

# Balanced Polymorphisms and the Evolution of Dominance

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**ABSTRACT:** We explore the evolution of dominance at polymorphisms maintained either by overdominant selection or by migration-selection balance. At such balanced polymorphisms, heterozygotes remain at appreciable frequencies over long periods of time, allowing extensive modification of dominance to occur. The strength of selection favoring a modifier of dominance is roughly proportional to the probability that a modifier allele is found in a heterozygote at the locus subject to balancing selection times the heterozygote fitness increase caused by the modifier. Using a two-locus model, we elucidate the interesting ways in which recombination and migration cause departures from this rough expectation. For example, with overdominance, a genetic association with the rarest allele favors a modifier that increases heterozygote fitness because the modifier occurs more often in heterozygotes. With migration-selection balance, dominance evolves more readily in patches experiencing the strongest selection. We also find that, while there are more heterozygotes in sink populations (which have higher rates of immigration than emigration), selection for dominance in sink and source populations is nearly equal because sink populations make a lower genetic contribution to future generations. We conclude that the evolution of dominance is likely to occur whenever polymorphism is maintained by either overdominance or migration.

**Keywords:** dominance modifiers, deleterious mutations, balanced polymorphism, insecticide resistance, variable environments, marginal overdominance.

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As a rule, hybrids do not represent the form exactly intermediate between the parental strains. ... Those traits that pass into hybrid association entirely or almost entirely unchanged, thus themselves representing the traits of the hybrid, are termed dominating, and those that become latent in the association, recessive. (Gregor Mendel [(1865) 1966, p. 9])

\* To whom correspondence should be addressed; e-mail: otto@zoology.ubc.ca. Am. Nat. 1999. Vol. 153, pp. 561–574. © 1999 by The University of Chicago. 0003-0147/99/5306-0001\$03.00. All rights reserved.

Mendel's classic hybridization experiments with peas demonstrated that one parental trait (e.g., round pea shape and violet red blossoms) is often dominant over the trait exhibited by the other parent. Initially, after the rediscovery of Mendel's work, dominance was viewed as an essential genetic property, akin to the phenomenon of segregation (recounted by Wright [1929*b*, 1934*a*]). This view was soon dispelled as alleles with various levels of dominance were discovered. Nevertheless, the prevalence of dominance, particularly the dominance of wild-type over mutant alleles, begged explanation.

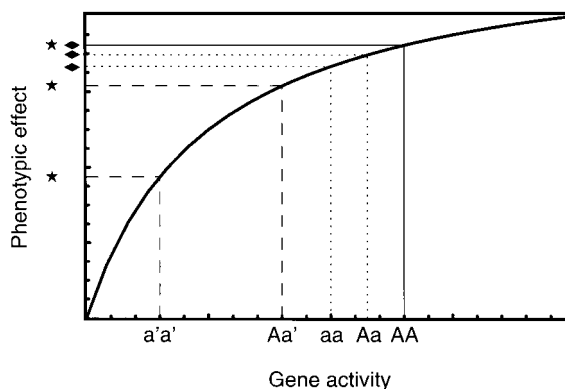
An early explanation, the presence-absence hypothesis (Bateson 1909; Punnett, cited in Wright 1934*a*), suggested that functional gene products either were or were not produced (by the dominant or recessive allele, respectively) and that even a half dose of the functional allele was sufficient to produce a normal phenotype. However, multiple alleles (e.g., ABO blood type alleles in humans) do not fall simply into two discrete categories. Furthermore, the dominance level of an allele is not absolute but depends on its genetic context (Morgan et al. 1925; Wright 1925; Dunn 1940). Mutant alleles that are fully recessive when paired with a wild-type allele often show intermediate levels of dominance when paired with different mutant alleles at the same locus. These observations, among others, led to the rejection of the presence-absence hypothesis and inspired Fisher (1928*a*, 1928*b*) to develop an evolutionary explanation for dominance.

Fisher (1928*a*, 1928*b*) proposed that wild-type alleles evolve increased dominance to reduce the fitness costs of recurrent deleterious mutations. Wright (1929*b*) doubted this explanation, arguing that selection on a modifier of dominance would be proportional to the frequency of mutant-bearing heterozygotes and hence only on the order of the mutation rate. Over the next few years, the debate between Fisher and Wright flared into an ongoing battle fought largely in the pages of the *American Naturalist* (Fisher 1929, 1930, 1934; Wright 1929*a*, 1934*a*, 1934*b*). The debate had deep philosophical roots reaching beyond the evolution of dominance: Fisher and Wright were essentially arguing over the power of selection (Fisher 1929; Wright 1934*a*; Provine 1986). Fisher claimed that, given sufficient time, even extremely weak selection would result

in a large cumulative impact on evolution. Wright countered that extremely weak selection would be overwhelmed by mutation (1929*b*), pleiotropic effects (1929*b*), and drift (1929*a*).

Wright (1929*b*, p. 277) instead advocated an “immediate physiological explanation” for dominance. He suggested that genes often act as catalysts and that metabolic throughput rises at a decreasing rate with catalytic activity as catalysis becomes less and less rate limiting (Wright 1934*a*; see fig. 1). Dominance of the wild type naturally arises whenever the phenotypic effects of a gene rise less than linearly with gene activity (as in fig. 1), since a deleterious mutation in homozygous form will have more than twice the phenotypic effects of a mutation in heterozygous form. Several theoretical and empirical studies have since bolstered Wright’s physiological theory of dominance. In particular, the metabolic theory developed by Kacser and Burns (1981) predicted that most enzymes would naturally function near the asymptote of the activity curve shown in figure 1, where dominance is expected to be greatest. Charlesworth (1979) noted that the physiological theory of dominance could explain the observed correlation between the level of dominance and the fitness effect of a mutation (fig. 1), but that Fisher’s evolutionary theory of dominance predicts no such correlation. More recently, Orr (1991) observed that wild-type alleles were as dominant over mutant alleles in “artificial” diploids of the normally haploid alga *Chlamydomonas* as they are in typically diploid organisms, which again is consistent with Wright’s physiological theory but not Fisher’s evolutionary theory of dominance.

Nevertheless, there is ample evidence that dominance levels can evolve (reviewed in Sheppard 1961, 1975; Sved and Mayo 1970; Mayo and Bürger 1997). Ford (1940) observed a rapid response to artificial selection for high and low levels of dominance of the yellow color variant in the currant moth *Abraxas grossulariata*. Similarly, by artificially selecting mice, Fisher and Holt (1944) successfully decreased the heterozygous effects of the  $S^l$  allele, which affects tail length when heterozygous and is lethal when homozygous. More importantly, there is evidence that dominance levels have evolved in natural populations. The melanic form of the peppered moth *Biston betularia* first appeared in British collections in the mid-1800s. At that time, melanic forms were rare and were presumably heterozygotes. These early specimens are not, however, completely black and contain many more white markings than heterozygous melanic forms from the next century, which suggests that increased dominance of the melanic form evolved over this time period (Haldane 1956; Sheppard 1975). Furthermore, Kettlewell (1965) found that dominance of the melanic form broke down upon outcrossing with Canadian strains, which is consistent with



**Figure 1:** Relationship between phenotypic effect and gene activity (based on Wright 1934*a*, fig. 7). The curve exhibits diminishing returns, since increased enzyme activity has less of an impact on the products of an enzyme reaction and so on phenotype when enzyme activity is already high and not limiting the rate of reaction. Compared to a wild-type genotype ( $AA$ ; solid thin line), minor mutations ( $a$ ; dotted thin lines) that are additive at the level of gene activity ( $X$ -axis) are partially recessive at the level of phenotype (diamonds on  $Y$ -axis), while major mutations ( $a'$ ; dashed thin lines) that are additive at the level of gene activity exhibit more pronounced recessivity at the level of phenotype (stars on  $Y$ -axis), which is consistent with observed patterns (Charlesworth 1979).

the existence of modifiers that augment dominance of the British melanic form. Another striking example comes from the mimetic butterfly *Papilio dardanus*. Clarke and Sheppard (1960) showed that alleles found together within a population often exhibit complete dominance (15 out of 22 cases), while alleles from different populations generally exhibit incomplete dominance (12 out of 14 cases), suggesting that complete dominance evolves when alleles are frequently found together in heterozygotes.

The above examples share one main feature: heterozygotes are (or have been) common. Selection for modifiers of dominance becomes much stronger when heterozygotes are common, a point on which Wright and Fisher consistently agreed. In this article, we examine the strength of selection on a modifier of dominance when heterozygotes are maintained within a population by balancing selection, either by overdominance or by migration among subpopulations with spatially heterogeneous selection. Selection on a modifier approaches the strength of selection acting at the balanced polymorphism, but the extent to which it does so depends on migration and recombination rates.

### Model Background

One may distinguish three main classes of theoretical models for the evolution of dominance, depending on whether the primary selected locus is at a mutation-selection bal-

ance, evolving to a new equilibrium, or held at an intermediate frequency by balancing selection. Most models (Fisher 1928a, 1929; Wright 1929a, 1929b, 1934a; Haldane 1930; Ewens 1965a, 1965b, 1966, 1967; Mayo 1966; Feldman and Karlin 1971; Karlin and McGregor 1974; Bürger 1983a, 1983b, 1983c) have focused on the evolution of a modifier locus when the primary selected locus is held at a balance between mutation and selection (Fisher's model). These models confirm Wright's (1929b) claim that the selective advantage of a modifier allele that causes mutant alleles to become more recessive is very small, being on the order of the mutation rate in most cases.

The second category of models (Haldane 1956; Parsons and Bodmer 1961; Bodmer 1963; Ewens 1966; Mayo 1966; O'Donald 1967, 1968a, 1968b; Wagner 1981; Bürger 1983a, 1983b, 1983c; Wagner and Bürger 1985) tracks the evolution of dominance when alleles at the primary locus are not at equilibrium. This approach was pioneered by Haldane (1956), who was motivated by the example of *Biston betularia* to model the evolution of dominance during the spread of a favorable allele. These models demonstrate that, when an allele is spreading through a population, selection on a modifier can be very efficient. Nevertheless, substantial selection for dominance will be restricted to the period of time during which genetic variation remains at the selected locus. This poses two problems for the evolution of dominance: modifier alleles that alter the dominance level of an advantageous allele may not happen to be present within a population during this window of opportunity, and, even if present, they may not rise to high frequency before fixation of the advantageous allele (Haldane 1956).

The third class of models (Clarke 1964; O'Donald 1968b; Wallace 1968; Feldman and Karlin 1971; Charlesworth and Charlesworth 1975) examines the evolution of dominance when the primary selected locus is at a balanced polymorphism. As pointed out by Fisher (1930) and Sheppard (1958, p. 140), dominance levels should evolve more readily when there is a balanced polymorphism, since heterozygotes are maintained at high frequencies for extended periods of time. Therefore, balanced polymorphisms represent the best case scenario for the evolution of dominance. Surprisingly, this scenario has been the least explored theoretically. Clarke (1964), O'Donald (1968b), and Charlesworth and Charlesworth (1975) explored the evolution of dominance for mimicry alleles maintained by frequency-dependent, disruptive selection, using mean fitness arguments and numerical analyses. Wallace (1968) considered a model of overdominant selection, again using mean fitness arguments. While mean fitness arguments predict the outcome of evolution by group selection and by simple one-locus models of individual selection, they do not generally predict the outcome of models of selection

at the individual level in more complex models (e.g., models with selected loci and modifier loci). A two-locus model was described by Feldman and Karlin (1971) to address the evolution of dominance by individual selection for loci at a balanced polymorphism, but the model was left unanalyzed. In no case has a full two-locus stability analysis been performed.

Here we propose and analyze a two-locus model for the evolution of dominance in the presence of a balanced polymorphism, where the balance is maintained by overdominant selection or by migration in a patchy environment. We are particularly interested in the case where polymorphism is maintained by migration between habitats in which different alleles are favored. This situation arises, for example, when pesticide applications are heterogeneous in space, providing a patchy environment with treated and untreated areas. Intensive pest management has selected for resistance alleles for a variety of chemicals in a wide range of species (Georghiou 1986). Dominance relationships among pesticide-resistance alleles have recently been explored (Bourguet et al. 1996, 1997; Bourguet and Raymond 1998), and there is some evidence that dominance levels vary in natural populations (Bourguet et al. 1997). Spatial models for the evolution of dominance will therefore provide more accurate estimates of the selective forces acting on dominance levels at loci involved in pesticide resistance.

### Overdominance

We first consider a model in which there is heterozygote advantage at a primary selected locus ( $A$ ), such that genotypes  $AA$ ,  $Aa$ ,  $aa$  have fitnesses  $W_1$ ,  $W_2$ ,  $W_3$ , respectively, with  $W_1 < W_2 > W_3$ . The fitness of  $Aa$  heterozygotes varies according to the genotype at a second, modifier locus ( $M$ ) and equals  $W_{2D}$ ,  $W_{2H}$ ,  $W_{2R}$  within  $MM$ ,  $Mm$ , and  $mm$  individuals. Here, and in all models considered, recombination occurs between the  $A$  and  $M$  loci at an arbitrary rate,  $r$ , and mutations are ignored. Recursion equations for this two-locus model (appendix) follow Feldman and Karlin (1971).

If the allele,  $M$ , is initially fixed at the modifier locus and if both alleles  $A$  and  $a$  are present (at frequencies  $p_A$  and  $p_a$ ), the system evolves to a globally stable polymorphic equilibrium at which the frequency of allele  $A$  is

$$\hat{p}_A = \frac{W_{2D} - W_3}{2W_{2D} - W_1 - W_3} \quad (1)$$

whenever  $W_{2D} > W_1, W_3$  (Fisher 1922). If allele  $m$  is introduced at low frequency into this polymorphic population, it will invade whenever the leading eigenvalue of the local stability matrix is  $>1$ . In the appendix, we determine the

leading eigenvalue ( $\lambda_L$ ; eq. [A2]) and demonstrate that it is  $>1$  whenever the new modifier allele increases heterozygote fitness ( $W_{2H} > W_{2D}$ ). We also demonstrate that, while allele  $m$  is rare, the strength of selection ( $s_m$ ) acting indirectly through its effects on dominance at the  $A$  locus can be measured by  $\lambda_L - 1$ . In addition, selection may act directly on the modifier locus, irrespective of its effects on the  $A$  locus. If the strength of direct selection is  $s_d$ , then invasion will occur if, approximately,  $s_m + s_d$  is positive (assuming weak selection). Thus the fate of a modifier allele will be governed by its effects on dominance, rather than any pleiotropic effects, only when indirect selection ( $s_m$ ) is large in magnitude relative to direct selection ( $s_d$ ).

When  $r = 0$ , we can consider the strength of selection acting on the new  $mA$  and  $ma$  haplotypes separately:

$$s_{mA} = \hat{p}_a \frac{W_{2H} - W_{2D}}{W}, \quad (2a)$$

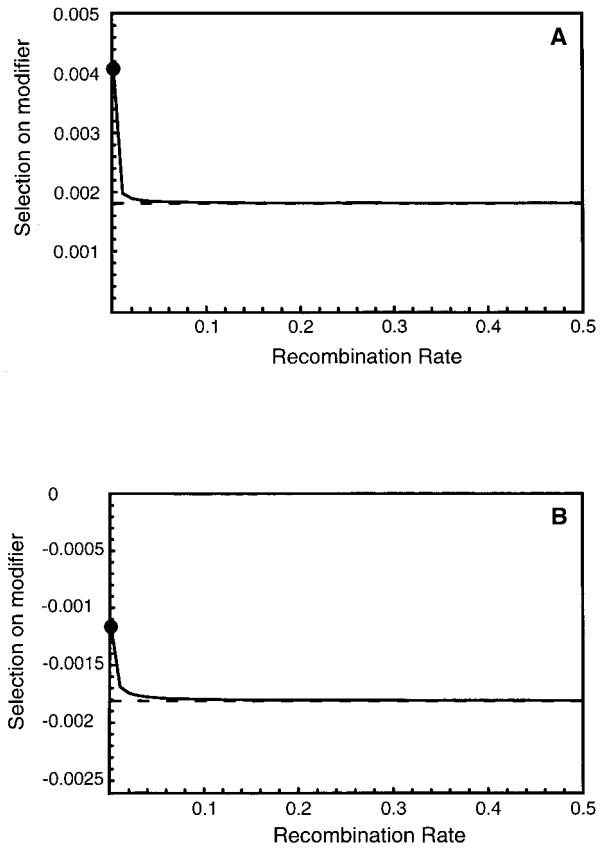
$$s_{ma} = \hat{p}_A \frac{W_{2H} - W_{2D}}{W}. \quad (2b)$$

These coefficients were obtained by Wallace (1968) from mean fitness considerations. As he noted, the advantage of the modifier allele “is greatest when it is linked with the rarer of the [ $A$ ] alleles” (p. 338) because this association increases the chance that the modifier will occur in a heterozygote. For higher rates of recombination ( $r \gg W_{2H} - W_{2D}$ ) and ignoring  $(W_{2H} - W_{2D})^2$  and smaller-order terms, selection in favor of the  $m$  allele becomes

$$s_m \approx 2\hat{p}_A\hat{p}_a \frac{W_{2H} - W_{2D}}{W}. \quad (3)$$

(Wallace [1968] also obtained [3] but then inappropriately halved it in comparison with [2].) For intermediate rates of recombination,  $\lambda_L$  (eq. [A2]) must be used to provide a precise measure of the selective advantage of a modifier.

In (2) and (3), the strength of selection acting on a modifier allele,  $m$ , equals the amount by which  $m$  increases the average relative fitness of  $Aa$  heterozygotes times the probability that  $m$  is found in a heterozygote. This latter quantity is highest for complete linkage to the rarer of the two selected alleles and lowest for complete linkage to the more common one. More generally, it can be shown that selection on the modifier ( $\lambda_L - 1$ ) is a decreasing (or constant) function of the rate of recombination. Consequently, new modifier alleles that increase dominance are more strongly selected under tight linkage (fig. 2A), but alleles that decrease dominance are more rapidly eliminated under loose linkage (fig. 2B). This has an interesting effect on the spread to fixation of a modifier allele (fig. 3). A completely linked modifier allele that increases dominance

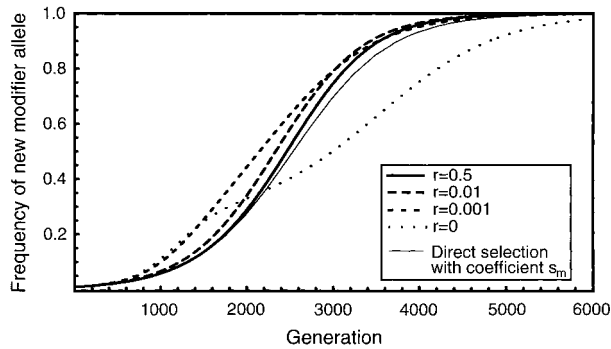


**Figure 2:** Selection ( $s_m$ ) for a modifier of dominance as a function of recombination with overdominant selection at the modified locus,  $A$ :  $W_1 = 0.95$ ,  $W_{2D} = 0.966$ ,  $W_3 = 0.91$ .  $A$ , Modifier allele increases heterozygote fitness to  $W_{2H} = 0.971$ .  $B$ , Modifier allele decreases heterozygote fitness to  $W_{2H} = 0.961$ . Solid curves give the exact value of  $s_m$ ; that is, the leading eigenvalue (eq. [A2]) minus one. Circles give the approximation for  $r = 0$  (from eq. [2a]). Dashed lines give the approximation for weak modifiers (from eq. [3]). Note that the figure also represents the evolution of dominance in the small-scale patch model with  $\alpha = 0.1$ ,  $s = 0.5$ ,  $h_{MM} = 0.5$ ,  $h_{Mm} = 0.4$  (in  $A$ ),  $h_{Mm} = 0.6$  (in  $B$ ),  $t = 0.1$ ,  $k_{MM} = 0.1$ , and  $k_{Mm} = 0.1$ .

initially spreads faster than a loosely linked modifier, but this effect is reversed once the modifier becomes common. This occurs because, while the initial rate of spread of a completely linked modifier is governed by the largest of the two selection coefficients given in equation (2), eventually the increase in frequency of the modifier depends on the spread of the  $m$ -bearing haplotype with the smaller of the two selection coefficients in equation (2).

### Migration-Selection Balance

A balanced polymorphism may also occur when selection is spatially heterogeneous, such that locally disfavored al-



**Figure 3:** Spread to fixation of a modifier of dominance. Simulations were run to follow the dynamics of a modifier of dominance beyond invasion. Parameters were identical to those used in figure 2A, with recombination set to 0, 0.001, 0.01, and 0.5. Additive gene action was assumed at the modifier locus ( $W_{2R} = 0.976$ ). In each case, the modifier allele spread to fixation. Although the initial rate of spread was higher for  $r = 0$ , the final rate of spread was lower because the haplotype experiencing weaker selection ( $mA$ ) was slow to spread with complete linkage. For comparison, the thin solid curve describes the spread of an allele,  $m$ , in a one-locus model with fitnesses  $W_{MM} = 1$ ,  $W_{Mm} = 1 + s_m$ ,  $W_{mm} = 1 + 2s_m$ , where  $s_m$  is given by equation (3). While  $s_m$  was calculated under the assumption that the modifier was rare, it provides a good measure of the strength of selection acting on an additive modifier throughout its spread, except for low rates of recombination.

les are maintained by migration from locations where they are favored (Levene 1953; Dempster 1955), a phenomenon known as multiple-niche polymorphism. We analyze the evolution of dominance in a population that is subdivided into two patches with heterogeneous selection. Fitness is determined by patch type and by an individual's genotype at the primary selected locus ( $A$ ), as shown in table 1. For the sake of clarity, we will assume that allele  $a$  is directionally favored in patch 1 and that allele  $A$  is directionally favored in patch 2. The modifier locus affects the level of dominance at the  $A$  locus in one or both of the patches; the dominance coefficient for an individual with modifier genotype  $i$  is  $h_i$  in patch 1 and  $k_i$  in patch 2. We explore two different models of migration and population regulation, corresponding to patches distributed over small or large spatial scales.

These models may be used, for example, to follow the evolution of dominance at loci involved in pesticide resistance. Let allele  $a$  increase pesticide resistance and so be favored in patches where pesticides are present (patch type 1), while allele  $A$  is favored in patches where pesticides are absent (patch type 2). Whether the small- or large-scale patch model will be more appropriate depends on the scale of pesticide application relative to the dispersal distance of the pest. A modifier of dominance may affect the ability of heterozygotes to resist pesticides (via the evolution of  $h$ ) and/or to tolerate the costs of resistance

(via the evolution of  $k$ ). Although this example indicates that dominance levels in the two patches may evolve independently, it might often be the case that a modifier increases the level of dominance of a particular allele in both patches (e.g., decreasing  $h$  and increasing  $k$ ). We now determine whether and to what extent such modifier alleles are favored.

### Small-Scale Patchiness

In the small-scale patch model, complete mixing occurs each generation among reproductive adults from each patch. Their offspring then settle randomly within one of the two habitats. The chance of encountering a patch depends on its area; patches 1 and 2 are assumed to account for a proportion  $\alpha$  and  $1 - \alpha$ , respectively, of the total area of the population. Each patch contributes to the adult mating pool in proportion to the area of the patch and to the average fitness of individuals within it. This model corresponds to a hard selection model for a multiple-niche polymorphism, as proposed by Dempster (1955). The analysis of this model is straightforward because the equations describing genotypic frequency change are identical to those for a single-patch model, but with the fitness of each type averaged over the two patches as shown in table 2. Consequently, the results are identical to the case of overdominant selection ("Overdominance"; figs. 2 and 3).

The stability of the internal equilibrium (1) now depends on the dominance coefficients (see table 2). The condition  $W_{2D} > W_1, W_3$  is most easily satisfied when  $h_{MM}$  and/or  $k_{MM}$  are small and cannot be satisfied if both  $h_{MM}$  and  $k_{MM}$  are  $\geq 1/2$  (Hoekstra et al. 1985). If a stable polymorphism is maintained, a new modifier allele can invade whenever  $W_{2H} - W_{2D}$  is positive, which in this case requires that

$$\alpha s(h_{MM} - h_{Mm}) + (1 - \alpha)t(k_{MM} - k_{Mm}) > 0. \quad (4)$$

This condition demonstrates that dominance will evolve more readily in frequently encountered habitats and in habitats where selection against migrant alleles is strong. Notice that a modifier allele that increases dominance of the locally favored allele in one patch but decreases it in the other patch can still invade a population if (4) holds. Interestingly, since invasion of the modifier increases the fitness of heterozygotes, the system evolves closer to  $\hat{p}_A = 1/2$ . Therefore, this process will reinforce the main-

**Table 1:** Patch fitnesses

Genotype	AA	Aa	aa
Fitness in patch 1	$1 - s$	$1 - hs$	1
Fitness in patch 2	1	$1 - kt$	$1 - t$

**Table 2:** Fitness averaged over two patch types

Genotype	AA	Aa	aa
<i>MM</i>	$W_1 = 1 - \alpha s$	$W_{2D} = 1 - \alpha h_{MM}s - (1 - \alpha)k_{MM}t$	$W_3 = 1 - (1 - \alpha)t$
<i>Mm</i>	$W_1 = 1 - \alpha s$	$W_{2H} = 1 - \alpha h_{Mm}s - (1 - \alpha)k_{Mm}t$	$W_3 = 1 - (1 - \alpha)t$
<i>mm</i>	$W_1 = 1 - \alpha s$	$W_{2R} = 1 - \alpha h_{mm}s - (1 - \alpha)k_{mm}t$	$W_3 = 1 - (1 - \alpha)t$

tenance of genetic variation at the selected locus and the potential for further evolution of dominance.

*Large-Scale Patchiness*

In the large-scale patch model, patches are spatially separated and individuals only occasionally migrate from one patch type to the other. In this model, population size is regulated by ecological factors and does not depend on the fitness of individuals within each patch (soft selection). Reproductively active, but unmated, adults (or gametes) migrate between patches. Following migration, mating occurs randomly within a patch. Among the juveniles in patch 1, a fraction ( $m_1$ ) of the chromosomes derive from parents that lived in patch 2, while the remaining fraction ( $1 - m_1$ ) derive from parents that lived in patch 1. Similarly, among the juveniles in patch 2, a fraction ( $m_2$ ) of the chromosomes derive from migrant parents, while the remaining fraction ( $1 - m_2$ ) are from parents local to patch 2. If  $m_1 \ll m_2$ , then patch 1 acts as a genetic source population and patch 2 acts as a genetic sink population. If migration occurs freely among the patches ( $m_1 = m_2 = 1/2$ ), then the model reduces to the Levene (1953) model for a multiple-niche polymorphism. Recursions are described in the appendix.

The conditions required to maintain a polymorphism are much easier to satisfy when migration is limited. Assuming a low rate of migration between patches and with only allele *M* present, the system evolves to an equilibrium with

$$\begin{aligned} \hat{p}_{A(\text{in patch } 1)} &\approx \frac{m_1}{h_{MM}s}, \\ \hat{p}_{a(\text{in patch } 2)} &\approx \frac{m_2}{k_{MM}t}. \end{aligned} \tag{5}$$

This migration-selection balance equilibrium is stable as long as the migration rates are small relative to the strength of selection acting against heterozygotes in each patch.

The fate of a modifier allele, *m*, introduced into these patches is again determined by a local stability analysis (see appendix). In the following results, it is assumed that migration rates are low and that second-order and higher terms involving migration rates may be ignored. Let  $W_i$  equal the fitness of genotype *i* in patch 1 (found by setting

$\alpha$  to 1 in table 2) and  $V_i$  equal the fitness of genotype *i* in patch 2 (found by setting  $\alpha$  to 0 in table 2).

When  $r = 0$ , invasion of the new *ma* haplotype occurs only if  $W_{2H} > W_{2D}$  (increased heterozygote fitness in patch 1). While this haplotype is rare, it experiences a selection coefficient of

$$s_{ma} \approx (W_{2H} - W_{2D})\hat{p}_{A(\text{in patch } 1)}. \tag{6a}$$

When  $W_{2H} > W_{2D}$ , the *ma* haplotype gains a double fitness advantage in patch 1: it has a higher fitness in heterozygotes and it carries the locally favored allele (*a*), yet the rate of loss due to migration to patch 2 is no different for *ma* and *Ma* haplotypes. Since allele *a* is disadvantageous in patch 2 and since migration is low, patch 2 acts as a genetic sink for the *a* allele and has a negligible influence on the evolution of *a*-bearing haplotypes. Overall, selection increases the frequency of the *ma* haplotype relative to the *Ma* haplotype as long as heterozygote fitness is increased in patch 1, regardless of the modifier's effect in patch 2. Similarly, when  $r = 0$ , invasion of the new *mA* haplotype will occur if  $V_{2H} > V_{2D}$  (increased heterozygote fitness in patch 2) and will experience a selection coefficient of

$$s_{mA} \approx (V_{2H} - V_{2D})\hat{p}_{a(\text{in patch } 2)}. \tag{6b}$$

Thus, with no recombination, a modifier allele that increases heterozygote fitness in a patch increases in frequency if it is linked to the allele favored in that patch. If the modifier increases heterozygote fitness in each patch, then both *ma* and *mA* haplotypes will increase when rare. In summary, with complete linkage, a rare modifier allele need only increase heterozygote fitness in one patch in order to increase in frequency.

Results are more complicated with nonzero recombination rates, because the fate of the modifier allele now depends on its effects on both genetic backgrounds (with alleles *a* and *A*). It can be shown that a modifier allele that increases heterozygote fitness in one patch and does not affect fitness in the other will always invade. To proceed further, we assume that the effects of the modifier on fitness are small and that second-order terms in these effects and second-order terms involving the migration rates may be ignored. In this case, the modifier will invade only if the following is positive:

$$\begin{aligned} \Psi &= (W_{2H} - W_{2D})(1 - V_{2D})V_{2D}[(1 - W_{2D}) + 2rW_{2D}] \\ &+ (V_{2H} - V_{2D})(1 - W_{2D})W_{2D}[(1 - V_{2D}) + 2rV_{2D}]. \end{aligned} \quad (7)$$

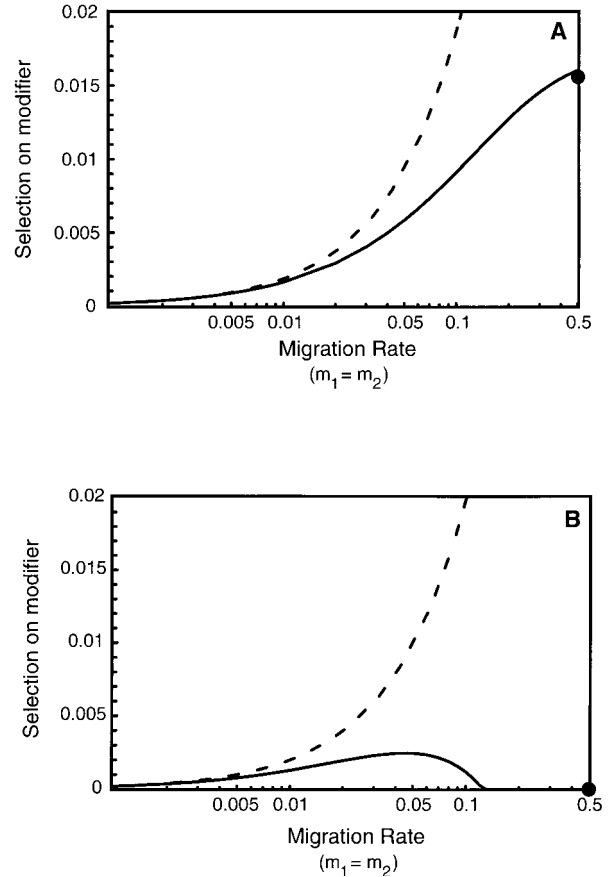
All terms, except the first term on each line, are always positive under the assumptions of the model. Therefore, equation (7) indicates that the modifier will invade if it increases heterozygote fitness on average across patches, where the average is weighted according to equation (7). The strength of selection on the modifier is then

$$s_m \approx \frac{\hat{p}_{A(\text{in patch 1})}\hat{p}_{a(\text{in patch 2})}\Psi}{m_1W_{2D}[1 - V_{2D}(1 - r)] + m_2V_{2D}[1 - W_{2D}(1 - r)]}. \quad (8)$$

If dominance is similar in the two patches ( $h_{MM} \approx k_{MM}$ ), there will again be stronger selection for modifiers that increase heterozygote fitness in the patch experiencing stronger selection (e.g., patches with pesticides). Notice that if one of the migration rates goes to 0, selection for dominance disappears ( $\hat{p}_{A(\text{in patch 1})}\hat{p}_{a(\text{in patch 2})} \rightarrow 0$ ). This occurs because only alleles from the patch that sends out emigrants and receives no immigrants (the source population) will ultimately leave descendants, but, in the absence of immigration into the source population, heterozygotes will be absent and dominance will not evolve.

Increasing the rate of migration in equation (8) increases the strength of selection acting on the modifier. (Recall that  $\hat{p}_{A(\text{in patch 1})}$  and  $\hat{p}_{a(\text{in patch 2})}$  increase with migration.) The reason for this is simple: the strength of selection on the dominance modifier depends on the frequency of heterozygotes, which increases with the immigration of locally rare alleles. However, if migration becomes very common and if dominance is initially low, then it may no longer be possible to maintain a polymorphism (if  $W_{2D}$  in table 2 is less than either  $W_1$  or  $W_3$ ). Hence, selection for dominance can be strongest at intermediate levels of migration because a balanced polymorphism is more likely to occur (fig. 4).

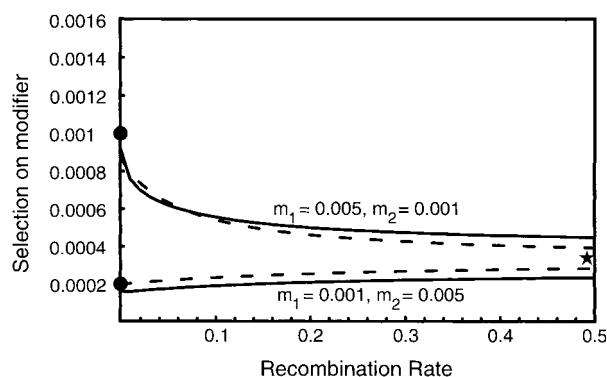
The role of recombination is more complex in the large-scale patch model. According to approximation (8), the fitness of a rare allele that modifies dominance at the  $A$  locus increases with the rate of recombination if the migration rates from patch to patch are low and nearly equal, which is the exact opposite of the result obtained with overdominance. For asymmetric migration, however, increased recombination can lower the fitness of a modifier of dominance (fig. 5). This behavior illustrates the complicated role that genetic associations play in models of the evolution of dominance (cf. Feldman and Karlin 1971; Wagner and Bürger 1985).



**Figure 4:** Selection for a modifier of dominance ( $s_m$ ) as a function of migration in the large-scale patch model. Parameters:  $s = 0.5$ ,  $h_{MM} = 0.5$ ,  $h_{Mm} = 0.4$ ,  $k_{MM} = 0.1$ ,  $k_{Mm} = 0.1$ ,  $r = 0.2$ . *A*, Strong selection against allele  $a$  in patch 2 ( $t = 0.5$ ). *B*, Weaker selection against allele  $a$  in patch 2 ( $t = 0.1$ ). Only in case *A* is a polymorphism maintained as migration becomes frequent. Solid curves give  $s_m$  calculated from the eigenvalues of a local stability analysis. Dashed curves represent approximation for weak modifiers and low migration rates (from eq. [8]). Circles represent selection coefficients (eq. [A2]) obtained from the Dempster (1955) model for a small-scale population structure with  $\alpha = 0.5$ . Note that predictions for the evolution of dominance based on the Dempster model for a multiple-niche polymorphism (circles) coincide well with predictions based on the Levene (1953) model (solid curves at  $m_1 = m_2 = 1/2$ ).

As recombination becomes increasingly large, equation (8) approaches

$$\begin{aligned} s_m(\text{for } r \text{ large}) &\approx (W_{2H} - W_{2D})(2\hat{p}_{A(\text{in patch 1})})\frac{m_2}{m_1 + m_2} \\ &+ (V_{2H} - V_{2D})(2\hat{p}_{a(\text{in patch 2})})\frac{m_1}{m_1 + m_2}. \end{aligned} \quad (9)$$



**Figure 5:** Selection for a modifier of dominance ( $s_m$ ) as a function of recombination in the large-scale patch model. The new modifier allele increases dominance of the wild type in patch 1, with  $s = 0.5$ ,  $h_{MM} = 0.5$ ,  $h_{Mm} = 0.4$ ,  $t = 0.1$ ,  $k_{MM} = 0.1$ , and  $k_{Mm} = 0.1$ . Solid curves give the exact value of  $s_m$  calculated from the eigenvalues obtained by a local stability analysis. Dashed curves represent approximation for weak modifiers and low migration rates (from eq. [8]). Circles represent approximation for  $r = 0$  (from eq. [6a]). The star represents the high recombination approximation (from eq. [9]).

The first two terms on each line are familiar (the change in heterozygote fitness times the approximate frequency of heterozygotes in each patch). The last terms involving the migration rates are interesting. For a neutral model with the same large-scale patch structure, it can be shown that  $m_2/(m_1 + m_2)$  is the expected fraction of individuals from a distant future population whose ancestry can be traced back to individuals currently living in patch 1. Equation (9) thus indicates that the strength of selection favoring a modifier of dominance is weighted by the expected future contribution of individuals from each patch. A sink population (say patch 1, so that  $m_1 \gg m_2$ ) will, on the one hand, contain a high frequency of immigrants and heterozygotes but, on the other hand, will not make a large contribution to the future gene pool since  $m_2/(m_1 + m_2)$  is small. With loose linkage, these two factors offset one another, so that sink and source subpopulations have nearly equal influences on the evolution of dominance. With tight linkage, however, dominance evolves more readily in sink populations (from eqq. [6a] and [6b] and fig. 5) because the sink population does contribute substantially to the future gene pool of the locally favored allele with which the modifier becomes associated.

### Discussion

Cases of polymorphism permanently maintained in a species by the stability of the frequency ratio of a pair of allelomorphs supply opportunities peculiarly favorable to the selective evo-

lution of dominance, for in these cases the heterozygotes are not extremely rare. (R. A. Fisher [1931, p. 360])

Despite a long and acrimonious history, the debate over the general recessivity of deleterious mutations has been largely resolved (Mayo and Bürger 1997). A consensus has formed that the recessivity (or partial recessivity) of mutant alleles results primarily from an insensitivity to small changes that is typical of many metabolic pathways (see fig. 1; Wright 1929b, 1934a; Kacser and Burns 1981; Keightley 1996). Nevertheless, there is clear evidence that dominance relationships can be, and indeed have been, altered by modifier loci under certain circumstances (reviewed in Sheppard 1961, 1975; Sved and Mayo 1970; Mayo and Bürger 1997).

### *Evolution of Dominance with Balanced Polymorphisms*

For dominance to evolve rapidly via selection on dominance modifiers, there must be substantial genetic variance at the loci involved. Fisher (1928a, 1928b) originally argued that the dominance of wild-type alleles would evolve to reduce the deleterious fitness effects of mutations, but this is an extremely slow and ineffective process because of the rarity of the genotypes affected. Dominance is much more likely to evolve when the affected genotypes are at intermediate frequency. We have developed models that examine the initial selective advantage of a modifier allele that alters dominance relations among alleles maintained at a balanced polymorphism, either by overdominant selection or migration-selection balance.

A modifier allele that increases heterozygote fitness can always invade a population at an overdominant equilibrium. While rare, the modifier allele will experience selection of strength equal to its effect on the heterozygote fitness times its probability of being found in a heterozygote. Selection on a modifier is thus comparable in strength to that at the primary selected locus. Since selection due to dominance modification can be strong, it is reasonable that the modifier will evolve in response to its effects on dominance ( $s_m$ ) rather than any direct effects on fitness ( $s_d$ ), a claim that cannot be made for dominance modifiers that affect alleles held at a mutation-selection balance (Wright 1929b). The spread of a modifier that increases dominance is hastened by tighter linkage while the modifier is rare but is hampered once the modifier becomes common as a result of genetic associations (fig. 3).

Perhaps a more likely scenario for the evolution of dominance involves spatial variation in selection. Spatial variation in the direction of selection can maintain substantial amounts of genetic variation under a broader range of parameters (reviewed in Felsenstein 1976; Hedrick et al.

1976), thereby increasing the opportunity for dominance levels to evolve. By investigating a two-patch model, we find that a modifier that increases the fitnesses of heterozygotes in each patch is positively selected when rare. Even if the modifier increases heterozygote fitness in one patch and decreases it in the second patch, the modifier can invade as long as it increases the weighted average heterozygote fitness (weighted according to table 2 if patchiness occurs on a small spatial scale or by equation [7] if patchiness occurs on a larger scale). Again, the strength of selection is proportional to the average effect of the modifier on heterozygote fitness and to the frequency of heterozygotes. Since migration rates may be much larger than mutation rates, the genetic variance observed at a migration-selection balance is likely to be orders of magnitude greater than that observed at a mutation-selection balance. Interestingly, the evolution of dominance causes deleterious alleles in each patch to become more recessive, which increases the fitness of heterozygotes. This, in turn, causes heterozygotes to become more frequent and increases the opportunity for dominance evolution in a self-reinforcing process (Parsons and Bodmer 1961; Sheppard 1961).

In short, heterozygotes are typically much more common at a polymorphism maintained by overdominance or by spatial variation in selection than they are at a mutation-selection balance. Consequently, strong selection for dominance levels to evolve may be observed whenever an overdominant or multiple-niche polymorphism is maintained, in contrast to the exceedingly weak selection coefficients found in mutation-selection models pioneered by Fisher (1928*a*, 1929) and Wright (1929*a*, 1929*b*, 1934*a*). Since Wright's objections to Fisher's theory of dominance were based on the rarity of heterozygotes at mutation-selection balance, they do not apply to the balanced polymorphisms considered here, as Wright (1929*b*, p. 277) himself pointed out.

#### *Evolution of Dominance with Pesticide Resistance*

One of our primary motivations for developing a spatial model was to explain the evolution of dominance at pesticide resistance genes. Pesticide resistance corresponds to a situation where an allele (i.e., an allele conferring pesticide resistance) is favored in treated areas but is often at a disadvantage in untreated areas because of the presumed fitness costs of resistance. Pesticide resistance varies from partial recessivity to complete dominance but is more often partially dominant in the presence of pesticides; that is,  $h < 1/2$  (Bourguet et al. 1996; Bourguet and Raymond 1998). Fitness costs associated with pesticide resistance may also be recessive (e.g., Roush and Plapp 1982), co-

dominant (e.g., McKenzie 1996, p. 69), or dominant (e.g., Chevillon et al. 1997).

Three major mechanisms are known by which dominance for pesticide resistance may be modified. First, the enzymatic targets of a pesticide may evolve increased activity through altered gene expression, duplication, or posttranslational modification (reviewed in Taylor and Feyereisen 1996). Recently, variation in the activity of the pesticide target acetylcholinesterase has been investigated by Bourguet et al. (1997) in the mosquito *Culex pipiens*. They found that four resistant strains from different geographical areas displayed varying levels of dominance with respect to insecticide resistance. A correlation between increased acetylcholinesterase activity and higher dominance levels was also found. Since the strains did not differ in their amino acid sequence in the catalytically active regions of acetylcholinesterase, Bourguet et al. (1997) concluded that the expression of acetylcholinesterase has been regulated by either neighboring or distant sites, thereby altering dominance levels. A second type of modifier confers additional resistance to heterozygotes. Such modifiers have been described by Grigolo and Openoorth (1966) and Rupes and Pinterova (1975). They found that resistance in houseflies to DDT conferred by the sodium channel modification (*kdr*) became more dominant in the presence of DDT-ase, a detoxifying enzyme that provides only a low level of resistance by itself. Third, evolution of dominance could occur by the replacement of less dominant wild-type alleles by more dominant wild-type alleles, a process suggested by Haldane (1930). Although cases of allele replacement have been described recently at pesticide resistance loci (e.g., Guillemaud et al. 1998; Lenormand et al. 1998), it is not yet clear to what extent dominance coefficients have changed. Since spatial heterogeneity in pesticide application helps to maintain genetic variance at pesticide resistance loci (as observed by Guillemaud et al. [1998]), we expect that increased dominance levels may evolve in natural populations through one or more of the above mechanisms.

Dominance of resistant alleles limits the effectiveness of pesticide treatments, so that efforts to reduce selection on dominance (e.g., by hindering migration between treated and untreated areas) may prolong their usefulness. This is of practical importance for managing resistance. For example, for cultivars of plants that have been genetically engineered to produce insecticidal toxins using a gene from *Bacillus thuringiensis*, strategies for delaying resistance within insects (Alstad and Andow 1995; Gould 1998) are based on the fact that resistance to the toxin is partially recessive (Bourguet and Raymond 1998). Evolution toward higher dominance levels would hasten the spread of resistance alleles and jeopardize the effectiveness of these transgenic crops.

We suggest that dominance levels commonly evolve whenever spatial heterogeneity maintains a polymorphism between alleles favored at different locations. Such a scenario is not restricted to pesticide resistance. Alleles responsible for any adaptation to a new environment (e.g., a new parasite, climate, or chemical challenge) may often have a fitness cost in the previous environment (see Carrière et al. 1994; Simms and Triplett 1994; Bergelson and Purrington 1996; McKenzie 1996). Furthermore, such environmental changes will often occur, at least initially, in limited regions, creating spatial heterogeneity in selection. There is evidence for just such a scenario with the peppered moth *Biston betularia*. Mani (1980) showed that accounting for spatial variation in selection (probably caused by varying degrees of industrialization) better explained the observed frequency distribution of the melanic allele. As a further example, Doebley et al. (1995) studied two quantitative trait loci responsible for the morphological differences between maize and teosinte. In each case where there was a significant effect on a trait, alleles present in maize were more dominant on their original maize genetic background than they were when introgressed onto a teosinte

genetic background. As Doebley et al. (1995, p. 344) conclude, "this change in gene action could have resulted from selection during the domestication process for modifier loci that enhanced the expression of the trait in the heterozygote." Gene flow from natural teosinte populations would have maintained heterozygotes within the domesticated strains and may have been critical for the evolution of dominance at these loci. Thus, even when a beneficial allele is spreading through a population, spatial heterogeneity in selection will prolong the time period during which heterozygotes are frequent, thereby widening the window of opportunity within which dominance may evolve.

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### APPENDIX

#### Models of the Evolution of Dominance at a Balanced Polymorphism

##### Overdominance

Let  $x_1$ ,  $x_2$ ,  $x_3$ , and  $x_4$  denote the frequencies of the chromosomes  $AM$ ,  $aM$ ,  $Am$ , and  $am$ , respectively. We assume nonoverlapping generations and census chromosomes among juveniles. Juveniles disperse at random, settle, and then experience viability selection. Adults mate randomly, producing gametes via meiosis with recombination. Consequently, among the next generation of juveniles, the chromosome frequencies are

$$\begin{aligned}\overline{Wx}'_1 &= x_1(x_1W_1 + x_2W_{2D} + x_3W_1 + x_4W_{2H}) - rDW_{2H}, \\ \overline{Wx}'_2 &= x_2(x_1W_{2D} + x_2W_3 + x_3W_{2H} + x_4W_3) + rDW_{2H}, \\ \overline{Wx}'_3 &= x_3(x_1W_1 + x_2W_{2H} + x_3W_1 + x_4W_{2R}) + rDW_{2H}, \\ \overline{Wx}'_4 &= x_4(x_1W_{2H} + x_2W_3 + x_3W_{2R} + x_4W_3) - rDW_{2H},\end{aligned}\tag{A1}$$

where  $D = x_1x_4 - x_2x_3$  is the linkage disequilibrium within the population,  $W_i$  is the relative fitness of genotype  $i$ , and  $W$  is the mean relative fitness, which equals the sum of the right-hand sides of equations (A1).

The fate of a new modifier allele,  $m$ , introduced into a population at low frequency can be determined by linearizing equations (A1) under the assumption that the system is very near the equilibrium defined by equation (1):  $x_1 = \hat{p}_A$ ,  $x_2 = 1 - \hat{p}_A$ ,  $x_3 = 0$ , and  $x_4 = 0$ . This system of linear equations breaks up into two separate sets of linear equations: one that describes the stability of the equilibrium in the absence of the  $m$  allele (internal stability) and one that describes the stability of the equilibrium to invasion of the  $m$  allele (external stability). As long as  $W_{2D} > W_1$ ,  $W_3$ , the equilibrium defined by equation (1) with allele  $M$  fixed is internally stable. Whether or not allele  $m$  will invade is then determined by the eigenvalues of the  $2 \times 2$  external stability matrix (J). If the leading eigenvalue ( $\lambda_L$ ) of this matrix is  $>1$ , allele  $m$  will increase in frequency (see Feldman 1970 for details about the methods).

Each element in the matrix J is strictly positive when  $r > 0$ . In this case, by the Perron-Frobenius theorem (Gantmacher 1989), the leading eigenvalue  $\lambda_L$  will be real and positive. It is given by

$$\lambda_L = 1 + \frac{W_{2H}(1-r) - W_{2D}}{2\bar{W}} + \frac{\sqrt{(\hat{p}_A - \hat{p}_a)^2 [W_{2H}(1-r) - W_{2D}]^2 + 4\hat{p}_A\hat{p}_a r^2 W_{2H}^2}}{2\bar{W}} \tag{A2}$$

To determine when  $\lambda_L > 1$ , we examine the characteristic polynomial of the local stability matrix, which is a quadratic with positive  $\lambda^2$  term. The characteristic polynomial evaluated at  $\lambda = 1$  is equal to

$$(W_{2H} - W_{2D}) \frac{\hat{p}_A\hat{p}_a [W_{2H}(1-2r) - W_{2D}]}{\bar{W}^2} \tag{A3a}$$

and has a slope of

$$-\frac{[W_{2H}(1-r) - W_{2D}]}{\bar{W}} \tag{A3b}$$

If either (A3a) or (A3b) is negative, the characteristic polynomial must cross the X-axis above  $\lambda = 1$  (as long as  $r > 0$ ), and hence the leading eigenvalue will be  $>1$ . If  $W_{2H} < W_{2D}$ , neither of these conditions will hold. If  $W_{2H} > W_{2D}$ , either (A3a) is negative (for  $(W_{2H} - W_{2D})/(2W_{2H}) < r \leq 1/2$ ) and/or (A3b) is negative (for  $r < (W_{2H} - W_{2D})/W_{2H}$ ). If  $r = 0$ , the eigenvalues may be found explicitly and equal  $1 + s_{mA}$  and  $1 + s_{ma}$ , given by equations (2). Again, the leading eigenvalue will be  $>1$  if  $W_{2H} > W_{2D}$ . Therefore, allele  $m$  will invade a population at the overdominant equilibrium (1) If  $W_{2H} > W_{2D}$  and will otherwise disappear from the population.

### Direct Selection on Modifier

First, consider a rare modifier allele,  $m$ , which experiences no direct selection and which is introduced into a population at equilibrium. Denote the leading eigenvalue of the external stability matrix,  $J$ , by  $\lambda_L$  and define  $1 + s_m = \lambda_L$ . If allele  $m$  also has a direct selective effect, such that  $Mm$  individuals have fitness  $(1 + s_d)$  even in the absence of dominance modification, every term in the external stability matrix becomes multiplied by  $(1 + s_d)$ , and the new external stability matrix can be written as  $J^* = (1 + s_d)J$ . The leading eigenvalue of  $J^*$  is then equal to  $(1 + s_d)(1 + s_m)$ , which demonstrates that  $s_m$  is equivalent to a standard selection coefficient ( $s_d$ ). Indirect and direct selection will exactly balance when  $(1 + s_d)(1 + s_m) = 1$ , or  $s_m + s_d \approx 0$  for weak selection. In this case, allele  $m$  will neither increase nor decrease at a geometric rate. Therefore, the selection coefficients  $s_m$  given in the text can be used to determine upper bounds for the strength of opposing direct selection that may act without reversing the direction of evolution of the modifier.

### Large-Scale Patch Model

Let  $x_1, x_2, x_3,$  and  $x_4$  denote the frequencies of the chromosomes  $AM, aM, Am,$  and  $am$  among juveniles in patch 1. The chromosome frequencies after selection in patch 1 ( $x'_i$ ) are described by equation (A1) using the fitnesses,  $W_i$  from table 2, with  $\alpha$  set to 1. Although recombination will occur later during reproduction, it is mathematically equivalent to allow recombination at this stage. Similarly, in patch 2, let  $y_1, y_2, y_3,$  and  $y_4$  denote the frequencies of the chromosomes  $AM, aM, Am,$  and  $am$  among juveniles. In patch 2, the fitnesses are given by  $V_i$ , where  $V_i$  is given by  $W_i$  from table 2 with  $\alpha$  set to 0. The chromosome frequencies after selection in patch 2 ( $y'_i$ ) are also described by equation (A1) with  $y_i$  and  $V_i$  replacing  $x_i$  and  $W_i$ . Migration of reproductive adults then occurs, followed by mating within a patch. The chromosome frequencies among juveniles in the next generation in the two patches ( $x''_i$  and  $y''_i$ ) are given by

$$\begin{aligned}
 x_i'' &= (1 - m_1) \frac{x_i'}{\bar{W}} + m_1 \frac{y_i'}{\bar{V}}, \\
 y_i'' &= (1 - m_2) \frac{y_i'}{\bar{V}} + m_2 \frac{x_i'}{\bar{W}},
 \end{aligned}
 \tag{A4}$$

where  $\bar{W}$  and  $\bar{V}$  are the mean fitnesses in patches 1 and 2, respectively.

As in the small-scale patch model, we determine stability of the initial equilibrium with  $M$  fixed to invasion by the modifier allele,  $m$ . With low rates of migration, the initial equilibrium is given by equations (5), describing a migration-selection balance. Following the same procedures as in the previous model, we determined the necessary and sufficient conditions for the leading eigenvalue to be greater than one and the approximate selection coefficient acting on the  $m$  allele while it is rare. The results are presented in equations (6a)–(9). A Mathematica 3.0 package (Wolfram 1996) with the complete analysis is available on request. This package also contains simulations that indicate that if  $s_m > 0$  and  $r > 0$ , an additive modifier will spread to fixation at a rate very nearly equal to that predicted from a simple one-locus model describing the spread of a beneficial allele,  $m$ , with fitness  $1 + s_m$  in heterozygotes and  $1 + 2s_m$  in  $mm$  homozygotes.

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