TÜBİTAK

Turkish Journal of Physics

http://journals.tubitak.gov.tr/physics/

Research Article

Turk J Phys
(2022) 46: 206 – 216

doi:10.55730/1300-0101.2727

Critical dynamics in biological Boolean networks follows from symmetric response to input genes

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Received: 11.11.2022 • **Accepted/Published Online:** 13.12.2022 • **Final Version:** 27.12.2022

Abstract: A recent observation on an extensive collection of biological gene regulatory networks suggests that the regulatory dynamics is tuned to remain close to the order-chaos boundary in the Lyapunov sense [1]. We here investigate, from a mathematical perspective, the structural/functional constraints which give rise to such accumulation around criticality in these systems. While the role of canalizing functions in this respect is well established, we find that critical sensitivity to small input variations also follows from an over-abundance of symmetrical inputs, i.e. regulatory genes invoking identical or complementary responses on their common target. A random network ensemble constructed to have the same distribution of symmetric inputs as in the above collection of biological networks captures the dependence of the sensitivity on mean activity bias, a nontrivial characteristic which the canalizing ensemble fails to fully reproduce.

Keywords: Biomolecular dynamics, gene expression, patterns in complex systems, self-organization, transcription

1. Introduction

Biological organization is often found to display self similarity across spatial and temporal scales, as observed in brain function [2], swarm behavior [3, 4]. It has been suggested that organisms benefit from proximity to a critical state since it facilitates energy economy [5], communication/transport efficiency, and optimal trade-off between robustness *vs* responsiveness [6]. Unveiling the mechanisms through which criticality emerges in biology has therefore been an active area of research for some time. In certain cases, the scaling laws can be explained by employing physical constraints (e.g., allometric observations [7]), evolutionary or developmental processes (e.g., protein networks [8], neural connectivity in the brain [9]), or mechanisms of self-organized criticality [10] (e.g., swarm behavior [11]). In others, such as the power-law distributed avalanche sizes in brain activity [12] or the probability distribution of protein production rates in a cell [13], the mechanisms are still not well understood.

Gene regulatory networks (GRNs) also display scale invariance in both structural and functional domains. The underlying interaction graph has been observed to be scale-free in multiple organisms [14], a property which has been attributed to gene duplication [8] or the physical mechanism of protein-DNA binding that initiates transcriptional regulation [15]. On the dynamics front, simple gene-activation (node-update) rules have been demonstrated to yield critical avalanches on

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scale-free networks [16], in agreement with experimental observations [17]. These models typically require a selection mechanism for fine tuning either the structural or the functional parameters (or both). For example Derrida and Pompeau showed in a seminal work [18] that a random Boolean network is critical when the node degree satisfies $K = 2$. Evolutionary pressures may fuel such fine tuning, since gene regulation networks are believed to have high plasticity (mutation rate per base is several orders of magnitude higher in the regulatory regions than in the coding segments [19]).

Vanishing of the Lyapunov exponent marks the tipping point between order and chaos and is often used as the indicator for criticality in regulatory dynamics [20]. A recent study on 72 regulatory networks from various organisms measured the corresponding Lyapunov exponents for the network-specific regulatory dynamics [1] and found an impressive collapse around one. A substantial body of literature has been devoted to the study of why biological systems may organize in the vicinity order-chaos boundary, most notably works by S.A. Kauffman [21, 22], but also many others [23–25]. Given the insufficient amount of evolutionary data on GRNs, it is difficult to point to a particular evolutionary mechanism or a selective pressure that might explain the observation above. On the other hand, the how question, exploring the means (in terms of structural and functional determinants) by which the 72 gene networks above are "tuned" to criticality, appears more accessible. We here address this question, motivated by the observation that the symmetry property is obeyed by virtually all of the approximately 3000 regulatory functions in the Cell Collective database [26].

2. Theoretical setup

We here adopt the common definition of criticality as the vanishing of the Lyapunov exponent. In the present context, this condition determines the borderline between order and chaos for the dynamical response of genes to small perturbations in the input. The time evolution of the expression state of a gene in discrete time is assumed to be given by

$$\vec{x}(t + dt) = \vec{f}[\vec{x}(t)] \ , \tag{2.1}$$

where each component of $\vec{x}$ refers to the (Boolean) expression level of a gene and each the corresponding component of $\vec{f}$ is a Boolean function encoding the connection between the expression levels of the regulatory proteins and that of the regulated gene. Recent studies link critical regulatory dynamics within cells to the "canalization" property of the underlying regulatory functions [27–29]. Here, canalization refers to a hierarchy order assigned to the regulatory inputs, allowing the response to be determined by a privileged subset of the inputs (see below).

While canalization is a widely observed feature of genetic regulatory functions, another related but not equivalent quality they almost universally demonstrate is the symmetry of the function $f()$ under a permutation of two or more input signals. We quantify this statement in the next section, over the regulatory functions obtained from the Cell Collective database (CC). Note that symmetry in the above sense in a (uniformly) random Boolean function with k inputs has a chance of occurrence which decays exponentially with k. Motivated by this observation, we here investigate the impact of symmetry on the criticality of the regulatory dynamics.

2.1. Symmetry and generalized symmetry

Symmetry can be defined as a relation between two inputs of a (binary) function. Two inputs are symmetric if they are interchangeable in any input state:

x_i, x_j pair is symmetric, if and only if $f(\vec{x}) = f(S_{ij}\vec{x})$ $\forall x \in \{0,1\}^n$, where S_{ij} is the exchange (permutation) operator which switches the components i and j of the state vector it acts on.

For a stability related analysis, a generalized definition ignoring negations is more appropriate. In the rest of the paper, "symmetry" is used only in this generalized sense:

x_i, x_j pair is generally symmetric, if and only if $f(\vec{x}) = f(S_{ij}\vec{x})$ or $f(N_i\vec{x}) = f(N_iS_{ij}\vec{x})$, $\forall x \in \{0,1\}^n$, where N_i negates the i^{th} component of a state vector.

We define a Boolean function $f : \{0,1\}^n \to \{0,1\}$ to be *partially k-symmetric* if and only if a partition $P = \{p_1, p_2, \ldots, p_k\}$, of the input set can be found with $k < n$, such that f is invariant under any permutation of the elements within p_i. *1-symmetric* functions are also called as totally symmetric functions.

2.1.1. 2-symmetric functions

An inspection of the Cell Collective database reveals that out of more than 2000 documented genes in 73 different regulatory networks, 81% have at most two symmetry classes. We, therefore, focus on *2-symmetric* functions in the form

$$f = g_1(x_1, \ldots, x_a) \vee g_2(x_{a+1}, \ldots, x_n) \ , \tag{2.2}$$

where g_1 and g_2 are totally symmetric and, without loss of generality, we assume $a \leq n/2$. If we rule out the *exclusive or (xor)* operation (which is almost never found in the Cell Collective database), $g_{1,2}$ must have their inputs related through $\wedge$ or $\vee$ operators exclusively. Consequently, f comes in four types listed below.

$$\begin{aligned}
&Type-0 && \text{, if } f = x_1 \vee \cdots \vee x_n \\
&Type-1 && \text{, if } f = (x_1 \wedge \cdots \wedge x_a) \vee x_{a+1} \vee \cdots \vee x_n \\
&Type-2 && \text{, if } f = x_1 \vee \cdots \vee x_a \vee (x_{a+1} \wedge \cdots \wedge x_n) \\
&Type-3 && \text{, if } f = (x_1 \wedge \cdots \wedge x_a) \vee (x_{a+1} \wedge \cdots \wedge x_n) \ .
\end{aligned} \tag{2.3}$$

While the possibility of a negated input is discarded above, our results for network stability/sensitivity -which are for generalized symmetric functions- apply without change to this case as well. We also note that, type-0 *2-symmetric* functions comprise a special case since they are totally symmetric, yet, they represent a significant portion of the GRNs.

2.2. Canalization

In the present context, canalization refers to the presence of a input or inputs which dictate the output of a function when they acquire their canalizing value. Formally f is canalizing in s_1 if

$$f(s_1, s_2, \ldots, s_n) \equiv \begin{cases} r_1, \text{ if } s_1 = \sigma_1 \\ \hat{f}(s_2, s_3, \ldots, s_n), \text{otherwise.} \end{cases} \tag{2.4}$$

More generally a subset of inputs may dictate the output:

$$f(s_1, s_2, \ldots, s_n) \equiv \begin{cases} r_1, \text{ if } (s_1, \ldots, s_m) = (\sigma_1, \ldots, \sigma_m) \\ \hat{f}(s_1, s_2, \ldots, s_n), \text{otherwise} . \end{cases} \tag{2.5}$$

Such collective canalization may be considered weaker, since the condition is more restrictive.

Canalization and symmetry are clearly distinct qualities. While a canalization property shared by two inputs, as in collective canalization, can promote symmetry between these inputs, it does not necessitate it. For example, consider the function $f(\vec{s}) = g_1(s_1, s_2, s_3) \vee g_2(\vec{s})$ where g_1 and g_2 are not symmetric. The inputs for which $g_1 = 1$ canalize f to 1, but f is not symmetric in the subset of inputs $\{s_1, s_2, s_3\}$.

An extreme case of canalization is when all inputs exert canalization in a (nonunique) hierarchical order:

$$f(s_1, \ldots, s_n) \equiv \begin{cases} r_1, \text{ if } s_1 = \sigma_1 \\ r_2, \text{ if } s_2 = \sigma_2, s_1 = \bar{\sigma_1} \\ \vdots \\ r_n, \text{ if } s_n = \sigma_n \text{ and } s_i = \bar{\sigma_i} \ \forall i \in \{1, \ldots, n-1\} \\ \bar{r}_n, \text{ otherwise} . \end{cases} \tag{2.6}$$

The hierarchy consists of layers, whose members have identical privileges and are interchangeable on the hierarchy list. For instance, considering the function $f = x_1 \vee (x_2 \wedge x_3)$, x_1 is at the top the hierarchy while x_2 and x_3 share the next layer. A nested canalizing function with r layers is *r-symmetric*. The connection between canalization and symmetry in the context of *2-symmetric* functions is shown as a Venn diagram in Figure 1.

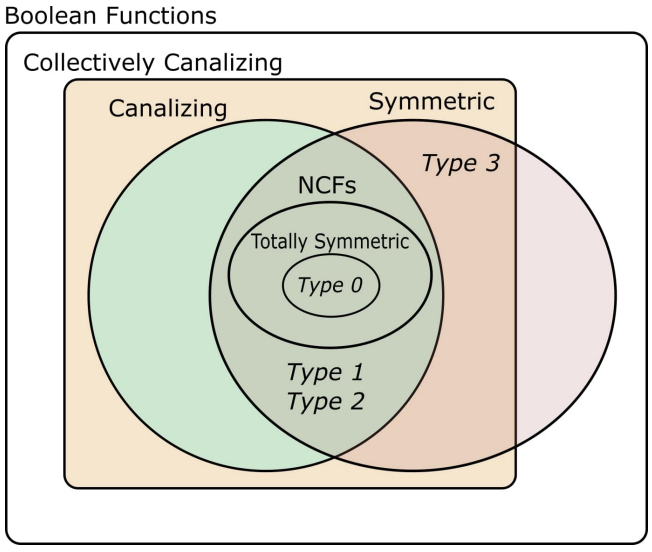

Figure 1. The Venn diagram depicting the relationship between various types of canalizing and symmetric functions.

2.3. Sensitivity

In order to investigate the dynamical stability of a system evolving under the rules in Eq.(2.1) we need to define the sensitivity of a Boolean function to small (one bit) variations in the input. To this end, we define

$$s \equiv \sum_{i=1}^{n} s_i, \text{ where } s_i = \left\langle \frac{\partial f}{\partial x_i} \right\rangle_{\vec{x}} , \tag{2.7}$$

as the sensitivity coefficient for the Boolean function f. The expected value is calculated over all possible inputs and the Boolean derivative is defined as

$$\frac{\partial f}{\partial x_i} \equiv f(\vec{x}^{(i,0)}) \oplus f(\vec{x}^{(i,1)}) , \tag{2.8}$$

where $\vec{x}^{(i,0)}$ is derived from the vector $\vec{x}$ by setting its i^{th} entry to 0.

By the annealed approximation, average sensitivity of a network is the average of the sensitivities of the nodes within the network. It describes the response of the network to a typical local perturbation. When the average sensitivity is lower than 1 a local perturbation decays before it traverses the network. Otherwise, it branches out to generate an avalanche spanning the whole system. A network with an average sensitivity of 1 is said to be critical, since, on average, a local perturbation is neither amplified nor diminished in time, propagating across the network with a constant mean amplitude. Hence, $s = 1$ corresponds to the maximally robust network which is still "aware" of a local perturbation at a global scale. GRNs are observed to be near this critical point. [28].

2.4. Sensitivity and activity bias for 2-symmetric functions

We can now calculate the sensitivity of 2-symmetric functions in terms of their activity bias, α. The activity bias is defined simply as the probability for a Boolean function returning a "true" value, subject to uniformly random inputs. Here, we are motivated by recent studies which demonstrate that the activity bias strongly dictates the sensitivity for GRNs [28, 29]. To start, one can easily show that the sensitivities to symmetric inputs are equal:

$$s_i = \left\langle \frac{\partial f(\vec{x})}{\partial x_i} \right\rangle_{\vec{x}} = \left\langle \frac{\partial f(S_{ij}\vec{x})}{\partial x_j} \right\rangle_{\vec{x}} = \left\langle \frac{\partial f(\vec{x})}{\partial x_j} \right\rangle_{\vec{x}} = s_j , \tag{2.9}$$

where in the last step we used $f(S_{ij}\vec{x}) = f(\vec{x}) \;\; \forall \; (i,j)$. Then, for the four types of 2-symmetric functions in Eq.(2.3), we have $s_1 = s_2 = \cdots = s_a$ and $s_{a+1} = s_{a+2} = \cdots = s_n$. In order to determine the sensitivity of f, it is therefore sufficient to calculate s_1 and s_n. Starting with Eq.(2.8), we find

$$\begin{aligned} \frac{\partial f}{\partial x_1} &= f(\vec{x}^{(1,0)}) \oplus f(\vec{x}^{(1,1)}) \\ &= \overline{g_2(x_{a+1}, \ldots, x_n)} \wedge \frac{\partial g_1}{\partial x_1} , \end{aligned} \tag{2.10}$$

where $\overline{x}$ indicates negation of x. We obtain s_1 after averaging over all possible states $\vec{x}$:

$$\begin{aligned} s_1 &= \frac{1}{2^n}\sum_{\vec{x}} \overline{g_2(x_{a+1},\ldots,x_n)} \wedge \frac{\partial g_1}{\partial x_1} \\ &= \begin{cases} 2^{1-n} & , \text{ if } \overline{g_2} = \overline{x_{a+1}} \wedge \cdots \wedge \overline{x_n} \\ (2^{n-a}-1)2^{1-n}, & \text{if } \overline{g_2} = \overline{x_{a+1}} \vee \cdots \vee \overline{x_n} \ . \end{cases} \end{aligned}$$

Using a similar approach one can also calculate s_n as

$$s_n = \begin{cases} 2^{1-n} & , \overline{g_1} = \overline{x_1} \wedge \cdots \wedge \overline{x_a} \\ (2^a-1)2^{1-n}, & \overline{g_1} = \overline{x_1} \vee \cdots \vee \overline{x_a} \ . \end{cases} \tag{2.11}$$

Finally, the sensitivity coefficients can be calculated exactly for all four choices of a 2-symmetric function, f, as

$$s(n,a) = \begin{cases} n2^{1-n} & , f = x_1 \vee \cdots \vee x_n \\ a2^{1-n} + (n-a)(2^a-1)2^{1-n} & , \ f = (x_1 \wedge \cdots \wedge x_a) \vee x_{a+1} \vee \cdots \vee x_n \\ a(2^{n-a}-1)2^{1-n} + (n-a)2^{1-n} & , \ f = x_1 \vee \cdots \vee x_a \vee (x_{a+1} \wedge \cdots \wedge x_n) \\ a(2^{n-a}-1)2^{1-n} + (n-a)(2^a-1)2^{1-n} & , \ f = (x_1 \wedge \cdots \wedge x_a) \vee (x_{a+1} \wedge \cdots \wedge x_n) \ , \end{cases} \tag{2.12}$$

and can be expressed in terms of the activity bias, α, as

$$s(\alpha^*) = \begin{cases} -2\log_2(\alpha^*)\alpha^* & , \ f = x_1 \vee \cdots \vee x_n \\ 2aK\alpha^* - 2\alpha^*\log_2(\frac{K}{L}\alpha^*) & , \ f = (x_1 \wedge \cdots \wedge x_a) \vee x_{a+1} \vee \cdots \vee x_n \\ 2a\alpha^* - 2\log_2(1-2^a\alpha^*)(L-\alpha^*) & , \ f = x_1 \vee \cdots \vee x_a \vee (x_{a+1} \wedge \cdots \wedge x_n) \\ 2aK + 2\log_2(-K+\frac{K}{L}\alpha^*)(L-\alpha^*) - 2a\alpha^*K & , \ f = (x_1 \wedge \cdots \wedge x_a) \vee (x_{a+1} \wedge \cdots \wedge x_n) \ , \end{cases} \tag{2.13}$$

where $\alpha^* = \min(\alpha, 1-\alpha)$, $K = \frac{1}{2^a-1}$, and $L = \frac{1}{2^a}$. Note that all sensitivity coefficients are symmetric functions of the activity bias. From these expressions, the maximum possible sensitivity for each 2-symmetric function class can be obtained as

$$s^{max} = \begin{cases} 1, & \text{for } (n,a) = (1,1) \text{ and } f = x_1 \vee \cdots \vee x_n \\ 1.25, & \text{for } (n,a) = (3,1) \text{ and } f = (x_1 \wedge \cdots \wedge x_a) \vee x_{a+1} \vee \cdots \vee x_n \\ 1.25, & \text{for } (n,a) = (3,1) \text{ and } f = x_1 \vee \cdots \vee x_a \vee (x_{a+1} \wedge \cdots \wedge x_n) \\ 1.5, & \text{for } (n,a) = (4,2) \text{ and } f = (x_1 \wedge \cdots \wedge x_a) \vee (x_{a+1} \wedge \cdots \wedge x_n) \ . \end{cases} \tag{2.14}$$

In order to put this result in perspective, we note that the expected sensitivity coefficient grows linearly with the number of inputs as $E[s]_{canal} = (n+1)/4$ for canalizing functions [30], and as $E[s]_{rand} = n/2$ for random Boolean functions. In contrast, we find here that the sensitivity of symmetric functions is bounded from above. For the majority of the biological cases found in the Cell Collective database Eqs. (2.12) & (2.14) give the exact sensitivities and their upper bound within

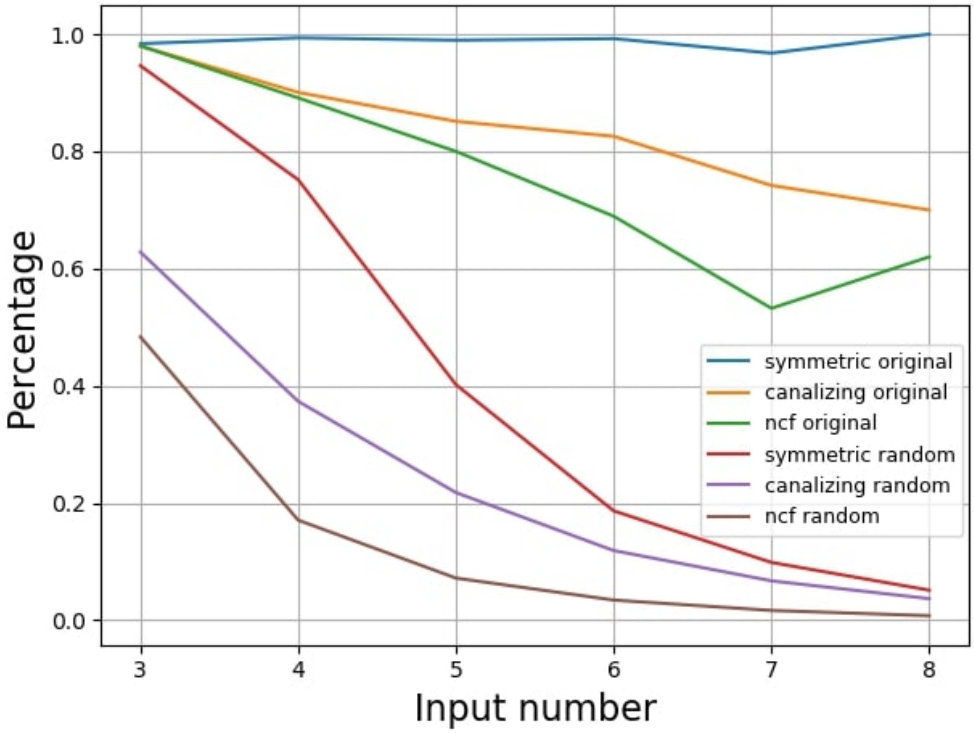

Figure 2. Frequency of symmetry, canalization and nested canalization vs. the number of inputs in the original (Cell Colletive) networks and in random Boolean functions with uniform activity bias.

each function class. As the input size is increased, the limiting behavior of the sensitivity of Type-2 and Type-3 functions and the activity bias can be obtained as

$$s \to \frac{2a}{2^a} \quad \text{and} \quad \alpha \to \frac{1}{2^a} \,. \tag{2.15}$$

An exhaustive compilation of the sensitivity coefficient as a function of the activity bias for at most 2-symmetric Boolean functions is given in Figure 3 where approach to the limit in Eq. (2.15) is clear.

3. Comparison with biological networks

The Cell Collective Database has full structural and functional specification of 79 GRNs which include 3476 genes. Out of these, 2140 are regulated by 1 or 2 genes and 25 by more than 11. We omit the second set due to the large computational time they require for sensitivity calculation. The dynamics of the first set, comprising the majority of the genes, are described by a handfull of 1-symmetric functions with a sensitivity of 1 with no room for variability. We find that the remaining 1311 target genes have an average sensitivity of 0.936, also very close to the critical value. Hence, symmetry of the regulatory functions alone appears to support criticality in gene regulation.

The frequency of symmetry and canalization in biological networks relative to their randomized counterparts is shown in Figure 2. While different priors used for randomization yield different estimates, it is clear that the likelihood of partial symmetry or canalization decays exponentially

Table 1. Distribution of genes with at most 2 symmetry classes.

Type	Count	Percentage %	Sensitivity average
Type-0	502	49.17	0.6028
Type-1	165	16.16	0.8057
Type-2	321	31.44	1.208
Type-3	27	2.64	1.4298
XOR	6	0.59	1.104

fast with the number of inputs, n. However, the frequency of symmetry is visibly higher than that of canalization both for the randomized networks and the original ones. In the CC database, 1.1% of the target genes lack any symmetry, while those without the canalization property amount to 10.8%. Our analysis based on symmetry therefore applies to practically all of the CC database. We observed that only 1.5% of the symmetric genes in CC database include an *xor* operation in their update function. Furthermore, 78.8% have at most 2 symmetry classes falling into one of the four types mentioned earlier. Their sensitivities and activity biases match exactly with those calculated above and yield the statistics given in Table 1.

Unlike canalizing functions, the expected sensitivity of 2-symmetric functions is independent of the number of inputs and depends only on the size of the small symmetry class, a. In the Cell Collective database we only encountered $a = 1, 2, 3$. For $a = 1, 3$ and $a = 2$ the average sensitivities are 0.86 and 0.946, respectively, which fall in the vicinity of the critical regime. Interestingly, nested canalizing functions have an average sensitivity of exactly 1 under a uniform activity bias distribution. However, the corresponding fractal curve in Figure 3, which is provably a lower bound [29] on the sensitivity, does not capture a fraction of the data points from Cell Collective. Random canalizing functions do not yield a better model either (also shown in Figure 3) since the scatter above the lower bound is concentrated away from $\alpha = 0.5$. In contrast, 2-symmetric functions yield a sensitivity distribution which is in better agreement with the database. They capture both the high density of genes on the boundary given by the nested canalizing functions and the scatter above the lower bound.

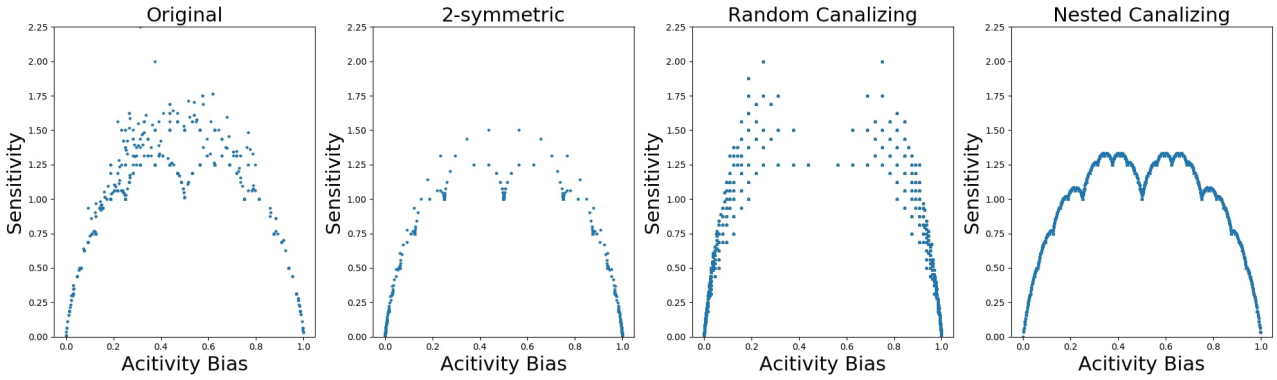

Figure 3. Sensitivities vs. activities for the original (Cell-Collective) gene regulatory functions and randomly chosen 2-symmetric, canalizing, and nested canalizing functions with similar number of inputs.

4. Conclusion

Biological benefits and origins of canalization in gene regulation have been discussed in the literature since the classic works of Waddington [31] and Schmalhausen [32]. Yet, the fractal lower bound on the sensitivity of Boolean functions (shown in the last panel of Figure 3), which is realized by nested canalizing functions, has been reported only recently [29]. This observation poses the near-criticality of gene regulation dynamics as -almost- a mathematical necessity. On the other hand, a small but nonnegligible portion of genes do not fall on this optimal boundary. While this can be interpreted as "evolution in progress", an alternative perspective may follow from the analysis provided here. Biological networks appear to adhere more closely to generalized symmetry than to canalization in the regulation processes. Although these two concepts are not far from each other (as was shown in Figure 1) asymmetric regulatory functions, unlike noncanalizing ones, are practically nonexistent.

We have shown here that this symmetry property alone yields an upper bound on the sensitivity (i.e. imposes robustness) of the regulatory dynamics, a desirable feature for any functional design. We then calculated the activity bias vs. sensitivity exhaustively for all 1- and 2-symmetric functions which correspond to the majority of the genes in Cell Collective. We finally argued that, a random ensemble of 2-symmetric functions may be a more faithful null-model for the biological networks than canalizing functions. Extending the above analysis to p-symmetric functions with $p > 2$ and exploring biological mechanisms for symmetry in gene regulatory functions are left for future work.

Acknowledgements

We dedicate this work to Prof. Nihat Berker whose lifelong commitment to and excellence in scientific inquiry and infinite energy for sharing his passion with generations of physics students continues to be an inspiration for many.

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