

# Monotonic Change of the Mean Phenotype in Two-Locus Models

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## ABSTRACT

It is shown that the mean phenotype monotonically approaches the optimum in a class of symmetric, two-locus, two-allele models with stabilizing selection. In this model, mean fitness does not change monotonically. Thus, Fisher's fundamental theorem does not hold, even though another quantity of evolutionary interest, the mean phenotype, can be shown to change monotonically. Using this quantity, it is proven that global stability results for this model.

ONE of the most celebrated results in theoretical population genetics is FISHER's (1930) fundamental theorem, which shows that mean fitness is nondecreasing in single locus models with constant fitnesses. Both because this notion is intuitively appealing and because it is useful in analyzing models, there have been many attempts to extend FISHER's theorem to multiple locus models (e.g., EWENS 1969; KARLIN and FELDMAN 1970a; NAGYLAKI 1976). However, early in the study of two-locus models, examples were found that showed that FISHER's result did not hold in general for multilocus models.

Another approach to studying multilocus models is to consider the change in the mean and variance of a phenotype, determined additively by a number of loci, undergoing selection. This quantitative genetics approach can be used to show that under stabilizing selection that the change in the mean phenotype is *approximately* proportional to the deviation of the mean from the optimum times the genetic variance (BULMER 1980; FALCONER 1981), ignoring the role of recombination, disequilibrium or epistasis.

Here, I describe a class of two locus models for which a quantity of evolutionary interest, namely the negative of (the absolute value of) the deviation of the mean phenotype from the optimum, can be shown to always increase. I then use this result to prove global stability results. The reason that the behavior of the model can be analyzed this way for two loci is that the mean of the phenotype is unchanged by recombination, and the number of different values (contributions to the phenotype) of gametes is only three. Thus, the selection aspect of the system can be described by two variables. Consequently, the mean and the variance provide an adequate description of the response to selection.

## MODEL AND RESULTS

Let there be two loci with two alleles each:  $A_0$  and  $A_1$  at the  $A$  locus and  $B_0$  and  $B_1$  at the  $B$  locus. Let the

frequency of the gametes  $A_0B_0$ ,  $A_0B_1$ ,  $A_1B_0$ ,  $A_1B_1$  be given by  $x_1$ ,  $x_2$ ,  $x_3$ ,  $x_4$ , respectively. Define the linkage disequilibrium  $D$  to be  $x_1x_4 - x_2x_3$  and let  $r$  be the recombination rate. Let  $\delta_i$  take the values  $-1$ ,  $1$ ,  $1$ ,  $-1$  for  $i = 1-4$ , respectively. Let  $w_{ij} = w_{ji}$  (with  $w_{23} = w_{14} = 1$ ) be the fitness of the individual with the gametes whose frequencies are  $x_i$  and  $x_j$ . Denote the marginal mean fitness of the gamete  $i$  by:

$$w_i = \sum_{j=1}^4 x_j w_{ij}, \quad (1)$$

and the mean fitness of the population by:

$$\bar{w} = \sum_{j=1}^4 x_j w_j. \quad (2)$$

Then the dynamics of this system are given by:

$$x'_i = (x_i w_i + \delta_i r D) / \bar{w} \quad (3)$$

for a discrete time system with nonoverlapping generations.

Let the allele subscripted 0 at each locus contribute 0 to the phenotype and let the allele subscripted 1 contribute 1. Assume that the phenotype is determined additively across alleles and loci in a model of stabilizing selection with an optimum of two, which is symmetric about the optimum. This leads to a special case of the symmetric model (KARLIN and FELDMAN 1970b), as in Table 1. It is easy to show that mean fitness can decrease in this model. The first result concerns the mean phenotype. (Sketches of proofs are given in the APPENDIX.)

**Result 1:** The mean phenotype of the population approaches its optimum monotonically, starting from any initial condition where the population is not homozygous for both '1' alleles or both '0' alleles.

Also, starting from initial conditions with all alleles present, the system either ends up homozygous for the gamete  $A_0B_1$  or the gamete  $A_1B_0$ , or possibly at an

TABLE 1

Fitnesses in a two-locus phenotypic model with an intermediate optimum

	$B_0B_0$	$B_0B_1$	$B_1B_1$
$A_0A_0$	$1-\delta$	$1-\beta$	1
$A_0A_1$	$1-\beta$	1	$1-\beta$
$A_1A_1$	1	$1-\beta$	$1-\delta$

In a model of stabilizing selection, either  $0 \leq \beta < \delta$ , or  $0 < \beta \leq \delta$ .

unstable balance where at each locus both alleles are equally represented.

**Result 2:** The only possible outcomes of the model (3) with the fitnesses in Table 1 are fixation with  $x_2 = 1$  or  $x_3 = 1$ , or an equilibrium with  $x_1 = x_4$  and  $x_2 = x_3$ . This last equilibrium is unstable, so it is approached only from initial conditions satisfying particular equality constraints.

DISCUSSION

The result here is that in a two-locus model of stabilizing selection, the mean phenotype changes monotonically. Note that the mean fitness does not always increase in this model. The result of the current paper represents the first step in providing an alternate way of extending the approach embodied in FISHER's fundamental theorem to more than two loci. While the result here is encouraging, it is important to recognize the strong limitations imposed here. First, the model is limited to two loci. Second, the optimum is assumed to be achieved when both loci are homozygous. Third, both loci are assumed identical and contribute additively to the character.

What are the positive implications of this result? Models of quantitative inheritance (e.g., FALCONER 1981; BULMER 1980) have predicted that the mean changes in proportion to the variance and approaches its optimum monotonically. The importance of the result here is that it is exact, and the effects of recombination and disequilibrium are explicitly included.

It is natural to consider the possibility of extensions to more loci. With more loci, the third moment may be important (cf. BARTON 1986), so extensions will not necessarily be straightforward. In a four (or more)-locus model there are additional unstable internal equilibria, where the mean of the character is not at the optimum. These correspond to cases where the third moment of the phenotype is nonzero (cf. BARTON 1986), and indicate that the mean of the phenotype cannot behave as it does in two-locus two-allele models. This necessarily complicates the analysis, but suggests the possibility of additional phenomena of evolutionary interest.

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APPENDIX

Here I sketch the proof of the results in the paper. Instead of  $x_i$ , use the following three variables (KARLIN and FELDMAN 1970b):

$$u = x_1 - x_4 \tag{A1}$$

$$v = x_2 - x_3 \tag{A2}$$

$$z = x_1 + x_4 - x_2 - x_3. \tag{A3}$$

Note that these three variables satisfy the inequalities:

$$1 \geq u, v, z \geq -1. \tag{A4}$$

The mean of the phenotype is  $2u + 2$ .

For the fitnesses in Table 1, the dynamics of the system are (KARLIN and FELDMAN 1970b):

$$\bar{w}u' = u - \delta u(1+z)/2 - \beta u(1-z)/2 \tag{A5}$$

$$\bar{w}v' = v - \beta u(1-z)/2 \tag{A6}$$

$$\bar{w}z' = z - \delta\{(1+z)^2 + 4u^2\}/8 - r(z + v^2 - u^2), \tag{A7}$$

where

$$\bar{w} = 1 - \delta\{(1+z)^2 + 4u^2\}/8 - \beta(1-z^2)/2. \tag{A8}$$

**Proof of Result 1:** Write equation (A5) as:

$$u' = u w_u / \bar{w}, \tag{A9}$$

where

$$w_u = 1 - \delta(1+z)/2 - \beta(1-z)/2. \tag{A10}$$

The conclusion of the theorem will follow immediately from the inequality:

$$\bar{w} > w_u > 0. \tag{A11}$$

To see that  $w_u > 0$ , note that  $\delta, \beta$  and  $|z|$  are less than one. To demonstrate the other half of the inequality, begin by noting that

$$u^2 \leq (x_1 + x_4)^2 = (z + 1)^2/4. \tag{A13}$$

where the equality comes from the constraint that the gametic frequencies sum to one. Equations A8, A10 and A13 imply

$$\bar{w} - w_u \geq \delta[(1+z)/2 - (1+z)^2/4] + \beta[(1-z)/2 - (1-z^2)/2]. \quad (\text{A14})$$

By taking derivatives, one can show that the minimum of the right hand side of (A14) in the range  $1 > z > -1$  is positive, which implies that (A11) holds for  $1 > z > -1$ .

**Proof of Result 2:** Result 1 implies that the system approaches a state where  $u = 0$ . If  $u = 0$ , the variable  $v$  either remains 0, or else monotonically increases (if initially positive)

or monotonically decreases (if initially negative), as shown by the following argument. If  $u = 0$ , Equation A8 becomes:

$$v' = v/\bar{w}. \quad (\text{A15})$$

For  $\bar{w} \leq 1$ , unless  $z = -1$ , the conclusion follows because  $z$  cannot remain at  $-1$ , and cannot approach  $-1$ , unless the system is fixed with  $x_2 = 1$  or  $x_3 = 1$ . Note that if  $z = -1$ ,

$$z' = -1 + r(1 - v^2), \quad (\text{A16})$$

so unless  $v$  is plus or minus 1,  $z'$  is greater than  $-1$ . Note that if  $v$  is plus or minus one and  $u$  is zero, the system is at an equilibrium where the population is homozygous for the gamete  $A_0B_1$  or for the gamete  $A_1B_0$ .