FITNESS LANDSCAPES AND EVOLUTION*

LUCA PELITI
Dipartimento di Scienze Fisiche and Unità INFM
Università “Federico II”, Mostra d’Oltremare, Pad. 19
I-80125 Napoli (Italy)†

February 1, 2008

Abstract

The concept of fitness is introduced, and a simple derivation of the Fundamental Theorem of Natural Selection (which states that the average fitness of a population increases if its variance is nonzero) is given. After a short discussion of the adaptative walk model, a short review is given of the quasispecies approach to molecular evolution and to the error threshold. The relevance of flat fitness landscapes to molecular evolution is stressed. Finally a few examples which involve wider concepts of fitness, and in particular two-level selection, are shortly reviewed.

1 Fitness and the fundamental theorem of natural selection

The term “fitness” derives from the phrase “survival of the fittest” that the philosopher Herbert Spencer suggested to use instead of “natural selection”. In the struggle made by the evolutionary theorists to avoid the
tautology lurking in the phrase, the term has been twisted to several meanings. R. Dawkins [6] distinguishes no less than five different meanings to the word in the evolutionary literature. From the point of view of model building, the most convenient meaning—and the one we shall adopt—is however the following:

The fitness of an individual is proportional to the average number of offspring it may have in the given environment.

In this definition, fitness is assigned to individuals rather than to genes or to groups of individuals. It is further assumed that reproduction takes place via a stochastic process, and that, in a given population, the average numbers of (immediate) offspring of two individuals have the same ratio as their fitnesses: therefore, only ratios of fitnesses have a well-defined meaning, and not their absolute value.

Let us consider a population formed by a certain number of individuals, whose inheritable characteristics (genotype) are summarized by the variable \( \sigma \). Let us further assume that the population reproduces asexually, that the offspring of an individual have the same genotype as the parent, and finally that the number of offspring is exactly proportional to the fitness of the parent: briefly, let us neglect mutations in the genotype and fluctuations in the number of offspring.

We can thus write down an equation expressing the number \( n_t(\sigma) \) of individuals carrying the genotype \( \sigma \) at generation \( t + 1 \), given the same quantity at generation \( t \), assuming that the fitness \( A(\sigma) \) of an individual is a function only of its genotype:

\[
n_{t+1}(\sigma) = \frac{1}{Z_t} A(\sigma) n_t(\sigma), \tag{1}
\]

where \( Z_t \) is a proportionality constant. In order to simplify the argument we have also assumed that the generations are nonoverlapping, i.e., that all individuals, once reproduced, die.

The total number \( N_t \) of individuals in the population at generation \( t \) is given by

\[
N_t = \sum_{\sigma} n_t(\sigma). \tag{2}
\]
We define the population average $\langle Q \rangle_t$ at generation $t$ of a quantity $Q(\sigma)$, which depends only on the genotype $\sigma$, in the following way:

$$\langle Q \rangle_t = \frac{1}{N_t} \sum_{\sigma} Q(\sigma)n_t(\sigma). \quad (3)$$

We can now prove that the average fitness $\langle A \rangle$ always increases, unless all individuals have the same fitness. We have in fact:

$$\langle A \rangle_{t+1} = \frac{1}{N_{t+1}} \sum_{\sigma} A(\sigma)n_{t+1}(\sigma) = \frac{1}{N_{t+1}Z_t} \sum_{\sigma} A^2(\sigma)n_t(\sigma). \quad (4)$$

On the other hand, one has

$$N_{t+1} = \frac{1}{Z_t} \sum_{\sigma} A(\sigma)n_t(\sigma) = \frac{N_t}{Z_t} \langle A \rangle_t. \quad (5)$$

Therefore

$$\langle A \rangle_{t+1} \langle A \rangle_t = \langle A^2 \rangle_t \geq (\langle A \rangle_t)^2, \quad (6)$$

and the equality holds only if all individuals in the population have the same fitness. In fact, the larger the variance in the fitness, the faster its average grows.

This result is a simplified version of the Fundamental Theorem of Natural Selection due to R. Fisher [16, p. 22ff]. Some authors have considered it as the key point of difference between the living and the inorganic world. As K. Sigmund puts it [32, p. 108]:

So we see, in physics, disorder growing inexorably in systems isolated from their surroundings; and in biology, fitness increasing steadily in populations struggling for life. Ascent here and degradation there—almost too good to be true.

In fact, the result depends on many unrealistic assumptions. Let alone the complications introduced by sex, which lead to maddeningly complex behavior, let us focus on the effects of mutation: on that set of causes which makes offspring different from their parent, even among bacteria.

We all know that genetic information is carried by the DNA, in the form of a sequence of nucleotide bases, which belong to four different types: $\text{A}$ adenine and $\text{G}$ guanine (purines); $\text{T}$ thymine and $\text{C}$ cytosine (pyrimidines). 3
In the double helix of DNA they are found in matching pairs: A-T and G-C. During the replication, it may happen that the replication mechanism, which associates one of the “old” strands to the “new” ones, stumbles in some errors. These errors can be divided in a few classes:

**Point mutations:** Substitution of one nucleotide base to another. They can be divided into two classes:

Transitions (the most common): substitution of one purine by the other, or of one pyrimidine by the other;

Transversions, in which a purine is replaced by a pyrimidine and vice versa.

**Insertions and deletions:** They correspond to the introduction of new bases in the strand or in their omission respectively. In the case of sequences coding for a protein, these mutations are often fatal, since they entail a frame shift in the translation into proteins, unless they occur by threes.

**Major rearrangements:** In this class one considers the insertions (or deletion) of comparatively long sequences. This is the case, e.g., of the transposable elements which are known to move easily from one place to another in the genotype. A subclass of special interest is gene doubling.

These processes do not have the same probability. If one considers two genotypes, i.e., two different nucleotide sequences in DNA, one may introduce a notion of distance between them by considering the probability of the most likely mutation path connecting them. This notion of distance (metrics) has a rather immediate evolutionary meaning, but is most often quite difficult to compute. For the sake of definiteness I shall consider in the following only point mutations, and I shall assign the same probability to transitions and to transversions. In this case all DNA sequences which may be connected to each other have the same length, and their distance is equal to the number of points in the sequence in which different bases are found: this is known as the Hamming distance.

To summarize: we have defined a genotype space as the space of all sequences $\sigma$ of a given length which can be built with the four-letter alphabet ATGC. This space is endowed with a metrics, defined by the Hamming
distance, i.e., by the number of corresponding positions in the sequence in which different nucleotide pairs are encountered. If we now assign to each such sequence its fitness value (assuming that the fitness of an individual is a function only of its genotype), we obtain a fitness landscape. The phrase goes back to S. Wright [37], but the concept can already be found in Fisher’s work in the ’twenties.

The Fundamental Theorem therefore implies that populations move on fitness landscapes striving to climb up their peaks, while we are accustomed to physical systems rolling down the slopes towards the points of smallest energy. In this sense, fitness plays in evolutionary theory a role similar to energy in mechanics.

2 Adaptative walks

The Fundamental Theorem intimates in fact that the population rapidly reaches the maximum fitness of all individuals that are already present in it. Higher values of the fitness can only arise if there are mutations. If mutations are rare, one can think of a regime in which mutants arise from time to time and, if they correspond to higher fitness, “draw” the population to the new fitness value. This justifies the evolutionary model known as the Adaptative Walk [21].

In order to simplify the discussion, we shall consider from now on a genotype written in a two-letter alphabet. The conclusions that we shall draw can be easily translated, in principle, in the four-letter alphabet of real life. We shall denote the two letters by \{-1, +1\}, and describe the genotype \(\sigma\) by a collection of \(N\) binary variables (units): \(\sigma = (\sigma_1, \sigma_2, \ldots, \sigma_N)\), where \(\sigma_i = \pm 1, \forall i\). The space of these genotypes is the hypercube in \(N\) dimensions, whose \(2^N\) vertices correspond to the genotypes, and the Hamming distance between genotypes \(\sigma\) and \(\sigma'\) is given by

\[
d_H(\sigma, \sigma') = \frac{1}{2} \sum_{\sigma} (1 - \sigma_i \sigma'_i) .
\]  

(7)

We shall also consider an equivalent measure of the similarity or dissimilarity of genotypes, namely the overlap \(q\), central to the theory of spin glasses [28].
and defined by

\[ q = \frac{1}{N} \sum_{i=1}^{N} \sigma_i \sigma_i' = 1 - \frac{2d_{H}(\sigma, \sigma')}{N}. \]  

(8)

The overlap between identical genotypes is equal to 1, and it decreases as the Hamming distance increases. Two completely independent genotypes will be different, on average, in half of their units, and the corresponding overlap will be close to zero.

We can now define the Adaptative Walk model [22], [21, p. 39–40]. To each genotype \( \sigma \) is associated its fitness \( A(\sigma) \). One assumes that the population is characterized by a single genotype \( \sigma(t) \) at each generation \( t \). The initial genotype \( \sigma(0) \) is chosen at random. Given the genotype \( \sigma(t) \), the next genotype is chosen according to the following procedure:

(i) One changes sign to one of the units of the genotype \( \sigma(t) \), chosen at random; in other words, one chooses at random one of the \( N \) vertices of the hypercube closest to \( \sigma(t) \); one thus obtains a tentative genotype \( \sigma'(t) \);

(ii) If \( A(\sigma'(t)) > A(\sigma(t)) \), then \( \sigma(t+1) = \sigma'(t) \); otherwise \( \sigma(t+1) = \sigma(t) \).

This procedure is reminiscent of a zero-temperature Monte-Carlo dynamics, where the Hamiltonian is a decreasing function of the fitness \( A(\sigma) \). Evolution is bound to finish on a local fitness maximum. More explicit predictions can only be made when more properties of the fitness landscape are known.

We do not know in general the intricate conditions which determine the fitness of a given species as a function of its genotype: we can only expect the fitness landscape to be rather irregular and complicated. It has been suggested \( \Pi \) to represent a given fitness landscape as a realization of a random function.

A rather general class of random functions defined on the \( N \)-dimensional hypercube has been introduced by B. Derrida in the context of spin-glass theory \([7]\). It is defined by the expression

\[ A^{(p)}(\sigma) = \sum_{\{i_1,i_2,\ldots,i_p\}} J_{\{i_1,i_2,\ldots,i_p\}} \sigma_{i_1} \sigma_{i_2} \cdots \sigma_{i_p}, \]  

(9)

where the sum runs over all different subsets of \( n \) indices, and for each such subset, the coefficient \( J_{\{i_1,i_2,\ldots,i_p\}} \) is an independent, identically distributed,
real random variable. This model is known as the \( p \)-spin model in spin-glass theory. A slightly different set of random functions has been independently introduced by S. A. Kauffman in the context of Adaptative Walks [22], [21, p. 54–62], where it is known as the \( NK \)-model.

The simplest case is of course \( p = 1 \). In this case the maximum fitness is reached for the single genotype \( \sigma^* \), satisfying
\[
\sigma^*_i = \text{sign} J_i. \tag{10}
\]
Moreover, since there are no local maxima but \( \sigma^* \), it is possible to reach this maximum simply by flipping one unit after the other in the good direction. Evolution is a simple matter in this “Fujiyama landscape”, as it has been called, because it is never necessary to undo the progress already made in order to go forward.

However, as soon as we go to \( p > 1 \), thing become much more complicated.

Two properties of the landscape are strictly related: the frequency of local fitness maxima (peaks), and the correlation (or its contrary, “ruggedness”) of the landscape. We say that a landscape is rugged if the value \( A^{(n)}(\sigma) \) of the fitness changes a great deal when the genotype \( \sigma \) changes slightly. A measure of the ruggedness of the landscape is provided by the correlation function
\[
C(\sigma, \sigma') = \mathbb{E}_{\text{av}} [A^{(p)}(\sigma)A^{(p)}(\sigma')] ,
\]
where \( \sigma \) and \( \sigma' \) are two different genotypes with overlap \( q \), and the average \( \mathbb{E}_{\text{av}} \) is taken over the probability distribution of the coefficients \( J \). In the “thermodynamic limit” \( N \to \infty \), this quantity is equal, with probability one, to the average of the product \( A^{(p)}(\sigma)A^{(p)}(\sigma') \) taken over all genotype pairs with overlap equal to \( q \). If this correlation function decays slowly with decreasing overlap \( q \), the landscape is smooth; otherwise, it is rugged. The more rugged the landscape, the larger the frequency of local optima.

Let us assume, with Derrida [7], that the distribution of the coefficients \( J \) is a Gaussian of mean zero, and variance equal to \( J_0^2 p!/\left(2N^{p-1}\right) \). One can then prove that the probability density \( P_\sigma(E) \) that the fitness \( A^{(p)}(\sigma) \) of any given genotype \( \sigma \) is equal to \( E \) is also a Gaussian:
\[
P_\sigma(E) = \mathbb{E}_{\text{av}} \delta \left(A^{(p)}(\sigma) - E\right) \propto \exp \left( -\frac{E^2}{NJ_0^2} \right). \tag{11}
\]
The properties of the landscape can be read off the joint probability distribution function
\[
P_{\sigma\sigma'}(E, E') = \mathbb{E}_{\text{av}} \delta \left(A^{(p)}(\sigma) - E\right) \delta \left(A^{(p)}(\sigma') - E'\right).
\]
\[ \propto \exp \left[ -\frac{(E + E')^2}{2N J_0^2 (1 + q^p)} - \frac{(E - E')^2}{2N J_0^2 (1 - q^p)} \right], \quad (12) \]

where \( q = (1/N) \sum_i \sigma_i \sigma'_i \) is the overlap of the two configurations. The correlation function \( C(\sigma, \sigma') \) then reads

\[ C(\sigma, \sigma') = \left[ A^{(p)}(\sigma) A^{(p)}(\sigma') \right]_{\text{av}} = \frac{1}{2} N J_0^2 q^p. \quad (13) \]

It decays more and more rapidly as \( p \) increases. As \( p \) increases, therefore, the landscape becomes more and more “rugged”. At the same time, the number of extrema becomes larger and larger. Already for \( p = 2 \), which corresponds to the Sherrington-Kirkpatrick model of spin glasses, this number increases exponentially with \( N \). Therefore, it becomes more and more likely that the adaptative walk, starting from an arbitrary initial genotype, ends up in a local fitness maximum instead of the absolute one.

Eventually, as \( p \to \infty \) one obtains, whenever \( |q| < 1 \),

\[ P_{\sigma\sigma'}(E, E') \sim P_{\sigma}(E) P_{\sigma'}(E'). \quad (14) \]

This is known as the “rugged landscape” limit, in which the fitnesses corresponding to different genotypes are independent random quantities. Adaptative walks in this limit have been thoroughly discussed by Kauffman and Levin [22] and more recently analyzed by H. Flyvbjerg and B. Lautrup [17].

Let us therefore consider adaptative walks in a landscape in which the fitness \( a = A(\sigma) \) of each different genotype \( \sigma \) is an independent random variable, with a given probability distribution function \( p(a) \). Several important properties of this model can be obtained almost immediately [21, p. 47–52]:

- The probability that a given genotype \( \sigma \) is a local fitness optimum is equal to \( 1/(N + 1) \). This can be simply evaluated in terms of the cumulative distribution function \( \Phi(a) = \int_a^\infty da' p(a') \), namely, the probability that the fitness of a given genotype is smaller than \( a \). Calling \( P_N \) the probability that a given genotype is a local maximum, we have indeed:

\[ P_N = \int_{-\infty}^{\infty} da \Phi(a) \Phi(a)^N = \frac{1}{N + 1}. \quad (15) \]

- A walk leading to a local optimum will touch on average \( \approx \log_2 N \) different genotypes. In fact, since there are no correlations between the
value of the fitness of one genotype and that of its next (fitter) mutant—except, of course, that it is larger—the value of $1 - \Phi$ will be halved, on average, at each mutation step. The previous result tells us that the walk will stop when $1 - \Phi \simeq 1/N$. Calling $\ell$ the length of the walk, we thus have $1 - 2^{-\ell} \simeq 1 - 1/N$, hence $\ell \simeq \log N / \log 2$.

- The expected time $T$ needed to reach an optimum is proportional to $N$. The idea is that the waiting time at each step is inversely proportional to the probability that any given mutant is fitter, i.e., to $1 - \Phi(a)$. Thus the waiting time doubles at each step. We obtain therefore, roughly

$$T \simeq \sum_{k=0}^{\ell-1} 2^k = 2^\ell - 1 = N - 1. \quad (16)$$

- The expected fitness $a^*$ of local optima satisfies the equation $\Phi(a^*) = 1 - 1/N$. This result has an important consequence, named by Kauffman “the complexity catastrophe”. As $N$ increases, it is reasonable to assume that the “typical” values of $a$ increase like some power of $N$. On the other hand, $1 - \Phi(a)$ usually decreases faster than any power as $a \to \infty$. Therefore, as $N$ increases, the fitness values of the local optima become closer and closer to the “typical” values.

Before going on, let us emphasize, following [21], that similar results are expected to hold qualitatively also for adaptative walks on correlated (smoother) landscapes. Let us consider such a landscape, and assume that the correlation function $C(\sigma, \sigma')$ vanishes when the Hamming distance $d_H(\sigma, \sigma')$ is larger than, say, $\delta$. Starting from one given genotype $\sigma_0$, after a certain number $\tau$ of evolutionary steps the genotype $\sigma(t)$ will be more than $\delta$ away from $\sigma_0$: its fitness will be therefore uncorrelated with $\sigma_0$ (except, of course, for the fact that it is larger). Therefore, in the long run, the walk will resemble a walk on a rugged fitness landscape, apart from a rescaling of the elementary step length from $\delta$ to one, and of the unit of time from $\tau$ generations to one.

One of the lessons to be taken from this result is that the adaptative walk framework is too narrow to allow for a high degree of adaptation, since the expected value of fitness of local optima is so low. In order to explain a higher degree of adaptation, one is led to introduce mechanisms that allow to
explore larger regions of genotype space. One possibility is the appearance of a “hopeful monster”, i.e., a mutant whose genotype is further away from the dominant genotype than one or two mutations. Another (already suggested by S. Wright) is the appearance of a chain of slightly unfit mutants, one after the other, which may “reach out” for further fitness peaks. I do not find these suggestions very convincing. However, these possibilities cannot be discussed without a closer look at the genetic structure of evolving populations.

3 The quasispecies approach

There is no analytically treatable model, to my knowledge, that describes fully the structure of a population evolving on a nontrivial fitness landscape. In the Adaptative Walk model, all genetic variability within the population is neglected. The quasispecies model, introduced by M. Eigen in the context of the theory of prebiotic evolution [13, 14], neglects fluctuations in the composition of the population. In the case of nonoverlapping generations that we consider here for simplicity, it may be simply derived by introducing the effects of mutation into eq. (1). Let us denote by \( W(\sigma \leftarrow \sigma') \) the conditional probability that, while attempting to reproduce an individual of genotype \( \sigma' \), one produces instead an individual of genotype \( \sigma \). Taking into account this effect, the equation (1) for the number \( n_{t+1}(\sigma) \) of individuals of genotype \( \sigma \) at generation \( t+1 \) becomes the quasispecies (QS) equation:

\[
    n_{t+1}(\sigma) = \frac{1}{Z_t} \sum_{\sigma'} W(\sigma \leftarrow \sigma') A(\sigma') n_t(\sigma').
\]

(17)

The normalizing constant \( Z_t \) must be chosen in a way to satisfy the external constraint imposed on the population. The simplest constraint is constant population size: \( \sum_{\sigma} n_t(\sigma) = M = \text{const.} \), which implies

\[
    Z_t = \frac{1}{M} \sum_{\sigma} A(\sigma) n_t(\sigma),
\]

(18)

where we have exploited the fact that \( \sum_{\sigma} W(\sigma \leftarrow \sigma') = 1, \forall \sigma' \).

This equation exposes its origin in the theory of chemical reactions in that it neglects fluctuations in the numbers \( n_t(\sigma) \). This neglect is warranted when these numbers are much larger than one, which is the case when the
different chemical species are few in number, and the number of interacting molecules is very large. However, in evolutionary theory, and even in the RNA replication experiments discussed by W. Grüner in this meeting [20], the number of points in genotype space is much larger than the population size $M$. It is possible nevertheless to take it as a starting point, and we shall see that it is valid at least in a particular regime.

It is easy to derive the explicit form of the mutation matrix $W(\sigma \leftarrow \sigma')$ when one considers only point mutations with uniform probability $\mu$:

$$W(\sigma \leftarrow \sigma') = \mu^d_H(\sigma, \sigma')(1 - \mu)^{N-d_H(\sigma, \sigma')}.$$  (19)

The Fundamental Theorem is recovered in the limit $\mu \to 0$. As soon as $\mu > 0$, however, the asymptotic composition of the population is dictated by a balance of the effects of selection and mutation not unlike the energy-entropy balance determining the equilibrium in thermodynamics. It is indeed possible to formulate the solution of the QS equation in terms of equilibrium statistical mechanics [24, 36]. The most interesting consequence of this analogy is the existence of a phase transition between an “ordered” (selection-dominated) regime and a “disordered” (mutation-dominated) one. This transition has been named the “error threshold”.

Let us consider the “single-peak landscape” defined by

$$A(\sigma) = \begin{cases} A_0, & \text{if } \sigma = \sigma^*; \\ A_1 < A_0, & \text{if } \sigma \neq \sigma^*. \end{cases}$$  (20)

The maximum fitness is reached for the isolated sequence $\sigma^*$, called the optimal or the master sequence. It is easy to solve numerically the QS equation by lumping together all sequences as a function of their Hamming distance. For $\mu = 0$, we have $n_t(\sigma) \to n_\infty(\sigma)$ as $t \to \infty$, where $n_\infty(\sigma^*) = M$ and $n_\infty(\sigma) = 0$ for $\sigma \neq \sigma^*$. In other words, all genotype sequences in the population are identical, and equal to the master sequence. When $\mu > 0$, the stationary distribution is sharply peaked on the master sequence, but sequences within a small Hamming distance from it (close mutants) also appear with nonnegligible frequency. This distribution of a master sequence with its close mutants is called a *quasispecies* [13, 14].

In this regime, the QS equation describes rather faithfully the structure of the population. Most of the genotypes are equal to the master sequence or are close to it (in terms of the Hamming distance): the frequency of these
genotypes is large enough for the corresponding fluctuations to be negligible. To be sure, further mutants appear and disappear from the population: their frequency is small and the relative fluctuations in \( n_\sigma(t) \) are large. However, they play essentially no role in the dynamics.

As the mutation rate increases, the concentration of the master sequence decreases. We can locate the critical value \( \mu^* \) of the mutation rate where the master sequence concentration (as estimated from first-order perturbation theory) vanishes. It satisfies

\[
(1 - \mu^*)^N = \frac{A_1}{A_0}.
\]

For \( \mu > \mu^* \), the population is no more “hooked” at the master sequence, and the QS equation predicts an almost uniform concentration of all sequences. Therefore \( \mu^* \) is a good estimate of the location of the error threshold. The error threshold becomes sharper and sharper as \( N \to \infty \), provided that the ratio \( A_0/A_1 \) increases exponentially with \( N \).

Beyond the error threshold, the predictions of the QS equation cannot be taken at face value. In the usual case in which the population size \( M \) is much smaller than the number of points in sequence space, \( 2^N \), it is impossible to reach a stationary sequence distribution with almost uniform concentration. One has instead a wandering cloud of sequences, whose structure is dictated by the reproduction-mutation mechanism, and where the effects of selection can be neglected to a first approximation. This regime is well described by the “neutral theory” due to M. Kimura [23]. It deserves a more thorough discussion, that is deferred to the next section.

It is instructive to solve the QS equation in the rugged fitness landscape discussed above [18]. One can identify the error threshold with a spin-glass transition if one assumes that the “typical” values of the fitness behave like \( \exp(N) \) for large \( N \). The role of the inverse temperature is played by \( \beta = \frac{1}{2} \log(\mu/(1 - \mu)) \). For \( \beta > \beta^* \), the population is essentially concentrated on a fitness optimum, while for \( \beta < \beta^* \) all consequences of selection disappear in the “thermodynamic limit”. It is therefore likely that the error threshold is a general feature of all generic fitness landscapes, independently of their ruggedness.

The concept of the error threshold is central to the theory of prebiotic evolution [13] [14]. A suggested mechanism for the emergence of life is the
formation of complex molecules capable of self-reproduction. Given the accuracy $1 - \mu$ of the replication mechanism, eq. (21) sets an upper bound to the length $N$ of these molecules. Reasonable estimates of $\mu$ lead to values of $N$ which appear too short to be able to start up a Darwinian evolutionary mechanism eventually leading to the first cell. One way out of this problem is to assume that the necessary biological information was separated in several different molecules, each with an $N$ smaller than the critical one, and related to one another in a structure of chemical reactions like the hypercycle [15] or more general ones [15, 33]. This problem may find a completely different solution within the theory of neutral networks expounded at this meeting by W. Grüner [20, 30].

4 Evolution in a flat fitness landscape

The relative weights of mutation and selection in shaping the evolution of natural population has been the subject of a hot debate since the late sixties, when Crow and Kimura introduced the Neutral Theory of Molecular Evolution [4, 23]. This theory was prompted by the observation that natural populations exhibit a much higher degree of genetic variability at the molecular level than was previously suspected. If selection were dominant, this would imply that most of the variants which are found in natural populations have *not yet* been eliminated by Natural Selection. This, however, would mean that actual populations have a much lower fitness than the optimal one.

Crow and Kimura suggested instead that most molecular variants in the genotype have the same fitness as the most common one. They are therefore *selectively neutral*. To be sure, there are mutants corresponding to a much smaller fitness that the dominant one, but they are fast eliminated by Natural Selection, in accordance with the Fundamental Theorem. But the variability that is left in the genotypes does not correspond to a measurable effect on the fitness, again in accordance with the Fundamental Theorem, which states that the *fitness* of all individuals (not their genotype) is the same at stationarity. Evolution by increasing adaptation, in this view, is a comparatively rare phenomenon, which has little bearing on the genetic structure of the populations at the molecular level.

It becomes therefore rather interesting to describe the structure of a population evolving in a flat fitness landscape, in which all genotypes have the
same fitness.

The results contained in this section are a translation of the results of the Neutral Theory in the “spin” language which we have used so far [3]. We consider a population of \( M \) individuals, whose genotype \( \sigma^\alpha, \alpha = 1, 2, \ldots, M \), is identified by \( N \) binary variables (units) \( \sigma^\alpha_i = \pm 1, i = 1, 2, \ldots, N \). Given the genetic structure \( (\sigma^1, \sigma^2, \ldots, \sigma^M) \) at generation \( t \), the corresponding structure at generation \( t + 1 \) is obtained according to the following procedure:

(i) For each individual \( \alpha \) of the new population, one chooses, independently and with uniform probability, the label \( \alpha' = G_t(\alpha) \) of its parent among the \( M \) possible ones;

(ii) The genotype \( \sigma^\alpha(t + 1) \) is given by \( (\sigma^\alpha_1(t + 1), \ldots, \sigma^\alpha_N(t + 1)) \), where

\[
\sigma^\alpha_i(t + 1) = \epsilon^\alpha_i(t)\sigma^\alpha_{i'}(t). \tag{22}
\]

In this equation, \( \epsilon^\alpha_i(t) = \pm 1 \) is for each \( i, \alpha, \) and \( t \), an independent random variable with average \( \overline{\epsilon^\alpha_i(t)} = e^{-2\mu} \). This equation defines the \textit{bare mutation rate} \( \mu \).

The reproduction process, by which each individual “chooses” its parent, is a random dynamical process applying a \( M \)-point set into itself. This process has been thoroughly studied by Derrida and Bessis [8], and their results have only to be translated into our language, to obtain results on the statistics of genealogies.

Let us fix our attention, for example, on the population at a given generation much later than the beginning of the process. Let us pick up at random \( n \) individuals: it is a simple matter to show that the probability \( \pi_n \) that all \( n \) individuals have \( n \) different parents is given by

\[
\pi_n = \left(1 - \frac{1}{M}\right)\left(1 - \frac{2}{M}\right)\ldots\left(1 - \frac{n - 1}{M}\right) \simeq 1 - \frac{n(n - 1)}{2M}, \tag{23}
\]

assuming \( n \ll M \). The probability \( p_n(t) \) that each of the \( n \) individuals had a different ancestor \( t \) generations ago is obviously given by

\[
p_n(t) = \pi_n^t \simeq \exp\left(-\frac{n(n - 1)t}{2M}\right). \tag{24}
\]

Let us now say that two individuals belong to the same \( t \)-family if they had the same ancestor \( t \) generations ago. The number \( F(t) \) of \( t \)-families
is a random variable, which changes as the population evolves. Let us fix again our attention on the population at a given time, and consider $F(t)$ as a function of $t$. This number is reduced, as $t \rightarrow t + 1$, if the ancestors of two different $t$-families had the same parent. This happens with a probability equal to $1 - \pi_{F(t)} = F(t)(F(t) - 1)/(2M)$. We can thus write down a “mean field equation” for the average $\Phi(t) = F(t)$:

$$\frac{d\Phi(t)}{dt} = -\frac{\Phi(t)(\Phi(t) - 1)}{2M}. \quad (25)$$

The solution of this equation reads

$$\Phi(t) = \left(1 - e^{-t/2M}\right)^{-1}. \quad (26)$$

Therefore, after a number of generations essentially equal to $M$, all individuals in the population share the same ancestor. Derrida and Bessis [8] have calculated the probability $Z_k(t)$ that $F(t) = k$. One can then obtain an exact expression for $\Phi(t)$:

$$\Phi(t) = \sum_{k=0}^{\infty} k Z_k(t) = \sum_{k=1}^{\infty} (2k - 1) \exp \left[ -\frac{k(k - 1)t}{2M} \right]. \quad (27)$$

This expression agrees with the mean-field one when $t \ll M$, yielding $\Phi(t) \simeq 2M/t$, but deviates from it in the fluctuation-dominated range $t \geq M$, where $F(t) \simeq 1$. It is actually possible to compute the probability distribution of the sizes of all $t$-families, obtaining the result that all possible ways of breaking the population of $M$ individuals into $k$ $t$-families have the same probability, once $k$ is given. As a result, the sizes of $t$-families fluctuate wildly.

It is indeed possible to calculate more explicitly the distribution of the genetic structure of the population. Let us remark first of all than in the infinite genotype limit $N \rightarrow \infty$, the genetic overlap $q^{\alpha \beta}$ between two individuals $\alpha$ and $\beta$ is a function of their relatedness. If the last common ancestor of $\alpha$ and $\beta$ had existed $\tau^{\alpha \beta}$ generations before the present, one would have $q^{\alpha \beta} = \exp(-4\mu\tau^{\alpha \beta})$. In fact, the genotypes of the two independent lineages of ancestors of the two individuals have performed two independent random walks on the hypercube, with an average rate of $\mu N$ steps per generation.

Therefore the distribution function $P(q) = \langle \delta(q^{\alpha \beta} - q) \rangle$ of the overlap reflects the genealogical structure of the population [19]. At any given time, a
peak in $P(q)$ represents a subpopulation of $\nu$ individuals whose last common ancestor existed $\tau$ generations ago: the location of the peak is given by $\exp(-4\mu \tau)$, while its height is proportional to $\nu^2$. As time goes on, these peaks move towards zero, according to the law just stated, while their height fluctuates. From time to time some of the peaks disappear, and new ones arise from the $q \sim 1$ region, as new subpopulations appear. The genetic structure of the population is therefore a stochastic process, which evolves in time according to the particular realization of the mapping $\alpha \rightarrow G_t(\alpha)$ of each individual to its parent. One must therefore distinguish two kinds of averages [3]:

- The population average denoted by $\langle \ldots \rangle$: for example, the average overlap $Q = \langle q \rangle$ in the population is defined by

$$Q = \langle q \rangle = \left[ \binom{M}{2} \right]^{-1} \sum_{(\alpha, \beta)} q^{\alpha \beta},$$

(28)

where the sum runs over all different pairs $(\alpha, \beta)$ of individuals in the population.

- The process average denoted by $\overline{\ldots}$. One has for example [34][3]:

$$\overline{Q} = \overline{\langle q \rangle} = \frac{1}{1 + \lambda};$$

$$\overline{Q^2} = \overline{\langle q \rangle^2} = \frac{\lambda^2(9\lambda^2 + 18\lambda + 4)}{(\lambda + 1)(\lambda + 2)(3\lambda + 1)(3\lambda + 2)},$$

(30)

where we have introduced the notation $\lambda = 1/(4\mu M)$.

It is obvious from the fact that $\overline{Q^2} > \overline{Q^2}$ that $Q$ is itself a random quantity. This observation implies that the genetic structure of any given sample, even of a very large population, will be in general very different from the average one: and therefore that predictions based on a “mean field” approach, like the QS equations, could be rather misleading.

The average overlap $\overline{Q}$ depends on population size $M$, and decreases as $M$ increases. Thus genetic variability increases with increasing population size. In most natural populations genetic variability is much smaller than expected on the basis of this result [23]. In fact, natural populations are
often the outcome of a comparatively recent “population boom” involving a rather small founder population. In order to reach the “equilibrium” value quoted above one should wait of the order of $M$ generations, where $M$ is population size. This is often too long, and the result is that the actual variability reflects the much smaller size of the founder population.

It is also interesting to monitor the evolution of the average genotype

$$\langle \sigma \rangle = (\langle \sigma_1 \rangle, \ldots, \langle \sigma_N \rangle). \quad (31)$$

The genetic drift of the population (a physicist would call it diffusion) is represented by the correlation function

$$K(t) = \frac{1}{N} \sum_{i=1}^{N} \frac{\langle \sigma_i \rangle_{t_0} \langle \sigma_i \rangle_{t_0+t}}{\langle \sigma_i \rangle_{t_0}}, \quad (32)$$

where $\langle \ldots \rangle_t$ denotes the population average at generation $t$. The exponential decrease of the correlation $K(t) \propto \exp(-2\mu^* |t|)$ defines the effective mutation rate $\mu^*$. A simple calculation from eq. (22) yields

$$K(t) = Q \exp(-4\mu |t|). \quad (33)$$

In our case therefore, the effective mutation rate is equal to the bare one, and in particular, it is independent of population size. This rather surprising result is known as the Kimura theorem [23].

The previous result hold almost without change if all fit genotypes have the same fitness value, while unfit ones have a negligible one. Let us assume that a fraction $x$ of the genotypes is unfit, and therefore practically unable to reproduce, and that fit and unfit genotypes are distributed at random on the hypercube. Therefore $N x$ neighbors of every fit genotype will be unfit on average. If a mutation appears, it will lead to an unfit genotype with probability $x$. It will be safer not to mutate, since one’s parent is fit by definition. Therefore the effective mutation rate $\mu^*$ will be smaller than the bare one $\mu$, and given approximately by $\mu^* \simeq \mu (1 - x)$ [23, 3].

The effective mutation rate $\mu^*$ can only be nonzero if the clusters of fit genotypes span the hypercube, i.e., if it is possible to connect two arbitrarily different fit genotypes via a chain of fit mutants. Let us say that the fit genotype $\sigma$ belongs to the same cluster as the fit genotype $\sigma'$ if it differs in only one unit $\sigma_i$ either from $\sigma'$ or from a fit genotype which belongs to the
same cluster of $\sigma'$. If $x$ is small, there is a large cluster of fit genotypes which spans the hypercube: starting from any point on it, one can reach genotypes whose overlap with the initial point is arbitrarily small. However, when $x > x^* \sim 1 - 1/N$, the space of fit genotypes breaks down into small clusters, and it is never possible to wander far away from the initial point stepping only on fit genotypes via single-point mutations. In this case memory of the initial genotype is maintained forever. This phenomenon is called the percolation threshold, and we see that it is closely related to the error threshold discussed in the previous section. We can introduce the order parameter

$$q_\infty = \lim_{t \to \infty} \frac{1}{N} \sum_i \langle \sigma_i(t) \rangle^2,$$

where it is understood to take the process average with a fixed initial genotype $\sigma(0)$. This order parameter is nonzero in the “trapped” regime $x > x^*$.

In the “wandering” regime $x < x^*$, the population evolves in a neutral network, and is able to explore larger and larger regions of sequence space as time goes on [20, 30]. At any given point, the number of fit mutants can be small, but the sequence space has a large connectivity, and the neutral network can efficiently span it.

In a number of proteins one can relate the number of aminoacid substitutions in different taxa to their respective time of divergence, i.e., the time of the existence of their last common ancestor. One obtains a well-defined substitution rate which is specific of the protein, except for very conservative proteins like histones [2]. This suggests that proteins also evolve along neutral networks: unfit aminoacid substitutions are eliminated at each step, but fit substitutions, which are selectively neutral, are retained in accordance with the neutral theory [23].

5 Two-parent reproduction and the origin of species

Since most of the organisms which are close to us in daily life reproduce sexually, it is interesting to ask if the results of the previous section hold for a two-parent reproduction mechanism [31, 19]. The model can be defined in analogy with eq. (22). One chooses, at each generation and for each
individual $\alpha$, two parents $\alpha'$ and $\alpha''$. The genotype $\sigma(t + 1)$ of the individual $\alpha$ in the new generation is then given (for $i = 1, 2, \ldots, N$) by

$$\sigma_i(t + 1) = \epsilon_i(t) \left[ \xi_i(t) \sigma_i'(t) + (1 - \xi_i(t)) \sigma_i''(t) \right].$$

(35)

Here $\epsilon_i(t) = \pm 1$ represents the effects of mutations as in the previous section, while $\xi_i(t) \in \{0, 1\}$ determines from which parent our individual inherits the state of its unit $\sigma_i$: if $\xi_i(t) = 0$, from $\alpha'$; otherwise, from $\alpha''$. One has $\xi_i(t) = \frac{1}{2}$.

The genetic variability is again expressed in terms of the average genetic overlap

$$A = Q = \langle q \rangle = \sigma_i\sigma_i'.$$

(36)

One obtains for $\overline{Q}$ the equation

$$\overline{Q} = e^{-4\mu \frac{1}{4} \left[ \frac{4}{M} + 4 \left( 1 - \frac{1}{M} \right) \overline{Q} \right]}.$$  

(37)

This equation implies $\overline{Q} = \lambda/(1 + \lambda)$, as for the one-parent reproduction mechanism. Fluctuations are determined by the quantities

$$B = \langle q^2 \rangle = \sigma_i\sigma_i'\sigma_j\sigma_j';$$

(38)

$$C = \overline{Q^2} = \langle q'^2 \rangle = \sigma_i\sigma_i'\sigma_j\sigma_j';$$

(39)

$$D = \sigma_i\sigma_i'\sigma_j\sigma_j'.$$

(40)

It is understood that different indices take on different values. We assume $M \to \infty$, but $4\mu M \to \lambda^{-1} = \text{const}$. In this limit, we have

$$3B = C + 2D;$$

(41)

$$\left( \frac{1}{\lambda} + 3 \right) C = A + 2D;$$

(42)

$$4D = 2D + 2C + A.$$  

(43)

These equations imply

$$A^2 = B = C = D = \frac{1}{(1 + \lambda)^2};$$

(44)

and therefore

$$\langle q \rangle^2 = \langle q'^2 \rangle = \langle q^2 \rangle.$$  

(45)
Stated in other words, this result implies that in a population in which all possible pairs have the same probability of producing offspring (such populations are called *panmictic*), the genetic difference between any two individuals has the same value with probability one. To be sure, this result has to be modified in actual populations: siblings are genetically more similar than strangers; however it is in agreement with the fact that specific genetic correlations are lost very rapidly as the genealogical relatedness decreases.

Higgs and Derrida [19] have taken advantage of this result to introduce a minimal model for the formation of biological species. They assume that a pair of individuals can produce offspring only if their genotypes are not too different: more explicitly, if their genetic overlap \( q \) is larger than a threshold \( q_0 \) (fecundity threshold). As long as \( M \) and \( \mu \) are such that \( Q \) (as obtained above) is larger than \( q_0 \), nothing happens; but if the mutation rate \( \mu \) is too large, the population splits into several subpopulations: the genetic overlap \( q \) of individuals belonging to the same subpopulation is larger than \( q_0 \), whereas the overlap belonging to different subpopulations is smaller. Therefore, offspring can only be produced by pairs of individuals belonging to the *same* subpopulation. This is exactly the definition of the biological species, according to Mayr [26]:

Species are groups of actually or potentially interbreeding natural populations which are reproductively isolated from other such groups.

The actual behavior of the population is extremely irregular: the size of the subpopulations fluctuates according to the irregularities in their sampling, much in the same way as family size in the one-parent reproduction mechanism; and the value of the corresponding characteristic overlap fluctuates in agreement with the expression obtained above which relates the genetic overlap of a panmictic population to its size. From time to time, a subpopulation becomes too large, and the corresponding overlap hits the threshold. After a short period of "confusion" two new subpopulations (species) arise. The mutual overlap between different species evolves in time according to the exponential law that we have derived in the previous section. The process average of the overlap \( Q \) over the whole population is, rather remarkably, given by the same expression valid for a panmictic population [19]. There has not yet been an explanation of this result which appears very clearly in the populations.
The same model can be generalized to treat the effects of geographic isolation [25]. One considers a population with reproduces with the same two-parent mechanism discussed above, but which is distributed in several “islands”. Reproducing pairs can only be formed among individuals inhabiting the same island, but before each “mating season” an individual can move from one island to a neighboring one with a small probability $\epsilon$. As a consequence, the overlap between individuals belonging to the same island is larger than between different islands. When the migration rate becomes so small that the average overlap between neighboring islands drops below the fecundity threshold, the system start behaving in the same irregular way as discussed above. Again, the average overlaps (either between islands or within one island) behave as in the absence of the fecundity threshold.

There is an interesting phenomenon which takes place in rings of islands. One may reach a regime in which the average overlap between neighboring islands is above threshold, while that between islands further away is below. In this case it is possible to start from one islands and to move in one direction in the ring, always finding mutually fecund populations in neighboring islands. However, coming back to the starting point, one finds a reproductive barrier, and possibly the coexistence, in the same islands, of two populations mutually sterile. This phenomenon appears rather frequently in the simulations [25] and can be related to the circular invasion phenomenon observed in natural populations [27]. For example, the northern skylark *Larus argentatus* exhibits a group of populations which are mutually interfecund if one starts from Scandinavia and moves towards the East, reaching, over Siberia, to North America. However, where the last American population overlaps with the first European one, they are no more mutually interfecund. Therefore the relation “being mutually interfecund” is not necessarily an equivalence relation.

If one goes over to consider all-or-none selection in the presence of a two-parent reproduction mechanism [29], one observes another peculiar phenomenon. The effective mutation rate $\mu^*$ does not appear to depend on the fraction $x$ of unfit genotypes, as long as $x$ is small. When $x$ crosses a threshold $x^*$ (which increases with the genome size $N$) the mutation rate drops suddenly and the average fitness of the population increases. This behavior can be understood in terms of collective adaptation, i.e., of the search for a region which optimizes the recombinational fitness of the individual, a quantity which measures also the likelihood that the offsprings of an indi-
individual, obtained by mating with the other members of the population, are fit. A quantitative theory of this transition (which is rather striking in the simulations) is still lacking.

6 Two-level selection and the maintenance of unselfish genes

The last observation prompts us to consider situations in which the selection process leads to potential conflicts. One case, much studied in the literature, is the possible existence of unselfish genes, which determine, in the individual which expresses them, a behavior disadvantageous to the carrier, but beneficial to the group to which it belongs. While the existence of such genes has not yet been proved beyond doubt, it is an interesting problem in itself to see whether the interaction between the two selection levels, the individual and the group, can lead to the permanence of these genes in the population. Here I shall only report briefly a model which has been introduced and analyzed by R. Donato, M. Serva and myself [10, 11].

We consider a population divided into groups (demes) of $L$ individuals. Mating is only allowed within a group. Heredity acts according to the usual Mendelian mechanism. There is a behavioral locus with two alleles: a selfish (S) allele (dominant), and an unselfish (U) one (recessive). (It is easy to modify the model to consider more alleles, different reproduction schemes, etc.) The fitness of an individual depends on two factors: (i) if it is unselfish homozygote (UU) it is reduced, by a factor $(1 - r)$, with respect to the other members of a group; (ii) if it belongs to a group with a large enough fraction $x$ of UU-individuals (larger than a threshold $x^*$), it is enhanced, by a factor $(1 + c)$, with respect to groups which do not satisfy this condition.

This definition can be summarized in the following table:

| Genotype: | $x < x^*$ | $x \geq x^*$ |
|-----------|------------|--------------|
| UU        | $1 - r$    | $(1 - r)(1 + c)$ |
| Other genotypes | $1$         | $1 + c$       |

Table 1: Fitness table
As a consequence of this selection scheme, the fraction \( x \) of unselfish individuals decreases within any given deme. On the other hand, demes with \( x > x^* \) have higher average fitness and tend to expand at the expenses of the others. When a deme grows too large, it splits into two demes, and its members are redistributed at random between the two new demes. We can represent this process via a “deme fitness” \( A(x) \), proportional to the total fitness of individuals which form each deme, and given by

\[
A(x) = \begin{cases} 
1 - x + x(1 - r), & \text{if } x < x^*; \\
(1 + c)[1 - x + x(1 - r)], & \text{if } x \geq x^*.
\end{cases}
\] (46)

In the limit of very large population (infinite number of demes) the process can be described by a quasispecies equation at the level of demes. Denoting by \( \rho_t(x) \) the fraction of demes with a fraction \( x \) of unselfish individuals, we have

\[
\rho_{t+1}(x) = \frac{1}{Z_t} \int_0^1 dx' P(x \leftarrow x') A(x') \rho_t(x').
\] (47)

In this equation, \( P(x \leftarrow x') \) is the conditional probability density to produce a deme with a fraction \( x \) of unselfish individuals, starting from one with a fraction \( x' \). This probability contains two effects: (i) the systematic decrease of \( x \), due to the disadvantage of altruism; (ii) the fluctuations due to random sampling, due to the finite deme size \( L \).

The quasispecies equation for the demes can be solved numerically for the steady state distribution. One finds a line \((1 - r)(1 + c) = f(L)\) which separates two regimes: when \( r \) is too large (or \( c \) is too small), the distribution is peaked at \( x = 0 \), and therefore unselfish genes are wiped out of the population; otherwise, the distribution is nontrivial, and the average value of \( x \) is different from zero. The transition appears to be discontinuous. It is interesting to remark that it is the competition between demes that keeps unselfish genes in the population: there is no “optimal value” for \( x \). Again, the “steady state” hides a complicated dynamical behavior: demes with high values of \( x \) increase in number, but their values of \( x \) decrease; however, new ones with high values of \( x \) arise from the splitting of old ones, and so on.

7 Conclusions

Fitness as an individual property, in the way we have used here, is a powerful tool for model building. However, it is not measurable in the field, because
the actual number of viable offspring of an individual is the outcome of its complex interaction with other members of the same population and with its environment. Some aspects of these interactions, from the point of view of evolutionary success, can be captured by the game theory approach [32]. The most important aspect is the difference between local optimization, i.e., fitness optimization at the level of individual, and global optimization, at the level of community.

Community can be formed by members of the same species, or of different species. One of the key problems in understanding evolutionary innovation is the evolution of individuality [4], i.e., of the organization of different units into a single integrated organism to which it is possible to assign a fitness. This is also the problem of the emergence of mutualism [12] and can be the key point in the understanding of the evolution of multicellular organisms.

Nevertheless the concept of fitness, with its strong aspects of "physicalism" related to its similarity with energy, is a very convenient stepping stone to enter, as physicists, in the arena of evolutionary theory.

Acknowledgments

I warmly thank my collaborators: U. Bastolla, B. Derrida, R. Donato, F. Manzo, M. Sellitto and especially M. Serva. I also thank W. Fontana for much-needed encouragement and illumination. The support of the INFN Sections of Napoli and Roma made possible much of my work in this area. And I am grateful to the organizers of the NATO ASI on Physics of Biomaterials, and in particular to Professor T. Riste, for having given me the opportunity for expressing my point of view on evolutionary theory.

References

[1] P. W. Anderson (1983) Suggested model for prebiotic evolution: The use of chaos, Proc. Natl. Acad. Sci. USA 80 3386.

[2] F. J. Ayala (ed.) (1976) Molecular Evolution, Sinauer Associates, Sunderland (Mass.).
[3] U. Bastolla, L. Peliti, Un modèle statistique d’une population en évolution avec sélection stabilisante, C. R. Acad. Sci. Paris, Série III, 313 101.

[4] L. W. Buss (1987) The Evolution of Individuality, Princeton University Press, Princeton.

[5] J. F. Crow, M. Kimura (1970) An Introduction to Population Genetics Theory, Harper and Row, New York.

[6] R. Dawkins (1982) The Extended Phenotype, Oxford University Press, Oxford.

[7] B. Derrida (1981) Random energy model: An exactly solvable model of disordered systems, Phys. Rev. B24 2613.

[8] B. Derrida, D. Bessis (1988) Statistical properties of valleys in the annealed random map model, J. Phys. A: Math. Gen. 21 L509.

[9] B. Derrida, L. Peliti (1991) Evolution in a flat fitness landscape, Bull. Math. Biol. 53 355.

[10] R. Donato (1995) Relazioni tra meccanismi di riproduzione e variabilità genetica in un approccio stocastico, Thesis, University of Rome “La Sapienza”.

[11] R. Donato, M. Serva, L. Peliti (1995) Two-level selection and the maintenance of unselfish genes. In preparation.

[12] G. Duchateau-Nguyen, G. Weisbuch, L. Peliti (1995) Emergence of mutualism, in: W. Banzhaf, F. H. Eeckman (eds.) Evolution and Biocomputation: Computational Models of Evolution, Springer Verlag, Berlin, p. 27.

[13] M. Eigen (1971) Selforganization of matter and the evolution of biological macromolecules, Naturwissenschaften 58 465.

[14] M. Eigen, J. McCaskill, P. Schuster (1989) The molecular quasi-species, Adv. Chem. Phys. 75 149.
[15] M. Eigen, P. Schuster (1979) *The Hypercycle: A Principle of Natural Self-Organization*, Springer Verlag, Berlin.

[16] R. A. Fisher (1958) *The Genetical Theory of Natural Selection*, (2nd edn) Dover, New York.

[17] H. Flyvbjerg, B. Lautrup (1992) Evolution on a rugged fitness landscape, *Phys. Rev. A* 46 6714.

[18] S. Franz, M. Sellitto, L. Peliti (1993) An evolutionary version of the Random Energy Model, *J. Phys. A: Math. Gen.* 26 L1195.

[19] P. G. Higgs, B. Derrida, Stochastic model for species formation in evolving populations, *J. Phys. A: Math. Gen.* 24 L985.

[20] W. Grüner (1995) Lectures at the present NATO ASI.

[21] S. A. Kauffman (1993) *The Origins of Order: Self-Organization and Selection in Evolution*, Oxford University Press, Oxford.

[22] S. A. Kauffman and S. Levin (1987) Towards a general theory of adaptative walks on rugged landscapes, *J. Theor. Biol.* 128 11.

[23] M. Kimura (1983) *The Neutral Theory of Molecular Evolution*, Cambridge University Press, Cambridge.

[24] I. Leuthäusser (1987) Statistical mechanics of Eigen’s evolution model, *J. Stat. Phys.* 48 343.

[25] F. Manzo, L. Peliti (1994) Geographic speciation in the Derrida-Higgs model of species formation, *J. Phys. A: Math. Gen.* 27 7079.

[26] E. Mayr (1942) *Systematics and the Origin of Species*, Columbia University Press, New York.

[27] E. Mayr (1963). *Animal species and evolution*, Belknap Press, Cambridge (Mass.).

[28] M. Mézard, G. Parisi, M. A. Virasoro (1987) *Spin Glass Theory and Beyond*, World Scientific, Singapore.
[29] L. Peliti, U. Bastolla (1994) Collective adaptation in a statistical model of an evolving population, *C. R. Acad. Sci. Paris*, Sciences de la Vie, 317 371.

[30] P. Schuster (1995) How to search for RNA structures: Theoretical concepts in evolutionary biotechnology, *Journal of Biotechnology* in press.

[31] M. Serva, L. Peliti (1991) A statistical model of an evolving population with sexual reproduction, *J. Phys. A: Math. Gen.* 24 L705.

[32] K. Sigmund (1993) *Games of Life: Explorations in Ecology, Evolution and Behaviour*, Oxford University Press, Oxford.

[33] P. F. Stadler, W. Fontana, J. H. Miller (1993) Random catalytic reaction networks, *Physica D63* 378.

[34] F. M. Stewart, Variability in the amount of heterozygosity, maintained by neutral mutations, *Theor. Pop. Biol.* 9 188.

[35] E. Szathmáry, L. Demeter (1987) Group selection of early replicators and the origin of life, *J. Theor. Biol.* 128 463.

[36] P. Tarazona (1992) Error threshold for molecular quasispecies as phase transitions: From simple landscapes to spin-glass models, *Phys. Rev. A45* 6038.

[37] S. Wright (1932) The roles of mutation, inbreeding, crossbreeding, and selection in evolution, *Proc. 6th Int. Cong. Genetics, Ithaca* 1 356.