On the Mutual Maintenance of a Polymorphism in Two Nonepistatic Loci with Partial Selfing

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Received May 21, 1976

In a two-locus system of multiplicative fitnesses with a mixed selfing and random mating, the maintenance of a polymorphism in each locus is not independent of its maintenance in the other one.

Introduction

An intriguing problem in theoretical population genetics is what conditions and limitation permit the analysis of a genetical structure of a natural population at one or a few loci, while ignoring the possible interaction of these with other loci. It is sometimes argued that for nonepistatic fitness expression and loose linkage, the biological realizations are determined by the individual loci effects. An empirical question, yet to be settled, is whether there is one locus (or even a small set of loci) which is virtually in epistasis with all other loci. On a theoretical level, however, it is correct that in any multilocus selection model of a randomly mating population in the presence of loose linkage, the existence of a stable polymorphism at a nonepistatic locus is independent of selection forces operating at other loci (e.g., see Karlin, 1975). Moreover, if nonepistasis is defined in terms of fitness multiplicity (which, in the case of relative fitness, seems to be the natural way to define it), the very selection forces—and, thus, the limit allelic frequencies at each nonepistatic locus—will not be affected by other loci.

This may not be the case in nonrandom mating patterns. It is definitely not the case in mixed selfing and random mating systems. An interesting result in this direction was first achieved by Strobeck (1977). As he has shown, a two-allele polymorphism being stably maintained at one locus will cause an increase in the frequency of heterozygotes at any neutral locus.

For a heuristic discussion of this result in relation to some new results, see the last section. As it is shown, the quantitative result of Strobeck can be extended to any two-locus multiplicative fitness model in which polymorphism is maintained in both loci. More importantly, it is shown that in a general two-locus multiplicative model subjected to a mixture of selfing and random mating, the very existence of a stable polymorphism at one locus changes the conditions that a

99

polymorphism be established at the other locus. More specifically, it is shown that as the heterozygote advantage at one locus increases up to a certain value (to be explicitly calculated), the range of parameters for which a protected polymorphism is maintained at the other locus enlarges. As the heterozygote advantage at the first locus increases above this level, the polymorphism-enhancing effect on other loci is reduced, tending to null as the heterozygote advantage tends to infinity.

Moreover, it is shown that a two-locus protected polymorphism can be maintained stably under conditions which are not sufficient to maintain a stable polymorphism at each separate locus. Actually, this is always the case for a high-enough rate of selfing and moderate values of heterozygote advantage at each locus. For two interesting cases—free recombination and homozygous–lethal mutation with any rate of recombination—the quantitative conditions for a two-locus polymorphism (which are different from the combination of conditions achieved for each locus separately) are explicitly calculated. It is interesting that in the special case of nonlinked homozygous–lethal mutants, an increase in the rate of selfing above a given value $(2 - 2^{1/2})$ does not affect the conditions for a protected polymorphism. For any rate of selfing above the critical one, the condition will be of a geometric mean heterozygote advantage in both loci being above $2^{1/2}$. This result stands in contrast to any result achieved for a one locus model with a mixed selfing and random mating.

MATHEMATICAL ANALYSIS OF THE GENERAL MULTIPLICATIVE MODEL WITH MIXED SELFING AND RANDOM MATING

We assume a two-locus model of an infinite size population undergoing recombination, mating, and selection in this order. Each generation, a proportion α $(0 \leqslant \alpha \leqslant 1)$ of the individuals in the population propagate by selfing, independently of their genotypes. The rest of the population mates at random (see, for comparison, Benet and Binet, 1956; Kimura, 1957; Parsons, 1957; Karlin, 1968). For mathematical tractability, we assume that recombination occurs only in one sex. We assume a general rate of recombination between the two loci, although part of the calculation is done under the assumption of free recombination. We believe that the qualitative results are likely independent of these restrictions. An important ingredient in the model is the assumption that selection operates according to a *multiplicative fitness model with heterozygote advantage at each locus*.

More specifically, we assume the following fitnesses and relative frequencies of the 10 genotypes:

Genotype	$\dfrac{AB}{AB}$	$\dfrac{AB}{Ab}$	$\dfrac{AB}{aB}$	$\dfrac{AB}{ab}$	$\dfrac{Ab}{Ab}$	$\dfrac{Ab}{aB}$	$\dfrac{Ab}{ab}$	$\dfrac{aB}{aB}$	$\dfrac{aB}{ab}$	$\dfrac{ab}{ab}$
Relative fitness	1	w_2	w_1	$w_1 w_2$	σ_2	$w_1 w_2$	$w_1 \sigma_2$	σ_1	$w_2 \sigma_1$	$\sigma_1 \sigma_2$
Relative frequency	x_1	x_2	x_3	x_4	x_5	x_6	x_7	x_8	x_9	x_{10}

$w_i > \sigma_i > 1$ $(i = 1, 2)$. Relative frequencies are measured after selection. We are interested in conditions for a simultaneous maintenance of a protected polymorphism in both loci. For this end, one should check the stability of the four monomorphic equilibria as well as of the four surface equilibria corresponding to situations of one-locus polymorphism. In the case of a multiplicative model, however, instability of the favorable fixation equilibrium ab (say, that of the *wild type*) readily implies instability of the other three fixation equilibria (say, the mutant monomorphisms). Moreover, we see that in an interesting situation, instability of the fixation states also implies instability of the other edge equilibria.

We thus start by local analysis of the stability of the monomorphic equilibrium ab. Denote $x_{10} = 1 - \sum_{i=1}^{9} x_i$. We are interested in changes in the relative frequencies $(x_1, ..., x_9)$ in the vicinity of the wild-type equilibrium state $(0, ..., 0)$. Discarding quadratic and smaller terms, we obtain the matrix of the state linear approximation for the changes in the relative genotype frequencies (Table I).

Two eigenvalues of the matrix are immediately extracted:

$$\lambda_1 = \alpha w_1/\sigma_1\sigma_2; \qquad \lambda_2 = \alpha w_2/\sigma_1\sigma_2 .$$

The other eigenvalues coincide with those of the matrixes

$$B_1 = \frac{1}{\sigma_1} \left\| \begin{matrix} \alpha & \dfrac{\alpha}{4} \\ 2(1 - \alpha)\, w_1 & \dfrac{2 - \alpha}{2}\, w_1 \end{matrix} \right\|,$$

$$B_2 = \frac{1}{\sigma_2} \left\| \begin{matrix} \alpha & \dfrac{\alpha}{4} \\ 2(1 - \alpha)\, w_2 & \dfrac{2 - \alpha}{2}\, w_2 \end{matrix} \right\|,$$

and

$$B_3 = \frac{1}{\sigma_1\sigma_2} \left\| \begin{matrix} \alpha & \dfrac{(1 - r)\,\alpha}{4} & \dfrac{r\alpha}{4} \\ 2(1 - \alpha)\, w_1 w_2 & \dfrac{2 - \alpha}{2}\, w_1 w_2 (1 - r) & \dfrac{2 - \alpha}{2}\, r w_1 w_2 \\ 0 & \dfrac{\alpha r w_1 w_2}{2} & \dfrac{\alpha(1 - r)\, w_1 w_2}{2} \end{matrix} \right\|.$$

The first two eigenvalues correspond to changes in the frequencies of AB/Ab and AB/aB, respectively. These eigenvalues are easily seen to be smaller than the largest eigenvalues of B_1 and B_2, respectively. The matrix B_1 corresponds

TABLE I

$$A = \frac{1}{\sigma_1\sigma_2}$$

α	$\dfrac{\alpha}{4}$	$\dfrac{\alpha}{4}$	$\dfrac{(1-r)\alpha}{4}$	0	$\dfrac{r\alpha}{4}$	0	0	0
0	$\dfrac{\alpha\sigma_2}{2}$	0	0	0	0	0	0	0
0	0	$\dfrac{\alpha w_1}{2}$	0	0	0	0	0	0
$2(1-\alpha)w_1w_2$	$(1-\alpha)w_1\sigma_2$	$(1-\alpha)w_1w_2$	$\dfrac{2-\alpha}{2}(2-r)w_1w_2$	0	$\dfrac{2-\alpha}{2}rw_1w_2$	0	0	0
0	$\dfrac{\alpha\sigma_2}{4}$	0	$\dfrac{\alpha r\sigma_2}{4}$	$\alpha\sigma_2$	$\dfrac{\alpha(1-r)\sigma_2}{4}$	$\dfrac{\alpha\sigma_2}{4}$	0	0
0	0	0	$\dfrac{\alpha r w_1 w_2}{2}$	0	$\dfrac{\alpha(1-r)w_1w_2}{2}$	0	0	0
0	$(1-\alpha)w_1\sigma_2$	0	$(1-\alpha)rw_1\sigma_2$	$2(1-\alpha)w_1\sigma_2$	$(1-r)(1-\alpha)w_1\sigma_2$	$\dfrac{(2-\alpha)w_1\sigma_2}{2}$	0	0
0	0	$\dfrac{\alpha\sigma_1}{4}$	$\dfrac{\alpha r\sigma_1}{4}$	0	$\dfrac{(1-r)\alpha\sigma_1}{4}$	0	$\alpha\sigma_1$	$\dfrac{\alpha\sigma_1}{4}$
0	0	0	$(1-\alpha)rw_2\sigma_1$	0	$(1-\alpha)(1-r)w_2\sigma_1$	0	$2(1-\alpha)w_2\sigma_1$	$\dfrac{2-\alpha}{2}w_2\sigma_1$

to changes in frequencies of the types Ab/Ab and Ab/ab. The matrix B_2 corresponds to changes in the frequencies of aB/aB and aB/ab. The matrix B_3 corresponds to changes in the frequencies of AB/AB, AB/ab, and aB/Ab (the homozygous double mutant and the two double heterozygotes).

Let μ_i denote the largest real eigenvalue of the matrix B_i ($i = 1, 2, 3$). By Frobenius' theorem, it follows that these eigenvalues are also the largest in absolute values. For $i = 1, 2$, it is readily shown that

$$\mu_1 > 1 \quad \text{if and only if} \quad \frac{w_1}{\sigma_1} > \frac{2(\sigma_1 - \alpha)}{(2 - \alpha)\,\sigma_1 - \alpha} = K(\alpha, \sigma_1), \quad (2.1)$$

$$\mu_2 > 1 \quad \text{if and only if} \quad \frac{w_2}{\sigma_2} > \frac{2(\sigma_2 - \alpha)}{(2 - \alpha)\,\sigma_2 - \alpha} = K(\alpha, \sigma_2). \quad (2.2)$$

Not surprisingly, these are exactly the conditions for a polymorphism being maintained stably in each locus separately. Thus, conditions for one-locus instability of the monomorphic states are sufficient for instability of the two-locus monomorphic state. A study of the matrix B_3, however, specifies conditions for which $\mu_3 > 1$ and μ_1, $\mu_2 < 1$. Under these conditions, the wild-type monomorphic equilibrium is unstable, and all other monomorphic equilibria are even more so. Moreover, in this case, having $w_i/\sigma_i < K(\alpha, \sigma_i)$, $i = 1, 2$, one can resort to one-locus analysis to show that no surface equilibrium corresponding to fixation at only one locus can be stable in respect to allelic frequencies at the other locus. Thus, when μ_1, $\mu_2 < 1$ but $\mu_3 > 1$, both the A and the B alleles are to be maintained stably in the population, yet none of them can be maintained alone. Quite surprisingly, this result is to be manifested even under the condition of no linkage (as well as of no biological epistasis) between the two loci, with linkage disequilibrium tending to zero. Heuristically, it may be explained on the basis of a statistical bias imposed by selection in one locus, on the frequency of surviving heterozygotes (though, without linkage disequilibrium, not directly on the allelic frequency) in the other locus.

Starting with the most interesting case of free recombination $r = \frac{1}{2}$, B_3 becomes

$$B_3\left(\frac{1}{2}\right) = \frac{1}{\sigma_1 \sigma_2} \left\| \begin{matrix} \alpha & \dfrac{\alpha}{8} & \dfrac{\alpha}{8} \\[2ex] 2(1 - \alpha)\,w_1 w_2 & \dfrac{2 - \alpha}{4}\,w_1 w_2 & \dfrac{2 - \alpha}{4}\,w_1 w_2 \\[2ex] 0 & \dfrac{\alpha w_1 w_2}{4} & \dfrac{\alpha w_1 w_2}{4} \end{matrix} \right\|$$

and the eigenvalues of B_3 are the solutions of the equation

$$|B_3 - Ix| = \frac{1}{\sigma_1{}^3\sigma_2{}^3} \begin{vmatrix} \alpha - \sigma_1\sigma_2 x & \dfrac{\alpha}{8} & \dfrac{\alpha}{8} \\[2ex] 2(1-\alpha)\,w_1 w_2 & \dfrac{2-\alpha}{4}\,w_1 w_2 - \sigma_1\sigma_2 x & \dfrac{2-\alpha}{4}\,w_1 w_2 \\[2ex] 0 & \dfrac{\alpha}{4}\,w_1 w_2 & \dfrac{\alpha}{4}\,w_1 w_2 - \sigma_1\sigma_2 x \end{vmatrix}$$

$$= -\frac{x}{\sigma_1{}^2\sigma_2{}^2} \begin{vmatrix} \alpha - \sigma_1\sigma_2 x & \dfrac{\alpha}{8} \\[2ex] 2(1-\alpha)\,w_1 w_2 & \dfrac{w_1 w_2}{2} - \sigma_1\sigma_2 x \end{vmatrix} = 0.$$

(The second equality is obtained by subtracting the second column from the third one and then adding the second row to the third one). μ_3 is, therefore, the largest eigenvalue of the matrix

$$\frac{1}{\sigma_1\sigma_2} \begin{Vmatrix} \alpha & \dfrac{\alpha}{8} \\[2ex] 2(1-\alpha)\,w_1 w_2 & \dfrac{w_1 w_2}{2} \end{Vmatrix}.$$

Hence, $\mu_3 > 1$ if either

$$\alpha + \frac{w_1 w_2}{2} > 2\sigma_1\sigma_2 \tag{2.3}$$

or

$$\frac{1}{\sigma_1\sigma_2}\left(\alpha + \frac{w_1 w_2}{2}\right) > 1 + \frac{(1+\alpha)\,w_1 w_2}{4\sigma_1{}^2\sigma_2{}^2}$$

which is equivalent to

$$\frac{w_1 w_2}{\sigma_1\sigma_2} > \frac{4(\sigma_1\sigma_2 - \alpha)}{2\sigma_1\sigma_2 - \alpha(\alpha+1)} = K_2(\alpha, \sigma_1\sigma_2), \tag{2.4}$$

say.

But it is readily shown that with $w_1 w_2 \geqslant \sigma_1\sigma_2 \geqslant 1$, $0 \leqslant \alpha \leqslant 1$, (2.3) implies (2.4). Hence (2.4) is a necessary and a sufficient condition for $\mu_3 > 1$. In this case we also have $|B_3 - I| > 0$.

We thus conclude that a necessary and a sufficient condition for instability of the wild-type equilibrium is that at least one of the inequalities (2.1), (2.2), or (2.4) holds. But for all $\sigma_1 > 1$, $\sigma_2 > 1$:

$$K(0, \sigma_1)\,K(0, \sigma_2) = 0 < 2 = K_2(0, \sigma_1\sigma_2) = K_2(1, \sigma_1\sigma_2) < 4 = K(1, \sigma_1)\,K(1, \sigma_2).$$

From the continuity of the functions K and K_2, we therefore infer that for a sufficiently high rate of selfing α

$$K_2(\alpha, \sigma_1\sigma_2, \tfrac{1}{2}) < K(\alpha, \sigma_1)\, K(\alpha, \sigma_2) \qquad (2.5)$$

and vice versa if α is sufficiently small.

For a low rate of selfing (depending on σ_1 and σ_2), we therefore conclude that the wild-type monomorphism is unstable in respect to two-locus nonepistatic mutation only if it is unstable in respect to the occurrence of the mutation in at least one of these loci. (The reverse of condition (2.5) means that if $\mu_1, \mu_2 < 1$, then indeed $\mu_3 < 1$.)

If, on the other hand, the rate of selfing is high enough, condition (2.5) indicates the existence of a nonempty range of values w_1 and w_2 for which

$$w_i/\alpha_i < K(\alpha, \sigma_i), \qquad i = 1, 2$$

and, therefore, $\mu_1, \mu_2 < 1$, but

$$w_1 w_2/\sigma_1\sigma_2 > K_2(\alpha, \sigma_1\sigma_2)$$

and, hence, $\mu_3 > 1$. As we have seen, this implies instability of all the other corners. Moreover, $\mu_1, \mu_2 < 1$ implies that no equilibrium exists on the edges.

COROLLARY. *With free recombination and a high enough rate of selfing a protected polymorphism can be maintained in both loci simultaneously when neither one-locus protected polymorphism can be maintained.*

Quite expectedly we now see that linkage only enhances simultaneous polymorphism in both loci (indeed, it does not affect the maintenance of polymorphism in each locus separately). More specifically we show that for any rate of recombination $0 \leqslant r < \tfrac{1}{2}$, a critical value $K_2(\alpha, \sigma_1\sigma_2, r)$ exists, $K_2(\alpha, \sigma_1\sigma_2, r) < K_2(\alpha, \sigma_1\sigma_2) = K_2(\alpha, \sigma_1\sigma_2, \tfrac{1}{2})$, such that if

$$w_1 w_2/\sigma_1\sigma_2 > K_2(\alpha, \sigma_1\sigma_2, r) \qquad (2.6)$$

then the wild-type equilibrium is unstable.

Recall that the wild-type equilibrium is unstable if $\mu_3 = \mu_3(r) > 1$ and $\mu_3(r)$ is the largest (positive) solution of the equation

$$|B_3(r) - Ix| = 0.$$

Since

$$\lim_{x \to \infty} |B_3(r) - Ix| = -\infty,$$

$\mu_3(r) > 1$ if (but not only if) $| Br(r) - I | > 0$. A straightforward calculation indicates that $| B_3(r) - Ix |$ is a linear function of r (all nonlinear terms are cancelled out). Thus

$$| B_3(r) - I | = (1 - 2r)| B_3(0) - I | + 2r | B_3(\tfrac{1}{2}) - I |. \qquad (2.7)$$

As we have seen, $| B_3(\tfrac{1}{2}) - I | > 0$ if and only if $w_1 w_2 / \sigma_1 \sigma_2 > K_2(\alpha, \sigma_1 \sigma_2)$. For $r = 0$ we get:

$$| B_3(0) - I | = \begin{vmatrix} \dfrac{\alpha}{\sigma_2 \sigma_2} - 1 & \dfrac{\alpha}{4\sigma_1 \sigma_2} & 0 \\[2mm] 2(1 - \alpha)\dfrac{w_2 w_2}{\sigma_1 \sigma_2} & \dfrac{2 - \alpha}{2}\dfrac{w_1 w_2}{\sigma_1 \sigma_2} - 1 & 0 \\[2mm] 0 & 0 & \dfrac{\alpha w_2 w_2}{2\sigma_1 \sigma_2} - 1 \end{vmatrix}$$

$$= \frac{\sigma_2{}^2 \sigma_2{}^2}{4}\left(2 - \alpha\,\frac{w_1 w_2}{\sigma_1 \sigma_2}\right)\left\{ [(2 - \alpha)\,\sigma_1 \sigma_2 - \alpha]\,\frac{w_1 w_2}{\sigma_1 \sigma_2} - 2(\sigma_1 \sigma_2 - \alpha)\right\}$$

which is positive if and only if

$$\frac{2}{\alpha} > \frac{w_1 w_2}{\sigma_1 \sigma_2} > \frac{2(\sigma_1 \sigma_2 - \alpha)}{(2 - \alpha)\,\sigma_1 \sigma_2 - \alpha}\,.$$

(It can also be shown that the right inequality is a necessary and a sufficient condition for $\mu_3(0) > 1$.) But

$$\frac{2(\sigma_1 \sigma_2 - \alpha)}{(2 - \alpha)\,\sigma_1 \sigma_2 - \alpha} < \frac{4(\sigma_1 \sigma_2 - \alpha)}{2\sigma_1 \sigma_2 - \alpha(\alpha + 1)} = K_2(\alpha, \sigma_1 \sigma_2).$$

It therefore follows from (2.7) that for any $0 \leqslant r < \tfrac{1}{2}$ there is a value $K_2(\alpha, \sigma_1 \sigma_2, r)$ in the interval

$$\left[\frac{2(\sigma_1 \sigma_2 - \alpha)}{(2 - \alpha)\,\sigma_1 \sigma_2 - \alpha}\,;\, K_2(\alpha, \sigma_1 \sigma_2) \right]$$

such that if

$$\frac{2}{\alpha} > \frac{w_1 w_2}{\sigma_1 \sigma_2} > K_2(\alpha, \sigma_1 \sigma_2, r)$$

then $| B_3(r) - I | > 0$, $\mu_3(r) > 1$, and the wild-type equilibrium is unstable. But if it is unstable for given values of w_1/σ_1 and w_2/σ_2, it will indeed be unstable for higher values of the relative fitnesses of the heterozygote mutants and we get $\mu_3(r) > 0$ for all

$$w_1 w_2 / \sigma_1 \sigma_2 > K_2(\alpha, \sigma_1 \sigma_2, r), \qquad (2.8)$$

In the special case where both mutant alleles A and B are lethal in their homozygous form, K_2 can be calculated explicitly for all $0 \leqslant r \leqslant \frac{1}{2}$. In order to study this case we let $\sigma_1, \sigma_2 \to \infty$ but keep the ratios w_i/σ_i (namely, the heterozygote advantage at each locus) fixed. By omitting rows of zeros (corresponding to lethal genotypes) together with their corresponding columns, the matrix A becomes:

$$A^* = \begin{Vmatrix} \dfrac{(2-\alpha)(1-r)\,w_1 w_2}{2\sigma_1\sigma_2} & \dfrac{(2-\alpha)\,w_1 w_2}{2\sigma_1\sigma_2} & 0 & 0 \\[2ex] \dfrac{\alpha r w_1 w_2}{2\sigma_1\sigma_2} & \dfrac{\alpha(1-r)\,w_1 w_2}{2\sigma_1\sigma_2} & 0 & 0 \\[2ex] 0 & \dfrac{(1-\alpha)\,w_1}{\sigma_1} & \dfrac{(2-\alpha)\,w_1}{2\sigma_1} & 0 \\[2ex] 0 & \dfrac{(1-\alpha)\,w_2}{\sigma_2} & 0 & \dfrac{(2-\alpha)\,w_2}{2\sigma_2} \end{Vmatrix}$$

with eigenvalues

$$\mu_1 = \left(1 - \frac{\alpha}{2}\right) \frac{w_1}{\sigma_1},$$

$$\mu_2 = \left(1 - \frac{\alpha}{2}\right) \frac{w_2}{\sigma_2},$$

$$\mu_3 = \frac{w_1 w_2}{2\sigma_1\sigma_2} (1 - r + ((1-2r)(1-\alpha)^2 + r^2)^{1/2}),$$

$$\mu_4 = \frac{w_1 w_2}{2\sigma_1\sigma_2} (1 - r - ((1-2r)(1-\alpha)^2 + r^2)^{1/2}).$$

Conditions (2.1) and (2.2) become:

$$\mu_i > 1 \quad \text{if and only if} \quad \frac{w_i}{\sigma_i} > \frac{2}{2-\alpha} \quad (i = 1, 2). \qquad (2.1a)$$

Condition (2.4) becomes

$$\frac{w_1 w_2}{\sigma_1 \sigma_2} > \frac{2}{1 - r + ((1-2r)(1-\alpha)^2 + r^2)^{1/2}} = K_2(\alpha, \infty, r). \qquad (2.4a)$$

$K_2(\alpha, \infty, r)$ is monotone increasing with r, from $K_2(\alpha, \infty, 0) = 2/(2-\alpha)$ to $K_2(\alpha, \infty, \frac{1}{2}) = 2 = \lim_{\sigma_1\sigma_2\to\infty} K_2(\alpha, \sigma_1\sigma_2)$.

Thus, for free recombination, if $\alpha \leqslant 2 - 2^{1/2}$, the wild-type equilibrium is stable if and only if

$$\mathrm{Max}\left(\frac{w_1}{\sigma_1}, \frac{w_2}{\sigma_2}\right) < \frac{2}{2-\alpha},$$

which is the exact condition for stability in each locus separately. For $\alpha > \alpha - 2^{1/2}$, an additional requirement is needed:

$$\frac{w_1 w_2}{\sigma_1 \sigma_2} < 2.$$

It is quite interesting that this additional condition is independent of any further increase in the rate of selfing. Thus, for $w_1/\sigma_1 = w_2/\sigma_2 = w/\sigma$, the condition for a protected polymorphism becomes

$$\frac{w}{\sigma} > \begin{cases} \dfrac{2}{2-\alpha} & \text{if} \quad \alpha \leqslant 2 - 2^{1/2} \\[2mm] 2^{1/2} & \text{if} \quad \alpha \geqslant 2 - 2^{1/2}. \end{cases} \tag{2.9}$$

COROLLARY. (i) *For a low rate of selfing $\alpha \leqslant 2 - 2^{1/2}$, the one-locus hetero-zygote advantage required for the establishment of two nonepistatic nonlinked homo-zygous–lethal mutations with the same heterozygous effect is equal to the one-locus heterozygote advantage $w/\sigma > 2/(2-\alpha)$ needed for the establishment of each of these mutants separately. This critical heterozygote advantage is increasing with α.*

(ii) *For a high-enough rate of selfing, $\alpha \geqslant 2 - 2^{1/2}$, the required one-locus heterozygote advantage becomes independent of any further increase in the rate of selfing, being $2^{1/2}$ for all $\alpha > 2 - 2^{1/2}$.*

We finally investigate the case where $\mu_1 < 1$ but $\mu_2 > 1$, i.e., the situation where a polymorphism could be maintained in the locus B but not in the locus A separately. In this case we know that (independently of μ_3) the wild-type equilibrium is unstable and so are all other corners. However (unlike in the case where $\mu_1 < 1$, $\mu_2 < 1$, $\mu_3 > 1$), there is an additional adge equilibrium $\hat{\mathbf{x}} = (\hat{x}_1, \dots, \hat{x}_9)$ corresponding to a polymorphism at the B locus alone. We assume fixation of the favorable a allele at the other locus. (It is readily shown that instability of this equilibrium indeed implies instability of the edge equilibrium corresponding to fixation of the less favorable A allele.) Equivalently we assume $\sum_{i=1}^{7} \hat{x}_i = 0$, while $\hat{x}_8$ and $\hat{x}_9$ satisfy the equations

$$\hat{x}_8 = \frac{\sigma_1}{w}\left\{(1-\alpha)\left(\hat{x}_8 + \frac{\hat{x}_9}{2}\right)^2 + \alpha\left(\hat{x}_8 + \frac{\hat{x}_9}{4}\right)\right\}, \tag{2.10}$$

$$\hat{x}_9 = \frac{\sigma_1 w_2}{w}\left\{2(1-\alpha)\left(\hat{x}_8 + \frac{\hat{x}_9}{2}\right)\left(1 - \hat{x}_8 - \frac{\hat{x}_9}{2}\right) + \frac{\alpha x_9}{2}\right\}, \tag{2.11}$$

$$w = \sigma_1 + (w_2 - \sigma_2)\left\{2(1-\alpha)\left(\hat{x}_8 + \frac{\hat{x}_9}{2}\right)\left(1 - \hat{x}_8 - \frac{\hat{x}_9}{2}\right) + \frac{\alpha x_9}{2}\right\}\sigma_1$$

$$+ (1 - \sigma_2)\left\{(1-\alpha)\left(1 - \hat{x}_8 - \frac{\hat{x}_9}{2}\right)^2 + \alpha\left(1 - \hat{x}_8 - \frac{3\hat{x}_9}{4}\right)\right\}\sigma_1. \tag{2.12}$$

The genetic frequencies among the newborn offspring of the selfing parents will be

$$\hat{x}_8' = \hat{x}_8 + (\hat{x}_9/4),$$
$$\hat{x}_9' = \hat{x}_9/2,$$

with an average fitness of

$$w_s = \left\{1 + (w_2 - \sigma_2)\frac{\hat{x}_9}{2} + (1 - \sigma_2)\left(1 - \hat{x}_9 - \frac{3\hat{x}_9}{4}\right)\right\}\sigma_1. \quad (2.13)$$

It is readily shown that for all $0 < \alpha < 1$, $w_s < w$. The frequency of offspring born to selfing in the entire population will therefore be

$$\alpha^* = w_s\alpha/w < \alpha. \quad (2.14)$$

Finally, it is not difficult to show that the point $\hat{x}$ will be unstable in respect to introduction of the mutant A if and only if

$$w_1/\sigma_1 > K(\alpha^*, \sigma_1). \quad (2.15)$$

(The arguments are exactly the ones given for a one-locus situation with α^* as the rate of selfing.) But since $K(\alpha, \sigma_1)$ is monotone increasing in α, $K(\alpha^*, \sigma_1) < K(\alpha, \sigma_1)$ and the condition (2.15) for instability of $\hat{x}$ is weaker than the condition (2.1) for a one-locus polymorphism.

COROLLARY. *For any rate of selfing $0 < \alpha < 1$ (though not for $\alpha = 0$ or $\alpha = 1$), and for any rate of recombination $0 < r \leqslant \frac{1}{2}$, a stable polymorphism at one locus always weakens the condition for a protected polymorphism at any other, nonepistatic locus.*

Again, it appears that a substantial heterozygote advantage in one locus, by imposing selection in favor of offspring born to random mating, weakens the relevant effect of selfing in all other loci. A natural question is thus whether a high-enough heterozygote advantage in one locus can practically null the effect of selfing in other loci. As we see, the answer to this question is always negative. Moreover, it is shown that, as the heterozygote advantage in one locus increases above some critical value, its polymorphism-maintaining effect in any other locus is reduced, tending to null as the heterozygote advantage tends to infinity.

In order to illustrate this phenomenon in quantitative detail, we analyze the symmetric viability case $\sigma_2 = 1$. In this case, a necessary and a sufficient condition for a polymorphism maintenance at the B locus is $w_2 > 1$. From (2.11)–(2.14) we then obtain

$$\alpha^* = \frac{2 + (w_2 - 1)\hat{x}_9}{2 + (1 - \alpha + \alpha\hat{x}_9)(w_2 - 1)} \quad (2.16)$$

and

$$\hat{x}_9 = 1 - \frac{w_2 + 1 - \alpha - ((w_2 + 1 - \alpha)^2 - 4\alpha(w_2 - 1))^{1/2}}{2\alpha(w_2 - 1)}. \quad (2.17)$$

(See, for example, Karlin, 1968). From (2.16) and (2.17) we readily get

$$\frac{\partial \alpha^*}{\partial w_2} = \frac{\alpha(1 - \alpha)[(w_2 + 1 - \alpha)^2 - 4\alpha(w_2 - 1)]^{1/2}}{2[2 + (1 - \alpha + \alpha\hat{x}_9)(w_2 - 1)]^2}$$

$$\times \{3w_2 - 5 - \alpha - ((w_2 + 1 - \alpha) - 4\alpha(w_2 - 1))^{1/2}\}. \quad (2.18)$$

This expression is negative for $w_2 < 2 + (1 - \alpha)^{1/2}$ and positive for $w_2 > 2 + (1 - \alpha)^{1/2}$. A maximal polymorphism-maintaining effect of a heterozygote advantage in a symmetric-viability locus is thus achieved for the critical heterozygote advantage

$$w_2^* = 2 + (1 - \alpha)^{1/2}. \quad (2.19)$$

This value is hard to estimate in the general, non-symmetric-viability case. Yet for all $\sigma_2 - 1$, it follows from (2.8) and (2.9) that

$$\hat{x}_9 \to 1 \qquad \text{as} \quad w_2/\sigma_2 \to \infty.$$

Hence, from (2.11), (2.12), and (1.13) we get

$$\alpha^* = w_3\alpha/w \to \alpha \qquad \text{as} \quad w_2/\sigma_2 \to \infty \quad (2.20)$$

and the polymorphism-maintaining effect of the extremely high heterozygote advantage is reduced to null. For heuristic understanding of this phenomenon, note that in this case of close-to-lethal homozygotes in the B locus, almost all the population will be heterozygote in respect to this locus. Hence, half of the offspring of random mating will die, compared with almost half of the offspring of the selfing—and the difference in the average fitness between offspring of the two mating systems becomes negligible.

3. Discussion

It is known that in a random-mating two-locus multiplicative model with free recombination, a stable two-locus polymorphism exists if and only if it can exist in each locus separately. As shown, this is not the case in a system with mixed selfing and random mating. In such a system, a stable polymorphism in one locus may enable the existence of a protected polymorphism in another locus which is neither linked nor epistatic. Moreover, a protected polymorphism can be main-

tained in the nonepistatic loci simultaneously when it cannot be maintained in either of them separately.

Intuitively, this phenomenon is explained on the basis of selection imposed by a heterozygote advantage in one locus in favor of offspring born to random mating. This, in turn, creates a statistical effect, similar to selection in favor of heterozygotes in other loci. This argument is also suggested as an explanation to the interesting phenomenon first revealed by Strobeck (1977). As he has shown, in a system with mixed selfing and random mating, heterozis at one locus increased the frequency of heterozygotes in another, neutral locus; this result motivated the present study. The result of both works (see also Eshel, 1977) leads to the same unfortunate conclusion that, unless we restrict ourselves to a system of a complete random mating, any investigation, either theoretical or empirical, of one locus or even of a finite set of loci, may be unsuitable. And it may be so even if one can assume that the investigated locus (or loci, or even a complete chromosome) is neither linked to nor biologically interacting with any other loci.

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