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Pleiotropy as a factor maintaining genetic variation in quantitative characters under stabilizing selection

A. GIMELFARB
Department of Ecology and Evolution, University of Chicago, Chicago, IL 60637, USA

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Summary

A model of pleiotropy with N diallelic loci contributing additively to N quantitative traits and stabilizing selection acting on each of the traits is considered. Every locus has a major contribution to one trait and a minor contribution to the rest of them, while every trait is controlled by one major locus and $N-1$ minor loci. It is demonstrated that a stable equilibrium with the allelic frequency equal to 0·5 in all N loci can be maintained in such a model for a wide range of parameters. Such a 'totally polymorphic' equilibrium is maintained for practically any strength of selection and any recombination, if the relative contribution by a minor locus to a trait is less than 20% of the contribution by a major locus. The dynamic behaviour of the model is shown to be quite complex with a possibility under sufficiently strong selection of multiple stable equilibria and positive linkage disequilibria between loci. It is also suggested that pleiotropy among loci controlling traits experiencing direct selection can be responsible for apparent selection on neutral traits also controlled by these loci.

1. Introduction

The maintenance of genetic variation under natural selection in multilocus genetic systems controlling quantitative traits is an important and long-standing problem in population biology. Given that phenotypic variation is practically always reduced by stabilizing selection (Shnoll & Kondrashov, 1993), what biological mechanisms can counterbalance the effect of selection and be responsible for the maintenance of genetic variation in natural populations? For some time the field of quantitative genetics was dominated by polygenic models assuming that a quantitative character is controlled by many loci contributing additively and equally to the trait. It has been demonstrated for such models that, if selection is weak relative to recombination, no genetic variation (except for a possible polymorphism in just one locus) can be maintained under stabilizing selection without an input of new variation (Wright, 1935; Robertson, 1956; Lewontin, 1964; Barton, 1986).

Models have been proposed in which mutations provide new variation, and genetic variation in a population is maintained by the balance between stabilizing selection and mutations (Lande, 1975; Turelli, 1984; Barton, 1986; Slatkin, 1987; Bürger, 1988; Bulmer, 1989). In spite of an intensive study of mutation–selection balance models, it remains uncertain whether this mechanism can account for the amounts of genetic variation in quantitative characters that are observed in natural populations (Barton & Turelli, 1989; Keightley & Hill, 1990).

In addition to models of natural selection acting directly on the character of interest, models have been proposed in which genetic variation for a given trait is a result of polymorphisms in the loci controlling the trait, but the forces maintaining the polymorphisms are not related to the trait itself. The polymorphisms can be maintained due to either overdominance for fitness (Robertson, 1956; Gillespie, 1984; Barton, 1990), or selection against unconditionally deleterious mutations (Barton, 1990; Keightley & Hill, 1990; Kondrashov & Turelli, 1992), or epistatic viability selection (Gavrilets & De Jong, 1993). Thus, the character itself is neutral, but differences in fitness between individuals with differing values of the trait give an appearance of stabilizing selection on the trait. It is important, however, that, while there is experimental evidence of unconditionally deleterious mutations, overdominance for fitness or the particular forms of epistasis for viability are just postulated in the above models, but no known developmental or hereditary mechanisms have been suggested which would produce these phenomena. On the other hand,

while the balance between deleterious mutations and selection can explain the maintenance of polymorphisms in mutating loci, it cannot explain the evolution of phenotypes, and, hence, different biological mechanisms are supposed to be responsible for the maintenance of genetic variation and for phenotypic evolution, yet there is no evidence of this. Also, while it is conceivable that some biological traits are neutral with respect to natural selection, there must also be traits (e.g. obvious adaptations) experiencing direct, and possibly quite strong, natural selection. Models are needed, therefore, that can explain the maintenance of genetic variation under selection acting directly on quantitative traits.

It has become quite evident by now that genetic variation can be maintained in a multilocus system controlling a quantitative trait, even if it is under direct stabilizing selection, if some of the assumptions of the polygenic model are relaxed. This was shown for unequal effects of loci (Gale & Kearsey, 1968; Kearsey & Gale, 1968; Nagylaki, 1989; Gavrilets & Hastings, 1993, 1994*a*, *b*), for selection strong relative to recombination (Gavrilets & Hastings, 1993, 1994*a*, *b*; Gimelfarb, 1995), for dominance (Lewontin, 1964) and for epistasis (Gimelfarb, 1989).

In spite of the scarcity of direct experimental evidence of pleiotropy among quantitative traits, it is supposed to be ubiquitous based on the widespread genetic correlations between different traits (Falconer, 1989), on the complexity and interconnection of biochemical processes underlying the development of quantitative traits (Wright, 1968; Barton, 1990) and on the general philosophical consequence of an organism being 'a unity of an infinite number of traits and finite number of genes' (Serebrovsky, 1973). Recently, evidence of pleiotropy among quantitative traits has been obtained experimentally based on spontaneous and P-element induced mutations (Mackay *et al.* 1992; Santiago *et al.* 1992; Clark *et al.* 1995). The effect of pleiotropy on genetic correlations between quantitative traits has been studied quite extensively, particularly in mutation–selection balance models (Lande, 1980; Turelli, 1985; Wagner, 1989; Slatkin & Frank, 1990). Relatively little work has been done, however, investigating pleiotropy among loci controlling several quantitative traits as a potential factor directly responsible for the maintenance of genetic variation in multilocus systems under natural selection. Rose (1982) has shown that a stable polymorphism can be maintained in two loci having antagonistic pleiotropic effects on components of fitness. Gimelfarb (1986) proposed a model of two loci contributing additively to two traits with the contributions by one locus being the same to both traits but with antagonistic contributions to the traits by the other locus. Such a model maintains a stable polymorphism in both loci for any recombination and any strength of stabilizing selection on each character. Hastings & Hom (1989, 1990) investigated multilocus multicharacter systems, and have concluded that, if selection is weak relative to recombination, the number of loci maintaining a stable polymorphism cannot be greater than the number of characters they control. A stable polymorphism can, however, be maintained in more loci than the number of traits they control, if selection is sufficiently strong (Gavrilets & Hastings, 1994*a*). Indeed, a model of several loci contributing additively to two traits with half the loci contributing similarly to both traits and the other half contributing antagonistically was shown to maintain a stable polymorphism in as many as six (Gimelfarb, 1992) and eight (Gavrilets & Hastings, 1994*a*) loci.

Even if as many loci are maintained polymorphic as the number of traits they control, pleiotropy can still be an important factor responsible for the maintenance of genetic variation in natural populations, since the number of pleiotropically related traits can be potentially quite large. In this paper, we shall investigate the maintenance of polymorphisms in a model of pleiotropy with N loci controlling N quantitative traits. The model is inspired by experimental evidence that not all loci controlling a trait contribute equally to the trait (Edwards *et al.* 1987; Paterson *et al.* 1990; Mackay *et al.* 1992). The majority of quantitative traits whose genetic basis has been investigated appear to be 'under control of a few major genes supported by numerous genes with smaller effects' (Shrimpton & Robertson, 1988).

2. The model

It is assumed that N diallelic loci contribute additively to N quantitative characters. Each locus has a major effect on one of the characters and a minor effect on the rest of them. On the other hand, each character is controlled by one major locus and by $N-1$ minor loci. The contribution to any trait by one of the alleles in each locus is zero. The contribution by the other allele depends on whether the locus is major or minor for the trait. If L_i is a minor locus for a trait $X_j (i \neq j)$, its contribution is assumed to be a fraction, b_{ij}, of the contribution to the trait by the major locus, L_j, i.e. major and minor loci contribute to a trait in a proportion $1 : b_{ij}$. It is also assumed without loss of generality that the minimum and the maximum of any trait are 0 and 1, respectively. Hence, the actual allelic contributions to a trait X_j are

$$\alpha_j = 0{\cdot}5/B_j \quad \text{(major locus)}, \tag{1a}$$

$$\beta_{ij} = 0{\cdot}5 b_{ij}/B_j \quad \text{(minor locus)}, \tag{1b}$$

where $B_j = 1 + \Sigma_{k \neq j} b_{kj}$. Notice that $\alpha_j + \Sigma_{k \neq j} \beta_{kj} = 0{\cdot}5$ for any j. Consequently, the genotypic value of a 'total heterozygote' (all N loci heterozygous) is 0·5 for any trait.

Each trait, $X_j (j = 1, 2, \ldots, N)$, is assumed, independently of other traits, to be under stabilizing selection with a quadratic fitness function:

$$w(X_j) = 1 - Q_j (X_j - \theta_j)^2, \tag{2}$$

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and the fitness of an individual with a set of characters $\{X_j\}$ is

$$\prod_{j=1}^{N} w(X_j). \tag{3}$$

Random mating is assumed, and the effect of environment is neglected.

The number of parameters (b_{ij}, Q_j and θ_j) is very large, making it impossible to analyse a general model. We shall, therefore, consider in detail a simplified model which assumes symmetry in the effects of loci ($b_{ij} = b$ for any $i \neq j$, hence $\alpha_j = \alpha$, $\beta_{ij} = \beta$) and symmetry in selection ($Q_j = Q$ and $\theta_j = \theta$). It will be demonstrated, however, that the symmetry assumptions are not necessary, and genetic polymorphisms can be maintained in models that are not symmetric. If $\theta = 0{\cdot}5$ (the optimum phenotype is that of a total heterozygote), the value of Q cannot, obviously, exceed four in order for fitness of any phenotype to be non-negative, and, hence, $Q = 4$ represents the strongest possible quadratic selection on a trait.

3. Weak selection analysis

A complete dynamical analysis is not possible even for a symmetric $N \times N$ model. It is possible, however, to analyse its 'weak selection' approximation, assuming selection sufficiently weak relative to recombination, so that linkage disequilibrium between loci can be neglected. An analysis of an $N \times N$ model under such selection is presented in Appendix A. It is demonstrated there that, if selection is weak, a symmetric model with $b_{ij} = b$, $\theta_j = \theta$, $Q_j = Q$, has an equilibrium with allelic frequency

$$p_i = p = \frac{\theta - \theta^*}{1 - 2\theta^*}, \quad \text{where } \theta^* = \frac{1 + (N-1)\,b^2}{4[1 + (N-1)\,b]^2} \tag{4}$$

at each locus. It is seen that, if the optimum phenotype, $\theta = 0{\cdot}5$, the equilibrium allelic frequency, $p = 0{\cdot}5$. Generally, in order for $0 < p < 1$, i.e. for a polymorphic equilibrium to exist, the optimum phenotype must be within the limits $\theta^* < \theta < 1 - \theta^*$. If, for example, $b = 0{\cdot}2$, the limit, $\theta^* = 0{\cdot}181$, $0{\cdot}138$, $0{\cdot}109$, $0{\cdot}090$ and $0{\cdot}043$ for $N = 2$, 3, 4, 5 and 10, respectively. Thus, if the number of loci in the model is large, a polymorphic equilibrium exists for practically any selection optimum.

It is also shown in Appendix A that, if the value of b (the relative contribution by a minor locus) is below a certain limit determined by N, the equilibrium (4) is locally stable. Thus, for values of b not exceeding $0{\cdot}268$, $0{\cdot}250$, $0{\cdot}236$, $0{\cdot}225$ and $0{\cdot}188$, a stable polymorphism is maintained under weak selection in a symmetric $N \times N$ model with $N = 2$, 3, 4, 5 and 10, respectively.

If minor loci do not contribute to traits, i.e., $b_{ij} = 0$ for $i \neq j$, a $N \times N$ model becomes a trivial model of N independent traits each controlled by one (major) locus. Since each trait experiences selection favouring the heterozygote, there is total overdominance for fitness (the fitness of an individual is an increasing function of the number of heterozygous loci in the individual's genotype) in such a model. The overdominance will, obviously, be preserved if contributions by minor loci are small. It can be said, therefore, that a $N \times N$ model of pleiotropy with small contributions by minor loci produces total overdominance for fitness. This is not necessarily true, however, if the contributions by minor loci are not very small. It follows from Appendix B that in order for total overdominance for fitness to exist in a symmetric model, the relative contribution by a minor locus must be below the following limits: $0{\cdot}268$, $0{\cdot}121$, $0{\cdot}079$, $0{\cdot}058$ and $0{\cdot}025$ for $N = 2$, 3, 4, 5 and 10, respectively. It is seen that for $N > 2$, these limits are below the limits required for the stability of a polymorphic equilibrium. Hence, polymorphisms in $N \times N$ pleiotropic models can be maintained without total overdominance for fitness.

4. General analysis

A symmetric 2×2 model under selection with $\theta = 0{\cdot}5$ represents a special case of the 'symmetric viability' model (e.g. Karlin & Feldman, 1970) whose parameters are as follows:

$$\left.\begin{aligned} \delta &= 0{\cdot}5Q - 0{\cdot}0625Q^2, \\ \gamma = \beta &= [(0{\cdot}5 - z)^2 + z^2]\,Q - z^2(0{\cdot}5 - z)^2Q^2, \\ \alpha &= 2(0{\cdot}5 - 2z)^2Q - (0{\cdot}5 - 2z)^4Q^2, \end{aligned}\right\} \tag{5}$$

where $z = 0{\cdot}5/(1 + b)$. Such a model always has a symmetric (allelic frequency $0{\cdot}5$ in both loci) equilibrium. It may also have asymmetric equilibria, but we shall not be concerned with them here. The linkage disequilibrium at a symmetric equilibrium is described by a cubic equation (e.g. equation 2.1 of Karlin & Feltman, 1970). The equation may have as many as three admissible solutions. Parameters (5), calculated for different values of relative allelic contribution, $0 \leqslant b \leqslant 1$, and strength of selection, $0 \leqslant Q \leqslant 4$, were substituted into the cubic equation, and the equation was solved to obtain the equilibrium values of linkage disequilibrium. The stability of a solution was tested for four values of recombination, $r = 0{\cdot}5$, $0{\cdot}3$, $0{\cdot}1$, $0{\cdot}05$, using criteria suggested by Karlin & Feldman (1970).

No analytical methods exist for obtaining equilibria explicitly and investigating their stability in models with more than two loci. It is possible, however, to find stable equilibria for such a model by numerically iterating equations describing the dynamics of gametic frequencies:

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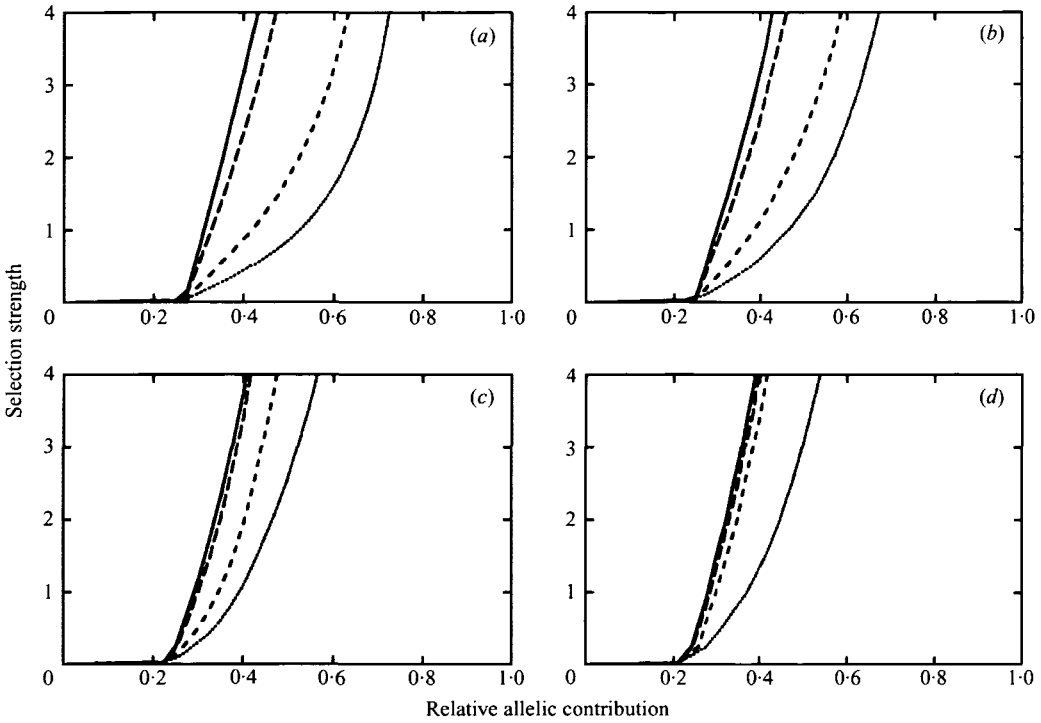

Fig. 1. Areas of existence of stable totally polymorphic equilibria on the plane of selection strength and relative allelic contribution for a given recombination rate, r (stable equilibria exist in areas above a corresponding curve). (*a*), 2×2; (*b*), 3×3; (*c*) 4×4, (*d*), 5×5. ·····, $r=0{\cdot}05$; – – –, $r=0{\cdot}1$; – – – –, $r=0{\cdot}3$; ——, $r=0{\cdot}5$.

$$\left.\begin{aligned} p_{k+1}(g_3) &= \frac{1}{W_k}\sum_{g_1}\sum_{g_2} p_k(g_1)\,p_k(g_2)\,w(g_1,g_2)\,H(g_3|g_1,g_2),\\ W_k &= \sum_{g_1}\sum_{g_2} p_k(g_1)\,p_k(g_2)\,w(g_1,g_2), \end{aligned}\right\} \quad (6)$$

where, g_1, g_2, g_3 are gametes, and p_k, p_{k+1} are the frequencies of gametes in generations k and $k+1$. The fitness, $w(g_1,g_2)$, of a genotype is obtained by computing the value of each of the N characters for the genotype and substituting the values into formulas (2) and (3). The function $H(g_3|g_1,g_2)$ in (6) is the probability that a gamete produced by an individual with the genotype (g_1,g_2) will be g_3. This function is determined by the pattern of recombination between the loci in a model. It is assumed throughout the paper that recombination is the same between any pair of adjacent loci and there is no interference.

For a given set of parameters, system (6) was iterated on a computer starting from an initial distribution of gametes, and when the distance,

$$\sqrt{\{\Sigma_g[p_{k+1}(g)-p_k(g)]^2\}},$$

between gametic distributions in two consecutive generations became less than 10^{-12}, it was assumed that an equilibrium had been reached. To test the local stability of the equilibrium, the equilibrium gametic frequencies were perturbed by adding to each of them its own very small (of the order 10^{-5}) random number, and then normalizing them so that their sum was unity. Iterations were repeated starting with the perturbed gametic frequencies, and an equilibrium was classified as stable or unstable depending on whether the perturbed system returned to it or not. Gimelfarb (1989) argued that it is impossible to misclassify an unstable equilibrium as stable by using this method, although it is possible in principle to miss a locally stable equilibrium with a very small domain of attraction. Computer iterations for any given set of parameters were initiated from a random point in the vicinity of the centre of the simplex of gametic frequencies. The centre is the point at which frequencies of all gametes are the same, i.e. the allelic frequency is 0·5 in each locus and the loci are in complete linkage equilibrium. If $\{x_i\}$ denotes coordinates of the centre of a simplex, a starting point was chosen with random coordinates $\{y_i\}$ such that, besides the usual constraints defining the simplex: $\Sigma_i y_i = 1$ and $y_i \geqslant 0$, they also satisfied an additional constraint:

$$\sum_i (x_i-y_i)^2 = \rho^2 \quad (7)$$

i.e. a starting point was located at a distance ρ from the centre. It is not a good idea to choose the same ρ for models with different numbers of loci, since a given distance may be regarded as 'small' in one simplex but as 'large' in a simplex of a higher dimension. For example, a sphere of radius 0·05 lies completely within the two-locus simplex, but the same sphere 'sticks out' of the five-locus simplex. For this reason, the distance for a starting point was chosen as $\rho=\rho^*/100$, where ρ^* is the maximum radius of a sphere completely contained within the N-locus

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simplex. For 3×3, 4×4 and 5×5 model, the distance is equal to 0·0013, 0·0006 and 0·0003, respectively.

Fig. 1 shows regions of existence of stable equilibria in $N \times N$ models on the plane of relative allelic contribution, b, and strength of selection, S, for four values of recombination, r. Only 'totally polymorphic', i.e. with allelic frequency 0·5 at each locus, equilibria are considered. Such equilibria are, obviously, symmetric for a 2×2 model, but not for a model with $N > 2$, since linkage disequilibria generally differ between different pairs of loci. For a given value of r, a locally stable totally polymorphic equilibrium exists in the area above the corresponding curve (left side of the graph), whereas no such equilibrium exists in the area below the corresponding curve (right side of the graph). It should be remembered that a stable equilibrium in Fig. 1 is approached from a random point in a vicinity of the centre of the simplex of gametic frequencies. Other totally polymorphic equilibria, to which trajectories originating in different parts of the simplex converge, may in principle exist.

It is seen in Fig. 1 that totally polymorphic stable equilibria exist in $N \times N$ models for a wide range of parameters, and, if the contribution by a minor locus is less than 0·2 of that by a major locus, there is a totally polymorphic stable equilibrium for any model with practically any strength of selection and any recombination, which is in accordance with the analysis of weak selection discussed previously. It can also be noticed that the effect of recombination diminishes with increased dimensionality of the model. In a 5×5 model, the existence and stability of totally polymorphic equilibria are mostly determined by the strength of selection, whereas recombination has very little effect, unless linkage is quite tight ($r = 0{\cdot}05$).

It is not possible to investigate completely the dynamics of $N \times N$ models. However, a good idea about dynamic properties of a model with a given set of parameters can be obtained by employing a computer procedure introduced by Karlin & Carmelli (1975) to investigate two-locus symmetric viability models, and used by Gimelfarb (1995) to investigate two- and three-locus models of a quantitative trait under strong stabilizing selection. A large number of trajectories of system (6) are generated starting from points randomly chosen in the total simplex of gametic frequencies, and equilibria are observed to which the trajectories converge. The proportion of trajectories converging to a particular equilibrium can be regarded as a measure of the size of the domain of attraction to the equilibrium. Obviously, only equilibria that are stable and have domains of attraction that are not extremely small can be discovered by this method, but on the other hand only such equilibria are of biological significance. If all the randomly initiated trajectories converge to one equilibrium, we shall call such an equilibrium 'apparently' globally stable.

This procedure (with 500 random trajectories generated for each set of parameters) was applied to quite a large number of parameter sets in 2×2 and 3×3 models, but to fewer parameter sets in models of a higher dimension (computing time becomes prohibitively long for the latter models). The general picture emerging from this is that the dynamic properties of $N \times N$ models are determined, not surprisingly, by the relative strength of recombination and selection. If $r > 0{\cdot}05$, i.e. linkage is not very tight, a totally polymorphic stable equilibrium, if it exists, seems to be the only equilibrium with non-zero allelic frequencies in all loci. It is apparently globally stable under selection that is only slightly stronger than the minimum required to maintain a stable equilibrium in a model with given b and r (the minimum strength of selection is represented in Fig. 1 by the vertical coordinate of the point on the curve for a given r, whose horizontal coordinate is b).

If, however, linkage is tight ($r = 0{\cdot}05$), dynamic properties of $N \times N$ models are more complex, particularly for small contributions by minor loci.

Table 1. *Percentage of trajectories converging to an equilibrium with linkage disequilibrium D under selection of strength Q in a 2 × 2 model with relative allelic contribution, b = 0·1, and recombination, r = 0·05 (all equilibria are symmetric)*

Q	D	%
0·1	−0·010	100
3·1	−0·198	100
3·2	−0·201	81
	0·147	19
4·0	−0·215	59
	0·208	41

Table 2. *Percentage of trajectories converging to an equilibrium with linkage disequilibria D_{ij} under selection of strength Q in a 3 × 3 model with relative allelic contribution, b = 0·1, and recombination, r = 0·05 (all equilibria are totally polymorphic with the allelic frequency 0·5 in each locus)*

Q	D_{12}	D_{13}	D_{23}	%
0·1	−0·008	−0·004	−0·008	100
1·5	−0·072	−0·032	−0·072	100
2·3	−0·091	−0·005	−0·091	100
2·4	−0·098	0·003	−0·098	100
2·6	−0·115	0·026	−0·115	100
2·7	−0·125	0·041	−0·125	70
	0·083	−0·084	−0·171	15
	−0·171	0·084	0·083	15
3·5	−0·182	0·129	−0·182	32
	0·178	−0·151	−0·204	32
	−0·204	−0·151	0·178	32
	0·186	0·142	0·186	4

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Multiple totally polymorphic stable equilibria may exist simultaneously under sufficiently strong selection in such a case. For example, Tables 1 and 2 show the percentage of trajectories (out of 500 initiated randomly) converging to totally polymorphic equilibria in 2×2 and 3×3 models with $r = 0{\cdot}05$ and $b = 0{\cdot}1$. The 2×2 model has only one stable symmetric equilibrium with negative linkage disequilibrium, which is apparently globally stable, under selection with $Q \leqslant 3{\cdot}1$. If, however, $Q \geqslant 3{\cdot}2$, two stable symmetric equilibria exist simultaneously, one with negative and the other with positive linkage disequilibrium. As for the 3×3 model, it has only one stable totally polymorphic equilibrium, which is apparently globally stable, under selection with $Q \leqslant 2{\cdot}6$, whereas three and even four stable totally polymorphic equilibria can exist simultaneously under stronger selection. It is also interesting that, while linkage disequilibria between adjacent loci, D_{12} and D_{23}, in the 3×3 model are always negative under selection with $Q \leqslant 2{\cdot}6$, and their absolute value increases with stronger selection, the behaviour of linkage disequilibrium between the distant loci, D_{13}, is more complex. It is negative and its absolute value increases with stronger selection until Q remains less than 1·5. If, however, $Q > 1{\cdot}5$, its absolute value decreases until it reaches zero, after which D_{13} becomes positive and increases with increasing strength of selection. If selection is sufficiently strong ($Q \geqslant 2{\cdot}7$), linkage disequilibrium can be positive between any two loci, including a possibility of all three linkage disequilibria being positive. Existence of stable equilibria with positive linkage disequilibrium was first discovered by Gavrilets & Hastings (1994*b*) in a two-locus model of an additive quantitative trait under strong stabilizing selection.

5. Discussion and conclusions

The results demonstrate that $N \times N$ models of pleiotropy can maintain a stable equilibrium with the allelic frequency 0·5 in all N loci for a wide range of parameters. If the relative contribution by a minor locus is less than 20% of that by a major locus, a 'total polymorphism' is maintained for practically any recombination and any strength of selection. Since contributions by loci to traits are additive, the genotypic variance of any trait is equal to the additive genetic variance of the trait, and it can be utilized by natural selection in the process of phenotypic evolution.

A question can be raised concerning symmetries in the $N \times N$ models analysed so far: it is assumed that the relative contributions of all minor loci to any trait are the same, and that any trait experiences the same selection. Are the models robust to deviations from these assumptions? The answer is 'yes'. It is easy to see from the analysis in Appendix A, that a stable totally polymorphic equilibrium may exist under weak selection, even in a model that is not symmetric. Also, consider a 5×5 model with parameters shown in Table 3. Even though the model is clearly not symmetric with respect to either contributions by minor loci or selection, there is a stable equilibrium with a polymorphism in all five loci (equilibrium allelic frequencies are shown in the bottom row of the table), and it is apparently globally stable. It is important to notice that the equilibrium mean value of a trait, m_j, deviates from the selection optimum, θ_j, which means, as discussed by Gavrilets & Hastings (1993), that each character will exhibit a directional component of selection even in a population at equilibrium. It can also be noted that the allelic contributions by minor loci in Table 3 are not of the same sign. This means that minor loci do not have to act in the same direction on all traits for a stable polymorphism to be maintained. Actually, Table 3 is only one example of a $N \times N$ model with parameters chosen randomly from the following intervals: $-0{\cdot}2 \leqslant b_{ij} \leqslant 0{\cdot}2$; $0{\cdot}3 \leqslant Q_j \leqslant 1{\cdot}0$; $0{\cdot}4 \leqslant \theta_j \leqslant 0{\cdot}6$. Five hundred such models were generated for each $N = 2, 3, 4, 5$, and a stable equilibrium with a polymorphism at all N loci existed for 96% of 2×2 models, 95% of 3×3 models, 81% of 4×4 models and 56% of 5×5 models.

Another potential concern about the models discussed here is the assumption that every locus contributes to all N characters, and, consequently, every character must be genetically correlated with all other characters, which may not be true in reality.

Table 3. *5×5 model without symmetry: relative contributions by locus L_i to character X_j, parameters of selection (θ_j and Q_j) on character X_j, the equilibrium mean, m_j, and variance, v_j, of character X_j, the equilibrium allelic frequencies, p_i. Recombination pattern, $r = \{0{\cdot}5, 0{\cdot}4, 0{\cdot}3, 0{\cdot}2\}$*

	L_1	L_2	L_3	L_4	L_5	θ_j	Q_j	m_j	v_j
X_1	1·00	0·13	−0·20	−0·19	0·17	0·49	0·32	0·47	0·047
X_2	−0·14	1·00	−0·13	0·18	−0·11	0·41	0·48	0·33	0·041
X_3	0·18	0·10	1·00	−0·14	0·09	0·56	0·36	0·61	0·048
X_4	0·15	−0·12	0·08	1·00	0·12	0·60	0·44	0·70	0·048
X_5	0·11	−0·10	−0·18	0·09	1·00	0·48	0·40	0·55	0·059
p_i	0·56	0·24	0·71	0·74	0·55				

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However, this assumption is also not necessary, and a total polymorphism can be maintained even more easily in a model of N loci controlling N traits with some of the loci contributing to fewer than N characters (an extreme and trivial case is that of every locus contributing to a different trait). Consider, for example, a model of five loci controlling five quantitative traits with $b_{i(i+1)} = b(i = 1\text{–}4)$, $b_{51} = b$ and $b_{ij} = 0$ otherwise, i.e. each locus contributes to only two traits, and any two traits have either one or no loci in common. It follows from Fig. 1*d* that the minimum strength of selection necessary to maintain a total polymorphism in a 5×5 model with $b = 0{\cdot}3$ and $r = 0{\cdot}5$ is $Q = 1{\cdot}5$. On the other hand, a totally stable polymorphism is maintained in the discussed model with the same parameters b and r under selection with Q as small as 0·01. Under such weak selection, linkage disequilibria are very close to zero and, consequently, only characters having a locus in common are genetically correlated (e.g. character X_1 is genetically correlated with characters X_2 and X_5, while its genetic correlation with other traits is practically zero).

The model of antagonistic pleiotropy for fitness components by Rose (1982) predicts a negative genetic correlation between the traits. Yet, many experimental estimates of the genetic correlation between fitness components are either zero or positive (Rose *et al.*, 1987). On the other hand, the genetic correlation between characters in models discussed here can be either positive or negative or zero, depending on the signs and values of allelic contributions and on the pattern of pleiotropy.

A question may be asked whether it is actually pleiotropy that is responsible for the maintenance of a total polymorphism in $N \times N$ models. Would not stabilizing selection acting on just one of the characters produce a similar result? Indeed, a stable polymorphism in several loci with unequal contributions to a quantitative trait can be maintained under stabilizing selection on the trait, provided selection is sufficiently strong relative to recombination (Gavrilets & Hastings 1993, 1994*a*, *b*; Gimelfarb, 1995). If, however, selection is relatively weak, it is in fact pleiotropy among traits, each experiencing selection, that is responsible for the maintenance of a total polymorphism in N × N models. Consider, for example, a 5×5 model with $b_{ij} = b = 0{\cdot}2$ and $r = 0{\cdot}5$ between any pair of loci. If selection acts only on one of the traits, no totally polymorphic equilibrium can be maintained under stabilizing selection of any strength (including the strongest possible stabilizing selection which culls all individuals except those whose phenotype is exactly θ). Yet, as Fig. 1*d* demonstrates, a stable totally polymorphic equilibrium exists for the same values of b and r even under extremely weak selection, if selection acts on each of the five traits.

Pleiotropy among characters experiencing stabilizing selection can also be a mechanism responsible for apparent selection on 'neutral' traits. Indeed, consider a $N \times N$ model, and let there be some other traits which do not experience direct selection but are controlled by the N loci (or some of them). If parameters of the $N \times N$ model are such that a total polymorphism is maintained, there will be apparent stabilizing selection on any 'neutral' trait to which these loci contribute. The apparent selection can be quite strong if the number of traits experiencing direct selection is large, even if selection on each individual trait is weak.

Appendix A

The following analysis was suggested by Nick Barton. Given that the loci controlling traits are at linkage equilibrium, i.e. the distribution of genotypes in the loci are independent, the mean and the variance of a character X_j are

$$\bar{X}_j = 2\sum_k \beta_{kj} p_k, \tag{A 1}$$

$$v(X_j) = 2\sum_k \beta_{kj}^2 p_k q_k, \tag{A 2}$$

where p_k is the frequency of the non-zero allele in locus $L_k (q_k = 1 - p_k)$ and β_{jk} is the actual contribution by locus L_k to character $X_j (\beta_{jj} = \alpha_j)$. According to equations (2) and (3) in the text, the fitness of an individual is

$$W = \prod_j [1 - Q_j (X_j - \theta_j)^2]. \tag{A 3}$$

Assuming that selection is sufficiently weak that terms in (A 3) of the order Q^2 and higher can be neglected, the fitness of an individual is approximately

$$W = 1 - \sum_j Q_j (X_j - \theta_j)^2. \tag{A 4}$$

Consequently, the average fitness in a population is

$$\bar{W} = 1 - \sum_j Q_j [(\bar{X}_j - \theta_j)^2 - v(X_j)], \tag{A 5}$$

The dynamics of allelic frequencies under weak selection is described approximately by the following system of differential equations (Wright, 1935; Barton, 1986):

$$\frac{dp_i}{dt} = p_i q_i \frac{\partial \bar{W}}{\partial p_i}. \tag{A 6}$$

Given (A 5), (A 1) and (A 2),

$$\frac{d\mathbf{p}}{dt} = \mathbf{A}\mathbf{p} - \mathbf{c}, \tag{A 7}$$

where $\mathbf{p}$ is a vector whose elements are allelic frequencies, whereas $\mathbf{A}$ and $\mathbf{c}$ are a matrix and a vector with elements

$$A_{ii} = -4\sum_k Q_k \beta_{ik}^2, \quad A_{ij} = -8\sum_k Q_k \beta_{ik} \beta_{jk} \quad (\text{for } i \neq j), \tag{A 8a}$$

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$$c_i = 2\sum_k Q_k \beta_{ik}(2\theta_k - \beta_{ik}). \quad (A\,8b)$$

Provided matrix **A** is non-singular, allelic frequencies at an equilibrium are obtained as

$$\mathbf{p} = \mathbf{A}^{-1}\mathbf{c}. \quad (A\,9)$$

For a symmetric model with $Q_j = Q$, $\theta_j = \theta$, $\beta_{ii} = \alpha$ and $\beta_{ij} = \beta$ for $i \neq j$, the elements of matrix **A** and vector **c** are

$$A_{ii} = -4Q[\alpha^2 + 2(N-1)\alpha\beta],$$
$$A_{ij} = -8Q[2\alpha\beta + (N-2)\beta^2] \quad (\text{for } i \neq j), \quad (A\,10a)$$
$$c_i = 2Q[\theta - \alpha^2 - (N-1)\beta^2]. \quad (A\,10b)$$

Consequently, the equilibrium allelic frequencies are

$$p_i = p = \frac{\theta - \theta^*}{1 - 2\theta^*}, \quad \text{where } \theta^* = \alpha^2 + (N-1)\beta^2. \quad (A\,11)$$

Substituting the values of α and β from equations (1 *a*, *b*) in the text,

$$\theta^* = \frac{1 + (N-1)b^2}{4[1 + (N-1)b]^2}. \quad (A\,12)$$

In order for $0 < p < 1$, the optimum phenotype must be within the limits $\theta^* < \theta < 1 - \theta^*$.

The local stability of the equilibrium (A 11) is determined by the eigenvalues of the matrix **A**. A $N \times N$ matrix with elements R on the main diagonal and elements S elsewhere has one eigenvalue $\lambda_1 = R + S(N-1)$ and $(N-1)$ eigenvalues $\lambda_2 = R - S$. For the matrix **A**,

$$\lambda_1 = -4Q[\alpha^2 + 6(N-1)\alpha\beta + 2(N-1)(N-2)\beta^2], \quad (A\,13a)$$
$$\lambda_2 = -4Q[\alpha^2 - 4\alpha\beta - (N-3)\beta^2]. \quad (A\,13b)$$

The first value is always negative, whereas in order for the second value to be negative, and, hence, for the equilibrium to be locally stable, the expression in square brackets of (A 13*b*) must be positive, i.e. the following inequality must hold:

$$1 - 4b - (N-3)b^2 > 0. \quad (A\,14)$$

This requires that

$$b < 2 - \sqrt{3} \quad (N = 2), \quad (A\,15a)$$
$$b < 1/4 \quad (N = 3), \quad (A\,15b)$$
$$b < (\sqrt{N} + 1 - 2)/(N-3) \quad (N > 3). \quad (A\,15c)$$

Appendix B

Consider individuals with identical genotypes in $N-1$ loci, but having different genotypes (*AA*, *Aa* or *aa*) at one locus, say L_j. In a symmetric $N \times N$ model, such individuals will have the following values of the characters:

$$X_j(AA) = x_j + 2\alpha, \quad X_k(AA) = x_k + 2\beta \quad (k \neq j) \quad (B\,1a)$$
$$X_j(Aa) = x_j + \alpha, \quad X_k(Aa) = x_k + \beta \quad (k \neq j) \quad (B\,1b)$$
$$X_j(aa) = x_j \quad X_k(aa) = x_k \quad (k \neq j) \quad (B\,1c)$$

where $\alpha = 0{\cdot}5/[1 + (N-1)b]$ and $\beta = 0{\cdot}5b/[1 + (N-1)b]$ are the actual contributions by a major and a minor locus, respectively, whereas x_i denotes the total contribution to character X_i by the identical $N-1$ loci. The fitness of an individual under weak selection is described by (A 4). Hence, the fitnesses of individuals differing only at locus L_j will be

$$W(AA) = 1 - Q[(x_j + 2\alpha - 0{\cdot}5)^2 + \sum_{k \neq j} (x_k + 2\beta - 0{\cdot}5)^2], \quad (B\,2a)$$

$$W(Aa) = 1 - Q[(x_j + \alpha - 0{\cdot}5)^2 + \sum_{k \neq j} (x_k + \beta - 0{\cdot}5)^2], \quad (B\,2b)$$

$$W(aa) = 1 - Q\sum_k (x_k - 0{\cdot}5)^2. \quad (B\,2c)$$

Total overdominance for fitness means that for any genotype at $N-1$ loci, a heterozygote at locus L_j has a higher fitness than a homozygote, i.e. the difference in fitness between a heterozygote and a homozygote must be positive. Hence the difference

$$W(Aa) - W(aa) = 2\alpha(x_j - 0{\cdot}5) + \beta\sum_{k \neq j} (x_k - 0{\cdot}5) + \alpha^2 + (N-1)\beta^2, \quad (B\,3)$$

must be positive for any values contributed by the $N-1$ loci, including their maxima. The maximum of x_j is $(N-1)\beta$, whereas the maximum of x_k is $\alpha + (N-2)\beta$. Hence, the following inequality must be satisfied:

$$8(N-1)\alpha\beta + (N-1)(4N-7)\beta^2 + \alpha^2 - 0{\cdot}5 > 0. \quad (B\,4)$$

Substituting the expressions for α and β from equations (1 *a*, *b*) of the text yields

$$(N-1)(2N-5)b^2 + 8(N-1)b - 1 < 0 \quad (B\,5)$$

It can be shown that the same inequality must hold in order for the difference $W(Aa) - W(AA)$ to be positive. Hence, total overdominance for fitness is present in a $N \times N$ model if

$$b < 2 - \sqrt{3} \quad (N = 2) \quad (B\,6a)$$
$$b < \frac{\sqrt{[3(N-1)(2N-3)]} - 2(N-1)}{(N-1)(2N-5)} \quad (N > 2). \quad (B\,6b)$$

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References

Barton, N. H. (1986). The maintenance of polygenic variation through a balance between mutation and stabilizing selection. *Genetical Research, Cambridge* **47**, 209–216.

Barton, N. H. (1990). Pleiotropic models of quantitative variation. *Genetics* **124**, 773–782.
Barton, N. H. & Turelli, M. (1989). Evolutionary quantitative genetics: how little do we know? *Annual Review of Genetics* **23**, 337–370.
Bulmer, M. G. (1989). Maintenance of genetic variability by mutation–selection balance: a child's guide through the jungle. *Genome* **31**, 761–767.
Bürger, R. (1988). Mutation–selection balance and continuum-of-alleles models. *Mathematical Biosciences*, **91**, 67–83.
Clark, A. G., Wang, L. & Hullenberg, T. (1995). P-element-induced variation in metabolic regulation in *Drosophila*. *Genetics* **139**, 337–348.
Edwards, M. D., Stuber, C. W. & Wendel, J. F. (1987). Molecular-marker-facilitated investigations of quantitative trait loci in maize. I. Numbers, genomic distribution and types of gene action. *Genetics* **116**, 113–125.
Falconer, D. S. (1989). *Introduction to Quantitative Genetics*, 3rd edn. London: Longman.
Gale, J. S. & Kearsey, M. J. (1968). Stable equilibria under stabilising selection in the absence of dominance. *Heredity* **23**, 553–561.
Gavrilets, S. & De Jong, G. (1993). Pleiotropic models of polygenic variation, stabilizing selection and epistasis. *Genetics* **134**, 609–625.
Gavrilets, S. & Hastings, A. (1993). Maintenance of genetic variability under strong stabilizing selection: two-locus model. *Genetics* **134**, 377–386.
Gavrilets, S. & Hastings, A. (1994*a*). Maintenance of multilocus variability under strong stabilizing selection. *Journal of Mathematical Biology* **32**, 287–302.
Gavrilets, S. & Hastings, A. (1994*b*). Dynamics of genetic variability in two-locus models of stabilizing selection. *Genetics* **138**, 519–532.
Gillespie, J. H. (1984). Pleiotropic overdominance and the maintenance of genetic variation in polygenic characters. *Genetics* **107**, 321–330.
Gimelfarb, A. (1986). Additive variation maintained under stabilizing selection: a two-locus model of pleiotropy for two quantitative traits. *Genetics* **112**, 717–725.
Gimelfarb, A. (1989). Genotypic variation maintained under stabilizing selection without mutations: epistasis. *Genetics* **123**, 217–227.
Gimelfarb, A. (1992). Pleiotropy and multilocus polymorphisms. *Genetics* **130**, 223–227.
Gimelfarb, A. (1996). Some additional results about polymorphisms in models of a quantitative trait under stabilizing selection. *Journal of Mathematical Biology* (in the press).
Hastings, A. & Hom, C. L. (1989). Pleiotropic stabilizing selection limits the number of polymorphic loci to at most the number of characters. *Genetics* **122**, 459–463.
Hastings, A. & Hom, C. L. (1990). Multiple equilibria and maintenance of additive genetic variation in a model of pleiotropy. *Evolution* **44**, 1153–1163.
Karlin, S. & Carmelli, D. (1975). Numerical studies of two-locus selection models with general selection. *Theoretical Population Biology* **7**, 399–421.
Karlin, S. & Feldman, M. (1970). Linkage and selection: two-locus symmetric viability model. *Theoretical Population Biology* **1**, 39–71.
Kearsey, M. J. & Gale, J. S. (1968). Stabilising selection in the absence of dominance: additional note. *Heredity* **23**, 617–620.
Keightley, P. D. & Hill, W. G. (1990). Variation maintained in quantitative traits with mutation–selection balance: pleiotropic side effects on fitness traits. *Proceedings of the Royal Society of London, Series B* **242**, 95–100.
Lande, R. (1975). The maintenance of genetic variability by mutation in a polygenic character with linked loci. *Genetical Research, Cambridge* **26**, 221–235.
Lande, R. (1980). The genetic covariance between characters maintained by pleiotropic mutations. *Genetics* **94**, 203–215.
Lewontin, R. C. (1964). The interaction of selection and linkage. II. Optimal model. *Genetics* **50**, 757–782.
Mackay, T. F. C., Lyman, R. F. & Jackson, M. S. (1992). Effects of P element insertions on quantitative traits in *Drosophila melanogaster*. *Genetics* **130**, 315–332.
Nagylaki, T. (1989). The maintenance of genetic variability in two-locus models of stabilizing selection. *Genetics* **122**, 235–248.
Paterson, A. H., De Verna, J. W., Lanini, B. & Tanksley, S. D. (1990). Fine mapping of quantitative trait loci using selected overlapping recombinant chromosomes in an interspecies cross of tomato. *Genetics* **124**, 735–742.
Robertson, A. (1956). The effect of selection against extreme deviants based on deviation or on homozygosis. *Journal of Genetics* **54**, 236–248.
Rose, M. R. (1982). Antagonistic pleiotropy, dominance and genetic variation. *Heredity* **48**, 63–78.
Rose, M. R., Service, P. M. & Hatchinson, E. W. (1987). Three approaches to trade-offs in life-history evolution. In *Genetic Constraints on Adaptive Evolution*, ed. V. Loeschcke. Berlin: Springer.
Santiago, E., Albornoz, J., Dominguez, A., Toro, M. A. & Lopez-Fanjul, C. (1992). The distribution of spontaneous mutations in quantitative traits and fitness in *Drosophila melanogaster*. *Genetics* **132**, 771–781.
Serebrovsky, A. S. (1973). *Nekotorye Problemi Organicheskoy Evolutsii*. Moscow: Nauka (in Russian).
Shnoll, E. E. & Kondrashov, A. S. (1993). The effect of selection on phenotypic variance. *Genetics* **134**, 995–996.
Shrimpton, A. E. & Robertson, A. (1988). The isolation of polygenic factors controlling bristle score in *Drosophila melanogaster*. II. Distribution of third chromosome bristle effects within chromosome sections. *Genetics* **118**, 445–459.
Slatkin, M. (1987). Heritable variation and heterozygosity under a balance between mutations and stabilizing selection. *Genetical Research, Cambridge* **50**, 53–62.
Slatkin, M. & Frank, S. A. (1990). The quantitative genetic consequences of pleiotropy under stabilizing and directional selection. *Genetics* **125**, 207–213.
Turelli, M. (1984). Heritable genetic variation via mutation–selection balance: Lerch's zeta meets the abdominal bristle. *Theoretical Population Biology* **25**, 138–193.
Turelli, M. (1985). Effects of pleiotropy on predictions concerning mutation–selection balance for polygenic traits. *Genetics* **111**, 165–195.
Wagner, G. P. (1989). Multivariate mutation–selection balance with constrained pleiotropic effects. *Genetics* **122**, 223–234.
Wright, S. (1935). Evolution in populations in approximate equilibrium. *Journal of Genetics* **30**, 257–266.
Wright, S. (1968). *Evolution and the Genetics of Populations*, vol. 1. Chicago: University of Chicago Press.