Stability of Boolean and continuous dynamics

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Regulatory dynamics in systems biology is often described by continuous rate equations for continuously varying chemical concentrations. Binary discretization of state space and time leads to Boolean dynamics. In the latter, the distinction between stable and unstable dynamics is usually made by checking damage after flip perturbations. Here we point out that this notion of stability is incompatible with the stability properties of the original continuous dynamics probed by small perturbations. In particular, random networks of nodes with large sensitivity yield stable dynamics, in contrast to the prediction of chaos obtained by flip perturbations in Boolean networks.

I. INTRODUCTION

The functioning of organisms on the molecular level is a research topic of increasing attention. Survival and reproduction requires an autonomous regulation of chemical concentrations in the living cell. Modeling such regulatory dynamics, various mathematical approaches have been studied, from discrete to continuous methods, from deterministic to stochastic techniques, from static to dynamical models, from detailed to coarse grained perspectives [1], see ref. [2] for an overview.

Boolean dynamics [3–7] is a framework for modeling regulatory systems, especially for precise sequence control as observed in morphogenesis [8] and cell cycle dynamics [9] but also in the regulation of the metabolism [10]. Using binary (on/off) concentrations as an idealization, Boolean dynamics directly implements the logical skeleton of regulation. Values of system parameters such as binding constants, production and degradation rates etc. are not needed. This abstraction simplifies computation and analytical treatment. Boolean networks have been extracted directly from the literature [6, 11] of known biochemical interactions or obtained by discretization of differential equation models [12]. Known state sequences and responses of several systems have been faithfully reproduced by the discrete models.[8, 9]

Despite these benefits, modelers do not employ Boolean dynamics as widely as ordinary or delay differential equations (ODE or DDE). The latter are embedded in an established framework for state-*continuous* dynamical systems [13] which itself builds on the mathematical foundations of linear algebra and infinitesimal calculus. In particular, the definition of *stability* of a solution is based on the consideration of infinitesimally small neighborhoods in state space. Stability checks for solutions of the dynamical equations are a salient part of mathematical modeling. Unstable solutions are not expected to be observed in a real-world system.

For the state-*discrete* Boolean dynamics, an analogous and consistent criterion of stability is lacking because infinitesimally small neighbourhoods in state space cannot be suitably defined. Modelers resort to treating stability in Boolean systems as the resilience with respect to *flip perturbations*. The state of one dynamical variable is changed ("flipped") and the evolution of the *damage* is tracked. The damage is the difference between the state of the perturbed and the unperturbed system. The return map of the expected size of the damage is known as Derrida plot [14]. Numerous statements on the stability of regulatory dynamics with Boolean states are based on flip perturbations [15–20].

Defining stability by the response to flip perturbations has advantages for practical computation and analytical tractability. However, the concept of flip perturbations is distinct from the usual notion of stability in continuous dynamical systems formulated as differential equations.

Here we show that the stability of regulatory dynamics cannot be inferred by probing the system with flip perturbations. In particular, the so-called chaotic phase in random Boolean networks does not appear under small perturbations, see Figure 1. We use a hybrid model based on differential equations while incorporating Boolean dynamics. In this hybrid dynamics both flip perturbations and small perturbations are applicable. Before quantifying the distinct effects of the two types of perturbations in large random networks, we illustrate concepts with the example of a bistable switch.

II. BOOLEAN AND CONTINUOUS DYNAMICS

An n-dimensional Boolean map $f : \{0,1\}^n \to \{0,1\}^n$ gives rise to a time-discrete dynamics

$$x(t+1) = f(x(t)) \tag{1}$$

with $x = (x_1, \dots, x_n)$ being a Boolean state vector (bit string) of n entries. Such a map is equivalent to a *Boolean network*. When f is pictured as a network, a node corresponds to a coordinate i of the Boolean state vector and a directed edge $j \to i$ (from node j to node i) is present if the Boolean function f_i explicitly depends on the j-th coordinate.

Let us now define a continuous dynamics whose discretization readily leads to the Boolean map in Eq. (1).

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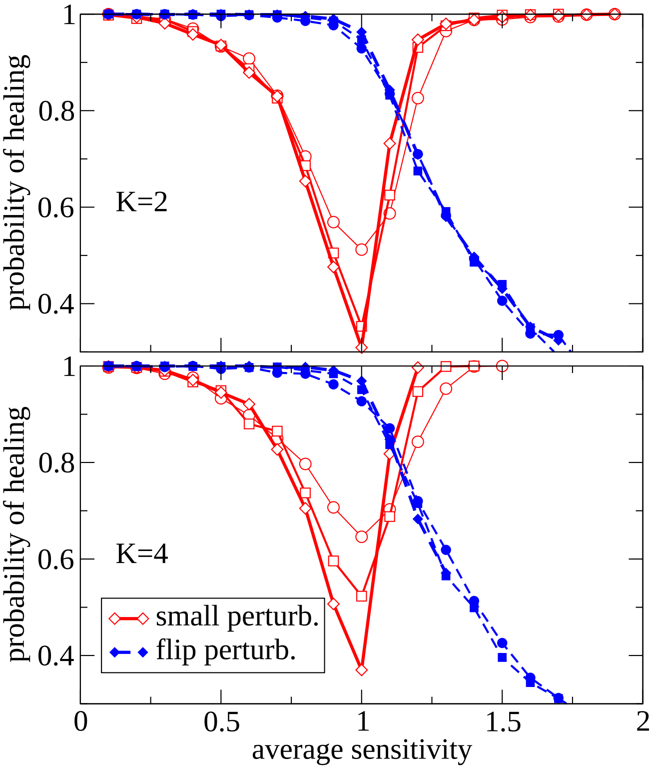

FIG. 1: Stability of dynamics in random networks under perturbation by spin flip (blue) and under continuous perturbation (red) in random networks with $K = 2$ and $K = 4$ inputs per node. Symbols distinguish system size $n = 300$ ($\circ$), 1000 ($\square$) and 3000 ($\diamond$). Each data point gives the relative frequency of healed out perturbations on a set of 10^4 independent random realizations of network, initial condition and perturbation.

Taking values $y_i(t) \in [0, 1]$, $i \in \{1, \ldots, n\}$, $t \in \mathbb{R}$, the states evolve according to the delay differential equation.

$$\dot{y}_i(t+1) = \alpha \operatorname{sgn}(\tilde{f}(y(t)) - y_i(t+1)) \tag{2}$$

with α an inverse time constant. For large α, this is essentially Boolean dynamics with fast but continuous switching between the saturation values. The simplest choice is $\tilde{f} = f \circ \Theta$ with Θ the component-wise step function, $\Theta_i(y) = 1$ if $y_i \geq 1/2$ and $\Theta_i(y) = 0$ otherwise. This choice of continuous dynamics is in close correspondence with the discrete dynamics in the following sense. Suppose $x(0), x(1), x(2), \ldots$ is a Boolean time series solving Eq. (1). Let $y(t)$ be a solution of Eq. (2) such that there is a time interval $[t_1, t_2]$ with $y(s) = x(0)$ for all $s \in [t_1, t_2]$. Then for all future times $t \in \mathbb{N}$ and all $s \in [t_1, t_2]$

$$x(t) = y(\beta t + s) \tag{3}$$

with $\beta = 1 + 1/(2\alpha)$. The closest resemblance between Boolean and continuous dynamics is obtained when choosing the same initial condition, that is $y(s) = x(0)$ for all $s \in [-1, 0]$. Similar correspondence between Boolean maps and ordinary differential equations has been studied earlier neglecting transmission delay [21] or implementing more complicated differential equations [22–25] compared to Equation (2).

III. PERTURBATIONS

Given a map f, the evolution of states is uniquely determined by Eq. (2) after giving an initial condition $y(t)$ on a time interval of unit length, here taken as $[-1, 0] =: I$. Here we restrict ourselves to initial conditions that do not vary on I, $y(t) = y(0)$ for all $t \in I$. An initial condition with a *small* perturbation is generated as

$$y'_i(t) := \epsilon_i(1 - y_i(t)) + (1 - \epsilon_i) y_i(t) \tag{4}$$

for $t \in I$. The perturbation amplitudes are arbitrary numbers $\epsilon_i \in]0, 1/2[$. An initial condition with a *flip* perturbation is generated as

$$y^!_i(t) := \begin{cases} 1 - y_i(t) & \text{if } i = l \\ y_i(t) & \text{otherwise} \end{cases} \tag{5}$$

for $t \in I$ and an arbitrary node $l \in \{1, \ldots, n\}$. Note that the total amplitude $\sum_i \epsilon_i$ of a small perturbation may exceed the unit amplitude of a flip perturbation. A small perturbation produces small deviations from the original state potentially at each node. A flip perturbation concentrates a maximal deviation at a single node.

We say that the system *heals* from the perturbation if the dynamics from perturbed and unperturbed initial condition eventually become the same except for an arbitrary time lag. Formally, healing from a small perturbation means that there are $t_0 > 0$ and $\tau > -t_0$ such that

$$y(t) = y'(t + \tau) \tag{6}$$

for all $t \geq t_0$. Healing from a flip perturbation means that Eq. (6) holds analogously for $y^!$ instead of y'. We define the heal time t_{heal} as the smallest time t_0 for which this holds. This definition of healing is stronger than the usual one requiring convergence towards but not equality to the unperturbed dynamics.

IV. FIXED POINTS AND BISTABLE CIRCUITS

Let us first consider a fixed point as the simplest dynamical behaviour. A fixed point of the continuous dynamics is a state vector y^* such that constant $y(t) = y^*$ is a solution of Eq. (2). This in turn means that the time derivative vanishes at all times, equivalent to $y^* = f(y^*)$. The fixed points of the continuous dynamics are exactly the fixed points of the discrete map f.

A small perturbation to a fixed point y^* always heals, because values after applying the treshold Θ remain unchanged, $\tilde{f}(y'(t)) = y^*$ for all $t \in I$. All fixed points are stable.

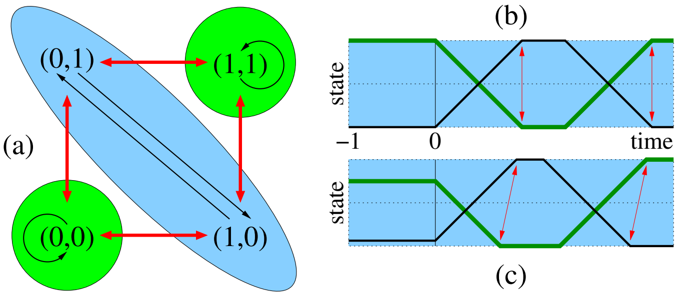

FIG. 2: Dynamics of two mutually activating nodes. (a) State space of the Boolean system described by Eq. (7). Thin arrows indicate the mapping f of states by the dynamics, thick bidirectional arrows stand for flip perturbations. Indicated by shaded areas, the system has three dynamical modes (attractors): two fixed points $(0,0)$ and $(1,1)$ and a cycle of length 2 involving the states $(0,1)$ and $(1,0)$. (b) Time evolution of the corresponding continuous system in Equation (2) with initial condition $x_1(0) = 1$ (thick curve) and $x_2(0) = 0$ (thin curve). The two nodes switch in a synchronous mode as indicated by vertical double arrows akin to the Boolean state sequence $(0,1),(1,0),(0,1),\ldots$. (c) Time evolution from perturbed initial condition, $x_1(0) < 1$, $x_2(0) > 0$. The perturbation translates into a phase lag in switching that does not heal out.

In contrast, a flip perturbation to a fixed point does not always heal. The *bistable switch* is an example. Consider a two-dimensional map f with $f(x_1,x_2) = (x_2,x_1)$. It gives rise to the dynamics

$$x_1(t+1) = x_2(t) \qquad x_2(t+1) = x_1(t) \tag{7}$$

with fixed points $(0,0)$ and $(1,1)$. After perturbing a fixed point by flipping one node's state, the system does not return to the fixed point. It remains in the set of the state vectors $(0,1)$ and $(1,0)$ constituting a limit cycle, cf. Figure 2(a). The stability of the fixed points is not obtained when probing the dynamics with flip perturbations. The bistable switch constitutes a first simple example to demonstrate that probing the dynamics with flip perturbations does not lead to correct stability classification.

In the continuous counterpart of the alternating Boolean state $(0,1)$ and $(1,0)$, small perturbations do not heal, see Figure 2(b,c). The effect of a small perturbation is to induce a phase lag in the oscillation, being discussed in earlier work [23, 26–28].

V. STABILITY IN RANDOM NETWORKS

We now assess the expected extent of misclassification of stability by comparing the effects of the two types of perturbations on dynamics in randomly constructed systems. These are generated drawing randomly for each node i a set of K input nodes and assigning i a Boolean function that is dependent only on the input nodes. Boolean functions are chosen maximally random among those with K inputs under the constraint of a given average sensitivity $\langle s\rangle$.

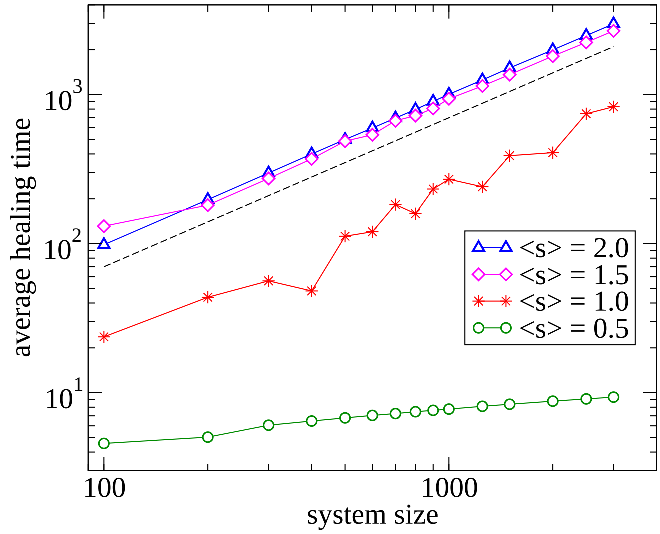

FIG. 3: The average time to heal from a small perturbation increases linearly with the number of nodes in the system for sensitivity $\langle s\rangle \geq 1$, and sublinearly otherwise. The dashed line has slope 1 in this double-logarithmic plot. Each data point is the average over t_{heal} for the subset of healing realizations. For each choice of $\langle s\rangle$ and system size N, 10000 random network realizations with $K = 2$ inputs per node are considered (same as in Figure 1).

Figure 1 shows how dissimilar dynamics reacts to two different kinds of perturbations. Under *flip perturbations*, the known result for random Boolean networks is reproduced as follows. For small values of the average sensitivity $\langle s\rangle$, the dynamics is frozen on a single fixed point such that flips are mostly irrelevant for asymptotic behaviour. In networks with increasing $\langle s\rangle$, the asymptotic state sequence is more and more dependent on the details of the initial condition such that flip perturbations tend not to heal. For large networks, a transition between the regimes of healing and non-healing flip perturbations is observed at $\langle s\rangle = 1$.

The healing of *small perturbations*, however, shows a quite different dependence on $\langle s\rangle$. Only in the so-called critical region of $\langle s\rangle \approx 1$, healing probability is low. Both for $\langle s\rangle \ll 1$ and $\langle s\rangle \gg 1$, healing probability tends towards 1. This effect is enhanced by increasing system size. In the limit of $n \to \infty$ one may expect a finite probability of non-healing only at $\langle s\rangle = 1$. Then the dynamics is almost always stable under small perturbations.

The average time t_{heal} to heal from small perturbations increases moderately with system size as shown in Figure 3. For average sensitivity above 1, we observe a linear increase

$$\langle t_{\text{heal}}\rangle \propto N\ . \tag{8}$$

For lower values of the average sensitivity, the increase is sublinear.

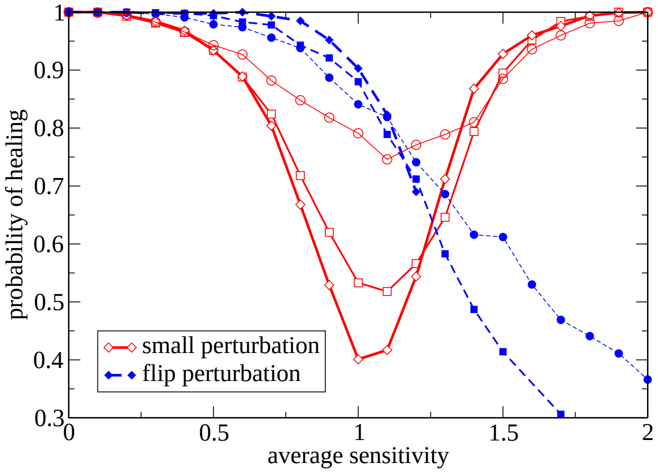

FIG. 4: Healing probabilities remain qualitatively the same (cf. Figure1) when using the alternative transfer function (12). Each data point is the healing fraction of 1000 realizations of with given average sensitivity and system size $n = 30$ (○), 100 (□) and 300 (◇). Small perturbations are generated by drawing ϵ_i from the flat distribution on $[0; 0.01]$ independently for each node i, cf. Equation (4).

sensitivity	$\langle s \rangle < 1$	$\langle s \rangle = 1$	$\langle s \rangle > 1$
flip perturbation	heals	prevails	prevails
small perturbation	heals	prevails	heals
number of attractors	small	large	large

TABLE I: Overview of dynamical regimes of random Boolean networks with respect to the average sensitivity as a parameter. The regime of large average sensitivity ($\langle s \rangle > 1$) combines dynamical versatility (many attractors) and responsiveness to environmental triggers (flip perturbations) with resilience to noise (small perturbations).

The dynamics we have studied so far is simple but not the only possibility to pass from the Boolean map to a continuous flow. In order to check to what extent our results depend on this choice we repeat simulations for $K = 2$ with an alternative function $\tilde{f}$ taking into account cooperative effects between regulatory inputs (see Methods). Figure 4 shows that the same qualitative result obtains under this choice.

VI. DISCUSSION

We have shown that the dynamics of large random networks of switch-like elements typically recovers from small perturbations of the state vector. Healing is observed naturally at low sensitivity. i.e. a weak dependence of the logic functions on their inputs. Surprisingly, however, also large sensitivities of functions lead to a system behaviour that is insensitive to small perturbations in the initial condition. Inherent instability is observed only in an intermediate sensitivity regime that shrinks as systems become larger.

This finding may at first sight appear to be incompatible with the established stability diagram of random Boolean networks (RBN), being the time- and state-discrete representations of the aforementioned systems of switch-like elements. RBN display a transition from healing to non-healing (damage spreading) behaviour at a critical average sensitivity of 1, when subject to *flip* perturbations. These particular perturbations tend not to heal in random networks of highly sensitive functions. The tacit assumption that flip perturbations are sufficient to probe the stability of the dynamics lead to the hypothesis that networks of regulatory switches position themselves at this transition [29], known as the *edge of chaos* [30]. This would cause some but not all flip perturbations to spread and therefore allow for complex information processing without rendering the system unreliable under noise.

We argue that the apparent conflict between responsiveness to input signals and resilience under noise dissolves when these influences are translated into perturbations at their respective scales: noise corresponds to small perturbations whilst trigger signals are interpreted as the flipping of a state. Under these assumptions, noise resilience and responsiveness are compatible rather than conflicting. Systems that combine both beneficial properties are obtained "for free" in random networks of sufficiently sensitive switch-like elements, see also Table I. On the other hand, tuning the average sensitivity of functions down to the transition point is unnecessary and undesirable since it renders the dynamics least noise resilient.

VII. METHODS

A. Random Boolean Networks

A random Boolean network with N nodes and in-degree K is generated as follows. For each node i, draw K pairwise different nodes $s(i,1), s(i,2), \ldots, s(i,K)$ from which i receives input. A self-coupling $s(i,j) = i$ is allowed. Then for each node i, a Boolean function $f_i : \{0,1\}^K \to \{0,1\}$ is drawn from a distribution π. This distribution π defines a statistical ensemble of Boolean functions.

B. Ensembles of Boolean functions

The important parameter for the ensemble is the average *sensitivity* [31]. The sensitivity of a Boolean function f with K inputs is

$$s(f) = 2^{-K} \sum_{x \in \{0,1\}^K} \sum_{i=1}^{K} |f(x) - f(x^{[i]})| \qquad (9)$$

where $x^{[i]}$ denotes the Boolean vector x after negating the i-th component. Thus $s(f)$ is K times the probability that the value of f changes when exactly one of its K arguments changes.

Here we specify π as the maximum entropy ensemble under a given average sensitivity

$$\pi_\lambda(f) \propto \exp(\lambda s(f)) \tag{10}$$

with appropriate normalization and λ as a free parameter. For $\lambda > 0$, average sensitivity $\langle s \rangle > 1$ is obtained for $K \leq 2$.

An alternative and more commonly used ensemble is

$$\pi_p(f) = p^{c_1(f)}(1-p)^{c_0(f)} \tag{11}$$

with $c_b(f)$ being the number of Boolean vectors x with $f(x) = b$, $b \in \{0, 1\}$. This amounts to a random generation of Boolean functions by independently placing rule table entries, a 1 occurring with probability p. For $K = 2$ and average sensitivity $\langle s \rangle = 1$, the two ensembles coincide.

C. Transfer functions

For the results in Figures 1 and 3, the standard transfer function $\tilde{f} = f \circ \Theta$ is used: each continuous state is mapped to a Boolean value separately by applying a threshold at 1/2. Then the node's Boolean function is applied to decide if its own state value would rise towards 1 or falls towards 0, cf. Equation (2).

The alternative transfer function $\tilde{f}$, used to obtain results in Figure 4, is defined by

$$\tilde{f}_i(y) = \Theta(h_i(y)) \tag{12}$$

with

$$h_i(y) = a y_j y_k + b_1 y_j + b_2 y_k + c \tag{13}$$

for node i taking inputs from nodes j and k. The parameters a, b_1, b_2, c are chosen such that $h_i(y) = f_i(y)$ for $y_j, y_k \in \{0, 1\}$. If, for instance, f_i is an AND then $a = 1$ and $b_1 = b_2 = c = 0$ so $\tilde{f}_i(y) = 1$ if and only if $y_j y_k \geq 1/2$.

D. Integration

Equation (2) is integrated with the standard Euler method using a time increment $\Delta t = 10^{-4}$ and cross-checking the results with $\Delta t = 10^{-5}$. Integration is speeded up by exploiting the piece-wise linearity of the solution. At any time t, a possibly large time horizon $t_{\text{bound}}(t)$ is calculated such that all target values $\tilde{f}(t'-1)$ are constant on $[t, t_{\text{bound}}(t)[$. Then the state values are calculated at time $t_{\text{bound}}(t)$ and the step is iterated.

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