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CYCLICAL ENVIRONMENTAL CHANGES AS A FACTOR MAINTAINING GENETIC POLYMORPHISM. 2. DIPLOID SELECTION FOR AN ADDITIVE TRAIT

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Abstract.—The subject of this paper is polymorphism maintenance due to stabilizing selection with a moving optimum. It was shown that in case of two-locus additive control of the selected trait, global polymorphism is possible only when the geometric mean fitnesses of double homozygotes averaged over the period are lower than that of the single heterozygotes and of the double heterozygote (with a multiplier $(1 - r)^p$, which depends on recombination rate r and period length p). *But local stability of polymorphism cannot be excluded even if geometric mean fitnesses of all double homozygotes are higher than that of all heterozygotes.* We proved, that for logarithmically convex fitness functions, cyclical changes of the optimum cannot help in polymorphism maintenance in case of additive control of the selected trait by two equal loci. However, within the same class of fitness functions, nonequal gene action and/or dominance effect for one or both loci may lead to local polymorphism stability with large enough polymorphism attracting domain. The higher the intensity of selection and closer the linkage between selected loci the larger is this domain. Note that even simple cyclical selection could result in two forms of polymorphic limiting behavior: (*a*) usually expected forced cycle with a period equal to that of environmental changes; and (*b*) "supercycles," nondamping auto-oscillations with a period comprising of hundreds of forced oscillation periods.

Key words.—Moving optimum, nonequal gene effects, polymorphism, supercycles, two-locus models.

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Among different explanations of high level of genetic variability in nature, spatial and temporal variations of selection were considered as very plausible for a long time. Theoretical analysis has confirmed this expectation, but strongly delimited the conditions of their applicability (Levene 1953; Haldane and Jayakar 1963; Maynard Smith and Hoekstra 1980; see also Felsenstein 1976; Hedrick et al. 1976; Hedrick 1986). The range of parameters compatible with stable polymorphism proved to be much narrower in cases of temporal fluctuations compared with spatial ones. The conditions for protected polymorphism could be relaxed under combined action of these two factors (Ewing 1979).

Most of the results related to selection variation in time are for the one locus case (e.g., Haldane and Jayakar 1963; Karlin and Levikson 1974; Nagylaki 1975). However, it is reasonable to assume that new conclusions may be obtained when considering two or more loci (Gillespie 1978). Here we will show on an additive two-locus model, that stabilizing selection with cyclically changing optimum can result in protected polymorphism.

DESCRIPTION OF THE MODEL

Consider an infinite diploid population with panmixia and non-overlapping generations. Let the individual fitnesses be dependent on two linked autosomic loci, *A/a* and *B/b*. We will be interested here with the effect of cyclical environmental changes on polymorphism. Namely, we can consider a situation when in each environmental state, stabilizing selection for an intermediate optimum of a selected trait occurs, and the optimum itself varies cyclically from generation to generation. This model was used in different studies including those concerned with the evolution of recombination (Maynard Smith 1988; Korol and Preygel 1989; Korol et al. 1994).

The evolutionary operator defined on the simplex $\Sigma_{i=1}^{4} x_i = 1, x_i \geq 0, i = \overline{1,4}$ can be written in the form:

$$\begin{aligned} x_1' &= (w_1x_1 - rw_dD)/\bar{w}, \\ x_2' &= (w_2x_2 + rw_dD)/\bar{w}, \\ x_3' &= (w_3x_3 + rw_dD)/\bar{w}, \\ x_4' &= (w_4x_4 - rw_dD)/\bar{w}, \end{aligned} \tag{1}$$

where x and x' are gamete frequencies in two consecutive generations; D is the linkage disequilibrium coefficient; $w_l = w_{l1}x_1 + w_{l2}x_2 + w_{l3}x_3 + w_{l4}x_4$, $(l = \overline{1,4})$ stays for the marginal fitness of gamete l and $\bar{w}$ is the mean fitness of the population: $\bar{w} = x_1w_1 + x_2w_2 + x_3w_3 + x_4w_4$; r is the rate of recombination between fitness loci. Coefficient w_{ij} is the fitness of the zygote (i,j); w_d denotes the fitness of double heterozygotes (we assume here that $w_d = w_{14} = w_{23}$).

For each environmental state, s, a set of fitness coefficients can be considered: $w_{ij} = w_{ij}(s)$. For further analysis we need the products $W_{ij} = w_{ij}(1)w_{ij}(2)\ldots w_{ij}(p)$, which will be referred to as "fitness products" of zygotes (i,j) over the period.

Let the selected trait z be dependent on the fitness loci *A/a* and *B/b* in accordance with the following matrix:

$$\begin{array}{c} \\ bb \\ Bb \\ BB \end{array} \begin{array}{c} \begin{array}{ccc} aa & Aa & AA \end{array} \\ \begin{vmatrix} m - (d_A + d_B) & m - d_B & m + (d_A - d_B) \\ m - d_A & m & m + d_A \\ m - (d_A - d_B) & m + d_B & m + (d_A + d_B) \end{vmatrix} \end{array}, \tag{2}$$

where m is the total mean, d_A and d_B—effects of alleles A and B on z (without loss of generality, we can assume that $d_A, d_B \geq 0$, $d_A \geq d_B$). The fitness of a genotype (i,j) with a trait value $z = z_{ij}$ at the environmental state s where the optimum value of the trait is Z_s can be defined by a fitness function, F, as $w_{ij}(s) = F(z_{ij} - Z_s)$.

Results

Conditions Favoring Genetic Polymorphism

Global Stability

The problem of *global* stability of polymorphism caused by stabilizing selection with cyclically moving optimum could be analyzed starting from of a more general case of cyclical selection. It can easily be shown, that the possibility for existence of *global* polymorphism due to cyclical selection is always conditioned by an advantage of fitness products of heterozygotes over those of double homozygotes:

Proposition 1.—For existence of a globally attracting polymorphism in a cyclical environment the following conditions should hold:

$$\begin{aligned} W_{11} &< \max(W_{12}, W_{13}, (1 - r)^p W_{44}), \\ W_{22} &< \max(W_{21}, W_{24}, (1 - r)^p W_{44}), \\ W_{33} &< \max(W_{31}, W_{34}, (1 - r)^p W_{44}), \\ W_{44} &< \max(W_{42}, W_{43}, (1 - r)^p W_{44}). \end{aligned} \tag{3}$$

If for some W_{ii} this necessary condition is violated, then the vertex $x_i = 1$ of the simplex is a locally attracting point. For proof see Appendix 1.

This proposition generalizes the results obtained earlier for constant environment (Bodmer and Felsenstein 1967; Gavrilets and Hastings 1994a). Note, that from the proof it follows, that proposition 1 is true also for a quasi-periodical environment, i.e., for a cyclical environment with nonfixed order of environmental states within the period. Therefore, according to proposition 1, the necessary condition for the vertex $x_i = 1$ to be a point of attraction is the superiority of the geometric mean fitness averaged over the period (GMF) of the respective double homozygotes (i,i) over GMF of single heterozygotes ($i,*$). The GMF of the double heterozygote can be higher than that of the homozygote (i,i) but not more than by a multiplier $(1 - r)^p$. The higher the recombination and longer the period the higher is the superiority of the double heterozygote compatible with local attraction to the point $x_i = 1$. On the other hand, if at least one of the heterozygotes is superior for the fitness products, then the corresponding vertex becomes repelling. In particular, with relatively high fitness of the double heterozygote, all the vertexes become simultaneously repelling. The above analysis allows us to assume that global polymorphism is impossible without some form of advantage of heterozygotes over the homozygotes.

How Important Is Superiority of Heterozygotes for Local Stability of Polymorphism?

Let us now analyze the spectrum of possible relationships between genotypic fitnesses produced by stabilizing selection with moving optimum. We will also consider how the local behavior near the vertexes depends on these relationships. Let, for definiteness, $d_A > 2d_B$. Then, according to (2), the following order of the genotype values z_{ij} of the selected trait holds:

$$\begin{aligned} z_{11} > z_{12} > z_{22} > z_{13} > z_{14} \\ = z_{23} > z_{33} > z_{24} > z_{34} > z_{44}. \end{aligned} \tag{4}$$

Consider a case of two-state environment, with optimal values of the trait Z_1 and Z_2, and let $Z_1 > z_{11} > z_{14} > Z_2$. We need also to assume that $Z_1 + Z_2 > 2z_{11}$. Then, in the first state, the fitness of the corresponding genotypes will be ordered in the same sequence as the trait values, while inverse order will occur in the second state:

$$\begin{aligned} &F(z_{11} - Z_1) > F(z_{12} - Z_1) > F(z_{22} - Z_1) > F(z_{13} - Z_1) \\ &\qquad > F(z_{14} - Z_1) \\ &= F(z_{23} - Z_1) > F(z_{33} - Z_1) > F(z_{24} - Z_1), \\ &F(z_{11} - Z_2) < F(z_{12} - Z_2) < F(z_{22} - Z_2) < F(z_{13} - Z_2) \\ &\qquad < F(z_{14} - Z_2) \\ &= F(z_{23} - Z_2) < F(z_{33} - Z_2) < F(z_{24} - Z_2). \end{aligned} \tag{5}$$

It is easy to see, that in logarithmic scale, the fitness products of a genotype (i,j) in case of a cycle of the length $p = 2$ have the form $\ln F(z_{ij} - Z_1) + \ln F(z_{ij} - Z_2)$. It is a well known that any function (or any sequence) can be represented as a sum of two monotonic functions (sequences). Therefore, any arbitrary sequence could be generated by the sum of the increasing and decreasing sequences $\{\ln F(z_{ij} - Z_1)\}$ and $\{\ln F(z_{ij} - Z_2)\}$ (see [5]), under an appropriate choice of the unimodal function F that characterizes stabilizing selection. We can conclude that, even in the simplest case, stabilizing selection with moving optimum may result in any arbitrary relationships between the fitness products.

It is worth mentioning, that an additional assumption of symmetry of F could be taken into account in these arguments. Without loss of generality, we can always suppose that $\min\{F[z_{ij} - Z_2]\} > \max\{F[z_{ij} - Z_1]\}$. Indeed, the set of fitness coefficients corresponding to the state with optimum Z_2, could be multiplied by a sufficiently small constant, without changing the dynamical properties of the system. Due to the above choice of Z_1 and Z_2, the two intervals of values, $-(z_{ij} - Z_1)$ and $(z_{ij} - Z_2)$, are not overlapping. Therefore, any unimodal F can be replaced by a symmetric one without changes in fitnesses.

The above model is rather general in terms of the possibilities of generating different types of systems of fitness products in two-state environments. Therefore, it is reasonable to use this simple model to understand how polymorphism stability depends on selective superiority of heterozygotes (for fitness products). In general, this problem still remains unsolved even in the case of constant environment (e.g., Hastings 1982; Nagylaki 1992).

Let us consider a situation where in one of the states the maximum of the unimodal fitness function lies to the right of the set of the genotypic trait values, and in the other state, to the left of this set. Using evenly distributed sets of fitness coefficients, we found that the mean proportion of stably polymorphic systems for recombination ranges $0 < r < 0.1$, $0.1 < r < 0.25$, and $0.25 < r < 0.5$ was 6.8%, 5.4%, and 7.8%, respectively. The proportion of starting points resulting in trajectories converged to polymorphic stable points could be referred to as "volume of polymorphism attracting domain," v. For the foregoing three ranges of r, we obtained respectively $v = 0.84$, 0.67, and 0.68. It should be mentioned here, that under even distribution of fitness coefficients, given the inequalities (5), the majority of the resulting systems will

manifest any form of heterozygote superiority for geometric mean fitness. It is no wonder that all the revealed polymorphic systems manifested some heterozygote advantage. Small proportion of systems manifesting no heterozygote advantage (assuming even distribution of fitness coefficients), poses some difficulties in numerical analysis aimed to check whether polymorphism is possible *without any form of heterosis at the level of geometric mean fitness*. As we showed above, it is impossible to construct such systems based on usually employed fitness functions.

Followed are two examples of polymorphic systems without superiority in fitness products of heterozygotes comparative to those of any homozygotes.

Example 1.—Consider a two-state environment with period of length 2 (we will refer to such environmental fluctuations as seasonal, assuming that each state corresponds to a season). Let the fitness matrices in the two states be:

$$c_1 S_1 = \begin{array}{c} \\ BB \\ Bb \\ bb \end{array} \begin{vmatrix} AA & Aa & aa \\ 2.6400 & 1.2200 & 0.1550 \\ 1.7180 & 0.8545 & 0.1185 \\ 1.3600 & 0.2090 & 0.1120 \end{vmatrix},$$

$$c_2 S_2 = \begin{vmatrix} AA & Aa & aa \\ 0.384 & 0.803 & 6.461 \\ 0.570 & 1.144 & 8.345 \\ 0.736 & 4.700 & 8.974 \end{vmatrix}, \quad (6)$$

here c_1 and c_2 are normalizing constants. These matrices correspond to selection for an additively forming trait controlled by two genes with unequal effects. Thus, if $m = 3$, $d_A = 2$ and $d_B = 1$ (see [2] for designation), then the values of the selected trait z will be ordered as

$$z(AABB) > z(AABb) > z(AAbb) > z(AaBB) > z(AaBb) > z(Aabb) > z(aaBB) > z(aaBb) > z(aabb). \quad (7)$$

Therefore, in the first environmental state the fitnesses are increasing with z, whereas, in the second state, they are correspondingly decreasing. The matrix of fitness products has, in this case, the following form:

$$\begin{array}{c} \\ BB \\ Bb \\ bb \end{array} \begin{vmatrix} AA & Aa & aa \\ 1.002240 & 0.979660 & 1.001455 \\ 0.979260 & 0.977548 & 0.988883 \\ 1.000960 & 0.982300 & 1.005088 \end{vmatrix}, \quad (8)$$

It is easy to see, that every homozygote is superior compared to the respective heterozygotes.

We tested, employing numerical iterations of the evolutionary operator (1), the dynamics of this system. For each chosen value of recombination rate (r), 500 random initial points were used to check for polymorphism stability of the respective trajectories during 500,000 generations. This analysis showed that stable polymorphism in this system with rather high volume of the attraction domain (say, $v > 80\%$ of the total volume of the simplex) is possible with sufficiently large r (say, $r > 0.34$). For example, at $r = 0.380519$ the stable point (starting from the first state as a beginning of the period) is: $x_1 = 0.027614$, $x_2 = 0.039576$, $x_3 = 0.559985$, $x_4 = 0.372825$. The spectrum of the linear approximation of the product of evolutionary operator along the period at this stable point is 0.981224, 0.869705, 0.386220. Notice that, in the vicinity of the stable point, linkage disequilibrium does not change the sign (D is negative).

Example 2.—Consider the same situation as in the previous example, but with different fitness matrices:

$$c_1 S_1 = \begin{array}{c} \\ BB \\ Bb \\ bb \end{array} \begin{vmatrix} AA & Aa & aa \\ 3.795 & 1.887 & 1.358 \\ 2.841 & 1.710 & 0.778 \\ 2.588 & 1.508 & 0.586 \end{vmatrix},$$

$$c_2 S_2 = \begin{vmatrix} AA & Aa & aa \\ 0.263435 & 0.529942 & 0.736377 \\ 0.351989 & 0.584795 & 1.285347 \\ 0.386399 & 0.663130 & 1.706485 \end{vmatrix}. \quad (9)$$

Here, all of the elements of the matrix of fitness products are equal to 1.00. Therefore, at the level of geometric mean fitness we have here a purely neutral case.

The same numerical simulations as described above have show that for each possible value of r ($0 < r \leq 0.5$) the system has a stable polymorphism. The volume of the attracting domain is ≈90% of the simplex for small r and it reduces to 80% with increasing r. At $r = 0.303$ the stable point (starting from the first state as a beginning of the period) is: $[x_1 = 0.025317, x_2 = 0.003442, x_3 = 0.829056, x_4 = 0.142183]$. The spectrum of the linear approximation of the product of evolutionary operator along the period in this stable point has an eigenvalue 0.482887 and a pair of complex roots with module 0.997963. Here, in the vicinity of the stable point, sign(D) is alternating within the period.

We would like to note, that in example 2 small variations of fitnesses may result in appearance of a heterozygote advantage and such systems are of no major interest in the framework of this section. However, we could not renounce the pleasure to pursue the bifurcation of the system and have been rewarded by a simple example of a "supercyclical" behavior in the model of seasonal environmental fluctuations (see below, example 3). For the first time we found such behavior in two-locus haploid systems with fluctuating selection (Kirzhner et al. 1994).

Example 3.—The fitness matrices in the two states can be presented, up to a multiplicative constant as:

$$S_1 = \begin{array}{c} \\ BB \\ Bb \\ bb \end{array} \begin{vmatrix} AA & Aa & aa \\ 3.6160 & 1.8870 & 1.3700 \\ 2.8360 & 1.7105 & 0.7630 \\ 2.6455 & 1.5080 & 0.5860 \end{vmatrix},$$

$$S_2 = \begin{vmatrix} AA & Aa & aa \\ 0.263435 & 0.529942 & 0.736377 \\ 0.351989 & 0.586295 & 1.285347 \\ 0.386399 & 0.663130 & 1.706485 \end{vmatrix}. \quad (10)$$

The phase portrait of the system for $r = 0.303$ is presented in Figure 1. We have here: (a) a stable polymorphism (initial point: $[x_1 = 0.057, x_2 = 0.01, x_3 = 0.761, x_4 = 0.172]$ at S_1 belongs to the attracting domain of this polymorphism); (b)

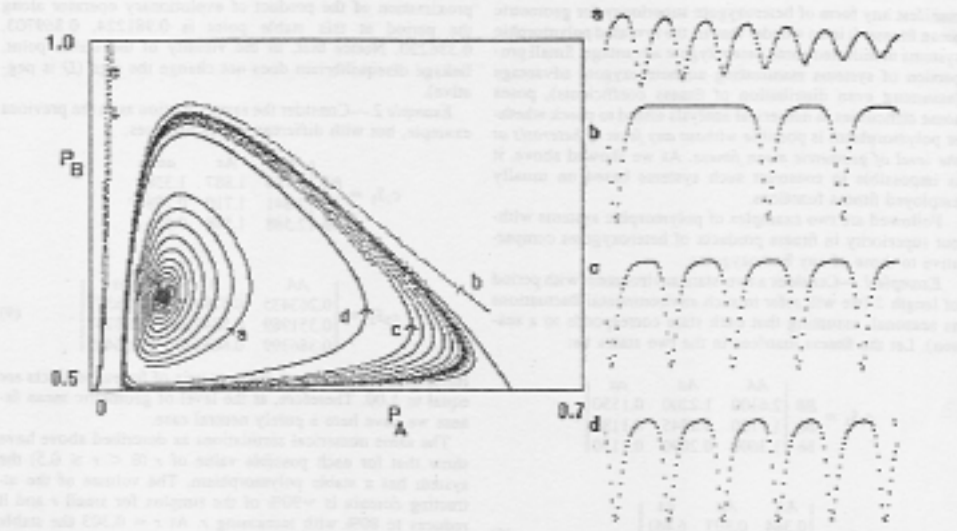

FIG. 1. A fragment of the phase space of the two-locus system subjected to two-state environmental fluctuations of selection coefficients with period $p = 2$ (a projection on the plane of allele frequencies) is shown at the end of each environmental period. For details of the selection regime, see description of example 3 in the text. Four types of limiting behavior of the system can be seen in the figure: (1) A stable polymorphic "point" (which trivially represents the forced oscillations caused by environmental changes). Trajectory **a** converges to this point as shown by damping oscillations of the frequency of allele A. (2) A stable limiting "supercycle" comprised of hundreds of environmental cycles. Trajectories **b** and **c** converge to the supercycle for outside and inside, respectively. (3) An unstable supercycle **d**, which subdivides the domains of attraction of the stable point and stable supercycle. (4) A stable point corresponding to fixation at locus *Aa*. Trajectory **c** converges to this point.

an attracting "supercycle" with the length of about 1000 environmental periods (the point $[x_1 = 0.4, x_2 = 0.0, x_3 = 0.41, x_4 = 0.19)$ at S_1 could be used as one of starts to obtain this limiting trajectory); (*c*) an unstable cycle dividing the attracting domains *a* and *b* (an example of a point which belongs to this cycle is $x_1 = 0.232201$, $x_2 = 0.002704$, $x_3 = 0.741072$, $x_4 \approx 0.024021$). This interesting pattern could be observed for r approximately from the interval 0.27–0.305. At $r < 0.26$ the limiting cycles disappear and the polymorphic stable point becomes repelling. At $r > 0.31$ both limiting cycles disappear, but the limiting point remains stable. For further details concerning this unexpected behavior see Kirzhner et al. (1995c). The described effect is, in a sense, analogous to autooscillations found earlier by Hastings (1981) for diploid constant selection in a discrete time model: in both cases the period of oscillations is very long.

Sign-Concordant Environments

In the more special, but important, case of sign-concordant environments, some additional constraints arise, in form of inequalities between the fitness products. We will refer to an environment as a *sign-concordant* one, if the variable $w_1w_4 - w_2w_3$ has one and the same sign across the environmental states. The environment is either *plus-concordant* or *minus-concordant* if $\text{sign}(w_1w_4 - w_2w_3)$ is always nonnegative or nonpositive. If in all states $w_1w_4 - w_2w_3 = 0$, the environment will be referred to as a zero-concordant. According to Kirzhner et al. (1995a), if F is log-concave or log-convex (i.e., $\log F(z)$ is either concave or convex), then the environment is sign-concordant. Such function are rather common in modeling. For example, $F(z) = \exp(-C|z - a|^m)$ ($C > 0$, $m = 1,2,\ldots$) is log-concave for any set of parameters C, m, and a. This property is characteristic also to $F(z) = 1 - C|z - a|^m$. Contrary to that, Monod's function $F(z) = c + (1 - c)(1 + a|z|^n/(a + z)$ employed by Gillespie (1978) in his SAS-CFF model of polymorphism maintenance is log-convex.

Proposition 2.—Let us consider stabilizing selection with cyclically moving optimum for a trait controlled by two additive loci. Additivity is assumed both for between and within loci effects. Let the selection function F be log-convex. Then, for each of the transhomozygotes (*AAbb* and *aaBB*), at least one of the "nearest" heterozygotes (i.e., *Aabb* and/or *AABb* for *AAbb*; and *AaBB* and/or *aaBb* for *aaBB*) will have a higher fitness products than the respective homozygote. A simultaneous fixation of alleles *A* and *b* or *a* and *B* is impossible. Let the selection function F be log-concave. Then, again, no more than two homozygotes can be found, such that the "nearest" heterozygotes have a higher fitness and no more than two combinations of allele fixations are possible, whereas these fixations are not necessary for transcombinations of the alleles at the two loci. For proof see Appendix 2.

This proposition indicates that a choice of a class of fitness functions F may lead (and in such cases necessarily so) to superiority of heterozygotes over homozygotes with respect to their fitness products, independently of the cycle structure. For example, it is easy to show that the superiority of heterozygotes will be automatically obtained for some of the usually employed fitness functions (e.g., Gaussian).

With equal effects of the genes, we have $d_A = d_B$ and, therefore, $w_2 = w_3$. The last equality allows to employ for the analysis of trajectories of the system (1) the relationship used for the haploid case by Feldman (1971).

Namely, it follows from (1) that $x'_2 - x'_3 = w_2(x_2 - x_3)/\bar{w}$, which means that the sign of $x_2 - x_3$ does not change along the trajectory. We can also find from (1) that

$$\frac{x'_2}{x'_3} = \frac{w_2x_2 + rw_4D}{w_3x_3 + rw_4D}. \tag{11}$$

Let us assume that the environment is minus-concordant and let, for definiteness, $x_2 < x_3$ at the initial point of the trajectory. It is important to mention, that in a minus-concordant environment, the sign of D, beginning from some generation, becomes negative and remains negative along the trajectory (Kirzhner et al. 1995a). Therefore, it can easily be obtained from the previous inequality, beginning from this moment

$$\frac{x'_2}{x'_3} = \frac{w_2x_2 + rw_4D}{w_3x_3 + rw_4D} \le \frac{x_2}{x_3}, \tag{12}$$

the equality being possible only when $D = 0$. Thus, $x_2 \to 0$ or $D \to 0$ or simultaneously $x_2 \to 0$ and $D \to 0$. But it follows from (1) that if $x_2 \to 0$ at $r > 0$, then $D \to 0$ too. 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 for the evolutionary operator (1). Then, if some point (x_1,x_2,x_3,x_4) belongs to the set $D = 0$, i.e., $x_1x_4 - x_2x_3 = 0$, then the operator (1) will transform it into the point $(w_1x_1/\bar{w}, w_2x_2/\bar{w}, w_3x_3/\bar{w}, w_4x_4/\bar{w})$ from the same set. Therefore, $w_1w_4x_1x_4 - w_2w_3x_2x_3 = 0$, and we have $w_1w_4 - w_2w_3 = 0$ or $x_1x_4 = x_2x_3 = 0$. Because of the condition of minus-concordance, at least for one of the states the inequality $w_1w_4 - w_2w_3 < 0$ takes place, and hence $x_1x_4 = 0$ and $x_2x_3 = 0$. This results in fixation for one or both loci. The case when $x_2 > x_3$, can be treated in the same way.

The situation with plus-concordant environment will be analyzed analogously to the above consideration of minus-concordant environment. Let $x_2 < x_3$. Then, starting from some moment, $D \equiv 0$ will be established in such environment (Kirzhner et al. 1995a) and for the following trajectory we obtain

$$\frac{x'_2}{x'_3} = \frac{w_2x_2 + rw_4D}{w_3x_3 + rw_4D} \ge \frac{x_2}{x_3}. \tag{13}$$

Equality is possible here when $x_2 = x_3$ or $D = 0$. But it was shown above, that from $D = 0$ it follows that $x_2x_3 = 0$, which is impossible because x_2/x_3 is monotonically increasing and we assumed that $x_2 < x_3$. Hence, each trajectory converges to the diagonal $x_2 = x_3$. Therefore, we proved the following proposition.

Proposition 3.—Cyclical selection for a trait controlled by two additive genes with equal effects resulting in sign-concordant environment leads to the following behavior of the system trajectories: in minus-concordant environment any trajectory with $x_2 = x_3$ at the initial state comes to the set $x_2x_4 = 0$ and $x_3x_1 = 0$. In other words, at least one of the loci becomes fixed. In plus-concordant environment the population trajectories come to the set $x_2 = x_3$. In both cases, the set $x_2 = x_3$ is invariant for the evolutionary operator (1).

Note that proposition 3 is partly overlapping with result 1 of Gavrilets and Hastings (1994b).

Consider now the behavior of the system on the set $x_2 = x_3$. Fixation in at least one locus is possible here only if either $x_1 = 1$ or $x_4 = 1$. Using proposition 1, it is easy to calculate that at the vertex $x_1 = 1$ in the subspace $x_2 = x_3$, the spectrum of linear approximation is $\{W_{12}/W_{11}, W_{14}(1 - r)^2/W_{11}\}$ (recall that with equal gene effects $W_{12} = W_{13}$). In the further analysis, let us normalize the genotype fitnesses with respect to that of the double heterozygote $W_{14} = 1$. Then, the spectrum can be presented in the form: $\{W_{12}/W_{11}, (1 - r)^2/W_{11}\}$. Analogously, the spectrum for $x_4 = 1$ will be $\{W_{24}/W_{44}, (1 - r)^2/W_{44}\}$. The evaluation of local stability of these vertexes will be done for the case of log-concave fitness functions. In such a case, if the environment is minus-concordant, then the fitnesses products should obey the following inequalities:

$$W_{11} - W_{12}^2 < 0, \qquad W_{11}W_{24} - W_{12} < 0,$$
$$W_{24}W_{12} - 1 < 0, \qquad W_{44}W_{11} - W_{24}W_{12} < 0,$$
$$W_{44}W_{12} - W_{24} < 0, \qquad W_{44} - W_{24}^2 < 0. \tag{14}$$

If W_{11} and W_{44} are small enough as compared to W_{12}, W_{24} and $(1 - r)^2$ (which agrees with [4]), then both vertexes, $x_1 = 1$ and $x_4 = 1$, will be locally unstable. Therefore, in spite of the fact that the diagonal is a repeller for the evolutionary operator, within this set we can have no fixation.

In plus-concordant environment the diagonal is an attracting set. For such an environment, a stable fixed point is possible at the diagonal in case of a sufficiently strong stabilizing *constant* selection, as follows from the results of Gavrilets and Hastings (1994b).

Numerical Simulations

We will analyze the behavior of diploid two locus systems (1) under different types of cyclical environmental changes, the changes being described by an ordered set $S_1t_1, S_2t_2, \ldots, S_qt_q$, where S_i is the matrix of selection coefficients at the ith environmental state, t_i is the longitude (i.e., number of generations) of the ith state, and $p = t_1 + t_2 + \ldots + t_q$ is the period length.

Numerical modelling will be conducted using three types of fitness functions $F(z - Z)$ representing three important classes of stabilizing selection systems with moving optimum. Here z is the selected trait value of a genotype, and Z is the current optimal trait value. In all of the three cases, the possibilities are provided to consider equal or nonequal effects of the participating loci on the selected trait and any level of dominance for one or both loci. The following matrix was used to specify the effects of the loci:

however, are possible unless r exceeds some level, r^*. The critical role of unequal effects of additive genes has also been shown for the maintenance of polymorphism under selection in constant environments (Hastings and Hom 1990).

Note that the volume of polymorphism attracting domain is proportional to strength of selection and intensity of linkage. However, with tight enough linkage even moderate selection is able to protect polymorphism. This point may be illustrated by the following example. For the above exponential fitness function with $k = 2$ and $\sigma = 6$, period structure $t_0 = 1$, $t_1 = 4$, $t_2 = 4$, $Z_1 = 3$, $Z_2 = 0$, $Z_3 = 6$ and gene effects $d_a = 1$, $d_b = 2$, $h_a = h_b = 0$, we obtained at $r = 0.01$ $v = 1.0$ and mean fitness (geometrical average over the stationary period) $w = 0.800$ (regime *); and $v = 1.0$ and $w = 0.804$ at $t_1 = 0$ (i.e., regime **).

Let $F(z) = 1/[1 + [(z - Z)/\sigma]^2$. Provided selection is intense enough, stable polymorphism is possible in this case even for $d_a = d_b$ and $h_a = h_b = 0$, and, needless to say, for $d_a = d_b$ or nonzero h_a or h_b. It is noteworthy, that with this fitness function, in case of equal additive genes, *constant selection* (for the intermediate trait state S_2) cannot maintain polymorphism. Indeed, as one could easily check, the criterion $2\beta \le \delta$ for no polymorphism existence proved by Gavrilets and Hastings (1994b; see their result 1, p. 523) holds in this situation. Also, variable selection with alternating S_2 and S_3 cannot maintain polymorphism. Only the full combination $S_1 \to S_2 \to S_1 \to S_3$ results in stable polymorphism.

Discussion

The role of fluctuating selection (in space and/or time) as a factor maintaining genetic polymorphisms is one of the central problems in population genetics and has a direct bearing on the general controversy about the causes of the variability observed in nature. Its solution is beset with difficulties even in the one-locus case, the more so when attempting to interpret the experimental evidence (Felsenstein 1976; Hedrick et al. 1976; Hedrick 1986).

The model discussed in this paper describes situations of the genotype-environment interaction, because it is assumed that when the environment is changed, there is a change in the ranking of selectively favored genotypes (Bell 1988). Via and Lande (1987) have shown the genotype-environment interaction to play an important role in the dynamics of genetic variation under disruptive selection in a spatially heterogeneous environment. Based on computer simulations of a two-locus phenotypic model, Zonta and Jayakar (1988) found that "temporally varying selection can maintain more genetic variability for a quantitative trait than constant selection." Stabilizing selection with a temporally fluctuating optimum was also shown to increase genetic variation in populations with overlapping generations (Ellner and Hairston 1994).

There are indications of positive association between spatial or temporal environmental heterogeneity and the amount of polymorphism (Allard and Kahler 1974; Nevo 1978, 1988; Mackay 1981; Nevo et al. 1984; Verdonck 1987; Mukai 1988). In particular, some evidence directly demonstrates the effect of temporal environmental changes on genetic variation in nature. Most such cases are related to the effect of seasonal changes in organisms with two or more generations per year (for a review see Hedrick et al. 1976). These include *Adalia bipunctata*, *Drosophila pseudoobscura*, *D. melanogaster*, and *Daphnia magna*. Another class of temporally fluctuating selection regimes in nature may be related to between-year variations of food resources where the conditions experienced by offspring generation are different from those of their parents (Finerty 1980). Another important source of temporal variation of environmental conditions may be the well known oscillations of population densities due to species interactions (Begon et al. 1986; Hanski et al. 1993). No matter what is the precise mechanism of such periodicity in each specific case, the resulting fluctuating selection regime may play an important role as a factor maintaining polymorphism (see also Hamilton 1993; Preygel and Korol 1990).

Few studies have dealt with the considered problem at the level of controlled laboratory experiments. Thus, Powell and Wistrand (1978) subjected cage populations of *D. pseudoobscura* to alternating warm and cold conditions every next generation. The conclusion they reached was that variable environments maintain more variation than stable environments. In *D. melanogaster*, Mackay (1981) has shown that experimental populations subjected to environmental fluctuations (addition of ethanol to the medium) can maintain substantially higher variation for some quantitative traits than control population at a constant environment. In this study, temporal environmental changes were not less, if not more, effective than spatial heterogeneity in promoting genetic variation.

Our results indicate that stabilizing selection with a cyclically fluctuating optimum can promote maintenance of polymorphism for additive genes (see also Korol et al. 1993, 1994). These findings are rather different from the conclusions reached by Lande (1976). He showed, that under assumptions that neglect linkage disequilibria (i.e., loose linkage and moderate or small selection intensity) temporal fluctuations of the optimum do not affect the amount of variability stored in the population. By contrast, in our simulations, cyclical fluctuations of the optimum did maintain polymorphism, provided strong or moderate selection and/or recombination rate between the involved loci is small enough. This mode of behavior is rather robust, with the volume of polymorphism attracting domain comprising about 0.5–1.0 for tightly linked loci, at selection intensity of 0.2–0.5. The numerical examples provided above show that removing the "constant selection component" (in cases of $t_1 = 0$) have no principal effect on polymorphism maintenance.

In the first part of the paper we studied some general conditions for polymorphism stability in diploid two-locus cyclical selection models. We found that global polymorphism is possible only when the geometric mean fitnesses of double homozygotes are lower than that of the respective single heterozygotes and of the double heterozygote. Analogous consideration was presented for constant environment (Bodmer and Felsenstein 1967; Hastings 1982; Gavrilets and Hastings 1994a). We should mention, however, that a stable local polymorphism in variable environment is possible even if an opposite condition holds. Two such numerical examples of cyclical selection (with period $p = 2$) were presented, with equal fitnesses products of all 10 two-locus genotypes (see example

2 above), and even with geometric mean fitnesses of *double homozygotes* and *double heterozygotes* being, correspondingly, *higher* and *lower*, than those of all other genotypes (see example 1). Notably, superiority of homozygotes with respect to geometric mean fitness is not necessarily an exclusive situation among two-locus systems exposed to stabilizing selection with a moving optimum. Many types of unimodal selection functions producing such selection regimes could be suggested.

Theoretical considerations (Global Stability and Sign-Concordant Environments) help to exclude the class of situations where stabilizing selection for an additively controlled trait with cyclically changing optimum is unable to maintain polymorphism, e.g., minus-concordant environments. Such selection regimes are generated by log-concave fitness functions, e.g., the Gauss function. Note, the importance of the fitness function properties, including convexity, in polymorphism maintenance and other aspects of population dynamics and evolution have been discussed by many authors (e.g., Karlin and Avni 1981; Schluter 1988; Charlesworth 1993; Kondrashov 1993; Gavrilets and Hastings 1994b).

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 selection (in stable environment) the existence of a critical value $r = r^*$ such that for $r > r^*$ the population reaches linkage equilibrium $D_- = 0$, while for $r < r^*$ $D_- \neq 0$. Moreover, Ewens (1968) found that for some selection regimes, the range of r values ($0 \leq r \leq 0.5$) is even noncontinuous and could include more than one subinterval corresponding to $D_- \neq 0$ (Ewens 1968).

Recombination may play a critical role in polymorphism stability under constant selection regime. Thus, Karlin and Avni (1981) have shown that stability of central polymorphism in a multilocus population depends on recombination, so that if polymorphism is stable at some recombination rate, it will be stable at higher rates too. We have demonstrated that, provided locally stable polymorphism results from cyclical selection, the volume of the polymorphism attracting domain, v, strongly depends on the rate of recombination, r, between the selected loci: the higher r the lower is v. And beginning with some critical $r = r^*$ we have no polymorphism for any $r > r^*$. The border r^* is increasing with selection intensity.

Fluctuating environment may, in principle, maintain polymorphism due to haploid selection as well (Karol et al. 1993; Kirzhner et al. 1995b). It is clear, that in this case, polymorphism stability is temporary changing environments, when existing, is precisely the result of environmental variation. Indeed, the obtained stability cannot be "inherited" in any form from the basic model of constant environment, because constant haploid selection is unable to maintain polymorphism (Rutschman 1994).

The results presented in this paper are directly related to the above mentioned problem of recombination evolution. We have seen that cyclical selection does not maintain polymorphism in case of Gaussian fitness function with equal additive genes. Earlier, Lande (1976) reached the conclusion that stabilizing selection with a temporally moving optimum does not help in the maintenance of genetic variation. This lead to a generalization that temporally changing environment is, in itself, not sufficient as a factor of recombination evolution (Kondrashov 1993). Our results indicate that either a change in the form of the fitness function, or using nonequal additive genes or genes with some dominance effect, relax the problem of polymorphism maintenance. This may help in a reevaluation of different hypotheses of recombination evolution (Korol et al. 1994).

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APPENDIX 1

Proof of Proposition 1

Let us consider the Jacobian J of the system (1) at the vertex $x_1 = 1$ of the simplex S:

$$w_{11}^{-1}\begin{vmatrix} (w_{14} + rw_{\delta}) & (w_{14} - w_{12} + rw_{\delta}) & (w_{14} - w_{13} + rw_{\delta}) \\ -rw_{\delta} & w_{12} - rw_{\delta} & -rw_{\delta} \\ -rw_{\delta} & -rw_{\delta} & w_{13} - rw_{\delta} \end{vmatrix}. \quad (1A)$$

It is easy to find out that the eigenvalues corresponding to the "right" eigenvectors of matrix (1A) $(1, -1, 0)$ and $(1, 0, -1)$ are w_{12}/w_{11} and w_{13}/w_{11}, respectively). The eigenvalue corresponding to the "left" eigenvector $(1, 1, 1)$ is $[1 - r]w_{\delta}/w_{11}$. Thus, it is clear that any vertex of the simplex will be stable, if w_{11} is the largest fitness (i.e., $w_{11} > w_{12}$, w_{13}, w_{14}), or if $w_{14} = w_{11} > w_{12}$, w_{13} but $(1 - r)w_{14} < w_{11}$.

Let the evolution occur in an environment with p states alternating in any order within the period of length p. Then, the linear approximation in a vertex of the evolutionary operator (1) reiterated over the period is a product of linear approximations in the form (1A) in each of the states: $J = J_1, J_2, \ldots J_p$. The spectrum of J can easily be calculated, because the eigenvectors $(1, -1, 0)$, $(1, 0, -1)$ and $(1, 1, 1)$ of each matrix J_i $(1 < i < p)$ are the same (do not depend on i). Therefore, those vectors are also eigenvectors for J. Hence, the eigenvalues of the Jacobian J are as follows:

$$w_{21}w_{22} \ldots w_{2\delta}/w_{11}w_{12} \ldots w_{1\delta} = W_2/W_1,$$

$$w_{31}w_{32} \ldots w_{3\delta}/w_{11}w_{12} \ldots w_{1\delta} = W_3/W_1,$$

$$(1 - r)^p w_{14}w_{24} \ldots w_{p4}/w_{11}w_{12} \ldots w_{1\delta} = (1 - r)^p W_4/W_1. \quad (1B)$$

From these formulae proposition 1 follows directly.

APPENDIX 2

Proof of proposition 2

In any cyclical environment with a period p, the fitness products of a genotype ij (resulting from union of gametes i and j) may be presented as $F(z_{i_1} - Z_1)^{\gamma}(z_{i_2} - Z_2)^{\gamma} \ldots F(z_{i_p} - Z_p)^{\gamma}$, where Z_s is the selected for (optimal) value of z in environmental state s ($s = 1, \ldots, k$, k being referred to the number of different states), i_s is the loegtinde of the state s. The length of the cycle $p = i_1 + \ldots + i_k$. Consider the heterozygotes $ij = 12$ and $ij = 24$, and the homozygote $ij = 22$. According to (3), $z_{12} > z_{11}$, and $z_{24} < z_{11}$. The superiority of the homozygote $ij = 22$ over the heterozygotes $ij = 12$ and $ij = 24$ means, that

$$F(z_{21} - Z_1)^{\gamma}F(z_{12} - Z_2)^{\gamma} \ldots F(z_{2\delta} - Z_p)^{\gamma}$$
$$> F(z_{11} - Z_1)^{\gamma}F(z_{21} - Z_2)^{\gamma} \ldots F(z_{12} - Z_p)^{\gamma},$$
$$F(z_{22} - Z_1)^{\gamma}F(z_{22} - Z_2)^{\gamma} \ldots F(z_{22} - Z_p)^{\gamma}$$
$$> F(z_{24} - Z_1)^{\gamma}F(z_{14} - Z_2)^{\gamma} \ldots F(z_{24} - Z_p)^{\gamma}, \quad (2A)$$

In the logarithmic form, we will have

$$\begin{aligned}&r_1\ln F(z_{11} - Z_1) + r_2\ln F(z_{12} - Z_2) + \ldots + r_k\ln F(z_{1k} - Z_k)\} \\ &\quad > r_1\ln F(z_{21} - Z_1) + r_2\ln F(z_{22} - Z_2) + \ldots + r_k\ln F(z_{2k} - Z_k)\} \\ &r_1\ln F(z_{21} - Z_1) + r_2\ln F(z_{22} - Z_2) + \ldots + r_k\ln F(z_{2k} - Z_k)\} \\ &\quad > r_1\ln F(z_{31} - Z_1) + r_2\ln F(z_{32} - Z_2) + \ldots + r_k\ln F(z_{3k} - Z_k)\end{aligned} \tag{2B}$$

Further: let $\alpha_1 z_{11} + \alpha_2 z_{14} = z_{13}$, where $\alpha_1, \alpha_2 \geq 0$, $\alpha_1 + \alpha_2 = 1$. Then, from (2B), we obtain:

$$\begin{aligned}&r_1\ln F(z_{11} - Z_1) + r_2\ln F(z_{12} - Z_2) + \ldots + r_k\ln F(z_{1k} - Z_k) \\ &\quad > r_1(\alpha_1\ln F(z_{12} - Z_1) + \alpha_2\ln F(z_{14} - Z_1)) \\ &\qquad + r_2(\alpha_1\ln F(z_{12} - Z_2) \\ &\qquad + \alpha_2\ln F(z_{24} - Z_2)) + \ldots \\ &\qquad + r_k(\alpha_1\ln F(z_{12} - Z_k) + \alpha_2\ln F(z_{24} - Z_k)).\end{aligned} \tag{2C}$$

If $\ln(F)$ is convex then the last inequality is false and by definition of a convex function we have:

$$\begin{aligned}&\ln F(z_{12} - Z_1) < (\alpha_1\ln F(z_{12} - Z_1) + \alpha_2\ln F(z_{24} - Z_1), \\ &\ln F(z_{22} - Z_2) < (\alpha_1\ln F(z_{12} - Z_2) + \alpha_2\ln F(z_{24} - Z_2), \\ &\quad\ldots \\ &\ln F(z_{22} - Z_k) (\alpha_1\ln F(z_{12} - Z_k) + \alpha_2\ln F(z_{24} - Z_k)).\end{aligned} \tag{2D}$$

Therefore, fitness products of at least one of the heterozygotes, $ij' = 12$ or $ij' = 24$, is higher than that of the homozygote $ij = 22$. By analogy, it can be shown that at least one of the heterozygotes, $ij' = 13$ or $ij' = 34$, is superior over the homozygote $ij' = 33$.

In case of concave $\ln(F)$, one can consider a triple of genotypes $ij = 11, 12, 22$. In a similar way, it is easy to show that the fitness products of at least one of the homozygotes, $ij = 11$ or $ij = 22$, is lower than that of the heterozygote $ij' = 12$. Analogous results can be obtained for the triples $ij = 33, 34, 44$ and $ij' = 22, 23, 33$.