The Quantitative Genetic Consequences of Pleiotropy Under Stabilizing and Directional Selection

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ABSTRACT

The independence of two phenotypic characters affected by both pleiotropic and nonpleiotropic mutations is investigated using a generalization of M. Slatkin's stepwise mutation model of 1987. The model is used to determine whether predictions of either the multivariate normal model introduced in 1980 by R. Lande or the house-of-cards model introduced in 1985 by M. Turelli can be regarded as typical of models that are intermediate between them. We found that, under stabilizing selection, the variance of one character at equilibrium may depend on the strength of stabilizing selection on the other character (as in the house-of-cards model) or not (as in the multivariate normal model) depending on the types of mutations that can occur. Similarly, under directional selection, the genetic covariance between two characters may increase substantially (as in the house-of-cards model) or not (as in the multivariate normal model) depending on the kinds of mutations that are assumed to occur. Hence, even for the simple model we consider, neither the house-of-cards nor the multivariate normal model can be used to make predictions, making it unlikely that either could be used to draw general conclusions about more complex and realistic models.

We will be concerned here with the extent to which two quantitative characters can be regarded as evolutionarily independent. Interactions between characters can arise from linkage disequilibrium of loci affecting each character, from pleiotropy of loci affecting both characters or from selection acting on both characters together. Linkage disequilibrium is thought often to be unimportant for maintaining genetic correlations in populations in approximate equilibrium (TURELLI 1985), a conclusion that is supported by the recent theoretical work of HASTINGS (1989) and BÜRGER (1989). In this paper, we will ignore linkage disequilibrium and focus attention on the role of pleiotropic alleles.

The question of importance to evolutionary discussions is whether characters that are apparently independent, both because they are genetically uncorrelated and because they are affected by different selection pressures, can indeed be treated as independent in evolutionary models. If they can be treated independently, then it is reasonable to model the evolution of one or a few characters separately and without regard to the evolution of most other characters. If they cannot be treated as independent, then considering some characters in isolation may yield misleading conclusions.

Models of maintenance of genetic variation and covariation in quantitative characters show that the extent of independence of quantitative characters depends on genetic details that are not currently known. The model analyzed by LANDE (1975, 1980), which assumes a multivariate normal distribution of allelic effects at each locus, predicts that the genetic correlation coefficient between two characters is sufficient to determine their evolutionary independence. Under these assumptions, if there is zero correlation between two characters, the equilibrium variance of one character does not depend on the intensity of stabilizing selection on the other. Further, directional selection applied to one or both characters will not change the genetic correlation between them.

In contrast, the model introduced by TURELLI (1984, 1985), the "house-of-cards" model, reaches a different conclusion. TURELLI (1985) showed that, under his assumptions, if two characters are affected by pleiotropic loci the equilibrium variance of one character will depend on the strength of stabilizing selection on the other even if the two characters are genetically uncorrelated at equilibrium. In each individual, both characters may be affected by pleiotropic alleles but the net effect in the population may still be no genetic correlation between the characters. If the house-of-cards model is a better description of the maintenance of genetic variation, then even genetically uncorrelated characters cannot be regarded as evolutionarily independent.

The two models mentioned, the multivariate nor-

mal model of LANDE (1980) and the house-of-cards model of TURELLI (1985), represent extremes in a continuum of possible models in which genetic variation is maintained by mutation-selection balance. Roughly speaking, the multivariate normal model is valid if selection affecting each allele at each locus is much weaker than mutation, and the house-of-cards model is valid when selection is much stronger than mutation (TURELLI 1984). Under the multivariate normal model there are numerous alleles in roughly equal frequencies at each locus, and under the house-of-cards model one allele at each locus is in high frequency and the others are in very low frequency. The important question is whether either of these extreme models makes predictions that are typical of models intermediate between them. We will show that neither model can be regarded as being typical, at least for predicting the evolutionary independence of uncorrelated characters. We reach this conclusion by considering a simple model that is intermediate between the two extreme models and show that the predictions of this model are in some ways similar to those of the house-of-cards model and in some ways similar to those of the multivariate normal model. Our results represent a counterexample to claims of generality for either extreme model.

STEPWISE MUTATION MODEL OF A PLEIOTROPIC LOCUS

We will introduce a model of pleiotropic alleles that will allow us to consider a wide range of selection intensities affecting individual alleles. This model is a generalization of SLATKIN's (1987) stepwise mutation model of a single quantitative character. We will consider a haploid locus in an infinite population and two characters with measurements x and y affected by alleles at this locus. We assume that each allele is characterized by a pair of indices i and j that indicate the contribution to each of the two characters ($i, j = 0, \pm1, \pm2, \ldots$). An individual carrying allele (i, j) will have $x = c_x i$ and $y = c_y j$. For simplicity, we will ignore the environmental component. It is easy to account for diploidy in a randomly mating population and for the presence of other loci under the assumption of linkage equilibrium.

We assume that mutation can change an allele into only one of the eight adjacent allelic classes. We will consider two kinds of mutation, those that change only i or j, which we will call *nonpleiotropic* mutations, and those that change both i and j, which we will call *pleiotropic* mutations. We assume that nonpleiotropic mutations occur at rate μ_1 and that pleiotropic mutations occur at rate μ_2. It will be convenient to denote the net mutation rate by $\mu = \mu_1 + \mu_2$ and the fraction of nonpleiotropic mutations by $\nu = \mu_1/(\mu_1 + \mu_2)$. If $p_{i,j}$ is the frequency of the (i, j) allele, then our assumptions imply that after mutation

$$\begin{aligned} p^*_{i,j} &= (1-\mu)p_{i,j} \\ &\quad + (\mu_1/4)(p_{i+1,j} + p_{i-1,j} + p_{i,j+1} + p_{i,j-1}) \\ &\quad + (\mu_2/4)(p_{i+1,j+1} + p_{i-1,j+1} + p_{i+1,j-1} + p_{i-1,j-1}) \end{aligned} \tag{1}$$

where the asterisk indicates the value after mutation.

This model of mutations differs from that assumed by WAGNER (1989) and allows for more flexibility in the mutation process. WAGNER assumed that each locus coded for single product that could be characterized by an underlying variable, y, and that phenotypic characters were all linear functions of y. In his model, mutations affected only the value of y, and the pleiotropic effects of mutations are constrained by the functional relationship between y and the phenotypic characters as specified by the "B matrix." In terms of our model, WAGNER's assumption is equivalent to assuming that only a subset of mutational states confined to a single line are possible. For example, only the mutational states identified by (i, i) for $i = 0, \pm1, \pm2, \ldots$ are possible, which in our model is equivalent to assuming that $\nu = 0$, *i.e.*, all mutations are pleiotropic.

We assume that stabilizing selection acts independently on each character. The fitness of an individual with phenotype (x, y) is $w(x, y) = \exp[-x^2/(2V_{sx}) - y^2/(2V_{sy})]$, which implies that the fitness of an individual carrying the ij allele is

$$w_{ij} = \exp(-s_x i^2 - s_y j^2) \tag{2}$$

where $s_x = c_x^2/(2V_{sx})$ and $s_y = c_y^2/(2V_{sy})$. After selection, at the beginning of the next generation, the frequency of the (i, j) allele is

$$p'_{i,j} = \frac{p^*_{i,j} w_{ij}}{\bar{w}} \tag{3}$$

where $\bar{w} = \Sigma(p_{i,j} w_{ij})$ is the mean fitness.

The numerical results presented later were obtained by iterating this set of equations. In the program that carries out these iterations, we assumed a sufficiently large range, n, of allelic classes, i and j, that the frequencies of the outer allelic classes were all less than 10^{-6} at equilibrium. We then iterated these equations for $p_{i,j} (-n \le i, j \le n)$ by assuming that frequencies outside this range were zero. In the calculations for each set of parameter values, we used two initial conditions, in one $p_{0,0} = 1$ and all other allele frequencies were zero, while in the other all allele frequencies were equal. We iterated the equations until the absolute value of the largest change in allele frequency per generation was less than 10^{-8}. We found that this criterion for stopping the iteration ensured that the maximum absolute difference between the final allele frequencies from the two sets of

initial conditions was less than 10^{-4}, thus indicating that the final frequencies in the iterations were close to the true equilibrium frequencies of the system of equations. We also found that increasing the bounds on the allelic classes, n, from the ones we chose had no effect on the equilibrium frequencies we found.

Nine-allele approximation: Equations 1 and 3 allow the prediction of allele frequencies given the mutation rates and the selection intensities. It is possible to obtain approximate results by assuming that selection is sufficiently strong relative to mutation that only the nine central alleles, $-1 \leq i, j \leq +1$, are contributing significantly to the genetic variance. Assuming all other frequencies are zero leads to a set of three coupled quadratic equations. Our approximation is a generalization of TURELLI's (1985) five-allele model but differs in two ways. TURELLI considered only the pleiotropic alleles (1, 1), (1, −1), (−1, 1) and (−1, −1), in addition to the central allele, (0, 0), which in our notation is equivalent to assuming that $\mu_1 = \nu = 0$. Also, TURELLI assumed that the alleles other than the central allele are all in low frequency. We will not assume those alleles are in low frequency, making our model a generalization of SLATKIN's (1987) model for a single character, but we will assume that the frequencies of alleles other than the nine central alleles are zero. Using SLATKIN's approach here, it would be possible to include the effects of the alleles for which i or j is ±2, but the small increase in accuracy does not justify the extra algebra needed.

The assumption that only nine alleles are needed to approximate the equilibrium for the stepwise mutation model leads to a closed set of equations for their equilibrium frequencies. Because we have assumed that both mutation and selection are symmetric in i and j it is reasonable to use the symmetry of the model to reduce the number of unknown allele frequencies. Therefore, we can assume that at equilibrium $p_{1,0} = p_{-1,0}$, $p_{0,1} = p_{0,-1}$ and $p_{1,1} = p_{1,-1} = p_{-1,1} = p_{-1,-1}$ giving three independent allele frequencies. To simplify notation, we will let $q_1 = p_{1,0}$, $q_2 = p_{0,1}$ and $q_3 = p_{1,1}$, and note that $p_{0,0} + 2q_1 + 2q_2 + 4q_3 = 1$. If we assume that both selection and mutation are weak forces, then we can combine Equations 1 and 3 into a single set of equations for the q's:

$$
\begin{aligned}
&-q_1 + \nu(1 - 2q_1 - 2q_2 - 2q_3)/4 + (1 - \nu)(q_1 + q_2)/4 \\
&\quad + q_1[\xi_x(2q_1 - 1) + 2\xi_y q_2 + 4(\xi_x + \xi_y)q_3] = 0 \\
&-q_2 + \nu(1 - 2q_1 - 2q_2 - 2q_3)/4 + (1 - \nu)(q_1 + q_2)/4 \\
&\quad + q_2[2\xi_x q_1 + \xi_y(2q_2 - 1) + 4(\xi_x + \xi_y)q_3] = 0 \\
&-q_3 + \nu(q_1 + q_2)/4 + (1 - \nu)(1 - 2q_1 - 2q_2 - 4q_3)/4 \\
&\quad + q_3[\xi_x(2q_1 - 1) + \xi_y(2q_2 - 1) + 4(\xi_x + \xi_y)q_3] = 0
\end{aligned}
\qquad (4)
$$

where $\xi_x = s_x/\mu$ and $\xi_y = s_y/\mu$ indicate the relative strengths of selection and mutation.

These three coupled quadratic equations do not have a general solution in closed form but can be solved for particular parameter values using programs such as Mathematica or Macsyma. Some results obtained using Mathematica are presented in Figure 1.

EQUILIBRIUM UNDER STABILIZING SELECTION

The first question is how the variance of one character depends on the intensity of stabilizing selection on the other character. TURELLI (1985, 1988) showed that, if the assumptions of the multivariate normal model are not satisfied, there will be some dependence of equilibrium variance of one character on the other. He did not show how strong the effect is for models intermediate between the house-of-cards and multivariate normal models and for mixtures of pleiotropic and nonpleiotropic mutations.

We have assumed complete symmetry of the mutation model and independence of selection on the two characters, so the genetic correlation between the characters is zero at equilibrium for any parameter values. In our numerical analysis, we assumed that the additive effects of the two loci are equal, $c_x = c_y = c$, and fixed the values of μ, the net mutation rate, and V_{sx}, the intensity of stabilizing selection on x. We then determined how the equilibrium variance of x, var(x) depends on V_{sy}, the intensity of stabilizing selection on y, and ν, the fraction of mutations that are nonpleiotropic.

Figure 1 shows results for both the exact numerical analysis and the nine-allele approximation that illustrate our main point. There are three pairs of results that are distinguished by different values of c. Parts a and b, $c = 1$, which implies that $s_x = 2.0 \times 10^{-2}$ and $5 \times 10^{-2} \geq s_y \geq 2.5 \times 10^{-4}$, so the selection intensities are both greater than μ, which is 10^{-4} in all the examples. For these parameter values, alleles other than the central allele are in very low frequency, and the results are consistent with TURELLI's (1985) results for his five-allele model. If there are any pleiotropic mutations ($\nu < 1$), then the var(x) does depend on V_{sy}. Figure 1, a and b, shows that, as expected, the larger the value of ν, the weaker the effect is. Surprisingly, the same pattern is found in parts c and d which were obtained when $c = 0.1$, for which alleles adjacent to the central allele are in higher frequency at equilibrium. For $c = 0.1$, $s_x = 2.5 \times 10^{-4}$ and $5 \times 10^{-4} \geq s_y \geq 2.5 \times 10^{-6}$. In this case, the nine-allele approximation described above is reasonably accurate. In parts e and f which were obtained for $c = 0.02$, only the exact numerical results are presented. The nine-allele approximation is not at all accurate for that range of parameter values.

Only when selection affecting each allele is much weaker ($c = 0.02$, *i.e.*, $s = 10^{-5}$) or when most mutations are nonpleiotropic ($\nu = 0.9$) are the results com-

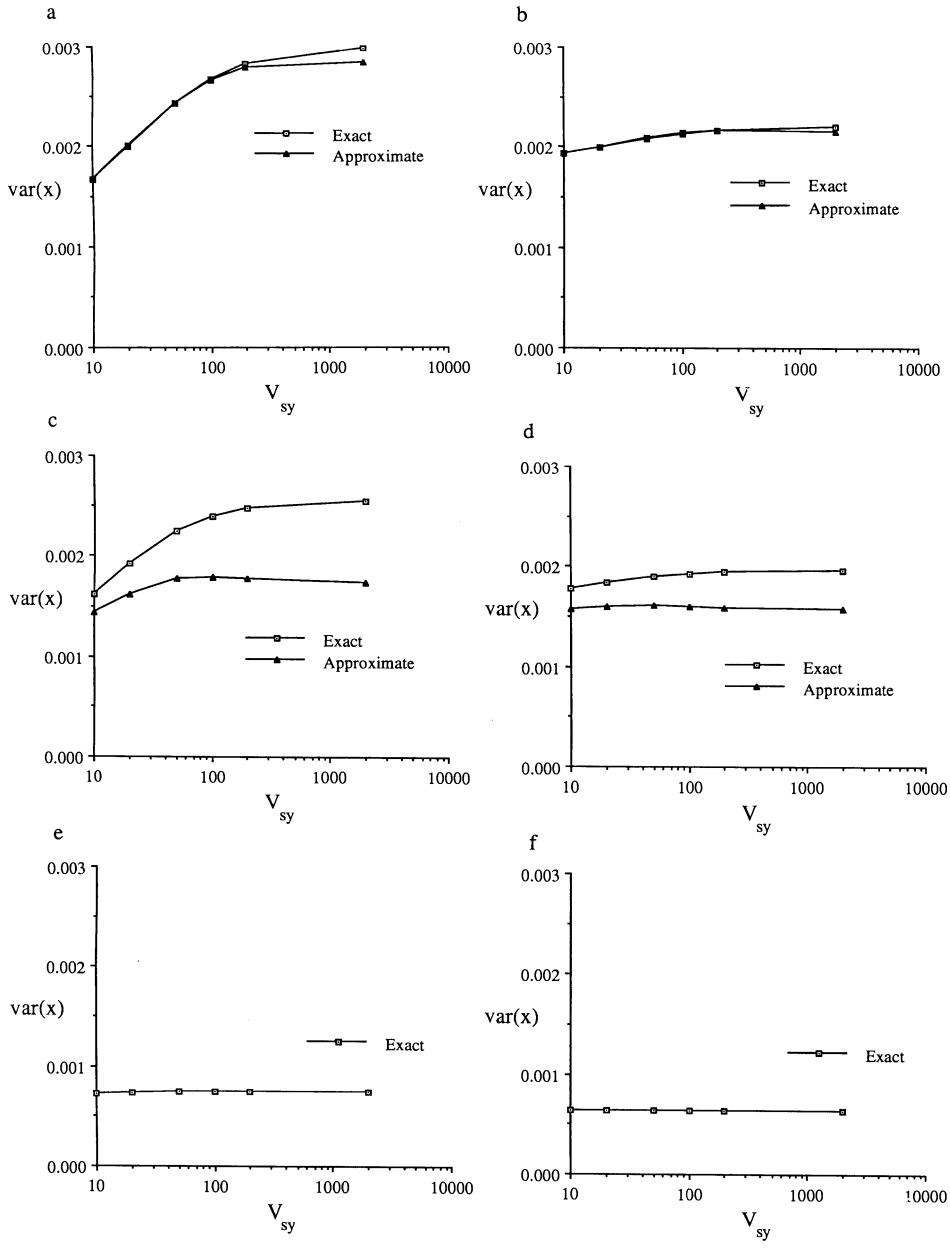

FIGURE 1.—The equilibrium variance of one character, var(x), plotted as a function of the strength of stabilizing selection on the other character, V_{sy}. In all cases, $\mu = 0.0001$ and $V_{sx} = 20$. The exact results were obtained by numerically iterating Equations 1 and 3 until the maximum change in allele frequency was less than 10^{-8} per generation. The approximate results in parts a–d were obtained by using the FindRoot function in Mathematica (WOLFRAM 1988) on a NeXT computer. Part a: $c = 1$, $\nu = 0.5$, part b: $c = 1$, $\nu = 0.9$, part c: $c = 0.1$, $\nu = 0.5$, part d: $c = 0.1$, $\nu = 0.9$, part e: $c = 0.02$, $\nu = 0.5$, and part f: $c = 0.02$, $\nu = 0.9$. c is the additive effect of each allelic step and ν is the fraction of nonpleiotropic mutations.

parable to those obtained using a normal approximation. In those cases, the equilibrium value of var(x) depends only slightly on V_{sy}. Therefore, we conclude that the house-of-cards approximation leads to predictions that are also valid if selection affecting each allele is comparable to mutation and if a substantial fraction of the mutations are pleiotropic. In contrast, predictions obtained using the normal approximation apply only when the effect of selection affecting each locus is weaker than mutation or if most mutations are nonpleiotropic.

DIRECTIONAL SELECTION

The other question of interest here is whether directional selection tends to cause a change in the genetic correlation between two characters. To answer this question, we assumed that an equilibrium was reached between mutation and selection. Then both mutation and stabilizing selection ceased acting and directional selection in favor of larger values of $x + y$ acted for 20 generations. The directional selection imposed was sufficiently strong that the previously acting forces can be ignored in the short term. To be specific, we assumed that the relative fitness of an (x, y) individual was $w(x, y) = 1 + \alpha(x + y)$, where α is the measure of the intensity of directional selection.

Figure 2 shows the effect of directional selection on correlation between the two characters. To obtain these results, we first iterated Equation 1 and 3 to obtain the equilibrium distributions of the characters and then assumed directional selection acted for 20

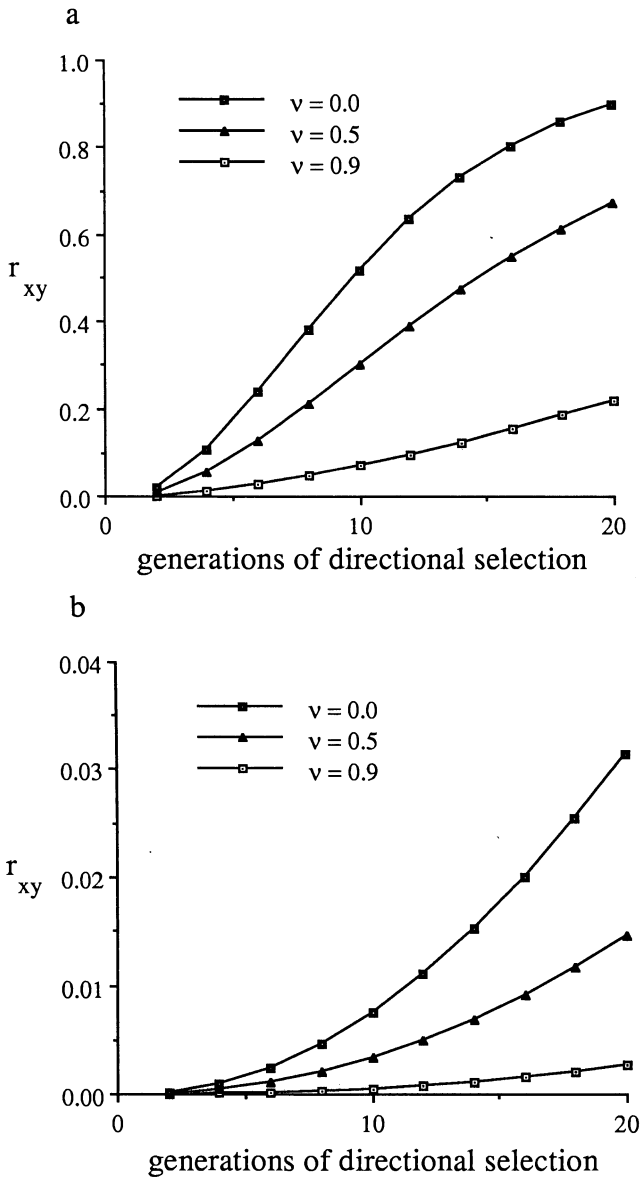

FIGURE 2.—The change in genetic correlation, r_{xy}, between two characters during 20 generations of directional selection. In both parts, $V_{sx} = V_{sy} = 20$ and $\mu = 10^{-4}$. Part a corresponds to Figure 1, a and b ($c = 1$), and part b corresponds to Figure 1, c and d ($c = 0.1$). In both parts the equilibrium was obtained as described in the caption to Figure 1 and then directional selection of the form $w(x, y) = 1 + \alpha(x + y)$ with $\alpha = 0.1$ was imposed.

generations. As shown in Figure 2, there is a dramatic increase in r_{xy}, the genetic correlation between the two characters, when the house-of-cards approximation is valid. The reason is that the response to directional selection is attributable primarily to the increase in frequency of the (1, 1) allele which also causes the increase in the correlation. The increase in r_{xy} is much less pronounced if variation is maintained by higher frequency alleles, as shown in Figure 2b. When alleles are present in higher frequency, the response to directional selection is absorbed by several of the allelic classes, making the increase in genetic correlation much smaller. (Note the difference in vertical scales in Figure 2, a and b.)

Another way to look at our numerical results is to consider the change in r_{xy} under directional selection when changes in the mean are the same. Because the dynamics of the variances and covariances are different for different values of c and ν, changes in the means after 20 generations of directional selection vary. For each case with $c = 1$ (the house-of-cards limit), we applied 20 generations of directional selection. We then computed the change in the mean of either character relative to its standard deviation at equilibrium. The symmetry of our model ensures that the results for both characters are the same. Then, with $c = 0.1$, we applied directional selection until the relative change in the mean was approximately the same as for 20 generations under $c = 1$. The results in Table 1 confirm the conclusions from Figure 2 that the increase in r_{xy} caused by directional selection is much smaller for our intermediate model than it is in the house-of-cards limit. For some levels of pleiotropic mutations, ν, significant changes do occur, contradicting the prediction of the multivariate normal model.

We conclude that, for the consequences of directional selection, neither the house-of-cards nor the normal approximation can predict all of the results for the intermediate model we have considered. The actual results for that model depend on both the strength of selection relative to mutation and the fraction of mutations that are pleiotropic.

EMPIRICAL STUDIES

Our results suggest two kinds of empirical studies that might indicate whether genetic variation is attributable primarily to alleles in relatively high or relatively low frequencies: stabilizing selection of differing intensities and directional selection on two traits simultaneously. We know of no studies of the effects of stabilizing selection of different strengths applied to two characters, but there have been several studies of the effect of directional selection on the genetic correlation between two characters. DEMPSTER, LERNER and LOWERY (1952) selected for increased egg production and found that the genetic correlation between two components of egg production, egg-laying rate and survival to the end of the first laying year, increased from 0.20 in years 1–3 to 0.49 in years 8–10. FRIARS, BOHREN and MCKEAN (1962) selected chickens for increased meat production and found a slight decrease in the genetic correlations in four pairs of component traits. SEN and ROBERTSON (1964) found a slight increase in genetic correlation in lines selected for both increased sternopleural and abdominal bristles in *Drosophila melanogaster*. BELL (1972) selected for four combinations of high and low larval

TABLE 1

A comparison of the numerical results for directional selection in the house-of-cards limit ($c = 1$) and for our intermediate case ($c = 0.1$) when the change in the mean relative to the equilibrium standard deviation is fixed

c	ν	t	Δx	var(x)	Δx/var(x)	r_{xy}
1.0	0.9	20	0.008	0.045	0.178	0.220
0.1	0.9	40	0.008	0.043	0.186	0.011
1.0	0.5	20	0.013	0.045	0.289	0.669
0.1	0.5	60	0.013	0.044	0.295	0.121
1.0	0.0	20	0.019	0.045	0.422	0.898
0.1	0.0	75	0.019	0.044	0.432	0.334

The model is the same as used to produce the results shown in Figure 2: c is the additive effect of each mutation; ν is the fraction of mutations that are nonpleiotropic; t is the number of generations of directional selection after the equilibrium was reached; Δx is the change in the mean of x after t generations of directional selection; var(x) is the equilibrium standard deviation; and r_{xy} is the genetic correlation coefficient between the two traits. The value of t for $c = 0.1$ was chosen so that Δx/var(x) is approximately the same for both values of c.

and pupal weights in *Tribolium casteneum* and found no trends in the genetic correlations.

In the most thorough study of the effects of directional selection on two characters, SHERIDAN and BARKER (1974) selected for four combinations of high (U) and low (D) numbers of coxal and sternopleural bristles in *D. melanogaster*. They selected four replicate lines in each of four treatments, making a total of 16 experimental lines. At the end of 10 and 22 generations, they computed the realized genetic correlations by performing an additional generation of selection on samples of individuals from each line. The initial average realized genetic correlation (ARGC) was 0.24 ± 0.08. After 10 generations, in one of the treatments (UU) the ARGC decreased to 0.15 ± 0.06 and in the other three it increased to between 0.37 to 0.45. After 22 generations, one of the treatments (UD) had almost the starting ARGC while the others increased to between 0.40 and 0.54.

The available evidence suggests that genetic correlations are affected by directional selection on two characters simultaneously, although that is not always true. A feature of the results that is difficult to explain is that directional selection on two characters simultaneously often increases the genetic correlation between them regardless of the direction of selection applied. In the SHERIDAN and BARKER (1974) study, the genetic correlation increased in lines selected upwards for one character and downwards for the other. If the genetic correlation increases in one treatment because of changes in the frequencies of pleiotropic alleles, then it should decrease in the opposite treatment. That was not found. SHERIDAN and BARKER (1974) discuss possible developmental causes for their results.

Available studies do not provide a direct test of the theory we have developed here. Our model is of two characters that are initially uncorrelated genetically and then subject to simultaneous directional selection. If the two characters are affected by pleiotropic alleles in low frequencies, as in the house-of-cards model, then small changes in the frequencies of those alleles will result in large changes in genetic correlations. If the two characters are affected by numerous pleiotropic alleles in comparable frequencies, as in the multivariate normal model, then little or no change in genetic correlation would be expected.

DISCUSSION AND CONCLUSIONS

We have found that neither the house-of-cards nor the normal approximations leads to robust predictions about the evolutionary relationships of genetically uncorrelated characters affected by pleiotropic loci. A model intermediate between the two extremes makes predictions that are sometimes consistent with the those of the house-of-cards model and sometimes with those of the multivariate normal model. Therefore, neither extreme can in any sense be regarded as typical of intermediate cases.

Our results are consistent with those of WAGNER (1989) when the assumptions are comparable. WAGNER assumed that mutation rates are low enough that TURELLI's (1985) one-locus house-of-cards results could be used. Wagner found that under his assumptions the equilibrium variance of one character is decreased by stabilizing selection on other characters and that the effect could be substantial if there are numerous characters affected by pleiotropic loci. For the case of selection much stronger than mutation, we reach the same conclusion for our model of mutation.

At the present time, the forces maintaining quantitative genetic variation are unknown. TURELLI (1988), BARTON and TURELLI (1989) and BARTON (1990) review various theories and available evidence but can reach no firm conclusion. There seem to be valid objections to any single theory. In attempting to understand different possibilities, it is worth distinguishing two questions: (i) What are the forces maintaining quantitative genetic variation? and (ii) What are the frequencies of alleles responsible for quantitative genetic variation? The answers are obviously related because the balance of forces achieved will determine

allele frequencies. But they are also somewhat independent.

The results described in this paper combined with the results of TURELLI (1985) lead to testable predictions that could restrict the possible answers to both of these questions. If genetic variability is maintained in part by alleles that are pleiotropic, then our results suggest that imposing stabilizing selection on one character may affect the variances of other characters. Only if allelic effects at different loci all have an approximately multivariate normal distribution would the variances of other characters be independent of the strength of stabilizing selection on related characters. This prediction does not depend on the mechanism maintaining pleiotropic alleles in the population. Even if pleiotropic alleles are maintained in the population by forces other than mutation and stabilizing selection, additional stabilizing selection on one character will alter their frequencies and hence alter the variance of the other character.

If genetic variation is maintained by pleiotropic alleles in very low frequencies as in the house-of-cards model, then directional selection would tend to increase the variances of characters and the genetic correlations between them. TURELLI (1988) has reviewed the experimental literature and concluded that large increases in genetic variance are not found in the first few generations of directional selection, an observation that argues against the general applicability of the house-of-cards model. KEIGHTLEY and HILL (1988), however, show that in relatively small populations, such an increase in variance might be difficult to detect. Our results lead to another prediction. If directional selection on two characters together is imposed, then pleiotropic alleles in low frequency would be expected to increase substantially the genetic correlation between those characters.

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