

Cell–Cell Interactions: How Coupled Boolean Networks Tend to Criticality

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Abstract Biological cells are usually operating in conditions characterized by intercellular signaling and interaction, which are supposed to strongly influence individual cell dynamics. In this work, we study the dynamics of interacting random Boolean networks, focusing on attractor properties and response to perturbations. We observe that the properties of isolated critical Boolean networks are substantially maintained also in interaction settings, while interactions bias the dynamics of chaotic and ordered networks toward that of critical cells. The increase in attractors observed in multicellular scenarios, compared to single cells, allows us to hypothesize that biological processes, such as ontogeny and cell differentiation, leverage interactions to modulate individual and collective cell responses.

Keywords

Cell–cell interactions, coupled Boolean networks, dynamical regimes, criticality, gene regulatory networks

1 Introduction

“Large, randomly assembled nets of binary elements behave with simplicity, stability, and order. It seems unlikely that Nature has made no use of such probable and reliable systems, both to initiate evolution and protect its progeny,” wrote Stuart Kauffman (1969) in his first paper on Boolean networks (BNs), which gave origin to a flourishing research area focusing on Boolean models for genetic networks. An important perspective of a large part of those studies is the ensemble approach (Kauffman, 2004), aimed at investigating generic properties of cells that can be matched by ensembles of parameterized models. One of the most relevant and far-reaching conjectures originating from those studies is the so-called *criticality hypothesis*, which states that systems in a dynamical regime between order and disorder are capable of optimally balancing robustness and adaptiveness during evolution and reliably reacting to external stimuli with a wide repertoire of actions (Roli et al., 2018). In these last 50 years, a profusion of results supporting the criticality hypothesis in biological systems has been published (see, e.g., Balleza et al., 2008; Nykter et al., 2008; Rämö et al., 2006; Shmulevich et al., 2005; Torres-Sosa et al., 2012; Villani et al., 2018). As Teuscher (2022) has stated, we have now accumulated enough evidence to consider this hypothesis valid, and there is no need to reconsider it. Nevertheless, there is still room for further investigations when interacting cells are concerned, including tissues and multicellular organisms. A natural question arises as to whether a colony of interacting cells, a tissue or even a multicellular organism, consists of atomically critical components from a dynamical point of view or whether its criticality emerges as a whole as a

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consequence of cell–cell interactions. Properties of interacting random Boolean networks (RBNs) have been explored from different perspectives. Damiani et al. (2011) have studied the attractor diversity of interacting RBNs arranged on a lattice. By varying the degree of interaction, they found that low and moderate interaction degrees produce new attractors in the networks, while high interaction degrees reduce the number of attractors. Furthermore, Damiani, Kauffman et al. (2010) found that, also, information transfer is maximized at moderate interaction degrees. The response to perturbations in interacting critical BNs has been also addressed (Damiani, Graudenzi et al., 2010), finding that interactions may introduce more variability in the kinds of responses. The dynamics of coupled BNs has been the subject of a detailed study considering several experimental conditions (Alonso-Sanz & Bull, 2009); notably, the authors reported that when a high-connectivity degree network is connected to a low-connectivity one, the former shows a drop in the state change per cycle, whereas the latter shows an opposite trend. Interesting results have also been reported by Flann et al. (2013), who studied the patterns created by interacting BN under different signaling settings. They found that ordered networks are able to produce as complex patterns as critical networks. Kim and Sayama (2018) focused instead on the study of robustness and evolvability upon genetic perturbations of interacting network systems. They found that critical RBNs exhibit the greater ability to conserve existing attractors while at the same time creating new ones at both the single-cell level and the level of the interacting multicellular system. Poblanno-Balp and Gershenson (2011) studied modular random Boolean networks (MRBNs), which can be regarded as a special instance of interacting Boolean network systems. They showed that the presence of modules blocks the spread of perturbations and makes MRBNs more robust than RBNs. Furthermore, preliminary results on their dynamical regime have shown that particular trade-offs between the numbers of intramodular and intermodular connections favor criticality.

In this work, we address the question how interacting RBNs change their dynamical features with respect to isolated ones. In particular, we focus on attractor properties and the response to perturbations. The results of our experiments suggest that not only is criticality maintained but it seems to attract networks from ordered and chaotic (disordered) regimes. This might be a clue explaining why living systems are driven by evolution toward criticality and are robustly settled on a dynamically critical state. In this contribution, we primarily define the interaction model used in our experiments, which takes inspiration from cell–cell interactions like direct signaling (Cooper & Adams, 2022). Subsequently, we describe the experimental setting and present the results. The results and their implications are discussed, and we conclude with an outlook toward future work.

2 Interaction Model

Multicellular organisms have a higher level of complexity than unicellular organisms, both structurally and dynamically. The increase in complexity is accompanied by an increase in the capacity, efficiency, adaptability, and fault tolerance of the organism, but at the cost of the need for coordination and, possibly, specialization of the different cells that compose the organism. Coordination is mediated by the interaction between cells, which makes interaction a crucial component in the orchestration of the complex functions of the multicellular organism (Armingol et al., 2021).

To unravel the general principles that have favored, on an evolutionary scale, the emergence of multicellularity—and consequently highlighted the advantages of cell–cell interactions—we propose a model of interaction based on the coupling of cells represented by BNs.

BNs are discrete models of gene regulatory networks proposed by Kauffman (1969). A BN can be mathematically described by a directed graph of N nodes in which each node represents a gene that can be in one of two states: “on” or “off.” So, the state of the system at a discrete time t is a tuple of N Boolean variables (x_1, \dots, x_N) whose evolution is determined by a Boolean function $f_i(x_{i_1}, \dots, x_{i_{K_i}})$, where K_i is the number of inputs of node i . Despite their simplicity, they can capture important qualitative biological cell properties (Braccini, Montagna, & Roli, 2019; Braccini, Roli et al., 2019; Braccini et al., 2017, 2021; Huang et al., 2005; Huang et al., 2009; Montagna et al., 2021; Serra et al., 2007; Shmulevich et al., 2005; Villani et al., 2018).

The types of basic cellular interaction models we study follow:

Unidirectional. In this interaction scheme, at least two BNs are involved. At each time step, the values of a selected subset of nodes in one network are a function of the values of a subset of nodes in the second network. In this configuration, without losing generality, we can refer to the former networks as receiving networks and to the latter as emitter networks. Mathematically, a receiving network node x_i^r affected by the interaction can be defined as $x_i^r = g(x_j^e \mid x_j^e \in X^e)$, where X^e is the set of nodes of the emitter network. In short, we can point out that the dynamics of the receiving network is partially steered by the emitter network, as it is continuously perturbed by the dynamics of the emitter network.

Bidirectional. In this setup, the BNs involved simultaneously play the role of receiver and emitter, mutually influencing each other’s dynamics. Thus each network will have (a) a defined subset of nodes whose dynamics will be determined by the values of some nodes in another network and (b) another subset of nodes that will determine the values of the nodes of the other network.

Unidirectional and bidirectional interaction schemes abstractly describe interaction mechanisms observed in biological cells. They can, in fact, summarize very different dynamics within a cell that can be described at different levels of abstraction, from the simplest receptor–ligand interaction to the most complex cellular physiological response mediated by intracellular signaling cascades. Whereas unidirectional interactions are ubiquitous in biology and appear at any level of biological organization, bidirectional interactions are more frequent in more complex cellular systems, examples of which can be found in the work of Munshi and Stack (2006), Reynolds and Woolf (1993), and Verdi et al. (1996).

With the abstract representation in Figure 1, we present the unidirectional interaction scheme and the mapping between BNs and biological cells.

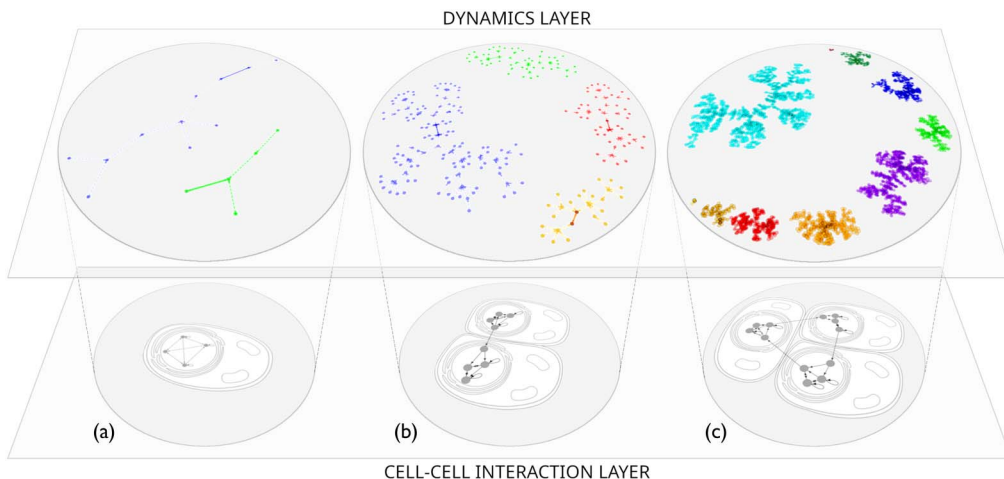


Figure 1. Relationships between Boolean networks (BNs) and biological cells. The bottom layer, that is, the cell–cell interaction layer, represents the level at which interactions between cells occur, so in our framework, it is the layer where the different models of interaction between BNs that we present will be tested. The layer above represents the space in which the dynamics of BNs (isolated and interacting) is represented. In the specific case reported, we can appreciate an increase in the number of attractors—and also in the related state space, since the overall composite network grows—as the number of interacting networks increases. (a) Unicellular system; experimental case modeled with an isolated BN. (b) Multicellular system composed of two interacting BNs with unidirectional interaction. (c) Multicellular system of three interacting BNs with unidirectional interaction.

3 Experiments

In this section, we summarize first the details of the experimental setting, then the results we obtained.

3.1 Experimental Setting

As we are interested in discovering statistical features that highlight the advantage of multicellularity over unicellularity under the lens of evolution, we analyze the dynamics of interacting RBNs drawn from ensembles of networks (Kauffman, 2004) generated with a number of incoming nodes $K = 3$ for each RBN node. In addition, the parameter p , which defines the probability of assigning the value 1 to each entry in an RBN truth table, will take on the values $\{0.1, 0.21, 0.5\}$ which, combined with $K = 3$, allow us to obtain, statistically, sets of ordered, critical, and chaotic networks, respectively (Bastolla & Parisi, 1997). We generated RBNs with 20 nodes.

Concerning the implementation of cell–cell interaction schemes with RBNs, we conduct experiments by selecting a number of interacting networks from the set $\{2, 3\}$ and refer to the scenario in which only one network is involved as an *isolated* network. Because an isolated network has 20 nodes, we replicate it—to produce an exact copy of its genotype—and interconnect it with its clone to create an overall network of 40 nodes for scenarios that require two interacting networks. Similarly, we iterate this process twice to obtain a network with 60 nodes in the case of three interacting networks. For the states used as initial conditions for the simulation of the BNs, we randomly generate a Boolean vector of size equal to the number of nodes of the isolated BN, whereas for the relative cases of interacting networks, where the same network is replicated x times, we juxtapose x times the exact copy of the previously randomly generated vector. This process is repeated 1,000 times to obtain a number of data sufficient to collect ensemble statistics. For each interaction model (i.e., unidirectional and bidirectional), we choose a number of connections from the set $\{1, 2, 3, 4\}$, where by “connections,” we identify the number of nonoverlapping nodes involved in the interaction between the networks. We choose to use the *identity function* to represent the type of information processing applied to data received from the emitter network. Consequently, in simulations involving a single node, the activation function that determines its state at time t will follow this scheme: $x_i^t(t) = x_j^t(t)$, with i and j randomly chosen without replacement in the respective node sets available.

The study of the dynamical features of isolated networks is of fundamental importance because they represent unicellular systems. They provide a term of comparison for the composition of interacting networks, which instead model multicellular systems. Therefore comparisons are made with isolated networks of the same size as the resulting system; as an example, if the interacting networks are three and the size of each is equal to 20 nodes, the isolated networks used for comparison will have 60 nodes. So, isolated networks used as a comparison term are ex novo randomly generated RBNs with a number of nodes corresponding to the sum of nodes of interacting networks.

To begin to empirically address the scientific questions raised, we collect statistics over 100 samples for each experimental configuration on the following quantitative metrics for both isolated and interacting RBN ensembles and for each configuration of parameters previously presented:

Basin entropy. Basin entropy measures the classification capacity of a dynamical system (Krawitz & Shmulevich, 2007). Indeed, making a parallel between a dynamical system and a classification process (Serra & Zanarini, 1990), the attractors represent the prediction classes, while their basins of attraction, and especially the way they partition the state space, represent the classification function. We calculated the basin entropy of a network X with a set of attractor \mathcal{A} as the Shannon entropy of the normalized basin sizes w : $b(X) = -\sum_{a \in \mathcal{A}} w_a \log_2 w_a$. For the basin size calculation, we do not consider the length of the attractors but only the number of states flowing into them.

Number of attractors. Statistics about the number of attractors of a dynamical system is an important feature in biological modeling because attractors, or sets of attractors, usually represent cell types (Huang, 2012; Huang et al., 2005; Huang & Ingber, 2000; Huang & Kauffman, 2013).

Derrida analysis. In its one-step version, the Derrida parameter λ provides a characterization of the dynamical regime of a BN by measuring the average level of propagation of a perturbation after one simulation step. Statistically, $\lambda > 1$ in chaotic networks, $\lambda < 1$ in ordered networks, and $\lambda = 1$ in critical networks. To calculate the Derrida value of a single state, we make a copy of it and perturb it with a logical negation applied to the value of a randomly chosen variable; we then perform a synchronous update for both the original and the perturbed state and, finally, measure the Hamming distance between the two resulting states. We determine the average value for each BN by repeating this procedure for 1,000 random states.

Lempel–Ziv (LZ) complexity. This metric is used to approximate the Kolmogorov complexity of a string of symbols s , defined in terms of the shortest program that produces s . As this measure cannot be effectively computed, it is common to resort to approximations of it. We chose LZ complexity to reckon the Kolmogorov complexity of the attractors of a BN (the attractors are appended to obtain a string of binary symbols). The LZ complexity metric (Lempel & Ziv, 1976) is based on a lossless compression algorithm that scans a given string s and splits it into words; it associates symbols to prefixes and suffixes of the words composing s , progressively introducing a new symbol when the combinations of previous ones cannot produce the incumbent word. The number of symbols used to encode s is an estimate of the Kolmogorov complexity of s . Because the LZ complexity provides an estimation of the compressibility of a sequence of symbols (the LZ complexity is anticorrelated with compressibility, which is high if the sequence contains repetitions), the higher its value is, the more diversified are the attractors.

Maximal attractor distance. The maximum among the distances between attractor pairs provides an estimation of the spectrum range of stationary behaviors exhibited by a BN. Among the possible distance metrics, we opted for an information-theoretic one, namely, the normalized compression distance (Cilibrasi & Vitányi, 2005). The rationale of this metric is to compare the compression ratio of two individual sets of data (i.e., files) with the compression ratio of the juxtaposition of the two sets of data. The more similar the two sets of data are, the smaller is the compression of the compound object with respect to the sum of the compressions of the individual objects. The normalized compression distance (NCD) between two objects A and B is defined as $\frac{\alpha(AB) - \min[\alpha(A), \alpha(B)]}{\max[\alpha(A), \alpha(B)]}$, where $\alpha(X)$ is the size of the compression of data object X and AB means the compound of A and B . This metric has been computed with the high quality data compressor bzip2, based on the Burrows–Wheeler (1994) algorithm.

3.2 Results

The first analysis considers the number of attractors detected in each configuration (see Figure 2). For this analysis, we control in which attractor the dynamics relaxes for each of the 1,000 random initial states, without truncating any trajectory. This implies that even for chaotic networks, characterized by very long attractors, we waited for each simulation to end. Ordered networks usually present a lower number of attractors than critical networks. Likewise, our critical networks present a lower number of attractors than chaotic ones. This pattern persists even in the case of interacting networks, indicating a common trend. Nevertheless, by comparing isolated and interacting networks of the same total size, we can see that the number of attractors of the latter greatly increases. Interestingly, the average and median values of some interacting critical network configurations even exceed those of chaotic isolated networks. Overall, the number of attractors seems also to be related to the number of connections between interacting networks. Specifically, attractor and connection numbers seem to be inversely correlated. This means that an increase in the number of connections

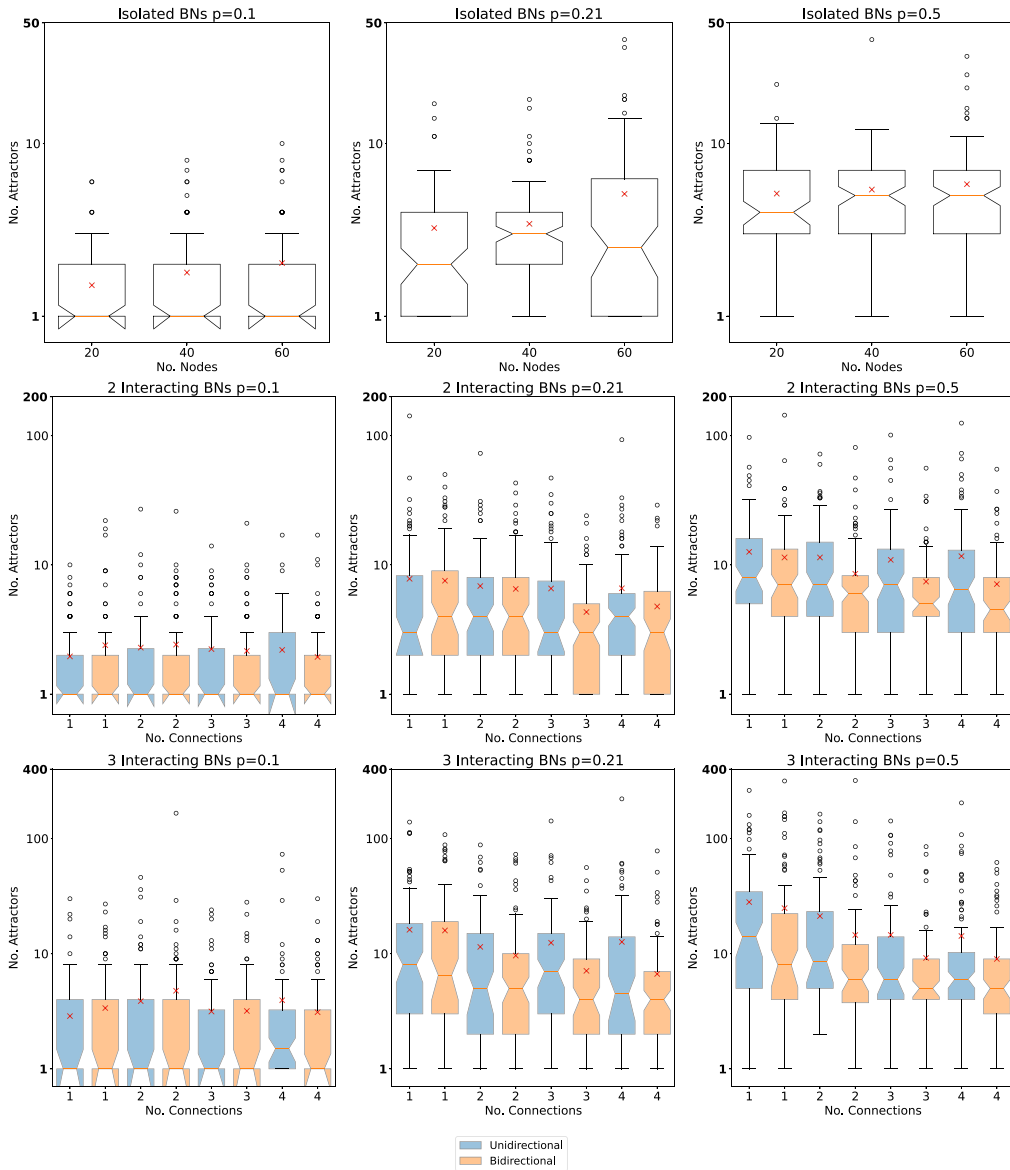


Figure 2. Number of attractors of isolated and interacting networks.

generally leads to a decrease in the number of attractors; these results are in agreement with Damiani et al. (2011).

The second analysis considers basin entropy (see Figure 3). Also in this case, we see an increment in the entropy value according to the degree of disorder of the network. Nevertheless, this difference is minimal between critical and chaotic networks. Congruently with the previous results on attractor number, the basin entropy value of interacting networks is higher than that of isolated networks. Specifically, in some cases, the basin entropy value even doubles that of an isolated network of the same size. Also in this case, the number of connections between interacting networks is negatively correlated with the basin entropy value. This is clearly visible in the bidirectional interaction in critical and chaotic networks. Because an increase in the value of basin entropy can be explained

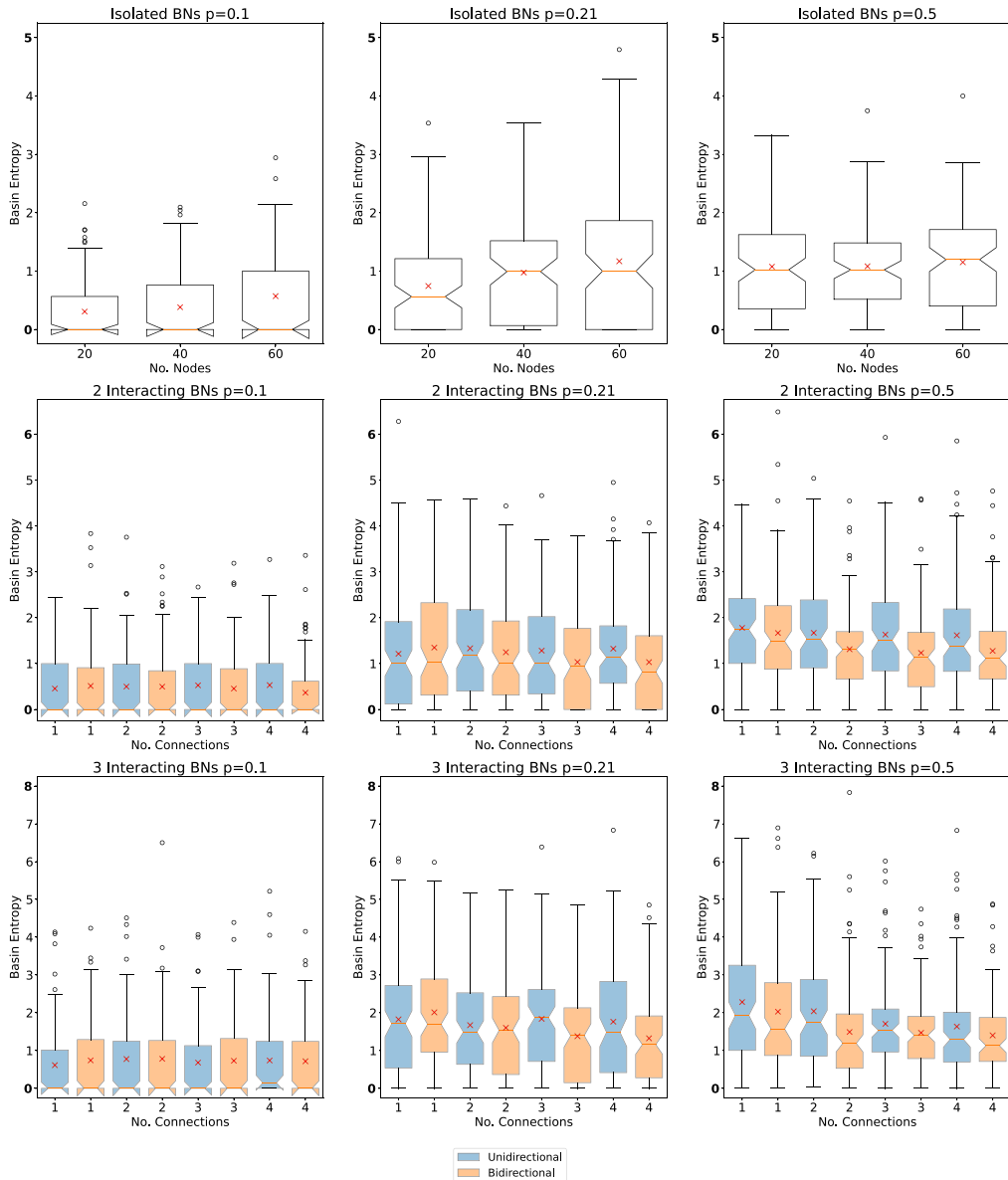


Figure 3. Basin entropy of isolated and interacting networks.

either primarily by an increase in the number of attractors or, alternatively, by a greater tendency toward a uniform discrete distribution, we introduce an additional analysis based on the measure of average absolute deviation (AAD) to get a clearer picture of what is happening to basin sizes. The AAD measure—which shows the AAD of the normalized basin sizes—is in our case defined as $\frac{1}{n} \sum_{i=1}^n |x_i - \mu|$, where n is the number of attractors, x_i is the normalized basin size of attractor i , and μ is the mean over all attractors. As can be seen in Figure 4 the increase in basin entropy of the interacting networks is underpinned mainly by an increase in the number of attractors compared to the isolated networks. However, it can be observed that the increase in the basin entropy of critical compared to chaotic networks is explained more by a reorganization of the size of their attractor basins (higher occurrences of values with low AAD around value 10 on the

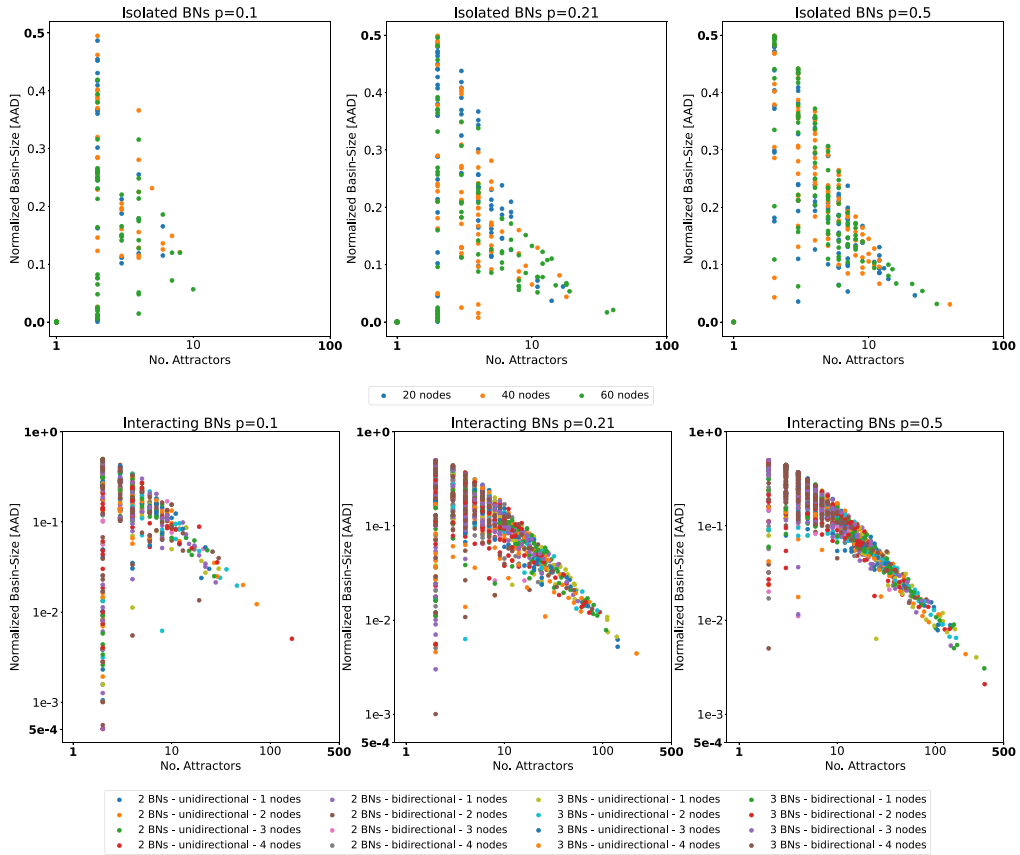


Figure 4. Average absolute deviation (AAD) of the normalized basin sizes for the isolated and interacting networks cases.

\times axis) than by the contribution of the number of attractors (longer tail corresponding to more attractors with low AAD values).

The third analysis consists of verifying the dynamical regime state of the network according to the Derrida value (see Figure 5). The isolated networks produce median values of 0.5 for ordered networks, 1 for the critical, and 1.5 for the chaotic, consistently with the theory on the critical line (Bastolla & Parisi, 1997). When considering the Derrida value of interacting networks, it is possible to see that the mean value moves toward 1 in the case of ordered and chaotic networks and remains stable for critical ones. This happens even when we consider the number of connections. As the number of connections increases, the joint dynamics of the interacting networks tends to 1. In other words, all three types of networks seem to converge toward a critical dynamics when they interact.

The fourth and fifth analyses involve complexity metrics to capture properties of the BN attractors. We first consider the similarity among the attractors of a given network: the more similar the attractors are, the more restricted is the repertoire of available stationary behaviors. For this study, we applied the LZ complexity as a practical estimate of the Kolmogorov complexity of the set of the attractors in each network. To compare the overall trends among each of the three dynamical regimes in the case of isolated and interacting BNs, we averaged across the median values computed on the 100 replicas for each type of configuration. The corresponding bar graphs are shown in Figure 6. We observe that isolated chaotic RBNs are characterized by a higher attractor complexity with respect to the interacting chaotic RBNs. This means that the attractors are more compressible—to some extent—in interacting networks; that is, interactions reduce disorder in chaotic networks. As for critical RBNs, we note that interacting critical networks are characterized

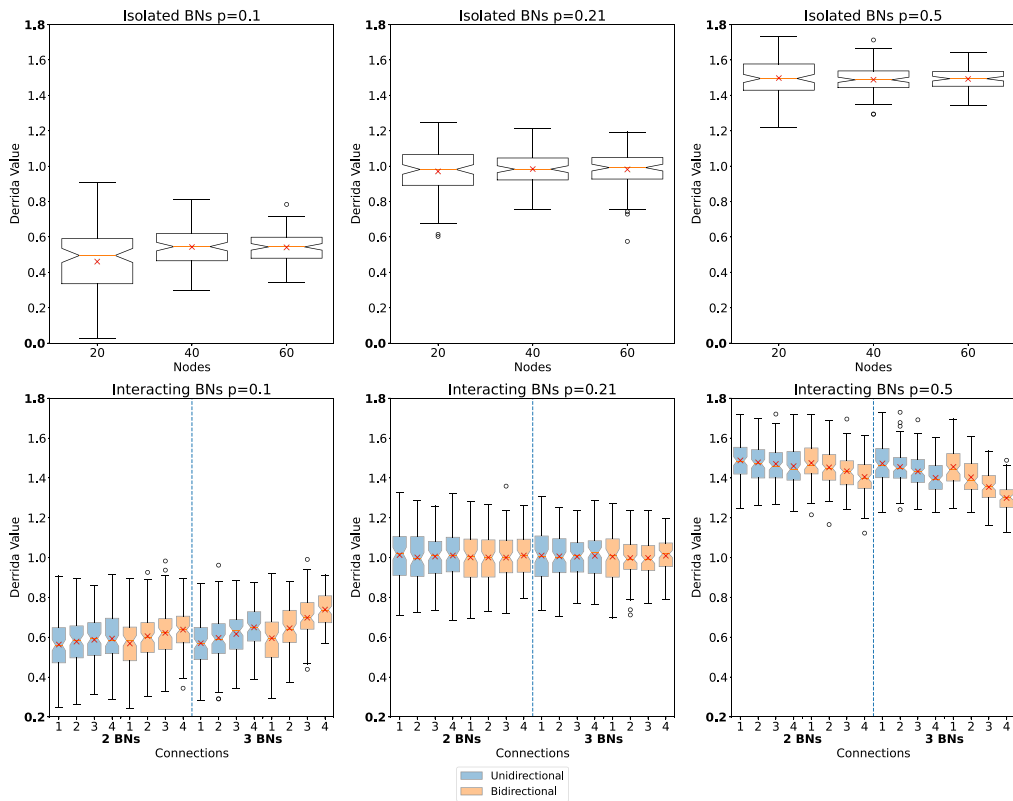


Figure 5. Derrida value of isolated and interacting networks.

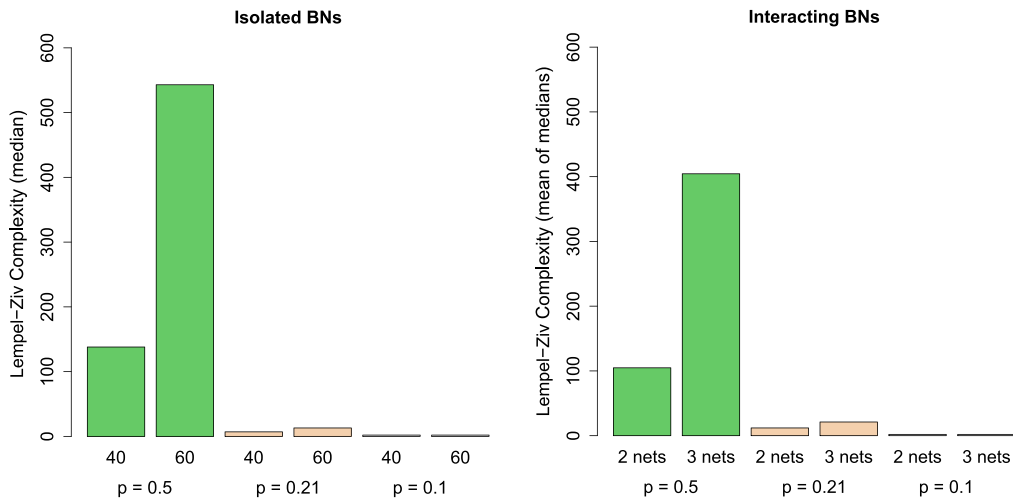


Figure 6. Lempel-Ziv complexity of attractors in isolated and interacting networks.

by a feebly higher attractor complexity, while ordered RBNs do not show differences between the isolated and interacting cases.

Finally, we consider the maximal attractor distance in terms of normalized compression distance. The corresponding results are shown in Figure 7. As for the previous case, we averaged the

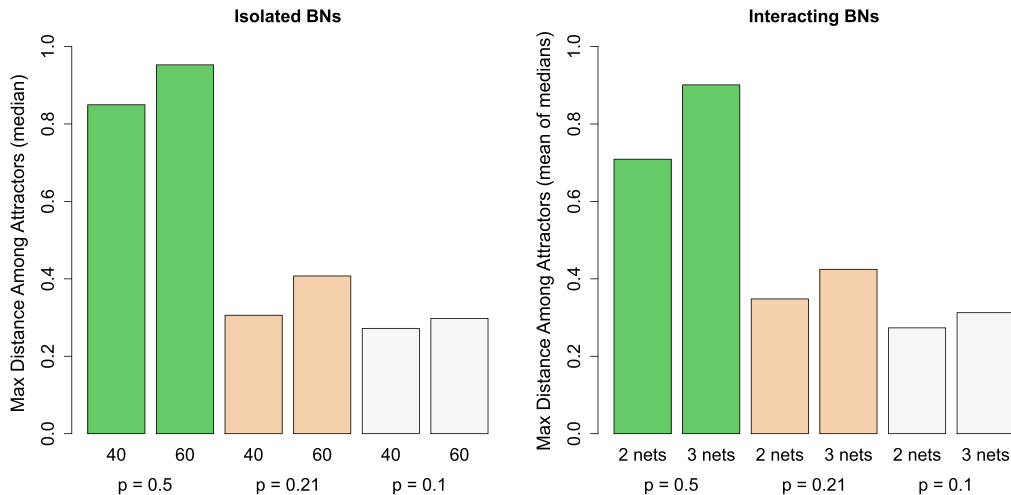


Figure 7. Maximal compression distance of attractors in isolated and interacting networks.

medians of the values of interest across the different kinds and numbers of connections in the case of interacting networks. For the statistics, we considered only the BNs with at least two attractors. The maximal attractor distance is the highest for chaotic RBNs, both isolated and interacting. This value decreases on average for interacting networks, moving toward values comparable to those of critical BNs. For these latter networks, the average maximal distance slightly increases. The differences between isolated and interacting ordered BNs are rather low as well, even though a moderate increase in the interacting case can be observed. Summarizing, the maximal attractor distance statistics seem to reduce the differences among different regimes when interactions take place. These last two analyses confirm the observations of the first ones, suggesting that interactions bias the dynamics of the network toward criticality.

4 Discussion

The previous results give us some insights into the characteristics of the interactions between models of single cells. The main consideration relates the dynamics of the coupled system and how it differs from its isolated components (i.e., the cells). We consider the case of cells in different dynamical regimes that interact with each other. Interestingly, the results indicate that the coupled dynamics of interacting cells always tends toward a critical state. This suggests that the starting dynamics of a single component loses importance as it starts to interact with its neighbors. If proved correct, this theory may allow abstracting away from single cells when studying tissues and focusing on the dynamics of the overall ensemble.

As the results of this study show that interaction can considerably change the dynamical properties of chaotic networks and mildly those of ordered ones, such that they tend to move toward properties characterizing the critical regime, we conjecture that not only is criticality favored by evolution but it also represents a sort of stable meta-attractor. This would provide a further explanation of why living systems are poised in critical regions, but it also raises new questions, such as whether multicellular organisms are composed of atomically critical components or are (also) the result of the interaction of disordered (or ordered) components.

5 Conclusion

In this work, we have studied dynamical properties of interacting RBNs. We have analyzed numbers of attractors, basin entropy, complexity of attractors, maximal attractor distance, and the

Derrida parameter of pairs and triplets of RBNs, under directional and bidirectional connections of varying size. The comparisons with isolated RBNs of the same size as the compound ones show a tendency of changing the properties of chaotic and ordered RBNs toward criticality. This outcome calls for further and deeper investigations of interacting genetic regulatory network models. First of all, we plan to extend the experiments to RBNs with a large size. Furthermore, instead of considering pairs and triplets of BNs, we plan to analyze the properties of tissue-like structures. Furthermore, the results stimulate further analyses involving multicellular configurations that also take into account the processes of cell reproduction, that is, mitosis and meiosis. Finally, as the role of interactions might be considerable in reducing disorder in chaotic networks, the relation between evolution and criticality should probably be investigated in more detail: Not only would evolution favor critical networks, but simple interactions might just be sufficient to create—or not disrupt—criticality upon which evolution can operate.

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