The interaction between effective population size and linkage intensity under artificial selection

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1. INTRODUCTION

The elegant mathematical theory developed by Kimura (1957) and Robertson (1960) has greatly increased our understanding of the long-term effects of artificial selection in finite populations. Under a régime of directional selection in which a proportion, P, of the population is selected each generation on the basis of individual performance, the expected total response can readily be determined for a system of independent loci each with two alleles. For an additive locus with alleles A_1, A_2 at initial frequencies p_1, p_2 the probability of ultimate fixation of the homozygote favoured by selection, which we shall assume to be A_2A_2, has been shown by Kimura (1957) to be

$$u(p_2) = [1 - \exp(-2vp_2)]/[1 - \exp(-2v)] \tag{1}$$

where $v = N\bar{\imath}a/\sigma$, N denoting the effective size of the breeding population each generation, $\bar{\imath}$ the standardized selection differential, and a/σ the proportionate effect of the locus as defined by Falconer (1960). The outcome of the selection process depends on the relative magnitudes of the directional changes in gene frequency, viz. $\frac{1}{2}\bar{\imath}(a/\sigma)q(1-q)$ per generation for an allele of frequency q, and the random changes in frequency due to genetic sampling, with an expected variance of $\frac{1}{2}q(1-q)/N$ (Robertson, 1960).

However, comparatively little is known of the quantitative effects of linkage on these selection limits predicted for independent loci, and our understanding of the behaviour of linked loci under selection in finite populations is far from complete. The particular case of a pair of identical loci of additive effect, initially in linkage equilibrium, has been examined by Latter (1965 *b*) in a computer simulation study. Linkage was shown to be responsible for a reduction in the mean response realized under long-term selection, but the effect was appreciable only for pairs of loci of fairly large effect at recombination values of 0·10 or less. When the effective population size was such as to reduce the expected response by 40% or more under free recombination, due simply to the effects of genetic sampling, the additional reduction due to linkage was considered to be unimportant for pairs of genes separated by as little as five map units.

In the present paper it is proposed to explore this symmetric model in far greater detail, and to discuss the essential features of the behaviour of linked genes of equal effect under selection in finite populations. The study has been restricted to combinations of parameter values which can give rise to marked linkage effects, i.e. to a consideration of genes of large effect under moderately intense selection pressure, the initial gene frequencies being such that approximately 70% of the potential response would be realized under selection in the absence of linkage. In this context, an approximate algebraic description can be given of the interaction between population size and linkage intensity in the determination of ultimate response. It must be stressed, however, that the formulae represent no more than a first step towards the development of a rigorous theory.

2. NUMERICAL RESULTS

The main experiment to be discussed in this paper involves twenty regimes, four population sizes in the range $N = 5$–40 having been tested in all possible combinations with five recombination values ranging from 0 to 0·5. The computer programme was the same as that described by Latter (1965 b). A selection intensity of $P = 0·10$ was imposed on all the simulated populations in this study, and the proportionate effect of each of the two loci was set at $a/\sigma = 0·5$. The loci were taken to be initially in linkage equilibrium with alleles A_1, A_2 and B_1, B_2. The recombination value has been denoted by y, and the initial frequency of the 'plus' alleles A_2 and B_2 by p_2.

The convention has been adopted of measuring total response to selection as a fraction R of the maximum possible advance, viz. $1 - p_2$. The total response due to unlinked genes (R^*) is expected to be

$$R^* = [u(p_2) - p_2]/(1 - p_2)$$

where $u(p_2)$ is given by equation (1). Initial gene frequencies have been chosen so that $R^* = 0·70$ for all population sizes, earlier studies having shown this to be the region of maximal linkage effects in small populations (Latter, 1965 b). This has the advantage that we are setting out to compare a number of regimes which are known to be equivalent as regards total response under free recombination. However, it is

Table 1. *The observed total response to selection expressed as a proportion of the maximum possible advance*

	Observed response (R)			
Recombination value (y)	$N = 5$ $p_2 = 0·156$	$N = 10$ $p_2 = 0·073$	$N = 20$ $p_2 = 0·035$	$N = 40$ $p_2 = 0·017$
0·00	0·541 ± 0·010	0·508 ± 0·008	0·484 ± 0·007	0·462 ± 0·006
0·01	0·564 ± 0·010	0·574 ± 0·009	0·609 ± 0·010	0·662 ± 0·010
0·05	0·605 ± 0·011	0·634 ± 0·010	0·679 ± 0·010	0·689 ± 0·010
0·10	0·635 ± 0·011	0·644 ± 0·010	0·688 ± 0·010	0·671 ± 0·010
0·50	0·669 ± 0·011	0·693 ± 0·011	0·698 ± 0·010	0·691 ± 0·010

essential in discussing the observed responses that phenomena due to the differences in initial gene frequency be clearly distinguished from those due directly to differences in effective population size.

The observed total responses, averaged over 1000 replicates for each regime, are presented in Table 1. Variation in the frequency of fixation of the least-favoured gamete (A_1B_1) has been found to be non-significant in this experiment, so that differences in total response depend only on the frequency with which one of the
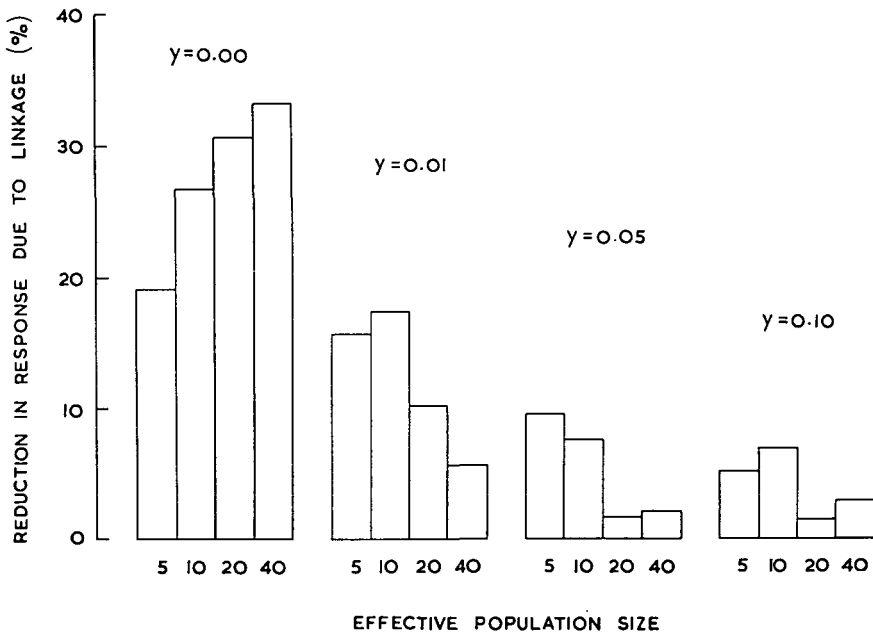

Fig. 1. The reduction in total response at each of four levels of linkage intensity, expressed as a percentage of the response observed under free recombination. Initial gene frequencies were chosen so that the expected response was the same for all population sizes at $y = 0.50$.

repulsion-phase gametes A_1B_2 or A_2B_1 is fixed by chance, before A_2B_2 can be increased in frequency to 100%. The interaction between the value of y on the one hand, and the tested combination of N and p_2 on the other, can most readily be appreciated from Fig. 1, which illustrates the percentage reduction in response at each linkage intensity by comparison with that observed under free recombination. Relevant data from the second experiment of Latter (1965 b) have been used in the preparation of the figure. Note in particular the effectiveness of recombination between loci separated by only one map unit at values of N greater than 10.

There are a number of separate phenomena involved in the observed interaction between linkage and population size at the chosen fixed level of R^*. We must first of all consider the probability of the chance elimination of the gamete A_2B_2 in a given replicate in the early generations of selection, which is a function primarily of the initial gene frequency p_2. This probability may be estimated empirically from observations of the effects of a complete suppression of recombination between

Table 2. *The probability of elimination of A_2B_2 for the tested combinations of population size and initial gene frequency, estimated in the absence of recombination*

N	p_2	Probability of elimination of A_2B_2
5	0·156	0·707 ± 0·014
10	0·073	0·840 ± 0·012
20	0·035	0·914 ± 0·009
40	0·017	0·968 ± 0·006

the two loci, and in Table 2 are given the observed frequencies of the loss of A_2B_2 for each of the four different regimes involved in the experiment. Note that at the chosen level of R^* the probability of the early loss of the gamete is high for each tested combination of N and p_2, being particularly high for N greater than 10 because of the low values of p_2 involved.

The remaining phenomena are the recovery of A_2B_2 by means of crossing-over, and its ultimate fixation in the population. Estimates of the expected frequency of this combined event can readily be calculated from the available data. For example, the frequency of fixation of A_2B_2 at $N = 40$, $p_2 = 0·017$, and $y = 0·01$ in the experiment under discussion was observed to be $0·414 \pm 0·016$. From the data of Table 2 we can estimate that a proportion $0·032 \pm 0·006$ of replicates retained this gamete throughout the entire selection process, so that the required probability of recovery and ultimate fixation of A_2B_2 in the remaining replicates is given by $(0·414 - 0·032)/0·968 = 0·395$. Comparable estimates for the other tested regimes are presented in Table 3. It is clear that the observed probabilities are determined both by the effective size of the population and the value of the initial gene frequency p_2, the latter influencing the probability of the survival of both repulsion-phase gametes through the early generations of selection. In the following section the effects of both these factors will be discussed in quantitative terms. It can be seen from the results presented in Table 3 that the probability of recovery and fixation of A_2B_2 with $N = 40$ and $y = 0·01$ is higher than the corresponding probability for $N = 5$ and $y = 0·50$. At low values of N the frequency of the combined event increases rapidly as the degree of recombination between the loci is increased, whereas at $N = 40$ there is little difference between values of y in the range $0·05$–$0·50$.

Table 3. *Estimated frequencies of the recovery and ultimate fixation of A_2B_2 in those replicates from which it has been eliminated*

Recombination value (y)	Frequency of recovery and fixation			
	$N = 5$ $p_2 = 0·156$	$N = 10$ $p_2 = 0·073$	$N = 20$ $p_2 = 0·035$	$N = 40$ $p_2 = 0·017$
0·01	0·071 ± 0·028	0·149 ± 0·021	0·260 ± 0·018	0·395 ± 0·016
0·05	0·174 ± 0·028	0·308 ± 0·021	0·400 ± 0·018	0·461 ± 0·016
0·10	0·236 ± 0·027	0·327 ± 0·021	0·421 ± 0·018	0·435 ± 0·016
0·50	0·338 ± 0·026	0·407 ± 0·020	0·455 ± 0·018	0·471 ± 0·016

3. AN APPROXIMATE THEORETICAL MODEL

Let g_{ij} denote the frequency of the gamete A_iB_j in the potentially infinite population of offspring derived from a given set of selected parents. If the parental genotypes do not include the gamete A_2B_2, this combination of alleles may be considered to have been eliminated from the population. The *recovery* of A_2B_2 then implies the inclusion of a crossover product of this constitution in a subsequent set of parental individuals. If the frequency of recombination is low, the composition of a population from which A_2B_2 has been eliminated will become dominated by genotypes $(A_1B_2)(A_1B_2)$, $(A_1B_2)(A_2B_1)$ and $(A_2B_1)(A_2B_1)$ because of the mean selective disadvantage of A_1B_1 gametes. The frequency of repulsion-phase heterozygotes among breeding individuals selected from the population will then be $2g_{12}g_{21} + \delta$, where $E(\delta) = 0$. If A_2B_2 is not represented in the chosen set of parents, its frequency in the following generation is given by $(g_{12}g_{21} + \frac{1}{2}\delta)y$, and its selective value relative to that of repulsion-phase gametes is approximately equal to $1 + \frac{1}{2}\bar{i}a/\sigma$. The probability of recovery of A_2B_2 in the selection of parents from this generation is then

$$1 - [1 - (g_{12}g_{21} + \tfrac{1}{2}\delta)\,y(1 + \tfrac{1}{2}\bar{i}a/\sigma)]^{2N}$$

which may be taken to be

$$\rho \;=\; 2Ng_{12}g_{21}\,y(1 + \tfrac{1}{2}\bar{i}a/\sigma) \tag{2}$$

with an error less in absolute magnitude than ρ^2. Where this is a satisfactory approximation, the probability of ultimate *fixation* of A_2B_2, given its occurrence among a group of selected individuals, is

$$u \;=\; [1 - \exp(-\bar{i}a/\sigma)]/[1 - \exp(-2N\bar{i}a/\sigma)] \tag{3}$$

Use is being made here of the formula given by Kimura (1957) for the chance of fixation of an individual mutant gene, since there is a negligible probability of the inclusion of more than one A_2B_2 gamete in the selected set of parents if ρ is small. For regimes in which $2N\bar{i}a/\sigma > 5$, the denominator in equation (3) may be taken to be unity so that the probability of fixation of A_2B_2, once recovered, is independent of population size. In the present study the value of $\bar{i}a/\sigma$ is $0\cdot8775$, and the probability given by equation (3) is equal to $0\cdot584$ for all N greater than 2.

Consider next the approximate frequency distribution of the variable $p = \frac{1}{2}(g_{21} - g_{12})$, $-\frac{1}{2} < p < +\frac{1}{2}$, over those replicates from which A_2B_2 has been lost by chance and A_1B_1 has been effectively eliminated by selection. The sum of the frequencies of gametes A_1B_2 and A_2B_1 among the original parents selected from the base population is expected to be approximately

$$\phi \;=\; 2p_2(1 - p_2)\,[1 + (\tfrac{1}{2}\bar{i}a/\sigma)\,(1 - 2p_2)] \tag{4}$$

and in populations from which A_2B_2 is eliminated, the drift variance in the frequency of A_1B_2 relative to that of A_2B_1 will initially be of the order of $(\frac{1}{2})(\frac{1}{2})/2N\phi$. In the numerical study under discussion, where $R^* = 0\cdot70$, $\bar{i}a/\sigma = 0\cdot8775$ and N is greater than 4, the value of $N\phi$ lies in the range $1\cdot7$–$2\cdot0$ for all regimes. The

probability of the preservation of *both* repulsion-phase gametes in the population through the early generations of selection will therefore be of much the same order for all regimes. The distribution of the variable p among those replicates in which a recombinational event is a prerequisite for further advance, can also be expected to be approximately uniform because of the large sampling variation in the frequency $g_{21} - g_{12}$. The rate of loss of heterozygosity in these replicates can be predicted to be $1/2N$ per generation in the absence of effective recombination (Kimura, 1955).

Given a uniform distribution of p, an approximate expression for the probability of the recovery and subsequent fixation of A_2B_2 can be derived for small values of ρ. In the selection of N breeding individuals from any given generation, the required probability is equal to ρu from equations (2) and (3). Since the variable p is restricted to values $(i-N)/2N$, $i = 1, 2, ..., 2N-1$, the expected value of this probability for p uniformly distributed is

$$\lambda = \tfrac{1}{3}Nyu(1 + 1/2N)(1 + \tfrac{1}{2}\bar{i}a/\sigma) \tag{5}$$

The parameter ρ is proportional to the prevailing frequency of repulsion-phase heterozygotes, so that the total probability of recovery and fixation of A_2B_2 is given to a first approximation by

$$\Pr(A_2B_2) = \sum_{n=1}^{\infty} [(1 - \lambda - 1/2N)^{n-1}\lambda]$$
$$= 2N\lambda(1 + 2N\lambda)^{-1} \tag{6}$$

In addition, the mean waiting time for *effective* recovery of A_2B_2 in these replicates is expected to be roughly equal to

$$W = \sum_{n=1}^{\infty} [n(1 - \lambda - 1/2N)^{n-1}\lambda](1 + 2N\lambda)(2N\lambda)^{-1}$$
$$= 2N(1 + 2N\lambda)^{-1} \tag{7}$$

A more comprehensive treatment of this process must of course take account of the fact that the distribution of p will not be strictly uniform if the probability of a crossover occurring is high. It should therefore be emphasized that equations (6) and (7) are based on the assumption that Ny is small.

4. EVIDENCE IN SUPPORT OF THE MODEL

The computer programme written for this study involves the calculation each generation of the coefficient of linkage disequilibrium,

$$D = g_{11}g_{22} - g_{12}g_{21}$$

and the mean and variance of D over those replicates still segregating at both loci (Latter, 1966). From the behaviour of these statistics at a recombination value of zero, indirect evidence as to the form of the frequency distribution of the variable p can be provided for each of the four combinations of population size and initial gene frequency. In the absence of recombination, selection in those replicates from which

Table 4. *The mean coefficient of linkage disequilibrium and its variance among replicate populations, averaged over the first ten generations of stability at a linkage value of* $y = 0.00$

Regimes		Generations to reach stability	Observations of D		Predictions for p uniformly distributed	
N	p_2		Mean D	Var. D	$E - (\frac{1}{4} - p^2)$	Var. (p^2)
5	0.156	13	-0.180	0.0037	-0.183	0.0034
10	0.073	15	-0.180	0.0041	-0.175	0.0045
20	0.035	21	-0.179	0.0041	-0.171	0.0050
40	0.017	19	-0.175	0.0047	-0.169	0.0053

A_2B_2 has been lost by chance will rapidly lead to the elimination of A_1B_1, so that $g_{12} + g_{21} = 1$ and the mean of D in a given generation becomes a measure of the average value of $-g_{12}g_{21}$, which can be shown to be equal to $-(\frac{1}{4} - p^2)$.

At $y = 0.00$ the mean value of D has been observed to change from its initial value of zero to that expected for p uniformly distributed in the interval $-\frac{1}{2} < p < +\frac{1}{2}$, thereafter stabilizing at the values given in Table 4. The number of generations of selection prior to the period of stability varied from 13 to 21, depending on the regime concerned. Note that there is consistent evidence at the higher values of N of a deficiency of extreme values of p during the period of stability, but the departure from expectation is in all cases of a relatively minor order.

Table 5. *The observed frequency of fixation of A_2B_2 in populations with initial gamete frequencies* $g_{12} = \frac{1}{2} - p$, $g_{21} = \frac{1}{2} + p$, *given initially a uniform distribution of* p *in the interval* $(-\frac{1}{2}, +\frac{1}{2})$

Recombination value (y)	Probability of fixation			
	$N = 5$	$N = 10$	$N = 20$	$N = 40$
0.01	0.131 ± 0.005	0.370 ± 0.007	0.662 ± 0.006	0.867 ± 0.005
0.05	0.388 ± 0.007	0.678 ± 0.006	0.868 ± 0.005	0.967 ± 0.003
0.10	0.512 ± 0.007	0.777 ± 0.006	0.904 ± 0.004	0.978 ± 0.002
0.50	0.710 ± 0.006	0.868 ± 0.005	0.967 ± 0.003	0.996 ± 0.001

Let us consider now the predictive value of equations (6) and (7) for genes of large effect, in giving the probability of recovery and subsequent fixation of A_2B_2 for p uniformly distributed, and the expected waiting time prior to effective recovery. To provide direct comparisons of predicted and estimated probabilities, selection has been simulated in a series of populations corresponding exactly to the regimes tested in the main experiment, except that the initial gamete frequencies were set at $g_{12} = \frac{1}{2} - p$, $g_{21} = \frac{1}{2} + p$ for values of p in the interval $(-\frac{1}{2}, +\frac{1}{2})$. The frequencies of fixation of A_2B_2 in these populations, taken over a uniform distribution of p, are given in Table 5. Figure 2 shows the relationship between the observed frequencies and those predicted by equation (6), for values of y in the

Y

range 0·01–0·10. The agreement is excellent for values of Ny up to 0·2, but at higher values the equation gives no more than a rough indication of the required probability. It should be pointed out here that the observed frequencies and predicted probabilities in Fig. 2 are not based on precisely the same definition of relative
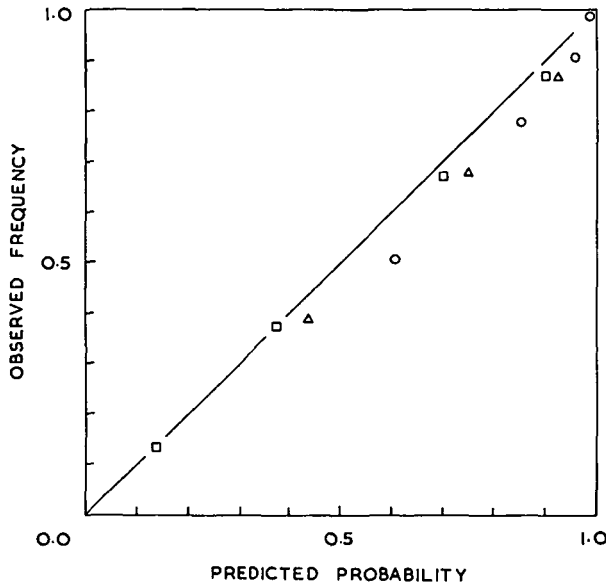

Fig. 2. The relationship between predicted probabilities based on equation (6) and the corresponding observed frequencies presented in Table 5. Symbols □, △, ○; refer to $y = 0·01$, 0·05 and 0·10 respectively. Population sizes of $N = 5$, 10, 20 and 40 are represented.

selective value. In all the simulated populations the selective value of a genotype has been taken to be that given by Latter (1965 a) for genes of large effect. In the derivation of equation (6) it was considered inappropriate to introduce this refinement.

Equation (7) leads us to expect the mean waiting time for effective recombination to be of the order of $2N$ generations for very small values of λ, i.e. for Ny close to zero. At a given recombination value, the waiting time is expected to increase with

Table 6. *The mean number of generations necessary for the fixation of A_2B_2 in populations with initial gamete frequencies $g_{12} = \frac{1}{2} - p$, $g_{21} = \frac{1}{2} + p$, given initially a uniform distribution of p in the interval $(-\frac{1}{2}, +\frac{1}{2})$*

Recombination value (y)	Observed mean time to fixation			
	$N = 5$	$N = 10$	$N = 20$	$N = 40$
0·01	19·8	26·1	28·0	27·9
0·05	15·6	18·3	19·6	20·8
0·10	13·8	16·2	17·4	18·8
0·50	10·6	12·4	14·1	15·5

increasing population size to a maximum at an intermediate value of N, thereafter falling off gradually at higher population sizes (Fig. 3). No direct observations of waiting time were made in the simulated populations with initial gamete frequencies of $g_{12} = \frac{1}{2} - p$, $g_{21} = \frac{1}{2} + p$, but the mean numbers of generations required for the
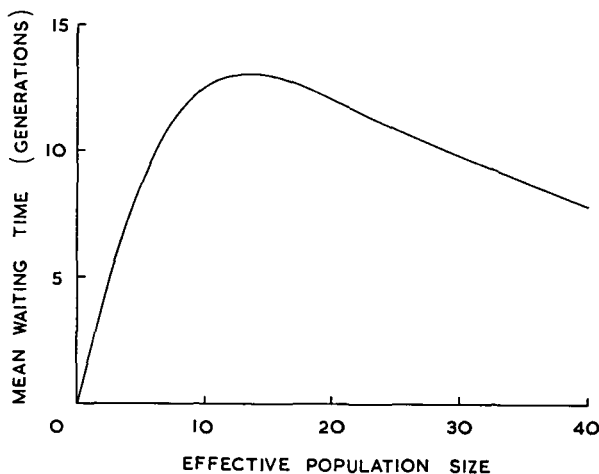

Fig. 3. The relationship between population size and the mean waiting time for effective recombination at $y = 0.01$, given by equation (7) for $\bar{i} = 1.755$ and $a/\sigma = 0.5$.

fixation of A_2B_2 were recorded (Table 6), so that the delay due to the *restriction* of recombination between the loci can be estimated. At $y = 0.01$ the increase in waiting time by comparison with that under free recombination was observed to be 9.2, 13.7, 13.9 and 12.4 generations at $N = 5$, 10, 20 and 40 respectively. The corresponding total waiting times predicted by equation (7) are 8.7, 12.6, 12.1 and 7.9 generations respectively. We might therefore expect equation (7) to give realistic predictions of the time scale of the process under discussion only for values of Ny less than 0.2.

5. DISCUSSION

The response to artificial selection due to a pair of linked additive loci of equal proportionate effect can be considered to involve four distinct phenomena. If the frequency of the gamete carrying both 'plus' alleles (A_2B_2) is low in the equilibrium base population, the initial response phase will be characterized by a high probability of its chance elimination from the population. The total probability of this event can be estimated in a computer study by setting the recombination value equal to zero, thereby precluding the possibility of the recovery of A_2B_2. In the main experiment under discussion, genes of large effect are considered to be segregating with the 'plus' alleles initially at low frequency, and the probability of elimination of A_2B_2 has been shown to be greater than 0.7 for all regimes (Table 2).

The second phenomenon is the increase in frequency of gametes A_1B_2 and A_2B_1 (which are equivalent as regards mean selective value in the symmetric model under study), the preservation of both being a requirement for the subsequent recovery

of A_2B_2 by recombination. However if the initial gene frequency p_2 is small, the variance of the difference in the frequency of these two repulsion-phase gametes will be high in the early generations of selection, the effective population size governing this process being initially of the order of *two* for each tested combination of N and p_2. A population from which A_2B_2 has been lost will come to consist almost exclusively of genotypes $(A_1B_2)(A_1B_2)$, $(A_1B_2)(A_2B_1)$ and $(A_2B_1)(A_2B_1)$ if the frequency of recombination is low, the distribution of $p = \frac{1}{2}(g_{21} - g_{12})$ being at this stage approximately uniform over the interval $(-\frac{1}{2}, +\frac{1}{2})$. A comparison of the frequencies of recovery of A_2B_2 given for $y = 0.01$ in Tables 3 and 5 suggests that at low values of y, the probability of the joint preservation of A_1B_2 and A_2B_1 through the early generations of selection is very nearly the same (approximately 0.45) for all regimes involved in the present study.

The third and fourth steps in the selection process involve the *recovery* of A_2B_2, defined as the inclusion of the gamete in a selected set of parental genotypes, followed by its *fixation* in the population through selection. Provided the probability of recovery of A_2B_2 in any particular generation is small (i.e. provided Ny is small), equations (2) and (3) give the probability of recovery and fixation respectively. For genes of large effect, the probability of fixation of A_2B_2 once recovered is expected to be independent of population size, and in this context it is convenient to speak of the product of the two component probabilities as the probability of *effective recovery* of A_2B_2. For p uniformly distributed, the approximate algebraic expressions given as equations (6) and (7) predict the mean probability of effective recovery of the required gamete, and the mean waiting time involved.

It has been shown that the probability of effective recovery of A_2B_2 depends upon the balance between the following two processes: (i) the frequency of repulsion-phase heterozygotes is expected to decrease by a fraction $1/2N$ per generation in the absence of effective recombination; and (ii) the probability of recovery of A_2B_2 in any particular generation is proportional to the value of Ny and to the prevailing frequency of repulsion-phase heterozygotes. At a given recombination value, the effect of an increase in population size (provided Ny remains less than 0.2) can be gauged from equation (6): due to the decrease in the rate of random fixation of A_1B_2 and A_2B_1, and the increase in the probability of recovery of A_2B_2 each generation, the total probability of effective recovery increases as a function of N^2.

SUMMARY

The effects of tight linkage on the total response due to pairs of identical additive loci, segregating in a population initially in linkage equilibrium, have been studied both algebraically and by means of computer simulation. Particular attention has been given to the effects of finite population size on the probabilities of (*a*) the elimination from the population of the gamete carrying both 'plus' alleles; (*b*) the joint preservation of the two types of repulsion gametes; (*c*) the recovery of the desired combination of plus alleles through crossing-over; and (*d*) the fixation of the gamete in the population following its recovery.

The study is restricted to situations in which linkage is known to have an appreciable effect on total selection response, i.e. to the case of genes of large effect initially at low frequency. A comparison of regimes with the same expected response under free recombination has shown the probability of (*a*) to be high, and the probability of (*b*) to be very nearly the same for all regimes tested. Provided that the recovery of the gamete carrying both plus alleles is an unlikely event at any given point in time, the probability of the fixation of the gamete, once reconstituted, is expected to be independent of population size for genes of large effect. In this context, approximate algebraic expressions have been derived for the probability of effective recovery of the required gamete, and for the mean waiting time involved.

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