Pleiotropic Stabilizing Selection Limits the Number of Polymorphic Loci to at Most the Number of Characters

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ABSTRACT

We demonstrate that, in a model incorporating weak Gaussian stabilizing selection on n additively determined characters, at most n loci are polymorphic at a stable equilibrium. The number of characters is defined to be the number of independent components in the Gaussian selection scheme. We also assume linkage equilibrium, and that either the number of loci is large enough that the phenotypic distribution in the population can be approximated as multivariate Gaussian or that selection is weak enough that the mean fitness of the population can be approximated using only the mean and the variance of the characters in the population. Our results appear to rule out antagonistic pleiotropy without epistasis as a major force in maintaining additive genetic variation in a uniform environment. However, they are consistent with the maintenance of variability by genotype-environment interaction if a trait in different environments corresponds to different characters and the number of different environments exceeds the number of polymorphic loci that affect the trait.

DETERMINATION of the forces responsible for the maintenance of additive genetic variability in natural populations has been a subject of great interest in recent years. One approach has used theoretical techniques to investigate the plausibility of potential mechanisms that include drift (LYNCH and HILL 1986), environmental variability (*e.g.*, GILLESPIE and TURELLI 1989), heterosis (GILLESPIE 1984) and mutation-selection balance (*e.g.*, BULMER 1972, 1980; LANDE 1976; TURELLI 1984; BARTON 1986; BARTON and TURELLI 1987).

Many authors, beginning with SEWALL WRIGHT (summarized in WRIGHT 1977), have noted that pleiotropy is another factor that may contribute to the maintenance of additive genetic variability. The interaction between pleiotropy and mutation-selection balance was examined by TURELLI (1985). Rather than focusing on pleiotropy, however, this work emphasized the robustness of predictions of mutation-selection balance for genetic systems in which there is hidden selection on characters connected by pleiotropy. ROSE (1985) studied the effects of pleiotropy on polymorphism in life history characters. He assumed that mortality and fecundity are controlled by a single diploid locus, with reversal of dominance at a fixed age. Under these conditions, he demonstrated that recessive deleterious alleles may be maintained in the population. More recently, GIMELFARB (1986) investigated the role of antagonistic pleiotropy alone in maintaining additive genetic variability. In a diploid model with two characters and stabilizing selection, he showed that two loci, which contributed additively to the two characters, could be polymorphic at a stable equilibrium. Consequently, substantial amounts of additive genetic variability could be maintained in this two locus model.

We sought to characterize the amount of additive genetic variability that could be maintained at loci that contribute additively to n characters all undergoing weak Gaussian stabilizing selection. We used a definition of character based on a change of coordinates determined by the form of selection: the number of characters is the number of independent components in the Gaussian selection scheme. We also assumed that we could approximate the mean fitness of the population using only the mean, variance, and covariances of the characters undergoing selection. As noted by BARTON and TURELLI (1987), this will hold under either of the following two conditions: (1) the number of loci is large enough so that the distribution of phenotypes in the population could be approximated as a multivariate Gaussian, or (2) weak stabilizing selection. As is common in studies of quantitative genetics (BULMER 1980), we assumed that we could ignore the effects of linkage disequilibrium. Under these assumptions, we obtained the result that at most n loci could be maintained at a stable polymorphism if selection were weak enough that the effects of disequilibrium could be ignored. Obviously, there are trivial cases where selection on n characters in fact maintains n loci polymorphic, *e.g.*, if each character were determined by a single locus, with the heterozygote corresponding to the optimum. There may also be stable equilibria with fewer segregating loci than the number of characters.

When assessing the importance of pleiotropy in

maintaining variability, it must be noted that pleiotropy may affect allele frequencies not only through correlated responses to selection, but also via differential expression of a single trait in different environments. That is, in some cases, pleiotropy may provide the genetic mechanism underlying the phenomenon interpreted as interaction between genotype and environment. This relationship can be described explicitly in our formulation. We regard a single trait with multiple states, each of which corresponds to a different environment, as separate characters. Thus, our results can be used to gain insight into the role of genotype-environment interaction in the maintenance of genetic variability (VIA and LANDE 1987; GILLESPIE and TURELLI 1989).

MODEL

We will describe a model with an arbitrary number of characters determined additively by n biallelic loci and multivariate Gaussian stabilizing selection. In this model, we assume that selection is weak, which allows a simple calculation of mean fitness. In accordance with our assumption of weak selection, we assume that we can ignore the role of linkage disequilibrium (BULMER 1980; TURELLI 1984). We also assume that mutation does not occur, and, because gene effects are additive, that epistasis and dominance do not affect the system.

The dynamics of the evolutionary system in our formulation can be understood in terms of the mean fitness because mean fitness always increases and is maximized at stable equilibria in a system where linkage equilibrium is assumed (FISHER 1930; AKIN 1979). By making an assumption that the population phenotypic distribution is approximately multivariate Gaussian and, once again, using the assumption of weak selection, we can determine an approximation for the mean fitness of the population. This assumption has been widely used in the analysis of quantitative genetic models (*e.g.*, BARTON 1986) and does not correspond to an assumption of Gaussian effects at a single locus (BARTON and TURELLI 1987). We use this expression for mean fitness to examine the existence and stability of polymorphic equilibria.

Our model is couched in terms of allele frequencies at the various loci. Let there be two alleles at each locus i, with frequencies p_i and $q_i = 1 - p_i$, respectively. Assume that the two alleles at locus i have effects $\alpha(i,k)$ and $\beta(i,k)$ on character k, and that contributions are additive within and between loci. Thus, in any individual, the genetic contribution to character k is given by:

$$\tilde{z}_k = \sum_{i=1}^{n} [x(i,k) + y(i,k)], \tag{1}$$

where the variables $x(i,k)$ and $y(i,k)$, representing the contributions from the two alleles at locus i to character k, take on the values $\alpha(i,k)$ or $\beta(i,k)$, depending on the identity of the alleles at locus i. Thus, the mean phenotype for a particular character is

$$\tilde{z}_k = \sum_{i=1}^{n} [\alpha(i,k)p_i + \beta(i,k)q_i], \tag{2}$$

with variance

$$v(\tilde{z}_k) = \sum_{i=1}^{n} [\alpha(i,k) - \beta(i,k)]^2 p_i q_i. \tag{3}$$

The covariance between any two characters $\tilde{z}_j$ and $\tilde{z}_k$ is

$$\begin{aligned} &\mathrm{cov}(\tilde{z}_j,\tilde{z}_k) \\ &= \sum_{i=1}^{n} [\alpha(i,j) - \beta(i,j)][\alpha(i,k) - \beta(i,k)]p_i q_i. \end{aligned} \tag{4}$$

Suppose that weak Gaussian stabilizing selection occurs around the optimum for each character. Without loss of generality, we assume that the optimum value for all characters is $\hat{\tilde{z}} = 0$, with a corresponding symmetric, positive definite selection matrix, $\tilde{\mathbf{C}}$. Note that in this formulation, unlike earlier studies (*e.g.*, GIMELFARB 1986), the optimum for a character need not equal its mean value. Consequently, in our model, the contribution to the fitness of an individual due to selection on the character states is given by

$$w(\tilde{\mathbf{z}}) = \exp[-(\tfrac{1}{2})\tilde{\mathbf{z}}^T\tilde{\mathbf{C}}\tilde{\mathbf{z}}] \tag{5}$$

Now consider the matrix of selection coefficients. We have made no assumptions about the selection matrix, $\tilde{\mathbf{C}}$, and character set, $\tilde{\mathbf{z}}$. However, it will be useful to transform this matrix and the set of characters to forms that are equivalent but analytically more tractable. Since the matrix of selection coefficients is symmetric and positive definite, it can be diagonalized by a linear change of variables. This is done using a unitary matrix, $\mathbf{B}$, i.e., a matrix whose transpose equals its inverse (see, for example, HORN and JOHNSON 1985):

$$\mathbf{B}^T = \mathbf{B}^{-1}.$$

Thus, (5) is equivalent to:

$$w(\tilde{\mathbf{z}}) = \exp[-(\tfrac{1}{2})\tilde{\mathbf{z}}^T\mathbf{B}^T\mathbf{B}\tilde{\mathbf{C}}\mathbf{B}^{-1}\mathbf{B}\tilde{\mathbf{z}}]. \tag{6}$$

Now define the diagonal matrix $\mathbf{C}$ as

$$\mathbf{C} = \mathbf{B}\tilde{\mathbf{C}}\mathbf{B}^{-1},$$

and a new set of characters z_k, which are linear combinations of the original characters, as

$$\mathbf{z} = \mathbf{B}\tilde{\mathbf{z}}.$$

In terms of $\mathbf{z}$ and $\mathbf{C}$, we can rewrite Equation 6 describing selection as

$$w(z) = \exp[-(\tfrac{1}{2})\mathbf{z}^T\mathbf{C}\mathbf{z}] = \exp[-(\tfrac{1}{2})\sum_{i=1}^{n} z_i^2 s_i], \quad (7)$$

where s_i represents the selection coefficient corresponding to the new character z_i, and $\mathbf{C}$ is diagonal.

In other words, *without loss of generality*, we change coordinate systems rather than analyzing the model in terms of the original coordinates. In the new coordinates, the matrix of selection coefficients is diagonal and the axes composing the coordinate system are mutually perpendicular. Each axis corresponds to a new character, which is formed from linear combinations of the original characters. Further, because each new character is independent of the others, the number of characters is the number of independent components in the Gaussian selection regime. Because the new characters are linear combinations of the original characters, it is straightforward to rewrite the means and variances (2)–(4) in terms of the new characters. Finally, the transformation means that we examine selection relative to the new set of characters. It is important to note that we are not restricting attention to the case where, in terms of characters observed, selection is on only a single character. *Our results hold for any Gaussian stabilizing selection regime.*

Now assume that the phenotypic structure of the population can be described by a multivariate normal distribution with mean $\bar{z}$ and variance covariance matrix $\mathbf{M}$. We will use (7) and the multivariate normal approximation to derive an approximation for the mean fitness of the population.

Following WRIGHT (1935) (see also BARTON 1986), we approximate the evolutionary dynamics of the multilocus system as:

$$dp_i/dt = p_i(1 - p_i)\partial \ln \bar{w}/\partial p_i. \quad (8)$$

Mean fitness, $\bar{w}$, is given by

$$\bar{w} = \int w(z)p(z)dz,$$

where $p(z)$ is the probability distribution describing the phenotypes in the population. After substitution and some algebra, using the assumption that the phenotypic distribution is given by a multivariate normal distribution, this becomes

$$\bar{w} = 1/[(2\pi)^n|\mathbf{M}|]^{1/2} \cdot \int \exp\{-\tfrac{1}{2}[(\mathbf{z}^T\mathbf{C}\mathbf{z}) + (\mathbf{z} - \bar{\mathbf{z}})^T\mathbf{M}^{-1}(\mathbf{z} - \bar{\mathbf{z}})]\}dz. \quad (9)$$

Equation 9 is simply the multidimensional version of the expression that often is used for single characters (*e.g.*, BARTON 1986). Now recall that under weak Gaussian stabilizing selection, mean fitness depends only on the mean and variance of the phenotypic distribution (BARTON and TURELLI 1987), since higher order moments are negligible. This is true for all phenotypic distributions. Also, $\bar{w}$ is a Lyapunov function (HOFBAUER and SIGMUND 1988). This means that small (higher order) changes in $\bar{w}$ will not alter its qualitative features. *Thus, regardless of the underlying phenotypic distribution, (9) and results derived from (9) are applicable to any genetic system in which mean fitness does not differ from (9) to terms of second order.*

Algebraic manipulation and application of the weak selection assumption (see Appendix) yields

$$\bar{w} \cong [1 - \mathrm{Tr}(\mathbf{MC})]^{1/2}\exp[-(\tfrac{1}{2})\bar{\mathbf{z}}^T\mathbf{C}\bar{\mathbf{z}}] \quad (10)$$

where Tr denotes the trace of the matrix. Therefore, using the relationship that

$$\ln[1 - \mathrm{Tr}(\mathbf{MC})] \cong -\mathrm{Tr}(\mathbf{MC})$$

when $\mathrm{Tr}(\mathbf{MC})$ is small (as it would be under weak selection), we find from (10):

$$\ln \bar{w} \cong -(\tfrac{1}{2})\mathrm{Tr}(\mathbf{MC}) - (\tfrac{1}{2})\bar{\mathbf{z}}^T\mathbf{C}\bar{\mathbf{z}}. \quad (11)$$

We will use this formulation to prove our main result, which follows: *In a system in which m characters* (defined below as independent components) *undergo weak Gaussian stabilizing selection, at most m loci will be polymorphic at a stable equilibrium, assuming linkage equilibrium.* We outline the proof of this result in biological terms.

A simple example of a system with m characters and m polymorphic loci is one in which each character is determined by only one locus and the heterozygote has the highest fitness. In this case, it is obvious that polymorphism can be maintained at all loci. Now consider the case where there are more loci than characters. We will use contradiction to show that this cannot yield a stable polymorphism. Assume that there is a stable polymorphic equilibrium with m characters determined by n loci, where n is larger than m. Denote the equilibrium values of the allele frequencies by the vector $\mathbf{p}^*$, and the corresponding population mean phenotype vector by $\bar{\mathbf{z}}^*$. Since there are more loci that characters, there are many combinations of allele frequencies that can produce a particular mean phenotype. More precisely, since there are more loci than characters, and the characters are determined additively, there must be a nonempty set of allele frequencies, $\mathscr{P}$, which contains $\mathbf{p}^*$ (linear subspace of dimension $n - m$), for which the population mean phenotype vector is $\bar{\mathbf{z}}^*$.

For $\mathbf{p}^*$ to be a stable equilibrium, $\ln \bar{w}$ must be maximized at $\mathbf{p}^*$. This also means that $\mathbf{p}^*$ must maximize $\ln \bar{w}$ when the set of possible allele frequencies is restricted to those in the set $\mathscr{P}$. Recall, however, that the mean phenotype is constant in $\mathscr{P}$. Conse-

quently, for those gene frequencies within $\mathscr{P}$, maximizing the logarithm of the mean fitness can be achieved only by altering the population genetic variance of the phenotype. Denote the term describing the contribution of variance of the log mean fitness by

$$f = -(\tfrac{1}{2})\mathrm{Tr}(\mathbf{MC}).$$

Since the selection matrix **C** is a positive diagonal matrix, f is a sum of terms of the form $-\gamma_i p_i(1 - p_i)$ for some positive constants γ_i. Consequently, any critical point of f, a point where the derivative of f with respect to the allele frequencies is zero, must correspond to a minimum of f. This also must be a minimum when restricted to the set $\mathscr{P}$. (Here we use linearity, which corresponds to our assumption that there is no epistasis.) As a result, because f represents the contribution of variance to $\ln \bar{w}$, mean fitness cannot be at a maximum. This is a contradiction, since mean fitness must be maximized at stable equilibria. Thus, in a system undergoing weak Gaussian stabilizing selection, a polymorphism in which m characters are determined by the sum of the effects of n loci cannot be stable if $n > m$.

DISCUSSION

The most obvious point of discussion is whether our arguments rule out the possibility that antagonistic pleiotropy is a valid explanation for the maintenance of additive genetic variability in natural populations. Obviously, in our model we have not specified the contribution of environmental variability to the characters that we consider. Since we cannot use this model to compare the level of observed variability to environmental variability, we propose to use the number of polymorphic loci per character as a measure of the importance of antagonistic pleiotropy as an explanation for maintaining variability. We consider that observed levels of additive genetic variability require the maintenance of polymorphism at somewhere between ten and one hundred loci. In our development, we have defined the number of characters as the number of independent components, *i.e.*, uncorrelated characters, undergoing Gaussian stabilizing selection. For selection in a single uniform environment, our arguments suggest that pleiotropy coupled with additive determination of characters will not lead to the levels of variability typically observed in natural populations, unless there are a large number of characters all controlled by the same loci. Weak mutation does not change our conclusions, as it will cause only a small change in the equilibrium.

Genotype-environment interaction, which is a ubiquitous feature of most natural systems, may be important in maintaining genetic variability (GILLESPIE and TURELLI 1989). This is consistent with our analysis because under our definition of a character, a single trait in several environments with differing selective pressures is treated as several distinct characters. Our deterministic results, which show that the number of polymorphic loci is less than or equal to the number of characters, with equality possible for a wide range of selective regimes, indicate that the number of polymorphic loci can be as large as the number of different environments. If the environmental variable is continuous, the number of characters can be unbounded.

However, with a continuous environmental variable, our deterministic analysis is inappropriate, and the actual level of polymorphism may be set by stochastic factors. It is possible that as the differences among characters diminish, drift may overcome selection, and the number of polymorphic loci will be smaller than predicted by a deterministic model. More work is needed to answer these questions.

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APPENDIX

Derivation of expression for mean fitness: Recall that we assume weak selection and Gaussian distribution of phenotypes. For notational simplicity, denote

$$\mathbf{M}^{-1} = \mathbf{Q}.$$

Throughout the appendix, we use the fact that since **C**, **M**, and **Q** are symmetric they commute. The mean fitness of the population is given by

$$\bar{w} = 1/[(2\pi)^n |\mathbf{M}|]^{1/2} \int \exp\{-\tfrac{1}{2}[(\mathbf{z}^T\mathbf{C}\mathbf{z}) + (\mathbf{z} - \bar{\mathbf{z}})^T\mathbf{Q}(\mathbf{z} - \bar{\mathbf{z}})]\}dz. \quad \text{(A1)}$$

The integration in (A1) can be performed by expanding terms in the exponent and completing the square, yielding:

$$\bar{w} = [|(\mathbf{Q} + \mathbf{C})^{-1}|/|\mathbf{M}|]^{1/2} \exp[(-\tfrac{1}{2})\bar{\mathbf{z}}^T(\mathbf{Q} - \mathbf{Q}^2(\mathbf{Q} + \mathbf{C})^{-1})\bar{\mathbf{z}}]. \quad \text{(A2)}$$

Because selection is weak by hypothesis, **C** is near zero, hence $\mathbf{Q}^{-1}\mathbf{C}$ is small. As a result, we can write

$$(\mathbf{Q} + \mathbf{C})^{-1} = \mathbf{Q}^{-1}(\mathbf{I} + \mathbf{Q}^{-1}\mathbf{C})^{-1} \approx \mathbf{Q}^{-1}(\mathbf{I} - \mathbf{Q}^{-1}\mathbf{C}). \quad \text{(A3)}$$

Thus, using (A3), terms in (A2) become

$$\mathbf{Q} - \mathbf{Q}^2(\mathbf{Q} + \mathbf{C})^{-1} = \mathbf{Q}(\mathbf{I} - \mathbf{Q}(\mathbf{Q} + \mathbf{C})^{-1}) \approx \mathbf{C}, \quad \text{(A4)}$$

and

$$[|(\mathbf{Q} + \mathbf{C})^{-1}|/|\mathbf{M}|]^{1/2} = |\mathbf{I} - \mathbf{MC}|^{1/2} \approx [1 - \mathrm{Tr}(\mathbf{MC})]^{1/2}. \quad \text{(A5)}$$

The final step in (A5) is an approximation which depends on **MC** being small. Substituting (A4) and (A5) into (A2) yields (10); we obtain (11) by taking the logarithm of both sides.