Interacting Random Boolean Networks

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Abstract. Random Boolean networks (RBN) have been extensively studied as models of genetic regulatory networks. While many studies have been devoted to the dynamics of isolated random Boolean networks, which may considered as models of isolated cells, in this paper we consider a set of interacting RBNs, which may be regarded as a simplified model of a tissue or a monoclonal colony. In order to do so, we introduce a cellular automata (CA) model, where each cell site is occupied by a RBN. The mutual influence among cells is modelled by letting the activation of some genes in a RBN be affected by that of some genes in neighbouring RBNs. It is shown that the dynamics of the CA is far from trivial. Different measures are introduced to provide indications about the overall behaviour. In a sense which is made precise in the text, it is shown that the degree of order of the CA is affected by the interaction strength, and that markedly different behaviours are observed. We propose a classification of these behaviours into four classes, based upon the way in which the various measures of order are affected by the interaction strength. It is shown that the dynamical properties of isolated RBNs affect the probability that a CA composed by those RBNs belongs to one of the four classes, and therefore also affects the probability that a higher interaction strength leads to a greater, or a smaller, degree of order.

Keywords: genetic network model, random Boolean network, cellular automaton, interaction, cell-criticality.

1 Introduction

The idea that evolution drives living organisms in a "critical" region of parameter space which is intermediate between that of ordered behaviour and that of chaotic dynamics has been proposed by one of us (S.A.K.) as a powerful unifying principle for understanding some deep features of life. Biology could benefit much by such general hypotheses, which must however be carefully investigated.

Random Boolean networks (briefly, RBN) are a classical, well-known representative of the "ensemble approach" to biological studies [Kauffman, 1971]. The statistical analysis of a collection of RBNs allows one to study the influence of the structural features of the networks (connectivity, topology, updating rules, etc.) on its dynamics [Kauffman, 1993; Kauffman, 1995]. It has recently been shown that these models provide a good description of the statistical features of changes in the expression of the whole set of genes of S. Cerevisiae after single knock-outs [Serra, Villani & Semeria, 2004; Serra, Villani, Graudenzi & Kauffman, 2007; Ramo, Kesseli & Yli-Harja, 2006]. Moreover, by analyzing these data it has been possible to start to address the important issue of cell criticality, since the distribution of avalanches in gene expression data turns out to be related to a parameter which also determines the network dynamical regime.

The results of the previous studies (and of other attempts at analyzing experiments whose results are related to the issue of criticality [Shmulevich & Kauffman, 2004; Shmulevich, Kauffman & Aldana, 2005] indicate that cells seem to be in an ordered regime close to the critical boundary. They are however not conclusive, in part because of scarcity of suitable experiments.

It has however been observed [Kauffman, 1993; 2000] that the remarks on the advantages of criticality apply to organisms as a whole, rather than to their individual cells. The distinction is obviously irrelevant for isolated unicellular organisms, but is important for those organisms which can live in colonies or for multicellular beings. It is indeed known that under these circumstances neighbouring cells communicate by means of chemical messengers, and are therefore not isolated.

It is therefore extremely important to understand the relationship between the dynamics of a single, isolated RBN – which has been extensively studied in the past – and that of a collection of interacting networks. We describe below a model which is well suited for this purpose: it is a 2-D cellular automaton where each cell of the automaton (which simulates a biological cell) is occupied by a RBN. While a related issue has been addressed in the context of scale-free Random Boolean Networks [Kauffman, Peterson, Samuelsson & Troein, 2004], here we investigate the effects of interactions among neighbouring cells using "classical" random Boolean networks (which have proven well suited to describe the experimental avalanches in S. Cerevisiae [Serra, Villani & Semeria, 2004; Serra, Villani, Graudenzi & Kauffman, 2007]).

In our model all the RBNs are structurally identical (same connections and same Boolean functions) and the interaction between neighbouring cells is modelled by allowing the activation of some nodes of the RBN in a given cell to depend upon the activation of some genes of a neighbouring cell (in a way which crudely simulates the fact that some proteins can cross the cellular membrane and influence the genes of another cell).

This model could be regarded as a simplified description of a tissue in a multicellular organism, or of a colony of unicellular organisms: at this level of modelling the two cases are approached in the same way. It should be remarked however that, according to the usual biological interpretation of RBNs, the attractor of a given cell is associated to the cell type: therefore a tissue should be composed by cells which are all in the same attractor. Since this latter condition is not imposed in our model, we will refer to it sometimes as a "colony".

CA models of groups of interacting cells have been proposed for the study of morphogenesis in different organisms [Glazier and Graner, 1993, Marée and Hogeweg, 2001, Alber et al, 2004]. The model we consider here might be extended in order to deal with morphogenetic processes, e.g. by associating different attractors to a different cell types, and by studying the spatial arrangement of these different attractors. In the present study we limit to a simpler question, namely that of finding under which conditions a given set of interacting cells can be found in the same attractor. While the analysis provides also information about conditions which allow the coexistence of different attractors, no attempt is made here to analyze the spatial patterns which may appear.

The model has been already subject to a preliminary investigation [Villani, Serra, Ingrami & Kauffman, 2006] which showed that its dynamics is far from trivial. While one might have thought that interaction might either lead to a more ordered or a more disordered behaviour, the simulation results showed a more complicated behaviour. Different behaviours were indeed observed, either highly ordered or disordered. It was suggested, on the basis of preliminary data, that the dynamical regime of the isolated network might be related to the effects of the interaction, which might enhance the features of the isolated network. It is therefore necessary to provide an in-depth investigation of the relationship between the dynamics of an isolated network and that of a collection of interacting RBN, and the results given here aim at elucidating this relationship.

The paper is organized as follows. In section 2 a brief description of RBN is given: since there are many excellent reviews we only introduce a few key definitions and properties. In section 3 our cellular automata model of interacting Boolean Networks is described. In section 4 the different variables which have been used to describe the aggregate behaviour of the colony are introduced. The way in which experiments were performed is described in Section 5, while the following section 6 is dedicated to the results of these experiments. The final section 7 includes critical comments and indications for further work.

2 Random Boolean Networks

For a complete description of the RBN model we refer the reader to [Kauffman, 1993; Harvey & Bossomaier, 1997; Aldana, Coppersmith & Kadanoff, 2003]. In this section we will only outline its main features, which will be used in the rest of the paper.

A RBN is an oriented graph composed by N Boolean nodes. Every node corresponds to a gene of a correspondent genetic network, and it is said to be active (value = 1) if its corresponding gene synthesises its protein; otherwise it is considered inactive and its value is 0. In real genetic networks, genes are able to influence the expression of other genes by means of their corresponding products and through the interaction of these products with other chemicals, by promoting or inhibiting the activation of target genes. In the RBN model this influences are

represented by directed links (if the product of gene A influences the activation of gene B, node A will be an input of node B). Thus, the activation value of a certain node depends on the value of its input nodes, according a specific Boolean function. Each Boolean function is generated at random, assigning to any combination of its inputs the output value "1" with probability p (which is called the bias and has the same value for every node). The updating of the network is synchronous and the time is discrete. In the approach we used the so-called *quenched* model [Aldana, Coppersmith & Kadanoff, 2003]: both the topology and the Boolean function associated to each node do not change in time. Hence, the system is deterministic: if $x_i(t) \in \{0,1\}$ is the activation value of node i at time t and $X(t)=[x_1(t), x_2(t) \ldots x_N(t)]$ is the vector of activation values of all the genes, once the connections and the Boolean functions of each node have been specified, $X(t)$ uniquely determines $X(t+1)$.

The main structural features of RBNs are: average connectivity, ingoing and outgoing connectivity distribution, set of allowed Boolean functions and bias of the Boolean functions.

In a so-called "classical" RBN each node has the same number of ingoing connections k_{in} and its k_{in} input nodes are chosen at random with uniform probability among the remaining $N-1$ nodes (self-coupling and multiple connections being forbidden). Consequently, outgoing connections follow a typical Poisson distribution [Kauffman, 1993].

There is a wide literature about the dynamical regimes which can be observed in RBNs. We can distinguish two typical behaviours, which are called "ordered" and "chaotic" [Kauffman, 1993; Aldana, Coppersmith & Kadanoff, 2003]. If we observe, for instance, the average number of attractors and the average attractors' length, we can note how in ordered regime networks these variables increase their values as a power law of N, while chaotic networks show an exponential divergence. The dynamical regime of a RBN depends primarily on two parameters, the average connectivity of the network $\langle k_{in} \rangle$ and the bias p. The critical regime condition is described by the equation: $\langle k_{in} \rangle^{-1}=2p(1-p)$ [Aldana, Coppersmith & Kadanoff, 2003].

While many theories and observations indicate that isolated biological cells tend to be found in the ordered region, rather close to the "edge of chaos", i.e. the border between ordered and disordered regimes [Kauffman 1993; Kauffman 2000], in this research we are interested in understanding what happens when cells interact among them, in a upper-level organization like a colony. Does this interaction bring any change in the behaviour of the cells? Does the order of the system increase or vice versa? In order to find answers to these questions we introduced the model we present in the next section.

3 RBN-CA

In order to model the interaction of RBNs let us consider a 2D square lattice cellular automaton with M^2 cells, each of them being occupied by a complete Random Boolean Network (in the text, it will be referred to as *RBN-CA*). The neighbourhood is of the von Neumann type (composed by the cell itself and its N, E, S, W neighbours). We assume wrap around so the overall topology is toroidal (Fig. 3.1).

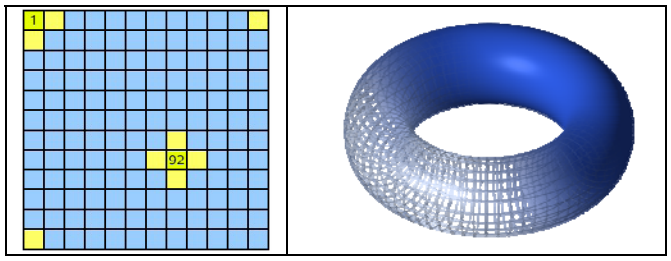

Figure 3.1. (a) Graphical visualization of a RBN-CA: each cell of the automaton hosts a complete random Boolean network; a subset of its nodes interacts with the first four neighbouring RBNs. (b) The spatial shape of the automata is that of a torus.

Every RBN of the automaton is structurally identical, while the initial activation states of the various genes may differ. In particular, each of the RBNs owns the following common features:

1. same number (N) of Boolean nodes;
2. same ingoing and outgoing connections for each node of the network;
3. same Boolean functions associated to each node.

The use of homogeneous RBNs for all the cells of the automata is due to the fact that, in general, all the cells of a given multicellular organism or monoclonal colony share the same genetic material: therefore, in each cell we have to consider a copy of the same RBN. Hence, the above common features (1-3) of the RBN define its *genome*.

A key aspect of the model is the representation of interactions: the fact that some proteins can pass from one cell to another is modelled by assuming that a cell can be affected by the activation of some genes of a neighbouring cell.

In our model, nodes able to interact with other cells are defined as *shared nodes* and they are a subset of the total number of nodes of the RBN (not all the proteins can cross the cellular membrane). Since all the RBN are structurally identical, the subset of shared nodes is exactly the same for all the cells of the automaton. Let f be the fraction of interacting nodes. We define as *elementary value* of a certain node the value computed according its Boolean function and the value of its input nodes, belonging to the same RBN. The *shared value* of a shared node, instead, is calculated taking into account also the activation value of the corresponding shared nodes of its neighbouring cells, depending on a precise interaction rule. Note that shared nodes own an elementary value as well, depending on the value of their input nodes. The output nodes of a shared node will receive as input of their Boolean function the shared value of that node.

It is possible to define different interaction rules. In this work we consider the rule "AT LEAST ONE ACTIVE" node (ALOA), according which the shared value of a node x in the cell A is 1 if its value or at least one of those of the nodes x in the four neighbouring cells is 1. See the figure 3.2. for an example.

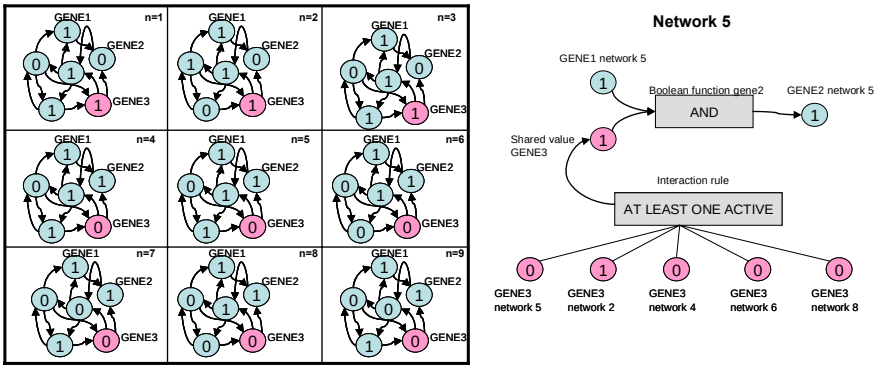

Figure 3.2. Example of a 3*3 automaton. Networks in the automaton are identified by a number from 1 to 9. Gene 3 (pink coloured) is chosen to be shared. In the scheme on the right we can see a section of network number 5 (central one): the input values for gene 2 are the elementary value of gene 1 and the shared value of gene 3 (gene 3 owns elementary value = 0 and shared value = 1). The shared value of gene 3 in the network 5 is 1 because gene 3 of the neighbouring network number 2 is active.

In order to use a consistent terminology, let us introduce the following definition. A *G-automaton* (or, equivalently, a G-colony) is a set of interacting cells (namely, a RBN-CA), defined by:

- the dimension of the lattice M,
- the topology of interaction T,
- the interaction rule R,
- the genome G of the RBNs which are placed in each cell of the automaton.

Most of the studies have been made on single G-automata, observing their behaviour when the interaction strength is varied (being understood that G, M, T and R are kept fixed). The whole analysis has involved G-automata different in terms of the genome G.

4 Analysis criteria

It is necessary to define suitable aggregate descriptors for the dynamical behaviour of the colony as a whole. The analysis is mainly focused on the search of the features of the attractors of the RBNs belonging to the to automata. Since the updating of each node of each RBN in the automata depends on the elementary value of the not-shared input nodes and on the shared value of the shared input nodes, it would not be meaningful to look for an attractor only on the elementary value of nodes. For this reason, we introduce the concept of *image* of a RBN: the image of a specific RBN is the vector constituted by the elementary value of the non-shared nodes and by the shared value of the shared ones. Since shared input nodes determine the state of their output nodes by means of their shared value, the dynamic of the image is deterministic and, thus, it is better suited than the vector of elementary values to describe the dynamics. In particular, the search for the attractors is made on the image of the RBNs of the automata.

Order in a spatial model like our RBN-CA may take two different (although not independent) meanings: *temporal order*, which is what is usually considered in isolated Boolean networks, has to do with the system attractors (number, period, basins of attraction), while *spatial order* refers to the fact that neighbouring cells

may reach the same or similar attractors, or be in completely different states. In order to quantify the two kinds of order, the following variables (which will collectively be referred to as *order indicators*) have been considered:

- the fraction of experiments α where all the cells of the automaton reach the same attractor;
- the fraction of experiments β where all the cells of the automaton reach an attractor;
- the fraction of experiments γ where no cell reaches an attractor[1];

and, for each experiment of each series:

- the number of different attractors present in the automaton at the end of the experiment;
- the number of cells of the automaton which do not reach any attractor at the end of the experiment;
- the number of different periods present in the automaton at the end of the experiment;
- the average length of the periods of the attractors on all the RBNs of the automaton at the end of the experiment;
- the structural factor *stfc* at the end of the run. It is an aggregate variable which provides indications of the presence of homogeneous zones inside the colony. For each RBN of the automata, we compute the number of nearest neighboring RBNs that are in its same attractor, and sum the quantities of all the cells. If all the RBNs share the same attractor this variable reaches its maximum value ($4*M^2$).

5 Experiments

In order to disentangle the effects of increasing interaction from the (possibly large) effects of G-automaton change, we decided to concentrate on the deep study of the specific behaviour of single G-automata: in particular the simulations have been made on a set of 150 G-automata, characterized by RBNs with different genomes G.

The parameters of the RBNs placed in the cells of the G-automata are chosen in such a way that they are "in the critical regime": this is of course a statistical property of these networks, and single realizations may have different number of attractors. In detail, the networks are "classical" RBNs, with an equal number of incoming connections per node ($k_{in} = K = 2$). The input nodes are chosen at random with uniform probability among the remaining N-1 nodes, auto and multiple connections being forbidden. The Boolean functions are generated at random independently for every node, with no restrictions and bias = 0.5. The initial states of the nodes are chosen at random for every RBN, independently from those of the other cells.

The G-automata are 20*20 square lattices, composed by RBNs with N = 100 nodes.

We set up 11 different sets of simulations, with different interaction strength f, ranging from 0 to 1, step 0.1 (f = 0, 0.1, 0.2, … 0.9, 1). For each G-automaton,

[1] Due to computational limits, we consider as cells without attractor those cells whose attractors' length is higher than a fixed value (see section 5).

when the fraction of shared nodes is increased, say from 0.1 to 0.2, the shared nodes at f=0.2 are a superset of those which were shared at 0.1. It is therefore possible to observe the variation of the measures of order for the same G-automaton according the different values of f. The search for an attractor starts after 200 time steps (a step being a complete update of each node of each RBN present in the automaton) and the maximum possible period (for attractor search) is set to 200: in this way, we do not consider attractors whose period is higher than 200 steps. The search ends when an attractor is found or when the system reaches 2000 steps (in this case we state that the RBN has found no attractor).

The whole simulation ends in correspondence of the value of f = 1. Every simulation on every G-automaton is repeated 150 times[2]. All the order indicators are averaged on their value in these 150 runs.

6 Results

Several preliminary experiments showed a very weak dependence of the order indicators on the initial conditions of the value of the nodes in the RBNs of the automata. Note that one initial condition of an automata implies 400 different initial conditions of identical RBNs and, even though 400 surely represents an undersampling of all the possible configurations of a RBN of 100 nodes, they seem to allow sufficient variability to identify the most relevant attractors.

Note however that the variance of the measured variables appears to increase with coupling strength f.

Other extensive analyses have been made to study the impact of the choice of the specific set of shared genes. A large variability in all the measures of order has been observed for the same G-automaton, for each value of f, changing randomly the set of shared nodes. The choice of a particular shared node instead of another one can provoke dramatic differences in the dynamic of the automata. That is why, as discussed in section 5, when comparing results for different values of f, we decided to generate the sets of shared nodes as a superset of those with smaller values of f.

In order to measure the influence of interaction on the degree of order, we introduced a further variable, defined as follows:

$$\Omega = DA + CWA,$$

where DA is the number of different attractors of a definite G-automaton, while CWA is the number of cells whose RBN reached no attractors. The number of different attractors can be considered as an indicator of the homogeneity of the cells in the G-automaton. Yet, in many cases some cells could reach no attractors and their number would not be computed into this variable. Adding the numbers of cells with no attractor to the number of different attractors is a way to compensate this effect. Thus, Ω is a variable whose value is minimum (1) where the order is maximum (all the cells reach the same attractor) and is maximum (400) where the order is minimum (all the cells do not reach any attractors or reach different attractors).

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[2] The 150 runs of the simulations on the same G-Automaton differ for the choice of the subset of shared nodes and for the initial condition of the RBNs.

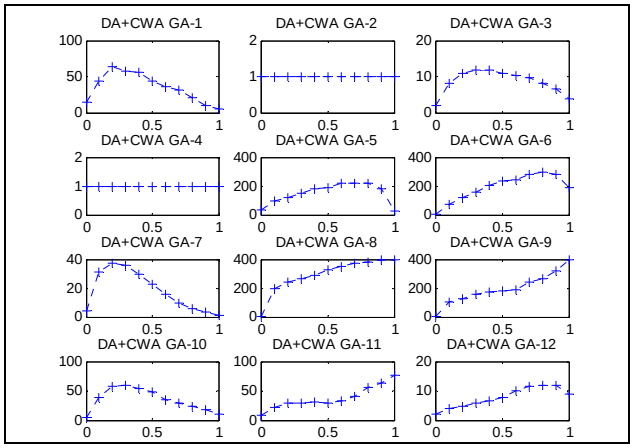


Figure 6.1. 12 example of G-automata: trend of Ω – mean on 150 simulation runs – (y axe) according different values of *f* (x axe).

The analysis on several G-automata (whose RBNs are characterized by different genomes) demonstrates the presence of three recognizable kinds of behaviour, concerning the dependency of Ω upon *f* (see figure 6.1):

- Ω constant and equal to 1: all the G-automata reach the same attractor, independently of the value of *f* and also in absence of interaction. The attractors of this class of G-automata are fixed points.
- increasing Ω.
- *bell-shaped* Ω: we define as bell-shaped a curve with a single maximum for $f \notin \{0,1\}$.

It has also proven convenient to introduce a further sub-distinction among the G-automata characterized by a bell-shaped curve of Ω:

- *left-oriented bell-shaped*: the maximum of the curve is for $f \leq 0.5$.
- *right-oriented bell-shaped*: the maximum is for $f > 0.5$.

On this basis, we classified the set of G-automata in four groups: constant (briefly *CO*), growing (*GR*), left-oriented bell-shaped (*LB*), right-oriented bell-shaped (*RB*). In the specific set of G-automata object of the study, we have:

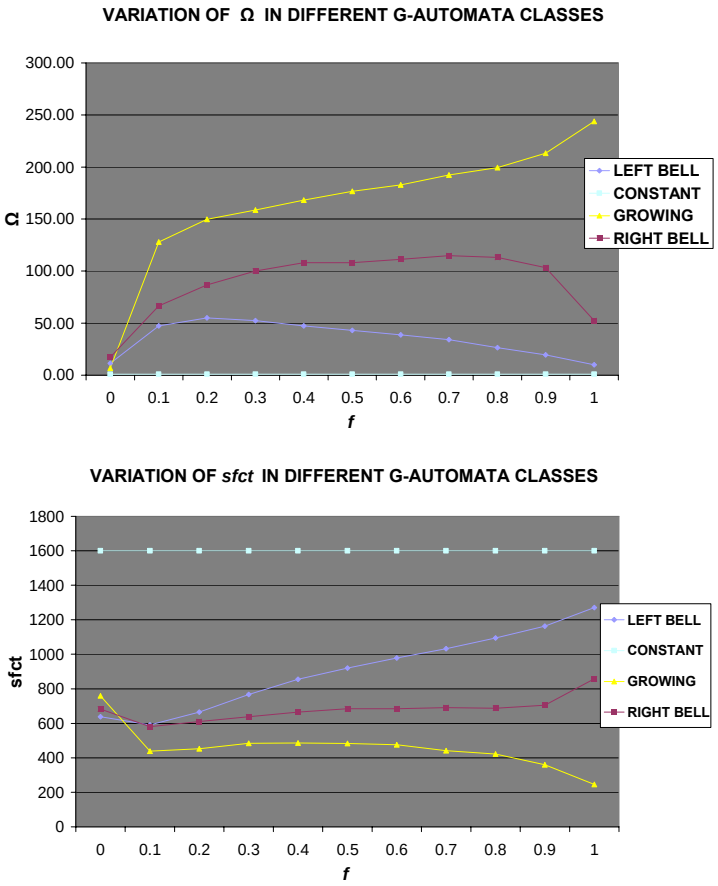
- CO G-automata: 11% of the total.
- GR G-automata: 17% of the total.
- LB G-automata: 55% of the total.
- RB G-automata: 10% of the total.
- not classifiable: 7% of the total. In this category we considered all the G-automata which do not clearly belong to one of the groups above.

Once the G-automata have been divided in homogeneous groups on the dependency of Ω on *f*, it has been possible to study the differences in behaviour according all the specific order indicators (see section 4). The analysis has been made on average values for every indicator on the G-automata belonging to each group.

Exception made for the attractors mean period, if there is no interaction among the cells of the G-automata, the value of the order indicators are very close for all the three non-constant classes. If the interaction is turned on, i.e. for values $f > 0$, the various classes of G-automata manifest different order degree and tendency. In

detail, for values of $f > 0$, the degree of order of CO G-automata is the highest[3], followed by RB, LB and GR ones[4]. Furthermore, in correspondence of higher f the differences among the groups accentuate: in particular, GR G-automata decrease their degree of order; RB and LB, after an initial diminution, increase their state of order; lastly, the degree of order of CO G-automata remain fixed to the maximum, notwithstanding the value of f.

In figures 6.2 (a)(b)(c) we can observe the dependency of Ω, *stfc* and α on f, for the four different G-automata classes. All the other indicators present similar shapes and give a support to the hypothesis of a different response to coupling strength for different classes of G-automata.



[3] Notice that an "increase of the degree of order" corresponds to a higher value of certain order indicators (e.g. *stfc*, α…) and to a lower value of certain other ones (e.g. Ω…).

[4] Note that for low values of f ($f \leq 0.2$) we can observe some inversions in the relation of order between RB and LB, probably due to some experimental noise.

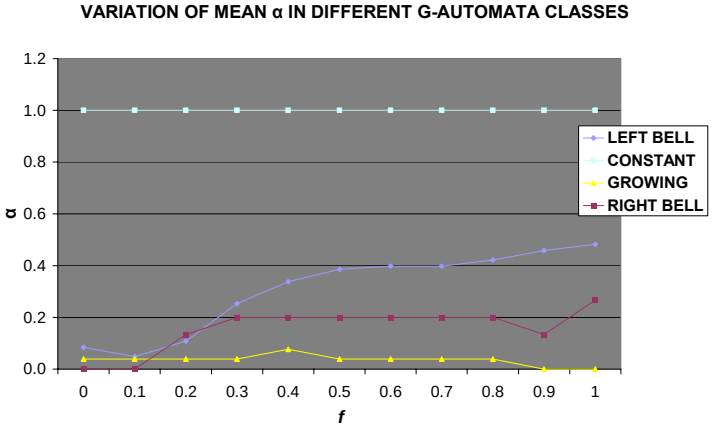


Figure 6.2. (a) Variation of Ω according different values of *f* for the 4 different classes of G-automata. (b) Variation of *stfc* according different values of *f* for the 4 different classes of G-automata. (c) Variation of *α* according different values of *f* for the 4 different classes of G-automata.

As stated above, attractors mean period (shortly, *AMP*) presents a different dependency on *f* compared to the other order indicators (see figure 6.3).

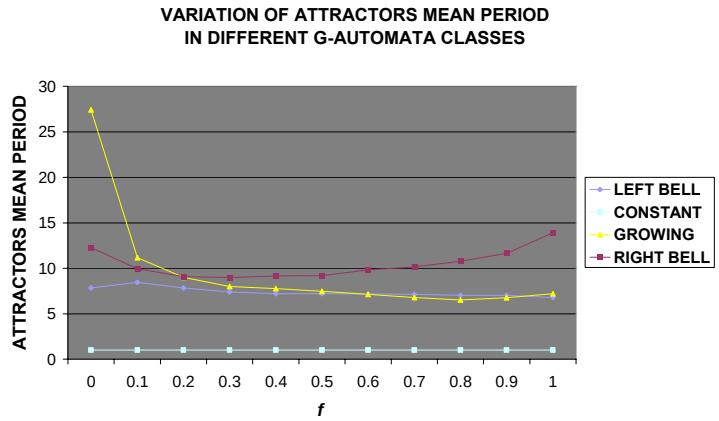


Figure 6.3. Variation of AMP according different values of *f* for the 4 different classes of G-automata.

In particular:

- the value of the AMP in case of no interactions ($f = 0$) is significantly different among the four G-automata classes: GR G-automata own the highest value, respectively followed by RB, LB and CO ones.
- in presence of interaction, AMP seems to be weakly dependent on the interaction strength[5] for $f \geq 0.1$.

[5] Note that the collapse in the attractors mean period for growing G-automata is probably due to the fact that in case of interaction the first cells to lose the attractor are the ones with

The significant difference in the value of AMP in case of no interaction suggests the existence of a relationship between the dynamics of the isolated cells (namely of the specific RBN hosted in the cell of the automata) and the different behaviours of the G-automata in response to the interaction. Moreover, they point to the possibility of using the value of the AMP in case of no interaction to estimate the probability that a given network belongs to one of the four classes and, as a consequence, to form meaningful expectations concerning their response to growing interaction.

On the basis of the observed distribution of AMP in case of no interaction for each G-automata class, we partitioned the range of values of AMP in 4 intervals: equal to 1, between 2 and 10, between 10 and 30 and higher than 30. In figure 6.4 one can see the relative frequency of G-automata of the four classes, in each of the four AMP intervals. The observed conditional frequencies of the various types of G-automata are the following:

- AMP = 1: CO: 94%, not classifiable: 6%.
- AMP comprised among 2 and 10: LB: 70%, RB: 10%, GR: 12%, 8%: not classifiable;
- AMP comprised among 10 and 30: LB: 50%, RB: 20%, GR: 27%; 3%: not classifiable;
- AMP > 30: LB: 19%, RB: 9%, GR: 63%, 9% not classifiable.

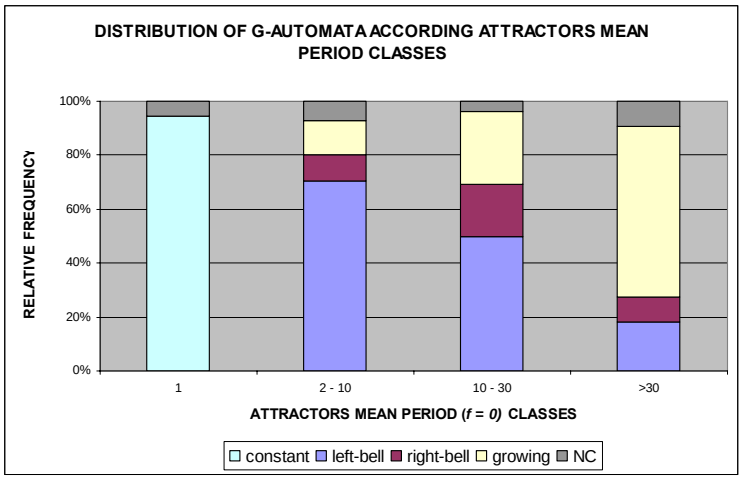


Figure 6.4. Repartition of G-automata classes for different ranges of attractors mean period in case of no interaction (1; 2 – 10; 10 – 30; >30).

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the largest periods. In this way, just the mean of the periods of the attractors on the cells that still reach an attractor only is computed.

7 Conclusions

Let us first remark the difficulty in understanding in a clear way the influence of the interaction strength on the dynamics of the whole system. While one might have expected a well defined tendency, the phenomena which have been observed are definitely more complicated.

On the basis of extensive simulations we could observe that different random Boolean networks can show substantially different behaviours when interacting with each other.

We introduced different order indicators, and we tentatively identified four classes of G-automata, on the basis of the dependency of most of these variables upon the interaction strength.

It was then found out that the average attractor period (AMP) of a single and isolated RBN seems providing fine indications on the behaviour of the automata in which this RBN would interact. RBNs that, taken singularly, present high values of AMP would, in fact, lead to a system of interacting RBNs tending to more disordered states while the interaction strength increases. On the contrary, RBNs characterized by AMP equal to 1 almost always lead to automata characterized by a constant and maximum state of order, unaffected by the interaction. Among these extreme dynamics, RBNs with intermediate values of AMP are likely to lead to G-automata which belong to the most frequent class, which was called "bell-shaped".

Possible future directions of research in this area may include:

- analyzing the behaviour of CA made by RBNs which have a non classical topology (e.g., scale free [Aldana, 2003; Darabos, Giacobini & Tomassini, 2006]);
- studying the behaviour of CA with different interaction rules (e.g. majority) and interaction topologies;
- studying the robustness of the behaviour of "artificial tissues", where each RBN starts in the same attractor as the others, but there are random flips (a tissue would be stable if the networks continue to remain in the original attractor).

Another open issue concerns the possible meaning of our findings from the viewpoint of evolutionary theory. In the case of a tissue made by cells of the same type it may be supposed that they all are in the same attractor. Then it might be guessed [Kauffman, 1995] that the evolutionary pressure towards critical (or slightly subcritical) states should operate at the tissue level and not at the level of single cells. Our findings here point to the fact that the overall order at the collective level is highly sensitive to the dynamical properties at the level of single cells. Therefore there is no screening of the individual properties, and the selective pressure should favour the development of cells with appropriate individual dynamical properties. It would be interesting to consider a system endowed with some evolutionary dynamics to better understand the interplay between the evolution at the system level and that at the level of single cells.

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