SYMMETRY BREAKING AND ADAPTATION: EVIDENCE FROM A “TOY MODEL” OF A VIRUS

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Abstract: We argue that the phenomenon of symmetry breaking in genetics can enhance the adaptability of a species to changes in the environment. In the case of a virus, the claim is that the codon bias in the neutralization epitope improves the virus’ ability to generate mutants that evade the induced immune response. We support our claim with a simple “toy model” of a viral epitope evolving in competition with the immune system. The effective selective advantage of a higher mutability leads to a dominance of codons that favour non-synonymous mutations. The results in this paper suggest the possibility of emergence of an algorithmic language in more complicated systems.
1. Introduction

How does evolution work? The XIX’th century witnessed a competition between two points of view, best described through the famous example of the giraffe’s neck. The first point of view, due to Lamarck, was that during a giraffe’s lifespan the need to constantly stretch to reach leaves high up in the trees was somehow understood by the reproductory system which would have the giraffes produce offspring with longer necks than their parents. The second point of view, due to Darwin, was that the offspring are born with a random distribution of neck sizes, with a mean value identical to that of their parents. The principle of natural selection is then assumed to favour longer neck sizes through the differential in reproduction rates.

Lamarck’s ideas have been mostly relegated to the role of historical anecdote with the improved understanding of the biomolecular mechanisms involved in the manipulation of genetic information. The “central dogma”, which is almost always true as far as we know today (Lewin, 1995), holds that information flows only one way: from chromosome to protein, but not the other way around. Yet the discussion has never completely died, mainly because the claim that mutations are strictly random is difficult to reconcile with the observed efficiency of evolution. Some of the main objections are:

1. Simultaneous changes of several apparently independent phenotypic traits, which are required to explain many “large” mutations (e.g. reptiles and birds), seem too improbable to occur without some form of organization.
2. The efficiency with which species adapt to changes in the environment suggests that there should be a mechanism for environment-feedback which favours useful mutations over random ones.

In this article, we will show that the environment (e.g. the immune system) can organise the search for new genetic solutions within the context of random mutations of the chromosome. The essential idea is that random mutations of the genotype (genetic makeup of an organism) produce “organised” mutations of the phenotype (shape and function of an organism). In other words, mutations at the phenotypic level can be “guided” without the need to appeal to a mechanism which would violate the central dogma or causality. What we mean by guided can be understood once again with the example of the giraffe; here the claim would be that the distribution of giraffe offspring is biased toward longer necks. To understand how this can occur it is important to recall how chromosomes encode genetic information.

The genetic information is encoded in ribonucleic acid (RNA) and deoxyribonucleic acid (DNA), these molecules being polymers of four types of nucleotides (monomers). A group of three nucleotides forms an aminoacid residue, called a “codon”. There are 64 possible codons ($4^3$), which encode a total of 20 possible aminoacids and a STOP sequence. The code is almost universal but variations exist (Lewin, 1995; Trifonov, 1987). Since there are 64 codons and only 20 amino acids, several codons can code for the same aminoacid, for example ATT, ATC and ATA all represent Isoleucine. In general, the genetic code can be represented most conveniently by placing the 64 codons on the vertices of a six-dimensional hypercube (Jiménez-Montaño, 1996).

The translation process produces a chain of amino acids which eventually folds into a particular shape that characterises a functional object at the microscopic level (protein or enzyme). Here again there is a great redundancy. There are many possible amino acid substitutions along the polymer that would leave the resulting protein unaltered. Finally, the chemical interactions and catalytic properties of these products underlie a complex biochemical “computer” which regulates the organism’s development and eventually determines the phenotype, e.g. the giraffe’s neck size. The entire process, which begins with...
t–RNA molecules binding to m–RNA anticodons in rybozymes to synthesise proteins and culminates with the macroscopic shape and function of each organ has been described as a process of “percolation through scales” (Conrad, 1996).

The importance of the distinction between phenotype and genotype in Darwinian evolution has been stressed previously by other authors (e.g. Gatlin, 1972; Ratner, 1983). Likewise, the concept of self-organization in evolution is not new (e.g. Kauffman, 1993). One might summarise this paper by saying that it is an attempt to apply the general ideas of self-organization to the genotype-phenotype map. The point which we stress here is that in general this map is non-injective there existing a great number of “synonymous” genotypes for each phenotype. In nature, not all synonyms are observed and those that are come in different proportions. It is known from the theory of branching processes (Taib, 1992) and the Neutral Theory of molecular evolution (Kimura, 1983) that symmetry-breaking occurs spontaneously in a finite breeding pool. In this paper we will show that induced symmetry breaking also occurs, due to the violation of the synonym symmetry by genetic operators.

A simple example shows the non-equivalence of different synonyms under the mutation operator: Consider the synonyms dead and defunct. A point mutation is defined to be the change of single letter. The word dead can mutate to deed, bead, lead, deaf, dean, dear, read or deal, but is difficult to generate a meaningful word by mutating the word defunct. As we will see synonymous codons can likewise differ in their mutability. Of course it would be very convenient to choose among the synonyms those that have the best mutation targets, thereby preparing the organism for mutation to useful products. The question is: how can this occur without violating causality or the central dogma? We answer this question in the following paragraphs.

The growth of an individual over many generations will take into account not only its own selective advantage, but also its ability to produce well-adapted offspring which can in turn produce well-adapted offspring, etc. One can define an average effective fitness (Stephens and Waelbroeck 1996, 1997) of an individual as its growth rate over many generations. This effective fitness function does not respect the synonym symmetry and gives rise to a selective pressure which enhances the production of potentially successful mutants by selecting, among the synonyms, those that have a higher probability to generate well-adapted offspring. This proposal implies the existence of a mechanism for environmental feedback in the genetic search. Since symmetry breaking is due in part to selective pressures, some of these by the environment, it is reasonable to expect that mutant phenotypes are produced in an organised manner. What we are saying is in no way in contradiction with the central dogma (like Lamarckism): Information from the environment is incorporated not through a single individual but indirectly through the symmetry breaking of the gene pool. There is also no violation of causality. The symmetry breaking supports the right mutability strategies only to the extent that the mutability strategies that were useful in the past will continue to be useful in the future.

According to this point of view, it is not the giraffe’s neck size that is being selected but the tendency to produce mutant offspring with longer necks than their parents. We stress once again that this does not require that mutations of the chromosomes be organised, as a modern interpretation of Lamarkism would suggest. This is important because transcription errors are known to occur without premeditation and when directionality is observed there is no evidence that this directionality is related to environmental constraints. The information which allows the mutations to be organised at the phenotypic level is encoded in the distribution of synonyms, and expressed through the action of a genetic “interpreter”, i.e. the genotype-phenotype map. Due to the complexity of the genetic interpreter, it is not difficult to imagine that two synonymous chromosomes for
identical giraffes could differ in the sense that one would mutate more easily to a longer 
neck and the other to a shorter neck length. For the sake of illustration we can mention one 
possible mechanism for this sort of predisposition in mutability: Some genes are repeated 
in several sites along the chromosome but without the required promoter, or with some 
other genetic “mistake” which impedes its expression. Such redundant copies of a gene 
for an enzyme which would stimulate the growth of longer necks can be activated with a 
simple mutation. This is just one of many examples of how the choice of a synonym can 
favour mutability. Of course this is a trivial example and almost certainly not the correct 
exploration of the giraffe phenomenon, but it serves its purpose as a feasibility proof.

The actual mechanism whereby the symmetry breaking and ensuing emergence of a 
genetic language (Popov, 1996) can organise mutations of the phenotype is likely to be at 
least as complicated as the genetic interpreter itself, in part because there is no evidence 
that short, compact “words” should be more important than non-local forms of information 
storage (Stephens and Waelbroeck 1996, 1997). This suggests using simple toy models to 
try to understand the phenomenon as a prerequisite to any serious attempt to explain or 
demonstrate the existence of analogous processes in natural evolution.

An example of a simple organism where a mutation strategy can be selected and where 
evidence of a language exists is the evolution of a viral neutralization epitope in vivo 
(Burgos, 1996; Vera and Waelbroeck, 1996). In this case in order to evade the induced 
immune response the best evolutionary strategy is to be as mutable as possible. Since this 
strategy is valid at all times, it is a situation where the symmetry breaking, which reflects 
the selective pressure to mutate in the past, can also be expected to function in the future, 
by again enhancing the ability of the epitope to mutate. In a separate article an analysis 
of the coding of the env proteins was carried out and provided evidence in favour of our 
proposal. However, in that case several other selective factors are competing with the need 
to mutate; for example m-RNA secondary structure, enzyme and t-RNA availabilities in 
the infected cells, and secondary structure constraints all play some role. It is also not 
known precisely what segment(s) of the V3 loop region or other hypervariable regions is 
(recognised as a neutralization epitope by immunoglobulins.

Our purpose in this paper is to provide cleaner evidence for our proposed mechanism 
(whereby adaptation is enhanced by symmetry breaking), using a simple toy model where 
the only selective factor is the need to adapt to the immune response.

2. Model and Results

In this section we will present the “toy” model with which we will illustrate our ideas. 
The model consists of a virus, of which we will consider the evolution of one “epitope” 
represented by six “amino acids”. There are three possible amino acids \(a, b, c\) at each 
position represented by three-bit “codons”. The genotype then is an 18-bit “chromosome”. 
The possible values for each “nucleotide” are 0 or 1, i.e. there are two bases, hence there 
are 8 possible codons. The total number of possible genotypes is \(2^{18} = 262,144\). The phenotype is a six-letter word, e.g. \(aabab\), each word representing a different “virus”. 
The total number of possible phenotypes is \(3^6 = 729\).

As there are eight possible codons and only three aminoacids the genotype-phenotype 
mapping will be degenerate. This is manifest in the difference between the total number 
of genotypes and the total number of phenotypes. If we think of the genotype-phenotype 
mapping, \(\phi\), as an “interpreter” then \(\phi\) is non-injective. We specify the interpreter map 
\(\phi\) at the level of codon and aminoacid. Specifically: \(\phi(000) = \phi(001) = \phi(010) = a, \phi(011) = \phi(100) = \phi(101) = b\) and \(\phi(110) = \phi(111) = c\).
Each codon has a different proper mutability, where by proper mutability we mean the number of different aminoacids reached by any point mutation in a particular codon. The relation between codon, aminoacid and proper mutability is shown below.

| Aminoacid | Codon | Proper mutability | Aminoacid reached |
|-----------|-------|-------------------|-------------------|
| a         | 000   | 1                 | b(100)            |
| a         | 001   | 2                 | b(101), b(011)    |
| a         | 010   | 2                 | b(011), c(110)    |
| b         | 011   | 3                 | a(010), b(001), c(111) |
| b         | 100   | 2                 | a(000), b(101)    |
| b         | 101   | 2                 | a(001), c(111)    |
| c         | 110   | 2                 | a(010), b(100)    |
| c         | 111   | 2                 | b(011), b(101)    |

Table 1

As can be seen, for most codons the proper mutability is 2. The codon 000 however has a proper mutability 1 whilst 011 is the most mutable codon with a proper mutability of 3. The proper mutability of the entire chromosome is by definition the sum of the proper mutabilities of its six constituent codons. In an initial random population it is 12 on average and ranges from 6 (when all codons are 000) to 18 (when all codons are 011).

The fitness, \( f_i(n) \), of the ith virus at generation \( n \) is a measure of how well the virus evades the immune system. Fitness, however, is associated with a phenotype not a genotype, hence to calculate the fitness the genotype must be translated to a phenotype. For example

| Genotype | Genotype number | Phenotype | Phenotype number |
|----------|-----------------|-----------|------------------|
| 000010111110110101 | 12213 | aacccb | 79 |
| 1011110000011010010 | 192617 | bcaaba | 408 |

The fitness of a particular viral strain, \( i \), obeys the equation

\[
f_i(n + 1) = f_i(n) - \gamma V_i(n),
\]

where \( V_i(n) \) is the amount of virus \( i \) present at time \( n \) and \( \gamma \) is a constant which represents the immune system’s success in recognizing a viral strain and responding by creating T-cells capable of attacking this particular strain. The decrease in fitness of a virus in proportion to its abundance is a representation of the action of macrophages which consume viruses and activate T-cells which recognise the specific neutralization epitope of the consumed virus.

For the evolution of \( V_i(n) \) we used a selection operator that replaced \( V_i(n) \) by the integer part of \( f_i(n)V_i(n)R\zeta \), where we introduce \( R \) as a reproduction parameter and \( \zeta \) is a random number uniformly distributed in the unit interval. After selection we implement mutation with probability \( \mu \) per bit. A mutation, which acts on genotypes in a completely random and symmetrical fashion, flips the gene value: if it was 1 it will be 0 and vice versa. The mutation rate is previously determined and is the same for the entire experiment.

The system is initialized with a single virus with unit fitness. A “generation” consists of: evaluation of the fitness of each virus; reproduction of each virus and finally mutation of the selected chromosomes. As the evolution proceeds the initial fitness of any mutant virus not previously present in the population is set to 1. When the fitness reaches 0 this signifies that the virus cannot survive the induced immune response (T cells) and so it disappears completely from the population. It can also disappear prior to this due to
the random sampling effect inherent in a finite breeding pool. A virus which has been successfully eliminated in one generation can of course reappear later through a mutation of a different strain. When this happens it reappears with a fitness value equal to 1.

The model above tries to represent faithfully the essence of a phenomenon which we claim is found in nature (Waelbroeck, 1997). A “virus”, which we have identified with the phenotype in our model, consists of a chain of just 6 amino acids which is roughly the size of the neutralization epitope. From the point of view of the immune system this is what characterises the virus.

When the total amount of virus exceeds a given number, $M$, the infected person dies and the evolution stops. If the total amount of virus does not exceed $M$ within $G$ generations then the patient has survived. The particular values of the parameters chosen were: $\mu = 0.001$, $\gamma = 0.001$, $M = 1000$ and $G = 3000$. The long “latency” period ($G = 3000$) is achieved by “weakening” the patient when his virus count reaches a low value and “treating” him when it is excessively large, to avoid both recovery and death of the patient. More precisely, if the total virus count is over 600 the reproduction parameter, $R$, is set to 3 and if it is below 5 the parameter is set to 8. For intermediate values we set $R = 4$. With these choices some runs with long incubation periods are observed; the code was designed to only retain information about the infections that lasted the full 3000 generations.

The fact that $\gamma = 0.001$ implies that if 1000 copies of a particular virus have been detected over a period of time, the induced immune response is perfect and the virus is necessarily eliminated as its fitness goes to zero. With the value 4 for the reproduction factor, the expected time for the immune response to eliminate an infection by a particular strain is about ten generations; if infection has a duration of 3000 generations this implies that we will be observing about 300 mutations.

The proper mutability was averaged during the 3000 generations of each experiment. In Figure 1 the results of 1000 experiments are represented. The graph shows that all the experiments had an average proper mutability greater than 12. This is evidence of environmental feedback wherein the environment is represented by the immune system in the way it decreases the fitness of a viral strain as it becomes recognised. Since the virus is constantly forced to mutate to new forms, which by definition start with a high fitness, to avoid extermination, a strategy is selected whereby codons which mutate more frequently to non-synonymous targets are preferred. As mentioned above this implies using more frequently the codon 011, which has a proper mutability of 3, and less frequently the codon 000 which mutates mostly to other synonyms.

In Fig. 2 we show the average virus diversity during the infection for each of the 1000 experiments. In all cases the ratio of virus strains present to the total number possible is less than 15%. Since mutation acts on every gene, if the population grows, the number of new viruses grows as well, so a high diversity is related to an increase in the population.

Figures 3 to 6 we show two “experiments” in extenso. In Figure 3 one can see that the patient almost eliminates the virus completely in the first generations; the proper mutability eventually increases to an exceptionally high value, above 13 (Figure 4). The run described in Figures 5,6 is more “generic”. One can note the fluctuations of the total infection during the process, where the total viral population ranges from 500 to 750. Figs. 4 and 6 show that the proper mutability is above 12 for almost all generations, thereby confirming our hypothesis about symmetry breaking.

4. Discussion and Conclusions
Our model shows the spontaneous emergence of structure in the production of mutants in spite of the purely random and non-directional nature of point mutations at the genotypic level. This reflects a self-organization process which improves the virus’ ability to adapt to changes in its environment. The proper mutability average for virus with a long lifetime in vivo is above the average value, reflecting the dominance of the more mutable codons in the chromosome. Thus, we have demonstrated that a virus can “organise” its mutations in order to avoid the immune system response through the choice of non-synonymous mutations over neutral ones.

From all possible epitopes that could be represented in our model, only a small proportion, approximately 15%, are actually present at any time during the infection. The only selective difference between one epitope and another is the extent to which the immune system has learned to recognise it. Thus, any mutation to one of the remaining 85% of as yet unrecognised epitopes is selectively favoured. The effective selective advantage in the long term of a high proper mutability leads to the dominance of codons that favour non-synonymous mutations.

The induced symmetry breaking which results in the enhanced usage of mutable codons is closely related to the non-injective property of the interpreter which carries out the translation process. This implies that synonyms can exist which differ from one another only by the action of the genetic operators; this action induces a hierarchy among synonyms, which leads to the symmetry breaking. For the case treated in this paper, the relevant genetic operator is point mutation and the hierarchy is due to proper mutability. The interpreter used in our experiment was trivial in that its only role was to establish three possible hierarchical states depending on proper mutability, with mutability values 1, 2 and 3. Since the codon bias occurred within this simple model one is led to the conclusion that the property of mutability itself is being selected. The interpreter is independent of the fitness landscape which depends only on the phenotype.

Of course, one may take the point of view that there is no fundamental difference between a non-injective fitness function on genotypes (i.e., direct encoding with a “symmetrical” fitness landscape) and a non-injective interpreter (indirect encoding). However, by following this point of view one misses the point, which is that by focusing on the role of the interpreter we can better understand how evolution works. In this case, identifying the interpreter allows us to understand that the origin of the symmetry of the induced fitness function on genotypes is that different codons can code for the same amino acid but differ from one another in mutability. This allows the system to better face the changes needed for adaptation.

In conclusion, our model proves that symmetry breaking can enhance the adaptability of a species to changes in the environment. The production of phenotypic mutations is not only a reflection of the random and non-directional nature of point mutations, but of the spontaneous emergence of structure in the gene pool through symmetry breaking.

For this mechanism to be useful towards understanding the self-organization of phenotypic evolution in more complex organisms the concept of synonym must be generalised beyond the simple codon-aminoacid redundancy considered here. The chromosome does not encode directly the size and shape of various parts of an organism, but rather the interpreter, in this case embodied by biochemical processes in living cells (and amongst them), translates the genotype into a phenotype. In this translation there are many possible sources of redundancy, the codon bias being only a relatively insignificant example. There are more subtle forms of synonyms, involving issues ranging from protein secondary structure to the machinery of gene regulation, for which symmetry breaking can be related to the emergence of an algorithmic language.
Considering the chromosome (genotype) as an algorithm, the interpreter is the “computer” which executes the algorithm and the phenotype is the solution. In this sense, the breaking of symmetry is related to the selection of a language, where “words” or “grammatical rules” are selected in order to facilitate the search for well-adapted offspring, i.e. successful mutants. The identification of such subunits of genetic information (Schmitt, 1996) which facilitate the search for mutant phenotypes is related to the standard problem of finding an approximate decomposition of an optimization problem into smaller sub-problems. The condition for such a strategy to succeed is that when the solutions to the subproblems are reached then a good approximation to the global solution is reached as well. This requires that the fitness landscape should have a certain amount of structure; by unravelling this structure the emergent language results in an effective smoothing of the induced landscape on the space of genotypes. By “effective smoothing” we mean the population-dependent property that mutations at the level of the genotype have better mutation targets on average than in a random population. This implies first of all a solution of the brittleness problem, since the first task is that mutant algorithms be meaningful, and secondly an enhanced ability to produce genetic improvements (better algorithms). For the proposed mechanism to work it is necessary that the landscape be sufficiently correlated, and that the interpreter be well adjusted to the structure of the problem. An example would be the Kauffman’s $N_k$ landscapes for $k \ll N$, together with his model of cellular automata for gene regulation. Another example (Angeles et al 1997) is the cell division interpreter in Kitano’s neurogenetic model (Kitano 1990, 1994).

In the case of complex interpreters that lead to algorithmic languages, in order that the symmetry breaking which necessarily reflects only past adaptation pressures should favour the search of future solutions, the evolution of the landscape must respect certain rules. Namely, the decomposition of the optimization problem into subproblems must be independent of time, so that the algorithmic language which has been successful in past should continue to be useful in future. This is the requirement of structural decomposition stability: The landscape evolution must preserve the structural decomposition of the adaptation problem.

One might conjecture that extinctions are related to a violation of structural decomposition stability. For instance, the algorithmic language guiding the search of new dinosaur species would presumably have been incapable of producing viable solutions in the environment which is assumed to have provoke their demise.

The symmetry breaking which we observe in these experiments support these ideas by suggesting that with a less trivial interpreter one might witness the emergence of an “algorithmic language” tuned to the interpreter.

We are currently analyzing several Genetic Algorithm models to this effect, (Holland, 1975; Goldberg, 1989), using certain classes of controlled rugged landscapes that are more realistic from a biological point of view (Kauffman, 1989,1990,1993). A related challenge is to exploit the emergence of a language to assist in the design of a new generation of genetic algorithms as an improved general purpose optimization method. A key for success in this direction is the codification method: The interpreter should have the sufficient flexibility to be able to solve the decomposition problem, but not so much flexibility that it could solve any possible problem, since in that case the search space for the desired algorithmic language would be far too large. Another application of the language emergence is the development of an GA to perform complex computational tasks (Crutchfield 1994), such as combinatorics. Interesting applications may also follow in adaptive systems modelling where adaptability is an important property, for example the forecasting problem in financial markets.
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