vol. 154, no. 4 the american naturalist october 1999

The Red Queen and Fluctuating Epistasis: A Population Genetic Analysis of Antagonistic Coevolution

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Submitted August 3, 1998; Accepted May 6, 1999

abstract: Host-parasite coevolution has been shown to provide an advantage to recombination, but the selective mechanism underlying this advantage is unclear. One possibility is that recombination increases the frequency of advantageous genotypes that are disproportionately rare because of fluctuating epistasis. However, for this mechanism to work, epistasis for fitness must fluctuate over a very narrow timescale: two to five generations. Alternatively, recombination may speed up the response to directional selection by breaking up linkage disequilibria that decrease additive genetic variance. Here we analyze the results of a numerical simulation of host-parasite coevolution to assess the importance of these two mechanisms. We find that linkage disequilibria may tend to increase, rather than decrease, additive genetic variance. In addition, the sign of epistasis changes every two to five generations under several of the parameter values investigated, and epistasis and linkage disequilibrium are frequently of opposite signs. These results are consistent with the idea that selection for recombination is mediated by fluctuating epistasis. Finally, we explore the conditions under which an allele causing free recombination can spread in a nonrecombining host population and find general agreement between the predictions of a population genetic model of fluctuating epistasis and our simulation model.

Keywords: coevolution, epistasis, linkage disequilibrium, recombination, Red Queen, fluctuating selection.

Because the primary consequence of recombination is to break up statistical associations among loci, recombination is only likely to be favored in populations that have disadvantageous linkage disequilibria (Barton 1995; Barton and Charlesworth 1998; Otto and Michalakis 1998). Linkage disequilibria may be disadvantageous in two ways. First, there may be a situation of rare advantage, in which disproportionately fit genotypes are disproportionately uncommon. In this case, recombination increases the frequency of these genotypes and directly increases the mean fitness of recombinant offspring. This circumstance is only likely to result from natural selection if the sign of epistasis for fitness changes every few generations such that combinations of alleles that are advantageous in one generation quickly become disadvantageous (Charlesworth 1976; Barton 1995). We refer to this mechanism as the "fluctuating epistasis" mechanism. Second, linkage disequilibria may slow down the response to selection by decreasing the additive genetic variance in the population (Barton 1995), in which case recombination increases fitness indirectly by increasing the rate of response to selection. Since this mechanism requires sustained directional selection to provide an advantage to recombination, we refer to it as the "directional selection" mechanism (following Barton 1995).

Population genetic analyses have suggested that the first mechanism, fluctuating epistasis, is unlikely to confer an advantage to sex or to select for increased recombination (Charlesworth 1976; Barton 1995). The reason is that fluctuating epistasis leads to selection for recombination only if the sign of epistasis for fitness changes over a small number of generations (Charlesworth 1976; Barton 1995). In other words, genotypes having high fitness in one generation must become unfit within the next few generations. More specifically, Barton (1995) has suggested that the sign of epistasis must change every two to five generations (based on a two-locus, two-allele model) for selection to favor recombination. Such a rapid change seems very unlikely for fluctuations caused by abiotic environmental factors (Barton 1995; Kondrashov and Yampolsky 1996). Antagonistic coevolution, however, may provide a mechanism by which rapid fluctuations are possible. For example, Nee (1989) has shown that host and parasite genotype frequencies are expected to cycle 90° out of phase. This produces fluctuations in the sign of epistasis, and, depending on the strength of selection against infection, the fluctuations may occur on the appropriate time-

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Am. Nat. 1999. Vol. 154, pp. 393–405.

scale. Since allele frequencies do not change in Nee's model, however, directional selection is impossible; therefore, it is not possible to assess the relative contributions of the directional selection and fluctuating epistasis models in providing an advantage to recombination under antagonistic coevolution (Barton 1995; Otto and Michalakis 1998). Thus, an important remaining question is, is the advantage to recombination caused by fluctuating epistasis, or is coevolution simply a particularly baroque mechanism to generate directional selection (Barton 1995; Barton and Charlesworth 1998)?

Here we examine a model of host-parasite coevolution in order to assess the relative importance of directional selection and fluctuating epistasis in selecting for some level of recombination. In order to quantify the potential effects of directional selection, we track several variance components of the natural logarithm of fitness: V_1', the additive variance caused by log fitness at individual loci (i.e., the strength of directional selection); v_1, the change in additive variance caused by linkage disequilibria; and V_2', the variance caused by epistasis (Barton 1995). In order for directional selection to provide an advantage to recombination, two conditions must be satisfied: directional selection must be strong enough to overcome the effects of epistasis (i.e., $V_1' > V_2'$), and linkage disequilibria must decrease additive genetic variance ($v_1 < 0$) (Barton 1995). We show that antagonistic coevolution leads to fluctuations in these variance components such that epistatic variance is periodically larger than additive variance, and linkage disequilibria may either increase or decrease the additive genetic variance. Thus, selection for recombination caused by antagonistic coevolution does not appear to be strictly caused by directional selection.

To quantify the potential importance of fluctuating epistasis, we examine the rate of fluctuations in the sign of epistasis and linkage disequilibrium. We show that when parasites are sufficiently virulent and/or common, the autocorrelation in epistasis becomes negative at a time lag of two to five generations; in other words, on average, the sign of epistasis changes every second, third, fourth, or fifth generation (as required by Barton's 1995 model). In addition, epistasis and linkage disequilibrium are periodically of opposite signs, and the proportion of time during which this occurs increases with the strength of selection in the host.

Finally, we alter the numerical simulation to consider the fate of a rare allele causing free recombination in the host population. The recombination allele increases in frequency when parasite-mediated selection on the host is intermediate to strong. The conditions under which the modifier allele can spread are slightly broader than those that cause the sign of epistasis to change within two to five generations, but in general these two sets of conditions closely correspond to each other.

Model

We examined recursion equations originally designed to explore the effects of migration on coevolution (Lively 1999). The model assumes that the success of a haploid parasite at infecting its haploid host is determined by the match between two diallelic "self" loci in the host and a complementary set of two diallelic "mimic" loci in the parasite. If the parasite matches the host at every locus, it can successfully infect the host and produce offspring, reducing the fitness of the host in the process ("matching alleles model," Hamilton 1980; Frank 1996*b*). If the parasite fails to match the host at any locus, it is killed by the host's self/nonself recognition system. With two alleles per locus, this model is also equivalent to one in which the parasite can only infect if it does not match the host at any locus ("inverse matching alleles model," Frank 1996*b*; Otto and Michalakis 1998). Before reproduction, mutation at each mimic locus occurs with some fixed probability in the parasite. Mutation in parasite alleles is necessary to ensure that no alleles are lost from the population, although this role could also be filled by migration. Since oscillations in the host population are less severe, no mutation parameter is required. Thus, the sequence of events for both the host and the parasite is reproduction → infection → selection → (mutation/migration) → reproduction.

Recursion Equations

The fitness of a host "self" genotype S is the proportion of that genotype that remains uninfected times its fitness plus the proportion infected times its fitness. The fitness of uninfected individuals is 1, the fitness of infected individuals is $1 - V$, where V is the virulence of the parasite. The probability of becoming infected is determined by the frequency of the complementary parasite "mimic" genotype and the number N of parasite propagules encountered by each host. The postselection frequency of a parasite mimic genotype M is simply its probability of successfully infecting a host. Thus, the frequencies of host self and parasite mimic genotypes after selection (p_S' and p_M') in generation t are

$$p_S'(t) = p_S(t)([1 - p_M(t)]^N + (1 - V)\{1 - [1 - p_M(t)]^N\}),$$
$$p_M'(t) = p_S(t)\{1 - [1 - p_M(t)]^N\}, \tag{1}$$

where p_S and p_M are the preselection frequencies of host

self and parasite mimic genotypes, respectively. For the following analyses, all values of p' are normalized so the frequencies sum to 1. For the purpose of this analysis, zero recombination was assumed, so the host genotype frequencies after reproduction are the normalized frequencies after selection. Since the parasite mimic loci are subject to mutation just before reproduction, the frequency of a mimic locus after reproduction is

$$p_M(t+1) = p'_M(t)(1-u)^2 + p'_M(t)(u)(1-u) + p'_{M2}(t)(u)(1-u) + p'_{M3}t(t)u^2, \quad (2)$$

where u refers to the mutation rate, p'_x refers to the post-selection frequency of genotype x, *M1* and *M2* refer to the genotypes that differ from *M* at only one locus, and *M3* refers to the genotype that differs from *M* at both loci. The variable u was set to 10^{-5} in all runs of the model. Values of *V*, the effect of parasite infection on host fitness, ranged from 0.2 to 1. These values may imply selection coefficients that are high compared with some population genetic models (e.g., Barton 1995). Though this constitutes a violation of the assumptions of the population-genetic models, these values for parasite virulence may be realistic for many host-parasite interactions. For example, digenetic trematodes often consume the reproductive organs of their first intermediate host, effectively sterilizing them. Such "parasitic castration" is also known for the fungal pathogens of grasses and the crustacean parasites of crabs (review in Kuris 1974). However, in general, the effects of infection in natural host populations are poorly known.

Analysis

Populations were allowed to evolve for 100 generations to reach quasi-equilibrium (i.e., until a stable limit cycle was established), then genotype frequencies and fitnesses, in both the host and the parasite populations, were measured every generation for the next 400 generations. The fitness of genotype or allele i, relative to the mean fitness, is defined as

$$\frac{W_i}{\overline{W}} = \frac{p'_i}{p_i}, \quad (3)$$

where p_i is the frequency of the genotype or allele before selection, and p'_i is the frequency after selection.

Linkage disequilibrium was calculated in the standard fashion to give the deviation of the frequency of genotype *ab* from that expected under random assortment (Felsenstein 1965):

$$D = p_{ab} - p_a p_b,$$

$$D = p_{AB}p_{ab} - p_{Ab}p_{aB}. \quad (4)$$

Epistasis was calculated as the deviation of the actual log fitness of genotype *ab* from its expected log fitness under multiplicative selection (Felsenstein 1965):

$$E = \ln(W_{ab}) - \ln(W_a W_b),$$

$$E = \ln\left(\frac{W_{AB}W_{ab}}{W_{Ab}W_{aB}}\right). \quad (5)$$

The important properties of this function are that it is negative if the *ab* (or *AB*) genotype's fitness is lower than expected and positive if the genotype's fitness is higher than expected and that it is symmetrical, in that the absolute value of E is the same for a genotype that is a factor f times as fit as expected as for a genotype that is a factor $1/f$ as fit as expected.

We calculated the components of genetic variance for fitness in the host each generation using the equations of Barton (1995):

$$V'_1 = [a'^2_A p_a(1-p_a) + a'^2_B p_b(1-p_b)], \quad (6a)$$

$$v_1 = 2a_A a_B D, \quad (6b)$$

$$V'_2 = E^2 p_a(1-p_a)p_b(1-p_b), \quad (6c)$$

where V'_1 gives the total contribution of individual loci to the additive genetic variance in the natural log of fitness, v_1 gives the additional contribution of linkage disequilibria to the additive variance, and V'_2 gives the epistatic variance (Barton 1995). The variable p_i gives the frequency of allele i, a_I denotes the additive selection coefficient for locus I (Barton and Turelli 1991), and $a'_I = a_I - a_I^2/2$ (Barton 1995). We calculated the selection coefficients a_I using the methods described in Barton and Turelli (1991):

$$a_A = \frac{W_{aB} - W_{AB} + p_b(W_{ab} - W_{aB} - W_{Ab} + W_{AB})}{\overline{W}},$$

and

$$a_B = \frac{W_{Ab} - W_{AB} + p_a(W_{ab} - W_{aB} - W_{Ab} + W_{AB})}{\overline{W}}$$

(see appendix).

In order to quantify the timescale over which the sign of epistasis changes, we calculated autocorrelations between epistasis for host genotypes one to 10 generations apart. A negative autocorrelation for a given time lag T

implies that, on average, epistasis measured T generations apart is of a different sign. The minimum value of T at which the autocorrelation is negative can be seen as the mean number of generations over which epistasis changes sign. According to Barton (1995), if this value is between two and five for a two-locus two-allele model, increased recombination has an advantage because of fluctuating epistasis.

Finally, in order to ascertain when epistasis and linkage disequilibrium are of opposite signs, we calculated the value of $E \times D$. When this value is negative, epistasis and linkage disequilibrium are of opposite signs. Under such circumstances, disproportionately fit offspring are rare, and common offspring are disproportionately unfit. Recombinant offspring therefore enjoy an immediate fitness benefit as these linkage disequilibria are broken up. The product $E \times D$ is expected to be positive under directional selection (Felsenstein 1965); it must be at least periodically negative for recombination to be advantageous under fluctuating epistasis (Barton 1995).

Introducing a Recombination Modifier

In order to determine the conditions under which increased recombination is favored and to compare those conditions with the predictions of Barton (1995), we introduced a modifier allele causing free recombination into a nonrecombining host population. The modifier allele was introduced at a frequency of 0.01 at generation 100 after the populations had reached a stable limit cycle. Two haplotypes are assumed to come together at random, and recombination is determined by the genotype of this transient diploid zygote at a recombination locus. The free-recombination allele R is assumed to be dominant to the nonrecombination allele r, so that only one copy of the R allele is required to code for free recombination. Thus, R haplotypes can arise from the fusion of two R haplotypes or of an R haplotype with an r haplotype. Similarly, r haplotypes can arise from the fusion of two r haplotypes or of an R haplotype with an r haplotype. Thus, the frequencies of haplotype xyR (i.e., the haplotype with parasite interaction alleles x and y and recombination allele R) and haplotype xyr (i.e., parasite interaction alleles x and y and recombination allele r) are

$$\begin{aligned} p_{xyR}(t+1) &= p_R^2\left(p_{x|R}p_{y|R} + \frac{D_{xy|R}}{2}\right) + (1/4)p_R(1-p_R) \\ &\quad \times [(p_x + p_{x|r})(p_{y|R} + p_{y|r}) + D_{xy|R} + D_{xy|r}], \\ p_{xyr}(t+1) &= (1-p_R)^2 p_{xy|r} + (1/4)p_R(1-p_R) \\ &\quad \times [(p_{x|R} + p_{x|r})(p_{y|R} + p_{y|r}) + D_{xy|R} + D_{xy|r}], \end{aligned} \tag{7}$$

where p_R is the frequency of the R allele, $p_{i|j}$ is the frequency of parasite interaction allele i among individuals carrying recombination allele j, $p_{xy|r}$ is the frequency of parasite interaction haplotype xy among individuals carrying recombination allele r, and $D_{xy|j}$ is the linkage disequilibrium associated with genotype xy among individuals carrying recombination allele j (i.e., $p_{xy|j} - p_{x|j}p_{y|j}$). All of these frequencies (p) refer to normalized frequencies after selection in the current generation.

Results

Directional Selection

In order to determine whether directional selection is an important factor in selecting for recombination under antagonistic coevolution, we calculated the components of genetic variance for host log fitness over 50 generations for a variety of parameter values. Additive genetic variance must outweigh epistatic variance, and linkage disequilibria must decrease the additive variance for directional selection to provide an advantage to recombination. Therefore, we calculated the relative strength of additive and epistatic variance, $\ln(V_1'/V_2')$, and the contribution of linkage disequilibria to additive variance, v_1 (fig. 1). When the first quantity is positive, directional selection outweighs epistasis; when the second quantity is negative, linkage disequilibria slow down the response to natural selection. Both of these conditions must exist for directional selection to provide an advantage to recombination.

Several important patterns emerge from an examination of these variance components. First, the relative strengths of additive and epistatic variance (i.e., $\ln[V_1'/V_2']$), fluctuate (fig. 1, *top panel*). This result suggests that periods during which directional selection is strong alternate with periods during which it is outweighed by epistasis. Second, the relative strength of directional selection appears to increase (i.e., $\ln[V_1'/V_2']$ becomes positive more frequently) as the effects of parasites on host fitness increase. Third, the contribution of linkage disequilibria to additive variance (v_1) fluctuates from positive (increasing the response to selection) to negative (decreasing the response to selection). Finally, as the effect of infection increases, this quantity (v_1) becomes positive more frequently and reaches greater magnitude when positive than when negative. In other words, linkage disequilibria tend to speed up the response to selection more than they slow it down. Indeed, for $N = 1$, $V = 0.8$ (fig. 1*C*), linkage disequilibria almost never slow down the response to selection and do so only very slightly when they do slow.

Overall, the patterns in variance for fitness suggest that directional selection is unlikely to provide an advantage to recombination under antagonistic coevolution. When

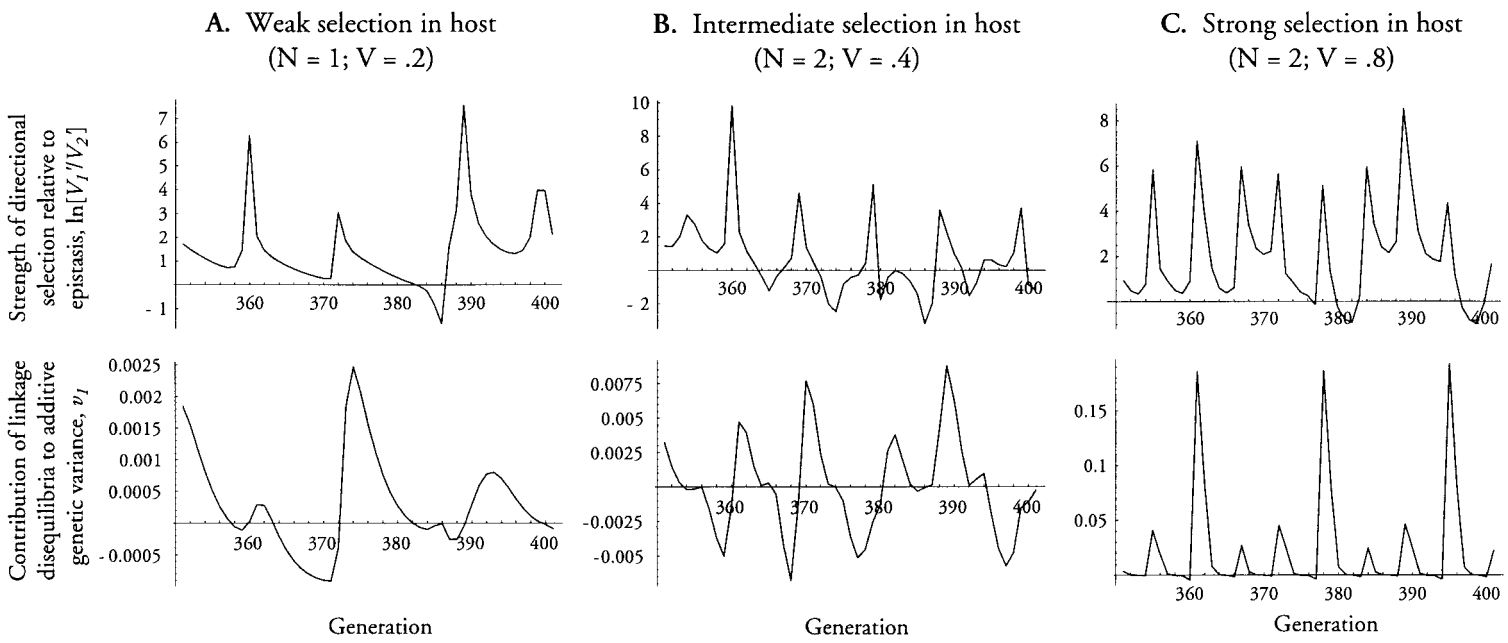
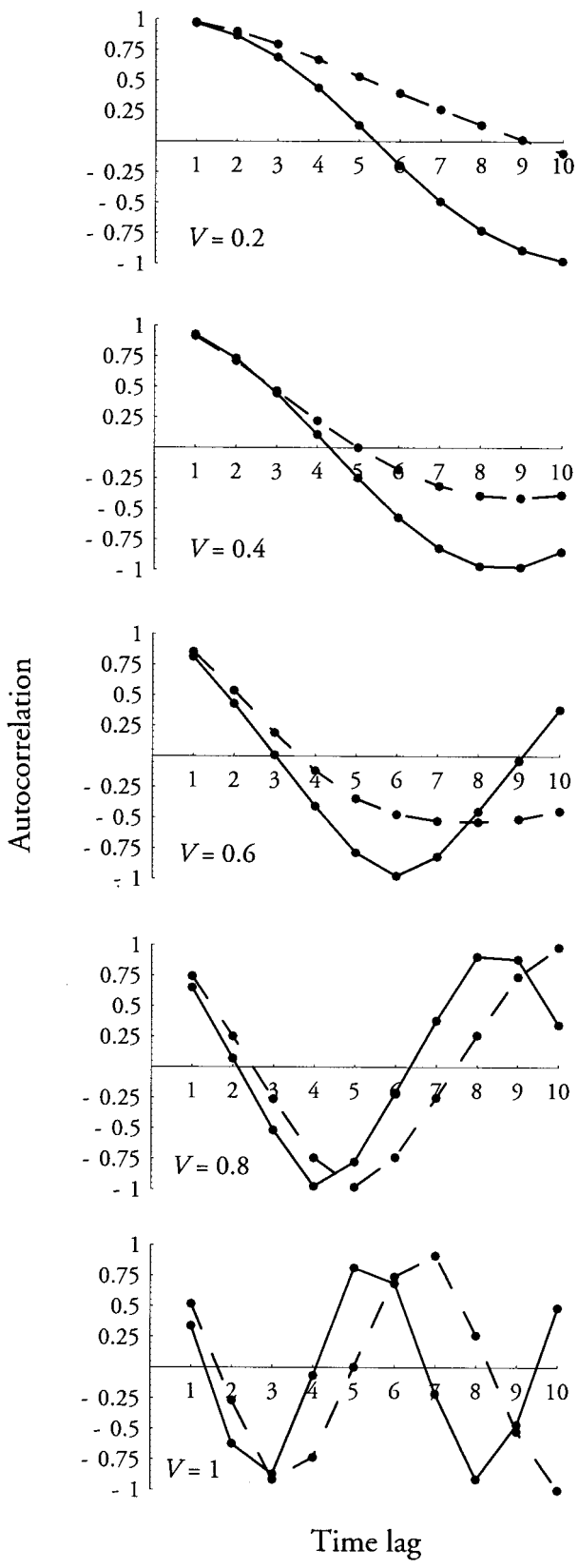


Figure 1: Components of genetic variance for log(fitness) in the host over 50 representative generations, for three selection regimes. *Top row*, Strength of directional selection relative to epistasis, $\ln(V_1'/V_2')$. If this quantity is positive, directional selection (measured as additive genetic variance in log[fitness]) outweighs epistasis; if it is negative, epistasis outweighs directional selection. For directional selection to provide an advantage to recombination, it must be positive. *Second row*, Contribution of linkage disequilibria to additive genetic variance, v_1. If this quantity is positive, linkage disequilibria speed up the response to directional selection; if it is negative, they slow down the response to selection. For directional selection to provide an advantage to recombination, $\ln(V_1'/V_2')$ must be positive and v_1 must be negative.



infection has intermediate effects on fitness (fig. 1*B*), directional selection may periodically provide an advantage to recombination: there are periods of time during which directional selection is relatively strong (i.e., $\ln[V_1'/V_2' > 0]$) and linkage disequilibria concurrently decrease the rate of response to selection ($v_1 < 0$), though this occurs only rarely. When infection has large effects on fitness (fig. 1*C*), linkage disequilibria effectively never decrease the rate of response to selection. Taken together, these results suggest that although the strength of directional selection increases with increasing parasite effect, it provides less of an advantage to recombination because linkage disequilibria tend to speed up the response to selection rather than slow it down. Thus, when the effects of parasites are large, the directional selection mechanism cannot provide an advantage to recombination. Even under intermediate parasite effect, the advantage to recombination through directional selection is likely to be relatively minor because the required conditions exist only infrequently.

Fluctuating Epistasis

Rate of Fluctuations. As the strength of selection in the host increases, by increasing either the virulence (V) of the parasite or the number of parasite propagules (N) encountered by each host individual, the average number of generations required for the sign of epistasis to change decreases (fig. 2). When each host is exposed to only one parasite propagule ($N = 1$), the sign of epistasis changes within five generations (Barton's [1995] upper bound), provided infection reduces host fitness by 60% or more ($V \geq 0.6$; fig. 2). For two parasite propagules per host ($N = 2$), the sign of epistasis changes within five generations if infection reduces host fitness by 40% or more ($V \geq 0.4$; fig. 2). More intense selection by the parasite results in a more rapid change in the sign of epistasis for fitness (fig. 2), but even when infection causes complete sterilization of the host ($V = 1$), the period of change is not less than two generations (Barton's lower bound). Although not analyzed, the parasite population must cycle with the same period. Thus, parasite virulence affects the period over which the sign of epistasis fluctuates in both

Figure 2: Temporal autocorrelations in epistasis in the host for five levels of parasite virulence, *V*. The time lag represents the number of generations between the measurements in each pair (i.e., the autocorrelation at a time lag of 3 is the correlation between epistasis measured three generations apart). The first point at which the autocorrelation becomes egative represents the average number of generations over which the sign of epistasis changes. *Dashed lines*, Number of parasite propagules per host $N = 1$; *solid lines*, $N = 2$. Barton (1995) predicts selection for recombination when the sign of epistasis changes between two and five generations.

the host and the parasite, and it is sufficient to meet Barton's conditions for selection for recombination provided virulence is moderate to strong.

The Sign of Epistasis and Linkage Disequilibrium. For fluctuating epistasis to provide an advantage to recombination, epistasis and linkage disequilibrium must be of opposite signs (Barton 1995). To quantify this, we calculated the value of $E \times D$ for each generation (fig. 3). Two important patterns emerge from this analysis. First, the value of $E \times D$ fluctuates from positive to negative, implying that epistasis and linkage disequilibrium are periodically of opposite signs; the period of these fluctuations decreases as the strength of selection in the host increases. Second, $E \times D$ becomes increasingly negative with increasing parasite-mediated selection on the host. Under stronger selection, both the relative amount of time during which $E \times D$ is negative and the relative magnitude of negative values increase.

Spread of a Recombination Modifier

Alleles causing free recombination were found to increase in frequency when infection decreased the fitness of the host by 0.4 or more ($V \geq 0.4$) for $N = 1$ or 2 (fig. 4). This is congruent with the rate of change in epistasis (fig. 2): where the sign of epistasis changes every two to five generations (i.e., when $N = 1$ and $V \geq 0.6$ or when $N = 2$ and $V \geq 0.4$), the modifier allele can spread as predicted by Barton (1995). The one exception to this congruence was found when $N = 1$ and $V = 0.4$. Under these parameter values, the sign of epistasis does not change until the sixth generation, but the modifier does increase in frequency. It is likely that these parameter values merely constitute a "boundary condition": the autocorrelation in epistasis is almost negative at the fifth generation (fig. 2), and the modifier spreads only slightly (fig. 4). It is also possible, however, that the process of antagonistic coevolution violates the assumptions of the genetic model and provides a slightly broader set of conditions under which recombination can spread. Our model explicitly violates two assumptions of Barton's (1995) model: the high parasite virulence violates the weak selection assumed in Barton's model, and the recombination modifier introduced causes free recombination, whereas Barton's (1995) model assumes the modifier has very small effect. In addition, the fluctuations in the relative strength of additive and epistatic variance arising from coevolution (fig. 1) may provide an advantage to recombination through both directional selection and fluctuating epistasis. Nonetheless, the correspondence between conditions that favor the spread of increased recombination in our model and Barton's (1995) predictions is striking.

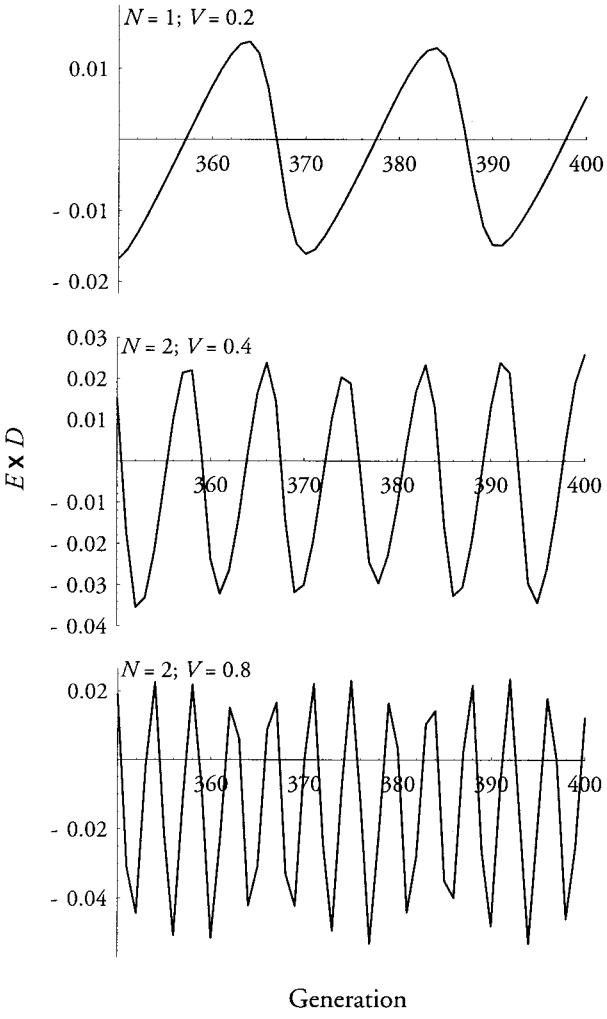


Figure 3: Value of $E \times D$ in the host over 50 representative generations for three selection regimes. *Top panel*, Parasites of minor effect; epistasis fluctuates too slowly to select for recombination. *Middle and bottom panels*, Parasites of intermediate to strong effect; epistasis fluctuates within the range required to select for recombination (Barton, 1995; fig. 2). When $E \times D$ is negative, epistasis and linkage disequilibrium are of opposite signs and recombinant offspring enjoy an immediate fitness advantage.

When the recombination modifier increases in frequency, it does not reach a strict equilibrium; rather, the frequency of the modifier oscillates around an attractor (fig. 4). These oscillations correspond with changes in the sign of $E \times D$. When $E \times D < 0$, the recombination allele increases in frequency; when $E \times D > 0$, it decreases in frequency. Since E and D must be of opposite signs ($E \times D < 0$) for fluctuating epistasis to provide an advantage to recombination, this result suggests strongly that it is fluctuating epistasis per se that selects for recombination under antagonistic coevolution.

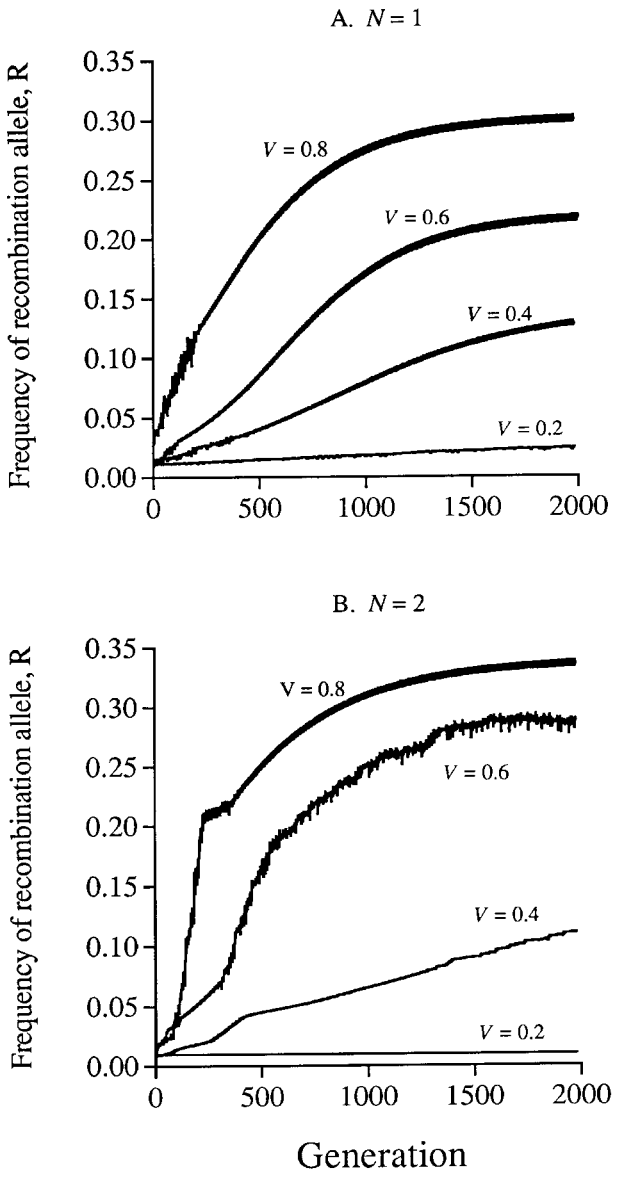


Figure 4: Spread of an allele causing free recombination (*R*) in a nonrecombining population under a variety of selection parameters. The initial frequency of the *R* allele was 0.01. Note that the frequency of the *R* allele fluctuates within a generally increasing trajectory for most parameter values. Also note that the conditions for spread of the *R* allele are slightly less restrictive than those suggested by Barton (1995); that is., the modifier can spread when $N = 1$ and $V = 0.4$, despite the fact that selection appears to fluctuate too slowly under these conditions (see fig. 2).

Discussion

Barton (1995) suggested that recombination can only increase under fluctuating epistasis when the sign of epistasis changes every few generations. Our results suggest that antagonistic coevolution may produce these conditions. This pattern can be understood by closely examining the patterns of epistasis and linkage disequilibrium in both the host and the parasite (fig. 5). The process of coevolution can be broken down into four components: parasite linkage disequilibrium, host epistasis, host linkage disequilibrium, and parasite epistasis. Each of these components affects the next in such a way that linkage disequilibrium in both the host and the parasite changes sign every few generations. Negative linkage disequilibrium in the parasite causes positive epistasis in the host (meaning that if a genotype is underrepresented in the parasite population, hosts of that genotype are unlikely to be infected and, therefore, have disproportionately high fitness). This positive epistasis in the host leads, after a time lag, to positive linkage disequilibrium in the host. Positive linkage disequilibrium in the host, in turn, causes positive epistasis in the parasite (so if a genotype is overrepresented in the host population, parasites mimicking that genotype will be more successful at infecting and, therefore, have disproportionately high fitness). At this point, the cycle continues but in the opposite direction: positive linkage disequilibrium in the parasite causes negative epistasis in the host, leading to negative linkage disequilibrium in the host, which leads back to negative epistasis in the parasite.

This four-step feedback loop demonstrates how antagonistic coevolution may lead to a situation in which the stringent conditions of Barton (1995) are met. Since linkage disequilibria do not build up immediately, there is a time lag between the moment at which epistasis changes sign and the moment at which linkage disequilibrium changes sign (fig. 5). During this time lag, epistasis and linkage disequilibrium are of opposite signs (fig. 3). These linkage disequilibria are maladaptive because fit genotypes are rare and common genotypes are unfit. Thus, recombination offers an immediate fitness benefit during these periods by breaking up these linkage disequilibria. If these periods occur frequently enough, recombination can increase because there is a net benefit to breaking up linkage disequilibria. As the rate of cycling speeds up, this time lag takes up an increasing proportion of each iteration of the cycle. In other words, epistasis and linkage disequilibrium are of opposite signs a greater proportion of the time. Under antagonistic coevolution, the rate of cycling is determined by the strength of selection against infection. As the strength of selection in the host increases (increasing virulence V and/or the number of exposures to parasites N), the rate of the response to selection increases, and the cycle speeds up. If selection is strong enough, epistasis changes sign on the order of every two to five generations, and linkage disequilibrium is of the opposite sign more than half the time (figs. 3, 5).

Even when the parasite imposes very strong selection

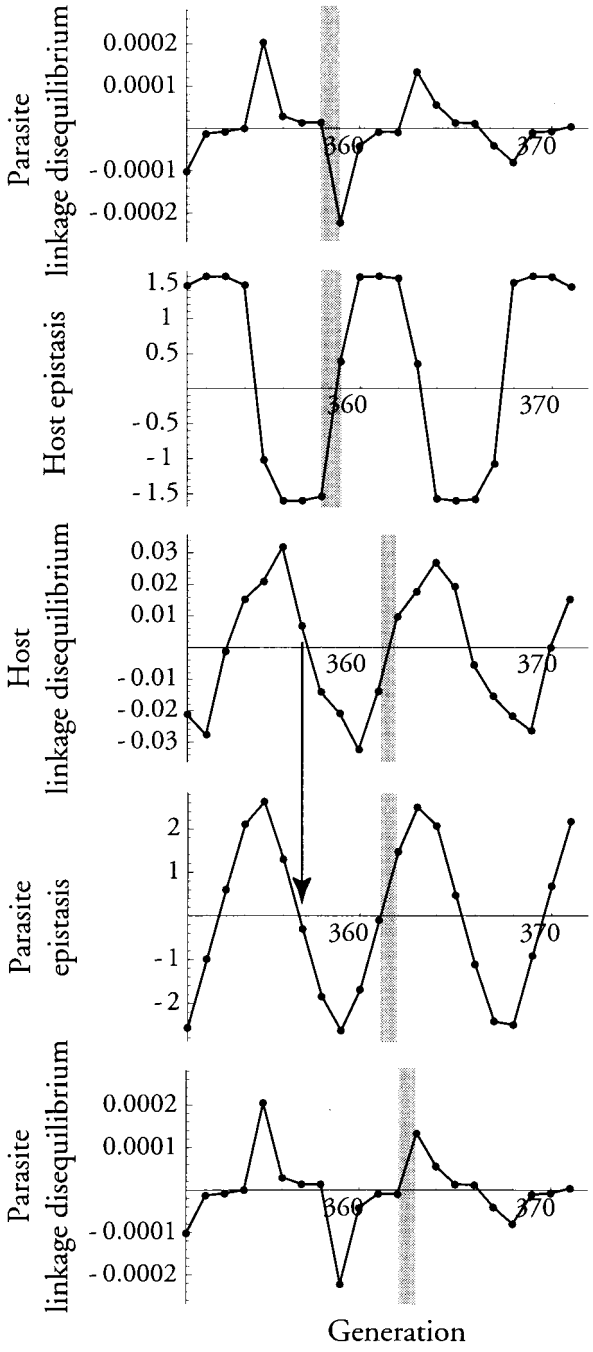


Figure 5: Patterns of linkage disequilibrium and epistasis in the parasite and the host over 21 representative generations under strong selection ($N = 2$; $V = 0.8$). Note that parasite linkage disequilibrium is shown twice (*top* and *bottom panels*) to illustrate a full iteration of the feedback loop. Gray bars denote points at which the epistasis or disequilibrium change sign, highlighting the phase relationships between the four components of the cycle. As linkage disequilibrium becomes negative in the parasite (*top panel*), epistasis becomes positive in the host (*second panel*). After a time lag, this leads to the buildup of positive linkage disequilibria in the host (*third panel*), which causes positive epistasis in the parasite (*fourth panel*). This, in turn, leads after a time lag to positive linkage disequilibria in the parasite (*bottom panel*). Note that selection is acting n gene frequencies, rather than directly on epistasis or linkage disequilibrium, so this pattern of fluctuations is not perfect (e.g., at the arrow, parasite epistasis becomes negative before host linkage disequilibrium). However, despite this periodic inconsistency, the overall pattern is maintained.

on the host, it seems unlikely that epistasis could change signs more frequently than every two generations (Barton's [1995] lower bound). In a coevolutionary model, linkage disequilibria must build up in order to elicit a response in the antagonistic population and continue the cycle. Since it takes at least one generation for linkage disequilibria to accumulate in response to changes in epistasis, the cycles should be constrained such that the sign of epistasis could not change in less than two generations.

One potential objection to the claim that antagonistic coevolution provides an advantage to recombination lies in the fitness cost to the host population from parasite infection (Kondrashov and Yampolsky 1996; Otto and Michalakis 1998). Since genotype frequencies in our model are normalized to sum to 1 every generation, the populations cannot go extinct. Thus, our model does not take into account the effects of genetic load that may be imposed on the host population by the very fluctuations we have investigated. To address this question, we have calculated the reduction in mean fitness (genetic load L) experienced by the host population across 1,000 generations (table 1). Since this is a multigenerational mean, it is based on geometric mean fitness: $L = 1 - \widetilde{\overline{W}}$, where $\widetilde{\overline{W}}$ is the multigenerational geometric mean of mean fitness in the host population. For the parameter values we have investigated, values of L range from 0.05 to nearly 1.0 in nonrecombining populations and from 0.05 to 0.58 after the recombination modifier has spread to its maximum. These compare favorably with values of mean fitness reduction imposed by other models of recombination. For a model of mutation-selection balance, for instance, Barton (1995, table 3) reports fitnesses that correspond to values of L from 0.06 to 0.66 in a free-recombining population. More telling is the comparison between parameter values that impart a small advantage to recombination: for mutation rate $U = 0.5$, Barton (1995) reports $L = 0.248$ ($\overline{W} = 0.752$) under free recombination; for $V = 0.4$ and $N = 2$, our model predicts $L = 0.16$ under no recombination. Presumably, genetic load is greater with no recombination in the mutation model, which implies that genetic load imparted by the coevolution model is substantially lower than that imparted by the mutation model when both are providing very small advantages to recombination.

Another factor worth considering is the genetic basis of

Table 1: Genetic load imposed on the host population under the parameter values investigated

		Genetic load	
N	*V*	No recombination	After spread of recombination modifier
1	.2	.05	.05
1	.4	.12	.11
1	.6	.20	.18
1	.8	.32	.26
1	1	>.999	.41
2	.2	.09	.09
2	.4	.16	.16
2	.6	.23	.22
2	.8	.34	.29
2	1	>.999	.58

the host-parasite interaction. Bell and Maynard Smith (1986) found that recombination spread in the parasite but not the host under a "quantitative" interaction model. In their model, the match between host and parasite was determined by summing allelic values across loci such that intermediate (i.e., *Ab* and *aB*) genotypes were identical. The explanation for the difference in results probably lies in the timescale over which the fluctuations occur: in the Bell and Maynard Smith model, selection appeared to change direction approximately once in 25 generations, probably because selection was weaker on both the host and the parasite. This is too slow for fluctuating epistasis to provide an advantage to recombination (Barton 1995); thus, any advantage must arise from the directional selection mechanism. This is corroborated by the fact that linkage disequilibria that slow down the response to selection are expected to build up in the parasite population but not the host population under the quantitative model (Otto and Michalakis 1998). Thus, the directional selection model is expected to provide an advantage to recombination in the parasite population but not the host population. Bell and Maynard Smith (1986) also explored an interaction model similar to ours. Under that model, recombination spread in both the host and parasite populations but only to a very low frequency (250×10^{-5}). Again, however, the fluctuations in selection may have been slow because of the weaker selection imposed; thus, fluctuating epistasis could not provide a substantial advantage to recombination.

A fundamentally different type of interaction model is the "gene-for-gene" (GFG) model often used to describe plant-pathogen interactions (Flor 1956; Parker 1994; Frank 1996*b*). Under this model, a "virulence" allele allows the parasite to infect any host and a "resistance" allele is required to protect the host from even "avirulent" parasites; under such a system, time-lagged cycles favoring increased recombination never occur (Parker 1994). Indeed, if the strict GFG model is the rule in plants, the model we describe may not be relevant in plants. However, the validity of the GFG model (at least to the degree that it excludes the possibility of matching-alleles models like the one used here) in plants is still a topic under debate (see, e.g., the exchange in Frank 1996*a*, 1996*c*; Parker 1996). In addition, like the quantitative model of Bell and Maynard Smith (1986), the GFG model may generate linkage disequilibria that slow down the response to selection (Otto and Michalakis 1998). If so, interactions of this type may select for recombination through the directional selection mechanism, even if they fail to do so through fluctuating epistasis. An analysis of the variance components for fitness in GFG models may shed light on this possibility.

Our model points out that, contrary to some recent assertions (e.g., Kondrashov and Yampolsky 1996), all fluctuating selection is not equal. Under arbitrary abiotic fluctuations, the period and amplitude of the fluctuations are insensitive to the evolutionary response. Under antagonistic coevolution, however, the fluctuations depend directly on the reaction of the population: changes in host linkage disequilibrium lead within a few generations to changes in parasite linkage disequilibrium, which lead within a few generations to changes in host linkage disequilibrium, and so on. This general fact has been pointed out on many occasions (Jaenike 1978; Bell and Maynard Smith 1986; Seger and Hamilton 1988; Nee 1989; Otto and Michalakis 1998), though our model is the first attempt to analyze the results of coevolutionary interactions specifically with respect to epistasis and linkage disequilibrium and to compare the results with specific predictions from population-genetic models.

In addition, our model imposes substantially less genetic load on the population than other models of fluctuating selection. Kondrashov and Yampolsky (1996) reported that load must be on the order of 0.3 or greater in order to achieve intermediate frequencies of a free-recombination allele under fluctuating selection. This difference is probably largely because of the fact that their model was primarily one of directional selection (i.e., epistasis changed sign on the order of at least 10 generations; Kondrashov and Yampolsky 1996). The directional selection mechanism works because recombination increases additive genetic variance for fitness. Recombination thus becomes associated with high-fitness genotypes over the long term because it causes a more rapid response to selection. In the short term, however, recombination may actually decrease mean fitness (i.e., cause recombination load) because it increases the frequency of both extremely advantageous genotypes and extremely disadvantageous genotypes (Charlesworth and Barton 1996; West et al.

1998). Thus, because the directional selection mechanism is a long-term process dependent on indirect increases in mean fitness and may potentially lead in the short term to decreased fitness, it requires strong, constant directional selection to provide an advantage to recombination. In order to maintain substantial directional selection under fluctuating selection, high-amplitude changes in the optimal phenotype are required, imposing a heavy genetic load. In other words, the directional selection mechanism requires that the population be poorly adapted most of the time. The fluctuating epistasis mechanism, however, works because recombination imposes a direct, immediate increase in fitness by increasing the frequency of rare, fit genotypes. It is therefore a relatively short-term process and not subject to recombination load during those periods when $E \times D < 0$. A relatively large advantage may accrue to recombination over a short period of time, requiring relatively small fluctuations in fitness. Thus, though the fluctuating epistasis mechanism does require periods of poor adaptation, those periods may be relatively short, interspersed by periods of high fitness; furthermore, they may involve relatively small drops in fitness.

Taken together, these results suggest that fluctuating epistasis is the main factor providing an advantage to recombination under antagonistic coevolution. There appears to be some directional selection under antagonistic coevolution, but the strength of this selection fluctuates. In addition, linkage disequilibria appear more likely to speed up the response to selection than to slow it down, particularly when parasite effects are strong (fig. 1). Under such conditions, interactions between directional selection and epistasis cannot select for increased recombination (Barton 1995). Further, antagonistic coevolution leads to fluctuations in epistasis on exactly the right timescale to provide an advantage to recombination (fig. 2). Finally, conditions under which increased recombination can spread (fig. 4) appear to be correlated with increases, rather than decreases, in additive genetic variance caused by linkage disequilibria (fig. 1). However, the spread of recombination is observed when epistasis and linkage disequilibrium are often of opposite signs (fig. 3), as is expected under the fluctuating epistasis mechanism. Furthermore, once the recombination modifier has spread, the frequency of the modifier follows stable limit cycles in which transient increases in the frequency of the modifier are associated with those periods when epistasis and linkage disequilibrium are of opposite signs. Whether directional selection, during those periods when additive variance outweighs epistatic variance, can interact with fluctuating epistasis to broaden the parameter space under which recombination is advantageous is unclear; further analysis of Barton's (1995) model may be necessary to address this issue.

Though we have shown that antagonistic coevolution can provide an advantage to recombination via fluctuating epistasis per se, this does not mean that other aspects of coevolutionary dynamics might not provide further advantages (Howard and Lively 1994, 1998; Lively and Howard 1994; Barton 1995; Otto and Michalakis 1998). Allele frequencies also fluctuate in response to selection, and recombination may speed up this response if there is negative epistasis between alleles when the level of additive genetic variance is high; these short bursts of "directional selection" might also provide an advantage to recombination (Bell and Maynard Smith 1986; Barton 1995; Otto and Michalakis 1998). This might explain the spread of the free recombination allele slightly outside of two to five generations (the "Barton zone") in our model at $N = 1$ and $V = 0.4$ (fig. 4*A*). In addition, antagonistic coevolution and mutation accumulation may interact in such a way that the parameter values under which sex is advantageous are much broader than under either mechanism alone (Howard and Lively 1994, 1998; Lively and Howard 1994), and these mechanisms may also apply to the evolution of recombination. These factors suggest that, in theory, antagonistic coevolution may be a particularly powerful mechanism selecting for recombination in natural populations. Whether sexual hosts are commonly confronted with parasites that are sufficiently virulent ($V > 0.4$) to select for host sex and recombination is an empirical issue. Estimates of the effects of parasites on host fitness in nature are needed before meaningful decisions can be made regarding a general role for antagonistic coevolution in selecting for sex/recombination in both of the interacting species.

Acknowledgments

We thank K. Lythgoe for extensive discussions. Thanks also to N. Barton, A. Burt, S. P. Otto, Y. Michalakis, S. West, and an anonymous reviewer for very useful comments and discussion on earlier versions of this manuscript. This study was supported in part by a National Science Foundation grant to C.M.L. (DEB-9629849), the Marsden Fund of New Zealand (Contract LL 0501), and a grant from the Indiana University Department of Biology to A.D.P.

APPENDIX

Calculation of Selection Coefficients

The selection coefficients a_I are calculated as described by Barton and Turelli (1991) by solving the set of equations

$$\frac{W_i}{\overline{W}} = 1 + a_A(X_A - p_a) + a_B(X_B - p_b) + a_{AB}[(X_A - p_a)(X_B - p_b) - D], \tag{A1}$$

where W_i is the fitness of genotype i. The X's are indicator variables denoting which allele at each locus is carried by genotype i: $X_A = 1$ if the allele at the A locus is a, and 0 if the allele is A; $X_B = 1$ if the allele at the B locus is b, and 0 if it is B (modified from Barton and Turelli 1991). Given this encoding, the mean value of the population for the A locus, for instance, is p_a, the frequency of allele a. Thus, the $(X - p)$ terms denote the deviation of a genotype from its mean value at each locus. Replacing the Xs with their appropriate values, the full set of equations becomes

$$\begin{aligned}
\frac{W_{AB}}{\overline{W}} &= 1 + a_A(-p_a) + a_B(-p_b) + a_{AB}(p_a p_b - D),\\
\frac{W_{Ab}}{\overline{W}} &= 1 + a_A(-p_a) + a_B(1 - p_b) + a_{AB}[(-p_a)(1 - p_b) - D],\\
\frac{W_{aB}}{\overline{W}} &= 1 + a_A(1 - p_a) + a_B(-p_b) + a_{AB}[(1 - p_a)(-p_b) - D],\\
\frac{W_{ab}}{\overline{W}} &= 1 + a_A(1 - p_a) + a_B(1 - p_b) + a_{AB}[(1 - p_a)(1 - p_b) - D].
\end{aligned} \tag{A2}$$

The additive effects of loci A and B on fitness are a_A and a_B, respectively; the nonadditive (epistatic) fitness effects are denoted by a_{AB}. Solving for these coefficients,

$$\begin{aligned}
a_A &= \frac{W_{aB} - W_{AB} + p_b(W_{ab} - W_{aB} - W_{Ab} + W_{AB})}{\overline{W}},\\
a_B &= \frac{W_{Ab} - W_{AB} + p_a(W_{ab} - W_{aB} - W_{Ab} + W_{AB})}{\overline{W}},\\
a_{AB} &= \frac{W_{ab} - W_{aB} - W_{Ab} + W_{AB}}{\overline{W}}.
\end{aligned} \tag{A3}$$

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Associate Editor: Sarah P. Otto