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Adaptive peak shifts in a heterogenous environment

Lilach Hadany*

School of Mathematical Science, Tel Aviv University, Tel Aviv, Israel

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Abstract

The problem of moving from one coadapted gene complex to a better one can be divided into two steps: first the advantageous combination has to appear and then it has to take over the population. Selection can have contrasting effects on the two stages. When selection is weak intermediate forms are frequent, and the advantageous combination appears easily. Spreading of that advantageous combination, on the other hand, tends to be hard, as recombination acts to break it. The opposite is true when selection is strong. Spreading is easier, but if selection is also strong against the intermediate forms, the appearance of the beneficial combination becomes an extremely rare event.

This inherent contrast in the optimal conditions for the two stages raises the possibility that *proximity* of areas differing in the intensity of selection may significantly shorten the expected waiting time for a peak shift. We studied this phenomenon in a haploid two-locus diallelic model of two neighboring subpopulations. Our results show that limited migration between the two areas might shorten the waiting time for a peak shift by orders of magnitude in comparison with either complete isolation or complete mixing. Implications for peripheral evolution and speciation are discussed.

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1. Introduction

In epistatic genetic systems, substitution of individual components may be separately harmful but jointly advantageous. In such a situation a population may become fixed on a genotype that is not the global optimum. Wright (1931, 1932) introduced the concept of fitness landscape to describe such situations. The problem, as defined by Wright, is how a species can evolve from one adaptive peak to a higher one, crossing a less fit “valley” (for an alternative view, see Gavrilets, 1997).

Wright suggested the shifting balance theory, based upon population subdivision into small demes, to solve that problem. A small deme might drift across the valley up to the point where selection would take it to the higher peak. Migration and inter-demic selection will afterwards spread the new combination in the population. Whereas this process seems feasible (Crow et al., 1990; Wade and Goodnight, 1991; Coyne et al., 1997),

the range of parameters for which it works appears to be quite limited (Moore and Tonsor, 1994; Gavrilets, 1996; Phillips, 1996).

Fisher (1958) emphasized the role of environmental changes. Such changes can enhance peak shift directly by altering individual fitnesses—changes in the direction or intensity of selection can allow peak shifts without drift (Kirkpatrick, 1982; Milligan, 1986; Whitlock, 1997). Alternatively, an environmental change can induce a change in the phenotypic variance of the population that may result in a peak shift (Kirkpatrick, 1982; Whitlock, 1995).

In the present study, it will be shown that if the population is divided into subpopulations with different selection intensities, then the probability of a peak shift increases considerably, even if the subpopulations are large, so that drift is ineffective.

Only a difference in the intensity of selection, not in its sign, is assumed here. Consider, for example, two color-defining loci, with alleles A/a and B/b, in a haploid population under predatory pressure. The green wild type, ab, is well hidden on leaves, yet the brown AB type is hidden even better on the bark. The intermediates are easily noticed everywhere. A difference in the intensity

*Current address: Department of Biological Sciences, Stanford University, CA 94305, USA.

E-mail address: lilach@charles.stanford.edu.

of selection between sites means a difference in the level of predation. The relative fitness of both the double mutant and the single mutants would be affected simultaneously, though in opposite directions.

A population confronts two contrasting difficulties in the transition from the lower peak to the higher one. The double mutant has to appear, and then it has to spread in the population (Slatkin and Michalakis, 1996). The first stage is most likely when selection is weak, and the second when selection is strong. When selection is weak, the fitness of the intermediates is close to that of the wild type, whereas the advantage of the “best” genotype is not large. On one hand, this means that a greater amount of the genetic variability created by mutation at each locus is left after selection, and the favorable combination is more likely to appear as a result of a recombination event. On the other hand, recombination tends to break up beneficial combinations more than to create them (Eshel and Feldman, 1970). Therefore, for this rare and beneficial combination to be able to spread in a large population, its advantage has to be larger than a certain threshold required to counteract recombination. Conversely, when selection is strong, the relative advantage of the rare combination is large, but the intermediates are very unfit. Thus, when selection is strong enough, a rare beneficial combination has a good chance of spreading in the population, whereas the waiting time for the appearance of such a combination might be very long.

Here we study the case where the intensities of selection in two neighboring areas are different. In one area there is strong selection (“harsh environment”). Once the beneficial combination appears there, it has a good chance of spreading, but the waiting time for its appearance is expected to be very long. In the other area there is weak selection (“mild environment”) and the beneficial combination is not likely to spread by means other than drift. We are interested in two questions: First, how does migration from the mild environment affect the timing of the transition to the higher peak in the harsh environment? Second, given that a peak shift had already occurred in the harsh environment, does migration enable it to spread to the mild environment?

We show that limited migration between the two areas may shorten the expected waiting time for a shift to the higher adaptive peak by orders of magnitude, in comparison with complete isolation. The shift occurs first in the harsh environment, but the individuals initiating it are usually migrants from the mild environment. Later, the advantageous combination may spread to the mild environment as well.

The concept of adaptive landscape has been used over the years in two different senses (Coyle et al., 1997). One is the individual landscape, where fitness is plotted as a function of genotype, and the other is the population landscape, where average population fitness

is plotted as a function of allele frequencies. Wright himself (1931, 1988) used both interpretations alternately. This ambiguity can be especially confusing in the context of the current paper: Had the two subpopulations been separated, the mean population fitness landscape in the mild environment would have two peaks (requiring drift in order to shift between the two), whereas in the harsh environment it would have a single peak (had the new combination appeared, it would spread deterministically, though waiting time can be long). Individual fitness landscape, on the other hand, would have two peaks in both environments. In the following, the term ‘peak shift’ will refer to a shift between the two individual optima.

2. The model

An individual fitness landscape consisting of two peaks is considered. The genetic system includes two haploid loci with alleles a/A at the first and b/B at the second. The frequent type in the population is ab , which has a relative fitness of 1. The genotypes with a single rare allele (Ab or aB) have a lower fitness, $1 - s$, whereas the genotype with the two rare alleles (AB) has a higher fitness than the wild type, $1 + sH$ (following Crow et al., 1990). This corresponds to a population occupying the lower of two adaptive peaks. Forward and backward mutation rates in both loci are assumed to be equal to the low rate μ , and the recombination rate is r .

2.1. Background: conditions for a peak-shift in an infinite population

Let us start with a single infinite population without mutation. In the absence of drift and mutation, fixation of the most fit genotype AB is always stable. The fixation of ab is stable if

$$s < \frac{r}{(1-r)H}. \quad (1a)$$

We refer to this as the case of mild selection.

Fixation of ab is unstable if

$$s > \frac{r}{(1-r)H}. \quad (1b)$$

In the latter case, fixation of AB is globally stable. We refer to this as the case of harsh selection. In both cases, the largest eigenvalues of the transformation near the stable equilibria are strictly less than one, hence convergence occurs at a geometrical rate. Employing the Karlin–McGregor principle of small perturbations near geometrically stable equilibria (Karlin and McGregor, 1972) we infer that a similar dynamical system with sufficiently small rates of mutation should maintain a stable equilibrium in the vicinity of the stable fixation points analyzed for the case without mutation.

Moreover, any of these fixation points would now be in the range of attraction of such a new equilibrium.

Still restricting our attention to infinite populations, this means that in the case of mild selection with low rates of mutation, a peak shift can never occur. Instead, starting from fixation of ab, small frequencies of single mutants and even smaller frequencies of double mutants would be maintained in the population in stable mutation-selection and mutation-selection–recombination balance, respectively. Neglecting terms of the order of μ^2 , we know that the frequency of each of the two single mutant types would then be

$$p = \frac{\mu}{s}.$$

Neglecting terms of the order of μ^3 , we thus know that at mutation-selection balance, each generation a proportion $r(\frac{\mu}{s})^2$ of the individuals in the population are born double mutants as a result of recombination between two single mutants. A proportion $2(\frac{\mu}{s})\mu$ of the individuals are AB because of a mutation occurring in a single mutant, and μ^2 of the individuals are AB because of a double mutation occurring in wild type individuals. Altogether, the proportion of “new” double-mutant offspring, born to parents that are not double mutants is

$$q_n = \left(\frac{\mu}{s}\right)^2 (r + 2s + s^2) + O(\mu^3). \quad (2)$$

Denote by q the total proportion of double mutants at equilibrium, we know that $q = q_n + q_o$, where q_o is the frequency of double mutants born to double mutant parents. Any double mutant parent in the population has a probability $1 - 2p - q = 1 + O(u)$ of mating with a non-mutant individual, in which case a proportion r of its chromosomes, passed to the next generation, would no longer be double mutant. Hence, ignoring terms of the order of μ , the expected number of double-mutant offspring born to a single double-mutant parent is given by

$$\alpha = (1 - r)(1 + Hs) + O(u), \quad (3)$$

since the fitness of the double mutant is $1 + sH$ relative to the average fitness $1 - 2ps + qHs = 1 + O(u)$ of the entire population. Under assumption (1a), $\alpha(s)$ is smaller than one.

At equilibrium, we then get

$$q_o = q\alpha = (q_n + q_o)\alpha.$$

Hence $q_o = \frac{q_n}{1-\alpha}$, which implies $q = \frac{q_n}{1-\alpha}$.

Inserting (2) and (3) this becomes

$$q = \left(\frac{\mu}{s}\right)^2 \frac{r + 2s + s^2}{r - Hs + rHs} [1 + O(u)], \quad (4)$$

the denominator being positive for $s < \frac{r}{(1-r)H}$.

In the case $s > \frac{r}{(1-r)H}$ of harsh selection with small rates of mutation, on the other hand, it readily follows from the classical, no-mutation model, that, on introducing small rates of mutations from a to A and from b to

B, fixation of AB would remain globally stable. In the case of small rates of mutations in all directions, a single, globally stable equilibrium should exist in the vicinity of fixation on AB.

2.2. Waiting time for a peak shift in an isolated finite population

Assume now a large but finite population of size N , with the same forces of selection, recombination, and mutation as in the infinite population model analyzed above.

In the case $s < \frac{r}{(1-r)H}$ of mild selection, the infinite population can serve as a good approximation when N is large and $\frac{1}{N}$, $\mu \ll s$ (Crow and Kimura, 1970). In that case a mutation-selection balance with the frequencies of mutant alleles drifting around $\frac{\mu}{s}$ is maintained. The right-hand side of (4) may then approximate the probability that an individual in the population would be a double mutant. For a peak shift to occur in such a case, the frequency of mutants should drift against selection up to a value within the range of attraction of the AB fixation. The waiting time for such an event is likely to be extremely long in large populations.

In the case $s > \frac{r}{(1-r)H}$ of harsh selection, the situation is different. The combined forces of selection and recombination are expected to increase the frequency of the double mutant even when it is very rare. Yet in a finite population the expected time for the first appearance and establishment of the double mutant could be quite long. This waiting time problem is especially crucial when the population size is not extremely large. Here, we estimate this waiting time for finite populations under harsh selection, concentrating on the range

$$\frac{s}{\mu} < N \ll \left(\frac{s}{\mu}\right)^2, \quad (5)$$

where drift due to small population size is unlikely, and production of AB is not too common. In the absence of the double mutant, the frequency of the two single mutants should approach the vicinity of the quasi-stable mutation-selection balance $p = \frac{\mu}{s}$. Hence, the probability that a random newborn individual in the population will be a double mutant is well approximated by the value $q_n = (\frac{\mu}{s})^2 (r + 2s + s^2)$ as given in Eq. (2). The right-hand side of condition (5) guarantees that this value multiplied by N would still be very small. Hence the probability $1 - (1 - q_n)^N$ that the first double mutant would appear in the population at a given generation, given that it had not appeared earlier, is well approximated by $q_n N$. The waiting time thus follows a geometric distribution with expectation

$$E[\tau(s)] \approx \frac{1}{Nq_n} = \frac{s^2}{Nu^2(r + 2s + s^2)}. \quad (6)$$

Christiansen et al. (1998) studied the waiting time for the appearance of a double mutant in a different selective regime—where each single mutation is either neutral or slightly beneficial. In these cases, the expected waiting time is considerably shorter than (6).

Once a double mutant first appears in the population, its fitness is $1 + sH$ relative to the average $1 - 2(\frac{\mu}{s}) + 2(\frac{\mu}{s})(1 - s) = 1 - 2\mu$ of the population. However, given the probability $1 - 2(\frac{\mu}{s})$ that it mates with a non-mutant, only a proportion $1 - r[1 - 2(\frac{\mu}{s})]$ of its offspring would be double mutants. The expected number of its double-mutant offspring would therefore be given by $\alpha = \frac{(1+sH)}{1-2\mu}\{1 - r[1 - 2(\frac{\mu}{s})]\}$ which, for $\mu \ll s$, can be well approximated by $\alpha = (1 - r)(1 + sH)$, similar to (3).

Note that α is larger than one if and only if condition (1b) for harsh selection holds. Moreover, this approximation is valid as long as the frequency of double mutants in the population is low. As long as the likelihood of a double mutant to meet another double mutant is negligible, the number of double mutants is well described by a Galton–Watson branching process. Denote by $\pi(s)$ the probability that the branching process would not become extinct. In the case of harsh selection, fixation of AB is globally stable for the infinite population model. Thus we know that once the double mutant is established, it is very likely to become fixed in the population. Hence $\pi(s)$ can approximate the probability of a peak shift, following the appearance of a single double mutant in the population, assuming the population is of considerable size (for example, when the left-hand side of (5) is satisfied). The expected time until the beginning of a successful peak shift can therefore be approximated by

$$E[T(s)] = \frac{E[\tau(s)]}{\pi(s)}. \tag{7}$$

For any one-dimensional Galton–Watson process we know that if the expected number of offspring $\alpha(s)$ per individual is slightly above one and if the variance in the number of these offspring is σ^2 , then the probability that the process does not become extinct can be approximated by $\pi = 2\frac{\alpha-1}{\sigma^2} + O(\alpha - 1)^2$ (Ewens, 1979; Eshel, 1981).

Assuming a Poisson distribution of offspring and ignoring terms of the order of $(\alpha - 1)^2$, this becomes $\pi = 2(\alpha - 1)$. Inserting (3) we thus get

$$\pi(s) = 2[(1 - r)Hs - r]. \tag{8}$$

Inserting (6) and (8) in (7) we finally get

$$E[T(s)] = \frac{s^2}{2N\mu^2(r + 2s + s^2)[(1 - r)Hs - r]}. \tag{9}$$

By finding the minimum of (9) we can bound the waiting time from below:

$$E[T(s)] > \frac{1}{3(2 + H)N\mu^2}. \tag{10}$$

For example, for $N = 10^4$, $\mu = 10^{-6}$, and $H = 1$, we get $E[T(s)] > 10^7$ generations.

2.3. Waiting time for a peak shift in two partially isolated populations

Now consider two partially isolated subpopulations. We are interested in the case in which the selection forces are harsh in one of the areas and mild in the other. Selection parameters in the two environments are denoted s_h and s_m . The sizes of the two subpopulations are N_h and N_m , respectively, and we concentrate on the case $N_h \leq N_m$. The two subpopulations are separated by a physical barrier, allowing only a small number of individuals, M , to migrate in each direction every generation. We denote the rate of migration to and from area i ($i = h, m$) by $m_i = \frac{M}{N_i}$, and assume M is small, at least in relation to the larger subpopulation, so that $m_m < 0.01$.

Once a double mutant first appears in the harsh area, the number of its double-mutant offspring, remaining in that zone, will now be $(1 - r)(1 + s_h H)(1 - m_h)$. If

$$m_h > 1 - \frac{1}{(1 - r)(1 + s_h H)}, \tag{11a}$$

then the double mutant is not likely to become established in the harsh environment even after its first appearance there. Hence we concentrate on the case of relatively small migration rates, satisfying a stronger version of condition (1b): $s_h > \frac{r+m_h(1-r)}{(1-r)(1-m_h)H}$, that is equal to

$$m_h < 1 - \frac{1}{(1 - r)(1 + s_h H)}. \tag{11b}$$

In any given generation, a mutant individual in the mild environment would be replaced by a migrant from the harsh environment at probability m_m . We assume the worst case, that migrants from the harsh area to the mild one (before a shift occurs in the harsh area) are all wild type. In that case each of the rare alleles in the mild area will be found at the mutation-selection–migration balance:

$$\tilde{p}_m = \frac{\mu}{s_m + m_m(1 - s_m)} \cong \frac{\mu}{s_m + m_m} = \frac{\mu}{\tilde{s}_m},$$

where $\tilde{s}_m = s_m + m_m$. The frequency of double mutants in the mild area at equilibrium would be, as with (4):

$$\tilde{q}_m = \left(\frac{\mu}{\tilde{s}_m}\right)^2 \frac{r + 2\tilde{s}_m + \tilde{s}_m^2}{1 - (1 - r)(1 + s_m H)(1 - m_m)} + O(\mu). \tag{12}$$

If, in addition, $s_m, m_m \ll r$, (13) reduces to

$$\tilde{q}_m = \left(\frac{\mu}{\tilde{s}_m}\right)^2.$$

The probability that at least one individual in the population of the harsh area is replaced by a migrant

double mutant can thus be approximated by

$$M\tilde{q}_m = M \left(\frac{\mu}{\tilde{s}_m} \right)^2 \frac{r + 2\tilde{s}_m + \tilde{s}_m^2}{1 - (1-r)(1+s_m H)(1-m_m)} \times [1 + O(u)]. \quad (13)$$

For $s_m, m_m \ll r$, the right-hand side of (13) becomes $M \left(\frac{\mu}{\tilde{s}_m} \right)^2$.

Note that the probability that a double mutant migrates to the harsh area from the mild one depends on the intensity of selection in the mild area and on the number of migrants. It depends only weakly on the selection in the harsh area, or the recombination rate.

In addition, the frequency of each of the rare alleles in the harsh environment increases to $\tilde{p}_h = \frac{\mu + m_h \tilde{p}_m}{s_h} \cong \frac{\mu}{s_h}$, where $\tilde{s}_h = \frac{s_h}{1 + \frac{s_h m_m}{s_m + m_m}}$, incorporating the effects of both selection in the harsh environment and migration of single mutants from the mild environment. The probability that a native in the harsh area is a new double mutant (i.e., born to non-double-mutant parents) thus increases to

$$\tilde{q}_{nh} = \left(\frac{\mu}{\tilde{s}_h} \right)^2 (r + 2\tilde{s}_h + \tilde{s}_h^2). \quad (14)$$

Under assumption (5), the overall probability of appearance of a new double mutant in the harsh area, either native or migrant, can be approximated by $\psi = N_h(\tilde{q}_{nh} + m_h \tilde{q}_m - m_h \tilde{q}_m \tilde{q}_{nh})$. Neglecting terms of the order of $N_h \mu^3$ we get

$$\psi = N_h(\tilde{q}_{nh} + m_h \tilde{q}_m), \quad (15)$$

where the expectation of the waiting time for the first appearance of a double mutant in the harsh environment is $E[\tilde{\tau}] = \frac{1}{\psi}$.

The effect of migration rate on $E[\tilde{\tau}]$ is complex: while $E[\tilde{\tau}]$ is an increasing function of m_m , it is also a decreasing function of m_h (Eq. (12)). Consider the extreme case: when m_m is larger than s_m , the single mutants in the mild area have a higher probability to be lost due to migration to the harsh environment than due to direct selection. Thus the effect of migration on $E[\tilde{\tau}]$ depends on the ratio N_m/N_h . When N_m/N_h is large m_m is much smaller than m_h and $E[\tilde{\tau}]$ is an increasing function of the migration rate (see the upper bound of K in Fig. 1). For low values of N_m/N_h , $E[\tilde{\tau}]$ is a unimodal function of the migration rate, and the whole effect is weaker. Note, however, that the importance of the relative sizes of the subpopulations results from the assumption that the same number of migrants, M , migrates in both directions. Had m_m been independent of m_h (as in the case of source and sink populations, for example) we would expect the waiting time $E[\tilde{\tau}]$ to increase with N_h and decrease with N_m .

Had a double mutant appeared in the harsh area, only $\tilde{\alpha} = (1-r)(1+s_h H)(1-m_h)$ of its $\alpha = (1-r)(1+s_h H)$ offspring would stay there. Thus its probability to be

established, $\tilde{\pi}$, is decreased in comparison with the isolated case. In the worst case, where α is only slightly larger than 1, the probability of spread is (similarly to (8)) $\tilde{\pi} = 2(\tilde{\alpha} - 1)$. The expected time until the first appearance of the first *successful* double mutant in the harsh environment is $E[\tilde{T}(s)] = \frac{E[\tilde{\tau}(s)]}{\tilde{\pi}(s)}$. That waiting time is K times shorter than the waiting time for the same event in an isolated population (Eq. (9)), where

$$K = \frac{E[T(s)]}{E[\tilde{T}(s)]} = \frac{E[\tau(s)] \tilde{\pi}(s)}{E[\tilde{\tau}(s)] \pi(s)}. \quad (16)$$

As the probability of spread is a convex function of the selective advantage, the ratio of the probability of spread with migration, $\tilde{\pi}$, to that probability without migration, π , can be bounded by

$$1 - \frac{m_h(1+s_h H)(1-r)}{(1-r)s_h H - r} \leq \frac{\tilde{\pi}}{\pi} < 1, \quad (17)$$

where the left-hand inequality is attained for the case that $(1+s_h H)(1-r)$ is slightly above one (Eq. (8)), and the right-hand inequality for the case that $(1+s_h H)(1-m_h)(1-r)$ is considerably above one. Using (15) we get

$$K = \left(\frac{r + 2\tilde{s}_h + \tilde{s}_h^2}{\tilde{s}_h^2} + m_h \frac{r + 2\tilde{s}_m + \tilde{s}_m^2}{\tilde{s}_m^2} \right) \times \left(\frac{s_h^2}{r + 2s_h + s_h^2} \right) \frac{\tilde{\pi}}{\pi} \quad (18)$$

and together with (17) we can find upper and lower bounds for the value of K . These bounds are shown in Fig. 1 as a function of m_h . For the high values of the ratio N_m/N_h considered (30, 90), $\frac{E[\tilde{\tau}]}{E[\tau]}$ is an increasing function of m_h , and so is the upper bound of K . The lower bound of $\frac{\tilde{\pi}}{\pi}$, on the other hand, decreases with m_h for any population sizes (Eq. (17)), and the lower bound of K is an unimodal function of m_h . Lower bound of the *absolute* values of the waiting time in the harsh environment is obtained in (10), and for reasonable parameter values would be of the order of tens, if not hundreds, of millions of generations.

For $s_m, m_m \ll s_h$ the component of migrating double mutants is much larger than that of migrating single mutants (see Fig. 2). Using (13), a good approximation of K is given by

$$K = \left(\frac{s_h}{\tilde{s}_m} \right)^2 \frac{m_h}{r + 2s_h + s_h^2} \frac{\tilde{\pi}}{\pi}$$

Note that if, in addition, $(1-r)(1+s_h H)(1-m_h)$ is considerably larger than 1, a better approximation for K would be given by $\left(\frac{s_h}{\tilde{s}_m} \right)^2 \frac{m_h}{r + 2s_h + s_h^2}$. If, in addition, $m_m \approx s_m$ and $s_h \approx r$ we get, using (13),

$$K \cong \frac{s_h N_m}{12 s_m N_h}. \quad (19)$$

As the migration rate increases, however, the relative contribution of migrating single mutants increases and

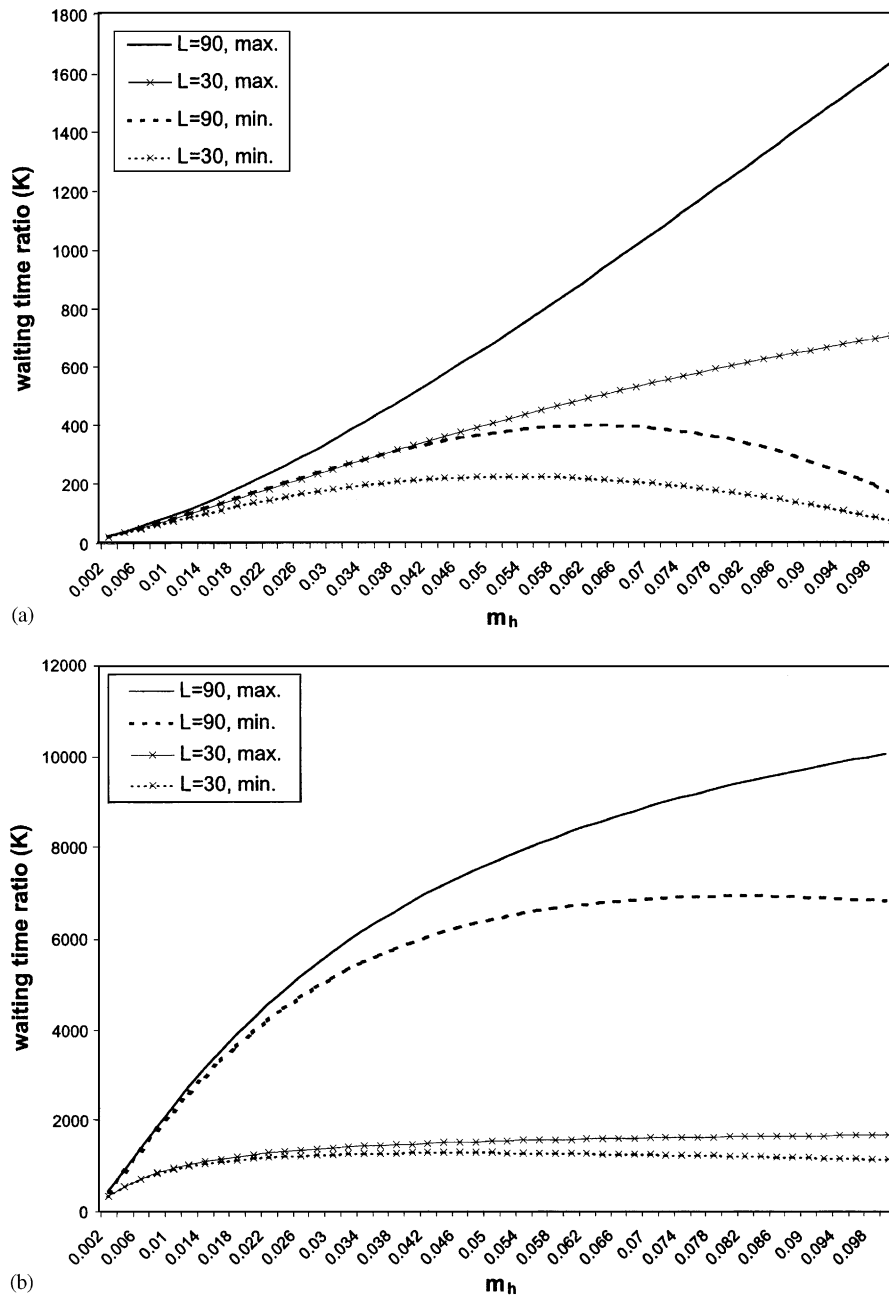


Fig. 1. Shortening of waiting time. Waiting time ratio (K) is the expected waiting time for the beginning of a peak shift in the harsh environment when isolated ($M = 0$), divided by the expected waiting time for a peak shift in the harsh environment with migration from the mild environment ($M > 0$), as found in Eq. (18). (Waiting time for a peak shift in the mild environment when isolated is orders of magnitude longer than in the harsh area under population sizes considered). Upper and lower bounds of K are shown as a function of the migration rate m_h into the harsh area. The mild subpopulation is L times larger than the harsh subpopulation, and $m_m = m_h/L$. $L = 30, 90$. $H = 1$, $s_h = 0.5$, $r = 0.5$, and (a) $s_m/s_h = 0.01$, (b) $s_m/s_h = 0.001$.

the under estimation of (19) becomes more significant (see Fig. 2).

As the above results depend upon various assumptions, including neglect of drift due to small population size, it is of interest to compare them with simulation results. In the simulation a population composed of two subpopulations is initialized with no mutants. At each generation, each subpopulation goes

through reproduction, mutation, and selection (with fitnesses determined by two haploid loci). Then M individuals are chosen at random from the mild subpopulation and replaced with M randomly chosen individuals from the harsh subpopulation (symmetric migration). The process continues until the frequency of double mutants in at least one of the subpopulations exceeds 0.5. The number of generations required is

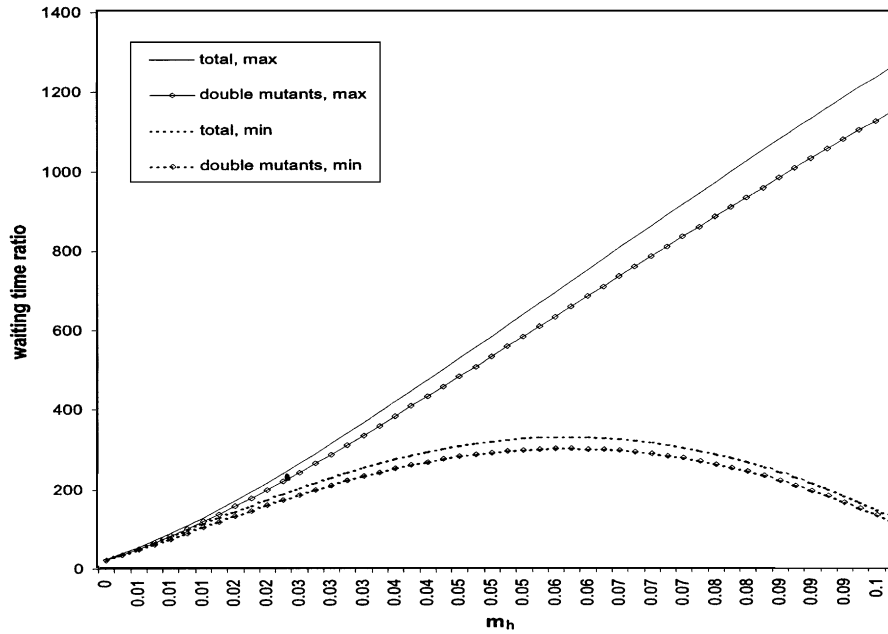


Fig. 2. The contributions of migrating double mutants and migrating single mutants to the shortening of the waiting time for a peak shift, as a function of migration rate m_h in the harsh area. Upper and lower bounds of waiting time ratios (expected waiting time without migration divided by expected waiting time with migration) are plotted for two cases of migration: (i) migration of wild-type and double mutants only (diamonds) and (ii) migration of all types (line and dashed line). The difference between the total and the double mutant contributions is the contribution of the migrating single mutants. $s_m/s_h = 0.01$, $H = 1$, $s_h = 0.5$, $r = 0.1$, and $N_m/N_h = 30$.

considered as the waiting time. The simulation above was repeated 50 times for each value of m_m , ranging from 0.002 to 0.1. As we can see (Fig. 3), when selection in the harsh area is strong, the simulated waiting time usually lies within the theoretical upper and lower bounds for $N_h = 500, 1000$. Allowing each of the two subpopulations to reach mutation-selection balance before the onset of migration showed qualitatively similar results.

2.4. Spread of AB to the mild environment

Had the mutation taken over the harsh area, the likelihood of a reverse peak shift is negligible for N_h satisfying condition (5). It requires a takeover by drift of either one of the deleterious alleles, with a higher relative disadvantage on the background of AB, or of type ab, against the joint forces of selection and recombination. In both cases selection against the rare types would be much stronger than drift. Migrants from the harsh area to the mild one would nearly all be of genotype AB. Hereafter we will neglect mutation and back-migration (migrants from the mild area to the harsh one and back to the mild) and consider the frequency of AB within the migrants from the harsh area to be 1. Let x_1, x_2, x_3, x_4 be the frequencies of genotypes AB, Ab, aB and ab in the mild area, respectively, and let $D = x_1x_4 - x_2x_3$. Assuming selection occurs prior to migration the frequen-

cies of the different genotypes in the mild area in the following generations can be described by the recursion equations:

$$\begin{aligned} x'_1 &= (x_1 - rD)(1 + s_mH)(1 - m_m)/\omega + m_m, \\ x'_2 &= (x_2 + rD)(1 - s_m)(1 - m_m)/\omega, \\ x'_3 &= (x_3 + rD)(1 - s_m)(1 - m_m)/\omega, \\ x'_4 &= (x_4 - rD)(1 - m_m)/\omega, \end{aligned} \tag{20}$$

where $\omega = (x_1 - rD)(1 + s_mH) + (x_2 + x_3 + 2rD)(1 - s_m) + x_4 - rD$.

The process described by Eqs. (20) may lead AB either to fixation or to a low selection-migration-recombination balance. From (20) it can easily be established that $\{x_1 = 1, x_2 = 0, x_3 = 0, x_4 = 0\}$ is always a stable solution. By running the equations forward to equilibrium, we found that where m_m is small enough, a stable polymorphic equilibrium exists as well. Starting from a frequency of AB of the order of $(\frac{\mu}{s_m})^2$ (Eq. (4)) and assuming $\mu \ll m_m$, the population is most likely to be found at the polymorphic equilibrium when the latter exists. Under this assumption, the equilibrium frequency of AB in the mild area (a numerical solution of 20) is shown in Fig. 4 as a function of m_m and s_m . The parameter range is clearly divided into two areas—fixation of AB and polymorphism, where the frequency of AB is extremely low. At the latter case, the harsh area would be dominated by AB type, whereas the mild area

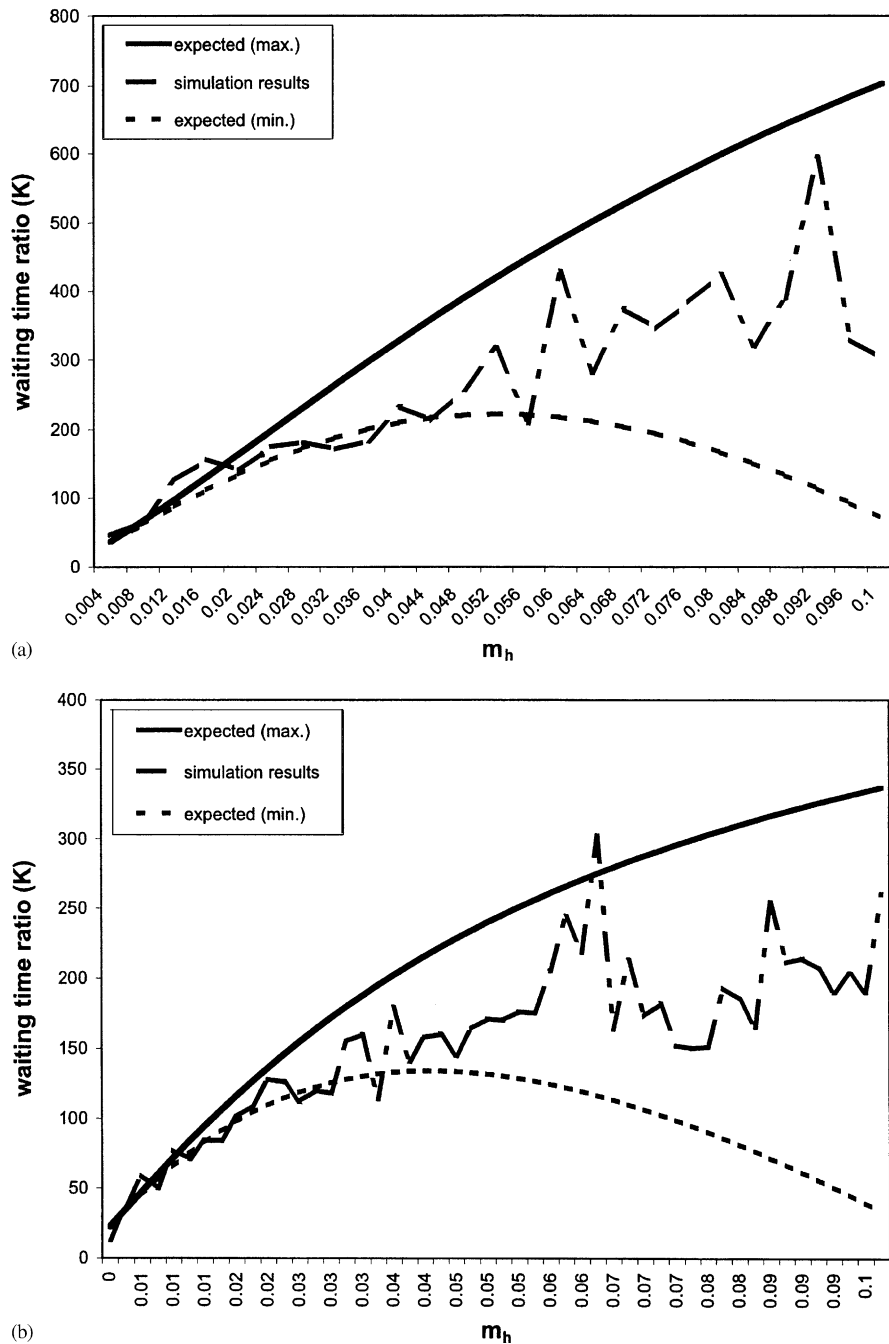


Fig. 3. Expected and observed values of the waiting time ratio K , as a function of migration rate in the harsh area, m_h . Plotted are upper and lower bounds of the expectation of K (based upon Eqs. (17) and (18)), and the simulation results. We can see that the average simulated waiting time tend to lie within the theoretical upper and lower bounds. $H = 1$, $r = 0.1$, $s_h = 0.5$, $s_m/s_h = 0.01$, $N_m = 15000$. (a) $N_h = 1000$. (b) $N_h = 500$.

would be dominated by ab . As we can see, the parameter range over which a stable polymorphic equilibrium exists consists mainly of low values of m_m . As low migration would also postpone the fixation of AB in the harsh environment, we would expect the two areas to be dominated by different genotypes most commonly when m_m is very low while m_h is not. That is, when the mild population is much larger than the harsh one.

2.5. The effect of linkage

Recombination has different effects on the different stages of the process suggested here. When the main source of type AB in the harsh environment is migrating double mutants from the mild environment, the waiting time for that event is almost independent of r (Eq. (13)). This is because type AB is (at the beginning) at a

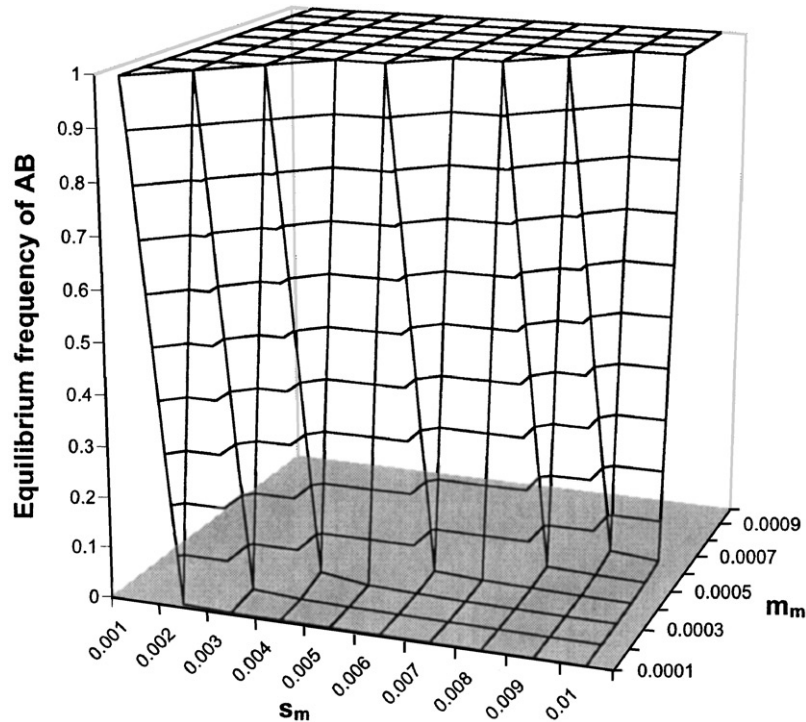


Fig. 4. AB equilibrium frequency in the mild area, after it has fixed in the harsh patch, as a function of the migration rate in the mild area, m_m , and the selection there, s_m . The parameter range is divided into two areas: fixation of AB, and a stable polymorphism, with a very low frequency of AB. We can see that as the value of s_m increases, the critical value of m_m , above which a shift in the mild area would occur, increases as well. $H = 1$, $r = 0.1$.

mutation-selection-recombination balance in the mild area. Recombination is at the same time the main force creating advantageous combinations and the main force breaking them in the mild environment and thus has almost no effect on the equilibrium frequency of AB there (Eq. (4)). The number of double mutants created in the harsh area is of course proportional to r , but we saw that this term is often minor (Fig. 2). The probability of spread of the double mutant in the harsh area, on the other hand, is affected by r . As r increases, the expected number of descendants of a rare AB individual decreases, and as a result the probability of spread decreases. Altogether, the waiting time for a peak shift in the harsh environment increases with r , almost independently of the proximity of the mild environment.

Had the double mutant taken over the harsh area, the main source of double mutants in the mild area would be migrants, and their number would be independent of r . Since recombination acts to destroy the migrating AB individuals, the migration threshold needed for a peak shift in the mild area increases with r . Everything else being equal, we expect that adaptive peak shifts would occur more easily in both areas as linkage becomes tighter. For a more general investigation of recombination and epistasis in a heterogeneous environment see Lenormand and Otto (2000).

3. Discussion

We have shown that environmental heterogeneity may be of great importance for adaptive peak shifts even when the direction of selection does not vary between the different patches. We considered two large subpopulations, separated by an environmental barrier. The two areas differ in the strength of selection operating on two haploid loci. While it would take a very long time for the double mutant to appear in the harsh environment, and an almost infinite amount of time for it to take over the mild environment (Phillips, 1996), migrant exchange between the two areas may shorten this time by orders of magnitude. Limited migration between the two subpopulations increases the likelihood of an adaptive peak shift much more than either complete isolation or complete mixing.

We showed that the double mutant would first take over the harsh area, but it is the proximity of the mild area that actually enables the double mutant to appear there within a reasonable amount of time, since migrants from the mild area are much more likely to carry the mutations. Later, migrants from the harsh environment may induce a peak shift in the mild environment. The proximity of a partially isolated patch of harsh environment can thus allow a peak shift where it would almost never occur otherwise.

These results depend on several factors: The strength of selection in the harsh environment, the difference in the intensity of selection between the two subpopulations, the migration rate, and the relative sizes of the subpopulations. It is necessary that, in the harsh environment, selection be strong enough to enable the double mutant to increase in frequency even when very rare. Under this condition, the expected waiting time for the peak shift is shorter in a population subdivided in the manner suggested here, than in a population composed of completely disconnected subpopulations, and the difference might be up to several orders of magnitude for reasonable parameter values. The ratio between the expected waiting time in partially disconnected populations to that in completely disconnected ones increases with the difference in intensity of selection between the two areas, and with the relative size of the mild area. The second step, the shift in the mild environment, depends upon population sizes, selection parameters, and migration rate. The probability of a peak shift in the mild environment increases with migration rate, and decreases with selection in the mild environment.

Several cases in which these conditions are likely to be met might have great importance in adaptive evolution, and in particular in the context of peripheral evolution and speciation. Our very simple model may give a clue to the understanding of these complex and important processes.

3.1. *Peripheral evolution*

Consider first the classical population structure of peripheries and mainland (Mayr, 1963). The mainland is the area to which the organisms are best adapted. The main selective factors there thus include intra-species competition, while parasites are also most frequent and well adapted in this area. In each periphery, by definition, population density is lower. The reason could be heat, aridity, salt etc. Most probably this reason is of minor importance in the mainland. If selection acts in the same direction in the mainland and in the periphery, selection in the periphery is strong enough, and a physical barrier (possibly distance) exists between the two areas, the conditions of our model are met. Surprisingly, this means that adaptation to the demands of the periphery, when there is a shift to a new adaptive peak, might be greatly enhanced by some low rate of migration from the mainland, where these demands are marginal and a shift to the new peak could never occur. Note that the very same process might be relevant, simultaneously, to different traits and in different directions. A peak shift required for intra-species competition or parasite resistance may occur much more rapidly in the mainland due to the low rate of migrants from all the low-density peripheries, where

these selective forces are weak. Adjacent but environmentally different peripheries can increase the frequency of peak shifts in each other. To avoid confusion, we continue hereafter to use the term ‘periphery’ referring to the harsh environment.

In the next step, double mutants from the periphery migrate into the mainland. An important question is whether this migration is sufficient to shift the mainland itself to the new peak. As we have seen, this may or may not occur, depending on population sizes, selection parameters, and migration rate. If migration is high enough, a peak shift would occur in the mainland, where it would be almost impossible without the presence of the periphery. If migration is not high enough, a peak shift in the mainland would not occur. In that case migrants from the mainland, and especially their descendants, will do very poorly in the periphery. This unidirectional reproductive barrier might contribute to divergence of the population into two subspecies. Once speciation occurs, however, the situation changes. Migrants from the periphery belonging to a new species, superior in the same niche of the parent species, can take over the mainland, as recombination is ineffective once a reproductive barrier exists.

Direct examination of these predictions is difficult. It is clear that other processes and especially drift might be of great effect. Everything else being equal, our model predicts that novel adaptations and even speciation might be most common not in a uniform environment but rather in border areas, where different environments meet.

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