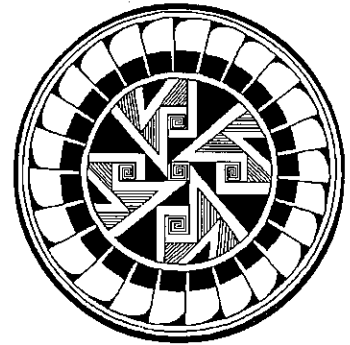


# Deleterious Mutations, Variable Epistatic Interac- tions, and the Evolution of Recombination

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## Abstract

In this paper, we examine the conditions that allow increased recombination to evolve in the presence of recurrent deleterious mutation. We focus on a three-locus model first studied by Feldman et al. (1980), which follows the dynamics of a modifier locus that alters the recombination rate between two loci subject to deleterious mutation. Although Feldman et al. (1980) indicated that increased recombination might be favored if there is diminishing-returns epistasis, we show that alleles that increase the recombination rate can only invade if there is synergistic epistasis between the loci under selection. Even with synergistic epistasis, evolution at the modifier locus will lead to *decreased* recombination if the modifier locus is loosely linked and epistasis is strong. Using multi-locus analysis of Barton (1995), we show that variability among loci in the sign and strength of epistasis also tends to select for decreased recombination. We conclude that the conditions that favor increased recombination in the presence of deleterious mutations are fairly restrictive, especially if, as seems likely, epistatic interactions are highly variable among loci.

## Introduction

By reducing genetic associations among loci, recombination can exert a strong influence on the genetic changes that occur within a population in response to selection (see recent reviews in Michod and Levin, 1988, and Kondrashov, 1993). In a variety of different selective models, recombination has traditionally been thought to have a beneficial influence on the efficiency of selection: recombination can generate beneficial genetic combinations (Fisher, 1930; Muller, 1932); it can assist in the tracking of fluctuating environments (Sturtevant & Mather, 1938; Hamilton, 1980); and it can hasten the elimination of deleterious mutations (Muller, 1964; Kimura & Maruyama, 1966; Feldman *et al.*, 1980; Kondrashov, 1982). In each of these cases, increased recombination may, under the appropriate conditions, have a selective advantage (Barton, 1995; Feldman *et al.*, 1996). As a general explanation for the evolution and maintenance of sex and recombination, the hypothesis that recombination aids in the elimination of deleterious mutations from the genome is especially compelling, since deleterious mutations pose such a common and persistent problem to all living organisms (Kondrashov, 1988; Kondrashov, 1993). In this paper, we will examine the evolution of recombination in a large population subject to recurrent deleterious mutations.

Mutations arise continuously despite the existence of several mechanisms that limit DNA damage and repair replication errors. Data on the rate of mutations across a genome are limited, but there is growing evidence that the average number of new mutations per diploid genome per generation,  $U$ , is at least  $\frac{1}{2}$  and perhaps substantially higher (Charlesworth *et al.*, 1990; Houle *et al.*, 1994; Keightley, 1994; Kondrashov & Crow, 1993; Mukai *et al.*, 1972). Although some of these mutations improve the functioning of an organism, the vast majority of mutations that affect fitness are deleterious. Purifying selection eliminates deleterious mutations, but the efficiency of this process depends upon several factors, including the epistatic interactions and recombination rates among mutant loci. In response to this process, the genetic system (e.g. linkage relationships) may itself evolve. One approach to modeling the evolution of the genetic system is to follow the dynamics of modifier alleles that alter some aspect of the genetic system such as the recombination rate or the mutation rate (Nei, 1967; Feldman, 1972; Feldman *et al.*, 1980; Brooks, 1988).

In this work, we will attempt to synthesize known results from three-locus and multi-locus models that examine the evolution of recombination at a modifier locus in response to recurrent deleterious mutations. This attempt has made us aware of an error in a previous

paper that examined the evolution of recombination in a three-locus model (Feldman *et al.*, 1980). This error is corrected in the appendix to this paper. We then use both the three-locus and multi-locus models to address the importance that variable epistatic interactions may have on the evolution of recombination. Previous multi-locus analyses of recombination in the presence of deleterious mutations tend to assume specific functional forms (e.g. truncational or quadratic fitness functions) for the way loci interact to effect fitness (Kondrashov, 1984; Charlesworth, 1990). In particular, these models assume that all loci interact in an equivalent manner with the strength of epistatic interactions depending only on the number of previous mutations and not on their nature. Although little is known about the distribution of epistatic interactions among loci, it is quite likely that much variation exists in the form and strength of these interactions (Whitlock *et al.*, 1995), with some loci interacting strongly and others weakly. We find that variation in epistasis tends to favor reduced recombination. Variable epistatic interactions thus limit the parameter space in which increased recombination evolves in response to recurrent deleterious mutation.

*The importance of epistasis* – If the fitness of an organism,  $W$ , were simply the product of the fitness,  $(1 - s_i)$ , of each mutation carried within the genome, i.e. if fitnesses were multiplicative and  $W = \prod_{i=1}^n (1 - s_i)$ , then selection would not create genetic associations between loci. Between two loci, for example, linkage disequilibrium is absent at an equilibrium between mutation and multiplicative selection (Feldman *et al.*, 1980). When genetic associations are absent, the level of recombination becomes immaterial since haplotypes cannot be further randomized (Maynard-Smith, 1968). This result breaks down, however, with epistatic interactions among loci (Eshel & Feldman, 1970). Epistasis (assumed in this paper to measure the departure from multiplicative selection) ensures that linkage disequilibrium will be maintained at a mutation-selection balance (Feldman *et al.*, 1980). These genetic associations allow indirect selection to act on modifier alleles that alter recombination rates.

Unfortunately, little empirical data exist about the epistatic relationships among random mutations. The data that best serve as an empirical guide come from experiments examining the effects of mutations on viability in *Drosophila melanogaster* (Mukai, 1964; Mukai, 1969; Mukai *et al.*, 1972). In these experiments, selection against deleterious mutations on the second chromosome was relaxed, allowing mutations to accumulate over time. From these experiments, Mukai *et al.* (1972) estimated that the rate of deleterious mutation on the second chromosome is approximately 0.12 per generation, leading to an estimate for the

rate of deleterious mutations across the diploid genome of  $U = 0.6$ . The average selection coefficient against mutations was  $\bar{s} \approx 0.038$ , with a mean dominance coefficient of  $\bar{h} \approx 0.21$ . In the Mukai *et al.* (1972) study, mean viability went down linearly over 40 generations, with no significant additive or multiplicative epistasis. In an earlier study that extended through 60 generations, however, Mukai (1969) observed a significant quadratic relationship among mutations, such that the deleterious effects of mutations were even greater in combination (“synergistic” or negative epistasis). Crow (1970) fitted a quadratic fitness function to these data, finding that the fitness of an individual bearing  $n$  homozygous mutations fitted the relation:

$$W(n) = 1 - an - bn^2 = 1 - 0.014n - 0.011n^2. \quad (1)$$

Here the quadratic term measures the extent of additive epistasis (departure from linear selection). To measure the extent of multiplicative epistasis among mutations that appear as heterozygotes, Charlesworth (1990) used Crow’s formula and Mukai’s data to find that approximately

$$\ln [W(n)] = -\alpha n - \frac{\beta}{2}n^2 = -0.002n - 0.0004n^2, \quad (2)$$

where  $\beta$  measures the departure from multiplicative selection. The general applicability of these fitness functions remains to be demonstrated; in particular, confirmation is needed that deleterious mutations do tend to interact synergistically and that the synergism is relatively weak, as in the quadratic functions (1) and (2).

A point to remember is that the quadratic fitness function was estimated using the *average* viability of seventy-two lines of *Drosophila melanogaster*. Each of these lines accumulated a different sequence of mutations, and it is likely that the actual fitness functions for the different lineages were quite different, with some sequences exhibiting stronger and others weaker epistatic interactions. Certainly, substantial variation in viability was observed among the lines (e.g. the mean viability after 60 generations was 0.51 with a standard deviation of 0.25), but this variability could have had several causes including (1) variation in the number of mutations accumulated (2) variance in the selective strength of these mutations (estimated by Keightley, 1994), and (3) variance in the epistatic interactions among them. No data currently exist on the variance in epistatic interactions among random mutations (although

experiments in progress will address this issue, T. Mackay pers. comm.). Nevertheless, the wide variety of ways in which gene products interact at a molecular level strongly suggests that epistatic interactions do vary dramatically depending on the loci involved (Whitlock *et al.*, 1995).

## Models for the evolution of recombination with epistasis

*Three locus model* – A three-locus model was developed by Feldman *et al.* (1980) to investigate the evolution of recombination between two loci subject to recurrent deleterious mutations. Although both haploid and diploid models were examined, we will focus on the simpler haploid model (the diploid model is briefly discussed at the end of the appendix). In this model, one locus  $M$  modifies the recombination rate between two viability loci ( $A$  and  $B$ ) as shown in Table 1. The gene order is assumed to be  $MAB$ , with the  $M$  locus located a distance,  $R$ , from the  $A$  locus. The model is unchanged if we assume that the modifier also changes the rate of recombination between itself and locus  $A$ .  $R$ , in this case, measures the rate of recombination between  $M$  and  $A$  in heterozygotes ( $Mm$ ) at the modifier locus (the rate of recombination between  $M$  and  $A$  in  $MM$  and  $mm$  homozygotes has no effect on the dynamics of the system). Both viability loci are subject to recurrent deleterious mutations (to  $a$  and  $b$ ) at a rate  $\mu$ . Selection acts against these mutations, such that the viabilities of  $AB$ ,  $Ab$ ,  $aB$ , and  $ab$  are 1,  $W_1 = 1 - s$ ,  $W_1 = 1 - s$ , and  $W_2 = (1 - s)^2 + \varepsilon$ , respectively. By assumption, additional mutations always decrease fitness ( $1 > W_1 > W_2$ ), and both  $\mu$  and  $s$  are the same for the  $A$  and  $B$  loci. When  $\varepsilon$  is negative, mutations have a more deleterious effect on fitness in combination than expected if fitnesses were multiplicative (“synergistic” or “negative” epistasis), whereas when  $\varepsilon$  is positive, mutations have a weaker effect on fitness when combined (“diminishing-returns” or “positive” epistasis). During reproduction, haploids fuse to form diploids, which then undergo recombination and mutation to regenerate the haploid stage. Censusing occurs at the adult haploid stage after selection.

With one modifier allele present,  $M$  say, the system approaches a two-locus mutation-selection balance. At this equilibrium, the linkage disequilibrium,  $\hat{D}$ , between the two viability loci has the same sign as  $\varepsilon$  (Feldman *et al.*, 1980). The stability of this equilibrium to invasion by a second modifier allele,  $m$ , was analysed by Feldman *et al.* 1980. One part of their analysis contains an error which is corrected in the appendix to this paper. Also in the appendix, we derive the stability conditions for weak epistasis and for free recombination between the modifier and the loci under direct selection. Here, we summarize the main

findings.

With either tightly linked modifiers ( $R$  small) or extremely weak epistasis, the sign of the epistasis governs evolution at the modifier locus. When epistasis is positive, modifiers that decrease the recombination rate are favored. When epistasis is negative, modifiers that increase the recombination rate are favored. Feldman et al. (1980) noted, however, that if linkage is sufficiently loose between the modifier locus and the loci under selection (such that  $R$  is above a critical value  $R^*$ ), a switch in stability can occur. Although their analysis implied that such a switch could occur with both positive and negative epistasis, the reanalysis presented in the appendix indicates that there is no switch in stability if epistasis is positive; that is, increased recombination is never favored with positive epistasis. When there is moderately strong *negative* epistasis, however, a critical value ( $R^*$ ) may be reached such that for all  $R > R^*$  increased recombination is no longer favored and modifiers that *decrease* recombination can invade. Consequently, for unlinked modifiers ( $R = \frac{1}{2}$ ), increased recombination is only favored if there is fairly weak negative epistasis. From equation (13) in the appendix, which assumes that the mutation rates are much smaller than the selection coefficients, increased recombination evolves when  $R = \frac{1}{2}$  only if

$$\frac{-s^2(3-s)}{(1-s)} < \varepsilon < 0. \quad (3)$$

As noted above, the results apply equally well if we assume that  $R$  is the modified recombination rate between  $M$  and  $A$  in  $Mm$  individuals. Thus, condition (3) must be met for the invasion of a modifier allele that, when heterozygous, produces free recombination between all loci, even if the modifier is tightly linked to the  $A$  locus in  $MM$  homozygotes. These results are consistent with an analysis of the three-locus special case of a more general multi-locus model in Barton (1995). Barton's method assumes that a modifier has only a slight effect on recombination rates ( $r_1 \approx r_2 \approx r_3$ ), an assumption which does not appear to be critical to the qualitative conclusions concerning the three-locus model.

*A heuristic explanation for the behavior of the three-locus model* – We have observed that recombination is never favored under positive (diminishing-returns) epistasis and is favored under negative (synergistic) epistasis when the modifier is tightly linked to the loci under selection or, if it is loosely linked, when epistasis is sufficiently weak. An explanation for these phenomena was provided by Barton (1995) and is adapted here. In this three-locus

model with purifying selection, the only genotype that is likely to give rise to descendants in the long-term is the fittest genotype ( $AB$ ), so that a genetic association with this genotype would cause a modifier to increase when rare. Negative epistasis creates an association between  $AB$  and modifiers that increase the recombination rate, because increasing the recombination rate produces the under-represented genotypes which are  $AB$  and  $ab$  with  $\hat{D} < 0$  (Eshel & Feldman, 1970). The opposite happens with positive epistasis;  $AB$  and  $ab$  are now over-represented in the population ( $\hat{D} > 0$ ) and a new modifier allele that increases recombination becomes associated with the single mutants  $Ab$  and  $aB$  that will, in the long-run, fail to leave offspring. Besides creating genetic associations, there is a second, immediate effect of changing the recombination rate: carriers of a new modifier allele have a different mean fitness than the rest of the population. With negative epistasis ( $\hat{D} < 0$ ), increasing recombination eliminates pairs of  $Ab$  and  $aB$  haplotypes (with an average fitness of  $2(1-s)$ ), producing pairs of  $AB$  and  $ab$  haplotypes (with an average fitness of  $1 + (1-s)^2 + \varepsilon$ ). Thus modifier alleles that increase recombination will have a higher fitness by eliminating the disequilibrium present in the equilibrium population only if  $2(1-s) < 1 + (1-s)^2 + \varepsilon$ , i.e. if epistasis is weak enough to be positive on an additive scale even though it is negative on a multiplicative scale ( $0 < \varepsilon + s^2$  and  $\varepsilon < 0$ ). With epistasis that is strong enough to be negative on both the multiplicative and additive scales ( $\varepsilon < -s^2$ ), modifier alleles that increase recombination suffer from an immediate reduction in the average fitness of their carriers. In this case, producing the best and the worst genotype by recombination leads to a lower fitness on average than having the intermediate genotypes. When the modifier is tightly linked to the major loci, its genetic association with the  $AB$  genotype is strong enough to overwhelm the decrease in mean fitness caused by eliminating linkage disequilibrium. Loosely linked modifiers have, however, only a weak genetic association with the fittest genotype, an advantage that is overwhelmed by the immediate fitness loss when, approximately, condition (3) holds. On the other hand, with positive epistasis ( $\hat{D} > 0$ ), increasing recombination produces the under-represented pair of haplotypes (now  $Ab$  and  $aB$ ), which always leads to a decrease in fitness since  $2(1-s) < 1 + (1-s)^2 + \varepsilon$  when multiplicative epistasis is positive. In this case, a modifier allele that increases recombination leads to genetic associations that are not in its favor and also leads to an immediate fitness decrease; these effects always act in concert (to favor decreased recombination) unlike the case with negative epistasis. Interestingly, this verbal argument also explains the behavior of modifiers of recombination in models with directional selection (Barton, 1995; Bergman *et al.*, 1995).

*A numerical example* – As a concrete example, we can use Mukai’s data (via equation (1)) to estimate the fitness of individuals carrying one mutation ( $W_1 = 0.975$ ) and two mutations ( $W_2 = 0.928$ ) so that  $s = 1 - W_1 = 0.025$  and  $\varepsilon = W_2 - W_1^2 = -0.023$ . Although equation (1) was developed using data on the fitness effects of homozygous mutants, we will assume that the fitness effects of haploid mutants are equivalent. Since  $\varepsilon$  does not obey condition (3), we expect decreased recombination to be favored when the modifier is loosely linked. In fact, for  $R$  greater than approximately 0.05, only modifiers that decrease recombination are able to invade (Figure 1).

In Mukai’s experiment, the average fitness loss caused by a mutation becomes more severe after further generations of mutation accumulation. If we examine a population of individuals that already carry five mutations, the baseline fitness of this population is  $W_5 = 0.655$  (from 1). The average selection coefficient against the next mutation is  $s = 1 - W_6/W_5 = 0.206$  and the epistasis observed upon the seventh mutation is  $\varepsilon = W_7/W_5 - (W_6/W_5)^2 = -0.076$ . In this case, epistasis is sufficiently weak relative to the strength of selection for  $\varepsilon$  to obey condition (3) and so increased recombination is favored for all values of  $R$  (Figure 2).

*Correspondence with polygenic models* – Many of the features observed in the three-locus model extend to the evolution of recombination in polygenic models (Kondrashov, 1984; Charlesworth, 1990). These models focus on the effects of recombination on the distribution of the number of mutations,  $n$ , carried by an individual. With synergistic epistasis, increased recombination is generally favored in the polygenic models, although decreased recombination evolves if (a) linkage is already loose, (b) epistasis is sufficiently strong, and (c) mutation rates are too low. Of these three caveats, the first two were also observed with the three-locus model. The dependence on the mutation rate, however, deserves some discussion.

In the three-locus model, the mutation rate did not have to be above a certain value for recombination to be favored. In fact, as long as the mutation rate is above zero and yet smaller than the selection coefficients, the stability conditions are fairly insensitive to the mutation rate (e.g. equation (11) in the appendix depends only weakly on  $\mu$ ). How is it, then, that the magnitude of the mutation rate comes to play such a critical role in the polygenic models? The polygenic models assume a large number of contributing loci, so that mutations at a locus are still rare even with high mutation rates. The main effect of a high mutation rate is to increase the average number of mutations carried by an individual

at different loci. This changes the selective context in which a new mutation finds itself (Kondrashov, 1984). To quantify the change in selective context, we can define the relative strength of epistasis as  $\varepsilon^* = \frac{\varepsilon}{s^2}$  where  $s = 1 - W_{n+1}/W_n$  and  $\varepsilon = W_{n+2}/W_n - (W_{n+1}/W_n)^2$ , using either fitness function (1) or (2). With synergistic epistasis (such that  $a, b, \alpha, \beta$  are all positive),  $\varepsilon^*$  falls rapidly from a maximum at  $n = 0$  and decreases, monotonically, towards an asymptote as  $n$  becomes large. Therefore, when an individual carries few mutations, a new mutation tends, on average, to have relatively strong interactions with other loci. Such strong epistatic interactions make it less likely for increased recombination to be favored, especially if linkage is already very loose (see example in Figure 1). If, however, the mutation rate is high and individuals already carry several mutations,  $\varepsilon^*$  is smaller, and modifiers that increase recombination are more likely to invade (as in Figure 2). The importance of the mutation rate in the polygenic models is therefore not related to the mutation rate, per se, but rather to the strength of epistatic interactions experienced by new mutations which depends strongly on how many other mutations are present within the genome.

*Variance in epistasis* – Condition (3) indicates that, when  $R = \frac{1}{2}$ , increased recombination is favored only for a small range of epistatic values. This point is further illustrated in Figures 3 and 4. Shown is the leading eigenvalue minus one,  $\lambda_L - 1$ , (obtained from a numerical evaluation of the stability matrix) as a function of the fitness of double mutants,  $W_2$  (note the different axes). Invasion of the new modifier allele (here an allele that increases recombination between  $A$  and  $B$  from 0.2 to 0.3) occurs only when  $\lambda_L - 1$  is positive. As can be seen from these graphs, increased recombination is favored over a very small parameter space when  $R = \frac{1}{2}$ . When  $W_1 = 1 - s = 0.9$  (Figure 3), the fitness of double mutants must lie between 0.78 and 0.81 for increased recombination to be favored. The situation is even less favorable for the evolution of recombination when selection is weaker. When  $W_1 = 1 - s = 0.99$  (Figure 4), the fitness of double mutants must lie between 0.9798 and 0.9801 for increased recombination to be favored.

The lower the recombination rate between the modifier and locus  $A$  the larger the range of  $W_2$  over which increased recombination will be favored. Even when  $R = 0.1$ , increased recombination is favored only if  $W_2$  lies between 0.65 and 0.81 when  $W_1 = 0.9$  (Figure 3) or between 0.9789 and 0.9801 when  $W_1 = 0.99$  (Figure 4). Similar graphs are observed for other modifier alleles (tested values include  $r_1 = 0$  with  $r_2 = 0.1$ ,  $r_1 = 0$  with  $r_2 = 0.01$ ,  $r_1 = 0.2$  with  $r_2 = 0.4$ ,  $r_1 = 0.2$  with  $r_2 = 0$ ), although the curves for  $R = 0.01$  and  $R = 0.1$

vary. The graphical analyses suggest that, as an approximate rule of thumb,  $R$  must be less than  $s$  for there to be a large range of values of  $W_2$  in which evolution favors increased recombination. When this range is small, however, the evolution of recombination may be quite sensitive to variation in the strength of synergistic epistasis.

When epistatic interactions vary among loci, some epistatic interactions will be too strongly negative or will be positive and will fall out of the range in which recombination is favored. Even if the average pair-wise epistasis favors recombination, many interactions may not. This indicates that variability in the strength of interactions among loci will tend to reduce the advantage of recombination. We can use the recent analysis of Barton (1995) to estimate the role of variable epistatic interactions on the evolution of recombination in a multi-locus model. Barton (1995) derived a formula for the selection coefficient ( $s_i$ ) acting upon a modifier of recombination at locus  $i$ , assuming that the effects of the modifier on recombination are weak (all terms used in this equation are defined in Table 2):

$$s_i \approx -\frac{1}{2} n^2 \mathbb{E}[\delta r_{jk} \varepsilon_{jk} \mu_j \mu_k] \mathbb{E}\left[\frac{1}{r_{ijk} r_{jk}} \left(\frac{1}{r_{ik}} + \frac{1}{r_{ij}} - 1\right)\right] \\ - \frac{1}{2} \sum_{|S|>1} \delta r_{|S|} V_{|S|} \mathbb{E}\left[\frac{1}{r_{iS} r_S}\right]. \quad (4)$$

The first half of equation (4) quantifies the amount of indirect selection on a modifier that arises from changing the efficiency of selection (Barton, 1995). Recombination can increase the efficiency of selection by creating genotypes with very many and very few mutations if these genotypes are less common than expected (which they will be if there is negative epistasis). The second half of equation (4) quantifies the immediate fitness consequences to a modifier that arise from changed genetic associations among sets of loci (Barton, 1995). The second half of (4), as defined, always selects for decreased recombination; those genetic combinations that are more common than expected because selection against them is weaker than expected are destroyed by recombination. Assuming weak selection and a weak modifier, this formula is accurate as long as the expected recombination rate between loci is not very small, although Barton discusses reasonable approximations for this case.

Any variability between loci in the amount of epistasis contributes only to the second half of equation (4), which, as noted by Barton, always favors decreased recombination. To simplify matters, assume that the mutation rate and the amount by which recombination is

modified ( $\delta r_{jk}$ ) are independent of the strength of epistasis at the relevant loci. Denote the average mutation rate by  $\bar{\mu}$  and the average  $\delta r_{jk}$  between pairs of loci by  $\bar{\delta r}$ . Equation (4) then becomes

$$s_i \approx -\frac{1}{2} \bar{\delta r} (n\bar{\mu})^2 \mathbb{E}[\varepsilon_{jk}] \mathbb{E}\left[\frac{1}{r_{ijk}r_{jk}} \left(\frac{1}{r_{ik}} + \frac{1}{r_{ij}} - 1\right)\right] - \frac{1}{2} \bar{\delta r} V_2 \mathbb{E}\left[\frac{1}{r_{ijk}r_{jk}}\right] - \frac{1}{2} \sum_{|S|>2} \delta r_{|S|} V_{|S|} \mathbb{E}\left[\frac{1}{r_{iS}r_S}\right]. \quad (5)$$

$V_2$  is approximately equal to

$$V_2 \approx n^2 \mathbb{E}[\varepsilon_{jk}^2 p_j q_j p_k q_k] \approx (n\bar{\mu})^2 \mathbb{E}\left[\frac{\varepsilon_{jk}^2}{\tilde{a}_{j,\phi} \tilde{a}_{k,\phi}}\right], \quad (6)$$

where  $\tilde{a}_{j,\phi}$  is a measure of the strength of selection at locus  $j$ , which equals the standard selection coefficient  $s_j$  when selection is weak (see Barton, 1995, for further details). The strength of selection at the modifier locus can therefore be written as

$$s_i \approx -\frac{1}{2} \bar{\delta r} (n\bar{\mu})^2 \mathbb{E}\left[\frac{1}{r_{ijk}r_{jk}} \left(\varepsilon_{jk} \left(\frac{1}{r_{ik}} + \frac{1}{r_{ij}} - 1\right) + \frac{\varepsilon_{jk}^2}{\tilde{a}_{j,\phi} \tilde{a}_{k,\phi}}\right)\right] - \frac{1}{2} \sum_{|S|>2} \delta r_{|S|} V_{|S|} \mathbb{E}\left[\frac{1}{r_{iS}r_S}\right], \quad (7)$$

For a modifier that increases recombination to invade, the expectation in the first half of this equation must be negative. This is not a sufficient condition since the last sum in the equation always favors decreased recombination, but there are reasons to believe this factor may be small (Barton, 1995). When linkage between the modifier and loci under selection is fairly tight, increased recombination will be favored whenever epistasis is on average negative, although technically the approximations leading to equation (4) are violated when recombination rates are too small (see Barton 1995). With a loosely linked modifier, however, variably epistatic interactions will make it less likely for recombination to be favored, especially when selection is weak. If there is little covariance between the strength of selection and the amount of epistasis (a fairly unlikely assumption), an unlinked modifier allele