Genet. Res. Camb. (1998), **71**, *pp.* 247–256. Printed in the United Kingdom © 1998 Cambridge University Press

Migration versus mutation in the evolution of recombination under multilocus selection

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(*Received 12 December 1996 and in revised form 15 August 1997 and 20 December 1997*)

Summary

We use modifier theory to compare the evolution of recombination under mutation–selection and migration–selection balance models. Recombination between loosely linked loci subject to weak multilocus selection is controlled by the genotype at a selectively neutral modifier locus. We show that the success of a new modifier depends on the sign and amount of epistasis as well as on the linkage of the modifier locus to the loci under selection. With both migration and mutation, for recombination to increase requires negative (synergistic) epistasis. When epistasis is sufficiently weak, increased recombination is always favoured under mutation–selection balance and never under migration–selection balance. With stronger negative epistasis, there exists a critical recombination value. In this case, a recombination-increasing allele invades the population under mutation–selection balance if its recombination rate with the major loci is less than the critical recombination value, whereas with weak migration it must be above this value. These results are the same for haploid and diploid populations.

1. Introduction

Genetic variation in the rate of recombination exists in many species. The structure of this variation is expected to influence how recombination evolves (Korol *et al*., 1994). Models for the evolution of recombination have used either optimality criteria (increase in the mean fitness, rate of accumulation of advantageous mutations, rate of disappearance of deleterious mutations, frequencies of favoured genotypes, time until production of a fitter genotype) or modifier theory based on the dynamics of recombination-modifying genes. Both approaches are reviewed by Feldman *et al*. (1996). The goal of modifier models is to ascertain when a new allele that alters the rate of recombination will invade a population.

Feldman and his colleagues have formulated the *reduction principle*, which claims that in a population at equilibrium under viability selection in a constant environment, only modifiers decreasing recombination rates are successful. This has been shown for two loci (Feldman, 1972; Feldman *et al*., 1980; Feldman & Liberman, 1986), for multiple loci if the new modifier eliminates recombination (Altenberg & Feldman, 1987), for sex-dependent selection with no recombination in one sex (Liberman & Feldman, 1996), and for density-dependent selection (Zhivotovsky & Feldman, 1995).

This principle may fail, however, and increased recombination may evolve under a special form of cyclic selection (Charlesworth, 1976; Hamilton, 1980) or under some forms of directional selection (Maynard Smith, 1988; Charlesworth, 1993; Barton, 1995). Other population forces, such as genetic drift (Felsenstein, 1974), mutation to deleterious alleles (Feldman *et al*., 1980; Kondrashov, 1984; Charlesworth, 1990; Barton, 1995; Otto & Feldman, 1997), meiotic drive (Feldman & Otto, 1991), and selfing (Charlesworth *et al*., 1979; Holsinger & Feldman, 1983), have been demonstrated to facilitate increased recombination under certain conditions.

Zhivotovsky *et al*. (1994) have considered a population at equilibrium under constant multilocus viability selection with pairwise epistatic interactions and concluded that the reduction principle holds *on average*, but that recombination among some of the loci may increase (*generalized reduction principle*).

The balance between deleterious mutation and

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directional selection is delicate in that recombination is favoured when epistasis (measured as the deviation from multiplicativity in fitness) is negative (synergistic) and sufficiently small (for a review see Feldman *et al.*, 1996). The only process whose interaction with epistasis and recombination has not yet been analysed is migration, which is certainly an important factor in evolutionary dynamics (Burt, 1995). It might be expected that migration and mutation, which often have similar evolutionary effects, would have similar effects on the fate of modifier alleles. However, migration creates correlations between loci, whereas mutation events at different loci are independent of each other.

In this paper, we use modifier theory to compare the evolution of recombination under mutation–selection and migration–selection balance models. Recombination between loosely linked loci subject to weak multilocus selection is controlled by the genotype at a selectively neutral modifier locus. For both migration and mutation we show that the invasion criterion involves an average over pairs of the loci under selection in which the contribution of any pair depends on the sign and amount of epistatic interaction between them as well as on the linkage of the modifier locus to these loci. Our results are the same for haploid and diploid populations.

For mutation–selection balance we confirm that increased recombination always evolves if, on average, epistasis is negative and weak. When epistasis is stronger, there exists a critical recombination value that is a decreasing function of the amount of epistasis, and a new recombination-increasing allele is successful provided that its rate of recombination with the loci under selection is less than that value. We show that the evolution of recombination under migration–selection balance between two populations, with weak disruptive epistatic selection favouring different alleles in the different populations, depends critically on the rate of migration. With rather strong migration the qualitative picture is the same as with mutation. With weak migration, for recombination to increase also requires negative (synergistic) epistasis. However, the detailed invasion conditions contrast with those for mutation: increased recombination is favoured only when epistasis is sufficiently strong (but still small relative to the directional effect of selection) and the recombination rate between the modifier locus and the major loci is above a critical value.

2. The model

(i) *Genotypic selection*

Consider a randomly mating diploid population and n autosomal loci. Each locus, i, has two alleles, A_i and a_i, labelled as 1 and 0 respectively, so that the state of locus i can be described by an indicator variable l_i that takes the value 1 if A_i is present and 0 otherwise. Each n-locus gamete can be represented by an n-dimensional vector $L = (l_1, \ldots, l_n)$. Hence the genotype of an individual may be written as the pair of gametes L_1/L_2 received from its parents. The population is assumed to be large enough that random drift is negligible. Generations are non-overlapping and viability selection precedes migration.

Denote the set of loci by $\mathcal{N} = \{1, \ldots, n\}$. For simplicity we will consider selection with pairwise epistasis so that the fitness of genotype L_1/L_2 in the population is given by the following fitness function:

$$w(L_1, L_2) = a_0 + \sum_i [a_i(l_{1i} + l_{2i}) + a_{i,i} l_{1i} l_{2i}] + \sum_i \sum_{j>i} [a_{ij}(l_{1_i} l_{1_j} + l_{2_i} l_{2_j}) + a_{i,j}(l_{1_i} l_{2_j} + l_{1_j} l_{2_i})], \quad (1)$$

where a_i is the additive (directional) effect of locus i, $a_{i,i}$ is the dominance effect within locus i, and the parameters a_{ij} and $a_{i,j}$ denote additive pairwise epistasis between the A-alleles in double *cis*- and *trans*-heterozygotes, respectively. To investigate the effect of this mode of selection on population dynamics, we apply perturbation techniques that have previously proved to be useful in exploring the behaviour of multilocus systems under weak selection (Fleming, 1979; Hastings, 1986; Zhivotovsky & Gavrilets, 1992). Introduce the small parameter ϵ and assume that the strength of directional selection can be written

$$a_i = \tilde{a}_i \epsilon, \quad (2a)$$

where $\tilde{a}_i \neq 0$ are of order one with respect to ϵ.

We assume that the magnitude of directional selection is stronger than that of dominance and epistasis according to the assumptions

$$a_{i,i}, a_{ij}, a_{i,j} = \mathcal{O}(\epsilon^2). \quad (2b)$$

Epistasis between more than two loci is ignored.

We denote by r_{ij} the probability of recombination between loci i and j and assume it to be positive and of order one with respect to ϵ.

A similar notation may be used for a haploid population. In this case the genotype of a haploid individual is described by the n-dimensional vector $L = (l_1, \ldots, l_n)$, and the fitness of L is

$$w(L) = a_0 + \sum_i a_i l_i + \sum_i^n \sum_{j>i} a_{ij} l_i l_j, \quad (1')$$

where a_i is the additive (directional) effect of locus i, and a_{ij} measures the additive pairwise epistatic interaction between loci i and j. The assumptions on the strength of the viability selection are again

$$a_i = \tilde{a}_i \epsilon \quad \text{and} \quad a_{ij} = \mathcal{O}(\epsilon^2). \quad (2')$$

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Introduce the relative pairwise epistasis:

$$e_{ij} = \frac{b_{ij}}{a_i a_j}, \tag{3}$$

where $b_{ij} = a_{ij} - a_i a_j$ is the multiplicative pairwise epistasis. We will demonstrate that the evolution of recombination under migration (mutation) is better described in terms of *relative* rather than the usual pairwise epistasis. It follows from (2) and (2′) that

$$e_{ij} = \mathcal{O}(1). \tag{4}$$

The following analysis will refer to both diploids and haploids unless it is necessary to specify the particular features of each. Without loss of generality we may assume that a_0, the fitness of the homozygous genotype with all 0-alleles, is equal to 1. For the population dynamics, it is sufficient to use the frequencies p_i of alleles A_i ($i \in \mathcal{N}$) and pairwise linkage disequilibria, $\mathcal{D}_{ij}$, whose dynamics under selection of the form (1) obey the recursions given in Zhivotovsky & Gavrilets (1992, eqns. 14–15) generalized to permit *cis–trans* differences in fitness (Zhivotovsky & Pylkov, unpublished).

The mean fitness for diploids is

$$\bar{w} = 1 + \sum_i [2a_i p_i + a_{i,i}(p_i)^2] + 2\sum_i \sum_{j>i} [a_{ij}\mathcal{D}_{ij} + (a_{ij} + a_{i,j}) p_i p_j],$$

and for haploids,

$$\bar{w} = 1 + \sum_i a_i p_i + \sum_i \sum_{j>i} a_{ij}(\mathcal{D}_{ij} + p_i p_j).$$

We assume that the number of loci is finite and parameter ϵ is close to zero, so that

$$n\epsilon \ll 1.$$

Therefore, we can neglect terms with linkage disequilibria of the third and higher order. In this case, under the weak-selection assumptions (2*a*), (2*b*), (2′),

$$\bar{w} = 1 + \mathcal{O}(\epsilon). \tag{5}$$

Near an equilibrium under selection of the form (1) for diploids (or (1′) for haploids), the changes in allele frequencies are described by the following equation (Barton & Turelli, 1991; Zhivotovsky & Pylkov, unpublished):

$$\delta p_i = a_i p_i q_i + \mathcal{O}(p_i q_i \epsilon^2). \tag{6a}$$

The dynamics of pairwise linkage disequilibria for diploids close to any equilibrium are given by

$$\delta\mathcal{D}_{ij} = -r_{ij}\mathcal{D}_{ij} + [b_{ij} - r_{ij}(a_{ij} - a_{i,j})] \times p_i q_i p_j q_j + \mathcal{O}(p_i q_i p_j q_j \epsilon^3). \tag{6b}$$

For haploids the term in brackets should be replaced by $(1 - r_{ij})b_{ij}$. Here $\delta p_i = p_i' - p_i$ and $\delta\mathcal{D}_{ij} = \mathcal{D}'_{ij} - \mathcal{D}_{ij}$ denote the total change in allele frequencies and linkage disequilibria between successive generations due to both selection and recombination.

(ii) *Migration*

Consider two populations labelled 1 and 2 that are connected by migration given by the backward matrix

$$\mathbf{M} = \begin{matrix} 1 - m_1 & m_1 \\ m_2 & 1 - m_2 \end{matrix}, \tag{7}$$

where m_1 is the fraction of migrants from population 2 in population 1, and m_2 the fraction in population 2 of migrants from population 1. We assume migration rates m_k are positive and constant over generations.

The dynamics of allele frequencies and pairwise linkage disequilibria under migration alone are (Li & Nei, 1974)

$$\begin{aligned} \delta^m p_i^{(1)} &= m_1(p_i^{(2)} - p_i^{(1)}), \\ \delta^m p_i^{(2)} &= m_2(p_i^{(1)} - p_i^{(2)}), \end{aligned} \tag{8a}$$

and

$$\left.\begin{aligned} \delta^m \mathcal{D}_{ij}^{(1)} &= m_1(\mathcal{D}_{ij}^{(2)} - \mathcal{D}_{ij}^{(1)}) \\ &\quad + m_1(1 - m_1)(p_i^{(2)} - p_i^{(1)})(p_j^{(2)} - p_j^{(1)}), \\ \delta^m \mathcal{D}_{ij}^{(2)} &= m_2(\mathcal{D}_{ij}^{(1)} - \mathcal{D}_{ij}^{(2)}) \\ &\quad + m_2(1 - m_2)(p_i^{(1)} - p_i^{(2)})(p_j^{(1)} - p_j^{(2)}), \end{aligned}\right\} \tag{8b}$$

where the supercript denotes the population.

The migration–selection balance and consequently the evolution of recombination depend critically on the migration strength. Two cases are considered separately:

Weak migration: migration rates can be written as

$$m_k = \tilde{m}_k \epsilon,$$

where $\tilde{m}_k \neq 0$ is of order one with respect to ϵ.

Strong migration: migration rates, m_k, are assumed to be of order one with respect to ϵ, i.e. $m_k \gg \epsilon$.

(iii) *Migration–selection balance*

(*a*) *Allele frequencies*

Let us assume that recombination, selection, and migration take place in that order. Therefore, the dynamics of allele frequencies close to any equilibrium under selection (6*a*) with fitness function (1) for diploids ((1′) for haploids), and migration according to (8*a*), are given by:

$$\left.\begin{aligned} \delta p_i^{(1)} &= m_1(p_i^{(2)} - p_i^{(1)}) \\ &\quad + (1 - m_1)(a_i^{(1)} p_i^{(1)} q_i^{(1)}) + m_1(a_i^{(2)} p_i^{(2)} q_i^{(2)}), \\ \delta p_i^{(2)} &= m_2(p_i^{(1)} - p_i^{(2)}) \\ &\quad + (1 - m_2)(a_i^{(2)} p_i^{(2)} q_i^{(2)}) + m_2(a_i^{(1)} p_i^{(1)} q_i^{(1)}), \end{aligned}\right\} \tag{9}$$

with error $\mathcal{O}(p_i^{(k)} q_i^{(k)} \epsilon^2)$.

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If the product $a_i^{(1)} a_i^{(2)}$ is positive, then locus i will eventually be monomorphic for the same allele in both populations. Such loci will be in linkage equilibrium and thus will not contribute to the evolution of recombination. These loci will not be considered further. Therefore, we assume that at each locus i, selection favours different alleles in the two populations, i.e. $a_i^{(1)} a_i^{(2)} < 0$, so that under selection alone there would be fixation of different alleles at each locus, for example, alleles a in the first population and alleles A in the second population. Without loss of generality we can suppose that

$$a_i^{(1)} < 0 \quad \text{and} \quad a_i^{(2)} > 0 \quad \text{for each} \quad i \in \mathcal{N}. \tag{10}$$

Thus, in the absence of migration, the two-population system, considered as a whole, is subject to disruptive selection. Weak migration between these populations may, however, maintain polymorphism (Karlin & McGregor, 1972). It has been emphasized (Zhivotovsky & Feldman, 1993) that the dynamics of a genetic system are determined by the ratio of migration and selection parameters rather than their absolute values (see also Haldane, 1932, p. 212). Analogously, set

$$\bar{m}_i^{(k)} = \frac{m_k}{a_i^{(k)}[1-m_1-m_2]}, \quad (k = 1, 2; \quad i \in \mathcal{N}).$$

The system (9) may have only one polymorphic equilibrium with allele frequencies within the biologically reasonable range $(0, 1)$:

$$\begin{aligned} p_i^{(1)*} &= \tfrac{1}{2} - \bar{m}_i^{(1)} - \sqrt{(\tfrac{1}{4} - \bar{m}_i^{(1)} \bar{m}_i^{(2)})}, \\ p_i^{(2)*} &= \tfrac{1}{2} - \bar{m}_i^{(2)} + \sqrt{(\tfrac{1}{4} - \bar{m}_i^{(1)} \bar{m}_i^{(2)})}, \end{aligned} \tag{11}$$

where * indicates values at equilibrium. This exists and is globally stable if and only if

$$|\bar{m}_i^{(1)} + \bar{m}_i^{(2)}| < 1. \tag{12}$$

Throughout the paper we assume that condition (12) is fulfilled.

It follows from (11) that $p_i^{(k)*} q_i^{(k)*}$ is of order one with respect to ϵ. Under weak migration the difference between corresponding allele frequencies in populations, $p_i^{(2)*} - p_i^{(1)*}$, is of order one. Note that under strong migration, $m_k \gg \epsilon$, a stable polymorphic equilibrium may still exist, although the required parameter range is narrow. However, the evolutionary properties of this equilibrium are different from those for weak migration (see below). Strong migration mixes populations considerably, so the two populations are genetically close at equilibrium, i.e. $p_i^{(2)*} - p_i^{(1)*}$ is of order ϵ.

(*b*) *Linkage disequilibria*

Linkage disequilibria are known to be generated by epistatic selection (e.g. Ewens, 1979). They can also be caused by gene flow (Li & Nei, 1974; Christiansen & Feldman, 1975; Barton, 1983; Barton & Bengtsson, 1986). The exact expression for the stationary value of the linkage disequilibria under both epistatic selection and migration can be obtained from system (30) in Appendix A. We shall demonstrate that the strength of migration crucially affects the evolution of a new modifier allele. Two cases will be considered:

Strong migration. For strong migration, explicit interpretation of results is difficult. To illustrate the possible behaviour of recombination modifiers when migration is substantial, we consider a symmetric model for which the effect of selection on A-alleles in one population is equivalent to that on a-alleles in the other population. In terms of selection, migration, and recombination parameters, this entails

$$\left.\begin{aligned} &a_i^{(1)} = -a_i^{(2)} = a_i > 0, \quad b_{ij}^{(1)} = b_{ij}^{(2)} = b_{ij}, \\ &m_1 = m_2 = m, \\ &r_{ij}^{(1)} = r_{ij}^{(2)} = r_{ij}, \quad \Delta r_{ij}^{(1)} = \Delta r_{ij}^{(2)} = \Delta r_{ij}. \end{aligned}\right\} \tag{13}$$

Here selection favours the different alleles at locus i in the different populations with equivalent directional pressure a_i and multiplicative pairwise epistasis b_{ij}.

In this case, for diploids we obtain from (A 1)

$$(\mathscr{D}_{ij})^* = ([b_{ij} - r_{ij}(a_{ij} - a_{i,j})] + e_{ij}^m) \frac{p_i^* q_i^* p_j^* q_j^*}{r_{ij}}, \tag{14}$$

with an error $\mathcal{O}(\epsilon^3)$, where superscript k is omitted owing to the symmetry in the corresponding values in the two populations, and e_{ij}^m, defined by

$$e_{ij}^m = \frac{1-m}{m} a_i a_j, \tag{15}$$

is the contribution of mixing to linkage disequilibria, scaled in units of epistasis. For haploids the term in brackets in (14) should be replaced by $(1 - r_{ij}) b_{ij}$.

Weak migration. In Appendix A we show that under the interaction of weak migration and selection defined by (10), linkage disequilibria are formed primarily by the mixing effect of migration rather than epistasis in selection. In (14) the term e_{ij}^m becomes of order ϵ (see (15)), and thus the term in brackets, which is of order ϵ^2, may be omitted. Therefore, we obtain for both diploids and haploids

$$(\mathscr{D}_{ij}^{(k)})^* = e_{ij}^{m(k)} \frac{p_i^{(k)*} q_i^{(k)*} p_j^{(k)*} q_j^{(k)*}}{r_{ij}^{(k)}}, \tag{16}$$

where $e_{ij}^{m(k)}$ is analogous to (15):

$$e_{ij}^{m(k)} = \frac{1-m_k}{m_k} a_i^{(k)} a_j^{(k)}. \tag{17}$$

The right-hand side of (16) is of the same order as m_k with respect to ϵ and thus gives an approximation for

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the equilibrium value of $\mathscr{D}_{ij}$ with an error $\mathcal{O}(\epsilon^2)$. It follows from (10) that $\mathscr{D}_{ij}^{(k)} > 0$, $k = 1, 2$.

For strong migration $\mathscr{D}_{ij}^{(k)}$ is of order ϵ^2, whereas for weak migration, $\mathscr{D}_{ij}^{(k)}$ is of order ϵ.

3. Invasion by a modifier

Nei (1967) considered the evolution of recombination in terms of the dynamics of modifier genes that control recombination rates among major loci subject to selection. Feldman (1972) formulated this theory in terms of the initial increase in the frequency of a recombination-modifying allele introduced into the population near its polymorphic genetic equilibrium. The most general form of the result of this analysis is the *reduction principle*, according to which the modifier allele invades the population at polymorphic equilibrium under selection if it decreases the recombination rate between two loci in linkage disequilibrium subject to this selection (Feldman & Liberman, 1986) or if it completely suppresses recombination among multiple loci (Altenberg & Feldman, 1987). The *generalized reduction principle* claims that a recombination-modifying allele increases when rare in a population close to a selection equilibrium if it decreases an appropriately weighted average recombination rate among multiple selected loci; this allows increased recombination between some of the loci (Zhivotovsky *et al.*, 1994*a*; Zhivotovsky & Feldman, 1995). Here we apply this approach to the case of a population at equilibrium under migration and selection.

Consider a neutral locus M that modifies recombination rates among the major loci that are under the selection regime described above. Assume that the populations are initially fixed at the modifier locus on the allele M_0, which produces recombination pattern $\{r_{ij}\}$ among the loci under selection that have already attained the polymorphic equilibrium with allele frequencies (11) and linkage disequilibria (16) or (14). Denote by r_{ijM} the probability of at least one recombination event among loci i, j, M.

Now suppose that a new modifier allele M_1 that changes recombination by Δr_{ij}, producing the new recombination rates $r'_{ij} = r_{ij} + \Delta r_{ij}$, is introduced near the equilibrium. Denote the frequency of M_1 in population k ($k = 1, 2$) by π_k. It was shown earlier (Zhivotovsky *et al.*, 1994*a*, eqn. 16) that the frequencies after selection and before migration, π'_k, satisfy

$$\pi'_k = \frac{\bar{v}_k}{\bar{w}_k^*}\pi_k, \tag{18}$$

where $\bar{w}_k^*$ is the equilibrium value of the mean fitness of population k homozygous for the allele M_0, and $\bar{v}_k$ is the mean fitness in population k of those individuals that received one gamete carrying M_0 and the other gamete carrying allele M_1 from their parents.

Following Zhivotovsky & Christiansen (1995), it can be shown that the relative difference between mean fitnesses, $\Delta\bar{v}_k/\bar{w}_k^*$, where $\Delta\bar{v}_k = \bar{v}_k - \bar{w}_k^*$, rapidly converges to a limit denoted here by ξ_k. Hence, the sign of ξ_k determines the fate of the new modifier allele in population k. It will increase in frequency when rare if $\xi_k > 0$, and will vanish from the population if $\xi_k < 0$.

(i) *Migration–selection balance*

Here we apply this approach to study the evolution of recombination in two populations initially at the migration–selection balance described above.

The initial dynamics of new modifier frequencies in the two populations under the joint operation of selection and migration can be expressed as

$$\begin{aligned}\pi'_1 &= (1-m_1)(1+\xi_1)\pi_1 + m_1(1+\xi_2)\pi_2,\\ \pi'_2 &= (1-m_2)(1+\xi_2)\pi_2 + m_2(1+\xi_1)\pi_1,\end{aligned} \tag{19}$$

for π_1 and π_2 sufficiently small.

Obviously, this linear system has only one stationary state $\pi_k = 0$, $k = 1, 2$, which is unstable (and thus the modifier invades the populations) if the maximal eigenvalue, λ, of the matrix in (19) is greater than 1. In Appendix B we calculate ξ_k for cases of both weak and strong migration and show that $\xi_k = o(m_k)$ (eqns. (B 4) and (B 7) respectively), which yields

$$\lambda - 1 = \frac{m_1\xi_2 + m_2\xi_1}{m_1 + m_2}. \tag{20}$$

Thus, the invasion criterion is

$$m_1\xi_2 + m_2\xi_1 > 0. \tag{21}$$

Define the new parameters:

$$\frac{1}{\rho_{ij}^{\prime(k)}} = \frac{1}{2}\left(\frac{1}{r_{iM}^{\prime(k)}} + \frac{1}{r_{jM}^{\prime(k)}}\right), \tag{22}$$

where $\rho_{ij}^{\prime(k)}$ is the harmonic mean of the recombination rates (superscript $'$ refers to the new modifier allele) between the modifier locus and major loci i and j. These may be viewed as measures of linkage of the modifier locus to a pair of major loci ij, and we assume it to be loose in that $\rho_{ij}^{\prime(k)}$ is of order one with respect to ϵ.

Also introduce

$$\rho_{ij}^{c(k)} = \frac{2}{1 - e_{ij}^{(k)}}, \tag{23}$$

which depends on the relative pairwise epistasis (3) and will be shown to determine the critical recombination rate (in terms of ρ'_{ij}).

Substituting (B 4) and (B 7) into (21), we obtain for both diploids and haploids:

Result 1 (Migration). *Consider a population at equilibrium between recurrent migration and weak disruptive*

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selection on loosely linked multiple autosomal loci. A recombination-modifying allele increases in the population when rare if the change in recombination rates due to this allele, averaged over all pairs of loci, with the weights $B_{ij}^{(k)}$, is negative:

$$\sum_{j}\sum_{j>i}(m_2\,\tilde{B}_{ij}^{(1)}\,\hat{B}_{ij}^{(1)}\,\Delta r_{ij}^{(1)}+m_1\,\tilde{B}_{ij}^{(2)}\,\hat{B}_{ij}^{(2)}\,\Delta r_{ij}^{(2)})<0, \tag{24}$$

where

$$\tilde{B}_{ij}^{(k)}=2\;\frac{1}{\rho_{ij}^{\prime(k)}}-\frac{1}{\rho_{ij}^{c,(k)}}\;\frac{a_i^{(k)}\,a_j^{(k)}}{r_{ijM}^{\prime(k)}},\quad (k=1,2). \tag{25}$$

For weak migration,

$$\hat{B}_{ij}^{(k)}=e_{ij}^{m(k)}\frac{p_i^{(k)*}\,q_i^{(k)*}\,p_j^{(k)*}\,q_j^{(k)*}}{r_{ij}^{(k)}}+\mathcal{O}(\epsilon^2),\quad (k=1,2), \tag{26a}$$

where we view $e_{ij}^{m(k)}$, defined by (17), *as a relative measure of epistasis contributing to linkage disequilibria due to mixing.*

For the symmetric model with strong migration,

$$\hat{B}_{ij}=(b_{ij}+e_{ij}^{m})\frac{p_i^*\,q_i^*\,p_j^*\,q_j^*}{r_{ij}}+\mathcal{O}(\epsilon^3), \tag{26b}$$

where the superscript k may be omitted because the corresponding values in the two populations are equal.

(ii) *Mutation-selection balance*

Barton (1995, eqn. 18*a*) obtained an expression for modifier dynamics at a balance between weak directional selection and deleterious mutation when the modifier changes the recombination rates among major loci slightly and there is no *cis–trans* fitness effect. Here we present a generalization of his result for arbitrary change in recombination rates under the assumption that linkage between all major loci is loose. We also show (Appendix B) that the *cis–trans* difference in fitness is irrelevant.

We use the fitness function (1) for diploids and (1′) for haploids with weak directional selection (2), (2′) acting against *A*-alleles, i.e. $a_i<0$. The balance is attained via recurrent deleterious mutations transforming the *a*-allele into *A* at locus *i* with probability μ_i. Mutation rates are typically assumed to be smaller than the strength of selection. The small parameter ϵ is used to scale the mutation rate μ_i:

$$\mu_i=\tilde{\mu}_i\epsilon^2.$$

Under the above assumptions the changes in allele frequencies due to mutation are $\delta p_i=-\mu_i p_i$. Combining this with the effect of selection in (6*a*), we obtain

$$p_i^*\,q_i^*=-\mu_i/a_i+\mathcal{O}(\epsilon^2). \tag{27}$$

The dynamics of linkage disequilibria under mutation are given by $\mathcal{D}_{ij}^{\prime}=(1-\mu_i)(1-\mu_j)\,\mathcal{D}_{ij}$, and after selection (6*b*) we obtain for diploids

$$\mathcal{D}_{ij}^{*}=\;e_{ij}-r_{ij}\frac{(a_{ij}-a_{i,j})}{a_i\,a_j}\;\frac{\mu_i\mu_j}{r_{ij}}, \tag{28}$$

which is of the same order as $\mu_i\mu_j$ with respect to ϵ and thus holds with an error $\mathcal{O}(\epsilon^4)$. For haploids the term in brackets should be replaced by $(1-r_{ij})\,e_{ij}$.

Neglecting recurrent mutation at the modifier locus, the initial dynamics of the new modifier frequency, $\pi^{\prime}$, near the mutation–selection balance can be expressed as

$$\pi^{\prime}=(1+\xi_{\mu})\,\pi,$$

where ξ_{μ} is the limiting value of $\Delta\bar{v}_{\mu}/\bar{w}_{\mu}^{*}$, with $\Delta\bar{v}_{\mu}$ and $\bar{w}_{\mu}^{*}$ similar to those in (18) in the case of mutation–selection balance for a single population. Thus the invasion criterion becomes $\xi_{\mu}>0$, or, using expression (B 8) in Appendix B, we obtain

$$\sum_{i}\sum_{j>i}\Delta r_{ij}\;\frac{1}{\rho_{ij}^{\prime}}-\frac{1}{\rho_{ij}^{c}}\;\frac{2e_{ij}\,a_i\,a_j\,\mu_i\,\mu_j}{r_{ij}\,r_{ijM}^{\prime}}<0 \tag{29}$$

(cf. Barton, 1995, eqns. 12, 18*a*). The expression obtained by Barton includes terms due to epistatic interactions between more than two loci, but only pairwise epistasis is actually relevant because at mutation–selection balance the higher-order epistatic terms appear in (29) with multipliers $(p^*\,q^*)^n$, where $n>2$, and thus are negligible since $(p^*\,q^*)^n$ are of order ϵ^3 or less (see (27)). For modifiers having an arbitrary effect on recombination rates, the term $\rho_{ij}^{\prime}$, which is the recombination rate due to the new modifier allele M_1, appears in (29), whereas for weak modifiers ($\Delta r_{ij}=\mathcal{O}(\epsilon)$), ρ_{ij}, corresponding to the resident modifier allele M_0, can be used since in that case $\rho_{ij}^{\prime}$ and ρ_{ij} are approximately equal (see definition (22)).

From (29) we obtain for both diploids and haploids:

Result 2 (Mutation). *Consider a population at equilibrium between recurrent deleterious mutations and weak disruptive selection on loosely linked multiple autosomal loci. A recombination-modifying allele increases in the population when rare if the change in recombination rates due to this allele, averaged over all pairs of loci, with the weights B_{ij}, is negative:*

$$\sum_{i}\sum_{j>i}\tilde{B}_{ij}\,\hat{B}_{ij}\,\Delta r_{ij}<0, \tag{24′}$$

where $\tilde{B}_{ij}$ has the same definition as for migration (25)*:*

$$\tilde{B}_{ij}=2\;\frac{1}{\rho_{ij}^{\prime}}-\frac{1}{\rho_{ij}^{c}}\;\frac{a_i\,a_j}{r_{ijM}^{\prime}}, \tag{25′}$$

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Table 1. *Change in recombination rate, favouring a new modifier in a two-locus model (see Corollary)*

Scenario	Factor	$e < -3$	$-3 < e < 0$	$e > 0$
I	Mutation, *Strong* migration	r increases if $\rho' < \rho^c$ r decreases if $\rho' > \rho^c$	r increases	r decreases
II	*Weak* migration	r decreases if $\rho' < \rho^c$ r increases if $\rho' > \rho^c$	r decreases	r decreases

and

$$\hat{B}_{ij} = \frac{\mu_i \mu_j e_{ij}}{r_{ij}} + \mathcal{O}(\epsilon^5). \tag{26'}$$

Consider the special case of two loci with symmetry in the model parameters (see (13)). Results 1 and 2 imply:

Corollary (Two-locus model). *Consider a population at equilibrium between recurrent migration or recurrent deleterious mutations and weak disruptive selection on two loosely linked autosomal loci. A recombination-modifying allele increases in the population when rare if*

$$\tilde{B}\hat{B}\,\Delta r < 0, \tag{24''}$$

where Δr *is the change in the recombination rate,* $\tilde{B}$ *is defined by* (25′) *and* $\hat{B}$ *by* (26) *for migration or* (26′) *for mutation* (*for simplicity, the indices and the superscripts are omitted*).

Note that

$$\tilde{B} > 0 \quad \text{if} \quad \begin{cases} e > -3 \\ e < -3, \quad \rho' < \rho^c, \end{cases}$$

and

$$\tilde{B} < 0 \quad \text{if} \quad e < -3, \quad \rho' > \rho^c.$$

The sign of $\hat{B}$ is due to epistasis for mutation–selection balance (see (26′)). It is always positive under weak migration (see (26*a*)), whereas for strong migration it depends on both selection and migration (26*b*).

It follows from (24″) that increased recombination is favoured if $\tilde{B}\hat{B} < 0$, and recombination decreases if $\tilde{B}\hat{B} > 0$. The corresponding conditions in terms of epistasis and recombination rates are listed in Table 1.

4. Discussion

The goals of this study have been to explore and compare the effects of migration and mutation on the evolution of recombination in populations of diploid and haploid individuals under multilocus selection. For these purposes we first outlined the conditions for maintaining polymorphism in a system of two populations connected by migration and subject to weak disruptive epistatic selection, favouring different alleles in the different populations.

It was shown earlier that maintenance of genetic polymorphism in a system under the joint operation of weak selection and migration is determined by the ratio of the corresponding parameters rather than by their absolute values (Zhivotovsky & Feldman, 1993). Our analysis confirms this observation (see (12)). We showed that the evolution of recombination depends qualitatively on the strength of migration. This feature is due to the different ways of forming linkage disequilibria. With weak migration, linkage disequilibria are created primarily by mixing and are always positive (under assumption (10)). For strong migration, polymorphism is still maintained unless condition (12) is violated. In this case, the two populations are genetically close at equilibrium, $p^{(2)*} - p^{(1)*} \sim \mathcal{O}(\epsilon)$, and linkage disequilibria are formed both by epistasis in selection and by mixing due to migration.

For mutation–selection balance, we obtained an invasion criterion that generalizes a previous result by Barton (1995) to include *cis–trans* fitness effects and arbitrary change by the modifiers.

For both migration and mutation, the invasion criterion for a new modifier is formulated in terms of the average change in the recombination rates *weighted over loci* as well as over populations (for migration–selection balance). This seems to be a general property of the evolution of recombination in multilocus systems (Zhivotovsky *et al.*, 1994*a*; Zhivotovsky & Feldman, 1995). The role of migration in the evolution of recombination differs qualitatively from that of mutation. To illustrate this, consider a two-locus model (see Corollary). In this model, recombination increases under mutation with weak negative epistasis ($-3 < e < 0$). If epistasis is stronger ($e < -3$) then the increase in recombination occurs when $\rho' < \rho^c$. We call this scenario I (Table 1, mutation).

The principal difference between the effects of migration and mutation on the evolution of recombination resides in the formation of linkage disequilibria. Mutations, acting independently, change the magnitude of linkage disequilibria but not the sign, which is still determined by the epistasis. With migration the situation is more complex. Under sufficiently strong migration, selection may play a major role in determining linkage disequilibria, and

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consequently recombination evolves according to scenario I (Table 1, *strong* migration). However, under the interaction of weak migration and disruptive selection, the equilibrium value of linkage disequilibria is created by mixing only and thus is always positive (assuming (10)), irrespective of the sign of epistasis. Thus for negative epistasis, $e < 0$, the invasion conditions are reversed relative to scenario I and increased recombination evolves in a population under weak-migration-selection balance according to scenario II (see Table 1, *weak* migration).

The conditions for recombination between any pair of major loci to decrease are opposite to those outlined above.

Scenario I requires migration to be sufficiently strong. For example, if the value e of epistasis is -3, the migration rate must be above 25%. For $e = -9$, the fraction of migrants must be greater than 10%. Although gene flow between populations may occasionally reach this level (Zhivotovsky *et al.*, 1994*b*), weaker migration seems to be more common in nature (Burt, 1995). We suggest, therefore, that with migration, recombination is more likely to evolve according to scenario II.

The fact that under migration–selection balance the invasion criterion is averaged over populations leads to the following interesting observation. Assume that in population 1, say, selection is much weaker than in population 2: $a_i^{(1)}/a_i^{(2)}, a_{ij}^{(1)}/a_{ij}^{(2)} \sim \mathcal{O}(\epsilon)$; and suppose that the rate of migration into population 1, m_1, is much smaller than into population 2: $m_1/m_2 \sim \mathcal{O}(\epsilon)$. Condition (12) can still be satisfied and stable polymorphism maintained. In this case, the values of $m_1 \hat{B}^{(2)}$ and $m_2 \hat{B}^{(1)}$ are of the same order with respect to ϵ, whereas $\tilde{B}^{(1)}/\tilde{B}^{(2)} \sim \mathcal{O}(\epsilon)$. Thus, the fate of a new recombination-modifying allele will be determined by its success in the population with the stronger selection pressure, namely 2, as if there were no migration. Thus the evolution of recombination in population 1 may appear anomalous relative to what would be expected if there were no other population.

To conclude, under migration–selection, recombination may evolve in a qualitatively different way compared with under mutation–selection balance. Studies of the evolution of recombination in subdivided populations subject to heterogeneous selection and more general migration and selection patterns may give different results and are worth pursuing.

Appendix A. Migration–selection balance: equations (16) and (14)

The dynamics of linkage disequilibria under selection (6*b*) and migration (8*b*) close to equilibrium are described by a linear system:

$$\bar{\mathscr{D}}'_{ij} = \mathbf{M}_{\mathbf{r}}(\mathbf{r_{ij}})\,\bar{\mathscr{D}}_{ij} + \mathbf{M} \times [\bar{\alpha} + \bar{\beta}(r_{ij})] + \bar{\gamma}, \qquad \text{(A 1)}$$

where $\bar{\mathscr{D}}_{ij}$ is the vector $(\mathscr{D}_{ij}^{(1)}, \mathscr{D}_{ij}^{(2)})$, $\mathbf{M}$ is given by (7), $\mathbf{M}_{\mathbf{r}}(\mathbf{r_{ij}})$ is the 2×2 matrix

$$\mathbf{M}_{\mathbf{r}}(\mathbf{r_{ij}}) = \begin{matrix} (1-m_1)(1-r_{ij}^{(1)}) & m_1(1-r_{ij}^{(2)}) \\ m_2(1-r_{ij}^{(1)}) & (1-m_2)(1-r_{ij}^{(2)}) \end{matrix}, \qquad \text{(A 2)}$$

$\bar{\alpha}$, $\bar{\gamma}$, and $\bar{\beta}$ are vectors whose kth ($k = 1, 2$) elements close to equilibrium are given by

$$\alpha_k = b_{ij}^{(k)}\, p_i^{(k)*}\, q_i^{(k)*}\, p_j^{(k)*}\, q_j^{(k)*},$$

$$\gamma_k = e_{ij}^{m(k)}\, p_i^{(k)*}\, q_i^{(k)*}\, p_j^{(k)*}\, q_j^{(k)*},$$

with $e_{ij}^{m(k)}$ defined by (17);

$$\beta(r_{ij})_k = \begin{cases} -r_{ij}^{(k)}\,(a_{ij}^{(k)} - a_{i,j}^{(k)})\, p_i^{(k)*}\, q_i^{(k)*}\, p_j^{(k)*}\, q_j^{(k)*}, \\ \quad \text{for diploids,} \\ -r_{ij}^{(k)}\, b_{ij}^{(k)}\, p_i^{(k)*}\, q_i^{(k)*}\, p_j^{(k)*}\, q_j^{(k)*}, \\ \quad \text{for haploids.} \end{cases}$$

Weak migration. When migration is weak, $m_k = \mathcal{O}(\epsilon)$, and linkage is loose, $r_{ij}^{(k)} \gg m_k$, the matrix (A 2) becomes diagonal to leading order, so that the local dynamics of $\mathscr{D}_{ij}^{(k)}$ in populations 1 and 2 are independent. We can neglect $\bar{\beta}$ since it becomes much smaller than $\bar{\gamma}$ and after some simple algebra, we obtain expression (16).

Symmetric model with strong migration. With symmetric parameters in the populations as in (13), at equilibrium for (A 1) we have $\mathscr{D}_{ij}^{(1)} = \mathscr{D}_{ij}^{(2)} = \mathscr{D}_{ij}$, and $\mathscr{D}_{ij}$ is easily obtained in the form (14).

Appendix B. Initial dynamics of a new modifier

Once a new modifier M_1 enters population k, we may distinguish two pools of gametes in this population: one consists of the gametes carrying only the resident modifier allele M_0, and the other has the new allele M_1. This subdivision enables us to define new variables, $\Delta p_i^{(k)}$ and $\Delta \mathscr{D}_{ij}^{(k)}$, the difference between the frequencies of allele A_i and the difference between gametic disequilibria in these pools, respectively.

The mean-fitness difference, $\Delta v = \bar{w} - w^*$, is (Zhivotovsky *et al.*, 1994*a*, eqn. 23):

$$\Delta \bar{v}^{(k)} = \sum_i F_i^{(k)*}\, \Delta p_i^{(k)} + \sum_i \sum_{j>i} a_{ij}^{(k)}\, (\Delta \mathscr{D}_{ij}^{(k)} + \Delta p_i^{(k)}\, \Delta p_j^{(k)}), \qquad \text{(B 1)}$$

where $F_i^{(k)*} = a_i^{(k)} + a_{i,i}^{(k)}\, p_i^{(k)*} + \Sigma_{j \neq i}(a_{ij}^{(k)} + a_{i,j}^{(k)})\, p_j^{(k)*}$ for diploids, and $F_i^{(k)*} = a_i^{(k)} + \Sigma_{j \neq i} a_{ij}^{(k)}\, p_j^{(k)*}$ for haploids. It follows from (2), (2′) that $F_i^{(k)*} = a_i^{(k)} + \mathcal{O}(\epsilon^2)$.

Migration–selection balance

For the limiting value of $\Delta \bar{v}^{(k)}$ in population k, we need the equilibrium values of $\hat{\Delta} p_i^{(k)}$ and $\hat{\Delta} \mathscr{D}_{ij}^{(k)}$ under

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selection and migration. We can again use matrix (A 2) to represent the local dynamics of differences in allele frequencies and linkage disequilibria using vector forms, $\overline{\Delta p}_i$ and $\overline{\Delta \mathscr{D}}_{ij}$, respectively.

Applying the method developed by Zhivotovsky *et al.* (1994*a*) to our model including migration, we obtain

$$\left.\begin{aligned}(\overline{\Delta \mathscr{D}}_{ij})' &\approx \mathbf{M}_{\mathbf{r}}(\mathbf{r}'_{\mathbf{ijM}})\,\overline{\Delta \mathscr{D}}_{ij} \\ &\quad + \mathbf{M}_{\mathbf{r}}(\Delta \mathbf{r}_{\mathbf{ij}})\,\bar{\mathscr{D}}^*_{ij} - \bar{\mathscr{D}}^*_{ij} + \mathbf{M}\bar{\beta}(\Delta r_{ij}), \\ (\overline{\Delta p}_i)' &\approx \mathbf{M}_{\mathbf{r}}(\mathbf{r}'_{\mathbf{iM}})\,\overline{\Delta \mathscr{D}}_{ij} + \sum_{j\neq i} \overline{a_j \Delta \mathscr{D}}_{ij},\end{aligned}\right\} \tag{B 2}$$

where $\overline{a_j \Delta \mathscr{D}}_{ij}$ denotes the vector $(a_j^{(1)}\,\Delta \mathscr{D}_{ij}^{(1)},\, a_j^{(2)}\,\Delta \mathscr{D}_{ij}^{(2)})$.

Weak migration. In this case, the matrix of the system (B 2) becomes diagonal to leading order, so that the local dynamics of $\Delta \mathscr{D}_{ij}^{(k)}$ occur independently in populations 1 and 2 and, near equilibrium under selection (6*a*, *b*) (see also Zhivotovsky *et al.*, 1994*a*, eqns. 32–33) and migration (8*a*, *b*), we have for diploids and haploids

$$(\Delta \mathscr{D}_{ij}^{(k)})' \approx (1 - r'^{(k)}_{ijM})\,\Delta \mathscr{D}_{ij}^{(k)} - \Delta r_{ij}\,\mathscr{D}_{ij}^{(k)*},$$

$$(\Delta p_i^{(k)})' \approx (1 - r'^{(k)}_{iM})\,\Delta p_i^{(k)} + (1 - r'^{(k)}_{iM}) \sum_{j\neq 1} a_j^{(k)}\,\Delta \mathscr{D}_{ij}^{(k)},$$

to terms of leading order. This yields the equilibrium values (denoted by superscript ˆ)

$$\hat{\Delta} \mathscr{D}_{ij}^{(k)} = -\frac{\Delta r_{ij}}{r'^{(k)}_{ijM}}\,\mathscr{D}_{ij}^{(k)*} + \mathscr{O}(\epsilon^2), \tag{B 3a}$$

where $(\mathscr{D}_{ij}^{(k)})^*$ is given by equations (16), and

$$\hat{\Delta} p_i^{(k)} = \frac{1 - r'^{(k)}_{iM}}{r'^{(k)}_{iM}} \sum_{j\neq i} a_j^{(k)}\,\hat{\Delta} \mathscr{D}_{ij}^{(k)} + \mathscr{O}(\epsilon^3). \tag{B 3b}$$

Substituting (B 3*a*) and (B 3*b*) into (B 1), and retaining terms of leading order, we obtain an expression for ξ_k with an error of $\mathscr{O}(\epsilon^4)$:

$$\xi_k = -\sum_i \sum_{j>i} \Delta r_{ij}^{(k)}\; a_i a_j \left(\frac{1}{r'_{iM}} + \frac{1}{r'_{jM}}\right) + b_{ij} - a_i a_j \times \frac{e_{ij}^{m(k)}\, p_i^{(k)*}\, q_i^{(k)*}\, p_j^{(k)*}\, q_j^{(k)*}}{r_{ij}^{(k)}\, r'^{(k)}_{ijM}}.$$

Applying definitions (3), (22), (23) and rearranging terms produces

$$\xi_k = -\sum_i \sum_{j>i} \Delta r_{ij}^{(k)}\; \left(\frac{1}{\rho'^{(k)}_{ij}} - \frac{1}{\rho^{c(k)}_{ij}}\right) \times \frac{2 e_{ij}^{m(k)}\, a_i^{(k)} a_j^{(k)}\, p_i^{(k)*}\, q_i^{(k)*}\, p_j^{(k)*}\, q_j^{(k)*}}{r_{ij}^{(k)}\, r'^{(k)}_{ijM}} + \mathscr{O}(\epsilon^4). \tag{B 4}$$

Substituting this into (21) produces Result 1 for weak migration.

Symmetric model with strong migration. Under assumptions (13), the system (B 2) simplifies considerably and at equilibrium we have $\Delta \mathscr{D}_{ij}^{(1)} = \Delta \mathscr{D}_{ij}^{(2)} = \hat{\Delta} \mathscr{D}_{ij}$ and $\Delta p_i^{(1)} = \Delta p_i^{(2)} = \hat{\Delta} p_i$, where for diploids

$$\hat{\Delta} \mathscr{D}_{ij} = -\frac{1}{r'_{ijM}} \times \{\Delta r_{ij} (\mathscr{D}_{ij})^* + \Delta r_{ij} [a_{ij} - a_{i,j}]\, p_i^*\, q_i^*\, p_j^*\, q_j^*\} + \mathscr{O}(\epsilon^3), \tag{B 5}$$

and $(\mathscr{D}_{ij})^*$ is given by equations (14). For haploids, the term in brackets should be replaced with b_{ij}. Substituting (14) into (B 5) produces

$$\hat{\Delta} \mathscr{D}_{ij} = -\frac{\Delta r_{ij}}{r'_{ijM}}\; (b_{ij} + e_{ij}^m) \frac{p_i^*\, q_i^*\, p_j^*\, q_j^*}{r_{ij}} + \mathscr{O}(\epsilon^3), \tag{B 6a}$$

where the term in braces is the linkage disequilibrium, (14), as if there were no *cis–trans* effect of loci *i* and *j*. Thus, the pairwise *cis–trans* differences in diploid fitness do not affect the evolution of recombination.

Also

$$\hat{\Delta} p_i = \frac{1 - r'_{iM}}{r'_{iM}} \sum_{j\neq i} a_j\,\hat{\Delta} \mathscr{D}_{ij} + \mathscr{O}(\epsilon^4). \tag{B 6b}$$

In the symmetric model, $\xi_1 = \xi_2 = \xi$. Substituting (B 6*a*) and (B 6*b*) into (B 1), and retaining the terms of leading order, we obtain an expression for ξ with an error of $\mathscr{O}(\epsilon^5)$:

$$\xi = -\sum_i \sum_{j>i} \Delta r_{ij}\; a_i a_j \left(\frac{1}{r'_{iM}} + \frac{1}{r'_{jM}}\right) + b_{ij} - a_i a_j \times (b_{ij} + e_{ij}^m) \frac{p_i^*\, q_i^*\, p_j^*\, q_j^*}{r_{ij}\, r'_{ijM}}.$$

Again, using definitions (3), (22), (23) and rearranging terms we obtain (superscript k is omitted because of symmetry)

$$\xi = -\sum_i \sum_{j>i} \Delta r_{ij}\; \left(\frac{1}{\rho'_{ij}} - \frac{1}{\rho^c_{ij}}\right)\; (b_{ij} + e_{ij}^m) \times \frac{2 a_i a_j\, p_i^*\, q_i^*\, p_j^*\, q_j^*}{r_{ij}\, r'_{ijM}} + \mathscr{O}(\epsilon^5). \tag{B 7}$$

Substitution of (B 7) into (21) gives Result 2 for the symmetric model with strong migration.

Mutation–selection balance

For the limiting value of $\Delta \bar{v}$ we need the equilibrium values of $\hat{\Delta} \mathscr{D}_{ij}$ and $\hat{\Delta} p_i$ under selection and deleterious mutations. Expressions for these variables are similar to (B 5), (B 6*a*), (B 6*b*) but with $(\mathscr{D}_{ij})^*$ given by (28). Substitution into (B 1) yields

$$\xi = -\sum_i \sum_{j>i} \Delta r_{ij}\; a_i a_j \left(\frac{1}{r'_{iM}} + \frac{1}{r'_{jM}}\right) + b_{ij} - a_i a_j \times \frac{\mu_i \mu_j \epsilon_{ij}}{r_{ij}\, r'_{ijM}} + \mathscr{O}(\epsilon^7) \tag{B 8}$$

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(cf. Barton, 1995, eqns. 12, 18*a*). Applying definitions (3), (22), (23) produces the invasion criterion for the mutation–selection balance model in the form (29).

Drs N. H. Barton and S. P. Otto provided valuable comments on the manuscript. Research was supported in part by NIH grants GM28016 and 1 R03 TW00491-01 and a grant to the Morrison Institute for Population and Resource Studies from the John D. and Catherine T. MacArthur Foundation.

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