J. evol. Biol. 8: 93–120 (1995)

1010–061X/95/010093–28 $ 1.50 + 0.20/0

Cyclical environmental changes as a factor maintaining genetic polymorphism. 1. Two-locus haploid selection

V. M. Kirzhner, A. B. Korol* and Y. I. Ronin

Institute of Evolution, University of Haifa, Haifa 31905, Israel

Key words: Polymorphism; cyclical selection; haploid; recombination.

Abstract

To classify different types of cyclic selection, a measure of fitness disequilibrium was used, and a class of systems were considered where this measure has the same sign in all states (sign-concordant environments). The necessary conditions for existence of a fixed point (considering any moment within the period as a referring one) are obtained for sign-concordant systems. However, analytical study of such systems, in the case of selection for equal additive genes, and numerical testing of more general situations, allowed us to conclude that no polymorphism is possible. In the alternative class of sign-nonconcordant systems, polymorphism is possible. However, we found that global stability is an exception rather than a rule for sign-nonconcordant systems. Massive numerical simulations of selection in a four-state environment were made for cycle lengths in the range 8–28 and with evenly distributed selection coefficients. The proportion of polymorphic regimes ranged up to about 1.5%, and was dependent on the recombination rate between the loci. It should be stressed, that polymorphism maintenance in the haploid systems, when it is possible, can not be considered as an effect derived from constant selection, or be a result of any hidden form of heterozygous advantage. In other words, polymorphism stability is causally connected with environmental fluctuations. Equally important is that this effect of fluctuations is only possible because of recombination: in single locus systems haploid cyclical selection is unable to produce protected polymorphism.

---

* Author to whom correspondence should be addressed.

Introduction

Among different explanations for high levels of genetic variability in nature, spatial and temporal variations of selection intensity were considered as very plausible for a long time. The first theoretical models have confirmed this expectation but strongly delimited the conditions of their applicability (Levene, 1953; Haldane and Jayakar, 1963; and others. For reviews see also Felsenstein, 1976; Gillespie and Langley, 1976; Hendrick et al., 1976; Hendrick, 1986). The range of parameters compatible with stable polymorphism proved to be much narrower in the case of temporal fluctuations as compared to spatial ones. The conditions for protected polymorphism may be relaxed under combined action of these two factors (Hendrick, 1978; Ewing, 1979).

Most of the results related to selection variation in time are for the one locus case (e.g., Karlin and Levikson, 1974). However, it is reasonable to assume that new conclusions may be obtained when considering two or more loci. For such a formulation the haploid case is of special interest. Indeed, with haploid selection there is no way to obtain a stable polymorphism due to any (hidden) form of heterozygote advantage, no matter how this advantage is defined. Here we will show that with haploid selection in a constant environment, and in a rather broad range of fluctuating environments stable polymorphism can not be maintained. However, a class of situations can be described where fluctuating selection can maintain stable polymorphism.

Necessary conditions for polymorphism. General selection regime

The dynamics of infinite haploid panmictic populations will be considered with selection acting on two diallelic autosomal loci. Generations are non-overlapping. The evolutionary operator can be written in the following form:

$$\begin{aligned} x_1' &= l_1(x_1 - rD)/W, \quad x_2' = l_2(x_2 + rD)/W, \\ x_3' &= l_3(x_3 + rD)/W, \quad x_4' = l_4(x_4 - rD)/W, \end{aligned} \tag{1}$$

which transforms the standard simplex Σ for the 4-dimensional space into itself. Here x_1, x_2, x_3, and x_4 are the frequencies of haplotypes *AB*, *Ab*, *aB*, and *ab*, respectively,

$$W = l_1 x_1 + l_2 x_2 + l_3 x_3 + l_4 x_4 + rD\sigma,$$

$$D = x_1 x_4 - x_2 x_3, \quad \sigma = -l_1 + l_2 + l_3 - l_4.$$

Fitnesses l_1, l_2, l_3, l_4 are dependent on the environment. We will consider changing environments with p different states ($p > 1$). If the states follow in a periodical sequence we can speak of a cyclical environment. For the state with number i we denote fitness coefficients as $l_{i1}, l_{i2}, l_{i3}, l_{i4}$. Due to normalization of (1), the maximal fitness in each environmental state is equal to unity.

For a better understanding of the nature of possible polymorphisms in fluctation environments, it is reasonable to first check the situation with a constant environment. The questions of: (a) existence, and (b) analytical form of stable states, have been solved earlier for the case $l_1 = l_4$ (Feldman, 1971). For the general case, the following statement can be proved.

Proposition 1

For existence of an internal fixed point of the system (1), in constant environment, it is necessary and sufficient that one of these two groups of inequalities hold:

$$l_1, l_4 > l_2, l_3; \quad r > (\max(l_1, l_4) - \min(l_2, l_3))/\max(l_1, l_4)\,,$$

or (2)

$$l_2, l_3 > l_1 l_4; \quad r > (\max(l_2, l_3) - \min(l_1, l_4))/\max(l_2, l_3)\,.$$

Only one internal fixed point could exist (if at all) with coordinates $(\bar{x}_1, \bar{x}_2, \bar{x}_3, \bar{x}_4)$:

$$\begin{aligned} \bar{x}_1 &= -l_1 \mu_2 \mu_3 \mu_4/(L\delta(L)), \quad \bar{x}_2 = -l_2 \mu_1 \mu_3 \mu_4/(L\delta(L))\,, \\ \bar{x}_3 &= -l_3 \mu_1 \mu_2 \mu_4/(L\delta(L)), \quad \bar{x}_4 = -l_4 \mu_1 \mu_2 \mu_3/(L\delta(L))\,, \end{aligned} \tag{3}$$

where $\mu_i = l_i - L$,

$$\begin{aligned} L &= \{(2-r)(l_1 l_4 - l_2 l_3) + \surd([(2-r)(l_1 l_4 - l_2 l_3)] \\ &\qquad - 4((l_1 - l_2 - l_3 + l_4)\delta(0)(1-r)))\}/(2(l_1 - l_2 - l_3 + l_4))\,, \\ \delta(L) &= -\mu_2\mu_3\mu_4 + \mu_1\mu_3\mu_4 + \mu_1\mu_2\mu_4 - \mu_1\mu_2\mu_3. \end{aligned}$$

For proof see Appendix 1.

The Jackobian of the transformation (1) at the fixed point can be written in the explicit form. However, its analytical treatment is cumbersome. Numerical examination showed that the characteristic polynomial of this Jacobian has, almost always, a positive root which exceeds unity. The only exceptions are cases where the parameters of the system obey some special conditions (equalities) and then the spectral radius is equal to unity. Thus, in these cases polymorphism will be, as a rule, unstable.

Generally, stable polymorphism is not an intrinsic characteristic of systems with haploid selection. Therefore, polymorphism stability, if possible at all, should be a phenomenon of some kind of variable selection (e.g., temporal fluctuations of fitness coefficients, frequency dependent selection, etc.). On the other hand, global stability of a set of polymorphic points (with the whole interior of the simplex being the domain of attraction) is also an exception for environments with a finite number of states. Under these conditions, as a rule, there exists a non-empty domain of attraction of fixation points for each of the participant loci. The direction of fixation depends on the integral fitnesses of haplotypes (as defined below) in all of the environmental states.

Let us define the integral fitness of the haplotype j, in a periodic environment with p states, as $L_j = l_{1j} l_{2j} \cdots l_{pj}$, where p is the period length, and $j = 1, 2, 3, 4$. If the sequence of the states is not fixed within the period, the environment can be called quasi-periodic.

Proposition 2

The equality $\max(L_1, L_4) = \max(L_2, L_3)$ is a necessary condition for global stability of polymorphisms in periodic and quasi-periodic environments. If $\max(L_1, L_4) = \max(L_2, L_3)$, then the vertex $x_m = 1$ of the simplex will be a point of local attraction, if $L_m = \max(L_1, L_2, L_3, L_4)$. The second locally attracting vertex will be $x_s = 1$, if

$$L_s = \max(\{L_1, L_2, L_3, L_4\} \backslash L_m) \quad \text{and} \quad (1-r)^p L_s < L_m\,, \tag{4}$$

where $\{L_1, L_2, L_3, L_4\} \backslash L_m$ denotes the set $\{L_1, L_2, L_3, L_4\}$ without the element L_m, and haplotype s complementary to m. For proof see Appendix 2.

Therefore, global stability of polymorphisms is practically an exception, and possible directions of fixation depend on integral fitnesses L_i, and the recombination rate r between the selected loci. The condition $\max(L_1, L_4) = \max(L_2, L_3)$ corresponds to a small set of systems and is, formally speaking, very special. Situations of this type are discussed in the literature (e.g., Sasaki and Iwasa, 1987, for the haploid case, the Charlesworth, 1976, for the diploid case) and, therefore, deserve further consideration.

As a simple example where the accomplishment of the necessary condition leads to global stability, we will study the model of the haploid two locus population considered in Sasaki and Iwasa (1987), where selection alternatively favours either *AB* and *ab*, or *Ab* and *aB* haplotypes. In our analysis the length of the period is $p = 2$.

Proposition 3

For a system defined by the evolutionary operator (1) in a two-state environment with $l_{11} = l_{14} = 1$, $l_{12} = l_{13} = C$ and $l_{22} = l_{23} = 1$, $l_{21} = l_{24} = C$, $C > 1$ and $p = 2$, a polymorphic fixed point exists, and is globally stable. For proof see Appendix 3.

Now we will formulate one important necessary condition for the existence of a polymorphic fixed point. A trajectory of the dynamic system (1) will be referred to as a *regular* one, if an environmental state (say, i) exists, such that for a finite time the sign of the sequence $\hat{D}_{ji}(n)$ becomes stabilized. Here,

$$\hat{D}_{ji} = \tau_j \sum_{s=0}^{s=p-1} (L_j^s / \Omega^s) D^{(i+s)}, \quad j = 1, 2, 3, 4\,; \tag{5}$$

j is the haplotype number; L is the integral fitness; $L_j^s = l_{i,j} l_{i+1,j} \cdots l_{i+s,j}$; $\Omega^s = W_i W_{i+1} \cdots W_{i+s}$; and $\Omega^{p-1} = \Omega$. Index $i+s$ is calculated modulo p, D^{i+s} is linkage disequilibrium at the environmental state $i+s$, $\tau_1 = \tau_4 = -1$, $\tau_2 = \tau_3 = 1$.

The coefficient $\hat{D}_{ji}$ is a linear combination (with constant coefficients) of the quantities D/Ω over all their values within the cycle, and it depends on genotype (j), and on the chosen starting point within the cycle (i). Thus, for each i ($1, \ldots, p$) we can define four sequences $\hat{D}_{ji}(n)$ ($j = 1, \ldots, 4$), where n is the period number. Stabilization of the sign of $\hat{D}_{ji}(n)$ means, that some $n = n_0$ exists and, that for any $n > n_0$ sign $(\hat{D}_{ji}(n)) = \text{sign}(\hat{D}_{ji}(n_0))$. A trajectory is regular if there exists at least one state i, for which stabilization of sign $\hat{D}_{ji}$ is possible for all j ($j = 1, \ldots, 4$).

Let us consider a case where L_j could be ranked in an increasing sequence

$$L_{j_1} > L_{j_2} > L_{j_3} > L_{j_4}. \tag{6$'$}$$

This ordering induces a corresponding sequence of coefficients $\hat{D}_{ji}$:

$$\hat{D}_{j_1 i}, \hat{D}_{j_2 i}, \hat{D}_{j_3 i}, \hat{D}_{j_4 i}. \tag{6$''$}$$

For each regular trajectory of the system (1) we can say that the signs of $\hat{D}_{ji}$ from (6) become stabilized within a finite time. Further consideration concerns the behavior of the system beginning from the moment of stabilization of the sequence of signs. We will refer to the sequence (6″) as an *increasing-for-sign* if it does not contain changes from plus to minus. In other words, the first m elements of (6″) are non-positive and the subsequent 4-m are non-negative, $0 \leq m \leq 4$. It should be noted that when some values of integral fitnesses are equal, their mutual order can be arbitrarily chosen, which leads to several possible sequences (6″). In particular, when all fitnesses are equal we can choose such an order that the sequence (6) will be an increasing-for-sign.

Proposition 4

Let all of the integral fitnesses be different. For convergence of any regular trajectory to an interior point of the simplex $x_1 + x_2 + x_3 + x_4 = 1$, it is necessary that the corresponding sequence (6″) be an increasing-for-sign. For proof see Appendix 4.

Remark

The case of non-equal fitnesses has been considered in Proposition 4. Clearly, definition (6) of a regular sequence is formally irrelevant to the case when all of the integral fitnesses are equal. Nevertheless, some elements of the above proof are also applicable in this case, provided that the sequence $\text{sign}(\hat{D}_{ji}(n))$ becomes stabilized. Namely, let a change in the sign be characteristic to the sequence (6″). Then, by a consideration analogous to that in the proof of Proposition 4, the following result could be obtained. Under the above conditions either the trajectory converges to the set $D = 0$ or at least one of the loci goes to fixation (this could be shown employing a chain of inequalities analogous to that of 22A–24A).

As important examples of the described situtation we can consider 'plus-concordant' ($l_{1i}l_{4i} > l_{2i}l_{3i}, i = 1, \ldots, p$) and 'minus-concordant' ($l_{1i}l_{4i} < l_{2i}l_{3i}, i = 1, \ldots, p$) environments (Kirzhner et al., 1993, 1994a). Environments of these types arise in schemes of stabilizing selection with moving optimum when the selected trait is controlled by additively acting genes (Maynard Smith, 1988; Kirzhner et al., 1993, 1994a). Earlier we showed that the sign of linkage disequilibrium in such environments becomes stabilized and equal for all environmental states (Kirzhner et al., 1993, 1994a). According to (5), the sign of $\hat{D}$ in these cases also becomes stabilized. Thus, each trajectory of the corresponding system (1) in this special case is regular. The signs of $\hat{D}_{11}$, $\hat{D}_{41}$ and $\hat{D}_{21}$, $\hat{D}_{31}$ are opposite, and depend on plus- or minus-concordance of the environment. Therefore, we conclude that each trajectory in the sign-concordant environment is regular. However, it is worth mentioning here, that in massive numerical experiments with this class we have not been able to find a stable polymorphic situation. Due to this fact, Proposition 4 for the class of sign-concordant environments should be reformulated as follows:

Corollary

If the environment is minus-concordant, i.e. $l_{i1} l_{i4} < l_{i2} l_{i3}$, then the full dominance of integral fitnesses of haplotypes 2 and 3,

$$L_2, L_3 > L_1, L_4 \tag{7}$$

is necessary for existence of an interior fixed point (because in this case we have $\hat{D}_{1j}, \hat{D}_{4i} \le 0, \hat{D}_{2i}, \hat{D}_{3i} \ge 0$).

For plus-concordant environments the direction of the inequality (7) should be reversed. It is worthwhile to note, that condition (7) is an analogue of Proposition 1 for a constant environment.

For example, let the sign-concordant environmental selection be the result of an optimum movement with a fitness function $F(\cdot)$, so that,

$$l_{ji} = F(t_j - a_i), \quad L_j = F(t_j - a_1) \cdots F(t_j - a_p),$$

where t_j stands for the selected trait value of haplotype j, and a_i is the optimum level of t at the state i. If the selected trait t depends on two equal additive genes, then the conditions (7) will be as follows:

$$\begin{aligned} F(t_1 - a_1) \cdots F(t_1 - a_p) &< F(t_2 - a_1) \cdots F(t_2 - a_p), \\ F(t_4 - a_1) \cdots F(t_4 - a_p) &< F(t_2 - a_1) \cdots F(t_2 - a_p). \end{aligned} \tag{8}$$

Clearly, these inequalities may be violated with some sets of a's. If $F = \exp(-\alpha u^2)$, then from (8) one can obtain:

$$\begin{aligned} pt_1^2 - 2t_1 \Sigma a_i + \Sigma a_i^2 &> pt_2^2 - 2t_2 \Sigma a_i + \Sigma a_i^2, \\ pt_4^2 - 2t_4 \Sigma a_i + \Sigma a_i^2 &> pt_2^2 - 2t_2 \Sigma a_i + \Sigma a_i^2. \end{aligned}$$

For a selected trait increasing with the genotype number,

$$(t_1 + t_2)/2 < (\Sigma a_i)/p < (t_2 + t_4)/2.$$

Therefore, the necessary condition for polymorphism is that the mean of the optimal values of the trait (over the environmental states) belongs to the interval $([t_1 + t_2)]/2, [t_2 + t_4]/2)$.

The significance of the above obtained necessary conditions for existence of a polymorphic fixed point in sign-concordant environments can be illustrated by the fact that these conditions are indeed satisfied in the corresponding cases of constant environments, as well as in cyclical environments with a long selection-free period (Kirzhner et al., 1994b).

Selection for an additively controlled trait

Let us consider in more detail the case of selection for an additively controlled trait. The trait values of the four haplotypes are as follows:

	a	A
b	m	$m + d_A$
B	$m + d_B$	$m + d_A + d_B$

Let $d_A = d_B$. Thus, fitness coefficients of Ab and aB are equal, $l_{*2} = l_{*3}$. In the case of a constant environment, this system has been investigated by Feldman (1971). Consider first the case of a minus-concordant environment. Then, according to our previous results (Kirzhner et al., 1993, 1994a), for any trajectory, starting from some generation the linkage disequilibrium D will become negative. Thus, we can study just this part of any trajectory. From (1) one can easily obtain:

$$x'_2 - x'_3 = l_{*2}(x_2 - x_3)/W.$$

Hence, the relations $x_2 < x_3$, $x_2 > x_3$, or $x_2 = x_3$ are reproducing along the trajectory. Clearly, the first two cases are analogous, thus we consider only one of them, and the case of equality.

Let $x_2 < x_3$. Then, for each of the environmental states, the following inequality holds:

$$x'_2/x'_3 = (x_2 + rD)/(x_3 + rD) < x_2/x_3, \tag{12}$$

the equality being possible only when $D = 0$. Thus, either $x_2 \to 0$ or $D \to 0$, or simultaneously $x_2 \to 0$ and $D \to 0$. However, it follows from (1) that, if $x_2 \to 0$ at $r = 0$, then $D \to 0$ also. We can conclude that for each trajectory with $x_2 = x_3$ at the beginning, the population converges to the set $D = x_1x_4 - x_2x_3 = 0$, which is, therefore, invariant with respect to the evolutionary operator (1). On any element of this set, and at any environmental state, the evolutionary operator gives $l_{i1}l_{i4}x'_1x'_4 = x'_2x'_3$. Hence, $x_1x_4 = 0$ and $x_2x_3 = 0$, because of the condition of minus-concordance, the inequality $l_{i1}l_{i4} \neq 1$ holds at least for only one of the states. This results in fixation for one or both loci.

Now let $x_2 = x_3$. This set is invariant for the evolutionary operation. Fixation on this set goes, if at all, simultaneously at both loci. Indeed, let fixation be for locus A/a, e.g. allele a is lost. Then, $x_3 \equiv 0$ and $x_4 \equiv 0$ and, therefore, $x_2 \equiv 0$. Thus, only

$x_1 = 1$ could be stable from the subset of points belonging to the border set of the simplex. It can be shown, that for local stability of the point $x_1 = 1$ on the set $x_2 = x_3$, it is necessary that either,

$$L_1 \geq L_2, L_4 \quad \text{or} \quad L_2 < L_1 \leq L_4, \quad L_4(1-r)^p \leq L_1 \tag{13}$$

takes place. This condition will also be sufficient if non-rigorous inequalities are replaced by rigorous ones. The last statement can be proved analogously with Proposition 2. Indeed, provided $x_2 = x_3$, the evolutionary operator can be written as

$$x'_1 = l_1(x_1 - rD)/W, \quad x'_2 = l_2(x_2 + rD)/W, \quad x'_4 = l_4(x_4 - rD)/W\,.$$

From the normalization condition $x_1 + 2x_2 + x_4 = 1$, we have $x_2 = (1 - x_1 - x_4)/2$, so that it is sufficient to consider the evolutionary operator in the two-dimensional space (x_1, x_4). Clearly, vertex $x_1 = 1$ is a fixed point for all environmental states. For any state i, the Jacobian J_i at this point can be represented as

$$\begin{vmatrix} l_{2i}/l_{1i} & J_{i21} \\ 0 & l_{4i}(1-r)/l_{1i} \end{vmatrix},$$

where the concrete value of the element J_{21} is not important for our analysis. The Jacobian J of the product of the evolutionary operators along the period is $J = J_1 \cdots J_p$. Consequently, the eigenvalue of J is the product of the eigenvalues of Jacobians taken over the states. Therefore, we have the conditions

$$l_{21} \cdots l_{2p}/l_{11} \cdots l_{1p} = L_2/L_1 < 1\,,$$

$$l_{41} \cdots l_{4p}(1-r)^p/l_{11} \cdots l_{1p} = L_4(1-r)^p/L_1 < 1\,,$$

from which (13) immediately follows.

In the same manner one can show the stability of the point $x_4 = 1$ is within the set $x_2 = x_3$. We should recall that for minus-concordant environments the inequality $L_1L_4 - L_2L_2 < 0$ is true. Therefore, in minus-concordant environments, for cases of selection for additively acting genes with equal effects, only two types of inequalities are possible, either $L_1, L_4 < L_2$ or $L_4 < L_2 < L_1$. Clearly, mutual replacement of L_1 and L_4 results in an essentially equivalent situation.

Let $L_1, L_4 < L_2$ and, as before, $x_2 = x_3$. Then, according to (13), both points $x_1 = 1$ and $x_4 = 1$ will be repelling and no alleles will lost along the trajectory. The limiting behavior of the trajectories remains, in general unclear, while the analytical results for the particular case of a constant environment (Feldman, 1971), and our numerical experiments for cyclically changing environments, show that all the trajectories starting from this set converge to one fixed polymorphic point.

Now let $L_4 < L_2 < L_1$, which is compatible, as before, with the conditions of minus-concordance, and with selection for additive genes with equal effects. Then, according to the previous analysis for the case $x_2 = x_3$, the point $x_1 = 1$ is locally attracting. Numerical experients enable the assumption that $x_1 = 1$ is also globally stable. We can now formulate two statements concerning population behavior under cyclical selection for a trait controlled by two equal additive genes in sign-concordant environments.

Proposition 5a

The trajectory of the population in minus-concordant environments with an initial state $x_2 \neq x_3$ converges to the set $x_1 x_4 = 0$ and $x_2 x_3 = 0$, losing, therefore, at least one allele. With the initial point $x_2 = x_3$, polymorphism is maintained if $L_1 > L_2 = L_3, L_4$ or $L_2 = L_3 < L_1 < L_4$ and $L_4(1-r)^p < L_1$.

For plus-concordant environments an analogous statement can be formulated.

Proposition 5b

The population trajectory in plus-concordant environments converges to the set $x_2 = x_3$. In this case, either a lost of polymorphism at both loci ($x_2 = x_3 = 0 \Rightarrow x_1 = 1$ or $x_4 = 1$) or convergence to a polymorphic state (if the last one exists) in the set $x_2 = x_3$ is possible.

Proof of this Proposition is similar the previous one. Thus, only specific points characteristic to the considered situation should be mentioned here. According to our previous results (Kirzhner et al., 1993, 1994a), in plus-concordant environments with any trajectory, starting from some generation linkage disequilibrium D, will become positive. Thus, we can study just this part of any trajectory. In this case, the sign of the inequality (12) will be opposite, which means a growth of the ratio x_2/x_3 along the trajectory. This growth continues as long as $x_2 \neq x_3$ or $D \neq 0$. The assumption of $D \equiv 0$ along the trajectory leads to the condition $x_2 = x_3 = 0$, because $L_1 L_4 - L_2 L_3 > 0$ in plus-concordant environments. If $D \neq 0$, then $x_2 - x_3 \rightarrow 0$, so that in all cases the trajectory converges to the diagonal.

Now consider the diagonal $x_2 = x_3$ which is an invariant set of the operator (1) (for the case of equal gene effects). It is worth mentioning that in a plus-concordant environment the inequality $\max(L_1, L_4) > L_2 = L_3$ occurs. It follows from the Proof of Proposition 2, that at least one of the points $x_1 = 1$ or $x_4 = 1$ is locally stable provided that $\max(L_1, L_4) > L_2 = L_3$. It is clear, that if both points, $x_1 = 1$ and $x_4 = 1$, are locally stable, then an interior saddle point should exist. In our numerical experiments all of the trajectories have converged to one of the border points of the simplex (i.e. we have here the case $x_2 = x_3 = 0$).

In the case of zero-concordant environments, the sign of linkage disequilibrium D depends on the initial state of the trajectory (Kirzhner et al., 1993, 1994a). It has been shown above, that the limiting behavior of a trajectory depends on the sign of D along the trajectory. Thus, the behavior of any trajectory in zero-concordant environments should follows that of a plus- or minus-concordant environment.

Therefore, haploid selection for an additively formed trait in sign-concordant environments is unable to maintain polymorphism, with the exception of the set $x_2 = x_3$ but, the mode of allele loss depends on the "sign" of the environment. In the case of a minus-concordant environment only one of the two loci may become monomorphic, while in plus-concordant environments both loci go to fixation.

The difference between these two types of limiting behavior can be better illustrated in the following terms. Consider a sign-concordant environment with an infinite set of states. The environment could be referred to as a *controlled* one if the sequence of the states follows any predetermined rule. Then, for any rule, if the environment is minus-concordant, the population loses some alleles. This result can be easily obtained by analogy with the case of a cyclical environment. However, if the environment is plus-concordant, then polymorphism maintenance is possible. Indeed, if for some state the inequalities $l_1 > l_2, l_3, l_4$ hold, then the point $x_1 = 1$ is attracting. If in some other state $l_4 > l_1, l_2, l_3$, then the point $x_4 = 1$ will be attracting. It is clear, that by a suitable alternation of these two states one can protect polymorphism for an unlimited time. The situation considered above with a regulated environment could appear in a program of pest population control using two pesticides (e.g. Mani, 1985).

In conclusion, we note that the above results allow exclusion of situations where haploid two-locus selection caused by temporal fluctuations in the environment are unable to maintain polymorphism. On the other hand, the disturbance of the sign-concordance property is very promising in terms of polymorphism maintenance. Polymorphism may be expected in situations where "the amounts of selection" in plus- and minus-concordant states are more or less balanced within the period. The simplest example of such types of environmental changes is a two-state cyclical environment where in half of the period selection favours *AB* and *ab* haplotypes and in the other half *Ab* and *aB* are selected for, the intensity of selection being equal in both states (e.g., Sasaki and Iwasa, 1987). In this example, polymorphism exists and is even globally stable (see also Proposition 3). Further analysis of the effect of alternating plus- and minus-concordant environments has been done numerically.

Computer simulations

The experimental design

The above analysis showed that polymorphism maintenance due to haploid selection in fluctuating environment, if possible at all, could be expected only in sign-nonconcordant environments. These expectations were tested based on massive numerical experiments. For each of the considered class of systems the following approach was employed in order to analyze the effect of the key parameters on polymorphism:

(i) The first step was to define the class of systems to be studied, including parameters characterizing the mode of the changes in enviornmental states, and the fitness coefficients (see below).

(ii) Generating random or deterministic samples of systems of the defined class. Uniformly distributed parameter values were used for each of the permissible sets.

(iii) For each of the parameter combinations, the volume of the set of initial points resulting in polymorphic trajectories was calculated using uniformly distributed random starting points.

Results

Three types of systems were studied using this methodology: (1) a relatively general case of cyclical selection with a four-state environment; (2) the simplest system with two-state, sign-nonconcordant environment and; (3) a special case of selection in a three-state cyclical environment favouring consequently genotypes *AB* then *Ab* and *aB*, and finally *ab*.

Cyclical selection with a four-state environment

Let the cycle be of the following structure: $C = (S_1 t_1, S_2 t_2, S_3 t_3, S_2 t_2)$, where $S_i = \{s_{1i}, s_{2i}, s_{3i}, s_{4i}\}$ is a set of selection coefficients of the considered genotypes and t_i is the number of consecutive generations in the ith environment. The chosen condition, that the selection regime is the same in the 2nd and 4th states within the period, allows analysis of several groups of situations previously considered in the literature, and which have simple interpretations. Thus, we studied situations with increased t_1 and t_3 given fixed t_2, and increased t_2 given fixed t_1 and t_3. For each of these cases the size of a random sample from the space $S_1 \times S_2 \times S_3 \times r$ was 300,000 (recall that r is recombination rate between the selected loci). The range of uniformity distributed selection coefficients in our Monte-Carlo simulations was [0, 1], and that of $r \in [0, 0.5]$. Each sample was iterated numerically from 100 random initial points in order to estimate the size of any stable polymorphism attracting domains.

The above analysis (see Sections 1 and 2) indicates that sign-concordant environments are unfavorable from the point of view of polymorphism maintenance. This assumption was tested numerically for the considered class of four-state environments. In the parametric space 25% of the systems correspond to sign-concordant situations. For them, we could expect fixation in, at least, one of the loci. In fact, in all cases of sign-concordant environment such a fixation was observed. For this reason, all subsequent comparisons were made with the sign-nonconcordant class (225,000 systems for each type of environment).

The selection regime will be referred to as one of the Sturtevant-Mather's type (*SM*-type) if the linkage disequilibria of the favoured haplotypes (say, *Ab* and *aB*), in the states S_1 and S_3, are of the same sign and opposite to those in S_2 (*AB* and *ab*) (Sturtevant and Mather, 1938). The situation when haplotype *AB* is favoured in S_1, both *Ab* and *aB* in S_2, and *ab* in S_3, will be referred to as selection with moving optimum (or moving selection, *MS*-type), if the following ordering for the fitnesses holds: $AB > Ab, aB > ab$ in S_1; $Ab, aB > AB, ab$ in S_2; $ab > Ab, aB > AB$ in S_3. It is clear, that these two modes of classifications, being applied simultaneously, will give us four classes of systems: $SM\&MS$, $\overline{SM}\&\overline{MS}$, $\overline{SM}\&MS$ and $SM\&\overline{MS}$.

Two series of variation of the period structure were considered, starting from the situation with equal longitudes ($t_i = 2$) of the four environmental states. In the first series, we consequently extended the proportion of longitudes t_2 and t_4 with identical selection regime (thereby making the environment more stable), while in the second series the longitudes of states with unequal selection regimes (t_1 and t_3) are extended. In other words, for any period length, the diversity of "environmental challenges" to the genetic pool in the second series is higher than in the first one. Table 1 shows the proportion of polymorphic cases among each of the four types of selection regimes ($SM\&MS$, $\overline{SM}\&\overline{MS}$, $\overline{SM}\&MS$, and$SM\&\overline{MS}$), and along all systems. As expected, polymorphic systems are more frequent in the second series.

As mentioned above, the simulated systems were cross-classified according to two types of selection. It can be seen from the results presented in Table 1 that moving selection is the most effective for polymorphism maintenance in more diverse environments (second series). Namely, within this type of system, the proportion of polymorphic cases is much higher than in the whole set. In the first series, where the environment is more stable, the proportion of polymorphic cases follows the average observed in the whole set.

The distribution of the recombination rates for the systems which where polymorphic is presented in Fig. 1. For the first series a tendency to a bimodality in

Table 1. Proportion of polymorphic cases among four classes of cyclical selection regimes as a function of the period structure.

Environment				Proportion of polymorphic regimes (%)				
t_1	t_2	t_3	t_2	Among all systems	Within the type			
					$\overline{SM}\&\overline{MS}$	$\overline{SM}\&MS$	$SM\&\overline{MS}$	$SM\&MS$
Series 1								
2	2	2	2	0.33	0.36	0.18	0.19	0.87
2	4	2	4	0.28	0.28	0.18	0.25	0.00
2	6	2	6	0.19	0.18	0.00	0.23	0.00
2	8	2	8	0.14	0.13	0.00	0.19	0.00
2	12	2	12	0.07	0.07	0.00	0.07	0.00
Series 2								
2	2	2	2	0.33	0.36	0.18	0.19	0.87
4	2	4	2	1.05	1.18	1.83	0.38	0.00
6	2	6	2	1.42	1.63	2.74	0.35	0.00
8	2	8	2	1.45	1.69	2.74	0.26	0.00
12	2	12	2	1.16	1.35	1.83	0.16	0.00

The values t_i ($i = 1, \ldots, 4$) stand for the number of generations in the ith environmental state within the period. SM and MS denote selection regimes of the Sturtevant-Mather and moving optimum types, respectively. The upper lines marks the absence of the respective property. The two series of experiments correspond to a consequent elongation of a certain part of the cycle.

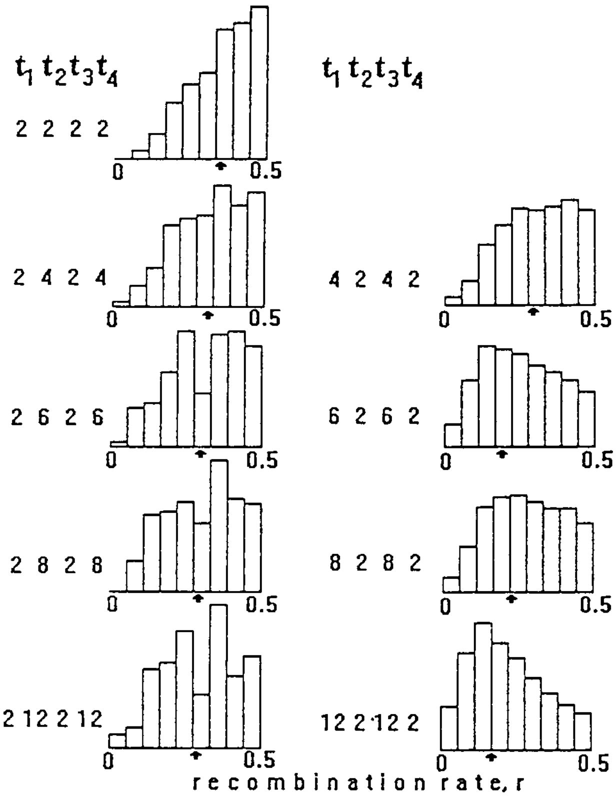

Fig. 1. The distribution of the recombination rate (r) in haploid two locus systems where cyclical selection results in stable polymorphism as a function of the period structure. The values t_i ($i = 1, \ldots, 4$) stand for the number of generations in the ith environmental state within the period. The mean value of r is marked by arrows on the axis r.

distribution could be seen with increased period length, the mean value of r decreased from 0.35 to 0.30. In the second series the distribution is unimodal with mean r decreasing from 0.35 to 0.22.

A system with two-state sign-nonconcordant environments

A two-state environment with fitness coefficients of genotypes *AB*, *Ab*, *aB*, and *ab* being 1, q_2, q_3, 1 in the first state and q_2, 1, 1, q_3 in the second one ($q_2, q_3 \leq 1$) was studied. Here, the coefficient of integral fitness disequilibrium is zero and the system is close to the model considered by Sasaki and Iwasa (1987). If $q_2 = q_3$ then, according to Proposition 3, the system has a globally stable polymorphism (see also Appendix A from Sasaki and Iwasa, 1987). It is reasonable to assume that the system is structurally stable, i.e. small deviations from the above conditions will not disturb

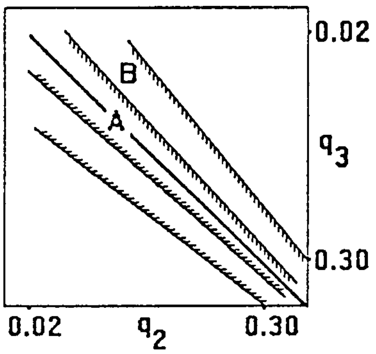

Fig. 2. Dependence of the size of the selection parameter domain corresponding to polymorphism maintenance by seasonal (alternating) changes in fitness coefficients: $(1, q_2, q_3, 1)$ in one season, and $(q_2, 1, 1, q_3)$ in the other, for haplotypes *AB*, *Ab*, *aB*, and *ab*, respectively. Domain *A* corresponds to recombination $r = 0.3$, while the broader domain *B* corresponds to $r = 0.5$.

the stability (at least not the local one). Our numerical studies are an attempt to estimate how large these deviations could be at different recombination values (r). We found that for each r the set of polymorphic systems corresponds in the space of parameters $q_2 \times q_3$ to some domain which is symmetric with respect to the diagonal $q_2 = q_3$. Figure 2 shows the results obtained for $r = 0.3$ (domain *A*) and $r = 0.5$ (domain *B*) for selection coefficients in the range 0.02–0.30. It is clear, that with increasing selection intensity or recombination rate the level of asymmetry compatible with polymorphism is also increasing.

Moving selection in a three-state environment (favoring genotypes AB; Ab and aB; and ab).

This class of situations could be considered as a special case of moving selection. The selection regime was defined by the formula (S_1t_1, S_2t_2, S_3t_3), where $S_1 = (1, q, q, q)$, $S_2 = (q, 1, 1, q)$, $S_3 = (q, q, q, 1)$, $q < 1$. For the results presented in Fig. 3 the following structure of the period was used: $t_1 = t_3 = 3$, $t_2 = 6$. It can easily be seen that with relaxed selection the size of the polymorphism attracting domain (v) is decreasing. The effect of recombination is non-linear: for every value of q (from some range $q_1 < q < q_2$) a pair of recombination rates r_1, r_2 can be found such that polymorphism is absent outside the interval $r_1 < r < r_2$ ($v = 0$) while within the interval $0 < v \leq 1$. For the chosen t_1, t_2, and t_3, we estimated that $q_1 \approx 0.3$ and $q_2 \approx 0.56$. It is clear that if selection is too weak, ($q > q_2$) polymorphism is impossible at any recombination rate. With strong enough selection ($q < q_1$) polymorphism is globally stable at any recombination rate. It is noteworthy that, selection intensity in nature is usually much weaker, but strong selection can not be considered as an exclusion (Ford, 1971).

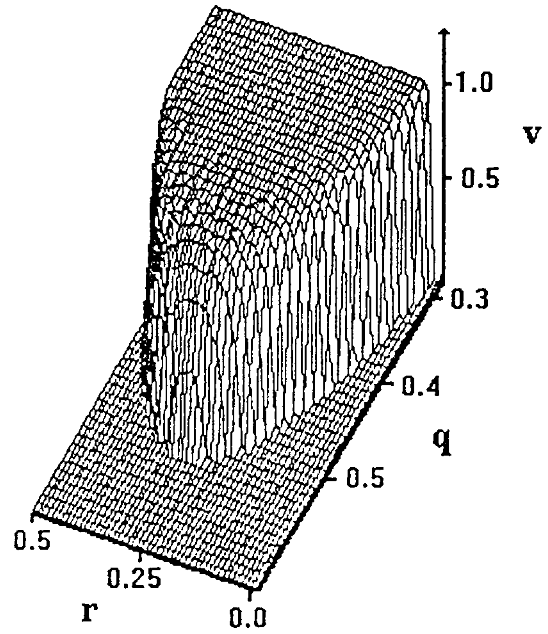

Fig. 3. The dependence of the volume (v) of the interior attracting set on selection intensity (q) and recombination rate (r) in a three-state cyclic environment. The sets of fitness coefficients of the four haplotypes are ($q, q, q, 1$), ($q, 1, 1, q$), and ($1, q, q, q$) ($0 \leq q \leq 1$), for the states 1, 2, and 3, respectively. If most of the trajectories are converging to the interior of the symplex, then v is close to unity. If most of the trajectories go to the border set, than v is close to zero. The Figure represents the results of estimation of v based on 500 random runs for each combination of the parameters.

Discussion

Haploid selection models are of special interest in evaluating putative factors promoting polymorphism in nature. This is due to the fact that these can be considered as pure models without any hidden form of heterozygote advantage. Fluctuating environment may, in principle, maintain polymorphism due to diploid selection as well (Haldane and Jayakar, 1963; Hedrick, 1986; Korol et al., 1993, 1994; but see Lande, 1976). However, to better understand the effect of interactions between recombination and fluctuating selection on polymorphism, haploid models are preferable because they are simpler and independent of heterosis for fitness. It is worthwhile to recall that cyclical haploid selection in the one-locus case can produce only neutral polymorphism (Nagylaki, 1975; Hendrick, 1978).

In addition to the problem of polymorphism maintenance, analysis of fluctuating haploid selection could be of interest for studies in other fields, for example recombination evolution (e.g. Sasaki & Iwasa, 1987) and evolution of life cycles (haploidy-diploidy). The last problem has been considered in terms of selection against harmful mutations (Kondrashov and Crow, 1991; Perrot et al., 1991), the selection in constant environments (Jenkins, 1993). However, fluctuating selection, acting simultaneously at the haploid and diploid level, could also play an important role in the evolution of the life cycle (Nevo et al., in preparation).

In the first part of this paper we have studied some general conditions for polymorphism stability in haploid, two-locus cyclical selection models. As a basic system we also considered general haploid selection in constant environments. For the latter case we showed that no more than one fixed polymorphic point could exist; a criterion for the existence of such a point was obtained, and the coordinates of the fixed point were found. Based on numerical analysis of the spectrum of linear approximation, it can be shown that a real eigenvalue exceeding unity always exists (with exception of special neutral cases, e.g. when all selection coefficients are equal to each other).

Therefore, it is clear, that polymorphism stability in temporarily changing environments (if it exists at all) is precisely the result of environmental variation, i.e. it can not be a "relic" of selection in a constant environment. However, in haploid systems with non-overlapping generations, polymorphism produced by changing environments can be globally stable. Indeed, according to Proposition 2, the necessary conditions for global stability are equalities. These conditions hold for the haploid model of selection regime of Sturtevant-Mather's type (for example, Sasaki and Iwasa, 1987). These conditions can also be sufficient, as shown in our Proposition 3. Proposition 2 practically precludes the existence of global stability of polymorphism. However, the internal stable equilibrium point is, to some extent, structurally stable (see Iwasa and Sasaki, 1987; and our simulation results in Section 3.2).

It was shown that in models with variable selection, the fitness functions usually used in the literature lead to a class of environmental changes which could be named as sign-concordant (Kirzhner et al., 1993, 1994a). For this class, the above considered necessary conditions for existence of a fixed point (Proposition 4) are close to analogous conditions for the case of a constant environment (which, in this situation, are also sufficient ones).

Consider a situation, where sign-concordant environmental selection occurs for a trait controlled by two additive genes with equal effects. In the case of minus-concordant environments we found no polymorphism for most of the trajectories. The only exceptions are the trajectories starting (and remaining) in the diagonal $x_2 = x_3$ (note also that the diagonal is a repeller for the trajectories starting outside of it). For plus-concordant environments, the diagonal $x_2 = x_3$ is an attracting set. However, numerical analysis shows that the system goes to fixation along the diagonal.

Therefore, we conclude, that the phase space of the population in fluctuating sign-concordant environments looks like that of constant selection. Even if it has a fixed point, this point is unstable. This conclusion was confirmed in our massive numerical experiments. Polymorphism, if possible at all, can be found in sign non-concordant environments where the effects of states with opposite signs are "balanced" within the environmental cycle.

Theoretical considerations in the first part of paper help to exclude the class of situations where stable polymorphism is impossible. Thus, we had to check, if polymorphism could exist in the remainder, presumably more perspective, class of systems (with sign non-concordant environments). This was done by numerical modelling. The results presented in the second part of the paper are concerned with polymorphism maintenance in two special cases, and one more general situation. The last one includes, among other regimes, selection with moving optimum and selection of the Sturtevant-Mather type. Polymorphism was found in all four types of the considered selection regimes, but the proportion of polymorphic systems depends on how the opposite selection tendencies are balanced within the period. In the special case of "non-Sturtevant-Mather, but moving selection" type, the proportion of polymorphic regimes is much higher than in the general case.

An important role of the recombination rate in polymorphism maintenance should be stressed. The distribution of the recombination rate among the systems which occurred to be polymorphic depends on the period structure and length: the less variable are the environmental conditions (e.g. due to increased period length) the lower is the recombination rate compatible with polymorphism.

In case (2) of two-state environment, with selection of Sturtevant-Mather type, recombination level is also critical for polymorphism maintenance: the higher r, the larger the size of the polymorphism attracting domain (see Fig. 2). Recall, that symmetric versions of this haploid selection regime were also considered earlier by Sasaki and Iwasa (1987).

In case (3) of moving selection we also have an appreciable proportion of polymorphic systems. And here again, the existence of polymorphism depends on r: for every level of selection intensity a pair of recombination values r_1, r_2 can be found such that polymorphism is possible only within the interval $r_1 < r < r_2$.

Strong dependence of the behavior of two- or multilocus systems on recombination has been found in different studies. Thus, Lewontin (1974) established for symmetric viability diploid selection (in constant environment) the existence of a critical value $r = r^*$ such that for $r > r^*$ the population reaches asymptotically linkage equilibrium $D_\infty = 0$ while for $r < r^*$ $D_\infty \neq 0$. Moreover, Ewens (1968) found that for some selection regimes the range of r values ($0 \leq r \leq 0.5$) is even non-continuous and could include more than one subinterval corresponding to $D_\infty \neq 0$ (Ewens, 1968).

These facts, as well as many other models showing the qualitative importance of recombination in the two locus system behavior are, to an extent, in contrast with some multilocus models assuming weak selection (e.g., Lande, 1976). Lande (1976) showed that weak diploid selection with a fluctuating optimum does not help in maintenance of polymorphism for additive genes. Our findings could be considered as complementary to these results. We demonstrated that with strong enough selection and some restrictions on recombination, fluctuating selection can result in stable polymorphism with a quite large volume of the polymorphism attracting domain. This result also hold in the case of diploid selection (Korol et al., 1993, 1994).

Acknowledgements

We acknowledge with thanks the support of the Israeli Ministry of Science (grant No 3675-1-91), the Institut Alain de Rothschild and the Wolfsen Family Charitable Trust. The authors are very grateful to the referees for their comments and suggestions which helped to clarify many important questions.

References

Clarlesworth, B. 1976. Recombination in a fluctuating environment. Genetics 83: 181–195.

Ewens, J. W. 1968. A genetic model having complex linkage behavior. Theor. Appl. Genet. 38: 140–143.

Ewing, E. P. 1979. Genetic variation in a heterogeneous environment. VII. Temporal and spatial heterogeneity in infinite population. Am. Nat. 114: 197–212.

Feldman, M. W. 1971. Equilibrium studies of two locus haploid populations with recombination. Theor. Popul. Biol. 2: 299–318.

Felsenstein, J. 1976. The theoretical population genetics of variable selection and migration. Ann. Rev. Genet. 10: 253–280.

Ford, E. B. 1971. Ecological Genetics, 3rd edn. Chapman & Hall, London.

Gillespie J. and C. Langley. 1976. Multilocus behavior in random environments. I. Random Levene models. Genetics 82: 123–137.

Haldane, J. B. S. and S. D. Jayakar. 1963. Polymorphism due to selection of varying direction. J. Genet. 58: 237–242.

Hedrick, P. W. 1978. Genetic variation in heterogeneous environments. V. Spatial heterogeneity in finite populations. Genetics 89: 389–401.

Hedrick, P. W., M. E. Ginevan and E. P. Ewing. 1976. Genetic polymorphism in heterogeneous environments. Ann. Rev. Ecol. Syst. 7: 1–32.

Hedrick, P. W. 1986. Genetic polymorphism in heterogeneous environments: A decade later. Ann. Rev. Ecol. Syst. 17: 535–566.

Jenkins, C. D. 1993. Selection and the evolution of genetic life cycles. Genetics 133: 401–410.

Karlin, S. and Levikson, B. 1974. Temporal fluctuation in selection intensities. Case of small population size. Theor. Popul. Biol. 7: 94–122.

Kirzhner, V. M., A. B. Korol and Y. I. Ronin. 1993. The dynamics of linkage disequilibrium under temporal environmental fluctuations. Two-locus selection. *In* Evolution 93 (Abstracts, the 4th Congr. Europ. Soc. Evol. Biol.) Montpellier (France), p. 219.

Kirzhner V. M., A. B. Korol and Y. I. Ronin. 1994a. The dynamics of linkage disequilibrium under temporal environmental fluctuation. Two-locus selection. Theor. Pop. Biol., in press.

Kirzhner, V. M., A. B. Korol, Y. I. Ronin and E. Nevo. 1994b. Cyclical like behavior of genotype frequencies in a two-locus population under fluctuating haploid selection. Proc. Natl Acad. Sci. USA 91 (in press).

Kondrashov, A. S. and J. F. Crow. 1991. Haploidy or diploidy: which is better? Nature 351: 314–315.

Korol, A. B., V. M. Kirzhner and Y. I. Ronin. 1993. Polymorphism caused by stabilizing selection with cyclically changing optimum. *In* Evolution 93 (Abstracts of the 4th Congr. Europ. Soc. Evol. Biol.) Montpellier (France), Univ. Montpellier II, p. 229.

Korol, A. B., I. A. Preygel and S. I. Preygel. 1994. Recombination Variability and Evolution. Chapman & Hall.

Lande, R. 1976. The maintenence of genetic variability by mutation in a polygenic character with linked loci. Genet. Res. 26: 221–235.

Levene, H. 1953. Genetic equilibrium when more than one ecological niche is available. Am. Nat. 87: 331–333.

Lewontin, R. C. 1974. The Genetic Basis of Evolutionary Change. Columbia University Press, New York.

Maynard Smith, J. 1988. The evolution of recombination, pp. 106–125. *In* R. E. Michod and B. R. Levin (eds.), The Evolution of Sex: An Examination of Current Ideas. Sinauer Associates, Sunderland, MA.

Mani, G. S. 1985. Evolution of resistance in the presence of two insecticides. Genetics 109: 761–783.

Nagylaki, T. 1975. Polymorphisms in cyclically-varying environments. Heredity 35: 67–74.

Perrot, V., S. Richerd and M. Valero. 1991. Transition from haploidy to dipoloidy. Nature 351: 315–317.

Sasaki, A. and Y. Iwasa. 1987. Optimal recombination rate in fluctuating environments. Genetics 115: 377–388.
Sturtevant, A. H. and K. Mather. 1938. The interrelations of inversions, heterosis and recombination. Am. Nat. 72: 447–452.

Received 24 November 1993;
accepted 6 June 1994.
Corresponding Editor: Y. Iwasa

Appendix 1

Proof of Proposition 1. Let us consider the process of transition from one generation to the next as the successive action of two operators – (a) random mating followed by crossing over, and (b) selection; as described by the following transformation:

$$\tilde{x}_1 = \hat{x}_1 - r\hat{D}, \quad \tilde{x}_4 = \hat{x}_4 - r\hat{D}, \quad \tilde{x}_2 = \hat{x}_2 + r\hat{D}, \quad \tilde{x}_3 = \hat{x}_3 + r\hat{D}, \tag{a}$$

$$\hat{x}'_1 = l_1\tilde{x}_1/L, \quad \hat{x}'_2 = l_2\tilde{x}_2/L, \quad \hat{x}'_3 = l_3\tilde{x}_3/L, \quad \hat{x}'_4 = l_4\tilde{x}_4/L, \tag{b}$$

where, $L = l_1\tilde{x}_1 + l_2\tilde{x}_2 + l_3\tilde{x}_3 + l_4\tilde{x}_4$.

At the initial state the population is characterized by a vector $\hat{x}$, which is transformed by the above two operators, (a) and (b), into $\tilde{x}$ and $\hat{x}$, consequently.

It is clear, that operator (a) does not change allele frequencies. Therefore, for stability of a polymorphic point it is necessary that the selection operator (b) does not change allele frequencies at this point.

Lemma A1

The set of population states with unchanged allele frequencies after the selection operator has the form,

$$\begin{aligned} x_1 &= -\mu_2\mu_3\mu_4/\delta(L), \quad x_2 = \mu_1\mu_3\mu_4/\delta(L), \\ x_3 &= \mu_1\mu_2\mu_4/\delta(L), \quad x_4 = -\mu_1\mu_2\mu_3/\delta(L), \end{aligned} \tag{1A}$$

where,

$$\delta(L) = -\mu_2\mu_3\mu_4 + \mu_1\mu_3\mu_4 + \mu_1\mu_2\mu_4 - \mu_1\mu_2\mu_3, \quad \mu_i = l_i - L,$$

if one of the following alternative inequalities holds:

$$l_1, l_4 \geq L \geq l_2, l_3 \quad \text{or} \quad l_1, l_4 \leq L \leq l_2, l_3.$$

Proof

The population state $\tilde{x} = (\tilde{x}_1, \tilde{x}_2, \tilde{x}_3, \tilde{x}_4)$ with unchanged allele frequencies after the selection operator action, should obey the equations,

$$l_1\tilde{x}_1 + l_2\tilde{x}_2 = L(\tilde{x}_1 + \tilde{x}_2), \quad l_1\tilde{x}_1 + l_3\tilde{x}_3 = L(\tilde{x}_1 + \tilde{x}_3),$$

$$l_2\tilde{x}_2 + l_4\tilde{x}_4 = L(\tilde{x}_2 + \tilde{x}_4), \quad l_3\tilde{x}_3 + l_4\tilde{x}_4 = L(\tilde{x}_3 + \tilde{x}_4),$$

or, (2A)

$$\mu_1\tilde{x}_1 + \mu_2\tilde{x}_2 = 0, \quad \mu_1\tilde{x}_1 + \mu_3\tilde{x}_3 = 0\,,$$
$$\mu_2\tilde{x}_2 + \mu_4\tilde{x}_4 = 0, \quad \mu_3\tilde{x}_3 + \mu_4\tilde{x}_4 = 0\,,$$

where $\mu_i = l_i - L$. It follows from (2A), that each of the products $\mu_1\mu_2$, $\mu_1\mu_3$, $\mu_2\mu_4$, and $\mu_3\mu_4$ should be negative, assuming that all of the haplotype frequencies are positive. Because of symmetry, it is enough to consider the case when l_1 has the largest fitness. It is clear that in this case $\mu_1 > 0$, so that $\mu_2 < 0$, which also leads to $\mu_4 > 0$ and therefore, $\mu_3 < 0$. Thus, if l_1 is the largest among selection coefficients, then $l_1 \geq l_4 \geq L \geq l_2, l_3$.

Using similar considerations we can easily obtain the necessary conditions for the existence of a positive solution to the system (2A) for a general case given either of the two following conditions: $l_1, l_4 \geq L \geq l_2, l_3$ or $l_1, l_4 \leq L \leq l_2, l_3$. Note, that the system (2A) is degenerated and the last equation of (2A) may be replaced by the normalization condition in the simplex, i.e.:

$$\mu_1 x_1 + \mu_2 x_2 = 0, \quad \mu_1 x_1 + \mu_3 x_3 = 0, \quad \mu_2 x_2 + \mu_4 x_4 = 0,$$
$$x_1 + \cdots + x_4 = 1\,. \tag{3A}$$

The solution of this system is,

$$\tilde{x}_1 = -\mu_2\mu_3\mu_4/\delta(L), \quad \tilde{x}_2 = \mu_1\mu_3\mu_4/\delta(L)\,,$$
$$\tilde{x}_3 = \mu_1\mu_2\mu_4/\delta(L), \quad \tilde{x}_4 = -\mu_1\mu_2\mu_3/\delta(L)\,,$$

where,

$$\delta(L) = -\mu_2\mu_3\mu_4 + \mu_1\mu_3\mu_4 + \mu_1\mu_2\mu_4 - \mu_1\mu_2\mu_3, \quad \mu_i = l_i - L\,. \tag{4A}$$

The solution depends on the parameter L, and the value L is a function of variables $\tilde{x}$:

$$L = l_1\tilde{x}_1 + l_2\tilde{x}_2 + l_3\tilde{x}_3 + l_4\tilde{x}_4\,.$$

Indeed, it follows from (4A) that

$$L \equiv -(l_1 - L + L)\mu_2\mu_3\mu_4/\delta(L) + (l_2 - L + L)\mu_1\mu_3\mu_4/\delta(L)$$
$$+ (l_3 + L + L)\mu_1\mu_2\mu_4/\delta(L) - (l_4 - L + L)\mu_1\mu_2\mu_3/\delta(L)\,.$$

Therefore, (4A) determines a one-parametric set (a curve) in the space of population states, each point of which is transformed by the selection operator without changing allele frequencies.

The solution 4A is valid only if $\delta(L) = 0$. Clearly, $\delta(L)$ is a polynomial of the third degree of L. Without loss of generality, we assume, that $l_1 \geq l_4 \geq l_2 \geq l_3$. The last ordering correspondings to Lemma A1 and because of symmetry it may be considered as a general one. It is easy to see that $\delta(l_1)$, $\delta(l_3) \geq 0$, $\delta(l_4)$, $\delta(l_2) \leq 0$. By taking into account the ordering of l_i, one can check that nowhere within the interval (l_4, l_2), is $\delta(L)$ zero. Thus, (4A) is always valid. The population states defined in accordance to Lemma A1 satisfy the necessary conditions for an internal fixed point. In order to get the sufficient conditions, let us now apply the mating and selection operators to the same states. Then,

$$\hat{x}_1 = -l_1\mu_2\mu_3\mu_4/(L\delta(L)), \quad \hat{x}_2 = l_2\mu_1\mu_3\mu_4/(L\delta(L)),$$
$$\hat{x}_3 = l_3\mu_1\mu_2\mu_4/(L\delta(L)), \quad \hat{x}_4 = -l_4\mu_1\mu_2\mu_3/(L\delta(L)),$$
$$L = (-l_1\mu_2\mu_3\mu_4 + l_2\mu_1\mu_3\mu_4 + l_3\mu_1\mu_2\mu_4 - l_4\mu_1\mu_2\mu_3/\delta(L)$$

and

$$\tilde{x}_1 = -l_1\mu_2\mu_3\mu_4/(L\delta(L)) - rD, \quad \tilde{x}_2 = l_2\mu_1\mu_3\mu_4/(L\delta(L)) + rD,$$
$$\tilde{x}_3 = l_3\mu_1\mu_2\mu_4/(L\delta(L)) + rD, \quad \tilde{x}_4 = -l_4\mu_1\mu_2\mu_3/(L\delta(L)) - rD, \qquad (5A)$$
$$D = \mu_1\mu_2\mu_3\mu_4(l_1l_4\mu_2\mu_3 - l_2l_3\mu_1\mu_4)/(L\delta(L))^2.$$

If the considered point is a fixed one, then the value $\tilde{x}$ is determined by the relations in (4A), so that from (4A) and (5A) we obtain,

$$-\mu_2\mu_3\mu_4/\delta(L) = -l_1\mu_2\mu_3\mu_4/(L\delta(L)) - rD,$$
$$\mu_1\mu_3\mu_4/\delta(L) = l_2\mu_1\mu_3\mu_4/(L\delta(L)) + rD,$$
$$\mu_1\mu_2\mu_4/\delta(L) = l_3\mu_1\mu_2\mu_4/(L\delta(L)) + rD,$$
$$-\mu_1\mu_2\mu_3/\delta(L) = -l_4\mu_1\mu_2\mu_3/(L\delta(L)) - rD.$$

Each of the last four relations can be transformed into the following equation for L:

$$\mu_1\mu_2\mu_3\mu_4[L\delta(L) + r(l_1l_4\mu_2\mu_3 - l_2l_3\mu_1\mu_4)] = 0 \qquad (6A)$$

The solutions of (6A) from the interval determined by the inequalities of Lemma A1 give the fixed values for the dynamic system (1). It has been assumed earlier that $l_1 \geq l_4 \geq l_2 \geq l_3$. However, it is clear that this assumption does not effect the generality of our consideration. According to Lemma A1 it is necessary to find the roots of (6A) in the range $l_2 \leq L \leq l_4$. However, the values $L = l_2, l_4$ are irrelevant because these solutions correspond, in accordance with (A1), to fixed states with no polymorphism. Thus, we should find the roots of the polynomial

$$P(L) = L\delta(L) + r(l_1l_4\mu_2\mu_3 - l_2l_3\mu_1\mu_4) = 0 \qquad (7A)$$

For analysis it is convenient to transform $P(L)$ to the form,

$$l_1l_4\mu_2\mu_3 - l_2l_3\mu_1\mu_4 = l_1l_4(l_2 - L)(l_3 - L) - l_2l_3(l_1 - L)(l_4 - L)$$
$$= L[L(l_1l_4 - l_2l_3) - \delta(0)],$$
$$\delta(L) = L^2(l_1 - l_2 - l_3 + l_4) - 2L(l_1l_4 - l_2l_3) + \delta(0),$$
$$\delta(0) = -l_2l_3l_4 + l_1l_3l_4 + l_1l_2l_4 - l_1l_2l_3.$$

Then, from (7A) we obtain,

$$P(L) = L\{(L^2(l_1 - l_2 - l_3 + l_4) + \delta(0)(1 - r)) - (2 - r)L(l_1l_4 - l_2l_3)\} = 0. \qquad (8A)$$

Therefore, polynomial $P(L)$ has the root $L = 0$ as well as others. Using (7A) we note

$$
\begin{aligned}
P(l_1) &= -l_1(l_2 - l_1)(l_3 - l_1)(l_4 - l_1) + r(l_1 l_4(l_2 - l_1)(l_3 l_1)),\\
P(l_2) &= l_2(l_1 - l_2)(l_3 - l_2)(l_4 - l_2) + r(-l_2 l_3(l_1 - l_2)(l_4 l_2)),\\
P(l_3) &= l_3(l_1 - l_3)(l_2 - l_3)(l_4 - l_3) + r(-l_2 l_4(l_1 - l_3)(l_4 l_3)),\\
P(l_4) &= -l_4(l_1 - l_4)(l_2 - l_4)(l_3 - l_4) + r(l_1 l_4(l_2 - l_4)(l_3 l_4)).
\end{aligned}
$$

At $r = 0$ $P(l_1) > 0$, $P(l_4) < 0$ and $P(l_2) < 0$, $P(l_3) > 0$, so that the non-zero roots are in the intervals (l_1, l_4) and (l_2, l_3), but outside of the demanded interval $l_2 \le L \le l_4$. An increase in r does not affect the sign of $P(l_2)$, but it may change the sign of $P(l_4)$, resulting in appearance of the root in the interval (l_4, l_2). The second root should always be in the interval $(l_2, -\infty)$, because in this interval the sign of the polynomial $P(L)$ is changed from $-$ to $+$. Therefore, we can consider the following inequality as a criterion for existence of a suitable root:

$$P(l_4) = -l_4(l_1 - l_4)(l_2 - l_4)(l_3 - l_4) + r(l_1 l_4(l_2 - l_4)(l_3 - l_4)) > 0$$

or,

$$-(l_1 - l_4) + r(l_1) > 0,$$

so that $r > (l_1 - l_4)/l_1$. Using (8A) we can find a corresponding root L:

$$
\begin{aligned}
L = \{&(2 - r)(l_1 l_4 - l_2 l_3) + \sqrt{}([(2 - r)(l_1 l_4 - l_2 l_3)]^2\\
&- 4(l_1 - l_2 - l_3 + l_4)\delta(0)(1 - r))\}/(2(l_1 - l_2 - l_3 + l_4))
\end{aligned}
\tag{9A}
$$

These calculations together with Lemma A1 prove Proposition 1.

Appendix 2

Proof of Proposition 2

We shall consider Jacobian J of system (1) in the vertex $x_1 = 1$ of simplex Σ, assuming variables x_1, x_2, x_4 are independent and $x_3 = 1 - x_1 - x_2 - x_4$:

$$
\begin{vmatrix}
l_2/l_1 & * & * \\
0 & l_3/l_1 & * \\
0 & 0 & (1 - r)l_4/l_1
\end{vmatrix},
\tag{10A}
$$

where the asterisk stays for some elements of Jacobian. It is clear, to a first approximation, that the vertex $x_1 = 1$ of the simplex is stable if either l_1 is the largest fitness $(l_1 > l_2, l_3, l_4)$, or $l_4 \ge l_1 > l_2, l_3$ and simultaneously $(1 - r)l_r/l_1 < 1$.

Let population evolution occur in an environment with p states, alternating in any order within a period of the length p (the order not necessarily being the same across periods). Then, at the end of a period the linear approximation at the vertex

$x_1 = 1$ of simplex Σ is a product of approximations of the form (10A): $J = J_1 J_2 \cdots J_p$. Hence, the values,

$$\begin{aligned} &l_{12}l_{22}\cdots l_{p2}/l_{11}l_{21}\cdots l_{p1} = L_2/L_1\,, \\ &l_{13}l_{23}\cdots l_{p3}/l_{11}l_{21}\cdots l_{p1} = L_3/L_1 \end{aligned} \qquad (11A)$$

and

$$(1-r)^p l_{14}l_{24}\cdots l_{p4}/l_{11}l_{21}\cdots l_{p1} = (1-r)^p L_4/L_1$$

are eigenvalues of the Jacobian J. Then, the form of the spectrum of linear approximation and the above inequalities give proof for Proposition 2.

Appendix 3

Proof of Proposition 3

According to (1), the evolutionary equations connecting two consecutive periods can be written as

$$\begin{aligned} x_1'' &= L_1 x_1/W'W - L_1 rD'/W'W - l_{11}rD/W\,, \\ x_2'' &= L_2 x_2/W'W + L_2 rD'/W'W + l_{12}rD/W\,, \\ x_3'' &= L_3 x_3/W'W + L_3 rD'/W'W + l_{13}rD/W\,, \\ x_4'' &= L_4 x_4/W'W - L_4 rD'/W'W - l_{14}rD/W\,. \end{aligned} \qquad (12A)$$

The variables characterizing the "omitted" generation are marked by stroke. It follows from (12A) that

$$1 = C/W'W + (-l_{11} + l_{12} + l_{13} - l_{14})rD/W\,. \qquad (13A)$$

It is worth noting that $\delta = 0$ and, according to Kirzhner et al. (1993, 1994a), along any trajectory sign(D) acquires an invariable sign for a finite number of steps, i.e. plus in one environmental state and minus in the other. More specifically, a positive sign of D is found when $l_{11} = l_{14} = 1$, and $l_{12} = l_{13} = C$, and a negative sign for D in the alternative state.

Consider a trajectory after sign stabilization. Let us assume, that we began with a state where $D \geq 0$. Then, from (13A) it follows $1 = C/W'W + (2C-2)D/W$, so that $C/W'W \leq 1$. The last inequality is strict if $D = 0$. We also assume that in the initial state $x_1 \geq x_4$ and $x_2 \geq x_3$. It is easy to see that these relations along the trajectory do not change. The last fact follows from (12A). Namely,

$$0 \leq x_2'' - x_3'' = (x_2 - x_3)C/W'W, \quad 0 \leq x_1'' - x_4'' = (x_1 - x_4)C/W'W\,.$$

Therefore, the consecutive values of $x_2 - x_3$, as well as $x_1 - x_4$, decrease along the trajectory (across periods). If in the initial state none of x_i is zero, then

$$0 \leq x_2 - x_3 < q_1 < 1, \quad 0 \leq x_1 - x_4 < q_2 < 1, \quad q_1 + q_2 < 1 \qquad (14A)$$

and these inequalities will remain along the trajectory. It follows from this, that extinction of alleles is impossible. Indeed, fixation at both loci (i.e. either $x_1 = 1$ or

$x_2 = 1$) contradicts to the inequalities (14A). If only one allele is lost, then $x_3 = x_4 = 0$ and $x_1 + x_2 = 1$, which also contradicts (14A).

It is easy to show that if there is no extinction of alleles, the surface $D = 0$ is not invariant for the operator (1). Indeed, for some generations let $D = 0$. According to (12A), D'' can be presented in the form

$$D'' = c^2[(x_1 - rD')(x_4 - rD') - (x_2 + rD')(x_3 + rD')]/WW' ,$$

so that,

$$D'' = c^2[D - rD']/WW' = c^2[-rD']/WW' , \tag{15A}$$

because $D = 0$. Therefore, if $D'' = 0$, then D' should also be zero. However, for $C > 1$ and $x_i > 0$, the variables $D' = C^2 x_1 x_4 - x_2 x_3$ and $D = x_1 x_4 - x_2 x_3$ can not be equal to zero simultaneously. Thus, if $D = 0$, then $D'' \neq 0$. Now consider an arbitrary trajectory and the set of the limiting states of the population. The differences $x_1 - x_4$ (as well as $x_2 - x_3$) will be equal for all elements of this limiting set, because they are not increasing along the trajectory. On the other hand, because of the above connection between D and D'', at least one state with $D \neq 0$ should exist in this limiting set. At this state, $1 > C/WW'$ and therefore, the differences $x_1 - x_4$ and $x_2 - x_3$ should decrease (if they were non-zero). This means the convergence of the trajectory to the diagonal $x_1 = x_4$, $x_2 = x_3$.

On this diagonal, the evolutionary transformation reduces to

$$x_1' = (x_1 - rD)/W, \quad x_2' = C(x_2 + rD)/W ,$$

$$x_1'' = C(x_1' - rD')/W', x_2'' = (x_2' + rD')/W' ,$$

where the values W and W' are calculated from the normalization condition; $x_1 + x_2 = 0.5$ and, hence, $D = x_1^2 - x_2^2 = 0.5(x_1 - x_2)$. From this operator it is easy to move on to the one-dimension problem: assuming that $x_1/x_2 = u$ we obtain for both of the environmental states a homographic transformation,

$$u' = (1/C)F(u), \quad u'' = CF(u') , \tag{16A}$$

where $F = ((2 - r)u + r)/((ru + (2 - r))$. For $u \geq 0$, the derivative of F, $dF/du = 4(1 - r)/(ru + (2 - r))^2$ is positive (recall that $r \leq 0.5$). It is easy to show that $dF/du \leq 1$ and $dF/du = 1$ only if $u = 0$ and $r = 0$. Clearly, the derivative of the superposition $u'' = CF(u') = CF((1/C)F(u))$ (from (16A)) does not exceed unity. Therefore, the transformation of the population genetic structure during an environmental cycle is defined by a compression evolutionary operator in one-dimensional space. Consequently, any trajectory from the diagonal set converges to one stable point (which will be referred to as $X^\infty = (X_1^\infty, X_2^\infty, X_3^\infty, X_4^\infty)$).

Remark

The final part of proof is easy to extend to a more general situation. If, for the operator (1), with $p > 2$ the diagonal $x_1 = x_4$, $x_2 = x_3$ is invariant, then in this invariant set stable polymorphism always exists.

Therefore, we proved that population trajectories starting outside the diagonal converge monotonically to the diagonal, while the trajectories starting at the diagonal converge to a unique stable point X^∞. One could assume that trajectories starting from any arbitrary point will converge to X^∞. Let us prove this statement. To do that it will be enough to consider the fate of a trajectory which starts in the vicinity of the diagonal.

Let $x_1 = x_4 + \tau_4$ and $x_2 = x_3 + \tau_3$, where τ_4 and τ_3 are small. Due to the conditions $x_1 \geq x_4$ and $x_2 \geq x_3$ accepted at the beginning of the consideration, the variables are non-negative. Clearly,

$$x_3 + x_4 = 0.5(1 - \tau_4 - \tau_3),$$

so that,

$$\begin{aligned} D &= x_1 x_4 - x_2 x_3 = 0.5(x_4 - x_3)(1 - \tau_4 - \tau_3) + \tau_4 x_4 - \tau_3 x_3 \\ &= 0.5(x_4 - x_3) + \tau, \end{aligned}$$

where τ is a small variable of the same order as τ_3 and τ_4. Let as now show the following. With a possible exception of the initial point, the trajectory started anywhere in the vicinity of the diagonal will enter by one step and remain in some domain M separated from zero. Indeed, according to the evolutionary equations, for any of the environmental states,

$$\begin{aligned} x_3' &= (x_3 + rD)/W = (x_3 + 0.5r(x_4 - x_3) + \tau r)/W \\ &= ((2 - r)x_3 + rx_4 + \tau r)/2W, \\ x_4' &= C(x_4 - rD)/W = C(x_4 - 0.5r(x_4 - x_3) + \tau r)/W \\ &= C((2 - r)x_4 + rx_3 + \tau r)/2W. \end{aligned} \tag{17A}$$

Assuming that $r \gg \tau$, we obtain, with a precision of $O(\tau)$,

$$x_3' > 0.5(1 - \tau_4 - \tau_3)C \min((2 - r), r)/2(1 + C),$$

$$x_4' > 0.5(1 - \tau_4 - \tau_3)C \min((2 - r), r)/2(1 + C),$$

because, $W < 2(1 + C)$.

Analogously, we can get estimates of x_3 and x_4 for the alternative environmental state. Thus, we can conclude, that all of the trajectories which interest us, belong to the set M.

From (17A) it follows that,

$$\begin{aligned} x_4'/x_3' &= C(x_4 - rD)/(x_3 + rD) \\ &= C((2 - r)x_4 + rx_3 + \tau r)/((2 - r)x_3 + rx_4 + \tau r). \end{aligned}$$

By substitution $u = x_4/x_3$, the last relationship could be represented as,

$$u' = C((2 - r)u + r + \tau r/x_3)/((2 - r) + ru + \tau r/x_3).$$

For the further consideration we can assume that $\tau r/x_3 = O(\tau)$, because the trajectories belong to set M separated from zero and, therefore, $x_3 > \alpha$, where α is some positive constant. Similarly, for the alternative state,

$$u'' = (1/C)((2-r)u' + r + \tau' r/x_3)/((2-r) + ru' + \tau' r/x_3)\,.$$

From the relationships for u' and u'' we can readily get,

$$u'' = (1/C)(Qu + 1 + \mu_1)/(u + Q + \mu_2), \tag{18A}$$

where μ_1 and μ_2 are of the same order as τ_3 and τ_4, and

$$Q = ((2-r)^2 + Cr^2)/(r(2-r)(1+C)) \quad (\text{provided } r \neq 0)\,.$$

Consider two population states which are close enough to the diagonal. Using (18A), we can get for these states,

$$\begin{aligned} |u_1'' - u_2''| &= (1/C)|(Qu_1 + 1 + \mu_{11})/(u_1 + Q + \mu_{12}) \\ &\quad - (Qu_2 + 1 + \mu_{21})/(u_2 + Q + \mu_{22})| = S|u_1 - u_2|\,, \end{aligned} \tag{19A}$$

where,

$$S = (1/C)|((Q^2 - 1) + \mu_{11}/|u_1 - u_2|)/(u_1 + Q + \mu_{12})(u_2 + Q + \mu_{22})|\,.$$

It is easy to see that,

$$(u_1 + Q + \mu_{12})(u_2 + Q + \mu_{22}) > (Q + O(\mu_{12} + \mu_{22}))^2\,.$$

Taking into account this inequality and assuming that $\mu_{11}/|u_1 - u_2| < 1$, we will obtain the following estimation:

$$\begin{aligned} S &\leq (1/C)(|Q^2 - 1| + |\mu_{11}/|u_1 - u_2||)/(u_1 + Q + \mu_{12})(u_2 + Q + \mu_{22}) \\ &< (1/C)(|Q^2 - 1| + 1)/(Q + O(\mu_{12} + \mu_{22}))^2\,. \end{aligned}$$

Now let us show that,

$$(1/C)(|Q^2 - 1| + 1)/(Q + O(\mu_{12} + \mu_{22}))^2 < 1\,. \tag{20A}$$

Indeed, if $Q \geq 1$, then $Q^2 - 1 + 1 < C(Q + O(\mu_{12} + \mu_{22}))^2$, given small enough values for μ_{12} and μ_{22}. If $Q < 1$ then

$$1 - Q^2 + 1 < C(Q + O(\mu_{12} + \mu_{22}))^2\,.$$

The last inequality is true if,

$$2 < (1 + C)Q^2 + O(\mu_{12} + \mu_{22})\,, \tag{21A}$$

Now, in the chain of the inequalities,

$$\begin{aligned} 4C/(1+C)^2 < Q^2 &\Leftrightarrow 4Cr^2(2-r)^2 < ((2-r)^2 + Cr^2)^2 \\ &\Leftrightarrow 0 < ((2-r)^2 - Cr^2)^2 \end{aligned}$$

the last one is trivially true. Thus, $2 < (1 + C)Q^2$, because from $C > 1$ it follows that $2 < 4C/(1 + C)$. It is clear, that for small enough values of $\mu_{12} + \mu_{22}$, the inequality (21A) holds, so that $S < 1$. Therefore, if $\mu_{11}/|u_1 - u_2| < 1$, then $S < 1$ and $|u_1'' - u_2''| < |u_1 - u_2|$.

Let the second of the considered population states coincide with the stable point $X^\infty = (X_1^\infty, X_2^\infty, X_3^\infty, X_4^\infty)$, so that $u_2 = X_4^\infty / X_3^\infty$. Let $x = (x_1, x_2, x_3, x_4)$ and $x'' = (x_1'', x_2'', x_3'', x_4'')$ be two consequent population states taken over the full period. The last result means, that if x deviates from the diagonal less than for $|x_4/x_3 - X_4^\infty/X_3^\infty|$, then x_4''/x_3'' is closer to X_4^∞/X_3^∞ than x_4/x_3. We can conclude, that each trajectory starting close enough to the diagonal enters into the neighborhood of the stable point X^∞, with a radius of the same order as that of the distance between the current point of the trajectory and the diagonal. Starting from this moment $\mu_{11} > |u_1 - u_2|$, i.e. $\mu_{11}/|u_1 - u_2| > 1$, and then the previous estimations are false. Thus, the trajectory could jump out of the neighborhood. Let us estimate the radius of the new neighborhood. According to (19A),

$$|u_1'' - u_2''| \le (1/C)\{|(Q^2 - 1)|u_1 - u_2|)/(u_1 + Q + \mu_{12})(u_2 + Q + \mu_{22})|\}$$
$$+ |\mu_{11}/(u_1 + Q + \mu_{12})(u_2 + Q + \mu_{22})| \,.$$

Using the above estimation of S, we can get from last inequality:

$$|u_1'' - u_2''| \le S_1|u_1 - u_2| + O(\mu_{11}) \,,$$

where $S_1 < 1$. It is clear, that μ_{11} vanishes, because the trajectory converges monotonically to the diagonal. Thus, the radiuses of the considered two neighborhoods should also vanish. Therefore, the trajectory converges to the stable point X^∞, possibly with dumping oscillations around X^∞.

This concludes the proof that a global stable polymorphism exists in this system.

Appendix 4

Proof of the Proposition 4

Consider some regular trajectory, i.e. some environmental state i exists such that the condition (6) holds. Starting from the state i and iterating the formulae of evolution (1) along the period, it is easy to connect x_j in the state i in two neighboring cycles:

$$\hat{x}_{ji}' = (L_j/\Omega)x_{ji} + r\hat{D}_{ji} \,, \tag{22A}$$

where $\hat{D}_{ji}$ is determined by (5); j is the haplotype number ($j = 1, 2, 3, 4$); and x_{ji} is the frequency of the haplotype j at environmental state i ($i = 1, \ldots, p$). Let us examine a regular trajectory beginning from a moment, when the signs of $\hat{D}_{ji}$ for all pairs ji become stabilized and the sequence (6″) is ordered in accordance with increasing integral fitnesses L. If the last sequence is not an increasing-for-sign one, then for some pair of numbers, j_q and j_{q+1}, the following inequality holds:

$$L_{j_q} > L_{j_{q+1}}, \quad \hat{D}_{j_q i} \ge 0, \quad \hat{D}_{j_{q+1}} i \le 0 \,. \tag{23A}$$

Using (22A), we obtain,

$$\hat{x}_{j_q i}' / \hat{x}_{j_{q+1} i}' = ((L_{j_q}/W)x_{j_q i} + r\hat{D}_{j_q i})/((L_{j_{q+1}} i/W)x_{j_{q+1} i} + r\hat{D}_{j_{q+1} i} \,.$$

then, taking into account the signs of D as determined by (23A), we finally obtain:

$$\hat{x}'_{j_q i}/\hat{x}'_{j_q+1 i} \geq (L_{j_q} x_{j_q i})/(L_{j_q+1 i} x_{j_q+1 i}) \,. \tag{24A}$$

Then, it follows from (23A), that

$$t = L_{j_q}/L_{j_q+1} > 1,$$

and, in accordance with (24A), the frequency of haplotype with number j_{q+1} converges to zero exponentially with the power $\ln(t)$.

Therefore, for regular trajectories the assumption of a disturbance of increasing-for-sign of an ordered sequence (6″) results in extinction of at least one allele along the trajectory. The proposition is thus proven.