Current trends in the modeling of biological networks

Yamir Moreno[*], Luis Mario Floría[†,*] and Jesús Gómez-Gardeñes[†,*]

[*]*Instituto de Biocomputación y Física de los Sistemas Complejos.*
Universidad de Zaragoza, E-50009 Spain.
[†]*Departamento de Física de la Materia Condensada.*
Universidad de Zaragoza, E-50009 Spain.

Abstract.

How does the interplay between complex structures and nonlinear dynamics may shed new light on what is going on at the cellular and molecular levels of organization of biological systems? As in other natural systems, on one hand, scientists have begun to look for patterns of interactions in biological systems. The idea behind this approach is that we can not completely understand the functioning of the cell by studying its components separately. The next step consists of taking into account the dynamics governing the unraveled interactions. This is certainly not an easy task as one has to deal with two sources of complexity: one coming from the unraveled structural patterns and the other from a dynamics in which analytical insights are difficult to take. Here we summarize some of the most recent and important works addressing the network approach to biological systems.

Keywords: Biological Networks, Boolean Dynamics, Power-law Distributions, Michaelis Menten Dynamics
PACS: 89.75.-k; 95.10.Fh; 89.75.Fb; 05.45.-a

INTRODUCTION

In 1999, Hartwell and collaborators published an influential paper discussing the new challenges of modern biology [1]. The authors pointed out that an issue of utmost importance is to develop a general framework in which biological functions could be understood as part of a complex modular organization of molecules or cell's constituents. In other words, modern biology should explain not only the functioning of individual cellular components, but also how these components are interconnected through a complex web of interactions leading to the function of a living cell. It is then natural to ask what these biological networks at the cell organization level look like and how their structure couples to the dynamics.

Cells are life's fundamental units of structure and function. It was expected that, once the complete instructions encoded in DNA would have been interpreted, one could map a gene (the basic information unit in the DNA) into a specific activity or function, with all the consequent potential applications such as targeted drug development [2]. On the contrary, although today the complete knowledge on the genes of several organisms is available, yet the relationship between blueprints in DNA and functional activities of the cell is not fully understood. For instance, the p53 gene and protein (having the function of controlling cell's life and death) are known as tumor-suppressor, since it was found that the p53 protein does not function correctly in most human cancers. However, despite the many studies performed on p53 gene and protein, the way on how effectively suppressing the growth of cancer cells is missing at a genetic level. Recently, it has been proposed that the understanding of such cancer cell growth mechanism would be gathered not only from the study of the p53 gene and protein, but taking into account the whole network interacting with them [3]. That is, the function of the gene should be analyzed through a network in which the gene participates. Similarly to p53 network case, several other observations prove that some functional activities of the cell emerge from interactions between different cell's components through complex webs. Moreover, it is expected that the large-scale network approach may lead to new insights on various longstanding questions on life, such as robustness to external perturbations, adaptation to external circumstances, and even hidden underlying design principles of evolution.

In what follows, we discuss the last advances in the characterization of some biological networks from two points of view: their structural organization and their functioning. The main point here is how to uncover the relationship between the two sources of complexity intimately linked (dynamics and structure) as both play a key role in the functioning of the system. We stress here that our main intention is to provide a brief overview of the current state in the field, and that many works may be overlooked due to space constraints. We invite the interested reader to follow the specialized literature.

STRUCTURE

A plenty of cellular and molecular networks have been unraveled in the last several years. We here refer to those that have been more used in subsequent studies or because they are considered to be essential for the cell's life.

The first of these complex biological networks is that formed by metabolic reactions:

the metabolic network. Jeong et al. have considered the metabolic reactions of 43 different organisms, representing the three domains of life, and have constructed directed graphs whose nodes are the metabolites and edges represent biochemical reactions [4]. A node receives an incoming edge when the corresponding metabolite is produced, and receives an outgoing edge when the metabolite is educed. Enzymes are not included in the graph. The total number of connections (edges) of a node is called the degree of the node. If the edges have a direction (incident to or going out from the node), the degree of a node is divided in in-degree and out-degree, respectively. For all investigated organisms, the resulting graphs for metabolic reactions exhibit scale-free properties for both incoming and outgoing degree distributions.

Scale-free networks refer to a class of graph in which the probability that a node is connected with k other nodes follows a power law distribution $P(k) \sim k^{-\gamma}$, with $2 \leq \gamma \leq 3$ in the vast majority of networks. This is a property not only found in biology, but in fields as diverse as social, technological and natural systems [5]. Besides, scale-free networks are characterized by what is known as *small-world property*, which means that the average distance between any two nodes of the graph scales at much as $logN$, where N is the size of the system. The power-law distribution for the degree of the vertices of a network and the small world property are common topological features of many real world networks [5].

The above-mentioned properties were found universally, irrespective of metabolic pathway databases and of the methods used to construct graphs from biochemical reactions. For example, instead of assuming virtual intermediate complexes, Wagner and Fell built up two networks (the metabolite and the reaction networks) from the metabolic pathways of *Escherichia coli* [6]. The metabolite network consists of nodes representing metabolites and bidirectional links between educt and product of a metabolic reaction. On the other hand, the reaction network is the network where the nodes correspond to metabolic reactions and two nodes are linked when the two reactions share a metabolite. In metabolite networks, scale-free properties are detected, while the reaction network does not show power-law degree distributions. Small-world properties and relatively high clustering (i.e, how probable it is that two nodes with a common neighbor are also connected together) are found in both networks. Other studies with different ways of obtaining graphs show almost identical results [7, 8, 9, 10].

Another class of well-studied cellular networks is that of protein-protein and protein-gene interaction networks. This is due to the increasing availability of data sets and new experimental techniques that allows a more detailed study of the interactions at the cellular level. On the other hand, interactions among proteins have a crucial role in several functional activities, such as signal transduction. According to the demand of understanding the protein interaction map, several high-throughput experiments have been performed. They provide evidence of a partial interaction map between proteins. In the graph representation, a node corresponds to a protein and two proteins are linked when they physically interact. The east two-hybrid screen method has been applied for revealing protein-protein interactions by Uetz et al. [11] and by Ito et al.[12]. Similarly to metabolic networks, scale-free properties, high-clustering and small-world properties have been found. Besides, the studies performed have allowed to address other questions such as the robustness of these networks against random and directed failures [13]. It should be noticed that the databases used in the analysis show very small overlap, while

the individual networks obtained from each database show a very similar structure. In particular, it has been argued that the biological functional organization and the spatial cellular organization are correlated significantly with the topology of the network, by comparing the connectivity structure with that of randomized networks.

Finally, we note that networks constructed from gene expression data are currently under exploration [14, 15]. For instance, Agrawal [15] have studied networks from gene expression of cancer data. By analyzing individual gene expression level at different samples, networks in which the degree distribution of the nodes shows a power-law behavior in the tails with an exponent 1 can be constructed. Stuart et al. have further shown that co-expressed gene networks of humans, flies, worms, and yeast have scale-free properties [14].

In summary, biological networks seems to share many topological properties. What do these properties mean in a biological system? And what basic principles in biology give rise to such universal features? Many steps toward the answers to these questions have been certainly given in the last several years. However, the majority of the issues addressed are based mainly on analyzing the structure of these networks without taking into account their dynamics, i.e., the fact that the structure correlates with the functioning of the underlying system. For instance, from a topological point of view, it has been argued that the nodes with a high degree (the hubs, those contributing to the tail of the degree distribution) are critical for the robustness of the system to intentional removal of them. On the other hand, the hubs have been shown to radically change the behavior of the system in front of several dynamical processes such as epidemic spreading [5, 16]. It is yet to see whether or not the same results hold when nonlinear dynamics coexists with complex topological structure. We next describe two promising approaches in this direction.

DYNAMICS

During the last several years a wealth of experimental data, obtained with technological advances such as cDNA microarrays, have allowed the dynamical characterization of several biological processes both on a genome-wide and on a multi-gene scales and with fine time resolution. From a theoretical side, compelling models on the dynamics governing metabolic and genetic processes are hard to build as these biological phenomena are highly nonlinear and with many degrees of freedom. However, scientists have certainly advanced towards a comprehensive global understanding of, for instance, gene regulation through genetic engineering that require a thorough understanding of the general principles that can guide the design process. It is impossible here to provide an exhaustive review of the subject. However, we think that it is important to provide at least some ideas about the research lines that relate the structure and the function of biological systems.

Concepts such as operon, regulator gene and transcriptional repression were first introduced in the literature by Jacob and Monod [17]. Their model has served as the basis for more elaborated models as different regulatory mechanisms have been discovered [18]. Recent theoretical studies capitalize on these kind of models in order to elucidate what are the system constituents, their properties and how they interact in order to give

rise to the collective behavior of the system. The final goal is to understand the relationship between structure and function as determined by the biological environment. In this sense, different gene circuit designs should be compared to determine which of them confers selective advantage in an ecological context and thus one should be able to advance what the functional consequences of different designs are. This is usually done by exploring the parameter space and looking for performance criteria such as the ability of a system to return to a steady state after a perturbation (called stability) or its responsiveness, that can be measured as the recovery time of the system after an environmental change (a change in an independent variable).

The results obtained for elementary gene circuits certainly provide answers to intriguing questions about how gene circuits could be organized, but at the same time pose new ones. With the recent advances in the characterization of the structure of gene networks, it is clear that genome-wide approaches will allow to discover new higher-order patterns. Therefore, more efforts in modeling the dynamics of increasingly complex gene circuits are expected in the near future. Some steps in this direction have been given.

Boolean modeling of regulatory networks

The first attempt to describe the functioning of genetic regulatory networks was performed by S.A. Kauffman [19]. This pioneering work settled the basis for modeling the complex nature of dynamics and interactions between genes and their products. In his work, each gene, i, and its product, I, were abstracted as a node of a random network having a fixed number, k, of neighbors that regulate its level of activation, g_i. This level of activation can be viewed as the concentration of the transcribed mRNA and/or the protein I encoded. The boolean character of the formulation done by Kauffman implies a qualitative description of whether a gene is activated ($g_i = 1$) or not ($g_i = 0$). Besides, time is considered as a discrete variable so that the dynamical behavior of the gene ensemble is described by the temporal series of their activity levels. At each time step the activity level of a single gene is updated considering the state of its k neighbors

$$g_i(t+\tau) = f_i(g_{j_1}(t), ..., g_{j_k}(t)) \; . \tag{1}$$

This is performed by means of booleans functions, f_i, that make use of the basic "AND", "OR" and "NOT" logical functions so that the results can be either 1 if the statement is true or 0 if it is false. The construction of each boolean function depends on the particular interactions that a gene shares with its regulators and has to be carefully analysed with the help of biochemical data. On the other hand, the work by Kauffman was performed from a general point of view and considered a random assignment of the boolean functions that governs the dynamical evolution of the gene's activity. The main result of the work is the existence of a phase transition on the number and length of the dynamical attractors. In particular, for $k > 2$ the number of cycles scales with the number of genes, N, and its length scales exponentially with N. On the other hand, for the case $k = 2$ these two quantities scale as $\sqrt{N}$. The above findings are biologically relevant if one considers that different genetic dynamics can be regarded as biologically differenciate cells. Taking into account that the cell diversity of a living organism scales

approximately with the square root of the genetic population Kauffman suggested that gene regulatory networks should operate just on the border of the dynamically ordered region.

The above findings represented the starting point of a lot of research on the so-called subject of "Kauffman networks" during the last 25 years. These works mainly focus on the search of a full description of the dynamically different regions as well as the characterization of the phase transition (recent work on the matter can be found in [20, 21, 22, 23, 24, 25]). On the other hand, "Kauffman networks" have served as a framework for performing a coarse-grained description of real gene regulatory networks. The availability of real regulatory networks inferred from DNA microarray data joined with the easy implementation and management of the boolean dynamics provides a useful tool for understanding the interplay between the topology and the function of biological networks.

The use of boolean dynamics to characterize real genetic regulatory networks has been recently applied to the case of the *segment polarity genes in the Drosophila Melanogaster* [26]. In this case the whole map of interactions between genes is known and Boolean dynamics is seen to reproduce the patterns of gene expression that appear in the wild type. Besides, it has been tested when mutations are present confirming the validity of the model. The application of this method can help to determine the effects of new mutations and constitute a test for the question of whether the topological features of the interaction network or the kinetic details play the key role in the functioning of biological networks. The success of the use of Boolean modeling points out that it is the former which is the relevant ingredient. Another recent application of Boolean dynamics to a real gene circuit is found in [27] where the *yeast transcriptional network* is considered. In this case the point of view is drastically different because neither the nature of the interactions between genes nor any dynamical state of the system is available. The starting point is simply a set of connected genes and the authors apply a Boolean modeling of the interactions for determining what set of (Boolean) interaction rules lead to a stable dynamics of the whole system. The authors also study the effect of rewiring links of the network and conclude that dynamical states on top of the original network is more stable than on the perturbed ones. The above two examples show how the coarse-grained Boolean modeling can help to analyze the large amount of available experimental data and answer the question on where the biological stability observed has its roots.

Finally, let us remark that the boolean modeling can be reformulated in order to incorporate realistic features of real regulatory networks. Perhaps, the most important ingredient is to reproduce the effects of noise (which is a substantial characteristic of a biological system). This is usually incorporated on the form of a non synchronous update rule, assigning a time delay to each variable of the Boolean functions, f_i. Another interesting extension of the formulation is considering multi-levels for the gene activity so that the model incorporates some quantitative description on how much the gene is activated.

Saturated response

There is a wide variety of situations in which the system response to an external action saturates. Perhaps the most familiar example of saturable behavior known to physicists is the adsorption of gas molecules on a solid surface: At thermodynamical equilibrium, the fraction (coverage ratio) θ of surface interstitial occupied by adsorbed molecules depends on the gas pressure P as [29]

$$\theta = \frac{P}{P_0(T)+P} \tag{2}$$

where the temperature-dependent constant $P_0(T)$ is the pressure value at which the coverage ratio reaches half of its possible maximal value $\theta = 1$. While for small values of P, compared to $P_0(T)$, θ increases linearly with P, for values of the pressure larger than $P_0(T)$ the coverage ratio becomes insensitive to pressure variations. Saturable behaviours of this type (and of a more general form; see below) have been introduced [30] in the modeling of interactions among species in ecological systems, where (most notably) they effectively provide robustness to the limit-cycle behaviour often observed in these systems [31, 32]. In the realm of Social Sciences, saturated response functions have been also used to model some type of social interactions like *e.g.* the effects of community investments in police pressure and/or educational programs on the street-gang growth phenomena [32].

Biological reaction rates are often saturable; while at small concentrations of a new chemical introduced in a cell, this responds sensitively, the response should not keep growing indefinitely as the new chemical concentration grows. The archetypal example of saturation in biological systems is the Michaelis-Menten equation [33] governing the concentration evolution of a product catalyzed from a substrate by an enzyme which binds to it. If x and y denote the concentrations of product and substrate respectively, then the reaction rate is given by

$$\frac{dx}{dt} = \frac{V_{max}y}{K_M+y} \tag{3}$$

where K_M is called the Michaelis constant and V_{max} is the value at which the rate saturates for high substrate concentrations. This saturation behaviour can be understood from the usual chemical kinetics (law of mass-action) in an intuitive way: when the enzyme molecules are mostly bound to substrate molecules, adding more substrate cannot speed up the reaction [34]. If n, instead of only one, substrate molecules bind to the enzyme, the reaction rate takes a more general functional form of saturation, often called Hill equation

$$\frac{dx}{dt} = \frac{V_{max}y^n}{K_M+y^n} \tag{4}$$

showing a sudden increase of the reaction rate towards saturation around $y = K_M$. The Hill parameter n often takes on non-integer values. Both Michaelis-Menten and

Hill equations are often used in models of biological reactions, even when the explicit mechanisms generating them are unknown in many cases.

Synthetic genetic networks

In cells, the proteins, RNA and DNA form a complex network of interacting chemical reactions governing all cellular functional activities like metabolism, response to stimuli, reproduction, ... While the understanding of the structure of these networks is growing rapidly, the current understanding of their dynamics is still rather limited. In this regard, an interesting body of research is currently addressed to synthetic genetic networks, which offer an alternative approach aimed at providing a controlled test bed for the detailed characterization of some isolated functions of natural gene networks, and also pave the way to engineering of new cellular behaviour.

An example of synthetic gene regulatory network, termed the "repressilator", is becoming one of the best studied model systems of this kind. The repressilator is a network of three genes, whose products (proteins) inhibit the transcription of each other in a cyclic way; they were added to the bacterium *E. coli*, so periodically inducing the synthesis of green fluorescent protein as a readout of the network state [35]. The authors of the work first argue that the represilator can show temporal fluctuations in the concentration of each of its components, by analyzing a system of six ODE's (which, in turn, were obtained by a process of integration-out or coarse-grain away of the promoter states involved in the regulation, and rescaling of the variables) modeling the network. If p_i ($i = 1,2,3$) denote the three repressor-protein concentrations (in units of the Michaelis constant K_M), and m_i their corresponding mRNA concentrations (appropriately rescaled), the repressilator equations are (assuming the symmetrical case in which all three repressors are identical except for their DNA-binding specificities):

$$\frac{dm_i}{dt} = -m_i + \frac{\alpha}{1+p_i^n} + \alpha_0 \tag{5}$$

$$\frac{dp_i}{dt} = -\beta(p_i - m_i) \tag{6}$$

where $i = 1,2,3$ and $j = 3,1,2$; α_0 ($\alpha + \alpha_0$) is the number of protein copies produced from a given promoter type in the pressence (absence) of saturating amounts of repressor, β is the ratio of the protein decay rate to the mRNA decay rate, and time is rescaled in units of the mRNA lifetime. This system of equations has a unique steady state which can be stable or unstable depending on the parameter values. In the unstable region of parameter space, the three protein concentrations fluctuate periodically. Experiments show temporal oscillations of fluorescence, which were checked to be due to the repressilator. Though admittedly oversimplified, the model of ODE's guided the experimental design, for it served to identify possible classes of dynamic behaviour and to determine which experimental parameters should be adjusted in order to obtain sustained oscillations.

Not surprisingly, the repressilator called attention from experts on (biological) synchronization, for it offers good prospectives for further insights into the nature of bio-

logical rythms, whose mechanisms remain to be understood. In this respect, in reference [36] the authors propose a simple modular addition (of two proteins) to the repressilator original design, which allows for a mechanism of coupling between cells containing the repressilator networks.

Modules

As seen in the previous subsection, even a very small gene network, like the repressilator, requires some simplifying assumptions for an analysis of its dynamic behaviour in terms of ordinary differential equations. With large networks involving thousands of regulatory genes, this approach would require a huge number of differential equations and, what is even more problematic, an exploding number of dimensions of the parameter space (decay rates, production rates, interaction strengths, etc.). Thus an important issue concerns the right level of description when constructing quantitative models of large genetic networks [28].

In this regard, several works (*e.g.* [37, 38, 39]) have focussed on the identification of general building blocks (motifs) in genetic networks, showing robust or "reliable" behaviour. These include small modules of a few genes, such as autoregulatory excitatory feedback loops, inhibitory feedback loops, feed-forward loops and dual positive-feedback loops, which represent different kinds of robust switching elements, whose occurrence as subgraphs in real networks is significantly higher than in their randomized versions. These works provide support to discrete models in which genes are modeled as switchlike dynamic elements that are either "on" or "off", of the Boolean type described in the previous section, and point toward strong correlations between structural and functional properties of genetic regulation networks.

The robustness of slightly larger modules, like the segment polarity genes of the fruit fly *Drosophila* (a subgraph of the segment determination network, responsible for the embryonic development of the insect body segments), has been convincingly tested with a realistic dynamical model [40] supporting the view that segmentation is modular, with each module autonomously expressing a characteristic intrinsic behaviour in response to transient stimuli. A connectionist model for the segment determination system of *Drosophila*, including cell-cell interaction via one-dimensional diffussion [41] has been thoroughly characterized (along with its continuum limit (PDE) equations [42]). These generalised reaction-diffusion models inspired further work in [43] which identified minimal gene networks associated to different segmentation patterns; also, extensive computer simulation of randomly generated networks showed that combinations of spatial patterns can be mapped into combinations of the basic modules.

The resistance of modules to variations (proxy for mutations of small effect) in the kinetic constants and various parameters that govern its dynamical behaviour, may suggest that evolution could rearrange inputs to modules without changing their intrinsic behaviour, or as conjectured in [43], that the target of selection would operate not only on single-gene level structures, but also on the available structures in the high-dimensional parameter space of the model equations.

Scale-free network topologies

The confluent interest of several scientific disciplines in the many aspects of the problem of Structure-Function correlations in systems made up of discretely many nonlinearly interacting components (of which gene regulatory networks are but a particular example), reccomends to pay some attention to general abstract models. These models should be both, conceptually simple and universal in their perceptions.

The universality of both saturability of the interactions and scale-free character of the interconnections among constituents in many real world systems, irrespective of the diverse nature of their components, interactions and time scales, motivated the study undertaken in [44], aimed at capturing in a simple model some general ingredients of the entangled complexity which arises from the competition of nonlinear interactions on top of complex connectivity topologies. In the model, each constituent unit (say substrate, or agent) sit on a node i ($= 1, \ldots N$) of a "small world" and "scale-free" network, and its activity level is a real function $g_i(t)$ of time. The interaction ($i \leftarrow j$) can be either activatory or inhibitory, and correspondingly the entry W_{ij} of the interaction matrix is defined respectively as $+1$ or -1, whenever interaction exists (or zero otherwise). The fraction of inhibitory interactions is a tunable parameter p of the model. The equations of motion for the activity vector $\mathbf{G}(t) = (g_1(t), \ldots g_N(t))$ are given by

$$\frac{d\mathbf{G}(t)}{dt} = -\mathbf{G}(t) + \alpha \mathbf{F}(\mathbf{W}\mathbf{G}(t)), \tag{7}$$

where $\mathbf{F}$ is a saturated response (Michaelis-Menten) vectorial function of the product of the interaction matrix $\mathbf{W}$ and the activity vector $\mathbf{G}$, and α (positive) is the interaction strength. The model has been extensively analyzed using numerical procedures which combine powerful methods of the nonlinear dynamics of many degrees of freedom and the statistical characterizations of Complex Networks. Note that for each given set of model parameters, one has to sample in network realizations and initial conditions, $\mathbf{G}(t = 0)$, in the N-dimensional phase space. Among the wealth of results obtained, we highlight here the following generic features:

- *Fluctuations over Stasis:* For intermediate values of the parameter p, the measure in phase space of asymptotic trajectories in which activities fluctuate (either periodically or chaotically) in time, prevails over stationary states.
- *Fragmentation:* In the asymptotic states (attractors) the network is fragmented, *i.e.* partitioned into islands of non-zero activity. Islands denote subgraphs which are interconnected between them by nodes which have evolved to null activity, so the dynamics of the islands are effectively disconnected. The genericity of the phenomenon of fragmentation extend to the tangent space: the instabilities experienced by the attractors when model parameters are varied, induce a partition of the dynamical island into (a) participating nodes, and (b) indifferent nodes. The later are nodes such that small single-node perturbations localised on them are orthogonal to instability.
- *Clustering:* The islands of positive activity invariably have a high clustering coefficient, which saturates with increasing network size N, in contrast to the underlying original network whose clustering coefficient tends to zero values when N is in-

creased. Moreover, the islands inherit from the original network the small-world and scale-free character, but it is the development of dynamical fluctuations what generates the clusterization of nodes.

CONCLUSIONS

In summary, a large number of systems have been studied in the last several years from the network perspective [5]. This approach has allowed the understanding of the effects of complex topologies in many well-studied problems. By comparing the results obtained with other topologies and those for real graphs in processes such as the spreading of epidemic diseases [16] and the tolerance of complex networks to random failures and attacks, we have realized that topology plays a fundamental role.

As we have argued throughout the present overview, biological networks are not an exception. They are, at all levels of organization, the subject of intense experimental and theoretical research. The topological analyses performed on these networks have provided new useful insights [13] and are expected to produce new tools to solve longstanding problems. For instance, it is believed that a better comprehension of gene and protein networks will help to elucidate the functions of a large fraction of proteins whose functions are unknown up to date. Moreover, it is a major challenge the discovery of how biological entities interact to perform specific biological processes and tasks, as well as how their functioning is so robust under variations of internal and external parameters. Such an achievement is only possible by merging the new knowledge gained from network analysis with nonlinear dynamics models relevant in biological processes. This is what is driving current theoretical efforts, in which new mathematical models and methods borrowed from nonlinear dynamics are being studied on top of the real architecture of biological networks.

ACKNOWLEDGMENTS

J.G.G. and Y.M. are supported by MEC through a FPU grant and the Ramón y Cajal Program, respectively. This work has been partially supported by the Spanish DGICYT Projects FIS2004-05073-C04-01, FIS2005-00337 and by DGA through a research grant to FENOL.

REFERENCES

1. L. H. Harwell, J. J. Hopfield, S. Leibler and A. W. Murray, Nature **402**, C47 (1999).
2. D. B. Searls, Nature Reviews **4**, 45 (2005).
3. B. Vogelstein, D. Lane, and A. J. Levine, Nature **408**, 307 (2000).
4. H. Jeong, B. Tombor, R. Albert, Z.N. Oltvai, A.-L. Barabási, Nature **407**, 651 (2000).
5. S. Boccaletti, V. Latora, Y. Moreno, M. Chavez, and D.-U. Hwang, *Complex networks: Structure and dynamics*, Phys. Rep. **424**, 175 (2006).
6. S.A. Wagner and D.A. Fell, Proc. R. Soc. London **B268**, 1803 (2001).
7. H. Ma and A.-P. Zeng, Bioinformatics **19**, 270 (2003).
8. H.-W. Ma and A.-P. Zeng, Bioinformatics **19**, 1423 (2003).
9. M. Arita, Proc. Natl. Acad. Sci. USA **101**, 1543 (2004).

10. R. Tanaka, Phys. Rev. Lett. **94**, 168101 (2005).
11. P. Uetz, L. Glot, G. Cagney, T. A. Mansfield and E. Al., Nature **403**, 623 (2000).
12. T. Ito, T. Chiba, R. Ozawa, M. Yoshida, M. Hattori and Y. Sakaki, Proc. Natl. Acad. Sci. USA **98**, 4569 (2001).
13. H. Jeong , S.P. Mason, A.-L. Barabási, Z.N. Oltvai, Nature **411**, 41 (2001).
14. J. M. Stuart *et al.*, Science **302**, 249 (2003).
15. H. Agrawal, Phys. Rev. Lett. **89**, 268702 (2002).
16. Y. Moreno, R. Pastor-Satorras, and A. Vespignani, Eur. Phys. J. **B26**, 521 (2002).
17. F. Jacob and J. Monod, J. Mol. Bio. **3**, 318 (1961).
18. M. E. Wall, W. S. Hiavacek and M. A. Savageau, Nature Review Genetics **5**, 34 (2004).
19. S.A. Kauffman, J. Theor. Biol. **22**, 437 (1969).
20. U. Bastolla and G. Parisi, Physica D **15**, 203 (1998).
21. U. Bastolla and G. Parisi, Physica D **15**, 219 (1998).
22. J.E.S. Socolar and S.A. Kauffman, Phys. Rev. Lett. **90**, 68702 (2003).
23. B. Samuelsson and C. Troein, Phys. Rev. Lett. **90**, 98701 (2003).
24. B. Drossel, T. Mihaljev and F. Greil, Phys. Rev. Lett. **94**, 88701 (2005).
25. B. Drossel, Phys. Rev. E **72**, 16110 (2005).
26. R. ALbert and H.G. Oltmer, J. Theor. Biol. **223**, 1 (2003).
27. S. Kauffman, C. Peterson, B. Samuelsson and C. Troein, Proc. Natl. Acad. Sci. U.S.A. **100**, 14796 (2003).
28. S. Bornholdt, Science **310**, 449 (2005).
29. B. Diu, C. Guthmann, D. Lederer, and B. Roulet, *Physique Statistique* (Hermann, Paris, 1989); I. Langmuir, J. Chem. Soc. **40**, 1361 (1918).
30. B. Drossel and A.J. McKane, in *Handbook of Graphs and Networks: From the Genome to Internet*, edited by S. Bornholdt and H.G. Schuster (Wiley-VCH, Berlin, 2002); C.S. Holling, Mem. Ent. Soc. Can. **45**, 1 (1965).
31. J. Hofbauer and K. Sigmund, *Evolutionary Games and Population Dynamics* (Cambridge University Press, Cambridge, 1998).
32. N. Boccara, *Modeling Complex Systems* (Springer, New York, 2004).
33. L.A. Segel, *Modeling Dynamic Phenomena in Molecular and Cellular Biology* (Cambridge University Press, Cambridge, 1984); L. Michaelis and L.M. Menten, Biochem. Z. **49**, 333 (1913).
34. J.P. Sethna, *Statistical Mechanics: Entropy, Order Parameters, and Complexity* (Oxford University Press, New York, 2006).
35. M.B. Elowitz and S. Leibler, Nature **403**, 335 (2000).
36. J. Garcia-Ojalvo, M.B. Elowitz, and S.H. Strogatz, Proc. Natl. Acad. Sci. USA **101**, 10955 (2004).
37. K. Klemm and S. Bornholdt, Proc. Natl. Acad. Sci. USA **102**, 18414 (2005).
38. O. Bradman, J.E. Ferrel Jr., R. Li, T. Meyer, Science **310**, 496 (2005).
39. A. Ma'ayan et al., Science **309**, 1078 (2005).
40. G. von Dassow et al., Nature **406**, 188 (2000).
41. E. Mjolsness, D.H. Sharp, J. Reitnitz, J. Theor. Biol. **152**, 429 (1991; J. Reitnitz, E Mjolsness, D.H. Sharp, J. Exp. Zoology **271**, 47 (1992).
42. V.V. Gursky, J. Reitnitz, A.M. Samsonov, Chaos **11**, 132 (2001).
43. R.V. Solé, I. Salazar-Ciudad, J. García-Fernández, Physica A **305**, 640 (2002); I. Salazar, J. García-Fernández, R.V. Solé, J. Theor. Biol. **205**, 587 (2000); R.V. Solé and R. Pastor-Satorras, in *Handbook of Graphs and Networks: From the Genome to Internet*, edited by S. Bornholdt and H.G. Schuster (Wiley-VCH, Berlin, 2002).
44. J. Gómez-Gardenes, Y. Moreno, L.M. Floría, Chaos **16**, 015114(1-11) (2006); Biophys. Chem. *115*, 225 (2005); Physica A **352**, 265 (2005).