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The circular topology of rhythm in asynchronous random Boolean networks

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Abstract

The analysis of previously evolved rhythmic asynchronous random Boolean networks [Biosystems 59 (2001) 185] reveals common topological characteristics indicating that rhythm originates from a circular functional structure. The rhythm generating core of the network has the form of a closed ring which operates as a synchronisation substrate by supporting a travelling wave of state change; the size of the ring corresponds well with the period of oscillation. The remaining nodes in the network are either stationary or follow the activity of the ring without feeding back into it so as to form a coherent whole. Rings are typically formed early on in the evolutionary search process. Alternatively, long chains of nodes are favoured before they close upon themselves to stabilize. Analysis of asynchronous networks with de-correlated (non-rhythmic, non-stationary) attractors reveals no such common topological characteristics. These results have been obtained using statistical analysis and a specifically developed bottom–up pruning algorithm. This algorithm works from local interactions to global configuration by eliminating redundant links. The suitability of the algorithm has been confirmed by both numerical and single lesion analysis. The ring topology solution for the generation of rhythm implies that it will be harder to evolve rhythmic networks for big sizes and small periods and for bigger number of connections per node. These trends are confirmed empirically. Finally, the identified mechanisms are utilised to handcraft rhythmic networks of different periods showing that a low number of connections suffices for a large variety of rhythms. Random asynchronous update forces the evolved solutions to be highly robust maintaining their performance in the presence of intrinsic noise. The biological implications of such robust designs for molecular clocks are discussed.

Keywords: Random Boolean networks; Random asynchronous updating; Ring topology; Genetic algorithms; Rhythmic phenomena

1. Introduction

Intracellular molecular clocks are a necessary, but not sufficient element in the generation of circadian and other biological rhythms (Roennenberg and Merrow, 2001). It is generally acknowledged that regulation across networks of oscillating cells, and entrainment with external signals are necessary for regulating a 24-h cycle. However, molecular clocks in themselves can be quite robust (Young, 1998) maintaining a rhythm even when cells divide faster than the period of oscillation, for instance in cyanobacteria (Kondo et al., 1997).

Random Boolean network (RBN) models of genetic regulation have naturally been associated with cell cycles and molecular oscillations due to the fact that their behaviour will always fall into some sort of cyclic attractor, (Kauffman, 1969, 1993; Bagley and Glass, 1996). When these cycles are very long (much larger than the size of the network) they are often called “chaotic”, but for smaller cycles it is possible to

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associate the activity of an RBN with that of a molecular clock. Consequently, they might provide some insight into the general properties of such clocks, albeit at an abstract level where gene activity is simplified to only two states: active or inactive.

The problem, as noticed before for these systems (Gunji, 1990; Harvey and Bossomaier, 1997; Ingerson and Buvel, 1984; Schonfisch and de Roos, 1999) and in general (Huberman and Glance, 1993; Ruxton and Saravia, 1998), is that the order expressed in RBN models depends crucially on the assumption of synchronous updating of its elements. This assumption is in general not justified empirically. It is also methodologically unsound when the states of the system are discrete (Di Paolo, 2001). The likelihood that all the infinitely fast transitions in the network occur at the same instant is zero in the absence of an external clock. In other words, the artifactual source of synchrony in the system makes parallel updating a bad choice when studying systems capable of generating rhythmic activity on their own.

Asynchronous updating of logical circuits has been studied by Thomas (Thomas, 1973, 1978) for situations when the order of update is known and therefore still deterministic. Later, these studies have been extended to many-valued logical gates, and the role of positive and negative feedback loops on determining attractor dynamics (Thomas, 1991; Thomas et al., 1995). This work is different from the ensemble approach mentioned above using random networks and not subject to the same criticism of synchronous update. However, it relies on a clearly distinct order of events which may not always be the case in large noisy circuits.

In contrast, random serial updating fits particularly well with the Boolean assumption where state transitions are considered of negligible duration and the system is noisy—but of course would be naturally superseded by other serial or parallel updating schemes when these are empirically justified. For instance, it is possible to replicate the behaviour of synchronous RBNs using especially constructed asynchronous networks where memory of a previous state and a local synchronising device is added to each node and restrictions are imposed on the update of visible states (Nehaniv, 2002). Finding a natural analogy of such mechanisms would validate the use of parallel update. So far, however, no biological justification has been offered for the necessary coordinating mechanisms and so we find that it is more appropriate to update these systems asynchronously using a random order. Such asynchronous RBNs (ARBNs) exhibit very different behaviour than their much studied synchronous counterparts as an ensemble, including much larger basins of attractions for fixed point attractors that promote rapid and widespread convergence to stationary states, the impossibility of strict cycles due to the randomness in the update, and the existence of non-stationary ‘loose’ attractors showing in general no distinct pattern (Harvey and Bossomaier, 1997). It is possible, however, to find within the latter attractors with marked rhythms using genetic algorithms (Di Paolo, 2001); but such attractors seem to be rare. Arguably, understanding when and how an asynchronous network will behave rhythmically is likely to provide information of interest regarding the abstract principles of molecular clocks. In this paper we propose to continue the study initiated in Di Paolo (2001) on the generation of rhythmic ARBNs. Although robust rhythmic networks have been found for different parameters using a genetic algorithm (GA), until now little attention has been paid to understanding how rhythm is produced. In most cases studied, rhythmic patterns are an emergent feature of the network dynamics exhibiting robustness to inherent noise in the system. Understanding which mechanisms are able of generating such robust patterns is of biological interest.

The observed robustness of rhythmic behaviour suggests a distributed rather than a central, localised underlying mechanism. However, as we shall see, this is not totally independent of the relations between network size (N), number of inputs per node (K), and the rhythmic period (P) and this fact may explain why certain combinations of parameters make rhythm more difficult to evolve using a GA.

We develop and apply a method for simplifying the topologies of evolved ARBNs and we discover that underlying the generation of rhythm in almost all cases studied lies a ring-shaped functional architecture whose size and Boolean properties correspond to the rhythmic period. Such topological solutions to the generation of rhythms are well-known in natural oscillators (Winfree, 2001). We compare this topology with the topologies found for non-rhythmic networks and study the effects of network size and connectivity on the likelihood of the GA finding adequate partial topologies. Finally, we use this knowledge to hand-craft rhythmic networks of increased complexity and discuss the biological and engineering implications.

2. Methods

Random asynchronous update of the network is implemented by updating a node at random using a uniform probability with replacement and repeating this operation N times per time-step. On average each node in the network is updated once per time-step. The new state is computed as a Boolean function of the states of the K corresponding input nodes.

As in Di Paolo (2001), we define rhythmic activity in a network using the concept of pseudo-periodicity. This measure uses the relational properties of a succession of states and indicates the degree to which a given state of N nodes approximately recurs after approximately P time-steps (i.e., $P \times N$ single node updates). Networks ranking high on this scale will be called pseudo-periodic. The similarity between states at time j and j' is defined as:

$$C(j, j') = \frac{1}{N} \sum_{i=1}^{N} s_i^*(j) s_i^*(j'),$$

where $s_i^*(j)$ is the scaling of $s_i(j)$ onto [-1, 1]. The overall correlation of a network's output is obtained by an average correlation between states and their kth successors over M successive states with $M \gg N$:

$$\mathrm{AC}(k) = \frac{1}{M} \sum_{j=1}^{M} C(j, j+k),$$

with $k = 0, 1, 2, \ldots$ and M being sufficiently large. This measure, called autocorrelation (AC), will return an estimate of how well each state is correlated to a state occurring k time-steps afterwards. In the case of rhythmic networks, there will be a distinct peak at values k close to the period P.

A generational GA with mutation, crossover and rank-based selection is used to search for rhythmic ARBNs (Di Paolo, 2001; Mitchell, 1996). Their properties are encoded in a genome of length:

$$G = N(K \log_2 N' + 2^K),$$

where N' is the first power of 2 greater than or equal to N. For each node, the K inputs and corresponding Boolean function are expressed as binary strings. Each network is run from a random initial condition for around 500–1000 time-steps over 5–8 trials, measuring the autocorrelation after each trial. The autocorrelation is estimated for $k = 0, 1, 2, \ldots, 2N - 1$ and averaged over all but the last $2N$ states of the run. The fitness is determined by the difference between the autocorrelation and the target function and is averaged over the number of trials. The value of one standard deviation is deducted to benefit networks with a low variance between trials. The size of the population is 90 and the rate of mutation is kept around 0.2 per genotype. The crossover is uniform and the entire population is replaced each generation. Other search methods may be used with similar results but using a GA can provide some information on how such networks could evolve in nature.

The original target correlation had been defined using steps between 0 and 1: The value of 1 is used around the chosen period P and it multiples such that the network will show high correlation around that period. Values of 1 are assigned to values of k in $[mP - e, mP + e]$, with $m = 0, 1, 2, \ldots$. The value of 0 is assigned to all other values of k. The fitness of a network is given by $1 - D$, where D is the normalised distance between the network's autocorrelation and the target function. Other target correlations have been used also, producing rhythmic networks with slightly different characteristics. These include other step values within the numerical range of [-1, 1] and measuring and maximising the relative distance between the period $k = P$ (where the peak should be) and $k = 0.5P$ (where the trough should be) and their multiples. A constant target correlation of $\mathrm{AC}(k) = 0$ may be used to evolve de-correlated networks that have non-stationary, non-rhythmic output.

A simple statistical procedure is used to prune individual connections in the evolved networks to approximate the functional architecture of a network that effectively corresponds to the output produced. The method is simple yet results have been confirmed as robust using both single lesions and statistical output analysis. The pruning algorithm utilises the concept of natural tendencies. Each Boolean function is classified as being determined, biased or neutral. If all the output values are identical (i.e., all 1's or 0's) then the function is determined as its outcome is always known (e.g., 0000). If the function is exactly divided between the two values, then it is neutral as it does not have a natural tendency to be in one state or the other (e.g., 0110). If one value is dominant, the function is biased as it is statistically more likely (other things being equal) to be in the state of the more frequent value (e.g., 0001). This information suffices to approximate the networks' determining structure (which we will call functional architecture) to a satisfactory degree.

The following steps of the pruning algorithm are applied for each node in turn:

1. Nodes whose Boolean function is either tautology or contradiction are labelled as "stationary". The inputs to these nodes can be pruned as they make no difference to the outcome of the node.
2. If the Boolean function of the node in question coincides with one of the columns of its truth table, the input node corresponding to that column is kept and all other inputs to this node may be pruned.
3. The Boolean functions of the input nodes are examined: If all are neutral, none can be pruned. If any of the functions is biased, the effect of this bias is used to determine how the influences of all inputs are affected: if one node has a natural tendency towards the value 1, for example, all inputs are measured against the part of the Boolean function where the value of the identified input is 1 in the truth table. This is done for every node (i.e., if two nodes are biased, the focus is shifted towards the part in the Boolean function that corresponds to the bias expressed by both inputs). If one input turns out to be determining the output while none of the others do, all other inputs are pruned. If several inputs have identical influences but some have none, they may be pruned.
4. Special attention has to be given if the same node serves as input multiple times. In these cases, only columns which have identical values need to be considered. This may lead to pruning despite all inputs being neutral.

The algorithm has successfully been applied to networks of size $N = 16$ to 64 and $K = 1$, 2 or 3. For higher values of K, different levels of certainty may be introduced to deal with the different degrees of tendencies so as to produce something similar to conditional probability tables.

3. Results

Different networks have been studied using the pruning algorithm. Twenty networks with $N = 16$,

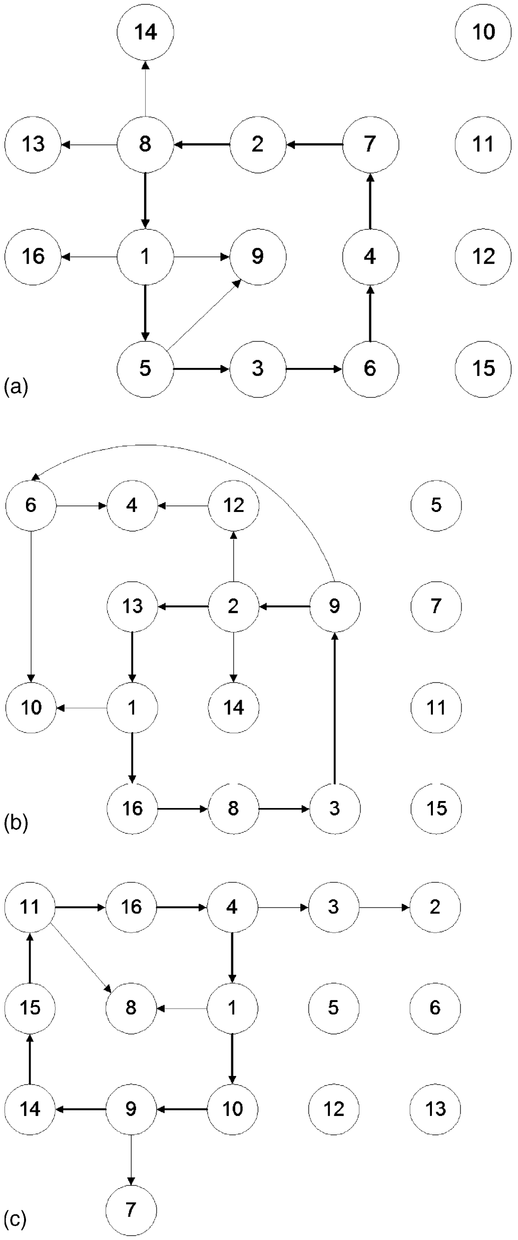

Fig. 1. Examples of three pruned networks ($N = 16$, $K = 2$, $P = N$). The number of nodes in the ring corresponds to half the period of the overall network (8 nodes = period 16), nodes without input are stationary; see text.

$K = 2$ and a target period $P = N$ were evolved using the target correlation [0, 1]. See Di Paolo (2001) for example runs of evolved autocorrelation functions of similar rhythmic networks. Their functional structure was then simplified using the pruning method. In all cases the reduced functional topology of the networks exhibited striking similarity to the topologies represented by the three examples shown in Fig. 1. Notice that many links have been pruned and most nodes show either one or no inputs.

A common feature of these topologies is the underlying directed ring structure. Upon analysis of the Boolean relation between links in the ring we find that this structure is the source of rhythm. Each node in the closed ring maintains a relational state to exactly one other node in the ring. The only possible Boolean dependencies on the input node are either to take the same or the opposite of its value. Each link in the ring may consequently be labelled as either "same" or "opposite". A node may only change its value given that the output of the previous node has been altered so as to disturb the relational synchronisation between the pair of nodes. In other words, a node only changes if and only if its input has been changed previously. The overall effect of this architecture is statistical optimality: only a single node within the ring changes its state per time-step on average with high probability. The other important feature of this topology (not shown in the figures) is there is an odd number of "opposite" links in the ring. It follows that a ring of N nodes will never settle into a stationary attractor and will have a natural frequency of $2N$ while covering the maximum Hamming distance possible during each cycle and so behaving like a logical Möbius band.

The other nodes in the network are either stationary or follow the centralised clock and are therefore entrained as well. They do so by taking inputs from nodes in the ring and typically not feeding back into it (although it is possible for a few links to feedback as long as the entrainment is maintained). All examined networks correspond well with the hypothesis that the ring topology underlies the generation of rhythm and the size of the centralised ring almost always accurately reflects the overall rhythm produced by the network. Lesion analysis confirms this hypothesis: rhythm breaks down if a node contributing functionally to the ring is lesioned but not in other cases.

Applying the pruning algorithm to random networks or networks that have been evolved to be de-correlated ($\mathrm{AC}(k) = 0$) neither results in ring structures nor in structures showing any common

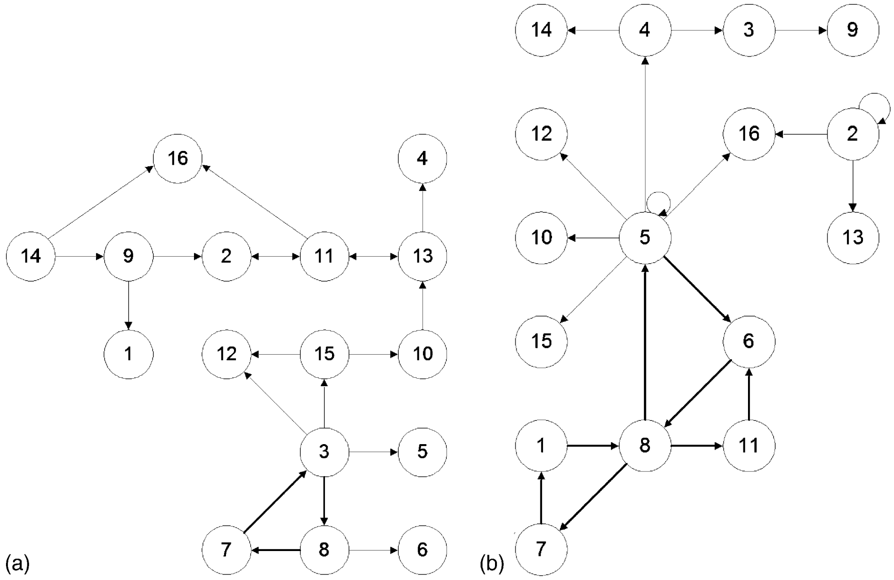

Fig. 2. Examples of (a) a de-correlated network ($N = 16$, $K = 2$, ring: [3, 8, 7] and a long chain) and (b) a synchronously evolved rhythmic network without a ring corresponding to the period ($N = 16$, $K = 2$, $P = N$, rings: [1, 8, 7], [5, 6, 8], [8, 11, 6]).

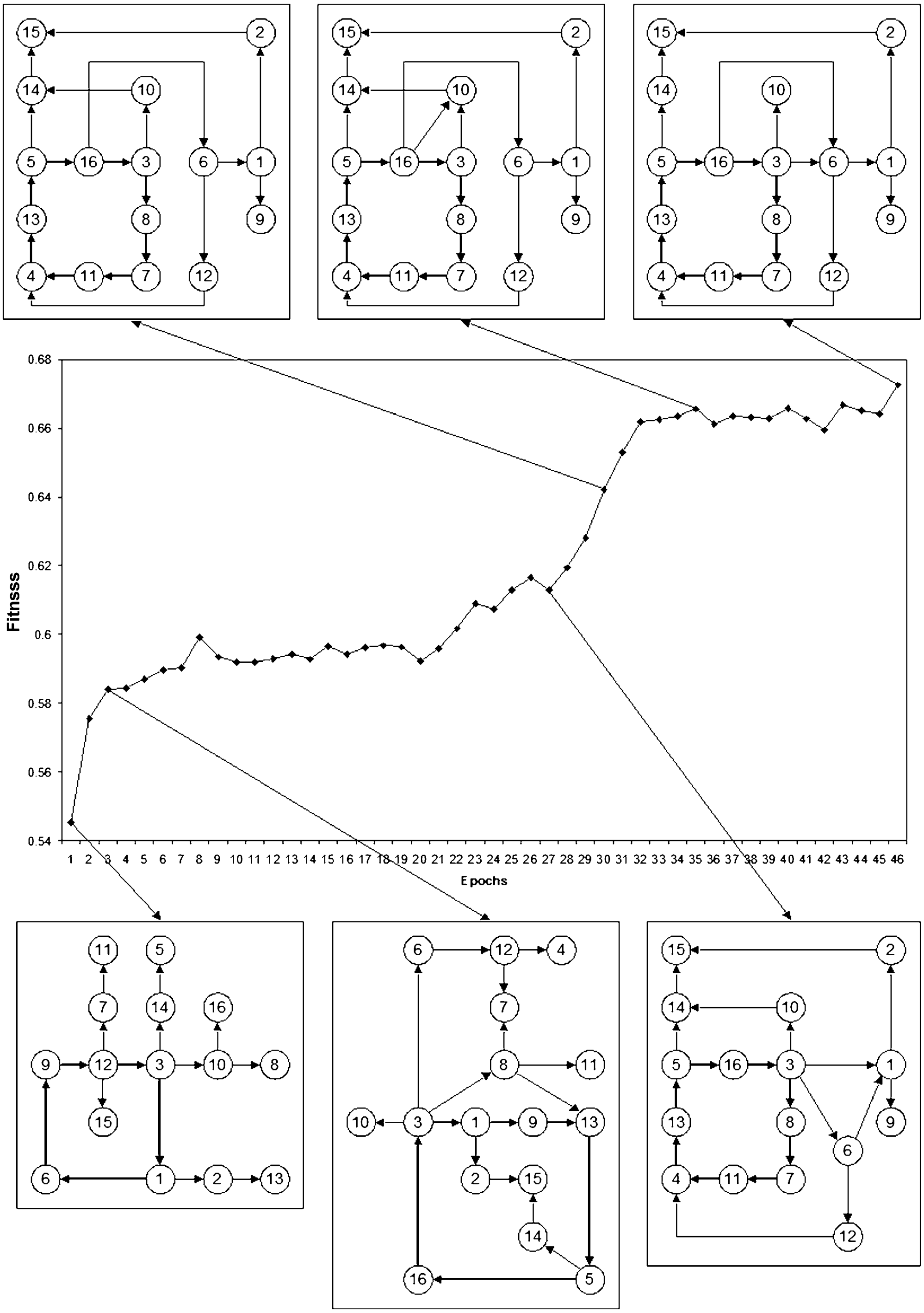

Fig. 3. The evolution of a robust rhythmic architecture with samples taken at different points. Central inset: plot of fitness vs. number of generations. A ring is formed early on; increases in fitness correspond to changes of the size of the ring and the distribution of Boolean functions.

characteristics. Evolving networks of identical parameters but using a synchronous update scheme may result in ordered topologies; rings are, however, not necessary for rhythm to emerge given the presence of synchrony (Fig. 2b). Most of these synchronous networks do not exhibit rhythmic properties when updated asynchronously. Asynchronously evolved networks, however, do exhibit their respective rhythm

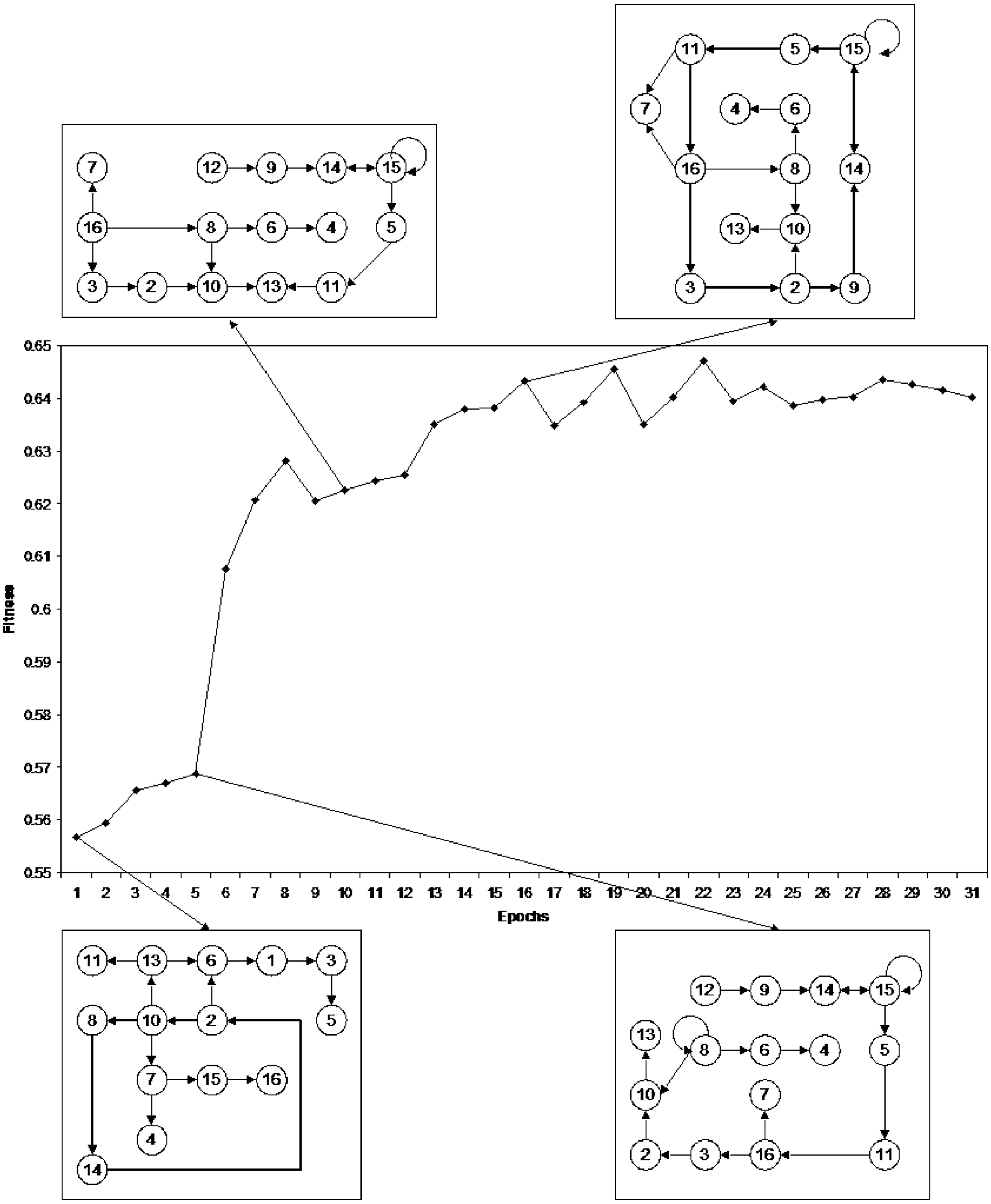

Fig. 4. The evolution of a robust rhythmic architecture with samples taken at different points. Central inset: plot of fitness vs. number of generations. At first a ring is formed but a network with long chains of nodes is favoured. Finally the topology falls into a ring and the fitness levels stabilize.

when updated synchronously indicating that the ring topology also works in this case.

Target periods of $0.5N$ and $2N$ have been evolved successfully but the number of epochs required to achieve a cut-off fitness comparable to that of networks with target period N is generally much higher. This highlights the organisational constraints of such architecture: the trade-off between the size of the ring and the number of nodes that are dependent on the ring or are stationary.

It seems plausible to hypothesize that ring structures will underlie the generation of rhythmic patterns in most ARBNs (although an exception is described below). If this is so, then it is valid to question how these structures evolve at all, as it would seem that they only become functional once the ring is complete. Figs. 3 and 4 show the structure of the best individual in the population across generations for two evolutionary runs. In the first case, we see an early formation

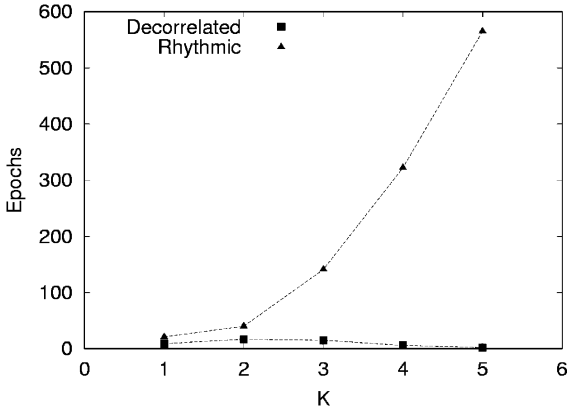

Fig. 5. Number of epochs needed to evolve de-correlated networks (filled square) and rhythmic networks (filled triangle) for $N = 16$, $P = N$ and varying K.

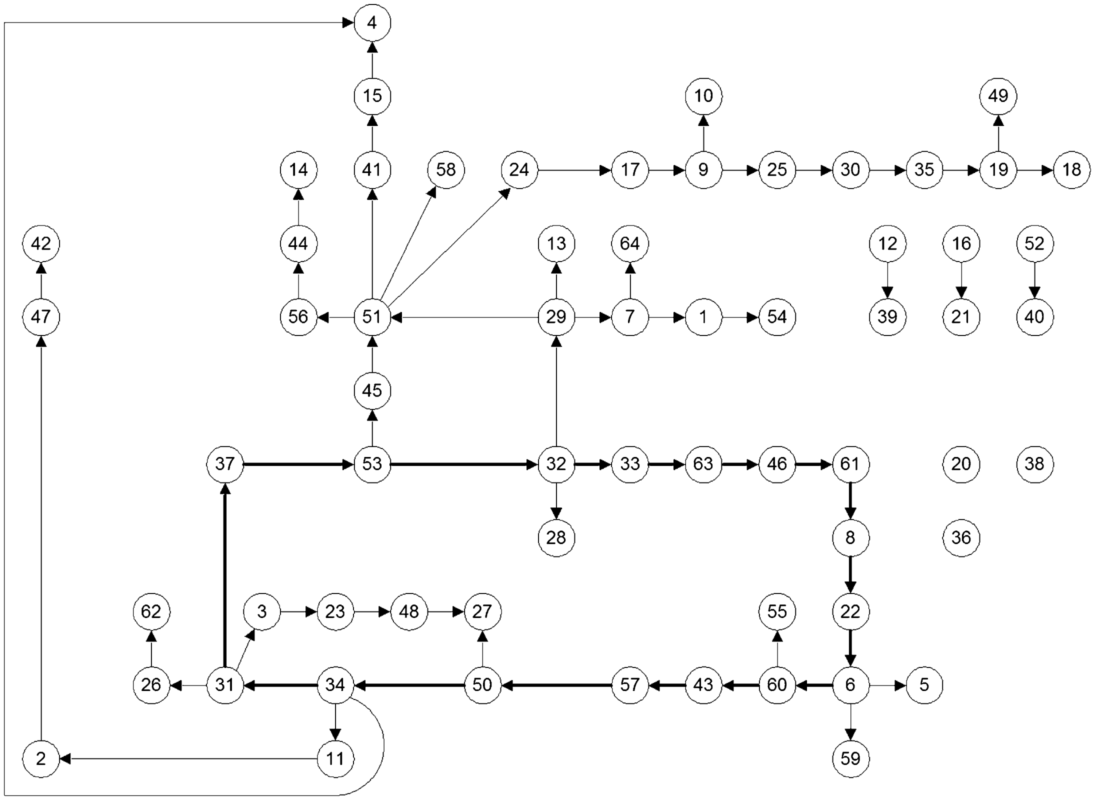

Fig. 6. A network with $N = 64$, $K = 2$ and $P = 32$. A central ring of 16 nodes underlies the rhythm produced by this network (ring: [37, 53, 32, 33, 63, 46, 61, 8, 22, 6, 60, 43, 57, 50, 34, 31]).

of a ring but with an insufficient number of nodes for the period of $P = 16$ (5 instead of 8). Across generations we see the insertion of two more nodes in the ring with fitness increasing in jumps when these events occur. The smooth increase in fitness between these events is assumed to correspond to a reordering of Boolean functions such that exterior nodes are properly orchestrated by the ring.

Evolutionary progress may also be achieved in other ways. Fig. 4 shows that partial rhythms may be obtained even when the ring is not yet complete. In the example shown, a small ring (4 nodes) is initially formed but a network with long open chains of nodes is favoured later on. The best individuals across generations show the formation of chains of nodes which only later end up forming a ring. The chains of nodes do encode relational states but it is as yet unclear how exactly the rhythm emerges. It can be assumed that self-connected nodes play a crucial role in driving the output patterns generated. More interesting in this example is the fact that the level of fitness stabilises once a ring is formed suggesting that a ring is the most robust architecture upon which it is very difficult to improve using this fitness function. Other experiments show that using mutation as the only operator throughout the evolutionary process is very successful, indicating that small change is more effective than the recombination of partial solutions.

The ring structure maintains the relational properties between nodes using a single link. With the exception of $K = 1$, low number of inputs usually interfere in such a way to produce a single effective input to a node as indicated by the pruning algorithm. Evolved networks with $K = 1$ also form ring structures identifiable without the need to prune links. Higher values of K would seem increasingly more unsuitable to evolve rhythmic networks as the design requires making $K - 1$ inputs to a node in the ring effectively

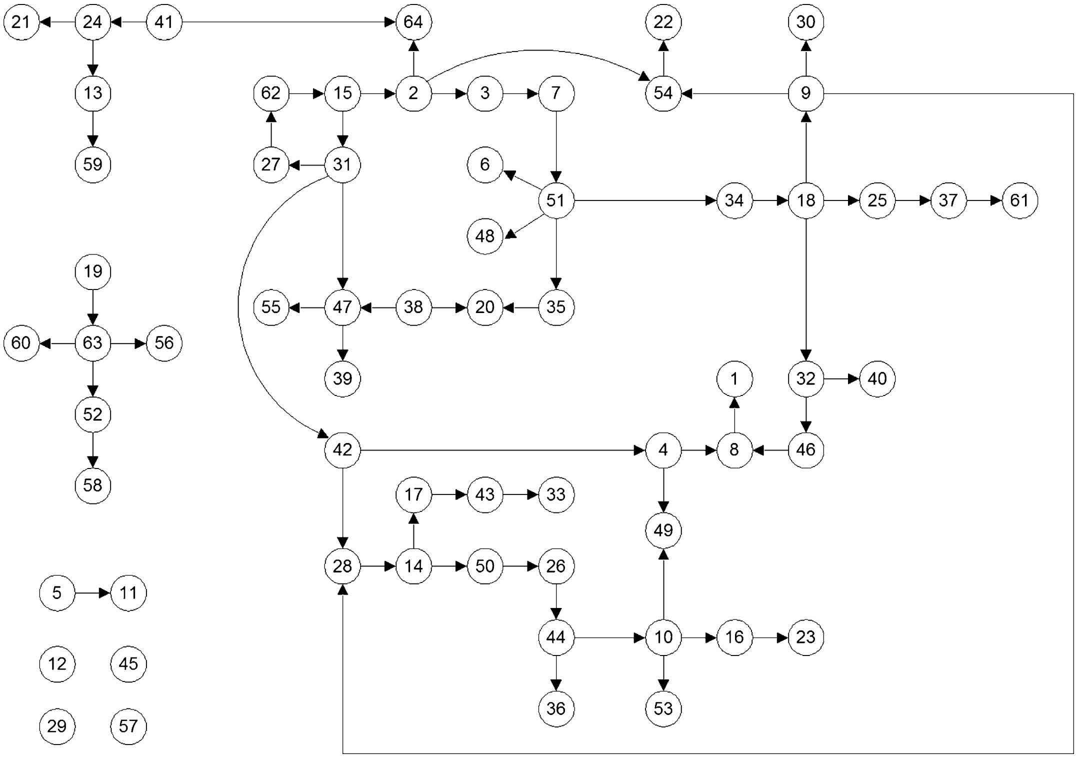

Fig. 7. A network with $N = 64$, $K = 2$ and $P = 32$. The only fit network found so far with no underlying ring structure (there is only one small ring: [62, 15, 31, 27]). Strategically located stationary nodes seem to produce a slightly different effective architecture as indicated by the pruning algorithm.

non-functional. Fig. 5 shows precisely this trend. The space of non-stationary attractors remains fairly constant across increasing values of K (Harvey and Bossomaier, 1997) but the number of epochs needed to evolve rhythmic networks (up to a cut-off fitness) increases with K. While this could be due to the increasing number of possible network configurations, the number of epochs needed to evolve de-correlated networks actually decreases slightly with K. Evolving rhythmic networks with high values of K has not yet been successful, although using the principle of the ring it would be trivial to design them by hand.

If rings underlie most cases of robust rhythmic ARBNs this means that the rest of the nodes must be organized so as functionally depend on the ring's activity and not feedback on it as discussed above. We can predict that such an arrangement will make it increasingly difficult to evolve networks with periods P much smaller than N (i.e., a comparatively small ring). Indeed, this is also the case. We have had no success so far evolving networks with $N = 64$ and $P = 16$ (i.e., a ring of 8 nodes and 56 functionally dependent nodes). The same reason underlies the more general difficulty of obtaining rhythm for larger values of N. Fig. 6 shows one rhythmic network for $N = 64$ and $P = 32$ with a central ring and the remaining nodes fully dependent. The only exception found so far of a highly robust rhythmic network that has not an underlying ring structure is also for the case of $N = 64$ and $P = 32$ and is shown in Fig. 7. The network's structure is characterised by long chains of nodes, closely related to a ring, often only missing a single link. Looking at the numerical output, however, indicates that the network uses strategically positioned stationary nodes to produce slightly different relational states as indicated by the functional architecture. This is not normally the case.

Once the generating principle is understood it is easy to handcraft robust networks with any specific rhythm. This has been done by using either several inter-connected rings or a combination of rings and chains. A maximum value for $K = 2$ has been found sufficient for a large variety of rhythms leading to mostly very distributed architectures. Fig. 8 shows some schematic examples of reliable networks with different periods. Networks with more than one marked frequency may be also constructed.

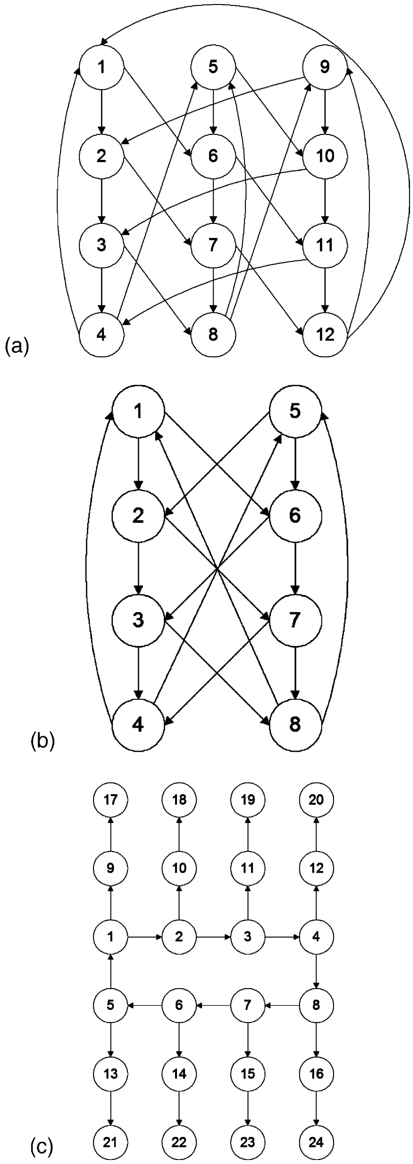

Fig. 8. Handcrafted networks with periods of (a) $2/3N$, (b) N and (c) $2/3N$.

4. Conclusions

We have analyzed evolved ARBNs capable of producing rhythm and found a common underlying mechanism in the form of a circular functional structure that produces travelling waves. The big advantage of such ring structure lies in the precision exhibited by the system as a whole: once nodes are arranged in the necessary manner, perturbations and errors do not matter, in particular the randomness of the update scheme. Once disturbed, the system will fall back into the same attractor as long as the functional topology is maintained. Such stochasticity is indeed inherent in every molecular event that takes place within the cell (McAdams and Arkin, 1997). Negative feedback in continuous models has been proposed as a mechanism for neutralising noise in gene networks (Becskei and Serrano, 2000) with the important difference that in this case the feedback is instantiated as a single-gene loop in a synthetic gene circuit. In contrast, rhythmic ARBNs make use of a structural solution in the form of a ring with some negative feedback elements such as the odd number of "opposite" links.

The reliability of the search method is statistically related to the size of the ring and the number of nodes. The fact that networks with a period of N have been by far the most successful to evolve indicates that the burden is equally shared between the two constraints (nodes within and outside of the ring) suggesting that small periods are simply more difficult to obtain as they entail a higher degree of centralisation. It would be, however, valuable to analyse the organisational constraints of nodes that lie within the ring and nodes that follow the ring in large networks. In fact, the overall attributes of large networks in general need to be investigated to determine how the current data scales up.

Using non-uniform connectivity is essential also for producing a more biologically plausible model. Fox and Hill (2001) found the mean number of connections in the Kohn map of mammalian cell cycles (Kohn, 1999) to be 3.65 but with a non-uniform distribution. They also explored the implications of different connectivity distributions $P(K)$ but updated their networks synchronously. Experiments using ARBNs with similar distributions should provide valuable insight towards this matter.

The experiments carried out so far clearly indicate that a ring is the most robust architecture for the generation of rhythm. Looking at the evolutionary history, however, indicates that other architectures, such as long chains of nodes, are also partially suitable topological arrangements. Amending the fitness function of the GA to favour networks which do not form rings could reveal further topologies that reliably produce rhythmic outputs. Multi-lesion analysis of contribution to fitness, as suggested by Aharonov et al. (2003), could be utilised in addition to the pruning algorithm for this purpose as well as for obtaining more accurate results for higher values of K.

The circular structure allows a stable trajectory through a non-deterministic state space. A reliable rhythmic behaviour is obtained from a network of noisy, unreliable elements. But the circularity found in rhythmic ARBNs is a functional one, and so it may or may not be related with other forms of genetic circularity, such as circular DNA molecules or circular maps (Thomas, 1967) of genetic linkage (Stahl, 1967), but it is in principle of a different sort.

This way of producing rhythm must also be contrasted with other clocks found in the organism where the interplay between fast and slow time scales and mutual inhibition or excitation result in a feedback oscillation through continuous states (Chay, 1981; Young, 1998). In the Boolean abstraction all nodes represent genes with similar time scales and so this implies that slower time scales (in this case the period of oscillation) can only be obtained by a suitable arrangement of a sufficient quantity of unitary time scales (in this case each node). As a consequence, rhythms with periods larger than $2N$ are not possible using a ring topology and all attempts to evolve such networks in search of alternative solutions have failed.

However, this is to some extent indicative of the evolutionary methodology utilised which does not encourage solutions organized in hierarchical or modular fashion, or the use of smaller feedback circuits (such as those found in gene networks). It would be possible to imagine a clever arrangement of ring circuits acting a role similar to counters or clocks with different time scales and therefore achieving rhythmic behaviour in a more complex fashion than the single ring topology. The search algorithm does not provide any selective pressure for solutions of this increased complexity and it would be very interesting to explore ways of incorporating these requirements into the fitness criteria.

In the absence of such modular or hierarchical organization, the difference in the mechanism between Boolean and continuous models may perhaps be pointing to a limitation of the Boolean idealisation for modelling oscillations in genetic regulatory networks. If we abandon the parallel update scheme (or deterministic alternatives), the results of this paper demonstrate that although it is possible to produce robust oscillations using asynchronous networks, the circular topologies that evolve reveal the constraints of working with a single time scale. A constraint that biological networks need not have and more complex design methodologies may help to break.

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