Proc. Natl. Acad. Sci. USA
Vol. 77, No. 8, pp. 4838–4841, August 1980
Evolution

Evolution of recombination in a constant environment

(evolution of sex/inversions/linkage disequilibrium/genetic modifiers)

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Communicated by Samuel Karlin, May 12, 1980

ABSTRACT **The theory of evolution at a selectively neutral locus that controls the recombination between two major loci that are under selection is studied. If the major loci are at a stable equilibrium in linkage disequilibrium under selection and recombination, then a mutation at the modifier locus will increase in frequency when rare if and only if it decreases the recombination fraction. If the major loci are in disequilibrium at a balance between selection against deleterious alleles and mutation towards them, then two new phenomena are observed. First, a recombination increasing mutation will succeed if the disequilibrium is negative and the modifier is sufficiently tightly linked to the major loci. Second, depending on the strength of selection, even if the disequilibrium is negative, recombination reduction may occur for looser linkage between the major and modifier loci.**

Most mathematical models for the evolution of recombination (often used interchangeably with sex in this context) in effectively infinite populations fall into one of two major classes. In the first, individuals are haploid and there are two loci with alleles A and a at the first and B and b at the second. There is recurrent mutation from A to a at rate μ_A and B to b at rate μ_B. Each of a and b are fitter than their alleles, and our interest is in the evolutionary rate of incorporation of the favorable double mutant ab into the population. Maynard Smith (1) showed that if the two loci are initially in linkage equilibrium and if the fitness of ab is the product of the fitnesses of Ab and aB, then recombination has no effect on the rate of change of the genotype frequencies. Eshel and Feldman (2) proved that if the fitness of ab is greater than the product of those of the advantageous single mutants Ab and aB and if the initial linkage disequilibrium is not negative, then from the first generation on there will always be more of the favored double mutants in the absence of recombination than in its presence. In this sense, recombination is disadvantageous. When the initial linkage disequilibrium is negative and mutation rates are sufficiently small, Karlin (3) showed that, for recombination rates bounded above by a specified function of the fitnesses, there can be more of the advantageous double mutants in the presence of recombination than in its absence and that this depends on the ordering of the fitnesses. In this class of deterministic models the criterion by which the success of recombination is evaluated is at the level of the population. That is, recombination succeeds if it produces a population with more of the favored double mutants.

In a second approach to the evolution of recombination initiated by Nei (4), a selectively neutral recombination-modifying gene, with alleles M and m, controls the recombination between two major loci A/a and B/b that are under selection. Recombination evolves as the alleles at the modifying locus change in frequency. Nei (4, 5) suggested that, in general, recombination would tend to be reduced as long as the selected loci were in linkage disequilibrium. Feldman (6) formulated the same problem as one of initial increase of a mutant allele at the modifier locus from an initial state at which the modifier locus was fixed and the selected loci were in equilibrium. For certain models of selection on the two major loci (additive, multiplicative, and symmetric viabilities; see, e.g., ref. 7), it was proven that if the initial equilibrium entailed linkage disequilibrium, then there was initial increase of the recombination-reducing allele.

Lewontin (8) argued that, at least for sufficiently tight linkage between the selected genes, recombination reduction would be expected because it would increase the mean fitness of the population. Karlin and McGregor (9) showed analytically that for any viability selection system and small enough recombination values, initial increase of a recombination-reducing allele would occur. They proposed that the evolution of recombination, as well as that of other evolutionarily important parameters such as rates of mutation and migration, would obey a mean fitness principle in that modifying loci would evolve in the direction of increasing the equilibrium mean fitness of the population. Although a number of examples counter to this principle for recombination modification have been exhibited (10, 11), the principle holds in considerable generality. Maynard Smith (12) conjectures (without specifying a model of recombination modification) that linkage disequilibrium at a stable equilibrium is sufficient for reduced recombination to be selected. Earlier, Teague (13) had made a similar suggestion based on studies of the evolution of inversions.

In this paper we address genetic modification of recombination in two different situations. The first is the original model of Nei (4) for which the conclusion of Feldman (6)—namely, that in the absence of interference *there is initial reduction of recombination from an equilibrium state in linkage disequilibrium*—will be shown to hold *regardless of the selection at the major loci* and of the linkage of the modifier to the related loci. This proves the conjectures of Teague and Maynard Smith.

The second situation to be discussed might be regarded as a "hybrid" between the two approaches described above. Again there is a locus controlling the recombination between two selected loci, but here the selected loci are held in a balance between selection against *deleterious* alleles and mutation towards them. It is shown that if the initial disequilibrium is negative, then increased recombination is favored, provided the modifier and selected loci are sufficiently tightly linked. As the latter linkage decreases, the result may reverse—i.e., reduced recombination between the selected genes may evolve.

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Model I: Recombination and selection (diploids)

There are three diallelic loci in the order M/m, A/a, and B/b. The M/m locus controls the recombination between A/a and B/b so that the recombination fractions between A/a and B/b produced by the modifier genotypes MM, Mm, and mm are r_1, r_2, and r_3, respectively. The recombination fraction between M/m and A/a is R, and there is no interference. There is random mating so that the evolution can be described in terms of the frequencies of the chromosomes MAB, MAb, MaB, Mab, mAB, mAb, maB, and mab—namely, x_1, x_2, x_3, x_4, x_5, x_6, x_7, and x_8, respectively. This order of the chromosomes will be retained throughout. Viability selection on the three-locus genotypes can be expressed in terms of an 8×8 matrix of relative viabilities W. Because the modifier locus is assumed to be selectively neutral, $W_{i,j} = W_{i+4,j} = W_{i,j+4} = W_{i+4,j+4}$ $(i,j = 1,2,3,4)$.

At the outset, the population is fixed on M and has reached the polymorphic equilibrium $E = (\hat{x}_1, \hat{x}_2, \hat{x}_3, \hat{x}_4, 0, 0, 0, 0)$ at which the linkage disequilibrium between A/a and B/b is $\hat{D} = \hat{x}_1\hat{x}_4 - \hat{x}_2\hat{x}_3$. (This equilibrium is stable in the frequency hyperplane $\Sigma_1^4 x_i = 1$.) Thus the initial recombination fraction is r_1. The fate of an initially small frequency of m introduced near E (for example, by mutation from M to m) can be analyzed in terms of the local stability of E in the simplex $\Sigma_{i=1}^8 x_i = 1$.

The recursion system specifying the evolution of the vector $\mathbf{x} = (x_1, x_2, \ldots, x_8)$ for the model above is given by equations 3 of Feldman (6). The local stability of E is determined by the properties of the linearized version of this recursion system whose 4×4 matrix, S, is given by equations 4 of Feldman (6), who pointed out that for $R > 0$, S is a strictly positive matrix. Thus, by the Perron–Frobenius theorem (14), S has a positive eigenvalue, denoted by λ_1, which is larger in magnitude than any of the other eigenvalues and which corresponds to a strictly positive eigenvector. If this largest eigenvalue is greater than unity, then E is unstable to the introduction of m, which will usually be incorporated into the population. It is clear from the structure of S, induced by the random mating, that r_3 will play no role in the initial increase of m. Of course, it is crucial for the later stages of evolution.

In those examples of W studied by Feldman (6), the necessary and sufficient condition for the instability of E, and hence the increase of m, in the cases where $\hat{D} \neq 0$, was that $r_2 < r_1$. If $\hat{D} = 0$, the leading eigenvalue of S is unity and the linear analysis fails to determine the local stability of E. We now outline a proof of the fact that for any W and E such that $\hat{D} \neq 0$, m increases in frequency if and only if it reduces recombination (i.e., $r_2 < r_1$).

Note first (see also ref. 6) that when $R = 0$, S decomposes into two positive 2×2 matrices, each of which has one eigenvalue larger than unity and one less than unity if $\hat{D} \neq 0$ and $r_2 < r_1$. If $r_2 > r_1 > 0$, then all four eigenvalues are less than unity [Karlin and McGregor (9) point out that the local analysis fails if $r_1 = 0$]. For any R, denote the characteristic polynomial $|S - \lambda I|$ by $f(\lambda)$. Then a series of elementary determinant operations similar to those of Teague and Deakin (15) produces the result

$$f(1) = r_1(r_1 - r_2)\hat{D}^4 W_{14}^4 g(R)/\hat{x}_1\hat{x}_2\hat{x}_3\hat{x}_4, \qquad [1]$$

in which

$$g(R) = R^2(1 - 2r_2)[1 - (\hat{Z}/\hat{D}^2 W_{14}^2)] + R[r_2(1 - \hat{Z}/\hat{D}^2 W_{14}^2) - 2r_1(1 - r_2)] + r_1(r_1 - r_2) \qquad [2]$$

and

$$\hat{Z} = \{\hat{x}_1(\hat{x}_2 W_{12} + \hat{x}_4 W_{14}) + \hat{x}_3(\hat{x}_2 W_{14} + \hat{x}_4 W_{34})\} \times \{\hat{x}_1(\hat{x}_3 W_{13} + \hat{x}_4 W_{14}) + \hat{x}_2(\hat{x}_3 W_{14} + \hat{x}_4 W_{24})\}. \qquad [3]$$

(Note that $W_{14} = W_{23}$ is the fitness of the double heterozygotes AB/ab and Ab/aB.) It is obvious that $\hat{Z} > \hat{D}^2 W_{14}^2$. Suppose first that $r_1 > r_2$. Then, as was remarked earlier, $f(\lambda)$ has two roots larger than unity and two less than unity for $R = 0$, and $g(0) > 0$. Now $g(R)$ has only one sign change in $R > 0$ and the roots of $f(\lambda)$ are continuous functions of R. Thus, the largest root of $f(\lambda)$, which is simple (i.e., cannot exhibit multiplicity) in view of the positivity of S, remains greater than unity as R increases. The conclusion is that if $\hat{D} \neq 0$, then $r_1 > r_2$ is sufficient for the instability of E and the consequent initial increase of m.

Now suppose $r_1 < r_2$. Then, at $R = 0$ all four eigenvalues of S are less than unity in magnitude and it is easy to see that $g(R) < 0$ for $R > 0$. Hence, the largest (positive) root of $f(\lambda)$ can never be larger than unity. Note that if $\hat{D} = 0$, the largest eigenvalue is unity and linear analysis fails to determine the local stability of E. *If $\hat{D} \neq 0$, then it is necessary and sufficient for the initial increase of* m *that it reduce recombination.*

Model IIA: Mutation, recombination, and selection (haploids)

The model is in some respects a hybrid between the two classes described earlier. There are three loci, M/m, A/a, and B/b, with mutation occurring from A to a and B to b at the rate μ per generation. (Extensive numerical iterations suggest that different mutation rates at the two loci do not qualitatively alter the conclusions.) The mutation rate is independent of the genotype at the M/m locus. After mutation, recombination occurs in a diploid phase with genotypes MM, Mm, and mm producing recombination fractions r_1, r_2, and r_3, respectively, with R the recombination fraction between M/m and A/a, and there is no interference. After recombination, selection occurs on the haploid products of recombination. The relative fitnesses of AB, Ab, aB, and ab are $1{:}W_1{:}W'_1{:}W_2$, irrespective of the genotype at the M/m locus, with $1 > W_1, W'_1 > W_2$. At the outset, the population is fixed on M and has attained a mutation–recombination–selection balance at the A/a and B/b loci; that is, the mutation towards a and b balances the loss in fitness to Ab, aB, and ab. Equilibria of this type have been studied by Karlin and McGregor (16). Such an equilibrium certainly exists, when $r_1 = 0$, if $1 - \mu > W_1$, $1 - \mu > W'_1$, $(1 - \mu)W_1 > W_2$, and $(1 - \mu)W'_1 > W_2$; that is, if the loss in fitness incurred by a deleterious mutation is greater than the mutation rate (see ref. 16). These inequalities are the analogs of those allowing mutation–selection balance at one locus (see, e.g., pp. 260–261 of ref. 17). They will be assumed to hold throughout our analysis of the haploid case. In addition, we assume that $W_1 = W'_1$, which entails $\hat{x}_2 = \hat{x}_3$ and reduces the algebra without affecting the qualitative findings.

These assumptions on the mutation and selection above differ from those of Eshel and Feldman (2) and Karlin (3).

The first and last of the eight recursion equations describing the evolution of the eight chromosomes are recorded below, where the frequencies $x_1, x_2, \ldots, x_8$ refer to the chromosomes in the same order as for model I:

$$\begin{aligned}\overline{W}x'_1 = {} & (1-\mu)^2(x_1 - r_1 D) - r_2(1-\mu)^2[x_1(x_6 + x_8) \\ & - x_2(x_5 + x_7)] + R(1-\mu)^2(x_5 p_M - x_1 p_m) \\ & + Rr_2(1-\mu)^2[x_1(x_6 + x_8) + x_6(x_1 + x_3) \\ & - x_2(x_5 + x_7) - x_5(x_2 + x_4)] \\ & \cdot \qquad \cdot \qquad \cdot \\ & \cdot \qquad \cdot \qquad \cdot \\ & \cdot \qquad \cdot \qquad \cdot \end{aligned} \qquad [4]$$

$$\overline{W}x'_8 = W_2\Big[\mu^2 x_5 + \mu x_6 + \mu x_7 + x_8 - r_3(1-\mu)^2 D^*$$

$$+ r_2(1-\mu)\{\mu[x_5(x_2+x_4)-x_6(x_1+x_3)] + x_7(x_2+x_4)-x_8(x_1+x_3)\} - R[\mu^2(x_5p_M - x_1p_m) + \mu(x_6p_M - x_2p_m + x_7p_M - x_3p_m) + x_8p_M - x_4p_m] - Rr_2(1-\mu) \times \{\mu[x_5(x_2+x_4)+x_2(x_5+x_7) - x_1(x_6+x_8)-x_6(x_1+x_3)] + x_7(x_2+x_4)+x_4(x_5+x_7) - x_3(x_6+x_8)-x_8(x_1+x_3)\}\Big].$$

Here $D = x_1x_4 - x_2x_3$, $D^* = x_5x_8 - x_6x_7$, $p_M = \sum_{i=1}^{4} x_i = 1 - p_m$, and $\overline{W} = (x_1+x_5)[(1-\mu)^2 + 2W_1\mu(1-\mu) + W_2\mu^2] + (x_2+x_3+x_6+x_7)[W_1(1-\mu)+W_2\mu] + (x_4+x_8)W_2 - [r_1D + r_3D^* + r_2(x_1x_8 + x_4x_5 - x_2x_7 - x_3x_6)](1-\mu)^2(1 - 2W_1 + W_2)$.

Under the hypothesis of the model there is an equilibrium $E_H = (\hat{x}_1, \hat{x}_2, \hat{x}_2, \hat{x}_4, 0, 0, 0, 0)$ that is stable in the hyperplane $\sum_{i=1}^{4} x_i = 1$; that is, with M fixed and recombination fraction r_1 if $\hat{\overline{W}} > W_1(1-\mu)$. We ask under what conditions will E_H be locally unstable to the introduction of m, that is, in the full simplex $\sum_{i=1}^{8} x_i = 1$? A few elementary relationships among the equilibrium frequencies at E_H are required.

Remark 1: The equilibrium value of $\overline{W}$ (namely, $\hat{\overline{W}}$) satisfies $\hat{\overline{W}} > W_1(1-\mu) > W_2$. From the sum of the first two equations of [4], at equilibrium, $\overline{W}(\hat{x}_1 + \hat{x}_2) = (1-\mu)W_1(\hat{x}_1+\hat{x}_2) + (1-\mu)^2(1-W_1)(\hat{x}_1 - r_1\hat{D})$, the first inequality is clear, and the inequality $W_1(1-\mu) > W_2$ is part of the hypothesis. In addition, the inequality $\hat{\overline{W}} > (1-\mu)^2(1-r_1)$ follows from the first equation of [4]. Thus, E_H is stable under the assumptions.

Remark 2: A direct evaluation by using [4] produces the equilibrium identity $[\hat{\overline{W}}^2 - W_2(1-\mu)^2(1-r_1)]\hat{D} = [(1-\mu)(\mu\hat{x}_1+\hat{x}_2) + r_1(1-\mu)^2\hat{D}]^2(W_2 - W_1^2)$. In view of *Remark 1*, this entails that the sign of the product $\hat{D}(W_2 - W_1^2)$ is positive. A similar identity holds when $\mu_A \neq \mu_B$ and

$$W_1 \neq W'_1$$
$$[\hat{\overline{W}}^2 - (1-\mu_A)(1-\mu_B)W_2(1-r_1)]\hat{D} = (W_2 - W_1W'_1) \times [(1-\mu_A)(\mu_B\hat{x}_1+\hat{x}_2) + r_1(1-\mu_A)(1-\mu_B)\hat{D}] [(1-\mu_B)(\mu_A\hat{x}_1+\hat{x}_3) + r_1(1-\mu_A)(1-\mu_B)\hat{D}].$$

For the stability of E_H, note first that the linearized version of [4] near E_H has a strictly positive matrix, S_H, for $R > 0$ while for $R = 0$ it splits into two positive 2×2 matrices $S_{1,2}$ and $S_{3,4}$ in which the subscripts denote the components of [4] from which they are derived. Both eigenvalues of $S_{3,4}$ are less than unity in magnitude if

$$K = [\hat{\overline{W}} - W_1(1-\mu)](\hat{\overline{W}} - W_2) - r_2(1-\mu) \times \{W_1(W_2 - \hat{\overline{W}}) + \hat{\overline{W}}(W_1 - W_2)(\hat{x}_1+\hat{x}_2)\} \quad [5]$$

is positive. In view of *Remark 1*, to show that $K > 0$, it is sufficient that the last factor be shown to be negative. This follows from a direct evaluation by using [4] and *Remark 2*. The larger eigenvalue of $S_{1,2}$ is greater than unity if and only if

$$(r_1 - r_2)\hat{D}(\overline{W} - W_1(1-\mu)) > 0. \quad [6]$$

In view of *Remark 1*, this demonstrates that when $R = 0$ the condition for the increase of the recombination-modifying allele m is that it increase recombination if $\hat{D} < 0$ and decrease it if $\hat{D} > 0$.

For $R > 0$, the characteristic polynomial $f_H(\lambda)$ of S_H is of fourth degree. By elementary determinant manipulations, $f_H(1)$ can be evaluated and shown to have the same sign as

$$(r_1 - r_2)\hat{D}g_H(R), \quad [7]$$

in which $g_H(R)$ is a quadratic function of R:

$$g_H(R) = R^2(1-\mu)^2(1-2r_2)[W_1^2(W_2 - \hat{\overline{W}}) + 2\hat{\overline{W}}W_1(W_1 - W_2)(\hat{x}_1+\hat{x}_2)] + R\{2[\hat{\overline{W}} - W_1(1-\mu)](1-r_2)(1-\mu)K + r_2(1-\mu)^2[W_1^2(W_2 - \hat{\overline{W}}) + 2\hat{\overline{W}}W_1(W_1 - W_2)(\hat{x}_1+\hat{x}_2)]\} - [\hat{\overline{W}} - W_1(1-\mu)]K, \quad [8]$$

and K is given in [5]. Because K is positive, either $g_H(R) < 0$ for all $R \geq 0$ or $g_H(R)$ has a single positive root denoted by R^*. In the former case, for all $R \geq 0$, E_H is unstable if

$$(r_1 - r_2)\hat{D} > 0. \quad [9]$$

In the latter, E_H is unstable if [9] holds, provided $R < R^*$. For $R > R^*$, there are two possibilities. The unique largest eigenvalue passes through 1 at $R = R^*$ and could be smaller than 1 for $R > R^*$. Alternatively, one of the three eigenvalues less than 1 in magnitude passes through 1 at $R = R^*$ so that two are larger than unity in magnitude for $R > R^*$. Now at $R = 1$, $f_H(\lambda)$ factors and it is possible to show that if $\hat{D} < 0$, only the first alternative is possible. If $\hat{D} > 0$, then for small enough mutation rates the first alternative is the only possibility. An extensive numerical survey of the properties of [4] under iteration has been made and in all cases where R^* exists, $R > R^*$ entails a reversal in the stability properties of E_H from $R < R^*$. Thus, if $(r_1 - r_2)\hat{D} > 0$, then $R < R^*$ ensures the increase of m near E_H, whereas $R > R^*$ entails its decrease. In the same way, if $(r_1 - r_2)\hat{D} < 0$, then either E_H is stable for all R or it is stable for $R < R^*$ and unstable for $R > R^*$. If $R^* > 1/2$, this threshold is not biologically relevant.

To summarize, in the haploid model I (under the hypotheses stated), when $\hat{D} < 0$ and $r_2 > r_1$, then for tight enough linkage of the modifier to the selected loci, m increases so that recombination increases. In the same way, when $\hat{D} > 0$, and $r_1 > r_2$, a modifier that decreases recombination will enter the population if it is linked to the major loci, but if the linkage is loose enough (when R^* exists), it may be eliminated. The sign of $\hat{D}$ is determined by the quantity $(W_2 - W_1W'_1)$.

Model IIB: Mutation, recombination, and selection (diploids)

In model I, the initial equilibrium near which the modifying allele m was introduced was maintained by selection interacting with recombination to produce stable linkage disequilibrium. Now we modify that model so that after selection and recombination there is mutation from A to a and B to b each at the rate μ per generation. After the selection and recombination, the frequencies $x_1^*, x_2^*, \ldots, x_8^*$ of $MAB, MAb, \ldots, mab$ are given by equations 3 of Feldman (6). After mutation these frequencies become

$$\begin{aligned} x'_1 &= (1-\mu)^2x_1^*, \\ x'_2 &= (1-\mu)[\mu x_1^* + x_2^*], \\ x'_3 &= (1-\mu)[\mu x_1^* + x_3^*], \\ x'_4 &= \mu^2x_1^* + \mu(x_2^* + x_3^*) + x_4^*, \\ x'_5 &= (1-\mu)^2x_5^*, \\ x'_6 &= (1-\mu)[\mu x_5^* + x_6^*], \\ x'_7 &= (1-\mu)[\mu x_5^* + x_7^*], \\ x'_8 &= \mu^2x_5^* + \mu(x_6^* + x_7^*) + x_8^*. \end{aligned} \quad [10]$$

As with model IIA, the mutant alleles are assumed to be deleterious and a mutation–selection–recombination balance is produced. Assumptions on the selection matrix **W** analogous to those relating the haploid fitnesses and the mutation rate are that the relative fitness loss due to the substitution of a for A or

b for B is greater than the mutation rate—for example, $(1-\mu)W_{11} > W_{12}$, etc. The notation for the various recombination frequencies is the same as was used earlier. The algebra is greatly simplified if the additional assumption $W_{2j} = W_{3j}$, $W_{i2} = W_{i3}$ is made for all i,j. (This is analogous to $W_1 = W_1'$ in model IIA.) Numerical work indicates that as long as the other assumptions hold, this does not qualitatively affect the results.

With M fixed, the population achieves the equilibrium $E_D = (\hat{x}_1, \hat{x}_2, \hat{x}_2, \hat{x}_4, 0, 0, 0, 0)$ when $\hat{\overline{W}} - (1-\mu)\hat{W}_{2\cdot} > (1-\mu)(W_{22} - W_{14})\hat{x}_2$. The fate of m upon introduction near E_D is determined by the local stability properties of E_D. The matrix of the linearization of [10] is $S_D = TS^*$, in which

$$T = \begin{pmatrix} (1-\mu)^2 & 0 & 0 & 0 \\ \mu(1-\mu) & 1-\mu & 0 & 0 \\ \mu(1-\mu) & 0 & 1-\mu & 0 \\ \mu^2 & \mu & \mu & 1 \end{pmatrix}$$

and S^* has the structure of S used in model I, but with equilibrium values from E_D replacing those from E.

Remark 3: Throughout this local analysis the quantities $\hat{W}_{i\cdot} = \sum_{j=1}^{4} W_{ij}\hat{x}_j$ for $i = 1, 2, 3, 4$ take the roles of the relative fitnesses $1, W_1, W_1', W_2$ in model IIA. Thus, if $\hat{D} < 0$, $\overline{W} > (1-\mu)^2 W_{1\cdot} > (1-\mu)\hat{W}_{2\cdot}$, whereas if $\hat{D} > 0$, $(1-\mu)^2\hat{W}_{1\cdot} > \overline{W} > (1-\mu)\hat{W}_{2\cdot}$. A sufficient condition for stability of E_D is $W_{14} > W_{22}$.

The characteristic polynomial, $f_D(\lambda)$ of S_D shares many qualitative properties with $f_H(\lambda)$ from model IIA. When $R = 0$, it factors into two quadratics and has a single root larger than unity if

$$(r_1 - r_2)\hat{D}L > 0, \qquad [11]$$

in which

$$L = (\hat{\overline{W}} - (1-\mu)\hat{W}_{2\cdot})(\hat{\overline{W}} - W_{4\cdot}) - r_2(1-\mu)[(\hat{W}_{2\cdot} - \hat{\overline{W}})(\hat{x}_2 W_{24} + \hat{x}_1 W_{14}) + (\hat{W}_{4\cdot} - \hat{\overline{W}})(\hat{x}_2 W_{22} + \hat{x}_4 W_{24})]. \qquad [12]$$

The quantity L is the diploid analog of K defined by [5]. To show that the term multiplying $-r_2$ in [12] is negative is much more difficult than the corresponding argument for [5]. The reason appears to lie in the viabilities W_{22} and W_{14}, both of which refer to genotypes with two mutant alleles. It is difficult to justify *ad hoc* assumptions about the relationship between these fitnesses. However, if the assumption in the hypothesis that $(1-\mu)\hat{W}_{1\cdot} > \hat{W}_{2\cdot}$ is strengthened to become $(1-\mu)^2\hat{W}_{1\cdot} > \hat{W}_{2\cdot}$, then it is not difficult to show that $\overline{W} > W_{2\cdot}$, so that $L > 0$. This is entirely reasonable if the mutation rate is small compared to the fitness loss incurred by carriers.

Under the conditions just described for $R > 0$, the same two possibilities arise as for the haploid model. Either the condition $(r_1 - r_2)\hat{D} > 0$ entails instability of E_D for all R or there exists R^* such that for $R < R^*$ there is instability for $(r_1 - r_2)\hat{D} > 0$, and, for $R > R^*$, instability requires $(r_1 - r_2)\hat{D} < 0$.

The conclusion is that under reasonable assumptions on the parameters a recombination-increasing allele will succeed if initially $\hat{D} < 0$ and if the modifier locus is linked sufficiently tightly to the major genes. For loose linkage, $\hat{D} < 0$ will result in the success of a recombination-reducing allele.

Discussion

Laboratory selection of recombination rates has not succeeded in defining the nature of genetic variation for recombination although there seems to be some evidence that low recombination is dominant to high (see ref. 12 for a review). On the other hand, most analytic theory has, up to now, suggested that recombination-reducing genes should succeed in random mating and self-fertilizing systems (18). It is true that in most cases this reduction is due to a concomitant increase in mean fitness. However, the result of model I suggests that under selection and recombination alone the more general principle, independent of the viability assumptions, is that originally suggested by Nei—namely, reduction.

From a comparison of the results of Eshel and Feldman (2) and Karlin (3), with the inclusion of mutation, some dependence on the sign of the initial linkage disequilibrium might have been expected. However, the selection–mutation interaction is different in the present study from the earlier ones. In addition, parallels between genetic and nongenetic criteria for evolution are often not easy to make. The models presented here are the first with constant selection to allow the genetic evolution of increased recombination from a stable equilibrium at the major loci, although numerical studies by Charlesworth (19) suggest that in a fluctuating environment recombination can increase. When this occurs, the value of the largest eigenvalue that determines the initial rate of increase will be greater than unity by an amount determined by the mutation rate; from the value of $f_H(1)$ this rate should be of the order 1 + (constant)μ. Evolution of recombination by these schemes would be extremely slow. If the genetic control of recombination were coarse (that is, modification could occur over large blocks of chromosome), then the presence of mutation–selection balance at many genes simultaneously would allow an increase in this rate.

It is of interest now to pursue the genetic theory of neutral modifiers of other evolutionary important factors, such as the mating system, from the mutation–selection perspective initiated above. In particular, it would be of interest to determine how general the differences between the spectral properties of the linearized model I and models II, shown here for recombination, really are.

Excellent computational assistance was provided by Phillip Krampat and Barbara Andersen. We are grateful to Prof. S. Karlin for his critical comments on the manuscript. This research was supported in part by National Institutes of Health Grant GM10452-16 and National Science Foundation Grant DEB77-05742.

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