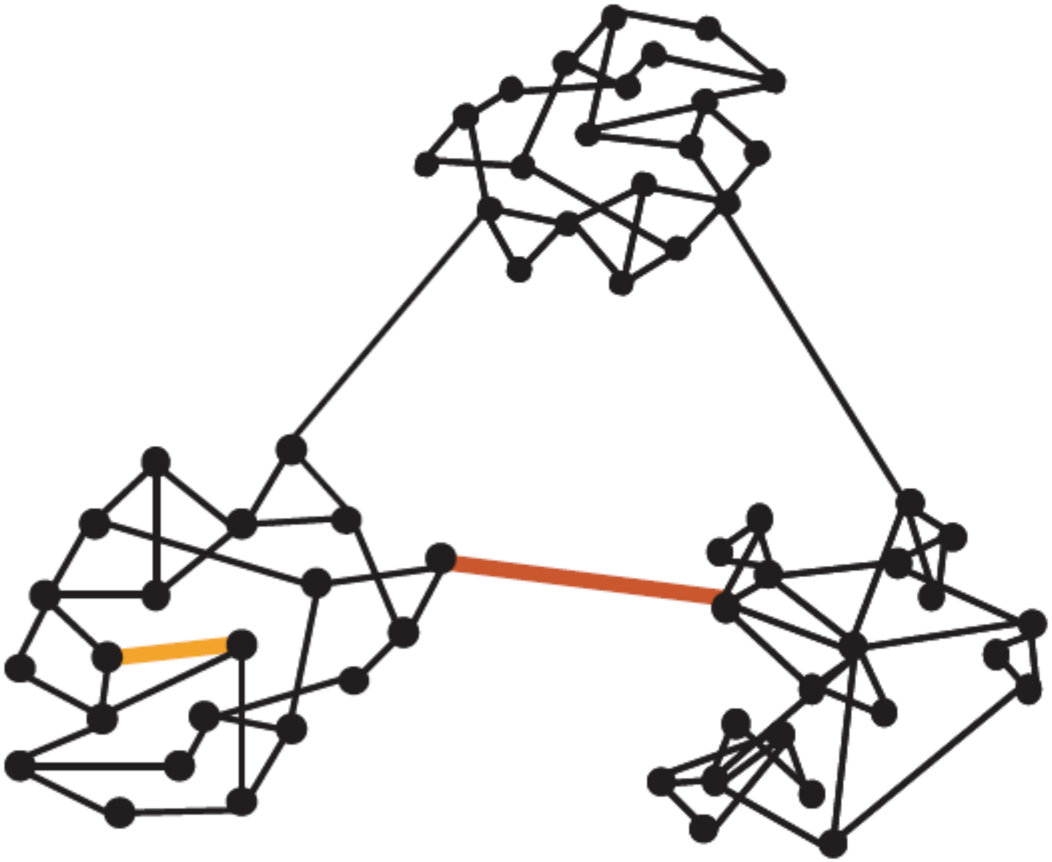
Node betweenness

- Node betweenness:
  number of shortest paths that go through one node



Edge betweenness

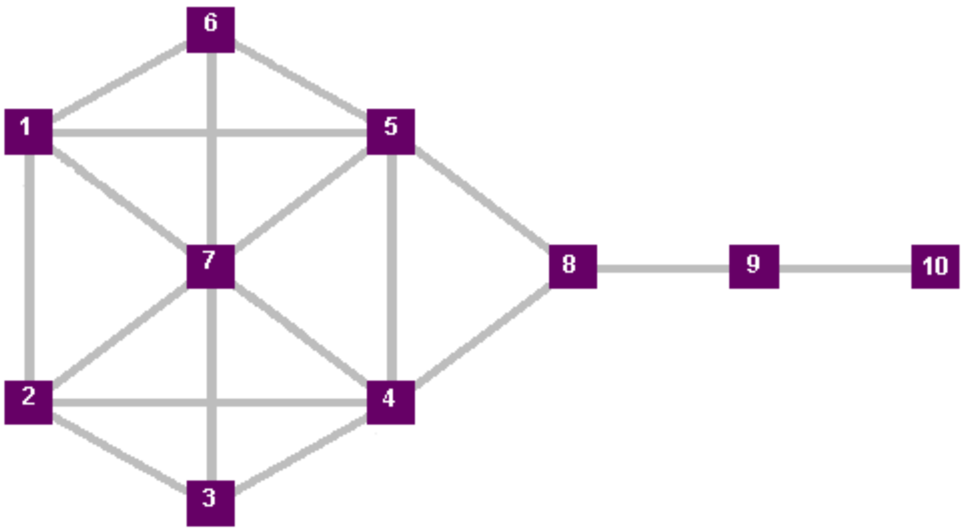
- Edge betweenness:
  number of shortest paths that go through one edge



High edge betweenness

Low edge betweenness

Centrality measure example



Node 8 has the highest node betweenness
Edge 8-9 has the highest edge betweenness

Motifs

Motifs

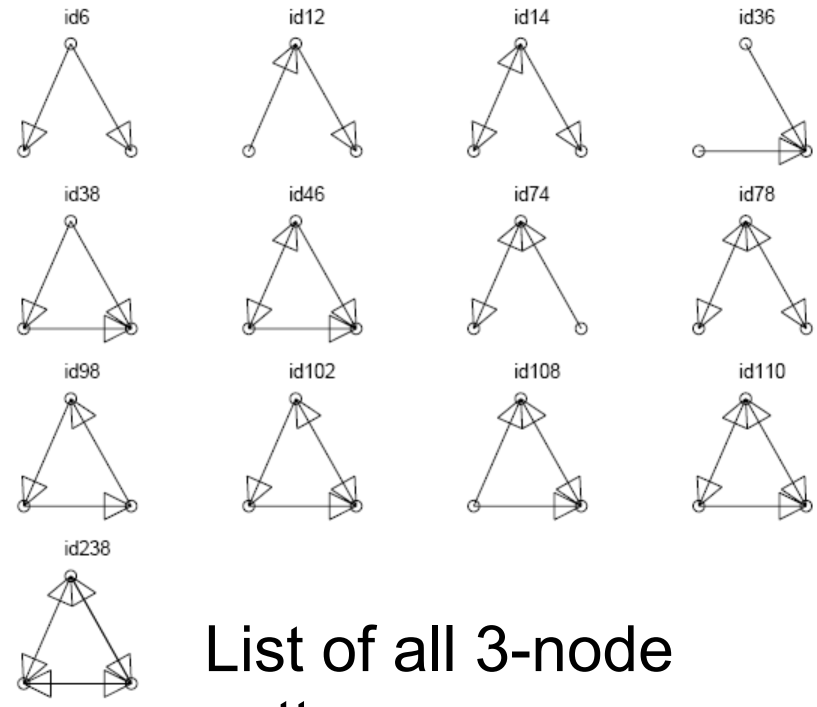
Idea: determine building blocks of networks.

Hope: structural building blocks correspond to functional units.

Pattern: possible connection configuration for a k-node subgraph

(see list of all 3-node configurations)

Motif: pattern that occurs significantly more often than for rewired benchmark networks
(same number of nodes and edges and same degree distribution)



List of all 3-node patterns

* Milo et al. (2002) Science;
http://www.weizmann.ac.il/mcb/UriAlon/groupNetworkMotifSW.html

Motif detection – algorithm

```
Network name: network_exmp.txt
Network type: Directed
Num of Nodes: 16 Num of Edges: 19
Num of Nodes with edges: 16
Maximal out degree (out-hub) : 3
Maximal in degree (in-hub) : 3
Roots num: 4 Leaves num: 4
Single Edges num: 19 Mutual Edges num: 0

Motif size searched  3
Total number of 3-node subgraphs : 21
Number of random networks generated : 100
Random networks generation method: Switches
Num of Switches range: 100.0-200.0,
      Success switches Ratio:0.652+0.01

The following motifs were found:

Criteria taken : Nreal Zscore > 2.00
                 Pval ignored (due to small number of random
networks)
                 Mfactor > 1.10
                 Uniqueness >= 4
```

Appearances in the real network

Random networks: mean+- SD

Uniqueness

Concentration X10-3

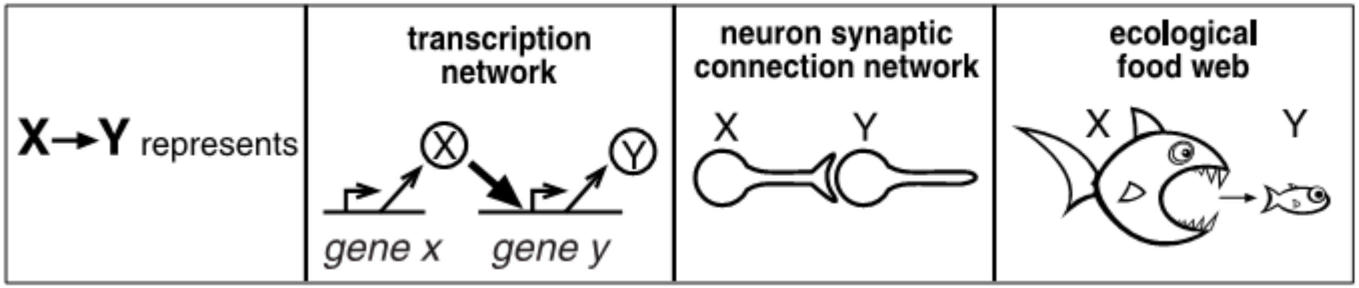
Full list includes 1 motifs

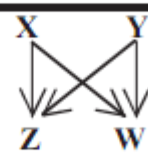
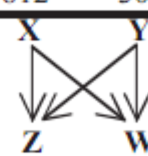
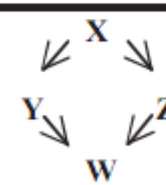
MOTIF ID	NREAL	NRAND STATS	NREAL ZSCORE	NREAL PVAL	UNIQ VAL	CREAL [MILI]
38	5	0.6+0.6	6.93	0.000	4	238.10

```
0 1 1
0 0 1
0 0 0
```

Motif Adjacency Matrix

Motif detection – results



Network	Nodes	Edges	N_{real}	$N_{rand} \pm SD$	Z score	N_{real}	$N_{rand} \pm SD$	Z score	N_{real}	$N_{rand} \pm SD$	Z score
Gene regulation (transcription)					**Feed-forward loop**			**Bi-fan**			
E. coli	424	519	40	7 ± 3	10	203	47 ± 12	13			
*S. cerevisiae**	685	1,052	70	11 ± 4	14	1812	300 ± 40	41			
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

Milo et al. Science, 2002

Motif detection – problems

Advantages:

- Identify special network patterns which *might* represent functional modules

Disadvantages:

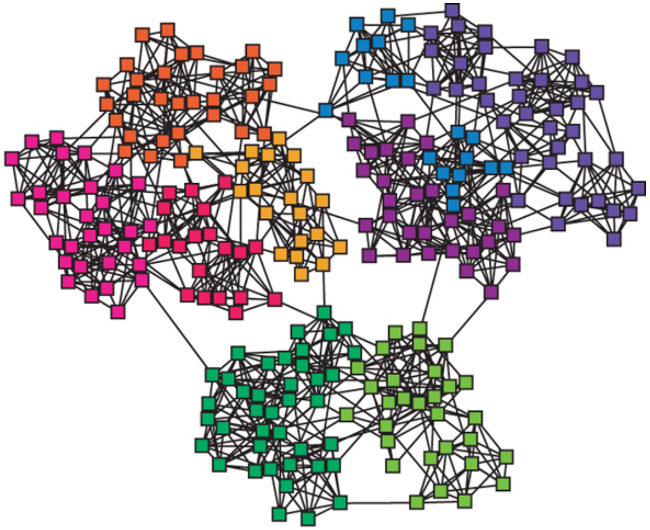
- Slow for large networks and
  unfeasible for large (e.g. 5-node) motifs
  (#patterns: 3-node – 13; 4-node – 199; 5-node: 9364; 6-node - 1,530,843)
- Rewired benchmark networks do not retain *clusters*;
  most patterns become insignificant for clustered benchmark networks*

* Kaiser (2011) Neuroimage

Clusters (or Modules or Communities)

Clusters

Clusters: nodes within a cluster tend to connect to nodes in the same cluster but are less likely to connect to nodes in other clusters



Quantitative measure: modularity Q
(Newman & Girvan, Physical Review E, 2004)

important terms:

hierarchical (cluster, sub-cluster, ...)

overlapping or *non-overlapping*
(one node can only be member of one cluster)

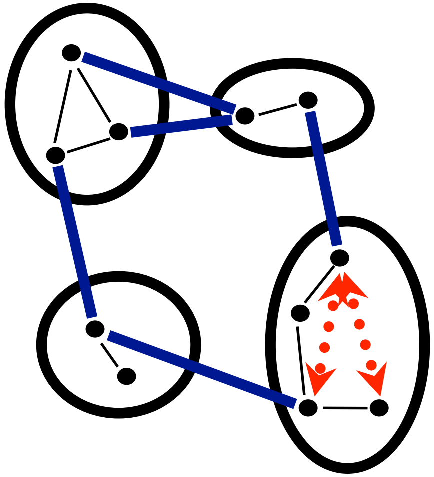
predefined number of clusters
(e.g. k-means algorithm)

Potential time problem for large networks, $O(k^N)$
Hundreds of algorithms for cluster detection!

Cluster detection – example

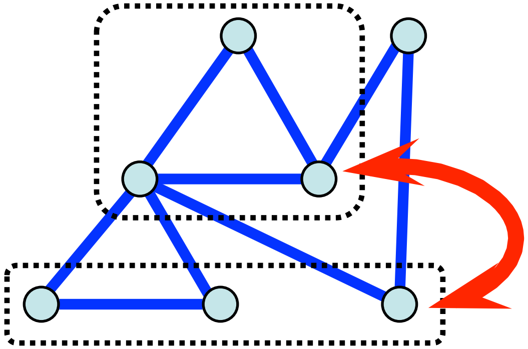
Non-hierarchical, overlapping

Genetic algorithm



- Have as few as possible connections ***between*** them
- Have as few as possible absent connections ***within*** them

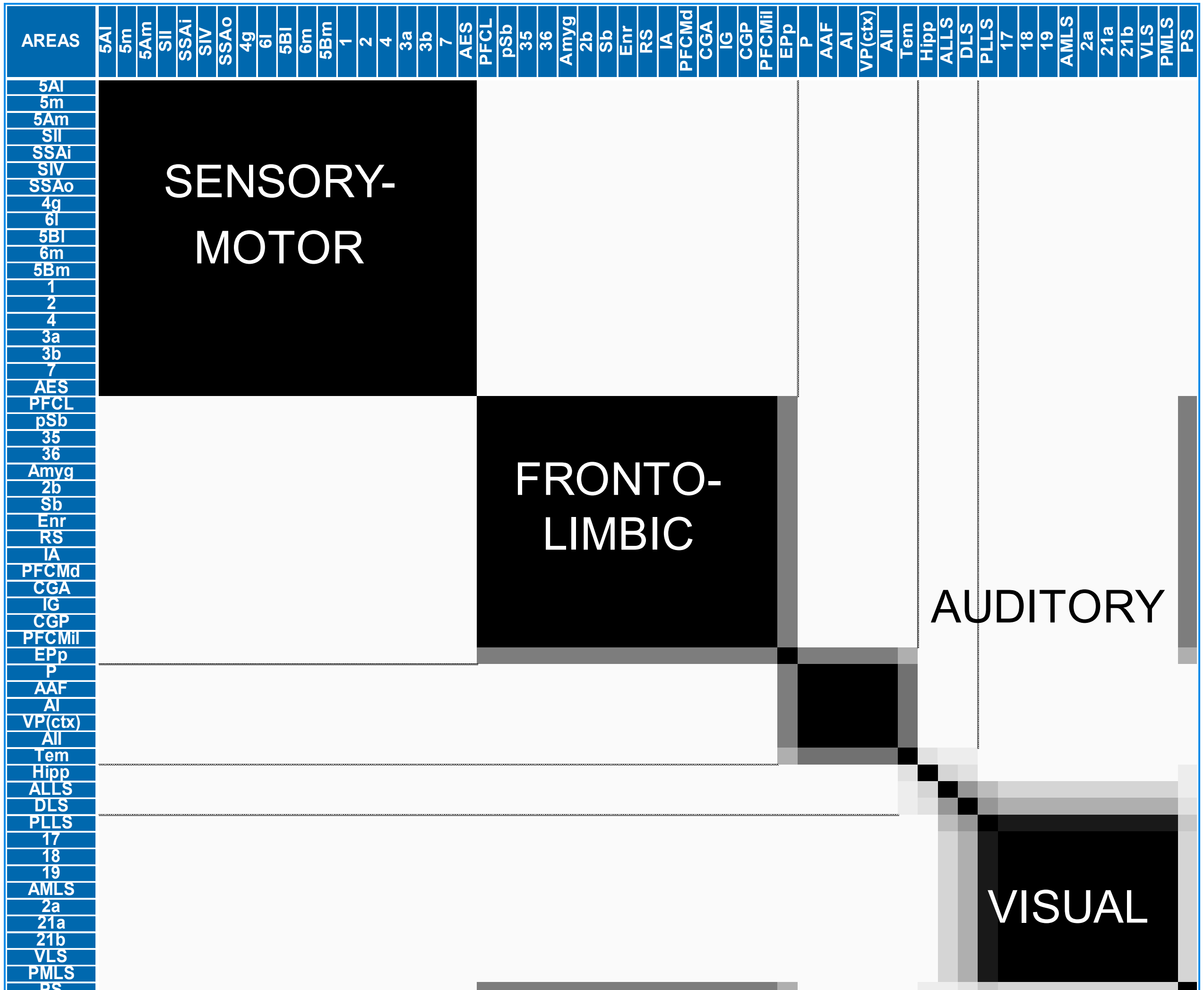
Procedure



- Random starting configurations
- Evolution:
  - Mutation : Area relocation
  - Evaluation : Cost function
  - Selection : Threshold
- Validation

Hilgetag et al. (2000) Phil. Trans. Roy. Soc. Lond. B.

Cluster detection



Example:

Cat cortical network

Black:

same cluster

Graylevel:

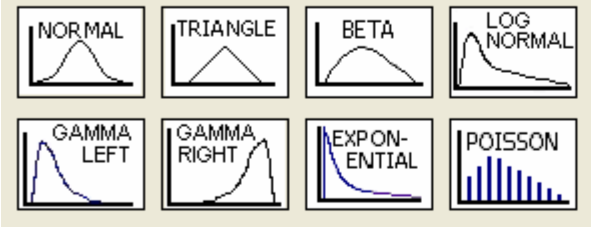
Ambiguous cases

Hilgetag et al. (2000) Phil Trans R Soc 355: 91

Random graphs

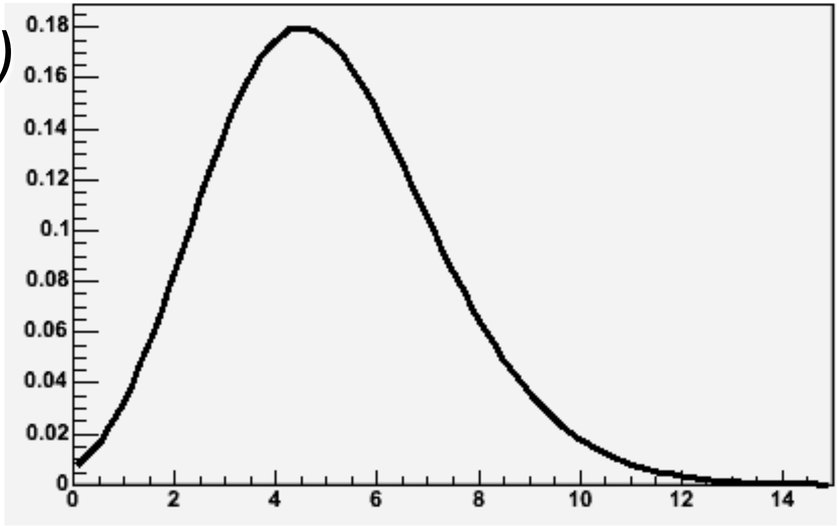
Preliminary: Degree distributions

Degree distributions



Theoretical (known properties): *P(k)* is the probability that a node with *k* edges exists in the network (probability distribution)

P(k)

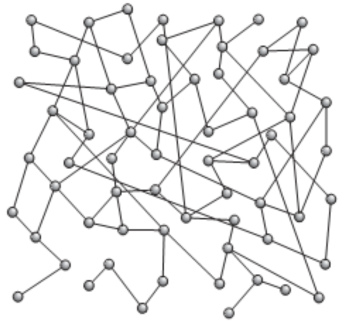


Node degree *k*

Degree distribution

Numerical (real-world network): use the number of occurrences of a node (histogram)

Random graphs



- often called Erdős–Rényi* random graphs

- Generation:
  For each potential edge
  (adjacency matrix element outside the diagonal),
  establish an edge
  (set that element of the adjacency matrix to 1)
  with probability *p*

$$A = \begin{pmatrix} 0 & 1 & 1 & 0 \\ 1 & 0 & 1 & 0 \\ 1 & 1 & 0 & 1 \\ 0 & 0 & 1 & 0 \end{pmatrix}$$

*Erdős, P.; Rényi, A. (1959). Publicationes Mathematicae 6: 290–297.

Properties of random graphs

- Edge density = *p*
- Binomial *degree distribution* (histogram of node degrees)

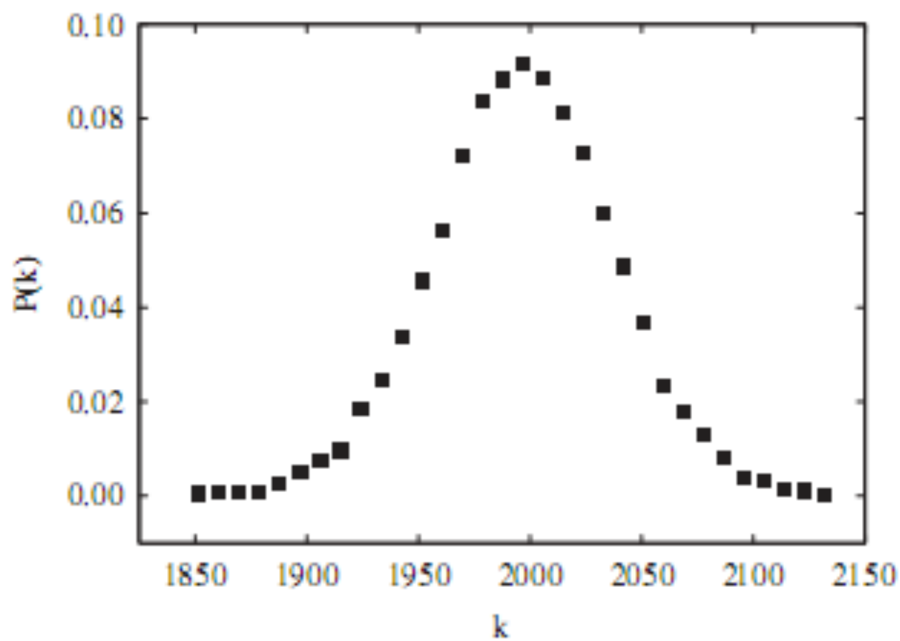
$$P(k) = \binom{n-1}{k} p^k (1-p)^{n-1-k}$$

Can be approximated as Poisson distribution

$$f(k;\lambda) = \frac{e^{-\lambda}\lambda^k}{k!} \qquad \lambda = n * p$$

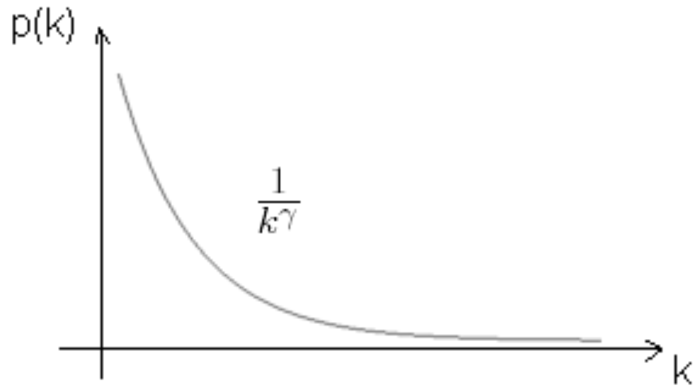
-> exponential *tail*

(networks are therefore sometimes called *exponential networks*)



Scale-free networks

Power-law degree distribution

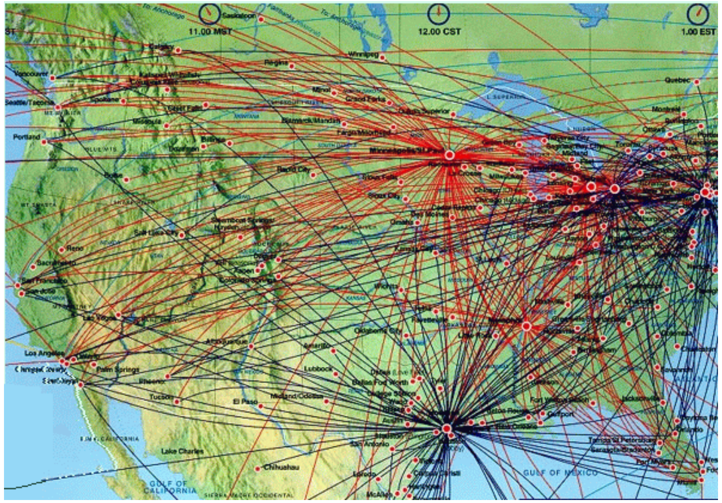


Barabasi & Albert, Science, 1999

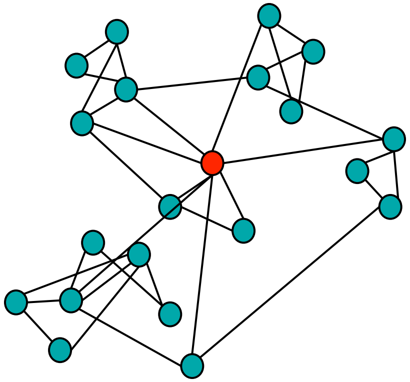
Power-law function:

$f(x) = x^{-a} = 1/x^a$

Scale-free = no characteristic scale



Airline network

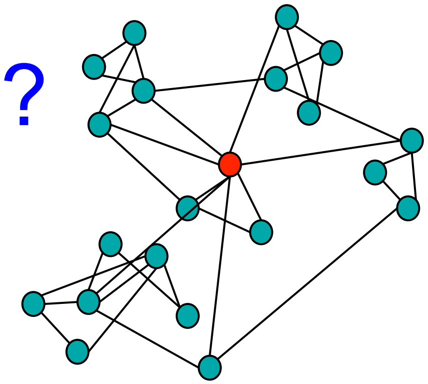


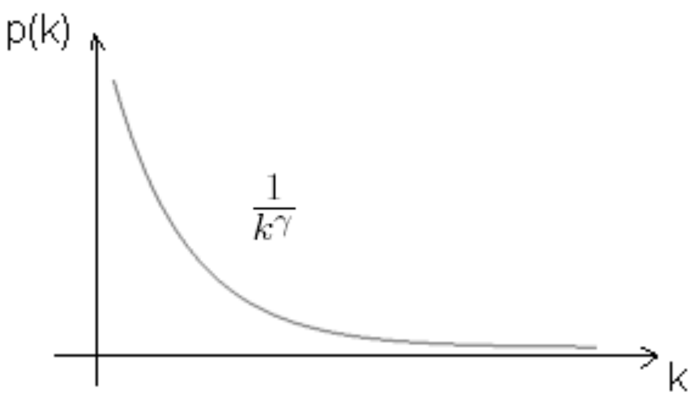
Hub =

highly-connected node

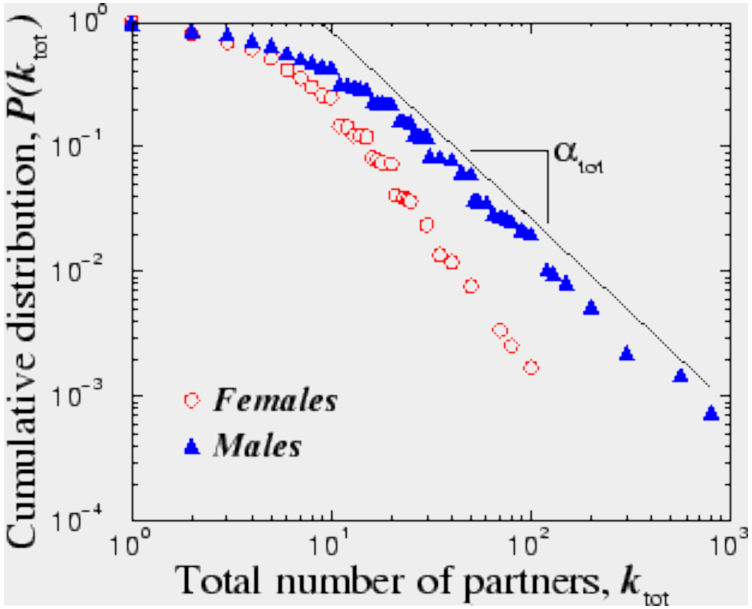
(potentially important for the network)

Is your network scale-free?





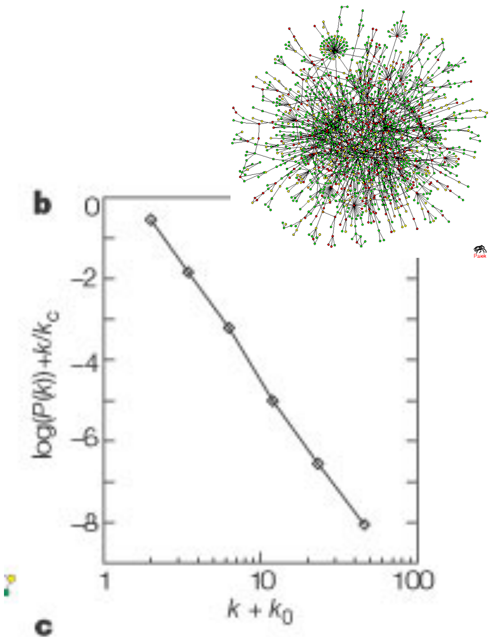
Log-log plot

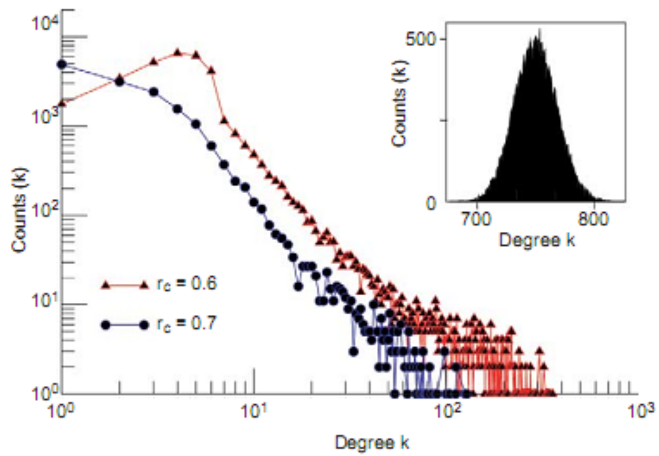


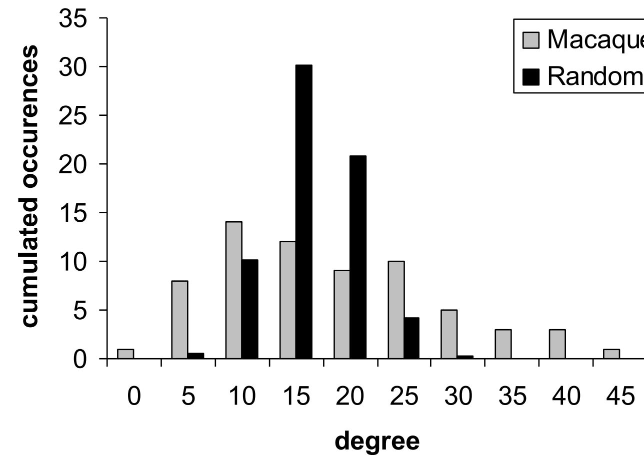
Barabasi & Albert, Science, 1999

Liljeros, Nature, 2001

Examples for biological scale-free networks







Protein-protein interaction network

Jeong et al., Nature, 2001

Correlation network between cortical tissue (fMRI voxels)

Eguiluz et al., Phys Rev Lett, 2005
Sporns et al., Trends Cogn Sci, 2004

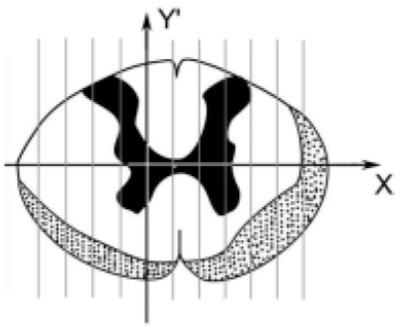
Cortical fibre tract network?

Kaiser et al., Eur J Neurosci, 2007

Robustness

Neural robustness against network damage (lesions)

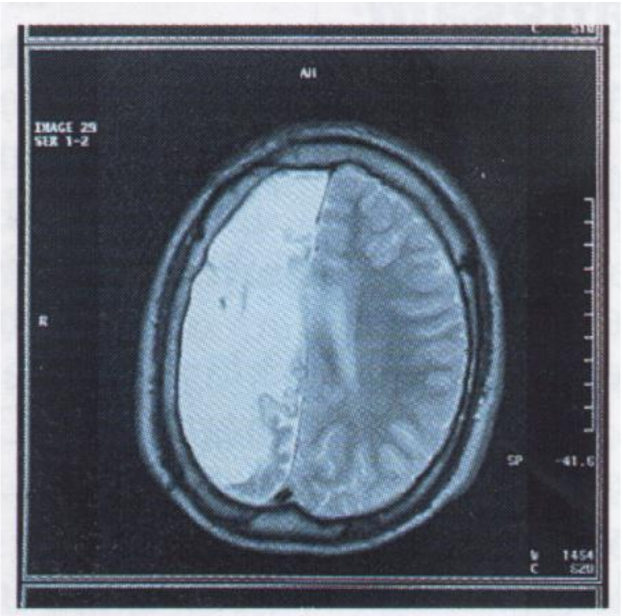
Rats: Spinal chord injury



large recovery possible with as few as 5% of remaining intact fibers

You et al., 2003

Human: Compensation for loss of one hemisphere at age 11

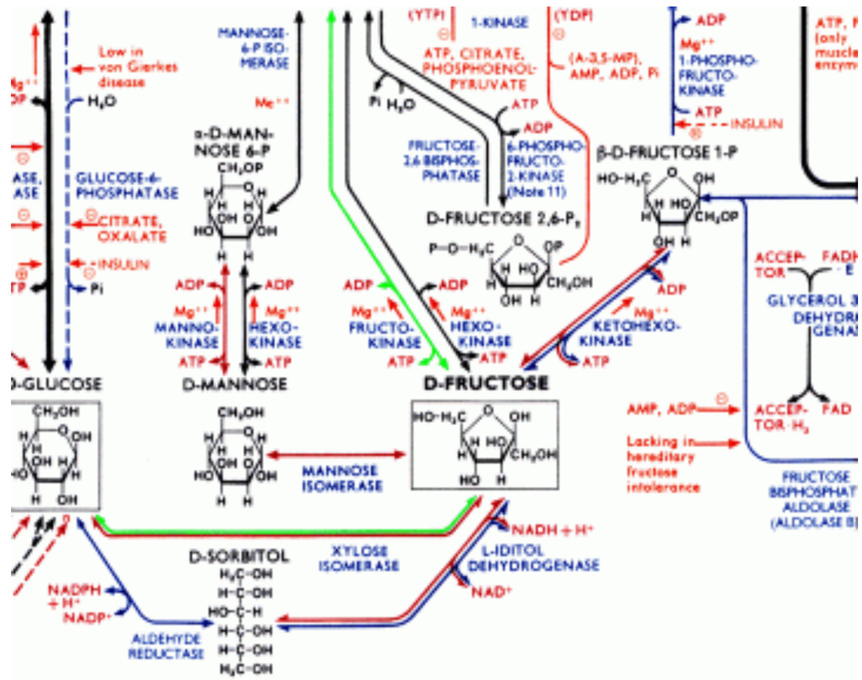


Cellular robustness against damage (gene knockouts)

- Mutations can be compensated by gene copies or alternative pathways*:

  ~70% of single-gene knockouts are non-lethal

- The metabolism can adjust to changes in the environment (e.g. switch between aerob and anaerob metabolism)



* **A. Wagner. Robustness against mutations in genetic networks of yeast.** ***Nature Genetics*, **24**, 355-361 (2000).**

Measures of structural integrity

How is the global topology of the network affected?

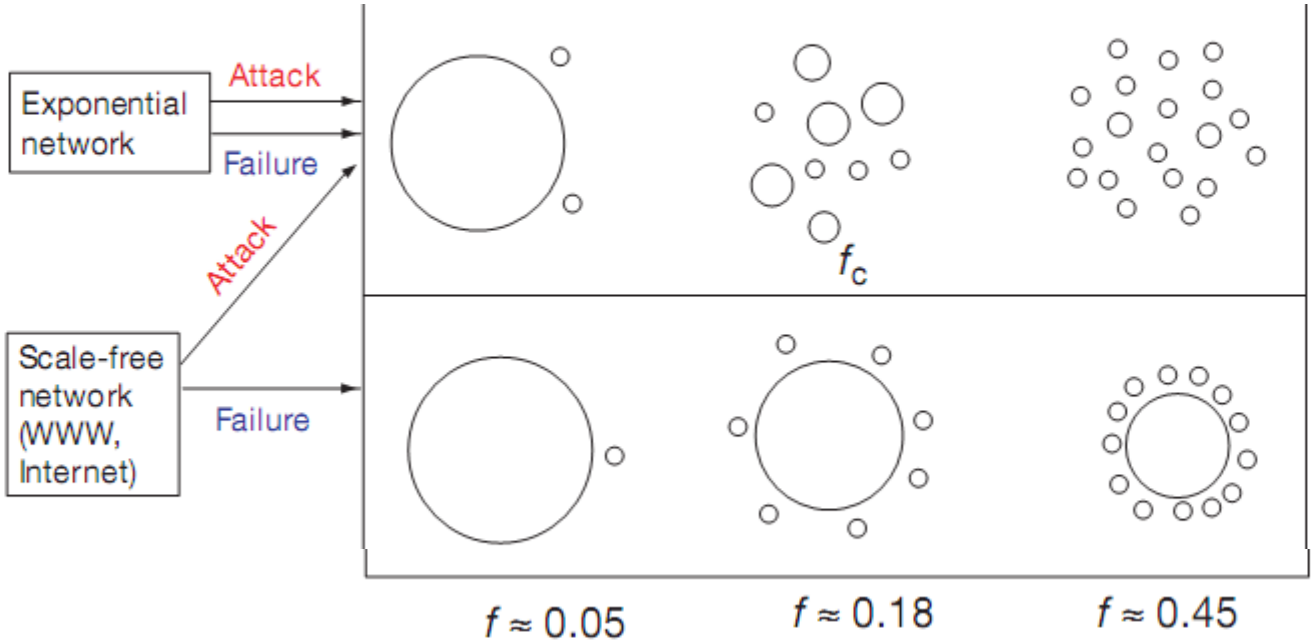
Idea: Changes in *structural* properties might indicate *functional* changes (like lower performance of the system)

Structural measure	Potential functional impact
⬆ All-pairs shortest path	longer transmission time
⬇ Reachability ⬆ Fragmentation	occurrence of isolated parts (components)
⬇ Clustering coefficient	less interaction within modules

Alzheimer

Schizophrenia

Example: fragmentation

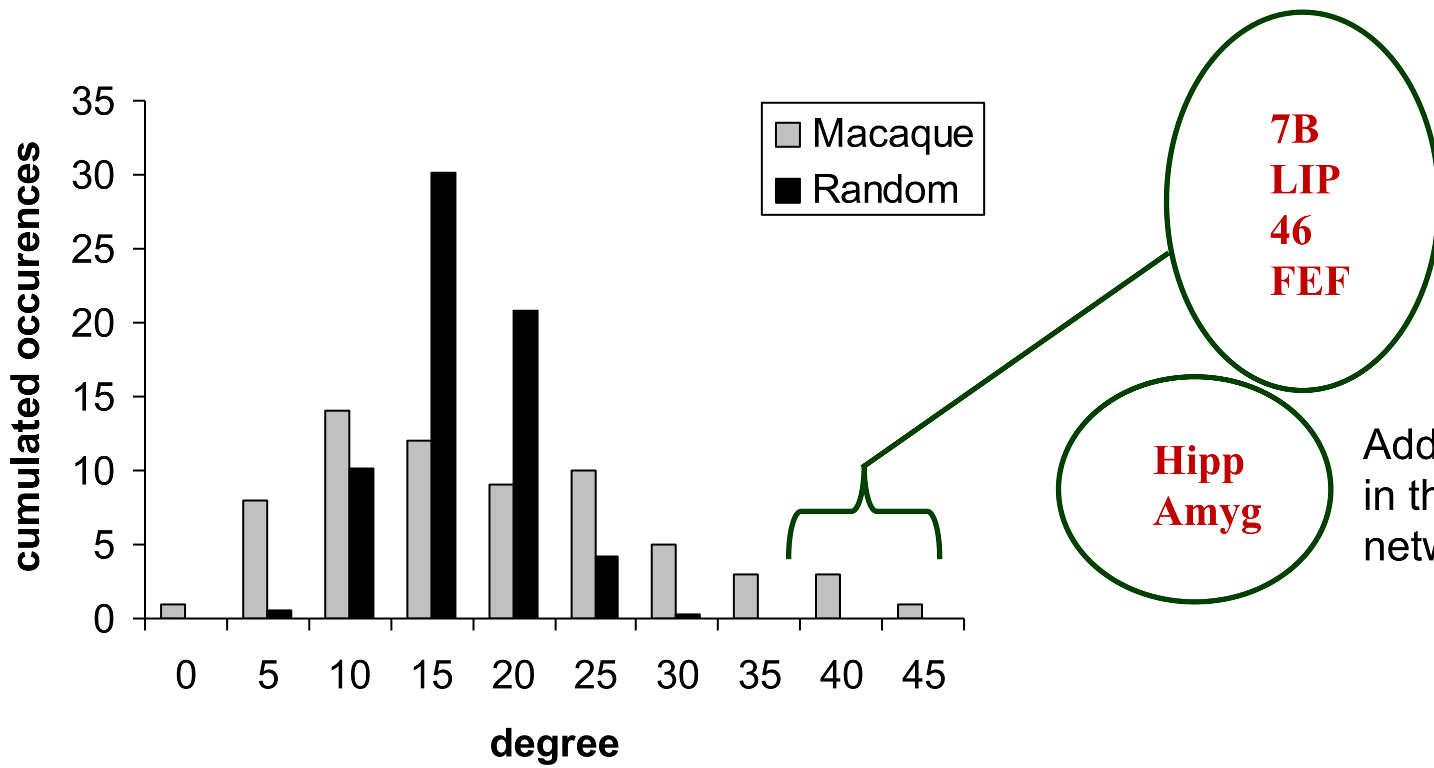


f: fraction of removed nodes
f_c: fraction where the network breaks into small fragments

Albert R, Jeong H, Barabasi AL (2000) Nature 406: 378–382

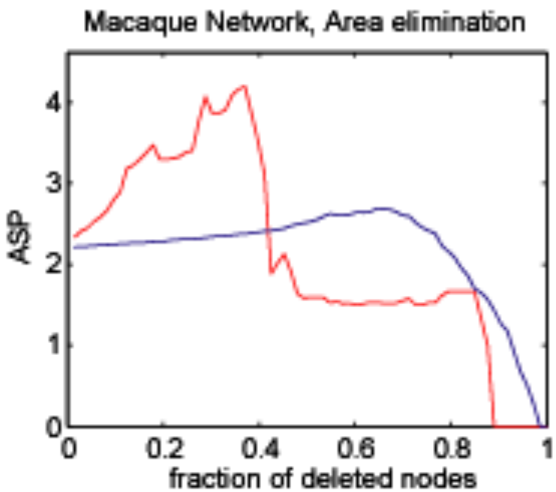
Example: simulated brain lesions

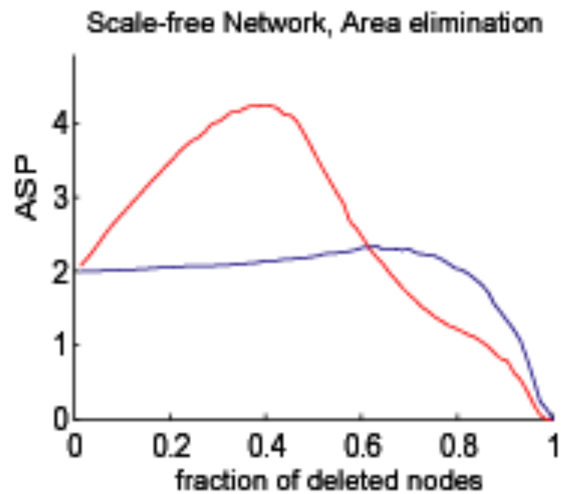
Is the brain similar to a scale-free network?

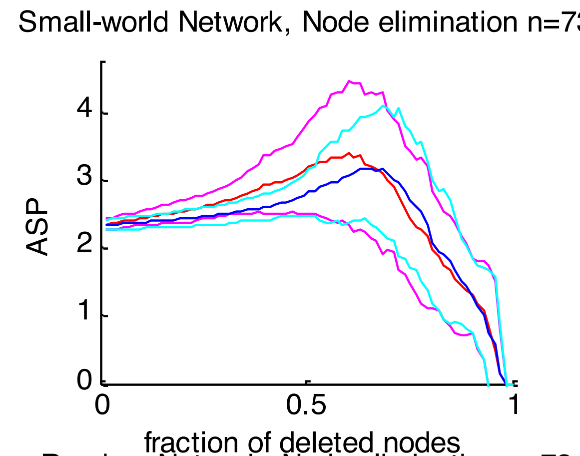


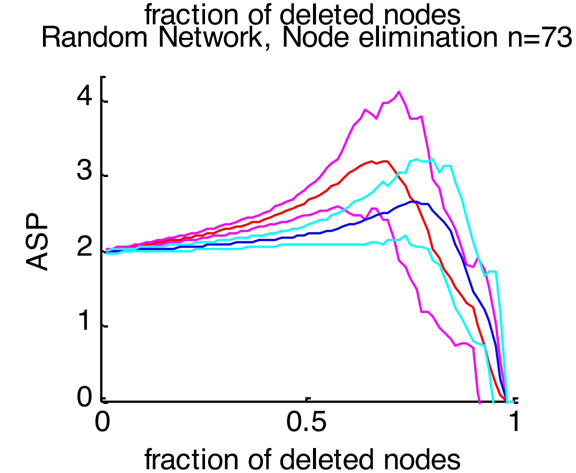
Additional hubs in the extended network of the cat

Sequential removal of brain areas









randomly = irrespective of degree

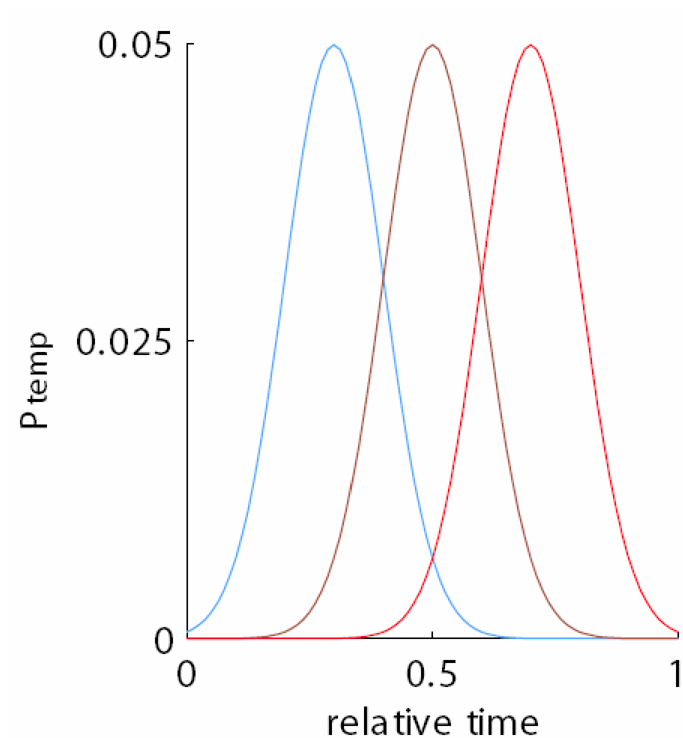
targeted = highly-connected nodes first

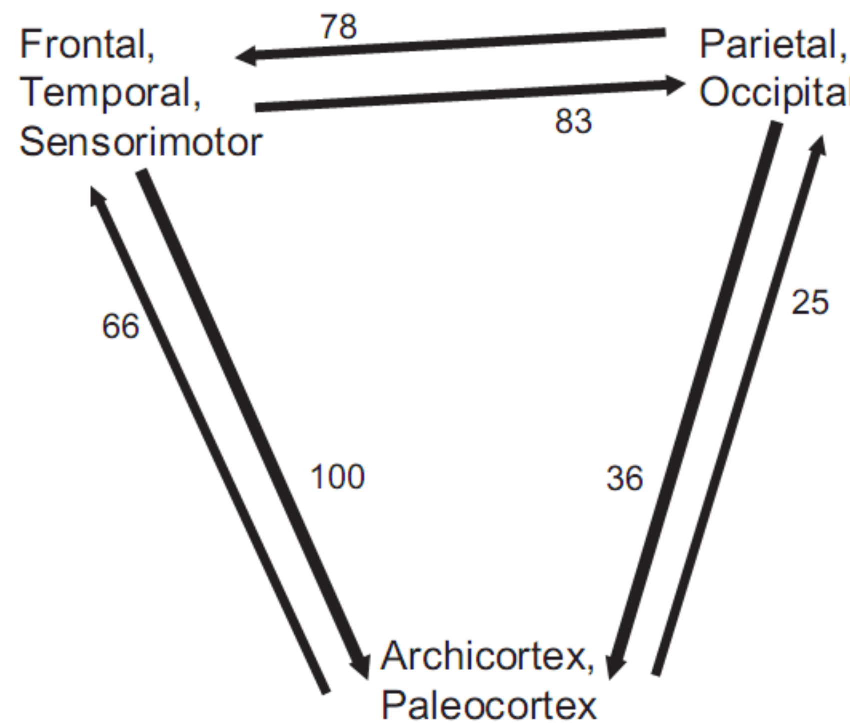
Kaiser et al. (2007) *European Journal of Neuroscience* 25:3185-3192

Where do 'hubs' come from?

Not from preferential attachment…

During individual development, early-established nodes have more time to establish connections:



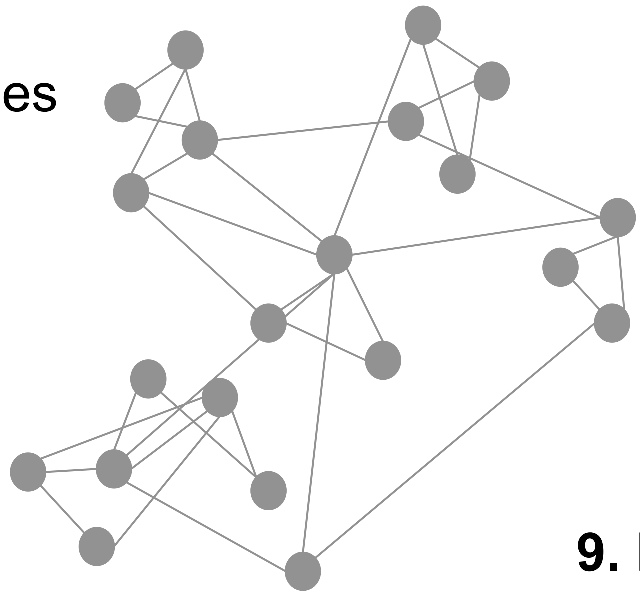


C. elegans network development: Varier & Kaiser (2011) PLoS Comput Biol
Nisbach & Kaiser (2007) *Eur Phys J B*
Kaiser et al. (2007) *European Journal of Neuroscience* 25:3185-3192

Summary

7. Mesoscale:
- Motifs
- Clusters/Modules

8. Macroscale:
- Degree distribution
  Random networks
  Scale-free networks
- *Small-world networks*
- *Hierarchical networks*



6. Microscale:
- Centrality
- *Node degree*
- *Local clustering coefficient*

9. Robustness:
- Change of network properties after edge or node removal
- simulated brain lesions

Further readings

Luciano da Fontoura Costa

Costa et al. Characterization of Complex Networks
Advances in Physics, 2006

Ed Bullmore

Olaf Sporns

Bullmore & Sporns. Complex Brain Networks
Nature Reviews Neuroscience, 2009

Malcolm Young

Kaiser et al. Simulated Brain Lesions
(brain as scale-free network)
European Journal of Neuroscience, 2007

Alstott et al. Modeling the impact of lesions in the human brain
PLoS Computational Biology, 2009