

Boolean networks with veto functions

Haleh Ebadi¹ and Konstantin Klemm^{1,2,3}

¹*Bioinformatics, Institute for Computer Science,
Leipzig University, Härtelstrasse 16-18, 04107 Leipzig, Germany*

²*Bioinformatics and Computational Biology, University of Vienna, Währingerstraße 29, 1090 Vienna, Austria*

³*Theoretical Chemistry, University of Vienna, Währingerstraße 17, 1090 Vienna, Austria*

(Dated: May 14, 2014)

Boolean networks are discrete dynamical systems for modeling regulation and signaling in living cells. We investigate a particular class of Boolean functions with inhibiting inputs exerting a veto (forced zero) on the output. We give analytical expressions for the sensitivity of these functions and provide evidence for their role in natural systems. In an intracellular signal transduction network [Helikar et al., PNAS (2008)], the functions with veto are over-represented by a factor exceeding the over-representation of threshold functions and canalizing functions in the same system. In Boolean networks for control of the yeast cell cycle [Fangting Li et al., PNAS (2004), Davidich et al., PLoS One (2009)], none or minimal changes to the wiring diagrams are necessary to formulate their dynamics in terms of the veto functions introduced here.

PACS numbers: 89.75.Fb, 87.16.Yc, 05.45.-a, 45.05.+x

I. INTRODUCTION

Networks of chemical interactions are responsible for the signalling and control in all living systems, from the unicellular bacteria to large multicellular organisms [1]. We are witnessing a rapid increase of biochemical measurements. These results need to be complemented by appropriate models in order to elucidate common principles of such systems and generate predictions testable by further experiments. A variety of modeling approaches exist, ranging from the chemical master equation or stochastic simulation of reactions for a few types of molecules to purely qualitative wiring diagrams that summarize existing interactions [2].

A particularly successful approach of simplification for control networks of up to hundreds of nodes is the discretization of chemical signals into on/off states evolving in discrete time [3, 4]. These kinds of models, called Boolean networks, are formally equivalent to circuits of digital electronics with logical gates.

For more and more control systems, the essential time course and response to perturbations are accurately reproduced by a dedicated Boolean network [5–8]. Such system-specific Boolean models are obtained from known interactions in the literature [9], by discretizing existing models of differential equations [10] or by direct inference from high-throughput experimental data [11, 12].

Long before the data-driven definition and refinement of system-specific networks, however, statistical ensembles of Boolean networks were studied, seeking generic properties of these discrete dynamical systems [3, 13]. There the Boolean functions are assigned to the nodes randomly over the set of all functions with a given number of inputs. When increasing the average number of interactions, such random Boolean networks display a transition from ordered behaviour dominated by fixed points to “chaotic” dynamics with transients and periodic attractors of length exponential in system size [14].

Random Boolean networks may now serve as null models in comparison to system-specific models. One way of refinement of these null models is by restricting the set of Boolean functions to realistic ones. Though the repertoire of combinatorial biochemical interactions, e.g. between transcription factors and binding sites [15], enables construction of complicated logical functions, relatively simple truth tables abound in real systems. One class of naturally occurring input-output relations are canalizing [16]: a certain truth value at one argument fully determines the output of the Boolean function. Using nested canalizing functions, where the residual function after removal of one canalizing input is again canalizing, the dynamics of the Boolean networks is ensured to be non-chaotic [17].

Beyond making null models more realistic, the usage of a specifically restricted set of Boolean functions also offers advantages in the numerical treatment of Boolean dynamics and, in particular, the evolution of the networks [18]. Such simulation scenarios frequently use threshold functions [19], whose output is active only if a weighted sum of the inputs exceeds a certain value. Similar to $\pm J$ -spin glasses [20] but keeping couplings asymmetric in general, these threshold functions employ binary weights taking values +1 (activation), -1 (inhibition), and an entry 0 representing absence of a coupling in the interaction matrix. For a function with k inputs, this choice reduces the set of available functions from 2^{2^k} to at most 3^k . Threshold functions, however, are not the only practical choice of Boolean functions where inputs are assigned binary labels in this manner.

Here we investigate a class of functions with strong inhibition, which we call veto functions. As is the case with threshold functions, inputs have binary labels, activating or inhibiting. However, the output is shut off by a single inhibitory signal regardless of other inputs. We calculate the sensitivity of these functions and provide two instances of relevance for biological systems. First, veto

functions preferentially occur in a large Boolean network of inter-cellular signalling. Second, known wiring diagrams for control of yeast cell cycles generate the correct trajectories under veto functions.

II. DEFINITIONS AND NOTATION

A Boolean function is a mapping

$$f : \{0, 1\}^k \rightarrow \{0, 1\} \quad (1)$$

of k binary valued inputs with a single binary output. The number of inputs k is called the *arity* of f . For testing the dependence of f on small displacements in input space, we define the negation (“flip”) of the i -th component on a Boolean vector $\sigma \in \{0, 1\}^k$ as the vector $\sigma^{\uparrow i}$ with

$$(\sigma^{\uparrow i})_j \neq \sigma_j \Leftrightarrow i = j. \quad (2)$$

In analogy to the usual partial derivative, $\partial^{(i)}f$ indicates whether a change in the i -th input variable causes a change of output. For an input vector $\sigma \in \{0, 1\}^k$,

$$\partial^{(i)}f(\sigma) = \begin{cases} 1 & \text{if } f(\sigma) \neq f(\sigma^{\uparrow i}) \\ 0 & \text{otherwise} \end{cases} \quad (3)$$

with $i \in \{1, \dots, k\}$ and $\uparrow i$ indicating negation at the i -th component (Eq. (2)).

A Boolean network is a time- and state-discrete dynamical system given by an iteration

$$\sigma(t+1) = \phi(\sigma(t)) \quad (4)$$

on a time-dependent binary state vector $\sigma \in \{0, 1\}^N$. The map

$$\phi : \{0, 1\}^N \rightarrow \{0, 1\}^N \quad (5)$$

is a collection of N Boolean functions $\phi_1, \phi_2, \dots, \phi_N$ each of arity N . In practical and realistic scenarios, the functions depend only on a small subset of all N inputs, see section VIII for a precise definition of input dependence. These systems are then characterized by their sparse interaction networks and hence the name Boolean network. See section VII for examples.

III. CANALYZING AND THRESHOLD FUNCTIONS

Canalyzing functions, sometimes called forcing functions, have been studied widely in the context of Boolean networks [5, 16]. Canalyzation means that a certain value at one of the inputs determines the output, regardless of the other inputs. For a Boolean function f , the input with index j is canalyzing if there are $b, c \in \{0, 1\}$ such that for all $\sigma \in \{0, 1\}^k$

$$\sigma_j = b \Rightarrow f(\sigma) = c. \quad (6)$$

Then b is the canalyzing value and c is the canalyzed value. A Boolean function f is called canalyzing if f has a canalyzing input.

A different widely used class of functions are those defined by a weight vector and a threshold [7, 9, 21]. A k -ary Boolean function f is a *general threshold function* if there is a weight vector $w = (w_1, w_2, \dots, w_k) \in \mathbb{R}^k$ and a threshold $\theta \in \mathbb{R}$ such that

$$f(\sigma) = H\left(\sum_{j=1}^k w_j \sigma_j - \theta\right) \quad (7)$$

for all $\sigma \in \{0, 1\}^k$, using the step function $H : \mathbb{R} \rightarrow \{0, 1\}$ with $H(x) = 1$ if and only if $x > 0$.

Here we consider the restriction to the case of discrete weights $w_j \in \{-1, 0, +1\}$ for all inputs j and a vanishing threshold $\theta = 0$. See the recent work by Rybarsch and Bornholdt for a motivation of this choice in the context of biochemical regulation. By *threshold function*, we denote a member of this restricted set of functions.

IV. VETO FUNCTIONS

For veto functions, similar to threshold functions, the set of inputs is divided into subsets of activating, inhibitory and irrelevant inputs. The output of a veto function is active if and only if all inhibitors are off and at least one activator is on. Formally, a k -ary Boolean function f is a veto function, if there are $A, I \subseteq \{1, \dots, k\}$ with $A \cap I = \emptyset$ such that for all $\sigma \in \{0, 1\}^k$,

$$f_v(\sigma) = 1 \Leftrightarrow \forall j \in I : \sigma_j = 0 \text{ and } \exists l \in A : \sigma_l = 1 \quad (8)$$

Equivalently, veto functions may be defined by restricting the set of general threshold functions. Then f is a veto function if there is a weight vector $w \in \{-k, 0, +1\}^k$ such that Eq. (7) holds for all state vectors $\sigma \in \{0, 1\}^k$ and threshold $\theta = 0$. The choice of $-k$ as the weight of an inhibitor keeps the sum below the threshold irrespective of activating inputs.

V. COUNTING FUNCTIONS THAT DEPEND ON ALL THEIR INPUTS

For the data analysis in the following section, further notation and considerations are required for the counting of Boolean functions. With the aim of providing methodology also for similar future work, we introduce the notions in detail now.

By \mathcal{B} we denote the set of all Boolean functions on finitely many inputs; for $k \in \mathbb{N} \cup \{0\}$, we call \mathcal{B}_k the set of all k -ary Boolean functions, so

$$\mathcal{B} = \bigcup_{k=0}^{\infty} \mathcal{B}_k. \quad (9)$$

We denote the restriction of \mathcal{B} to functions with a given property π as $\mathcal{B}^{(\pi)}$, and the further restriction to k inputs as $\mathcal{B}_k^{(\pi)}$. Here we are concerned with the three properties canalizing, threshold and veto, so $\pi \in \{\text{can}, \text{thr}, \text{veto}\}$ and the corresponding function sets \mathcal{B}^{can} , \mathcal{B}^{thr} , $\mathcal{B}^{\text{veto}}$.

Not all k -ary functions actually depend on all k inputs. For instance, a k -ary function f is trivially obtained from an l -ary function g with $l < k$ as $f(\sigma_1, \dots, \sigma_k) = g(\sigma_1, \dots, \sigma_l)$, thus ignoring the last $k - l$ inputs. We call input j of function f *spurious* if $f(\sigma) = f(\sigma^{\downarrow j})$ for all input vectors σ . Thus input j is spurious if f can be computed without knowing the value at input j . Spurious inputs are absent in empirical data of networks, where each input of a node represents a real regulatory interaction that does influence the output. In order to assess if functions with a certain property are over- or under-represented in real data, a reasonable null model is to be based only on functions that depend on all inputs. By \mathcal{B}^* we denote the restriction of \mathcal{B} to functions without spurious inputs; applying the same restriction to \mathcal{B}_k and $\mathcal{B}_k^{(\pi)}$, we use the symbols \mathcal{B}_k^* and $\mathcal{B}_k^{*,(\pi)}$.

We assume that property π is closed under permutations of inputs and removal / addition of spurious inputs, an assumption fulfilled for unrestricted Boolean functions as well as the three properties $\{\text{can}, \text{thr}, \text{veto}\}$. The number of functions with property π without spurious inputs, is obtained recursively as

$$|\mathcal{B}_k^{*,(\pi)}| = |\mathcal{B}_k^{(\pi)}| - \sum_{j=0}^{k-1} \binom{k}{j} |\mathcal{B}_j^{*,(\pi)}|. \quad (10)$$

For each k -ary function with exactly $k - j$ spurious inputs, these may be removed to arrive at a unique j -ary function. The multiplicity of such k -ary functions reducing to the same j -ary function in this way is given by the binomial factor, counting the combinations in which spurious and non-spurious inputs are assigned.

A Boolean function with k inputs takes 2^k different input vectors, to each of which an output value is assigned independently. Thus there are $|\mathcal{B}_k| = 2^{2^k}$ Boolean functions of arity k . By inserting this result into Eq. (10), the number of Boolean functions without spurious inputs is obtained. For canalizing functions, $|\mathcal{B}_k^{*,\text{can}}|$ is calculated by the same equation using the results $|\mathcal{B}_k^{\text{can}}|$ from Just and co-authors [22].

For a threshold function or a veto function, each zero entry in a representing weight vector w is a spurious input. So let us consider only functions with weight vectors $w \in \{-1, +1\}^k$ (for threshold functions) or $w \in \{-k, +1\}^k$ (veto functions). For these, the weight vector is unique and a single activating input (j with $w_j = +1$) renders all inputs non-spurious. Therefore, each combination of admissible non-zero weights, except for the all-negative weight vector, represents a function in $\mathcal{B}_k^{*,\text{thr}}$ and $\mathcal{B}_k^{*,\text{veto}}$, so we obtain

$$|\mathcal{B}_k^{*,\text{veto}}| = |\mathcal{B}_k^{*,\text{thr}}| = 2^k - 1. \quad (11)$$

TABLE I: Counts in the data set. The column a_k is for the total count of k -ary functions, the following three columns count veto, canalizing and threshold functions. The last line gives the summation over all arities.

k	a_k	a_k^{veto}	a_k^{can}	a_k^{thr}
1	27	27	27	27
2	23	12	21	12
3	21	5	18	2
4	29	4	15	2
5	11	1	4	1
6	10	0	5	0
7	8	0	3	0
8	10	0	4	0
9	5	0	3	0
10	5	0	5	0
11	1	0	1	0
12	1	0	0	0
13	0	0	0	0
14	1	0	1	0
\sum_k	152	49	107	44

TABLE II: Over-representation of the three types of functions

k	r_k^{veto}	r_k^{can}	r_k^{thr}
1	0.3	0	0.3
2	0.25	0.07	0.25
3	0.87	0.33	0.47
4	2.78	1.04	2.48
5	6.30	3.25	6.30
6		7.94	
7		17.40	
8		36.63	
9		75.28	
10		152.52	
11		306.61	
14		2464.29	

VI. OVER-REPRESENTATION OF FUNCTIONS IN A SIGNALING NETWORK

In order to evaluate applicability of the veto function in natural systems, we analyze the functions in a Boolean network based on a real living system. The data set is a collection of biological input-response of 152 nodes of intracellular signal transduction network in the form of Boolean truth tables each of which corresponds to the update function of a node [8, 23]. We investigate the over-representation of veto functions, threshold functions and canalizing functions in this system.

For each property π , we count the k -ary functions in the data set as:

$$a_k^{(\pi)} = |\{i \in 152 : f_i \text{ is } k\text{-ary with property } \pi\}|. \quad (12)$$

Table I provides an overview of these counts.

Then $a_k^{(\pi)}/a_k$ is the fraction of these functions, a_k being the total count of k -ary functions in the data set. In order to quantify the preference of property π , we compare this fraction to a null model of uniformly drawing

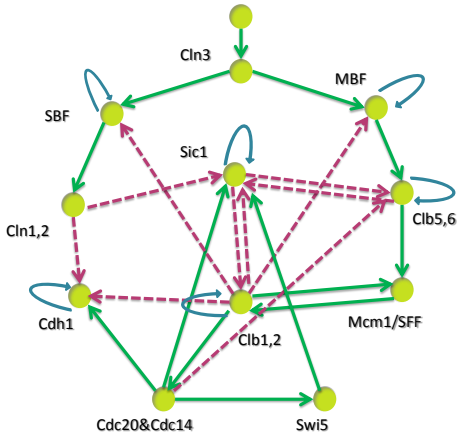


FIG. 1: (Color online) Functional network using veto functions for the budding yeast cell cycle. Solid arrows represent activators, dashed arrows inhibitors. Departing from the wild type network based on threshold functions [24], the depicted network is obtained by deleting six interactions: the two activations from Mcm1/SFF to Swi5 and to Cdc20&Cdc14; and the four inhibitions from Clb5,6 to Cdh1, from Cdh1 to Clb1,2, from Cdc20&Cdc14 to Clb1,2, and from Clb1,2 to Swi5.

k -ary functions without spurious inputs. Under this null model, the expected fraction of functions with property π is $|\mathcal{B}_k^*(\pi)|/|\mathcal{B}_k^*|$. We call the *over-representation* of property π at arity k , the logarithm of the ratio between the observed fraction and that expected under the null model, so

$$r_k^{(\pi)} = \log \left(\frac{a_k^{(\pi)}}{a_k} \right) - \log \left(\frac{|\mathcal{B}_k^*(\pi)|}{|\mathcal{B}_k^*|} \right) \quad (13)$$

Table II lists these values. The over-representation of veto functions is at least as large as that of threshold functions and strictly larger than that of canalizing functions, considering the value of $r_k^{(\pi)}$ for arities $k \leq 5$ where all these types of functions are present.

VII. CELL CYCLE NETWORKS

Cell division has been one of the first biological processes to be described in terms of Boolean networks, using with few (around 10) nodes [7, 9, 21, 24, 25]. In the Boolean discretization, the cell cycle is a sequence of state vectors $\sigma(0), \sigma(1), \dots, \sigma(T) \in \{0, 1\}^N$ where $\sigma_j(t)$ indicates the presence or absence of molecular species j at time step t . A Boolean network on N nodes is called *functional* if it generates the cell cycle sequence given $\sigma(0)$ as an initial condition. Most earlier approaches describe functional networks using threshold functions. Here we investigate functional networks using veto functions.

In a functional network, each node i independently fulfills the input-output mapping given by the sequence.

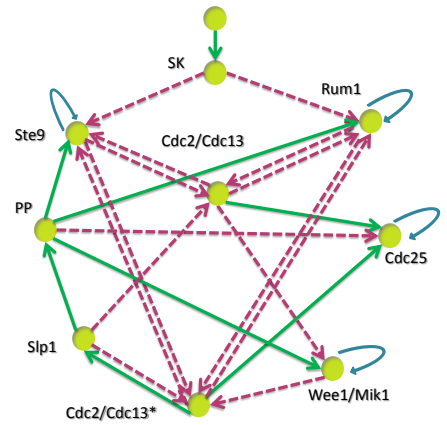


FIG. 2: (Color online) Functional network using veto functions for the fission yeast cell cycle. Solid arrows represent activators, dashed arrows inhibitors. The wiring is identical to the one given by Rybarsch and Bornholdt [24], bottom of Figure 5 there.

Thus the problem of finding *all* functional networks is fully solved by independently finding the set S_i^{veto} of functions generating this mapping [21].

$$S_i^{\text{veto}} = \{f \in \mathcal{B}_N^{\text{veto}} \mid \forall t \in \{1, \dots, T\} : f(\sigma(t-1)) = \sigma_i(t)\} \quad (14)$$

with $\mathcal{B}_N^{\text{veto}}$ denoting the set of all N -ary veto functions (cf. section V). Since the solutions at each node i combine independently, the number of functional networks based on veto functions is

$$H^{\text{veto}} = \prod_{i=1}^N |S_i^{\text{veto}}|. \quad (15)$$

For the cell cycle of the species *S. cerevisiae* (budding yeast, $N = 11$) [7], we compute $H^{\text{veto}} = 1.15 \times 10^{28}$, to be compared to $H^{\text{thr}} = 1.6 \times 10^{33}$ functional networks using threshold functions. Fig. 1 shows one of the functional networks with veto functions. It has been selected such that the wiring is closest to the so-called wild type [7, 24] based on interactions with evidence in the literature. Departing from the wiring of the wild-type, the network in Fig. 1 is obtained by deleting six interactions, see the caption for details.

For the cell cycle of the species *S. pombe* (fission yeast, $N = 10$) [9], we compute $H^{\text{veto}} = 2.97 \times 10^{27}$, to be compared to $H^{\text{thr}} = 2.4 \times 10^{27}$ functional networks using threshold functions. Fig. 2 shows one of the functional networks with veto functions. The wiring is identical to the wild type network using threshold functions [24]. We remark that node Cdc2/Cdc13 is treated different from the other nodes. This node does not have an activating connection in the wild type wiring. Here we use a varied type of veto function making node is active in the absence of inhibiting inputs (even though there is no activating input). This is analogous to the treatment with thresh-

old functions where a negative threshold is assigned to Cdc2/Cdc13.

VIII. SENSITIVITY

The tendency of a Boolean function to change output value in response to a changing input is quantified by the activity [26], defined as

$$\alpha_l(f) = 2^{-k} \sum_{\sigma \in \{0,1\}^k} \partial^{(l)} f(\sigma), \quad (16)$$

with ∂ as defined in Eq. (3). Thus the activity is the probability that a perturbation (negation of state) at input l propagates to the output of the function when all other inputs are kept fixed.

Let us consider a k -ary veto function f . As before, we denote the activating inputs by A , inhibiting inputs by I . Let $m := |I| = m$ and assume absence of spurious inputs, so $|A| = k - m$. Let us consider the set X_l of state vectors where flipping the state of the l -th component causes f to change output,

$$X_l = \{\sigma \in \{0,1\}^k : f(\sigma^{\uparrow l}) \neq f(\sigma)\} \quad (17)$$

so $\alpha_l(f) = 2^{-k} |X_l|$.

An inhibiting input l switches the output if and only if there is at least one activation and all other inhibitors are off,

$$X_l = \{\sigma \in \{0,1\}^k : (\forall i_l \setminus \{l\} : \sigma_i = 0) \wedge \exists j \in A : \sigma_j = 1\} \quad (18)$$

This comprises $|X_l| = 2(2^{k-m} - 1)$ state vectors, so the activity of an inhibitor is

$$\alpha_l(f) = \frac{2(2^{k-m} - 1)}{2^k}. \quad (19)$$

When switching the state at an activating input $l \in A$, the output of f changes if and only if all other inputs are off,

$$X_l = \{\sigma \in \{0,1\}^k : \forall i \in \{1, \dots, k\} \setminus \{l\} : \sigma_i = 0\}. \quad (20)$$

Here we have $|X_l| = 2$ state vectors only. The activity of an activator is

$$\alpha_l(f) = \frac{2}{2^k} \quad (21)$$

The sensitivity is the sum of activities of all inputs

$$s(f) = \sum_{i=1}^k \alpha_i. \quad (22)$$

For the veto functions with m inhibitors and $k - m$ activators, we obtain

$$s(f) = \frac{m(2^{k-m} - 2) + k}{2^{k-1}}. \quad (23)$$

TABLE III: Characterization of veto functions by sensitivity s . Depending on the total number of inputs k and the number m of inhibitors among these, functions would lead to frozen ($s < 1$), critical ($s = 1$), chaotic ($s > 1$) dynamics in the annealed approximation. Only functions without irrelevant (spurious) inputs are considered, so the number of activators is $k - m$.

k	$m = 0$	$m = 1$	$m = 2$	$m = 3$	$m = 4$	$m > 4$
1	critical	frozen	—	—	—	—
2	critical	critical	frozen	—	—	—
3	frozen	chaotic	chaotic	frozen	—	—
4	frozen	chaotic	critical	frozen	frozen	—
> 4	frozen	chaotic	chaotic	frozen	frozen	frozen

The sensitivity is the crucial parameter in the annealed approximation [13, 26]. It predicts a transition from ordered (convergent) to chaotic (divergent) dynamics at a sensitivity value 1 in large networks. For networks homogeneously built with veto functions of m inhibitors and $k - m$ activators, the expected dynamic phase is obtained by evaluating Eq. (23) and listed in Table III. Non-frozen dynamics is rarely obtained. For $k \geq 4$, only $m = 1$ or $m = 2$ lead to $s > 1$, otherwise $s < 1$.

Now let us consider a statistical ensemble of veto functions with k inputs where the number of inhibitors m is distributed binomially with parameter γ . Thus in generating a function, we decide for each of the k inputs independently, if it is taken as an inhibitor (with probability γ) or an activator (with probability $1 - \gamma$). Then the ensemble averaged sensitivity is

$$\langle s \rangle = \sum_{m=0}^k \binom{k}{m} \gamma^m (1 - \gamma)^{k-m} \left[\frac{m(2^{k-m} - 2) + k}{2^{k-1}} \right]. \quad (24)$$

Using

$$\gamma^m (1 - \gamma)^{k-m} 2^{k-m} = (2 - \gamma)^k \left(\frac{\gamma}{2 - \gamma} \right)^m \left(1 - \frac{\gamma}{2 - \gamma} \right)^{k-m} \quad (25)$$

the $m 2^{k-m}$ effectively sums as a binominal distribution with parameter $\gamma/(2 - \gamma)$. We arrive at:

$$\langle s \rangle = \frac{1}{2^{k-1}} [(2 - \gamma)^{k-1} k \gamma - 2k\gamma + k] \quad (26)$$

$$= \frac{k}{2^{k-1}} [(2 - \gamma)^{k-1} \gamma - 2\gamma + 1] \quad (27)$$

This ensemble averaged sensitivity is plotted in Fig. 3. These values $\langle s \rangle$ never exceed 1. In contrast to concrete choices (k, m) , cf. Table III, the ensemble of independent stochastic assignment of inhibitors and activators to veto functions always gives ordered dynamics.

IX. CLOSING REMARKS AND OUTLOOK

The idea of strong inhibitory inputs of veto type has been used in models of neurons before. It dates back

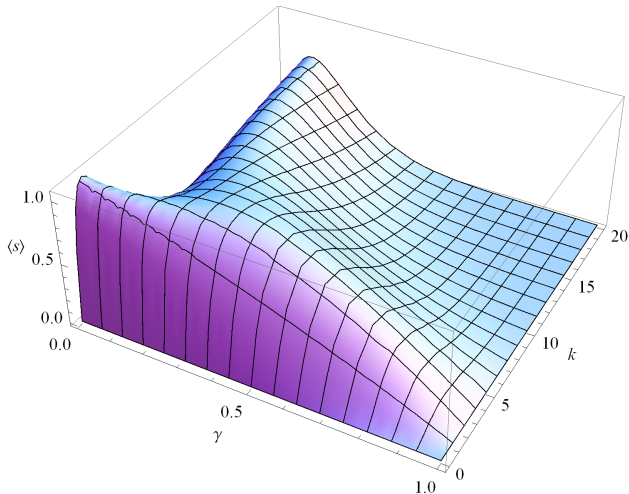


FIG. 3: (Color online) Average sensitivity according to Equation (24) for an ensemble of veto functions with inhibitor probability γ . The number of inputs k is a fixed integer parameter of the ensemble (no averaging over k).

at least to the work by McCulloch and Pitts [27] where the veto of an inhibitor is made explicit as a rule of the model: “The activity of any inhibitory synapse absolutely prevents excitation of the neuron at that time.” Strong inhibition is also used in studies of cell cycle networks in a model with graded (non-Boolean) response

by Burda, Zagorski and co-authors [28, 29]. Networks with veto functions are obtained when discretizing the response functions used in their model.

We identify two directions for immediate further work. Simulations and analytical estimates of networks with veto functions will give a clearer picture of their dynamics in comparison to the other types of functions. Random networks would be taken as a starting point. Similar to recent work on threshold functions [24], the annealed approximation for networks of veto functions would be refined by a self-consistent calculation of the expected intensity, i.e. the fraction of nodes in the on-state.

Classes of functions and their parametrizations are to be explored further, under comparison with empirical data sets. This will lead to more and refined null models being able to separate global effects from network architecture from local ones given by the use of logical functions with particular properties.

X. ACKNOWLEDGMENTS

The authors acknowledge helpful comments from Johannes Rauh (MPI-MiS Leipzig), This work has been funded by VolkswagenStiftung under the call Complex Networks as Phenomena across Disciplines. K. K. acknowledges partial funding by FWF (Austria) through project SFB F43, RNA regulation of the transcriptome.

-
- [1] U. Alon, *An Introduction to Systems Biology: Design Principles of Biological Circuits* (Chapman and Hall, 2006).
- [2] H. de Jeong, *J Comput Biol* **9**, 67 (2002).
- [3] S. A. Kauffman, *J. Theor. Biol.* **22**, 437 (1969).
- [4] S. Bornholdt, *Science* **310**, 449 (2005).
- [5] S. Kauffman, C. Peterson, B. Samuelsson, and C. Troein, *Proc. Natl. Acad. Sci. U.S.A.* **100**, 14796 (2003).
- [6] R. Albert and H. Othmer, *J Theor Biol* **223**, 1 (2003).
- [7] F. Li, T. Long, Y. Lu, Q. Ouyang, and C. Tang, *Proc Natl Acad Sci USA* **101**, 4781 (2004).
- [8] T. Helikar, J. Konvalina, J. Heidel, and J. A. Rogers, *Proc. Natl. Acad. Sci. USA* **105**, 1913 (2008).
- [9] M. I. Davidich and S. Bornholdt, *PLoS ONE* **3**, e1672 (2008).
- [10] M. Davidich and S. Bornholdt, *J. Theor. Biol.* **255**, 269 (2008).
- [11] R.-S. Wang, A. Saadatpour, and R. Albert, *Physical Biology* **9**, 055001 (2012).
- [12] A. Saadatpour and R. Albert, *Methods* **62**, 3 (2013).
- [13] B. Derrida and Y. Pomeau, *Europhys Lett* **1**, 45 (1986).
- [14] B. Drossel, *Reviews of Nonlinear Dynamics and Complexity* **1**, 69 (2007).
- [15] N. E. Buchler, U. Gerland, and T. Hwa, *Proceedings of the National Academy of Sciences* **100**, 5136 (2003).
- [16] S. E. Harris, B. K. Sawhill, A. Wuensche, and S. Kauffman, *Complexity* **7**, 23 (2002), ISSN 1099-0526.
- [17] S. Kauffman, C. Peterson, B. Samuelsson, and C. Troein, *Proceedings of the National Academy of Sciences of the United States of America* **101**, 17102 (2004).
- [18] S. Bornholdt and K. Sneppen, *Phys. Rev. Lett.* **81**, 236 (1998).
- [19] T. Rohlf and S. Bornholdt, *Physica A: Statistical Mechanics and its Applications* **310**, 245 (2002), ISSN 0378-4371.
- [20] K. Binder and A. P. Young, *Rev. Mod. Phys.* **58**, 801 (1986).
- [21] K.-Y. Lau, S. Ganguli, and C. Tang, *Physical Review E* **75**, 051907 (2007).
- [22] W. Just, I. Shmulevich, and J. Konvalina, *Physica D: Nonlinear Phenomena* **197**, 211 (2004).
- [23] P. Rue, A. J. Pons, N. Domedel-Puig, and J. Garcia-Ojalvo, *Chaos* **20**, 045110 (2010).
- [24] M. Rybarsch and S. Bornholdt, *Phys. Rev. E* **86**, 026114 (2012).
- [25] G. Boldhaus, N. Bertschinger, J. Rauh, E. Olbrich, and K. Klemm, *Phys. Rev. E* **82**, 021916 (2010).
- [26] I. Shmulevich and S. A. Kauffman, *Phys. Rev. Lett.* **93**, 048701 (2004).
- [27] W. S. McCulloch and W. H. Pitts, *Bull. Math. Biophys.* **5**, 115 (1943).
- [28] Z. Burda, A. Krzywicki, O. C. Martin, and M. Zagorski, *Proceedings of the National Academy of Sciences* **108**, 17263 (2011).
- [29] M. Zagorski, A. Krzywicki, and O. C. Martin, *Phys. Rev. E* **87**, 012727 (2013).