The rate of polygenic mutation

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Summary

By application of the neutral model of phenotypic evolution, quantitative estimates of the rate of input of genetic variance by polygenic mutation can be extracted from divergence experiments as well as from the response of an inbred base population to selection. The analytical methods are illustrated through a survey of data on a diversity of organisms including *Drosophila*, *Tribolium*, mice, and several crop species. The mutational rate of introduction of genetic variance (V_m) scaled by the environmental variance (V_E) is shown to vary between populations, species, and characters with a range of approximately 10^{-4} to 5×10^{-2}. V_m/V_E for *Drosophila* viability is somewhat below this range, while hybrid dysgenesis may temporarily inflate V_m/V_E beyond 10^{-1}. Potential sources of bias and error in the estimation of V_m are discussed, as are the practical implications of the observed limits to V_m/V_E for projecting the long-term response to selection and for testing adaptational hypotheses.

1. Introduction

The rate of phenotypic evolution ultimately depends on the frequency at which new adaptive mutations arise. Little information exists on this phenomenon. The vast majority of studies on the mutation rate have involved major mutations with individually discernible and primarily deleterious effects. Mutations with small effects (often called micromutations, minor mutations, or polygenic mutations) are obviously less amenable to quantitative investigation and consequently have attracted little attention from empiricists. Yet there are a number of reasons to suspect that polygenic mutation plays an important role in the evolution of complex characters in natural populations.

Even when the fixation of a macromutation does result in a major evolutionary advance, fine-tuning of the polygenic background is likely to be essential for the persistence of a population in a variable environment. As an aggregate, polygenic mutations often appear at a much higher frequency than macromutations (Mukai, 1979), and some evidence suggests that the mutation rate varies inversely with mutational effect (Gregory, 1965). Unlike macro-mutations, mutations with small effects often arise in a non-directional manner, having little or no average effect on the mean of a character in an unselected base population (Oka *et al.* 1958; Gregory, 1965;

Hollingdale & Barker, 1971; Mukai *et al.* 1984). If the pleiotropic effects of mutant polygenes are also highly variable (and little information on this exists), then polygenic mutation would provide a potential mechanism for the evolution of adaptive suites of characters that is unlikely to be matched by macromutation.

Recent work based on fundamental principles of quantitative genetics has helped clarify the relationship between polygenic mutation and the evolutionary response to selection. In an early model, Kimura (1965) considered a character exposed to mutation and a selection function with fixed optimum and fitness declining with the squared deviation from the optimum. More recently, the case for characters exposed to Gaussian selection has been evaluated for sexual (Latter, 1970; Bulmer, 1972, 1980; Lande 1975; Barton, 1986; Barton & Turelli, 1987; Turelli, 1987) and for asexual and heterogonic life cycles (Lynch & Gabriel, 1983). Lande (1980) and Turelli (1985) have extended the analysis to multivariate evolution, while Hill (1982*a*, *b*), Keightley & Hill (1983), and Zeng & Hill (1986) have investigated the special case of truncation selection. Turelli (1984, 1986) provides a broad overview of the stabilizing selection theory and analyses its sensitivity to violation of the underlying assumptions; Felsenstein (1977, 1981) and Fleming (1979) also address the latter issue. Although variation exists between the quantitative

predictions of these studies, all are in agreement that mutation plays a significant role in determining the amount of genetic variance circulating in a population.

It is a major challenge to obtain quantitative estimates of the parameters underlying these models and to establish the degree to which they vary between species and characters. With respect to polygenic mutation there are three phenomena to consider at each locus: μ, the mutation rate, σ_a^2, the variance of mutational effects (effect being measured as one-half the deviation between the homozygous states of the mutant and original allele), and k, the degree of dominance of mutations. Except in the study of Hill (1982*a*), only the case of pure additivity of mutations ($k = 0.0$) has received much attention and epistasis has been ignored uniformly. Consequently, the composite parameter

$$V_m = 2 \sum_{i=1}^{n} \mu_i \sigma_{ai}^2, \qquad (1)$$

where n is the number of loci underlying the trait, plays a prominent role in much of the stabilizing (Latter, 1970; Lande, 1975; Fleming, 1979) and truncation (Hill, 1982*a*, *b*) selection theory. Turelli (1984), however, has made a clear case that depending upon the magnitude of selection, mutation rate per locus, and variance of mutational effects, the total mutation rate,

$$\lambda = 2 \sum_{i=1}^{n} \mu_i,$$

may be a more significant quantity from the standpoint of stabilizing selection than V_m (see also Latter, 1970; Bulmer, 1972, 1980).

Since the accurate domains of the Kimura–Lande–Fleming models and Latter–Bulmer–Turelli models are largely non-overlapping (Turelli, 1984), and since both sets of models are likely to be useful under some circumstances, it is premature to dismiss V_m as a relevant parameter in issues of stabilizing selection. Moreover, as pointed out by Hill (1982*a*, *b*), V_m is of significance in forecasting the outcome of long-term truncation selection programs; and it is V_m, not simply λ, which determines the rate of divergence of unselected characters (Chakraborty & Nei, 1982; Lynch & Hill, 1986).

My intentions here are to summarize existing data on the rate of polygenic mutation. I will begin by considering in some detail the manner in which estimates of V_m may be extracted from various laboratory and field experiments. Before proceeding, however, some clarification of the definition of the polygenic mutation rate is required.

2. Definition of V_m

Throughout the theoretical literature (Kimura, 1965; Latter, 1970; Lande, 1975; Chakraborty & Nei, 1982; Hill, 1982*a*, *b*) the rate of *input* of new genetic variance by polygenic mutation is defined as in equation (1) or as

$$V_m = 2n\mu\sigma_a^2 \qquad (2)$$

for the special case in which all loci are considered to have equivalent properties. An attractive feature of equations (1) and (2) is that V_m is independent of the total population size, N.

There are, however, problems in strictly defining V_m as the rate of *input* of new genetic variance via mutation. It may seem that such a definition ought only to involve first-generation mutations whose gene frequencies (and hence influences on the variance) have not been altered by random sampling drift. However, first-generation mutants have not yet segregated into the homozygous state; in the case of separate sexes, this requires two generations. The problem with a 'first generation' focused definition for the production of new genetic variance is most apparent for purely recessive mutations which have zero influence on the observed variance until they have segregated out. Only in the case of purely additive mutations is the first generation variance produced by new mutations equal to V_m [Lynch & Hill, 1986, equation (2)].

Thus, an accurate description of the rate of production of genetic variance by mutation needs to involve the effects of mutant alleles on the variance in their first generation of segregation. Once this point is accepted, however, then it is clear that the rate of production of genetic variance via mutation is not density-independent since, prior to segregation, the gene frequency moments will be altered by random drift.

For these reasons, it seems best simply to regard V_m as a fundamental quantitative genetic parameter which, in the special case of additive effects, becomes equivalent to the amount of new genetic variance introduced/generation via mutation. In the absence of drift and selection, V_m is the steady-state rate of increase in within-population variance regardless of the degree of dominance. In the absence of selection, $2V_m$ is the expected steady-state rate of increase of between-population variance regardless of population size and degree of dominance (Lynch & Hill, 1986).

The following analyses are performed under the assumption of additivity, and the traditional definition of V_m is relied upon. As will be discussed below, the assumption of additivity has empirical support for most of the studies cited, and extreme and unlikely deviations from this assumption would be necessary to alter significantly the major conclusions of this paper (Lynch & Hill, 1986).

For comparative purposes, it is useful to record the rate of polygenic mutation in dimensionless form. Generally, this is accomplished by dividing V_m by the environmental component of variance for the trait, V_E, a procedure that will be adhered to below. A conceptual advantage of such a scaling is that V_m/V_E

is approximately the expected heritability of an initially homozygous population following one generation of mutation. We may refer to this quantity as the mutational heritability. The usual precautions should be exercised in extrapolating scaled estimates of V_m since V_E may vary with experimental circumstances and with the degree of inbreeding.

3. Estimation of V_m

(i) Drosophila *bristle numbers*

Two types of experiments, both utilizing long-inbred stocks of *D. melanogaster*, provide an ample basis for estimating V_m for bristle number, a character known for its primarily additive genetic basis (Falconer, 1981). The first approach entails the analysis of selection responses in highly inbred lines and is best exemplified by an experiment of Mather & Wigan (1942). After maintaining a line by full-sib mating for 78 generations, Mather & Wigan (1942) relaxed the inbreeding and attempted to select for higher and lower bristle numbers. A response to truncation selection was observed in all of their experiments, the magnitude of response increasing with the experimental duration. Data on the progressive response of mean bristle number to upward and downward selection (Tables 1 and 2; Mather & Wigan, 1942) can be utilized to estimate V_m as follows.

Assuming no selection for bristle number in the initial inbred line, the expected genetic variance, var$(w,0)$, will represent a balance between the opposing forces of drift and mutation. Under full-sib mating the expected equilibrium is reached within ~ 15 generations (Lynch & Hill, 1986), and by use of Robertson's (1952) transition matrix is found to be $4V_m$ for additive mutations [Lynch & Hill, 1966, equation (21)]. During their selection experiments, Mather & Wigan allowed three single-pair matings each generation, each selected individual being the extreme of 20 measured sibs of its sex. Brother–sister matings were avoided intentionally, but there were a few unavoidable instances. Therefore, I have assumed the effective number of breeding adults to be 5 for the experimental period.

With such a small effective population size, random drift is the dominant force in the erosion of genetic variance, and as the population adjusts to the new N, the expected dynamics of var(w, t) will be closely approximated by a drift-mutation model. One simple model, first suggested by Clayton & Robertson (1955) for additive genes, is

$$E[\text{var}(w, t) \mid \text{var}(w, t-1)]$$
$$= \left(1 - \frac{1}{2N}\right)\text{var}(w, t-1) + V_m. \quad (3)$$

Although the random generation of linkage disequilibrium can temporarily cause the rate of erosion of genetic variance to deviate substantially from $[1 - (1/2N)]$, computer simulations of Bulmer (1976)

support the use of this expression for calculating the *expected* loss of genetic variance via random drift (see also Lynch & Hill, 1986). Lynch & Hill (1986) have shown that the Clayton–Robertson model consistently overestimates the expected genetic variance by a factor of $\sim (1/2N)$, an amount that is of negligible importance for large N but that can be an important consideration for N in the range of those for Mather & Wigan's (1942) experiment. Thus, in all of the following analyses, the more precise formulation of Lynch & Hill [1986; equation (29)] has been used. With the assistance of a computer, the latter model generates the expected dynamics of var(w, t) in terms of V_m given the effective population sizes before and after the transition. By equating observed and expected estimates of var(w, t), mutiple estimates of V_m are obtained. Although the model of Lynch & Hill (1986) was not formally derived for the extreme case of full-sib mating, it provides an excellent fit to those conditions if N is set equal to 2·33.

Under truncation selection, the additive genetic variance can be estimated by the rearrangement of the standard selection equation, var$(w, t) = [\Delta \bar{z}(t) \cdot V_T^{\frac{1}{2}}]/i$, where $\Delta \bar{z}$ is the change in mean phenotype, V_T is the phenotypic variance, and i, the standardized selection differential, is a function of the proportion of selected individuals (Falconer, 1981). For Mather & Wigan's experiment, $i = 1·867$. I used the mean of the upward and downward responses to selection in each generation as an estimate of $\Delta \bar{z}(t)$ and Mather & Wigan's measures of phenotypic variance in the inbred base population as estimates of V_T. In order to calculate V_m/V_E, V_E was estimated by subtracting the mean estimate of var(w, t) for Mather & Wigan's (1942) first experiment from their pooled estimate of V_T (their table 3) for the same experiment.

Mather & Wigan performed four selection experiments, one for sternopleural bristle number and three for abdominal bristle number. The upward-selected lines in the last two abdominal selection experiments were branched off from the initial downward-selected line at generations 17 and 34 and were treated as starting with levels of genetic variance predicted by equation (29) of Lynch & Hill (1986). The three estimates of V_m/V_E obtained for abdominal bristle number (0·0006, 0·0050, 0·0028) do not appear to be related to this change in genetic background, and their mean (0·0028) is similar to the single estimate for sternopleural bristles (0·0023). Several other bristle selection experiments with inbred *Drosophila* lines provide the information necessary to calculate V_m/V_E in the above manner (Table 1).

A second approach to estimating V_m in *Drosophila* takes advantage of the Curly/Plum marker technique and the lack of recombination in males to isolate second chromosomes on an isogenic background. The amount of genetic variance attributable to second chromosomes can be determined by performing a diallel cross and dividing the difference between

Table 1. *Survey of estimates of V_m/V_E for four characters in* Drosophila melanogaster. *S refers to selection on an inbred base population, C to chromosomal divergence.*

Trait	Method	V_m/V_E				Reference
		Mean	Range	S.D.	n	
Abdominal bristle number	S	0·0028	0·0006–0·0050	0·0022	3	Mather & Wigan (1942)
	S	0·0006	—	—	1	Clayton & Robertson (1955)
	S	0·0003	0·0001–0·0009	0·0003	6	Clayton & Robertson (1964)
	S	0·0034	0·0000–0·0102	0·0050	7	
	S	0·0006	—	—	1	Kitagawa (1967)
	S	0·0007	—	—	1	Hollingdale & Barker (1971)
	C	0·0016	0·0024–0·0041	0·0012	2	Durrant & Mather (1954)
	C	0·0017	—	—	1	Paxman (1957)
Sternopleural bristle number	S	0·0023	—	—	1	Mather & Wigan (1942)
	C	0·0034	0·0058–0·0077	0·0013	2	Durrant & Mather (1954)
	C	0·0008	—	—	1	Paxman (1957)
Viability	C	0·00004	—	—	1	Mukai (1964)
	C	0·00003	0·00001–0·000 06	0·00003	3	Mukai et al. (1972)
	C	0·00001	—	—	1	Cardellino & Mukai (1975)
	C	0·00002	—	—	1	Ohnishi (1977a)
ADH activity	C	0·0006	0·000 59–0·000 65	0·00004	2	Mukai et al. (1984)

chromosome and error mean square by twice the number of times that the chromosome appeared in the assay. By these means, Durrant & Mather (1954) and Paxman (1957) were able to establish the amount of genetic variance for bristle number in the Oregon line of *D. melanogaster* after 300 and 400 generations of continuous full-sib mating. Prior to the two experiments reported by Durrant & Mather (1954), full-sib mating was relaxed for an average of 2·5 and 8 generations and var (w) was assumed to be equal to $6·5V_m$ and $12V_m$ respectively. Paxman (1957) reports a pooled analysis of variance for second chromosomes that were allowed to diverge via spontaneous mutation for an average of 34 generations, and I assumed var (w) = $38V_m$ at the time of the diallel cross. In order to scale var (w) estimates for second chromosomes to the entire genome, I multiplied by 2·5 based on observations that the second chromosome constitutes approximately 40% of the *Drosophila* genome. Estimates of V_E for these experiments were obtained by summing chromosomal and error sums of squares and dividing by the total degrees of freedom to obtain an estimate of V_T free of sex and block effects, subtracting the estimate of var (w), and multiplying by 10 to account for the usage of means of 10 measures. This procedure yielded estimates of V_E that averaged twice as high as the estimates derived from the previously cited selection experiments. This was possibly because of the confounding of background genetic variation in the experiment of Durrant &

Mather (1954) but not in Paxman (1957) for which the genetic background was randomized. Since both chromosomal studies yielded similar estimates of V_E, these estimates were used. The resultant estimates of V_m/V_E are quite comparable to those derived from selection experiments (Table 1).

Some small differences exist among the V_m/V_E estimates obtained for *Drosophila* bristle numbers by myself, Lande (1975), and Hill (1982b), most likely because of slightly different approaches and rounding errors, but in general we are in good agreement. The 11 independent estimates have a mean and standard deviation equal to 0·0017 and 0·0012.

(ii) Drosophila *viability*

Another series of mutation-accumulation experiments involves polygenes encoding for viability in *Drosophila melanogaster*. By use of the Curly/Plum marker technique, several investigators have isolated initially identical second chromosomes into different sublines, allowed them to diverge by spontaneous mutation with a minimum of selection, and then periodically determined their viability properties using a standard assay developed by Wallace (1956). As expected in the absence of selection, the temporal increase in genetic variance for viability of quasi-normal lines (those with viabilities > ~ 60% of that expected for second chromosomes without mutations) is generally linear. A parameter recorded in all of the viability mutation

studies is ΔV, the average increase in genetic variance for *homozygous* second chromosomes per generation. (The scale on which V is measured varies between studies.) Since mutant viability alleles act in an additive fashion (Mukai & Yamazaki, 1964, 1968; Ohnishi, 1977*b*; Mukai & Nagano, 1983) and the second chromosome constitutes approximately 40% of the *Drosophila* genome, $5\Delta V/2$ is an approximate measure of $4n\mu\sigma_a^2$ for the entire genome. Dividing by 2, we then have an estimate of V_m as in equation (2). All estimates of V_E were obtained by multiplying the variance of replicate means (within chromosomal lines) by the number of flies assayed/replicate. As an estimate of V_E in Mukai *et al.* (1972) and Cardellino & Mukai (1975), I used the mean of the individual estimates provided in Mukai (1964), Mukai *et al.* (1982), and Mukai & Nagano (1983), after conversion to the appropriate scale by Taylor expansion. The average within-line mean square from Ohnishi (1977*b*) was used to compute V_E for Ohnishi (1977*a*).

All of the resultant estimates of V_m/V_E for viability are certainly too low since they do not include mutations of major effects and since the environmental variance estimates, based on within-line variance, are potentially inflated by the existence of any genetic variance for viability in the marker strain. Nevertheless, the average of the four independent estimates of V_m/V_E for viability in Table 1, 0·000025 (S.D. = 0·000013) is nearly two orders of magnitude less than that for bristle numbers. Given that mutational properties are subject to modification by natural selection, it is perhaps not surprising that V_m/V_E for viability, a major fitness component, should be relatively low. A fifth estimate for viability obtained from Mukai & Yamazaki (1968) but not included in Table 1 is anomalously high ($V_m/V_E = 0·00061$). While this estimate was obtained with the same set of lines employed by Mukai (1964) that yielded an estimate of $V_m/V_E = 0·00004$, it was measured after a much greater period of chromosomal divergence. All of the estimates of V_m are expected to be quite accurate since most of the cited studies involved assays of approximately 10^6 flies.

Yoshimaru & Mukai (1985) have shown that the pleiotropic effects of viability mutations on development time are very great, the genetic correlation being nearly 1·0. The reported data, however, do not allow a computation of V_m/V_E for the latter character.

(iii) Drosophila *ADH activity*

A final result of interest for *D. melanogaster* concerns the activity of alcohol dehydrogenase (ADH). Using essentially the same procedures as described above for the experiments with viability polygenes, Mukai *et al.* (1984) performed an analysis of variance of second chromosomes in an isogenic background after 300 generations of divergence. Two experiments were run, each initiated with a different wild and marker

chromosome. Significant between-line variance was detected in both experiments. The authors convincingly demonstrated that the variation was unlikely to be a product of structural gene mutations and argued for the modification of ADH activity by multiple factors in non-coding regions.

The ADH assays were performed on Cy/+ heterozygotes on an isogenic genetic background. Therefore, I took the between-line variance of the experimental populations to be an estimate of $(300 \times \frac{2}{5} V_m$. The error mean square, multiplied by 10 to account for pooling in individual assays, was taken to be the estimate of V_E. The two estimates of V_m/V_E for ADH activity are in excellent agreement with each other and are intermediate to those for viability and bristle numbers (Table 1).

(iv) Tribolium *pupal weight*

Goodwill & Enfield (1971) successfully selected for 21-day pupal weight in two highly inbred lines of *Tribolium castaneum* (CSI-5 and CSI-10). Prior to selection both lines had passed through 46 generations of single full-sib matings. The fact that 13 additional generations of full-sib mating in CSI-10 did not result in a depression of genetic variance is consistent with these populations being in approximate drift-mutation equilibrium with var$(w) = 4V_m$. Two-way selection was imposed on both sexes in each population for 17 generations. During this period, each selected male was randomly mated with 3–5 selected females. The number of selected individuals varied somewhat each generation, but the population size was maintained at 40–50 full-sib families. Assuming a mean male:female ratio of 1/4 and an average of 45 females, the effective population size estimated by $4N_mN_f/(N_m+N_f)$ is 36. This is similar to the estimate ($N_e = 30$) that the authors provide without explanation (p. 11; Goodwill & Enfield, 1971). Accepting the latter estimate, the expected dynamics of genetic variance generated by equation (29) of Lynch & Hill (1986) yield an expected mean genetic variance over the 17 generations of selection of $10·5V_m$.

In their tables 4 and 5 the authors provide two heritability estimates pooled over sexes and selection directions for three experiments. The first estimate is based on the regression of cumulative selection response on cumulative selection differential, the second on parent–offspring and sib analyses. For the six data sets, I estimated var(w) by h^2V_T and V_E by $(1-h^2)V_T$. The average phenotypic standard deviations $(\sqrt{V_T})$ for lines CSI-5 and CSI-10 over 17 generations are approximately 225 and 250 respectively (Figures 1 and 2; Goodwill & Enfield, 1971). The four estimates of V_m/V_E obtained for line CSI-10 (0·0100, 0·0100, 0·0134, 0·0183) are substantially higher than those for line CSI-5 (0·0028, 0·0000) for unknown reasons. These yield a pooled estimate of V_m/V_E for *Tribolium* pupal weight of 0·0091 ±0·0034.

More recent work on the CSI-5 line (Enfield, 1987) yields estimates of $V_m/V_E = 0.001$, consistent with my derivations from the earlier work on this line.

(v) Mouse *skeletal traits*

In order to maintain as uniform a genetic background as possible for biomedical research, many laboratory strains of mice have been maintained by brother–sister mating for decades. Several such strains have been subdivided periodically and the sublines extended by further brother–sister mating. Two studies involving continuously distributed skeletal characteristics have been performed to quantify the rate of divergence of such sublines.

Baily (1959) performed a nested analysis of variance on four skull measures and lengths of the ulna and ilium of two sublines from the C57BL/6 and BALB/cAn strains. Prior to subdivision, the two strains had been maintained by full-sib mating for 30 and 78 generations respectively. The sublines were also maintained by single full-sib matings (D. Bailey, pers. comm.) and were allowed to diverge for an average of 46.5 and 9 generations respectively. Bailey (1959) detected significant subline divergence (within strains) in 8 of 12 comparisons. Since the effective population size of the original lines and the derived sublines was stable for a long period, the expected genetic variance between sublines after t generations of divergence is simply $2V_m t$ (Lande, 1976; Chakraborty & Nei, 1982; Lynch & Hill, 1986). The sum of the variances between individuals within litters and between litters within mothers provides an estimate of $(V_E + 4V_m)$. The data suggest that V_m/V_E for skull metrics (0.0046 ± 0.0015) is lower than that for lengths of limb bones (ilium: 0.0158 ± 0.0105; ulna: 0.0311 ± 0.0192), there being almost no overlap between the two types of characters (Table 2).

Festing (1973) performed a multivariate analysis of variance on 13 linear measures of the mandibles of specimens from nine British sublines of strain C57BL/

Gr. Ten of the characters were found to vary significantly between sublines. The ancestral strain had been full-sib mated for at least 40 generations prior to its subdivision and the subsequent pedigree is well-known (Deol *et al.* 1957; Yong, 1972). Table 1 in Festing (1973) contains the phenotypic means ($\bar{z}$) of the 13 characters for each of the nine strains as well as the pooled within-subline standard deviations ($MS_w^{\frac{1}{2}}$). The square of the latter provides an estimate of $(V_E + 4V_m)$. For any two sublines, the between-subline variance, var($\bar{z}$) can be estimated by analysis of variance as $[(\bar{z}_1 - \bar{z}_2)^2/2] - [2MS_w/(n_1 + n_2)]$, where n_1 and n_2 are the sample sizes for the two populations. From the nine sublines, 36 estimates of var($\bar{z}$) were made for each character, and then regressed on the respective divergence times. The expected value of the slope of such a regression is $2V_m$. Following these procedures, the mean value of V_m/V_E ($\pm$ S.E.) obtained for the thirteen mandible traits (0.0231 ± 0.0065) appears to be significantly greater than the previous estimates for the skull but is of the same order as that for limb bones.

A second set of studies with inbred mice has involved discontinuous skeletal characteristics. Such traits are believed to be dependent upon an underlying continuous variable that is influenced by mutiple loci and that, upon reaching a critical threshold, produces the variant (Gruneberg, 1955; Falconer, 1981). Using the same sublines that were studied by Festing (1973) plus three American sublines, Carpenter *et al.* (1957), Deol *et al.* (1957), and Yong (1972) have recorded the incidences of 25 skull variants. Sample size were on the order of 100–200 for most sublines. Assuming the underlying distribution to be standard normal, then the variance within populations can be equated to $1 = V_E + 4V_m$. The incidence of the trait can be transformed into the deviation of the mean phenotype on the underlying scale from the threshold, x_p, by use of approximation (26.2.23) in Abramowitz & Stegun (1972). An unbiased estimate of the variance between any two sublines is then $[(x_{p1} - x_{p2})^2/2] - [2/(n_1 + n_2)]$,

Table 2. *Survey of estimates of* V_m/V_E *for skeletal traits of inbred lines of mice*

Trait	V_m/V_E Mean	Range	S.D.	n	Reference
Skull measures (metric)	0.0046	0.0000–0.0118	0.0039	8	Bailey (1959)
Skull measures (threshold)	0.0057	0.0000–0.0426	0.0088	25	Carpenter *et al.* (1957), Deol *et al.* (1957), Yong (1972)
Mandible measures	0.0231	0.00004–0.0716	0.0235	13	Festing (1973)
Ilium length	0.0158	0.0084–0.0233	0.0105	2	Bailey (1959)
Ulna length	0.0311	0.0175–0.0447	0.0192	2	Bailey (1959)

the expectation of which is $2tV_m$. This quantity was estimated for all 66 possible pairs of sublines, the divergence times for which varied widely, and then regressed on t to obtain an estimate of $2V_m$. V_m/V_E was then equated to $V_m/(1-4V_m)$. The mean estimates of V_m/V_E for metric and threshold skull characters are not significantly different (Table 2).

(vi) Daphnia *life history traits*

Obligately asexual organisms provide a useful opportunity for measuring the rate of polygenic mutation since the random drift that normally accompanies the sampling of gametes is not a factor and since divergence between lines cannot possibly be caused by segregation of residual heterozygosity. For such organisms, however, the mutational variance cannot be dissected into its additive and dominance components. Experimental and statistical procedures for measuring V_m with divergent clones are outlined in Lynch (1985) where 11 estimates of V_m/V_E for a lineage of *Daphnia pulex* are presented for life-history characters (several of which are pleiotropically constrained). The mean value of V_m/V_E for that study, 0·0017 ($s.d. = 0·0010$), is on the order of that observed for spontaneous mutations for bristle number in *Drosophila*.

(vii) *Corn vegetative and reproductive traits*

Utilizing several long-time (> 10 generation) inbred lines of corn, Russell *et al.* (1963) performed a lengthy mutation–accumulation experiment that provides information on V_m/V_E for nine polygenic traits. During the experiment each line was maintained by selfing ($N = 1$) with a minimum of selection (only ears with > 150 seeds were utilized) and subdivided each generation, thereby resulting in 16 sublines/line in the fifth generation. In order to eliminate year-to-year variation in environmental effects, seed stored from each generation was simultaneously grown for the final analysis of variance. Pooled estimates of the total genetic variance between sublines for each character

(Table 4; Russell *et al.* 1963) exhibit pronounced and approximately linear increases for generations 2–5.

The interpretation of the dynamics of the variance between sublines is somewhat complicated under the dichotomous branching scheme because many pairs of sublines are not independent and the degree of independence varies depending on the position in the hierarchy. Taking this covariance structure into consideration, it can be shown that the variance between sublines after t generations of branching has expectation

$$E[\text{var}(\bar{z}, t)] = 2V_m\left[t - 2^{t-1}\sum_{x=1}^{t-1}2^x(2^t\text{-}1)\right],$$

so at the 2, 4, 8, and 16 subline stages, $E[\text{var}(\bar{z}, t)] = 2·00V_m$, $3·33V_m$, $4·86V_m$, and $6·53V_m$. For the experiment of Russell *et al.* (1963), a pooled estimate of V_m was obtained by equating the four observed $\text{var}(\bar{z}, t)$ with their expectations and averaging the individual estimates of V_m. The error variances of plot means given by Russell *et al.* (1963) have expectations of $(V_E + 2V_m)/10$. The nine resultant estimates of V_m/V_E for vegetative and reproductive characters have an average of 0·008 (Table 3).

An additional set of conservative estimates of V_m/V_E for these same characters can be derived from a divergence experiment performed on doubled haploid strains of corn (initially homozygous at all loci) (Sprague *et al.* 1960). The experimental design was basically the same as that of Russell *et al.* (1963), but instead of performing an analysis of variance, the authors detected mutants by t test comparisons (0·05% significance level) of the mean phenotypes of individuals and their ancestors. Differences that were detected at one point in a pedigree but later disappeared (possibly due to segregation and drift) were not included in these mutation rate estimates. Thus, the reported estimates of the mutation rate are too low since they primarily include mutations of relatively large effects that became fixed. With this in mind, an average of 0·060 (range 0·032–0·088) mutations/attribute/gamete ($n\mu$ in the notation of equation (2)) was detected. This compares favourably

Table 3. *Survey of V_m/V_E for vegetative and reproductive characters in plants*

	Mean	Range	S.D.	n	Reference
Barley	0·0001	0·0000–0·0004	0·0002	8	Cox *et al.* (1987)
Corn	0·0078	0·0031–0·0192	0·0054	9	Russell *et al.* (1963)
	> 0·0024	0·0012–0·0034	0·0009	9	Sprague *et al.* (1960)
Rice	0·0028	0·0015–0·0038	0·0017	2	Oka *et al.* (1958)
	0·0034	0·0018–0·0056	0·0014	6	Sakai & Suzuki (1964)

with an estimate of 0·064 obtained in the study of Russell et al. (1963).

Lande (1975) suggested how such incidence measures might be used to compute a minimum estimate of V_m/V_E. Let V_w be the within-line variance. Then, in units of $\sqrt{V_w}$, the minimum detectable difference between two samples of equal size n is $\bar{z}_1 - \bar{z}_2 = t_{0·05} [2V_w/n]^{\frac{1}{2}}$. In the experiment of Sprague et al. (1960), 100 seeds were sown for each plant, so $t_{0·05} = 1·982$, and the minimum value of $\bar{z}_1 - \bar{z}_2$ that would be recorded as a mutation was $0·280 \sqrt{V_w}$. If it is assumed that mutants were only detected in the homozygous state, then $(0·280\sqrt{V_w}/2)^2 = 0·0196 V_w$ provides a lower bound for the variance of mutational effects, σ_a^2. Substituting into equation (2) and dividing by V_w, which will be approximately V_E for a selfed line, we obtain $V_m/V_E > 0·0392 \ (n\mu)$. Based on these computations, it appears that the mean V_m/V_E can be no less than 0·0024. The two types of studies are therefore in rough accord.

(viii) Barley biomass and grain yield

Cox et al. (1987) recently completed an experiment with three inbred lines of barley grown at two nutrient levels following the design of Russell et al. (1963) In their table 3, the authors record successive variance components for new sublines within lines. The expectation of each of these is $2V_m$. The sampling variance of mean phenotypes is reported in Table 2 (Cox et al. 1987) as Error (b); multiplication of these by the sample size (30) generates estimates of V_E. The resultant estimates of V_m/V_E for biomass (0·0001 and 0·0004) and grain ($< 0·0001$ and 0·0004) yield are quite low, the higher estimates arising under low nutrient conditions. Grain yield behaved erratically, its total genetic variance remaining stable for the first five generations and then increasing dramatically in generation 6 under both nutrient conditions. Two additional characters, plant height and 100-kernel weight, exhibited no genetic variation, at least not enough to prompt the authors to publish the results.

(ix) Rice vegetative and reproductive traits

Data on the control of an irradiation experiment provide two estimates of V_m/V_E for the self-fertilizing Oryza sativa (rice) (Oka et al. 1958). A 'pure line' obtained by repeated self-fertilization of a single plant formed the base population. Prior to analysis the plants were propagated in bulk for four generations. Assuming the genetic variance of the base population to be in drift-mutation equilibrium, then from equation (11) of Lynch & Hill (1986) var $(w, 0) = 1·5V_m$, and the expected genetic variance for the unselected population in the fifth generation is $[1·5 + (5 \times 2)] V_m = 11·5V_m$. At that time the authors grew 75 families in 3 subplots with 10 plants/family in each subplot and performed an analysis of variance

on family means for two traits (heading data and plant height). For each character I estimated $(V_E + 1·5V_m)$ by multiplying the error mean square (Table 2; Oka et al. 1958) by 10. The between-family variance was obtained by equating the mean squares to the expectations and provided an estimate of $10V_m$. The resultant estimates of V_m/V_E for heading data and plant height are 0·0038 and 0·0015. There are reasons to suspect that these are underestimates, since prior to analysis, an unknown number of recognizable deviants (dwarfs, etc.) were intentionally discarded.

The control of another irradiation experiment performed by Sakai & Suzuki (1964) provides the basis for several estimates of V_m/V_E of a less reliable nature. The commerical breed of rice, described as 'almost completely self-fertilizing', was separated into 160 lines each of which was subsequently maintained as a single plant for four generations. In their table 3, the authors provide estimates of genetic and environmental variance for six vegetative and reproductive traits in the fourth-generation plants. A more appropriate description of the reported environmental variance is $(V_E + 1·5V_m)/12$, since the analysis was performed on means of 12 family members. The expected genetic (between-family) variance in generation 4 is $8V_m$. The mean estimate of V_m/V_E over six characters is not significantly different from that of Oka et al. (1958) (Table 3).

4. Discussion

It is important to be cognizant of factors that could result in biased estimates of V_m in the preceding computations. I have operated under the assumption of perfect additivity of new mutations. Based on the properties of complex biochemical pathways, Kacser & Burns (1981) present an argument for why this might be so for genes of small effect; and as noted above, the assumption does not appear to be unreasonable for bristle number and viability mutations in Drosophila. It is not possible to draw any inferences about dominance effects in the Daphnia study since the clone was an obligate parthenogen (Lynch, 1985), and I am aware of no pertinent data for the mouse skeletal traits, the rice or barley attributes, or several of the maize characters. However, Enfield et al. (1966) suggest partial dominance in the direction of higher pupal weight in Tribolium; letting $\bar{k} = 0$ denote perfect additivity, $\bar{k} = 1$ complete dominance, and $\bar{k} = -1$ complete recessivity, their results indicate $\bar{k}$ is between 0·1 and 0·5. Data from Moll et al. (1964) provide estimates of $\bar{k}$ for four of the maize characters analysed above: grain yield (1·4), ear diameter ($-0·1$), ear length (0·5), and plant height ($-0·2$). These estimates may in part be an artifact of linkage disequilibrium. Thus, with the possible exception of grain yield in corn, the existing evidence suggests that the alleles underlying the traits focused

upon in this paper exhibit partial dominance approaching additivity.

This is not an entirely satisfactory answer to the question of dominance since the properties of new mutations may differ from those of alleles that are well-established in a population. Nevertheless, even if mutant polygenes do tend to be non-additive, most of the computations presented above would not be influenced greatly. For divergence experiments in which the base population is in drift-mutation equilibrium and the lines are maintained at the same effective population size, the expected rate of increase in between-line variance is $2V_m$ regardless of the level of dominance (Lynch & Hill, 1986). This result arises because only the homozygous effects of alleles contribute to the development of between-lines variance as new mutations ultimately become fixed or lost. Thus, an experiment of the form utilized by Russell *et al.* (1963) is a useful design when one is interested in measuring V_m, i.e. the variance due to homozygous effects of mutant alleles.

When selection experiments are used to estimate V_m, dominance becomes a more serious problem. The dominance properties of mutant alleles have a direct influence on the additive component of genetic variance which in turn determines the response to selection (Falconer, 1981). Relative to the case for additive mutations, the additive genetic variance is inflated two-fold when new mutations are completely dominant, and variance in the level of dominance results in a further inflation by a factor of approximately $2\sigma_k^2/3$ (Lynch & Hill, 1986). On the other hand, recessivity of new mutations ($\bar{k} < 0$) results in a reduction of the additive component of variance (by approximately 40 % for complete recessives). Thus, depending upon whether new mutations are dominant or recessive in the direction of selection, V_m may be over- or underestimated when it is calculated from the realized heritabilities of selection experiments. Since the genes underlying *Drosophila* bristle numbers tend to be additive, the estimation of V_m for this trait from the selection response does not seem inappropriate and indeed does not give greatly different results than divergence experiments (Table 1). However, given the results of Enfield *et al.* (1966), it is possible that my estimate of V_m for 21-day pupal weight in *Tribolium* using the selection results of Goodwill & Enfield (1971) may be inflated.

Another reason for concern with the data analysed above is the potential existence of residual heterozygosity (in excess of that expected for drift-mutation equilibrium) in some of the inbred lines. It is well-known that heterozygote superiority can result in a balanced polymorphism in infinitely large populations. However, in small populations, selection for heterozygotes can at best reduce the rate of fixation and under a range of circumstances may even enhance the fixation process relative to completely neutral alleles (Robertson, 1962). While I have provided

arguments against the presence of excess heterozygosity in the inbred lines that I have analysed above, to avoid any possibility of such a problem in the future, attempts to measure V_m might start with lines that are known with certainty to contain no heterotically-maintained genetic variance. Doubled haploid plants are logical candidates (Sprague *et al.* 1960; Lange, 1971; Deaton *et al.* 1982).

On the other hand, in the estimation of V_m it is not necessarily desirable to start with a completely homozygous base population since, for example, the simple rule that the variance of population mean phenotypes increases at the rate $2V_m$ applies only to populations in drift-mutation equilibrium. The initial divergence rate of lines derived from a homozygous base will be less than $2V_m$ by an amount that depends on the effective population size (Lynch & Hill, 1986). Failure to correct for the departure from this equilibrium assumption will result in underestimates of V_m whenever the effective size of the initial population is smaller than that of the divergent lines.

Selection is always a potential source of bias in estimates of V_m. It is difficult to quantify the magnitude of such bias but it will usually be in the downward direction. A conflict between stabilizing natural selection and directional artificial selection will result in underestimates of V_m/V_E derived from long-term selection experiments. Stabilizing selection will also reduce the rate of divergence of 'unselected' lines. The problem will be minimized if the effective sizes of lines are kept as small as possible so that the force of random genetic drift is large relative to that of selection, but such a procedure has the negative aspect of increasing the probability of loss of extreme lines.

Consideration also needs to be given to the inherent difficulties in measuring V_m due to the random production of mutations. For replicate populations in drift-mutation equilibrium, the coefficient of variation of var (w) is approximately $[(4Nn\mu)^{-1} + (2/3N) - n^{-1}]^{\frac{1}{2}}$ for mutations with normally distributed effects (Lynch & Hill, 1986). If a large number of loci contribute to the character so $(4n\mu) \simeq 1$ and $n \gg N$, this is very roughly $(2/N)^{\frac{1}{2}}$. Thus, for small laboratory populations ($N < 10$), the standard error of V_m based on L replicate analyses of the within-population variance is on the order of $V_m\sqrt{(2/NL)}$ or larger. This ignores the additional variation that can arise from measurement error, maternal effects, etc. For mutations with normally distributed effects, the standard error of V_m based on between-lines variance is essentially independent of the effective population size of the lines and of the divergence time, and equal to $V_m\sqrt{(2/L)}$ (Lynch & Hill, 1986). Thus, when the divergence is assayed for only two lines, the standard error will be on the order of V_m. Since these computations involve only the variance in the realization of the drift-mutation process and do not

include sampling variance on the part of the investigator, it is clear that the inaccuracies in estimates of V_m are not trivial.

Since Lande (1975) first suggested that $V_m/V_E \simeq 10^{-3}$ for a variety of species and characters, reference to this figure has frequently been made in the literature (Franklin, 1980; Hill, 1982 a, b; Lynch & Gabriel, 1983; Turelli, 1984). However, in light of the preceding analyses, the general application of this estimate may be questioned. Considerable variation for V_m/V_E appears to exist between species, populations, and characters. The only generalization possible is that, with the exception of viability mutations, V_m/V_E is almost always within the range of 10^{-4} to 5×10^{-2}.

Occasionally, rates of polygenic mutation may even exceed $V_m/V_E \simeq 5 \times 10^{-2}$. Mackay (1985, 1986, 1987, 1988) and Yukuhiro et al. (1985) have documented that the enhancement of transposon acitivity in dysgenic cultures of *Drosophila melanogaster* is associated with greatly elevated rates of mutation for genes affecting many quantitative traits. For abdominal and sternopleural bristle number, the results of selection and mutation accumulation experiments consistently indicate that $V_m/V_E \simeq 0.1-0.2$ during periods of hybrid dysgenesis (Mackay, 1985, 1987, 1988). This is an approximately 100-fold inflation above the spontaneous rate and even greatly exceeds rates computed from X-ray induced lines (Mackay, 1987). In a study of a P-element-bearing but non-dysgenic strain, Mackay (1988) found a threefold inflation of V_m/V_E over the normal rate, further supporting the idea that V_m is a function of the genetic background.

Despite a potential range to V_m/V_E of three orders of magnitude, a knowledge of these limits may be of some practical use. For example, Hill (1982 a) has argued that the response to truncation selection will ultimately approach $\Delta \bar{z} = (2NV_m) i/\sqrt{V_T}$ as the utilizable genetic variance from the base population becomes exhausted. This may be rewritten as $\Delta \bar{z} = 2Ni(V_m/V_E)/[(1+2NV_m/V_E)/V_E]^{\frac{1}{2}}$. Taking 10^{-4} as the lower limit to V_m/V_E and $i \simeq 2$ for 5% truncation selection, then the lower limit to the asymptotic selection response is $0.0004N/[(1+0.0002N)/V_E]^{\frac{1}{2}}$. The data for V_m/V_E in Table 3 suggest that substantially higher expectations may be reasonable for many crop species. Thus, if conventional selection programs can be applied to large outbred populations, considerable advance due to new mutations can be anticipated. A doubling in N, the number of selected individuals, will magnify the asymptotic response by a factor of $\sqrt{2}$ (for large N) to 2 (for small N).

As discussed in the introduction, V_m is also a central element in the neutral model of phenotypic evolution. Such models are needed for the resolution of a number of problems in palaeontology and evolutionary ecology (Lande, 1976; Gould, 1980; Charlesworth et al. 1982; Reyment, 1983). In comparing the mean phenotypes of isolated populations or species, it is often assumed that the observed differences are adaptive. If the divergence time (t generations) of the lineage is known, the validity of such an assumption can be explicitly tested by reference to the expectation that the between-line variance is $2V_m t$ for neutral characters. Taking $5V_E \times 10^{-2}$ to be the upper limit to V_m and noting that $V_E < V_T$, then observed levels of var$(\bar{z})$ that are significantly greater than $0.1 V_T t$ can be taken as evidence of significant diversifying selection on the lineages. Provided the phenotypic expression of the isolated lineages has not been differentially affected by the environment, this test requires only phenotypic data. By similar reasoning, measures of var$(\bar{z})$ that are significantly less than $0.0002V_E t$ can be taken as support of stabilizing or convergent selection on the isolates. This leaves a range in var$(\bar{z})$ of approximately three orders of magnitude that is consistent with neutral expectations.

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