

# Mathematical Biology 3

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- Proteins → Protein-protein interaction networks  
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- Metabolites → Metabolic networks
- Cells → Cell-cell interaction networks
- Animals → Social networks
- Ecosystems → Overlaps of distributions of species
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Formalized by a **graph**, where the vertices represent the elements and the links the interactions between them.

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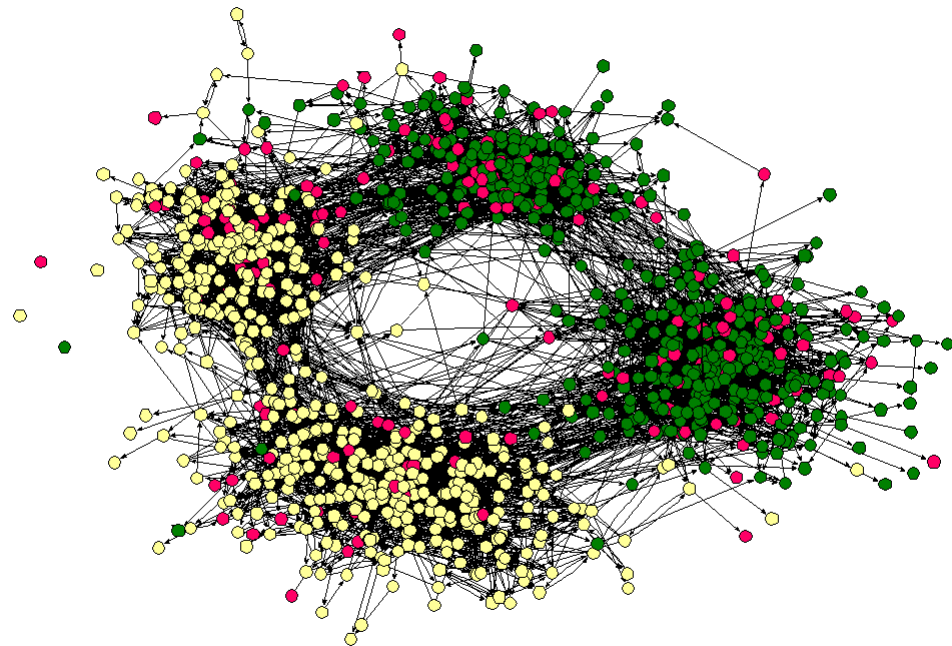
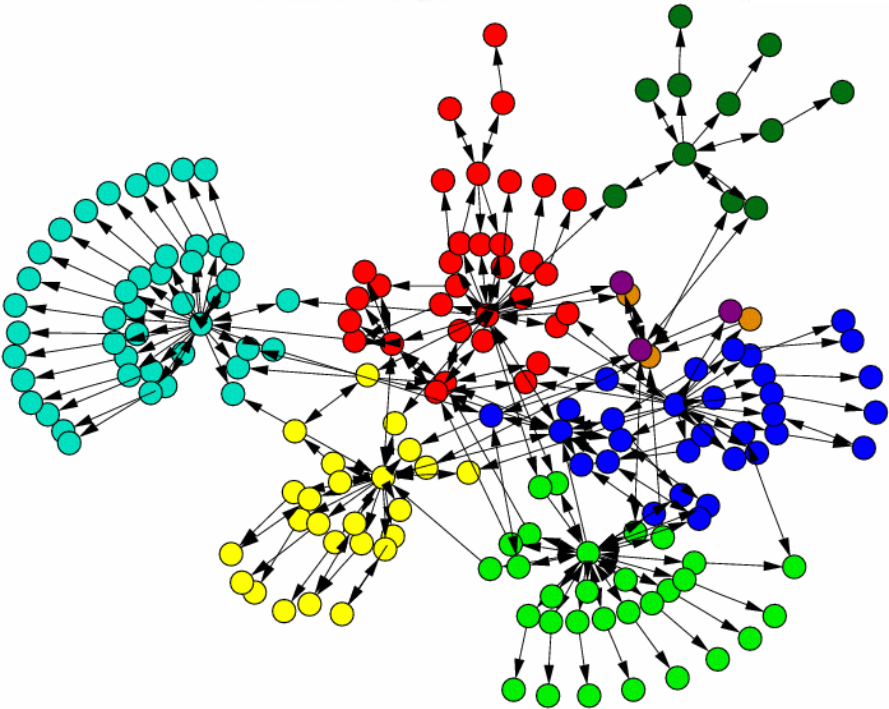
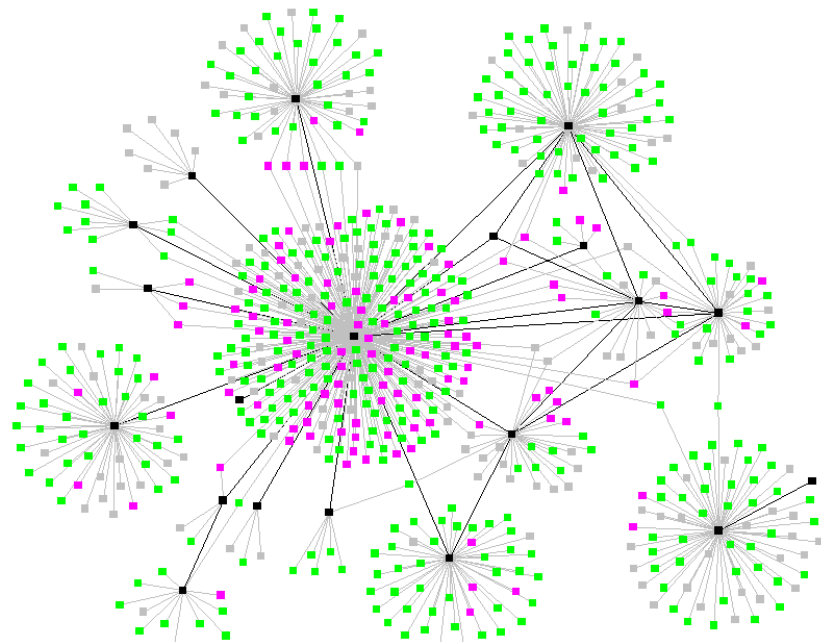
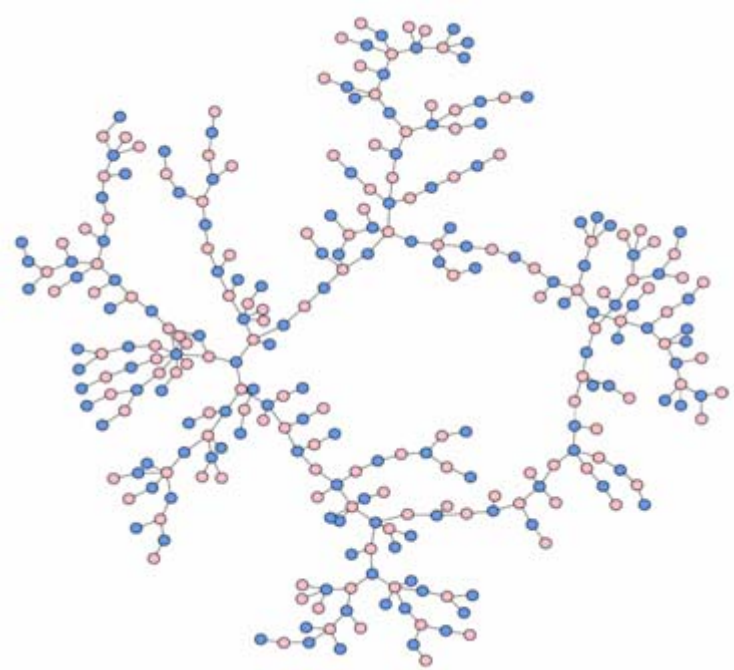
The formal analysis does not care about the physical nature or the biological content and the implementation of the interactions. That is its weakness and its strength.

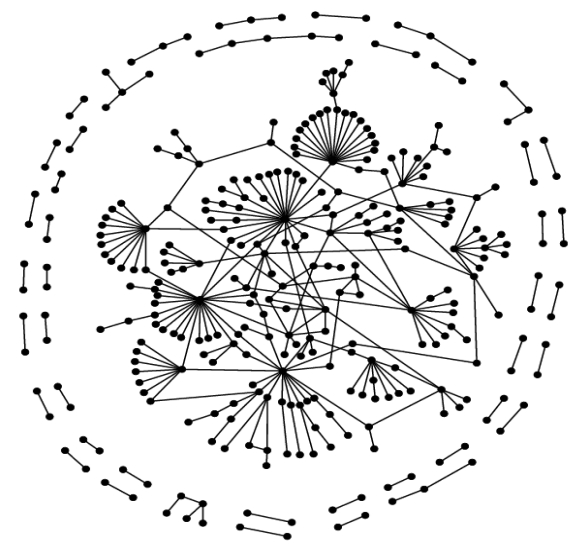
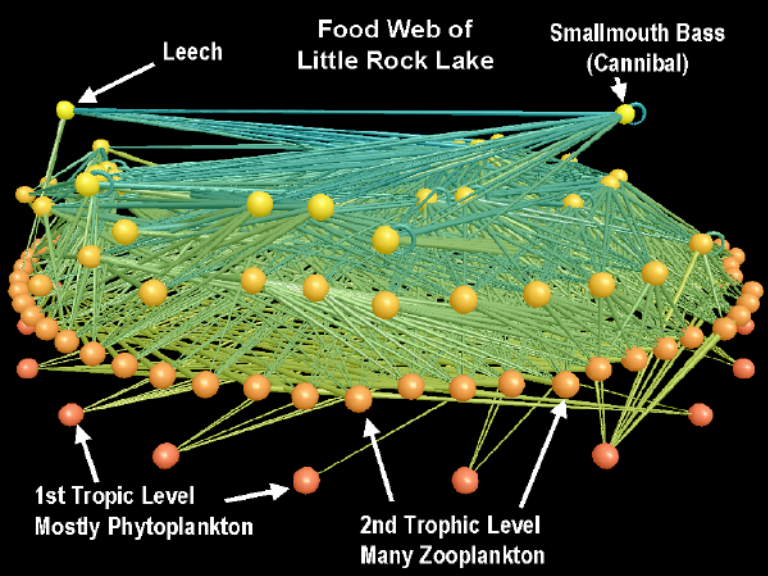
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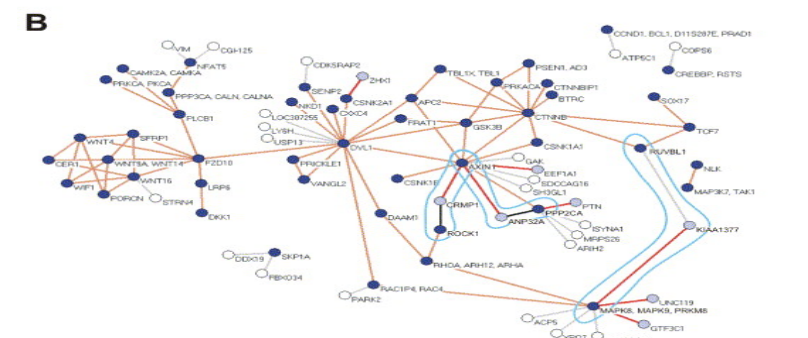
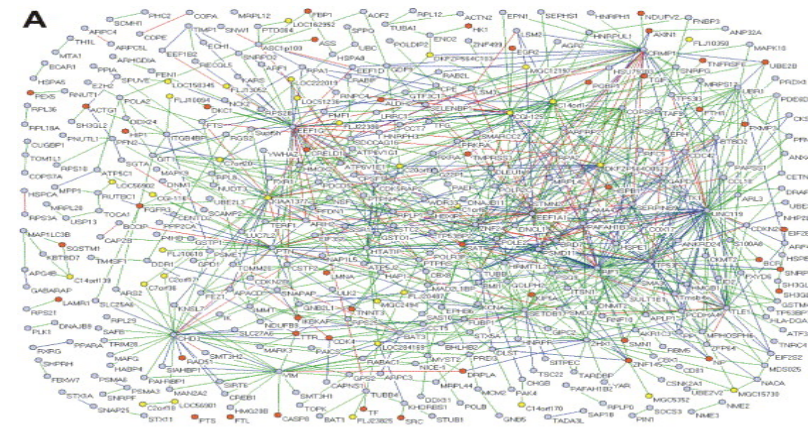
The links can either be binary, that is, simply present or absent (1 or 0), or they can have weights, possibly also negative, in case of inhibition.

→ We need formal mathematical tools to analyze graphs and to distinguish different types of graphs.





• How can we compare these different network representations?



# Graph Laplacian

$\Gamma$ : finite and connected graph with  $N$  vertices.

Vertices  $i, j \in \Gamma$  that are connected by an edge of  $\Gamma$  are called neighbors,  $i \sim j$ .

Degree  $n_i$  of vertex  $i \in \Gamma$  := number of neighbors.

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For functions  $v$  from the vertices of  $\Gamma$  to  $\mathbb{R}$ , we define the (normalized) Laplacian as

$$\Delta v(i) := \frac{1}{n_i} \sum_{j, j \sim i} v(j) - v(i).$$

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$\Delta$  compares the value at the vertex  $i$  with the average of the values at the neighbors of  $i$ .

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Properties:

- Random walks
- Conservation law

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• Symmetric for the product

$$(u, v) := \sum_{i \in V} n_i u(i) v(i),$$

that is,

$$(\Delta u, v) = (u, \Delta v)$$

for all  $u, v$ .

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•  $\Delta$  is nonpositive:

$$(\Delta u, u) \leq 0$$

# Eigenvalues

$$\Delta u_k + \lambda_k u_k = 0$$

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Order the eigenvalues as

$$\lambda_0 < \lambda_1 \leq \dots \leq \lambda_K$$

$$(K := N - 1)$$

# Examples

Complete graph **iff**

$$\lambda_1 = \dots = \lambda_{N-1} = \frac{N}{N-1}.$$

For a complete graph, all eigenvalues are the same.

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Complete graph **iff**

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Bipartite graph (two classes of vertices (male and female), links only between different classes) **iff**

$$\lambda_{N-1} = 2$$

**iff** ( $\lambda$  eigenvalue  $\Leftrightarrow 2 - \lambda$  eigenvalue.)

For a bipartite graph, the spectrum is symmetric about 1

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In general:

$$\lambda_1 \leq \frac{N}{N-1}$$

$$\frac{N}{N-1} \leq \lambda_{N-1} \leq 2$$

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**iff** ( $\lambda$  eigenvalue  $\Leftrightarrow 2 - \lambda$  eigenvalue.)

Lower bound for  $\lambda_1$  estimates how difficult it is to cut graph into two pieces, or how easily coupled dynamics on the graph synchronize.

## Eigenvalue equation

$$\Delta u + \lambda u = 0,$$

that is,

$$\frac{1}{n_i} \sum_{j, j \sim i} u(j) - u(i) + \lambda u(i) = 0$$

rewritten as

$$\frac{1}{n_i} \sum_{j \sim i} u(j) = (1 - \lambda)u(i) \text{ for all } i.$$

In particular, when the eigenfunction  $u$  vanishes at  $i$ , then also

$$\sum_{j \sim i} u(j) = 0,$$

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the average of the neighboring values vanishes for each  $i$ .  
A solution  $u$  is called **balanced**.

Multiplicity  $m_1$  of eigenvalue 1 = number of linearly independent balanced functions on  $\Gamma$ .

Equivalent algebraic formulation:  $A = (a_{ij})$  adjacency matrix of  $\Gamma$ :  $a_{ij} = 1$  if  $i$  and  $j$  are connected by an edge and  $=0$  else.

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**Mathematical question:** How to determine the kernel of a symmetric 0-1 matrix?

Estimate multiplicity  $m_1$  of eigenvalue 1 on a graph.

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Simple observation: *Let  $q$  be vertex of degree 1 in  $\Gamma$  (called a pending vertex). Then any eigenfunction  $f_1$  for the eigenvalue 1 vanishes at the unique neighbor of  $q$ .*

Follows from  $\sum_{j \sim q} u(j) = 0$

# Vertex doubling

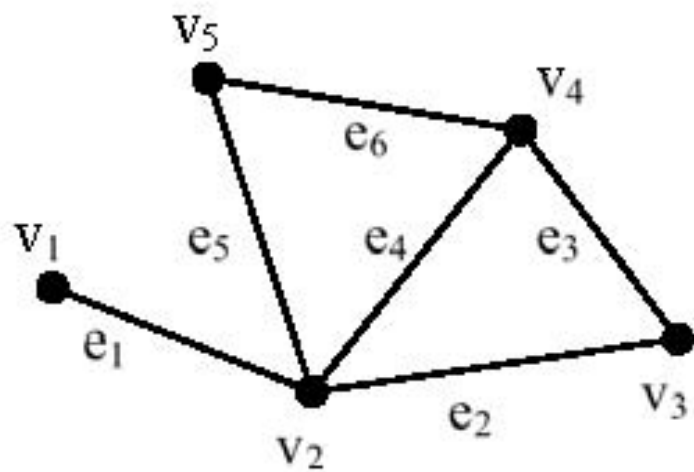
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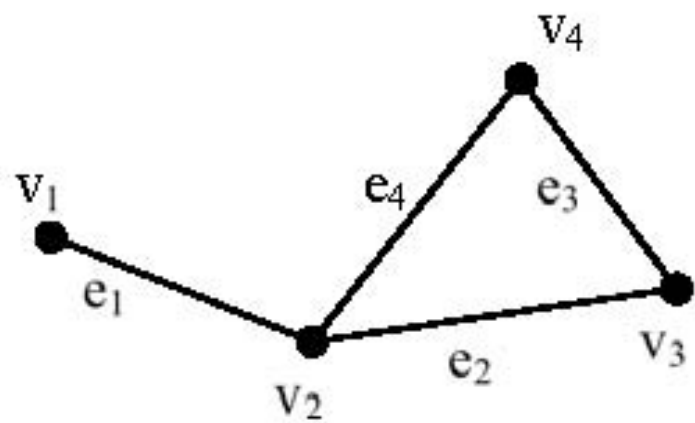
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New eigenfunction  $f_1$ :

$$\begin{aligned} f_1(i) &= 1 \text{ for } i = p \\ &= -1 \text{ for } i = q \\ &= 0 \text{ else.} \end{aligned}$$



(a)



(b)

# Vertex doubling

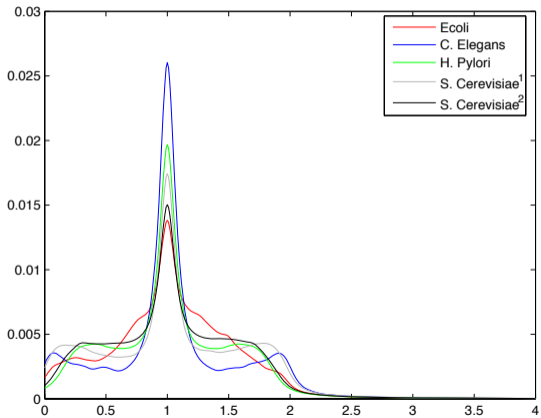
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Satisfies  $\sum_{j \sim i} f_1(j) = 0$  because each  $i$  either has both  $p$  and  $q$  as neighbors or neither of them.

Thus, if we wish to produce a high multiplicity for the eigenvalue 1, we can perform many vertex doublings. We could either duplicate different vertices, or we could duplicate one vertex repeatedly.



Thus, if we wish to produce a high multiplicity for the eigenvalue 1, we can perform many vertex doublings. We could either duplicate different vertices, or we could duplicate one vertex repeatedly. The effects can be distinguished by counting of small motifs.

# Edge doubling

$$\frac{1}{n_i} \sum_{j \in \Sigma, j \sim i} f(j) = (1 - \lambda) f(i) \text{ for all } i \in \Sigma \text{ and some } \lambda.$$

Consider edge connecting two vertices  $p_1, p_2$ . Let  $f$  satisfy

$$\frac{1}{n_{p_1}} f(p_2) = (1 - \lambda) f(p_1), \quad \frac{1}{n_{p_2}} f(p_1) = (1 - \lambda) f(p_2).$$

This admits the solutions

$$\lambda = 1 \pm \frac{1}{\sqrt{n_{p_1} n_{p_2}}}$$

(symmetric about 1).

# Edge doubling

We double the edge, that is, we add a new edge  $q_1, q_2$  and connect  $q_i, i = 1, 2$  with all neighbors of  $p_i$ . This doubling produces a graph  $\Gamma'$  with eigenvalue  $\lambda$  and an eigenfunction  $f'$  agreeing with  $f$  on the edge  $p_1, p_2$ , with  $-f$  on the new edge  $q_1, q_2$ , and being 0 on the rest of  $\Gamma'$ .

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When  $p_1$  or  $p_2$  has a large degree, these eigenvalues

$\lambda = 1 \pm \frac{1}{\sqrt{n_{p_1} n_{p_2}}}$  become close to 1.

# Spectral plots

Spectral plots of (formal and biological) networks: convolve the eigenvalues with a Lorentz kernel, i.e., plot the graph of the function

$$f(x) = \sum_{\lambda_j} \frac{\gamma}{(\lambda_j - x)^2 + \gamma^2}$$

where the  $\lambda_j$  are the eigenvalues and we choose the parameter value  $\gamma = .03$ .

# Spectral plots

Spectral plot with Lorentz kernel

$$f(x) = \sum_{\lambda_j} \frac{\gamma}{(\lambda_j - x)^2 + \gamma^2}.$$

Could as well take some other kernel; general formula

$f(x) = \sum_{\lambda_j} \int k(x, \lambda) \delta(\lambda - \lambda_j) d\lambda$  where  $k(x, \lambda)$  is some kernel function. For example, a Gaussian kernel, or a piecewise constant kernel  $k(x, \lambda) = \frac{1}{2\gamma}$  if  $|x - \lambda| \leq \gamma$  and 0 else.

# Spectral plots

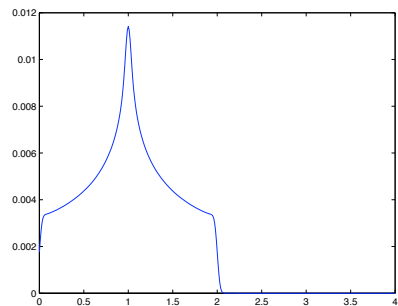
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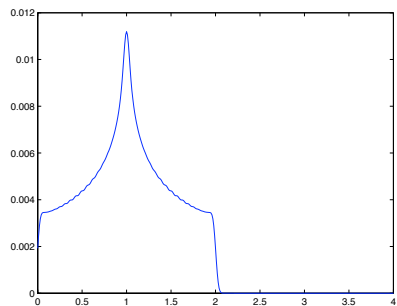
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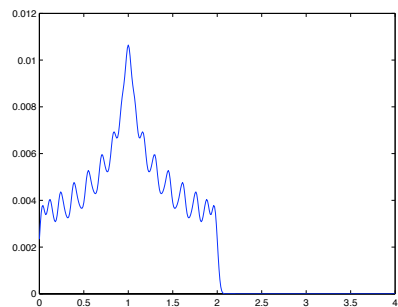
Shape of kernel less important than careful choice of the parameter  $\gamma$ . **For small  $\gamma$ , plot obscures global features**  $\leftrightarrow$   
**For large  $\gamma$ , details become blurred.**



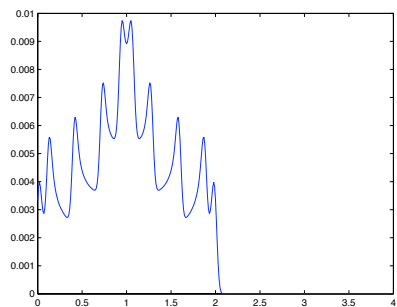
(a)



(b)

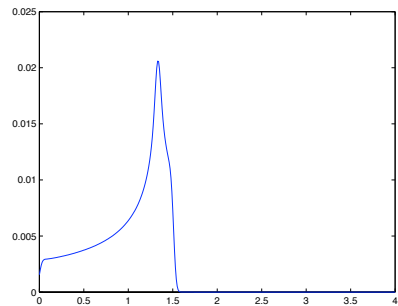


(c)

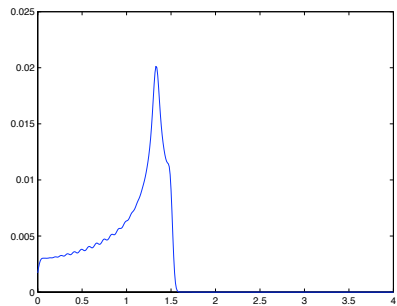


(d)

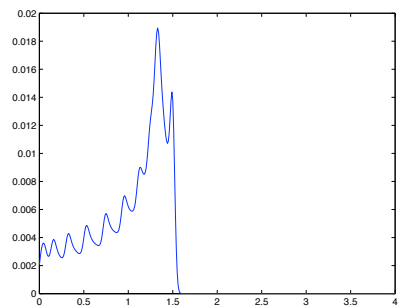
Figure 1: 2-dimensional grid with dimension  $M$  by  $N$ . (a)  $M=100$ ,  $N=100$ . (b)  $M=25$ ,  $N=400$ . (c)  $M=10$ ,  $N=1000$ . (d)  $M=5$ ,  $N=2000$ .



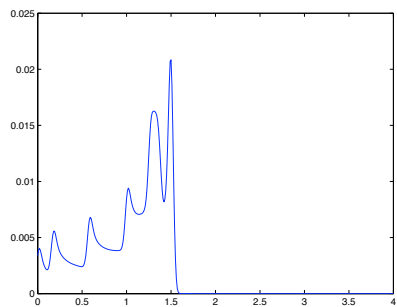
(a)



(b)



(c)



(d)

Figure 2: 2-dimensional grid with one diagonal in each square with dimension  $M$  by  $N$ . (a)  $M=100$ ,  $N=100$ . (b)  $M=25$ ,  $N=400$ . (c)  $M=10$ ,  $N=1000$ . (d)  $M=5$ ,  $N=2000$ .

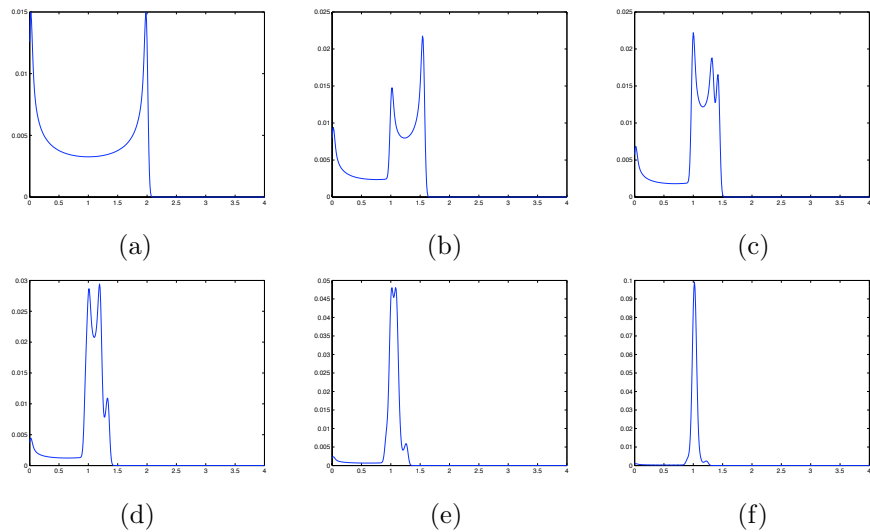


Figure 3: 1-dimensional regular ring lattice of size 1000 with degree of each vertex (a) 2 (b) 4 (c) 6 (d) 10 (e) 20 (f) 50.



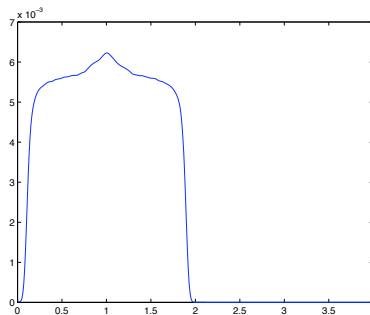


Figure 5: Spectral plot of a small-world network created by rewiring a 2-dimensional grid of dimension 100 by 100 with rewiring probability 0.3. *Single realization.*

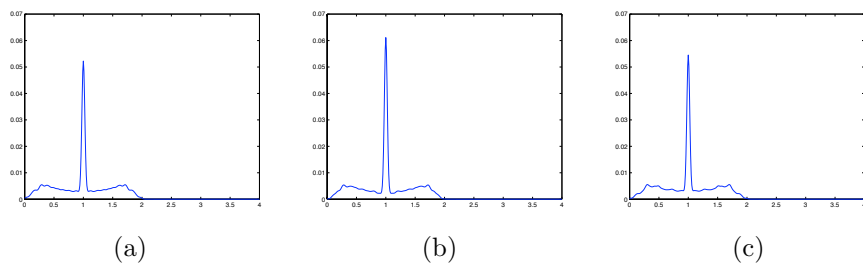


Figure 6: Metabolic networks. Nodes represent substrates, enzymes and intermediate complexes. Data used in [14]. Data Source: <http://www.nd.edu/~networks/resources.htm/>. [Download date: 22nd Nov. 2004] (a) *Archaeoglobus fulgidus*. Network size 1268. (b) *Escherichia coli*. Network size 2268. (c) *Saccharomyces cerevisiae*. Network size 1511.

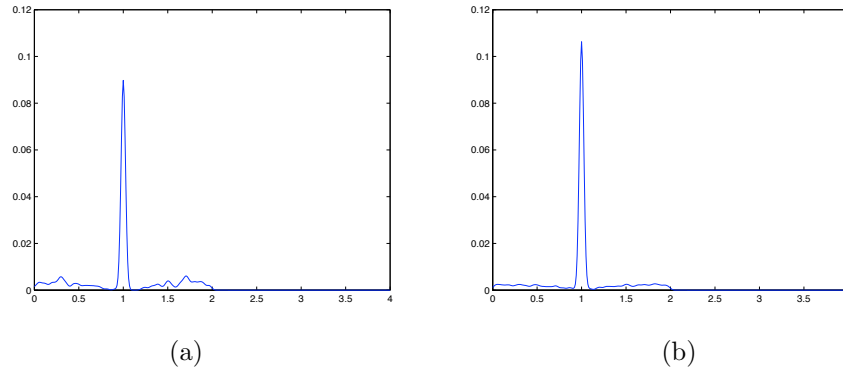


Figure 7: Transcription networks. Data source: Data published by Uri Alon (<http://www.weizmann.ac.il/mcb/UriAlon/> ). [Download date: 13th Oct. 2004]. Data used in [20, 26]. (a) *Escherichia coli*. Network size 328. (b) *Saccharomyces cerevisiae*. Network size 662.

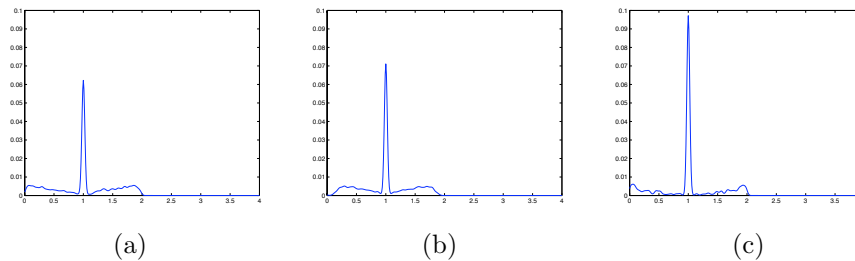


Figure 8: Protein-protein interaction networks. (a) *Saccharomyces cerevisiae*. Network size 1458. Data downloaded from <http://www.nd.edu/~networks/> and data used in [15] [download date: 17th September, 2004]. (b) *Helicobacter pylori*. Network size 710. (c) *Caenorhabditis elegans*. Network size 314. (b,c) Data collected from <http://www.cosin.org/> [download date: 25th September, 2005].

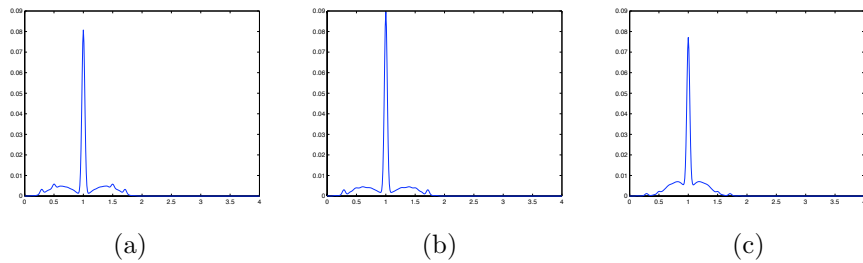


Figure 9: Word-adjacency networks of a text in (a) French. Network size 8308. (b) Japanese. Network size 2698. (c) English. SNetwork size 7377. Data downloaded from <http://www.weizmann.ac.il/mcb/UriAlon/> [Download date 3rd Feb. 2005]. Data used in [21].

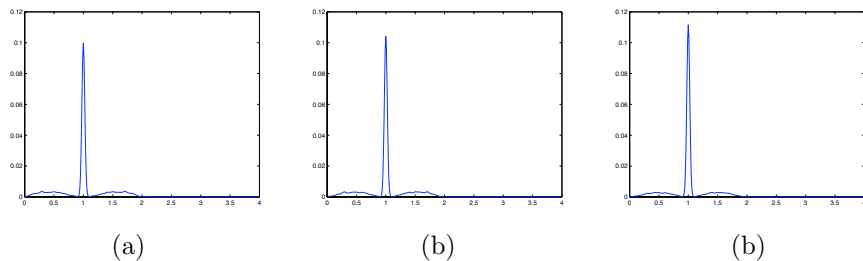


Figure 10: Autonomous Systems topology of the Internet. Every vertex represents an autonomous system, and two vertices are connected if there is at least one physical link between the two corresponding Autonomous Systems. (a) AS graph of 1997/11/08. Network size 3015. (b) AS graph of 1999/07/02. Network size 5357. (c) AS graph of 2001/03/16. Network size 10515. Data collected from <http://151.100.123.37/extra/data/internet/nlanr.html> and data used in [10] [download date: 23rd September, 2005]. Main source: BGP routing data collected by University of Oregon Route Views Project, then processed and made available in various formats at the Global ISP interconnectivity by AS number page of NLNR (National Laboratory of Applied Network Research).

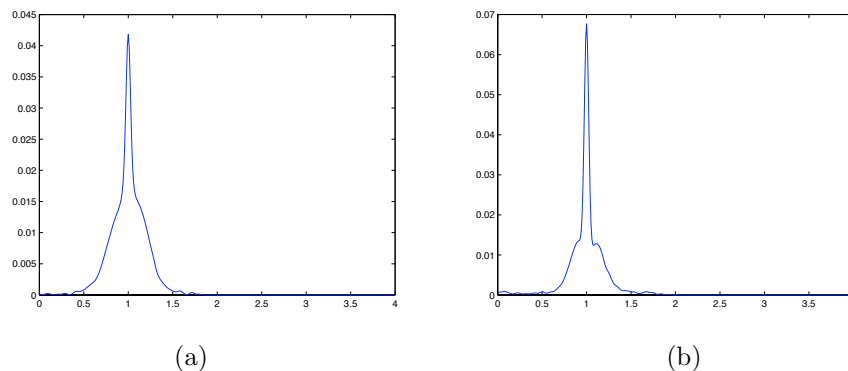


Figure 11: (a) The network of hyperlinks between weblogs on US politics, recorded in 2005 by Adamic and Glance [1]. Network size 1222. Data downloaded from <http://www-personal.umich.edu/~mejn/netdata/> [Download date: 23rd April 2007]. (b) Network of conformation space (Only conformations that are visited at least 20 times during the simulation are considered in the building of the network.) of a 20 residue antiparallel beta-sheet peptide sampled by molecular dynamics simulations [25]. Snapshots saved along the trajectory are grouped according to secondary structure into nodes of the network and the transitions between them are links. Network size 1199. Downloaded from Caffisch group, University of Zurich, <http://www.biochem-caffisch.unizh.ch/> [Download date: 18th Dec. 2006].

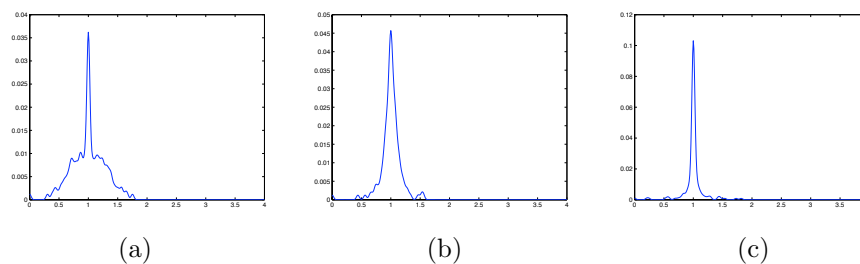


Figure 12: Food-web. (a) From "Ythan estuary". Data downloaded from <http://www.cosin.org/>. [Download Date 21st December, 2006]. Network size 135. (b) From "Florida bay in wet season". Data downloaded from <http://vlado.fmf.uni-lj.si/pub/networks/data/> (main data resource: Chesapeake Biological Laboratory. Web link: <http://www.cbl.umces.edu/>). [Download Date 21st December, 2006]. Network size 128. (c) From "Little rock lake". Data downloaded from <http://www.cosin.org/>. [Download Date 21st December, 2006]. Size of the network is 183.

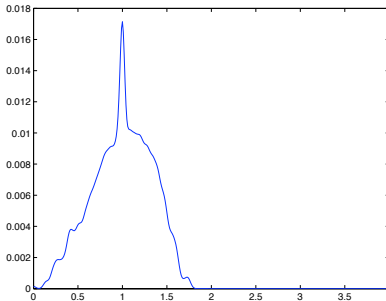


Figure 13: E-mail interchanges between members of the Univeristy Rovira i Virgili (Tarragona) [12]. Network size 1133. Data downloaded from <http://www.etse.urv.es/~aarenas/data/welcome.htm> [Download date: 21st March, 2007].

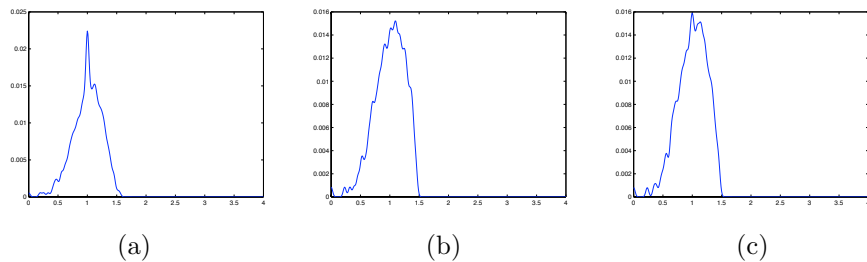


Figure 14: Neuronal connectivity. (a) *Caenorhabditis elegans*. Network size 297. Data used in [28, 29]. Data Source: <http://cdg.columbia.edu/cdg/datasets/> [Download date: 18th Dec. 2006]. (b) *Caenorhabditis elegans* (animal JSH, L4 male) in the nerve ring and RVG regions. Network size 190. Data source: Data assembled by J. G. White, E. Southgate, J. N. Thomson, S. Brenner [29] and revisited by R. M. Durbin (Ref. <http://elegans.swmed.edu/parts/>). [Download date: 27th Sep. 2005]. (c) *Caenorhabditis elegans* (animal N2U, adult hermaphrodite) in the nerve ring and RVG regions. Network size 199. Data source: Data assembled by J. G. White, E. Southgate, J. N. Thomson, S. Brenner [29] and revisited by R. M. Durbin (Ref. <http://elegans.swmed.edu/parts/>). [Download date: 27th Sep. 2005].

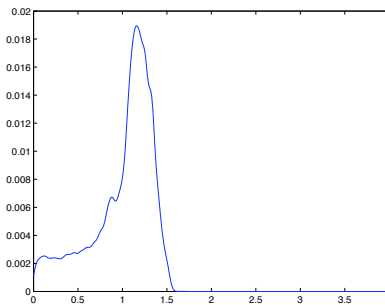
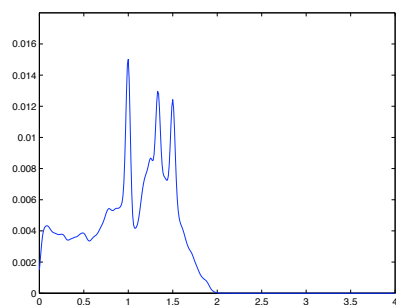
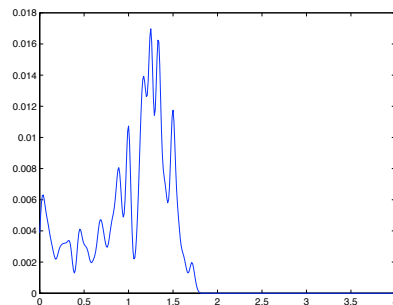


Figure 15: Topology of the Western States Power Grid of the United States [28]. Network size 4941. Data downloaded from <http://cdg.columbia.edu/uploads/datasets/> [Download date: 1st March, 2007].

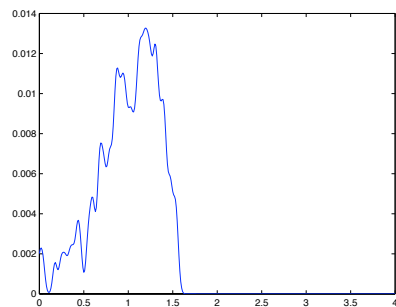


(a)

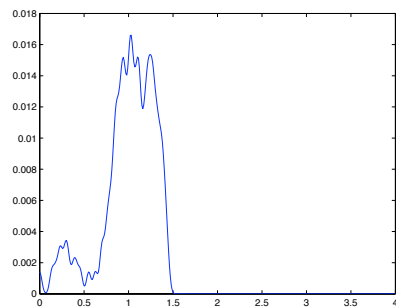


(b)

Figure 16: (a) Coauthorships between scientists posting preprints on the High-Energy Theory E-Print Archive, <http://arxiv.org/archive/hep-th> between 1st Jan, 1995 and 31st December 1999 [22]. Network size 5835. (b) Coauthorships of scientists working on network theory and experiment [23]. Network size 379. Data downloaded from <http://www-personal.umich.edu/~mejn/netdata/> [Download date: 23rd April, 2007].

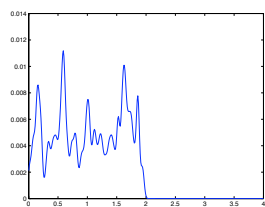


(a)

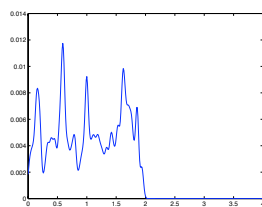


(b)

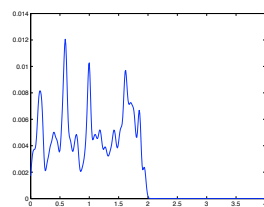
Figure 17: (a) Books about recent US politics sold by the online bookseller Amazon.com. Edges between books represent frequent copurchasing of books by the same buyers. Network compiled by V. Krebs (unpublished). Network size 105. Data downloaded from <http://www-personal.umich.edu/~mejn/netdata/> [original source <http://www.orgnet.com/>. Download date: 23rd April, 2007]. (b) American football games between Division IA colleges during regular season Fall 2000, as compiled by M. Girvan and M. Newman [11]. Network size 115. Data downloaded from <http://www-personal.umich.edu/~mejn/netdata/> [Download date: 23rd April, 2007].



(a)



(b)



(c)

Figure 18: Electronic circuits. (a) With size = 122. (b) With size = 252. (c) With size = 512. Data downloaded from <http://www.weizmann.ac.il/mcb/UriAlon/> [Download date: 15th March, 2005]. Data used in [20].

# More structure

Links in a network can be

- weighted (e.g. synaptic strength), possibly also with negative weights (inhibitory synapses)
- directed (synapse goes from pre- to postsynaptic neuron)
- changing in time (mobile phone networks, intracellular interactions)
- randomly failing
- ...

Spectral analysis of biological networks is joint work with  
[Anirban Banerjee](#)

Spectra of non-symmetric (directed) and weighted graphs:  
[Frank Bauer](#)

Synchronization of nonlinear dynamics is joint work with  
Joy, Fatihcan Atay, Wenlian Lu, Frank Bauer, and others.