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Measures for information propagation in Boolean networks

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Abstract

Boolean networks provide a large-scale model of gene regulatory and neuronal networks. In this paper, we study what kinds of Boolean networks best propagate and process signals, i.e. information, in the presence of stochasticity and noise. We first examine two existing approaches that use mutual information and find that these approaches do not capture well the phenomenon studied. We propose a new measure for information propagation based on perturbation avalanches in Boolean networks and find that the measure is maximized in dynamically critical networks and in subcritical networks if noise is present.

Keywords: Gene regulatory network; Boolean network; Information propagation; Perturbation avalanche; Criticality

1. Introduction

The concept of measuring information processing and propagation in complex dynamical networks, such as gene regulatory or neuronal networks, has lately gained attention in the literature [1,2]. It has been proposed that gene regulatory and neuronal networks operate in the so-called dynamically critical regime [3–6,1]. A long-standing idea has been that critical dynamics maximize the complexity, information processing, or information propagation capabilities of the system [3,7]. In this paper, we examine different measures for information propagation in dynamical systems with Boolean networks.

We first study how mutual information could be used to measure information propagation by analyzing the methods presented by Beggs and Plenz [1] and Luque and Ferrara [8]. We find that these methods fail to measure the information propagation in many general cases. For this reason, we propose a new measure that uses instead of mutual information the entropy of perturbation avalanches caused by small initial perturbations.

Perturbation avalanches and branching processes have been successfully used to understand how perturbations propagate in dynamical networks [6,9,10]. We derive the size distribution of perturbation avalanches in Boolean networks and propose a new measure for information propagation based on the entropy of avalanche size distributions. A similar approach has been recently used by Kinouchi and Copelli [2]. In addition, we introduce a stochastic model where some nodes are randomly perturbed at each time step to study the effects of noise on the proposed measure. Finally, we compare the analytical results to results obtained from numerical experiments. We find that the measure is maximized in dynamically critical networks and in subcritical networks if noise is present.

2. Boolean networks

Boolean networks are mainly used as simplified models of gene regulatory networks [11,12,3]. A Boolean network is a directed graph with N nodes. The nodes represent genes and the graph arcs represent biochemical interactions between the genes. Each node is assigned a binary state variable and a

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Boolean function as an update rule whose inputs are determined according to the graph connections. Value 1 of the state represents an active gene and value 0 represents a non-active gene. Boolean function f associated with the node represents the regulatory rule affecting the gene in question. We denote the distribution over the set of functions in the network by $\mathfrak{F}$. The in-degree and the function distribution are connected in such a way that the degree distribution of the function distribution matches the network in-degree distribution. The state x of the network is the vector of state variable values x_i of all the nodes at time t. The network nodes are synchronously updated. In mathematical terms, the state x_i of the ith node of the network is updated as

$$x_i(t+1) = f_i(x_{i_1}(t), x_{i_2}(t), \ldots, x_{i_K}(t))$$

where x_{i_j} is the jth connection to node i and K is the in-degree of Boolean function f_i. Boolean networks can be viewed also as maps between different states as $x(t+1) = F(x(t))$. In quenched Boolean networks the network connections and functions do not change over time.

The annealed approximation provides a probabilistic framework in which to study the dynamics of Boolean networks. In the approximation we shuffle the network connections and functions after every time step. All the analytical results in this paper are based on the annealed approximation. The functions are taken from a given function distribution $\mathfrak{F}$. Annealed networks can be constructed with any in-degree $p_{\text{in}}(k)$ and out-degree $p_{\text{out}}(j)$ distribution. Of course, the two distributions must have the same expectation $\langle p_{\text{in}}(k)\rangle$. In addition, we assume that the network size approaches infinity, $N \to \infty$. In practice, these approximations mean that we can consider every node in the network as a probabilistic entity that has a probability of having a specific in-degree, out-degree, and Boolean function.

To make the analysis as general as possible, we assume that the Boolean network may have any distribution of functions. The bias b_t is the probability that a node has value 1 at time t. The bias-map $b_{t+1} = g(b_t)$ gives the evolution of b_t as

$$b_{t+1} = g(b_t) = \mathop{E}_{f\in\mathfrak{F}}\left[\sum_{x\in\{0,1\}^K} f(x)P(x|b_t)\right],$$

where

$$P(x|b_t) = b_t^{|x|}(1-b_t)^{K-|x|}$$

is the probability for the input vector x when b_t is known. f is a Boolean function drawn from the distribution $\mathfrak{F}$ and K is the in-degree of function f. We assume that all the bias-maps of the biologically realistic distributions $\mathfrak{F}$ have a single stable fixed point $b^* = g(b^*)$ [13]. The average influence I is defined as the probability that a perturbation of an input to $f(x)$ has an influence on its output value in the stationary state characterized by b^*:

$$I = \mathop{E}_{f\in\mathfrak{F}}\left[\frac{1}{K}\sum_{i=1}^{K}\sum_{x\in\{0,1\}^K} f(x)\oplus f(x\oplus e_i)P(x|b^*)\right].$$

Here, e_i is the unit vector with value 1 at the ith position and $\oplus$ refers to the exclusive or operator. We define the network order parameter λ as

$$\lambda = \langle p_{\text{in}}(k)\rangle I,$$

where $\langle p_{\text{in}}(k)\rangle$ is the expected value of the distribution $p_{\text{in}}(k)$. The order parameter λ is the average amount of nodes that are perturbed one time step after we have flipped the value of a randomly chosen node, given that the network has reached the bias-map fixed point before the perturbation. Networks with $\lambda < 1$ are stable, networks with $\lambda = 1$ are critical, and networks with $\lambda > 1$ are chaotic.

A Derrida map [14,15] is a one-dimensional mapping $\rho_{t+1} = h(\rho_t)$, $\rho \in \{0, 1\}$ that illustrates the propagation of perturbations in annealed Boolean networks. ρ_t is the proportion of perturbed nodes in the network at time t. The Derrida map has a stable fixed point at zero for stable and critical networks and a non-zero fixed point for chaotic networks [14]. The fixed point of the Derrida map gives the final probability that a node is perturbed after the network has been run for many time steps. The slope of the Derrida map is the order parameter λ [15].

3. Mutual information in dynamical networks

Mutual information is commonly used to study how much information can be passed through a system. Beggs and Plenz [1] and Luque and Ferrara [8] proposed two different approaches that use mutual information to measure information propagation in dynamical networks. They claim that their measures are maximized in critical networks. We will find in this section that these results do not apply in many general cases. We think this is an important note since the result presented in [1] is cited by many other papers; see for example [2,16,17].

Mutual information MI can be defined as follows:

$$MI = H_1 + H_2 - H_{12},$$

where H_1 is the input entropy:

$$H_1 = -\sum_{s_i\in S} P_1(s_i)\log(P_1(s_i)),$$

H_2 is the output entropy:

$$H_2 = -\sum_{s_j\in S} P_2(s_j)\log(P_2(s_j)),$$

and $H_{1,2}$ is the joint entropy of the input and output:

$$H_{1,2} = -\sum_{s_i\in S}\sum_{s_j\in S} P(s_i, s_j)\log(P(s_i, s_j)).$$

Here, S refers to the set of possible symbols, $P_1(s_i)$ is the probability that symbol s_i occurs in the input, and $P_2(s_j)$ is the probability that symbol s_j occurs in the output.

Beggs and Plenz [1] used feed-forward networks with a finite number of nodes on each layer. The nodes are randomly connected to the next layer, and the update rules are chosen so that a perturbation of a node is transmitted, on average, to λ nodes on the next layer. The first layer is the input layer and the last layer is the output layer. They calculated the average mutual information between the symbols in the input and output layers given the distribution of input symbols and given λ. See [1] for the exact model definition.

Let us now concentrate on this approach in more detail. The setting corresponds to annealed Boolean networks with a finite number of nodes on each layer. Here, instead of the actual state the configuration of perturbed nodes constitute a symbol. We note that the probability $P_2(s_2)$ that the output symbol $s_2 \in S$ occurs is only related to the probability that an output node is perturbed. This is true because the layers are randomly connected, i.e. there are no logical connections between a pair of input and output nodes. If there are enough layers, all initial perturbations finally die out in stable and critical networks because the corresponding Derrida map has a fixed point at zero. In these cases, the output contains only non-perturbed nodes. Therefore, any output symbol is uncorrelated with the input symbols. From this, we directly see that the mutual information is not maximized in critical networks. In chaotic networks the analysis becomes a bit more complicated. We have feed-forward networks with a finite number of nodes in each layer. Therefore, the perturbation size may reach zero and stay there. In addition, we know from the theory of branching processes that the perturbation size may converge also in chaotic networks when the initial perturbations have a finite size; see the next section for details. In a typical (Boolean network) case, however, the perturbation propagates so that the probability of a node being perturbed in the output layer is close to the non-zero Derrida map fixed point. This result may vary depending on how we define the case where a node gets a perturbation from multiple sources. Therefore, for some particular parameters of the model the mutual information may have a small non-zero value for chaotic networks. In conclusion, the maximum of the mutual information is not found in critical networks in this model as claimed.

Luque and Ferrara [8] have used a different approach to use mutual information in annealed Boolean networks. They found that the mutual information between the consecutive states of a node in the network is

$$
\begin{aligned}
MI = & -p\log p - (1-p)\log(1-p) + \frac{a-1+2p}{2} \\
& \times \log\left(\frac{a-1+2p}{2p}\right) + \frac{1-a}{2}\log\left(\frac{1-a}{2p}\right) + \frac{a+1-2p}{2} \\
& \times \log\left(\frac{a+1-2p}{2(1-p)}\right) + \frac{1-a}{2}\log\left(\frac{1-a}{2(1-p)}\right).
\end{aligned}
$$

Here, a is the probability that a node keeps its value in the Boolean network over a single time step, and p is the probability that a random Boolean function outputs one. In other words, a is one minus the fixed point of the corresponding Derrida map [15,18]. The authors found that this measure for complexity is maximized in critical Boolean networks in networks with constant in-degree $K = 3$. However, the measure fails to make a separation between stable networks. For example, the measure does not separate the networks with constant in-degrees $K = 1$ and $K = 1.5$, since all stable networks have the Derrida map fixed point at zero ($a = 1$). In addition, the analysis presented can only be directly applied to random Boolean networks with random functions.

4. Measure for information propagation based on perturbation avalanches

A perturbation is a random flip to a node in the network. The size of a perturbation avalanche is the total number of nodes that have behaved differently than the nodes in the non-perturbed network. We may interpret the initial perturbation as the signal and the perturbation avalanche as the system's response to the signal. We propose to use the entropy of the avalanche size distribution as a measure for information propagation in Boolean networks. The measure illustrates how wide the scale of responses that the system can have to the initial signal is. We define the measure H as

$$H = -\sum_{n=1}^{\infty} p_n \log p_n,$$

where p_n is the probability that the perturbation avalanche has magnitude n.

Let us assume that we have a Boolean network with a Poisson out-degree distribution

$$p_{\text{out}}(j) = \frac{K^j}{j!}\mathrm{e}^{-K}.$$

Here, $p_{\text{out}}(j)$ is the probability that a node has j out-going connections, and K is the distribution parameter. Randomly constructed graphs have a Poisson out-degree distribution. However, real gene regulatory or neural networks may have a scale-free out-degree distribution [19].

The propagation of a perturbation that has an absolute size $Z_t \in \mathbb{Z}$ at time t can be studied by using the theory of branching processes [10,9]. In our analysis we use the initial perturbation size $Z_0 = 1$. The perturbation size Z_t is the non-normalized Hamming distance after t time steps between the network states with and without the perturbation. When we use the annealed approximation in the limit $N \to \infty$, all perturbed nodes at any time step are independent of each other. With probability one a perturbation of finite size will spread to nodes that were not previously perturbed. In addition, if $Z_t = 0$, then $Z_{t+a} = 0$ for any $a > 0$. Therefore, the propagation of a perturbation in Boolean networks ($N \to \infty$) is a branching process. For a branching process the branching probability distribution $q_k = P(Z_1 = k)$ is the probability that a node in the process produces k daughters. For a Boolean network it is given by

$$
\begin{aligned}
q_k &= \sum_{j=k}^{\infty} \binom{j}{k} p_{\text{out}}(j) I^k (1-I)^{j-k} \\
&= \left(\frac{I}{1-I}\right)^k \sum_{j=k}^{\infty} \binom{j}{k} p_{\text{out}}(j)(1-I)^j.
\end{aligned}
$$

When the out-degree distribution is Poissonian this can be calculated to be

$$q_k = \left(\frac{\lambda}{K-\lambda}\right)^k \sum_{j=k}^{\infty} \frac{j!}{(j-k)!k!} \frac{K^j}{j!} \mathrm{e}^{-K} (1-I)^j$$
$$= \frac{\lambda^k}{(K-\lambda)^n} \frac{\mathrm{e}^{-K}}{k!} \sum_{j=k}^{\infty} \frac{1}{(j-k)!} (K-\lambda)^{j-k} (K-\lambda)^k$$
$$= \frac{\lambda^k}{k!} \mathrm{e}^{-K} \mathrm{e}^{K-\lambda} = \frac{\lambda^k}{k!} \mathrm{e}^{-\lambda}.$$

The generating function of this branching probability distribution is given by

$$Q(s) = \sum_{n=0}^{\infty} \frac{\lambda^n}{n!} \mathrm{e}^{-\lambda} s^n = \mathrm{e}^{\lambda(s-1)}.$$

The iterates of the generating function $Q(s)$ are defined as

$$Q_0(s) = s,$$
$$Q_{t+1}(s) = Q(Q_t(s)).$$

In general, the generating function of Z_t is $Q_t(s)$ [9]. Let $\lambda = E[Z_1] = Q'(1)$ and $\sigma^2 = E[Z_1^2] - \lambda^2 = Q''(1) + \lambda - \lambda^2$. The expectation $E[Z_t]$ and variance $V[Z_t]$ are

$$E[Z_t] = Q_t'(1) = \lambda^t,$$
$$V[Z_t] = \begin{cases} \dfrac{\sigma^2 \lambda^t (\lambda^t - 1)}{\lambda^2 - \lambda}, & \lambda \neq 1 \\ t\sigma^2, & \lambda = 1. \end{cases}$$

The limit $\lim_{t\to\infty} Q_t(s) = q$ is $q = 1$ for ordered and critical networks ($\lambda \leq 1$) and constant $q < 1$ for chaotic networks ($\lambda > 1$). Moreover, we can prove that $Z_t \to \infty$ with probability $1 - q$ and $Z_t \to 0$ with probability q when $t \to \infty$ [9]. This means that even if the Boolean network is chaotic, there is a considerable probability q that the perturbation size will converge to zero. Perturbation spread in the network can be interpreted as a Markov random walk with adsorbing boundary at $i = 0$. Let us define $p_{i,j}$ as

$$p_{i,j} = P(Z_{t+1} = j | Z_t = i), \quad i, j \in \mathbb{Z}$$

and the generating function of the random walk as

$$P_i(s) = \sum_{j=0}^{\infty} p_{i,j} s^j.$$

It is well known that the generating function of a sum of i independent random variables, each distributed with q_k, can be expressed as

$$P_i(s) = Q(s)^i.$$

From this we get the Markov random walk for a Boolean network with a Poisson out-degree distribution as

$$p_{i,j} = \frac{(\lambda i)^j}{j!} \mathrm{e}^{-\lambda i}.$$

The avalanche size n is the total number of nodes generated by the branching process. The probability p_n that the avalanche size is n can be conveniently expressed as [10,20]

$$p_n = \frac{1}{n} p_{n,n-1}. \tag{1}$$

This result applies for all Markov random walks [20]. For the Poisson case we have

$$p_n = \frac{(n\lambda)^{n-1}}{n!} \mathrm{e}^{-n\lambda}.$$

By using Stirling's approximation $n! \approx \sqrt{2\pi n}(\frac{n}{e})^n$ we have

$$p_n \approx \frac{1}{\sqrt{2\pi}} \mathrm{e}^{n(1-\lambda)} \lambda^{n-1} n^{-\frac{3}{2}},$$

from which we see that for critical Boolean networks ($\lambda = 1$)

$$p_n \sim n^{-\frac{3}{2}}.$$

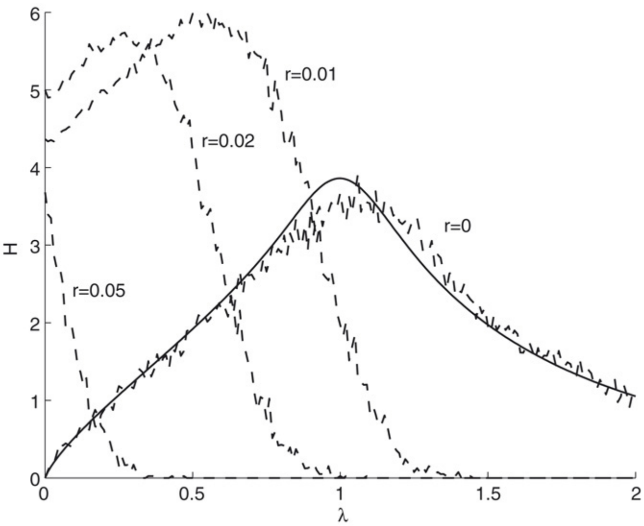

Fig. 1. Entropies of avalanche size distributions for Boolean networks generated with varying order parameter λ. The solid line is the theoretical estimate without noise and the broken lines are the numerical experiments with and without noise ($r = 0$). The amount of noise in the numerical experiments was $r = 0.01$, $r = 0.02$, and $r = 0.05$.

This result coincides with the well known result that in critical branching processes the avalanche size distribution is scale-free with exponent $\gamma = -\frac{3}{2}$. Fig. 1 shows how the measure H changes when the order parameter λ is varied. We note that the measure is maximized in critical networks.

We compared the analytical result to a numerical result obtained from randomly generated quenched Boolean networks. The quenched networks had random functions chosen so that the whole network had the desired λ. In the numerical experiments, we generated 400 Boolean networks with $N = 100$ nodes. Then, we ran each of them for 100 time steps. The starting point was a random state and a perturbed state with one node having a different value than the random initial state. The total number of nodes that, at some time point, had a different value was the avalanche size. The experiment was repeated for different values λ in small intervals.

Sometimes in quenched networks the initial perturbation causes the network to settle down in a different attractor. In this case, the perturbation size defined in the above-mentioned way approaches infinity when the number of steps is increased. In addition, especially in chaotic networks, the perturbation avalanche size may approach extremely large values. Therefore, we interpreted avalanche sizes that were larger than the network size as avalanches that percolate throughout the whole system. We included all such large avalanches in the probability of avalanche size $n = 100$.

Most biological systems are stochastic and random fluctuations are common. For these reasons, it is important to study how random perturbations affect the proposed measure. As a simple experiment, we flipped the value of a node with probability r at each time step. We repeated the above-mentioned numerical experiments with $r = 0.01$, $r = 0.02$, and $r = 0.05$. See the broken lines in Fig. 1 for the numerical results. We note that, if noise is present, the maximum is shifted into the ordered regime. In addition, the peak is higher for networks with noise and the measure has much lower values for chaotic networks when noise is present.

5. Discussion

We have investigated what kind of Boolean networks best propagate information. We have shown that some methods presented in the literature using mutual information do not correctly measure the information propagation capabilities of the network.

We have proposed a new measure for the propagation of information in Boolean networks. The measure is based on the entropy of the size distributions of perturbation avalanches and illustrates the range of possible changes in the network as a consequence of an initial small perturbation. We have found that the measure is maximized in critical networks and in subcritical networks if noise is present. In addition, we have verified with numerical experiments the analytically derived result.

Many complex dynamical systems, such as gene regulatory or neuronal networks, should have a wide range of possible ways to react to external signals. At the same time, the system should be robust against stochasticity and noise. Critical systems show perturbation avalanches with a power law distribution that compromises between these two conflicting constraints. Reactions of a large magnitude are relatively probable, while most perturbations do not lead to large avalanches. In addition, we have shown that if noise is present in the system, information propagation is maximized in slightly subcritical networks. In fact, critical networks with additional noise would be slightly chaotic and therefore difficult to control. The results suggest that in the presence of stochasticity and noise, subcritical networks could appear critical. However, this hypothesis requires further exploration.

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