Quasispecies and recombination

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Abstract

Recombination is introduced into Eigen’s theory of quasispecies evolution. Comparing numerical simulations of the rate equations in the non-recombining and recombining cases show that recombination has a strong effect on the error threshold and, for a wide range of mutation rates, gives rise to two stable fixed points in the dynamics. This bi-stability results in the existence of two error thresholds. We prove that, under some assumptions on the fitness landscape but for general crossover probability, a fixed point localized about the sequence with superior fitness is globally stable for low mutation rates.

1 Introduction

The quasispecies concept was introduced by Eigen in 1971 [1] to describe populations of self-replicating molecules. A quasispecies is an equilibrium distribution of closely related gene sequences, localized in sequence space around one or a few sequences of high fitness. The quasispecies model can be viewed as a simple framework that contains all the basic ingredients of Darwinian evolution. In particular, it captures the critical relation between mutation rate and information transmission [1, 2]. The behavior of these systems has been extensively studied, see for instance [1, 2, 3, 4, 5]. Quasispecies have also been fruitfully studied using concepts and techniques from statistical physics, see, e.g., [6, 7, 8].

In the quasispecies model, the population dynamics is described on the gene level, and a fitness landscape [9] is used to define the degree of adaptation directly from the gene sequence. Considerable amounts of work has gone into defining models of rugged landscapes and analyzing their consequences for the evolutionary dynamics (e.g. [10, 11, 12, 13, 14]).

In this paper we introduce recombination into the quasispecies model. With some exceptions (see, e.g., [15, 16, 17, 18]) previous work on quasispecies has only considered non-recombining populations where variation is created only by mutation. However,
most species in nature use crossover during replication, at least to some degree, which
makes this an important case to study. Besides applications to evolutionary biology,
developing an understanding for the dynamics of systems under recombination is also
important for gaining theoretical insights into the behavior of genetic algorithms [21] in
combinatorial optimization problems.

Recombination introduces a non-linearity in the rate equations, which in general
results in the appearance of two stable fixed points. For a wide range of mutation
rates this divides the space of initial distributions into two regions: one where the
population converges to a distribution localized around the genome with highest fitness,
and another where it converges to an approximately uniform distribution. This behavior
is qualitatively different from that of non-recombining populations. Another interesting
observation is the shift in the error threshold.

The main contribution of the paper is a proof that, for a class of fitness landscapes
(see Section 5 for details), independent of the crossover probability, there exist exactly
one globally stable fixed point. The single peaked fitness landscape is a special case
that belongs to this class.

The rest of this paper is organized as follows:

Section 2 gives a short review of quasispecies evolving under mutation only, for
comparison with the recombination case. In section 3 we introduce the rate equations
for quasispecies with mutation and recombination, and formulate a condition for the
equilibrium distribution as a generalized non-linear eigenvalue problem.

Section 4 contains results from numerical simulations of the rate equations for a
recombining population. We demonstrate how the equilibrium distribution changes with
mutation rate for different initial distributions. As in the non-recombining case, a phase
transition from a localized to a uniform distribution occurs when the mutation rate is
increased. The dependence of the phase transition point on the initial distribution is
investigated.

In section 5 we prove that, under some assumptions on the fitness landscape but
without constraint on the crossover, when the mutation rate is low enough all initial
distributions converge to a fixed point localized around the genome with highest fitness.
Finally, section 6 contains a discussion and conclusions.

2 Quasispecies

In this section we give a short review of relevant results for quasispecies with non-
recombining replication [1] [2], to allow us to compare with the results when recombina-
tion is included. In the model, a self-replicating molecule is represented by a sequence
of bases $s_k = (s_1 s_2 \cdots s_n)$. The bases are assumed to be binary \{0, 1\}, and all sequences
have equal length $n$. A genome is then given by a binary string $(011001 \cdots)$, which also
can be represented by an integer $k$ \((0 \leq k < 2^n)\). The space of all gene sequences in
the model is called sequence space [22]. A quasi-species is defined as a distribution of
sequences localized in sequence space.

Selection in the quasispecies model is expressed in terms of a fitness landscape, which
is a function of the phenotype and the environment. The environment describes direct interactions with other organisms as well as the physical environment. In the quasispecies model we assume that the phenotype is directly determined by the genotype. There is no direct interaction between individuals in the population, only indirect competition for resources. The fitness landscape can then be expressed as a function of the genotype only. In the following, we only consider a simple landscape with a single sequence of high fitness $A_0$, called the master sequence, and with all other sequences $i$ having equal fitness $A_i < A_0$.

Mutations are described by $Q^l_k$, the probability that replication of genome $l$ gives genome $k$ as offspring. If the mutation rate per base, $p_m = 1 - q$, where $q$ is the copying accuracy per base, is assumed to be constant in time and independent of position in the genome, we obtain

$$Q^i_k = p_m^{h_{ki}} q^{n-h_{ki}} = q^n \left(\frac{1 - q}{q}\right)^{h_{ki}}$$

where $h_{ki}$ is the Hamming distance between genomes $k$ and $i$.

The rate equations that describe the dynamics of the population are then given by (where $x_k$ denotes the relative concentration of species $k$):

$$\dot{x}_k = \sum_l Q^l_k A_l x_l - e x_k$$

where $e = \sum_l A_l x_l$. The second term ensures the total normalization of the population ($\sum_l x_l = 1$).

These differential equations can be solved analytically [23, 24]. Equation (2) can be made linear through a change of variables and we can then use standard techniques to find $x_k$. If all the elements of the matrix $Q^l_k$ are strictly positive, $x_k$ always converges to a unique stable fixed point [25], given by the eigenvector corresponding to the largest eigenvalue $l = e$ of the matrix $Q^l_k A_l$.

For a landscape where the fitness only depends on the Hamming distance from the master sequence, we can divide sequence space into error classes containing sequences with the same number of ones. The effective dimension of the system of equations (2) can then be reduced from $2^n$ to $n + 1$ by summing over error classes. In this way we obtain the new equations

$$\dot{x}_K = \sum_L \tilde{Q}^L_K A_L x_L - E x_K$$

where the indices $K$ and $L$ denote error classes, and $\tilde{Q}^L_K$ describes mutation probabilities between error classes rather than sequences.

We now consider a fitness landscape with $A_0 = 10$, and $A_L = 1$ for all $L \neq 0$. The sequences are indexed by their Hamming distance from the master sequence. The equilibrium distributions corresponding to different mutation rates, $p_m$, are shown in figure 1. There is a sharp transition between a state where the population is localized
around the master sequence $x_0$ and a state where the distribution is approximately binomial. This is the error catastrophe (or error threshold) of Eigen and coworkers. 

Fig. [1] here.

The error catastrophe occurs approximately when $q^n A_0 / A_i = 1$, or when the selective advantage of the master sequence, $A_0 / A_i$, is compensated by the finite probability $q^n < 1$ for the master sequence to replicate to itself.

This observation is important for theories of prebiotic evolution of life. When polynucleotides replicate without replicase enzymes, the copying fidelity is unlikely to exceed 0.99, which means that $n$ cannot be larger than 100 [1]. This is much smaller than coding regions for replicase enzymes, which are needed to increase the copying fidelity. This contradiction is often called Eigen’s paradox. There have been several different attempts to resolve this problem, such as hyper-cycles [2].

In the following sections we consider quasispecies where both recombination and mutation can occur during replication. The introduction of recombination will cause major changes in the population dynamics. As an example, we observe that the rate equations have multiple stable fixed points. The error threshold also also significantly shifted.

3 Recombination

The crossover operator, $T_{lm}^{km}$, denotes the probability that parents $l$ and $m$ give rise to the offspring $k$ in one recombination event [15, 17]. The crossover operator $T_{lm}^{km}$ depends on the crossover probability $p_c \in [0,0.5]$, i.e., the probability per base pair for the reading process to switch from one parent to the other. As an example, $p_c = 0.5$ (uniform crossover) means that each position in the genome is chosen with equal probability from each parent. Another extreme case is $p_c = 0$ which means that the offspring inherits all its genome from a single randomly chosen parent.

The crossover operator has the following properties

$$0 \leq T_{lm}^{km} \leq 1$$

$$\sum_k T_{lm}^{km} = 1 \quad \forall l, m$$

For uniform crossover we can write $T_{lm}^{km}$ explicitly as

$$T_{lm}^{km} = \begin{cases} 2^{-h_{lm}} & \text{if } O(k,l,m) = 1 \\ 0 & \text{if } O(k,l,m) = 0 \end{cases}$$

where $O(k,l,m) = 1$ if at each position where the parents genome $l$ and $m$ are identical, the same base also appears in the child genome $k$, else $O(k,l,m) = 0$. New genes can only be created by mutations.
The most realistic and interesting population dynamics involves both recombination and mutations. In our model we have only recombining individuals and the point mutations will come in as limited reading accuracy in the crossover process. We have chosen to let the number of offsprings depend on both parents. The rate equations for a population of sequences which both recombine and mutate are then given by

\[
\dot{x}_k = \sum_{lm} V_{lm}^k A_l x_l A_m x_m - c x_k
\]

where \( V_{lm}^k = \sum_i Q_{k}^i T_{lm}^i \) and \( c = (\sum_l A_l x_l)^2 \) (which is used to normalize the total growth as before).

The rate equations in the case of recombination are in general much harder to analyze than in the case of pure mutations. The crossover operator acts on pairs of sequences, which gives rise to a non-linearity in the growth term. We are mainly interested in the equilibrium distribution, i.e., the concentration of sequences after long time. In the pure mutation case the stable equilibrium distribution could be calculated by solving a standard eigenvalue problem. When recombination is used the fixed points of the rate equations (7), \( \vec{y} \), are solutions to the generalized eigenvalue problem:

\[
\sum_{lm} V_{lm}^k A_l y_l A_m y_m = \lambda y_k \forall k
\]

All normalized (\( \sum_l y_l = 1 \)) solutions to (8) are also fixed points to the rate equations, since summing over \( k \) gives the relation \( \lambda = (\sum_l A_l y_l)^2 = c \). There may however exist solutions to equation (8) which cannot be normalized to a vector of concentrations, since all elements must be non-negative.

In general there exists more than one solution to (8) which can be normalized to a concentration vector. It turns out that these multiple fixed points can be stable, see section 4. One of the most important differences between the non-recombining and the recombining case is in fact the uniqueness of the equilibrium distribution. As we will see in section 4, the equilibrium distribution of the rate equation (7) depends on the initial distribution (as was previously observed in other models, e.g. [18]). This behavior is very different from the pure mutation case, where all initial distributions converge to a unique stable fixed point, as discussed in section 2.

However, in Section 5 we present a proof that in the zero mutation rate limit, the only globally stable fixed point corresponds to a population totally localized on the fitness peak.

The dimension of sequence space scales exponentially with the number of bases in the genome. In the non-recombining case we saw that the degrees of freedom in the rate equations (7) could be reduced from \( 2^n \) to \( n + 1 \) by dividing the sequences into error classes. This symmetry is in general broken by recombination (see figure 2). The only non trivial case when the rate equation (7) preserves the symmetry between the error classes, is when \( p_c = 0.5 \) (uniform crossover). In this case we can write the reduced rate equations as
\[
\dot{x}_K = \sum_{L,M} \tilde{V}_K^{LM} A_L x_L A_M x_M - C x_K
\]  
(9)

where we use the same notation as in equation (3). For \( p_c = 0.5 \) and \( p_m = 0 \) the transition probabilities between error-classes \( \tilde{V}_K^{LM} \) are given by

\[
\tilde{V}_K^{LM} = \frac{\sum_{d=|M-L|}^{M+L+2\min(n-L-M,0)} \binom{L}{\min(l,m) - \frac{2d-|l-m|}{2}} \binom{n}{M}}{M} 
\]  
(10)

In the more realistic case when \( p_c < 0.5 \), we either have to be satisfied with rather small genome sizes or need to use some approximation method.

Fig. 2 here.

4 Numerical Results

Fig. 3 here.

In this section we present results from computer simulations of the rate equations (7). We concentrate on the asymptotic behavior as time goes to infinity, and do not consider detailed dynamics of the transients. Equilibrium distributions are obtained by a straight-forward simulation of the differential equations. All the simulations in this section use uniform crossover (\( p_c = 0.5 \)), which preserves the error class symmetry.

We now consider a fitness landscape with an isolated peak (\( A_0 = 10 \), and \( A_L = 1 \) \( \forall L \neq 0 \)). The equilibrium distributions for recombining and non-recombining populations are presented in figure 3 where the initial distribution is binomial over the error classes. The phase transition between the localized and non-localized state is extremely sharp in the recombination case. The phase transition occurs at a mutation rate which is orders of magnitude lower than in the non-recombining population.

Figure 4 shows the equilibrium distribution of recombination dynamics with the same fitness landscape as figure 3; the only difference is the initial distribution which is completely localized to the master sequence (\( x_0 = 1 \), and \( x_K = 0 \) \( \forall K \neq 0 \)). We see that the equilibrium distributions depend strongly on the initial distributions. The error threshold is still lower than in the pure mutation case, however the difference is much smaller. In general recombination in single peak fitness landscapes tends to mix the gene sequences and push the population above the error threshold.

Fig. 4 here.
Figure 6 and 7 show how the equilibrium distributions and the phase transition point varies with the initial distribution. The initial distributions are given by

\[ x_k(s) = \frac{2^{-s}k \binom{N}{k}}{(1 + 2^{-s})^N} \]  \hspace{1cm} (11)

This gives a uniform distribution for \( s = 0 \) and a distribution concentrated to the master-sequence for large \( s \). The graphs in figure 5 show the initial distributions for some discrete parameter values, \( s = 0, 1, \cdots, 5 \). Figure 6 shows that there are two different regions in the space of initial distributions, converging to two different fixed points. In one corner of this space all the genomes are master-sequences. If the concentration vector starts out far from this corner it will not converge into the corner unless the mutation rate is extremely low (as illustrated in figure 3 or by the case of \( s \in [0,1] \) in figure 7). If the initial distribution starts near the corner it will converge into the corner for much larger mutation rates (see figure 4 or the region \( s \in [3,5] \) in figure 7). Figure 7 shows the location of the phase transition point for different initial distributions defined by equation 11. This phase diagram shows how the border between the two regions in figure 6 changes with mutation rate. A change of \( p_m \) from \( 9 \cdot 10^{-6} \) to 0.055, changes the border from \( s = 1 \) to 3. When the mutation rate is too low or too high only one region exists corresponding to a single stable fixed-point.

That there is an upper bound on the mutation rate where a stable localized fixed point ceases to exist is obvious. The existence of a lower bound, below which all initial distributions converge to a localized distribution, is however non-trivial. This lower bound always exists and we will present a proof of this in section 5.

The main conclusion to be drawn from these numerical simulations is that, for a wide range of mutation rates, one finds a coexistence of two different equilibrium distributions to the rate equations involving both recombination and point mutations. Which of these fixed points the population will converge to depends on the initial distribution. This means that the space of initial distributions consists of two regions, with the border between this regions depending on the mutation rate. The whole range of mutation rates where a localized fixed point exists is however lower than the phase transition point in the non-recombining case. This shows that a recombining population is more sensitive to mutation than a non-recombining one on a single peak landscape. Similar conclusions have been reached in a simpler model by Bergman and Feldman [18]. Similar results have also been shown in other work, see e.g., [15].
5 Existence of a single fixed-point at zero mutation rate.

In this section we investigate the behavior of the rate equations when \( p_m \to 0^+ \). In section 4 it was shown numerically that at very low mutation rates, all initial distributions converge to a highly localized equilibrium distribution. Here we show that this region always exists for fitness landscapes fulfilling certain assumptions, to be specified below.

The idea behind the proof is to study the dynamics of one position or loci in the genome and sum over all possibilities at the other positions. Let \( S_{\alpha}^{(N,n,i)} \) denote all genomes of length \( N \) that contain the sequence \( \alpha \) starting at position \( 1 \leq i \leq N-n \), where \( \alpha \) is an index coding for genomes of length \( n \). For example; \( S_{3}^{(10,2,1)} \) will be all genomes of length 10 that starts with (11). We also introduce the notation \( x_k^{(N)} \), where \( N \) simply indicates the genome length and affects decoding of the index \( k \). We can now write the rate equations (7) as

\[
\dot{x}_k^{(N)} = \sum_{l,m} V_k^{(N)lm} A_l x_l^{(N)} A_m x_m^{(N)} - \left( \sum_l A_l x_l^{(N)} \right)^2 x_k^{(N)} \tag{12}
\]

The crossover operator has the following property

\[
\sum_{k \in S_{\alpha}^{(N,n,i)}} T_{lm}^{k} = T_{\alpha}^{\beta\gamma} \text{ for } l \in S_{\beta}^{(N,n,i)}, m \in S_{\gamma}^{(N,n,i)}, \forall i \tag{13}
\]

where no assumptions on the crossover probability in made.

Since the point mutation operator \( Q_{k}^{(N)} \) has the same property, so will the combined operator \( V_{k}^{(N)lm} \). We can now use this property and sum the rate equations over all sequences in \( S_{\alpha}^{(N,1,i)} \)

\[
\sum_{k \in S_{\alpha}^{(N,1,i)}} \dot{x}_k^{(N)} = \sum_{k \in S_{\alpha}^{(N,1,i)}} \left( \sum_{l,m} V_k^{(N)lm} A_l x_l^{(N)} A_m x_m^{(N)} - \left( \sum_l A_l x_l^{(N)} \right)^2 x_k^{(N)} \right) \tag{14}
\]

\[
\dot{x}_\alpha^{(1)} = \sum_{\beta,\gamma} V_{\alpha}^{(1)\beta\gamma} \sum_{l \in S_{\beta}^{(N,1,i)}} A_l x_l^{(N)} \sum_{m \in S_{\gamma}^{(N,1,i)}} A_m x_m^{(N)} - \left( \sum_{\beta} \sum_{l \in S_{\beta}^{(N,1,i)}} A_l x_l^{(N)} \right)^2 x_\alpha^{(1)} \tag{15}
\]

The following, compact, notation is now introduced:
\[
\sum_{l \in S^{(N,1,i)}_{\beta}} A_l x^{(N)}_i = \begin{cases} 
\Delta_0^{(i)} & \text{if } \beta = 0 \\
\Delta_1^{(i)} & \text{if } \beta = 1 
\end{cases}
\] (17)

Eq. 16 simplifies to
\[
\dot{x}^{(1)}_0 = q \left( \Delta_0^{(i)} \right)^2 + \Delta_0^{(i)} \Delta_1^{(i)} + (1 - q) \left( \Delta_1^{(i)} \right)^2 - \left( \Delta_0^{(i)} + \Delta_1^{(i)} \right)^2 x^{(1)}_0 
\] (18)
\[
x^{(1)}_1 = 1 - x^{(1)}_0 
\] (19)

which, in the limit \( q \to 1^- \), simplify to
\[
\dot{x}^{(1)}_0 = \left( \Delta_0^{(i)} + \Delta_1^{(i)} \right) \left( \Delta_0^{(i)} x^{(1)}_1 - \Delta_1^{(i)} x^{(1)}_0 \right) 
\] (20)
\[
x^{(1)}_1 = 1 - x^{(1)}_0 
\]

To continue the following assumption on the fitness landscape is needed:

\[
A_l \leq A_m \text{ if } l \in S^{(N,1,i)}_1, m \in S^{(N,1,i)}_1 
\] (21)

We further assume that there exist a gene sequence \( M \in S^{(N,1,i)}_0 \) such that

\[
A_l < A_M \forall l \in S^{(N,1,i)}_1 
\] (22)

These two assumptions mean that no sequences with a zero at position \( i \) have a fitness inferior to any sequence with a one at this position, and that there exist at least one sequence with with a zero at position \( i \) with strictly larger fitness than the sequences with a one at this position. Under these assumptions, the following inequalities hold

\[
\Delta_0^{(i)} \geq \Delta_{0,min}^{(i)} x^{(1)}_0 \\
\Delta_1^{(i)} \leq \Delta_{1,max}^{(i)} x^{(1)}_1 
\] (23)

where \( \Delta_{0,min}^{(i)} \) (\( \Delta_{1,max}^{(i)} \)) denotes the minimum (maximum) fitness of the sequences with a 0 (1) at position \( i \). We further note that at least one of the inequalities in Eq. 23 is strict unless \( x^{(N)}_M = 0 \) for all \( M \) fulfilling Eq. 22. Eq. 23 implies the following estimate

\[
\dot{x}^{(1)}_0 \geq \left( \Delta_{0,min}^{(i)} - \Delta_{1,max}^{(i)} \right) x^{(1)}_1 x^{(1)}_0 
\] (24)
with equality if and only if $x_M^{(N)} = 0$ for all $M$ fulfilling Eq. 22 or $x_1^{(1)} = 0$ or $x_0^{(1)} = 0$.

Note however that $x_0^{(1)} = 0$, $x_1^{(1)} = 1$ is an (unstable) fixed-point since no mutations implies no inventions of new genes.

From Eq. 24 it is clear that the rate equations will converge to a state where all sequences has a zero at position $i$. This fixed point is unstable and it is clear that they cease to exist when the mutation rate is non-zero.

We conclude that all sequences with a one at position $i$ will diminish after long time, and can therefore be discarded. We can then search for a new position such that the remaining half of the fitness landscape satisfies the assumptions in Eq. 21 and 22. If this can be repeated (possibly interchanging the zero and one as being superior, since this choice is arbitrary) until the last position, we conclude that the rate equations converge to a state completely dominated by genomes with the same sequence (which necessarily is a global optimum). Loosely, we may describe such fitness landscapes as having a natural ordering of the importance of its loci. One example of a fitness landscape fulfilling these requirements is a single peaked fitness landscape, describing a degenerate case where the positions can be chosen arbitrarily.

6 Conclusions and discussion

We have studied Eigen’s quasispecies model extended to include crossover as well as mutations. The numerical simulations of section 4 show that there are significant changes in the dynamics of the rate equations because of the non-linearity arising from the introduction of crossover. For a wide range of mutation rates, two simultaneous stable fixed points exist. One fixed point is concentrated around the master sequence while the other describes a uniform distribution. For extremely low and rather high mutation frequencies there is only a single fixed point, corresponding to the localized distribution and the uniform one, respectively. The mutation frequency at the point where the localized fixed point ceases to exist is still lower than the error threshold without recombination.

In this paper we prove that, for a class of fitness landscapes having a hierarchical ordering of the loci in the genome (see Section 5 for details), a single globally stable fixed point exist in the limit of zero mutation rate. Since the proof is valid for all crossover probabilities, the only natural generalization is to expand the class of fitness landscapes. A possible generalization of the technique in Section 5 could be to prove that; within larger class of fitness landscapes, for any point in time, i.e., for any distribution $\vec{x}^{(N)}$, we can always find a position $i$ such that Eq. 24 is fulfilled. The position $i$ would now depend on the distribution (which changes in time), not only the fitness landscape which is the case in our proof. Technically however, this generalization is non-trivial since the changing of position with the distribution makes it complicated to argue that all locus in the global fixedpoint will dominate completely in the infinite time limit.
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Figure 1: The relative equilibrium concentrations of the 51 different error classes for sequences of length 50 for different mutation rates. The fitness landscape has a single peak $A_0 = 10$, and $A_L = 1 \forall L \neq 0$. The error catastrophe occurs around $p_m \approx 0.045$. 
Figure 2: The equilibrium distribution for the concentration of genomes at different mutation rates. The genomes have length 4 and the crossover probability $p_c$ is 0.1. There is a small difference in concentration between genomes in the same error class. Genomes 1 and 4 have the same concentration due to the mirror symmetry in the binary strings. The symmetry breaking tends to increase with genome length.
Figure 3: The equilibrium distributions for recombination (upper graph) and pure mutation (lower graph) dynamics, when the initial distribution is binomial between the error classes. The gene sequences has length 25 and the fitness landscape has an isolated peak ($A_0 = 10$, and $A_L = 1 \forall L \neq 0$).
Figure 4: The equilibrium distribution for a recombining population when the initial distribution is concentrated to the master sequence, $x_0 = 1$, and $x_K = 0 \ \forall K \neq 0$. The gene sequences have length 25 and the fitness landscape has an isolated peak ($A_0 = 10$, and $A_L = 1 \ \forall L \neq 0$).

Figure 5: Initial distributions for different values of the parameter $s$. 

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Figure 6: Equilibrium distributions for different values of the parameter $s$. The copying fidelity is constant $q = 0.97$. Note that there are only two different equilibrium distributions.

Figure 7: The copying fidelity at the phase-transition for different initial distributions $x_k(s)$ (as defined in equation 11). The gene sequence has length 25 and the fitness landscape has an isolated peak ($A_0 = 10$, and $A_L = 1 \forall L \neq 0$).