Genet. Res., Camb., (1986), **47**, *pp.* 209–216 *With 4 text-figures Printed in Great Britain*

The maintenance of polygenic variation through a balance between mutation and stabilizing selection

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(Received 14 November 1985 and in revised form 5 February 1986)

Summary

The maintenance of polygenic variation through a balance between mutation and stabilizing selection can be approximated in two ways. In the 'Gaussian' approximation, a normal distribution of allelic effects is assumed at each locus. In the 'House of Cards' approximation, the effect of new mutations is assumed to be large compared with the spread of the existing distribution. These approximations were developed to describe models where alleles may have a continuous range of effects. However, previous analyses of models with only two alleles have predicted an equilibrium variance equal to that given by the 'House of Cards' approximation. These analyses of biallelic models have assumed that, at equilibrium, the population mean is at the optimum. Here, it is shown that many stable equilibria may coexist, each giving a slight deviation from the optimum. Though the variance is given by the 'House of Cards' approximation when the mean is at the optimum, it increases towards a value of the same order as that given by the 'Gaussian' approximation when the mean deviates from the optimum. Thus, the equilibrium variance cannot be predicted by any simple model, but depends on the previous history of the population.

1. Introduction

Despite the importance of continuously varying characters in both natural adaptation and artificial selection, we know almost nothing about their genetic basis. The most that can be measured in the majority of organisms are the phenotypic mean, and the genetic and environmental components of the variance. We would therefore like to find a simple model which would describe the evolution of the mean and the variance, and which would be independent of the unknown relationship between genotype and phenotype. Since many characters are known to be under stabilizing selection in nature (see Lande, 1975, and Turelli, 1984), a particularly important problem is to predict the genetic variance maintained at equilibrium under such selection; this may be seen as a special case of the general problem of predicting the evolution of continuous characters under arbitrary patterns of selection, mutation, and drift.

If no other forces were acting, and if a finite number of loci were responsible for polygenic variation, stabilizing selection would eventually eliminate all variability. The simplest explanation for the maintenance of high levels of genetic variation in natural populations is that it is generated by mutation (Kimura, 1965; Lande, 1975; Turelli, 1984); recurrent mutation may also be an important source of variation in populations under artificial selection (Hill, 1982). Of course, this is not the only possibility: polygenic variation could be caused by the pleiotriopic effects of balanced polymorphisms. This explanation would be more likely if most electrophoretic polymorphism is maintained by balancing selection, but is still plausible even if the majority of such variation is neutral. However, if polygenic variation were simply the side effect of balancing selection, it would not be possible to predict the evolution of the character of interest without understanding the underlying polymorphisms (though see Gillespie, 1984). It therefore seems reasonable to begin by analysing models of mutation/selection balance, in order to find whether measured rates of mutation and stabilizing selection could account for the abundant genetic variation which is observed for most continuous characters.

Kimura (1965) showed that, if the mutation rate to new alleles is sufficiently high, the distribution of effects of each locus will be Gaussian. Lande (1975, 1980) has used this assumption of normally distributed effects to account for the effects of linkage and pleiotropy; his model has been applied to a variety of problems (see review in Turelli, 1984). In the simplest case, where variation is due to n equivalent loci, and where linkage disequilibrium is negligible, the vari-

ance maintained at equilibrium is $\sqrt{(2nU/s)}$; here, U is the variance produced by new mutations per zygote per generation, and s is the strength of stabilizing selection (as defined below). The Gaussian model can be extended, under the same assumptions, to describe the general dynamics of the mean and the variance under selection and drift (section 3 below).

Unfortunately, the genetic variance which is maintained in even a simple balance between mutation and stabilizing selection depends on the nature of the variation at the underlying loci. Turelli (1984) has argued that the mutation rate per locus is unlikely to be high enough to maintain an approximately normal distribution of effects; he shows that the alternative 'House of Cards' approximation (appropriate for low mutation rates (Kingman, 1978)) predicts an equilibrium variance equal to $4\Sigma\mu/s$, where μ is the mutation rate at each locus. This is a qualitatively different form from that derived using the 'Gaussian' approximation. The 'House of Cards' approximation can be extended in a similar way to the 'Gaussian' approximation to describe the dynamics of a quantitative character under arbitrary selection pressures (section 3 below).

Both Lande's 'Gaussian' models, and Turelli's application of the 'House of Cards' approximation, assume that there is continuous distribution of allelic effects at each locus. However, Turelli (1984) predicts the same equilibrium variance as Wright (1935*a*), Latter (1960), Bulmer (1972, 1980) and Kimura (1981), who use models in which only two alleles segregate at each locus. Turelli (1984) shows, using computer simulations of a three allele model, that the distinction between the 'Gaussian' and the 'House of Cards' approximations depends on the mutation rate, and not on the number of alleles involved: the latter approximation is relevant whenever the loci responsible for polygenic variation are close to fixation.

In this paper, I extend Wright's (1935*a*, *b*) biallelic model to include mutation as well as stabilizing selection. Analysis of this model shows than when allelic effects are limited to a discrete set of values (in this case, two), the evolution of the genetic variance is much more complex than is suggested by either Lande's (1975) or Turelli's (1984) continuum-of-alleles models. Over the range of mutation rates for which polygenic variation is maintained by a balance between mutation and stabilizing selection, many alternative equilibria are possible. The genetic variance depends strongly on which equilibrium is reached. At the optimal equilibrium, the variance is minimized, and roughly equals that predicted by the 'House of Cards' approximation; this was the case assumed implicitly by Wright (1935*a*), Latter (1960), Bulmer (1972) and Kimura (1981). However, at other stable equilibria, the variance may be much greater, and approaches that predicted by the 'Gaussian' approximation. Since the equilibrium variance depends critically on the history of the population, it cannot be predicted from the observed distribution of the character: without detailed knowledge of the genetic basis of continuous characters, only a crude description of their evolution is possible.

2. The model

(i) *Selection*

Consider a single character, z', which is determined by the sum of the effects of n loci. The effect of the ith locus is α_i, and the states of the two homologous genes in a diploid individual are denoted by l_i, l_i^*; l_i is 0 or 1, depending on the state of the locus. Thus:

$$z' = \Sigma\, \alpha_i(l_i + l_i^* - 1). \tag{1}$$

The character is assumed to be completely heritable; the effect of environmental variability would merely be to dilute the effects of selection, and would not significantly alter the conclusions. The fitness, W, of an individual with phenotype z' is assumed to follow a Gaussian curve centred on some optimum, z_0, and with variance $1/s$:

$$\log W = -s(z' - z_0)^2/2. \tag{2}$$

The mean fitness of a population with mean z and variance v (assuming that the phenotype, z', is normally distributed, and $sv \ll 1$) is:

$$\log \overline{W} = -s(z - z_0)^2/2 - sv/2 \tag{3a}$$

where

$$z = 2\Sigma\alpha_i(p_i - \tfrac{1}{2}), \tag{3b}$$

$$v = 2\Sigma\alpha_i^2 p_i q_i. \tag{3c}$$

(Here, p_i, q_i are the frequencies of the two alleles at the i'th locus.)

Provided that selection is much slower than recombination, linkage disequilibrium will be negligible; Bulmer (1980) and Turelli (1984) argue that this is a reasonable assumption for most natural populations. Thus, changes in allele frequency are given by the general relation $dp_i/dt = (p_i q_i/2)(\partial \log \overline{W}/\partial p_i)$. (Selection is here assumed to be weak enough that evolution is approximately continuous in time; this condition is automatically satisfied if selection is much weaker than recombination). I will assume that all loci have equal effects. The equations can then be simplified by rescaling time relative to $s\alpha^2/2$, which is a measure of the selection pressure associated with each individual locus. The equation for the effects of selection which results is equivalent to equation 19 in Wright (1935*a*):

$$dp_i/dt = p_i q_i\,((p_i - q_i) - 2\delta). \tag{4}$$

Here, δ is the deviation from the optimum, relative to the effect of a single gene, α: $\delta = (z - z_0)/\alpha = 2\Sigma((p_i - \tfrac{1}{2}) - (z_0/\alpha))$. Two forces are acting in (4). First, stabilizing selection acts to reduce the phenotypic variance, and hence to reduce the heterozygosity at

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each of the underlying loci. This causes disruptive selection on the allele frequency, and hence a tendency for fixation of one or other allele. Second, selection acts to pull the mean towards the optimum, and so to reduce δ. I will begin by considering the equilibria under selection alone, and their stabilities, and will later introduce mutation.

At each locus, there are, in principle, three equilibrium frequencies: $p = 0, \frac{1}{2}+\delta$, or 1; the number of loci at these frequencies will be denoted by m, v, M, respectively. The state of the whole system is described by these three numbers. For each set of numbers, $\{m, v, M\}$, a large number of equilibria is available, corresponding to different permutations of loci. However, since the effects of each locus have been assumed identical, these permutations will have identical properties. We will therefore only be concerned with the differences between different *classes* of equilibria, characterized by different $\{m, v, M\}$.

The deviation from the optimum is given by:

$$\delta = (M-m-(z_0/\alpha))/(1-2v) \qquad (5)$$

The stability of the class of equilibria $\{m, v, M\}$ is determined by the eigenvalues of the matrix $S_{ij} = \partial^2 \log \bar{W}/\partial p_i\, \partial p_j$. These are:

$$\lambda = -2(\tfrac{1}{2}+\delta) \quad (m \text{ times}) \qquad (6a)$$

$$= -2(\tfrac{1}{2}-\delta) \quad (M \text{ times}) \qquad (6b)$$

$$= -(4v-2)(\tfrac{1}{4}-\delta^2) \quad (\text{once when } v > 0) \qquad (6c)$$

$$= 2(\tfrac{1}{4}-\delta^2) \quad (v-1 \text{ times when } v > 1). \qquad (6d)$$

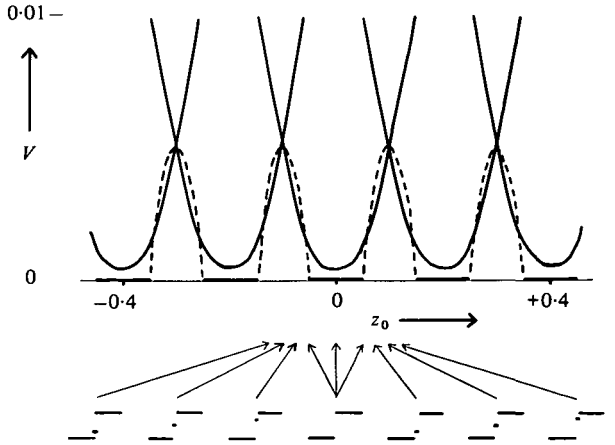

Fig. 1. The variance, V, plotted against the optimum, z_0, for two values of the mutation rate, μ. When there is no mutation, ($\mu = 0$), only one class of equilibria is possible for a given optimum. For half the values of z_0, polymorphism is maintained at one locus (dotted curves); for the other half, no polymorphism is possible ($v = 0$; solid horizontal lines). The series of diagrams below the main graph illustrate these two types of equilibria; they show the equilibrium allele frequency at each of the polygenes. Even a low mutation rate (here, $\mu = 10^{-6}$) causes a qualitative change. The polymorphic equilibria become unstable for all values of z_0, whilst the monomorphic equilibria become stable for a wide range of optima (solid parabolas): two equilibria may now be stable simultaneously. (Here, there are $n = 100$ loci, each with effect $\alpha = 0{\cdot}1$. Stabilizing selection has strength $s = 1$).

The equilibrium can only be stable to the introduction of new alleles at fixed loci, or to perturbations at polymorphic loci, if all these eigenvalues are negative. Thus, (6*d*) implies that stability is only possible when $v = 0$ or 1. Unless either M or m is zero, (6*a*, *b*) require that $|\delta| < (\frac{1}{2})$ (as shown by Wright, 1935*a*). Equation 5 can therefore be rearranged to show that the optimum must lie inside the range $(M-m)-(\frac{1}{2}) < (z_0/\alpha) < (M-m)+(\frac{1}{2})$. We can see that, for any particular z_0, stable equilibria are only possible for one combination of $\{m, v, M\}$.

Now, imagine that z_0 is gradually increased, and that mutations are supplied at a rate high enough to keep the population at the stable equilibrium, but not so high as to distort that equilibrium. The population will pass from a state in which all loci are fixed for one or other allele, through polymorphism at a single locus, to a new state of fixation (Fig. 1). Thus, for roughly half the parameter values, selection maintains no genetic variance at all, whilst for the other half, variation is maintained at only a single locus.

(ii) *Mutation/selection balance*

Suppose that we now introduce recurrent mutation. It is simplest to assume that mutation occurs at an equal rate μ in each direction; I do not believe that relaxing this assumption of mutational symmetry would introduce any qualitative change in the results. Equation 4 becomes, at equilibrium:

$$dp_i/dt = 0 = p_i q_i ((p_i-q_i)-2\delta)-2\gamma(p_i-q_i). \qquad (7)$$

(Here, γ is a measure of the rate of mutation, relative to the selection pressure on a single locus: $\gamma = \mu/s\alpha^2$.)

This equation is identical to Wright's (1935*a*) equation 42, except that Wright assumed unidirectional mutation, and more important, assumed that the mean lies at the optimum ($\delta = 0$). The present analysis differs from those of Wright (1935*a*, *b*), Latter 1960), and Bulmer (1972) primarily in the inclusion of deviations from the optimum; though these are small in magnitude, being less than half the effect of a single substitution, ($|\delta| < \frac{1}{2}$), we will see that they introduce significant complications.

I will first consider the conditions for the existence of equilibria. In the absence of mutation ($\gamma = 0$), we have seen that, provided the mean does not deviate too far from the optimum ($|\delta| < \frac{1}{2}$), three equilibria are available at each locus. We will concentrate on those equilibria in which all loci are near to fixation: m for the '$-$' allele, and M for the '$+$' allele. The frequencies at these loci are denoted by (p, q) and (P, Q), respectively. Both p and P are solutions of (7); no loci lie at the intermediate equilibrium, which is the solution of (7) lying between p and P. When there is no mutation, the above analysis shows that this class of equilibria cannot be realized for roughly half the values of z_0. However, I show here that unless mutation is extremely low ($(n+1)^2\,\gamma < 1$), this class exists and is stable for a wide range of z_0. As γ increases, this range be-

https://doi.org/10.1017/S0016672300023156 Published online by Cambridge University Press

comes wider, and the number of alternative equilibria increases. As γ increases still further, the heterozygosity at each locus increases, until eventually all the equilibria collapse into a single state, in which variation is maintained primarily by mutation pressure. The first problem, then, is to find the parameter values which allow the existence of each class of equilibria; this is the most important part of the analysis, since it will be shown that if these equilibria exist, they will be stable.

Equation 7 is a cubic polynomial. Although there is an explicit formula for its roots (Abramowitz & Stegun, 1965), it is complicated; analytic progress will not be possible without some more tractable approximation. First, assume that γ is small enough that each locus is very close to fixation ($\gamma, p, Q \ll 1$). Taking leading terms in γ gives:

$$p = \frac{\gamma}{(\frac{1}{2}+\delta)} \qquad Q = \frac{\gamma}{(\frac{1}{2}-\gamma)}. \tag{8a}$$

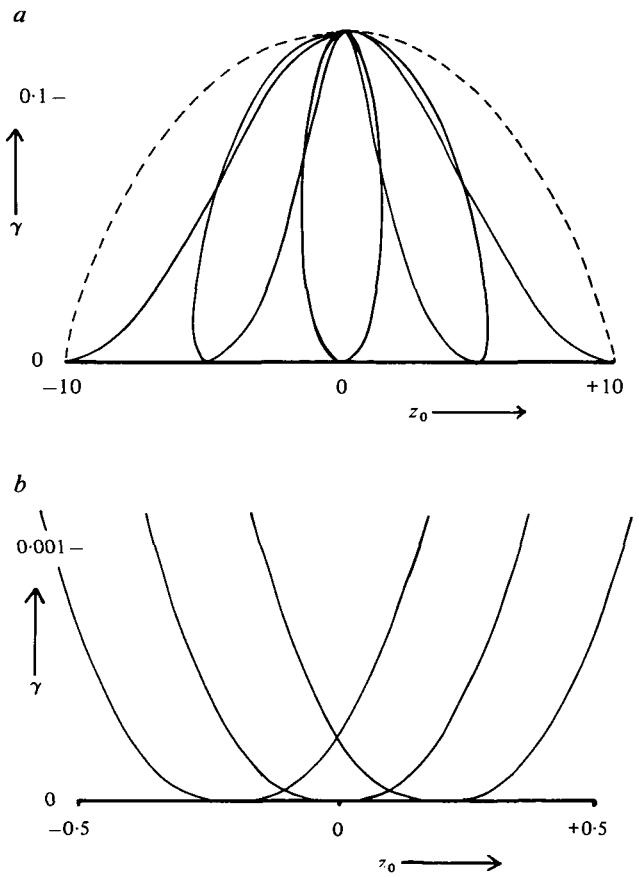

Fig. 2. The range of mutation rates ($\gamma = \mu/s\alpha^2$) and optima (z_0) for which each class of equilibria is stable. Parameter values are as in Fig. 1; the five areas in Fig. 2*a* correspond to (from left to right) the classes of equilibria $\{m, v, M\} = \{100, 0, 0\}, \{75, 0, 25\}, \{50, 0, 50\}, \{25, 0, 75\}$ and $\{0, 0, 100\}$. The equilibrium in which all loci are near fixation for the '+' allele (i.e. $\{0, 0, 100\}$) is stable for arbitrarily large z_0; the right-hand dotted line shows the parameter values beyond which only a single class of equilibria is stable. (A similar comment applies to the left-hand dotted line.) Fig. 2*b* shows details for the region near $z_0 = 0$, $\gamma = 0$, for the classes $\{51, 0, 49\}, \{50, 0, 50\}$ and $\{49, 0, 51\}$.

This approximation breaks down when $|\delta|$ is close to $\frac{1}{2}$; since this may happen over a significant range of parameter values, we must find a better approximation. Let $\delta = \frac{1}{2}-\varepsilon$, and retain leading terms in ε, γ. Then:

$$p = \gamma, \quad Q = (\varepsilon - \sqrt{[\varepsilon^2 - 4\gamma]})/2. \tag{8b}$$

A similar approximation can be derived for $\delta = -\frac{1}{2}+\varepsilon$:

$$p = (\varepsilon - \sqrt{[\varepsilon^2 - 4\gamma]})/2, \quad Q = \gamma. \tag{8c}$$

When $|\delta|$ is not close to $\frac{1}{2}$, ε^2 is much greater than 4γ, and so $\sqrt{(\varepsilon^2 - 4\gamma)} \simeq (\varepsilon - 2\gamma/\varepsilon)$. Hence, the expressions for Q, p in (8*b*, *c*) reduce to those in (8*a*). Equation 8*b*, *c* are therefore accurate whenever $\gamma \ll 1$, even when ε is large.

We can now use these approximations to find the range of equilibria which exist for given γ, z_0. First, suppose that $(M-m)$ is much greater than its optimal value, z_0/α, so that the mean of the character is pulled far above the optimum (δ close to $+\frac{1}{2}$). The closest possible approach to $\delta = \frac{1}{2}$ is, from (8*b*), when $\varepsilon = \frac{1}{2}-\delta = 2\sqrt{\gamma}$, so that $Q = \sqrt{\gamma}$; if the mean is pulled beyond this point, the solution in (8*b*) becomes imaginary, and so cannot be realised. We can now substitute these solutions into (3*b*) and find the smallest value of z_0 for which the class of equilibria $\{m, 0, M\}$ exists. The same method can be used to find the largest value of z_0:

$$(M-m)-(\tfrac{1}{2})-2(M-1)\sqrt{\gamma}+O(M\gamma) < z_0/\alpha < (M-m)+(\tfrac{1}{2})+2(m-1)\sqrt{\gamma}+O(m\gamma). \tag{9}$$

We can see that, if $n\sqrt{\gamma}$ is large (i.e. $\mu \gg s(\alpha/n)^2$), a large number of equilibria is possible for each value of the optimum: roughly, $1+(n-2)\sqrt{\gamma}$ (Figs. 1–4). By comparing the allowable ranges of z_0 for consecutive equilibria ($\{m, 0, M\}, \{m-1, 0, M+1\}$), one can show that, for some z_0, no equilibrium in the class with all loci close to fixation ($v = 0$) can exist when $(n+1)\sqrt{\gamma} < 1$. When mutation becomes extremely low, (9) shows that this class of equilibria becomes impossible for half the values of z_0, a result consistent with the earlier treatment of selection alone (Fig. 1).

Turelli (1984) gave numerical results for a biallelic model identical to that analysed here, and involving up to six loci. However, he did not find multiple equilibria. This was because, with six loci, two equilibria can only be simultaneously stable over a narrow range of optima. For example, in Turelli's table VII, results are presented for $\mu = 10^{-4}$, $s = 0{\cdot}05$ ($= 1/V_s$), and α^2 ($= c^2$) $= 0{\cdot}05$; thus $\gamma = 0{\cdot}04$. The equilibria $\{3, 0, 3\}$ and $\{2, 0, 4\}$ are only simultaneously stable when z_0 is between 0·11 and 0·22. Only the class $\{3, 0, 3\}$ is stable when $z_0 = 0$, as in Turelli (1984). For any of the alternative parameters used ($\mu = 10^{-3}$, $s = 0{\cdot}01$, $\alpha^2 = 0{\cdot}01$), γ would be greater than $\frac{1}{8}$, and multiple equilibria would be impossible for any number of loci. In general, multiple equilibria are never possible when $n < 4$, whilst when $n < 7$, they are impossible for some values of z_0 (Fig. 4).

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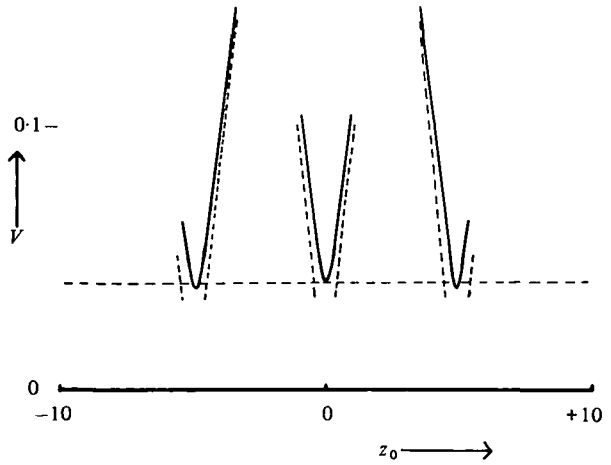

Fig. 3. A graph of the variance, V, against the optimum, z_0, for the classes of equilibria {75, 0, 25}, {50, 0, 50} and {25, 0, 75} (reading from left to right). The mutation rate is $\mu = 10^{-4}$; other parameters are as in Figs. 1 and 2, and so $\gamma = 0{\cdot}01$. The horizontal dotted line shows the variance expected from the 'House of Cards' approximation, $v = 4n\mu/s = 0{\cdot}04$. The slanted dotted lines show the variance expected on the assumption that $\gamma \ll 1$ (equations 8*b*, *c*; $v = \alpha^2\{|(M-m)-z_0/\alpha|-(\frac{1}{2})\}$).

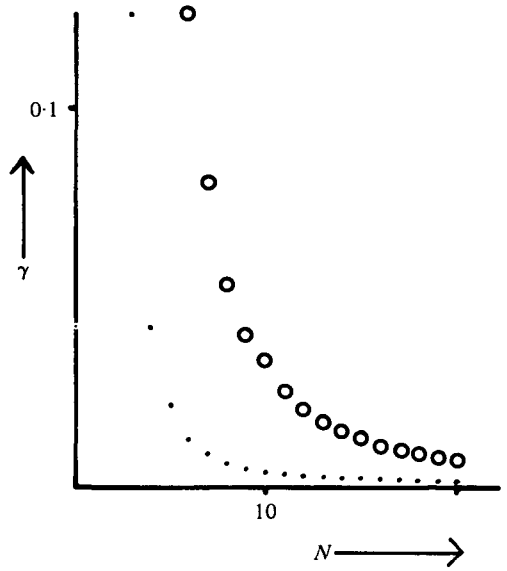

Fig. 4. The dots show the values of the mutation rate ($\gamma = \mu/s\alpha^2$) above which at least one equilibrium of the class {*m*, 0, *M*} is stable for all values of the optimum. The circles show the mutation rate ($\gamma = \mu/s\alpha^2$) above which at least two equilibria of the class {*m*, 0, *M*} are stable for all values of the optimum. Thus, several stable equilibria can coexist for some z_0 when more than three loci are involved ($n > 3$), and coexistence is possible for all z_0 when more than six loci are involved ($n > 6$). These limits are derived from (10); when $z_0 \neq 0$, there will also be an upper limit to γ (see Fig. 2).

The variance maintained at equilibrium for any given {*m*, 0, *M*} can be calculated by solving (5) and (7). When the mean is at the optimum ($\delta = 0$), the variance is $4n\gamma\alpha^2$, which is equal to $4n\mu/s$ (Wright, 1935*a*; Latter, 1960; Bulmer, 1972); this value is equal to that obtained for a continuum of alleles model under the 'House of Cards' approximation (Turelli, 1984). The minimum variance may be very slightly less than this value when the optimum is away from the centre (Fig. 3, Table 1). However, stable equilibria may exist in which the variance is much greater. At the lower extreme of z_0, the variance is (to leading order in γ) $2\alpha^2 M\sqrt{\gamma}$, whilst at the upper extreme, it is $2\alpha^2 m\sqrt{\gamma}$. The approximations of (8*b*, *c*) can be used to find an approximation for the variance: $v = \alpha^2\{|(M-m) - z_0/\alpha| - (\frac{1}{2})\}$. This becomes accurate when the mean is far from the optimum ($|\delta| \approx \frac{1}{2}$; Fig. 3, Table 1).

For the symmetric equilibrium ($m = M = n/2$), the maximum possible variance reduces to $\alpha^2 n\sqrt{\gamma} = \alpha n\sqrt{(\mu/s)}$; if we define $2n\mu\alpha^2$ as U, the variance in the character which is introduced per gamete per generation, we see that the maximum possible variance in this biallelic model ($\sqrt{[nU/2s]}$) is equal to half the variance predicted by the Gaussian approximation ($\sqrt{[2nU/s]}$): the maximum variance depends in the same way on n, U, and s. Thus, the system lies between the predictions of the Gaussian and the 'House of Cards' approximation, at a point which depends on its previous history.

This analysis has assumed that mutation is weak relative to selection ($\gamma \ll 1$). To find the highest mutation rate which is compatible with the existence of multiple equilibria, a more general treatment is needed. The condition that (7) has three real roots is (from Abramowitz & Stegun, 1965):

$$\delta^2 < ((\tfrac{1}{4}) + 5\gamma - 2\gamma^2) - 2\sqrt{[\gamma(1+\gamma)^3]}. \qquad (10)$$

This inequality defines a critical value of $|\delta|$, above which only a single real equilibrium is available at each locus. When γ is small, this value is approximately $\frac{1}{2} - 2\sqrt{\gamma}$, as found above; as γ increases, the allowable range of δ decreases, until above $\gamma = \frac{1}{8}$, only a single equilibrium is possible. Equation 10 can be combined with (3*b*) to find the combinations of mutation rate and optimum (γ, z_0) which allow the existence of multiple equilibria (Fig. 2). When large numbers of loci are involved, many different classes of equilibria may be available for a given combination of parameters (Figs. 2, 4).

(iii) *Stability of the equilibria*

The stability of the equilibria can be found from the matrix of derivatives of (7) with respect to allele frequency: $S_{ij} = \partial(\partial p_i/\partial t)/\partial p_j$. An equilibrium is only stable if the real component of every eigenvalue of S is negative.

$$S_{ii} = (2p_i q_i - 1 - 4\gamma) + 2\delta(p_i - q_i) \quad (i = j) \qquad (11a)$$

$$S_{ij} = -4p_i q_i \quad (i \neq j). \qquad (11b)$$

If M loci are at P, and m at q, the eigenvalues are:

$$\lambda = (6pq - 1 - 4\gamma) + 2\delta(p - q) \quad (\equiv g) \quad (m - 1 \text{ times}) \qquad (12a)$$

$$= (6PQ - 1 - 4\gamma) + 2\delta(P - Q) \quad (\equiv G) \quad (M - 1 \text{ times}) \qquad (12b)$$

$$= (C + c + \sqrt{[(C-c)^2 + 64mMpqPQ]}/2 \quad \text{(once)} \qquad (12c)$$

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$$= (C+c-\sqrt{[(C-c)^2+64mMpqPQ]}/2 \quad \text{(once)} \tag{12d}$$

(where: $c = (2pq-1-4\gamma)+2\delta(p-q)$
$-4(m-1)\,pq = g-4mpq,$

$$C = (2PQ-1-4\gamma)+2\delta(P-Q)$$
$$-4(M-1)\,pq = G-4MPQ)$$

In order for this class of equilibria to be stable, all these eigenvalues must have negative real parts. Since the first two sets of eigenvalues (denoted by g, G above) are equal to the differentials of the cubic polynomial (7), and since p, P are the smallest and largest roots of (7), these two sets of eigenvalues must be negative whenever the equilibria exist (g, $G < 0$). The other two eigenvalues will have negative real parts whenever $c+C < 0$, and $cC > 16mMpqPQ$. Since $c = g-4mpq$, and $C = G-4MPQ$, the first condition is satisfied. The remaining condition can be rewritten as $gG-4mpqG-4MPQg > 0$, which is also satisfied. Thus, this class of equilibria is stable whenever it exists. This is confirmed by numerical calculations of the eigenvalues (Table 1).

3. The phenotypic moments

Barton & Turelli (In prep; Eq. 4*b*) show that, provided the alleles responsible for polygenic variation are rare, the evolution of the mean and variance of a quantitative character can be approximated by:

$$\begin{pmatrix} dz/dt \\ dv/dt \end{pmatrix} = \begin{pmatrix} v & m_3 \\ m_3 & vv_0/n \end{pmatrix} \begin{pmatrix} \partial(\log \overline{W})/\partial z \\ \partial(\log \overline{W})/\partial v \end{pmatrix}. \tag{13}$$

Here, v_0/n is the ratio between the fourth moment and the variance of the character. When all loci have an equivalent distribution of effects, and when alleles are close to fixation, v_0/n remains constant; in the biallelic model analysed here, it is equal to α^2, so that $v_0 = n\alpha^2$ is a measure of the maximum variance which could be maintained. If the third moment of the character (m_3) were negligible, (13) would describe the effects of an arbitrary pattern of selection. In particular, it could be combined with an equation for the variance introduced by mutation to give the variance maintained in a mutation/selection balance. This approximation gives the same result as that obtained by Wright (1935*a*), Latter (1960), and Turelli (1984). However, we have seen that this result can only be

Table 1. *The stable classes of equilibria with 100 loci*; $s = 1$, $\alpha = 0{\cdot}1$, $\mu = 0{\cdot}0001$, *and hence* $\gamma = 0{\cdot}01$

m	v	M	p	P	z	v	v_1	v_2	λ	m_3
(*a*) Optimum at $z_0 = 0$										
45	0	55	0·0124	0·9018	+0·0311	0·1084	0·095	0·0905	−0·00009	−0·0068
46	0	54	0·0124	0·9182	+0·0307	0·0924	0·075	0·0803	−0·00076	−0·0057
47	0	53	0·0127	0·9394	+0·0292	0·0763	0·055	0·0689	−0·00167	−0·0045
48	0	52	0·0133	0·9517	+0·0255	0·0604	0·035	0·0568	−0·00303	−0·0031
49	0	51	0·0151	0·9676	+0·0169	0·0465	0·015	0·0455	−0·00535	−0·0016
50	0	50	0·2042	0·9796	0	0·0400	—	0·0400	−0·00920	0
51	0	49	0·3241	0·9850	−0·0169	0·0465	0·015	0·0455	−0·00535	+0·0016
52	0	48	0·0483	0·9867	−0·0255	0·0604	0·035	0·0568	−0·00303	+0·0031
53	0	47	0·0651	0·9873	−0·0292	0·0763	0·055	0·0689	−0·00167	+0·0045
54	0	46	0·0818	0·9876	−0·0307	0·0924	0·075	0·0803	−0·00076	+0·0057
55	0	45	0·0982	0·9876	−0·0311	0·1084	0·095	0·0905	−0·00009	+0·0068
(*b*) Optimum at $z_0 = 5$										
17	0	83	0·0124	0·9030	5·0311	0·1496	0·155	0·1349	−0·00013	−0·0113
18	0	82	0·0124	0·9138	5·0309	0·1336	0·135	0·1245	−0·00056	−0·0103
19	0	81	0·0125	0·9249	5·0303	0·1173	0·115	0·1133	−0·00109	−0·0091
20	0	80	0·0127	0·9361	5·0290	0·1007	0·095	0·1011	−0·00175	−0·0079
21	0	79	0·0131	0·9476	5·0267	0·0839	0·075	0·0880	−0·00263	−0·0065
22	0	78	0·0139	0·9591	5·0225	0·0673	0·055	0·0742	−0·00391	−0·0050
23	0	77	0·0157	0·9703	5·0144	0·0515	0·035	0·0602	−0·00596	−0·0035
24	0	76	0·0210	0·9801	4·9987	0·0395	0·015	0·0476	−0·00892	−0·0019
25	0	75	0·0382	0·9859	4·9789	0·0393	—	0·0403	−0·00430	−0·0003
26	0	74	0·0686	0·9874	4·9036	0·0516	0·015	0·0427	−0·00145	+0·0011

Note: since the equilibria only depend on the ratio $\mu/s\alpha^2$, these tables can be rescaled to describe many other parameters. $\{m, v, M\}$ are the numbers of loci at the three alternative solutions of (7); p, P are the frequencies of '+' alleles at loci at the upper and lower solutions. z, v, and m_3 are the mean, variance, and third moment of the character. v_1 is the value derived from (8*b*, *c*) and is accurate when $\gamma \ll 1$, and when the mean is far from the optimum. v_2 is the value derived from the third moment, using (14). λ is the largest eigenvalue; it must be negative if the equilibrium is to be stable.

https://doi.org/10.1017/S0016672300023156 Published online by Cambridge University Press

produced by the biallelic model when the equilibrium is such that the mean lies at the optimum. At other equilibria, the variance may be very much greater.

This discrepancy arises because the third moment can become large enough to alter the variance substantially. Provided that $\gamma \ll 1$, the effect of mutation pressure on the mean is negligible, and the increase in variance per generation is $2n\mu\alpha^2$. Hence, (13) becomes:

$$\begin{pmatrix} dz/dt \\ dv/dt \end{pmatrix} = \begin{pmatrix} v & m_3 \\ m_3 & v\alpha^2 \end{pmatrix} \begin{pmatrix} -s\alpha\delta \\ -s/2 \end{pmatrix} + \begin{pmatrix} 0 \\ 2n\mu\alpha^2 \end{pmatrix}. \qquad (14)$$

Hence, at equilibrium:

$$dz/dt = 0 = -s\alpha\delta v - sm_3/2, \qquad (15a)$$

$$dv/dt = 0 = -s\alpha\delta m_3 - sv\alpha^2/2 + 2n\mu\alpha^2. \qquad (15b)$$

When $m_3 = 0$, (15*b*) gives $v = 4n\mu/s$, as expected on the 'House of Cards' approximation. However, when the third moment is large enough that the third term in (15*b*) can be neglected ($|s\alpha m_3| \gg (2n\mu\alpha^2)$), $v = -2m_3\delta/\alpha$. Substituting for δ from (15*a*) gives $v = |m_3/\alpha|$. In the model analysed above, m_3 is approximately equal to $-2M\alpha^3\sqrt{\gamma}$ when the optimum is as low as possible (9). Hence, the greatest possible value of the variance is given correctly, in the limit of very small γ, by the above equation: $v = 2M\alpha^2\sqrt{\gamma}$. The exact values of v, given in Table 1 for $\gamma = 0{\cdot}01$, do not agree very well with the simple prediction, $|m_3/\alpha|$, even at extreme equilibria. This is because the third term in (15*b*) has been neglected; if δ is substituted into (15*b*) from (5), and the resulting quadratic is solved for v, given the observed m_3, agreement is good (v_2 in Table 1).

The present analysis is therefore consistent with the approximation of (13); however, it shows that the third moment of the character is not usually negligible, so that the approximation cannot, in general, give an explicit formula for the equilibrium variance.

4. Discussion

In this simple biallelic model, many alternative equilibria may exist, and may give a wide range of variances. This complex behaviour only occurs at intermediate mutation rates. When mutation is so rare that only a single class of equilibria exists, most of the genetic variance is associated with a single locus. Conversely, when mutation is so frequent that the multiple equilibria merge together, selection becomes negligible: variation is maintained primarily by recurrent mutation. Thus, *for the range of mutation rates for which polygenic variation is maintained by a mutation/selection balance*, several stable equilibria will coexist.

This range of mutation rates is likely to include those found in nature. Turelli (1984) and Lande (1975) suggest that the total mutation rate to genes affecting quantitative characters, $\Sigma\mu$, is typically 10^{-2} or greater; that the variance produced by mutation per generation, $\Sigma\mu\alpha^2$, is $\approx 10^{-3}V_e$, where V_e is the environmental variance; that the number of genes, n, is in the range 10^2 to 10^4; and that a selection pressure $s \approx 0{\cdot}05$ is typical of values measured in natural and laboratory populations (s is expressed in units of the standard deviation of environmental fluctuations, $\sqrt{V_e}$). The behaviour of the model depends on the relative rates of mutation and selection, $\gamma = \mu/s\alpha^2$. This can be rewritten in terms of the observed values, giving $\gamma = (\Sigma\mu)^2/(ns(\Sigma\mu\alpha^2)) = 2\times10^{-2}$ to 2×10^{-4}, well within the range which allows multiple equilibria ($1/n^2 = 10^{-4}$ to $10^{-8} < \gamma < \frac{1}{8}$).

This model is, of course, unrealistic in many respects. Mutation rates, allelic effects, and numbers of alleles are likely to vary from locus to locus; random fluctuations in selection pressures, and random drift, may shift the population between different equilibria; and linkage disequilibrium may reduce the phenotypic variance. I will consider these effects in a later paper; though the details are complicated, it seems that variation in allelic effects will reduce the observable differences between different classes of equilibria, and that sampling drift, for a wide range of population sizes, may be able to keep the population close to the optimal equilibrium. Thus, the 'House of Cards' approximation may in fact be applicable to natural populations, even though the results here show it to be misleading in simple systems.

Thanks are due to J. Felsenstein, J. Gillespie, S. Rouhani, M. Slatkin, and M. Turelli for stimulating discussions, and for their comments on the manuscript. This work was supported by a travel grant from the Royal Society, and by a research grant from the SERC.

References

Abramowitz, M. & Stegun, I. A. (1965). *Handbook of Mathematical Functions*. Dover, New York.

Bulmer, M. G. (1972). The genetic variability of polygenic characters under optimising selection, mutation and drift. *Genetical Research* **19**, 17–25.

Bulmer, M. G. (1980). *The Mathematical Theory of Quantitative Genetics*. Oxford University Press, Oxford.

Gillespie, J. (1984). Pleiotropic overdominance and the maintenance of genetic variation in polygenic characters. *Genetics* **107**, 321–330.

Hill, W. G. (1982). Rates of change in quantitative traits from fixation of new mutations. *Proceedings of the National Academy of Sciences, U.S.A.* **79**, 142–145.

Kimura, M. (1965). A stochastic model concerning the maintenance of genetic variability in quantitative characters. *Proceedings of the National Academy of Sciences, U.S.A.* **54**, 731–736.

Kimura, M. (1981). Possibility of extensive neutral evolution under stabilizing selection with special reference to non-random usage of synonymous codons. *Proceedings of the National Academy of Sciences, U.S.A.* **78**, 5773–5777.

Kingman, J. F. C. (1978). A simple model for the balance between selection and mutation. *Journal of Applied Probability* **15**, 1–12.

Lande, R. (1975). The maintenance of genetic variability by mutation in a polygenic character with linked loci. *Genetical Research* **26**, 221–236.

Lande, R. (1980). The genetic covariance between characters maintained by pleiotropic mutation. *Genetics* **94**, 203–215.

Latter, B. D. H. (1960). Natural selection for an intermediate optimum. *Australian Journal of Biological Sciences* **13**, 30–35.

Turelli, M. (1984). Heritable genetic variation via mutation-selection balance: Lerch's zeta meets the abdominal bristle. *Theoretical Population Biology* **25**, 138–193.

Wright, S. (1935*a*). The analysis of variance and the correlation between relatives with respect to deviations from an optimum. *Journal of Genetics* **30**, 243–256.

Wright, S. (1935*b*). Evolution in populations in approximate equilibrium. *Journal of Genetics* **30**, 257–266.