The phase diagram of random Boolean networks with nested canalizing functions

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Abstract. We obtain the phase diagram of random Boolean networks with nested canalizing functions. Using the annealed approximation, we obtain the evolution of the number \( b_t \) of nodes with value one, and the network sensitivity \( \lambda \), and we compare with numerical simulations of quenched networks. We find that, contrary to what was reported by Kauffman et al. [Proc. Natl. Acad. Sci. 2004 101 49 17102-7], these networks have a rich phase diagram, were both the "chaotic" and frozen phases are present, as well as an oscillatory regime of the value of \( b_t \). We argue that the presence of only the frozen phase in the work of Kauffman et al. was due simply to the specific parametrization used, and is not an inherent feature of this class of functions. However, these networks are significantly more stable than the variants where all possible Boolean functions are allowed.

1 Introduction

Boolean networks (BN) were introduced by Kauffman [12] as a simple model of gene regulation. In this model the transcription states of the genes are described by Boolean variables, and their dependency to other genes by Boolean functions. In Kauffman’s original model, which is usually called a Random Boolean Network (RBN) [3], both the functions and their inputs are randomly distributed among all possible choices. Since this clearly discards any possible structure which may be selected by the evolutionary process, these networks are null models of gene regulation, from which general features may be derived, which are independent of the missing details [4]. Indeed this simple model already shows an emergent behaviour which may be applicable to real system, namely the existence of two dynamical phases: Frozen and “chaotic”. In the frozen phase, small perturbations have a limited propagation, and eventually stop. In the chaotic phase, small perturbations propagate exponentially fast, often reaching a finite portion of the system. It has been argued [1] that real systems may share features with RBNs which lie exactly at the interface between these two phases — the so-called critical networks. In this point of the configuration space, small perturbations propagate only linearly; thus the system retains some stability of the frozen phase, as well as some of the excitability of the chaotic phase, which may be necessary for the system to respond to external signals. Although this a very interesting feature, a more plausible comparison with real gene regulation can only be made if more realistic properties are included, such as more realistic topologies [5-11] or update functions [12-14], for instance. In this paper we will consider RBNs with nested canalizing functions (NCFs), introduced in [15,16]. These functions are a natural extension of the concept of canalization often present in biological systems [17-19]. A function with a canalizing input is such that if this input is at its canalizing value (either 1 or 0), then the output of the function is automatically defined, for any combination of the remaining input values. It has been observed that many real functions have a canalizing input [18]. If this concept is carried out to the remaining inputs, such that a hierarchy of canalization is present, the resulting function is a nested canalizing function. Interestingly, the majority of the real functions studied in [16] are also NCFs [16]. In this work we will obtain the phase diagram of RBNs with NCFs. Contrary to what was claimed in [16], such networks possess a rich phase diagram, where both the chaotic and frozen phases occupy sizable portions of the configuration space. We also observe oscillations in the number of values of 1’s in the network, for a portion of the parameter space.

This paper is divided as follows. In Sec. 2 we define the model, as well as nested canalizing functions, and review some known facts. In Sec. 3 we obtain the evolution of fraction \( b_t \) of 1’s, and in Sec. 4 we obtain the network sensitivity \( \lambda \) and the phase diagrams. We then conclude in Sec. 5 and provide some final considerations.

2 The Model

A BN is defined as a directed network of \( N \) nodes representing Boolean variables \( \sigma \in \{1,0\}^N \), which are subject to a dynamical update rule,

\[ \sigma_i(t+1) = f_i(\sigma(t)) \] (1)
where $f_i$ is the update function assigned to node $i$, which depends exclusively on the states of its inputs. In this work we consider that all nodes are updated in parallel. All nodes have the same number of inputs $k$ which are chosen randomly.

Starting from a random configuration, the dynamics of the system evolves and eventually settles on an attractor, after a transient time. We will characterize the properties of the system after this transient time by the fraction $b_t$ of the number of 1’s in the network, and by the network sensitivity $\lambda$, which will differentiate between the dynamical phases.

### 2.1 Nested canalizing functions

As introduced in [15], a nested canalizing function $f(\{\sigma_i\})$, with inputs $\{\sigma_i\}, \ i \in [0..k-1]$, is defined as

$$f(\{\sigma_i\}) = \begin{cases} 
  s_0 & \text{if } \sigma_0 = c_0 \\
  s_1 & \text{if } \sigma_0 \neq c_0 \text{ and } \sigma_1 = c_1 \\
  s_2 & \text{if } \sigma_0 \neq c_0 \text{ and } \sigma_1 \neq c_1 \text{ and } \sigma_2 = c_2 \\
  \vdots \\
  s_{k-1} & \text{if } \sigma_0 \neq c_0 \text{ and } \ldots \text{ and } \sigma_{k-1} = c_{k-1} \\
  s_d & \text{otherwise},
\end{cases}$$

where $c_i \in [0, 1]$ is the canalizing value of input $i$ and, and $s_i \in [0, 1]$ is the output value associated with input $i$. The value $s_d$ is the default output of the function, when no input is at its canalizing value. It is usually assumed that $s_d = 1 - s_{k-1}$, so that every input is sensitive. However, in this paper we will also consider the situation where $s_d$ is a free parameter. We will call an input with $s_i = 1$ an activator, and a deactivator otherwise; and if an input is at its canalizing value, we will say it is canalized.

We will consider RBNs where the functions are chosen randomly from all possible Nested Canalizing functions, which are weighted according to the following parameters: $a$, the probability that an input is an activator (i.e. $s_i = 1$), $c$, the probability that the canalizing value of an input is 1, and $d$, the probability that the default output is 1. In the situation where $s_d = 1 - s_{k-1}$ this last parameter is omitted.

In [18] it was shown that many eukaryotic genes seem to be regulated by canalizing functions, and in [15] it was further identified that all but 6 of the 139 genes studied in [15] are in fact regulated by NCFs. There is a simple interpretation for the existence of nested canalizing functions in real gene regulation networks: Genes are used to encode mRNA via a protein called RNA Polymerase (RNAP). This protein binds to a region of the DNA called the promoter region, which starts shortly before the gene itself. Genes which serve as inputs for other genes encode proteins which are called transcription factors (TF). These proteins bind to the upstream region of the gene, i.e. the region preceding (and including) the promoter region. The presence of a TF close to the promoter region may increase or decrease the probability that the RNAP will bind, and initiate the transcription. It is easy to imagine a situation where an hierarchy of TFs exists, where a TF which binds closer to the promoter region has more relevance, and increases or decreases the binding probability of RNAP by such a factor that it overrides the TFs which are bound further away, giving rise to a (nested) canalizing input.

Let us appreciate how much of a deviation is the occurrence of NCFs, in comparison to canalizing functions on only one input, as well as to all possible functions, by considering the total number of functions belonging to each class. Nested canalizing functions are identical to the unate cascade functions known in computer science [19], which have optimal properties regarding their computation time via binary decision diagrams [20], and for which many properties are known. According to [21], the number of different NCFs with $k$ inputs scales as $N_{nc} \sim 4 k 2^{k-1}$. Although the fraction of both these classes relative to the total number $2^k$ of functions with $k$ inputs vanishes for large $k$, using the Stirling approximation for $k!$, we can easily see that the fraction of NCFs is smaller by a factor of $N_{nc}/N_c \sim 1/2^{k-1}$. Thus the presence of nested canalization is a much stronger deviation from a random distribution than single-input canalization.

### 3 The evolution of number of 1’s, $b_t$.

In order to obtain the fraction $b_t$ of 1’s in the network at time $t$, we will employ the annealed approximation [23]. This is a mean-field approximation, which assumes that the inputs of each function are randomly chosen at each time step. By construction, this forbids local correlations from arising, which makes the analysis easier. Since a quenched disorder should be indistinguishable from an annealed one, in the limit of large networks, this approximation is expected to be exact for large RBNs.

We begin by defining the probability $\gamma(b_t)$ that a random input in the network is at its canalizing value,

$$\gamma(b_t) = b_t c + (1 - b_t)(1 - c).$$

Thus, the probability that the output of a randomly chosen function will be 1 at the next time step is given simply by the probability that at least one input is canalized and is an activator, or that the default output value is 1,

$$b_{t+1} = (1 - (1 - \gamma(b_t))^k)a + (1 - \gamma(b_t))^kd = a + (d - a)(1 - \gamma(b_t))^k.$$  

The situation where $s_d = 1 - s_{k-1}$ can be obtained simply by setting $d = 1 - a$. The equilibrium value $b^* = b_{\infty}$ can then be obtained by solving the above equation for $b_{t+1} = b_t = b^*$. We note that $\lim_{t \to \infty} b_t = a$, except for $(a, c) \in \{(0, 1), (1, 0)\}$, in which case $b^* = d$. In Fig. 1 it is shown some of the solutions as a function of $a$, compared...
with numerical simulations. There are two interesting behaviors: 1. If $c = 1$ and $d = 0$ (or symmetrically if $c = 0$ and $d = 1$, not shown), there is a second-order transition of the value of $b^*$ at $a = 1/k$ (or $a = 1 - 1/k$), below which $b^* = 0$ and above which $b^* > 0$. For other values of $c$ and $d$, this behaviour is replaced by a continuous variation of $b^*$ (not shown); 2. If $|d - c|$ is small enough, the value of $b_i$ shows an oscillatory behaviour after a transient time, between two values of $b^*$. These oscillations happen when most of the default output values correspond to the canalizing values of a large portion of the inputs, and most canalized outputs are different from the canalizing values. In such situation, the canalized inputs tend to deactivate themselves, which in turn will increase the default activations, and so on. The transition from this period-2 oscillation to a fixed point is through a pitchfork bifurcation, where the fixed point becomes unstable ($|db_{i+1}/db_i(b^*)| > 1$) and gives rise to the oscillation (as shown in the bottom of Fig. 1).

**4 The network sensitivity, $\lambda$.**

The response of the system to small perturbations is characterized by the network sensitivity $\lambda$, which is defined as $k$ times the probability that the output of randomly selected function will change if a randomly selected input is flipped. Thus, for large networks, the average number of nodes flipped after some small time $t \ll \ln N$ should be $\lambda^t$. Therefore if $\lambda < 1$ the number of affected nodes will tend to zero after some time, and the dynamics is said to be in the frozen phase. If $\lambda > 1$, the number of affected nodes will increase exponentially, and the dynamics is said to be in the “chaotic” phase. For the special value of $\lambda = 1$, the average number of affected nodes increases linearly with time, and the dynamics is said to be in the critical line between the two phases.

We can obtain the value of $\lambda$ for RBNs with NCFs with the annealed approximation, as we did for the values of $b^*$. We start by defining the probability $\eta$ that two consecutive inputs have the same canalized output,

$$\eta = a^2 + (1-a)^2,$$

and the probability $\eta_0$ that the last input has the same canalized output as the default output,

$$\eta_0 = ad + (1-a)(1-d).$$

Using this, we can write the probability $\lambda_i$ that the output will be flipped if input $i$ is flipped,

$$\lambda_i = \left(1 - \gamma(b^*)\right)\left(1 - \gamma(b^*)\right) + \gamma(b^*)\gamma(b^*) \eta_0 (1 - \gamma(b^*)).$$

which accounts for the probability that all the inputs $j < i$ are not canalized, and that the output of $i$ is different than any input $j > i$ which may be canalized. The sensitivity value $\lambda = \sum_i \lambda_i$ amounts then simply to,

$$\lambda = (1-\eta)\frac{1 - (1 - \gamma(b^*))k}{\gamma(b^*)} + k(1 - \gamma(b^*))^{k-1}(\eta - \eta_0).$$

The situation where $s_d = 1 - s_{k-1}$ can be obtained by setting $d = 1 - a$, as before, and making the substitution $\eta^i \rightarrow \eta^i(1 - \delta_{i,k-1})$ in Eq. (2), which yields

$$\lambda^i = (1-\eta)\frac{1 - (1 - \gamma(b^*))k}{\gamma(b^*)} + \left(1 - \gamma(b^*)\right)^{k-1}\left[k(\eta - 1) + (1 - \eta_0)(k - 1) + 1\right].$$

We note that $\lambda^i \geq \lambda$ for small values of $k$, but for $k \gg 1$ we have $\lambda^i \sim \lambda$, and this value approaches $\lim_{k \to \infty} \lambda = (1-\eta)/\gamma(b^*)$, for $\gamma(b^*) > 0$. This means that in the limit of
large \( k \), NCFs tend to be much more stable than randomly chosen functions, which have \( \lambda = k/2 \).

In Figs. 2 and 3 are the phase diagrams for several parameter values. We note that these diagrams are symmetric in respect to the appropriate parameter transformations, such as \( (c, d) \leftrightarrow (1-c, 1-d) \). For \( d = 0 \) and \( c = 1 \), we observe that the critical line is composed of the \( a = 1/2 \) line plus the \( a = 1/k \) line, which corresponds to the critical values of \( a \) where \( b^* > 0 \), as discussed previously. We note that, since \( \lambda \cong (1-\eta)/\gamma(b^*) \) for \( k > 1 \), there is a universal critical line at \( a = 1/2 \) for which \( \eta = 1/2 \) and \( \gamma(b^*) \cong 1/2 \), and thus \( \lambda \cong 1 \), independent of \( c \) and \( d \). This is interesting, since it means that the most entropic situation \( a = c = d = 1/2 \) leads to a critical network, if \( k \) is not too small, and either changing \( c \) or \( d \) leaves the value of \( \lambda \) unmodified. Thus criticality can be attained for a large number of possible configurations, which is maybe a reason why this class of functions are favoured biologically. However, there are large portion of the configuration space where \( \lambda > 1 \), and the dynamics finds itself in the chaotic phase. Additionally, there are significant regions where the fixed point of \( b^* \) is unstable ans is replaced by a period-2 oscillation, as discussed previously. In this situation (which are marked in white in Figs.2 and 3), the value of \( \lambda \) is not meaningful, since it supposes that \( b^* \) is a stable fixed point, and the networks are neither in the frozen nor in the chaotic phase.

The values of \( \lambda \) and \( \lambda^* \) in Eqs. 8 and 9 can be verified empirically, by constructing RBNs and obtaining the so-called Derrida plots [26], as shown in Fig. 4. These plots show the normalized hamming distance \( r_{t+1} \) at time \( t+1 \) between two identical copies of the network, after only one of them had a random fraction of \( r_t \) nodes flipped at time \( t \). As can be seen on the top of Fig. 4 the different

Fig. 2. Network sensitivity \( \lambda \) (Eq. 8) for several parameter values, as indicated in the labels and axes. The critical line \( \lambda = 1 \) is indicated by the solid lines. The regions in white correspond to parameter regions where the system displays oscillations, and thus the value of \( \lambda \) is not well defined. The points marked with stars (*) were verified empirically in Fig. 4.

Fig. 3. Network sensitivity \( \lambda^* \) (Eq. 9) for the case were \( s_2 = 1 - s_{k-1} \), for several parameter values, as indicated in the labels and axes. The critical line \( \lambda^* = 1 \) is indicated by the solid lines. The regions in white correspond to parameter regions where the system displays oscillations, and thus the value of \( \lambda^* \) is not well defined. The points marked with stars (*) were verified empirically in Fig. 4.
networks (even those with the same value of $\lambda$) have a different perturbation propagation. However, if we only consider small values of $r_t$, these curves are matched quite exactly by slopes of type $r_{t+1} = \lambda r_t$, as can be seen on the bottom of Fig. 4.

5 Conclusion

We have obtained the phase diagram of random Boolean networks with nested canalizing functions. Using the annealed approximation, we have analytically calculated the fraction $b_t$ of nodes with value one, and the sensitivity $\lambda$ of the network to small perturbations. We compared the results with numerical realizations of quenched networks, which have shown an excellent agreement. We have seen that the steady state value $b^* = \lim_{t \to \infty} b_t$ displays two interesting features for some parameter combinations: 1. For a probability $c = 1$ that the canalizing value of a random input is one, and a probability $d = 0$ that the default output of a random input is one (and symmetrically for $d = 1$ and $c = 0$), there is a second-order transition from $b^* = 0$ to $b^* > 0$ at critical fraction $a = 1/k$ of inputs which are activators; and 2. If $|d - c|$ is small enough, $b_t$ will oscillate between two values of $b^*$, up to a value of $a$ for which the fixed point of $b_t$ will become stable again. A similar oscillation is also observed in RBNs with threshold functions [27].

We have also observed that the phase diagram has large regions where $\lambda > 1$, and thus the system is in the chaotic phase. This contradicts the claim by Kauffman et al. [10] that this class of functions always leads to $\lambda < 1$. The results in [10] were obtained for specific in-degree distributions, and a selection of the canalizing values according to specific probabilities. These probabilities were chosen so that they match the experimental data they analysed, but for which no other explanation was offered. This distribution was then extrapolated to obtain the entire phase diagram, which resulted only in values of $\lambda < 1$. In this work, the functions were chosen with different probabilities, according to the simple parameters $a$, $c$ and $d$, which resulted in a phase diagram with large portions where $\lambda > 1$. Therefore, since there seems to be no reason to believe the specific parametrization in [10] has a general character, it should not be concluded that the existence of NCFs always leads to $\lambda < 1$. On the other hand, the values of $\lambda$ for RBNs with NCFs are much smaller than RBNs with all functions chosen with equal probability. Thus the conclusion in [10] that NCFs convey more stability to the system seems well justified, and it may indeed be a reason why these functions are observed in real biological systems.

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