EFFECTS OF PLEIOTROPY ON PREDICTIONS CONCERNING MUTATION-SELECTION BALANCE FOR POLYGENIC TRAITS

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ABSTRACT

Previous mathematical analyses of mutation-selection balance for metric traits assume that selection acts on the relevant loci only through the character(s) under study. Thus, they implicitly assume that all of the relevant mutation and selection parameters are estimable. A more realistic analysis must recognize that many of the pleiotropic effects of loci contributing variation to a given character are not known. To explore the consequences of these hidden effects, I analyze models of two pleiotropically connected polygenic traits, denoted P_1 and P_2. The actual equilibrium genetic variance for P_1, based on complete knowledge of all mutation and selection parameters for both P_1 and P_2, can be compared to a prediction based solely on observations of P_1. This extrapolation mimics empirically obtainable predictions because of the inevitability of unknown pleiotropic effects. The mutation parameters relevant to P_1 are assumed to be known, but selection intensity is estimated from the within-generation reduction of phenotypic variance for P_1. The extrapolated prediction is obtained by substituting these parameters into formulas based on single-character analyses. Approximate analytical and numerical results show that the level of agreement between these univariate extrapolations and the actual equilibrium variance depends critically on both the genetic model assumed and the relative magnitudes of the mutation and selection parameters. Unless per locus mutation rates are extremely high, *i.e.*, generally greater than 10^{-4}, the widely used gaussian approximation for genetic effects at individual loci is not applicable. Nevertheless, the gaussian approximations predict that the true and extrapolated equilibria are in reasonable agreement, *i.e.*, within a factor of two, over a wide range of parameter values. In contrast, an alternative approximation that applies for moderate and low per locus mutation rates predicts that the extrapolation will generally overestimate the true equilibrium variance unless there is little selection associated with hidden effects. The tendency to overestimate is understandable because selection acts on all of the pleiotropic manifestations of a new mutation, but equilibrium covariances among the characters affected may not reveal all of this selection. This casts doubt on the proposal that much of the additive polygenic variance observed in natural populations can be explained by mutation-selection balance. It also indicates the difficulty of critically evaluating this hypothesis.

IT is not known what accounts for the persistence of heritable polygenic variation. Based on a mathematical analysis and empirical estimates of the

This paper is dedicated to my friend and colleague John Gillespie on the occasion of his fortieth birthday.

relevant parameters, LANDE (1975) argued that mutation-selection balance may play a major role. This hypothesis, discussed earlier by FISHER (1930), LATTER (1960), KIMURA (1965) and BULMER (1972), is extremely appealing because it involves an equilibrium between two ubiquitous forces: stabilizing phenotypic selection, which tends to eliminate additive genetic variance (*e.g.*, FISHER 1930; ROBERTSON 1956; LEWONTIN 1964; WRIGHT 1969; BULMER 1972) and mutation, which continually reintroduces it. Previous mathematical analyses of mutation-selection balance for quantitative characters (reviewed in TURELLI 1984) assume that selection acts on the relevant loci only through the character(s) under study. This implies that all of the relevant mutation and selection parameters are empirically estimable. However, the complex pathways that connect DNA to phenotypes ensure that the alleles contributing variation to any one character will also affect numerous other characters, not under study, that are also under selection. Naturally, one expects these hidden effects to obscure the relationship between estimable mutation and selection parameters and the actual mutation-selection equilibrium. This paper presents mathematical analyses that display how this relationship changes with alternative genetic assumptions and mathematical approximations. The mathematics is coupled with an attempt to determine the biological conditions under which the alternative models and approximations are appropriate. A major corollary of the calculations is that genetic conclusions based on a set of mathematical assumptions introduced by LANDE (1975) may not be robust.

LANDE's (1975) treatment of mutation-selection balance, which he has extended to multiple characters connected by pleiotropy (LANDE 1980), uses a generalization of the CROW and KIMURA (1964) continuum-of-alleles model for polygenic traits. This model assumes that alleles and loci contribute additively to the trait(s) of interest (*i.e.*, dominance and epistasis are ignored) and that the segregating alleles at each locus have an essentially continuous range of effects. The cornerstone of Lande's analyses is the additional assumption that at each locus the distribution of allelic effects in a population is approximately gaussian. The additivity assumptions of Lande's generalization of the continuum-of-alleles model together with the use of gaussian distributions to approximate the effects of the segregating alleles will be referred to as the *gaussian genetic model*. Unlike traditional population genetic analyses which derive gamete and allele frequencies from specified recursions, the gaussian genetic model *assumes* that the form of the distribution of effects is known. This profoundly simplifies the mathematics. Consequently, the gaussian genetic model is now the most commonly applied genetic analysis for polygenic traits, with applications including mutation-selection balance (LANDE 1975, 1977, 1980), sexual selection (LANDE 1981), spatially varying selection (FELSENSTEIN 1977; SLATKIN 1978), disruptive selection (FELSENSTEIN 1979), and rapid phenotypic evolution (KIRKPATRICK 1982).

It is important to recognize that the gaussian genetic model is not interchangeable with gaussian-based models for phenotypes (*e.g.*, FISHER 1918; LANDE 1976, 1979). The latter are grounded in the empirical observation that, on an appropriate scale of measurement, the distributions of quantitative

traits in populations are often nearly gaussian (see WRIGHT 1968, chap. 15). In contrast, the gaussian genetic model stems from KIMURA'S (1965) mathematical derivation of an approximate gaussian distribution for allelic effects at individual loci under mutation-selection balance. Although KIMURA'S (1965) result is frequently invoked, the underlying biological assumptions have generally been unknown and ignored. Using the single character mutation and selection model of LANDE (1975), I have shown (TURELLI 1984) that the gaussian approximation for segregating alleles is likely to be applicable at equilibrium only if the relevant loci experience extremely high mutation rates, *e.g.*, in excess of 10^{-4} per locus. An alternative approximation, named after KINGMAN'S (1978) "house-of-cards" model, was demonstrated to be applicable for more usual per locus mutation rates, *i.e.*, $\leq 10^{-4}$. However, this conclusion was based on a one-character analysis that ignored confounding effects in the estimation of the intensity of stabilizing selection. One objective of this paper is to describe biological and mathematical conditions under which the gaussian and house-of-cards approximations for the continuum-of-alleles model are valid when pleiotropy is considered.

The basis for the house-of-cards approximation is the empirically motivated assumption that among mutants at a given locus, the variance of phenotypic effects exceeds the variance of effects associated with currently segregating alleles (see Turelli 1984, pp. 147–148). Unlike LANDE'S (1975) predictions and the closely related results of KIMURA (1965) and FLEMING (1979), the house-of-cards predictions agree with those derived from a diallelic model by LATTER (1960) and BULMER (1972, 1980) and from a triallelic model by TURELLI (1984). Thus, a key result from the single-character house-of-cards analysis is that the equilibrium genetic variance maintained by mutation-selection balance is approximately independent of the number of available alleles at each locus. The analysis below shows that pleiotropy destroys this property. Thus, the validity of multivariate predictions for mutation-selection balance hinges on the validity of assumptions concerning the number and effects of segregating alleles. This is one source of uncertainty that confounds equlibrium predictions based on single-character analyses.

As noted previously, the other major source is the estimation of selection intensity. Selection estimates for quantitative characters generally come from observing the frequency distribution of a character, or set of characters, in a cohort at two stages of the life cycle (JOHNSON 1976; LANDE and ARNOLD 1983). These estimates are used to predict selection intensities at the underlying loci (see TURELLI 1984), but there are confounding influences. As shown by LANDE and ARNOLD (1983), changes in a given character are caused not only by direct selection on that character, but also by selection on correlated characters. This suggests that selection intensities may tend to be overestimated. Conversely, however, all of the selection experienced by new mutations may not be reflected accurately by phenotypic correlations. The goal of the analyses below is to sort out these contradictory effects.

My analysis is broken into three parts. In MODELS AND METHODS, I introduce a two-character model and dual method of analysis that displays the conse-

quences of hidden pleiotropic effects. Within this general framework, I present two extreme alternative models for the number and effects of segregating alleles at each locus. The first is the continuum-of-alleles model of LANDE (1980), the second is a five-allele generalization of the triallelic model of TURELLI (1984). To simplify the subsequent analyses, I argue for assuming complete linkage equilibrium so that only single-locus equilibria need be approximated.

In the second section, APPROXIMATE ANALYTICAL RESULTS are presented for each model. Two alternative approximations are used for the continuum-of-alleles model: a gaussian approximation based on LANDE (1980), which is shown to be appropriate for relatively high per locus mutation rates, and a generalization of the house-of-cards approximation from TURELLI (1984), which is shown to be appropriate for relatively low per locus mutation rates. Only a low mutation rate analysis is presented for the five-allele model. Qualitative differences between the models and approximations are highlighted by simple special cases. In addition, I present some asymptotic results for the low-mutation approximations which display the range of possible discrepancies between actual equilibrium variances and extrapolations based on incomplete information. Detailed calculations are relegated to appendices.

The third part of my analysis consists of two sorts of NUMERICAL RESULTS. The first is numerical approximations for mutation-selection equilibria which exhibit the accuracy and domains of applicability of the alternative approximations. The second consists of graphical and numerical comparisons of actual and extrapolated equilibria for various parameter values. Finally, the DISCUSSION elaborates the difficulties of experimentally evaluating the power of mutation-selection balance to account for observed heritable variation.

MODELS AND METHODS

To unravel the connection between observed phenotypic selection and unknown pleiotropic effects, it seems reasonable to begin with a simple model. A minimal model that captures the phenomena of interest involves stabilizing phenotypic selection acting on two polygenic traits, denoted P_1 and P_2, which share variance-contributing loci. For simplicity, let us assume that these loci experience selection only through their effects on these characters and that correlations between them are due solely to pleiotropy and environmental effects (*i.e.*, linkage effects are ignored, *cf.* DAVIES 1971). To reveal the consequences of hidden pleiotropic effects, this bivariate system will be approached from two perspectives. First, we can assume, as in LANDE (1980), that all of the selection and mutation parameters are known. This allows a complete bivariate analysis of equilibrium genetic and phenotypic means, variances and covariances. Second, we can mimic the dilemma faced by experimental studies and assume that observations are available only on one of the two characters, say P_1. In this context, the single character P_2 crudely represents all of the unknown effects of the loci that contribute variation to P_1, the character under

study. The complexity of the results from this simple model dampens enthusiasm for more realistic models of unknown pleiotropic effects.

As in empirical studies, we can estimate the intensity of stabilizing selection on P_1 by measuring the reduction in phenotypic variance through the life cycle. If it is assumed that both characters are at mutation-selection equilibrium, this within-generation reduction in variance can be calculated from a bivariate analysis. This yields a stabilizing selection estimate for P_1, denoted $\tilde{V}_{s,1}$, which will be called the *realized* intensity of selection in P_1. Assuming that the mutation parameters relevant to P_1 are known, we can put them and $\tilde{V}_{s,1}$ into the formulas derived from single-character mutation-selection balance theory. This produces an extrapolated prediction, denoted $\tilde{V}_{g,1}$, for the equilibrium genetic variance for P_1. In this model system, it can be directly compared to the true equilibrium genetic variance, denoted $\tilde{V}_{g,1}$, obtained from a complete bivariate analysis. Thus, we can assess the accuracy of mutation-selection equilibrium predictions based on incomplete knowledge of genotype-phenotype relationships.

Basic assumptions: We assume an effectively infinite, randomly mating, diploid population with nonoverlapping generations. To facilitate comparison with existing gaussian and single-character results, we assume additive genetic effects, no genotype-environment interaction and gaussian stabilizing selection as in LANDE (1980). Let $\mathbf{P} = (P_1, P_2)$, $\mathbf{G} = (G_1, G_2)$ and $\mathbf{E} = (E_1, E_2)$ denote the bivariate phenotype and its genetic and environmental components. We assume

$$\mathbf{P} = \mathbf{G} + \mathbf{E}, \tag{1}$$

with the random vector $\mathbf{E}$ independent of $\mathbf{G}$ and distributed as a bivariate gaussian with mean (0,0), variances $V_{e,1}$ and $V_{e,2}$ and correlation ρ_e. Letting n denote the number of loci contributing variance to either character, additivity of allelic effects implies

$$\mathbf{G} = \sum_{i=1}^{n} (\mathbf{x}_{\delta}^{(i)} + \mathbf{x}_{\varphi}^{(i)}), \tag{2}$$

in which $\mathbf{x}^{(i)} = (x_1^{(i)}, x_2^{(i)})$ denotes the average phenotypic contributions of an allele at the ith locus and the subscripts δ and φ denote maternal *vs.* paternal inheritance.

Fitnesses are assigned to phenotypes by

$$w(P_1, P_2) = \exp\{-\tfrac{1}{2}[(P_1/w_1)^2 - 2\rho_w(P_1/w_1)(P_2/w_2) + (P_2/w_2)^2]/(1 - \rho_w^2)\}. \tag{3}$$

Thus, both characters are subject to stabilizing selection with selection intensities proportional to w_1^{-2} and w_2^{-2} and optima scaled to 0. The correlation parameter ρ_w satisfies $-1 < \rho_w < 1$ and measures the extent to which selection acts to produce covariance between P_1 and P_2. Assumptions (1) and (3) imply that the mean fitness of genotype $\mathbf{G}$ is

$$w(G_1, G_2) = c \exp[-\tfrac{1}{2}(G_1^2 V_{s,1}^{-1} - 2\rho_s G_1 G_2 (V_{s,1} V_{s,2})^{-\frac{1}{2}} + G_2^2 V_{s,2}^{-1})/(1 - \rho_s^2)], \tag{4}$$

in which c is a genotype-independent constant,

$$V_{s,i} = w_i^2 + V_{e,i}, \quad \text{and} \tag{5a}$$

$$\rho_s = (\rho_w w_1 w_2 + \rho_e V_{e,1} V_{e,2})(V_{s,1} V_{s,2})^{-1/2}. \tag{5b}$$

Note that, as $V_{s,i}$ increases, the intensity of selection against nonoptimal genotypes for character i decreases.

Calculation of realized selection: The key step in understanding the effects of pleiotropy is calculating $\tilde{V}_{s,1}$, the intensity of realized selection on P_1, in terms of the parameters and phenotypic equilibrium of the bivariate model. To calculate $\tilde{V}_{s,1}$, we assume that P_1 experiences univariate stabilizing selection and we estimate its intensity from the within-generation reduction of phenotypic variance. The bivariate and univariate calculations for the change in phenotypic variance rely on the approximation that the equilibrium distribution of phenotypes is gaussian. Because of the assumptions of polygenic inheritance (2) and gaussian environment effects (1), this approximation for phenotypes is consistent with nongaussian distributions of allelic effects at the underlying loci. The accuracy of this approximation is discussed in APPENDIX 1 and in FISHER (1918).

Let $V_{p,1}$ ($V'_{p,1}$) denote the variance of P_1 before (after) selection, once the population has reached mutation-selection equilibrium. If we assume univariate gaussian stabilizing selection with intensity $\tilde{w}^2$, *i.e.*,

$$w(P_1) = \exp(-P_1^2/2\tilde{w}^2), \tag{6}$$

it is easy to show that

$$\frac{V'_{p,1}}{V_{p,1}} = \frac{\tilde{w}^2}{\tilde{w}^2 + V_{p,1}} \quad \text{and, hence,} \tag{7a}$$

$$\frac{V_{p,1}^2}{V_{p,1} - V'_{p,1}} = \tilde{w}^2 + V_{p,1}. \tag{7b}$$

Under weak selection, *i.e.*, $\tilde{w}^2 \gg V_{p,1}$,

$$\tilde{V}_{s,1} \equiv \tilde{w}^2 + V_{e,1} \cong \tilde{w}^2 + V_{p,1}; \tag{8}$$

thus (7) implies that

$$\tilde{V}_{s,1} \cong \frac{V_{p,1}^2}{V_{p,1} - V'_{p,1}}. \tag{9}$$

The weak selection approximation (8) is consistent with empirical estimates of $\tilde{V}_{s,1}/V_{e,1}$ which generally fall between 10 and 20 (TURELLI 1984).

As (9) shows, predicting $\tilde{V}_{s,1}$ from the bivariate model requires an approximation for $V_{p,1} - V'_{p,1}$ at equilibrium. Let $\mathbf{\Sigma}_p$ ($\mathbf{\Sigma}'_p$) denote the variance-covariance matrix for phenotypes before (after) selection, let $\mathbf{\Sigma}_e$ denote the variance-covariance matrix for environmental effects, and let $\mathbf{\Sigma}_w$ denote the variance-covariance matrix of the bivariate gaussian fitness function (3). As noted by LANDE (1980),

$$\mathbf{\Sigma}_p - \mathbf{\Sigma}'_p = \mathbf{\Sigma}_p(\mathbf{\Sigma}_w + \mathbf{\Sigma}_p)^{-1}\mathbf{\Sigma}_p \tag{10a}$$

$$\cong \mathbf{\Sigma}_p(\mathbf{\Sigma}_w + \mathbf{\Sigma}_e)^{-1}\mathbf{\Sigma}_p, \tag{10b}$$

under weak selection. Thus, for two characters, approximations (9) and (10b)

yield

$$\tilde{V}_{s,1} \cong \frac{V_{s,1}(1 - \rho_s^2)}{1 - 2\rho_s y + y^2}, \tag{11a}$$

with

$$y = \left[\frac{V_{s,1}}{V_{s,2}}\right]^{1/2} \frac{\text{cov}(P_1, P_2)}{V_{p,1}}. \tag{11b}$$

As expected from LANDE and ARNOLD's (1983) discussion of indirect selection,

$$\tilde{V}_{s,1} \leq V_{s,1} \tag{12}$$

with equality if and only if $\rho_s = y$.

Continuum-of-alleles model: To carry out this analysis, we must specify the number and effects of alleles at each locus and the mutation scheme. Two models will be considered. The first is a special case of LANDE's (1980) multivariate extension of the continuum-of-alleles model. It assumes that at each locus there is an effectively infinite number of alleles with a continuous range of effects on one or both of the characters. Mutation at locus i occurs with probability μ_i and transforms an allele of effect $\mathbf{x} = (x_1, x_2)$ into an allele of effect $\mathbf{x}' = (x_1', x_2')$ with

$$\mathbf{x}' = \mathbf{x} + \mathbf{M}. \tag{13}$$

The mutation-induced displacement, $\mathbf{M}$, is assumed to follow a bivariate gaussian distribution with mean (0, 0), variances $m_{1,i}^2$ and $m_{2,i}^2$ and correlation $\rho_{m,i}$. Apart from the existence of correlation in the mutation-induced changes of P_1 and P_2, this model assumes that no constraints are imposed by the genetic system. In particular, every locus affecting both characters is capable of producing essentially any effect on each character.

Five-allele model: The alternative model that will be considered is a five-allele generalization of the triallelic model of TURELLI (1984). It is a simple attempt at introducing genetic constraints associated with a limited range of potential bivariate allelic effects. For locus i, the alleles are denoted $A_{0,0}^{(i)}$ and $A_{j,k}^{(i)}$ for $j, k = \pm 1$; allele $A_{j,k}^{(i)}$ contributes $(jc_{1,i}, kc_{2,i})$ to (G_1, G_2) with $c_{1,i}, c_{2,i} \geq 0$. This model is most plausible when allele $A_{0,0}^{(i)}$ is nearly fixed. Then, mutation affects the equilibrium genetic structure primarily through the mutation rates from $A_{0,0}^{(i)}$ to the other four alleles. The mutation rate from $A_{0,0}^{(i)}$ to $A_{j,k}^{(i)}$ is

$$\mu_{(0,0),(j,k)}^{(i)} = \tfrac{1}{4}\mu_i(1 + jk\rho_{m,i}) \tag{14}$$

with $-1 < \rho_{m,i} < 1$. For simplicity, the mutation model will be completed by assuming that each of the alleles $A_{j,k}^{(i)}$ for $j, k = \pm 1$ mutates only to $A_{0,0}^{(i)}$ at rate μ_i. This simplifying assumption has little effect on the low mutation rate approximations presented in the next section. This model assumes that among mutants from $A_{0,0}^{(i)}$, the variance introduced for P_1 (P_2) is $c_{1,i}^2$ ($c_{2,i}^2$) and the correlation between the changes in P_1 and P_2 is $\rho_{m,i}$. Thus, the parameters $c_{1,i}^2$ and $c_{2,i}^2$ are analogous to $m_{1,i}^2$ and $m_{2,i}^2$ in the continuum-of-alleles model, and $\rho_{m,i}$ has the same interpretation in both models.

The five-allele model differs from the continuum-of-alleles model in one critical respect. In both models nonzero $\rho_{m,i}$ imposes a probabilistic coupling between the effects of mutation on the two characters. The five-allele model imposes an additional deterministic coupling between the variances contributed to the two traits, namely, their ratio must be $c_{1,i}^2/c_{2,i}^2$ irrespective of other parameter values. Given our lack of knowledge of the genetic variants underlying quantitative variation, it is difficult to determine whether this strict constraint is more or less realistic than the weaker coupling imposed by $\rho_{m,i}$. Unfortunately, these alternative assumptions lead to quantitatively different consequences for hidden pleiotropic effects.

Linkage equilibrium and weak selection approximation: To complete the description of these polygenic models, the linkage relationships among the n loci should be specified. However, several lines of evidence presented in TURELLI (1984) suggest that the overall genetic variances and covariances will be essentially independent of the recombination scheme under realistic selection values and reasonable constraints on the recombination rates. For instance, although both LANDE (1975) and FLEMING (1979) account for linkage disequilibrium and diploidy in their analyses, their final results for $\hat{V}_g$ can be very well approximated by applying their analyses to each locus in isolation as done earlier by LATTER (1960), KIMURA (1965) and BULMER (1972). Moreover, several numerical multilocus calculations show that, unless many of the loci are very tightly linked, so that the harmonic mean recombination rate falls below 0.05, the polygenic equilibria can be well approximated by extrapolating from single-locus haploid results (*cf.* LANDE 1980). This holds even with selection as strong as $V_s/V_e = 10$.

This simplification will be exploited below. Let $\hat{V}_{g,1}^{(i)}$ denote a one-locus haploid prediction for the equilibrium genetic variance contributed to P_1 by locus i, and let $\hat{C}_g^{(i)}$ denote the covariance for effects on P_1 and P_2 of the alleles at locus i. We assume that the overall variances and covariances can be approximated by summing over loci, *i.e.*,

$$\hat{V}_{g,1} \cong 2 \sum_{i=1}^{n} \hat{V}_{g,1}^{(i)} \quad \text{and} \tag{15a}$$

$$\hat{C}_g \cong 2 \sum_{i=1}^{n} \hat{C}_g^{(i)}. \tag{15b}$$

APPROXIMATE ANALYTICAL RESULTS

Continuum of alleles

Let $p_{i,t}(\mathbf{x})$ denote the bivariate distribution of allelic effects at locus i among zygotes in generation t, let $m_i(\mathbf{x})$ denote the gaussian distribution of mutant effects at this locus as described by (13), and let $w(\mathbf{x})$ denote the gaussian fitness function for genotypes (4). Denote by $\mathbf{\Sigma}_{g,t}^{(i)}$, $\mathbf{\Sigma}_m^{(i)}$ and $\mathbf{\Sigma}_s = \mathbf{\Sigma}_w + \mathbf{\Sigma}_e$ the respective variance-covariance matrices. Following section 2 of TURELLI (1984), the linkage equilibrium and weak selection approximations imply that it suffices to analyze the equilibrium genetic variance-covariance structure gen-

erated by the recursion

$$p_{i,t+1}(\mathbf{x}) = (1 - \mu_i)p'_{i,t} + \mu_i \int p'_{i,t}(\mathbf{y})m_i(\mathbf{x} - \mathbf{y})d\mathbf{y} \tag{16}$$

with

$$p'_{i,t}(\mathbf{x}) = p_{i,t}(\mathbf{x})w(\mathbf{x})/\bar{w}_{i,t},\ \bar{w}_{i,t} = \int p_{i,t}(\mathbf{x})w(\mathbf{x})d\mathbf{x},$$

and μ_i the mutation rate at locus i. (All integrals here and below are taken over the entire domain of the integrands unless otherwise specified.) For convenience of notation, I have assumed that each locus has a mean effect of $\mathbf{0}$ at equilibrium.

Gaussian approximation: following LANDE (1980), if we assume that $p_{i,t}(\mathbf{x})$ and $p_{i,t+1}(\mathbf{x})$ are gaussian, (16) implies

$$\mathbf{\Sigma}^{(i)}_{g,t+1} = \mathbf{\Sigma}^{(i)}_{g,t} - \mathbf{\Sigma}^{(i)}_{g,t}(\mathbf{\Sigma}_s + \mathbf{\Sigma}^{(i)}_{g,t})^{-1}\mathbf{\Sigma}^{(i)}_{g,t} + \mu_i\mathbf{\Sigma}^{(i)}_m. \tag{17}$$

For weak selection (*i.e.*, $\mathbf{\Sigma}_s + \mathbf{\Sigma}^{(i)}_g \cong \mathbf{\Sigma}_s$), the equilibrium is approximated by

$$\hat{\mathbf{\Sigma}}^{(i)}_g \cong \mathbf{\Sigma}_s^{1/2}(\mu_i\mathbf{\Sigma}_s^{-1/2}\mathbf{\Sigma}^{(i)}_m\mathbf{\Sigma}_s^{-1/2})^{1/2}\mathbf{\Sigma}_s^{1/2}, \tag{18}$$

with positive semidefinite matrix square roots. Together with (15), this provides explicit, albeit cumbersome, formulas for $\hat{V}_{g,1}$ and $\tilde{V}_{s,1}$. The single-character extrapolation analogous to (18) is given by KIMURA'S (1965) formula

$$\tilde{V}^{(i)}_{g,1} \cong \sqrt{\mu_i m^2_{1,i}}\tilde{V}_{s,1}; \tag{19}$$

from which (15) produces

$$\tilde{V}_{g,1}(\mathrm{G}) \cong \sqrt{2n_{E,1}\sigma^2_{m,1}}\tilde{V}_{s,1}, \tag{20}$$

$$\text{with}\quad \sigma^2_{m,1} = 2\sum_{i=1}^{n}\mu_i m^2_{1,i}\quad\text{and}\quad n_{E,1} = 2(\sum_{i=1}^{n}\sqrt{\mu_i m^2_{1,i}})^2/\sigma^2_{m,1}$$

as in LANDE (1975).

Because of the complexity of the expressions for $\hat{V}_{g,1}$ and $\tilde{V}_{g,1}$, algebraic comparisons are not generally informative. However, one special case is worth considering, despite being biologically implausible, because it reveals a critical difference between the gaussian and house-of-cards predictions. Suppose there is no environmental correlation, no correlation in the phenotypic fitness function (3) and no correlation in the mutant effects at the pleiotropic loci, *i.e.*, $\rho_e = \rho_w = \rho_{m,i} \equiv 0$. This reduces all of the matrices in (18) to diagonals, so that

$$\hat{V}^{(i)}_{g,1} = \sqrt{\mu_i m^2_{1,i}V_{s,1}}\quad\text{and}\quad \hat{C}^{(i)}_g = 0\quad\text{for}\quad i = 1, \cdots, n. \tag{21}$$

It follows from (11), (15) and (20) that in this special case

$$\tilde{V}_{g,1}(\mathrm{G}) = \hat{V}_{g,1}(\mathrm{G}). \tag{22}$$

This applies for any number of hidden characters. Thus, in the absence of correlation, hidden pleiotropic effects do not confound equilibrium predictions when the gaussian analysis applies. Although (22) is not preserved when correlation is introduced (*e.g.*, $\tilde{V}_{g,1}(\mathrm{G}) < \hat{V}_{g,1}(\mathrm{G})$ if $\rho_e \neq 0$ but $\rho_s = \rho_{m,i} \equiv 0$), the numerical results of the next section show that $\tilde{V}_{g,1}(\mathrm{G})$ is within a factor of two

of $\hat{V}_{g,1}(G)$ for a wide range of parameter values. This is in marked contrast to the house-of-cards predictions.

House-of-cards approximation: The central argument presented in TURELLI (1984) in favor of the house-of-cards (HC) approximation is not affected by pleiotropy. When the variance associated with new mutants exceeds the segregating allelic variance, *i.e.*, $m_{j,i}^2 \gg V_{g,j}^{(i)}$, the equilibrium of (16) can be approximated by

$$\hat{p}_i(\mathbf{x}) = \frac{\mu_i m_i(\mathbf{x})}{1 - cw(\mathbf{x})} \tag{23}$$

if a constant $c = (1 - \mu_i)/\hat{w}_i < 1$ can be found so that $\int p_i(\mathbf{x})d\mathbf{x} = 1$ (see KINGMAN 1978). APPENDIX 2 displays an approximation for the equilibrium genetic variance and covariance produced by this distribution. The general algebraic expressions are complex and will not be repeated. However, if $\rho_s = \rho_{m,i} \equiv 0$, they reduce to

$$\hat{V}_{g,1}(\mathrm{HC}) = 4V_{s,1} \sum_{i=1}^{n} \mu_i/(1 + \beta_i) \quad \text{and} \quad \hat{C}_g(\mathrm{HC}) = 0, \quad \text{with} \tag{24}$$

$$\beta_i^2 = s_{2,i}/s_{1,i} \quad \text{and} \quad s_{j,i} = m_{j,i}^2/V_{s,j}. \tag{25}$$

The composite parameter β_i plays a critical role in what follows. Note that, if an allele of optimal effect at locus i mutates, it will suffer a decrease in relative fitness of order $s_{j,i}$ from selection on character j. Thus, when the house-of-cards approximation is applicable, β_i^2 quantifies the relative intensity of selection on new mutants that is attributable to their effect on the hidden character (P_2) *vs.* their effect on the observed character (P_1). Even with nonzero correlations, β_i remains central parameter. As shown by approximation (2.6b) in APPENDIX 2, for each value of ρ_s, $\hat{V}_{g,1}$ depends on $V_{s,2}$, $m_{1,i}^2$ and $m_{2,i}^2$ only through β_i.

From TURELLI (1984), the general single-character extrapolation is

$$\tilde{V}_{g,1}(\mathrm{HC}) = 4\tilde{V}_{s,1}(\mathrm{HC}) \sum_{i=1}^{n} \mu_i. \tag{26}$$

For $\rho_e = \rho_w = \rho_{m,i} \equiv 0$, $\tilde{V}_{s,1} = V_{s,1}$ so that (24) implies $\hat{V}_{g,1}$ (HC) $< \tilde{V}_{g,1}$ (HC). In the special case $\beta_i \equiv \beta$, the relationship is simply

$$\tilde{V}_{g,1}(\mathrm{HC}) = (1 + \beta)\hat{V}_{g,1}(\mathrm{HC}). \tag{27}$$

A simple generalization to k hidden characters is available under complete symmetry, *i.e.*, $m_{j,i}^2 \equiv m^2$ and $V_{s,j} \equiv V_s$, and no correlation. Under these assumptions (27) generalizes to

$$\tilde{V}_{g,1}(\mathrm{HC}) = (1 + k)\hat{V}_{g,1}(\mathrm{HC}), \tag{28}$$

whereas $\tilde{V}_{g,1}(G) = \hat{V}_{g,1}(G)$ irrespective of k.

These cases without correlation illustrate an important difference between the gaussian and house-of-cards predictions for the consequences of pleiotropy. Under the gaussian genetic model, characters, even if pleiotropically con-

nected, can affect each other's evolution only through phenotypic correlation. Because $\tilde{V}_{s,1}$ relies on phenotypic correlation for information about selection induced by hidden pleiotropic effects, $\tilde{V}_{g,1}(G)$ may often reasonably approximate $\hat{V}_{g,1}(G)$. In contrast, under the house-of-cards approximation, pleiotropic effects that are not revealed by correlation can decisively influence the genetic equilibrium. The reason is clear. The house-of-cards analysis assumes that all mutants arise from nearly optimal genotypes. These mutants will experience selection associated with all of the characters they affect, whether or not those characters, or the mutational displacements, are correlated. Thus, hidden characters that are pleiotropically connected to observed ones can produce hidden selection that is not detected by $\tilde{V}_{s,1}$. Even with correlation, it is generally true that, as β increases, $\tilde{V}_{g,1}(HC)$ increasingly overestimates $\hat{V}_{g,1}(HC)$. However as shown below, literally any relationship is possible.

Although algebraic comparisons of the general expressions for $\hat{V}_{g,1}(HC)$ and $\tilde{V}_{g,1}(HC)$ are not practical, three special cases, with $\beta_i \equiv \beta$ and $\rho_{m,i} \equiv \rho_m$, are tractable: $\beta \ll 1$, $\beta = 1$ with $\rho_m = \rho_s$, and $\beta \gg 1$. These cases reflect: selection on pleiotropic loci primarily through the character observed, equally through the observed and unobserved characters and primarily through the unseen character, respectively. From the general expressions for $\hat{V}_{g,1}(HC)$ and $\tilde{V}_{g,1}(HC)$ in APPENDIX 2, it follows that

$$\lim_{\beta \to 0} \hat{V}_{g,1}(HC)/\tilde{V}_{g,1}(HC) = 1 \tag{29}$$

if $V_{s,2}/V_{s,1} \to \infty$ as $\beta \to 0$. Thus, as expected intuitively, if selection acts essentially only on character 1, $\tilde{V}_{g,1}$ accurately approximates $\hat{V}_{g,1}$. However, the ratio in (29) can approach one either from above or below depending on the signs of the correlation parameters. Thus, hidden pleiotropic effects need not bias $\tilde{V}_{g,1}$ upward.

If $\beta_i \equiv 1$ and $\rho_{m,i} \equiv \rho_s$, it follows from (2.6a) and (2.7a) that

$$\tilde{V}_{g,1}(HC) \leq 2\hat{V}_{g,1}(HC) \tag{30}$$

with equality if and only if

$$\rho_s = y = \left[\frac{V_{s,1}}{V_{s,2}}\right]^{1/2} \frac{\mathrm{cov}(P_1, P_2)}{\mathrm{var}(P_1)}. \tag{31}$$

Thus for $\beta = 1$ and $\rho_m = \rho_s$, the results obtained without correlation supply an upper bound for the error introduced by hidden pleiotropic effects. However, the numerical results of the next section show that this bound does not apply for other parameter combinations.

The full complexity of the problem emerges as $\beta \to \infty$ with nonzero correlations. LANDE and ARNOLD's (1983) multivariate analysis of phenotypic selection suggests that this case, in which most selection experienced by the observed character is indirect, may frequently apply. Unfortunately, the results depend critically on how this selection occurs. Note that selection can be concentrated on P_2 by (1) letting $m_2^2/m_1^2 \to \infty$ with $V_{s,1}/V_{s,2}$ fixed or (2) letting $V_{s,2}/V_{s,1} \to 0$ with m_2^2/m_1^2 fixed or (3) by taking both limits simultaneously. Biolog-

ically, cases 1 and 2 reflect pleiotropic selection through large phenotypic effects on an unseen character that is under moderate selection *vs.* moderate phenotypic effects on an unseen character that is under strong selection. If it is assumed that $V_{s,2}$ is bounded above, it can be shown that in case 1

$$\lim_{\beta\to\infty} \hat{V}_{g,1}/\tilde{V}_{g,1} = 0; \tag{32}$$

whereas in cases 2 and 3

$$\lim_{\beta\to\infty} \hat{V}_{g,1}/\tilde{V}_{g,1} = \infty. \tag{33}$$

Thus, $\tilde{V}_{g,1}$ can either greatly overestimate or underestimate $\hat{V}_{g,1}$ depending on the nature of pleiotropic selection. These asymptotic results must be interpreted cautiously because the numerical analyses in the next section show that there are combinations of parameters for which β^2 is large, *e.g.*, 10–100, but $\tilde{V}_{g,1}$ is within a factor of two of $\hat{V}_{g,1}$.

Predicted domains of applicability: Reasonable conjectures concerning the domains of applicability of the alternative approximations can be obtained by requiring that the predictions be consistent with the assumptions used to derive them. To keep the algebra manageable, I will consider only $\rho_e = \rho_m = \rho_w = 0$. The numerical results in the next section show that these predictions suffice to produce useful guidelines.

LANDE (1975) motivated his gaussian analysis by assuming $m_i^2 \ll \hat{V}_g^{(i)}$. The natural extension under pleiotropy is

$$m_{j,i}^2 \ll \hat{V}_{g,j}^{(i)} \quad \text{for} \quad j = 1,2. \tag{34}$$

In the absence of correlation, substitution of $\hat{V}_{g,j}^{(i)}$(G) leads to

$$\mu_i \gg \max(m_{1,i}^2/V_{s,1},\ m_{2,i}^2/V_{s,2}). \tag{35}$$

Thus, the effects and selection coefficients associated with both characters must satisfy the corresponding single-character constraints.

The house-of-cards predictions are based on (23) which assumes the converse of (34), namely,

$$m_{j,i}^2 \gg \hat{V}_{g,j}^{(i)} \quad \text{for} \quad j = 1,2. \tag{36}$$

In the absence of correlation, substitution of $\hat{V}_{g,j}^{(i)}$(HC) leads to

$$\mu_i \ll m_{1,i}m_{2,i}/(V_{s,1}V_{s,2})^{1/2}. \tag{37}$$

This suggests that the house-of-cards approximation may apply to loci affecting two characters even when the single-character consistency criterion, $\mu_i \ll m_i^2/V_s$, is not met for both characters. The numerical results of the next section confirm this. They also show that the strong inequalities in (35) and (37) can be relaxed to requiring only that the right- and left-hand sides differ by a factor of three.

House-of-cards approximation for the five-allele model

APPENDIX 3 presents five-allele approximations for $\hat{V}_{g,1}$ and $\tilde{V}_{g,1}$ that are analogous to the house-of-cards approximation for the continuum-of-alleles

model. Two levels of approximations are given. The less precise ones, denoted $\hat{V}_{g,1}(5)$ and $\tilde{V}_{g,1}(5)$, are simpler and are used for the comparisons below. As for the continuum-of-alleles approximations, a comparison of the general expressions for $\hat{V}_{g,1}$ and $\tilde{V}_{g,1}$ is not helpful. However, as before, the comparison is illuminating when $\rho_e = \rho_w = \rho_{m,i} \equiv 0$. In this case, the approximations reduce to

$$\hat{V}_{g,1}(5) = 4V_{s,1} \sum_{i=1}^{n} \mu_i/(1 + \beta_i^2), \qquad \hat{C}_g(5) = 0, \quad \text{and} \tag{38}$$

$$\tilde{V}_{g,1}(5) = 4V_{s,1} \sum_{i=1}^{n} \mu_i > \hat{V}_{g,1}(5) \tag{39}$$

with $\beta_i^2 = s_{2,i}/s_{1,i}$, as in the continuum-of-alleles model, but $s_{j,i} = c_{j,i}^2/V_{s,j}$. For $\beta_i \equiv \beta$, we have the simple relationship

$$\tilde{V}_{g,1}(5) = (1 + \beta^2)\hat{V}_{g,1}(5). \tag{40}$$

Thus, under these conditions, $\tilde{V}_{g,1}$ always overestimates $\hat{V}_{g,1}$ as it does under the house-of-cards analysis for the continuum-of-alleles model. However, here the overestimate is proportional to β^2 rather than β [*cf.* (27)].

This discrepancy between the continuum and five-allele predictions arises from a change in $\hat{V}_{g,1}$. Thus, in contrast to the single-character results of TURELLI (1984), pleiotropy makes the house-of-cards predictions dependent on the number and effects of segregating alleles at each locus. Given our ignorance of these, this result is not reassuring.

The discrepancy between $\tilde{V}_{g,1}$ and $\hat{V}_{g,1}$ can be increased or decreased by the presence of nonzero correlations. As for the continuum-of-alleles, three cases, with $\beta_i \equiv \beta$ and $\rho_{m,i} \equiv \rho_m$, will be considered: $\beta \ll 1$, $\beta = 1$ and $\beta \gg 1$. As with the house-of-cards approximations for a continuum-of-alleles,

$$\lim_{\beta \to 0} \hat{V}_{g,1}(5)/\tilde{V}_{g,1}(5) = 1 \tag{41}$$

if $V_{s,2}/V_{s,1} \to \infty$ as $\beta \to 0$. For $\beta = 1$ and $\text{sgn}(\rho_m) = \text{sgn}(\rho_s)$,

$$\tilde{V}_{g,1}(5) \leq 2\hat{V}_{g,1}(5) \tag{42}$$

with equality if and only if $\rho_e = \rho_m = \rho_w = 0$. However, this bound is not preserved if $\text{sgn}(\rho_m) = -\text{sgn}(\rho_s)$.

A significant difference from the continuum-of-alleles HC predictions arises with $\beta \gg 1$. As before, it is informative to consider selection piling up on character 2 in three separate ways: (1) $c_2^2/c_1^2 \to \infty$ with $V_{s,1}/V_{s,2}$ fixed, (2) $V_{s,2}/V_{s,1} \to 0$ with c_2^2/c_1^2 fixed and (3) $c_2^2/c_1^2 \to \infty$ and $V_{s,2}/V_{s,1} \to 0$. As for the continuum, case 1 leads asymptotically to $\tilde{V}_{g,1}(5) \gg \hat{V}_{g,1}(5)$; whereas case 2 leads to $\tilde{V}_{g,1}(5) \ll \hat{V}_{g,1}(5)$. The difference is that here case 3 also produces

$$\lim_{\beta \to \infty} \tilde{V}_{g,1}(5)/\hat{V}_{g,1}(5) = \infty \tag{43}$$

Thus, this model, which constrains the relative amount of variance contributed to each character, produces a greater tendency for $\tilde{V}_{g,1}$ to overestimate $\hat{V}_{g,1}$,

even in the presence of correlation. This is illustrated by the numerical results of the next section.

We can again apply the consistency criterion to delimit parameter values for which the five-allele approximation is expected to be accurate. The assumption $\hat{p}_0^{(i)} \cong 1$ that leads to (3.3) is equivalent to the house-of-cards assumption

$$c_{j,i}^2 \gg \hat{V}_{g,j}^{(i)} \quad \text{for} \quad j = 1, 2 \tag{44}$$

[*cf.* (36)]. If no correlation is assumed, substitution of $\hat{V}_{g,j}^{(i)}(5)$ yields

$$\mu_i \ll \max(c_{1,i}^2/V_{s,1},\ c_{2,i}^2/V_{s,2}). \tag{45}$$

Thus, for this bivariate model, the house-of-cards approximation is expected to apply to a locus if the single-character criterion, $\mu_i \ll c_i^2/V_s$, is satisfied by *either* of the characters affected. Because this model directly couples the variances contributed to each character, constraint (45) is weaker than the analogous constraint (37) for a bivariate continuum of alleles.

NUMERICAL RESULTS

The analytical approximations of the previous section will be supplemented by numerical analyses of two sorts. The first treats the accuracy and domains of validity of the various predictions for the equilibrium genetic variances and covariances. Supported by the analytical and numerical results underlying the linkage equilibrium and weak selection assumptions, I will consider only one-locus haploid models. Second, multilocus predictions for $\tilde{V}_{g,1}$ and $\tilde{V}_{g,1}$ will be compared over a range of parameter values. These will extend and generalize the qualitative results obtained from the analytical comparisons for special cases. All calculations were performed in double precision on a DEC LSI 11/23 microcomputer (providing approximately 17 accurate decimal digits).

One-locus haploid equilibria

All of the equilibria were calculated by the same method. The first step for the continuum-of-alleles model is to approximate the recursion (16) by a finite allele analog of the form

$$p_{j,t+1} = \sum_{i \in S} p_{i,t} w_i u_{ij} / \sum_{i \in S} p_{i,t} w_i \quad \text{for} \quad j \in S \tag{46}$$

with S a set of allele indices, $p_{i,t}$ the frequency of allele i among gametes in generation t, w_i the (marginal) fitness of allele i and u_{ij} the mutation rate from allele i to allele j. The haploid version of the five-allele model (3.1) is already in this form. MORAN (1976) proved that under (46) the allele frequencies globally converge to the normalized (*i.e.*, $\Sigma p_i = 1$) elements of the unique, positive left eigenvector for the dominant eigenvalue of $V = (w_i u_{ij})$. This eigenvector was approximated via the EISPACK algorithms (SMITH *et al.* 1976) and was used to approximate the equilibrium variances and covariances.

Continuum of alleles: The major obstacle to approximating equilibria for (16) is choosing an appropriate discretization. The numerical results in TURELLI (1984) show that the equilibrium structure of the one-dimensional continuum-

of-alleles model can be very well approximated by 21 alleles with equally spaced effects. When the house-of-cards approximation is applicable, even fewer alleles suffice to approximate $\hat{V}_g$. This is expected because the same analytical approximation applies with two, three and a continuum of alleles per locus. In contrast, with pleiotropy the house-of-cards predictions for five alleles and a bivariate continuum differ appreciably. This suggests that a larger number of alleles may be needed to accurately approximate a two-dimensional continuum. Surprisingly, the number needed to achieve accuracy comparable to that obtained in one dimension (*i.e.*, relative errors of predictions in the neighborhood of 1–5%) is very large. In fact, 121 alleles (11 possible effects for each of the two characters) do not generally suffice if effects are assigned by a direct extension of the discretization procedure in TURELLI (1984). Because the available computer could not easily manipulate matrices larger than 121 × 121, I used the more elaborate discretization procedure described in APPENDIX 4.

A brief review of the single-character continuum-of-alleles results from TURELLI (1984) will be helpful in interpreting the two-dimensional results, particularly the restricted range of parameters for which the gaussian approximation is accurate. One-locus haploid equilibria were calculated to determine the relative accuracy and domains of validity for four alternative approximations: house-of-cards, KIMURA (1965), LANDE (1975) and FLEMING (1979). The non-gaussian approximation of FLEMING (1979), reviewed in NAGYLAKI (1984) and TURELLI (1984), refines the gaussian approximations of KIMURA (1965) and LANDE (1975). Over the range of parameter values used, the house-of-cards approximation was the most accurate for $20\mu \leq m^2/V_s$, whereas the FLEMING (1979) approximation was generally the most accurate for $20\mu > m^2/V_s$. These bounds are not sharp. Near the boundary both approximations err by 10–20% in opposite directions. If the estimates $m^2/V_e \geq 0.03$ from LANDE (1975) and $V_s/V_e \cong 10$–20 from TURELLI (1984) are used, the numerical results supported the house-of-cards approximation of $\hat{V}_g$ for $\mu \leq 10^{-4}$ and the Fleming approximation for $\mu > 10^{-4}$. Even when the Fleming approximation was extremely accurate (*e.g.*, for $\mu = 10^{-2}$–10^{-3}, its relative error was less than 1%), the gaussian approximations overestimated $\hat{V}_g$ by 10–40%. With $m^2/V_e = 0.05$, $V_s/V_e = 20$ and $\mu = 10^{-4}$–10^{-5}, they overestimated $\hat{V}_g$ by a factor of three to ten, with larger errors for smaller mutation rates.

In all of the tables below, the accuracy of the analytical predictions is estimated by computing the percent relative discrepancy between the predicted and numerically determined values of $\hat{V}_{g,i}$. These error estimates, which are confounded somewhat by the numerical approximations, are denoted $\%(G)_i$ and $\%(HC)_i$ for the gaussian and house-of-cards predictions, respectively. They are computed by

$$\%(G)_i = 100(\hat{V}_{g,i}(G) - \hat{V}_{g,i})/\hat{V}_{g,i}. \tag{47}$$

Without loss of generality, we assume henceforth that $V_{e,1} = V_{e,2} = 1$.

Table 1 displays the effects of varying the mutation rate. Of the two approximations, the HC is the more accurate for $\mu \leq 10^{-3}$; for $\mu \leq 10^{-4}$, it is

TABLE 1

Effects of varying the mutation rate on the numerically determined equilibrium genetic variances, $\hat{V}_{g,1}$ and $\hat{V}_{g,2}$, with $V_{s,1} = 20$, $V_{s,2} = 40$, and $\rho_e = \rho_m = \rho_w = 0$

μ	$m_1^2 \times 10^2$	$m_2^2 \times 10^2$	$\hat{V}_{g,1}$	$\hat{V}_{g,2}$	$\%(G)_1$	$\%(G)_2$	$\%(HC)_1$	$\%(HC)_2$
10^{-2}	5.44	2.47	9.79×10^{-2}	9.64×10^{-2}	6.8	3.2	176.9	167.6
10^{-3}	5.21	2.68	2.20×10^{-2}	2.31×10^{-2}	45.7	41.6	19.7	16.4
10^{-4}	5.21	2.61	2.67×10^{-3}	2.65×10^{-3}	282.5	284.5	−0.2	0.3
10^{-5}	5.21	2.61	2.69×10^{-4}	2.63×10^{-4}	1102.9	1127.0	−0.7	1.3

TABLE 2

Effects of varying μ with $V_{s,1} = 20$, $V_{s,2} = 40$ and $\rho_e = \rho_w = 0.8$, $\rho_m = 0.79$–0.82[a]

μ	$m_1^2 \times 10^2$	$m_2^2 \times 10^2$	$\hat{V}_{g,1}$	$\hat{V}_{g,2}$	$\hat{\rho}_g$	$\%(G)_1$	$\%(HC)_1$	$\hat{\rho}^b - \hat{\rho}_g$
10^{-2}	5.14	2.62	9.34×10^{-2}	9.95×10^{-2}	0.81	−0.3	137.3	−0.06
10^{-3}	5.41	2.75	1.96×10^{-2}	2.07×10^{-2}	0.76	54.0	16.0	0.00
10^{-4}	5.39	2.69	2.24×10^{-3}	2.16×10^{-3}	0.75	325.2	1.4	0.01
10^{-5}	5.39	2.69	2.25×10^{-4}	2.11×10^{-4}	0.75	1239.8	1.1	0.01

[a] $\rho_m = 0.79$ for $\mu = 10^{-2}$, $\rho_m = 0.82$ for $\mu = 10^{-3}$–10^{-5}.
[b] ρ = equilibrium correlation predicted by the gaussian and house-of-cards analyses.

extremely accurate. The parameters in Table 1 yield $m_1 m_2/(V_{s,1}V_{s,2})^{1/2} \cong 1.3 \times 10^{-3}$ and $\max(m_1^2/V_{s,1}, m_2^2/V_{s,2}) \cong 2.6 \times 10^{-3}$. The results show that the strong inequalities in predictions (35) and (37) for the domains of applicability are conservative. A factor of three suffices for good agreement. For instance, with $\mu = 4 \times 10^{-4}$ and the remaining parameters as in Table 1, $\%(HC)_1 = 3.3$ and $\%(HC)_2 = 0.5$. Like the single-character results in TURELLI (1984), these suggest that the gaussian approximation is accurate only for extraordinarily high per locus mutation rates. For a "typical" rate of order 10^{-5}, it overestimates $\hat{V}_g$ by a factor of ten. The relatively small errors in the regions of parameter space for which the gaussian or house-of-cards predictions were expected to apply support both the numerical approximations and the analytical predictions.

Table 2 shows that the qualitative results of Table 1 are not influenced by the addition of correlation. It also illustrates an unexpected relationship between the gaussian and house-of-cards predictions. For these parameter values as well as all others examined, both approximations make identical predictions for the equilibrium genetic correlation. Further examination of the numerical results showed that

$$\frac{\hat{V}_{g,1}(G)}{\hat{V}_{g,1}(HC)} = \frac{\hat{V}_{g,2}(G)}{\hat{V}_{g,2}(HC)} = \frac{\hat{C}_g(G)}{\hat{C}_g(HC)} \tag{48}$$

for all parameter values used. The first equality is easily verified analytically when $\rho_e = \rho_m = \rho_w = 0$.

Table 3 displays the effects of simultaneously varying the mutation variance parameters m_1^2 and m_2^2. As in Table 1, the house-of-cards approximation is

TABLE 3

Effects of simultaneously varying the mutation variance parameters m_1^2 *and* m_2^2 *with* $\mu = 10^{-4}$, $V_{s,1} = 20$, $V_{s,2} = 40$, *and* $\rho_e = \rho_m = \rho_w = 0$

m_1^2	m_2^2	$\hat{V}_{g,1} \times 10^3$	$\hat{V}_{g,2} \times 10^3$	%(G)$_1$	%(G)$_2$	%(HC)$_1$	%(HC)$_2$
2.61×10^{-1}	1.30×10^{-1}	2.70	2.64	747.7	765.0	−1.1	1.0
5.21×10^{-2}	2.61×10^{-2}	2.67	2.65	282.5	284.5	−0.2	0.3
1.04×10^{-2}	5.21×10^{-3}	2.53	2.60	80.8	75.5	5.5	2.4
2.09×10^{-3}	1.09×10^{-3}	1.64	1.76	24.6	18.5	61.4	53.4
4.33×10^{-4}	1.96×10^{-4}	0.89	0.85	5.1	4.0	205.6	202.4

TABLE 4

Effects of varying ρ_w *with* $\mu = 10^{-4}$, $m_1^2 = 5.39 \times 10^{-2}$, $m_2^2 = 2.69 \times 10^{-2}$, $\rho_m = 0.82$, $\rho_e = 0.8$, $V_{s,1} = 20$ *and* $V_{s,2} = 40$

ρ_w	$\hat{V}_{g,1} \times 10^3$	$\hat{V}_{g,2} \times 10^3$	$\hat{\rho}_g$	%(G)$_1$	%(G)$_2$	%(HC)$_1$	%(HC)$_2$	$\hat{\rho} - \hat{\rho}_g$
0.8	2.24	2.16	0.75	325.2	334.8	1.4	3.7	0.01
0.4	3.04	2.61	0.63	241.3	241.9	−0.2	0.0	0.00
0.0	2.85	2.39	0.51	249.9	247.8	0.3	−0.3	0.00
−0.4	2.19	1.87	0.36	301.7	302.5	0.2	0.4	−0.01
−0.8	1.14	1.04	0.13	483.8	509.9	0.7	5.2	−0.04

more accurate than the gaussian once $\mu < m_1 m_2/(V_{s,1}V_{s,2})^{1/2}$, whereas the gaussian is more accurate for $\mu > \max(m_1^2/V_{s,1}, m_2^2/V_{s,2})$. Again, both approximations are quite accurate once a factor of three separates the two sides of the inequalities. The same qualitative results were obtained by varying the selection intensities and in the presence of correlation. Table 4 illustrates one of many sets of calculations showing that the house-of-cards approximations apply over a wide range of correlation parameters. It also displays the complex dependence of the equilibrium genetic variance on the correlation structure of the model.

Table 5 presents a test of prediction (37) concerning the domain of applicability of the house-of-cards approximation. In the first five rows, m_2^2 decreases while the parameters μ, m_1^2 and $V_{s,1}$ are held constant in the domain for which the single-character house-of-cards prediction is accurate, *i.e.*, $10\mu \leq m_1^2/V_{s,1}$. The house-of-cards approximation is quite accurate for the first three sets of parameters which satisfy $3\mu < m_1 m_2/(V_{s,1}V_{s,2})^{1/2}$. It is reasonably accurate even for the fifth set with $\mu \cong m_1 m_2/(V_{s,1}V_{s,2})^{1/2}$. Adding $\rho_e = \rho_w = 0.8$ and $\rho_m \cong 0.8$ produces comparable house-of-cards errors but eliminates the decrease in the gaussian error as m_2^2 decreases. Similar results were obtained by increasing $V_{s,2}$. For instance, the house-of-cards predictions are reasonably accurate for the parameters in the sixth row of Table 5 even though $\mu = 10^{-4}$ and $m_1 m_2/(V_{s,1}V_{s,2})^{1/2} \cong 1.8 \times 10^{-4}$.

These calculations demonstrate an important difference between the gaussian and house-of-cards approximations. The gaussian approximation accurately describes the variance contributed to P_1 by a locus only if *both* of the characters affected by the locus satisfy $\mu > m_i^2/V_{s,i}$. Thus, its applicability can be destroyed by unknown pleiotropic effects involving strong selection (*i.e.*,

TABLE 5

Effects of extreme asymmetry, with $\mu = 10^{-4}$, $m_1^2 = 3.13 \times 10^{-2}$, $V_{s,1} = 20$, *and* $\rho_e = \rho_m = \rho_w = 0$

m_2^2	$V_{s,2}$	$\hat{V}_{g,1} \times 10^3$	$\hat{V}_{g,2} \times 10^3$	%(G)$_1$	%(G)$_2$	%(HC)$_1$	%(HC)$_2$
3.13×10^{-2}	40	2.35	3.31	237.5	238.5	−0.1	0.2
1.04×10^{-2}	40	2.82	2.34	180.6	176.5	0.7	−0.8
3.18×10^{-3}	40	3.18	1.51	148.7	136.0	2.6	−2.7
1.09×10^{-3}	40	3.35	0.97	136.6	115.3	5.6	−3.9
3.00×10^{-4}	40	3.43	0.54	131.1	104.0	9.2	−3.7
3.25×10^{-2}	1500	3.37	32.88	135.2	112.3	6.3	−4.0
1.09×10^{-2}	5000	3.46	28.59	128.8	158.8	11.4	26.0
1.13×10^{-3}	5000	3.48	4.79	127.9	398.9	13.5	148.5

large m^2/V_s). In contrast, the house-of-cards approximation accurately predicts both $\hat{V}_{g,1}$ and $\hat{V}_{g,2}$ as long as (37) is satisfied even if $\mu > m_2^2/V_{s,2}$. Additional calculations were performed to determine its behavior when (37) is violated but $\mu \ll m_1^2/V_{s,1}$. Two examples appear in the last rows of Table 5. For the first, $m_1 m_2/(V_{s,1}V_{s,2})^{1/2} = 5.8 \times 10^{-5}$; for the second, it is 1.9×10^{-5}. Even though the house-of-cards approximation overestimates $\hat{V}_{g,2}$, it reasonably approximates $\hat{V}_{g,1}$. This suggests that the house-of-cards approximation can adequately approximate $\hat{V}_{g,1}$ as long as $\mu \ll m_1^2/V_{s,1}$, irrespective of the parameters describing other effects of the locus. Clearly, this is a useful property when the pleiotropic effects are unknown.

Five alleles: Equilibria for the haploid version of (3.1) were approximated for a wide range of parameter values to test the prediction that the house-of-cards approximations for both $\hat{V}_{g,1}$ and $\hat{V}_{g,2}$ would be accurate as long as

$$\mu \ll \max(c_1^2/V_{s,1},\ c_2^2/V_{s,2}). \tag{49}$$

The results of extensive calculations analogous to those presented in Tables 1–5 can be simply summarized. The "more precise" approximation (3.5) is within 10% of the observed equilibria as long as a factor of five separates the sides of (49). This holds irrespective of the correlation values used. For the cruder approximations (3.7) to reach this level of accuracy, a factor of 20 must separate the sides of (49). For such parameters, the "more precise" approximation errs by less than 1%.

Multilocus comparisons of $\tilde{V}_{g,1}$ *and* $\hat{V}_{g,1}$

Despite the availability of analytical approximations for $\hat{V}_{g,1}$ and $\tilde{V}_{g,1}$, their complexity rules out simple conclusions concerning their relative magnitudes, except in special cases. Even the asymptotic results for the house-of-cards approximations are of limited value because it is difficult to determine the actual parameter values for which they apply. To provide some insight into the behavior of the multilocus predictions, two sorts of numerical results will be presented. The first are graphs of $\hat{V}_{g,1}$ and $\tilde{V}_{g,1}$ for each approximation under various combinations of parameters. To make the choices of parameter values manageable, only the simplest case of interchangeable loci, each having the

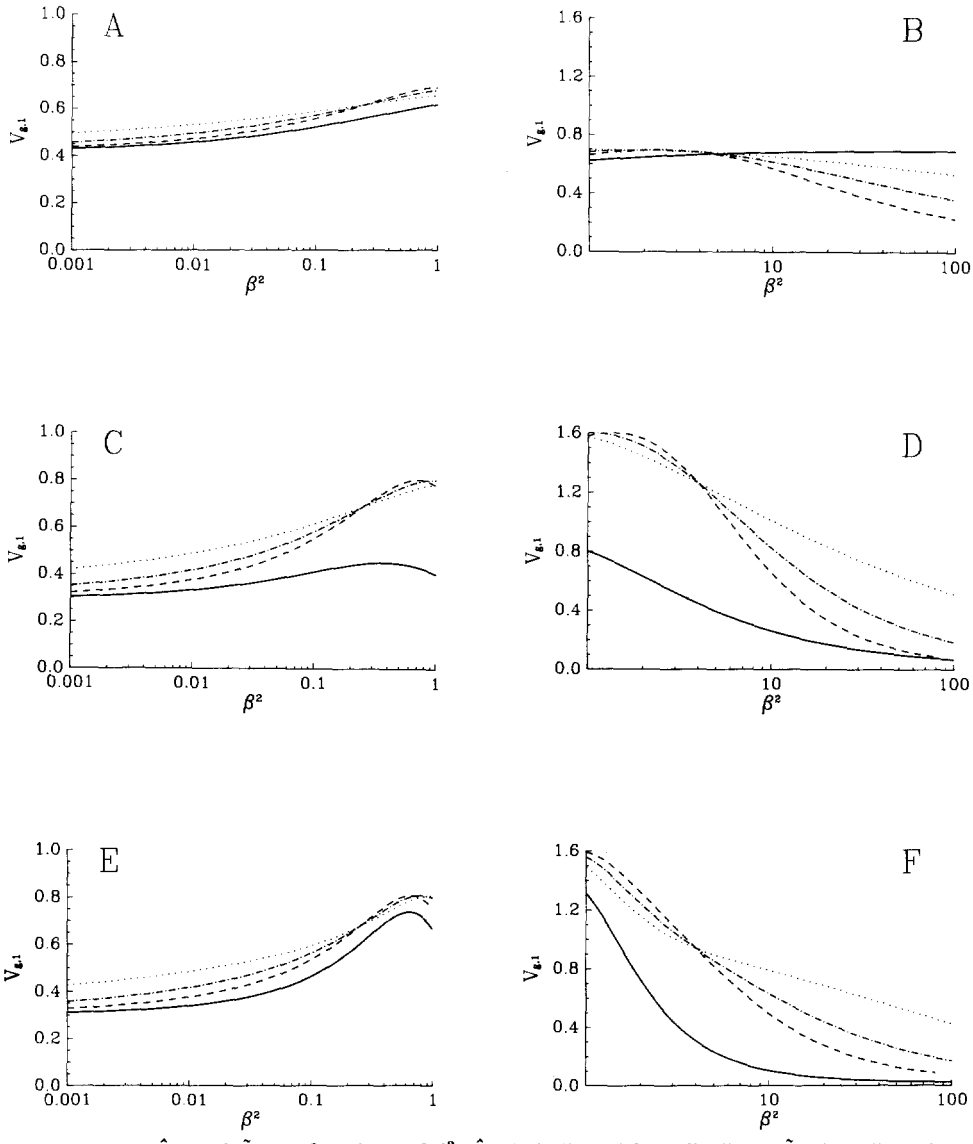

FIGURE 1.—$\hat{V}_{g,1}$ and $\tilde{V}_{g,1}$ as functions of β^2. $\hat{V}_{g,1}$ is indicated by solid lines; $\tilde{V}_{g,1}$ is indicated by broken lines with dashes for $mp = 0.25$, dots and dashes for $mp = 0.50$ and dots for $mp = 0.75$. A and B use the gaussian approximation, C and D use the house-of-cards approximation for a continuum-of-alleles and E and F use the house-of-cards approximation (3.5) for five alleles. See text for parameter values.

same mutation parameters, will be treated. Second, I present statistical summaries of comparisons between $\hat{V}_{g,1}$ and $\tilde{V}_{g,1}$ obtained with parameter values chosen randomly subject to various constraints. Both interchangeable and non-interchangeable loci are considered.

The six graphs in Figure 1 display $\hat{V}_{g,1}$ and $\tilde{V}_{g,1}$ as functions of β^2. The parameters were chosen to produce patterns representative of those found in

the statistical summaries below. Note that in each graph, there is a single curve for $\hat{V}_{g,1}$ but several for $\tilde{V}_{g,1}$. To produce them, initial values were chosen for all of the parameters; then, m_2^2 and $V_{s,2}$ were varied to obtain the desired range of β^2 values. The alternative curves for $\tilde{V}_{g,1}$ result from varying m_2^2 and $V_{s,2}$ at different rates. This was parameterized as follows. An initial choice of parameter values gives $\beta^2(0) = m_2^2(0)V_{s,1}/m_1^2V_{s,2}((0)$. To achieve $\beta^2(x) = 10^x\beta^2(0)$, m_2^2 and $V_{s,2}$ were varied as

$$m_2^2(x) = m_2^2(0)10^{x \cdot mp} \quad \text{and} \tag{50a}$$

$$V_{s,2}(x) = V_{s,2}(0)10^{-x(1-mp)} \tag{50b}$$

with $0 \leq mp \leq 1$. Thus, for $mp = 0.5$ both parameters vary at the same rate; whereas for $mp > 0.5$, m_2^2 varies more rapidly. Only a single $\hat{V}_{g,1}$ curve appears in each graph because $\hat{V}_{g,1}$ depends on m_2^2 and $V_{s,2}$ only through β^2 once $V_{s,1}$, m_1^2 and ρ_s are specified.

All of the graphs in Figure 1 assume $\Sigma\mu_i = 10^{-2}$ and $\rho_e = \rho_m = \rho_s = 0.8$. Other correlation patterns are discussed below. The graphs on the left assume that selection on new mutants is concentrated on character 1, *i.e.*, $\beta^2 = m_2^2V_{s,1}/m_1^2V_{s,2} < 1$, and use as initial parameters $V_{s,1} = 20$, $V_{s,2} = 40$, $m_1^2 = 0.06$ and $m_2^2 = 0.03$. The graphs on the right assume that selection is concentrated on character 2, *i.e.*, $\beta^2 > 1$, and use $V_{s,1} = 40$, $V_{s,2} = 20$, $m_1^2 = 0.03$ and $m_2^2 = 0.06$. The gaussian predictions, Figure 1A and B, assume ten loci so that $\mu_i \equiv 10^{-3}$. The house-of-cards predictions for five alleles, Figure 1E and F, assume 100 loci so that $\mu_i \equiv 10^{-4}$. The five-allele predictions are based on (3.5).

The graphs on the left show, as expected, that, if selection acts primarily through the observed character, the predictions, $\tilde{V}_{g,1}$, are always close to the true equilibria, $\hat{V}_{g,1}$, irrespective of the model or approximation used. However, even as $\beta^2 \to 0$, $\tilde{V}_{s,1}$ accurately reflects the selection on the underlying loci only if $V_{s,2} \to \infty$. Thus, although all of the $\tilde{V}_{g,1}$ curves tend toward $\hat{V}_{g,1}$ as $\beta^2 \to 0$, those with smaller mp values, corresponding to a more rapid increase of $V_{s,2}$, converge more quickly.

The consensus among the models and analyses disappears for $\beta^2 > 1$. Figure 1B shows that, according to the gaussian analysis, $\tilde{V}_{g,1}$ accurately approximates $\hat{V}_{g,1}$ for $\beta^2 < 10$ and then becomes increasing conservative as β^2 increases. In contrast, Figure 1D shows that under the house-of-cards analysis of the same model, $\tilde{V}_{g,1}$ overestimates $\hat{V}_{g,1}$ for this range of parameters. Recall from (32) and (33) that, if $m_2^2/m_1^2 \to \infty$ with $V_{s,1}/V_{s,2}$ constant, we expect $\tilde{V}_{g,1}/\hat{V}_{g,1} \gg 1$ eventually; whereas if m_2^2/m_1^2 and $V_{s,1}/V_{s,2}$ both increase, we expect $\tilde{V}_{g,1}/\hat{V}_{g,1} \ll 1$ eventually. This is reflected in the approach of $\tilde{V}_{g,1}$ to $\hat{V}_{g,1}$ as mp decreases from 0.75 to 0.25. However, even with $mp = 0.5$, so that m_2^2/m_1^2 and $V_{s,1}/V_{s,2}$ increase at the same rate, $\tilde{V}_{g,1}$ overestimates $\hat{V}_{g,1}$ by a factor of two or three for $1 < \beta^2 < 100$. As expected from the analytical results of the previous section, Figure 1F shows that, for the five-allele model, the house-of-cards analysis predicts a larger discrepancy between $\tilde{V}_{g,1}$ and $\hat{V}_{g,1}$ than seen with a continuum of alleles. For $mp = 0.5$, $\tilde{V}_{g,1}$ overestimates $\hat{V}_{g,1}$ by a factor of eight or more for $20 < \beta^2 < 100$. For instance, with $\beta^2 = 30$, $\hat{V}_{g,1} = 0.35$ corresponds to a predicted heritability of $h^2 = 0.26$; whereas $\hat{V}_{g,1} \cong h^2 \cong 0.03$.

To circumvent partially the biases inherent in choosing examples and to understand the consequences of interlocus mutation differences, $\tilde{V}_{g,1}$ and $\hat{V}_{g,1}$ were computed for parameter values chosen at random subject to various constraints. Three regions of parameter space for mutation and selection were explored: $0 < \beta^2 < 1$, $1 < \beta^2 < 10$ and $10 < \beta^2 < 100$. To illustrate the effects of changing $\beta^2 = m_2^2 V_{s,1}/m_1^2 V_{s,2}$ via m_2^2/m_1^2 *vs.* $V_{s,1}/V_{s,2}$, either the m's, the V_s's or both were chosen at random. When both were sampled, each ratio was restricted to the square root of the range of β^2. Thus, for $10 < \beta^2 < 100$, m_2^2/m_1^2 and $V_{s,1}/V_{s,2}$ were both restricted to $(\sqrt{10}, 10)$. Over a given range, the values of m_i^2 and $w_i^2 = V_{s,i} - 1$ were chosen independently and uniformly on a log scale. For $\beta^2 < 1$ (>1), the random values were ordered so that $m_1^2 \geq m_2^2$ ($m_1^2 \leq m_2^2$) and $V_{s,1} \leq V_{s,2}$ ($V_{s,1} \geq V_{s,2}$). Only pairs satisfying the appropriate constraints were used to compute $\tilde{V}_{g,1}$ and $\hat{V}_{g,1}$.

In addition to picking random mutation and selection parameters, several patterns of correlation were considered. The simplest, $\rho_e = \rho_m = \rho_w = 0$, provides a standard of comparison for the house-of-cards predictions with nonzero correlations; it yields $\tilde{V}_{g,1} \equiv \hat{V}_{g,1}$ for the gaussian prediction. The constraints $0.6 < \rho_e, \rho_m, \rho_w < 1$ will be called "complementary" correlations. Based on the frequent agreement in sign of empirical estimates for genetic and environmental correlations (see, for instance, HEGMANN and DEFRIES 1970; FALCONER 1981, TABLE 19.1), this pattern may be the most reasonable, although the magnitudes imposed are large. Three other correlation patterns were also investigated in which the sign of one of ρ_e, ρ_m or ρ_w differed from the other two; these will be referred to as "antagonistic" correlations. Among them, $\text{sgn}(\rho_e) = \text{sgn}(\rho_m) = -\text{sgn}(\rho_w)$ seems most reasonable because environmental and genetic perturbations of development may tend to have similar effects. In the tables below, only the pattern $0.6 < \rho_e, \rho_m, -\rho_w < 1$ is considered, but results from the other two antagonistic correlation patterns will be briefly described. To condense the results, only the estimated means and standard deviations for $\tilde{V}_{g,1}/\hat{V}_{g,1}$ will be presented. For each range of parameters, the estimates are based on 10,000 values for interchangeable loci and 1000 for noninterchangeable loci.

Table 6 presents results obtained with the gaussian approximation for ten interchangeable loci. The central qualitative result is that $\tilde{V}_{g,1}$ is generally within a factor of two of $\hat{V}_{g,1}$. Given the difficulty of estimating $\hat{V}_g$ and estimating the parameters that enter $\tilde{V}_g$, this level of agreement seems quite satisfactory. When $\tilde{V}_{g,1}$ is not within $(\frac{1}{2}\hat{V}_{g,1}, 2\hat{V}_{g,1})$, it is generally less than $\frac{1}{2}\hat{V}_{g,1}$. As illustrated by Figure 1B, the gaussian analysis predicts that $\tilde{V}_{g,1}$ tends to increasingly *underestimate* $\hat{V}_{g,1}$ as β^2 increases through both m_2^2/m_1^2 and $V_{s,1}/V_{s,2}$. Apart from this distinguishing feature of the gaussian predictions, the other two major trends that appear in Table 6 also show up in Tables 7 and 8, which present results from the house-of-cards analyses. For each we see (1) for a given range of β^2, the mean of $\tilde{V}_{g,1}/\hat{V}_{g,1}$ is largest when only m_2^2/m_1^2 varies among replicates, smallest when only $V_{s,1}/V_{s,2}$ varies and intermediate when both vary, and (2) for a given range of parameters, the antagonistic correlation pattern, $\text{sgn}(\rho_e) = \text{sgn}(\rho_m) = -\text{sgn}(\rho_w)$, provides a lower mean for $\tilde{V}_{g,1}/\hat{V}_{g,1}$ than

TABLE 6

Estimated means and standard deviations for $\tilde{V}_{g,1}/\hat{V}_{g,1}$ obtained from the gaussian approximation for ten identical loci with $\sum\mu_i = 10^{-2}$ and randomly chosen parameters

Ranges for selection and mutation parameters			Ranges for correlation parameters (Mean ± SD)	
β^2	$-\log_{10}m_i^2$	$\log_{10}w_i^2$	$0.6 < \rho_e, \rho_m, \rho_w < 1$	$0.6 < \rho_e, \rho_m, -\rho_w < 1$
0–1	0–3	0–3	1.06 ± 0.11	0.88 ± 0.09
0–1	1.5	0–3	0.94 ± 0.07	0.87 ± 0.11
1–10	0–3	0–3	1.00 ± 0.14	0.73 ± 0.17
1–10	0–3	1.5	1.09 ± 0.21	0.73 ± 0.18
1–10	1.5	0–3	0.86 ± 0.16	0.65 ± 0.15
10–100	0–3	0–3	0.84 ± 0.30	0.59 ± 0.22
10–100	0–3	1.5	1.50 ± 0.68	0.76 ± 0.33
10–100	1.5	0–3	0.48 ± 0.15	0.42 ± 0.13

For details see text.

TABLE 7

Estimated means and standard deviations for $\tilde{V}_{g,1}/\hat{V}_{g,1}$ obtained from the house-of-cards approximation with interchangeable loci, $\sum\mu_i = 10^{-2}$ and randomly chosen parameters

Ranges for selection and mutation parameters			Ranges for correlation parameters (Mean ± SD)		
β^2	$-\log_{10}m_i^2$	$\log_{10}w_i^2$	$\rho_e = \rho_m = \rho_w = 0$	$0.6 < \rho_e, \rho_m, \rho_w < 1$	$0.6 < \rho_m, \rho_m, -\rho_w < 1$
0–1	0–3	0–3	1.18 ± 0.18	1.39 ± 0.52	0.85 ± 0.15
0–1	1.5	0–3	1.44 ± 0.27	1.28 ± 0.39	1.02 ± 0.15
1–10	0–3	0–3	2.79 ± 0.43	2.83 ± 1.20	1.22 ± 0.40
1–10	0–3	1.5	2.81 ± 0.61	3.66 ± 2.53	1.23 ± 0.45
1–10	1.5	0–3	2.79 ± 0.60	2.04 ± 0.87	0.98 ± 0.36
10–100	0–3	0–3	6.68 ± 1.34	4.00 ± 2.09	1.63 ± 0.74
10–100	0–3	1.5	6.54 ± 1.86	15.36 ± 13.92	2.97 ± 1.81
10–100	1.5	0–3	6.51 ± 1.84	1.06 ± 0.65	0.70 ± 0.36

does the complementary correlation pattern, $\text{sgn}(\rho_e) = \text{sgn}(\rho_m) = \text{sgn}(\rho_w)$. Although the results do not appear in the tables, $\text{sgn}(\rho_e) = \text{sgn}(\rho_w) = -\text{sgn}(\rho_m)$ generally produces larger values than the complementary pattern; whereas $\text{sgn}(\rho_m) = \text{sgn}(\rho_w) = -\text{sgn}(\rho_e)$ produces values comparable to those with $\text{sgn}(\rho_e) = \text{sgn}(\rho_m) = -\text{sgn}(\rho_w)$. Irrespective of their signs, as the magnitudes of the correlation coefficients decrease, the results converge to those obtained without correlation. For instance, using the gaussian approximation with $10 < \beta^2 < 100$ obtained from random values for m_2^2/m_1^2 and $V_{s,1}/V_{s,2}$, the mean and standard deviation of $\tilde{V}_{g,1}/\hat{V}_{g,1}$ are 0.93 ± 0.08 for $0.2 < \rho_e, \rho_m, \rho_w < 0.6$ and 0.78 ± 0.11 for $0.2 < \rho_e, \rho_m, -\rho_w < 0.6$.

Tables 7 and 8 present results from the house-of-cards analyses of the continuum-of-allele and five-allele models, respectively. As expected, $\tilde{V}_{g,1}$ approximates $\hat{V}_{g,1}$ well for $\beta^2 < 1$. For $10 < \beta^2 < 100$, $\tilde{V}_{g,1}/\hat{V}_{g,1}$ depends critically on whether β^2 is large due to m_2^2/m_1^2 or $V_{s,1}/V_{s,2}$ or both. It is also significantly influenced by the correlation pattern. The main conclusion is that, unless the

TABLE 8

Estimated means and standard deviations for $\tilde{V}_{g,1}/\hat{V}_{g,1}$ obtained from the house-of-cards approximation (3.5) for 100 identical five-allele loci with $\sum\mu_i = 10^{-2}$ and randomly chosen parameters

Ranges for selection and mutation parameters			Ranges for correlation parameters (Mean ± SD)		
β^2	$-\log_{10}m_i^2$	$\log_{10}w_i^2$	$\rho_e = \rho_m = \rho_w = 0$	$0.6 < \rho_e, \rho_m, \rho_w < 1$	$0.6 < \rho_e, \rho_m, -\rho_w < 1$
0–1	0–3	0–3	1.05 ± 0.10	1.29 ± 0.68	0.85 ± 0.14
0–1	1.5	0–3	1.20 ± 0.22	0.95 ± 0.17	1.01 ± 0.17
1–10	0–3	0–3	3.08 ± 1.53	2.64 ± 4.19	1.57 ± 0.50
1–10	0–3	1.5	3.29 ± 1.84	4.88 ± 11.11	1.90 ± 0.94
1–10	1.5	0–3	3.20 ± 1.71	1.58 ± 1.05	1.25 ± 0.36
10–100	0–3	0–3	16.05 ± 12.83	11.53 ± 9.69	4.58 ± 1.98
10–100	0–3	1.5	15.86 ± 10.66	55.17 ± 110.0	11.26 ± 6.90
10–100	1.5	0–3	14.40 ± 8.51	1.99 ± 0.86	1.51 ± 0.41

TABLE 9

Estimated means and standard deviations for $\tilde{V}_{g,1}/\hat{V}_{g,1}$ for noninterchangeable loci with randomly chosen selection and mutation parameters satisfying $10 < \beta_i^2 < 100$ for each locus

Approximation	No. of loci	Range of $-\log_{10}\mu_i^2$	Ranges for correlation parameters		
			$\rho_e = \rho_m = \rho_w = 0$	$0.6 < \rho_e, \rho_m, \rho_w < 1$	$0.6 < \rho_e, \rho_m, -\rho_w < 1$
Gaussian	20	2.5–5.2	1.00	0.82 ± 0.17	0.57 ± 0.12
House-of-cards	100	3.3–5.5	6.48 ± 0.92	3.81 ± 1.67	1.53 ± 0.56
House-of-cards/ five-allele	100	3.3–5.5	13.31 ± 5.91	8.98 ± 5.21	4.00 ± 0.98

[a] These ranges give average gametic mutation rates approximately equal to those in Tables 6–8.

large β^2 is determined primarily by $V_{s,1}/V_{s,2}$, $\tilde{V}_{g,1}$ generally overestimates $\hat{V}_{g,1}$. For $10 < \beta^2 < 100$, the overestimate is usually five-fold or less under the continuum-of-alleles model; but it frequently exceeds ten-fold under the five-allele model. Although correlation tends to moderate the confounding effects predicted without correlation, the large mean values for $\tilde{V}_{g,1}/\hat{V}_{g,1}$ obtained with $V_{s,1} = V_{s,2}$ correctly indicate that correlation can also enhance the confounding effects of unseen characters. Use of noninterchangeable loci in the calculations has essentially no effect for $\beta_i^2 < 1$, a slight effect for $1 < \beta_i^2 < 10$ and a somewhat larger effect for $10 < \beta_i^2 < 100$. Table 9 shows that even for $10 < \beta_i^2 < 100$, the mean values of $\tilde{V}_{g,1}/\hat{V}_{g,1}$ are fairly similar to those in Tables 6–8.

DISCUSSION

Understanding the consequences of hidden variables is a fundamental problem in all areas of science. Ignoring them for modeling convenience does not make their effects disappear. In the last 10 yr, theoretical population biologists

have increasingly turned to this problem. In community ecology, SCHAFFER (1981) developed a mathematical framework for evaluating the consequences of ignoring some interacting species in community analyses. The diverse results of EWENS and THOMSON (1977), HASTINGS (1981, 1984) and NICHOLAS and ROBERTSON (1980) suggest that analogous problems in population and quantitative genetics are generally less tractable. From this perspective, it is hardly surprising that no simple message emerges from my analysis of mutation-selection balance with hidden pleiotropic effects. Indeed, the results raise more questions than they answer. However, these are substantive biological questions concerning models and conclusions that have been widely, and perhaps prematurely, accepted. The two key issues are (1) the validity of the gaussian genetic model when applied to mutation-selection balance and (2) the ability of mutation-selection balance to account for a significant fraction of the observed heritable variation in metric traits.

The analytical and numerical approximations suggest that the gaussian approximation for $\hat{V}_{g,1}$ will be reasonably accurate only when

$$\mu_i > \max(m_{1,i}^2/V_{s,1},\ m_{2,i}^2/V_{s,2}). \tag{51}$$

The analytical extension to k uncorrelated characters is trivial, but checking it will be a formidable numerical task for $k \geq 3$. Nevertheless, it is a reasonable conjecture that, if sufficient genetic flexibility is available to justify the continuum-of-alleles model, the distribution of alleles at a locus will be nearly gaussian if

$$\mu_i > \max_k(m_{k,i}^2/V_{s,k}), \tag{52}$$

where k ranges over the characters affected. LANDE (1980) assumes that all of these characters are under stabilizing selection. LANDE (1975) estimated $m_k^2 > 0.033$ for mutations of nine maize characters studied by RUSSELL, SPRAGUE and PENNY (1963). Estimating $V_{s,k}$ is more problematic. As shown by LANDE and ARNOLD (1983), estimates are confounded by both directional and stabilizing selection on correlated characters. Thus, the univariate data used in TURELLI (1984) to produce $V_s \cong 10$–20 may uniformly overestimate the intensity of stabilizing selection. However, it should be recognized that the available data are generally restricted to viability selection over only a portion of the life cycle. Because of these limitations, indirect estimates must be considered.

Note that a new mutation arising in a nearly "optimal" genotype experiences a selection coefficient proportional to $\boldsymbol{m}^T\boldsymbol{\Sigma}_s^{-1}\boldsymbol{m}$, where $\boldsymbol{m}^T = (m_1, \cdots, m_k)$ is the vector of standard deviations for mutant effects and $\boldsymbol{\Sigma}_s$ is the variance-covariance matrix of the genotypic fitness function. Thus, the right-hand side of (52) is proportional to the largest single-character contribution to this selection coefficient. The extensive data on spontaneous viability mutants in *D. melanogaster* yield average selection coefficients on the order of 0.01 against heterozygotes for new mutations (CROW and SIMMONS 1983). Even if this is associated with effects on as many as 20 characters, it suggests 5×10^{-4} as an upper bound for the right-hand side of (52). Similarly, if $V_{s,k} \leq 100$ for at least one of the characters affected by the locus, LANDE's (1975) estimate of m^2 and (52)

imply that $\mu_i > 3 \times 10^{-4}$ is needed for the gaussian approximation to apply. TURELLI (1984, pp. 147–148) presents an independent argument, based on estimates of σ_m^2, which also predicts that the gaussian approximation is unlikely to be accurate unless per locus mutation rates significantly exceed 10^{-4}. As reviewed previously (TURELLI 1984), there are no data to support the prevalence of such high mutation rates. Thus, there is no apparent biological justification for using the gaussian genetic model to understand polygenic mutation-selection balance.

Given this, the problem of explaining observed levels of additive genetic variances via mutation-selection balance will be discussed only with respect to the house-of-cards predictions. As noted in TURELLI (1984), the estimates $\Sigma\mu_i \cong 0.01$ and $\tilde{V}_{s,1} \cong 10$–20 produce univariate house-of-cards heritability predictions ranging from 0.29 to 0.44. Thus, if these parameter estimates are reasonably accurate and $\tilde{V}_{g,1}$ is not inflated by pleiotropy, mutation-selection balance may well account for much of the observed additive variance. However, both the continuum-of-alleles and five-allele analyses imply that $\tilde{V}_{g,1}$ is generally accurate only when most of the selection experienced by new mutants is attributable to the character observed, *i.e.*, $\beta_i^2 < 1$. This seems unlikely.

Based on a multivariate phenotypic selection study, LANDE and ARNOLD (1983) concluded that most observed stabilizing selection may be due to indirect selection, *i.e.*, selection acting on correlated characters. This may be due either to linkage (as indicated by the data of DAVIES 1971) or pleiotropy (as emphasized by WRIGHT 1968). If, as the models here assume, most indirect selection is due to pleiotropy, the LANDE and ARNOLD (1983) observation would imply that β^2 tends to be large. But there are insufficient data, and insufficient information in obtainable data, to estimate it accurately. As shown by LANDE and ARNOLD (1983), multivariate selection studies can, with considerable effort, estimate the ratio of intrinsic selection on a character to realized selection. At best this might approximate the $V_{s,1}/V_{s,2}$ ratio in β^2. However, it would be biased downward (assuming most selection is stabilizing) by selection on pleiotropically connected characters not included in the study and by selection on included characters that are pleiotropically connected to, but only weakly correlated with, the character of interest. Thus, the hidden selection that tends to bias $\tilde{V}_{g,1}$ upward would also act to bias estimates of β^2 downward.

The difficulties imposed by pleiotropy may well preclude accurate predictions concerning mutation-selection balance for polygenic traits. However, it is important to recognize that, if β^2 is large, as seems likely, the true equilibrium genetic variance, $\tilde{V}_{g,1}$, is generally overestimated by $\tilde{V}_{g,1}$, the univariate prediction based on the empirically estimable realized intensity of selection, $\tilde{V}_{s,1}$. Thus, the house-of-cards predictions noted above, $h^2 \cong 0.29$–0.44, should be viewed as upper bounds based on the parameter estimates given. As demonstrated in the previous section, the extent of overestimation depends on the details of pleiotropic selection, correlation patterns and the model used. Because of the number of alleles needed to approximate accurately a two-dimensional continuum of effects, the multivariate continuum-of-alleles model seems highly implausible. Thus, the overestimates predicted by the continuum-of-

alleles model should be regarded as conservative. Conversely, the rigid constraints imposed by the five-allele model probably inflate the overestimates unrealistically. Nevertheless, there seems to be no reason to doubt that $\tilde{V}_{g,1}$ may overestimate $\hat{V}_{g,1}$ by five- to ten-fold as seen in Tables 7–9. If this is taken into account, the range of "explained" heritabilities is reduced from $h^2 \cong 0.29$–0.44 to $h^2 \cong 0.04$–0.14. Hence, without additional data to support the gaussian approximation or additional insight to circumvent the pleiotropy-induced problems raised here, LANDE's (1975) mutation-selection hypothesis for extant heritable variation must remain an appealing but unsubstantiated conjecture.

Finally, the artificiality of the models analyzed should be acknowledged. The complexity of the predictions from these simple models makes it very unlikely that robust predictions based on empirically estimable quantities will emerge from more realistic models. However, one of the central mathematical results may be artifactual. The house-of-cards prediction that increasing intensity of pleiotropic selection drives the equilibrium genetic variance downward depends critically on the assumption that stabilizing selection acts on every aspect of the phenotype affected by loci contributing variation to the character of interest. Following the tradition of ROBERTSON (1956), GILLESPIE (1984) has cogently criticized this assumption. He has shown that, if pleiotropic effects involve balancing selection rather than phenotypic stabilizing selection, pleiotropy can be a potent force *maintaining* additive variance. Similarly, ROSE (1982) has shown that opposing directional selection on pleiotropically connected traits can also maintain variation. The punchline is obvious. Sorting out the mechanisms responsible for observed levels of heritability will be no simpler than explaining protein polymorphisms.

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APPENDIX 1

Suppose the allelic effects at each of n loci are independent and identically distributed. Assuming only additive genetic effects, we want to assess how well the distribution of phenotypes approximates a gaussian. A simple index is the kurtosis. According to the gaussian model, the kurtosis of the distribution of effects at individual loci satisfies $\kappa_L = E(X^4)/3[E(X^2)]^2 = 1$ (for simplicity, I've assumed $E(X) = 0$). According to the house-of-cards approximation $\kappa_L > 1$, with typical values on the order of 10. It is easy to show that according to model (1), if a trait has heritability h^2, the kurtosis of its phenotypic distribution satisfies

$$\kappa_P - 1 = h^4(\kappa_L - 1)/2n. \tag{1.1}$$

The simple fact that the kurtosis (and skewness) of the phenotypic distribution approach their gaussian expectations as n^{-1} was observed by FISHER (1918). Note that $h^2 \leq \frac{1}{2}$, $\kappa_L \leq 10$ and $n \geq 10$ yield $\kappa_P \leq 1.11$. Thus, relatively few loci are needed to produce a gaussian-like distribution for phenotypes even if the allelic effects are markedly nongaussian.

APPENDIX 2

When approximation (23) holds, the genetic quantities of interest can be obtained from an approximate evaluation of

$$\mathbf{I}_{n,m} = \mu_i \int\int \frac{x_1^n x_2^m m_i(x_1, x_2) dx_1 dx_2}{1 - cw(x_1, x_2)}. \tag{2.1}$$

By analogy with the analysis in TURELLI (1984), I will assume

$$\mu_i \ll m_{j,i}^2/V_{s,j} \ll 1 \tag{2.2}$$

for at least one of $j = 1, 2$. Without loss of generality, assume that (2.2) holds with $j = 1$ for all loci that affect both characters. A messy change of variables transforms (2.1) into

$$I_{n,m} = K_i \int_0^{2\pi} (\cos\theta)^m (\rho_{m,i}\cos\theta + (1-\rho_{m,i}^2)^{1/2}\sin\theta)^n \int_0^{\infty} \frac{\exp(-a_i r^2) r^{m+n+1} dr d\theta}{1 - c\exp[-r^2 f(\theta)]} \tag{2.3}$$

with

$$K_i = \{\mu_i (m_{2,i}/m_{1,i})^n [2V_{s,1}(1-\rho_s^2)]^{(1/2)(m+n+2)}\}/(2\pi m_{1,i}^2),$$

$$a_i = V_{s,1}(1-\rho_s^2)/m_{1,i}^2,\ f(\theta) = b_{1,i}(\cos\theta)^2 + b_{2,i}\cos\theta\sin\theta + b_{3,i}(\sin\theta)^2,$$

$$\beta_i = (V_{s,1}m_{2,i}^2/V_{s,2}m_{1,i}^2)^{1/2},\ b_{1,i} = 1 - 2\rho_{m,i}\rho_s\beta_i + \rho_{m,i}^2\beta_i^2,$$

$$b_{2,i} = 2(1-\rho_{m,i}^2)^{1/2}\beta_i(\rho_{m,i}\beta_i - \rho_s),\ \text{and}\ b_{3,i} = (1-\rho_{m,i}^2)\beta_i^2.$$

Condition (2.2) implies that c in (2.3) is approximately 1 and a_i is very large so that the inner integral can be approximated by the first term of the Watson's lemma expansion (*cf.* chap. 6 of CARRIER, KROOK and PEARSON 1966) for

$$\int_0^{\infty} \frac{\exp(-a_i r^2) r^{m+n+1} dr}{1 - \exp[-r^2 f(\theta)]} \tag{2.4}$$

as $a_i \to \infty$. Thus, (2.3) can be approximated by

$$I_{m,n} \cong K' \int_0^{2\pi} (\cos\theta)^m (\rho_{m,i}\cos\theta + (1-\rho_{m,i}^2)^{1/2}\sin\theta)^n / f(\theta) d\theta, \tag{2.5}$$

with $K' = \frac{1}{2}K\Gamma[\frac{1}{2}(m+n)]a_i^{-(1/2)(m+n)}$, $\Gamma[\cdot]$ denoting the γ function, and the remaining terms as in (2.3). The integral in (2.5) can be explicitly evaluated to obtain

$$\hat{V}_{g,1}^{(i)} \cong 2\mu_i V_{s,1}/(1+\beta_i) \tag{2.6a}$$

if $\rho_{m,i} = \rho_s = 0$, or $\beta_i = 1$ and $\rho_{m,i} = \rho_s$, and

$$\hat{V}_{g,1}^{(i)} \cong \mu_i V_{s,1}(1-\rho_s^2)A_i[2(b_{1,i} - b_{3,i}) + B_i C_i^{-1}] \tag{2.6b}$$

otherwise, with $A_i = [b_{2,i}^2 + (b_{1,i} - b_{3,i})^2]^{-1}$, $B_i = b_{2,i}^2 + 2b_{3,i}(b_{3,i} - b_{1,i})$, and $C_i = \beta_i[(1-\rho_{m,i}^2)(1-\rho_s^2)]^{1/2}$. Note that for a given value of ρ_s, $V_{s,2}$, $m_{1,i}^2$ and $m_{2,i}^2$ enter $\hat{V}_{g,1}^{(i)}$ only through β_i. Similarly, (2.5) yields

$$\hat{C}_g^{(i)} \cong \mu_i V_{s,1}\rho_s m_2/m_1 \tag{2.7a}$$

if $\rho_{m,i} = \rho_s$ and $\beta_i = 1$, and

$$\hat{C}_g^{(i)} \cong \mu_i V_{s,1}(1-\rho_s^2)(m_{2,i}/m_{1,i})A_i\{\rho_{m,i}[2(b_{1,i} - b_{3,i}) + B_i C_i^{-1}] + b_{2,i}(1-\rho_{m,i}^2)^{1/2}[2 - (b_{3,i} + b_{1,i})C_i^{-1}]\} \tag{2.7b}$$

otherwise. The final bivariate house-of-cards approximations, $\hat{V}_{g,1}$ (HC) and $\tilde{V}_{s,1}$ (HC), follow from (11), (15), (2.6) and (2.7).

APPENDIX 3

Let $p_{\mathbf{j},t}$ with $\mathbf{j} = (j_1, j_2)$ denote the frequency of allele $A_{j_1,j_2}^{(i)}$ among zygotes in generation t. If we ignore linkage disequilibrium and assume selection is sufficiently weak that each locus experiences approximately the genotypic fitness function (4), the dynamics of $p_{\mathbf{j},t}^{(i)}$ with $j_1 = \pm 1$, $j_2 = \pm 1$ can be approximated by

$$p_{\mathbf{j},t+1}^{(i)} = (1-\mu_i)\hat{p}_{\mathbf{j},t}^{(i)} + \mu_{\mathbf{0},\mathbf{j}}^{(i)}\hat{p}_{\mathbf{0},t}^{(i)} \tag{3.1}$$

with

$$\hat{p}_{\mathbf{j},t}^{(i)} = p_{\mathbf{j},t}^{(i)}\bar{w}_{\mathbf{j},t}^{(i)}/\bar{w}_t^{(i)},$$

$$\bar{w}_{\mathbf{j},t}^{(i)} = \sum_{\mathbf{k}\in K} p_{\mathbf{k},t}^{(i)} w[(j_1+k_1)c_{1,i}, (j_2+k_2)c_{2,i}],$$

$$\bar{w}_t^{(i)} = \sum_{\mathbf{j}\in K} p_{\mathbf{j},t}^{(i)}\bar{w}_{\mathbf{j},t}^{(i)},$$

$K = \{(1,1), (1,-1), (0,0), (-1,1), (-1,-1)\}$, $\mu_{\mathbf{0},j}^{(i)}$ defined by (14) and $w(\cdot,\cdot)$ defined by (4). To

approximate the equilibrium, we can mimic the mutation and selection assumptions used in the house-of-cards approximation for the continuum-of-alleles, *i.e.*,

$$\mu_i \ll c_{j,i}^2/V_{s,j} \ll 1 \quad \text{for} \quad j = 1 \text{ or } 2 \tag{3.2}$$

[*cf.* (2.2)]. This implies that mutation is weaker than selection, so we expect the equilibrium to satisfy $\hat{p}_{\mathbf{j}}^{(i)} \ll 1$ for $\mathbf{j} \neq \mathbf{0}$. Thus, the equilibrium of (3.1) may be approximated by

$$\hat{p}_{\mathbf{j}}^{(i)} \cong (1 - \mu_i)\hat{p}_{\mathbf{j}}^{(i)} w(j_1 c_{1,i}, j_2 c_{2,i}) + \mu_{\mathbf{0},\mathbf{j}}^{(i)} \quad \text{for} \quad \mathbf{j} \neq \mathbf{0}. \tag{3.3}$$

Note that the same approximation applies if we replace (3.1) by the analogous haploid model.

Equation (3.3) produces the simple approximation

$$\hat{p}_{\mathbf{j}}^{(i)} \cong \mu_{\mathbf{0},\mathbf{j}}^{(i)}/[1 - (1 - \mu_i)w(j_1 c_{1,i}, j_2 c_{2,i})]. \tag{3.4}$$

Using the linkage equilibrium approximation, this implies

$$\hat{V}_{g,1} \cong 4 \sum_{i=1}^{n'} (\hat{p}_{1,1}^{(i)} + \hat{p}_{1,-1}^{(i)}) c_{1,i}^2 \quad \text{and} \tag{3.5a}$$

$$\hat{C}_g \cong 4 \sum_{i=1}^{n'} (\hat{p}_{1,1}^{(i)} - \hat{p}_{1,-1}^{(i)})\, c_{1,i} c_{2,i}. \tag{3.5b}$$

To obtain expressions analogous to those derived for the continuum-of-alleles model, the μ_i in the denominator of (3.4) can be ignored and the fitness term can be approximated using $e^{-x} \cong 1 - x$ if we assume relatively weak selection on both characters, *i.e.*,

$$c_{j,i}^2/V_{s,j} \ll 1 \quad \text{for} \quad j = 1, 2, \tag{3.6}$$

in addition to (3.2). This yields the somewhat cruder five-allele approximations

$$\hat{V}_{g,1}(5) = 4V_{s,1}(1 - \rho_s^2) \sum_{i=1}^{n} \mu_i \frac{1 + 2\rho_{m,i}\rho_s\beta_i + \beta_i^2}{1 + 2(1 - 2\rho_s^2)\beta_i^2 + \beta_i^4} \quad \text{and} \tag{3.7a}$$

$$\hat{C}_g(5) = 4(V_{s,1}V_{s,2})^{1/2}(1 - \rho_s^2) \sum_{i=1}^{n} \mu_i \frac{\rho_{m,i}(\beta_i + \beta_i^{-1}) + 2\rho_s}{\beta_i^2 + 2(1 - 2\rho_s^2) + \beta_i^{-2}}. \tag{3.7b}$$

Here, as in the continuum-of-alleles model, $\beta_i^2 = V_{s,1}c_{2,i}^2/V_{s,2}c_{1,i}^2$ measures the relative intensity of selection at pleiotropic loci attributable to P_2 *vs.* P_1. Also, once ρ_s is fixed, $V_{s,2}$, $c_{1,i}^2$ and $c_{2,i}^2$ enter $\hat{V}_{g,1}^{(i)}$ only through β_i.

Corresponding to (3.5) and (3.7), there are two approximate single-character extrapolations $\hat{V}_{g,1}$. The more precise approximation corresponding to (3.5) is

$$\hat{V}_{g,1} = 4 \sum_{i=1}^{n'} \hat{p}_1^{(i)} c_{1,i}^2 \tag{3.8}$$

with $\hat{p}_1^{(i)} = \frac{1}{2}\mu_i/[1 - (1 - \mu_i)\exp(-\frac{1}{2}c_{1,i}^2/\tilde{V}_{s,1})]$ and $\tilde{V}_{s,1}$ given by (11) with (3.5) used to compute $\text{cov}(P_1, P_2)$ and $\text{var}(P_1)$. The analogous approximation corresponding to (3.7) is

$$\hat{V}_{g,1}(5) = 4 \sum_{i=1}^{n'} \mu_i \tilde{V}_{s,1}(5) \tag{3.9}$$

with $\tilde{V}_{s,1}(5)$ computed via (11) and (3.7).

APPENDIX 4

Given values for the parameters μ, m_1^2, m_2^2, ρ_m, w_1^2, w_2^2, ρ_w and ρ_e, the gaussian approximations $\hat{V}_{g,1}(\text{G})$ and $\hat{V}_{g,2}(\text{G})$ were computed from (18). Based on four additional parameters, Sd_1,

Sd_2, N_1 and N_2 with N_1 and N_2 integers, a grid was established for allele effects, denoted (a_i, a_j) with $-(N_1 + N_2) \leq i, j \leq N_1 + N_2$, by first setting

$$s_i = \sqrt{\max(\hat{V}_{g,i}(G), m_i^2)} \quad \text{for} \quad i = 1, 2, \text{ then} \tag{4.1}$$

$$h_{i,1} = s_i Sd_1/N_1 \quad \text{and} \quad h_{i,2} = s_i (Sd_2 - Sd_1)/N_2. \tag{4.2}$$

Values of a_i were assigned according to

$$a_i = ih_{1,1} \quad \text{for} \quad 0 \leq |i| \leq N_1 - 1, \tag{4.3a}$$

$$a_{N_1} = -a_{-N_1} = N_1 h_{1,1} + \tfrac{1}{4}(h_{1,2} - h_{1,1}) \quad \text{and} \tag{4.3b}$$

$$a_i = N_1 h_{1,1} + (i - N_1)h_{1,2} \quad \text{for} \quad N_1 + 1 \leq |i| \leq N_1 + N_2. \tag{4.3c}$$

Thus, alleles range in effect on P_1 from $-s_1 Sd_2$ to $s_1 Sd_2$ with different spacings between the effects of alleles near the origin *vs.* near the extremes. Values for a_j were assigned as above with $h_{1,j}$ replaced by $h_{2,j}$. Letting $N = N_1 + N_2$, $K = 1 + 2N$ is the number of different effects considered for each character and K^2 is the total number of alleles. For all of the calculations presented in Tables 1–5, $Sd_1 = 0.5$, $Sd_2 = 2.5$, $N_1 = 3$ and $N_2 = 2$ so that $K^2 = 121$. These values were chosen by trial and error to produce reasonable agreement between the predicted and observed results over the range of parameter values used.

After allele effects were assigned allele (a_i, a_j) was assigned fitness

$$w_{ij} = w(a_i, a_j) \tag{4.4}$$

using the genetic fitness function (4). Last, the mutation rate from (a_i, a_j) to $(a_{i'}, a_{j'})$ was determined from

$$u_{(i,j),(i',j')} = (1 - \mu)\delta_{(i,j),(i',j')} + \mu v_{(i,j),(i',j')} \tag{4.5a}$$

with $\delta_{(i,j),(i',j')} = 1$ if $(i, j) = (i', j')$ and 0 otherwise,

$$v_{(i,j),(i',j')} = m(a_i - a_{i'}, a_j - a_{j'}) / \sum_{k=-N}^{N} \sum_{l=-N}^{N} m(a_i - a_k, a_j - a_l), \tag{4.5b}$$

and $m(x_1, x_2)$ the gaussian mutation density as in (16). This mutation scheme is a cruder approximation than that used in TURELLI (1984). It results in an appreciable discrepancy (up to 10%) between the input variance and correlation parameters and the actual variances and correlation of mutant effects. In Tables 1–5, the actual variances and correlation associated with mutants from (0, 0) are given. For the parameters used in the calculations, (4.5) also generally produces slightly platykurtic (*i.e.*, $\kappa = E(X^4)/3[E(X^2)]^2 < 1$) distributions of mutant effects, instead of the gaussian $\kappa = 1$. Despite its limitations, this algorithm produces equilibria that agree well with both the gaussian and house-of-cards predictions for appropriate parameter values. Finally, the discretization introduces a discrepancy between the mutation rates relevant to the gaussian and house-of-cards predictions [see (4.5) of TURELLI 1984]. For the parameters used, they differ by less than 0.5% and only the house-of-cards mutation rate is given in the tables but both were used in calculating the predicted equilibria.