# **Introduction to Random Boolean Networks**

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#### **Abstract**

The goal of this tutorial is to promote interest in the study of random Boolean networks (RBNs). These can be very interesting models, since one does not have to assume any functionality or particular connectivity of the networks to study their generic properties. Like this, RBNs have been used for exploring the configurations where life could emerge. The fact that RBNs are a generalization of cellular automata makes their research a very important topic.

The tutorial, intended for a broad audience, presents the state of the art in RBNs, spanning over several lines of research carried out by different groups. We focus on research done within artificial life, as we cannot exhaust the abundant research done over the decades related to RBNs.

# Introduction

Random Boolean networks (RBNs) were originally developed by Stuart Kauffman as a model of genetic regulatory networks (Kauffman, 1969; Kauffman, 1993). They are also known as N-K models, or Kauffman networks. RBNs are generic, because one does not assume any particular functionality or connectivity of the nodes: these are generated randomly. This is a useful approach if the specific structure and/or function of a system are very complex and unknown. The generic properties found in the model can be then applied to the particular system, in order to attempt to unveil its mechanisms.

Mathematical and computational modelling of genetic regulatory networks promises to uncover the fundamental principles of living systems in an integrative and holistic manner. It also paves the way toward the development of systematic approaches for effective therapeutic intervention in disease (Shmulevich et al., 2002). Single-gene studies are very limited for such intertwined networks.

Even when there is a Boolean simplification, many systems can be studied with near-binary states. This is because the behaviour of many systems is determined by thresholds, such as the ones determined by firing potentials of synapses in neurons, or activation potentials of chemical reactions in metabolic networks.

Furthermore, random Boolean networks have been applied and used as models in many different areas, such as evolutionary theory, mathematics, sociology, neural networks, robotics, and music generation.

In the next section, we will review the classic RBN model, its three characteristic phases (ordered, chaotic, and critical, some explorations of the model, alternatives, and extensions. Next we will review the effect of the updating scheme in RBNs: syncrhonous-asyncrhonous, deterministic-non-deterministic. We mention briefly some applications of RBNs, tools availabe for their study, and future lines of research.

### **Classical Model**

Kauffman proposed the original RBN model, supporting the hypothesis that living organisms could be constructed from random elements, without the need of precisely programmed elements (Kauffman, 1969). Certain types of RBNs are very robust, and have many analogies to living organisms.

A RBN consists of N nodes, which can take values of zero or one (Boolean). The state (zero or one) of each node is determined by K connections coming from other (or the same) nodes. The connections are wired randomly, but remain fixed during the dynamics of the network, i.e. "quenched". The way in which nodes affect each other is not only determined by their connections, but by logic functions, which are generated randomly, simply using lookup tables for each node, which take the states of the connecting nodes as inputs, and the state of the node as output. These also remain fixed (quenched) during the dynamics of the network.

We can see that RBNs are a generalization of Boolean cellular automata (CA) (von Neumann, 1966; Wolfram, 1986; Wuensche and Lesser, 1992), where the state of each node is not affected necessarily by its neighbours, but potentially by any node in the network. RBNs with N=K are also called random maps.

The updating of the nodes in classic RBNs is *synchronous*: the states of nodes at time t+1 depend on the states of nodes at time t, so that all nodes "march in step". We will see below that there can be drastic differences if we

change the updating scheme.

Usually, an initial random state is chosen for the RBN, and the dynamics flow according to the updating functions and scheme. Since the state space is finite  $(2^N)$ , eventually a state will be repeated. Since the dynamics are deterministic, this means that the network has reached an *attractor*. If the attractor consists of one state, it is called a *point* attractor or steady state, whereas if it consists of two or more states, it is called a *cycle* attractor or state cycle. The set of states that flow towards an attractor is called the attractor *basin*. An example of a RBN with N = 3 and K = 3 is shown in Figure 1.

If we try to imagine all possible networks, for each node there will be  $2^{2^K}$  possible functions. And each node has N!/(N-K)! possible ordered combinations for K different links. Therefore all the possible networks for given N and K will be (Harvey and Bossomaier, 1997):

$$\left(\frac{2^{2^K}N!}{(N-K)!}\right)^N \tag{1}$$

Note that many of these will be equivalent, but nevertheless we can see that the space of networks is immense. This makes things complicated for statistical studies. There is not enough computational power to exhaust all possible networks, so only "representative" properties can be studied. We should also mention that there is a very high variance in the statistical studies of RBNs.

However, general properties can be extracted from this huge universe of possible networks.

## Order, Chaos, and the Edge

In RBNs, as well as in many dynamical systems, three phases can be distinguished: *ordered*, *chaotic*, and *critical*. These phases can be identified with different methods, since they have several unique features.

If we plot the states of a network in a square lattice where the state of a node depends topologically on its neighbours, and let the dynamics flow, we can easily see which states change, and which ones are stable. In other words, we can observe how much the network changes. We can colour changing states with green, and static ones with red. In the ordered phase, we will see that after we select an initial random state, initially many states are changing (green), but quicky the dynamics stabilise, and most of the nodes will be static (red). There will be only few green "islands", surrounded by a red "frozen sea". In the chaotic regime, most of the states are changing constantly, so we have a green sea of changes, typically with red stable islands. The phase transition from the ordered to the chaotic regime, also known as the "edge of chaos", occurs when the ordered green sea breaks into green islands, and the red islands join and percolate through the lattice (Kauffman, 2000, pp. 166-167).

A second feature of these dynamical phases is related to "sensitivity to initial conditions", "damage spreading", and "robustness to perturbations" which are different ways of measuring the *stability* of a network. We can "mutate", "damage" or "perturb" a node of a RBN by flipping its state. We can also change a connection between two nodes, or in the lookup table of a node. Since nodes affect other nodes, we can measure how much a random change affects the rest of the network. In other words, we can measure how the damage spreads. This can be done by comparing the evolution of a "normal" network and a "perturbed" network. In the ordered regime, usually the damage does not spread: a "perturbed" network "returns" to the same path of the "normal" network. This is because changes cannot propagate from one green island to another. In the chaotic phase, these small changes tend to propagate through the network, making it highly sensitive to perturbations. This is because perturbations can propagate through the percolating green sea (Kauffman, 2000, pp. 168-170). This "butterfly effect" is a common characteristic of chaotic systems, where small perturbations can cause large consequences, and systems are sensitive to their initial conditions. At the edge of chaos, changes can propagate, but not necessarily through all the network.

A third feature is the convergence versus divergence of the trajectories in state space of the network dynamics. In the ordered phase, similar states tend to converge to the same state. In the chaotic regime, similar states tend to diverge. At the edge of chaos, nearby states tend to lie on trajectories that neither converge nor diverge in state space (Kauffman, 2000, p. 171).

Living systems, or computing systems, need certain stability to survive, or to keep information; but also flexibility to explore their space of possibilities. This has lead people to argue that life and computation occur more naturally at the edge of chaos (Langton, 1990), or at the ordered regime close to the edge of chaos (Kauffman, 2000). There could be ordered or chaotic systems able to perform the same computations, but the first ones would need more time, and the second more redundancy to cope with their instabilities. Therefore, we can assume that an adequate balance of order and chaos is more economic, thus preferable by natural selection.

**Phase Transitions in RBNs** Very early in the studies of RBNs, people realized in simulations that the networks with  $K \le 2$  were in the ordered regime, and networks with  $K \ge 3$ , were in the chaotic regime. In Figure 2 we can appreciate characteristic dynamics of RBNs in different phases.

We can identify phase transitions in RBNs in different ways. The main idea is to measure the effect of perturbations, the sensitivity to initial conditions, or damage spreading. This is analogous to Lyapunov exponents in continuous dynamics.

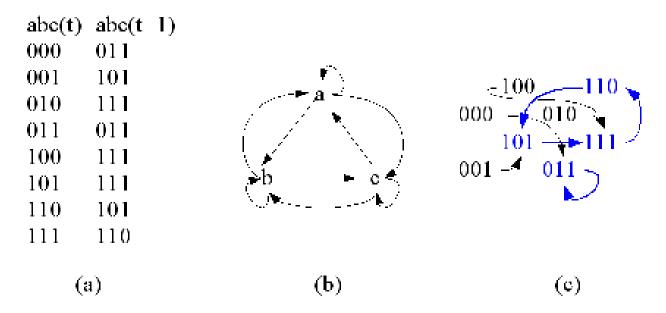


Figure 1: a) Lookup table for the state transitions. b) Wiring diagram: in this case, all nodes affect all nodes. c) State space diagram. There is one point attractor (011), with one state flowing into it (000), and one cycle attractor of period three  $(111 \rightarrow 110 \rightarrow 101)$ , with three states flowing into it (001, 010, 100).

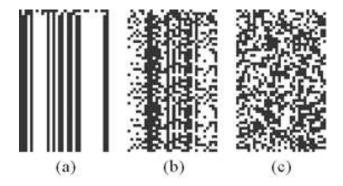


Figure 2: Trajectories through state space of RBNs within different phases, N = 32. A square represents the state of a node. Initial states at top, time flows downwards. a) ordered, K = 1. b) critical, K = 2. c) chaotic, K = 5

The phase transitions can be statistically or analytically obtained. Derrida and Pomeau were the first to determine analytically that the critical phase (edge of chaos) was found when K=2 (Derrida and Pomeau, 1986). They also introduced two generalizations of the classical model: one where they consider nonhomogeneous networks (K is not necessarily the same for all nodes, so we use as a parameter the mean connectivity  $\langle K \rangle$ ), and another where the values of lookup tables have a probability p of being one (and thus 1-p of being zero).

The method they used, also known as the Derrida annealed approximation, takes two random initial configura-

tions, and measures their overlap. This can be done with the normalized Hamming distance (2). Then one time step of the dynamics is computed, and the overlap is measured again. Then, a new set of rules and connections is chosen at random. It can be shown that this evolves in a onedimensional map.

$$H(A,B) = \frac{1}{n} \sum_{i=1}^{n} |a_i - b_i|$$
 (2)

For p=0.5, the map converges to the stable point H=0 when K<2, meaning that different states tend to converge (ordered dynamics). At K=2, this point becomes unstable, meaning that for K>2, different states tend to diverge (chaotic dynamics). It can be shown that the curve for critical K's depending on the value of p follows the equation (3), both for homogeneous and nonhomogeneous normal distributions of K. The plot of this equation can be seen in Figure 3.

$$\langle K \rangle = \frac{1}{2p(1-p)} \tag{3}$$

Luque and Solé made a simpler analytic determination of the phase transitions in networks, where they study the damage spreading when single nodes are perturbed (Luque and Solé, 1997b). They consider trees of nodes that can affect the state of other nodes in time. As a node has more connections, there will be an increase in the probability that a damage in a single node  $(0\rightarrow 1 \text{ or } 1\rightarrow 0)$  will percolate through the network.

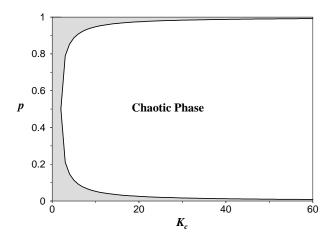


Figure 3: Phase diagram for the classical model, reprinted from (Aldana, 2003) with permission from Elsevier

Let us focus only in one node i at time t, and a node j of the several i can affect at time t+1. There is a probability p that j will be one, and a damage in i will modify j towards one with probability 1-p. The complementary case is the same. Now, for K nodes, we could expect that at least one change will occur if  $\langle K \rangle 2p(1-p) \geq 1$ , which leads to (3). This method can be also used for other types of networks. Luque and Solé later used the concept of Boolean derivative to define Lyapunov exponents in RBNs (Luque and Solé, 2000):

$$\lambda = \log\left[2p\left(1 - p\right)K\right] \tag{4}$$

where  $\lambda < 0$  represents the ordered phase,  $\lambda > 0$  the chaotic phase, and  $\lambda = 0$  the critical phase.

Statistical studies confirm these analytical results. However, it seems that, *in practice*, the size of the network can play a role in the phase transitions (Gershenson, 2004a; Gershenson, 2004b). We have seen that for large RBNs the phase transition (measured with the average of differences of normalized Hamming distances at  $t \to \infty$  and t = 0, for minimum initial distances of 1/N) is given for K shifted towards one, and for very small networks for K shifted towards three. This is probably because for large networks, there is a higher probability that a *subnetwork* will be generating more noise than "average", thus propagating damage.

In practice, there are very high standard deviations in RBN studies, which are normal in this type of systems (Mitchell et al., 1993). We can clearly find (or design) ordered networks for  $K \gg 3$  but on average, statistical studies confirm the analytical ones. Therefore, when we generate a random network, there are high probabilities that it will be in a specific regime according to K and p.

## **Explorations of the Classical Model**

There have been several explorations of different properties of RBNs, e.g. (Wuensche, 1997; Aldana-González et al., 2003). One can measure, for example, the number and length of attractors, the sizes and distributions of their basins, and how these depend on different parameters of RBNs, such as N, K, p, or the topology.

The structure of the nodes is very important for the dynamics of RBNs. The *descendants* of a node are the nodes that it affects, while the *ancestors* of a node are those that affect it. To have cycle attractors, i.e. of period greater than one, there should be at least one node that will be its own ancestor. A circuit of auto-activating nodes is called a *linkage loop*, and when there is no feedback, *linkage trees* are formed. Note that loops spread activation through trees, but not vice versa. The *relevant* elements of a network are those nodes that form linkage loops, and do not have constant functions, for these cause instabilities in the network, which might or not propagate. Note that as there are more connections in a network (higher *K*), the probability of having loops increases. Therefore, finding less stable dynamics for high values of *K* is natural.

We should not confuse the node diagrams with the state space diagrams. These show the dynamic trajectories of states of the network, while the first show the relations of the network elements. Classic RBNs are dissipative systems: a state can have only one *successor*, since the dynamics are deterministic, but more than one *predecessor* or *pre-image* can flow into a single state. The *in-degree* of a state is the number of predecessors it has. States without predecessors are called *garden-of-Eden* states. In this way, the dynamics flow from garden-of-Eden states, converging towards attractors. The time it takes to reach an attractor is called *transient* time

**Attractor Lengths** There have been analytic solutions of RBNs for K = 1 (Flyvbjerg and Kjaer, 1988), and for K = N (Derrida and Flyvbjerg, 1987). The challenging problem of finding a general analytic solution is still open. Some statistical studies have matched the analytic solutions for the special cases. People have observed the following, considering p = 0.5 (Kauffman, 1993; Bastolla and Parisi, 1998; Aldana-González et al., 2003):

For K = 1, the probability of having long attractors decreases exponentially, and the average number of cycles seems to be independent of N (Bastolla and Parisi, 1998). The median lengths of state cycles are of order  $\sqrt{N/2}$ .

For  $K \ge N$ , the average length of attractors and the transient times required to reach them grow exponentially. This restricts numerical investigations to small networks. The typical cycle length grows proportional to  $2^{N/2}$ .

For K = 2, at the critical phase, both the typical attractor lengths and the average number of attractors grow

algebraically with N. However, the precise dependence of N is a matter of dispute. People long believed that the average number of attractors and their length was proportional to  $\sqrt{N}$ , (Kauffman, 1969; Kauffman, 1993; Bastolla and Parisi, 1998). This result was very attractive, because the number of cell types and cell replication times for different organisms seem to scale also as the square root of genes for different species, although the precise number of genes of organisms keeps on changing. However, Bilke and Sjunnesson did a full exploration of networks, "decimating" irrelevant variables, and found that there is a linear dependence of number of attractors depending on N (Bilke and Sjunnesson, 2002). This linear dependence has been confirmed in other complete statistical studies (Gershenson, 2002; Gershenson et al., 2003). The difference seems to lie on the bias caused by undersampling the state space.

Since there are  $2^N$  states, full statistical studies are possible only for very small networks. For example, for N=20 there are more than a billion initial states. Therefore, these studies either concentrate on small networks, or take into account only very few initial states. In the first case, some properties of large networks will not be observed, whereas in the second, some attractors would not be found, especially if their basins consist of very few states.

More research is needed in this direction. One argument could be that even when there would be potentially more attractors than the ones found by limited sampling, in practice one would obtain the same result, since nature does not exhaust all possible configurations (e.g. there could be more cell types for a given number of genes, but *developing* into them is impossible, i.e. their basins are very small). Also, if we could get the general analytical solution, it could be that it would not match statistical studies, since a bias should be expected in the statistical sampling, due to very high standard deviations. However, for different purposes we might be more interested in the practical than the theoretical results, or vice versa.

**Convergence** One can measure the convergence of states with different parameters. One of them is the *G*-density, which is the density of garden-of-Eden states. Another is the in-degree frequency distribution, which can be plotted as a histogram (Wuensche, 1998). These measures reveal features at different phases.

At the **ordered** phase, there is a very high *G*-density, and high in-degree frequency. This leads to a high convergence, and very short transient times. The basins of attraction are very compact, with many states flowing into few states.

At the **critical** phase, the in-degree distribution approximates a power-law, i.e. there are few states with high in-degree, and many states with low in-degree. There is medium convergence.

At the **chaotic** phase, there are a relatively lower G-

density, and a high frequency of low in-degrees. The basins of attraction are very elongated, with few states flowing into other states. This makes average transient times very long, and in some cases infinite in practice. Therefore, there is low convergence.

Other parameters that can be useful for measuring convergence include Walker's "internal homogeneity" (Walker and Ashby, 1966), Langton's  $\lambda$  parameter (Langton, 1990), and Wuensche's Z parameter (Wuensche, 1999). The latter one, together with the "inputentropy variance", can be also used to automatically classify rules of CA into ordered, complex (critical), and chaotic (Wuensche, 1999). This is useful, since "interesting" behaviour in CA tends to occur within complex rule space.

#### **Multi-Valued Networks**

There have been some extensions to the Boolean idealization of classical RBNs, namely where nodes can take more than two values.

Solé, Luque, and Kauffman, and more recently Luque and Ballesteros have studied such multi-valued networks, and calculated their phase transitions (Solé et al., 2000; Luque and Ballesteros, 2004). For the special case where only two states are allowed, the results of Derrida are recovered.

In nature, the components of certain systems exhibit a behaviour that is better described with more than two states. Particular models should go beyond the boolean idealization. However, for theoretical purposes, we could combine several boolean nodes to act as a multi-valued one (codifying in base two its state).

### **Topologies**

Many systems have been found to have a scale-free topology. It seems to be a persistent feature of complex networks (Barabási, 2002): The Internet, molecular and genetic networks, social networks, technology graphs, language networks, food webs... they all share similar topological features: they have few elements with many links, and many elements with few links. This distribution seems to have several adaptive advantages, thought it is still not very well understood.

However, most RBNs which have been studied have homogeneous or normal topologies. Oosawa and Savageau studied the effects of topology in the properties of RBNs (Oosawa and Savageau, 2002). Their results showed that the topology can change drastically these properties. Networks with the more uniform rank distributions exhibit more and longer attractors and less entropy and mutual information (less correlation in their expression patterns), whereas more skewed topologies exhibit less and shorter attractors and more entropy and mutual information. A topology based on E. coli, which is scale-free, balances the parameters to avoid the disadvantages of the extreme topologies.

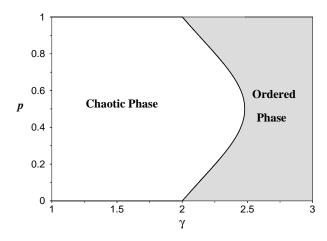


Figure 4: Phase diagram for the scale-free model, reprinted from (Aldana, 2003) with permission from Elsevier

Having this in mind, Aldana studied many properties of RBNs with scale-free topology (Aldana, 2003). The connectivity of scale-free RBNs can be generated randomly using the probability distribution  $P(k) = [\zeta(\gamma)k^{\gamma}]^{-1}$ , where  $\gamma > 1$  and  $\zeta(\gamma) = \sum_{k=1}^{\infty} k^{-\gamma}$  is the Riemann Zeta function. In this way, every node has at least one connection, but there are few ones with many connections. The properties of the network are no longer determined by the average connectivity, but by the exponent  $\gamma$ .

Following Derrida's method, Aldana found that the critical value of the exponent  $\gamma_c$  where the phase transition from order to chaos occurs is determined by the transcendental equation:

$$2p(1-p)\frac{\zeta(\gamma_c-1)}{\zeta(\gamma_c)} = 1$$
 (5)

The values for which (5) is satisfied are plotted in Figure 4. We can see that  $\gamma_c \in [2,2.5]$  for any value of p. The maximum value of  $\gamma_c \approx 2.47875$  is reached when p = 0.5.

The network properties at each phase (e.g. number and length of attractors, transient times) are analogous to the ones obtained with homogeneous RBNs.

An important result is that evolvability has more space in scale-free networks, since these can adapt even in the ordered regime, where changes in well-connected elements do propagate through the network. However, experimental evidence shows that most biological networks are scale free with exponent  $2 < \gamma < 2.5$  (Aldana, 2003), i.e. "at the edge of chaos". The advantages of scale-free topologies are beginning to become evident, although they have been not embraced by most researchers of RBNs.

### **RBN Control**

RBNs usually do not consider external inputs. However, real systems such as genetic networks can be influenced by ex-

ternal signals, such as molecular clocks related to sunlight.

Methods of chaos control have been successfully applied to chaotic **RBNs** (Luque and Solé, 1997a; Luque and Solé, 1998; Ballesteros and Luque, 2002). The main idea is to use a periodic function to drive a very chaotic network into a stable pattern. If a periodic function determines the states of some nodes at some time, these will have a regularity that can spread through the rest of the network, developing into a global periodic pattern. A high percentage of nodes should be controlled to achieve this. However, once we control a small chaotic network, we can use this to control a larger chaotic network, and this one to control an even larger one, and so on. This shows that it is possible to design chaotic networks controlled by few external signals to force them into regular behaviour.

# **Different Updating Schemes**

Kauffman has argued that the small average number of attractors found in RBNs compared with the number of possible states can account for the number of cell types and cell replication time in organisms compared with their number of genes (Kauffman, 1969; Kauffman, 1993). In those days, about eighty thousand genes were thought to conform the human genome. Therefore, if the genome is seen as a RBN close to the edge of chaos, the expected number of attractors would be less than three hundred, matching the observed number of cell types in humans. However, there are many drawbacks to this calculation. The Boolean idealization has been roughly accepted, since multi-valued networks have shown similar results. Now that the human genome has been mostly sequenced, it seems to consist of less than thirty five thousand genes. The topology seems to be scale-free. There is certain amount of junk or structural DNA, without functionality. Many functions seem to be biassed ( $p \neq 0.5$ ). But the heaviest argument has been the following: genes do not march in step. Genes do not change their states all at the same moment, but some do it earlier than others. There was no argument for the synchronicity in RBNs. In the next sections we will review research made related to this criticism.

# **Asynchronous RBNs**

Harvey and Bossomaier introduced the criticism to the synchronicity of classic RBNs (Harvey and Bossomaier, 1997). It was well known that asynchronicity could change drastically the dynamics of a synchronous system, such as the prisoner's dilemma (Huberman and Glance, 1993) or Conway's game of life (Bersini and Detours, 1994), and they did a similar thing for RBNs. Instead of updating the nodes synchronously, they defined asynchronous RBNs (ARBNs), where a node is picked up at random, and updated. We have to notice that ARBNs are not only asynchronous, but also non-deterministic. This destroys the cycle attractors of classical RBNs (CRBNs), since it is very difficult that a sequence of states will be repeated with a non-deterministic

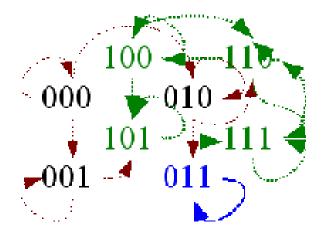


Figure 5: State space diagram of an ARBN, using the lookup table and wiring of Figure 1. Dotted arcs indicate stochastic transitions. There is one point attractor (011) and one loose attractor (100,101,110,111). The state (0,0,0) could lead to either attractor, via (010) or (001), respectively; i.e. it is in the basin of both attractors

updating. Point attractors still appear in ARBNs. There are also "loose" attractors, which can be seen as a subset of the state space which "traps" the dynamics after some time (all the possible states would rarely be visited).

The behaviour of ARBNs changes drastically from the one presented by CRBNs. Not only cycle-attractors disappear, but their basins can change. Also, states in ARBNs can be in more than one basin of attraction: they have the potentiality to fall into different attractors depending on which nodes are updated. An example of an ARBN can be appreciated in Figure 5.

Harvey and Bossomaier found that in theory, there is on average exactly one point attractor for any ARBN family. However, since we do not exhaust all possible networks, a skewed distribution of the point attractors is made evident: for some values ARBNs have more skewed distributions, i.e. few networks with many point attractors, several with none, so the averages tend to be lesser than one (except for the special case K = 0, where it is exactly one), reaching a minimum for K = 3 (Gershenson, 2002). It seems that there are no loose attractors for K = 1, and the probability of having one increases with K.

The properties of ARBNs, being so different to the ones of RBNs, casted a doubt on the validity of CRBNs as models of genetic regulatory networks.

**Rhythmic** Asynchronous RBNs If ARBNs were to model biological systems, how could they have any rhythm? An artificial way of solving this could be to implement a CRBN in an ARBN using Nehaniv's method (Nehaniv, 2002), but such a network would be very unre-

alistic. Another option could be to introduce proportionally large time delays in each node, so that each node could be updated only when most probably all the other nodes would have been updated (Klemm and Bornholdt, 2003). However, this is in a way a disguised synchronicity, and not more realistic than it.

Trying to find a solution, Di Paolo used genetic algorithms to explore the space of possible ARBNs, and found networks that do have rhythmic behaviour (Di Paolo, 2001). Recently, Rholfshagen and Di Paolo analysed the topology of such rhythmic ARBNs (Rholfshagen and Di Paolo, 2004). They found that invariably this consists of a "ring" of nodes that affect only one to the next, i.e. a linkage loop. The rest of the nodes affect nodes only outside the ring, so that activation can spread only outwards of the ring. In other words, there is a single linkage loop in the network, and the dynamics of this propagate only towards linkage trees. The number of nodes in the ring determines the average period of the rhythm in epochs (time steps $\times N$ ). This is because only one node can change the guiding dynamics of the network at a time, and any node is updated on average once an epoch. These results are very promising, but there are open tasks, such as the exploration of rhythmic ARBNs with more than one rhythmic attractor.

# **Deterministic Asynchronous RBNs**

I agree with the criticisms to the synchronous assumption: genes do not march in step. But I do not believe that they are random. Having this in mind, I proposed Deterministic Asynchronous RBNs (**DARBNs**) (Gershenson, 2002).

For having nodes that do not update simultaneously, we can introduce two parameters per node,  $P_i$  and  $Q_i$  ( $P_i, Q_i \in \mathbb{N}, P_i > Q_i$ ). All  $P_i$ 's and  $Q_i$ 's are generated randomly with maxima  $P_{max}$  and  $Q_{max}$ , and remain fixed. A node i will be updated when the modulus of the time step over  $P_i$  equals  $Q_i$ . Like this,  $P_i$  can be seen as the *period* of the node update, i.e. the number of time steps that will pass between updated, and  $Q_i$  can be seen as the *translation* of the node update. If at a certain time step more than one node fulfills its updating condition, then the nodes will be updated in an arbitrary order (e.g. from left to right), and the whole network will be updated with each node.

We can also define Deterministic Generalized Asynchronous RBNs (**DGARBNs**), where if more than one node fulfills its updating condition, all of these nodes will be updated synchronously. This makes DGARBNs semisynchronous.

For completeness, we also defined Generalized Asynchronous RBNs (**GARBNs**), which are like ARBNs, only that at each time step, some nodes are randomly selected, and these are updated synchronously. In this way, GARBNs are semi-synchronous, but non-deterministic. We can see examples of these RBNs in Figure 6.

We found out that all types of networks have the same

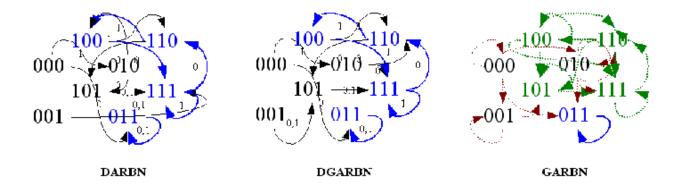


Figure 6: State space diagrams of a DARBN, a DGARBN, and a GARBN, using the lookup table and wiring of Figure 1. For the deterministic networks,  $\overline{P} = \{1,1,2\}$  and  $\overline{Q} = \{0,0,0\}$ . Numbers near arcs indicate the transitions which will occur at time modulus two. There is one point attractor (011) and one cycle attractor, but different than the one of a CRBN  $(100_1 \rightarrow 111_0 \rightarrow 111_1 \rightarrow 110_0)$ , but the basins are different. For the GARBN, there is the same point attractor and loose attractor than for the ARBN, but there are more possible stochastic transitions, i.e. changes can potentially propagate faster

point attractors (Gershenson, 2002). This is because no matter which node is updated, the state will not change. Therefore, the updating scheme does not affect point attractors. However, the attractor basins do change, and other types of attractor. DARBNs and DGARBNs have properties much closer to the ones of CRBNs (Gershenson, 2002). Since they are deterministic, cycle attractors are present. The number of attractors, like in CRBNs, increases linearly with N, but more slowly, meaning that there are even fewer attractors for a high possible number of states<sup>1</sup>. Also, the percentage of states in attractors is reduced exponentially, as with CRBNs, but even faster. These results imply that DGARBNs and DARBNs can perform even more *complexity reduction* than CRBNs. We also concluded that the difference of CRBNs and ARBNs lies more in non-determinism than in asynchronicity.

Moreover, we proposed a method for mapping any deterministic asynchronous RBN into a CRBN. The main idea is to introduce new nodes, connected to every other previous node, which codify in base two the maximum period of the DARBN. This is the least common multiple of all  $P_i$ 's.

Asynchronicity and Feedback We have to mention that Thomas developed much earlier an asynchronous model of RBNs using delays, which could be both deterministic or stochastic, depending on the certainty of the delays (Thomas, 1973; Thomas, 1978; Thomas, 1991). However, these models were proposed and used mainly for the analysis of precise networks, their circuits, and feedback loops, and to my knowledge they have been not used for analytical or statistical studies of ensembles ("families") of networks. An

interesting finding of Thomas and coworkers was the following: a positive feedback loop (direct or indirect autocatalysis) in a network implies the choice of two stable states, i.e. point attractors. This gives the property of *multistationarity*. On the other hand, a negative feedback loop implies periodic behaviour, i.e. point or cycle attractors. This can be described as *homeostasis*. The combinations of positive and negative feedback loops give RBNs a plethora of possible behaviours, many of which are found in living systems.

### **Mixed-context RBNs**

We can see the sets  $\overline{P}$  and  $\overline{Q}$ , consisting of all  $P_i$ 's and  $Q_i$ 's respectively, as the *context* of a network. This is because external factors, such as temperature, can change the updating periods of elements of a system. Like this, the same DGARBN can have different behaviours in different contexts, i.e. for different  $\overline{P}$  and  $\overline{Q}$ .

Having this in mind, we can introduce non-determinism in contextual RBNs in a very specific way (Gershenson et al., 2003). For a given DGARBN, we can have M "pure" contexts. Then, each R time steps we select randomly one of these contexts, and use it in the network. Thus, we have defined Mixed-context RBNs (**MxRBNs**). An example is shown in Figure 7.

We should note that the non-determinism in MxRBNs is introduced in a very controlled fashion. In GARBNs we have N "coin flips" per time step (selecting which nodes will be updated). In ARBNs we have one coin flip per time step (selecting which node will be updated). In MxRBNs we have one coin flip per R time steps (selecting which context will be used). The higher the value of R and the lower number of R contexts, the less stochasticity there will be.

MxRBNs have very similar number of attractors than ARBNs and GARBNs (considering loose attractors), and also their number increases linearly and slowly with *N*.

<sup>&</sup>lt;sup>1</sup>ARBNs and GARBNs have also a linear increase in the average number of attractors, when we consider loose attractors in the statistics (Gershenson, 2004b). These RBNs have less attractors than deterministic RBNs, but their sizes are much larger.

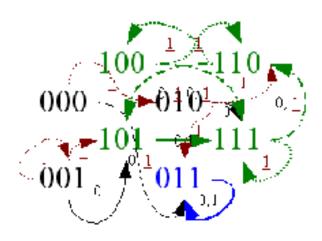


Figure 7: State space diagram of a MxRBN, using the lookup table and wiring of Figure 1. M=2 contexts.  $\overline{P}_1 = \{1,1,2\}, \overline{P}_2 = \{2,1,1\}$  and  $\overline{Q}_1 = \overline{Q}_2 = \{0,0,0\}$ . Therefore, the dynamics are deterministic and context independent when the modulus of time over two is zero, and depend on the context when it is one. There is one point attractor (011) and one loose attractor (100,101,110,111)

However, they can perform significantly more *complexity reduction* (Gershenson, 2004b), even more than CRBNs, but not as much as DGARBNs or DARBNs. This means that very few states, from all their possible states, lie in their attractors.

We can see that the *context* in RBNs allows a high increase in complexity reduction, since it allows information to be "thrown" into the context. We can restate this with the following argument. Any updating scheme can perform in theory any computation. The more non-determinism we introduce, the more redundancy in the network we need to perform the computation. We require more elements. On the other hand, *contextual* RBNs can exploit information in their contexts, which CRBNs need to codify explicitly. In terms of number of elements required for a computation, less will be required in a DGARBN. Then the ascending order would be of DARBNs, MxRBNs, CRBNs, ARBNs, and finally GARBNs.

### **Classification of RBNs**

We can classify different types of RBNs according to their updating scheme (Gershenson, 2002). All RBNs are discrete dynamical networks (DDNs) (Wuensche, 1997), since they have discrete time, states, and values. The most general type of RBNs are GARBNs, since all of the others can be seen as special cases of them. If, on one hand, we make them deterministic with a context conformed by  $\overline{P}$  and  $\overline{Q}$ , then we would have DGARBNs. MxRBNs would be more general than DGARBNs, since they have M contexts. DGARBNs are a special case, when M=1 or  $R\to$ 

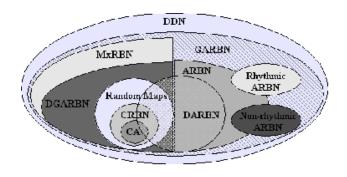


Figure 8: Classification of random Boolean networks, according to their updating scheme

∞. Random maps would be a special case, of DGARBNs when  $\overline{P} = \overline{1}$ ,  $\overline{Q} = \overline{0}$ , and N = K. Random maps can simulate with redundancy any CRBN, but not vice versa, so the latter can be seen as a special case of the former. Boolean CA are special cases of CRBNs, where the connectivity and functionality are the same, i.e. symmetrical, for all nodes. From GARBNs, on the other hand, we can limit to the update of only one node at a time, and we will have ARBNs (Harvey and Bossomaier, 1997). If we make them deterministic with a context, then we have DARBNs. These and DGARBNs overlap on the special cases when one and only one node is updated at a time step. There are special ARBNs with rhythmic and nonrhythmic attractors (Di Paolo, 2001), and probably there are also GARBNs with these types of attractors. We should note that particular instantiations of Thomas' asynchronous RBNs (Thomas, 1973; Thomas, 1978; Thomas, 1991) could be seen as ARBNs or DARBNs, depending on the certainty of the delays. We can see a diagram of the proposed classification in Figure 8.

We could add a third dimension to Figure 8, indicating the number of allowed states per node, to include multi-valued networks. Special cases of the different RBNs presented can be also interesting, such as networks with scale-free or another particular topology, or CA with different updating schemes. We can see that DDNs offer a rich variety of models, many of which have not been yet studied.

The more general a type of RBN is, the more trajectories in state space it can have. Note that since we only change the updating scheme, we can easily compare the behaviour of the same network, i.e. rules and connectivity, with different schemes. We have seen that the dynamics and the basins of attraction can change considerably as we switch updating scheme, although in extreme cases, such as K=0 or when the number of attractors equals N, different network types do have the same behaviour. An example can be seen in Figure 9. However, we have recently found that, even when the precise stability of RBNs depends on the updating scheme, the phase transition seems to be very similar independently



Figure 9: Dynamics of the same RBN under different updating schemes, with N = 32, K = 2, p = 0.5, for the same initial state. For contextual RBNs, maxP = 5, maxQ = 4. For MxRBN, M = 2, R = 10. Few states are frozen (e.g. second from left to right is always black, the fourth is always white), but dynamics change drastically with updating scheme. Note that in spite of being non-deterministic, the dynamics of the MxRBN are visually more similar to the ones of DARBN or DGARBN than ARBN or GARBN.

of the updating scheme (Gershenson, 2004a).

# **Applications**

The generality of RBNs makes them applicable in a wide range of domains. In this section we review some of the main areas where RBNs have been applied.

## **Genetic Regulatory Networks**

Most cells in multicellular organisms have the same genetic information, although the genes that are expressed or "on" change at every moment. Genes interact with each other via proteins, but there are so many of them, that genetic regulation is not fully understood. RBNs were originally proposed to tackle this problem (Kauffman, 1969). They have been used not only to explore their generic properties, but also to analyse and predict genomic interactions (Somogyi and Sniegoski, 1996; Somogyi et al., 1997; D'haeseleer et al., 1998). Since the genomic data is incomplete, and certain knowledge about real genetic networks is required for disease treatment, probabilistic boolean networks (**PBNs**) were introduced by Shmulevich and coworkers. These are useful for inferring possible gene functionality from incomplete data (Shmulevich et al., 2002).

There has been experimental evidence for Kauffman's interpretation of cell types as attractors of RBNs (Huang and Ingber, 2000), which encourages more RBN research. It seems that many genes do not play a role in the type of a cell. They certainly might have other functions, for example related to the cell's metabolism. Nevertheless, there is a very strong correlation for some genes as a cell type is mechanically forced, which shows that the activation patterns of a subset of genes can indicate the type of a cell.

There have been also other models of genetic regulatory networks which include continuos states (Glass and Kauffman, 1973; Kappler et al., 2002). Using differential equations in which gene interactions are incorporated as logical functions, there is no need for a clock to calculate the dynamics.

### **Evolution and Computation**

RBNs are very tempting models for studying evolution, since we do not assume any functionality. It is now known that evolvability is expected at the edge of chaos, where small changes do not destroy previous functionality, but can explore their space of possibilities incrementally. RBNs also present naturally modules, a desired feature in evolvable systems.

Fernández and Solé have studied issues related to the evolvability of networks, such as robustness, redundancy, degeneracy, and modularity (Fernández and Solé, 2004). This is a very abstract study of the requirements of life,

since one way we can distinguish physical from biological systems is to note that the latter perform computations (Hopfield, 1994). By understanding how a network can evolve to perform certain computations, we are answering questions on how complex organisms evolved on Earth. There have been some studies of evolution of RBNs using genetic algorithms with promising results (Stern, 1999; Lemke et al., 2001).

Related work is the one carried out in the area of evolvable hardware, where complex logical circuits are evolved in reconfigurable hardware (Thompson, 1998). Also, research in RBNs could provide valuable feedback for evolving logical circuits.

#### Other areas

RBNs have been used in several other areas, such as neural networks (Huepe-Minoletti and Aldana-González, 2002), social modelling (Shelling, 1971), robotics (Quick et al., 2003), and music generation (Dorin, 2000).

Finally, RBNs are interesting mathematical objects by themselves. Since cellular automata are special cases of RBNs, we can find many more applications there, e.g. in percolation theory (Stauffer, 1985).

## **Tools**

There are several software applications available for the exploration of different properties of RBNs:

**DDLab.** Developed by Andy Wuensche, Discrete Dynamics Lab is probably the most powerful tool for studying discrete dynamical networks: synchronous RBNs and CA, including multi-valued networks. One can observe the dynamics of the networks, explore their basins of attraction. It includes a wide variety of measures, data, analysis and statistics. It is very well documented, and runs on most platforms. It is available at http://www.ddlab.com

**RBN Toolbox** for Matlab was developed by Christian Schwarzer and Christof Teuscher. It is useful for simulating and visualizing RBNs. It includes different updating schemes, statistical functions, and other features. It is available at http://www.teuscher.ch/rbntoolbox

**RBNLab** was developed by the author. It can graphically simulate the dynamics of RBNs with different updating schemes. It can find attractors (point, cycle, and loose), and generate different statistics. It is implemented in Java, so it runs on most platforms. The source code and the program are available at http://rbn.sourceforge.net

**BN/PBN Toolbox** for Matlab is maintained by Harri Lähdesmäki and Ilya Shmulevich. It can be used to work with CRBNs and Probabilistic Boolean Networks. It includes functions for simulating the network dynamics, computing network statistics (numbers and sizes of attractors, basins, transient lengths, Derrida curves, percolation on 2-D lattices, influence matrices), computing state transition matrices and obtaining stationary distributions, inferring net-

works from data, generating random networks and functions, visualization and printing, intervention, and membership testing of Boolean functions. It is available at http://www2.mdanderson.org/app/ilya/PBN/PBN.htm

## **Future Lines of Research**

There are many promising lines to be followed in RBN research. The ensemble approach is promising for understanding and predicting properties of cells and organisms (Kauffman, 2004). The use of RBNs for data mining and genetic network analysis is being propagated (D'haeseleer et al., 1998; Shmulevich et al., 2002). Because of their generality, RBNs are also interesting for studying evolvability and adaptability at an abstract level. Generalizations, combinations, and refinements of the different types of RBNs presented are also worth pursuing, e.g. ensemble studies on Thomas' ARBNs or PBNs, scale-free multi-valued DGARBNs, etc. Also, the challenging problem of finding analytical solutions for CRBNs is still evading us. In short, there is plenty of RBN research to do in the years to come.

#### **Conclusions**

This tutorial was a brief introduction to some of the research related to random Boolean networks in the past decades. There has been much more work that could not be included because of different constrains. However, the readers are invited to deepen their knowledge in RBNs following the references of this tutorial.

There will be many arguments on which will be the "best" model for different purposes and phenomena. CRBNs may be not very close to reality, but full ARBNs are even farther, since genes are not updated in a fully stochastic manner<sup>2</sup>. Models such as DGARBNs or MxRBNs seem to be more realistic, although they are more complicated. For ensemble studies, for simplicity, CRBNs can be justifiable (Gershenson, 2004b). For modelling particular genetic networks, other models might be more realistic and useful, such as PBNs, or the models of Thomas, Glass, or Somogyi. However, their complexity would make difficult, but still interesting, ensemble studies on them. We can say that different models will be more suitable for different purposes, and most of them are worth exploring.

We can say that RBNs are very inviting, because of their generality: one can model at a very abstract level many phenomena, and study generic properties of networks independently of their functionality. They have also raised important

<sup>&</sup>lt;sup>2</sup>We have found out that ARBNs and GARBNs perform less complexity reduction than deterministic RBNs or MxRBNs (Gershenson, 2004a). This indicates that determinism or quasi-determinism is a desirable property of natural systems. How could this evolve, is a different question, and studies such as the ones on rhythmic ARBNs (Di Paolo, 2001) are providing interesting answers.

questions related to the differences between theory and practice, since some analytical or statistical results do not match each other. This can be explained with skewed distributions and very high standard deviations found in RBN statistics. However, this brings deeper philosophical questions: how much should we care about theory, and how much should we care about practice? Which one will help us understand better the phenomena we try to study? It seems that a careful *balance* of both is required. However, it is unknown how this balance might be like.

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