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ADAPTIVE DISTANCE AND THE GENETIC BASIS OF HETEROSIS

DAVID HOULE[1]
Department of Ecology and Evolution, State University of New York, Stony Brook, New York 11794 and
Department of Biology, University of Oregon, Eugene, Oregon 97403

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Smouse (1986) proposed an analysis of marker-associated heterosis which he claimed would aid in distinguishing whether it was due to overdominance or directional dominance. I analyze two of the cases most likely to cause heterosis due to directional dominance, nonrandom mating and linkage between a marker and a selected locus, and show that the consequences in the Smouse model are precisely equivalent to overdominance at the marker locus. The Smouse model is therefore unlikely to be useful in determining the genetic basis of heterosis.

Plant and animal breeders have long known that crosses between genetically dissimilar parents often produce superior offspring, and crosses of closely related individuals tend to produce inferior ones (Darwin 1868). These observations, termed heterosis and inbreeding depression, respectively, are genetically the same phenomenon. There are two genetic mechanisms which can explain both heterosis and inbreeding depression: directional dominance and overdominance. The overdominance hypothesis supposes that heterosis is due to increased heterozygosity for loci at which the heterozygote is superior to both homozygotes. The directional dominance hypothesis builds on the observation that deleterious genes tend to be recessive. Heterosis on crossing is due to reduced homozygosity for these recessives. Heterosis and inbreeding depression are descriptions of the phenomena; dominance and overdominance are genetic mechanisms which can explain them (Charlesworth and Charlesworth 1987).

In recent years, many populations where heterozygosity at allozyme loci is positively correlated with fitness-related traits have been identified (Mitton and Grant 1984; Zouros and Foltz 1987). In these cases, marker heterosis has been detected as a correlation between the number of heterozygous loci and a phenotype. I will refer to this method of analysis as the heterozygosity-counting (HC) model. Like heterosis of offspring of genetically dissimilar parents, marker-associated heterosis may result from directional dominance or overdominance, or a combination of the two (Houle 1989).

Smouse (1986) reasoned that if overdominance at the marker locus is causing heterosis, then the marker allele frequencies will reflect the relative fitnesses measured for each genotype. For example, in a two-allele case, the fitness of the rare homozygote would be less than that of a common homozygote. Smouse derived a regression model, the adaptive-distance (AD) model, which would explain all of the genetic variance in fitness at equilibrium in this case. In several cases, the AD model has given a better fit than the HC model (Bush et al. 1987; Mitton 1993). The AD model is of interest because Smouse (1986) asserted that it would explain more variance than the HC model if heterosis was due to overdominance, and therefore provides a method for determining the cause of allozyme-associated heterosis. This is questionable, as previous work has demonstrated that rarer homozygotes at neutral loci will have lower induced fitness under the dominance hypothesis (Ohta 1971; Ohta and Cockerham 1974; Charlesworth 1991), in qualitative agreement with the overdominant AD model. Smouse did not analyze any cases where heterosis was due to directional domi-

[1] Present address: Department of Zoology, University of Toronto, Toronto, Ontario M5S 1A1, Canada.

nance, although he did mention the possibility that heterosis could be caused by the chromosome segment around the marker locus, rather than the marker locus itself.

Smouse assumed random mating in his analysis, although the plants to which the AD model has been applied self at an appreciable rate (Bush et al. 1987; Bush and Smouse 1991; Mitton 1993). Strobeck (1979) showed that in a partially selfing population overdominance at any locus in the genome causes heterozygosity at all neutral loci to be correlated with fitness. Thus, with nonrandom mating, the apparent fitness of a marker locus will be influenced by selection pressure at other loci, even if overdominance is responsible for variance in fitness.

Directional dominance will cause marker-associated heterosis when genotypes at the marker locus are correlated with those at loci which affect fitness. Here I consider partial nonrandom mating and linkage in finite populations as potential sources of these genotypic correlations. Nonrandom mating causes correlations between homozygosity at all loci in the genome, as inbreds are less likely to be heterozygous at all loci. This process promotes marker-associated heterosis, even with unlinked loci (Haldane 1949; Ohta and Cockerham 1974). In this case, genotypic associations are due to identity disequilibria, and not to the more familiar gametic-phase (linkage) disequilibria. Identity disequilibria reflect associations between genotypes that are not explained by gametic-phase disequilibria (Weir and Cockerham 1969, 1973; Ohta and Cockerham 1974). In the case of linkage in finite populations, heterosis occurs as a result of gametic-phase disequilibria (Ohta 1971). I show that in each case, the AD model fits as well with dominance as it does when there is overdominance at the marker locus.

The Adaptive Distance Model

Smouse (1986) constructed the overdominant adaptive distance (OAD) model on the assumptions that the marker loci are overdominant for fitness, are unlinked with each other, interact multiplicatively in determining fitness, and the gene frequencies are at equilibrium. Smouse also implicitly assumed random mating by assuming Hardy-Weinberg equilibrium. For a single locus with two alleles, a standard representation of an overdominant relative-fitness array is the following:

Genotypes:	A_1A_1	A_1A_2	A_2A_2
Relative fitness:	$1 - t_1$	1	$1 - t_2$
	w_{11}	w_{12}	w_{22}
Frequency:	p^2	$2pq$	q^2

In a panmictic population at gametic equilibrium, the equilibrium frequencies of the two alleles are

$$\hat{p} = \frac{t_2}{t_1 + t_2} \quad \text{and} \quad \hat{q} = \frac{t_1}{t_1 + t_2}.$$

If t_1 and t_2 are both much less than 1, then $-t_1 \approx \ln(1 - t_1)$ and $-t_2 \approx \ln(1 - t_2)$. Then the expected log fitness for genotype A_1A_1, relative to w_{12}, is

$$\ln(w_{11}) \approx -t_1 = -\left(\frac{t_1 t_2}{t_1 + t_2}\right)\left(\frac{t_1 + t_2}{t_2}\right) = -L\frac{1}{\hat{p}}, \quad (1)$$

where $L = w_{12} - \bar{w}$, the segregational load for the locus, the reduction of population mean fitness from that of a population consisting solely of the optimal genotype. Similarly, $\ln(w_{22}) \approx -L(1/\hat{q})$ and $\ln(w_{12}) = 0$. Smouse called the inverse of the observed allele frequency of the corresponding homozygote the adaptive distance, symbolized X. Heterozygotes have an adaptive distance of 0. Adaptive distances are thus easily obtained from genotype frequencies and associated measures of individual fitness, and linear regression of adaptive distance on log-relative fitness yields an estimate of the segregational load for the locus.

Overdominance with Nonrandom Mating

Recurrent nonrandom mating affects the equilibrium frequencies of alleles at overdominant loci (Li 1955; Kimura and Ohta 1971), and therefore the OAD model must be modified to take this into account. With the overdominant fitness array outlined above, and recurrent inbreeding to degree $\hat{f}$, there is an equilibrium when

$$t_2(\hat{q} + \hat{f}\hat{p}) = t_1(\hat{p} + \hat{f}\hat{q}), \quad (2)$$

a quantity I define as Λ. This condition restricts balanced polymorphisms to regions where $\hat{p}$ and $\hat{q}$ are not close to 0 (Li 1955; Kimura and Ohta 1971). For A_1, the equilibrium is

$$\hat{p} = \frac{t_2 - t_1\hat{f}}{t_2(1 - \hat{f}) + t_1(1 - \hat{f})}. \quad (3)$$

This requires that the AD model be adjusted to

$$\ln(w_{11}) \approx -t_1 = -\Lambda(p + \hat{f}q)^{-1}, \quad (4)$$

and

$$\ln(w_{22}) \approx -t_2 = -\Lambda(q + \hat{f}p)^{-1}. \quad (5)$$

The appropriate adaptive distance for genotype A_1A_1 is the quantity $(p + \hat{f}q)^{-1}$; for A_2A_2 it is $(q + \hat{f}p)^{-1}$. I define these quantities as inbreeding adaptive distances (IADs). As with random mating, these more general adaptive distances may be calculated from readily measurable quantities, and are linearly related to log-standardized fitness at equilibrium for a single overdominant two-allele polymorphism. However, Strobeck's (1979) results make it clear that the apparent fitnesses of each genotype also reflect overdominant selection elsewhere in the genome.

Induced Fitnesses of Neutral Loci as a Result of Nonrandom Mating

Ohta and Cockerham (1974) have demonstrated that marker heterosis arises under partial selfing when a neutral marker locus is linked to a single locus, polymorphic for alleles maintained by mutation–selection balance. Charlesworth (1991) has simulated a multiple-locus analog, where inbreeding depression arises at many loci, either by overdominance or mutation–selection balance, and again showed that heterosis at a neutral-marker locus arises under partial selfing. Both noted that the rare homozygote at a marker locus has lower induced fitness than the common homozygote, in qualitative agreement with the AD models.

I take the more general, but less rigorous, approach of Cockerham and Rawlings (1967), and make no assumption about the cause of inbreeding depression to derive the expected fitnesses of marker genotypes under a single type of nonrandom mating. I consider a large diploid population with nonoverlapping generations, in which consanguineous matings take place with probability S, and random matings with probability $1 - S$, where $S \ll 1$. I assume that the fitness of outbred individuals is 1, while inbred individuals have fitness $1 - C$. This simplifying assumption is unrealistic if inbreeding is recurrent, although if $S(1 - C) \ll 1$ the inaccuracy is small. The marker locus itself is assumed to be neutral. Inbreeding depression arises through variation at unlinked loci and could be the result of either directional dominance or overdominance. Since many observations of allozyme heterosis involve growth rates or sizes of prereproductive individuals, I assume that viabilities of inbred and outbred individuals are equal until the time of measurement, and that the phenotype measured is perfectly correlated with fitness. If the phenotype measured is growth rate, for example, I assume that inbred individuals grow at a rate $1 - C$, which eventually results in relative fitness of $1 - C$.

In this simple system, there are two subpopulations, one inbred to degree f_I, and the other outbred. The degree of inbreeding of the offspring of consanguineous matings, f_I, depends on the system of matings which brings it about. For example, following selfing, $f_I = 0.50$. I consider a neutral locus, A, with two alleles, A_1 and A_2, with frequencies p and q. The outbred subpopulation is at Hardy-Weinberg equilibrium. The inbred subpopulation has genotype frequencies

$$g_{I\cdot 11} = p^2 + pq[f' + f_I(1 - f')], \quad (6)$$

$$g_{I\cdot 12} = 2pq[1 - f' - f_I(1 - f')], \quad (7)$$

$$g_{I\cdot 22} = q^2 + pq[f' + f_I(1 - f')], \quad (8)$$

where f' is the inbreeding coefficient of the entire population in the previous generation. The inbreeding coefficient of the total population before selection is $\bar{f} = S[f' + f_I(1 - f')]$. The genotype frequencies in the combined population of inbred and outbred individuals are the usual $p^2 + \bar{f}pq$, $2pq(1 - \bar{f})$, and $q^2 + \bar{f}pq$. Standardizing by the relative fitness of the heterozygote, the relative fitnesses of the two homozygotes are

$$w_{11} = \left(1 - C\frac{pS + q\bar{f}}{p + q\bar{f}}\right)\left(1 - C\frac{S - \bar{f}}{1 - \bar{f}}\right)^{-1}, \quad (9)$$

$$w_{22} = \left(1 - C\frac{qS + p\bar{f}}{q + p\bar{f}}\right)\left(1 - C\frac{S - \bar{f}}{1 - \bar{f}}\right)^{-1}. \quad (10)$$

Taking the log of these fitnesses yields

$$\ln(w_{11}) \approx -\left(\frac{C\bar{f}(1 - S)}{1 - \bar{f} - C(S - \bar{f})}\right)(p + \bar{f}q)^{-1}, \quad (11)$$

$$\ln(w_{22}) \approx -\left(\frac{C\bar{f}(1 - S)}{1 - \bar{f} - C(S - \bar{f})}\right)(q + \bar{f}p)^{-1}, \quad (12)$$

assuming that $1 - w_{11}$ and $1 - w_{22} \ll 1$. Note that the first term of each equation is the same, and does not depend on allele frequencies, while the second terms are the adaptive distances un-

der inbreeding from equations 4 and 5, assuming $\bar{f} = \hat{f}$. When the population is not at inbreeding equilibrium, the IAD model is not entirely accurate if the marker locus is overdominant. The discrepancy is related to the difference between $\bar{f}$ and a weighted average $\tilde{f}$ for the previous generations. Unless the variance of $\bar{f}$ is large, such discrepancies are likely to be small. If the marker locus is linked to some of the loci responsible for inbreeding depression, the IAD still fits precisely, with the magnitude of marker heterosis increased slightly (analysis not shown).

If consanguineous mating is recurrent, f' reaches an equilibrium state $\hat{f}$, which depends on the co-ancestry of mating relatives, the rate of inbreeding, and C. The rate of inbreeding is reduced by the lowered fitness of inbreds to

$$S^* = S\frac{1 - C}{1 - SC}. \qquad (13)$$

S* may be plugged into standard equations (Li 1976) for $\hat{f}$, assuming, as above, that $S(1 - C)$ is not very large. For example, with partial selfing $\hat{f} = S^*/(2 - S^*)$.

In figure 1, I graph the proportion of genetic variance of log fitness due to inbreeding explained by the IAD, OAD, and HC models for a population at selfing equilibrium for three different selfing rates when $C = 0.3$. The selfing rates and level of inbreeding depression used are common among self-compatible plants (Charlesworth and Charlesworth 1987). Recall that I have made no assumption as to the genetic causes of inbreeding depression; these results hold for either overdominance or directional dominance. The total genetic variance resulting from nonrandom mating on a log scale is $[\ln(1 - C)]^2 S(1 - S)$. The IAD model explains the most genetic variance in all cases; closely followed by OAD, so closely that the two models overlap in the upper panels of figure 1. The HC model is equivalent to both the OAD and IAD models at $P = 0.5$, but explains less variance as allele frequencies become less equitable. Notice that the magnitude of the variance explained is in line with experimental observations of allozyme heterosis. The AD models explain on the order of a few percent of the genetic variance caused by inbreeding per locus. Assuming that other sources of genetic and environmental variance are not of a larger order of magnitude than the variance due to nonrandom mating, this is in line with the levels of variance explained in studies showing allozyme heterosis and the simulation results of Charlesworth (1991).

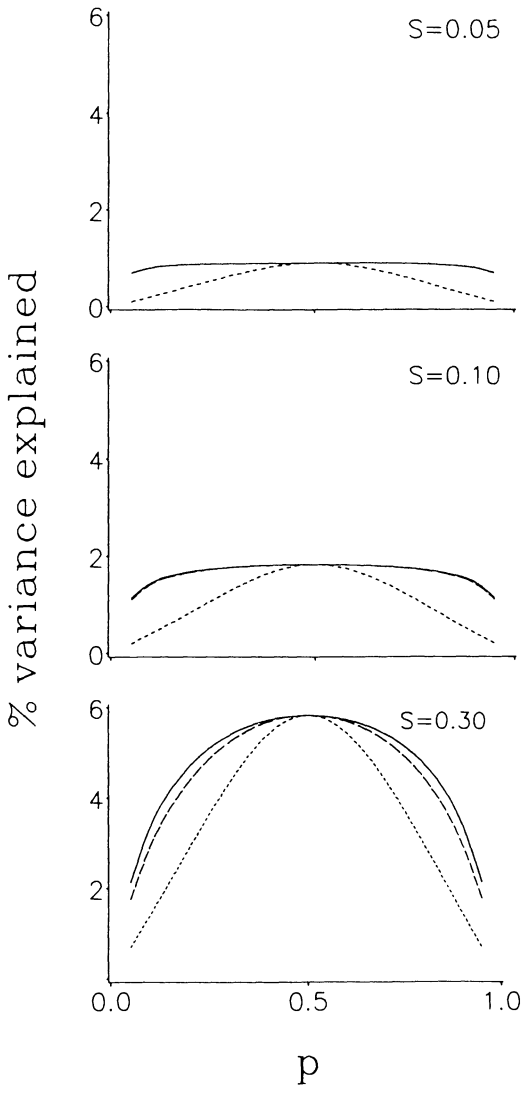

FIG. 1. Fit of the adaptive-distance and heterozygosity-counting models when variance in fitness is entirely due to inbreeding depression under partial selfing. The X axis is the gene frequency at the neutral marker locus, and the Y-axis is the percentage of the total variance explained. The population selfs at rate S each generation, and the fitness of selfed individuals is 0.7 times that of outcrossed individuals. Fitnesses were log transformed before analysis. Solid lines represent IAD; long dashed lines represent OAD; and short dashed lines represent HC.

It is important to realize that heterosis generated by nonrandom mating does not influence the allele frequencies at neutral loci (Haldane 1949; Strobeck 1979; Charlesworth 1991). The

reduced fitness of rare alleles in homozygotes is exactly compensated by the increased relative fitness of heterozygotes bearing the same alleles, with no net impact on allele frequencies.

Finite Population Size

In finite outbreeding populations, gametic-phase disequilibria may arise between linked loci (Hill and Robertson 1968; Kimura and Ohta 1971). Ohta (1971) has shown, using diffusion approximations, that a neutral locus linked to another locus at which deleterious mutations occur is expected to show heterosis, and that the rarer homozygotes are expected to have the lowest fitness. Heterosis arises because new mutations occur on a single chromosome and remain associated with the alleles of nearby loci to a degree controlled by the recombination rate. As long as this association exists, homozygosity of deleterious alleles tends to occur in individuals also homozygous at closely linked loci. Since a pair of rare marker alleles tends to share a more recent common ancestor than common alleles, this effect is most pronounced for rare homozygotes.

In Ohta's model, the load-bearing locus mutates at rate μ to a deleterious allele with fitnesses $1 - hs$ in heterozygotes and $1 - s$ in homozygotes. The effective population size is N. She assumes that allele frequencies at the marker locus change much more slowly than those at the selected locus, so that population size cannot be too small ($4Nhs \gg 1$), and that the deleterious allele is only partially recessive. The relevant equations (equations 6 and 7 in Ohta 1971) have the form

$$s_1' = s(1 - 2h)(\hat{x}_1^2 - \widehat{x_1x_2}), \tag{14}$$

where s_1' is the apparent selection on neutral genotype $A_1A_1[s_1' \approx \ln(w_{11})]$, "^" denotes an expectation, and x_1 and x_2 are the frequencies of the detrimental allele on chromosomes bearing A_1 and A_2, respectively. The necessary moments are

$$\hat{x}_1 = \hat{x}_2 = \frac{\mu}{hs}, \tag{15}$$

$$\widehat{x_1^2} = [4Npqc\widehat{x_1x_2} + \hat{x}_1(Np\mu + 1)](\alpha^{-1}), \tag{16}$$

and

$$\widehat{x_1x_2} = \hat{x}_1 \frac{\begin{array}{c}2\mu\alpha\beta + pc\beta(4Np\mu + 1) \\ + qc\alpha(4Nq\mu + 1)\end{array}}{\begin{array}{l}\alpha\beta(c + 2sh) \\ - 4Npqc^2[\alpha + 4Nshp(1 - 2p)]\end{array}}, \tag{17}$$

where

$$\alpha = 4Np(qc + sh) + 1$$

and

$$\beta = 4Nq(pc + sh) + 1,$$

and c is the recombination fraction between the two loci.

If N is not very large ($N \ll 1/\mu$), equation 14 can be approximated

$$s_1' \approx s(1 - 2h)\frac{\mu}{hs}\left[\frac{1}{\alpha} - \frac{c(\alpha + p\beta)}{(c + 2hs)\alpha\beta}\right]. \tag{18}$$

Finally, with the assumption that the load-bearing locus is closely linked to the marker locus ($c < hs$),

$$s_1' \approx \frac{\mu(1 - 2h)}{4Nh(c + sh)}\frac{1}{p}, \tag{19}$$

and

$$s_2' \approx \frac{\mu(1 - 2h)}{4Nh(c + sh)}\frac{1}{q}. \tag{20}$$

Once again, standardized log fitness is linearly related to the inverse of the allele frequency of the marker locus. A single load-bearing locus would clearly have a small impact on the apparent fitnesses of marker genotypes, although each marker locus may be closely linked to many such loci. An analysis of the magnitude of heterosis expected from linkage in finite populations would have to include these additional loci. Circumstances which restrict recombination, such as inversion polymorphisms, would increase the number of loci capable of influencing the fitness of marker loci. Analyses of multilocus cases have never been done.

Discussion

I have analyzed the properties of Smouse's (1986) adaptive-distance model in two cases where directional dominance causes marker-associated heterosis. Both cases are fairly restricted. To analyze nonrandom mating, I have assumed that individuals with different degrees of inbreeding are so rare that they may be ignored. It is encouraging that Charlesworth's (1991) more realistic simulations of heterosis under partial selfing give qualitatively similar conclusions. Similarly, a more satisfying analysis of heterosis due to linkage in finite populations would include multiple-linked loci, and not assume away changes in allele frequency at the neutral locus.

In addition, other cases where heterosis due to dominance may arise such as migration, and recent strong directional selection (Houle 1989), have never been investigated. However, since all cases of marker heterosis which have been analyzed fit the adaptive distance models, it appears very unlikely that such models are of any use in distinguishing the genetic basis of heterosis. Any claims to the contrary should be verified by explicit analyses of alternative hypotheses.

The two cases analyzed here are relevant to some of the more convincing cases where heterosis has been observed. Of the many species in which marker-associated heterosis has been observed, many have small effective population sizes, and there are very few whose genetics are known well enough to rule out the existence of chromosomal inversions. Both finite population size and inversion polymorphism promote gametic-phase disequilibria. Two of the most famous examples of heterosis involve inversions (Lewontin and White 1960; Dobzhansky 1970). In *Drosophila psuedoobscura* allozyme alleles are in gametic disequilibrium with the heterotic inversions (Prakash and Lewontin 1968, 1971). In the absence of karyotypic information, heterosis associated with these loci would seem consistent with the overdominance hypothesis.

The possibility that random gametic disequilibria could generate substantial heterosis is made more plausible by measurements of mutational load in *D. melanogaster* (Crow and Simmons 1983). These studies suggest that the average heterozygous selection coefficient against deleterious mutations is approximately $hs = 0.03$, so loci within about 6 centi-Morgans (cM) would fall within the range where equations 19 and 20 apply. With 15,000 loci in the *Drosophila* genome spread over 260 cM, deleterious mutations at approximately 350 loci fall in this region. The total haploid genomic mutation rate of 0.25 to 0.5 estimated in these studies suggests each such region would have a total mutation rate of 0.005–0.01.

Nonrandom mating is likely to be the cause of allozyme-associated heterosis in a number of plant species (Schaal 1975; Ledig et al. 1983). Such observations should be expected if a species is self-compatible. They may also arise in any organism through matings of relatives, as long as inbreeding depression is high. There is evidence for such nonrandom mating in some plants, probably due to limited dispersal (Hedrick and Cockerham 1986; Campbell and Dooley 1992; Waser 1993). The increasing number of direct studies in animal populations have found a wide variety of mating structures, including cases of isolation by distance, although analyses of these data are quite controversial (Rowley et al. 1993; Shields 1993; Smith 1993). The results in figure 1 make it clear that it does not take much nonrandom mating to generate detectable heterosis. Low levels of nonrandom mating are very difficult to detect, especially through deviations from Hardy-Weinberg equilibrium (Ward and Sing 1970). Detailed pedigree analyses may ultimately prove more useful for this purpose.

Smouse (1986) argued that variation in degree of heterosis indicated the importance of selection at the marker loci. Note that there is no expectation that loci show the same degree of heterosis under directional dominance. As is apparent from figure 1, loci with more equitable allele frequencies explain the most variance. For the case of consanguineous mating, the genotype of a marker locus is more highly correlated with identity by descent for loci on its own chromosome than those elsewhere in the genome, so loci on large chromosomes should show slightly more heterosis than those on small chromosomes. For heterosis due to gametic-phase equilibria, in a finite population only a small proportion of loci capable of mutating to a recessive deleterious state will actually be variable, and these will differ greatly in their heterozygosity, leading to locus-specific differences in heterosis. Another source of variance among marker loci is variance in fitness that is not due to overdominance or directional dominance. If, for example, the population is also experiencing directional selection, this may well contribute to the genotypic variance apparent at linked loci.

In species with significant heterozygote deficiencies, Gaffney et al. (1990) argued that if such deficiencies were the result of nonrandom mating, they should be consistent in magnitude across loci. In the species they studied, there was significant variation in f among loci, which led them to reject inbreeding as the source of heterosis and heterozygote deficiencies. This argument needs to be made somewhat cautiously for two reasons (Charlesworth 1991). First, in addition to the experimental sampling variation in f values, there will also be variation in the true f values among loci within populations due to finite population size (Weir et al. 1980; Cockerham and Weir 1983). Perhaps more important

is the possibility that selection has obscured evidence of inbreeding by changing genotype frequencies since the zygote stage.

In spite of the inability of the AD models to distinguish the genetic basis of heterosis, they can explain more of the variance in fitness in some cases. The question then arises whether any information can be gleaned from departures from the AD models. One troublesome source of discrepancy is the bias due to using log fitness as an estimate of the disadvantage of a genotype. Using a Taylor approximation, it is easy to show that the bias in estimating the selection coefficient for a given genotype is at least $-s^2 - V_P$, where V_P is the phenotypic variance of the trait. V_P enters into the estimates of all genotypes, and thus is not troublesome if genotypes have uniform variances. However, the fitness of rare homozygotes will be not only difficult to estimate (Bush and Smouse 1991), but will be the most biased. Even without such biases, the AD model may fail if any of its assumptions are not met. Perhaps the most important of these are that the phenotype measured is perfectly correlated with fitness, and, for the overdominant case, that the population is at equilibrium. It is difficult to see how a useful interpretation of the departures from the adaptive distance model could be constructed.

The appeal of the adaptive-distance model is that it apparently offered a tractable approach to the fundamental, unsolved problem of which forces are responsible for the maintenance of genetic variation. Fortunately, alternative experimental approaches to investigate marker-associated heterosis are also feasible. Any attempt to identify overdominant polymorphisms must reduce or eliminate the potential for genotypic correlations to influence the phenotypes of the marker loci. This may be accomplished with a variety of approaches, from simple crosses which manipulate the genotypic correlations which could generate heterosis caused by directional dominance (Strauss 1986), to the extremely complex process of mapping, cloning, and then transforming with loci which harbor putative overdominant polymorphisms.

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Corresponding Editor: G. Vermeij