SYMMETRY BREAKING AND ADAPTATION: THE GENETIC CODE OF RETROVIRAL ENV PROTEINS

S. Vera Noguez
Facultad de Ingeniería, UNAM,
Circuito Exterior, C.U.,
México, D.F. 04510.

H. Waelbroeck
Instituto de Ciencias Nucleares, UNAM,
Circuito Exterior, A.Postal 70-543,
México, D.F. 04510.
email: hwael@roxanne.nuclecu.unam.mx

Abstract: Although several synonymous codons can encode the same aminoacid, this symmetry is generally broken in natural genetic systems. In this article, we show that the symmetry breaking can result from selective pressures due to the violation of the synonym symmetry by mutation and recombination. We conjecture that this enhances the probability to produce mutants that are well-adapted to the current environment. Evidence is found in the codon frequencies of the HIV env protein: the codons most likely to mutate and lead to new viruses resistant to the current immunological attack, are found with a greater frequency than their less mutable synonyms.
1. Introduction

Darwin’s proposal that evolution proceeds by random mutation and natural selection has been the keystone of evolution theory since the XIX’th century (Darwin 1859, Simpson 1964). Yet objections linger on: Large mutations require coordinated changes of several phenotypic traits, which seems unlikely to occur at random. Also the efficiency with which species adapt to changes in the environment has led some to suggest that there should be a mechanism for environmental feedback which favors useful mutations over random ones (Steele 1979).

Proposals for a direct environmental feedback that would pre-determine the mutations have been largely discarded: The so-called “central dogma” (Lewin 1995) states that information from the environment cannot be tranfered to DNA. Actually this “dogma” is not quite true, although the conclusion that there is no direct environment feedback probably is. Viruses can incorporate their own coding in the germ line cells, as inherited endogenous proviruses. The enzyme methylase can induce a mutation hotspot, which allows for indirect information transfer through the location of the hotspot, etc. Yet it seems difficult for information from the environment to be usefully transfered through such mechanisms, and this is why the central dogma is so well accepted.

In this article, we will show that the environment can organize the search of new genetic solutions within the context of random mutations of the chromosome. The essential idea is that random mutations of the genotype produce non-random mutations of the phenotype. This results from the existence of synonyms, together with the claim that the gene pool breaks the synonym-symmetry in a way which incorporates information about the environment.

How this comes about is illustrated in the following simple example [Fig. 1]. Suppose that one has four possible genotypes, \( A \rightarrow D \), and that each genotype can mutate to the
two adjacent genotypes when the letters $A$, $B$, $C$, $D$ are placed on a circle. For example, $A$ can mutate to $B$ or $D$ but not to $C$. $A$ and $D$ both encode the phenotype $a$, $B$ encodes $b$ and $C$ encodes $c$. In a random population, $p(A) = \cdots = p(D) = \frac{1}{4}$ and the phenotype distribution is $p(a) = \frac{1}{2}$, $p(b) = p(c) = \frac{1}{4}$. The distribution of mutant phenotypes in that case is the same as for the population prior to mutation. But if the gene pool is organized so that phenotype $a$ is always encoded as $A$, then with the same distribution of phenotypes one gets the mutant distribution $p(a) = \frac{1}{2}$, $p(b) = \frac{1}{3}$ and $p(c) = \frac{1}{6}$. Vice-versa, if the synonym $D$ is chosen instead of $A$ then the mutations to the phenotype $c$ are more probable than to $b$. Information in the genotype probability distribution is expressed through a non-random distribution of mutant phenotypes.

The next step is to explain how selective forces can induce the symmetry breaking of the gene pool, thereby incorporating information about the environment into the genotype distribution.

Symmetry breaking would occur spontaneously in a finite breeding pool, by the theory of branching processes (Taib 1994, García-Pelayo 1994) (this observation is the backbone of the Neutral Theory of molecular evolution (Kimura 1983). However, we will show that there is also an induced symmetry breaking from the violation of the synonym symmetry by the genetic operators, such as mutations and recombination.

If one considers the growth of an allele not from one generation to the next but over many generations, selection forces will take into account not only the selective advantage of this allele but its ability to produce well-adapted offspring, which can themselves produce well-adapted offspring, etc. Since mutation and recombination act differently on synonymous alleles, the synonyms will differ in their descendence, both in the passive sense of genes surviving mutations, and in the active sense, to generate new genetic solutions. This implies that the time-averaged effective fitness function, defined as the growth rate of an allele over many generations, does not respect the synonym symmetry.
Thus, that the time-averaged effective fitness function provides 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 is a highly non-trivial proposal, in that it implies an environmental feedback in the genetic search: if the symmetry breaking is due in part to selective pressures, then the section of the symmetry group naturally incorporates information about the current environment, so that mutant phenotypes are produced not at random, but to some extent tuned to the current environment. Although this suggestion brings back the ghost of Lamarckism (Simpson 1964), we stress that what we are saying is in no way in contradiction with the central dogma. Information from the environment is incorporated indirectly through the symmetry breaking of the gene pool, not at the level of a single individual.

The simplest manifestation of synonym symmetry in the genetic code is the codon redundancy. Since $4^3 = 64$ possible codons encode 20 aminoacids and a STOP sequence, most aminoacids can be represented by several codons. Synonymous codons differ in terms of their products following a mutation of a single nucleotide.

It is easy to see how different synonyms can have different mutabilities. Consider for example the synonymous words *dead* and *defunct*, and assume that a mutation changes a single letter. The word *dead* can mutate to *deed*, *bead*, *lead*, *deaf*, *dean*, *dear*, *read* or *deal*, but it is difficult to generate a meaningful word by mutating the word *defunct*. As we will see below, the situation with codons is similar. The time-averaged effective fitness will give a selective edge to codons with the ability to mutate to another useful form. Since what is “useful” is generally environment-dependent, this implies that the symmetry-breaking process incorporates information about the environment into the gene pool.

In this paper, we will consider the code of retroviral enveloping proteins, which are
a key component in the detection of a virus by the immune system. We will show that the codons which have a higher probability to mutate to a different allowed aminoacid are preferred, thereby enhancing the ability to escape detection by the immune system. This demonstrates that phenotype mutations are organized, and furthermore that this organization is guided by environmental factors. They are *organized* because certain mutant aminoacids are produced more frequently than with a random choice of codons, and *guided by environmental factors* because these more frequent aminoacids are precisely the ones that are allowed (and thus presumably lead to a successful infection).

In order for this mechanism to usefully guide the search of new genetic solutions in a more complex organism, one must generalize the concept of “synonym” beyond the single-codon degeneracy of the genetic code. The central concept which allows selection among synonyms to take place is that of indirect encoding. The chromosome does not encode directly the size and shape of various parts of an organism, but an *interpreter*, embodied by the biochemical processes in living cells, translates the genotype into a phenotype. The decoder allows for several types of synonyms. The most trivial example is that of various codons encoding the same amino-acid, but there are more subtle synonyms, related to the machinery of gene expression, for which symmetry breaking can be related to the emergence of an *algorithmic language*.

If one views the chromosome as an algorithm, the interpreter is the “computer” which executes the algorithm and the phenotype is the solution. In this sense, the breaking of synonym symmetry is related to the selection of a language, where “words” or “grammatical rules” are selected if they facilitate the search for successful mutants. This will be the case if they are related to an approximate decomposition of the optimization problem into smaller subproblems. This in turn requires that the genetic interpreter be sufficiently flexible to realize the required decomposition, and that the fitness landscape be sufficiently correlated to allow for a decomposition of the optimization problem into smaller subprob-
lems. An example would be Kauffman’s $Nk$ landscapes for $k \ll N$, together with his model of cellular gene regulation (Kauffman 1993).

The importance of viewing the genotype as an algorithm for a solution rather than the solution itself has been discussed previously in the context of genetic algorithms (Asselmeyer et al. 1995, Adami 1994), as has the idea that intelligence is an emerging collective property (e.g., Rauch et al. 1995). Our claim is that the existence of synonyms and a mechanism of symmetry breaking are the key to understanding how such ideas are realized in practice.

Since the algorithmic language is necessarily evolved in the causal past, it will facilitate the search of future solutions only if the decomposition of the optimization problem is stable. We will refer to this condition as structural decomposition stability: the evolution of the landscape must preserve the structural decomposition of the adaptation problem, so that the language which was successful in the past continues to be successful in the immediate future.

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 provoked their demise.

In the following sections, we will focus on the simplest possible example of symmetry breaking in the genetic code, in order to demonstrate both analytically and experimentally the concept of induced symmetry breaking. We should stress that our results by no means exclude the possibility of spontaneous symmetry breaking, which is postulated in the Neutral Theory and strongly backed by empirical evidence. Likewise, our proposal and Cocho and Martínez-Mekler’s views on symmetry breaking by the genetic transcription machinery (Cocho et al. 1992, 1994, 1995) are not mutually exclusive.
We will consider the synonymous codons at each amino-acid in the \textit{env} protein from an HIV database (Myers 1992). The synonymous codons differ in their products following a point mutation. Some of these products are “allowed”, in the sense that they give rise to a functional virus, others may be neutral (same amino-acid), or forbidden. We will show that codons with a higher probability to mutate to a different allowed amino-acid are favored over their less “mutable” synonyms. This enhances the probability that the virus generate mutants capable of escaping detection by the immune system.

2. Symmetry breaking through codon mutability

The data on \textit{env} proteins gives sequences which can be aligned in the usual way to identify a total of 978 codon positions, some of which may be unoccupied in a particular strain of the virus. Let us focus on one position in particular, and make a list of the different aminoacids that are found at that position: these will be called “allowed aminoacids”, by definition. We will be interested in the effect of point mutations in the transcription of the \textit{env} protein in the HIV-1 viruses from our database.

Some point mutations lead to a synonymous codon which represents the same aminoacid; we will refer to such point mutations as \textit{neutral}. When the mutation leads to a \textit{different} amino-acid, we will say that the non-neutral mutation is “allowed” if the aminoacid obtained is an “allowed aminoacid”, i.e. if it can be found in another sequence at the same position.

For a given codon there are 9 possible point mutations. We will call the “mutability” of a codon the number of allowed mutations. When only non-neutral allowed mutations are counted one gets the “proper mutability”. Following our reasoning in the introduction, one expects that the codons with the highest mutability will be selected, since they have a higher probability to sucessfully infect a cell. The codon with a high \textit{proper mutability} has
an extra selective advantage since its offspring may be able to fool the immune system, if
the mutation happens to be picked out by macrophages and displayed as part of an epitope.
Thus, statistically speaking, codons with a higher mutability are selected for resistance to
mutations and those with a high proper mutability are selected for adaptation, in this case
to the immune system.

For example, at position number 186 one finds the aminoacids leucine, which can be
encoded by (TTA,TTG,TCT,TCC,TCA,TCG), glutamic acid (AGG,AGA), triptophan
(GTG) and STOP (ATA,ATG,GTA), i.e. 12 possible codons for four allowed aminoacids.
The mutability and proper mutability of each codon are represented in [Table 1]. Note
that synonyms differ in terms of their mutabilities and proper mutabilities: For example,
TTA can mutate in three different ways to the STOP sequence, but its synonym TCT
allows no non-neutral mutations.

Let us define the frequency of a codon as the number of times this codon is found at
that position, as one scans through the sequences in the database. If selection is behind the
symmetry breaking phenomenon, as we have speculated, the more mutable codons should
have a higher frequency.

To represent the relation between the frequency with which codons are observed and
their mutabilities, we computed the linear correlation coefficient between frequency and
mutability at every position where the variance is non-zero, and likewise for frequency and
proper mutability. The correlation coefficients are represented in the form of a histogram
in both cases. In the case of mutability [Figure 2a] there seems to be a preference for
positive correlation coefficients: there are 114 positive correlation coefficients against 42
negative ones. The next histogram however is even more dramatic: The weight of the
histogram [Figure 2b] is clearly shifted towards positive correlations, a result which would
be difficult to explain without recognizing that codons with a higher proper mutability are
prefered.
Considering the importance of proper mutability to help the virus adapt to the attacks of the immune system, these results are evidence that natural genetic systems can use symmetry breaking to organize the distribution of mutants. As we speculated in the Introduction, the genetic search through random mutations of the genotype produces an intelligent search at the level of mutant phenotypes, as the information in the probability distribution of codons is revealed through an better-than-random probability distribution of mutant phenotypes.

In some positions one finds a negative correlation with mutability but a positive correlation with proper mutability. This may imply that non-neutral mutations at such a site are important to escape the immune system, i.e. that the site is frequently picked as part of an epitope. The adaptability criterion would then overrule the slight selective advantage of resistance to mutations. Vice-versa, those sites with a positive correlation to mutability but negative correlation to proper mutability may simply never be picked as part of epitopes. Negative or null correlations can also indicate violations of the assumptions underlying our definitions of “allowed aminoacids” and “allowed mutation”, namely that codons act independently of each other and that our dataset is complete, or simply be the result of statistical fluctuations, e.g. neutral drift.

3. A simple model for symmetry breaking

In this section we will provide a simple model which allows one to calculate the value of the correlation coefficients represented in [Figure 2]. The model relies on highly simplistic assumptions, so our purpose here is to obtain an order of magnitude for the expected correlation coefficient, not a precise result.

We will assume that any one of the three bases which constitute the codon is replaced at random. Since there are four possible bases, the mutation probability is $p = 1/3$ to each
of the other bases. Considering the three bases which constitute a codon, the probability of each point mutation will then be 1/9. We will further assume that one can analyze each codon position independently of the others. The probability that a virus in the population successfully infect a cell and thereby perpetuates itself will be taken to be one if the transcribed codon is allowed and zero if it is not. So the “fitness” is a binary number. Clearly these assumptions are too simplistic for a serious model of a virus; however, they can be expected to provide a rough upper bound for the expected correlation coefficient: Indeed, non-local effects related to the “cooperation” of different codons, or restrictions on the genotype mutations, all dilute the effect which we are trying to observe by reducing the amount of information available to organize the phenotype mutations and by bringing in other competing motives for symmetry breaking.

The codons which represent allowed aminoacids will be labeled by a latin index \( i = 1, 2, \cdots, N \), where \( N \) is the total number of allowed codons at that site. Their mutability will be denoted by \( m_i \). A point mutation is assumed to occur at the given position with probability \( p \).

The equation which determines the evolution of the frequency of a codon in the population given these assumptions is

\[
n_i(t+1) = (1-p)n_i(t) + \frac{p}{9} \sum_{j=1}^{N} M_{ij} n_j(t),
\]

where \( n_i(t) \) is the number of times that an individual in the population has the codon \( i \) at that site, and \( M_{ij} = 1 \) if \( i \) can mutate to \( j \) with a point mutation and zero otherwise. The mutability of codon \( i \) is given by \( m_i = \sum_j M_{ij} \).

In the limit \( p \to 0 \) and taking an infinite population \( P \to \infty \),

\[
P_i(t) = \frac{n_i(t)}{\sum_{j=1}^{P} n_j(t)}
\]
is well-approximated by a real variable and the equation above becomes equivalent to the
differential equation

\[ \frac{dP_i}{dt} = p \sum_{j=1}^{N} N_{ij} P_j(t), \]

where \( N_{ij} = M_{ij} - \delta_{ij} \). This is set of linear differential equations. The population has an
asymptotic conformal fixed point as \( t \to \infty \) given by the eigenvector of the matrix \( N \) with
the largest eigenvalue, or “Liapunov exponent”.

Given this eigenvector one can compute the correlation between the mutability and
the frequency of a codon in the population, defined by

\[ C = \lim_{t \to \infty} \frac{1}{N} \sum_{i=1}^{N} \frac{(m_i - \bar{m})(P_i(t) - \bar{P})}{\sigma_m \sigma_P}, \]

where \( \sigma_m \) and \( \sigma_P \) are the root mean squares of mutability and codon frequency, respecti-
vely, and \( \bar{m}, \bar{P} \) their mean values.

Several correlation coefficients were computed using this model and gave values which
fluctuate about the mean of the observed correlation coefficients. For example, at position
186 one finds the aminoacids leucine, glutamic acid, triptophan and \( STOP \), i.e. 12 possible
codons with the mutability matrix given in [Table 1]. The eigenvector which corresponds to
the least negative eigenvalue, \( \Lambda_0 = -5.19 \), is given. This eigenvector gives the asymptotic
value for the frequency of the various codons in the population according to our simple
model. The relation between mutability and codon frequency is manifest and gives a
correlation coefficient of 0.164. This does not compare well to the observed correlation at
this position, which was anomalously high at 0.74, but is the same order of magnitude as
the mean observed correlation coefficient.

A similar model can be constructed to examine the correlation with proper mutability.
The only required modification is in the definition of the fitness function: the probability
of successful infection, or “fitness”, is assigned a larger value if the allowed mutation is non-neutral.

Note that the arguments given above are reversible: if sections of genetic code are best kept invariant then the favored codons would be the less mutable ones. This effect would be represented in a model which assigns fitness zero to non-neutral mutants.

4. Statistical evidence for a coding language

The results of section 2 suggest that there is a language in the genetic code which enhances the production of non-neutral mutations of the env protein.

Various statistical tests are available to check whether a sequence can be based on a coding language; all have been applied recently to search for evidence of a language in both coding and non-coding DNA. We shall mention only a few of them. Zipf analysis with fixed word-length yields the exponent ζ (Mantegna 1995), the Shannon entropy (Crisanti et al. 1993) is usually represented by giving percentage of redundancy defined by

\[ R(l) = 100 \times \left( 1 - \frac{H_1(l)}{\ln(4^l)} \right). \]

The “digital walks” (Peng et al. 1992, Buldyrev et al. 1993) yield the correlation exponent α which describes the scaling of the variance (Peng et al. 1992, Li and Kaneko 1992), as well as some other less-used exponents (Voss 1992). In [Table 2] we give a few of the results of these analyses, taken from the references in this paragraph.

There is some controversy in the literature regarding these methods (Israeloff et al. 1996, Bonhoeffer et al. 1996, Voss 1996, Mantegna et al. 1996). The results of Zipf analysis and entropy measurements can be reproduced with stochastic sequences; also the binary walks are similar to those from generalized Levy walks (Buldyrev et al. 1993). The bottom line seems to be that any statistical measure of a language can be reproduced
with a stochastic sequence tailored to have the appropriate characteristics. This should come as no surprise: statistical methods can only test statistical properties, and one can always construct a stochastic sequence with any desired statistical properties. A *language* presumably involves something more than statistics, namely it requires the assumption of an underlying intelligence. The only way to prove the existence of a language, then, is to unravel its meaning!

Statistics may provide evidence for a language, but for a proof one must demonstrate the existence of a meaning. This is essentially what we have attempted to do in this article.

In any case, to supplement our results we have carried out these standard statistical tests. The results are summarized in [Table 2] and in [Figs. 3, 4]; they are consistent with the possibility of a coding language for viral RNA.

5. Conclusions

We have proposed a mechanism whereby the environment can organize the genetic search by condensing the gene pool into an “intelligent” broken symmetry phase. This would optimize the probability that mutant offspring are well adapted to the current environment.

To search for evidence that such a mechanism is at work, we considered the enveloping protein of the retrovirus HIV, and found that codons with a high mutability are more frequent than their less mutable synonyms. Results from an analysis of genetic data show positive correlation coefficients, especially between proper mutability and codon frequency. The observed correlation coefficients are of the same order of magnitude as those derived from the theoretical model, and the average value $C \approx 0.25$ is consistent with expectations.

In the language of optimization theory and artificial life, mutability reduces brittleness, while proper mutability organizes the generation of mutants as an “intelligent” search. Our
results suggest that for viral populations the organization of mutant production to adapt to the immune system is more important than reducing brittleness.

The results also confirm the importance of non-neutral mutations in the dynamics of the AIDS virus. This appears to support a conjecture by Nowak (Nowak 1992) concerning the latency period of the virus prior to the manifestation of AIDS: Nowak has argued that the number of mutant forms of the virus increases until the immune system is overwhelmed by the uneven battle between the specific immune response, which must target every one of the mutant viruses individually, and the non-specific attack of the virus on the CD4 cells. Our arguments concerning the self-organization of the gene pool also suggest what may be another part of the explanation for the long latency period: If the gene pool can organize to enhance the mutation rate of the epitopes which provoke the strongest immune response specific to the particular infected individual, this would effectively disable the strongest sector of the individual’s immune system. Preliminary numerical simulations with the help of genetic algorithms indicate that the timescale for adaptation of the gene pool to the specificities of an individual’s immune system is of the order of several thousand generations of viruses. The mutation rate of HIV is consistent with a rate of roughly one thousand generations per calendar year. Therefore, observed latency periods give the right amount of time to evolve the symmetry-broken phase of the gene pool, to adapt to the individual’s MHC and epitopal response specificities.

The relation between symmetry breaking of the gene pool and adaptability of the virus may also have implications in disease control and therapy. For example, the identification of a segment of DNA dominated by codons with a low proper mutability would naturally signal a possible conserved region. This can be useful both with regard to detection tasks, through the polymerase chain reaction (PCR) (Lewin 1995), or in vaccine design, if a conserved part of the envelope of a dangerous virus can be incorporated in that of a controlled one (e.g. smallpox), to provoke a persistent induced immune response. From
this perspective, it would be interesting to consider the reversed situation, where conserved regions would be identifiable by their preference for non-mutable codons over mutable ones.

Our results show that induced symmetry breaking does in fact play a role in molecular evolution, but falls short of actually demonstrating environmental feedback and the emergence of a more sophisticated form of intelligence in the genetic search, that would be non-local along the chromosome. This more ambitious proposal is difficult to check empirically, due to our lack of a detailed understanding of the genetic interpreter. For this reason we are currently developing genetic algorithms based on Kauffman’s model of the genetic interpreter (Kauffman 1993) and other indirect encoding models, with which we hope to demonstrate the possibility that an algorithmic language emerge from the symmetry breaking.

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FIGURE CAPTIONS

Figure 1. The genetic interpreter translates a genotype (left) to a phenotype (right). When this is a surjection, the domain set of a particular phenotype consists of “synonyms”. Different synonyms may differ in terms of their mutability; when that is the case, mutant phenotypes can be predetermined to some extent by choosing among the equivalent codes for each phenotype.

Figure 2. The correlation coefficients between codon mutability and codon frequency (a), and between proper mutability and frequency (b), are represented. The vertical axis gives the number of correlation coefficients in each interval, out of the 978 positions of the HIV env segment. Since most positions allow only one possible aminoacid, the total number of correlation coefficients computed is less than 978.

Table 1. The mutability matrix is given for the 12 possible codons at position 186 of the HIV env segment, considering only single point mutations. The total mutability of each codon and the dominant eigenvector of the matrix $I - \frac{1}{9}M$ are given in the last two columns. The dominant eigenvector represents the theoretical expected values for the asymptotic frequencies of each codon in the population as $t \to \infty$. The calculation is based on a single-codon model where the offspring survives if and only if the inherited codon encodes an allowed aminoacid.

Table 2. The correlation exponent $\alpha$, the Zipf analysis exponent $\zeta$ and the Shannon redundancy $R(4)$ are given for various examples of genetic code. These figures are in general agreement with the conjectured existence of a coding language.
Figure 3. The Zipf plots are given for the coding of HIV \textit{env} proteins. Words of a given length are ranked from the most probable to the least probable, for word lengths ranging from 3 to 6. The data is not quite sufficient to obtain an accurate evaluation of $\zeta$, but a power law behavior is observed over $1\frac{1}{2}$ decades in all cases.

Figure 4. The Shannon redundancy $R(l)$ is given for $l = 1, 2, 3, 4$, for the coding of HIV \textit{env} proteins. This gives a measure of the percent reduction of entropy as compared to a random sequence.