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On the robustness of complex heterogeneous gene expression networks

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Abstract

We analyze a continuous gene expression model on the underlying topology of a complex heterogeneous network. Numerical simulations aimed at studying the chaotic and periodic dynamics of the model are performed. The results clearly indicate that there is a region in which the dynamical and structural complexity of the system avoid chaotic attractors. However, contrary to what has been reported for Random Boolean Networks, the chaotic phase cannot be completely suppressed, which has important bearings on network robustness and gene expression modeling.

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1. Introduction

In the last several years, many scientists working on fields as diverse as technological, social and biological problems have realized that seemingly diverse systems such as the Internet and protein interaction networks share universal features when represented as graphs (or networks) [1–3]. For instance, the small-world property and a power law distribution of the number of interacting partners of a given element, pervade social [4], biological [5,6] and technological systems [7]. This observation has the invaluable advantage that statistical tools, concepts and even results within a specific field can be borrowed or extrapolated to other networked systems.

Biological systems constitute a topical field in which network modeling is bringing out important results. Recent analysis of protein–protein interaction networks has provided new useful insights into biological essentiality at this level of organization [8] and may help to elucidate the functions of a large fraction of proteins whose functions are unknown [9]. On the other hand, it is known that biological networks show a striking degree of robustness in that their functioning is preserved under variations of biochemical parameters, different environmental conditions or even different levels of their components [10]. Network's approach to cell functioning consists of studying the dynamical and structural properties of the intricate patterns of interconnections that made up cellular networks. Behind this approach, it is hidden the belief that many processes at the cellular level could be understood without a full and detailed knowledge of all the chemical pathways, reactions and molecular details involved in the functions performed by cells [3]. This is the kind of analysis that we will use here.

In the present paper, we are interested in studying how the topological properties of complex networks affect the robustness of biological systems. Specifically, we analyze the dynamical phase diagram of a continuous gene expression model on top of heterogeneous networks. We provide evidences that both dynamics and structure determine the ability of the network to reach stable (robust)

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configurations, that is, regimes where small initial perturbations do not grow in time (hereafter referred as dynamical robustness). We also discuss the connections of our study with other results recently reported for random heterogeneous networks with Boolean rules [11].

2. The model

The mathematical description of the gene expression mechanisms is a tough task. Up to now, there is no model that efficiently and accurately represents this complex phenomenon. However, with the advent of modern computer and laboratory techniques, scientists have unraveled some of the essential features of these mechanisms as well as the topological features of genetic networks. For instance, by analyzing several datasets obtained from DNA microarray experiments, it has been recently shown that gene-coexpression networks are highly heterogeneous [12]. This means that there are a few genes that participates in the regulation of many others, whereas the majority of them are only involved in a few interactions. The previous observation, in terms of current network's literature, translates into a scale-free (SF) network [13]. They are characterized by a power law degree distribution, $P(k)\sim k^{-\gamma}$, which measures the probability that a given element interacts with other k elements. Moreover, gene networks are also directed, that is, interactions are unidirectional [14].

In order to take into account all previous features of real genetic networks, we study the following model on top of complex heterogeneous and directed networks. We consider that the activity of the genes is described by the vector $\mathbf{G}(t)=\{g_1(t),g_2(t),\ldots,g_N(t)\}$, where g_i, $i=1,\ldots,N$ accounts for the activity level of each individual gene i in a network made up of N elements. The time evolution of $\mathbf{G}(t)$ is described by the set of first-order differential equations [3,15]

$$\frac{\mathbf{G}(t)}{\mathrm{d}t} = -\mathbf{G}(t) + \mathbf{F}(\mathbf{G}(t)), \tag{1}$$

where $\mathbf{F}(\mathbf{G}(t))$ is assumed to follow a continuous Michaelis–Menten description [3,15],

$$\mathbf{F}_i(\mathbf{G}(t)) = \delta \frac{\Phi\left[h\sum_{j=1}^{k_i} w_{ij}g_j(t)\right]}{1+\Phi\left[h\sum_{j=1}^{k_i} w_{ij}g_j(t)\right]}. \tag{2}$$

The dynamics contained in Eq. (1) is a generalization of the successful Random Boolean Networks (RBNs) models [16–18], which consider that each gene's activity is either 0 or 1. In Eq. (2), W_{ij} is the interaction matrix linked to the underlying network, $\delta>0$ and $h>0$ are constants, $\Phi(z)=z$ if $z\geq 0$ and zero otherwise, and k_i is the connectivity (degree) of gene i. We have set $\delta=3$ hereafter and varied h. As to the underlying network, we follow the procedure introduced in [19]. It consists of generating first a random scale-free network [2] with a desired degree distribution $P(k)\sim k^{-\gamma}$ and a given average connectivity $\langle k\rangle$. At a second stage, we assign directions to the already generated interactions. Specifically, we look over the nonzero elements of the connectivity matrix C_{ij} of the SF network (if node i and j are connected $C_{ij}=1$) and with probability p consider that the interaction $i\rightarrow j$ is inhibitory, $W_{ij}=-1$, and with probability $1-p$ it is excitatory, $W_{ij}=1$. In this way, the parameter p controls the average output (input) connectivity of each regulatory unit or gene. In this representation, two nodes at the ends of a link are considered to be transcriptional units which include a regulatory gene. On the other hand, the parameter h controls the degree of nonlinearity in the genes' interactions.

We have performed extensive numerical simulations of the set of Eqs. (1–2). Starting from small values of h, the time evolution of the local dynamics g_i is obtained by means of a fourth-order Runge–Kutta integration scheme [20]. The set of simulations carried out screens the parameter space (h, p), where h goes form *1* to 10 and p from 0 to 1. For each pair (h, p), different realizations corresponding to many initial conditions were performed. The behavior of the model turns out to be very rich with a plenty of steady, periodic and chaotic states. Recently, we have fully characterized these regimes [19,21]. However, motivated by another study on the influence of the degree of heterogeneity (here represented by the exponent γ) in the dynamical robustness of the system [11], we present here numerical results for different heterogeneous networks. The results show that, contrary to what has been claimed, heterogeneous networks cannot completely avoid the onset of chaotic behavior in a region of the parameter space (h, p).

3. Results and discussions

To this end, we first generate different networks characterized by distinct exponents of the degree distribution. The method employed is known as the generalized Barabási–Albert model [2] and allows to tune γ between 2 and 3. In this range, the mathematical properties of the degree distribution are peculiar. While an average connectivity can be formally defined, the second moment of the distribution diverges in the thermodynamics limit, which means that the fluctuations around $\langle k\rangle$ are not bounded. This property has been shown to change radically the behavior of several processes ran on top of these networks [3,22–24]. For instance, both epidemic and percolation thresholds are suppressed in the infinite system size limit, contrary to what happens in random graphs where the thresholds are nonzero. Thus, we generate three networks with $\gamma=3$, 2.33 and 2.2 with $\langle k\rangle=6$, assign directions to the genes' interactions as explained before and look at the phase diagram of the system (for details of numerical simulations, see [21]).

The results are depicted in Fig. 1 for a network made up of N=300 genes and h=4. It is evident that as we vary the topological parameter p, the probability of having chaotic behavior, P_{ch} departs from zero at a threshold value, p_1 which depends on the exponent γ, i.e., on the degree of heterogeneity of the network (the lower γ is, the more heterogeneous the network is). This probability is defined as the relative number of realizations, corresponding to different initial conditions, where at least one gene's activity ended up in a chaotic attractor. The inset is a zoom of the region around the threshold value for the three networks studied. The linear-log scale shows that near p_1, the probability exponentially grows as p is increased. More important, the thresholds are clearly distinct for the three cases illustrated. This confirms that the topological properties of the underlying network greatly affect the onset of dynamical instabilities (chaotic behavior). Additionally, we note that there is a second threshold value for large values of p which avoids chaotic behavior. This is a consequence of the dynamics expressed in Eq. (1). In this region, most of the interactions are inhibitory and the dynamics of the genes die out due to the damping term in Eq. (1). Thus, the nontrivial threshold is p_1.

As we said before, the dynamical behavior of the system is very rich. In fact, chaotic behavior is usually interpreted as a prohibited regime in which living organisms may not operate [14]. There is no experimental observation of such a behavior. However, periodic attractors are allowed as they point to a rich behavioral repertoire while keeping the robustness of the system under variations of initial conditions, internal parameters or environmental pressures. In Fig. 2, we represent the subtraction between P_{per} and P_{ch} for the same networks of Fig. 1. Here, P_{per} is also defined as the portion of the total number of realizations in which

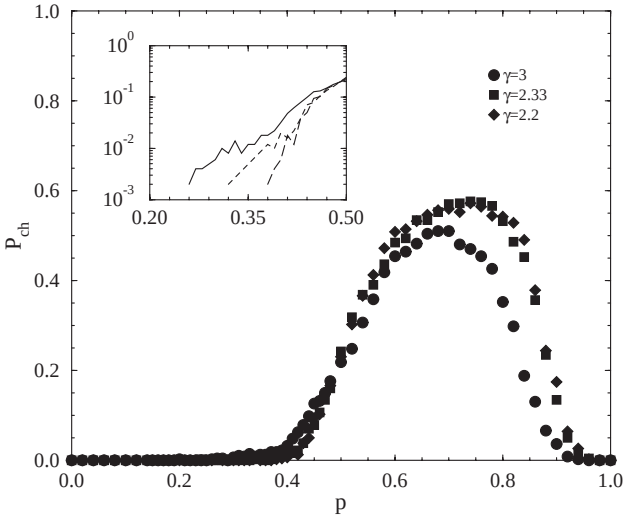

Fig. 1. Probability of having chaotic behavior as a function of the topological parameter p for three different heterogeneous networks. The inset is a zoom of the parameter region in which P_{ch} departs from zero. See the text for further details on the definitions and network parameters.

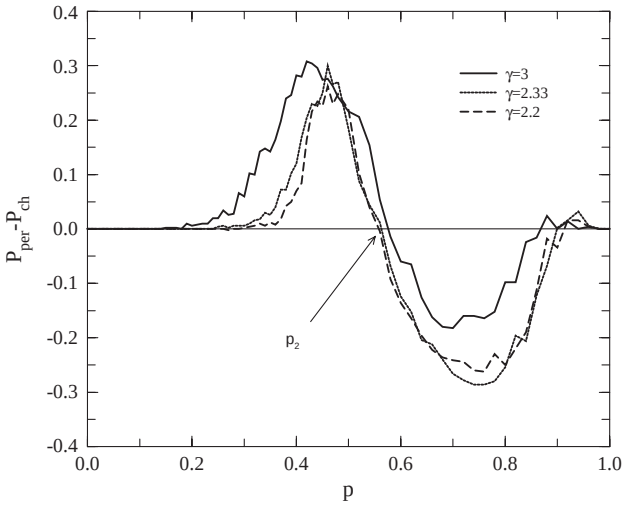

Fig. 2. Probability that the system displays dynamical robustness as a function of p for different γ. The network consists of N=300 nodes and h=4. The straight line marks the threshold beyond which chaotic attractors are more likely than periodic ones.

chaotic behavior was not attained by any node and at least one periodic orbit was observed. The straight line simply marks the threshold value for p beyond which the chaotic regimes are more likely than periodic behavior. In other words, the system dynamics can be regarded as dynamically robust in the region $(0,p_2)$ (neglecting the parameter space near p=1, see Fig. 2), where the specific value of p_2 depends on the degree of heterogeneity of the underlying network. Additionally, as the heterogeneity of the network increases (smaller values of γ), the parameter space that allows for more robust behavior is larger.

The results here obtained are not always in the same lines of a recent study where Random Boolean rules are implemented on top of scale-free networks for the same values of γ [11]. Specifically, we found that the region in which chaotic behavior is observed cannot be avoided completely contrary to the results of [11]. There are several reasons that explain the differences in the results. First of all, it is known that there is no exact correspondence between the numbers of behavioral patterns in RBNs and continuous models of real gene networks [25]. On the other hand, the directness of the networks studied in [11] differs from the one implemented here which may be the source of additional differences. As a matter of fact, Fig. 2 reveals that regardless of the value of γ employed, the dynamical robustness of the system is mainly determined by the topological properties given by p, as the differences in the threshold values for the three networks is not too significant. Finally, we point out that the analytical treatment used in [11] may not take into account properly the fluctuations in the degree distribution. As an example, we mention that in epidemic and percolation problems, the mean-field approximation, though still neglecting higher order correlations, must be modified in order to account for the heterogeneous character of the networks [3,22–24].

In summary, we have studied a continuous gene expression model on top of complex scale-free networks. We have focussed on the influence of the fluctuations around the mean average connectivity on the dynamical robustness of the system's dynamics. We have found that for heterogeneous distributions, the system cannot completely avoid the existence of chaotic attractors, contrary to what was previously suggested for RBNs models. Finally, we would like to stress that our results do not imply that these networks are not advantageous from the perspective of biological networks' design and evolution. In a previous work, we showed that even in the presence of chaotic attractors, heterogeneous networks are more favored than homogeneous ones [19,21]. We belief that the kind of study performed here may provide hints for more complex theoretical models and the experimental validation of the topology of gene networks.

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