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The Conflict Between Natural and Artificial Selection in Finite Populations

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Summary. A single locus model of the interaction between natural selection and artificial selection for a quantitative character in a finite population, assuming heterozygote superiority in natural fitness but additive action on the character, has been studied using transition probability matrices.

If natural selection is strong enough to create a selection plateau in which genetic variance declines relatively slowly, then the total response to artificial selection prior to the plateau will be much less than that expected in the absence of natural selection, and the half-life of response will be shorter. Such a plateau is likely to have a large proportion, if not all, of the original genetic variance still present. In selection programmes using laboratory animals, it seems likely that the homozygote favoured by artificial selection must be very unfit before such a plateau will occur. A significant decrease in population fitness as a result of artificial selection does not necessarily imply that the metric character is an important adaptive character.

These implications of this model of natural selection are very similar to those derived by James (1962) for the optimum model of natural selection. In fact, there seems to be no aspect of the observable response to artificial selection that would enable anyone to distinguish between these two models of natural selection.

Key words: Homeostatic natural selection – Artificial selection – Finite populations – Selection plateau

Introduction

An important gap in current artificial selection theory is the lack of proper understanding of the intermediate generations of artificial selection in the presence of natural selection, before homozygosity has occurred. The conditions under which a selection plateau is reached with dynamic equilibrium between natural and artificial selection are of particular interest. There is then no further response though there is still considerable genetic variation for the character under artificial selection.

Two extreme models have been proposed for the action of natural selection on quantitative characters. Both assume additive gene action for the quantitative character. The homeostatic model, in which heterozygotes at the loci affecting the quantitative character are assumed to have higher fitness, was first proposed by Lerner (1950, 1954). For this model, Robertson (1956) has shown that, because individuals around the population mean are likely to be more heterozygous, fitness of individuals will be a maximum at the mean phenotypic value of the heterozygote and will decline as the square of the phenotypic deviation from that value.

The optimum model relates fitness directly to the phenotype for the quantitative character, irrespective of the underlying genotype. One version that has received considerable attention is the 'nor-optimal' model (Cavalli-Sforza and Bodmer 1971), originally introduced by Haldane (1954). The decline of fitness from the mean or optimum phenotype in this model has the same function as the normal distribution.

Both models give the same relationship at the phenotypic level, namely, that individuals with intermediate values for a particular quantitative character have the highest fitness.

The implications of the optimum model for artificial selection have been considered by Latter (1960) and James (1962), the second paying particular attention to the limits of artificial selection. Robertson (1956) has examined the effects of the homeostatic model in the context of artificial selection in terms of the consequent change in fitness, and of the relaxation of artificial selection. However, it was not until recently that any theoretical consideration was given to the role of the homeostatic

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model in determining limits to artificial selection. Verghese (1974) extended Robertson's (1960) theory of selection limits to include the interaction between artificial selection and homeostatic natural selection. In finite populations, she obtained expressions for chance of fixation and total change in gene frequency, but these are only relevant for very small parameter values, as Verghese rightly points out. A more serious restriction is that they apply only to advance at the limit *when total homozygosity has been achieved.*

However, one of the most important aspects of homeostatic natural selection in the context of artificial selection is that it provides a possible reason for the cessation of response – a plateau – *long before complete homozygosity*. Indeed, such an explanation has often been invoked for the observed lack of response to artificial selection while additive genetic variance still remains, e.g. Lerner (1950, 1954), Clayton and Robertson (1957), Roberts (1966), Verghese and Nordskog (1968). Under what conditions in a finite population is such a model likely to be valid? The theoretical consideration of Verghese suggests that initial and equilibrium gene frequency will be important but we have no idea which actual combinations of artificial and natural selection are likely to result in a plateau.

The problem can be tackled using a transition probability matrix, with which it is possible to obtain the expected values of gene frequency, genetic veriance, and other parameters over subsequent generations under any relevant combinations of artificial and natural selection for any given effective population size, N.

This paper presents the results of such a study, with the principal aim of obtaining a greater insight into the intermediate generations of selection response.

The Model

Consider two alleles at a single locus, affecting a metric character under artificial selection, at which natural selection is acting in a manner described by the homeostatic model of Lerner (1950, 1954).

At the time of conception in generation t, the relative frequencies of zygotes will be $(1-q)^2$, $2q(1-q)$ and q^2 for genotypes A_2A_2, A_1A_2 and A_1A_1 respectively, where q is the frequency of allele A_1 in the group of individuals selected as parents at the time of mating in generation t-1. Natural selection may occur at any time within the diploid phase of a generation, i.e. at any time between conception of zygotes and mating of individuals resulting from those zygotes. In addition, artificial selection occurs at some specified time within that generation.

The total effect of natural selection can be represented by relative fitnesses of $1-s_2$, 1 and $1-s_1$ for genotypes A_2A_2, A_1A_2 and A_1A_1 respectively. Assuming additive gene action for the metric character at this locus, the effect of artificial selection on gene frequency can be expressed (following Haldane 1931) in terms of the selection coefficient $i\alpha$, where i is the standardized selection differential, and α is the difference (a) between the metric means of the two homozygotes, divided by the phenotypic standard deviation (σ_p). As usual, this relationship is only valid when a is small relative to σ_p.

For such a model, the metric value and overall selective value of each genotype can be represented as

	A_2A_2	A_1A_2	A_1A_1
Mean metric value relative to the heterozygote	$\frac{-a}{2}$	0	$\frac{+a}{2}$
Selective value relative to the heterozygote	$(1-\frac{i\alpha}{2})(1-s_2)$	1	$(1+\frac{i\alpha}{2})(1-s_1)$

Discussion can be simplified by the reasonable assumption that the population was at equilibrium with natural selection before artificial selection commenced, in which case initial gene frequency (q_o) is equal to equilibrium gene frequency for natural selection alone ($\bar{q}$), which is $\frac{s_2}{s_1+s_2}$ in the current model.

The most suitable form of transition probability matrix for the present model is the one used by Hill and Robertson (1968) who provided a full description of its derivation. The general theory involved in the use of such matrices has been developed in the context of artificial selection alone by Narain and Robertson (1969).

Changes in Various Population Parameters

When artificial selection occurs before natural selection, the metric mean is a simple linear function of the frequency of allele A_1 before any selection, being equal to $\frac{a}{2}(2q-1)$. For additive genetic variance, $V_A = \frac{a^2}{2}q(1-q)$ in which case change in variance also measures change in heterozygosity. Thus, changes in gene frequency (and hence metric mean) can be followed by setting an initial vector $\underset{\sim}{y}_o$ as

$$\underset{\sim}{y}_{o(j)} = j/2N \qquad j = 0, \ldots, 2N$$

where N is the effective population size, while the progress of heterozygosity (and hence additive genetic variance) can be traced by starting with

$$\underset{\sim}{y}_{o(j)} = (j/2N)(1-j/2N) \qquad j = 0, \ldots, 2N.$$

These simple relationships no longer hold if any natural selection occurs prior to artificial selection. However, several matrix runs have indicated that changes in metric mean and genetic variance follow the same trends irrespective of the stage of the generation at which natural selection occurs. It has been found that the effect of natural selection prior to artificial selection is most commonly to reduce the metric mean as observed at the time of measurement by a relatively small and fairly constant proportion. The same conclusion applies in general for the additive genetic variance.

The matrix operations have been carried out with an effective population size of N = 20 for various lengths of time with different combinations of artificial and natural selection. This value was chosen as being in the range of most of the artificial selection experiments reported in the literature. Analogous runs were carried out at other values of N in order to check the generality of conclusions drawn from the runs at N = 20. Differences in detail were of course observed, but the general trends and overall predictions observed and obtained from N = 20 were still evident in the other runs.

It may help to recall some theoretical effects of heterozygote superiority, both in infinite and finite populations. Using the earlier notation, the equilibrium frequency of A_1 in an infinite population with no artificial selection is $\bar{q} = s_2/(s_1 + s_2)$ and the fitness of a population at this equilibrium is $1-s_1 s_2/(s_1 + s_2)$. Any departure from this equilibrium frequency involves a loss of fitness of $(s_1 + s_2)\ (q-\bar{q})^2$. With artificial selection producing a difference in selective value between the two homozygotes of $i\alpha$, the new equilibrium frequency of A_1 will be $(s_2 + i\alpha/2)/(s_1 + s_2)$. It follows that if artificial selection is sufficiently strong so that $i\alpha > 2s_1$, then A_1 will be fixed, and the resultant loss of fitness will be $s_1^2/(s_1 + s_2)$. Increasing strength of natural selection increases this loss of fitness until $s_1 > i\alpha/2$, at which stage the new equilibrium frequency of A_1 is less than one, and the loss of fitness is $(i\alpha)^2/4(s_1 + s_2)$. Further increases in s_1 now result in a reduction in the loss of fitness. Thus, as the strength of natural selection is increased for a given value of $i\alpha$, the fitness first declines and then increases again.

If $s_1 > i\alpha/2$, then the combined effect of natural and artificial selection is overdominance for fitness and, in infinite populations as we saw above, a consequent prevention of homozygosity. In finite populations, however, overdominance for fitness does not prevent homozygosity – at best it merely retards it (Robertson 1962). The retardation is highest at intermediate values of the equilibrium frequency, and, if this is outside the range of 0.2 to 0.8, selection increases the rate of approach to homozygosity. There is a change in the mean gene frequency in favour of the allele which was initially more frequent.

In our computer work with transition matrices we make use of the fact that the process is determined by $Ni\alpha$, $N(s_1 + s_2)$ and the initial gene frequency (which in all cases we assume to be $\bar{q}$) with the time scale expressed as t/N. As the effect on fitness can be expressed as $(s_1 + s_2)(q-\bar{q})^2$, it follows that the loss in fitness should be expressed in units of 1/N. Because the relationship of s_1 to $i\alpha$ is the critical one in infinite populations, we have presented the results in terms of Ns_1, $Ni\alpha$ and $\bar{q}$.

Results

The behaviour of populations with a given parameter set can be described in terms of

(i) the asymptotic rate of decline of the genetic variance

(ii) the chance of fixation of the desirable allele.

Figure 1 illustrates the joint action of artificial and natural selection as described by these two independent measures.

We took as our criterion for the maintenance of genetic variation and hence as our definition of a selection plateau, a reduction in genetic variance of 1/80 each generation – one half the value expected with genetic drift alone with N = 20. Inside the shaded area, and corresponding to the above definition of a plateau, approach to homozygosity is retarded by a factor of more than two, compared to the rate in the absence of selection. Thus the shaded area represents a selection plateau in which genetic variance is maintained for a relatively long time by the interaction of artificial and natural selection, while the unshaded area describes situations in which genetic variance is exhausted relatively quickly. It should be noted that in both cases genetic variance is eventually exhausted; the above distinction is solely in terms of the rate of decline of genetic variance.

The chance of fixation of the desirable allele is indicated by the contours labelled 0.1, 0.3, 0.5 and 0.8.

With $\bar{q} = 0.5$, there are in effect only two outcomes; relatively rapid exhaustion of genetic variance, with a high chance of fixation of A_1 (greater than 0.8), or a selection plateau, but also with a quite high chance of ultimately fixing the desirable allele. Only in a small region with low values of $Ni\alpha$ and Ns_1 is there rapid exhaustion of genetic variance without a high chance of fixation of A_1; in this small area, the chance of fixation of A_1 varies between 0.5 and 0.8. With $\bar{q} = 0.3$, a further outcome is possible – again in a very small region – a rapid exhaustion of genetic variance with a high probability of loss of A_1, corresponding to a chance of fixation of less than 0.1. This region is again present with $\bar{q} = 0.1$, but is now larger. For instance, with $\bar{q} = 0.1$ and $Ni\alpha = 4$, there is rapid exhaustion of genetic variance with moderate changes of gene frequency up to an Ns_1 value of approximately 3, follow-

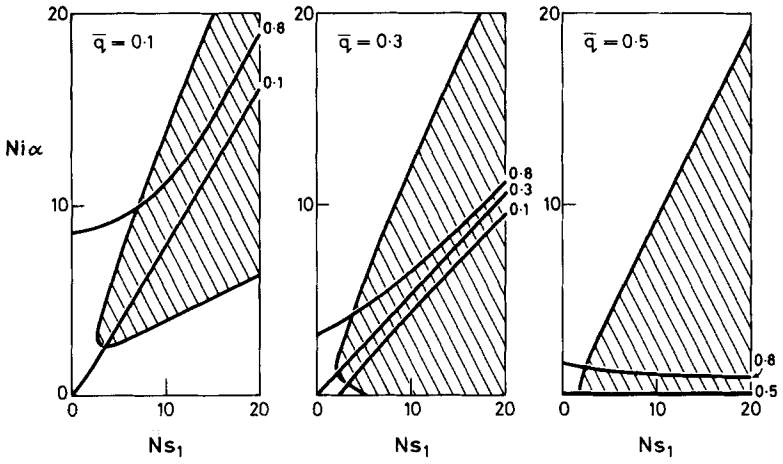

Fig. 1. Result of the conflict between natural selection (expressed in terms of Ns_1) and artificial selection (Niα) in finite populations, with the desirable allele at initial frequencies of 0.1, 0.3 and 0.5. The shaded area represents a selection plateau in which genetic variance declines relatively slowly. The other contours indicate the chance of fixation (0.1, 0.3, 0.5 or 0.8) of the desirable allele.

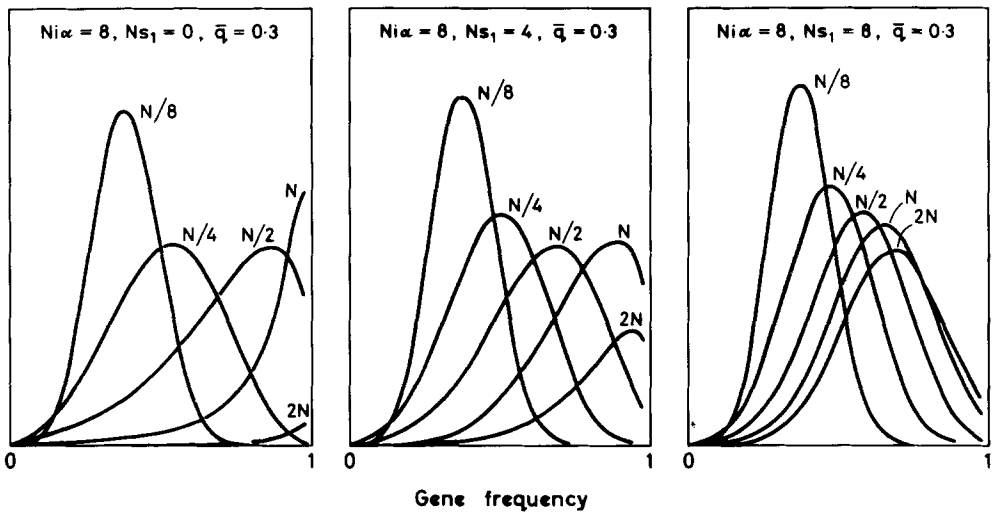

Fig. 2. Frequency distribution of the desirable allele after N/8, ..., 2N generations of artificial selection, for three levels of natural selection (Ns_1).

ed by a region of plateau up to $Ns_1 = 10$ and then rapid exhaustion of variance with a high probability of loss of the desirable allele. Note that at higher Niα values the critical region for long term segregation is not very dependent on the initial gene frequency. A further phenomenon is possible at very low initial frequencies of the desirable allele under artificial selection – that although the parameters permit long term maintainance of segregation, a particular line may not always get into that state as the allele may be lost in the early generations. Thus when $\bar{q} = 0.025$, Ns_1 must be greater than 6.2 to satisfy our criteria for the maintenance of segregation. Nevertheless it appears that such a line has a probability of only about one-third of reaching such a state.

In the remaining figures, we illustrate in detail the behaviour of a locus with Niα = 8 and $\bar{q} = 0.3$. Figure 2 shows the gene frequency distribution at different times. With no natural selection, the population proceeds rapidly to homozygosity, with a rapid increase and high final frequency of allele A_1. With $Ns_1 = 4$ the allele still has a high final frequency but the process is slowed down. With $Ns_1 = 8$, however, the distribution becomes fairly stable with a mode of approximately 0.75 after the Nth generation, though the early generations are little affected.

The other figures give the values of various observables during the selection process such as

(i) the mean gene frequency, linearly related to the metric mean

(ii) the genetic variance in the selected character
(iii) the loss of fitness due to artificial selection.

The response in gene frequency (Fig. 3) reaches a plateau for both high and low values of Ns_1, but for different reasons. When Ns_1 is low, A_1 is almost certain to be fixed – when it is high, quasi-permanent segregation is almost certain. At intermediate values, there may be, towards the end of selection, a long period of very slow change in mean gene frequency, as with $Ns_1 = 8$ in the figure. The total response is $1-\bar{q}$ when Ns_1 is small and $i\alpha/2(s_1 + s_2)$ when it is large, and in both cases the initial change of gene frequency is $i\alpha q(1-q)/2$ per generation. If we divide the initial rate of change into the total response to give a crude measure of the time taken to reach the plateau, we obtain values of $2/i\alpha\bar{q}$ and $1/s_1\bar{q}$ respectively.

Another measure of the time scale of selection response is the half-life of response, which is the time taken to get half-way to the limit. When $Ns_1 = 0$ and $Ni\alpha = 8$, the half-life is expected to be less than 1.4N generations (Robertson 1960), and from Figure 3, is approximately 0.4N. What is the expected half-life when natural selection is sufficiently strong to produce a plateau as defined earlier? From Figure 1, it appears that if $\bar{q} = 0.3$ and $Ni\alpha = 8$, a value of Ns_1 of at least 7 is required to produce a plateau. Thus the curves in Figure 3 for $Ns_1 = 8$ and 12 are the only ones that represent selection plateaux. For these curves, it can be seen from Figure 3 that the half-life is less than 0.4N. Thus, if natural selection is strong enough to produce a selection plateau at which genetic variance is maintained for a long time, then the half-life of response is expected to be less than that expected in the absence of natural selection.

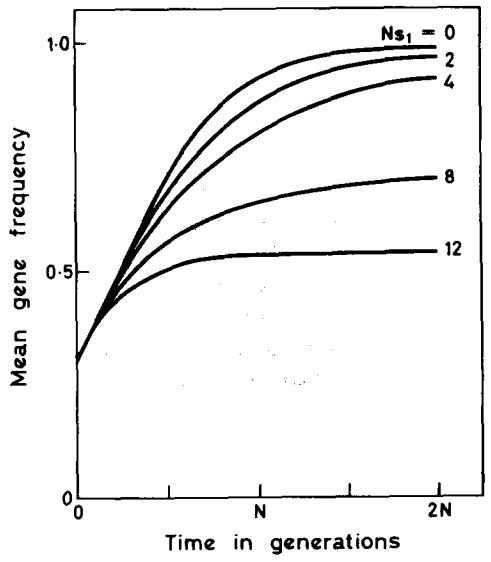

Fig. 3. Response to artificial selection with $\bar{q} = 0.3$ and $Ni\alpha = 8$, for various levels of natural selection (Ns_1)

Figures 4 and 5 give the change in the genetic variance during selection. At all values of Ns_1, there is a slight increase in the early generations due to the change in mean frequency but at the highest values the subsequent change with time is slow. The critical value of Ns_1 for the maintenance of genetic variation according to the criterion used in Figure 1, is here 7.

Figures 6 and 7 give the loss in fitness due to artificial selection, expressed in units of 1/N. In the early genera-

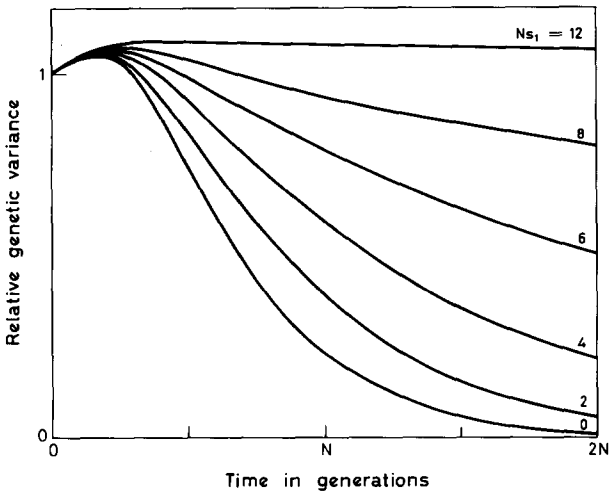

Fig. 4. Genetic variance, relative to the initial value, during artificial selection with $\bar{q} = 0.3$ and $Ni\alpha = 8$, for various levels of natural selection (Ns_1)

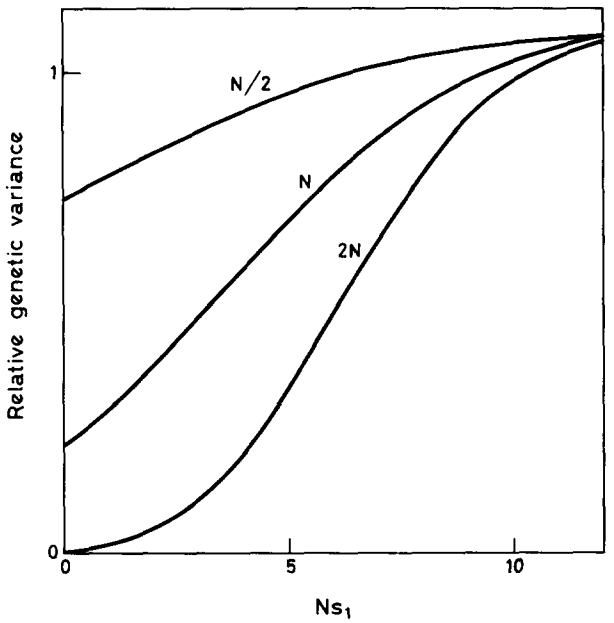

Fig. 5. Relative genetic variance remaining after N/2, N and 2N generations of artificial selection with $\bar{q} = 0.3$ and $Ni\alpha = 8$, as a function of Ns_1

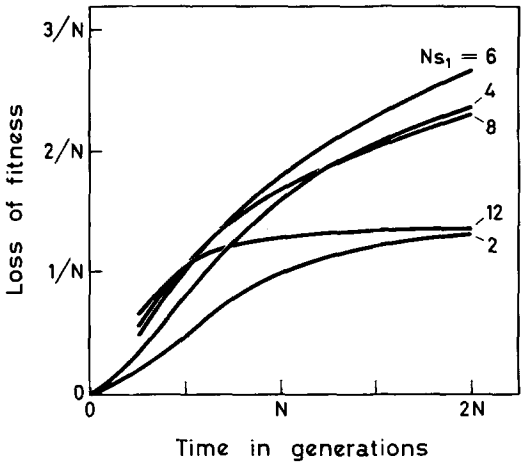

Fig. 6. Loss of fitness during the course of artificial selection with $\bar{q}$ = 0.3 and Niα = 8, for various levels of natural selection (Ns_1)

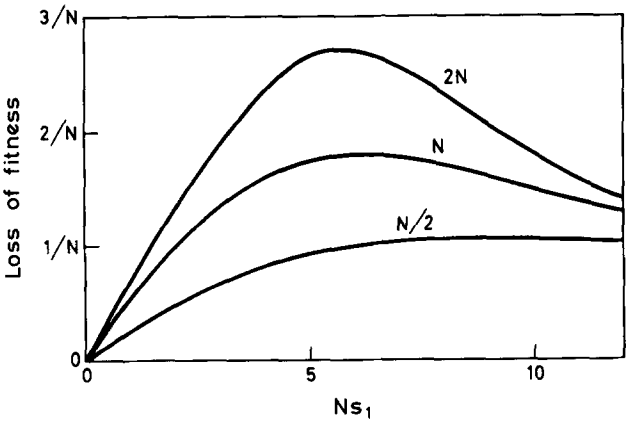

Fig. 7. Loss of fitness after N/2, N and 2N generations of artificial selection with $\bar{q}$ = 0.3 and Niα = 8, as a function of Ns_1

tions, the stronger the natural selection the greater the loss in fitness but, later, as the strong natural selection leads to permanent segregation, the loss passes through a maximum with Ns_1 around 6. The maximum loss appears to be of the order of 3/N. Note that this occurs in the range of values of Ns_1 where there is a slow change of gene frequency over a long period.

These figures refer to particular values of Niα and $\bar{q}$. For larger values of the effect of the locus on the selected character, it appears that the value of s_1 required to produce a plateau will be proportionately higher, the plateau will be reached more quickly and the maximum loss of fitness will be greater. It also appears that the closer $\bar{q}$ is to 0.5, the greater the value of s_1 needed to produce a plateau and the more quickly it will be reached but the loss of fitness at the maximum seems not to be much affected.

It must be emphasised that all the above discussion is concerned with loci affecting the character under artificial selection. Changes in fitness associated with overall inbreeding depression have not been considered. To the extent that this might occur if effective population size is relatively small, the loss of fitness given above will be underestimated: any general depression of fitness due to inbreeding will tend to increase further the loss of fitness for a particular strength of artificial selection.

Discussion

What are the main conclusions of this study? Verghese (1974) studied the joint effects of natural and artificial selection in infinite populations and her treatment of finite populations was limited to small values of $N(s_1 + s_2)$ in which natural selection could not prevent fixation but merely alter the mean gene frequency at the limit. In our analyses, we have been mostly concerned with the situation in which natural selection in a finite population results in the maintenance of segregation which declines with time at a very slow rate.

Verghese showed that for infinite populations we should be mainly concerned with those cases in which the desirable allele under artificial selection has an equilibrium frequency under natural selection of less than 0.5. This holds even more strongly for finite populations since now a new equilibrium is unlikely with a gene frequency greater than 0.8 (Robertson 1962). She showed that the condition for equilibrium with permanent segregation in an infinite population is that $s_1 > i\alpha/2$. Because of the above condition, in finite populations higher values of s_1 are necessary and are now dependent on the initial equilibrium frequency $\bar{q}$. For example, with $\bar{q}$ = 0.5, the value of s_1 necessary to maintain segregation is almost equal to $i\alpha$.

The values of Ni in many selection experiments with laboratory animals lie between 20 and 30. As gene frequencies at equilibrium under the joint action of natural and artificial selection will range from 0.2 to 0.8, such a locus will contribute a proportion $\alpha^2/10$ approximately of the observed phenotypic variance. Thus for the locus to contribute 10% of the phenotypic variance α would have to equal unity and selection against the desirable allele as a homozygote would have to be very strong to maintain the segregation. If this model holds, therefore, one might expect to find that strong natural selection operating on single loci would be the major cause of maintenance of genetic variation in artificial selection programmes. It seems unlikely that linkage between loci with small effects on the character or between such loci and loci affecting fitness only would lead to a plateau, unless the linkage were so tight that in effect only one 'factor' is segregating.

Robertson (1977) has shown that in simulation of artificial selection with a very large number of linked loci on a chromosome, each with an extremely small effect ($Ni\alpha \ll 1$) on the character under selection, natural selection of the kind discussed here has very little effect on the response to selection at the limit. Sved (1977) reached similar conclusions when the loci affecting the metric character are distinct from but closely linked with those affecting fitness. It is very usual to find continued genetic variation with a lack of response to artificial selection in *Drosophila* and in many of the cases analysed this has been shown to be due to continued selection for heterozygotes of a lethal recessive (Hollingdale 1971).

Recently Carmelli and Karlin (1975) and Karlin and Carmelli (1975) have discussed the joint action of natural and artificial selection. They criticise such approaches as the present one as 'vague and restrictive' because, we rely strongly on the proportionality between the difference in mean between two genotypes and the consequent difference between the two in 'artificial' fitness. They are particularly worried that the frequency-dependent aspects of artificial selection are in consequence ignored. This is true, but the latter effect is only of importance if the locus in question controls a large part of the total phenotypic variance. We believe their approach is unreal and restrictive for several reasons:

(i) they do not deal with the effects of finite population size.

(ii) they assume no variation due to the environment (or to loci other than the one or two they consider directly) in the variable to which artificial selection is applied so that genotypes, of groups or genotypes, can be placed with certainty in order of preference. This clearly leads to frequency dependent selective advantage. The smaller the effect of the locus, relative to effects at other loci and to the environmental component, the closer does the selective advantage come to proportionality to genetic effect on the character under selection. Numerical analysis would suggest that frequency dependence is probably not of importance if the locus controls less than 10% of the total variance.

(iii) they do not deal with the homeostatic model, with additive action for the character under selection but heterozygote superiority for fitness. In their two-locus paper, Karlin and Carmelli (1975) discuss two situations in which the phenotype is determined by the 'cumulative effects at the two loci', an additive model. However, by dividing the genotypes into two classes containing, in the first case at least three desirable alleles and in the second at least two, they in effect introduce dominance into the artificial selection.

It must be emphasised that this study has been in terms of single loci whereas results of artificial selection experiments must be interpreted in terms of at least several loci. The effective value of s_1 at any particular locus (or unit of segregation) will lie somewhere between 0 and 1. Furthermore this value may alter during the course of artificial selection as the result of mutation and/or recombination; Hollingdale's (1971) analysis of lethal recessives in selected *Drosophila* populations would suggest that in some cases they were absent from the base population. We are then describing what happens to particular components of response during selection. The response is probably a combination of the effects of loci at which natural selection does not act ($s_1 = 0$) and others with intermediate values together with one or two loci with maximum values of s_1. The latter type of locus may only have commenced its contribution to selection response after many generations of selection.

The implications of the homeostatic model of natural selection for artificial selection experiments have been explored in some detail. How do our conclusions accord with the results from artificial selection experiments where natural selection has been thought to have played a significant role?

A logical starting point would be the experiment of Lerner and Dempster (1951) from which the homeostatic model of natural selection arose. In an earlier reanalysis of this experiment, James (1962) estimated the limit to selection as being 0.6N times the gain in the first generation which is much less than the value of 2N expected if natural selection had been absent.

Furthermore, from page 78 of Lerner and Dempster (1951), it appears that the limit was reached after approximately 0.7N generations and that most of the original variance still remained. All these observations are compatible with relatively strong homeostatic natural selection opposing artificial selection. Finally, from their Table 3 it can be concluded that fitness at the limit was roughly one third or 4/N less than at the commencement of selection. In relating this observed decline in fitness with the expectations from our model, it must be noted that the curves in Figures 6 and 7 refer only to a single locus, and as such provide only a lower limit of the decline in fitness to be expected when several loci contribute to the response in the metric character. Thus an observed decline of this magnitude is not unexpected with the homeostatic model.

All the data are therefore compatible with the hypothesis that the observed plateau was caused by the opposition of homeostatic natural selection to artificial directional selection. But James (1962) was able to conclude that the same data could be explained with a hypothesis of directional selection opposed by nor-optimal natural selection. In fact, a general comparison of results of this study for the homeostatic model with that of James for the optimum model shows that, despite the profound differences between the two models, the practical implica-

tions of each are essentially the same *in the context of artificial selection*. Consequently there seems to be no aspect of observable response to artificial selection which would enable a distinction to be made between the two models.

It was shown earlier that the relative fitness at the plateau was at a minimum at the value of Ns_1 just strong enough to prevent complete fixation. It follows that some loci which contribute to a decline in fitness may not contribute at all to the maintenance of genetic variation at the limit. It would therefore not be surprising to find a line undergoing artificial selection for a metric character of apparent peripheral importance to fitness, in which fitness had declined considerably but in which there was no sign of the formation of a plateau with continued segregation. Indeed it is quite possible that fitness in a line could decline to such an extent that the line was in danger of extinction whereas had the opposing natural selection been stronger, a plateau might have resulted at which relative fitness was still quite high.

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