STABLE EQUILIBRIA UNDER STABILISING SELECTION IN THE ABSENCE OF DOMINANCE

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1. INTRODUCTION

It has frequently been suggested that the extensive genetic variation found in natural populations might be due in part to the action of stabilising selection. Models which do not require overdominance on the primary scale but which nevertheless lead to stable equilibria under stabilising selection have been discussed by Kojima (1959), Lewontin (1964), Jain and Allard (1965) and Singh and Lewontin (1966). However, such models do require that the loci controlling the character exhibit partial but fairly substantial dominance on the primary scale. Moreover, in the models described, the dominance is unidirectional.

However, the available evidence strongly suggests that many characters under stabilising selection are controlled by genes showing either no dominance or fairly weak ambidirectional dominance on the primary scale (Kearsey and Kojima, 1967), in accordance with the hypothesis first proposed by Mather (1960). The best substantiated example of this is sternopleural chaeta number in *Drosophila melanogaster*, where Barnes (1968) has demonstrated that a cage population, originating from an F_2 derived from crosses between two inbred lines, exhibited strong stabilising selection. The genes controlling sternopleural chaeta number in this experiment exhibited no dominance; absence of potency for this character has been found in nearly all investigations. Models of stabilising selection previously put forward would not be applicable in such cases.

In this paper, we shall show that this difficulty can be resolved if we assume that the effects of different loci on the primary character are unequal, which will be the usual situation in practice. In such situations, stable equilibria may occur in the absence of dominance on the primary scale.

If the inequality between the effects of the different loci is small, linkage is required for stability of equilibria. With sufficiently large differences between loci, we obtain the situation described by Kimura (1956), where one locus shows unconditional overdominance in fitness; under these circumstances, the loci need not be linked for stable equilibria to arise. We shall therefore restrict ourselves in the main to those situations where the difference between loci is relatively small, using a 2-locus model to illustrate the situation. In all cases described, we shall locate the fittest genotype at the midpoint of the phenotypic range.

2. NON-TRIVIAL EQUILIBRIUM POINTS

We consider first the contribution of the two loci to the phenotype of the primary character. In the absence of dominance we may represent the contribution of the first locus as

<i>AA</i>	<i>Aa</i>	<i>aa</i>
2	1	0

and that of the second locus as

<i>BB</i>	<i>Bb</i>	<i>bb</i>	
$2+2k$	$1+k$	0	$(0 \leq k \leq 1)$

If the two loci act jointly in a purely additive manner, the (mean) phenotypes will then be as shown in table 1.

TABLE 1
Phenotypes for the primary character

	<i>AA</i>	<i>Aa</i>	<i>aa</i>
<i>BB</i>	$4+2k$	$3+2k$	$2+2k$
<i>Bb</i>	$3+k$	$2+k$	$1+k$
<i>bb</i>	2	1	0

We now take the fitness of an individual as proportional to the mean phenotypic value of his genotype on the primary scale. The range of such values is $4+2k$ with midpoint $2+k$. We now suppose that individuals at the midpoint have fitness 3 and that the fitness falls by 1 for unit change of value on either side of the optimum. This simple model is easy to handle, although probably less realistic than the quadratic models which are frequently described. We then have the fitnesses given in table 2.

TABLE 2
Fitness of different genotypes

	<i>AA</i>	<i>Aa</i>	<i>aa</i>
<i>BB</i>	$1-k$	$2-k$	$3-k$
<i>Bb</i>	2	3	2
<i>bb</i>	$3-k$	$2-k$	$1-k$

It should perhaps be emphasised that, in this model, the fitnesses are directly related to mean phenotypic values on the primary scale. The selective advantage of the double heterozygote arises in virtue of its position at the midpoint of the range and not from heterozygosity as such. Thus in this important respect the present model differs from that put forward by Bodmer and Parsons (1962, p. 79).

While this paper was in preparation, a paper appeared by Bodmer and Felsenstein (1967) which gave conditions under which stable equilibria would be obtained for a variety of 2-locus models. Although their discussion was not specifically related to stabilising selection, the model we have put forward is easily seen to be a special case of their "general symmetrical viability model". It follows, therefore, from their analysis that, given sufficiently intense linkage, stable equilibria must exist for the model we have discussed. We shall locate equilibria by an approach essentially similar to that of Bodmer and Felsenstein, but in a notation more convenient in the present context.

We write the gametic frequencies in a given generation as

AB	aB	Ab	ab
c_1	c_2	c_3	c_4

and in the next generation as c'_1, c'_2, c'_3, c'_4 . If R is the recombination fraction and $\bar{W}$ the average fitness in the earlier generation, we find, following Lewontin and Kojima (1960),

$$c'_1 \bar{W} = c_1^2 + 2c_1c_3 + 2c_1c_2 + 3(1-R)c_1c_4 + 3Rc_2c_3 - k(c_1^2 + c_1c_2) \quad (1)$$

$$c'_2 \bar{W} = 3c_2^2 + 2c_2c_4 + 2c_1c_2 + 3(1-R)c_2c_3 + 3Rc_1c_4 - k(c_2^2 + c_1c_2) \quad (2)$$

$$c'_3 \bar{W} = 3c_3^2 + 2c_1c_3 + 2c_3c_4 + 3(1-R)c_2c_3 + 3Rc_1c_4 - k(c_3^2 + c_3c_4) \quad (3)$$

$$c'_4 \bar{W} = c_4^2 + 2c_3c_4 + 2c_2c_4 + 3(1-R)c_1c_4 + 3Rc_2c_3 - k(c_4^2 + c_3c_4) \quad (4)$$

We shall be interested in equilibria for which none of the c 's are zero. Putting $c'_1 = c_1, \dots, c'_4 = c_4$ we find that such equilibria will exist if the four expressions for $\bar{W}$

$$c_1 + 2c_2 + 2c_3 + 3(1-R)c_4 + 3Rc_2c_3/c_1 - k(c_1 + c_2) \quad (5)$$

$$2c_1 + 3c_2 + 2c_4 + 3(1-R)c_3 + 3Rc_1c_4/c_2 - k(c_1 + c_2) \quad (6)$$

$$2c_1 + 3c_3 + 2c_4 + 3(1-R)c_2 + 3Rc_1c_4/c_3 - k(c_3 + c_4) \quad (7)$$

$$c_4 + 2c_2 + 2c_3 + 3(1-R)c_1 + 3Rc_2c_3/c_4 - k(c_3 + c_4) \quad (8)$$

are equal.

If $c_1 = c_4, c_2 = c_3$ we find (5) = (8), (6) = (7). The four expressions for $\bar{W}$ now reduce to two, namely

$$4c_1 + 4c_2 - 3Rc_1 + 3Rc_2^2/c_1 - k(c_1 + c_2) \quad (9)$$

$$4c_1 + 6c_2 - 3Rc_2 + 3Rc_1^2/c_2 - k(c_1 + c_2) \quad (10)$$

which will be equal if

$$2c_2 - 3R(c_2 - c_1) + 3R(c_1^2/c_2 - c_2^2/c_1) = 0 \quad (11)$$

Moreover, if $c_1 = c_4, c_2 = c_3$ we have

$$c_1 + c_2 = \frac{1}{2} \quad (12)$$

Substituting (12) in (11) we find

$$2c_1^3 - 2c_1^2 + \frac{1}{2}(1 + 3R)c_1 - \frac{3}{8}R = 0 \quad (13)$$

This cubic will have one real root, except for the case $R = 0$, when the problem reduces to that of a four-allele system at a single locus (Mandel 1959). Numerical values for c_1 are given in table 3.

Although these equilibrium values are independent of k , the stability of such equilibria does indeed depend on k , as will now be shown. We may note, however, for 2-locus models, that when conditions are such that the equilibria are unstable, frequencies may remain in the neighbourhood of such equilibrium points for a considerable number of generations (Lewontin, 1964). Computer simulations show that this may happen in the present case.

TABLE 3
Equilibrium values for c_1

R	c_1
0.05	0.037257
0.10	0.072821
0.15	0.104623
0.20	0.131068
0.25	0.151838
0.30	0.167698
0.35	0.179772
0.40	0.189071
0.45	0.196359
0.50	0.202179

3. STABILITY OF EQUILIBRIA

We follow the procedure given by Moran (1964). Suppose in a given generation, that the gametic frequencies are

$$(c_1 + \delta_1, c_2 + \delta_2, c_3 + \delta_3, c_4 + \delta_4) \quad (14)$$

the c 's being now the equilibrium frequencies, so that the δ 's sum to zero. In the next generation, we write the frequencies as

$$(c_1 + \delta'_1, c_2 + \delta'_2, c_3 + \delta'_3, c_4 + \delta'_4) \quad (15)$$

We wish to show that, in the course of time, the deviations from equilibrium value tend to zero. In the neighbourhood of the equilibrium values, the δ 's are small and we may neglect second order terms in the δ 's. The δ 's may then be written as linear functions of the δ 's. In matrix form, we have

$$\delta' = A\delta \quad (16)$$

where

$$\delta = \begin{pmatrix} \delta_1 \\ \delta_2 \\ \delta_3 \\ \delta_4 \end{pmatrix} \quad \delta' = \begin{pmatrix} \delta'_1 \\ \delta'_2 \\ \delta'_3 \\ \delta'_4 \end{pmatrix}$$

Moran derives the matrix A for the case where the loci are unlinked, but his procedure is equally applicable to the case of linkage. We write

$$\begin{aligned} D &= c_2c_3 - c_1c_4 \\ l(i) &= 1 \quad \text{when } i = 1 \text{ or } 4 \\ &= -1 \quad \text{when } i = 2 \text{ or } 3 \end{aligned} \quad (17)$$

For convenience, we may write the fitnesses given in table 2 as shown in table 4.

TABLE 4
Alternative notation for fitnesses

W_{11}	W_{12}	W_{13}
W_{21}	W_{22}	W_{23}
W_{31}	W_{32}	W_{33}

The mean fitness at equilibrium will be

$$\bar{W} = W_{11}c_1^2 + 2W_{12}c_1c_2 + W_{13}c_2^2 + 2W_{21}c_1c_3 + 2W_{22}c_1c_4 + 2W_{23}c_2c_3 + 2W_{23}c_2c_4 + W_{31}c_3^2 + 2W_{32}c_3c_4 + W_{33}c_4^2 \quad (18)$$

If, as usual, a_{ij} denotes the element in the i th row, j th column of A , it may now be shown that

$$\bar{W}a_{ii} = \frac{1}{2} \frac{\partial \bar{W}}{\partial c_i} + \frac{1}{2} c_i \frac{\partial^2 \bar{W}}{\partial c_i^2} + R W_{22} l(i) \frac{\partial D}{\partial c_i} - c_i \frac{\partial \bar{W}}{\partial c_i} \quad (19)$$

$$\bar{W}a_{ij} = \frac{1}{2} c_i \frac{\partial^2 \bar{W}}{\partial c_j \partial c_i} + R W_{22} l(i) \frac{\partial D}{\partial c_j} - c_i \frac{\partial \bar{W}}{\partial c_j} \text{ when } i \neq j \quad (20)$$

where appropriate values for the c 's are substituted *after* differentiation.

To illustrate the use of these formulae, we shall calculate $\bar{W}a_{12}$. We have

$$\begin{aligned} \frac{1}{2} \frac{\partial \bar{W}}{\partial c_2} &= W_{12}c_1 + W_{13}c_2 + W_{22}c_3 + W_{23}c_4 \\ &= (2-k)c_1 + (3-k)c_2 + 3c_3 + 2c_4 \\ &= (4-k)c_1 + (6-k)c_2 \\ &= 3 - \frac{1}{2}k - 2c_1 \end{aligned} \quad (21)$$

since $c_1 = c_4$, $c_2 = c_3 = \frac{1}{2} - c_1$

Similarly

$$\frac{1}{2} \frac{\partial^2 \bar{W}}{\partial c_2 \partial c_1} = W_{12} = 2-k \quad (22)$$

$$\frac{\partial D}{\partial c_2} = c_3 = \frac{1}{2} - c_1 \quad (23)$$

$$l(i) = 1 \quad (24)$$

whence

$$\bar{W}a_{12} = \frac{3}{2}R - c_1(4+3R-4c_1) \quad (25)$$

The complete matrix is given in table 5, where, for convenience, columns 3 and 4 are given below columns 1 and 2.

TABLE 5

Transition matrix **A**

$(2-\frac{1}{2}k) - 3c_1(1+R)$	$\frac{3}{2}R - c_1(4+3R-4c_1)$
$-1 + c_1(2+3R)$	$\frac{3}{2} - \frac{1}{2}k - \frac{3}{2}R + c_1(3+3R-4c_1)$
$-1 + \frac{1}{2}k + c_1(2+3R-k)$	$-\frac{3}{2} + \frac{1}{2}k - \frac{3}{2}R + c_1(5+3R-k-4c_1)$
$-c_1(1+3R-k)$	$\frac{3}{2}R - c_1(4+3R-k-4c_1)$
$\frac{3}{2}R - c_1(4+3R-k-4c_1)$	$-c_1(1+3R-k)$
$-\frac{3}{2} + \frac{1}{2}k - \frac{3}{2}R + c_1(5+3R-k-4c_1)$	$-1 + \frac{1}{2}k + c_1(2+3R-k)$
$\frac{3}{2} - \frac{1}{2}k - \frac{3}{2}R + c_1(3+3R-4c_1)$	$-1 + c_1(2+3R)$
$\frac{3}{2}R - c_1(4+3R-4c_1)$	$(2-\frac{1}{2}k) - 3c_1(1+R)$

All $\div \bar{W}$

An equilibrium will be stable if and only if all the latent roots of **A** are less than unity in absolute value. Values for the numerically largest latent root, for various values of k and R are given in table 6, where 1.00- indicates a root marginally less than one.

TABLE 6
Numerically largest latent roots of *A*

		<i>k</i>										
		0.0	0.1	0.2	0.3	0.4	0.5	0.6	0.7	0.8	0.9	1.0
<i>R</i>	0.05	1.02	1.01	0.99	0.97	0.96	0.94	0.92	0.90	0.88	0.86	0.85
	0.10	1.05	1.03	1.02	1.00	0.98	0.97	0.95	0.93	0.92	0.90	0.88
	0.15	1.06	1.05	1.03	1.02	1.01	0.99	0.98	0.96	0.95	0.93	0.92
	0.20	1.08	1.06	1.05	1.04	1.02	1.01	1.00	0.98	0.97	0.96	0.94
	0.25	1.09	1.07	1.06	1.05	1.04	1.02	1.01	1.00	0.99	0.97	0.96
	0.30	1.09	1.08	1.07	1.06	1.04	1.03	1.02	1.01	1.00	0.99	0.98
	0.35	1.10	1.08	1.07	1.06	1.05	1.04	1.03	1.02	1.01	1.00	0.99
	0.40	1.10	1.09	1.08	1.07	1.06	1.04	1.03	1.02	1.01	1.00	0.99
	0.45	1.10	1.09	1.08	1.07	1.06	1.05	1.04	1.03	1.02	1.01	1.00
	0.50	1.10	1.09	1.08	1.07	1.06	1.05	1.04	1.03	1.02	1.01	1.00

We see that for any given value of *k*, there is a critical value of *R*; if *R* falls below this critical value, a stable equilibrium exists. For values of *R* where the numerically largest root is only slightly greater than unity, frequencies will move away from the neighbourhood of unstable equilibrium values, but only slowly, as mentioned earlier, giving rise to a transient but long lived polymorphism.

4. APPROACH TO EQUILIBRIUM

We have shown that, if we start with gametic frequencies close to their stable equilibrium values, a balanced polymorphism will result. In natural populations, however, initial frequencies will usually be far away from equilibrium values. Thus we may suppose, (1) that in a population, selection for a character was originally in the upward direction. The population would then consist almost entirely of *AB/AB*, the other genotypes being maintained at low frequency by recurrent mutation. Alternatively, (2) that the fittest genotype was intermediate but not at the midpoint of the range, such that an homozygote, say *Ab/Ab*, was at an advantage over all other genotypes. Suppose now that the environment changed in such a way that the fitnesses became those given in table 2. Would a balanced polymorphism arise in these circumstances?

An attempt to investigate these points has been made using computer simulations. Initial gametic frequencies were taken as follows:

	<i>AB</i>	<i>Ab</i>	<i>aB</i>	<i>ab</i>
Case (1)	0.9702	0.0198	0.0098	0.0002
Case (2)	0.0198	0.9702	0.0002	0.0098

While frequencies for the originally unfavoured combinations are, of course, unreasonably high, the results should give a guide to what would happen in practice. Frequencies were printed out every 50 generations. Results are given in tables 7 and 8. For those cases where a stable equilibrium was attained, the number of generations, in 50's, required for equilibrium values (to 5 decimal places) to be reached has been entered; an asterisk indicates that the population went to fixation.

TABLE 7
Generations to equilibrium, when AB is initially in excess

		k								
		0.2	0.3	0.4	0.5	0.6	0.7	0.8	0.9	1.0
R	0.05	700	300	200	150	100	100	100	100	100
	0.10	$\gg 2000$	500	300	200	150	150	100	100	
			0.15	1100	450	300	200	150	150	
				0.20	> 2000	550	300	250	200	
					0.25	*	700	400	250	
						0.30	*	750	400	
							0.35	*	750	
								0.40	*	
								0.45	*	

* = No equilibrium.

The results suggest that, when a stable equilibrium exists, it is usually attained, even when initial frequencies are a long way from their equilibrium values. For the cases considered, equilibrium is attained if

$$3R < k$$

except in one situation where $3R > 1$. When $3R = k$, equilibrium is reached in case (1) but not in case (2). However, it turns out that, in the latter case, the approach to fixation is exceedingly slow. For example, if $R = 0.2$, $k = 0.6$ frequencies in generation 50 are

<i>AB</i>	<i>Ab</i>	<i>aB</i>	<i>ab</i>
0.000454	0.999063	0.000302	0.000181

and differ from these only in the sixth decimal place in generation 1000. In contrast, if $R = 0.3$, $k = 0.8$, the frequency of *Ab* (to six decimal places) has reached unity by generation 200. The significance of these relationships between R and k is under investigation.

5. EXTREME DISPARITY BETWEEN LOCI

The two loci may differ substantially in their effects on the primary character, so that k is greater than one. In such a case the *Bb* heterozygote

will be at a selective advantage over both BB and bb , irrespective of the genotype at the A/a locus; hence (Kimura, 1956) stable equilibria with both loci segregating will arise even in the absence of linkage. The situation may be illustrated for the cases $k = 2$ and $k = 3$. To avoid negative fitnesses, $(1 - k)$ was added to the fitness of every genotype. Computer runs were started with frequencies as in case (1), above. Equilibrium frequencies proved to be:

k	AB	Ab	aB	ab	No. of generations
2	0.21508	0.28492	0.28492	0.21508	270
3	0.22259	0.27741	0.27741	0.22259	226

TABLE 8

Generations to equilibrium, when Ab is initially in excess

		k									
		0.2	0.3	0.4	0.5	0.6	0.7	0.8	0.9	1.0	
R	0.05	1150	400	250	200	150	150	100	100	100	
	0.10		*	700	350	250	200	150	150	100	
				0.15	1450	550	350	250	200	150	
					0.20	*	700	400	300	200	
						0.25	*	1000	450	300	
							0.30	*	*	550	
								0.35	*	*	
									0.40	*	
										0.45	*

* = No equilibrium.

6. SUMMARY

1. A metrical character under stabilising selection will usually be controlled by several loci, at which the effect on the character of gene substitutions will differ from one locus to another.

2. With a 2-locus model incorporating such unequal effects, stable equilibria may arise, even though the genes act on the primary character in a purely additive manner.

3. If the disparity between effects at the two loci is not very large, such equilibria will occur only if the two loci are linked, the intensity of linkage required falling off as the disparity between the loci increases.

4. Computer simulations suggest that in situations where stable equilibria exist, frequencies will usually, but not always, move to equilibrium values, even when initial frequencies are remote from those at equilibrium.

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