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ADDITIVE VARIATION MAINTAINED UNDER STABILIZING SELECTION: A TWO-LOCUS MODEL OF PLEIOTROPY FOR TWO QUANTITATIVE CHARACTERS

A. GIMELFARB

Department of Biology (Whitman), The University of Chicago, Chicago, Illinois 60637

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ABSTRACT

A model with two diallelic loci controlling two additive quantitative characters is suggested. One of the loci has a similar effect on both characters, whereas the second locus has an antagonistic effect on the two characters. Both characters experience direct stabilizing selection. The model yields a stable polymorphic state, with both characters maintaining genetic variation. The genetic correlation between the characters at the equilibrium is zero, in spite of the pleiotropic effects of the loci controlling them.

THE question about the amount of genetic variation that can be maintained in a population under stabilizing selection is prominent in theoretical population genetics; however, an answer to this question is far from being certain. Starting from the work by FISHER (1930), who showed that genetic variation is always reduced by stabilizing selection, it has been amply demonstrated that, in the absence of other forces, no genetic variation can be permanently maintained under stabilizing selection for an additive quantitative character controlled by several loci having similar effects on the character (except for the variation due to a maximum of one segregating locus if the number of loci is odd) (BULMER 1971; KOJIMA 1959; LEWONTIN 1964; ROBERTSON 1956; WRIGHT 1935).

A number of models have been developed that incorporate mutations as a source of variation, and suggestions have been made that mutation-selection balance can possibly account for the relatively high levels of genetic variation maintained in natural populations (BULMER 1972; KIMURA 1965; LANDE 1976; LATTER 1960; TURELLI 1984). The mutation-selection balance hypothesis, however, has not won unanimous acceptance. One of the main arguments against it is that mutation rates must be very high and selection very weak in order for mutation-selection balance to maintain the levels of genetic variation found in natural populations. The argument could have been settled if reliable estimates were available of mutation and selection parameters for quantitative characters in real populations. Unfortunately, the difficulties in obtaining re-

liable estimates of such parameters make a settlement of this argument virtually impossible (TURELLI 1984).

An important point to keep in mind concerning the result that no genetic variation can be maintained for an additive character under stabilizing selection is that the majority of models dealing with a quantitative character under stabilizing selection assume that the fitness of an individual depends exclusively on the value of this particular character. Any effects that other characters may have on the individual's fitness are ignored. This can be a valid approximation in the case of artificial selection for one particular character, but this is definitely not true in the case of natural selection, which is known to act on the whole organism and not just on one isolated character.

PEARSON (1903) already recognized that natural selection may have not only a direct effect on a character but also an indirect effect due to correlations with other characters under selection. PEARSON's ideas were developed and extended in a recent work by LANDE and ARNOLD (1983), who suggested ways of measuring direct and indirect effects of natural selection on multiple correlated characters. TURELLI (1985) discussed the errors in measuring parameters of selection on a quantitative character that can arise when indirect effects of selection for other characters are ignored.

ROBERTSON (1956; see also FALCONER 1981, chap. 20) considered a model of a quantitative character that is not under direct selection, but rather is under indirect stabilizing selection resulting from superior fitnesses of heterozygotes in the loci which also have an additive pleiotropic effect on the quantitative character. He showed that genetic variation can be maintained for such a character without mutations. BULMER (1973) suggested a diallelic model where direct stabilizing selection for an additive quantitative character is combined with an indirect effect of superior fitnesses of heterozygotes in the loci controlling the character. GILLESPIE (1984) extended BULMER's model to an arbitrary number of alleles per locus. It has been demonstrated that this model of "pleiotropic overdominance" may result in maintenance of genetic variation by an additive character in absence of mutations.

A simple model with two diallelic loci having a specific pleiotropic effect on two additive quantitative characters is presented in this paper. Both characters experience direct stabilizing selection. The model yields a stable equilibrium with genetic variation maintained by both characters in absence of mutation.

THE MODEL

Consider two quantitative characters, X_1 and X_2, both being controlled by the same two loci: locus A with alleles A,a and B with alleles B,b. Let the contributions of the alleles to the two characters be as follows:

	X_1	X_2
A	0	0
a	1	1
B	0	1
b	1	0

Also, let the genotypic values of the characters for an individual be equal to the sum of the respective contributions from the alleles constituting the individual's genotype. Notice that, since both characters are strictly additive, neither of them may have a nonadditive genetic component of variance, no matter what genotypic distribution may be in the population. Notice also that although locus A has the equivalent pleiotropic effect on both characters, locus B has an antagonistic pleiotropic effect: an increasing contribution by this locus to one of the characters is accompanied by a decreasing contribution to the other. ROSE (1982) investigated the role of antagonistic pleiotropy of genes affecting components of fitness in maintaining genetic variation.

Let us assume that natural selection operates in the following manner. Each of the two characters experiences direct selection with fitnesses $w_1(X_1)$ for the first and $w_2(X_2)$ for the second character. The total fitness, $w(X_1,X_2)$, of an individual with genotypic values X_1 and X_2 is the product of the two fitnesses:

$$w(X_1,X_2) = w_1(X_1)w_2(X_2). \tag{1}$$

This implies that the selection acts independently on the two characters, *i.e.*, the characters are functionally unrelated as far as selection is concerned.

Let direct selection on each of the characters be stabilizing around the "optimal" genotypic value θ with a quadratic fitness function:

$$w_i(X) = 1 - s_i(X - \theta_i)^2 \qquad (i = 1, 2). \tag{2}$$

Parameter s characterizes the strength of the stabilizing selection. Assuming for convenience that selection on both characters is around the same "optimal" genotypic value of 2, the fitness functions w_1 and w_2 are as follows:

$$w_i(X) = 1 - s_i(X - 2)^2 \qquad (i = 1, 2) \tag{2a}$$

where $s_i \leq 0.25$ in order for the fitnesses to be nonnegative over the range of genotypic values $0 \leq X_i \leq 4$. We shall ignore environmental components in the analysis, although their effects can be easily incorporated by substituting $s/(s - v_e)$ instead of s in (2) in the case of an independent additive environmental component with variance v_e.

The total fitnesses of the genotypes as computed from (1) and (2) are presented in the following fitness matrix:

	AA	*Aa*	*aa*
BB	$1 - 4s_1$	$(1 - s_2)(1 - s_2)$	$1 - 4s_2$
Bb	$(1 - s_1)(1 - s_2)$	1	$(1 - s_1)(1 - s_2)$
bb	$1 - 4s_2$	$(1 - s_1)(1 - s_2)$	$1 - 4s_1$

(3)

A two-locus genetic system with such a fitness matrix represents a special case of the general symmetric viability model, a detailed analysis of which has been presented by BODMER and FELSENSTEIN (1967) and by KARLIN and FELDMAN (1970). When applied to a genetic system with the fitness matrix, as in (3), the analysis reveals that for any set of selection parameters, s_1 and s_2, there always exists a unique symmetric equilibrium with allelic frequencies equal to 1/2 in

TABLE 1

Stable polymorphic states for the two-locus model

s_1	Parameters	s_1/s_2 = 1	2	3	4	5	10	20
0.25	r^*	0.5	0.5	0.5	0.4621	0.2704	0.1054	0.0506
	D	0.0	−0.0299	−0.0398	−0.0481	−0.0810	−0.1578	−0.2019
	$V1$	1.0	0.8805	0.8408	0.8078	0.6758	0.3689	0.1923
	$V2$	1.0	1.1195	1.1592	1.1922	1.3242	1.6311	1.8077
	r_c				0.25	0.20	0.10	0.05
0.15	r^*	0.5	0.5	0.5	0.2743	0.1614	0.0632	0.0303
	D	0.0	−0.0184	−0.0246	−0.0488	−0.0820	−0.1583	−0.2021
	$V1$	1.0	0.9262	0.9017	0.8047	0.6722	0.3668	0.1916
	$V2$	1.0	1.0738	1.0983	1.1953	1.3278	1.6332	1.8084
	r_c				0.15	0.12	0.06	0.03
0.10	r^*	0.5	0.5	0.5	0.1819	0.1073	0.0421	0.0202
	D	0.0	−0.0124	−0.0165	−0.0492	−0.0824	−0.1586	−0.2022
	$V1$	1.0	0.9504	0.9338	0.8032	0.6703	0.3657	0.1912
	$V2$	1.0	1.0496	1.0662	1.1968	1.3297	1.6343	1.8088
	r_c				0.10	0.08	0.04	0.02
0.05	r^*	0.5	0.5	0.5	0.0905	0.0535	0.0210	0.0101
	D	0.0	−0.0062	−0.0083	−0.0496	−0.0829	−0.1588	−0.2023
	$V1$	1.0	0.9750	0.9667	0.8016	0.6685	0.3547	0.1908
	$V2$	1.0	1.0250	1.0333	1.1984	1.3315	1.6353	1.8092
	r_c				0.05	0.04	0.02	0.01
0.01	r^*	0.5	0.5	0.5	0.0180	0.0107	0.0042	0.0020
	D	0.0	−0.0012	−0.0017	−0.0499	−0.0832	−0.1591	−0.2024
	$V1$	1.0	0.9950	0.9933	0.8003	0.6671	0.3636	0.1905
	$V2$	1.0	1.0050	1.0067	1.1997	1.3329	1.6364	1.8095
	r_c				0.01	0.008	0.004	0.002

Abbreviations: s_1 and s_2 = selection parameters; r^* = critical value of recombination coefficient; D = linkage disequilibrium; $V1$ and $V2$ = genetic variances; $r_c = 4s_2$.

both loci and with the gametic frequencies

$$p_{AB} = p_{ab} = 1/4 + D,$$
$$p_{Ab} = p_{aB} = 1/4 - D, \tag{4}$$

where D is the equilibrium value of linkage disequilibrium that can be found as a solution of a cubic equation (BODMER and FELSENSTEIN 1967, eq. 17). The stability of this equilibrium depends on the value of the recombination coefficient. The critical values of the recombination coefficient, r^*, below which there is a stable polymorphic equilibrium, are presented for different sets of selection parameters in Table 1, where it is assumed for definiteness that $s_1 \geq s_2$, *i.e.*, $s_1/s_2 \geq 1$. The following procedure was employed to obtain r^* for a given set of selection parameters. The initial value of the recombination coefficient was chosen as 0.5, and the equilibrium value of D was computed for the chosen recombination coefficient by solving the cubic equation (BODMER and FELSENSTEIN 1967, eq. 17). Following that, the system of recur-

rent equations for the dynamics of a two-locus genetic system (*e.g.*, BODMER and FELSENSTEIN 1967, eq. 1) was linearized around the equilibrium (4), and the eigenvalues of the linear system were calculated. If the absolute values of all the eigenvalues were <1, the chosen value of the recombination coefficient was considered as r^*. If the absolute value of at least one of the eigenvalues was >1, a smaller value of the recombination coefficient was chosen, and the calculations were repeated with the new value. Thus, for a given set of selection parameters the critical value, r^*, in Table 1 represents the largest (to five decimal points) recombination coefficient for which there is a stable polymorphic equilibrium. Also shown in Table 1 are the equilibrium values of linkage disequilibrium, D, corresponding to r^*.

The gametic frequencies (4) can be used to compute the means and variances of the two characters at the equilibrium. The means are the same for both characters, and they are equal to the "optimal" value:

$$M_1 = M_2 = 2.$$

The equilibrium variances, V_1 and V_2, of the two characters are presented in Table 1. Notice that the amount of genetic variation maintained by either of the two characters at the equilibrium (as measured by the variances V_1 and V_2) can be quite high. In the case of similar selection on both characters, *i.e.*, when $s_1/s_2 = 1$, it is equal to the maximum amount of genetic variation that can be maintained under random mating without selection, which is 1. In the case of $s_1 > s_2$, the genetic variation maintained by the second character is even higher than under random mating without selection. Notice also that a substantial negative linkage disequilibrium can be generated in the latter case.

It should be noted that the polymorphic equilibrium (4) may not be the only stable equilibrium for a given recombination coefficient. According to BODMER and FELSENSTEIN (1967, table 6), the monomorphic equilibria $p_{Ab} = 1$ and $p_{aB} = 1$ are stable when $1 - 4s_2 > (1 - s_1)(1 - s_2)$, if $r > r_c$, where $r_c = 4s_2$. Thus, there can be three simultaneously stable equilibria: one polymorphic (4) and two monomorphic when $s_1/s_2 < 3 + s_1$ and $r_c < r < r^*$. The values of r_c are presented in Table 1.

Because of the interaction between direct and indirect effects of selection, individuals with the same value of one of the characters, say X_1, may have different fitnesses. It makes no sense, therefore, to consider the fitness of an individual with a specified value of one of the characters, but only to consider the expected fitness of such an individual. The expected fitness, $w_1^*(X_1)$, of an individual whose value of the first character is X_1, resulting from the direct as well as indirect effects of selection on the character, can be computed as

$$w_1^*(X_1) = \sum_k w(G_k)p(G_k|X_1),$$

where G_k ($k = 1, \cdots, 9$) denotes a two-locus diallelic genotype; $w(G_k)$ is the fitness of the genotype G_k that can be found from the fitness matrix (3), and $p(G_k \mid X_1)$ is the probability for an individual with the value of the first character X_1 to have genotype G_k. The latter probability is easily computed for

TABLE 2

Fitness "profiles" of additive characters

s_1/s_2	Fitness	X				
		0	1	2	3	4
1	w_1^*	0.0000	0.5625	0.6667	0.5625	0.0000
	w_2^*	0.0000	0.5625	0.6667	0.5625	0.0000
2	w_1^*	0.0000	0.6563	0.8091	0.6563	0.0000
	w_2^*	0.5000	0.6563	0.7235	0.6563	0.5000
3	w_1^*	0.0000	0.6875	0.8680	0.6875	0.0000
	w_2^*	0.6667	0.6875	0.7436	0.6875	0.6667
4	w_1^*	0.0000	0.7031	0.8983	0.7031	0.0000
	w_2^*	0.7500	0.7031	0.7607	0.7031	0.7500
5	w_1^*	0.0000	0.7125	0.9115	0.7125	0.0000
	w_2^*	0.8000	0.7125	0.8288	0.7125	0.8000
10	w_1^*	0.0000	0.7313	0.9512	0.7313	0.0000
	w_2^*	0.9000	0.7313	0.9536	0.7313	0.9000
20	w_1^*	0.0000	0.7406	0.9751	0.7406	0.0000
	w_2^*	0.9500	0.7406	0.9889	0.7406	0.9500

Abbreviations: X = value of a character; s_1 and s_2 = selection parameters; w_1^* and w_2^* = expected fitnesses of characters X_1 and X_2; $s_1 = 0.25$.

any given gametic frequencies under the assumption of random mating. The expected fitness of an individual with a given value of the second character can be determined in the same way. The expected fitnesses for different values of a character, X, at the stable polymorphic equilibrium are shown in Table 2 for $s_1 = 0.25$, and a number of values s_1/s_2. Notice that when $s_1/s_2 < 3$ (actually, when $s_1/s_2 < 3 + s_2$), the "profiles" of the fitnesses for both characters at the equilibrium have a distinct "stabilizing" shape with the "optimum" value at $X = 2$ and with descending fitnesses for values farther away from the optimum. When $s_1/s_2 > 3 + s_2$, the fitness profile for the first character remains strictly "stabilizing," whereas the profile for the second character has two intermediate minima with the value of 2 still being the "optimum," *i.e.*, having the maximum fitness.

Thus, the two-locus model presented in this paper demonstrates that there can be a situation when two additive quantitative characters will maintain genetic variation with both characters being under direct stabilizing selection, if the two characters have the specific pleiotropic relation. Notice that antagonistic pleiotropy may be a common phenomenon for quantitative characters controlled by more than two loci and, therefore, can be a source of additive genetic variation maintained by multilocus characters. It is not clear, however, how results of the presented two-locus model can be generalized to a greater number of loci. Analytical results for multilocus characters can hardly be expected, and extensive computer simulations should be conducted.

DISCUSSION

Imagine an investigator whose interests are in one of the characters, say X_1, and who may not even be aware of the existence of the other character, X_2. He (or she) observes that a substantial amount of genetic variation is maintained in a population by the character X_1, and in an attempt to discover the source of the maintained variation, he undertakes a thorough analysis of the character. It is clear that, whatever methods of analysis he chooses, the correct outcome should be that only an additive component of genetic variance is present, because allelic contributions to the character are actually additive, and that the fitness function for the character has a profile similar to one of the rows marked as w_1^* in Table 2, indicating that the character is under stabilizing selection.

To an investigator who knows that no genetic variation can be maintained by an additive quantitative character under stabilizing selection, this outcome should clearly indicate a necessity to look for an additional source of variation. The most obvious source to consider would be mutation, since mutation-selection balance could possibly account for the presence of genetic variation maintained by the character X_1 in equilibrium. However, the high level of genetic variation maintained even under strong selection would require unrealistically high mutation rates, and therefore, mutation should be ruled out as a significant factor contributing to the maintenance of genetic variation by the character X_1.

If the investigator is aware of the possibility of an indirect effect on character X_1 of selection for some other character biologically connected with X_1, he may try to find such a character. Notice, however, that it will be a very difficult task to identify X_2 as being such a character. Indeed, there are two main indicators of a biological connection between two characters: the characters may be functionally related (due to correlated effects on fitness) or they can be genetically correlated (due to pleiotropy or linkage). As for the characters X_1 and X_2, they are functionally unrelated [see (1)], and what is more, they are genetically *uncorrelated* in a population in equilibrium. Indeed, as it is shown in the APPENDIX, the genetic correlation between characters X_1 and X_2 is zero at the polymorphic equilibrium (4), even though they are pleiotropically related. Hence, even if the investigator will be lucky enough to come across the character X_2, he is almost certain to discard it as having no biological connection with the character X_1.

Thus, the model presented in this paper demonstrates that two additive quantitative characters, each being under direct stabilizing selection, can maintain a high level of genetic variation in absence of mutation, if the characters have a particular (mixture of equivalent and antagonistic) pleiotropic relation. Unfortunately, the model also demonstrates that such a pleiotropic relation between characters may be quite difficult to detect.

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APPENDIX

Let x_1 and x_2 be the contributions by a gamete to the first and second characters, respectively. The contributions of the four types of gametes are as follows:

	x_1	x_2
AB	0	1
Ab	1	0
aB	1	2
ab	2	1

At the equilibrium (4) the mean values of x_1 and x_2:

$$m_1 = m_2 = 1. \tag{A1}$$

If Cov_{12} is the covariance between characters X_1 and X_2, then under random mating,

$$\mathrm{Cov}_{12} = 2\mathrm{cov}_{12}, \tag{A2}$$

where cov_{12} is the covariance between x_1 and x_2, which can be computed as

$$\mathrm{cov}_{12} = E(x_1x_2) - m_1m_2$$

$$= 2p_{aB} + 2p_{ab} - m_1m_2.$$

Substituting (4) and (A1) yields $\mathrm{cov}_{12} = 0$, and hence, $\mathrm{Cov}_{12} = 0$. Thus, the coefficient of correlation between X_1 and X_2 is zero.