MULTIPLICATIVE GENOTYPE-ENVIRONMENT INTERACTION AS A CAUSE OF REVERSED RESPONSE TO DIRECTIONAL SELECTION

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ABSTRACT

In experiments with directional selection on a quantitative character a "reversed response" to selection is occasionally observed, when selection of individuals for a higher (lower) value of the character results in a lower (higher) value of the character among their offspring. A sudden change in environments or random drift is often assumed to be responsible for this. It is demonstrated in this paper that these two causes cannot account for the reversed response at least in some of the experiments. Multiplicative genotype-environment interaction is discussed as a possible cause of a reversed response to directional selection. Such interaction entails either disruptive or stabilizing genotypic selection, even when the phenotypic selection is directional.

It is well known that the response to directional selection in experimental populations quite often does not follow the regular patterns predicted by quantitative genetics theory (cf. FALCONER 1981). One of the most striking manifestations of the irregularities is the "reversed response," when selecting individuals for an increased (decreased) value of a character results in a decreased (increased) value of the character among their offspring. It is a curious fact that a reversed response occurred in the very first generation of one of the earliest selection experiments in the history of quantitative genetics. In an experiment started by CASTLE on hooded rats (CASTLE and WRIGHT 1916; see also WRIGHT 1977, p. 193), the response to selection for increased amount of coat color was negative in the first generation. Other experimenters also encountered a similar situation. Thus, in experiments by FALCONER (1960) with selection in mice for growth on high and on low planes of nutrition, the downward selection resulted in an increase of the character in the first generation on both planes, but especially on the low plane. In an experiment by F. ROBERTSON (1955; see also FALCONER 1981, p. 197) the response to selection for increased thorax length in Drosophila melanogaster was negative in the first generation. In our own (unpublished) experiments with selection for abdominal bristle number in D. melanogaster, the first generation of downward selection produced a reversed response.

It is especially surprising that reversed responses are observed during the
first generations of selection experiments before any changes in genetic structure could have occurred, i.e., exactly when one would expect the best agreement between experimental results and those predicted by the well-known formula of quantitative genetics theory: \( R = h^2 \cdot S \) (FALCONER 1981, p. 172). In the case of a reversed response to selection, this formula yields a negative estimate of heritability, which is, of course, totally incompatible with the notion of the heritability as the proportion of the genotypic out of the total phenotypic variance.

A reversed response in selection experiments is rarely given serious consideration, and its significance is usually dismissed with one of two explanations: a sudden change in environmental conditions or random drift caused by the finite size of the experimental population. Caution is needed, however, before either of the two explanations is accepted in a particular case. Indeed, with regard to the argument of a sudden change in the environment, it should be kept in mind that, for some quantitative characters, even a substantial change in environmental conditions, such as temperature, nutrition and density, have small and often negligible effect on the character. Moreover, it has been demonstrated that for some characters, e.g., abdominal bristle number and the ovary size in *D. melanogaster* (see FALCONER 1981, pp. 126-129), the main portion of environmental variation is not due to external environmental conditions but, rather, due to the “accidents” or “errors” of development. Therefore, in order to account for a reversed response to selection by such characters a drastic change in environmental conditions must occur, which is highly improbable in laboratory experiments where these conditions are usually kept under control by the experimenter.

As for the random drift argument, it may seem quite plausible, especially in view of the high variation between replicate lines often observed in selection experiments. Let us, however, take a look at Table 1; this displays the results of a computer simulation of directional selection on a quantitative character under the following assumptions, which are quite common in quantitative genetics. The character, \( X \), is a sum of the genotypic value, \( x \), and an environmental component, \( e \):

\[
X = x + e. \tag{1}
\]

The genotypic value and environmental component are independent random variables normally distributed with zero means and variances \( v_x \) and \( v_e \), so that the broad heritability, \( H^2 = v_x / (v_x + v_e) \). A random sample of \( N \) individuals is taken, and out of these \( N \) individuals the proportion \( q \) of those with the lowest values of the character \( X \) are selected as parents (downward threshold selection). The mean genotypic value among the \( N \)-sampled individuals, \( m_x \), as well as among those selected as parents, \( m_s \), are computed, and the difference, \( m_s - m_x \), is calculated. This procedure has been repeated 3000 times for a given set of parameters \( N \), \( H^2 \) and \( q \). The last column in Table 1 presents the proportion (out of 3000) of the cases when the difference \( m_s - m_x \) was positive. In the case of a character controlled by additive genes, this difference is equal to the expected response to selection by the offspring of the selected parents.
Therefore, an entry in the last column of Table 1 can be regarded as the probability of a reversed response to threshold selection by an additive character in a population of size $N$ with the heritability $H^2$ when proportion $q$ of the individuals are selected as parents. Notice that, for sample sizes greater than 50, the probability of a reversed response is negligible even if the heritability is as low as 0.15 and selection is very strong (only 10% of individuals are selected as parents). Even in a population of size 20 a reversed response is quite improbable, unless the heritability is very low and selection is very strong. Thus, it follows that, even though high variation may exist between replicate lines in response to selection due to random drift (Hill 1977), a reversed response is not very likely to occur under the standard assumptions of quantitative genetics theory. In the above-mentioned experiment by Robertson (1955) a reversed response to selection occurred when 20 of 100 pairs were selected as parents. Table 1 seems to indicate that random drift can hardly be responsible for the reversed response in this case. In our experiments with selection for abdominal bristles, the average of the responses in nine replicate lines was reversed. This, also, can hardly be accounted for by random drift.

Thus, it appears that, at least in some cases, an explanation other than a
sudden change in environment or random drift is necessary in order to account for reversed responses to directional selection. Haldane (1931, also 1966, pp. 176–179) was the first to suggest that genotype-environment interaction can be such a cause. He considered a population consisting of a mixture of two clones, with one of the clones having the higher mean value but the lower variance of the character, and the second clone having the lower mean but the higher variance. Haldane argued that if, say, upward directional selection is applied to such a population, then for sufficiently strong selection, when only very few individuals with the highest values of the character are selected, individuals from the clone with the higher variance have a better chance of being selected, even though the mean value of the character is lower in this clone. Thus, very strong directional selection will favor the clone with the higher variance rather than with the higher mean value, which may, of course, result in a reversed response to selection. Having arrived at this conclusion, Haldane makes the following remarkable statement: “Were this not so, I expect that the world would be much duller than is actually the case” (Haldane 1966 pp. 178–179). Wright (1969, pp. 152–155) discusses Haldane’s model and expands it to the case of one diallelic locus. He confirms the conclusion that genotype-environment interaction can result in a reversed response to selection, and also demonstrates that it can lead to a polymorphism.

Genotype-environment interaction is often treated in quantitative genetics literature as merely a scaling problem. It is assumed that a scale transformation of a quantitative character can be found such that the effects of genotype and environment will become additive, or near additive, on the new scale, and the whole problem of the genotype-environment interaction is thus regarded simply as a matter of choosing an appropriate scale for measuring the character. Although it is indeed true that a transformation reducing the genotype-environment interaction can be found in some instances, in practice, however, selection experiments are usually conducted with a character on the original, untransformed scale, and conclusions are drawn and predictions are made with respect to the character measured on this scale. Since there is absolutely no a priori reason for genotypic and environmental contributions to be additive on a scale chosen by an experimenter, it is important to know what can be expected when these two contributions interact in a nonadditive way.

Consider a model of a quantitative character where the phenotype, \( X \), of an individual is not a sum but rather a product,

\[
X = xe, \tag{2}
\]

of the genotypic, \( x \), and environmental, \( e \), contributions (we shall use the word contribution for the genotypic and environmental components in the multiplicative case to distinguish it from the additive case in which these components are usually called genotypic and environmental effects). This model of genotype-environment interaction has been considered by Mather (1975), who discusses instances when it may be a better description of reality than an additive model and who also suggests a method for statistical analysis of the
model. We shall assume that $e$ is an independent normally distributed random variable.

Considering the multiplicative model (2), it may seem that it can be converted into a standard additive model by a log-transformation. Notice, however, that a log-transformation cannot be applied to (2) under the assumption of $e$ being an independent normally distributed random variable, since in this case $xe$ can take a negative value and a logarithm of $xe$ will not exist. It should also be pointed out that the "pure multiplicative" model (2) represents a special case ($A = 0$) of the more general "additive + multiplicative" model of environmental effects,

$$X = A(x + e) + B(xe).$$  \hfill (2a)

When both $A$ and $B$ are not equal to zero, there is no scale transformation that can make this model additive, no matter how $x$ and $e$ are distributed. Results of the paper are applicable to the "additive + multiplicative" model, but the formulas and computations become more complicated in this case.

Assuming that the mean value of $e$ is 1 and the variance is $v_e$, it is not difficult to show that for model (2) the mean value of the character, $M$, is equal to the mean genotypic contribution, $m_x$,

$$M = m_x,$$ \hfill (3a)

and that the variance of the character,

$$V = v_x(1 + v_e) + v_mm^2_x,$$ \hfill (3b)

where $v_x$ is the variance of genotypic contributions (genotypic variance). Computing the broad heritability of the character as the regression of the genotypic contribution on phenotype or as the ratio of the genotypic variance, $v_x$, to the phenotypic variance, $V$, yields

$$H^2 = v_x/(v_x(1 + v_e) + v_mm^2_x).$$ \hfill (3c)

It is worth noticing that, in the multiplicative model, the heritability depends not only on the genotypic and environmental variances but also on the mean genotypic contribution. Therefore, a change in the mean genotypic contribution may result in the heritability of a character being changed even if the genotypic variance remains unchanged.

Let the character be under downward threshold selection, when those and only those individuals whose character value is less than or equal to some threshold value $T$ are selected as parents. Such selection implies the following
fitness, \( W(x, e) \), of an individual with genotypic contribution \( x \) and environmental contribution \( e \):

\[
W(x, e) = \begin{cases} 
1 & (xe \leq T) \\
0 & (xe > T)
\end{cases}
\]

Depending on the sign of \( x \),

\[
W(x, e) = \begin{cases} 
1 & (e \geq T/x) \\
0 & (e < T/x)
\end{cases}
\]

if \( x > 0 \),

\[
W(x, e) = \begin{cases} 
1 & (T \geq 0) \\
0 & (T < 0)
\end{cases}
\]

if \( x = 0 \).

The genotypic fitness, \( w(x) \), is the expected fitness of an individual with genotypic contribution \( x \) and is computed as the average of \( W(x, e) \) over \( e \):

\[
w(x) = \int_{-\infty}^{\infty} W(x, e)\psi(e)de,
\]

where \( \psi(e) \) is the distribution of environmental contributions. The substitution of (5) into (6) yields

\[
w(x) = \int_{-\infty}^{T/x} \psi(e)de, \quad \text{if} \quad x > 0,
\]

\[
w(x) = \int_{T/x}^{\infty} \psi(e)de, \quad \text{if} \quad x < 0,
\]

\[
w(0) = \begin{cases} 
1 & (T \geq 0) \\
0 & (T < 0)
\end{cases}
\]

Taking into consideration that \( \psi(e) \) is the density of a normal distribution with the mean 1 and variance \( \nu \), equations (7a–c) can be rewritten as

\[
w(x) = 0.5 + \Phi( | (T - x)/x\sigma_x | ), \quad \text{if} \quad x \leq T,
\]

\[
w(x) = 0.5 - \Phi( | (T - x)/x\sigma_x | ), \quad \text{if} \quad x > T,
\]

where \( | \ | \) denotes absolute value, \( \sigma_x = \sqrt{\nu} \), and \( \Phi(z) \) is the integral from 0 to \( z \) of the standard normal density that is equal to \( \text{erf}(z/\sqrt{2})/2 \), where \( \text{erf} \) is the “error function.” The function \( \Phi \) increases from 0 to 0.5 when its argument changes from 0 to \( \infty \).

Equations (8a and b) express the genotypic fitness function, \( w(x) \), in the case of downward threshold selection. It can be shown in a similar manner that in the case of upward selection, i.e., when those and only those individuals whose character value is greater than or equal to a threshold value \( T \) are selected,

\[
w(x) = 0.5 + \Phi( | (T - x)/x\sigma_x | ), \quad \text{if} \quad x \geq T,
\]

\[
w(x) = 0.5 - \Phi( | (T - x)/x\sigma_x | ), \quad \text{if} \quad x < T.
\]
FIGURE 1.—Genotypic fitness function, \( w(x) \), under phenotypic threshold selection (solid curves represent \( w(x) \) when the phenotypic threshold \( T < 0 \); broken curves represent \( w(x) \) when \( T > 0 \); straight lines represent \( w(x) \) when \( T = 0 \)). A, Downward phenotypic selection, \( W(X) = 1 \) if \( X \leq 0 \), and \( W(X) = 0 \) if \( X > 0 \). B, Upward phenotypic selection, \( W(X) = 1 \) if \( X < 0 \), and \( W(X) = 0 \) if \( X \geq 0 \).

It can be shown that function \( w(x) \) in (8) and in (9) has either a maximum or a minimum at \( x = 0 \), depending on the sign of \( T \). It has a maximum, \( w(0) = 1 \), for downward selection with \( T > 0 \) and upward selection with \( T < 0 \). On the other hand, it has a minimum, \( w(0) = 0 \) for downward selection with \( T < 0 \) and upward selection with \( T > 0 \).

Figure 1 provides a graphic illustration of equations (8) and (9) for genotypic fitness functions for downward (Figure 1A) and upward (Figure 1B) selection. Solid curves in these figures represent \( w(x) \) in the case of the phenotypic threshold, \( T < 0 \), whereas broken curves represent \( w(x) \) in the case of \( T > 0 \). The straight lines represent \( w(x) \) in the case of \( T = 0 \), when equations (8a and b) reduce to

\[
\begin{align*}
  w(x) &= 0.5 + \Phi(1/\sigma), \quad \text{if} \quad x \leq T, \\
  w(x) &= 0.5 - \Phi(1/\sigma), \quad \text{if} \quad x > T,
\end{align*}
\]

and equations (9a and b) reduce to

\[
\begin{align*}
  w(x) &= 0.5 + \Phi(1/\sigma), \quad \text{if} \quad x \geq T, \\
  w(x) &= 0.5 - \Phi(1/\sigma), \quad \text{if} \quad x < T.
\end{align*}
\]

The slope of a curve representing \( w(x) \) for a nonzero threshold is determined by the value of \( T \) and by the environmental variance, \( \sigma \). For a given \( T \), greater \( \sigma \) results in a larger slope. The distance between the straight lines representing \( w(x) \) for \( T = 0 \) also depends on the environmental variance. Greater \( \sigma \) results in a smaller distance between the straight lines. If \( \sigma \) is infinitely large, \( w(x) = 0.5 \) for all \( x \) irrespective of \( T \), and there is no genotypic selection (as expected).

An important conclusion following from Figure 1 is that, even though the character itself is under directional selection, the genotypic contributions experience either disruptive or stabilizing selection around \( x = 0 \). Such genotypic selection may, of course, produce a variety of responses, depending on the particular distribution of the genotypic contributions in the population under selection and on the specifics of the genetic system underlying the character.
Consider, as an example, downward threshold selection with $T < 0$. The selection on genotypic contributions is disruptive in this case (Figure 1A, broken curve), and, hence, not only individuals with high negative genotypic contributions will be favored by such selection but also individuals with high positive genotypic contributions. Therefore, for a genotypic distribution located in the area $x > 0$, i.e., when the majority of individuals in the population have positive genotypic contributions, there is a possibility of a reversed response to selection.

Table 2 presents results of numeric computations based on equations (8a and b) for downward selection with different threshold values, $T$. It is assumed that the distribution of genotypic contributions, $p(x)$, is normal with the mean, $m_x = 2.0$, and variance, $v_x = 1.0$. It is also assumed that environmental variance $v_e = 1.0$ and, hence, $H^2 = 0.167$ (equation 3c). The proportion, $q$, of selected individuals was computed as

$$q = \int_{-\infty}^{\infty} p(x)w(x)dx,$$

(12)

The last column in Table 2 represents the difference, $m_s - m_x$, where $m_s$ is the mean genotypic contribution among selected individuals,

$$m_s = \frac{1}{q} \int_{-\infty}^{\infty} xp(x)w(x)dx.$$

(13)

In the case of a character controlled by additive genes, the mean genotypic contribution among offspring is equal to the mean genotypic contribution among their parents, $m_x$. According to (3a), the mean value of the character among the offspring will also be equal to $m_x$. Therefore, the difference $m_s - m_x$ will represent, in this case, the expected response to selection.

It is seen from Table 2 that, when selection is not sufficiently strong (thresh-
old is greater than \(-0.15\), the response to downward selection is negative ("normal"). When, on the other hand, selection is sufficiently strong (threshold is less than \(-0.15\)) the response becomes positive ("reversed"), and stronger selection produces a greater reversed response. Notice also that, for the "critical" threshold value of \(-0.15\), there is not any response to selection, even though selection is quite strong (\(q = 0.135\), i.e., only 13.5\% of individuals are selected) and the heritability is not zero (\(H^2 = 0.167\)).

It should be noted that in the derivation of equations for the genotypic fitness function, \(w(x)\), it is not necessary to assume that either the character, \(X\), or the genotypic contribution, \(x\), are measured from zero. Indeed, the following generalization of model (2) can be considered:

\[
X = A + (x - \alpha)e,
\]

where \(A\) and \(\alpha\) are some constants, and \(x\) and \(e\) are, as before, the genotypic and environmental contributions, respectively. The mean and variance of the character become

\[
M = A - \alpha + m_x,
\]

\[
V = v_x(1 + v_e) + v_e(m_x - \alpha)^2,
\]

and the heritability

\[
H^2 = \frac{v_e}{v_x(1 + v_e) + v_e(m_x - \alpha)^2}.
\]

Under the same assumptions as before about the distribution of \(e\), the genotypic fitness functions take the following form:

\[
w(x) = 0.5 + \Phi(\frac{1}{(T - A + \alpha - x)/(x - \alpha)\sigma_e}, \text{ if } x \leq T - A + \alpha),
\]

\[
w(x) = 0.5 - \Phi(\frac{1}{(T - A + \alpha - x)/(x - \alpha)\sigma_e}, \text{ if } x > T - A + \alpha),
\]

for downward selection, and

\[
w(x) = 0.5 + \Phi(\frac{1}{(T - A + \alpha - x)/(x - \alpha)\sigma_e}, \text{ if } x \leq T - A + \alpha),
\]

\[
w(x) = 0.5 - \Phi(\frac{1}{(T - A + \alpha - x)/(x - \alpha)\sigma_e}, \text{ if } x < T - A + \alpha),
\]

for upward selection. The shape of the genotypic fitness function will depend in this more general case not on the sign of \(T\) but, rather, on whether \(T < A - \alpha\) or \(T > A - \alpha\).

An obvious question with regard to the reversed response to directional selection due to multiplicative environment is whether such response can be sustained during several generations of selection. The answer is, most probably not. Indeed, whether there will be a reversed response to selection or not critically depends on the shape of the genotypic fitness function, \(w(x)\), and on the location of the genotypic distribution, \(p(x)\), with respect to \(w(x)\). Assuming that the environmental variance, \(v_e\), is constant, the genotypic fitness function is determined by the value of \(T\). If the threshold does not change from one generation to another, then \(w(x)\) will remain the same in any generation. If, on the other hand, the threshold changes, then \(w(x)\) will also change. In real
experiments, directional selection is usually conducted not with a fixed threshold, $T$, but rather with a fixed proportion of selected individuals, $q$. It is known (Falconer 1981) that to maintain the same value of $q$ for different phenotypic distributions requires different threshold values. Therefore, if the phenotypic distribution is changed by selection, the threshold needed to maintain the same proportion of selected individuals will also change. If, for example, a reversed response occurs in a given generation of downward selection, it will result in a phenotypic distribution in the new generation moved more toward positive phenotypes. Therefore, the threshold required to maintain the same proportion of selected individuals in the new generation will also have to be moved toward positive values. This will lead (see Table 2) to weakening of the reversed response and to eventually switching to a "normal" response. Notice that, if the response to selection is reversed (recall that it requires strong selection), an attempt to continue selection with a fixed threshold will very soon lead to only very few or even zero individuals being selected, and the experiment will have to be terminated.

In conclusion, it is worth noting that a reversed response to selection caused by the multiplicative genotype-environment interaction is a deterministic, not a stochastic, phenomenon; therefore, it has nothing to do with finite population size. If anything, the reversed response caused by such interaction will be more pronounced in experimental populations of a larger size and in the average over several replicate lines. It should also be noted that multiplicative interaction is only one of many types of genotype-environment interaction that may exist for quantitative characters. Other types of the interaction as well as other nonadditive effects, such as dominance, epistasis and maternal effect, may also result in a reversed response to selection and, possibly, in some other "unexpected" phenomena.

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LITERATURE CITED


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