ICTP SAIFR

International Centre for Theoretical Physics
South American Institute for Fundamental Research

SCHOOL ON COMPLEX NETWORKS AND APPLICATIONS TO NEUROSCIENCES

APPLICATIONS TO BIOLOGY: FROM RNA TO BRAIN NETWORKS (I)

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OVERVIEW

I.- Biological Networks

- Complex Networks & Biology
- Different kind of networks

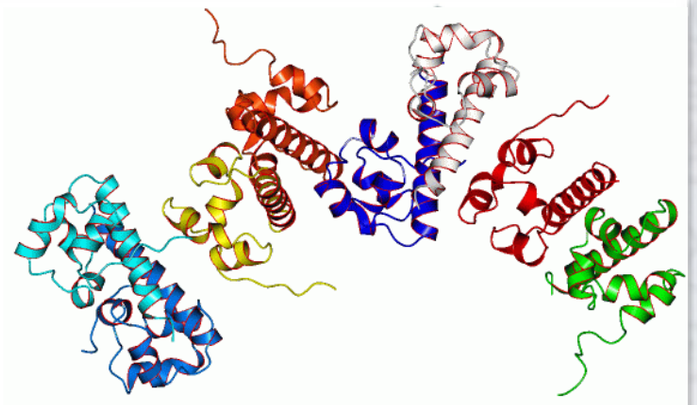
II.- RNA networks

- What is a RNA neutral network
- Topological properties
- Population dynamics

III.- Functional Brain Networks

- How to obtain them
- Risks and challenges

Biological Networks



(I-III)

COMPLEX BIOLOGICAL NETWORKS

One of the first contributions of the Complex Network Theory to biological systems is the seminal paper of Watts and Strogatz:

Collective dynamics of 'small-world' networks

Duncan J. Watts* & Steven H. Strogatz

Department of Theoretical and Applied Mechanics, Kimball Hall, Cornell University, Ithaca, New York 14853, USA

	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
C. elegans	2.65	2.25	0.28	0.05

The small-world of C. Elegans neural network, with an edge joining two neurons if they are connected by either a synapse or a gap junction (n= 282, <k>= 14). Table from Watts & Strogatz, 393, 440 (1998).

COMPLEX BIOLOGICAL NETWORKS

Biological networks are very heterogeneous, but one thing is sure, they are complex networks:

	network	type	n	m	z	ℓ	α	C	r
biological	metabolic network	undirected	765	3 686	9.64	2.56	2.2	0.67	−0.240
	protein interactions	undirected	2 115	2 240	2.12	6.80	2.4	0.071	−0.156
	marine food web	directed	135	598	4.43	2.05	–	0.23	−0.263
	freshwater food web	directed	92	997	10.84	1.90	–	0.087	−0.326
	neural network	directed	307	2 359	7.68	3.97	–	0.28	−0.226

Network parameters of several biological networks: n, number of nodes; m, number of links; z, mean degree,; l average shortest path; α, power-law exponent; C, clustering coefficient, and r, assortativity. From Newman, SIAM, 45, 167 (2003).

COMPLEX BIOLOGICAL NETWORKS

How are Biological Networks?:

- Biological networks are **small-world**.
- They are (typically) organized in **sub-modules** and, as a consequence, they have high modularity and community structures.
- It is common to observe **dissasortative** mixing (i.e., most connected nodes are not preferentially connected with each other).

Nevertheless, **each network deserves its own interpretation**

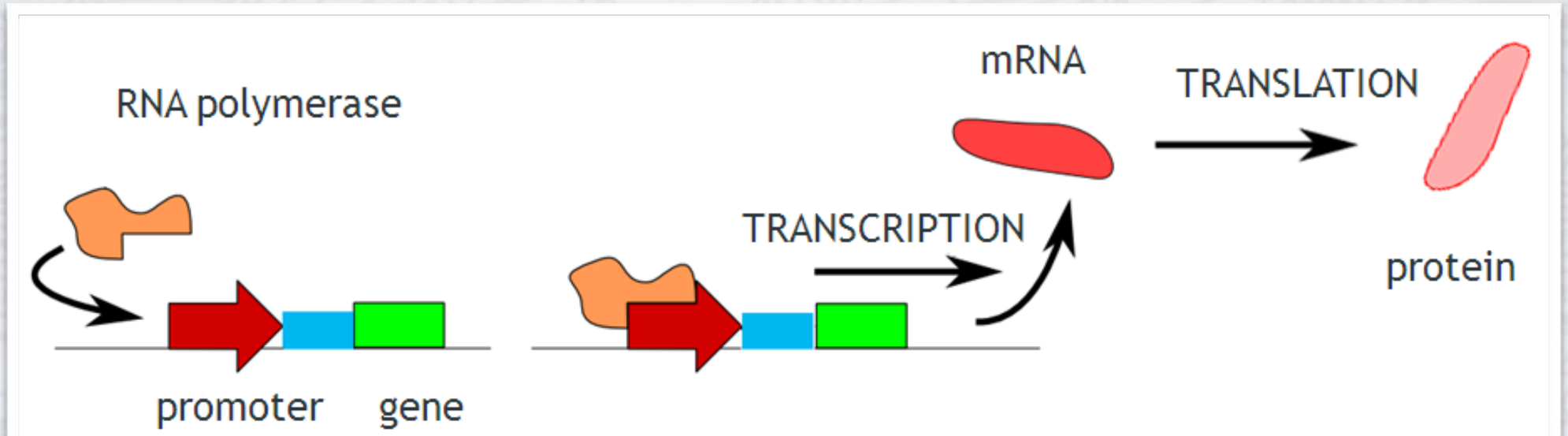
COMPLEX BIOLOGICAL NETWORKS

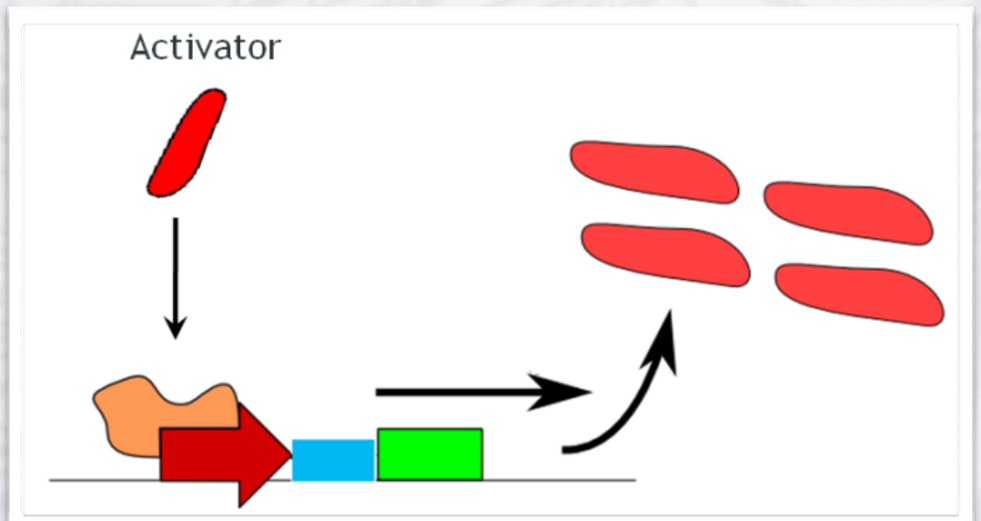
There is a **diversity** of biological networks, each one with its own particularities:

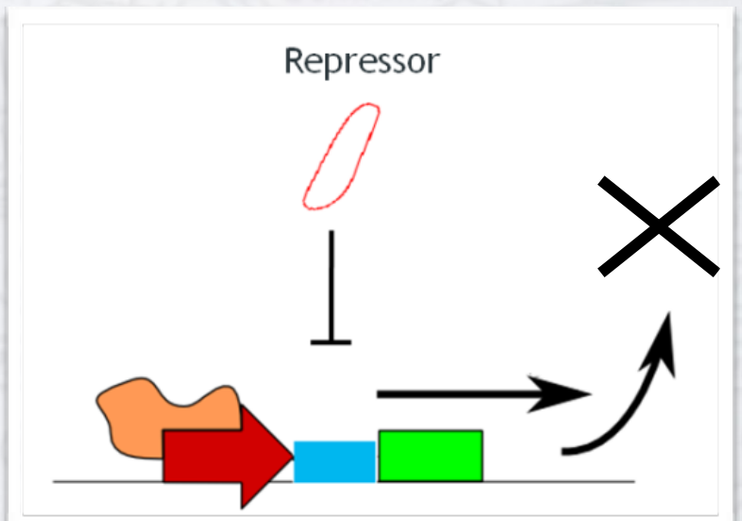
- Metabolic, protein and genetic networks
- Networks of neurons
- Functional and anatomical brain networks
- Food webs in ecosystems
- Animal grouping and swarm movement
- and many others …

GENETIC, PROTEIN AND METABOLIC NETWORKS

Interactions between genes (through transcription factors) lead to a network of promotor/repressor interactions

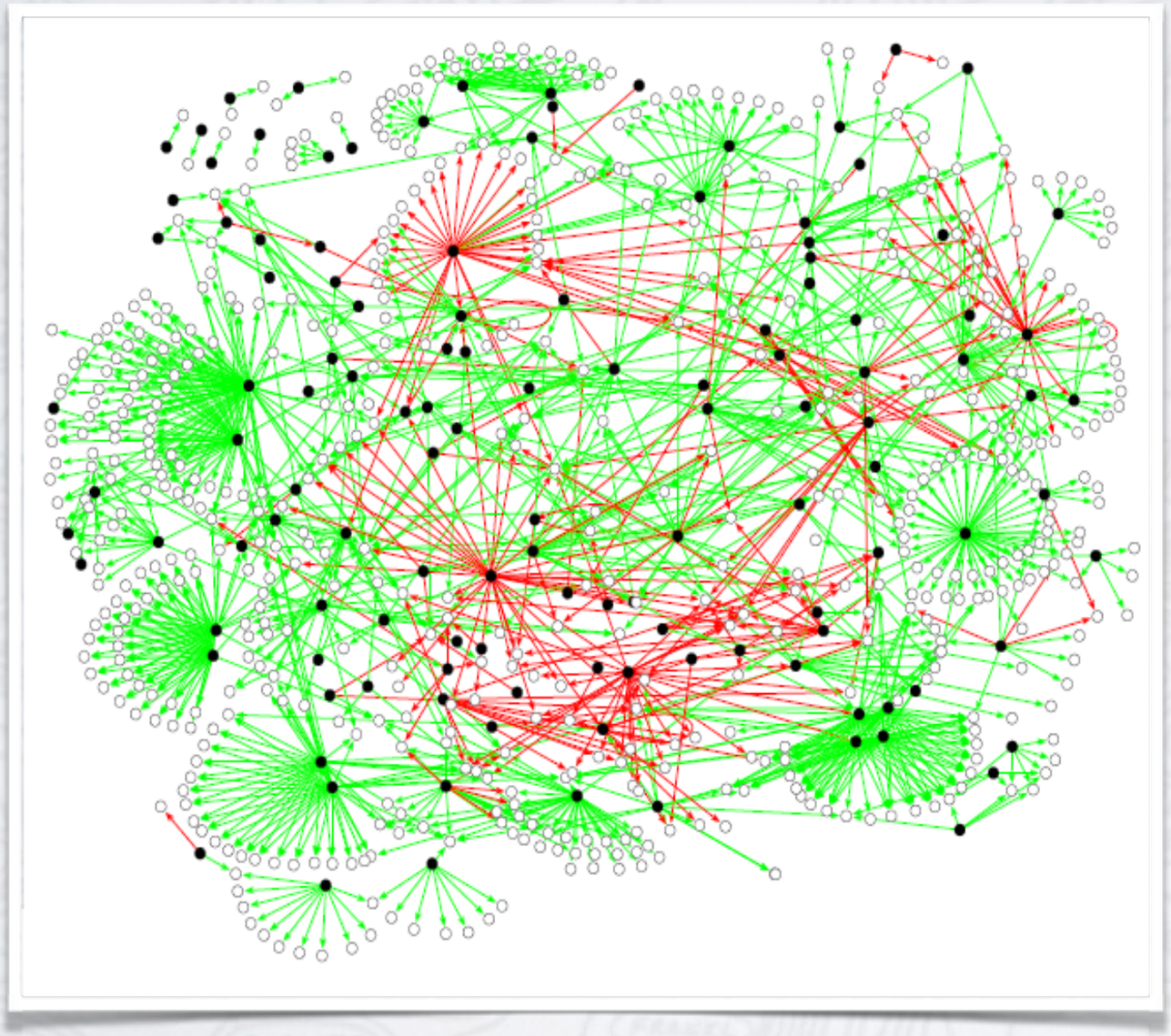






GENETIC, PROTEIN AND METABOLIC NETWORKS

Genetic transcription networks are directed (digraphs) with positive/negative regulations:



- transcription factor
- protein
- negative regulation
- positive regulation

Yeast (S. Cerevisiae) network of transcriptional regulation (N=682 proteins and M=1289 interactions). From Maslov et al., Large-Scale Topological Properties of Molecular Networks (Springer 2003).

GENETIC, PROTEIN AND METABOLIC NETWORKS

Despite their complexity, it is possible to analyze them and extract some conclusions:

The $P_{in}(k)$ distribution is limited by the system (due to the finite space of the promoter). $P_{out}(k)$ is not limited and, as a consequence, has a heavy tail.

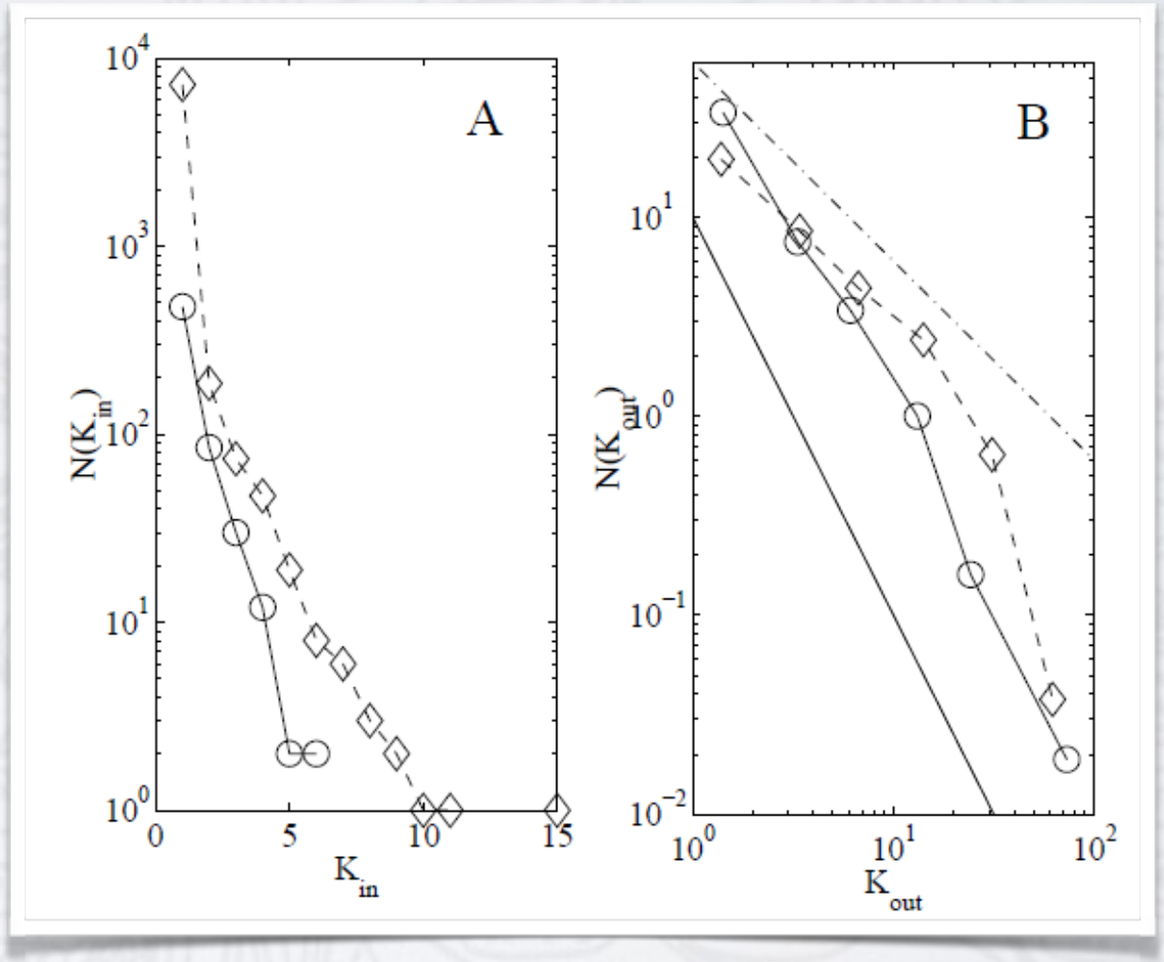
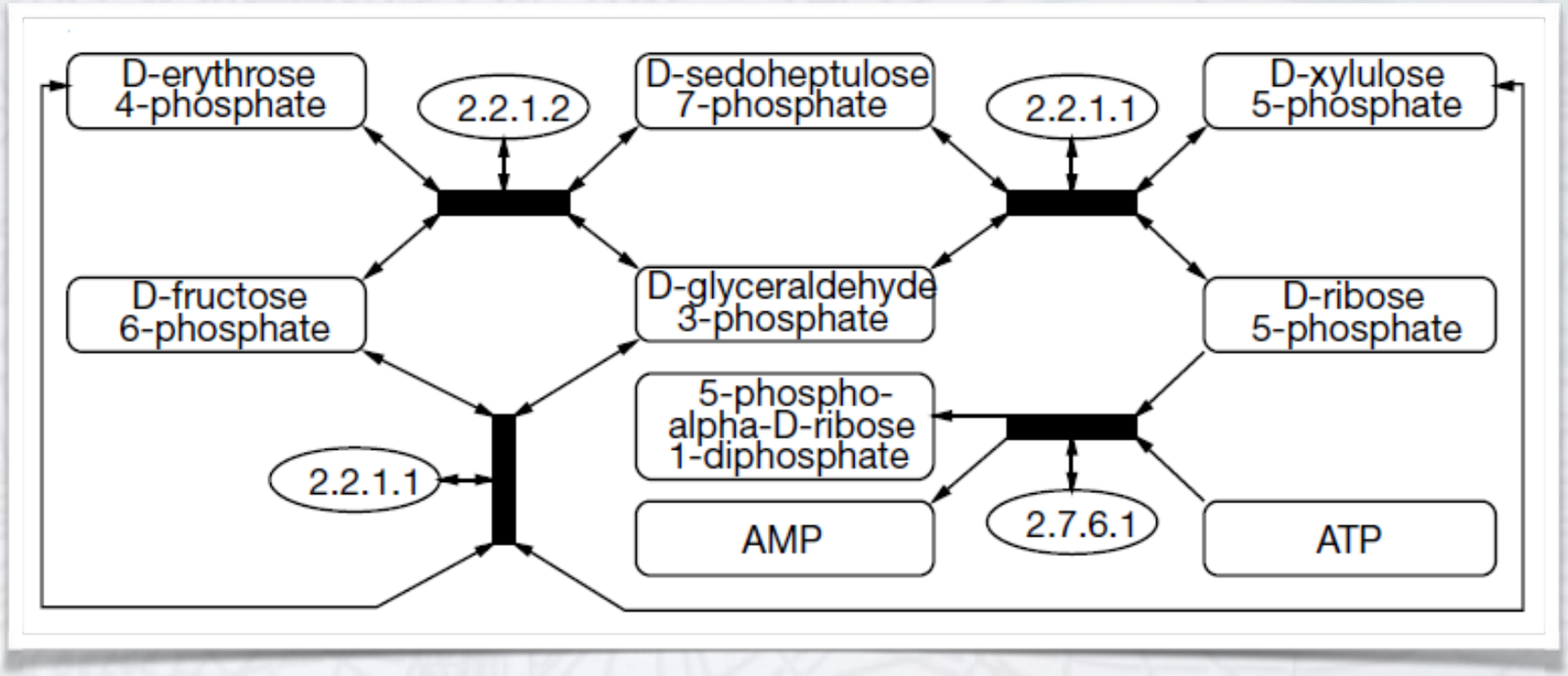


Figure: (a) The histogram N(Kin) of nodes' in-degrees Kin in transcription regulatory networks of yeast (diamonds, dashed line), and E. coli (circles, solid line). (b) the same as (a) but considering the N(Kout.). From Maslov et al., (2003).

GENETIC, PROTEIN AND METABOLIC NETWORKS

Metabolic networks are obtained from the biochemical reactions involving the transformation of energy and matter in the cell:

The participating substrates are called metabolites and are catalyzed and regulated by enzymes.

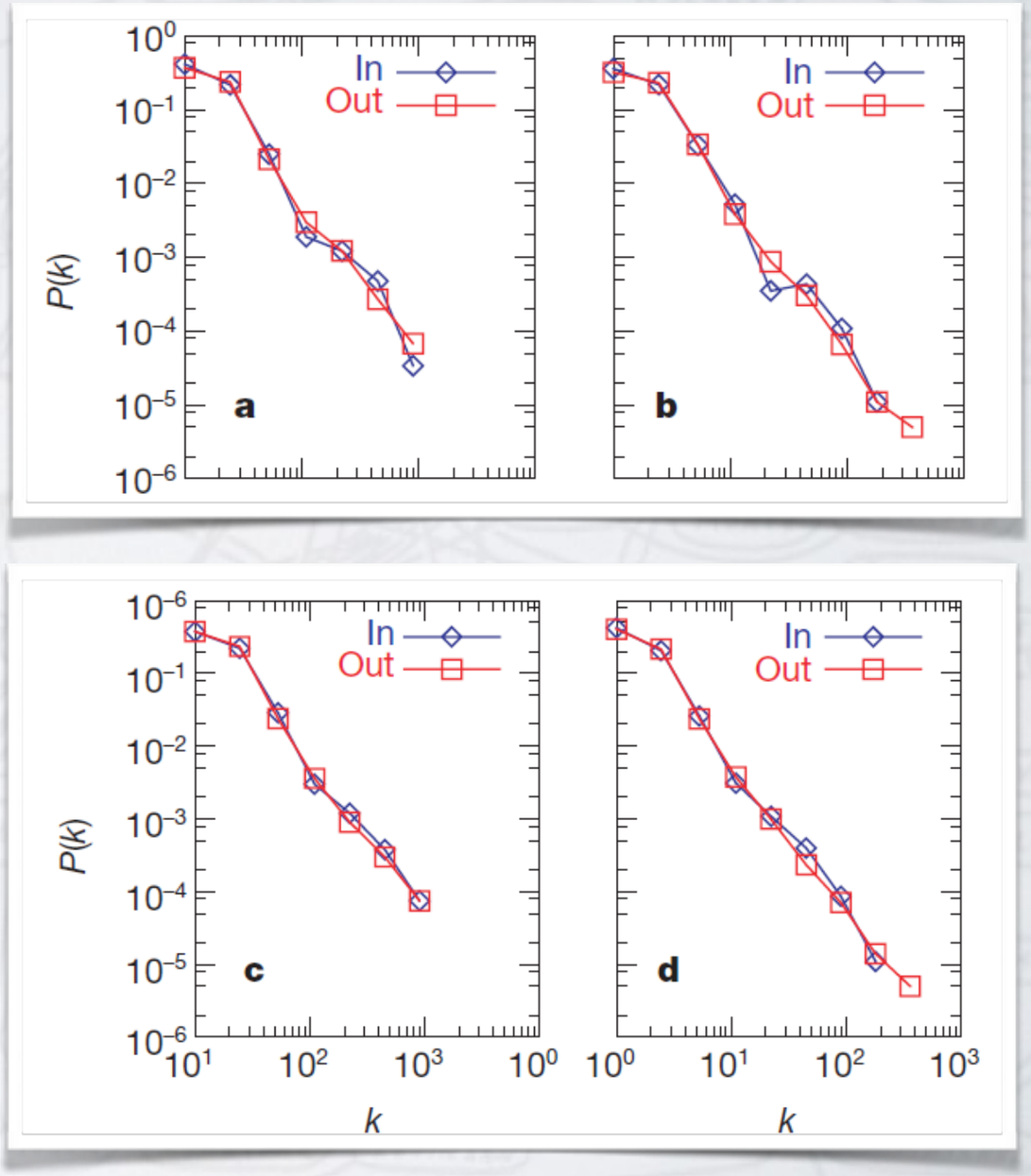


A portion of the WIT database for E. coli. Each substrate can be represented as a node of the graph, linked through temporary educt-educt complexes (black boxes) from which the products emerge as new nodes (substrates). The enzymes, which provide the catalytic scaffolds for the reactions, are shown by their EC numbers. From Jeong et al., Nature, 407.651 (2000).

GENETIC, PROTEIN AND METABOLIC NETWORKS

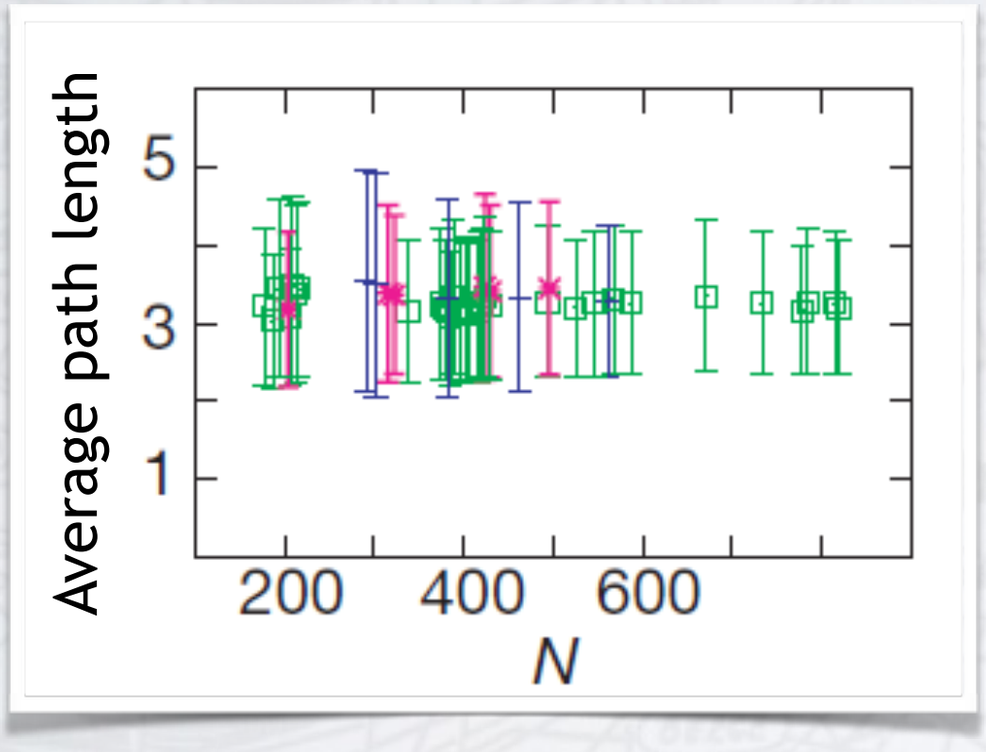
Metabolic networks have scale-free degree distribution

Connectivity distributions P(k) for: (a) Archaeoglobus fulgidus (archae); (b) E. coli (bacterium); (c) Caenorhabditis elegans (eukaryote), counting separately the incoming (In) and outgoing links (Out) for each substrate. k_{in} (k_{out}) corresponds to the number of reactions in which a substrate participates as a product (educt). (d) The connectivity distribution averaged over all 43 organisms. From Jeong et al., Nature, 407.651 (2000).

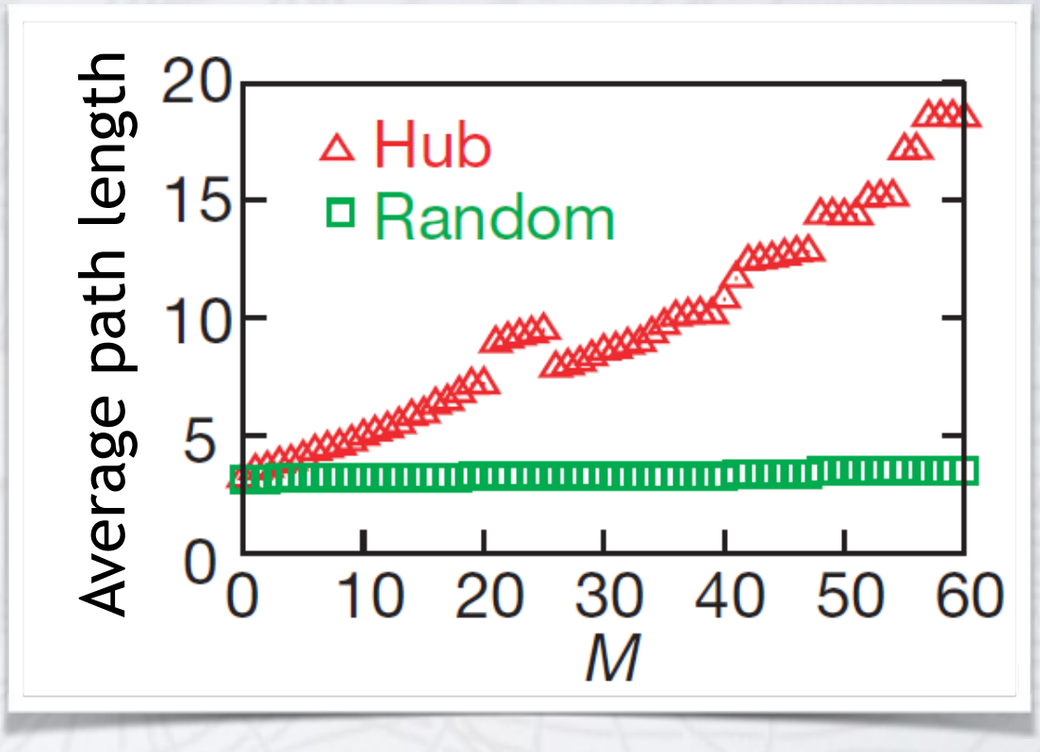


GENETIC, PROTEIN AND METABOLIC NETWORKS

Metabolic networks also show the **small-world property** and resilience to failures similar to scale-free networks:



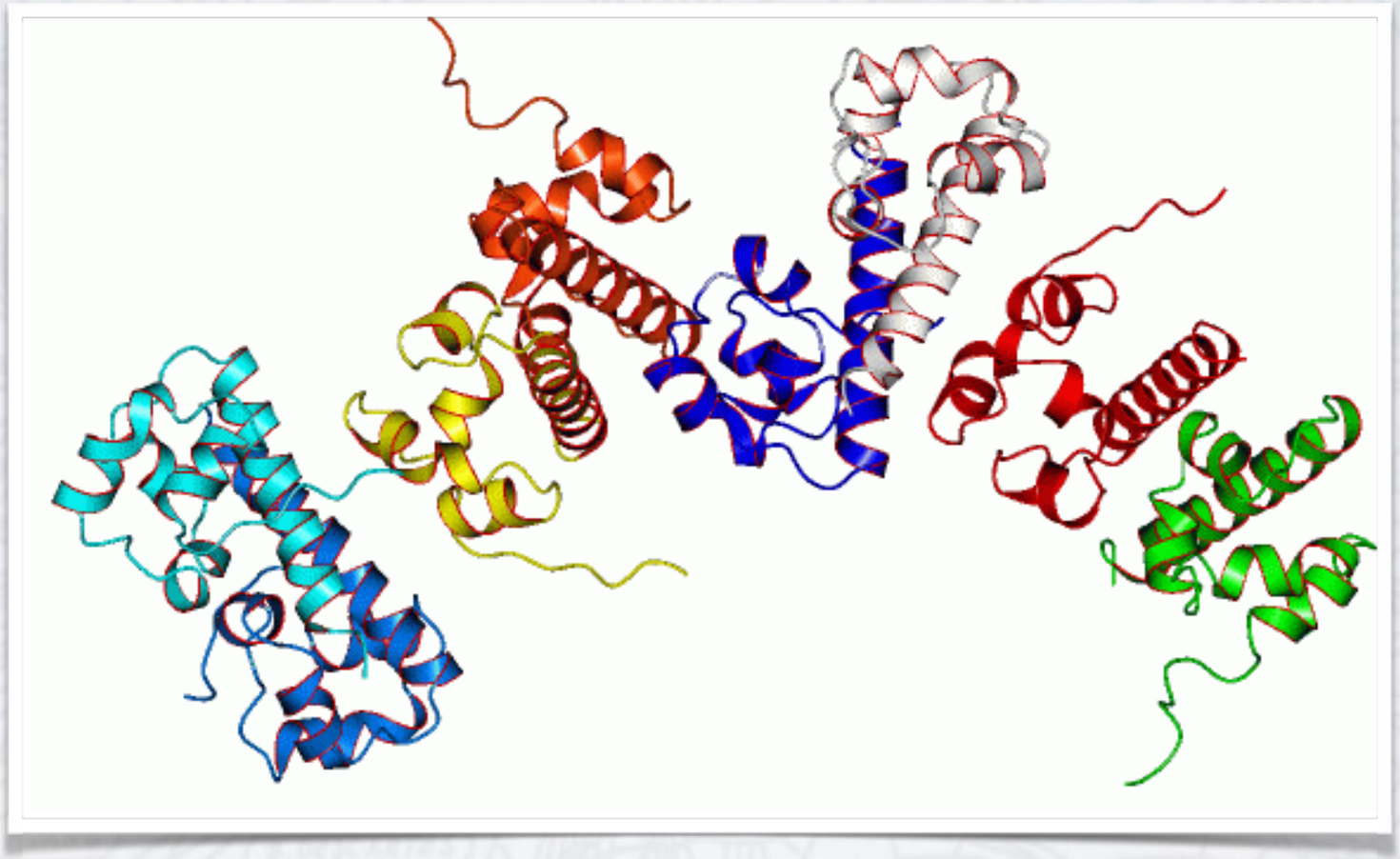
Average path length of the metabolic network of 43 organisms. From Jeong et al., Nature, 407, 651 (2000).



The effect of substrate removal on the metabolic network of E. coli. M=60 corresponds to the ~8% of the network metabolites. From Jeong et al., Nature, 407, 651 (2000).

GENETIC, PROTEIN AND METABOLIC NETWORKS

Protein-protein interaction networks reflect physical or chemical interactions between proteins:

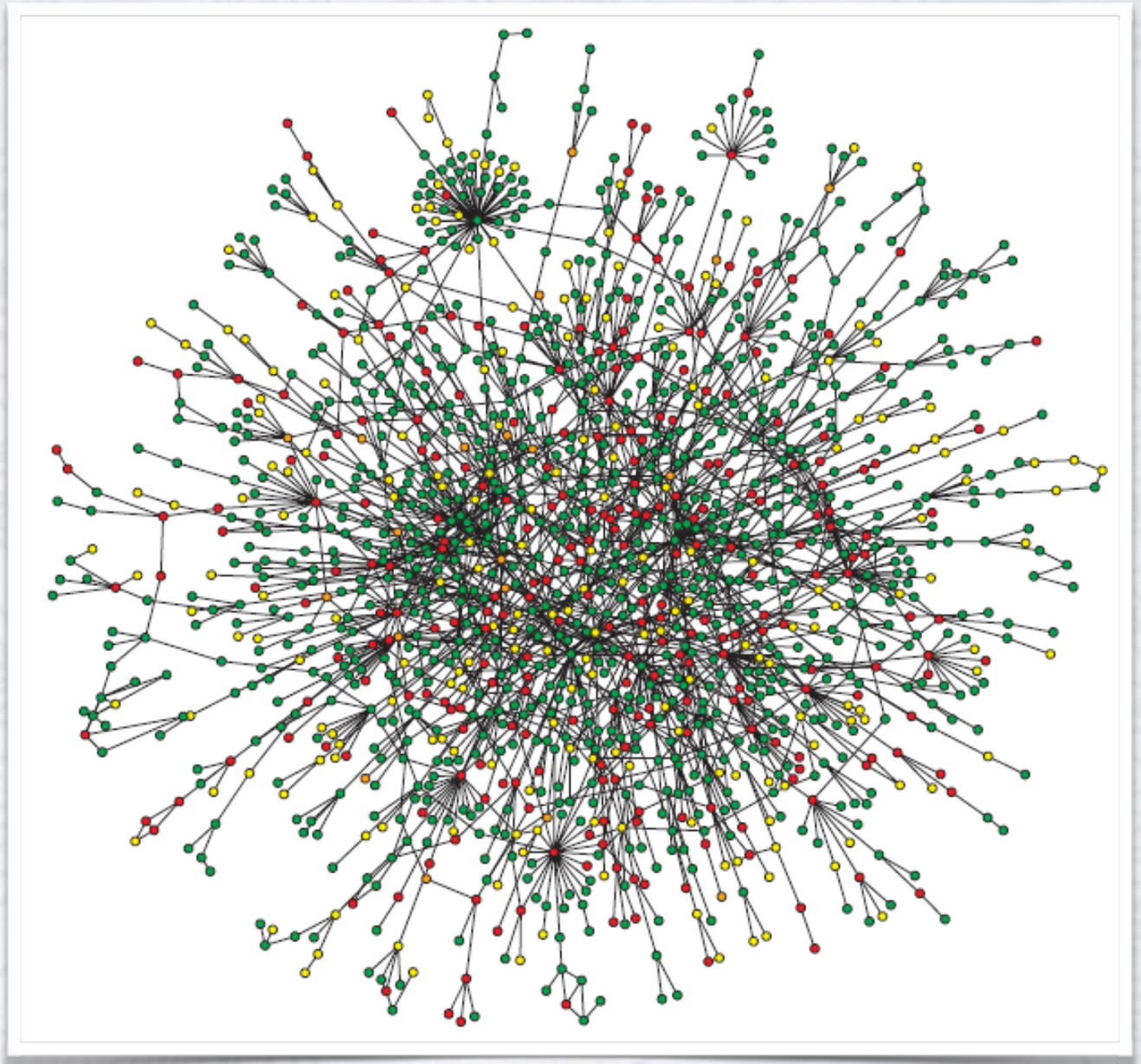


It is estimated that even simple single-celled organisms such as yeast have their roughly 6000 proteins interacting by at least 3 interactions per protein, i.e. a total of 20,000 interactions or more. By extrapolation, there may be on the order of ~100,000 interactions in the human body.

GENETIC, PROTEIN AND METABOLIC NETWORKS

Protein-protein (bidirectional) interactions lead to complex networks (I know you are not surprised anymore…):

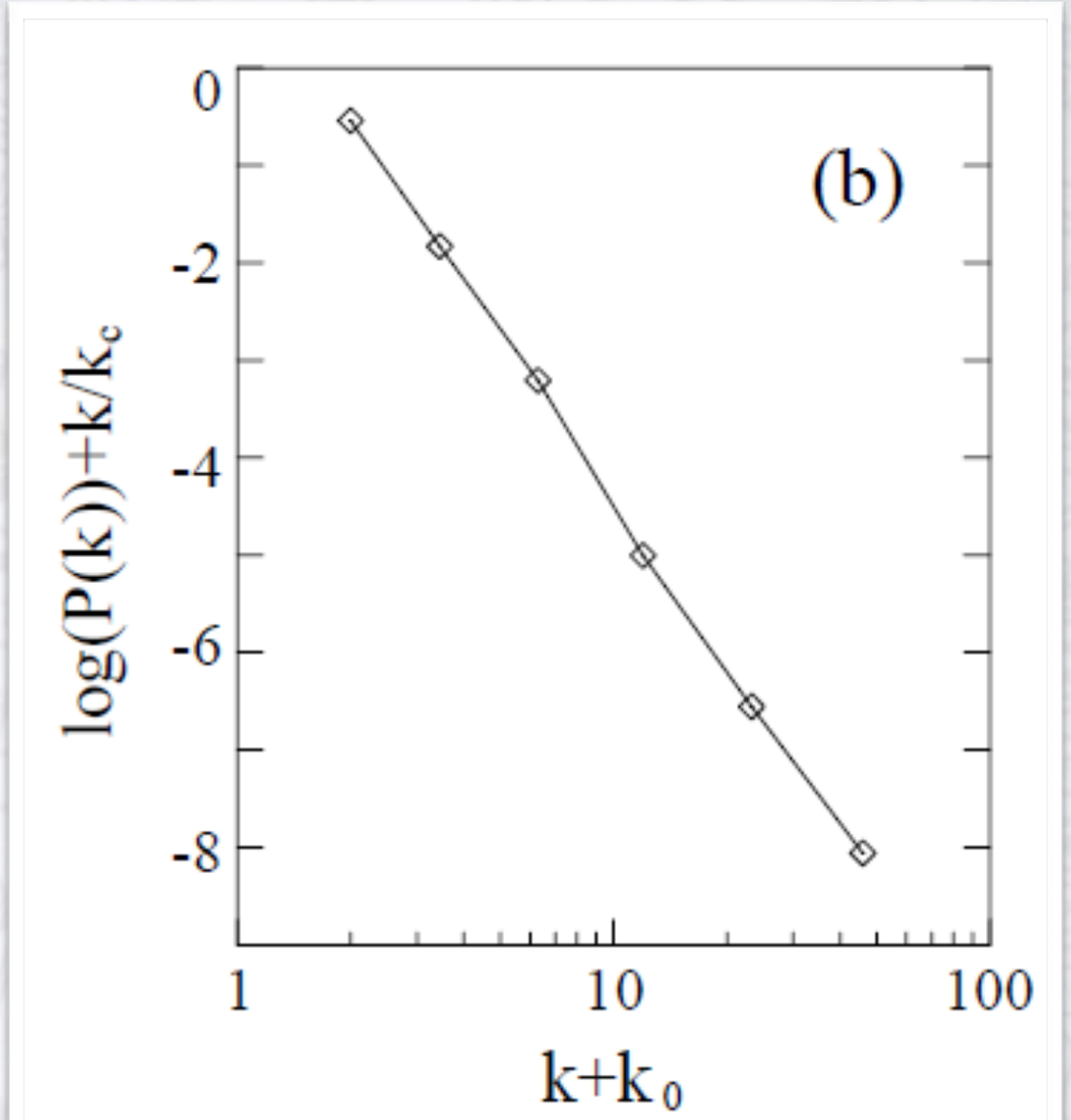
Protein-protein interaction in the yeast S. Cerevisiae, (N=1870 and M=2240). From Jeong et al., Nature, 411, 41 (2001). The colour of a node signifies the phenotypic effect of removing the corresponding protein (red, lethal; green, non-lethal; orange, slow growth; yellow, unknown).



GENETIC, PROTEIN AND METABOLIC NETWORKS

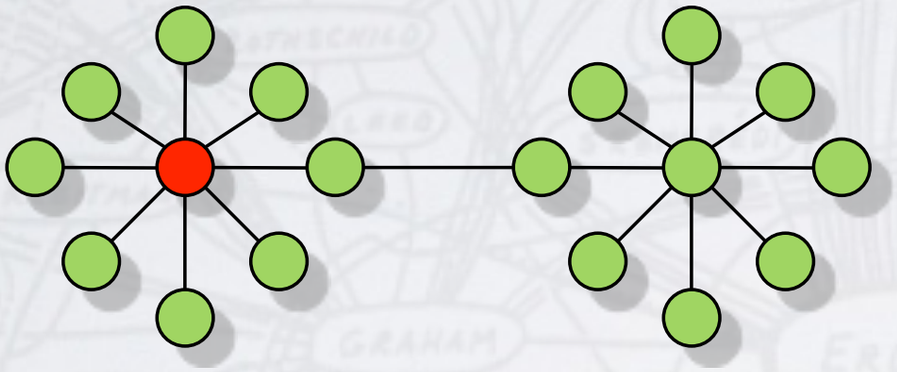
Protein-protein interaction networks are typically scale-free with an exponential cut-off:

Figure: Probability distribution of the protein-protein interaction in the yeast S. cerevisiae, (N=1870 and M=2240). The distribution is scale-free with an exponential cut-off (around k_c~20). From Jeong et al., Nature, 411, 41 (2001).



GENETIC, PROTEIN AND METABOLIC NETWORKS

Protein-protein networks are dissasortative:



- Interestingly, dissasortative structures are robust against failures of the hubs due to the reduced propagation to the neighbors.

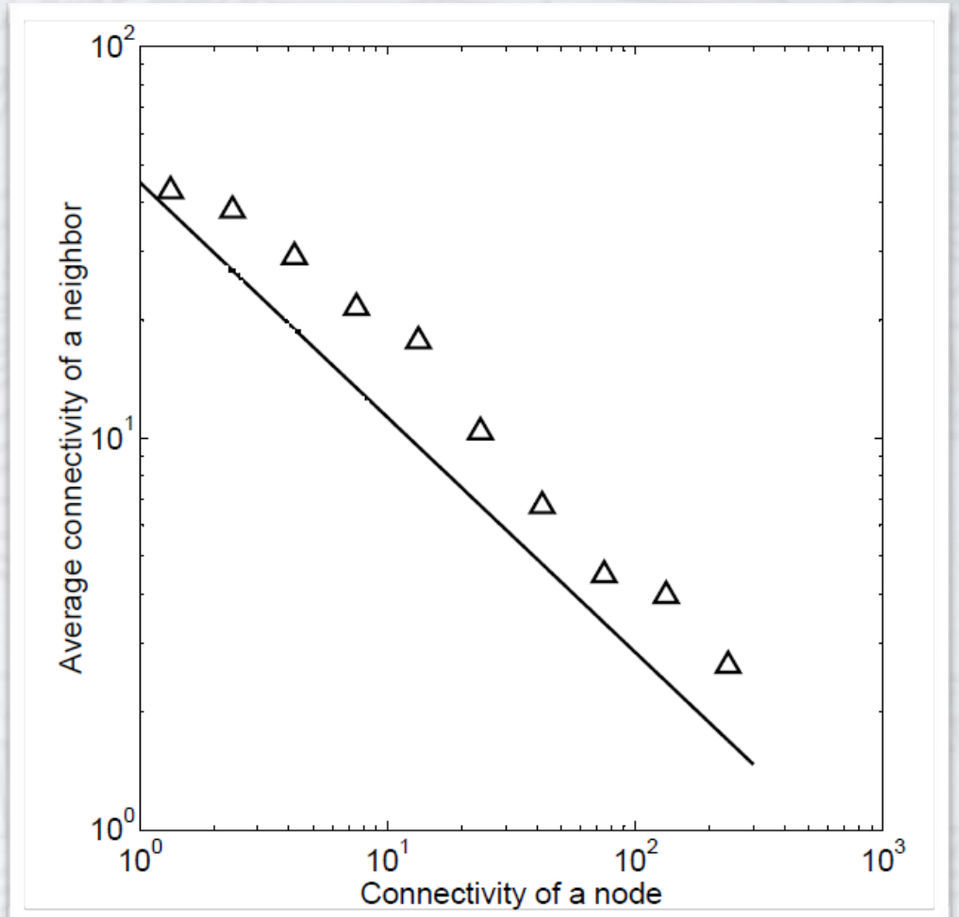


Figure: Distribution of the average neighbor connectivity for the yeast protein-protein interaction network. Here, N=3278 and M= 4549. From Maslov et al., Science., 296, 910 (2002).

NEURON AND BRAIN NETWORKS

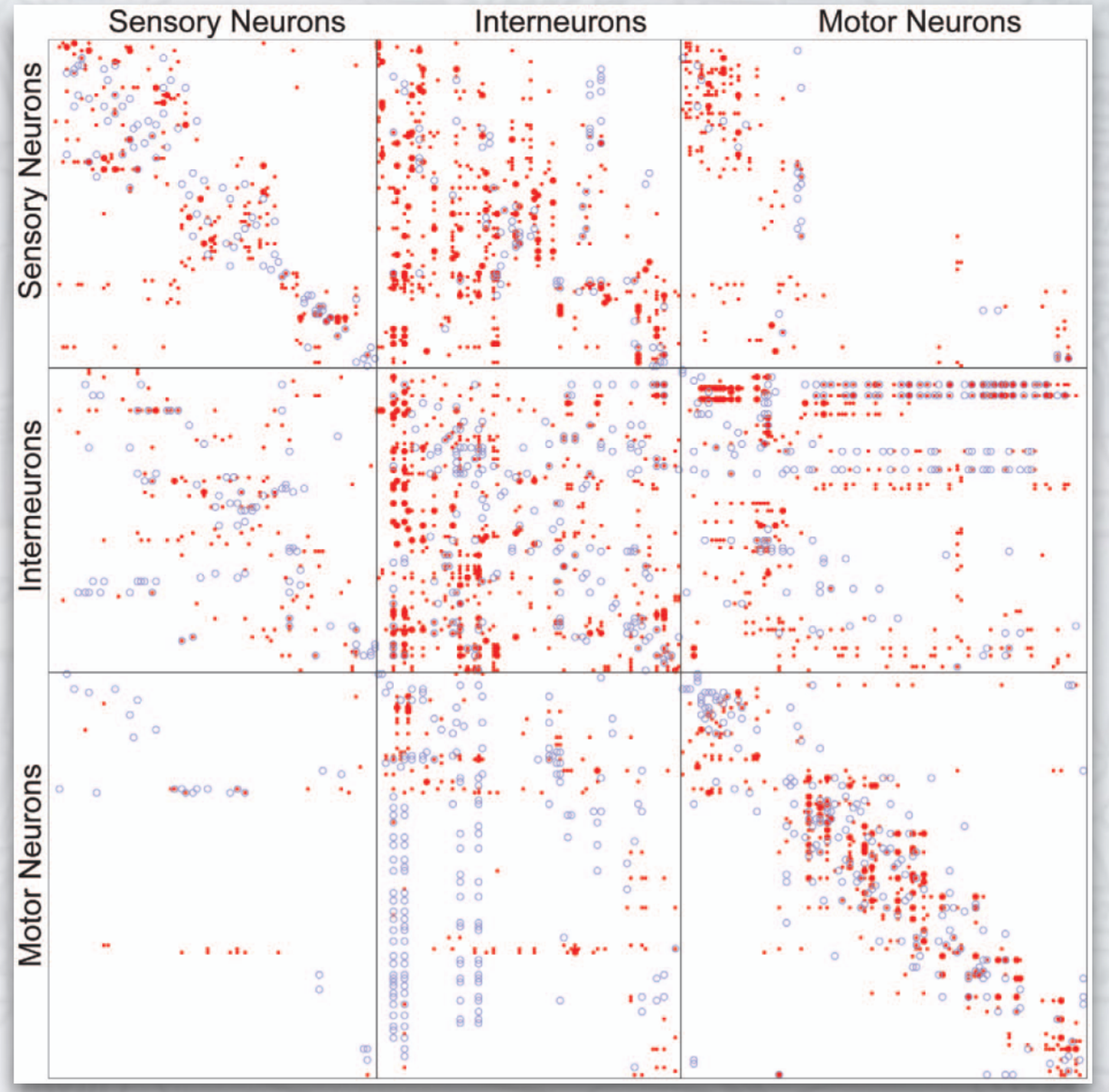
Networks of neurons:

- C. Elegans: It is the only living system that has been fully mapped. It has 302 neurons and average degree $\langle k \rangle \approx 29$.

- It has low shortest path and high clustering: it is a **small-world** network.

- Existence of **network motifs**.

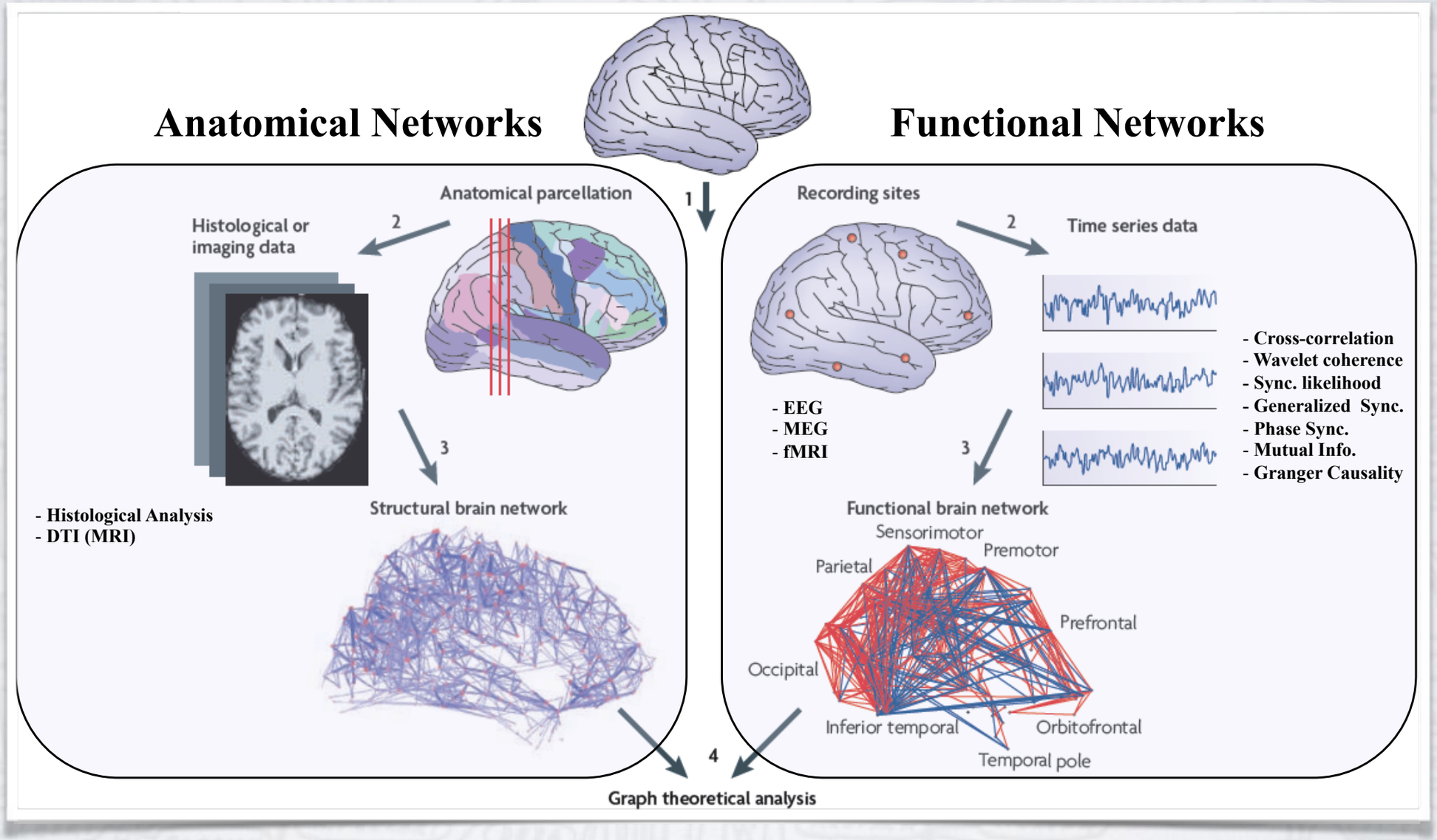
- The tail of the distribution of degrees p(k) is **power-law**.



Gap junctions connections and chemical synapses of C. Elegans neurons. From Varshney, PLoS Comp. Biol, 7, 1001066 (2011)

NEURON AND BRAIN NETWORKS

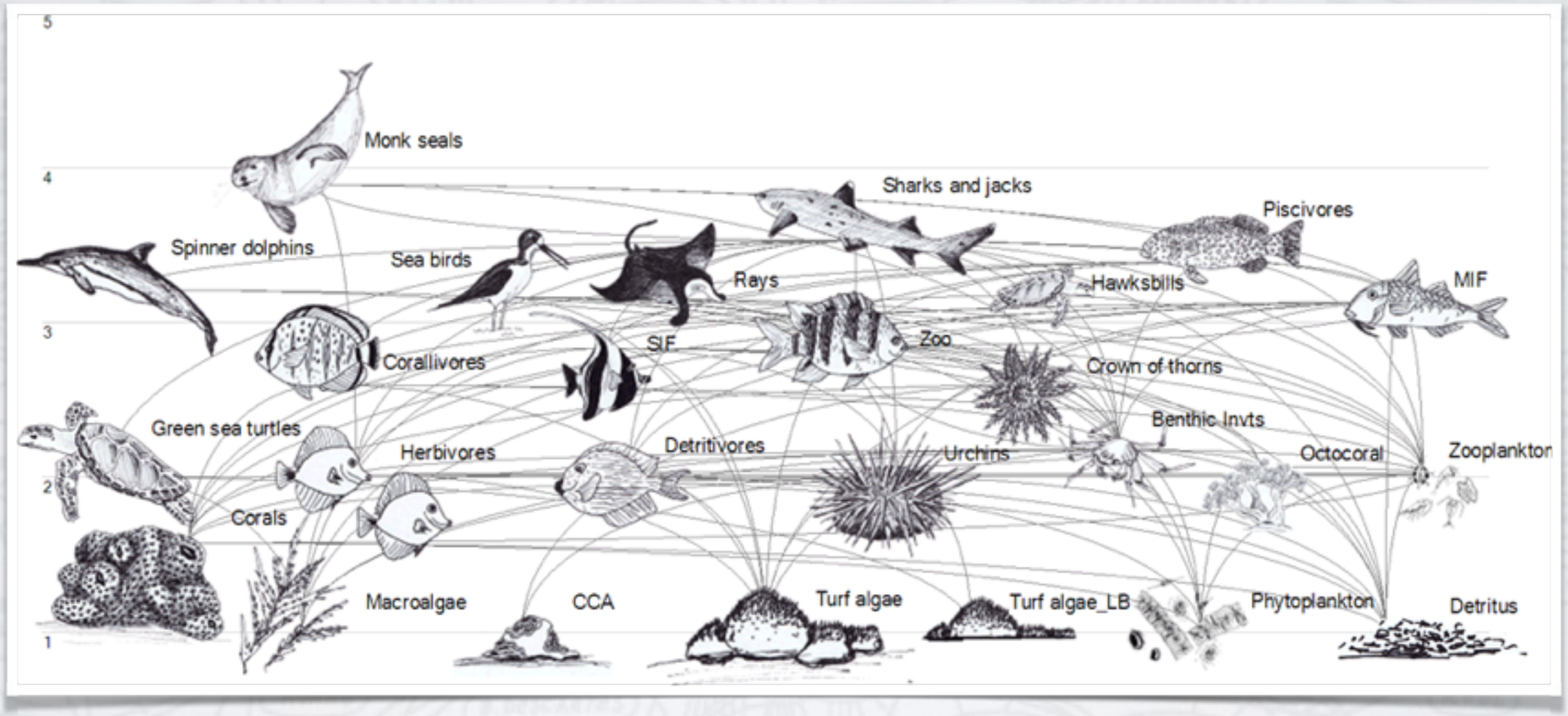
Let's go to higher spatial scales: Brain Networks



From Bullmore & Sporns, Nature Rev. 10, 186 (2009)

ECOSYSTEMS & FOOD WEBS
(INTERACTION BETWEEN NON-HUMAN ANIMALS)

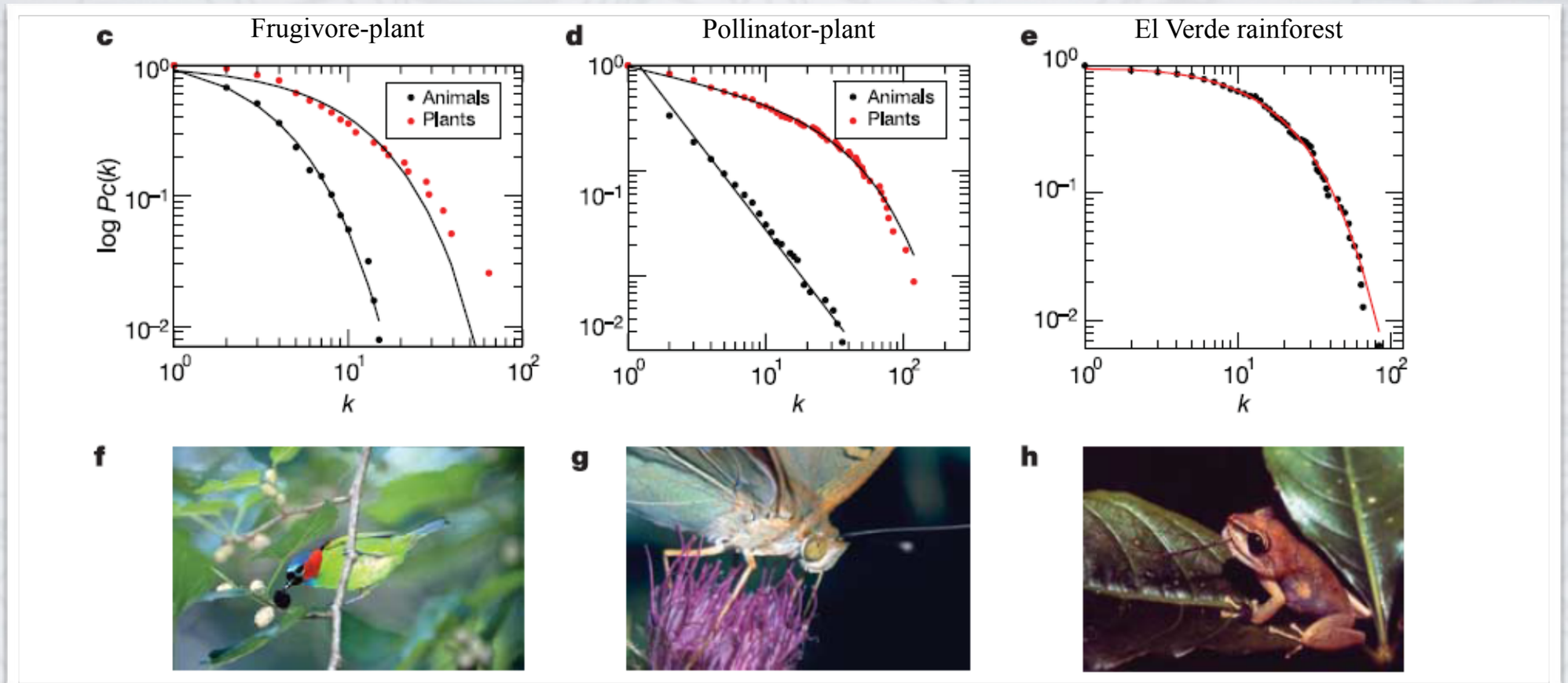
Ecosystems are networks:



Example of trophic interactions within a marine ecosystem.

ECOSYSTEMS & FOOD WEBS
(INTERACTION BETWEEN NON-HUMAN ANIMALS)

Food Webs = Trophic interactions



An exponential

$P(k) = e^{-k/3.998}$

Pl truncated power law

$P(k) = k^{-0.013} e^{-k/11.22}$

A power law

$P(k) = k^{-1.512}$

Pl truncated power law

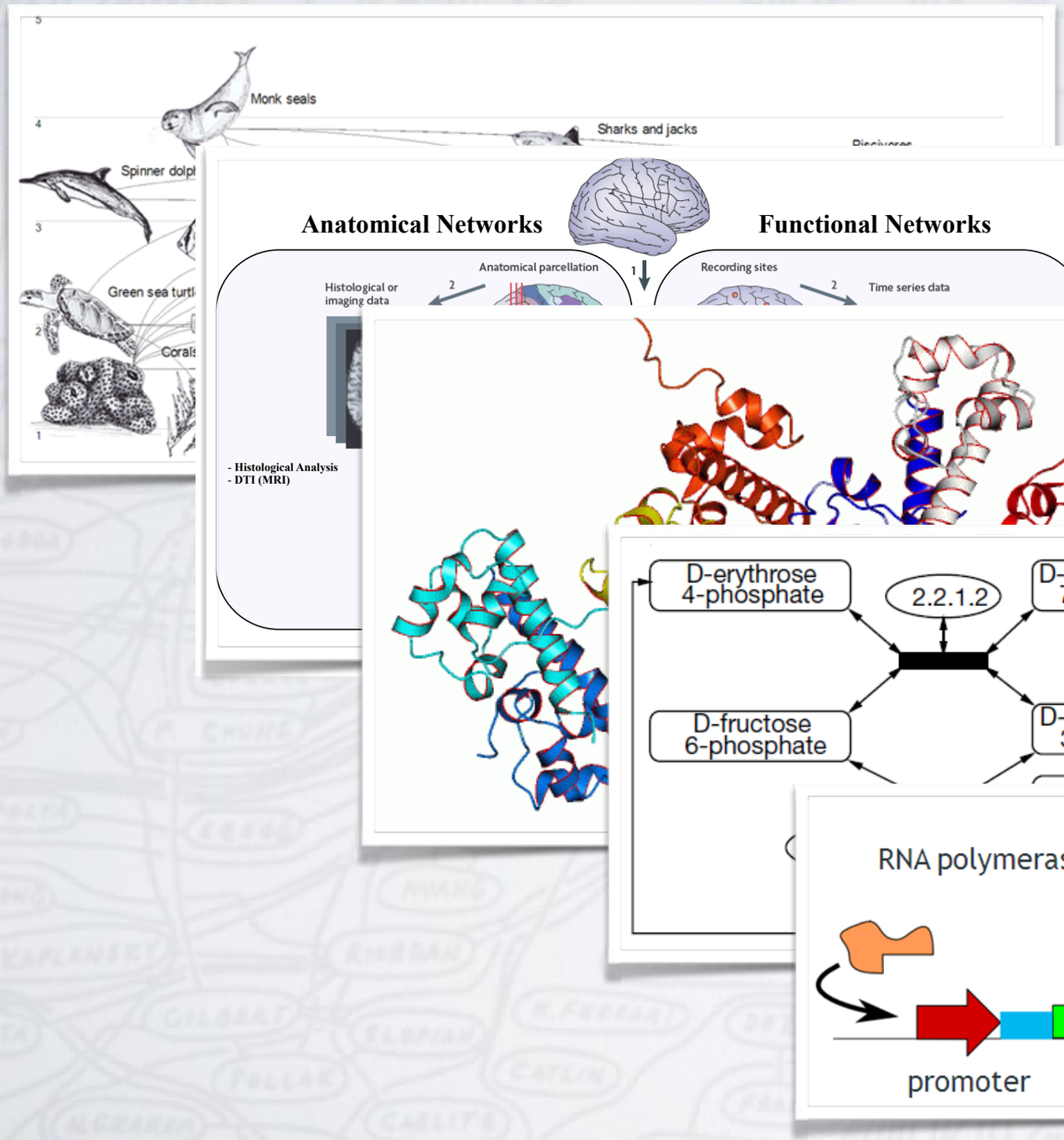
$P(k) = k^{-0.2822} e^{-k/42.55}$

exponential

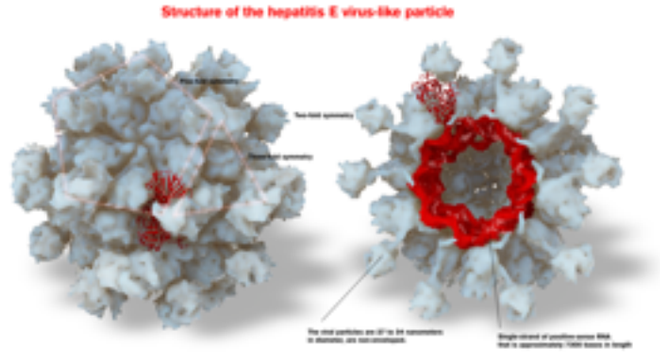
$P(k) = e^{-k/8.861}$

Montoya, J, S L Pimm, R V Sole Nature, 442 (2006)

ECOSYSTEMS & FOOD WEBS
(INTERACTION BETWEEN NON-HUMAN ANIMALS)



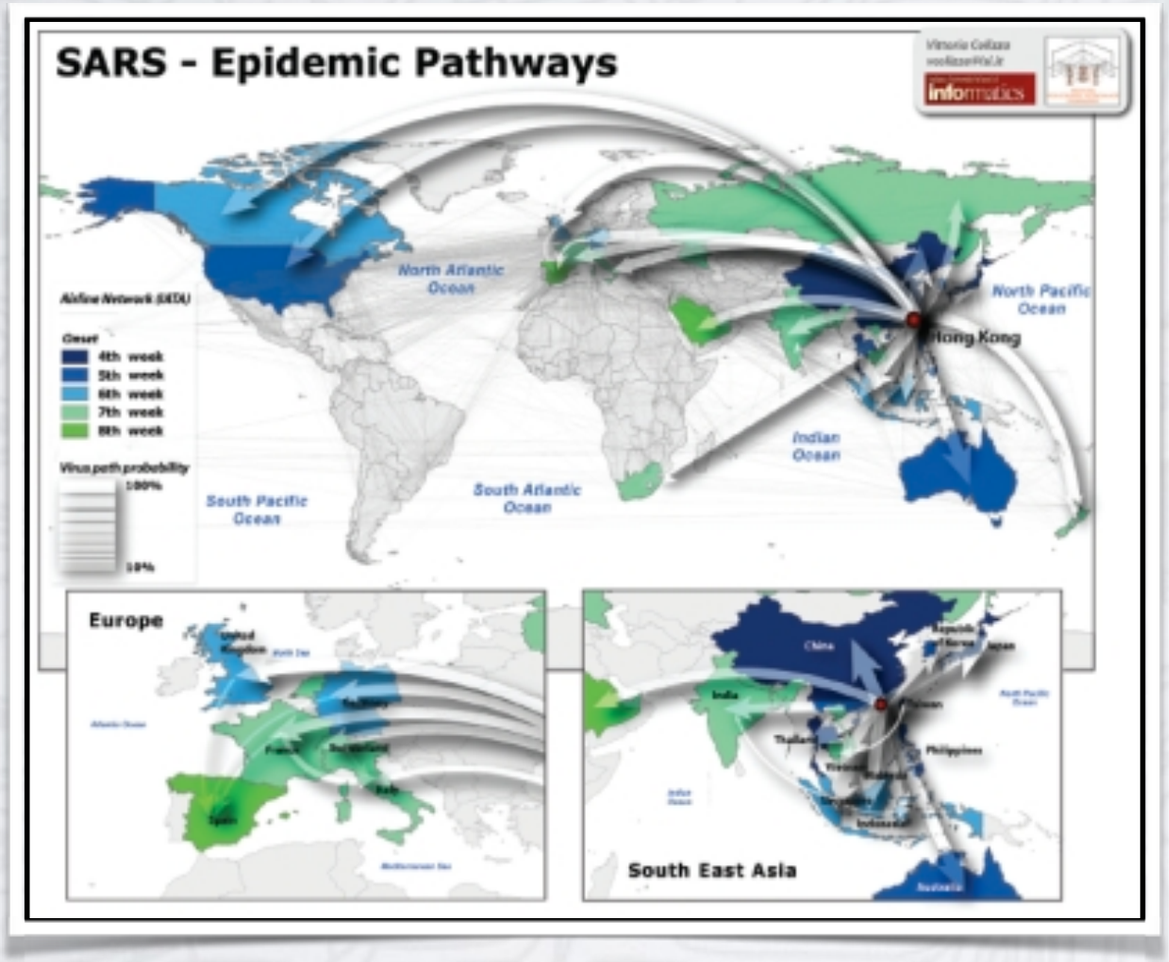
RNA Networks

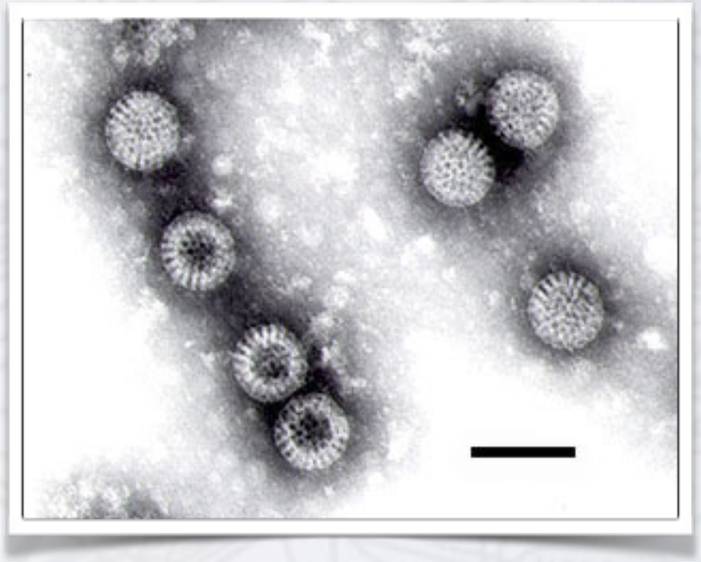


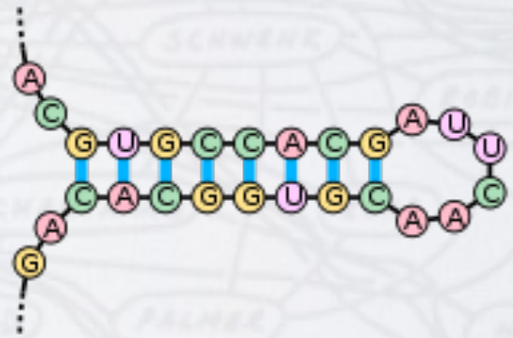
(II-III)

WHAT IS A RNA NEUTRAL NETWORK?

(example) A RNA virus is a virus that has ribonucleic acid (RNA) as its genetic material. Some examples are SARS, influenza and hepatitis C.





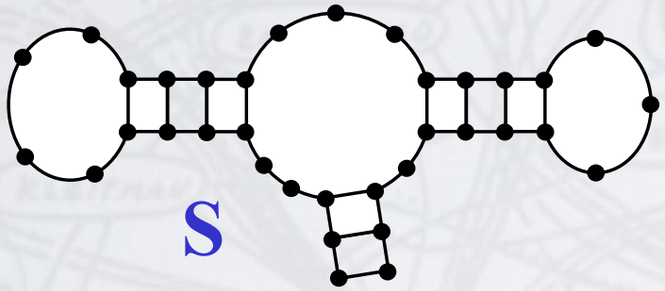


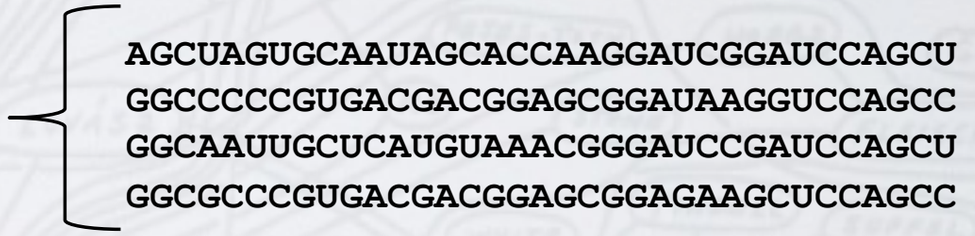
G≡C - 3 Kcal/mol
A=U - 2 Kcal/mol
G-U - 1 Kcal/mol

A: adenine (A)
C: cytosine (C)
G: guanine (G)
U: uracil (U) (instead of thymine)

WHAT IS A RNA NEUTRAL NETWORK?

There exists a huge **degeneracy** between sequence (genotype) and function (phenotype):





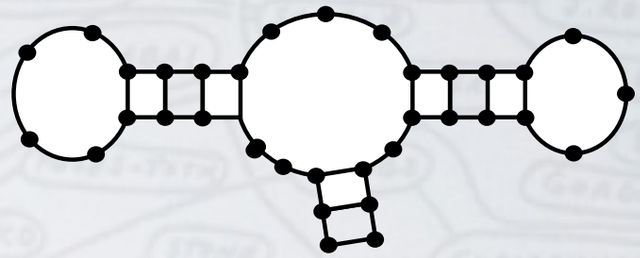
```
AGCUAGUGCAAUAGCACCAAGGAUCGGAUCCAGCU
GGCCCCCGUGACGACGGAGCGGAUAAGGUCCAGCC
GGCAAUUGCUCAUGUAAACGGGAUCCGAUCCAGCU
GGCGCCCGUGACGACGGAGCGGAGAAGCUCCAGCC
```

A: adenine (A)
C: cytosine (C)
G: guanine (G)
U: uracil (U) (instead of thymine)

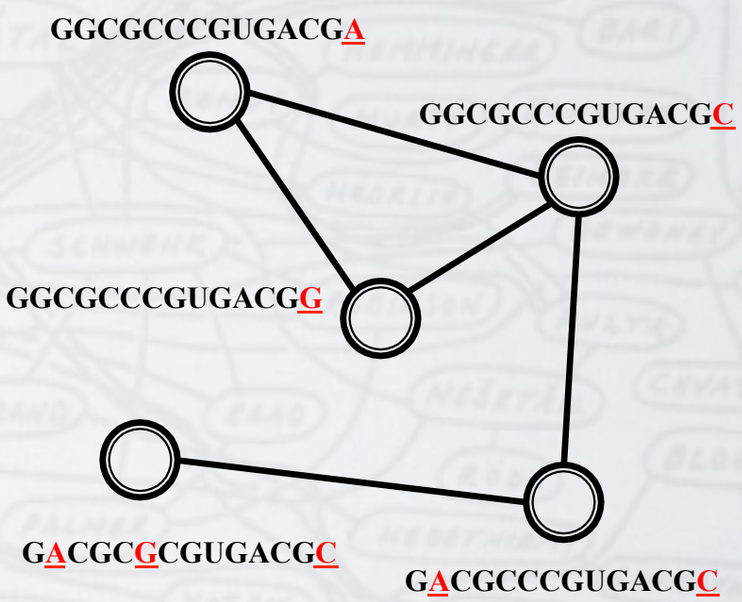
WHAT IS A RNA NEUTRAL NETWORK?

Construction of a RNA neutral network:

- We choose a secondary structure S.



- A node corresponds to a sequence that has S as a m.f.e. structure.
- A link is drawn between two nodes if they are at a Hamming distance of one.
- A sequence of length *l* is linked to at most *3l* other nodes and the maximum size of such network is 4^l (since there are 4 bases).



WHAT IS A RNA NEUTRAL NETWORK?

RNA "real" neutral network of length 12:

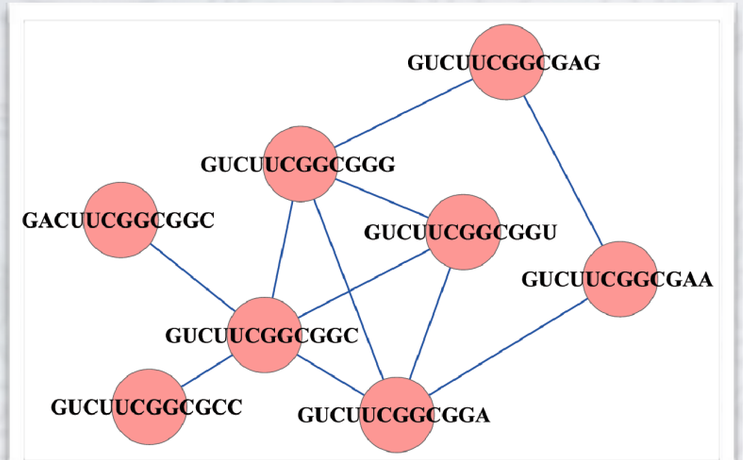
- Real and complete neutral networks can be obtained through exhaustive enumeration and folding of the space of sequences. For length *l=12* there are 4^{12}=16.777.216 sequences.

- "Real" RNA neutral networks can be obtained computationally with the *Vienna package*, which computes the folding energy of all possible secondary structures.

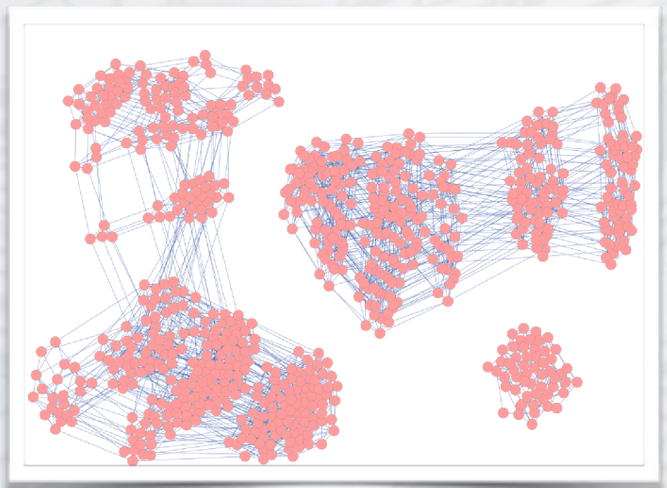
- For *l=12* we obtain 57 different neutral networks (with 44.000 sequences per structure on average).

WHAT IS A RNA NEUTRAL NETWORK?

Sequences of l=12:



(example) 46th rank



Structures and neutral networks for $n=12$

rank	frequency	subnetw.	structure	rank	frequency	subnetw.	structure
1	218567	16	(((.....)))..	30	23260	8	...(((...)))
2	183335	10	.(((.....))).	31	15350	6	..((......))
3	161765	26	(((.....))).	32	11365	7	...((.....))
4	152393	9	((.....)))....	33	6940	3	......(....)
5	152221	15	..(((.....)))	34	3638	28	((.(....))).
6	121861	8	...((.....)).	35	3519	27	(((.....).)).
7	117253	21	((((.....))))	36	2963	39	((.(.....).))
8	113896	8	.((.....))...	37	2244	12	(.((....))).
9	110842	22	.(((.....)))	38	2208	1	((.........))
10	105538	8	..((.....))..	39	1520	16	.(.(.....).).
11	93866	7	((.....))...	40	1379	15	(.(.....).)..
12	76439	5	..((......)).	41	1368	2	.((.........))
13	74626	12	(((.......)))	42	1308	22	.((.(....)))
14	71904	5	((.......))..	43	1189	34	(..(.....)..)
15	70375	5	.((.....))...	44	1140	23	.(((.....).))
16	61792	7	.((.......)).	45	860	3	..(.(.....)).
17	61613	27	(((((...))))).	46	800	3	(.(.....))...
18	46510	10	....((.....))	47	713	3	.(.(.....))..
19	45288	42	.((((...))))	48	665	15	(.((.....)).)
20	41618	18	..(((...))).	49	414	11	..(.(.....).)
21	41092	15	(((...)))...	50	314	3	(..(...)..).
22	39740	19	.(((...)))..	51	240	3	(.((...)).).
23	37472	5	((........)).	52	220	4	((((...)).))
24	31848	3	(....).....	53	211	4	((.((...))))
25	31498	3	.....(....).	54	165	4	..((.....).).
26	27522	3	....(.....)..	55	153	4	.((.....).)..
27	27312	3	.(....).....	56	107	6	(((....)).).
28	25053	3	..(....)....	57	54	1	(.(.....).).
29	24366	3	...(....)...	-	14325304	-	.....

Additional properties of the $l=12$ RNA neutral networks space can be found in [10].
doi:10.1371/journal.pone.0026324.t001

TOPOLOGICAL PROPERTIES OF RNA NEUTRAL NETWORKS

Size ranking:

- **Base pairs are indicated by parenthesis ()**
- **Unpaired bases are indicated by dots .**

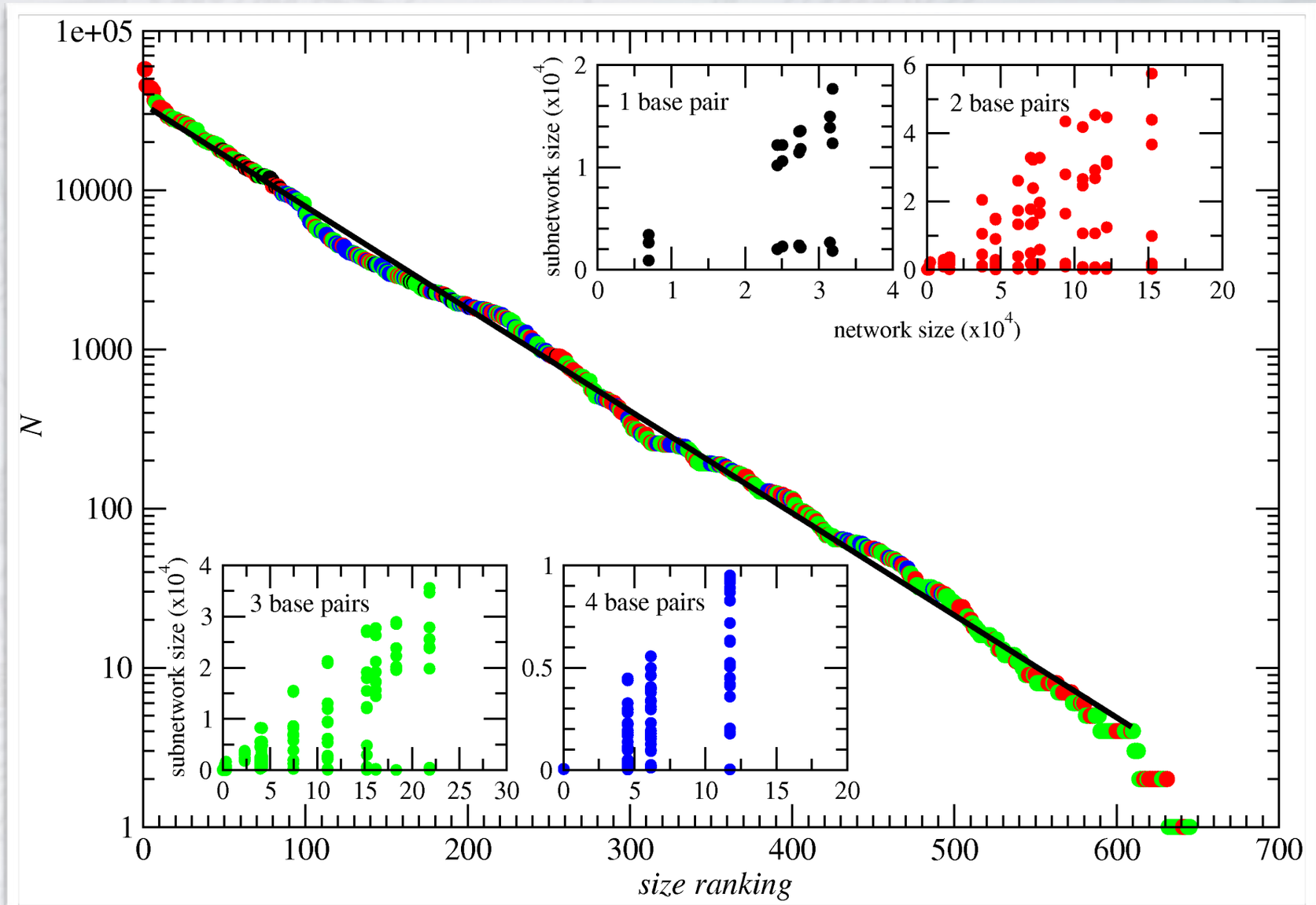


Figure 2. Subnetworks size ranking. In linear-logarithmic scale, ranking distribution of subnetwork sizes. Colors indicate the number of base pairs L_p in the secondary structure: one pair (black), two pairs (red), three pairs (green) and four pairs (blue). The solid line corresponds to an exponential fitting. Insets show for each group of structures (with the same L_p) the size of the subnetworks (in the *y*-axis) that belong to the same neutral network as a function of the corresponding neutral network size (in the *x*-axis). Note changes of scale in both axes.

TOPOLOGICAL PROPERTIES OF RNA NEUTRAL NETWORKS

Degree Distribution:

$$k_{max} = (b-1)l$$

- with:
- b = 4 (number of different nucleotides)
- l = 12 the sequence length (i.e., kmax = 36)

- Average degree grows with the size:

$$\langle k \rangle \sim 1.79 \ln(N)$$

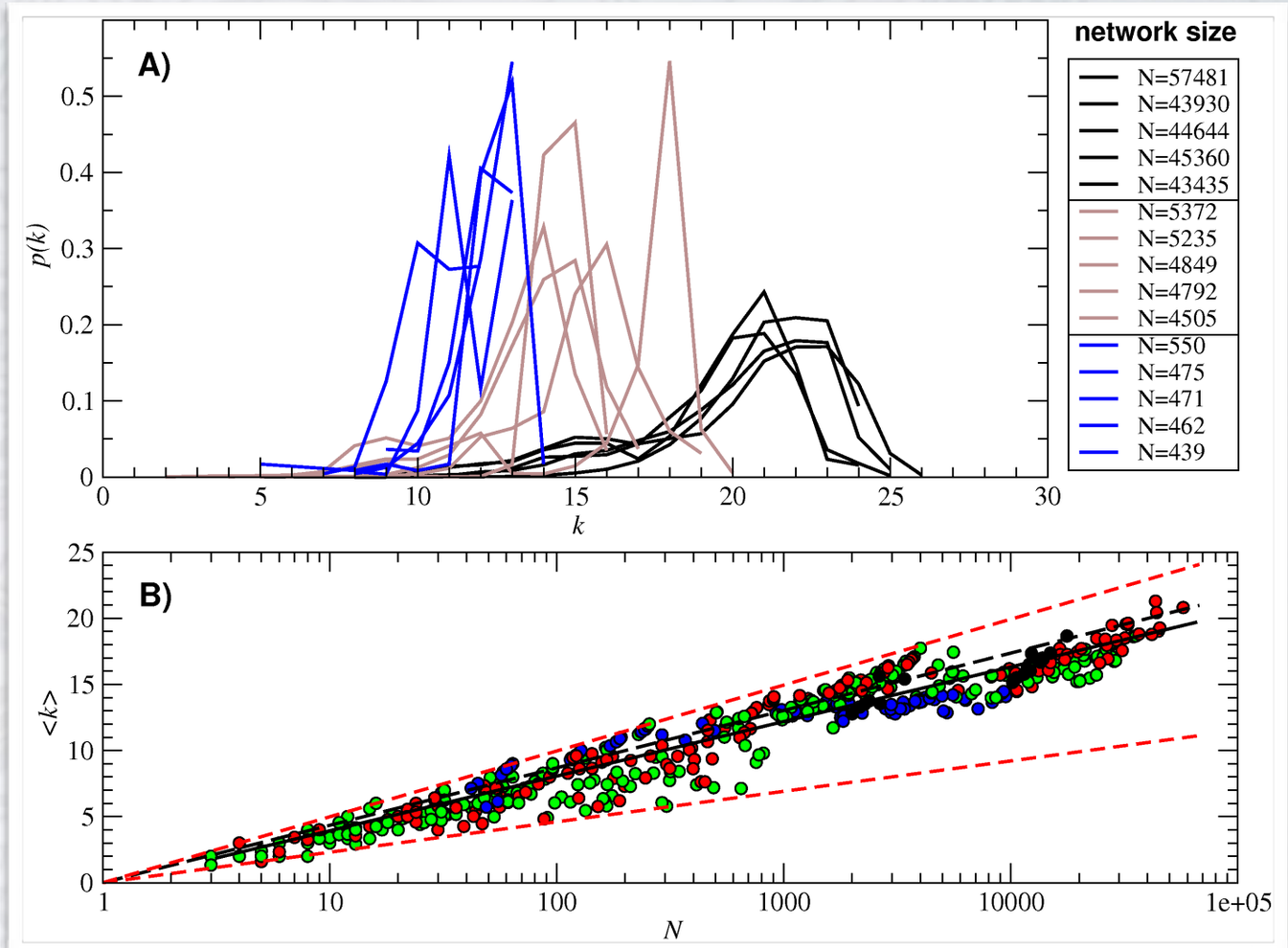


Figure 3. Degree distribution $p(k)$ and average degree $\langle k \rangle$. (A) Degree distribution $p(k)$ of fifteen subnetworks. They are the five largest (black curves), five of intermediate size (brown curves, one order of magnitude smaller) and five small subnetworks (blue curves, two orders of magnitude smaller). (B) Average degree $\langle k \rangle$ as a function of the subnetwork size N. Colors correspond to one (black), two (red), three (green) and four (blue) base pairs in the secondary structure. The solid line corresponds to the numerical fitting $\langle k \rangle \sim 1.79 \ln N$ (note the logarithmic-linear scale). The analytical approximation to $\langle k \rangle$ making use of the values of $\bar{u}$, $\bar{p}$ and α obtained from all the 12-nt folded sequences (and implying $A_S = 0.53$) is plotted in long-dashed black line. The upper and lower bounds to coefficient A_S yield $\langle k \rangle = \ln N$ and $\langle k \rangle = (3/\ln 4) \ln N$ (plotted in short-dashed red lines).

TOPOLOGICAL PROPERTIES OF RNA NEUTRAL NETWORKS

Clustering

- Neutral networks:

$$C_k \propto \frac{n^o\, triangles}{\frac{1}{2}k(k-1)} \approx \frac{3(L-2b)}{\frac{1}{2}k(k-1)} \approx \frac{2}{k}$$

$$C \propto \frac{2}{\bar{k}} \approx \frac{2\ln(4)}{3\ln(N)}$$

- Random networks:

$$C_{RND} \propto \frac{\bar{k}}{N} \approx \frac{3}{\ln(4)}\frac{\ln(N)}{N}$$

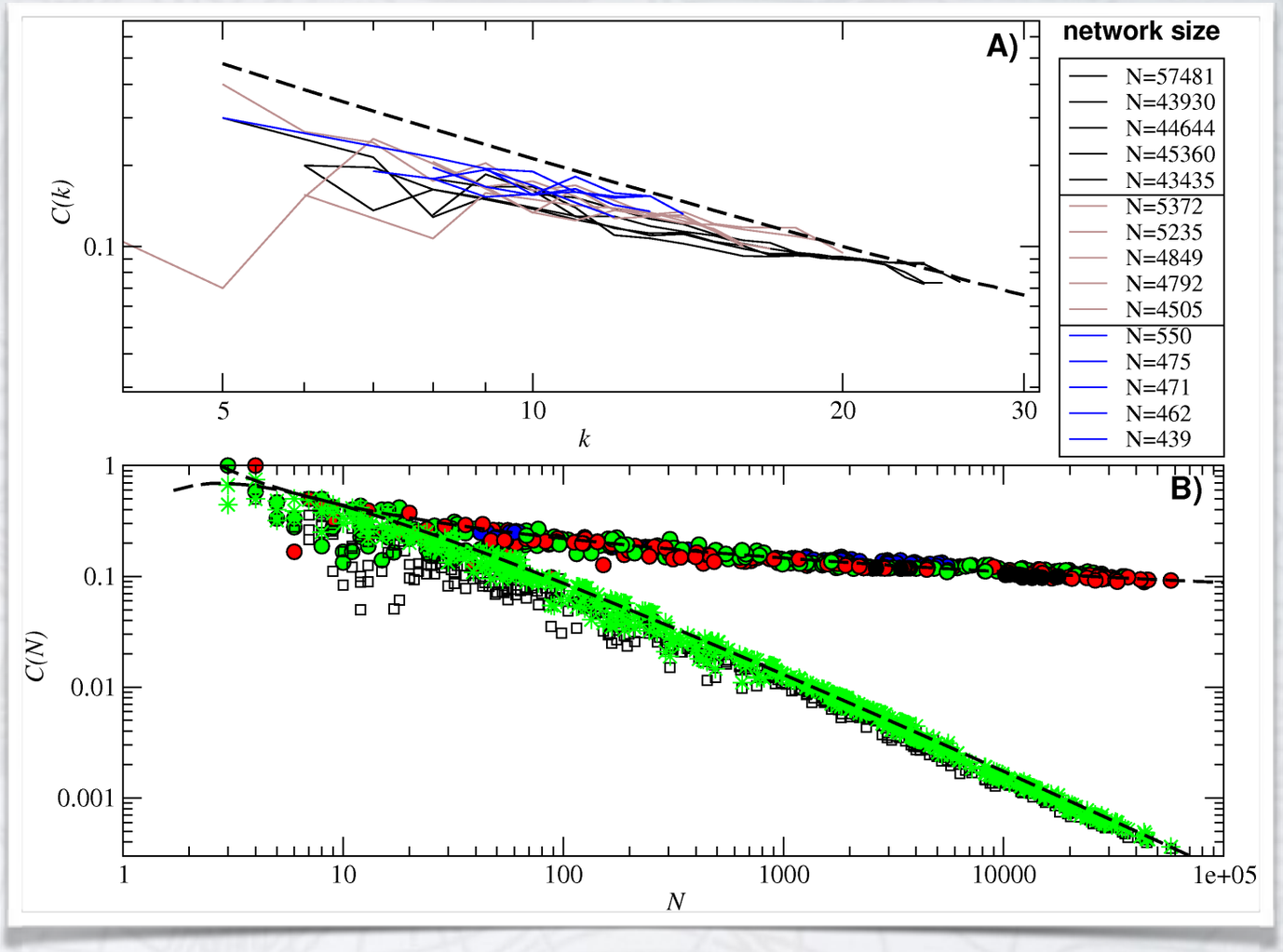


Figure 4. Clustering. (A) Clustering distribution $C(k)$ for the fifteen networks analyzed in Fig. 3. (B) Average clustering $C(N)$ as a function of the subnetwork size N for all folded neutral networks (colored circles), equivalent random networks (black squares) and theoretical predictions with a classical random model ($C(N) \simeq \langle k \rangle N^{-1}$, green stars). Circle colors correspond to the number of base pairs of each subnetwork (see caption of Fig. 3). In both plots (A) and (B), the analytical approximations using the values of $\bar{u}$, $\bar{p}$ and α obtained from all the 12-nt folded sequences are plotted in long-dashed black lines.

TOPOLOGICAL PROPERTIES OF RNA NEUTRAL NETWORKS

Assortativity:

- Yes, they are assortative…

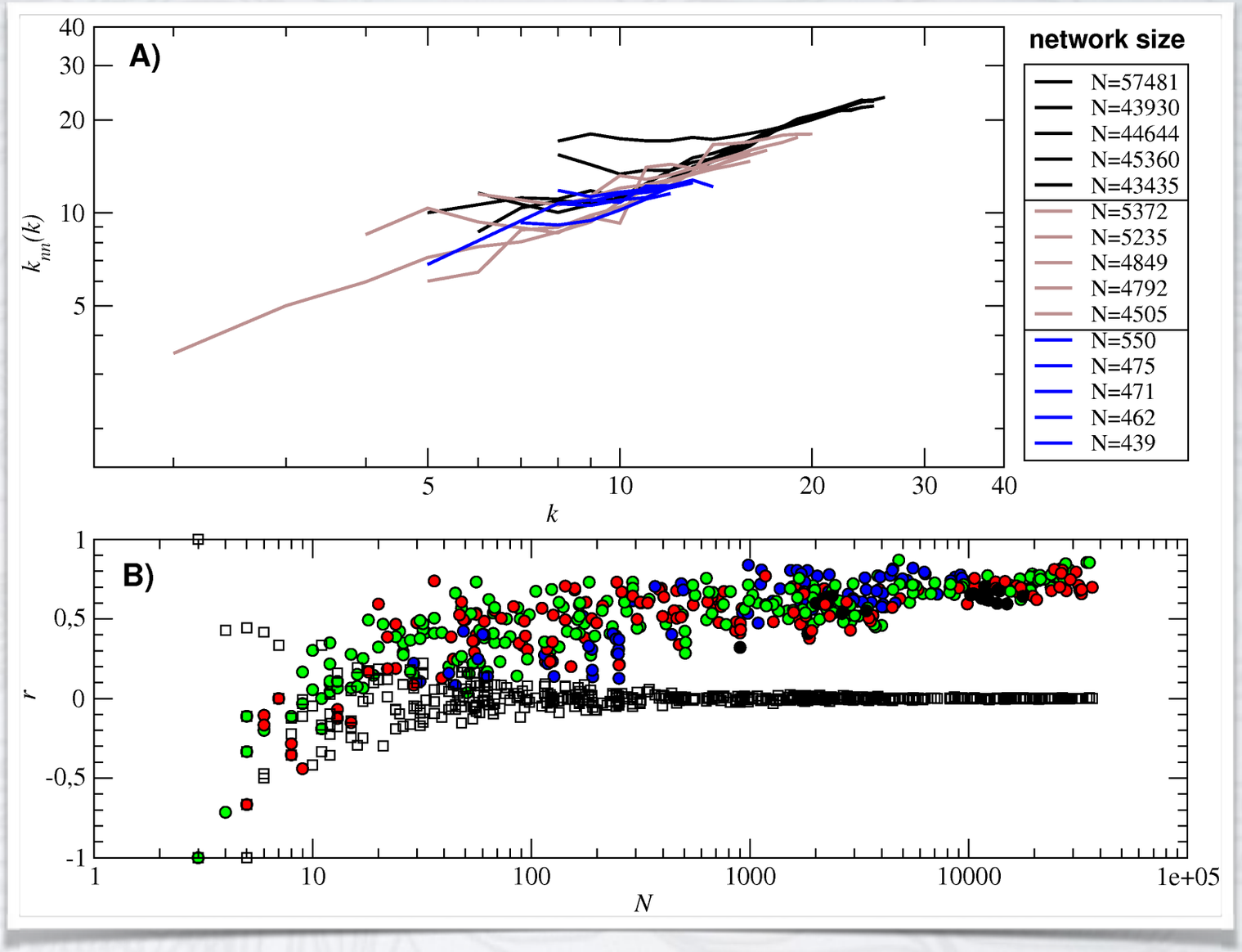


Figure 5. Assortativity. (A) Average nearest neighbors degree $k_{nn}(k)$ as a function of k for fifteen networks of different sizes. (B) Assortativity parameter r as a function of the network size. As in previous figures, colors correspond to the number of base pairs of the subnetwork: one (black), two (red), three (green) and four (blue). The r for equivalent random networks are plotted in black squares.

TOPOLOGICAL PROPERTIES OF RNA NEUTRAL NETWORKS

Point mutations:

- Mutations, i.e. neighbors, appear where bases are unpaired…

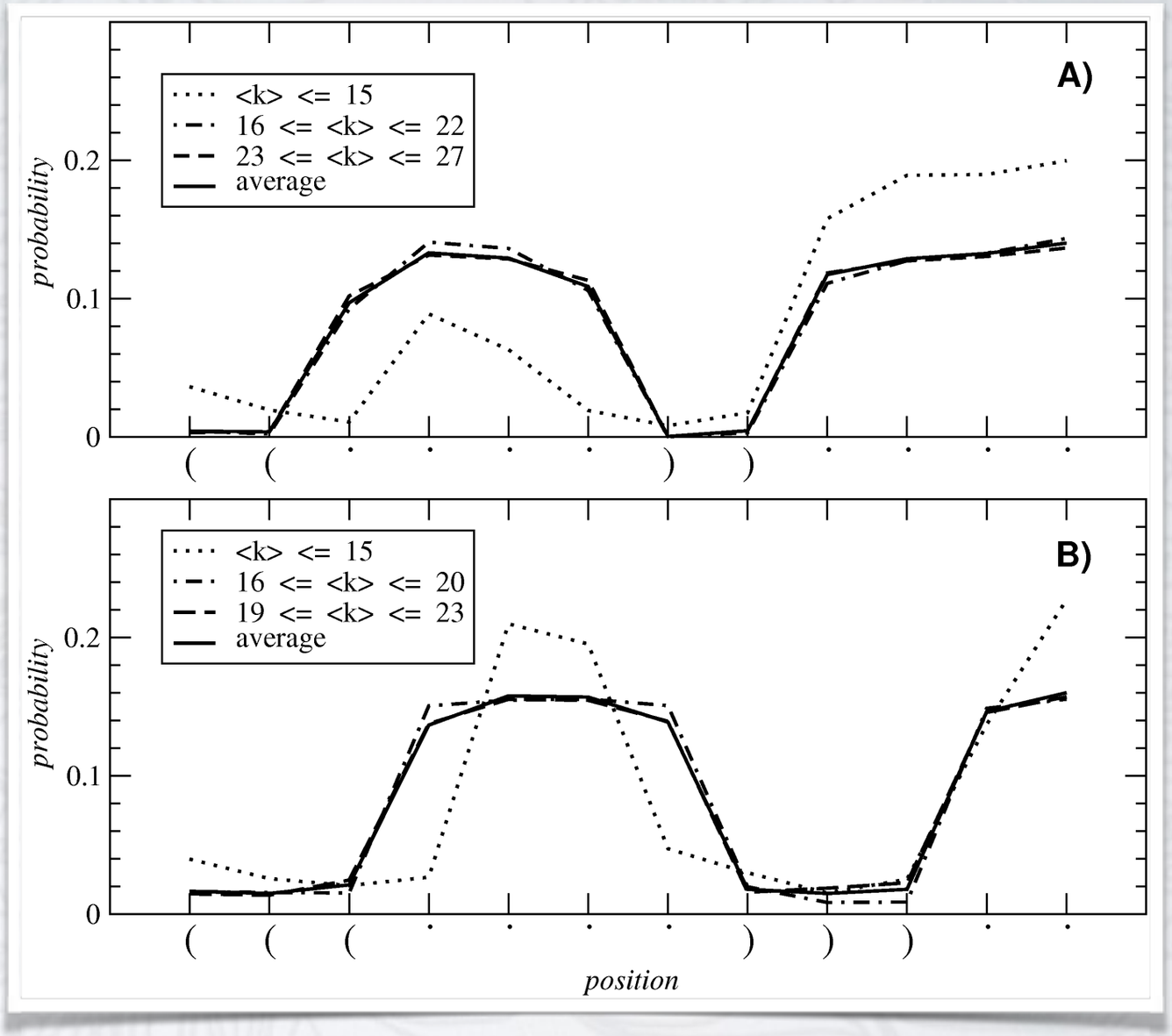


Figure 6. Probability of mutation. Probability of mutation at each position of the sequence for two different secondary structures (see *x*-axis labels of both plots). (A) corresponds to the largest subnetwork $N = 57481$, whose secondary structure is fourth by abundance. (B) corresponds to the largest subnetwork $N = 35594$ of the most abundant secondary structure. We plot the sequences grouped by degree (dotted, dashed and dashed-dotted lines) together with their averages (solid lines).

TOPOLOGICAL PROPERTIES OF RNA NEUTRAL NETWORKS

Shortest path:

- Shortest path <d> grows with the size:

$$\langle d \rangle \sim 0.63 \ln(N)$$

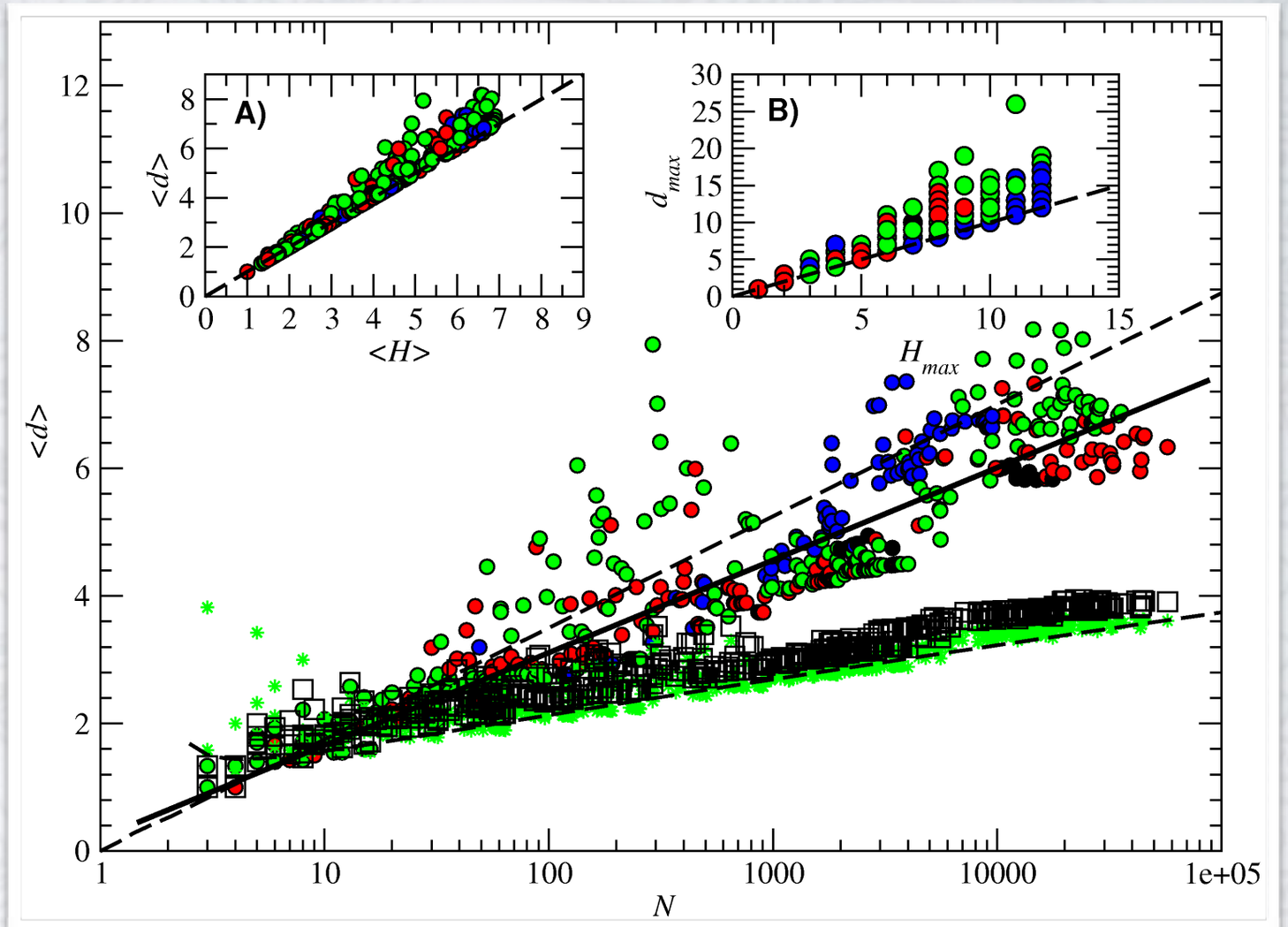


Figure 7. Average shortest path $\langle d \rangle$. Dependence of the average shortest path on the subnetwork size N for all folded neutral networks (colored circles), equivalent random networks (black squares) and theoretical predictions with a classical random model ($\langle d \rangle \sim \ln N / \ln \langle k \rangle$, green stars). Circle colors correspond to the number of base pairs of each subnetwork (see caption of Fig. 3). The numerical fitting is plotted as a solid black line, while the analytical approximations correspond to the long-dashed black lines (for values of α and A_S numerically obtained from the folding of all 12-nt sequences). Inset (A): relation between the average shortest path $\langle d \rangle$ and the average Hamming distance $\langle H \rangle$ of the subnetworks. Inset (B): relation between the longest distance between any pair of nodes of the network d_{max} and the maximum number of different bases between sequences H_{max} (maximum Hamming distance). In the insets, the dashed lines are $\langle d \rangle = \langle H \rangle$ and $d_{max} = H_{max}$, which correspond to the lower bounds of $\langle d \rangle$ and d_{max}, respectively.

TOPOLOGICAL PROPERTIES OF RNA NEUTRAL NETWORKS

Largest eigenvalue:

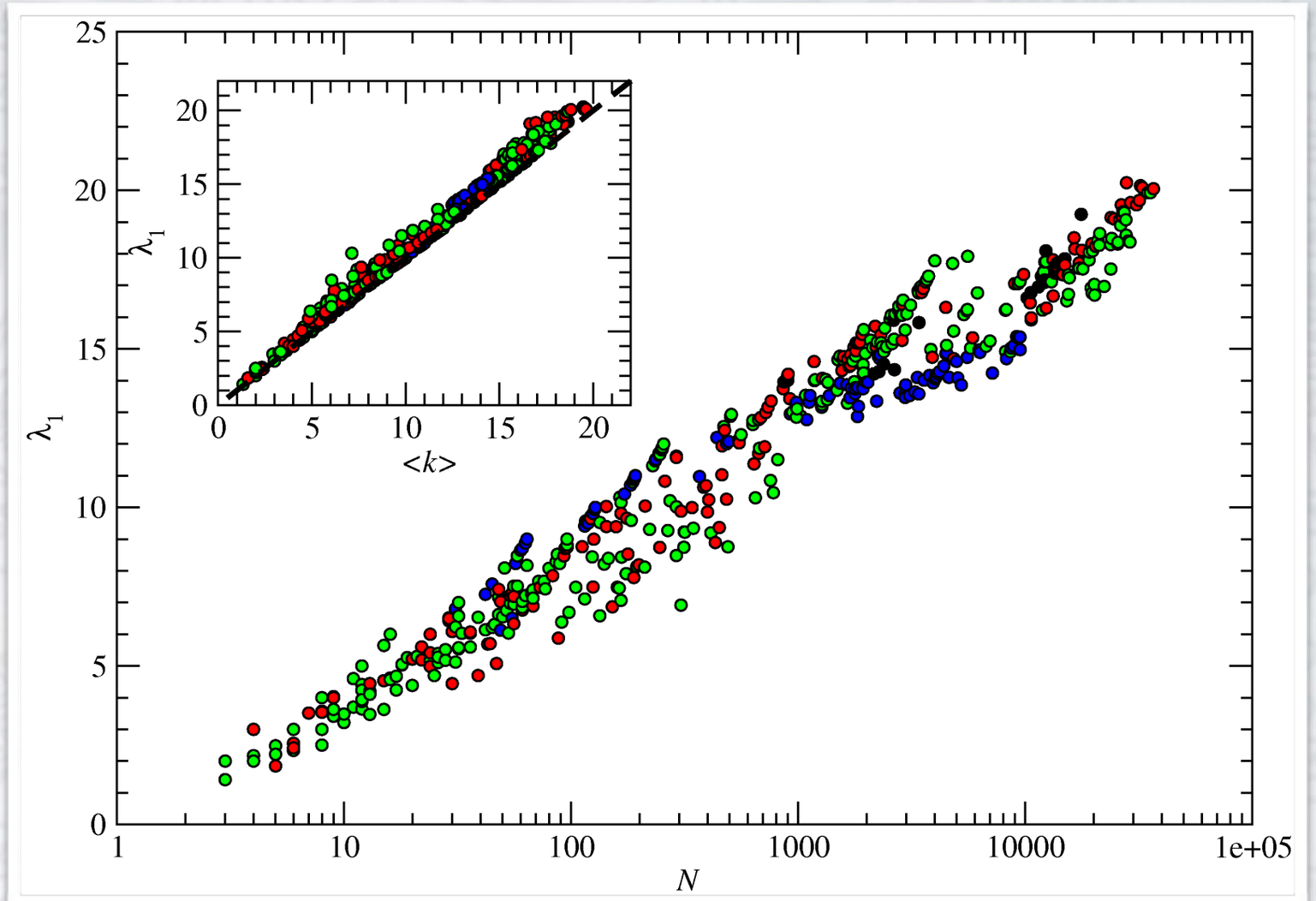


Figure 8. Eigenvector centrality. Largest eigenvalue λ_1 of the adjacency matrix **A** as a function of the network size N. The inset shows the linear relationship between λ_1 and the network average degree $\langle k \rangle$. Solid line in the inset is $\lambda_1 = \langle k \rangle$.

TOPOLOGICAL PROPERTIES OF RNA NEUTRAL NETWORKS

Centrality & Communities:

- Surprisingly, eigenvector centrality is a good indicator of community structure… why?

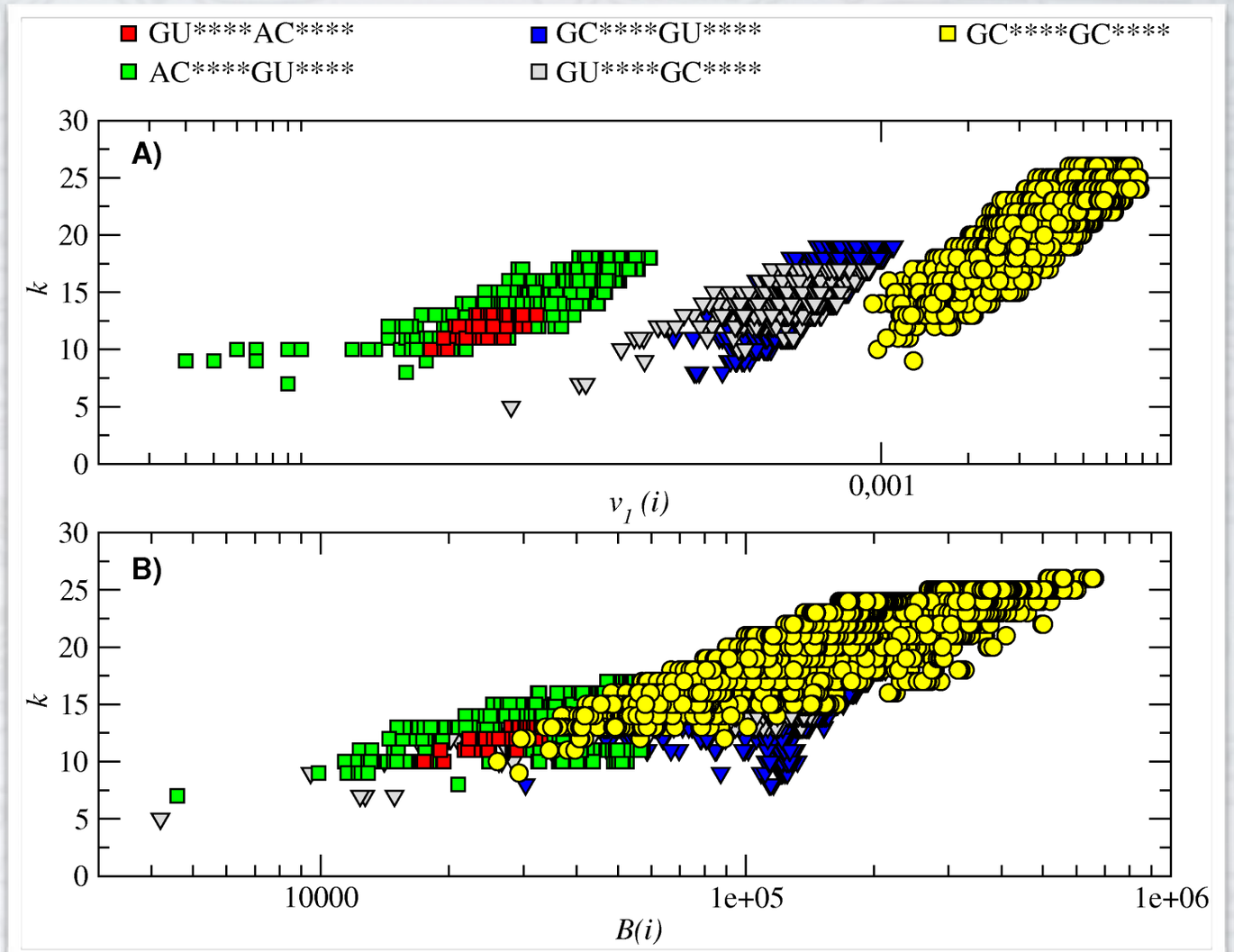


Figure 9. Sequence centrality. Evaluation of the sequence centrality for the largest subnetwork $N = 57481$, whose secondary structure is ((....))..... In (A), degree k_i versus eigenvector centrality $v_1(i)$. In (B), degree k_i versus betweenness centrality $B(i)$. Colors and shapes denote the type of base pairs the sequences have (see Figure's legend). Note the community division created by the eigenvector centrality, which is related to the type of nucleotides participating in the base pair: GC+UA and AU+CG for low eigenvector centrality, GU+CG and GC+UG and for intermediate $v_1(i)$ and GC+CG for high $v_1(i)$.

TOPOLOGICAL PROPERTIES OF RNA NEUTRAL NETWORKS

Some conclusions:

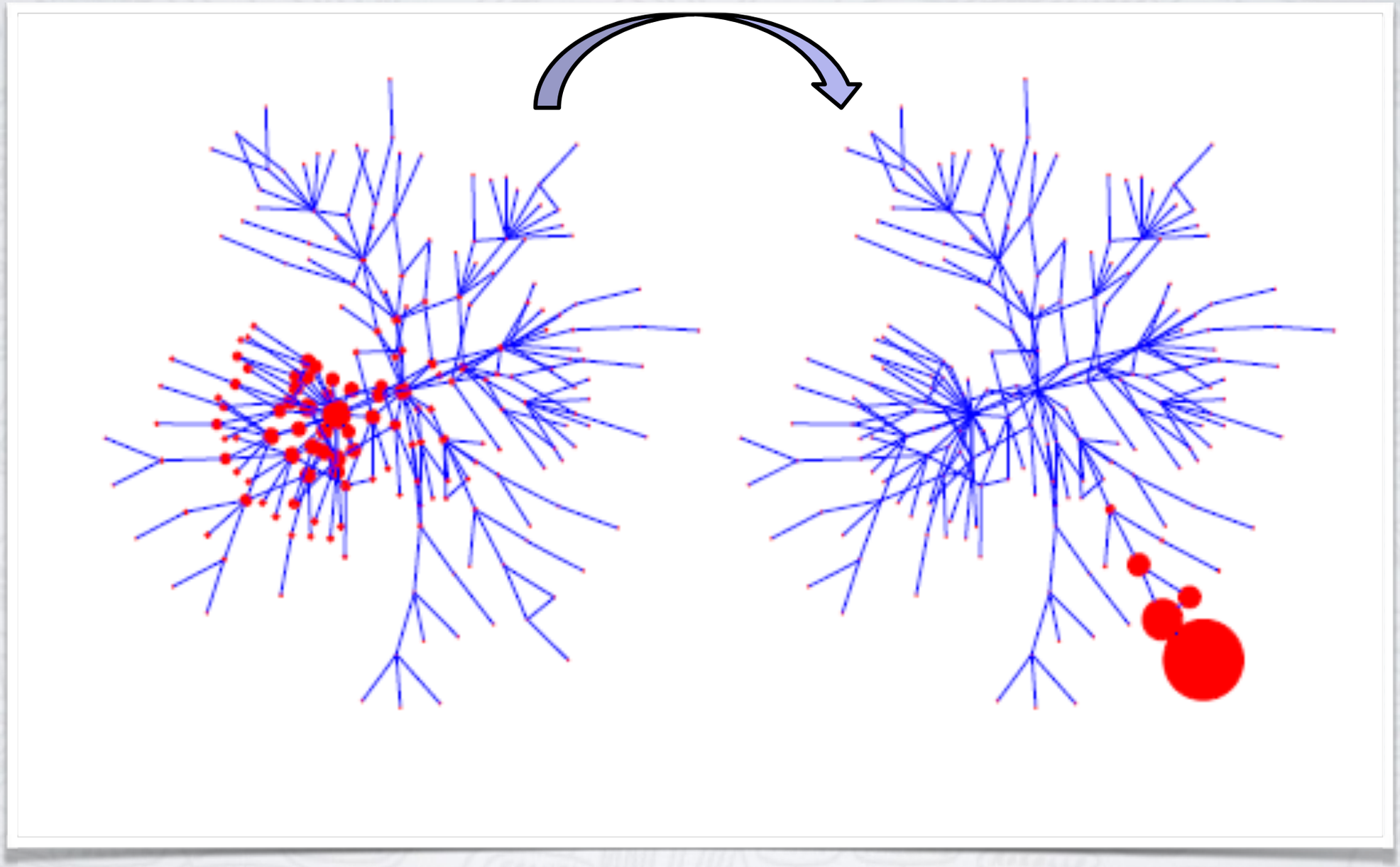
- We have overviewed the topological structure of neutral networks formed by **12-nucleotides** RNA sequences. A total of 412 sequences fragments into 465 subnetworks corresponding to 57 different secondary structures.

- The topological analysis reveals that RNA neutral networks are far from being random: they have a **degree distribution with a well-defined average** and **small dispersion**, **high clustering** and a **low average shortest path**.

- Several topological relationships can be extracted from the **structural (biological) restrictions** and generic properties of the folding process.

- The **average degree** of these phenotypic networks **grows logarithmically** with their size, such that abundant phenotypes have additional advantage of being more robust to mutations.

POPULATION DYNAMICS IN RNA NEUTRAL NETWORKS



POPULATION DYNAMICS IN RNA NEUTRAL NETWORKS

- Study of the **evolution** of populations of **genomes replicating** at high mutation rate (e.g. RNA) on artificial neutral networks (where populations evolve towards highly connected regions of the genome space).

- Analytical study (numerical if not possible) of the evolution of replicators on small networks where a **second selective pressure is included: the folding energy.**

- **Application** of the results to large and complex **"real" neutral networks.**

POPULATION DYNAMICS IN RNA NEUTRAL NETWORKS

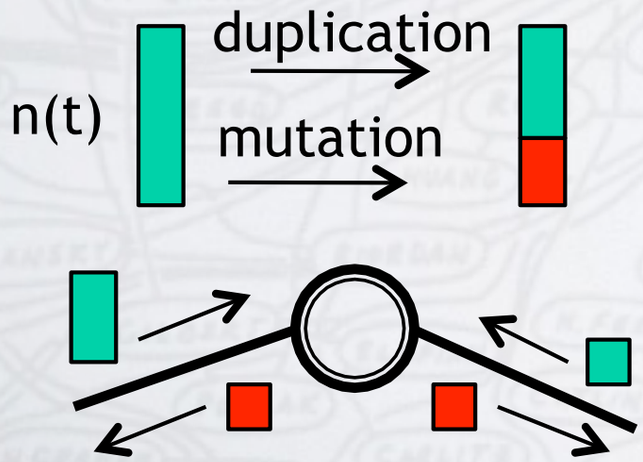
How do sequences move?

A. Initial condition: Each node *i* contains a number $n_i(0)$ of sequences.

B. At each time step (or generation) the population of a node duplicates.

C. The new sequence mutates with probability **μ**.

D. The population is constant.



$$n_i(t+1) = \underbrace{(2-\mu)n_i(t)}_{\text{Duplication - mutation}} + \underbrace{\frac{\mu}{3l}\sum_{\{nn\}_i} n_j(t)}_{\text{Network topology}} .$$

Population coming from neighbors

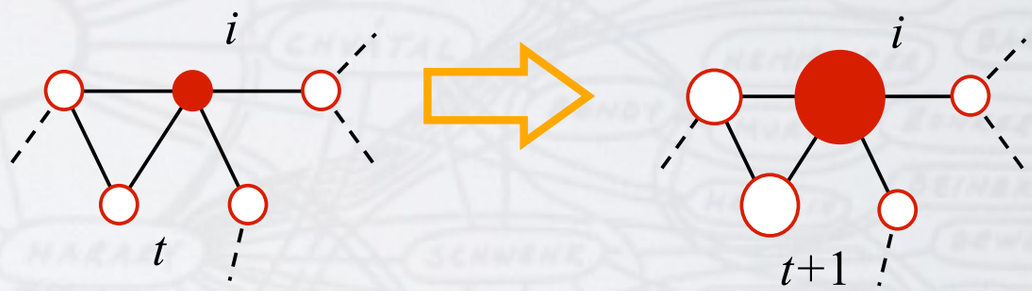
POPULATION DYNAMICS IN RNA NEUTRAL NETWORKS

Interplay between dynamics and topology:

$$n_i(t+1) = (2-\mu)n_i(t) + \frac{\mu}{3l}\sum_{\{nn\}_i} n_j(t)\ .$$

The topology is contained in the adjacency matrix **C**

n_i: population at node i
μ: mutation rate



Knowledge of C permits to calculate the final state (population in each node i) and the time required to attain equilibrium:

- The final state only depends on C
- Time to equilibrium depends on C and on the mutation rate

POPULATION DYNAMICS IN RNA NEUTRAL NETWORKS

Interplay between dynamics and topology:

$$n_i(t+1) = (2-\mu)n_i(t) + \frac{\mu}{3l}\sum_{\{nn\}_i} n_j(t)\,.$$

$$\vec{n}(t+1) = M\vec{n}(t)$$

M=Transition matrix
C=Adjacency matrix (topology)

$$\mathbf{M} = (2-\mu)\mathbf{I} + \frac{\mu}{3l}\mathbf{C}\,.$$

$$\lambda_i = (2-\mu) + \frac{\mu}{3l}\gamma_i$$

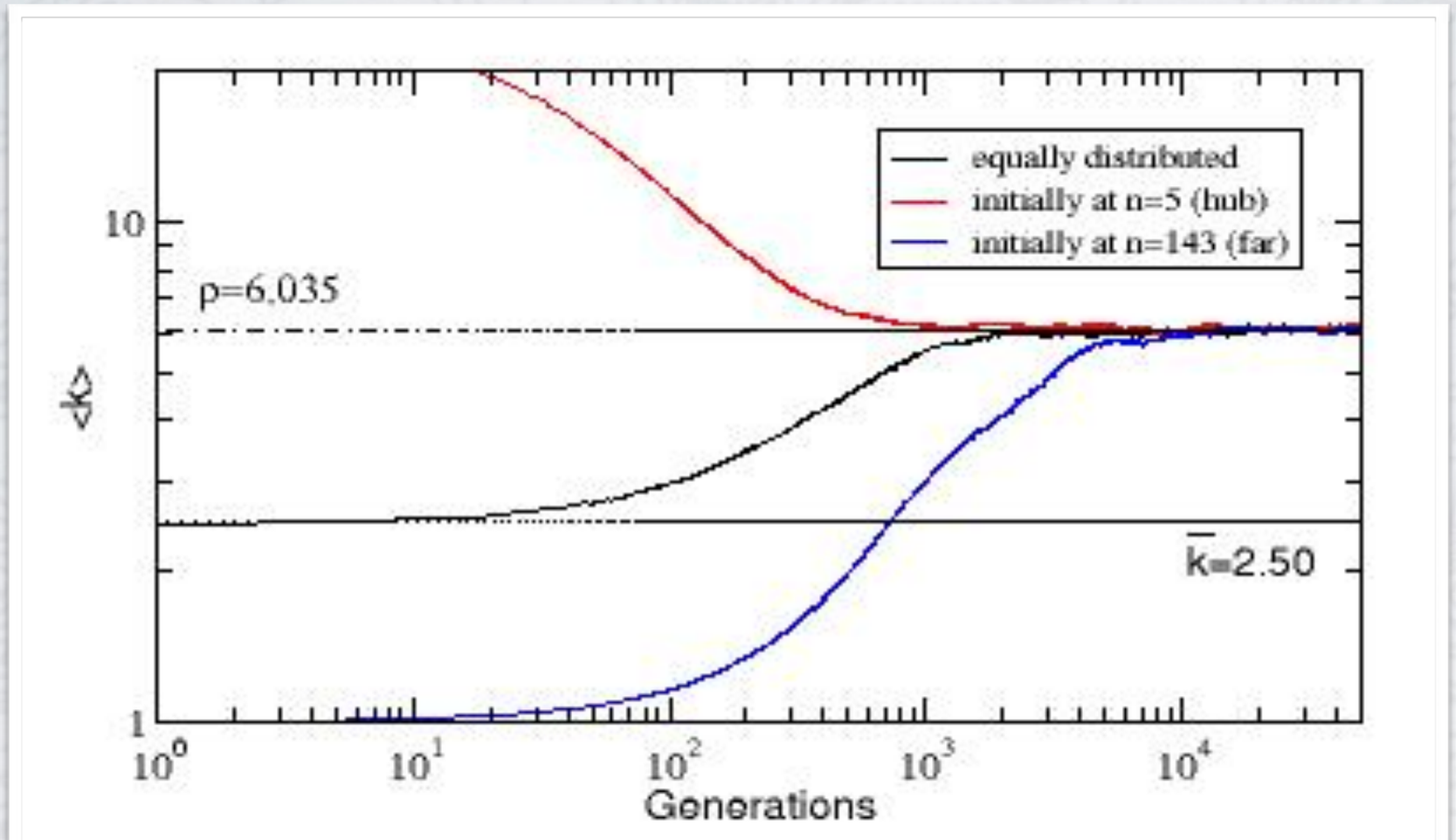
λi=eigenvalues of M
γi=eigenvalues of C

$$\vec{u}_i = \vec{w}_i$$

w_i=eigenvectors of M
u_i=eigenvectors of C

POPULATION DYNAMICS IN RNA NEUTRAL NETWORKS

How does the RNA population evolve in the network?



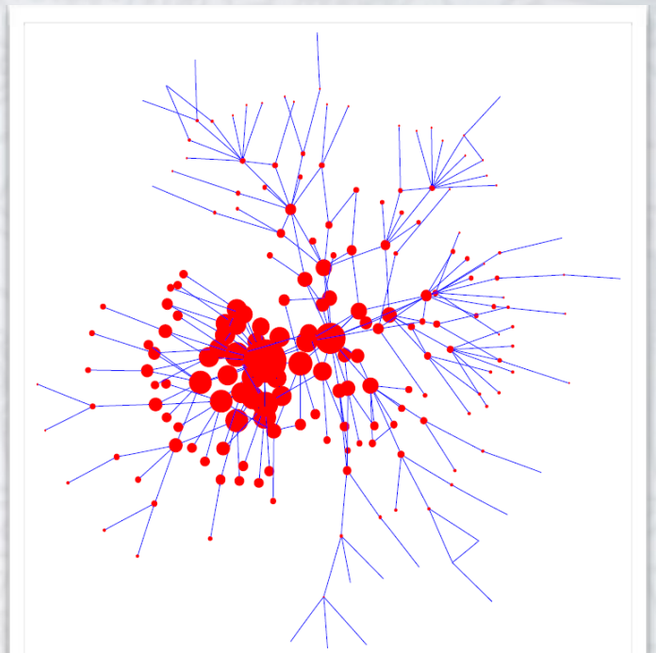


Figure: Average degree of the population as a function of time for a scale-free network. The final value ρ corresponds to the spectral radius of the adjacency matrix. Here μ=0.1 (N=200).

POPULATION DYNAMICS IN RNA NEUTRAL NETWORKS

- Transition matrix M has the same eigenvectors as the Adjacency matrix C:

$$n_i(t+1) = (2-\mu)n_i(t) + \frac{\mu}{3l}\sum_{\{nn\}_i} n_j(t)\,. \longrightarrow \begin{cases} \mathbf{M} = (2-\mu)\mathbf{I} + \frac{\mu}{3l}\mathbf{C}\,. \\ \vec{n}(t+1) = M\vec{n}(t) \end{cases}$$

- The final state is given by the first eigenvector of M (or C).

$$k_{min} < \langle k \rangle < \gamma_1 = \langle K_{pop} \rangle < k_{max}$$

- The average degree of the population $\langle K_{pop} \rangle$ is given by the first eigenvalue of C:

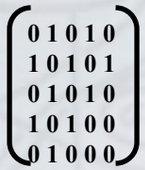
- The time to equilibrium t_ε depends on C (eigenvalues), on the initial condition and on the mutation rate μ:

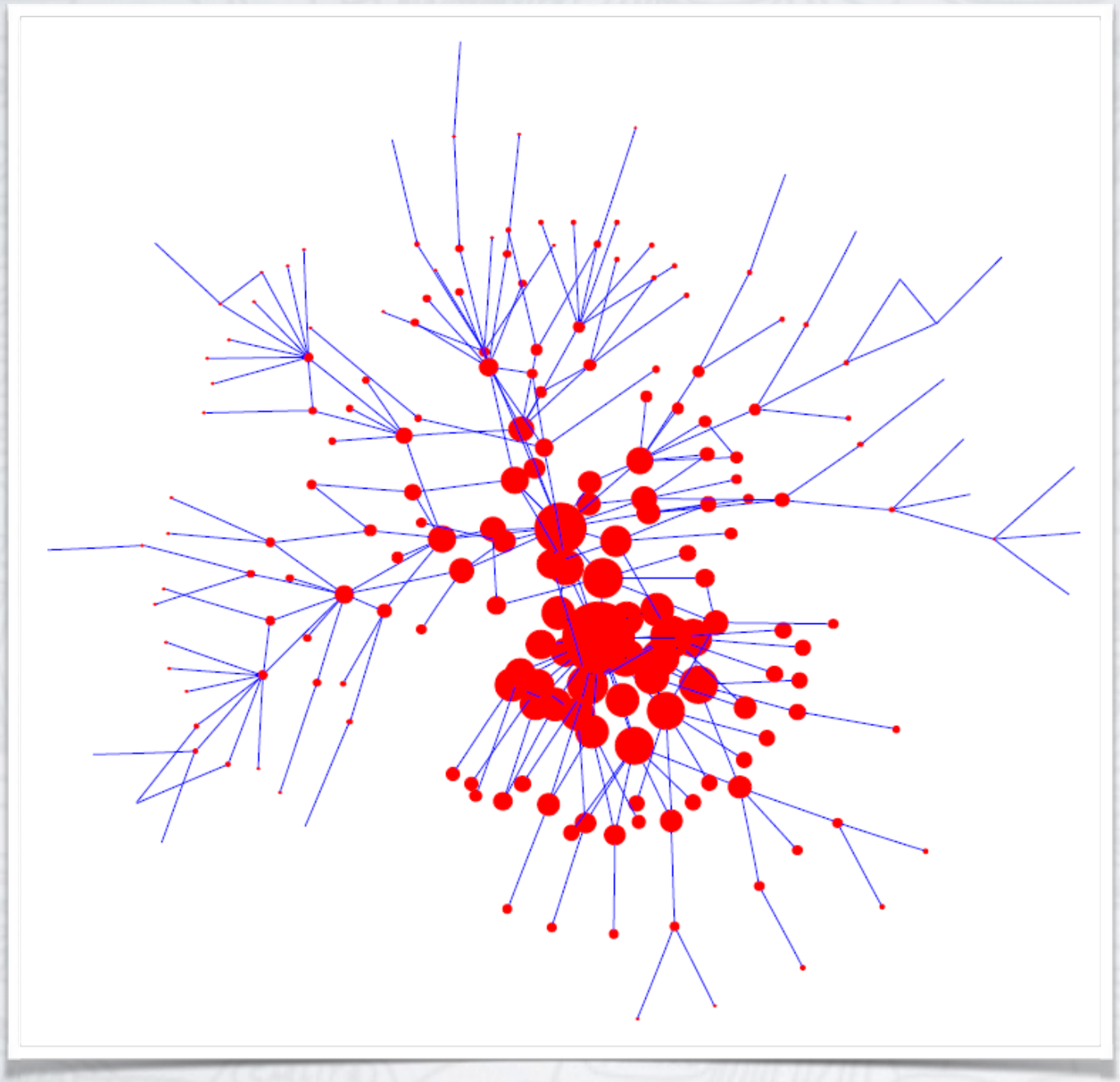
$$t_\epsilon^1 \simeq \frac{\ln|\alpha_2/\alpha_1| - \ln\,\epsilon}{\ln|\lambda_1/\lambda_2|}$$

For a given network and set of initial conditions: $t_\epsilon^1 \propto \mu^{-1}$

POPULATION DYNAMICS IN RNA NEUTRAL NETWORKS

Population finds robustness in the more connected regions!





- No matter where the initial distribution is (in the network), if the RNA has enough time, it will evolve toward the **same final distribution.**

- The population **evolves to the more connected areas.** In this way, it is more robust to mutations. This property is known as **neutrality.**

POPULATION DYNAMICS IN RNA NEUTRAL NETWORKS

- Next, we consider a second selective pressure: the folding energy E_i.

- The probability of occupying a node depends on its energy:

$$p_i = \exp\{-\beta(E_i - E_{min})\}\,.$$

- The folding energy depends on the base pairs:

G≡C - 3 Kcal/mol
A=U - 2 Kcal/mol
G-U - 1 Kcal/mol

$$E_i = -(3N_{\mathrm{GC}} + 2N_{\mathrm{AU}} + N_{\mathrm{GU}})\,,$$

- The parameter β quantifies the relative importance of high connectivity versus low energy:

$$\mathbf{M}' = \mathbf{E}\left[(2-\mu)\mathbf{I} + \frac{\mu}{3l}\mathbf{C}\right] = \mathbf{EM}$$

β → 0 the population evolves to the most connected nodes (neutrality).

β → ∞ the population evolves to nodes with lower energy (stability).

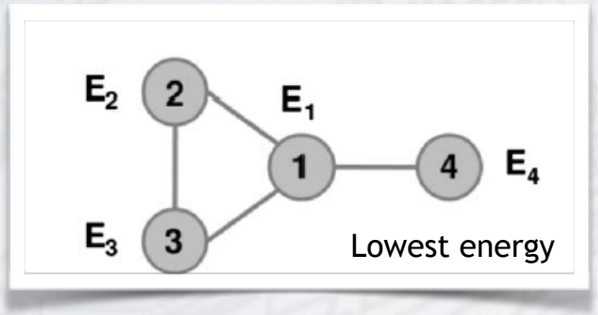
POPULATION DYNAMICS IN RNA NEUTRAL NETWORKS

Analytical results on (small) networks:

A) Eigenvectors of M' ≠ Eigenvectors of C: Topology is not enough!

B) The interplay and evolution of the eigenvalues and eigenvectors is the keystone of the complex dynamics.

Example:

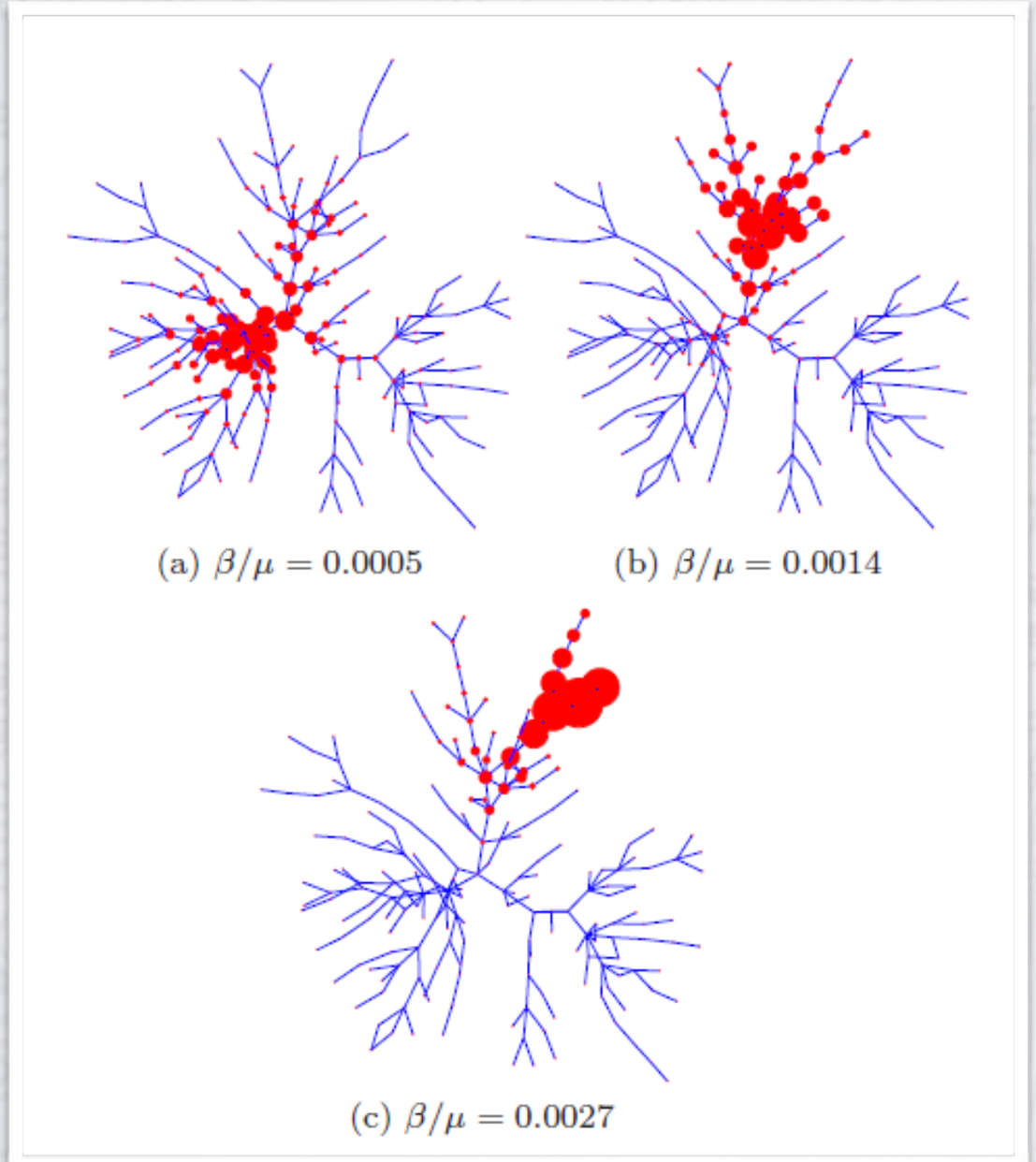


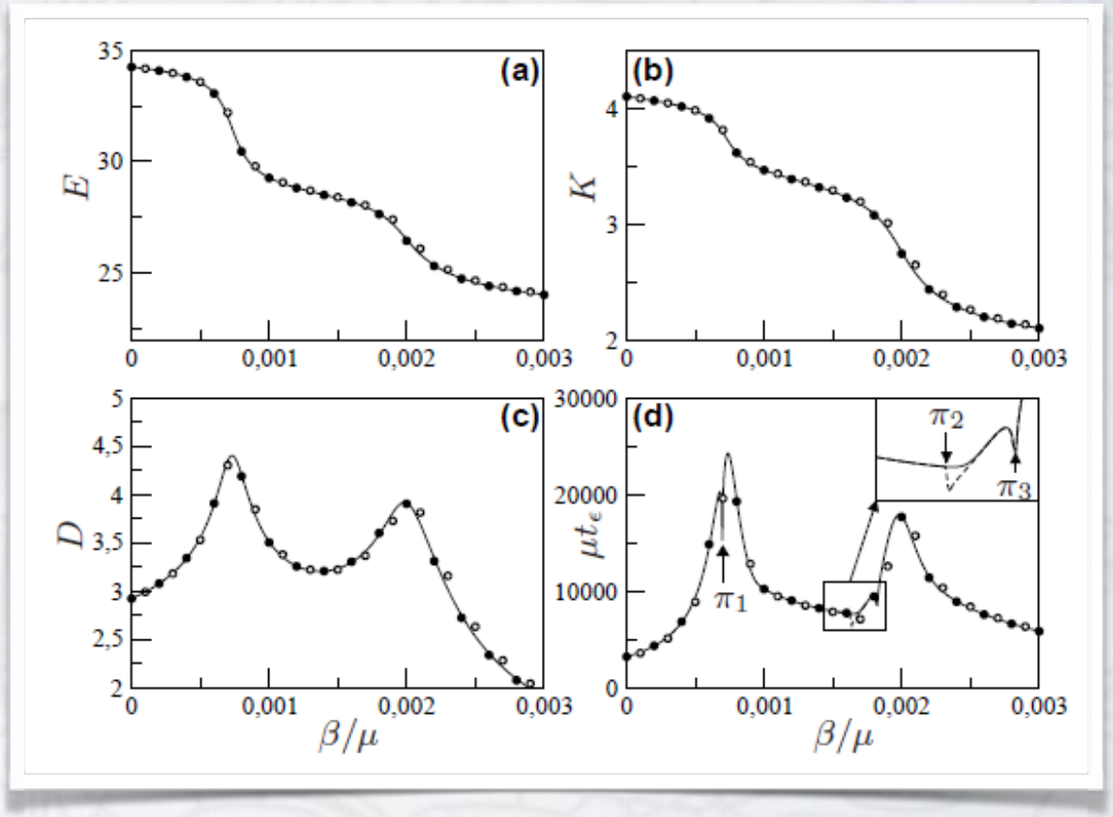
C)The mutation rate μ and the stability rate β represent opposite forces: μ promotes neutrality and β promotes stability.

D) **Correlations** between degree and energy will be crucial in the transition dynamics.

POPULATION DYNAMICS IN RNA NEUTRAL NETWORKS

- Energy versus topology in random networks:

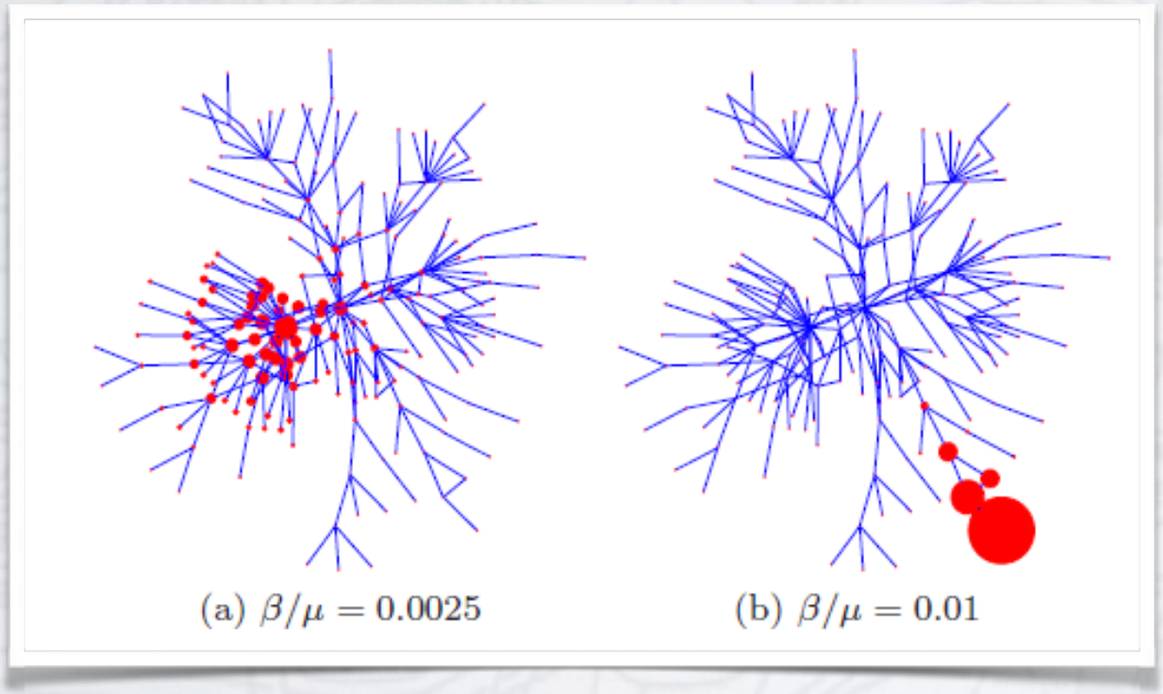


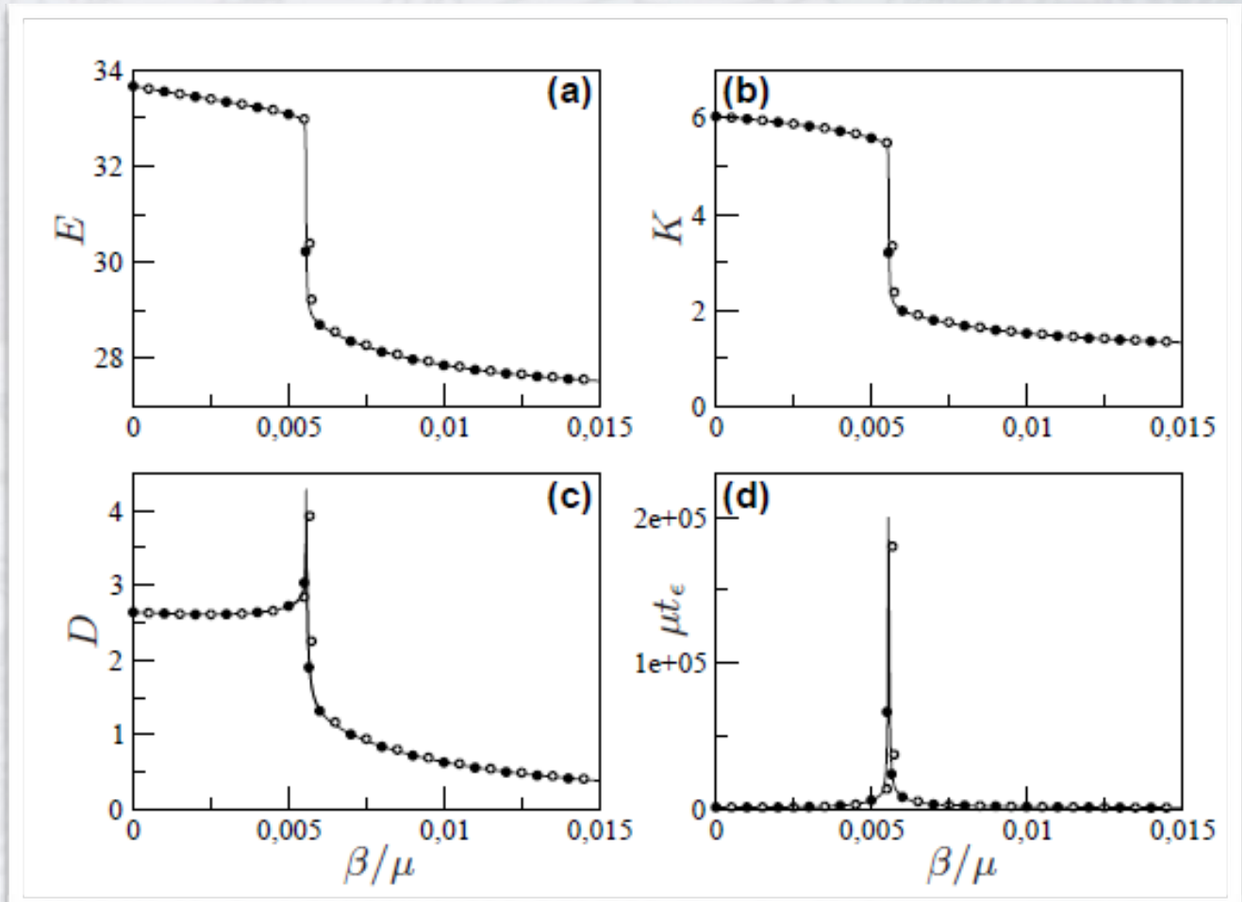


Dependence of the properties of the random mutation network on ß and μ when neutrality and energetic stability are negatively correlated (NS−). Each curve is plotted for μ = 0.001 (•), 0.01 (solid line), and 0.05 (◦). (a) Average energy *E*, (b) Average degree *K*, (c) Average dispersion *D*, (d) Dependence of the rescaled time to equilibrium

POPULATION DYNAMICS IN RNA NEUTRAL NETWORKS

Energy versus topology in scale-free networks



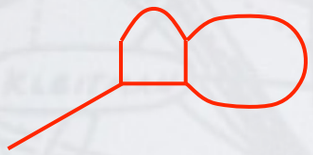


Dependence of the properties of the preferential mutation network on ß and μ when neutrality and energetic stability are negatively correlated (NS−). Each curve is plotted for μ = 0.001 (•), 0.01 (solid line), and 0.05 (◦). (a) Average energy *E*, (b) Average degree *K*, (c) Average dispersion *D*, (d) dependence of the rescaled time to equilibrium

POPULATION DYNAMICS IN RNA NEUTRAL NETWORKS

Energy versus topology in scale-free networks

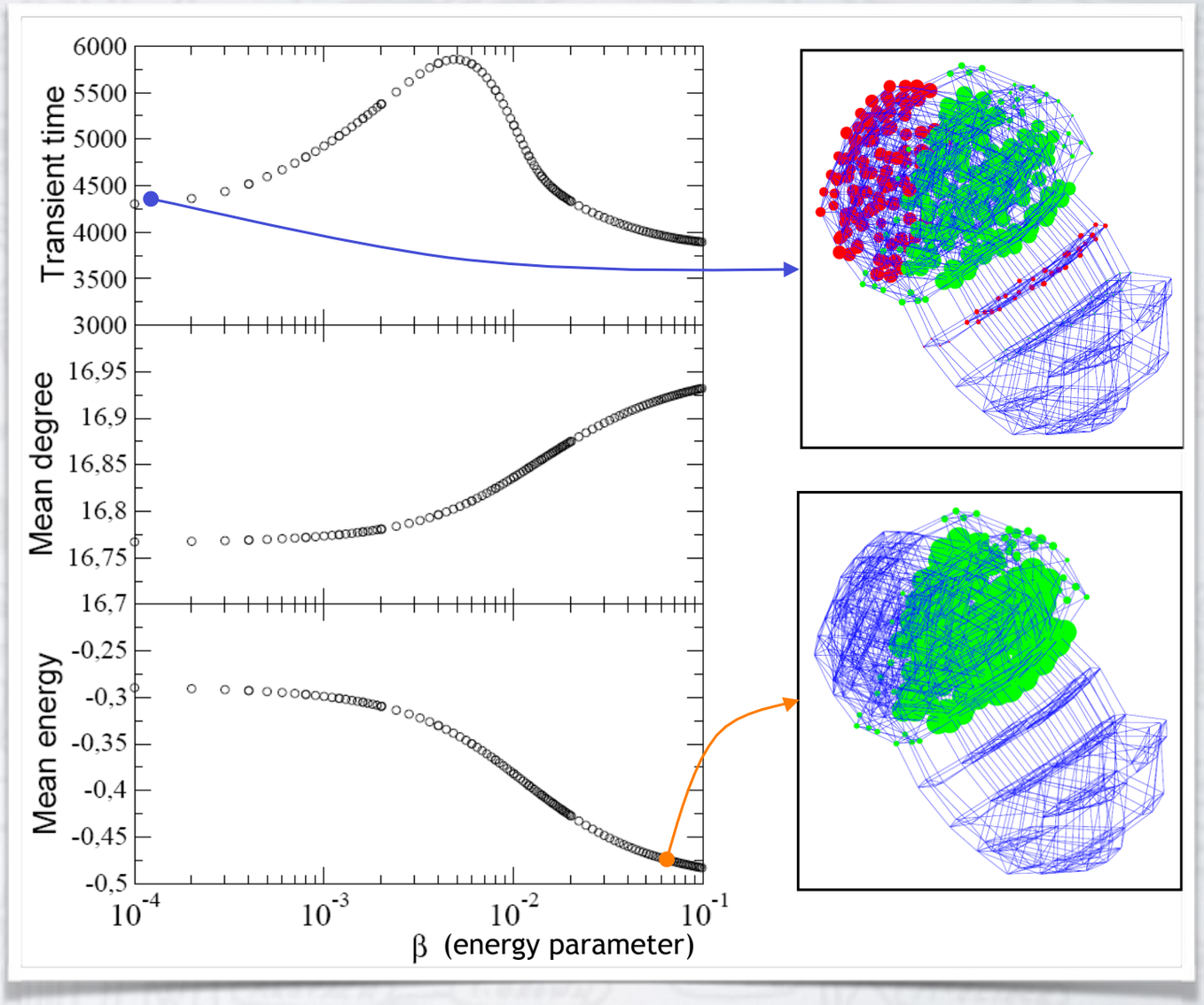
In this example, there are 404 different sequences leading to this secondary structure (l=12):



(.(....))...

- *Nodes of minimal energy (equal)*
- *Rest of nodes*

Interestingly, **correlation between energy and degree promotes neutrality** (robustness to mutations).



POPULATION DYNAMICS IN RNA NEUTRAL NETWORKS

Conclusions:

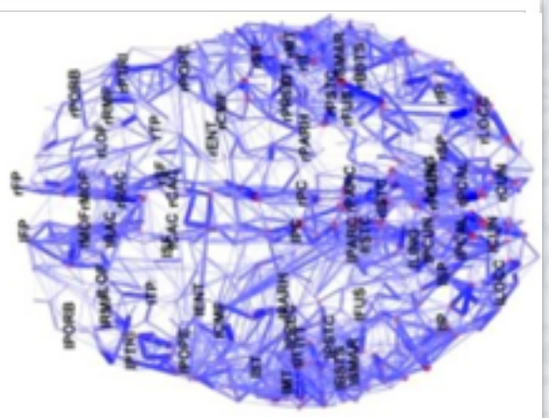
- Evolutionary dynamics on neutral networks leads populations to highly connected areas in the space of genomes: **neutrality (connectivity) is optimized, thus increasing robustness to mutations**

- When the energy of the folded state is taken into account, the **population concentrates around sequences of minimal energy**, thus increasing robustness to perturbations

- **Robustness** arises as a compromise between **minimizing the effect of mutations and maximizing structural stability**

- The **time** required to reach the asymptotic state has to be shorter than the time between changes in the environment

- **Correlation between energy and degree** in real RNA neutral networks can **increase the robustness** of the population

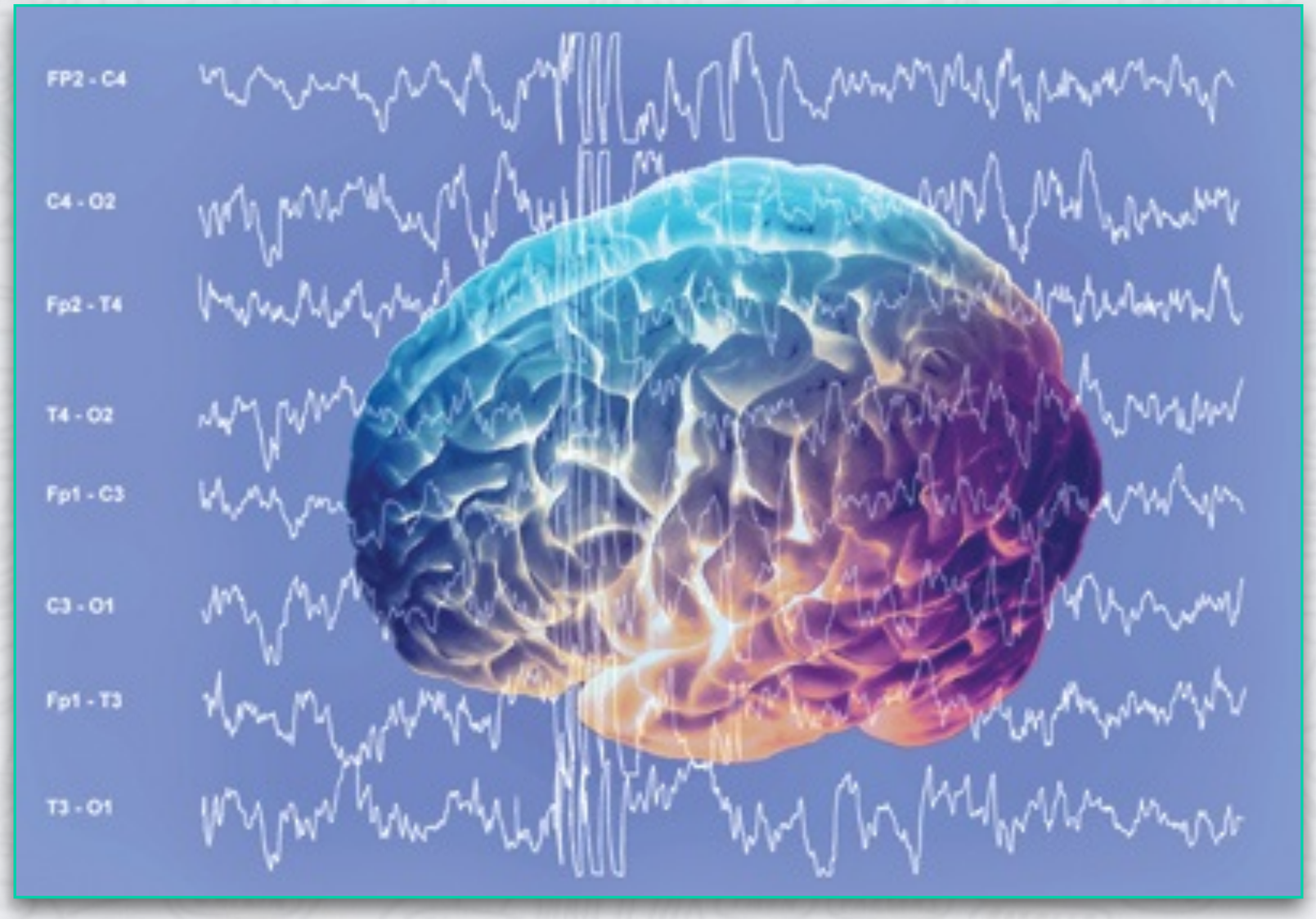


Functional Brain Networks

(III-III)

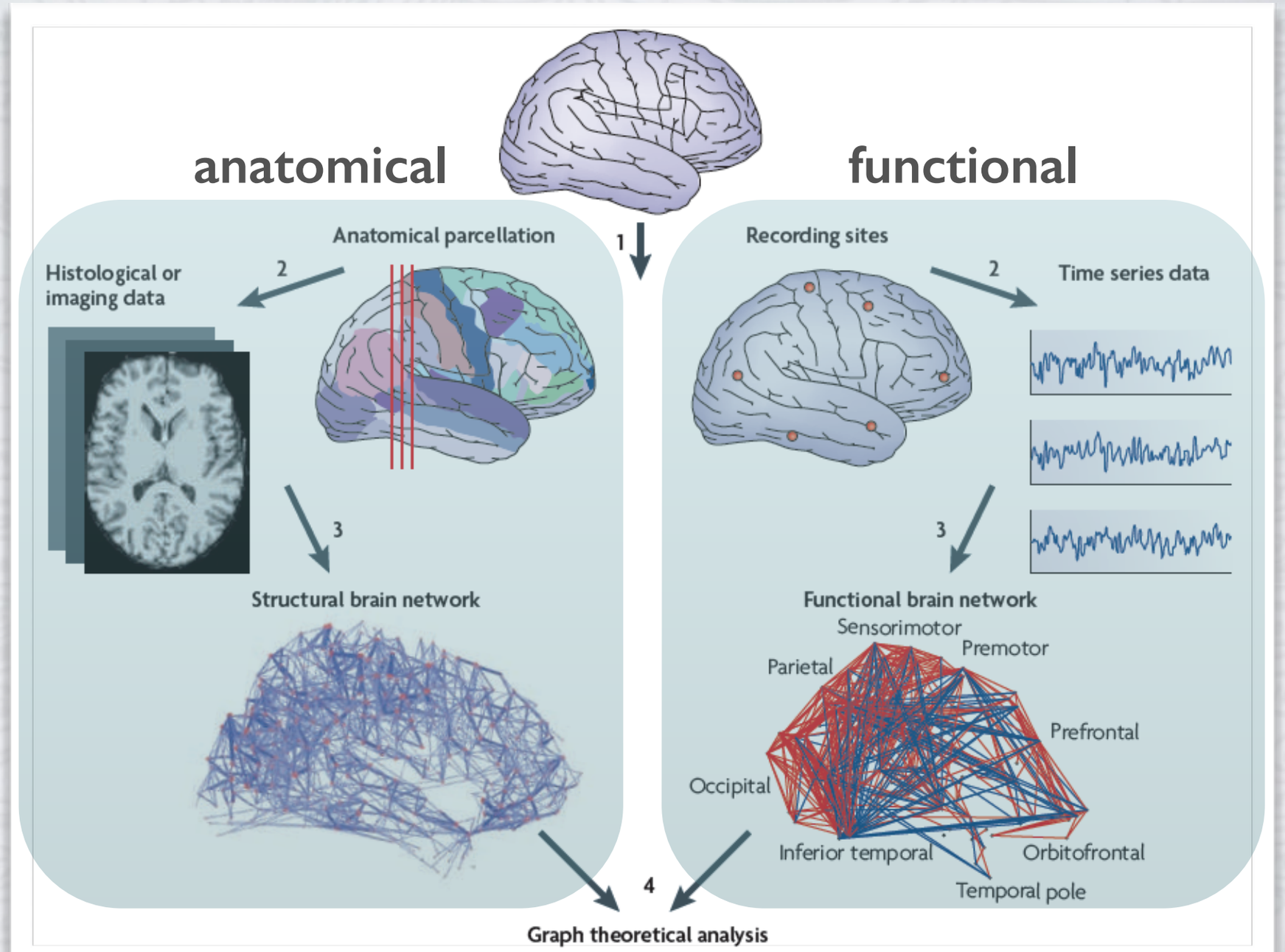
APPLYING NETWORK SCIENCE TO THE BRAIN

What if we apply network science to the most challenging system we are facing?



APPLYING NETWORK SCIENCE TO THE BRAIN

In brief, (main) types of brain networks



From Bullmore & Sporns, Nature Rev. 10, 186 (2009)

Measure	Binary and undirected definitions
Basic concepts and measures	
Basic concepts and notation	N is the set of all nodes in the network, and n is the number of nod L is the set of all links in the network, and l is number of links. (i, j) is a link between nodes i and j, $(i, j \in N)$. a_{ij} is the connection status between i and j: $a_{ij} = 1$ when link (i, j) exists (when i and j are neighbors); $a_{ij} = 0$ otherwise ($a_{ii} = 0$ for a We compute the number of links as $l = \sum_{i,j \in N} a_{ij}$ (to avoid ambiguity with directed links we count each undirected link twice, as a_{ij} and as a_{ji}).
Degree: number of links connected to a node	Degree of a node i, $$k_i = \sum_{j \in N} a_{ij}.$$
Shortest path length: a basis for measuring integration	Shortest path length (distance), between nodes i and j, $$d_{ij} = \sum_{a_{uv} \in g_{i \leftrightarrow j}} a_{uv},$$ where $g_{i \leftrightarrow j}$ is the shortest path (geodesic) between i and j. Note that $d_{ij} = \infty$ for all disconnected pairs i, j.
Number of triangles: a basis for measuring segregation	Number of triangles around a node i, $$t_i = \frac{1}{2} \sum_{j,h \in N} a_{ij} a_{ih} a_{jh}.$$
Measures of integration	
Characteristic path length	Characteristic path length of the network (e.g., Watts and Strogatz, 1998), $$L = \frac{1}{n} \sum_{i \in N} L_i = \frac{1}{n} \sum_{i \in N} \frac{\sum_{j \in N, j \neq i} d_{ij}}{n - 1},$$ where L_i is the average distance between node i and all other nodes
Global efficiency	Global efficiency of the network (Latora and Marchiori, 2001), $$E = \frac{1}{n} \sum_{i \in N} E_i = \frac{1}{n} \sum_{i \in N} \frac{\sum_{j \in N, j \neq i} d_{ij}^{-1}}{n - 1},$$ where E_i is the efficiency of node i.
Measures of segregation	
Clustering coefficient	Clustering coefficient of the network (Watts and Strogatz, 1998), $$C = \frac{1}{n} \sum_{i \in N} C_i = \frac{1}{n} \sum_{i \in N} \frac{2t_i}{k_i(k_i - 1)},$$ where C_i is the clustering coefficient of node i ($C_i = 0$ for $k_i < 2$).
Transitivity	Transitivity of the network (e.g., Newman, 2003), $$T = \frac{\sum_{i \in N} 2t_i}{\sum_{i \in N} k_i(k_i - 1)}.$$ Note that transitivity is not defined for individual nodes.
Local efficiency	Local efficiency of the network (Latora and Marchiori, 2001), $$E_{\text{loc}} = \frac{1}{n} \sum_{i \in N} E_{\text{loc},i} = \frac{1}{n} \sum_{i \in N} \frac{\sum_{j,h \in N, j \neq i} a_{ij} a_{ih} \left[d_{jh}(N_i) \right]^{-1}}{k_i(k_i - 1)},$$ where $E_{\text{loc},i}$ is the local efficiency of node i, and d_{jh} (N_i) is the length of the shortest path between j and h, that contains only neighbors of i.

Measure	Binary and undirected definitions
Modularity	Modularity of the network (Newman, 2004b), $$Q = \sum_{u \in M} \left[e_{uu} - \left(\sum_{v \in M} e_{uv} \right)^2 \right],$$ where the network is fully subdivided into a set of nonoverlapping modules M, and e_{uv} is the proportion of all links that connect nodes in module u with nodes in module v. An equivalent alternative formulation of the modularity (Newman, 2006) is given by $Q = \frac{1}{l} \sum_{i,j \in N} \left(a_{ij} - \frac{k_i k_i}{l} \right) \delta_{m_i, m_j}$, where m_i is the module containing node i, and $\delta_{m_i, mj} = 1$ if $m_i = m_j$, and 0 otherwise.
Measures of centrality	
Closeness centrality	Closeness centrality of node i (e.g. Freeman, 1978), $$L_i^{-1} = \frac{n - 1}{\sum_{j \in N, j \neq i} d_{ij}}.$$
Betweenness centrality	Betweenness centrality of node i (e.g., Freeman, 1978), $$b_i = \frac{1}{(n - 1)(n - 2)} \sum_{\substack{h,j \in N \\ h \neq j, h \neq i, j \neq i,}} \frac{\rho_{hj}(i)}{\rho_{hj}},$$ where ρ_{hj} is the number of shortest paths between h and j, and ρ_{hj} (i) is the number of shortest paths between h and j that pass through i.
Within-module degree z-score	Within-module degree z-score of node i (Guimera and Amaral, 2005), $$z_i = \frac{k_i(m_i) - \bar{k}(m_i)}{\sigma^{k(m_i)}},$$ where m_i is the module containing node i, k_i (m_i) is the within-module degree of i (the number of links between i and all other nodes in m_i), and $\bar{k}(m_i)$ and $\sigma^{k(m_i)}$ are the respective mean and standard deviation of the within-module m_i degree distribution.
Participation coefficient	Participation coefficient of node i (Guimera and Amaral, 2005), $$y_i = 1 - \sum_{m \in M} \left(\frac{k_i(m)}{k_i} \right)^2,$$ where M is the set of modules (see modularity), and k_i (m) is the number of links between i and all nodes in module m.
Network motifs	
Anatomical and functional motifs	J_h is the number of occurrences of motif h in all subsets of the network (subnetworks). h is an n_h node, l_h link, directed connected pattern. h will occur as an anatomical motif in an n_h node, l_h link subnetwork, if links in the subnetwork match links in h (Milo et al., 2002). h will occur (possibly more than once) as a functional motif in an n_h node, $l'_h \geq l_h$ link subnetwork, if at least one combination of l_h links in the subnetwork matches links in h (Sporns and Kotter, 2004).
Motif z-score	z-Score of motif h (Milo et al., 2002), $$z_h = \frac{J_h - \langle J_{\text{rand},h} \rangle}{\sigma^{J_{\text{rand},h}}},$$ where $\langle J_{\text{rand},h} \rangle$ and $\sigma^{J_{\text{rand},h}}$ are the respective mean and standard deviation for the number of occurrences of h in an ensemble of random networks.
Motif fingerprint	n_h node motif fingerprint of the network (Sporns and Kotter, 2004), $$F_{n_h}(h') = \sum_{i \in N} F_{n_h,i}(h') = \sum_{i \in N} J_{h',i},$$ where h' is any n_h node motif, $F_{n_h,i}$ (h') is the n_h node motif fingerprint for node i, and $J_{h',i}$ is the number of occurrences of motif h' around node i.

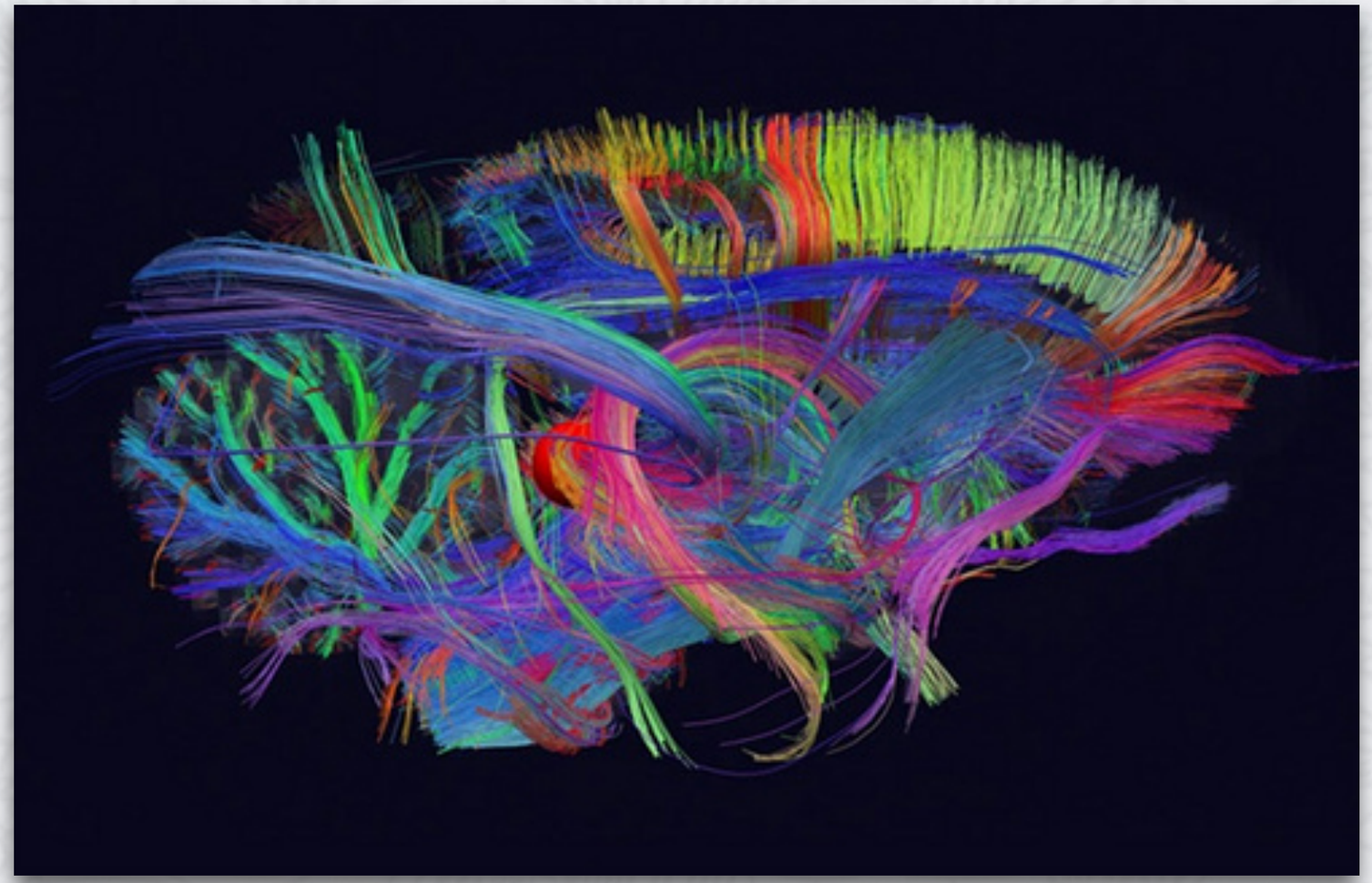
Measure	Binary and undirected definitions
Measures of resilience	
Degree distribution	Cumulative degree distribution of the network (Barabasi and Albert, 1999), $$P(k) = \sum_{k' \geq k} p(k'),$$ where $p(k')$ is the probability of a node having degree k'.
Average neighbor degree	Average degree of neighbors of node i (Pastor-Satorras et al., 2001), $$k_{\text{nn},i} = \frac{\sum_{j \in N} a_{ij} k_j}{k_i}.$$
Assortativity coefficient	Assortativity coefficient of the network (Newman, 2002), $$r = \frac{l^{-1} \sum_{(i,j) \in L} k_i k_j - \left[l^{-1} \sum_{(i,j) \in L} \frac{1}{2} \left(k_i + k_j \right) \right]^2}{l^{-1} \sum_{(i,j) \in L} \frac{1}{2} \left(k_i^2 + k_j^2 \right) - \left[l^{-1} \sum_{(i,j) \in L} \frac{1}{2} \left(k_i + k_j \right) \right]^2}.$$
Other concepts	
Degree distribution preserving network randomization.	Degree-distribution preserving randomization is implemented by iteratively choosing four distinct nodes $i_1, j_1, i_2, j_2 \in N$ at random, such that links (i_1, j_1), $(i_2, j_2) \in L$, while links (i_1, j_2), $(i_2, j_1) \notin L$. The links are then rewired such that (i_1, j_2), $(i_2, j_1) \in L$ and (i_1, j_1), $(i_2, j_2) \notin L$, (Maslov and Sneppen, 2002). "Latticization" (a lattice-like topology) results if an additional constraint is imposed, $\lvert i_1 + j_2 \rvert + \lvert i_2 + j_1 \rvert < \lvert i_1 + j_1 \rvert + \lvert i_2 + j_2 \rvert$ (Sporns and Kotter, 2004).
Measure `of network small-worldness.	Network small-worldness (Humphries and Gurney, 2008), $$S = \frac{C / C_{\text{rand}}}{L / L_{\text{rand}}},$$ where C and C_{rand} are the clustering coefficients, and L and L_{rand} are the characteristic path lengths of the respective tested network and a random network. Small-world networks often have $S \gg 1$.

… and many more!!

M. Rubinov and O. Sporns,
NeuroImage 52, 1059–1069 (2010)

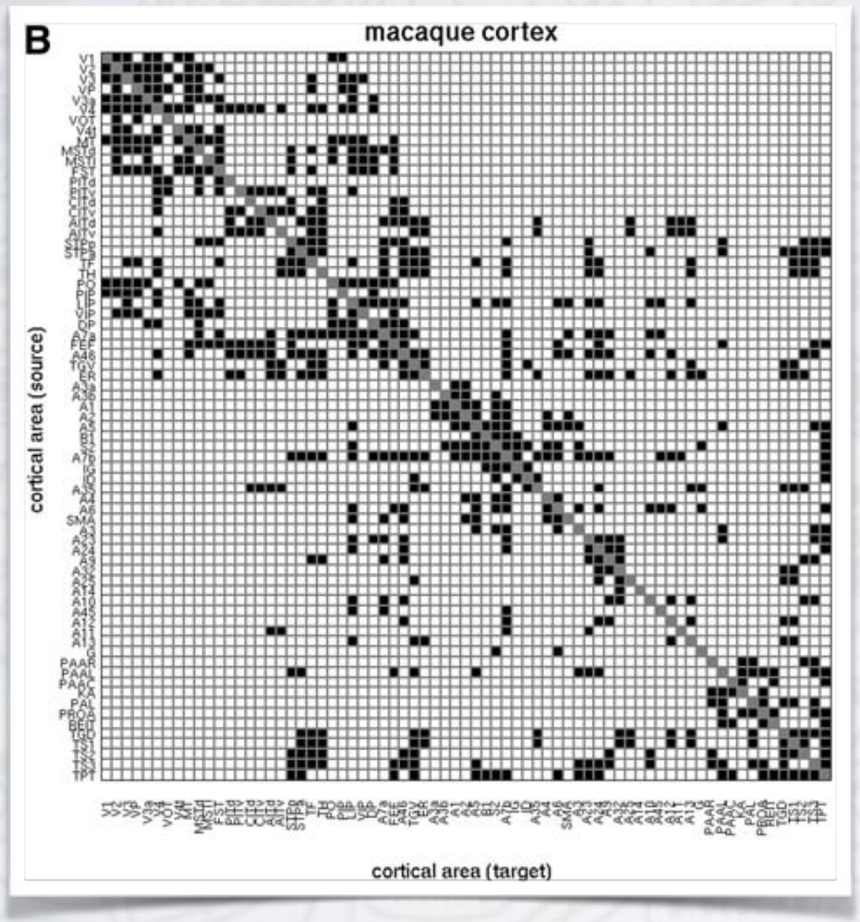
ANATOMICAL BRAIN NETWORKS

The **connectome** is a comprehensive map of neural connections in the brain. The production and study of connectomes, known as connectomics, **may range in scale from a detailed map of the full set of neurons and synapses of an organism to a macro scale description** of the structural connectivity between all cortical areas and subcortical structures.

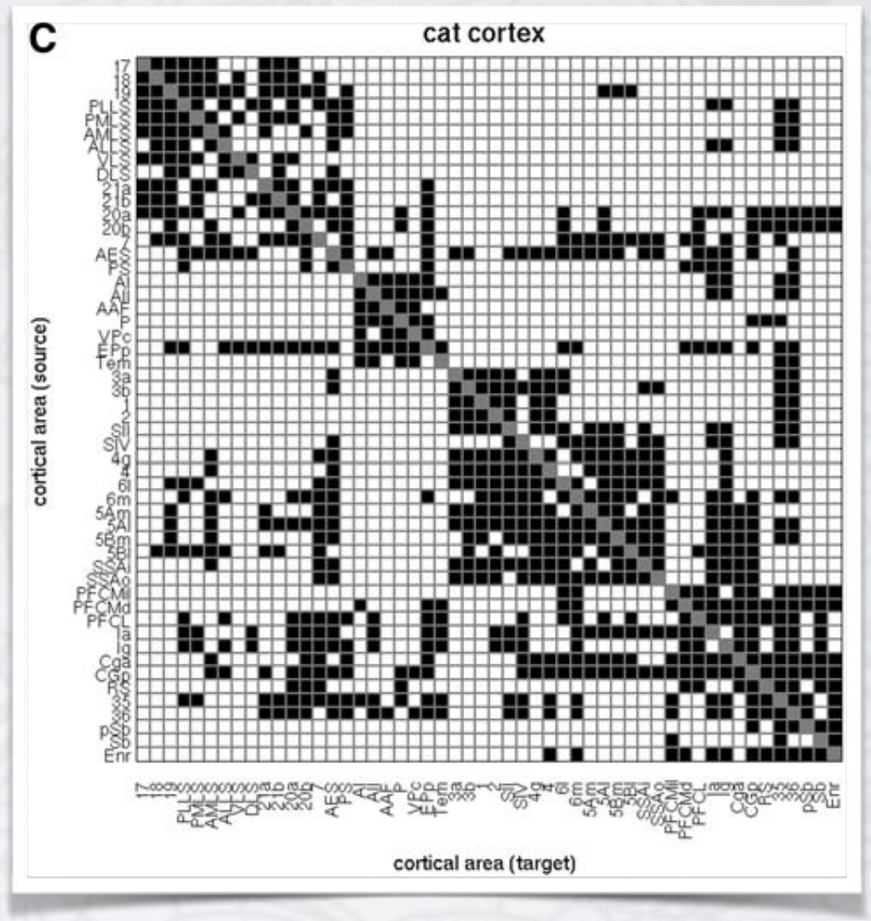


ANATOMICAL BRAIN NETWORKS

We can analyze the structure of anatomical networks in order to learn something from them:



N=71 Brain Areas and L=746
Small-world
No power-law



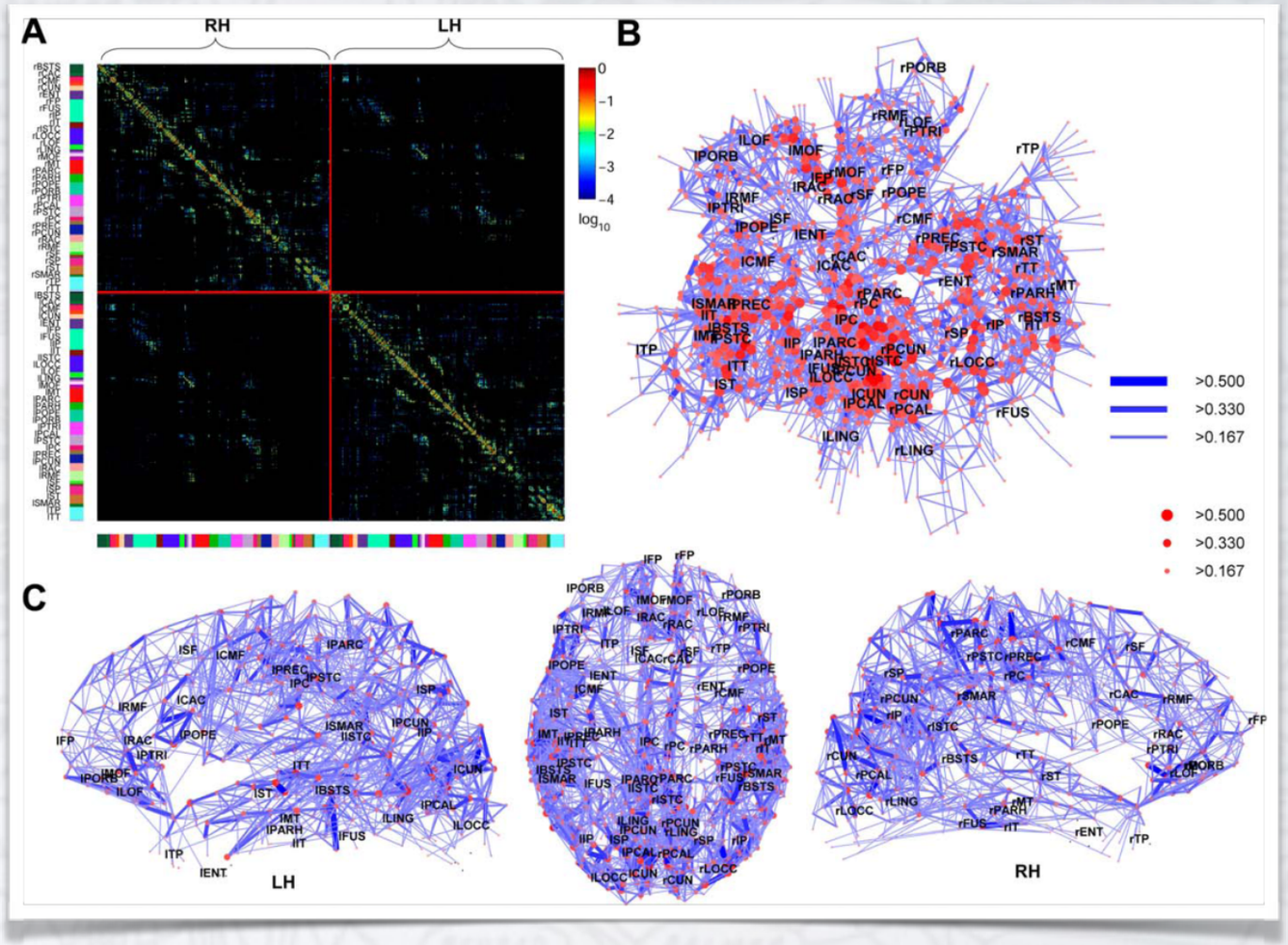
N= 52 Brain Areas and L=820
Small-world
No power-law

From Sporns et al., Neuroinformatics, 2, 145 (2004)

ANATOMICAL BRAIN NETWORKS

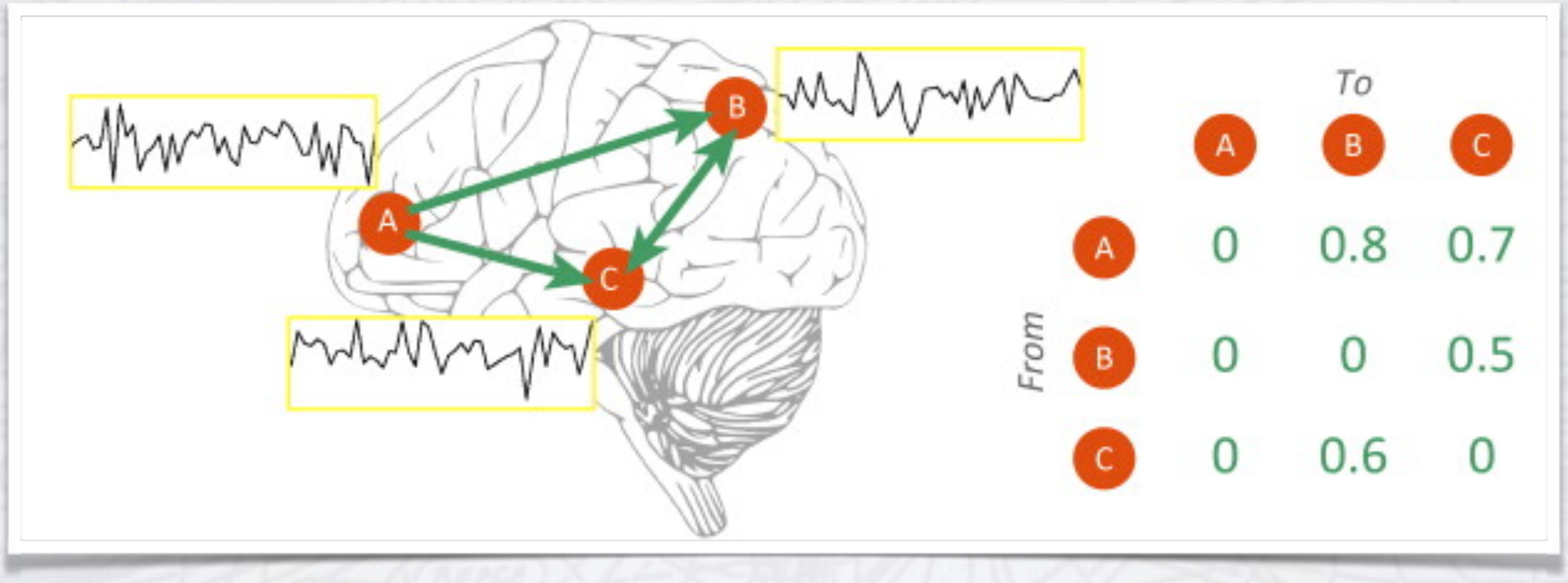
The human brain has been also translated into a network:

- **Exponential** (not scale-free) degree distribution (note that there are 66 subregions and 998 ROIs).
- **Small-world** attributes.
- Multiple **modules** interlinked by hub regions.
- Positive **assortativity**.



Hagmann et al. (2008) PLoS Biol. 6, e159

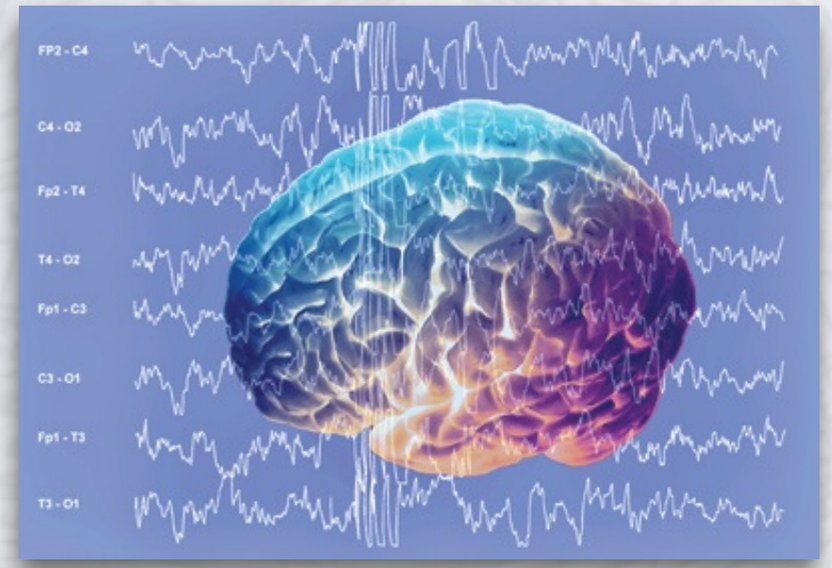
FUNCTIONAL BRAIN NETWORKS



IT'S A LONG ROAD… FULL OF TROUBLE!

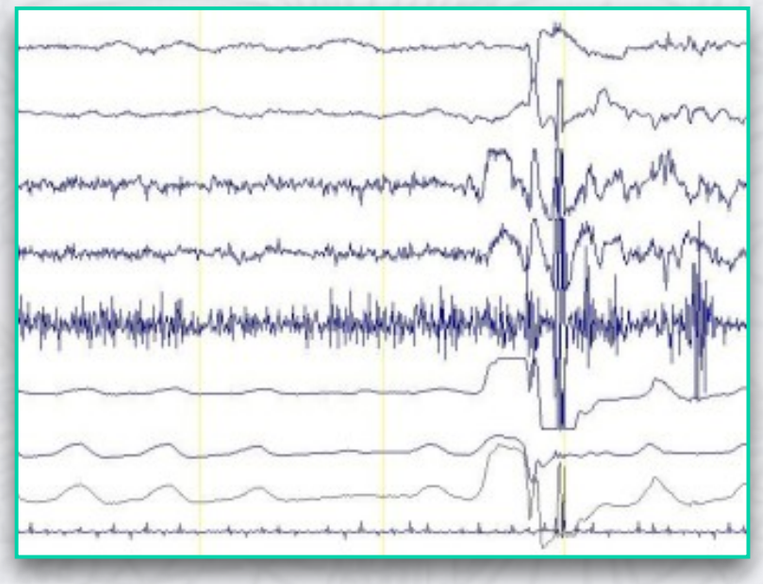
Obtaining a functional brain network in three steps:

STEP 1



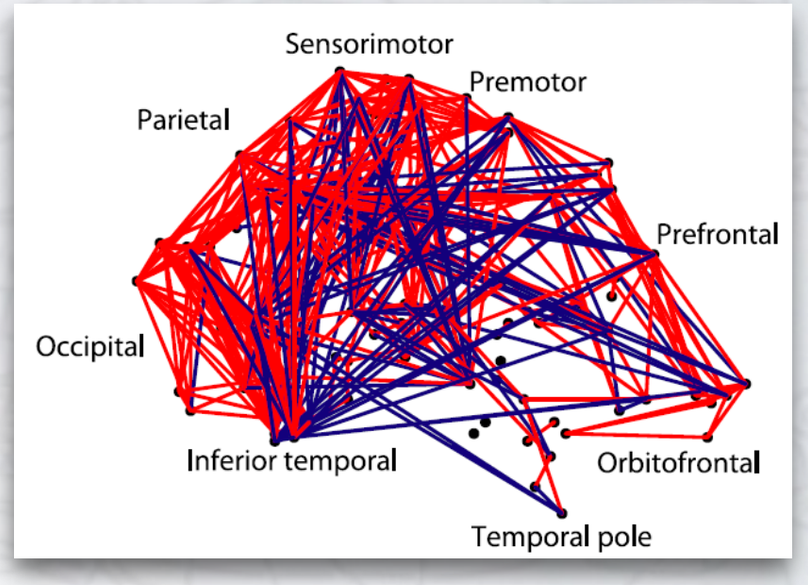
Measuring Brain Activity

STEP 2



Time Series Analysis &
Network Construction

STEP 3



Network Analysis

OBTAINING FUNCTIONAL BRAIN NETWORKS

STEP 1: Measuring Brain Activity

- **Functional MRI (fMRI).** The detection of changes in regional brain activity through their effects on blood flow and blood oxygenation (which, in turn, affect magnetic susceptibility and tissue contrast in magnetic resonance images). **High spatial resolution** (~mm3) but **low temporal resolution** (~seconds).

- **Electroencephalography (EEG).** A technique used to measure neural activity by monitoring electrical signals from the brain, usually through scalp electrodes. EEG has **good temporal resolution** but relatively **poor spatial resolution**.

- **Magnetoencephalography (MEG).** A method of measuring brain activity by detecting perturbations in the extracranial magnetic field that are generated by the electrical activity of neuronal populations. Like EEG, it has **good temporal resolution** but relatively **poor spatial resolution**. It has better resolution than EEG.

- **Others…**

OBTAINING FUNCTIONAL BRAIN NETWORKS

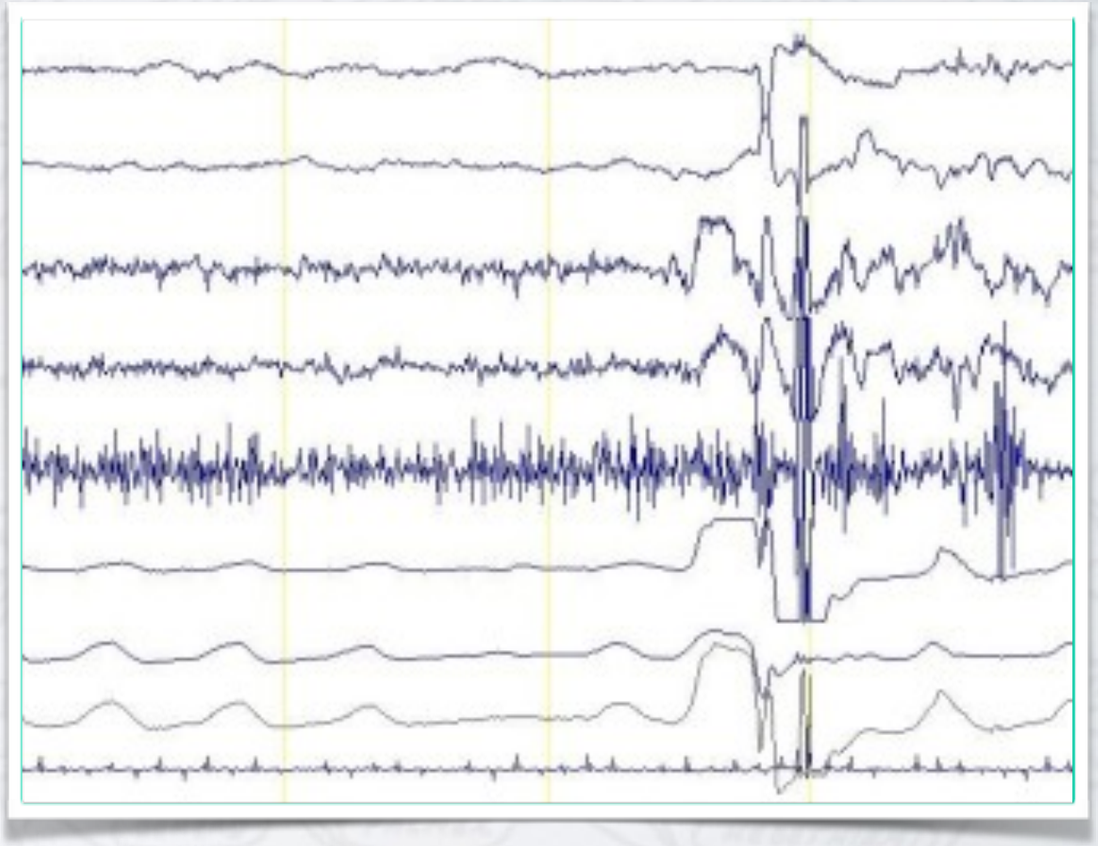
STEP 1: Measuring Brain Activity

- Low spatial resolution (we have ~10^{11} neurons)
- In EEG and MEG, we only measure cortical activity
- Overlapping of measurements
- Brain is not an isolated system
- High variability in the results

OBTAINING FUNCTIONAL BRAIN NETWORKS

STEP II: Time Series Analysis & Network Construction

- Several linear and nonlinear techniques*:
  - Cross-correlation
  - Wavelet coherence
  - Synchronization Likelihood
  - Generalized Synchronization
  - Phase Synchronization
  - Mutual Information
  - Granger Causality



- Once coordination is evaluated, we construct the functional network.

* For a review: Pereda et al, Prog. Neurobiol, 77 (2005)

OBTAINING FUNCTIONAL BRAIN NETWORKS

STEP 1I: Time Series Analysis & Network Construction

- Defining the nodes is a complex task
- It is difficult to evaluate causality and weights
- Several kinds of synchronization exist at the same time
- Where to put a threshold? (normalization, comparison,…)
- High variability in the results
- In EEG and MEG, we only measure cortical activity (missing interactions)

OBTAINING FUNCTIONAL BRAIN NETWORKS

STEP III: Network Analysis

A. Characterize the **topology of brain functional networks** and its influence on the processes occurring in them.

B. Identify **differences between healthy brains** and those with a certain **pathology.**

C. **Develop models** in order to explain the changes found in impaired functional networks.

ANALYZING FUNCTIONAL BRAIN NETWORKS

A. Characterize the topology of brain functional networks and its influence in the processes occurring in them:

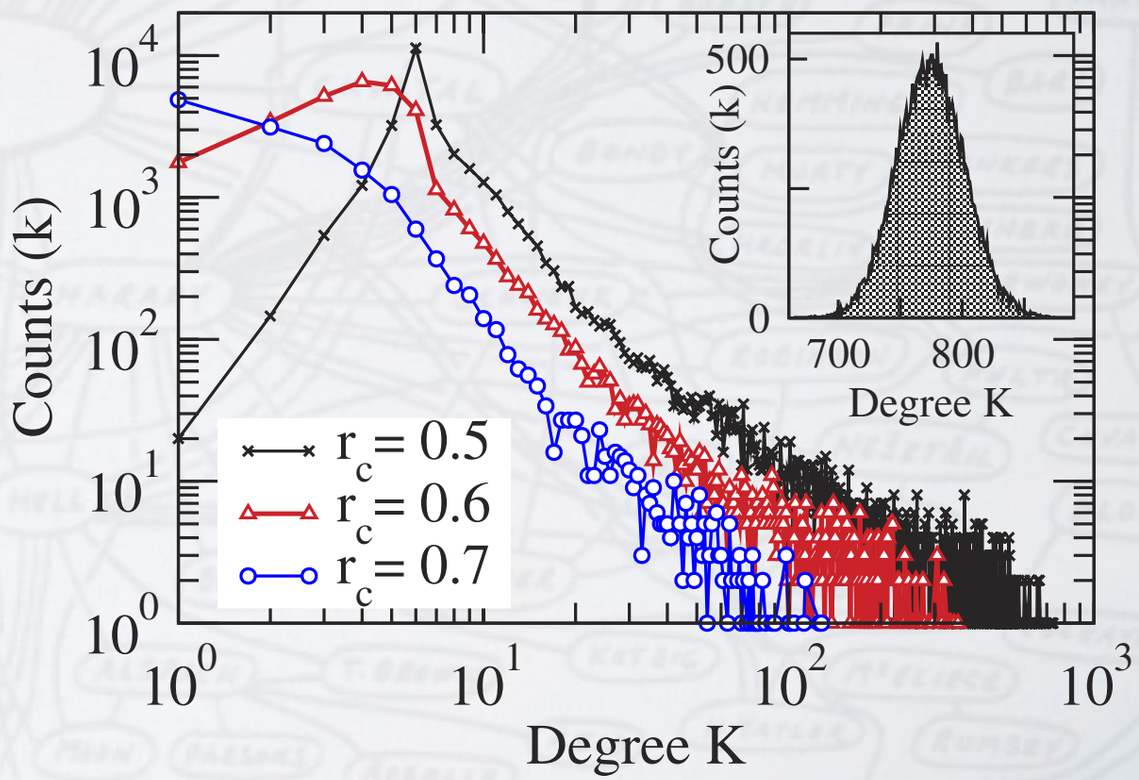
- Small-world topology -> High efficiency in information transmission?
- High clustering -> Good local resilience?
- Modularity -> Segregation & integration of information?

Eguiluz VM, Chialvo DR, Cecchi GA, Baliki M, Apkarian Scale-free brain functional networks. Phys Rev Lett 94: 018102 (2005).

TABLE I. Average statistical properties of the brain functional networks.

r_c	N	C	L	$\langle k \rangle$	γ	C_{rand}	L_{rand}
0.6	31 503	0.14	11.4	13.41	2.0	4.3×10^{-4}	3.9
0.7	17 174	0.13	12.9	6.29	2.1	3.7×10^{-4}	5.3
0.8	4891	0.15	6.0	4.12	2.2	8.9×10^{-4}	6.0

"…scale-free complex networks are known to show ***resistance to failure, facility of synchronization, and fast signal processing****…"*



ANALYZING FUNCTIONAL BRAIN NETWORKS

B. Identify differences between healthy brains and those with a certain pathology:

- Quantify evolution towards random topologies.
- Evaluate the loss of modularity in the networks.
- Quantify the increase of energy expenses.

J.M. Buldú, R. Bajo, F. Maestú et al., "Reorganization of Functional Networks in Mild Cognitive Impairment", PLoS ONE 6(5): e19584 (2011)

*"…the **distortion of the functional network is related to an evolution towards random structures**, as indicated by a clustering coefficient and shortest path length that is closer to the random configuration…"*

Figure S1: Percentage of variation of the average degree K, average shortest path L and its normalized value $\hat{L} = \frac{L}{L_{ran}}$, network outreach O and normalized outreach $\hat{O} = \frac{O}{O_{ran}}$, clustering C and normalized clustering $\hat{C} = \frac{C}{C_{ran}}$ and network modularity Q. Circles (•) correspond to $p < 0.03$ and stars (*) to $p < 0.01$, specifically: K ($p = 0.018$), L_z ($p = 0.025$), O ($p = 0.007$), $\hat{O}$ ($p = 0.027$), $\hat{C}$ ($p = 0.002$) and Q ($p = 0.0033$) .

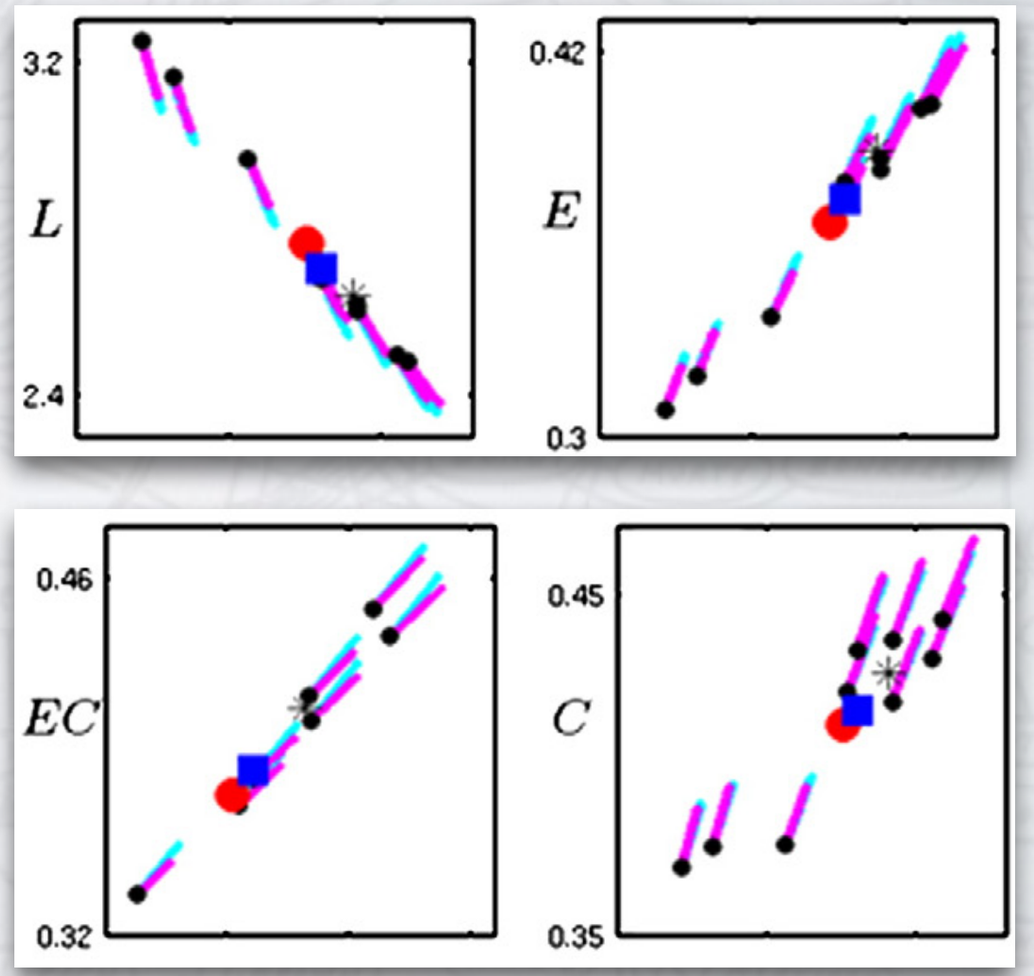
ANALYZING FUNCTIONAL BRAIN NETWORKS

C. Develop models in order to explain the changes found in impaired functional networks:

- Identify what are the rules that determine the network distortion.

N.P. Castellanos, I. Leyva, J.M. Buldú, et al., "Principles of recovery from traumatic brain injury: reorganization of functional networks", Neuroimage, 55, 1189-1199 (2011).

"…These results point to the hypothesis that in the alpha band the structural ***reorganization after recovery corresponds to an increase of the strength in the most active links*** *rather than in the rest of the edges…"*



Modeling Recovery after Traumatic Brain Injury: Shortest path L, Efficiency E, Energetic Cost EC and Clustering C. In all panels, the average parameters of the pre (red circle), post (blue square) and control (black star) groups are plotted.

ANALYZING FUNCTIONAL BRAIN NETWORKS

STEP III: Network Analysis

- We are accumulating errors from the previous two steps
- Functional networks are not static
- High variability in the results
- Functional networks do not evaluate function
- **But… above all…**

ANALYZING FUNCTIONAL BRAIN NETWORKS

STEP III: Network Analysis

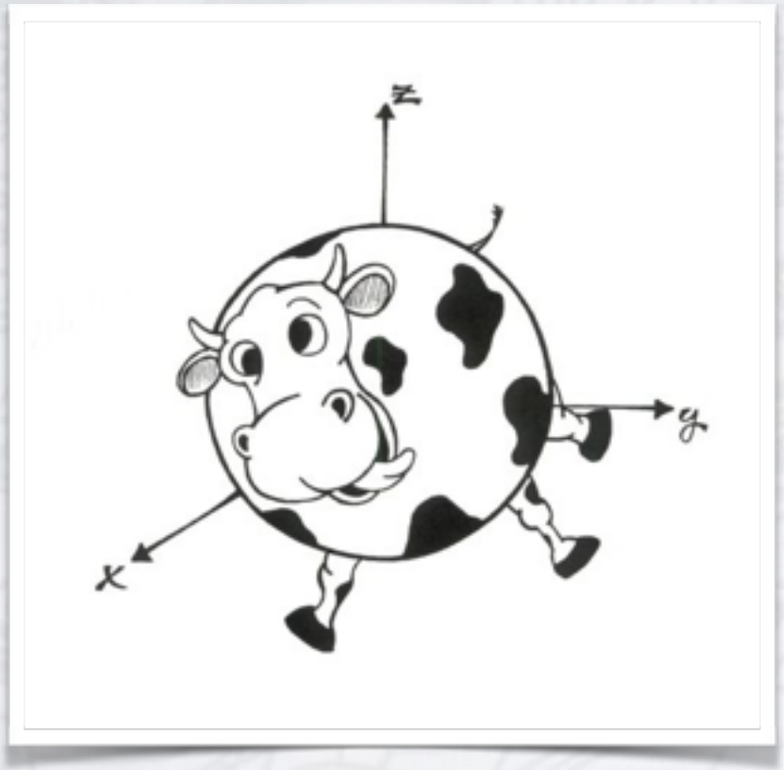
… NETWORK MEASURES ARE COMMONLY **MISINTERPRETED**….

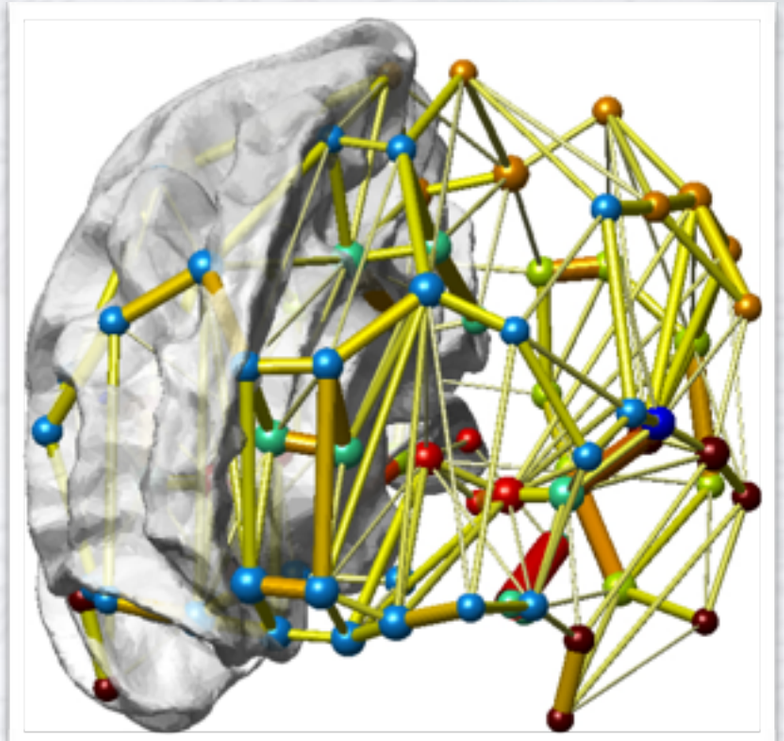
… SINCE WE NORMALLY FORGET THAT WE ARE ANALYZING THE BRAIN!

Risks & Challenges

FUNCTIONAL BRAIN NETWORKS: RISKS & CHALLENGES

When projecting the brain activity into a network, we are loosing a lot of information…





… and we may forget what is behind…

FUNCTIONAL BRAIN NETWORKS: RISKS & CHALLENGES

EXAMPLE 1: Synchronizability

Computers in Biology and Medicine 41 (2011) 1178–1186

Contents lists available at ScienceDirect

Computers in Biology and Medicine

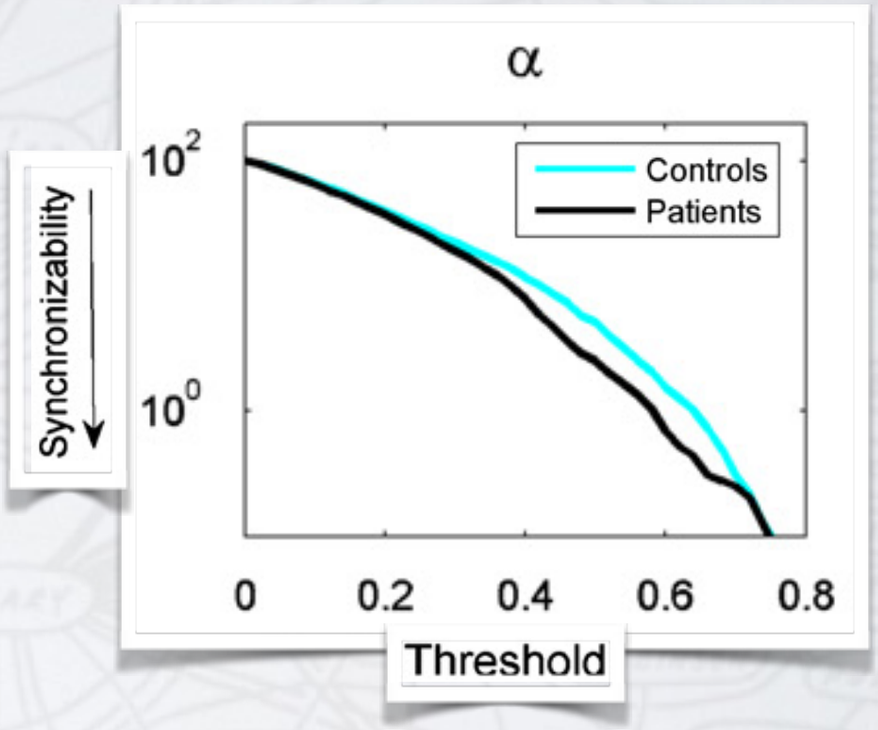
journal homepage: www.elsevier.com/locate/cbm

EEG-based functional networks in schizophrenia

Mahdi Jalili [a,*], Maria G. Knyazeva [b,c]

[a] Department of Computer Engineering, Sharif University of Technology, Tehran, Iran
[b] Department of Clinical Neuroscience, Centre Hospitalier Universitaire Vaudois (CHUV), and University of Lausanne, Lausanne, Switzerland
[c] Department of Radiology, Centre Hospitalier Universitaire Vaudois and University of Lausanne, Switzerland

"…the analysis reported here looks at the **synchronizability** from different perspective and considers the **synchronization properties of the brain networks** rather than looking for a synchronous pattern in the original EEG signal…"



Synchronizability parameter for the control and patient (schizophrenia) group in the alpha band.

FUNCTIONAL BRAIN NETWORKS: RISKS & CHALLENGES

EXAMPLE 1: Synchronizability

CHAOS **18**, 033119 (2008)

Evolving functional network properties and synchronizability during human epileptic seizures

Kaspar A. Schindler,[1,2,a)] Stephan Bialonski,[1,3] Marie-Therese Horstmann,[1,3,4]
Christian E. Elger,[1] and Klaus Lehnertz[1,3,4,b)]
[1]*Department of Epileptology, University of Bonn, Sigmund-Freud-Strasse 25, 53105 Bonn, Germany*
[2]*Department of Neurology, Inselspital, Bern University Hospital and University of Bern, Switzerland*
[3]*Helmholtz-Institute for Radiation and Nuclear Physics, University of Bonn, Nussallee 14-16, 53115 Bonn, Germany*
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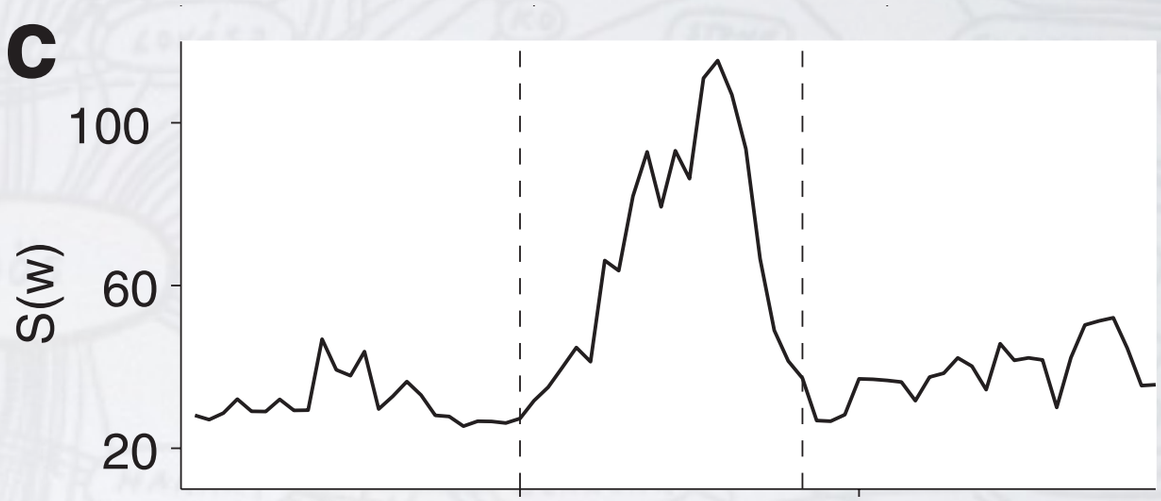
(Received 21 May 2008; accepted 10 July 2008; published online 15 August 2008)

"…we observed a concave-like temporal evolution, **with highest values of S i.e., lowest synchronizability in the middle of the seizure**, followed by a decline i.e., an increasing synchronizability…"

"…while the aforementioned interpretation **WOULD** indicate that the transient **evolution in graph properties is an active process** of the brain to abort a seizure, **our findings could also be understood as a passive consequence of the seizure itself**."

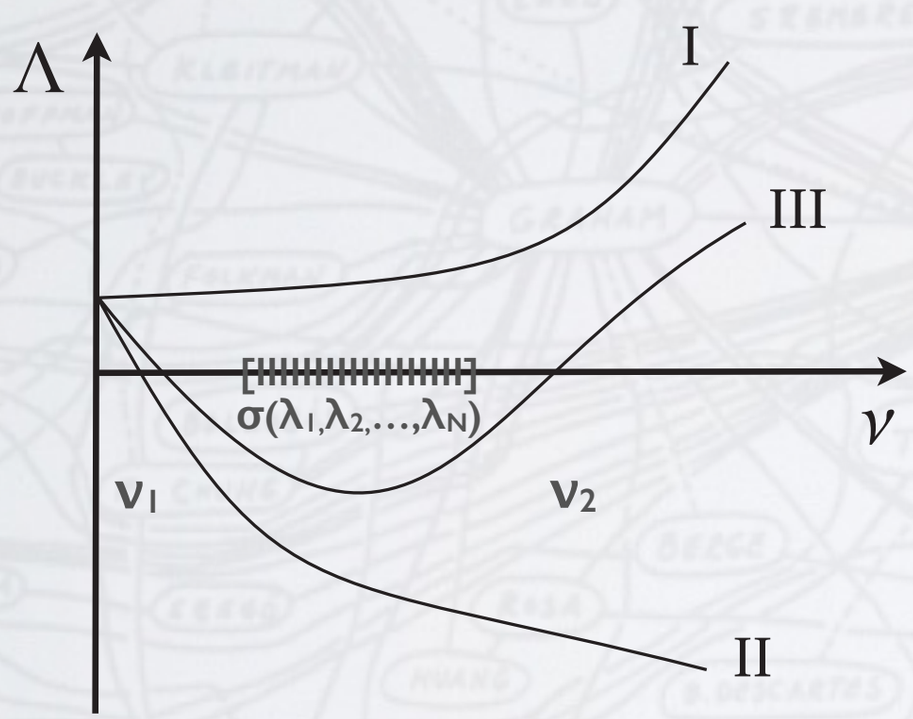


Evolving synchronizability during an epileptic seizure. The synchronizability parameter increases, thus being the network LESS synchronizable.

FUNCTIONAL BRAIN NETWORKS: RISKS & CHALLENGES

The Master Stability Function* (MSF) is a tool to evaluate the **stability of the synchronized state of diffusively coupled dynamical systems**:

$$\dot{\mathbf{x}}_i \;=\; \mathbf{F}(\mathbf{x}_i) + \sigma \sum_{i=1}^{N} a_{ij} w_{ij} [\mathbf{H}(\mathbf{x}_j) - \mathbf{H}(\mathbf{x}_i)] \;=\; \mathbf{F}(\mathbf{x}_i) - \sigma \sum_{j=1}^{N} G_{ij} \mathbf{H}(\mathbf{x}_j)$$



ν is related with σλi where σ is the coupling strength and λi are the eigenvalues of the Laplacian matrix (G=S-M) and $\lambda_1 < \lambda_2 < \ldots < \lambda_N$.

*** Pecora & Carroll, PRL 1998**

Class I system: Not synchronizable

Class II system: $\sigma\lambda_2 > \nu_1$

↓

(the higher, the better)

Class III system: $\sigma\lambda_2 > \nu_1$

$\sigma\lambda_N < \nu_2$

↓

$r = \lambda_N / \lambda_2$

(the lower, the better)

ANALYZING FUNCTIONAL BRAIN NETWORKS

STEP III: Network Analysis

A) IS THE BRAIN A CLASS I/II/III SYSTEM?

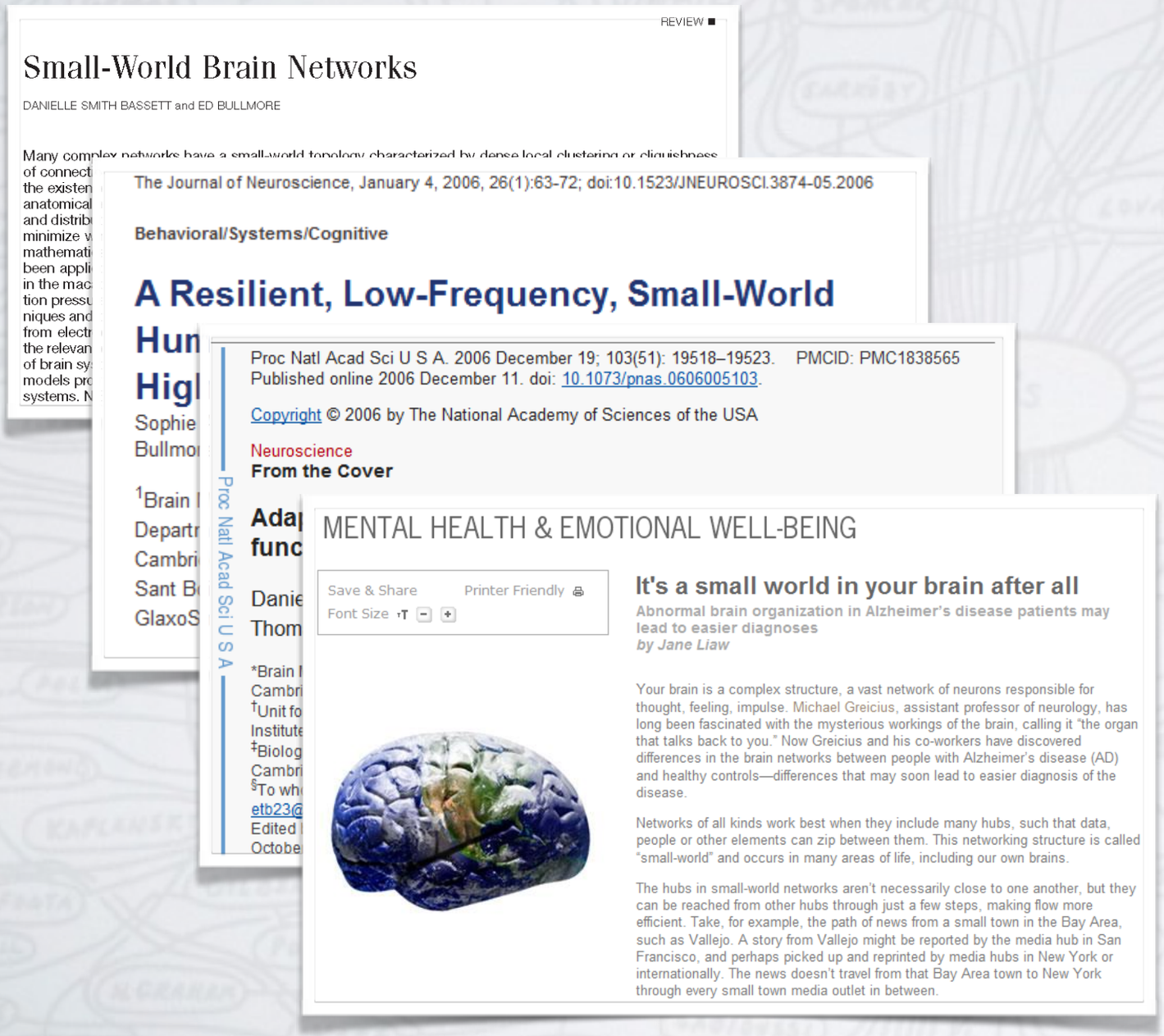
B) DOES THE BRAIN SHOW COMPLETE SYNCHRONIZATION?

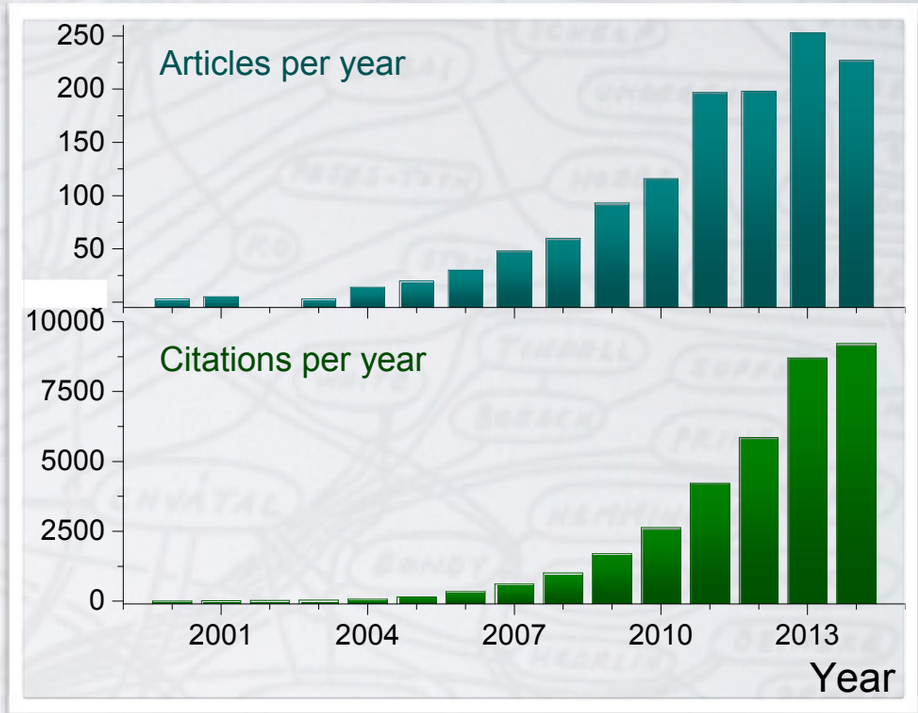
C) IS THE BRAIN COMPOSED OF IDENTICAL SYSTEMS?

D) ARE BRAIN REGIONS DIFFUSIVELY COUPLED?

FUNCTIONAL BRAIN NETWORKS: RISKS & CHALLENGES

EXAMPLE 11: Small-worldness





From Web of Science: (a) number of articles with a topic containing the terms "small-world" and "brain" and (b) number of citations.

FUNCTIONAL BRAIN NETWORKS: RISKS & CHALLENGES

EXAMPLE 11: Small-worldness

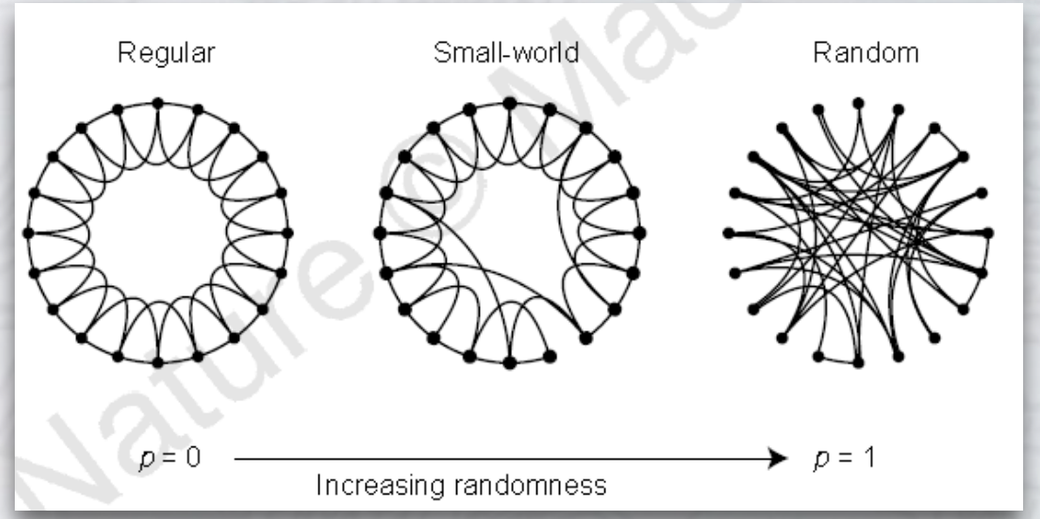
Shortest-path L: corresponds to the lowest number of steps to reach a node from any other node of the network. The average shortest path is obtained by averaging the shortest paths between all pair of nodes of the network.

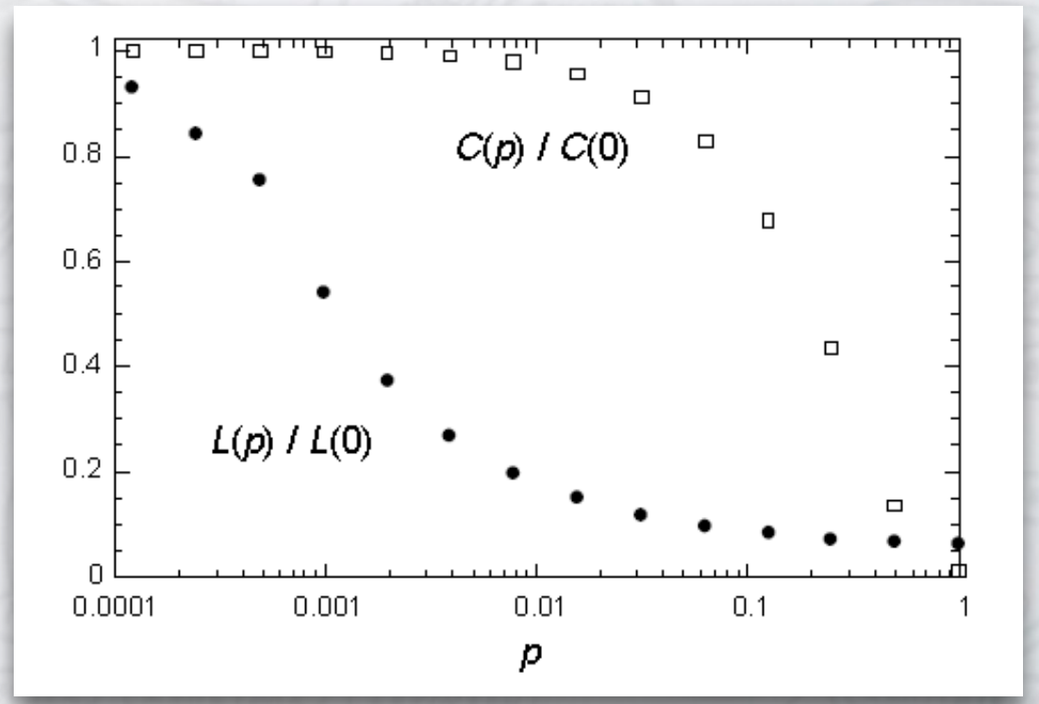
Clustering coefficient C: quantifies the percentage of neighbours of a node that, in turn, are themselves neighbours. It is an indicator of the number of triangles in the network. In real networks, including the brain, C typically has much higher values than in an equivalent random network.

Small-world (SW) network: network with high local clustering C and low average path length L, the latter scaling as L~ln(N). Many social, biological and technological networks are small-world.

Watts-Strogatz model: theoretical model proposed to generate SW networks [4]. Starting from a regular network with an average number of links per node K and a clustering coefficient C=1, links are randomly rewired with probability p. For small values of p, C remains high, but L dramatically decreases, fulfilling a logarithmic dependence on the network size N and leading to a SW network.

Small-worldness is defined as the ratio between C and L normalized by the L_{ran} and C_{ran} of a set of equivalent random networks, i.e., $\sigma = (C/Cran)/(L/Lran)$.





FUNCTIONAL BRAIN NETWORKS: RISKS & CHALLENGES

EXAMPLE II: Small-worldness

- **Brain recording devices and standard analyses** used to construct networks from neural data can **distort** the extent to which a network may appear **SW** (defining the nodes, spurious links, thresholds, …).

- **Quantifying** small-worldness parameter is **non-trivial**. (normalization)

- The **true Aquilles heel of the SW measure lies in interpreting its significance** (meaning of shortest path, efficiency, transmission of information,…)

FUNCTIONAL BRAIN NETWORKS: RISKS & CHALLENGES

EXAMPLE 11: Small-worldness

OPEN ACCESS Freely available online

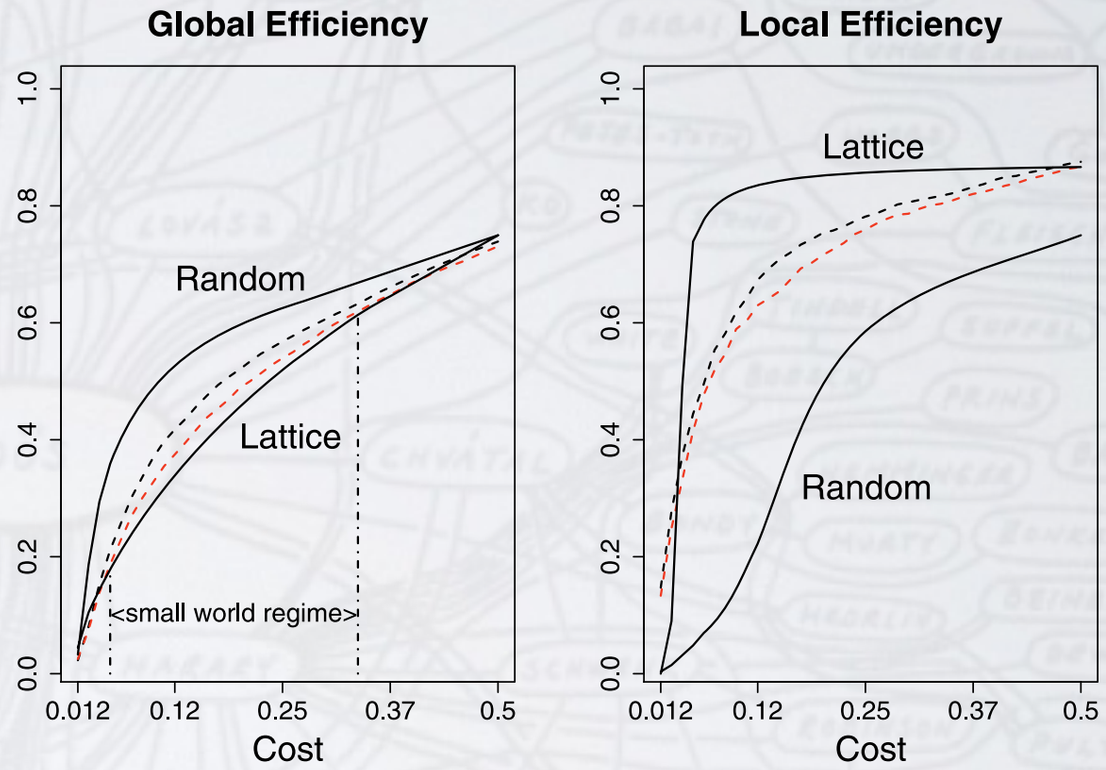
PLoS COMPUTATIONAL BIOLOGY

Efficiency and Cost of Economical Brain Functional Networks

Sophie Achard, Ed Bullmore*

Brain Mapping Unit, Department of Psychiatry, Addenbrooke's Hospital, University of Cambridge, Cambridge, United Kingdom

"… brain functional networks have economical small-world properties—**supporting efficient parallel information transfer at relatively low cost**—"



Small-World Properties of Human Brain Functional Networks. Global and local efficiency (y-axis) as a function of cost (x-axis) for a random graph, a regular lattice, and brain networks. For all networks, global and local efficiency increase with cost; the random graph has greater global efficiency than the lattice; the lattice has greater local efficiency than the random graph. On average, over all subjects in each group, young brain networks (black broken lines) and old brain networks (red broken lines) have efficiency curves located between the limiting cases of random and lattice topology. **The small-world regime is conservatively defined as the range of costs 0.34<K<0.5 for which the global efficiency curve for the old networks is greater than the global efficiency curve for the lattice.**

FUNCTIONAL BRAIN NETWORKS: RISKS & CHALLENGES

EXAMPLE 11: Small-worldness

JOURNAL OF THE ROYAL SOCIETY Interface

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doi:10.1098/rsif.2011.0840
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Dynamics and processing in finite self-similar networks

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[3]*Santa Fe Institute, 1399 Hyde Park Road, Santa Fe, NM 87501, USA*

"**Smaller diameter networks** adjust **more slowly,** have **shorter correlation lengths** and **cannot achieve the levels of non-local integration** seen in those nested systems."

"… show how the **existence of (multiple) paths allows for the more rapid dissipation of inhomogeneity.** Multiple paths are thus central for both information-processing and the time scales of coordination."

FUNCTIONAL BRAIN NETWORKS: RISKS & CHALLENGES

EXAMPLE 11: Small-worldness

RAPID COMMUNICATIONS

PHYSICAL REVIEW E **83**, 025102(R) (2011)

Small but slow world: How network topology and burstiness slow down spreading

M. Karsai,[1,*] M. Kivelä,[1] R. K. Pan,[1] K. Kaski,[1] J. Kertész,[1,2] A.-L. Barabási,[2,3] and J. Saramäki[1]
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(Received 12 June 2010; revised manuscript received 8 November 2010; published 18 February 2011)

"While communication **networks show the small-world property of short paths, the spreading dynamics in them turns out slow.** Here, the time evolution of information propagation is followed through communication networks by using empirical data on contact sequences and the susceptible-infected model."

3 SEPTEMBER 2010 VOL 329 **SCIENCE**

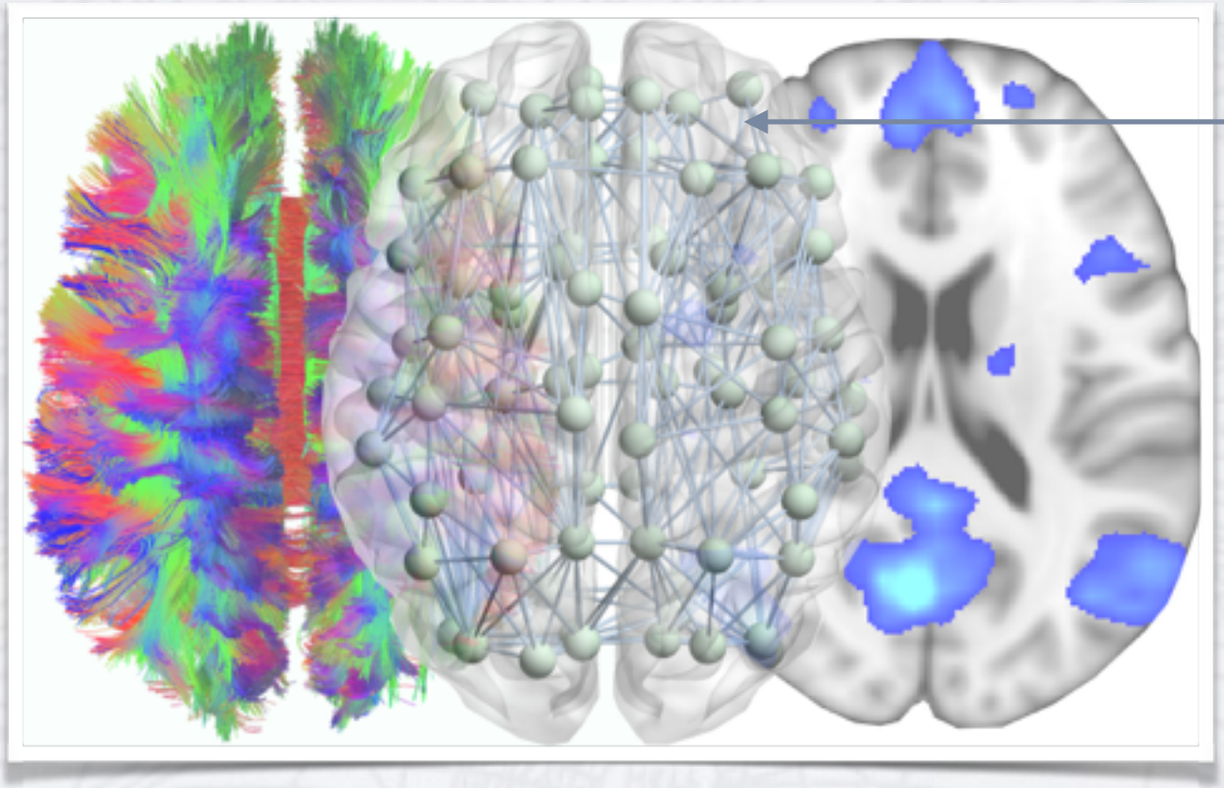
The Spread of Behavior in an Online Social Network Experiment

Damon Centola

"I investigated the effects of network structure on diffusion … **The behavior spread farther and faster across clustered-lattice networks than across corresponding random networks.**"

FUNCTIONAL BRAIN NETWORKS: RISKS & CHALLENGES

The brain is not a usual network: Not a single scale…. not a single dimension! (topology vs. space vs. time)… not static … nodes are not equivalent!



dynamics?
time?
space?
function?

A possible solution: A network-based reduction of the problem may be too strict. We should include as many biological information as possible in the network.

TAKE HOME MESSAGE

Just one and simple message…

… we face the challenge of creating a
neuro-inspired network science!

some related references…

PHILOSOPHICAL TRANSACTIONS OF THE ROYAL SOCIETY B

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Complex network theory and the brain

David Papo[1], Javier M. Buldú[1,2], Stefano Boccaletti[3] and Edward T. Bullmore[4,5]

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[5]GlaxoSmithKline, Alternative Discovery and Development, Addenbrooke's Centre for Clinical Investigations, Cambridge, UK

PHILOSOPHICAL TRANSACTIONS OF THE ROYAL SOCIETY B

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Opinion piece

Functional brain networks: great expectations, hard times and the big leap forward

David Papo[1], Massimiliano Zanin[2,3], José Angel Pineda-Pardo[1], Stefano Boccaletti[4] and Javier M. Buldú[1,5]

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frontiers in HUMAN NEUROSCIENCE

OPINION ARTICLE
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Reconstructing functional brain networks: have we got the basics right?

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Beware of the small-world, neuroscientist!

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THE (B) TEAM

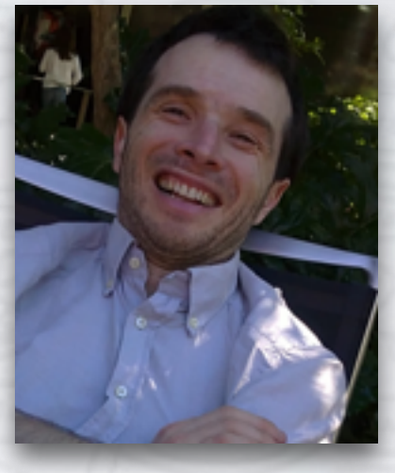
"…they survive as soldiers of fortune. If you have a problem, if no one else can help, and if you can find them, maybe you can hire them…"

Johann H. Martínez
(Universidad del Rosario, Colombia)

David Papo
(La Puta Calle Institute, Spain)

Jose A. Pineda
(Hospital HM Puerta Sur, Spain)

Massimiliano Zanin
(Innaxis, Spain)



More information at
www.complexity.es/jmbuldu