Effects of Mutation on Selection Limits in Finite Populations With Multiple Alleles

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ABSTRACT

The ultimate response to directional selection (i.e., the selection limit) under recurrent mutation is analyzed by a diffusion approximation for a population in which there are k possible alleles at a locus. The limit mainly depends on two scaled parameters \( S = 4N\sigma_a^2 \) and \( \theta = 4Nu \) and \( k \), the number of alleles, where \( N \) is the effective population size, \( u \) is the mutation rate, \( s \) is the selection coefficient, and \( \sigma_a^2 \) is the variance of allelic effects. When the selection pressure is weak (\( S \leq 0.5 \), the limit is given approximately by \( 2S\sigma_a^2(1 - (1 + c^2)/k)/(\theta + 1) \) for additive effects of alleles, where \( c \) is the coefficient of variation of the mutation rates among alleles. For strong selection, other approximations are devised to analyze the limit in different parameter regions. The effect of mutation on selection limits largely relies on the potential of mutation to introduce new and better alleles into the population. This effect is, however, bounded under the present model. Unequal mutation rates among alleles tend to reduce the selection limit, and can have a substantial effect only for small numbers of alleles and weak selection. The selection limit decreases as the mutation rate increases.

The cause of responses to directional selection with recurrent mutation can be generally divided into two phases. In the first phase, the response to selection is rapid and mostly due to genetic variance existing in the base population. As the genes in the initial population approach fixation, gradually more response to selection comes from new genetic variation introduced by mutation and the process of response is transformed into the second phase. Compared with the first phase, the second phase of selection response, largely relying on new genetic variation, covers a much longer time scale with a relatively small response per generation. But, sooner or later, the response will reach a plateau balanced by mutation and directional selection because the potential genetic variance accessible by mutation in a locus must be finite. In this paper, we formulate this equilibrium and analyze in particular the population mean at this mutation-selection limit. The analysis is directly related to the evaluation of mutation effects on the long-term response of populations to artificial selection. It has also some relevance to evolutionary problems, such as selection for fitness in natural populations. However, due to the nature of the problem, this kind of analysis depends very much on the mutation model.

Two extreme polygenic mutation models have been used in recent theoretical analyses. One is the constant variance model, originally proposed by CLAYTON and ROBERTSON (1955, 1964) for estimating the amount of new genetic variance. This mutation model assumes that the genetic variance produced by mutation per generation is constant over time independent of the background level of population mean and genetic variance. Many recent theoretical analyses used this mutation model, which include KIMURA (1965), LANDE (1975) and TURELLI (1984) on the maintenance of genetic variance with mutation and stabilizing selection; LANDE (1976, 1977) and TURELLI, GILLESPIE and LANDE (1988) on the prediction and estimation of the rate of evolution of quantitative characters from genetic drift; CHAKRABORTY and NEI (1982) and LYCH and HILL (1986) on the genetic variation within and between populations; and HILL (1982a,b) and HILL and RASBASH (1986) on long-term response to artificial selection. This model has the appeal of relating various evolutionary quantities to the parameter \( V_m \), the rate of input of new genetic variance by polygenic mutation, which is estimable from divergence and selection experiments under certain assumptions (LANDE 1975; HILL 1982b; LYNCH 1988). But it also has some limitations. Since the model does not produce a bound of genetic variance in an infinite population in the absence of selection, it is subject to the restrictions that the genetic variance in a population is not near saturation (LANDE 1975) and the population mean is not very far from the original value, because in reality there must be a limit to the range of allelic effects and hence the genetic variance at a locus. The observations that the between-population genetic variance (CHAKRABORTY and NEI...
1982; LYNCH and HILL 1986) and the cumulative selection response from mutation (HILL 1982b) asymptotically increase linearly with time without bound by using this mutation model reflect these limitations.

The other model is the $k$-allele model in which mutation is assumed to occur among $k$ alleles. In many papers $k$ is restricted to two or three or five and in others $k$ is set to be arbitrary, even to be infinite. These papers include LATTER (1960), BULMER (1972), TURELLI (1984), BARTON (1986) and SLATKIN (1987) on the maintenance of genetic variance with mutation and stabilizing selection; Cockerham (1984) and Cockerham and Tachida (1987) on the genetic variation within and between populations; Kimura (1981) on the molecular evolution under stabilizing selection; and Li (1977) and Watterson (1977) on the heterozygosity under mutation and selection. In contrast with the constant variance model, the $k$-allele model behaves properly in different time horizons (Cockerham and Tachida 1987) and depends much more on the parameter $4N\mu$ than $V_a$, where $N$ is the effective population size and $\mu$ is the mutation rate at a locus. In some problems, the results do not critically depend on which mutation model is used (e.g., Turelli 1984). But in some other problems (the problems involving long-term response to drift and selection), the results differ markedly for different models. By using the $k$-allele model, Cockerham and Tachida (1987) observed that without selection the between-population genetic variance does not increase indefinitely, but to a finite equilibrium value, which is in sharp contrast with the analyses of CHAKRABORTY and Nei (1982) and Lynch and Hill (1986). Despite this difference, however, the two models give comparable results as to the predictions of the short-term change of genetic variances within and between very small populations starting from a fixed population.

It is not possible to distinguish between the two polygenic mutation models from experimental results, because the two models do not differ markedly on the short-term accumulation of genetic variance from mutation and it is also very difficult to experimentally eliminate the confounding effects from selection and drift. Most mutation accumulation and selection experiments are carried out on unselected base populations for a relatively short time, yet the results are usually ambiguous as to the pattern of effects of polygenic mutation (see Clayton and Robertson 1964; Hollingdale and Barker 1971; Mukai 1979).

In this paper, we determine the population mean at the equilibrium between mutation and directional selection by using the $k$-allele model. This equilibrium mean is the limit to selection under recurrent mutation. (Note that no limit is expected under the constant variance model, see HILL 1982b). In the following discussion we analyze only the response from one locus with the understanding that a summation over all loci is implied provided that we are willing to ignore the effects of linkage disequilibrium. While linkage disequilibrium builds up in transient states with directional selection, the influence may be minor at equilibrium.

MODEL AND SELECTION LIMITS

Consider the conventional diffusion model of multiple-allele selection with mutation in a finite population of effective size $N$. Assume that there are $k$ possible alleles at a locus available for mutation in a population. Let $x_i$ and $a_i$ be the frequency and phenotypic effect respectively of the $i$th allele, $A_i$, and let $\bar{W} = \bar{W}(x_1, \ldots, x_{k-1})$ denote the mean fitness of the population, assumed to be approximately constant, but varying by amounts of order $O(1/N)$, due to the effect of small selective forces, as allele frequencies vary. For additive effects of genes and directional selection, $\bar{W} = 1 + 2s(x_1 + \cdots + 2s_kx_k)$, where $s$ is the selection coefficient of the $i$th allele. (For example, in the case of phenotypic truncation selection $s_i = (a_i - \bar{a})/\sigma_p$ where $\bar{a}$ is the intensity of selection, $\sigma_p$ is the phenotypic standard deviation of the character, and $\bar{a}$ is the mean effect of the alleles.)

Suppose that in each generation $A_i$ mutates to $A_j$ with probability $u_{ij}$ ($i \neq j$). Then, subject to the usual multinomial-type sampling variation from one generation to the next, the change, $\delta x_i$, in the $i$th allele's relative frequency in one generation has a mean

$$M_i = \sum_j x_ju_{ji} - x_i \sum_j u_{ij} + \frac{x_i}{2\bar{W}} \left[ \partial \bar{W} / \partial x_i - \sum_{j=1}^{k-1} x_j \partial \bar{W} / \partial x_j \right]$$

a variance $V_{ii} = x_i(1 - x_i)/2N$, and $\delta x_i$, $\delta x_j$ have a covariance $V_{ij} = -x_ix_j/2N$. If we denote $\Phi(x_1, \ldots, x_{k-1}; t)$ as the joint probability density of the first $k - 1$ allele frequencies at generation $t$, the Kolmogorov forward equation is

$$\partial \Phi / \partial t = \left( \frac{k}{2} \right) \sum_{i=1}^{k-1} \sum_{j=1}^{k-1} \partial^2(V_{ij}\Phi)/\partial x_i \partial x_j - \sum_{i=1}^{k-1} \partial(M_i\Phi)/\partial x_i$$

Unfortunately no equilibrium solution seems to have been obtained under this general condition. However, for the special case where $u_{ij} = u$ for all $i \neq j$, the above equation has a stationary solution as was first shown by Wright (1949)

$$\Phi = C \bar{W}_t^{2N \prod_{i=1}^{k} x_i^{e_i}},$$

where $e_i = 4Nu_i$, $x_i = 1 - x_1 - \cdots - x_{k-1}$, and $C$ is a normalizing constant. If $\bar{W}$ is close to one so that the
The population mean of the character at equilibrium is thus given by

$$\Phi = C \exp\{2N\bar{W}\} \prod_{i=1}^{k} x_i^{n_i-1}. \quad (3)$$

In the past several years a great deal of work (e.g., Li 1977; WATTERSON 1977) has been published using (2) or (3) as a starting point to discuss the maintenance of genetic variance and the number of alleles in natural populations. In this paper, we use (2) and (3) as a starting point to discuss the properties of selection limits.

The difference between (2) and (3) is negligible when $\bar{W}$ is close to one. The advantage of using (2) is that the normalizing constant $C$ can be formulated as a finite series. This facilitates numerical evaluation of the population mean of the character at equilibrium, i.e., the selection limit. But the direct evaluation is restricted to the cases of small numbers of alleles, $k$, and small population size, $N$, (see below). Some approximations of the selection limit can be made on (3) for some parameter regions of scaled parameters $\theta = \Sigma^k_{i=1} e_i$ and $S = a_{a_2} = 4N\sigma_a$ where $\sigma_a$ is the standard deviation of allelic effect $a_i$ and $s = S/a_i$. (For phenotypic truncation selection $s = a_i/\sigma_a$. Different choices of $a$ do not influence this parameterization.)

The normalizing constant, $C$, of (2) is determined by the relation $\int_{\mathbb{R}^k} \Phi dx_1 \ldots dx_k = 1$ where the integration is over the region $R: 0 \leq x_1 \leq x_1 + \ldots + x_k \leq 1$, which is given in the present model as

$$C^{-1} = \sum_{n_0}^{2N} \frac{(2N)!/(2^n)^n}{(2N - n)!\Gamma(\theta + n + 1)} \prod_{i=1}^{k} \frac{a_i^2\Gamma(e_i + n_i)}{n_i!},$$

where the last summation is over all vectors $\mathbf{n} = (n_1, \ldots, n_k)$ such that $n_1 + \ldots + n_k = n$. This constant is evaluated by using multinomial expansion and the Dirichlet integral formula (JOHNSON and KOTZ 1972).

The expected gene frequency at equilibrium is then

$$E(x_1 | a_1, \ldots, a_k) = \int_{\mathbb{R}^k} \Phi dx_1 \ldots dx_k$$

$$= C \sum_{n_0}^{2N} \frac{(2N)!/(2^n)^n}{(2N - n)!\Gamma(\theta + n + 1)} \prod_{i=1}^{k} \frac{a_i^2\Gamma(e_i + n_i)}{n_i!},$$

where $\mathbb{E}$ denotes the expectation with respect to $x$.

The population mean of the character at equilibrium is thus given by

$$R = 2 \mathbb{E} \left( \sum_{j=1}^{k} E(x_j | a_1, \ldots, a_k) a_j \right)$$

$$= 2 \mathbb{E} \left( \sum_{j=1}^{k} \left( \frac{\sum_{i=1}^{k} (e_i + n_i) a_i}{n_i!} \frac{a_i^2\Gamma(e_i + n_i)}{n_i!} \right) \right),$$

where $\mathbb{E}_a$ denotes the expectation with respect to $a$. If the initial population is maintained at equilibrium with respect to mutation in the absence of selection in which the population mean is zero, (4) represents the ultimate response to selection (the selection limit) that could be obtained from that initial population with mutation. This formula is general for the values of parameters appropriate for a diffusion approximation, i.e., the scaled parameters $\theta$ and $S$ are of order one. But since no further simplification can be made, the numerical calculation is restricted to the cases of small $N$ and $k$. When $N$ and $k$ become large, the computation becomes intractable because there are too many possible alternatives of $n_i$ to be considered. For this reason we consider the following two approximations.

**WEAK SELECTION APPROXIMATION**

The case of weak selection is special. For that, considerable analyses can be made on the moments of gene frequencies. When $\theta$ is small (<1), we can put $\exp[a\Sigma x a_i] = 1 + a\Sigma x a_i + O(a^2\sigma^2)$. Then (3) can be approximated as (EWENS 1979; p. 173)

$$\Phi = \frac{\Gamma(\theta)}{\prod_{i=1}^{k} \Gamma(\epsilon_i)} \left( 1 + \frac{\alpha}{\theta} \sum_{i=1}^{k} x_i a_i - \frac{\theta}{\theta + 1} \sum_{i=1}^{k} \epsilon_j a_j \right) + O(a^2\sigma^2) \prod_{i=1}^{k} x_i^{n_i-1}. \quad (5)$$

By ignoring the terms of $a^2\sigma^2$ and higher order, we can calculate from (5) the expected gene frequency at equilibrium given the allelic effects,

$$E(x_i | a_1, \ldots, a_k) = \frac{\epsilon_i}{\theta} + \frac{\alpha \epsilon_i}{\theta(\theta + 1)} \left( a_i - \sum_{j=1}^{k} \epsilon_j a_j / \theta \right).$$

Assuming that the effects of alleles are independent of each other and also independent of mutation rates, the selection limit is thus given by

$$R = 2 \mathbb{E} \left( \sum_{j=1}^{k} E(x_i | a_1, \ldots, a_k) a_j \right)$$

$$= \sum_{j=1}^{k} \left( \frac{\sum_{i=1}^{k} (e_i + n_i) a_i}{n_i!} \frac{a_i^2\Gamma(e_i + n_i)}{n_i!} \right),$$

for any distribution of $a$ with mean zero and variance $\sigma^2$. This limit is proportional to $2\sigma^2a^2[1 - \Sigma \epsilon^2/\theta^2]$, which is the equilibrium additive genetic variance in the absence of selection in an infinite population (Cockerham and Tachida 1987). For equal mutation rates among alleles, i.e., $u_i = u_j$ for all $i$ and $j$, $\Sigma \epsilon_i^2/\theta^2 = 1/k$. If the mutation rates are different, $\Sigma \epsilon_i^2/\theta^2 = (1 + \epsilon^2)/k$, where $\epsilon$ is the coefficient of variation of the mutation rates. Thus the limit increases as $k$ increases to a maximum when $k = \infty$ and decreases as $\epsilon^2$ increases.
if \( k \) is finite. Cockerham and Tachida (1987) point out that this latter effect can be substantial for few alleles. The limit is linearly related to \( \alpha/(\theta + 1) \), increasing linearly with \( \alpha \) and decreasing with \( \theta \) at the rate \((\theta + 1)^{-1}\). However, as shown later, this relation does not hold well when \( S \) is large (roughly \( S > 0.5 \)).

**WEAK MUTATION APPROXIMATION**

Another method to approximate the selection limit is to assume that mutation is very weak. As \( \theta \to 0 \), the population will be mostly monomorphic at equilibrium. This is assured by the assumption of additivity of gene effects (Kimura 1956). When \( S \) is large (\( \to \infty \)), the population will be mostly monomorphic for the best allele available for mutation. For moderate and small \( S \), the chance to be nearly fixed in the population is, however, distributed among alleles, and the probability of the population being monomorphic for allele \( A_i \), at equilibrium is approximately proportional to \( \exp[aa_i] \), since

\[
\text{Prob}[\text{monomorphic for } A_i] = \text{Prob}[1 \gtrless x_i \gtrless 1 - 1/2N, 1/2N \gtrless x_i \gtrless 0, i \neq 1] = \int_{1/2N}^{1} \int_{0}^{1/2N} \ldots \int_{0}^{1/2N} C \exp\left\{ \alpha \sum_{j=1}^{k} x_j a_j \right\} \prod_{i=1}^{k} x_i^{-1} \, dx_k \ldots \, dx_1 \\
\approx C \exp[aa_i] \int_{1/2N}^{1} \int_{0}^{1/2N} \ldots \int_{0}^{1/2N} \prod_{i=1}^{k} x_i^{-1} \, dx_k \ldots \, dx_1.
\]

Thus

\[
\text{Prob}[\text{monomorphic for } A_i] = \exp[aa_i] / \sum_{j=1}^{k} \exp[aa_j].
\]

From this expression we expect the selection limit to be

\[
R = 2 \mathcal{O} \left( \sum_{i=1}^{k} a_i \exp[aa_i] / \sum_{j=1}^{k} \exp[aa_j] \right) \tag{7}
\]

where \( \theta \to 0 \).

This is an expectation of a ratio. When \( k \) is finite, there is no simple expression for the limit for a given distribution of \( a \). However as \( k \to \infty \), we can use the law of large numbers for both numerator and denominator, that is

\[
R = 2 \mathcal{O} [ae^{aa}] / \mathcal{O}[e^{aa}] \tag{8}
\]

With (8) we can derive the limit for different distributions of \( a \). For example, if \( a \) is normally distributed with mean zero and variance \( \sigma_a^2 \) [denoted \( a \sim \mathcal{N}(0, \sigma_a^2) \)],

\[
R_s = 2a \sigma_a^2. \tag{9}
\]

For a double gamma distribution reflected about zero with density function \( f(a) = \frac{\lambda}{2} \frac{1}{(\sqrt{\pi} \sigma_a)^d} \exp(-\lambda |a|) \) where \( \lambda = \sqrt{\frac{3}{2}} \sigma_a \) [denoted \( a \sim \mathcal{D}(0, \sigma_a) \)] (Hill 1982b), the limit is

\[
R_s = \frac{\sqrt{\frac{3}{2}} \sigma_a \exp[\sqrt{\frac{3}{2}} \sigma_a |1| + 1] - 2}{\exp[\sqrt{\frac{3}{2}} \sigma_a |1|] - 1} \cdot a^2.
\]

When \( S \) is small, all these limits converge to (6) for \( k \to \infty \) and \( \theta \to 0 \). \( R_s \) is necessarily bounded. \( R_s \) is bounded except when \( S = \infty \) or \( S = 0 \); but \( R_s \) is bounded only when \( |S| < \sqrt{3}/2 \). In any case \( |R_s| \geq |R_s| \) for \( k \to \infty \).

When the number of alleles is finite, we can numerically evaluate (7) for different distributions of \( a \).

**NUMERICAL ANALYSIS**

The limit given by (7) is the maximum limit for given \( k, \alpha \) and \( a_i \)'s, since, as \( \theta \) increases, the limit decreases as shown by (6). So we begin with the numerical evaluation of (7) for random effects of \( a_i \)'s. We simulated two kinds of distributions of \( a \): normal distribution and double gamma distribution, both with mean zero and variance one. Both distributions are symmetrical. We used the same definition of double gamma distribution as Hill (1982b), which gives a highly leptokurtic distribution for allelic effects. The value of \( R \) is evaluated by repeatedly sampling values of \( a_i \)'s from the given distributions for various values of \( k \) and \( S \). The results of numerical calculations are shown in Table 1 for the normal distribution and in Table 2 for the double gamma distribution. Each value in the tables (except those for \( k = \infty \) in Tables 1 and 2 and \( S \to \infty \) in Table 1) is the average of 10,000 replicate samples, ± standard error. The values of \( R \) for \( S = \infty \) in Table 1 are the expected largest normal order statistics, and in Table 2 are the averages of the largest values of \( a \) in the samples. It is seen that \( R \) increases with \( S \) and \( k \) and is bounded in both directions (except in the case of \( S \to \infty \) and \( k = \infty \)) in Table 1. The values of \( R \) for the double gamma distribution are less than or equal to those for the normal distri-
the limit is reduced by a proportion of compared with that of equal mutations. This proportion is predicted by (6).

Roughly, the weak mutation approximation works for fixed number of alleles, an increase in as selection decreases the selection limit, and the rate of decrease is satisfactorily predicted by \((\theta + 1)^{-1}\) when \(S \leq 0.5\) approximately. For larger, \((\theta + 1)^{-1}\) overestimates the rate. When \(S = 5\) and \(\theta = 5\) (for \(k = 2, 3, 5\)), the limits are only reduced by about a half of those for \(\theta \to 0\). Roughly, the weak mutation approximation works well for \(\theta < 0.1\).

The effect of unequal mutation rates among alleles is to reduce the selection limit. When selection is weak, the limit is reduced by a proportion of \(c^2/(k - 1)\) compared with that of equal mutations. This proportion decreases as \(k\) increases. When selection is strong, the limit is less proportionally reduced. This is illustrated in Table 4 as an example with \(\epsilon_1 = 0.80\), \(\epsilon_5 = 0.15\), and \(\epsilon_5 = 0.05\) for three alleles (\(\theta = 1\) and \(c^2 = 1\)). Comparing Table 4 with Table 3 (\(k = 3\) and \(\theta = 1\)) shows that the proportion of reduction of limit decreases from about 0.5 when \(S = 0.1\) and 0.5 as expected to about 0.03 when \(S = 5\). Thus \(c^2/(k - 1)\) is the conservative estimate of proportional reduction. When the number of alleles is not small and selection is not weak, the effect of unequal mutation on selection limits is small and can be ignored.

**DISCUSSION**

Recently, Hill (1982a,b) and Hill and Rabash (1986) extensively analyzed the mutation effect on the response to artificial selection with the constant mutation variance model on a time scale observable in an artificial selection experiment and concluded that mutations in the broad sense occurring during the experiment from whatever sources could be important to long-term response to selection. However, due to the mutation model used, their prediction of mutation effect is not appropriate for an evolutionary time scale.

Here we discuss the eventual effect of mutation on selection response. By using Wright's formula of stationary distribution of alleles, we have obtained the selection limit under recurrent mutation. For weak selection (roughly \(S \leq 0.5\)) the limit is \(8N\sigma^2(1 - (1 + c^2)/k)/(\theta + 1)\) approximately. It is then of interest to compare this limit with that without mutation to assess

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<th>(k)</th>
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<th>(S = 5.0)</th>
<th>(S \to \infty)</th>
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<tr>
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<td>0.098 ± 0.014</td>
<td>0.436 ± 0.015</td>
<td>0.750 ± 0.016</td>
<td>0.977 ± 0.017</td>
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<tr>
<td>5</td>
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<td>0.765 ± 0.010</td>
<td>1.335 ± 0.012</td>
<td>1.912 ± 0.014</td>
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<tr>
<td>10</td>
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<tr>
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<tr>
<td>100</td>
<td>0.199 ± 0.002</td>
<td>1.357 ± 0.012</td>
<td>3.747 ± 0.030</td>
<td>6.509 ± 0.032</td>
<td>7.307 ± 0.027</td>
<td>7.466 ± 0.027</td>
</tr>
<tr>
<td>∞</td>
<td>0.203</td>
<td>1.551</td>
<td>∞</td>
<td>∞</td>
<td>∞</td>
<td>∞</td>
</tr>
</tbody>
</table>
the eventual contribution of mutation to response. This comparison may be best presented in terms of the ratio of the limit to initial response. Suppose that we draw an initial population from an infinite equilibrium population with respect to mutation. The mean of this initial population is then expected to be zero (since the mean of \( a \) is scaled to zero) and the genetic variance is approximately \( 2s^2_{\mu}[1 - (1 + \phi)/k] \). The initial response from this population is thus about \( 2s^2_{\mu}[1 - (1 + \phi)/k] \) and the ratio of the limit with mutation to the initial response is \( 4N/\theta' + 1 \). If, however, the initial population is from a finite equilibrium population with effective size \( N' \), and has genetic variance \( 2s^2_{\mu}[1 - (1 + \phi)/k]/\theta' + 1 \), the ratio becomes \( 4N/(\theta' + 1)/\theta' + 1 \) where \( \theta' = 4N'/\mu \). This ratio decreases as \( \theta \) and \( \theta' \) increase and is independent of the number of alleles. When \( \theta' < 1 \), the ratio is larger than \( 4N \). (It is important to point out that, if the parameters \( \theta' \) and \( \theta \) are such that \( \theta' + 1 \)\( \theta' + 1 = \frac{1}{2} \), mutation will not increase selection response since the ratio without mutation is about \( 2N \) for weak selection (ROBERTSON 1960) \( 2N \) ratio applies for multiple alleles as well). This condition requires \( \theta > 1 \) and hence \( \theta \gg S \), which appears unlikely in real situations.)

In the case that the initial population is a hybrid from two random inbred populations (with two alleles at a locus and each having frequency 0.5), the initial response is \( s^2_{\mu} \) and the ratio with mutation becomes \( 8N[1 - (1 + \phi)/k]/(\theta + 1) \), which is about \( 8N/(\theta + 1) \) as \( k \to \infty \). Since the ratio without mutation is about \( 2N \) for weak selection, the eventual contribution of mutation to the response to selection is therefore about \( 2N \) to \( 6N \) of the initial response for small \( \theta \), depending on initial populations, and could be higher than that if \( \theta' \) is also small.

As \( S \) increases the relative contribution of mutation to response increases as well. To show this, let us consider first the case of an initial hybrid population with the selection parameter \( S = 4N_s/\sigma_p = 5 \). By using KIMURA’s (1957) formula of fixation probability for two alleles in conjunction with normally distributed allelic effects, we can show that the selection limit without mutation is about \( 0.8N \) of the initial response. Thus by using (9) for \( \theta \to 0 \) and \( k \to \infty \), the maximal

---

**Table 3**

<table>
<thead>
<tr>
<th>( \theta )</th>
<th>( S = 0.1 )</th>
<th>( S = 0.5 )</th>
<th>( S = 1.0 )</th>
<th>( S = 2.0 )</th>
<th>( S = 5.0 )</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.01</td>
<td>0.098 ± 0.014a</td>
<td>0.436 ± 0.015a</td>
<td>0.750 ± 0.016a</td>
<td>0.977 ± 0.017a</td>
<td>1.085 ± 0.017a</td>
</tr>
<tr>
<td>0.1</td>
<td>0.035 ± 0.014</td>
<td>0.180 ± 0.014</td>
<td>0.329 ± 0.015</td>
<td>0.529 ± 0.015</td>
<td>0.750 ± 0.015</td>
</tr>
<tr>
<td>0.5</td>
<td>0.062 ± 0.014</td>
<td>0.359 ± 0.015</td>
<td>0.664 ± 0.016</td>
<td>0.918 ± 0.017</td>
<td>1.060 ± 0.017</td>
</tr>
<tr>
<td>1.0</td>
<td>0.049 ± 0.014</td>
<td>0.228 ± 0.015</td>
<td>0.414 ± 0.015</td>
<td>0.689 ± 0.016</td>
<td>0.930 ± 0.016</td>
</tr>
<tr>
<td>2.0</td>
<td>0.034 ± 0.014</td>
<td>0.180 ± 0.014</td>
<td>0.296 ± 0.015</td>
<td>0.513 ± 0.014</td>
<td>0.776 ± 0.016</td>
</tr>
<tr>
<td>5.0</td>
<td>0.012 ± 0.014</td>
<td>0.121 ± 0.014</td>
<td>0.155 ± 0.014</td>
<td>0.312 ± 0.015</td>
<td>0.532 ± 0.015</td>
</tr>
</tbody>
</table>

---

**Table 4**

Selection limits \( R \) ± standard error numerically evaluated from (4) for unequal mutation rates with \( c_1 = 0.00, c_2 = 0.15, \) and \( c_3 = 0.05 \) for three alleles \( [N = 20, a = \mathcal{N}(0,1)] \)

<table>
<thead>
<tr>
<th>( \theta )</th>
<th>( S = 0.1 )</th>
<th>( S = 0.5 )</th>
<th>( S = 1.0 )</th>
<th>( S = 2.0 )</th>
<th>( S = 5.0 )</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.0</td>
<td>0.036 ± 0.016</td>
<td>0.174 ± 0.016</td>
<td>0.362 ± 0.016</td>
<td>0.731 ± 0.015</td>
<td>1.268 ± 0.015</td>
</tr>
</tbody>
</table>
Mutation effect is calculated to be about $7.2N$ of the initial response (in this case the selection limit with mutation is $2aN\sigma_{a}^{2}/\sigma_{a}^{2} = 8N$ of the initial response).

If the initial population is from a finite equilibrium population with mutation parameter $\theta'$, the number of alleles in a sample is likely to be more than two if $\theta' \geq 0.5$ (Ewens 1972). To determine the selection response without mutation with multiple initial alleles, we have carried out simulation experiments by using Kimura and Takahata’s (1983) improved sampling technique (the detailed results will be presented elsewhere). We used Ewens’ (1972) sampling probability to determine the initial frequencies for fixed numbers of initial alleles ($2$, $5$, $10$, and $20$), which covers the value of $\theta'$ from about $0.2$ to $5$ and $a \sim M(0,1)$, and found that the selection limits without mutation are about $N$ times the initial responses for $S = 5$ for all the initial allele numbers. Thus when $S = 5$, by using (9) the eventual contribution of mutation to response is

$$ (4 + 3\theta')N/\theta' = \frac{8NS\sigma_{a}^{2}}{2s_{a}^{2}\theta'/(\theta' + 1)} - N $$

times the initial response, which is larger than

$$ (4 + 2\theta')N/\theta' = \frac{8NS\sigma_{a}^{2}}{2s_{a}^{2}\theta'/(\theta' + 1)} - 2N $$

when $S < 1$. So it seems that for random neutral initial populations the maximal effect of mutation is about $2.8N$ to $23N$ of the initial response for $\theta'$ ranging from $5$ to $0.2$.

From these examples we have seen the importance of parameters $\theta'$ and $\theta$ on the effect of mutation on the selection limit. The parameter $\theta'$ does not influence the selection limit, but does influence the initial response. As $\theta'$ decreases, initial response becomes smaller and the ratio of response due to mutation over initial response will become larger. The parameter $\theta$, however, influences the limit, not the initial response. As $\theta$ increases, the limit becomes smaller. When $\theta \gg S$, the selection limit with mutation can even be reduced to that without mutation.

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**LITERATURE CITED**


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