Genotype-Environment Interactions and the Maintenance of Polygenic Variation

John H. Gillespie and Michael Turelli

Department of Genetics, University of California, Davis, California 95616

Manuscript received April 18, 1988
Accepted for publication September 23, 1988

ABSTRACT

Genotype-environment interactions may be a potent force maintaining genetic variation in quantitative traits in natural populations. This is shown by a simple model of additive polygenic inheritance in which the additive contributions of alleles vary with the environment. Under simplifying symmetry assumptions, the model implies that the variance of the phenotypes produced across environments by a multilocus genotype decreases as the number of heterozygous loci increases. In the region of an optimal phenotype, the mapping from the quantitative trait into fitness is concave, and the mean fitness of a genotype will increase with the number of heterozygous loci. This leads to balancing selection, polymorphism, and potentially high levels of additive genetic variance, even though all allelic effects remain additive within each specific environment. An important implication of the model is that the variation maintained by genotype-environment interactions is difficult to study with the restricted range of environments represented in typical experiments. In particular, if fluctuations in allelic effects are pervasive, as suggested by the extensive literature on genotype-environment interactions, efforts to estimate genetic parameters in a single environment may be of limited value.

THE mechanisms responsible for genetic variation in quantitative traits in natural populations remain a mystery. The most frequently analyzed mechanism is the balance between mutation and stabilizing selection (reviewed by BULMER 1988). Using an analysis which assumes that the distributions of effects of alleles at individual loci are Gaussian, LANDE (1975) showed that observed heritabilities could be explained with reasonable estimates of selection intensity and the amount of new variation introduced by mutation. The mutation-selection-balance hypothesis has been reanalyzed by TURELLI (1984, 1985) who argued that LANDE's analysis requires per locus mutation rates that are unrealistically high. When more defensible mutation rates are used, and the effects of pleiotropy are considered (TURELLI 1985, 1986), the mutation-selection-balance hypothesis remains a viable, but much less compelling, explanation for genetic variance in quantitative traits. Given these problems, there is a need to investigate other mechanisms for maintaining heritable variation.

Models that involve balancing selection produced by pleiotropic effects are obvious candidates (*e.g.*, LERNER 1954, Ch. 17; ROSE 1982; GILLESPIE 1984), but experimental demonstration of the appropriate pleiotropic effects is extraordinarily difficult. A related class of models, based on genotype-environment interactions, appears to have received surprisingly little attention. Genotype-environment interactions are commonly observed in many quantitative traits (*e.g.*, COMSTOCK and MOLL 1963; PANI and LASLEY 1972; GUPTA and LEWONTIN 1982) including fitness components (DOBZHANSKY *et al.* 1955; TACHIDA and MUKAI 1985). They would seem to provide a natural explanation for the maintenance of quantitative variation because genotype-environment interactions in fitness can produce a robust form of balancing selection (*e.g.*, FELSENSTEIN 1976). However, the most recent theoretical treatment of genotype-environment interactions (VIA and LANDE 1987) concluded they are not, in fact, a plausible mechanism for the maintenance of polygenic variation. Here we will argue the opposite. Our qualitative conclusion differs from VIA and LANDE's because our model, unlike theirs, does not allow the existence of a single genotype that is most fit in all environments.

Our model is very similar in spirit, if not in detail, to one used by LEWONTIN (1964) who investigated the multilocus behavior of "optimum models," with additive contributions across loci (*i.e.*, no epistasis) and stabilizing selection on the resulting phenotype. Among the models considered, he found that only "homeostatic models" tended to maintain appreciable genetic variance at equilibrium. In these models, the environmental variance experienced by multilocus genotypes decreases with their number of heterozygous loci; thus the models reflect LERNER's (1954, Ch. 2) hypothesis of increased "developmental homeostasis" in multilocus heterozygotes. As demonstrated by

This paper is dedicated to Professor Timothy Prout on the occasion of his promotion to emeritus professor.

LEWONTIN, this hypothesis when combined with stabilizing selection will produce heterozygote advantage and lead to the maintenance of genetic variation. Our approach differs from his in that we begin with the standard model of additive polygenic inheritance then show that developmental homeostasis increases with heterozygosity if the additive allelic contributions randomly vary with the environment. Thus, we provide a simple mechanism that is consistent with the experimental observations cited by LERNER (1954) and the assumption used by LEWONTIN (1964). By "deriving" developmental homeostasis from lower-level assumptions, our analysis produces additional predictions that can be used to test the plausibility of this mechanism for maintaining variation.

Although our model is based on spatial and temporal heterogeneities, we assume constant fitnesses for phenotypes across environments. We recognize that different environments will often favor different phenotypes and that this too may promote the maintenance of genetic variation. While such models are of obvious biological importance, we have chosen to emphasize the effects of genotype-environment interactions. Clearly the critical question with respect to maintaining variation is whether a single genotype is most fit in all environments, not whether phenotypic fitnesses vary. As will be apparent, our results may be readily extended to more complex situations, including varying phenotypic fitnesses. Our aim in this paper, however, is to illustrate as simply as possible that genotype-environmental interactions can maintain variation.

A QUASI-SYMMETRIC MODEL

The approach used in this section is sufficiently unusual that a brief overview may be helpful. Our analysis begins by including genotype-environment interactions in the standard additive-effects quantitative genetics model, then we obtain the average fitness of each genotype over all environments. Because variances in fitness are negligible in our model, the average fitness of a genotype can be viewed as a constant and plugged into the standard equations of population genetics to obtain the dynamics and equilibria of the model. Thus most of the effort goes into calculating the average fitnesses. The main result is that, under certain symmetry assumptions, the fitness of a genotype is an increasing function of the number of heterozygous loci. Because the equilibrium behavior of multilocus systems for which fitness increases with the number of heterozygous loci is known in detail (KARLIN 1979), no new analysis of the dynamics is necessary. This overview glosses over the difficult technical issue of explicitly incorporating temporal and spatial fluctuations in the environment. Fortunately, the details of the environmental fluctuations are irrelevant to the dynamics when a weak-selection approximation is used. The Appendix includes the details of this approximation for the one-locus version of the model.

The first problem is to describe the nature of the environment's contribution to the phenotype. We will assume that the effect of the environment has two stochastically independent components, one that depends on the genotype of the individual and one that does not. The genotype-independent component, call it E, will be normally distributed with mean zero and variance V_e. The phenotype of each individual will be assumed to be affected additively by a genotype-independent contribution that is independent of those affecting all other individuals in the population. This definition of E is standard in theoretical quantitative genetics.

The genotype-dependent component of environmental effects will be called Z and will depend on both the genotype and the state of the environment that an individual experiences. This component differs from the genotype-independent component in that it will, in general, be shared by many individuals in the population. For example, if the population lives in an environment that fluctuates in time but not in space, then each individual of a particular genotype will have the same genotype-dependent contribution each generation, and this contribution will change from one generation to the next. If the variation is entirely spatial, then each individual of a particular genotype that occupies the same environmental subdivision will receive the same genotype-dependent contribution. It is tempting to call this contribution macroenvironmental, and the genotype-independent contribution microenvironmental. Although these terms do fit the model, they do not describe all situations where the model might apply. The expected value of Z, averaged across all environments (including both temporal and spatial components), will be assumed to be zero. Our Z is essentially the same as FALCONER's (1981, p. 122), I_{GE} and YAMADA's (1962) (GE). Our definition differs from theirs only in that we allow correlations between the Z's for different genotypes that are not a part of their approaches. This comparison will be expanded in the DISCUSSION.

Under our assumptions, the phenotype of an individual may be written

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

where G is the average phenotype produced by its genotype averaged over all environments. In order to describe the evolutionary dynamics of this model, we need an explicit representation of the genotypes in terms of specific alleles and a mapping of the phenotype into fitness.

We assume that a finite number of alleles segregate at each of m loci and denote the contribution to the phenotype of allele j at the ith locus by $\mu_j^{(i)} + Z_j^{(i)}$.

Assuming that there is neither dominance nor epistasis, the genetic plus genotype-environment contribution to the phenotype may be written

$$G + Z = \sum_{i=1}^{m} [\mu_j^{(i)} + \mu_k^{(i)}] + \sum_{i=1}^{m} [Z_j^{(i)} + Z_k^{(i)}], \quad (2)$$

where j and k label the alleles at locus i. In this representation, $Z_j^{(i)}$ is a random variable that reflects the genotype-dependent contribution of the environment. With k alleles at each locus, a fully parameterized model would require mk variances for the $Z_j^{(i)}$ and $mk(mk - 1)/2$ correlations between the pairs of $Z_j^{(i)}$. Rather than tackling such a model, we will assume a large amount of symmetry. The first two moments of the $Z_j^{(i)}$ will be written

$$\begin{aligned} E\{Z_j^{(i)}\} &= 0, \\ \mathrm{Var}\{Z_j^{(i)}\} &= V_Z, \\ \mathrm{Cov}\{Z_j^{(i)}, Z_k^{(i)}\} &= V_Z\rho_w \text{ for } j \neq k, \text{ and} \\ \mathrm{Cov}\{Z_j^{(i)}, Z_k^{(h)}\} &= V_Z\rho_b \text{ for } i \neq h, \end{aligned} \quad (3)$$

where the subscripts w and b of the correlations, ρ, refer to "within" and "between" loci. The expectations are taken over the full distribution of temporal and spatial fluctuations and hold for all i, j, k and h. This symmetry is not critical for the maintenance of variation, but it does tremendously simplify the algebra and the exposition.

The most important property of this simple model may be uncovered by examining the variance of $G + Z$ across environments for a particular genotype,

$$\begin{aligned} &\mathrm{Var}_Z\{G + Z \mid \text{genotype}\} \\ &= 2V_Z \sum_{i=1}^{m} [1 + \delta_{jk}^{(i)} + (1 - \delta_{jk}^{(i)})\,\rho_w] \\ &\quad + 4V_Z\rho_b m(m - 1) \\ &= 2mV_Z[1 + \rho_w + r(1 - \rho_w) + 2(m - 1)\rho_b] \\ &\equiv V_{ZG}, \end{aligned} \quad (4)$$

where $\delta_{jj}^{(i)} = 1$, $\delta_{jk}^{(i)} = 0$ if j $\neq k$, r is the fraction of homozygous loci in the genotype, and V_{ZG} is defined as the genotype-specific component of the variance in $G + Z$ due to fluctuations in the environment. Equation 4 demonstrates that the variance of the average phenotypes across environments produced by a genotype is a decreasing function of the number of heterozygous loci. Thus, the model implies developmental homeostasis. An immediate consequence of this property is that heterozygotes will be favored by natural selection for a broad range of fitness functions. This will be demonstrated below. To anticipate the argument, recall that the fitness function is concave in the region of an optimum. Since, approximately, the expected value of a concave function of a random variable decreases with the variance of the random variable, more heterozygous individuals should be more fit, on average, under stabilizing selection.

Although our qualitative results hold for any form of stabilizing selection, we assume for specificity that the fitness of an individual is determined by its phenotype, P, through the Gaussian fitness function

$$\Phi(P) = \exp\left(-\frac{P^2}{2w^2}\right), \quad (5)$$

where w^2 is a measure of the strength of selection, with large w corresponding to weak selection. We assume without loss of generality that the optimum phenotype is zero and express the mean contributions of alleles, $\mu_j^{(i)}$, as deviations from zero. Note that we are assuming that a single phenotype is optimal in all environments. One could extend the model to include both a fluctuating optimum and genotype-environment interactions, but this will not be pursued here. We can speculate that the extension will not have a significant effect unless there is a strong correlation across environments between the optimum phenotype and the allelic effects. Using (5), the relative fitness of a particular genotype, G, randomized over the distribution of E, may be written

$$\phi(G + Z) = \exp\left(-\frac{(G + Z)^2}{2V_s}\right), \quad (6)$$

where $V_s = w^2 + V_e$ (see LANDE 1975). We will investigate the dynamics of this selection model without genetic drift or mutation.

Our approach is based on a limiting argument which assumes that the contributions of each allele are very small. Formally this is accomplished by assuming that $\mu_j^{(i)}$ and V_Z are proportional to a small quantity ε that is allowed to approach zero to obtain a limiting process. In mathematical terms, we assume that $\mu_j^{(i)} = O(\varepsilon)$ and $V_Z = O(\varepsilon)$, where O means "of the same order of magnitude as." Usually we will proceed in a more casual fashion by simply ignoring terms proportional to ε^k for $k > 1$, *i.e.*, ignore terms that are $o(\varepsilon)$, where o means "of smaller order of magnitude than." These order of magnitude assumptions are used so that the variance of allelic effects, which reflect genotype-environment interactions, dominate the dynamics.

In our model, $G + Z$, the average phenotype of a given genotype, is a random variable that depends on the environment encountered. The mean fitness of a particular genotype, averaged across environments, could be derived by averaging (6) over the distribution of Z. However, without specifying the exact distribution of Z, this is not possible. Here we present two approaches, the first uses a Taylor series expansion of ϕ, the second a particular distribution for Z. If the variance of Z is small, and if higher-order moments of Z are negligible, then we can write, using (4),

$$E_Z\{\phi(G + Z) \mid \text{genotype}\}$$

$$\approx \phi(0) + (1/2)\phi''(0)V_{ZG} = 1 + \phi''(0)mV_Z[1 + \rho_w + r(1 - \rho_w) + 2(m - 1)\rho_b]. \quad (7)$$

The assumption that the mean effects are of order ε and the dependence of ϕ on $(G + Z)^2$ rather than $G + Z$ are responsible for the mean effects not appearing in the leading term of this expansion. Because the maximum of ϕ is at zero, $\phi''(0)$ will be negative. Because V_{ZG} is a decreasing function of the number of heterozygous loci, the mean fitness of a genotype is an increasing function of the number of heterozygous loci. This is one of the main results of the paper. Note that this is not a particularly surprising result. That such a property should hold for quantitative traits was thought to be obvious by both LERNER (1954) and LEWONTIN (1964) who argued that this property will lead to the maintenance of variation in natural populations. Here we have merely provided a mechanistic model that yields properties that were assumed by these authors on the basis of experimental results. It should be emphasized that overdominance need not be manifest in any particular environment. Overdominance is only evident when the fitnesses are averaged over all of the environmental heterogeneities.

A tractable parametric alternative to the Taylor series approach is to assume that Z is normally distributed across environments for each genotype. This follows from assuming that the additive contributions of each allele across environments follow a Gaussian distribution. This is equivalent to neither LANDE's (1975) assumption that the distribution of effects across alleles at a given locus is Gaussian nor to the classical quantitative genetic assumption (BULMER 1980, Ch. 8) that the distribution of breeding values is Gaussian. If Z is Gaussian across environments for each genotype,

$$E_Z\{\phi(G + Z) \mid \text{genotype}\} = \sqrt{\frac{V_s}{V_s + V_{ZG}}} + o(\varepsilon). \quad (8)$$

As before, the mean effects do not appear in the leading term of this expansion, and the mean fitness of a genotype is an increasing function of the number of heterozygous loci. Note that the same qualitative results would emerge if we assumed, as LEWONTIN (1964) did, that the allelic effects are constant but the environmental variance, V_e, experienced by a genotype decreases with the number of heterozygous loci it contains.

The fact that the mean fitness of a genotype increases with the number of heterozygous loci immediately suggests that genotype-environment interactions will lead to the maintenance of variation through balancing selection. However, an analytic demonstration of this that explicitly incorporates random fluctuations in the environment must take the traditional route through diffusion theory (see GILLESPIE [1978] for a review and references). This is accomplished in the APPENDIX for a one-locus, multiple-allele model. The remarkable fact that emerges from this analysis is that the limiting model (as $\varepsilon \to 0$) is a deterministic model described by a system of differential equations (see below), even though the model is defined with stochastic elements. The reason is that the variance in the fitness of a genotype is of order ε^2. Thus, as $\varepsilon \to 0$, mean fitness effects dominate, producing a deterministic solution. The APPENDIX is based on the SAS-CFF model (Stochastic Additive Scale-Concave Fitness Function) of selection in a random environment (GILLESPIE 1978). The SAS-CFF model is formally equivalent to the quantitative genetic model presented here, except that the temporal and spatial fluctuations are explicitly modelled. Dusting off the SAS-CFF machinery to analyze the quantitative genetics model shows that the terms reflecting properties of the environment other than the variance and correlations are unimportant as $\varepsilon \to 0$.

The other important result from the APPENDIX is that the deterministic model that is obtained as $\varepsilon \to 0$ is the same as a constant fitness model with the fitness of a genotype being the average of its fitnesses across environments. Thus the fitnesses given by (7) may be used directly in the standard deterministic equations of population genetics. While the APPENDIX applies only to the one-locus case, it is readily extended to multiple loci when linkage is loose. By loose linkage we mean that recombination dominates selection, leading in the weak-selection limit to zero linkage disequilibrium between all loci. In this case, the fitness of a genotype at a particular locus may be obtained by averaging its fitness over all other loci, assuming no disequilibrium. Consider, for example, the ith locus. Using (7), the marginal fitness of a homozygote at the ith locus may be written

$$w(\text{homozygote}) = 1 + a, \quad (9)$$

where

$$a = \phi''(0)mV_Z[1 + \rho_w + \bar{r}(1 - \rho_w) + 2(m - 1)\rho_b],$$

and $\bar{r}$ is the average fraction of homozygous loci in an individual homozygous at locus i. The average fitness of a heterozygote at this locus is

$$w(\text{heterozygote}) = 1 + a + b, \quad (10)$$

where

$$b = -\phi''(0)V_Z(1 - \rho_w)$$

and a is as in (9). Interestingly, the fitness excess of

the heterozygote, b, does not depend on the number of loci. Let $p_j^{(i)}$ be the allele frequency of the jth allele at the ith locus, then, using (9) and (10), we have

$$\Delta p_j^{(i)} = \frac{b p_j^{(i)}[F_i - p_j^{(i)}]}{1 + a + (1 - F_i)b}, \qquad F_i = \sum_{i=1}^{k} (p_j^{(i)})^2. \tag{11}$$

As $\varepsilon \to 0$, a and b also approach zero, suggesting the following differential equation as an approximation to (11)

$$\frac{dp_j^{(i)}}{dt} = - p_j^{(i)} \phi''(0) V_Z (1 - \rho_w)(F_i - p_j^{(i)}). \tag{12}$$

The equilibrium solution of (12) is, trivially,

$$p_j^{(i)} = \frac{1}{k_i}, \tag{13}$$

If there are k_i alleles at the ith locus. It is easy to apply the criteria of KIMURA (1956) to verify that this equilibrium is stable. The fact that the equilibrium solution depends only on the number of alleles at a locus demonstrates that genotype-environment interactions could lead to the maintenance of very large amounts of genetic variation. (For tighter linkage, other solutions may be possible but will not be considered here. See KARLIN [1979] for a general theory of selection in symmetric models with fitness depending on the number of heterozygous loci.)

DISCUSSION

There are two points that should be made concerning the comparison of our model of genotype-environment interactions to those commonly employed in statistical studies. The first involves correlations. The most common statistical models of genotype-environment interactions, *e.g.*, as developed by YAMADA (1962), implicitly assume that the $Z_j^{(i)}$ are independent in order that variances may be partitioned in a convenient manner. However, nothing in our development requires this restriction. In particular, negative correlations between alleles are allowed and, in fact, may be common in natural populations, reflecting constraints that prevent any particular allele from performing well in all environments.

The second point concerns the definition of the environmental variance, V_E. Under most experimental designs, variance due to genotype-environment interaction is included in the estimate of V_E (see FALCONER 1981, p. 122). Thus estimates of V_E usually include both the variance of the genotype-independent component of the environment (our E) and the genotype-environment interaction component (our Z). However, while this may be useful for certain statistical procedures, the genotype-environment interaction component may maintain genetic variation and should not be relegated to obscurity in the V_E term.

Support for our model may come by checking its basic prediction of greater developmental homeostasis in more heterozygous genotypes. There are two separate questions: Do heterozygotes generally exhibit greater "environmental buffering"? And, if so, is the buffering a consequence of heterozygosity *per se*? Unfortunately, the experimental literature is ambiguous on both questions. With respect to the first, it appears that the commonly held view that developmental homeostasis is greater in more heterozygous genotypes is not born out in all experiments. In his review of the effects of inbreeding on environmental variation for quantitative traits. FALCONER (1981, pp. 243–245) states that, although exceptions can be found, inbreds are "often" subject to greater environmental variation than are the F_1 between them. This certainly was LERNER's (1954) view. An alternative is presented by WRIGHT (1968, Ch. 15; 1977, Ch. 4). For over half of the cases reported in Tables 15.1–3 and 15.5 of WRIGHT (1968), the estimated coefficient of variation for the F_1 is not lower than those of both inbred parental lines. In his summary of the (mostly very old) experimental literature, WRIGHT (1977) clearly favors the view that increased heterozygosity does not invariably lead to increased developmental homeostasis. When it does, he felt that it is often associated with heterosis. While the failure to find a significant association between heterozygosity and developmental homeostasis would not, by itself, lead to a rejection of our model for reasons discussed below, our model is inconsistent with an association between heterosis, developmental homeostasis and heterozygosity.

Much of the experimental literature reviewed by WRIGHT and FALCONER may not be directly applicable to our model. The most obvious reason is that the variances are measured between individuals raised within a single laboratory or field situation. To be directly applicable, the individuals would have to be raised in the same spectrum of environmental conditions that caused the maintenance of variation in a natural population. Of equal importance is the fact that many of the experiments use inbred parental strains that were selected for certain traits. Since selection in small populations could lead to the fixation of unconditionally deleterious alleles, the decreased developmental homeostasis of homozygotes may be caused by these alleles rather than by homozygosity *per se*. In addition, the alleles that differentiate these strains will often have a large effect on the phenotype, rather than the nearly equal effects as-

sumed by our model. There is clearly a need for experiments that look at the effects of low levels of inbreeding on the variance between individuals raised in a variety of macroenvironments.

Paralleling the work on developmental homeostasis in phenotypes are a number of experiments on viability. If the mapping of phenotype to fitness is as assumed in this paper, then these experiments provide tentative support for our model. In a follow-up of DOBZHANSKY and LEVENE's (1955) classic study of developmental homeostasis for viability in Drosophila, MUKAI, CHIGUSA and KUSAKABE (1982) compared the across-replicate variability of lines heterozygous or homozygous for new mutations accumulated on chromosomes sheltered by balancers with the across-replicate variability of lines heterozygous or homozygous for chromosomes from a natural population. They found greater homeostasis for heterozygotes only among the chromosomes extracted from nature. They argued that this might be expected if only a small fraction of new mutations are destined to reach significant frequencies and that natural selection may preferentially retain those that exhibit developmental homeostasis. Hence, although counterexamples to increased developmental homeostasis in heterozygotes can be found easily, they need not rule out the applicability of our model.

Another problem is to determine whether examples of increased buffering in heterozygotes are attributable to their genotypes or average phenotypes. As described by LANDE (1980), in many crosses between divergent inbred phenotypes, the hybrid heterozygotes may be nearer the phenotypic optimum and therefore subject to greater canalization. Using a Taylor series argument that is essentially identical to our (7), LANDE argued that selection favors reduced environmental variance, *i.e.*, increased canalization, for genotypes whose mean phenotype is near an optimum. This effect of reduced environmental variance for intermediate phenotypes can be disentangled from the effects of heterozygosity by comparing the environmental variation experienced by heterozygotes and homozygotes with the same mean phenotype. We know no studies that have done this for characters expected to be under stabilizing selection; but MUKAI, CHIGUSA and KUSAKABE (1982) demonstrated that heterozygotes for chromosomes from nature exhibited increased homeostasis by comparing homozygous and heterozygous lines with nearly equal mean viabilities. Thus, despite numerous ambiguities, our model is not refuted by available data.

Although genotype-environment interactions can maintain large amounts of genetic variation, it is uncertain whether they can account for observed heritabilities. This question leads to some fundamental conceptual and methodological problems. They stem from the fact that experiments can only be carried out in a very restricted subset of the environments experienced by natural populations, and that the states of the environment responsible for the genotype-environment interactions may not, in general, be observed. Consider, for example, a population studied in one particular environment. In this situation, what will be the additive genetic variation found by standard estimation procedures? The answer is clearly

$$V_A = \mathrm{Var}\{G + Z \mid Z\} \approx 2\sum_{i=1}^{m}\sum_{j=1}^{k_i} x_j^{(i)}(Z_j^{(i)} - \bar{Z}_i)^2, \quad (14)$$

where $x_j^{(i)}$ is the frequency of the jth allele at the ith locus, k_i is the number of alleles at this locus, and $\bar{Z}_i$ is the average value of the additive allelic contributions. The mean effects are of a smaller order of magnitude and are not included in this approximation. If allelic effects vary appreciably across environments, this variance estimate is no more informative than is, say, a single observation of a normal random deviate for estimating the mean of the distribution from which it is drawn. By taking the expected value of (14) we see that, on average, an experimenter working in one environment would observe

$$E_Z\{V_Z\} = E_Z\{\mathrm{Var}\{G + Z \mid Z\}\} \approx 2mV_Z(1 - \rho_w)(1 - \bar{F}), \quad (15)$$

where $\bar{F}$ is the mean homozygosity of the population. We have included a subscript Z to emphasize that the expectation in (15) is taken across all of the environments. Because our model imposes no restrictive limitations on the parameters in (14) and (15), appreciable additive variances are easily accommodated. Unfortunately, there is little else to be said on this point. At present, we have no estimates of $2mV_Z(1 - \rho_w)$, so there is no method either to judge whether this model is compatible with observed heritabilities or to compare the level variation predicted by this model to predictions based on mutation-selection balance.

This view of experiments in a single environment should be contrasted to experiments involving a pair of environments. PROUT (1958) introduced experimental estimates of heritabilities based on offspring-parent regression with the parent from the wild and the offspring raised in the laboratory. Published results vary, sometimes a significant positive regression is observed (*e.g.*, COYNE and BEECHAM, 1987) and sometimes the regressions are not significantly different from zero, even though $h^2 > 0$ for the same traits studied in the lab [*e.g.*, PROUT (1958) and UNDERHILL (1969) who compared immature laboratory-reared offspring to wild-caught adults]. To interpret these experiments in the context of our model, we follow FALCONER (1952) and consider a trait's expression in two different environments as two separate charac-

ters. With this approach, LANDE (APPENDIX to COYNE and BEECHAM 1987) showed that the offspring-parent regression in this case is proportional to the genetic correlation of the two characters. The genetic correlation will therefore depend on the particular values of $Z_j^{(i)}$ that occur in the two environments. Since, in general, additive genetic effects in nature may not be correlated with those in the laboratory, we might expect to see as many positive as negative correlations when these experiments are performed. We are not aware of any published instances of statistically significant negative correlations. Thus, we must conclude that either these have been observed but not published since they would be difficult to interpret, or that there is a serious problem with our model. In fact, this problem leads to an important generalization of the model that will be introduced but not fully explored.

A natural resolution of the two-environment problem is to incorporate larger differences in the mean effects of alleles. These differences would carry over across environments, leading to positive offspring-parent regressions even without environmental similarities. The model described thus far was called "quasi-symmetric" because mean effects of order ε have been included, but they play an insignificant role in the approximate dynamics. Even though the mean effects do not appear in our final approximations (see (7) and (8)), they can account for small positive regressions in some two-environment experiments. The idea is that in the absence of correlation between the environments in nature and in the lab, the random effects would produce a small contribution (either positive or negative) to the observed regression, while the mean effects would always produce a small positive contribution to the regression. Thus, if the correlations of allelic effects across environments are negligible, we would expect in two-environment experiments to see either no significant regression or a positive regression that is smaller than that seen in a single-environment experiment.

If more experiments, like those of COYNE and BEECHAM (1987), show that two-environment parent-offspring regressions tend to be similar in magnitude to one-environment regressions, then either the relevant features of the environment are more similar than expected or the assumptions concerning the relative magnitudes of mean and variance effects will have to be modified. The obvious modification is to assume that $\mu_j^{(i)}$ is proportional to $\varepsilon^{1/2}$, i.e., $\mu_j^{(i)} = O(\varepsilon^{1/2})$, so that differences among the mean effects of alleles across environments would be larger than the across-environments variances experienced by each allele. In this case, the expectation of the fitness of a genotype will depend not only on the number of heterozygous loci, but also on the mean effects of the particular alleles that make up the genotype. The differential equations that emerge when the dynamics are approximated turn out to be, coincidentally, the same equations that were used in the pleiotropic overdominance analysis of GILLESPIE (1984). Some significant mathematical problems arise in analyzing this asymmetrical model, which we will address in a future paper. Here we will only note that the asymmetrical model differs from the quasi-symmetric model in that not all alleles are maintained in the population, and the segregating alleles at a locus are no longer equally frequent at equilibrium. The equilibrium behavior of this more realistic model may be understood as a tension between the random effects pushing allele frequencies toward the interior and the mean effects pushing alleles toward the boundaries. Although it will differ significantly in detail, this model shares with the quasi-symmetric model the qualitative prediction that significant levels of additive variance can be maintained by genotype-environment interactions.

Complexities also arise when attempting to define the additive variance of a population in which allelic effects fluctuate in space and time (*cf.* GUPTA and LEWONTIN 1982). One extreme model would have all of the environmental variation being spatial. In this case, the additive variance of the population would be due solely to mean effects and, in the quasi-symmetric model, smaller on average than that observed in a single environment. However, it is not clear that the "net" additive variance could ever be estimated due to the difficulty of performing an experiment in which the entire range of relevant environmental variation that is experienced by the population is present. An important exception may be provided by long-established laboratory populations, whose native environments can be easily replicated. Our model also suggests difficulties in trying to relate realized to estimated heritabilities. Under our model, the relationship between realized heritabilities and those estimated in the base population will depend critically on the magnitudes, patterns, and correlations of the environmental fluctuations. In general, realized heritabilities will be more similar to estimated heritabilities as larger asymmetries are incorporated.

The results presented here appear to contradict those of VIA and LANDE (1987), who concluded that genotype-environment interactions will not maintain significant levels of genetic variation, except under very restrictive conditions. Their approach is very different from ours, being based on spatially varying phenotypic fitnesses and FALCONER's (1952) representation of characters in different environments as genetically correlated character states. However, their qualitative conclusion is not due to the difference in mathematical formulation so much as to an implicit assumption in their model. Namely, they assume that unless there are complete correlations of breeding

values across environments, there exists a single genotype that is superior to all others in all of the environments. Such an assumption will clearly lead to monomorphism in classical population genetics models such as the LEVENE (1953) model, as well as in quantitative genetics models. In contrast, our symmetry assumptions ensure that no single genotype will produce an average phenotype that is optimal in all environments. This leads to our prediction of stable polymorphism. It will be difficult to refute VIA and LANDE's assumption, because it may be claimed that the optimal genotype has not yet appeared, and disruptive selection may maintain variation for a long period while the equilibrium is approached. However, it seems worthwhile to understand the consequences of assuming that no uniformly most fit genotype exists.

Another approach to the general question, can environmental fluctuations maintain polygenic variation, is to assume that the position of the optimum phenotype fluctuates, *i.e.*, to consider fluctuations in ϕ rather than in the additive effects. Analyzing such models demonstrates that the maintenance of polygenic variation is not ensured by there being no uniformly most fit genotype. Fluctuations in ϕ are formally the same as fluctuations in the additive effects with complete correlation, *i.e.*, $\rho_w = \rho_b = 1$. This can be mimicked in our model by setting each of the $Z_j^{(i)}$ equal to a single random variable that fluctuates. Since this is equivalent to setting $\rho_w = 1$, equation (6b) shows that polymorphism will not be maintained in this case. This claim is supported by analyses of mutation-selection balance. Using his Gaussian allelic model, LANDE (1977) showed that the equilibrium variance maintained by mutation-selection balance is not changed by temporal fluctuations in the position of the phenotypic optimum. Under a model with non-Gaussian distributions of allelic effects, TURELLI (1988 and unpublished data) has shown via both analytical and numerical approximations that temporal fluctuations of the optimum lead to only very small increases in the amount of variation over that maintained by mutation-selection balance with a constant optimum.

These theoretical results concerning fluctuating optima seem contrary to the experimental results of MACKAY (1981) who found that Drosophila populations kept in temporally or spatially fluctuating food regimes maintained much higher additive variances for two out of three characters than control populations kept under constant conditions. She postulated that the environmental fluctuations may be favoring heterozygotes, and this interpretation is consistent with our model of fluctuating allelic effects. Determining the importance of this mechanism will require additional theoretical analysis incorporating realistic asymmetries and more experiments that monitor additive variances under constant and variable conditions.

We would like to thank JERRY COYNE, RUSS LANDE, BRUCE RISKA, MONTY SLATKIN and SARA VIA for helpful comments. We hasten to add that we failed to convince all of them of our conclusions. This research was supported by National Science Foundation grant BSR-8806548.

LITERATURE CITED

BULMER, M. G., 1980 *The Mathematical Theory of Quantitative Genetics.* Oxford University Press, Oxford.

BULMER, M. G., 1988 Maintenance of genetic variability by mutation-selection balance: a child's guide through the jungle. Genome (in press).

COMSTOCK, R. E., and R. H. MOLL, 1963 Genotype-environment interactions, pp. 164–194. In *Statistical Genetics in Plant Breeding*, Edited by W. D. HANSON and H. F. ROBINSON. NAS-NRC Publ. 982, Washington, D.C.

COYNE, J. A., and E. BEECHAM, 1987 Heritability of two morphological characters within and among natural populations of *Drosophila melanogaster.* Genetics **117:** 727–737.

DOBZHANSKY, TH., O. PAVLOVSKY, B. SPASSKY and N. SPASSKY, 1955 The genetics of natural populations. XXIII. Biological role of deleterious recessives in populations of *Drosophila pseudoobscura.* Genetics **40:** 781–796.

DOBZHANSKY, TH., and H. LEVENE, 1955 The genetics of natural populations. XXIV. Developmental homeostasis in natural populations of *Drosophila pseudoobscura.* Genetics **40:** 797–808.

FALCONER, D. S., 1952 The problem of environment and selection. Amer. Natur. **86:** 293–298.

FALCONER, D. S., 1981 *Introduction to Quantitative Genetics*, Longman, London.

FELSENSTEIN, J., 1976 The theoretical population genetics of variable selection and migration. Annu. Rev. Genetics **10:** 253–280.

GILLESPIE, J. H., 1978 A general model to account for enzyme variation in natural populations. V. The SAS-CFF model. Theor. Popul. Biol. **14:** 1–45.

GILLESPIE, J. H., 1984 Pleiotropic overdominance and the maintenance of genetic variation in polygenic characters. Genetics **107:** 321–330.

GUPTA, A. P., and R. C. LEWONTIN, 1982 A study of reaction norms in natural populations of *Drosophila pseudoobscura.* Evolution **36:** 934–948.

KARLIN, S., 1979 Principles of polymorphism and epistasis for multilocus systems. Proc. Natl. Acad. Sci. USA **76:** 541–545.

KIMURA, M., 1956 Rules for testing stability of a selective polymorphism. Proc. Natl. Acad. Sci. USA **42:** 336–340.

LANDE, R., 1975 The maintenance of genetic variability by mutation in a polygenic character with linked loci. Genet. Res. **26:** 221–234.

LANDE, R., 1977 The influence of the mating system on the maintenance of genetic variability in polygenic characters. Genetics **86:** 485–498.

LANDE, R., 1980 Genetic variation and phenotypic evolution during allopatric speciation. Am. Nat. **116:** 463–479.

LERNER, I. M., 1954 *Genetic Homeostasis.* Wiley, New York.

LEVENE, H., 1953 Genetic equilibrium when more than one ecological niche is available. Am. Nat. **87:** 331–333.

LEWONTIN, R. C., 1964 The interaction of selection and linkage. II. Optimum models. Genetics **50:** 757–782.

MACKAY, T. F., 1981 Genetic variation in varying environments. Genet. Res. **37:** 79–93.

MUKAI, T., S. I. CHIGUSA and S.-I. KUSAKABE, 1982 The genetic structure of natural populations of *Drosophila melanogaster.* XV.

Nature of developmental homeostasis for viability. Genetics **101:** 279–300.

PANI, S. N., and J. F. LASLEY, 1972 Genotype × Environment Interactions in Animals. Missouri Agricultural Experiment Station Research Bull. 992, Columbia, Mo.

PROUT, T., 1958 A possible difference in genetic variance between wild and laboratory populations. Drosophila Inform. Serv. **32:** 148–149.

ROSE, M. R., 1982 Antagonistic pleiotropy, dominance, and genetic variation. Heredity **48:** 63–78.

TACHIDA, H., and T. MUKAI, 1985 The genetic structure of natural populations of *Drosophila melanogaster*. XIX. Genotype-environment interaction in viability. Genetics **111:** 43–55.

TURELLI, M., 1984 Heritable genetic variation via mutation-selection balance: Lerch's zeta meets the abdominal bristle. Theor. Popul. Biol. **25:** 138–193.

TURELLI, M., 1985 Effects of pleiotropy on predictions concerning mutation-selection balance for polygenic traits. Genetics **111:** 165–195.

TURELLI, M., 1986 Gaussian versus non-Gaussian genetic analyses of polygenic mutation-selection balance. pp. 607–628. In: *Evolutionary Processes and Theory*, Edited by S. KARLIN and E. NEVO. Academic Press, New York.

TURELLI, M., 1988 Population genetic models for polygenic variation and evolution, pp. 601–618. In: *The Second International Conference on Quantitative Genetics*, Edited by B. S. WEIR, E. J. EISEN, M. M. GOODMAN and G. NAMKOONG. Sinauer, Sunderland, Mass.

UNDERHILL, D. K., 1969 Heritability of some linear body measurements and their ratios in the leopard frog *Rana pipiens*. Evolution **23:** 268–275.

VIA, S., and R. LANDE, 1987 Evolution of genetic variability in a spatially heterogeneous environment: effects of genotype-environment interaction. Genet. Res. **49:** 147–156.

WRIGHT, S., 1968 *Evolution and the Genetics of Populations*, Vol. 1. University of Chicago Press, Chicago.

WRIGHT, S., 1977 *Evolution and the Genetics of Populations*, Vol. 3. University of Chicago Press, Chicago.

YAMADA, Y., 1962 Genotype by environment interaction and genetic correlation of the same trait under different environments. Jpn. J. Genet. **37:** 498–509.

Communicating editor: B. S. WEIR

APPENDIX

Here we will review a property of the SAS-CFF model of selection in a random environment that is key to our analysis of the quantitative genetic model. The one-locus SAS-CFF model (GILLESPIE 1978) is very similar to a quantitative genetic model in that there is an underlying additive scale (representing enzyme activity in the SAS-CFF model) and a concave, monotonic increasing fitness function, ϕ, mapping the additive scale onto fitness. Consider a particular locus with k alleles, A_i, and let the contribution of the ith allele to the enzyme activity be $1 + Z_i$ in a specific environment. The Z_i are viewed as random variables that fluctuate in both time and space. Their moments are defined by

$$\begin{aligned} E\{Z_i\} &= \mu_i \\ \mathrm{Var}\{Z_i\} &= \sigma^2 \\ \mathrm{Cov}\{Z_i,Z_j\} &= \sigma^2\rho_w. \end{aligned} \tag{A-1}$$

If the first two moments of Z_i are small, say of order ε with ε much less than one, then the dynamics of the allele frequency may be modelled by a diffusion process with

$$E\{dx_i\} = x_i(\phi'(1)/2)\sum_{j=1}^{k}[x_j(\mu_i-\mu_j)+VB(F-x_i)]dt$$

and

$$E\{dx_idx_j\} = Vx_ix_j(\delta_{ij}+F-x_i-x_j)dt, \tag{A-2}$$

where

$$F = \sum_{i=1}^{k} x_i^2,\ V = \phi'(1)^2\sigma^2(1-\rho)[1-\pi(1-c)]/2,$$

and

$$B = \frac{2-[\phi''(1)/\phi'(1)^2]-2\pi p(1-c)}{1-\pi(1-c)} \tag{A-3}$$

(GILLESPIE 1978). Here, π is a measure of the number of subdivisions of the environment, c is a measure of the correlation of the enzyme activity between separate patches, and p is a measure of the "hardness" of selection. Most of the details are not of immediate concern here. What should be noted is that the parameter B is a measure of the strength of balancing or centripetal selection relative to the strength of the centrifugal selection as measured by V. As B grows, so does the heterozygosity of the population.

The key difference between the SAS-CFF model and a model of genotype-environment interactions for a quantitative trait is that in the latter case the function ϕ is assumed to have an optimum. At the optimum the derivative of ϕ is zero. If we set $\phi'(1) = 0$ in (A-2), the diffusion degenerates to a system of ordinary differential equations,

$$\frac{dx_i}{dt} = -x_i\phi''(1)\,\sigma^2(1-\rho_w)(F-x_i), \tag{A-4}$$

whose equilibrium solution is simply $x_i = 1/k$. This result is somewhat unsettling in that a model that is based on a stochastic difference equation has produced a nonrandom dynamical system. The reason for this behavior may be found by examining the fitnesses of genotypes directly. The fitness of the genotype A_iA_j in a particular environment may be written

$$\begin{aligned} W_{ij} = \phi(1+(Z_i+Z_j)/2). &\approx \phi(1)+\phi'(1)[(Z_i+Z_j)/2] \\ &+\phi''(1)[(Z_i+Z_j)/2]^2+\cdots \end{aligned} \tag{A-5}$$

The first two moments of this fitness are

$$\begin{aligned} E\{W_{ij}\} &= \phi(1)+\phi'(1)(\mu_i+\mu_j)/2+\phi''(1)\sigma^2\cdot[1 \\ &\quad +\delta_{ij}+(1-\delta_{ij})\rho_w]/4+o(\varepsilon) \end{aligned} \tag{A-6}$$

$$\mathrm{Var}\{W_{ij}\} = \phi'(1)^2\sigma^2[1+\delta_{ij}+(1-\delta_{ij})\rho_w]/2+o(\varepsilon), \tag{A-7}$$

where $\delta_{ii} = 1$, $\delta_{ij} = 0$ for $i \neq j$, and $o(\varepsilon)$ means that there are additional terms of smaller order of magnitude than ε, the order of magnitude of μ and σ^2. If $\phi'(1) = 0$, these moments become

$$\begin{aligned} E\{W_{ij}\} &= \phi(1)+\phi''(1)\sigma^2(1+\delta_{ij} \\ &\quad +(1-\delta_{ij})\rho_w)/4+o(\varepsilon) \end{aligned} \tag{A-8}$$

$$\mathrm{Var}\{W_{ij}\} = o(\varepsilon). \tag{A-9}$$

The variance in fitness is of smaller order of magnitude than the difference in the mean fitnesses of homozygotes and heterozygotes. Furthermore, the mean fitness of a heterozygote always exceeds that of a homozygote whenever $\rho_w < 1$. Thus the main effect of the model is overdominance for mean fitnesses, and the variances in fitness are asymp-

totically (as $\varepsilon \to 0$) insignificant when compared to this mean effect. This accounts for the deterministic dynamics.

With this insight it is clear how to obtain the differential equation (A-4) directly without going through the intermediate diffusion step. Simply assume at the outset that fitnesses are constant and given by (A-8) then use standard deterministic population genetics theory to obtain the limiting differential equation as $\varepsilon \to 0$. It should be emphasized, however, that the full diffusion approximation is necessary to justify this approach.