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The effect of linkage on limits to artificial selection

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1. INTRODUCTION

A theory of limits to artificial selection in small populations was given by Robertson (1960) in terms of single genes, and was extended to selection for a quantitative character governed by many loci by ignoring linkage and epistatic interactions between loci. In this paper we include the effect of linkage in a very simple situation, that of two additive loci, though it is hoped to deal with more complex models in further papers. No general algebraic solution to this problem has been found, so that most of our information has come from Monte Carlo simulation on computers. When there is no recombination between the two loci, an algebraic treatment has been developed which will be described in a later paper.

Griffing (1960) investigated the effect of linkage on response to artificial selection in infinitely large populations, assuming that gene effects were small enough that changes in genetic parameters, other than the population mean, could be ignored. Using a model of two loci in an infinite population, Nei (1963) and Felsenstein (1965) have developed formulae for the effect of directional selection on changes in linkage disequilibrium. But, in infinite populations, linkage cannot affect the selection limit but only the rate of advance to that limit. Simulation by Monte Carlo methods has shown that, though populations may initially be in linkage equilibrium, the advance under selection can be reduced when genes are tightly linked, even with no interactions between loci (Martin & Cockerham, 1960; Qureshi, 1963). These workers used models in which the initial gene frequency of 0·5 and the effect on the character under selection were the same for all loci. Latter (1965*b*), using only two loci, considered the consequences of varying the initial gene frequency though this and the effect on the character under selection were the same for both loci. We shall also restrict ourselves here to two loci with additive action, but shall not restrict the effects of the loci on the character under selection or the initial gene frequency. We will in general assume that the population is initially in linkage equilibrium.

2. BASIC THEORY

To give a framework for the theoretical consideration of the problem with two loci, it will be useful to repeat some of Robertson's earlier conclusions on selection in a finite population at a locus with additive gene action, which relied heavily on a paper by Kimura (1957). The basic concept underlying this is the gene frequency

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distribution. This can be regarded as either that of the frequencies at equivalent loci in one population or that at a single locus replicated in many equivalent populations. Similarly, the chance of fixation when the selection limit is reached can be considered either as the proportion of such loci fixed in the same direction in a single line, or as the proportion of replicate lines in which the same allele is fixed. The situation in which no further selection response can be made but in which not all loci are fixed, due to heterozygote superiority or opposing natural selection, will not be discussed.

At a locus at which there is additive action in selective advantage (as would be brought about by artificial selection acting on a locus with additive effect on the character under selection), the change in the distribution (ϕ) of gene frequencies with time can be described reasonably well by the diffusion equation

$$\frac{\partial\phi}{\partial(t/N)} = \frac{1}{4}\frac{\partial^2}{\partial p^2}[p(1-p)\phi] - \frac{Ns}{2}\frac{\partial}{\partial p}[p(1-p)\phi] \tag{1}$$

where p is the gene frequency, t is the time in generations, N is the population size and s is the difference in selective advantage between the two homozygotes. From a given initial gene frequency, the pattern of the selection process is then entirely determined by the parameter Ns on a time scale t/N. Kimura (1957) showed that the chance of eventual fixation, $u(p_0)$, of a gene with initial frequency p_0 is then a function only of Ns and is given explicitly by

$$u(p_0) = \frac{1-e^{-2Nsp_0}}{1-e^{-2Ns}} \tag{2}$$

Examination of equation (1) shows that any computer simulation of the selection process need only be done at one population size as the above generalization allows extrapolation to all values of N and s. In practice this is limited by the restriction that s shall not be greater than unity. From equation (2) it can be shown that if Ns is small ($< 0{\cdot}5$) then the expected change in gene frequency at the limit is $2N$ times the change in gene frequency in the first generation and that the time for the gene frequency to change by half this amount is $1{\cdot}4N$ generations. Under most conditions, this value is an upper limit for the 'half-life' of the selection process.

When more than one locus segregates, the differential equation describing the selection process can be written in terms of gametic frequencies in the general form as follows (e.g. Kimura, 1955):

$$\frac{\partial\phi}{\partial t} = \frac{1}{2}\sum_{j=1}^{n}\frac{\partial^2}{\partial f_j^2}[V(\delta f_j)\phi] + \sum_{j<k}\sum\frac{\partial^2}{\partial f_j\,\partial f_k}[\mathrm{cov}(\delta f_j, \delta f_k)\phi] - \sum_{j=1}^{n}\frac{\partial}{\partial f_j}[M(\delta f_j)\phi] \tag{3}$$

where $\phi(f_1, f_2 \ldots f_n, t)$ is the density function of the distribution of gametic frequencies, f_j, at time t. The dimension (n) of the equation is the number of degrees of freedom amongst the gametic frequencies. Thus for two loci, each with two alleles, $n = 3$. From the multinomial distribution, the variance of change in gametic frequency is given by

$$V(\delta f_j) = [f_j(1-f_j)]/2N$$

and the covariance of changes by

$$\text{cov}\,(\delta f_j, \delta f_k) \;=\; -f_j f_k/2N$$

For the simplest model of two loci each with two alleles, let the frequencies of the gametes, AB, Ab, aB and ab be f_1, f_2, f_3 and f_4 respectively. Also let p and q be the frequencies of the alleles A and B, and define linkage disequilibrium by the determinant $D = f_1 f_4 - f_2 f_3$. Finally, assume that these loci have additive selective values r and s, the differences in selective values between the homozygotes at loci A and B respectively, and let c be the recombination fraction between these loci, assumed to be the same for both sexes. Then

$$\begin{aligned} M(\delta f_1) &= \tfrac{1}{2} f_1[r(1-p)+s(1-q)]+\delta D \\ M(\delta f_2) &= \tfrac{1}{2} f_2[r(1-p)-sq]-\delta D \\ M(\delta f_3) &= \tfrac{1}{2} f_3[-rp+s(1-q)]-\delta D \end{aligned} \tag{4}$$

and

$$\delta D \;=\; -cD\{1+\tfrac{1}{2}[r(1-2p)+s(1-2q)]\} \tag{5}$$

In equations (4) and (5), r and s are assumed small so that terms in the denominator have been ignored. Also, for the diffusion equation to hold, r, s and c must be small such that terms in their products can be ignored relative to $1/N$. Thus we can take

$$\delta D \;=\; -cD$$

Multiplying (3) by N and inserting the above equations, we obtain for two additive loci

$$\begin{aligned} \frac{\partial \phi}{\partial (t/N)} = {} & \frac{1}{4}\sum_{j=1}^{3} \frac{\partial^2}{\partial f_j^2}[f_j(1-f_j)\,\phi] - \frac{1}{2}\sum_{j<k}\sum \frac{\partial^2}{\partial f_j\,\partial f_k}[f_j f_k \phi] \\ & -\tfrac{1}{2}Nr\left\{\frac{\partial}{\partial f_1}[f_1(1-p)\,\phi]+\frac{\partial}{\partial f_2}[f_2(1-p)\,\phi]-\frac{\partial}{\partial f_3}[f_3 p\phi]\right\} \\ & -\tfrac{1}{2}Ns\left\{\frac{\partial}{\partial f_1}[f_1(1-q)\,\phi]-\frac{\partial}{\partial f_2}[f_2 q\phi]+\frac{\partial}{\partial f_3}[f_3(1-q)\,\phi]\right\} \\ & +Nc\left\{\frac{\partial}{\partial f_1}(D\phi)-\frac{\partial}{\partial f_2}(D\phi)-\frac{\partial}{\partial f_3}(D\phi)\right\} \end{aligned} \tag{6}$$

where, formally, in (6), p must be replaced by f_1+f_2, q by f_1+f_3 and D by $f_1(1-f_1-f_2-f_3)-f_2 f_3$. Thus, on a time scale proportional to N, the selection process is described completely by the initial conditions p_0, q_0 and D_0 and the parameters Nr, Ns, and Nc, and the chance of fixation at either locus is then a function of these alone.

A general solution of (6) has not been obtained though some results for Nr, $Ns < 0{\cdot}5$ can be given specifically in algebraic terms and we shall present later some results using matrix methods for $u(p_0)$ when $Nr < 0{\cdot}5$ but with no restriction on Ns.

Consider the rate of breakdown of linkage disequilibrium in small populations in the absence of selection. The recurrence equation for the mean value of D is then

$$D_t \;=\; (1-c)\,(1-1/2N)\,D_{t-1}$$

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If c and $1/2N$ are small, so that their product can be ignored, we have

$$\begin{aligned} D_t &= (1-c-1/2N)\,D_{t-1} \\ &= D_0\,e^{-(2Nc+1)\,t/2N} \text{ approximately.} \end{aligned}$$

The half-life of the decline of the linkage disequilibrium coefficient to zero is given approximately by $t=1{\cdot}4N/(2Nc+1)$ generations. If Nr and Ns are small ($<0{\cdot}5$) it can be assumed that changes in the variance of gene frequency and in the disequilibrium coefficient will occur mainly as a result of genetic sampling and crossing-over and not as a result of selection. In any generation the expected change in p in any line is given by

$$\delta p = rp(1-p)/2+sD/2$$

and in q by

$$\delta q = sq(1-q)/2+rD/2.$$

We may assume, following Robertson (1960), that the average value of $p(1-p)$ will decline by a proportion $1/2N$ each generation and that the average value of D will similarly decline by a proportion $(c+1/2N)$. We have then for the expected total change in gene frequency

$$u(p_0) = p_0+Nrp_0(1-p_0)+NsD_0/(2Nc+1)$$

The expected change of gene frequency is then a linear expression in $2Nc/(2Nc+1)$. A linear relationship of change in gene frequency with this expression is in fact found in computer runs over a much wider range of Nr and Ns than that used in this derivation and this has very considerably simplified our discussion of the effect of linkage. If linkage is not initially at equilibrium, then the expected change in gene frequency may be greater or less than $2N$ times the change in the first generation, depending on the sign of the disequilibrium determinant.

Under the conditions of this derivation, segregation at a second locus has no effect on the chance of fixation of the first if linkage is in equilibrium at the start. We shall see later that, when we move to higher values of Nr and Ns, this is no longer true.

In most selection experiments, selection is for a quantitative character and changes in gene frequency are not directly observable. The selective advantages are then consequences of the effects of the loci on the character under selection. If these are small, we have approximately $r=i\alpha$, $s=i\beta$, where i is the selection intensity in standard units and α, β are the effects of the two loci on the metric character, expressed as the difference between the two homozygous genotypes divided by the phenotypic standard deviation, σ. Latter (1965*a*) has investigated the errors involved in this approximation. If considered in terms of the effect on changes in gene frequency, the errors appear to be compensatory in that the expression used above underestimates the selective advantage of genotypes with both positive and negative deviations from the population mean. If $i\alpha$ and $i\beta$ are small, additive action on the character under selection implies additive action on selective advantage, though this breaks down to some extent under intense selection, as we shall see later. The probable chance of fixation at the two loci can then be described in

terms of $Ni\alpha$, $Ni\beta$ and Nc and the consequent total change, R, in the population mean will be given by

$$R = \{\alpha[u(p_0)-p_0]+\beta[u(q_0)-q_0]\}\sigma \quad (7)$$

At any instant, the additive genetic variance can be expressed as

$$V_A = \sigma^2\{\tfrac{1}{2}\alpha^2 p(1-p)+\tfrac{1}{2}\beta^2 q(1-q)+\alpha\beta D\}.$$

This expression can be generalized to any number of loci with additive gene action and is then interesting in showing that, in the prediction of immediate response to artificial selection, the linkage disequilibrium need only be specified in terms of the disequilibrium determinants between the loci taken in pairs.

3. THE MONTE CARLO SIMULATION PROCEDURE

The simulation process was carried out on a high-speed computer, the I.C.T. Atlas. It was rather more abstract than that of other workers (Fraser, 1957; Martin & Cockerham, 1960; Gill, 1965; Latter, 1965*b*). Selection, recombination and sampling were all done at the gametic level and gametes were never paired into zygotes. Using the previous notation of gene effects, expressing all measurements in terms of the phenotypic standard deviation and taking the mean value of the genotype *aabb* as an arbitrary zero, the mean, m, of the population at any time is given by $m=p\alpha+q\beta$. Changes in gametic frequency are given by (4) and (5) with the selective values r and s replaced by $i\alpha$ and $i\beta$, and these equations include both the effect of selection and recombination. From the gamete frequencies so produced, the $2N$ gametes in the next generation were obtained by sampling from a multinomial distribution with parameters f_j by generating $2N$ uniform pseudo-random numbers X, $0<X<1$, and comparing each with the gametic frequencies. If $0<X\leqslant f_1$, then a gamete AB was generated; if $f_1<X\leqslant f_1+f_2$, then a gamete Ab was generated, and so on. Each of the parameters, N, $i\alpha$, $i\beta$, c, and the initial frequencies could be altered. In all runs, linkage equilibrium in the initial population was assumed. At the start of any run, the first step was one of selection by applying the above formulae to the initial frequencies, followed by the drawing of a random sample of gametes.

Each replication was continued to fixation or for $6{\cdot}25N$ generations, whichever occurred first. After this time, at least 99·9% of the total response at a single locus can be expected to be made if $Ni\alpha\geqslant 4$, 98·5% if $Ni\alpha=2$, or 96·6% if $Ni\alpha=1$. The average gene frequency at this time was then taken as the limit even if all lines had not reached fixation. Usually 400 replicates were run for each set of parameters. At fixation, the proportion of lines in which any allele is fixed is binomially distributed so that the standard error of the chance of fixation may easily be calculated. The chance of fixation at one locus when there was no segregation at the other was obtained by matrix iteration (Allan & Robertson, 1964), using the same population size as in the Monte Carlo runs rather than by using (2). This avoids small differences in the chance of fixation observed at a single locus when different population sizes are used for the same $Ni\alpha$ value (Ewens, 1963). These results for a single locus only

must also apply when the second locus has no effect on the character under selection or when Nc is very large, as in independent segregation of the two loci in a large population. In a very small population, for example $N = 8$, when the maximum biological value of Nc is 4, we have in fact detected some influence of independent segregation at the second locus on the chance of fixation of the first.

4. RESULTS

The outcome of any particular run is affected by five independently varying parameters, $Ni\alpha$ and p_0 referring to the first locus, $Ni\beta$ and q_0 to the second, and Nc. The output of any set of runs can be expressed in terms of the average chance of fixation at the two loci, $u(p_0)$ and $u(q_0)$, and the 'between line' disequilibrium determinant, calculated from the observed frequencies of fixation of the four gametes. It soon became clear to us that the results could be discussed most meaningfully in terms of the influence of segregation at a second locus on the chance of fixation at the first. The view of the results that we shall present here represents the combination of the Monte Carlo results with the insights we could gain into them by the application of algebra to the simpler situations.

We found no situations in which the chance of fixation at the first locus was significantly increased by simultaneous segregation at the second. We found none in which the between-line disequilibrium determinant was significantly positive at fixation and very many in which it was significantly negative.

(i) *The influence of the effect and initial frequency at the second locus*

Figures 1–4 have been chosen to illustrate various general aspects of the results. First we shall discuss the influence of changes in the parameters at the second locus. Concentrating on those situations in which there is no crossing-over ($Nc = 0$), segregation at the second has no detectable influence on the chance of fixation at the first until its effect is greater than one-half that of the first and, even when the gene effect is three-quarters that of the first, the influence on the chance of fixation is very small. We have found these conclusions to apply quite generally. An example is shown in Fig. 2. As the effect at the second increases further, the chance of fixation at the first passes through a minimum and then increases again. Figure 1 shows that the reduction is very dependent on the initial frequency of the preferred allele at the second locus. Clearly there has to be a minimum in this curve, as the second locus will have no influence when its initial gene frequency is zero or unity. The initial frequency at which segregation at the second produces the greatest reduction is dependent on the magnitude of its gene effect. We have found empirically that the minima in the chance of fixation $u(p_0)$, when plotted either against the gene effect or the gene frequency at the second locus, occur roughly when $Ni\beta q_0 = 0{\cdot}8$, whatever the parameters at the first. The chance of fixation of the preferred allele at the second is then also approximately 0·8. At this minimum, the reduction in the chance of fixation at the first increases as the gene effect at the second increases.

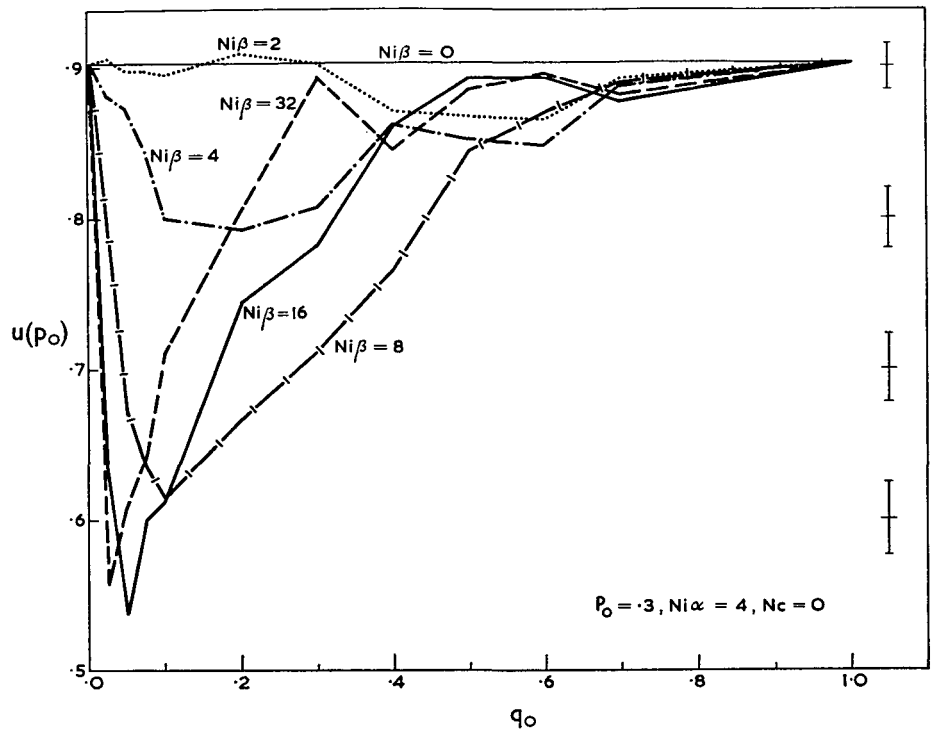

Fig. 1. The relationship between the chance of fixation at the first locus and the effect and initial frequency of the second. No crossing over. Typical ranges, of length two standard deviations, are shown.

(ii) *The influence of recombination frequency*

When $Ni\beta$ is small, the chance of fixation at the first locus is approximately linear in $2Nc/(2Nc+1)$ and this is well illustrated in Figs. 2–4. This expression goes from 0 to 1 as c increases from zero to infinity and the values $Nc=\frac{1}{4}$ and 1 divide this range into three equal intervals. Figure 4 shows that the curves for the three different crossover values are in fact equally spaced for all values of q_0, but, in Figs. 2 and 3, it will be seen that, although this prediction is reasonably satisfactory when $Ni\beta$ is less than 12, it obviously breaks down at higher values when the effect of increasing Nc from 0 is less than expected. In consequence, the value of $Ni\beta$ at which the minimum occurs is not independent of Nc and increases as the latter increases. At the high values of $Ni\beta$ the three curves become almost indistinguishable.

Runs not shown in these diagrams were made with a wide range of parameter sets ($p_0, q_0 = 0{\cdot}05$, $0{\cdot}1$, $0{\cdot}3$, $0{\cdot}5$ and $0{\cdot}7$; $Ni\alpha = 2, 4, 8$ and 16, and either $Nc = 1, \frac{1}{4}$ and 0, or $Nc = 4, 1, \frac{1}{4}, \frac{1}{16}$ and 0). For each set of the other four parameters, the linear regression of $u(p_0)$ against $2Nc/(2Nc+1)$ was calculated, the line being forced through the matrix iteration result for $Nc=\infty$. It was found that 97·4% of the variation in $u(p_0)$ between different Nc values could be removed by the linear regressions.

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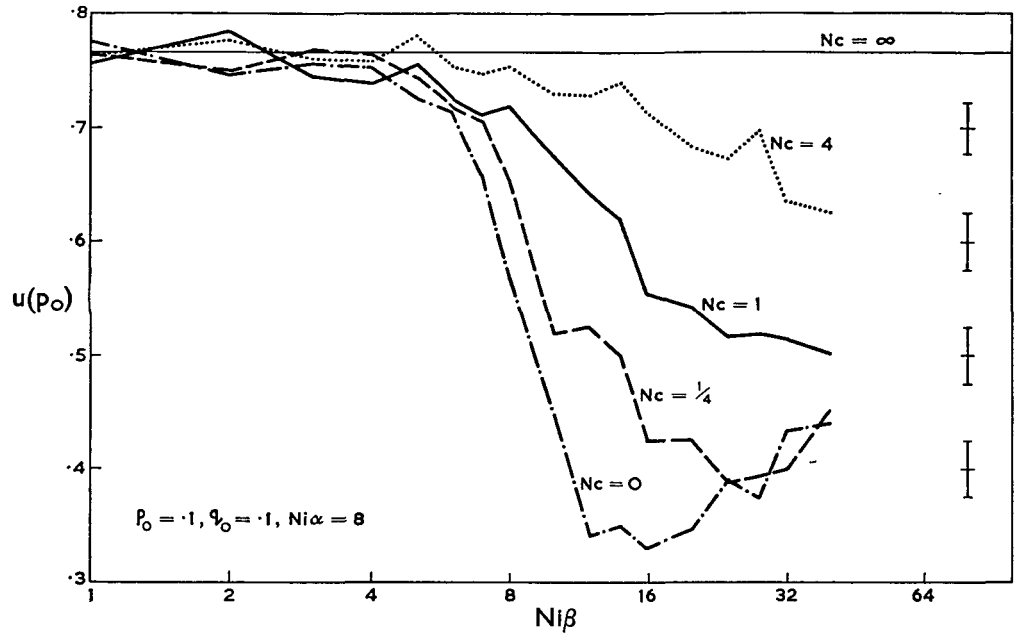

Fig. 2. The relationship between the chance of fixation at the first locus and the effect at the second, for various recombination values. Typical ranges, of length four standard deviations if $Ni\beta \leqslant 8$, or two standard deviations if $Ni\beta > 8$ are shown.

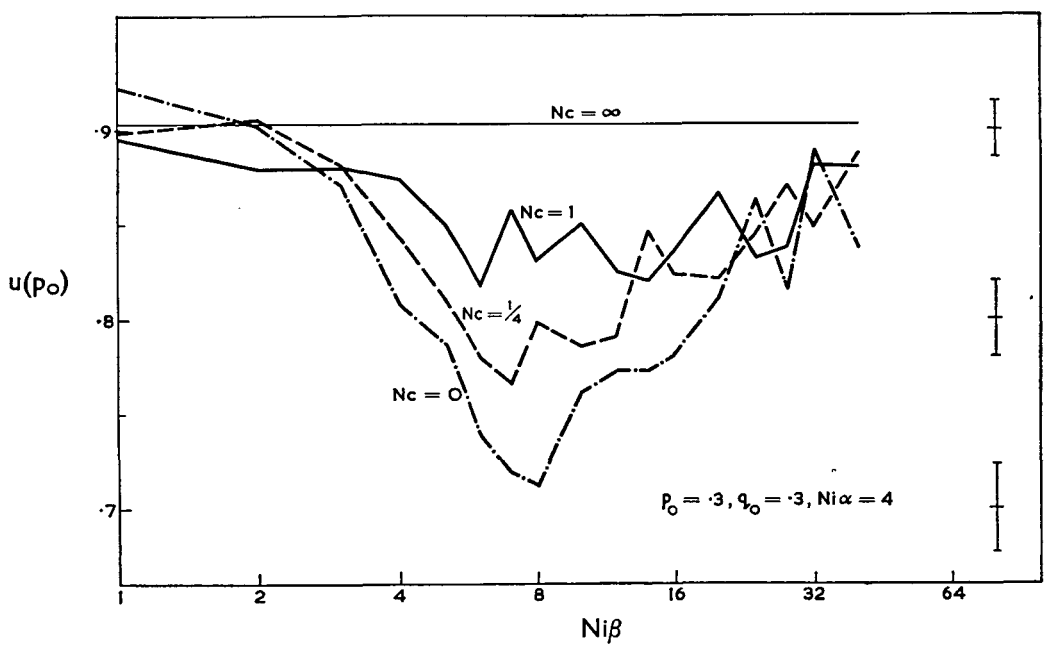

Fig. 3. As Fig. 2, but with the effect halved at the first locus. Typical ranges of length two standard deviations are shown.

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Nevertheless the residual variation due to curvilinearity was highly significant in many cases.

Figure 4 also shows the effect of altering population size in the computer runs for fixed values of $Ni\alpha$, $Ni\beta$ and Nc. The curves for a population size of 8 are indistinguishable from those with a population size of 16.

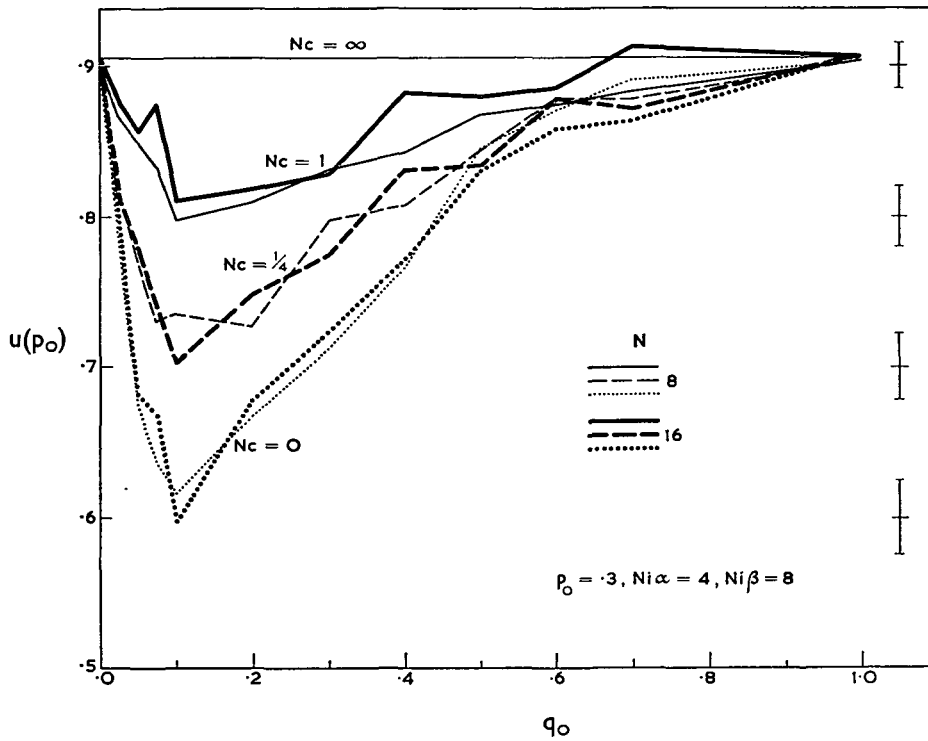

Fig. 4. The relationship between the chance of fixation at the first locus gene and the initial frequency at the second for various recombination values. Estimates were made at two levels of population size. Typical ranges, of length two standard deviations, are shown.

(iii) *Changes in the parameters at the first locus*

Any discussion of the influence of changes in the parameters at the first locus is complicated by the fact that in the absence of segregation at the second, variations in these will affect the chance of fixation. We are then concerned to find a description of the effects of this segregation on the chance of fixation which will be as far as possible independent of the parameters at the first locus. Segregation at the second reduces the chance of fixation at the first. This can be thought of as a reduction of the effective selection intensity at the first locus. From each computer run, we calculated from Kimura's formula (2) the effective value of $Ni\alpha$ (denoted $\widehat{Ni\alpha}$) which, from the given initial gene frequency, would give the observed chance of fixation if the first alone was segregating. Figure 5 gives examples of the use of this

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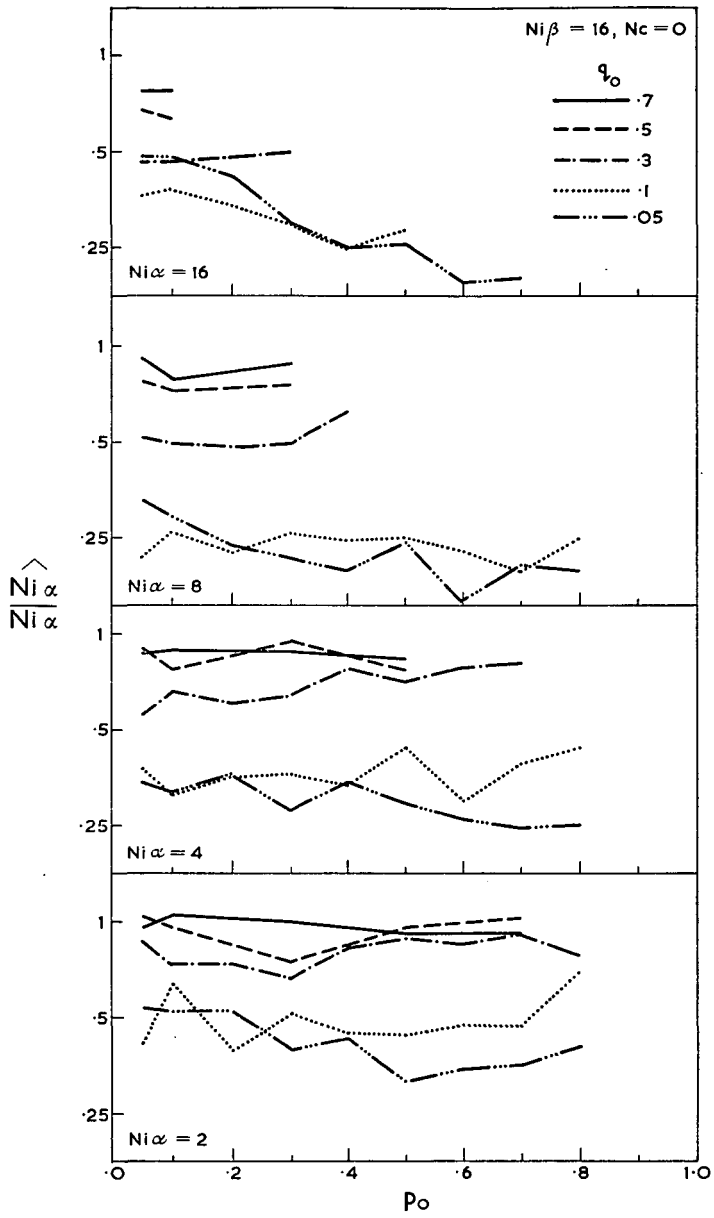

Fig. 5. The effective selection parameter, $\hat{Ni\alpha}/Ni\alpha$, at the first locus as influenced by segregation at the second ($Nc = 0$).

transformation in evaluating the interaction of $Ni\alpha$ and p_0 with the other variables. Because the sampling variance becomes very high as $u(p_0)$ approaches unity, no points are plotted when the observed value exceeds 0·99. It is quite clear that the effect of the segregation at the second locus, if expressed in this way, is almost independent of the gene frequency at the first for values of $Ni\alpha$ up to about 4.

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However, this independence breaks down at low values of q_0, when $\hat{Ni\alpha}$ is reduced as p_0 increases.

It is a necessary consequence of the theoretical model of the process which will be presented in a subsequent paper that $\hat{Ni\alpha}/Ni\alpha$ will be independent of both p_0 and $Ni\alpha$ when $Ni\alpha < 0{\cdot}5$. However, it will be seen that as $Ni\alpha$ increases, the

Table 1. *The relationship between* $\hat{\text{Ni}}\alpha/\text{Ni}\alpha$ *and* $\text{Ni}\alpha$ *for a model with* $\text{Ni}\beta = 16$, $\text{q}_0 = 0{\cdot}1$, $\text{Nc} = 0$, *averaged over a range of* p_0 *from* $0{\cdot}05$ *to* $0{\cdot}8$

$Ni\alpha$	$\hat{Ni\alpha}/Ni\alpha$
0	0·56
2	0·49
4	0·37
8	0·24
16	0·32

observed value of $\hat{Ni\alpha}/Ni\alpha$ declines. An example is given in Table 1. As $Ni\alpha$ increases still further to values greater than $2Ni\beta$, when $u(p_0)$ will cease to be affected by the segregation at the second locus, $\hat{Ni\alpha}/Ni\alpha$ must obviously approach unity.

(iv) *The rate of selection advance*

We have so far only discussed the final chance of fixation at the two loci. Typical response curves are shown in Fig. 6, which give the smoothed averages of 3200 Monte Carlo replications with $N = 8$ for $Nc = 1$, $\frac{1}{4}$ and 0 respectively. The results for $Nc = \infty$ were obtained by iteration of the matrix of transition probabilities for a single locus. Clearly in the first few (say, $N/2$) generations, linkage has little influence on the rate of response, but then with tight linkage the latter rapidly slows down. After about $2N$ generations, the response has almost ceased for both $Nc = 0$ and $Nc = \infty$ but there is continued response for the two intermediate frequencies of crossing over. Since the approach to the limit is asymptotic, Robertson (1960) used the half-life of the selection process, the time taken for the mean gene frequency to get half-way to the limit, as a measure of the time scale of the response. Approximate half-lives for the example of Fig. 6 are shown in Table 2. It can be seen that as it is only the response in later generations which is reduced by tight linkage, the half-life is reduced at the lower values of Nc.

Latter (1966*a*) gives further results for the case of equal initial frequencies and selective advantages with two loci. He finds that while the half-life of the selection process is reduced the time taken to obtain 95% of the total advance is usually increased with intermediate recombination values, because of the prolonged period of late response.

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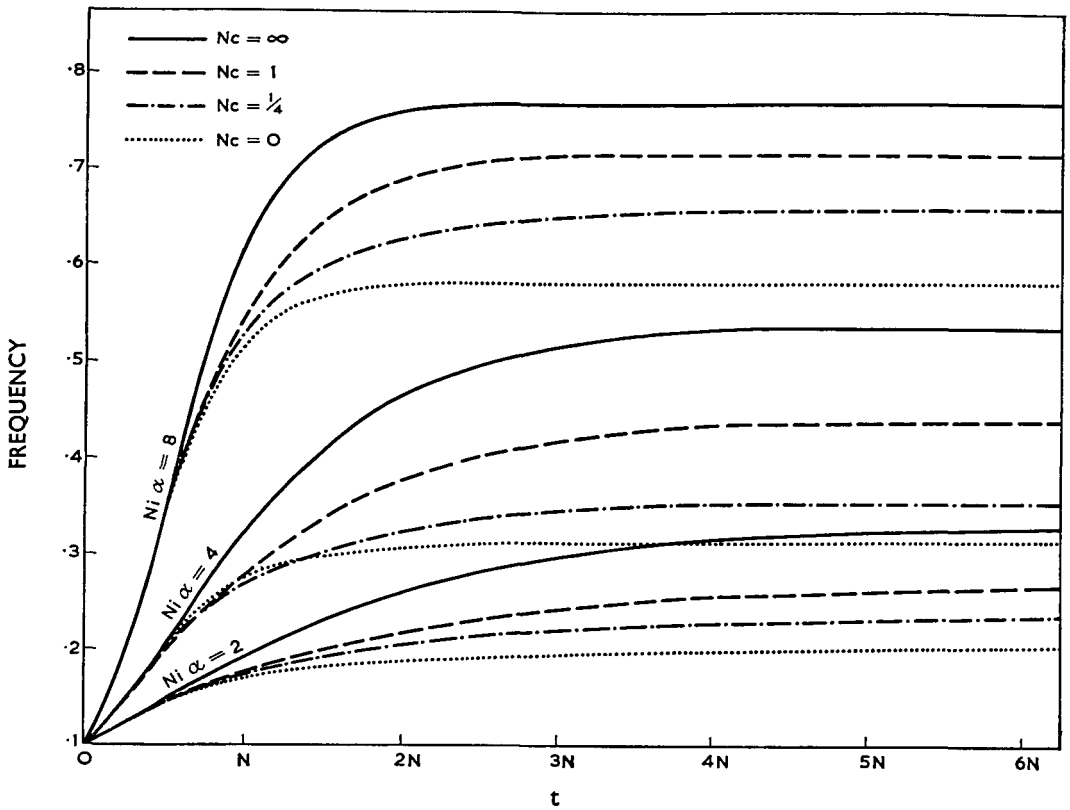

Fig. 6. Response curves at the first locus as influenced by its effect and tightness of linkage to the second. Time is measured in generations.

Table 2. *Half-lives* (× N *generations*) *of the selection process for* $p_0 = q_0 = 0{\cdot}1$ *and* $Ni\beta = 8$

	Nc			
Niα	∞	1	¼	0
2	1·31	1·19	0·86	0·65
4	1·00	0·95	0·66	0·57
8	0·64	0·62	0·57	0·50

Another view of the effect of tight linkage is given in Fig. 7, in which the mean value of p after varying numbers of generations is plotted against q_0. The effect of the segregation at the second locus is seen as the depression of p at low values of q_0. Before $N/2$ generations, this segregation has no effect on the gene frequency at the first, but at N generations p, at the value of q_0 which has maximum effect, is below that at other values and there is little change in p after this point. The diagram shows why the half-life of the process is reduced when the preferred allele at the second locus is at its most effective frequency. Examination of the curves for

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$Ni\beta = 8$ and 16 in Fig. 7 shows that at $q_0 = 0{\cdot}2$, both the total response and the half-life are greater for the higher value of $Ni\beta$.

Figure 8, which is of the same kind as Fig. 7, shows the effect of variation in $Ni\beta$ on the mean values of p at different times and includes curves for three values of Nc. When $Ni\beta$ has its maximum effect on $u(p_0)$ at the given initial frequency ($Ni\beta = 8$) there is again little effect of linkage in less than $N/2$ generations, but as $Ni\beta$ increased further it will be seen that almost all the reduction in response due to tight linkage now occurs in the earlier generations. This is to be expected since, for such high

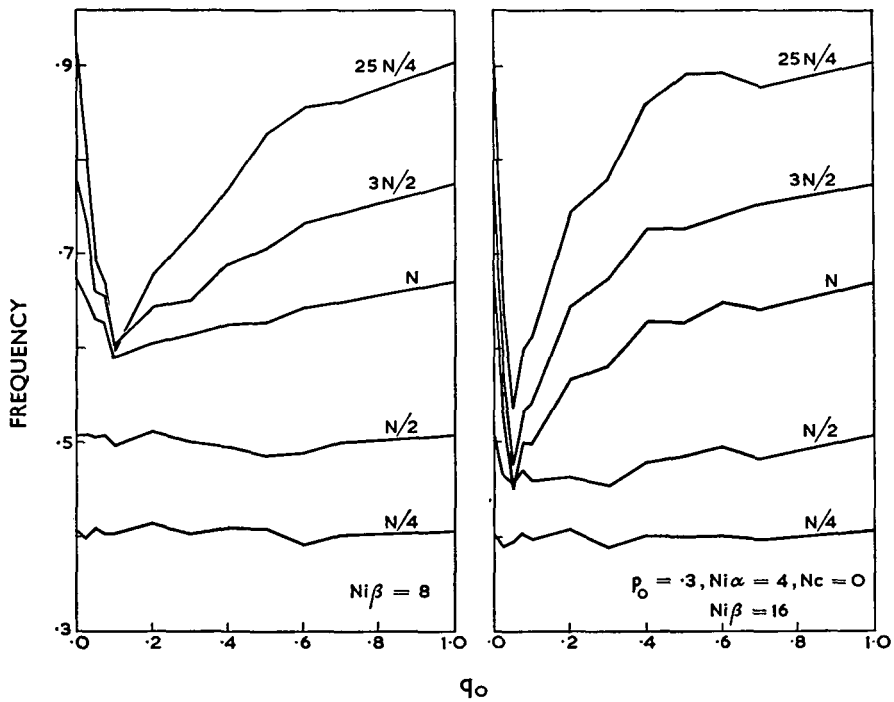

Fig. 7. The average frequency at the first locus at various times during the selection process, measured in generations, as influenced by the initial frequency and effect at the second.

values of $Ni\beta$, the second locus becomes fixed very quickly and only during this period is there segregation at both loci. It can be shown, by iteration of the transition probability matrix, that for a single gene with $Ni\beta = 32$ and $q_0 = 0{\cdot}3$, 99% of the expected change in gene frequency has been made in the first $0{\cdot}33N$ generations, whereas for a gene with a much smaller effect ($Ni\beta < 0{\cdot}5$) it takes $4{\cdot}61N$ generations for this point to be reached. When one locus goes to fixation so quickly it is clear that crossing-over has very little time to affect the outcome. In Fig. 8 it can be seen that at high values of $Ni\beta$, no more progress is made with $Nc = 1$ than with $Nc = 0$. With smaller values of $Ni\beta$, however, there is more time for recombination to occur. The shortened period of response when $Ni\beta$ is high then provides an explanation

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of the unexpectedly small effect of the relaxation of linkage at high $Ni\beta$ values in Figs. 2 and 3.

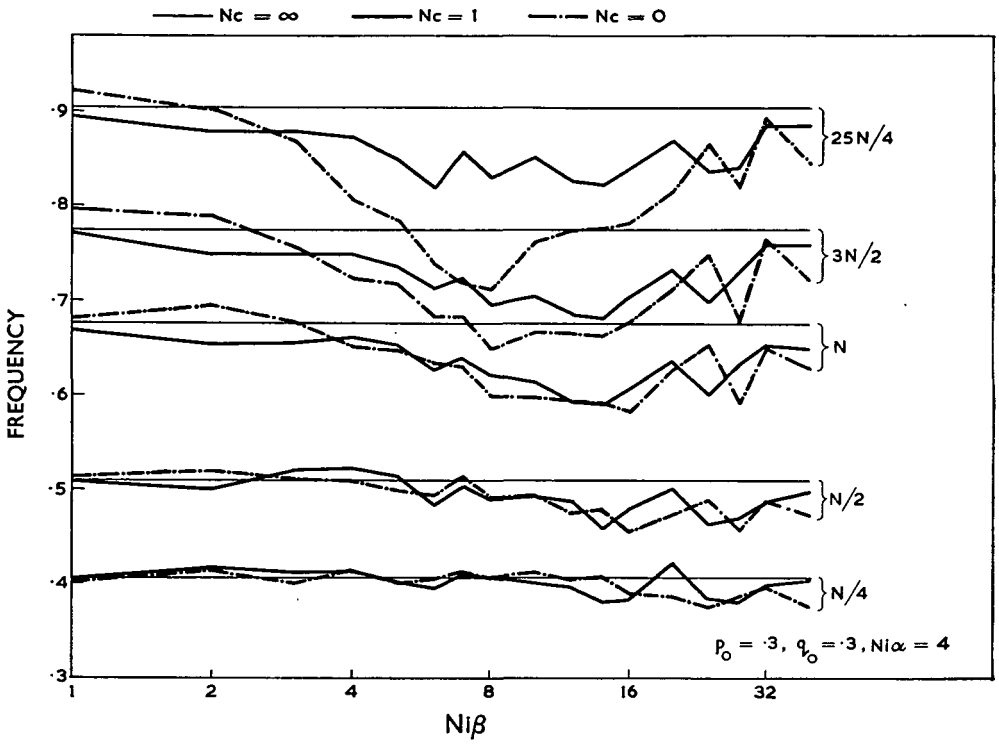

Fig. 8. The average frequency at the first locus at various times during selection, as influenced by the effect and tightness of linkage with the second.

(v) *The chance of fixation of the different gametes*

We have so far considered only the chance of fixation of the individual alleles; we shall now discuss their joint chance of fixation. Figure 9 shows, for $p_0 = q_0 = 0{\cdot}1$, $Ni\alpha = 8$, the effect of variation in Nc and in $Ni\beta$. Of these diagrams two are chosen so that $\beta \leqslant a/2$, one so that β is almost as large as α, and the final diagram shows the case of equal effects. Data from these runs have also been seen in Fig. 2. In Fig. 9 the results are plotted against $2Nc/(2Nc+1)$. As would be expected, at the lower values of β only the chance of fixation at the locus with the smaller effect is reduced as linkage becomes tighter. When the two effects are equal, the chance of fixation of the preferred alleles is reduced at both loci by tight linkage.

Latter (1965*b*) has shown that with equal effects at the two loci the chance of fixation of the unfavourable coupling gamete, *ab*, is not influenced by the degree of recombination and we find in Fig. 9 that this result holds even when the effects are unequal. The chance of fixation of the gamete aB is affected by linkage only as β approaches α. On the other hand, the chances of fixation of the gametes AB and Ab are influenced by the tightness of the linkage in all the cases. When $\beta \leqslant \alpha/2$, the favourable coupling gamete AB is less frequently fixed and the repulsion gamete

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Ab more frequently fixed with tight linkage, in such a way that the sum of their frequencies is not affected. So, if one gene has a much smaller effect than the other, the reduction in its chance of fixation as linkage becomes tighter takes place only amongst gametes in which the preferred allele at the other locus is fixed. This is to be expected in view of the results in the previous section. The gametes *ab* and *aB* are most likely to be fixed in the early generations of the selection process before the tightness of the linkage much affects it.

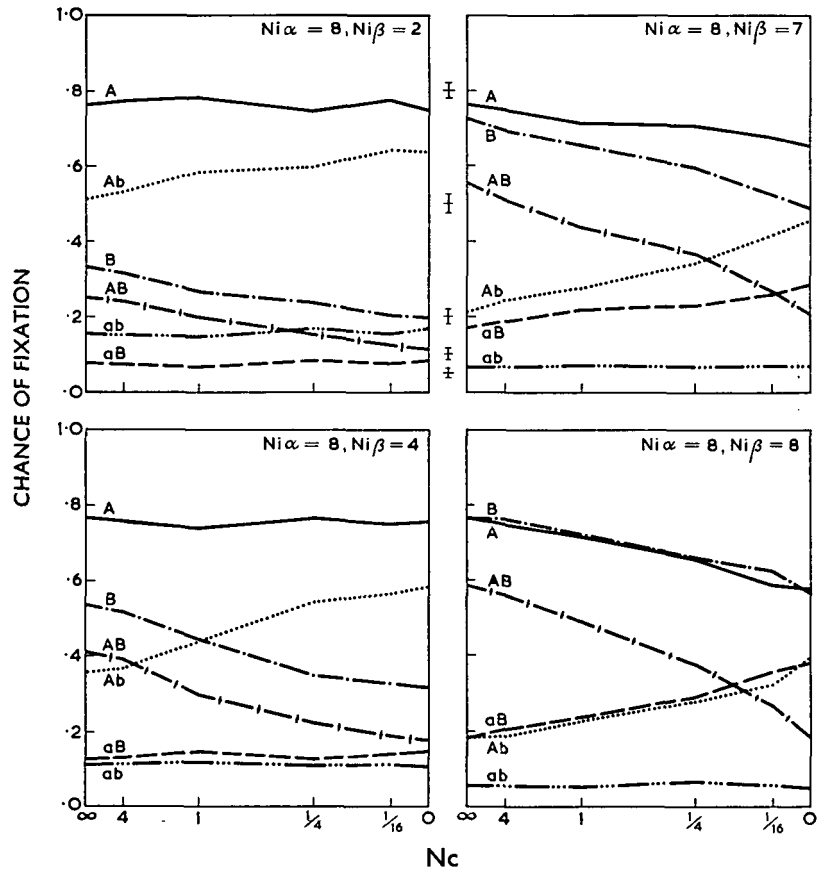

Fig. 9. The chance of fixation of the favourable alleles and the four gametic types with initial frequencies $p_0 = q_0 = 0{\cdot}1$.

We see in Fig. 9 that, as linkage becomes tighter, the chances of fixation of the repulsion gametes *Ab* and *aB* either remain constant or increase, that of *ab* remains constant and that of *AB* is reduced. As a consequence there is a negative disequilibrium D_L between lines at the limit, where

$$D_L = u(AB)\,u(ab) - u(Ab)\,u(aB)$$

where $u(-)$ is the chance of fixation of the specified gamete. In Fig. 9 with $Nc = 0$, the values of D_L are $-0{\cdot}0351$, $-0{\cdot}0667$, $-0{\cdot}1129$ and $-0{\cdot}1383$ when $Ni\beta = 2$, 4, 7 and 8 respectively. In general in our computer runs we have found an excess of

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repulsion gametes at the limit. Of the 210 runs having 400 replicates with the wide range of parameter sets mentioned earlier, D_L was zero in 72 cases (because a particular allele was fixed in all replicates), it was negative in 130 and positive in only 8. In none of the latter did D_L differ significantly from zero at the 5% level. Similarly, the observation that the chance of fixation of the *ab* gamete was not altered by the degree of linkage was found to hold at all levels of effects. Where the gene effects differed by a factor of at least 2, it was generally found that the chance of fixation of the repulsion gamete containing the unfavourable allele at the locus with the larger effect was little affected by the tightness of linkage.

(vi) *Change in the population mean under artificial selection*

We have discussed the results so far in terms of the chance of fixation of the individual gametes, but in a selection experiment for a quantitative character all that can usually be observed is the change in the population mean. This is a function

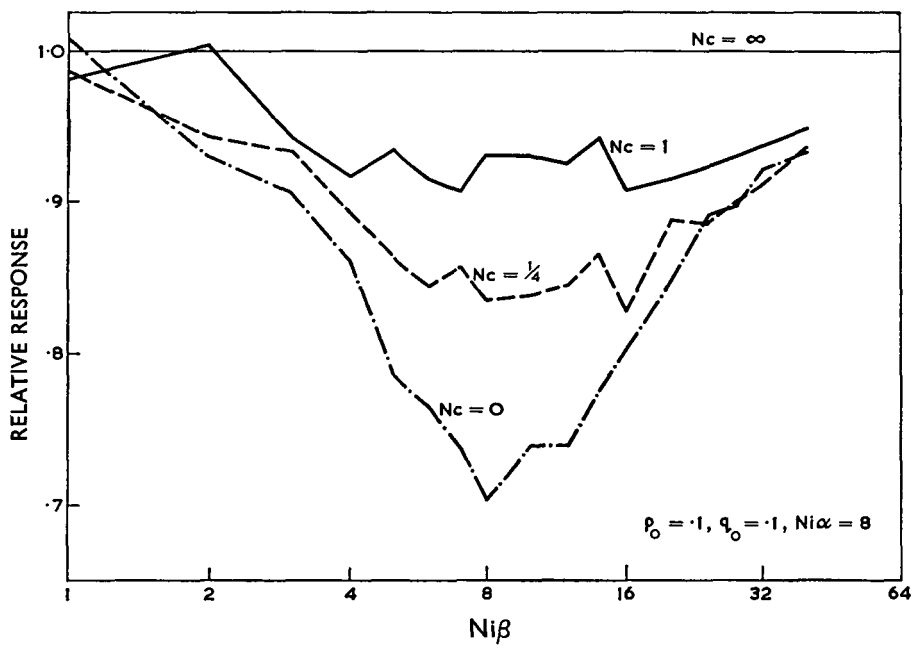

Fig. 10. The total change in the population mean expressed as a proportion of that expected from independent genes with the same effects and initial frequencies.

of the effects and changes in frequency at all loci contributing to the trait and in our case will be given by (7). To compare results from different initial frequencies and effects, we shall consider the response R observed for some parameter set as a proportion of that expected from the same set with free recombination between the loci. The greatest proportional reductions in R caused by tight linkage are found when α and β are approximately equal. An example is shown in Fig. 10, in which $Ni\alpha$ is kept constant and $Ni\beta$ is varied. The minimum of the curve of relative response occurs when the effects are approximately equal at the two loci. This

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result could have been anticipated from the earlier data for, in a model in which one locus has a much larger effect than the other, it has been shown that the change in gene frequency at the former (which will contribute most to changes in the mean of the population) is scarcely influenced by the smaller linked gene. Thus, the response in the mean will not be much influenced by the tightness of linkage when the genes have widely unequal effects on the quantitative trait.

The greatest reduction in response with tight linkage occurs when both genes have a low initial frequency and large effect. There are two reasons for this. We have to consider the same locus both as influencing the other one and being influenced by it. We showed earlier that the effect of one locus on another can best be expressed in terms of the proportional reduction in the effective value of $Ni\alpha$, and that this occurs when $Ni\beta q_0$ is in the region of 0·8, when the chance of fixation of the B allele is itself about 0·8. For the effects to be perceptible, $Ni\beta$ should be greater than 2. Now consider the sensitivity of the second locus to the segregation at the first. We can consider this as the proportional change in advance under selection, $u(q_0)-q_0$, for a given proportional change in $Ni\beta$. If the values of $Ni\beta$ are sufficiently large that we can ignore the denominator in equation (2), it can be shown that the sensitivity is at a maximum when $Ni\beta q_0(1-q_0)=\frac{1}{2}$. When $q_0=0{\cdot}2$, the maximum sensitivity will be achieved when the chance of final fixation (given by $Ni\beta=3{\cdot}125$) is 0·71. As q_0 declines, the chance of fixation for maximum sensitivity approaches the value of 0·64. Thus, for maximum influence we require a value of $u(q_0)$ of 0·8 and for maximum sensitivity we require a value slightly more than 0·64. It is not surprising then that Latter (1965*b*) found, when investigating two loci with equal effects and equal gene frequencies, that tight linkage had most effect on the advance under selection when $(u(q_0)-q_0)/(1-q_0)$ was in the region of 0·7.

It is sometimes possible in artificial selection programmes to vary the effective amount of crossing-over. One could, for instance, insert between each generation of selection a generation of relaxation with a large number of parents. This would effectively double the value of c in our equations. It is therefore of interest to know what effect this would have on the selection advance. In the situation in which linkage has its greatest effect (see Fig. 8) there appears to be an almost linear regression of change in gene frequency on $2Nc/(2Nc+1)$ in that the values for $Nc=\frac{1}{4}$ and 1 are equally spaced between $Nc=0$ and ∞. With $Nc=0$, about 30% of the total advance is lost. Assuming the linear relationship on $2Nc/(2Nc+1)$ to hold exactly, the expected responses with $N=20$, expressed as a proportion of the advance with free recombination, would be as follows:

Cross-over frequency c	*Proportional advance*
1/160	0·771
1/80	0·811
1/40	0·862
1/20	0·913
1/10	0·953
1/2	1·000

Doubling the recombination fraction produces at most an increase of 6% in the advance under selection. This occurs at $2Nc = 1$, when the curve of $2Nc/(2Nc+1)$ against $\log Nc$ has its greatest slope.

These results have some bearing on the intensity of artificial selection which should be applied in order to maximize the advance. In a mass selection programme, the number of individuals that can be measured in any generation (T) can be regarded as fixed. If selection affects only a single locus, or several independently segregating loci, it can be shown that the advance will be a function of Ni, where N is the number of animals selected to be used as parents and i is the selection intensity in standard units. This is at a maximum when the proportion of individuals selected is 0·5 (Dempster, 1955; Robertson, 1960), and the advance is symmetrical for variation about this value in the proportion selected. When two linked loci are under selection it might be expected that for two values of the proportion selected (say, 0·4 and 0·6) which give the same value of Ni, the selection advance would be greater for that with the lesser intensity of selection because Nc will then be greater. The advance under selection will no longer be symmetrical about $N/T = 0{\cdot}5$. In Table 3 we have therefore chosen for consideration a situation in which this effect should be most easily detected, i.e. two loci with equal effects on the character under selection at initial frequencies chosen so that the effect of linkage will be at its maximum and the linkage distance chosen so that the advance will be most sensitive to changes in Nc ($T = 40$, $\alpha = \beta = 0{\cdot}5$, $p_0 = q_0 = 0{\cdot}1$, and $c = 0{\cdot}025$). Figure 10 shows that in this situation the advance is almost linear on $2Nc/(2Nc+1)$. We have therefore used this relationship for interpolation of our Monte Carlo data.

Table 3. *Chance of fixation of an additive gene when* 40 *individuals* (T) *are recorded,* $\alpha = \beta = 0{\cdot}5$ *and* $p_0 = q_0 = 0{\cdot}1$

	Proportion selected								
	0·05	0·1	0·25	0·4	0·5	0·6	0·75	0·9	0·95
No linkage	0·34	0·51	0·71	0·78	0·80	0·78	0·71	0·51	0·34
$c = 0{\cdot}025$	0·31	0·46	0·61	0·66	0·70	0·70	0·65	0·49	0·33
$c = 0$	0·30	0·45	0·52	0·60	0·61	0·60	0·52	0·45	0·30

Both when the genes are segregating independently and when there is no recombination, the expected selection advance will be proportional to Ni and will be symmetrical about $N/T = 0{\cdot}5$. The second line of the table shows that, when $c = 0{\cdot}025$, the maximum in the chance of fixation, considered as a function of N/T, is only slightly shifted and occurs when N/T is about 0·55. Considerations of linkage should not greatly influence the intensity of selection to be practised if only two loci are involved. However, more drastic effects might be found with more than two.

5. DISCUSSION

There may appear to have been some contradiction between our earlier theoretical discussion and the Monte Carlo results. We stated that, when both $Ni\alpha$ and $Ni\beta$ were small, the expected advance under selection could be specified in terms of the

initial gene frequencies and the initial disequilibrium determinant and the distance between the two loci appeared only in the term containing the latter. Nevertheless, in the Monte Carlo studies it appeared that, even though we start with linkage initially at equilibrium, the advance under selection is dependent on the tightness of linkage between the two loci. How has this come about?

Felsenstein (1965) has presented a discussion of the effect of selection on linkage in infinite populations. He points out that if the genes concerned affect fitness in a multiplicative manner (i.e. if w_1, w_2, w_3 and w_4, are the relative fitnesses of the AB, Ab, aB and ab gametes and $w_1 w_4 = w_2 w_3$) then an infinite population in initial linkage equilibrium will remain in equilibrium during selection. He points out that truncation selection on a metric character will generally lead to immediate linkage disequilibrium. Nei (1963) showed that a large population initially in linkage equilibrium exposed to truncation selection has in the first generation a disequilibrium determinant given in our terminology by

$$D_1 = -\tfrac{1}{4} i^2 \alpha\beta p(1-p)\, q(1-q)$$

This formula assumes that the genes are acting additively on the character under selection. It is in fact only an approximation and inclusion in the expressions for selective advantages of squared terms in the gene effects leads to the expression

$$D_1 = \tfrac{1}{4}(ix - i^2)\, \alpha\beta p(1-p)\, q(1-q)$$

where x is the truncation point in standard units. Since $ix - i^2$ is always negative, a negative disequilibrium will be set up and the rate of response will therefore be reduced by tight linkage. In our case we have assumed an additive combination of the genes at the different loci in their effect on the fitness of the four gametes. Such selection will certainly lead to some negative disequilibrium in a large population and we decided to investigate whether this was responsible for the effect of linkage on selection limits in our case. We therefore set up for some values of the parameter sets a system of multiplicative selective advantage of the gametes. Such a modification is not as simple as it sounds, as starting from a given initial gene frequency, we wish to have the same chance of fixation in both cases with free recombination between the loci. A comparison of the additive and multiplicative model was run for a total of 80 different parameter sets and the results showed little, if any, difference in chance of fixation with tight linkage in the two models. The differences between the additive and multiplicative models obviously depend on the range of variation in the selective values of the different gametes. Although we used values for $i\alpha$ and $i\beta$ as large as one (a magnitude which would very rarely be encountered in practice) no differences were obtained between the two models. We therefore conclude that the reductions in chance of fixation with our model are not due to any great extent to a build-up of negative disequilibrium due to selection alone, predicted by Felsenstein's equation.

The solution to this problem comes from an examination of the effect of multiplicative selection when the disequilibrium determinant is not zero. It can then easily be shown that

$$D_1 = k_1 D_0 / (1 + k_2 D_0)^2$$

where k_1 and k_2 are functions of the gene frequencies and selection coefficients and are always positive. If we now consider the joint effect of genetic sampling and multiplicative selection, we see that in the first finite samples taken from the population initially at equilibrium, D will be distributed about a mean of zero with a variance depending on the sample size. After multiplicative selection, in which the D distribution will be modified according to the above formula, the average value will now be negative. A consideration of our computer runs would suggest that, even with multiplicative action, the mean negative disequilibrium determinant decreases as the square of time in the early generations, passes through a minimum and then rises to zero at final fixation.

We have not found the analysis of this process in terms of the development of the disequilibrium determinant during selection particularly illuminating and have come rather to a view of the situation in terms of the effective population size in which gene frequency changes at the locus with the smaller effect take place. This view will be given a mathematical treatment in a subsequent paper, but we may well sketch it out here for tight linkage. Consider a situation in which the B allele is at low frequency in the initial population but in which the selection process is such that, if in the initial sample there is a gamete containing B, it will almost certainly be fixed. There will then be two kinds of initial samples. In the first, no gametes containing B will be present and the expected change in p will be that calculated from equation (2). The other kind of initial sample will contain very few gametes containing the B allele. These will spread rapidly through the population under selection. With tight linkage, the change in frequency of the A allele in such lines has to take place within a population of gametes which may be very small in the early generations though, of course, as B becomes fixed it will approach $2N$. We may then expect that the average change of gene frequency at the A locus will be less in those lines in which the B gene becomes fixed and that tight linkage will therefore reduce the overall chance of fixation of A. As the initial frequency of B decreases, we have two opposing effects which lead to the minimum in the curve in Fig. 1. The first consequence will be a reduction of the number of B alleles in the initial sample (thus reducing the chance of fixation of A) until this effect is overcome by an increase in the proportion of initial samples contain no B alleles at all (so increasing the chance of fixation of A).

From this way of visualizing the problem, we can also obtain insight into some of the other surprising results. We have said that when segregation at the second locus has its greatest influence, only the changes of gene frequency at the first locus among gametes containing the desirable allele at the second are of importance in determining the final chance of fixation. The number of such gametes may be very small in the early generations of the selection process. Consider the situation in which almost all initial samples contain at least one gamete with the desirable allele at the second locus. If we then double the effect at the second locus, such gametes will increase in frequency more rapidly and as a consequence, the effective population size within which frequency changes at the first locus have to take place will be small for a shorter period of time. The expected change in gene frequency at the

first locus is then increased by increasing the effect at the second locus. We have here then an explanation of the minima in the curve of $u(p_0)$ plotted against $Ni\beta$, which we showed in Figs. 2, 3 and 4.

Now consider the effect of an increase in the gene effect at the first locus. Table 2 then shows that a greater part of the advance under selection will take place in the early generations but it is precisely in these early generations that the effective population size, with respect to changes in gene frequency at the first locus, is at its smallest. It then follows that the relative effect on the chance of fixation at the first locus will be greater as its own effect increases. This will hold until the latter approaches the same size as the effect at the second locus. This then provides us with a satisfactory explanation of the minimum value of $\widehat{Ni\alpha}/Ni\alpha$ found in Table 1.

Latter (1966*b*) has discussed in some detail the interaction of linkage intensity and population size, using computer simulation with two additive loci with equal gene effects and initial gene frequency. He concentrated attention on the situation in which he had found that the restrictive effect of linkage was greatest, i.e. when, under free recombination, $u(p_0)-p_0=0{\cdot}70(1-p_0)$. We were interested to see to what extent the interactions might be removed when linkage intensity was measured on the scale $2Nc/(2Nc+1)$. At his lower population sizes ($N=5$ and 10) the regression of response in the transformed linkage value was reasonably linear but this was clearly not so for the higher values ($N=20$ and 40). There was then a higher chance of fixation for intermediate values of c than would be expected from a linear relationship, i.e. the curve was concave downwards. This is opposite to the curvilinearity we found for high values of $Ni\beta$ when $\beta \gg \alpha$ (see Fig. 3).

Latter's experiments at the higher two population sizes correspond in our notation to runs with $Ni\alpha=Ni\beta=18$, $p_0=q_0=0{\cdot}035$ and $Ni\alpha=Ni\beta=36$, $p_0=q_0=0{\cdot}017$ respectively, somewhat higher values of Ns than we have dealt with. However, it is interesting that the curve of the chance of fixation of the AB gamete is concave downwards in our Fig. 9 when $Ni\alpha=Ni\beta=8$, $p_0=q_0=0{\cdot}1$, our most comparable experiment. In his theoretical treatment of the results, Latter lays particular stress on that phase of such selection runs in which only the equivalent gametes Ab and aB are segregating, a phase in which no selection is taking place even though the original $Ni\alpha=Ni\beta$ values were high. This phase is ended either by random fixation of one of the two or by the production of an AB gamete by crossing-over.

We would suggest that such a situation is a very special case due to the equality of gene effects at the two loci. With two alleles segregating and low selection pressures, it is known that the half-life of the process is $1{\cdot}4N$ generations. Selection reduces this by a factor which is dependent on Ns, where s is the difference in selective advantage between the two. Figure 11 (an extension of Fig. 3 in Robertson (1960)) shows the magnitude of this reduction. At higher values of Ns, the half-life at a given initial frequency is proportional to $1/Ns$. In the nomenclature of this paper, Ns is equal to $Ni(\alpha-\beta)$. If a value of $Ni(\alpha-\beta)$ of four can greatly reduce the period of joint segregation of the Ab and aB alleles, when $Ni\alpha$ and $Ni\beta$ are of the order of 40, we would suggest that we are here dealing with a very special case which

would be much altered at the higher population size by a relative difference of only 10% between the gene effects at the two loci. This should perhaps suggest caution in generalizing too much from selection simulation studies on models in which all loci have equal effects.

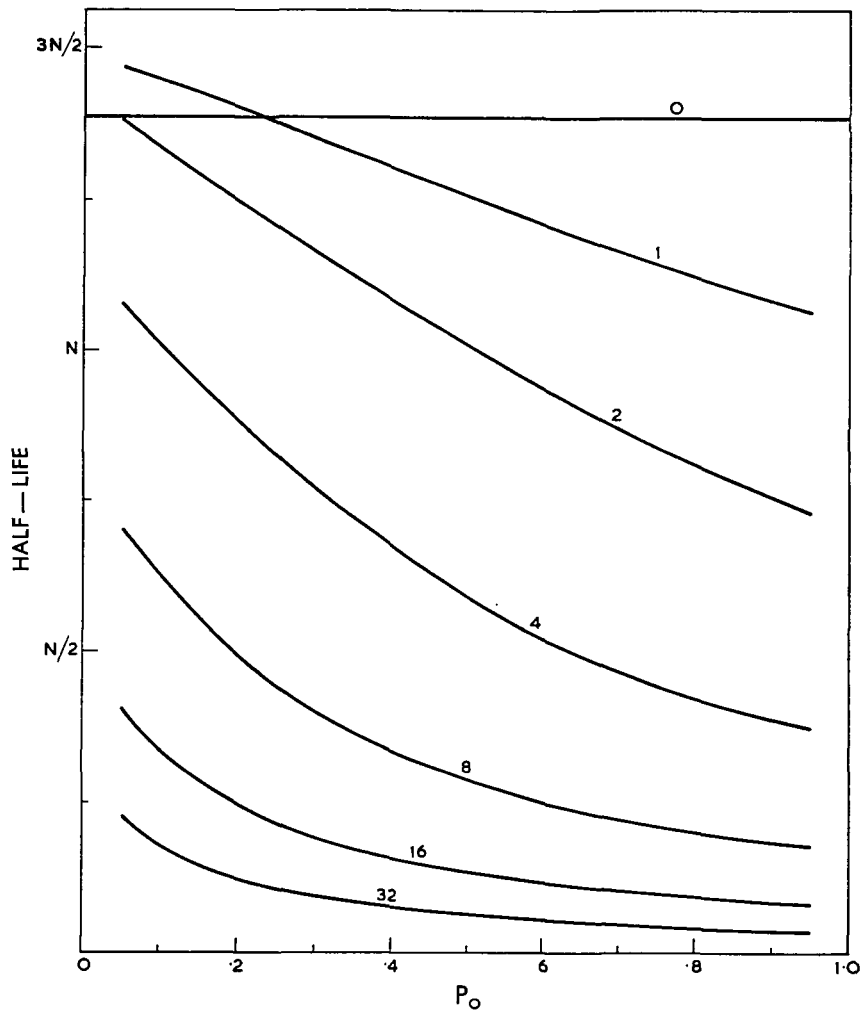

Fig. 11. The half-life of the selection process when two alleles are segregating at one locus.

We should now turn to some of the assumptions and limitations of this study. From the diffusion equation, it was argued that computer runs need only be made at one level of population size but the parameters $i\alpha$, $i\beta$ and c used were frequently much larger than those required for the diffusion approximation to hold. Nevertheless our results, including those of Fig. 4, indicate that the use of $Ni\alpha$, $Ni\beta$ and Nc as sufficient parameters is highly robust against departures from the underlying assumptions. Again, some approximations were made in the simulation procedure,

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partly to reduce computing time. In particular, the algebra developed for infinite populations which was used to simulate selection and recombination entirely in terms of gametes, assumes that Hardy–Weinberg equilibrium holds and also that there is no distinction between the sexes and that self-fertilization is permitted. Errors introduced by these approximations will become smaller, the larger the population size used, but small N values were usually run to minimize computation. A similar kind of inaccuracy was introduced in the definition of the selective advantage in terms of the effects of the genes on the character under selection, which are precise only for genes of small effect. Strictly speaking, second and higher order terms in effects should have been included but then we could not have generalized to populations of different sizes.

The selective values $i\alpha$ and $i\beta$ of the favourable alleles have been kept constant throughout the selection process and here two important assumptions have been made. Firstly, the gene effects α and β have been defined as the difference in genotypic value between the homozygotes at the two loci as a proportion of the phenotypic standard deviation, σ. Thus, for the selective values to remain constant during selection, σ itself must remain unchanged. As selection proceeds, it would be expected that the genetic variance at other loci would decline although at the same time the environmental variance might increase as the level of homozygosity rises. We may perhaps be encouraged by the general agreement of our results with those of Latter (1965*b*) on selection effects at two additive loci within the restrictions that he imposed on the gene effects and frequencies, in that there were less assumptions made in his approach. Finally, we have taken no account of natural selection, which might be expected to alter the effective selective values of genes having correlated effects on fitness as the gene frequencies move away from their initial equilibrium values.

This work is to be continued to include more than two loci segregating simultaneously as well as non-additive gene effects. There have been several Monte Carlo studies with many loci but these have all been restricted to equal gene effects with all initial gene frequencies at one-half. Using only two loci, we have been able to analyse the interactions of the parameters at the two loci more clearly than we could have done with many loci segregating at the same time. In this restricted study, we have been able to draw attention to a situation in which linkage is likely to be important which may be of fairly general occurrence, i.e. a desirable allele in the initial population at a low frequency but with a sufficiently large effect on the character under selection that its chance of fixation is high.

Although we have succeeded in finding a reasonably simple model to explain our results, they are nevertheless a little disappointing from one point of view. Even in this simplest of all situations, we find not only curvilinearity of effects but minima in the curves. It would therefore seem rather unlikely that any general theory could be constructed to be useful in the more complex situations which must exist in practice.

A further restriction of the results, but one which can easily be removed, is that we have dealt only with populations in initial linkage equilibrium. Mather (1943)

has argued that natural selection will favour a balance between alleles at linked loci with similar effects on the character under selection, but Wright (1952) has shown that selection values have to be large and linkage very tight for such equilibrium to be maintained. In general, if loci have no epistatic effects on fitness, an unselected closed random-mating population would be expected to remain in equilibrium (Lewontin & Kojima, 1960). On the other hand, our results show that linkage disequilibrium (in the form of an excess of repulsion gametes) is likely in populations derived from crosses between selected lines or between selected lines and unselected populations. These situations need further investigation, for they have particular relevance to problems of breaking through selection limits in artificial selection.

SUMMARY

(i) A computer simulation study has been made of selection on two linked loci in small populations, where both loci were assumed to have additive effects on the character under selection with no interaction between loci. If N is the effective population size, i the intensity of selection in standard units, α and β measure the effects of the two loci on the character under selection as a proportion of the phenotypic standard deviation and c is the crossover distance between them, it was shown that the selection process can be completely specified by $Ni\alpha$, $Ni\beta$ and Nc and the initial gene frequencies and linkage disequilibrium coefficient. It is then easily possible to generalize from computer runs at only one population size. All computer runs assumed an initial population at linkage equilibrium between the two loci. Analysis of the results was greatly simplified by considering the influence of segregation at the second locus on the chance of fixation at the first (defined as the proportion of replicate lines in which the favoured allele was eventually fixed).

(ii) The effects of linkage are sufficiently described by Nc. The relationship between chance of fixation at the limit and linkage distance (expressed as $2Nc/(2Nc+1)$) was linear in the majority of computer runs.

(iii) When gene frequency changes under independent segregation were small, linkage had no effect on the advance under selection. In general, segregation at the second locus had no detectable influence on the chance of fixation at the first if the gene effects at the second were less than one-half those at the first. With larger gene effects at the second locus, the chance of fixation passed through a minimum and then rose again. For two loci to have a mutual influence on one another, their effects on the character under selection should not differ by a factor of more than two.

(iv) Under conditions of suitable relative gene effects, the influence of segregation at the second locus was very dependent on the initial frequency of the desirable allele. The chance of fixation at the first, plotted against initial frequency of the desirable allele at the second, passed through a minimum when the chance of fixation at the second locus was about 0·8.

(v) A transformation was found which made the influence of segregation at the second locus on the chance of fixation at the first almost independent of initial gene frequency at the first and of gene effects at the first locus when these are small.

(vi) In the population of gametes at final fixation, linkage was not at equilibrium and there was an excess of repulsion gametes.

(vii) The results were extended to a consideration of the effect of linkage on the limits under artificial selection. Linkage proved only to be of importance when the two loci had roughly equal effects on the character under selection. The maximum effect on the advance under selection occurred when the chance of fixation at both of the loci was between 0·7 and 0·8. When the advance under selection is most sensitive to changes in recombination value, a doubling of the latter in no case increased the advance under selection by more than about 6%. The proportion selected to give maximum advance under individual selection (0·5 under independent segregation) was increased, but only very slightly, when linkage is important.

(viii) These phenomena could be satisfactorily accounted for in terms of the time scale of the selection process and the effective size of the population within which changes of gene frequency at the locus with smaller effect must take place.

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