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Heritable variation and heterozygosity under a balance between mutations and stabilizing selection

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Summary

A model of the balance between mutations and stabilizing selection affecting a quantitative character is developed and analysed. This model is essentially a discretized version of the continuum-of-alleles models analysed previously by Kimura, Lande, Turelli and others, and is formally similar to the stepwise mutation models used to interpret electrophoretic data. The complete model cannot be solved even for a haploid species, but there are useful approximations for most parameter values of interest. The 'house-of-cards' approximation can be used when selection is strong relative to mutation, and a normal approximation can be used when selection is relatively weak. For intermediate levels of selection a new 'five-allele' approximation provides accurate results over a wide range of parameter values. The house-of-cards and five-allele approximations applied to recessive alleles in a diploid population show that, for a given mutation rate, a somewhat larger genetic variance is maintained at equilibrium than in a comparable model of additive alleles. Under directional selection, the increase in genetic variance is largest for alleles of large effect and is much smaller for alleles of intermediate or small effect. At an equilibrium under stabilizing selection, homozygotes would tend to have a higher average fitness than heterozygotes when each mutation has a relatively large effect (the house-of-cards approximation), with the reverse if each mutation has a small effect (the normal approximation).

1. Introduction

The maintenance of heritable variation in a quantitative character has proved to be a particularly difficult problem to model in a simple way because of the potentially large number of alleles to be accounted for. Several models have been proposed that describe the balance between stabilizing selection and mutations of additive effect, with each model using different simplifying assumptions. One class of models, introduced by Latter (1960) and extended by Bulmer (1972, 1980), assumes that there are only two possible alleles at each of n loci, with the allele frequencies being the same at every locus. These assumptions reduce the problem to one of finding the equilibrium allele frequency. A different type of model was introduced by Kimura (1965) and developed further by Lande (1975), Fleming (1979) and Turelli (1984). This class of models assumes a continuum of alleles that are distinguished by their additive effect and predicts the equilibrium distribution of additive effects under different assumptions about mutation and selection. The continuum-of-alleles models do not predict the heterozygosity or other properties of the loci affecting the character of interest, because their results are in terms of the distribution of additive effects, not in terms of the frequencies of alleles producing those effects. Nor do they allow analysis of non-additive mutations.

In this paper I shall introduce and analyse a model of allelic effects that is closely related to the continuum-of-alleles model. The present model is similar to the 'stepwise mutation model' suggested by Bulmer (1971) to account for patterns observed in allozyme data. The complete model is not analytically tractable, even assuming infinite population size, but for most parameter values of biological interest there are useful approximations possible. This model is sufficiently simple for a number of analytic results to be obtained, yet is sufficiently flexible that it can make useful predictions about the heterozygosity and other quantities of interest to population geneticists. This model also provides a simple way to explore the effects of varying degrees of dominance on a quantitative character.

2. Haploid species

We shall begin with a model of additive alleles at a single locus in an infinite haploid population. Assume that the locus has a large number of possible alleles, $A_i (i = 0, \pm 1, \pm 2, \ldots)$ with allele A_i having additive effect ic on a quantitative character, where c is a parameter of the model. The allele frequencies will be denoted by $p_i (\Sigma p_i = 1$, where throughout sums are taken over all possible values of i). Mutation occurs at a rate μ per generation with A_i mutating to A_{i+1} or A_{i-1} with equal probability. This is the 'stepwise mutation' model, with c representing the additive effect of each mutational step. The contribution of this locus to the mean of the character is $c\Sigma\, ip_i$ and the contribution to the variance is $c^2 V_i$, where $V_i = \Sigma i^2 p_i - (\Sigma i p_i)^2$ is the variance of i.

The relative fitness of an individual carrying A_i is w_i. We will be concerned initially with stabilizing selection, which will be modelled by a 'nor-optimal' selection function, $w_i = \exp[-(ic)^2/(2V_s)]$. The optimal value of the character is at 0 and the strength of selection indicated by the parameter V_s. If a character were affected by only one locus, there would be no reason to assume that the optimum is exactly at 0 and coincides with one of the possible allelic states. However, if a character was affected by several loci, then the mean effect of a particular locus is not strongly constrained (Lande, 1975) and it is reasonable to assume that the maximum fitness at a particular locus can be achieved. The methods used in this paper could be applied to a model in which the optimum is not at one of the possible allelic states, but I will not do so here. Selection and mutation are assumed to be relatively weak forces so their order in a generation is not important, but to be specific we will assume that mutation follows selection. Throughout, we will ignore the environmental component of the variance because it can be absorbed into V_s (Lande, 1975; Turelli, 1984).

At the beginning of a generation the allele frequencies are p_i, and after selection they will change to p_i':

$$p_i' = p_i w_i / W \tag{1}$$

where $W = \Sigma p_i w_i$ is the mean fitness. Mutation then changes the allele frequencies to p_i'',

$$p_i'' = (1-\mu)p_i' + \mu(p_{i+1}' + p_{i-1}')/2. \tag{2}$$

At equilibrium $p_i'' = p_i$, and Equations (1) and (2) predict the equilibrium values. Without more assumptions, this infinite system of coupled, nonlinear equations seems intractable. For different ranges of the parameter values, however, we can obtain useful approximate solutions.

(i) *The house-of-cards approximation for strong selection*

If selection is much stronger than mutation, we can obtain an accurate approximation by assuming that at equilibrium the frequencies of only three alleles, A_0, and $A_{\pm 1}$ need be accounted for. This approximation is then equivalent to Turelli's (1984, pp. 153–154) three-allele model because the other alleles in the present model are ignored. Turelli called this the 'house-of-cards' approximation after Kingman's (1978) house-of-cards model of mutation. Kingman assumed that the mutational state of each new mutant is independent of the allele that mutated. The name of the model comes from the idea that each allele is so complicated that a mutation causes it to collapse 'like a house of cards' and then be restructured according to general properties of the locus. Although this metaphor may not describe real mutations, it does lead to models with desirable mathematical properties. Turelli found that by making this assumption, he could find an approximate solution to the continuum-of-alleles model, and his three-allele model is based on the same approximation. Barton (1986) discusses other aspects of the house-of-cards approximation.

Following Turelli's derivation, the symmetry of the selection and mutation processes makes it reasonable to assume that $p_1 = p_{-1}$ at equilibrium. The relative fitness of $A_{\pm 1}$ is approximately $1-s$ where $s = c^2/(2V_s)$. If we assume that $p_{\pm i} = 0$ for $i > 2$ and that both μ and s are much less than one, (1) and (2) can be combined to form a single approximate equation for p_1 at equilibrium:

$$p_1 = (1-s-\mu)p_1 + \mu/2 \tag{3}$$

because $p_0 = 1 - 2p_1$. Equation (3) depends on the assumption that μ and s are both small and that p_1 is small. As Turelli pointed out, this equation is similar to the equations obtained when considering a model of a balance between selection and mutation at a diallelic locus.

We can see in Equation (3) where the house-of-cards assumption enters. The second term on the right-hand side is the increase in p_1 due to mutation and does not depend on the frequencies of the three alleles. In this model that result was derived as an approximation to the complete model.

Equation (3) implies

$$p_1 = \mu/[2(\mu+s)]. \tag{4}$$

This result is a solution to (3) for any μ and s if they are both small, but it is an approximate solution to the complete model only if $p_1 \ll 1$ because only then is it reasonable to assume that the frequencies of alleles other than A_0 and $A_{\pm 1}$ are negligible. Therefore, (4) is a valid approximation to the complete model only if $\mu \ll s$. In that case $p_1 \approx \mu/(2s)$, the genetic variance of the character attributable to this locus is $c^2 V_i = 2p_1 c^2 = 2\mu V_s$, and the 'heterozygosity', H_e, is $1 - p_0^2 - 2p_1^2 \approx \mu/s$.

(ii) *Normal approximation for weak selection*

In the other extreme, we can assume that selection is much weaker than mutation. Turelli (1984) showed

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that this assumption is necessary for the continuum-of-alleles model to have a normal distribution of allelic effects at equilibrium. We will take advantage of the result to show that the distribution of p_i in this case is approximated by a discretized normal distribution. For values of i such that $V_s \gg i^2$, $w_i \approx 1 - si^2$ and $W = \Sigma p_i w_i \approx 1 - sV_i$. Equations (1) and (2) can then be approximated by

$$\mu(p_{i+1} - 2p_i + p_{i-1})/2 + s(V_i - i^2)p_i = 0. \quad (5)$$

The first term is nearly $(\mu/2)d^2p_i/di^2$, so (5) is approximated by a differential equation whose solution is a normal distribution, $p_i = [1/\sqrt{(2\pi V_i)}]$ $\exp[-i^2/(2V_i)]$, where the value of V_i has to be determined by substituting this expression into (5). This derivation follows those of Kimura (1965) and Turelli (1984) for the continuum-of-alleles model. Using a scaling argument similar to Turelli's (1984, pp. 143–144), this approximation is seen to be valid when $\mu \gg s$, i.e. when mutation is a much stronger force than selection. The equilibrium value of V_i is approximately $\sqrt{(\mu/2s)} = \sqrt{(\mu V_s/c^2)}$ which implies that the equilibrium genetic variance, $V_g = c^2 V_i$, is $\sqrt{(c^2 \mu V_s)}$. The equilibrium heterozygosity, $H_e = 1 - \Sigma p_i^2$, is approximately $1 - 1/\sqrt{(4\pi V_i)}$ which is, under these assumptions, nearly one.

(iii) *Five-allele approximation for intermediate selection*

For selection intensities that are intermediate between those for which the two preceding approximations are valid we can obtain another approximation by keeping track of five alleles. The analysis is in the same spirit as the house-of-cards approximation, but the extra flexibility provided by an additional allelic class yields accurate results for a larger range of parameter values.

We will keep track of the frequencies of only five alleles, A_0, $A_{\pm 1}$, and $A_{\pm 2}$, and use the symmetry to assume $p_{-1} = p_{+1} = p_1$ and $p_{+2} = p_2$. We will assume for now that selection and mutation are balanced in such a way that $p_2 \ll 1$ at equilibrium and later will find the range of parameter values for which that is true. When $p_{\pm 2} \ll 1$, we are justified in ignoring the presence of alleles with larger additive effects.

The equilibrium can be found from the two approximate equations

$$p_1 = (1-\mu)(1-s)p_1/W + \mu(p_0 + p_2)/2 \quad (6a)$$

$$p_2 = (1-\mu)(1-4s)p_2/W + \mu p_1/2, \quad (6b)$$

where $W = 1 - 2s(p_1 + 4p_2)$. Because $p_2 \ll 1$, $W \approx 1 - 2sp_1$ and (6*b*) can be solved for p_2 in terms of p_1:

$$p_2 \approx \mu p_1/[2(\mu + 4s - 2sp_1]. \quad (7a)$$

Equation (7*a*) can be combined with (6*a*) to provide a single quadratic equation for p_1,

$$2sp_1^2 - (2\mu + s)p_1 + \mu/2 = 0$$

which has the solution

$$p_1 \approx [1 + 2\mu/s - \sqrt{(1 + (2\mu/s)^2)}]/4. \quad (7b)$$

This solution is unique because the other root of the quadratic would imply $p_1 > 1/2$. Both p_2 and p_1 depend on the ratio μ/s, as expected in a model of a mutation–selection balance.

We can now ask for what values of μ/s is (7) an accurate approximation to the complete model, by using the criterion that p_2 must be sufficiently small. As μ/s increases from very small values, for which the house-of-cards approximation is valid, to very large values, for which the normal approximation is valid, Equation (7*b*) predicts that p_1 increases from a small value to 1/4. If μ/s is small, then (7*b*) implies $p_1 \approx \mu/(2s)$, which is the value in the house-of-cards approximation, and, for μ/s in that range, p_2 is much smaller, ensuring that this approximation is valid. The question is how large μ/s can be with p_2 still being sufficiently small that the five-allele approximation is valid. We can find this value by putting an upper bound on p_2, B, and say the approximation is consistent if $p_2 < B$. Equation (7*a*) implies that if $p_2 < B$,

$$p_1 < 2B(\mu/s + 4)/(\mu/s + 4B). \quad (8)$$

Inequality (8) combined with (7*b*) implies that this approximation is valid if approximately

$$\mu/s < [9B - \sqrt{(4B + 49B^2)}]/[2(2B - 1/4)] \quad (9)$$

when $B \ll 1$. For example, if $B = 0{\cdot}05$, (9) implies that $\mu/s < 0{\cdot}39$. Therefore, this approximation to the complete model is still valid when μ/s becomes relatively large but still less than one, and it reduces to the house-of-cards approximation when μ/s is very small.

(iv) *Comparison of loci with different additive effects*

If there is no or effectively no linkage disequilibrium among loci affecting a particular character, the additive genetic variance of a character is obtained by adding the genetic variances over all loci affecting the character. The assumption of linkage equilibrium is supported by both analytic and numerical results (Turelli, 1984). In effect, weak selection on a quantitative character acts almost independently on different loci with alleles of additive effect. That property combined with the independence of mutations at different loci ensures that there will be no correlation of allele frequencies among the loci.

We can interpret the above results by imagining that in a particular species there are different classes of loci with additive effects that vary from relatively small to relatively large. If V_s is much greater than the phenotypic variance of the character, then V_s is the intensity of stabilizing selection experienced at each locus, and the above results can be used to predict the relative contributions of these different classes of loci to the additive genetic variance.

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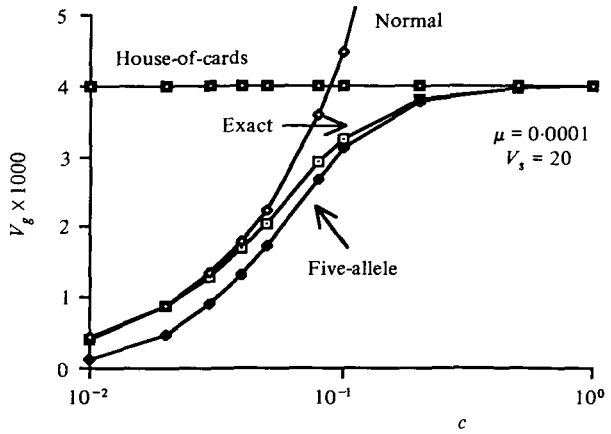

Fig. 1. A comparison of the exact and approximate predictions for the equilibrium genetic variance maintained under a balance between stabilizing selection and mutation in haploids. The exact results were obtained by numerically iterating Equations (1) and (2) as described in the text.

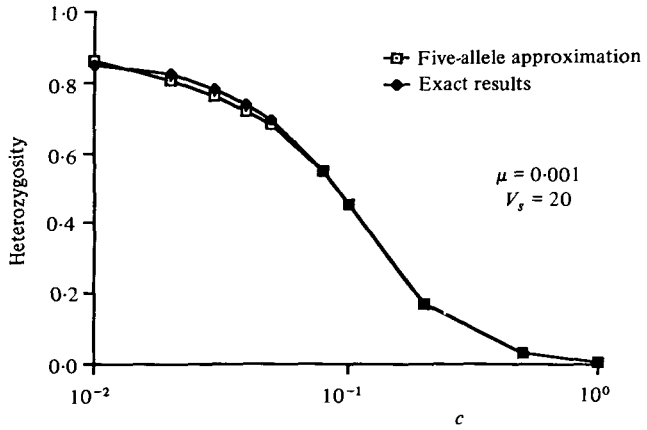

Fig. 2. A comparison of the exact and approximate predictions for the computed heterozygosity, defined as Σp_i^2, maintained under a balance between stabilizing selection and mutation in haploids. That quantity is the heterozygosity that would be observed in a comparable randomly mating diploid population.

If we consider all loci with the same mutation rate, μ, the contributions of the different types of loci to the additive genetic variance can be plotted as a function of c, the additive effect. The results are shown in Fig. 1, which shows the values of V_g obtained from each of the three approximations described above and the exact values obtained by iterating Equations (1) and (2). The iteration was carried out by choosing a large enough number of allelic classes for the equilibrium frequency in the outermost classes to be less than 10^{-7}. Fig. 1 shows that loci with small additive effects contribute far less than loci with larger additive effects. It also shows that the five-allele model provides an accurate approximation to the complete model over a wide range of values of c. That model becomes less accurate for smaller values of c and always underestimates V_g, but because V_g decreases with c, the absolute error is never very large.

We can also use these results to examine the heterozygosity. Fig. 2 shows the exact results and the results obtained using the five-allele approximation. Under the house-of-cards approximation the heterozygosity is almost zero, and under the normal approximation it is almost one. The five-allele model provides an excellent approximation throughout the range of parameter values.

3. Diploid species

We can now model a diploid species in a similar way, with the principal difference being that we can now allow for different degrees of dominance. As in the haploid model, there is an unlimited number of alleles, A_i, $i = 0, \pm 1, \pm 2 \ldots$ Each allele mutates at a rate μ per generation, with the allele A_i having probability μ of mutating to A_{i+1} and A_{i-1}. The relative fitness of an individual with genotype A_iA_j is w_{ij}, which is determined both by the selection and by the dominance relationships of the alleles. Equations (1) and (2) describe the model if w_i is interpreted now as the marginal fitness of A_i: $w_i = \Sigma p_j w_{ij}$. The mean fitness is $W = \Sigma p_i w_i = \Sigma p_i p_j w_{ij}$.

We assume that selection on the phenotypes is nor-optimal, with the optimum at 0 and the strength V_s. If alleles are additive in their effect, the phenotype of an individual with genotype A_iA_j is $(i+j)c$, so $w_{ij} = \exp[-(i+j)^2 c^2/(2V_s)]$. If we use the same three ways of approximating the diploid model as we did for the haploid model, we can show that the approximate equilibrium allele frequencies are unchanged by the assumption of diploidy as long as selection is weak. As discussed by Turelli (1984), when selection is weak and alleles are additive in their effects, selection acts on each allele essentially independently.

The interesting questions for the model of a diploid species are about the effects of dominance. The analysis is made somewhat difficult by the large number of possible dominance relationships among alleles. I will explore one class of assumptions about complete dominance to illustrate how this problem can be approached.

(i) *Recessive alleles*

It is relatively easy to examine the effects of recessive mutants under the assumption of strong and intermediate selection if we assume that high-frequency alleles are dominant to the lower-frequency alleles. This assumption corresponds to the idea of 'wild type' alleles being dominant. We will begin with the house-of-cards approximation and then examine the five-allele approximation, which allows for somewhat weaker selection. There seems to be no easy way to obtain an approximation comparable to the normal one used above.

In the house-of-cards approximation, we keep track of only A_0 and $A_{\pm 1}$. Under our assumptions about dominance, A_0 is dominant to $A_{\pm 1}$ and A_{-1}. There

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seems no reason to assume a particular dominance relationship for A_{+1} and A_{-1} so we let the phenotypic value of $A_{\pm 1}A_{-1}$ be dc. The nine genotypic and three marginal fitnesses are given in Table 1.

If $\mu \ll s$, then we can use Table 1 and equations (1) and (2) to find the two approximate equations for p_1 and p_{-1} that must be satisfied at equilibrium:

$$sp_1^2 + d^2sp_{-1}p_1 \approx \mu/2 \tag{10a}$$

$$sp_{-1}^2 + d^2sp_{-1}p_1 \approx \mu/2, \tag{10b}$$

where smaller terms have been dropped. These equations imply

$$p_1 \approx p_{-1} \approx \sqrt{[\mu/2s(1+d^2)]}. \tag{11}$$

Equation (11) is less accurate than the corresponding approximation for additive alleles, Equation (4). For additive alleles $p_{\pm 1}$ is of order μ/s in magnitude, and in deriving (4), terms of order $(\mu/s)^2$ were ignored. In (11), $p_{\pm 1}$ is of order $\sqrt{(\mu/s)}$ and terms of order μ/s were ignored.

Equation (11) resembles the standard result for a balance between mutation and selection against recessive alleles. The dominance relationships are not completely symmetric because the contribution of $A_{+1}A_{-1}$ to the character is dc, which may be positive or negative. Nevertheless, $p_1 \approx p_{-1}$ at equilibrium. A non-zero value of d does increase the selection affecting both alleles. The equilibrium genetic variance, V_g, under this model is

$$V_g = p_1^2c^2 + 2p_1p_{-1}(dc)^2 + p_{-1}^2c^2 = 2\mu V_s, \tag{12}$$

which contains both additive and dominance components. Using standard quantitative genetic methods, $V_g = V_A + V_D$, where $V_A \approx 4c^2(1+d^2)p_1^3$ is the additive component and $V_D \approx 2p_0p_1^2(1+d^2)c^2$ is the dominance component. Because $p_1 \ll 1$ at equilibrium, nearly all the genetic variance is dominance variance.

Table 1. Genotypic and marginal fitnesses for the house-of-cards approximation for completely recessive alleles

	Phenotypic values		
	A_{-1}	A_0	A_{+1}
A_{-1}	-1	0	d
A_0	0	0	0
A_{+1}	d	0	1

	Genotypic fitnesses		
	A_{-1}	A_0	A_{+1}
A_{-1}	$1-s$	1	$1-d^2s$
A_0	1	1	1
A_{+1}	$1-d^2s$	1	$1-s$

	Marginal fitnesses		
	w_{-1}	w_0	w_1
	$1-sp_{-1}-d^2sp_1$	1	$1-d^2sp_{-1}-sp_1$

For weaker selection, we can use the five-allele approximation. This is easiest to do if the assumptions about the dominance relationships ensure symmetry of the solution. One such choice is given in Table 2, in which A_0 is dominant to the other four alleles, A_{+1} and A_{-1} are dominant to A_{+2} and A_{-2}, A_{+1} and A_{-1} are codominant, and A_{+2} and A_{-2} are codominant. The parameter k indicates the increase in phenotypic value of the $A_{-2}A_{-2}$ and $A_{+2}A_{+2}$ individuals. There are other possible choices for the dominance relationships and they can be analysed in the same way.

We assume $p_1 = p_{-1}$ and $p_2 = p_{-2}$ at equilibrium and use Equations (1) and (2) and Table 2 to obtain the two equations for p_1 and p_2:

$$p_1 = (1-\mu)(1-sp_1)p_1/W + \mu(p_0+p_2)/2 \tag{13a}$$

$$p_2 = (1-\mu)(1-k^2s)p_2/W + \mu p_1/2, \tag{13b}$$

where $W = 1-2sp_1^2-4sp_1p_2-2k^2sp_2^2$. These equations correspond to (6) for the additive haploid model.

If $p_2 \ll 1$, then $W \approx 1-2sp_1^2$ and (13a) and (13b) imply

$$p_2 \approx \mu p_1/[4s(1-p_1)] \tag{14a}$$

and

$$p_1 \approx \sqrt{(\mu/2s)}. \tag{14b}$$

Although (14b) is the same as (11) with $d = 0$, the derivation of (14b) did not require the assumption that $\mu \ll s$. This approximation is valid even when μ and s are of the same order of magnitude, as long as $p_2 \ll 1$. Note that (14a) implies that the equilibrium frequency of $A_{\pm 2}$ does not depend on k, the phenotypic effect of the homozygotes. It does depend on the assumption about the dominance of $A_{\pm 1}$ to $A_{\pm 2}$. Other assumptions about those dominance relationships would lead to different values of p_2.

At the equilibrium given by (14), the genetic variance is $V_g \approx 2\mu V_s$ if p_2 is small, which is the same as the value obtained from the house-of-cards model of recessive alleles. This result predicts that V_g is approximately independent of c although the heterozygosity, $H_e = 1-\mu V_s/c^2$, does depend on c. The decrease of H_e with increasing c is consistent with the result for the house-of-cards approximation. Under the five-allele approximation, $V_A \approx 4c^2p_1^3$ and $V_D \approx 2p_0p_1^2c^2$, which are the same expressions as in the house-of-cards approximation (with $d = 0$). Because $p_2 \ll 1$, the outer alleles do not contribute significantly to the components of the variance. Now, p_1 is not necessarily small, implying that there may be a substantial additive component of the variance at equilibrium due to completely recessive alleles.

Both the three-allele and five-allele approximations for recessive alleles are less accurate than the corresponding approximations for additive alleles.

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Table 2. Phenotypic values and the genotypic and marginal fitnesses for the five-allele approximation for completely recessive alleles

Phenotypic values

	A_{-2}	A_{-1}	A_0	A_1	A_2
A_{-2}	$-kc$	$-c$	0	c	0
A_{-1}	$-c$	$-c$	0	0	$-c$
A_0	0	0	0	0	0
A_1	c	0	0	c	c
A_2	0	$-c$	0	c	kc

Genotypic fitnesses, w_{ij}

	A_{-2}	A_{-1}	A_0	A_1	A_2
A_{-2}	$1-ks$	$1-s$	1	$1-s$	1
A_{-1}	$1-s$	$1-s$	1	1	$1-s$
A_0	1	1	1	1	1
A_1	$1-s$	1	1	$1-s$	$1-s$
A_2	1	$1-s$	1	$1-s$	$1-ks$

Marginal fitnesses

$w_0 = 1 \quad w_1 = w_{-1} = 1-sp_1-2sp_2 \quad w_2 = w_{-2} = 1-2sp_1-ksp_2$

For comparable parameter values, selection on recessive alleles is weaker than selection on additive alleles, which means that the allelic classes that are ignored in the approximations will be more important. Fig. 3 shows the predictions of the three-allele and five-allele approximations for recessive alleles ($V_g = 2\mu V_s$), with the results from the iteration of the exact equations for recessive alleles and for additive alleles in a diploid. In the numerical iteration, the selection function of the recessive alleles was the obvious generalization of Table 2. The fitness of the A_iA_i homozygotes was $w_{ii} = \exp[-(ic)^2/2V_s]$. The selection function for the diploid model with additive alleles was chosen to be $w_{ij} = \exp[-c^2(i+j)^2/8V_s)$, so that the fitnesses of the homozygotes for a given value of c were the same for the recessives.

The numerical results show that the approximate results are not very accurate, especially for smaller values of c. The approximate results are qualitatively correct, however, in predicting that recessive alleles of a given effect will contribute more to the genetic variance than will additive alleles of the same effect.

It does not seem possible to find a useful approximation for a model of recessive alleles under weak selection. By making explicit assumptions about all the dominance relationships among alleles, it is possible to obtain an equation with a form similar to (5), but the resulting equation does not have a solution that can be approximated by a normal distribution and does not appear to be tractable.

Other assumptions about dominance relationships among alleles will of course lead to different results, and it is difficult to generalize about how other models would behave. If low-frequency alleles tended to be dominant, the results would be similar to a comparable model of additive alleles, because the low-frequency alleles would only rarely occur as homozygotes.

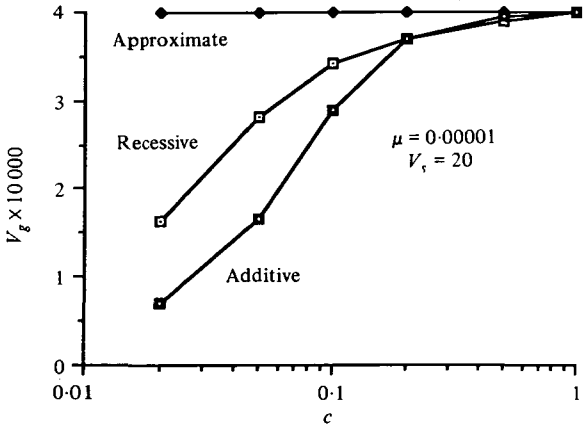

Fig. 3. A comparison of the exact and approximate predictions for the total genetic variance, V_g, maintained under a balance between stabilizing selection and mutation in diploids. The approximate results are the same for the house-of-cards and five-allele approximations. Selection on recessive and additive alleles was defined to ensure that they would have the same value of V_g for large values of c.

4. Directional selection

We can also ask how the mean and variance of a trait will change if a population that is at an equilibrium under stabilizing section is suddenly subject to strong directional selection. This situation models artificial

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selection applied to a population previously at a genetic equilibrium under natural selection. It is of particular interest to know how much the genetic variance increases during the first few generations of artificial selection under the assumptions of the model, because a large body of experimental data show that in general the genetic variance of traits subject to relatively strong directional selection does not increase substantially, even though the mean values change by several standard deviations. The complete one-locus model can be easily iterated numerically to give a quantitative picture of the results. We shall see, though, that the same class of approximations as used above are useful to describe the first few generations of response to directional selection, during which the average contribution of a locus changes by only a few multiples of the standard deviation of genetic effects at that locus.

We consider the population modelled above to be initially at equilibrium under the balance between mutation and stabilizing selection. Then directional selection is imposed with selection modelled by $w_i = 1+\alpha ic$, which means that directional selection is sufficiently strong for stabilizing selection to be ignored. A more complete analysis would include the effects of both stabilizing and directional selection, a problem that has recently been examined by Zeng & Hill (1987). This way of modelling directional selection is an approximation to the effect on a single locus of truncation selection, which is the kind used in studies of artificial selection, if the locus under consideration contributes a small fraction of the total phenotypic variance, with the remainder of the variance due to other loci and to environmental effects.

Using the house-of-cards approximation, we still assume that both p_1 and p_{-1} are small but now no longer equal. Under the assumption that α is small, $w_{\pm 1} = 1 \pm \alpha c$. Equation (1) implies that in the first few generations,

$$p_{\pm 1} \approx (w_{\pm 1})^t p_1(0) \tag{15}$$

because W, the mean fitness, is approximately 1. Assuming $\alpha > 0$, i.e. directional selection favours larger values of the character, $p_1(t)$ will increase and $p_{-1}(t)$ will decrease exponentially with time. Initially $p_{-1}(0) = p_1(0) \ll 1$. After several generations, the contribution of this locus to the mean of the character will be $c[p_1(t)-p_{-1}(t)]$ and the contribution to the variance approximately $c^2[p_1(t)+p_{-1}(t)]$.

One way to consider the effect of directional selection is to find the change in the genetic variance of the trait when the mean has changed by some multiple of the equilibrium standard deviation. In this way we need not be concerned with the particular value of α as long as selection is weak enough for these approximations to be valid. If we consider first a character governed by a single haploid locus, the initial value of V_g is $V_g(0) = 2c^2p_1(0) = 2\mu V_s$. The mean of the character will change by one standard deviation when

$$c[p_1(t)-p_{-1}(t)] = c[(1+\alpha c)^t-(1-\alpha c)^t]p_1(0) = \sqrt{[2c^2p_1(0)]}, \tag{16}$$

or

$$\sinh(\alpha ct) \approx 1/\sqrt{[2p_1(0)]} \tag{17}$$

Equation (17), which depends on the assumption that $\alpha c \ll 1$, can be solved for t to find the number of generations of selection of the specified intensity needed to achieve this change in the mean. The variance after that number of generations is approximately

$$\begin{aligned} V_g(t) &\approx c^2[(1+\alpha c)^t+(1-\alpha c)^t]p_1(0) \\ &\approx 2c^2\cosh(\alpha ct)\,p_1(0) \\ &= 2c^2p_1(0)\sqrt{[1+1/(2p_1(0))]}. \end{aligned} \tag{18}$$

Therefore, after the mean changes by one standard deviation,

$$V_g(t)/V_g(0) = \sqrt{[1+1/(2p_1(0))]} \approx \sqrt{(s/\mu)}. \tag{19}$$

The house-of-cards approximation is valid only when $\mu/s \ll 1$, so (19) tells us that under these assumptions $V_g(t)$ increases substantially.

Equation (17) shows that this approximation is consistent, because after directional selection has changed the mean by one standard deviation, $p_1(t) \approx \sqrt{[2p_1(0)]}$ and so is still small enough for $A_{\pm 2}$ and the other alleles to be ignored.

In the five-allele approximation the three central alleles, A_0 and $A_{\pm 1}$, contribute most of the genetic variance. We can use that fact to approximate the behaviour of the five-allele model in the first few generations of directional selection. For the haploid model,

$$p_i(t+1) = p_i(t)\,(1+i\alpha c)/W, \tag{20}$$

where

$$W \approx 1+\alpha c[p_1(t)-p_{-1}(t)] \tag{21}$$

is the mean fitness. Assuming $\alpha c \ll 1$, we obtain

$$p_1(t+1) \approx p_1[1+\alpha c-\alpha c(p_1-p_{-1})] \tag{22}$$

and

$$p_{-1}(t+1) \approx p_{-1}[1-\alpha c-\alpha c(p_1-p_{-1})]. \tag{23}$$

where, for notational convenience, t is suppressed on the right-hand sides. These difference equations can be approximated by two first-order differential equations for $dp_1(t)/dt$ and $dp_{-1}(t)/dt$. A simpler pair of equations can be obtained by adding and subtracting these equations to obtain

$$du/dt = \alpha cv(1-u) \tag{24}$$

and

$$dv/dt = \alpha c(u-v^2) \tag{25}$$

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where $u = p_1 + p_{-1}$ and $v = p_1 - p_{-1}$. Note that, except for the contributions of $A_{\pm 2}$, v is proportional to the contribution to the mean of the character and u is proportional to the contribution to the variance. By multiplying (24) by v, (25) by u, and subtracting, we obtain

$$d(v/u)/dt = \alpha c[1-(v/u)^2] \tag{26}$$

which implies

$$v(t)/u(t) = \tanh \alpha ct, \tag{27}$$

because $v(0) = 0$. Substituting (27) into (24) we obtain

$$du/dt = \alpha cu(1-u) \tanh \alpha ct \tag{28}$$

which can then be integrated to yield

$$u(t) = K \cosh \alpha ct/(1 - K \cosh \alpha ct) \tag{29}$$

where $K = u_0/(1+u_0)$, which is chosen to ensure that $u(0) = u_0$.

If we ignore the contributions of $A_{\pm 2}$ to the mean and variance, the mean of the character is $cv(t)$ and the variance is $c^2u(t)$. Therefore, the mean has increased by one standard deviation when $v(t) = \sqrt{u_0}$, which, according to (27), will occur when $u(t) = \sqrt{u_0} \coth \alpha ct$. Substituting that into (29) we can solve the resulting equation for $\cosh \alpha ct$, the time at which $v(t)$ has changed by the required amount. That equation is a quadratic whose solution is

$$\cosh \alpha ct = -[u_0 + \sqrt{(u_0 + K^2 - u_0K^2)}]/[K(1-u_0)]. \tag{30}$$

From this expression, $\coth \alpha ct$ can be found and from that the value of $u(t)$. The general expression is not very informative. For a particular value of u_0, finding the increase in u and hence V_g is easy. For example, if $u_0 = 0{\cdot}2$ (*i.e.* $p_1(0) = 0{\cdot}1$), $\cosh \alpha ct = 2{\cdot}04$ and $\coth \alpha ct = 1{\cdot}15$. Therefore, $u(t)$ would increase from u_0 to roughly $1{\cdot}15\sqrt{u_0} = 0{\cdot}51$ and the variance would increase by a factor of roughly 2·5. If, instead, $u_0 = 0{\cdot}6$, the corresponding increase in the variance would be by a factor of about 1·8. These values of u_0 bracket the range of values of $p_1(0)$ for which the five-allele approximation can be applied. Therefore we can conclude that, in contrast to the results for the house-of-cards approximation, the contribution of a single locus to the variance in this case is increased by approximately a factor of 2.

For a locus approximated by a normal distribution of allelic effects, an argument analogous to that in Lande (1975) will show that the variance does not change under weak directional selection. That property of the normal approximation has played an important role in the development of evolutionary theories based on Lande's results.

The increase in the total genetic variance under directional selection decreases as the number of loci affecting a character increases. That is true regardless of the relative importance of selection and mutation at each locus. To see this, assume that there are n loci with the same additive effect, c, and the same mutation rate, μ. If directional selection is weak, each locus experiences directional selection of the same intensity, so the relative fitnesses at each locus are the same as in the one-locus model. The difference is in the amount of change at each locus that is needed to change the mean of the character by one standard deviation. If the equilibrium variance at each locus is V_g, the variance of the character is nV_g. If directional selection changes the mean effect at each locus from 0 to x, the mean of the character is nx. The mean of the character will then change by one initial standard deviation when $nx = \sqrt{(nV_g)}$ or $x = \sqrt{(V_g/n)}$. The amount of change in the mean effect of each locus needed to achieve a specified net change decreases with the square root of the number of loci.

Using the house-of-cards approximation, we found that at a single locus the variance increases by roughly a factor of $\sqrt{(s/\mu)}$, so the above argument shows that with n loci of equal effect

$$V_g(t)/V_g(0) \approx \sqrt{(s/n\mu)}. \tag{31}$$

Therefore, μ/s might be small enough that the house-of-cards approximation is valid at each locus yet n might be large enough that only a small increase in the genetic variance is expected under sustained directional selection. This result is consistent with that of Barton & Turelli (1987). Under the five-allele approximation, the variance increased by roughly a factor of two, so even with relatively few loci of that type, only a small increase in the variance would be expected.

5. Apparent overdominance

There is a growing literature showing a positive correlation between heterozygosity of electrophoretically detectable alleles and physiological traits such as growth rates that are presumed to be correlated with fitness (Mitton & Grant, 1984). The two most common explanations for this phenomenon are inbreeding depression due to population subdivision and overdominance (Smouse, 1986). We can use the present model to ask whether loci with additive effects on a quantitative character and at equilibrium under a balance between mutation and stabilizing selection would appear to be over- or underdominant. To answer this question, we use the present model of a single locus in a diploid population to compute the average fitness of an individual that is heterozygous or homozygous at that locus:

$$W_{\text{hom}} = \Sigma_i p_i^2 w_{ii}/\Sigma_i p_i^2,$$

$$W_{\text{het}} = \Sigma_{i \neq j} p_i p_j w_{ij}/\Sigma_{i \neq j} p_i p_j. \tag{32}$$

Assuming weak stabilizing selection of strength V_s, $w_{ij} \approx 1 - c^2(i+j)^2/(2V_s)$.

Under the house-of-cards approximation $W_{\text{hom}} \approx 1$ and $W_{\text{het}} \approx 1 - c^2/(2V_s) < W_{\text{hom}}$. When selection is strong, A_1 and A_{-1} are sufficiently rare that nearly all

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the homozygotes are A_0A_0, which have fitness 1, and nearly all the heterozygotes are $A_0A_{\pm 1}$ which have fitness $1-c^2/(2V_s)$. Therefore, under the assumptions of this model, strongly selected loci would exhibit the opposite pattern from what is usually observed, with homozygotes on the average having a higher fitness than heterozygotes.

Using the five-allele approximation and ignoring $A_{\pm 2}$,

$$W_{\text{het}} \approx 1-4sp_0p_1/(4p_0p_1+2p_1^2) \tag{33}$$

and

$$W_{\text{hom}} \approx 1-8sp_1^2/(p_0^2+2p_1^2), \tag{34}$$

where $s=c^2/(2V_s)$. Because $p_0 \approx 1-2p_1$, $W_{\text{het}} < W_{\text{hom}}$ if roughly $p_1 < 0{\cdot}21$ and $p_0 > 0{\cdot}58$. As $A_{\pm 1}$ became more frequent, more of the heterozygotes are A_1A_{-1} and more of the homozygotes are A_1A_1 and $A_{-1}A_{-1}$, making the average fitness of the two groups more equal. For most parameter values for which the five-allele approximation is valid, heterozygotes will on the average be less fit than homozygotes, but the difference between them will be much less than for a strongly selected locus. If selection is weak, using the normal approximation for p_i and approximating the sums in (32) by integrals, we find that $W_{\text{het}} \approx 1-sV_i/2$ and $W_{\text{hom}} \approx 1-sV_i$. Therefore, $W_{\text{het}} > W_{\text{hom}}$, because the variance of the trait in heterozygotes is necessarily smaller than the variance of the trait in homozygotes.

These results suggest that under the assumptions of this model weakly selected loci would appear to be overdominant and more strongly selected loci would appear to be underdominant, with the transition occurring for parameters for which the five-allele approximation is valid. Of course, this model does not allow for more than one allele with the same additive effect on the character. A model that did not allow for that possibility could be analysed using the same approximations, because within an allelic class alleles would be effectively neutral.

These results are not presented as an explanation for observed patterns of heterosis and apparent overdominance of electrophoretic loci. It seems most unlikely that allozymes chosen for their convenient biochemical properties would fortuitously have significant effects on a quantitive character subject to stabilizing selection. These results do show, however, that there are other explanations possible for heterosis besides inbreeding depression and overdominance. Recurrent mutation balanced by selection can also result in different average fitnesses of heterozygotes and homozygotes.

6. Discussion and conclusions

Models of the balance between mutation and selection on a quantitative character generally assume either two alleles per locus or effectively an infinite number. Neither type of model leads to an understanding of the relationship between the phenotypic character and the frequencies of alleles at loci affecting that character. The model developed in this paper is intended to be intermediate between those two extremes. It makes relatively simple assumptions, and shows that for a wide range of parameter values useful approximate solutions can be found. It also allows the analysis of recessive alleles and predicts the increase in genetic variance due to directional selection.

A question of current interest to evolutionary biologists is the extent to which explicit genetic models of a quantitative character are necessary for evolutionary theories. There is a growing literature on quantitative genetic models of evolutionary processes, and most of the models are motivated by Lande's (1975) analysis of the balance between mutations and natural selection and on the generalization to two or more characters (Lande, 1980). This approach has been especially fruitful because it predicts that the genetic and phenotypic variances of a character approach their equilibrium values even though the mean values may still evolve. As a consequence, many evolutionary models become essentially phenotypic models in which the phenotypic variances and heritabilities are constants. The constancy of phenotypic variances and heritabilities, which is generally observed in short-term studies of directional selection, does not imply that the underlying distribution of allelic effects at each locus is normal. Turelli (1984) has argued that the assumptions needed for Lande's analysis are unrealistic, and that in general a normal or approximately normal distribution of allelic effects at each locus is not to be expected. But Turelli (1984) did not address the question of whether Lande's approach to predicting phenotypic evolution remains valid even though the underlying assumptions are not.

The above results show that the variance of a quantitative character can increase under directional selection, but that both the additive effect of alleles and the number of loci affecting the character determine the extent of the increase. If the house-of-cards approximation is an accurate description of most loci controlling quantitative characters, there must be a large number of such loci affecting each character in order for the genetic variances not to increase significantly under directional selection. If additive effects of mutations are smaller, implying that the five-allele or normal approximations are more accurate, there is relatively little increase in the variance. In many selection experiments the genetic variances remain relatively constant under several generations of directional selection (Falconer, 1981).

The present results call attention to a potentially important difference between Turelli's and Lande's assumptions about the maintenance of genetic variability by a balance between mutation and stabilizing selection. If loci affecting a character differ

substantially in their additive effects and if mutation rates at different loci are of the same order of magnitude, Turelli's assumptions pertain to loci with relatively large additive effects and Lande's assumptions pertain to loci with relatively small additive effects. However, Fig. 1 shows that each locus with a relatively large additive effect will contribute far more to the equilibrium genetic variance of a character than will each locus with a relatively small mutational effect. For the two types of loci to contribute equally to the genetic variance of a character, either there would have to be many more loci with small additive effects or mutation rates at loci with small additive effects would have to be much larger.

The approach taken in this paper is complementary to that of Barton & Turelli (1987), who also analyse the response to directional selection. They derive equations for the moments of allele frequencies and then close the system of equations under assumptions that are equivalent to the house-of-cards and normal approximations used here. Their approach is more general because it does not assume a particular model of mutational change of each allele and does not require any assumption about symmetry. It does require some assumption about the relationship among the moments of the allele frequency distribution, and consequently does not allow analysis of intermediate parameter values that correspond to the five-allele approximation used here. The results from the two models are consistent where they can be compared.

The present model is of only a single phenotypic character. An extension to two characters, using a generalization of Turelli's (1985) five-allele model, will be difficult but necessary. Without such an analysis, evolutionary biologists will be left in the lurch.

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References

Barton, N. H. (1986). The maintenance of polygenic variation through a balance between mutation and stabilizing selection. *Genetical Research* **47**, 209–216.

Barton, N. H. & M. Turelli (1987). Adaptive landscapes, genetic distance, and the evolution of quantitative characters. *Genetical Research* (In the Press.)

Bulmer, M. G. (1971). Protein polymorphism. *Nature* **234**, 410–411.

Bulmer, M. G. (1972). The genetic variability of polygenic characters under optimizing selection, mutation, and drift. *Genetical Research* **19**, 17–25.

Bulmer, M. G. (1980). *The Mathematical Theory of Quantitative Genetics*. Oxford University Press.

Fleming, W. H. (1979). Equilibrium distributions of continuous polygenic traits. *SIAM Journal of Applied Mathematics* **36**, 148–168.

Kimura, M. (1965). A stochastic model concerning the maintenance of genetic variability in quantitative characters. *Proceedings of the National Academy of Sciences, U.S.A.* **54**, 731–736.

Kingman, J. F. C. (1978). A simple model for the balance between selection and mutation. *Journal of Applied Probability* **15**, 1–12.

Lande, R. (1975). The maintenance of genetic variability by mutation in a polygenic character. *Genetical Research* **26**, 221–235.

Lande, R. (1980). The genetic covariance between characters maintained by pleiotropic mutations. *Genetics* **94**, 203–215.

Latter, B. D. H. (1960). Natural selection for an intermediate optimum. *Australian Journal of Biological Science* **13**, 30–35.

Mitton, J. B. & Grant, M. C. (1984). Associations among protein heterozygosity, growth rate, and developmental homeostatis. *Annual Review of Ecology and Systematics* **15**, 479–499.

Smouse, P. E. (1986). The fitness consequences of multiple-locus heterozygosity under the multiplicative overdominance and inbreeding depression models. *Evolution* **40**, 946–957.

Turelli, M. (1984). Heritable genetic variation via mutation–selection balance: Lerch's zeta meets the abdominal bristle. *Theoretical Population Biology* **25**, 138–193.

Turelli, M. (1985). Effects of pleiotropy on predictions concerning mutation–selection balance for polygenic traits. *Genetics* **111**, 165–195.

Zeng. Z.-B. & Hill, W. G. (1986). The selection limit due to the conflict between truncation and stabilizing selection with mutation. *Genetics* **114**, 1313–1328.