A general model for the evolution of recombination

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Summary

A general representation of multilocus selection is extended to allow recombination to depend on genotype. The equations simplify if modifier alleles have small effects on recombination. The evolution of such modifiers only depends on how they alter recombination between the selected loci, and does not involve dominance in modifier effects. The net selection on modifiers can be found explicitly if epistasis is weak relative to recombination. This analysis shows that recombination can be favoured in two ways: because it impedes the response to epistasis which fluctuates in sign, or because it facilitates the response to directional selection. The first mechanism is implausible, because epistasis must change sign over periods of a few generations: faster or slower fluctuations favour reduced recombination. The second mechanism requires weak negative epistasis between favourable alleles, which may either be increasing, or held in check by mutation. The selection (s_i) on recombination modifiers depends on the reduction in additive variance of log(fitness) due to linkage disequilibria ($v_1 < 0$), and on non-additive variance in log(fitness) (V_2', V_3', .. for epistasis between 2, 3.. loci). For unlinked loci and pairwise epistasis, $s_i = -(v_1 + 4V_2'/3)\delta r$, where δr is the average increase in recombination caused by the modifier. The approximations are checked against exact calculations for three loci, and against Charlesworth's analyses of mutation/selection balance (1990), and directional selection (1993). The analysis demonstrates a general relation between selection on recombination and observable components of fitness variation, which is open to experimental test.

1. Introduction

The prevalence of recombination seems paradoxical, since on the simplest view, the breakup of favourable gene combinations should impede adaptation. This is one of the several puzzles concerning the evolution of sexual reproduction, but may be more amenable to explanation than most. Recombination rates can readily evolve, as is shown both by heritability measures in the laboratory (Chinnici, 1971; Charlesworth & Charlesworth, 1985 *a, b*; Brooks & Marks, 1986), and by differences between species (Burt & Bell, 1987) and between the sexes (Trivers, 1988). Thus, the processes responsible for current levels of recombination can be investigated by short-term observations. Moreover, because recombination is constrained by the structure of classical population genetics, theory may help us to interpret such observations in a general way.

Recombination may be favoured for its direct effects on fitness (for example, through repair of DNA

– Bernstein *et al.* 1988), or because it breaks up unfavourable associations between genes. The population-genetic mechanisms can be classified by whether unfavourable linkage disequilibria are produced by stochastic forces (including both hitch-hiking and random drift), or by selection (Felsenstein, 1988). This paper deals solely with the latter class of deterministic models. Most theoretical work has concentrated on populations at equilibrium under selection, in which case the 'reduction principle' applies: with random mating, modifiers which reduce recombination will invade if there is any linkage disequilibrium. This principle has been established when two loci affect either haploid or diploid viability (Feldman *et al.* 1980), and for weak viability selection on many loci, with pairwise epistasis (Zhivotovsky *et al.* 1994). More generally, Altenberg & Feldman (1987) proved that modifiers that completely eliminate recombination will invade a population at an equilibrium under arbitrary selection. The mechanism here is straightforward: modifiers that reduce recombination

become associated with gene combinations that are favoured by selection, and thereby gain an advantage themselves. Recombination can increase if selection fluctuates, so as to sometimes favour one combination, and sometimes another (Sturtevant & Mather, 1938). However, it is hard to see why epistasis should fluctuate in sign over just the right timescale, making this implausible as a general explanation (Charlesworth, 1976; Maynard Smith, 1978, p. 98).

Recombination can be favoured through an interaction between directional selection and epistasis, by a mechanism quite distinct from the model of fluctuating epistasis described above. If the increase in fitness due to two favourable alleles is less than the product of their individual effects, then negative linkage disequilibria build up. These reduce the additive genetic variance, and hence impede the response of the population to directional selection (Mather, 1943; Felsenstein, 1965; Eshel & Feldman, 1970; Feldman *et al.* 1980). This effect gives an advantage to individual modifiers that increase recombination when directional selection is balanced by deleterious mutations (Feldman *et al.* 1980; Kondrashov, 1988; Charlesworth, 1990), and also when there is stabilizing selection on a polygenic trait, with a moving optimum (Maynard Smith, 1980, 1988; Charlesworth, 1993). In both cases, the mechanism is the same. Modifiers that increase recombination become associated with genomes that cause greater additive genetic variance. These respond more rapidly to directional selection, and so in turn become associated with favourable alleles, causing the modifier to hitch-hike to higher frequency.

This paper develops a general representation of the evolution of recombination in multilocus systems, and uses it to analyse the interaction between epistasis and directional selection. The method extends Barton & Turelli's (1991) techniques to describe modifiers of recombination. First, I summarize the notation, and show how it extends to describe recombination that depends on genotype. The formulae are greatly simplified when the modifier has very small effects, and further simplify when epistasis is weak, leading to general results for arbitrary multilocus systems. The simplest system of three loci (one modifier plus two selected genes) is analysed in detail, both to make clear the general results, to apply them to particular cases, and to check the approximations against numerical results (Appendix 1). Constant directional selection, fluctuating selection and mutation/selection balance are considered.

2. A general model

(i) *Summary of notation*

A more detailed exposition of the methods used here is set out in Barton & Turelli (1991) and Turelli & Barton (1994); only a brief summary is given here.

The state of a diploid individual is represented by the vectors $\mathbf{X}$ and $\mathbf{X}^*$, which give the states of the genes derived from the mother and father, respectively. The X_i's may represent the contribution of each gene to some additive trait, or they may simply act as labels for alleles. Throughout this paper, two alleles are assumed at each locus, and the X's take the values 0 or 1. Natural selection can act on the viability and fertility of both the haploid and diploid stage; however, variation in diploid fertility must be multiplicative across the two parents. Sexual selection can act to produce non-random mating between haploid gametes, but must be based solely on the haploid genotype. Generations must not overlap. These assumptions ensure that the population can be described by the distribution of haploid genotypes immediately after meiosis, and that selection can be described by the contributions of each diploid genotype to the next haploid generation, relative to the frequencies expected from random union of haploid gametes.

The population of haploid gametes generated by recombination is described by the mean effect of each locus, $m_i = E(X_i)$, and by the various multilocus linkage disequilibria. The linkage disequilibria are defined as central moments of effects across loci: $C_U = E(\zeta_U)$, where U is some set of loci, $\zeta_U = \prod_{i \in U} \zeta_i$, $\zeta_i = X_i - m_i$, and $E()$ is the expectation across a population formed by random union of haploid gametes. Immediately after selection and before meiosis, the state of the population of diploids after selection is described by $m_i' = E'(X_i)$, $m_i'^* = E'(X_i^*)$, and $C_{U,V}' = E'(\prod_{i \in U} \zeta_i \prod_{j \in V} \zeta_j^*)$. These variables are more complicated, because selection might act differently on male and female gametes ($m_i' \neq m_i'^*$, $C_{U,V}' \neq C_{V,U}'$), and because it builds up associations among genes on different chromosomes, reflecting deviations from multilocus Hardy–Weinberg proportions ($C_{U,V}' \neq C_{U,\varnothing}' C_{\varnothing,V}'$, where $\varnothing$ represents the empty set). With biallelic loci, the X_i take the values 0 or 1, and allele frequencies are denoted by $p_i = m_i$, $q_i = 1 - m_i$. Using the moments of binomial variables, repeated indices reduce according to simple rules; for example, $C_{ii} = p_i q_i$, $C_{iijk} = p_i q_i C_{jk} - C_{ijk}(p_i - q_i)$ (eqn A8 of Barton, 1986). Therefore, all that are needed are the means m_i and moments $C_{U,V}$ in which U and V contain distinct indices.

The relative fitness of diploid individuals is represented as a polynomial function of genotype, with selection coefficients $a_{U,V}$ (eqn 6 of Barton & Turelli, 1991):

$$\frac{W}{\overline{W}} = 1 + \sum_U a_{U,\varnothing}(\zeta_U - C_U) + \sum_V a_{\varnothing,V}(\zeta_V^* - C_V)$$

$$+ \sum_{U,V} a_{U,V}(\zeta_U - C_U)(\zeta_V^* - C_V). \tag{1}$$

Here, $a_{U,\varnothing}$ is the selection coefficient acting on the set U of the loci derived from female gametes. For

example, $a_{i,\varnothing}$ represents selection on the i'th locus, and $a_{ij,\varnothing}$ represents the epistatic interaction between loci i and j. Similarly, $a_{\varnothing,V}$ is the selection coefficient on the set V of loci derived from male gametes, and $a_{U,V}$ is the selection favouring associations between alleles derived from different gametes. $\tilde{a}_{U,V}$ denotes the symmetrized coefficient, $(a_{U,V}+a_{V,U})/2$. In this paper, we assume two alleles per locus, so that only coefficients involving distinct indices are required (for example, $a_{ii,jj}$ is unnecessary, and can be absorbed into $a_{i,j}$). Following the convention used in previous papers, the coefficients $a_{ij,\varnothing}$ and $a_{ji,\varnothing}$ are kept separate, and sums over sets U include both $\{ij\}$ and $\{ji\}$. This simplifies results for additive traits. Cross-gamete coefficients such as $a_{i,j}$ and $a_{j,i}$ are also kept separate: these differ if selection acts differently on male and female gametes. (Turelli & Barton (1994) describe an alternative notation, based on multilocus cumulants and selection gradients. This is more convenient for selection on additive polygenic traits, but is a more cumbersome description of recombination. The two approaches are mathematically equivalent; (Turelli & Barton, 1994.)

Recombination is described by the proportion $r_{S,T}$ of gametes produced with the set S of loci derived from one parent, and T from the other. For example, $r_{i,jk}$ is the proportion of gametes containing locus $\{i\}$ from one genome, and loci $\{jk\}$ from the other. When dealing with recombination, we pool permutations $r_{S,T}$ and $r_{T,S}$; thus, $r_{i,jk}+r_{j,ik}+r_{k,ij}+r_{ijk,\varnothing}=1$, because $r_{i,jk}$ includes both the possibility of getting $\{i\}$ from the mother, and $\{jk\}$ from the father, and *vice versa*. All sums over the possible partitions caused by recombination are therefore over distinct sets; such sums are denoted by $\sum_{S,T}^{*}$. In contrast, sums over selection coefficients, $\sum_{U,V}$, are taken over all the $|U|!|V|!$ permutations of the sets U, V. (Thus, the sets $\{ij,k\}$ and $\{k,ij\}$ would be counted separately in $\sum$, but absorbed into one term $\{ij,k\}$ in $\sum^{*}$). For brevity, the total frequency of recombination events that disrupt the set N is written r_N (i.e. $r_N = (1-r_{N,\varnothing}) = \sum_{S,T}^{*} r_{S,T}$, where the sum excludes $N,\varnothing$).

This extends to cover modifiers by letting recombination rates as well as fitnesses be polynomial functions of genotype. Let the rate of recombination between the sets S and T be a polynomial function of X, X^* with coefficients $\delta r_{S,T|U,V}$:

$$r_{S,T} = \bar{r}_{S,T} + \sum_U \delta r_{S,T|U,\varnothing}(\zeta_U - C_U)$$

$$+ \sum_V \delta r_{S,T|\varnothing,V}(\zeta_V^* - C_V)$$

$$+ \sum_{U,V} \delta r_{S,T|U,V}(\zeta_U - C_U)(\delta_V^* - C_V). \qquad (2a)$$

In most of the following, recombination rates are assumed to be influenced by only the additive effects at one locus (i, say). Hence, we need only consider

$\delta r_{S,T|i,\varnothing}$ and $\delta r_{S,T|\varnothing,i}$. Plausible models would give equal effects to maternal and paternal alleles, so that both can be written as $\delta r_{S,T|i}$:

$$r_{S,T} = \bar{r}_{S,T} + \delta r_{S,T|i}(\zeta_i + \zeta_i^*). \qquad (2b)$$

The recombination rates of the three genotypes $(X_i, X_i^*) = (0,0)$, $(0,1)$, $(1,1)$ are thus $\bar{r}_{S,T}-2\delta r_{S,T|i}p_i$, $\bar{r}_{S,T}-\delta r_{S,T|i}(p_i-q_i)$, $\bar{r}_{S,T}+2\delta r_{S,T|i}q_i$. Since these rates will usually be fixed, this implies that $\bar{r}_{S,T}$ is frequency dependent, being the mean across all genotypes. However, this is a negligible effect if $\delta r \ll \bar{r}$, as will be assumed below. The difference in recombination rates between the two homozygous genotypes is just $2\delta r_{S,T}$. It will be shown that assuming a single additive modifier is not restrictive if the modifier has a small effect.

(ii) *The effect of genotype-dependent recombination*

The effect of recombination on the disequilibria can be derived in the same way as eqn 2.19 of Turelli & Barton (1990) and eqn 14 of Barton & Turelli (1991), but using the genotype-dependent eqn 2a instead of fixed rates $r_{S,T}$:

$$C_N'' = \sum_{S+T=N}^{*} \bar{r}_{S,T} \tilde{C}_{S,T}' + \sum_{S+T=N}^{*} \sum_{A,B} \delta r_{S,T|A,B}$$

$$\times (C_{SA,TB}' - C_A' C_{S,TB}' - C_B' C_{SA,T}' + C_A' C_B' C_{S,T}'$$

$$+ C_{TA,SB}' - C_A' C_{T,SB}' - C_B' C_{TA,S}'$$

$$+ C_A' C_B' C_{T,S}')/2, \qquad (3a)$$

where $\tilde{C}_{S,T} = (C_{S,T}+C_{T,S})/2$, and the sum includes the non-recombinant $S,T = N,\varnothing$. Eqn 3a allows for the possibility that selection acts differently on female and male loci or gametes, so that $C_{S,T}' \neq C_{T,S}'$. (Recall that the $C_{S,T}'$ are the cross-gamete associations after selection.) Equation 3a is not as bad as it looks: the eight components in the last term arise because both permutations S,T and T,S contribute.

With a single additive modifier:

$$C_N'' = \sum_{S+T=N}^{*} \bar{r}_{S,T} \tilde{C}_{S,T}' + \sum_{S+T=N}^{*} \delta r_{S,T|i}(\tilde{C}_{Si,T}' + \tilde{C}_{S,iT}'). \qquad (3b)$$

The algorithms which constitute this general model of multilocus systems have been written in the symbolic programming language *Mathematica* (Wolfram, 1991). These include eqn 3b above, eqns 10, 12 of Barton & Turelli (1991), and an algorithm based on eqn 1 which derives the selection coefficients from a definition of relative fitness in terms of X, X^*.

The equations simplify considerably if the modifier is assumed to have small effects ($\delta r \ll r, 1$), and to have no direct effects on fitness ($\tilde{a}_{U,V} = 0$ if $i \in U$ or $i \in V$). The dynamics of the selected loci are then, to a first approximation, unaffected by the presence of the modifier. This is because the fate of the modifier is determined by the weak associations ($C_{iN} \approx \delta r$) which

build up between it and the selected loci; the effect of the modifier on the selected loci is also $\approx \delta r$, and so causes a negligible perturbation to the modifier. Thus:

$$\Delta p_i = \sum_N \tilde{a}_{N,\varnothing} C_{iN}, \tag{4}$$

where the sum is over all sets N of selected loci. The association between the modifier and a set N of loci immediately after recombination is found by replacing N by iN, and S by iS in eqn 3b. The second sum on the right then involves terms like $C'_{iiS,T}$; since associations between the modifier and the selected loci are $O(\delta r)$, this is approximately $C'_{ii} C'_{S,T}$. With two alleles per locus, $C_{ii} = p_i q_i$; since the frequency of the modifier allele only changes slowly, $C'_{ii} = p_i q_i + O(\delta r)$. Hence:

$$C''_{iN} = \sum^*_{S+T=N} \bar{r}_{iS,T} \tilde{C}'_{iS,T}$$
$$+ p_i q_i \sum^*_{S+T=N} \delta r_{iS,T|i} \tilde{C}'_{S,T} + O(\delta r^2). \tag{5a}$$

Here, the sums are over all distinct partitions (iS,T) of (iN), and hence include $(S,T) = (\varnothing, N)$ and $(N,\varnothing)$. Because $\bar{r}_{iS,T} + \bar{r}_{S,iT} = \bar{r}_{S,T}$, and $\delta r_{iS,T|i} + \delta r_{S,iT|i} = \delta r_{S,T|i}$, and because $\bar{r}_{iS,T|i}$ and $\delta r_{iS,T|i}$ have the same coefficient as $\bar{r}_{S,iT|i}$ and $\delta r_{S,iT|i}$, eqn 5a simplifies to:

$$C''_{iN} = \sum^*_{S+T=N} \bar{r}_{S,T} \tilde{C}_{iS,T}$$
$$+ p_i q_i \sum^*_{S+T=N} \delta r_{S,T|i} \hat{C}'_{S,T} + O(\delta r^2). \tag{5b}$$

This shows that the evolution of a modifier of small effect only depends on how it alters recombination among the selected loci ($\delta r_{S,T|i}$), and not on how it alters its own linkage to those loci ($\delta r_{iS,T|i}$, etc.). Third and higher-order associations (C_{ijk} etc.) between the modifier and particular gene combinations are generated directly, from terms such as $\delta r_{jk,\varnothing|i} C'_{jk,\varnothing}$. Pairwise associations between the modifier and particular genes such as C_{ij} are not generated directly, since the second sum in eqn 5b is then zero to $O(\delta r)$. However, they are produced indirectly from the first sum in eqn 5b. We will see later that they have an important role in mediating the interaction between directional selection and epistasis.

The assumption that modifiers have small effects is the key simplification. Since we retain only the first-order terms in δr, the equations for the associations between modifiers and selected loci form a linear set. Though only a single modifier is dealt with explicitly, modifiers with small effects will evolve independently of each other, through the linear effects of the various δr's. Moreover, dominance coefficients such as $\delta r_{S,T|i,i}$ can be neglected. This is because such coefficients introduce terms of the form $C'_{Si,Ti}$ into eqn 3a. These could only contribute to leading order if both S and T contained the index i, which is impossible if the N contains only distinct indices. With two or more modifier loci (i, i'), cross-locus interactions such as $\delta r_{S,T|i,i'}$ generate associations between the modifiers

such as $C_{ii'}$. However, these do not significantly influence the change in modifier frequency ($\Delta p_i, \Delta p_{i'}$). Of course, dominance itself can be important; for example, if heterozygotes at the modifier locus cause lower recombination than either homozygote, a polymorphism can be maintained (Feldman & Krakauer, 1976; Feldman & Liberman, 1986). However, in the present notation this is because the average effect of a modifier allele when paired with random homologues, $\delta r_{S,T|i}$, depends on its frequency, p_i. There is no influence of coefficients such as $\delta r_{S,T|i,i}$.

The sum which generates the association between the modifier and the selected loci can be rewritten using the constraint that $\sum^*_{S+T=N} \bar{r}_{S,T} = 1$, and hence $\sum_{S+T=N} \delta r_{S,T|i} = 0$, where the sum is taken over all partitions $S+T=N$, including $N+\{\varnothing\}$ and $\{\varnothing\}+N$. If the latter are separated out, we can write:

$$C''_{iN} = \sum^*_{S+T=N} \bar{r}_{iS,T} \tilde{C}'_{iS,T}$$
$$- p_i q_i \sum^*_{S+T=N} \delta r_{S,T|i} (\tilde{C}'_{N,\varnothing} - \tilde{C}'_{S,T}) + O(d^2). \tag{5c}$$

The effect of the modifier depends on the difference between the cross-gamete associations $C'_{S,T}$ and the within-gamete associations. The linkage disequilibria after selection, $C'_{S,T}$, can be substituted into eqn 5c (from eqn 12 of Barton & Turelli, 1991), leading to a complicated recursion for the associations C_{iN}. As an example, the full expressions for three loci are given in Appendix 1 (eqns A1.2): the dedicated reader should work through these, so as to better understand the general results.

(iii) *Weak selection*

Insight can be gained by approximating eqn 5 in the case where selection is weak. Suppose that linkage is loose, and all the selection coefficients are small ($a_{U,\varnothing}$, $a_{\varnothing,V}, a_{U,V} \ll r, 1$). To begin with, assume that epistasis and directional selection are of the same order ($a_{i,\varnothing} \approx a_{ij,\varnothing}$ etc.). Assume also that the selection coefficients change slowly, and can be taken to be approximately constant over the timescale of recombination. (This assumption is relaxed below, in the section on *Fluctuating selection*.) Then, the population rapidly approaches 'quasi-linkage equilibrium' (QLE), in which the linkage disequilibria are approximated by eqn 25 of Barton & Turelli (1991, Appendix B):

$$C_N = \frac{\{|N|! \tilde{a}_{N,\varnothing}(1-r_N) + \sum^*_{S+T=N} |S|! |T|! \tilde{a}_{S,T} r_{S,T}\} p_N q_N}{r_N}$$
$$+ O(a^2), \tag{6}$$

where $p_N = \prod_{i \in N} p_i$, $q_N = \prod_{i \in N} q_i$. Combining this with eqn 12 of Barton & Turelli (1991) gives approximations for the linkage disequilibria after selection, $C'_{U,V}$, which can be substituted into eqn 5c. Applying the QLE approximation shows that the association

between the modifier and the selected loci rapidly approaches:

$$C_{iN} = -\frac{p_i q_i p_N q_N}{r_N r_{iN}}$$

$$\times \delta r_{N|i} \{|N|! \tilde{a}_{N,\varnothing} + \sum_{S+T=N}^{*} \delta r_{S,T|i}$$

$$\times \sum_{A+B=N}^{*} (|A|!|B|! \tilde{a}_{A,B} r_{A,B} - |S|!|T|! \tilde{a}_{S,T} r_N)\} + O(a^2), \quad (7a)$$

where r_N is the total rate of all recombination events that break up the set N. If selection acts only on diploid viability, so that fitness does not depend on whether genes are in couping or repulsion, then necessarily $|S|!|T|! \tilde{a}_{S,T} = |N|! \tilde{a}_{N,\varnothing}$. Eqn 7a then simplifies to:

$$C_{iN} = -\delta r_{N|i} \frac{p_i q_i p_N q_N |N|! \tilde{a}_{N,\varnothing}}{r_N r_{iN}} + O(a^2). \quad (7b)$$

The association between the modifier and any set of selected loci N now only depends on the effect of the modifier on the net rate of all recombination events that break up the set N, $\delta r_{N|i} = \sum_{S+T=N} \delta r_{S,T|i}$. The modifier frequency changes at:

$$\Delta p_i = \sum_N \tilde{a}_{N,\varnothing} C_{iN}$$

$$= -\sum_N^{*} \delta r_{N|i} \frac{p_i q_i p_N q_N (|N|! \tilde{a}_{N,\varnothing})^2}{r_N r_{iN}} + O(a^3). \quad (8)$$

The extra factor of $|N|!$ appears because the first sum (over $\tilde{a}_{N,\varnothing}$) uses the convention appropriate for selection, that we sum over all permutations of N, whereas the second sum (over $\delta r_{N|i}$) uses the convention appropriate for recombination, when only distinct sets are counted. A modifier which never decreases the rate of recombination ($\delta r_{N|i} \geqslant 0$ for all N) cannot increase ($\Delta p_i \leqslant 0$). Zhivotovsky *et al.* (1994, eqns 27–28) proved this result for populations at equilibrium under strictly pairwise epistasis and weak selection. Equation 8 is a generalization to arbitrary epistasis, and to changing allele frequencies; however, it is more restrictive in that it requires in quasi-linkage equilibrium, and hence loose linkage.

(iv) *Weak epistasis*

Thus far, we have assumed that all the selection coefficients are weak, and of the same order. This leads to the conclusion that unless epistasis fluctuates rapidly (see below), recombination must decrease (at least, on average). This conclusion does not hold if directional selection is much stronger than epistasis. Suppose now that $a_{U,\varnothing}$ and $a_{\varnothing,U}$ are $O(s^2)$ for $|U| > 1$, $a_{U,V}$ is $O(s^2)$ for $|U|$ and $|V| > 0$, $U \neq V$, $a_{j,j}$, $a_{j,\varnothing}$, $a_{\varnothing,j}$ are $O(s)$, and recombination is $O(1)$. ($|U|$ is the number of elements in U.) The approximation can be developed for tight linkage ($r = O(s)$), but is somewhat more complicated (see Appendix 1 for the three-locus

case). Linkage disequilibria between the selected loci are still given by eqn 6, except for the pairwise associations:

$$C_{jk} = \frac{\{2\tilde{a}_{jk,\varnothing}(1-r_{jk}) + \tilde{a}_{j,k} r_{jk} - \tilde{a}_{j,\varnothing} \tilde{a}_{k,\varnothing}\} p_j q_j p_k q_k}{r_{jk}} + O(s^3). \quad (9a)$$

The extra term $\tilde{a}_{j,\varnothing} \tilde{a}_{k,\varnothing}$ arises from the change in allele frequencies, $\Delta p_j \Delta p_k$, which is now of the same order as epistasis; the analogous term is negligible for third and higher-order disequilibria. With selection on diploid viability, $2\tilde{a}_{jk,\varnothing} = \tilde{a}_{j,k}$, and so:

$$C_{jk} = \frac{\epsilon_{jk} p_j q_j p_k q_k}{r_{jk}} + O(s^3), \quad (9b)$$

where C_{jk} is now proportional to the deviation from multiplicative fitnesses, $\epsilon_{jk} = 2\tilde{a}_{jk,\varnothing} - \tilde{a}_{j,\varnothing} \tilde{a}_{k,\varnothing}$.

Because the associations C_{ijk} between the modifier and pairs of selected loci are driven by the pairwise linkage disequilibria C_{jk}, these must also include the term due to $\Delta p_j \Delta p_k$ when epistasis is weak. Applying eqn 5c to find the QLE approximation for C_{ijk} in terms of C_{jk}, using the fact that $2\tilde{a}_{jk,\varnothing} = \tilde{a}_{j,k}$ for selection on diploid viability, and then substituting for C_{jk} from eqn. 9b:

$$C_{ijk} = -\delta r_{jk|i} p_i q_i \frac{\{C_{jk} + (2\tilde{a}_{jk,\varnothing} - \tilde{a}_{j,k}) p_j q_j p_k q_k\}}{r_{ijk}}$$

$$= -\delta r_{jk|i} p_i q_i \frac{C_{jk}}{r_{ijk}}$$

$$= -\delta r_{jk|i} \frac{p_i q_i p_j q_j p_k q_k \epsilon_{jk}}{r_{ijk} r_{jk}} + O(s^3). \quad (9c)$$

Higher-order associations (C_{iN} for $|N| > 2$) are still given by eqn 7b.

The change in the modifier frequency (eqn 4) can be separated into two parts:

$$\Delta p_i = \sum_j \tilde{a}_{j,\varnothing} C_{ij} + \sum_{|N|>1} \tilde{a}_{N,\varnothing} C_{iN}. \quad (10)$$

These two sums describe the interaction between directional selection and epistasis (*via* $\tilde{a}_{j,\varnothing} C_{ij}$), and the effect of epistasis alone (*via* $\tilde{a}_{N,\varnothing} C_{iN}$). The second sum is still given by eqn 8, and is $O(s^4)$. However, the first sum is now of the same order, because although $C_{ij} \ll C_{iN}$, $a_{j,\varnothing} \gg a_{N,\varnothing}$. If epistasis is of the same order as directional selection, the first sum is negligible, and eqn 10 reduces to eqn 8. Retaining the leading terms from eqn 5c, applying the QLE approximation, and substituting for C_{ijk} from eqn 9c gives:

$$C_{ij} = \left(\frac{1}{r_{ij}} - 1\right) \sum_{k \neq i,j} \tilde{a}_{k,\varnothing} C_{ijk}$$

$$= -p_i q_i p_j q_j \left(\frac{1}{r_{ij}} - 1\right) \sum_{k \neq i,j} \tilde{a}_{k,\varnothing} \delta r_{jk|i} \frac{p_k q_k \epsilon_{jk}}{r_{jk} r_{ijk}}$$

$$+ O(s^4). \quad (11)$$

Substituting from eqn 7*b* and 11 into eqn 10 gives the net change in the modifier frequency:

$$\Delta p_i = -\sum_{j<k}^* \delta r_{jk|i} \frac{p_i q_i p_j q_j p_k q_k}{r_{jk} r_{ijk}}$$

$$\times \left\{ \tilde{a}_{j,\varnothing} a_{k,\varnothing} \left(\frac{1}{r_{ij}} + \frac{1}{r_{ik}} - 1 \right) + \epsilon_{jk} \right\} \epsilon_{jk}$$

$$- \sum_{|N|>2}^* \delta r_{N|i} (|N|! \tilde{a}_{N,\varnothing})^2 \frac{p_i q_i p_N q_N}{r_N r_{iN}} + O(s^5) \qquad (12)$$

The sums have been reorganised so as to bring together pairwise terms. Note that both sums are taken only over distinct sets; for example, only one of the permutations {*jk*}, {*kj*} is counted in the first sum.

Pairwise epistasis (represented by the first sum) will tend to increase recombination if there are negative interactions between favourable alleles ($\epsilon_{jk} < 0$), and if the product of the directional selection on pairs of loci is stronger than the epistasis between them ($\tilde{a}_{j,\varnothing} \tilde{a}_{k,\varnothing}(1/r_{ij} + 1/r_{ik} - 1) > -\epsilon_{jk}$ in eqn 12). (Recall that ϵ_{ij} is the deviation from multiplicative fitnesses.) Linkage between the modifier and the selected loci (r_{ij}, $r_{ik} < 1/2$) encourages the evolution of recombination. If recombination is to be favoured through the interaction between directional selection and epistasis, then epistasis must be weak. Unlinked modifiers (r_{ij}, $r_{ik} = 1/2$) increase most rapidly when pairwise epistasis equals $(-3/2)$ times the product of the coefficients of directional selection ($\epsilon_{jk,\varnothing} = -3\tilde{a}_{j,\varnothing}\tilde{a}_{k,\varnothing}/2$; see first sum in eqn 12), and there is no higher-order epistasis.

In applying the QLE approximation, the selection coefficients have been assumed to stay constant, at least for the timescale over which recombination dissipates linkage disequilibria. The approximation can still be applied with rapidly varying coefficients, in which case the linkage disequilibria are given by a sum of the epistasis in preceding generations, discounted by a factor $(1-r)$ for each generation (Appendix 4). If epistasis fluctuates rapidly, so that gene combinations which were favoured in one generation become unfavourable in the following generations, then recombination can increase. This mechanism is analysed in detail in Appendix 4, for three loci.

(v) *Interpretation in terms of the variance in fitness*

Equation 12 gives a general approximation for the selection on a modifier of recombination, which is valid when epistasis is weak, and selection acts on diploids. An intuitive interpretation can be found by considering fitness itself as a quantitative trait. The aim is to find a way of estimating the direction and strength of selection on recombination from observable properties of whole organisms, without the need to know the detailed genetic basis of fitness variation. To do this, we must first define measures of fitness and of the variance in fitness which are valid with epistasis and linkage disequilibrium. This is not straightforward (Weir & Cockerham, 1977; Cockerham, 1984; Ewens, 1989; Barton & Turelli, 1991).

To be definite, take fitness to be the absolute number of zygotes produced by a newly formed zygote after one generation. The mean fitness changes because allele frequencies change, because linkage disequilibria change, and because the fitness of each genotype changes as the external environment changes. (Here, the 'environment' includes changes in physical conditions, in the influence of other species, in the density of the same species, and in the frequencies of genotypes within the same species.) The effect of changing genotype frequencies can be isolated by holding the fitnesses of genotypes constant at their values in the initial environment. From Fisher's (1930) 'Fundamental Theorem of Natural Selection', the increase in mean fitness due to selection is precisely equal to the total genetic variance in relative fitness, $\mathrm{var}(W/\overline{W})$. Segregation and recombination then dissipate part of the increase, so that the net change in mean fitness caused by changing genotype frequencies equals the additive genetic variance in relative fitness.

Several different measures of fitness can be defined for each genotype, along with their corresponding variances. The expected fitness of a diploid genotype (W) is given by eqn 1; the corresponding variance includes components due to dominance ($a_{j,j}^2$), and due to the interaction between dominance and epistasis ($a_{j,jk}^2$). One can also consider the expected fitness of zygotes formed by taking one intact haploid genome from the genotype in question, and pairing it with another, taken at random from the population. By analogy with the breeding value, define ($W^* - \overline{W}$) as twice the deviation of such zygotes from the population mean. W^* is given by eqn 1, but without the third sum, which represents the contribution of dominance ($a_{U,V}$): $W^*/\overline{W} = 1 + \sum_U \tilde{a}_{U,\varnothing}(\zeta_U + \zeta_U^* - 2C_U)$. This definition is not the same as the breeding value of fitness, if that is defined as twice the deviation of the offspring's fitness (e.g. Falconer, 1985). The parental genome has gone through one round of recombination, and the breeding value therefore depends in a complex way on recombination rates. One can define a simpler quantity, $W^{**}/\overline{W} = 1 + \sum_j \tilde{a}_{j,\varnothing}(\zeta_j + \zeta_j^*) - 2\sum_U \tilde{a}_{U,\varnothing} C_U$. This can be thought of as the deviation of offspring after many generations of random mating, by which time only additive effects will remain. (More precisely, ($W^{**} - \overline{W}$) is the limit of 2^n times the deviation of offspring in the n'th generation, for large n.) Note that the mean of $W^{**}/\overline{W}$ is reduced by $2\sum_U \tilde{a}_{U,\varnothing} C_U$, which represents the loss of fitness due to the breakup of advantageous linkage disequilibria. On Ewens' (1989, p. 170) interpretation, W^{**} is close to Fisher's (1930) concept of 'fitness' as the sum of average effects. However, the average effect is defined by a least-squares procedure,

which differs from the $a_{i,\varnothing}$ in eqn 1 if there are linkage disequilibria (see Nagylaki, 1993, p. 639).

Assuming weak epistasis $(\tilde{a}_{j,k,\varnothing} \approx s^2, \tilde{a}_{j,\varnothing} \approx s)$, the variance in W^* is:

$$\mathrm{var}\left(\frac{W^*}{\bar{W}}\right) = 2\sum_j \tilde{a}_{j,\varnothing}^2 p_j q_j + 2\sum_{j+k} \tilde{a}_{j,\varnothing}\,\tilde{a}_{k,\varnothing}\,C_{jk}$$

$$+2\sum_{j<k}^* (2\tilde{a}_{jk,\varnothing})^2 p_j q_j p_k q_k + \sum_{|N|>2} V_{|N|} + O(s^5)$$

$$= V_1 + v_1 + V_2 + \sum_{|N|>2} V_{|N|} + O(s^5), \qquad (13a)$$

where $V_{|N|} = 2\sum_{j<k}^* (|N|!\tilde{a}_{jk,\varnothing})^2 p_N q_N$. The first two terms, $V_1 + v_1$ give the variance due to the additive effects of the individual genes, $\mathrm{var}(W^{**}/\bar{W})$; V_1 is the contribution from heterozygosities at individual loci, and v_1 is due to pairwise linkage disequilibria. The remaining terms give the non-additive variance in fitness due to two-, three- and higher-order epistasis $(V_2, V_3, ...)$. There are also terms involving the product of linkage disequilibrium and epistasis $(v_2, v_3$ etc.), which are negligible for weak epistasis. The discrepancy between $V_1 + v_1$ and the additive genetic variance (defined conventionally as the variance in breeding values) is also negligible for weak epistasis $(\approx v_2 \approx O(s^5))$; $V_1 + v_1$ is referred to below as the 'additive variance', despite the difference in definition.

This analysis of the variance of fitness into its components (eqn 13a) involves coefficients such as $\tilde{a}_{jk,\varnothing}$, which express deviations from additive inheritance. Linkage disequilibria, and the consequent selection on recombination, more naturally involve deviations from multiplicative inheritance, ϵ_{jk}. It is then appropriate to analyse the variance in log (fitness), since non-additive variance in this quantity expresses multiplicative epistasis. This analysis is non-linear, and hence leads only to approximate relations with the selection coefficients $\tilde{a}_{U,\varnothing}$, and with the 'Fundamental Theorem'. However, it gives a more natural expression for the selection on modifiers. By taking the logarithm of eqn 1, expanding in a Taylor's Series, and dropping terms $O(s^5)$:

$$\mathrm{var}(\log(W)) = 2\sum_j \tilde{a}_{j,\varnothing}'^2 p_j q_j + 2\sum_{j+k} \tilde{a}_{j,\varnothing}\,\tilde{a}_{k,\varnothing}\,C_{jk}$$

$$+2\sum_{j<k}^* \epsilon_{jk}^2 p_j q_j p_k q_k + \sum_{|N|>2} V_{|N|} + O(s^5)$$

$$= V_1' + v_1 + V_2' + \sum_{|N|>2} V_{|N|} + O(s^5), \qquad (13b)$$

where $\tilde{a}_{j,\varnothing}' = (\tilde{a}_{j,\varnothing} - \tilde{a}_{j,\varnothing}^2/2)$. Note that because the additive coefficients $(\tilde{a}_{j,\varnothing}', \tilde{a}_{j,\varnothing})$ differ in the expansions of W and $\log(W)$, the variance components (V_1, V_2) also differ. However, the perturbation to the additive variance (v_1) due to linkage disequilibria, and the higher-order components $(V_{|N|} = V_{|N|}'$ for $|N| > 2)$ are not affected to leading order.

Equation 12 can now be used to express the selection on a modifier in terms of the variance in log (fitness):

$$s_i = \frac{\Delta p_i}{p_i q_i} \approx -\frac{v_1}{4}E\left[\frac{\delta r_{jk|i}}{r_{ijk}}\left(\frac{1}{r_{ij}}+\frac{1}{r_{ik}}-1\right)\right]$$

$$-\frac{1}{2}\sum_{|N|>1} V_{|N|}' E\left[\frac{\delta r_{N|i}}{r_N r_{iN}}\right]. \qquad (14)$$

We see that if linkage disequilibria reduce the additive variance $(v_1 < 0)$, thereby reducing the rate of increase of mean fitness, then these disequilibria favour increased recombination. This is counterbalanced by the non-additive components of fitness variation, $V_{|N|}$, which always select for reduced recombination. Equation 14 can be compared with Altenberg & Feldman's (1987) Result 4, which showed that the initial increase of a modifier invading an equilibrium population is approximately the variance in marginal fitnesses. However, Altenberg & Feldman (1987) assumed tight linkage, whereas eqn 14 assumes loose linkage.

Selection on recombination can also be related to another quantity: the difference in log fitness between the current population $(\overline{\log(W)})$, and one with the same allele frequencies and genotypic fitnesses, but no linkage disequilibria $(\overline{\log(W^*)})$:

$$\delta\log(W) = (\overline{\log(W/W^*)}) = 2\sum_{j,k}^* \epsilon_{jk,\varnothing}\,C_{jk}$$

$$+2\sum_{|U|>2}^* (|U|!\tilde{a}_{U,\varnothing})\,C_U + O(s^5) \qquad (15a)$$

$\delta\log(W)$ tends to be positive, because selection builds up linkage disequilibria that increase mean fitness. However, it can be negative if epistasis fluctuates rapidly, since then $\epsilon_{jk,\varnothing}$ and C_{jk} can have different signs (see section on 'Fluctuating selection'). If epistasis changes slowly, the C_U can be substituted from eqns 6, 9b giving:

$$\delta\log(W) = 2\sum_{j<k}^* \frac{\epsilon_{jk}^2 p_j q_j p_k q_k}{r_{jk}} + 2\sum_{|U|>2}^* \frac{(|U|!\tilde{a}_{U,\varnothing})^2 p_U q_U}{r_U}$$

$$= V_2' E\left[\frac{1}{r_{jk}}\right] + \sum_{|U|>2}^* V_{|U|} E\left[\frac{1}{r_U}\right] + O(s^5) \qquad (15b)$$

(assuming that epistasis is uncorrelated with recombination).

In principle, $\delta\log(W)$ could be measured by relaxing selection, under constant conditions, and observing the change in log (fitness). It is more feasible to compare the effect on fitness of intact genomes, with genomes that have gone through one round of recombination. The difference in log (W) is then given by the non-additive component of $\mathrm{var}(\log(W))$, $V_2' + \sum_{|N|>2} V_{|N|}$. (cf. Charlesworth & Charlesworth (1975) and Mukai (1977); see Discussion).

Equations 13a and 15b can now be used to express

the selection on the modifier in terms of the contribution of linkage disequilibria to the additive genetic variance in fitness (v_1), and to the mean log fitness ($\delta \log(W)$). Denote the contributions of the various orders ($|N|$) of epistasis to the mean fitness by $\delta \log(W)_{|N|}$. Then, from eqn 12:

$$s_i = \frac{\Delta p_i}{p_i q_i} \approx -\frac{v_1}{4} E\left[\frac{\delta r_{jk|i}}{r_{ijk}}\left(\frac{1}{r_{ij}} + \frac{1}{r_{ik}} - 1\right)\right]$$
$$-\frac{1}{2}\sum_{|N|>2} \delta \log(W)_{|N|} E\left[\frac{\delta r_{|N||i}}{r_{iN}}\right]. \quad (16a)$$

For unlinked modifiers, $r_{ij} = r_{ik} = 1/2$, and $r_{iN} = (1 + r_N)/2$. Bringing together the terms due to pairwise epistasis:

$$s_i = \frac{\Delta p_i}{p_i q_i} \approx -\left(\frac{3v_1}{2} + \delta \log(W)_2\right) E\left[\frac{\delta r_{jk|i}}{(1 + r_{jk})}\right]$$
$$-\sum_{|N|>2} \delta \log(W)_{|N|} E\left[\frac{\delta r_{|N||i}}{(1 + r_N)}\right]. \quad (16b)$$

Here, $\delta r_{|N||i}$ is the average increase in recombination between sets of $|N|$ loci caused by the modifier, the average being weighted appropriately. If linkage disequilibria tend to decrease the additive genetic variance ($v_1 < 0$), then this causes selection in favour of recombination $s_i = -(3/2)v_1 E[\delta r_{jk|i}/(1 + r_{jk})]$ for unlinked modifiers; selection will be stronger if the modifier is linked. This effect arises because recombination increases the additive genetic variance in fitness, and hence accelerates the increase in mean fitness. It is offset by the immediate loss of fitness due to the breakup of linkage disequilibria ($\delta \log(W)$). Equation 16b shows that for unlinked modifiers, with negligible higher-order epistasis, recombination is favoured if linkage disequilibria reduce the additive genetic variance by more than the immediate loss of mean fitness ($v_1 < \delta \log(W)$), regardless of the genetic map.

The following argument suggests that higher-order epistasis indeed has a negligible effect on recombination. The expectation of $1/r_N$ depends on the genetic map, and should decrease towards 1 as the set gets larger. With no linkage, it is 2, 4/3, 8/7.. for 2, 3, 4.. loci. If the set N contains many widely scattered loci, then we may expect $r_{N,\emptyset} = (1 - r_N)$ to be very small, and hence hard to modify substantially; hence, $\delta r_{N,\emptyset|i}$ should be small for large sets N. Moreover, the variance in fitness associated with higher-order epistasis may also decline as the size of the set $|N|$ increases. Both factors give reason to expect the main force on recombination rates to be due to pairwise epistasis. However, it is not obvious that higher order epistasis can be neglected, since the number of such interactions is very large with many loci. It is hard to go further without a biological model of epistasis – for example, randomly assigning fitnesses to genotypes.

3. Applications

(i) *Directional selection*

What is the net effect on recombination rates of substitutions at two interacting loci? Suppose that genotypic fitnesses are constant (Table 1) and the two loci are equivalent. An explicit solution for the net effect of substitutions at both loci is then possible (see Appendix 1 for details, and Barton & Turelli, 1991, pp. 241–244, for a simple two-locus example of the multilocus method). Suppose that $\tilde{a}_{j,\emptyset} = s + \eta\Delta_k$, $\tilde{a}_{k,\emptyset} = s + \eta\Delta_j$, $\tilde{a}_{j,k} = 2\tilde{a}_{jk,\emptyset} = \eta$, and that $\epsilon_{jk} = (\eta - s^2) < 0$ ($\eta \ll s \ll 1$; $\bar{W} \approx 1$; $\Delta_j = p_j - q_j$). Then, the frequencies of the selected alleles grow logistically ($(p_j/q_j) = (p_k/q_k) = \exp(st)$). The net change in frequency of the modifier can be found by integrating eqn A1.5f over the whole timecourse of the substitutions:

$$\Delta p_i = -\frac{\delta r_{j,k|i}(\eta - s^2)p_i q_i}{6 r_{jk} r_{ijk}}\left[s\left(\frac{1}{r_{ij}} + \frac{1}{r_{ik}} - 1\right) + \frac{(\eta - s^2)}{s}\right]$$
$$(r_{ij}, r_{ik} \gg s). \quad (17)$$

Because epistasis is assumed weak ($\eta \approx s^2$), the two terms in eqn 17 are of the same order (i.e. $s \approx (\eta - s^2)/s$). In contrast, if the modifier is tightly linked to the selected loci ($r_{ij}, r_{ik} \approx s$), directional selection dominates, and recombination is strongly favoured. This is because the modifier becomes tightly associated with the favourable alleles, and hitch-hikes towards fixation with them.

Figure 1 compares the approximation for loose linkage (eqns A1.5, 12) with the exact solution (eqns A1.2), for three unlinked loci. Genotypic fitnesses are fixed, as in Table 1. Two alleles, each with advantage $s = 0{\cdot}1$, substitute in parallel. There is negative epistasis between them ($\eta = -0{\cdot}02$, $\epsilon = -0{\cdot}03$), which generates negative linkage disequilibrium (Fig. 1a). This disequilibrium in turn generates a positive three-way association (C_{ijk}; Fig. 1c), which then leads to positive pairwise associations (C_{ij}, C_{ik}; Fig. 1b). The loose linkage approximation to the linkage disequilibria is in good agreement with the exact results

Table 1. *Fitnesses of the nine genotypes, which are fixed. The corresponding selection coefficients are* $a_{j,\emptyset} = a_{\emptyset,j} = (s_j + \eta\Delta_k)/\bar{W}$, $a_{k,\emptyset} = a_{\emptyset,k} = (s_k + \eta\Delta_j)/\bar{W}$, $a_{j,k} = a_{k,j} = \eta/\bar{W}$, $a_{jk,\emptyset} = a_{kj,\emptyset} = a_{\emptyset,jk} = a_{\emptyset,kj} = \eta/2\bar{W}$

$X_k X_k^*$	X_j X_j^*	0 0	0 or 1 1 0	1 1
0 0		$1 - s_j - s_k + \eta$	$1 - s_k$	$1 + s_j - s_k - \eta$
0 1 or 1 0		$1 - s_j$	1	$1 + s_j$
1 1		$1 - s_j + s_k - \eta$	$1 + s_k$	$1 + s_j + s_k + \eta$

$W = 1 + s_j(X_j + X_j^* - 1) + s_k(X_k + X_k^* - 1) + \eta(X_j + X_j^* - 1)$
$\quad \times (X_k + X_k^* - 1)$
$\bar{W} = 1 + s_j\Delta_j + s_k\Delta_k + \eta(\Delta_j\Delta_k + 2C_{jk})$
$\epsilon_{jk} = (2\tilde{a}_{jk,\emptyset} - \tilde{a}_{j,\emptyset}\tilde{a}_{k,\emptyset}) = [(\eta - s_j s_k) + 2\eta^2 C_{jk}]/\bar{W}^2 \approx (\eta - s_j s_k)$
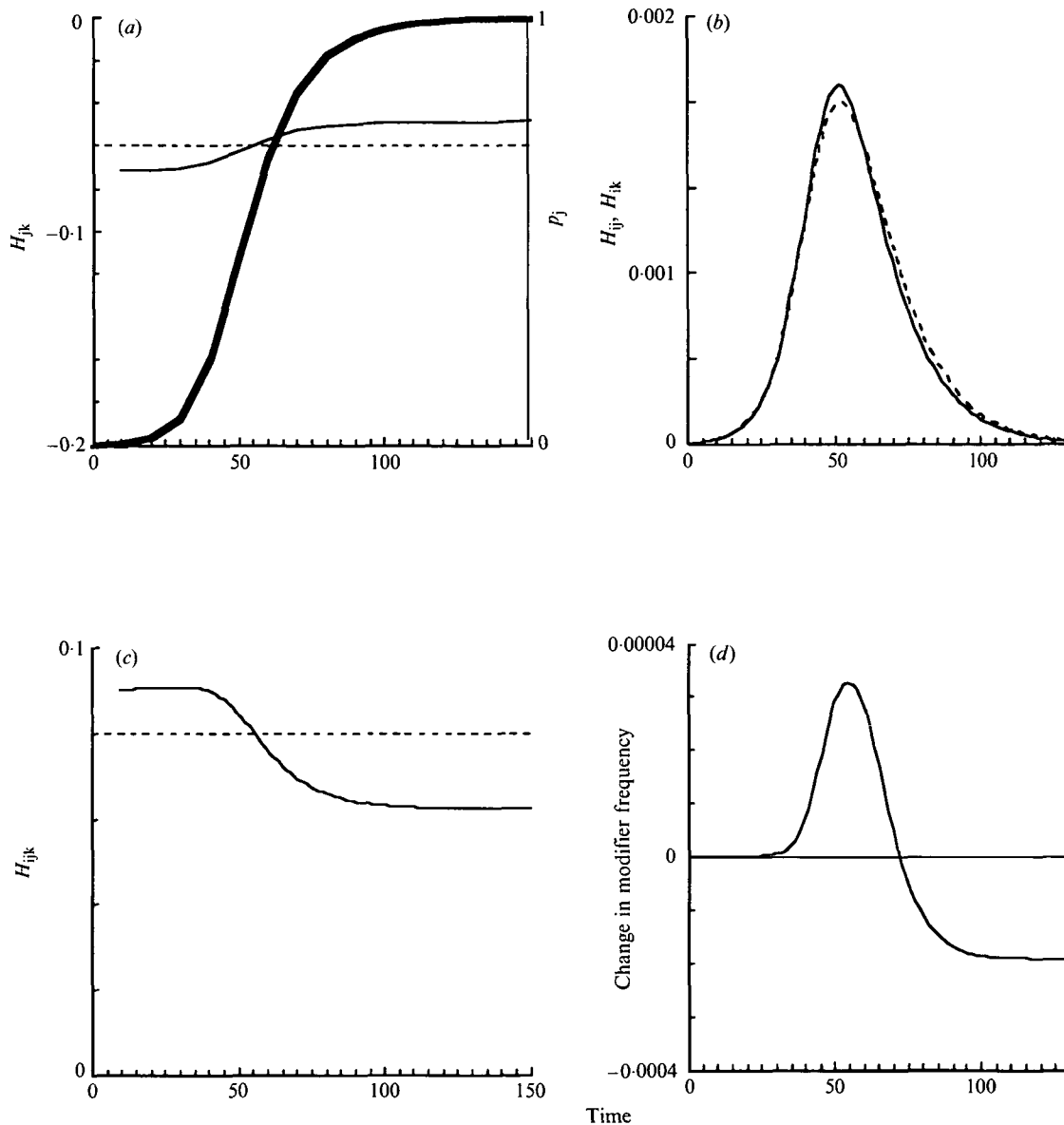
Fig. 1. Favourable alleles substitute at two loci (j, k), thereby changing the frequency of a modifier allele at a third locus (i). Genotypic fitnesses are constant, as specified by Table 1. The favourable alleles have selective advantage $s_j = s_k = 0.1$, and interact with negative epistasis $\eta = -0.02$. The favourable alleles both start at the same frequency, and increase in parallel. All three loci are unlinked. (a) shows the frequency of the favourable alleles ($p_j = p_k$; heavy sigmoid curve), together with the scaled linkage disequilibrium between them ($H_{jk} = C_{jk}/p_j q_j p_k q_k$; light sigmoid curve). This is close to the approximation of eqn A1.5a, $(\eta - s^2)/r_{jk} = -0.06$ (dotted line). (b) shows the pairwise associations $H_{ij} = H_{ik}$ (solid curve), together with the approximations of eqn A1.5b, c (dotted line). (c) shows the three-way association H_{ijk} (solid curve), together with the approximation of eqn A1.5d (dotted line). Finally, (d) shows the change in frequency, Δp_i, of a modifier which increases recombination by $\delta r_{j,k|i}$. Values of H_{ij}, H_{ik}, H_{ijk} and Δp_i are scaled relative to $\delta r_{j,k|i} p_i q_i$. The evolution of the system was calculated by exact iteration of eqns A1.2, using the selection coefficients in Table 1. The loose linkage approximation of eqns 19 was applied with the additional approximation that because selection is weak, so $W \approx 1, a_{jk,o} \approx \eta, a_{j,o} = a_{k,o} \approx s$.

(compare solid with dotted lines in Figs. 1 a–c). The effect of three-way associations is to decrease recombination, whilst that of the pairwise associations is to increase recombination. For these parameters, the two effects cancel, giving almost no net change in the modifier, as predicted by the loose linkage approximation (Fig. 1d).

Figure 2 shows the same comparison, but with linkage. Recombination is now strongly favoured: over the whole substitution, the modifier increases by

$0.254\delta r_{j,k|i} p_i q_i$. The loose linkage approximation now performs less well, though the predictions for the linkage disequilibria (dotted lines in Figs. 2a–c) and for the net change ($0.242\delta r_{j,k|i} p_i q_i$) are still reasonably accurate. Figure 3 shows the net change in modifier frequency as a function of epistasis. As expected from the above analysis, there is an intermediate range of epistasis which favours recombination. (Bergman *et al.* come to the same conclusion by considering the signs of the linkage disequilibria that develop as a
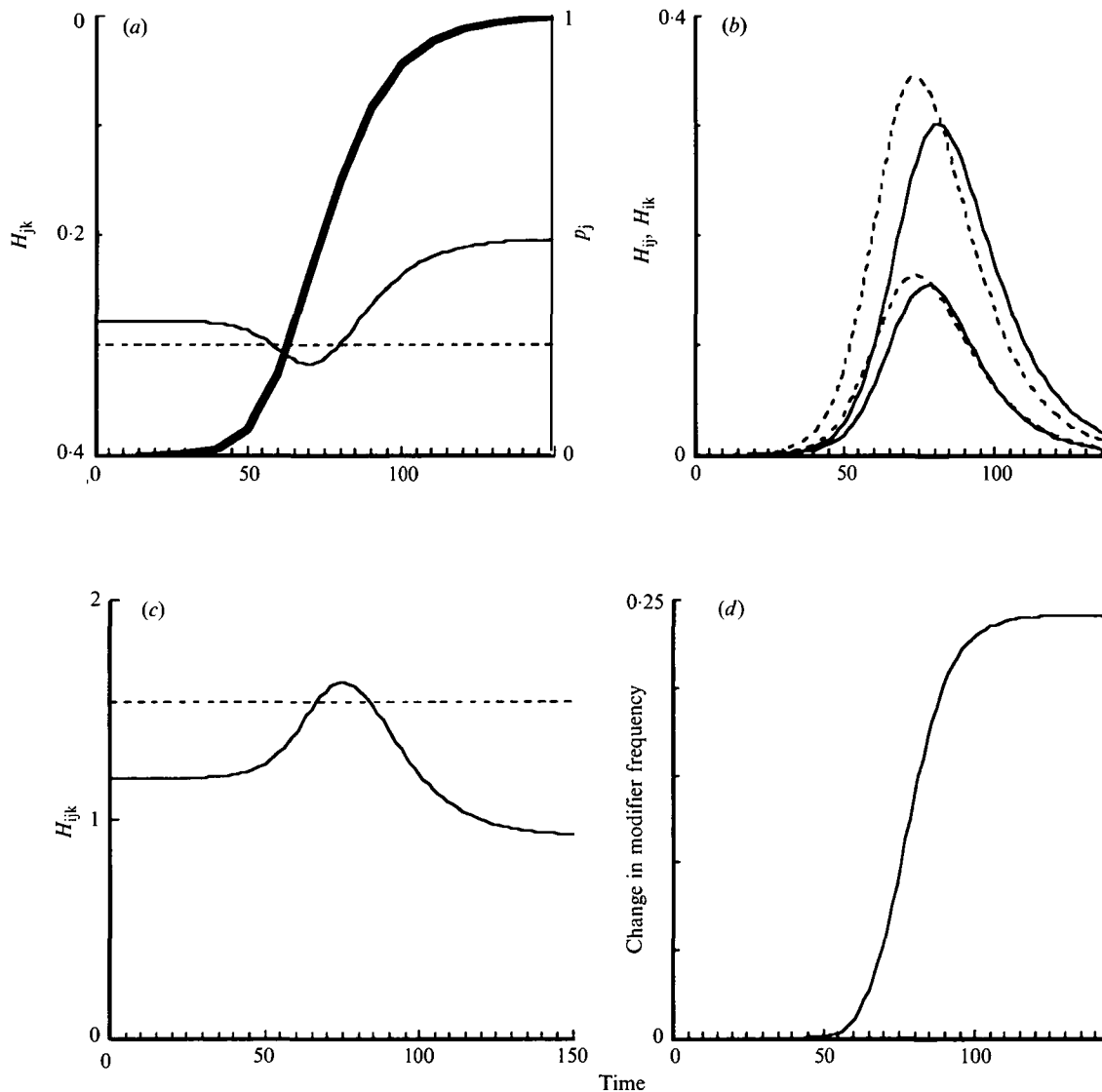
Fig. 2. As in Fig. 1, but with the three loci linked in the order $i-j-k$. $r_{ij} = r_{jk} = 0.1$. There is no interference, and so $r_{ik} = 0.18$, $r_{ijk} = 0.19$.

population evolves away from initial linkage equilibrium.)

With no linkage (Fig. 3a), the approximation of eqns A1.5 (solid curve), 17 works well over the whole range of epistasis, and is accurate even when $\epsilon \approx s$. With tight linkage, this approximation is still accurate for weak epistasis, but fails for stronger epistasis (Fig. 3b). The approximation based on the variance in log (fitness) (eqn 14) performs similarly: it is accurate with no linkage (dotted curve in Fig. 3a), but breaks down with tight linkage and strong epistasis (Fig. 3b).

Some insight into the opposing forces on recombination can be gained by considering the mean fitness of the population. Suppose that substitutions are in progress at two loci, and that there is negative epistasis between the favourable alleles. If linkage disequilibrium is suddenly set to zero, the negative associations built up by epistasis will be destroyed, and mean fitness will decrease (the 'recombination load'). This is shown by the lower curve in Fig. 4b.

However, the abolition of linkage disequilibrium will, in the long run, speed up the response to selection (Fig. 4a). The mean fitness of a population which evolves with no linkage disequilibrium is thus greater throughout (upper curve in Fig. 4b), because the faster increase of favourable alleles outweighs the immediate loss of fitness due to the breakup of favourable gene combinations. In this example, the net increase in mean fitness due to the faster response to selection is much greater than the total immediate load due to linkage disequilibrium (0.656 vs. −0.283, comparing the areas under the upper and lower curves). Nevertheless, unlinked modifiers that increase recombination are eliminated ($\Delta p_i = -0.00827 \delta r_{j,k|i} p_i q_i$ with r_{ij}, $r_{ik} = 0.5$). Recombination can increase if modifiers are linked to the selected loci: for example, with the parameters of Fig. 3b ($r_{ij} = 0.1$, $r_{ik} = 0.18$), the modifier will increase by $\Delta p_i = 0.299 \delta r_{j,k|i} p_i q_i$. The evolution of modifiers that decrease overall mean fitness, and the dependence on linkage between
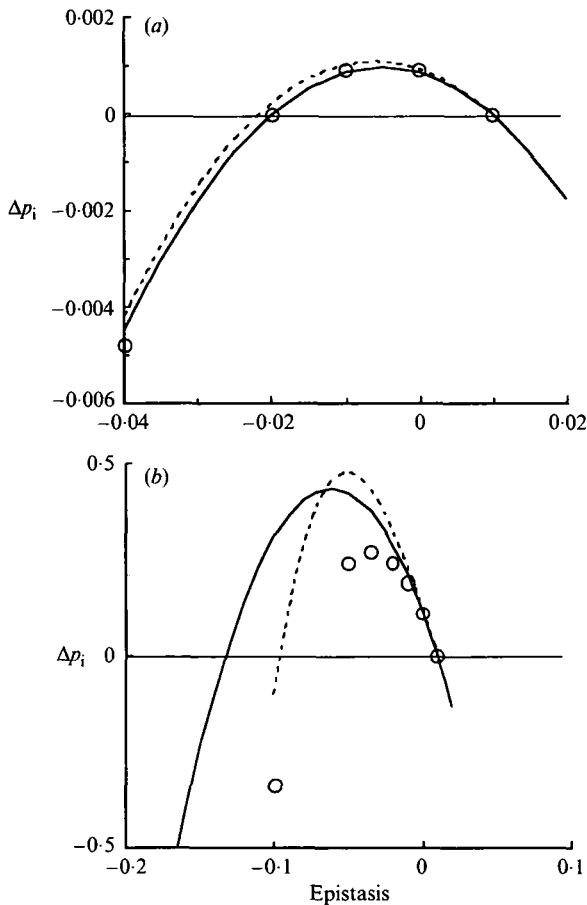
Fig. 3. The net change in modifier frequency over the course of the substitution (scaled relative to $\delta r_{\mathrm{j,k|i}} p_i q_i$), as a function of the strength of epistasis, η. (Note that $\eta = 0$ corresponds to additive fitnesses, and $\eta = s^2$ corresponds to multiplicative fitnesses). The model is as in Figs. 1, 2, but with η varying. The solid curve shows the loose linkage approximation (eqn 17), while the open circles show results from exact iteration of eqns A1.1. The dotted curve shows the approximation based on the variance in log (fitness) (eqn 14). (a) No linkage, as in Fig. 1. (b) Linkage as in Fig. 2; $r_{\mathrm{ij}} = r_{\mathrm{jk}} = 0.1$, $r_{\mathrm{ik}} = 0.18$.
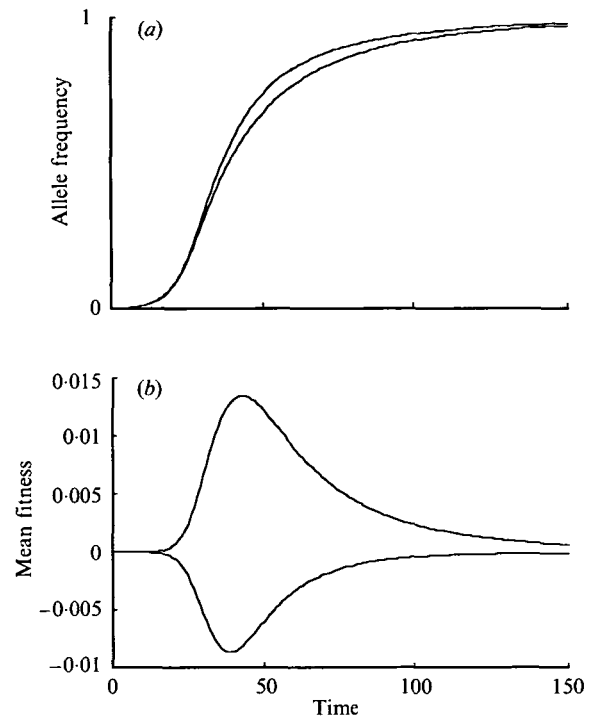

Fig. 4. (a) The frequency of favourable alleles in populations with and without linkage disequilibrium (lower and upper curves, respectively), parameters are as in Fig. 2, but with stronger epistasis ($s = 0.1$, $\eta = -0.08$, $r_{\mathrm{jk}} = 0.1$). (b) The lower curve shows the loss in mean fitness caused if linkage disequilibrium is suddenly set to zero. The upper curve shows the gain in mean fitness if a population evolves with no linkage disequilibrium (i.e. the difference in mean fitness between the two populations whose allele frequencies are shown in (a)).

modifier and selected loci illustrates the failure of group-level arguments based on mean fitness (see Brooks, 1988, pp. 96–98).

Table 2 shows how selection on the modifier is related to the components of log(fitness). The parameters are as in Figs. 1, 2 ($\eta = -0.02$, $s = 0.1$). Whether or not the selected loci are linked (Table 2a vs. 2b), the variance in log fitness is mostly additive. Epistasis produces only slight non-additive variance ($V_2' \ll V_1$), linkage disequilibria only slightly perturb the additive variance ($v_1 \ll V_1$), and the interaction between epistasis and linkage disequilibrium is negligible ($v_2 \ll v_1, V_2'$). The rate of increase in $\log(W^*)$ is close to the additive variance $V_1' + v_1$, as expected. The difference in fitness $\delta \log(W)$ between intact and fully recombined genomes is close to V_2/r_{jk}, again as expected. With unlinked loci, the effects of v_1 and V_2 almost exactly cancel, giving almost no selection on the modifier at any time (Fig. 1d, Table 2a). The

approximation based on variance in log(fitness) (eqn 14) is accurate over the whole range of epistasis (dotted curve in Fig. 3a). With linked loci, linkage disequilibria are so strong that eqn 14 breaks down (Table 2b); however, it is still accurate for weaker epistasis (Fig. 3b).

(ii) *Mutation/selection balance*

If mutation balances directional selection, and if there is negative epistasis between favourable alleles, then recombination can increase even when the population is at equilibrium with constant fitnesses. This was first proved for two loci by Feldman (Feldman *et al.* 1980), was given an intuitive explanation by Kondrashov (1984, 1988), and was analysed in detail for the polygenic case by Charlesworth (1990). A similar process occurs when meiotic drive balances selection (Thomson & Feldman, 1974; Feldman & Otto, 1989). Negative (or 'synergistic') epistasis generates linkage disequilibria which reduce the variance in number of deleterious mutations. Recombination restores the variance; the immediate effect is to reduce mean fitness, but in the long term, increased genetic variance allows selection to eliminate deleterious alleles more

Table 2. *The change in log (fitness) during the course of a substitution. Parameters are as in Figs. 1, 2; s = 0·1, $\eta = -0·02$. $\overline{\log(W)}$ gives the mean $\log(W^*)$ through time; values are given every 10 generations. $\Delta \log(W)$ gives the rate of change in mean $\log(W)$, which is close to its additive genetic variance, $V'_1 + v_1$. V'_2 is the non-additive variance in $\log(W^*)$. $\delta \log(W)$ is the contribution of linkage disequilibria to mean $\log(W)$, and is close to V'_2/r_{jk}, where r_{jk} is the recombination between selected loci. The last two columns give the (scaled) selection on the modifier, as predicted by eqn 14, and as given exactly by eqns A1.2. The last row gives totals over the whole substitution. Results for unlinked loci. The prediction from eqn 14 is $\Delta p_i/(p_i q_i \delta r_{jk|r})$ $= -v_1 - 4V'_2/3$; these opposing forces almost exactly cancel. Results for linked loci, in which case recombination is favoured. Because linkage disequilibria are strong, eqn 14 substantially overestimates selection on the modifier*

t	p	$\overline{\log(W)}$	$\Delta \log(W)$	V'_1	v_1	V'_2	$\delta \log(W)$	$\dfrac{\Delta p_i}{p_i q_i \delta r_{jk\|i}}$ (eqn 14)	$\dfrac{\Delta p_i}{p_i q_i \delta r_{jk\|i}}$ (exact)
a No linkage									
20	0·0170	−0·23878	0·001431	0·001340	−0·000002	0·000001	0·0000015	0	0
30	0·0652	−0·21193	0·004810	0·004581	−0·000020	0·000010	0·0000192	0·000007	0
40	0·2045	−0·13881	0·010236	0·010162	−0·000115	0·000064	0·0001249	0·000030	0·000002
50	0·4440	0·02828	0·010687	0·011098	−0·000177	0·000120	0·0002394	0·000017	0·000002
60	0·6740	0·06160	0·006740	0·007109	−0·000091	0·000079	0·0001562	−0·000014	−0·000002
70	0·8259	0·11321	0·003529	0·003710	−0·000029	0·000030	0·0000585	−0·000011	−0·000002
80	0·9108	0·13958	0·001762	0·001841	−0·000008	0·000009	0·0000173	−0·000004	−0·000001
90	0·9551	0·15269	0·000872	0·000907	−0·000002	0·000002	0·0000046	−0·000001	0
100	0·9776	0·15917	0·000431	0·000448	0	0·000001	0·0000012	0	0
110	0·9889	0·16237	0·000213	0·000221	0	0	0·0000003	0	0
Total					−0·004428	0·003149	0·0062340	0·000231	−0·000019
b Linked loci: $r_{ij} = r_{jk} = 0·1$, $r_{ik} = 0·19$									
40	0·0149	−0·23998	0·001257	0·001178	−0·000005	0·000001	0·000005	0·000073	0·000019
50	0·0572	−0·21624	0·004287	0·004100	−0·000064	0·000008	0·000062	0·000963	0·000272
60	0·1817	−0·14998	0·009459	0·009575	−0·000439	0·000054	0·000469	0·006636	0·002279
70	0·4022	−0·04532	0·010458	0·011458	−0·000899	0·000118	0·001171	0·013417	0·007163
80	0·6278	0·04554	0·007160	0·008084	−0·000582	0·000092	0·000951	0·008271	0·007940
90	0·7912	0·10226	0·004062	0·004491	−0·000200	0·000040	0·000393	0·002627	0·004294
100	0·8898	0·13330	0·002134	0·002296	−0·000054	0·000013	0·000119	0·000650	0·001565
110	0·9436	0·14936	0·001084	0·001156	−0·000014	0·000004	0·000032	0·000152	0·000469
120	0·9716	0·15747	0·000543	0·000568	−0·000003	0·000001	0·000008	0·000036	0·000128
130	0·9858	0·16152	0·000271	0·000282	−0·000001	0	0·000002	0·000009	0·000033
Total					−0·02271	0·00331	0·03212	0·32834	−0·24202

effectively. This process involves essentially the same interaction between epistasis and directional selection as described above. Equation 12 can therefore be used to relate the selective advantage of a modifier to the net mutation rate and the strength of epistasis. This extends Charlesworth's (1990) analysis to arbitrary patterns of selection. The relation with that analysis is set out in Appendix 3, where it is shown that the methods agree for weak selection (see Table 3).

Suppose that mutation occurs at meiosis; with biallelic loci, define the rate of mutation as μ_i from $X_i = 1$ to 0, and v_i from 0 to 1. Then, allele frequencies change by $\Delta p_i = (v_i q_i - \mu_i p_i)$, and the central moments C_N are multiplied by a factor $\prod_{i \in N}(1 - \mu_i - v_i)$, where N is a set of distinct loci. (This is because if a mutation occurs at any of the $|N|$ loci, the association is reduced to zero.) Since mutation rates are typically much smaller than recombination, this reduction in linkage disequilibria will be neglected. Then, the equations for linkage disequilibria (e.g. eqns 5, 9, 11) are unaffected, and eqn 12 still applies.

Suppose now that there is no back mutation ($v_i = 0$); deleterious mutations occur a rate μ_i from $X_i = 1$ to 0. If we neglect for the moment the perturbation to allele frequencies caused by linkage disequilibria, we have $\tilde{a}_{j,o} q_j \approx \mu_j$. Assuming that mutant alleles are rare ($p_j \approx 1$), the selective advantage of the modifier is:

$$s_i = \frac{\Delta p_i}{p_i q_i} = -\frac{\overline{\delta r_{2|i} \epsilon} U^2}{8} E\left[\frac{1}{r_{ijk} r_{jk}}\left(\frac{1}{r_{ik}} + \frac{1}{r_{ij}} - 1\right)\right]$$

$$-\frac{1}{2}\sum_{|N|} \delta r_{|N|:i} V_{|N|} E\left[\frac{1}{r_{iN} r_N}\right]. \qquad (18a)$$

The first term is due to the interaction between directional selection and epistasis. $U = 2\sum_{j|} \mu_j$ is the total mutation rate per diploid genome, and $\overline{\delta r_{2|i} \epsilon}$ is the average of $\delta r_{jk|i} \epsilon_{jk}$, weighted by the mutation rates $\mu_j \mu_k$; the modifier tends to increase if this average is negative. The second term is due to epistasis alone, and always tends to reduce recombination. (The second term is as in eqn 13, but with $V_2 = 2\sum^*_{j<k} \epsilon^2_{jk} p_j q_j p_k q_k$

Table 3. *Comparison with Charlesworth's (1990) analysis of mutation/selection balance. The fitness of an individual carrying n deleterious mutations is $exp(-\alpha n - \beta n^2/2)$, where $\alpha = 0{\cdot}002$, $\beta = 0.0008$. There is free recombination. (a), The first set of three columns give exact values for the mean fitness ($\overline{W}$), the average number of deleterious mutations ($\bar{n}$), and the variance in that number (V) (Charlesworth, 1990, table 3). The next three columns give the approximations derived above (eqns A3.1, A3.3, A3.5). ($V-\bar{n}$) is the reduction in variance due to linkage disequilibria. (b), Charlesworth's (1990, table 4) estimates of the selection gradient on the modifier ($d = \Delta p_i/(\delta r p_i q_i)$), and the difference in mean ($\delta\bar{n}/\delta r$) and variance ($\delta V/\delta r$) of n between individuals heterozygous for the modifier, and the rest of the population. The last three columns give the approximations derived here: $d = \beta(U^2 - \beta V^2/3).(eqn A3.10b)$; $\delta\bar{n} = -U\delta V/V$ (eqn A3.8); $\delta V = \delta\bar{n} + 2\beta V^2 \delta r/3$ (eqn A3.9). See Appendix 3 for details*

	Exact			This paper		
U	$\overline{W}$	$\bar{n}$	$V-\bar{n}$	$\overline{W}$	$\bar{n}$	$V-\bar{n}$
a						
2·0	0·329	50·8	−1·6	0·343	49·79	−1·98
1·5	0·434	43·6	−1·2	0·445	42·84	−1·47
1·0	0·571	35·0	−0·8	0·578	34·63	−0·96
0·5	0·752	24·1	−0·4	0·753	24·03	−0·46
0·1	0·940	9·84	−0·07	0·938	10·05	−0·08

	Charlesworth (1990)			This paper		
U	d	$\delta\bar{n}/\delta r$	$\delta V/\delta r$	d	$\delta\bar{n}/\delta r$	$\delta V/\delta r$
b						
2·0	0·00234	−0·0443	1·170	0·00271	−0·0490	1·170
1·5	0·00126	−0·0293	0·881	0·00143	−0·0319	0·881
1·0	0·00050	−0·0163	0·589	0·00056	−0·0174	0·587
0·5	0·00007	−0·0059	0·289	0·00008	−0·0062	0·290
0·1	−0·00001	−0·0005	0·052	−0·00001	−0·0005	0·052

representing the variance due to pairwise deviations from *multiplicative* fitness.)

Expectations over the genetic map, such as $E[1/r_{jk}r_{ijk}]$, diverge, because the contribution of very tightly linked loci becomes infinite. In fact, the approximations used to derive eqns 12, 15a break down when recombination is comparable with selection ($r \approx s$). Approximations can be derived for this case and, for rare deleterious alleles, lead to denominators of the form ($r_{jk} + \tilde{a}_{j,\sigma} + \tilde{a}_{k,\sigma}$) rather than r_{jk} (see Appendix 2, and Charlesworth, 1990). However, the averages only depend logarithmically on the strength of selection, and are only reduced substantially below the values for free recombination if there are few chromosomes, and the genetic map is short (e.g. fig. 2 of Charlesworth, 1990). With unlinked loci, $r_{ij} = r_{jk} = 1/2$, $r_{ijk} = 3/4$, and $r_N = 1 - 2^{-|N|}$. Then:

$$s_i = \frac{\Delta p_i}{p_i q_i} = -\overline{\delta r_{2|i}} \epsilon U^2$$

$$-\frac{1}{2}\sum_{|N|}\frac{\delta r_{|N|,i} V_{|N|}}{(1-2^{-|N|-1})(1-2^{-|N|})}. \quad (18b)$$

(iii) Fluctuating selection

The above analyses considered constant fitnesses, and identified two opposing forces on recombination. There is a term proportional to $\tilde{a}_{j,k,\sigma}^2$ which tends to reduce recombination, and which corresponds to the immediate loss in mean fitness caused by the breakup of favourable gene combinations. There is also a term proportional to $\tilde{a}_{j,\sigma}\tilde{a}_{k,\sigma}\tilde{a}_{jk,\sigma}$ which tends to increase recombination, and which corresponds to the long-term gain in fitness caused by a faster response to directional selection. At equilibrium, only the first term acts, and recombination necessarily decreases. This section extends the analysis to fluctuating selection, and shows that if epistasis changes sign over the right timescale, recombination can increase. This was the effect identified by Sturtevant & Mather (1994), and analysed by Maynard Smith (1978, p. 98). However, it only favours recombination over a narrow range of parameters.

Assume that selection fluctuates, with coefficients $\tilde{a}_{j,\sigma}[t]$, $\tilde{a}_{jk,\sigma}[t]$ etc. in generation t. If selection is weak, so that allele frequencies change slowly, the expected

change in modifier frequency per generation is given by:

$$E[\Delta p_i] = -\delta r_{j,k|i} p_i q_i p_j q_j p_k q_k$$

$$\times \left(\sum_{\tau=0}^{\infty} E[\epsilon[t] \epsilon[t-\tau-2]] f(\tau) \right.$$

$$- \sum_{\tau'=0}^{\infty} E[(g_{jk}(0) \epsilon[t-\tau'-2])] f(\tau')$$

$$+ \sum_{\tau=0,\tau'=0}^{\infty\infty} E[(g_{jk}(\tau)(1-r_{ij})^{\tau+1}$$

$$\left. + g_{kj}(\tau)(1-r_{ik})^{\tau+1}) \epsilon[t-\tau-\tau'-3]] f(\tau') \right),$$
(19)

where

$$f(t) = \left(\frac{(1-r_{jk})^{t+1} - (1-r_{ijk})^{t+1}}{r_{ijk} - r_{jk}} \right),$$

$$g_{jk}(\tau) = \tilde{a}_{j,\varnothing}[t] \tilde{a}_{k,\varnothing}[t-\tau-1].$$

The derivation is given in Appendix 4, for two selected loci. The effects of pairwise epistasis in a multilocus system can be obtained by summing eqn 19 over all loci; however, there will be additional terms due to higher-order epistasis, analogous to the second sum in eqn 12. Equation 19 separates into three terms, each consisting of the expected product of selection coefficients across generations, multiplied by a factor $f(\tau)$ which depends on linkage, and which decays rapidly over time. For example, with unlinked loci ($r_{jk} = 1/2$, $r_{ijk} = 3/4$), the factor $f(\tau)$ decreases as $1, 3/4, 7/16, 15/64 \ldots$.

First, suppose that directional selection is negligible ($\tilde{a}_{j,\varnothing}, \tilde{a}_{k,\varnothing} \approx 0$), so that only the first term contributes. In order for recombination to increase, $E[\epsilon[t] \epsilon[t-\tau-2]]$ must be negative. This requires predominantly negative autocorrelations between epistasis two to five generations apart. In other words, combinations of alleles that are favoured in one generation must be unfavourable in the next few generations. Note that the main term is due to the covariance between epistasis two generations apart, $E[\epsilon[t] \epsilon[t-2]]$. This is because the increase in the modifier in generation t is $2\tilde{a}_{jk,\varnothing}[t] C_{ijk}[t]$. $C_{ijk}[t]$ is proportional to $(C'_{jk} - C'_{j,k})$; since both terms are increased by the same amount by selection in generation $t-1$, $(C'_{jk} - C'_{j,k})$ is proportional to $C_{jk}[t-1]$, which in turn was generated by epistasis in generation $t-2$. This leads to the counter-intuitive conclusion that if epistasis alternates in every generation, recombination will tend to decrease, whereas if it alternates over a somewhat longer timescale, recombination may tend to increase. The stringent conditions required for fluctuating epistasis to favour recombination were stressed by Charlesworth (1976) and by Maynard Smith (1978). This analysis further emphasizes their stringency.

If epistasis is weak relative to directional selection, the second term dominates. Since the labelling of alleles is arbitrary, there is no reason to expect the coefficients of directional selection to have any particular sign, or to be correlated with each other (i.e. $E[\tilde{a}_{j,\varnothing}]$, $E[\tilde{a}_{k,\varnothing}]$, $E[\tilde{a}_{j,\varnothing} \tilde{a}_{k,\varnothing}]$, $E[\epsilon] = 0$. Any tendency for recombination to increase must therefore be due to a consistent relation between directional selection and epistasis, such that $E[a_{j,\varnothing}[t] a_{k,\varnothing}[t-\tau-1] \epsilon[t-\tau-\tau'-3]]$ is negative for times, τ, τ' separated by a few generations.

4. Discussion

Assuming that modifiers have small effects on recombination leads to substantial simplifications. The evolution of such modifiers is governed by a set of linear equations (eqn 5c), which depend only on the effect on recombination between the selected loci, and do not involve dominance in modifier effects even when modifiers are common. These equations apply to arbitrary selection and linkage; they simplify further when selection is weak relative to recombination, and yield a general relation between the variance in log fitness, and selection on recombination (eqns 14, 16). While modifiers of large effect can evolve in qualitatively different ways (e.g. Altenberg & Feldman, 1987; Charlesworth et al. 1990), concentrating on minor modifiers should isolate the key factors that determine overall levels of recombination.

Recombination can be favoured in two ways: because it impedes the response to fluctuating epistasis, or because it facilitates the response to directional selection. If directional selection, and hence changes in allele frequency, are negligible, recombination can only be favoured if unfavourable combinations of genes tend to be associated with each other (i.e. ϵ_{jk} and C_{jk} have opposite signs). Such perverse linkage disequilibria can only build up if epistasis changes sign over just the right timescale (eqn 19), making the mechanism implausible (Charlesworth, 1976; Maynard Smith 1978). Nee (1989) argues that while this conclusion may hold when epistasis fluctuates in response to physical conditions, biological coevolution (for example, between host and parasite: Hamilton, 1980; Jaenike, 1978) will tend to produce fluctuations on the right timescale. In Nee's model, allele frequencies stay constant, and so any advantage to recombination must indeed be due to fluctuating epistasis. Epistasis tends to act against gene combinations that are in excess because the epistasis imposed by one species is a direct response to the linkage disequilibria that have evolved in the other. In more realistic cases, where allele frequencies are free to vary, and where many species interact on a variety of timescales, it seems unlikely that epistasis would change in the right way. More complex models of host–parasite coevolution (Hamilton, 1980; Bell & Maynard Smith, 1986; Hamilton, 1993) generate selection for recombination; however, this may be due to changing allele frequencies rather than to changing

epistasis. The mechanisms could be distinguished by following the components of fitness variation (V'_1, v_1, V'_2). Without knowing the underlying mechanism, it is hard to extrapolate from simulations of a few loci to many, and hard to know whether the effect is specifically due to coevolution, or is a general consequence of fitness variation.

If epistasis changes slowly, eqn 14 gives a simple relation between the net selection on recombination and the distribution of log (fitness). If there is negative epistasis between favourable alleles, then linkage disequilibria will reduce the additive genetic variance in log (fitness) ($v_1 < 0$), which reduces the response to directional selection, and hence selects for recombination ($s \approx -v_1 \delta r$ for unlinked loci). This is counterbalanced by the immediate gain in log(fitness) caused by linkage disequilibria between favourable gene combinations ($s \approx -2\delta \log (W)/3$ for unlinked loci). Because the effect of linkage disequilibria on additive variance is proportional to epistasis, whereas their effect on mean fitness is proportional to (epistasis)^2, recombination is favoured only when epistasis is weak and negative.

If recombination is to be favoured because it increases the response to directional selection, then epistasis must be both weak and negative. It is plausible that the selection coefficient on particular pairs of loci is typically weaker than that on each locus just because fitness depends on so many loci. For example, Charlesworth (1990) supposes that fitness decreases with the number of deleterious mutations, as $W(n) = \exp(-\alpha n - \beta n^2/2)$. For a given mean and variance of fitness, the coefficients α and β must scale with $1/\bar{n}$, $1/\bar{n}^2$ respectively. Since α, β correspond to the coefficients $\tilde{a}_{j,o}$, ϵ_{jk}, this implies that epistasis is weak enough that recombination can be favoured (see Appendix 3). The argument could be developed more generally by finding how the selection coefficients scale with the number of loci. When applied to selection on a quantitative trait, this approach leads to a generalization of the 'infinitesimal limit' (Bulmer, 1980; Turelli & Barton, 1994, Appendix B).

While it is plausible that epistasis is weak ($\epsilon_{jk} \approx \tilde{a}_{j,o} \tilde{a}_{ko}$) because selection acts on large numbers of genes, it is not clear why it should be negative ($\epsilon_{jk} \tilde{a}_{j,o} \tilde{a}_{k,o} < 0$). Why should two favourable alleles increase fitness by less than the product of their separate effects? Negative epistasis would result if fitness is mediated *via* stabilizing selection on additive quantitative traits (Maynard Smith, 1988; Charlesworth, 1993). More generally, one can argue that negative epistasis is necessary if the 'genetic load' is to be avoided. An asexual population has mean fitness reduced by $\exp(-U)$, where U is the genomic mutation rate; however, a sexual population can eliminate deleterious mutations much more effectively if epistasis is negative, and indeed, may not survive if epistasis is positive (Kondrashov, 1988). Similarly, the segregation and substitution loads can be much

reduced if there is truncation selection on some measure of overall genetic quality (Sved *et al.* 1967; Maynard Smith, 1976; Wills, 1978). Of course, this argument does not explain why epistasis should in fact be compatible with substantial fitness variation. It is not clear whether epistasis has itself been shaped by natural selection, or whether (by analogy with dominance – Kacser & Burns, 1981) there are general physiological reasons why epistasis should be negative.

Selection on recombination depends primarily on the contribution of linkage disequilibria to the additive variance in log (fitness) (v_1), and to the mean log (fitness), $\delta \log (W)$ (eqn 16). These quantities can, in principle, be measured by comparing the distribution of fitness effects of genomes before and after recombination. This is essentially what was done by Charlesworth & Charlesworth (1975), and by Mukai (1977), who compared the effect on fitness of second chromosomes extracted from either male or female *Drosophila melanogaster*. Both sets of chromosomes had undergone selection on viability, but only those from females had undergone recombination. Charlesworth & Charlesworth (1975) found that chromosomes derived from females caused slightly lower mean viability, and significantly lower mean fecundity ($\approx 7\%$). Mukai (1977) found that flies currying two chromosomes derived from males ('MM') had substantially lower variance in relative viability (0·0036, 0·0057, 0·0059 for MM, MF, and FF, respectively). Surprisingly, Mukai (1977) also found that MF flies had highest viability (0·995, 1·015, 0·997, respectively).

These results suggest that that there might be substantial selection on recombination modifiers. (Bear in mind that the second chromosome makes up only about 40% of the *Drosophila* genome, that the chromosomes had only undergone viability selection before being isolated, and that only some components of fitness were measured.) However, before we can decide whether recombination is prevalent because it facilitates the response to directional selection, more extensive measurements of its effects on fitness variation are needed. Though laborious, such measurements are feasible, and are essential if we are to understand the evolution of this key feature of the genetic system.

Appendix 1: Detailed analysis of three loci

(i) *The model*

As an example of the general equations, consider now the simplest non-trivial model for the evolution of

recombination. A modifier is labelled i, and has no direct effect on fitness. Two loci j,k are directly selected, and interact epistatically with each other. For simplicity, assume that selection acts symmetrically on male and female gametes, so that $C'_{S,T} = C'_{T,S}$, and $C'_{S,\varnothing} = C'_{\varnothing,S}$ can be written as C'_S. The full equations were produced automatically using *Mathematica* (Wolfram, 1991), and then simplified by assuming that the modifier has small effects ($\delta r \ll 1$):

$$C''_{jk} = C'_{jk} - \bar{r}_{j,k}(C'_{jk} - C'_{j,k})$$
$$+ \delta r_{j,k|i}(C'_{ji,1} + C'_{j,ik} - C_{jki} - C'_{jk,i}) \quad (A1.1a)$$

Here, I have used the constraint that $1 = r_{jk,\varnothing} + r_{j,k}$, and $0 = \delta r_{jk,\varnothing|i} + \delta r_{j,k|i}$. Similarly:

$$C''_{ij} = C'_{ij} - \bar{r}_{i,j}(C'_{ij} - C'_{i,j}) + \delta r_{i,j|i}(C'_{ii,j} - C'_{iij}) \quad (A1.1b)$$

This is just eqn 3b, with $N = \{ij\}$. We see that if, after selection, there is no association between the modifier and the selected loci, then recombination modification does not build it up. Writing out $(C'_{ii,j} - C'_{iij})$ explicitly using eqn 12 of Barton & Turelli (1991), shows that it involves only terms like C_{ij} and C_{ijk}, which are $O(\delta r)$, and hence makes a negligible contribution.

The primary effect involves third-order disequilibrium:

$$C''_{ijk} = C'_{ijk} - \bar{r}_{i,jk}(C'_{ijk} - C'_{i,jk})$$
$$- \bar{r}_{j,ik}(C'_{ijk} - C'_{j,ik}) - \bar{r}_{k,ij}(C'_{ijk} - C'_{k,ij})$$
$$+ \delta r_{i,jk|i}(C'_{ii,jk} + C'_{i,ijk} - C'_{iijk} - C'_{ijk,i})$$
$$+ \delta r_{j,ik|i}(C'_{ij,ik} + C'_{j,iik} - C'_{iijk} - C'_{ijk,i})$$
$$+ \delta r_{k,ij|i}(C'_{ik,ij} + C'_{k,iij} - C'_{iijk} - C'_{ijk,i}). \quad (A1.1c)$$

Here, I have used the constraint that $0 = \delta r_{ijk,\varnothing|i} + \delta r_{i,jk|i} + \delta r_{j,ik|i} + \delta r_{k,ij|i}$. Most of these terms are negligible if associations between the modifier and the other loci are weak. The leading terms, which are $O(\delta r)$, involve $C'_{iijk} \approx C'_{ii,jk} \approx C_{ii}C'_{jk}$, $C'_{j,iik} \approx C_{ii}C'_{j,k}$ etc. This was confirmed by writing out the $C'_{U,V}$ explicitly in terms of the selection coefficients, assuming that C_{ij}, C_{ik}, $C_{ijk} \approx O(\delta r)$, and $C_{jk} \approx O(1)$, and retaining only leading terms in d. Using the relation $(\delta r_{j,ik|i} + \delta r_{i,jj|i}) = \delta r_{j,k|i}$ gives the key driving term as just $-\delta r_{j,k|i}C_{ii}(C'_{jk} - C'_{j,k})$ – a special case of eqn 5c, with $N = \{jk\}$. This confirms that a modifier of small effect only evolves because it changes recombination between the selected loci, and not because it alters its own linkage to the selected loci ($\delta r_{i,jj|i}$ etc).

For simplicity, assume that there is no dominance, and that there is no distinction between *cis* and *trans* combinations. Then, fitness is a function of $(X_i + X_i^*)$, rather than the individual X's. The dominance coefficients ($\tilde{a}_{j,j}$ etc.) are defined such that they would not directly affect the change in allele frequencies. However, they would cause deviations from Hardy–Weinberg proportions after selection ($C'_{j,j}$ etc), which would alter the rate at which recombinations reduces linkage disequilibria. (Note that viability

selection on haploids produces small 'dominance' coefficients, because the fitness of each diploid genotype is then the product of the haploid fitnesses, rather than the sum.)

With these assumptions, only three distinct coefficients contribute: $a_{j,\varnothing} = a_{\varnothing,j}$, $a_{k,\varnothing} = a_{\varnothing,k}$, and $a_{j,k} = a_{k,j} = 2a_{jk,\varnothing} = 2a_{\varnothing,jk} = 2a_{kj,\varnothing} = 2a_{\varnothing,kj}$. All others are zero. (Note that as in Barton & Turelli (1991), we use the convention the coefficients $a_{jk,\varnothing}$ and $a_{kj,\varnothing}$ are counted separately; this simplifies sums over loci.) If genotypic fitnesses are fixed, as in Table 1, the selection coefficients are $\tilde{a}_{j,\varnothing} = (s_j + \eta\Delta_k)/\bar{W}$, $\tilde{a}_{k,\varnothing} = (s_k + \eta\Delta_j)/\bar{W}$, $\tilde{a}_{j,k} = 2\tilde{a}_{jk,\varnothing} = \eta/\bar{W}$, where $\Delta_k = p_k - q_k$, s_j, s_k are the selection coefficients on loci j and k, and η is a measure of (additive) epistasis. However, the equations below will be written in terms of the selection coefficients ($\tilde{a}_{U,V}$), since they apply even when selection is frequency-dependent. Selection coefficients enter as the average over the two sexes, $\tilde{a}_{U,V} = (a_{U,V} + a_{V,U})/2$. There is no dominance, so that coefficients such as $\tilde{a}_{j,j}$ and $\tilde{a}_{jk,k}$ do not enter.

$$\Delta p_j = \tilde{a}_{j,\varnothing} p_j q_j + \sigma_k C_{jk} \quad (A1.2a)$$

$$\Delta p_k = \tilde{a}_{k,\varnothing} p_k q_k + \sigma_j C_{jk} \quad (A1.2b)$$

$$\Delta C_{jk} = 2\tilde{a}_{jk,\varnothing} p_j q_j p_k q_k - C_{jk}(r_{jk} + (1 - r_{jk})S)$$
$$- 2\tilde{a}_{jk,\varnothing}(1 - 2r_{jk})C_{jk}^2 - \Delta p_j \Delta p_k \quad (A1.2c)$$

$$\Delta C_{ij} = C_{ijk}(1 - r_{ij})\sigma_k - C_{ij}(r_{ij} + (1 - r_{ij})\tilde{a}_{j,\varnothing}\Delta_j$$
$$+ 2\tilde{a}_{jk,\varnothing} C_{jk}(1 - 2r_{ij}))$$
$$+ 2\tilde{a}_{jk,\varnothing} C_{ik} p_j q_j - \Delta p_i \Delta p_j \quad (A1.2d)$$

$$\Delta C_{ik} = C_{ijk}(1 - r_{ik})\sigma_j - C_{ik}(r_{ik} + (1 - r_{ik})\tilde{a}_{k,\varnothing}\Delta_k$$
$$+ 2\tilde{a}_{jk,\varnothing} C_{jk}(1 - 2r_{ik})) + 2\tilde{a}_{jk,\varnothing} C_{ij} p_k q_k - \Delta p_i \Delta p_k \quad (A1.2e)$$

$$\Delta C_{ijk} = -\delta r_{j,k|i} p_i q_i C_{jk}(1 - S - 4\tilde{a}_{jk,\varnothing} C_{jk})$$
$$- C_{ijk}(r_{ijk} + (1 - r_{ijk})S + 2\tilde{a}_{jk,\varnothing} C_{jk}(1 - 2r_{ijk}))$$
$$+ C_{ij}((1 - r_{ij})\sigma_k p_k q_k + r_{ik}\sigma_j C_{jk})$$
$$+ C_{ik}((1 - r_{ik})\sigma_j p_j q_j + r_{ij}\sigma_k C_{jk})$$
$$- \Delta p_i C_{jk}^* - \Delta p_j C_{ik}^* - \Delta p_k C_{ij}^* - \Delta p_i \Delta p_j \Delta p_k \quad (A1.2f)$$

$$\Delta p_i = \tilde{a}_{j,\varnothing} C_{ij} + \tilde{a}_{k,\varnothing} C_{ik} + 2\tilde{a}_{jk,\varnothing} C_{ijk}, \quad (A1.2g)$$

where $C_{jk}^* = C_{jk} + \Delta C_{jk}$, $\sigma_k = \tilde{a}_{k,\varnothing} - 2\tilde{a}_{jk,\varnothing}\Delta_j$, $\sigma_j = \tilde{a}_{j,\varnothing} - 2\tilde{a}_{jk,\varnothing}\Delta_k$, $S = \tilde{a}_{j,\varnothing}\Delta_j + \tilde{a}_{k,\varnothing}\Delta_k - 2\tilde{a}_{jk,\varnothing}\Delta_j\Delta_k$. These equations can be derived from eqns 4 and 5c. They are valid for strong selection on loci j and k, and for any pattern of recombination, with modifiers of small effect. Bergman *et al.* (1994, eqns 1–5) give equations for a similar three-locus model, which apply with weak selection on haploids, and which are consistent with eqns A1.2. The full equations derived using their methods are exactly equivalent to eqns A1.2 (Otto, pers. comm.).

A modifier which increases recombination ($\delta r_{j,k|i} > 0$) tends to become associated with pairs of alleles which are in negative linkage disequilibrium ($C_{jk} < 0$), because the term $-\delta r_{j,k|i} p_i q_i C_{jk}$ in eqn A1.2f then

generates positive C_{ijk}. This three-way association in turn causes the modifier to decrease if, as is likely, the negative disequilibrium C_{jk} between the selected alleles is caused by negative epistasis (the term $2\tilde{a}_{jk,\sigma}C_{ijk}$ is then negative in eqn A1.2g). It is this process which causes recombination to decrease in a population which is at equilibrium. However, the modifier may also increase if it becomes associated with individual alleles that are favoured (the terms $\tilde{a}_{j,\sigma}C_{ij}$, $\tilde{a}_{k,\sigma}C_{ik}$ in eqn A1.2g). Such associations build up indirectly, *via* the terms $C_{ijk}(1-r_{ij})\sigma_k$, $C_{ijk}(1-r_{ik})\sigma_j$ in eqns A1.2d, A1.2e, respectively. If directional selection is strong relative to epistasis, this indirect effect dominates, and leads to an increase in recombination.

(ii) *Weak linkage disequilibrium*

The full recursions given by eqns A1.2 can be simplified if selection is weak ($a \ll 1$), and if the selected loci are only weakly associated ($C_{jk} \ll p_j q_j p_k q_k$). Associations will be weak if linkage is loose, and both selection and epistasis are weak ($\tilde{a}_{j,\sigma}, \tilde{a}_{k,\sigma}, \tilde{a}_{jk,\sigma} \approx s \ll r_{jk} \approx 1$. Associations can also be weak if linkage is tight, provided that epistasis is much weaker than directional selection and recombination ($\tilde{a}_{jk,\sigma}$ and ($\tilde{a}_{j,\sigma}\tilde{a}_{k,\sigma}$) $\approx s^2 \ll r_{jk}$, $\tilde{a}_{j,\sigma}$, $\tilde{a}_{k,\sigma} \approx s$). These assumptions ensure that the effect of directional selection increasing recombination is of the same order as the effect of epistasis reducing it, and so allows their relative importance to be assessed. Because the equations derived here are valid for tight linkage ($r \approx s$) among the selected loci, and for fluctuating selection, they are more general than the formulae for arbitrary multilocus systems which lead to eqn 12.

The approximate equations are derived by keeping the leading-order selection terms in eqn A1.2:

$$\Delta p_j = \tilde{a}_{j,\sigma} p_j q_j \qquad (A1.3a)$$

$$\Delta p_k = \tilde{a}_{k,\sigma} p_k q_k \qquad (A1.3b)$$

$$\Delta C_{jk} = \epsilon_{jk} p_j q_j p_k q_k - (r_{jk} + \tilde{a}_{j,\sigma}\Delta_j + \tilde{a}_{k,\sigma}\Delta_k)C_{jk} \quad (A1.3c)$$

$$\Delta C_{ij} = (1 - r_{ij})\tilde{a}_{k,\sigma}C_{ijk} - (r_{ij} + \tilde{a}_{j,\sigma}\Delta_j)C_{ij} \qquad (A1.3d)$$

$$\Delta C_{ik} = (1 - r_{ik})\tilde{a}_{j,\sigma}C_{ijk} - (r_{ik} + \tilde{a}_{k,\sigma}\Delta_k)C_{ik} \qquad (A1.3e)$$

$$\Delta C_{ijk} = -\delta r_{j,k|i} p_i q_i C_{jk} - (r_{ijk} + \tilde{a}_{j,\sigma}\Delta_j + \tilde{a}_{k,\sigma}\Delta_k)C_{ijk}$$
$$+ \tilde{a}_{k,\sigma}p_k q_k(1 - r_{ij})C_{ij} + \tilde{a}_{j,\sigma}p_j q_j(1 - r_{ik})C_{ik} \quad (A1.3f)$$

$$\Delta p_i = \tilde{a}_{j,\sigma}C_{ij} + \tilde{a}_{k,\sigma}C_{ik} + 2\tilde{a}_{jk,\sigma}C_{ijk} \qquad (A1.3g)$$

where $\epsilon_{jk} = (2\tilde{a}_{jk,\sigma} - \tilde{a}_{j,\sigma}\tilde{a}_{k,\sigma})$. Note that the last term in eqn A1.3c should appear in full $(r_{jk} + (1 - r_{jk})(\tilde{a}_{j,\sigma}\Delta_j + \tilde{a}_{k,\sigma}\Delta_k))C_{jk}$. However, when $r_{jk} \gg s$, it approximates to $r_{jk}C_{jk}$, whereas when $r_{jk} \approx s$, it approximates to $(r_{jk} + (\tilde{a}_{j,\sigma}\Delta_j + \tilde{a}_{k,\sigma}\Delta_k))C_{jk}$. The form given in eqn A1.3c therefore covers both cases. The same comment applies to the corresponding terms in eqns A1.3d–f. With weak epistasis, S reduces to $\tilde{a}_{j,\sigma}\Delta_j + \tilde{a}_{k,\sigma}\Delta_k$, and σ_j, σ_k to $\tilde{a}_{j,\sigma}$, $\tilde{a}_{k,\sigma}$. The factor $\epsilon_{jk} = (2\tilde{a}_{jk,\sigma} - \tilde{a}_{j,\sigma}\tilde{a}_{k,\sigma})$ which produces linkage dis-

equilibrium C_{jk} (eqn A1.3c) arises from the first and last terms in eqn A1.2c. If fitnesses are multiplicative across loci, it is zero. If genotypes have fixed fitnesses, the selection coefficients will stay approximately constant. However, all the coefficients may change through time, because of changing conditions or frequency-dependent fitnesses.

Equations A1.3 can be simplified further by scaling the linkage disequilibria relative to the heterozygosities. Let $H_{jk} = C_{jk}/p_j q_j p_k q_k$, $H_{ij} = C_{ij}/p_j q_j$, $H_{ik} = C_{ik}/p_k q_k$, $H_{ijk} = C_{ijk}/p_j q_j p_k q_k$. Then, because $\Delta(p_j q_j) = -\Delta_j \Delta p_j - \Delta p_j^2 \approx -\tilde{a}_{j,\sigma}\Delta_j p_j q_j$, we have:

$$\Delta H_{jk} = \epsilon_{jk} - r_{jk}H_{jk} \qquad (A1.4c)$$

$$\Delta H_{ij} = (1 - r_{ij})\tilde{a}_{k,\sigma}p_k q_k H_{ijk} - r_{ij}H_{ij} \qquad (A1.4d)$$

$$\Delta H_{ik} = (1 - r_{ik})\tilde{a}_{j,\sigma}p_j q_j H_{ijk} - r_{ik}H_{ik} \qquad (A1.4e)$$

$$\Delta H_{ijk} = -\delta r_{j,k|i}p_i q_i H_{jk} - r_{ijk}H_{ijk}$$
$$+ \tilde{a}_{k,\sigma}(1 - r_{ij})H_{ij} + \tilde{a}_{j,\sigma}(1 - r_{ik})H_{ik}. \quad (A1.4f)$$

(One could define the associations as $C_{ij}/p_i q_i p_j q_j$ instead; however, because the modifier frequency p_i changes slowly, $p_i q_i$ is approximately constant, and so this rescaling makes no difference.) The scaled linkage disequilibria $H_{ij} = C_{ij}/p_j q_j$, $H_{ik} = C_{ik}/p_k q_k$, have a simple interpretation. They are the differences in frequency of the modifier allele between the two genetic backgrounds defined by loci j and k, respectively, and decrease steadily at rates r_{ij}, r_{ik} regardless of how frequencies at the selected loci change.

Equations A1.4c–f form a set of linear recursions, with coefficients which vary arbitrarily through time. An explicit solution can be found, but is complicated: it involves the exponential of the matrix of coefficients. However, if linkage is loose relative to the rates of change of the allele frequencies and the selection coefficients, the linkage disequilibria rapidly approach a 'quasi-equilibrium'. For slowly changing coefficients:

$$H_{jk} = \frac{\epsilon_{jk}}{r_{jk}} \qquad (A1.5a)$$

$$H_{ij} = \frac{(1 - r_{ij})H_{ijk}\tilde{a}_{k,\sigma}p_k q_k}{r_{ij}} \qquad (A1.5b)$$

$$H_{ik} = \frac{(1 - r_{ik})H_{ijk}\tilde{a}_{j,\sigma}p_j q_j}{r_{ik}} \qquad (A1.5c)$$

$$H_{ijk} = -\frac{\delta r_{j,k|i}p_i q_i H_{jk}}{r_{ijk}}. \qquad (A1.5d)$$

(The more general case where selection coefficients fluctuate rapidly is dealt with in Appendix 4 (eqn A4.1).) Substituting into eqn A1.3g gives the rate of change of the modifier:

$$\Delta p_i = -\frac{\delta r_{j,k|i}p_i q_i C_{jk}}{r_{ijk}}\left(\epsilon_{jk} + \tilde{a}_{j,\sigma}\tilde{a}_{k,\sigma}\left(\frac{1}{r_{ij}} + \frac{1}{r_{ik}} - 1\right)\right).$$
$$(A1.5e)$$

In eqn A1.5e, I have assumed that the modifier is loosely linked to the selected loci ($r_{ij}, r_{ik} \approx 1/2$). If the selected loci are tightly linked ($r_{jk} \approx s$), C_{jk} is given by the solution of eqn A1.4c. If all loci are loosely linked ($r_{ij}, r_{ik}, r_{jk} \approx 1/2$), C_{jk} is given by eqn A1.5a, and eqn A1.5e simplifies further to:

$$\Delta p_i = -\frac{\delta r_{j,k|i} p_i q_i p_j q_j p_k q_k \epsilon_{jk}}{r_{ijk} r_{jk}}$$

$$\times \left(\epsilon_{jk} + \tilde{a}_{j,\varnothing} \tilde{a}_{k,\varnothing} \left(\frac{1}{r_{ij}} + \frac{1}{r_{ik}} - 1 \right) \right). \quad (A1.5f)$$

This is a special case of eqn 12.

Appendix 2: Comparison with Charlesworth's (1993) analysis of direction selection

Charlesworth (1993) modelled directional selection on a quantitative trait, z, applying Bulmer's (1980) infinitesimal model to both haploid and diploid populations. I will only consider the haploid case here, since Charlesworth (1993) treats this in more detail, and since it differs instructively from the diploid case assumed in much of this paper. The trait has mean $\bar{z}$, and genetic and environmental variances V_g, V_e respectively. There is Gaussian selection of strength $1/\omega^2$ around an optimum at θ ($W(z) = \exp(-(z-\theta)^2/2\omega^2)$; the relative importance of directional and stabilizing selection depends on the deviation of the mean from the optimum, $(\bar{z}-\theta)$. If there is a steady movement of the optimum by $\Delta\theta$ per generation, the deviation settles to a steady lag $(\bar{z}-\theta) = -\Delta\theta V_s/V_g$.

From eqn 4 of Charlesworth (1993), the logarithm of mean fitness is:

$$\log(\bar{W}) = \log(\omega) - \tfrac{1}{2}\log(V_g+V_s) - \frac{(\bar{z}-\theta)^2}{2(V_g+V_s)}, \quad (A2.1)$$

where $V_s = V_e + \omega^2$.

The selection coefficients can be found from the selection gradients with respect to the mean and variance of z (see Appendix B of Turelli & Barton, 1994). Suppose that the effect of locus j on the trait is α_j; thus, for the haploid population, $\bar{z} = \sum_j \alpha_j p_j$. The genetic variance consists of components due to genic heterozygosity (V_{g0}) and linkage disequilibrium (C_L):
$V_g = \sum_j \alpha_j^2 p_j q_j + \sum_{j \neq k} \alpha_j \alpha_k C_{jk} = V_{g0} + C_L$. I assume throughout that selection is weak ($V_s \gg V_g$). Then:

$$\tilde{a}_{j,\varnothing} = \frac{\partial \log(\bar{W})}{\partial \bar{z}} \frac{\partial \bar{z}}{\partial p_j} = -\alpha_j \frac{(\bar{z}-\theta)}{V_s} = \alpha_j \frac{\Delta\theta}{V_g} \quad (A2.2a)$$

$$\tilde{a}_{jk,\varnothing} = \frac{\partial \log(\bar{W})}{\partial V} \frac{\partial V}{\partial C_{jk}} = -\alpha_j \alpha_k \left(\frac{1}{2V_s} - \frac{(\bar{z}-\theta)^2}{2V_s^2} \right) \quad (A2.2b)$$

$$\epsilon_{jk,\varnothing} = (2\tilde{a}_{jk,\varnothing} - \tilde{a}_{j,\varnothing} \tilde{a}_{k,\varnothing}) = -\frac{\alpha_j \alpha_k}{2V_s}. \quad (A2.2c)$$

$\epsilon_{jk,\varnothing}$ is a measure of the deviation from multiplicative fitnesses. With random mating and selection on haploid viability, the contribution of each diploid genotype is the product of the fitnesses of its haploid components. Hence, $\tilde{a}_{U,V} = \tilde{a}_U \tilde{a}_V$, which ensures that there are no cross-gamete associations after selection ($C'_{U,V} = 0$).

First, consider linkage disequilibria among the selected loci. Under the QLE approximation (eqn 6), these are $C_{jk} \approx (1-r_{jk}) \epsilon_{jk} p_j q_j p_k q_k / r_{jk}$. Summing over loci, and substituting for ϵ_{jk} from eqn A2.2c, the

$$C_L \approx -\left(\frac{1}{r_H} - 1 \right) \frac{p_j q_j p_k q_k}{V_s}, \quad (A2.3)$$

where r_H is the harmonic mean recombination rate among selected loci. This agrees with Charlesworth's (1993) eqn A3c.

Charlesworth (1993) calculates the rate of spread of a rare modifier from the difference between the mean and variance of the trait in the individuals heterozygous for the modifier, and the rest of the population ($\delta\bar{z}, \delta V_g$). In terms of the linkage disequilibria between the modifier and the selected loci:

$$\delta\bar{z} = \sum_j \frac{\alpha_j C_{ij}}{p_i q_i} \quad (A2.4a)$$

$$\delta V_g = \delta V_{g0} + \delta C_L = -\sum_{j,k} \frac{\alpha_j^2 (p_j - q_j) C_{ij}}{p_i q_i}$$

$$+ \sum_{j,k} \frac{\alpha_j \alpha_k C_{ijk}}{p_i q_i} \quad (A2.4b)$$

(assuming $C_{ij} C_{ik} \ll C_{ijk}$). Substituting C_{ij} from eqn 11 into eqn A2.4a, and substituting for $a_{k,\varnothing}$ from eqn A2.2a:

$$\delta\bar{z} = \sum_{j \neq k} \alpha_j \left(\frac{1}{r_{ij}} - 1 \right) \tilde{a}_{k,\varnothing} \frac{C_{ijk}}{p_i q_i}$$

$$= \frac{\Delta\theta}{V_g} \sum_{j \neq k} \alpha_j \alpha_k \left(\frac{1}{r_{ij}} - 1 \right) \frac{C_{ijk}}{p_i q_i}$$

$$= \frac{\Delta\theta}{V_g} \left(\frac{1}{\rho_H} - 1 \right) \delta C_L, \quad (A2.5)$$

where ρ_H is the harmonic mean recombination rate between the modifier and the selected loci. This corresponds to eqn A2c for $V_g \ll V_s$, provided that $\delta C_L \gg \delta V_{g0}$. Substituting C_{ij} from eqn 11 into eqn A2.4b shows that this condition holds for small α; under the infinitesimal model, the modifier acts primarily by changing linkage disequilibria rather than gene frequencies.

To find C_{ijk}, apply eqn 5c, noting that selection on haploids cannot generate cross-gamete associations ($C'_{U,V} = 0$):

$$C''_{ijk} = (1-r_{ijk}) C'_{ijk} + \delta r_{jk|i}(C'_{jk} - C_{jk}). \quad (A2.6a)$$

At quasi-linkage equilibrium,

$$C_{jk} = (1-r_{jk}) \epsilon_{jk} p_j q_j q_k q_k / r_{jk}$$

(from eqn 6), and $(C'_{jk} - C_{jk}) = \epsilon_{jk} p_j q_j p_k q_k / r_{jk}$. Hence, at QLE:

$$C_{ijk} = \frac{1}{r_{ijk}} \left((1 - r_{ijk})(C'_{ijk} - C_{ijk}) + \frac{\delta r_{jk|i}}{r_{jk}} \epsilon_{jk} p_j q_j p_k q_k \right).$$

$$(A2.6b)$$

This corresponds to Charlesworth's (1993) eqns A5, 8: his $\delta\Delta/m(m-1)$ is the change in δC_{jk} due to selection $(C'_{ijk} - C_{ijk})/p_i q_i$, and his $\Delta/m(m-1)$ is the change in C_{jk} due to selection $(C'_{jk} - C_{jk}) \approx \epsilon_{jk} p_j q_j p_k q_k$. The first term is negligible for weak selection ($V_g \ll V_s$), giving an explicit formula for C_{ijk}.

The selection on the modifier can be found from δV_g, $\delta \bar{z}$ using Charlesworth's (1993) eqn A10, which corresponds to the sum over loci of eqn 8, above:

$$s_i = \frac{\Delta p_i}{p_i q_i} \approx \frac{\partial \log(\bar{W})}{\partial \bar{z}} \delta \bar{z} + \frac{\partial \log(\bar{W})}{\partial V_g} \delta V_g$$

$$\cong \frac{\Delta\theta}{V_g} \delta \bar{z} - \frac{1}{2} \left(\frac{1}{V_s} - \frac{\Delta\theta^2}{V_g^2} \right) \delta V_g. \quad (A2.7a)$$

Substituting for $\delta \bar{z}$ from eqn A2.5, and then for δV_g from eqn A2.6 (neglecting the first term) gives:

$$s_i \approx \frac{1}{2} \left(\frac{\Delta\theta^2}{V_g^2} \left(\frac{2}{\rho_H} - 1 \right) - \frac{1}{V_s} \right) \delta V_g$$

$$\approx \frac{1}{2} \left(\frac{\Delta\theta^2}{V_g^2} \left(\frac{1}{\rho_H} - 1 \right) - \frac{1}{V_s} \right) \frac{\delta r_{jk|i}}{r_{jk} r_{ijk}} \epsilon_{jk} p_j q_j p_k q_k. \quad (A2.7b)$$

This corresponds to Charlesworth's (1993) eqn A11a, for $V_g \ll V_s$. It can be derived from eqn 12 (discarding the third and higher-order terms due to the second sum), even though eqn 12 was derived for selection on diploids rather than haploids. (The factor of (1/2) multiplying eqn A2.7b arises because the sum Σ^* in eqn 12 is over only pairs $j < k$, rather than over all pairs.)

Appendix 3: Comparison with Charlesworth's (1990) analysis of mutation/selection balance

Charlesworth (1990) analysed the modification of recombination under a mutation/selection balance, treating the number of deleterious mutations in a diploid individual, n, as a quantitative trait with mean $\bar{n}$ and variance V. His crucial assumptions were that n is normally distributed, and is approximated by the infinitesimal model. Selection is Gaussian, with $W(n) = \exp(-\alpha n - \beta n^2/2)$. From eqn A2 of Charlesworth (1990), the log mean fitness is precisely:

$$\log(\bar{W}) = -\tfrac{1}{2} \log(1 + \beta V) - \frac{(2\alpha\bar{n} + \beta\bar{n}^2 - \alpha^2 V)}{2(1 + \beta V)}. \quad (A3.1)$$

The selection coefficients can be found from the selection gradients with respect to the mean and variance of n (using eqn A3 of Turelli & Barton, 1994, and neglecting higher-order coefficients such as $a_{jk,l}$). I will assume throughout that $\beta V \ll 1$. This is a good

approximation over the relevant range of parameters, and greatly simplifies the algebra. Then:

$$\tilde{a}_{j,o} = -\frac{\partial \log(\bar{W})}{\partial \bar{n}} = (\alpha + \beta\bar{n}) \quad (A3.2a)$$

$$\tilde{a}_{jk,o} = \frac{\partial \log(\bar{W})}{\partial V} = -\frac{(\beta - (\alpha + \beta\bar{n})^2)}{2} \quad (A3.2b)$$

$$\epsilon_{jk,o} = (2\tilde{a}_{jk,o} - \tilde{a}_{j,o} \tilde{a}_{k,o}) = -\beta \quad (A3.2c)$$

Treating n as a quantitative trait, with selection gradient $(\alpha + \beta\bar{n})$, gives a balance between mutation and selection (eqn 2 of Charlesworth, 1990):

$$U = (\alpha + \beta\bar{n}) V, \quad (A3.3)$$

where $U = 2\Sigma_j \mu_j$ and $V = 2\Sigma_j q_j$. At linkage equilibrium, the number of deleterious mutations is Poisson distributed, and approximates to a normal distribution with variance $V = \bar{n}$. Solving the consequent quadratic equation gives $\bar{n}$, V. (The same can be derived at the level of discrete loci, from $\Delta p_j = 0 = a_{j,o} p_j q_j - \mu_j p_j$.)

Assuming weak epistasis, linkage disequilibria are given by eqn 9b:

$$C_{jk} \approx \frac{\epsilon_{jk} p_j q_j p_k q_k}{r_{jk}} \approx -\frac{\beta q_j q_k}{r_{jk}} \quad (A3.4)$$

The variance is reduced by these linkage disequilibria to:

$$V = 2\sum_j q_j + 2\sum_{j \neq k} C_{jk} = \bar{n} - \frac{\beta\bar{n}^2}{2} E\left[\frac{1}{r_{jk}} \right]. \quad (A3.5)$$

Substituting into eqn A3.3 gives a cubic for $\bar{n}$. Solutions for this substitution are compared with exact results from Charlesworth (1990) in Table 3a, for unlinked loci ($E[1/r_{jk}] = 2$). There is reasonable agreement even for high total mutation rates ($U = 2$).

The expectation of $(1/r_{jk})$ over a linear genetic map is infinite, because of the divergent contribution of very closely linked pairs. The QLE approximation which leads to eqns 6 and A4 breaks down when recombination is comparable to selection. Charlesworth used an improved approximation, suggested by analogy with Thomson's (1977) analysis of the effect of selection at one locus on linked neutral loci. He replaced $1/r_{jk}$ by $1/(r_{jk} + 2hs)$ (his eqn 10a), where $hs = U/\bar{n}$ is the effective selection on each locus. This approximation is hard to justify in the multilocus framework used here. The exact equations for the change in allele frequency due to directional selection and pairwise epistasis, are (from Barton & Turelli, 1991):

$$\Delta p_j = -\mu_j p_j + a_{j,o} p_j q_j$$

$$+ \sum_{k \neq j} (a_{k,o} - 2a_{jk,o} \Delta_j) C_{jk} + \sum_{k \neq l \neq j} a_{kl,o} C_{jkl},$$

$$(A3.6a)$$

where $\Delta_j = (p_j - q_j)$. Neglecting skew, C_{jkl}, and assuming that epistasis is weaker than directional

selection $(a_{jk,\varnothing} \ll a_{j,\varnothing})$, this reduces to eqn A3; the 'effective selection' which balances mutation at each locus is then $hs_j = a_{j,\varnothing} + \sum_{k \neq j} a_{k,\varnothing} C_{jk}/p_j q_j$, which corresponds to Charlesworth's hs. The exact equation for the change in pairwise linkage disequilibrium is:

$$\Delta C_{jk} = (1 - \mu_j)(1 - \mu_k)(2\tilde{a}_{jk,\varnothing} p_j q_j p_k q_k$$
$$+ (1 - r_{jk})(1 - \tilde{a}_{j,\varnothing} \Delta_j - \tilde{a}_{k,\varnothing} \Delta_k$$
$$+ 2\tilde{a}_{jk,\varnothing} \Delta_j \Delta_k) C_{jk} - 2(1 - 2r_{jk})$$

$$\times C_{jk}(\tilde{a}_{jk,\varnothing} C_{jk} + \sum_{k \neq l \neq j} (\tilde{a}_{jl,\varnothing} C_{jl} + \tilde{a}_{kl,\varnothing} C_{kl})$$

$$- \Delta p_j \Delta p_k + \sum_{k \neq l \neq j} (\tilde{a}_{l,\varnothing} - 2\tilde{a}_{jl,\varnothing} \Delta_j - 2\tilde{a}_{kl,\varnothing} \Delta_k) C_{jkl}$$

$$+ \sum_{k \neq l \neq j} 2r_{jk}(\tilde{a}_{jl,\varnothing} p_j q_j C_{kl} + \tilde{a}_{kl,\varnothing} p_k q C_{jl}$$

$$+ \sum_{l \neq m \neq k \neq j} \tilde{a}_{lm,\varnothing}((1 - r_{jk})(C_{jklm} - C_{jk} C_{lm})$$

$$+ 2r_{jk} C_{jl} C_{km})) - C_{jk}. \tag{A3.6b}$$

For two loci, and no mutation, this reduces to eqn A1.2c. If linkage disequilibrium is weak enough that $2(1 - 2r_{jk})\tilde{a}_{jk,\varnothing} C_{jk}^2$ is negligible, and if deleterious alleles are rare $(\Delta_j, \Delta_k \approx 1)$, then the solution at equilibrium is approximately $C_{jk} = 2\tilde{a}_{jk,\varnothing} p_j q_j p_k q_k/(r_{jk} + \tilde{a}_{j,\varnothing} + \tilde{a}_{k,\varnothing})$, which corresponds to Charlesworth's eqn 10a if $hs \approx \tilde{a}_{j,\varnothing}$. However, if the cumulative effect of linkage disequilibrium is to be great enough to substantially perturb allele frequencies, the effective selection will differ from the direct selection. In order to allow for the effect of multiple loci, Charlesworth replaces $\tilde{a}_{j,\varnothing}$ by hs_j, giving his eqn 10a: $C_{jk} \approx 2\tilde{a}_{jk,\varnothing} p_j q_j p_k q_k/(r_{jk} + hs_j + hs_k)$. While this substitution is plausible, I do not see that it can be derived from eqn A1.6b. Taking the limit of weak epistasis $(\tilde{a}_{jk,\varnothing} \approx s^2, r_{jk}, \tilde{a}_{j,\varnothing} \approx s, \text{but} \sum_{k \neq j} a_{k,\varnothing} C_{jk}/p_j q_j \approx Us \approx 1)$, and assuming normality $(C_{jkl} \approx 0, C_{jklm} \approx C_{jk} C_{lm} + C_{jl} C_{km} + C_{jm} C_{kl})$ shows that the only sum that contributes to eqn A3.6b is $2\sum_{l,m} \tilde{a}_{lm,\varnothing} C_{jl} C_{km}$, which cannot be expressed in terms of the 'effective selection', hs. It seems that no simple approximation can be rigorously derived when linkage is tight and when linkage disequilibria have a substantial net effect. However, this problem is not serious, because the expectation of $1/(r_{jk} + 2hs)$ only depends logarithmically on hs, and is close to $1/r_{jk}$ for all but short genetic maps.

Charlesworth (1990) calculates the rate of spread of a rare modifier by finding the difference between the mean and variance of the number of deleterious alleles in the individuals heterozygous for the modifier, and the bulk of the population $(\delta \bar{n}, \delta V)$. In terms of the linkage disequilibria between the modifier and the selected loci:

$$\delta \bar{n} = \sum_j \frac{C_{ij}}{p_i q_i}. \tag{A3.7a}$$

The variance in number of deleterious mutations consists of contributions from the individual loci, and from linkage disequilibria: $V = \bar{n} + \sum_{j,k} C_{jk}$. Hence:

$$\delta V = \delta \bar{n} + \sum_{j,k} \frac{C_{ijk}}{p_i q_i} \quad \text{(assuming } C_{ij} C_{ik} \ll C_{ijk}). \tag{A3.7b}$$

Substituting C_{ij} from eqn 11 into eqn A3.7a, setting $r_{ij} = 1/2$ for an unlinked modifier, substituting for $a_{k,\varnothing}$ from eqn A3.2a, and then using eqn A3.3:

$$\delta \bar{n} = \sum_{j,k} a_{k,\varnothing} \frac{C_{ijk}}{p_i q_i} = -(\alpha + \beta \bar{n}) \delta V = -\frac{U \delta V}{V}. \tag{A3.8}$$

This agrees with Charlesworth's eqn 21 for $\beta V \ll 1$. To find δV, substitute C_{ijk} from eqn 7b into eqn A3.7b, set $r_{ij} = 1/2$, $r_{ijk} = 3/4$ for unlinked loci, and substitute $\epsilon_{jk,\varnothing} = -\beta$ from eqn A3.2c:

$$\delta V = \delta \bar{n} + \frac{2\beta \delta r_{jk|i} V^2}{3}. \tag{A3.9}$$

This agrees with Charlesworth's eqn 23 for βV, $\beta \bar{n}$, $hs \ll 1$.

The selection coefficient on the modifier can now be found by summing eqn 10 over all loci. Noting that $\delta V \gg \delta \bar{n}$:

$$s_i = \frac{\Delta p_i}{p_i q_i} \approx \frac{\partial \log(\bar{W})}{\partial \bar{n}} \delta \bar{n} + \frac{\partial \log(\bar{W})}{\partial V} \delta V$$
$$\approx -(\alpha + \beta \bar{n}) \delta \bar{n} - \frac{(\beta - (\alpha + \beta \bar{n})^2)}{2} \delta V. \tag{A3.10a}$$

Substituting for δV from eqn A3.9, and then using eqn A3.3:

$$s_i \approx \beta \left(U^2 - \frac{\beta V^2}{3} \right) \delta r_{jk|i}. \tag{A3.10b}$$

The selection gradient on the modifier (Charlesworth's d) is just $d = s_i/\delta r_{jk|i}$. This formula agrees with eqn 18b (setting $\epsilon = -\beta$, and $V_2 = \beta^2 V^2/4$). Table 3b shows numerical values, which agree well with Charlesworth's (1990, table 4). As expected, agreement is closest for low net mutation rates.

Appendix 4: Fluctuating selection

Suppose that selection fluctuates $(\tilde{a}_{j,\varnothing}[t], \tilde{a}_{jk,\varnothing}[t]$ etc. in generation t). Then, from the approximation of eqns A1.4:

$$H_{jk}[t] \approx \sum_{\tau=0}^{\infty} \epsilon[t - \tau - 1](1 - r_{jk})^{\tau} \tag{A4.1a}$$

$$H_{ij}[t] \approx \sum_{\tau'=0}^{\infty} \tilde{a}_{k,\varnothing}[t - \tau' - 1] p_k q_k$$
$$H_{ijk}[t - \tau' - 1](1 - r_{ij})^{\tau'+1} \tag{A4.1b}$$

$$H_{ik}[t] \approx \sum_{\tau'=0}^{\infty} \tilde{a}_{j,\varnothing}[t - \tau' - 1] p_j q_j$$
$$H_{ijk}[t - \tau' - 1](1 - r_{ik})^{\tau'+1} \tag{A4.1c}$$

$$H_{ijk}[t] \approx -\delta r_{j,k|i} p_i q_i \sum_{\tau'=0}^{\infty} H_{jk}[t - \tau' - 1](1 - r_{ijk})^{\tau}$$

$$= -\delta r_{j,k|i} p_i q_i \sum_{\tau'=0}^{\infty} \sum_{\tau=0}^{\infty} \epsilon[t - \tau - \tau' - 2]$$

$$\times (1 - r_{jk})^{\tau} (1 - r_{ijk})^{\tau'}$$

$$= -\delta r_{j,k|i} p_i q_i \sum_{\tau=1}^{\infty} \epsilon[t - \tau - 1]$$

$$\times \left(\frac{(1 - r_{jk})^{\tau} - (1 - r_{ijk})^{\tau}}{r_{ijk} - r_{jk}} \right), \qquad (A4.1\,d)$$

where $\epsilon[t] = (2\tilde{a}_{jk,\varnothing}[t] - \tilde{a}_{j,\varnothing}[t] \tilde{a}_{k,\varnothing}[t])$. Equation A4.1$d$ neglects the last two terms in eqn A1.4f ($\tilde{a}_{k,\varnothing}(1 - r_{ij})$ $H_{ij}, \tilde{a}_{j,\varnothing}(1 - r_{ik}) H_{ik}$). These are negligible if linkage is loose, but may not be if linkage is tight ($\tilde{a}_{jk,\varnothing} \ll r_{ij}, r_{ik}, r_{jk} \approx \tilde{a}_{j,\varnothing}, \tilde{a}_{k,\varnothing} \ll 1$).

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