Interplay between Boolean rules and topology in the stability of Boolean networks

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Empirical evidence has revealed that biological regulatory systems are controlled by high-level coordination between topology and Boolean rules. In this study, we study the joint effects of topology and Boolean functions on the stability of Boolean networks. To elucidate these effects, we focus on i) the correlation between the sensitivity of Boolean variables and the degree, and ii) the coupling between canalizing inputs and degree. We find that negatively correlated sensitivity with respect to local degree enhances the stability of Boolean networks against external perturbations. We also demonstrate that the effects of canalizing inputs can be amplified when they coordinate with high-degree nodes. Numerical simulations confirm the accuracy of our analytical predictions at both the node and network levels.

I. INTRODUCTION

The random Boolean network proposed by Kauffman in 1969\(^1\) has been widely used in physics, biology, and computer science for modeling biological regulatory systems in an abstract manner\(^2\,^6\). Many functions in living systems can be modeled by Boolean networks, including genetic regulation\(^1\,^4\,^5\), neural firing\(^7\), and social activity\(^8\). The dynamical patterns of Boolean networks fall into two phases, namely stable and unstable (chaotic) phases. In a stable phase, most nodes rapidly reach a steady state and remain unchanged. In contrast, in an unstable phase most nodes change their states in a chaotic manner. It has been suggested that many biological regulatory systems ranging from genetic systems to neural systems tend to hover near the borderline between these two phases, achieving both stability and evolvability\(^9\,^{11}\). Empirical evidence supports the hypothesis that biological networks remain near criticality\(^9\,^{12}\), especially for knockout experiments for single genes in \textit{Saccharomyces cerevisiae}\(^13\) and gene expression dynamics in macrophages\(^14\).

Theoretical predictions regarding the dynamics of Boolean networks are based on stability against perturbations\(^15\,^{16}\). While damage caused by perturbations dies out quickly in a stable phase, it can spread through an entire system in an unstable phase. Pioneering research on the theoretical prediction of the stability of random Boolean networks has revealed that the mean degree \(\langle k \rangle\) of a network and the mean bias \(\langle p \rangle\) of Boolean functions typically determine the location of criticality\(^15\,^{16}\). Since then, many studies have attempted to assess the effects of structural and dynamical features, including scale-free structures\(^17\), noise\(^18\,^{19}\), multi-level interactions\(^20\), asynchronous updates\(^21\), continuous dynamics\(^22\), veto functions\(^23\), bipartite interactions\(^24\), knockout\(^25\,^{26}\), adaptive dynamics\(^27\), and canalizing functions\(^28\). Recently, an exhaustive search of real-world networks revealed that biological regulatory circuits achieve stable and adaptive functionality based on the interplay between logical variables and causal structures, such as anti-correlated sensitivity to the local degrees of nodes and abundant canalizing functions\(^12\). There have been several attempts to study the role of the correlations between structural and dynamic properties in Boolean networks\(^29\,^{31}\), but this role is still not fully understood, particularly for the correlations between node degrees and Boolean functions.

In this study, we analyze the stability of a random Boolean network incorporating interplay between network topology and Boolean variables. Specifically, we aim to assess the effects of the correlation between local node degrees and Boolean functions in terms of sensitivity\(^29\,^{30}\) and canalizing inputs\(^28\). In this paper, we elucidate the role of the coupling between local topology and Boolean rules in promoting the stability of Boolean networks. Specifically, we demonstrate that negatively correlated sensitivity to degree enhances the stability of Boolean networks. Additionally we find that coordination between high-degree nodes and canalizing inputs can enhance stability. Numerical simulations are conducted to verify our analytical predictions, revealing excellent agreement.

II. THEORY

The Boolean network considered in this paper consists of a set of nodes whose states are binary (i.e., on or off). The bias \(p_i\) of a Boolean function is assigned to each node and Boolean variables for every combination (total of \(2^k_i\) combinations, where \(k_i\) is the degree of node \(i\)) of inputs are assigned according to the bias \(p_i\). Starting from an initial state selected at random, the state of each node is updated synchronously according to its Boolean function and input signals. After a transient period, the dynamics of the Boolean network eventually arrives at a set of restricted patterns among of total of \(2^N\) possible states,
where $N$ is the number of nodes. To simulate a perturbation, a small fraction of the nodes are randomly selected and flipped. To check the network responses to such perturbations, we define the stability of the network as its ability to eliminate damage. In a stable phase, nodes flipped by a perturbation quickly return to their initial states. However, in an unstable phase, the majority of the nodes in a system fall under the influence of perturbations and evolve to exhibit chaotic dynamics.

To quantify the stability of a Boolean network, we measure the (normalized) Hamming distance $H$ between the initial and final states following a perturbation. We define the state of the nodes as $\bar{s} = \{s_1, s_2, \ldots, s_N\}$, where $s_i \in \{0, 1\}$. The average Hamming distance between an initial $(t_0)$ and final $(t)$ state is defined as

$$H = \frac{1}{N} \sum_i |s_i(t) - s_i(t_0)|.$$

While $H$ remains at zero in a stable phase within the thermodynamic limit as $N \to \infty$, it takes on non-zero values in unstable phases. Therefore, $H$ represents the degree of network instability.

For a given bias $p_i$ of node $i$, the probability that node $i$ changes its state when one of its input changes, which is referred to as sensitivity, is defined as $q_i = 2p_i(1 - p_i)$. We define $H_i$ as the probability that the state $s_i$ of node $i$ changes based on a change in one of its neighbors. For a locally tree-like network, we can derive the following self-consistency equations for a set of Hamming distances $H_i$ for each node $i$:

$$H_i = q_i \left[ 1 - \prod_{j \in \bar{d}i} (1 - H_j) \right],$$

where $\bar{d}i$ represents the set of neighbors of node $i$. When iterating Eq. 2 from an initial value of $H_i$, $H_i$ converges to a fixed point. We can then obtain the average Hamming distance for an entire network as follows:

$$\langle H \rangle = \frac{1}{N} \sum_i H_i.$$

Note that Eq. 2 can be interpreted as a percolation process with an occupation probability of $q_i$.

By expanding $H_i$ near a small value of $\epsilon_i$, we get

$$\epsilon_i = q_i \sum_j A_{ij} \epsilon_j,$$

where $A_{ij}$ are the elements of the adjacency matrix. It should be noted that we neglect second- and higher-order terms. Next, the critical point can be identified by calculating the inverse of the principal eigenvalue $\Lambda$ of the matrix $\mathcal{Q}$ as follows:

$$\mathcal{Q}_{ij} = q_i a_{ij}.$$

By using Eqs. 2-5, we can calculate the stability and critical point for a fixed network structure.

By ignoring different $H_i$ values for each node in an “annealed approximation”, we can treat the $H_i$ value for each node as the same value $H_a$. In this approximation, analysis at a single node level is no longer possible, but we can easily compute the stability of a Boolean network by solving a single equation for $H_a$ with given degree and sensitivity distributions. We obtain the following equation for a degree distribution $P(k, k_o)$, where $k$ and $k_o$ are the in and out degrees, respectively:

$$H_a = 1 - \sum_{k,k_o} k_o P(k, k_o) q(k)(1 - H_a)^k,$$

where $q(k)$ is the sensitivity distribution as a function of degree. Assuming that $k$ and $k_o$ are uncorrelated, we get

$$H_a = 1 - \sum_k P(k) q(k)(1 - H_a)^k.$$

We now define $f(H_a) = 1 - \sum_k P(k) q(k)(1 - H_a)^k - H_a$. By applying the linear stability criterion, the critical point can be identified by the condition $f'(0) = 0$, which yields

$$\sum_k k P(k) q(k) = 1.$$

Assuming that the sensitivity has no correlation with the degree, we can recover the well-known prediction of the critical point $\langle k \rangle = 1/(2p(1-p))$.

### III. RESULTS

We analyze the effects of the correlation between node degree and sensitivity using the general framework described above. First, we constructed an Erdős-Rényi (ER) graph and assign the sensitivity $q_i = 2p_i(1 - p_i)$, where $p_i$ is the bias. We consider three representative cases of the coupling between sensitivity and node degree: uncorrelated (UC), positively correlated (PC), and negatively correlated (NC). For UC case, we assign the same $\langle p \rangle$ to each node to obtain uncorrelated coupling. For the PC case, we assign the linearly correlated bias $p_i$ of node $i$ to its degree $k_i$ as $p_i = C_p k_i$. Here, $C_p$ determines the average bias for a given mean degree as $\langle p \rangle = C_p \langle k \rangle$. In contrast, for the NC case, $p_i$ is assigned as $p_i = -C_N k_i + 1/2$, where $C_N$ determines the average bias as $\langle p \rangle = -C_N \langle k \rangle + 1/2$. The factor of $1/2$ ensures that the maximum value of bias is $1/2$. The exact linear relationships in the PC and NC cases do not sustain all possible ranges of $\langle p \rangle$ because $0 \leq p_i \leq 1/2$. However, the range of linear dependency is still sufficiently broad to examine the impact of the correlation. By substituting all of these parameters into Eq. 7, we can derive the self-consistency equations for $H_a$ for the three coupling
cases as follows:

\[ H_a = 2p(1 - p)(1 - e^{-(H_a)}) \]
\[ PC: H_a = 2C_p\langle k \rangle \left\{ 1 - C_p(1 + \langle k \rangle) + (1 - H_a)e^{-(H_a)} \left[ C_p + C_p\langle k \rangle(1 - H_a) - 1 \right] \right\} \]
\[ NC: H_a = \frac{1}{2} - 2C_N^2\langle k \rangle(1 + \langle k \rangle) - \langle k \rangle H_a \times \left[ \frac{1}{2} - 2C_N^2\langle k \rangle(1 - H_a)(1 + \langle k \rangle - \langle k \rangle H_a) \right] \]

By solving these self-consistency equations, we can obtain the average Hamming distances and identify the critical points.

We implemented numerical simulations on ER networks with \( \langle k \rangle = \langle k_{out} \rangle = 4 \) without any degree-degree correlation. We assigned the biases and corresponding Boolean variables according to the process described above. From initial states selected randomly, the state of each node is updated synchronously according to the Boolean variables. After a transient period, the dynamics should arrive at a steady state. To simulate a perturbation, we flipped a fraction of 0.01 of the nodes by force. When the system reached a steady state again following the perturbation, we measured the Hamming distance over all nodes.

In Fig. 1, we compare the analytical predictions from Eq. 10 to the numerical simulations. The agreement between the theory and the simulations is excellent. We find that a negatively correlated sensitivity to degree enhances stability when comparing the UC and PC cases. For the NC case, the transition point of mean bias \( \langle p \rangle_c \) is delayed and \( H \) is lower than in the other cases. In contrast, the PC case exhibits an enlarged chaotic region compared to the other cases, making it more vulnerable to perturbations. These results demonstrate that the correlation between sensitivity and degree can significantly affect the stability in terms of the location of the critical point and the size of Hamming distance.

To evaluate the impact of the interplay between node degree and sensitivity more clearly, we consider a transparent example with a bimodal degree distribution with \( P(k) = (1/2)\delta_{k,10} + (1/2)\delta_{k,6} \) and \( N = 10^3 \). The bias distribution is also bimodal and defined as \( Q(p) = (1/2)\delta_{p,2} + (1/2)\delta_{p,0.1} \). Analytical predictions (lines) and numerical results (symbols) are presented together. (b) Phase diagram between stable and chaotic phases obtained theoretically as a function of the mean node degree \( \langle k \rangle \) and \( p \). We use \( K_1 = \langle k \rangle + 2 \) and \( K_2 = \langle k \rangle - 2 \).
We consider three different correlations between node sensitivity and node degree: (a) PC, (b) UC, and (c,d) NC. We consider a network with $P(k) = (1/2)\delta_{k,10} + (1/2)\delta_{k,6}$ and $N = 10^4$, and a bimodal bias distribution defined as $Q(p) = (1/2)\delta_{p,2} + (1/2)\delta_{p,0.1}$. Figure (d) is an enlarged view of Fig. (c). The average Hamming distances for nodes with high degrees ($k = 10$) and low degrees ($k = 6$) are denoted by green and blue arrows, respectively. The average Hamming distance over all nodes is denoted by a filled circle.

The average Hamming distance for nodes with high degrees ($k = 10$) and low degrees, respectively. For the sake of simplicity, we consider a random network with a bimodal degree distribution defined as $P(k) = (1/2)\delta_{k,K_1} + (1/2)\delta_{k,K_2}$, where $K_1 = 6$ and $K_2 = k - 2$. An increasing value of $p_c$ for the NC coupling can be observed consistently over a wide range of parameter sets.

In addition to the global stability of Boolean networks, we can also assess the stability of each node in a given network topology using Eq. (2). Fig. 3 reveals perfect agreement between the numerical results $H_i^{\text{sim}}$ and theoretical predictions $H_i^{\text{th}}$ for the probability that a node $i$ changes its state when a perturbation occurs. We computed the average Hamming distances $\langle H_{k=10} \rangle$ and $\langle H_{k=6} \rangle$ for nodes with high degree ($k = 10$) and low degree ($k = 6$), respectively, as indicated by the green and blue arrows in Fig. 3, respectively. The average Hamming distance over all nodes is denoted by a filled circle. One can see two clearly separated groups of nodes with different stability values and Hamming distances $H_i$ for the PC coupling. We can confirm that in the PC coupling, damage can spread through high-degree nodes with high sensitivity, which are prone to instability. However, for the NC coupling, these two groups merge and perturbations terminate quickly. From the perspective of a percolation problem, NC coupling corresponds to the case where high-degree nodes have low occupation probabilities, leading to stable dynamics, which is analogous to degree-based removal in network percolation [35].

Finally, we consider the role of the interplay between local node degree and canalizing inputs, which are observed frequently in biological systems [13 28]. Canalizing functions have a single input that forces the corresponding output to a specific value, regardless of the values of other inputs. The average Hamming distance $H_i$ with a fraction $c_i$ of canalizing inputs is calculated as

$$H_i = \langle H_i \rangle = c_i q_i (1 - H_i) + \frac{1}{2} c_i q_i (1 - H_i) \left[ 1 - \prod_{j \in \partial_i/c} (1 - H_j) \right] + (1 - c_i) q_i \left[ 1 - \prod_{j \in \partial_i} (1 - H_j) \right], \quad (11)$$

where $q_j = 2p_j (1 - p_j)$ and $\partial_j/c$ define a set of inputs excluding a canalizing input [22]. By definition, canalizing functions lead to stable dynamics [28] because they effectively reduce the sensitivity of non-canalizing inputs connected to nodes shared by canalizing inputs. However, the effects of canalizing inputs are not solely determined by the fraction of canalizing inputs. The topological locations of canalizing links also affect stability, which can be predicted using Eq. (11).

We consider three different correlations between node degree and the locations of canalizing inputs, which are again denoted as UC, PC, and NC. For the UC case, the canalizing inputs are distributed randomly. PC and NC indicate that canalizing inputs tend to connect nodes with high and low degrees, respectively. For the sake of simplicity, we consider a random network with a bimodal degree distribution defined as $P(k) = (1/2)\delta_{k,K_1} + (1/2)\delta_{k,K_2}$.
We analyzed the stability of random Boolean networks incorporating dynamic rules, as well as the topological properties of each node. We find that correlation between node degree and Boolean functions plays an important role in determining Hamming distances and critical point. Specifically, negatively correlated sensitivity to the degree of each node increases stability. We also find that a correlation between high-degree nodes and canalizing inputs can increase global stability. Our results reveal that analysis based on the naive mean-field approach may fail to predict dynamical consequences in Boolean networks with intertwined structural and functional properties, which are often observed in real-world biological systems. Further study is required to examine the effects of more complex features in Boolean networks, such as loops and feedback in network topologies, and hierarchical dynamics.

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