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A computer simulation evaluation of the role of mutations in finite populations on the response to directional selection: The generations required to attain maximum genetic variance

M. D. Li and F. D. Enfield

Department of Genetics and Cell Biology, 270 Bioscience Center, University of Minnesota St Paul, MN 55108, USA

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Summary. The role of mutations in finite populations on response to artificial selection was investigated by a computer simulation model designed to mimic the biological model of pupal weight of *Tribolium*. Given the model, the results showed that with selection about 25–55 generations were needed for genetic variances to reach a maximum value depending on population size, selection intensity, and gene number. When effective population size was larger than 40 or the intensity of selection was high (less than 50% selected), selection had a dramatic effect in reducing the time to approach the maximum point of genetic variance. Furthermore, the genetic variance after that point often declined as a function of selection instead of remaining at a steady state in the subsequent generations.

Key words. Mutations – Selection – Generation – *Tribolium* – Simulation

Introduction

The papers of Hill (1982a, b) and subsequent papers from the Edinburgh group (Keightley and Hill 1983, 1987, 1989; Hill and Rasbash 1986a, b; Hill and Keightley 1988; Lynch and Hill 1986) have generated considerable renewed interest in the role of new mutations as a source of quantitative genetic variation that can contribute to response to directional selection. As a follow-up to several long-term selection experiments in our laboratory that were designed to study the nature of quantitative genetic variation for pupa weight in *Tribolium* (Katz and Enfield 1977; Kaufman et al. 1977; Enfield 1980; Enfield and Braskerud 1989), we now have underway a new set of experiments to test the importance of new mutations and effective population size on the accumulation of genetic variance. In designing these experiments we have resorted to the use of computer simulation to address several questions that have been raised by the theoretical expectations of the Hill papers (1982a, b). It should be emphasized that the simulation is not a direct test of the Hill theory since, in most cases, different assumptions have been employed. In the simulation we have chosen to model pupa weight in *Tribolium* since we have more than 20 years of experimental data on this trait and it is the trait of choice in the new experiments.

One of the intuitively troublesome aspects of the Hill theory is that selection per se has no effect on the asymptotic rate of response ultimately attained in the balance between mutational variance and effective population size. A primary question we addressed in the simulation deals with the impact of selection on the accumulation of genetic variance when gene number is large but finite. In other words, when does the average effect of a new mutation become large enough that drift is not the only driving force in the distribution of allelic frequencies if the population is under directional selection? We have also focused on the time frame required, with and without selection, for the accumulation of significant genetic variance from mutation since this has a direct bearing on how important new mutations might be in the life of a plant or animal improvement program. It is also a significant question in the interpretation of laboratory selection experiments that would rarely be carried until an asymptote is reached.

Methods

The model of population structure and breeding programs underlying the simulation used in this study is somewhat similar to

Correspondence to: F. D. Enfield

the experimental schemes of Enfield (1986), and of Enfield and Braskerud (1989) for pupa weight in *Tribolium*. All of the initial parameters used in this study were determined from a series of experimental reports from this laboratory in past years (Comstock and Enfield 1981; Enfield 1986; Enfield and Braskerud 1989). Each individual in a population was assumed to have n loci that determined its genotypic value according to the mode of gene action for those loci. All loci in the simulation results to be reported are additive in their effects and unlinked. Every individual in the foundation population of any replication is homozygous for those genes affecting pupa weight; that is, there is no genetic variance present in the base population, and all genetic variance in the following generations is the result of new mutations. The phenotypic value of an individual is the sum of genotypic values for each locus and a normally distributed environmental effect with mean zero and a variance (V_e) of 40,000 (Comstock and Enfield 1981). Because all individuals in the foundation population are homozygous for genes affecting the trait, the phenotypic variance, therefore, is equal to the environmental variance.

Each replication was initiated at generation zero from a homozygous foundation population with T individuals. N individuals were chosen from those T individuals to be parents for the next generation by either truncation or random selection depending on a selection or no selection (control) model. Either directional selection or random selection was continued for t generations. In any generation, all N individuals were assigned randomly to be either males or females with an equal number $N/2$ offspring of each sex. $2T/N$ gametes were produced by every individual. For every gamete, all genes were allowed to mutate according to the probability of a mutation, i.e., 10^{-5}. If there was a mutation, the genetic effect of the new allele was assigned a value based on a given distribution of gene effects. It was randomly assigned a positive or negative sign. Thus, all mutation effects had a symmetrical distribution around zero. Each male was mated randomly to a female, and a total of $2T/N$ offspring were produced from such a mating by a random combination of male gametes with female gametes. A total of T individuals was produced and used as the base population for next generation.

The first implementation of the simulation was tested on a very small population so that a trace could be made using selective outputs of the data structures. The program was constructed usign stepwise refinement, tested after each refinement, and generally followed the assumptions for the Hill model in terms of the *Tribolium* data except that a finite number of genes affecting the trait was considered (Hill 1982a, b). The next group of tests consisted of replication of a subset of Lynch and Hill (1986) simulations. These served as a foundation check as well as verification (replication) of their experiments.

The statistics of genetic variance (V_G), phenotypic variance (V_p), cumulative response summed over all generations (CR), realized response per generation (R), estimated heritability (h^2), and realized heritability ($r(h^2)$) were computed for each generation. Only the cumulative response, realized response per generation, and genetic variance are reported in this paper. For figures given in the paper, the data points were the mean of those statistics for every five generations. The time (change point) required to attain maximum genetic variance for all cases in this study was estimated using Quandt's (1958) method. His model is:

$$Y_i = \begin{cases} a_1 + b_1 X_i + e_{1,i} & i = 1, 2, \ldots\ldots, k \\ a_2 + b_2 X_i + e_{2,i} & i = k+1, \ldots\ldots, n \end{cases}$$

where the error variances are permitted to change. The $e_{1,i}$'s are independent, identical, and normally distributed with mean zero and variance s_1^2. The $e_{2,i}$'s have the same properties except that the variance is s_2^2. The likelihood ratio statistic L* for testing H_0 of no change point in the regression regime against H_1 of one change point at an unknown position is:

$$L^* = (S^2_{1,k^*}/S^2_{1,n})^{k^*/2} (S^2_{k^*+1,n}/S^2_{1,n})^{n-k^*/2}$$

where k* maximizes the likelihood ratio statistic,

$$L_k = (S^2_{1,k}/S^2_{1,n})^{k/2} (S^2_{k+1,n}/S^2_{1,n})^{n-k/2}$$

In addition, the following parameters were given consideration before every run.

The estimates of mutational variance (V_m) for pupa weight of *Tribolium* ranged from 8 to 49 (measured in micrograms) depending on the assumptions made concerning the effective population sizes that had been maintained in the population cages (Enfield and Braskerud 1989). The initial parameters for different distributions of gene effects were determined first by the statistical properties of corresponding distributions and then repeatedly adjusted based on the pre-simulation results of more than 30 replications so that a reasonable mutational variance could be generated for all considered cases.

Since mutation rate (μ) was set to be 10^{-5} and a mutant occurred very rarely, the results varied significantly for different replications. In order to have an accurate assessment of these simulation results, many replications were required. The number of replications required were determined based on the patterns of response as well as on changes in genetic variance over generations. If there was no clear trend for a specific pattern over time, the number of replicates was increased.

Three different distributions (i.e. Normal, Uniform and double Gamma) were simulated. With the double Gamma distribution, major mutant effects having values of more than $\alpha\beta + 3V_m$ were deleted. The reason for this restriction was that there was not any indication of major mutations occurring from our long-term selection experiments on pupa weight of *Tribolium*. Although such a limitation on the mutant gene effect existed, it should not affect the conclusions drawn from this study, because there were only a very few times that a mutant with a very large effect was deleted during the simulation. There was very little difference observed among these three distributions in terms of the patterns of response and genetic variances. Therefore, even though the true distribution of mutant effects is not known, this does not seem to be an important factor, given the symmetrical distributions that were evaluated. Although the choice of distribution of gene effects is arbitrary, it has been suggested that the double Gamma distribution is a proper distribution for gene effects because it has a suitable range of properties (Hill and Rasbash 1986a). Thus, we have chosen the double Gamma distribution of mutant gene effects in all simulations in this paper. The density function of a Gamma distribution is

$$f(a) = a^{\alpha-1} e^{-a\beta} / \Gamma(\alpha) \beta^{\alpha}$$

where $\Gamma(\alpha)$ is the Gamma function. Its moments are $E(a) = \alpha\beta$, $V(a) = \alpha\beta^2$. The parameter α is the shape parameter, and β is the scale parameter. The effect of every mutant is mainly determined by the shape parameter of the Gamma distribution.

The empirical standard error was an important parameter in determining the number of replications required in this study. Generally speaking, the amount of replication for every case was adequate to address all considered questions. Empirical standard errors were calculated for a given output for every generation and pooled for the five generation sets.

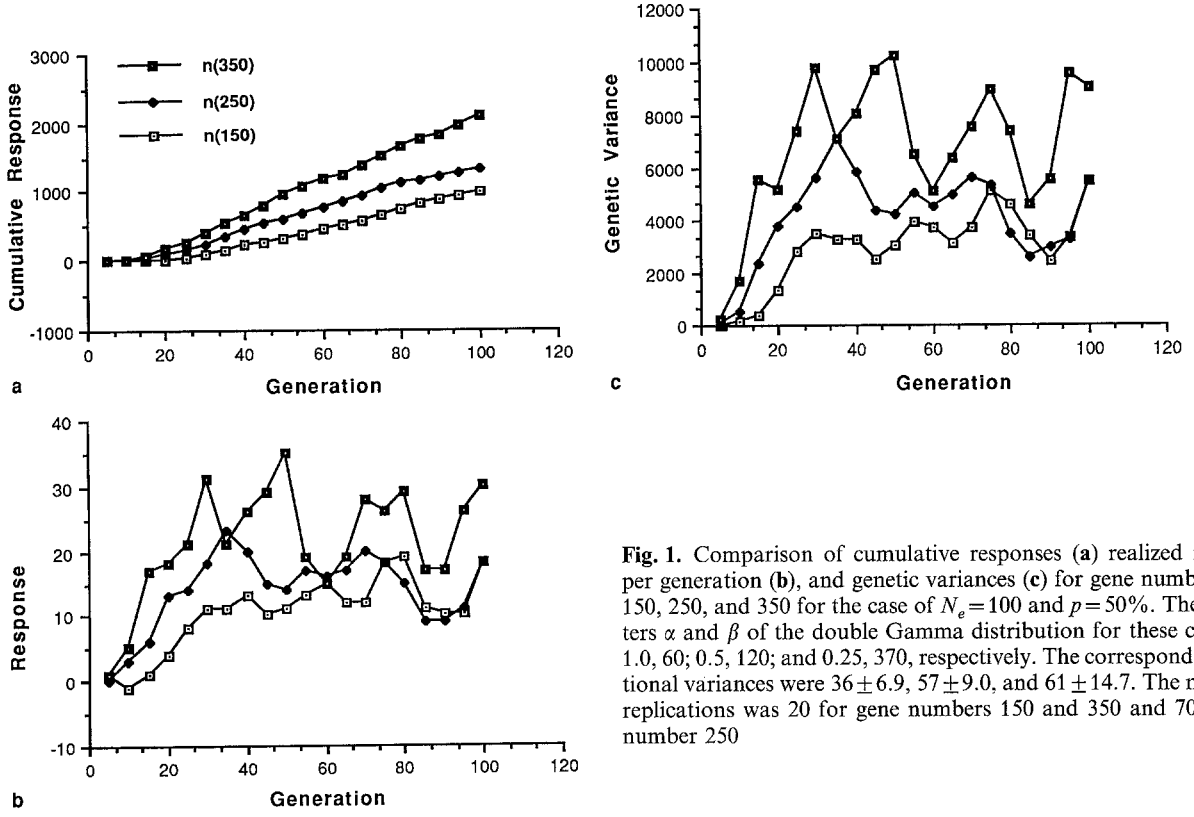

Fig. 1. Comparison of cumulative responses (**a**) realized responses per generation (**b**), and genetic variances (**c**) for gene numbers (n) of 150, 250, and 350 for the case of $N_e = 100$ and $p = 50\%$. The parameters α and β of the double Gamma distribution for these cases were 1.0, 60; 0.5, 120; and 0.25, 370, respectively. The corresponding mutational variances were 36 ± 6.9, 57 ± 9.0, and 61 ± 14.7. The number of replications was 20 for gene numbers 150 and 350 and 70 for gene number 250

Results and discussion

Gene number (n)

One important question in quantitative genetics that has persisted since the early development of the science concerns the number of genes affecting quantitative traits. While there is likely a great deal of variation in gene number from trait to trait the question remains whether some important measures of phenotype are affected in a significant way by genes numbering in the dozens to hundreds. By conventional selection procedures, directional selection will potentially lead to a much greater change in mean phenotype when variation is due to many genes with small effects rather than a few genes of large effects given the same amount of initial additive genetic variation. On the basis of the response patterns of long-term selection experiments for a diversity of organisms from plants to animals (Dudley 1977; Enfield 1980; Yoo 1980; Bell 1981), one can infer that many genes with small effects affect those quantitative traits. For example, the gene numbers for pupa weight of *Tribolium* were estimated to be 150–450 depending upon the assumptions made for the models (Comstock and Enfield 1981). In our simulation a constant mutational variance was used, while gene numbers that could affect the trait were varied. For the case of variable gene number, the effective population size was set at 100 and the fraction selected was 50%. Generally speaking, as the number of genes affecting a trait is increased, each mutation will have a smaller effect, on average, and vice versa. This rule was realized by arbitrarily changing the shape parameter (α) of the double Gamma distribution in this study. When the gene number for pupa weight was assumed to be 150, 250, and 350, the parameter α was assigned to be 1.0, 0.5 and 0.25, respectively. To generate a constant mutational variance for those three cases, the scale parameter (β) of the double Gamma distribution also had to be adjusted based on the pre-simulation results with many replications such that equal or very similar mutational variances (i.e., statistically non-significant at $P < 0.05$) could be produced for those cases. The final values of parameter β were 60, 120, and 370 for gene numbers of 150, 250, and 350, respectively.

Figure 1 presents the results of 20 replications for gene numbers of 150 and 350, and 70 replications for a gene number of 250. Figure 1 a and b shows the patterns of average cumulative responses as well as realized responses for every five generations, and Fig. 1 c shows the average genetic variances for every five generations for these three cases. The average mutational variances for gene numbers of 150, 250, and 350 were 36, 57, and 61, respectively, and were not significantly different from each other at $P < 0.10$ (data not shown). The differences in genetic variances for these three cases after the maximum point in the population was reached were largely a function of mutational variances. Based on Quandt's

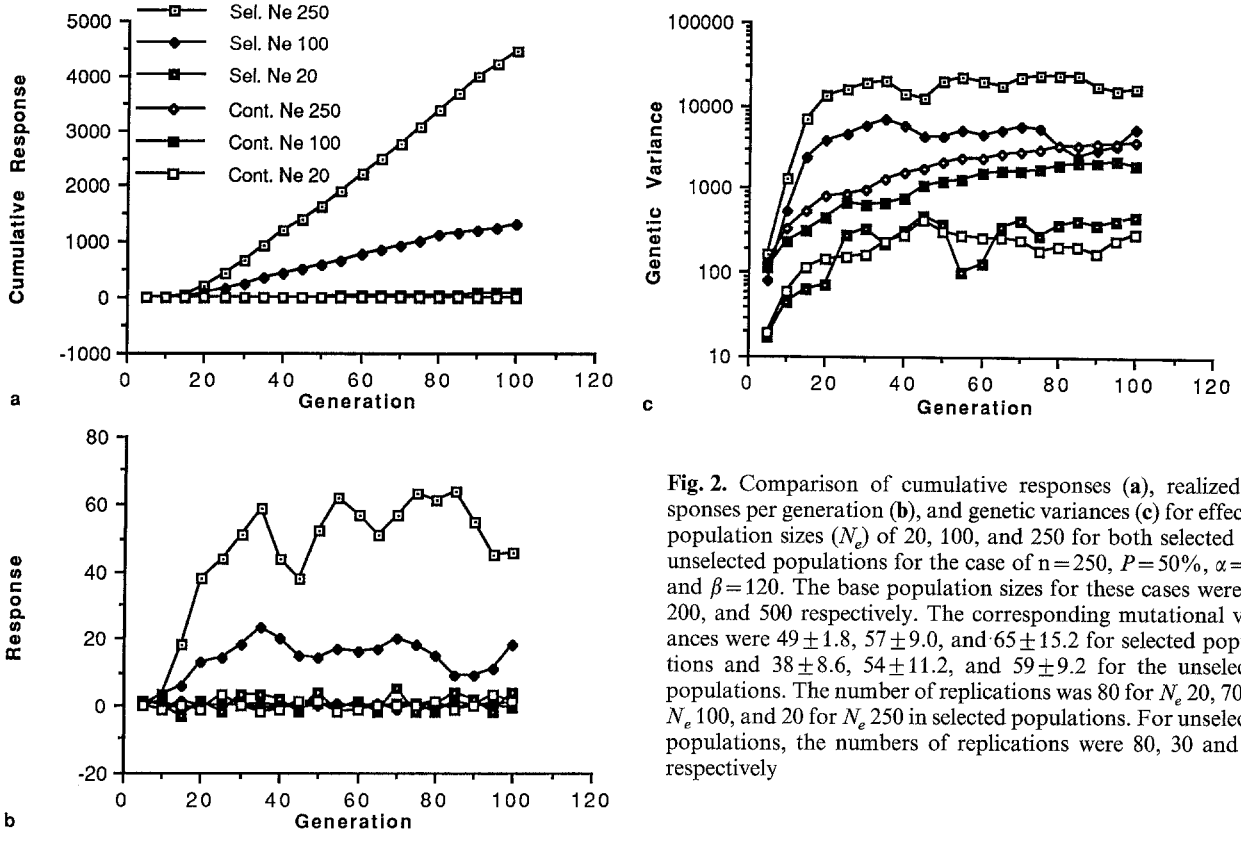

Fig. 2. Comparison of cumulative responses (**a**), realized responses per generation (**b**), and genetic variances (**c**) for effective population sizes (N_e) of 20, 100, and 250 for both selected and unselected populations for the case of n=250, $P=50\%$, $\alpha=0.5$ and $\beta=120$. The base population sizes for these cases were 40, 200, and 500 respectively. The corresponding mutational variances were 49 ± 1.8, 57 ± 9.0, and 65 ± 15.2 for selected populations and 38 ± 8.6, 54 ± 11.2, and 59 ± 9.2 for the unselected populations. The number of replications was 80 for N_e 20, 70 for N_e 100, and 20 for N_e 250 in selected populations. For unselected populations, the numbers of replications were 80, 30 and 25, respectively

model, it was expected that about 30, 35, and 50 generations were needed for populations with gene numbers of 150, 250, and 350, respectively, to reach the maximum point of genetic variance. This implies that more generations will be required for genetic variance to reach a maximum state if the traits are controlled by many genes with small effects. In other words, gene number is an important factor in determining time frame for a selection experiment when evaluating the importance of mutation effects.

Effective population size (N_e)

Effective population sizes of 20, 100, and 250 were simulated for both selected and unselected populations for a gene number of 250 and 50% selection. The parameters α and β of the double Gamma distribution were the same for different population sizes because mutational variance was assumed independent of population size (Lande 1976; Clayton and Robertson 1964; Hill 1982a). The results of average cumulative response, realized response, and genetic variance over every five generations for these six populations are given in Fig. 2. The number of replications were 80, 70, and 20 for selected population sizes of 20, 100 and 250, respectively, and 80, 30, and 25 for corresponding unselected populations. As expected, the smaller the population size, the greater the replicate variance and thus the need for increased replications.

There were very significant differences among the patterns of cumulative response, realized response per generation, and genetic variance for these selected populations. The differences were small for the first few generations, but after that the differences became obvious for the different population sizes. Approximately 30, 35, and 55 generations were needed for genetic variances to approach the maximum points for the selected population sizes of 20, 100, and 250, respectively. The genetic variance after the maximum point in the populations was directly proportional to the population size for both selected and unselected populations (see Fig. 2c). This result was consistent with Hill's model that equilibrium genetic variance is directly related to effective population size.

Hill's results indicated that equilibrium genetic variances for a given effective population size should be the same with or without selection. Our simulation showed that these predictions hold better for the smaller population sizes than for the larger populations within the simulated 100 generations. For example, the results were almost the same for population 20 with and without selection, but were very different for populations 250 and 100. Lynch and Hill (1986) have shown theoretically that 1.4 N_e generations are required for the genetic variance to reach half of the equilibrium genetic variance in a neutral population. Based on the fact that the genetic

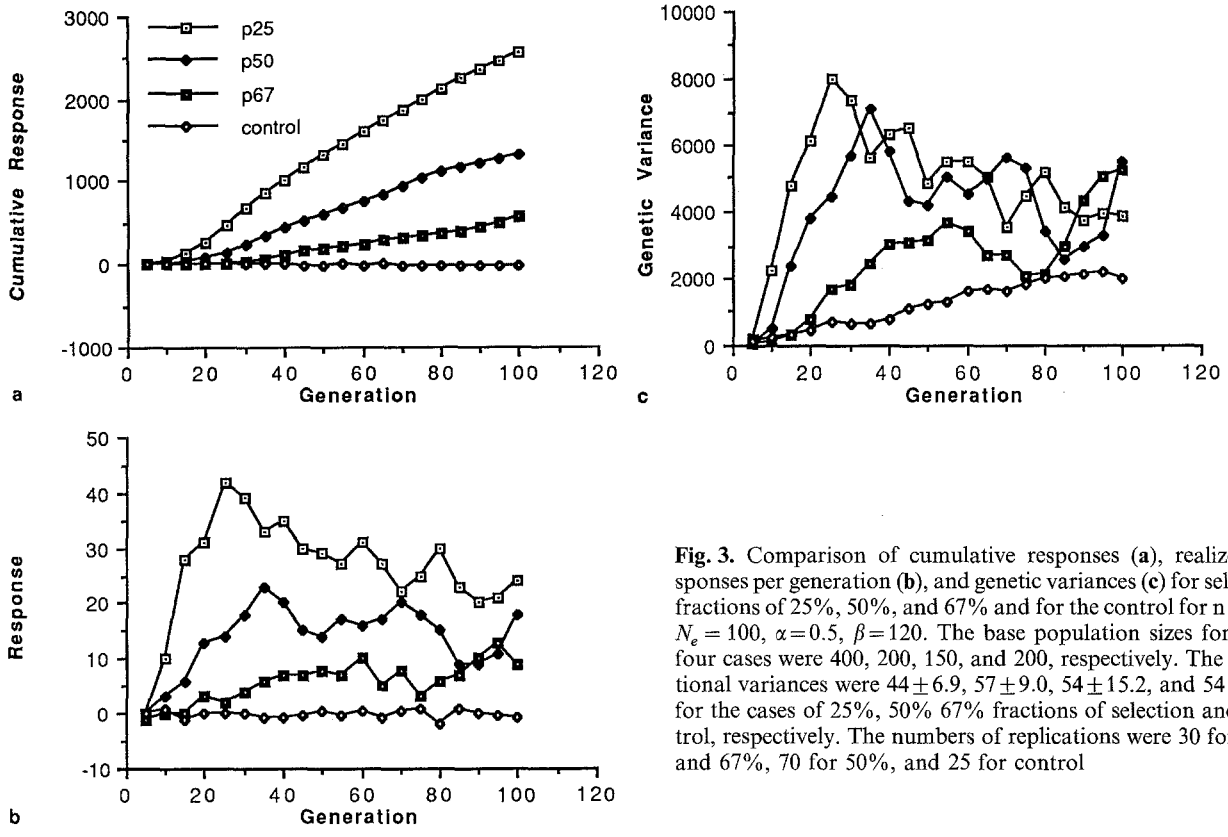

Fig. 3. Comparison of cumulative responses (**a**), realized responses per generation (**b**), and genetic variances (**c**) for selection fractions of 25%, 50%, and 67% and for the control for n = 250, $N_e = 100$, $\alpha = 0.5$, $\beta = 120$. The base population sizes for these four cases were 400, 200, 150, and 200, respectively. The mutational variances were 44 ± 6.9, 57 ± 9.0, 54 ± 15.2, and 54 ± 11.2 for the cases of 25%, 50% 67% fractions of selection and control, respectively. The numbers of replications were 30 for 25% and 67%, 70 for 50%, and 25 for control

variances in the unselected population sizes of 100 and 250 increased slowly with time, they may have become more similar (with and without selection) after a very long time period, but we can not be sure at the moment since only 100 generations were simulated. It is very clear, however, in terms of population sizes 100 and 250 that selection had a significant effect on the changes of genetic variances within our simulated time frame (see Fig. 2c). In other words, because of a faster approach toward q = 0.5 when genetic variance is maximum, selection greatly enhanced the rate of increase in genetic variance in populations where the effects of selection were not overwhelmed by drift.

Considering the patterns of realized response per generation as well as cumulative response for those selected and non-selected populations, there were very significant differences for populations 100 and 250. There were no significant differences for cumulative response between selected and unselected populations of size 20 over many generations, however, and this was probably indirect proof for Robertson's limited selection theory (Robertson 1960) where small population size was one of the basic and critical assumptions (Fig. 2a). The reason for this may be that the favorable mutations did not have enough opportunity to accumulate such that they cannot become the major force for creating new genetic variances after selection has started.

Fraction selected (p)

In the preceding section we have noted that selection had a very significant effect on the time required to attain equilibrium genetic variance. The next question we addressed was whether the time required to attain maximum genetic variance was a function of selection intensities. The issue of selection was not well explored in the original Hill papers (1982a, b), but we think it to be one of the major issues that has an impact on the general relevancy of the Hill model to biological populations.

Three different selection fractions, 25%, 50%, 67%, and one randomly selected control were simulated for the case of effective population size of 100 and gene number of 250. To show clearly the effects of selection and simplify conditions, effective population size was held constant for these three experiments so that different fractions of selection for the same N_e could be implemented by only changing the base population size (T). The base population sizes for the fractions of selection 25%, 50%, 67% were 400, 200, and 150, respectively. A randomly selected population of 100 individuals from 200 served as the unselected control. The parameters α and β of the double Gamma were 0.5 and 120 for all populations. The replication numbers were 30 for both 25% and 67%, 80 for 50%, and 25 for the randomly selected control.

Average cumulative responses, realized responses per generation, and genetic variances over every five genera-

tions for these experiments are given in Fig. 3. As expected, the cumulative responses differed significantly as the fraction of selection was varied (see Fig. 3a); the stronger the selection intensity (lower selection proportion), the larger the cumulative responses. The patterns of realized response per generation and genetic variances were quite similar for the cases of 25% and 50% but were very different for the cases of 25% and 67%.

To examine the effect of different selection intensities on genetic variances over generations, the genetic variance data were split into two parts based on the patterns given in Fig. 3c. Regression equations for different generation sets are summarized in Table 1. For the strongest selection fraction of 25% both realized responses per generation and genetic variances showed almost linear increases for the first 25 generations, after which they had a very significant decrease as selection continued within the simulated period of time. In the case of 50% selection, realized response per generation and genetic variance increased linearly for the first 35 generations after which both decreased, although not as dramatically as for 25% selection (see Table 1). With the weak selection of 67%, about 55 generations were required for both the realized response per generation and genetic variance to reach a maximum point, after which there was no significant decrease. It should be emphasized that the term maximum point of genetic variance instead of the equilibrium genetic variance is used here because there is no apparent equilibrium state.

Based on the definition, if genetic variance attains an equilibrium state it should remain constant in subsequent generations. Equilibrium did not appear to be the case for the selection fractions of 25% and 50%. At lower selection fractions (e.g., 67%) the loss of genetic variance from fixation due to selection had less impact. This was in contrast with Hill's results, indicating that when selection was strong and mutant effects large, a steady state was not attained. Therefore, his results may not apply for strong selection with finite gene numbers. For the control population, there was no indication that the population had attained a maximum point within the simulated 100 generations.

Table 1. Regression equations for change in genetic variances per generation of selection for fractions selected

Fraction selected	Generation (t)	Regression equation	*t*-value	Probability (*P*)
p25	1– 25	$Vg = -1610.3 + 391.58\,t$	18.929	0.0003
	25–100	$Vg = 8256.8 - 48.58\,t$	6.773	0.0001
p50	1– 35	$Vg = -1332.4 + 238.38\,t$	19.47	0.0001
	35–100	$Vg = 6920.0 - 34.04\,t$	2.408	0.033
p67	1– 55	$Vg = -551.3 + 79.59\,t$	16.636	0.0001
	55–100	$Vg = 262.2 + 40.83\,t$	1.887	0.0959
Control	1–100	$Vg = 7.8 + 23.25\,t$	24.495	0.0001

Table 2. Comparison of observed with expected V_G

Experiment		r	$V_m \pm$SE	t	R	V_G	$V_G/E(V_G)$
150[a]	Observed	20	36±6.9	30	13.04±0.67	3,640±110	
	Experimental				26.45	7,200	0.51
250	Observed	70	57±8.97	35	15.49±0.65	4,466±136	
	Experimental				40.13	11,400	0.39
350	Observed	20	61±14.7	50	22.88±1.09	7,059±256	
	Experimental				42.61	12,200	0.58
20[b]	Observed	80	49±1.8	30	1.27±0.80	338±15	
	Experimental				8.24	2,120	0.16
100	Observed	70	57±8.97	35	15.49±0.65	4,466±136	
	Experimental				40.13	11,400	0.39
250	Observed	20	65±15.2	55	55.65±1.20	20,192±435	
	Experimental				96.32	32,500	0.62
25%[c]	Observed	30	44±6.94	25	27.79±0.82	5,078±164	
	Experimental				50.63	8,800	0.58
50%	Observed	70	57±8.97	35	15.49±0.65	4,466±136	
	Experimental				40.13	11,400	0.39
67%	Observed	30	54±15.2	55	7.96±1.17	3,409±167	
	Experimental				25.78	10,800	0.32

Abbreviations: r, Replications; t, generations required to approach the maximum genetic variance; V_m, mutational variance mean; R, realized response; V_G average of genetic variance after maximum point; $E(V_G)$, the expected equilibrium genetic variance from Hill's equation

[a] Gene number

[b] Effective population size

[c] Fraction selected

Since there were many variables in our model, factors were considered one at a time and other factors were held constant for each run such that the effect of any variable on the model could be well explored. The results for the cases discussed above are summarized in Table 2. The mutational variance (V_m), realized response per generation (R), and genetic variance (V_G) shown in this table were computed from the average of all those replications for the corresponding parameters. The mutational variance of every replicate was determined following exactly the definition given by Hill (1982a). As shown earlier, both realized response per generation and genetic variance showed a linear increase with time for the first 30–50 generations, then reached a maximum point (for the cases of strong selection) or an equilibrium state (relatively weak selection) after which they varied in amount of decrease with generations. The average realized response per generation and genetic variance given in Table 2 were computed from the generations after the maximum was attained. The expected response and genetic variance were based on Hill's prediction equation (Hill 1982a). The time (generations) required to attain the maximum point of genetic variance increased as effective population size and gene number increased, and as selection intensity decreased.

The results in Table 2 show that the realized responses and genetic variances were about half the values expected from Hill's prediction equation. The ratios of realized to expected asymptotic genetic variance are given in the last column of Table 2 and ranged from 0.16 to 0.62 with the average of these ratios being 0.47. This is smaller than the minimum value of 0.7 shown by Hill's simulation (Hill 1982b). For the small population of 20, the average of the ratios was much smaller than the value expected from Hill's prediction equation. This means that with a finite number of genes the Hill prediction equation holds better for larger populations than for a small one.

In modelling a quantitative trait where the potential number of genes that can affect the trait is more restricted than in the theory of Hill and when the magnitude of gene effects is larger on average, the implications of the impact of mutation on plant and animal breeding programs become much more apparent. Constant selection pressure is important if one hopes to make use of potential genetic variance created by a new mutation. Our results indicate that from a practical breeding perspective the rate of increase in genetic variance may be more important than the ultimate equilibrium state attained.

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