Criticality Distinguishes the Ensemble of Biological Regulatory Networks

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The hypothesis that many living systems should exhibit near-critical behavior is well motivated theoretically, and an increasing number of cases have been demonstrated empirically. However, a systematic analysis across biological networks, which would enable identification of the network properties that drive criticality, has not yet been realized. Here, we provide a first comprehensive survey of criticality across a diverse sample of biological networks, leveraging a publicly available database of 67 Boolean models of regulatory circuits. We find all 67 networks to be near critical. By comparing to ensembles of random networks with similar topological and logical properties, we show that criticality in biological networks is not predictable solely from macroscale properties such as mean degree $\langle K \rangle$ and mean bias in the logic functions $\langle p \rangle$, as previously emphasized in theories of random Boolean networks. Instead, the ensemble of real biological circuits is jointly constrained by the local causal structure and logic of each node. In this way, biological regulatory networks are more distinguished from random networks by their criticality than by other macroscale network properties such as degree distribution, edge density, or fraction of activating conditions.

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A key and oft-debated concept in the physics of life is the criticality of living matter [1–6]. Criticality, or tuning to a point of marginal stability, is hypothesized to drive both the robustness and evolvability of living processes [7,8]. Systems far from their critical point are expected to be less adaptive than critical systems, being either too stable to be responsive in the ordered phase or too unstable to maintain memory in the chaotic phase. Many examples of living systems are now known to be poised at the boundary between these two regimes, with proximity to criticality reported across a variety of biosystems with very different functions, such as neural firing, animal motion and social behavior, and gene regulation [2,9–14]. Yet, despite these many examples of critical behavior in biology, the true pervasiveness of criticality across living systems remains to be illuminated.

Regulatory networks were among the first proposed and are among the most widely discussed candidates for critical systems in biology [8]. Evidence that biological regulatory networks operate near criticality has been so far limited to a handful of experimental examples, but these are increasing in frequency. The effects of experimental perturbations of single genes in *Saccharomyces cerevisiae* [15,16], the dynamics of gene expression in the macrophage [17], and a handful of networks with experimentally derived network topology [18,19] have been shown to be consistent with being near criticality. These isolated experimental cases indeed suggest criticality plays an important role in at least some biological regulatory networks. However, it is currently unknown how widespread criticality is across diverse systems with different structure and function. Characterizing the ubiquity (or lack thereof) of criticality would enable the systematic identification of those properties that give rise to collectively critical states in regulatory networks. To accomplish this requires a survey of criticality across a diverse sample of biological regulatory networks, enabling isolating properties of the ensemble of biological networks that give rise to criticality. We provide the first such survey here, revealing that critical states in biological regulatory networks are ubiquitous and, surprisingly, the critical states observed in the biological ensemble differ from naïve theoretical predictions based on random network ensembles.

To study criticality across diverse regulatory systems, we use Boolean networks, as these are among the most widely used models of complex regulation in biology. Their ubiquity is due in part to their successful approximation of complex regulatory interactions of genes essential to cellular function [20–26]. Boolean network models have successfully predicted cellular behavior including the robustness of the cell cycle, cell differentiation processes, and cellular response to DNA damage [27–30]. With few fine-tuned parameters, Boolean models are simple to build and simulate, and yet they still capture many important

dynamical features of the real biological systems which they model [31]. This has led to a proliferation of Boolean network models of a wide range of real biological processes, and researchers can now capitalize on the availability of such models to identify and study the drivers of criticality in real biological systems.

For our study, 67 Boolean network models were obtained from the Cell Collective database [32]. The networks represent biological processes including virus and cell cycles, cell differentiation, cell plasticity, cell apoptosis, cell migration, and signaling pathways, among other gene regulatory functions. They encapsulate a wide range of biological processes across humans, animals, plants, bacteria, and viruses and range in size from five nodes to 321 nodes. Each of the network models originated in a specific cited study, with a list of citations provided in Supplemental Material [33]. Most of the models (63 of 67) were constructed including interactions gathered from previously published literature. Some include interactions inferred from published data (eight networks) or inferred from data taken explicitly for that model (nine networks). About one-third of the models (25 of 67) were constructed or validated using experimental data taken explicitly for the corresponding study. In total, the networks we study encompass more than 6500 biological interactions, which were originally identified in a diverse set of laboratories using a diverse set of methods, e.g., by investigating specific pairs of interacting proteins (e.g., [36]) or inferring interactions from time series data (e.g., [37]).

Before proceeding to present our results analyzing these networks, it is important to emphasize that observations of criticality in real systems have so far been primarily motivated by the theory of random Boolean networks (RBNs) (e.g., [38–40]). By constructing ensembles of RBNs with fixed mean in-degree $\langle K \rangle$ and mean activity bias $\langle p \rangle$, one can readily determine thresholds for criticality as a function of $\langle K \rangle$ and $\langle p \rangle$ for the ensemble. The results indicate that mean connectivity and mean bias of Boolean logic functions both play a role in determining criticality. However, while the ensemble of random networks in these theoretical studies subsumes those we expect to exhibit a biological function, the ensemble is not exclusive to living examples. As we will show, $\langle K \rangle$ and $\langle p \rangle$, as statistical characterizations of connectivity and logic, are not specific enough to explain the criticality observed across the ensemble of networks with biological function.

To infer criticality in the 67 biological networks in our data set, we use a measure of average sensitivity [41]. This measure of criticality is related to others such as Derrida curves [18] and perturbation avalanches [16], but it is advantageous for this study where we consider large ensembles of biological and random networks, because it can be calculated efficiently even for large networks when all node in-degrees are sufficiently small, as they are for most existing biological network models (and our controlled randomizations of them). The average sensitivity s was defined in Ref. [41] by starting with the Boolean derivative that measures the number of inputs for which flipping a bit at time step t changes the value of the output at time step $t+1$ and then averaging over nodes and over all possible input states $\vec{x}$. Defining the discrete dynamics as $\vec{x}(t+1) = \vec{f}[\vec{x}(t)]$,

$$s = \frac{1}{N}\sum_{i}^{N}\left\langle \sum_{j}^{N}\frac{\partial f_i(\vec{x})}{\partial x_j}\right\rangle_{\vec{x}}. \tag{1}$$

Here $\partial f_i(\vec{x})/\partial x_j$ represents the sensitivity of node i to changing node j when starting in state $\vec{x}$ [42]:

$$\frac{\partial f_i(\vec{x})}{\partial x_j} = f_i(x_1,\ldots,x_j,\ldots,x_N) \oplus f_i(x_1,\ldots,\bar{x}_j,\ldots,x_N), \tag{2}$$

with $\bar{x}_j$ representing the logical negation of x_j and $\oplus$ representing the exclusive-OR function. Defined in this way, the average sensitivity s is the expected number of nodes whose state is changed at the next time step given an intervention that flips the state of one node at the current time step. It is equivalent to the average Hamming distance between the perturbed and unperturbed state at time $t+1$ when a random bit is flipped at time t (see Supplemental Material [33]).

The average sensitivity was defined in Ref. [41] to be an indicator of the critical transition in RBNs from an ordered to a chaotic phase. In an infinite ergodic system, this transition happens at $s = 1$ [43,44]. In the ordered phase bit-flip interventions have effects that become smaller over time, while in the chaotic phase these changes grow in time and spread to affect most of the network [42]. The original results exploring this damage-spreading transition [42,45] make this connection analytically under two assumptions: (i) As in other spreading processes [9], this critical transition happens when the local measure of spreading (here, the average sensitivity) is equal to 1 only in the limit of $N \to \infty$, where finite-size effects of saturation are not important, and with the assumption of ergodicity [43]; (ii) the dynamics were assumed to be synchronous, with all nodes updated at each time step. We note that a large fraction of the models we test were not designed to be used with synchronous updating. Yet, even in the asynchronous case, we expect $s = 1$ to correspond to the damage-spreading critical transition as $N \to \infty$. In this limit and as $t \to \infty$, regardless of the specifics of how nodes are updated, we can treat the damage spreading as a simple branching process with a branching ratio equal to the average sensitivity s. Thus, we expect that networks run asynchronously will have similar bulk behavior to those run synchronously, with a critical transition at $s = 1$ in the infinite limit.

Using s as a measure of criticality, we find *all* 67 biological regulatory networks are critical or near critical. We show that the explanation of this ubiquitous nearness to criticality requires stricter conditions on the causal structure and logic of each node for the ensemble of biological regulatory networks than merely constraining average network properties such as $\langle K \rangle$ and $\langle p \rangle$ as predicted previously based on RBN theory. In particular, our results demonstrate that biological networks differ from the ensemble of critical RBNs with fixed $\langle K \rangle$ and $\langle p \rangle$ predicted from RBN theory in three important ways: The Boolean functions in each biological network typically (i) display covariance in K and p, in that functions with a larger in-degree tend to have a smaller $p(1-p)$, (ii) depend on most or all inputs (making connectivity coincide with causal structure), and (iii) are mostly canalizing, such that there is nearly always at least one input which, when set to a particular value, specifies the output independent of the values of the other inputs. Each of these constraints significantly affects the sensitivity, yet we nonetheless find that all biological networks we measure have sensitivity near one (Fig. 1). Our results indicate that the ensemble of biological regulatory networks is more distinguished by its criticality than other macroscale network properties such as the degree distribution, edge density, or fraction of activating conditions.

To determine the properties of regulatory networks most important for achieving their near-critical state, we compare the analysis of the sensitivity of the 67 biological networks to the same analysis performed on three different ensembles of random networks, each designed to successively isolate the properties of the real regulatory networks driving their average sensitivity. Each random ensemble is therefore constructed with reference to one of the 67 biological models [such that there are 67×3 random ensembles in our study [33]; see Fig. 1(b)].

In prior work, most ensembles of RBNs are defined such that the probability of a given node i to be activated by a given condition, the activity bias p_i, is equal for all nodes. The average sensitivity s_i can be calculated for each node separately (such that $s = \sum_i s_i/N$), and it is known that, when calculating the sensitivity for each Boolean function with K_i inputs and activity bias p_i, $\langle s_i \rangle = 2K_i p_i(1-p_i)$, where the average is taken over possible Boolean functions [41]. When naïvely assuming $p_i = p \ \forall \ i$, or, more generally, when K_i is not correlated with $p_i(1-p_i)$, the average sensitivity for the network is simple:

$$s_{\text{naïve}} = 2\langle K \rangle \langle p(1-p) \rangle, \tag{3}$$

where each average is taken over nodes i. But, as shown in Fig. 2(a), we find that most networks in our database display anticorrelation between K_i and $p_i(1-p_i)$, meaning that a more accurate estimate of the average sensitivity for real regulatory circuits would require knowledge of the magnitude of this covariance:

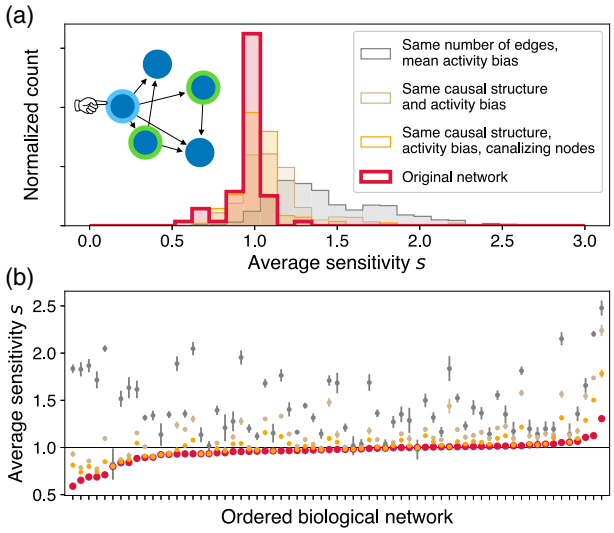

FIG. 1. Biological networks are close to critical sensitivity. (a) The 67 published Boolean network models of biological regulation (red) have sensitivity near the critical value of 1. The schematic depicts the sensitivity measure, equal to the average number of nodes whose states are changed at time step $t+1$ (green) when one node's state is changed at time step t (light blue). Also shown are sensitivities of random ensembles preserving various aspects of the original biological networks. Preserving only the number of edges and mean activity bias (gray) produces much more chaotic networks. Preserving the causal structure and activity bias of each node in the network (tan) produces sensitivity generally nearer to 1. Further restricting the random ensemble to have the same number of canalizing functions (yellow) even more closely approaches the criticality of the biological ensemble. This indicates that, beyond average connectivity, the specific structure and types of Boolean functions are important for predicting criticality in the biological ensemble. (b) Naïve random Boolean network theory does not correctly predict the average sensitivity for the majority of biological networks. Plotting individually the average sensitivities for each biological network and its randomized ensembles reveals most networks in the biological ensemble have a sensitivity significantly different from that predicted by the random ensembles. The mean and standard deviation for each ensemble are shown for 100 samples from each ensemble.

$$s_{\text{random}} = 2\langle K \rangle \langle p(1-p) \rangle + 2C, \tag{4}$$

where C is the covariance over nodes between K_i and $p_i(1-p_i)$. Random networks that conserve $\langle K \rangle$ and $\langle p \rangle$ but do not conserve this covariance (Fig. 1) should therefore be expected to have very different s than the biological networks, as we indeed observe.

We can conclude that random networks conserving the global structure and logic of biological networks (e.g., same $\langle p \rangle$ and $\langle K \rangle$) do not reproduce the criticality of real regulatory networks. We therefore next constructed random network ensembles that control for the local (nodewise) causal and logical properties of biological networks, not just their global ones. Specifically, we note that network

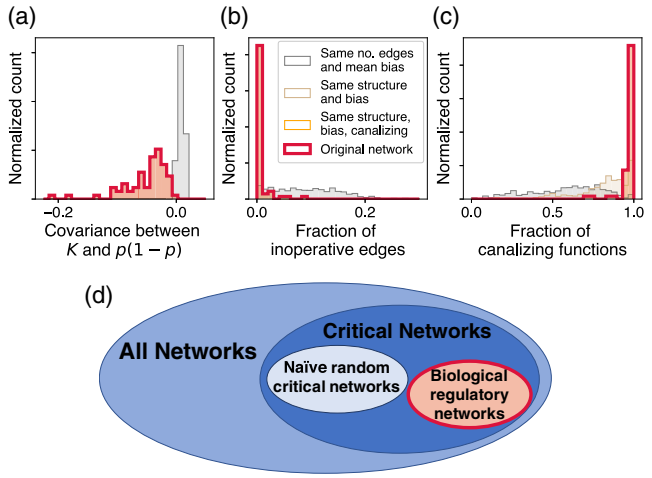

FIG. 2. Boolean models of biological networks are atypical in theoretical random ensembles. (a) The activity bias p and in-degree K covary in observed networks, such that the simple expected sensitivity in constant p, constant K networks [Eq. (3)] is not valid. (b) Inoperative edges, which never affect the output state, are much more rare in biological networks than in randomized ensembles. (c) Compared to uniform sampling over Boolean functions, a much larger fraction of functions in biological networks are canalizing. (d) These differences imply that biological networks form an ensemble distinct from naïve RBNs with independent K and p selected for criticality.

structure encapsulates the causal interactions of each node defined by its number of inputs and outputs. To test the role of this structure in driving criticality, we constructed a random ensemble of Boolean networks that conserves the local causal structure of each node, changing only the specific Boolean functions implemented by each node. That is, we constructed random networks keeping the same causal inputs and outputs and the same activity bias p_i for each node, but with randomized Boolean logic functions (labeled as "same causal structure and activity bias"). This ensemble explicitly retains the covariance between K and $p(1-p)$. It also retains the fact that most connected inputs in biological models are "operative" in the sense that there is at least one state for which the output value of the node depends on each input; this is not necessarily true in traditional RBNs [Fig. 2(b)]. We find that even this very restricted ensemble (tan color in Fig. 1) is often distinctly more chaotic than the original biological networks. This is due to a third way the random ensembles are distinct from biology: We find that biological regulatory networks have an overabundance of canalizing Boolean functions, meaning that these functions have at least one input that can be fixed to a value that forces the output to a specific value regardless of the other inputs. We find that the biological networks indeed overwhelmingly consist of canalizing functions [Fig. 2(c)], as previously hypothesized [46,47]. As has been argued before [46–50], canalizing functions tend to have smaller sensitivity: Random ensembles not taking this into account will appear more chaotic than those that sample from canalizing functions. We test the role of canalizing functions in driving criticality by constructing a third ensemble of random networks, which control for causal structure, activity bias, and canalizing nodes (yellow color in Fig. 1). Of the random ensembles tested, this ensemble most closely matches the criticality observed for the biological networks of the ensembles tested.

In summary, we find that knowing only the mean properties (mean in-degree $\langle K \rangle$ and activity bias $\langle p \rangle$) is not enough to predict criticality in the ensemble of biological regulatory networks. Nor is knowing the exact network structure. We must additionally include Boolean functions that tend to both be canalizing and depend on most inputs in order to model networks with the same critical sensitivity as biological networks. We can conclude that the ensemble of biological regulatory networks differs from what naïve RBN theory would predict [Fig. 2(d)].

Isolating the properties that uniquely distinguish the ensemble of biological networks is a necessary step toward statistical approaches to characterizing living matter and therefore toward developing a bona fide physics of life. Our results indicate that an average sensitivity close to critical is sufficient to distinguish biological regulatory networks from random networks with similar global topological structure and logic. This suggests that the most distinguishing features of biological networks are not their macroscale connectivity patterns, such as degree distribution or edge density, or even the average bias of their logic operations. Instead, criticality in biological regulatory networks is better explained by the relationship between local causal and logical structure, quantified in terms of the covariance of K and $p(1-p)$, with a much higher frequency of canalizing functions in their implemented logic than naïve models would predict. While critical sensitivity is a collective property of the interactions of many components, we find that its explanation in regulatory networks relies on constraining the properties of individual nodes. This suggests that evolution optimizes the macroscale behavior of regulatory networks, as quantified by their criticality, by jointly tuning the microscale causal structure and logic of individual components.

Constraining the relationship between K and $p(1-p)$ for critical biological networks has implications for experimental investigations of regulatory networks. For example, characterizing this relationship provides new, testable criteria for assessing criticality of regulatory networks in the lab and can inform better constrained evolutionary models. Our results also confirm that neither network structure nor logic alone can predict the behavior of biological networks: Knowing both is necessary to characterize their behavior. In addition, our results provide new criteria for the design of robust, adaptive regulatory circuits, e.g., in the design of synthetic cells [51]. In order for a genetic circuit to be critical, our results indicate that genes regulated by many others must remain largely

insensitive to many of their inputs. In this sense, criticality in regulatory networks, which captures something of their collective properties, can be considered as an emergent property of their logical *and* causal structure together. This has implications for our understanding of the physics of living processes, where the connection between information processing (aggregate logic) and causation (aggregate connectivity) has yet to be fully explicated [52–54].

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[1] C. Adami, Self-organized criticality in living systems, Phys. Lett. A **203**, 29 (1995).
[2] M. A. Muñoz, Colloquium: Criticality and dynamical scaling in living systems, Rev. Mod. Phys. **90**, 031001 (2018).
[3] D. Krotov, J. O. Dubuis, T. Gregor, and W. Bialek, Morphogenesis at criticality, Proc. Natl. Acad. Sci. U.S.A. **111**, 3683 (2014).
[4] J. Hidalgo, J. Grilli, S. Suweis, M. A. Muñoz, J. R. Banavar, and A. Maritan, Information-based fitness and the emergence of criticality in living systems, Proc. Natl. Acad. Sci. U.S.A. **111**, 10095 (2014).
[5] A. Roli, M. Villani, A. Filisetti, and R. Serra, Dynamical criticality: Overview and open questions, J. Syst. Sci. Complex. **31**, 647 (2018).
[6] P. Bak, *How Nature Works: The Science of Self-Organized Criticality* (Springer, New York, 2013).
[7] C. G. Langton, Computation at the edge of chaos: Phase transitions and emergent computation, Physica (Amsterdam) D **42**, 12 (1990).
[8] S. A. Kauffman, *The Origins of Order: Self-Organization and Selection in Evolution* (Oxford University, New York, 1993).
[9] B. C. Daniels, D. C. Krakauer, and J. C. Flack, Control of finite critical behaviour in a small-scale social system, Nat. Commun. **8**, 14301 (2017).
[10] J. M. Beggs, The criticality hypothesis: How local cortical networks might optimize information processing, Phil. Trans. R. Soc. A **366**, 329 (2008).
[11] C. Haldeman and J. Beggs, Critical Branching Captures Activity in Living Neural Networks and Maximizes the Number of Metastable States, Phys. Rev. Lett. **94**, 058101 (2005).
[12] T. Mora and W. Bialek, Are biological systems poised at criticality?, J. Stat. Phys. **144**, 268 (2011).
[13] R. V. Solé, S. C. Manrubia, M. Benton, S. Kauffman, and P. Bak, Criticality and scaling in evolutionary ecology, Trends Ecol. Evolution **14**, 156 (1999).
[14] W. Bialek, A. Cavagna, I. Giardina, T. Mora, O. Pohl, E. Silvestri, M. Viale, and A. M. Walczak, Social interactions dominate speed control in poising natural flocks near criticality, Proc. Natl. Acad. Sci. U.S.A. **111**, 7212 (2014).
[15] R. Serra, M. Villani, and A. Semeria, Genetic network models and statistical properties of gene expression data in knock-out experiments, J. Theor. Biol. **227**, 149 (2004).
[16] R. Serra, M. Villani, A. Graudenzi, and S. A. Kauffman, Why a simple model of genetic regulatory networks describes the distribution of avalanches in gene expression data, J. Theor. Biol. **246**, 449 (2007).
[17] M. Nykter, N. D. Price, M. Aldana, S. A. Ramsey, S. A. Kauffman, L. E. Hood, O. Yli-Harja, and I. Shmulevich, Gene expression dynamics in the macrophage exhibit criticality, Proc. Natl. Acad. Sci. U.S.A. **105**, 1897 (2008).
[18] E. Balleza, E. R. Alvarez-Buylla, A. Chaos, S. Kauffman, I. Shmulevich, and M. Aldana, Critical dynamics in genetic regulatory networks: Examples from four kingdoms, PLoS One **3**, e2456 (2008).
[19] S. Chowdhury, J. Lloyd-Price, O.-P. Smolander, W. C. V. Baici, T. R. Hughes, O. Yli-Harja, G. Chua, and A. S. Ribeiro, Information propagation within the genetic network of Saccharomyces cerevisiae, BMC Syst. Biol. **4**, 143 (2010).
[20] G. Karlebach and R. Shamir, Modelling and analysis of gene regulatory networks, Nat. Rev. Mol. Cell Biol. **9**, 770 (2008).
[21] R.-S. Wang, A. Saadatpour, and R. Albert, Boolean modeling in systems biology: An overview of methodology and applications, Phys. Biol. **9**, 055001 (2012).
[22] I. Albert, J. Thakar, S. Li, R. Zhang, and R. Albert, Boolean network simulations for life scientists, Source Code Biol. Med. **3**, 16 (2008).
[23] T. Helikar, B. Kowal, S. McClenathan, M. Bruckner, T. Rowley, A. Madrahimov, B. Wicks, M. Shrestha, K. Limbu, and J. A. Rogers, The cell collective: Toward an open and collaborative approach to systems biology, BMC Syst. Biol. **6**, 96 (2012).
[24] T. Helikar, B. Kowal, and J. A. Rogers, A cell simulator platform: The cell collective, Clinical pharmacology and therapeutics **93**, 393 (2013).
[25] T. Helikar and J. A. Rogers, Chemchains: A platform for simulation and analysis of biochemical networks aimed to laboratory scientists, BMC Syst. Biol. **3**, 58 (2009).
[26] S. Bornholdt, Boolean network models of cellular regulation: Prospects and limitations, J. R. Soc. Interface **5**, S85 (2008).
[27] F. Li, T. Long, Y. Lu, Q. Ouyang, and C. Tang, The yeast cell-cycle network is robustly designed, Proc. Natl. Acad. Sci. U.S.A. **101**, 4781 (2004).
[28] M. I. Davidich and S. Bornholdt, Boolean network model predicts cell cycle sequence of fission yeast, PLoS One **3**, e1672 (2008).
[29] S. Huang, G. Eichler, Y. Bar-Yam, and D. E. Ingber, Cell Fates as High-Dimensional Attractor States of a Complex Gene Regulatory Network, Phys. Rev. Lett. **94**, 128701 (2005).
[30] M. Choi, J. Shi, S. H. Jung, X. Chen, and K.-H. Cho, Attractor landscape analysis reveals feedback loops in the p53 network that control the cellular response to dna damage, Sci. Signal. (Online) **5**, ra83 (2012).
[31] M. Davidich and S. Bornholdt, The transition from differential equations to boolean networks: A case study in simplifying a regulatory network model, J. Theor. Biol. **255**, 269 (2008).

[32] The cell collective, https://cellcollective.org.
[33] See Supplemental Material at http://link.aps.org/supplemental/10.1103/PhysRevLett.121.138102 for more information about computational methods, including the handling of external nodes, inoperative edges, and inoperative nodes; details about the 67 original biological networks; and the relationship between sensitivity and in-degree. Supplemental Material also includes Refs. [34,35].
[34] C. E. Giacomantonio and G. J. Goodhill, A Boolean model of the gene regulatory network underlying mammalian cortical area development, PLoS Comput. Biol. **6**, e1000936 (2010).
[35] Neet: Analysis of dynamical network models, https://github.com/elife-asu/neet.
[36] A.-M. O'Farrell, D. A. Parry, F. Zindy, M. F. Roussel, E. Lees, K. W. Moore, and A. L. -F. Mui, Stat3-dependent induction of p19INK4D by IL-10 contributes to inhibition of macrophage proliferation, J. Immunol. **164**, 4607 (2000).
[37] E. Sontag, A. Kiyatkin, and B. N. Kholodenko, Inferring dynamic architecture of cellular networks using time series of gene expression, protein and metabolite data, Bioinformatics **20**, 1877 (2004).
[38] A. A. Moreira and L. A. N. Amaral, Canalizing Kauffman Networks: Nonergodicity and Its Effect on Their Critical Behavior, Phys. Rev. Lett. **94**, 218702 (2005).
[39] P. Rämö, J. Kesseli, and O. Yli-Harja, Perturbation avalanches and criticality in gene regulatory networks, J. Theor. Biol. **242**, 164 (2006).
[40] A. Goudarzi, C. Teuscher, N. Gulbahce, and T. Rohlf, Emergent Criticality through Adaptive Information Processing in Boolean Networks, Phys. Rev. Lett. **108**, 128702 (2012).
[41] I. Shmulevich and S. A. Kauffman, Activities and Sensitivities in Boolean Network Models, Phys. Rev. Lett. **93**, 048701 (2004).
[42] B. Luque and R. V. Solé, Lyapunov exponents in random Boolean networks, Physica (Amsterdam) A **284**, 33 (2000).
[43] M. Villani, D. Campioli, C. Damiani, A. Roli, A. Filisetti, and R. Serra, Dynamical regimes in non-ergodic random Boolean networks, Nat. Comput. **16**, 353 (2017).
[44] Finite size effects cause $s = 1$ to correspond to a slightly subcritical regime.
[45] B. Derrida and Y. Pomeau, Random networks of automata: A simple annealed approximation, Europhys. Lett. **1**, 45 (1986).
[46] S. E. Harris, B. K. Sawhill, A. Wuensche, and S. Kauffman, A model of transcriptional regulatory networks based on biases in the observed regulation rules, Complexity **7**, 23 (2002).
[47] S. Kauffman, C. Peterson, B. Samuelsson, and C. Troein, Genetic networks with canalyzing Boolean rules are always stable, Proc. Natl. Acad. Sci. U.S.A. **101**, 17102 (2004).
[48] S. Kauffman, C. Peterson, B. Samuelsson, and C. Troein, Random Boolean network models and the yeast transcriptional network, Proc. Natl. Acad. Sci. U.S.A. **100**, 14796 (2003).
[49] P. Rämö, J. Kesseli, and O. Yli-Harja, Stability of functions in Boolean models of gene regulatory networks, Chaos **15**, 034101 (2005).
[50] R. B. Correia, A. J. Gates, X. Wang, and L. M. Rocha, CANA: A python package for quantifying control and canalization in boolean networks, Front. Physiol. **9**, 1046 (2018).
[51] K. P. Adamala, D. A. Martin-Alarcon, K. R. Guthrie-Honea, and E. S. Boyden, Engineering genetic circuit interactions within and between synthetic minimal cells, Nat. Chem. **9**, 431 (2017).
[52] H. Kim, P. Davies, and S. I. Walker, New scaling relation for information transfer in biological networks, J. R. Soc. Interface **12**, 20150944 (2015).
[53] S. I. Walker, H. Kim, and P. C. W. Davies, The informational architecture of the cell, Phil. Trans. R. Soc. A **374**, 20150057 (2016).
[54] P. C. W. Davies and S. I. Walker, The hidden simplicity of biology, Rep. Prog. Phys. **79**, 102601 (2016).