

# Letter to the Editor

## Apparent Stabilizing Selection and the Maintenance of Neutral Genetic Variation

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A central paradox of quantitative genetic theory is the strong statistical relationship between character values and fitness and the comparatively high heritability of the same traits (BARTON and TURELLI 1989). The relationship between character values and fitness is often consistent with the model of stabilizing selection, although the actual frequency and intensity of stabilizing selection remains a matter of debate (ENDLER 1986). If all or most of the drop in fitness is caused by selection against the character itself, the observed levels of heritability would be difficult to explain by mutation-selection balance (TURELLI 1984, 1985). However, a correlation between deviation from the mean and fitness can also be caused by deleterious side effects, so-called apparent selection (ROBERTSON 1956; HILL and KEIGHTLEY 1988). This possibility has been explored extensively in recent years, both by theoretical investigations (BARTON 1990; KEIGHTLEY and HILL 1990; KONDRASHOV and TURELLI 1992; GAVRILETS and DEJONG 1993) as well as experimental studies (MACKAY *et al.* 1992, 1994, 1995; NUZHIDIN *et al.* 1995). It has been concluded that strong apparent selection can only be explained by either a strong correlation between pleiotropic fitness effects and additive effects on the character (KEIGHTLEY and HILL 1990; BARTON 1990), or by epistatic interaction among the fitness effects (GAVRILETS and DEJONG 1993; KONDRASHOV and TURELLI 1992). However, apparent selection on a trait can also be induced by phenotypic (for instance environmental) correlations with characters under stabilizing selection (also called indirect selection: LACK 1954; LANDE and ARNOLD 1983; PRICE and LIU 1989; RAUSHER 1992), while the genes affecting the trait may experience little if any selection (see below). Below, a simple model is analyzed showing that apparent selection is compatible with effectively neutral variation of the genes affecting the trait.

The basic idea of pleiotropic models of quantitative genetic variation is to find a scenario, where the genes responsible for the heritability of the character are not eliminated by selection on the character itself (BARTON 1990). The HILL-KEIGHTLEY (1988) model assumes that

the apparent selection comes from unconditionally deleterious side effects of the genes that cause heritability, but there is no selection on the character itself. However, if the correlation between the mutational effects on the trait value and the pleiotropic effects on fitness is not very strong, there is always a fraction of alleles with little effect on fitness (KEIGHTLEY and HILL 1990). These are then the genes that cause most of heritability, which in turn leads to weak apparent stabilizing selection (BARTON 1990). A way to accommodate strong apparent selection is the assumption of epistasis among fitness effects, (KONDRASHOV and TURELLI 1992; GAVRILETS and DEJONG 1993). Below, an alternative model is proposed, which also makes the strength of apparent stabilizing selection independent of the selection coefficient of the genes. But in this model the causality between apparent selection and genetic variation is inverted: the assumption is that apparent stabilizing selection is due to correlations in nonheritable variation (so-called environmental variation), while the genes have no deleterious pleiotropic effects.

Let us consider two characters with phenotypic values  $z_1$  and  $z_2$ , one of which, say character 1, is neutral, as abdominal bristle number seems to be (ROBERTSON 1967; KEARSEY and BARNES 1970; SPIERS 1974; NUZHIDIN *et al.* 1995), and the second character is under strong stabilizing selection. Let us further assume that all the genes that affect the neutral character have no pleiotropic effects, neither on the second character nor on fitness in general. Let us further assume that the two characters are phenotypically correlated due to environmental effects. It is also assumed that the breeding values of both characters are distributed according to a Gaussian distribution function. The environmental effects are also assumed to be Gaussian and independent of the genotype, *i.e.*, it is assumed that there is no genotype environment interaction:  $\mathbf{z} = \mathbf{x} + \mathbf{e}$ , where  $\mathbf{z} = (z_1, z_2)$  is the vector of phenotypic values,  $\mathbf{x} = (x_1, x_2)$  is the vector of genotypic values, and  $\mathbf{e} = (e_1, e_2)$  is the vector of the environmental values. Then the phenotype distribution is also Gaussian. Certainly this is an extreme model, but it is chosen to illustrate the mechanism suggested in this paper. Of course, it is compatible with more complex mixed models with weak

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direct selection on the first character or some weak pleiotropic effects, *etc.*

Since we assume that the first character is phenotypically neutral, the fitness function is simply

$$w(\mathbf{z}) = \exp\left\{-\frac{z_2^2}{2\omega^2}\right\}.$$

In this equation the strength of stabilizing selection is determined by the parameter  $\omega$ , which is analogous to a standard deviation in a Gaussian probability distribution. The smaller the  $\omega$ , the steeper the function  $w(\mathbf{z})$  along the direction  $z_2$ , and the stronger the stabilizing selection on character 2. Without loss of generality  $\bar{z}_1 = 0$  can be assumed. If the population is in equilibrium,  $\bar{z}_2$  also equals 0. The apparent selection function of the first character can be calculated as

$$w(z_1) = \int_{-\infty}^{\infty} w(\mathbf{z})p(z_2|z_1)dz_2$$

with  $p(z_2|z_1) = p(\mathbf{z})/p(z_1)$ . By straight-forward integration, this leads to

$$w(z_1) = \exp\left\{-\frac{z_1^2\rho^2V_2}{2V_1[\omega^2 + V_2(1 - \rho^2)]}\right\}$$

where  $V_1$  and  $V_2$  are the phenotypic variances of the characters, and  $\rho$  is the phenotypic correlation between them. The equation means that the phenotypically neutral character 1 experiences apparent Gaussian stabilizing selection, with the strength of apparent stabilizing selection being

$$\frac{\rho^2V_2}{2V_1[\omega^2 + V_2(1 - \rho^2)]}.$$

Clearly apparent stabilizing selection is possible due to phenotypic correlations. A rough upper limit of the strength of apparent stabilizing selection can be obtained by observing that in this model the phenotypic correlation is only due to environmental covariance, and assuming that the environmental covariance is close to its maximal absolute value  $\sqrt{V_{e1}V_{e2}}$ , where  $V_{e1}$  and  $V_{e2}$  are the environmental variances of characters 1 and 2. If we further scale the two characters such that  $V_{e1} = V_{e2} = 1$ , the upper limit reads

$$\frac{1}{(V_{g1} + 1)^2 2\omega^2}$$

in which  $V_{g1}$  is the genetic variance of character 1. This upper limit is very rough and only serves to show that the strength of apparent stabilizing selection due to environmental correlations is inversely related to the amount of genetic variance for the neutral character. This is the case since the phenotypic correlation decreases with the amount of (uncorrelated) genetic variation. In the wild most heritabilities are less than 30%, such that  $1 \leq (V_{g1} + 1)^2 \leq 1.7$ . This leads to an estimate where the strength of apparent stabilizing selection on

the first character is up to half the strength of direct stabilizing selection on the second character.

The next question is what the fitness function of the breeding values is. The fitness function for the genotypic values  $\mathbf{x} = (x_1, x_2)$  is calculated by averaging over the environmental effects

$$w(\mathbf{x}) = \iint p(\mathbf{e}|\mathbf{x})w(\mathbf{x} + \mathbf{e})d\mathbf{e}.$$

In the absence of genotype-environment interaction, we have  $p(\mathbf{e}|\mathbf{x}) = p(\mathbf{e})$ . If, in addition, the environmental effects are Gaussian and the phenotypic fitness function is written as

$$w(\mathbf{z}) = w(\mathbf{x} + \mathbf{e}) = \exp\left\{-\frac{(x_2 + e_2)^2}{2\omega^2}\right\}.$$

The fitness function for the breeding values is obtained by integration and ignoring constant factors. This leads to the usual result of

$$w(\mathbf{x}) = \exp\left\{-\frac{x_2^2}{2[\omega^2 + V_{e2}]}\right\}.$$

The important point here is that the selection surface for the breeding values is qualitatively the same as that for the phenotype, which means that the genotypic values of the first character are neutral in spite of the apparent stabilizing selection on the phenotypic values of this character. This implies that mutations that have only an effect on the first character remain selectively neutral in spite of apparent stabilizing selection. This is in agreement with ROBERTSON's conclusions on genes affecting abdominal bristles (ROBERTSON 1967).

In this model, the selection against genetic variation causing heritability of the first character is completely independent of the strength of *apparent* stabilizing selection on the first character. The genetic variation can thus reach the values expected under mutation-drift equilibrium:  $V_{g1} = 2N_eV_{m1}$  (LYNCH and HILL 1986), where  $N_e$  is the effective population size and  $V_{m1}$  is the amount of genetic variance for character 1 produced by mutation in each generation. Note that in this model the genes affecting the first character are assumed to have no pleiotropic effects on the second. In a more realistic model one needs to correct the prediction to  $V_{g1} = 2N_e f V_{m1}$ , where  $f$  is the fraction of genes which have no pleiotropic effects.<sup>1</sup> If  $f$  is not too small, the amount of genetic variation maintained by mutation-drift equilibrium is more than adequate to account for the observed levels of heritability (BÜRGER *et al.* 1989).

As mentioned above, the scenario that leads to complete independence of apparent stabilizing selection and neutral genetic variation is extreme: phenotypic correlation caused by environmental correlations only, complete neutrality of the character, and no pleiotropic

<sup>1</sup> I thank an anonymous reviewer for pointing this out to me.

effects. However, these conditions can be easily relaxed but still hold the potential for stronger apparent selection than the genes experience. For instance, if there are pleiotropic effects between the two characters, but the correlation is not very strong there will be selection against the mutations. However, as in the HILL-KEIGHTLEY model, the majority of the genetic variation of the neutral character will be caused by alleles with weak or no pleiotropic effects on fitness (KEIGHTLEY and HILL 1990). Consequently, a high amount of genetic variation can be maintained by mutational input.

The mechanism for apparent stabilizing selection discussed here is compatible with any other model proposed, *i.e.*, additional pleiotropic effects, epistasis, *etc.* But it points out that the strength of apparent stabilizing selection may be determined by two factors: deleterious pleiotropic effects and environmental correlations. The relative importance of deleterious pleiotropic effects and indirect selection is an empirical question. The pleiotropic model predicts that the strength of apparent stabilizing selection is positively related to the amount of genetic variation in the population in which it is measured. If all apparent stabilizing selection is due to deleterious pleiotropic effects, the strength of apparent stabilizing selection should approach zero as the inbreeding coefficient approaches one in an inbreeding line. Any residual apparent stabilizing selection can be attributed to selection on environmentally correlated characters. In fact the discussion of the formula for the apparent stabilizing selection shows that its strength may even increase as genetic variance is decreasing. Hence the pleiotropic and the environmental correlation models for apparent stabilizing selection make different predictions about the effect of inbreeding on the strength of apparent stabilizing selection.

Another prediction of a model assuming unconditionally deleterious pleiotropic effects is that the offspring fitness shall depend on the parental deviation from the mean (M. LYNCH, personal communication). The experiment could look like this: take pairs of parents that deviate from the mean of the population but that have midparental values equal to the mean. Then the fitness of the offspring should be negatively correlated with the deviation of the parental values from the mean. No such correlation is predicted by the model proposed here.<sup>2</sup>

These two predictions, effect of inbreeding on apparent stabilizing selection and offspring fitness in relation to parental deviations from the mean, make the proposed model for the maintenance of genetic variation directly testable.

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<sup>2</sup> Another remote possibility for the absence of a correlation between offspring fitness and parental deviation from the mean is if the pleiotropic effects are exactly additive and affect a second character under stabilizing selection.

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