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The founder effect and response to artificial selection

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SUMMARY

The response to selection in any line depends on the size of the initial sample by which the line is founded. For a single locus with additive gene action the effects of number of founders on early rate of response and on final limits are studied in relation to selection intensity and number of parents in the selected line. The reduction in total response caused by a small number of founders is greatest for large populations under intense selection, especially when the desirable alleles are rare in the base population. If these alleles are at high frequencies it is possible that a line which has gone through a bottleneck may be more sensitive to a reduced population size during subsequent selection than a line which has not. Under some conditions replicate selection lines founded with small samples are likely to be less variable in response than lines founded with moderately large samples.

INTRODUCTION

It has long been recognized that random fluctuations may lead to changes of gene frequency. This phenomenon has been extensively studied by Wright since his classic paper (1931) and by others. There has been disagreement over its importance in the evolution of natural populations, but there can be no doubt of its influence on the results of laboratory experiments in quantitative genetics. In such experiments population sizes are typically small and the results must be interpreted in the light of the effects of random genetic drift.

The effects of restricted population size on limits of response to artificial selection have been analysed by Robertson (1960) for a single locus, and by Latter (1965) and by Hill & Robertson (1966) for pairs of linked loci.

Random sampling effects may conveniently be divided into two classes: those which depend on the initial sample ('founder effects'), and those consequent upon a continued restriction of population size during selection. Robertson (1960) briefly discussed some aspects of the interaction of these factors, and in a later paper (1966) described some experimental results for selection lines which had been subjected to a severe initial restriction in population size. In this paper I give a rather more detailed treatment of the problem than that of Robertson.

These questions are of some practical importance in plant and animal breeding, especially when a new breed or species is introduced to a country. The initial

introduction may well be of only a small number of individuals. In such circumstances one would like to know how response to subsequent selection will be affected by the number of founders.

THE GENETIC MODEL

The analysis will be of selection at a single locus and most attention will be given to the case of additive gene action. For unlinked loci with no epistasis, these results may be applied to polygenic traits in the usual way by taking the selection coefficient at a locus as the product of the standardized selection differential and the effect of the locus measured as a proportion of the phenotypic standard deviation (Falconer, 1960, p. 206).

We consider a very large random mating base population in which a locus is segregating for two alleles A_1 and A_2, the frequency of the allele A_2 being p. From this base population lines are started by taking a random sample of n individuals from whose progeny selection is begun. During the selection phase the effective population size is N and the selective values of the three genotypes are

A_1A_1	A_1A_2	A_2A_2
$1-\frac{1}{2}s$	1	$1+\frac{1}{2}s$.

This model should give a reasonably accurate description of the effect of selection on a locus with additive effects on a quantitative character.

THE RATE OF RESPONSE IN THE FIRST GENERATION

For the above model the rate of response to selection in a large population with gene frequency x is given with sufficient accuracy by

$$\Delta x = \tfrac{1}{2}sx(1-x),$$

provided s is not too large. In a sample of n individuals from the base population the number of A_2 alleles will have a binomial distribution with probability p and index $2n$. If we let x be the frequency of A_2 in such a sample, then x will also be the gene frequency in a very large group of progeny produced by the members of the sample, and the response to selection in such a large progeny group will be given by the above equation. We may find the average response over all such samples by using the moments of the binomial distribution to obtain

$$E(\Delta x) = \tfrac{1}{2}sp(1-p)\left(1-\frac{1}{2n}\right).$$

Thus for selection among large numbers of progeny produced by samples of size n the expected rate of response in the first generation is proportional to $(1-[1/2n])$.

Similarly we may use the moments of the binomial distribution to find the variance of the selection response between initial samples. This gives the result

$$\text{var }(\Delta x) = \frac{1}{8n}\left(1-\frac{1}{2n}\right)p(1-p)s^2\left[\left(1-\frac{1}{2n}\right)(1-2p)^2+\frac{1}{n}p(1-p)\right].$$

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If we write $C^2 = \text{var}(\Delta x)/[E(\Delta x)]^2$ so that C is the coefficient of variation of response rate,

$$C^2 = \frac{(1-2p)^2}{2np(1-p)} + \frac{1}{2n^2(1-[1/2n])}.$$

The coefficient of variation is least when $p = 0{\cdot}5$ and rises as p departs from this value.

Next we consider the variation in rate of response between replicate lines, each with an effective number of parents equal to N, taken from the same initial sample. Kojima (1961) showed that for an initial sample with gene frequency x the variance of response was given by

$$\frac{1}{2N} x(1-x)[1+\tfrac{1}{2}s(1-2x)].$$

The expected variance between replicate lines within founder groups may then be found by averaging this expression over all initial samples. Since for such binomial samples

$$E[x(1-x)] = p(1-p)\left(1-\frac{1}{2n}\right),$$

$$E[x(1-x)(1-2x)] = p(1-p)(1-2p)\left(1-\frac{1}{2n}\right)\left(1-\frac{1}{n}\right),$$

we find the variance to be

$$\text{var}\,(\Delta x) = \frac{1}{2N} p(1-p)\left(1-\frac{1}{2n}\right)\left[1+\tfrac{1}{2}s(1-2p)\left(1-\frac{1}{n}\right)\right].$$

This component of variance would usually be rather larger than the component of variance between initial samples, especially when s is small. If selection lines are founded from separate and independent samples the variance in rate of response will be the sum of the two components. The variance would be dominated by the within founder group component except when loci with large s values were involved. For example, when $p = 0{\cdot}5$ the ratio of the between to the within initial sample component is $Ns^2/16n^2$.

SELECTION LIMITS

Of perhaps greater interest is the effect of a small number of founders on limits to selection response. Robertson (1960) gave results for an initial sample of one pair and also for three generations of single pair matings before selection began. We now consider an arbitrary initial sample size.

If a selection line is taken from an initial sample in which the favoured allele has frequency x then, as shown by Kimura (1957), the chance of fixing the desirable allele under our model is

$$u(x) = \frac{1-e^{-2Nsx}}{1-e^{-2Ns}}.$$

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We must find the expected value of $u(x)$ for samples of size n from a population with gene frequency p. Denoting this as $u_n(p)$ we have

$$u_n(p) = \frac{1-E(e^{-2Nsx})}{1-e^{-2Ns}}.$$

Now

$$E(e^{-2Nsx}) = \sum_{j=0}^{2n} \binom{2n}{j} p^j (1-p)^{2n-j} e^{-2Nsj/2n},$$

$$= (1-p+pe^{-Ns/n})^{2n},$$

and consequently

$$u_n(p) = \frac{1-(1-p+pe^{-Ns/n})^{2n}}{1-e^{-2Ns}}.$$

The limit of this expression as $n \to \infty$ is Kimura's result, as of course it should be.

For small values of Ns a power series expansion is

$$u_n(p) = p + Nsp(1-p)\left(1-\frac{1}{2n}\right) + \ldots,$$

showing that the total response is approximately $2N$ times the initial response, as was shown by Robertson (1960) in the absence of a founder effect. For small values of Ns the founder effect is to reduce the total genetic gain by a fraction $1/2n$. For large values of Ns we take the limit as $Ns \to \infty$ and obtain

$$u_n(p) = 1-(1-p)^{2n}.$$

This is intuitively obvious, since if Ns is large the favoured allele will be fixed if it occurs in the initial sample, for which the probability is $1-(1-p)^{2n}$. In this case if p is small and n not large $u_n(p) \simeq 2np$. The selection limit for rare alleles is thus much more strongly influenced by number of founders when Ns is large than when Ns is small.

The precise treatment of recessive genes is much more difficult, but a little may be deduced easily. When Ns is very large the favoured recessive will be fixed if included in the initial sample so that $u_n(p)$ will be the same as for additive genes. For a given initial sample with frequency x for the desirable recessive allele, the chance of fixation given by Kimura (1957) may be expanded in a power series for small Ns values to give

$$u(x) = x + \tfrac{2}{3}Nsx(1-x^2) + \ldots.$$

Averaging this over all initial samples of size n gives

$$u_n(p) = p + \tfrac{2}{3}Nsp(1-p^2)\left(1-\frac{1}{2n}\right)\left(1+\frac{1-2p}{2n(1+p)}\right) + \ldots.$$

For $p = 0{\cdot}5$ the total gain is a fraction $(1-[1/2n])$ of that from a large founder group; for very small p the fraction is $(1-[1/4n^2])$; and for p near to 1 the fraction is nearly $(1-[3/4n])$. Thus for small Ns values the founder effect on response due

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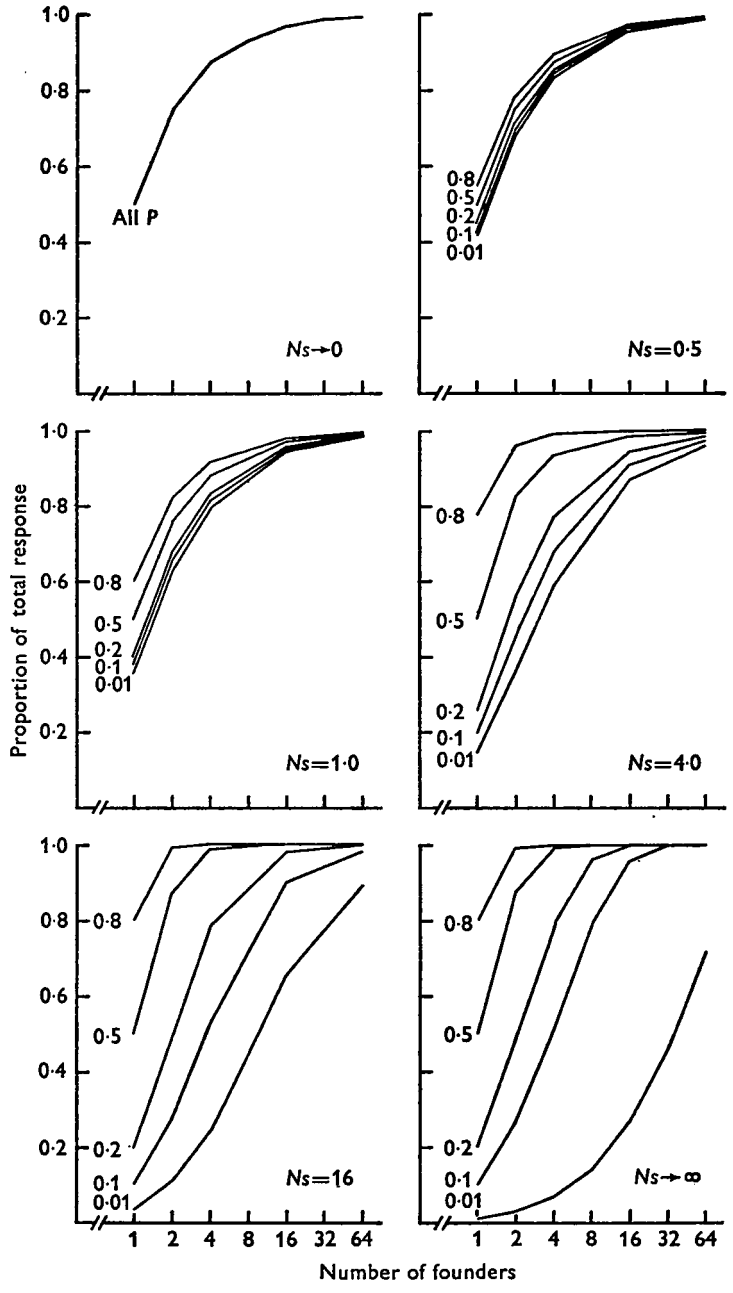

Fig. 1. Total selection response for a given number of founders as a fraction of that for an infinite number. Curves are drawn for base population gene frequencies of 0·8, 0·5, 0·2, 0·1 and 0·01.

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to recessive alleles resembles that for additive alleles. The same is true for large Ns values, but no results have been found for intermediate values.

We return now to further consideration of the chance of fixation at an additive locus. It is convenient to work with the ratio

$$w_n(p) = \frac{u_n(p)-p}{u_\infty(p)-p},$$

which is the average total gain from a group of n founders as a fraction of that expected from an infinitely large founder group under the same conditions of selection. It is thus a useful measure of the limitations on total gain which are imposed by a reduction in the initial sample size, and we now consider its behaviour as p, Ns and n vary.

When Ns is small

$$w_n(p) \simeq 1-\frac{1}{2n},$$

while for large values of Ns

$$w_n(p) \simeq 1-(1-p)^{2n-1}.$$

For a range of values of n, p and Ns the values of $w_n(p)$ have been calculated and the results are presented in Fig. 1.

Table 1. *Total selective gain for a given value of* Ns *as a fraction of that when* Ns = ∞

(n is the initial sample size, p the gene frequency in the base population.)

					n		
Ns	p	1	2	4	16	64	∞
0·5	0·01	0·2449	0·1344	0·0715	0·0208	0·0080	0·0058
	0·1	0·2449	0·1451	0·0910	0·1561	0·0556	0·0562
	0·5	0·2449	0·2105	0·2164	0·2374	0·2430	0·2449
	0·8	0·2449	0·2826	0·3191	0·3468	0·3535	0·3557
4	0·01	0·9640	0·8214	0·5870	0·2205	0·0906	0·0676
	0·1	0·9640	0·8349	0·6539	0·4752	0·4898	0·5010
	0·5	0·9640	0·9062	0·9120	0·9536	0·9617	0·9640
	0·8	0·9640	0·9642	0·9839	0·9918	0·9930	0·9934

For low values of Ns, $w_n(p)$ is little affected by gene frequency. But when Ns is high $w_n(p)$ is very sensitive to differences in gene frequency, the founder effect being particularly drastic for alleles rare in the base population. For alleles common in the base population ($p \geqq 0{\cdot}5$) $w_n(p)$ is less affected by number of founders when Ns is large than when Ns is small, while the opposite is true when p is small.

Another way of looking at the results is to ask how the fraction of the possible total advance varies with Ns for a given initial sample size. To do this we consider the function

$$v_{Ns}(p) = \frac{u_n(p)-p}{1-p-(1-p)^{2n}}.$$

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The possible advance is $1-p$ except for the $(1-p)^{2n}$ cases where the desirable allele is not included in the initial sample, hence the denominator of $v_{Ns}(p)$.

Table 1 gives the results of a few calculations. It can be seen from the table that $v_{Ns}(p)$ does not change very markedly with n when the desirable allele is common in the base population, but declines appreciably as n increases if the favoured allele is rare in the base population. The value of Ns which is required in order to obtain a given fraction of the possible response is thus greatest for large initial samples from a base population in which the favoured allele is rare.

VARIATION BETWEEN LINES AT FIXATION

Selection lines obtained by the same procedure from one base population will vary in total response both because different initial samples are used and because of different sampling accidents during selection. For independent lines the variance between lines at the limit is given by the binomial sampling variance

$$u_n(p)[1-u_n(p)].$$

This variance is greatest when $u_n(p) = 0{\cdot}5$. One result of this is that under some conditions replicate selection lines founded by fairly large groups may respond more variably than similarly selected lines founded by only a few individuals. For example, when $p = 0{\cdot}01$ and Ns is large the between line variance is greatest when $n = 34$. Thus in selection for a trait whose response depends mainly on loci of large effect where the desirable allele is rare, the results may be more variable in lines founded by a moderate number of individuals than in lines founded by very few or very many. The reason is simply that in initial samples of moderate size appreciable proportions would include and fail to include the favoured alleles. Virtually all very small samples would fail to include them while virtually all very large samples would include them.

AN EXAMPLE

Dr D. E. Robertson has kindly allowed me to quote some of his data which are relevant to the above considerations. A full account of the experiment is to be published later. From the Canberra base population (Latter, 1964) a number of initial samples were taken, some consisting of one pair ($n = 2$), some of five pairs ($n = 10$) and some 20 pairs ($n = 40$). From each founder group two samples of progeny were taken. One was at once subjected to selection, and the other was kept for five generations of random mating with 40 pairs of parents and then selected in the same way as the first sample. All lines were selected for high sternopleural bristle number on the left side at an intensity of 20%. Some lines had five pairs of parents per generation ($N = 10$) and some 20 pairs ($N = 40$). The number of replicate lines varied between treatments. After 30 generations of selection (i.e. after generation 35 in the lines with a lag period) selection was discontinued, although some lines appeared to be still responding. In Table 2 the mean increase

in bristle number, averaged over both sexes, is given for each treatment. I shall take these values as approximating to relative values of selection limits. The lag period had no consistent effect so I shall discuss averages over lag and direct selection lines.

Clearly N has had a marked effect on the limits. But the number of founders seems to have had an appreciable influence only when $N = 10$ and not when $N = 40$. Alternatively, we might say a reduction in N has had more serious consequences for small than for large founder groups. Can such results be explained in terms of the theory given above?

Table 2. *Gains in sternopleural bristle number from* 30 *generations of selection*

(n is the number of founders, N the number of selected parents. Direct lines were selected at once, lag lines after five generations of random mating.)

n	N	Replicates	Direct	Lag	Average
2	10	8	2·3	2·8	2·6
	40	6	8·6	5·8	7·2
10	10	6	4·6	4·5	4·6
	40	4	7·5	6·9	7·2
40	10	6	3·4	4·6	4·0
	40	4	6·5	6·1	6·3

From Fig. 1 we see that for loci with high values of p, the proportion of possible response which is achieved is less sensitive to number of founders at high Ns values, than at low Ns values. This suggests as an interpretation that most of the response was obtained from loci at which the desirable alleles were common in the base population. For example if we take $p = 0{\cdot}8$ we can calculate selection gains as $u_n(0{\cdot}8)$–$0{\cdot}8$. For $n = 2$ and 16 and $Ns = 1$ and 4 the gains are

	$n = 2$	$n = 16$
$Ns = 1$	0·1016	0·1206
$Ns = 4$	0·1913	0·1984

Without pressing the comparison too far we may note that in relative value these are somewhat similar to the observed pattern. An explanation along these lines is thus possible. However, Mr Robertson tells me there is evidence that a good deal of the response is due to alleles rare in the base population. It is therefore not clear that the theory presented here can provide a valid explanation.

DISCUSSION

Perhaps the most striking feature of the theory is the way in which the founder effect varies with the subsequent level of selection pressure as measured by Ns. This is especially marked for rare desirable alleles. For such alleles, especially at loci of large effect, a bottleneck will have drastic effects on the limits if thereafter

selection lines have many parents which have been intensely selected. The effect will be much less drastic if selected lines are maintained by only a few parents under mild selection. On the other hand, when the favoured alleles are common, a bottleneck will affect limits less in large intensely selected lines than in small mildly selected ones.

Robertson (1960) wrote: 'Highly selected populations or those which have passed through a severe "bottleneck" in population size will be tolerant of any further size restrictions in the sense that the desirable alleles will be harder to lose because, if they are present at all, they will have a reasonable frequency.' This is certainly so if one is thinking of favourable alleles which are rare in the base population. But if the statement is interpreted as suggesting that once a line has gone through a bottleneck subsequent selection may safely be done with small numbers, our theory shows this interpretation to be incorrect, since in at least some cases a line would be more sensitive to such a reduced Ns value than it was before the bottleneck.

The reason for this is not hard to see. If an allele is very common before the bottleneck then it will probably be included in all samples, even small ones. Intense selection in large populations thereafter should fix the favoured allele in nearly all cases. Mild selection in small populations thereafter has a high probability of fixing the desirable allele in samples in which its frequency is high, but not in samples in which its frequency is, by chance, low. Only in small samples will the frequency be likely to fall sharply, so they will be more seriously affected than large samples. In a sense this is Robertson's argument looked at from the other side, with the rare allele being now the unfavourable one.

Leaving the subject of bottlenecks for the moment, let us suppose a line had been selected for some time and that the frequency of a desirable allele had reached 0·8 in the line. If at this point the line is subdivided and one replicate is continued with $Ns = 4$ while a second is run with $Ns = 1$, the respective probabilities of fixation are 0·9987 and 0·9230. The relative further gains are thus 0·1987 and 0·1230 so that the line with smaller Ns value achieves only 60% of the further response of that with $Ns = 4$. This may be relevant to the interpretation of results reported by Jones, Frankham & Barker (1968). From lines which had been selected for 16 generations with 40 pairs of parents they took lines with 10 pairs of parents selected at the same intensity while continuing the 40-pair lines. In all three cases the 10-pair lines gave a good deal less further response than the 40-pair lines over the next 30 generations. Discussing this, the authors wrote: 'Robertson also suggested that restricting population size after a number of generations of selection would have little effect on the total response... Thus there were desirable genes still at low frequencies.' Though this conclusion may well be true it does not necessarily follow from the observations.

An alternative explanation would be that all loci of large effect had become fixed, and only loci of small effect remained segregating. Subsequent response from such loci would be highly susceptible to reduction in the value of Ns.

It is of course possible in such a situation that a high proportion of the total

response obtainable from the foundation sample has been achieved when the restriction is imposed, and that the loss of response due to the reduction in number of parents is a small fraction of this total response. However, in animal breeding practice the important question is not 'how far have we come?' but rather 'how far can we go?'

The present theory suggests that the effect of a bottleneck on limits to selection may be severe or mild, depending on gene frequency and on the subsequent selection programme. It is, moreover, a single locus theory, and it is important to know the extent to which the results are affected when selection acts on linked systems of genes. A general analysis of this problem raises very considerable difficulties which will probably require extensive simulation studies for their elucidation.

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