The Evolution of Recombination in a Heterogeneous Environment

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Manuscript received January 18, 2000
Accepted for publication May 19, 2000

ABSTRACT

Most models describing the evolution of recombination have focused on the case of a single population, implicitly assuming that all individuals are equally likely to mate and that spatial heterogeneity in selection is absent. In these models, the evolution of recombination is driven by linkage disequilibria generated either by epistatic selection or drift. Models based on epistatic selection show that recombination can be favored if epistasis is negative and weak compared to directional selection and if the recombination modifier locus is tightly linked to the selected loci. In this article, we examine the joint effects of spatial heterogeneity in selection and epistasis on the evolution of recombination. In a model with two patches, each subject to different selection regimes, we consider the cases of mutation-selection and migration-selection balance as well as the spread of beneficial alleles. We find that including spatial heterogeneity extends the range of epistasis over which recombination can be favored. Indeed, recombination can be favored without epistasis, with negative and even with positive epistasis depending on environmental circumstances. The selection pressure acting on recombination-modifier loci is often much stronger with spatial heterogeneity, and even loosely linked modifiers and free linkage may evolve. In each case, predicting whether recombination is favored requires knowledge of both the type of environmental heterogeneity and epistasis, as none of these factors alone is sufficient to predict the outcome.

U NDERSTANDING the evolution of recombination is a key component to understanding why sex is so ubiquitous in higher organisms (Michod and Levin 1988). Various hypotheses for the evolution of genetic mixis have been classified by Kondrashov (1993) into two categories: (1) physiological hypotheses and (2) generative hypotheses. Examples of the immediate physiological benefits of recombination are its roles in DNA repair and in the proper disjunction of chromosomes (reviewed in Otto and Barton 1997). Our focus here is on the second category of hypotheses and specifically on the idea that recombination has evolved because it reduces genetic associations ("linkage disequilibria") that are detrimental among loci. Several models have been proposed for the evolution of recombination. They differ mainly in the way they generate linkage disequilibria. Disequilibria can be generated stochastically by random genetic drift (Fisher 1930; Muller 1932; Hill and Robertson 1966; Felsenstein 1974; Barton 1995b; Otto and Barton 1997). They can also be generated deterministically by epistatic selection (Feldman *et al.* 1980; Kondrashov 1982; Charlesworth 1990; Barton 1995a; Otto and Feldman 1997) or by selection that varies through time (Charlesworth 1976, 1990; Hamilton 1980; Barton 1995a; Peters and Lively 1999). Clearly, the various sources

of linkage disequilibria are not mutually exclusive, and a major theoretical challenge is to understand how the different effects combine to influence the evolution of recombination. However, one potential source of linkage disequilibria has been largely neglected in this body of theory: the effect of migration in a heterogeneous environment. Natural selection varying across space maintains local differences in gene frequency. With migration, these differences in frequency in turn generate linkage disequilibria within a patch and create a selective pressure on recombination.

Spatial heterogeneity in selection: Spatial variation in selection is commonplace. Genotype-by-environment interactions for fitness-related traits are often present when measured (*e.g.*, Tachida and Mukai 1985; Bell 1991; Via 1991; and for reviews, Felsenstein 1976; Hedrick *et al.* 1976; Bell 1987; Fry *et al.* 1996). Spatial heterogeneity in selection can take several forms. The first possibility is that different alleles are favored in different environments. This scenario predominates in the literature, both in the context of the maintenance of genetic variation (*e.g.*, Levene 1953; Dempster 1955) and in the context of life-history theory (*e.g.*, in the evolution of specialization; Futuyma and Moreno 1988; Van Tienderen 1991). Such opposing selection pressures are also easily detected in natural populations and have been extensively demonstrated in the study of clines (*e.g.*, Kettlewell and Berry 1961; Bishop 1972; Koehn *et al.* 1980; Johannesson *et al.* 1995; Lenormand *et al.* 1999). The second possibility is that the

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strength but not the sign of selection varies among environments. This scenario is more difficult to observe in natural populations, because it requires careful measurements over space of either deleterious mutations at low frequency or spreading beneficial alleles. Nevertheless, evidence is accumulating that variation in the strength of selection is more common than variation in its sign (KONDRASHOV and HOULE 1994; FRY *et al.* 1996, 1998). Finally, there may be variation among environments in the way alleles interact, either at the same locus (variation in dominance; *e.g.*, BOURGUET *et al.* 1996) or different loci (variation in epistasis; *e.g.*, BARNES *et al.* 1989; BOHANNAN *et al.* 1999). With the exception of environment-dependent dominance, we consider all of the above possibilities in this article.

The modifier approach: NEI (1967) introduced a modifier approach to study the evolution of genetic systems. By tracking changes in allele frequency at a neutral modifier locus that affects some aspects of the genetic system, the modifier approach allows one to analyze precisely and quantitatively the outcome of indirect selection on transmission-related traits, for example, rates of recombination among loci. This approach is based on the assumption that there is genetic variation for recombination rates. This has been demonstrated by heritability measurements in the laboratory and by observed differences between sexes or closely related species (CHARLESWORTH and CHARLESWORTH 1985a,b; BURT and BELL 1987; TRIVERS 1988; BURT *et al.* 1991; KOROL *et al.* 1994). Recombination is also extremely variable within a genome, with areas of low recombination (such as centromeres and telomeres) as well as hotspots (the physical gap between two chromosomes being an extreme example; see review in KOROL *et al.* 1994, pp. 122–130). In both direct and indirect selection experiments, it has been shown that recombination rates can evolve through either chromosomal rearrangement (inversion, fusion, fission, etc.) or changes at recombination "modifier" loci (NEI 1967; KOROL and ILIADI 1994; KOROL *et al.* 1994, pp. 186–192).

Models have shown that it is generally not possible to ignore the exact genetic details of loci under selection to predict the outcome of modifier evolution (FELDMAN *et al.* 1980). On the other hand, the dynamics of modifier models can be enormously complex and difficult to study when several interacting factors are included. One approach, which we take in this article, is to determine the effects of including an additional factor in a modifier model. Here, we add spatial heterogeneity to a modifier model that includes mutation, selection, and epistasis. Our primary goal is to determine the sensitivity of results concerning the evolution of recombination to the inclusion of spatial variation in selection.

Previous models: Any model that generates polymorphism and linkage disequilibria at some selected loci potentially allows for the evolution of recombination. However, for a given locus there are many ways to maintain a polymorphism (recurrent mutation, migration-selection balance, frequency-dependent selection, etc.). Plus, for a set of loci, there are many ways to generate linkage disequilibria (epistatic selection, mutation, drift, migration). Given the large number of factors that might influence the evolution of recombination, the number of possible combinations that could be tested using a modifier model is enormous.

Previous modifier models considering the evolution of recombination with spatial heterogeneity have been restricted to cases where migration and selection balance to maintain polymorphisms. CHARLESWORTH and CHARLESWORTH (1979) considered numerically the evolution of recombination along clines that either were or were not coincident across loci. PYLKOV *et al.* (1998) analyzed the simplest case of coincident clines, where there is balancing selection in two demes such that alleles favorable in one deme are disadvantageous in the other. Other studies have examined the effects of environmental heterogeneity on the evolution of sex and recombination in the context of local competition among relatives. In "lottery selection" models (WILLIAMS and MITTON 1973; MAYNARD SMITH 1976, 1977; TAYLOR 1979; BULMER 1980), a genetically diversified brood is more likely to include the winning genotype under very strong truncation selection than a genetically uniform brood. In "tangled bank" models (GHISELIN 1974; BELL 1982; CASE and TAPER 1986; GAGGIOTTI 1994), a genetically diversified brood makes a more complementary use of local resources than does a genetically uniform brood. Unfortunately, epistasis is often present in these models (for instance, with the truncation selection of the lottery models), as well as migration among selectively different patches, both of which exert selection on a modifier of recombination. Consequently, it is difficult to determine the extent to which past results are due to epistatic selection, migration with spatial heterogeneity, or sib competition. None of these models considered the evolution of recombination in a heterogeneous environment when only the strength (and not the sign) of selection varies from patch to patch.

This article elucidates how environmental heterogeneity affects the evolution of recombination in populations subject to directional selection and epistasis. In addition to migration-selection balance, we consider the case of mutation-selection balance and the case of selective sweeps occurring with different selection intensities in different populations. We first review the results obtained in one population, and then we extend these results to two populations. We show that previous results for the evolution of recombination with directional selection and epistasis no longer hold when more than one population is considered. Indeed, the combined model including both epistasis and environmental heterogeneity makes predictions that are qualitatively and quantitatively different than predictions based on either factor alone.

MODEL

In this article, we analyze the evolution of recombination when the selected loci are polymorphic for one of three different reasons: (1) an equilibrium is reached between mutations that are deleterious in both patches and selection (mutation-selection equilibrium); (2) a balance is struck by migration between a patch where an allele is favored and one where it is disfavored (migration-selection equilibrium); and (3) alleles that are beneficial in both patches are increasing in frequency (sweep of beneficial mutations). We make the simplifying assumption that the same form of polymorphism occurs at all selected loci for each case. Linkage disequilibria are generated by both epistatic selection and migration.

Genetic setting: Consider a haploid population with n autosomal loci; results hold for diploids as long as selection on the diploid genotype is the geometric average of selection on its component haplotypes. Each locus i has two alleles: B_i and b_i. We let $L = (l_1, \ldots, l_n)$ represent an individual's genotype, where the variable l_i takes the value 0 when B_i is present and 1 when b_i is present at locus i. The rate of recombination between loci i and j is r_{ij}, and we assume that there is no interference among crossover events. In deme k, the frequency of the b_i allele is measured by $p_{i,k}$ ($p_{i,k} = 1 - q_{i,k}$), and the linkage disequilibrium between the two loci is measured by $D_{ij,k}$. As described below, the haplotypes are subject each generation to selection, mutation, and migration among patches, in this order.

Selection: We utilize the quadratic fitness function employed by PYLKOV *et al.* (1998) and let the fitness of an individual with genotype L in deme k be

$$w(L, k) = 1 + \sum_i a_{i,k}\, l_i + \sum_i^n \sum_{j>i} a_{ij,k} l_i l_j, \qquad (1)$$

where $a_{i,k}$ is the additive effect of allele b_i and $a_{ij,k}$ is the additive pairwise epistasis between loci i and j in deme k. The multiplicative pairwise epistasis, $\varepsilon_{ij,k}$, between loci i and j in deme k is therefore $\varepsilon_{ij,k} = a_{ij,k} - a_{i,k}\, a_{j,k}$. When considering a single deme, the subscript k is omitted. We assume throughout the analysis that viability selection is weak, *i.e.*,

$$a_{i,k} = O(\xi), \quad a_{ij,k} = O(\xi^2) \qquad (2)$$

(where ξ is a small parameter) and that the direction of selection at a locus within a patch does not depend on its genetic context (*i.e.*, epistasis is weak and does not change the sign of selection). Under these assumptions, the least or most fit haplotype within one population is also the least or most fit haplotype in the second population, and the least and the most fit haplotypes within a deme contain different alleles at both loci i and j. These properties allow us to adopt the following convention. We define the linkage disequilibrium between loci i and j within a patch such that a positive disequilibrium implies that the least fit and the most fit genotypes at these loci are overrepresented.

When considering only two loci, the mean fitness is approximately one, and the change in allele frequency due to one generation of viability selection is

$$\delta^s p_{i,k} = a_{i,k} pq_{i,k} + O(pq_{i,k}\, \xi), \qquad (3)$$

where $pq_{i,k}$ equals $p_{i,k} q_{i,k}$. Similarly, the change in linkage disequilibrium due to one generation of viability selection and recombination, provided that r_{ij} is of higher order than ξ, is

$$\delta^s D_{ij,k} = -r_{ij} D_{ij,k} + (1 - r_{ij})\varepsilon_{ij,k} pq_{ij,k} + O(pq_{ij,k}\xi^2), \qquad (4)$$

where $pq_{ij,k}$ equals $p_{i,k}q_{i,k}p_{j,k}q_{j,k}$ (BARTON 1995a).

Mutation: With deleterious mutations, we assume that the most fit B_i allele is subject to recurrent mutation at rate μ, with mutations occurring independently at each locus. The mutation rate is assumed small, of order ξ^2, and back mutations are ignored. The change in the frequency of the mutant allele, b_i, due to one generation of mutation, is

$$\delta^\mu p_{i,k} = \mu q_{i,k}. \qquad (5)$$

Since mutations are rare and since the disequilibrium generated at mutation-migration-selection balance will also be small, the linkage disequilibrium is, to leading order, unchanged by mutation:

$$\delta^\mu D_{ij,k} = [(1 - \mu)^2 - 1]D_{ij,k} = O(D_{ij,k}\xi^2). \qquad (6)$$

Migration: We consider two populations k and l of equal density (except where noted) connected by migration at rate m. The change in allele frequencies due to migration is

$$\delta^m p_{i,k} = m\Delta_i = -\delta^m p_{i,l}, \qquad (7)$$

where $\Delta_i \equiv p_{i,l} - p_{i,k}$. The change in linkage disequilibria due to migration is

$$\delta^m D_{ij,k} = m(D_{ij,l} - D_{ij,k}) + m(1 - m)\Delta_i\Delta_j$$
$$\delta^m D_{ij,l} = m(D_{ij,k} - D_{ij,l}) + m(1 - m)\Delta_i\Delta_j \qquad (8)$$

(see BARTON and GALE 1993).

Recombination modifier: A modifier allele at another locus (M) modifies the recombination rate between the viability loci by a small amount ρ (of order ξ). For clarity in the text, we assume that the M allele increases recombination ($\rho > 0$), although the equations apply equally to a modifier that decreases recombination ($\rho < 0$). The modifier locus is located at a distance r_{iM} (of higher order than ξ) from the i locus (the order of the loci is supposed to be M, i, j). For the cases of mutation-selection and migration-selection balance, we follow the dynamics of the modifier allele after it is introduced at low frequency into populations at equilibrium. For the case of selective sweeps, the total change in the modifier allele over the course of the substitutions is calculated. All qualitative results were checked by simulation using

the exact three-locus recursions of FELDMAN *et al.* (1980).

EVOLUTION AT THE MODIFIER LOCUS

The outcome of selection on the modifier locus (whether or not allele M will spread) depends on the balance of its effect on the mean fitness and on the variance in fitness among offspring carrying the new modifier allele. This can be interpreted as a short-term and a long-term effect, respectively (BARTON 1995a). We discuss these effects in turn. We first consider the roles of linkage disequilibria and epistasis separately, and then we discuss their relationship in one population and in two populations.

Short-term effect: This effect depends directly on the relative fitness of extreme genotypes ($b_i b_j$ and $B_i B_j$) *vs.* intermediate genotypes ($b_i B_j$ and $B_i b_j$). First, consider the case where $a_{ij,k}$ is positive, so that the average fitness of extreme genotypes is greater than that of intermediate genotypes. In this case, there is an immediate advantage for an individual to produce more of these extreme genotypes. In a population where extreme genotypes are underrepresented ($D_{ij,k} < 0$), an individual that recombines more often (*i.e.*, carriers of the M allele) will produce more of these extreme and, on average, more fit offspring. The M allele will therefore gain a short-term fitness advantage. Conversely, if $D_{ij,k} > 0$, the extreme genotypes are already overrepresented and will be broken apart by recombination, causing a modifier that increases recombination to have an immediate fitness disadvantage. The situation is symmetrical, and M will also gain a short-term fitness advantage if $a_{ij,k} < 0$ and $D_{ij,k} > 0$. An analytical approximation for the short-term effect on the frequency of the M allele is

$$(\delta p_{M,k})_{\text{short-term}} = -D_{ij,k} a_{ij,k} K p q_{M,k} \qquad (9)$$

(BARTON 1995a), where $K \equiv \rho/r_{ijM}$ combines the intensity of the effect of the modifier and the probability that a recombination event breaks the $\{M, i, j\}$ set of loci $[r_{ijM} = 1 - (1 - r_{iM})(1 - r_{ij})]$. This short-term effect has the sign of $-D_{ij,k}$ ($\varepsilon_{ij,k} + a_{i,k} a_{j,k}$) and is not strongly dependent on the linkage between the selected loci and the modifier (only through K, which is scaled by the $\{M, i, j\}$ map length). Figure 1a represents this short-term effect graphically.

Long-term effect: Since we have assigned a positive sign to $D_{ij,k}$ when extreme genotypes are overrepresented, the additive genetic variance in fitness in a population increases with $D_{ij,k}$ (everything else being equal). Since recombination reduces the linkage disequilibrium [$D_{ij,k}$ decreases in magnitude by a factor $(1 - r_{ij})$ each generation in the absence of other forces], recombination increases the additive genetic variance in fitness when $D_{ij,k}$ is initially negative and decreases it when $D_{ij,k}$ is initially positive. Since the response to directional selection is proportional to this variance, a modifier

allele that increases recombination will hitchhike with favorable alleles whenever $D_{ij,k}$ is negative. That is, when $D_{ij,k} < 0$, the most fit genotypes are more often generated by recombination, and they thus tend to be associated with modifier alleles that increase recombination. Of course, this long-term effect will be more pronounced if the modifier allele is tightly linked to the selected loci (it will then hitchhike for a longer period). An analytical approximation for the long-term effect on the frequency of a modifier allele, M, that increases recombination is

$$(\delta p_{M,k})_{\text{long-term}} = -D_{ij,k} K a_{i,k} a_{j,k} \left(\frac{1 - r_{iM}}{r_{iM}} + \frac{1 - r_{jM}}{r_{jM}} \right) p q_{M,k}$$

$$(10)$$

(BARTON 1995a), where K is defined as before and $r_{jM} = r_{ijM} - r_{iM} r_{ij}$. The sign of this long-term effect is the same as the sign of $-D_{ij,k}$, and its magnitude increases when the modifier locus is closer to the selected loci (r_{iM} and/or r_{jM} low). Figure 1b represents the long-term effect graphically.

Total effect: A modifier that increases recombination will thus invade if the sum of the short- and long-term effects is positive. This yields

$$\delta p_{M,k} = -D_{ij,k} K (\varepsilon_{ij,k} - \lambda_k) p q_{M,k} + O(D_{ij,k} p q_{M,k} \xi^2),$$

$$(11)$$

where

$$\lambda_k \equiv -a_{i,k} a_{j,k} \left(\frac{1}{r_{iM}} + \frac{1}{r_{jM}} - 1 \right). \qquad (12)$$

In deme k, increased recombination is selected for if

$$(D_{ij,k} > 0 \text{ and } \varepsilon_{ij,k} < \lambda_k) \quad \text{or} \quad (D_{ij,k} < 0 \text{ and } \varepsilon_{ij,k} > \lambda_k).$$

$$(13)$$

As illustrated in Figure 1, the short- and long-term effects both influence the evolution of recombination in the same direction when $\varepsilon_{ij,k} > -a_{i,k} a_{j,k}$: recombination is favored if $D_{ij,k}$ is negative but disfavored if $D_{ij,k}$ is positive. However, if $\varepsilon_{ij,k}$ is sufficiently negative, the short- and long-term effects oppose each other. The total effect on the modifier then depends on the relative magnitude of $\varepsilon_{ij,k}$ and λ_k. If $\varepsilon_{ij,k} < \lambda_k$, the short-term effects are more powerful, and recombination is only favored when $D_{ij,k}$ is positive. Conversely, if $\varepsilon_{ij,k} > \lambda_k$, the long-term effects predominate, and recombination is only favored when $D_{ij,k}$ is negative. These conditions are summarized in Figure 1c.

Two demes: The behavior described above must be slightly modified when there are two demes. From (11), we can define a selection coefficient acting on the modifier in each deme:

$$a_{M,k} \equiv \frac{\delta p_{M,k}}{p q_{M,k}} = -D_{ij,k} K (\varepsilon_{i,k} - \lambda_k) + O(D_{ij,k} \xi^2). \quad (14)$$

With migration between the demes, the frequency of the modifier is given by the system of equations:

$$\begin{bmatrix} p_{M,k} \\ p_{M,l} \end{bmatrix}_{t+1} = \begin{bmatrix} (1-m)(1+a_{M,k}) & m(1+a_{M,l}) \\ m(1+a_{M,k}) & (1-m)(1+a_{M,l}) \end{bmatrix} \cdot \begin{bmatrix} p_{M,k} \\ p_{M,l} \end{bmatrix}_t. \quad (15)$$

A migration-selection balance might be maintained at the modifier locus provided that there is disruptive selection ($a_{M,k} a_{M,l} < 0$) and low migration. More precisely, this will occur if

a

$D_{ij,k}$

$\varepsilon_{ij,k}$

$-a_{i,k}a_{j,k}$

b

$D_{ij,k}$

$\varepsilon_{ij,k}$

c

$D_{ij,k}$

$\varepsilon_{ij,k}$

λ_k $-a_{i,k}a_{j,k}$

$$m < \left| \frac{a_{M,k}a_{M,l}}{a_{M,k}+a_{M,l}} \right|. \quad (16)$$

However, assuming that condition (16) is not met, the modifier will either spread or go extinct. The leading eigenvalue of the transition matrix in (15) minus one is

$$\bar{a}_M = (a_{M,k}+a_{M,l})/2, \quad (17)$$

where the selection coefficient in each deme is given by (14). This eigenvalue indicates the asymptotic rate at which the modifier changes in frequency when rare. Consequently, a modifier allele will spread if the arithmetic mean of the selection coefficients over the two demes is positive. The above discussion was based on the values of $D_{ij,k}$ and $\varepsilon_{ij,k}$ present within a population, regardless of how these are achieved. In fact, the expected disequilibrium depends on the epistasis, and we turn now to an exposition of the relationship between them.

ONE POPULATION CASE

In this section, we briefly rederive the results found in one population (for mutation-selection balance and for sweeps of beneficial alleles) to compare them to the two-population case (see BARTON 1995a; OTTO and FELDMAN 1997).

Mutation-selection balance: In this model, a mutation-selection balance is reached at the two viability loci, where the linkage disequilibrium approaches

$$D_{ij} = \varepsilon_{ij} \frac{(1-r_{ij})pq_{ij}}{r_{ij}} + O(\xi^4) \quad (18)$$

(see Equation 4). This approximation shows that linkage disequilibrium is generated by viability selection in proportion to the amount of epistasis. Equation 18 reduces the two-dimensional (D_{ij}, ε_{ij}) space of Figure 1c to a one-dimensional line of equilibria with an intercept of zero (Figure 2, dashed line). In this situation, a modifier that increases recombination is favored only if $\lambda < \varepsilon_{ij} < 0$. Within this region, there is a long-term advantage to recombination, which is partly but not completely offset by a short-term disadvantage when $\lambda < \varepsilon_{ij} < a_i a_j$. Since λ becomes more negative as the recombination rate between the modifier and the se-
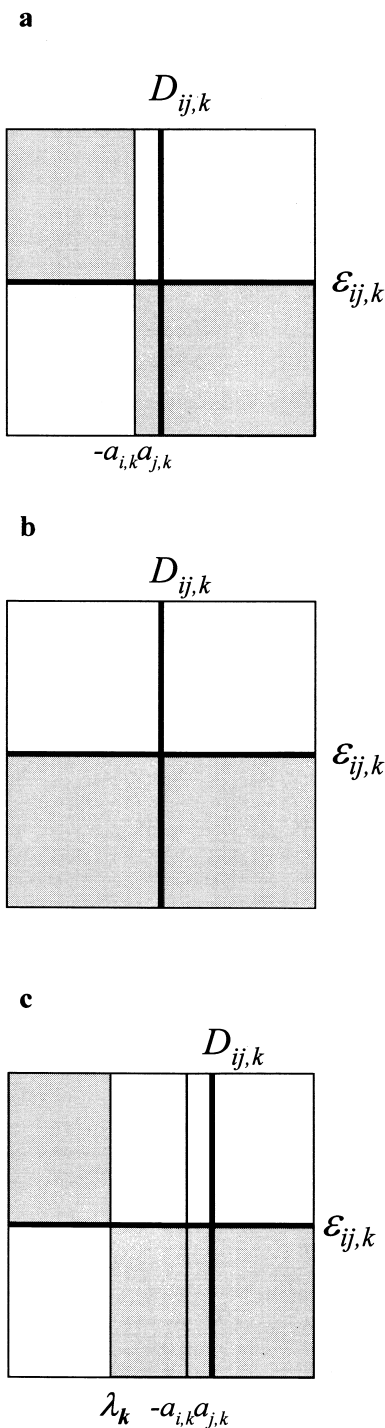
FIGURE 1.—General model for the evolution of recombination. $D_{ij,k}$ is the linkage disequilibrium, and $\varepsilon_{ij,k}$ is the multiplicative epistasis between the selected loci i and j. The index k refers to a given population. The origin of the ($D_{ij,k}, \varepsilon_{ij,k}$) space is the intersection of the bold axis. There is an advantage of a modifier that increases recombination in shaded areas: (a) the short-term advantage of recombination; (b) the long-term advantage; and (c) the combined effect of both the long- and short-term effects (see text). λ_k is given by (12).
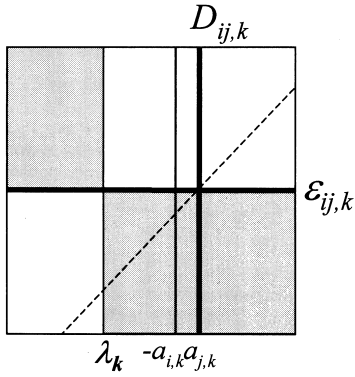
FIGURE 2.—Line of equilibria in one deme. The dashed line represents the possible $(D_{ij,k}, \varepsilon_{ij,k})$ space in a single isolated population k. The intercept of this line is zero and recombination is favored only for weak negative epistasis (shaded area). See Figure 1 for definitions.

lected loci decreases (see definition 12), the parameter space within which recombination is favored is larger for a tightly linked modifier.

As recombination evolves, λ will change, which alters the conditions for further changes at modifier loci. We can assess the ultimate evolutionary behavior of the system by asking what the evolutionary stable strategy (ESS) is for the rate of recombination. This ESS is defined as the rate of recombination $\hat{r}_{ij}$ that, if fixed within the population, is able to resist the invasion of any other modifier allele. Here we assume that the modifier only alters the recombination rate between the selected loci (r_{ij}). If, for all r_{ij}, $\lambda < \varepsilon_{ij} < 0$, recombination is always favored, and $\hat{r}_{ij} = 0.5$ is the ESS. If, for all r_{ij}, $\varepsilon_{ij} < \lambda$, or if $\varepsilon_{ij} > 0$, then recombination is always disfavored, and $\hat{r}_{ij} = 0$ is the ESS. If, however, $\lambda < \varepsilon_{ij}$ for small but not for large r_{ij} (or vice versa), that is, if

$$\frac{1 + r_{iM}}{r_{iM}} \leqslant -\varepsilon_{ij}^* \leqslant \frac{2 - r_{iM}}{r_{iM}}, \qquad (19)$$

where $\varepsilon_{ij}^* = \varepsilon_{ij}/(a_i\, a_j)$, then the ESS occurs at $\lambda = \varepsilon_{ij}$, with an intermediate recombination rate equal to

$$\hat{r}_{ij} = \frac{r_{iM}\,[2 + (\varepsilon_{ij}^* - 1)\,r_{iM}]}{(2r_{iM} - 1)\,[1 + (\varepsilon_{ij}^* - 1)\,r_{iM}]}. \qquad (20)$$

This summarizes the results for the evolution of recombination in the presence of epistasis at mutation-selection balance.

Sweep of beneficial mutations: Linkage disequilibria created by epistasis during the course of two simultaneous substitutions at different loci may also create an important selective pressure on recombination, although this effect lasts only as long as the process of substitution. With a single large population and no initial disequilibria, the sign of D_{ij} becomes the same as the sign of epistasis, and its magnitude varies with the genetic variance at the substituting loci during the selective sweep. Therefore the direction of evolution of re-

combination is predicted by the same conditions as found with a mutation-selection balance [conditions (13)]. With certain simplifying assumptions it is possible to integrate (11) over the course of the selective sweeps to determine the net change in frequency of the modifier (see BARTON 1995a, Equation 17). For instance, when both loci are subject to the same selection pressure, we have

$$p_i/\, q_i = p_j/\, q_j \approx \mathrm{Exp}(a_i t) = \mathrm{Exp}(a_j t), \qquad (21)$$

where t measures the number of generations since the midpoint of the selective sweep (i.e., $p_i = q_i = 1/2$ when $t = 0$). Assuming large r_{ij} such that D_{ij} rapidly approaches and remains at quasi-linkage equilibrium (QLE), we also have

$$D_{ij}(t) \approx \frac{\varepsilon_{ij}\,(1 - r_{ij})}{r_{ij}}\, pq_{ij}(t). \qquad (22)$$

Assuming a modifier of weak effect such that changes in pq_M over time may be ignored, the change in frequency at the modifier locus throughout the course of the substitution is

$$\Delta p_M \approx -K(\varepsilon_{ij} - \lambda)\, pq_M \int_{-\infty}^{\infty} D_{ij}(t)\, dt$$

$$= -\frac{K(\varepsilon_{ij} - \lambda)\varepsilon_{ij}(1 - r_{ij})\, pq_M}{6 a_i r_{ij}} \qquad (23)$$

(BARTON 1995a).

TWO POPULATIONS

Selection in two demes: We consider the following matrix of selection coefficients:

$$
\begin{array}{ccc}
\text{deme} & k & l \\
\text{locus } i & \begin{bmatrix} a_{i,k} & a_{i,l} \\ a_{j,k} & a_{j,l} \end{bmatrix}. \\
\text{locus } j &
\end{array}
$$

If the selection coefficients do not vary in space for at least one of the loci, then the selection coefficients cannot covary across patches. As shown in the following analysis, if there is no covariance in selection across space, linkage disequilibria will be created only by epistasis, and recombination will evolve with weak negative epistasis, as in the one-population case. Although the equations hold whether or not covariance is present, we concentrate our discussion on the more interesting case where there is a nonzero covariance in selection coefficients across demes between loci:

$$\mathrm{Cov}(a_i, a_j) = (a_{i,l} - a_{i,k})(a_{j,l} - a_{j,k})/4. \qquad (24)$$

The factor $\frac{1}{4}$ arises in this covariance because we assumed demes of equal density. We first consider the case where all a are negative and where the polymorphism is maintained at a mutation-selection balance. We then consider the case where all the a are positive and where the polymorphism occurs transiently during the sweep of selected alleles introduced at low frequency. In both

these cases, $\text{Cov}(a_i, a_j)$ can be positive or negative. It will be positive when alleles at both loci are selected more strongly in one patch than in the other, as may occur if the two loci carry out functions that are more essential in the same patches. The covariance will be negative, however, when mutations at one locus experience stronger selection in deme k than in deme l, while mutations at the other locus experience stronger selection in deme l than in deme k. This pattern might be expected when the two loci carry out functions that are more essential in different patches. Finally we consider the case where, for each locus, one a is positive (say in deme k) and the other negative (in deme l). In this last case, the polymorphism can be maintained at selection-migration equilibrium, and the covariance will always be positive as will be explained in detail.

Linkage disequilibria in the two demes: With spatial heterogeneity in selection, epistasis is not the only source of linkage disequilibria. The mixing of the two populations by migration creates some linkage disequilibria because the frequencies of selected alleles are different in the two demes. Even when $m = \frac{1}{2}$, there is a difference immediately after selection equal to $\delta^{(s)}p_{i,l} - \delta^{(s)}p_{i,k}$ for locus i. We thus compare the relative effects of epistasis and migration on the linkage disequilibrium D_{ij}.

Assuming weak selection and a population near QLE, the recurrence for the linkage disequilibrium is given by the system of equations,

$$\begin{bmatrix} \delta D_{ij,k} \\ \delta D_{ij,l} \end{bmatrix} = \begin{bmatrix} \delta^s D_{ij,k} \\ \delta^s D_{ij,l} \end{bmatrix} + \begin{bmatrix} \delta^m D_{ij,k} \\ \delta^m D_{ij,l} \end{bmatrix}. \tag{25}$$

Substituting from (4) and (8) and solving for the QLE, the linkage disequilibrium therefore approaches

$$D_{ij,k} = \frac{\Delta_i \Delta_j (1 - m) m}{r_{ij}}$$
$$+ \frac{(1 - r_{ij}) [\varepsilon_{ij,k} pq_{ij,k}\{r_{ij} + m\} + m\varepsilon_{ij,l} pq_{ij,l}]}{r_{ij}[2m + r_{ij}]}. \tag{26}$$

The first term ($D_{ij,k}^{(m)}$) is the contribution to the linkage disequilibrium of differences in allele frequency between the two demes, whereas the second term ($D_{ij,k}^{(\varepsilon)}$) is the contribution due to departures from multiplicative epistasis in the two demes. If $r_{ij} \gg m$, then the dynamics of the linkage disequilibria in the two demes are nearly independent, and

$$D_{ij,k} \approx \frac{\Delta_i \Delta_j (1 - m) m}{r_{ij}} + \frac{(1 - r_{ij}) [\varepsilon_{ij,k} pq_{ij,k}]}{r_{ij}}. \tag{27}$$

Conversely, when $r_{ij} \ll m$, the linkage disequilibria are nearly equal in the two demes

$$D_{ij,k} \approx D_{ij,l} \approx \frac{\Delta_i \Delta_j (1 - m) m}{r_{ij}} + \frac{(1 - r_{ij}) [\varepsilon_{ij,k} pq_{ij,k} + \varepsilon_{ij,l} pq_{ij,l}]}{2r_{ij}}. \tag{28}$$

Mutation-selection equilibrium: *Finding the linkage disequilibria:* When a polymorphism is maintained at a mutation-selection balance,

$$\delta^\mu p_{i,k} + \delta^s p_{i,k} + \delta^m p_{i,k} \approx 0$$
$$\delta^\mu p_{i,l} + \delta^s p_{i,l} + \delta^m p_{i,l} \approx 0. \tag{29}$$

From (3), (5), and (7), the difference in allele frequency between the two demes at equilibrium is given by

$$\Delta_i \approx \frac{\mu(a_{i,l} - a_{i,k})}{a_{i,k}a_{i,l} - m(a_{i,k} + a_{i,l})}. \tag{30}$$

Therefore, the linkage disequilibrium between a pair of selected loci at equilibrium (from Equation 26) is

$$D_{ij,k} = [4m(1 - m)$$
$$\cdot \text{Cov}(a_i, a_j)\mu^2] / [r_{ij}[a_{i,k}a_{i,l} - m(a_{i,k} + a_{i,l})]$$
$$\cdot [a_{j,k}a_{j,l} - m(a_{j,k} + a_{j,l})]]$$
$$+ (1 - r_{ij}) [\varepsilon_{ij,k} pq_{ij,k}\{r_{ij} + m\}$$
$$+ m\varepsilon_{ij,l} pq_{ij,l}] / [r_{ij}(2m + r_{ij})]$$
$$\equiv D_{ij,k}^{(m)} + D_{ij,k}^{(\varepsilon)}, \tag{31}$$

which is a line of equilibria in the ($\varepsilon_{ij,k}$, $D_{ij,k}$) space with an intercept different from zero [compare with (18) in one population].

Comparison of $D_{ij,k}^{(m)}$ and $D_{ij,k}^{(\varepsilon)}$: If we assume that $\text{Cov}(a_i, a_j)$ is of the same order of magnitude as the epistasis (ξ^2), then from Equation 31 and assumption (2), we have

$$D_{ij,k}^{(\varepsilon)}/D_{ij,k}^{(m)} = O(1) \tag{32}$$

if the migration is either of order 1 or ξ^2 and

$$D_{ij,k}^{(\varepsilon)}/D_{ij,k}^{(m)} = O(\xi) \tag{33}$$

if the migration is of order ξ. Indeed, $D_{ij,k}^{(m)}$ reaches a maximum at a low value, $\hat{m}$, of the migration rate

$$\hat{m} \approx \sqrt{\frac{a_{i,k}a_{i,l}a_{j,k}a_{j,l}}{(a_{i,k} + a_{i,l})(a_{j,k} + a_{j,l})}}. \tag{34}$$

Thus, the effect of migration on linkage disequilibria can never be neglected whereas the effect of epistasis is negligible for low migration rates (near 34). Thus the direction and speed of the evolution of recombination may well be very different than expected from the sign and intensity of epistasis.

Evolution at the modifier locus: Selection at the modifier locus is given by (17), with $D_{ij,k}$ given by (31). When $r_{ij} \ll m$ or when linkage disequilibria are primarily formed by migration [*i.e.*, $D_{ij,k}^{(m)} \gg D_{ij,k}^{(\varepsilon)}$ and $D_{ij,l}^{(m)} \gg D_{ij,l}^{(\varepsilon)}$], the linkage disequilibria in the two demes are approximately equal. In this case, Equation 17 simplifies, and increased recombination will be favored overall if

$$(D_{ij} > 0 \text{ and } \bar{\varepsilon}_{ij} < \bar{\lambda}) \quad \text{or} \quad (D_{ij} < 0 \text{ and } \bar{\varepsilon}_{ij} > \bar{\lambda}),$$
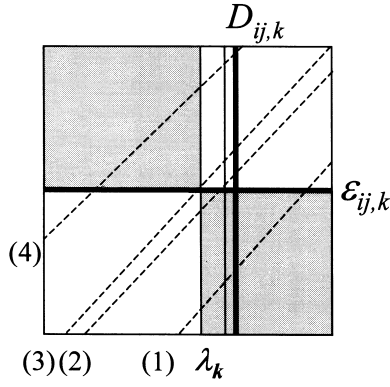
FIGURE 3.—Lines of equilibria with two demes. Line (1) illustrates a case where $\mathrm{Cov}(a_i, a_j)$ is negative, lines (2), (3), and (4) represent cases where $\mathrm{Cov}(a_i, a_j)$ is positive with increasing values of $D_{ij,k}^{(m)}$. The different lines correspond to four cases described in the text. There is an advantage of a modifier that increases recombination in shaded areas. Note that when $\mathrm{Cov}(a_i, a_j)$ is large relative to the epistasis, the slope of the line becomes negligible compared to the intercept. In that case, the lines of equilibria would be almost horizontal. See Figure 1 for definitions.

where $\bar{\lambda} = (\lambda_k + \lambda_l)/2$ and $\bar{\varepsilon}_{ij} = (\varepsilon_{ij,k} + \varepsilon_{ij,l})/2$. This case can be easily represented graphically since the line of equilibria in the $(\varepsilon_{ij,k}, D_{ij,k})$ space is the same for the two demes. If the covariance is negative (Figure 3, line 1), increased recombination will evolve as long as $\bar{\varepsilon}_{ij}$ is greater than the average $\bar{\lambda}$ threshold and $D_{ij} < 0$. Thus increased recombination may evolve despite substantial positive epistasis. If the covariance is positive, we can distinguish three cases. In the first case (Figure 3, line 2), $D_{ij,k}^{(m)}$ is very low such that recombination is only favored if $\bar{\varepsilon}_{ij} > \bar{\lambda}$ and $D_{ij} < 0$, mimicking the results found with only one population. At a slightly larger value of $D_{ij,k}^{(m)}$ (Figure 3, line 3), there comes a point where neither the short-term nor the long-term advantages of recombination are sufficiently strong, and decreased recombination evolves regardless of the epistasis. Finally, for large $D_{ij,k}^{(m)}$ (Figure 3, line 4), recombination is favored if $\bar{\varepsilon}_{ij} < \bar{\lambda}$ and $D_{ij} > 0$. In contrast to the classic results for a single population, weak negative epistasis now selects against recombination, while stronger epistasis selects for recombination. We refer to these different situations as cases 1, 2, 3, and 4, respectively.

The rate of recombination between the modifier and the selected loci also plays an important role (through $\bar{\lambda}$) in determining whether or not recombination is favored. For a tightly linked modifier, $\bar{\lambda}$ is lower (more negative), whereas for a loosely linked modifier $\bar{\lambda}$ is close to $-3a_i a_j$. Therefore, we are more likely to see case 2 when there is a tightly linked modifier (in which case results are similar to those obtained in a single population), while we are more likely to observe case 4 with a loosely linked modifier (in which case even high recombination rates may be favored if epistasis is strong and negative).

Sweep of beneficial mutations: When two loci are substituting at different rates in two populations connected by migration, some linkage disequilibria are created by the difference in frequency between the two demes, which can again result in different selective pressures on a modifier of recombination.

Finding the linkage disequilibria: For tractability, we assume that the two loci are subject to the same selection pressure overall, that is,

$$\bar{a}_i = \bar{a}_j = (a_{i,k} + a_{i,l})/2 = (a_{j,k} + a_{j,l})/2, \quad (36)$$

and that they spread simultaneously so that

$$\bar{p}_i(t) = 1 - \bar{q}_i(t) = (p_{i,k} + p_{i,l})/2 = \bar{p}_j(t) \quad (37)$$

and

$$\bar{p}_i/\bar{q}_i = \bar{p}_j/\bar{q}_j = \mathrm{Exp}(\bar{a}_i t) = \mathrm{Exp}(\bar{a}_j t). \quad (38)$$

Assuming that the linkage disequilibria are at QLE throughout the course of the substitution and are equal in the two demes (*i.e.*, migration and recombination are sufficiently frequent), the difference in allele frequency between the two demes is given by

$$\Delta_i(t) \approx \frac{\bar{p}\bar{q}_i(t)\,(a_{i,l} - a_{i,k})}{2m}. \quad (39)$$

The linkage disequilibria are thus

$$D_{ij,k}(t) \approx D_{ij,l}(t) \approx \frac{\mathrm{Cov}(a_i, a_j)(1 - m)\bar{p}\bar{q}_i(t)^2}{m\,r_{ij}}$$

$$+ \frac{\bar{\varepsilon}_{ij}(1 - r_{ij})\,\bar{p}\bar{q}_i(t)^2}{r_{ij}}$$

$$\equiv D_{ij,k}^{(m)} + D_{ij,k}^{(\varepsilon)} \quad (40)$$

(see Equation 28).

Comparison of $D_{ij,k}^{(m)}$ and $D_{ij,k}^{(\varepsilon)}$: If we assume that $\mathrm{Cov}(a_i, a_j)$ is of the same order of magnitude as the epistasis (ξ^2), then from Equation 40 and assumption (2), we have

$$D_{ij,k}^{(\varepsilon)} / D_{ij,k}^{(m)} = O(m). \quad (41)$$

Thus, the effect of migration on linkage disequilibria cannot be neglected whereas the effect of epistasis is negligible for low migration rates.

Evolution at the modifier locus: Over the course of the substitutions we then have

$$\int_{-\infty}^{\infty} D_{ij}(t)\,dt = \int_0^1 D_{ij}(\bar{p})\frac{dt}{d\bar{p}}d\bar{p}$$

$$\approx \frac{\mathrm{Cov}(a_i, a_j)(1 - m)}{6\bar{a}_i m r_{ij}} + \frac{\bar{\varepsilon}_{ij}(1 - r_{ij})}{6\bar{a}_i r_{ij}}. \quad (42)$$

Integrating (11) over the course of the selective sweeps gives the total effect of the sweeps on the modifier of recombination, Δp_M. Ignoring the small changes in pq_M for a weak modifier, we have

$$\Delta p_M = -K(\bar{\varepsilon}_{ij} - \bar{\lambda}) pq_M \int_{-\infty}^{\infty} D_{ij}(t) \, dt$$

$$= -\frac{K(\bar{\varepsilon}_{ij} - \bar{\lambda}) pq_M}{6a_i r_{ij}}$$

$$\cdot \left(\frac{\text{Cov}(a_i, a_j)(1 - m)}{m} + \bar{\varepsilon}_{ij}(1 - r_{ij}) \right). \quad (43)$$

If the selection coefficients covary positively (selection favors both mutant alleles more intensely in one of the two demes), then $D_{ij}^{(m)}$ becomes positive, while if they covary negatively (selection favors one mutant more intensely in one deme and the other mutant more intensely in the other deme), then negative $D_{ij}^{(m)}$ are created. For the most part, the results are analogous to the case of a mutation-selection balance. When $\text{Cov}(a_i, a_j)$ and $\bar{\varepsilon}_{ij}$ have the same sign, then the direction of the evolution of recombination is predicted by the same conditions as in the case of a single population [compare (43) with (23)]; *i.e.*, recombination is favored with weak negative epistasis as in case 2 (Figure 3). When their signs are different though, and when $\text{Cov}(a_i, a_j)$ is substantial, the outcome of the selection on recombination is the opposite of that found in one population (Figure 3, cases 1 and 4).

Balanced selection: In this case, we are free to define alleles b_i and b_j as favored in the same deme (say k) or in different demes without loss of generality. We make the former choice, so that $a_{i,k}$ and $a_{j,k}$ have the same sign. In this case, D_{ij} measures whether the B_iB_j and b_ib_j are overrepresented ($D_{ij} > 0$) or underrepresented ($D_{ij} < 0$), which is consistent with our previous convention. Because B_iB_j will be favored in one deme and b_ib_j in the other, balanced selection will always lead to a positive covariance across the two demes.

Finding the linkage disequilibria: When a polymorphism is maintained at migration-selection balance between the two demes, the effect of mutation is negligible, and we have near the equilibrium

$$\delta^s p_{i,k} + \delta^m p_{i,k} \approx 0$$
$$\delta^s p_{l,j} + \delta^m p_{i,l} \approx 0. \quad (44)$$

The difference in allele frequency between the two demes at equilibrium is given by

$$\Delta_i = \frac{a_{i,k} pq_{i,k}}{m}. \quad (45)$$

Thus, from (26), the linkage disequilibrium between a pair of selected loci at equilibrium is

$$D_{ij,k} = \frac{(1 - m) a_{i,k} a_{j,k} pq_{ij,k}}{r_{ij}m}$$

$$+ \frac{(1 - r_{ij}) [\varepsilon_{ij,k} pq_{ij,k}\{r_{ij} + m\} + m\varepsilon_{ij,l} pq_{ij,l}]}{r_{ij}[2m + r_{ij}]}$$

$$\equiv D_{ij,k}^{(m)} + D_{ij,k}^{(\varepsilon)}, \quad (46)$$

which is a line of equilibria in the $(\varepsilon_{ij,k}, D_{ij,k})$ space with an intercept different from zero.

Comparison of $D_{ij,k}^{(m)}$ and $D_{ij,k}^{(\varepsilon)}$: From Equation 47 and assumption (2), we have

$$D_{ij,k}^{(\varepsilon)} / D_{ij,k}^{(m)} \approx O(m). \quad (47)$$

$D_{ij,k}^{(\varepsilon)}$ is therefore negligible compared to $D_{ij,k}^{(m)}$ as long as the rate of migration is small. This is because, with low migration, the linkage disequilibrium created by migration is high as a result of the large allele frequency differences between the two demes (*i.e.*, Δ_i becomes of order 1). However, if migration is high, the frequency of selected alleles is almost the same in the two demes.

Evolution at the modifier locus: The strength of selection on the modifier is given by (17) with $D_{ij,k}$ given by (47), which gives results equivalent to those of PYLKOV *et al.* (1998). Since the covariance in the case of a migration-selection balance is positive and likely to be strong, positive disequilibria will generally develop among the selected loci (as expected for coadapted gene complexes). As indicated in Figure 1c, we would therefore expect increased recombination to evolve only when there is strong negative epistasis within each patch and when λ_k is near zero, *i.e.*, when there are already reasonably high levels of recombination within the population [see definition (12)]. An important difference from the results of a mutation-selection is that case 1 of Figure 3 never occurs. $D_{ij,k}^{(m)}$ is always positive (by convention and without loss of generality, $a_{i,k}$ and $a_{j,k}$ were chosen to have the same sign). Therefore, recombination is never favored if epistasis is absent or positive in a two-deme model at migration-selection balance. These results are consistent with the results of PYLKOV *et al.* (1998), the simulations of CHARLESWORTH and CHARLESWORTH (1979), and the suggestion of SLATKIN (1975).

SEVERAL LOCI AND SEVERAL POPULATIONS

More than two demes: It is important at this point to discuss whether a two-deme model can capture all of the essential features of spatial heterogeneity. Clearly, there are some types of selection that cannot be modeled with two demes. For example, staggered clines, as studied by CHARLESWORTH and CHARLESWORTH (1979), cannot be analyzed using two demes since they require at least three different environments. The case of a clinal migration-selection balance is biologically important, and it can lead to results not observed with two patches. For example, unlike the case of a two-patch migration-selection balance, linkage disequilibria (as defined in this article) switch signs between the clines when they are staggered over space. With a right scale for the spatial lag between the two environmental transitions, recombination can be favored in the absence of epistasis in that model (see MAYNARD SMITH 1977; CHARLESWORTH and CHARLESWORTH 1979). On the other hand, when migration rates are high across all

environments (such that all demes have approximately equal genotype frequencies after migration), the results of the two-deme model continue to hold; all that matters is the covariance of selective effects across environments (see APPENDIX).

An interesting test case is a two-locus two-allele model (A/a, B/b) with four types of environments, each favoring a different haploid genotype. If the four types of environment are equally represented and selection is perfectly symmetrical, then the $\text{Cov}(a_i, a_j)$ will equal zero over all environments. With only two demes, this would imply that linkage disequilibrium would not be generated by migration. With four demes, however, disequilibrium is still generated as long as dispersal is limited (because $\Delta_i\Delta_j$ in Equation 26 is not zero). Essentially, the most fit genotype reaches a higher frequency than expected based on the local allele frequencies, which are skewed away from the most fit genotype by migration from the other patches. With our definition of disequilibrium (which is positive locally if the most fit and least fit genotypes are overrepresented), this argument suggests, and simulations confirm, that positive disequilibria develop in each patch. Besides the disequilibria and covariance terms, everything else in this four-patch migration-selection model is the same as in the two-deme model. Consequently, recombination may be favored by its short-term advantage when there is sufficiently strong negative epistasis as was seen with two patches. However, this example points out that care must be taken in defining the disequilibrium and its relationship to the covariance in selection with multiple demes.

More than two selected loci: Here we consider how the results developed so far depend on having only two loci subject to selection. We consider only pairwise epistasis as defined in Equation 1 and ignore more complex epistasis involving several loci. Even in that case, higher-order disequilibria could develop among the selected loci that may alter the dynamics. Assuming that these higher-order associations can be ignored (which is probably less and less accurate when the number of loci increases; KIRKPATRICK and SERVEDIO 1999), it is possible to average the change at the modifier locus over all the pairs of loci (whose linkage relationships are affected by the same modifier locus) to determine the direction of evolution of the modifier. The condition for increased recombination is then

$$\sum_i \sum_{j>i} \sum_k - KD_{ij,k}(\epsilon_{ij,k} - \lambda_k) > 0 \quad (k = 1, 2), \quad (48)$$

where the linkage disequilibrium is given by (31), (40), or (46) with mutation-selection, selective sweeps, or migration-selection, respectively. The difference between this case and the two-locus case is that some pairs of loci will exhibit positive covariance and others will exhibit negative covariance (except at migration-selection balance), and it is the total influence of these covariance terms that determines when recombination will evolve.

If n_1 is the number of loci selected more strongly in deme k than in deme l (we denote these loci using i), and n_2 is the number of loci selected more strongly in deme l than in deme k (we denote these loci using j), then the number of pairs of loci characterized by a negative covariance is

$$n_{\text{neg}} = n_1 n_2,$$

while the number of pairs of loci characterized by a positive covariance is

$$n_{\text{pos}} = \binom{n_1}{2} + \binom{n_2}{2}.$$

As a consequence, n_{neg} will be greater than n_{pos} if n_1 is close to n_2. Pairs of loci characterized by a positive ($\{i, i\}$ and $\{j, j\}$ pairs) or negative covariance ($\{i, j\}$ and $\{j, i\}$ pairs) do not, however, have an equally strong effect on a modifier of recombination. As a simple example, we assume that all loci are at mutation-selection equilibrium, that the deleterious mutations are all selected against by an amount a and αa in the least and most selected deme, respectively ($\alpha > 1$), that epistasis is absent ($\epsilon = 0$), and that these loci are distributed such that on average $\bar{r} = \bar{r}_{ij} = \bar{r}_{ii} = \bar{r}_{jj}$ and $\bar{r}_{iM} = \bar{r}_{jM}$. Under these assumptions, the average pairwise linkage disequilibrium will have the same magnitude for all pairs and will be positive for $\{i, i\}$ and $\{j, j\}$ pairs and negative for $\{i, j\}$ and $\{j, i\}$ pairs. Condition (48) reduces in this simple example to

$$-\frac{K\mu^2 a^2(\alpha - 1)^2 m(1 - m)[n_{\text{pos}}(1 + \alpha^2) - 2\alpha n_{\text{neg}}]}{2\bar{r}(a\alpha - m(\alpha + 1))^2} > 0. \quad (49)$$

Consequently, pairs of loci with a positive covariance ($\{i, i\}$ and $\{j, j\}$) receive greater weight than pairs with a negative covariance ($\{i, j\}$ and $\{j, i\}$) by a factor

$$\frac{1 + \alpha^2}{2\alpha}, \quad (50)$$

which is >1 and increases as $|\text{Cov}(a_i, a_j)| = a^2(\alpha - 1)^2/4$ increases. From (49), recombination will be favored if

$$1 < \alpha < \frac{n_{\text{neg}} + \sqrt{n_{\text{neg}}^2 - n_{\text{pos}}^2}}{n_{\text{pos}}}. \quad (51)$$

Condition (51) is most easily satisfied when the number of loci is small and when n_{pos} and n_{neg} are nearly equal. When (51) holds, negative covariance in selection predominates, generating negative disequilibria and selecting for increased recombination (recall that epistasis is absent in this example). With only two patches, however, condition (51) often fails, especially with many loci (even in the most favorable case where $n_1 = n_2$, the ratio $n_{\text{neg}}/n_{\text{pos}}$ tends to one when the number of loci increases). That is, positive covariance often dominates with only two patches and several loci. In this case, if epistasis were added, spatial heterogeneity in selection

would generate positive disequilibria and select for recombination only if there were strong negative epistasis (case 4). On the other hand, adding more than two demes increases the realm of possibilities and makes it more likely that negative covariance will predominate. As an extreme example, imagine that there are n patches and n loci and that $\alpha = 1$ in all patches except in patch i for locus i. In this extreme case, no pairs of loci will exhibit positive spatial covariance, many will exhibit negative covariance (those involving patch i and locus i), and the remainder will exhibit no spatial covariance between pairs of patches. These considerations suggest that, with few patch types and with many loci exhibiting the same spatial pattern in selection, positive covariance will tend to develop and, if this covariance is strong, will favor the evolution of recombination only when there is strong negative epistasis. Conversely, if there are many patch types and each locus has a unique pattern of selection over space, then negative covariance is more likely, which will favor the evolution of recombination if epistasis is weakly negative, absent, or even positive (case 1).

DISCUSSION

Spatial heterogeneity alone

> Models incorporating an unpredictable environment have two drawbacks: they require an extreme and implausible type of unpredictability, and they imply selection for reduced recombination whenever several loci are concerned with the same environmental feature.
>
> Maynard Smith (1977)

The idea that environmental heterogeneity alone does not favor recombination is old. However, this idea is based on a single type of spatially variable selection, where different alleles are favored in different patches (balanced selection). It may be more common, however, that spatial heterogeneity does not alter which allele is most fit but only the strength of selection acting locally. We have considered this case at both mutation-selection equilibrium and during sweeps of beneficial alleles and have found that spatial heterogeneity can indeed select for increased recombination when the covariance in selection coefficients is negative and epistasis absent or weak. This result is not robust, however, to the presence of strong epistasis. Furthermore, as we have shown, it may be difficult in a simple two-patch environment to generate negative covariance for a large number of loci.

Epistasis alone

> If recombination is to be favoured because it increases the response to directional selection, then epistasis must be both weak and negative.
>
> Barton (1995a)

The idea that epistatic selection can select for recombination can be traced back to Feldman et al. (1980) and has been cited (Kondrashov 1988) as one of the more plausible factors favoring sex and recombination. There are several weaknesses in this explanation (we do not discuss here temporal variation in epistasis). First, recombination is only favored when epistasis is negative and weak (Figure 2), with the conditions favoring recombination being more lax when recombination rates are low. This conclusion is, however, not very robust to small variation in the model. We have shown that introducing a small covariance in selection coefficients completely alters the results. For instance, with a small positive covariance, weak and negative epistasis actually selects against recombination. A second difficulty is that even if the epistasis is weak and negative, on average, recombination will be favored only if there is little variance in epistasis between pairs of loci (Otto and Feldman 1997), which is contrary to empirical evidence (e.g., Elena and Lenski 1997). A third difficulty is that the strength of selection favoring recombination plummets as recombination rates rise within the genome and can become negative before typical rates of recombination are reached.

The joint effect of spatial heterogeneity and epistasis

We investigated the joint effects of spatially heterogeneous selection and epistasis on the evolution of recombination in a two-patch model. We found that epistasis and spatial heterogeneity in selection interact strongly in their influence on linkage disequilibria. Because of this interaction, predictions about the magnitude and sign of disequilibria and about the evolution of recombination are sensitive to the inclusion of both factors. We found that the main criticisms of either theory considered in isolation no longer hold when both processes are taken into account.

The mean epistasis and the type of spatial heterogeneity: Including spatial heterogeneity alters the results of models of recombination in many ways, the most important of which is that disequilibria present within a population may be different than expected based on local epistatic selection. As a consequence, recombination can be favored in three distinct situations: by the short-term effect alone (when the epistasis is strongly negative and the covariance in selection is positive enough to generate positive disequilibria), by the long-term effect alone (when the epistasis is weak and negative and the covariance is negative, absent, or slightly positive), or by both the short- and the long-term effects (when additive epistasis is positive and the covariance in selection across environments is negative enough to generate negative disequilibria). These results differ radically from those in a single population where recombination is favored almost only by the long-term effect.

The first important conclusion is that with appro-

TABLE 1

Conditions favoring increased recombination between a pair $\{i, j\}$ of loci within a deme

		$\varepsilon_{ij} < \lambda$	$\lambda < \varepsilon_{ij} < 0$	$\varepsilon_{ij} = 0_j$	$\varepsilon_{ij} > 0_j$
$\mathrm{Cov}(a_i, a_j)$	$< 0^a$	Never	Always[1]	Always[1]	If $D_{ij} < 0$ [1]
	$= 0^{a,b,c}$	Never	Always[2]	Never	Never
	$> 0^{a,b}$	If $D_{ij} > 0$ [4]	If $D_{ij} < 0$ [2]	Never	Never

$\mathrm{Cov}(a_i, a_j)$ is the covariance between the selection coefficients across demes (see Equation 24). ε_{ij} is the multiplicative epistasis and λ the threshold between strong and weak negative epistasis (Equation 12). Cases 1, 2, and 4 described in the text are in parentheses.

[a] Conditions that favor recombination in two populations at mutation-selection equilibrium or during sweeps of beneficial alleles.

[b] Conditions that favor recombination in two populations at migration-selection equilibrium.

[c] Conditions that favor recombination in the absence of environmental heterogeneity.

priate spatial heterogeneity, recombination can be favored for any form of epistasis. The reciprocal is also true; with appropriate epistasis, recombination can be favored for any covariance in selection coefficients. This can be easily visualized in Table 1 where all the results are summarized.

The second important conclusion is that recombination is favored overall if a negative correlation exists between $\mathrm{Cov}(a_i, a_j)$ and $a_{i,j}$ (see Table 1). Thus, we expect that high levels of recombination would evolve if pairs of loci with a positive covariance in space tend to exhibit negative epistasis whereas pairs of loci with a negative covariance tend to exhibit positive epistasis. Is such a pattern reasonable? Considering the physiological basis of epistasis, the answer may be yes.

Epistasis results from nonlinear effects of gene products at the physiological level. For simple metabolic pathways, it has been shown that mutations in the same enzyme tend to exhibit negative (synergistic) epistasis (SZATHMARY 1993). In contrast, mutations in different enzymes within a pathway tend to exhibit positive (diminishing returns) epistasis (SZATHMARY 1993). These patterns arise because enzymes with a single deleterious mutation exert greater control over the flux through a pathway, making further mutations in the same gene even more deleterious (saturation effect), but making mutations in other genes less critical (limiting factor effect). These patterns may also appear under more general conditions as long as (1) small deleterious mutations in a function ("function A") are buffered by some form of homeostasis (*e.g.*, WAGNER 2000), (2) the presence of these mutations makes further mutations in the same function even more harmful, but (3) their presence decreases the importance to fitness of functions besides function A. Under these conditions, we would expect that deleterious mutations affecting the same function would exhibit negative epistasis. Furthermore, because these mutations affect the same function, which will differ in importance from location to location, we would expect these mutations to exhibit a positive covariance over space in the intensity of selection. Conversely, if the two mutations affect different func-

tions, they will be more likely, on average, to exhibit positive epistasis and a negative covariance in space. Thus it may be relatively common that epistasis and spatial covariance in selection are negatively correlated, which would generate a short-term advantage to recombination and could potentially explain why recombination and sex are found in so many organisms.

The variance in epistasis: When $D_{ij}^{(m)}$ is larger than $D_{ij}^{(\varepsilon)}$, recombination can be favored in a very large proportion of the parameter space (Figure 4). The range of values that favor recombination is increased by more than two orders of magnitude compared to the case of a single population. Consequently, the advantage of recombination may be much less sensitive to variation in epistasis among loci than in the one-population model (OTTO and FELDMAN 1997).

The evolution of high recombination rates: With spatial heterogeneity, the disequilibria that accumulate locally depend on epistasis but also on selective differences among patches. The disequilibria and epistasis can thus have opposite signs. Under this circumstance, selection within a patch favors the elimination of disequilibria, and there is a strong short-term advantage to high rates of recombination. These results may thus provide a key to understanding why high rates of recombination and multiple chromosomes have evolved, which was difficult to explain in most previous models where the advantage of recombination lay in its long-term effects (which tend to be weak when linkage is loose). In particular, if selection tends to be similar in strength at different loci within a patch (positive covariance in selection), high recombination rates are expected to evolve when epistasis is strongly negative, while if selection tends to act more strongly on different loci in different patches (negative covariance in selection), high recombination rates are favored whenever epistasis is positive.

Structure of the genome

The recombination rate per unit of physical distance is in general quite variable within a particular chromo-
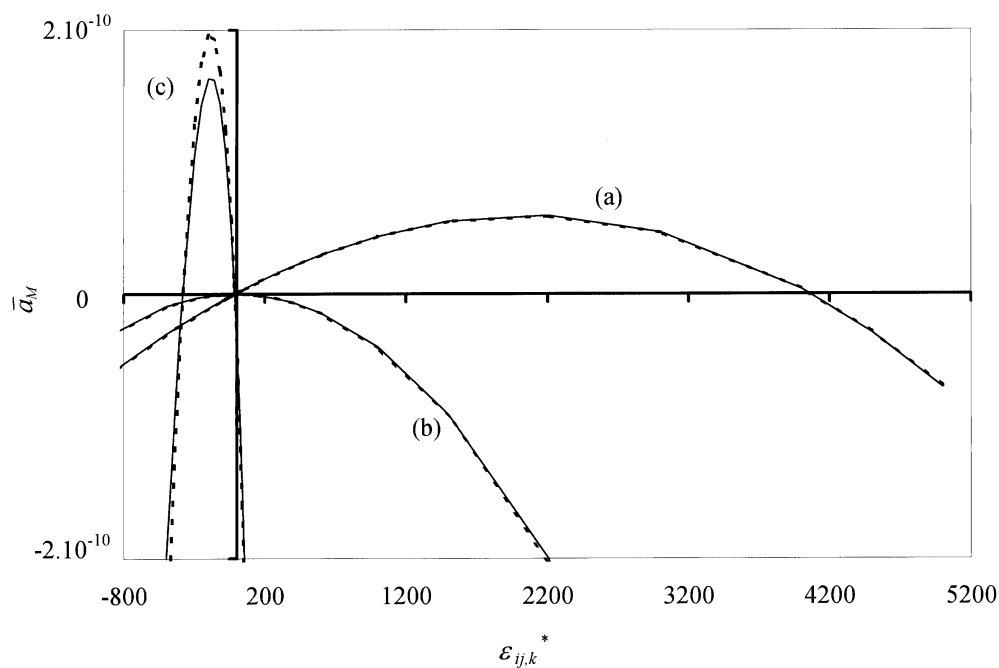
FIGURE 4.—Selection coefficient on the modifier $\overline{a}_M$ as a function of the relative epistasis $\varepsilon_{ij,k}^*$ ($= \varepsilon_{ij,k}/[a_{i,k}\,a_{j,k}]$) for different values of $\mathrm{Cov}(a_i, a_j)$. The relative epistasis is the same in the two demes and the selected loci are at mutation-selection balance. Three cases are presented: (a) negative covariance $a_{i,k} = a_{j,l} = -0.01$, $a_{j,k} = a_{i,l} = -0.0001$; (b) zero covariance $a_{i,k} = a_{i,l} = -0.01$, $a_{j,k} = a_{j,l} = -0.0001$; (c) positive covariance $a_{i,k} = a_{j,k} = -0.01$, $a_{i,l} = a_{j,l} = -0.0001$. In each case, $r_{ij} = r_{iM} = 0.1$, $\rho = 0.01$, $m = 0.0005$, and $\mu = 10^{-5}$. Values represented by lines are computed using exact three-loci recursions whereas dashed lines are computed using analytical results (in most cases they cannot be distinguished). Note that the region where recombination is favored for case (b) is $-15 < \varepsilon_{ij,k}^* < 0$. This corresponds to the weak negative epistasis region where recombination is favored in one population.

some and even between chromosomes (a phenomenon referred to as "pseudolinkage"; KOROL et al. 1994). This variability can, to some extent, be accounted for by physiological explanations (for instance, recombination near centromeres may interfere with segregation; KOEHLER et al. 1996). Interestingly, heterogeneity in the environment as well as variation in epistasis also predicts different selection pressures on recombination between different pairs of loci. For instance, in the absence of epistasis, natural selection would favor tighter linkage among genes whose effects on fitness covary positively among environments and loose linkage among those whose fitness effects covary negatively. Given the appropriate genetic variation at recombination modifier loci, these evolutionary forces may partially explain the current structure of a genome. This may be tested, for example, by comparing the relative position of genes in domesticated species and their wild relatives. Given that gene flow was probably prevalent early during domestication between domesticated and wild populations and that there was strong spatial heterogeneity in selection (with and without artificial selection), we would expect loci that were positively selected in domesticated species to have lower recombination rates between them, on average, than in the ancestral genome if epistasis is weak overall. Conversely, we would expect higher rates of recombination between these artificially selected loci and loci subject to natural but not artificial selection, which exhibit negative covariance in selection.

Comparison with temporal heterogeneity

Interestingly, modeling spatial heterogeneity generates substantially different results than modeling temporal heterogeneity. With temporal heterogeneity in selection, the conditions favoring the evolution of recombination are not much broader than if there were no variation in selection over time. Specifically, recombination is not favored unless the selective environment varies rapidly between cases with positive epistasis and negative epistasis (CHARLESWORTH 1976; BARTON 1995a) or unless there is weak negative epistasis (in which case, recombination would be favored by epistatic selection alone). Only with rapid oscillations is the disequilibrium (built up by past selection) frequently of opposite sign to the current epistasis, in which case recombinant offspring are more fit than nonrecombinant offspring, and there can be a short-term advantage to modifiers that increase recombination. If the environment cycles over periods longer than about five generations, the signs of the disequilibrium and epistasis are more often the same, and this short-term advantage disappears. That selection caused by abiotic factors would be so capricious as to vary over time with rapid changes in the sign of epistasis seems highly unlikely (MAYNARD SMITH 1977; BARTON 1995a; KONDRASHOV and YAMPOLSKY 1996) but may occur for some coevolutionary models (reviewed in OTTO and MICHALAKIS 1998; PETERS and LIVELY 1999). In contrast, it is not unusual for spatially heterogeneous selection to permanently maintain local

disequilibria that are opposite in sign to local epistasis. All that is required is that, for a pair of loci, the strength of selection varies over space with a covariance that is substantial in magnitude and opposite in sign compared to the degree of epistasis. Consequently, it may be possible that spatial heterogeneity more often provides a short-term advantage to recombination than does temporal heterogeneity.

Empirical aspects

These results indicate that understanding the evolution of recombination may require more field work focused on measuring covariance in selection across environments. Knowing epistasis is not sufficient, because any value of epistasis can favor recombination in the proper set of environments. Similarly, knowing the extent of variation in selection across environments is of little help without knowing the amount of epistasis.

Measuring this covariance is a difficult task. For example, in a reciprocal transplant experiment, negative covariance in fitness across environments can equally be the consequence of negative covariance in selection coefficients for loci subject to recurrent deleterious mutations or of alleles that are favored in one patch and selected against in another. On the other hand, a positive covariance between the fitness of different genotypes in two environments would provide evidence for positive covariance for selection coefficients (see Fry 1993).

With spatial heterogeneity, the disequilibria present within a population may be opposite in sign to the local epistatic selection. In this case, recombinant offspring are generally more fit, on average, than nonrecombinant offspring, and there will be a short-term advantage to recombination. This result is almost never observed in models with epistasis alone, unless ε_{ij} lies within the extremely small range between $-a_i a_j$ and 0, in which case the disequilibrium produced is negligible and the short-term fitness advantage of recombination would be nearly impossible to detect. Therefore, the presence of a short-term advantage of recombination would be an appropriate test for the role of spatial heterogeneity in the evolution of recombination. If recombinant offspring are more fit on average than nonrecombinant offspring in a natural population assessed under natural conditions, then disequilibria and epistasis are opposing, and the short-term advantages of recombination are likely to contribute to the evolution of recombination. Previous laboratory experiments on Drosophila in a single population have found that there is a short-term disadvantage to recombination (recombination resulted in a lower fitness among progeny; see Charlesworth and Barton 1996). This is consistent with one-population models, where disequilibria and epistasis have the same sign [see (18)], and where there is almost always a short-term disadvantage to recombination [see (9)].

Similar tests incorporating spatial heterogeneity would be extremely valuable.

Conclusion

We have seen that the structure of the environment, the intensity of migration, and the variability of selection across environments can have a large impact on how recombination will evolve. Single-population models clarified our understanding of the processes important in the evolution of recombination but neglected environmental heterogeneity. This heterogeneity can affect models of the evolution of recombination because even slight variation in natural selection across environments can produce linkage disequilibria that will interfere or even outweigh other sources of disequilibria, such as epistasis, drift, mutation, and temporal variation (including due to coevolution). Furthermore, our results demonstrate that not all forms of spatial heterogeneity are equivalent. Previous models incorporating environmental heterogeneity have assumed that the direction of selection varies from location to location, but a more common phenomenon may be that the strength (not the direction) of selection varies spatially. Indeed, our results from a mutation-selection model and from a model of selective sweeps differed from results of a migration-selection balance.

We have shown that recombination can evolve in the absence of epistasis, drift, sib competition, temporal variation, or parasites. Unfortunately, we have also shown that predictions from a model including multiple factors that affect recombination (epistasis and spatial heterogeneity) can be quite different than predictions from models incorporating each factor in isolation. Indeed, interactions among these effects may be more important than their main effects: epistasis does not give a clue about the evolution of recombination if the form and extent of spatial heterogeneity are unknown, and vice versa. However, including spatial heterogeneity greatly increases the range of values of epistasis that can favor recombination, increases the selection pressure upon recombination-modifier loci, allows tightly as well as loosely linked modifiers to evolve, and allows free linkage to evolve. For these reasons, including spatial heterogeneity broadens the conditions under which recombination may be favored and may provide a key to understanding the prevalence of sex and recombination.

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APPENDIX

The results in the limiting case where $m = \frac{1}{2}$ can be derived in a straightforward way since allele frequencies and disequilibria are equal in the two patches after migration. This case is useful as it also describes the scenario where individuals experience different selective pressures for any nongenetic reason, for example, if there is random variability in development or food quality even in a single population. In this case, the overall departure from multiplicative fitness (which is responsible for generating the linkage disequilibrium) is different from in one population and equals

$$E[1 + a_i)(1 + a_j) + \varepsilon] - E(1 + a_i)E(1 + a_j) = E(\varepsilon) + \mathrm{Cov}(a_i, a_j),$$
$$(A1)$$

where E and Cov stand for the expectation and the covariance in selection across any number of environments, respectively. At QLE, the linkage disequilibrium modified from (18) is therefore

$$D_{ij} \approx (E(\varepsilon_{ij}) + \mathrm{Cov}(a_i, a_j))\frac{(1 - r_{ij})}{r_{ij}} pq_{ij} \qquad (A2)$$

with error of order ξ^5. This result can also be obtained from (31), taking into account the fact that (30) reduces to

$$\Delta_i = \delta^{(s)}p_{i,l} - \delta^{(s)}p_{i,k}. \qquad (A3)$$

With free migration, however, the effect of fitness covariance is relatively minor and will only alter the outcome qualitatively if epistasis is weak (on the order of the covariance term). The maximum covariance occurs when the selected alleles are each neutral in one of the patches, indicating that, with free migration

$$\left|\mathrm{Cov}(a_i, a_j)\right| \leq \frac{a_i a_j}{4}. \qquad (A4)$$

Combining (17) and (A2), recombination will be favored when

$$\bar{\lambda} < \bar{\varepsilon}_{ij} < -\mathrm{Cov}(a_i, a_j), \qquad (A5)$$

where $\bar{\lambda} = (\lambda_k + \lambda_l)/2$ is always smaller than $-3a_i a_j$. Thus, a positive $\mathrm{Cov}(a_i, a_j)$ decreases the range where recombination is favored whereas a negative $\mathrm{Cov}(a_i, a_j)$ increases it. Note that even if epistasis is absent or positive in both patches and $m = \frac{1}{2}$, higher recombination can still evolve as long as there is a negative covariance between the patches in terms of selection on the two loci.