WHEN natural selection acting on two loci contains nonadditive interactions, that is, when selection is epistatic, the properties of the system cannot necessarily be predicted from the behaviour of single loci. Lewontin and Kojima (1960) and others since have noted that there is frequently permanent gametic excess (linkage disequilibrium) at equilibrium, that there may be alternative stable equilibria, and that the amount of gametic excess, and the equilibrium gene frequencies (and even the stability of the equilibrium) are dependent upon the recombination fraction between the loci. With weak epistasis and loose linkage most of these complexities can be ignored (Kimura 1965).

There are four properties of such systems which do not seem to receive as much attention as they deserve: the analogy between one- and two-locus systems in the properties of some of the derivatives of mean fitness; a similar analogy between the way in which dominance and epistasis affect the position of equilibria; the similarity between multiplicative selection for one and two loci; and the conditions leading to gametic equilibria whose stability varies with the recombination fraction. This paper deals briefly with these properties. Random mating is assumed throughout.

**THE DERIVATIVES OF FITNESS**

*One Locus:* Let the alleles be \( A_0, A_1 \), with frequencies \( q_0, q_1 \), and the genotypes \( A_0A_0, A_0A_1, A_1A_1 \) have the Wrightian fitnesses \( W_{00}, W_{01}, W_{11} \). Then the average effect of the gene substitution, being the difference between the frequency-dependent fitnesses of the alleles (Fisher 1941) is

\[
W_0 - W_1 = \frac{1}{2} \left( \frac{d \overline{W}}{dq_0} \right)
\]

where

\[
W_0 = q_0 W_{00} + q_1 W_{01}
\]

\[
W_1 = q_0 W_{01} + q_1 W_{11}
\]

and the mean fitness \( \overline{W} \) is

\[
\overline{W} = \sum_i q_i \overline{W}_i = \sum_{ij} q_i q_j W_{ij} (i \geq j)
\]

Further, the dominance interaction is

\[
W_{01} - \frac{1}{2} (W_{00} + W_{11}) = - \frac{1}{4} \left( \frac{d^2 \overline{W}}{dq_0^2} \right)
\]

*Two loci:* Represent the gametes \( A_0B_0, A_0B_1, A_1B_0, A_1B_1 \) by their binary values
TABLE 1

Fitnesses and frequencies at two loci

<table>
<thead>
<tr>
<th>Genotype</th>
<th>Frequency</th>
<th>I</th>
<th>II</th>
<th>III</th>
<th>IV</th>
</tr>
</thead>
<tbody>
<tr>
<td>$A_0B_0/A_0B_0$</td>
<td>$(q_0^* + D)^2$</td>
<td>$W_{00}$</td>
<td>$wz$</td>
<td>$w^2z^2$</td>
<td>00</td>
</tr>
<tr>
<td>$A_0B_1/A_0B_1$</td>
<td>$(q_1^* - D)^2$</td>
<td>$W_{11}$</td>
<td>$wx$</td>
<td>$w^2x^2$</td>
<td>11</td>
</tr>
<tr>
<td>$A_0B_0/A_0B_0$</td>
<td>$(q_2^* - D)^2$</td>
<td>$W_{22}$</td>
<td>$yz$</td>
<td>$y^2z^2$</td>
<td>22</td>
</tr>
<tr>
<td>$A_1B_1/A_1B_1$</td>
<td>$(q_3^* + D)^2$</td>
<td>$W_{33}$</td>
<td>$xy$</td>
<td>$x^2y^2$</td>
<td>33</td>
</tr>
<tr>
<td>$A_0B_0/A_1B_2$</td>
<td>$2(q_0^* + D)(q_3^* - D)$</td>
<td>$W_{01}$</td>
<td>$w$</td>
<td>$w^2xz$</td>
<td>01</td>
</tr>
<tr>
<td>$A_0B_0/A_0B_0$</td>
<td>$2(q_0^* + D)(q_3^* + D)$</td>
<td>$W_{03}$</td>
<td>$w$</td>
<td>$w^2y^2z$</td>
<td>02</td>
</tr>
<tr>
<td>$A_1B_2/A_1B_2$</td>
<td>$2(q_1^* - D)(q_3^* + D)$</td>
<td>$W_{13}$</td>
<td>$x$</td>
<td>$wx^2y$</td>
<td>13</td>
</tr>
<tr>
<td>$A_0B_0/A_0B_0$</td>
<td>$2(q_2^* - D)(q_3^* + D)$</td>
<td>$W_{23}$</td>
<td>$y$</td>
<td>$wy^2z$</td>
<td>23</td>
</tr>
</tbody>
</table>

Alternative form of I:

$W_{00} = W_{01} - W_{03} + W_{02} - U_0$
$W_{11} = W_{13} - W_{03} + W_{01} - U_1$
$W_{22} = W_{02} - W_{03} + W_{25} - U_2$
$W_{33} = W_{23} - W_{03} + W_{13} - U_3$
$W_{12} = W_{03} - K$

0, 1, 2, 3, write fitnesses as in scheme I of Table 1, and define the gametic determinant as

$$D = q_0q_3 - q_1q_2$$

(5)

In Table 1, the $U_i$ are parameters of epistasis identical in value but not sign with those used by Cockerham (1954); $K$ is an epistasis parameter expressing the difference in fitness between coupling and repulsion heterozygotes. By multiplying the genotype frequencies in Table 1 by the corresponding fitnesses in scheme I, we (Bodmer and Felsenstein 1967; Turner 1967b,c) find that

$$W_0 = W_{00} - 2D [q_0^*(U_0 + K) - q_1^*U_1 - q_2^*U_2 + q_3^*(U_3 + K)]$$
$$- D^2(\sum_i U_i + 2K)$$

(6)

where the asterisk denotes the value of the parameter which would obtain if the gene frequencies were held constant and $D$ were made zero. If $K$ is zero the term in $D$ is a function of the additive $\times$ additive interaction, and that in $D^2$ of the dominance $\times$ dominance interaction. Then it is possible to show that (Turner 1967d), with $K$ finite or zero,

$$W_0 - W_1 - W_2 + W_3 = \frac{1}{2}(d\bar{W}/dD)$$

(7)

$W_i$ being frequency-dependent fitnesses of the gametes (as in (2)), defined as

$$W_i = \sum_j q_j W_{ij}$$

(8)

The left-hand side of (7) occurs quite frequently in two-locus theory; the analogy
with (1) is striking. Further, in analogy to (4), when \( K \) is zero the dominance \( \times \) dominance interaction is

\[
-\frac{1}{2} \sum_i U_i = \frac{1}{4} \left( d^2\bar{W}/dD^2 \right).
\]  

(9)

Similarly, when \( K \) is finite

\[
-\frac{1}{2} (\sum_i U_i + 2K) = \frac{1}{4} \left( d^2\bar{W}/dD^2 \right).
\]  

(10)

These relations help to clarify two-locus theory, particularly by analogy to that for single loci. Equation (6) includes a linear term which is a function of the additive \( \times \) additive interaction, and a quadratic term which is a function of the dominance \( \times \) dominance interaction; \( \bar{W} \) for a single locus can similarly be partitioned into a linear term in the additive effect and a quadratic term for dominance (Falconer 1961).

As the second derivatives determine the type of equilibria in the system, (4), (9), and (10) will be important in the next section.

**EQUILIBRIA**

**One locus:** Overdominance and underdominance are central to the theory of single locus equilibria—the first gives a single stable equilibrium with both alleles present, the second two stable equilibria, each with only one allele present. Thus imagine that Figures 1a and 1b are graphs of \( \bar{W} \) against gene frequency. If the heterozygote is fitter than both homozygotes (overdominance in fitness) the curve is convex upwards, and there is a single stable equilibrium at maximum \( \bar{W} \). If both homozygotes are fitter than the heterozygote (underdominance) the curve is concave upward, and there are two stable equilibria, each with only one allele in the population (Li 1955). This follows from the fact that the dominance is the second derivative of mean fitness with respect to gene frequency (4).

**Two loci:** Just as certain kinds of dominance can be called overdominance and underdominance, so certain kinds of epistasis can be called overepistasis and underepistasis. The definitions are:

*Overepistasis:* the epistatic part of selection acts against both the double homozygotes and the repulsion heterozygote, so that \( (\Sigma U_i + 2K) \) in (6) is positive; *Underepistasis:* the epistatic part of selection favours both the double homozygotes and the repulsion heterozygote, so that \( (\Sigma U_i + 2K) \) in (6) is negative.
When $2K$ (the position effect) is zero, over- and underepistasis are the same as a negative or positive dominance $\times$ dominance interaction. In earlier papers (e.g., Turner 1967b) I have called over- and underepistasis respectively, relative (or epistatic) overdominance and underdominance, but since "dominance" should be restricted to interactions within a locus, I have dropped these misleading terms.

Over- and underepistasis govern equilibria at two loci in a way very similar to that of over- and underdominance at a single locus, as a result of their relation with the second derivative of the mean fitness with respect to $D$, (9) and (10). Thus imagine that Figures 1a and 1b represent graphs of $\bar{W}$ against $D$ and assume recombination is zero. If there is overepistasis, the graph is convex upward, and there is one stable equilibrium with a moderate value of $D$ (and hence with all four gametes in the population), at the maximum of $\bar{W}$. If there is underepistasis, the concave graph produces two stable equilibria each with $D$ at its extreme value, and hence with one or two gametic types missing from the population.

Recombination and mutation move the equilibria away from the peaks of the curves in Figure 1 (Turner 1967a,b). As can be seen from the shape of Figures 1a and 1b, recombination and mutation will produce a greater loss of fitness, and thus a greater genetic load, when there is underepistasis. With overepistasis, the load is much smaller.

So overepistasis permits at most a single nontrivial equilibrium with up to four gametic types in the population and produces a comparatively small genetic load as a result of recombination and mutation. Underepistasis permits up to two stable equilibria, each with at most two or three gametic types in the population, when recombination is zero, and produces a comparatively large genetic load as a result of recombination and mutation.

The analogy with single locus theory is not precise; with a single locus, there is one stable equilibrium with only one allele present if the fitness of the heterozygote lies between that of the homozygotes (additivity or simple dominance; Figure 1c). With two loci, there is at most a single equilibrium with two or three gametes if there is simple epistasis (neither over- nor underepistasis, $\Sigma U_i + 2K = 0$), or if the second term in (6) is numerically large at equilibrium. These conditions are roughly equivalent to additivity and simple dominance.

When an inversion polymorphism is established because of the selective advantage of reduced recombination (Fisher 1930; Sheppard 1953; Ford 1964; Turner 1967b), the equilibrium differs according to the type of epistasis. If an inversion containing the arrangement, say $A_B$, spreads with underepistasis, it reaches equilibrium with all representatives of this gene sequence contained in the inversion (as described by Fraser, Burnell and Miller 1966); with overepistasis the equilibrium population contains both inverted and normal $A_B$ sequences (Turner 1967d).

**MULTIPLICATIVE SELECTION**

*One locus:* If the fitnesses of the three genotypes $A_A A_a$, $A_a A_A$, $A_A A_A$ are in the proportions $x_a^2$, $x_a x_A$, $x_A^2$ it is easy to see that after random mating followed by a
The fitnesses are here said to show "no multiplicative dominance" (Cannings and Edwards 1968).

**Two loci:** If the fitnesses for two loci are as in Table 1, column II, they can be said to show “no multiplicative epistasis” and if in the initial population there is random mating and there is also gametic equilibrium (i.e., \( D = 0 \)) there will still be gametic equilibrium after a round of selection. Thus starting with gametic frequencies \( q_0^*, q_1^*, q_2^*, q_3^* \), after random mating and selection we have gametic frequencies in the ratios

\[
q_0 = wz(q_0^*)^2 + wzq_1^*q_2^* + zq_0^*q_2^* + q_0^*q_3^* \\
q_1 = wz(q_1^*)^2 + wzq_0^*q_3^* + zq_1^*q_3^* + q_1^*q_2^* \\
q_2 = wz(q_2^*)^2 + wzq_3^*q_0^* + zq_2^*q_0^* + q_2^*q_3^* \\
q_3 = wz(q_3^*)^2 + wzq_1^*q_0^* + zq_3^*q_0^* + q_3^*q_1^* 
\]

and similarly for the other gametes. Substitution in (5) gives, after some algebra, and substituting gene frequencies \( q_0^* = q_Aq_B, \text{etc.} \)

\[
D = q_Aq_Bq_Aq_B[(wx_Aq_B + wz_Aq_B + wz_Aq_B + x_Aq_B) \times \\
(y_Aq_B + x_Aq_B + y_Aq_B + q_Aq_B) \\
-(wx_Aq_B + wz_Aq_B + x_Aq_B + y_Aq_B) \times \\
(y_Aq_B + x_Aq_B + y_Aq_B + q_Aq_B)] \\
= 0 
\]

It is easy to show that the genotypes are not in Hardy-Weinberg equilibrium.

If selection is as in Table 1, column III, there is neither multiplicative epistasis nor multiplicative dominance, and after random mating and selection the population is both in Hardy-Weinberg and gametic equilibrium, as is easily seen.

**QUASI STABLE EQUILIBRIA**

The equilibria discussed by Lewontin and Kojima (1960) and some of those noted by Parsons (1963) and other authors have a peculiar property not shown by single-locus equilibria; an equilibrium remains stable for a range of high recombination fractions, but if recombination drops below a certain critical value it becomes unstable, and a pair of stable equilibria appear on either side of it. It is easy enough to show that, provided the coupling and repulsion heterozygotes are equally fit \( (K = 0) \), then the necessary and sufficient conditions are underepistasis and a value of \( D = 0 \) at equilibrium; equilibria with other values of \( D \) cannot show this property. With overepistasis, an equilibrium in \( D = 0 \) is stable and remains in \( D = 0 \) for all values of recombination, unlike equilibria outside \( D = 0 \) whose position varies with the recombination fraction (Turner 1967c).

These two kinds of equilibria, the quasi stable and the permanently stable with constant values of \( D \), are probably rare, except when selection is multiplicative, for as was shown above, populations under multiplicative selection tend to remain in \( D = 0 \) if they start in \( D = 0 \), and their equilibria will therefore be quasi stable or permanently stable.

To find a general solution for the kinds of selection resulting in these two kinds
of equilibria, one needs a general solution giving an equilibrium in $D = 0$; this seems to be very difficult, but one special case can be found comparatively easily.

If we write fitnesses of the ten genotypes as in the last column of Table 1 (that is, simply represent them by the paired binary digits representing the genotypes, 00 indicating the fitness of $A_oB_o/A_oB_o$ etc.), then they can be written as two forms of matrix:

\[
\begin{array}{ccc}
A_oA_o & B_oB_o & B_oB_1 \\
A_oA_1 & 02 & 03 \\
A_1A_1 & 22 & 23 \\
\end{array}
\]

\[
\begin{array}{cccc}
A_oB_o & A_oB_1 & A_1B_0 & A_1B_1 \\
A_oB_1 & 01 & 11 & 13 \\
A_1B_0 & 02 & 12 & 23 \\
A_1B_1 & 03 & 13 & 33 \\
\end{array}
\]

(13) is easier to visualise; (14) is necessary for solutions. With no recombination, the nontrivial equilibrium with all four gametes present is given by TALLIS (1966) and LI (1967). The complete solution is not needed, and we use only the quantities $q_o'$, $q_1'$, $q_2'$, $q_3'$ which are proportional to the equilibrium frequencies of the gametes, for we are interested in the property $q_0'q_3' - q_1'q_2' = 0$, which is not affected by using proportional values. The actual solutions are found simply by dividing the $q_i'$ by $\sum q_i'$. The proportional solutions are

\[
q_o' = \begin{bmatrix} 1 & 01 & 02 & 03 \\ 1 & 11 & 12 & 13 \\ 1 & 12 & 22 & 23 \\ 1 & 13 & 23 & 33 \end{bmatrix}, \quad q_3' = \begin{bmatrix} 00 & 01 & 02 & 03 \\ 01 & 11 & 12 & 13 \\ 02 & 12 & 22 & 23 \\ 03 & 13 & 23 & 33 \end{bmatrix}
\]

the 1 in this case being unity (remembering that 00 etc. are convenient abbreviations for $W_{oo}$). For the four-gamete equilibrium to be quasi stable or truly stable for all degrees of recombination, it must be in linkage (gametic) equilibrium, i.e. $D = 0$, so we need a solution giving

\[
q_0'q_3' - q_1'q_2' = 0
\]

or

\[
q_0'q_3' = q_1'q_2'
\]

Using the solutions (15) in (16) yields a very difficult equation, and although a general solution may be possible it will not be attempted. However one special solution has been found.
One of the ways (16) can be satisfied is if

\[ q'_0 = q'_3, \quad q'_2 = q'_3 \]  

(17)

Again a general solution to (17) is difficult, but a special case can be solved. Expand the determinants in (15) by rows:

\[ q'_0 = + \begin{vmatrix} 11 & 12 & 13 \end{vmatrix} - \begin{vmatrix} 01 & 02 & 03 \end{vmatrix} + \begin{vmatrix} 01 & 02 & 03 \end{vmatrix} - \begin{vmatrix} 01 & 02 & 03 \end{vmatrix} \]
\[ = + \begin{vmatrix} 12 & 22 & 23 \end{vmatrix} - \begin{vmatrix} 12 & 22 & 23 \end{vmatrix} + \begin{vmatrix} 12 & 22 & 23 \end{vmatrix} - \begin{vmatrix} 12 & 22 & 23 \end{vmatrix} \]  

(18)

\[ q'_1 = - \begin{vmatrix} 01 & 12 & 13 \end{vmatrix} + \begin{vmatrix} 00 & 02 & 03 \end{vmatrix} - \begin{vmatrix} 00 & 02 & 03 \end{vmatrix} + \begin{vmatrix} 00 & 02 & 03 \end{vmatrix} \]
\[ = - \begin{vmatrix} 02 & 22 & 23 \end{vmatrix} + \begin{vmatrix} 02 & 22 & 23 \end{vmatrix} - \begin{vmatrix} 02 & 22 & 23 \end{vmatrix} + \begin{vmatrix} 02 & 22 & 23 \end{vmatrix} \]  

(19)

\[ q'_2 = + \begin{vmatrix} 01 & 11 & 13 \end{vmatrix} - \begin{vmatrix} 00 & 01 & 03 \end{vmatrix} + \begin{vmatrix} 00 & 01 & 03 \end{vmatrix} - \begin{vmatrix} 00 & 01 & 03 \end{vmatrix} \]
\[ = + \begin{vmatrix} 02 & 12 & 23 \end{vmatrix} - \begin{vmatrix} 02 & 12 & 23 \end{vmatrix} + \begin{vmatrix} 02 & 12 & 23 \end{vmatrix} - \begin{vmatrix} 02 & 12 & 23 \end{vmatrix} \]  

(20)

\[ q'_3 = - \begin{vmatrix} 01 & 11 & 12 \end{vmatrix} + \begin{vmatrix} 00 & 01 & 02 \end{vmatrix} - \begin{vmatrix} 00 & 01 & 02 \end{vmatrix} + \begin{vmatrix} 00 & 01 & 02 \end{vmatrix} \]
\[ = - \begin{vmatrix} 02 & 12 & 22 \end{vmatrix} + \begin{vmatrix} 02 & 12 & 22 \end{vmatrix} - \begin{vmatrix} 02 & 12 & 22 \end{vmatrix} + \begin{vmatrix} 02 & 12 & 22 \end{vmatrix} \]  

(21)

It will be seen that, as the value of a determinant is not altered if it is transposed about its leading diagonal, the first element of (19) equals the second element of (18). If each of the other elements of (18) was equal to a separate element of (19), \( q'_0 \) would equal \( q'_3 \), and if by a similar process \( q'_2 \) equalled \( q'_3 \), \( D \) would be zero.

Transposition of adjacent columns or rows of a determinant alters its sign but not its absolute value. Thus the third element of (18) can be changed:

\[ + \begin{vmatrix} 01 & 02 & 03 \end{vmatrix} = - \begin{vmatrix} 11 & 13 & 12 \end{vmatrix} = + \begin{vmatrix} 12 & 13 & 12 \end{vmatrix} \]
\[ 11 \quad 13 \quad 12 \]
\[ 12 \quad 23 \quad 33 \]
\[ = + \begin{vmatrix} 12 & 13 & 12 \end{vmatrix} \]
\[ 13 \quad 33 \quad 23 \]
\[ 13 \quad 33 \quad 23 \]

(22)

and in this final form the determinant is equal to the last determinant of (19), if

\[ 00 = 11, \quad 13 = 02, \quad 03 = 12, \quad 22 = 33 \]

(23)

that is, if the fitness matrix has the form

\[
\begin{bmatrix}
  a & e & c & d \\
  e & a & d & c \\
  c & d & b & f \\
  d & c & f & b
\end{bmatrix}
\]

or

\[
\begin{bmatrix}
  a & e & a \\
  c & d & c \\
  b & f & b
\end{bmatrix}
\]

(24)

(25)
These conditions also cause the first and fourth elements of $q_0'$, suitably rearranged, to equal the second and third elements of $q_1'$; similarly $q_2' = q_3'$ and we have the required property $D = 0$. There is a similar solution giving $q_0' = q_2'$, $q_1' = q_3'$, and matrices with more elements equal give $q_0' = q_1' = q_2' = q_3'$, or are trivial. (25) is a little less symmetrical than the most general form discussed by Lewontin and Kojima (1960).

This solution of the problem of the fitness matrix giving the central equilibrium in $D = 0$ is probably only one of a whole set of solutions.

DISCUSSION

I feel that the relationship between equilibria and over- and under-epistasis, and the similarity of certain equations and phenomena with one and two loci, help in understanding and remembering the rather complicated dynamics of two-locus polymorphisms. Also, they suggest ways in which it may be possible to understand three-locus systems, as presumably there will be properties of the second order epistasis in such a system which are analogous to those of the first order epistasis of two loci.

When multilocus systems are made simple enough for explicit solution, they tend to give special results, such as the quasi stable equilibria described above; we should therefore be cautious about generalizations based on explicit solutions.

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SUMMARY

The derivatives of mean fitness on other population parameters have closely similar properties in the theories of one and two loci.—As would be expected, dominance and epistasis have similar properties; in particular, the sign of the dominance $\times$ dominance interaction for two loci determines the number and position of stable equilibria in the way that the sign of the dominance determines them for a single locus; and the effects of multiplicative dominance and multiplicative epistasis are analogous.—The sign of the dominance $\times$ dominance interaction influences the fate of inversion polymorphisms.—Some two-locus equilibria have unusual properties; among the conditions producing such equilibria are selection schemes symmetrical enough for explicit solution.

LITERATURE CITED


SELECTION AT TWO LOCI WITH EPISTASIS


