

Stable and unstable attractors in Boolean networks

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Boolean networks at the critical point have been a matter of debate for many years as, e.g., the scaling of numbers of attractors with system size. Recently it was found that this number scales superpolynomially with system size, contrary to a common earlier expectation of sublinear scaling. We point out here that these results are obtained using deterministic parallel update, where a large fraction of attractors are an artifact of the updating scheme. This limits the significance of these results for biological systems where noise is omnipresent. Here we take a fresh look at attractors in Boolean networks with the original motivation of simplified models for biological systems in mind. We test the stability of attractors with respect to infinitesimal deviations from synchronous update and find that most attractors are artifacts arising from synchronous clocking. The remaining fraction of attractors are stable against fluctuating delays. The average number of these stable attractors grows sublinearly with system size in the numerically tractable range.

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Boolean networks at the critical point (sometimes also called Kauffman networks) have been discussed as simplified models for gene regulation networks for many years [1–3]. We currently experience a renewed interest in these models, as the structure and dynamics of the genetic network in a living cell become visible thanks to new powerful experimental techniques (DNA chips) [4]. From the theorist's point of view, Boolean networks exhibit interesting statistical mechanics with a prominent order/disorder phase transition [5]. Earlier, the critical state has been postulated to have some relevance in the biological context as the scaling properties of numbers of attractors with network size appeared to resemble how numbers of cell types scale with the amount of genetic information when comparing simple and complex organisms [3]. Until recently it was believed that the total number of attractors increased as \sqrt{N} [3]. This has been falsified by improved simulation techniques [6] and subsequently it was shown that the total number of attractors grows even faster than any polynomial [7,8].

Let us step back for a moment and reconsider Kauffman networks, in the context of their original motivation, as models for biological systems. While the use of models discrete in time is an established approach in many circumstances of biological modeling, such idealizations always have to be treated with special care. In the case of Kauffman networks, the system evolves by a synchronous update of all nodes at integer values of time. Such a clocking, however, can produce spurious synchrony. For instance, subsystems are kept phase synchronized even if they are not interacting at all. In order to circumvent computational artifacts it has been suggested to use a more natural updating schedule [9]. For example, it has been shown that the complex spatiotemporal patterns observed under synchronous update often disappear when units are updated asynchronously [9–11].

In this paper we reconsider Boolean networks at criticality, while destroying spurious synchrony by equipping the nodes with weakly fluctuating response delays. This allows

us to analyze the stability of dynamical attractors in the discrete network model. A deterministic Kauffman network at an attractor is perturbed by a slight shift of update events forward or backward in time. If all such perturbations die out, i.e., the system returns to the identical attractor, we call this attractor “stable.” Otherwise ongoing temporal fluctuations accumulate and drive the system away from the attractor. These latter cases correspond to attractors that are an artifact caused by synchronous update of the deterministic system. When systematically applying this method to Kauffman networks we obtain as a main result that the number of stable attractors grows sublinearly with system size [see Fig. 1(a)].

Let us study a Kauffman network composed of N binary nodes where each node determines its state x_i by applying a Boolean function (a rule table) $f_i: \{0, 1\}^2 \rightarrow \{0, 1\}$ on inputs received from two other nodes $a(i)$ and $b(i)$, according to a randomly chosen quenched topology. To be definite, we exclude self-couplings. States of the nodes are synchronously updated at integer times t according to the Boolean function

$$x_i(t+1) = f_i(x_{a(i)}(t), x_{b(i)}(t)). \quad (1)$$

The network itself as defined by f_i , $a(i)$, and $b(i)$ remains constant in time. For arbitrary initial condition $[x_1(0), x_2(0), \dots, x_N(0)]$, the finite discrete state space of 2^N possible states ensures that, eventually, a state reappears that has been encountered before. From thereon, the deterministic system will indefinitely follow the attractor it reached. Different initial conditions may lead to the same or to a different attractor. The total number of attractors is a characteristic property of a network. The expected number of cycles in an ensemble of random Kauffman networks has been shown to increase superpolynomially with system size N [7].

Let us now define a criterion for stability of an attractor in the presence of deviations from deterministic parallel update.

For this purpose, we replace the discrete update times by a continuous time variable t where nodes may update at any point in time. Our goal is to slightly desynchronize the dynamics of the network by shifting the individual updates of nodes to earlier or later time points. To prevent this from generating spurious spikes during transitional phases (e.g., when several signals interact that used to be simultaneous, but now arrive at different times), nodes have to be prevented from switching on a time scale s much shorter than the original integer update time step (i.e., $s \ll 1$). This is implemented by a low-pass filter that averages out fluctuations on short characteristic times scales s , namely by averaging over the input signal according to

$$x_i(t+1) = \Theta \left[(2s)^{-1} \int_{t-s}^{t+s} f_i(x_{a(i)}(t), x_{b(i)}(t)) dt - 1/2 \right], \quad (2)$$

where Θ is the step function with $\Theta(h)=1$ for $h \geq 0$ and $\Theta(h)=0$ otherwise. Let us briefly check how this works. Imagine node $a(i)$ switches on at time t , node $b(i)$ switches off at time $t+\epsilon$, while f_i is the function AND. Without a low-pass filter ($s=0$), node i switches on at time $t+1$ and off again at time $t+1+\epsilon$. For $s > \epsilon$, the spurious spike is filtered out, i.e., node i remains constant. In the limit of fast switching time scale $s \rightarrow 0$, Eq. (2) converges towards Eq. (1). In particular, all synchronous solutions of Eq. (1), i.e., solutions with nodes switching precisely at integer values of t , are solutions of Eq. (2) for arbitrary $s < 1/2$, as well.

In order to check the stability of a network against small fluctuations in the timing of the switching events, we perturb the system at some time T by temporarily retarding a fraction of the switching events. Thereby, a subset of nodes that would normally change state at time T is kept frozen in their present state during the time interval $[T, T+\epsilon]$ with $\epsilon < s$. After $t=T+\epsilon$, we let the system evolve as usual according to Eq. (2). The original and the perturbed solutions differ only on time intervals $[t, t+\epsilon]$ for integer t . In general, the perturbation may propagate, i.e., for each integer $t \geq T$ some units flip at time t while others flip at time $t+\epsilon$ in the perturbed solution. If, however, there is a later integer time $t^* > T$ such that either (I) no flips occur at time $t^*+\epsilon$ or (II) no flips happen at time t^* , the perturbation has healed out and the system has regained synchrony. Then, at times $t \geq t^*$, the perturbed and the original solutions are either identical [case (I)] or identical up to a global phase shift ϵ [case (II)]. We call an attractor stable if for all possible perturbations of the above type (i.e., for all possible permutations of perturbed and non-perturbed nodes) the system regains synchrony and the original attractor is stabilized within a finite time interval. Otherwise the attractor is called unstable. This stability criterion is robust under variation of the perturbation scheme, including the case of different time lags ϵ_i for different nodes i . In real-world situations, ongoing perturbations may cause accumulating phase shifts in the unstable case. This eventually leads to a change in time ordering of the switching events, which may shift the system into a different attractor. With this we choose here a particularly simple criterion for the stability of an attractor in a discrete dynamical network in

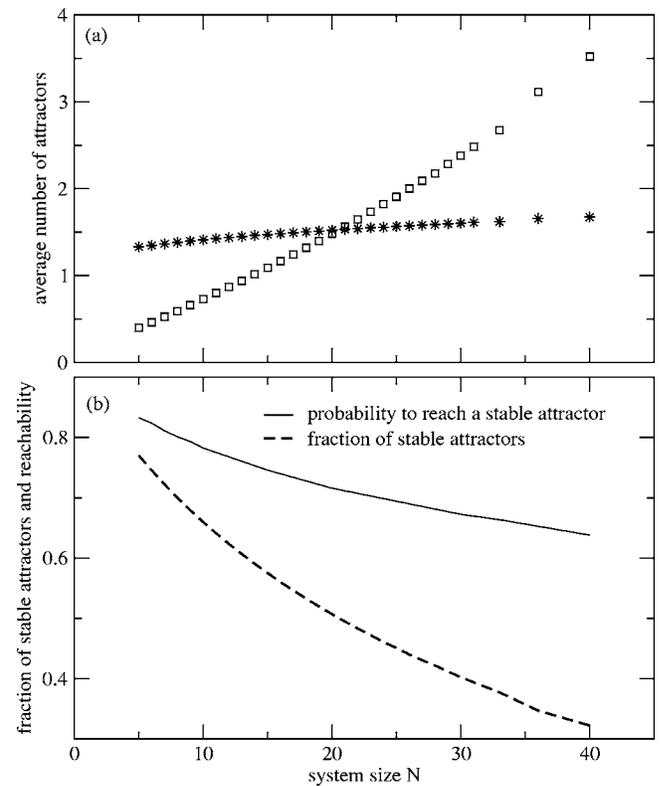


FIG. 1. Frequency and accessibility of stable and unstable cycles in Kauffman networks. (a) Average number of stable (*) and unstable (□) attractors as a function of the number of nodes in the network. (b) Fraction of initial conditions leading to a stable attractor (solid line) and the ratio between numbers of stable and all attractors (dashed line). Data points in (a) are averages over R independent realizations of the Kauffman network, $R=10^7$ for $N < 24$, $R=10^6$ for $24 \leq N \leq 31$, and $R=10^4$ otherwise. For increasing computational speed the networks are subject to the decimation procedure [6] before simulation. For the decimated network we fully enumerate the state space such that it is certain that all cycles are detected. Sizes of basins of attraction in (b) have been estimated in 10^5 networks, testing 100 randomly chosen initial conditions in each original network (no decimation applied).

the presence of noise. The system is on a stable attractor if after each small perturbation it reaches the attractor again. On unstable attractors, such time lags do not relax. This scenario is better suited as a stability criterion than stochastically adding or removing switching events [12,13], which does not allow for the limit of infinitesimally weak perturbations. Furthermore, the low-pass filter characteristics used here are well motivated by the dynamics of biochemical switches [14] where molecule concentrations typically respond slowly, leading to overall low-pass filter characteristics of the switch. This natural property of genes is a simple means of stabilization which is of low cost and ubiquitous in nature.

Applying our stability criterion to random Boolean networks at criticality, one observes that the average number of all attractors, stable and unstable ones, grows much faster than the average number of stable attractors alone [see Fig. 1(a)]. In large networks, almost all attractors are expected to be unstable. Interestingly, the probability to reach a stable

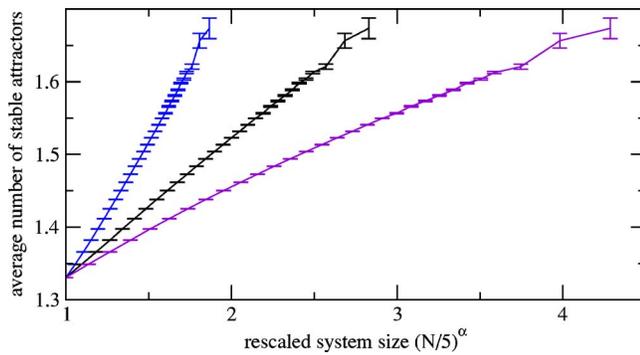


FIG. 2. (Color online) System size scaling of the number of stable attractors plotted as a function of the rescaled number of nodes $(N/5)^\alpha$ with $\alpha=0.3, 0.5, 0.7$ (left to right). Error bars in (b) indicate standard deviation divided by \sqrt{R} with ensemble size R (cf. Fig. 1).

attractor from a random initial condition is much larger than the fraction of stable attractors, as shown in Fig. 1(b). Thus, unstable attractors typically have significantly smaller basins of attraction than stable attractors. The main result is that, with system size N , the number of stable attractors grows sublinearly as $\sim N^\alpha$ with $\alpha \approx 0.5$, as shown in Fig. 2 in the numerically feasible range of $N \leq 40$. A least-squares fit of the form $c + bN^\alpha$ fits best ($\langle \chi^2 \rangle = 0.00013$) with the parameter values $\alpha = 0.448$, $c = 1.107$, and $b = 0.108$ (with a correlation coefficient for this fit of $r = 0.999742$). The number of stable attractors varies broadly around the mean value, e.g., for $N = 30$, where we observe a mean value of 1.6, the fraction of realizations with more than k stable attractors is 0.009 for $k=5$ and 8.7×10^{-4} for $k=9$. The Poisson distribution with the same mean has $P(>5) \approx 0.006$ and $P(>9) \approx 7 \times 10^{-6}$.

Let us further analyze the number l of states contained in the attractors. While stable attractors are shorter on average

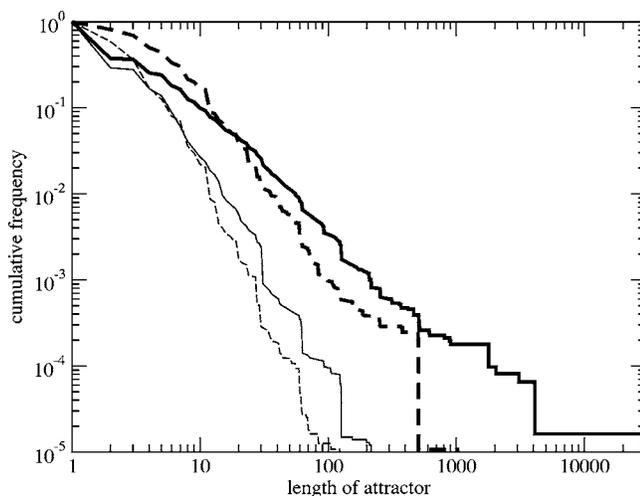


FIG. 3. Statistics of attractor lengths for networks with $N=10$ (thin curves) and $N=30$ (thick curves). The cumulative distribution is shown for stable attractors (solid lines) and unstable attractors (dashed lines). For $N=10$ nodes the average length of stable attractors is $\langle l \rangle_{\text{nat}} = 2.59$; of unstable attractors $\langle l \rangle_{\text{art}} = 3.56$; for $N=30$ we find $\langle l \rangle_{\text{nat}} = 5.50$ and $\langle l \rangle_{\text{art}} = 7.16$.

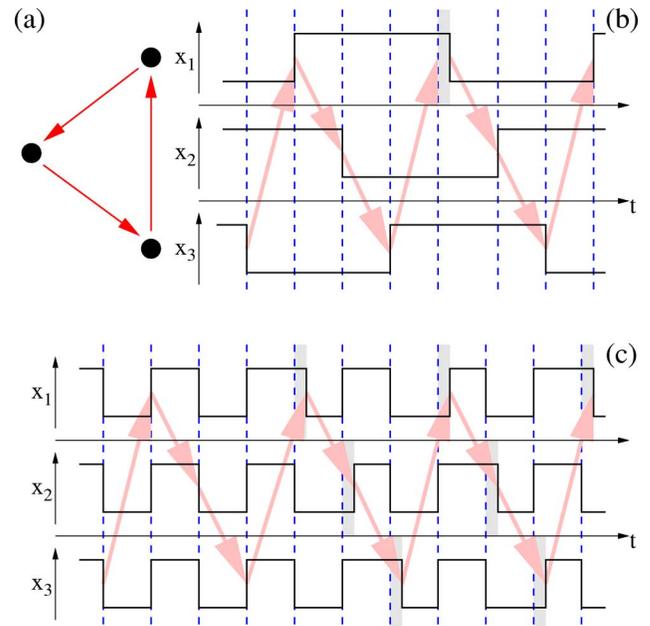


FIG. 4. (Color online) A stable and an unstable attractor in the same system. (a) Three nodes forming a feedback loop. Each node i performs the Boolean function negation on the input from its predecessor j , i.e., $x_i(t+1) = 1 - x_j(t)$. (b) Temporal evolution of a stable attractor. There is a unique causal chain of flipping events (thick arrows). A retarded update (shaded box) retards all subsequent events by the same amount of time. Thus, perturbations heal immediately. (c) An unstable attractor consisting of three independent chains of flipping events propagating along the cycle of nodes. One of these chains is indicated by thick arrows. Retarding an event affects subsequent events in the same causal chain only. Causal chains remain phase shifted. The system does not regain synchrony after a perturbation.

than unstable attractors, the distribution of attractor lengths is broader for stable than for unstable attractors, as shown in Fig. 3. The majority of long attractors with lengths far above average are stable.

Can we understand by a simple picture how unstable attractors differ from stable ones? Most obviously, unstable attractors occur when the network falls into two or more noninteracting clusters. When all updates in one of the clusters are delayed by the time ϵ , this phase lag with respect to all other clusters cannot heal. All attractors with flipping events in more than one network cluster are unstable. However, also in networks consisting of a single cluster unstable attractors are found. Figure 4 illustrates the coexistence of a stable and an unstable attractor in a small connected network. The example suggests that an attractor is stable if there is a single cascade of switching events. Let us consider the minimal number of simultaneous flipping events

$$m = \min_t \{ | \{ i | x_i(t) \neq x_i(t+1) \} | \} \quad (3)$$

for a given attractor. The attractors with $m=0$ are the fixed points. These are stable by definition because no flipping events are to be retarded. Attractors with $m=1$ are stable as well. These attractors contain a step with only a single flip-

ping event. Going through this step the system always regains synchrony. For $m \geq 2$ the attractor is likely to contain several chains of causal events as in Fig. 4(c). In the simulations we find that a large fraction u of the attractors with $m \geq 2$ is unstable, $u=0.856, 0.882, 0.899, 0.9094$ for $N=10, 20, 30, 36$, respectively. Thus the minimal number of simultaneous flipping events m allows for an almost perfect distinction between stable and unstable attractors, where m is measured in the decimated networks [6].

Comparing these results to past studies of random Boolean networks at criticality ($K=2$ inputs per node), we obtain a distinctly different picture: Only a small fraction of attractors are at all stable against small amounts of noise. Or, put differently, the effect of spurious synchronization due to a parallel update mode has been underestimated in previous studies, at least where these studies have been made with a potential application to biological systems in mind. In particular, characteristic properties of the attractor statistics are different when considering the subset of stable attractors: The average number of stable attractors scales less than linearly while the number of unstable attractors shows a faster, superlinear growth with N in the simulations. A similar scaling has been observed in a different approach to asynchronous Boolean networks [15]. Also, stable attractors have a significantly larger basin of attraction than unstable ones.

This latter property might have been the reason for the long prevalence of the opinion that the total number of attractors scales as \sqrt{N} [3]. Mainly these stable attractors were likely to be found in the early studies using sparse sampling.

Biological networks are of course far from random and random network models can at best describe few aspects of real systems (we study the role of specific topologies elsewhere [11]). If one aims at discussing random Boolean networks as simplest models for biological signaling networks, our study suggests to consider more carefully the question of which attractors are at all relevant to the biological system. Kauffman's hypothesis, that the number of attractors in critical random Boolean networks exhibits a similar scaling with system size as the number of cell types with genome size in organisms [3], seems to be wrong in light of the results by Troein and Samuelsson [7]. However, it appears to be still open to debate when considering solely the subset of stable attractors.

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