

The Incorporation of Epigenetics in Artificial Gene Regulatory Networks

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Abstract

Artificial gene regulatory networks are computational models that draw inspiration from biological networks of gene regulation. Since their inception they have been used to infer knowledge about gene regulation and as methods of computation. These computational models have been shown to possess properties typically found in the biological world, such as robustness and self organisation. Recently, it has become apparent that epigenetic mechanisms play an important role in gene regulation. This paper describes a new model, the Artificial Epigenetic Regulatory Network (AERN) which builds upon existing models by adding an epigenetic control layer. Our results demonstrate that AERNs are more adept at controlling multiple opposing trajectories when applied to a chaos control task within a conservative dynamical system, suggesting that AERNs are an interesting area for further investigation.

Keywords: Artificial Gene Regulation, Epigenetics, Dynamical Systems, Chaos Control, Evolutionary Algorithms

1. Introduction

Gene regulatory networks are complex dynamical structures that underpin an organism's ability to control its internal environment (Turner, 2001). From a biological perspective, the study of gene regulation is of significant scientific importance because it determines cellular differentiation, which is responsible for the development of the different tissues and organs that underpin the structure of higher organisms (Latchman, 2005). From a computational perspective, gene networks are interesting because they are robust control structures, capable of dealing with environmental perturbations, whilst maintaining structure and order. Because of this, there has been significant interest in modelling gene regulatory networks *in silico* in order to capture these features e.g. (Lones et al., 2010; Quick et al., 2003). Due to the complexity of biological gene regulation, computational analogues are simplified. Research has shown that relatively simple networks, such as the random Boolean network, can exhibit emergent properties such as self-organisation and robustness and, in addition to this, can model real regulatory circuits (Kauffman, 1969; Kauffman et al., 2003).

However, current computational analogues of gene regulation fail to include models of one of the most pervasive methods of gene regulation in higher organisms, epigenetics. In this sense, the regulatory nature of these computational analogues may be limited in terms of their complexity and performance. In this paper, we define a computational representation of epigenetic information for the control of a complex dynamical system.

2. Gene Regulation and Epigenetics

A gene is a unit of hereditary information within a living organism, most commonly considered to be a region of DNA that specifies the primary structure of a protein. The genetic code is a biological blueprint that details which proteins can be produced, and ultimately, the phenotypic space within which the organism can exist. The lowest known threshold on the number of genes required to naturally facilitate life is that of *Mycoplasma genitalium*, which has approximately 470 genes (Fraser et al., 1995). Even in nature's most minimalist example of a gene regulatory network, 470 genes have to be coordinated in such a way as to maintain the optimum internal environment of the organism, highlighting that even the simplest of gene regulatory networks are inherently complex.

2.1. DNA Methylation

One of the principal epigenetic mechanisms is DNA methylation, which refers to the addition of a methyl group

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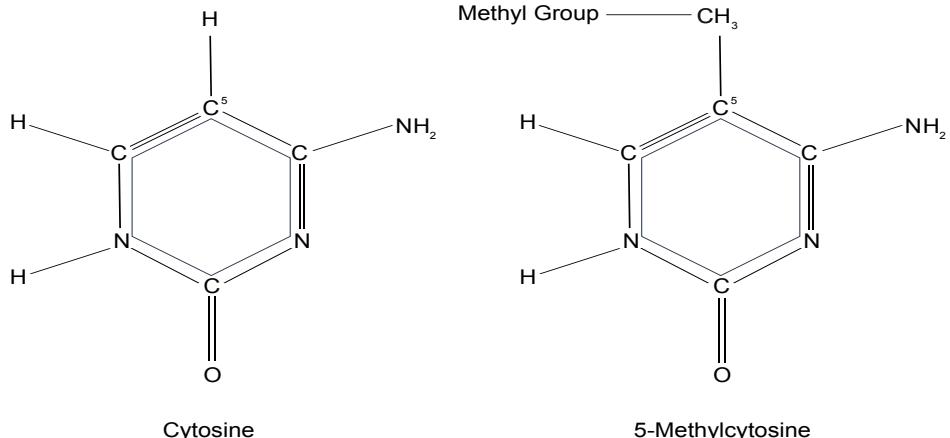


Figure 1: DNA methylation. The attachment of a methyl group to a cytosine nucleobase has been shown to be able to regulate physiological processes (Bird, 2002; Hattman, 2005)

to either the cytosine or adenine nucleobase in DNA (Figure 1). It acts as an epigenetic marker that can regulate many physiological processes (Bird, 2002; Hattman, 2005). In mammals, DNA methylation is most commonly present within CpG islands (Kim et al., 2009), locations in the DNA sequence with an abundance of cytosine guanine dinucleotides. In mice it has been shown that methylated cytosine bases account for approximately 1% of all the DNA bases within the genome, and therefore is representative of between 70-80% of all CpG dinucleotides in the genome (Kim et al., 2009).

2.2. Chromatin Modifications

Especially in complex organisms, higher order structures such as chromatin have been shown to have significant influence over gene expression. Chromatin is a molecular complex consisting of a combination of DNA and proteins which is contained within the cell nucleus (Figure 2). Chromatin has two functions. First, in the case of human cells, there are approximately 3400Mb of DNA of approximately 2.3m in length. Chromatin provides a structure for the condensation of DNA, so that it can be fully contained in a nucleus of approximately $6\mu\text{m}$ (Alberts et al., 1994; Allis et al., 2007; Bushman, 2002). This is accomplished in multiple stages. The first is the wrapping of 145 base pairs of DNA in 1.67 toroidal superhelical turns around a histone octamer (Schones and Zhao, 2008). This forms the basis of the nucleosome, which moves through further levels of condensation into a solenoid fibre which ultimately folds into a chromosome (Figure 2).

The second function of chromatin is to control access to the DNA, which in turn acts as an additional level of genetic control. This is because, in order for a gene to be expressed, the DNA has to be physically accessible by the transcriptional machinery within the cell. When it is tightly packed the structure of chromatin prevents this, allowing access to underlying DNA only when it is in its least condensed state.

2.3. Genes and Epigenetic Molecules

There is no clear separation between DNA methylation and chromatin modification in terms of gene expression. Research suggests that chromatin modification and DNA methylation are intrinsically linked (Jackson et al., 2002), and frequently, DNA methylation causes an underlying change to chromatin structure and gene expression (Jones and Takai, 2001). Generally, DNA methylation provides a more long term, stable effect on gene expression when compared to relatively short term reversible chromatin modifications (Cedar and Bergman, 2009). One of the more interesting aspects of epigenetics is that, in certain instances, epigenetic traits can be inherited by successive generations of cells, and sometimes organisms (Bird, 2007). In addition to this, epigenetic modifications can give the genetic code a relative genetic memory (Bird, 2002), which can then be used in such processes as cellular differentiation (Mohn and Schübeler, 2009).

It has been hypothesised that the characteristics of epigenetic molecules allows for a genetic plasticity which plays a major part in the development of complex phenotypes (Petronis, 2010). This plasticity creates the ability for organisms to express high levels of adaptability via utilisation of the dynamical reconfiguration afforded by epigenetic processes. In the following sections the idea of incorporating a level of artificial epigenetic information in an existing artificial gene regulatory network model is introduced.

3. Artificial Genetic Regulatory Networks

Gene regulation in biology is a set of mechanisms that maintains homeostasis within an organism's internal environment. The aim of artificial gene regulation is to create a computational model of genetic behaviour that exhibits the useful and interesting properties of gene regulation in nature, namely self organisation, robustness and

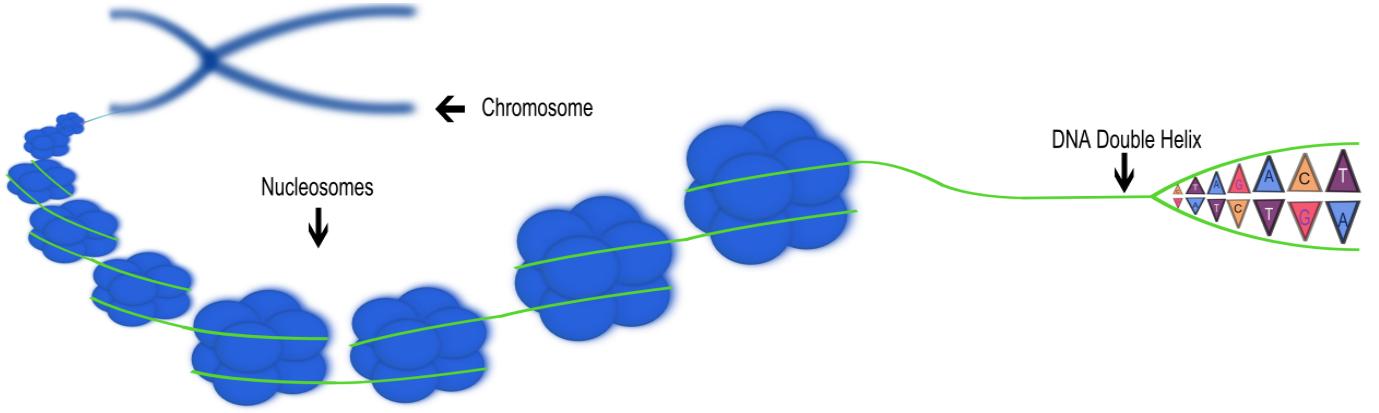


Figure 2: An illustration of the process of folding DNA into the higher order structure of a chromosome, adapted from (Schones and Zhao, 2008)

the expression of complex behaviours. The earliest example of this is the random Boolean network (RBN) (Kauffman, 1969). RBNs represent genes as Boolean expressions. These artificial genes are referred to as nodes. The network has a connectivity value, k , which specifies how many nodes influence a given node's expression level. The state of a node is defined by randomly initiated state transition rules. Upon execution, the network is iterated over a number of time steps, during which each node modifies its value depending upon its connectivity and its state transition rules. These networks demonstrate that with a k value of 2 or 3, distinct order and repetitive patterns can be generated. Moreover, for certain parameter ranges, the RBNs express high levels of robustness, maintaining relative order when exposed to external perturbations (Harvey and Bossomaier, 1997).

Subsequent models of gene regulation draw inspiration from the RBN. However there has been a shift towards continuous-valued models (Kumar, 2004; Lones et al., 2010), as they are computationally more flexible. In addition, it has been shown that these models can be applied to the control of complex systems (Lones et al., 2010).

3.1. Artificial Epigenetic Regulatory Networks

This paper, a revised and extended version of (Turner et al., 2012) extends the model of artificial gene regulation (AGN) described in (Lones et al., 2010) by incorporating epigenetic information. The aim is to ascertain if an additional level of regulatory control will result in a performance benefit over the previous model. The Artificial Epigenetic Regulatory Network (AERN) uses an analogue of DNA methylation in combination with chromatin modifications as its epigenetic elements. This gives the network the ability to change its epigenetic information both during evolution, and during execution via the changing of epigenetic frames (\mathbf{E}_G in definition below). Table 1 gives an example of the data within an AERN, and Figure 3 provides a graphical description.

The AERN can be formally described as: $\langle G, L_G, I_G, O_G, E_G \rangle$ where :

$G = \text{Indexed genes } \{g_0, \dots, g_n : g_i = \langle \lambda_i, R_i, f_i \rangle\}$, where:
 $\lambda_i : R$ is the expression level of a gene
 $R \subseteq G$ is the set of regulatory inputs used by the genes
 $f_i : R_i \rightarrow \lambda_i$ is a gene's regulatory function
 L_G is an indexed set of initial expression levels, where,
 $|L_G| = |G|$
 $I_G \subseteq G$ are the external inputs applied to the network
 $O_G \subseteq G$ are the outputs of the network
 $E_G \subseteq G$ is the epigenetic data structure specifying which genes are *active* at a given instance

The AGRN is iterated over a series of timesteps. At each time step, each gene updates its current expression value by calculating the weighted expressions of its connected genes, and then processing that through the sigmoid function. The result is the current gene's expression for the next time step. This process is repeated for each gene within the network to complete a single iteration of the network. This is described in Algorithm 1.

The expectation is that epigenetic control will enable the network to evolve in such a way that it will have certain subsets of genes that are more able to perform a given objective. The inclusion of epigenetic information gives the network the ability to allocate different genes to different tasks, effectively regulating gene expression according to the environment in which it is operating.

Each gene uses a parametrisable sigmoid function which has been shown in (Lones et al., 2010) to be the most effective at controlling the dynamics of a conservative dynamical system. The variable ranges are summarised in Table 2.

4. Dynamical Systems

A dynamical system is a system whose current state is a product of its previous state and an evolution rule. For any given point within a dynamical system, its trajectory through the space is governed by the iteration of this rule over a given period of time. One of the most interesting

Variable	External Inputs (\mathbf{I}_G)		Genes					Outputs ($\mathbf{O}_G \subset \mathbf{G}$)
Gene Expression Values (\mathbf{I}_G)	0.18	0.81	0.54	0.38	0.95	0.14	0.05	0.47
Weights	0.47	-0.27	0.24	0.99	-0.87	-0.02	-0.47	0.97
Sigmoid Offset	-0.18	0.24	0.14	-0.50	-0.21	0.57	0.31	0.38
Sigmoid Slope	1	10	5	19	2	14	3	7
Connections	3 8 7	2 7 5	2 8 8	4 8 8	2 7 3	3 2 5	2 2 7	3 3 7
Epigenetic Frame A ($\mathbf{E}_G \subset \mathbf{G}$)	1	0	1	1	0	0	0	1
Epigenetic Frame B ($\mathbf{E}_G \subset \mathbf{G}$)	0	1	1	0	1	1	1	1
Network Iterations	15							

Table 1: Example data attributes for an AERN of size 8. The only difference between the AERNs and the AGNs is the introduction of 2 epigenetic frames, which specify which genes will be active for each objective

Algorithm 1 Execute single iteration of network

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if First Execution then
     $\lambda_0, \dots, \lambda_n$  are initialised from  $\mathbf{L}_G$ 
end if

Expression levels of enzymes in  $\mathbf{I}_G$  are set by the external inputs

for  $i = 1 \rightarrow NetworkIterations$  do
    for  $i = 1 \rightarrow NetworkSize$  do
        if Epigenetics Layer specifies gene is active then
            Each active gene  $g_i$  applies its regulatory function  $f_i$  to the current expression levels of its active regulating genes  $R_i$ 
        end if
    end for
end for

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Expression levels of enzymes in \mathbf{O}_G are copied to the external outputs

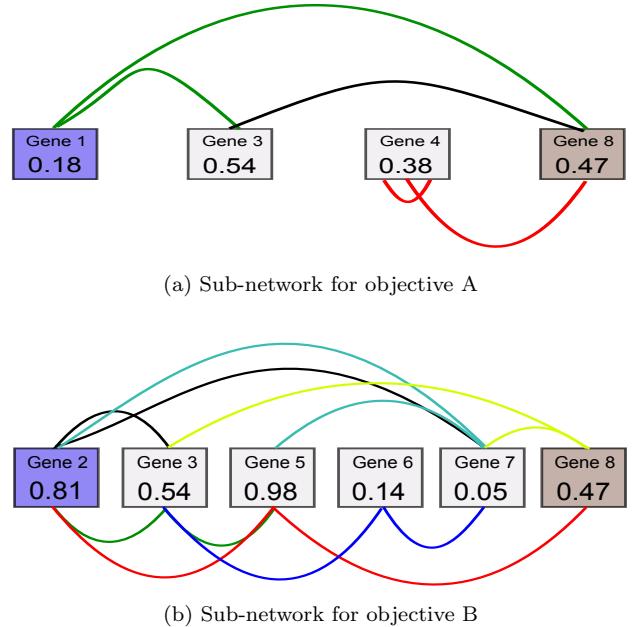


Figure 3: An illustration of the two sub-networks which the epigenetic layer partitions. The data used is from Table 1

groups of dynamical systems are those that exhibit chaotic dynamics. Chaos can be recognised as irregular and unpredictable behavior within a system, due to extreme sensitivity to initial conditions (Tél and Gruiz, 2006). Unlike random behaviour, this is the result of applying a deterministic evolution rule.

4.1. Chirikov's Standard Map

Chirikov's standard map (Chirikov and Sanders, 1971) is a two dimensional dynamical system that, models co-existing and ordered and chaotic dynamics . Its behaviour results from two difference equations :

$$\begin{aligned}
 x_{n+1} &= (x_n + y_{n+1}) \bmod 1 \\
 y_{n+1} &= y_n - \frac{k}{2\pi} \sin(2\pi x_n)
 \end{aligned} \tag{1}$$

Modulation of the k parameter affects the balance between ordered and chaotic dynamics within the system's state space. For low k values, the dynamics of the map (Fig. 4a) are ordered. For high values, (Fig. 4c), chaotic dynamics dominate the state space. For intermediate values (Fig. 4b), the system displays co-existing regions of ordered and chaotic dynamics. At $k = 0.972$, the system has a behavioural inflection point. Below this value, it

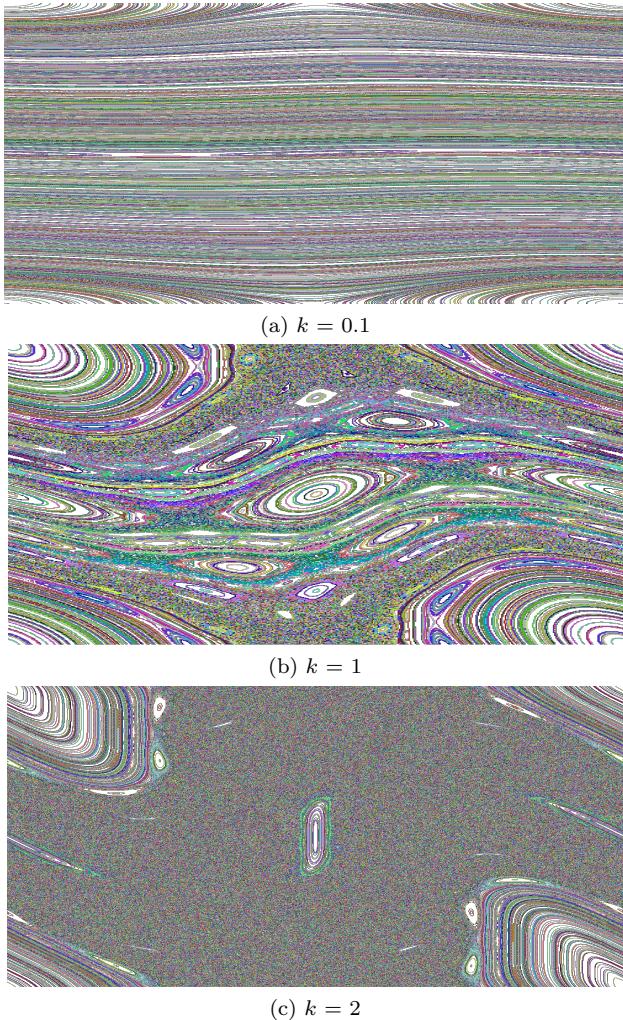


Figure 4: Orbits of Chirikov's Standard Map during ordered (a and c) and chaotic (b) dynamical phases

is not possible for trajectories to move between the upper and lower chaotic regions by following the system's natural dynamics. Above this value, it is possible, and transport across the central region continues to become easier as k increases.

4.2. State Space Targeting

The presence of chaos within a system makes it difficult to predict future behaviours. However, research has shown that targeting within the standard map during periods of chaos is possible via the use of perturbations, allowing navigation to different regions of the state space (Lones et al., 2010; Bollt and Meiss, 1995).

5. Experimentation

In order to test the relative performance of AERNs, they were compared to the same model without the use of epigenetics when controlling two opposing trajectories within the standard map (Lones et al., 2010).

Variable	Type	Range
Gene Expression	Real	0;1
Weights	Real	-1;1
Sigmoid Offset	Real	-1;1
Sigmoid Slope	Int	0;20
Epigenetic Objective	Int	0:1
Network Iterations	Int	1;20

Table 2: Ranges of the variables within the AERN

5.1. Evolution Of The Networks

A genetic algorithm (GA) is used to evolve the networks. GAs are population based search algorithms (Mitchell, 1998), which often find near optimal solutions within a tractable time frame, making them a favorable approach for this experiment. The genome representation can be seen in Table 1. The GA uses a crossover rate of 0.5, a mutation rate of 0.001 and tournament selection of size 4 to evolve networks containing 20 genes. The GA is run for 50 generations, and the fittest individual at the 50th generation is the score for that run. 50 runs were carried out for each network type.

5.2. State Space Targeting Using Artificial Gene Regulatory Networks

Previous work demonstrates that the AGN can be used to target specific regions of Chirikov's map (Lones et al., 2010). This paper builds upon this by using the networks to control two opposing trajectories within the standard map. There are two objectives. (A). The networks have to guide a trajectory from the bottom to the top of the map, and thus (B). guide the trajectory from the top to the bottom. The overall aim is to achieve both these tasks in the lowest number of steps.

Each network receives 3 inputs and produces 1 output. The three inputs are the x and the y co-ordinate representing the map's current trajectory and the current Euclidean distance between the trajectory and the centre of the target. The output of the network is the new k value (see Eqn 1), which is used in the next iteration of the standard map equations. The output of the network, a real value (Table 2) is scaled to the interval [1,1.1] to ensure that the map remains in a region where it is difficult, but not impossible, to traverse the map by following the system's natural dynamics. Upon initialisation, the starting point for the trajectory is a randomly initiated point within the starting region, and the networks are randomly initiated with values from ranges shown in Table 2. The epigenetic frame changes when either the first objective is completed, or when the maximum number of steps for that objective has been reached.

When travelling from the bottom to the top of the map, the initial start point is in [0.45,0.55] for the x co-ordinate, and in [0,0.05] for the y co-ordinate. For the other direction, the randomly initialised start point is in [0.45,0.55]

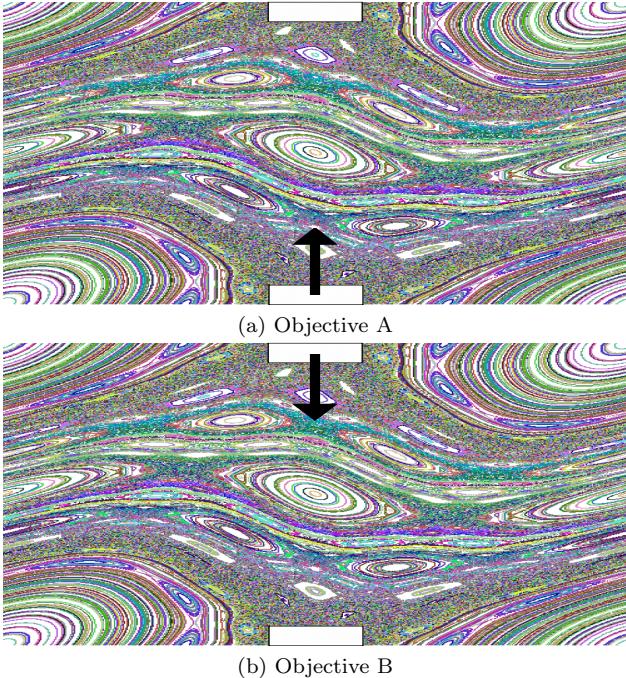


Figure 5: Chirikov’s standard map showing two start and finish areas for each objective

for the x co-ordinate and $[0.95,1]$ for the y co-ordinate. The score for both objectives is the average number of steps to traverse the map in both directions, up to a maximum number of 1000 steps. During execution, the scores for the 40 repeats (20 for each objective) are collated, and if there is an instance where the network completed both objectives, the fitness is rewarded by 250 steps. If only one objective is completed, the score is decremented by 100 steps up to a maximum of 1000 steps (the final results will not take into consideration rewards and punishments, only solutions that complete both objectives are able to achieve a score less than 1000). Otherwise, fitness is the mean number of steps over 40 repeats). This is to place emphasis on the networks completing both objectives, whilst allowing strong solutions that only complete one objective to remain in the population.

5.3. Analysis of Network Dynamics

In order to gain insight into the dynamics of the network, time delay embedding is used to reconstruct the underlying attractor structure of the controller (equation 2, figure 10). This allows for the visualisation of the underlying dynamics of the network by observing the output of the network over a delayed time margin, and then plotting this to create a phase portrait (Tél and Gruiz, 2006).

$$S_n = (S_n - (m - 1)r, S_n - (m - 2)r, \dots, S_n) \quad (2)$$

A delay embedding is formed (equation 2) by using the vector S_n (A list of network outputs over time), and taking

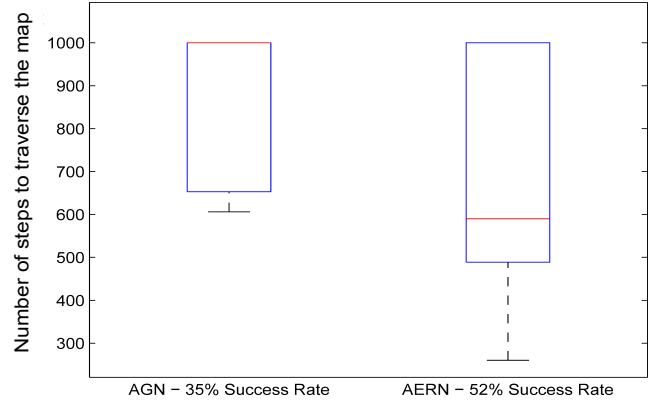


Figure 6: Summary of the fitness distributions (low numbers are better). The results for the AGN show less than a 50% success rate, and a best value of approximately 600 steps. The AERNs show a significant increase in success rate, and better solutions overall.

the embedding dimension m (set to 3 to allow visualisation) with a delay r (set to 1).

6. Results

The results show that both the AGNs and the AERNs were able to produce solutions that could control both trajectories (A typical solution can be seen in Figure 8). However, the results indicate that the tasks were difficult (Figure 6), as only 35% of the AGNs and 52% of the AERNs were able to complete both objectives. Notably the results demonstrate that the AERNs perform significantly better than the AGNs. The trend is more evident when the unsuccessful instances are removed, as can be seen in Figure 7.

In particular Figure 7 shows that the vast majority of the successful AERNs outperform almost all of the successful results from the AGNs. On average the AERNs produce an improvement of approximately 150 steps in terms of mean path length.

6.1. Phase Portraits

The reconstruction of phase portraits show the networks’ attractor structure during execution. Figures 9a and 9b show the phase portraits in each direction for the best evolved AGRN. The portrait’s structure in Figure 9a suggests the presence of ordered dynamics which are manifested primarily as two interlocked triangles, approximately translating to a cycle of length 6. Figure 9b demonstrates similar properties, however there appear to be two interlocked triangles of varying size. Visually it is clear that the networks are behaving differently depending on which epigenetic frame is being used.

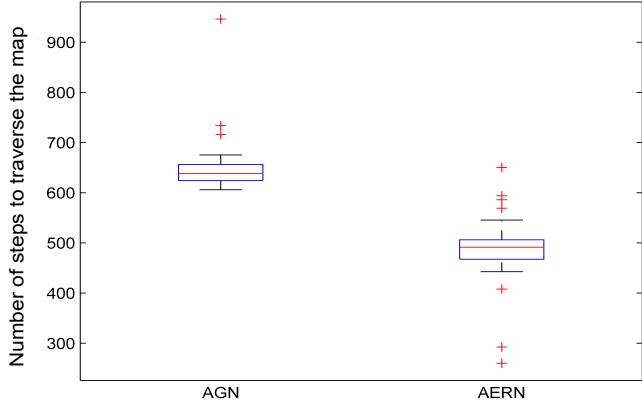


Figure 7: Data from Figure 6 with the unsuccessful results omitted (low numbers are better). This shows a much clearer trend in the data, and the addition of the artificial epigenetic information can be seen to increase performance.

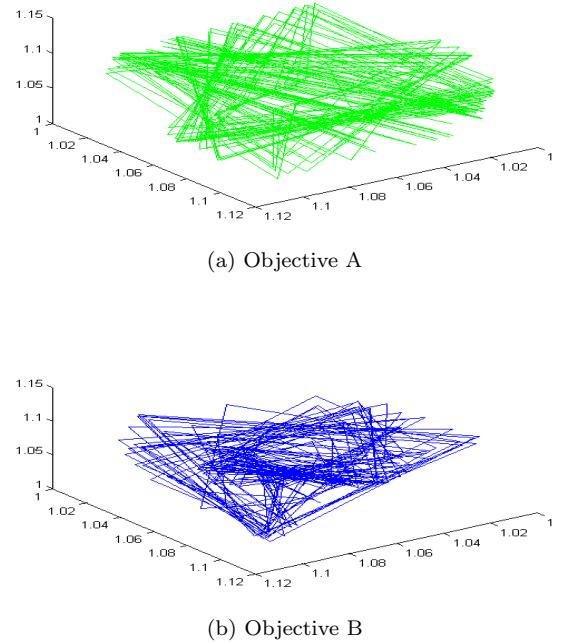


Figure 9: Phase portraits of the best evolved network that used epigenetic information

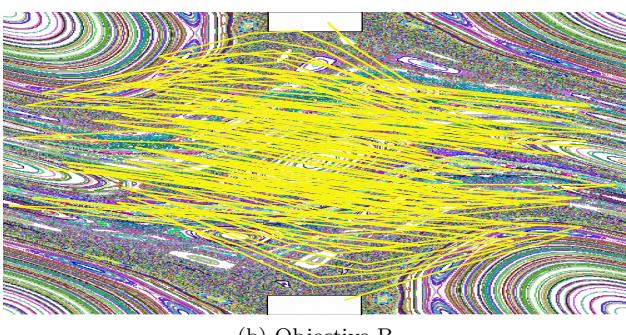
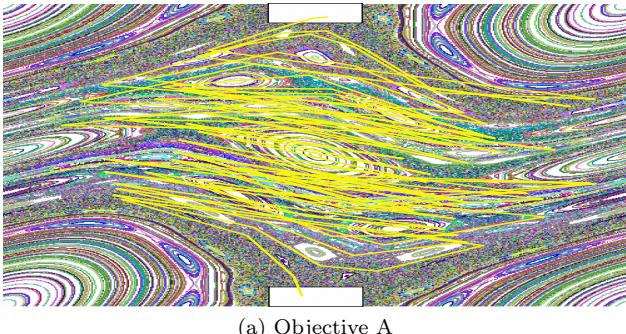
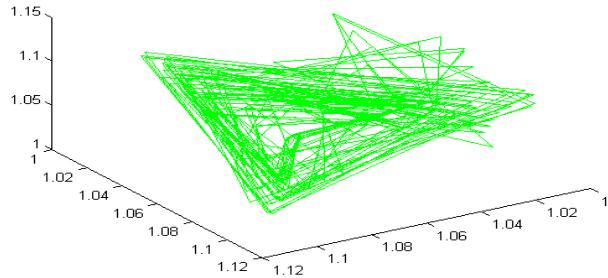


Figure 8: Example of the trajectories being controlled by an evolved AGRN in both directions

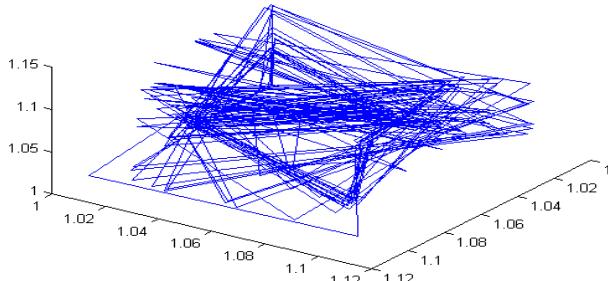
Figures 10a and 10b show the phase portraits for the best network with the epigenetic frames omitted. These show a clear difference between behaviours depending on the direction of the trajectory. Hence, a distinction can be made between networks with epigenetic control omitted and those that contain epigenetic information. This suggests they have evolved differently, both in task differentiation and in network dynamics.

6.2. Efficiency and Qualitative Analysis

As well as the significant performance advantages provided by the introduction of the epigenetic frames, there were other benefits from using this approach. First, the inherent nature of the epigenetic frames specifying which genes are on and off for a given objective means that there will be an increase in computational efficiency. At the end of the evolutionary process, the networks that used epigenetics were using approximately 54% of the genes compared to those of the AGN. Second, the epigenetic frames allowed for a level of qualitative analysis which would otherwise have not been possible. Upon network dissection, it is possible to see which of the internal inputs are being used for each task. During experimentation, it became apparent that not all three external inputs were needed to solve either task, and furthermore, there were multiple instances that only used one of the three inputs and were able to complete the task. This allows information to be generated about the problem domain which would have not been possible with the epigenetic frames omitted.



(a) Objective A



(b) Objective B

Figure 10: Phase portraits of the best evolved network that omitted epigenetic information

7. Conclusions

This paper has illustrated the potential for incorporating epigenetic information in computational models of gene regulation, and the initial results are very promising. The results demonstrate that evolved Artificial Epigenetic Regulatory Networks (AERN) are able to assign certain genes to certain tasks, improving functionality and efficiency. This ties in well with the biology of epigenetics, which allows for a higher level of genetic control without compromising efficiency (Jeanteur, 2008).

There is a significant amount of further research required to assess the full functionality of the AERNs. In future work, the AERNs will be applied to a range of tasks in order to evaluate their computational capabilities. Additionally, the topologies of the networks will be looked at in more detail to ascertain the role and function of varying epigenetic mechanisms. Furthermore, we are also interested in implementing metabolic constraints to increase the efficiency of the AERNs.

Acknowledgments

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