# STUDIES ON ARTIFICIAL AND NATURAL SELECTION

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## SUMMARY

A theoretical study has been made of the interplay between natural selection and artificial selection for a quantitative character. The implications of two models of stabilizing natural selection in which an intermediate metric phenotype is more fit than extreme phenotypes, have been examined in this context.

The homeostatic model, in which extreme metric phenotypes are less fit because they are more homozygous, has been described in terms of the strength of homeostatic natural selection, S. Under this model each locus can be considered independently and natural selection does not necessarily act at all loci. For any particular locus, an understanding has been obtained of the strength of natural selection necessary to produce a selection plateau prior to complete fixation, and of the time at which such a plateau will first appear. It has been found that the total advance in the metric mean at a plateau due to opposing natural selection is never greater than $2N(1-2S)^2$ times the change in metric mean in the first generation of artificial selection, where N is the effective population size. It should be possible to break through any such plateau by increasing the strength of artificial selection if sufficient reproductive excess still exists in the population.

The optimum model of natural selection, in which extreme metric phenotypes are less fit solely because they have extreme phenotypes, has also been considered. Quantitative predictions of limits to artificial selection due to opposing optimum natural selection may not have very much value when derived from single locus selective values, as the equilibria they represent are transient. The problem is that under this model, epistasis is of vital importance. Thus all loci that contribute to the metric character are subject to natural selection, the effect of which at

any one locus varies from generation to generation, being determined by gene frequencies and gene effects at all other loci. The problem of epistasis can be avoided by considering an extreme situation in which there is no crossing over between the loci. In this particular case, if the initial distribution of chromosome effects is approximately normal, then the predictions of Latter (1960) and James (1962) provide a realistic description of the results of the interaction between artificial and optimum natural selection.

In general, the implications of each model of stabilizing natural selection in the context of artificial selection appear to be very similar.

The effect of t' generations of reverse selection after t generations of forward selection has been described in terms of the ratio of the change in metric mean resulting from reverse selection (R) to the change in metric mean due to the previous forward selection ($\Delta x$). In the absence of natural selection, and for equal periods of reverse and previous forward selection (t'=t), $\frac{R}{\Delta x}$ equals 1-F where F is the inbreeding coefficient for a neutral locus at generation t, being estimated as $[1 - (1-\frac{1}{2N})^t]$ where N is the effective population size for both forward and reverse selection. And for a single generation of reverse selection in which response in metric mean was $R_1$ following t generations of forward selection, $\frac{NR_1}{\Delta x}$ equals $\frac{1-F}{2F}$. The presence of natural selection opposing forward artificial selection increases the observed values of the ratios above those expectations.

In a separate study, the effect of directional and heterotic selection on the standardized variance of gene frequency (f) has been examined. It has been found that heterotic selection always results in f values lower than those expected due to drift alone. Additive selection usually results in similarly low f values, but f values larger

than those expected due to drift will be observed under additive selection with low initial gene frequency, or when the populations have been separated for a relatively long period of time in which case f expected due to drift is quite high (around 0.7 or greater). The effect of selection on f is unlikely to be detected if the observed value of f is less than 0.1.

Included as an appendix is the following paper which has been submitted for publication under joint authorship, with Dr W.G. Hill: "Estimation of heritability by both regression of offspring on parent and intra-class correlation of sibs in one experiment".

# PART A

# THE THEORY AND PRACTICE OF ARTIFICIAL SELECTION

In his attempts to increase the production of food and other products from domestic animals, man has been for many years selecting only certain animals to act as parents for the next generation. To the extent that the various selection criteria adopted by man have not been directly related to an animal's ability to contribute to the next generation if left to fend for itself in the "wild", it can be said that man has been carrying out artificial selection, as distinct from natural selection. The latter type of selection can be thought of as the natural processes which result in some individuals contributing more progeny to the next generation than others.

Man has complete control over the first but not the second type of selection, so that some artificial selection programmes are bound to involve the often unwelcome action of natural selection as well.

A large majority of characteristics of importance in artificial selection over the centuries have been continuously varying (quantitative or metric) characters, but it was not until the advent of the sciences of genetics and statistics during the early years of this century that man was able to objectively describe and analyse the process of artificial selection for such characters.

The early theory of artificial selection for a quantitative character, as summarised by Lush (1945), provided a simple prediction of the gain to be expected from artificial selection. Thus the change in metric mean $\Delta G$ in the next generation as a result of selecting individuals whose mean phenotype is $\Delta P$ metric units above

the population mean is given by $\Delta G = h^2 \Delta P$, where $h^2$ is the heritability of the metric character. This prediction has been demonstrated to be quite useful during the early generations of selection in a variety of different species including Drosophila (Clayton, Morris and Robertson, 1957), Tribolium (summarised by Bell, 1969), mice (Falconer, 1953), poultry (Lerner, 1950), pigs (Hetzer and Harvey, 1967) and sheep (Turner and Young, 1969, chapter 11).

Even the early workers in this field, however, recognised the limitations or inherent assumptions of the simple prediction equation especially in the context of longer term selection. Lush (1945) was fully aware that factors such as epistasis, linkage and over-dominance for the metric character were not included in the simple prediction, and the potential importance of natural selection opposing artificial selection was soon emphasised by Lerner (1950). In addition it has become apparent more recently that the inherent assumption of a large number of loci, each making a small and equal contribution to genetic variance, may not be realistic in all situations. Finally, the relatively small numbers of parents used in most selection programmes certainly violates the implicit assumption of a large population size. Thus it was not surprising to find that the simple equation was of little use in predicting the long term outcome of a selection programme (see, for example, Clayton and Robertson, 1957, and Jones, Frankham and Barker, 1968).

Since the inception of the use of the simple equation therefore, a major aspect of the theoretical study of artificial selection has been the extension of the validity of prediction through the gradual incorporation of the extraneous factors into the prediction itself.

A brief review will now be made of some of the more important theoretical studies, looking not so much at actual results but more at the methods of approach that have been utilized.

A number of algebraic studies have been conducted with relatively simple models. Dominance, epistasis, linkage, genes of large effect and finite population size have been incorporated into a variety of predictions, either singly or in various combinations. In general, however, the algebraic description of more realistic models incorporating several of the above items has not been possible. The increasing number of parameters required to define such a model, and the associated increase in complexity of parameter interactions have so far defied any attempt to achieve a purely algebraic prediction.

The need for increasingly complex models coincided with the development of Monte Carlo simulation techniques that could be carried out at high speed by automatic computers. Monte Carlo methods, which involve computer simulation of "the random aspects of inheritance and computing the history of a number of replicate populations" (Fraser and Burnell, 1970), were first applied to artificial selection of a quantitative character by Fraser (1957, et seq.), Martin and Cockerham (1960) and Gill (1965, et seq.). Making use of the binary nature of arithmetic computation in a digital computer, these workers started with relatively complex models involving many loci, linkage, intra- and inter-locus interactions and finite population size. With so many parameters interacting and with only a few values of each parameter specified, conclusions tended to be descriptive rather than predictive. Broad generalisations sometimes emerged, but

few of these had immediate predictive value. Fraser and Burnell (1970) have recently reviewed the various simulation studies which made use of this approach.

Latter (1965, 1966a, 1966b) used computer simulation to study a simpler two-locus model in greater detail, searching for conclusions of greater predictive value. A literal simulation of the binary nature of the problem was not used. Rather, an algebraic (and hence deterministic) description of the selection process, supplemented by the use of random numbers to simulate gamete sampling and recombination, was employed. Such an approach is more abstract than that of Fraser but is more efficient in use of computer time, and facilitates the finding of generalised predictions. Hill and Robertson (1966), using an even more abstract method of simulation, studied a more general form of Latter's model. With the aid of some preliminary algebra it was shown that the whole selection process could be specified by three parameter combinations and three other single parameters. Since each of the parameter combinations contained N, useful conclusions and predictions could be drawn from all computer runs at only one population size.

More recently, Robertson (1970) has reported the results of a simulation study of the effect of linkage with many loci on the limits to artificial selection. Some of the seven parameters needed to define the initial population were "reparameterised" into combinations of two or more, thus reducing the number of variables to a more manageable level. As with the earlier studies of Robertson (1960) and Hill and Robertson (1966), such a reparameterisation offered a guideline as to which parameter values would be relevant, and enabled

more useful conclusions and predictions to be obtained. The predictions arising from the latest study have already been subjected to an experimental test with reasonable success, by McPhee and Robertson (1970).

Robertson's approach was similar to that of Latter and Novitski (1969) who also used some algebra to provide guidelines for their subsequent simulation of directional selection in a finite population using a single locus model with many alleles. They were also able to make successful use of reparameterisation. In addition they obtained several empirically derived relationships and predictions just as Robertson did, as a result of certain patterns appearing in the simulation results.

Algebraic studies, therefore, when judiciously combined with computer simulation have incorporated several of the more important original limitations into the theory of artificial selection for a quantitative character.

However, one important assumption has still been made in each of the theoretical studies described above. In particular, each of those studies has neglected the potential effect of natural selection.

The interplay of natural selection and artificial selection has been observed during the course of many artificial selection experiments, Mather and Harrison (1949) reported a large and negative correlated response in reproductive fitness when selecting for abdominal bristle number of Drosophila, while Lerner and Dempster (1951) were able to attribute the cessation of response to selection for increased shank length in poultry, at least in part to adverse natural selection, in the form of a negative correlation between shank length

and hatchability in dams.

More recent selection experiments in several species have provided further evidence of a resultant decrease in reproductive fitness. Such observations were reported by Latter and Robertson (1962) in Drosophila; Kress, Enfield and Braskerud (1971) and Orozco (1972) in Tribolium; Eisen, Hanrahan and Legates (1973) in mice, and Verghese and Nordskog (1968) in poultry. On the other hand, not all artificial selection has led to a decrease in reproductive fitness. Hetzer and Miller (1970) for example, found no consistent changes in fitness during 13 generations of selection for backfat thickness in pigs.

In any discussion of the interplay between natural and artificial selection, care must be taken to differentiate between those aspects of natural selection associated directly with artificial selection for a particular character, and the more general effects of finite population size on reproductive fitness. The remainder of this review will concentrate only on the former, and will thus assume that the inbreeding effects of artificial selection with reference to the whole genome (as discussed by Robertson, 1961) have negligible effects on reproductive fitness.

The proper analysis and explanation of the above selection results requires a far greater understanding of the basic processes involved in the interaction of artificial and natural selection. As an initial step in the study of these processes, the relationship between natural selection and quantitative characters must be considered.

## Natural selection and quantitative characters

Robertson (1955) and Mather (1966) have both described the range of relationships between a quantitative character and natural selection as extending from those characters very closely associated with fitness to those with only an unimportant, peripheral relationship. Such a scale corresponds to increasing additive genetic variance for the quantitative character as might be expected in the light of Fisher's (1930) fundamental theorem of natural selection.

It has been argued that only fitness itself is subjected to directional natural selection alone, and that all other quantitative characters including components of fitness, must be subjected to a degree at least of stabilizing selection in which an intermediate metric phenotype is more fit than extreme phenotypes. Indeed such an opinion now seems to have acquired the status of text-book dogma (see, for example, Falconer, 1960; Crow and Kimura, 1970; and Cavalli-Sforza and Bodmer, 1971). The strength of such stabilizing selection is proportional to the degree of relationship between the character and fitness, with characters of peripheral importance to fitness being subjected to negligible strengths of stabilizing selection.

The concept of stabilizing natural selection thus seems to be of major importance in any discussion of natural selection and quantitative characters.

## Models of stablizing selection

Essentially two main models have been proposed for the action of stabilizing selection on a quantitative character. In their

simplest forms, both of them involve the assumption of additive gene action for the metric character.

The homeostatic model, in which extreme metric deviants are less fit because they are more homozygous, was first proposed by Lerner (1950, 1954). It has since been shown (Robertson, 1956) that fitness in this model will be a maximum at the mean phenotypic value of heterozygotes, and will decline as the square of the phenotypic deviation from that mean. This observation, however, is not an integral component of the model. It is simply a consequence of fitness decreasing with increasing homozygosity. In the same study, Robertson made much use of a parameter which he called the homeostatic strength of a character (S for a single locus, $\bar{S}$ for many loci where $\bar{S}$ is the average of all S values, weighted according to the proportion of additive genetic variance contributed by each locus). Having zero value for characters unassociated with fitness, the magnitude of S increases with increasing strength of natural selection. Its main virtue lies in the fact that the value of S for a particular metric character can be estimated from an artificial selection experiment, as will be shown later.

The optimum model, in direct contrast to the homeostatic model, relates reproductive fitness directly to the phenotype for the quantitative character, irrespective of the underlying genotype. Its most popular version, the "quadratic deviation" optimum model, was first described by Fisher (1930, page 105) and Wright (1935). In this model fitness declines as the square of the deviation of the metric phenotype from either the population mean which may be variable (Fisher) or from some fixed optimum phenotype (Wright).

Gale and Kearsey (1968) and Kearsey and Gale (1968) have studied a simpler "linear" optimum model in which fitness declines linearly from a fixed intermediate optimum. Another version (Robertson, 1956; Curnow, 1964; and Van Valen, 1965) is the "double truncation" optimum model in which there are two vertical cut-off points, one on either side of the population mean or some optimum phenotype. All individuals between the two truncation points (and hence near the mean or optimum) are selected, while all those having metric phenotypes outside the cut-off points are rejected. Such a model is more relevant to artificial than to natural selection, in the sense that natural selection is rarely as absolute in its effect as this model requires.

Yet another version that has received considerable attention is the "nor-optimal" model (Cavalli-Sforza and Bodmer, 1971) which was originally introduced by Haldane (1954). The decline of fitness from the mean or optimum phenotype in this version follows the shape of the normal distribution. A notable contribution to the study of the nor-optimal model was that of Latter (1970) who introduced a parameter called the coefficient of centripetal selection, C, which has the logical and convenient property of ranging from zero (for no selection) to unity (for absolute selection of the optimum phenotype only). Latter was able to show that C also had the valuable property of being estimable from an artificial selection experiment, analogous to the situation already described (Robertson, 1956) for the strength of homeostatic natural selection, S. In addition, C was shown to be simply related to Haldane's (1954) intensity of nor-optimal natural selection, I.

Of all the versions of the optimum model, those which have been most thoroughly studied are the quadratic deviation and the nor-optimal. It is important to note that for metric characters that are normally distributed and for the relatively weak natural selection usually encountered, both versions amount to essentially the same thing (Bulmer, 1972; O'Donald, 1970, 1973). From now on therefore, any reference to the optimum model will be in terms of one or other, or both of these versions.

It has already been seen that both the homeostatic and optimum models give rise to exactly the same relationship at the observational level, namely that individuals with intermediate phenotypes for a particular quantitative character have the highest fitness.

The validity of such a relationship has been questioned by Robertson (1963, 1966, 1967) who has suggested that we say nothing about the way in which natural selection acts if we simply observe the relationship between fitness and a single character considered at one point in time and in complete isolation from the totality of characters which go to make up an individual's overall or 'global' phenotype. Natural selection, claims Robertson, surely does not partition the global phenotype into the arbitrary component characters which we have defined for our own purposes.

Despite these valid objections, the concept of stabilizing natural selection has received considerable attention from many workers, including those attempting to explain the results of artificial selection experiments in which fitness has declined and/or selection plateaux have been observed (see for example, Verghese and Nordskog, 1968; and Orozco, 1972). Indeed, Eisen, Hanrahan and Legates (1973)

have recently attempted to use their artificial selection results to differentiate between the two models of stabilizing natural selection. However, despite a thorough and careful analysis of fitness changes in their lines, these authors were unjustified in concluding that their results favour the optimum model; they have failed to realise that exactly the same results in this case could have occurred under the homeostatic model. Analyses of this type are potentially useful, but a far greater understanding of the ramifications of each model is needed before a valid conclusion can be reached from such selection data.

One way to obtain more knowledge of the implications of the homeostatic and optimum models would be to use these two models as the basis for a theoretical study of the interplay between artificial and natural selection especially now that we have, in S and C, biologically meaningful and measureable parameters for each of the models. In order to provide a framework for such a study it is first necessary to determine whether or not each model is a valid description of natural selection in natural populations.

The homeostatic model is relatively straightforward, having the maintenance of genetic variability as one of its basic premises. This model could therefore be used to describe the way in which natural selection maintains the genetic variability which is observed in quantitative characters in natural populations, and which is subsequently subjected to artificial selection. The ability of the optimum model to maintain genetic variability, on the other hand, has been the subject of considerable study, and controversy. In particular, each new publication on the topic seems to alter the conditions under which the various versions of the optimum model may or may not

maintain significant genetic variation. Despite numerous papers from a wide variety of workers, the exact implications of the optimum model still remain to be clarified beyond dispute.

The most recent study of the nor-optimal model has been reported in a series of papers by Bulmer. All of these papers were based on an initial, more general, study of stabilizing and disruptive selection (Bulmer, 1971a) from which it was concluded that stabilizing selection never results in stable equilibria in a single population, unless gene action for the metric character is overdominant at all loci. However, nor-optimal selection for different optimum phenotypes in two (Bulmer, 1971b) or more than two (Bulmer, 1971c) partially isolated populations was shown to be a mechanism capable of maintaining genetic variability. It was also concluded that some variability could be maintained in a single population of finite size under the nor-optimal model with the addition of recurrent mutation (Bulmer, 1972) and/or independent selection in favour of heterozygotes (Bulmer, 1973). For the purpose of this study it will be assumed that the optimum model is capable of maintaining a reasonable amount of genetic variation and is thus sufficiently valid to act as a comparison for the homeostatic model, which has the maintenance of genetic variability as one of its basic premises.

Differences of opinion also exist as to the relationship between particular metric characters and fitness. Robertson (1955, 1966) and Latter (1962, 1963), for example, have examined this relationship theoretically and experimentally for several Drosophila characters. Their conclusion for abdominal and sternopleural bristle number, as an example, was that such characters were of peripheral importance to

fitness, and are therefore subjected to only very weak natural selection. On the other hand, O'Donald (1970, 1971) has produced evidence suggesting intense stabilizing natural selection for sterno-pleural bristle number in adult Drosophila (but only in males) under crowded conditions. Barnes (1968), Kearsey and Barnes (1970) and Linney, Barnes and Kearsey (1971) have also reported experimental results indicating that relatively intense natural selection acts on genes that determine bristle number, in some cases producing an observable effect which accords well with the optimum rather than the homeostatic model. These same authors have expressed further doubts about the validity of the homeostatic model because of what they claim to be the general paucity of evidence of single locus overdominance for fitness. However, a recent investigation in pigeons (Frelinger, 1972), seemed to indicate that single locus overdominance for fitness is a feasible proposition.

More importantly, in his initial detailed proposal of the homeostatic model, Lerner (1954) emphasised that single locus overdominance for fitness was not an integral requirement of the model. Rather, he was very careful to point out that it was "fitness as a whole" which exhibited overdominance.

The design of a definitive experiment that will enable a final decision to be made in favour of one of the two models has still to be determined. Indeed such an experiment may never be conceived if, as is quite likely, the real situation in nature lies somewhere in between. The current position is that both models continue to be discussed whenever natural selection appears to have counteracted the effect of artificial selection. A brief review will now be made of

the theory which is currently available to assist in such discussions.

## Interaction of artificial and natural selection

The result of artificial selection for a metric character in the presence of natural selection has been considered by superimposing artificial directional selection for the metric character onto each of the two models of stabilizing natural selection.

The homeostatic model was shown by Robertson (1956) to lead to certain predictions about the consequences of artificial selection when applied to a genetic system which could be described by the following single locus model:

| Genotype | $A_1A_1$ | $A_1A_2$ | $A_2A_2$ |
|---|---|---|---|
| Relative frequency | $(1-q)^2$ | $2q(1-q)$ | $q^2$ |
| Metric mean as deviation from heterozygote | $-\frac{1}{2}a$ | 0 | $+\frac{1}{2}a$ |
| Relative fitness | $1-s_1$ | 1 | $1-s_2$ |

In particular, it was demonstrated that the relative fitness of the population declines by $\frac{\bar{S}(\Delta x)^2}{2h^2\sigma_P^2}$ as a result of a change in the population mean of $\Delta x$, where

$$\bar{S} = \frac{\sum_i k_i S_i}{\sum_i k_i}$$ = weighted average of the $S_i$,

given that $S_i = \frac{s_1 s_2}{s_1 + s_2}$ / in which case $1-S_i$ is the average fitness of the equilibrium population relative to that of the heterozygote, at the $i^{th}$ locus,

and $k_i = \frac{a^2}{2} q(1-q)$ = genetic variance contributed by the $i^{th}$ locus. It was the parameter $\bar{S}$ that Robertson called the homeostatic strength of a metric character.

In addition

$$\sum_i k_i = \sigma_G^2 ,$$

$\sigma_P^2$ = phenotypic variance prior to selection, and

$$h^2 = \frac{\sigma_G^2}{\sigma_P^2} .$$

In comparison, the decline in fitness expected of individual deviants with a phenotype of x metric units in the original unselected population was given as $\frac{\bar{S}h^2x^2}{2\sigma_P^2}$. Since $\frac{\bar{S}(\Delta x)^2}{2h^2\sigma_P^2} > \frac{\bar{S}h^2x^2}{2\sigma_P^2}$ as long as heritability is less than unity, it was concluded that the decline in fitness as a result of artificial selection to a new phenotypic mean x, would be greater than that of individual deviants having phenotype x in the original population. Finally, it was predicted that upon relaxation of artificial selection, the return to the mean in the first generation would be equivalent to $\bar{S}\Delta x$, or a proportion S of the total phenotypic gain achieved by the previous artificial selection. Thus it was possible to estimate the value of $\bar{S}$, the homeostatic strength for a particular metric character, after a few generations of artificial selection.

Despite its apparent potential usefulness, the homeostatic model has received little subsequent theoretical attention in the context of artificial selection. In particular, there has been no attempt to investigate the interaction between homeostatic natural selection and artificial selection in a finite population. Predictions of the

limit to artificial selection, especially where genetic variance still remains, would be useful in providing a greater understanding of the implications of this type of natural selection.

The optimum model of natural selection has received more attention than the homeostatic model in the context of artificial selection. Expressions analogous to those of Robertson (1956) were first derived for the nor-optimal model by Latter (1960). The decline in fitness with artificial selection was predicted to be $\frac{(\Delta x)^2}{2\sigma^2}$ where $\sigma^2 = \sigma_p^2 + \sigma_f^2$ and $\sigma_f^2$ is a constant whose value is inversely proportional to the strength of natural selection. In terms of Latter's (1970) coefficient of centripetal selection, which is defined as $C = \frac{\sigma_p^2}{\sigma^2}$, the decline in fitness would be $C\,\frac{(\Delta x)^2}{2\sigma_p^2}$. Robertson's equivalent prediction was $\frac{\bar{S}}{h^2}\,\frac{(\Delta x)^2}{2\sigma_p^2}$. The return to the mean during the first generation of relaxation was shown to be a proportion $\frac{h^2\sigma_p^2}{\sigma^2}$ or $h^2C$ of the total gain previously achieved, in comparison with a proportion $\bar{S}$ for the homeostatic model. Both $\bar{S}$ and C can therefore be estimated for any metric character after a few generations of artificial selection, with the product $Ch^2$ corresponding operationally to $\bar{S}$ (Latter, 1970).

In two other papers Latter (1962, 1963) further examined the theoretical implications of the two models in the context of artificial selection, using as his examples data published by Latter and Robertson (1962) on the Kaduna population of Drosophila, and further data collected from artificial selection in the Canberra population. He was able to show, for example, that the total intensity of natural selection, I, as defined by Haldane (1954) could be expressed as

$$I = h^2\left[-\frac{\log_e \bar{w}}{g^2}\right] \qquad (1)$$

or

$$I = \frac{1}{h^2}\left[-\frac{\log_e \bar{w}}{g^2}\right] \qquad (2)$$

for the homeostatic and nor-optimal models respectively, where $\bar{w}$ is the mean fitness of selected lines, relative to controls after artificial selection has altered the mean of the metric character by g additive genetic standard deviations.

Having previously obtained values of $\frac{-\log_e \bar{w}}{g^2}$ of $0.022 \pm 0.005$ and $0.021 \pm 0.002$ at generations 5 and 10 respectively of artificial selection for abdominal bristle number in the Kaduna population (in which $h^2 = 40\%$), Latter estimated the heterozygote superiority for fitness to be $0.4 \times 0.022 = 0.5\%$ at the relevant loci, assuming the homeostatic model to be appropriate. Similar calculations can be performed on data supplied by Verghese and Nordskog (1968, p.233), to provide equivalent estimates in the range 0.5% to 1.5% approximately. Estimates such as these may be useful as guidelines to further theoretical studies, although several rather important assumptions are implicit in their use. Verghese and Nordskog pointed out that their own data are not in good agreement with the rather basic assumption that the decline in fitness with response to selection can be represented simply as $\frac{-\log_e \bar{w}}{g^2}$. Latter and Robertson (1962) also observed significant alterations in this quantity between generations 5 and 10 of selection for body size in Drosophila. As a first approximation, however, the above estimates may be of some value.

The interplay between directional artificial selection and natural selection for a phenotypic intermediate optimum was further investigated by James (1962) who developed expressions based on a

single locus additive model, to describe the effect of opposing non-optimal natural selection on the limits to artificial selection. The shortcomings of the model were considerable, as James pointed out, but the conclusions may be useful in that they indicate possible ways in which the measure of intensity of natural selection might interact with the other parameters commonly used to describe artificial selection in finite populations. The mean $\mu$, after t generations of artificial selection in this system was shown to be

$$\mu_t = \frac{i\sigma_P}{2I}\{1-(1-2Ih^2)^t\} \quad , \tag{3}$$

where i is the standardised selection differential, and I is Haldane's intensity of natural selection in a population with mean at the optimum.

The corresponding half-life of the selection process was predicted to be

$$H = \frac{0.35}{Ih^2} \quad . \tag{4}$$

Both these expressions are essentially relevant only to infinite populations. It was shown that the analogous expression for $\mu_t$ in a population of finite size N could be represented as

$$\mu_t = \frac{i\sigma_P}{2I}\left[1-\exp\left\{-4NIh^2\left(1-\left(1-\frac{1}{2N}\right)^t\right)\right\}\right] \quad , \tag{5}$$

and an estimate of the asymptotic limit would then be

$$\mu_\infty = 2N\frac{i\sigma_G^2}{\sigma_P}(1-2NIh^2) \tag{6}$$

which reduces to Robertson's (1960) prediction of $2N\frac{i\sigma_G^2}{\sigma_P}$ or 2N times the response in the first generation, when natural selection is absent.

Very little experimental evaluation of these predictions has been reported, although James (1965) did use equation (4) to estimate half-life in several previously reported selection experiments. Agreement between observed half-lives and those expected by James was not particularly evident, with predictions being much greater than those observed, but then Robertson's (1960) half-life prediction of 1.4N generations (for additive loci) was likewise a considerable over-estimate. Such a result, however, may simply indicate that artificial selection has successfully achieved fixation of most of the desired alleles, as Robertson has pointed out.

James' study was useful in that it was the first attempt to analyse the effect of the interaction between natural and artificial selection on the limit to artificial selection. In dealing with the optimum model of natural selection, however, the study did not emphasise that interactions between loci are a vital component. James' selective values took this into account, but his derivation of expressions for the metric mean at any time t, and at the limit tended to play down the importance of these interactions, with the result that the expression obtained do not necessarily apply to the type of limit most likely to be reached with the optimum model. A more detailed discussion of this problem is given later.

It would seem then, that both the homeostatic and optimum models of stabilizing natural selection need to be more fully explored in the context of artificial selection, before a proper understanding of the interplay between artificial and natural selection can be achieved.

# LIMITS TO ARTIFICIAL SELECTION IN THE PRESENCE OF NATURAL SELECTION

## Introduction

One of the more important gaps in current artificial selection theory is the lack of a proper understanding of what happens during the intermediate generations of artificial selection in the presence of natural selection, before total fixation has occurred. In particular, it would be useful to be able to predict in a population of finite size the occurrence of selection plateaux at which genetic variance still remains due to opposing natural selection.

Using the available algebra as a basis, it should be worthwhile to explore more fully both the optimum and homeostatic models of natural selection in the context of artificial selection, studying in some detail the implications of each with respect to the nature of response to artificial selection. Such a study has therefore been conducted, with the aim of determining the consequences of the interplay between these two selective forces.

First to be examined will be the homeostatic model of natural selection, with its implications for artificial selection in very large and in small populations being investigated in turn. The algebraic predictions so obtained for the latter situation will then be expanded with the aid of computer operation of a suitable transition probability matrix, to obtain a greater insight into the intermediate generations of selection. In all cases the aim of the matrix study will be to look for general patterns rather than specific results from a particular set of parameter values. An attempt will be made to express conclusions and predictions in terms of population parameters,

or combinations of parameters, which are relevant to the overall concept of artificial selection.

The optimum model of natural selection will then be considered with the aim of obtaining a greater understanding of its implications in the light of theory which has already been developed by other workers in this field.

Finally, the results of reverse and relaxed selection following forward selection will be examined. Predictions initially obtained for an additive model of artificial selection in the absence of natural selection will be compared with transition probability matrix results including the effect of natural selection.

## I. THE HOMEOSTATIC MODEL OF NATURAL SELECTION

Consider two alleles at a single locus in a large population undergoing artificial selection for a metric character, and in 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.

For a single locus 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 can be expressed (following Haldane, 1931) in terms of the selection coefficient $i\alpha$, where i is the standardized selection differential, and $\alpha$ is the difference (a) between the metric means of the two homozygotes, divided by the phenotypic standard deviation ($\sigma_p$). As usual, this relationship is only valid when a is small relative to $\sigma_p$.

For such a model, the metric mean 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 : | $(1 + \frac{i\alpha}{2})(1-s_1)$. |

## 1. ALGEBRAIC APPROXIMATIONS

### Change in gene frequency

The end result of a single generation of such artificial and natural selection will be a change in frequency of allele $A_1$ given by

$$\Delta q \doteq \frac{i\alpha}{2}q(1-q) + (s_1+s_2)q(1-q)(\bar{q}-q) - \frac{i\alpha}{2}(s_1+s_2)q(1-q)\{q+\bar{q}(1-2q)\} \qquad (1)$$

where $\bar{q}$ is the equilibrium frequency of allele $A_1$ with natural selection alone in a large population, and is given by $\bar{q} = \frac{s_2}{s_1+s_2}$ in the usual manner. The three terms of equation (1) correspond to artificial selection, natural selection and the interaction between these two forces, in that order.

The conditions necessary for the attainment of a selection plateau, which is in effect an equilibrium between artificial and natural selection, could obviously be obtained by setting $\Delta q = 0$ in equation (1). A far easier, and more enlightening approach is to consider the relative selective values of the three genotypes as a result of the combined forces of artificial and natural selection. In a large population the necessary and sufficient condition for an equilibrium is that the overall selective values should exhibit over-dominance. This will occur when $(1 + \frac{i\alpha}{2})(1 - s_1) < 1$ which gives

immediately the condition for equilibrium between artificial and natural selection as $s_1 > \frac{i\alpha}{2+i\alpha}$. Such a conclusion makes sense when it is considered that the direction of artificial selection in this model is in favour of the homozygote $A_1A_1$. Natural selection can only produce an equilibrium, or selection plateau, when it transfers maximum overall fitness in the presence of artificial selection from that homozygote to the heterozygote. It is to be expected then, that the only parameters of importance in determining whether or not a selection plateau will result, would be the strength of artificial selection and the natural fitness of the homozygote most favoured by artificial selection. This indeed turns out to be the case. Such an equilibrium is bound to be stable in a large population, since it arises out of a simple overdominance situation. The frequency of allele $A_1$ at the plateau can be written as

$$\hat{q} = \frac{(s_1+s_2)\ \bar{q}\ (2-i\alpha) + i\alpha}{(s_1+s_2)\ [2+i\alpha(1-2\bar{q})]}$$

which can have a value anywhere between $\bar{q}$ and 1, depending on the relative strengths of natural and artificial selection. If $\hat{q}$ does equal unity then there is no longer a plateau due to opposing natural selection but rather a plateau due to fixation of the favourable allele and hence exhaustion of genetic variance. Conversely, an equilibrium gene frequency less than unity corresponds to what might be called a pre-fixation plateau at which segregation still occurs and hence genetic variance still remains. Because the value of $\hat{q}$ depends solely on the relative strengths of natural and artificial selection, it follows that it should be possible to break through any such pre-fixation plateau by increasing the strength of artificial selection.

This could be most easily achieved by increasing the value of i, the intensity of artificial selection, if reproductive excess is sufficient.

Change in the mean of the metric character

The metric mean of the population is $\frac{a}{2}(2q - 1)$ when the genotypes are in Hardy-Weinberg equilibrium. A change in gene frequency of $\Delta q$ will therefore result in a corresponding change in the mean of the metric character given by

$$\Delta x = \frac{a}{2}[2(q+\Delta q) - 1] - \frac{a}{2}[2q-1]$$
$$= a\Delta q$$

providing that the measurement of phenotype is carried out prior to any action of natural selection. If some of the natural selection has already occurred prior to measurement, the genotypes will no longer be in Hardy-Weinberg equilibrium and the above relationship between change in gene frequency and change in metric mean will no longer hold. Therefore, when discussing change in the metric mean as a result of artificial selection in the presence of natural selection consideration must be limited for the time being to natural selection which occurs between measurement of an individual and conception of its progeny.

Relaxation of artificial selection

Robertson (1956) introduced the parameter $\bar{S}$ which he called the homeostatic strength of a character and which he defined as

$$\bar{S} = \frac{\sum_i k_i S_i}{\sum_i k_i}$$

where

$$S_i = \frac{s_1 s_2}{s_1 + s_2}$$

and

$$k_i = \tfrac{1}{2} a_i^2 q_i(1-q_i) .$$

$1-S_i$ is then the average fitness of the equilibrium population relative to that of the heterozygote at the $i^{th}$ locus, and the homeostatic strength is simply the mean of the $S_i$, weighted according to the proportion of additive genetic variance contributed by each locus. In the same paper, Robertson was able to show that $\bar{S}$ could be estimated by observing the change in metric mean resulting from one generation of relaxation in a large population after artificial selection has altered the mean by an amount $\Delta x$. For a single locus, the change in metric mean resulting from a single generation of relaxation at generation t will be

$$R_1 = a(s_1+s_2)\ q_t(1-q_t)(\bar{q}-q_t)$$

where $q_t$ is the frequency of allele $A_1$ after t generations of artificial selection. But

$$S = \frac{s_1 s_2}{s_1+s_2} = (s_1+s_2)\ \bar{q}(1-\bar{q})$$

which gives

$$R_1 = a \frac{S}{\bar{q}(1-\bar{q})}\ q_t(1-q_t)(\bar{q}-q_t) \quad ,$$

and therefore

$$S = \frac{R_1}{\Delta x} \frac{\bar{q}(1-\bar{q})}{q_t(1-q_t)} \cdot \frac{\Delta q}{(\bar{q}-q_t)} \qquad (2)$$

This expression can be simplified by making the likely assumption that the population was at equilibrium with natural selection before artificial selection was commenced. In this case $\Delta q = -(q_t - \bar{q})$ which gives

$$S = -\frac{R_1}{\Delta x} \frac{\bar{q}(1-\bar{q})}{q_t(1-q_t)} \qquad (3)$$

and $$|S| = \left|\frac{R_1}{\Delta x}\right| \qquad (4)$$

providing artificial selection has not altered gene frequency too far from the original equilibrium value. Equation (4) was first derived by Robertson (1956) using a different approach: the conditions under which it is likely to be useful are now quantified in equation (2). In particular, $\frac{R_1}{\Delta x}$ will be a reasonable estimate of S only if relaxation is carried out in one of the early generations of artificial selection, before $q_t(1-q_t)$ has altered very much from $\bar{q}(1-\bar{q})$. Even if this condition is met, a number of replicate selection/relaxation lines would be necessary in practice to obtain a useful estimate of S, because of the large sampling variances inevitably associated with single estimates of $\Delta x$ and $R_1$.

It was noted above that the only important parameter of homeostatic natural selection in the context of artificial selection is $s_1$, the natural selection coefficient of the homozygote most favoured by artificial selection. Since $s_1 = S/\bar{q}$, the same purpose can be achieved by using the parameter S to describe the strength of natural selection, so long as the associated equilibrium gene frequency $\bar{q}$ is also mentioned.

Chance of fixation

It is well known that the change in gene frequency distribution with time in a finite population of size N under a continuous model can be described approximately by the Kolmogorov forward equation

$$\frac{\partial \phi}{\partial t} = \frac{\partial^2}{\partial q^2}\left[\frac{q(1-q)\phi}{4N}\right] - \frac{\partial}{\partial q}[\phi''\Delta q] \qquad (5)$$

where $\phi(q,t)$ represents the distribution of gene freqnency at time t,

given an initial frequency $q_o$. In the current model, $\Delta q$ is the change in gene frequency resulting from artificial selection in the presence of natural selection. By following Kimura (1957) and solving the associated Kolmogorov backward equation for $t = \infty$, it is possible to obtain

$$u(q_o) = \frac{\int_0^{q_o} f(y)dy}{\int_0^1 f(y)\,dy} \quad , \quad (6)$$

where

$$f(y) = \exp[-2Ni\alpha y + 2N(s_1+s_2)(y-\bar{q})^2 + N(s_1+s_2)i\alpha\{2y\bar{q} + y^2(1-2\bar{q})\}],$$

and where $u(q_o)$ is the chance of fixation of allele $A_1$. For the present model $u(q_o)$ is best thought of as the proportion of loci expected to be fixed for the favoured allele within one line, or the proportion of lines expected to be fixed for allele $A_1$ in a replicated selection programme. Equation (6) reduces to the relevant equations of Robertson (1960) and Robertson (1962) for artificial selection alone, and natural selection alone, respectively. For $Ni\alpha<1$ and $N(s_1+s_2)<1$, an expansion of equation (6) gives

$$u(q_o) = q_o + 2Nq_o(1-q_o)\frac{i\alpha}{2} + 2Nq_o(1-q_o)\frac{s_1+s_2}{3}(3\bar{q}-1-q_o)$$

$$- 2Nq_o(1-q_o)\frac{s_1+s_2}{3}\frac{i\alpha}{2}[1+\bar{q}+q_o(1-2\bar{q})]+\ldots \quad . \quad (7)$$

Consideration of this expression and indeed the whole topic of this model can be simplified by assuming as was done in the previous section that the population was at equilibrium with natural selection before artificial selection was commenced. Thus it is now being assumed that homeostatic natural selection was acting in a large population maintaining the large-population equilibrium frequency of $\bar{q}$. At the commencement of artificial selection, a finite sample of individuals was withdrawn at random from the large population, giving

$E[q_o] = \bar{q}$. Unless otherwise stated therefore, during the rest of this study it will be assumed that $q_o = \bar{q}$.

By neglecting the interaction term, which will be considerably smaller than either of the other two terms in N, and by substituting $S = (s_1+s_2)\bar{q}(1-\bar{q})$, the expression for chance of fixation now becomes

$$u(\bar{q}) = \bar{q} + 2N\bar{q}(1-\bar{q})\frac{i\alpha}{2} + \frac{2}{3}NS(2\bar{q}-1) \quad . \quad (8)$$

The term representing artificial selection is always positive thereby indicating that any form of artificial selection will tend to increase the chance of fixation above the equilibrium and initial gene frequency of $\bar{q}$, as would be expected.

On the other hand, the term for natural selection can be positive or negative, depending on whether $\bar{q}$ is greater or less than 0.5. It can be seen from equation (8) that heterozygote superiority for fitness in a small population will decrease the limit to artificial selection only if $\bar{q}<0.5$. Conversely, if the allele most favoured by artificial selection is at an initial and equilibrium frequency of greater than 0.5, then heterozygote superiority for fitness in a small population will increase the chance of fixation above that expected from artificial selection alone.

This conclusion follows directly from Robertson's (1962) study in which it was shown that heterozygote superiority alone in small populations exerts essentially a twofold effect. The first and obvious effect is to decrease the rate of loss of heterozygosity (although it even fails to do this for equilibrium frequencies outside the range of approximately 0.2 to 0.8). Equally important, however, is what could be called a directional effect imposed on gene frequency

by heterozygote superiority in which the least frequent allele decreases in frequency over generations, ultimately having a lower chance of fixation than that expected with drift alone. In other words, heterozygote superiority alone in small populations results in the preferential fixation of the allele which forms the fitter of the two homozygotes. This directional effect is absent for $\bar{q} = 0.5$ because in this case both homozygotes are equally fit. Graphs showing the way in which heterozygote superiority decreases the frequency of the least frequent allele during the intermediate generations of selection have been presented and explained by Hill and Robertson (1968).

It would appear then, that if $\bar{q} > 0.5$ natural selection will always be aiding and never hindering the ultimate results of artificial selection, in which case a plateau due to conflict between artificial and natural selection could never be expected. This conclusion becomes more apparent by considering that artificial selection is attempting to establish homozygosity for the favoured (with respect to artificial selection) allele. If $\bar{q} > 0.5$, then this favoured homozygote will also be fitter (with respect to natural selection) than the other homozygote, and artificial selection will simply be accelerating and exaggerating a process which was inevitable in a small population under homeostatic natural selection anyway, namely the preferential fixation of the allele which forms the fitter of the two homozygotes.

The curves in figure 1, obtained from equation (6), illustrate the effect of heterozygote superiority for fitness on the chance of fixation due to artificial selection. The effect of natural

selection is expressed in terms of S which, as we have noted earlier, is a biologically meaningful parameter which can be estimated relatively early in a selection programme.

A word of explanation must be given on the use of S alone as the parameter of natural selection. Substitution of equation (1) for $\Delta q$ into the diffusion equation (5) and multiplying throughout by N would lead to the conclusion that the change in the gene frequency distribution could be described in terms of $Ni\alpha$ and $N(s_1+s_2)$ if the time scale were to be measured in units of t/N. Since $S = (s_1+s_2)\bar{q}(1-\bar{q})$, and $\bar{q}\ (1-\bar{q})$ is a constant, the above statement is equivalent to saying that the whole process can be described in terms of $Ni\alpha$ and NS. The big disadvantage however, of using NS in the present context is that it completely obscures the fact that S has very definite and, as it so happens, very convenient maximum values depending on $\bar{q}$.

Consider for example, $\bar{q} = 1-\bar{q} = 0.5$ which gives $S = \frac{2s}{4}$, since for $\bar{q} = 0.5$, $s_1 = s_2 = s$. S will obviously be maximum when both homozygotes have zero fitness (s=1), giving maximum $S = 0.5 = \bar{q} = 1-\bar{q}$. For $\bar{q}$ other than 0.5 the maximum value of S must reflect the situation in which the least fit of the two homozygotes has zero fitness. By expressing S in terms of the equilibrium frequency $\bar{q}$ and the selection coefficient of the least fit homozygote, S can be written as $\bar{q}s_1$, and $(1-\bar{q})s_2$ for $\bar{q} < 0.5$ and $\bar{q} > 0.5$ respectively. Setting $s_1 = 1$ and $s_2 = 1$ in turn, to give the relevant homozygote zero fitness, it can be seen that the maximum value of S is $\bar{q}$ for $\bar{q}<0.5$, and $1-\bar{q}$ for $\bar{q}>0.5$. Of particular interest in the context of artificial selection is the case in which $\bar{q}<0.5$ and $S = \bar{q}$ because this describes a situation reported

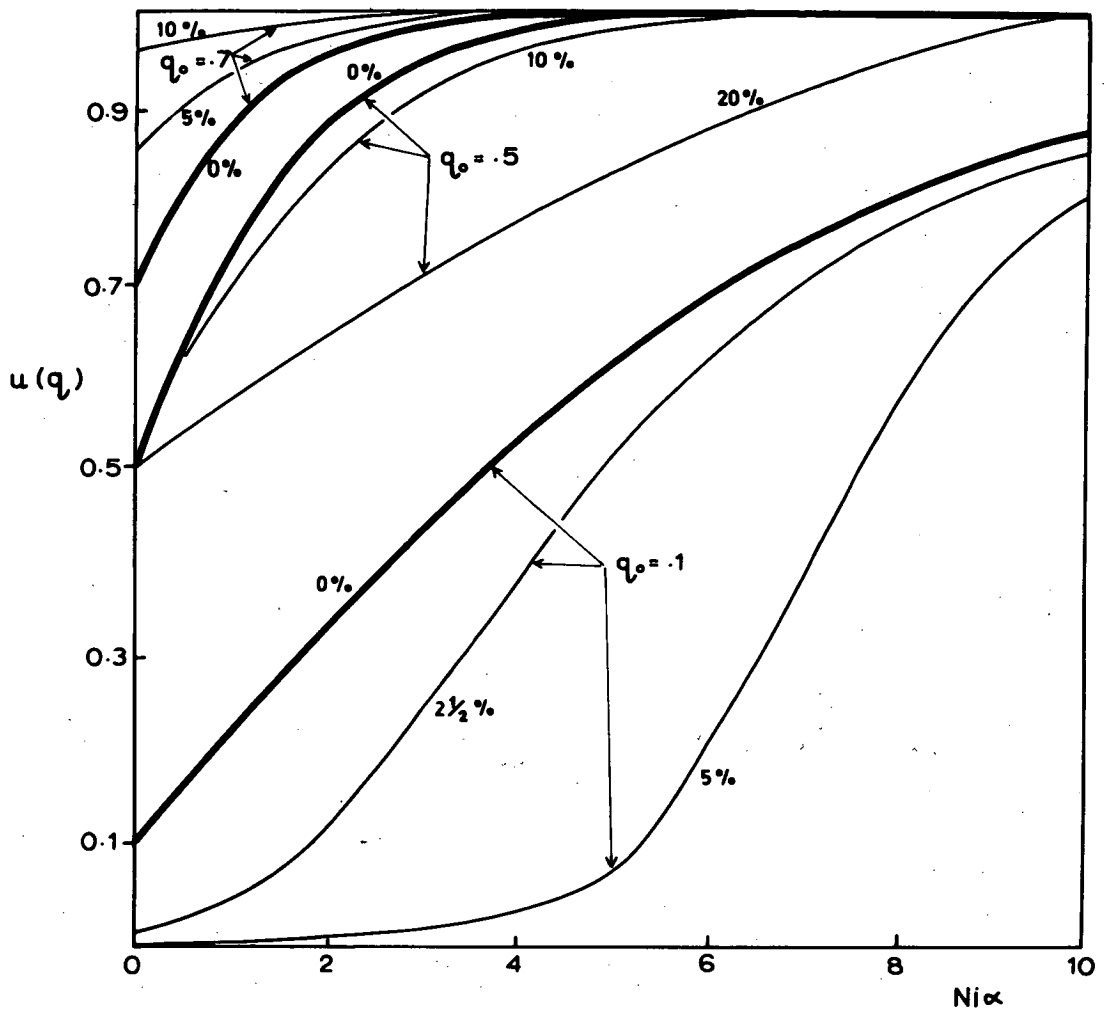


Figure 1. The effect of heterozygote superiority for fitness on the chance of fixation due to various strengths ($Ni\alpha$) of artificial selection. Curves are drawn for $q_o = \bar{q}$ equal to 0.1, 0.5 and 0.7, each for several values of S, the strength of natural selection.

several times in the literature, where artificial selection favours an allele which is lethal or sterile when homozygous (see for example, Clayton and Robertson, 1957; and Hollingdale, 1971). Another advantage of the use of S alone will be brought out below in the discussion of the matrix results, where it will be shown that a description in terms of S rather than NS enables more fruitful predictions to be obtained. Finally, it can be shown by a simple analysis of variance (see Appendix I) that over three population sizes (5, 10 and 20) and with four strengths of natural selection combined in all possible ways with four strengths of artificial selection, more than 85% of the variation in response can be accounted for by describing the selection process in terms of Nia and S.

Returning now to figure 1, it should be noted that the three curves representing no natural selection (S=0%) correspond exactly to the relevant curves in figure 1 of Robertson (1960). And as long as artificial selection is carried out prior to any natural selection, then the value of the metric mean at the limit could be represented on the same scale as chance of fixation, because only additive gene action for the metric character is being considered. Included in figure 1 is an example of the way in which homeostatic natural selection actively favours the effect of artificial selection at the limit for alleles with equilibrium frequencies greater than one half, in this case 0.7. The curves for $q_o = \bar{q} = 0.5$ illustrate that artificial selection will be opposed by natural selection if both homozygotes have the same natural fitness. The reason for this again derives directly from Robertson (1962), who showed that although the directional effect on gene frequency is absent for $\bar{q} = 0.5$, retardation of fixation for either allele is at a

maximum for this equilibrium frequency. Natural selection in this situation is acting therefore by favouring heterozygosity and would be expected to oppose artificial selection. The situation for $\bar{q}<0.5$ (in this case 0.1) brings out another point which can also be determined from equation (8), namely that it is conceivable that natural selection may exert a stronger influence than artificial selection in which case the chance of fixation will be less than the initial and equilibrium frequency, if $\bar{q}<0.5$. While such a result is unlikely to be achieved in practice for a number of loci, it does emphasise that the end result of the interaction of artificial and natural selection is quite simply a function of the relative strengths of each force.

It can be concluded from the graphs that natural selection will not seriously affect the ultimate results of artificial selection unless S is of the order of 0.05, or even greater for genes with intermediate initial frequencies.

Total advance in the mean at the limit

The effect of natural selection on the limit to artificial selection can be further analysed by considering the total change in gene frequency $[u(q_o)-q_o]$ which corresponds to a total change in metric mean of $a[u(q_o)-q_o]$. This can be written as $L_{AH}$, for the expected advance of the metric mean at the limit under the combined effects of Artificial selection and the Homeostatic model of natural selection. Equation (7) can be rewritten as

$$u(q_o)-q_o \doteq Ni\alpha q_o(1-q_o)(1-W)$$

where, for $q_o = \bar{q}$, $W = \frac{2}{3}S - \frac{s_1+s_2}{3}\left[\frac{2}{1\alpha}(2\bar{q}-1)-1\right]$ , (9)

which gives $L_{AH} \doteq 2N\Delta G\ (1-W)$ (10)

where $\Delta G$ is the change in metric mean in the first generation of artificial selection alone, being estimated as a $\frac{i\alpha}{2} q_o(1-q_o)$.

Under assumptions similar to those used here, Robertson (1960) predicted that the total advance at the limit due to artificial selection alone will be 2N times the change in the first generation. Equation (10) shows that this prediction will be altered by a factor 1-W in the presence of homeostatic natural selection. From equation (9) it can be seen that initial and equilibrium gene frequencies of 0.5 will give $W = 2S$, while relatively low frequencies will produce values of W well in excess of 2S. It is reasonable therefore to take

$$L_{AH} \doteq 2N\Delta G\ (1-2S) \qquad (11)$$

as a maximum estimate of the advance at the limit to artificial selection in the presence of homeostatic natural selection.

This equation however, is limited in usefulness by the assumptions inherent in its derivation, some of which have been described above. More importantly, it applies only to advance at the limit when total fixation has been achieved. On the other hand, it is obvious that the homeostatic model of natural selection may produce a plateau in the relatively early generations of selection, long before genetic variation has been exhausted. It will be shown later that the metric mean at such a pre-fixation plateau may not be exactly the same as the mean represented by $L_{AH}$, at total fixation. It remains to be seen therefore whether or not equation (11) is a useful prediction of advance in the mean at a prefixation plateau.

Intermediate generations

Expansion of the relevant transition probability matrix as in Robertson (1952) and more thoroughly in Narain and Robertson (1969) will provide relatively simple algebraic expressions which are adequate over a limited range of parameter values. For small $Ni\alpha$ and $N(s_1+s_2)$ it is possible to obtain from equation (1)

$$E[\Delta q_{t+1}] \doteq q_o(1-q_o)\{\frac{i\alpha}{2} + (s_1+s_2)(\bar{q}-\tfrac{1}{2}-\frac{i\alpha}{4})\}(1-\frac{1}{2N})^t + q_o(1-q_o)(s_1+s_2)(\tfrac{1}{2}-q_o)\{1 + \frac{i\alpha}{2}(1-2\bar{q})\}(1-\frac{3}{2N})^t \quad (12)$$

which for $q_o = \bar{q}$ gives

$$E[\Delta q_{t+1}] \doteq \{\frac{i\alpha}{2}\bar{q}(1-\bar{q}) + S(\bar{q}-\tfrac{1}{2}-\frac{i\alpha}{4})\}(1-\frac{1}{2N})^t + S(\tfrac{1}{2}-\bar{q})\{1 + \frac{i\alpha}{2}(1-2\bar{q})\}(1-\frac{3}{2N})^t \quad (13)$$

where $\Delta q_{t+1}$ is the change in gene frequency between generations t and t+1. Equation (12) reduces to

$$E[\Delta q_{t+1}] \doteq \frac{i\alpha}{2} q_o(1-q_o)(1-\frac{1}{2N})^t$$

for artificial selection alone as in Robertson (1960), and to

$$E[\Delta q_{t+1}] \doteq (s_1+s_2)q_o(1-q_o)\{(\bar{q}-\tfrac{1}{2})(1-\frac{1}{2N})^t + (\tfrac{1}{2}-q_o)(1-\frac{3}{2N})^t\}$$

for natural selection alone.

From equation (12) expectations can be derived for the frequency of allele $A_1$ at time t $[q_t]$ and at the limit $[q_\infty]$. The former turns out to be

$$E[q_t] \doteq q_o + 2Nq_o(1-q_o)\{\frac{i\alpha}{2} + (s_1+s_2)(\bar{q}-\tfrac{1}{2}-\frac{i\alpha}{4})\}[1-(1-\frac{1}{2N})^t] + 2Nq_o(1-q_o)\frac{s_1+s_2}{3}(\tfrac{1}{2}-q_o)\{1 + \frac{i\alpha}{2}(1-2\bar{q})\}[1-(1-\frac{3}{2N})^t] , \quad (14)$$

while the expression for E $[q_\infty]$ is exactly the same as that for $u(q_o)$ in equation (7) as would be expected. Equation (14) could be used to follow the course of gene frequency change from generation to generation during the whole period of selection. However, being derived from equation (12), it too is limited in usefulness to situations in which $Ni\alpha<1$ and $N(s_1+s_2)<1$. A more fruitful method of predicting changes in gene frequency over time involves the use of a transition probability matrix which will be described in the next section.

Half-life

Equation (14) can be used to obtain an expression for the half-life of the selection process. Following Narain and Robertson (1969) the half-life ($t_h$) can be estimated by solving for t in the equation

$$E[q_t] - q_o = \frac{u(q_o)-q_o}{2} \quad .$$

Substitution of the expressions already obtained for $E[q_t]$ and $u(q_o)$ eventually results in

$$Ax^3 + Bx + C = 0$$

where $x = e^{-t/2N}$ ,

$$A = \frac{s_1+s_2}{3}(\tfrac{1}{2}-q_o) + \frac{i\alpha}{6}(s_1+s_2)(\tfrac{1}{2}-q_o-\bar{q}+2\bar{q}q_o) \quad ,$$

$$B = \frac{i\alpha}{2} + (s_1+s_2)(\bar{q}-\tfrac{1}{2}) - \frac{i\alpha}{4}(s_1+s_2) \quad ,$$

and $$C = -\tfrac{1}{2}[\frac{i\alpha}{2} + \frac{s_1+s_2}{3}(3\bar{q}-q_o-1) + \frac{i\alpha}{6}(s_1+s_2)(2q_o\bar{q}-q_o-\bar{q}-1)] \quad .$$

Knowing that $x_o = \tfrac{1}{2}$ is one possible solution, and utilizing the Newton-Raphston method to obtain a better estimate, results in

$$x = x_o - \frac{Ax^3 + Bx + C}{3Ax^2 + B}$$

which gives

$$e^{-t/2N} = \tfrac{1}{2}\left[\frac{2A-8C}{3A+4B}\right] .$$

Solving for t results in

$$\hat{t}_h \doteq N[1.4 + 2A + 8B + 16C]$$

$$\doteq 1.4N + N(s_1+s_2)\{2q_o-1+i\alpha[q_o(1-2\bar{q}) + \bar{q}-\tfrac{1}{2}]\} \quad . \qquad (15)$$

This expression for half-life is only strictly valid for $Ni\alpha<1$ and $N(s_1+s_2)<1$. Within these limits it can be seen that the absence of natural selection results in a half-life of 1.4N generations, as was first predicted by Robertson (1960). With initial and equilibrium gene frequencies less than one half, $t_h$ will be less than 1.4N, this being a reflection of the decreased limit to artificial selection resulting from such natural selection. Conversely, with $\bar{q}>0.5$, it has already been shown that the chance of fixation will be increased above that expected from artificial selection alone, in which case it will take longer than 1.4N generations to achieve half this response.

Change in fitness with selection

The tendency for artificial selection to produce homozygosity for favourable alleles at loci associated with the character under selection would be expected under the homeostatic model to produce a decrease in fitness over and above that which could be attributed to the average inbreeding at all loci in the genome, the latter resulting simply from the effects of finite population size. It has not been possible to obtain a simple expression describing the way in which fitness will alter with artificial selection in a small population. A minimum estimate of the change in fitness can, however, be obtained by deriving an expression for the change in fitness due to the effect of

small population size alone in the absence of selection.

The mean fitness of $\bar{w}$ of a population under homeostatic natural selection can be represented as

$$E[\bar{w}_o] = 1 - S$$

at generation zero, for $q_o = \bar{q}$, and

$$E[\bar{w}_t] = 1 - S - E[(s_1+s_2)(q_t-\bar{q})^2]$$

at generation t. Both of these expressions have been derived in the usual manner directly from the single locus heterozygote superiority model, in the absence of artificial selection. Following the method used to derive equation (14) it is possible to obtain

$$E[\bar{w}_t] = 1 - S[2 - (1-\frac{1}{2N})^t]$$

$$= 1 - S(1+F)$$

where F is the coefficient of inbreeding which, with random mating in the absence of selection, is simply a function of population size and generation number. The mean fitness at complete fixation (F=1) is then rather obviously $E[\bar{w}_\infty] = 1-2S$. A useful way in which to express the change in fitness as a result of inbreeding and/or selection is to talk in terms of the ratio $\frac{\bar{w}_t}{\bar{w}_o}$ which is that proportion of the original fitness remaining at time t. It can now be seen that this ratio has an expectation of $\frac{1-S(1+F)}{1-S}$ for inbreeding alone (which arises solely from small population size) in the absence of artificial selection. Loci at which alleles had been subjected to artificial selection in a small population would be expected to be more homozygous than any estimate of F for that population would indicate. It can therefore be concluded that $\frac{1-S(1+F)}{1-S}$ will be a maximum estimate of the proportion of original fitness still remaining at a particular generation of artificial

selection in a small population. Furthermore, the best estimate available of the proportion of original fitness remaining at complete fixation will be $\frac{1-2S}{1-S}$. This too will be a maximum estimate because artificial selection may have resulted in the fixation of a larger proportion of alleles which produce relatively unfit homozygotes than would have occurred simply due to chance with inbreeding alone.

Summary

1. Only two parameters are of importance in determining whether or not Lerner's model of homeostatic natural selection will result in cessation of response to artificial selection. These are the natural fitness of the homozygote most favoured by artificial selection ($1-s_1$), and the strength of artificial selection ($i\alpha$).

2. In a large population, a selection plateau will result whenever $s_1 > \frac{i\alpha}{2+i\alpha}$.

3. The nature of the equilibrium between the two selective forces is such that it should be possible to break through any such 'prefixation' plateau by increasing the strength of artificial selection.

4. The strength of homeostatic natural selection (S) can be estimated as the ratio of response in the metric mean following a single generation of relaxation in a large population ($R_1$), to the response in the metric mean to all previous forward selection ($\Delta x$), but only if such relaxation is carried out quite early in the selection programme before gene frequencies have been altered substantially.

5. Since the natural selection coefficient $s_1$ can be written as $S/\bar{q}$,

the effect of natural selection can be described in terms of S and the large population equilibrium gene frequency ($\bar{q}$).

6. For a single locus, S has a potential maximum value of $\bar{q}$ for $\bar{q}<0.5$ and $1-\bar{q}$ for $\bar{q}>0.5$, and such maxima correspond to the least fit homozygote having zero fitness. The case in which $q_o = \bar{q}<0.5$ and $S=\bar{q}$ describes the situation where artificial selection favours an allele which is sterile or lethal when homozygous.

7. At a single locus, and assuming that artificial selection in a small population is commenced by random sampling from a very large population with equilibrium frequency $\bar{q}$ such that $E[q_o] = \bar{q}$, heterozygote superiority for fitness in the subsequent small population will decrease the chance of fixation due to artificial selection alone only for alleles with initial frequencies less than one half. Under such circumstances, the advance in the metric mean at the limit for alleles with initial frequencies less than but close to one half will have been reduced by a factor 1-2S from its usual expectation of 2N times the change in the first generation. The reduction will be greater for alleles which are initially less frequent.

8. The half-life of the selection process will be greater than 1.4N generations for alleles which are initially common ($q_o = \bar{q}>0.5$) and will be less for less frequent alleles ($q_o = \bar{q}<0.5$).

9. The proportion of original fitness remaining at the limit will never be greater than $\frac{1-2S}{1-S}$.

## 2. THE USE OF A TRANSITION PROBABILITY MATRIX

Most of the consideration so far has been of the effect of homeostatic natural selection on the ultimate results of artificial selection. We have seen the ways in which such natural selection can alter the expected metric mean at the limit, when total fixation has occurred. But one of the more 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 fixation has been achieved. Indeed, such an explanation has often been invoked to explain the observed lack of response to artificial selection in the continuing presence of additive genetic variance e.g., Lerner (1950, 1954), Clayton and Robertson (1957), Roberts (1966b), Verghese and Nordskog (1968). Under what conditions is such a model likely to be valid?

Our previous considerations would suggest that initial and equilibrium gene frequency will be important factors, but we have no idea as to what actual combinations of artificial and natural selection are likely to result in a pre-fixation plateau in a small population. It would appear that some indication could be obtained by setting $\Delta q=0$ and solving equation (12) for t, which would then be the generation at which cessation of response first appeared. However, being an approximation, and being relevant only for small $Ni\alpha$ and $N(s_1+s_2)$, equation (12) represents an ever increasing function in which case $\Delta q$ will never be zero. Unfortunately, therefore, a plateau prior to fixation could never be predicted from such an algebraic approximation.

The problem can be tackled with the aid of a transition probability

matrix, with which it is possible to obtain the expected value of gene frequency, genetic variance, and other parameters over subsequent generations under any relevant combination of artificial and natural selection. 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 recently been developed in the context of artificial selection alone by Narain and Robertson (1969).

Derivation of the matrix

From the model described previously, it can be seen that for a given gene frequency $q=j/2N$, the proportion $g_j$ of each genotype in the population of parents at the time of their mating will be

$$g_{j22} = \frac{1}{\bar{r}}(1-q)^2(1-s_2)(1-\frac{i\alpha}{2})$$

$$g_{j12} = \frac{1}{\bar{r}}2q(1-q)$$

$$g_{j11} = \frac{1}{\bar{r}}q^2(1-s_1)(1+\frac{i\alpha}{2})$$

where $\bar{r}$ is the proportion of the zygotes which remain to be included as parents, and is given by

$$\bar{r} = (1-q)^2(1-s_2)(1-\frac{i\alpha}{2}) + 2q(1-q) + q^2(1-s_1)(1+\frac{i\alpha}{2}) \quad .$$

The probability of obtaining exactly x $A_2A_2$, y $A_1A_2$ and z $A_1A_1$ genotypes ($x + y + z = N$) in a population of N survivors, given that there were j $A_1$ alleles in the population of zygotes in the same generation can be expressed as

$$f_j(x,y,z) = \binom{N}{xyz} g_{j22}^{x}\, g_{j12}^{y}\, g_{j11}^{z} \quad ,$$

and can easily be evaluated on a computer for all j=0,1,...,2N. It then follows that the probability $p_{jk}$ of obtaining k $A_1$ alleles in a population of N zygotes at generation t+1, given that there were j $A_1$ alleles in the N zygotes of generation t, will be

$$p_{jk} = \sum_{\substack{2z+y \\ =k}} f_j(x,y,z) \qquad j,k = 0,1,\ldots,2N,$$

which is an element of the transition probability matrix $\underset{\sim}{U}$. If all lines are considered, both fixed and unfixed, then $\underset{\sim}{U}$ is square of dimension 2N+1, and within each row $\sum_{k=0}^{2N} p_{jk} = 1$. Deletion of the first and last row and column, and adjustment of all remaining $p_{jk}$ to obtain $\sum_{k=1}^{2N-1} p_{jk}=1$ for each row, will result in a square matrix $\underset{\sim}{W}$ of dimension 2N-1, which will be relevant to segregating populations only.

Changes in various population parameters

Both matrices are independent of generation because the selective values used to calculate them are assumed to be independent of generation. At any generation t therefore, post-multiplication of $\underset{\sim}{U}$ or $\underset{\sim}{W}$ by a suitable column vector $\underset{\sim}{v}_t$ will result in a column vector $\underset{\sim}{v}_{t+1}$ expressing the results of that one generation of selection. For the parameters metric mean (x) and additive genetic variance ($\sigma_A^2$), the values of the vector at any generation will depend among other things, on whether natural selection occurs before or after artificial selection.

Consider for example the metric mean. For the present model it can be written most generally as $\frac{a}{2}[f_{11}-f_{22}]$ where $f_{11}$ and $f_{22}$ are the frequencies of genotypes $A_1A_1$ and $A_2A_2$ respectively at the time when metric phenotypes are actually observed, and $f_{11}+2f_{12}+f_{22}=1$. If artificial selection is carried out prior to the occurrence of natural

selection, then the genotypes will be in Hardy-Weinberg equilibrium at the time of observation, in which case $f_{11}=q^2$ and $f_{22}=(1-q)^2$, giving $x=\frac{a}{2}[2q-1]$ as noted previously. On the other hand, if natural selection has acted prior to artificial selection, then the genotypes will no longer have Hardy-Weinberg frequencies. Instead, the homeostatic model of natural selection will give

$$f_{11} = q^2(1-s_1)/\bar{w} \tag{1}$$

$$2f_{12} = 2q(1-q)/\bar{w} \tag{2}$$

and

$$f_{22} = (1-q)^2(1-s_2)/\bar{w} \tag{3}$$

where

$$\bar{w} = 1-s_1q^2 - s_2(1-q)^2$$

$$= 1 - S - (s_1+s_2)(q-\bar{q})^2$$

which is the natural fitness of a population with gene frequency q. The metric mean after natural selection will then be

$$\frac{a}{2}[f_{11}-f_{22}]$$

$$= \frac{a}{2\bar{w}}\left[2q-1 + S\left\{\frac{(1-q)^2}{1-\bar{q}} - \frac{q^2}{\bar{q}}\right\}\right]$$

which is equal to $\frac{a}{2}[2q-1]$ only if $S=0$ or $q=\bar{q}$. Thus the value of the metric mean at the time of artificial selection will depend on whether or not natural selection has already occurred, except at generation zero for which it has already been assumed that $q=\bar{q}$. It is possible to compare the two extreme cases of all natural selection prior to artificial selection, and artificial selection before any natural selection by a suitable choice of initial values for the column vector $v_o$. For the

latter situation, the changes in metric mean can be followed by setting

$$v_{o(j)} = 2(j/_{2N}) - 1 \qquad \begin{matrix} j = 0,\ldots,2N \text{ for } \underset{\sim}{U} \\ j = 1,\ldots,2N-1 \text{ for } \underset{\sim}{W} \end{matrix} .$$

Alternatively, the metric mean after natural selection and at the time of artificial selection can be followed by commencing with

$$v_{o(j)} = f_{11(j)} - f_{22(j)}$$

where

$$f_{11(j)} = (j/_{2N})^2(1-s_1)/\bar{w}_{(j)} \tag{4}$$

$$f_{22(j)} = (1-j/_{2N})^2(1-s_2)/\bar{w}_{(j)} \tag{5}$$

and $$\bar{w}_{(j)} = 1 - S - (s_1+s_2)(j/_{2N}-\bar{q})^2 \quad . \tag{6}$$

It should be noted that for the case of artificial selection prior to natural selection, the metric mean is a simple linear function of the frequency of allele $A_1$ before any selection has occurred. Changes in the metric mean in this situation will therefore indicate changes in the frequency of allele $A_1$ at the time of conception in any generation.

Turning now to additive genetic variance, it is convenient to follow Crow and Kimura (1970, section 5.6) and start by expressing the metric means (and frequencies) of the genotypes $A_2A_2$, $A_1A_2$ and $A_1A_1$ as $\mu + \bar{y}_{22}$, $(f_{22})$, $\mu + \bar{y}_{12}$, $(2f_{12})$, $\mu + \bar{y}_{11}$, $(f_{11})$ respectively, where again, $f_{22} + 2f_{12} + f_{11} = 1$. For the present additive model, $\bar{y}_{22} = -aq$, $\bar{y}_{12} = -a(q-\frac{1}{2})$ and $\bar{y}_{11} = -a(q-1)$. It can then be shown (for example, Crow and Kimura used the method of least squares) that the additive genetic variance is given by

and $\mu$ is the overall population mean.

$$\sigma_A^2 = 2q\ a_1\ \alpha_1 + 2(1-q)\ a_2\ \alpha_2 \tag{7}$$

where $\alpha_1 = q\bar{y}_{11} + (1-q)\bar{y}_{12}$

$= (1-q)\frac{a}{2}$ ,

$a_1 = [f_{11}\bar{y}_{11} + f_{12}\bar{y}_{12}]/q$

$= (1-q)\frac{a}{2}[2\frac{f_{11}}{q} + 2(\tfrac{1}{2}-q)\frac{f_{12}}{q(1-q)}]$ ,

$\alpha_2 = q\bar{y}_{12} + (1-q)\bar{y}_{22}$

$= -q\frac{a}{2}$ ,

and $a_2 = [f_{12}\bar{y}_{12} + f_{22}\bar{y}_{22}]/(1-q)$

$= -q\frac{a}{2}[2(q-\tfrac{1}{2})\frac{f_{12}}{q(1-q)} + 2\frac{f_{22}}{1-q}]$ .

The above relationships indicate that $\alpha_1$ and $\alpha_2$ are the average effects (Falconer, 1960), while Crow and Kimura (1970) have called $a_1$ and $a_2$ the average excesses, of alleles $A_1$ and $A_2$ respectively. If the population is observed when the genotypes are in Hardy-Weinberg proportions, then $f_{11} = q^2$ [and $f_{12} = q(1-q)$] giving $a_1 = \alpha_1$ for example, in which case

$$\sigma_A^2 = 2q\alpha_1^2 + 2(1-q)\alpha_2^2$$

$$= \frac{a^2}{2}q(1-q) \qquad (8)$$

as expected. In the context of the present model, however, if natural selection has occurred prior to artificial selection then the additive variance actually observed at the time of artificial selection will be, from (7)

$$\sigma_A^2 = \frac{a^2}{2}q(1-q)[2(1-q)\frac{f_{11}}{q} + 4(\tfrac{1}{2}-q)^2\frac{f_{12}}{q(1-q)} + 2q\frac{f_{22}}{1-q}] \qquad (9)$$

where $f_{11}$, $f_{12}$ and $f_{22}$ are given by expressions (1), (2) and (3). The two extreme situations can once again be represented by a suitable choice of initial values for the column vector $\underset{\sim}{v}_o$. When artificial selection is carried out prior to the occurrence of any natural selection, it can be seen from (8) that changes in additive genetic variance observed at the time of artificial selection can be followed from generation to generation by setting

$$v_{o(j)} = j/_{2N}(1-j/_{2N}) \quad .$$

On the other hand, if all natural selection has occurred before artificial selection, then the additive genetic variance actually observed at the time of artificial selection in any generation can be determined by setting $q = j/2N$ and commencing with

$$v_{o(j)} = q(1-q)\left[2(1-q)\frac{f_{11(j)}}{q} + \frac{4(\frac{1}{2}-q)^2}{\bar{w}_{(j)}} + 2q\,\frac{f_{22(j)}}{1-q}\right]$$

where $f_{11(j)}$, $f_{22(j)}$ and $\bar{w}_{(j)}$ are given by expressions (4), (5) and (6).

It must be emphasised that the end result of the interaction of artificial selection and homeostatic natural selection within any one generation is the same irrespective of when each type of selection occurs. Reference to the generalised derivation of selection coefficients for artificial selection in appendix II shows that these coefficients depend only on the deviation of the phenotypic mean of each homozygote from that of the heterozygote, the intensity of artificial selection (i) and the phenotypic standard deviation ($\sigma_p$). They do not depend on relative frequencies of genotypes, nor do they depend on the amount of additive genetic variance present. If we assume therefore, that homeostatic natural selection will cause negligible alteration to the phenotypic

variance within a generation, then the selection coefficients due to artificial selection will be the same irrespective of the stage or stages of the generation at which natural selection occurs.

Consider for example, selection occurring in the following manner:-

| | $A_2A_2$ | | $A_1A_2$ | | $A_1A_1$ |
|---|---|---|---|---|---|
| viability from conception to maturity | $(1-s_2)^p$ | : | 1 | : | $(1-s_1)^r$ |
| artificial selection | $1-\frac{i\alpha}{2}$ | : | 1 | : | $1+\frac{i\alpha}{2}$ |
| adult viability, mating ability and fertility | $(1-s_2)^{1-p}$ | : | 1 | : | $(1-s_1)^{1-r}$ |

For any values of the proportions p and r, the overall selective values of the three genotypes after all selection will be

$$(1-s_2)(1-\tfrac{i\alpha}{2}) \quad : \quad 1 \quad : \quad (1-s_1)(1+\tfrac{i\alpha}{2})$$

as has been assumed throughout this study.

The reason for looking at the two extreme situations is that all conceivable intermediate situations involving some natural selection prior to, and further natural selection following artificial selection, must lie somewhere in between the results predicted for the two extreme cases.

Another parameter of interest in the present model is natural fitness, and it is possible to predict the absolute fitness of the population at any generation by starting with

$$v_{o(j)} = 1 - S - (s_1+s_2)(j/_{2N}-\bar{q})^2 \quad .$$

Changes in the distribution of gene frequencies

Pre-multiplication of the matrix $\underset{\sim}{U}$ by a row vector $\underset{\sim}{u}_0$ of order 2N+1 with all elements zero except the jth which is unity, will produce a row vector $\underset{\sim}{u}_1$ describing the distribution of gene frequencies at generation 1, including the probabilities of fixation and loss, given an initial gene frequency of j/2N. Continual pre-multiplication of $\underset{\sim}{U}$ by $\underset{\sim}{u}$ will provide the gene frequency distribution at all subsequent generations.

## 3. THE PATTERN OF RESPONSE TO SELECTION

The matrix operations described above have been carried out with an effective population size of N=10 for t=8N generations with various combinations of artificial and natural selection. This has enabled curves to be drawn showing the way in which various population parameters alter during the selection process. The final generation was chosen as t=8N simply because it represents a convenient multiple of N, and corresponds to almost all (in this case 98.2%) of the inbreeding process for a locus with neutral alleles. In addition, it represents a period of selection longer than most experiments reported in the literature, and thus should include all periods of relevance to practical selection programmes.

An effective population size of N=10 was chosen because it represents a realistic value of N when compared with most of the artificial selection experiments reported in the literature, and also because of its arithmetic convenience. Several analogous runs were carried out at N=5 and N=20, in order to check the generality of conclusions drawn from the

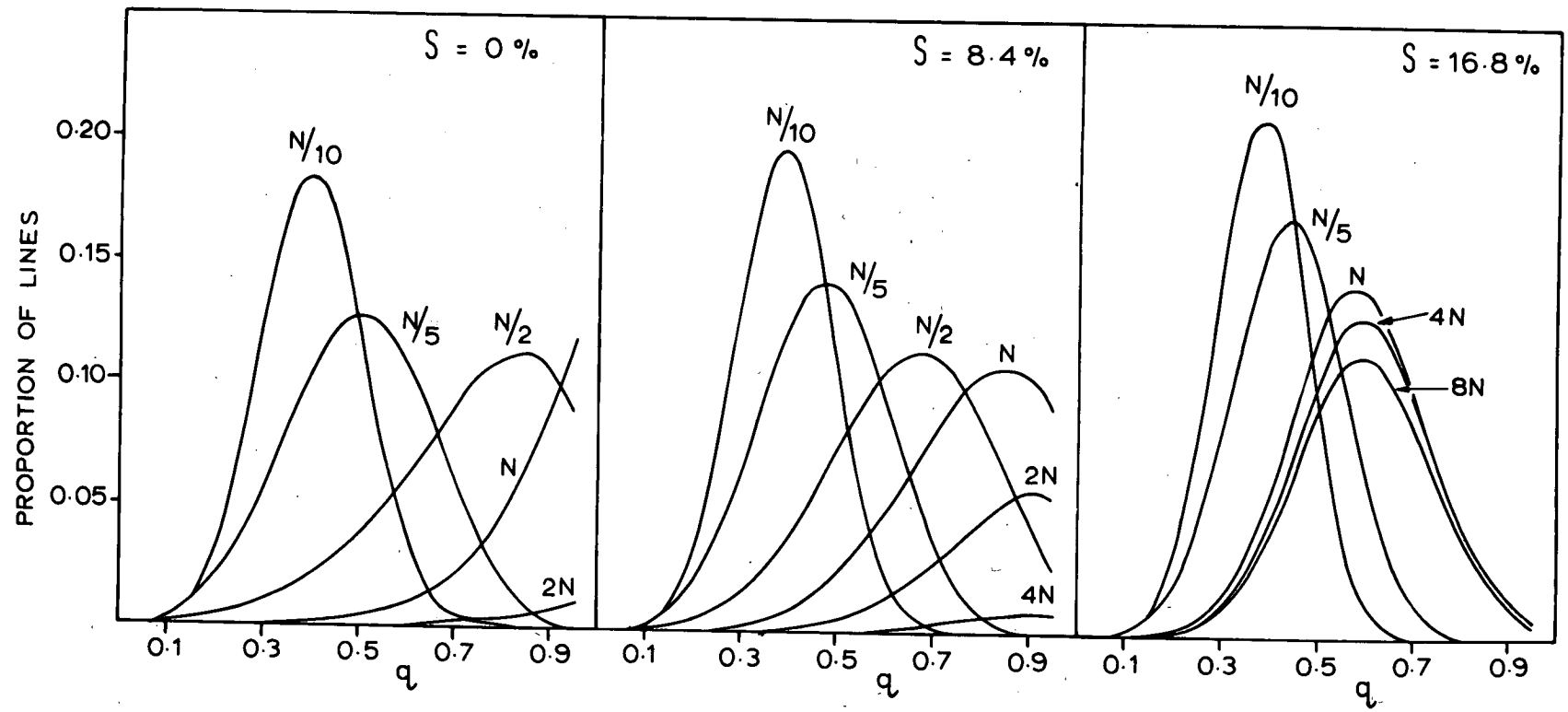


Figure 2. The change in frequency distribution of allele $A_1$ during the course of artificial selection in favour of that allele, with no natural selection (S = 0%) and with natural selection corresponding to S values of 8.4% and 16.8%. Curves are drawn for various generations, expressed in terms of effective population size, N. In this example $q_o = \bar{q} = 0.3$ and $Ni\alpha = 8$.

majority of runs at N=10. Differences in detail were of course observed, but the general trends and overall predictions observed and obtained from N=10 were still evident in the other runs. An analysis of the correspondence between analogous runs at different population sizes can be seen in Appendix I.

Changes in gene frequency distribution

An initial understanding of the interaction between artificial and natural selection can best be achieved by considering the changes of the gene frequency distribution during the selection process. An example of the way in which various strengths of natural selection can alter the effect of artificial selection is given in figure 2, which shows for one strength of artificial selection and three strengths of natural selection, the shape of the frequency distribution of allele $A_1$ at various generations during the selection programme.

With no natural selection (S=0%) the distribution moves quickly towards fixation of the favoured allele which is completely achieved soon after generation 3N. An intermediate strength (S=8.4%) of natural selection slows down the progression of the distribution, postponing the attainment of total homozygosity until much later, around generation 6N. Still stronger natural selection (S=16.8%) produces a distinctly non-linear steady-state representing an equilibrium between natural and artificial selection which is reached as early as generation N. Fixation and loss occur at a much reduced rate from such a steady state. More $A_1$ alleles will be fixed than lost simply because the mode of the steady state distribution is at a point greater than 0.5. The mean gene frequency will therefore continue to increase slowly, in spite of

a stable equilibrium between natural and artificial selection. This, then, is a stable equilibrium which does not appear as a selection plateau. On reflection, such a result would be expected for any situation in which a stable equilibrium is reached at a gene frequency above one half providing that the steady state distribution is reasonably symmetrical. Similarly, if a stable equilibrium steady state is reached at a gene frequency of less than 0.5, the mean gene frequency and hence metric mean may actually decrease, because now the mode of the steady state distribution is closer to loss of the favoured allele than to fixation.

The one exception to this conclusion will be associated with very strong natural selection, of the order of $\bar{q}$ for equilibrium frequencies less than one half and $1-\bar{q}$ for those greater than 0.5. Natural selection of this strength confers effectively zero fitness on the homozygote of the most favoured allele, and the least favoured allele respectively, in which case fixation of the relevant allele is effectively prevented. Since artificial selection has as its aim the fixation of the favoured allele, the latter situation of $S=1-\bar{q}$ for $\bar{q}>0.5$ will be assisting rather than hindering artificial selection. It is therefore only in the case of very strong natural selection on alleles with initial and equilibrium frequencies less than one half that a stable equilibrium with a stable gene frequency could be expected. Even this type of equilibrium would eventually produce a decrease in gene frequency and metric mean because fixation, which is inevitable in a small population, will essentially be of only the homozygote with the lower metric mean. The generations at which such a decrease in mean is likely to be observed however (for example, some time after

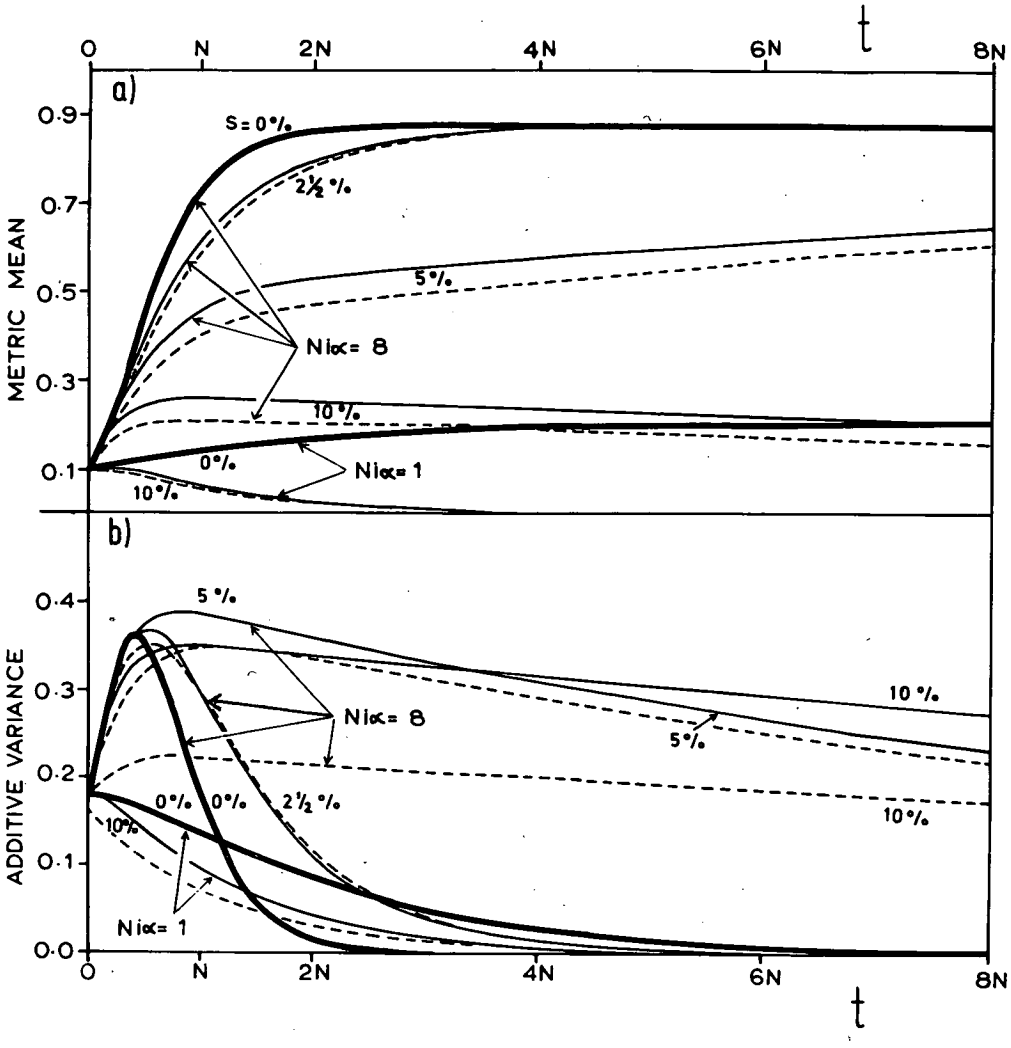


Figure 3. $q_o = \bar{q} = 0.1$. Expected response in metric mean and change in additive genetic variance resulting from artificial selection in a population of effective size N, during 8N generations, with natural selection occurring before (dotted lines) or after (solid lines) artificial selection. Curves are drawn for various strengths (S) of natural selection, with relatively weak (Niα = 1) and relatively strong (Niα = 8) artificial selection. The scale for metric mean x is drawn as $\frac{x}{a} + \frac{1}{2}$ so as to also represent gene frequency for the solid lines. Similarly additive variance $\sigma_A^2$ is shown on a scale $\frac{2\sigma_A^2}{a^2}$ so as to also represent heterozygosity for the solid lines.

generation 10N) are hardly likely to be the concern of a person carrying out an artificial selection programme in large animals.

Changes in metric mean and genetic variance

The effect of the interaction between artificial and natural selection on the metric mean is illustrated in figures 3a, 4a, 5a and 6a, while the corresponding changes in additive genetic variance are shown in figures 3b, 4b, 5b and 6b. For the case of artificial selection prior to natural selection (solid lines), the graphs for metric mean also indicate frequency of allele $A_1$ at conception. Similarly, the solid lines in figures 3b to 6b indicate heterozygosity at conception as well as additive genetic variance. In either case, the graphs for additive genetic variance also indicate total genetic variance because of the additive model being considered here.

It must be emphasised that the graphs in figures 3a to 6a correspond exactly to the curves so often used in the reporting of results of artificial selection programmes, namely selection response against time in generations. Furthermore, because the transition probability matrix is always expressed in terms of expected values, there is no sampling variance around the response curves obtained from it. Only one run of the computer for each combination of artificial selection and natural selection is needed, as there is no stochastic element at all in the actual computer manipulations. The response curves represent therefore the result which would be expected for the mean of a large number of replicate selection lines for one locus, or the mean response to selection for a quantitative character determined by a large number of independent equivalent loci within one line. It is

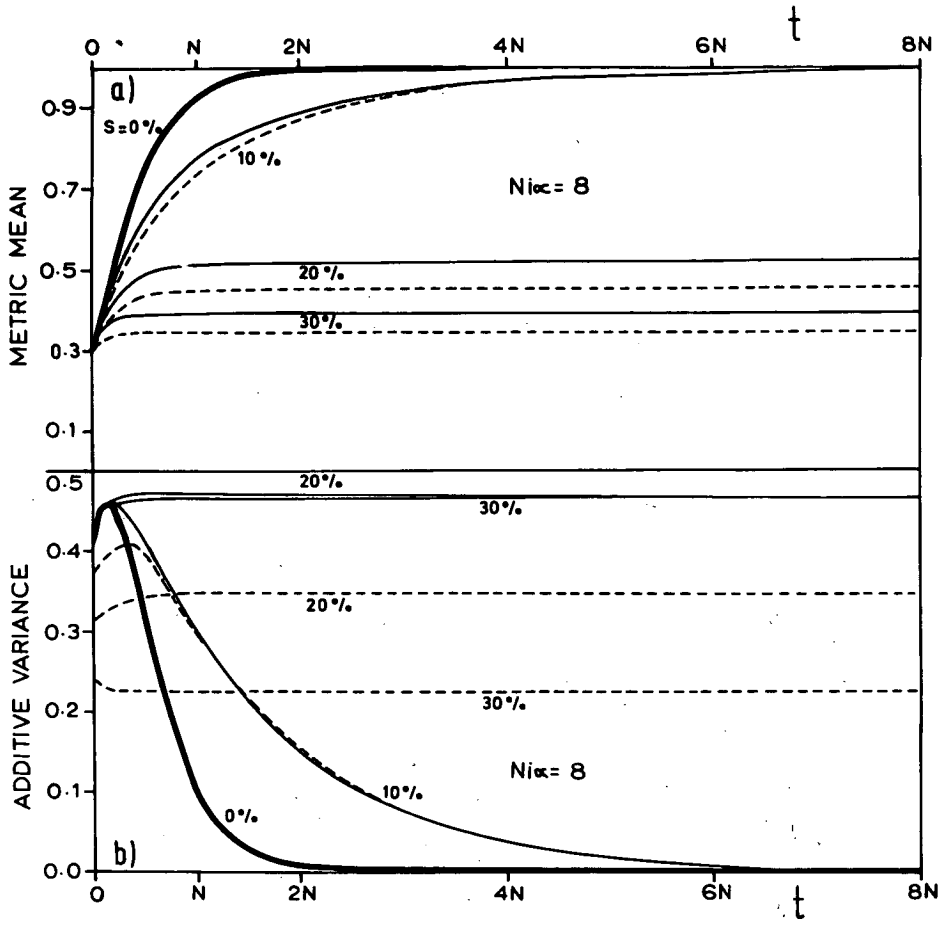


Figure 4. $q_o = \bar{q} = 0.3$. Expected response in metric mean and change in additive genetic variance resulting from artificial selection in a population of effective size N, during 8N generations, with natural selection occurring before (dotted lines) or after (solid lines) artificial selection. Curves are drawn for various strengths (S) of natural selection, with artificial selection of Niα=8. The scale for metric mean x is drawn as $\frac{x}{a} + \frac{1}{2}$ so as to also represent gene frequency for the solid lines. Similarly, additive variance $\sigma_A^2$ is shown on a scale of $\frac{2\sigma_A^2}{a^2}$ so as to also represent heterozygosity for the solid lines.

important to note that unless otherwise stated, the values of population parameters so obtained refer to the average over all lines, or all loci, including both those that have already reached fixation and those that are still segregating, at any particular generation. Allan and Robertson (1964), being the first to make use of transition probability matrix multiplication on a computer in the study of artificial selection in small populations, have discussed the implications of this method in more detail.

In general, it can be seen that the changes in metric mean and genetic variance follow the same trends irrespective of what stage of the generation natural selection occurs. The effect of any 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 to additive genetic variance, at least for relatively weak natural selection. However, reductions of over one half in the variance actually observed can be seen for very strong natural selection prior to the time of observation, especially at intermediate initial gene frequencies.

Of particular interest are the dotted lines for S=10% and 30% in figures 3a and 4a respectively, as these represent the situation in which the allele most favoured by artificial selection is lethal when homozygous. The progress of such alleles is seen to be similar to that followed at loci where the favoured allele is sterile when homozygous (solid lines for S=10% and 30%). In either case, the metric mean is prevented from being moved away very far from its original value and may even decrease due to chance fixation of the alternative allele.

Because of the overall similarity in trends for natural selection occurring before and after artificial selection, the following discussion will be mostly in general terms, not necessarily distinguishing between the different possible stages of occurrence of natural selection.

Looking now more closely at the curves for $q_o = \bar{q} = 0.1$ and relatively strong artificial selection ($N i\alpha = 8$) it can be seen that, in the absence of natural selection (S=0%), a plateau is reached fairly early in the selection programme, at around generation 3N. Reference to figure 3b shows that this plateau is due to exhaustion of genetic variance, because of complete homozygosity. The fact that the final gene frequency is around 0.9 indicates that approximately 10% of lines, or loci, were fixed for the wrong allele because of small population size. Even higher values of $N i\alpha$ would therefore have been needed to achieve complete fixation for the favourable allele alone, in which case the frequency of the favourable allele at the limit would have been unity. It can be seen from the curve for $N i\alpha = 8$ and S=0% that it is quite possible to run out of genetic variance and thus reach a fixation plateau relatively early in a selection programme. The curve for $N i\alpha = 8$ and S=2½% indicates that weak natural selection decreases the rate of selection advance and hence postpones but does not prevent the attainment of a fixation plateau. The ultimate limit is not reduced. Stronger natural selection (S=5%) causes a further decrease in the rate of selection advance and also decreases the ultimate limit, while the maximum possible strength of natural selection (S=10%) produces a prefixation plateau at which much genetic variance remains as early as generation N.

The continual advance in the metric mean and gene frequency for

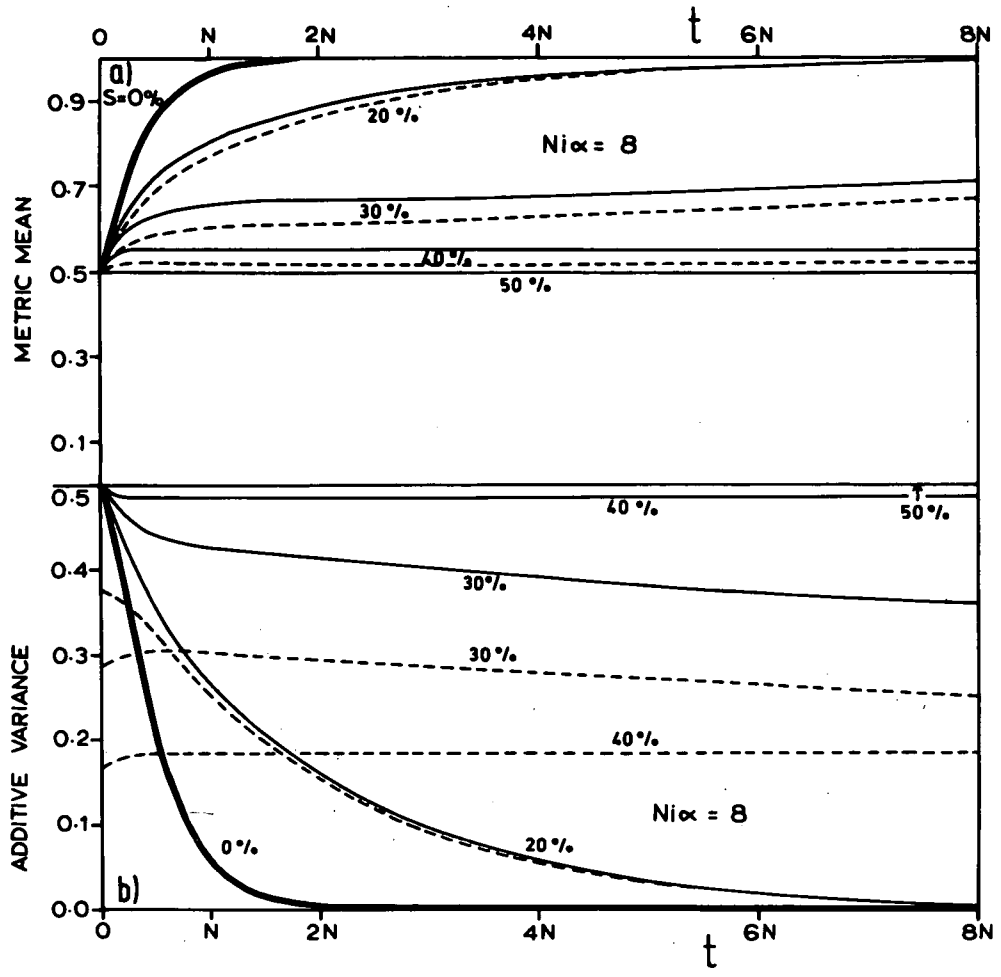


Figure 5. $q_o = \bar{q} = 0.5$. Expected response in metric mean and change in additive genetic variance resulting from artificial selection in a population of effective size N, during 8N generations, with natural selection occurring before (dotted lines) or after (solid lines) artificial selection. Curves are drawn for various strengths (S) of natural selection with artificial selection of $Ni\alpha = 8$. The scale for the metric mean x is drawn as $\frac{x}{a} + \frac{1}{2}$ so as to also represent gene frequency for the solid lines. Similarly additive variance $\sigma_A^2$ is shown on a scale of $\frac{2\sigma_A^2}{a^2}$ so as to also represent heterozygosity for the solid lines.

S=5% is due solely to continual fixation of the more frequent allele. Indeed it has been found that in this case the gene frequency in segregating lines has actually reached an equilibrium value of 0.614 corresponding to a steady state frequency distribution at about generation 2.5N. This then is an example of an equilibrium between artificial and natural selection which does not appear as a selection plateau. Likewise the eventual decrease in mean with S=10% is due to the inevitable fixation of allele $A_2$, since the homozygote $A_1A_1$ now has zero fitness. Again it has been found that the frequency of allele $A_1$ in those lines still segregating has remained constant ever since the plateau first appeared.

The associated changes in genetic variance illustrate the same conclusions in a different manner. With intense artificial selection ($Ni\alpha=8$) and no natural selection (S=0%), genetic variance increases as gene frequency increases until with gene frequency above 0.5 and with fixation proceeding quite rapidly, genetic variance quickly decreases to effectively zero at a time (t=3N) corresponding to the time when a plateau was observed in the population mean. Weak natural selection (S=2½%) simply maintains variance for a slightly longer period prior to a similar decrease to a somewhat later exhaustion of genetic variance. In both cases a plateau does not occur until total fixation has been achieved. Stronger natural selection (S=5% and 10%) maintains variance at a relatively high level for a much longer period, during which time a plateau has been observed in the population mean. Considerable heterozygosity and genetic variance will thus be associated with these plateaux. For less intense artificial selection ($Ni\alpha=1$) increasing strength of natural selection tends to decrease heterozygosity at least

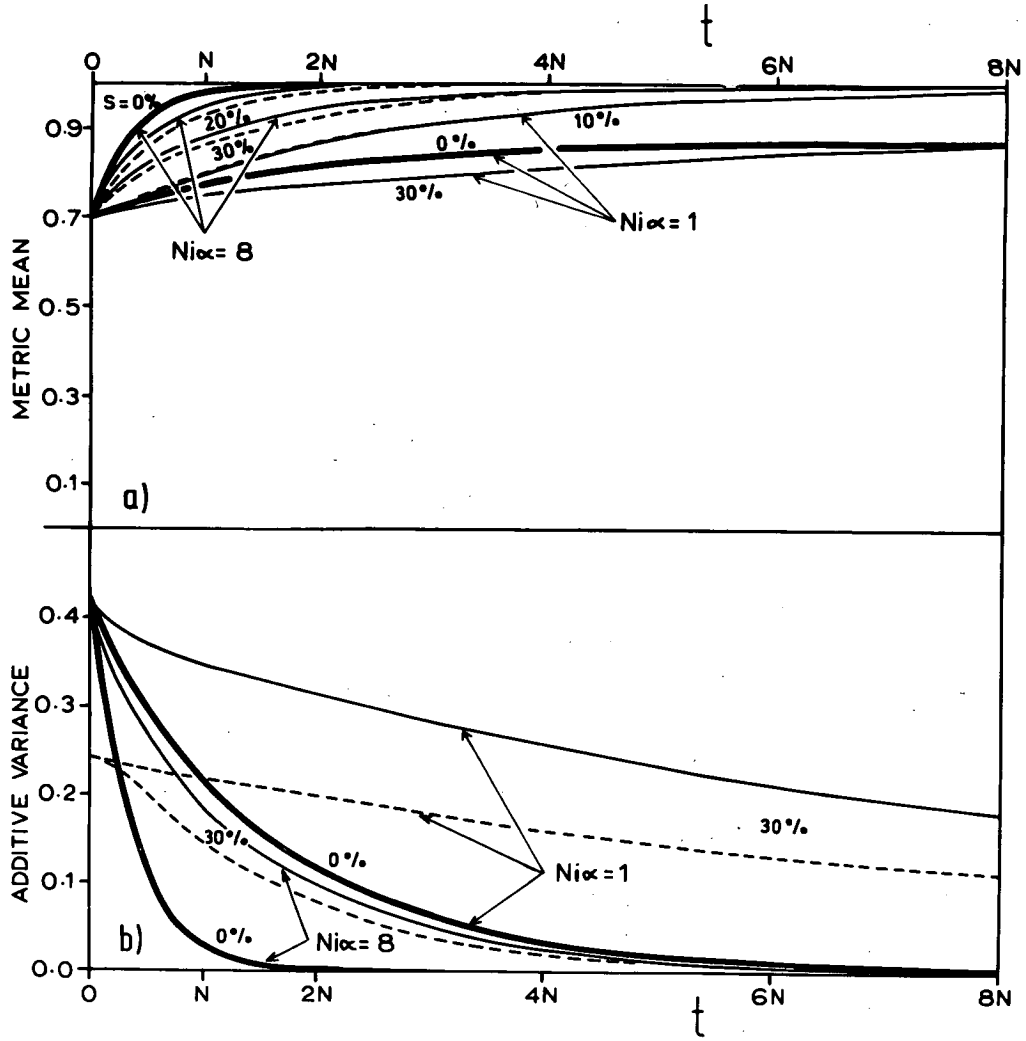


Figure 6. $q_o = \bar{q} = 0.7$. Expected response in metric mean and change in additive genetic variance resulting from artificial selection in a population of effective size N, during 8N generations, with natural selection occurring before (dotted lines) or after (solid lines) artificial selection. Curves are drawn for various strengths (S) of natural selection, with relatively weak (Niα = 1) and relatively strong (Niα = 8) artificial selection. The scale for metric mean x is drawn as $\frac{x}{a} + \frac{1}{2}$ so as to also represent gene frequency for the solid lines. Similarly additive variance $\sigma_A^2$ is shown on a scale of $\frac{\sigma_A^2}{a^2}$ so as to also represent heterozygosity for the solid lines.

during the first half of the selection process, but this is only because heterozygote superiority tends to maintain the mode of the distribution of gene frequency closer to its original position of $q=0.1$ and hence to increase the chances of loss of allele $A_1$ due to sampling.

The curves for $q_o=\bar{q}=0.3$ and 0.5 illustrate that a similar pattern of selection response and plateau formation results from the whole range of initial and equilibrium gene frequencies equal to or below 0.5.

It has previously been stated that heterozygote superiority for fitness will increase the chance of fixation of an allele undergoing artificial selection, for initial and equilibrium frequencies greater than 0.5. But alleles commencing at such relatively high frequencies have a high chance of fixation anyway due to artificial selection alone. What will be the effect of homeostatic natural selection on the pattern of selection response of an allele which was bound to be fixed [$u(q_o)=1$] due to artificial selection alone? The curves for $q_o=\bar{q}=0.7$ in figure 6a show that natural selection will retard the selection advance at such loci, but will not alter the ultimate result of complete fixation for the favoured allele. Natural selection in such circumstances would therefore be expected to increase the half-life of the selection process, in agreement with the earlier algebraic prediction. If the strength of artificial selection is not sufficient to produce inevitable fixation of allele $A_1$ however, ($Ni\alpha=1$), then relatively weak natural selection is seen to increase the mean at the limit, as predicted. Relatively strong natural selection ($S=30\%$) is now still sufficient to establish an equilibrium between the two forces of selection, and the change in mean which is actually observed

here is solely due to chance fixation of allele $A_1$ in a relatively high proportion of lines. The corresponding graphs for genetic variance illustrate the range of possible effects of natural selection (S = 0% to the maximum of 30%) on the changes in these parameters brought about by artificial selection. Natural selection is seen to maintain heterozygosity for a longer period of the selection process.

## 4. PREDICTION OF A PLATEAU

From a practical point of view, it would be useful to be able to predict approximately the generation at which a plateau will first occur ($\hat{t}$), the advance in the mean at the plateau (L) and the proportion of heterozygosity or genetic variance remaining at that time. An indication of the relative fitness of the population at the plateau would also be of use. Algebraic expressions which are relevant to some of these predictions have already been obtained. They can now be tested against the much more general results obtained from the transition probability matrix.

### a) Time to reach a plateau

The difficulty in pinpointing the generation at which a plateau first appears, or indeed whether or not a plateau actually exists in any curve in figures 3 to 6 is very similar to the difficulty met by those (for example, Roberts, 1966a) who have tried in practice to identify a plateau in an actual selection line. At what point does a decreased rate of selection advance correspond to a plateau? Realizing that any decision, in theory or in practice, is bound to be

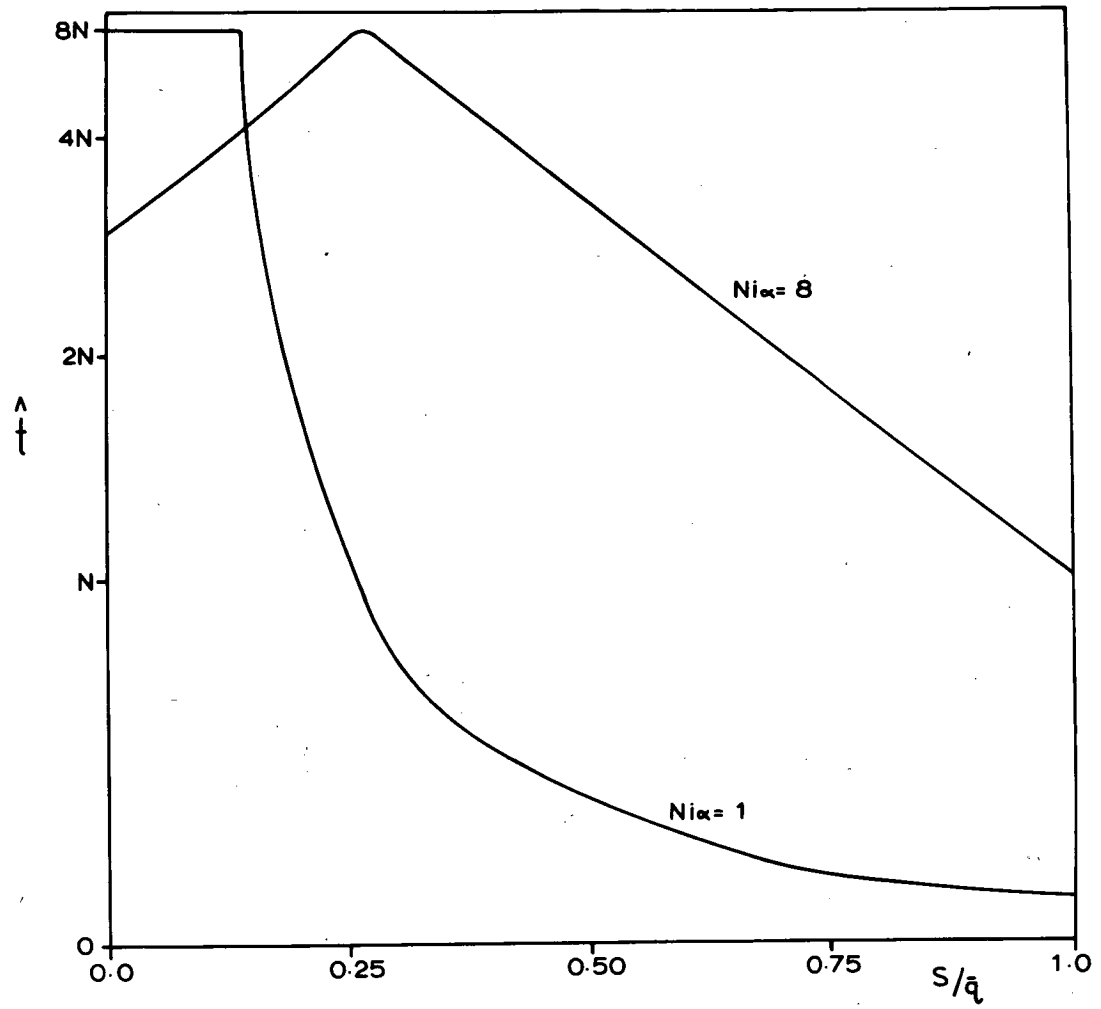


Figure 7. The effect of strength of homeostatic natural selection ($S/\bar{q} = s_1$) on time to reach a plateau, $\hat{t}$, expressed in terms of effective population size N. Curves are drawn for relatively weak ($Ni\alpha = 1$) and relatively strong ($Ni\alpha = 8$) artificial selection. The time scale is expressed in the modified form of $1-e^{-t/2N}$ which has a linear relationship with the inbreeding coefficient for neutral loci. It is used here to provide a better presentation of the trends.

an arbitrary one, it has been decided here to define a plateau as that which begins to exist when the mean gene frequency (or metric mean), rounded to the second decimal point, has not altered for three consecutive generations. If such a definition is too conservative, then it will serve to lessen the apparent effect of natural selection. As it turns out, the general conclusions obtained from this analysis are quite robust against alterations in the definition of a plateau.

The effect of natural selection on the time to reach a plateau is illustrated in figure 7. For ease of presentation of the curves, time has been expressed in a scale of $1-e^{-t/2N}$. The x-axis has been expressed in units of $S/\bar{q}$, from 0 to 1, to enable all initial and equilibrium gene frequencies to be represented in the one figure. With $q_o = \bar{q} = 0.1$ for example, the scale represents all possible values of S from 0% to 10%, and for $q_o = \bar{q} = 0.3$, the corresponding S values range from 0% to 30%. The same scale also applies to initial and equilibrium frequencies greater than one half, but the maximum value of S then corresponds to a value of $S/\bar{q}$ which is less than unity. With $q_o = \bar{q} = 0.7$ for example, the maximum value of S (30%) corresponds to $S/\bar{q} = 0.43$. The disadvantage of the scale $S/\bar{q}$ is that it contains a parameter $\bar{q}$ which can not be directly estimated from the population. It should be remembered, however, that $S/\bar{q} = s_1$ which is the coefficient of natural selection for the homozygote most favoured by artificial selection. It has already been concluded that in large populations the effect of natural selection on artificial selection can be described solely in terms of $s_1$. It would seem then that the parameter $s_1$ $(=S/\bar{q})$ is the main factor determining the effect of the interaction between the two selective forces in both large and small populations, and this is what might have been expected. Since artificial

selection is attempting to achieve complete fixation of allele $A_1$, it comes as no surprise to see that the relative fitness of this homozygote is of crucial importance.

It has been found that the shapes of the curves of $\hat{t}$ against $S/\bar{q}$ are not exactly the same for all initial and equilibrium frequencies. Even at S = 0% for example, $\hat{t}$ varies slightly with $q_o$, with $\hat{t}$ decreasing as $q_o$ increases, this being a result predicted by Robertson (1960). The results have been summarised in one figure, however, in the interests of obtaining a generalised understanding and prediction. The differences between curves for different initial and equilibrium frequencies have been found to be differences in detail only; the important general trend is represented in figure 7, the curves in which happen to have been obtained from $q_o = \bar{q} = 0.3$.

For any initial and equilibrium gene frequency then, figure 7 shows the effect of natural selection on the time to reach a plateau. It can be seen that even in the absence of natural selection (S = 0 and hence $S/\bar{q} = 0$), $\hat{t}$ occurs relatively early with strong artificial selection ($Ni^{\alpha} = 8$). This is because high values of $Ni^{\alpha}$ lead to complete fixation at a time well before that of $\hat{t} = \infty$ expected for a locus with neutral alleles. Such a plateau would be due to exhaustion of genetic variance. Increasing strength of natural selection at first increases $\hat{t}$, because heterozygote superiority for fitness tends to increase the time required to achieve complete fixation. A stage is reached, however, at around $S/\bar{q} = 0.3$, when such natural selection is sufficiently strong to prolong complete fixation until effectively $\hat{t} = \infty$. Any stronger natural selection then reduces $\hat{t}$, but now because fixation has been prevented and thus a plateau has been reached

due to an equilibrium between natural and artificial selection. Increasing strength of natural selection now simply produces an equilibrium and hence a plateau increasingly early in the selection programme. Genetic variance will still now exist at such equilibrium plateaux.

With less intense artificial selection ($Ni\alpha = 1$) complete fixation is never reached prior to $\overset{\circ}{t} = \infty$ even with no natural selection. With increasing strength of natural selection a point is reached, at about $S/\bar{q} = 0.2$, after which complete fixation is prevented. Stronger natural selection then produces an equilibrium plateau at ever earlier generations. It has been found that the results for intermediate strengths of artificial selection all fall within the two curves shown in figure 7, which can thus be taken to represent the majority of situations likely to exist in a selection programme.

It has also been found that natural selection prior to artificial selection slightly reduces $\overset{\circ}{t}$ for any strength of natural selection. This reduction is sufficiently small however, to enable the curves in figure 7 to be taken as representative of the effect of natural selection at any stage of the generation.

b) Advance in the mean at the plateau

For an additive model in the absence of natural selection, and for $Ni\alpha<1$, Robertson (1960) predicted that the advance in the metric mean at the limit would be 2N times the change in the first generation. The ratio $\frac{L}{2N\Delta G}$ is thus expected to be unity under the above conditions. Figure 8 illustrates the way in which homeostatic natural selection affects the value of this ratio. Natural selection has been expressed on the same scale as in the previous figure, again to enable

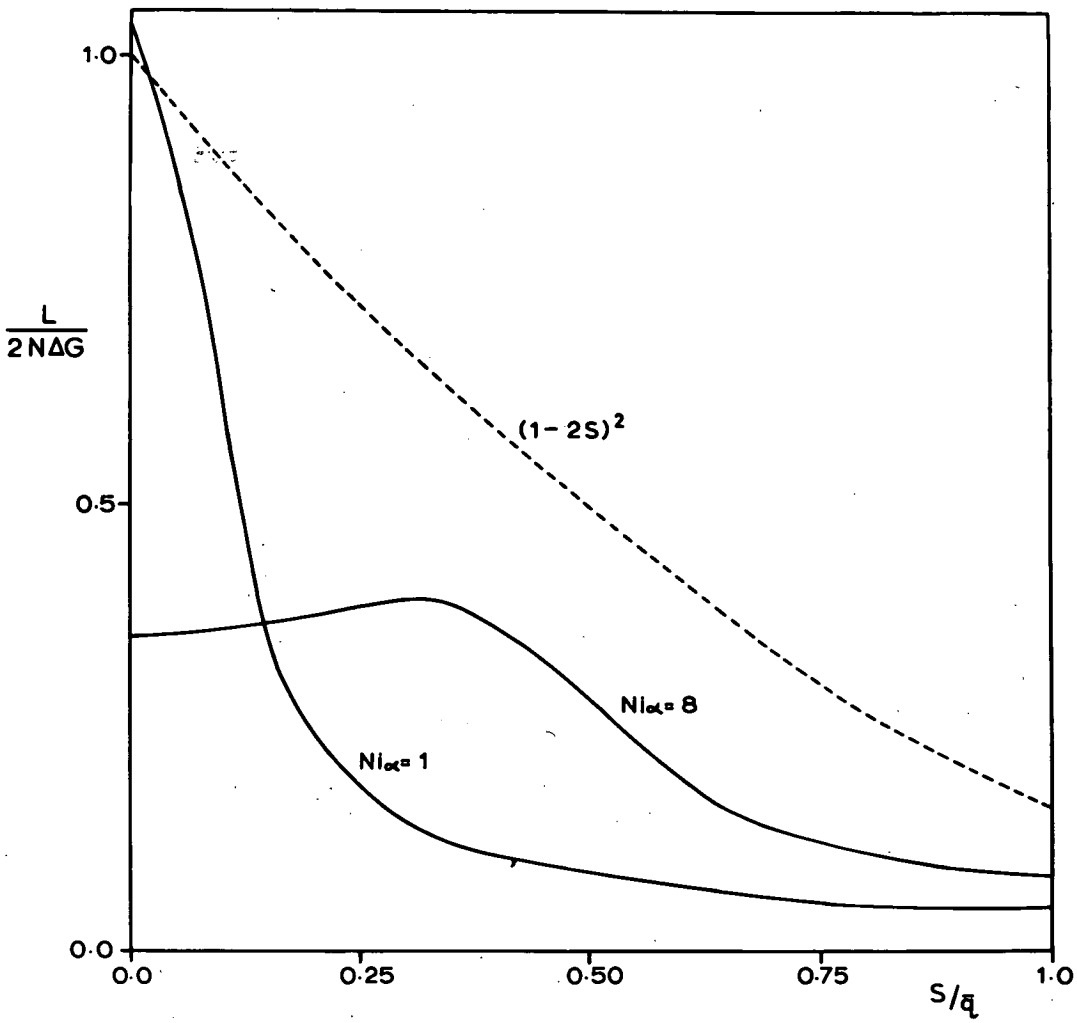


Figure 8. The effect of strength of homeostatic natural selection ($S/\bar{q} = s_1$) on the ratio $\frac{L}{2N\Delta G}$, where L is the total advance in metric mean at the plateau, $\Delta G$ is the change in metric mean during the first generation of selection and N is effective population size. Curves are drawn for relatively weak ($Ni\alpha = 1$) and relatively strong ($Ni\alpha = 8$) artificial selection. The curve of $\frac{L}{2N\Delta G} = (1-2S)^2$ has been drawn for $q_o = \bar{q} = 0.3$.

generalised conclusions to be drawn for all gene frequencies from the one figure. (The actual data represented in figure 8 have been obtained from $q_o = \bar{q} = 0.3$).

For relatively weak artificial selection ($Ni\alpha = 1$) the ratio $\frac{L}{2N\Delta G}$ declines rapidly from unity as $S/\bar{q}$ increases until, at around $S/\bar{q} = 0.2$ it has a value of about 0.2. It will be recalled that this was the minimum strength of natural selection required to produce a pre-fixation plateau. If a plateau due to opposing natural selection is observed for relatively weak artificial selection, then the ratio $\frac{L}{2N\Delta G}$ is expected to be less than 0.2, corresponding to points on the curve for $Ni\alpha = 1$ to the right of $S/\bar{q} = 0.2$.

Relatively strong artificial selection, represented here by $Ni\alpha = 8$, can be seen to produce a relatively low value of the ratio even in the absence of natural selection, the reason for this being that such artificial selection is sufficient to achieve complete fixation of the favoured allele and hence the maximum value of L, relatively early in the selection programme. Thus L is "prevented" from attaining that value which the relatively large $\Delta G$ would have inferred. As natural selection increases in strength, the ratio also increases gradually in value until around $S/\bar{q} = 0.3$, the point at which pre-fixation plateaux first appear. For $S/\bar{q} < 0.3$ therefore, L has remained constant at its maximum value, while $\Delta G$ has gradually decreased due to increasing strength of natural selection. Pre-fixation plateaux occur at ever earlier generations as $S/\bar{q}$ increases, thus resulting in a decreasing L beyond $S/\bar{q} = 0.3$. The value of the rationtherefore declines toward a relatively low value around 0.1 very similar to that observed for $Ni\alpha = 1$.

In very general terms it appears that the ratio $\frac{L}{2N\Delta G}$ will always

be less than unity in the presence of natural selection and will probably be less than one half at a pre-fixation plateau. It has been found that an approximate and simple algebraic prediction to this effect can be obtained by setting $\frac{L}{2N\Delta G} = (1-2S)^2$. This result was achieved empirically from graphical examination of the results, but obviously with the algebraic prediction of equation (11) in mind. The relationship $L = 2N\Delta G(1-2S)^2$ is drawn in figure 8, in this case for $\bar{q} = 0.3$. Its position on the graph will obviously alter with different $\bar{q}$, but it has been found that the relationship provides quite a useful prediction of the upper limit of the value of $\frac{L}{2N\Delta G}$ in the presence of homeostatic natural selection.

As in the previous figure, it has been found that the stage of the generation at which natural selection acts has very little effect on the shape or position of the curves. Thus the total advance in the metric mean at a pre-fixation plateau will usually not be greater than $2N\Delta G(1-2S)^2$ irrespective of when natural selection occurs.

c) Genetic variance remaining at the plateau

Selection plateaux at which some genetic variance still remains have been commonly observed in practice, and opposing natural selection has often been invoked as the cause. The changes in additive genetic variance as a result of artificial selection in the presence of homeostatic natural selection have already been presented in figures 3b to 6b, and some idea as to the time, $\hat{t}$, at which selection plateaux occur has been obtained from figure 7. It should now be possible to combine both these sources of information by expressing the additive genetic variance at time $\hat{t}$, $\hat{\sigma}_A^2$, as a proportion of the original additive genetic variance, $\sigma_A^2$. This ratio has been chosen

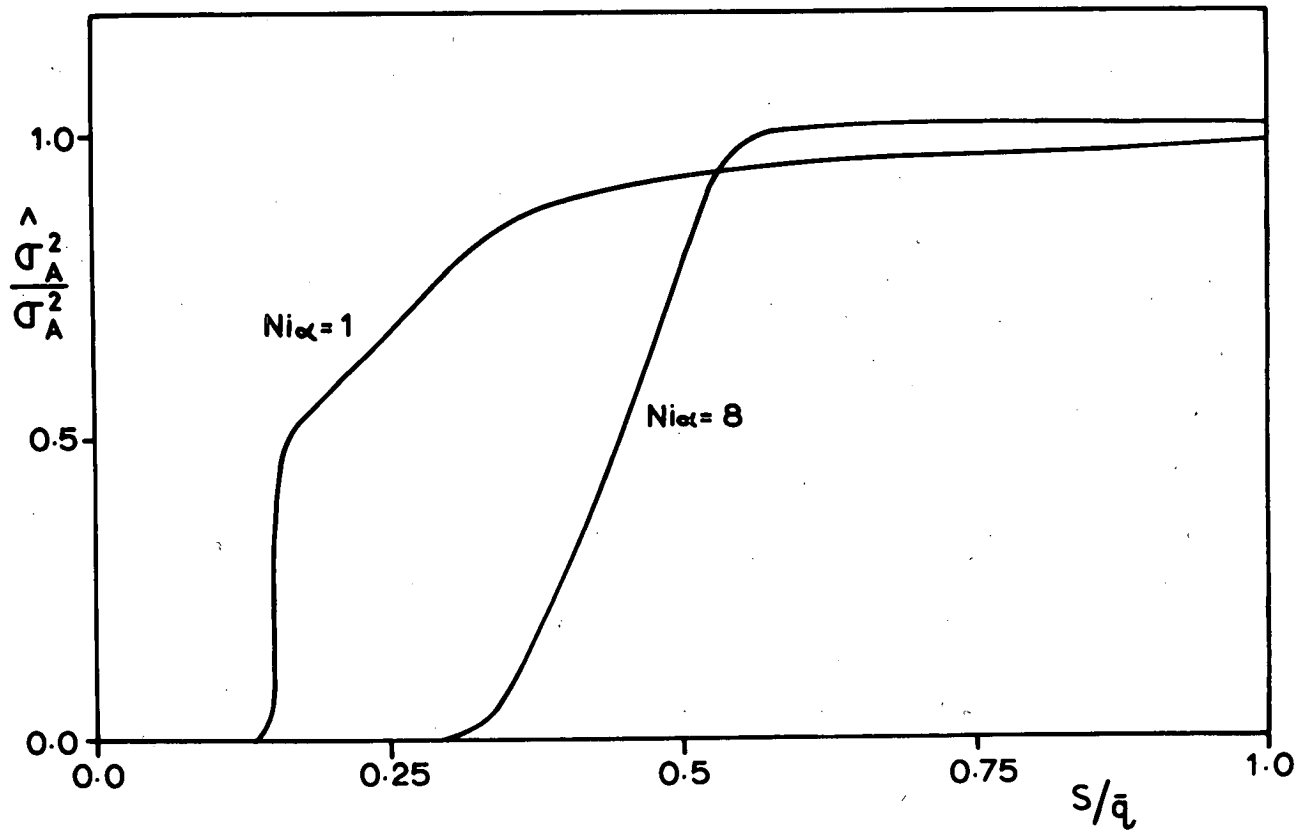


Figure 9. The effect of strength of homeostatic natural selection ($S/\bar{q} = s_1$) on the proportion of original additive genetic variance remaining at a selection plateau. Curves are drawn for relatively weak ($Ni\alpha = 1$) and relatively strong ($Ni\alpha = 8$) artificial selection.

because of its practical relevance, in that an estimate of $\frac{\hat{\sigma}_A^2}{\sigma_A^2}$ can be obtained in principle from any selection experiment.

Lerner and Dempster (1951, table 2), for example, estimated heritability from intra-class correlation of sibs for every generation of their shank length selection experiment. Associated estimates of phenotypic variance then enabled them to estimate $\sigma_A^2$ from each generation.

Figure 9 shows the ratio $\frac{\hat{\sigma}_A^2}{\sigma_A^2}$ plotted against strength of natural selection, expressed as $S/\bar{q}$ as before. Again, although the curves actually shown have been obtained from just one initial and equilibrium gene frequency, namely 0.3, they represent the general pattern obtained for all initial and equilibrium gene frequencies.

The main point to note from figure 9 is that, in general, a selection plateau will have either very little or almost all of the original genetic variance remaining. It has already been determined from figure 7, that values of $S/\bar{q}$ at least around 0.2 are necessary to prevent complete fixation, even for relatively weak artificial selection. The curve for $N i\alpha_2 = 1$ in figure 9 supports this conclusion, by showing that $\frac{\hat{\sigma}_A^2}{\sigma_A^2} \sim 0$ if $S/\bar{q}$ falls much below 0.2. Values of $S/\bar{q}$ around 0.3 or greater, on the other hand, are sufficient to result in almost all of the original variance remaining at the plateau. The same trend is evident for relatively strong artificial selection ($N i\alpha=8$), for which it has already been seen that an $S/\bar{q}$ value of around 0.3 is necessary to prevent complete fixation.

The results for $S=\bar{q}$ indicate that essentially all of the genetic variance contributed by a locus at which the favoured allele is sterile will remain at a plateau, irrespective of the strength of artificial selection.

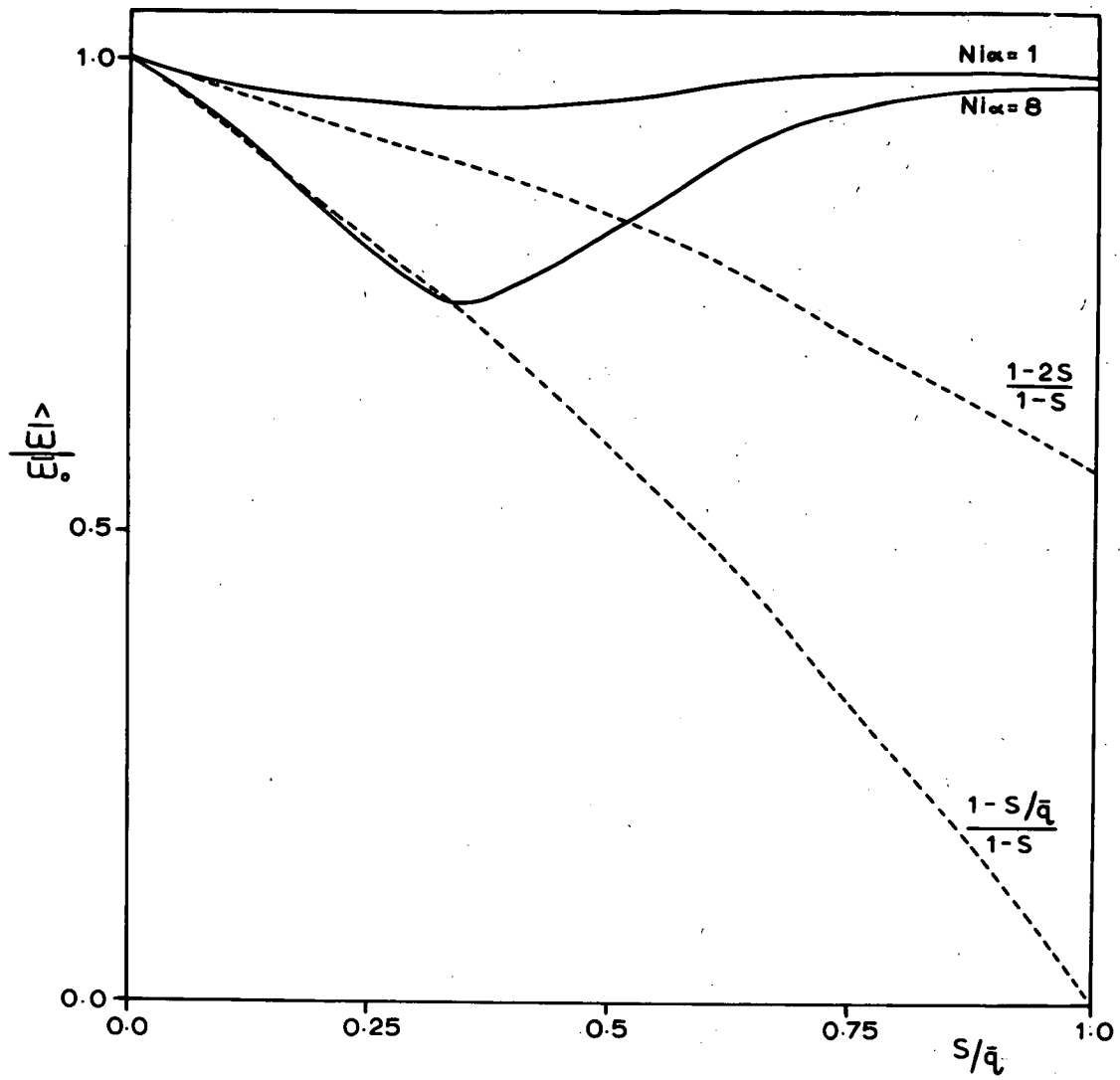


Figure 10. The effect of strength of homeostatic natural selection ($S/\bar{q} = s_1$) on the relative fitness at a selection plateau. Curves are drawn for relatively weak ($Ni\alpha = 1$) and relatively strong ($Ni\alpha = 8$) artificial selection. The curve of $\frac{\hat{w}}{w_o} = \frac{1-2S}{1-S}$ has been drawn for $q_o = \bar{q} = 0.3$.

Finally, it has been found that the general trends outlined above apply to natural selection occurring at any stage during the generation, either before or after artificial selection. Thus selection plateaux due to opposing homeostatic natural selection will in general be characterised by the continuing presence of a large proportion, if not all, of the original genetic variance. It will be seen below (in section III) that this continuing presence of most of the original genetic variance at such plateaux will be reflected in relatively large responses to subsequent reverse selection.

d) Relative fitness at the plateau

Changes in absolute fitness during the whole process of artificial selection have been obtained from the matrix results for all relevant combinations of initial gene frequency, $N_{i\alpha}$ and S. Rather than presenting these as a series of graphs showing fitness against time, an attempt has been made to summarise all the important features in one figure. Consideration will thus be given to the ratio of $\frac{\bar{w}^*}{\bar{w}_o}$ where $\bar{w}^*$ is the fitness at the limit to artificial selection, and $\bar{w}_o$ is the original fitness. The ratio $\frac{\bar{w}^*}{\bar{w}_o}$ is plotted against strength of natural selection in figure 10.

It can be seen that stronger artificial selection tends to decrease fitness for any strength of natural selection, as might be expected. Of greater interest is the observation that $\frac{\bar{w}^*}{\bar{w}_o}$ is at a minimum when $S/\bar{q}$ is just sufficient to prevent complete fixation, i.e. is just sufficient to result in a pre-fixation plateau. The decrease in $\frac{\bar{w}^*}{\bar{w}_o}$ up to this value of $S/\bar{q}$ is easy enough to explain. Fitness at any generation in the homeostatic model is a function of the strength of natural selection ($s_1+s_2$ in this case), the equilibrium gene frequency ($\bar{q}$) and the actual

gene frequency ($q_t$), such that $\bar{w}_t - \bar{w}_o = (s_1+s_2)(q_t-\bar{q})^2$. If $t=\hat{t}$ then $q_t-\bar{q}$ will be the same for all values of $S/\bar{q}$ less than that required to produce a prefixation plateau: the total change in gene frequency will have been the same in all cases. This conclusion follows from, say, figure 4a, in which it can be seen that for $S\leq 10\%$ ($S/\bar{q}\leq 0.33$), the only effect of natural selection is to retard the rate of advance. The final gene frequency is the same in all cases. Thus for $S/\bar{q}$ less than around 0.3, the value of $\hat{\bar{w}}$ will depend only on the strength of natural selection, expressed in this case as $s_1+s_2$, and will obviously decrease as $s_1+s_2$ increases. Hence the value of $\bar{w}$ decreases until $S/\bar{q}$ is about 0.3.

The subsequent increase in $\frac{\hat{\bar{w}}}{\bar{w}_o}$ as $S/\bar{q}$ increases beyond this point (and as pre-fixation plateaux begin to form) is due to a gradual decrease in $q_t-\bar{q}$ at the limit, as natural selection becomes increasingly able to decrease the total change in gene frequency. Exactly the same trend is shown for the two relatively extreme values of $Ni\alpha$, so that the same trend would be observed at all intermediate strengths of artificial selection.

Is it possible to relate the earlier prediction of $\frac{\hat{\bar{w}}}{\bar{w}_o} = \frac{1-2S}{1-S}$ to these more realistic results? The curve of $\frac{1-2S}{1-S}$ is given in figure 10, in this case assuming that $\bar{q} = 0.3$. It is indeed an accurate estimate for small $Ni\alpha$ and small S, but completely fails to take into account the relatively high values of $\frac{\hat{\bar{w}}}{\bar{w}_o}$ at pre-fixation plateaux. In general then, for small $Ni\alpha$ it appears that $\frac{1-2S}{1-S}$ is an overestimate rather than an underestimate of $\frac{\hat{\bar{w}}}{\bar{w}_o}$ as was initially concluded from the algebraic derivation. But at higher values of $Ni\alpha$ it turns out to be an underestimate.

It has been found that a far more accurate prediction of $\frac{\hat{\bar{w}}}{\bar{w}_o}$ is

given by $\frac{1-S/\bar{q}}{1-S}$, at least for values of $S/\bar{q}$ less than that required to achieve a pre-fixation plateau. The curve of $\frac{1-S/\bar{q}}{1-S}$ is also shown in figure 10, where it can be seen that this empirically derived curve follows the curve for $N_{ia} = 8$ obtained from the computer matrix operations, almost exactly until $S/\bar{q}$ is approximately 0.3. However, it is hopelessly inaccurate as a predictor of $\frac{\hat{w}}{\bar{w}_o}$ at pre-fixation plateaux.

One final conclusion can be drawn from figure 10, and this is to do with loci at which $S=\bar{q}$. It can be seen that such loci, at which the favoured allele is sterile or lethal, do not really contribute to a decrease in fitness at the limit. This must be mainly because gene frequency at such loci alters relatively little from what it was originally.

It must be emphasised that the whole of the above discussion has been concerned with loci at which artificial selection is attempting to achieve homozygosity. Changes in fitness associated with overall inbreeding depression have not been considered. To the extent that inbreeding depression of fitness might occur if effective population size is relatively small, the predictions obtained above would tend to be overestimates: any general inbreeding depression of fitness will tend to lower the curve of $\frac{\hat{\bar{w}}}{\bar{w}_o}$ against $S/\bar{q}$ for any particular strength of artificial selection.

## 5. DISCUSSION

The ramifications of the homeostatic model of natural selection in the context of artificial selection have been explored in some detail. How well do the implications of the homeostatic model accord with results observed in artificial selection experiments where natural selection has been thought to have played a significant role?

A logical starting point seems to be a reconsideration of the selection experiment of Lerner and Dempster (1951) from which the homeostatic model of natural selection first arose. In an earlier reanalysis of this experiment, James (1962) estimated L as 1.33, $\Delta G$ as 0.19 and N as 12 approximately. Thus the ratio of $\frac{L}{2N\Delta G}$ is roughly 0.3, which is considerably less than the value of unity expected for genes of small effect and/or small population size under an additive model in the absence of natural selection. Furthermore, from page 78 of Lerner and Dempster (1951) it can be determined that $\hat{t} = 8 = 0.67N$ generations, and $\frac{\hat{\sigma}_A^2}{\sigma_A^2} = 1$ approximately. Finally, from their table 3, it can be concluded that $\frac{\hat{\bar{w}}}{\bar{w}_o} = \frac{2.47}{3.75} = 0.66$.

How well do these results tie in with the implications of the homeostatic model described above? Firstly, it must be remembered that this study of the homeostatic model 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 at any particular locus (or unit of segregation) will lie somewhere between zero and $\bar{q}$ (or $1-\bar{q}$). Furthermore, this value may alter during the course of artificial selection as a result of mutation and/or recombination. Witness, for example, the appearance after many generations of artificial selection in Drosophila, of lethal or sterile genes that were apparently absent from the base population (Hollingdale, 1971).

In drawing conclusions about the homeostatic model in terms of single loci, we are describing what happens to particular components of the actual response observed during an artificial selection programme. To the extent that these components operate independently of each other, any observed selection response is probably the combination of the response curves of several loci where natural selection does not

with intermediate values of S, together act (S=0), and other loci with one or two loci with maximum values of S. And the latter type of locus may only have commenced its contribution to selection response after many generations of selection.

Considering Lerner and Dempster's results in this light, the value of the ratio $\frac{L}{2N\Delta G}$ of 0.3 is certainly compatible with a model of homeostatic natural selection opposing artificial selection. Similarly, the $\hat{t}$ value of 0.67N generations, and $\frac{\sigma_A^2}{\sigma^2} = 1$ are also to be expected with relatively strong homeostatic natural selection opposing artificial selection. With respect to fitness, it must be noted that the curves in figure 10 only give a direct prediction of the overall population fitness for a single locus, and as such provide only an upper limit of the actual value of relative population fitness to be expected where several loci are contributing to the metric character. Thus the value of $\frac{\hat{w}}{w_o} = 0.66$ observed by Lerner and Dempster is not unexpected with the homeostatic model.

All the data therefore are compatible with an hypothesis that the observed plateau was caused by the opposition to directional selection of homeostatic natural selection.

It remains now to mention two implications of the homeostatic model which follow from the predictions obtained in this study. Firstly, it has been seen how the formation of a pre-fixation plateau is simply the result of an equilibrium between two opposing selective forces, and consequently that the plateau can be broken through by increasing the strength of artificial selection. But if the stronger artificial selection is still not sufficiently strong to achieve complete fixation, then a new pre-fixation plateau, at a slightly higher level of metric mean will be expected to result. Even stronger artificial selection will be required to break through this plateau, and so on. It has

already been mentioned that the easiest way to increase the strength of artificial selection is to increase the value of i, which involves decreasing the proportion selected, p. And if the effective population size is to remain constant, a decrease in p requires a larger number of offspring scored, which may not be possible if the overall population fitness has declined. Thus in practice it may be impossible to break through a pre-fixation plateau because of an insufficient number of offspring.

Secondly, it was seen in figure 10 that the relative fitness at the plateau was at a minimum at the value of $S/\bar{q}$ which corresponded to a strength of natural selection just sufficient to prevent complete fixation. It follows that some of the loci which contribute most to a decline in fitness may not contribute at all to the maintenance of genetic variance at the limit. It would not therefore 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 pre-fixation plateau. Indeed it is quite conceivable that fitness in such a line could decline to an extent that the line was in danger of extinction, whereas had the opposing natural selection been stronger then a pre-fixation plateau at which relative fitness was still quite high could have resulted.

Thus a significant decrease of population fitness as a result of artificial selection need not necessarily imply that the metric character concerned is an important adaptive character with respect to natural selection.

## 6. SUMMARY

1. A study has been made of the effect of homeostatic natural selection on the limits to artificial selection for a metric character. The treatment has been in terms of two alleles at a single locus and the conclusions apply to natural selection occurring at any diploid stage of the generation.

2. The effect of homeostatic natural selection can be described in terms of the strength of natural selection, S, and the large population equilibrium gene frequency, $\bar{q}$. S can be estimated as the ratio of response in the metric mean following a single generation of relaxation in a large population, $R_1$, to the response in the metric mean to all previous forward selection, $\Delta x$, but only if such relaxation is carried out quite early in the selection programme before gene frequencies have been altered substantially. It is reasonable to assume that the gene frequency at the start of artificial selection is equal to $\bar{q}$.

3. For any particular locus at which initial gene frequency does equal $\bar{q}$, a cessation of selection response due to opposing natural selection (a 'pre-fixation' plateau) in a population of finite size generally occurs only for genes with equilibrium frequencies equal to or less than one half, and then only if the value of $S/\bar{q}$ is around 0.2 or greater. Values of $S/\bar{q}$ less than this are not sufficient to prevent complete fixation and hence exhaustion of genetic variance.

4. The generation at which a pre-fixation plateau first appears, $\hat{t}$, is determined by the relative strengths of artificial and natural selection such that $\hat{t}$ is increased by stronger artificial and/or weaker natural selection.

5. The total advance in the metric mean at a pre-fixation plateau is never greater than $2N(1-2S)^2$ times the change in metric mean in the first generation of artificial selection, where N is the effective population size.

6. The time taken to achieve half this predicted response is less than 1.4N generations.

7. A large proportion, if not all of the original genetic variance remains at a pre-fixation plateau.

8. A significant decrease in population fitness as a result of artificial selection does not necessarily imply that the metric character concerned is an important adaptive character.

9. For the particular case of a locus at which the favoured allele is sterile or lethal ($S=\bar{q}$) a pre-fixation plateau always results. For that particular locus, the plateau first occurs sometime during the first N generations of artificial selection and corresponds to a total advance in the metric mean of less than $\frac{N}{5}$ times the change in the first generation. At such a pre-fixation plateau, the population retains all its original genetic variance, and the locus does not contribute to a decrease in overall population fitness from the fitness that existed when selection commenced at that locus.

10. It should be possible to break through any pre-fixation plateau due to opposing homeostatic natural selection by increasing the strength of artificial selection if sufficient reproductive excess still exists in the population. The single exception to this is the situation in which the favoured allele is sterile or lethal and where artificial selection is already sufficiently strong so that none of the fertile or viable homozygotes are selected.

## II. THE OPTIMUM MODEL OF NATURAL SELECTION

A normally distributed quantitative character with population mean $\mu$ and phenotype variance $\sigma_p^2$ can be represented by the normal probability density function

$$f(x) = \frac{1}{\sigma_p\sqrt{2\pi}} \exp\left[-\frac{(x-\mu)^2}{2\sigma_p^2}\right]$$

where x is an observation of the metric phenotype on a single member of the population.

Consider natural selection to be acting on such a quantitative character in the manner described by the nor-optimal model of Haldane (1954), in which the decline in fitness from some optimum phenotype $\theta$ follows the shape of the normal distribution. Thus the fitness of an individual with phenotype x is

$$\emptyset(x) = \exp\left[-K(x-\theta)^2\right] \qquad (1)$$

where K is a scale constant directly proportional to the strength of natural selection. Of the different notations which have been used in the various studies of this model, by far the most useful appears to be that of Latter (1970) who introduced a parameter which he called the coefficient of centripetal selection, C. It has the logical and convenient property of ranging from zero for no natural selection, to unity for absolute selection of the optimal phenotype only. Latter has shown that C is simply related to Haldane's (1954) intensity of natural selection (I) by the expression

$$I = -\tfrac{1}{2}\log(1-C) \qquad \text{when } \theta = \mu,$$

which at low strengths of natural selection can be approximated by C=2I.

In terms of Latter's notation, the scale constant K in equation (1) is equivalent to $\frac{C}{(1-C)2\sigma_p^2}$.

To facilitate comparisons with other papers it should be noted that $\sigma_1^2$ of Haldane (1954) is equal to $\sigma_p^2$ while his $\sigma_2^2$ equals $\sigma_p^2(1-C)$. Futhermore,

$$C = \frac{\sigma_p^2}{\sigma_p^2+\sigma_f^2} = \frac{\sigma_p^2}{\sigma^2}$$

in the notation of Latter (1960) and James (1962) where $\sigma_f^2$ is a scale constant which is inversely proportional to the strength of natural selection, and $\sigma^2 = \sigma_p^2+\sigma_f^2$. In O'Donald's (1970) notation, $C=\frac{2KV}{1+2KV}$ where V is the phenotypic variance and K is a scale constant equivalent to $\frac{1}{2\sigma_f^2}$. Bulmer (1971 b, 1971 c, 1972 and 1973) made occasional use of a parameter K which, as he noted in his 1972 and 1973 papers, is exactly the same as Latter's coefficient of centripetal selection. However, most of Bulmer's work was carried out in terms of a scale constant c which is equivalent to O'Donald's K. (The K used in equation (1) above is identical with O'Donald's K and Bulmer's c). Finally, Cavalli-Sforza and Bodmer (1971) standardized the distribution of phenotypes so as to have mean zero and variance unity ($\sigma_p^2 = 1$), and then chose a scale constant $\sigma^2$ such that $C = \frac{1}{1+\sigma^2}$.

A sample of individuals with phenotypic mean $\bar{x}$ has a mean fitness given by

$$\bar{w} = \int_{-\infty}^{\infty} \phi(x)\ f(x)\ dx$$

which becomes, after completing the square (O'Donald, 1970; Bulmer, 1972)

$$\bar{w} = \sqrt{1-C}\ \exp\ [-C\frac{(\bar{x}-\theta)^2}{2\sigma_p^2}] \quad . \qquad (2)$$

For a single locus with two alleles the total population can be divided into three samples corresponding to the genotypes $A_2A_2$, $A_1A_2$ and $A_1A_1$, which are assumed to be additive for the metric character and to be in Hardy-Weinberg frequencies at conception:

| | $A_2A_2$ | $A_1A_2$ | $A_1A_1$ |
|---|---|---|---|
| Relative frequencies | $(1-q)^2$ | $2q\ (1-q)$ | $q^2$ |
| Mean metric phenotype relative to the heterozygote | $\frac{-a}{2}$ | 0 | $\frac{+a}{2}$ |

The metric means of the genotypes at generation t are $\mu_t - aq_t$, $\mu_t - a(q_t - \frac{1}{2})$ and $\mu_t - a(q_t - 1)$ respectively, where $\mu_t$ is the overall population mean at generation t. Thus at generation zero for example, the relative fitnesses of the three genotypes can be expressed as

$$A_2A_2 \qquad A_1A_2 \qquad A_1A_1$$

$$\exp\left[\frac{-C}{2\sigma_P^2}\{\mu_o - aq_o - \theta\}^2\right] : \exp\left[\frac{-C}{2\sigma_P^2}\{\mu_o - a(q_o - \tfrac{1}{2}) - \theta\}^2\right] : \exp\left[\frac{-C}{2\sigma_P^2}\{\mu_o - a(q_o - 1) - \theta\}^2\right] \quad (3$$

which for low values of C can be written approximately as

$$1 - \frac{C}{2\sigma_P^2}\{\mu_o - aq_o - \theta\}^2 : 1 - \frac{C}{2\sigma_P^2}\{\mu_o - a(q_o - \tfrac{1}{2}) - \theta\}^2 : 1 - \frac{C}{2\sigma_P^2}\{\mu_o - a(q_o - 1) - \theta\}^2 . \quad (4$$

The relative fitnesses in (4) correspond to the quadratic deviation version of the optimum model in which fitness declines as the square of the deviation of the metric phenotype from the optimum phenotype, $\theta$. This is an illustration of the well known fact that the nor-optimal and quadratic deviation versions of the optimum model are effectively the same for relatively low strengths of natural selection. The finer points of difference between the two versions have been debated recently by Manly

(1973) and O'Donald (1973).

Returning to the nor-optimal version, the relative fitnesses (selective values) in (3) can be expressed more simply as

$$\begin{matrix} A_2A_2 & & A_1A_2 & & A_1A_1 \\ \exp\left[\frac{-Ca}{2\sigma_P^2}\{a(q_o-\tfrac{1}{2})+\theta-\mu_o\}\right] & : & 1 & : & \exp\left[\frac{-Ca}{2\sigma_P^2}\{a(\tfrac{1}{2}-q_o)+\mu_o-\theta\}\right] . \end{matrix} \qquad (5)$$

## 1. THE NATURE OF THE SELECTIVE VALUES

The majority of recent studies of the nor-optimal model have considered only the case where the optimum phenotype is a certain constant value, this appearing to be a more realistic model than the alternative one involving a variable optimum. This study will therefore concentrate on the case of a constant optimum phenotype, and only a brief comparison with the model of a variable optimum will be made towards the end.

The important thing to note about the relative selective values which result from the nor-optimal model is that for a single locus model they will remain constant over time, if the optimum phenotype $\theta$ remains constant. Given a particular strength of natural selection C and phenotypic variance $\sigma_P^2$, the relative selective values are determined solely by the extent to which the phenotypic mean of each genotype deviates from the fixed optimum phenotype $\theta$. For a single locus model any change in population mean resulting from a change in gene frequency is simply a reflection of an alteration in the relative frequencies of the three genotypes: the actual phenotypic mean of each genotype does not alter. A constant fixed optimum phenotype and a constant mean phenotype for each genotype will therefore result

in a constant selective value for each genotype, irrespective of changes in gene frequency and associated alteration of the overall population mean at that single locus.

The fixed optimum is often taken to be the population mean at time zero in which case $\theta = \mu_o$ for the present study.

An examination of the relative selective values in (5) for $\theta = \mu_o$ indicates that they will be heterotic for all initial frequencies of either allele between $\frac{1}{4}$ and $\frac{3}{4}$. This is because over that range of gene frequencies the population mean and hence the optimum is closer to the mean of the heterozygote than to that of either homozygote. It should be possible to compare these heterotic selective values with those considered previously in the homeostatic model. The relative fitness of genotype $A_2A_2$ can be expressed as

$$1 - s_2 = \exp\left[\frac{-Ca^2}{2\sigma_p^2}(q_o - \tfrac{1}{4})\right]$$

which gives

$$s_2 \sim \frac{Ca^2}{2\sigma_p^2}(q_o - \tfrac{1}{4})$$

for small C. Similarly,

$$1 - s_1 = \exp\left[\frac{-Ca^2}{2\sigma_p^2}(\tfrac{3}{4} - q_o)\right] \qquad (6)$$

and

$$s_1 \sim \frac{Ca^2}{2\sigma_p^2}(\tfrac{3}{4} - q_o)$$

for genotype $A_1A_1$. It then follows that

$$s_1 + s_2 \sim \frac{Ca^2}{4\sigma_p^2}$$

In addition

$$\bar{q} = \frac{s_2}{s_1 + s_2}$$

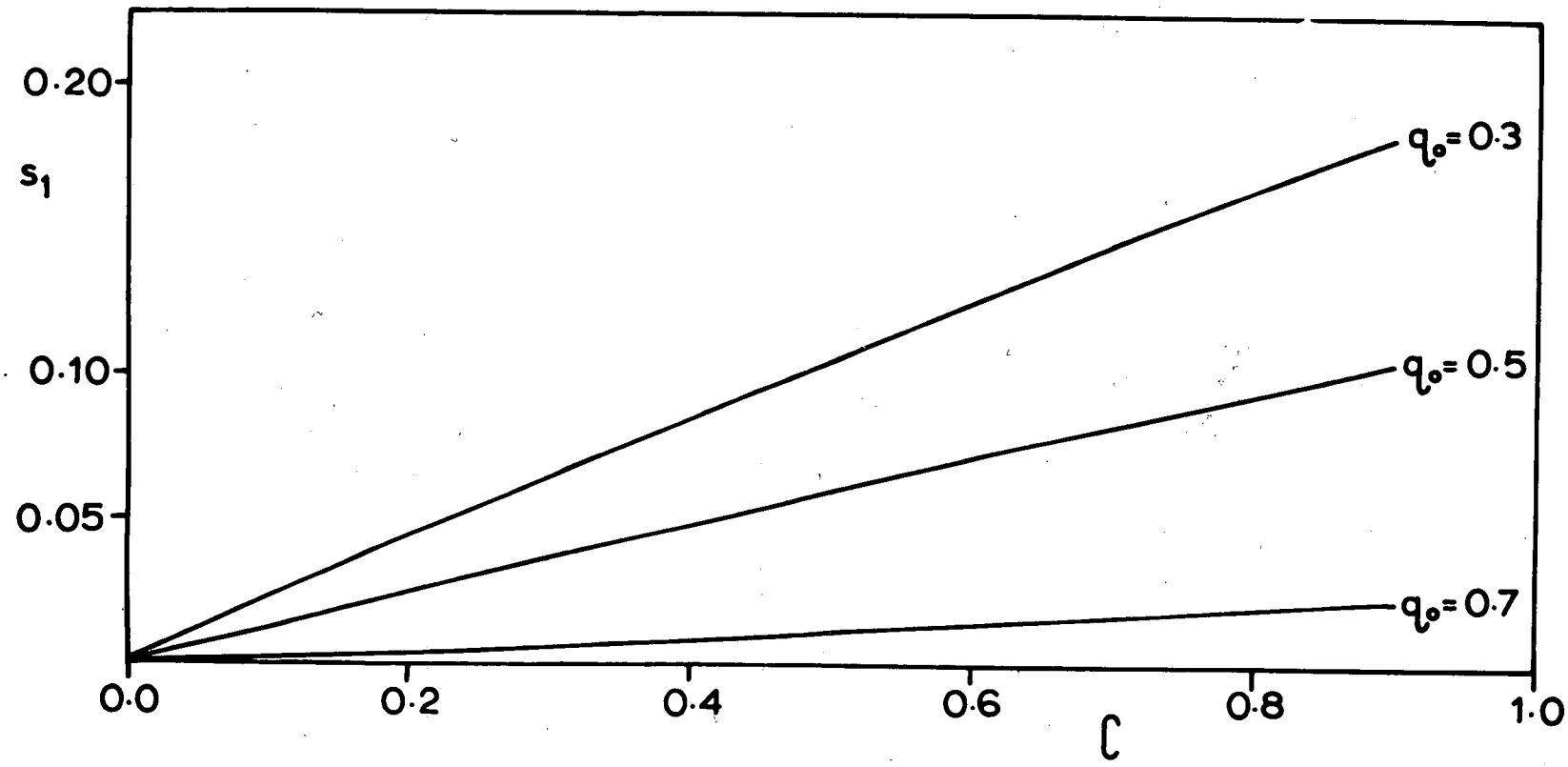


Figure 1. The relationship between strength of nor-optimal natural selection, C, and strength of homeostatic natural selection ($S/\bar{q} = s_1$). The three different initial gene frequencies were chosen so as to represent almost the whole range of initial gene frequencies for which selective values are heterotic with $\theta = \mu_o$.

$$= 2(q_o - \tfrac{1}{2}) \qquad (7)$$

and

$$S = (s_1+s_2)\,\bar{q}\,(1-\bar{q})$$

$$- \frac{Ca^2}{\sigma_P^2}[q_o(1-q_o) - \frac{3}{16}]$$

Equation (7) was previously derived for the nor-optimal model by Wright (1935, a) and Robertson (1956), who discussed its consequences. Briefly, these are that for a single locus undergoing such selection against a constant genetic background in a large population, a stable non-zero equilibrium will eventually be reached providing the initial gene frequency lies midway between the equilibrium frequency and 0.5. In terms of the metric character, the fixed optimum phenotype which is the overall population mean at time zero, will lie halfway between the population mean at equilibrium and the mean of the heterozygotes. Initial gene frequencies between $\frac{1}{4}$ and $\frac{3}{4}$ therefore account for equilibrium frequencies covering the whole possible range from zero to unity.

It has already been shown that the only important parameter of heterozygote superiority for fitness in the context of artificial selection is the natural selective coefficient of the homozygote most favoured by artificial selection. For the homeostatic model this parameter is $s_1$, which equals $S/\bar{q}$ with values ranging from zero to unity. What values of this parameter will result from the nor-optimal model of natural selection? The values of $s_1$ corresponding to various values of C have been obtained from equation (6) and are shown in figure 1. The graphs have been drawn for $\frac{a}{\sigma_P} = 1$ so as to show some of the largest possible $s_1$ values for a given C. Smaller, more realistic values of $\frac{a}{\sigma_P}$ would depress each of the curves thereby indicating

even smaller $s_1$ values for a particular C.

For situations in which the nor-optimal model results in heterotic selective values it can therefore be concluded, for $\theta = \mu_o$, that even the strongest conceivable strengths of nor-optimal natural selection at the most favourable initial frequencies will only be equivalent to relatively weak homeostatic natural selection. A similar conclusion can be inferred from James (1962). More precisely, nor-optimal natural selection will never produce an $s_1$ value of greater than around 0.25 if the optimum phenotype is equal to the population mean at generation zero. This result is not surprising when it is considered that nor-optimal selection is acting indirectly (on phenotypes), whereas homeostatic selection acts on genotypes directly.

Finally for $\theta = \mu_o$, it must be noted that initial gene frequencies outside the range of $\frac{1}{4}$ to $\frac{3}{4}$ give rise to directional selective values in favour of the homozygote of the allele with initial frequency greater than $\frac{1}{2}$, eventually producing fixation of that allele. This is a simple consequence of the population mean and hence optimum lying closer to one or other homozygote than to the heterozygote for gene frequencies outside the range $\frac{1}{4}$ to $\frac{3}{4}$.

These directional selective values will never be very strong. With $\frac{a}{\sigma_p} = 1$ again as an extreme example, the relative fitness of the three genotypes is approximately, from (5)

$$\begin{array}{ccccc} A_2A_2 & & A_1A_2 & & A_1A_1 \\ 1 - \frac{C}{2}(q_o - \frac{1}{4}) & : & 1 & : & 1 - \frac{C}{2}(\frac{3}{4} - q_o) \end{array}$$

which, for a gene frequency outside the range $\frac{1}{4}$ to $\frac{3}{4}$, say 0.1, and for a relatively large C of 20%, reduce to 1.015 : 1 : 0.935 in favour of

the homozygote $A_2A_2$. More realistic values of $\frac{a}{\sigma_P}$ and C will obviously result in even smaller differences in fitness between the three genotypes.

What if the constant optimum phenotype is different from the population mean at generation zero? Since the relative selective values are a function of the deviation of the mean of each genotype from the fixed optimum, then the selective values will be directional rather than heterotic whenever the fixed optimum is closer to the mean of either homozygote than to that of the heterozygote. An optimum phenotype less than that of the homozygote $A_2A_2$ for example, would thus give rise to directional natural selection in favour of that homozygote. In such a situation it is more useful to express all the selective values relative to that of genotype $A_2A_2$, in which case they can be written as

$$\begin{array}{ccccc} A_2A_2 & & A_1A_2 & & A_1A_1 \\ 1 & : & \exp\left[\frac{Ca}{2\sigma_P^2}\{a(q_o-\frac{1}{2}) + \theta - \mu_o\}\right] & : & \exp\left[\frac{Ca}{\sigma_P^2}\{a(q_o-\frac{1}{2}) + \theta - \mu_o\}\right] . \end{array}$$

If, for example, the optimum phenotype is the metric mean of genotype $A_2A_2$ at generation zero, then $\theta = \mu_o - aq_o$, and the relative selective values become approximately

$$1 \quad : \quad 1 - \frac{1}{8}\frac{Ca^2}{\sigma_P^2} \quad : \quad 1 - \frac{1}{2}\frac{Ca^2}{\sigma_P^2}$$

which are directional but not additive. The selective values are approximately additive only if the optimum is quite some distance from the population mean. The best way to represent this situation is to follow Latter (1960) and James (1962) by setting $\theta = 0$ and $\mu_o >> a$ in

which case the relative fitnesses are given approximately as

$$1 \quad : \quad 1 - \frac{1}{2}\frac{Ca\mu_o}{\sigma_P^2} \quad : \quad 1 - \frac{Ca\mu_o}{\sigma_P^2}$$

which are additive.

It can be concluded therefore that relatively weak heterotic selective values will result if the constant optimum phenotype is closer to the mean of the heterozygote than to that of either homozygote. Otherwise, the selective values will be directional in favour of that homozygote whose metric mean is closest to the fixed optimum. These directional selective values will be additive only if the fixed optimum is several multiples of a away from the population mean at generation zero.

The above results can be extended to any generation by considering the more realistic situation of several loci contributing to the metric character. At any generation t, the relative selective values at any one of the loci can be written as

$$A_2A_2 \qquad\qquad A_1A_2 \qquad\qquad A_1A_1$$

$$\exp\left[\frac{-C}{2\sigma_P^2}\{\mu_t - aq_t - \theta\}^2\right] : \exp\left[\frac{-C}{2\sigma_P^2}\{\mu_t - a(q_t - \tfrac{1}{2}) - \theta\}^2\right] : \exp\left[\frac{-C}{2\sigma_P^2}\{\mu_t - a(q_t - 1) - \theta\}^2\right]$$

where $q_t$ is the frequency of allele $A_1$ at generation t at that locus. The selective values are no longer constant but vary from generation to generation, because $\mu_t$ (the overall population mean) is altered by changes in gene frequency at the other loci.

Making direct use of the previous results it can now be concluded more generally that heterotic selective values will result at a given locus only if the constant optimum phenotype is closer to the mean of

the heterozygote than to that of either homozygote. For this to be so at any generation t, $\theta$ must in fact be equal to or not very different from $\mu_t$, because $\mu_t$ always lies somewhere between the means of the two homozygotes if gene action is additive. Otherwise the selective values at any particular locus will be directional in favour of that homozygote whose metric mean is closest to the fixed optimum. These directional selective values will only be additive if $\theta$ is several multiples of a away from $\mu_t$.

The remainder of this study will concentrate on the case of several loci contributing to the metric character. Thus, although natural selective values will be expressed for only one locus, they will be considered to have arisen as a result of selection at all loci contributing to the metric character, in which case the natural selective values for any one locus at generation t will be a function of the gene frequency at that particular locus $q_t$, and the overall population mean $\mu_t$.

## 2. ARTIFICIAL SELECTION VERSUS NOR-OPTIMAL NATURAL SELECTION

The effect of artificial selection can now be superimposed on this model of natural selection. Before doing so, however, it must firstly be noted that the nor-optimal model results in an alteration of the phenotypic mean and variance within every cycle of selection (see James, 1962; Latter, 1970; O'Donald, 1970 and Bulmer, 1971, b, 1972, 1973). It is possible to determine from each of these papers that this alteration amounts to a decrease of a proportion C of the phenotypic variance. The phenotypic mean, on the other hand, may be increased or decreased according to whether the optimum phenotype is greater than or less than

the sample mean. The magnitude and sign of this alteration are given by $C(\theta-\bar{x})$ where $\bar{x}$ is the phenotypic mean before selection. In other words, the phenotypic variance after selection is $(1-C)\sigma_p^2$, and the phenotypic mean is $\bar{x}+C(\theta-\bar{x})$.

The simplicity of these statements illustrates another advantage of the parameter C over all the other different parameters described previously. A description of the same change in mean and variance in terms of any other parameters involves more complex expressions which are more difficult to interpret biologically.

For the present model, there seems to be no reason for believing that this non-genetic effect of nor-optimal natural selection alters the phenotypic variance between generations: it is merely an effect that is observed within each generation. Therefore the assumption of a constant $\sigma_p^2$ between generations, which is implicit in all the selective values discussed above, is still valid. Indeed, it appears that all the various studies in which expression for, say, $\Delta q$ have been derived have involved this assumption. For an effectively infinite number of loci, it has recently been shown (Bulmer, 1971, d) that a change in phenotypic variance in the parental generation of $-C\sigma_p^2$ (using Latter's (1970) notation) under the nor-optimal model does result in a decrease of phenotypic variance in the offspring generation of $\frac{1}{2}h^4C\sigma_p^2$ compared with $\sigma_p^2$ in the parental generation before selection. However, with heritabilities usually less than 0.5, and values of C less than say 0.2, it would seem that the expected change in phenotypic variance between generations can be safely assumed to be negligible in the present context.

If natural selection occurs prior to artificial selection, then the phenotypic means of the three sub-populations representing the

genotypes $A_2A_2$, $A_1A_2$ and $A_1A_1$ will be altered relative to one another as a result of the non-genetic effect of nor-optimal selection. The selective values of the three genotypes with respect to subsequent artificial selection within the same generation will consequently be different to what they would have been in the absence of natural selection, even though the genotypic means have not altered. As this effect of nor-optimal natural selection within a generation is phenotypic and not genetic, it is of no relevance if natural selection occurs after artificial selection.

Two separate situations must therefore be considered when artificial selection is superimposed on nor-optimal natural selection.

a) Artificial selection prior to natural selection

When artificial selection occurs before the phenotypic means have been altered by natural selection, the relative selective values at generation t after both artificial and natural selection can be represented as

$$\begin{array}{ccccc} A_2A_2 & & A_1A_2 & & A_1A_1 \\ (1-\frac{i\alpha}{2}) \exp[\frac{-Ca}{2\sigma_P^2}\{a(q_t-\frac{1}{2})+\theta-\mu_t\}] & : & 1 & : & (1+\frac{i\alpha}{2}) \exp[\frac{-Ca}{2\sigma_P^2}\{a(\frac{1}{2}-q_t)+\mu_t-\theta\}] \end{array} .$$

The resultant change in gene frequency is

$$\begin{aligned} \Delta_q \doteq & \frac{i\alpha}{2} q(1-q) \\ & + \frac{Ca^2}{4\sigma_P^2} q(1-q)\{q-\tfrac{1}{2}+\tfrac{2}{a}(\theta-\mu_t)\} \\ & - \frac{i\alpha}{2}\frac{Ca^2}{4\sigma_P^2} q(1-q)\{4q(1-q)-\tfrac{1}{2}+\tfrac{2}{a}(\theta-\mu_t)(1-2q)\} \end{aligned} \qquad (8)$$

where q is specifically $q_t$.

The condition necessary to achieve a selection plateau is that the relative fitness of $A_1A_1$ be less than unity in which case

$$(1+\frac{i\alpha}{2})\exp[\frac{-Ca}{2\sigma_p^2}\{a(\tfrac{1}{2}-q_t)+\mu_t-\theta\}] < 1$$

and this condition reduces approximately to

$$C > \frac{i\alpha}{2+i\alpha}\left[\frac{2\sigma_p^2}{a\{a(\tfrac{1}{2}-q_t)+\mu_t-\theta\}}\right] \quad . \qquad (9)$$

The expression on the right hand side is composed of two parts, the first being the same as that which appeared in the condition for equilibrium of the homeostatic model. The term enclosed by square brackets represents the part played by the other parameters used in the optimum model. It shows that the strength of nor-optimal natural selection necessary to produce a pre-fixation plateau increases with phenotypic variance but is reduced by larger values of the effect of the gene, a, and the deviation of the optimum phenotype from the population mean. It also shows that if $\theta = \mu_t$ an equilibrium can only be achieved if $q_t < \frac{1}{2}$, thus reinforcing the earlier conclusion that frequencies above this level result in directional selective values, in this case in the same direction as artificial selection. And even if $q_t < \frac{1}{2}$ for $\theta = \mu_t$, the term enclosed by square brackets will have a value much larger than two for all values of $\frac{a}{\sigma_p}$ less than unity. With $q_t = 0.5$ and $\frac{a}{\sigma_p} = 0.5$ for example, a strength of nor-optimal natural selection in excess of $32\frac{i\alpha}{2+i\alpha}$ will be needed to achieve an equilibrium. It can therefore be concluded that all but the weakest strengths of artificial selection will be sufficient to override the effect of nor-

optimal natural selection if the optimum phenotype is equal to the population mean.

If, however, artificial selection eventually produces an overall mean $\mu_t$ much greater than a fixed $\theta$ (which may have equalled $\mu_o$), then $\mu_t - \theta$ becomes relatively large in which case expression (9) indicates that a selection plateau is quite likely.

b) Artificial selection after natural selection

It has already been noted that a single cycle of nor-optimal natural selection alters the phenotypic variance to $(1-C)\sigma_p^2$ and the phenotypic mean to $\bar{x} + C(\theta - \bar{x})$. How will such alterations affect the relative selective values of the three genotypes with respect to subsequent artificial selection within the same generation? Firstly, by expressing the altered mean of each genotype as a deviation from the heterozygote mean, it is shown in appendix II that the genotype means after natural selection can be represented as

| $A_2A_2$ | $A_1A_2$ | $A_1A_1$ |
|---|---|---|
| $-\frac{a}{2}(1-C)$ | 0 | $\frac{a}{2}(1-C)$ , |

in which case the relative selective values of each genotype with respect to artificial selection turn out to be

$$1 - \frac{i\alpha}{2}\sqrt{1-C} \quad : \quad 1 \quad : \quad 1 + \frac{i\alpha}{2}\sqrt{1-C} \quad .$$

The effect of nor-optimal natural selection prior to artificial selection is therefore to reduce the strength of artificial selection by a factor $\sqrt{1-C}$. The combined action of the two selective forces can be expressed as

$$\left[\exp\left[\frac{-Ca}{2\sigma_p^2}\{a(q_t-\tfrac{1}{2})+\theta-\mu_t\}\right]\right]\left(1-\frac{i\alpha}{2}\sqrt{1-C}\right) \; : \; 1 \; : \; \left[\exp\left[\frac{-Ca}{2\sigma_p^2}\{a(\tfrac{1}{2}-q_t)+\mu_t-\theta\}\right]\right]\left(1+\frac{i\alpha}{2}\sqrt{1-C}\right)$$

which will result in expressions for $\Delta q$ etc. exactly the same as before, except with $i\alpha\sqrt{1-C}$ instead of $i\alpha$. Thus by again reading $q$ as $q_t$, $\Delta q$ is now given by

$$\Delta q = \frac{i\alpha}{2}\sqrt{1-C}\, q(1-q) + \frac{Ca^2}{4\sigma_P^2} q(1-q)\{q-\tfrac{1}{2}+\frac{2}{a}(\theta-\mu_t)\} - \frac{i\alpha\sqrt{1-C}}{2}\frac{Ca^2}{4\sigma_P^2} q(1-q)\{4q(1-q) - \tfrac{1}{2}+\frac{2}{a}(\theta-\mu_t)(1-2q)\} \quad , \tag{10}$$

which reduces to the various expressions for $\Delta q$ obtained by James (1962), who assumed throughout that $\theta = 0$. It should be noted from the second lines of equations (8) and (10) that the contribution of nor-optimal natural selection <u>per se</u> to the change in gene frequency is exactly the same whether natural selection occurs prior to or after artificial selection.

The condition for a selection plateau in a large population if natural selection occurs first now becomes

$$C > \frac{i\alpha\sqrt{1-C}}{2+i\alpha\sqrt{1-C}}\left[\frac{2\sigma_P^2}{a\{a(\tfrac{1}{2}-q_t) + \mu_t - \theta\}}\right]$$

which is slightly less stringent than the analogous condition (9) when artificial selection is carried out prior to natural selection.

As well as altering the phenotypic mean of each genotype, nor-optimal natural selection also alters the relative frequencies of the three genotypes so that they are no longer in Hardy-Weinberg equilibrium. The overall metric mean and genetic variance actually observed at the time of artificial selection are thus not the same as the simple predictions of $\frac{a}{2}(2q_t-1)$ and $\frac{a^2}{2} q_t(1-q_t)$ if any nor-optimal natural selection occurs prior to artificial selection. This is the same effect as was

investigated earlier with the homeostatic model, for which it was shown that the result of natural selection prior to artificial selection is generally to reduce the metric mean and genetic variance actually observed.

## 3. THE PROBLEM OF FURTHER PREDICTION

It would be a relatively straight forward matter now to proceed along lines similar to those used with the homeostatic model of natural selection. Thus expressions could be derived for chance of fixation, advance in the metric mean at the limit, half-life and fitness in a finite population. Indeed James (1962) has already obtained an expression for advance in the metric mean at the limit in a finite population, using a somewhat different approach.

But how useful are such predictions, derived as they are from the above selective values? It has already been noted that in reality, selection acts at a number of loci in which case the background genotype of any one locus will be continually altering. If, for example, artificial selection is increasing the frequency of favoured alleles at several loci, then the metric mean of any one genotype considered alone will be continually increasing. The difference between the optimum phenotype and the metric mean of any genotype at generation t thus increases as selection proceeds,if the optimum is constant, with the result that the natural selective values of various genotypes alter over time. These selective values thus become more and more additively directional in opposition to artificial selection, and increase in intensity as well. Consequently, artificial selection is increasingly opposed as it moves the population mean further and further from the optimum.

One way partly around this problem is to utilize the alternative type of optimum model, namely that in which the optimum phenotype is no longer constant, but rather always equals the population mean whatever that may be at any given generation. Several factors tend to decrease the attractiveness of this hypothesis not the least of which is that it is hard to imagine nature acting in this way. Furthermore, it has already been shown above that nor-optimal natural selection will never cause significant opposition to artificial selection when $\theta = \mu_t$, and will certainly never result in a pre-fixation plateau.

Hence an optimum model with a fixed optimum appears to be much more realistic and potentially fruitful. But the problem of continually altering selective values still remains. For a fixed optimum, it has not been possible to represent the gradual alteration in natural selective values algebraically, but the end result (with the population mean much greater than the fixed optimum) can be depicted as already shown, by following Latter (1960) and James (1962) and setting $\theta = 0$ and $\mu_t \gg a$, where $\mu_t$ is now the change in overall population mean resulting from t generations of changes in gene frequency at all relevant loci. It has already been shown that the natural selective values resulting from such a situation are essentially additive.

At a single locus therefore, additive artificial selection will be opposed by additive natural selection. At generation t, this conflict of selection forces can be represented approximately as

$$\begin{array}{ccccc} A_2A_2 & & A_1A_2 & & A_1A_1 \\ 1 & : & (1+\frac{i\alpha}{2})\exp\{-\frac{C\alpha\mu_t}{2\sigma_p^2}\} & : & (1+i\alpha)\exp\{-\frac{C\alpha\mu_t}{\sigma_p^2}\} \end{array},$$

where the natural fitnesses are variable over time. Having obtained an analogous set of selective values for natural selection occurring prior to artificial selection, James (1962) then proceeded to derive expressions for the resultant change in gene frequency and for the asymptotic limit of response in metric mean in large and finite populations. An asymptotic limit in metric mean is certainly to be expected with the above type of selective values, because as $\mu_t$ continues to increase a stage is reached at which the two opposing selection forces are balanced. At this time the relative fitness of each genotype is unity, in which case if $i\alpha$ is small

$$i\alpha = \frac{Ca\mu}{\sigma_P^2}$$

Solving this expression for $\mu$ gives the metric mean at the limit as

$$\hat{\mu} = \frac{i\sigma_P}{C}$$

which is slightly greater than James' large population result of $\frac{i\sigma_P}{C}\sqrt{1-C}$ for the case of natural selection occurring prior to artificial selection.

However, not all loci will reach this point of balance at the same time unless all loci have alleles of the same effect which started at the same frequency and have not been subjected to chance deviations from the change in frequency expected as a result of selection. Consequently for any one locus, $\mu_t$ must continue to increase above the level which produced the balance at that locus, in which case the overall combined selective values of the three genotypes at any one locus will, sooner or later alter in direction from that which favours artificial selection to that which opposes it: the situation in which the

three genotypes have equal fitness for any one locus will only last for a single generation. The single locus equilibrium is therefore not stable, and the limit to response in metric mean considered by James will thus not be permanent.

Considering all the loci contributing to the metric character, continued artificial selection will generate stronger/and stronger natural selection until, conceivably, an equilibrium will result at which the 'negative' overall selective values at some loci just balance the 'positive'overall selective values at all the other loci. And such an equilibrium could exist without any single locus having equal selective values. Here then is a model of natural selection which certainly appears able to produce a plateau in artificial selection response, but its mechanism is very different from anything that has so far proved amenable to algebraic analysis.

The importance of interactions between alleles at different loci in the optimum model is evident from the above discussion: the relative selective values of the three genotypes at any one locus are determined by the gene frequencies at all other loci which contribute to the expression of the metric character. This interaction between loci seems to preclude any simple algebraic prediction of a plateau in artificial selection due to opposing nor-optimal natural selection.

## 4. SELECTION IN THE ABSENCE OF CROSSING OVER

The single exception to this impasse is the extreme case in which there is no crossing-over between the loci which contribute to genetic variance in the metric character, because in this case the changes in frequency of alleles at all loci on a particular chromosome will all

be the same, irrespective of their effects on the metric character, and will all be equal to the change in frequency of that particular chromosome. Thus changes in the population metric mean can be predicted at any generation: the problem of interaction between loci does not exist. For this situation it is possible to utilize the theory of selection with multiple alleles already developed by Latter and Novitski (1969) and Latter (1970). This can be done by making the reasonable assumption that for a chromosome within which there is no crossing-over between loci which contribute to the metric character, the initial distribution of chromosomal effects tends to be normal. Thus, as Latter and Novitski (1969) pointed out, the single locus model with a potentially infinite number of alleles whose effects are initially normally distributed, is analogous to a model of a potentially infinite number of different chromosomes whose metric values are initially normally distributed.

Combining the relevant expressions of Latter and Novitski (1969) and Latter (1970), it can be shown that the change in frequency of chromosome j resulting from a single generation of artificial selection followed by nor-optimal natural selection is

$$\Delta p_j = \frac{i}{\sigma_P} p_j a_j + \frac{C}{2\sigma_P^2} p_j \left[\tfrac{1}{2}\sigma_G^{*2} - 2(\mu-\theta)a_j - a_j^2\right] \qquad (11)$$

where $p_j$ = frequency of chromosome j prior to that generation of selection,

$a_j$ = the metric effect of chromosome j, scaled such that $\Sigma_j p_j a_j = 0$,

and $\sigma_G^*$ = square root of the genetic variance contributed by all loci in the chromosome at time zero.

The first term on the right hand side of equation (11) represents the effect of artificial selection and the second that of natural selection. Interaction terms have been neglected in this case, for simplicity.

The total change in the population metric mean resulting from the single generation of selection is

$$\Delta x = 2 \sum_j a_j \Delta p_j$$

which reduces to

$$\Delta x = ih^*\sigma_G^* + (\theta-\mu)\, C\, h^{*2} \quad , \qquad (12)$$

where $h^* = \frac{\sigma_G^*}{\sigma_P}$ as in Robertson (1970). Thus the genetic variance contributed by all loci in the chromosome is a proportion $h^{*2}$ of the total phenotypic variance. It can be seen that the effect of non-optimal natural selection increases in importance as the population metric mean ($\mu$) moves further from the optimum, with the result that artificial selection is increasingly opposed by natural selection.

With the problem of interaction between loci removed by considering only complete linkage between all relevant loci, equation (12) is a realistic prediction of the change in metric mean at any generation. But equation (12) is exactly analogous to the expression for $\Delta x$ obtained by James (1962, p.492) from a single locus model with two alleles, in which he assumed $\theta = 0$ and in which i was multiplied by the factor $\sqrt{1-C}$ because natural selection occurred prior to artificial selection. This result is simply an indication of the fact that James effectively assumed that the changes in allelic frequency at all loci were the same. It seems, therefore, that all the predictions analogous to those of James can be realistically applied in the case of no crossing-over between loci.

Thus a selection plateau due to opposing natural selection will be observed when $\Delta x = 0$ in which case the metric mean at the plateau is

$$\hat{\mu} = \theta + \frac{i\sigma_p}{C} \quad .$$

If the original population metric mean was equal to the optimum phenotype $\theta$, then the total advance at the plateau will be

$$\hat{\mu} - \theta = \frac{i\sigma_p}{C} \quad , \qquad (13)$$

which is analogous to the prediction obtained above for a two allele, single locus model in which the changes in allelic frequency at all loci were assumed to be the same, following the approach of James (1962).

Furthermore, the response to a single generation of relaxation from this plateau will be, from (12),

$$R = (\theta - \hat{\mu})\, Ch^{*2}$$
$$= - ih^{*2}\sigma_p \quad ,$$

which gives the ratio of the first generation of relaxation response ($R_1$) to previous forward selection response ($\Delta x = \hat{\mu} - \theta$) as

$$\left|\frac{R_1}{\Delta x}\right| = h^{*2}C \qquad (14)$$

which is effectively the same as the prediction obtained by Latter (1960) for a model of two alleles at a single locus.

The mean fitness at the plateau will be, from (2)

$$\hat{\bar{w}} = \sqrt{1-C}\, \exp\left[ \frac{-C}{2\sigma_p^2}(\hat{\mu} - \theta)^2 \right]$$
$$= \sqrt{1-C}\, \exp\left[ - \frac{i^2}{2C} \right]$$

But at generation zero, $\bar{w}_o = \sqrt{1-C}$ if $\mu_o = \theta$. Therefore, the fitness of the plateaued population relative to that of the original population is approximately, for low values of C,

$$\frac{\bar{w}}{w_o} = 1 - \frac{C}{2\sigma_P^2}(\hat{\mu} - \theta)^2$$

$$= 1 - \frac{i^2}{2C} \quad .$$

Once again, this is analogous to the prediction obtained by James (1962, p.491).

Finally, by making direct use of James' predictions, the value of the metric mean at any time t is

$$\mu_t - \theta = \frac{i\sigma_P}{C}\left[1-(1-Ch^{*2})^t\right]$$

in large populations, and

$$\mu_t - \theta = \frac{i\sigma_P}{C}\left[1 - \exp\left\{-2NCh^{*2}\left[1-\left(1-\frac{1}{2N}\right)^t\right]\right\}\right]$$

approximately, for populations of effective size N. From this last expression James obtained an approximation for the total advance in the metric mean due to Artificial selection in the presence of the Optimum model of natural selection which can be written as

$$L_{AO} = 2N\Delta G\,(1-NCh^{*2})$$

where $\Delta G$ is the change in metric mean during the first generation of selection.

## 5. DISCUSSION

There is little point in describing the detailed ramifications of the predictions given above for the case of no crossing-over, because Latter (1960) and James (1962) have already discussed the implications of analogous expressions. The only value in restating these predictions in the above forms is to emphasise that they can be most safely thought of in the context of completely linked loci, where assumptions of equal gene frequencies and equal gene effects are no longer necessary.

Furthermore, if all loci contributing to the metric character are completely linked, then the predictions for selection in a finite population are much more realistic. This can be most clearly understood by considering the other possibility of incomplete linkage or even independence. Any deviation due to sampling from the deterministic prediction of change in gene frequency at any such locus will result in a population metric mean in the next generation different from its deterministic prediction. Hence the selective values (which are a function of the population metric mean) at all other loci will be different from the deterministic prediction, and it thus becomes impossible to predict accurately the result of even a few generations of selection.

This is in direct contrast with the homeostatic model of natural selection in a finite population where the deviations from deterministic prediction at one locus have no effect on the selective values at other loci.

Returning to the optimum model, it must be noted that the predictions arising from the case of no crossing-over do not necessarily indicate the lowest possible advance in the metric mean, as they do for artificial selection in the absence of natural selection (Robertson, 1970). With several unlinked loci, for example, the initial response to artificial selection in the presence of natural selection could indeed be greater than that predicted with no crossing-over. But as a direct consequence of this relatively rapid response, it seems quite possible to achieve a plateau of the type in which the 'negative' overall selective values at some loci are balanced against the 'positive' overall selective values at all the other loci. And such a plateau

could conceivably occur before the total advance in the mean had reached the plateau level predicted for no crossing-over.

What is needed in order to obtain a greater understanding of this situation is a multi-locus computer simulation of artificial selection in the presence of nor-optimal natural selection. While such a study would not be simple it does appear to be the only way by which to gain a better understanding of the optimum model of natural selection in the context of artificial selection.

## 6. SUMMARY

1. The nor-optimal model of natural selection, in which the fitness decline from some optimum metric phenotype follows the shape of the normal distribution, has been considered.

2. The whole model can be best described in terms of the optimum phenotype $\theta$, the overall population metric mean $\mu$, the phenotypic variance $\sigma_p^2$ and Latter's (1970) coefficient of centripetal selection C.

3. If $\theta$ equals $\mu$ at a given generation, the resultant selective values at any particular locus are either heterotic if gene frequency at that locus lies between $\frac{1}{4}$ and $\frac{3}{4}$, or weakly directional for gene frequencies outside this range. If the selective values are heterotic, then even the strongest conceivable strengths of nor-optimal selection at the most favourable frequencies are only equivalent to relatively weak homeostatic selection.

4. A model in which $\theta$ is variable, being always equal to the overall population mean at any time, will thus never cause significant opposition

to artificial selection, and will certainly never result in a prefixation plateau. The alternative model, in which $\theta$ is a fixed constant phenotype, will likewise never produce serious oppoaition to artificial selection in the early generations, if, as is commonly assumed, $\theta$ equals $\mu$ at generation zero.

5. If $\theta$ is not equal to $\mu$, then the selective values at any particular locus are directional rather than heterotic whenever the optimum is closer to the mean of either homozygote than to that of the heterozygote. The directional selective values are additive only if the optimum is several multiples of a (the metric difference between the two homozygotes) away from the population mean.

6. With a fixed optimum phenotype for which $\theta = \mu_o$, continued artificial selection produces an ever increasing difference between $\theta$ and $\mu_t$ in which case the natural selective values become increasingly additive and increasingly opposed to artificial selection as the selection programme proceeds. A selection plateau is quite likely to result from such a situation, but a realistic algebraic method of describing this process has yet to be discovered.

7. A single cycle of nor-optimal natural selection alters the phenotypic metric mean from $\bar{x}$ to $\bar{x}+C(\theta-\bar{x})$ and alters the phenotypic variance from $\sigma_p^2$ to $(1-C)\sigma_p^2$ within each generation, but this selection has no effect on genotypic means and variances within generations, and can be assumed to result in a negligible alteration of $\sigma_p^2$ between generations. If such selection occurs prior to artificial selection, then the effect is to reduce the artificial selection coefficient from $i\alpha$ to $i\alpha\sqrt{1-C}$. Nor-optimal natural selection prior

to artificial selection thus acts by reducing the strength of artificial selection, as well as contributing per se to a change in gene frequency. Nor-optimal natural selection therefore produces greater opposition if it occurs before the time of artificial selection.

8. Quantitative predictions of limits to artificial selection due to opposing nor-optimal natural selection may not have very much value when derived from single locus selective values, as the equilibria they represent are transient.

9. It is possible to consider one extreme multi-locus case, namely that in which there is no crossing-over between the loci contributing to the metric character. If the initial distribution of chromosome effects is approximately normal, then the predictions of Latter (1960) and James (1962) provide a realistic description of the results of the interaction between artificial and natural selection.

10. For all other cases except no crossing-over, a proper understanding of the implications of the nor-optimal model in the context of artificial selection will only be achieved if interactions between loci are taken into account. A multi-locus computer simulation thus appears to be the only way in which more useful predictions can be obtained.

# III REVERSE AND RELAXED SELECTION

## Introduction

Reverse and relaxed selection have been used quite commonly in laboratory selection experiments as diagnostic tools, especially in situations where selection response seems to have plateaued. The results of such selection have usually been interpreted in the light of common sense arguments which say that any alteration in the metric mean after relaxation must be an indication of opposing natural selection, and that response to reverse selection indicates the remaining presence of at least some additive genetic variance.

What is lacking at present is a quantitative prediction as to what the results of reverse and relaxed selection at a particular stage of the selection programme might be, for specific models of artificial selection. One method by which some understanding of the problem can be obtained for various single locus models involves the use of a suitable transition probability matrix. Such an approach has already been used by Allan and Robertson (1964), but they were concerned specifically with the effects of initial reverse selection on the ultimate result of subsequent forward selection to the limit. In the present context, this amounts to a study of the total change in gene frequency or metric mean resulting from a given period of forward selection followed by reverse selection to the limit. In the present study, the methods and results of Allan and Robertson are extended to cover any number of generations of both forward and reverse selection for several single locus models of artificial selection.

Operations with a transition probability matrix

It has already been seen how repeated multiplication of a suitable matrix by a relevant vector enables the course of artificial selection in the absence or presence of natural selection to be followed over generations. For example, the method of setting up a suitable transition probability matrix for forward selection, and pre-multiplying this matrix by a row vector of the gene frequency distribution at generation t (given a particular initial gene frequency) to obtain the gene frequency distribution in the next generation, has already been described. Subsequent multiplication of the row vector of gene frequency distribution at generation t+1 by a column vector of all possible initial gene frequencies then produces a scalar whose value is the frequency of allele $A_1$ at generation t+1, given the particular initial frequency.

More specifically, the initial step is to set up a transition probability matrix $\underset{\sim}{U}$ for forward selection as described previously. Having then established a row vector $\underset{\sim}{u}_o$ of order 2N+1 with all elements zero except the jth which is unity, the gene frequency distribution at generation t=1 for an initial gene frequency of j/2N is obtained as

$$\underset{\sim}{u}_1 = \underset{\sim}{u}_o \underset{\sim}{U}$$

For subsequent generations,

$$\underset{\sim}{u}_2 = \underset{\sim}{u}_1 \underset{\sim}{U}$$

$$= \underset{\sim}{u}_o \underset{\sim}{U}^2$$

and $$\underset{\sim}{u}_t = \underset{\sim}{u}_{t-1} \underset{\sim}{U} \qquad (1)$$

$$= \underset{\sim}{u}_o \underset{\sim}{U}^t \qquad (2)$$

Expression (2) indicates more clearly the principle of the use of a transition probability matrix, in that the element $p_{jk}$ of $\underset{\sim}{U}^t$ represents the probability of obtaining k $A_1$ alleles at generation t given there were j $A_1$ alleles at generation 0. The $j^{th}$ row of $\underset{\sim}{U}^t$ therefore represents the gene frequency distribution at generation t for an initial gene frequency of j/2N.

In practice, however, it is less expensive to follow Allan and Robertson (1964) and actually use operations of the form given by (1), involving only the repeated multiplication of the matrix by a vector rather than the matrix by the matrix, as is needed in (2).

The expected frequency of allele $A_1$ at generation t is then obtained as

$$E[q_t | q_o = j/2N] = \underset{\sim}{u}_t \underset{\sim}{v}_o$$

$$= \underset{\sim}{u}_o \underset{\sim}{U}^t \underset{\sim}{v}_o$$

where $\underset{\sim}{v}_o$ is a column vector of all possible initial gene frequencies with elements $v_{o(j)} = j/2N$.

Reverse selection

The commencement of reverse selection involves recalculation of the transition probability matrix, with -i substituted for i in the selective values of the three genotypes. All subsequent pre-multiplications of the row vector $\underset{\sim}{u}$ of gene frequency distribution are then carried out onto the recalculated matrix $\underset{\sim}{D}$ for as many generations of reverse selection as required. Thus the results of the first generation of reverse selection are obtained as

Table 1

Changes in gene frequency distribution and in mean gene frequency during 10 generations of forward selection followed by 40 generations of reverse selection in a population of effective size N=10. All probabilities are expressed x 1000. Only every second possible class is shown so that the probabilities do not sum to 1000 except at t=0. In this example $q_o$=.3 and Niα=8.

| Generations | | Frequency distribution of allele $A_1$ | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| t | t' | 0 | .1 | .2 | .3 | .4 | .5 | .6 | .7 | .8 | .9 | 1 | E[q] | $\frac{R}{\Delta x}$ |
| 0 | | | | | 1000 | | | | | | | | 0.300 | |
| 1 | | | 3 | 33 | 125 | 184 | 118 | 34 | 4 | | | | 0.400 | |
| 2 | | | 4 | 21 | 57 | 103 | 127 | 107 | 59 | 19 | 3 | | 0.499 | |
| 3 | | 1 | 4 | 12 | 30 | 59 | 90 | 108 | 100 | 66 | 26 | 4 | 0.591 | |
| 4 | | 1 | 3 | 8 | 17 | 34 | 59 | 86 | 104 | 100 | 68 | 24 | 0.672 | |
| 5 | | 2 | 2 | 5 | 10 | 21 | 38 | 62 | 90 | 110 | 105 | 75 | 0.740 | |
| 6 | | 2 | 1 | 3 | 6 | 13 | 24 | 44 | 71 | 103 | 126 | 157 | 0.797 | |
| 7 | | 2 | 1 | 2 | 4 | 8 | 16 | 30 | 54 | 90 | 130 | 259 | 0.842 | |
| 8 | | 2 | 1 | 1 | 2 | 5 | 10 | 21 | 40 | 74 | 123 | 370 | 0.878 | |
| 9 | | 2 | | 1 | 2 | 3 | 7 | 14 | 30 | 59 | 109 | 478 | 0.906 | |
| 10 | | 3 | | 1 | 1 | 2 | 4 | 10 | 22 | 46 | 93 | 576 | 0.928 | |
| 10 + | 1 | 3 | 1 | 2 | 3 | 6 | 12 | 20 | 33 | 48 | 62 | 602 | 0.902 | 0.04 |
| 10 + | 2 | 3 | 2 | 4 | 8 | 14 | 20 | 28 | 34 | 38 | 36 | 614 | 0.872 | 0.09 |
| 10 + | 3 | 5 | 5 | 10 | 16 | 21 | 25 | 28 | 29 | 27 | 22 | 621 | 0.840 | 0.14 |
| 10 + | 4 | 9 | 11 | 18 | 22 | 25 | 26 | 25 | 22 | 18 | 13 | 625 | 0.809 | 0.19 |
| 10 + | 5 | 18 | 19 | 24 | 26 | 25 | 23 | 19 | 15 | 12 | 8 | 628 | 0.780 | 0.24 |
| 10 + | 6 | 33 | 28 | 29 | 27 | 23 | 19 | 14 | 11 | 8 | 5 | 629 | 0.754 | 0.28 |
| 10 + | 7 | 55 | 34 | 31 | 25 | 19 | 14 | 10 | 7 | 5 | 3 | 630 | 0.731 | 0.31 |
| 10 + | 8 | 83 | 38 | 30 | 22 | 15 | 11 | 7 | 5 | 3 | 2 | 630 | 0.711 | 0.35 |
| 10 + | 9 | 115 | 39 | 28 | 18 | 12 | 8 | 5 | 3 | 2 | 1 | 631 | 0.694 | 0.37 |
| 10 + | 10 | 149 | 38 | 24 | 15 | 9 | 5 | 3 | 2 | 1 | 1 | 631 | 0.681 | 0.39 |
| 10 + | 11 | 182 | 35 | 21 | 12 | 7 | 4 | 2 | 1 | 1 | | 631 | 0.670 | 0.41 |
| 10 + | 12 | 214 | 31 | 17 | 9 | 5 | 3 | 1 | 1 | 1 | | 631 | 0.661 | 0.43 |
| 10 + | 13 | 242 | 27 | 14 | 7 | 3 | 2 | 1 | 1 | | | 631 | 0.654 | 0.44 |
| 10 + | 14 | 266 | 22 | 11 | 5 | 3 | 1 | 1 | | | | 631 | 0.649 | 0.44 |
| 10 + | 15 | 287 | 18 | 9 | 4 | 2 | 1 | | | | | 631 | 0.644 | 0.45 |
| 10 + | 16 | 304 | 15 | 7 | 3 | 1 | 1 | | | | | 631 | 0.641 | 0.46 |
| 10 + | 17 | 318 | 12 | 5 | 2 | 1 | | | | | | 631 | 0.639 | 0.46 |
| 10 + | 18 | 329 | 9 | 4 | 2 | 1 | | | | | | 631 | 0.637 | 0.46 |
| 10 + | 19 | 338 | 7 | 3 | 1 | | | | | | | 631 | 0.636 | 0.47 |
| 10 + | 20 | 345 | 6 | 2 | 1 | | | | | | | 631 | 0.634 | 0.47 |
| 10 + | 21 | 351 | 4 | 2 | 1 | | | | | | | 631 | 0.634 | 0.47 |
| 10 + | 22 | 355 | 3 | 1 | | | | | | | | 631 | 0.633 | 0.47 |
| 10 + | 23 | 359 | 3 | 1 | | | | | | | | 631 | 0.633 | 0.47 |
| 10 + | 24 | 361 | 2 | 1 | | | | | | | | 631 | 0.632 | 0.47 |
| 10 + | 25 | 363 | 1 | 1 | | | | | | | | 631 | 0.632 | 0.47 |
| 10 + | 26 | 364 | 1 | | | | | | | | | 631 | 0.632 | 0.47 |
| 10 + | 27 | 366 | 1 | | | | | | | | | 631 | 0.632 | 0.47 |
| 10 + | 28 | 366 | 1 | | | | | | | | | 631 | 0.632 | 0.47 |
| 10 + | 29 | 367 | | | | | | | | | | 631 | 0.631 | 0.47 |
| 10 + | 30 | 367 | | | | | | | | | | 631 | 0.631 | 0.47 |
| 10 + | 31 | 368 | | | | | | | | | | 631 | 0.631 | 0.47 |
| 10 + | 32 | 368 | | | | | | | | | | 631 | 0.631 | 0.47 |
| 10 + | 33 | 368 | | | | | | | | | | 631 | 0.631 | 0.47 |
| 10 + | 34 | 368 | | | | | | | | | | 631 | 0.631 | 0.47 |
| 10 + | 35 | 368 | | | | | | | | | | 631 | 0.631 | 0.47 |
| 10 + | 36 | 369 | | | | | | | | | | 631 | 0.631 | 0.47 |
| 10 + | 37 | 369 | | | | | | | | | | 631 | 0.631 | 0.47 |
| 10 + | 38 | 369 | | | | | | | | | | 631 | 0.631 | 0.47 |
| 10 + | 39 | 369 | | | | | | | | | | 631 | 0.631 | 0.47 |
| 10 + | 40 | 369 | | | | | | | | | | 631 | 0.631 | 0.47 |

$$\underset{\sim}{u}_{t+1} = \underset{\sim}{u}_{t}\,\underset{\sim}{D}$$

$$= \underset{\sim}{u}_{o}\,\underset{\sim}{U}^{t}\,\underset{\sim}{D}$$

and, in general,

$$\underset{\sim}{u}_{t+t'} = \underset{\sim}{u}_{t+t'-1}\,\underset{\sim}{D}$$

$$= \underset{\sim}{u}_{o}\,\underset{\sim}{U}^{t}\,\underset{\sim}{D}^{t'}$$

Finally, the expected value of gene frequency after t' generations of reverse selection is given by

$$E[q_{t+t'} \mid q_o = j/2N] = \underset{\sim}{u}_{t+t'}\,\underset{\sim}{v}_{o}$$

$$= \underset{\sim}{u}_{o}\,\underset{\sim}{U}^{t}\,\underset{\sim}{D}^{t'}\,\underset{\sim}{v}_{o} \quad .$$

Table 1 illustrates the way in which the course of artificial selection can be followed, in this case with forward selection for N generations followed by reverse selection for 4N generations, starting with an initial frequency of 0.3, with $N i\alpha = 8$ in a population of size N = 10. Natural selection is assumed to be absent. It can be seen how the gene frequency distribution is quickly moved to the right by strong forward selection, towards fixation of the allele favoured by artificial selection ($A_1$). By generation t=N, the probability of fixation of that allele is 0.576 in contrast to the very low probability of loss (0.003). The mode of the frequency distribution is now at q = 0.9, and the frequency of the favoured allele over all populations or loci, both segregating and fixed, is already 0.93.

Reverse selection of equivalent strength ($i\alpha = -0.8$) exerts an immediate and marked effect. The frequency distribution is moved

quickly to the left towards fixation of the allele which is now favoured ($A_2$), until, at generation $t' = 0.7N$, the mode is down at $q = 0.1$. The probability of fixation of allele $A_2$ increases, but its upper limit has already been determined by the proportion of lines or loci previously fixed for the other allele, $A_1$. In fact, this latter proportion continues to increase until $t' = 0.9N$ simply because the upper tail of the frequency distribution is still continuous with the fixation class of allele $A_1$ during the early generations of reverse selection. It is not until $t' = 1.1N$ that a discontinuity develops in the distribution. However, as soon as the separation occurs, the ultimate frequency of each allele at the limit of reverse selection is decided. For allele $A_1$, it is obviously the proportion of lines or loci already fixed for that allele (0.631), and for allele $A_2$ it is the remainder (0.369): all those lines or loci still segregating after the discontinuity appears must eventually become fixed for allele $A_2$ if reverse selection is continued. In this particular example, complete fixation is achieved around generation $t' = 2.9N$ but it would have taken far longer with weaker artificial selection.

The overall frequency of allele $A_1$ decreases quite rapidly during the first few generations of reverse selection, because of the associated shift of the frequency distribution to the left. Although the lower limit of frequency of allele $A_1$ is set at 0.631 as soon as the discontinuity in the distribution develops, it can be seen that this actual value is not and can not be achieved until complete fixation: so long as any part of the distribution remains in the segregating classes, the final possible frequency of allele $A_1$ as a

result of reverse selection can not be obtained.

This then is an example of the way in which the course of artificial selection, both forward and reverse, can be followed, generation by generation through the selection process.

Relaxation

In laboratory selection programmes, relaxation of artificial selection involving the random choice of individuals to become parents of the next generation, is most commonly conducted in relatively large populations. Under such conditions the simple prediction is that no subsequent change in metric mean will occur unless natural selection is interacting with artificial selection. For the homeostatic model of natural selection, the change in metric mean as a result of $t'$ generations of relaxation in a large population is $R_{t'} = a \sum_{i=1}^{t'} \Delta q_i$ where $\Delta q_i = (s_1+s_2)q_i(1-q_i)(\bar{q}-q_i)$, this being the usual equation for change in gene frequency due to heterozygote superiority. The metric mean thus continues to alter until the gene frequency returns to its large population equilibrium value of $\bar{q}$.

It is possible, however, that relaxation may be carried out by the random sampling of only the same number of individuals as have previously been selected for high expression of the metric character, in which case the effective population size remains unaltered. As before it might be expected that natural selection will result in a change in metric mean following relaxation, but the manner of this change will almost certainly be different from that which would be expected in a large population.

The effect of relaxation of artificial selection in finite

populations can be studied in a manner analogous to that already described for reverse selection, the only difference being that for relaxation, zero is substituted for i in the recalculation of the transition probability matrix after t generations of forward selection.

In order to provide a framework in which to discuss the results obtained from the transition probability matrix approach, some consideration will now be given to several theoretical predictions which can be obtained from a simple algebraic model.

1. THE ADDITIVE MODEL

For small $N\alpha$, the frequency of allele $A_1$ after t generations of forward selection with an additive model in the absence of natural selection is

$$E[q_t] = q_o + N\alpha\, q_o(1-q_o)(1-e^{-t/2N}) \qquad (3)$$

where $q_o$ is the initial gene frequency (Robertson, 1960). It is usually assumed that during this time the effect of finite population size is to reduce $q_o(1-q_o)$ by a fraction 1/2N per generation, in which case it will have the value $q_o(1-q_o)e^{-t/2N}$ after t generations of forward selection. It is then possible to express the expected frequency of allele $A_1$ after t' subsequent generations of reverse selection ($i<o$) in a form analogous to that given above:-

$$E[q_{t+t'}] = E[q_t] + N(-i\alpha)[q_o(1-q_o)e^{-t/2N}](1-e^{-t'/2N}) \qquad (4)$$

$$= q_o + Ni\alpha q_o(1-q_o)(1-2e^{-t/2N}+e^{-(t+t')/2N}) \quad .$$

The difference between the initial frequency $q_o$ and the ultimate frequency after t+t' generations is then

$$E[q_{t+t'}] - q_o \doteq Ni\alpha q_o(1-q_o)(1-2e^{-t/2N}+e^{-(t+t')/2N}) \quad .$$

When $t' = \infty$, implying reverse selection to the limit, this expression reduces to

$$E[q_{t+\infty}] - q_o = Ni\alpha q_o(1-q_o)(1-2e^{-t/2N}) \qquad (5)$$

which is analogous to the result obtained by Allan and Robertson (1964) who were studying the effect of t generations of initial reverse selection on the ultimate result of subsequent forward selection to the limit.

A prediction for small $Ni\alpha$

A general description of the effects of reverse selection following forward selection can be achieved by considering the change in metric mean due to reverse selection (R) in terms of the change in metric mean resulting from the previous forward selection ($\Delta\bar{x}$). From equations (3) and (4), it can be seen for an additive model that

$$\Delta\bar{x} = a\{E[q_t] - q_o\}$$

$$\doteq a\, Ni\alpha q_o(1-q_o)(1-e^{-t/2N})$$

and

$$R = a\{E[q_{t+t'}] - E[q_t]\}$$

$$\doteq -a\, Ni\alpha q_o(1-q_o)e^{-t/2N}(1-e^{-t'/2N})$$

which gives

$$\left|\frac{R}{\Delta\bar{x}}\right| \doteq \frac{e^{-t/2N}\,(1-e^{-t'/2N})}{1-e^{-t/2N}} \quad . \qquad (6)$$

The ratio of reverse selection response to previous forward selection response is thus the same for all initial gene frequencies and is

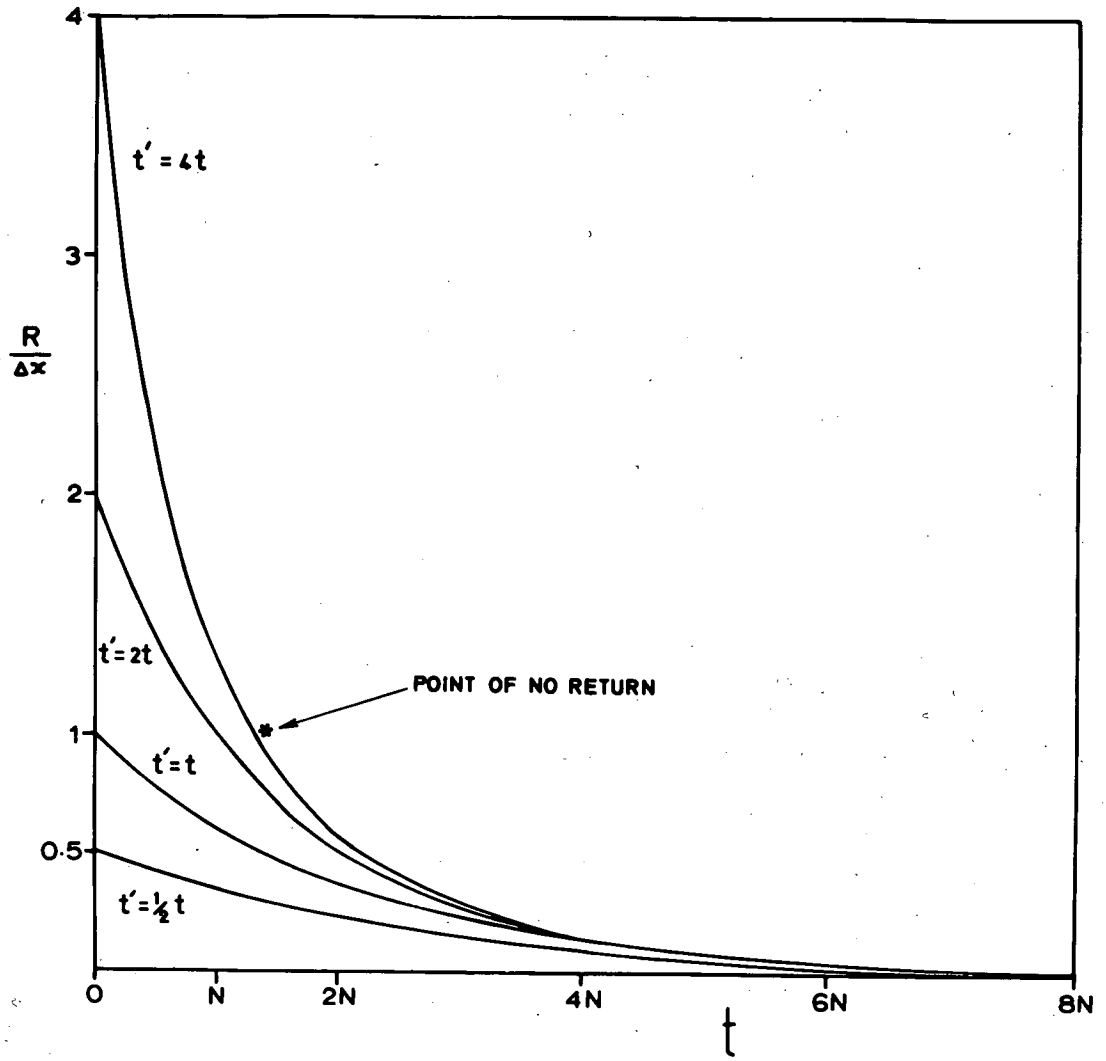


Figure 1. The relationship between length of forward selection, t, and the ratio $\frac{R}{\Delta x}$ after various lengths of subsequent reverse selection, t', corresponding to $\frac{1}{2}$t, t, 2t and 4t generations, with t and t' being expressed in terms of effective population size N. Curves have been obtained from equation (6).

independent of the size of the gene effect ($\frac{a}{\sigma_P} = \alpha$), and the intensity of artificial selection (i), so long as Nia is small.

An even more simple prediction is obtained if reverse selection is carried out for the same number of generations as the previous forward selection, in which case t' = t, and equation (6) reduces to

$$\frac{R}{\Delta \bar{x}} \doteq e^{-t/2N}$$
$$\doteq 1 - F$$

where F is the inbreeding coefficient at a neutral locus after t generations of random mating in a population of effective size N. Thus, if forward selection is followed by an equal number of generations of reverse selection, the response to reverse selection is never as great as the previous forward selection response. Furthermore, the effectiveness of reverse selection decreases as the period of previous forward selection is lengthened, as might be expected. It must be emphasised that these conclusions apply only to a model of additive gene action in the absence of natural selection.

The general relationship between $\frac{R}{\Delta \bar{x}}$ and the length of forward and reverse selection is shown in figure 1, having been obtained from equation (6). The first point to note is that the time scale on the x-axis corresponds exactly to the time scale used earlier in the presentation of expected selection response curves. Thus all possible periods of initial forward selection are included, from t=0 to t=8N. Each curve in the figure represents the value of $\frac{R}{\Delta \bar{x}}$ to be expected from a particular length of subsequent reverse selection. The curve for equal numbers of generations of forward and reverse selection (t'=t) is simply the plot of 1-F for a neutral locus against time in units of N. It shows, for example, that an equal number of generations

of reverse selection after forward selection of length equivalent to the half-life of the overall selection process (1.4N generations), results in the metric mean returning half way to its original level.

The asterisk in the figure represents the 'point of no return', a concept introduced by Allan and Robertson (1964) and which in the present context can be defined as the number of generations of forward selection beyond which it is impossible for even an infinite number of generations of reverse selection to return the metric mean to its original level. For genes of small effect, Allan and Robertson found that the point of no return was 1.4N generations and indeed this conclusion derives directly from equation (5) by setting $E[q_{t+\omega}]-q_o = 0$. The curve for $t' = \infty$ would thus pass through the point of no return, and would then approach asymptotically a value of $\frac{R}{\Delta x} = \infty$ as $t \to 0$. All other curves for all finite values of t' will be situated to the left of this curve and will therefore always pass to the left of the point of no return. If $t<1.4N$, the number of generations of reverse selection necessary to return the metric mean to its original value, (that is, to obtain $\frac{R}{\Delta x} = 1$) decreases as t decreases. Beyond $t=1.4N$, on the other hand, even reverse selection to the limit (complete fixation) will not return the metric mean to its original value.

Finally, it can be seen that the magnitude of $\frac{R}{\Delta x}$ approaches a limit of $t'/t$ as the number of generations of forward selection decreases. Forward selection for $t=0.2N$ generations, for example, followed by $t'=0.1N$ generations of reverse selection results in an $\frac{R}{\Delta x}$ value approaching 0.5, in this case 0.47.

It is possible to obtain one more simple prediction from equation (6), in this case for a single generation of reverse selection ($t'=1$) following t generations of forward selection. If response to the first generation of reverse selection is denoted by $R_1$, then equation (6) reduces to

$$\frac{R_1}{\Delta x} \doteq \frac{1}{2N} \frac{e^{-t/2N}}{1-e^{-t/2N}}$$

or $$\frac{NR_1}{\Delta x} \doteq \frac{1-F}{2F} .$$

Thus the results of a single generation of reverse selection following any period of forward selection can be described in terms of the parameter combination $\frac{NR_1}{\Delta x}$. It follows from the above expression that beyond $t=1.4N$, $\frac{NR_1}{\Delta x}$ is less than 1-F, while if the single generation of reverse selection is carried out before the point of no return, then $\frac{NR_1}{\Delta x}$ is greater than 1-F.

All the conclusions so far reached refer to a specific model of additive gene action with no natural selection and $N\bar{i}\alpha<1$, inferring genes of small effect and/or small population size. How will the conclusions be altered if the model is extended to include larger values of $N\bar{i}\alpha$?

## Stronger artificial selection

Since larger $N\bar{i}\alpha$ values tend to decrease genetic variance more quickly thus leaving relatively less genetic variance for subsequent reverse selection, it could be expected that the value of $\Delta x$ will be increased by a greater proportion than the value of R by larger values of $N\bar{i}\alpha$, for any particular t and t'. Thus with equal periods of forward and reverse selection, the ratio $\frac{R}{\Delta x}$ is expected to be less than the 1-F

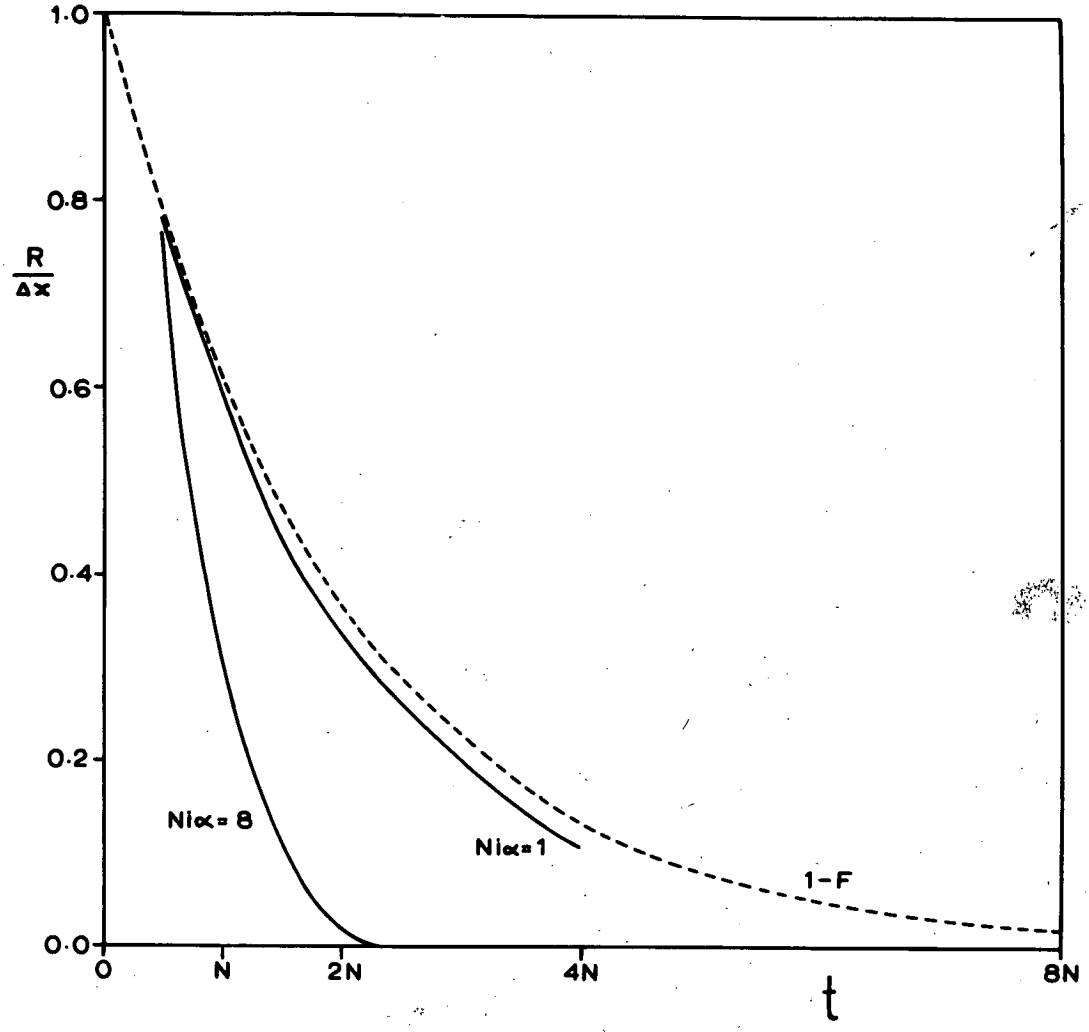


Figure 2. The relationship between length of forward selection, t, and the ratio $\frac{R}{\Delta x}$ after as many generations of reverse selection as previous forward selection (t'=t). Transition probability matrix results (solid lines) for relatively weak (Niα=1) and relatively strong (Niα=8) artificial selection with $q_o$=0.5 are compared with the prediction of $\frac{R}{\Delta x}$ = 1-F (dotted line) from equation (6).

predicted for $Ni\alpha<1$. For $t=t'$ and $q_o = 0.5$, figure 2 shows this to be true.

The values of $\frac{R}{\Delta x}$ have been obtained from continued multiplication of the row vector of gene frequency distribution onto the appropriate transition probability matrix, and the subsequent determination of gene frequency, as described previously. Firstly, it can be seen that the points for $Ni\alpha = 1$ correspond very closely to the expectation of $e^{-t/2N}$ for small $Ni\alpha$. Increasing the strength of artificial selection reduces the value of $\frac{R}{\Delta x}$ for any particular t, until with say $Ni\alpha = 8$, forward selection for as little as 2N generations is sufficient to effectively prohibit any response to subsequent reverse selection.

Similar conclusions in general have been obtained for all possible initial gene frequencies, with the exception that for $t'=t$ the value of $\frac{R}{\Delta x}$ may be slightly greater than $e^{-t/2N}$ if reverse selection is commenced after only a few generations of forward selection and if initial gene frequency is less than one half. The reason for this is simply that any forward selection favouring alleles with an initial frequency less than one half initially increases the genetic variance at that locus (until $q_t = 0.5$) thus enhancing the prospects of response to any reverse selection which occurs before $q_t$ has reached 0.5. More generally, it has been found that the value of $\frac{R}{\Delta x}$ observed from the matrix operations for any initial gene frequency and for any value of t' and t corresponds very closely to the value predicted from equation (6), if $Ni\alpha<1$, so that the matrix results for $Ni\alpha = 1$ could have been used to draw figure 1. Once again, the observed value of $\frac{R}{\Delta x}$ for any t' and any t tends to decrease below that predicted from equation (6) as $Ni\alpha$ increases, for all initial gene frequencies.

Relaxation

It is quite evident that no change in metric mean as a result of relaxation of selection is expected to occur with an additive model in the absence of natural selection. Matrix results have confirmed this expectation, and have shown that the only result of relaxation is a gradual widening and flattening of the gene frequency distribution, with fixation and loss occurring in the ratio of $q_t/(1-q_t)$ where $q_t$ is the frequency of the allele favoured by artificial selection at the final generation of forward selection.

## 2 SUMMARY

1. The effect of t' generations of reverse selection after t generations of forward selection can be described by expressing the change in the metric mean resulting from reverse selection (R) in terms of the change in the metric mean due to the previous forward selection ($\Delta x$).

2. An additive model of artificial selection in a population of effective size N with no natural selection has been considered.

3. If reverse selection is continued for as many generations as the previous forward selection (t' = t), then the ratio $\frac{R}{\Delta x}$ equals 1-F where F is the inbreeding coefficient for a neutral locus at generation t and is estimated as $[1 - (1-\frac{1}{2N})^t]$. This prediction is expected to hold for genes of small effect and/or small population size such that $Ni\alpha<1$.

4. Stronger artificial selection ($Ni\alpha>1$) tends to decrease the observed value of $\frac{R}{\Delta x}$ below 1-F. On no occasion will $\frac{R}{\Delta x}$ be greater than 1-F, for t=t'.

5. For any period of reverse selection following any period of forward

selection, the value of $\frac{R}{\Delta x}$ never exceeds $\frac{t'}{t}$, and tends to decrease exponentially from this value as t increases, and as the strength of artificial selection (Nia) increases.

6. The result of a single generation of reverse selection (t'=1) following t generations of forward selection can be described in terms of the ratio $\frac{NR_1}{\Delta x}$ where $R_1$ is the response to the first generation of reverse selection. With genes of small effect and/or small population size for which $Nia \leq 1$, the value of $\frac{NR_1}{\Delta x}$ is expected to be $\frac{1-F}{2F}$.

## 3. THE HOMEOSTATIC MODEL OF NATURAL SELECTION

It would be convenient if the simple algebraic prediction of the results of reverse selection already obtained for the additive model could be extended to include the effect of homeostatic natural selection. Suitable expressions for R and $\Delta x$ have already been obtained in the earlier consideration of the homeostatic model, but the resultant ratio $\frac{R}{\Delta x}$ has so far defied all attempts at simplification.

What has been done therefore, is to go straight to the transition probability matrix results, and to use as a basis for comparison the results already obtained for an additive model in the absence of natural selection. Thus the question being asked is how does homeostatic natural selection alter the results of reverse selection from those expected under a simple additive model in the absence of natural selection?

In line with the earlier study of the homeostatic model, the assumption made here is that the base population for artificial selection is obtained by randomly sampling a finite number of individuals from a conceptually infinite population which is in equilibrium with natural selection, such that E[q] in the base population equals $\bar{q}$. Forward and reverse selection are then carried out in exactly the same manner as described in the previous section, with the transition probability matrices being calculated from overall selective values $(1-\frac{i\alpha}{2})(1-s_2):1:(1+\frac{i\alpha}{2})(1-s_1)$ for forward selection, and $(1+\frac{i\alpha}{2})(1-s_2):1:(1-\frac{i\alpha}{2})(1-s_1)$ for reverse selection for genotypes $A_2A_2$, $A_1A_2$ and $A_1A_1$ respectively. For the time being it will be assumed that natural selection occurs after artificial selection, i.e., that the genotypes are in Hardy-Weinberg frequencies at the time of artificial selection. The effect of relaxing this assumption will be considered in a subsequent section.

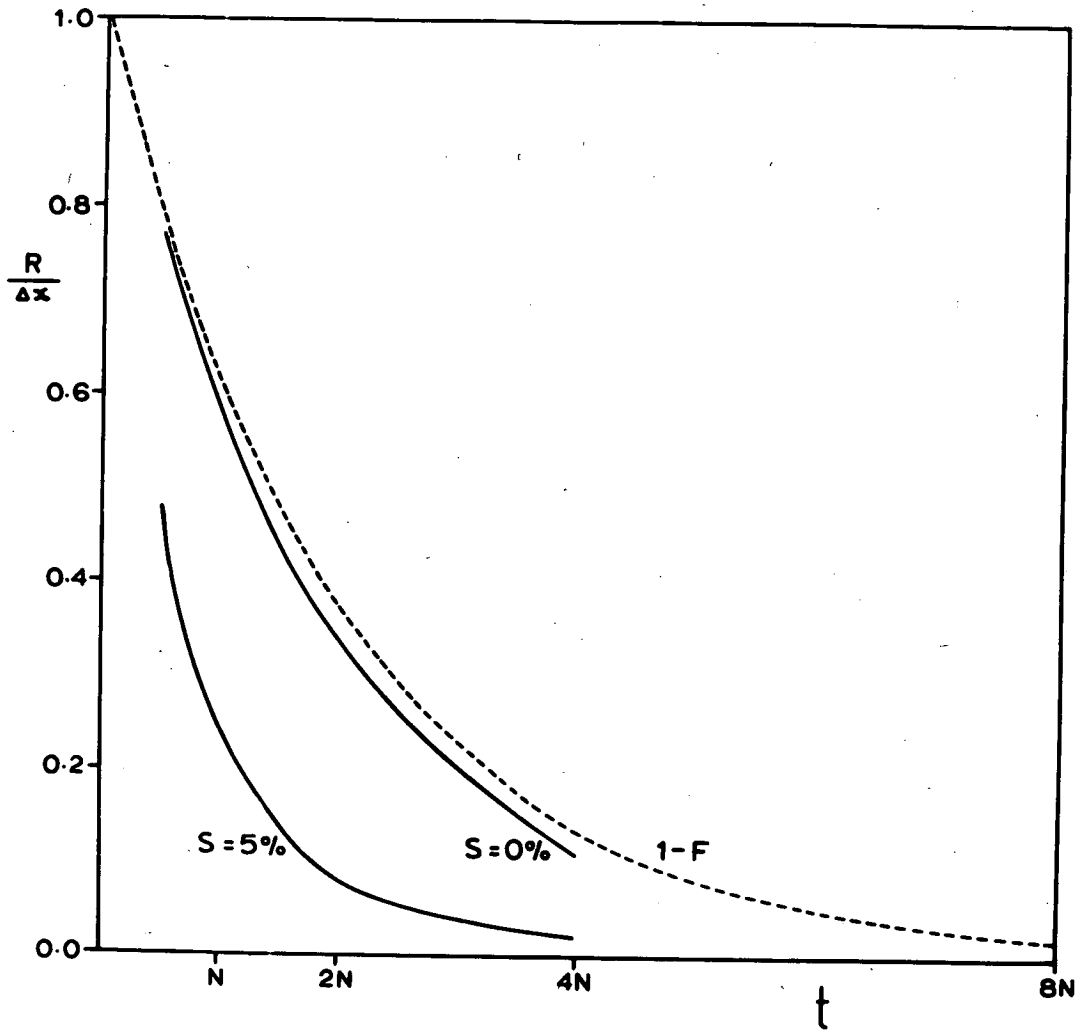


Figure 3. The relationship between length of forward selection, t, and the ratio $\frac{R}{\Delta x}$ after as many generations of reverse selection as previous forward selection (t'=t). Transition probability matrix results (solid lines) for no natural selection (S=0%) and relatively weak natural selection (S=5%) with $q_o = \bar{q} = 0.7$ are compared with the prediction of $\frac{R}{\Delta x} = 1-F$ (dotted line) for no natural selection from equation (6).

The importance of equilibrium gene frequency

It has been found that the results of reverse selection under the present model are dependent to a large extent on initial and equilibrium gene frequency $\bar{q}$. In other words the value of $\frac{R}{\Delta x}$ is dependent on the relative natural fitnesses of the two homozygotes.

For $\bar{q}>0.5$, the homozygote favoured by artificial selection ($A_1A_1$) has a higher natural fitness than the other homozygote, with the result that natural selection and artificial forward selection in small populations are both tending to work towards the same end, namely fixation of allele $A_1$. More importantly, if $\bar{q}>0.5$, it follows that natural selection will oppose reverse selection because the homozygote most favoured by artificial reverse selection ($A_2A_2$) is the least fit of all the genotypes. An example of this effect is given in figure 3 where it can be seen for $q_o = \bar{q} = 0.7$ and $t' = t$, that even relatively weak natural selection (S=5%) is sufficient to reduce $\frac{R}{\Delta x}$ well below that expected under the additive model alone. Stronger natural selection reduces $\frac{R}{\Delta x}$ even further. The same trends have been found with any value of t and t' for any $\bar{q}>0.5$.

On the other hand, with $\bar{q}$ equal to or less than 0.5 natural selection opposes forward artificial selection and consequently enhances the result of reverse selection. The expected results of reverse selection with $q\leq 0.5$ will now be examined with the aim of obtaining an understanding of the extent of this enhancement.

A single generation of reverse selection

It has previously been shown that the value of $\frac{NR_1}{\Delta x}$ after a single generation of reverse selection is expected to be $\frac{1-F}{2F}$ in the absence of natural selection. What effect will homeostatic natural selection have on this prediction? For $t' = 1$, figure 4 illustrates the effect of

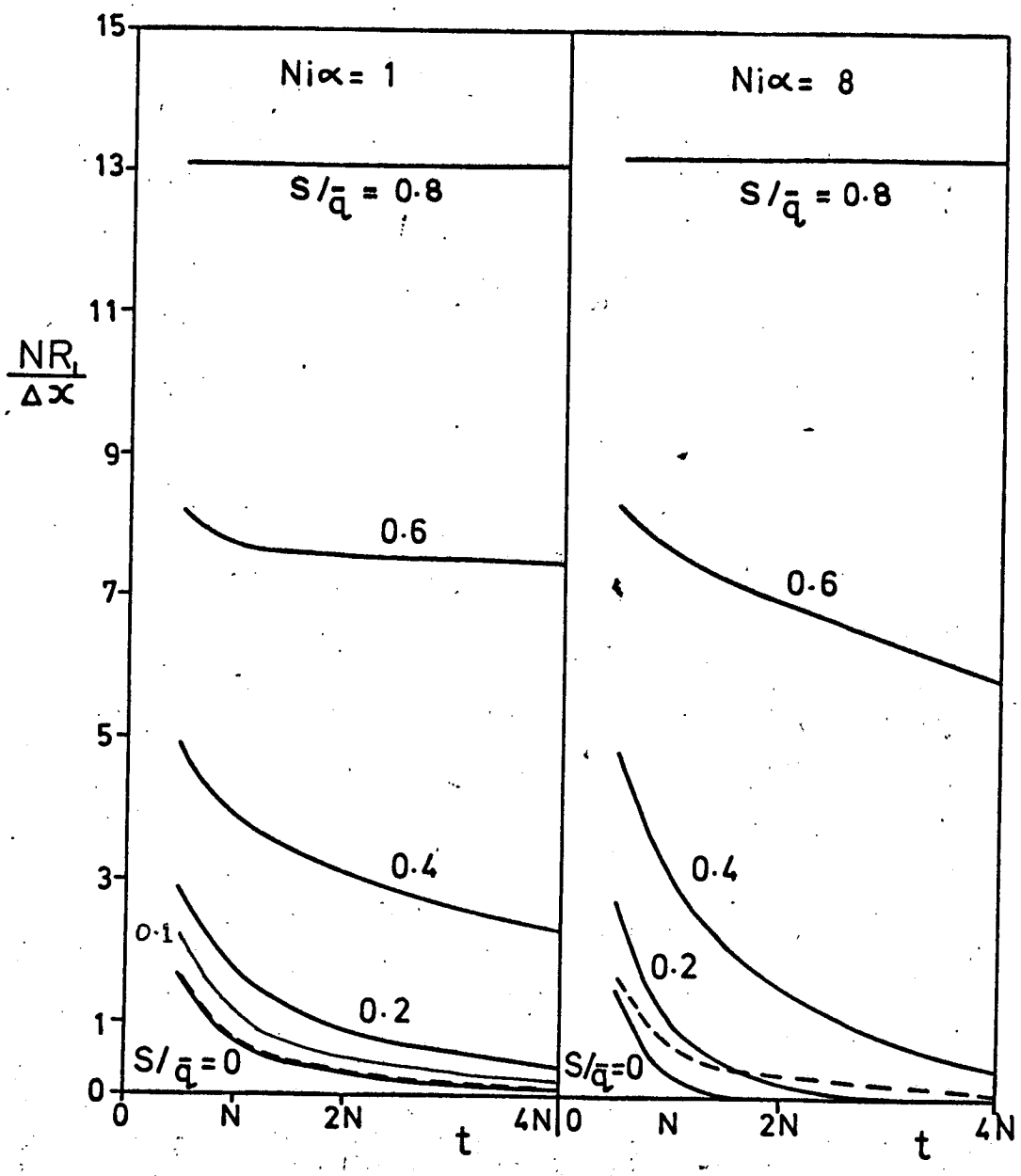


Figure 4. The effect of strength of homeostatic natural selection ($S/\bar{q} \doteq s_1$) on the relationship between length of forward selection, t, and the ratio $\frac{NR_1}{\Delta x}$ after one generation of reverse selection. Curves are drawn for relatively weak ($Ni\alpha=1$) and relatively strong ($Ni\alpha=8$) artificial selection from matrix results (solid lines). The two dotted lines represent the prediction of $\frac{NR_1}{\Delta x} = \frac{1-F}{2F}$ for no natural selection from equation (6).

homeostatic natural selection on the ratio $\frac{NR_1}{\Delta x}$ for relatively weak (Nia =1) and relatively strong (Nia =8) artificial selection.

It can be seen that the effect of natural selection is to increase $\frac{NR_1}{\Delta x}$. With Nia=1 the result is that even weak natural selection ($S/\bar{q}$ = 0.1) increases $\frac{NR_1}{\Delta x}$ above the prediction of $\frac{1-F}{2F}$ with no natural selection. Stronger natural selection ($S/\bar{q} \geq 0.2$) is needed to achieve the same result for Nia=8, because for stronger artificial selection with no natural selection $\frac{R}{\Delta x}$ for any t' is very much less than the simple prediction, as has already been seen in the previous section. A general conclusion can be drawn from this figure by recalling that homeostatic natural selection does not produce a pre-fixation plateau unless $S/\bar{q}$ is at least around 0.2 for Nia=1, and 0.3 for Nia=8. The curves in figure 4 infer that a value of $S/\bar{q} > 0.3$ results in $\frac{NR_1}{\Delta x}$ being greater than $\frac{1-F}{2F}$, even for relatively strong artificial selection of Nia=8. It can therefore by concluded that if a pre-fixation plateau occurs as a result of homeostatic natural selection, then for a single generation of reverse selection from that plateau, $\frac{NR_1}{\Delta x}$ is most likely to be greater than $\frac{1-F}{2F}$, for any strength of artificial selection.

The results in figure 4, although obtained specifically from the case of $q_o = \bar{q} = 0.5$, are representative of results expected for all $q_o = \bar{q} \leq 0.5$, except for relatively strong natural selection of say $S/\bar{q} > 0.7$ in which case the exact values of $\frac{NR_1}{\Delta x}$ tend to vary with $\bar{q}$. However, it has been found that the values of $\frac{NR_1}{\Delta x}$ for large $S/\bar{q}$ with any $\bar{q}$ essentially fall within the range of 10 to 15 so these values can be taken as the expected upper limit of $\frac{NR_1}{\Delta x}$.

In general, therefore, a single generation of reverse selection from a pre-fixation plateau is expected to result in a value of $\frac{NR_1}{\Delta x}$ somewhere between $\frac{1-F}{2F}$ and 15, with values greater than 10 indicating very

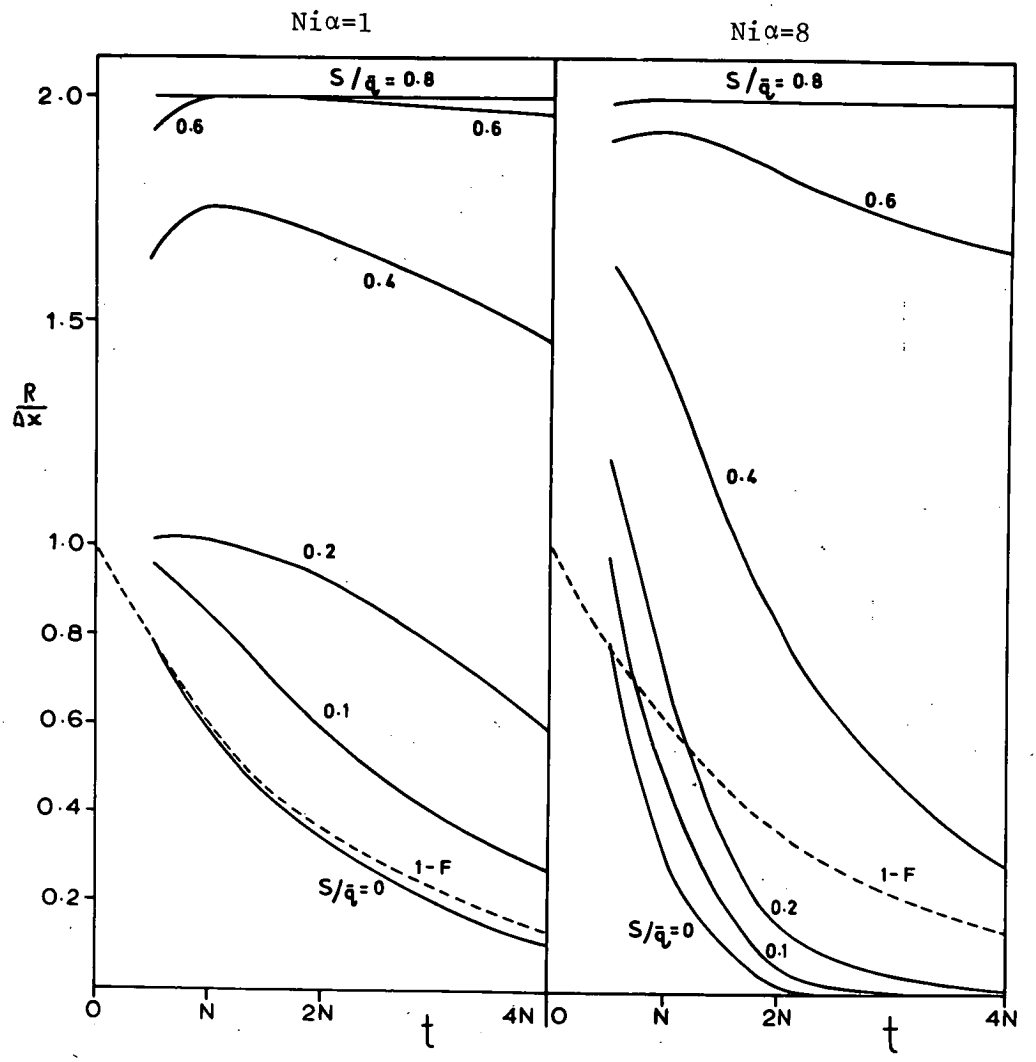


Figure 5. The effect of strength of homeostatic natural selection ($S/\bar{q} = s_1$) on the relationship between length of forward selection, t, and the ratio $\frac{R}{\Delta x}$ after/as many generations of reverse selection as previous forward selection (t' = t). Curves are drawn for relatively weak (Niα = 1) and relatively strong (Niα = 8) artificial selection from matrix results (solid lines) with $q_o = \bar{q} = 0.5$. The two dotted lines represent the prediction of $\frac{R}{\Delta x} = 1 - F$ for no natural selection from equation (6).

strong opposing natural selection as a reason for the plateau.

Equal periods of forward and reverse selection

Figure 5 is analogous to the previous figure in that it shows the effect of homeostatic natural selection on the ratio $\frac{R}{\Delta x}$ for two values of Nia.

As before, the effect of increasing strength of natural selection is to increase the value of $\frac{R}{\Delta x}$ for a given t=t'. This time it can be concluded in general that reverse selection from a pre-fixation plateau for a number of generations equal to the previous forward selection is expected to result in a value of $\frac{R}{\Delta x}$ greater than 1-F, for any strength of artificial selection.

How much greater than 1-F is $\frac{R}{\Delta x}$ likely to be? It can be seen from figure 5 that the value of $\frac{R}{\Delta x}$ increases to a maximum of two as the strength of natural selection increases. This particular limit of $\frac{R}{\Delta x}$ is peculiar to $q_o=\bar{q}=0.5$ and arises simply because in this case both homozygotes have the same natural fitness. If, having started with $q_o=\bar{q}=0.5$, a selection plateau is reached at say q=0.7, then reverse selection from this plateau will decrease q until a new plateau (this time to reverse selection) is established at a point as far below 0.5 as the initial plateau was above, in this case at q=0.3. Thus the equal fitnesses of homozygotes result in "symmetrical" equilibria between artificial and natural selection, from which it simply follows that R will be no more than twice $\Delta x$. Any fixation of allele $A_1$ during forward selection will tend to decrease the ability of subsequent reverse selection to return q to its symmetrical equilibrium value. Hence intermediate strengths of natural selection, which are not sufficiently strong to prevent some fixation, will result in values of $\frac{R}{\Delta x}$ less than two.

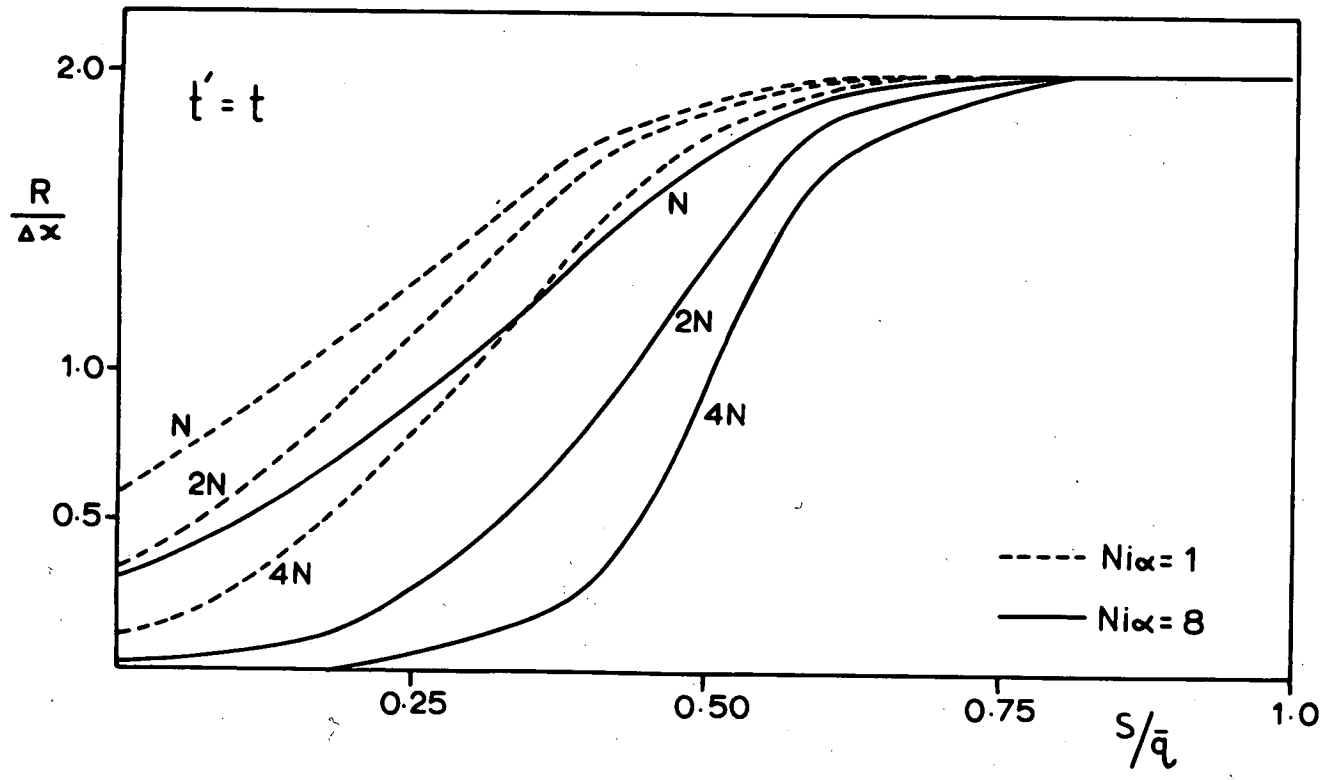


Figure 6. The effect of strength of homeostatic natural selection ($S/\bar{q} = s_1$) on the ratio $\frac{R}{\Delta x}$ after as many generations of reverse selection as previous forward selection (t'=t). Curves are drawn for relatively weak (Niα = 1, dotted lines) and relatively strong (Niα = 8, solid lines) artificial selection, with t'=t=N, 2N and 4N generations where N is effective population size.

The effect of natural selection on the results of reverse selection can also be viewed in a manner analogous to that which was used earlier to study its effect on forward selection. Thus figure 6 shows the effect of increasing strength of homeostatic natural selection (expressed in terms of $S/\bar{q}$ as before) on the ratio $\frac{R}{\Delta x}$. Although the curves actually shown are for $q_o=\bar{q}=0.5$, the nature of the scale on the x-axis enables figure 6 to illustrate the general trends for any $q_o=\bar{q}\leq 0.5$. Once again it can be seen that $\frac{R}{\Delta x}$ increases as the strength of natural selection increases. Recalling that selection plateaux only occur if $S/\bar{q}$ is greater than about 0.2 or 0.3, it can be seen that reverse selection from a prefixation plateau, for $t'=t$, will result in $\frac{R}{\Delta x}$ values at least equal to unity if previous forward selection has been carried out for anything less than N generations. Indeed, $\frac{R}{\Delta x}$ soon becomes greater than unity for all $t'=t$ as $S/\bar{q}$ increases.

An interesting aspect of figure 6 is its resemblance to figure 9 in section I which shows the relative proportion of additive genetic variance remaining at a selection plateau, as a function of $S/\bar{q}$. Comparison of these two figures indicates that there is a high correlation between the amount of additive genetic variance remaining at the plateau, and the response to subsequent reverse selection from the plateau.

One aspect of figure 6 which is not representative of all $q_o=\bar{q}\leq 0.5$ is the position of the curves for very strong natural selection, say beyond $S/\bar{q}=0.6$. It has been previously noted with $\bar{q}=0.5$ that the value of $\frac{R}{\Delta x}$ for very strong natural selection is largely an artifact of the relative fitness of the two homozygotes. The end result of this in very general terms has been found to be that $\frac{R}{\Delta x}$ for very strong natural selection may vary between 1 and 4 approximately depending on initial

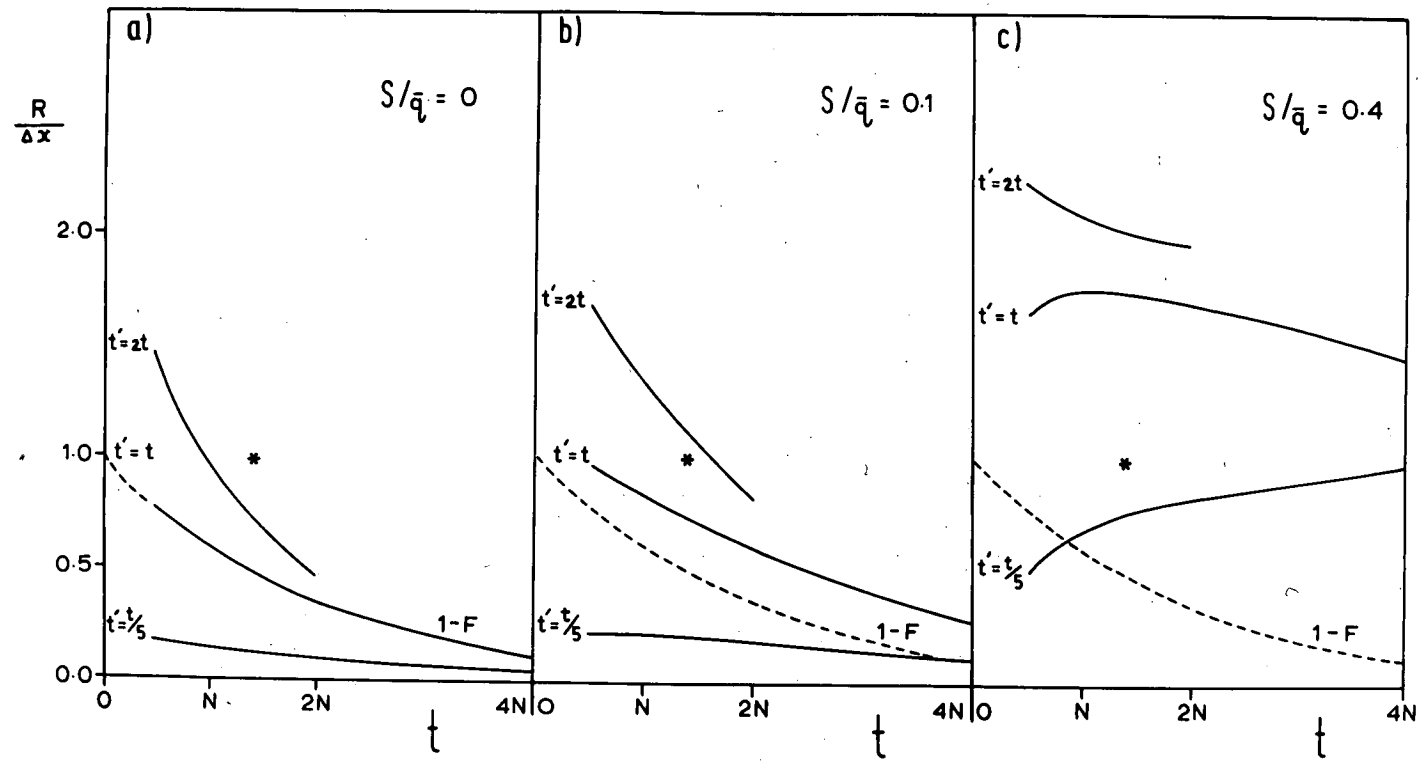


Figure 7. The effect of strength of homeostatic natural selection ($S/\bar{q} = s_1$) on the relationship between length of forward selection, t, and the ratio $\frac{R}{\Delta x}$ after various lengths of subsequent reverse selection, t', corresponding to $\frac{t}{5}$, t and 2t generations. Solid lines are matrix results for $Ni^{\alpha} = 1$ and $q_o = \bar{q} = 0.5$. Dotted lines are the prediction of $\frac{R}{\Delta x} = 1-F$ for no natural selection from equation (6).

and equilibrium frequency.

Any period of forward and reverse selection

Finally an example of the effect of homeostatic natural selection on reverse selection for any t and any t' is shown in figure 7. In the previous section it was concluded that the matrix results for $Ni\alpha=1$ in the absence of natural selection correspond very closely to the prediction $\frac{R}{\Delta x} = \frac{e^{-t/2N}(1-e^{-t'/2N})}{1-e^{-t/2N}}$. Thus the matrix results in figure 7a, for which S=0%, show the value of $\frac{R}{\Delta x}$ which would be predicted from the above expression for any period of forward selection from $t=\frac{N}{2}$ to t=4N, and for periods of reverse selection equivalent to $\frac{t}{5}$, t and 2t generations. The effect of natural selection is shown in figures 7b and 7c. The general way in which $\frac{R}{\Delta x}$ increases with increasing strength of natural selection for any t and any t' can be plainly seen.

Relaxation of selection

Only the most common situation, namely that of relaxation in a large population, will be considered here.

For a single generation of relaxation, it has already been seen how Robertson (1956) predicted that $\frac{R_1}{\Delta x}$ is expected to equal S, but that this prediction is only expected to be valid if the previous forward selection has not altered gene frequency substantially. Figure 8 illustrates the results of one generation of relaxation following any period of forward selection from $t=\frac{N}{2}$ to t=4N generations, in this case for $q_o=\bar{q}=0.5$ with weak ($Ni\alpha=1$) and strong ($Ni\alpha=8$) artificial selection. It can be seen that $\frac{R_1}{\Delta x}$ is indeed a good estimate of S for $Ni\alpha=1$, because such relatively weak artificial selection does not alter the gene frequency very much at any stage. Stronger artificial selection, however, results in values of

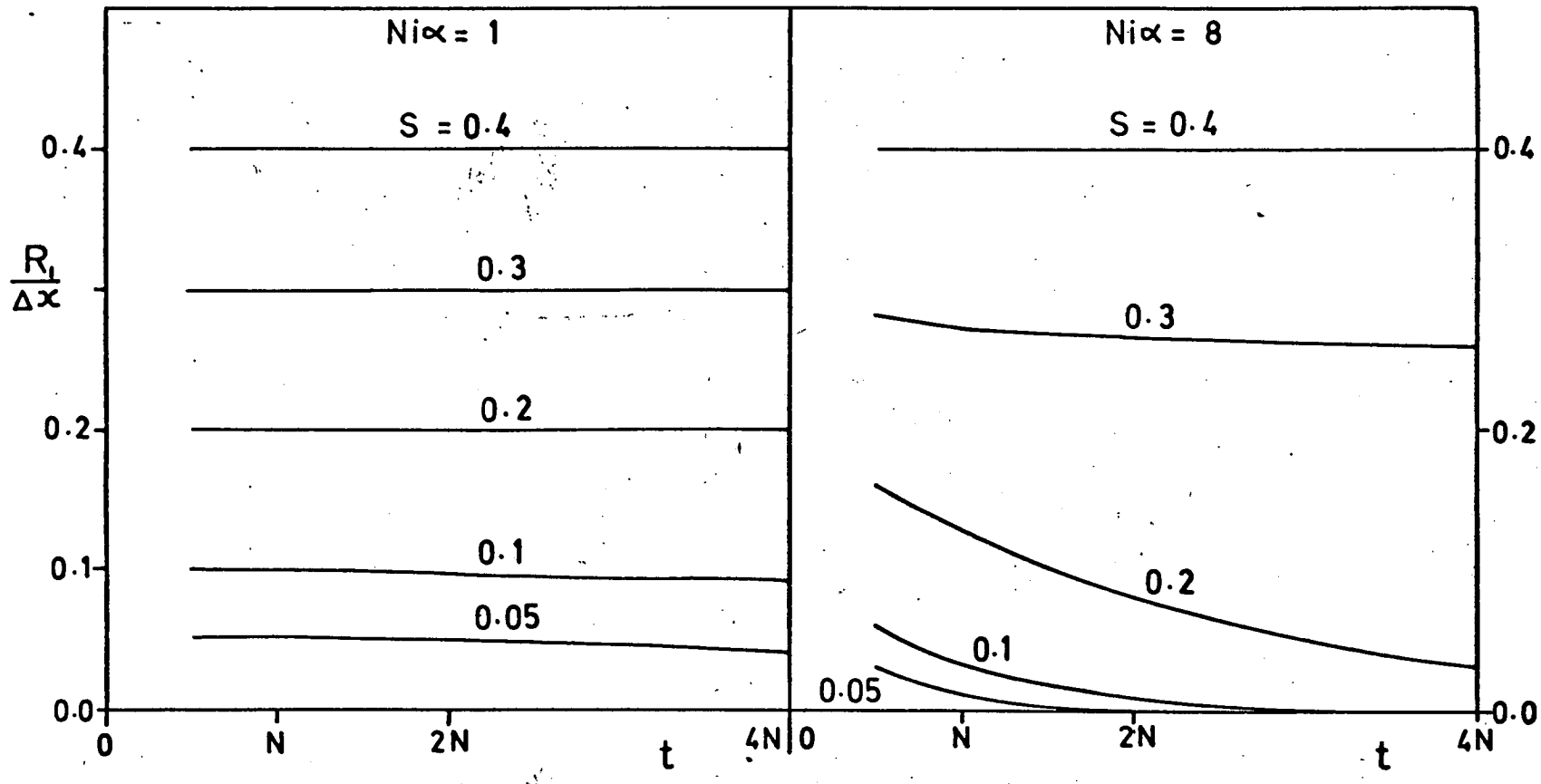


Figure 8. The effect of length of forward selection, t, on the ratio $\frac{R_1}{\Delta x}$ after a single generation of relaxation in a large population with various strengths of homeostatic natural selection (S). Curves are drawn for relatively weak ($Ni\alpha = 1$) and relatively strong ($Ni\alpha = 8$) artificial selection with $q_o = \bar{q} = 0.5$. $\Delta x$ was calculated from matrix results while $R_1$ was calculated as $(s_1 + s_2)\, q(1 - q)\, (\bar{q} - q)$.

$\frac{R_1}{\Delta x}$ much less than S if relaxation is carried out after even just a few generations of forward selection, because such strong artificial selection does alter gene frequency substantially. The results of one generation of relaxation for other equilibrium gene frequencies are very similar to those shown in figure 8, except of course that the maximum possible value of S is $\bar{q}$, which means that one generation of relaxation at a locus with for example $\bar{q}=0.1$ is never expected to result in an $\frac{R_1}{\Delta x}$ value greater than 0.1.

The results in figure 8 thus confirm the earlier conclusion that $\frac{R_1}{\Delta x}$ is expected to equal S if the single generation of relaxation is carried out relatively early in the selection programme.

For a longer period of relaxation, the simple expectation under the homeostatic model of natural selection is that the metric mean will continue to decrease until the large population equilibrium gene frequency $\bar{q}$ is reached. If $q_o=\bar{q}$, as has been assumed throughout this study, the above statement amounts to a prediction that the maximum value of $\frac{R}{\Delta x}$ for relaxation in a large population will be 1, for any $q_o=\bar{q}$. Figure 9 shows the value of $\frac{R}{\Delta x}$ expected as a result of relaxation after various periods of forward selection from $t=\frac{N}{2}$ to $t=4N$, in this case with $t'=t$ and $q_o=\bar{q}=0.5$. The value of $\frac{R}{\Delta x}$ is seen to increase as the strength of natural selection increases, and, except at very low values of $S/\bar{q}$, also increases with t. The reason for this latter trend is that in a large population, where chance fixation is unlikely to occur, the value of $\frac{R}{\Delta x}$ for any t is largely a function of t', the number of generations of relaxation carried out. Obviously as t' continues to increase, a value of $\frac{R}{\Delta x}=1$ will eventually be reached. Figure 9 is of the same form as figure 6, in that it represents the general relationship between $\frac{R}{\Delta x}$ and the strength of natural selection for all $q_o=\bar{q}\leq 0.5$. It can therefore

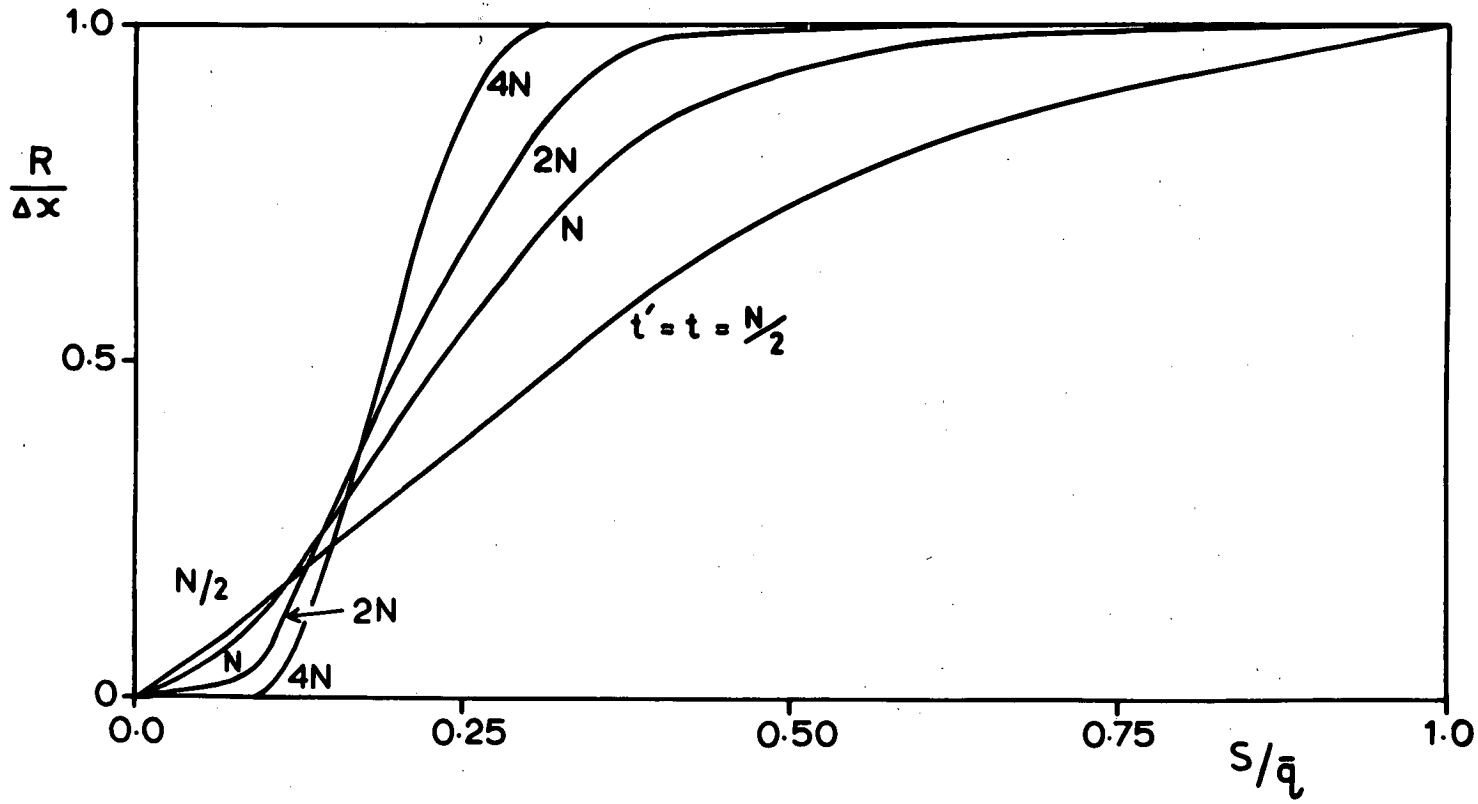


Figure 9. The effect of strength of homeostatic natural selection ($S/\bar{q} = s_1$) on the ratio $\frac{R}{\Delta x}$ after as many generations of relaxation in a large population as previous forward selection (t'=t) corresponding to $\frac{N}{2}$, N, 2N and 4N generations, where N is effective population size during forward selection. Curves are drawn from matrix results with $Ni\alpha = 8$ and $q_o = \bar{q} = 0.5$.

be concluded that the result of relaxation of selection with the homeostatic model in a large population will be an $\frac{R}{\Delta x}$ value between zero and unity, with larger strengths of natural selection and longer periods of relaxation tending to give values of $\frac{R}{\Delta x}$ approaching unity.

Natural selection prior to artificial selection

It was stated at the beginning of this section that the results obtained from the above matrix operations are only valid if the genotypes are in Hardy-Weinberg equilibrium at the time of observation, or in other words, all natural selection occurs after artificial selection. Is it possible to extend these results to cover the action of natural selection at any stage of the life cycle? The matrix operation in which $E[q_t]$ is calculated from the gene frequency distribution is no longer useful because alterations in q do not directly reflect alterations in the metric mean if the genotypes are not in Hardy-Weinberg equilibrium. In the initial discussion of this situation, it was noted that the metric mean can be expressed as

$$x = \frac{a}{2}[f_{11}-f_{22}]$$

if $f_{11}+2f_{12}+f_{22}=1$, where $f_{ij}$ is the frequency of genotype $A_iA_j$ at the time when the metric phenotypes are actually observed. Thus if homeostatic natural selection occurs prior to artificial selection,

$$f_{11} = q^2(1-s_1)/\bar{w}$$

$$2f_{12} = 2q(1-q)/\bar{w}$$

and

$$f_{22} = (1-q)^2(1-s_2)/\bar{w}$$

where

$$\bar{w} = 1-S-(s_1+s_2)(q-\bar{q})^2 \quad .$$

The course of artificial selection in the presence of natural selection was then followed by post-multiplication of the matrix $\underline{\underline{U}}$ with a column vector $\underline{v}_o$ having elements

$$v_{o(j)} = f_{11(j)} - f_{22(j)}$$

where

$$f_{11(j)} = (j/2N)^2(1-s_1)/\bar{w}_{(j)}$$

$$f_{22(j)} = (1-j/2N)^2(1-s_2)/\bar{w}_{(j)}$$

and

$$\bar{w}_{(j)} = 1-S(s_1+s_2)(j/2N-\bar{q})^2 \quad .$$

Thus the results of forward selection were obtained as

$$\underline{v}_1 = \underline{\underline{U}}\underline{v}_o \quad ,$$

$$\underline{v}_2 = \underline{\underline{U}}\underline{v}_1$$

$$= \underline{\underline{U}}^2\underline{v}_o$$

and in general

$$\underline{v}_t = \underline{\underline{U}}\underline{v}_{t-1}$$

$$= \underline{\underline{U}}^t\underline{v}_o \quad .$$

How can the course of subsequent reverse selection be followed? In principle what is wanted is a final result which can be written as

$$\underline{v}_{t+t'} = \underline{\underline{U}}^t\underline{\underline{D}}^{t'}\underline{v}_o \qquad (7)$$

but it would be much more economical if continual multiplications of matrix by matrix could be avoided. Examination of expression (7) indicates that one way to achieve such economy is to do the reverse selection before the forward selection. Indeed in their initial use of a transition probability matrix in the study of artificial selection, Allan and Robertson (1964) used this very technique, but did not report it explicitly.

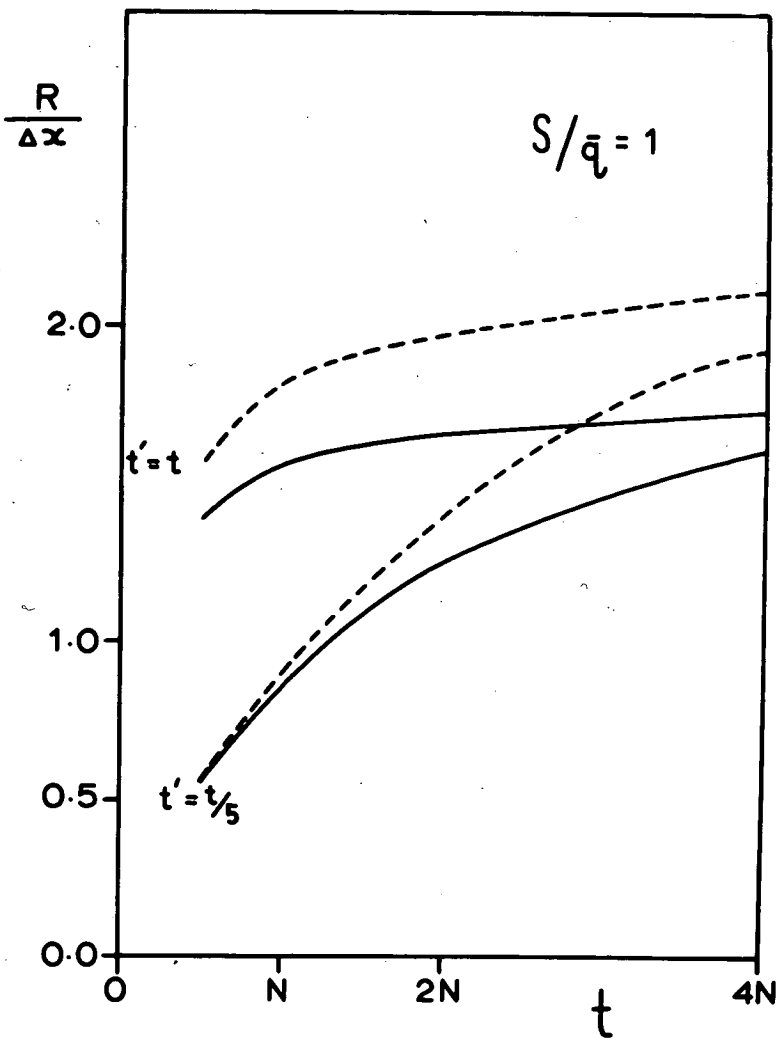


Figure 10. The relationship between length of forward selection, t, and the ratio $\frac{R}{\Delta x}$ at a locus where the favoured allele is sterile (solid lines) or lethal (dotted lines), after two periods of reverse selection, t', corresponding to $\frac{t}{5}$ and t generations. Curves are drawn from matrix results with $q_o = \bar{q} = 0.1$ and $N_i\alpha=8$.

Thus matrix operations have been carried out in the manner of expressions (8) and (9) below:

$$\underset{\sim}{v}_{1'} = \underset{\sim}{\underset{\sim}{D}}\underset{\sim}{v}_{o}$$

$$\underset{\sim}{v}_{2'} = \underset{\sim}{\underset{\sim}{D}}\underset{\sim}{v}_{1'}$$

$$= \underset{\sim}{\underset{\sim}{D}}^{2'}\underset{\sim}{v}_{o}$$

and

$$\underset{\sim}{v}_{t'} = \underset{\sim}{\underset{\sim}{D}}\underset{\sim}{v}_{t'-1} \qquad (8)$$

$$= \underset{\sim}{\underset{\sim}{D}}^{t'}\underset{\sim}{v}_{o} \quad .$$

Then

$$\underset{\sim}{v}_{1+t'} = \underset{\sim}{\underset{\sim}{U}}\underset{\sim}{v}_{t'}$$

$$\underset{\sim}{v}_{2+t'} = \underset{\sim}{\underset{\sim}{U}}\underset{\sim}{v}_{1+t'}$$

$$= \underset{\sim}{\underset{\sim}{U}}^{2}\underset{\sim}{v}_{t'}$$

$$= \underset{\sim}{\underset{\sim}{U}}^{2}\underset{\sim}{\underset{\sim}{D}}^{t'}\underset{\sim}{v}_{o}$$

and

$$\underset{\sim}{v}_{t+t'} = \underset{\sim}{\underset{\sim}{U}}\underset{\sim}{v}_{t-1+t'} \qquad (9)$$

$$= \underset{\sim}{\underset{\sim}{U}}^{t}\underset{\sim}{v}_{t'}$$

$$= \underset{\sim}{\underset{\sim}{U}}^{t}\underset{\sim}{\underset{\sim}{D}}^{t'}\underset{\sim}{v}_{o} \quad .$$

An example of the results so obtained is given in figure 10, which illustrates that any natural selection prior to artificial selection (broken lines) tends to increase the observed value of $\frac{R}{\Delta \bar{x}}$ above that which would have been expected if artificial selection had been carried out prior to natural selection (solid lines). It has been found that the difference between the two situations decreases as the strength of natural selection decreases, so the curves in figure 10 represent an extreme example. The value of $S/\bar{q}$ was chosen as unity in this case so as to illustrate speci-

fically the results of reverse selection at a locus where the allele favoured by forward artificial selection is lethal (broken lines) or sterile (solid lines). The value of $\frac{R}{\Delta \bar{x}}$ is of the same order in both cases, and for t'=t is relatively constant for any value of t. The actual values of $\frac{R}{\Delta \bar{x}}$ in figure 10, however, are very much a reflection of the initial and equilibrium frequency, in this case $q_o=\bar{q}=0.1$, but the general trends and the relationship between the results for lethal and sterile alleles represent results which can be generalised.

## Discussion

In very general terms, the results of reverse selection and relaxation of selection under the homeostatic model of natural selection have been found to be in agreement with current expectations of results of reverse selection and relaxation in the presence of natural selection. Thus a decrease of the metric mean occurs following relaxation, and reverse selection results in a greater change in the mean than that produced by relaxation.

To a certain extent it has been possible to quantify these expectations but, as in section I, only in terms of single loci. The actual result of reverse selection or relaxation for any metric character determined by a number of different loci will represent a completely unpredictable combination of the various results discussed above. The predictions obtained in this study can therefore only be used in a very general sense, to provide a feeling of the order of magnitude of the results which might be expected. They also should be of some use in the interpretation of results already obtained.

One aspect of the importance of equilibrium gene frequency which has not been mentioned above is the difficulty associated with low values

of $N_i\alpha$ and $q_o=\bar{q}<0.5$. The directional effect of heterozygote superiority in small populations for $\bar{q}\neq 0.5$ has already been mentioned, and it has been seen that this effect may be stronger than artificial selection with low $N_i\alpha$, in which case the metric mean decreases under the action of forward artificial selection for $\bar{q}<0.5$. Measures of $\frac{R}{\Delta x}$ for subsequent reverse selection in such situations cease to have much relevance. What can be concluded quite generally is that the homeostatic model may give rise to quite a strong natural selection force in favour of actively decreasing the metric mean for genes with initial and equilibrium frequencies less than one half. It remains to be seen whether other models of natural selection also have the same implications.

Finally, it must be noted that certain different models involving no natural selection at all can give rise to results of the type which have been shown above to arise from the homeostatic model of natural selection. For example, forward and reverse selection under a model of non-additive gene action could conceivably produce trends of the same type as those discussed above. A study of the formation of pre-fixation plateaux, and the effects of subsequent reverse selection and relaxation for non-additive gene action would be helpful in this regard.

## 4. SUMMARY

1. The implications of the homeostatic model of natural selection for reverse selection and relaxation have been considered. It has been assumed in all cases that $q_o=\bar{q}$ at the commencement of forward artificial selection. The results of reverse selection or relaxation have been described in terms of the ratio of reverse selection or relaxation response (R) to previous forward selection response ($\Delta x$), where t generations of forward selection are followed by t' generations of reverse selection

or relaxation. If t'=1 then the response to reverse selection or relaxation is denoted by $R_1$. Consideration has been given to forward and reverse selection in a finite population of size N, and to relaxation in a very large population.

2. For alleles initially common in the base population ($q_o=\bar{q}>0.5$) the value of $\frac{R}{\Delta x}$ for reverse selection is expected to be much less than that predicted in the absence of natural selection, for any t and any t'. Conversely, natural selection is expected to enhance the effect of reverse selection at loci where $q_o=\bar{q}<0.5$. and hence at loci where selection plateaux due to opposing natural selection are likely to form.

3. There is a high correlation between the proportion of original additive genetic variance remaining at a selection plateau, and the magnitude of response to reverse selection from that plateau.

4. A single generation of reverse selection from a pre-fixation plateau is expected to result in a value of $\frac{NR_1}{\Delta x}$ greater than $\frac{1-F}{2F}$ but less than 15, where F is the inbreeding coefficient for a neutral locus at generation t. Values of $\frac{NR_1}{\Delta x}$ around 10 or greater indicate very strong opposing natural selection as a reason for the plateau.

5. For reverse selection from a pre-fixation plateau equal in length to the previous forward selection, $\frac{R}{\Delta x}$ is expected to have a value greater than 1-F but less than 4.

6. A single generation of relaxation in a large population is expected to result in an $\frac{R_1}{\Delta x}$ value of S providing that the single generation of relaxation is carried out relatively early in the selection programme.

7. Relaxation of selection for any t' in a large population results in

$\frac{R}{\Delta x}$ values between zero and unity, with $\frac{R}{\Delta x}$ tending toward the latter value with increases in t' and increases in the strength of natural selection.

8. Any natural selection which occurs prior to the time of artificial selection tends to increase the value of $\frac{R}{\Delta x}$ actually observed.

9. Reverse selection from plateaux due to alleles which are sterile or lethal when homozygous generally results in $\frac{R}{\Delta x}$ values greater than unity.

## LIMITS TO ARTIFICIAL SELECTION IN THE PRESENCE OF NATURAL SELECTION

### Discussion

The implications of the homeostatic and optimum models of stabilizing natural selection for forward artificial selection have been investigated in turn. It was possible to obtain a reasonable insight into the homeostatic model but the optimum model proved to be much more intractable. The reason for this lies in the essential difference between the two models: the one in which each locus can be considered independently and in which natural selection does not necessarily act at all loci, and the other in which epistasis is of critical importance. Thus under the optimum model, all loci which contribute to the metric character are subject to natural selection, the effect of which at any one locus varies from generation to generation, being determined by gene frequencies and gene effects at all other loci.

Are we any closer to being able to interpret the results of artificial selection experiments where natural selection has been implicated, in terms of one rather than the other model? All present indications are that we are not. For example, it has been concluded in section I that the results of Lerner and Dempster's (1951) selection experiment are compatible with the homeostatic model, as indeed they should be. But James (1962) was able to conclude that the same data could be explained with an hypothesis of directional selection opposed by nor-optimal natural selection. And the consideration given to the nor-optimum model in section II supports this conclusion. In fact, there seems to be no aspect of the observable response to artificial selection which would enable one to distinguish between the two models of natural selection.

An example of the way in which one can not differentiate between the two models is the recent analysis of an artificial selection experiment for body weight in mice reported by Eisen, Hanrahan and Legates (1973). The authors concluded that their data favoured the optimum model rather than the homeostatic model, because artificial selection had been seen to move the population mean for body weight and percent body fat away from an optimum, in lines of relatively large effective population size. However, the relatively large responses to selection observed in these large populations would be expected to have resulted in a greater degree of fixation of favourable alleles specifically at loci contributing to the genetic variance in body weight than in the smaller lines where response was not as great. And, under the homeostatic model, a greater degree of fixation of favourable alleles is associated with a larger decrease in fitness. Thus the observed fitness decline at the large effective population size is equally compatible with the homeostatic or the optimum model of natural selection. It appears therefore, that the detailed analysis of such artificial selection experiments is unlikely to provide evidence in favour of one or other model of natural selection, at least in the light of present knowledge.

The nor-optimal model remains to be explored in more detail in the context of both forward and reverse artificial selection, and such a study may then point out differences in the ramifications of the two models.

For the present at least, it remains apparently impossible to differentiate between the two models by analysis of artificial selection data. What are the type of experiments which would enable a useful comparison to be made? The difficulty in answering this question is

probably an indication that the real situation in nature lies somewhere in between the extreme situations described by the two models. What would be useful is a new conceptual approach to the whole question of the inter-relationship between a metric character and fitness; an approach in which the genetic consequences of natural selection on the whole 'global' phenotype can be described; an approach that does not involve confusion between cause and effect.

What then has been the use of considering the two models in this study? The main reason is that the two models in their present state represent essentially two extreme (and, incidently, the only) descriptions of the way in which natural selection acts with respect to metric characters. And it is these two models which are always discussed during the analysis of any artificial selection programme in which natural selection seems to have been of importance. To the extent that the implications of each model of natural selection are similar in the context of artificial selection, then knowledge obtained from either one can be utilized in discussing the effects of natural selection in artificial selection programmes.

Thus for any particular locus under the homeostatic model, natural selection is expected to be the cause of a pre-fixation plateau in a population of finite size only for genes with initial and equilibrium frequencies equal to or less than one half, and then only if the value of $S/\bar{q}$ is around 0.2 or greater. The total advance in the metric mean at a pre-fixation plateau is never greater than $2N(1-2S)^2$ times the change in metric mean in the first generation of artificial selection, and a large proportion if not all of the original genetic variance remains at such a plateau. An indication of the amount of genetic variance remaining is given by the magnitude of response to

reverse selection from the plateau. And finally, a significant decrease in population fitness as a result of artificial selection does not necessarily imply that the metric character concerned is an important adaptive character with respect to natural selection.

With the optimum model, it has not been possible to obtain quantitative predictions with the same generality as those above, but it has been seen that the implications of the model are essentially the same. Thus a pre-fixation plateau will result if natural selection is sufficiently strong, the total advance in the metric mean will probably be something less than 2N times the change in metric mean in the first generation of artificial selection, and the natural fitness of the population will have declined at the plateau from what it was originally.

The results of this study may also be of use in the analysis of artificial selection lines in which fitness has declined and/or a selection plateau has resulted. If, for example, the investigation of the nature of a selection plateau involves reverse selection, then certain predictions are now available of the results expected from reverse selection with and without natural selection. In its most general form the value of the ratio of the change in metric mean resulting from t' generations of reverse selection (R) to the change in metric mean due to t generations of previous forward selection ($\Delta x$) is expected to be $\frac{e^{-t/2N}(1-e^{-t'/2N})}{1-e^{-t/2N}}$ in the absence of natural selection. Values of the ratio larger than this prediction are expected if natural selection has been opposing the previous forward selection.

Further work is needed on other possible causes of selection plateaux such as non-additive gene action (especially overdominance) for the metric character. It would be particularly helpful to be able

to distinguish the effect of natural selection from the effect of non-additive gene action on the response to reverse selection.

Finally, it is evident that many relevant aspects of response to forward and reverse selection and relaxation have not been treated in detail here. However, it should be quite possible to use the matrix operations described in this study, especially for reverse selection, to simulate a particular practical situation and consequently study it in more detail.

**PART B**

# THE EFFECT OF SELECTION ON THE STANDARDIZED VARIANCE OF GENE FREQUENCY

## Introduction

The relative importance of selection and random drift in determining the observed pattern of evolution is still a major topic of debate in population genetics. For loci at which gene frequency can be determined, one of the lines of study currently being followed is based on an idea apparently first suggested by Cavalli-Sforza (1966), in which the standardized variance of gene frequency $f = \frac{\sigma_q^2}{q(1-q)}$ is estimated for various loci over several populations. Thus f is estimated from the mean gene frequency at a particular locus over several populations (q), and the variance of the gene frequency distribution ($\sigma_q^2$) over the same populations, at a particular point in time. Since all loci in a given group of populations have been subjected to exactly the same breeding structure, f values obtained from any number of such loci will be homogeneous unless selection has been acting at some of the loci. Lewontin and Krakauer (1973) have recently developed various statistical tests for the homogeneity of f values, and the use of these tests has, for example, led Nevo (1973) to conclude that selection is acting at various loci in the pocket gopher Thymomys talpoides. Lewontin and Krakauer (1973) reached a similar conclusion from their analysis of some of Cavalli-Sforza's (1966) data on human populations.

Each of these papers has also drawn some conclusions as to the type of selection which is acting. Thus it has been argued that f values lower than those expected due to drift alone could be due to some form of stabilizing selection (e.g. heterozygote superiority),

and relatively large f values may be indicative of different strengths of directional selection at the same locus in different populations. But these generalisations are the only knowledge currently available: what is lacking is a proper understanding of the way in which various models of selection affect the standardized variance of gene frequency.

It is not only natural populations which are being subjected to this type of study. The advent of suitable electrophoretic techniques has recently led to studies of the effect of selection on gene frequency and the variance of gene frequency in laboratory populations of, for example, Drosophila (Dolan, 1974) and mice (Garnett, 1973). The latter study was concerned solely with the effect of artificial selection for a metric character on gene frequency and variance of gene frequency at various 'electrophoretic' and coat colour loci. A better knowledge of the way in which selection affects the standardized variance of gene frequency would assist in the interpretation of such artificial selection experiments.

In attempting to trace the history of human evolution, Cavalli-Sforza (1969) developed an algebraic relationship between f and the time (t) since separation of two populations, for a model of constant but different directional selective values in different populations at the same locus and compared it to the relationship $f = 1-e^{-t/2N}$ expected in the absence of selection. These two relationships were then used to obtain lower and upper limits respectively of t, the time since divergence. But other models of selection could give completely different relationships between f and t and hence completely different estimates of time since divergence.

Once again, therefore, a greater understanding of the effect of selection on f would be useful.

For human populations, Cavalli-Sforza and Zei (1967) and Bodmer and Cavalli-Sforza (1968) have obtained the expected value of f for more complex but more realistic models using the Monte-Carlo and migration matrix methods respectively, on a computer. Expected values of f so obtained for situations where sufficient migration and general demographic data are available have been compared with observed f values. But it is difficult to use these methods to determine the effect of selection on f in general terms, as so many parameters of migration and/or demography are required to obtain any specific answer. The cost in computer time is also quite substantial.

It is possible, however, to obtain a general impression of the effect of selection on f by firstly considering an algebraic model of additive directional selection. A further understanding can then be acquired by the use of a transition probability matrix with which it is possible to calculate the expected value of $\sigma_q^2$ and q and hence f at any time under various models of selection.

The aim of this study is to obtain a greater insight into the behaviour of the standardized variance of gene frequency under simple models of selection.

## The additive model

Consider a single locus with two alleles $A_1$ and $A_2$, and assume the relative fitnesses of the three genotypes $A_2A_2$, $A_1A_2$ and $A_1A_1$ are $1 - \frac{s}{2}$, 1 and $1 + \frac{s}{2}$ respectively. If the genotypes are in Hardy-Weinberg equilibrium at the time of conception, then the change in frequency of allele $A_1$ as a result of one generation of selection in a large population is

$$\Delta q \doteq \frac{s}{2} q(1-q) \qquad (1)$$

where q is the frequency of allele $A_1$ at the time of conception.

For a locus at which such selection is acting, the value of f actually observed at any time is an expression of the end result of a combination of selection and random genetic drift. Is it possible to disentangle the effects of these two components, in order to see more clearly how the observed f is achieved? The change in f due to one generation of random drift alone is well known as $\frac{1}{2N}$, where N is the effective population size. But what is the equivalent expression for selection alone? And is the observed f simply the sum of these two components?

Some understanding of the effect of selection alone on f can be obtained by considering selection acting in a similar manner at a single locus in a number of populations. Each of these populations must be sufficiently large to justify the assumption that random sampling is not going to alter the result of selection in any one population from that predicted by equation (1).

Assume that the gene frequency at a particular time (t=0) in the $i^{th}$ population is $q_{o(i)}$. If the $q_{o(i)}$ are all the same, then $\sigma_{q_o}^2 = 0$ and $f_o = 0$. Alternatively, if at least some of the $q_{o(i)}$ are different, then $\sigma_{q_o}^2 > 0$ and $f_o = \frac{\sigma_{q_o}^2}{q_o(1-q_o)}$, where $q_o$ is the mean gene frequency at t=0. How will the value of f be altered after t generations of selection in each of these populations?

Following Haldane (1924), equation (1) can be expressed as a differential equation

$$\frac{dq}{dt} \doteq \frac{s}{2} q(1-q) \qquad (2)$$

provided that dq is small. The solution of this equation is

$$\frac{q_t}{1-q_t} \doteq (1+\frac{s}{2})^t \frac{q_o}{1-q_o} \quad . \qquad (3)$$

In order to obtain $f_t$, we firstly need $\sigma_{q_t}^2$, which can be obtained by noting that for any q,

$$\text{Var}\left[\frac{q}{1-q}\right] \doteq \frac{\text{Var}[q]}{(1-q)^4} \quad .$$

Thus

$$\frac{\sigma_{q_t}^2}{(1-q_t)^4} \doteq (1+\frac{s}{2})^{2t} \frac{\sigma_{q_o}^2}{(1-q_o)^4} \quad . \qquad (4)$$

The term in s can be removed by dividing equation (4) by the square of equation (3), to give

$$\frac{\sigma_{q_t}^2}{q_t^2(1-q_t)^2} \doteq \frac{\sigma_{q_o}^2}{q_o^2(1-q_o)^2}$$

$$\text{or} \quad \frac{f_t}{q_t(1-q_t)} \doteq \frac{f_o}{q_o(1-q_o)} \quad . \qquad (5)$$

Recalling that $f_o$ and $q_o$ are particular and constant values describing the state of the populations at t=0, equation (5) can be written as

$$f_t \doteq k\, q_t\, (1-q_t) \qquad (6)$$

where k is constant for any particular set of initial conditions. If all populations have the same initial gene frequency, then $f_o$ and hence k are both zero, and $f_t$ is zero as expected : in the absence of drift there can be no variance in gene frequency at any stage if all populations start with the same gene frequency. On the other hand, if there is some variation in initial gene frequency, then $f_t$ is

directly proportional to $q_t(1-q_t)$, in which case it is expected to increase until $q_t=0.5$. Once the mean gene frequency of all the populations passes beyond $q_t=0.5$, then $f_t$ decreases.

Another way to look at this is to consider the change in f with change in q which can be written, from (6), as

$$\frac{df_t}{dq_t} \doteq k(1-2q_t) \quad . \tag{7}$$

Thus the change in f is positive if $q_t$ is less than 0.5, and negative for all values of $q_t$ above one half.

It remains now to obtain a more useful expression for change in f. For a single generation, equation (7) can be written as

$$\Delta f \doteq \frac{f(1-2q)}{q(1-q)} \Delta q \quad . \tag{8}$$

And for drift alone in the absence of selection, change in f can be written as

$$\Delta f \doteq \frac{1}{2N}(1-f) \tag{9}$$

where the last term ensures that $\Delta f$ is zero when f = 1.

Is it now possible to describe the change in f due to selection in a finite population by simply combining the two expressions for $\Delta f$? The simplest way to do this is to add the two terms together so that

$$\Delta f \doteq \frac{1-f}{2N} + \frac{f(1-2q)}{q(1-q)} \Delta q$$

When f has reached its maximum value of unity, complete fixation has occurred so that changes in gene frequency are no longer possible. In general, therefore,

$$\Delta q \doteq \frac{s}{2}q(1-q)(1-f)$$

where the last term is simply a reflection of heterozygosity declining by a proportion $\frac{1}{2N}$ every generation in a finite population.

The way in which f alters with changes in mean gene frequency due to selection is then given by

$$\frac{df}{dq} \doteq \frac{\frac{1}{Ns} + f(1-2q)}{q(1-q)} \qquad (10)$$

which can be solved to give

$$f \doteq \frac{1}{Ns}\left[2q-1 + 2q(1-q)\log\frac{q}{1-q}\right] + Kq(1-q) \qquad (11)$$

where K is a constant whose value for a particular initial gene frequency $q_o$ and value of Ns can be determined by setting f=0 in equation (11). In other words, equation (11) gives the value of f expected at any particular time when the mean gene frequency is q, given that all lines or populations were derived from a single population in which the initial gene frequency was $q_o$ at the time of separation. Thus $E[q_o]$ in all lines is $q_o$, and the expected value of f at the time of separation is zero.

The usefulness of expression (11) as a prediction will be checked below by comparing its prediction to the exact results which have been obtained by the use of a transition probability matrix.

The matrix operations

The derivation and subsequent use of a suitable matrix have been described in full, for example, by Hill and Robertson (1968). Only a brief description, therefore, of the matrix operations will be given here.

Consider a population of N diploid individuals mating at random (including selfing). At a particular single locus with two alleles $A_1$ and $A_2$, the genotypes $A_2A_2$, $A_1A_2$ and $A_1A_1$ are assumed to have Hardy-

Weinberg frequencies of $(1-q)^2$, $2q(1-q)$ and $q^2$ respectively at conception, where q is the frequency of allele $A_1$ at conception. The relative fitnesses of these three genotypes are assumed to be $S_{22}$, 1 and $S_{11}$ respectively.

For a given gene frequency i/2N, the proportion $g_i$ of each genotype in the population of parents at the time of their mating is

$$g_{i22} = \frac{1}{\bar{w}} (1-q)^2 S_{22}$$

$$g_{i12} = \frac{1}{\bar{w}} 2q(1-q)$$

$$g_{i11} = \frac{1}{\bar{w}} q^2 S_{11}$$

where q=i/2N and $\bar{w}$ is the proportion of zygotes which remain to be included as parents, and is given by

$$\bar{w} = (1-q)^2 S_{22} + 2q(1-q) + q^2 S_{11} \quad .$$

The probability of obtaining exactly x $A_2A_2$, y $A_1A_2$ and z $A_1A_1$ genotypes (x+y+z=N) in a population of N survivors, given that there were i $A_1$ alleles in the population of zygotes in the same generation can be expressed as

$$f_i(x,y,z) = \binom{N}{x\ y\ z} g_{i22}^{x} g_{i12}^{y} g_{i11}^{z} \quad ,$$

and can easily be evaluated on a computer for all i=0,1,...,2N. It then follows that the probability $p_{ij}$ of obtaining j $A_1$ alleles in a population of N zygotes at generation t+1, given that there were i $A_1$ alleles in the N zygotes at generation t is

$$p_{ij} = \sum_{\substack{2z+y \\ =j}} f_i(x,y,z) \qquad i,j = 0,1,\ldots,2N,$$

which is an element of the transition probability matrix $\underset{\sim}{P}$. The matrix

is square of dimension 2N+1, and within each row $\sum_{j=0}^{2N} p_{ij} = 1$.

The expected value of q and $\sigma_q^2$ can then be obtained by post multiplication of $\underset{\sim}{P}$ by column vectors representing the first and second moments about zero of the distribution of gene frequency. Thus the selection process is commenced by setting up a column vector $\underset{\sim}{u}_o$ with elements $u_i = i/2N$ and a second vector $\underset{\sim}{v}$ with elements $v_i = i/2N \times i/2N$. Then the matrix operations

$$\underset{\sim}{u}_1 = \underset{\sim}{P}\ \underset{\sim}{u}_o$$

and

$$\underset{\sim}{v}_1 = \underset{\sim}{P}\ \underset{\sim}{v}_o$$

result in vectors $\underset{\sim}{u}_1$ and $\underset{\sim}{v}_1$ representing the first and second moments after one generation of selection. The results for subsequent generations are then obtained as

$$\underset{\sim}{u}_2 = \underset{\sim}{P}\ \underset{\sim}{u}_1$$

$$= \underset{\sim}{P}^2\ \underset{\sim}{u}_o$$

and

$$\underset{\sim}{u}_t = \underset{\sim}{P}\ \underset{\sim}{u}_{t-1} \qquad (a)$$

$$= \underset{\sim}{P}^t\ \underset{\sim}{u}_o \qquad (b)$$

and similarly for $\underset{\sim}{v}$. While operations of the form of (b) indicate more clearly the principle of the use of a transition probability matrix, it is operations of the type shown in (a) which are actually carried out, because they involve only the repeated multiplication of the matrix by a vector, rather than the matrix by the matrix as is needed in (b).

At any generation t, the $i^{th}$ element of $\underset{\sim}{u}_t$ represents $E[q_t | q_o = i/2N]$, and the $i^{th}$ element of $\underset{\sim}{v}_t$ is equivalent to $E[q_t^2 | q_o = i/2N]$. Thus

$$E[\sigma_q^2 | q_o = \tfrac{i}{2N}] = v_{t(i)} - [u_{t(i)}]^2$$

and

$$E[f \mid q_o=\tfrac{i}{2N}] = \frac{v_{t(i)} - [u_{t(i)}]^2}{u_{t(i)}\{1-u_{t(i)}\}} .$$

Matrix operations of the type shown above have been carried out with a diploid population size of N=10, for a total of t=8N generations, with various strengths of selection under two simple models, additive and heterotic. The final generation was chosen as 8N simply because it represents a convenient multiple of N, and corresponds to almost all (in this case 98.2%) of the inbreeding process for a locus with neutral alleles. Extrapolation from t=8N to t=∞ for the parameter f is a relatively easy matter, as E [f] at t=∞ is 1.

An effective population size of N=10 was chosen because it represents a convenient value for matrix operations. It is now commonly realised (see for example, Crow and Kimura, 1970) that generalisations to a wide range of population sizes can be made by expressing the results obtained from one value of N as Ns for the additive model, and as $N(s_1+s_2)$ for the heterotic model, where s is the selection coefficient for additive selection, and $s_1$ and $s_2$ are the selection coefficients for heterotic selection. Thus the two models can be represented as

| | $A_2A_2$ | | $A_1A_2$ | | $A_1A_1$ | |
|---|---|---|---|---|---|---|
| Relative fitness | $1-\frac{1}{2}s$ | : | 1 | : | $1+\frac{1}{2}s$ | additive model |
| | $1-s_1$ | : | 1 | : | $1-s_2$ | heterotic model |

It follows that the transition probability matrix P can be set up by taking $S_{22}=1-\frac{1}{2}s$ and $S_{11}=1+\frac{1}{2}s$ for the additive model, and $S_{22}=1-s_2$ and $S_{11}=1-s_1$ for the heterotic model.

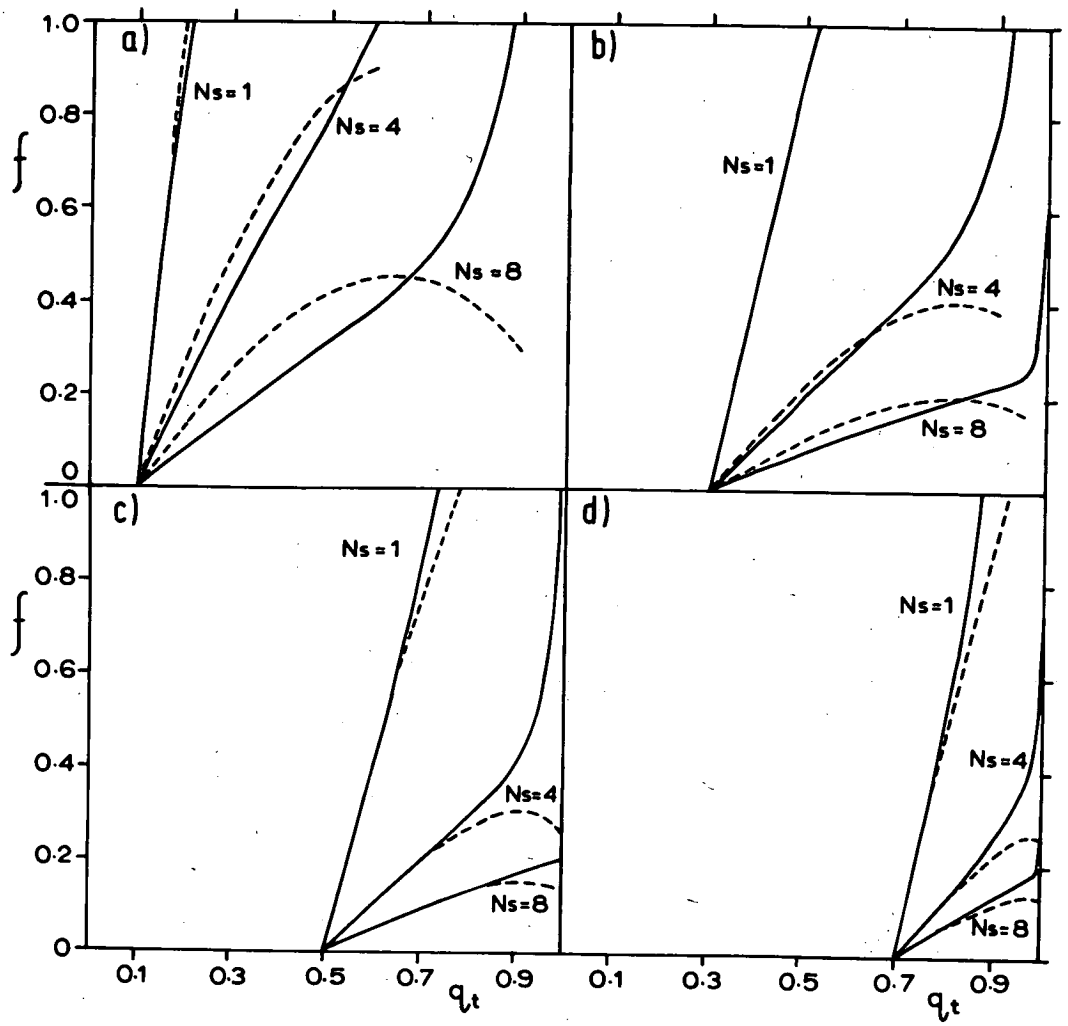


Figure 1. The effect of various strengths of additive selection on the relationship between gene frequency at time t, and the corresponding standardized variance of gene frequency, for initial gene frequencies of $q_o$ = 0.1, 0.3, 0.5 and 0.7. Curves are drawn from transition probability matrix results (solid lines) and from the prediction of equation (11) (dotted lines).

The effect of selection on f

An example of the behaviour of f under additive selection in a finite population is given in figure 1, in which f is shown as a function of mean gene frequency at time t, for the four initial gene frequencies of $q_o$=0.1, 0.3, 0.5 and 0.7. Thus a conceptually infinite population has been subdivided randomly at time t=0 into several subpopulations each of effective size N. The value of $q_o$ is the same in all subpopulations, giving $f_o$=0. Additive directional selection then occurs with exactly the same coefficient of selection in all subpopulations : the variance of s is zero. The exact matrix results (solid lines) represent the mean value of f which would be observed if the whole process of subdivision followed by selection within subpopulations were repeated a large number of times. The broken lines represent the prediction of equation (11).

It can be seen that equation (11) provides an accurate prediction of f for $Ns \leq 1$ and values of f up to about 0.5. (Only one line is shown for $q_o$=0.3 and Ns=1 because observation and prediction coincide exactly in this case, for all values of f). As f approaches its ultimate value of unity, the prediction generally tends to become less accurate. For larger values of Ns, equation (11) tends to overestimate for $q_o < 0.5$ and underestimate for $q_o \geq 0.5$. However, at intermediate initial frequencies ($0.3 \leq q_o \leq 0.7$) the prediction is quite useful for f values up to 0.1 even for large Ns.

The discrepancy between observation and prediction at higher values of f is most likely an indication that some type of interaction term has been omitted from equation (10). An exact description of the whole process is not therefore possible by the simple addition of $\Delta f$

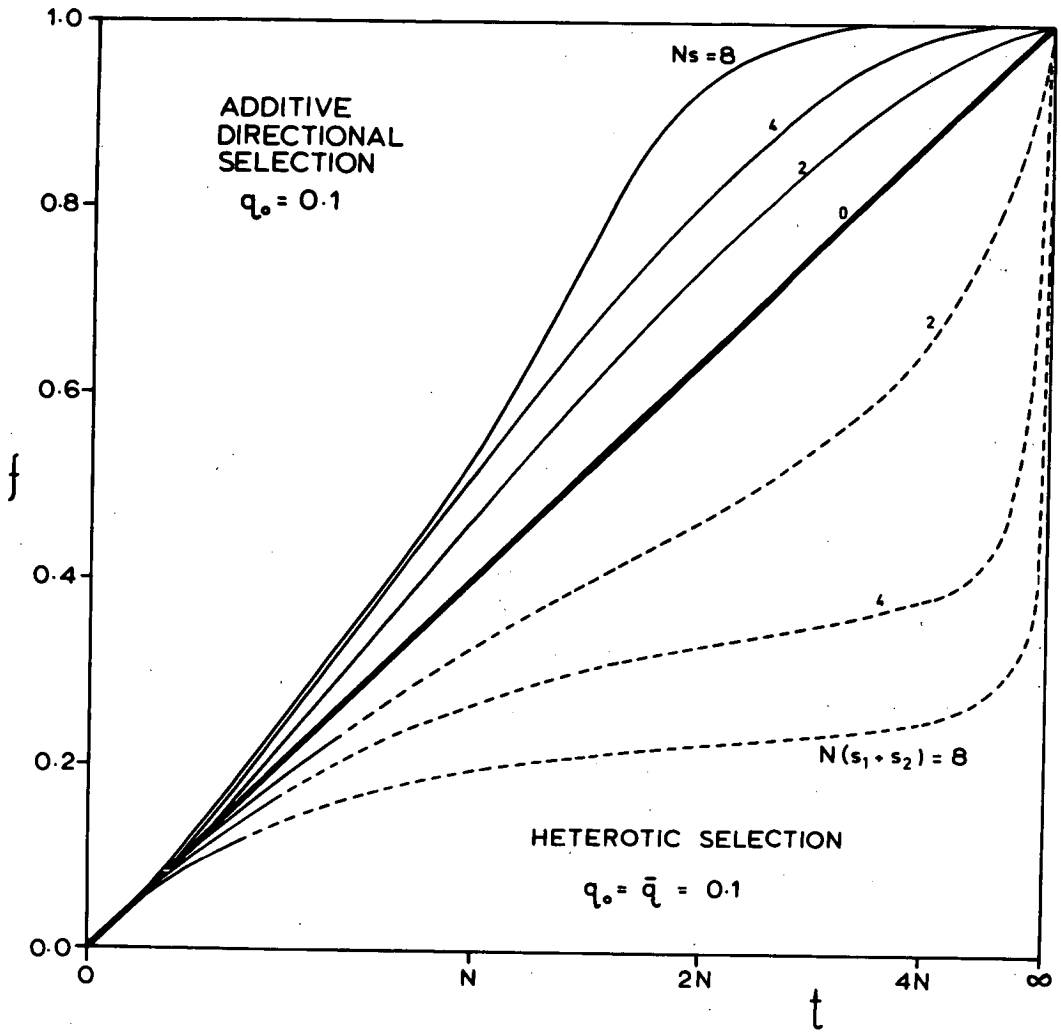


Figure 2. The effect of various strengths of additive directional selection (solid lines) and heterotic selection (dotted lines) on the standardized variance of gene frequency, f, during the whole inbreeding process from generation zero to generation infinity. Time scale is expressed as $1-e^{-t/2N}$ so as to provide a linear relationship with f for no selection. In this example matrix results are given for additive selection with $q_o = 0.1$, and for heterotic selection with $q_o = \bar{q} = 0.1$.

due to drift and $\Delta f$ due to selection. However, to the extent that some useful prediction is indicated in figure 1, at least for $Ns \leq 1$ and/or low f values, it can be concluded that equation (10) is a valid first approximation to a proper description of the effect of selection on f in finite populations.

Another illustration of the way in which f behaves under different strengths of selection for the additive model is given in figure 2. The results for the heterotic model are also included. The time scale on the x-axis is expressed as $1-e^{-t/2N}$ so as to provide a straight line relationship between f and t in the absence of selection. All the curves in figure 2 have been obtained for the same initial frequency of allele $A_1$, namely $q=0.1$: results for other initial gene frequencies will be discussed below. In addition, for the heterotic model, it has been assumed that $q_o=\bar{q}$, where $\bar{q}$ is the large population equilibrium gene frequency, and is given by $\frac{s_2}{s_1+s_2}$. This assumption is probably quite a valid description of the situation in real life, because $t=0$ in the context of this study represents the time of divergence or separation of one relatively large population into two or more relatively smaller ones. If selection were favouring the heterozygote at a particular locus, then it would not be surprising to find $q=\bar{q}$ in the large population, and hence for any newly formed subpopulation the assumption that $E[q_o] = \bar{q}$ would seem to be quite realistic.

It can be seen from figure 2 that at any time t, additive selection results in f values larger than that expected due to drift alone, and that heterotic selection has the opposite effect. The difference between f under selection and f under drift alone at any time t increases as the values of Ns or $N(s_1+s_2)$ increase. More

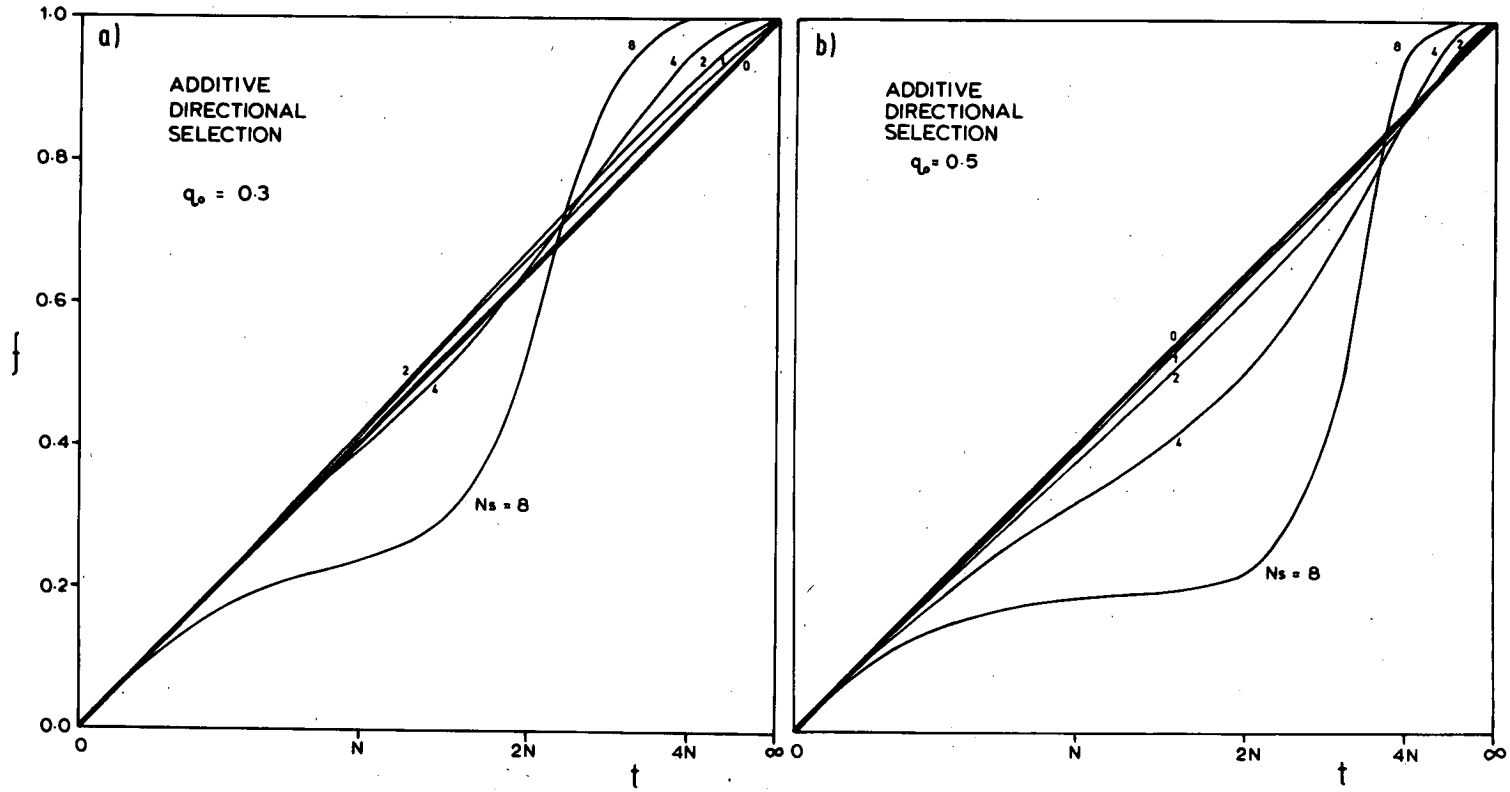


Figure 3. The effect of various strengths of additive directional selection on the standardized variance of gene frequency, f, during the whole inbreeding process from generation zero to generation infinity. Time scale is expressed as $1-e^{-t/2N}$ so as to provide a linear relationship with f for no selection. In this example matrix results are given for additive selection with $q_o = 0.3$ and $q_o = 0.5$.

generally, it has been found that the shape and position of the curves for heterotic selection are very similar for all initial gene frequencies, if $q_o = \bar{q}$. The effects of heterozygote advantage are thus well in accord with the verbal predictions of Cavalli-Sforza (1966, 1969) and Lewontin and Krakauer (1973).

The effect of additive selection, however, is not so easily generalised. For higher initial gene frequencies, in this case 0.3 and 0.5, figure 3 shows the effect of various values of Ns on f. It can be seen that f under selection is almost the same as or less than f with drift alone for the majority of the selection process. In fact with $q_o = 0.5$ the curves for additive selection now resemble the curves for heterotic selection, except for relatively high values of f, of the order of 0.8 or more.

An explanation of the difference between the curves for additive selection at various initial frequencies can be obtained by considering the way in which $\sigma_q^2$ and q alter during the selection process. For initial frequencies less than one half, $\sigma_q^2$ is always greater than it would be in the absence of selection at least until q reaches 0.5. Thus the numerator of f is larger with additive selection than it would have been in the absence of selection. However, as q increases from a low initial value towards 0.5, the value of q(1-q), which is the denominator of f, also increases up to a maximum of 0.25. Thus the denominator is tending to decrease f over this range. The observation that f continues to increase in the early stages of selection is then simply an indication that the increase in $\sigma_q^2$ is more than sufficient to offset the increase in q(1-q).

As q continues to increase above 0.5, the rate of increase in

$\sigma_q^2$ begins to decline. Relatively large Ns values even result in an absdute decline in the value of $\sigma_q^2$. But this relative or absolute decline in $\sigma_q^2$ will be associated with a decline in q(1-q), as q proceeds beyond 0.5, which will tend to increase f. The observed fact that f continues to increase throughout the selection process merely indicates that the decline in the value of q(1-q) is relatively greater than any decline in $\sigma_q^2$ which may occur.

The curve for Ns=8 with $q_o$=0.3 indicates that during the relatively early stages of selection, the decline in q(1-q) may not be sufficient to completely offset the decline in $\sigma_q^2$, so that although the value of f continues to increase, it falls below that expected due to drift alone. It is only when q(1-q) has become much smaller, towards the later stages of selection, that f becomes larger than that expected with drift. The same trends are evident to a greater extent with $q_o$=0.5. In this case, and indeed for all $q_o \geq 0.5$, the value of $\sigma_q^2$ is never as great as that which would be observed with drift alone, and can be much smaller for relatively large Ns values. It therefore takes somewhat longer for the decreasing value of q(1-q) to compensate for the relatively low $\sigma_q^2$, with the result that f with selection is always less than f with drift alone, unless the value of f with drift alone is quite high.

It can be concluded that heterotic selection always results in f values lower than those expected with drift in the absence of selection. Additive directional selection will produce similarly low values of f unless initial gene frequency is low, or unless observations are made relatively late in the selection process, when f values expected due to drift alone are of the order of 0.7 or greater. In these two

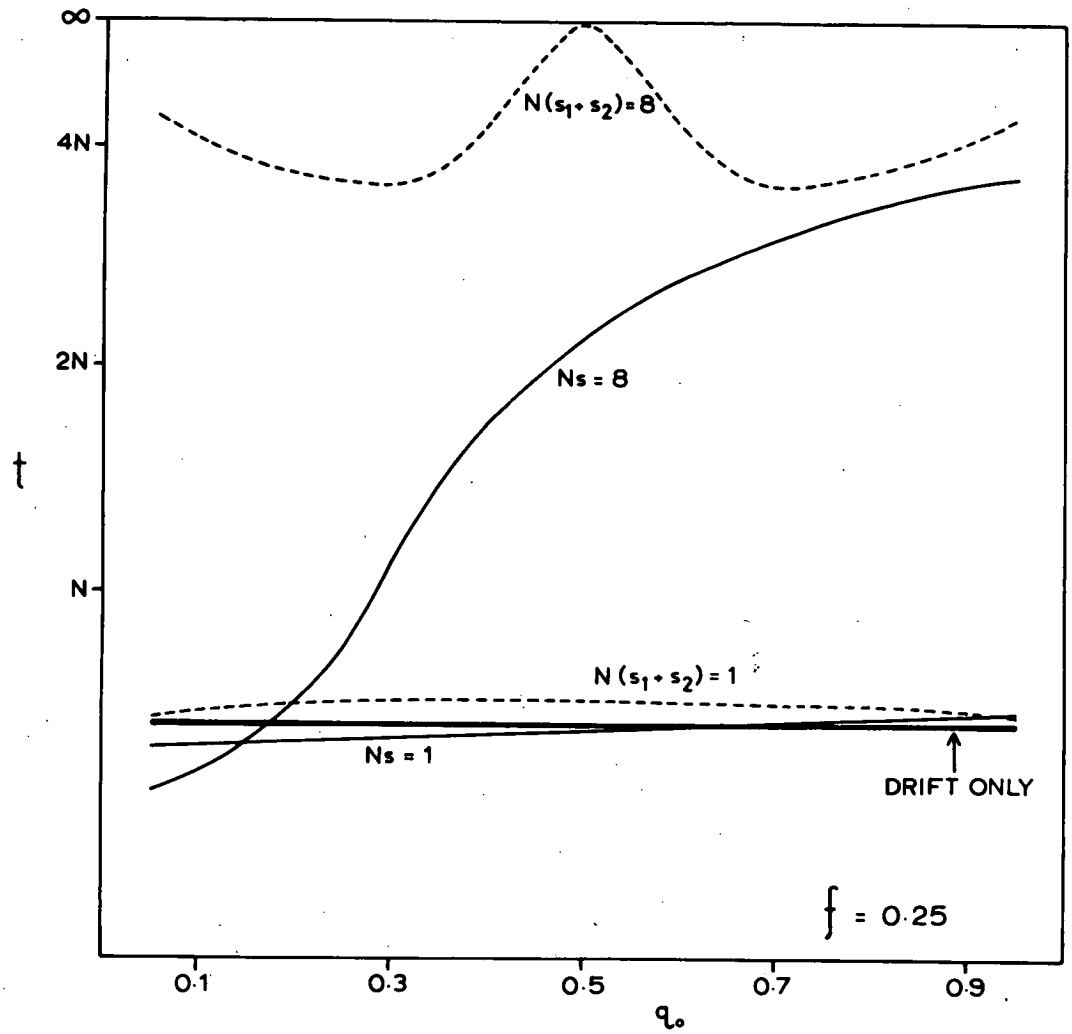


Figure 4. The effect of selection and initial gene frequency on the value of t that would be inferred from an observed f value of 0.25 for relatively weak additive [$Ns = 1$] and heterotic [$N(s_1 + s_2) = 1$] selection, and for relatively strong additive [$Ns = 8$] and heterotic [$N(s_1 + s_2) = 8$] selection. All curves are drawn from matrix results. The straight line for no selection (drift only) is also included. The time scale is expressed in the modified form of $1 - e^{-t/2N}$.

situations f with selection is greater than f with drift alone.

Another general point can be obtained from the curves in figures 2 and 3. It is very evident that even with quite large values of Ns or $N(s_1+s_2)$, the effect of selection on f will never be detected if the observed value of f is less than say 0.1. The effect of selection on f becomes most apparent as f due to drift approaches intermediate values.

It remains now to consider the effect of selection on the results of two different methods of analysis currently used for observations on the standardized variance of gene frequency.

Standardized variance between populations averaged over loci

This is the type of analysis conducted by Cavalli-Sforza (1966, 1969) who used the mean f values so obtained to estimate times since separation or divergence of the populations concerned. Thus a particular value of f is observed, and a value of t is inferred from the observed f. Figure 4 illustrates the way in which the value of t so inferred from a particular value of f is influenced by initial gene frequency, for the two models of selection considered above.

Firstly, it can be seen that for low values of Ns or $N(s_1+s_2)$, the estimate of t is very similar to that which would have been obtained with an hypothesis of no selection (drift only), as expected, and this result holds for all initial gene frequencies. Larger Ns or $N(s_1+s_2)$ values, however, result in much larger estimates of t, except for relatively low initial gene frequencies. The effect of selection therefore, is generally to provide much higher estimates of t than would have been inferred under an hypothesis of drift alone. Estimates

of time since divergence based on an assumption of no selection may thus be considerable underestimates of the true value if additive or heterotic selection has occurred.

But what if the forces of selection vary between loci or between populations? If, for example, alleles at some loci are effectively neutral, while alleles at other loci are subject to either type of selection considered here, then the individual f values from which the mean f is calculated will simply be drawn from different conceptual populations of f values, with the population mean of f for any particular value of Ns or $N(s_1+s_2)$ being situated at the relevant position shown in figures 2 and 3. Thus exactly the same conclusions apply as before.

The situation considered specifically by Cavalli-Sforza (1966, 1969) and Lewontin and Krakauer (1973) involved variable selection coefficients in space for a particular locus. Any such variation in s or $(s_1+s_2)$ would surely increase the value of f at any given time over that which exists for the smallest value of s or $(s_1+s_2)$ on its own. Thus the effect of variation in selection coefficients with space will be to increase the expected value of f above those predicted from the models of constant s and $s_1+s_2$ considered here. However, to the extent that the f values expected under either heterotic or additive selection are generally well below those expected due to drift alone, it would seem to be quite possible that variation in s or $s_1+s_2$ may not be sufficient to give an f value greater than that due to drift alone.

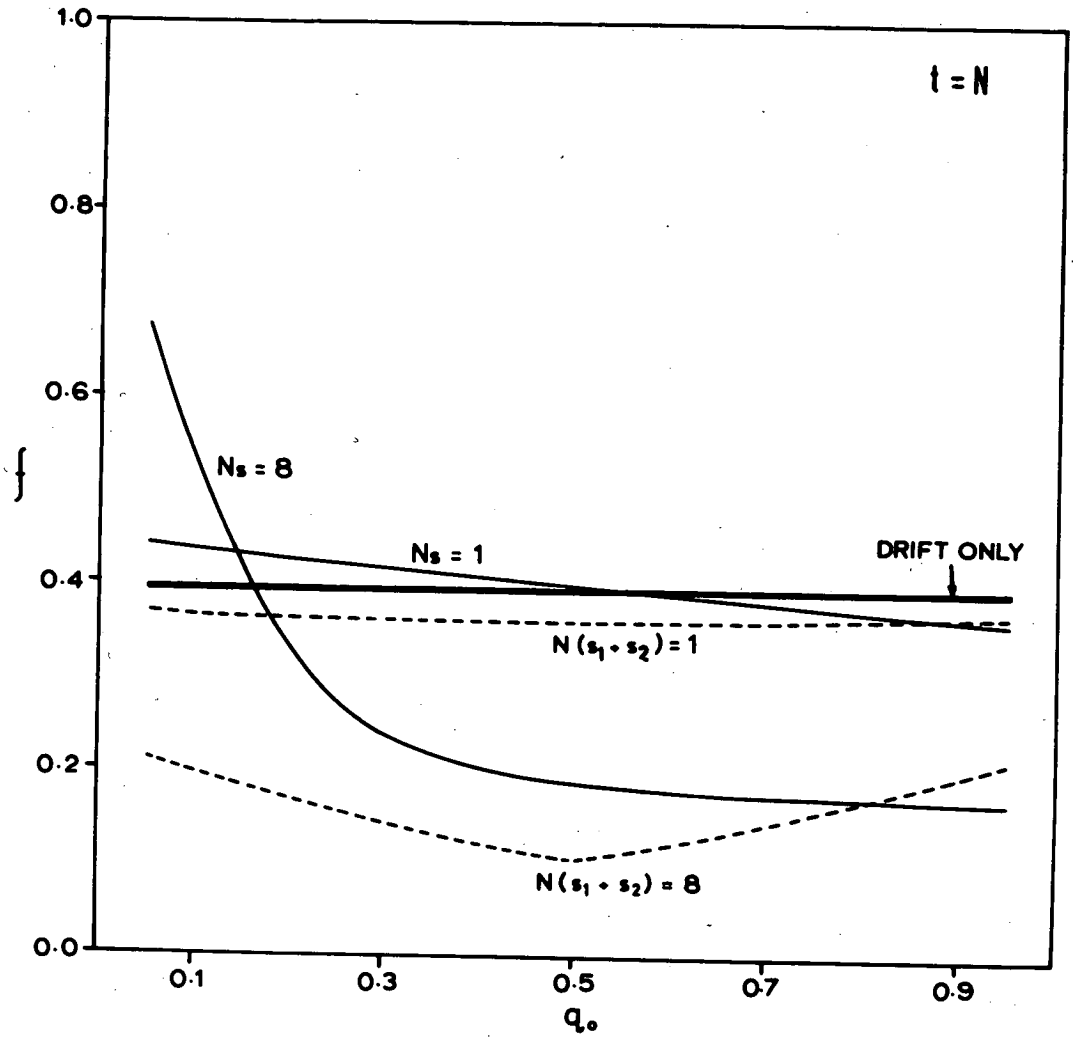


Figure 5. The effect of selection and initial gene frequency on the value of f that would be observed at a time t=N generations after all populations first diverged from one another. Curves are drawn from matrix results for relatively weak additive [$Ns$=1] and heterotic [$N(s_1+s_2)$=1] selection, and for relatively strong additive [$Ns$=8] and heterotic [$N(s_1+s_2)$=8] selection. The straight line for no selection (drift only) is also included.

Standardized variance between populations within loci

Lewontin and Krakauer (1973) have considered two possible types of analysis in this category. The first of these, as utilized by Nevo (1973), involves observation of gene frequency at as many loci in as many different populations as possible, at a particular point in time. A value of f is then estimated for each locus, and significant heterogeneity between f values is taken as evidence of selection at least at some loci. Figures 5 and 6 show the way in which selection determines the value of f actually observed at two particular points in time, namely t=N and 4N generations, for all possible initial gene frequencies. In this context, initial gene frequency refers to the gene frequency at time zero, the time at which all observed populations are assumed to have diverged from each other.

For t=N, which is fairly soon after separation, it can be seen that selection in general, either additive or heterotic, results in relatively low f values compared to those expected due to drift alone. Later on, when the populations have been separated for much longer (t=4N), f due to drift alone is quite high, in this case around 0.86. Once again, heterotic selection results in lower f values, but the situation for additive selection is now somewhat different, in that f values resulting from this type of selection are larger than those expected due to drift alone, except for loci at which the most favoured allele was quite common at the time of separation.

The second type of analysis considered by Lewontin and Krakauer, and actually used by Krimbas and Tsakas (1971), involves observing the variation of gene frequency over time, rather than over space as above. This was done in the case of Krimbas and Tsakas by calculating f for

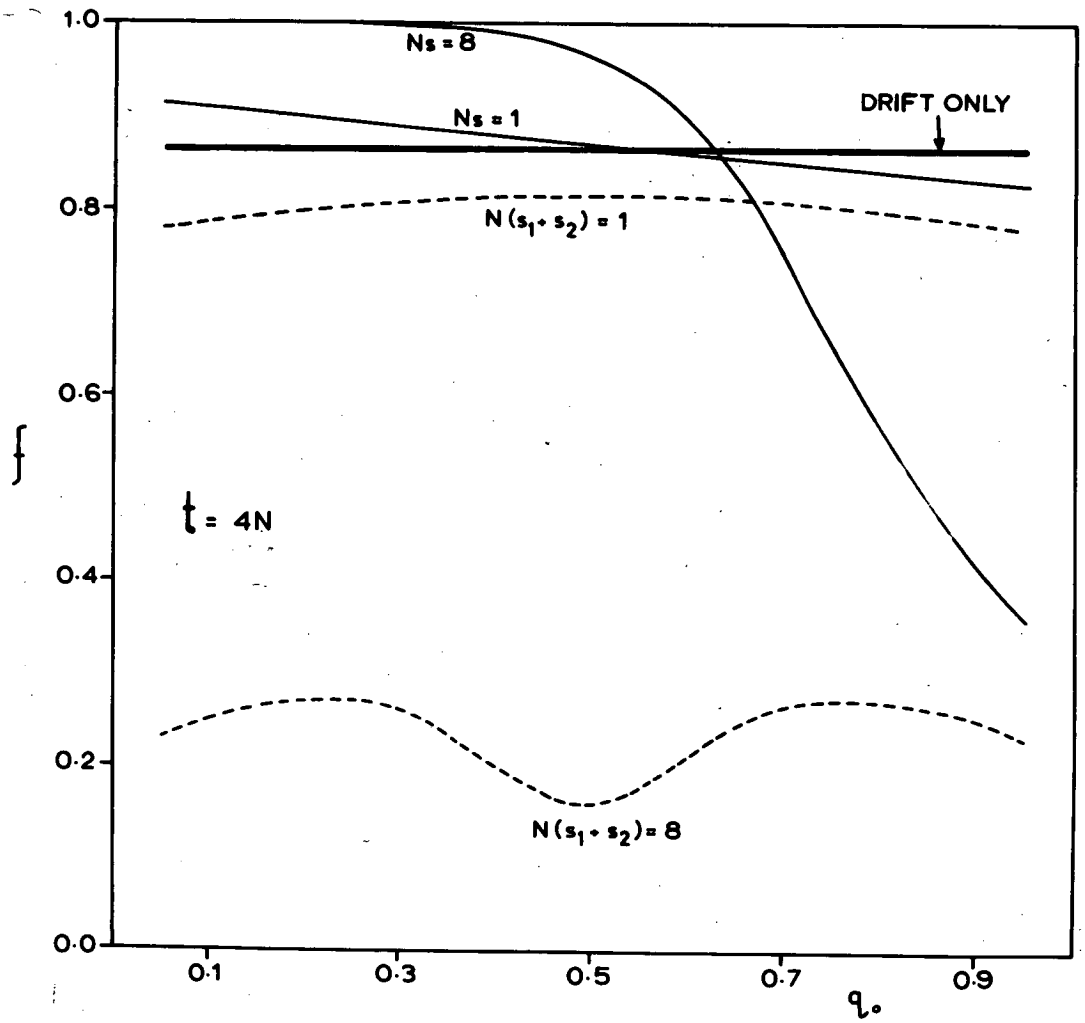


Figure 6. The effect of selection and initial gene frequency on the value of f that would be observed at a time t = 4N generations after all populations first diverged from one another. Curves are drawn from matrix results for relatively weak additive [$Ns_i = 1$] and heterotic [$N(s_1+s_2) = 1$] selection, and for relatively strong additive [$Ns_i = 8$] and heterotic [$N(s_1+s_2)=8$] selection. The straight line for no selection (drift only) is also included.

each of two loci between adjacent years of sampling in a natural population of the olive fruit fly Dacus oleae. It is interesting to note that in their discussion of the sensitivity of such an analysis, Lewontin and Krakauer assumed that the effect of additive selection would be to increase the value of f over and above that expected due to drift alone. It would appear, however, from the results obtained above, that the effect of additive selection is generally to result in f values lower than those expected due to drift except when initial gene frequency is low, or when f due to drift is high.

## Discussion

The results of this study are in broad agreement with verbal predictions already available, of the effect of selection on the standardized variance of gene frequency. What has become evident, however, is the way in which two simple models of selection are sufficient to provide expected values of f which cover almost the entire possible range of f values. Furthermore, the possible range of f values at any particular time t can be substantially extended when consideration (not described here) is given to directional selection for a recessive, and for a dominant gene. It must therefore be concluded that while heterogeneous f values certainly can be taken as evidence of selection, any subsequent inference as to the type of selection operating is bound to be of very limited validity in the absence of knowledge of initial gene frequencies.

It is interesting to note that if the mean initial gene frequency were known, and if it were around 0.5, then equation (11) can be used to estimate the value of Ns for that particular situation, because K=0 for any Ns if $q_o$=0.5. Thus the estimate of Ns is, from (11)

$$\hat{Ns} = \frac{1}{f}\left[2q-1 + 2q(1-q)\log\frac{q}{1-q}\right] \qquad (12)$$

where q is the mean gene frequency and f the corresponding standardized variance of gene frequency actually observed at time t. This type of calculation would be especially valid in the case of, say, artificial directional selection in several lines where each line was initiated from the same base population which in turn was the $F_2$ resulting from the crossing of two distinct inbred lines. The advantage of applying the results of this study to artificial selection is that the assumption of a constant selection coefficient at a given locus is more likely to be valid than in the context of natural selection. With the continuing developments in electrophoretic techniques, investigations are now being made into the way in which artificial directional selection affects gene frequency at various loci, providing estimates of $q_o$, $q_t$ and $f_t$. Equations (11) and (12) can then be used to obtain an approximate estimate of s due to artificial selection at each available locus, if a suitable estimate of effective population size is available.

Summary

1. The effect of directional and heterotic selection on the standardized variance of gene frequency (f) has been studied.

2. For the additive model of directional selection, the change in f per generation due to selection in a finite population of effective size N can be described quite simply in terms of an effect due to drift alone and an effect due to selection alone, such that

$$\Delta f = \frac{1-f}{2N} + \frac{f(1-2q)}{q(1-q)}\Delta q \ ,$$

where $\Delta q$ is the change in gene frequency due to selection in a finite population, and q is the frequency of the allele favoured by selection.

3. A prediction of the relationship between f and q at any generation has been found to be quite accurate for $Ns \leq 1$ or for relatively low values of f.

4. The use of a transition probability matrix has shown that heterotic selection always results in f values lower than those expected due to drift alone.

5. Additive selection usually results in similarly low f values. But f values larger than those expected due to drift will be observed under additive selection with low initial gene frequency (around 0.1 or less), or when the populations have been separated for a relatively long period of time, in which case f expected due to drift is quite high (around 0.7 or greater).

6. The effect of selection on f is unlikely to be detected if the observed value of f is less than 0.1. The effect of selection becomes most apparent as f due to drift approaches intermediate values.

7. Estimates of the type considered by Cavalli-Sforza (1969) of time since divergence or separation of two or more populations, when based on an hypothesis of no selection, may be considerable under estimates of the true value if additive or heterotic selection has occurred.

8. Not withstanding the above generalisations, any inferences as to the type of selection which has produced a particular set of heterogeneous f values are bound to be of limited validity, because the

possible range of f values expected at any given time under any particular model overlaps considerably with those expected from other models.

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# APPENDIX I

## Analysis of variance of selection response

A simple nested analysis of variance was conducted to determine what proportion of the total variation of response could be accounted for by variation in Niα and S. The model used was

$$x_{ijk} = \mu + S_i + Ni\alpha_{ij} + N_{ijk} \qquad \begin{matrix} i = 1,\ldots,4 \\ j = 1,\ldots,4 \\ k = 1,\ldots,3 \end{matrix},$$

where $x_{ijk}$ is the observed frequency of allele $A_1$ in the $k^{th}$ population size (5, 10 or 20) under a selection regime specified by the $j^{th}$ value of Niα (1, 2, 4 or 8) and the $i^{th}$ value of S (0, 0.1, 0.2 or 0.3). Three separate analyses were performed on the observed gene frequency at generations N, 3N and 6N. Initial gene frequency was 0.3 in all cases.

The following results were obtained:-

| | | M.S. | | | E[M.S.] |
|---|---|---|---|---|---|
| | d.f. | gen N | gen 3N | gen 6N | |
| Between S | 3 | 0.195 | 0.460 | 0.567 | $\sigma_N^2 + 3\sigma_{Ni\alpha}^2 + 12\sigma_S^2$ |
| Between Niα within S | 12 | 0.081 | 0.111 | 0.135 | $\sigma_N^2 + 3\sigma_{Ni\alpha}^2$ |
| Between N within Niα | 32 | 0.004 | 0.009 | 0.013 | $\sigma_N^2$ |
| TOTAL | 47 | | | | |

The proportion of total variation in response which can be attributed to variation in Niα and S is then given by $\frac{\sigma_S^2 + \sigma_{Ni\alpha}^2}{\sigma_S^2 + \sigma_{Ni\alpha}^2 + \sigma_N^2}$ which has values of 90%, 87% and 86% for response at generations N, 3N and 6N respectively.

## APPENDIX II

### Derivation of selective values of genotypes

A large proportion of what follows is not original. Derivations arriving at the same end result for additive gene action have been given for example by Griffing (1960) and Latter (1965a), following on from the initial idea of Haldane (1931).

The derivation presented here is different in that it obtains selective values which are explicitly functions of the metric deviation of each homozygote from the heterozygote. It is then possible to use the selective values expressed in this manner, to obtain a simple expression for selective values under a particular model of interest in section II. The selective values for this particular model have already been given without derivation by James (1962), but in a less evident form and in terms of parameters which are more difficult to interpret biologically.

For the genotype $A_jA_k$, the distribution of a metric phenotype prior to artificial selection can be represented as

$$f(x) = \frac{1}{\sigma_p\sqrt{2\pi}} \exp\left[\frac{-(x-\bar{x}_{jk})^2}{2\sigma_p^2}\right]$$

where $\bar{x}_{jk}$ is the mean metric phenotype of genotype $A_jA_k$, and $\sigma_p^2$ is the phenotypic variance of the metric character at the time of artificial selection.

Assume that the effect of artificial selection is to select all individuals whose metric phenotype is equal to or greater than a particular truncation value $x_c$. The probability of an individual being selected is then

$$\text{Prob}\,[x \geq x_c] = \frac{1}{\sigma_p\sqrt{2\pi}} \int_{x_c}^{\infty} \exp\left[\frac{-(x-\bar{x}_{jk})^2}{2\sigma_p^2}\right] dx$$

$$= \frac{1}{\sigma_p\sqrt{2\pi}} \int_{x_c-\bar{x}_{jk}}^{\infty} \exp\left[\frac{-t^2}{2\sigma_p^2}\right] dt.$$

If we let

$$f(x_c) = \frac{1}{\sigma_p\sqrt{2\pi}} \int_{x_c}^{\infty} \exp\left[\frac{-t^2}{2\sigma_p^2}\right] dt$$

then

$$\text{Prob}\,[x \geq x_c] = f(x_c+h)$$

where $h = -\bar{x}_{jk}$ for genotype $A_jA_k$. Expressing $f(x_c+h)$ as a Taylor's expansion results in

$$f(x_c+h) = f(x_c) + h\,f'(x_c) + \ldots$$

Thus it should be possible to evaluate Prob $[x \geq x_c]$ in terms of $f(x_c)$ and $f'(x_c)$. Firstly it is evident that

$$f(x_c) = p$$

where p is the proportion of the population selected. Also

$$f'(x_c) = \frac{-1}{\sigma_p\sqrt{2\pi}} \exp\left[\frac{-x_c^2}{2\sigma_p^2}\right]$$

$$= \frac{-z_c}{\sigma_p}$$

where $z_c$ is the height of the ordinate of the normal curve at the standardised cut-off point $x_c/\sigma_p$. For the genotype $A_jA_k$, it then follows that

$$\text{Prob}\,[x \geq x_c] \sim p + (-\bar{x}_{jk})\left[\frac{-z_c}{\sigma_p}\right] \sim p\left\{1 + \bar{x}_{jk}\,\frac{i}{\sigma_p}\right\},$$

where i is the standardised selection differential, equal to $z_{c/p}$. The relative selective values of the three genotypes can then be expressed as

| $A_2A_2$ | | $A_1A_2$ | | $A_1A_1$ |
|---|---|---|---|---|
| $1 + \bar{x}_{22}\frac{i}{\sigma_p}$ | : | $1 + \bar{x}_{12}\frac{i}{\sigma_p}$ | : | $1 + \bar{x}_{11}\frac{i}{\sigma_p}$ |
| or $1 + \frac{i}{\sigma_p}(\bar{x}_{22}-\bar{x}_{12})$ | : | 1 | : | $1 + \frac{i}{\sigma_p}(\bar{x}_{11}-\bar{x}_{12})$ . |

The well known selective values for additive gene action in the absence of natural selection are obtained directly by noting that $\bar{x}_{22}-\bar{x}_{12} = \frac{-a}{2}$ and $\bar{x}_{11}-\bar{x}_{12} = \frac{a}{2}$ .

Of greater interest in the present study is a somewhat different model, involving nor-optimal natural selection prior to artificial selection with additive gene action.

In their most general form, the metric means of the genotypes can be expressed as

$$\bar{x}_{22} = \mu - aq$$

$$\bar{x}_{12} = \mu - a(q-\tfrac{1}{2})$$

and

$$\bar{x}_{11} = \mu - a(q-1) \quad .$$

It has already been noted in section II that the effect of nor-optimal natural selection is to alter any metric mean $\bar{x}$ to $\bar{x}+C(\Theta-\bar{x})$, and to alter $\sigma_p^2$ to $\sigma_p^2(1-C)$. Thus, using primes to indicate metric means after natural selection,

$$\bar{x}'_{22} - \bar{x}'_{12} = \mu - aq + C[\Theta - \mu + aq] - \left\{\mu - a(q-\tfrac{1}{2}) + C[\Theta - \mu + a(q-\tfrac{1}{2})]\right\}$$

$$= -\frac{a}{2}(1-C)$$

irrespective of the value of $\Theta$ and $\mu$. Similarly

$$\bar{x}'_{11} - \bar{x}'_{12} = \frac{a}{2}(1-C) \quad .$$

The relative selective values of the three genotypes with respect to artificial selection, if nor-optimal natural selection has already taken place, will then be

$$1 + \frac{i}{\sigma_p\sqrt{1-C}}\left[\frac{-a}{2}(1-C)\right] \quad : \quad 1 \quad : \quad 1 + \frac{i}{\sigma_p\sqrt{1-C}}\left[\frac{a}{2}(1-C)\right]$$

which reduce to

$$1 - \frac{i\alpha}{2}\sqrt{1-C} \quad : \quad 1 \quad : \quad 1 + \frac{i\alpha}{2}\sqrt{1-C} \quad .$$

# APPENDIX III

## ESTIMATION OF HERITABILITY BY BOTH REGRESSION OF OFFSPRING ON PARENT AND INTRA-CLASS CORRELATION OF SIBS IN ONE EXPERIMENT.

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## 1. INTRODUCTION

In laboratory or field experiments data are sometimes available on the performance of both the parents and several of their progeny. It is then possible to estimate heritability in two ways, either from the regression of progeny on parent performance or from the intra-class correlation of sibs in the progeny generation [e.g. Falconer (1960)]. In the regression method, no use is made of the variance between members of the same family, nor, directly, of the variance between family means. In the intra-class correlation method, no use is made of parental performance. When all the information is available heritability is customarily estimated by both methods from the same data, but no attempt is made to find the correlation between the estimates, or to pool them to obtain a single, best estimate. Alternative estimates of heritability from the same data have been obtained by Sheridan, Jones, Frankham, Rathie and Barker [ 1968 ], who commented on the poor agreement obtained between the offspring-parent and sib covariance estimates, but thought this due to sampling. Clayton, Morris and Robertson [1957 ] obtained the different kinds of estimates, but each from a different set of data. Alternatively all the information could be utilised to form a maximum likelihood (ML) estimate, which is not commonly done in practice, but has been suggested in this context by Dr J. Felsenstein [ personal communication ].

In this paper we derive formulae for the expected values of the sampling correlation between regression and intra-class correlation heritability estimates, of the variance of pooled estimates derived from these, and of ML estimates. Thus we envisage, in concept, a

large number of separate experiments, of identical design, in each of which a heritability is estimated by offspring-parent regression and by the covariance of sibs. The sampling correlation we compute is that between the pairs of estimates obtained in each experiment taken over the population of replicated experiments.

In Section 2 we discuss the concepts and derive in some detail the formulae for a very simple situation, full sib families from pair matings. In Section 3 we give without details of derivation equivalent formulae for the more involved, but more impprtant hierarchical design in which males are each mated to several females, to give both full-sib and half-sib family groups. In Section 4 we compare the efficiency of alternative estimators and in Section 5 we discuss the optimum designs for estimating heritability using all the available information by ML.

We assume that random mating is practised. For simplicity, balanced designs are considered which, though rarely encountered in field data, illustrate the principles more clearly.

## 2. FULL SIB STRUCTURE

If the correlation of full sibs is to be an unbiased estimator of heritability we need to assume that gene action is additive and that there is no covariance among sibs produced by common environmental (maternal) effects; and for the regression of offspring on parent to be an unbiased estimator, there must be no environmental covariance of maternal and progeny performance. We make all these assumptions here, but relax some of them in the half sib analysis discussed subsequently.

Let us assume that s pair matings are made, and that n progeny

are reared from each mating. Although some information is contained in the variance between individual parents, we shall ignore this, and utilise only the parental means, $X_i$, $i = 1,\ldots,s$. Let $Z_{ij}$ be the score of the $j$th individual in the $i$th family, with $j = 1,\ldots,n$. We assume that the $X_i$ and $Z_{ij}$ are multivariate normally distributed, each with mean $\mu$, and that individual observations have variance $\sigma^2$. The typical variance-covariance structure, based on formulae given by Falconer [1960], is shown below:

$$\begin{array}{c} \\ X_i \\ Z_{ij} \\ Z_{ij'} \end{array} \begin{array}{c} \begin{array}{ccccc} X_i & Z_{ij} & Z_{ij'} & X_{i'} & Z_{i'j} \end{array} \\ \begin{pmatrix} \frac{1}{2} & \frac{1}{2}H & \frac{1}{2}H & 0 & 0 \\ \frac{1}{2}H & 1 & \frac{1}{2}H & 0 & 0 \\ \frac{1}{2}H & \frac{1}{2}H & 1 & 0 & 0 \end{pmatrix} \end{array} \sigma^2 \qquad (1)$$

where $i \neq i'$, $j \neq j'$, and $H$ is the heritability ($h^2$).

## Regression and intra-class correlation

In the usual offspring-parent and sib covariance analyses the following mean squares or products are computed:

$$M_{XX} = \sum_i (X_i - \bar{X}_.)^2/(s-1), \quad M_{XZ} = \sum_i (X_i - \bar{X}_.)(\bar{Z}_{i.} - \bar{Z}_{..})/(s-1),$$

$$M_{BZ} = n\sum_i (\bar{Z}_{i.} - \bar{Z}_{..})^2/(s-1), \quad M_{WZ} = \sum\sum_{ij} (Z_{ij} - \bar{Z}_{i.})^2/s(n-1);$$

and the following estimators of heritability may be used:

regression of offspring on mid-parent: $H_{bf} = M_{XZ}/M_{XX}$,

twice the intra-class correlation of full sibs:

$$H_{tf} = 2(M_{BZ} - M_{WZ})/[M_{BZ} + (n-1)M_{WZ}].$$

While $H_{bf}$ is an unbiased estimator of $H$, $H_{tf}$ is not, for it is the ratio of two random variables, for which only the ratio of their expectations is $H$. We have

$$V(\bar{Z}_i . |X_i) = [\tfrac{1}{2}H(1-H) + (1-\tfrac{1}{2}H)/n]\sigma^2 ,$$

and since $\sum_i (X_i-\bar{X})^2/(\sigma^2/2)$ is distributed as chi-square with $s-1$ d.f.,

$$E[1/\Sigma_i (X_i-\bar{X})^2] = 2/[(s-3)\sigma^2]$$

which can be shown directly, or inferred from Kendall and Stuart [1973, p.305]. Hence

$$V(H_{bf}) = \frac{2 + (n-1)H - nH^2}{(s-3)n}$$

(Latter and Robertson [1960]). Here and elsewhere we shall assume that $s$ is sufficiently large that terms of order $s^{-1}$ can be ignored relative to 1, giving

$$V(H_{bf}) = [2 + (n-1)H - nH^2]/sn \qquad (2)$$

By taking logarithms and expanding, or using Taylor's series, we obtain

$$V(H_{tf}) = \frac{(2-H)^2[2 + (n-1)H]^2(sn-1)}{2s(s-1)n^2(n-1)} ,$$

which reduces to Fisher's [1925, sect. 39] formula

$$V(H_{tf}) = \frac{(2-H)^2[2 + (n-1)H]^2}{2sn(n-1)} \qquad (3)$$

approximately, if $s$ is large.

We find cov ($H_{bf}$, $H_{tf}$) by the same expansion method. For four random variables $w_1, \ldots, w_4$ with means $\mu_1, \ldots, \mu_4$ and small coefficients of variation such that terms of order $(w_i - \mu_i)^3/\mu_i^3$ and higher can be ignored, then

$$\operatorname{cov}\left(\frac{w_1}{w_2}, \frac{w_3}{w_4}\right) = \frac{\mu_1\mu_3}{\mu_2\mu_4}\left[\frac{\operatorname{cov}(w_1,w_3)}{\mu_1\mu_3} - \frac{\operatorname{cov}(w_1,w_4)}{\mu_1\mu_4} - \frac{\operatorname{cov}(w_2,w_3)}{\mu_2\mu_3} + \frac{\operatorname{cov}(w_2,w_4)}{\mu_2\mu_4}\right] . \tag{4}$$

In our case we have

$$w_1 = M_{XZ},\ \mu_1 = \tfrac{1}{2}H\sigma^2 \ ;\ w_2 = M_{XX},\ \mu_2 = \tfrac{1}{2}\sigma^2$$

$$w_3 = 2(M_{BZ} - M_{WZ}),\ \mu_3 = nH\sigma^2 \ ;\ w_4 = M_{BZ} + (n-1)M_{WZ},\ \mu_4 = n\sigma^2.$$

Tallis [1959] gives a general formula for variances and covariances of mean squares and products of normal deviates. For some $m_{qr}$, $m_{st}$ which are unbiased estimators of population moments with $f$ d.f.,

$$\operatorname{cov}(m_{qr}, m_{st}) = [\operatorname{cov}(q,s)\operatorname{cov}(r,t) + \operatorname{cov}(q,t)\operatorname{cov}(r,s)]/f$$

where cov($q$,$s$) etc. are the appropriate covariances. We have

$$\operatorname{cov}(M_{XX}, M_{BZ}) = 2n\ \operatorname{cov}^2(X_i, \bar{Z}_{i.})/(s-1) = \tfrac{1}{2}nH^2\sigma^4/(s-1)$$

$$\operatorname{cov}(M_{XX}, M_{WZ}) = \operatorname{cov}(M_{XZ}, M_{WZ}) = 0$$

$$\operatorname{cov}(M_{XZ}, M_{BZ}) = 2n\ \operatorname{cov}(X_i, \bar{Z}_{i.})V(\bar{Z}_{i.})/(s-1) = \tfrac{1}{2}H(nH+2-H)\sigma^4/(s-1).$$

Substituting the above into (4), rearranging, and assuming $s$ is large we obtain

$$\operatorname{cov}(H_{bf}, H_{tf}) = \frac{H(2-H)[2+(n-1)H-nH^2]}{sn} \tag{5}$$

which is, of course, approximate since high order terms are ignored in (4).

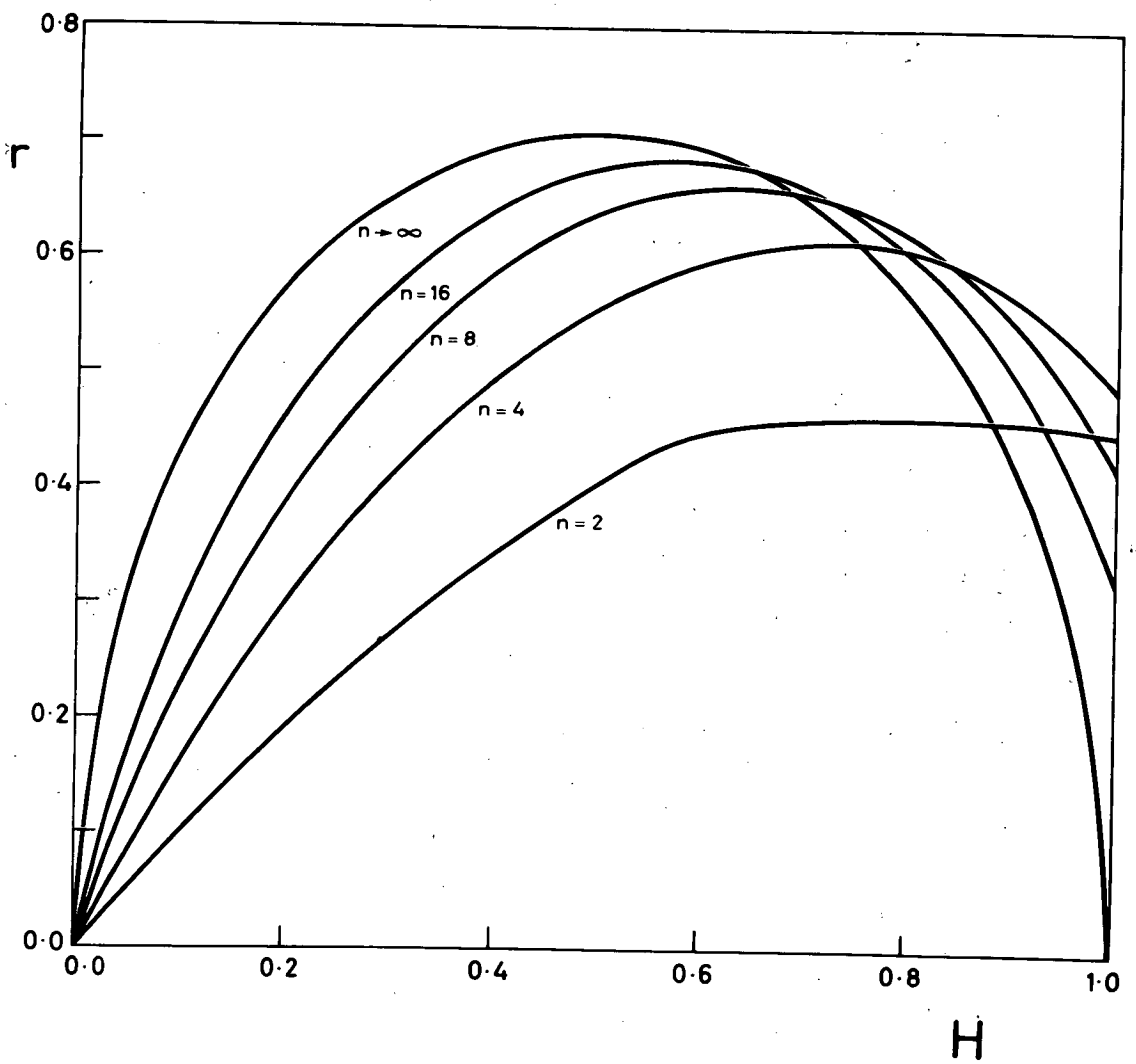


Figure 1. Correlation, r, between estimates of heritability from the covariance of full sibs ($H_{tf}$) and the regression of offspring on mid parent ($H_{bf}$) with full sib families of specified size.

From (2) and (5) we find that, asymptotically for large $s$, the regression of $H_{tf}$ on $H_{bf}$ is given by $H(2-H)$, and from (2), (3) and (5) that the correlation between $H_{tf}$ and $H_{bf}$ is

$$r = \frac{H\{2(n-1)[2+(n-1)H-nH^2]\}^{\frac{1}{2}}}{2 + (n-1)H} \qquad (6)$$

which does not depend on the number of families. With large family sizes ($n \to \infty$) and $H>0$, equation (6) reduces to $r = \sqrt{2H(1-H)}$. In Figure 1 the correlation is shown for some values of $n$ and $H$.

Some verbal but non-rigorous explanation of the positive covariance and hence correlation of the two estimators can be given. If, for example, the genetic variance among the sample of parental pairs taken exceeds its expectation ($\frac{1}{2}H\sigma^2$), then the variance between progeny means and the covariance of progeny and parental scores will both exceed their appropriate expectation, so that both $H_{tf}$ and $H_{bf}$ will tend to exceed $H$. However, both $H_{tf}$ and $H_{bf}$ will generally be less than $H$ if there is reduced genetic variance among parental pairs, so there is a positive covariance between $H_{tf}$ and $H_{bf}$.

It is clear from Figure 1 that the correlation between estimates of heritability from offspring on mid parent regression and from the covariance of full sibs is not trivially small unless the true heritability ($H$) is close to zero or, only if family sizes are very large, close to unity. Thus, in a single experiment in which heritability is estimated by both methods, we should expect to find a better agreement between the two estimates than if they were obtained independently.

Maximum likelihood estimation

The available information on heritability in the experiment can be utilised by ML. We are concerned here primarily with the efficiency of such estimators, relative to using the simple regression or sib correlation estimators, rather than with the ML estimation procedure.

Let $\underset{\sim}{V}$ of dimension $s(n+1)$ be the variance-covariance matrix of the observations, which, for simplicity in the later analysis, we take as the transformed vector:

$$(X_1, \bar{Z}_{1.}, Z_{11} - \bar{Z}_{1.}, Z_{12} - \bar{Z}_{1.}, \ldots, Z_{1,n-1} - \bar{Z}_{1.}; \ldots; X_s, \bar{Z}_{s.}, Z_{s1} - \bar{Z}_{s.}, \ldots, Z_{s,n-1} - \bar{Z}_{s.})'.$$

Since families are distributed independently, $\underset{\sim}{V}$ is block diagonal, with the block $\underset{\sim}{V}_i$ of dimension $n+1$ specifying the variance-covariance structure of a single family. We can write $\underset{\sim}{V} = \underset{\sim}{I} * \underset{\sim}{V}_i\sigma^2$, where $*$ denotes direct product [Searle (1966)]. From the model (1)

$$\underset{\sim}{V}_i = \begin{pmatrix} \underset{\sim}{T} & \underset{\sim}{0} \\ \underset{\sim}{0} & (1-\frac{H}{2})(\underset{\sim}{I}-\frac{1}{n}\underset{\sim}{J}) \end{pmatrix}, \quad i = 1, \ldots, s$$

where $\underset{\sim}{I}$ (the identity matrix) and $\underset{\sim}{J}$ (with all elements unity) are of dimension $n-1$; and $\underset{\sim}{T}$ of dimension 2 is given by

$$\underset{\sim}{T} = \begin{pmatrix} \frac{1}{2} & \frac{1}{2}H \\ \frac{1}{2}H & \frac{1}{2}H + (1-\frac{1}{2}H)/n \end{pmatrix}$$

Noting that $E(X_i) = E(\bar{Z}_{i.}) = \mu$ and $E(Z_{ij} - \bar{Z}_{i.}) = 0$, the log likelihood becomes

$$\text{Log } L = -\tfrac{1}{2}s(n+1)\,(\log 2\pi + \log \sigma^2) - \tfrac{1}{2}s \log |\underset{\sim}{T}| + \tfrac{1}{2}s \log n - \tfrac{1}{2}s(n-1)$$

$$\times \log (1-\tfrac{1}{2}H) - (1/2\sigma^2) \sum_{i=1}^{s} [(\underset{\sim}{y}_i-\mu\underset{\sim}{1})'\underset{\sim}{T}^{-1}(\underset{\sim}{y}_i-\mu\underset{\sim}{1}) + \sum_{j=1}^{n} (Z_{ij}-\bar{Z}_{i.})^2/(1-\tfrac{1}{2}H)] \qquad (7)$$

where $\underset{\sim}{y}_i' = (\underline{X}_i, \underline{\bar{Z}}_{i.})$, $\underset{\sim}{1}' = (1, 1)$. Explicit solutions for the ML estimators of $\underline{\mu}$, $\underline{\sigma^2}$ and $\underline{H}$ have not been found, but with any set of data estimates can be obtained numerically. For example Felsenstein [personal communication] has written a computer program for this specific problem. However, large sample variances can be obtained in the usual way from the inverse of the matrix of expected second partial derivatives of the likelihood with respect to the parameters.

Let $\underline{\theta_1} = \underline{\mu}$, $\underline{\theta_2} = \sigma^2$ and $\underline{\theta_3} = \underline{H}$, and the information matrix $\underset{\sim}{M}$ have elements

$$m_{ij} = -E(\partial^2 \log L/\partial\theta_i\partial\theta_j), i,j = 1,2,3.$$

In differentiating (7) and taking expectations we utilise some results given by Searle [1970]. In our context these are

$$\underline{E}\left\{\frac{\partial}{\partial \underline{H}}[(\underset{\sim}{y}_i-\mu\underset{\sim}{1})'(\sigma^2\underset{\sim}{T})^{-1}(\underset{\sim}{y}_i-\mu\underset{\sim}{1})]\right\} = -\text{tr}\left[\underset{\sim}{T}^{-1}\frac{\partial \underset{\sim}{T}}{\partial \underline{H}}\right] = -\underline{\partial} \log |\underset{\sim}{T}|/\underline{\partial H},$$

where tr denotes the trace; and

$$E\left\{\frac{\partial^2}{\partial H^2}[(\underset{\sim}{y}_i-\mu\underset{\sim}{1})'(\sigma^2\underset{\sim}{T})^{-1}(\underset{\sim}{y}_i-\mu\underset{\sim}{1})]\right\} = -\text{tr}\left[\underset{\sim}{T}^{-1}\frac{\partial^2 \underset{\sim}{T}}{\partial H^2} - 2\underset{\sim}{T}^{-1}\frac{\partial \underset{\sim}{T}}{\partial H}\underset{\sim}{T}^{-1}\frac{\partial \underset{\sim}{T}}{\partial H}\right],$$

$$= -\frac{2\partial^2}{\partial H^2} \log |\underset{\sim}{T}| + \text{tr}\left[\underset{\sim}{T}^{-1}\frac{\partial^2 \underset{\sim}{T}}{\partial H^2}\right]$$

$$= -2\partial^2 \log |\underset{\sim}{T}|/\partial H^2,$$

since $\underline{\partial^2 \underset{\sim}{T}/\partial H^2} = 0$. We obtain from (7)

$$m_{11} = \frac{2s[n+2 - (n+1)H]}{\sigma^2[2+(n-1)H - nH^2]}, \quad m_{22} = \frac{s(n+1)}{2\sigma^4}$$

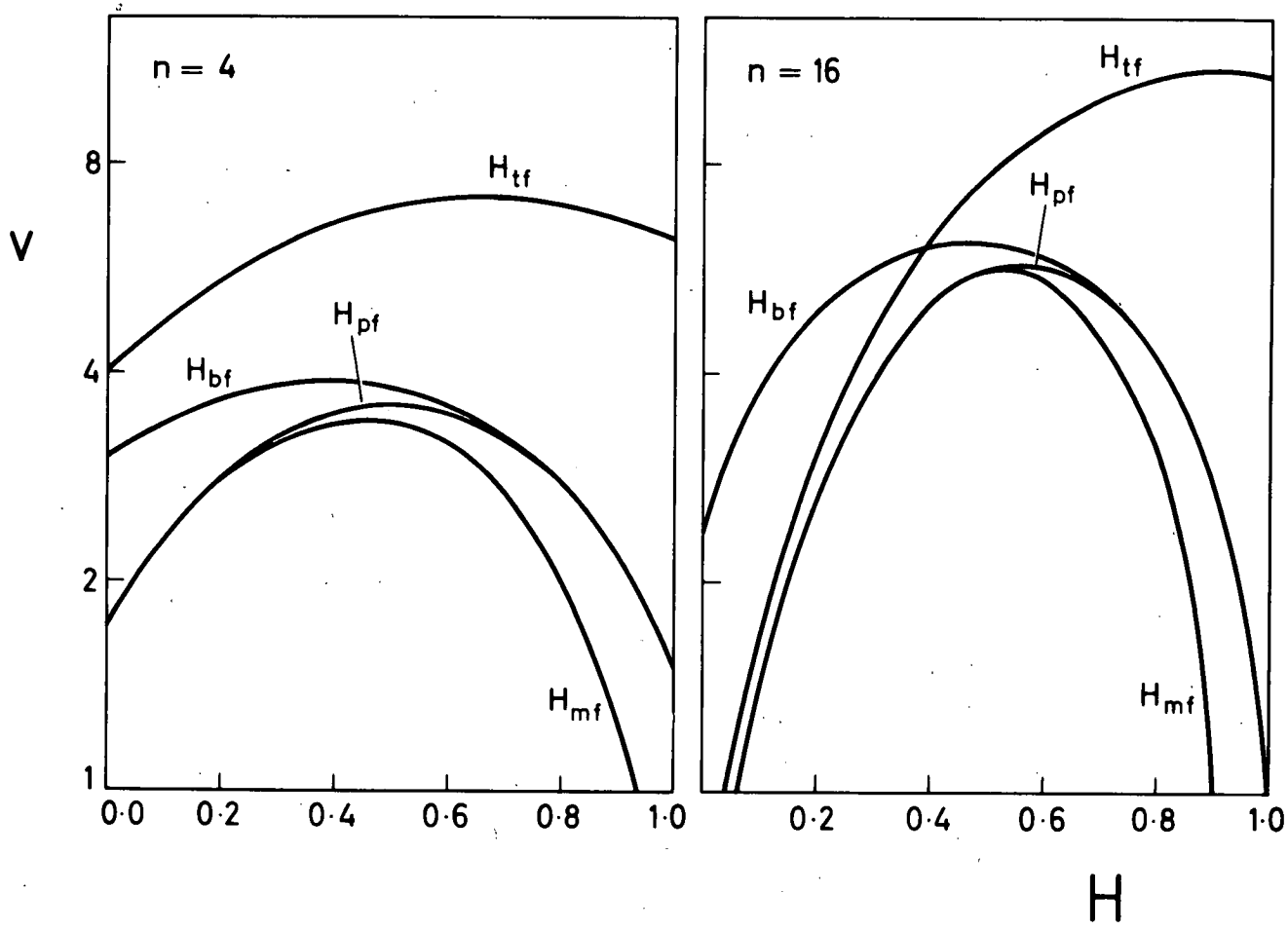


Figure 2. Sampling variance per observation (v) of alternative heritability estimators with full sib families of two different sizes: $H_{tf}$ from sib covariance, $H_{bf}$ from regression on mid-parent, $H_{pf}$ a pooled estimate of $H_{tf}$ and $H_{bf}$, and $H_{mf}$ from maximum likelihood.

$$m_{12} = m_{21} = m_{13} = m_{31} = 0$$

$$m_{23} = m_{32} = \frac{s}{2\sigma^2}\left[\frac{n-1 - 2nH}{2+(n-1)H-nH^2} - \frac{n-1}{2-H}\right]$$

$$m_{33} = s\left\{\frac{2n[2+(n-1)H-nH^2]+(n-1-2nH)^2}{2[2+(n-1)H-nH^2]^2} + \frac{n-1}{2(2-H)^2}\right\}$$

The estimates of $\underline{\mu}$ and $\underline{H}$ are uncorrelated, since they are the mean and a function of the variance, respectively, in a mixed model (Searle [1970]). Let $\underline{V(H_{mf})}$ denote the sampling variance of the ML estimator of heritability, which is given by the (3,3) element of $\underline{M}^{-1}$, i.e.

$$V(H_{mf}) = m_{22}(m_{22}m_{33} - m_{23}^2)^{-1} .$$

Relative efficiency of estimators

The variance of $\underline{H_{mf}}$ is compared with that of the simple estimators $\underline{H_{bf}}$ and $\underline{H_{tf}}$ in Figure 2. The total number of observations made for the estimates is $\underline{T} = \underline{s(n+2)}$, so to enable comparisons between estimates obtained for different values of $\underline{n}$, variances are expressed as $\underline{T.V(H_{mf})} = v$, for example. Thus for any experiment with $\underline{T^*}$ individuals, the variance is $\underline{v/T^*}$. The computed sampling variance of the ML estimator is proportional to $\underline{s}$, and we have seen that those of $\underline{H_{tf}}$ and $\underline{H_{bf}}$ are inversely proportional to $\underline{s} - 1$ and $\underline{s} - 3$, respectively, and approximately to $\underline{s}$ if the number of sires is large. We therefore assume that many sires are used, and the results of Figure 2 do not depend on $\underline{s}$.

It is also possible to obtain a pooled heritability estimate, $\underline{H_{pf}}$, as a linear weighted function of $\underline{H_{bf}}$ and $\underline{H_{tf}}$. We take

$$H_{pf} = \alpha H_{bf} + (1-\alpha)H_{tf} \qquad (8)$$

in which $\alpha$ is chosen so as to minimise $V(H_{pf})$. This value of $\alpha$ is

$$\alpha = [V(H_{tf}) - \mathrm{cov}(H_{bf},H_{tf})]/[V(H_{bf}) + V(H_{tf}) - 2\ \mathrm{cov}(H_{bf},H_{tf})], \qquad (9)$$

giving

$$V(H_{pf}) = [V(H_{bf})V(H_{tf}) - \mathrm{cov}^2(H_{bf},H_{tf})]/[V(H_{bf}) + V(H_{tf}) - 2\ \mathrm{cov}(H_{bf},H_{tf})]. \qquad (10)$$

In practice only estimates of $V(H_{bf})$, $V(H_{tf})$ and $\mathrm{cov}(H_{bf},H_{tf})$ are available to insert into (9), since they depend on the parameter $H$. An iterative procedure has to be used in which a value, $\hat{H}$ is guessed, used to estimate $H_{pf}$ from (8), and subsequently $V(H_{bf})$ etc. These values are substituted into (9), $\hat{\alpha}$ is estimated again and the process repeated.

Values of $T.V(H_{pf})$ are also shown in Figure 2. Since the best weighting factor, $\alpha$, is not known, the variances given in the figure may be biased downwards. While no exact formula for this bias has been obtained, a simple argument shows that it becomes proportionately smaller as $s$ increases, and thus is negligible in large samples. Rewriting (8) as

$$H_{pf} = H_{tf} + \hat{\alpha}(H_{bf} - H_{tf})$$

we see that the contribution of error of estimation of $\hat{\alpha}$ to $V(H_{pf})$ is roughly proportional to $E(H_{bf} - H_{tf})^2 V(\hat{\alpha})$. Now $E(H_{bf} - H_{tf})^2$ and the variance of all of the terms on the right hand side of (9), and thus $V(\hat{\alpha})$, are proportional to $1/s$, so the product $E(H_{bf}-H_{tf})^2 V(\hat{\alpha})$ is proportional to $1/s^2$ and in large samples becomes a trivial part of

$V(H_{pf})$. (The same arguments can be applied to the ML estimators, which are themselves weighted estimates, with the weights inaccurately determined in small samples).

It appears (Figure 2) that except at high heritabilities the pooled estimator, $H_{pf}$, is almost as efficient as the ML estimator. Since parental observations are not required to enable estimation of intra-class correlation, the appropriate value of $T$ in an experiment designed only to obtain $H_{tf}$ and in which parents are not recorded for regression estimates is $sn$. The value of $T.V(H_{tf})$ in Figure 2 could then be reduced by the factor $n/(n+2)$.

The loss of efficiency in ML estimation from excluding the information on the individual parents can be obtained using the methods described in section 3, but omitting the environmental covariance of sibs term ($K$). For heritabilities near zero there is no loss in efficiency. Taking values of $H$ of 0.1, 0.2,...,0.9, the greatest losses obtained were 6.5% and 7.5% for $n$ = 16 and 8 respectively, both at $H$ = 0.7, and 9.5%, 12.2% and 11.9% for $n$ = 4, 2 and 1 respectively, all at $H$ = 0.9.

## 3. ESTIMATORS IN A HIERARCHICAL STRUCTURE

An important assumption in our analysis of the full sib family model is that the only covariance between family members is that from additive genetic variance (i.e. $\frac{1}{2}H\sigma^2$). Usually there is some additional covariance, $K\sigma^2$, of full sibs from two sources; maternal or other environment effects common to full sibs and non-additive genetic effects, especially dominance (Falconer [1960]). Therefore intra-class correlation estimates of heritability are normally made from

the covariance of half sibs. Regressions of progeny on parental performance do not include dominance effects, but there could be some maternal environmental covariance between progeny and dam. However, this covariance is unlikely to be of the same magnitude as the environmental covariance of sibs and we shall assume in the following analysis that it can be ignored. Thus the only major change from the simple full sib model described previously is that a term $K\sigma^2$ is added to the covariance of full sibs. We again assume there is no epistatic variance.

Let $s$ sires each be mated to $d$ dams with $n$ progeny reared from each mating and we shall assume throughout that $s$ is sufficiently large that terms in $s^{-1}$ can be ignored relative to 1. This simplifies the formulae and makes them more directly comparable with each other. Let $X_i$ be the measurement on sire $i$, $Y_{ij}$ that on the $j$th dam mated to sire $i$, and $Z_{ijk}$ the measurement on her $k$th progeny. The observations are assumed to be multivariate normally distributed with mean $\mu$. There are no covariances between members of different sire families, and typical variances and covariances for a single family are shown below:

$$
\begin{array}{c}
 \\
X_i \\
Y_{ij} \\
Z_{ijk} \\
Z_{ijk'} \\
Y_{ij'} \\
Z_{ij'k}
\end{array}
\begin{array}{c}
\begin{array}{cccccc} X_i & Y_{ij} & Z_{ijk} & Z_{ijk'} & Y_{ij'} & Z_{ij'k} \end{array} \\
\begin{pmatrix}
1 & 0 & \frac{1}{2}H & \frac{1}{2}H & 0 & \frac{1}{2}H \\
0 & 1 & \frac{1}{2}H & \frac{1}{2}H & 0 & 0 \\
\frac{1}{2}H & \frac{1}{2}H & 1 & \frac{1}{2}H+K & 0 & 1/4H \\
\frac{1}{2}H & \frac{1}{2}H & \frac{1}{2}H+K & 1 & 0 & 1/4H \\
0 & 0 & 0 & 0 & 1 & \frac{1}{2}H \\
\frac{1}{2}H & 0 & 1/4H & 1/4H & \frac{1}{2}H & 1
\end{pmatrix}
\end{array}
\sigma^2 \qquad (11)
$$

where $j \neq j'$, $k \neq k'$. Within this structure we shall also include

the case of sex limited traits, where if no measurement is made on males, no $X_i$ are available, or if none on females, there are no $Y_{ij}$. There are clearly many other relevant models which we do not consider: for example where males and females have different means and variances, or where the mean performance differs between the two generations.

With this kind of data estimators of heritability can be obtained in several ways:

i) Intra-class correlation between half sibs. (The correlation between full sibs is biased.)

ii) Regression of offspring on parent performance:

a) Progeny on dam within sires.

b) Progeny on sire.

c) Progeny on sire plus dam average.

d) Progeny on mid-parent.

e) Various pooled regression estimators.

iii) Pooled estimators from intra-class correlation and regression.

iv) Maximum likelihood.

We shall compare the variances of the alternative estimators, together with the sampling correlations between estimates obtained from the same data, using the methods described in section 2.

i) Intra-class correlation between half-sibs ($H_{ts}$)

The intra-class correlation between half sibs, $H_{ts}$, is too well known to require definition here. The approximate sampling variance, modified from Osborne and Patterson [1952] or Robertson [1959], is

$$V(H_{ts}) = \frac{1}{8sd^2n^2}\{(4-H)^2[4-2H-4K + n(H + 4K) + ndH]^2 + [4 + (d-1)H]^2[4 - 2H - 4K + n(H + 4K)]^2/(d-1) + 4d(n-1)H^2(2 - H - 2K)^2\} \quad (12)$$

where the variances deriving from the mean squares for sires, dams and individuals are shown in order. The method can, of course, be used for sex limited traits.

ii) Regression of offspring on parent performance

Each of the following regression estimators, not necessarily an exhaustive list, can be shown to be unbiased, for $H$.

a) Progeny on dam within sires ($H_{bd}$). The estimator,

$$H_{bd} = 2\Sigma\Sigma_{ij}(Y_{ij}-\bar{Y}_{i.})(\bar{Z}_{ij.}-\bar{Z}_{i..})/\Sigma\Sigma_{ij}(Y_{ij}-\bar{Y}_{i.})^2 \quad (13)$$

makes no use of differences between sires, and is the typical daughter-dam regression technique used for traits expressed only in females, such as milk yield in cattle where there is often only one daughter for each dam ($n = 1$). From regression theory,

$$V(H_{bd}) = \frac{4-2H+nH(1-H) + 4(n-1)K}{s(d-1)n} \quad (14)$$

and we can show that

$$\mathrm{cov}(H_{bd},H_{ts}) = \frac{-H}{2sd(d-1)n}[4+(d-1)H][4-2H+nH(1-H)+4(n-1)K].$$

The regression of $H_{ts}$ on $H_{bd}$ is simply $-H[4+(d-1)H]/2d$, but the correlation of the two estimates has a lengthy formula. The correlation is negative if $H>0$, in contrast to that between the estimates from covariance of full sibs and offspring on mid-parent regression described

earlier. Presumably a sample of dams with a genetic variance above expectation induces a regression above average and a sire variance component, estimated from the difference between sire and dam mean squares, below average. Since $V(H_{bd})$, $V(H_{ts})$ and $cov(H_{bd},H_{ts})$ are all inversely proportional to $s$, (under our assumptions), the correlation does not depend on $s$. Also, if $d$ and $s$ are large, $n = 1$ and $H>0$, it can be shown that the correlation between $H_{bd}$ and $H_{ts}$ approaches $-H/\sqrt{2d}$.

b) Progeny on sire ($H_{bs}$). The estimator,

$$H_{bs} = 2\Sigma_i(\bar{X}_i-\bar{X}_.)(\bar{Z}_{i..}-\bar{Z}_{...})/\Sigma_i(\bar{X}_i-\bar{X}_.)^2$$

can be used for traits expressed only in males, since it makes no use of information on the dams. We can show that

$$V(H_{bs}) = \frac{4-2H + nH + ndH(1-H) + 4(n-1)K}{sdn} \qquad (15)$$

and

$$cov(H_{bs},H_{ts}) = \frac{H(4-H)}{2sdn}\ [4-2H+nH+ndH(1-H)+4(n-1)K].$$

Thus the regression of $H_{ts}$ on $H_{bs}$ is $\frac{1}{2}H(4-H)$ and, like the correlation, does not decrease to zero as the size of the experiment increases.

c) Progeny on sire plus dam average ($H_{ba}$). The information available on the mean performance of dams mated to each sire is excluded from the regressions $H_{bd}$ and $H_{bs}$. It can be incorporated by regressing the mean performance of progeny in a sire family on the sire plus average dam performance. Thus

$$H_{ba} = 2\Sigma_i(\bar{X}_i+\bar{Y}_{i.}-\bar{X}_.-\bar{Y}_{..})\ (\bar{Z}_{i..}-\bar{Z}_{...})/\Sigma_i(\bar{X}_i+\bar{Y}_{i.}-\bar{X}_.-\bar{Y}_{..})^2$$

and

$$V(H_{ba}) = \frac{4-2H+n(d+1)H(1-H)+4(n-1)K}{s(d+1)n} \qquad (16)$$

which is slightly less than $V(H_{bs})$. Also

$$cov(H_{ba},H_{ts}) = cov(H_{bs},H_{ts}) - H^3(4-H)/2sd$$

d) Progeny on mid-parent ($H_{bm}$). If the hierarchical structure is disregarded, a straightforward regression of offspring on mid-parent can be computed in which the sire performance is included with each of his mates. It is a simple method of utilising all the observations on the parents for traits expressed in both sexes, and

$$H_{bm} = 2\Sigma\Sigma_{ij}(X_i+Y_{ij}-\bar{X}_{.}-\bar{Y}_{..})(\bar{Z}_{ij.}-\bar{Z}_{...})/\Sigma\Sigma_{ij}(X_i+Y_{ij}-\bar{X}_{.}-\bar{Y}_{..})^2.$$

The error structure of this estimator is more complicated since the errors about regression of dam families in the same sire family are correlated, but when $s$ is large the variance reduces to

$$V(H_{bm}) = \frac{4[2-H+nH(1-H)+2(n-1)K]+(d-1)nH(1-H)}{4nsd} \qquad (17)$$

The covariance between $H_{bm}$ and $H_{ts}$ is not required in our subsequent analysis.

e) Pooled regression estimators ($H_{bp}$). It can be shown that $H_{bd}$ (from within sire families) is uncorrelated with both $H_{bs}$ and $H_{ba}$ (from between sire families). For a trait which is expressed in both sexes, it seems reasonable to assume that $H_{bd}$ and $H_{ba}$ contain all the information which can be obtained by regression. From these a pooled estimator, $H_{bp}$, can be obtained by substituting into (8), (9) and (10), but they simplify such that

$$\alpha = V(H_{ba})/[V(H_{bd}) + V(H_{ba})]$$

and

$$V(H_{bp}) = [1/V(H_{bd}) + 1/V(H_{ba})]^{-1},$$

since $H_{bd}$ and $H_{ba}$ are uncorrelated.

In limiting cases of family size, several of these regression estimators are the same. If $d = 1$ (i.e. one dam per sire), then $H_{bm} \equiv H_{ba} \equiv H_{bf}$ (the latter refers to full sib families, see section 2) and since there is no information on $H_{bd}$, it follows that $H_{bp} \equiv H_{bm}$ also. Our formulae are not precise if $s = 1$ (only one sire family), but it follows that there is no information on either $H_{bs}$ or $H_{ba}$ and $H_{bd} \equiv H_{bm} \equiv H_{bp}$.

iii) Pooled estimators from covariance of half sibs and regression

Estimators can also be obtained by pooling those from the covariance of half sibs and from one or more regression estimators. The appropriate method will depend on whether or not the trait is sex limited. For traits expressed only in males we define $H_{ps}$, which is a linear function of $H_{ts}$ (from the covariance of half sibs) and $H_{bs}$ (from the regression of progeny on sire). The optimal weighting and $V(H_{ps})$ are based on (8), (9) and (10). For traits expressed only in females, we define $H_{pd}$, which is a linear function of $H_{ts}$ and $H_{bd}$ (from the regression of progeny on dam), obtained by the same weighting procedure. If a trait is expressed in both sexes, we have suggested that all information from regression is included in $H_{bd}$ and $H_{ba}$ and these can be combined with $H_{ts}$ to form a pooled estimate $H_{pa}$, given by

$$H_{pa} = \alpha_1 H_{bd} + \alpha_2 H_{ba} + \alpha_3 H_{ts}$$

with $\sum_i \alpha_i = 1$ and the $\alpha_i$ chosen to minimise $V(H_{pa})$. The solution can

be shown to be as follows. Let $c_{ij}$ be the covariance between estimates $i$ and $j$, and let $A = c_{12} - c_{13} - c_{23} + c_{33}$, $B = c_{11} - 2c_{13} + c_{33}$ and $C = c_{22} - 2c_{23} + c_{33}$. Then

$$\alpha_1 = [(c_{33}-c_{23})A - (c_{33}-c_{13})C]/[A^2-BC]$$

$$\alpha_2 = (c_{33}-c_{13}-\alpha_1 B)/A, \quad \alpha_3 = 1-\alpha_1-\alpha_2$$

Of course, only estimates of the $c_{ij}$ are available, so exact weightings are not possible.

The sampling variances of these estimators are compared with those expected from ML methods in section 4.

iv) Maximum likelihood ($H_m$)

Consider the model in which observations are available on both sexes, so that a total of $s+sd+sdn$ measurements are made with the variance-covariance structure given by (11). However, as in the full sib case, it is useful to transform the observations into the following order for each sire family, say sire $i$:

$$X_i, \bar{Y}_{i.}, \bar{Z}_{i..}; \; Y_{i1}-\bar{Y}_{i.}, \bar{Z}_{i1.}-\bar{Z}_{i..}, \ldots, Y_{i,d-1}-\bar{Y}_{i.}, \bar{Z}_{i,d-1,.}-\bar{Z}_{i..};$$

$$Z_{i11}-\bar{Z}_{i1.}, \ldots, Z_{i1,n-1}-\bar{Z}_{i1.}, \; Z_{i21}-\bar{Z}_{i2.}, \ldots, Z_{id,n-1}-\bar{Z}_{id.} \quad .$$

Let this set of observations have variance-covariance matrix $\underset{\sim}{W}_i\sigma^2$, of dimension $1+d+dn$. Since $\underset{\sim}{W}_i$ is the same for all $i$, and sire families are uncorrelated, the overall variance-covariance matrix $\underset{\sim}{W}$ of dimension $s+sd+sdn$ is given by

$$\underset{\sim}{W} = \underset{\sim}{I} * \underset{\sim}{W}_i\sigma^2$$

We have

$$\underset{\sim}{W}_i = \begin{pmatrix} \underset{\sim}{S}_1 & 0 & 0 \\ 0 & (\underset{\sim}{I}-\frac{1}{d}\underset{\sim}{J}) * \underset{\sim}{S}_2 & 0 \\ 0 & 0 & \underset{\sim}{I} * (\underset{\sim}{I}-\frac{1}{n}\underset{\sim}{J})(1-\tfrac{1}{2}H-K) \end{pmatrix}$$

where, in the (2,2) block of $\underset{\sim}{W}_i$, $(\underset{\sim}{I} - \frac{1}{d}\underset{\sim}{J})$ is of dimension $d - 1$, and in the (3,3) block, $\underset{\sim}{I}$ is of dimension $d$ and $(\underset{\sim}{I} - \frac{1}{n}\underset{\sim}{J})$ of dimension $n-1$.

Also

$$\underset{\sim}{S}_1 = \begin{pmatrix} 1 & 0 & \frac{H}{2} \\ 0 & \frac{1}{d} & \frac{H}{2d} \\ \frac{H}{2} & \frac{H}{2d} & \frac{H}{4} + \frac{H}{4d} + \frac{K}{d} + \frac{1-\frac{1}{2}H-K}{nd} \end{pmatrix}$$

$$\underset{\sim}{S}_2 = \begin{pmatrix} 1 & \frac{1}{2}H \\ \frac{1}{2}H & \frac{1}{4}H+K+(1-\frac{1}{2}H-K)/n \end{pmatrix}$$

From the properties of direct products e.g.[Searle, (1966)] and utilising the special form of these "$\underset{\sim}{I} + \underset{\sim}{J}$" matrices [Searle (1970)] we obtain

$$\underset{\sim}{W}^{-1} = \underset{\sim}{I} * \underset{\sim}{W}_i^{-1}$$

$$\underset{\sim}{W}_i^{-1} = \begin{pmatrix} \underset{\sim}{S}_1^{-1} & 0 & 0 \\ 0 & (\underset{\sim}{I} + \underset{\sim}{J}) * \underset{\sim}{S}_2^{-1} & 0 \\ 0 & 0 & \underset{\sim}{I} * (\underset{\sim}{I}+\underset{\sim}{J})/(1-\tfrac{1}{2}H-K) \end{pmatrix}$$

and $|\underset{\sim}{W}| = |\underset{\sim}{S}_1|^{s} (\frac{1}{d^2}|\underset{\sim}{S}_2|^{d-1})^{s} [\frac{1}{n}(1-\frac{1}{2}H-K)^{n-1}]^{sd}$ .

Hence, the log likelihood can be shown to be

$$\text{Log } L = \text{constant terms} - \tfrac{1}{2}(s+sd+sdn)\log\sigma^2 - \tfrac{1}{2}s\log|\underset{\sim}{S}_1| - \tfrac{1}{2}s(d-1)\log|\underset{\sim}{S}_2|$$

$$-\tfrac{1}{2}sd(n-1)\log(1-\tfrac{1}{2}H-K) - \tfrac{1}{2}\sigma^2\Big[\sum_{i=1}^{s}(\underset{\sim}{x}-\mu\underset{\sim}{1})'\,\underset{\sim}{S}_1^{-1}(\underset{\sim}{x}_i-\mu\underset{\sim}{1})$$

$$+\sum_{i=1}^{s}\sum_{j=1}^{d}\underset{\sim}{W}_{ij}\,\underset{\sim}{S}_2^{-1}\,\underset{\sim}{W}_{ij}$$

$$+\sum_{i=1}^{s}\sum_{j=1}^{d}\sum_{k=1}^{n}(Z_{ijk}-\bar{Z}_{ij.})^2/(1-\tfrac{1}{2}H-K)\Big]$$

where $\underset{\sim}{x}'_i = (X_i, \bar{Y}_{i.}, \bar{Z}_{i..})'$, $\underset{\sim}{1}' = (1,1,1)$ and $\underset{\sim}{W}'_{ij} = (\bar{Y}_{ij} - \bar{Y}_{i.}, \bar{Z}_{ij.} - \bar{Z}_{i..})$.

Differentiation of the likelihood and obtaining expectations of the second partial derivatives are straightforward, and the results can be evaluated on a computer. The matrix $\underset{\sim}{P}$, of dimension, 4 x 4, has elements $P_{ij} = -E(\partial^2 \log L/\partial\theta_i\partial\theta_j)$, where we take $\theta_1 = \mu$, $\theta_2 = \sigma^2$, $\theta_3 = H$ and $\theta_4 = K$. The inverse of $\underset{\sim}{P}$ gives the sampling variances and covariances of the ML estimators.

If information is available only on females a total of $s(d + nd)$ observations is available. The sampling variances of the ML estimators are found in the same way, but the first row and column of $\underset{\sim}{S}_1$ together with the relevant terms in the observations which relate to information on sire performance, are deleted. Similarly, if there is no information available on females, there are $s(1 + nd)$ observations and the second row and column of $S_1$, the first row and column of $S_2$ and the appropriate observations are deleted.

When no parental data are available, deletion of the first and second rows and columns of $S_1$ and the first row and column of $S_2$ is required. In such a balanced design the estimates of variance components by the analysis of variance are minimum-variance quadratic unbiased (Graybill and Hultquist [1961]) and equal to the ML estimators after correction for bias with normally distributed observations (Graybill [1954]). Thus the large sample variances of heritability estimates by ML($H_m$) and intra-class correlation ($H_{ts}$) are the same when only progeny data are available.

Pooling of Sheridan et al's results

An example of the use of the theory developed in this section can be given by considering the alternative heritability estimates of Sheridan et al [1968]. From the same data they obtained estimates of $H_{ts}$, $H_{bd}$ and $H_{bs}$, for total abdominal and sternopleural bristle number in both male and female Drosophila melanogaster with a balanced hierarchical design of $s = 62$, $d = 3$ and $n = 10$. Using the method outlined in section 3(iii) we can obtain a single pooled estimate of heritability for each character in each sex. [In the absence of the original data it has not been possible to pool the male and female estimates, nor has it been possible to obtain an ML estimate]. We do this by firstly guessing a value for the pooled heritability which is then substituted as H into the equations for $V(H_{bd})$, $V(H_{bs})$, $V(H_{ts})$, $\text{cov}(H_{bd}, H_{ts})$, $\text{cov}(H_{bs}, H_{ts})$ and $\text{cov}(H_{bd}, H_{bs})$. The values thus obtained are substituted into the equations for $\alpha_1$, $\alpha_2$ and $\alpha_3$ to provide estimates of these three weights which are then used to obtain a second estimate of pooled heritability as

$$H_p = \alpha_1 H_{bd} + \alpha_2 H_{bs} + \alpha_3 H_{ts}.$$

The cycle is repeated until the estimate of $H_p$ stabilises.

TABLE 1. Results of analysis of data of Sheridan et al on abdominal and sternopleural bristle numbers in D. melanogaster.

| | | Total Abdominal | | Sternopleural | |
|---|---|---|---|---|---|
| | | Males | Females | Males | Females |
| Heritabilities & standard errors calculated by Sheridan et al | $H_{bd}$ (1) | 0.28 ± 0.09 | 0.21 ± 0.08 | 0.18 ± 0.08 | 0.26 ± 0.08 |
| | $H_{bs}$ (2) | 0.22 ± 0.10 | 0.40 ± 0.15 | 0.16 ± 0.09 | 0.18 ± 0.13 |
| | $H_{ts}$ (3) | 0.29 ± 0.13 | 0.67 ± 0.18 | 0.17 ± 0.08 | 0.29 ± 0.10 |
| Pooled H | | 0.26 ± .062 | 0.35 ± .065 | 0.17 ± .046 | 0.25 ± .050 |
| Expected | (1) | 0.093 | 0.094 | 0.072 | 0.074 |
| Standard | (2) | 0.097 | 0.102 | 0.078 | 0.085 |
| Errors | (3) | 0.123 | 0.139 | 0.076 | 0.092 |
| Expected | (1,2) | 0.00 | 0.00 | 0.00 | 0.00 |
| Sampling | (1,3) | -0.15 | -0.19 | -0.12 | -0.15 |
| Correlations | (2,3) | +0.39 | +0.47 | +0.34 | +0.43 |

This final estimate of $H_p$ is then used to obtain final estimates of the expected sampling variances and covariances, and hence the relevant sampling correlation coefficients. The results of these calculations, together with the estimates and standard errors of Sheridan et al, are presented in Table 1.

Each of the pooled estimates is seen to be weighted in favour of the separate estimates with lowest variance, and the standard error of each of the pooled estimates is lower than any of those of the separate estimates, as we would expect. The standard errors expected for each separate estimate are in reasonable agreement with those observed. It can also be seen that the expected sampling correlation between $H_{bs}$ and $H_{ts}$ is never greater than 0.47, and that the correlations between $H_{bd}$ and $H_{bs}$, and $H_{bd}$ and $H_{ts}$ are expected to be zero and slightly negative respectively. In view of these relatively low correlations, we should not necessarily expect good agreement among the estimates.

## 4. RELATIVE EFFICIENCY OF ESTIMATORS IN A HIERARCHICAL STRUCTURE

The relative magnitudes of the sampling variances of different heritability estimates from the same set of data depend, of course, on the design parameters, $n$, $d$ and $s$, and also the underlying parameters $H$ and $K$. Thus we can only compare the estimators for a few examples. All but one of the designs have been chosen such that for an inter-

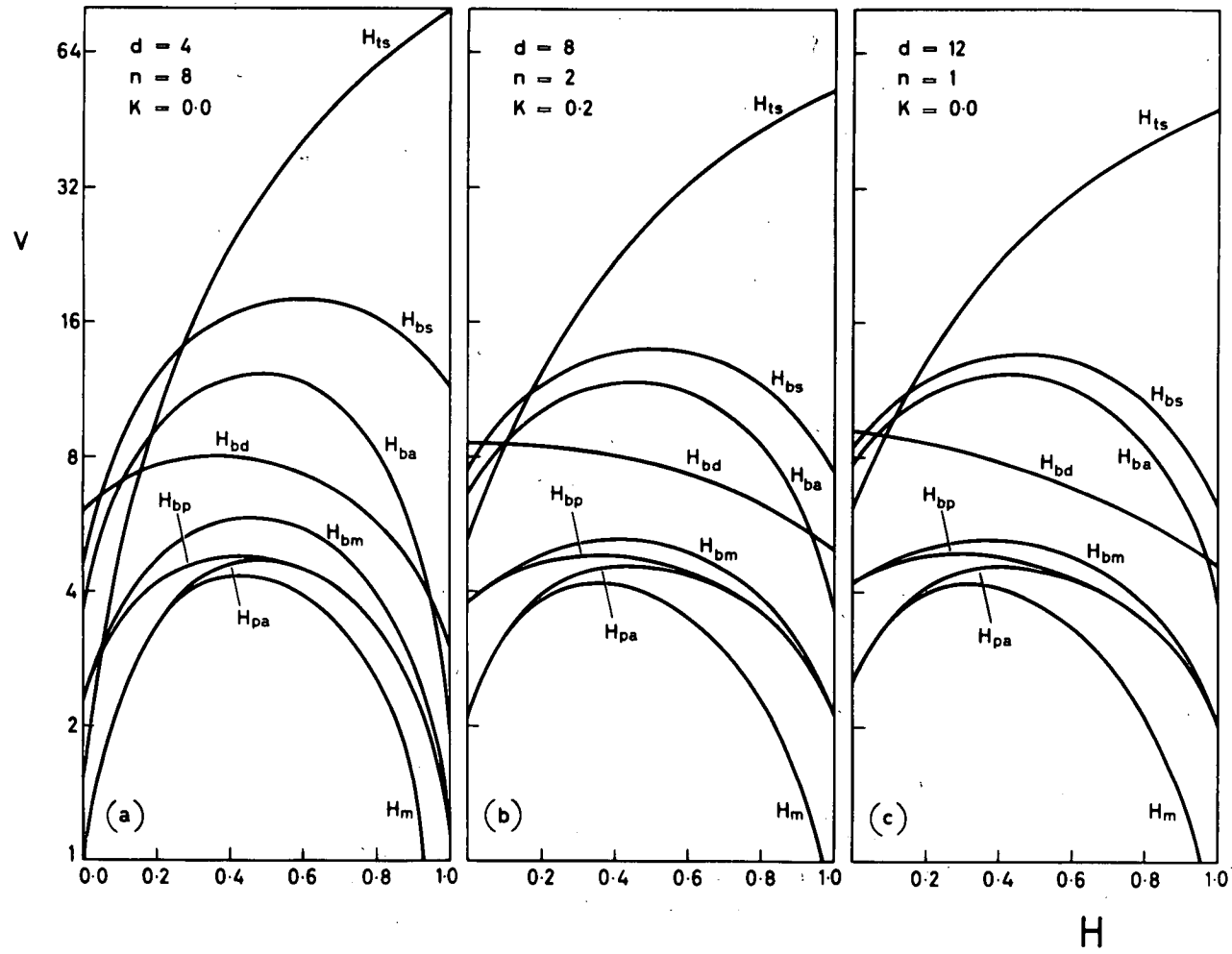


Figure 3. Sampling variance per observation (v) of alternative heritability estimators with half and full sib families of specified size on traits measured in both sexes: from half sib covariance ($H_{tss}$), from regression on sire performance ($H_{bs}$), on sire and mean dam performance ($H_{ba}$), on dam performance ($H_{bd}$) on mid parent ($H_{bm}$), using a pooled regression estimator ($H_{bp}$), a pooled estimator from regression and sib covariance ($H_{pa}$) and maximum likelihood ($H_m$).

mediate $\underline{H}$ value (0.2), they are the optimum for ML estimation, given a fixed total number scored, $\underline{T}$. The single exception is the design used for the comparison of estimators in Figure 3a. This design, which is far from optimum, has been chosen to illustrate that the conclusions drawn from comparisons are quite robust over different designs.

The results are given in Figures 3, 4 and 5 for traits in which both sexes are scored, only females are scored and only males are scored, respectively. In each case variances are expressed on a single observation basis, i.e. they are the inverses of the Fisherian information per observation. A large number of sires is assumed to be used, so that the variance of each estimator is inversely proportional to the number of sires. This assumption is less satisfactory for estimators such as the regression of progeny on sire ($\underline{H_{bs}}$) or the half sib intra-class correlation ($\underline{H_{ts}}$), for with only one sire available $\underline{H_{bs}}$ and $\underline{H_{ts}}$ cannot be estimated. Then the only unbiased information on heritability comes from the regression of progeny on dam ($\underline{H_{bd}}$), so the ML estimator ($\underline{H_m}$) must then have the same efficiency.

In Figure 3 and in other examples we have investigated in which the estimators can be compared, it is seen that $\underline{H_{bd}}$ has a considerably lower variance than the other single parent regression estimator $\underline{H_{bs}}$. Also $\underline{H_{ba}}$, the regression on sire and dam average, has a variance intermediate between the single parent regression estimators over most heritability values. The regression on mid parent $\underline{H_{bm}}$, is more efficient than $\underline{H_{bd}}$. The only intra-class correlation estimator which is unbiased, $\underline{H_{ts}}$, may be more efficient than any regression estimator at low heritabilities, but becomes

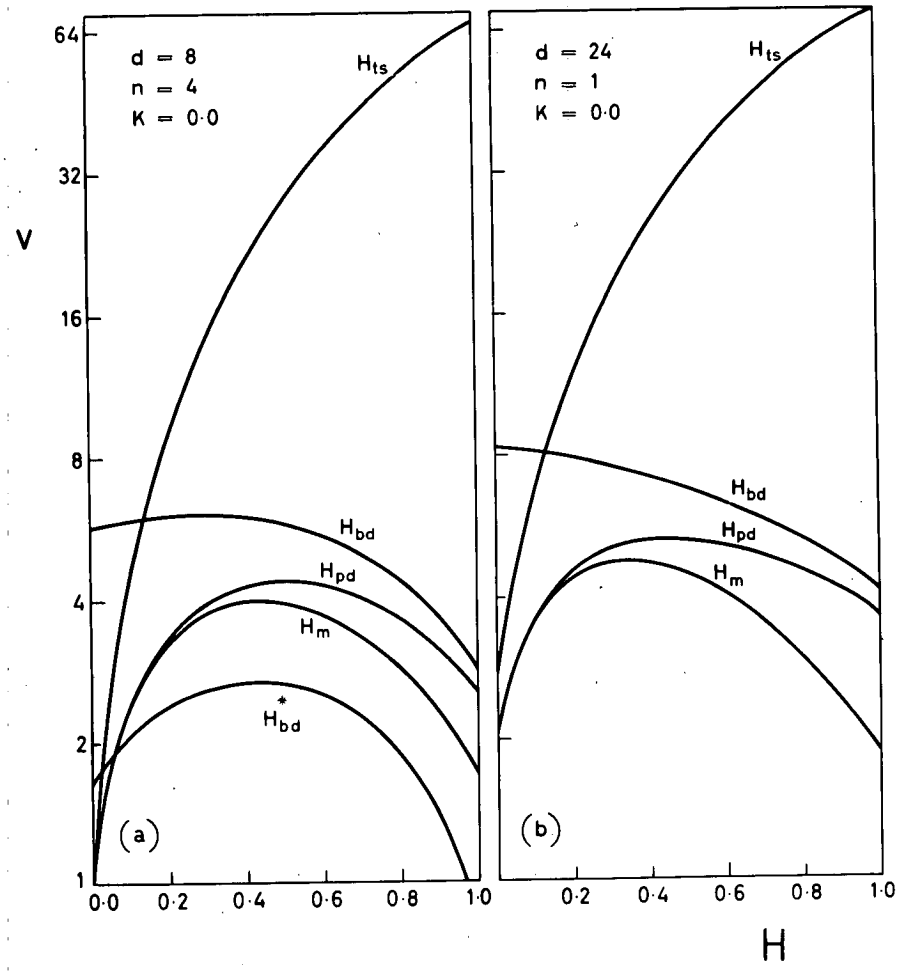


Figure 4. As Figure 3, but for traits recorded only on females, together with $H^*_{bd}$, estimated from regression on selected parents.

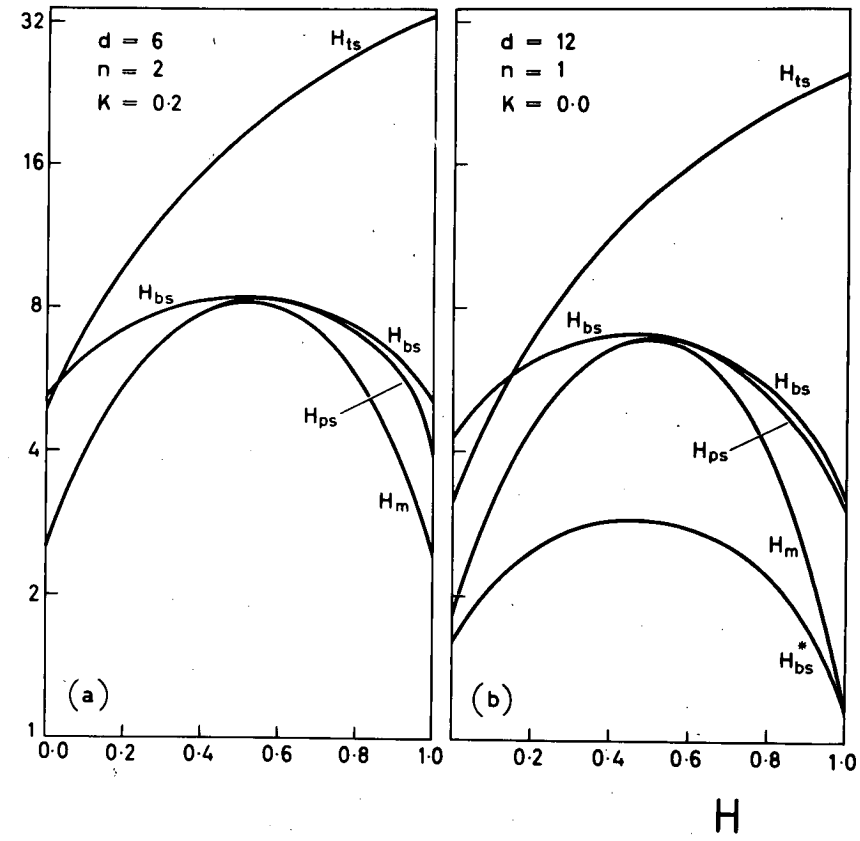


Figure 5. As Figure 3, but for traits recorded only on males, together with $H^*_{bs}$, estimated from regression on selected parents.

very much worse at high heritabilities. This was shown for some of the estimators by Robertson (1959). The variance of the maximum likelihood estimator, $H_m$, is much smaller than that of the best commonly used estimator, but the pooled estimators, $H_{bp}$, based only on regression estimators and $H_{pa}$ based on all estimators, are not much less efficient than $H_m$. At low heritabilities $H_{pa}$ and $H_m$ have almost the same sampling variance. A few assumptions need to be emphasised, however: the exact weightings for the pooled estimates could not be achieved exactly, the designs have been chosen to be near optimal for ML estimation without regard to their efficiency for other estimators, and the variances are expressed in terms of all observations in the experiment, $s + sd + sdn$. However $H_{ts}$ is based on $sdn$ observations, $H_{bs}$ on $s + sdn$ and $H_{bd}$ on $sd + sdn$. Thus, if the parents are not measured the values for $H_{ts}$ in Figure 3 could be reduced by the factor $dn/(1 + d + dn)$.

For sex limited traits scored only in females (Figure 4), the pooled estimator $H_{pd}$ is considerably more efficient than the simple regression estimator $H_{bd}$ and is as efficient as ML at low heritabilities. At higher heritabilities, $H_{pd}$ is little better than $H_{bd}$ and somewhat poorer than $H_m$. When the trait is scored only in males (Figure 5) similar conclusions hold for the regression estimator $H_{bs}$ rather than $H_{bd}$, and the pooled estimator $H_{ps}$ rather than $H_{pd}$.

In Figures 3, 4 and 5 examples are also given for designs in which only half-sib data is available (i.e. $n = 1$). In these it is assumed that $K = 0$, since there are no full sib families from which it can be estimated. The general patterns are seen to be very similar to those of the relevant full hierarchical structure shown in the same

figure.

As well as providing comparisons of efficiency of various heritability estimators, Figures 3, 4 and 5 also provide information of potential use in the planning of experiments to estimate heritability. Given an optimum sire family design, Figures 3, 4 and 5 can then be used to provide a direct indication of the total number of observations required to achieve an estimate of heritability with a particular variance. Suppose, for example, that we wished to obtain an estimate of $H_{bm}$ with a standard error of 0.1 for a character in which we expect both the heritability and $K$ to be around 0.2. Using Table 2, the optimum values of $d$ and $n$ are 8 and 2 respectively, and from Figure 3b, we see that $v^{*}$ 5 for $H_{bm}$ at $H = 0.2$ with this design. Since $v = T.V(H_{bm})$ and $T = s[1 + d(n + 1)] = 25s$ in this case, we have $V(H_{bm}) = \frac{5}{25s}$. But we want $V(H_{bm}) = 0.01$ which therefore requires $s = \frac{5}{25} \times \frac{1}{0.01} = 20$ sire families or a total of 500 observations over the two generations. More generally, a similar type of conclusion can be obtained by the use of the relevant equation in section 3, for any commonly used heritability estimator and for any particular combination of $H$, $K$, $d$ and $n$. Again it should be noted that such a conclusion will often be quite robust for a range of values of the parameters $H$ and $K$. In Figure 3b for example, it can be seen that our conclusion for $H = 0.2$ would equally apply to all values of $H$ between 0.2 and 0.6.

Some indication of the probable value of $K$ may be available from previous analyses, as is often the case with heritability. In terms of the model of section 3, we have $K = \frac{\frac{1}{4} V_D + V_{Ec}}{V_P}$, using the notation of Falconer [1960]. An indication of its probable value can

therefore be obtained as $\hat{K} = \frac{H_{td} - H_{ts}}{4}$, where $H_{td}$ is the half-sib heritability estimate based on the dam component of variance. Such an estimate must of course be interpreted with considerable caution, because of sampling errors involved in estimating $H_{td}$ and $H_{ts}$.

The optimum values of $d$ and $n$ for use in calculations such as those just outlined have been determined by Robertson [1959] for intra-class correlation estimates and by Latter and Robertson [1960] for regression estimates. Now that we have an expression for $V(H_m)$, we can examine the relative efficiencies of different experimental designs for ML estimation of heritability, and compare these optimum values of $d$ and $n$ with those relevant to the regression and intra-class correlation estimates.

## 5. OPTIMUM DESIGNS FOR HERITABILITY ESTIMATION

We now find optimum designs for ML estimation using both parent and progeny data, making the same assumptions as Robertson [1959] and Latter and Robertson [1960] of random mating among unselected parents. It has not proved possible to find the optimum designs for ML analytically so our results have been obtained by trial and error numerical evaluation of $V(H_m)$ on a computer. In all cases we define the optimum design as that giving the most information, i.e. $V(H_m)^{-1}$, per observation on either parent or progeny. Since the large sample variance of $H_m$ that we have to use is inversely proportional to $s$ (the number of sires) the optimum design depends only on $d$ and $n$.

TABLE 2. Optimum family structure ($d,n$) for maximum likelihood estimation of heritability in a hierarchical design with parents and progeny scored.

| K | H 0.05 | 0.10 | 0.20 | 0.40 | 0.60 | Sexes Scored |
|---|---|---|---|---|---|---|
| 0.00 | 11,8 | 8,5 | 5,4 | 3,3 | 3,2 | ♂ & ♀ |
| | 36,2 | 16,2 | 6,2 | 2,2 | 2,2 | ♂ |
| | 11,9 | 10,5 | 8,4 | 7,3 | 9,2 | ♀ |
| 0.05 | 22,4 | 13,3 | 6,3 | 3,2 | 3,2 | ♂ & ♀ |
| | 38,2 | 16,2 | 6,2 | 2,2 | 2,2 | ♂ |
| | 25,4 | 23,2 | 13,2 | 9,2 | 9,2 | ♀ |
| 0.20 | 44,2 | 20,2 | 8,2 | 4,2 | 3,2 | ♂ & ♀ |
| | 43,2 | 18,2 | 6,2 | 2,2 | 2,2 | ♂ |
| | 50,2 | 27,2 | 15,2 | 11,2 | 10,2 | ♀ |

For the heirarchical structure analysed in section 3, the optimum designs for ML estimation are given in Table 2 for a range of values of $H$ and $K$, and for characters measured either in both sexes or in males or females alone. The optimum values of $d$ increase if there is a decrease in $H$ or an increase in $K$. A similar trend is observed in $n$ at low $K$, but as the covariance between full sibs becomes increasingly inflated by maternal environment or non-additive genetic effects, the optimum value of $n$ soon reduces to 2, which is the lowest value of $n$ for which $K$ can be estimated. For characters scored only in males, the optimum design does not depend greatly on $K$, and at higher $H$ values is close to the optimum design for traits measurable

in both sexes. Only at high heritabilities does the optimum design for traits measured just in females differ greatly from that appropriate for both sexes. Thus it should be possible to select a design which provides a high degree of efficiency for the simultaneous estimation of heritability of several sex-limited and non sex-limited traits. Table 2 shows, however, that it is more difficult to find a suitable compromise for traits of widely differing heritability or maternal environment correlation. It can be seen in Table 2 that, for constant $\underline{H}$, the optimum value of nd does not depend greatly on $\underline{K}$. With both sexes scored, these optima are roughly 88, 40, 18, 7 and 6 for $\underline{H}$ = 0.05, 0.1, 0.2, 0.4 and 0.6 respectively. As a good approximation, the value of nd at the optimum is $4/\underline{H}$, giving $\underline{nd}$ = 80, 40, 20, 10 and 7 respectively. If only males are scored, the optimum for nd is $3/\underline{H}$ approximately, and if only females are scored it becomes $5/\underline{H}$ approximately.

These results do not differ greatly from those derived by Robertson [1959] for heritability estimation from the covariance of half sibs. He found that a dam family size ($\underline{n}$) of one with $\underline{d} = 4/\underline{H}$, approximately, to be the optimum. If both sire and dam intra-class correlations are to be estimated Robertson showed that the optimum value of $\underline{n}$ was $2/\underline{H}$, with $\underline{d}$ = 3 or 4. These values of $\underline{n}$ are slightly larger and $\underline{d}$ slightly smaller than those given in Table 2 for ML estimation using both parental and progeny data. As we have noted previously, the half-sib intra-class correlation estimator and the ML estimator are essentially the same when only progeny data are available, and so therefore are their respective optimum designs.

The optimum designs have also been found by computation for

cases in which both parents and progeny are measured, but where only half sib families (i.e. $\underline{n} = 1$) are available in the progeny generation. A value of $\underline{K} = 0$ has been assumed since it can not be estimated. The results are shown in Table 3, and it is seen that the optimum value of $\underline{d}$ (and hence $\underline{nd}$) is generally somewhat smaller than the optimum value of nd when both full and half sibs are available (Table 2). If only full sib families are available the optimum design if $\underline{K}$ is to be estimated is close to that given by Latter and Robertson [1959], presumably since all information on $\underline{H}$ comes from regression of offspring on parent.

TABLE 3. Optimum half-sib family size ($\underline{d}$) for maximum likelihood estimation of heritability where observations are available on parents and half-sib progeny only.

| $\underline{H}$ | | | | | |
|---|---|---|---|---|---|
| 0.05 | 0.10 | 0.20 | 0.40 | 0.60 | Sexes Scored |
| 71 | 31 | 12 | 5 | 4 | ♂ & ♀ |
| 70 | 30 | 10 | 4 | 4 | ♂ |
| 82 | 43 | 24 | 15 | 14 | ♀ |

Many of the optimum designs shown in Tables 2 or 3 may be impracticable, especially those requiring large values of $\underline{d}$. However, apparently large departures from the optimum design often involve only a small reduction in the amount of information per observation. Some examples to illustrate this are given in Figure 6; similar results have been found for other combinations. We see that for a trait

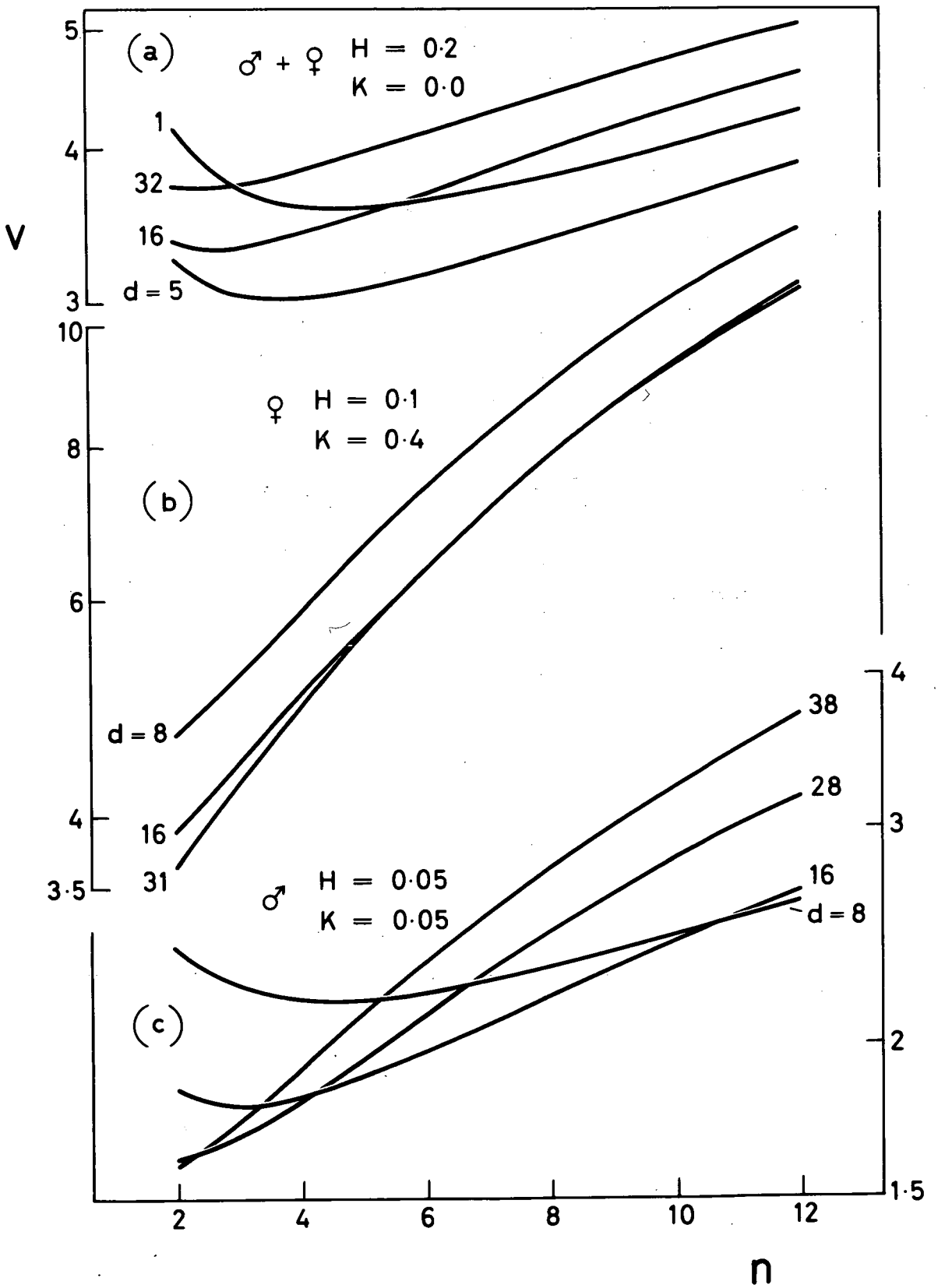


Figure 6. Sampling variance per observation (v) of an ML estimator of heritability for different family sizes, records on both sexes (a), only females (b), or only males (c).

scored only in females with a low $\underline{H}$ and high $\underline{K}$, a reduction in $\underline{d}$ from the optimum of 31 down to 16 increases the variance per observation by only 6% if $\underline{n}$ remains at 2.

Although tables 2 and 3 give the optimum designs when there is prior knowledge of $\underline{H}$ and $\underline{K}$, there is also need to specify designs likely to be efficient over a wide range of parameter values when this prior knowledge is absent. We find that a satisfactory design has a dam family size ($\underline{n}$) of 2, and 6 dams per sire ($\underline{d}$) for characters scored in both sexes or in males alone and 12 dams per sire for characters scored only in females. If only parental and half sib information is available ($\underline{n} = 1$), then the optimum number of dams per sire is around 12 and 24 respectively. When only parental and full sib data are available ($\underline{d} = 1$), a full sib family size of 3 is efficient over a wide range of parameters.

## 6. DISCUSSION

Let us first review our more important assumptions and consider their implications. The omission of a term for dominance or common environment ($\underline{K}$) in the full sib model was made primarily to enable simpler demonstration of the principles; it can not be defended too strongly in practice. We also ignored any environmental covariance of dam and offspring in the hierarchical case. Such covariances certainly exist, for example in litter size in mice (Falconer [1955]). It would not be difficult to include such a term in the model; then all the unbiased information on heritability would come from the regression of progeny on sire (only for traits expressed

in males) and the covariance of half sibs, whose properties have been analysed in section 3. The assumptions of equality of means and variances in the two generations and sexes are likely to have biased the sampling variances downwards, but few degrees of freedom would be lost in their estimation. Experiments from which heritability estimates are obtained are rarely balanced, except perhaps in Drosophila. Removal of this assumption should introduce no conceptual difficulties in ML estimation, but would make the form of the variance-covariance structure of the alternative regression and sib covariance estimators rather involved. The mechanics of the ML estimation procedure have not been considered, but a specific program for this sort of data has been written [Felsenstein, personal communication] and there are many general programs for finding maxima.

Throughout we have assumed that there is no selection or assortative mating of the parents, yet both can give much reduced sampling variances of regression estimators in a properly designed experiment (Hill [1970]). Two examples are given for sex-linked traits in Figures 4(a) and 5(b), with the optimum designs appropriate for selection of parents with $\underline{H} = 0.2$, the same value used to choose the design for ML estimation. In Figure 4(a) we have used $\underline{n} = 14$ and a proportion of 5.5% of potential female parents selected (from Hill [1970]). The estimator of regression of progeny on selected parents, $H^*_{bd}$, has a variance approximately half of the ML estimator, $\underline{H_m}$, per individual scored, except at very low heritabilities. Similarly, in figure 5(b), selection of males gives an estimator, $\underline{H^*_{bs}}$, with substantially lower sampling variance than $\underline{H_m}$, particularly at intermediate heritabilities. Thus where selection can be practised,

we advocate that it be done. Even then there will be some information available from the variance between families. Maximum likelihood methods which could deal with such data have been developed by Thompson [1973].

There are several situations where selection or assortative mating of the parents may not be desirable, however. One such case is a control population being maintained for several generations alongside selected populations to establish whether trends are genetic or environmental. Usually no selection is practised in these, but if selection or assortative mating were practised in a control it would be to reduce rather than inflate the variance between parents (Hill [1972]), and would reduce the efficiency of heritability estimators. The other main case where neither selection nor assortative mating is desirable is where heritabilities and genetic correlations are to be estimated simultaneously on several traits.

We make two essential recommendations. Firstly, people obtaining estimates of heritability by several methods from essentially the same set of data should take note of the correlation structure among their estimates before concluding that agreement between them is good or bad. Secondly, all available data should be used to obtain a single estimate; we have considered just pairs of generations, but in a control population several generations might be combined.

SUMMARY:

The analysis and design of experiments to estimate heritability when data are available on both parents and offspring are discussed. It is shown that there is a substantial positive sampling correlation

between the regression of offspring on mid-parent and the covariance of full sibs estimated from the same data, and that in a hierarchical structure the covariance of half sibs has a negative correlation with the regression of offspring on dam and a positive correlation with the regression of offspring on sire.

The efficiency of alternative estimators of heritability by regression and sib covariance, pooled estimators based on these and maximum likelihood (ML) are compared. The ML estimator does not reduce the variance substantially below that from the pooled estimators, but both are often much better than either regression or sib covariance estimators alone.

The optimum designs of experiments for ML estimation are obtained. It is found that these do not differ very much from those appropriate for either offspring on parent regression or half sib covariance estimators, and that optimum designs are fairly robust against changes in parameter assumptions.

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