Polygenic Variation Maintained by Balancing Selection:
Pleiotropy, Sex–Dependent Allelic Effects
and GxE Interactions

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Pleiotropy, sex-dependent allelic effects and G×E interactions

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ABSTRACT

We investigate three alternative selection-based scenarios proposed to maintain polygenic variation: pleiotropic balancing selection, G×E interactions (with spatial or temporal variation in allelic effects) and sex-dependent allelic effects. Each analysis assumes an additive polygenic trait with \( n \) diallelic loci under stabilizing selection. We allow loci to have different effects and consider equilibria at which the population mean departs from the stabilizing-selection optimum. Under weak selection, each model produces essentially identical, approximate allele-frequency dynamics. Variation is maintained under pleiotropic balancing selection only at loci for which the strength of balancing selection exceeds the effective strength of stabilizing selection. In addition, for all models, polymorphism requires that the population mean be close enough to the optimum that directional selection does not overwhelm balancing selection. This balance allows many simultaneously stable equilibria; and we explore their properties numerically. Both spatial and temporal G×E can maintain variation at loci for which the coefficient of variation (across environments) of the effect of a substitution exceeds a critical value greater than one. The critical value depends on the correlation between substitution effects at different loci. If these correlations exceed 1/2, even extreme fluctuations in allelic effects cannot maintain variation. Surprisingly, this implies that sex-dependent allelic effects cannot maintain polygenic variation. We present numerical results that support our analytical approximations and discuss our results in connection to relevant data and alternative variance-maintaining mechanisms.
It remains a challenge for evolutionary geneticists to understand the additive genetic variance observed for most traits in most populations. Given the ubiquity of additive genetic variation, it is natural to seek an explanation in terms of ubiquitous forces. Lande (1975) proposed mutation-selection balance. However, over the past 25 years, attempts to explain standing levels of quantitative genetic variation in terms of mutation-selection balance have been at best only partially successful (e.g., Caballero and Keightley 1994, Charlesworth and Hughes 2000; but see Zhang and Hill 2002). One alternative is that some form of balancing selection, unconnected to the trait of interest, may account for persistent polymorphism at the underlying loci (e.g., Robertson 1965, Bulmer 1973, Gillespie 1984, Barton 1990). In contrast to such pleiotropic explanations, balancing selection might arise from variation in the effects of alleles that contribute to the trait, for instance, through genotype-by-environment interactions (G×E). Here we explore four scenarios in which variance-depleting stabilizing selection interacts with pleiotropic balancing selection, environment-dependent allelic effects (with spatial or temporal heterogeneity) or sex-dependent allelic effects. The thread that unites these scenarios is that, under weak selection, each produces very similar allele-frequency dynamics and polymorphism conditions. An empirical motivation for these analyses is that alleles of intermediate frequency contribute to phenotypic variation in natural populations (e.g., Mackay and Langley 1990, Long et al. 2000). Polymorphic alleles are incompatible with mutation-selection balance for plausible levels of selection and mutation.

The mathematical motivation for these analyses is Wright’s (1935) approximations showing that stabilizing selection tends to eliminate polygenic variation. Using a weak-selection approximation, he showed that at most one locus is expected to remain polymorphic at equilibrium. More recent analyses of strong selection (Nagylaki 1989, Bürger and Gimelfarb 1999) have demonstrated that two-locus polymorphisms can be stably maintained with sufficiently strong selection and sufficient interlocus variation in allelic effects. We provide new simulations that further illustrate the restrictive conditions needed to maintain stable two-locus polymorphisms for additive traits under stabilizing selection and loose linkage.

Robertson (1965) proposed that additive variation may be maintained by pleiotropically
induced overdominant selection which counteracts the effects of stabilizing selection. His conjecture was explored analytically by Bulmer (1973) for diallelic loci and extended to multiple alleles by Gillespie (1984). Both assumed equal allelic effects across loci, symmetric overdominance of equal intensity at all loci, and that the population mean at equilibrium coincided with the optimal trait value. They found lower bounds on the intensity of overdominant selection required to maintain symmetrical polymorphisms at all of the loci in the face of balancing selection. Our diallelic analyses generalize theirs, and that of Zhivotovsky and Gavrilets (1992), by allowing for unequal allelic effects and arbitrary overdominance across loci and by considering the simultaneous stability of alternative equilibria at which the population mean can depart from the optimum.

Gillespie and Turelli (1989) showed how balancing selection could arise at individual loci by averaging over randomly fluctuating allelic effects. In their symmetric model of genotype-by-environment (G×E) interactions, all alleles have essentially the same mean and variance of effects. With this extreme symmetry assumption, even slight fluctuations can maintain indefinitely many alleles at an arbitrary number of loci. However, the essential interchangeability of the alleles implies that there will be essentially no correlation between the phenotypes produced by a given genotype across unrelated environments (i.e., two environments chosen at random from the distribution of environments responsible for maintaining variation) (Gillespie and Turelli 1989, 1990; Gimelfarb 1990). Genetic variation that shows so little consistency of effects would severely limit the resemblance between parents and offspring across different environments. As discussed below, it may, nonetheless, be compatible with experimentally observed additive variance.

Below we explore the consequences of allowing appreciable differences in the mean effects of different alleles. We will show that under simple forms of spatial and temporal variation in allelic effects, the conditions for the maintenance of variation become much more restrictive than indicated by Gillespie and Turelli (1989). Nevertheless, a surprisingly simple necessary condition for the maintenance of variation emerges. Our weak-selection approximations apply to a broad class of selection regimes in which balancing selection acts on the loci that contribute to trait variation. In
particular, we show that the approximate dynamics obtained for average allele frequencies under G×E interactions and stabilizing selection are very similar to those arising from pleiotropic balancing selection.

The consequences of sex-dependent allelic effects, as extensively documented by Mackay, Langley and their collaborators (e.g., Lai et al. 1995, Long et al. 1996, Nuzhdin et al. 1997, Wayne and Mackay 1998, Gurganus et al. 1998, Vieira et al. 2000, Dilda and Mackay 2002), are approximated by a special case of the model for spatial variation. Contrary to the expectation from single-locus analyses that such sex-dependent effects may promote the maintenance of variation, we show that sex-dependent allelic effects do not stably maintain polygenic variation for additive traits.

All of our analyses assume that selection is weak enough relative to recombination that linkage disequilibrium is negligible. We also assume diallelic loci. It is not clear to us how restrictive this assumption is. In models of mutation/selection balance, two-allele and continuum-of-allele models give similar results provided that the alleles responsible for variation are rare (Turelli 1984, Slatkin and Frank 1990). However, when loci are highly polymorphic (as might occur under balancing selection), continuum-of-allele models can give qualitatively different results (Waxman and Peck 1999, Bürger 1999). Nevertheless, we believe that models with two alleles are a better approximation to reality (where usually there will be a few discrete alleles) than a continuum of alleles, particularly when pleiotropy is considered, because it takes an extraordinary number of discrete alleles to approximate even a two-dimensional continuum (Turelli 1985; Wagner 1989).

Another critical assumption is that the temporal and spatial scales of fluctuating allelic effects are sufficiently small, relative to the time scale of selection, that we can average over these fluctuations to approximate the allele-frequency dynamics with deterministic differential equations. Both the linkage equilibrium and averaging approximations were made by Gillespie and Turelli (1989), and we explore their validity numerically with temporal fluctuations in allelic effects (and sex-dependent allelic effects). We conjecture that more highly autocorrelated temporal fluctuations would maintain less variation (Gillespie and Guess 1978), whereas a coarser spatial variation can maintain more variation (Barton and Turelli 1989, Barton 1999).
Our analyses show that balancing selection can maintain variation at loci for which the intensity of balancing selection exceeds the strength of stabilizing selection. With pleiotropy, this follows from sufficiently strong balancing selection; and hence, this provides a plausible mechanism for the maintenance of variation if there exists sufficient balancing selection. In general, we find multiple alternative stable equilibria, but these tend to produce similar mean phenotypes and levels of variation. With fluctuating allelic effects, stable polymorphism requires sufficiently large fluctuations in the effects and sufficient independence of the fluctuations across loci. The restrictiveness of the conditions is illustrated by the fact that sex-dependent allelic effects cannot maintain stable polygenic variation. Although fluctuations of allelic effects that are extreme enough to maintain variation significantly limit the consistency of genotypic effects, this lack of consistency is apparent only if the genotypes are assayed across the entire range of environments responsible for maintaining variation. This may reconcile the polymorphism conditions with experimental observations.

MODELS AND APPROXIMATE ANALYSES

We will analyze in turn pleiotropic balancing selection, G×E with spatial variation and complete mixing, sex-dependent allelic effects, and G×E with temporal variation. The connection between these alternative scenarios is that in the weak-selection limit, they lead to essentially identical allele-frequency dynamics, and hence similar stability properties for equilibria. This is somewhat surprising, since temporal G×E leads to stochastic fluctuations in allele frequencies whereas pleiotropic balancing selection, spatial variation and sex-dependent allelic effects are wholly deterministic (but see Gillespie and Turelli (1989) for motivation of this deterministic approximation and our results below for numerical support). We start with the simplest deterministic model to illustrate our stability analyses, then apply essentially the same analyses to “averaged” versions of more complex models involving environment- or sex-dependent allelic effects. We support our average-based analytical approximations with exact multilocus numerical analyses and also use numerical analyses to explore the properties of simultaneously stable
alternative equilibria.

**Pleiotropic Balancing Selection**

Let $B_i$ and $b_i$ denote the alleles at locus $i$. We let $p_{i,t}$ denote the frequency of $B_i$ in generation $t$ and set $q_{i,t} = 1 - p_{i,t}$. We assume that selection is sufficiently weak and linkage sufficiently loose that we can ignore linkage disequilibrium. Let $\beta_i$ ($\gamma_i$) denote the additive contribution of $B_i$ ($b_i$) to the trait of interest. We set $\alpha_i = \beta_i - \gamma_i$, so that $\alpha_i$ denotes the average effect of a substitution at locus $i$ (Falconer and Mackay, 1996, Ch. 7). (Table 1 provides a glossary of notation.) Assuming that there is no dominance or epistasis for the trait, the population mean and additive genetic variance in generation $t$ are

\[
\bar{z}_t = 2 \sum_{i=1}^{n} (p_{i,t} \beta_i + q_{i,t} \gamma_i) \quad \text{and} \quad V_{A,t} = 2 \sum_{i=1}^{n} \alpha_i^2 p_{i,t} q_{i,t}.
\]  

(1)

We assume constant Gaussian stabilizing selection on this trait with optimum $\theta$ and strength $S$, so that the fitness assigned to genotypes producing mean phenotype $G$ (averaged over non-genetic sources of variation) is $w(G) = \exp\left(-\frac{S}{2}(G - \theta)^2\right)$. For weak selection, we can approximate $w(G)$ by a linear function of $S$. In the weak-selection limit, the population’s mean fitness is

\[
\bar{w} = 1 - \frac{S}{2} \left( V_{A} + (\bar{z} - \theta)^2 \right) + o(S),
\]  

(2)

where $o(S)$ denotes a quantity that vanishes faster than $S$ does as $S \to 0$. At linkage equilibrium, the allele-frequencies dynamics can be approximated by

\[
\Delta p_i = \frac{p_i q_i}{2} \frac{\partial \ln \bar{w}}{\partial p_i} = \frac{S p_i q_i}{2} \left( \alpha_i^2 (p_i - q_i) - 2 \alpha_i (\bar{z} - \theta) \right) + o(S)
\]  

(3)
(Wright 1937). (The first equation above is exact for one locus; the approximation is the calculation of mean fitness for the one-locus genotypes.) Assuming weak selection, we can approximate (3) by

$$\frac{dp_i}{dt} = \frac{Sp_iq_i}{2} \left( \alpha_i^2(p_i - q_i) - 2\alpha_i(\bar{z} - \theta) \right).$$  \hspace{1cm} (4)

Note that the allele-frequency dynamics depend on the allelic effects only through $\alpha_i = \beta_i - \gamma_i$ and $\bar{z} - \theta = 2\sum_{i=1}^{n} p_i\alpha_i - 2\sum_{i=1}^{n} \gamma_i - \theta$. Because the scale of measurement of our trait is arbitrary, $\theta$ can absorb any constants that enter the determination of the mean phenotype (such as the $\gamma_i$ and the contributions of monomorphic loci not considered in our analyses). Thus, we are free to choose any values for the $\beta_i$ and $\gamma_i$ that satisfy $\alpha_i = \beta_i - \gamma_i$. Without loss of generality, we will assume that

$$\beta_i = \alpha_i/2$$ and $\gamma_i = -\alpha_i/2$ for all $i$, so that $\bar{z} = \sum_{i=1}^{n} \alpha_i(p_i - q_i).$ \hspace{1cm} (5)

As shown initially by Wright (1935) from an approximation like (4) (cf. Bulmer 1971), stabilizing selection will generally eliminate additive polygenic variation (see Bürger and Gimelfarb 1999 for a recent review). To maintain variation, we assume that the loci experience balancing selection of some sort. The simplest such mechanism is overdominance, but our analysis also covers cases in which additive effects on fitness are linear functions of allele frequencies. This may be a good approximation for a wide range of models of negative frequency-dependence, especially if allele frequencies are not perturbed too far from equilibrium.

We assume that the relative contributions to fitness from pleiotropic effects are $1 - s_i\hat{p}_i$, 1 and $1 - s_i\hat{p}_i$ for $B_iB_i$, $B_ib_i$ and $b_ib_i$, respectively, with $0 < s_i << 1$ and $0 < \hat{p}_i < 1$ for all $i$. These fitnesses
lead to a stable equilibrium at $\hat{p}_i$. For definiteness, we assume that these pleiotropic fitness effects are multiplicative across loci and that this pleiotropic selection acts before stabilizing selection in the life cycle. However, neither assumption matters in our weak-selection approximation. With weak-selection, we can, like Bulmer (1973) and Gillespie (1984), superimpose the pleiotropic overdominant selection on the trait-induced selection to approximate the allele-frequency dynamics by

$$\frac{dp_i}{dt} = -\frac{S}{2} p_i q_i \left( -\alpha_i^2 (p_i - q_i) + 2 \alpha_i (z - \theta) + 2 \frac{S_i}{S} (p_i - \hat{p}_i) \right)$$

$$= \frac{S \alpha_i^2}{2} p_i q_i \left( (p_i - q_i) - 2 \delta_i - 2 v_i (p_i - \hat{p}_i) \right),$$

where

$$v_i = \frac{s_i}{\alpha_i^2 S}, \delta_i = \frac{\Delta}{\alpha_i}, \text{ and } \Delta = z - \theta. \quad (7a)$$

Note that a deviation from the optimum of $\alpha_i$ reduces fitness by $S \alpha_i^2 / 2$; hence, $v_i$ quantifies the intensity of balancing selection at locus $i$ relative to stabilizing selection. To make the stability analysis more transparent, we can rewrite (7a) as

$$\frac{dp_i}{dt} = -S \alpha_i^2 p_i q_i \left( p_i - \frac{1}{2} + \frac{1}{\alpha_i} (z_i^* - \theta) + v_i (p_i - \hat{p}_i) \right). \quad (8)$$

where $z_i^* = \sum_{j \neq i} \alpha_j (p_j - q_j)$ denotes the contribution to the mean phenotype from all loci but $i$.

**Stability of fully polymorphic equilibria:** From (7a) we see that each locus can fall into one of three possible equilibria: $p_i = 0$, $p_i = 1$, or $p_i$ satisfying

$$\frac{2v_i \hat{p}_i - 1 - 2 \delta_i}{2(v_i - 1)}, \quad (9)$$
with \( v_i \) and \( \delta_i \) defined in (7b).  (Because the approximate dynamics form a gradient system, complex equilibria are excluded and only point equilibria can occur, Hofbauer and Sigmund 1998, Ch. 19.)  As expected, the polymorphic equilibrium (9) becomes \( \hat{p}_i \) if \( v_i \) is very large, and becomes 1/2 if pleiotropic balancing selection is eliminated and the population mean is at the optimum (\( \Delta = \delta_1 = 0 \)).  Condition (9) creates a system of linear equations for the \( p_i \) that will generally have a unique solution for a fixed set of polymorphic loci.  We will first focus on the stability of fully polymorphic equilibria at which all \( n \) loci satisfy (9), but we show below that precisely the same stability conditions emerge whenever two or more loci are polymorphic.  Conditions for the uniqueness and feasibility of fully polymorphic equilibria are discussed below, along with boundary equilibria at which some or all of the loci are fixed.

As shown in Appendix A, stability of the polymorphic equilibrium is determined solely by the \( v_i \).  In order to maintain a stable polymorphism, balancing selection must be sufficiently strong relative to stabilizing selection (Bulmer 1973).  The stability of the fully polymorphic equilibrium depends on the eigenvalues of the Jacobian matrix \( A = (a_{ij}) \), with

\[
a_{ii} = \frac{\partial}{\partial p_i} \left( \frac{dp_i}{dt} \right) = -Sp_i q_i \alpha_i^2 (1 + v_i) \quad \text{and} \quad (10a)
\]

\[
a_{ij} = \frac{\partial}{\partial p_j} \left( \frac{dp_i}{dt} \right) = -2Sp_i q_i \alpha_i \alpha_j \quad \text{for} \ i \neq j, \quad (10b)
\]

evaluated at allele frequencies that satisfy (9).  The fully polymorphic equilibrium is locally stable if all of the eigenvalues of this matrix have negative real parts.  In general, it is difficult to calculate the eigenvalues.  Nevertheless, the stability conditions can be determined because of symmetries imposed by our model.  We consider first a completely symmetric model, as discussed by Bulmer (1973), for which all of the eigenvalues and the equilibrium allele frequencies can be explicitly determined.
Suppose that the loci are interchangeable with \( \alpha_i = \alpha \), \( s_i = s \), and \( \hat{p}_i = \hat{p} \); then \( \nu_i = \nu \) for all \( i \) and the equations (9) for the equilibrium allele frequencies have a unique solution:

\[
p_i = p = \frac{2\theta + (2n - 1)\alpha + 2\nu\alpha\hat{p}}{2\alpha(2n - 1 + \nu)}. \tag{11}
\]

In this symmetric case, the stability matrix \( A \) has all diagonal elements equal and all off-diagonal elements equal. \( A \) has only two distinct eigenvalues,

\[
\lambda_1 = -Spq\alpha^2(v - 1) \text{ and } \lambda_2 = -Spq\alpha^2(2n + v - 1), \tag{12}
\]

where \( \lambda_1 \) has multiplicity \( n - 1 \). Obviously, \( \lambda_2 \) is always negative; but \( \lambda_1 \) is negative if and only if

\[
v > 1. \tag{13}\]

Thus, as Bulmer (1973) found under the assumption that \( \bar{z} = \theta \), \( s = \alpha^2S \) is the lower bound on the intensity of balancing selection relative to stabilizing selection that must be exceeded to produce a stable polymorphism. Essentially the same constraint on \( \nu_i \) arises for the general model (7a).

The necessary and sufficient conditions derived in Appendix A for stability are that either:

\[
\nu_i > 1 \text{ for all } i, \tag{14}
\]

or one locus (locus 1, say) has \( \nu_1 < 1 \), but this locus obeys

\[
\nu_1 > 1 - \frac{1}{\frac{1}{2} \sum_{i=2}^{n} \frac{1}{\nu_i - 1}}. \tag{15}
\]

For large numbers of polymorphic loci, the sum in the denominator is large, and so this condition is
barely different from the simpler sufficient condition (14). Indeed, as shown in Appendix A, a necessary condition for stability is

$$(v_i + 1)(v_j + 1) > 4 \text{ for all } i \neq j; \quad (16)$$

so that condition (14) is not far from being both necessary and sufficient. Conditions (14) and (15) can be understood from Wright’s (1935) result that in the absence of balancing selection, i.e., $v_i = 0$ for all $i$, at most one locus is expected to be polymorphic in the weak-selection limit. At loci with $v_i > 1$, balancing selection is strong enough to be able to maintain polymorphism. Our weak-selection analysis indicates that at most one such locus can be polymorphic with $1 > v_i > -1$.

**Multiple characters:** The model readily generalizes to multiple characters. We suppose that stabilizing selection of intensity $S_\omega$ acts towards an optimum $\theta_\omega$, independently across a set of characters, labeled $\omega$, i.e., $w(G) = \text{Exp}[-\frac{1}{2}(G_\omega - \theta_\omega)^2]$. Following the arguments leading to (7a), we obtain

$$\frac{dp_i}{dt} = \frac{\tilde{S}_T}{2} p_i q_i \left((p_i - q_i) - 2\tilde{\delta}_i - 2\tilde{v}_i (p_i - \hat{p}_i)\right), \text{where} \quad (17a)$$

$$\tilde{S}_T = \sum_\omega S_\omega \alpha_{i,\omega}, \quad \tilde{\delta}_i = \frac{\sum_\omega S_\omega \alpha_{i,\omega}^2 \delta_{i,\omega}}{S_T}, \quad \delta_{i,\omega} = \frac{z_{\omega} - \theta_\omega}{\alpha_{i,\omega}}, \quad \text{and} \quad \tilde{v}_i = \frac{s_i}{S_T}. \quad (17b)$$

The polymorphic equilibria can still be represented by (9) with $v_i$ replaced by $\tilde{v}_i$ and $\delta_i$ replaced by $\tilde{\delta}_i$. However, the stability conditions are more complex than for the one-dimensional model, because the stability-determining matrix $A$ in (10) is replaced by

$$a_{ij} = -S_T p_i q_i (1 + \tilde{v}_i) \text{ and} \quad (18a)$$
\[ a_{ij} = -2p_ip_j\Sigma_{\omega}S_{\omega}\alpha_{i,0}\alpha_{j,0} \quad \text{for } i \neq j. \] (18b)

Because of the summation in (18b), the signs of the eigenvalues of (18) do not depend solely on the \( \tilde{v}_i \). Unlike the one-character model in which at most one locus is expected to be polymorphic with \( v_i < 1 \), for multiple characters with \( \tilde{v}_i = 0 \) for all \( i \) and equal allelic effects, the number of stably polymorphic loci can be as large as the number of traits (Hastings and Hom 1989). We will not pursue this model here, but will return to it when we consider sex-dependent allelic effects.

**Stability, feasibility and positions of alternative equilibria:** Next, we consider equilibria for the one-character model in which some loci are monomorphic. Several complexities arise due the possible simultaneous stability of multiple equilibria with different numbers of polymorphic loci and fixation of either \( B_i \) or \( b_i \) at the monomorphic loci. First consider the conditions for polymorphic equilibria to be feasible. The conditions will depend on whether \( v_i > 1 \) (recall that at most one stably polymorphic locus can violate this). If \( v_i > 1 \), (9) implies that
\[
0 < p_i < 1 \quad \text{only if} \quad v_i > \max\left(\frac{1 + 2\delta_i}{2\hat{p}_i}, \frac{1 - 2\delta_i}{2\hat{q}_i}\right),
\] (19a)

If \( v_i < 1 \), feasibility requires
\[
v_i < \min\left(\frac{1 + 2\delta_i}{2\hat{p}_i}, \frac{1 - 2\delta_i}{2\hat{q}_i}\right),
\] (19b)

Unless \( \Delta = 0 \), (19a) constrains at least all but one of \( v_i \) to exceed one by an amount that depends \( \Delta \). Conversely, if stability is achieved with one locus satisfying \( v_i < 1 \), (19b) puts an upper bound on this \( v_i \) that must be satisfied along with the lower bound given by (15). Overall, these feasibility
conditions for polymorphisms and the conditions described next for stability of fixation equilibria require allele frequencies that make $\Delta$ very small.

Consider an equilibrium at which $p_i = 0$ for all $i$ in the set $\Omega_0$, $p_i = 1$ for $i$ in $\Omega_1$, and $0 < p_i < 1$ for $i$ in $\Omega_p$. In this case, the stability matrix $A$ can be partitioned into pieces corresponding to the fixed and polymorphic loci, because

$$a_{ij} = 0 \text{ for } i \neq j \text{ if } i \text{ is in either } \Omega_0 \text{ or } \Omega_1,$$

$$a_{ii} = \frac{S\alpha_i^2}{2}(2\hat{p}_i v_i - 1 - 2\delta_i) \text{ for } i \in \Omega_0, \text{ and}$$

$$a_{ii} = \frac{S\alpha_i^2}{2}(2\hat{q}_i v_i - 1 + 2\delta_i) \text{ for } i \in \Omega_1.$$ 

Thus, the eigenvalues governing the stability of the fixed loci (i.e., $i \in \Omega_0 \cup \Omega_1$) are simply $\lambda_i = a_{ii}$; and the stability conditions for the subsystem of polymorphic loci (i.e., $i \in \Omega_p$) are just (14, 15). Equations (20b,c) show that the stability conditions for the fixed loci are

$$v_i < \frac{1 + 2\delta_i}{2\hat{p}_i} \text{ if } p_i = 0, \text{ and}$$

$$v_i < \frac{1 - 2\delta_i}{2\hat{q}_i} \text{ if } p_i = 1.$$ 

Hence, the conditions for the stability of the fixed equilibria are complementary to the feasibility conditions (19a) for the polymorphic equilibria with $v_i > 1$. The implications of (21) can be seen by assuming, without loss of generality, that $\Delta = \bar{z} - \theta$ is negative and all of the $\alpha_i$ are positive. In this case, increasing $p_i$ at each locus moves the population mean closer to the optimum. Then, inequalities (21) with $v_i = 0$ imply that, whenever possible, the multilocus system will equilibrate so that $|\Delta|$ is less than $\min_{i \in \Omega_0}(\alpha_i/2)$. Inequalities (21) imply that $|\Delta|$ is even smaller with $v_i > 0$. 

15
Because alternative multilocus equilibria will generally produce different values of $\Delta$, and hence different $\delta_i$ for each locus, conditions (19) and (21) do not preclude a locus from having stable alternative fixation and polymorphic equilibria (cf. Hastings and Hom 1990). In particular, if $v_i$ is only slightly above one, the locus can be stably polymorphic at an equilibrium with $\Delta$ very near 0, but stably monomorphic at equilibria with larger $|\Delta|$. This will be illustrated numerically below.

Now consider $\Delta$ at equilibria. Assuming as above that $p_i = 0$ for $i \in \Omega_0$, $p_i = 1$ for $i \in \Omega_1$, and $0 < p_i < 1$ for $i \in \Omega_p$, we have

$$\Delta = \sum_{i \in \Omega_1} \alpha_i - \sum_{i \in \Omega_0} \alpha_i + \sum_{i \in \Omega_p} \alpha_i(p_i - q_i) - \theta. \quad (22)$$

Substituting expression (9) for the equilibrium allele frequencies and rearranging, we find that

$$\Delta = \frac{\Delta_f}{1 + 2C}, \quad \text{where} \quad (23a)$$

$$\Delta_f = \sum_{i \in \Omega_1} \alpha_i - \sum_{i \in \Omega_0} \alpha_i + \sum_{i \in \Omega_p} \frac{\alpha_i v_i (\hat{p}_i - \hat{q}_i)}{v_i - 1} - \theta, \quad \text{and} \quad (23b)$$

$$C = \sum_{i \in \Omega_p} \frac{1}{v_i - 1}. \quad (23c)$$

Assuming that only the loci in $\Omega_p$ are polymorphic, the population mean would depart from the optimum by $\Delta_f$ in the absence of stabilizing selection returning the trait towards the optimum. (Note that in the absence of stabilizing selection, the terms in the final summation in (23b) reduce to $\alpha_i(\hat{p}_i - \hat{q}_i)$.) In this sense, $\Delta_f$ represents a natural resting point of the system under balancing selection alone. Stabilizing selection generally reduces this deviation by a factor $B = 1/(1 + 2C)$ (as noted in Appendix B, the factor is negative if $v_i < 1$ for one of the $i$ in $\Omega_p$, but we will ignore this special case). Thus, $B$ is a cumulative measure of the strength of stabilizing selection relative to balancing selection. As noted above, we generally expect $v_i > 1$ at stably polymorphic loci. For any
fixed lower bound on the $v_i$, (23c) shows that as the number of polymorphic loci increases, the population mean will converge to the optimum by slightly perturbing the polymorphic allele frequencies away from $\hat{p}_i$ as described by (9).

The stability conditions for the full system, including fixed and polymorphic loci, are detailed in Appendix B. The qualitative conclusion is that for a wide range of parameter values, loci with $v_i > 1$ can be stably polymorphic and loci with $v_i < 1$ are generally monomorphic. Moreover, although alternative equilibria may be simultaneously stable, they generally produce mean phenotypes very near the optimum. These generalizations are illustrated by our numerical examples below, which also suggest that the alternative equilibria produce similar equilibrium levels of genetic variation.

**Consequences of GxE with Spatial Variation and Complete Mixing**

Next we consider a deterministic model that involves only stabilizing selection on the trait, but allows for environment-specific allelic effects, which can produce balancing selection at individual loci (Gillespie and Turelli 1989). Following Levene (1953), we assume that each environment contributes a constant proportion to the random mating pool that forms the next generation of zygotes. In our weak-selection limit, this means that we can simply average the equations that emerge in each environment, weighting each environment by its fractional contribution to the next generation (cf. Gillespie and Langley 1976). Let $\beta_{i,k} (\gamma_{i,k})$ denote the effect of $B_i (b_i)$ in environment $k$. With weak selection, we can approximate the allele frequency dynamics in this environment by

$$ \frac{dp_i}{dt} = -Sp_iq_i \left( (p_i - q_i)(\beta_{i,k} - \gamma_{i,k})^2 + 2(\beta_{i,k} - \gamma_{i,k})(\bar{z} - \theta) \right). $$

(24)

We assume that $S$ and $\theta$ remain fixed across environments. Averaging over environments, we define

$$ E(\beta_i - \gamma_i) = \alpha_i \text{ and } Var(\beta_i - \gamma_i) = v_i \alpha_i^2. $$

(25)
Thus, the effect of a substitution at locus $i$ has mean $\alpha_i$ and variance is $v_i\alpha_i^2$, so that $v_i$ is the square of the coefficient of variation of the substitution effect. We will demonstrate that these $v_i$ play the same role in the stability analysis of this model as do the $v_i$ defined by (7b) for the pleiotropy model. Averaging over environments, as done in Gillespie and Turelli (1989), we obtain

$$\frac{dp_i}{dt} = -\frac{Sp_iq_i}{2} \left(-\alpha_i^2(1 + v_i)(p_i - q_i) + 2\alpha_i[E(\bar{z}) - \theta] + 2\text{Cov}(\beta_i - \gamma_i, \bar{z})\right). \quad (26)$$

As discussed after Eq. (4), we can absorb constants that enter $E(\bar{z})$ into $\theta$, so we assume $E(\beta_i) = \alpha_i/2$ and $E(\gamma_i) = -\alpha_i/2$, without loss of generality. Thus, $E(\bar{z}) = \sum_i (p_i - q_i)\alpha_i$. Rearranging (1), we have

$$\bar{z} = \sum_{i=1}^{n} (p_i - q_i)(\beta_i - \gamma_i) + \sum_{i=1}^{n} (\beta_i + \gamma_i), \quad (27)$$

where the $\beta_i$ and $\gamma_i$ have environment-specific values. Hence, the term $\text{Cov}(\beta_i - \gamma_i, \bar{z})$ that enters (26) and the analyses below depends on the scaled covariances, $\tilde{c}_{ij}$ and $\tilde{d}_{ij}$, defined by

$$\text{Cov}(\beta_{i,t} - \gamma_{i,t}, \beta_{j,t} - \gamma_{j,t}) = \tilde{c}_{ij}\alpha_i\alpha_j = \rho_{ij}\alpha_i\alpha_j\sqrt{v_i}v_j \quad \text{and} \quad (28a)$$

$$\text{Cov}(\beta_{i,t} - \gamma_{i,t}, \beta_{j,t} + \gamma_{j,t}) = \tilde{d}_{ij}\alpha_i\alpha_j, \quad (28b)$$

where $\tilde{c}_{ii} = v_i$ and $\rho_{ij}$ denotes the correlation of substitution effects at loci $i$ and $j$. Note that $\tilde{c}_{ij} = \tilde{d}_{ij} = 0$ for all $i \neq j$ if either the allelic effects at different loci fluctuate independently or we impose the symmetry constraints, $\text{Cov}(\beta_i, \beta_j) = \text{Cov}(\gamma_i, \gamma_j) = \text{Cov}(\gamma_i, \beta_j) = \text{Cov}(\beta_i, \gamma_j)$ for all $i \neq j$. Gillespie and Turelli (1989) assumed the latter. Under the less restrictive assumptions that $\text{Cov}(\beta_i, \beta_j) = \text{Cov}(\gamma_i, \gamma_j)$ and $\text{Cov}(\gamma_i, \beta_j) = \text{Cov}(\beta_i, \gamma_j)$, we have $\tilde{d}_{ij} = 0$ for all $i$ and $j$. In particular, $\tilde{d}_{ii} = \text{Var}(\beta_i)$ –
Var(γ_i), so that \( \bar{d}_{i} = 0 \) if Var(β_i) = Var(γ_i). Separating the terms in (26) that depend on locus i, we have

\[
\frac{dp_i}{dt} = -\frac{Sp_i q_i}{2} \left( \alpha_i^2 (1 + v_i)(p_i - q_i) + 2\alpha_i [E(z_i^*) - \theta] + 2\alpha_i^2 \bar{d}_{i} + 2\text{Cov}(\beta_i - \gamma_i, z_i^*) \right),
\]

(29)

where \( E(z_i^*) = \sum_{j\neq i}(p_j - q_j)\alpha_j \) denotes the average contribution to the mean phenotype from the loci other than i. It is easy to see that Cov(β_i - γ_i, z_i^*) = 0 if \( \bar{c}_{ij} = 0 \) for all i \neq j. Gillespie and Turelli (1989) assumed this and found that interlocus correlations did not affect their polymorphism condition. We show below that this conclusion depends critically on their symmetry assumption concerning interlocus correlations.

**Analysis of fully polymorphic equilibria:** At equilibrium, each locus must satisfy: \( p_i = 0, \) \( p_i = 1, \) or

\[
p_i - q_i = -\frac{2\alpha_i [E(z_i^*) - \theta] + 2\alpha_i^2 \bar{d}_{i} + 2\text{Cov}(\beta_i - \gamma_i, z_i^*)}{\alpha_i^2 (1 + v_i)}. \tag{30}
\]

Note that increasing \( \bar{d}_{i} \), corresponding to raising the variance of effect for allele B_i relative to the variance for b_i, decreases the equilibrium \( p_i \), consistent with the general principle that selection in variable environments tends to favor more homeostatic genotypes (Gillespie 1974). The stability of the fully polymorphic equilibrium depends on the eigenvalues of the Jacobian matrix \( A = (a_{ij}) \) with elements

\[
a_{ii} = \frac{\partial}{\partial p_i} \left( \frac{dp_i}{dt} \right) = -Sp_i q_i \alpha_i^2 (1 + v_i) \text{ and} \tag{31a}
\]

\[
a_{ij} = \frac{\partial}{\partial p_j} \left( \frac{dp_i}{dt} \right) = -2Sp_i q_i \alpha_i \alpha_j (1 + \bar{c}_{ij}) \text{ for } i \neq j, \tag{31b}
\]
evaluated at allele frequencies that satisfy (30), with \( \tilde{c}_{ij} \) as defined in (28a). If \( \text{Cov}(\beta_i - \gamma_i, \tilde{z}_i^+ ) = 0 \), the terms \( \tilde{c}_{ij} \) in (31b) vanish and the stability conditions are precisely those for the pleiotropy model, (14) and (15). In this case, the G\( \times \)E model reduces to the pleiotropic balancing selection model (apart from \( \tilde{d}_{ii} \) which does not affect stability of polymorphic equilibria) with \( \hat{p}_i = 0.5 \) at all loci. Following the argument in Appendix A, it is easy to see that in general the stability properties of (31) depend only on the \( v_i \) and the \( \rho_{ij} \) defined in (28a).

In general, positive correlations across loci are destabilizing in the sense that larger \( v_i \) are needed to achieve stability with \( \rho_{ij} > 0 \) than with \( \rho_{ij} = 0 \). The destabilizing effect is quite dramatic. For instance, the necessary condition for stability, analogous to (16), is

\[
(v_i + 1)(v_j + 1) > 4(1 + \rho_{ij}\sqrt{v_i}v_j)^2 \text{ for all } i \neq j. \tag{32}
\]

Note that if \( \rho_{ij} > 1/2 \) for all \( i \) and \( j \), (32) cannot be satisfied for any values of \( v_i \). The general stability conditions can be explicitly obtained following the procedure given in Appendix A, but they seem too complicated to be informative. However, the qualitative effects of correlations across loci can be seen under the symmetry assumptions \( v_i = v \) and \( \rho_{ij} = \rho \). In this case, a feasible fully polymorphic equilibrium is stable if and only if

\[
\rho < 1/2 \text{ and } v > \frac{1}{1 - 2\rho}. \tag{33}
\]

Hence, polygenic variation can be stably maintained under this model of G\( \times \)E interactions only if the loci experience at most moderate positive correlations among their fluctuating allelic effects, and the variance in effects is sufficiently large.

**Stability, feasibility and position of alternative equilibria:** Consider an equilibrium with \( p_i = 0 \) for \( i \in \Omega_0 \), \( p_i = 1 \) for \( i \in \Omega_1 \), and \( 0 < p_i < 1 \) for \( i \in \Omega_p \). First note that if
Cov(\beta_i - \gamma_i, \bar{z}_i^*) = 0 and \bar{d}_{ii} = 0, we can use the results for the pleiotropic balancing selection model with the additional constraint \hat{p}_i = 0.5 for all i. This generally simplifies the analysis. For instance, the stability conditions for the fixed loci reduce to

\[ v_i < 1 + 2\delta_i, \text{ if } i \in \Omega_0, \text{ and } v_i < 1 - 2\delta_i, \text{ if } i \in \Omega_1, \]  \tag{34}  

where \delta_i = [E(\bar{z}) - \theta]/\alpha_i. Numerical examples of pleiotropic overdominance presented below, which assume \hat{p}_i = 0.5, illustrate the approximate equilibria and dynamics of this model.

New phenomena appear with Cov(\beta_i - \gamma_i, \bar{z}_i^*) \neq 0 and \bar{d}_{ii} \neq 0. As noted above, positive correlations across loci make stable polymorphisms more difficult to obtain and positive values of \bar{d}_{ii} tend to lower \pi. Hence, we expect that positive correlations between loci and \bar{d}_{ii} > 0 will broaden the conditions for stability of \pi. As before, the stability matrix A can be partitioned into pieces corresponding to the fixed and polymorphic loci, because

\[ a_{ij} = 0 \text{ for } i \neq j \text{ if } i \text{ is in either } \Omega_0 \text{ or } \Omega_1, \text{ whereas } \]  \tag{35a}  

\[ a_{ii} = -\frac{S\alpha_i^2}{2} (v_i - 1 - 2e_i) \text{ for } i \in \Omega_0, \text{ and } \]  \tag{35b}  

\[ a_{ii} = -\frac{S\alpha_i^2}{2} (v_i - 1 + 2e_i) \text{ for } i \in \Omega_1, \text{ with } \]  \tag{35c}  

\[ e_i = \delta_i + \bar{d}_{ii} + \frac{\text{Cov}(\beta_i - \gamma_i, \bar{z}_i^*)}{\alpha_i^2}. \]  \tag{35d}  

Thus, the eigenvalues governing the stability of the fixed loci (i.e., \(i \in \Omega_0 \cup \Omega_1\)) are simply \(\lambda_i = a_{ii}\); and that the stability conditions for the subsystem of polymorphic loci (i.e., \(i \in \Omega_p\)) are determined by the eigenvalues of (31), which depend only on the parameters for the polymorphic loci.
Equations (35b, c) show that the stability conditions for the fixed loci are

\[ v_i < 1 + 2e_i, \text{ if } p_i = 0, \text{ and } v_i < 1 - 2e_i, \text{ if } p_i = 1. \quad (36) \]

As expected, positive values of \( \text{Cov}(\beta_i - \gamma_i, Z_i^*) \) and \( \tilde{d}_{ii} \) promote the stability of \( p_i = 0 \).

**Properties of polymorphic equilibria:** One of our central motivations for allowing significant differences in the mean effects of the alleles was to determine whether appreciable heritable variation could be maintained by \( G \times E \) that could provide persistent selection response. We have shown that maintaining variation requires a sufficiently large coefficient of variation of the allelic effects and sufficient independence of the fluctuations across loci. At least two biologically interesting questions follow. First, how similar are the phenotypes of various relatives, for instance, parents and offspring; and second, how variable are the phenotypes produced by specific genotypes across the range of environments responsible for maintaining the variation (cf. Yamada 1962, Gimelfarb 1990, Gillespie and Turelli 1990). The second question is more easily answered than the first, because the similarity of relatives will depend on the similarity of their environments. Even if this is known, the correlations between relatives will depend on additional parameters, which do not enter the polymorphism conditions, that describe the covariance of the fluctuating effects of alleles within and across loci. These parameters also enter the variance for the mean phenotypes produced by specific genotypes across environments. To illustrate this, we calculate the expected variance of the mean phenotype of a randomly drawn genotype, then partition the equilibrium variance in mean phenotypes to quantify the consistency of genotypic differences across environments.

Let \( G_t(g) \) denote the average phenotype of a specific multilocus genotype \( g \) in a specific environment \( t \). Under our additivity assumption,

\[ G_t(g) = \sum_{i=1}^{n} G_{i,t}(g), \quad (37) \]
where $G_{t,i}(g)$ denotes the contribution of the diploid genotype at locus $i$ in environment $t$. Under the assumptions that lead to (24), the allele-frequency dynamics depend on the moments of allelic effects only through the means and variances of the substitution effects. Thus, we had to specify only $E(\beta_{i,t} - \gamma_{i,t}) = \alpha_i$ and $\text{Var}(\beta_{i,t} - \gamma_{i,t}) = v_i\alpha_i^2$. However, we will see that the variance of genotypic values depends separately on the variances and covariances of the allelic effects within and between loci. We assume that

$$\text{Var}(\beta_{i,t}) = \text{Var}(\gamma_{i,t}) = c_i\alpha_i^2/2 \quad \text{and} \quad \text{Cov}(\beta_{i,t},\gamma_{i,t}) = \rho_i c_i\alpha_i^2/2; \quad (38)$$

so that

$$\text{Var}(\beta_{i,t} - \gamma_{i,t}) = c_i\alpha_i^2(1 - \rho_i). \quad (39)$$

Hence, in the calculations above, e.g., Equation (8), $v_i = c_i(1 - \rho_i)$. (Note that $\rho_i$ describes correlations between allelic effects within loci; whereas $\rho_{ij}$ in (28a) describes correlations between substitution effects at different loci.)

First, assume uncorrelated fluctuating allelic effects across loci, so that

$$\text{Var}[G_t(g)|g] = \sum_{i=1}^n \text{Var}[G_{i,t}(g)|g] \quad \text{and} \quad E\{\text{Var}[G_t(g)]|g]\} = \sum_{i=1}^n E\{\text{Var}[G_{i,t}(g)]|g]\}. \quad (40)$$

A central feature of all random environment models is that $\text{Var}[G_{t,i}(g)]$ depends on whether genotype $g$ is homozygous or heterozygous at locus $i$ (Gillespie and Turelli 1989). Using (38), $\text{Var}[G_{t,i}(g)] = 2c_i\alpha_i^2$ if $g$ is homozygous for either allele at locus $i$, and $\text{Var}[G_{t,i}(g)] = c_i\alpha_i^2(1 + \rho)$ if $g$ is heterozygous at locus $i$. Thus,
\[ E\{ \text{Var}[G_{i,t}(g)|g]\} = 2c_i \alpha_i^2 [1 - p_i q_i (1 - \rho)] = 2v_i \alpha_i^2 \left( \frac{1}{1 - \rho_i} - p_i q_i \right). \] (41)

Note that this depends on both \( v_i \) and \( \rho_i \). With independent fluctuations across loci, we have

\[ E\{ \text{Var}[G_{t}(g)|g]\} = 2 \sum_{i=1}^{n} v_i \alpha_i^2 \left( \frac{1}{1 - \rho_i} - p_i q_i \right). \] (42)

To understand the implications of (42), we need a scale-independent quantification of this expected within-genotype variance. By analogy to broad-sense heritability, we can define an index for the stability of environment-dependent genetic effects as the fraction of the total genetic variance (across both genotypes and environments) attributable to the mean effects of different genotypes. In general, we have

\[ \text{Var}[G_{t}(g)] = \text{Var} \{ E[G_{t}(g)|g]\} + E\{ \text{Var}[G_{t}(g)|g]\}, \] (43)

where, as indicated, the inner expectations are taken over environments and the outer expectations are taken over genotypes. The first term is the variance of the mean genotypic values (i.e., the “main effect” of genotypes) and the second is the average across-environment variance for individual genotypes (i.e., the G×E term in an ANOVA of experimental data). We define the “consistency” of these genotypes as

\[ K = \frac{\text{Var} \{ E[G_{t}(g)|g]\}}{\text{Var}[G_{t}(g)]}. \] (44)

\( K \) near 0 implies that the differences among mean effects are small relative to the standard deviations of genotypes’ effects across environments, and \( K \) near 1 implies relatively large mean effects (e.g., \( K = 1 \) with constant allelic effects).
Our linkage equilibrium assumption and the definition of $\alpha_i$ imply that irrespective of correlations in fluctuations within or among loci,

$$\text{Var}\{E[G_i(g)]\} = 2 \sum_{i=1}^{n} \alpha_i^2 p_i q_i. \quad (45)$$

Hence, for independent fluctuations across loci,

$$K = \frac{\sum_{i=1}^{n} \alpha_i^2 p_i q_i}{\sum_{i=1}^{n} \alpha_i^2 p_i q_i + \sum_{i=1}^{n} v_i \alpha_i^2 \left( \frac{1}{1 - p_i} - p_i q_i \right)} . \quad (46)$$

The qualitative implications are most easily seen with exchangeable loci (i.e., $\alpha_i = \alpha$, $c_i = c$, $p_i = \rho$, and $q_i = p$), for which

$$K = \frac{pq(1 - \rho)}{pq(1 - \rho) + v[1 - pq(1 - \rho)]}, \quad (47)$$

and the stability criterion is simply $v > 1$. For fixed $v$, as $\rho \to 1$, $c \to \infty$ and $K \to 0$. Equation (47) implies that $K$ decreases as $\rho$ and $v$ increase and as $p$ departs from 0.5. Hence, for stable equilibria, $K$ is maximized when $\rho = -1$, $v = 1$, and $p = 0.5$. At this point, $K = 0.5$. However, when the within-locus effects are uncorrelated, as the between-locus effects are assumed to be, $K \leq 0.25$.

In general, positive between-locus covariances reduce $K$ because the numerator remains constant but $E\{\text{Var}[G_i(g)|g]\}$ in the denominator increases. The effects of these covariances depend not only on the covariances of substitution effects, i.e. $\text{Cov}(\beta_{i,t} - \gamma_{i,t}, \beta_{j,t} - \gamma_{j,t})$ as described by (28), but also on the covariances between the individual alleles at each locus, i.e., $\text{Cov}(\beta_{i,t}, \beta_{j,t})$, $\text{Cov}(\gamma_{i,t}, \gamma_{j,t})$ and $\text{Cov}(\beta_{i,t}, \gamma_{j,t})$. Nine different expressions for $\text{Cov}\{[G_{i,t}(g)|g], [G_{j,t}(g)|g]\}$ are generated by the three genotypes at each locus. To illustrate the
quantitative effects, we focus on the completely symmetrical case explored by Gillespie and Turelli (1989) and Gimelfarb (1990) with

$$\text{Cov}(\beta_{i,t},\beta_{j,t}) = \text{Cov}(\gamma_{i,t},\gamma_{j,t}) = \text{Cov}(\beta_{j,t},\gamma_{i,t}) = \frac{\rho_B \sqrt{c_i \alpha_i^2 c_j \alpha_j^2}}{2}. \quad (48)$$

As discussed following Eqs. (28), this implies that Cov($\gamma_{i,t}$,$\gamma_{j,t}$) = 0 for all $i \neq j$; so that the allele frequency dynamics are still approximated by (29). In particular, in the symmetrical case with $c_i(1 - \rho_i) = v$ for all $i$, the polymorphic equilibrium is stable whenever $v > 1$. For exchangeable loci satisfying (48), (47) is replaced by

$$K = \frac{pq(1 - \rho)}{pq(1 - \rho) + v[1 - pq(1 - \rho) + (n - 1)\rho_B]}. \quad (49)$$

Thus, for any positive $\rho_B$, $K$ approaches 0 for large numbers of loci (see Gimelfarb 1990 for an analogous result). The implications of these upper bounds on $K$ for the maintenance of variation by G\times E interactions are considered in the Discussion.

**Sex-dependent allelic effects**

A special case of this multiple-environment model approximates allele-frequency dynamics with sex-dependent allelic effects. In this case, the two sexes are the alternative “environments.”

As first argued by Haldane (1924) and demonstrated rigorously for one locus by Nagylaki (1979), the dynamics of weak, sex-dependent viability selection can be approximated by simply averaging the fitnesses of each genotype over the two sexes. This is equivalent to averaging the allele-frequency dynamics as in (26), but now each random variable takes on only two values. This greatly simplifies and constrains the expressions for the coefficients of variation and the correlations of substitution effects across loci. For instance, if $\alpha_{f,i}$ ($\alpha_{m,i}$) denotes the effect of a substitution at locus $i$ on females (males), we have
The condition \( v_i > 1 \) requires that \( \alpha_{f,i} \) and \( \alpha_{m,i} \) have different signs. Thus, if we use the convention that each \( B_i \) denotes the allele that increases the trait value in females, the polymorphism condition \( v_i > 1 \) implies that each \( B_i \) must decrease the trait in males. By considering the symmetrical model with \( \theta = 0 \), it is easy to see, however, that condition (50) cannot suffice to maintain polymorphism. The multilocus recursions for the allele frequencies depend separately on the fitnesses assigned to each genotype in males and females. When \( \theta = 0 \), our symmetrical selection model implies that altering the signs of all of the allelic effects in one sex will not change the fitnesses. Hence, for any assignment of allelic effects, identical dynamics must emerge if all of the signs of allelic effects in one sex are reversed. If the initial assignment of effects satisfies \( v_i > 1 \) for all \( i \), by reversing the signs of effects in one sex, we get identical dynamics but the new values of \( v_i \) are the reciprocals of the old.

The additional constraint required for stable polymorphism involves the correlations in the fluctuating effects across loci. Our convention of labeling the alleles so that \( B_i \) increases the trait values in females implies that

\[
\rho_{ij} = 1 \text{ for all } i \neq j \tag{51}
\]

(indeed, a two-valued bivariate random variable can only have correlations \( \pm 1 \)). Thus, constraint (32) implies that a fully polymorphic equilibrium cannot be stable, although sex-dependent selection can readily maintain polymorphism at one locus (Kidwell et al. 1977).

Below we present numerical analyses that support the qualitative conclusion that sex-dependent, additive allelic effects cannot maintain stable polygenic variation. From our sexes-averaged approximation, we expect that at most one locus can remain stably polymorphic under
weak selection. In fact, however, several numerical examples described below indicate that up to
two loci may be stably polymorphic for loose linkage. This shows that our averaging
approximation misses some of the subtleties of sex-dependent selection, while accurately capturing
its inability to maintain variation at many loci. The stable two-locus polymorphisms we find are
reminiscent of Hastings and Hom’s (1989, 1990) results concerning pleiotropic effects on two
characters. A more careful analysis of sex-dependent allelic effects requires distinguishing the
allele frequencies in the two sexes, so that at linkage equilibrium the stability analysis for n loci
involves 2n variables rather than n. This will be discussed elsewhere.

**Temporal variation and G×E**

Finally, we apply the analyses above to generalize the treatment by Gillespie and Turelli (1989)
of temporally fluctuating allelic effects. Our approximation is based on averaging over the
distribution of allelic effects to approximate the stochastic dynamics by a set of deterministic
equations identical to those obtained for G×E with spatial variation. We know that this
approximation can be misleading, because spatial variation generally leads to broader conditions for
the maintenance of polymorphism than does temporal variation. With haploid selection, for
instance, spatial variation as described by the Levene model can maintain a stable polymorphism
(Gliddon and Strobeck 1975), but temporal variation cannot (Dempster 1955). In this case,
averaging leads to the correct approximate polymorphism condition for the spatial model (namely,
the haploid fitnesses must satisfy E(w₁/w₂) > 1 but E(w₁/w₂) – Var(w₁/w₂) < 1); but produces a
qualitatively incorrect conclusion for temporal variation. This extreme discrepancy seems
uncharacteristic, however. For instance, under one-locus diploid selection, averaging again leads to
the correct approximate polymorphism conditions for the Levene model but suggests that the
correct “average” fitness than for the temporal model involves E(w) – Var(w) instead of the correct
approximation, E(w) – (Var(w)/2) (Gillespie 1974). Ultimately, the usefulness of our
approximations depends on their ability to predict the maintenance of variation with biologically
plausible levels of selection and environmental fluctuation. We present numerical results below
suggesting that our approximate polymorphism conditions are surprisingly accurate. Our
deterministic analysis does not address the fluctuations of allele frequencies inherent in stable
polymorphisms maintained by temporal fluctuations. This is explored numerically below.

As with spatial variation, under particular symmetry assumptions concerning the interlocus
correlations in fluctuating allelic effects (see 28 and 29), the deterministic approximation is
precisely equivalent to the pleiotropy model analyzed above. As with spatial variation, the critical
parameter governing the stability of polymorphism at each locus is just \( v_i \), the squared coefficient of
variation of the substitution effect at that locus. Because we obtain identical approximations for
temporal and spatial variation, we discuss the analytical approximations only briefly.

The assumptions of this model are the same as with spatial variation, except that the allelic
effect parameters, \( \beta_{i,t} \) and \( \gamma_{i,t} \), vary across generations. Note that (25) allows for arbitrary
correlation between the fluctuating effects of the two alleles at a locus. Within-locus correlations of
\( \beta_{i,t} \) and \( \gamma_{i,t} \) do not explicitly affect the dynamics, because selection depends only on \( \beta_{i,t} - \gamma_{i,t} \).
However, as discussed in the context of spatial variation, intra-locus correlations can significantly
affect the properties of the genetic variation maintained, depending on the time-scale of parameter
variation. As before, the basic recursion is

\[
\Delta p_{i,t} = -\frac{S p_i q_i}{2} \left( (p_{i,t} - q_{i,t})(\beta_{i,t} - \gamma_{i,t})^2 + 2(\beta_{i,t} - \gamma_{i,t})(\overline{z_{i,t}} - \theta) \right) + o(S). \tag{52}
\]

A central assumption of our analysis is that the time-scale of allele-frequency change is slower
than the time-scale of the environmental fluctuations. This allows us to: (i) average the random
fluctuations over time, and (ii) approximate the dynamics of the discrete-generation stochastic
model (52) by a system of deterministic differential equations. These approximations are
consistent with the weak-selection diffusion limit of Gillespie and Turelli (1989). Taking the
expectation of the right hand side of (52) over the fluctuations in allelic effects, ignoring the higher-
order terms and going to the continuous-time limit, we obtain the time-averaged, weak-selection
approximation (26) used above to discuss spatial variation with complete mixing. We have not made any explicit assumptions about the temporal correlations of the fluctuating parameters. However, our analysis implicitly assumes that autocorrelations decay faster than the time-scale of allele frequency change (1/S).

The approximate polymorphism conditions are precisely those obtained for the spatial model considered above. Again, the central parameters governing the stability of polymorphisms are the $v_i$, which describe the squared coefficient of variation of substitution effects at individual loci (see 25), and $\rho_{ij}$, which describe the correlations between substitution effects at different loci (see 28a). In particular, when $\rho_{ij} = 0$, we expect that loci satisfying $v_i > 1$ will tend to remain polymorphic if the expected population mean is close enough to the optimum. Loci with $v_i < 1$ will generally not be stably polymorphic, and they will fix for alleles that produce an expected population mean very near $\theta$. As before, we predict that no stable multilocus polymorphisms can be maintained for loci with $\rho_{ij} \geq 1/2$.

One important difference between the spatial and temporal models concerns the interpretation of the consistency index, K, defined by (44), and its relationship to empirical observations. The key point, as made by Gillespie and Turelli (1989, 1990), is that the temporal variation responsible for maintaining variation need not be observable over a few generations. For instance, even though the “true” value of K, obtained by averaging over all of the environments responsible for maintaining variation, may be quite small; the value observed in any one generation is one, since allelic effects are assumed to be fixed within any one generation. With high levels of positive autocorrelation for allelic effects, K would remain high even when averages are taken over several generations. Thus, temporal G×E may maintain high levels of genetic variation with consistent differences among genotypes over the time scale of reasonable experimental analyses. This point is elaborated below.

**NUMERICAL ANALYSES**

**Pleiotropic Balancing Selection**

The number of parameters in this model make it impractical to explore equilibria and dynamics
systematically across the parameter space. However, the qualitative features of alternative equilibria and dynamics are illustrated by the following numerical examples. In both examples, we assume for simplicity that \( p_i = 1/2 \) at all loci. Loci with extreme values of \( p_i \) are less likely to be polymorphic because of the constraints associated with the feasibility conditions (19) and the increased influence of genetic drift. We concentrate on observable quantities such as mean fitness, deviation of the trait mean from the optimum, and genetic variance.

**Example 1—Alternative equilibria:** To illustrate the implications of the stability and feasibility conditions, we first consider an example in which the \( \alpha_i \) and \( v_i \) at 20 loci were drawn independently from gamma distributions (Table 2), and the optimum is \( \theta = 0 \). Because of this symmetry, the equilibria come in pairs, the elements of which have \( \Delta \) of opposite sign, produced by replacing each \( p_i \) by \( 1 - p_i \). Appendix C describes the procedure for finding the alternative stable equilibria. Note that since all of the equilibria discussed have some monomorphic loci, the polymorphic loci must produce a mean near an optimum different from 0, which cannot be achieved by multilocus heterozygotes or by any combination of homozygotes. This “effective optimum,” denoted \( \theta_{\text{eff}} \), is

\[
\theta_{\text{eff}} = \theta - \sum_{i \in \Omega_1} \alpha_i + \sum_{i \in \Omega_0} \alpha_i;
\]

its values are given in Table 2.

For the parameter values given in Table 2, there are seven pairs of distinct stable equilibria (or, more accurately, seven pairs of allele frequencies that satisfy the constraints for stable equilibria given by our approximations); only the stable allele frequencies that produce negative \( \Delta \) are shown. All of the equilibria share similar properties: mean fitnesses are within 0.55S of each other, and the deviation from the optimum is \( |\Delta| < 0.373 \) (relative to a mean allelic effect of \( \bar{\alpha} = 1 \) and a range of genotypic values \( |G| < 21.07 \)). Barring the most extreme pair of equilibria (presented in the first column of Table 2), mean fitnesses are within 0.0051S of each other, and the deviation from the
optimum is $|\Delta| < 0.021$. The main differences among the equilibria are in the number of polymorphic loci, and in the combinations of fixed loci. As expected from the stability conditions for fixation equilibria (21), the polymorphic loci that differ among equilibria tend to be those of small effect; and the different combinations of polymorphic and monomorphic loci all bring the population mean very close to the optimum. This explains the similarity in overall fitness properties of the different equilibria. Given that selection is simply tending to climb towards local fitness optima, it is not clear whether equilibria with higher mean fitness will tend to be reached preferentially.

We can gain some insight by considering the feasibility conditions for the polymorphic equilibria, (19), and the stability conditions for the fixation equilibria, (21). For definiteness, we assume that $\Delta < 0$ and $\alpha_i > 0$ for all $i$, so that directional selection will tend to increase the $p_i$. As before, we let $\Omega_p$ denote the set of polymorphic loci and $\Omega_0$ the set of loci with $p_i = 0$. With $\hat{p}_i = 1/2$, the feasibility condition (19) requires that for the loci in $\Omega_p$ to avoid fixation at $p_i = 1$,

$$|\Delta| < \frac{\alpha_i(v_i - 1)}{2}$$

for all $i \in \Omega_p$. (54)

Hence, for these loci to remain polymorphic, $|\Delta|$ must be less than $\min_{i \in \Omega_p}\{\alpha_i(v_i - 1)/2\}$.

Conversely, if the loci in $\Omega_0$ are to remain stably fixed, (21a) requires

$$|\Delta| < \frac{\alpha_i(1 - v_i)}{2}$$

for all $i \in \Omega_0$. (55)

With multiple loci contributing to the character, (54) and (55) insure a very close approach to the optimum. Because the deviation from the optimum is small, allele frequencies at polymorphic loci with significant effects are close to $\hat{p}_i$. For small $\Delta$, the allele frequencies should be near $\frac{1}{2}\left(\frac{1}{1 - v_i}\right) + \hat{p}_i\left(\frac{v_i}{v_i - 1}\right)$, which is a compromise between the unstable equilibrium under stabilizing selection (first term) and the stable equilibrium under balancing selection (second term). For $\hat{p}_i$ near 0.5, the
genetic variance will be approximately \( \frac{1}{2} \sum \alpha_i^2 \), where the sum is over those loci for which \( v_i > 1 \), and which are hence polymorphic at \( \Delta = 0 \). For example, the model of Table 2 gives a genetic variance that varies across equilibria from 41.2927 to 43.6166; the value when all loci with \( v_i > 1 \) are polymorphic with \( p_i = 0.5 \) is 43.6166. If \( \Delta \) deviates slightly from zero, then loci with small effects fix; however, such loci have little effect on the genetic variance.

In general, the mean relative fitness of the population is less than one because of balancing selection at the individual loci, contributing an amount denoted \( L_B \) to the genetic load, and stabilizing selection. The stabilizing selection component of the load can be partitioned into the portion attributable to departures of the population mean from the optimum, denoted \( L_\Delta \), and variance in the population around the population mean, denoted \( L_V \). In our weak-selection limit, the contributions to the load are additive, i.e.

\[
L = 1 - \bar{W} = L_V + L_\Delta + L_B, \tag{56a}
\]

\[
L_V = \frac{SV_A}{2} = S \sum_{i \in \Omega_p} \alpha_i^2 p_i q_i, \tag{56b}
\]

\[
L_\Delta = \frac{SA^2}{2}, \tag{56c}
\]

\[
L_B = \sum_{i=1}^n s_i (\hat{p}_i q_i^2 + \hat{q}_i p_i^2) = \sum_{i=1}^n s_i (\hat{p}_i - p_i)^2 + \sum_{i=1}^n s_i \hat{p}_i \hat{q}_i = L_{BS} + L_{BB}, \tag{56d}
\]

where \( L_{BS} \) in (56d) denotes the segregation load from balancing selection attributable to allele frequencies being perturbed by stabilizing selection from their balancing-selection equilibria, and \( L_{BB} \) denotes the equilibrium segregational load under balancing selection alone. From Table 2, we see that \( L_\Delta \), the loss in mean fitness due to \( \Delta \), is much smaller than that due to stabilizing selection \( (L_V) \), which is in turn smaller than \( L_B \), the segregational load.
This numerical procedure was repeated, with 100 random choices of the set of allelic effects and strengths of balancing selection \( \{ \alpha_i, v_i \} \) at 20 loci. In all but one case, the results were similar to those shown in Table 2. (In the one exceptional case, the largest allelic effect was much greater than the rest: \( \alpha_1 = 17.8 \), compared with a maximum of 1.78 among the remainder. Thus, a single polymorphism was maintained by overdominance at this locus, with the remaining loci fixed for ‘1’ alleles.) In the remaining discussion, we discard this outlier.

In the other 99 cases, multiple polymorphisms were maintained; on average, 6.8 loci were polymorphic (with standard deviation, SD, 2.3). In 12% of cases, one of these polymorphic loci had \( v_i < 1 \) as allowed by our stability condition. Conversely, 40% of the monomorphic loci had \( v_i < 1 \); these loci had small allelic effects relative to the deviation from the optimum, so that \( \alpha_i(v_i - 1) < 2|\Delta| \). Typically, many alternative equilibria were stable for any given set of \( \{ \alpha_i, v_i \} \): on average, 17.7, with a range from 2 to 178. However, these equilibria had very similar properties. This is because the equilibria differ in whether loci with small effects (namely, \( \alpha_i(v_i - 1) < 2|\Delta| \)) are fixed for 0 or 1. Every allowable set of these loci leads to almost the same (small) deviation from the optimum, and this set contributes very little to the overall genetic variance.

Over our replicates, the mean deviates from the optimum by an average \( \Delta = 0.17 \) (SD 0.28). This can be compared with a mean allelic effect \( \bar{\alpha} = 1 \), and with an average genetic variance of 31.1 (SD 39.9). The loss of mean fitness caused by this deviation is negligible (mean 0.06S, SD 0.17S) compared with the genetic load due to variation around the optimum (mean 15.5S, SD 20.1S) and due to balancing selection (mean 59.1S, SD 73.6S). In the great majority of cases, most of the genetic load is due to the perturbation of loci away from their equilibrium under balancing selection.

**Example 2—Response to changes in selection:** Next we consider the consequences of varying the intensity of stabilizing selection and the position of the optimum. We explore how these alter the amount of variation maintained and the portions of the genetic load attributable to: departures of the mean phenotype from the optimal phenotype (as described by \( L_\Delta \), 56c), genetic variation about the mean (\( L_V \), 56b), and loss of fitness under balancing selection caused by stabilizing selection perturbing allele frequencies away from their balancing selection equilibria.
In general, we expect that a moderate number of loci under balancing selection might affect a specific trait (10-100 with \( s_i > 0 \), say). There will be a distribution of strengths of balancing selection, \( s_i \); and for each \( s_i \), a distribution of allelic effects \( \alpha_i \) that may be correlated with the \( s_i \). In Figure 1, we show a bivariate distribution of \((\alpha_i, s_i)\) for 100 loci, where the \( s_i \) were chosen from a gamma distribution with mean 0.01 and coefficient of variation (CV) 1; and for each \( s_i \), \( \alpha_i \) was chosen from a gamma distribution with mean 0.05 + 5\( s_i \) and CV = 1, then made negative with probability 0.5 (i.e., a gamma distribution reflected around 0). There may also be many loci that affect the trait, but are not under balancing selection. These will not be considered because they are expected to be fixed and thus will not affect the properties we discuss. For any given optimum, there may be many stable equilibria, as illustrated in Table 2. We circumvent this by considering equilibria that produce a specific departure from the optimum, \( \Delta \). Although alternative equilibria may exist even for fixed \( \Delta \) (i.e., monomorphic loci may fix at either 0 or 1), the statistics we discuss have unique values because they depend only on polymorphic loci.

Suppose the set of fixed loci is such that the natural resting point of the system coincides with the optimum, i.e. \( \Delta_f = 0 \) (see 23b). In this case, the conditions for feasible and stable polymorphism are just \( v_i > 1 \) or \( s_i > S\alpha_i^2 \); that is, polymorphic loci must have \((\alpha_i, s_i)\) that lie above the parabola in the top panel of Figure 1. Because the mean coincides with the optimum and \( \hat{p}_i = 1/2 \) at all of the loci, the equilibrium allele frequency at each locus is 1/2, and the genetic variance is \( V_A = \frac{1}{2} \sum_{i \in \Omega_p} \alpha_i^2 \).

Figure 2A shows the genetic variance, \( V_A \), as a function of the strength of stabilizing selection: it decreases inversely with \( S \). These calculations assume that \( \Delta = 0 \) as in Figure 1A. Figure 2B shows \( L_V \), the load due to variation around the optimum, as a function of \( S \). Initially, \( L_V \) increases linearly. However, as polymorphic loci start to fix, \( L_V \) decreases and remains almost constant for a wide range of \( S \). It is not clear how general this pattern is, since it depends on the joint distribution of \((\alpha_i, s_i)\).

Now, consider the short-term response to a decrease in the optimum. There will be an immediate increase in the “natural” deviation, to \( \Delta_f > 0 \). Polymorphic allele frequencies will adjust rapidly, and some loci will fix. Overall, the new deviation from the optimum will be \( \Delta_f^*/(1 + 2C^*) \).
(see 23), which may be very much smaller than Δf. Note that the natural resting point will shift from Δf to Δf* because some initially polymorphic loci have fixed, which also decreases C* from its initial value, C. In this new selection regime, the loci depicted in Figure 1A are scattered over seven stability regimes as shown in Figure 1B. Reading from left to right, we see: i) loci that could fix at 0 or 1 under the old and new positions of the optimum; ii) loci with αi < 0 that were originally fixed for 0 or 1 are now forced to fix for p_i = 0, increasing the trait value; iii) loci that were polymorphic are now forced to fix for p_i = 0; iv) loci that were polymorphic, and remain so; v) loci that were polymorphic with αi > 0 are forced to fix for p_i = 1; vi) loci that were originally fixed for 0 or 1 are now forced to fix for p_i = 1; and finally, vii) loci that were fixed for 0 or 1 and remain so.

Figure 3 shows the short-term deviation from the optimum, Δ, as a function of Δf, the difference between the natural resting point and the optimum. Figure 3A shows the results on the original scale, Figure 3B presents the same results as a log-log plot. In these calculations, we assume that the polymorphic loci are those found assuming Δ = 0, as in Figure 1A. The question addressed is how those specific polymorphic loci are expected to respond to changes in the optimum. As the optimum changes, all of the polymorphic allele frequencies adjust to produce a new value Δ, as described by Eq. 23a. As Δf increases, there is remarkably little change in Δ, provided that Δf does not approach the maximum that can be compensated by shifts in polymorphic allele frequencies (corresponding to Δf = 2.38 in this example, see Figure 3A). For small deviations, Δ is only ~ 0.01Δf^{1.85} (as determined by a least-squares fit of the log-log results in Figure 3B). The main effect of a small perturbation, Δf, is to reduce the genetic variance (Figure 4), as polymorphic allele frequencies shift from 0.5 and eventually fix. The efficiency with which selection optimizes the mean of a polygenic trait, despite underlying constraints, is seen in other models of this sort (Barton 1986, 1999).

Using the same procedure as described for Figure 3, Figure 5 shows how three components of load, L_Δ, L_V and L_BS, and the total load, L (all scaled by the intensity of stabilizing selection S), increase as the mean is perturbed from the optimum. We ignore the contribution L_BB to the total load, described in (56d), because this does not vary with changes in the polymorphic allele
frequencies. As expected from the close adjustment of the trait mean to the new optimum (Figure 3), the load due to deviations of the mean, $L_{\Delta}$, is negligible until most variation is lost. The load due to variation around the optimum, $L_V$, decreases as variation is lost, but this is almost exactly compensated by the load due to perturbing the allele frequencies away from their equilibria under balancing selection, $L_{BS}$. The overall load, $L$, barely changes as the mean is perturbed slightly.

Long-term responses of the mean and the additive variance to changes in the intensity of selection or the position of the optimum are complex and depend on a large number of parameters describing the underlying genetics and the history of population size changes. However, the qualitative behavior is roughly as follows.

If the strength of stabilizing selection increases, genetic variation will be rapidly lost, as some polymorphic loci become unstable (as illustrated in Figure 4); the time scale for this loss is set by $S\alpha_i^2$. If stabilizing selection weakens again, then polymorphism will be recovered much more slowly, since the particular alleles under balancing selection must arise by mutation. Our assumption here is that the alleles would be lost for many plausible population sizes rather than being retained at mutation-selection equilibrium. This follows because the mutation rates relevant to these particular alleles under balancing selection would be on the order of the per-nucleotide mutation rate, say $10^{-8}$ or smaller. The chance that one such mutation at locus $i$ will be fixed is twice the selection coefficient, $s_i - S\alpha_i^2$; hence, the time scale for recovery in a population of effective size $N$ is set by $2N\mu_i(s_i - S\alpha_i^2)$. Because $\mu_i$ is likely to be of the order of the per-nucleotide mutation rate, recovery of polymorphism could be very slow, unless the population is large enough to retain the previously polymorphic alleles through mutation-selection balance. For example, with an average $s_i = 0.01$ as assumed in the example of Figure 1, $N = 10^6$ and $\mu = 10^{-8}$, the rate of recovery of polymorphism at each locus individually is $2 \times 10^{-4}$. To make this argument in a little more detail, suppose that a population with loci as illustrated in Figure 1 is initially under stabilizing selection with $S = 1$. Balancing selection then maintains genetic variance $V_A = 0.072$, due to the pleiotropic effects of 36 polymorphic loci. If this variation is lost as a result of strong stabilizing selection, which then relaxes to its original intensity, the rate of increase in the number of
polymorphic loci is \(2N \sum_i \mu_i (s_i - S \alpha_i^2) = 0.008\); thus, it will take \(\sim 4500\) generations to return to the original 36 polymorphic loci.

Similarly, if the optimum changes, different responses occur on different time scales. After the first phase of response to a new optimum, in which allele frequencies adjust to approach the new optimum (Figure 3) and some polymorphic loci fix, there will be a loss of genetic variation (Figure 4). We now expect a second phase, in which the very many loci that may affect the trait but are not under balancing selection accumulate mutations, so as to bring the mean back towards the optimum. After this phase, we expect \(\Delta f = \Delta = 0\) to a very close approximation; and so the stability regimes return essentially to those depicted in Figure 1A. A third, and much slower phase, now occurs, in which variation at loci under balancing selection and lying above the parabola \(s_i = S \alpha_i^2\), is recovered.

**Sex-dependent allelic effects**

To test the accuracy of our weak-selection approximations, multilocus diploid calculations were performed using the full multilocus, diploid gamete-frequency recursions with selection, random mating and recombination. Our goal was to test the prediction that sex-dependent allelic effects cannot maintain stable multilocus polymorphisms, at least with weak selection. Given that stable two-locus polymorphisms can be maintained under strong selection for sex-independent effects (Gimelfarb 1996, Bürger and Gimelfarb 1999), we performed comparable sets of simulations with sex-dependent and sex-independent allelic effects. We started a set of simulations by choosing independent random values for the allelic effects assigned to males and females. The effects were chosen using gamma-distributed, pseudo-random numbers, as described below. For each set of allelic effects and selection parameters, we generally used 10 randomly chosen initial conditions. We started at linkage equilibrium with each allele frequency chosen from a uniform distribution over the allowable allele frequencies (explained below). Iterations were stopped when the sum of absolute changes of gamete frequencies fell below a specified threshold. For all results reported here, with equilibrium allele frequencies restricted to \((0.01, 0.99)\), a threshold of \(10^{-9}\) or \(10^{-10}\).
proved adequate (the smaller value was used with weaker selection). For all cases in which two or more loci remained polymorphic, an output file was generated giving the parameter values and initial gamete frequencies. This allowed us to test the adequacy of our stopping criterion by lowering the threshold value and determining whether the same approximate equilibria were obtained. It also allowed us to reuse specific allelic effects and initial frequencies with different selection intensities, as discussed below.

Each set of simulations involved specifying: the number of loci; the number of replicate sets of allelic effects, the number of initial conditions for each set of allelic effects, the mean and CV of the allelic-effect parameters, $\beta_{i,f}$, $\beta_{i,m}$, $\gamma_{i,f}$, and $\gamma_{i,m}$ (for simplicity we assumed the same mean and CV for each); the intensity of stabilizing selection, $S$; the optimal trait value, $\theta$; the recombination rates between adjacent loci (assuming no interference); a threshold for minimum acceptable polymorphic allele frequencies (to avoid artifacts associated with slow convergence to fixation, we set this threshold at 0.01); and a threshold for the sum of the absolute changes in gamete frequencies. For the sex-dependent simulations, four independent pseudo-random, gamma-distributed deviates were chosen for each locus, denoted $g_i$ for $i = 1, ..., 4$; and we set $\beta_{i,f} = g_1$, $\gamma_{i,f} = -g_2$, $\beta_{i,m} = g_3$, and $\gamma_{i,m} = -g_4$. For sex-independent effects, we set $\beta_{i,f} = \beta_{i,m} = g_1$ and $\gamma_{i,f} = \gamma_{i,m} = -g_2$. To reduce the dimensionality of the parameter space and facilitate investigating many sets of allelic effects, we used 5 unlinked loci, chose 10 sets of random initial allele frequencies for each set of allelic effects, assumed that each $g_i$ has mean 1, and set $\theta = 0$ for all calculations. Our assignment of sex-specific allelic effects implies that the effects of substitutions have the same sign in both sexes. However, as explained above, with $\theta = 0$, identical results are obtained by specifying $\beta_{i,f} = g_1$, $\gamma_{i,f} = -g_2$, $\beta_{i,m} = -g_3$, and $\gamma_{i,m} = g_4$, so that the effects of substitutions in the two sexes have different signs.

Several thousand sets of parameters were explored, all with unlinked loci. These led to four simple generalizations: (i) there were no stable equilibria involving three or more polymorphic loci, (ii) sex-dependent allelic effects facilitate stable two-locus polymorphisms, (iii) for both sex-dependent and sex-independent effects, choosing the effects from a distribution with larger CV facilitates stable two-locus polymorphisms, and (iv) for sex-dependent effects, unlike sex-
independent allelic effects, stable two-locus polymorphisms can be found even with extremely weak selection. We briefly describe some results supporting these generalizations.

Over thousands of sets of allelic effects, each run with 10 sets of initial allele frequencies, no stable equilibria were found with more than two polymorphic loci. This is consistent with the numerical results of Bürger and Gimelfarb (1999) for sex-independent effects (see their Table 1). Although stable three-locus polymorphisms can be obtained even with sex-independent effects when recombination is weak relative to selection (Gimelfarb 1996), such polymorphisms seem unlikely with loose linkage and weak selection.

Table 3 presents numerical results that illustrate the effects of sex-dependence, interlocus variation in allelic effects, and the intensity of selection. The fact that larger CV for allelic effects produces more two-locus polymorphisms is expected from the analytical work of Nagylaki (1989) and Bürger and Gimelfarb (1999), showing that strong selection and significant asymmetries of effects across loci are required to maintain stable two-locus polymorphisms with stabilizing selection on an additive trait. The effect of asymmetries and the effect of sex-dependence is illustrated with $S = 0.2$ in Table 3 by comparing results from $CV = 0.5$ versus $CV = 1$ for sex-dependent versus sex-independent allelic effects. In each case, larger CV produces significantly more sets of allelic effects leading to two-locus polymorphisms (under Fisher’s exact test, $P < 10^{-9}$ for sex-dependence and $P < 10^{-4}$ for sex-independence). Similarly, for each CV, sex-dependence facilitates two-locus polymorphisms ($P < 0.01$ for $CV = 0.05$, $P < 10^{-9}$ for $CV = 1$).

The qualitative difference between sex-dependent and sex-independent allelic effects with respect to maintaining stable two-locus polymorphisms under weak selection can be seen by concentrating on initial conditions and sets of allelic effects that produce stable two-locus polymorphisms with $S = 0.2$. Using 30 such sets of allelic effects and initial conditions, we set $S = 0.02$ and iterated to a new equilibrium. The results are shown in the third row of Table 3. For sex-independent selection, of the 30 sets that led to stable two-locus polymorphism with $S = 0.2$, only one produced a stable two-locus polymorphism with $S = 0.02$. (As expected, that example had one polymorphic locus with very large effects, $\beta_1 = 5.19973$ and $\gamma_1 = -8.78685$, and one with much
smaller effects, $\beta_2 = 0.319015$ and $\gamma_2 = -0.144994$.) When these same allelic effects and initial conditions were used with $S = 0.002$, only the locus of large effect remained polymorphic. In contrast, for sex-dependent effects, 17 of the 30 sets of allelic effects and initial conditions also produced a stable two-locus polymorphism with $S = 0.02$ (even though only a single initial frequency was used). Moreover, for all 17, a very similar two-locus polymorphism was also reached with $S = 0.002$ and $S = 0.0002$. As noted above, these stable two-locus polymorphisms obtained with sex-dependent allelic effects are analogous those found by Hastings and Hom (1989, 1990) when alleles pleiotropically affect two characters under stabilizing selection. Although sex-dependent allelic effects do produce stable two-locus polymorphisms, our results suggest that they cannot maintain stable polygenic variation, even with strong selection.

**Temporal variation and G×E**

As with sex-dependent allelic effects, we tested our polymorphism conditions, based on weak-selection, deterministic approximations, by performing exact multilocus iterations with temporally varying allelic effects. The joint distribution of the fluctuating allelic effects depends on many parameters. As noted in our analytical approximations, intralocus correlations between allelic effects do not affect the polymorphism conditions, but interlocus correlations between substitutions effects dramatically affect the levels of variation required to maintain polymorphism (see 33). To test our predictions concerning variances and interlocus correlations of substitution effects, we used symmetry assumptions to simplify the model description and our predictions. For all of our simulations, we assumed that $\theta = 0$, $E(\beta_i) = \alpha/2$, $E(\gamma_i) = -\alpha/2$, $\text{Var}(\beta_i) = \text{Var}(\gamma_i) = \nu \alpha^2$, $\text{Cov}(\beta_i, \gamma_i) = 0$, $\text{Cov}(\gamma_i, \beta_j) = \text{Cov}(\beta_i, \gamma_j) = 0$, $\text{Cov}(\beta_i, \beta_j) = \text{Cov}(\gamma_i, \gamma_j)$, and no autocorrelation in the effects across generations. The allelic effects were chosen as multivariate pseudo-random, Gaussian deviates with the appropriate mean and covariance structure, which depends on only three parameters: $\alpha$, the mean effect of a substitution at each locus; $\nu$, the CV of substitution effects (see 25); and $\rho$, the interlocus correlation in substitution effects (see 28a). Our calculations assumed six unlinked loci. With these symmetry assumptions, our approximate polymorphism criterion reduces to (33),
namely \( \rho < 1/2 \) and \( v > 1/(1 - 2\rho) \). This prediction is independent of \( \alpha \) and \( S \).

Even with these symmetry assumptions, no attempt will be made to present simulations spanning the entire parameter space. Instead, we provide some illustrative examples, using biologically plausible parameter values for selection intensity and average allelic effects, that focus on our predicted critical values for \( v \) and \( \rho \). Figure 6 shows the effects of varying either \( v \) or \( \rho \), holding all other parameters fixed. These simulations assume \( \alpha = 0.7 \) and \( S = 0.05 \) (corresponding to the canonical values used in Turelli (1984) and many other papers to explore polygenic mutation-selection balance). To summarize the asymptotic behavior of the stochastically fluctuating allele frequencies, we first iterated the recursions for 500,000 generations starting with random initial allele frequencies and global linkage equilibrium. We then ran the recursions for an additional 500,000 generations, during which we calculated the mean and standard deviation of allele frequencies at each of the six loci. We report in Figure 6 the means and standard deviations (SDs) of the two loci whose average allele frequencies depart least and most from 0.5. The former is called the “most polymorphic locus,” the latter, the “least polymorphic.” To standardize the results, we report the average frequency of the less common allele.

Figure 6A shows the consequences of varying \( v \) with \( \rho = 0.17 \). According to (33), all loci should remain stably polymorphic if \( v > 1.515 \) and all loci should become monomorphic if \( v < 1.515 \). The critical value for \( v \) is indicated by the dashed line in Figure 6A. As predicted, for \( v \leq 1.4 \), all loci become monomorphic, with mean = SD = 0. Conversely, for \( v \geq 1.6 \), all six loci remain polymorphic. For \( v = 1.5 \), very near the predicted threshold value, we see that at least one locus has become monomorphic; but at least one remains polymorphic. As expected given the high level of stochastic fluctuations, the polymorphic loci always show considerable fluctuations in allele frequencies. To put the observed SDs in perspective, note that if the allele frequencies fluctuated between 1 and 0 in an extremely rapid manner so that the allele frequency is essentially 1 with probability \( p \) and 0 with probability \( 1 - p \), we would observe an average allele frequency of \( p \) and SD near the maximum value \( \sqrt{p(1-p)} \). When \( v = 1.5 \), the SD of the most polymorphic locus is about 86% of this maximum value. In contrast, for \( v = 1.6 \), the SD for the most polymorphic locus
is 0.78 of the maximum; and this ratio declines somewhat as \( v \) increases, despite the increasing intensity of the stochastic fluctuations.

Figure 6B considers varying \( \rho \) with \( v = 1.5 \). Prediction (33) implies that all loci should remain stably polymorphic if \( \rho < 0.167 \) (see the dashed line in Figure 6B), and all loci should become monomorphic if \( \rho > 0.167 \). As predicted, all loci become monomorphic when \( \rho \approx 0.18 \), and all loci remain polymorphic when \( \rho \leq 0.16 \). With \( \rho = 0.17 \), very near the predicted threshold, we see that at least one locus has become monomorphic; but at least one remains polymorphic.

As expected from way the allele frequency dynamics in (29) depend on \( \alpha^2 \) and \( S \), varying each of these parameters has a similar effect on polymorphisms. For instance, if we set \( v = 1.6 \), \( \rho = 0.17 \) and \( \alpha = 0.07 \), the mean allele frequency at the most polymorphic locus remains very close to 0.5 for \( S = 0.01, 0.05 \) and 0.25, but the SD increases from 0.32 with \( S = 0.01 \) to 0.45 with \( S = 0.25 \). This reflects the fact that with stronger selection, allele frequencies respond faster to changing selection forces produced by varying allelic effects. Similarly, if we set \( v = 1.6 \), \( \rho = 0.17 \), \( S = 0.05 \), and vary \( \alpha^2 \) from 0.09 to 2.56 (roughly a factor of 25, as with \( S \) above), again the mean stays very near 0.5 while the SD increases from 0.30 to 0.45.

Overall, our simulations suggest that our approximations provide useful guidelines concerning the maintenance of polygenic variation through fluctuating allelic effects. As shown in Figure 6, the simulations switch from stable multilocus polymorphisms to complete fixation near the predicted threshold values for \( v \) and \( \rho \). As the parameters near the threshold values, interlocus differences become greater and allele frequency fluctuations become more extreme.

**DISCUSSION**

There are two basic classes of models to explain the maintenance of stable polygenic variation: those that rely on mutation to maintain variation that would otherwise be largely eliminated by selection and those in which selection itself maintains variation. For a broad range of biologically reasonable parameter values, mutation-selection balance models imply that the variation maintained will generally be attributable to rare alleles at many loci (Turelli 1984). This remains true even for
the most recent models of mutation-selection balance that consider both direct and pleiotropic selection (e.g., Zhang and Hill 2002). In contrast to this theoretical expectation, molecular studies have found that variants at intermediate frequency contribute significantly to polygenic variation in natural populations (e.g., Mackay and Langley 1990, Long et al. 2000). This provides one of the primary empirical motivations for our study of alternative models for balancing selection, because such models generally lead to intermediate allele frequencies at the polymorphic loci. We will discuss in turn the results from each of our models, then make some general comments comparing these mechanisms for the maintenance of variation to others.

Pleiotropic balancing selection

Our analysis has revealed straightforward conditions under which balancing selection can maintain variation in a quantitative trait, despite stabilizing selection which reduces this variation. At each locus, polymorphism can be maintained provided that two conditions are met. First, balancing selection must be stronger than stabilizing selection ($v_i = s_i/(\alpha_i^2 S) > 1$); at most one polymorphic locus can violate this condition. Second, the net balancing selection must be stronger than the directional selection that arises when the trait mean deviates from its optimum. At equilibrium, the trait mean closely matches the optimum. The genetic variance is maintained by a set $\Omega_p$ of loci that are highly polymorphic, and is approximately equal to half the sum of squared allelic effects at these loci. At each polymorphic locus, the allele frequency is a compromise between the equilibrium favored by balancing selection and a slight shift that brings the overall trait mean close to the optimum.

How likely is it that genetic variation is maintained as a pleiotropic side-effect of balancing selection? We have little idea of how many balanced polymorphisms there might be, but it is plausible that variation is maintained by selection at a substantial fraction of genes (at some thousands of loci in multicellular eukaryotes, say). There is then no difficulty in accounting for high levels of genetic variance in any particular trait. However, this explanation does face two difficulties in explaining variation in most quantitative traits. First, balancing selection must be
strong enough in total to counterbalance the stabilizing selection acting on all traits. Roughly speaking, we expect that the total strength of balancing selection, $\Sigma_i s_i$, should be greater than the net load due to variation of quantitative traits around their optima. Unfortunately, we do not know the magnitude of either of these quantities. If balancing selection is due to overdominance, then $\Sigma_i s_i$ is proportional to the segregation load, which could in principle be measured as a component of inbreeding depression. However, if frequency-dependent selection predominates, it is hard to relate $\Sigma_i s_i$ to observable quantities. The net genetic load due to deviation of traits under stabilizing selection from their optima is still harder to estimate; indeed, it is hard even to define the number of traits under stabilizing selection (though see Orr 2000). Despite these uncertainties, however, it is at least possible that there is sufficient balancing selection to counterbalance stabilizing selection on very many traits. For example, selection coefficients of 5% on 2000 loci would give $\Sigma_i s_i = 100$. This could counterbalance genetic loads of a few percent due to stabilizing selection on some thousands of independent traits.

More naively, we can ask how much balancing selection is required to maintain variation at a particular locus that affects a single trait under stabilizing selection. If we assume a heritability near 0.5 and scale genetic and environmental variance to 1, we can ask how much balancing selection is needed to maintain a polymorphism contributing about 10% of the total genetic variance. From (1), we have $\alpha^2_i$ near 0.2. Hence, if stabilizing selection is on the order of $S = 0.05$, we require balancing selection on the order of $s_i = 0.01$. If stabilizing selection is often much weaker than assumed (Kingsolver et al. 2001), the required intensity of balancing selection decreases.

A second constraint is that episodes of directional selection on quantitative traits must not eliminate variation at polymorphic loci. In our analysis, we assumed stabilizing selection towards a constant optimum. In reality, optima may vary, and so allele frequencies at the underlying loci will fluctuate. If directional selection is sufficiently strong for long enough, alleles will fix, and variation will be regenerated only when lost alleles are recovered. Clearly, if balancing selection is sufficiently strong, and if traits depend on very many loci, then the mean can be adjusted by small changes at each locus, avoiding fixations. Moreover, if selection varies from place to place in a
spatially subdivided population, alleles can be retrieved by migration rather than by mutation. Finally, it may be that balanced polymorphisms are usually transient (as seems to be the case for inversions in Drosophila [Andolfatto et al. 2001] and for human adaptations to malaria [Hamblin et al. 2002]) rather than being maintained for very long times (as for example with incompatibility loci in flowering plants, or the HLA system in vertebrates; Hughes, 1999). This idea is related to the transient maintenance of variation through fluctuating selection on traits themselves, as discussed below.

**Relation with mutation/selection balance:** Combining mutation with stabilizing selection leads to substantial mathematical complications. The polymorphic equilibria are now given by the solution to a system of cubic equations, and there may be multiple stable polymorphic equilibria for a fixed set of polymorphic loci. In contrast, the model analyzed here gives a unique polymorphic equilibrium for any fixed set of polymorphic loci. However, the two cases are similar; indeed, they must be because mutation represents a small perturbation of the model analyzed here and thus will give qualitatively similar results (e.g., Karlin and McGregor 1972). Both stabilizing selection and mutation-selection balance generally have the property that the mean can be adjusted to small changes in the optimum by slight changes in allele frequencies at many loci. In both models, many combinations of fixed or nearly fixed loci can give stable equilibria, all of which produce a population mean very close to the optimum.

Our numerical results suggest that with unequal allelic effects, the properties of different equilibria become more similar to each other than in the case where loci are equivalent. The same may hold for mutation-selection balance. When allelic effects are equal, the variance can become much larger than its minimal value when the mean deviates above the optimum. This is because all the loci near \( p = 0 \) climb in frequency together, until a critical value is approached when some set switch to the alternative equilibrium. Near this critical value there can be a large increase in genetic variance (Barton 1986). However, with varying allelic effects and equilibrium allele frequencies, a single locus approaches the critical value and then fixes, greatly reducing the magnitude of the deviation from the optimum without giving much increase in genetic variance.
Fluctuating allelic effects

Under our models of temporal or spatial fluctuations, a necessary condition for the maintenance of polymorphism at a locus is that $v_i$, the squared coefficient of variation of the effects of a substitution (across the distribution of environments), exceed one. To address the biological plausibility of this condition, we first describe its mathematical implications by specifying distributions for the substitution effects. The range of implications can be illustrated by considering two particular distributions: Gaussian and gamma. In general, $v_i > 1$ implies that the standard deviation of substitution effects exceed the mean. Under a Gaussian distribution, this implies that the sign of substitution effects at this locus must frequently change with environmental conditions. If we assume that the mean effect of a substitution is positive, the probability of a negative effect will be $\Phi(-1/\sqrt{v_i})$, where $\Phi$ denotes the cumulative distribution function of the standard normal distribution. This probability must be at least 0.16 for $v_i > 1$, it is 0.24 for $v_i = 2$, and it approaches 0.5 as $v_i$ increases. Such sign reversals are not necessary, however, because $v_i > 1$ can also be achieved with a gamma distribution, which remains positive. In this case, $v_i > 1$ puts a lower bound on the magnitude of fluctuations of the substitution effects. One way to quantify this is as the ratio of the 75th percentile of the distribution of substitution effects to the 25th percentile (which depends only on $v_i$). This ratio must be at least 4.82 for $v_i > 1$, it is 13.0 for $v_i = 2$, and it approaches infinity rapidly as $v_i$ increases (e.g., it is 100 for $v_i = 4.01$).

Are such dramatic fluctuations in substitution effects plausible? The most relevant data concerning the fluctuating effects of individual loci are the QTL-based G×E studies by Mackay and her collaborators (e.g., Gurganus et al. 1998, Vierra et al. 2000, Dilda and Mackay 2002). These studies estimate the effects of individual QTL, which presumably correspond to one or a small number of closely linked loci, over a range of environmental conditions, such as alternative rearing temperatures, heat shock and starvation, as well as determining sex dependence. It is important to recognize, however, that the genotypes used in these analyses are generally recombinant inbred lines derived from selection experiments or long-held laboratory stocks. Hence, the variation described
may not be representative of variation in natural populations. Nevertheless, these studies
demonstrate that QTL effects are generally sex- or environment-dependent. Scanning the data
tables in these papers (see, for instance, Table 4 of Vieira et al. 2000), examples can be found where
statistically significant marker effects within a sex vary by more than a factor of ten or change sign
depending on the rearing environment. Hence, these data seem broadly compatible with the levels
of variation required to maintain polymorphism in our analysis. However, there is another
important caveat that Mackay and collaborators clearly recognize (e.g., Dilda and Mackay 2002, p.
1671). We do not know whether the environments chosen for these laboratory experiments are
representative of the environmental variation in nature that may be responsible for maintaining
genetic variation. It seems reasonable, however, to assume that the range of conditions in nature
would fluctuate in many more ways than considered in these experiments, with temperature,
crowding and food quality, for instance, all varying simultaneously in time and space.

Analyzing fluctuating allelic effects for individual loci is extremely difficult. A more traditional
quantitative-genetic approach is to consider the “consistency index,” K (see Eq. 44), the ratio of
the variance of mean effects of genotypes to the total genetic variance, which includes mean effects
plus interaction terms related to G×E. As noted above, the polymorphism conditions constrain K to
be quite small, especially when the fluctuations in effects across loci are positively correlated (see
Eqs. 47 and 49). Indeed, 0.5 is an upper bound for K if all fluctuating allelic effects, both within
and across loci, are uncorrelated; but this bound quickly falls to values on the order of 0.1 or less
under more plausible assumptions. Relevant data appear in several experimental studies of G×E
that partition the total genetic variance observed across genotypes and environments into main
effects of genotypes and interaction effects. For instance, Wayne and Mackay (1998) used three
temperatures to study ovariole number and body size in mutation-accumulation lines of Drosophila
melanogaster. Treating temperature and block as the environmental variables (see their Tables 1
and 2), we see that for ovarioles, about 57% of the newly arising variation for genotypes (lines) plus
interactions between genotypes and environments is attributable to mean effects of genotypes. The
comparable figure for body size is 42%. Given that these estimates come from a sample of newly
arising variation, not all of which would be expected to remain stably polymorphic because of G\times E, there is no reason to expect them to satisfy the constraints described above for K. Nevertheless, they demonstrate that mutation provides environment-sensitive variants that could plausibly satisfy the G\times E polymorphism conditions. Similar data are available for life span (Vieira et al. 2000) and bristle number (Gurganus et al. 1998); but in these studies, the genetic variation originates from recombinant inbred lines derived from long-held laboratory stocks. Again, these studies indicate the ubiquity of environment- (and sex-) dependent genetic effects. However, they cannot tell us whether the variation segregating in natural populations satisfies the constraints expected for stable G\times E-maintained polymorphisms. Many other recent studies demonstrate G\times E either at the level of QTLs (e.g., Shook and Johnson 1999) or whole genotypes (Shaw et al. 1995), but none provide data that allow us to estimate the relevant parameters.

**Sex-dependent allelic effects**

We have shown for diallelic loci that sex-dependent additive allelic effects are no more effective at maintaining stable polygenic variation than the classic sex-independent additive model investigated by Wright (1935). (Although sex-dependent effects can maintain variation at two loci whereas sex-independent effects maintain variation at only one, this distinction is negligible in the context of understanding polygenic variation.) In contrast, sexually antagonistic fitness effects can easily maintain single-locus polymorphisms (e.g., Kidwell et al. 1977). This distinction between the propensity of sex-dependent effects to facilitate one-locus polymorphism but inability to maintain polygenic variation is analogous to findings concerning antagonistic pleiotropic effects on life histories (compare Rose 1982 and Curtsinger et al. 1994).

Sex-dependent allelic effects have been extensively documented for several traits in *D. melanogaster* (summarized in Dilda and Mackay 2002). Our analytical and numerical results indicate that such effects *per se* cannot account for the maintenance of polygenic variation for traits under stabilizing selection.
**Comparisons to alternative mechanisms**

We have considered models in which selection alone maintains quantitative variation. Many other models of this type have been proposed. For example, multiple polymorphisms can be maintained by stabilizing selection on an additive trait if allelic effects are sufficiently different, even when selection is weak (Nagylaki 1989). When selection is strong enough that linkage disequilibrium is significant, polymorphism may be further facilitated (Gavrilets and Hastings 1994). However, Bürger and Gimelfarb (1999) used numerical investigations to show that when more than a few loci influence a trait, polymorphism at multiple loci becomes much less likely; moreover, the loci of smallest effect tend to be polymorphic, so that very little genetic variance is maintained. This pattern arises because with multiple loci, the optimum can be closely matched by a homozygous genotype; selection then acts against deviations from this optimal genotype. With multiple traits, it is harder to match the trait mean to the optimum, and so relatively more polymorphism is expected: in Hastings and Hom’s (1989) model, there can be as many polymorphic loci as there are traits under stabilizing selection. A serious criticism of these models is that they apply only to outcrossing diploids, and so cannot account for quantitative variation in haploid or selfing organisms that do not contain heterozygotes. There is surprisingly little known about polymorphism conditions in multilocus haploid models with recombination. However, it is reasonable to conjecture that epistatic selection cannot maintain variation in the absence of dominance interactions. In contrast, provided that balancing selection acts through negative frequency-dependence rather than overdominance, the pleiotropic balancing selection model we analyze is quite generally applicable. Fitness might depend on genotype frequencies through a number of selective mechanisms mediated by quantitative traits (see the theoretical analyses of Bulmer 1974, Slatkin 1979, and Bürger 2002 and the data analyzed by Bolnick et al. 2003). However, it seems simplest to treat variation in some arbitrarily chosen trait as being due to the pleiotropic effects of balanced polymorphisms, without detailing the causes of that balancing selection.

In the models just discussed, selection on the trait remains constant through time and we focus
on stable equilibria. In contrast, Bürger (1999), Waxman and Peck (1999) and Bürger and Gimelfarb (2002) have recently shown that a changing optimum can generate substantially more genetic variance than would be generated in a balance between mutation and static stabilizing selection. Bürger (1999) and Waxman and Peck (1999) assumed a continuum of allelic effects at each locus, and it is unclear how far variation can be inflated with discrete alleles under their selection regimes. Kondrashov and Yampolsky (1999) demonstrate an increased genetic variance under fluctuating selection in a model with discrete alleles. However, at any one time, most of the variance in their model is contributed by a single locus as it sweeps between near-fixation for alternative alleles. This does not seem an adequate explanation of polygenic variation. In the context of our pleiotropy model, adding balancing selection to these models might have rather little effect, because fluctuating selection would tend to eliminate the particular alleles that are required for balanced polymorphism. Bürger and Gimelfarb (2002) consider fluctuating optima under stabilizing selection for moderate numbers of diallelic loci. They demonstrate that considerably more variation can be maintained than expected under mutation-selection balance alone; but their results seem to depend on fairly extreme fluctuations in the position of the optimum relative to the width of the stabilizing selection function (cf. Turelli 1988). If, as Kingsolver et al. (2001) have recently argued, stabilizing selection is typically much weaker than usually assumed, the fluctuating-optimum hypothesis will be less credible.

Epistatic interactions have been widely documented (e.g., Shook and Johnson 1999, Dilda and Mackay 2002) and some numerical work has suggested that epistasis may help maintain polygenic variation (e.g., Gimelfarb 1989). However, recent analytical work by Hermisson et al. (2003) suggests that epistasis is likely to lower rather than raise the amount of variation explained by mutation-selection balance.

**Future directions**

We have shown that pleiotropic balancing selection and temporally or spatially varying allelic effects can maintain stable polygenic variation, but sex-dependent allelic effects cannot. Recent
studies have championed varying selection pressures as a way to explain the maintenance of alleles at intermediate frequencies (e.g., Waxman and Peck 1999, Bürger and Gimelfarb 2002) and pleiotropic effects of deleterious alleles on weakly selected traits (Zhang and Hill 2002) as a way to explain abundant additive variance attributable to rare alleles at many loci. These models and ours present a daunting challenge to experimentalists to estimate the relevant parameters. As with molecular variation at individual loci, the explanation of polygenic variation may well depend on the simultaneous action of many of alternative mechanisms, both across characters and across loci. Mutation-selection balance surely explains some of the variation we observe, but it is generally expected to explain only the persistence of rare alleles (but see Slatkin and Frank 1990). Intermediate allele frequencies might be explained either by some form or balancing selection, as we have discussed, or transient polymorphisms associated with fluctuating selection (or hitchhiking effects from linked sites under directional selection). Studies of the molecular variation at and near individual loci that contribute to polygenic variation may help unravel the relevant evolutionary forces. In particular, elevated levels of molecular variation in regions that contribute to quantitative variation would support the role of persistent balancing selection (Barton and Keightley 2002).
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APPENDIX A: STABILITY CONDITIONS FOR POLYMORPHIC EQUILIBRIA

Here we will establish that the eigenvalues of the stability matrix (13) are real and that necessary and sufficient conditions for them all to be negative are (17) and (18), respectively. Our demonstration rests on the fact that the eigenvalues of a real symmetric matrix are real (Lancaster 1969, p. 75) and some elementary properties of determinants and quadratic forms. First note that \( A \) can be written as

\[
A = -2SBC, \tag{A1}
\]

with \( B \) a diagonal matrix whose \( i \)th diagonal element is \( 2p_iq_i \), the equilibrium heterozygosity at locus \( i \) [denoted \( B = \text{diag}(2p_iq_i) \)], and \( C \) is a symmetric, positive matrix whose elements are

\[
c_{ij} = \alpha_i \alpha_j \left[ 1 + \delta_{ij} \left( \frac{y_i - 1}{2} \right) \right] \text{ for } i, j = 1, ..., n, \tag{A2}
\]

where \( \delta_{ij} \) denotes the Kronecker delta, with \( \delta_{ii} = 1 \) and \( \delta_{ij} = 0 \) for \( i \neq j \). Equation (A1) implies that
the eigenvalues of A are the eigenvalues of BC multiplied by –2S. The remaining argument has four steps. First we show that the eigenvalues of BC are real, then we show that they are all positive—implying that G×E maintains a stable polymorphic equilibrium—if and only if all of the eigenvalues of C are positive. Next, we reduce the problem further by showing that we can set all of the \( \alpha_i = 1 \) without loss of generality. The constraints on the \( v_i \) that lead to stability then follow from properties of quadratic forms.

By definition, the eigenvalues of BC satisfy

\[
\text{det}(BC - \lambda I) = 0, \tag{A3}
\]

where I denotes the \( n \times n \) identity matrix and \( \text{det}(D) \) denotes the determinant of D. Let \( B^{1/2} = \text{diag}(\sqrt{2} sp_{qi}) \) and \( B^{-1/2} = \text{diag}(1/\sqrt{2} sp_{qi}) \). Clearly, \( \text{det}(B^{1/2}) = 1/\text{det}(B^{-1/2}) > 0 \). From the product rule for determinants, (A3) holds if and only if \( \text{det}(B^{-1/2}(BC - \lambda I)B^{1/2}) > 0 \), or equivalently,

\[
\text{det}(B^{1/2}CB^{1/2} - \lambda I) > 0. \tag{A4}
\]

Thus, the eigenvalues of BC are the eigenvalues of \( B^{1/2}CB^{1/2} \). Because \( B^{1/2}CB^{1/2} \) is real and symmetric, its eigenvalues are real.

Next we will show that the eigenvalues of \( B^{1/2}CB^{1/2} \) (and BC) are all positive if and only if the eigenvalues of C are positive. Real symmetric matrices have all positive eigenvalues if and only if they are positive definite (Lancaster, p. 94). Hence the eigenvalues of \( B^{1/2}CB^{1/2} \) are all positive if and only if for all nonzero vectors \( x \)

\[
x^T B^{1/2}CB^{1/2} x > 0. \tag{A5}
\]

This is equivalent to
\[ y^T C y > 0 \]  \hspace{1cm} (A6)

for all nonzero \( y \). Hence, stability of the polymorphic equilibrium is equivalent to determining when \( C \) is positive definite.

The problem can be simplified further by noting that

\[ C = D V D, \]  \hspace{1cm} (A7)

where \( D = \text{diag}(\alpha_1, \alpha_2, \ldots, \alpha_n) \) and \( V \) is the positive, symmetric matrix with elements

\[ v_{ij} = 1 + \delta_{ij} \left( \frac{v_i - 1}{2} \right), \]  \hspace{1cm} (A8)

with \( \delta_{ij} \) as in (A2). By the logic used in (A6), we see that \( C \) is positive definite if and only if \( V \) is. This demonstrates that the stability conditions depend only on the \( v_i \) and are independent of the mean effects, \( \alpha_i \), as well as the equilibrium allele frequencies, \( p_i \). When is \( V \) positive definite? It is easy to derive a sufficient condition by considering the quadratic form associated with \( V \). Note that for any vector \( x \),

\[ x^T V x = \left( \sum_{i=1}^{n} x_i \right)^2 + \sum_{i=1}^{n} x_i^2 \left( \frac{v_i - 1}{2} \right). \]  \hspace{1cm} (A9)

This is obviously positive for all nonzero \( x \) if

\[ v_i > 1 \text{ for all } i. \]  \hspace{1cm} (A10)

Hence (A10) suffices for stability. The necessary condition (18) can be obtained by considering \( V \)
as a variance-covariance matrix. To be positive definite, all correlations must be less than one. Thus, a necessary condition for stability is

\[(v_i + 1)(v_j + 1) > 4 \quad (A11)\]

for all pairs with \(i \neq j\).

Necessary and sufficient conditions follow from the fact that a real symmetric matrix is positive definite if and only if all its “principal minors” (i.e., submatrices obtained by deleting rows and columns with identical indices) have positive determinants (Lancaster 1969, p. 96). To present the conditions for stability of the equilibria (12) concisely, assume that the \(v_i\) are ordered from smallest, \(v_1\), to largest, \(v_n\). The necessary and sufficient conditions are

\[
\prod_{i=1}^{m} (v_i - 1) + 2 \sum_{i=1}^{m} \prod_{j \neq i}^{m} (v_j - 1) > 0, \quad (A12)
\]

for all \(m \leq n\). Condition (A11), which corresponds to \(m = 2\) in (A12), implies that \(v_i > 1\) for \(i \geq 2\). Consider (A12) with \(m = n\). Then, if \(v_1 < 1\), we must have

\[
v_1 > 1 - \frac{1}{\frac{1}{2} + \sum_{i=2}^{n} \frac{1}{v_i - 1}}. \quad (A13)
\]

Thus, if there are many loci, or if some loci have \(v_i\) near 1, the lower bound on \(v_1\) will be not much below 1. Hence, for stable polygenic variation, the sufficient condition (A10), \(v_i > 1\) for all \(i\), is effectively also necessary. This qualitative conclusion is supported by our analysis of boundary equilibria (see (21) and Appendix B).

The special case in which only one locus is polymorphic deserves comment. In this case, the stability condition reduces to
\[ v_1 > -1. \] (A14)

This trivially generalizes Wright’s (1935) result by showing that even underdominant selection can be balanced by stabilizing selection to retain one polymorphic locus if the heterozygote produces a near-optimal phenotype in a genetic background in which all other loci are fixed.

**APPENDIX B: STABILITY CONDITIONS FOR BOUNDARY EQUILIBRIA**

Let \( A = (a_{ij}) \) denote the stability matrix corresponding to an equilibrium with \( p_i = 0 \) for \( i \in \Omega_0 \), \( p_i = 1 \) for \( i \in \Omega_1 \), and \( 0 < p_i < 1 \) for \( i \in \Omega_p \). As shown by (20), the eigenvalues governing the stability of the loci fixed at 0 and 1 are simply \( \lambda_i = a_{ii} \) for \( i \in \Omega_0 \cup \Omega_1 \) (20b,c). Moreover, the eigenvalues governing the polymorphic loci are generated by a matrix whose elements are given by (10). The stability conditions for this subsystem are given by (14, 15) if \( \Omega_p \) has at least two elements (or A14 if there is just one polymorphic locus), and depend only on the \( v_i \). What remains is to find the conditions for stability of the fixed equilibria in an explicit form, rather than in terms of the \( \delta_i = \Delta / \alpha_i \), which depend on the allele frequencies.

For definiteness, suppose that the mean lies above the optimum (\( \Delta > 0 \)) and that all \( \alpha_i > 0 \) (hence \( \delta_i > 0 \)); the argument is similar for the other cases. With \( \Delta > 0 \), directional selection on the trait is tending to reduce the \( p_i \). First, suppose that the polymorphic loci all satisfy \( v_i > 1 \). Then, from (23), \( \Delta_f > 0 \). For the polymorphic equilibria to be feasible, (19a) implies that we must have

\[
\alpha_i \left( 2\hat{p}_i v_i - 1 \right) > 2\Delta = \frac{2\Delta_f}{1 + 2C} \quad \text{and} \quad (B1a)
\]

\[
\alpha_i \left( 2\hat{q}_i v_i - 1 \right) > -2\Delta = -\frac{2\Delta_f}{1 + 2C} \quad \text{for } i \in \Omega_p, \quad (B1b)
\]

with \( \Delta_f \) and \( C \) as in (23). Note that even with \( v_i > 1 \), (B1a) implies that polymorphism may not be feasible for any \( \Delta_f \) if \( \hat{p}_i \) is too small (e.g., \( \hat{p}_i < \frac{1}{2v_i} \)). In contrast, if \( \hat{p}_i = \frac{1}{2} \), then \( v_i > 1 \) insures that
polymorphism is feasible if $\Delta f$ is sufficiently small. Note that conditions (B1) are more easily satisfied with $C$ large, corresponding to many polymorphic loci and/or relatively weak balancing selection (i.e., $v_i$ slightly over 1). For the fixed loci to be stable, conditions (21) imply that

$$\alpha_i(2\hat{p}_i v_i - 1) < 2\Delta \text{ for } i \in \Omega_0, \text{ and}$$

$$\alpha_i(2\hat{q}_i v_i - 1) < -2\Delta \text{ for } i \in \Omega_1 \quad (B2a)$$

Thus, for $\hat{p}_i = \frac{1}{2}$, loci with $p_i = 1$ can be stable only if $\alpha_i(v_i - 1) < -2\Delta$, which requires $v_i < 1$; but loci may fix for $p_i = 0$ even if $v_i > 1$, provided that $\alpha_i(v_i - 1) < 2\Delta$. If $\hat{p}_i$ deviates from $\frac{1}{2}$, then the conditions for stability generally become more restrictive.

Now, consider an equilibrium with $v_I < 1$ for one $I \in \Omega_p$. As before, we assume that $\Delta > 0$. From stability condition (A11), we know that $v_i > 1$ for $i \in \Omega_p$ if $i \neq I$. Then, from (A12), $1 + 2C < 0$, with $C$ as in (23c). Condition (A13) implies that

$$v_I > 1 - \left( \frac{2}{1 + 2 \sum_{j \in \Omega_p, j \neq I} \frac{1}{v_j - 1}} \right) > 0. \quad (B3)$$

Conditions (19b) require

$$\alpha_I(2\hat{p}_I v_I - 1) < 2\Delta \text{ and } \alpha_I(2\hat{q}_I v_I - 1) < -2\Delta. \quad (B4)$$

Overall, the constraints on the one polymorphic locus with $v_I < 1$ are very restrictive.

**APPENDIX C: FINDING ALTERNATIVE STABLE EQUILIBRIA**

We restrict attention to the special case $\hat{p}_i = 0.5$ and $\theta = 0$ considered in our first numerical example concerning pleiotropic balancing selection. Because of the symmetry, we can restrict
attention to equilibria with $\Delta > 0$, as the complementary equilibria with $\Delta < 0$ can be found by simply reversing the frequencies of $B_i$ and $b_i$ at each locus. We seek an exhaustive list of multilocus equilibria that satisfy our stability and feasibility constraints. The key idea is to recognize that these alternative equilibria fall into classes that are determined by the relationship of $2\Delta$ to the intervals defined by the sequence of values for $\pm\alpha_i(v_i - 1)$. For any assignment of the $\alpha_i$ and $v_i$, we first order the sequence $\pm|\alpha_i(v_i - 1)|$, then find the possible equilibria that fall into each of these intervals, including the regions below $\min_i\{-|\alpha_i(v_i - 1)|\}$ and above $\max_i\{|\alpha_i(v_i - 1)|\}$.

The strategy is to start with a trial value of $\chi = 2\Delta$ in one of these intervals, then to determine for this value the sets of loci that can be fixed for 0, fixed for 1, or polymorphic, then from these to determine which values of $\Delta$ in the interval being considered can be realized. The crucial observation is to realize that according to our stability and feasibility conditions, the qualitative equilibrium state of each locus depends only on the value of $\alpha_i(v_i - 1)$ relative to $\pm\Delta$. Because of this, we need only consider one trial value of $\chi$ in each interval.

First, consider equilibria where all polymorphic loci have $v_i > 1$. A trial value of the threshold $\chi = 2\Delta$ is chosen. If $\chi < 0$, then the complementary case is considered, with $\chi > 0$; loci fixed for 0 and 1 are then reversed. For fixed $\chi$, all of the loci are sorted into three classes according to their value of $\alpha_i(v_i - 1)$. According to (B2), those loci with $v_i > 1$ and $\alpha_i(v_i - 1) > \chi$ must be polymorphic, and those with $\chi > \alpha_i(v_i - 1) > -\chi$ must fix at 0. Finally, those with $-\chi > \alpha_i(v_i - 1)$ may fix at 0 or 1. Thus, the task reduces to considering all of the equilibria with the loci in this final class fixed for either 0 and 1 and determining which of these configurations produces values of $\Delta$ in the interval being considered. All that do are feasible stable equilibria. By trying values of $\chi$ in each interval, all possible stable equilibria can be found.

Finally, for each $\chi$, we consider possible stable equilibria at which one of the polymorphic loci has $v_i < 1$. Let I denote such a locus. For it to be feasibly polymorphic, it must satisfy $\alpha_I(v_I - 1) < -\chi$ (B2b); and it must also satisfy the stability criterion (B3). This condition can be written as $2\Delta/\theta_{eff} > 0$. Jointly, these conditions are very restrictive. The algorithm is to find all loci that satisfy
\[- \frac{2\alpha_I}{1 + 2 \sum_{j \in (\Omega_\alpha - 1)} \frac{1}{v_j - 1}} < \alpha_I (v_I - 1) < -\chi, \] (C1)

assign them individually as polymorphic, then carry out the procedure described above with all of
the remaining polymorphic loci satisfying \( v_i > 1 \). Configurations of monomorphic loci that lead to
values of \( 2\Delta \) in the target interval are accepted as stable polymorphic.
TABLE 1
Glossary of repeatedly used notation.

<table>
<thead>
<tr>
<th>Symbol</th>
<th>Usage, (relevant equation in the text)</th>
</tr>
</thead>
<tbody>
<tr>
<td>$B_i$</td>
<td>one of the two alleles at locus $i$ ($b_i$ is the other), (1)</td>
</tr>
<tr>
<td>$K$</td>
<td>fraction of the total genetic variance attributable to mean effects of genotypes, (44)</td>
</tr>
<tr>
<td>$S$</td>
<td>strength of stabilizing selection, (2)</td>
</tr>
<tr>
<td>$V_A$</td>
<td>additive genetic variance, (1)</td>
</tr>
<tr>
<td>$p_{i,t}$</td>
<td>frequency of $B_i$ in generation $t$, (1)</td>
</tr>
<tr>
<td>$\hat{p}_i$</td>
<td>equilibrium frequency of $B_i$ under balancing selection alone, (7)</td>
</tr>
<tr>
<td>$q_i$</td>
<td>frequency of $b_i$, (1)</td>
</tr>
<tr>
<td>$s_i$</td>
<td>intensity of balancing selection at locus $i$, (7)</td>
</tr>
<tr>
<td>$v_i$</td>
<td>$s_i/(\alpha_i^2 S)$ in the model of pleiotropic balancing selection, (7), or squared coefficient of variation of the effect of substitution at locus $i$ in the model of pleiotropic balancing selection, (25)</td>
</tr>
<tr>
<td>$\bar{z}$</td>
<td>average trait value in the population, (1)</td>
</tr>
<tr>
<td>$\bar{z}_i^*$</td>
<td>contribution to the mean phenotype from all loci but $i$, $\sum_{j \neq i} \alpha_j (p_j - q_j)$, (8)</td>
</tr>
<tr>
<td>$\alpha_i$</td>
<td>(mean) effect of a substitution at locus $i$, (1) and (25)</td>
</tr>
<tr>
<td>$\beta_i$ ($\gamma_i$)</td>
<td>additive contribution of $B_i$ ($b_i$) to the trait, (1) and (25)</td>
</tr>
<tr>
<td>$\Delta$</td>
<td>departure of the population mean from the optimum, $\bar{z} - \theta$, (7b)</td>
</tr>
<tr>
<td>$\Delta_f$</td>
<td>under pleiotropic balancing selection, the amount by which the population would depart from the optimum in the absence of stabilizing selection, (23c)</td>
</tr>
<tr>
<td>$\delta_i$</td>
<td>$\Delta$ normalized by the (mean) effect of a substitution at locus $i$, i.e., $\Delta/\alpha_i$, (7)</td>
</tr>
<tr>
<td>$\theta$</td>
<td>optimum trait value under stabilizing selection, (2)</td>
</tr>
<tr>
<td>$\rho_{ij}$</td>
<td>the correlation between the substitution effects at loci $i$ and $j$, (28a)</td>
</tr>
</tbody>
</table>
TABLE 2

Multiple stable equilibria maintained by stabilizing selection on a single trait and overdominance.

<table>
<thead>
<tr>
<th>Locus</th>
<th>$\alpha_i$</th>
<th>$v_i$</th>
<th>$e_1$</th>
<th>$e_2$</th>
<th>$e_3$</th>
<th>$e_4$</th>
<th>$e_5$</th>
<th>$e_6$</th>
<th>$e_7$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2.27458</td>
<td>0.048</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>1.92538</td>
<td>0.181</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>3</td>
<td>0.320365</td>
<td>0.220</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>4</td>
<td>0.054810</td>
<td>0.099</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>5</td>
<td>0.03597</td>
<td>0.486</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>6</td>
<td>0.004355</td>
<td>0.906</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>7</td>
<td>0.000191</td>
<td>0.792</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>8</td>
<td>0.000042</td>
<td>0.102</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>9</td>
<td>0.000053</td>
<td>3.364</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>10</td>
<td>0.761252</td>
<td>1.034</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>0.6995</td>
<td>0.7657</td>
<td>0.5248</td>
</tr>
<tr>
<td>11</td>
<td>0.011769</td>
<td>3.528</td>
<td>1</td>
<td>1</td>
<td>0.5534</td>
<td>0.5174</td>
<td>0.5232</td>
<td>0.5022</td>
<td>0.5057</td>
</tr>
<tr>
<td>12</td>
<td>0.02935</td>
<td>2.720</td>
<td>1</td>
<td>0.9072</td>
<td>0.5315</td>
<td>0.5103</td>
<td>0.5137</td>
<td>0.5013</td>
<td>0.5034</td>
</tr>
<tr>
<td>13</td>
<td>0.21609</td>
<td>1.387</td>
<td>1</td>
<td>0.7457</td>
<td>0.5190</td>
<td>0.5062</td>
<td>0.5082</td>
<td>0.5008</td>
<td>0.5020</td>
</tr>
</tbody>
</table>
Allelic effects $\alpha_i$ and relative overdominance $v_i$ for 20 loci were drawn from independent Gamma distributions with means 1, 2 respectively, and variance 4. The range of the trait is $|z|<21.07$, and the maximum possible variance is $V_A = 48.11$. With an optimum at $\theta = 0$, there are 14 stable equilibria (according to our approximate stability criteria); only 7 are shown here, since the other 7 differ only by a sign change (and replacing the $p_i$ by $1 - p_i$). The last four rows give total genetic load and its three components (as defined in 56), scaled relative to $S$. 

<table>
<thead>
<tr>
<th>Loci</th>
<th>$\theta_{eff}$</th>
<th>$\Delta$</th>
<th>$V_A$</th>
<th>$L/S$</th>
<th>$L_{A}/S$</th>
<th>$L_{V}/S$</th>
<th>$L_{B}/S$</th>
</tr>
</thead>
<tbody>
<tr>
<td>14</td>
<td>0.325396</td>
<td>1.038</td>
<td>1</td>
<td>0.7048</td>
<td>0.5158</td>
<td>0.5052</td>
<td>0.5069</td>
</tr>
<tr>
<td>15</td>
<td>0.0502681</td>
<td>3.936</td>
<td>1</td>
<td>0.6393</td>
<td>0.5108</td>
<td>0.5035</td>
<td>0.5047</td>
</tr>
<tr>
<td>16</td>
<td>0.037032</td>
<td>5.905</td>
<td>1</td>
<td>0.6132</td>
<td>0.5086</td>
<td>0.5029</td>
<td>0.5038</td>
</tr>
<tr>
<td>17</td>
<td>0.224072</td>
<td>1.906</td>
<td>1</td>
<td>0.6012</td>
<td>0.5078</td>
<td>0.5025</td>
<td>0.5034</td>
</tr>
<tr>
<td>18</td>
<td>4.50501</td>
<td>1.357</td>
<td>0.7321</td>
<td>0.5128</td>
<td>0.5010</td>
<td>0.5003</td>
<td>0.5004</td>
</tr>
<tr>
<td>19</td>
<td>3.70138</td>
<td>4.877</td>
<td>0.5260</td>
<td>0.5014</td>
<td>0.5001</td>
<td>0.5000</td>
<td>0.5000</td>
</tr>
<tr>
<td>20</td>
<td>7.28178</td>
<td>5.723</td>
<td>0.5108</td>
<td>0.5006</td>
<td>0.5000</td>
<td>0.5000</td>
<td>0.5000</td>
</tr>
</tbody>
</table>

$\theta_{eff}$ = 2.8141, $\Delta$ = –0.3728, $V_A$ = 41.2927, $L/S$ = 122.3500, $L_{A}/S$ = 0.0695, $L_{V}/S$ = 20.6464, $L_{B}/S$ = 101.3340


TABLE 3

Effects of sex-dependence, CV of allelic effects, and intensity of stabilizing selection on the occurrence of stable two-locus polymorphisms with five-locus selection

<table>
<thead>
<tr>
<th></th>
<th>Sex-dependent</th>
<th>Sex-independent</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Na</td>
<td>poly (total)</td>
</tr>
<tr>
<td>CV = 0.5, S = 0.2</td>
<td>1000</td>
<td>7 (12)</td>
</tr>
<tr>
<td>CV = 1.0, S = 0.2</td>
<td>1000</td>
<td>117 (315)</td>
</tr>
<tr>
<td>S = 0.02d</td>
<td>30</td>
<td>17</td>
</tr>
<tr>
<td>S = 0.002e</td>
<td>17</td>
<td>17</td>
</tr>
<tr>
<td>S = 0.0002e</td>
<td>17</td>
<td>17</td>
</tr>
</tbody>
</table>

a Number of sets of allelic effects generated.

b Number of those sets in which at least one stable two-locus polymorphic equilibrium was found when iterating from 10 random initial frequencies.

c Total number of calculations (out of 10n) that produced stable two-locus polymorphisms.

d For S ≤ 0.02, each of these sets of allelic effects produced a stable two-locus polymorphism with S = 0.2. For each one, we iterated from only one of the initial frequencies that led to a stable two-locus polymorphism with S = 0.2.

e Only sets of allelic effects and initial frequencies that produced stable two-locus polymorphisms with S = 0.2 and S = 0.02 were used.
FIGURE LEGENDS

FIGURE 1.—Values of $\alpha_i$ and $s_i$ for 100 loci separated by lines indicating their stable equilibria. The upper panel (A) assumes $\Delta = 0$, the lower assumes $\Delta = 0.05$; both assume $S = 1$. With $\Delta = 0$, there are only two stability regimes; loci with $\{\alpha_i, s_i\}$ above the parabola must be polymorphic, while those below the parabola can fix for 0 or 1. With $\Delta = 0.05$, there are seven stability regimes, as described in the text.

FIGURE 2.—Additive genetic variance, $V_A$, as a function of the intensity of stabilizing selection, $S$. We assume that $\Delta = 0$ as in Figure 1A. $V_A$ declines inversely with the strength of stabilizing selection (top panel). However, the load due to variation around the optimum, $L_V = \frac{S}{2} V_A$, is almost constant for a wide range of $S$ (lower panel).

FIGURE 3.—The deviation of the mean from the optimum, $\Delta$, as a function of $\Delta_f$. The line $\Delta = \Delta_f$ is also plotted. The left panel shows the original scale, and the right panel a log-log scale. This plot depends on the assumption that the polymorphic loci are those identified with $\Delta = 0$ in Figure 1A.

FIGURE 4.—The genetic variance as a function of the deviation of $\Delta_f$. This is based on the same assumptions as Figure 3. $V_A = 0.072$ when $\Delta = 0$ and declines to zero when the deviation is so large that all loci have fixed.

FIGURE 5.—Genetic load and its components, scaled by $S$, as functions of $\Delta_f$. The total load is the solid line at the top, the load due to deviations of the mean from the optimum is the heavy curve that stays near 0. The portions of the load attributable variation around the optimum (short dashes) and perturbations of the allele frequencies from their overdominant equilibria (long dashes) change relative magnitude as $\Delta_f$ increases.
FIGURE 6.—Stable equilibria under fluctuating allelic effects. Each panel shows the mean allele frequency (across generations) and the standard deviation of allele frequencies for the “most polymorphic” and “least polymorphic” (explained in the text) of six diallelic loci. The average frequency of the least common allele is given for each locus. The dashed vertical lines indicate the predicted critical values of the parameter varied. In panel A, stable polymorphism is expected only for values of v above the critical value; monomorphism is expected for smaller values of v. In panel B, stable polymorphism is expected only for values of ρ below the critical value.
Figure 1. (Note that the x-axis label should be $\alpha$ rather than a.)
Figure 2.
Figure 3. (In this preliminar version of the figure, $\Delta$ prints as $D$ and $\Delta_f$ prints as $D_f$.)
Figure 4. (Note that the x-axis label should be $\Delta$ rather than $D$.)
Figure 5. (There is a technical glitch in the pdf. The x-axis should be labeled Δ instead of D, and the y-axis should be labeled L/S.)