Editors' Suggestion

Proof for Minimum Sensitivity of Nested Canalizing Functions, a Fractal Bound, and Implications for Biology

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We prove that nested canalizing functions are the minimum-sensitivity Boolean functions for any activity ratio and we determine the functional form of this boundary which has a nontrivial fractal structure. We further observe that the majority of the gene regulatory functions found in known biological networks (submitted to the Cell Collective database) lie on the line of minimum sensitivity which paradoxically remains largely in the unstable regime. Our results provide a quantitative basis for the argument that an evolutionary preference for nested canalizing functions in gene regulation (e.g., for higher robustness) and for plasticity of gene activity are sufficient for concentration of such systems near the "edge of chaos."

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Canalization in biological systems refers to the capacity of a dynamical process to reach a definite fate or a product, despite inherent or external fluctuations. Waddington [1] and Schmalhausen [2] recognized the significance of canalization in biological development and evolution early on, suggesting it as a mechanism that promotes coordinated response to environmental and genetic perturbations and suppresses genetic variation. Biological signatures and implications of canalization are still active research areas [3–8]. The concept entered the radar of the biophysics community due to seminal works by Kauffman *et al.* [9–12] on gene regulation networks (GRNs), which observed that canalization is particularly suited to describe the transcriptional states of genes subject to multiple regulatory inputs.

A common simplification of regulatory dynamics widely adopted in the literature is to consider genes to be either on or off. Despite its simplicity, a binary representation is sufficient to capture many essential features of the complex gene expression dynamics [13,14]. In this framework, a GRN reduces to a Boolean network where the vertices represent genes, directed edges encode regulatory interactions, and the state of a gene is updated at each time step by a gene-specific Boolean function. The average transcriptional activity of a gene is largely determined by the "activity ratio" of its update function which is the fraction of input combinations that turn the gene "on."

Canalization, in this narrowed down context, is defined as the presence of a subset of genes which are privileged in dictating the output when in a particular "canalizing" state. Abundance of canalization in real-life GRNs is well established [7,10] and rationalized both in physical terms, through the mechanisms of interaction between transcription factors and the DNA [15], and in biological terms, by the advantage it lends the organism through stabilization of the regulatory dynamics against random fluctuations [16]. In fact, a Boolean network utilizing random vertex update functions with k inputs on average and a mean activity ratio p is typically unstable (i.e., sensitive to random fluctuations of gene expression levels) for

$$k^{-1} < 2p(1-p), \tag{1}$$

while a network utilizing canalizing rules is not [11,15,17,18].

This Letter reports observations on a specific subclass of Boolean functions called "nested canalizing functions" (NCFs), or "unate cascade functions" [19], for which *all* of the inputs manifest the canalizing property in an order of hierarchy (see Fig. 1). In particular, we prove that NCFs realize the minimum possible sensitivity (or maximum robustness) across all Boolean functions subject to a given activity ratio. Despite numerous studies attesting to the improved robustness of Boolean network dynamics under the canalization rule [12,15,20–23], this central mathematical fact appears to have been overlooked so far. We also derive a mathematical expression for the sensitivity lower bound which we find to be a fractal function of the activity ratio, and finally demonstrate the relevance of our results to biological systems by measuring the sensitivity of more

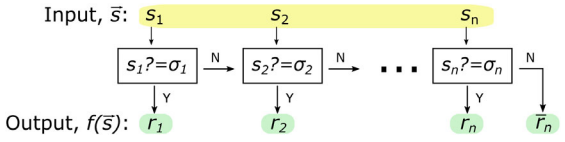

FIG. 1. Schematic representation of the decision algorithm for the output of a nested canalizing function $f(\vec{s})$ as a function of the defining parameters $\{\sigma_i\}$ and $\{r_i\}$, where $s_i, \sigma_i, r_i \in \{0,1\}$. The input vector is shaded yellow and the possible outputs are shaded green.

than 2000 known regulatory functions and their distance from the obtained bound.

We start with some preliminaries: (1) A *NCF* $f(\vec{s})$ of n variables $\vec{s} = (s_1, \ldots, s_n)$ is a Boolean function which is canalizing in all of its inputs, as shown in Fig. 1. A NCF is defined in terms of a set of canalizing (input) values $\{\sigma_i\}$ and canalized (output) values $\{r_i\}$ as

$$f(s_1, s_2, \ldots, s_n) \equiv \begin{cases} r_1, & \text{if } s_1 = \sigma_1 \\ r_2, & \text{if } s_2 = \sigma_2, s_1 = \bar{\sigma}_1 \\ \vdots & \\ r_n, & \text{if } s_n = \sigma_n \text{ and } s_i = \bar{\sigma}_i \; \forall \, i \in \{1, \ldots, n-1\} \\ \bar{r}_n, & \text{otherwise} \end{cases}, \tag{2}$$

where $s_i, \sigma_i, r_i \in \{0, 1\}$. The last condition in Eq. (2) (with the notation $\bar{r}_n \equiv 1 - r_n$) ensures that all input variables are relevant, that is, for all j there exists at least one input $\vec{s}$ such that $s_j \to \bar{s}_j$ changes the output. Relaxing the last condition yields "generalized NCFs" which may have input variables inconsequential to the output. (2) The *activity*, α, of a Boolean function is the Hamming weight (the number of "1" s) of the output column in the truth table. It follows that the activity of a NCF as in Eq. (2) can be expressed in base two as

$$\alpha_{\mathrm{NCF}} = (r_1 r_2 .. r_{n-1} 1)_2. \tag{3}$$

Since the ith condition in Eq. (2) dictates a truth value for 2^{n-i} inputs. The activity ratio is accordingly given by $p = \alpha/2^n$. (3) The *sensitivity*, $\xi_i[f]$, of a Boolean function to its ith input is defined as the fraction of states for which $s_i \to \bar{s}_i$ flips the output. The overall sensitivity $\xi[f]$ is then their sum $\sum_i \xi_i[f]$, or

$$\xi[f] = 2^{-n} \sum_{i=1}^{n} \sum_{\{s_j\}} f(.., s_i, ..) \oplus f(.., \bar{s}_i, ..), \tag{4}$$

with $\oplus$ representing the "xor" operation. Since an average over all inputs is evaluated by the inner summation in Eq. (4), $\xi[f]$ for a NCF is independent of the choice of canalizing inputs $\{\sigma_i\}$. Furthermore, we show below that it is uniquely determined by the activity ratio. A tight upper bound of $4/3$ was derived earlier for the sensitivity of NCFs [24], while for a random Boolean function with n inputs one can calculate the average sensitivity to be $\xi = n/2$ [25]. The stability—in the Lyapunov sense—of the discrete-time dynamics on a Boolean network can be approximated by the average of vertex sensitivities given in Eq. (4) [26,27]. The boundary separating stable and chaotic regimes is at $\xi = 1$.

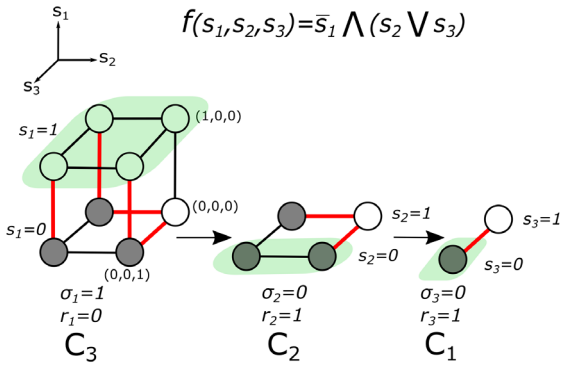

FIG. 2. The hypercube representation and the boundary edges (red) for a NCF with $\{r_1, r_2, r_3\} = \{0, 1, 1\}$. The hyperfaces which correspond to the canalization condition $s_i = \sigma_i$ at each decision step of Fig. 1 are shaded green. The presented proof by induction rests on the observation that the hyperface $s_1 = \bar{\sigma}_1$ itself encodes a NCF whose sensitivity can be related to that of f (and iteration of this observation to lower dimensions).

In order to prove that the NCFs are the minimum-sensitivity Boolean functions for given (n, α), we employ a geometric approach: A Boolean function with n inputs can be mapped to an n-dimensional hypercube graph, $\mathcal{C}_n$, where each vertex (corner) of the hypercube represents one of 2^n possible inputs and the vertex color encodes the corresponding output (white for "0" and dark gray for 1 in Fig. 2). In this picture, the sensitivity of a Boolean function f, given in Eq. (4), becomes $\xi[f] = b[f]/2^{n-1}$, where $b[f]$ counts the edges which have different terminal colors, henceforth called "boundary edges" (shown in red in Fig. 2).

A lower bound on the sensitivity ξ is provided by spectral graph theory, by means of a well-known inequality about the number of edges connecting two disjoint subsets of vertices in a graph [28]. For a Boolean function which splits the vertices of a hypercube graph into two such sets according to their color, the inequality translates to $\xi[f] \geq 2\lambda p(1-p)$, where p is the activity ratio of the function f and $\lambda = 2$ is the smallest nonzero eigenvalue of the graph Laplacian for $\mathcal{C}_n$ (see Sec. S1 in the Supplemental Material [29] for further details). The similarity between this bound and Eq. (1) is not coincidental. The role of λ on the stability of network dynamics is well documented and has multiple applications (see, e.g., Refs. [30,31] and references therein).

We now outline a proof by induction for the fact that the sensitivity minimum is realized by NCFs. To this end, let $\mathcal{B}_{n,\alpha}$ be the set of all Boolean functions with n inputs and activity α, and let $\beta(n, \alpha)$ be the number of boundary edges of the NCF in $\mathcal{B}_{n,\alpha}$. Our objective is to prove that

$$\beta(n, \alpha) = \min_{f \in \mathcal{B}_{n,\alpha}} b[f], \quad \forall \; n, \alpha. \tag{5}$$

We first seed the induction with $n = 2$. NCFs with $\alpha = 1$, 2, and 3 (for example, $s_1 \wedge s_2$, s_1, and $s_1 \vee s_2$,

respectively) have exactly two boundary edges. And we observe that

$$\beta(2,\alpha) = 2 = \min_{f\in\mathcal{B}_{2,h}} b[f], \quad \text{for } \alpha = 1,2,3 \tag{6}$$

since any nonuniform coloring of $\mathcal{C}_2$ (square graph) will yield at least two boundary edges. $\alpha = 0, 4$ correspond to constant functions (which, too, are NCFs in the generalized sense) and trivially realize the minimum, since $b(2,0) = b(2,4) = 0$.

Now, assume that Eq. (5) is true for functions with $2, 3, \ldots, n-1$ variables (the induction hypothesis) and prove it for n. Consider the following search algorithm for $\min_{f\in\mathcal{B}_{n,\alpha}} b[f]$: We distribute α black corners of $\mathcal{C}_n$ to two opposite $\mathcal{C}_{n-1}$ hyperfaces by α_1 and $\alpha-\alpha_1$, thus defining two functions $f_1 \in \mathcal{B}_{n-1,\alpha_1}$ and $f_2 \in \mathcal{B}_{n-1,\alpha-\alpha_1}$. The number of boundary edges *connecting* the two hyperfaces is at least $|\alpha - 2\alpha_1|$, while the remaining ones *on* the hyperfaces add up to $b[f_1] + b[f_2]$, by definition. Then, it suffices to show that no such assignment will yield a total number of boundary edges smaller than that of a NCF, i.e.,

$$\begin{aligned}&\beta(n,\alpha) \le b[f_1] + b[f_2] + |\alpha - 2\alpha_1| \\ &\forall\, f_1 \in \mathcal{B}_{n-1,\alpha_1} \quad \text{and} \quad \forall\, f_2 \in \mathcal{B}_{n-1,\alpha-\alpha_1}\end{aligned} \tag{7}$$

subject to $\alpha \le 2^n$, $\alpha_1 \le 2^{n-1}$, and $\alpha - \alpha_1 \le 2^{n-1}$. By the induction hypothesis, a sufficient condition for Eq. (7) is

$$\beta(n,\alpha) \le \beta(n-1,\alpha_1) + \beta(n-1,\alpha-\alpha_1) + |\alpha - 2\alpha_1|, \tag{8}$$

which we prove below.

Without loss of generality, we assume $\alpha \le 2^{n-1}$ (more white corners than black), since $f \to \bar{f}$ (inverting colors) preserves both the sensitivity and the NCF designation. As a corollary,

$$\beta(n,\alpha) = \beta(n, 2^n - \alpha). \tag{9}$$

Also, since all α black corners of the NCF lie on the hyperface $s_1 = \bar{\sigma}_1$ (see Fig. 2), the boundary edges between it and the opposite (all white, $s_1 = \sigma_1$) face is α. This yields the recursion relation

$$\beta(n,\alpha) = \beta(n-1,\alpha) + \alpha. \tag{10}$$

The proof of Eq. (8) rests on using Eqs. (9) and (10) in conjunction with the induction hypothesis. We consider two disjoint intervals of the activity α separately: (i). *Case I:* $\alpha \le 2^{n-2}$.—Employing the method of induction, we assume Eq. (8) is satisfied for $n \to n-1$:

$$\beta(n-1,\alpha) \le \beta(n-2,\alpha_1) + \beta(n-2,\alpha-\alpha_1) + |\alpha - 2\alpha_1|.$$

Note that both α_1 and $\alpha - \alpha_1$ above are within the allowed range ($\le 2^{n-2}$). Substituting Eq. (10) in the form $\beta(n-1,\alpha) = \beta(n,\alpha) - \alpha$ above, first arguments of the three $\beta(\cdot)$ terms can be promoted by one to reach the sought relation in inequality (8). (ii). *Case II:* $2^{n-2} < \alpha \le 2^{n-1}$.—The argument used in Case I still applies when

$$\alpha - 2^{n-2} \le \alpha_1 \le 2^{n-2}. \tag{11}$$

For the remaining values of α_1 on either side of the interval in Eq. (11), we make use of an auxiliary relation which follows from Eqs. (9) and (10):

$$\beta(n-1,\alpha-2^{n-2}) = \beta(n,\alpha) + \alpha - 3\times 2^{n-2}. \tag{12}$$

On the left of the interval in Eq. (11), $0 \le \alpha_1 \le \alpha - 2^{n-2}$, we again employ the induction hypothesis by assuming equation (8) is satisfied with $n \to n-1$ and $\alpha \to \alpha - 2^{n-2}$:

$$\begin{aligned}\beta(n-1,\alpha-2^{n-2}) \le{}& \beta(n-2,\alpha_1) \\ &+ \beta(n-2,\alpha-2^{n-2}-\alpha_1) \\ &+ |\alpha - 2^{n-2} - 2\alpha_1|\end{aligned} \tag{13}$$

and substitute Eq. (12) and (10) to obtain

$$\begin{aligned}\beta(n,\alpha) \le{}& \beta(n-1,\alpha_1) + \beta(n-1,\alpha-\alpha_1) \\ &+ 2^{n-2} - 2\alpha_1 + |\alpha - 2^{n-2} - 2\alpha_1|.\end{aligned} \tag{14}$$

The desired relation in Eq. (8) follows from Eq. (14) by algebra (Sec. S2 in the Supplemental Material [29]).

Finally, on the right of the interval in Eq. (11), $2^{n-2} \le \alpha_1 \le \alpha$, the Eq. (13) can be used again after replacing α_1 by $(\alpha_1 + 2^{n-2})$, yielding

$$\begin{aligned}\beta(n,\alpha) \le{}& \beta(n-1,\alpha_1) + \beta(n-1,\alpha-\alpha_1) \\ &+ 2\alpha_1 - 2\alpha + 2^{n-2} + |\alpha + 2^{n-2} - 2\alpha_1|,\end{aligned} \tag{15}$$

which reduces to Eq. (8) after minimal algebra, completing the proof. A full derivation with all intermediate steps is given in the Supplemental Material [29], Sec. S2.

We have shown that a NCF has the minimum sensitivity across Boolean functions in $\mathcal{B}_{n,\alpha}$. We now investigate this minimum as a function of the activity ratio. Let us first observe that such a function exists: Note that $\mathcal{B}_{n,\alpha}$ accommodates exactly one NCF. If α is even, it has one or more irrelevant arguments which can be discarded to yield a NCF with less variables and odd α [consistent with Eq. (2)]. Since the number of boundary edges is halved after discarding each irrelevant argument, that is, $\beta(n,\alpha) = 2\beta(n-1,\alpha/2)$ for α even, we observe that both the activity ratio $p = \alpha/2^n$ and the sensitivity $\xi_{\mathrm{NCF}} = \beta(n,\alpha)/2^{n-1}$ are preserved in the reduction process. Therefore, the sensitivity of a NCF for a given activity ratio is unique. We can then define the function $\xi_{\mathrm{NCF}}(p)$, the *exact lower bound* for the sensitivity of Boolean functions subject to a given

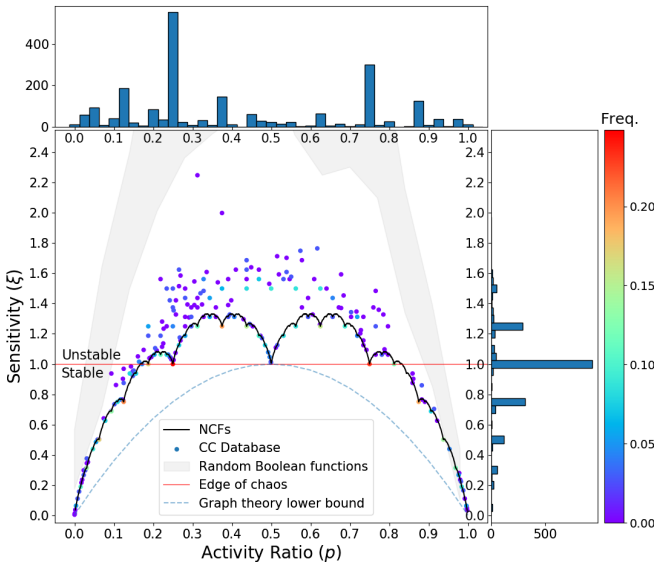

FIG. 3. Sensitivity vs activity ratio for NCFs corresponding the minimum of $\xi(p)$ (solid) as proven here, and for biological examples from from Cell Collective database [34] (circle) with hot colors representing higher frequency of occurrence in the database. Activity and sensitivity histograms for the latter are also shown on the side panels. Note that, the sensitivity histogram has been discussed earlier in Ref. [6]. The shaded region corresponds to 1σ neighborhood of the mean sensitivity for randomized versions of the biological examples. The horizontal red line marks the stability boundary (edge of chaos). The lower bound adopted from spectral graph theory in the text is also shown (dashed).

activity ratio, as the closure of the set of points $(p, \xi_{\rm NCF})$, $\forall\ n, \alpha$ (see Sec. S3 in the Supplemental Material [29]). $\xi_{\rm NCF}(p)$ is given in Fig. 3 and can be compared with the lower bound derived above from spectral graph theory. Its evidently self-similar structure (also hinted at in Ref. [32]) is a consequence of the recursion relation

$$\frac{\xi_{\rm NCF}(p)}{2} = \xi_{\rm NCF}\left(\frac{p}{2}\right) - \frac{p}{2}, \tag{16}$$

which follows from Eq. (10). In fact, Eq. (16) and the symmetry condition $\xi_{\rm NCF}(p) = \xi_{\rm NCF}(1-p)$ by Eq. (9) comprise a complete mathematical description of $\xi_{\rm NCF}(p)$, together with the boundary condition $\xi_{\rm NCF}(1) = 0$. By inspection (analytical and also visual from Fig. 3), we find that $\xi_{\rm NCF}(p) \geq 1$ (i.e., at or above the order or chaos boundary) when $p \in [(1/6), (5/6)]$ and $\xi_{\rm NCF}(p) < 1$ otherwise. The significance of the shape of $\xi_{\rm NCF}(p)$, known as the "blancmange curve" or "Takagi curve" [33], for the accumulation of biological networks at the edge of chaos (previously reported in Ref. [6]) is discussed below.

Having characterized the lower bound on the sensitivity, we next ask whether it is consequential to biology at all. Hence, we downloaded all regulatory functions of the 78 biochemical networks in the Cell Collective database [34] which contains models curated from earlier published studies on a wide selection of cellular processes in multiple organisms. Out of 3460 regulatory functions, we discarded 1310 which take a single variable as input (they convey no valuable information for our study) and calculated the activity ratio and sensitivity for the rest, using Eq. (4).

Superimposing the resulting scatter plot with $\xi_{\rm NCF}(p)$ in Fig. 3 reveals the biological significance of the calculated exact minimum. For comparison, the range of sensitivities for an ensemble of randomized functions (obtained by shuffling the truth table of each function in the database) is also shown as an overhanging gray region in the same figure. It is remarkable that most of the biological regulatory functions are situated on the minimal curve and the rest are visibly closer to it than their random counterparts. For a quantitative assessment of this observation, we define the "normalized excess sensitivity" of a regulatory function as $\delta[f] \equiv \xi[f]/\xi_{\rm NCF}(p_f) - 1$. In Fig. 4(a), we show the distribution of δ for the functions in the Cell Collective database and for their randomized versions. The dominating feature of the shown distributions is the peak at $\delta = 0$ which reflects the fact that all but 215 functions out of 2150 in Cell Collective lie on the sensitivity minimum (i.e., are NCFs, consistent with an earlier analysis on a smaller set [10]). The remaining 10% (non-NCFs) have $\langle\delta\rangle \simeq 0.2$, as opposed to $\langle\delta\rangle \simeq 0.85$ for the randomized functions.

It is interesting to consider our findings in conjunction with a recent analysis on the same dataset by Daniels *et al.* [6], which found an impressive concentration around the order-chaos boundary $\xi = 1$ (also reproduced here on side panel of Fig. 3). The observation serves as a confirmation of the well-known "edge-of-chaos" hypothesis by Kauffman, which posits that most biological systems are tuned to remain in the vicinity of the critical point [13,16], striking a balance between robustness to transient environmental changes and adaptability to persistent shifts. Mechanisms leading to criticality in living organisms are still unclear [35,36]. Our results underline the somewhat counterintuitive fact that, gene regulatory networks not

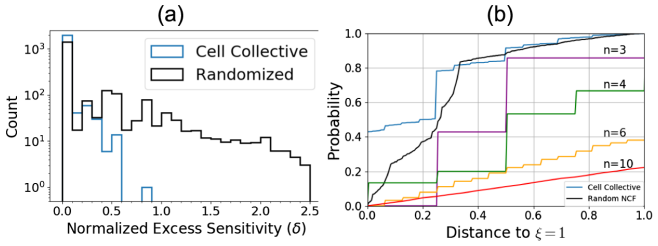

FIG. 4. (a) The histogram for the percentage deviation from the sensitivity minimum $\xi_{\rm NCF}(p)$, for the regulatory functions in the Cell Collective database and their randomized counterparts. (b) The probability of finding $\xi \in [1-x, 1+x]$ for functions in the Cell Collective database (blue), NCFs (black), and random Boolean functions with $n = 3$, 4, 6, and 10 inputs.

only "live at the edge of chaos," but they also barely stray away from the boundary of minimum sensitivity. Upon inspection, this is facilitated by the abundance of functions with two or three inputs in the dataset (hot spots in Fig. 3), which induces a bias for certain activity ratios (Fig. 3, top panel) with $\xi = 1$. Yet, it is evident that the shape of $\xi_{\mathrm{NCF}}(p)$ favors the vicinity of the critical point, even in the absence of any activity bias. Figure 4(b) shows that the sensitivities of 50% and 85% of NCFs selected randomly from a uniform distribution on p remain within 1 ± 0.25 and 1 ± 0.35, respectively.

We conclude that, a selective pressure for robustness combined with a sufficient spread in the distribution of activity ratios suffices for the gene regulatory functions to populate the neighborhood of marginal stability, although an additional preference for a small number of regulatory inputs per gene appears responsible for the sharp peak observed at $\xi = 1$ for biological functions [6] (compare blue and black curves in Fig. 4). Thus, the exact bound $\xi_{\mathrm{NCF}}(p)$ we report here offers a quantitative reference point which helps one gauge the role and the limits of the competition between robustness and plasticity in shaping the marginal stability of these systems.

Finally, it is worth noting that, although the network sensitivity can be expressed as $\langle \xi_\alpha \rangle$ (averaged over the network nodes, α) in an annealed approximation, existence of correlations between the inputs of different nodes generally necessitates a more refined treatment [15,37,38]. It would be interesting to investigate the limits of sensitivity at the network scale, in conjunction with the bound derived here at the node level.

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