Dynamical Robustness in Gene Regulatory Networks

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Abstract

We investigate the robustness of biological networks, emphasizing gene regulatory networks. We define the robustness of a dynamical network as the magnitude of perturbation in terms of rates and concentrations that will not change the steady state dynamics of the network. We find the number of dynamical networks versus their dynamical robustness follows a power law. We observe module robustness to increase with node degree in published gene regulatory networks. Finally, based on dynamical robustness, we propose a growth model for producing networks with power law degree distributions.

1. Introduction

Many biological, social and technological networks have scale free characteristic, that is, the degree of the nodes follows a power law distribution. This differs from random networks where node degrees follow a Poisson distribution. In order to generate random graphs with power law distributions, specific schema have been developed, such as growth through preferential attachment [1], or node duplication followed by edge deletion [2]. There is still much debate about whether or not these growth models are appropriate when dealing with gene and protein networks. In addition, these models do not take dynamics into account, even though dynamical robustness is an important aspect of gene and protein networks. Quoting Uri Alon [3], biological networks are robust to component tolerance and this should impose severe constraints on their design. Furthermore, it has been shown that power law networks exhibit robust behavior for power law exponents greater than two [4], and such exponent values are generally observed in most published protein and gene networks. In this paper, we further explore the relationship between dynamical robustness and scale free properties.

2. Methodology

We focus on gene regulatory networks and define the robustness of such networks as the magnitude of perturbation (in rates and concentrations) that can be carried out without changing the steady state dynamics of that network. If the network is limited to the Boolean activation/inhibition model, robustness becomes the number of different networks having the same set of attractors. Indeed, as illustrated in Figure 1, different networks can lead to the same steady state dynamics.

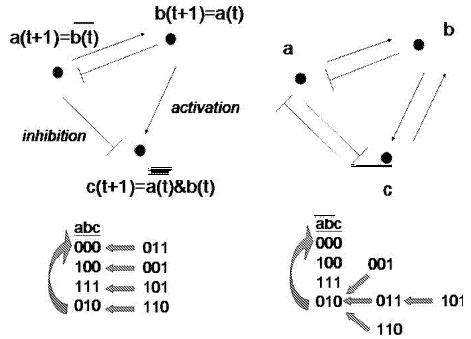

Figure 1. Networks with identical attractors. Both networks cycle in the attractor composed of states (000,100,111,010).

In order to search for robust networks, we have systematically generated all activation/inhibition networks with up to five nodes. Undirected graphs were first enumerated using McKay s orderly enumeration algorithm [5]. Next, for each enumerated graph, the two possible edge directions and the activation/inhibition labels were added in all possible ways. All resulting non-isomorphic networks were then run using Boolean dynamics. Each run was performed over all possible initial conditions until an attractor was reached. A binary string was compiled representing the Boolean states of the nodes within the attractors. That string was canonized considering all node permutations. Finally, networks were clustered according to their dynamical canonical string. Figure 2 plots the number of clusters versus cluster sizes.

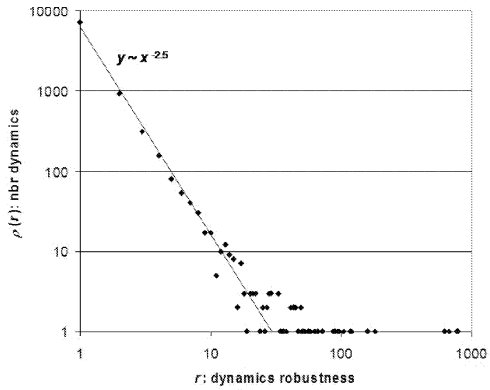

Figure 2. Number of dynamics vs. dynamical robustness for activation/inhibition networks.

3. Results and Discussion

Figure 2 demonstrates that most networks do not share their steady state dynamics with others, while a few networks are highly robust. Precisely, the number of different steady state dynamics versus the dynamic robustness seems to follow a power law with exponent 2.5. This result is surprising, since according to the theory of random graphs, network characteristics should follow Poisson distributions. We hypothesize that power law behavior observed in biological networks is a consequence of dynamic robustness.

To test this hypothesis we analyzed the dynamics of three activation inhibition networks: a transcriptional regulation network for E-coli [6], and two Yeast gene regulatory networks ([7], and a network we inferred from microarray data [8]). In all of these networks, we found that the number of subgraphs (or modules) with up to five nodes increased with the dynamical robustness. We also found that dynamical robustness increased with node degree. These results can be explained by considering that biological networks are composed of modules connected together [9], and that networks composed of modules can be constructed with a power law degree distribution, $P(k)$, if the modules have a fitness (robustness in the present case) also following a power law, $\rho(r)$. Precisely, Caldarelli *et al.* [10] have shown that networks of N modules can be constructed with the following distribution of node degrees $P(k) = r_M^2/(N\langle r\rangle)\rho[r_M^2/(N\langle r\rangle)\ k]$, where $\langle r\rangle$ and r_M^2 are the averaged and maximum robustness of the modules. Note that $P()$ follows a power law as long as $\rho()$ does. The growth of such networks is simply carried out by linking modules, one with robustness r and the other with robustness s, with probability rs/r_M^2. Figure 3 was compiled for a network of 150,000 modules grown using the above probability and following the robustness distribution of Figure 2. Clearly both figures follow the same power law distribution. Thus, we conclude that the distribution of module robustness can be used to explain the node degree distribution found in gene regulatory networks.

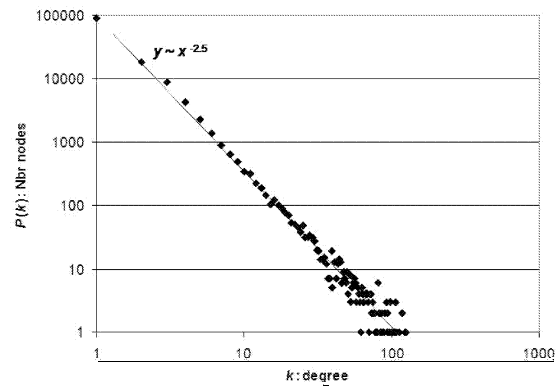

Figure 3. Degree distribution for networks generated using $\rho(r) \sim r^{-2.5}$ and edge probability rs/r_M^2.

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