Scale-free networks are not robust under neutral evolution

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Recently it has been shown that a large variety of different networks have power-law (scale-free) distributions of connectivities. We investigate the robustness of such a distribution in discrete threshold networks under neutral evolution. The guiding principle for this is robustness in the resulting phenotype. The numerical results show that a power-law distribution is not stable under such an evolution, and the network approaches a homogeneous form where the overall distribution of connectivities is given by a Poisson distribution.

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There are many different areas of contemporary science where the concept of networks are of special importance. Recently, the amazing result that such diverse networks as the World Wide Web [1], collaborations of movie actors [2], the electrical power grid of western USA [2], citation patterns of scientific publications [3] and metabolic networks [4], all have distributions of connectivities that are scale-free, i.e., obey some power-law. One reason for this quite general behaviour seems to be that the networks are grown by addition of new nodes and that each such new node preferentially attaches to other nodes with high number of connections [2]. These networks are also more robust against unintelligent attacks than homogeneous networks, where each node has approximately the same number of connections [6]. For the case of genetic regulatory networks, mutation is an example of such an “unintelligent attack”, and it is perhaps not surprising that the same type of scale-free distributions are found in the metabolic networks of so far 43 different organisms from all three domains of life (bacteria, eukarya, and archaea) [1].

The evolution of life is a random process with selection [6], although all details about how this occur with interactions among genotypes, phenotypes, and environment are not totally clear. Neutral evolution is the hypothesis that evolution mainly proceeds as a random walk which does not affect the phenotypes [7]. Experimentally, it is supported on the microlevel by the fact that most of the important macromolecules of life have forms which are functionally identical variants. If this idea of neutrality is correct also on a higher level, it means that the usefulness of fitness landscapes for describing the evolution of life as a hill climbing process is limited.

Here we explore the idea of neutral evolution and how the distribution of connectivities in a genetic regulatory network changes under mutations that are phenotypically silent. The fundamental constituents in our model are the genes of the organism, represented by the nodes of the network. It has been suggested that such a system can be well approximated by a Boolean network [5], because of the “on-off” nature of the biochemical switches. The exploration is performed by simulating evolution in discrete threshold networks with robustness as the guiding principle for when a mutation will survive to future generations. We find by numerical simulations that the scale-free distribution cannot be maintained under neutral evolution in such networks. Instead, the networks evolve towards a Poisson distribution, regardless of the actual realization of the initial scale-free distribution.

The discrete threshold network is composed of $N$ nodes, $\sigma_i$, which are connected by a square matrix with elements $w_{ij}$. The values of the nodes are $\sigma_i \in \{-1, 1\}$, representing the corresponding gene to be expressed (+1) or not (-1). The coupling matrix takes values $w_{ij} \in \{-1, 0, 1\}$, with +1 if gene $j$ is an activator of gene $i$, -1 if it is a repressor, and 0 if no connection exist. The dynamics of the network is described by the updating rule

$$\sigma_i(t+1) = \text{sgn} \left( \sum_{j=1}^{N} w_{ij} \sigma_j(t) \right),$$  \hspace{1cm} (1)$$

where the sign-function is defined as $-1$ for all negative arguments, and +1 otherwise (including zero). Of special importance is the mean number of connections to each node, $K$, which is calculated as

$$K = \frac{1}{N} \sum_{i=1}^{N} \sum_{j=1}^{N} |w_{ij}|,$$  \hspace{1cm} (2)$$

that is, we make no distinction between repressors and activators, and it has the same value for both ingoing and outgoing connections.

This is a special case of Boolean networks, with similar structural and statistical properties [5]. These properties include both transients and limit cycles (attractors), as well as phase transitions for a specific critical connectivity, $K = K_c$. An analytical approach is limited due
to the non-Hamiltonian character of the system, but results within the so-called annealed approximation show, for Boolean networks, that for \( K \) below the critical connectivity \( K_c = 2 \), there are many disconnected regions, while above \( K_c \) most of the nodes are connected and the limit cycle period increases exponentially with the number of nodes. Also, at least in some intervals above \( K_c \), the size of the attractors diverges almost exponentially with increasing connectivity \( \gamma \). Note here that we use a form where the number of ingoing connections might differ from the number of outgoing, i.e., the matrix does not have to be symmetric, and that we do not impose the restriction that the number of connections should be the same for all nodes \( \sigma_i \).

If every two nodes in a network are connected with the same probability \( p \), we have the Erdős-Rényi model for random graphs \( \mathbb{G}_p \), sometimes referred to as a homogeneous network. It is well known that in such networks, the number of connections to each node follows a Poisson distribution (with exponential decaying tails), and hence there will hardly be any nodes with a large number of connections. Loosely speaking, this is the most common form of a random graph.

To simulate neutral evolution, we start by generating a network with elements \( w_{ij} \) by the procedure described in \( \mathbb{G}_p \), i.e., we start from a small random network, and add new nodes by preferential attachment. The result is a scale-free network with a probability for a given node to have \( K \) links (either ingoing or outgoing) proportional to \( K^{-\gamma} \) for \( K \geq 2 \), with, in our case, \( \gamma \approx 1.63 \) (solid line in Fig. 1). We use consequently in this paper \( N = 1024 \), which results in an average connectivity value initially slightly below the critical value \( K_c = 2 \). Interestingly, a recent letter showed that another form for evolving a discrete threshold network (adding links to quiet nodes, removing links from active) leads to an average connectivity of 2.55 for this size of network \( \mathbb{G}_p \). The sign of a specific connection specifies if we have an activator (positive value) or a repressor (negative value). These signs are here chosen randomly with equal probabilities.

The evolution now proceeds by the following procedure: The network is mutated by either

1. One non-zero element is put to zero (connection removed)
2. One zero element is turned into \( \pm 1 \) (with equal probability) (connection added)
3. Both of the above, i.e., one connection is added and another removed

These three alternatives (in the order given) occur with the probabilities \( 0.300 : 0.333 : 0.367 \), forming a new, mutated network. The values of these probabilities were chosen to obtain a network with a relatively constant mean number of connections also for the comparatively small number of generations and the initially low number of mean connectivity we consider. However, also other values have been tried, and the results do not depend critically on their exact magnitudes. To either reject or accept the new, mutated network, we use robustness as the guiding principle. This is achieved by picking by random an initial state, \( \{\sigma_i\} \), with equal probability for each single node \( \sigma_i \) being either positive or negative. This state is iterated in both the original and the mutated network until we either enter into the same limit cycle in both networks, or the two iterations cease to coincide. In the former case we accept the mutated network, and replace the original one with the mutated version. This is then an evolutionary step within the neutral evolution. In the latter case, we reject the new, mutated network, since the effect of the mutation were not silent. Finally, we return to the mutation step and repeat the procedure. Notice this introduces two different time scales in the evolution. The one corresponding to the iteration of states \( \{\sigma_i\} \) relates to a single generation, while the much slower process of accepting or rejecting new networks, i.e., the rewiring of connections \( w_{ij} \), corresponds to the evolution over generations.

This way of simulating neutral evolution has earlier been explored by Bornholdt and Sneppen, both by truly Boolean networks \( \mathbb{B}_p \) and by discrete threshold networks \( \mathbb{B}_t \). They studied, however, the phenomenon of punctuated equilibrium and distribution of waiting times, and ignored the distribution of connections. Their study clarified that this model exhibit many of the known properties of evolution, such as \( 1/f \) power spectra \( \mathbb{B}_p \) and \( 1/t^2 \) stability distribution \( \mathbb{B}_t \), in accordance with similar scalings found in the statistics of birth and death in the evolutionary record.

In Fig. 1 we show the initial distributions of connections and the distribution after 30 000 generations in one evolutionary run for the number of connections leading into the nodes. The result for connections leading out from them are quite similar, and are for clarity not shown. Although the limited number of nodes (due to computational constraints) makes the statistics somewhat fuzzy, it is still clear that the distribution changes from a power-law to an approximately Poisson distribution. To get a better picture, we have used the well-established technique of binning the values for the initial distribution. The solid and dotted lines are a power-law and a Poisson distribution, respectively. The exponent of the straight line \( P(K) \sim K^{-\gamma} \) is found by a least squares fit to be \( \gamma \approx 1.63 \). This should be compared to the theoretical value given in \( \mathbb{G}_p \) for a fully directed graph of infinite size, which is \( \gamma = 2 \). Although the number of nodes we use is small compared to the networks considered there, the correspondence seems acceptable. The Poisson distribution drawn is for the expectation value estimated by the mean value of connectivities, \( K \), at the actual generation. This means that in the general Pois-
son distribution function

\[ P(K) = \frac{K^K}{K!} \exp(-\mu), \tag{3} \]

we estimate the parameter \( \mu \) with the mean connectivity \( \bar{K} \). No curve fitting is used this time, but nevertheless the correspondence is quite striking.

In Fig. 2, we show the variation of mean connectivity, \( \bar{K} \), for the first 30 000 generations. Because of the definition (2), this is the same value both for outgoing and ingoing connections. The curve shows that the mean number of connections remains fairly constant, although the detailed dynamics is non-trivial (with punctuated equilibria, etc., as discussed in [13,14]). It also shows that we in this run constantly are below the critical value of \( K_c = 2 \). This is, however, not a critical aspect of the simulation, which other runs (not shown) have indicated. Hence any change in distribution among these connections cannot be due to changes in the mean connectivity. Nevertheless, there is according to Fig. 1 a real change in distribution from the start of the simulated evolution to the end of our calculations. To shed some further light onto the transition from a scale-free network with a power-law distribution to a homogeneous network with a Poisson distribution, we calculate the weighted mean square deviation

\[ d^2 = \frac{1}{N} \sum_{K=1}^{N} K[n(K) - NP(K)]^2, \tag{4} \]

where \( n(K) \) is the number of nodes with \( K \) connections and \( P(K) \) is the Poisson distribution (3). For each comparison, we use the actual value of \( \bar{K} \) as estimate for the expectation value \( \mu \), but no other fitting is performed. Because the tail of the distribution function is the most critical, we give higher weight to larger number of connections by multiplying each term with the actual number of connections. The results are shown in Fig. 3. Although the exact details for the ingoing and outgoing connections differ, and it is clearly seen that the distributions eventually approach the Poisson distribution, regardless of which measure we consider.

The lengths of the limit cycles for the accepted networks in this evolutionary scenario vary between 1 and 20, with an average of approximately 6. The transients have lengths between 10 and 35 steps. Both these results indicate that we are in the regime of many, small, disconnected attractors, which is fully consistent with the mean connectivity \( \bar{K} \) being less than the critical value \( K_c = 2 \).

Better statistics, i.e., less fuzzy distributions, are obtained if we change the mutation rule above somewhat. Instead of having the possibility to separately add or remove a connection, we stick solely to alternative three, which means that the number of connections, and hence \( \bar{K} \), remains constant. This is clearly a less realistic scenario than before from a biological point of view, but can help to see what distributions we really have. In Fig. 4, we show the mean values of the distributions for all generations between number 200 000 and 300 000, when we start with the same initial scale-free network used to obtain the results of Fig. 2. The dotted line is the theoretical Poisson distribution for the actual mean connectivity (\( \bar{K} = 1.9678 \)). The weighted mean square deviations from this theoretical value are 1.18 for the ingoing connections and 0.06 for the outgoing, respectively. To the prize of having incorporated an unrealistic restriction, we have obtained distributions which are considerably closer to the theory.

To check the robustness of these results, we have repeated the calculations many times with different forms of initial network in the construction of the original scale-free network, as well as checked many different realizations. We have also started with networks with a power-law distributed number of connections obtained directly from a random number generator, i.e., without the process described in [2]. In all these cases, our results do not change, i.e., the systems always end up with a Poisson distribution consistent with the random graph theory.

In conclusion, we have studied the evolution of initially scale-free networks, i.e., networks where the distribution of the number of connections to each node follows a power-law. The networks are evolved under the hypothesis of neutral evolution, which is implemented as a robustness criterium for the limit cycles in discrete threshold networks. The result is that the scale-free distribution is not robust under such an evolution, but instead all networks end up in a homogeneous form, with a Poisson distribution of connectivities. This result is surprising, since it has been shown that a scale-free network is more robust towards random attacks than an exponential network [3]. Although one should be very careful with inferring any definite statements with respect to biology from such simple models as the one presented here, we can speculate and draw the tentative conclusion that the addition of new nodes with preferential attachment seems to be a force that manages to repress the changes due to neutral evolution. Future studies might shed some light on the presumably different time-scales that are active here.

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FIG. 1. Distribution functions for number of ingoing connections for an initially scale-free network with $N = 1024$ nodes at two different generations. Diamonds: Initial power-law distribution. Crosses: Distribution after 30 000 generations of neutral evolution. The full line is a power-law, $P(K) \sim K^{-\gamma}$ with $\gamma = 1.63$, and the dotted line is a Poisson distribution (see text for details).

FIG. 2. Mean connectivity for an initially scale-free network evolving under neutral evolution.

FIG. 3. Weighted mean square deviations from the Poisson distribution for an initially scale-free network, evolving under neutral evolution, where the expectation value at each generation is estimated by the actual mean connectivity. Full line represents ingoing connections, dotted line represents outgoing connections.

FIG. 4. Mean distribution for all generations between 200 000 and 300 000 for an initially scale-free network evolving under neutral evolution with constant connectivity. Diamonds are ingoing connections and crosses outgoing. The dotted line is a Poisson distribution with expectation value estimated as the mean connectivity.