Rates of change in quantitative traits from fixation of new mutations
(population genetics/evolution/animal breeding/finite population size)

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Communicated by Alan Robertson, September 1, 1981

ABSTRACT Expressions are derived for the response to directional selection for a quantitative trait that comes from fixation of new mutations in a finite population. For additive genes with a distribution of mutant gene effects symmetric about zero, the response from fixing mutations occurring in a single generation is \(2N\sigma^2_i/\sigma\), in which \(N\) is the effective population size, \(i\) is the selection intensity, \(\sigma\) is the phenotypic standard deviation, and \(\sigma^2_i\) is the increment in variance in the generation immediately after occurrence of the mutations. This response is \(2N\) times that immediately after occurrence of the mutations. With continuous mutation each generation, the asymptotic rate of response is also \(2N\sigma^2_i/\sigma\) and the asymptotic variance is independent of \(i\). For completely dominant mutations with symmetric effects, the rates are \(N\sigma^2_i/\sigma\), and for recessive mutations the rates are proportional to \((N\sigma^2)^{1/2}\). If the distribution of mutation gene effects, \(a\), is not symmetric about zero, responses depend on the mean square of effects of mutations with positive effect, rather than on the variance of their effects. Rates of change in fitness and of traits correlated with fitness are also analyzed. It is argued that new mutations have contributed substantially to long-term responses in many laboratory selection experiments.

Theory for predicting rates of response and limits to selection of quantitative traits deals with the utilization of existing variation in the population rather than with the possible role of new mutations that occur while selection is proceeding (1, 2). In artificial selection programs the time scale is usually considered too short for mutations to influence the rates or limits substantially, but this view has been questioned (3). There have been continued responses over periods of 50 or more generations in some selection experiments (4–6); genes of visible phenotype and large effect have been detected in several selection lines but not in the base population (3) and, if recessive, have been detected later than would be expected if initially segregating (7); the “bobbed” phenotype, with reduced copy number at the rRNA tanden, has been found in selected Drosophila populations (8); and long-term selection from highly inbred populations has, in some cases, led to responses in Drosophila bristle number (9).

On an evolutionary time scale new variation from mutation is obviously utilized by natural selection, but there is little theory to indicate the rates of change possible and how they might be related to observations. Most theoretical studies of evolutionary rates have focused on gene or base substitution rates and the role of neutral mutations (10) rather than on the consequent changes in fitness or mean performance of other traits. The role of mutations in maintaining quantitative variation with stabilizing, but not directional, selection has been analyzed, however (11, 12).

An attempt is made here to develop a theory for predicting selection responses from directional selection due to fixing new mutations in finite populations, which extends Robertson’s (2) theory of selection limits from existing variation. The analysis is in terms of simple point mutations, but other sources of new variability are also covered by this analysis—e.g., insertion elements and duplication or deletion of a single copy of a gene; but changes in number of multiple-repeat copies of a gene require extensions of Ohta’s theories (13).

ANALYSIS

Let us assume that a population has constant size and breeding structure, in which \(T\) individuals are scored each generation and \(N\) is the effective population size. Mutations affecting some quantitative trait under selection are assumed to be unlinked and to show no epistasis for the trait.

Consider some locus currently fixed for allele \(A\), which can mutate to allele \(A’\). The relative genotypic values for the trait and consequent fitnesses, expressed in two equivalent ways, are as follows:

<table>
<thead>
<tr>
<th>Genotype</th>
<th>AA</th>
<th>AA’</th>
<th>A’A’</th>
</tr>
</thead>
<tbody>
<tr>
<td>Genotypic value</td>
<td>0</td>
<td>(ha)</td>
<td>(a)</td>
</tr>
<tr>
<td>Fitness</td>
<td>(1)</td>
<td>(1 + hs)</td>
<td>(1 + s)</td>
</tr>
<tr>
<td></td>
<td>(1)</td>
<td>(1 + hia/\sigma)</td>
<td>(1 + ia/\sigma)</td>
</tr>
</tbody>
</table>

The selective value is \(s = ia/\sigma\), in which \(i\) is the selection intensity (standardized selection differential) and \(\sigma\) is the phenotypic standard deviation of the trait under directional selection (1). This linear relationship between \(s\) and \(a\) depends on \(ia/\sigma\) not being too large, say less than 0.5. Heterozygote superiority or inferiority (i.e., \(h > 1\) or \(h < 0\)) is ignored.

The mutation rate per chromosome from \(A\) to \(A’\) is \(\mu\), and the total number of mutants per chromosome set is \(\lambda = \Sigma \mu\), in which \(L\) denotes summation over all possible mutants at all loci. The frequency of \(A’\) is \(q_i\); its initial frequency, if it appears, is \(1/2T\).

The mutation rates at any locus are assumed to be sufficiently small that simultaneous segregation of more than two alleles at a locus can be ignored. For selectively neutral genes, which require \(4N\mu\) generations for fixation, this implies \(4N\mu < 1\), but advantageous genes are fixed more rapidly and larger mutation rates can be incorporated.

The initial increase in variance in the population from one mutation to \(A’\) is \(2\sigma^2h^2(1 - q) = \sigma^2h^2/T\), so the expected initial increase in variance is \(2T\mu \times \sigma^2h^2/T = 2\mu h^2\sigma^2\). From all loci, the increase in variance per generation \((\sigma^2_i)\) is expected to be...
\[ \sigma_M^2 = 2 \sum_L \mu a^2 h^2 \]
\[ = 2 \lambda \int_{-\infty}^{\infty} \int_{0}^{1} a^2 h^2 f(a,h) dh da = 2\lambda E(a^2), \]
\[ \text{where } f(a,h) \text{ is the joint density function of effect and dominance of mutant genes—i.e., the relative frequency of mutants of specified effect and degree of dominance—and is assumed to remain constant over time. Many mutations may be neutral with respect to the trait—e.g., third-base substitutions. The density } f(a,h) \text{ may thus have a spike at } a \approx 0; \text{ alternatively, such mutations can be ignored, and } A \text{ can be defined as the expected number of those having any effect on the trait. As noted previously (12, 14), } \sigma_M^2 \text{ does not depend on the population size. The expected response to selection in the generation immediately after the mutation is } \sigma_M^2/\sigma \text{ because all variance is initially additive. Subsequent responses depend on the effects and on changes in gene frequency and the total selection advance from these mutants on their probability of fixation.} 

The probability that a mutant gene with initial frequency 1/2T is ultimately fixed in the population is, from Kimura’s formula (15),
\[ u(s, h) = \frac{1}{\sqrt{2\pi T}} e^{-2Nas^2(2h - 2as + s)^2} \int_{0}^{1} \frac{au(\alpha, \sigma, h) f(a, h) dh da}{e^{-2Nas^2(2h - 2as + s)^2}}. \]

If this gene is fixed there is an increment in mean performance of the metric trait of a units, so the expected advance from a single mutant is \( au(s, h) = au(\alpha/\sigma, h) \), providing sufficient time is allowed for its fixation. The total selection advance \( R \), from new mutations at all loci in any generation that are ultimately fixed, is
\[ R = 2T \sum L \mu au(\alpha/\sigma, h) \]
\[ = 2T \lambda \int_{-\infty}^{\infty} \int_{0}^{1} au(\alpha/\sigma, h) f(a, h) dh da. \]

Assuming mutations appear at the same rate continuously, Eq. 4 is also the asymptotic rate of response per generation. Although Eqs. 2 and 3 can be integrated numerically for any set of assumptions, insight into the formulas can be obtained only by considering special cases. Most attention will be given to additive genes.

**Additive Genes (h = \( \frac{1}{2} \)).** If all genes are additive Eq. 1 reduces to \( \sigma_M^2 = \frac{1}{2} \lambda E(a^2) \) and Eq. 2 to
\[ u(s, \frac{1}{2}) = (1 - e^{-Nas^2}/(1 - e^{-2Nas^2}) \]
(15). The fixation probability in Eq. 4 can be approximated as follows:
\[ Ns > 1 : u = Ns/T \]
\[ |Ns| \leq 1 : u = 1/2T + Ns/2T \]
\[ Ns < -1 : u = 0. \]

The approximation for large \( Ns \) is given by Kimura (15) and requires that \( Ns/T < \frac{1}{2} \). If for small \( Ns \) derives from Robertson’s (2) expression, \( u(q) = q + \frac{Ns}{2q}(1 - q) \). Eqs. 4 and 5 are compared in Fig. 1 with \( Tu(s, \frac{1}{2}) \) plotted against \( Ns \), assuming \( N \) to be very large; only for \( |Ns| \) near 1 is much error involved. Also in Fig. 1 values of \( Tu(s, \frac{1}{2}) \) are shown computed for a smaller value of \( N \), using a Wright–Fisher haploid model (ref.

**Fig. 1.** Curves a, relationship between fixation probability, expressed as \( Tu \), and gene effect or selective value, expressed as \( Ns = Nia/\sigma \) for additive mutations computed by using the exact formula 4 and approximation 5 for large \( N \) values, and by matrix iteration for \( N = 25 \), assuming an initial frequency of 1/2N. For large \( N \) and \( Ns \), \( Tu = Ns \). Curves b, relationship between expected response, expressed as \( NiaTu/a \) and gene effect, expressed as \( Ns = Nia/\sigma \), using formulas 4 and 5 with 6. For large \( N \) and \( Ns \), \( NiaTu = (Nia)^2 \).

16, p. 16) with 2N = 50. Eqs. 4 and 5 based on a diffusion model give a good fit until \( s \) values become large.

The expected selection advance, \( r = au(\alpha/\sigma, \frac{1}{2}) = au(s, \frac{1}{2}) \), for a gene with effect \( a \), using the approximation of Eq. 5, is as follows:
\[ Nia/\sigma > 1 : r = (Nia/T)a^2 \]
\[ \text{or } Nia < 1 : r = 2Ns(Tu/a) a^2 + a/2T. \]

The relationship between the expected advance and the gene effect is also shown in Fig. 1, in which \( (NTu/\sigma)^2 \) is plotted against \( Nia/\sigma = Ns \), with fixation probabilities computed by using Eqs. 4 and 5. The approximation is again seen to be generally satisfactory. Fig. 1 illustrates the quadratic relationship between the gene effect and its contribution to selection advance because for mutant genes with \( a > 0 \) both the fixation probability and the response, if fixed, are proportional to \( a \).

Integrating over loci in Eq. 3 by using the approximations of Eq. 5, and writing the density function for additive genes, \( f(a, \frac{1}{2}) \), as \( f(a) \),
\[ R = (2N\lambda a/\sigma) \left\{ \int_{-\infty}^{\sigma N} a^2 f(a) da + \frac{1}{2} \int_{-\sigma N}^{\sigma N} a^2 f(a) da \right\} \]
\[ + \lambda \int_{-\sigma N}^{\sigma N} a f(a) da. \]

Several special cases lead to simpler results.

(i) **Mutant effects distributed symmetrically about zero.** If \( E(a) = 0 \) and \( Var(a) = \sigma_a^2 \), from Eq. 1, \( \sigma_M^2 = \frac{1}{2} \lambda \sigma_a^2 \), and Eq.
This value of $R$ is $2N$ times the response in the first generation after the mutations appear. Robertson (2) showed that the ratio of the limit to the initial response was $2N$ for additive genes already segregating in the population, providing they had small values of $N_s$—i.e., $|a| < \sigma/\text{Ni},$ approximately. Eq. 8, however, applies for any value of $N_s$ because, as shown by Eq. 5, for all $|a| < \sigma/\text{Ni},$ the coefficient of $a$ in the fixation probability is $N_s/2T\sigma,$ and this is the average of the values, $N_s/T\sigma$ and 0, for $a > \sigma/\text{Ni}$ and $a < -\sigma/\text{Ni},$ respectively.

Eq. 8 also shows that the additive genetic variance in the population with continued mutation reaches $2N\sigma_M^2,$ because the response equals $(f/\sigma) \times$ the additive variance. This value of $2N\sigma_M^2$ would also be that achieved if no selection were practiced and a balance were reached between new variance deriving from mutation and that lost by drift (14). The somewhat surprising result is that, for this model of a symmetric distribution of effects of additive genes, the equilibrium variance in the population depends only on the effective population size and not on the selection intensity. The model here is quite different from that of Lande (12), who considers stabilizing selection in a population of infinite size.

(ii) **Divergent selection.** In some experiments selection is practiced in opposite directions in two lines. If these are maintained with the same size and selection intensity, the asymptotic rate of divergence ($D$) between high and low lines is, from Eq. 7,

\[ D = (2N\lambda/\sigma) \int_{-\infty}^{\infty} a^2 f(a) da = (4N\lambdai/\sigma)\sigma_M^2 \]

for any distribution, $f(a),$ in which $\sigma_M^2$ is given by Eq. 1 with $h = 1/4.$ The rate of divergence reaches $2N$ times the initial rate, regardless of the mean effect of mutant alleles.

(iii) **$N_i\sigma/\sigma$ large.** In this case the terms involving small selective values, $s \leq |\sigma/\text{Ni}|,$ can be ignored in Eq. 7, which reduces to

\[ R = (2N\lambda/\sigma) \int_{-\infty}^{\infty} a^2 f(a) da = (2N\lambdai/\sigma)E^+(a^2) \]

\[ = \{4N\lambdai/\sigma\}(E^+(a^2)/\sigma^2_M), \]

in which $E^+(a^2)$ denotes the mean square of effects of mutants having positive effect. For example, if effects are normally distributed with mean $\mu_0,$ $E^+(a^2) = p(\sigma_a^2 + \mu_0^2) - z\sigma_a\mu_0,$ in which $p = \Pr(a > 0)$ and $z$ is the ordinate of the standardized normal corresponding to $p.$ For:

\[ \mu_0/\sigma_a = -1.00 -0.75 -0.50 -0.25 0.00 0.25 \]

\[ E^+(a^2)/\sigma_M^2 = 0.075 0.128 0.210 0.329 0.500 0.733. \]

This shows how substantially the rate depends on the mean effect of the mutants. Other distributions could be considered: Kimura (17), for example, assumed that mutants were all unfavorable for fitness with selective disadvantage ($-s$) having a gamma distribution, such that fitness or a similarly distributed metric trait would gradually decline; incorporation of some mutants with selective advantage would require specification of four parameters in all.

(iv) $\sigma/\sigma$ large.** Eq. 5 no longer holds adequately, as seen in Fig. 1, if $N\lambda/T$ exceeds 0.5 or so. A better approximation to the fixation probability is, by expansion of Eq. 4, $\mu = (N\lambdai/T)(1 - 1/2N\sigma_0/T)$ and Eq. 10 can be extended to give

\[ R = (2N\lambdai/\sigma)(E^+(a^2) - 1/2(N\lambda/T\sigma)E^+(a^2)). \]
counted because they are rarely fixed, so, assuming a range of dominance
variances \( h \) around the additive value of \( h = 1/2 \), the 
asymptotic response seems unlikely to differ far from the 
values for additive genes of \( R = 2N \sigma_a^2/\sigma \), if effects are 
symmetrically distributed or, more generally, \( R = \{4N\sigma_a^2/\sigma\} \times \). 

**DISCUSSION**

Some data are available for evaluating the formulas derived. Analyses of bristle number in *Drosophila melanogaster* have shown that most genetic variation is additive (19) and that natural or induced mutants do not change the mean (14), so it seems reasonable to assume a symmetric distribution around zero of additive effects for such traits. Summarized from several analyses, the amount of new mutational variance for abdominal and sternopleural bristle number has been estimated as \( \sigma_M^2 = 10^{-4} \sigma_E^2 \), in which \( \sigma_E^2 \) is the environmental variance (12). In an isogenie line, the phenotypic variance \( \sigma^2 \) equals \( \sigma_E^2 \) and for abdominal bristle number, \( \sigma_M = 2 \), approximately. Thus \( \sigma_M^2 = 4 \times 10^{-3} \) and with 20% selection, typical of *Drosophila* experiments, \( i = 1.4 \), giving an initial response of \( \sigma_M^2/\sigma_M = 0.0028 \) bristle per generation. The rate of response ultimately achieved in an isogenie line with recurrent mutation is 2N times as large for a symmetric distribution of effects (from Eq. 8)—i.e., about 0.06 bristle per generation for \( N = 10 \) and 0.6 for \( N = 100 \), or \( 1/2 \alpha \) and \( 1/2 \alpha \) standard deviations, respectively. Yoo (6) observed an almost linear response of 0.3 bristle per generation from generations 50 to 80 in a selection with \( \sigma_M = 2 \), 20% selection, and 50 pairs of parents. Assuming \( N = 70 \), the predicted rate is 0.4 bristle per generation from mutations occurring after the experiment started.

Theory and observations on rates and patterns of response 
to selection in laboratory experiments derived from isogeneic 
lines or continued for many generations will be discussed in 
more detail in another paper, but an important point needs to 
be made here. Until mutations accumulate and reach frequencies 
at which their additive variance is appreciable, the rates of 
response in initially isogeneic lines, whether or not extra 
variation is induced by mutation, are expected to be small. 
Depending on the variance of gene effects, and thus on the 
magnitude of selective values, it may take 20 or so generations for 
responses to become noticeable and many more for rates of 
response due to mutations to approach values such as \( 2N\sigma_M^2/\sigma \) 
given here. Similarly, mutations are unlikely to contribute sig-
ificantly to response in early generations of selection from 
segregating populations. Nevertheless, the magnitude of the 
figures calculated here suggests that, in populations maintained 
in large size, new variants eventually contribute a substantial 
response. The selection limits frequently observed in selection 
experiments (1) may thus be due to opposing natural selection 
or other influences, rather than to lack of useful variation unless, 
of course, the number of useful mutations is so restricted that 
all have appeared.

The formulas derived here can be extended in a straightforward 
way to natural rather than artificial selection, providing 
interactions among loci in fitness can be ignored. Fitness itself 
can be regarded as the quantitative trait, and in formulas for 
responses both the effect \( a \) and the selective value \( ia/\sigma \) are 
replaced by \( s \). Thus rates of change in fitness are computed rather 
than rates of gene substitution as by Kimura (17). For example, 
Eq. 7 becomes

\[
R_s = 2N\lambda \left\{ \int_{-1/N}^{1/N} s f_s(s)ds + \int_{-1/N}^{1/N} s^2 f_s(s)ds \right\} + \lambda \int_{-1/N}^{1/N} s f_s(s)ds,
\]

in which \( f_s(s) \) is the density function of fitness, and if the con-
tribution from the "effectively neutral" genes (10) with \( |N_s| \leq 1 \) 
can be ignored, Eq. 10 becomes \( R_s = 2N\lambda \sigma_s^2(s^2) \). The 
distribution of effects of mutants on viability and the relationship 
of effects to degree of dominance can be obtained from the study 
of Mukai et al. (20). The distribution is clearly not symmetric 
about zero, and a gamma distribution of deleterious effects (17) 
may be more reasonable; if, however, the distribution were 
symmetric, the initial rate would be \( 1/2 \lambda \sigma_s^2 \), corresponding to 
Fisher's fundamental theorem, and the asymptotic rate would 
be 2N times as large. Similarly, the correlated changes in 
another quantitative trait due to natural selection would be 
\( N \Sigma \sigma_s^2(s,\sigma) \), in which \( \Sigma \sigma_s^2(s,\sigma) \) is the covariance of effects and 
fitness, and the change in a quantitative trait from a combination 
of artificial and natural selection would be \( N \Sigma \sigma_s^2(s,\sigma) \).

A feature of the formulas, whatever the distribution of effects or 
fitness, is the proportionality of response to population size, 
simply because the number of mutations per generation is pro-
portional to population size and their fixation probability is 
most independent of it unless the mutations are selectively 
neutral. The formulas become less relevant as population size 
gets very large, because more than two alleles per locus segregate, 
the initial mutant frequencies are so low that the asymptotic rate 
of response takes very long to achieve and the assumption of a 
constant distribution of mutant effects becomes less reasonable 
if much progress is made. Nevertheless, in situations in which 
selection objectives remain constant, faster rates in breeding 
programs and of evolution in nature are possible in larger pop-
ulations; that, as Kimura (17) remarked, this is 'contrary to ac-
tual observations' on evolution indicates the changing or non-
directional mode of selective forces in nature.

Further theoretical analysis will be required to remove many 
of the simplifying assumptions, notably of no linkage, epistasis, 
or multilocus genes.

I thank Dick Frankham, Trudy Mackay, and Alan Robertson for useful 
comments and Maureen Edwards for computational assistance.

   (Longman, London), 2nd Ed.
3. Frankham, R. (1980) in *Selection Experiments in Laboratory and 
   London), pp. 56–68.
   ence on Quantitative Genetics*, ed. Pollack, E., Kemphorne, O. 
5. Enfield, F. D. (1980) in *Selection Experiments in Laboratory and 
   London), pp. 69–86.
   (London)* 272, 80–81.
   131, 50–64.
   (Springer-Verlag, Berlin).
   Verlag, Berlin).
   55, 131–151.
   *Genetics* 72, 335–355.