Cell-cell interactions: How coupled Boolean networks tend to criticality

Michele Braccini[1], Paolo Baldini[1] and Andrea Roli[1,2]

[1]Department of Computer Science and Engineering, Università di Bologna, Campus of Cesena, I-47521 Cesena, Italy
[2]European Centre for Living Technology, Venice, Italy
Corresponding author: Michele Braccini, m.braccini@unibo.it

Abstract

Biological cells are usually operating in conditions characterized by inter-cellular signalling 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 towards 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.

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" writes Stuart **?** in its first paper on Boolean networks, 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 (**?**), aimed at investigating generic properties of cells that can be matched by ensembles of parametrized models. One of the most relevant and far-reaching conjecture originated 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 (**?**). In these last fifty years, a profusion of results supporting the criticality hypothesis in biological systems have been published (see e.g. (**??????**)). As stated by **?**, we have now accumulated enough evidence to consider this hypothesis valid and there is no need for reconsidering 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 dynamic point of view or its criticality emerge as a whole as a consequence of cell-cell interactions. Properties of interacting random Boolean networks have been explored from different perspectives. **?** have studied attractor diversity of interacting random Boolean networks 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, **?** found that also information transfer is maximized at moderate interaction degrees. The response to perturbations in interacting critical Boolean networks has been also addressed (**?**), finding that interactions may introduce more variability in the kinds of response. The dynamics of coupled Boolean networks has been the subject of a detailed study considering several experimental conditions (**?**); notably, the authors report 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 **?** who studied the patterns created by interacting Boolean networks under different signaling settings. They found that ordered networks are able to produce as complex patterns as critical networks. **?** focused instead on the study of robustness and evolvability upon genetic perturbations of interacting networks 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 at the level of the interacting multicellular system. **?** 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 number of intramodular and intermodular connections favor criticality.

In this work we address the question as to how interacting random Boolean networks change their dynamical fea-

This version of the contribution has been accepted for publication, after peer review. Cite it with: "Michele Braccini, Paolo Baldini, Andrea Roli; Cell–Cell Interactions: How Coupled Boolean Networks Tend to Criticality. Artificial Life 2024; doi: https://doi.org/10.1162/artl_a_00444". Artificial Life: https://direct.mit.edu/artl

tures with respect to isolated ones. In particular we focus on attractor properties and the response to perturbations. The results of our experiments suggest that criticality not only is maintained, but it seems to attract networks from ordered and chaotic (disordered) regimes. This might a be a clue for explaining why living systems are driven by evolution towards 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 such as direct signaling (**?**). Subsequently, we describe the experimental setting and present the results. The results and their implications are discussed, and we conclude with an outlook to future work.

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 (**?**).

In order to unravel the general principles that have favored, on an evolutionary scale, the emergence of multicellularity—and consequently highlighted the advantages of cell-to-cell interactions—we propose a model of interaction based on the coupling of cells represented by Boolean networks.

Boolean networks (BNs) are discrete models of gene regulatory networks proposed by Kauffman in 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 Booolean variables $(x_1, \ldots, x_N)$ whose evolution is determined by a Boolean function $f_i(x_{i_1}, \ldots, x_{i_{K_i}})$ where K_i is the number of inputs of node i. In spite of their simplicity, they can capture important qualitative biological cell properties (**??????????**).

The types of basic cellular interaction models we study are as follows:

Unidirectional In this interaction scheme, at least two Boolean networks 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 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 Boolean networks involved simultaneously play the role of receiver and emitter, mutually influencing each other's dynamics. Thus, each network will have *(i)* a defined subset of nodes whose dynamics will be determined by the values of some nodes in another network and *(ii)* another subset of nodes that will determine the values of the nodes of the other network.

Unidirectional and bidirectional interaction schemes abstractly describe interactions 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. While 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 following works **???**.

With the abstract representation in Figure **??**, we present the unidirectional interaction scheme and the mapping between Boolean networks and biological cells.

Experiments

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

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 random Boolean networks drawn from ensembles of networks (**?**) 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 following 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 (**?**). 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 where only one network is involved as an *isolated* network. Since 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

This version of the contribution has been accepted for publication, after peer review. Cite it with: "Michele Braccini, Paolo Baldini, Andrea Roli; Cell–Cell Interactions: How Coupled Boolean Networks Tend to Criticality. Artificial Life 2024; doi: https://doi.org/10.1162/artl_a_00444". Artificial Life: https://direct.mit.edu/artl

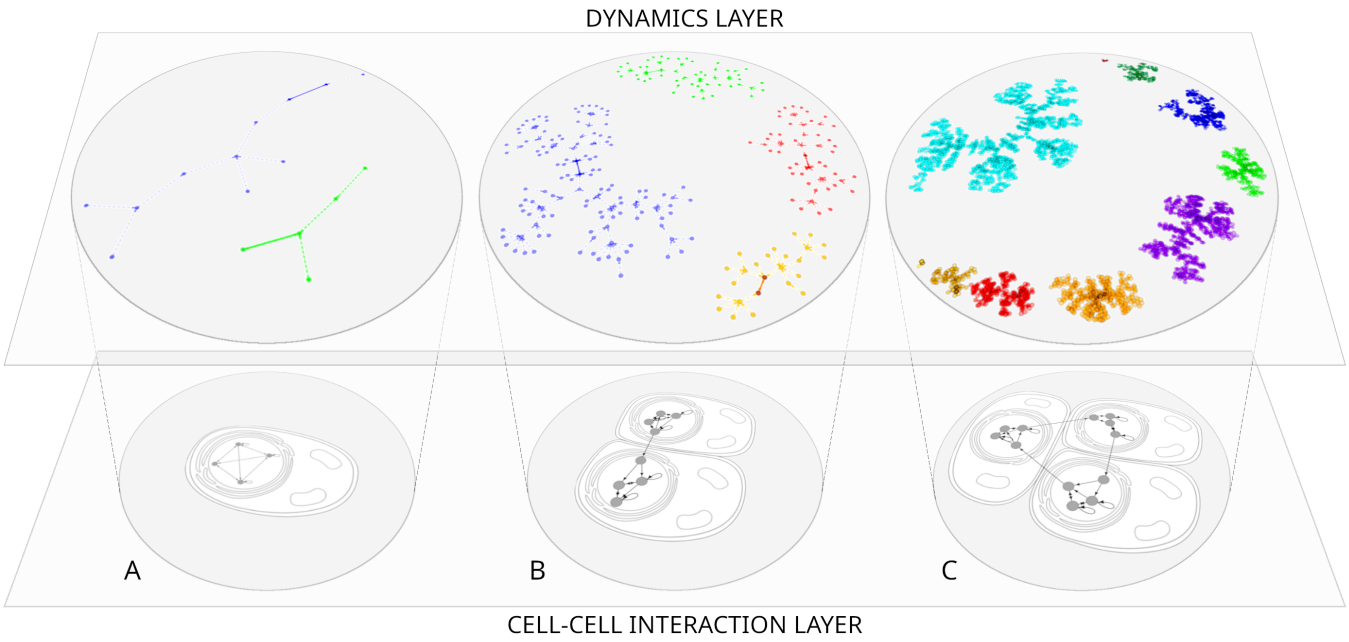

Figure 1: This figure explains the relationships between Boolean networks (BNs) and biological cells. The bottom layer, i.e. the cell-cell interaction layer, represents the level at which interactions between cells occur, so in our framework, it is the layer where the different models of interaction between Boolean networks that we present will be tested. Instead, the layer above represents the space in which the dynamics of Boolean networks (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 Boolean network. **(B)** Multicellular system composed of two interacting BNs with unidirectional interaction. **(C)** Multicellular system of three interacting BNs with unidirectional interaction.

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. While 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 1000 times to obtain a number of data sufficient to collect ensembles 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 non-overlapping 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: $x_i^r(t) = x_j^e(t)$, 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 will be made with isolated networks of the same size as the resulting system; as an example, if the interacting networks are 3 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 above, 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 (**?**). Indeed, making a parallel between a dynamical system and a classification process (**?**), 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 attractors A as the Shannon entropy of the normalized basins sizes w: $h(X) = -\sum_{a \in A} w_a \log_2 w_a$. For the basins sizes calculation, we do not consider the length

This version of the contribution has been accepted for publication, after peer review. Cite it with: "Michele Braccini, Paolo Baldini, Andrea Roli; Cell–Cell Interactions: How Coupled Boolean Networks Tend to Criticality. Artificial Life 2024; doi: https://doi.org/10.1162/artl_a_00444". Artificial Life: https://direct.mit.edu/artl

of the attractors, but only the number of states flowing into them.

No. of attractors Statistics about the number of attractors of a dynamical system is an important feature in biological modeling since attractors, or sets of attractors (**?**), usually represent cell types (**????**).

Derrida analysis In its one-step version, the Derrida parameter λ provides a characterization of the dynamical regime of a Boolean network 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 $\lambda = 1$ 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 Boolean network by repeating this procedure for 1000 random states.

Lempel-Ziv 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 (**?**) 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. Since 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 is its value, 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* (**?**). The rationale of this metric is to compare the compression ratio of two individual set of data (i.e. *files*) with the compression ratio of the juxtaposition of the two sets of data. The more similar are the two sets of data, the smaller 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: $\frac{c(AB)-min\{c(A),c(B)\}}{max\{c(A),c(B)\}}$, where $c(X)$ 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 algorithm (**?**).

Results

The first analysis considers the number of attractors detected in each configuration (see Figure **??**). For this analysis, we control in which attractor the dynamics relaxes for each of the 1000 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 amount of attractors than critical networks. Likewise, our critical networks present a lower amount of attractors than chaotic ones. This pattern persists even in 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 networks configurations even exceed that of chaotic isolated networks. Overall, the number of attractors seems to be also related to the number of connections between interacting networks. Specifically, attractors and connections number seems to be inversely correlated. This means that an increase in the amount of connections generally leads to a decrease in the number of attractors, these results are in agreement with **?**.

The second analysis considers basin entropy (see Figure **??**). 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. Since an increase in the value of basin entropy can be explained 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 basins sizes. The AAD measure—which show the average absolute deviation of the normalized basin sizes—is in our case defined as $\frac{1}{n}\sum_{i=1}^{n}|x_i - \mu|$, where n are the number of attractors, x_i the normalized basin size of attractor i and μ the mean over all attractors. As can be seen in Figure **??** the increase in basin entropy of the interacting net-

This version of the contribution has been accepted for publication, after peer review. Cite it with: "Michele Braccini, Paolo Baldini, Andrea Roli; Cell–Cell Interactions: How Coupled Boolean Networks Tend to Criticality. Artificial Life 2024; doi: https://doi.org/10.1162/artl_a_00444". Artificial Life: https://direct.mit.edu/artl

works is mainly underpinned 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 to value 10 on the x-axis) than by the contribution of the number of attractors (longer tail corresponding to more attractors with low AAD values).

The third analysis consists in verifying the dynamical regime state of the network according to the Derrida value (see Figure **??**). 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 (**?**). When considering the Derrida value of interacting networks, it is possible to see that the mean value moves toward 1 in 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 dynamic of the interacting networks tends to 1. In other words, all the 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, the more restricted the repertoire of available stationary behaviors. For this study we applied the Lempel-Ziv complexity as a practical estimate of the Kolmogorov complexity of the set of the attractors in each network. To compare the overall trend 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 barplots are shown in Figure **??**. 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, i.e. interactions reduce disorder in chaotic networks. As for critical RBNs, we note that interacting critical networks are characterized 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 **??**. As for the previous case, we took the medians of the values of interest and we averaged them across the different kinds and number of connections in the case of interacting networks. For the statistics we only considered 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 towards 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 towards criticality.

Discussion

The previous results give us some insights on the characteristic 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, which interact with each other. Interestingly, the results indicate that the coupled dynamic of interacting cells always tends towards a critical state. This suggests that the starting dynamic of a single component lose 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 property of chaotic networks and mildly those of ordered ones, such that they tend to move towards properties characterizing the critical regime, we conjecture that not only criticality is 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 if multicellular organism are composed of atomically critical components or they are (also) the result of the interaction of disordered (or ordered) components.

Conclusion

In this work we have studied dynamical properties of interacting RBNs. We have analyzed number 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 comparison with isolated RBNs of the same size as the compound ones show a tendency of changing the properties of chaotic and ordered RBNs towards 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 large size. Furthermore, instead of considering pairs and triplets of BNs, we plan to analyze the properties of tissue-like structures. More, the results stimulate further analyses involving multicellular configurations that also take into account the pro-

This version of the contribution has been accepted for publication, after peer review. Cite it with: "Michele Braccini, Paolo Baldini, Andrea Roli; Cell–Cell Interactions: How Coupled Boolean Networks Tend to Criticality. Artificial Life 2024; doi: https://doi.org/10.1162/artl_a_00444". Artificial Life: https://direct.mit.edu/artl

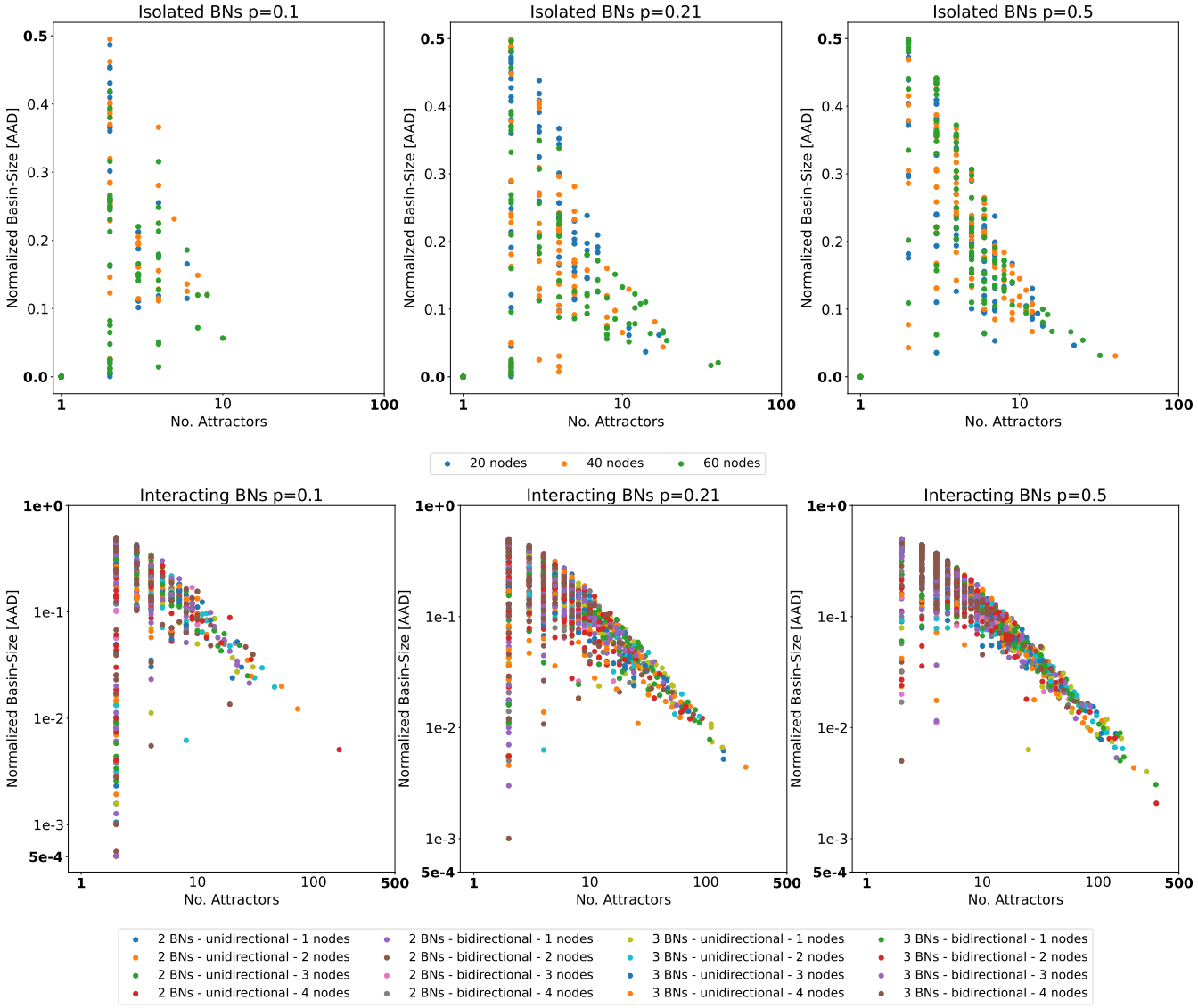

Figure 2: Average absolute deviation (AAD) of the normalized basin sizes for the isolated and interacting networks cases.

cesses of cell reproduction, i.e. 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 evolution would favor critical network, but simple interactions might just be sufficient to create—or not disrupt—criticality upon which evolution can operate.

Acknowledgements

AR acknowledges support from the PRIN 2022 research project of the Italian Ministry of University and Research titled *Org(SB-EAI) – An Organizational Approach to the Synthetic Modeling of Cognition based on Synthetic Biology and Embodied AI* (Grant Number: 20222HHXAX).

References

Alonso-Sanz, R. and Bull, L. (2009). On minimally coupled boolean networks. *International Journal of Bifurcation and Chaos*, 19(04):1401–1414.

Armingol, E., Officer, A., Harismendy, O., and Lewis, N. E. (2021). Deciphering cell–cell interactions and communication from gene expression. *Nature Reviews Genetics*, 22(2):71–88.

Balleza, E., Alvarez-Buylla, E., Chaos, A., Kauffman, S., Shmulevich, I., and Aldana, M. (2008). Critical dynamics in genetic regulatory networks: Examples from four kingdoms. *PLoS ONE*, 3:e2456:1–10.

Bastolla, U. and Parisi, G. (1997). A numerical study of the

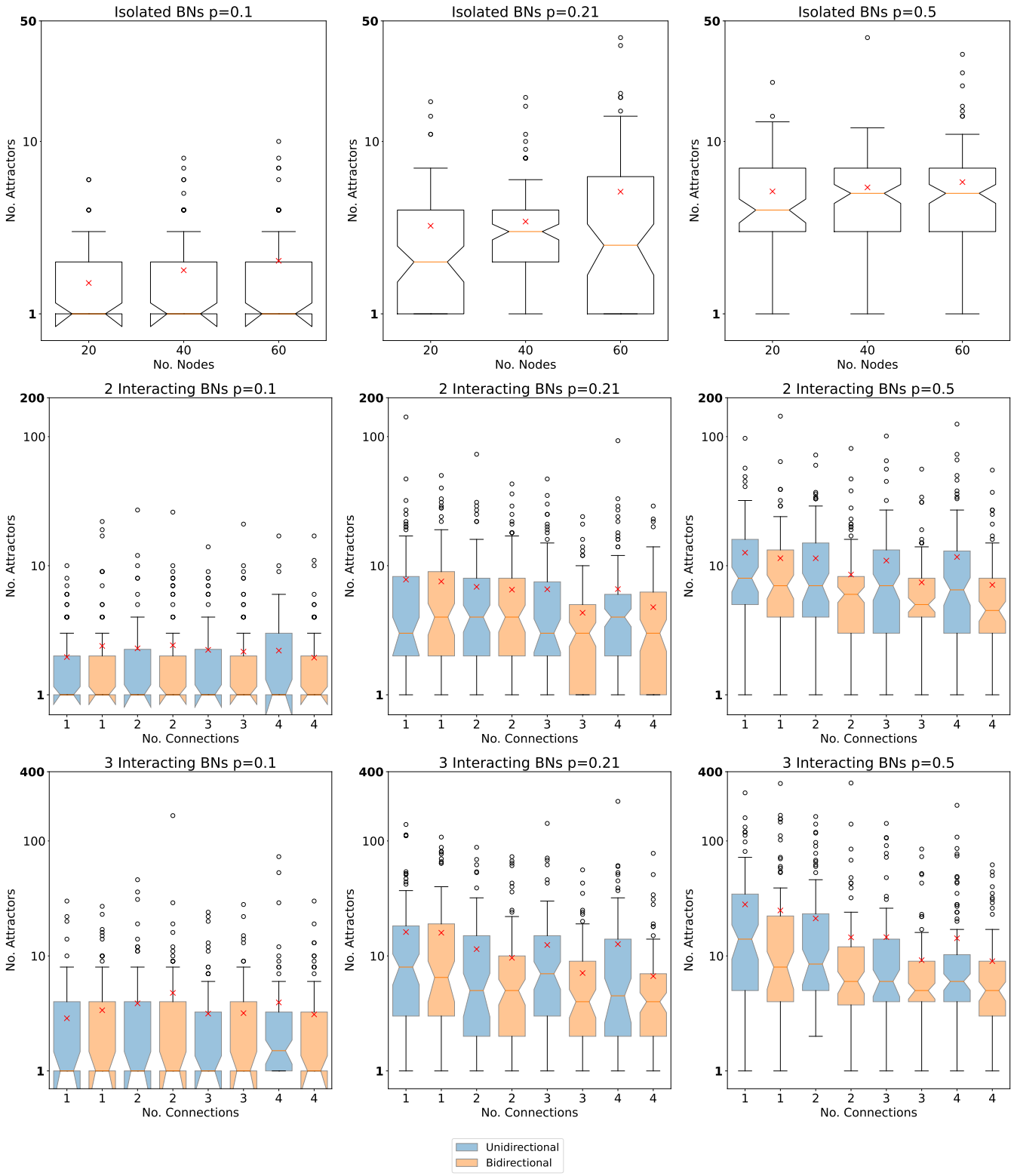

Figure 3: Number of attractors of isolated and interacting networks.

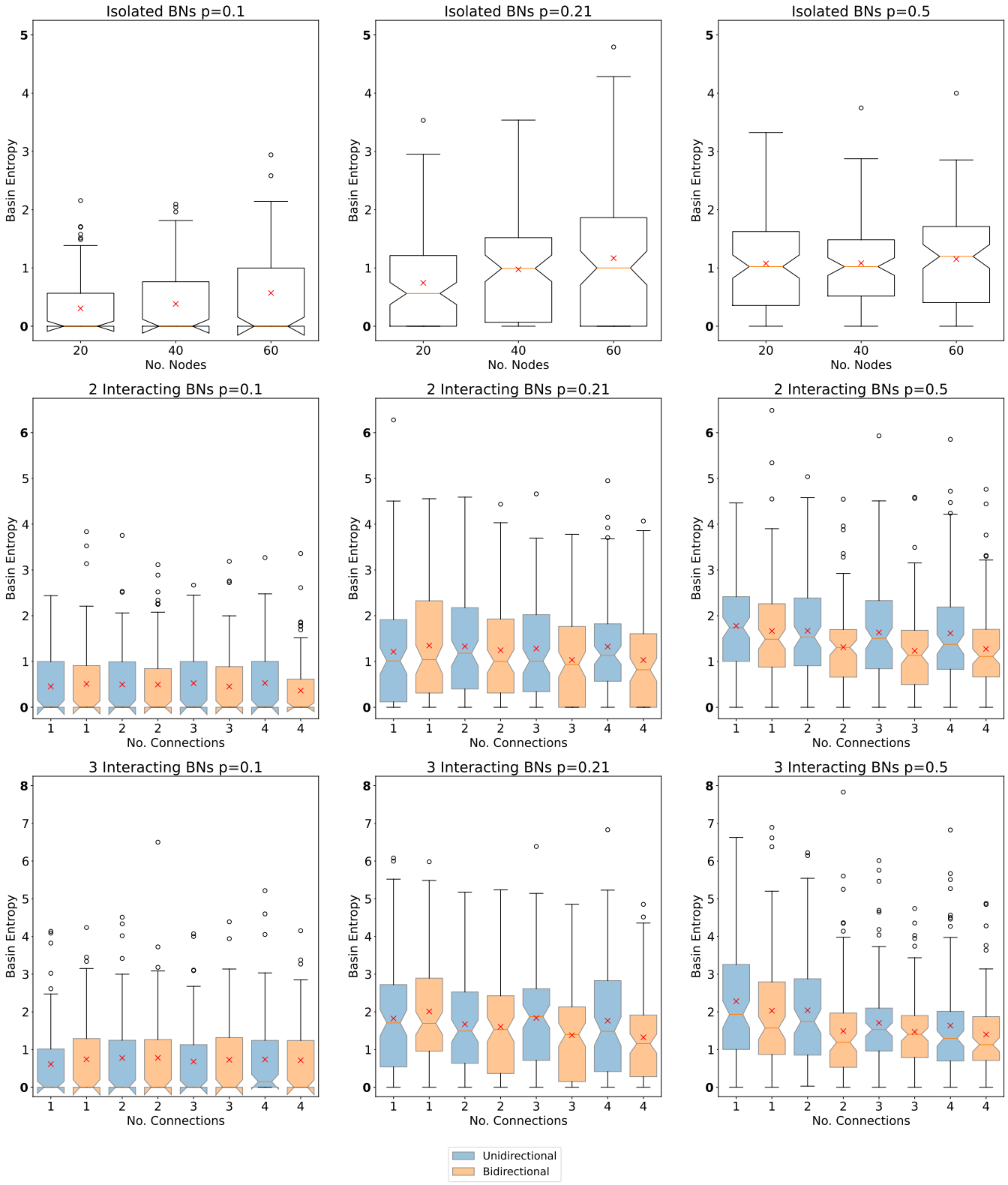

Figure 4: Basin entropy of isolated and interacting networks.

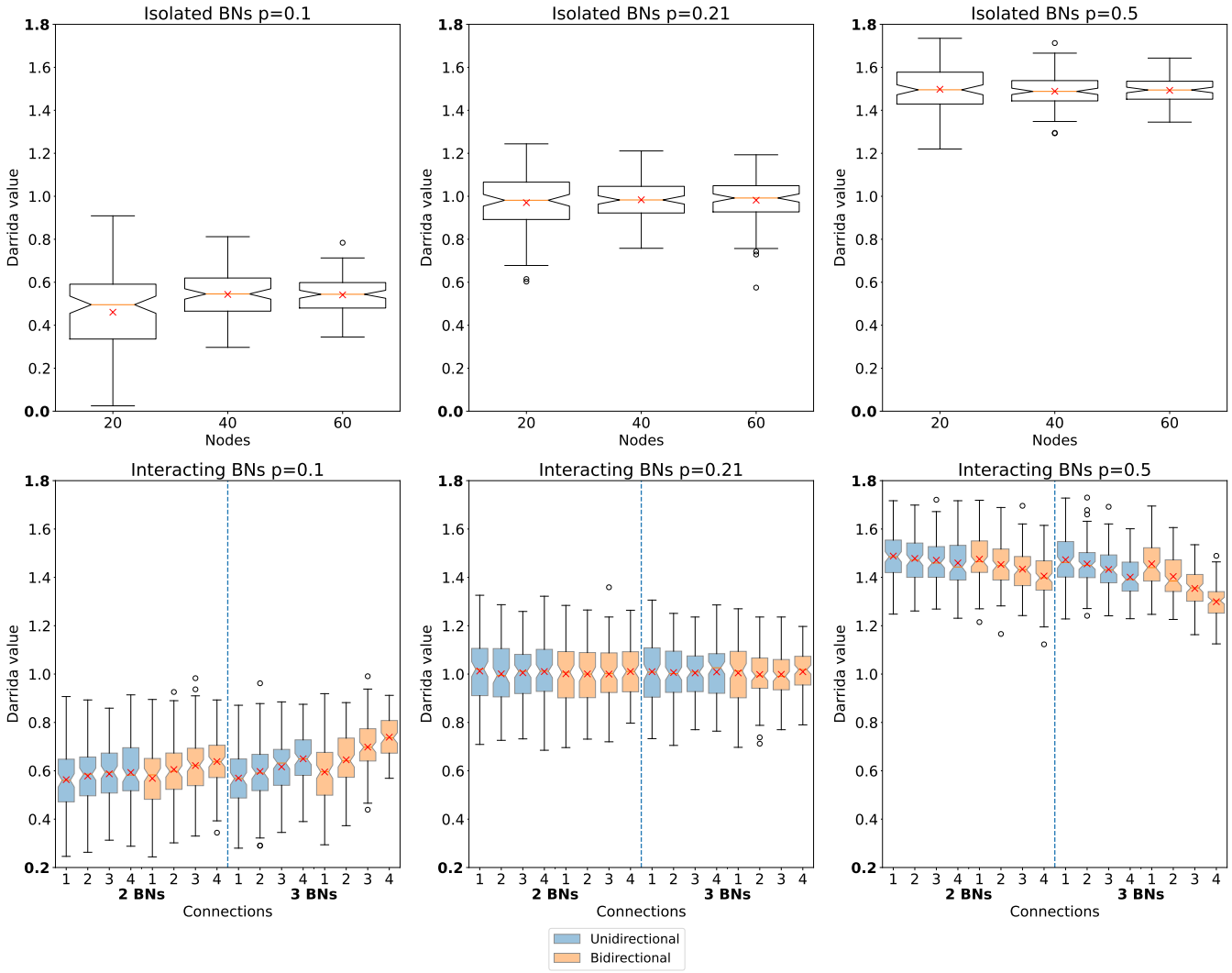

Figure 5: Derrida value of isolated and interacting networks.

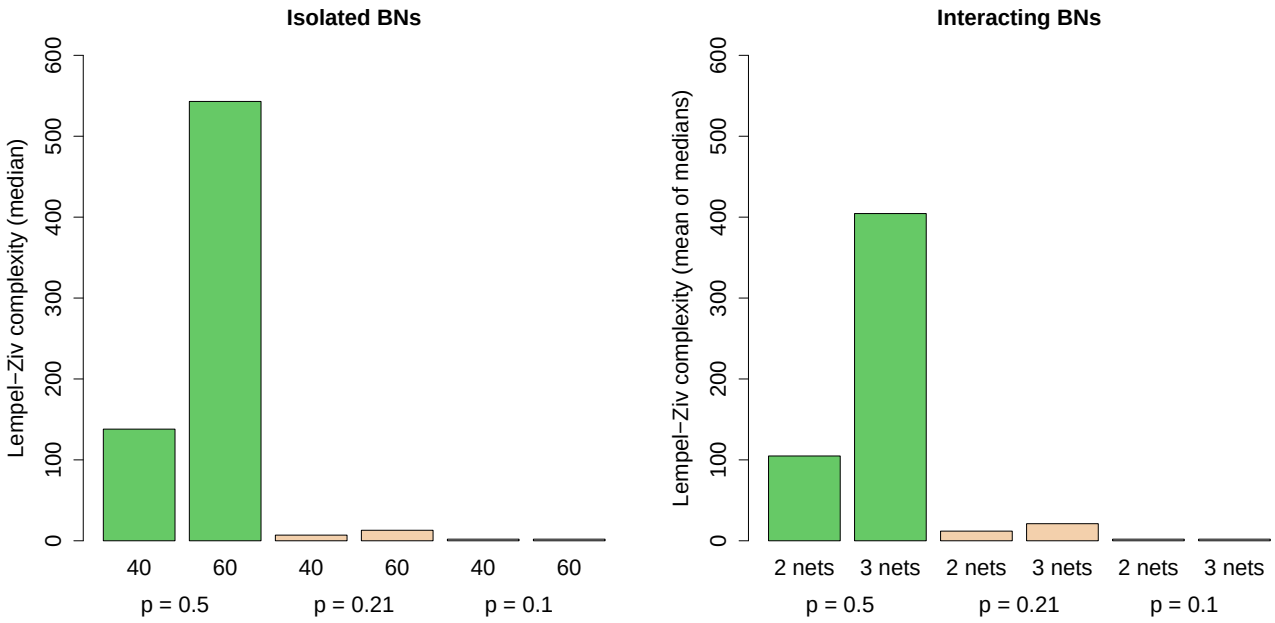

Figure 6: Lempel-Ziv complexity of attractors in isolated and interacting networks.

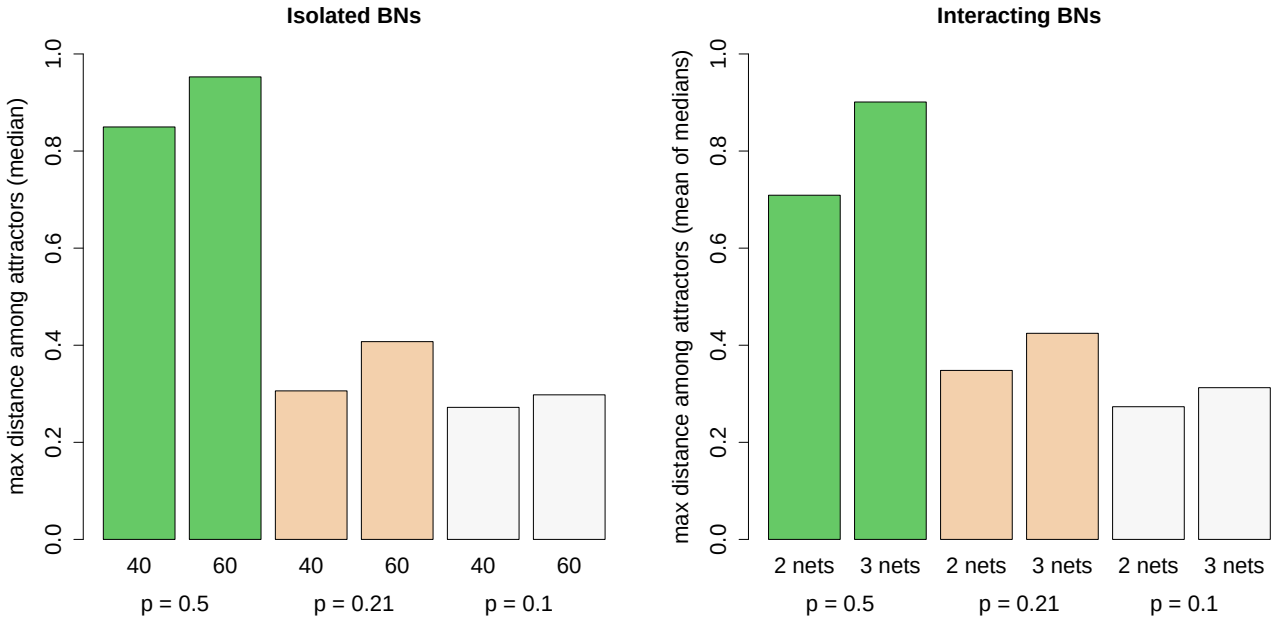

Figure 7: Maximal compression distance of attractors in isolated and interacting networks.

critical line of kauffman networks. *Journal of Theoretical Biology*, 187(1):117 – 133.

Braccini, M., Montagna, S., and Roli, A. (2019a). Self-loops favour diversification and asymmetric transitions between attractors in boolean network models. In Cagnoni, S., Mordonini, M., Pecori, R., Roli, A., and Villani, M., editors, *Artificial Life and Evolutionary Computation*, pages 30–41, Cham. Springer International Publishing.

Braccini, M., Roli, A., Villani, M., Montagna, S., and Serra, R. (2019b). A simplified model of chromatin dynamics drives differentiation process in boolean models of grn. In *Artificial Life Conference Proceedings*, volume ALIFE 2019: The 2019 Conference on Artificial Life, pages 211–217.

Braccini, M., Roli, A., Villani, M., and Serra, R. (2017). *Automatic Design of Boolean Networks for Cell Differentiation*, pages 91–102. Springer International Publishing, Cham.

Braccini, M., Roli, A., Villani, M., and Serra, R. (2021). Dynamical properties and path dependence in a gene-network model of cell differentiation. *Soft Computing*, 25(9):6775–6787.

Burrows, M. and Wheeler, D. (1994). A block sorting lossless data compression algorithm. Technical report, Digital Equipment Corporation, Palo Alto, CA, USA.

Cilibrasi, R. and Vitányi, P. (2005). Clustering by compression. *IEEE Transactions on Information theory*, 51(4):1523–1545.

Cooper, G. and Adams, K. (2022). *The cell: a molecular approach*. Oxford University Press.

Damiani, C., Graudenzi, A., and Villani, M. (2010a). How critical random boolean networks may be affected by the interaction with others. In *Artificial Life and Evolutionary Computation*, pages 259–269. World Scientific.

Damiani, C., Kauffman, S., Serra, R., Villani, M., and Colacci, A. (2010b). Information transfer among coupled random Boolean networks. In *Cellular Automata: 9th International Conference on Cellular Automata for Research and Industry, ACRI 2010, Ascoli Piceno, Italy, September 21-24, 2010. Proceedings 9*, pages 1–11. Springer.

Damiani, C., Serra, R., Villani, M., Kauffman, S., and Colacci, A. (2011). Cell–cell interaction and diversity of emergent behaviours. *IET systems biology*, 5(2):137–144.

Flann, N., Mohamadlou, H., and Podgorski, G. (2013). Kolmogorov complexity of epithelial pattern formation: The role of regulatory network configuration. *Biosystems*, 112(2):131–138.

Huang, S. (2012). The molecular and mathematical basis of waddington's epigenetic landscape: A framework for po st-darwinian biology? *Bioessays*, 34(2):149–157.

Huang, S., Eichler, G., Bar-Yam, Y., and Ingber, D. (2005). Cell fates as high-dimensional attractor states of a complex gene regulatory network. *Physical Review Letters*, 94:128701:1–4.

Huang, S., Ernberg, I., and Kauffman, S. (2009). Cancer attractors: a systems view of tumors from a gene network dynamics and developmental perspective. In *Seminars in cell & developmental biology*, volume 20, pages 869–876. Elsevier.

Huang, S. and Ingber, D. E. (2000). Shape-dependent control of cell growth, differentiation, and apoptosis: switching between attractors in cell regulatory networks. *Experimental cell research*, 261(1):91–103.

Huang, S. and Kauffman, S. (2013). How to escape the cancer attractor: rationale and limitations of multi-target drugs. In *Seminars in cancer biology*, volume 23, pages 270–278. Elsevier.

Kauffman, S. (1969). Metabolic stability and epigenesis in randomly constructed genetic nets. *J. Theor. Biol.*, 22:437–467.

Kauffman, S. (2004). A proposal for using the ensemble approach to understand genetic regulatory networks. *Journal of Theoretical Biology*, 230:581–590.

Kim, H. and Sayama, H. (2018). Robustness and evolvability of multilayer gene regulatory networks. In *Artificial Life Conference Proceedings*, volume ALIFE 2018: The 2018 Conference on Artificial Life of *Artificial Life Conference Proceedings*, pages 546–547.

Krawitz, P. and Shmulevich, I. (2007). Basin entropy in boolean network ensembles. *Phys. Rev. Lett.*, 98:158701–1:4.

Lempel, A. and Ziv, J. (1976). On the complexity of finite sequence. *IEEE Trans. on Info. Theory*, 22(1):75–81.

Montagna, S., Braccini, M., and Roli, A. (2021). The impact of self-loops on boolean networks attractor landscape and implications for cell differentiation modelling. *IEEE/ACM Transactions on Computational Biology and Bioinformatics*, 18(6):2702–2713.

Munshi, H. G. and Stack, M. S. (2006). Reciprocal interactions between adhesion receptor signaling and mmp regulation. *Cancer and Metastasis Reviews*, 25(1):45–56.

Nykter, M., Price, N., Aldana, M., Ramsey, S., Kauffman, S., Hood, L., Yli-Harja, O., and Shmulevich, I. (2008a). Gene expression dynamics in the macrophage exhibit criticality. *PNAS*, 105:1897–1900.

Poblanno-Balp, R. and Gershenson, C. (2011). Modular random boolean networks. *Artificial Life*, 17(4):331–351.

Rämö, P., Kesseli, J., and Yli-Harja, O. (2006). Perturbation avalanches and criticality in gene regulatory networks. *J. Theor. Biol.*, 242:164–170.

Reynolds, M. L. and Woolf, C. J. (1993). Reciprocal schwann cell-axon interactions. *Current Opinion in Neurobiology*, 3(5):683–693.

Roli, A., Villani, M., Filisetti, A., and Serra, R. (2018). Dynamical criticality: overview and open questions. *Journal of Systems Science and Complexity*, 31(3):647–663.

Serra, R., Villani, M., Graudenzi, A., and Kauffman, S. (2007). Why a simple model of genetic regulatory network describes the distribution of avalanches in gene expression data. *J. Theor. Biol.*, 246:449–460.

Serra, R. and Zanarini, G. (1990). *Complex systems and cognitive processes*. Springer.

Shmulevich, I., Kauffman, S., and Aldana, M. (2005). Eukaryotic cells are dynamically ordered or critical but not chaotic. *PNAS*, 102(38):13439–13444.

Teuscher, C. (2022). Revisiting the edge of chaos: Again? *Biosystems*, 218:104693:1–6.

Torres-Sosa, C., Huang, S., and Aldana, M. (2012). Criticality is an emergent property of genetic networks that exhibit evolvability. *PLOS Computational Biology*, 8:1–18.

Verdi, J. M., Groves, A. K., Fariñas, I., Jones, K., Marchionni, M. A., Reichardt, L. F., and Anderson, D. J. (1996). A reciprocal cell–cell interaction mediated by nt-3 and neuregulins controls the early survival and development of sympathetic neuroblasts. *Neuron*, 16(3):515–527.

Villani, M., Barbieri, A., and Serra, R. (2011). A dynamical model of genetic networks for cell differentiation. *PloS one*, 6(3):e17703.

Villani, M., La Rocca, L., Kauffman, S., and Serra, R. (2018). Dynamical criticality in gene regulatory networks. *Complexity*, 2018:1–14.