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Random Boolean networks response to external periodic signals

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Abstract

Random Boolean networks have been proposed as discrete models of genetic networks. Depending on the values of their control parameters, these networks fall by themselves in order or disorder phases. These networks are autonomous systems: no external inputs are considered. Nevertheless, in the real world the genetic networks are influenced by external signals. Many biological rhythms have 24-h periods related to sunlight, coupled with molecular clocks. In this work we study the response of Random Boolean Networks to analytical and non-analytical external periodic signals. The relationship between external and internal parameters for the determination of the dynamical behaviour of this networks is theoretically determined and simulations in agreement with these theoretical results are reported.

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1. Introduction

Discrete models have been employed as a description of several biological networks such as neural networks, immune system or ecological networks for example [1,2]. Given that modelling those biological system through thousand of coupled differential equations results impracticable, a statistical approach to study the discrete models has been widely used, reporting a great amount of understanding about biological systems.

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A classical example are random Boolean networks (RBN) which were proposed [2,3] as discrete genetic networks models. RBN are composed by several genes (automata). The state of a gene is represented by only two possible values (on–off). This state is only influenced by the states of another genes and vice versa. The mutual interaction is, then, done by the connection diagram of the system and the local dynamical rules. The dynamical behaviour of RBN exhibit a order–disorder phase transition: the order presented by these networks is a typical example of global emergence from local rules in complex systems [4]. The similarity of RBN with another theoretical random disorder models, such as spin glasses, is clear. However, it is not possible to define a Hamiltonian for RBN. For this reason RBN have become a theoretical challenge and new approaches to study them have been developed [5–9].

The dynamical behavior of the RBN is not influenced by external inputs. The system is, therefore, autonomous, using the language of dynamical systems [1]. Nevertheless, in the genome there are also external signals that affect it and regulate its behaviour [10]. In fact, the first well-known gene regulation, the operon model, shows this behaviour: the presence or absence of lactose in the medium activates or inhibits the transcription of the β-galactosidase gene in a *E. coli* bacteria.

More important for the purpose of this article are the possible periodical external inputs to the genome. Many biological rhythms have 24-h periods related to sunlight [11]. A recent example of this type of circadian rhythm is the molecular control of the daily flight cycle in Drosophila, regulated via genes [12]. Two proteins, PER and TIM, expressed by the genes *per* and *tim*, respectively, are directly involved in this control. Two other proteins, CYCLE and CLOCK, activate the genes *per* and *tim*. On the contrary, the abundance of the so expressed proteins PER and TIM deactivates the genes *per* and *tim*, acting as a negative feedback which stops the production of PER and TIM. During the day, light disintegrates the molecules PER and TIM. Then the molecules CYCLE and CLOCK activate again the genes. Therefore, *per* and *tim* genes have a cycle of activation–disactivation controlled by the sunlight. The recent discovery of PER homologues in mice and humans suggests that a related mechanism controls mammalian circadian rhythms [13].

Inspired by the existence of extracellular signals to genome in the real world, we will study the influence of external inputs to the RBN. In concrete, in this work we want to study how the dynamical behaviour of the RBN changes with the presence of periodic external signals. In previous articles [14,15] it was shown how a disordered RBN could be controlled (its behaviour changes from disordered to ordered) with a concrete kind of pulse function. In this work we are going to generalise previous results using any periodic function.

The article is organised in the following manner: in Section 2, RBN are defined. Their possible dynamical behaviours are described and their critical transition is pointed out. In Section 3 we present how to control RBN using periodic functions, we determine the relationship between parameters in the system to achieve control and we report simulations in agreement with these theoretical results. In Section 4 we show how to extend the results to non-analytical inputs in the form of networks controlling networks. And finally, in Section 5, a summary of the general results and possible extensions is given.

2. RBN

RBN [2] are systems composed of a number N of automata ($i = 1,\ldots,N$) with only two states available (say 0 and 1 for instance). Each automaton represents a gene active ($1 \equiv$ transcription process is active) or inhibited ($0 \equiv$ no transcription process is present). Each automaton i has associated a Boolean function f_i of K Boolean arguments that will be used to update the automaton state at each time step. These functions describe how a gene is regulated by other genes. Each automaton i will then have associated K other automata $i_1, i_2, \ldots, i_K$ (the inputs or vicinity of i), whose states $(x_{i_1}, x_{i_2}, \ldots, x_{i_K})$ will be the entries of f_i. That is, the automaton i will change its state x_i at each time step according to the rule

$$x_i(t+1) = f_i(x_{i_1}(t), x_{i_2}(t), \ldots, x_{i_K}(t)) . \tag{1}$$

Both f_i and its K input automata are initially assigned to the automaton i at random. The Boolean functions f_i are created in the following way: for each of the 2^K possible inputs we generate a random output with value 1 with a probability p, and with value 0 with a probability $1-p$. Where p is called the bias of the network [6]. This initial random assignment of neighbours and functions will be maintained (quenched) through the evolution of the system.

It has been shown [2] that RBN exhibit two different phases separated, for a given value of p, by a critical value of K, K_c:

(1) an ordered phase for $K < K_c$ in which the networks freeze in a pattern after a short transient. In this phase all of the automata remain in a completely frozen state or in a periodic pattern of activity and
(2) a disordered phase for $K > K_c$. All patterns are lost and the automata appear to be in a completely disordered state, switching from one state to another seemingly at random.

This behaviour naturally induced the conjecture that at K_c the RBN undergo a second-order phase transition. This conjecture has been proved correct and some more information about the transition has been gained [5]. For instance, as we change the value of p the critical value K_c at which the transition takes place also changes and a "critical line" appears, as shown in Fig. 1. As it was demonstrated in Refs. [5,6] this line corresponds to

$$K = 1/2\, p(1-p) . \tag{2}$$

In the insets of Fig. 1, three examples of different dynamic behaviours are depicted. Each RBN have $N = 50$ automata and connectivity $K = 3$. The behaviour ranges from disordered to ordered states by changing p. Each example contains 50 consecutive network states. Time increases along the upward direction in vertical axis. Automata with value 1 are represented as black points and automata with value 0 as white points.

RBN are by definition discrete (N cells) deterministic systems with a finite number of states ($\{0,1\}$), and therefore periodic patterns are expected after a maximum of 2^N steps. Thus, if we follow strictly the standard definition of low-dimensional

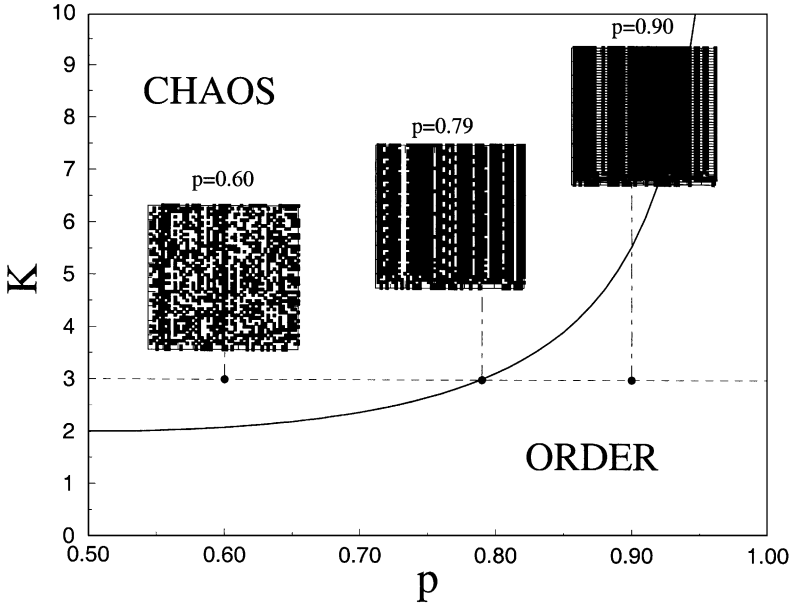

Fig. 1. The boundary (continuous line) between the chaotic and the ordered phase is shown in a K vs. p phase diagram. For a constant value of connectivity, $K = 3$, three examples of RBN with $N = 50$ automata are shown: $p = 0.60$ (disordered phase), $p = 0.79$ (over the critical line), and $p = 0.90$ (ordered phase). Each run contains 50 consecutive network states. Time increases along the upward direction in vertical axis.

deterministic chaos, chaotic behaviour is not possible in these systems. But it is possible, in analogy with continuous system, to define a Lyapunov exponent λ for RBN [16]:

$$\lambda = \log[2p(1-p)K]\,, \tag{3}$$

which determines the two classical regimes: $\lambda < 0$ (order) and $\lambda > 0$ (chaos) with the marginal case $\lambda = 0$, in agreement with the boundary phase transition (Eq. (2)). Thus, we will indistinctly use the terms disordered and chaotic.

3. Control using periodic functions

In previous works [14,15] we managed to control RBN by means of periodic pulses. By control we mean to force a RBN in chaotic phase to behave in an ordered way. Given a RBN in chaotic phase, we forced periodically some fixed percentage of automata (control) to have fixed values and we obtained that the RBN behaved as in ordered phase. Our goal now is to generalise this work to a more general input control: any periodic function controlling the percentage fixed, changing periodically in time.

Let us suppose a RBN with parameters p and K into disordered phase and N automata. Let us choose $N\gamma^{\max}$ automata randomly, being $0 < \gamma^{\max} < 1$. This will be the total subset of automata that will control the later evolution of the network.

Although these control automata are initially randomly chosen, they are kept as controllers throughout all the simulation (quenched). If the control automata were randomly chosen each iteration, we will not manage control. Moreover, even in the case of a initially ordered network, this procedure will destroy its periodicity.

Let us establish an arbitrary order numbering the automata: $1,2,\ldots,N\gamma^{\max}$. We assign randomly to each one a state: 0 or 1. Every time an automaton is being controlled, it will adopt this assigned value, independently of its state in t. Let $F\tau(t)$ be any positive function with period τ and with values normalised between 0 and 1. The fraction of automata to be controlled each iteration is defined by

$$\gamma(t) = \gamma^{\max} F\tau(t)\,. \tag{4}$$

The number of controlled automata in time-step t will therefore be $N\gamma(t)$. That is, in time-step t only automata $1,2,\ldots,N\gamma(t)$ will have frozen their states to their respective assigned values, meanwhile the remaining control automata $N\gamma(t)+1, N\gamma(t)+2,\ldots,N\gamma^{\max}$ keep free. Depending on the chosen function, this amount will vary between 0 and $\gamma^{\max}$.

To illustrate the method, three different simulations are shown in Fig. 2. The control function chosen is $F_\tau(t)=\sin^2(\pi t/\tau)$. The used RBN (the same in all three simulations) has $N=100$ automata with bias $p=0.5$ and connectivity $K=3$, that is, in disorder regime (see Eq. (2)). The difference among the simulations is the different period used in the control function. The value of $\gamma^{\max}$ is 0.4. In such a manner that, when the control function is equal to 1, the 40% of automata will be fixed. And when the control function is equal to 0, all automata are "free", i.e., their values depend strictly of their inputs and functions.

In each simulation a–c, we show three graphics. The top graphic, Automata vs. Iteration, represents the network evolution in time. As in Fig. 1 insets, automata in state 1 are represented in black and in state 0 in white. The bottom graphic in each simulation, Activity vs. Iteration, represents the temporal evolution of the number of active automata, i.e. the fraction of automata with value 1 (activity). And finally, the central graphic in each simulation is the value of the function control, $F_\tau(t)$ applied as input to each RBN along the time.

As it can be seen, initially the three RBN display chaotic behaviour. When the control begins at iteration $t=200$, the RBN changes quickly from a chaotic behaviour to a periodic and controlled behaviour, with periods equal to 75 in (a), 100 (a multiple of $\tau=50$) in (b) and 25 in (c). The period of the controlled RBN is always the same or an integer multiple of the control function period. The disordered behaviour is recovered when the control ends, at iteration 800.

The controlled automata are located in the lower part of the graphics Automata vs. Iteration. This has been done for programming simplicity and to locate them easily. This choice makes no difference in the conclusions as the connection among automata is chosen randomly and the position in the net is just a label.

In order to determine the relationship among the different parameters to reach control, we are going to analyse how perturbations propagate in the RBN [17]. Suppose a standard RBN with connectivity $K=2$ and bias p. In Fig. 3 top-left we have represented a tree which has one arbitrary automaton of this RBN with value 1 at time t, as initial

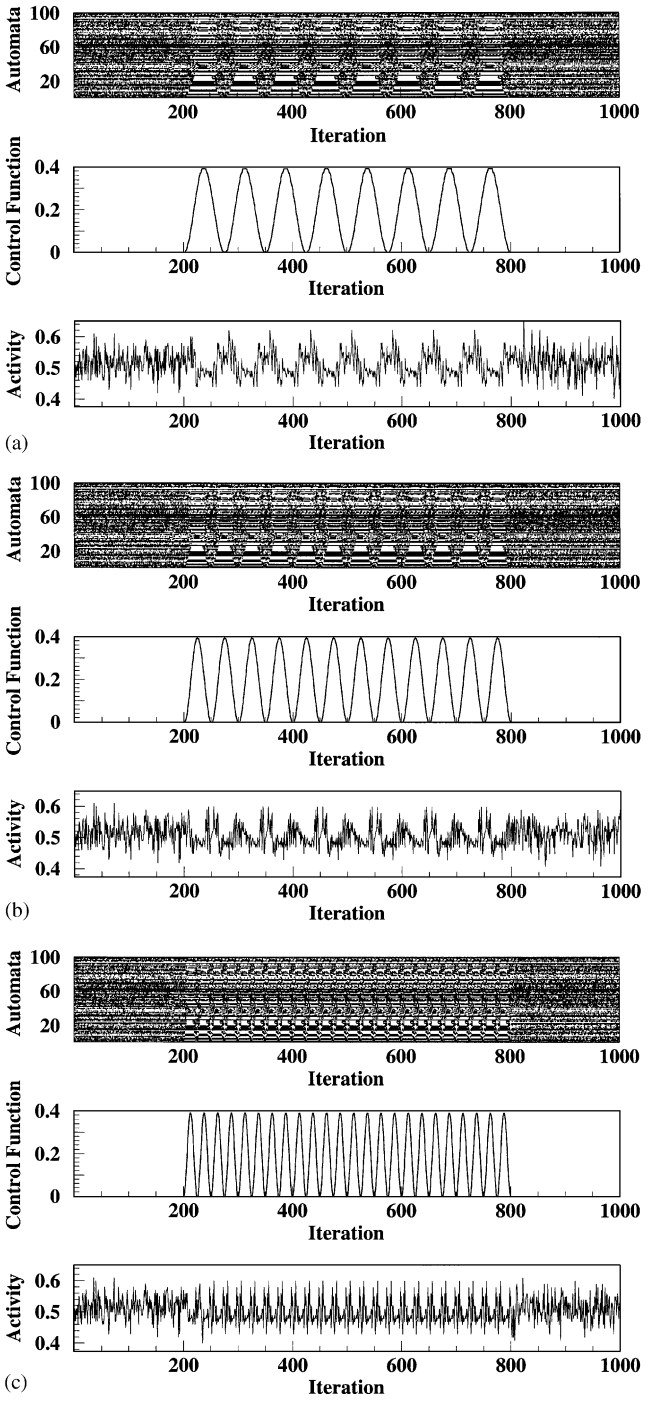

Fig. 2. Control in a chaotic RBN with $K = 3$ and $p = 0.5$ using a $\sin^2(\pi t/\tau)$ periodic function. The periods used in each case have been (a) $\tau = 75$, (b) $\tau = 50$ and (c) $\tau = 25$.

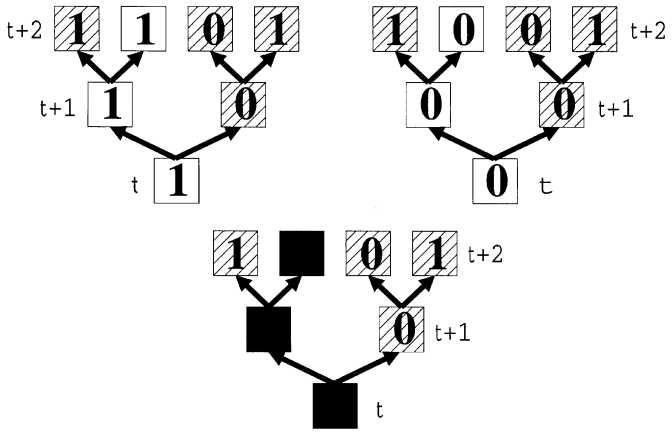

Fig. 3. Spreading of perturbations in a RBN. Top-left: evolution tree of automata states in time. Top-right: replica evolution with minimal perturbation in base automaton. Bottom: tree of cumulative differences between replicas or tree of percolation damage.

branch. This automaton acts as input for $K = 2$ others automata (in average each automaton will have K outputs if the connectivity of the system is K). In the second row (the first branches) is represented these two automata at time $t + 1$. Their value states are 1 and 0. For each automaton in level two we can draw their respective branches and so on. In this manner we have a representation of the network dynamic in branching form.

In Fig. 3 top-right we display the same tree, but now with the initial value of the arbitrary automata flipped. Its value now is 0. This represents a minimal perturbation onto the network. If we follow the dynamic of the network in time, this initial damage may or may not produce differences between two system replicas. In our case we can see that the left automaton in level $t + 1$ changes its state: now its value is 0. The automata with different values in the two replicas are represented in the bottom tree in grey colour.

The ordered and chaotic phase in RBN can be defined from the response of the network to minimal perturbations or damages. If the network is in ordered phase the damage is absorbed. In such a manner that, at certain level the two replicas above mentioned are indistinguishable: no more automata with grey colour appear in down tree. If the network is in chaotic phase then the damage spreads without stop (sensibility to initial conditions). This fact appears in the lower tree as a percolation of the damage trough all levels. The critical point can be defined then as the point at which one single damage percolates at each level.

The probability that the state at $t + 1$ in one automata changes in the replica tree (due to the fact that its input automaton in t changes) is: $2p(1 - p)$. Because the number of output are K, then the mean number of changes is: $K2p(1 - p)$. When the mean number is exactly one at each level, the RBN will be in the critical point, i.e.: $K2p(1 - p) = 1$ which coincides with the critical curve described in Eq. (2).

Let us suppose that we have an RBN in chaotic phase, and suppose that we want to control it with a periodic function as the one described by Eq. (4). The maximum fraction of frozen automata in the network, $\gamma^{\max}$, acts as a barrier that difficults the propagation of perturbations. If $\gamma(t) = \gamma^{\max} = 1$ all automata have frozen state and the RBN reaches exactly the same configuration each τ iterations independently of external perturbations or damages. The system is obviously cyclic. In the other extreme, when $\gamma^{\max} = 0$ the RBN is not controlled, being a classical disordered or chaotic RBN. The value of $\gamma^{\max}$ that defines the transition from chaotic to ordered behaviour, is given by the marginal condition which allows for first time one perturbation to percolate across the temporal evolution of the net as pointed out before. In Fig. 3 we have marked the frozen automata as dashed. For them, the damage percolation is not possible: the state of these automata is imposed externally. As the percentage of frozen automata is temporally dependent, at each step the probability of damage spreading varies. In fact as the variation is periodic, only it is necessary to compute one period. Thus, in the first step, the mean probability that one damage percolates is: $(2p(1-p)K)(1-\gamma^{\max}F_\tau(t))$. In the second step we have: $(2p(1-p)K)(1-\gamma^{\max}F_\tau(t+1))$, and so on to the step $t+\tau$ where the situation repeats. Therefore the critical condition for non-percolating damage is given by

$$[2p(1-p)K]^\tau \prod_{t=0}^{\tau} (1-\gamma^{\max}F_\tau(t)) \leqslant 1\,. \tag{5}$$

Given a fixed connectivity K, this equation establishes which is the limit boundary value of $\gamma^{\max}$ for each bias p that will be necessary to control a chaotic RBN.

To check the validity of our analysis, we have performed 100 simulations for each pair of values $(p, \gamma^{\max})$ using RBN with size $N = 1000$, connectivity $K = 3$ and the same periodic control function used in Fig. 2 with a period of $\tau = 50$. The pixels in Fig. 4 represent the fraction of the 100 simulations for each pair $(p, \gamma^{\max})$ that have not managed to reach a controlled state. We define a controlled state as that reaching a

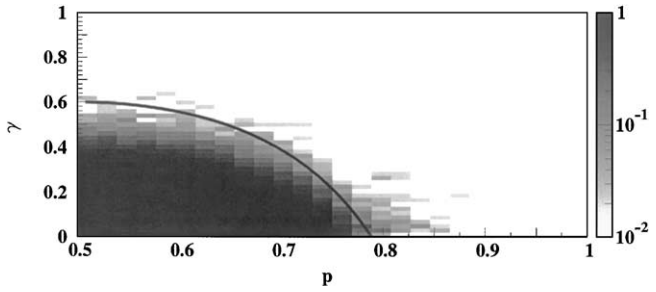

Fig. 4. The theoretical boundary (continuous line) for control chaotic RBN with $K = 3$ given by equality in Eq. (5) (upwards, control; downwards, chaos) and results from computer simulations. Each concrete point (p_0, γ_0) in the p–γ space is the result of 100 simulations. If all 100 simulations have been controlled then the pixel (p_0, γ_0) is painted in white. If no one has been controlled then the pixel is painted in black. Intermediate fractions are represented in grey tones according to the intensity scale shown.

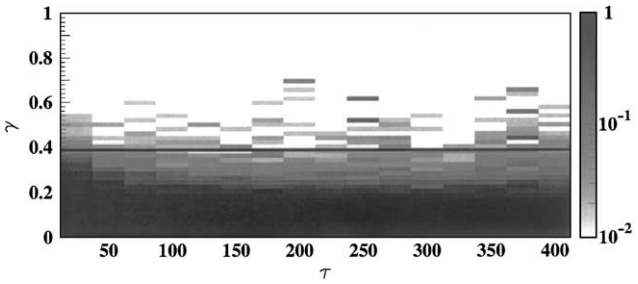

Fig. 5. The theoretical boundary for controlling chaotic RBN given by Eqs. (5) and (3) is independent of the control function period. The horizontal straight line is the theoretical boundary value for $K=3$ and $p=0.7$, superimposed to the results from computer simulations: each pixel stands for 100 simulations, meaning their grey tone the fraction of these simulations that have not been controlled (black = none has been controlled; white = all of them have been controlled).

periodic behaviour. Obviously, this period will be resonance with the control function period. Each pixel ranges from black (i.e., value = 1) when none of the 100 simulations has been controlled, to white (value = 0) when all of them have been controlled. The superimposed curve is the theoretical value for $\gamma^{\max}$ obtained from equality in Eq. (5). The region lying above the line is controlled, reassuring our simulations.

Using our definition of Lyapunov exponent (3), from Eq. (5) one obtains the following relationship:

$$\lambda \leqslant -\frac{1}{\tau}\sum_{t=0}^{\tau} \log(1-\gamma^{\max}F_{\tau}(t))\,. \tag{6}$$

The right-hand side of Eq. (6) is the average of a periodic function along its period. Therefore it should not have explicit dependence on the period. In order to test if there is any kind of dependence with the period, we have performed several sets of simulations for RBN with size $N=1000$, bias $p=0.7$ and connectivity $K=3$, using different values of the period and $\gamma^{\max}$. The results are shown in Fig. 5. Again, each pixel represent a set of 100 simulations for each pair of values $(\tau,\gamma^{\max})$, standing the grey tone the fraction of non-controlled RBN for each set of simulations. The horizontal line is the theoretical value of $\gamma^{\max}$ for $p=0.7$ and $K=3$ above which the system should be controlled. It can be observed how in fact the response of the system is independent of the control function period.

Approximating $\log(1-\gamma^{\max}F_{\tau}(t)) \approx -\gamma^{\max}F_{\tau}(t)$ and approximating the sum in Eq. (6) to an integral for $\tau \gg 1$, it follows:

$$\lambda \leqslant \frac{\gamma^{\max}}{\tau}\int_0^{\tau} F_{\tau}(t)\,\mathrm{d}t\,, \tag{7}$$

that is

$$\lambda \leqslant \gamma^{\max}\bar{F}_{\tau}(t)\,. \tag{8}$$

The non-trivial result is that to control the RBN, the Lyapunov exponent has to be equal to, or smaller than, the time average of the controlled automata without any

dependence on the period τ and on the shape of the control function. The only clear dependence with τ is that the period of the RNB in the controlled state is in resonance with the period of the control function, being equal to it or to an integer multiple, as our simulations proved.

Note that the result is valid for any function and it includes the result obtained in the previous articles [14,15], where a pulse function was used:

$$F_\tau(t) = \delta_\tau(t) = \begin{cases} 1 & \text{if } t \bmod \tau = 0\,, \\ 0 & \text{otherwise}\,, \end{cases} \tag{9}$$

then

$$\bar{F}_\tau(t) = \frac{1}{\tau}\int_0^\tau \delta_\tau(t)\,\mathrm{d}t = \frac{1}{\tau}\,, \tag{10}$$

the next relationships follows:

$$\lambda \leqslant \frac{\gamma^{\max}}{\tau}\,, \tag{11}$$

as already obtained in Ref. [14].

4. Networks controlling networks

Obviously, non-analytic periodic functions can be used for controlling the net. Specifically, it is very suggesting, from a biological point of view, to use a RBN with size n in ordered state to control a chaotic RBN with size $N > n$. This control is related to synchronisation of coupled elements in a variety of complex systems [18].

Let the ordered smaller RBN have a given period τ. To control the chaotic RBN, we will connect the ordered RBN to the chaotic one. At each iteration, the n values of the ordered RBN will be adopted by n automata of the chaotic RBN. These n automata are randomly chosen at the beginning and kept as controllers throughout all the simulation (quenched). The fraction of controlled automata γ does not change now. It can be easily found that in this case the critical condition to control the RBN is given by

$$2p(1-p)K(1-\gamma) \leqslant 1\,. \tag{12}$$

Unlike in previous section, now the controlled automata have not frozen values but they change with the evolution of the ordered control RBN. It is enough that their state is adopted periodically and predetermined independently of the chaotic RBN dynamics of the controlled network, acting (like in the previous case) as a blockage for the evolution of any possible perturbation, as can be checked in Fig. 6. As in Fig. 2 the simulation has three graphics. Now the control (central graphic) is not an analytical periodic function, but the control RBN with $n = 40$ automata.

This idea can be extended: the smaller ordered RBN controlling the bigger chaotic RBN can be in its turn a chaotic RBN controlled by a smaller ordered one and so on, like Russian dolls. Thus, it is enough an ordered small RBN with size for instance $n = 30$ to control a whole set of consecutively connected chaotic RBN with increasing sizes. The final RBN can be as big as one desires, for instance $N = 10^8$, and when the

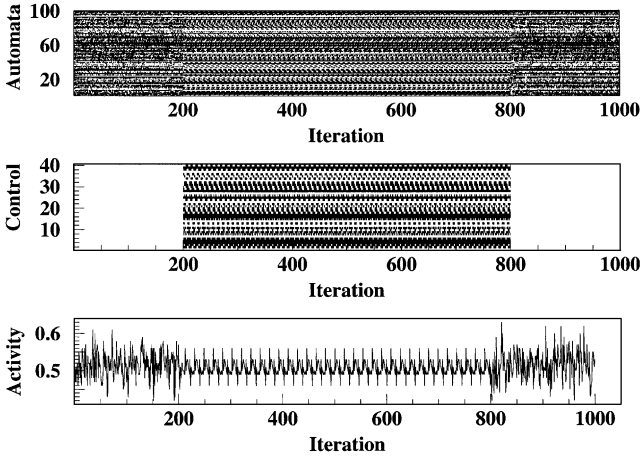

Fig. 6. RBN of size $n = 40$ in ordered state ($K = 2$, $p = 0.5$) and period $\tau = 9$ controlling the chaotic RBN described in Fig. 2. It can be seen how the first one induces an ordered behaviour of period 18 in the chaotic RBN.

first one is disconnected of the set (or its control parameters changed to turn it into a chaotic state), all the set becomes chaotic.

5. Summary

In this paper, it has been shown how an external control can induce an ordered behaviour in a network which in principle is in a chaotic state. The stability properties of the different cell types are basically determined by the outcome of gene interaction and such stability could be the result of a self-organisation mechanism to the critical point [2]. Our focus proves how external control mechanisms are another possibility of stability in the genome.

Inspired by the investigation in the molecular mechanism in genome responsible of the circadian rhythms [11,12], it has been shown how when a small fraction of a chaotic RBN is controlled by a periodic external signal, the whole RBN reaches a periodic controlled behaviour in resonance with this signal, and how the analytical result is independent of the period and shape of the control function.

The case of networks controlling networks is extremely interesting. More recently, it has been reported that the circadian clock operates during early embryogenesis in zebrafish. It seems that there is some synchronisation mechanism with the mother clock [19]. The mechanism network–control–network has already been proposed to neural networks (NN) [20] for modelling the relationship between the thalamus (the controller network) and the cortex (the controlled network).

This way of control suggests a possible hierarchy in several levels (networks controlling networks controlling networks) and the stability of large system by means of very small ordered networks. We believe that this is a interesting theoretical unexplored via.

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