Models of long-term artificial selection in finite population with recurrent mutation

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Summary

The effects of mutation on mean and variance of response to selection for quantitative traits are investigated. The mutants are assumed to be unlinked, to be additive, and to have their effects symmetrically distributed about zero, with absolute values of effects having a gamma distribution. It is shown that the ratio $R_t^M/(N^2 R_1^M)$ of expected cumulative response to generation t from mutants, R_t^M, and expected response over one generation from one generation of mutants, R_1^M, is a function of t/N, where t is generations and N is effective population size. Similarly, $\mathrm{SD}(R_t^M)/(N\sigma_M^2)^{\frac{1}{2}}$, is a function of t/N, where σ_M^2 is the increment in genetic variance from one generation of mutants. The mean and standard deviation of response from mutations relative to that from initial variation in the population, R_1^I in the first generation, are functions of NR_1^M/R_1^I. Evaluation of these formulae for a range of parameters quantifies the important role that population size can play in response to long-term selection.

Introduction

Based on observations of long-term selection experiments (e.g. Dudley, 1977), on particular events in Drosophila populations (Frankham, 1980) and on estimates of *de novo* variation (e.g. Clayton & Robertson, 1955; Lynch, 1986), theoretical analyses and simulations have indicated that new mutations could contribute substantially to responses in long-term breeding programmes and selection experiments (Hill, 1982). In a preceding paper, models of distributions of gene effects and frequencies have been constructed and analysed to assess the long-term mean and variance of response from variation initially existing in the population (Hill & Rasbash, 1986, subsequently referred to as HR86) which generalize some of the calculations of Robertson (1960). Here, the effects of mutation are added to the HR86 analysis in order to predict the course of response from both existing and *de novo* variation, to show how the relative importance of these sources depends on the population size and duration of the experiment or breeding programme and to indicate satisfactory ways of parameterizing the process. The generality extends to distributions of effects and frequencies rather than to modes of gene action, for additive gene action and no linkage are assumed; and rates of mutation and population sizes are assumed sufficiently small that not more than two alleles segregate at each locus.

Analysis

Experiments designed to estimate variation from mutation generally yield estimates of the new genetic variation (σ_M^2) or new heritability σ_M^2/σ^2, where σ^2 is the phenotypic variance, and σ_M^2 is independent of population size (N) (Clayton & Robertson, 1955; Hill, 1982). It is convenient to describe the response in terms of $R_1^M = i\sigma_M^2/\sigma$, the expected response in the first generation, contributed by this new variation where i is the selection intensity. Let r_t be the expected response from a single generation of mutants t generations previously, and

$$r_\infty = \lim_{t \to \infty} r_t$$

be the expected response when these mutants are ultimately fixed or lost. (Note that r and R denote expected responses, the $E(\ )$ being excluded for brevity). Also let $R_t^M = r_t + r_{t-1} + \ldots + r_1$ be the expected cumulative response from recurrent mutations each generation from the outset until generation t. Note that $R_1^M = r_1$.

Parametrization

Let a be the effect of a mutant on the trait, expressed as the difference between homozygotes, and $s = ia/\sigma$

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be its selective value as a consequence of artificial selection.

It has been shown previously (Hill, 1982) that for a symmetric distribution of mutant effects, as is assumed here, the asymptotic response from one generation of mutants is given by $r_\infty = 2Nr_1$. The basic explanation is that the initial frequency of a gene in a population of size N is $1/2N$ and the genetic variance and response it contributes in one generation are $a^2/4N$ and $ia^2/(4N\sigma)$ respectively. Consider first genes for which $Ni|a|/\sigma > 1$. If a mutant is favourable, its fixation probability equals its selective value, ia/σ, so the contribution to response is ia^2/σ; and if it is unfavourable it has a fixation probability of 0 and contributes no response. Averaging for each such pair of mutants and integrating over the distribution of a, $r_\infty = 2Nr_1$. A similar argument shows that $r_\infty = 2Nr_1$ for pairs of genes for which $Ni|a|/\sigma < 1$ and the fixation probabilities are $1/2N + ia/2\sigma$, approximately (Hill, 1982).

Now consider the time scale of this process. For given Ns and initial frequency q, the diffusion approximation shows that the time scale of change of frequency is inversely proportional to N (Robertson, 1960), a feature we have already used in describing response from existing variation where the gene frequency is not a function of population size (HR86). The case of mutation is more complicated, because N and q are related. Bearing in mind that we are not interested in making comparisons over very wide ranges of population sizes in the artificial selection context, we use a heuristic argument to examine the dependency on population size taking, as examples, the case of $N = 10$ and $N = 20$. (Presumably a more formal proof could be obtained using diffusion models, but this has not been achieved.)

A mutant gene of positive, but not large, selective value arising in a population of $N = 20$ with initial frequency 0·025 has only a little greater than even chance of reaching a frequency 0·05 before being lost, i.e. reaching a frequency of 0·0. At a frequency of 0·05, its subsequent fate and time passage are known from the diffusion process to be approximately the same as that of a mutant gene arising in a population of size $N = 10$, except that the time scale for the large population will be twice as slow (Robertson, 1960). Thus, as an approximation, a mutant gene arising in a population of size $N = 20$ has a fixation probability one-half that of a mutant arising in a population of size $N = 10$, but having the same Ns value (i.e. the latter has double the s value), and a rate of passage through the population one-half as fast. The argument holds providing selective values are not so great as to substantially change the probability that the first transition of gene frequency is equally likely to be up or down. In summary, therefore, for genes of given Ns value, $r_t/R_1^M \propto N$ on a time scale proportional to N.

Now consider recurrent mutation and cumulative response over a period of N generations, on which the time scale has been standardized. The number of generations of mutants is thus proportional to N and because r_t/R_1^M is proportional to N it follows that the cumulative response relative to that in the first generation, given by R_t^M/R_1^M, is proportional to N^2 for genes of specified Ns value.

In summary and extending the argument over the range of gene effects or selective value, $r_t^M/(NR_1^M)$ and $R_t^M/(N^2R_1^M)$ are functions of the distribution of Ns values on a time scale proportional to N.

The total expected response, TR_t, is the sum of the responses from variation initially present, R_t^I, and from mutational variance arising subsequently, R_t^M, to give

$$TR_t = R_t^I + R_t^M.$$

In our previous paper (HR86), R_t^I was reparametrized in terms of the expected response in the first generation, $R_t^I/(NR_1^I)$, which is a function of the distribution of Ns values. Extending this, we obtain a convenient expression for subsequent analysis:

$$TR_t/(NR_1^I) = R_t^I/(NR_1^I) + (NR_1^M/R_1^I)(R_t^M/N^2R_1^M). \quad (1)$$

Similar arguments can be used to establish a suitable parametrization of the variation in response. It can be shown that $V(R_t^M)/(N\sigma_M^2)$ or, alternatively $V(R_t^M)/(Nh_M^2\sigma^2)$, where h_M^2 is the increment in heritability from mutation, is a function of t/N and the distribution of Ns values, as similarly is $V(R_t^I)/(h_I^2\sigma^2)$ (HR86). Combining initial and mutational variation, a suitable parametrization which gives a function of the same parameters as (1) is

$$V(TR_t)/(h_I^2\sigma^2) = V(R_t^I)/(h_I^2\sigma^2)$$
$$+ (NR_1^M/R_1^I)\,V(R_t^M)/(Nh_M^2\sigma^2). \quad (2)$$

Evaluation of expressions

Mutant genes are assumed to be equally likely to increase or decrease the trait, the absolute value of their effects having a gamma distribution. So

$$f(|a|) = \alpha^\beta e^{-\alpha|a|}|a|^{\beta-1}/\Gamma(\beta) \quad (0 < |a| < \infty). \quad (3)$$

Note that $E(|a|) = \beta/\alpha$ and $E(|a|^2) = E(a^2) = \beta(\beta+1)/\alpha^2$. With selective values given by $s = ia/\sigma$, the parameter Ns has a gamma distribution with parameters $\alpha^* = \alpha\sigma/(Ni)$ and β (cf HR86, where the same distribution is assumed for the value of the allele initially segregating which increases the trait). The density function of mutant effects, regardless of sign, is $\tilde{f}(a) = f(|a|)/2 \quad (-\infty < a < \infty)$.

Assuming there are a possible total of n_T loci in the genome of which k mutate in some generation, k is Poisson distributed and

$$E(k) = 2Nn_T\mu = 2N\lambda,$$

where μ is the mutation rate per locus and λ is the total number of mutants per genome per generation. The

expected response r_t from one generation of mutations is

$$r_t = 2N\lambda \int_{-\infty}^{\infty} aE(q_t \mid 1/2N, Nia/\sigma)\tilde{f}(a)\,da \tag{4}$$

for genes with current frequency q_t, initial frequency $1/2N$ and population size $\times$ selective value of Nia/σ. Because of symmetry, the response obtained (by usually eliminating) mutant genes with deleterious effects $-a$ and initial frequency $1/2N$ is the same as that obtained (by usually fixing) a gene with advantageous effect $+a$ and initial frequency $1-1/2N$, there being no expected change in mean when they actually occur because their effects balance. Hence

$$r_t = N\lambda \int_0^{\infty} a[E(q_t \mid 1/2N, Nia/\sigma) \\ - E(1-q_t \mid 1-1/2N, Nia/\sigma)]f(a)\,da.$$

Transforming into the distribution of Ns, with density $f^*(Ns)$, $0 < Ns < \infty$, and noting that $a = s\sigma/i$,

$$r_t = [N\lambda\sigma/(Ni)] \int_0^{\infty} Ns[E(q_t \mid 1/2N, Ns) \\ - E(1-q_t \mid 1-1/2N, Ns)]f^*(Ns)\,d(Ns). \tag{5}$$

Variance in response due to mutation can be partitioned into that variation which is conditional on the number of mutants and is due to sampling of mutant effects, random changes in gene frequency and uncertain ultimate fate of mutants, and that which is due to variation in the number of mutants that occur:

$$V(r_t) = E_k[V_a(r_t \mid k)] + V_k[E_a(r_t \mid k)],$$

where expectations are taken over the subscript a or k. Now

$$E_a(r_t \mid k) = k \int_{-\infty}^{\infty} aE(q_t \mid 1/2N, Nia/\sigma)\tilde{f}(a)\,da$$

and

$$E_a[(r_t)^2 \mid k] = k \int_{-\infty}^{\infty} a^2 E(q_t^2 \mid 1/2N, Nia/\sigma)\tilde{f}(a)\,da \\ + k(k-1)\left[\int_{-\infty}^{\infty} aE(q_t \mid 1/2N, Nia/\sigma)\tilde{f}(a)\,da\right]^2.$$

Therefore

$$V_a(r_t \mid k) = k \int_{-\infty}^{\infty} a^2 E(q_t^2 \mid 1/2N, Nia/\sigma)\tilde{f}(a)\,da \\ - k\left[\int_{-\infty}^{\infty} aE(q_t \mid 1/2N, Nia/\sigma)\tilde{f}(a)\,da\right]^2$$

and taking expectation over k replaces the k by $2N\lambda$. Because k is Poisson distributed, $V(k) = E(k) = 2N\lambda$ and

$$V_k[E_a(r_t \mid k)] = 2N\lambda\left[\int_{-\infty}^{\infty} aE(q_t \mid 1/2N, Nia/\sigma)\tilde{f}(a)\,da\right]^2.$$

Thus

$$V(r_t) = 2N\lambda \int_{-\infty}^{\infty} a^2 E(q_t^2 \mid 1/2N, Nia/\sigma)\tilde{f}(a)\,da. \tag{6}$$

Using the symmetry and transforming in terms of Ns, we get

$$V(r_t) = [N\lambda\sigma^2/(N^2 i^2)] \int_0^{\infty} (Ns)^2 [E(q_t^2 \mid 1/2N, Ns) \\ + E((1-q_t)^2 \mid 1-1/2N, Ns)]f^*(Ns)\,d(Ns). \tag{7}$$

Because mutations in successive generations are assumed to be independent,

$$R_t^M = \sum_{t'=1}^{t} r_{t'} \quad \text{and} \quad V(R_t^M) = \sum_{t'=1}^{t} V(r_{t'}),$$

and the rate of mutation and distribution of mutant effects are assumed to be independent of variability existing initially in the population.

Standardization in terms of R_1^M is obtained by recalling the previous arguments from Hill (1982) and noting that

$$R_1^M = 2N\lambda(i/\sigma) \int_{-\infty}^{\infty} (a^2/4N)\tilde{f}(a)\,da \\ = \lambda i E(a^2)/2\sigma = (i/\sigma)\sigma_M^2, \tag{8}$$

because the variance is approximately $a^2/4N$ for a gene of effect a and frequency $1/2N$, for large N. Hence, transforming,

$$R_1^M = [\lambda\sigma/(2N^2 i)] \int_0^{\infty} (Ns)^2 f^*(Ns)\,d(Ns). \tag{9}$$

Values of $E(q_t)$ and $E(q_t^2)$ were obtained for successive values of t and $q_0 = 1/2N$ and $1-1/2N$ by transition probability iteration for given N and a range of s ($\geqslant 0$) and subsequently integrated numerically over s. Details were given previously (HR86).

Limiting case of small effects

If selection forces are small relative to those of drift, i.e. $E(Ns) \to 0$, simple formulae can be obtained which, as limiting values, provide useful checks and reference points. In these it is assumed that the changes in variance within and between lines are a consequence solely of drift, an approach used by Robertson (1960), i.e

$$E[q_t(1-q_t)] \doteq (1-1/2N)^t q_0((1-q_0) \doteq e^{-t/2N}q_0(1-q_0),$$

the exponential approximation also requiring large N. Therefore

$$E(q_t) \doteq q_0 + Nsq_0(1-q_0)(1-e^{-t/2N}) \text{ and} \\ E(q_t^2) \doteq q_0^2 + q_0(1-q_0)(1-e^{-t/2N}),$$

which, for a rare mutant, reduce to

$$E(q_t) \doteq 1/2N + s(1-e^{-t/2N})/2 \text{ and}$$

$$E(q_t^2) \doteq (1-e^{-t/2N})/2N.$$

The limiting formula for $E(q_t)$ can now be inserted into (4) to give

$$r_t \doteq Ni\lambda(1-e^{-t/2N})E(a^2)/\sigma = 2NR_1^M(1-e^{-t/2N}) \tag{10}$$

from (8). Therefore, after summing over generations,

$$R_t^M \doteq 2NR_1^M[t-2N(1-e^{t/2N})] \tag{11}$$

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(Hill, 1982). Similarly, from (6),

$$V(r_t) \doteq (1-e^{-t/2N})\,E(a^2) = 2(1-e^{-t/2N})\,\sigma_M^2, \qquad (12)$$

$$V(R_t^M) \doteq 2[t-2N(1-e^{-t/2N})]\,\sigma_M^2, \qquad (13)$$

a result derived elsewhere for the variance between lines deriving from neutral mutation (Lynch & Hill, 1986). With this approximation the response and variance of response are proportional to each other. Note that, providing t/N is small, R_t^M and $V(R_t^M)$ increases in proportion to $(t/N)^2$, and thus $SD(R_t^M)$ increases in proportion to t/N. Further, these equations illustrate for the special case of small Ns the validity of the reparametrization deduced earlier.

Results

Tests of approximation. The arguments used to show the reparametrization in terms of products such as NR_1^M were heuristic (the only critical element being the dependence of the mutant's initial frequency on population size). Examples of checks on approximations are given in Fig. 1. For fixed $\beta = 1$ and $(\beta+1)/\alpha^* = 4$ values of $R_t^M/(N^2 R_1^M)$ computed by numerical integration of results from transition probability matrix iteration are plotted for three values of N. To show the fit of the equivalent approximations for the variance, values of $[R_t^M \pm SD(R_t^M)]/(N^2 R_1^M)$ are also plotted for $\beta = 1$. In these examples, the standard deviation of response is computed on the assumption that $2N\lambda = 1$ (i.e. one mutant expected per generation), but note that $SD(R_t^M)/(N^2 R_1^M)$ is then inversely proportional to N. The agreement between the repara-
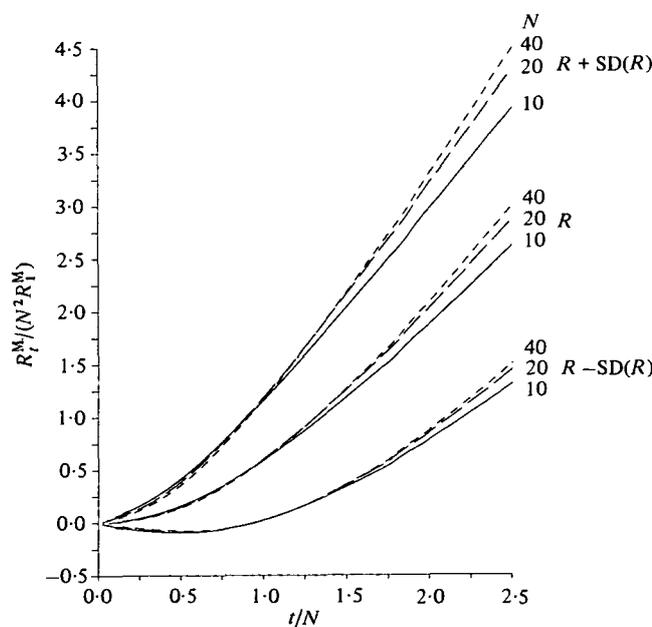
Fig. 1. Values of $R_t^M/(N^2 R_1^M)$, of $(R_t^M+SD(R_t^M))/(N^2 R_1^M)$ and of $(R_t^M-SD(R_t^M))/(N^2 R_1^M)$ plotted against t/N for $N = 10$, 20 and 40, $\beta = 1$, $(\beta+1)/\alpha^* = 4$ and $2N\lambda = 1$, in order to illustrate that this parametrization gives responses and standard deviations of response approximately independent of N.
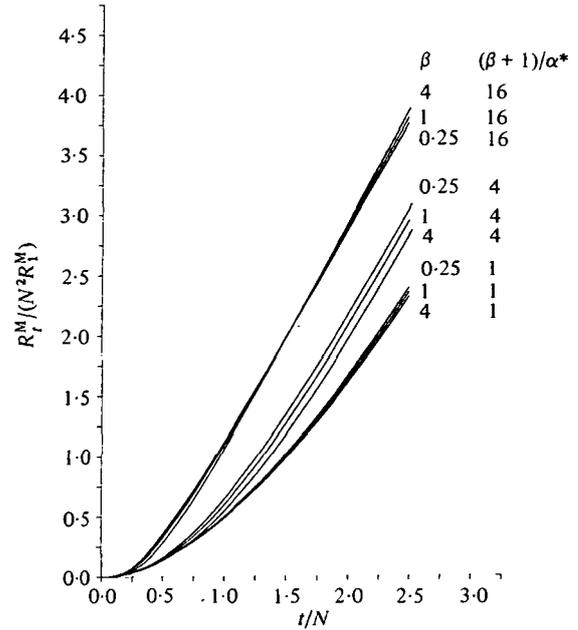
Fig. 2. Values of $R_t^M/(N^2 R_1^M)$ plotted against t/N for a range of values of β and $(\beta+1)/\alpha^*$ to show the relationship of response from mutations to the distribution of mutant gene effects.

metrized results for different values of N, in particular between the larger values of 20 and 40, illustrate that the approximations are satisfactory for practical purposes.

Response from mutation alone. For a wider range of parameters, values of cumulative response from mutation are plotted in Fig. 2. This illustrates that the value of β, the shape parameter of the gamma distribution or function of the ratio of effective to actual number of loci, $n_e/n = \beta/(\beta+1)$, in Wright's sense (see HR86), has little effect on the expected response. The steady state rate of response, i.e.

$$\lim_{t\to\infty} (R_t^M - R_{t-1}^M) = r_\infty,$$

expressed in terms of $N^2 R_1^M$, does not depend on the expected number of mutants contributing to the response, i.e. on $(\beta+1)/\alpha^* = (n/n_e)\,E(Ns)$. However, if gene effects are on average large (i.e. α^* small) the response is relatively higher in early generations (Hill, 1982), and the ratio of expected responses for $t/N < 0.5$ can be very large indeed. In other words, if mutant effects are infinitesimal, it takes a long time for the genes to change much in frequency and contribute substantially to response.

The standard deviation of cumulative response is shown in Fig. 3, and is plotted as $SD\ (R_t)/(N\sigma_M^2)^{0.5}$ since results plotted on this scale are independent of number of mutants/generation. As the mean effects of individual mutants rise (i.e. lower α^* and higher $(\beta+1)/\alpha^*$), the variation of response increases markedly, because the response in any replicate line depends critically on which specific mutants appear.

Response from existing and mutational variance. The two components are shown together in Fig. 4. In this
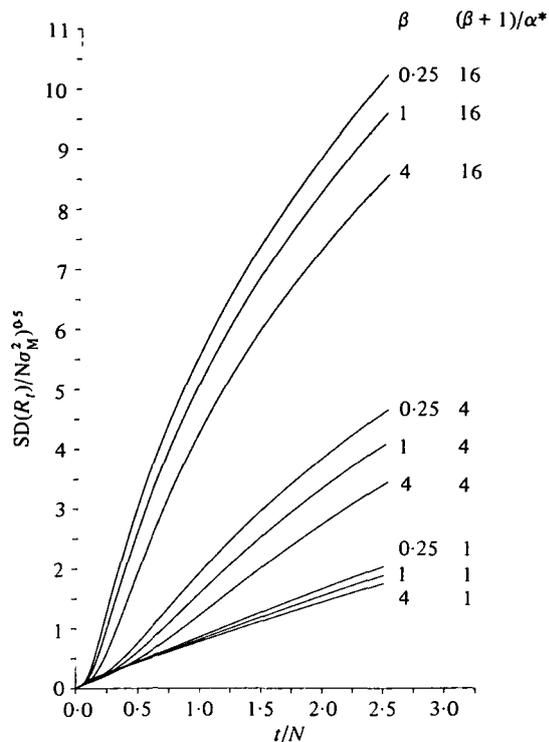
Fig. 3. Values of $SD(R_t^M)/(N\sigma_M{}^2)^{\frac{1}{2}}$ plotted against t/N for a range of values of β and $(\beta+1)/\alpha^*$ to show the relationship of standard deviation of response from mutations to the distribution of mutant gene effects.
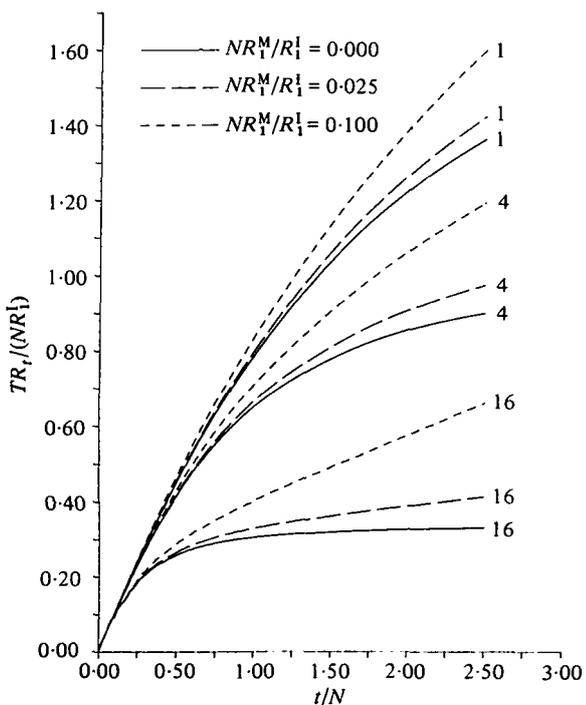
Fig. 4. Values of $TR_t/(NR_1^I)$ plotted against t/N for $\beta = 1$ and a range of values of $(\beta+1)/\alpha^*$, and NR_1^M/R_1^I. The same distribution of initially segregating and mutant gene effects is assumed. Note that the increment due to mutation is proportional to NR_1^M/R_1^I and that curves can be substituted if initially segregating and mutant genes have a different distribution of effects. For $\beta = 1$, $(\beta+1)/\alpha^* = 2N\bar{s}$, where $\bar{s}$ is the mean selective value of the genes.
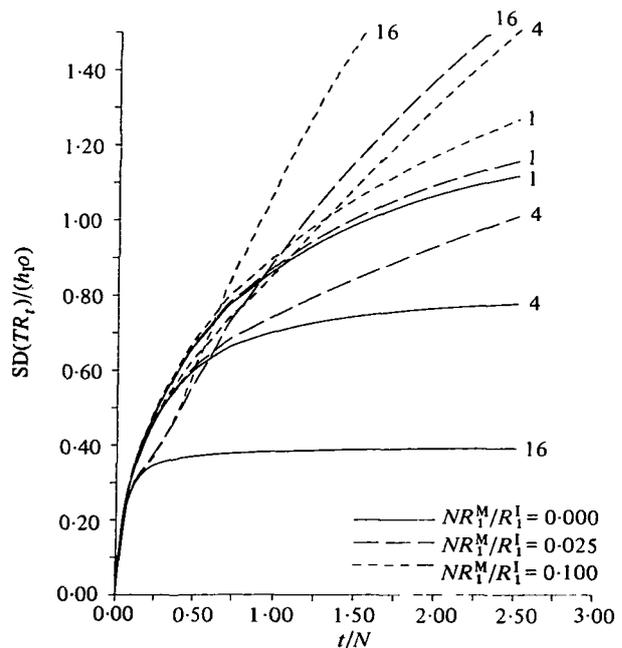
Fig. 5. As Fig. 4, but for values of the standard deviation of the total response expressed as $SD(TR_t)/(h_I\sigma)$.

example the initial frequencies are assumed to be uniformly distributed over the interval 0–1. However, as shown in HR86, the alternative initial conditions of either all gene frequencies equal to 0·5 or gene frequencies having a U-shaped distribution,

$$g(q) \propto q^{-1}(1-q)^{-1} \quad (0 < q < 1),$$

such as would derive from a recurrent mutation model, give rather similar expected responses for the time period and parameter range shown. Results are given for response from existing variance alone and for two values of NR_1^M/R_1^I, but since the contribution at any generation from mutations is proportional to NR_1^M/R_1^I, other values can be inferred immediately. As an example, bristle number in *Drosophila melanogaster* has a heritability of about 0·4 and estimates of the increase in heritability from mutation are about 0·001 per generation (Hill, 1982; Lynch, 1986); thus $R_1^M/R_1^I = 0·0025$, so the curves are drawn for values of N of 10 and 40, approximately. As argued previously, mutations have a proportionately greater effect early when there are relatively few genes of large effect: the initial variance then contributes less and the mutants more. In these graphs the same distribution of effects of original and mutant genes is assumed. The separate curves of Fig. 4 can be combined to give new combinations.

The standard deviation of response, with the initial and mutational components combined as in Fig. 4 and expressed relative to the initial genetic standard deviation, $h_I\sigma$, is shown in Fig. 5. It is seen that if gene effects are small then mutation contributes little to the variance, whereas as gene effects become large, mutation contributes almost all the variance, particularly in later generations.

Discussion

The main objective of this paper has been to present a comprehensive theoretical analysis of the response from mutations due to unlinked additive genes, reparametrizing the formulae in such a way that most of the relevant results can be read from a few graphs. There are, of course, many limitations to the analysis. Of these the lack of linkage is not critical, certainly for species with many chromosomes (Keightley & Hill, 1983); nor is the additivity essential unless almost all mutants are recessive, because the critical factor is whether mutant genes have effect in the heterozygote, and if they do not, they contribute little to response (Hill, 1982). More fundamental assumptions are that the distribution of mutant effects is symmetric and does not change as selection proceeds, i.e. that the amount of useful variation being generated remains unchanged, and that natural selection does not oppose artificial selection. If natural selection acted solely on the phenotype as a stabilising selection force, the population would be expected to reach a plateau where the artificial and stabilising selection balanced (James 1962; Zeng & Hill, 1986) and which would not depend much on the amount of *de novo* variation. If natural selection acted through the effects of individual genes, i.e. if genes increasing the trait also reduced fitness, the rate of response would be impeded and selection intensities might drop to the extent that response ceased.

Results of long-term selected populations do not give a uniform picture. For example, the Illinois high corn-oil selection has responded without obvious attenuation for almost 80 ($\doteq 2.5$ N) generations (Dudley, 1977), some *Drosophila* experiments have yielded responses for long periods with some possible signs of late reductions in response and certainly in fitness (e.g. Yoo, 1980*a*), others have shown plateaux after relatively few generations (e.g. F. W. Robertson, 1955, for body size in *Drosophila*). In Yoo's experiment (Yoo, 1980*b*) and, for example, that of Clayton & A. Robertson (1957), the fitness reductions were associated with genes with a large effect in the heterozygote but lethal in the homozygote. There is good but not unequivocal evidence that attenuation of response is due to stabilizing selection, i.e. due to the mean level of the trait *per se*. Thus Latter (1966) observed continuing reductions in fitness as his scutellar bristle selected lines of *Drosophila* became more extreme, and there was a substantial reduction in bristle number on relaxation of selection. Similarly, F. W. Robertson (1955) observed reductions in performance on relaxation of response but points out this does not prove the mechanism is stabilizing selection acting directly on the trait.

In previous papers (e.g. Hill, 1982) the variability of response from mutations has been noted, but here the first complete analysis is given. As Fig. 3 shows, this variance depends markedly on the number and distribution of effects of mutant genes: if they are rare, but can have a large effect, the pattern is quite different from that where there are likely to be several mutants, each generation having a small effect on the trait. Consequently, if individual mutants can have large effects they may cause substantial variation in response after a few generations even in a population which is large in size and initially has substantial variation (Fig. 5).

The analysis, as exemplified by Fig. 4, shows that mutations are expected to contribute substantially to response in long-term experiments. For bristle number in *Drosophila* the increment in heritability deriving from mutations is usually estimated at around 0·001, and Lynch (1986) has found a range of estimates over species (including mice and maize) from 0·0001 to 0·1. An increment in heritability of 0·25% would, for example, be equivalent to $R_1^M/R_1^I = 0.01$ for typical values of 25% for initial heritability. Thus, for experiments run with effective population sizes of much more than 10, Fig. 4 does not show values of NR_1^M/R_1^I as large as may be found in practice (because the intercrossing of lines made the graph very confusing). For example, for $N = 20$, $R_1^M/R_1^I = 0.01$ and genes of relatively large effect (i.e. $(\beta+1)/\alpha^* = (n/n_e) E(Ns) = 16$), a significant amount of the response could be due to mutations after 10 generations and over one-third after 20 generations. The role of mutations should not be ignored when planning and interpreting long-term selection experiments and breeding programmes. Although the linearity relation between response and population size will break down if the mutation-derived variance becomes a large part of the phenotypic variance, there are obvious potential benefits from maintaining large populations.

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