THE EFFECT OF LINKAGE ON DIRECTIONAL SELECTION

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RECENT studies of the joint effects of linkage and selection have concentrated on equilibrium populations, and on the effect of recombination on the position and stability of the equilibrium (BODMER and PARSONS 1962; HALDANE 1962; PARSONS 1963; LEWONTIN 1964 a,b). Less attention has been given to cases in which alleles are increasing towards fixation, with no intermediate equilibrium possible. Selection of this type, whether natural or artificial, may be referred to as directional selection. Linkage will affect gene and genotype frequencies only in the presence of linkage disequilibrium, which may be defined as nonrandom association of alleles at different loci. Linkage disequilibrium can arise during directional selection, although it must inevitably disappear when the favored alleles become fixed. Consequently, computer stimulation studies of artificial selection have often shown significant linkage effects. This paper will examine the qualitative effects of directional selection on linkage disequilibrium, and will discuss the effects of linkage on the rate of change of gene frequencies.

With two loci, A and B, each having two alleles, there are four types of gametes or haploid genotypes possible: A_1B_1, A_1B_2, A_2B_1 and A_2B_2. In the equations which follow, the gamete frequencies will be described by two systems of parameters, one involving the gamete frequencies themselves, the other using the gene frequencies and a linkage disequilibrium parameter. These systems can be summarized as follows:

$$\begin{array}{ll} A_1B_1 & x_1 = pq + D \\ A_1B_2 & x_2 = p(1-q) - D \\ A_2B_1 & x_3 = (1-p)q - D \\ A_2B_2 & x_4 = (1-p)(1-q) + D. \end{array} \tag{1}$$

$p = x_1 + x_2$ is the frequency of A_1, and $q = x_1 + x_3$ is the frequency of B_1. D is the excess of the A_1B_1 gametes over the frequency which would be predicted with random association of A_1 and B_1. Note that

$$D = x_1x_4 - x_2x_3.$$

Another measure of linkage disequilibrium, Z, will also be used:

$$\begin{aligned} Z &= \log_e (x_1x_4) - \log_e (x_2x_3) \\ &= \log_e x_1 - \log_e x_2 - \log_e x_3 + \log_e x_4. \end{aligned}$$

Note that Z and D always have the same sign, and are both zero when there is

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linkage equilibrium. Note also that Z is not defined when any of the x_i are zero.

MORAN (1964) has defined a useful function to keep track of sign changes in the equations for two-locus systems:

$$k(i) = \begin{cases} 1 & i = 1,4 \\ -1 & i = 2,3. \end{cases}$$

The following properties of $k(i)$ should be noted:

$$k^2(i) = 1$$

$$\sum_{i=1}^{4} k(i) = 0.$$

Using this function, we can rewrite the definition of Z as:

$$Z = \sum_{i=1}^{4} k(i) \log_e x_i.$$

Infinitely large random-mating populations of organisms having both a haploid stage and a diploid stage in their life cycle will be considered. Models of selection can be constructed with either continuous or discontinuous generations, with selection occurring in either the haploid or the diploid stage. These possibilities will be examined to determine the type of linkage disequilibrium produced by directional selection. In all cases r will denote the recombination fraction between A and B.

Haploid selection, continuous generations: Let the probability that in a small interval of time dt a haploid individual mates at random and produces one offspring be given by $b\,dt$. Let the probability that an individual of type i dies in the interval dt be given by $d_i dt$. Let $m_i = b - d_i$. Then by a derivation similar to that given by KIMURA (1956) we obtain

$$\frac{dx_i}{dt} = x_i(m_i - \bar{m}) - k(i) rbD \tag{2}$$

where $\bar{m} = \sum_i x_i m_i$. The m_i would be the malthusian parameters of populations containing only type i individuals.

Each of the m_i can be represented as the sum of a mean effect, individual locus effects, and an interaction effect, as follows:

$$\begin{array}{ll} A_1B_1 & m_1 = \mu \\ A_1B_2 & m_2 = \mu + \beta \\ A_2B_1 & m_3 = \mu + \alpha \\ A_2B_2 & m_4 = \mu + \alpha + \beta + E. \end{array}$$

We can write an equation for the interaction parameter E in terms of the m_i:

$$E = m_1 - m_2 - m_3 + m_4 = \sum_{i=1}^{4} k(i) m_i. \tag{3}$$

In direct analogy with the linkage disequilibrium parameter D, the epistasis parameter E measures the excess of m_4 over the value it would assume if the m_i were determined additively by the two loci.

We are now in a position to examine the effect of selection on linkage disequilibrium.

$$\frac{dZ}{dt} = \frac{d}{dt}\Big[\sum_i k(i) \log_e x_i\Big] = \sum_i k(i)\frac{1}{x_i}\frac{dx_i}{dt} \tag{4}$$

Substituting (2) and (3) into (4), we obtain

$$\frac{dZ}{dt} = E - rbD\Big(\sum_i \frac{1}{x_i}\Big).$$

Note that $\sum_i \frac{1}{x_i} > 0$, and recall that Z and D always have the same sign. Then if E is positive, Z will increase whenever Z and D are negative or zero. If E is negative Z will decrease whenever Z and D are positive or zero. If $E = 0$, Z will move towards zero, provided that r is not zero. In general, Z will change until it has the same sign as E.

Haploid selection, discontinuous generations: If x_1 is the frequency of the haploid genotype A_1B_1 before fertilization, then the frequency immediately after meiosis will be $x_1^2 + x_1x_2 + x_1x_3 + x_1x_4(1 - r) + x_2x_3r$ or $x_1 - rD$. If W_i is the probability that type i survives from meiosis to fertilization, then if we count the genotypes immediately before fertilization, we obtain

$$x_i' = W_i(x_i - k(i)rD)/\overline{W} \tag{5}$$

where $\overline{W} = \sum_i (x_i - k(i)rD)W_i$.

Each of the W_i can be represented as the product of individual locus effects and an interaction effect:

$$\begin{aligned} A_1B_1 \quad & W_1 = 1 \\ A_1B_2 \quad & W_2 = \beta \\ A_2B_1 \quad & W_3 = \alpha \\ A_2B_2 \quad & W_4 = \alpha\beta\,\gamma. \end{aligned}$$

We can write an equation for the interaction effect in terms of the W_i:

$$\gamma = \frac{W_1W_4}{W_2W_3}.$$

The measure of epistasis in this model will be the logarithm of γ

$$E = \log_e\gamma = \log_e\Big(\frac{W_1W_4}{W_2W_3}\Big)$$

$$E = \sum_i k(i)\log_e W_i.$$

E is a measure of the excess of $\log_e W_4$ over the value it would assume if the W_i were determined multiplicatively by the two loci.

As before, we can write an equation for the change in Z:

$$\Delta Z = Z' - Z = \log_e\Big(\frac{x'_1x'_4}{x'_2x'_3}\frac{x_2x_3}{x_1x_4}\Big)$$

From (5)

$$\begin{aligned} \Delta Z &= \log_e\Big[\frac{W_1(1 - rD/x_1)W_4(1 - rD/x_4)}{W_2(1 + rD/x_2)W_3(1 + rD/x_3)}\Big] \\ &= \sum_i k(i)\log_e W_i + \sum_i k(i)\log_e(1 - k(i)rD/x_i). \end{aligned} \tag{6}$$

Noting that the sign of $\log(1 + y)$ is the same as the sign of y, the second term of

(6) will be a sum of terms each having the same sign as $-k^2(i)rD/x_i$. Then

$$\Delta Z = E + Q.$$

Where Q has the same sign as $-rD$. As before, Z will change until it has the same sign as E.

Diploid selection, continuous generations: Let a diploid individual composed of gamete types i and j be denoted by ij. Let the probability that any individual dies in a time interval of width dt be $d\ dt$. With probability $b_{ij}\ dt$ an individual of type ij selects a mate at random from the whole population and produces a single offspring during the time interval dt. Thus each mating consists of an active and a passive partner. Type ij participates during a time interval dt in $n_{ij}\ b_{ij}\ dt$ matings as the active partner, and in $n_{ij}\ \bar{b}\ dt$ matings as the passive partner, where $\bar{b}\ dt$ is the probability that a randomly chosen individual will mate during the interval dt, and n_{ij} is the number of type ij individuals. Although this model may seem unnecessarily limited and complicated, it can be shown that it will not generate departure from Hardy-Weinberg proportions, as will many other possible diploid-continuous models (such as, for example, almost any model in which the probability of death varies with the genotype). Other models will, however, approach Hardy-Weinberg proportions as selection is made infinitely slow. If the genotypes are in Hardy-Weinberg proportions, the diploid genotype frequencies are the products of the corresponding gamete frequencies. Note that Hardy-Weinberg proportions are not incompatible with the existence of linkage disequilibrium.

Letting $m_{ij} = \frac{1}{2}\ b_{ij} - d$ and assuming that the coupling and repulsion double heterozygotes have the same birth rates, so that $b_{14} = b_{23}$, it can be shown that

$$\frac{dx_i}{dt} = x_i(m_i - \overline{m}) - k(i)r(\tfrac{1}{2}\ b_{14} + \tfrac{1}{2}\ \bar{b})D \qquad (7)$$

where $m_i = \sum_j x_j\ m_{ij}$, and $\overline{m} = \sum_i x_i\ m_i = \sum_{ij} x_i x_j\ m_{ij}$. Equations similar to (7) were first derived by KIMURA (1956).

If the m_{ij} are the sums of the effects of loci A and B, knowing the fitness of the double heterozygote, $m_{14}(= m_{23})$, and the single heterozygote fitnesses m_{12}, m_{13}, m_{24}, and m_{34}, we can predict the double homozygote fitnesses m_{11}, m_{22}, m_{33}, and m_{44}. Define the presence of epistasis by the deviation of any of these four fitnesses from their expected values. Then there will be four independent parameters measuring epistasis. Four such parameters are:

$$\begin{aligned} E_1 &= m_{11} - m_{12} - m_{13} + m_{14} \\ E_2 &= m_{12} - m_{22} - m_{23} + m_{24} \\ E_3 &= m_{13} - m_{23} - m_{33} + m_{34} \\ E_4 &= m_{14} - m_{24} - m_{34} + m_{44} \end{aligned}$$

or, in general,

$$E_i = \sum_j k(j) m_{ij} \qquad i = 1,2,3,4. \qquad (8)$$

Epistasis parameters of this sort were first used by FISHER (1918) to measure epistasis on a phenotypic scale. KOJIMA and KELLEHER (1961) used the above parameters to measure epistasis on a fitness scale.

The effect of selection on linkage disequilibrium can be derived by obtaining an equation for the change in Z:

$$\frac{dZ}{dt} = \sum_i k(i) \frac{1}{x_i} \frac{dx_i}{dt}.$$

Substituting from (7) and (8),

$$\frac{dZ}{dt} = \sum_i k(i) \frac{1}{x_i} \left[x_i(m_i - \bar{m}) - k(i) r(\tfrac{1}{2} b_{14} + \tfrac{1}{2} \bar{b}) D \right]$$

$$= \sum_j x_j E_j - (\tfrac{1}{2} b_{14} + \tfrac{1}{2} \bar{b}) r D \sum_i \frac{1}{x_i}.$$

If all of the E_i have the same sign, then $\bar{E} = \sum_j x_j E_j$ will have this sign. We have

$$\frac{dZ}{dt} = \bar{E} - (\tfrac{1}{2} b_{14} + \tfrac{1}{2} \bar{b}) r D \sum_i \frac{1}{x_i}.$$

If all of the E_i are positive, Z will increase whenever Z and D are negative or zero. If all of the E_i are negative, Z will decrease whenever Z and D are positive. If all of the E_i are zero, Z will tend to zero if r is not zero. As in the haploid cases we can say that Z will ultimately have the same sign as the E_i. Although the only cases treated here have been those in which the E_i are all the same sign, these cases will later be shown to be of particular importance.

Diploid selection, discontinuous generations: Let $W_{ij} (= W_{ji})$ be the probability that an individual of type ij survives from fertilization until it reproduces by mating at random. The equation for the frequency of gamete type 1 at fertilization can be seen to be

$$x'_1 = [x_1 x_1 W_{11} + x_1 x_2 W_{12} + x_1 x_3 W_{13} + x_1 x_4 W_{14}(1 - r) + x_2 x_3 W_{23} r] / \bar{W}.$$

If $W_{14} = W_{23}$,

$$x'_1 = [x_1(x_1 W_{11} + x_2 W_{12} + x_3 W_{13} + x_4 W_{14}) - r(x_1 x_4 - x_2 x_3) W_{14}] / \bar{W}$$

and in general,

$$x'_i = (x_i W_i - k(i) r D W_{14}) / \bar{W}$$

where $W_i = \sum_j x_j W_{ij}$ and $\bar{W} = \sum_i x_i W_i = \sum_{ij} x_i x_j W_{ij}$. These equations were first derived by LEWONTIN and KOJIMA (1960).

Assume that in the absence of epistasis, the W_{ij} are the products of the effects of loci A and B. We can then predict the viabilities of the double homozygotes from the double heterozygote and single heterozygote viabilities. Four epistasis parameters are needed. In this case our parameters will represent the deviation of the logarithms of the double homozygote viabilities from the values they would assume in the absence of epistasis:

$$E_i = \sum_j k(j) \log_e W_{ij}. \tag{10}$$

If there is no epistasis all the E_i will be zero. The meaning of the epistasis parameters is illustrated by the set of parameters in Table 1.

As in the previous cases, we can examine the equation for the change in Z to find the effect of selection on linkage disequilibrium. In contrast to the previous

TABLE 1

Fitness of genotypes in diploid-discontinuous model

	B_1B_1	B_1B_2	B_2B_2
A_1A_1	abe^{E_1}	a	ace^{-E_2}
A_1A_2	b	1	c
A_2A_2	bde^{-E_3}	d	cde^{E_4}

cases, clear results can be obtained only when $D = 0$. The equation for the change in Z is

$$\Delta Z = Z' - Z = log_e \left(\frac{x'_1 x'_4}{x'_2 x'_3} \frac{x_2 x_3}{x_1 x_4} \right) .$$

From (9),

$$\Delta Z = log_e \left[\frac{(W_1 - rDW_{14}/x_1)(W_4 - rDW_{14}/x_4)}{(W_2 + rDW_{14}/x_2)(W_3 + rDW_{14}/x_3)} \right]$$

and when $D = 0$,

$$\Delta Z = log_e \left(\frac{W_1 W_4}{W_2 W_3} \right)$$

which will have the same sign as $W_1W_4 - W_2W_3$. Using the parameters of Table 1 in place of the W_{ij}, we can write

$$\begin{aligned} W_1 &= abe^{E_1}x_1 + ax_2 + bx_3 + x_4 \\ W_2 &= ax_1 + ace^{-E_2}x_2 + x_3 + cx_4 \\ W_3 &= bx_1 + x_2 + bde^{-E_3}x_3 + dx_4 \\ W_4 &= x_1 + cx_2 + dx_3 + cde^{E_4}x_4. \end{aligned}$$

If the E_i are all zero,

$$\begin{aligned} W_1W_4 - W_2W_3 &= (x_1x_4 - x_2x_3)(ad - 1)(bc - 1) \\ &= D(ad - 1)(bc - 1) \\ &= 0 . \end{aligned}$$

If the E_i are all positive, W_1 and W_4 are increased and W_2 and W_3 are decreased, so that $W_1W_4 - W_2W_3 > 0$. If the E_i are all negative, W_1 and W_4 are decreased, and W_2 and W_3 are increased, so that $W_1W_4 - W_2W_3 < 0$. Then when the E_i are all of the same sign and Z and D are zero, the linkage disequilibrium will increase if the E_i are positive and decrease if the E_i are negative.

Equations for the change in D were derived by NEI (1963), in the only previous derivation of the effects of directional selection on linkage disequilibrium. His equations differed from the above in that they treated the change in D rather than the change in Z, and did not utilize the above fitness parameters.

The conclusions for the diploid-discontinuous model are weaker than for the other models since we cannot say that when D is opposite in sign to the E_i it will change in the direction of the E_i. If we choose r very small, ΔZ will have the same sign as $W_1W_4 - W_2W_3$. If we choose fitnesses such that the E_i are small in magnitude and $(ad - 1)(bc - 1)$ is positive and large, then ΔZ will have the same sign as D for large D regardless of the signs of the E_i. Thus our conclusion for this model is the same as for the other models, with the restriction that it need hold only at or near $D = 0$.

We have seen that directional selection will tend to generate linkage disequilibrium of the same sign as the epistatic parameters. It must be emphasized that although the effect of recombination will be to reduce the amount of linkage disequilibrium generated, linkage disequilibrium can be produced by selection even when the two loci are unlinked. This point has been made for equilibrium populations by BODMER and PARSONS (1962) and LEWONTIN (1964). It is often assumed, especially in the literature of biometrical genetics, that the absence of linkage is sufficient to guarantee the absence of linkage disequilibrium. Although this assumption has been shown to be invalid, nothing has been said about the magnitude of the linkage disequilibrium generated by selection. When the loci are unlinked or loosely linked, the linkage disequilibrium generated by selection will often be so small that it can effectively be ignored.

It may be useful at this point to establish that there is a certain equivalence between the epistasis parameters defined for the continuous and discontinuous models. If we have haploid-discontinuous and haploid-continuous models whose fitness parameters are related by

$$m_i = \log_e W_i$$

then since

$$m_1 - m_2 - m_3 + m_4 = \log_e W_1 - \log_e W_2 - \log_e W_3 + \log_e W_4$$

the epistasis parameters in the two models will be equal. Likewise, if we have diploid-discontinuous and diploid-continuous models whose fitness parameters are related by

$$m_{ij} = \log_e W_{ij}$$

since

$$\sum_j k(j) m_{ij} = \sum_j k(j) \log_e W_{ij}$$

the epistasis parameters in the continuous model will be equal to the epistasis parameters in the discontinuous model.

Epistasis produced by a simple transformation

We now examine an important type of epistasis, namely, epistasis produced when fitness is a function of an additive phenotype. Let a phenotype P be the sum of contributions from loci A and B, and let the fitness of a genotype which has phenotype P be given by

$$\log_e W = m = f(P).$$

Then the haploid cases can be summarized:

	P	m or $\log_e W$
A_1B_1	c	$f(c)$
A_1B_2	$b + c$	$f(b + c)$
A_2B_1	$a + c$	$f(a + c)$
A_2B_2	$a + b + c$	$f(a + b + c)$

Assume $a > 0$ and $b > 0$. Our measure of epistasis becomes

$$E = m_1 - m_2 - m_3 + m_4 = f(a + b + c) - f(a + c) - f(b + c) + f(c). \quad (11)$$

The diploid cases are summarized in Table 2.

Suppose that in the determination of P the fitness of every heterozygote is

TABLE 2

Phenotype and fitness when fitness is a function of an additively determined phenotype in diploid selection

	Phenotype (P)				Fitness (m or $\log_e W$)		
	B_1B_1	B_1B_2	B_2B_2		B_1B_1	B_1B_2	B_2B_2
A_1A_1	c	b_1+c	b_2+c	A_1A_1	$f(c)$	$f(b_1+c)$	$f(b_2+c)$
A_1A_2	a_1+c	a_1+b_1+c	a_1+b_2+c	A_1A_2	$f(a_1+c)$	$f(a_1+b_1+c)$	$f(a_1+b_2+c)$
A_2A_2	a_2+c	a_2+b_1+c	a_2+b_2+c	A_2A_2	$f(a_2+c)$	$f(a_2+b_1+c)$	$f(a_2+b_2+c)$

between the fitnesses of the corresponding homozygotes. Then $a_2 > a_1 > 0$ and $b_2 > b_1 > 0$, and $\alpha = a_2 - a_1 > 0$ and $\beta = b_2 - b_1 > 0$. From the definition of the epistatic parameters in equations (8) and (10) we obtain

$$\begin{aligned}
E_1 &= f(a_1 + b_1 + c) - f(a_1 + c) - f(b_1 + c) + f(c) \\
E_2 &= f(a_1 + b_2 + c) - f(a_1 + b_1 + c) - f(b_2 + c) + f(b_1 + c) \\
E_3 &= f(a_2 + b_1 + c) - f(a_2 + c) - f(a_1 + b_1 + c) + f(a_1 + c) \\
E_4 &= f(a_2 + b_2 + c) - f(a_2 + b_1 + c) - f(a_1 + b_2 + c) + f(a_1 + b_1 + c)
\end{aligned}$$

which can be written as

$$\begin{aligned}
E_1 &= f(a_1 + b_1 + c) - f(a_1 + c) - f(b_1 + c) + f(c) \\
E_2 &= f(a_1 + \beta + (b_1+c)) - f(a_1 + (b_1+c)) - f(\beta + (b_1+c)) + f(b_1 + c) \\
E_3 &= f(\alpha + b_1 + (a_1+c)) - f(\alpha + (a_1+c)) - f(b_1 + (a_1+c)) + f(a_1 + c) \\
E_4 &= f(\alpha + \beta + (a_1+b_1+c)) - f(\alpha + (a_1+b_1+c)) - f(\beta + (a_1+b_1+c)) \\
&\quad + f(a_1 + b_1 + c). \qquad (12)
\end{aligned}$$

We can now make use of the

Theorem: If f is continuous and has continuous first and second derivatives on the interval $[c, a + b + c]$, where $a > 0$ and $b > 0$, then $f(a + b + c) - f(a + c) - f(b + c) + f(c)$ has the same sign as $f''(x)$ for some x in $[c, a + b + c]$.

This theorem is proved in the Appendix. Assume that f has the continuity properties required, and that its second derivative $f''(x)$ has the same sign for all values of x. This means that the graph of f is either concave upward ($f''(x) > 0$) everywhere or concave downward ($f''(x) < 0$) everywhere. By equation (11), since $a > 0$ and $b > 0$, E will have the same sign as the second derivative of f. And by equations (12), since $a_1 > 0$, $b_1 > 0$, $\alpha > 0$, and $\beta > 0$, all of the E_i will have the same sign as the second derivative of f. Since $m = \log_e W$, these conclusions will hold in both continuous and discontinuous cases.

We have seen that selection will tend to produce linkage disequilibrium of the same sign as the epistasis parameters. Then we can conclude that if fitness, as measured by m or $\log_e W$, is a function of a phenotype which is determined additively by two non-overdominant loci, selection will tend to produce linkage disequilibrium of the same sign as the second derivative of the function, provided that the second derivative does not change sign in the interval of interest. In this context, positive linkage disequilibrium represents association of the two alleles which increase the phenotype and association of the two alleles which decrease the phenotype, while negative linkage disequilibrium represents association of

the allele at one locus which increases the phenotype with the allele at the other locus which decreases the phenotype.

It may be helpful at this point to give a semi-intuitive justification of the results obtained so far. Suppose we have selection at a single locus in the haploid phase. Suppose that there are two alleles, A_1 and A_2, whose frequencies are x_1 and x_2. The fitnesses of the two alleles are m_1 and m_2 in the continuous model and W_1 and W_2 in the discontinuous model. As an indirect measure of the gene frequency let us use

$$u = log_e\,(x_2/x_1) = log_e\,x_2 - log_e\,x_1\,.$$

Then it can be shown that in the continuous model $du/dt = m_2 - m_1$ and in the discontinuous model $\Delta u = log_e\,W_2 - log_e\,W_1$, so that the rate of change of gene frequencies will depend on the difference in m or $log_e\,W$ between the two alleles.

Suppose we have a two-locus model with haploid selection and no recombination. Then if we have the situation shown in Figure 1, where the second derivative of f is positive, the frequency of B_2 among chromosomes containing A_2 will increase faster than the frequency of B_2 among chromosomes containing A_1. This will result in an excess of A_2B_2 chromosomes, making D positive. If we have the situation shown in Figure 2, where the second derivative of f is negative, the frequency of B_2 among A_1 chromosomes will increase faster than the frequency of B_2 among A_2 chromosomes. There will be an excess of A_1B_2 and A_2B_1 chromosomes, making D negative. Thus the sign of the linkage disequilibrium will tend to become the same as the sign of the second derivative of f. The effect of recombination will be to randomize the B_2 alleles among the A_1 and A_2 chromosomes, but since the randomization is incomplete, the sign of the disequilibrium will not be affected by recombination.

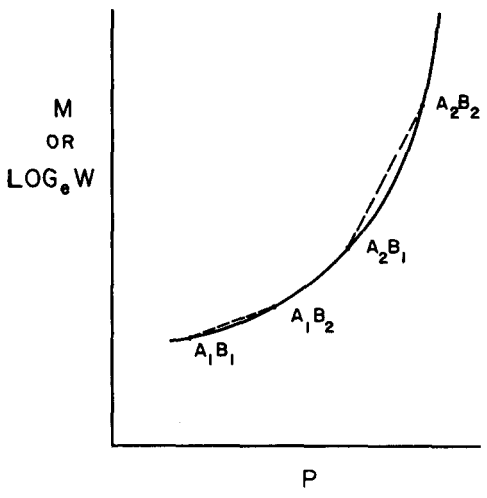

FIGURE 1.—Fitness as a function of phenotype. In this case the function has a positive second derivative. Dashed lines connect genotypes having the same allele at locus A.

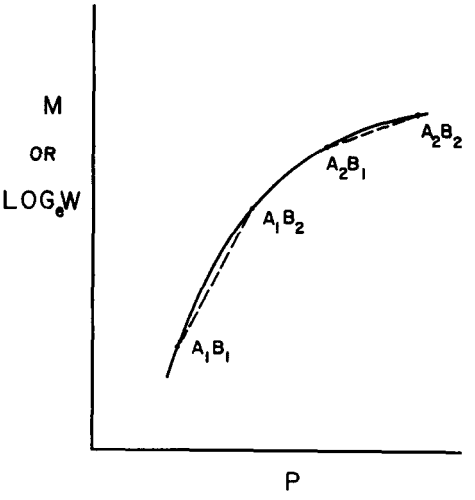

FIGURE 2.—Fitness as a function of phenotype. In this case the function has a negative second derivative. Dashed lines connect genotypes having the same allele at locus A.

Effect of linkage on the change in gene frequencies

The effects of linkage on the rate of progress under selection, as measured by the change in gene frequencies, can now be examined. An intuitive argument will be presented, followed by more formal proofs. It should be evident that the effect of recombination is to break down linkage disequilibrium. Selection will tend to produce linkage disequilibrium if there is any epistasis. The amount of linkage disequilibrium actually attained will be due to a balance between these opposing forces, a balance which will shift with changing gene frequencies. A smaller value of r will lead to more linkage disequilibrium.

If D is positive, the two favored alleles will tend to be associated and the two unfavored alleles will also be associated. If we examine the difference in average fitness between chromosomes containing A_2 and chromosomes containing A_1, this association of alleles can be seen to increase the difference in average fitness, and thus increase the rate of change of gene frequencies. Likewise, a negative value of D tends to associate the favored allele at each locus with the unfavored allele at the other locus, reducing the difference between the average fitnesses of A_1 and A_2, and decreasing the rate of change of gene frequencies. Since tight linkage increases the magnitude of linkage disequilibrium produced by selection, if the disequilibrium produced by selection is positive, tight linkage will increase the rate of change of gene frequencies. If the linkage disequilibrium produced by selection is negative, tight linkage will slow the rate of change of gene frequencies.

This argument can be made more exact by proving that $\frac{\partial}{\partial D}\left(\frac{dp}{dt}\right) > 0$ in the continuous models, and $\frac{\partial}{\partial D}\Delta\left(\frac{p}{1-p}\right) > 0$ in the discontinuous models, showing that positive disequilibrium speeds and negative disequilibrium retards the change of gene frequencies.

Haploid-discontinuous:

$$\frac{\partial}{\partial D}\Delta\left(\frac{p}{1-p}\right) = \frac{\partial}{\partial D}\left(\frac{p'}{1-p'} - \frac{p}{1-p}\right) = \frac{\partial}{\partial D}\left(\frac{p'}{1-p'}\right)$$

Substituting from equations (5),

$$\frac{\partial}{\partial D}\left(\frac{p'}{1-p'}\right) = \frac{\partial}{\partial D}\left[\frac{W_1(x_1 - rD) + W_2(x_2 + rD)}{W_3(x_3 + rD) + W_4(x_4 - rD)}\right]$$

Using equations (1),

$$\frac{\partial}{\partial D}\left(\frac{p'}{1-p'}\right) = \{[W_3(x_3 + rD) + W_4(x_4 - rD)][W_1 - W_2][1 - r]$$
$$-[W_1(x_1 - rD) + W_2(x_2 + rD)][W_4 - W_3][1 - r]\}/$$
$$[W_3(x_3 + rD) + W_4(x_4 - rD)]^2.$$

If we assume that A_1B_1 has the highest fitness and A_2B_2 the lowest fitness, then $W_1 > W_2$ and $W_3 > W_4$, so that

$$\frac{\partial}{\partial D}\Delta\left(\frac{p}{1-p}\right) > 0. \tag{13}$$

Haploid-continuous. From (2),

$\frac{\partial}{\partial D}\left(\frac{dp}{dt}\right) = \frac{\partial}{\partial D}(x_1m_1 + x_2m_2 - p\bar{m})$. Since $\bar{m} = x_1m_1 + x_2m_2 + x_3m_3 + x_4m_4$,

by (1),

$$\frac{\partial}{\partial D}\left(\frac{dp}{dt}\right) = m_1 - m_2 - p_1(m_1 - m_2 - m_3 + m_4)$$
$$= (1-p)(m_1 - m_2) + p(m_3 - m_4).$$

If A_1B_1 has the highest fitness and A_2B_2 the lowest, $m_1 > m_2$ and $m_3 > m_4$, so that

$$\frac{\partial}{\partial D}\left(\frac{dp}{dt}\right) > 0.$$

Diploid-continuous:

$$\frac{dp}{dt} = x_1m_1 + x_2m_2 - p\bar{m}.$$

From (1) and (8),

$$\frac{\partial}{\partial D}\left(\frac{dp}{dt}\right) = m_1 - m_2 + x_1E_1 + x_2E_2 - 2p\bar{E}$$

which after some algebra becomes

$$\frac{\partial}{\partial D}\left(\frac{dp}{dt}\right) = (1-q)(m_{14} - m_{24}) + q(m_{13} - m_{14})$$
$$+ 2(1-p)(x_1E_1 + x_2E_2) - 2p(x_3E_3 + x_4E_4)$$

assuming that $m_{14} = m_{23}$. m_{13}, m_{14}, and m_{24} are the fitnesses of the three genotypes at locus B provided locus A is heterozygous. If the interaction parameters are small relative to $m_{14} - m_{24}$ and $m_{13} - m_{14}$, then

$$\frac{\partial}{\partial D}\left(\frac{dp}{dt}\right) \cong (1-q)(m_{14} - m_{24}) + q(m_{13} - m_{14})$$

If locus B is not overdominant and if A_1 and B_1 are the favored alleles, $m_{14} > m_{24}$ and $m_{13} > m_{14}$, so

$$\frac{\partial}{\partial D}\left(\frac{dp}{dt}\right) > 0.$$

If the E_i are too large to be ignored, we can derive the inequality only under restricted conditions. The E_i must all be of the same sign, and the fitnesses must be such that substitution of an A_1 for an A_2 allele or a B_1 for a B_2 allele always increases fitness. The most important restriction is that D must be zero. When these restrictions are imposed, after some algebra we obtain

$$\frac{\partial}{\partial D}\left(\frac{dp}{dt}\right) \geq [(1-q)(m_{14} - m_{24}) + q(m_{13} - m_{14})] \cdot [1 - 2p(1-p)] \geq 0.$$

When D is nonzero we can find counterexamples to the inequality.

It has not been possible to prove an inequality similar to (13) for the diploid-discontinuous case.

Bodmer and Parsons (1962) have shown that if alleles at two loci are individually deleterious, but advantageous in combination, they will both increase when initially rare only if linkage between the loci is sufficiently tight. When the alleles are rare they will occur primarily in heterozygotes, and almost all of the diploid genotypes in the population will be A_1B_1/A_2B_2, A_1B_2/A_2B_2, $A_2B_1/$

A_2B_2, or A_2B_2/A_2B_2. Selection can be treated as if it occurred in the haploid phase. Since the selective values correspond to E positive and very large, selection would produce a positive value of D, and tight linkage would indeed be expected to increase the rate of change of gene frequencies. KOJIMA and SCHAFFER (1964) have treated the same case in terms of the probability of loss of the mutant alleles when initially rare, and have reached the same conclusion.

When initial linkage disequilibrium is either zero or of the type which directional selection tends to produce, tight linkage will increase the rate of change under selection if selection tends to produce positive linkage disequilibrium, and decrease the rate of change if selection tends to produce negative linkage disequilibrium. When the initial value of D is opposite in sign from its final value, tight linkage will at first slow the approach to zero, then speed the divergence from zero once D has passed zero. In terms of the effect of linkage on the rate of change of gene frequencies, this creates a very complex situation which awaits further investigation.

In the above treatment, the rate of change of gene frequencies has been used as the measure of the rate of progress under selection. A more natural measure would be the rate of change of the mean fitness, $\overline{m}$ or $\overline{W}$. When epistasis is small, changes in mean fitness will largely reflect changes in the gene frequencies, so that the results given above can be extended to mean fitness. But when epistasis is large, the rate of change in D will be an important factor determining the rate of change of mean fitness, complicating the analysis considerably. It should be obvious that our understanding of the effect of linkage on the rate of advance under directional selection is far from complete.

Application to Artificial Selection

Artificial selection of an additively determined trait can be considered as a case in which fitness is a function of phenotype. Let the phenotype be determined additively by two non-overdominant loci. Let the environmental component be normally distributed around the genotypic mean with constant environmental variance σ^2. During a given generation let us save all animals whose phenotypes exceed the value c. Then fitness is a function of the genotypic mean of the phenotype. For a genotype whose mean phenotype is μ_i, the probability that an animal of that phenotype survives is

$$W_i = \int_c^\infty \frac{1}{\sigma\sqrt{(2\pi)}} exp\left[\frac{(x-\mu_i)^2}{2\sigma^2}\right] dx$$

or

$$W_i = \int_{\left(\frac{c-\mu_i}{\sigma}\right)}^\infty \frac{1}{\sqrt{(2\pi)}} e^{-\frac{x^2}{2}} dx.$$

W_i as a function of μ_i is plotted in Figure 3. The curve is obviously an inte-

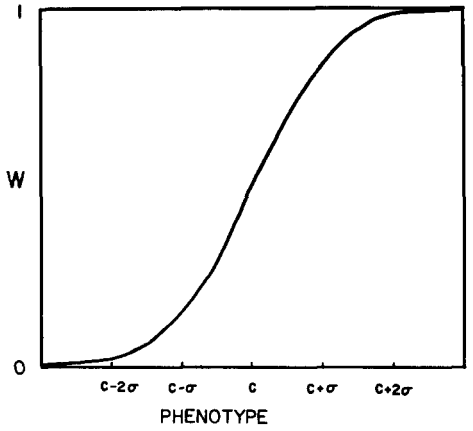

FIGURE 3.—Fitness as a function of the genotypic mean of the phenotype for the case of truncation selection. Individuals whose actual phenotypes exceed c are saved. σ^2 is the environmental variance of the phenotype.

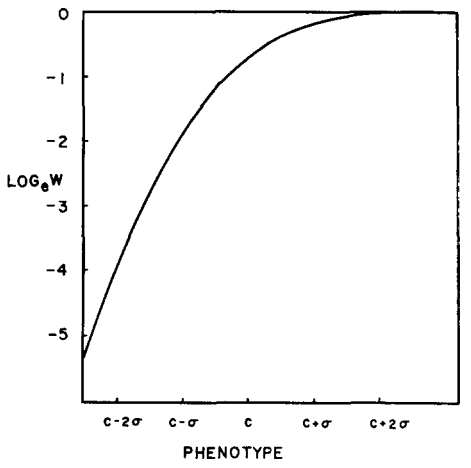

FIGURE 4.—$log_e W$ as a function of the genotypic mean of the phenotype for the same case as Figure 3.

grated normal curve. We can also write

$$log_e W_i = log_e \int_{\left(\frac{c-\mu_i}{\sigma}\right)}^{\infty} \frac{1}{\sqrt{(2\pi)}} e^{-\frac{x^2}{2}} \, dx.$$

$Log_e W_i$ is plotted as a function of μ_i in Figure 4. The second derivative of the function is negative, so that selection will tend to produce negative linkage disequilibrium. This conclusion will hold whether the cutoff point c remains the same in all generations or changes from generation to generation, as it would if a constant fraction of the population were being saved. If we assume that the effects of linkage are the same as those observed in the haploid cases and in the diploid-discontinuous case under restricted conditions, we can predict that if initial linkage disequilibrium is either zero or negative, tight linkage will reduce the response to selection.

FRASER (1957) used Monte Carlo methods to simulate artificial selection of a phenotype which was determined additively by six loci. The initial populations were in strong negative linkage disequilibrium. Tight linkage drastically reduced the response to selection. MARTIN and COCKERHAM (1960) carried out an essentially similar Monte Carlo simulation study. They found that tight linkage reduced the response to selection not only when the population was initially in negative linkage disequilibrium, but also when the population was initially in linkage equilibrium. If the phenotype is additively determined by more than two loci, the theory developed above can be applied to all pairs of loci, provided that the genetic variance at the other loci is added to the environmental variance σ^2.

If the linkage disequilibrium is not extreme, this residual variance should be approximately the same for all of the genotypes at a given pair of loci, so that the conclusions given above can be extended to multiple locus cases. The conclusions seem to explain some of the results of Monte Carlo studies of linkage.

A natural extension of this theory would involve consideration of epistasis on the phenotypic scale. GRIFFING (1960) has shown that epistasis on the phenotypic scale can generate linkage disequilibrium when the character is under artificial selection, although his approximations cause him to ignore the linkage disequilibrium generated when the phenotype is additively determined. In many cases it would seem that phenotypic epistasis could be taken into consideration by regarding the actual phenotype as a function $g(P)$ of an additive phenotype. Fitness would be a function of the actual phenotype, so that $log_e W_i = f[g(P)]$ and conclusions could be drawn once the second derivative of the composite function $f[g(P)]$ were known.

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SUMMARY

Four models of natural selection in two-locus, two-allele, random-mating populations are described, in which selection may occur either during the haploid or the diploid phase of the life cycle, and generations may be either continuous or discontinuous. Epistasis is defined as deviation from additive locus effects on fitness in the continuous-generation models, and deviation from multiplicative locus effects on fitness in the discontinuous-generation models. It is shown that there is a simple relation between the signs of the epistasis parameters and the type of linkage disequilibrium generated by selection. Cases are considered in which fitness is a function of a phenotype determined additively by two non-overdominant loci. It is shown that the linkage disequilibrium generated by selection has the same sign as the second derivative of the function which relates phenotype to fitness in the continuous-generation models, or which relates phenotype to the logarithm of fitness in the discontinuous-generation models. It is shown that if the linkage disequilibrium generated by selection is positive, tight linkage will increase the rate of change of the gene frequencies, while if the linkage disequilibrium generated by selection is negative, tight linkage will decrease the rate of change of the gene frequencies. Artificial selection on an additive phenotype is considered. It is shown that negative linkage disequilibrium will be generated, and hence tight linkage will reduce the response to artificial selection.

APPENDIX

Theorem: If f is continuous and has continuous first and second derivatives on the interval $[c, a+b+c]$, where $a > 0$ and $b > 0$, then $f(a+b+c) - f(a+c) - f(b+c) + f(c)$ has the same sign as $f''(x)$ for some x in $[c, a+b+c]$.

Proof: Without loss of generality we can take $b \geq a$. By the Mean Value Theorem, found in any calculus text, since f is continuous and has a continuous derivative, there is an x_1 in $(c, a+c)$ and an x_2 in $(b+c, a+b+c)$ such that

$$f(a+b+c)-f(b+c)=af'(x_2)$$

and $$f(a+c)-f(c)=af'(x_1)$$

so that

$$f(a+b+c)-f(a+c)-f(b+c)+f(c)=a[f'(x_2)-f'(x_1)].$$

Since $b \geq a$, $b+c \geq a+c$, so that $x_2 > x_1$. Since $f'(x)$ is continuous and has a continuous derivative, there is an x_3 in (x_1, x_2) such that $f'(x_2)-f'(x_1)=(x_2-x_1)f''(x_3)$.

Thus there is an x_3 in $(c, a+b+c)$ such that

$$f(a+b+c)-f(a+c)-f(b+c)+f(c)=a(x_2-x_1)f''(x_3).$$

Since $a>0$ and $x_2-x_1>0$. $f(a+b+c)-f(a+c)-f(b+c)+f(c)$ has the same sign as $f''(x_3)$.

LITERATURE CITED

BODMER, W. F., and P. A. PARSONS, 1962 Linkage and recombination in evolution. Advan. Genet. **11:** 1–99.

FISHER, R. A., 1918 The correlation between relatives on the supposition of Mendelian inheritance. Trans. Royal Soc. Edinburgh **52:** 399–433.

FRASER, A. S., 1957 Simulation of genetic systems by automatic digital computers. II. Effects of linkage on rates of advance under selection. Australian J. Biol. Sci. **10:** 492–499.

GRIFFING, B., 1960 Theoretical consequences of truncation selection based on the individual phenotype. Australian J. Biol. Sci. **13:** 307–343.

HALDANE, J. B. S., 1962 The selection of double heterozygotes. J. Genet. **58:** 125–128.

KIMURA, M., 1956 A model of a genetic system which leads to closer linkage by natural selection. Evolution **10:** 278–287.

KOJIMA, K., and T. KELLEHER, 1961 Changes of mean fitness in random mating populations when epistasis and linkage are present. Genetics **46:** 527–540.

KOJIMA, K., and H. E. SCHAFFER, 1964 Accumulation of epistatic gene complexes. Evolution **18:** 127–129.

LEWONTIN, R. C., 1964a The interaction of selection and linkage. I. General considerations; heterotic models. Genetics **49:** 49–67. —— 1964b The interaction of selection and linkage. II. Optimum models. Genetics **50:** 757–782.

LEWONTIN, R. C., and K. KOJIMA, 1960 The evolutionary dynamics of complex polymorphisms. Evolution **14:** 458–472.

MARTIN, F. G., JR., and C. C. COCKERHAM, 1960 High speed selection studies. pp. 35–45. *Biometrical Genetics*. Edited by O. KEMPTHORNE. Pergamon Press, New York.

MORAN, P. A. P., 1964 On the nonexistence of adaptive topographies. Ann. Human Genet. **27:** 383–393.

NEI, M., 1963 Effect of selection on the components of genetic variance. *Statistical Genetics and Plant Breeding*. Edited by W. D. HANSON and H. F. ROBINSON. Natl. Acad. Sci.-Natl. Res. Council Publ. **982:** 501–515.

PARSONS, P. A., 1963 Polymorphism and the balanced polygenic combination. Evolution **17:** 564–574.