

Does complex always equal robust?

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Summary

Mutation is a source of disturbance to the functionality of a genetic network. Recent research has focused in the arrangement that a genetic network should have to keep functioning in presence of noise. Results points that a complex genetic architecture is robust to noise. But the definitions of complexity used by different authors are not similar and partially contradictory.

I describe the genetic architecture underlying a phenotypic trait in terms of redundancy, connectance and diversity. Complexity is a global characteristic that incorporates these three components. Increase in either redundancy, connectance or diversity increases complexity.

Using my description of complexity I investigate if a more complex genetic network is more robust. My answer challenges the paradigm recently emerged in the realm of genetic networks research: "complex equals robust". This paradigm occurs because the theoretical research done so far does not consider the strength of genetic interaction as variable. Adding strength of interaction in analytical and simulated models of genetic networks I show that intermediate strength of interaction provides robustness.

Traditionally, complexity and homeostasis have been associated with feedback loops built in a network. However, feedback loops, besides homeostasis, produces instability. Surprisingly, the inherent instability of a feedback loop has not been addressed in recent genetic networks models. Redundancy has been also associated with increases in complexity and robustness. These counteracting forces (feedback loops producing instability and multiple equilibria, redundancy producing robustness) result in robustness, when the interaction strength is intermediate.

Keywords

Mutational disturbance, intermediate strength of genetic interaction, redundancy and connectance

Introduction

a) Defining complexity for genetic networks

With recently developed tools, the understanding of molecular interactions is a renewed topic of attention for evolutionary biologists. A question has recently arisen: Given a set of complexly interacting genes, are they more robust to perturbations than their simpler counterparts? The robustness of a gene network facing perturbations is important since we believe that organisms developed mechanisms to buffer noise, and simultaneously, evolution is fueled with mutational perturbations. Recent papers focus on the relation robustness-complexity from different viewpoints. The word complexity had been used to cover different aspects of an assemblage of genes. In this paper, I discuss these aspects, providing an inclusive definition of complexity, readdressing then the relation among complexity and robustness.

Connectance, redundancy and number of genes have been considered as aspects of the complexity of a gene network. Different authors have focused on these different aspects of complexity, separately. Lenski and co-workers produced artificial genomes in a computer and let them evolve. Afterwards they perturb the evolved genomes and analyze their responses. Results of the analyses points that increase in complexity increase genetic robustness. The measure of complexity used by Lensky and coworkers is interaction among genes, id est epistasis. The appearance of redundant genomes among their simulated systems is considered as a problem for the argument that complexity-as-epistasis is robustness, since complexity-as-redundancy might be the provider of robustness (Lenski *et al.* 1999). In a set of interacting entities, as a network of interacting genes is, the average number of connections that an entity has with others is called connectance. Connectance is the most used measurement of complexity. In trophic networks, connectance is the

estimation of trophic interactions per species. In genetic networks, connectance becomes an estimation of the number of epistatic interactions (Weng *et al.* 1999). Another definition of epistasis as interaction among genes is discussed in recent papers of G. Wagner and coworkers (Hansen & Wagner 2001a; Hansen & Wagner 2001b; Wagner *et al.* 1998; Wagner *et al.* 1997; Wagner & Mezey 2000). In their latest definition (Hansen & Wagner 2001b), epistasis occurs when the effect of a mutation depends on the genetic background of the affected loci. This is to say that epistasis occurs if there are interactions among genes able to modify their outcome.

Accordingly, Lensky and coworkers are mainly focused on complexity-as-connectance, or epistasis.

Nowak and co-workers see the evolution of redundancy as a provider of genetic complexity (Nowak *et al.* 1997) **cambiar este fraseo, indeed.** Traditional work on genetics considers redundancy as a measurement of the complexity of a genetic network. Redundancy is clearly a cause of robustness, since a redundant set of genes can provide backup functioning in the case of impeding mutations to the original set of genes (Wagner 1999). A problem is that redundancy is a concept intertwined with epistasis. For a gene be able to backup another gene, they must interact or be connected, id est, a certain amount of epistasis must occur. This relation is not addressed in the research of Nowak and coworkers.

Last but not least, the view of Adami's collaboration points that an increase in genome size also increases the amount of information that a genome can potentially store (Adami *et al.* 2000). Relating the information carried by a genome with its survival's abilities results in an increase of fitness and genome robustness. An increase of the number of genes coding for a phenotypic trait also increases the complexity of the corresponding genetic network. The number of different coding

genes can be called the “diversity” of the gene-network. Adami and coworkers discusses and use this definition of complexity.

Above I have mentioned how different concepts of complexity are present in recent literature. In the following, I discuss why connectance, redundancy and diversity together are needed to characterize the complexity of a gene network. Consider the three schematic gene networks depicted in Figure 1a. The circles are genes involved in the production of a phenotype, depicted as a square. The product of a gene pointed by an arrow depends on the product of the gene from which the arrow departs.

Figure 1a

Figure 1a illustrates that neither connectance, diversity nor redundancy alone are enough to characterize complexity. It is easy to see that in Figure 1a complexity increases from left to right. Diagrams (a) and (b) have the same connectivity, but different redundancy and diversity. Diagrams (b) and (c) have same redundancy and diversity but different connectance. A definition of complexity should integrate these three aspects. In principle, I state that increase either in connectance, redundancy or diversity increases the complexity of a network. Now, lets make the important question. Does an increase in complexity –as just defined– leads to an increase in the stability of a genetic network?

b) Is complexity robustness or fragility?

Recent literature states that an increase in complexity will increase the robustness of a gene network. An increase in number of coding genes could decrease the effect of a point mutation (Dall & Cuthill 1999). An increase in redundancy provides backup

functioning (Nowak *et al.* 1997; Wagner 1999). Finally, an increase in epistasis empirically enhances robustness (Lenski *et al.* 1999). These arguments are easy to check in Figure 1a. Assume that each set of vertical genes backups the other. The net (b), having some redundancy, is more robust than (a). Damage in a gene of one line would be hampered by the set of genes in the other line. Comparing the net (b) with the net (a), we see that redundancy increases robustness. Now compare the net (c) against (b). The corresponding gene in the other line will cover a damaged gene. Comparing (c) and (b), we see that an increase in connectance also increases robustness. So far, my definition of complexity as redundancy and connectance conforms the rule “more complex, more robust”. However, this is not necessarily the case. Depending on the type of interaction that connects two genes, more complexity might produce less robustness. Consider the pathway (c) from Figure 1a. Robustness depends whether the cross-arrows depict redundancy or connectance. If the cross-arrows are used only in case of failing of the vertical arrows, (redundancy) more connectance provides more stability, and this complex pathway is the most robust one from Figure 1a. If the cross-arrows and the vertical arrows are both strictly needed to produce the gene that they point to (connectance) a more connected system is less robust. (c) Would be then less robust than (b), since it is more complex.

With the simple example presented so far, which architecture induces robustness seems to be clear. Robustness is produced, most likely, by an increase in redundancy. An increase in connectance is expected to produce fragility. If an increase in complexity occurs by increasing connectance and redundancy, it is not clear that an increase in robustness will follow. However, it is important to go further this simplistic conclusion. In first place, there is empirical evidence supporting that artificially engineered feedback loops in alive cells produce robust genetic networks (Becskei & Serrano 2000; Elowitz & Leibler 2000; Gardner *et al.* 2000). One could say that an increase in connectance induces fragility in a genetic network, but also

induces the existence of robust feedback loops. On the other side, even though redundancy induces robustness, it must be remembered that for two genes to be redundant, they must interact. So any increase in redundancy will also increase the number of potentially de-stabilizing connections. It could be said then, that connectance and redundancy are related by a tradeoff, regarding robustness. The more redundancy, the more robustness, but at the same time more redundancy implies more connectance, which decreases the overall robustness. Or said in the other way, the less connectance, the less un-stability, but also less redundancy, which should bring less robustness.

If this tradeoff really exists, scenarios with mayor robustness must not be looked upon the extremes of the tradeoff, maximizing redundancy, minimizing connectance, or maximizing feedback loops. The consequence of the verbal argument so far is that networks with intermediate redundancy and connectance should provide the highest robustness. In the following, I quantify this intuitive idea, and test the corresponding prediction.

c) Modelling intermediate complexity using strength of interaction

So far, I have been talking of connectance or redundancy as architectures that occurs or not. But the verbal argument underscores that it is important to look with more detail at the intermediate cases, between redundancy and connectance. They might be modeled as the two extremes of a continuum of possible gene interactions. Consider a detail of the pathway (c) in Figure 1a.

Figure 1b

Figure 1b shows gene g_1 activated by the product of genes g_2 and g_3 . One extreme in the interaction portrayed is that g_1 is produced if g_2 or g_3 are produced. If so, g_2 is fully redundant with g_3 , providing backup functionality in the activation of g_1 . On the

other extreme, it could be that both g_2 and g_3 must be produced to activate g_1 . If so, g_2 and g_3 are connected -or epistatic- genes, since their joint action is needed to activate another gene. How to model cases among these two extremes? One way is to add a conversion factor from g_2 and g_3 to g_1 . Setting such a conversion factor to low (so that few product of g_2 or g_3 controls g_1) will model a more redundant network, since impeding mutation in g_2 or in g_3 will not impede the production of g_1 . On the other side, having such a conversion factor set to high values (so that a lot of product of g_2 and g_3 controls g_1) is to model more connected networks, in which the impeding mutation in g_2 or g_3 could account until 50% of the control of g_1 .

In figure 1b, the strength of interaction measured by the conversion factor k_{i1} quantifies the importance of the product of a gene for the expression of another gene. Varying k_{i1} would change the interaction strength of the network. Recent work from theoretical community ecology points that intermediate interaction strength produces stability of trophic networks (a.o.: (McCann *et al.* 1998)). Once introduced interaction strength in the picture of genetic networks, I predict that networks with intermediate strength of interaction will be more stable, or robust, facing perturbations.

So far, I have discussed different definitions of complexity in genetic networks. With this discussion I expect to have underscored that a complete definition of complexity must incorporate three aspects of a network (connectance, redundancy and diversity). Consideration of only one aspect of complexity drives to contradictory predictions. After setting an inclusive concept of complexity, I point to a tradeoff-like relation among complexity-as-redundancy and complexity-as-connectance (or epistasis). With this relation in mind, we must not expect robustness arising from highly connected gene networks nor from highly redundant gene networks. I expect to observe networks with intermediate levels of complexity as the most robust ones.

In the following part of this paper, I test this prediction. To do so I adapt a standard mathematical description of genetic networks, including a parameter to vary the strength of interactions among genes. This model is explored analytically and numerically to show that genetic networks with intermediate strengths of interaction are the most stable ones.

Methods

a) Analytical approach

Let us expand traditional descriptions of gene networks, to include the strength of interaction as a parameter. Equation 1 is a classic model of a genetic network (for a recent review see (Smolen *et al.* 2000)), with a simple addition, the parameter S .

$$\dot{X}_i = S \sum_k X_k H_k - X_i \sum_m \gamma_m \quad \text{Equation 1}$$

Here X_i stands for the concentration of the product of the gene X_i . The dot on top denotes the first derivative. Changes in the concentration of X_i are the balance between the product of all controlling genes and the degrading rate of X_i . S is interaction strength, there are k controlling substances to X_i and m degrading products from X_i . γ_m stands for the degrading rate. H is a Hill function:

$$H_i = \frac{x^p}{x^p + \theta^p} \quad \text{Equation 2}$$

p and θ are parameters determining the shape of control interaction and the position of the threshold in which control becomes active, respectively. For high values of p , H 's behavior is sigmoidal, and for lower values of p , the control occurs in a switch fashion. This function is widely used because the sigmoid shape is adjustable, as much as the threshold in which the control is activated. Normally it is used as $1-H$, for negative feedback control.

With the model just introduced, a genetic network is summarized into a system of coupled differential equations, one equation such as Equation 1 by each gene present in the network. The standard analysis of the stability of such systems is an eigenvalue analysis (a.o. (Thomas 1998)). In this analysis, the sign of the real part of the dominant eigenvalue of the transition matrix (made by the system of coupled differential equations) measures the stability of the corresponding equilibrium point of the dynamical system. This approach, aka perturbation analysis, has a long tradition in community and evolutionary ecology. The name emphasizes the information that we can obtain. The sign of the real part of the dominant eigenvalue tells us the behavior of the system after facing a small perturbation in the state of any X_i , the state variable. The system in itself is not affected, no change of its parameters is assumed. The stability that we are able to measure refers to the behavior of a gene network facing changes in, for example, the products of a gene. As I will use it, eigenvalue analysis does not measure the stability of the genetic network facing mutations that changes its architecture. Due to the inherent restrictions of solving systems of many differential equations, this analysis is restricted to gene networks of reduced number of genes. In the results, I use this analysis to show how epistasis can introduce instability in an arrangement of few interacting genes. Or, in other words, I show how complex networks can be more fragile than their simpler counterparts.

b) Numerical approach

To study the stability of larger networks and to compare *in extenso* different degrees of complexity, I devised numerical simulations to evaluate stability facing mutational perturbation. In this part of my research, I assessed which configurations of genes are able to produce the same outcome after random mutation. I consider a mutation as able to shut down the functioning of a gene.

Assume that the interaction of genes occurs in discrete time intervals. Then, the system portrayed above as a differential equation system can be converted to a set of difference equations, amenable to iterations with a simple computer code (The code is in C, and available upon request). The state of each gene in a network was recorded after transient behavior. This gives me a portrait of the un-perturbed genetic network behavior. The run is repeated after a random and small change in the gene products values, again discarding transients. Comparison of the behavior of the perturbed and the unperturbed system at each time step informs if the perturbed system converges to the behavior of the un-perturbed system, or not. I repeat the task hundreds of times and with the help of a binomial test, I checked whether the described genetic network converges a significant amount of times, i.e. it is a stable network. The simulations, so far, produces information comparable to the eigenvalue analysis. To add the mutational perturbation to the simulation analysis, in each gene network a random gene stops to work. Then I assess the perturbation stability of this mutated network. The networks that are less perturbed by noise after mutational perturbations are considered more robust, since they are able to dampen a perturbation. Figure 2 depicts the algorithm for the assessment of mutational robustness.

Figure 2.

Results

a) Connectance introduces instability

In the first group of results I show that gene arrangements with more connectivity can have a more unstable behaviour. Figure 3a shows the sign of the dominant eigenvalue of a system of two interacting genes. As expected, two genes that control each other are stable, all the real part of the eigenvalues are negative. Figure 3b

shows a lineal assemblage of interacting genes. They present a slightly more complex behaviour. Still the sign of the dominant eigenvalue is negative for most of the parameter space, reaching only zero, when interaction strength is equal to degrading rate. Finally, two connected sets of lineal assemblages of genes have a more complicated eigenvalue behaviour. The region not portrayed in the graph corresponds to complex eigenvalues with positive real parts. Such eigenvalues represents asymptotically unstable spirals.

In Figure 3 we can see that for some parameters combinations, the real part of the dominant eigenvalue are positive, implying that the system is not always stable. The parameter space in which this occurs increases with the increase of connectance. I explored widely the parameter space, noting that changes in parameters like the threshold or the shape of the Hill function (θ and p in equation 2) changes the region in which eigenvalues that indicates stable gene networks are found. But it is a repeated result that an increased number of genes, and connectance among them, enlarges the parameter space in which a gene network has unstable behaviours. From this extremely simple progression of complexity in the genetic network and the eigenvalues depicted we can see how the increase of complexity might lead to the increase of instability.

Figure 3

b) Simulations and connectance in parallel and vertical

I have discussed above that the complexity of a gene network can be increased increasing its connectance. Figure 4 depicts the gene networks that I analyse using the numeric algorithm. Starting with an arrangement of 16 genes, connectance 2 and having 3 parallel lines, I increase the connectance of the network in vertical or parallel fashion. Here, network architecture is differentially altered. Gene networks

P+ and P++ have connectance increased connecting genes that are parallel to each other. This is expected to create more redundancy. On the other side, gene networks V+ and V++ have connectance increased connecting genes that are in the same vertical line. This increase in “vertical” connectance increases the number of feedback loops. It is expected, accordingly to the discussion above, that an increase in parallel connectance increase the robustness facing mutational perturbation.

Figure 4

Figure 5

Accordingly, Figure 5 shows the results of noise dampening after mutational perturbation applied to the gene network. First, it is true that an increase in vertical connectance adds less robustness than an increase in parallel connectance. Moreover, it is interesting to see that the increase in vertical connectance adds robustness, but the increase in interaction strength, adding instability, can even reverse the robustness added by vertical connectance. The reverse is emphasized with the circle in Figure 5, which marks the level of interaction strength that reverse the gene network that is more robust. This situation illustrates perfectly the case in which more complex is not more robust.

Discussion

A long time ago, Glass and Kauffman reported that high connectivity in a boolean network might be cause of instability (Glass & Kauffman 1973). In particular, they identify feedback loops as providers of many unstable behaviors for a system. Nowadays it is a common place to relate feedback loops with stable behavior of genetic networks (Becskei & Serrano 2000; Freeman 2000). I noticed this historical disagreement in the literature. This work builds on classic models of genetic networks, adds the strength of genetic interactions as a parameter and, after

analytical and simulated explorations of the models find results that are closer to the classic work than to the recent phrase “complex is more robust”. Here I show that the statement “complexity due to feedback loops enhances robustness” is just part of the full picture. To this we must considerate that feedback loops also enlarge the range of available dynamical behaviors, introducing instability.

Nevertheless my results that “complex might not be more robust”, we are faced with a reality in which both empirical and theoretical results indicates that real systems (Barkai & Leibler 1997; Barkai & Leibler 2000; Lenski *et al.* 1999; Little *et al.* 1999; Ueda *et al.* 2001) and engineered systems (Elowitz & Leibler 2000; Gardner *et al.* 2000) are complex and robust. So a dilemma is posed. If mathematical models of complex gene networks are unstable, why their real counterpart seems to be stable? To answer this question I discussed that several aspects of complexity must be included to provide a meaningful definition of complexity. In doing so, I predict that intermediate complex networks should be more robust. By adding the strength of interaction of a genetic network, I showed that intermediate interaction strength provides robustness. This result, predicted after a discussion of the different aspects that complexity of gene networks must incorporate, is precluded in recent work on the stability of trophic networks (McCann *et al.* 1998)

Using eigenvalue analysis, I showed that at least two aspects of complexity: connectance and number of interacting genes, increase the instability of a gene network. This is so because more complex networks adds possible behaviours to a gene network. Some of the added behaviours can be unstable.

In a more realistic analysis, I showed that noise dampening is less affected by mutations in complex networks. The increase in redundancy is the element of complexity that maximizes the increase of robustness to face mutations. Nevertheless, high interaction strengths of connected and redundant genes can affect the noise dampening of a complex gene network, making it less robust than a

simpler gene network. Here intermediate strength of interaction is a source of robustness.

Other authors consider the evolution of canalization and modularity as sources of stability in a highly connected network (Somogyi & Sniegowski 1996). Here I identify another source of stability and robustness, intermediate strength interaction. The strength of interaction could be a more proximate cause for stability, being a molecular phenomenon. It is a tempting speculation to say that intermediate strength actually produces canalization. This is so because canalization is a developmental phenomenon in which mutational perturbation is shielded from being expressed. Recent work addresses the connection among robustness and canalization (Hansen & Wagner 2001b). Future and more specific modeling is required to test this idea. A long-standing debate in evolutionary biology regards the causes of long-term stability of certain phenotypes. In the literature, this is called stasis. Stasis, then, refers to the presence of un-perturbed phenotypes through geological times, despite environmental perturbation. It is interesting to speculate that if intermediate strength of interaction produces robustness, perhaps it also produces stasis.

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Figure Captions

Figure 1a

Three hypothetical genetic networks (a, b and c) are depicted here. The circles are genes that produces a phenotype, the square. The product of a gene pointed by an arrow depends on the product of the gene from which the arrow departs. In this figure, complexity increases from left to right.

Figure 1b

Detail of genetic network (c), to describe how redundancy and connectance might be modeled as two extremes among a continuum of interaction strengths. K_{21} and k_{31} are conversion factors that scales the influence of the products of g_2 and g_3 to the production of g_1 .

Figure 2

This figure depicts the algorithm used for the numerical analysis of the robustness facing mutations. The steps followed are:

- 1) Iterate the network and record last values after transient behavior
- 2) Record the following behavior carefully
- 3) Restart the iteration from the values recorded in one (1)
- 4) Perturb this second iteration with random noise
- 5) Record the following behavior carefully
- 6) Compare the recorded values from (2) and (5). Do they converge?

From (1) to (6) is the assessment of robustness to perturbations due to small changes in gene product. This test is repeated hundred times, and the significance of the times in which the system converge is assessed with a binomial test, since at each trial the system can converge, or not.

After I have done this, the system is mutated with a random in-habilitating mutation. This means that a random gene in the network does not function any more. And the procedure from (1) to (6) is repeated. In the results I report the frequencies in which a mutated system still is significantly stable.

Figure 3

Three simple genetic networks (left side) and the value of the real part of their dominant eigenvalue (right side). The networks increase in complexity from up to down. The real part of their dominant eigenvalue is plotted in the vertical axe against the Strength of Interaction (S in equation 1) and the Degrading Rate (γ_m in Equation 1). Negative values indicates parameter space in which the genetic network is stable to a small perturbation in the concentrations of the products of their genes. The parameters of the Hill function are .8 for θ and 10 for p . Initial concentration of the genes are set equal.

Figure 4

In the top a starting gene network is depicted. As in figure 1, the product of a gene pointed by an arrow depends on the product of the gene from which the arrow departs. The left side below the starting gene network (16 genes, 4 parallel lines, connectance 2), shows V+ and V++. These two genetic networks have been increased in vertical connectivity. The right side shows P+ and P++, networks in which the increase in connectance has been adding parallelism.

Figure 5

Results from the simulated analysis of robustness to mutational perturbation. The percentage of times that the products of a mutated genetic network did converge to the un-mutated genetic networks products is plotted in the “y” axe against strength of interaction (S in equation 1), in the “x” axe.

P+ and P++ depicts the behavior of the original net in which the parallel connectance have been increased. This figure shows that still with strong interaction strength, genetic networks in which connectance has been increased in parallel are more robust than less connected-in-parallel genetic networks. V+ and V++ are networks in which the vertical connectance has been increased. For high strength of interaction we can see that more connected networks are less robust, which is to say that the strength of interaction compromises the stability given by connectivity. This illustrate the case in which complex is not more robust, but intermediate interactions strength provides stability.

Short title

When complex is not robust

Figure 1a

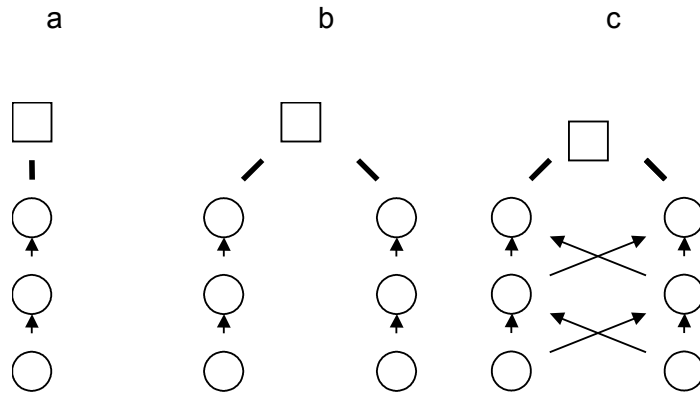


Figure 1b

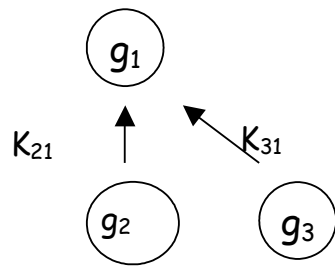


Figure 2

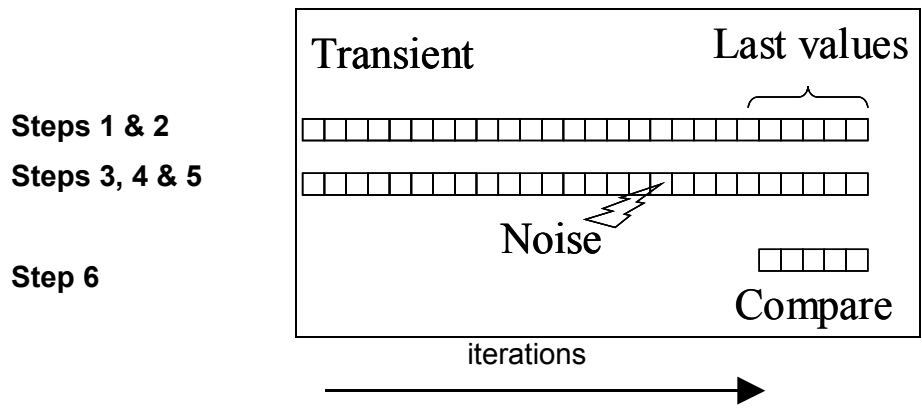


Figure 3

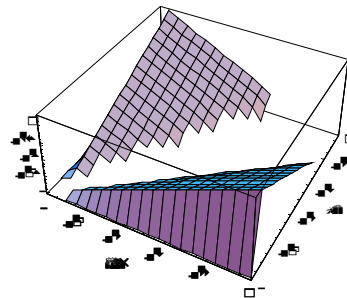
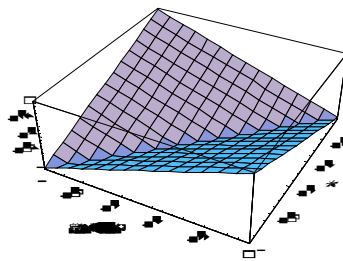
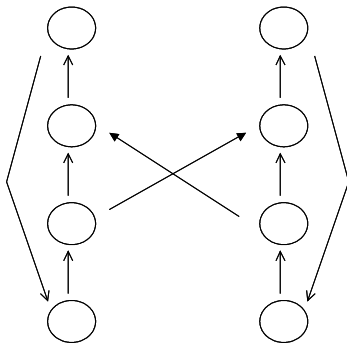
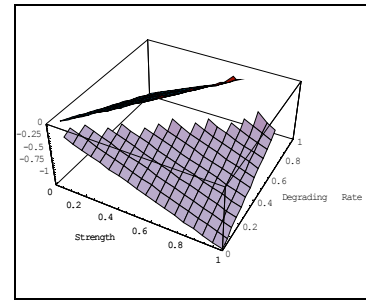
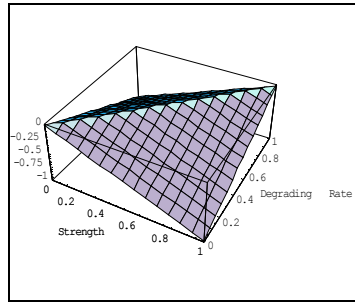
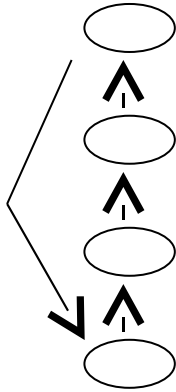
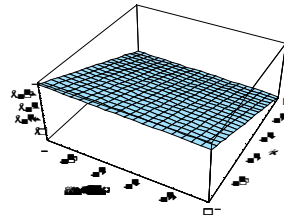
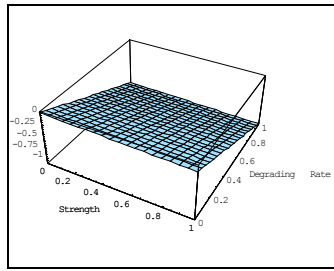
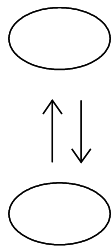


Figure 4

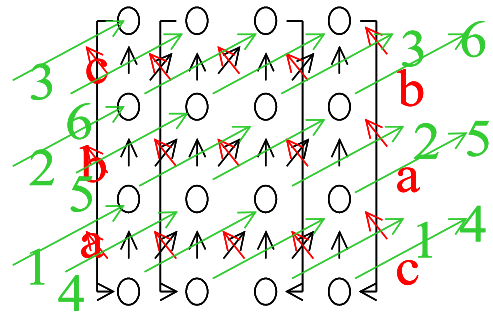
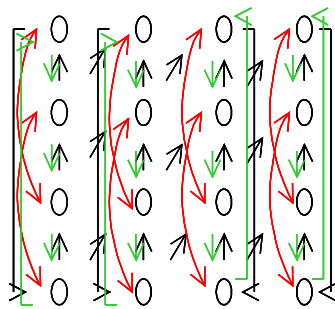
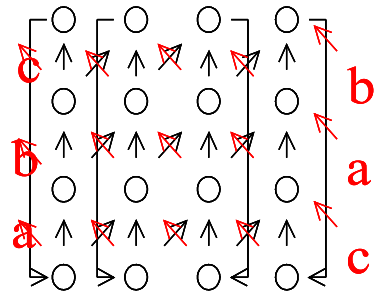
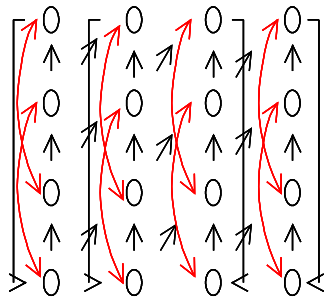
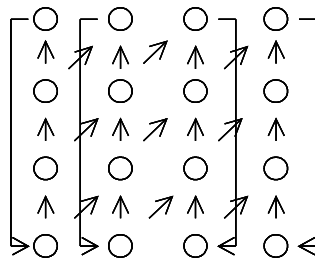


Figure 5

