

Predictions of response to artificial selection from new mutations

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SUMMARY

The pattern of response expected from fixation of mutant genes for quantitative traits in finite populations is investigated for a range of distributions of mutant gene effects. The eventual rate depends on the total variance of mutant effects per generation, but the initial rate and the variance of response is higher if the distribution of mutant effects has a large standard deviation or is leptokurtic. The difference between initial and eventual rates of response is greater with large population sizes.

For a range of assumptions, new mutants are unlikely to have much influence on response for 20 or so generations, but then may contribute substantially, such that no plateaux are obtained. However, information on the variance contributed by mutants is almost entirely on bristle number in *Drosophila*.

It is argued that the role of new mutants should be considered in designing breeding programmes, in particular in utilizing large populations.

1. INTRODUCTION

In artificial selection programmes in laboratory and farm animals the possible contributions of mutations occurring after the selection has started are usually ignored. There are several reasons for this attitude: mutation rates are estimated to be very low and the duration of the experiment so short that the number of useful mutants is likely to be small (Falconer, 1981); most experiments designed to enhance response by artificially increasing mutation rates by X-irradiation have produced little, if any, extra grains (Clayton & Robertson, 1955, 1964; Kitagawa, 1967; Hollingdale & Barker, 1971); and in many selection experiments plateaux have been reached beyond which no further response has been made (Falconer, 1981, p. 194 et seq.). There are, however, some experiments which indicate that mutations (the term being used here in a general way to indicate point mutations, insertions, duplications or other changes in the DNA) during the course of the experiment may be contributing to total response: in selection for over 50 generations in corn (Dudley, 1977), *Tribolium* (Enfield, 1980) and *Drosophila* (Yoo, 1980) there was a continued response with no clear indication of a plateau; the

'bobbed' phenotype, presumably due to reduced copy number at the rRNA tandon, has been found in *Drosophila* populations selected for low abdominal bristle number (Frankham, Briscoe & Nurthen, 1978; 1980); genes of visible phenotype and large effect on the selected traits have been discovered in several selection lines but not in the source population (Frankham, 1980*a*), and in several cases recessives have been observed later than would have been expected had they been initially segregating (Robertson, 1978); long-term selection from highly inbred populations has led to responses in some instances (Mather & Wigan, 1942); in experiments with artificial mutagenesis, responses, albeit small ones, were usually made (Clayton & Robertson, 1955, 1964; Scossiroli & Scossiroli, 1959; Kitagawa, 1967; Hollingdale & Barker, 1971); and in some selection experiments substantial 'jumps' in response were made after periods of little response, indicative of a mutation or rare crossover event (e.g. Mather & Harrison, 1949; Thoday, Gibson & Spickett, 1964; Lopez-Fanjul & Hill, 1973). Reviewing the evidence, Frankham (1980*a*) concluded that new variation, whether from point mutation, unequal crossing over, intragenic crossing-over or other sources, could not be ignored in artificial selection experiments.

The response from mutations occurring after a selection programme begins depends on the rate at which they are generated, their effect on the trait under selection and their subsequent increase in frequency and fixation probability. In a recent theoretical analysis (Hill, 1982) it was shown that, for additive mutants having effects on the trait under selection with zero mean and contributing variance σ_M^2 in the first generation, the rate of response ultimately reached from fixing new mutants would equal $2Ni\sigma_M^2/\sigma$, where N is the effective population size, i the selection intensity and σ the phenotypic standard deviation. For bristle number in *Drosophila*, on which data on σ_M^2 are available, this would be sufficient to explain the continued response in Yoo's (1980) lines. The previous paper (Hill, 1982) discussed only the responses due to ultimate fixation of the mutants and not the pattern of response from the time of their occurrence in single copy to fixation. This report deals, therefore, with the expected responses and variation in responses from new mutants both in isogenic and initially segregating populations, reviews some of the experimental work in terms of this theory and considers the implications for animal and plant improvement.

2. MODEL

The model is that used previously (Hill, 1982). The population is assumed to have constant size and breeding structure, with T individuals scored each generation and an effective population size of N . Mutations are unlinked, show no epistasis for the trait and are not affected by natural selection. We consider a locus currently fixed for allele A which can mutate to A' . The relative genotypic values and fitnesses of the trait are as follows, where i is the selection intensity, σ the

phenotypic standard deviation, and we consider for the present only additive genes:

Genotype	<i>AA</i>	<i>AA'</i>	<i>A'A'</i>
Genotypic value	0	$\frac{1}{2}a$	<i>a</i>
Fitness (equivalent formulae)	1	$1 + \frac{1}{2}ia/\sigma$	$1 + ia/\sigma$
	1	$1 + \frac{1}{2}s$	$1 + s$

The relation between gene effect and selective value, $s = ia/\sigma$, applies providing ia/σ is not too large, say less than 0.5 (Latter, 1965).

The mutation rate per chromosome from *A* to *A'* is μ and the total number of mutants per chromosome set is $\lambda = \sum_L \mu$ where *L* denotes summation over all possible mutants at all loci. The expected number of mutants in the population is therefore $2T\mu$ at the locus and $2T\lambda$ in all. The frequency of *A'* is *q*; its initial frequency, when it appears, is $1/2T$. Mutation rates and population size are assumed sufficiently small that simultaneous segregation of more than two alleles at a locus can be ignored.

The initial increase in variance from one mutation to *A'* is $\frac{1}{2}a^2q(1-q) \sim a^2/4T$, so the expected initial increase is $2T\mu \times a^2/4T = \frac{1}{2}\mu a^2$. From all loci, the increase in variance per generation (σ_M^2) is expected to be.

$$\sigma_M^2 = \frac{1}{2} \sum_L \mu a^2 = \frac{1}{2} \lambda \int_{-\infty}^{\infty} a^2 f(a) da = \frac{1}{2} \lambda E(a^2), \tag{1}$$

where $f(a)$ is the density function of mutant effects, assumed to remain constant over time. The expected response to selection in the generation immediately following the mutation is $i\sigma_M^2/\sigma$, and subsequent responses depend on the effects and frequency changes of mutant genes.

Let $g(q, a, t)$ be the density function of gene frequency (*q*) of a mutant gene of effect *a* at *t* generations after initial occurrence. The mean frequency at generation *t* of such genes is therefore

$$Q(a, t) = \int_0^1 qg(q, a, t) dq.$$

The mean response in performance from all mutants occurring *t* generations earlier is thus

$$\begin{aligned} R_t &= 2T \sum_L \mu a Q(a, t) \\ &= 2T\lambda \int_{-\infty}^{\infty} a Q(a, t) f(a) da. \end{aligned} \tag{2}$$

The expected response when all these genes are fixed is obtained by replacing $Q(a, t)$ by the ultimate fixation probability $u(a)$ of genes of effect *a*, and simple formulae can be obtained as follows (Hill, 1982), based on Kimura's formula (Crow & Kimura, 1970, p. 426):

$$\begin{aligned} a < -\sigma/Ni: & \quad u(a) \doteq 0 \\ |a| < \sigma/Ni: & \quad u(a) \doteq 1/2T + Nia/2T\sigma \\ a > \sigma/Ni: & \quad u(a) \doteq Nia/T\sigma. \end{aligned}$$

On replacing $Q(a, t)$ by these approximations for $u(a)$ in (2),

$$\lim_{t \rightarrow \infty} R_t = R = (2N\lambda i/\sigma) \int_{\sigma/Ni}^{\infty} a^2 f(a) da + \lambda \int_{-\sigma/Ni}^{\sigma/Ni} \{(Ni/\sigma) a^2 + a\} f(a) da \quad (3)$$

(Hill, 1982). If $f(a)$ is symmetrically distributed about zero, $R = 2Ni\sigma_M^2/\sigma$, using the definition of σ_M^2 given in (1). More generally, if population size and the variance of gene effects are sufficiently large, terms where $|a| < \sigma/Ni$ can be ignored in (3) (so the fixation probability of favourable mutants is then simply the product of selective value ($s = ia/\sigma$) and the ratio (N/T) of effective to total population size (Crow & Kimura, 1970, p. 426)),

$$R = (4Ni\sigma_M^2/\sigma) E^+(a^2)/E(a^2),$$

where

$$E^+(a^2) = \int_0^{\infty} a^2 f(a) da.$$

In these cases R is seen to be proportional to population size.

If the rate of occurrence and distribution of mutant effects and the phenotypic variance remain constant each generation, R becomes the steady-state rate of response per generation. Its proportional relation to population size clearly becomes inappropriate for very large populations because the steady state will take a very long time to be reached, the assumption of only two alleles segregating at each locus more tenuous, and useful mutations will be more likely to have been used already. Other factors are also likely to change the rate of response: for example the phenotypic variance may depend on the rate of input of genetic variance and on the mean level of the trait, and natural selection effects may become more important as selection proceeds.

The cumulative response, C_τ , up to generation τ from mutations occurring in generations 1, 2, ..., τ is simply

$$C_\tau = \sum_{t=1}^{\tau} R_t = 2T\lambda \int_{-\infty}^{\infty} a \left\{ \sum_{t=1}^{\tau} Q(a, t) \right\} f(a) da. \quad (4)$$

If most variation is due to genes of small effect such that $|Nia/\sigma| < 1$, the expected response to generation t after the mutations is, from Robertson (1960),

$$\begin{aligned} R_t &= (2Ni\sigma_M^2/\sigma) \{1 - (1 - 1/2N)^t\} \\ &\sim (2Ni\sigma_M^2/\sigma) (1 - e^{-t/2N}). \end{aligned} \quad (5)$$

The cumulative response to generation τ from repeated mutations with small effect is therefore, from (4) and (5)

$$\begin{aligned} C_\tau &= (2Ni\sigma_M^2/\sigma) \{ \tau + 1 - 2N [1 - (1 - 1/2N)^{\tau+1}] \} \\ &\sim (2Ni\sigma_M^2/\sigma) \{ \tau - 2N (1 - e^{-\tau/2N}) \}. \end{aligned} \quad (6)$$

For small τ and large N , C_τ increases in proportion to τ^2 , i.e. the variance increases in proportion to τ and the cumulative response in proportion to $(1 + 2 + \dots + \tau)$.

Variation in response

Variability in response from mutants is contributed by several sources: variation in the number of mutants each generation, variation in their effects and binomial variation in fixation probability. Details of the analysis are unnecessary here, but it can be shown that, ignoring genes with very small values of ia/σ , the variability in ultimate response from mutants in a single generation equals $2N\lambda(i/\sigma) E^+(a^3)$ approximately. (The main terms are: the expected number of mutants, $2T\lambda$, the variance in fixation probability given a , approximately equal to the fixation probability $Nia/T\sigma$, and the consequent squared response, a^2 .) The variation in observed response each generation is more difficult to handle analytically. As a first approximation it would seem reasonable to assume that, because the expected response in one generation from a gene of effect a is proportional to $E^+(a^2)$, the variance in response is proportional to $E^+(a^4)$.

3. METHODS

(i) *Simulation*

Equations (2)–(4) can be evaluated by transition matrix iteration accompanied by numerical integration using a set of a values. It seemed simpler to use Monte Carlo simulation and sample both the a values and the subsequent fate of the mutant. For fixed values of a , used as an extreme type of mutant distribution, transition probability matrices were used, otherwise simulation. In both cases, for simplicity, a haploid model with binomial transition probabilities among the N effective parents of each generation was used:

$$P(q_{t+1} = j | 2N | q_t) = \binom{2N}{j} \left[\frac{q_t(1 + \frac{1}{2}s)}{1 + \frac{1}{2}s q_t} \right]^j \left[1 - \frac{q_t(1 + \frac{1}{2}s)}{1 + \frac{1}{2}s q_t} \right]^{2N-j}$$

where $s = ia/\sigma$. For a mutant initially occurring in single copy in the $2T$ chromosomes of the total population, a probability of $(1 + \frac{1}{2}s)N/T$ was assumed for its occurrence in single copy in the $2N$ effective parents of generation one, otherwise it was assumed to be lost. For very small effects, $Ns \sim 0$, equations (5) and (6) were used.

(ii) *Distributions of effects*

Several alternative distributions of gene effects were simulated; although each was symmetric about $a = 0$ they differed substantially in the degree of kurtosis. These were: E, with all effects of equal absolute value; N, with effects having a normal distribution; Γ , with effects having a 'double gamma' distribution, essentially a gamma distribution with one parameter set to $\frac{1}{2}$ (chi-square with 1 d.f.), reflected about zero; G, with effects having a 'double geometric' distribution, essentially $f(a) \propto 1/|a|$, reflected about zero. For the G distribution, upper and lower bounds to $|a|$ had to be specified, but the lower bound was set very close to 0 and the upper

Table 1. *Symmetric distributions of gene effects used in simulation*

Name	Density function	Moments*			
		$E^+(a)/\sigma_a$	$E^+(a^2)/\sigma_a^2$	$E^+(a^3)/\sigma_a^3$	$E^+(a^4)/\sigma_a^4$
Equal (E)	$f(a) = \frac{1}{2}, a = -\sigma_a, a = \sigma_a$ = 0, otherwise	$\frac{1}{2}$	$\frac{1}{2}$	$\frac{1}{2}$	$\frac{1}{2}$
Normal (N)	$f(a) = \frac{1}{\sigma_a\sqrt{2\pi}} \exp(-a^2/2\sigma_a^2) \quad (-\infty < a < \infty)$	$\frac{1}{\sqrt{2\pi}} \doteq 0.40$	$\frac{1}{2}$	$\sqrt{(2/\pi)} \doteq 0.80$	$\frac{3}{2}$
Double gamma (Γ)†	$f(a) = \frac{1}{2} \left(\frac{\lambda}{\pi a } \right)^{\frac{1}{2}} \exp(-\lambda a) \quad (-\infty < a < \infty)$ $\lambda = \sqrt{3}/\sigma_a$	$\frac{1}{\sqrt{12}} \doteq 0.29$	$\frac{1}{2}$	$\frac{5}{\sqrt{12}} \doteq 1.44$	$\frac{35}{6}$
Double geometric (G)‡	$f(a) = \frac{1}{2 a \ln(U/L)} \quad (L < a < U)$ = 0, otherwise (value used: $U = 8\sigma_a, L = 8e^{-32}\sigma_a$)	$\frac{1}{8}$	$\frac{1}{2}$	$\frac{8}{3}$	16

* Conditional on positive values and standardized relative to σ_a , where $E^+(a^r) = \int_0^\infty a^r f(a) da$.
 † Simulated by squaring random normal deviates and randomly allocating sign.
 ‡ Simulated by sampling values of the cumulative distribution, $F(a) = \{\ln(a/L)/\ln(U/L)\}$ and randomly allocating sign.

sufficiently large to give a very leptokurtic form. The functions are listed in Table 1, together with expected values of a over the positive range, which feature in formulae for means and variability of response. In each of these cases strictly neutral genes, i.e. $a = s = 0$, are not sampled, so the numbers of mutants and distribution of effects apply to those having some effect, however small, on the selected trait. Because changes in the shape of the distribution affect the rate of response in early generations and the variance of response in different ways, no general formulation in terms of, for example, effective numbers of mutant genes, has been obtained.

In practice, selective values rather than gene effects were simulated, but the shapes of the distributions are the same because with i and σ constant $E^+(s^r)/\sigma_s^r = E^+(a^r)/\sigma_a^r$, where σ_s^2 and σ_a^2 are the variances of selective value and effect.

(iii) Number of mutants

Comparisons of the patterns of response for different distributions of gene effect were made in terms of fixed values of σ_M^2/σ^2 . When considering single replicate experiments the expected number of mutants in the whole population, $\Lambda = 2T\lambda$, was computed as follows. From (1), for symmetric distributions of effects, $\sigma_M^2 = \frac{1}{2}\lambda\sigma_a^2$ so $\Lambda = 4T\sigma_M^2/\sigma_a^2$. In terms of σ_s^2 , where $\sigma_s = i\sigma_a/\sigma$, $\Lambda = 4Ti^2\sigma_M^2/\sigma_s^2\sigma^2$. Assuming typical values of $i = 1.4 \doteq \sqrt{2}$ and $\sigma_M^2/\sigma^2 = 10^{-3}$ (appropriate for *Drosophila* bristles, as discussed subsequently), $\Lambda = 8 \times 10^{-3} T/\sigma_s^2$. In the simulations T was taken for convenience to equal $2N$, unrelated to the subsequent selection intensity, so, for example, with $\sigma_s = 0.5$ and $N = 25$, $\Lambda = 1.6$.

4. RESULTS

(i) Response from mutations occurring in one generation

Let us consider first the expected response (R_t) over successive generations (t) of selection of the mutations which occur in a single generation. The initial expected response is $R_1 = i\sigma_M^2/\sigma$, for any population size and distribution of gene effects, so to standardize results the values plotted in Figs. 1 and 2 are of R_t/R_1 . In Fig. 1 results are given for several values of population size and standard deviation of selective value, $\sigma_s = i\sigma_a/\sigma$, where σ_a^2 is the variance of gene effects defined by the distribution, $f(a)$. Thus for a fixed value of initial mutational variance, σ_M^2 , a fourfold decrease in σ_s implies a 16-fold increase in the expected number of mutants. While in Fig. 1 all gene effects are assumed to have the double gamma distribution, in Fig. 2 curves are drawn for different distributions.

As predicted (Hill, 1982), $R_t/R_1 \rightarrow 2N$, approximately, for large t , except that either when σ_s is very large (0.5) or the distribution is highly leptokurtic with a smaller value of σ_s (0.125 for the double geometric) a rather lower value is achieved; but in all the simulations shown, R_t/R_1 is at least $0.7 \times 2N$, so there is little need in practice to assume asymptotic values other than $2N$ for this ratio. The pattern

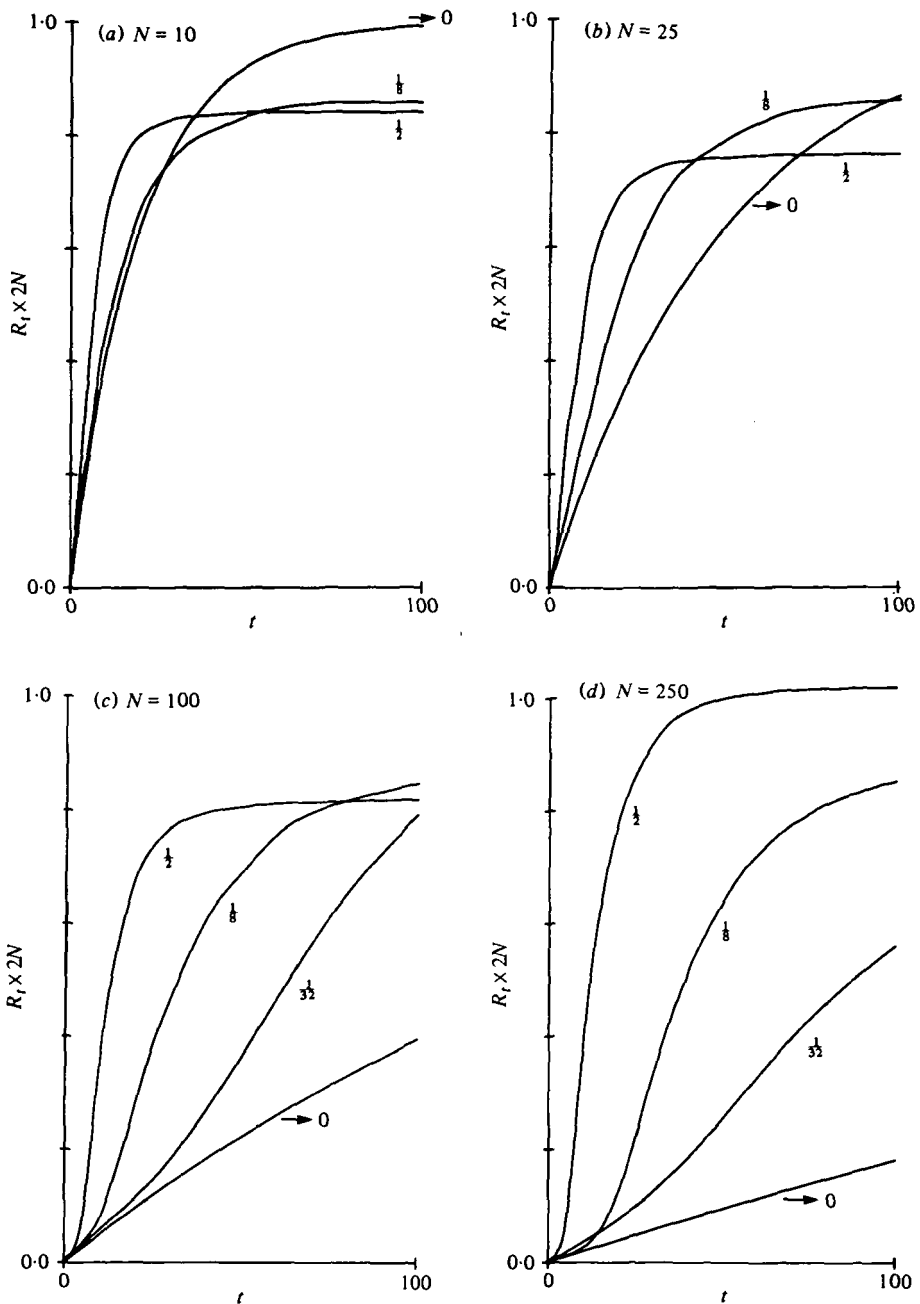


Fig. 1. Expected response (R_t) from mutants with additive effects occurring in a single generation, expressed relative to response in the first generation after the mutation ($R_1 = i\sigma_M^2/\sigma$). Mutants have a double gamma distribution with standard deviation of selective value $\sigma_s (= i\sigma_a/\sigma)$. Curves are drawn for a range of population size (N) and σ_s values. (For *Drosophila* bristles 350 units of R_t/R_1 is approximately equal to one bristle.)

of response is influenced rather more by the distribution of effects or selective values, more for large values of population size ($N \geq 100$) than for small ($N \leq 25$). A higher variance of selective value or higher kurtosis leads to higher expected responses in early generations. The reason is that, for a gene which is not lost almost immediately, its contribution to genetic variance and thus increase in means is proportional to a^2 during the period prior to approaching fixation.

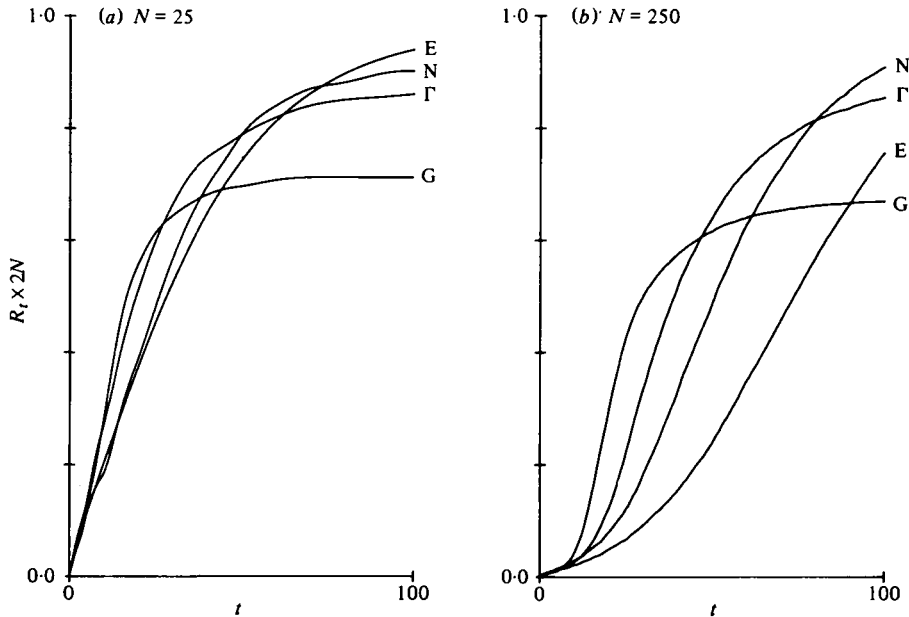


Fig. 2. As Fig. 1 except that curves are drawn for $\sigma_s = \frac{1}{8}$ and different distributions of gene effects (E = equal, N = normal, Γ = double gamma, G = double geometric).

In subsequent graphs of expected responses only the double gamma distribution is used, but it should be noted that in terms of response pattern an increase in kurtosis is equivalent to an increase in σ_s and vice versa.

(ii) Cumulative responses

Under the assumption that the distribution of mutant effects remains constant each generation, expected cumulative responses from mutations occurring continually each generation are plotted in Fig. 3. To show the effect of population size, the same scale is used for each value of N , and is in units of response in the first generation, (C_1/R_1) , because the response in the first generation does not depend on N . As in Fig. 1, results are given for a range of values of σ_s . The most striking feature is, of course, the dependency on population size, but the results also show how slowly response accumulates when N is large and σ_s is small. There is a

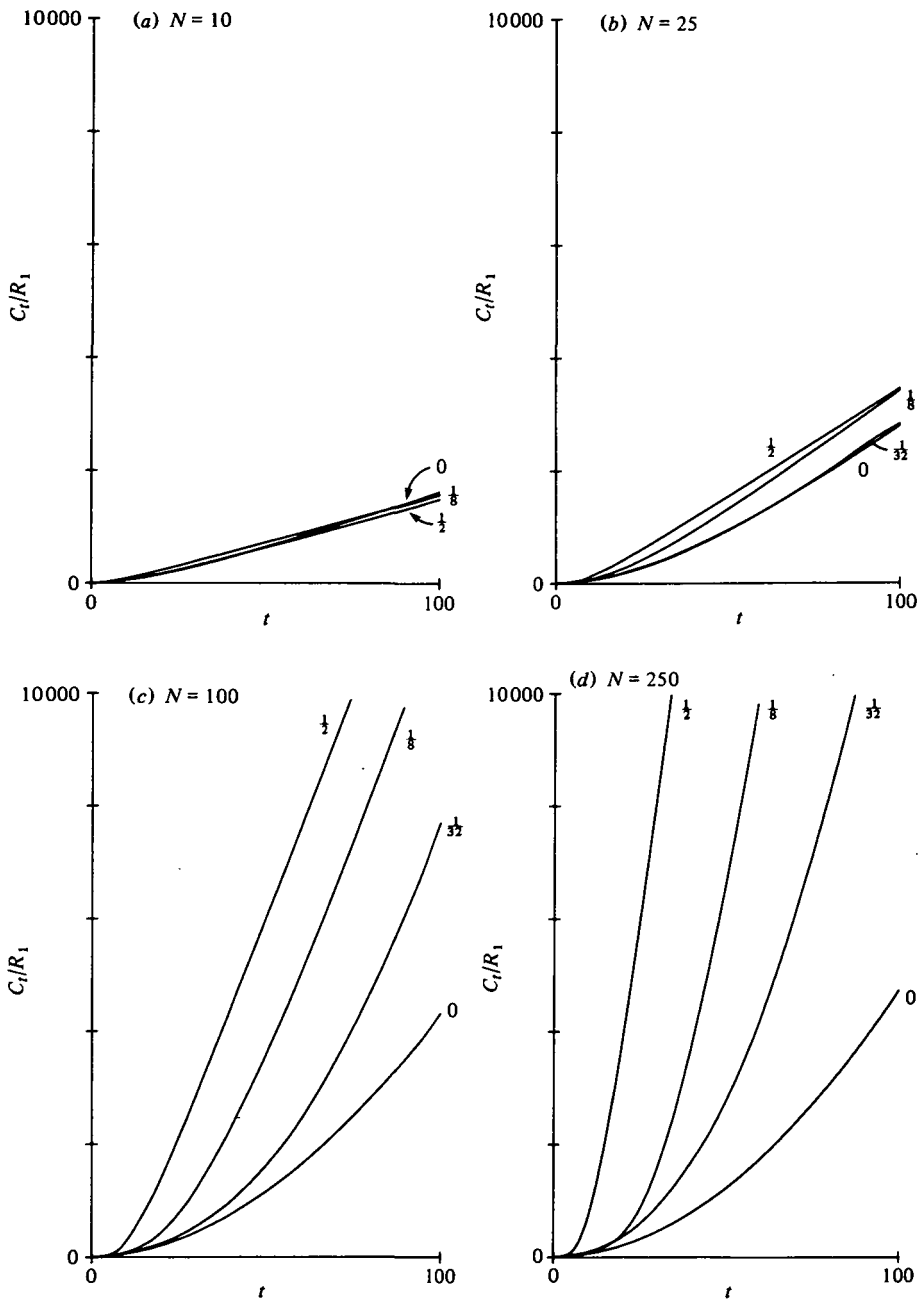


Fig. 3. Expected cumulative response from mutants with additive effects occurring at the same rate each generation, expressed as a ratio of the response from the first generation of selection of mutants of one generation, i.e. C_i/R_1 . Effects have a double gamma distribution, with parameters as in Fig. 1.

quadratic type of response curve for small σ_s , essentially because the variance increases approximately linearly with generation number, and thus the cumulative response, proportional to the integral of the variance, increases as the square of the generation number for a limited period (see equation (6) et seq.).

The results of Fig. 3 are expected responses in initially isogenic populations and there is obviously likely to be substantial variation in response: first due to random sampling of the mutations, and secondly due to drift of mutant frequency after they have occurred. Some examples of simulated experiments are shown in Fig. 4 for different values of N , σ_s and the distributions of effect. The larger σ_s and the kurtosis of the distribution, the greater the variability of response and, although expected responses may be small up to 20 or so generations (Fig. 3), in some replicates the actual response may be quite large. At larger population sizes the variance of response increases, but the coefficient of variation decreases (i.e. as in the Poisson distribution, $E(X) = V(X) = \mu$, but $CV(X) = \mu^{-1/2}$) such that overall appearance is of less erratic progress.

(iii) Dominance

The previous analyses and figures refer solely to additive genes, and here we briefly extend the results to include completely dominant or recessive mutants. The genotypic values are now assumed to be $AA:0$, $AA':ha$, $A'A':a$, with $h = 0$, $\frac{1}{2}$ and 1 for recessive, additive and dominant mutants, respectively. The initial variance contributed by such mutants, σ_M^2 , equals, 0, $\frac{1}{2}\lambda E(a^2)$ and $2\lambda E(a^2)$, respectively (cf. equation (1)). Comparisons between the responses from the different types of mutant can be made in several ways, for example by equating the number of mutants, their initial variance or their expected contribution to response. For the results shown in Fig. 5, the initial variance has been equated for completely dominant and additive mutants, i.e. for specified σ_M^2 and σ_a^2 , λ (dominant) = $\frac{1}{2}\lambda$ (additive). Because recessives contribute nothing to σ_M^2 , their numbers cannot be determined in the same way, so an equal frequency of completely dominant and recessive mutants has been assumed, i.e. λ (recessive) = λ (dominant).

The expected response at fixation from dominant mutants is, for the same initial variance, rather less than one-half that for additive genes. (A value of one-half was computed previously (Hill, 1982), but this applies only in very large populations for two reasons: the approximation $u = 2Nia/T\sigma$ for dominant genes with large Nia/σ holds less well than the approximation $u = Nia/T\sigma$ for corresponding additive genes; and with small Nia/σ there is a proportionately larger reduction in u for dominant than for additive genes.) The general pattern of response is similar for dominant and additive genes, although the early responses are relatively larger with dominants, i.e. the half-life of the response is somewhat shorter. Recessive mutants at the same rate of occurrence contribute less response and later response than dominants. The responses from one generation of mutant recessives are proportional to $\sqrt{N} E^+(a^3)$ rather than $NE^+(a^2)$, so with graphs in

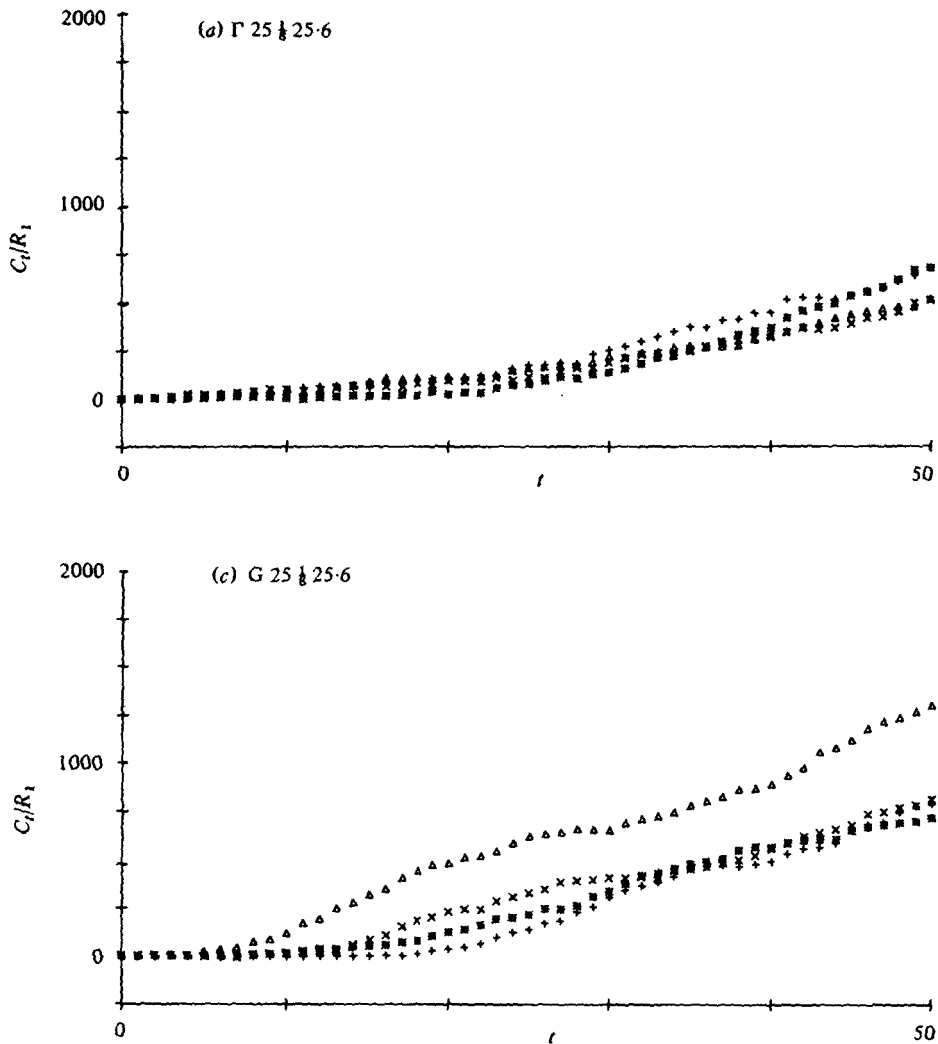


Fig. 4. For legends to (a) and (c) see opposite.

Fig. 5 shown for equal values of λa_a^2 there are proportionally large differences in the eventual rates of response.

For a combination of recessive and dominant mutants with the same distribution of effects and mutation frequency, the contribution to response is obtained by adding the appropriate curves in Fig. 5, and these can be compared directly with the curves for additive genes because all the initial variance is contributed by the dominant genes.

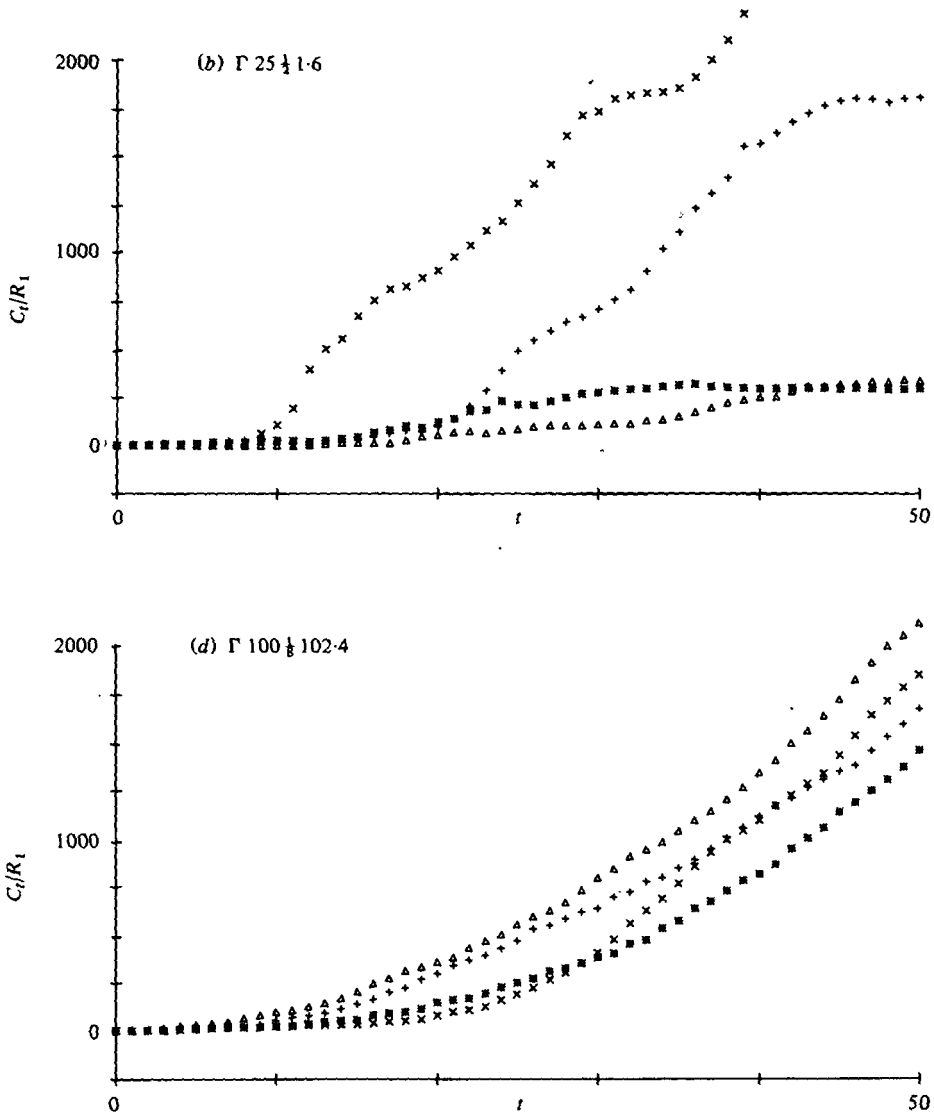


Fig. 4. Examples of cumulative response in replicates of experiments with different distributions of additive gene effects (see caption to Fig. 2), population size (N), standard deviation of selective value ($\sigma_s = i\sigma_a/\sigma$) and expected number of mutants per generation ($\Lambda = 2T\lambda$).

5. DISCUSSION

(i) Magnitude of mutational variance

Let us first attempt to put the theoretical results into the context of experiments and breeding programmes with actual traits. For this we need information on the distribution of mutant effects. There are extensive data on values of σ_M^2 (the initial

variance due to mutants) for bristle number in *Drosophila melanogaster* but not on other traits or species, and little direct information on the shape of the distribution of mutant effects. The analyses have all utilized highly inbred or isogenized populations. Estimates of σ_M^2 for *Drosophila* have been obtained by: direct analysis of variation among chromosomes on which mutants have accumulated (Durrant

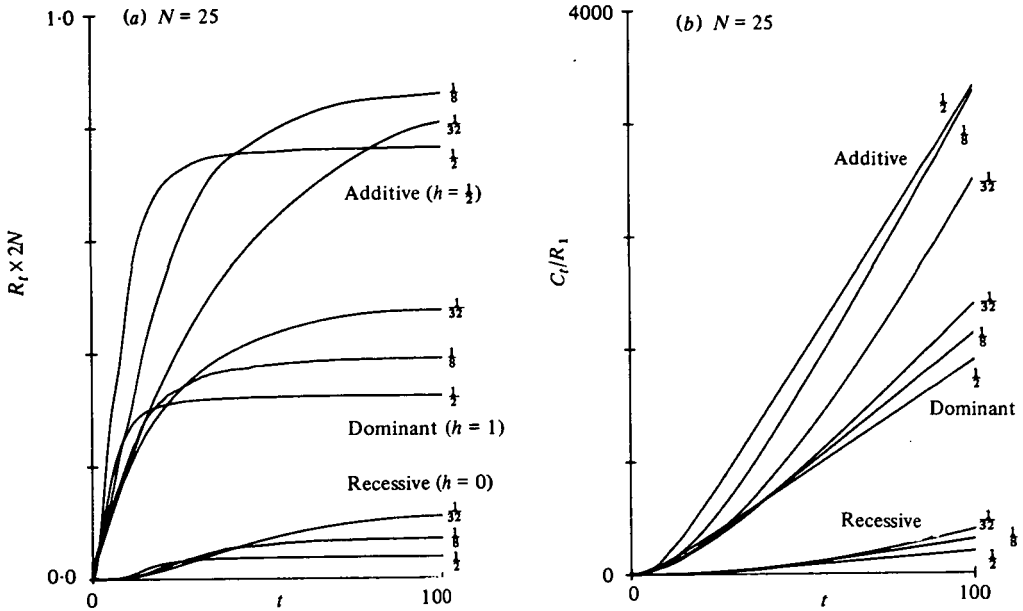


Fig. 5. Expected responses and cumulative responses from completely dominant and recessive mutants. Values are expressed (as Figs 1 and 3) relative to the response in one generation of dominant genes. The mutation rate for recessives is assumed to be the same. Mutant effects have a double gamma distribution and curves are for different σ_s values.

& Mather, 1954; Paxman, 1957), a procedure subsequently extended by Mukai *et al.* (1972) for analysis of mutant effects on fitness; by allowing mutations to accumulate in a random breeding population with subsequent selection to estimate variance (Clayton & Robertson, 1964); and from cumulative selection responses in initially inbred populations (other references in Table 2). All are summarized in Table 2, some on calculations given by the authors, others derived from the selection responses. In all cases these have been based on equation (6), by assuming that mutant effects were very small. Examination of Fig. 3 indicates that if a larger standard deviation of effects were assumed, the estimates of σ_M^2 would be smaller because responses up to a specific time, rather than asymptotic rates are being used. With the exception of Hollingdale & Barker's (1971) experiment, population sizes were rather small, so the estimate is less dependent on the values of σ_a^2 . The experiment of Mather & Wigan (1942) involved repeated subdivision of a line, so three estimates could be obtained.

Values in Table 2 are expressed as σ_M^2/σ_E^2 , where σ_E^2 is the environmental variance appropriate to the inbred line. The estimates range on either side, but not by far, of the value $\sigma_M^2/\sigma_E^2 \sim 10^{-3}$ initially suggested by Clayton & Robertson (1955) (although they obtained this as an 'upper limit' from their data) and obtained in a review of some of these values by Lande (1976). But of particular

Table 2. Estimates of σ_M^2/σ_E^2 (ratio of new mutational to environmental variance) for bristle number in *Drosophila melanogaster*

Authors	Method	Estimate $\sigma_M^2/\sigma_E^2 \times 10^{-3}$
	Abdominal bristles	
Durrant & Mather (1954)	Chromosome analysis	1.2
Paxman (1957)	Chromosome analysis	0.7*
Mather & Wigan (1942)	Selection response from inbred base for generation	
	0-17	1.1†
	18-34	2.2†
	35-53	1.1†
Clayton & Robertson (1955)	Selection response from inbred base	0.2‡
Kitagawa (1967)		
Hollingdale & Barker (1971)		
	Sternopleural bristles	
Durrant & Mather (1954)	Chromosome analysis	0.9
Paxman (1957)	Chromosome analysis	0.5*
Mather & Wigan (1942)	Selection response from inbred base	1.3
Clayton & Robertson (1964)	Selection in mass mated population from inbred base	0.4

Notes: estimates from inbred base using equation (5), i.e. assuming small gene effects.

* Estimate on one chromosome scaled by 2.5.

† Successive periods of splitting of lines.

‡ Figure of 1.0 published by Clayton & Robertson as 'upper limit'.

interest is that the values obtained from Mather & Wigan (1942), Kitagawa (1967) and Hollingdale & Barker (1971) also correspond. (Scossiroli & Scossiroli (1959) did not include an unselected control population, so no estimate of spontaneous rate can be obtained.) Mather & Wigan selected for a total of 53 generations for abdominal bristles and obtained such large responses, and jumps in response, that they concluded 'these jumps are due to the recombination of the mutations to which individual polygenes have given rise'. Examination of Fig. 4 suggests that occasional sampling of mutant genes of large effect will give such a pattern, especially in view of the fact that the effective population size was only 12 (three pairs and selection within families). Kitagawa (1967) and Hollingdale & Barker (1971), who selected for only 20 generations, obtained comparatively very small responses.

The general agreement (in view of the sampling error, e.g. Fig. 4) of the estimates obtained with and without selection lends some credence to the formulae being

used. They rely, however, on the assumptions that mutant effects are distributed approximately symmetrically around zero, such that $E^+(a^2) = \frac{1}{2}\sigma_a^2$, and that gene effects are additive. This seems a not unreasonable assumption for bristle number in *Drosophila*, which shows little non-additive genetic variance (Clayton, Morris & Robertson, 1957), and for which accumulation of mutants, either spontaneous or X-ray induced, leads to little change in mean (Clayton & Robertson, 1964). (For traits more closely associated with fitness, or for highly selected populations, these assumptions are less likely to hold, as we shall discuss later.) It is also possible to convert the arbitrary units used in Figs 1–5 into standard deviation units, or bristles. For example, with 20% selection $i = 1.4$, for sternopleural bristles $\sigma_E = 2$, approximately, and taking $\sigma_M^2/\sigma_G^2 = 10^{-3}$, the response in generation 1 is $R_1 = i(\sigma_M^2/\sigma_E^2)\sigma_E = 2.8 \times 10^{-3} \sim 3 \times 10^{-3}$ bristles. Therefore one unit in Figs 1–5 is equivalent to 3×10^{-3} bristles, i.e. 350 units/bristle, or 700 units/standard deviation.

The scale of change is also illustrated by considering the experiment of Hollingdale & Barker (1971) who used 50% selection ($i = 0.8$), 100 pairs of parents (say $N = 140$ to allow for variation in family size (Falconer, 1981, p. 66)) and abdominal bristle number with a phenotypic standard deviation of 1.8. The predicted response in generation 1 is 0.0014 bristles, too small to measure, the actual response observed by generation 20 was 0.27 bristles, but the predicted asymptotic rate is $140 \times 0.8 \times 1.8 \times 10^{-3} = 0.20$ bristles *per generation*.

Information on the distribution of mutant effects, even on the magnitude of σ_a , is essentially lacking. Estimates of the 'effective number of genes', whether based on Wright's formula (Falconer, 1981, p. 199), or on patterns of selection response (e.g. Roberts, 1966) generally have to assume that the genes have equal effect. This seems a quite unrealistic assumption. From analyses of recombinant chromosomes from selected lines of *Drosophila* it is possible to identify the effects of individual genes, more formally, of short segments of chromosome (Thoday, 1961). In such an analysis Shrimpton (1982) found values of a/σ up to about 1.8, with an increasing frequency down to $a/\sigma = 0.5$, below which there were substantial ascertainment problems. Of course, the estimates are based on pre-existing and new mutant genes, and are biased towards genes of large a/σ since these are most likely to be fixed, but suggest values of σ_a/σ in the range 0.25–0.5, the lower value corresponding to a more leptokurtic distribution.

(ii) Responses in segregating populations

It is clear that spontaneous mutation rates of $\sigma_M^2/\sigma_E^2 \sim 10^{-3}$, equivalent to an increase in heritability of 10^{-3} , have a trivial effect on response in early generations of selection in segregating or previously unselected populations, but presumably lead to responses later. This is illustrated in Fig. 6, appropriate for bristle number in *Drosophila* in which the population is assumed to have a heritability of 0.33, i.e. $\sigma_M^2/\sigma_G^2 = 2 \times 10^{-3}$, where σ_G^2 is the (additive) genetic variance. The previously segregating variance is assumed to be caused by genes with the same distribution

and variance of effect, σ_a^2 , and to have frequency uniformly distributed over the range 0 to 1. The phenotypic variance is assumed to remain constant, notwithstanding fixation and new mutations. The response due to initially segregating genes and the total response due to these and new mutants are shown separately. As predicted by Robertson's (1960) theory of limits, for specified initial variance the total response from genes segregating in the base population increases with

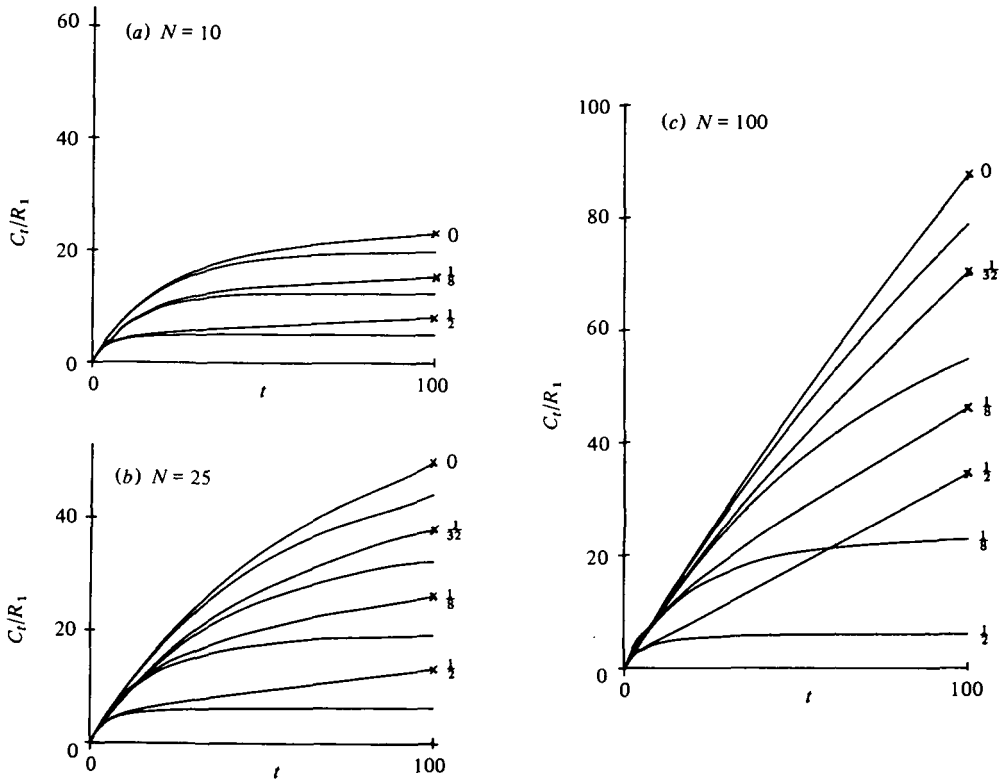


Fig. 6. Expected cumulative response from populations initially segregating (—) and from initial segregation together with new mutations (x—x). The standard deviation of selective value of existing and mutant genes is the same and shown on the figures for a range of values. Response is expressed relative to the response ($i\sigma_G^2/\sigma$) in the first generation. In each case $\sigma_M^2 = \sigma_G^2 \times 2 \times 10^{-3}$, where σ_G^2 is the initial additive genetic variance. Effects have a double gamma distribution; the distribution of gene frequency of initially segregating genes is uniform 0 to 1.

reduced variance of gene effect, because the range increases with the sum of gene effects, the initial variance with their sum of squares. Response from genes segregating in the base population also increases with population size, but with diminishing returns from ever greater sizes. The contribution from new mutants does not depend so much on σ_a , and always increases with increase in population

size, because more mutants occur with the same fixation probability. The overall pattern is therefore of very slow responses with small population sizes, such that when sampling of mutants and errors of estimates of mean are taken into account, plateaux are likely to be observed in many replicates, but in large populations plateaux are unlikely to be seen. Does this accord with practice, and if not, why not?

The most long-term applications of artificial selection have not, of course, been under controlled conditions, although the range of sizes of breeds of dogs illustrates the possibilities. Cob length in maize has increased at an almost linear rate for 7000 years in Mexico (Cavalli-Sforza & Feldman, 1981, p. 331), presumably largely due to genetic change.

In the experiment of Yoo (1980) with selection for up to 89 generations with 50 pairs of parents for abdominal bristle number in a scute stock of *D. melanogaster*, no plateau was reached in any replicate until about generation 80, when some replicates appeared to stop responding. The responses were almost linear over generations 50–80, at a rate of about 0.3 bristles per generation. The predicted rate, on the assumption that new mutants with symmetric effects were occurring at the rate of $\sigma_M^2/\sigma_E^2 = 10^{-3}$, $N = 70$ and $i = 1.4$ (20% selection) is 0.4 bristles per generation. This suggests that the calculation used previously for unselected, isogenic populations, can be carried forward to long-term selected populations, at least for bristle number in *Drosophila melanogaster*. Such analyses are complicated by scale effects, however, in that the standard deviation typically rises with mean, and a linear response can correspond to a declining heritability compensated by an increase in variance. This occurred in some of Yoo's lines.

There are other long-term experiments in which no plateaux have been reached (Dudley, 1976, for oil in corn) or have only been approached after long-continued selection (Enfield, 1980, for pupa weight in *Tribolium*). Yet there seem to be others, see e.g. Falconer (1981, pp. 194 et seq.) for a review, in which plateaux have been reached. How do these accord with any theory which at first sight predicts that responses proceed linearly for ever? There are a number of explanations.

(i) Responses have not actually reached a plateau, but the small changes are missed by sampling.

(ii) There is opposing natural selection, for example through a correlated change in fertility, as in small body weight lines of mice (Falconer, 1981, p. 197) or from segregation of a gene with large positive effect in the heterozygote, but lethal in the homozygote (Clayton & Robertson, 1957), such that effective population size is reduced and the variance is much inflated, so selection pressure on other genes is reduced.

(iii) The distribution of mutant effects after continued selection is such that no more useful mutants occur, i.e. all the positive mutants have already been fixed. Alternatively, all new mutants increasing the trait have a deleterious effect on fitness and are lost.

(iv) Some practical limit to response is being approached, for example no bristles in *Drosophila*, or one egg/day in chickens, such that positive mutants can have

little effect. Such a limit, or 'physiological limit' is really an alternative statement of point (iii).

Some answer to these questions, at least for *Drosophila*, could be obtained by analysing the distribution of mutant effects for a range of traits in unselected populations and for the selected trait in highly selected populations. It is reasonable to infer, as in the previous section, that bristle effects of mutants are symmetrically distributed in unselected populations, and that mutants' effects on fitness are necessarily negative, and have been shown to be so, by Mukai *et al.* (1972). There is no direct information about the distribution in selected populations, except for the continued linearity of response obtained by Yoo (1980). In practice it may be necessary to use mutagens to increase rates and enable analysis with limited facilities.

(iii) *Limitations of the analysis*

The analysis has been restricted in many ways. All mutants have been assumed unlinked, but analyses of the consequences of linkage on response in populations initially segregating in linkage equilibrium have shown the effects to be rather small (Robertson, 1970), particularly for species with many chromosomes. It would seem that, for diploid species, with new mutants of substantial effect occurring rarely, linkage is unlikely to be important; were we concerned with haploids the situation might be different (Maynard Smith, 1978). Nevertheless, some analysis is necessary.

A more interesting question, in view of our increasing knowledge of DNA structure, is how does the nature of mutational change influence predictions? There is evidence that changes in copy number at the rRNA tandon, or 'bobbed locus', can contribute to response for low bristle number in *Drosophila* (Frankham *et al.* 1978, 1980), and it is possible that such changes in copy number are a feature of selection response. There is yet no theory for predicting response in copy number from artificial selection and consequent changes in quantitative traits, although there exists a theory for random changes (Ohta, 1980). One-step changes, for example an initial duplication, are included in the theory for simple mutations, but subsequent multiple repeats would require some assumption of the relation between copy number and performance, and the selection response could not be predicted from the initial variance, σ_M^2 , created. There is evidence that many 'mutants' are due to insertion elements rather than base changes in *Drosophila* (Rubin *et al.* 1981), but provided these are reasonably stable it would seem that such mutations do not need to be handled in quantitative genetics any differently from conventional mutations caused by base substitutions.

Epistasis has also been ignored; but in the context of initially isogenic populations, few genes segregate for many generations, so epistatic interactions seem less important in determining the mutant's fate.

(iv) *Practical implications*

The theoretical analysis shows that mutations are likely to yield only small short-term responses, but in the long term can lead to large responses as the mutant

genes increase from their initial very low frequency. This theory, coupled with the review of experiments by Frankham (1980*a*), suggests that new mutants should not be ignored when considering long-term selection experiments or breeding programmes. The following are some of the possible implications in practice.

Population size and selection intensity

The asymptotic rate of response from new mutants is proportional to Ni , assuming they have no side effects on fitness, in contrast to the limit from existing variation when the limit is an increasing function of Ni , but typically (e.g. Fig. 6) of a diminishing returns form. Although the theory predicts proportionality of asymptotic response and population size, this becomes irrelevant as N becomes very large: the same mutants will recur and an infinite time will be taken to reach the asymptotic rate. Nevertheless, large populations may be justified and, if facilities (T) for animals are limited, the optimum proportion to select is 50%, which maximizes Ni for fixed T (Robertson, 1960). At first sight this is an anomalous result: at any time the *rate* of response is maximized by selecting at a rather low intensity; but this is a steady-state value: the response in the *next* generation is increased by more intense selection. If favourable mutants for the trait under selection have, on average, a deleterious effect on fitness, the asymptotic rate of response is maximized when fewer than 50% are selected, so in practice it seems better to use more intense selection.

Analyses of the relation between response and values of Ni from experiments are complicated by the dual contribution to response from pre-existing and new variation. Eisen (1980) in a review of data found that total selection response for post-weaning gain in mice increased linearly with Ni and suggested 'the need to re-evaluate aspects of selection limit theory which predict a curvilinear change'. Jones, Frankham & Barker (1968) plotted (their Fig. 6) the relation between response to 50 generations of selection for *Drosophila* bristle number against Ni ; although they present a curvilinear relationship it is apparent that a straight line would have fitted almost as well.

For experiments of only a few, say up to five generations, response is closely proportional to selection intensity (i) and not dependent on population size. For long-term experiments, say in excess of 30 generations, it appears that response becomes proportional to Ni although, as Fig. 6 indicates, the pattern depends on the distribution of gene effects.

Duration of experiments and programmes

It is also clear, for example from Fig. 3, that experiments designed to detect response from new mutants by selection must be continued for at least 20 generations to enable the mutants to contribute substantially to response. Experiments designed to detect spontaneous mutants or X-ray-induced mutants have typically been continued for only 20 or less generations (Clayton & Robertson,

1955; Scossiroli & Scossiroli, 1969; Kitagawa, 1967; Hollingdale & Barker, 1971). The theory suggests that their conclusions might have been quite different had they continued for longer periods.

The long time taken before new mutations contribute any substantial response, particularly when the variance of mutant effects is small and the population size is large, suggests that in modern breeding programmes for cattle and sheep only existing variation is likely to have been utilized so far. But in poultry there have been over 30 generations of continued selection and at least 20 in pigs. This suggests that some current improvement is coming from mutations subsequent to the start of the programmes; albeit progress may be slow, as for egg productions in poultry, but that may reflect the distribution of mutant effects and the circadian rhythm of the bird's egg-laying pattern. The theoretical analysis indicates that contributions from mutants should certainly not be ignored in the design of long term programmes.

(v) *Utilization of mutants*

Apart from emphasizing the role of population size, little attention has been given to optimizing procedures to utilize mutants. Essentially, because the mutant is initially unique, any procedure must maximize the probability of fixing useful mutants. For recessive genes the fixation probability can be improved by subdividing the population (Madalena & Hill, 1972): because the probability of fixation in any subline is proportional to \sqrt{N} , over all lines it is roughly proportional to the square root of the number of subpopulations. For additive genes subdivision is of no benefit (Robertson, 1960) and similarly for dominant genes which, when rare, behave as if they were additive. In view of the low probabilities of fixing recessives, even with subdivision, it is doubtful whether subdivision is justified.

Little benefit has accrued from induced mutagenesis in practical breeding. In animals this may be because the time scale was too short, in plants because the practice of inbreeding to produce new lines is a much less efficient procedure than the gradual accumulation of mutants by selection in large populations. If large selected synthetics are used as sources of inbred lines more might be achieved. There seems to be a need to reinvestigate the role of induced mutagenesis in the light of current theories, and also to consider mutagens other than X-rays with their consequent damage to chromosome structure.

If a new mutant has a very harmful effect on fitness, such as a lethal in *Drosophila* with effects in the heterozygote, it may be better to eliminate the gene and then reselect on the expectation of finding new mutants, rather than persisting. This approach to long-term selection, namely of waiting for more mutants, has other corollaries.

Bottlenecks of population size to a few individuals are predicted to reduce selection response, both in the short term and in the limit (Robertson, 1960; James, 1971). Experiments have been reviewed by Frankham (1980*b*) and these indicate

that short-term effects have been as predicted, but not long-term. The explanation suggested by Frankham and shown by the theory given here is that long-term responses derive largely from mutants occurring subsequent to the bottleneck. The practical conclusion is that long-term breeding programmes can be based on narrow populations provided the population size is large subsequently. Similarly, it is a moot point whether it is worth maintaining germ plasm resources with a view to eventual utilization rather than practising continued selection in commercial populations. If it would necessarily take many generations to utilize the stored population, it might be better to wait for mutants.

Conclusions

The theoretical foundations of this work are quite straightforward. The practical implications are more speculative and based almost entirely on data on bristle number in unselected populations of *Drosophila*. More data on different traits, selected populations and commercial species seem necessary before it is worth taking the theory much further. But there is already sufficient evidence to suggest that we should take mutation more seriously in designing our breeding programmes and consider not just how to utilize existing variation but how to obtain and utilize new variation.

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