SELECTION FOR LINKAGE MODIFICATION II. A RECOMBINATION BALANCE FOR NEUTRAL MODIFIERS*

MARCUS W. FELDMAN*

Department of Biological Sciences, Stanford University, Stanford, California 94305

BEVERLEY BALKAU

Department of Mathematics, La Trobe University, Bundoora, Victoria 3083, Australia

Manuscript received November 3, 1972
Revised copy received April 27, 1973
Transmitted by RICHARD C. LEWONTIN

ABSTRACT

A stable polymorphic equilibrium may be established at a selectively-neutral gene locus which controls the extent of recombination between two other selected loci. The condition for the existence of the stable polymorphism is analogous to heterozygous advantage. The heterozygote at the modifying locus should produce a recombination fraction allowing the greatest linkage disequilibrium. In the models treated this has the effect of producing the highest mean fitness. The relationship of these findings to general problems of coadaptation is discussed.

IN a recent paper one of us (FELDMAN 1972) made an analysis of a model, originally due to NEI (1967, 1969), for the control of linkage between two gene loci by a third locus. Briefly, suppose A/a and B/b are two linked loci at which selection occurs. The modifying locus M/m is such that with genotypes MM, Mm and mm the recombination fractions between A/a and B/b are r_1, r_2 and r_3, respectively. Suppose further that the recombination fraction between M/m and A/a is r for each genotype at the M/m locus and that this locus is *selectively neutral*. That is, the viability of a given A/a-B/b genotype is the same for each genotype at the M/m locus.

In the analysis made by FELDMAN (1972) the selection schemes chosen for A/a and B/b were those for which the two-locus equilibrium theory is known, namely the additive, multiplicative and symmetric viability models. It was supposed that a small frequency of 'm' arose at a stable (in the two-locus sense) equilibrium of the MAB, MAb, MaB, Mab system and the conditions for 'm' to increase, namely for the initial equilibrium to be unstable in the three-locus sense, were determined.

It was shown that provided MAB, MAb, MaB and Mab are in linkage disequilibrium at the initial equilibrium, then 'm' will increase if and only if $r_2 < r_1$, so that linkage between A/a and B/b will then be tightened. On the other hand, if the initial state was one of linkage equilibrium the leading stability eigenvalue

---

* Research supported in part by National Institute of Health Grant PHS 10452–09–10.

was unity and no advance of the '*m*' gene was possible. It was pointed out, with reference to the former case, that selection may occur at a locus at which the genotypes are equally fit. That is, a selectively neutral gene may be selected by virtue of its effect on the other loci rather than on viability or fertility. It was also pointed out that in the special cases examined the mean fitness was a decreasing function of the recombination fraction in the initial state of disequilibrium.

It has since been shown by KARLIN and MCGREGOR (1972) that when mating is random, what determines the fate of selectively neutral modifiers is the mean fitness of the population. For a modifying gene to increase from its initially low frequency, it must reduce a parameter of which the equilibrium mean fitness is a decreasing function. This result of KARLIN and MCGREGOR encompasses a much wider class of models than just linkage modification.

When heterozygote advantage at the modified loci is sufficiently strong FELDMAN and BALKAU (1972) have also shown that, as with random mating, a selectively neutral recombination reducer is favored in the case of pure selfing. When the modifiers are not assumed to be neutral in the models described above the results are not usually as clear-cut. Examples include the classical case of evolution of dominance (FELDMAN and KARLIN [1971]) and segregation distortion (PROUT, BUNGAARD and BRYANT [1971]; THOMSON and FELDMAN [1974]).

Clearly the model of linkage modification by a selectively neutral modifier, as described in the first paragraph above, is in a sense symmetric in the alleles M and m at the modifying locus. Thus if mAB, mAb, maB and mab are the original chromosomes which are in linkage disequilibrium when the new allele M arises, M will increase if $r_2 < r_3$ just as, in the corresponding situation, M increased, when it was rare, if $r_2 < r_1$. Clearly, if $r_2 < r_1$ and $r_2 < r_3$, and the stable equilibria for the two-locus system $A/a - B/b$ are at linkage disequilibrium, then all the boundary equilibria of the full three-locus system $M/m - A/a - B/b$ are unstable. In this paper we confine ourselves to two of the examples treated by FELDMAN (1972), namely the LEWONTIN-KOJIMA (1960) and the WRIGHT (1952) version of the symmetric viability model (see KARLIN and FELDMAN [1970] for details on this model).

The consequences of the analyses are, we believe, very interesting for evolutionary theory. The natural inference to draw is that a stable interior polymorphism exists. We describe two classes of such polymorphisms in the case where $r_1 = r_3$ (so that the alleles M and m are indeed symmetric) and outline the conditions under which they are stable. We would like to characterize these equilibria as being caused by a *recombination balance*. In general perhaps the term "modifier balance" might be more appropriate. These isolated polymorphisms are stable in spite of the neutrality of the M/m locus.

2. *Recursion System*

Let r be the recombination fraction between the modifier locus M/m and the modified loci A/a-B/b with the order M/m–A/a–B/b. The genotypes MM, Mm, and mm are responsible for the A/a-B/b recombination fractions r_1, r_2 and r_3, respectively, in the models we shall consider. The chromosomes MAB, MAb,

MaB, *Mab*, *mAB*, *mAb*, *maB* and *mab* have frequencies $x_1, x_2, \ldots, x_8$ respectively, and the selection matrix is in general $||w_{ij}||$ with w_{ij} the relative viability of the genotype having chromosomes i and j. Since the modifier locus is neutral this 8×8 matrix consists of four identical 4×4 blocks. The recursion system relating x'_1, in the next generation to x_1, is then given by (1) below.

$$\begin{aligned}\bar{w}x'_1 = x_1w_{1\cdot} &+ r[x_2x_5w_{25}+x_3x_5w_{35}+x_4x_5w_{45}-w_{17}x_1x_7-w_{18}x_1x_8-w_{16}x_1x_6] \\ &+ r_1[x_2x_3w_{23}-w_{14}x_1x_4] \\ &+ r_2[x_2x_5w_{25}+x_2x_7w_{27}-x_1x_8w_{18}-x_1x_6w_{16}] \\ &+ rr_2[2w_{16}x_1x_6-2w_{25}x_2x_5+x_3x_6w_{36}+x_1x_8w_{18}-x_4x_5w_{45}-w_{27}x_2x_7]\end{aligned} \tag{1}$$

where

$$\bar{w} = \sum_i \sum_j w_{ij}x_ix_j$$

and

$$w_i = \sum_i w_{ij}x_j \text{ etc.}$$

The product rr_2 arises because we assume that there is no interference. The corresponding transformations for the other frequencies are given in FELDMAN (1972).

Throughout this paper we shall consider only the case where the selective regime at the *A/a-B/b* loci is that of symmetric viabilities, as discussed by LEWONTIN and KOJIMA (1960), BODMER and FELSENSTEIN (1967) and KARLIN and FELDMAN (1970), namely

$$\begin{array}{c|cccc} & AB & Ab & aB & ab \\ AB & 1-\delta & 1-\beta & 1-\gamma & 1 \\ Ab & 1-\beta & 1-\alpha & 1 & 1-\gamma \\ aB & 1-\gamma & 1 & 1-\alpha & 1-\beta \\ ab & 1 & 1-\gamma & 1-\beta & 1-\delta \end{array} \tag{2}$$

Under the hypothesis of selective neutrality at the *M/m* locus, (2) is the matrix in each of the four 4×4 blocks of the full three-locus fitness matrix. The two cases of (2) we shall consider here are the LEWONTIN-KOJIMA model $\alpha = \delta$ and the WRIGHT model $2(\beta+\gamma) = \alpha + \delta$. For both of these models the stable equilibria of the two-locus system we consider are symmetric, i.e., at the equilibria *AB* and *ab* have the same frequencies, as do *Ab* and *aB*. The complete stability conditions for these may be found in KARLIN and FELDMAN (1970).

In terms of the three-locus model these equilibria are on the boundaries of the frequency simplex. Thus when $\alpha = \delta$ the two-locus theory produces the symmetric equilibria, with $l = 2(\beta+\gamma-\delta)$,

$$\hat{x}_1 = \hat{x}_4 = 1/4(1 \pm \sqrt{1-\frac{8r_1}{l}}); \; \hat{x}_2 = \hat{x}_3 = 1/4(1 \mp \sqrt{1-\frac{8r_1}{l}}), \tag{3a}$$

$$\hat{x}_1 = \hat{x}_2 = \hat{x}_3 = \hat{x}_4 = 1/4, \tag{3b}$$

when only M is present, with $\hat{x}_5 = \hat{x}_6 = \hat{x}_7 = \hat{x}_8 = 0$, and

$$\hat{x}_5 = \hat{x}_8 = \tfrac{1}{4}(1 \pm \sqrt{1 - \frac{8r_3}{l}}); \; \hat{x}_6 = \hat{x}_7 = \tfrac{1}{4}(1 \mp \sqrt{1 - \frac{8r_3}{l}}), \quad \text{(3c)}$$

$$\hat{x}_5 = \hat{x}_6 = \hat{x}_7 = \hat{x}_8 = \tfrac{1}{4}, \quad \text{(3d)}$$

when only m is present, with $\hat{x}_1 = \hat{x}_2 = \hat{x}_3 = \hat{x}_4 = 0$.

In the WRIGHT model $l = 2(\beta+\gamma) - (\alpha+\delta) = 0$ the corresponding equilibria are, with $k = \delta - \alpha > 0$,

$$\hat{x}_1 = \hat{x}_4 = \tfrac{1}{4} + \frac{r_1}{k} - \tfrac{1}{4}\sqrt{1 + \frac{16r^2_1}{k^2}}, \; \hat{x}_2 = \hat{x}_3 = \tfrac{1}{2} - \hat{x}_1 \quad \text{(4a)}$$

when only M is present, with $\hat{x}_5 = \hat{x}_6 = \hat{x}_7 = \hat{x}_8 = 0$, and

$$\hat{x}_5 = \hat{x}_8 = \tfrac{1}{4} + \frac{r_3}{k} - \tfrac{1}{4}\sqrt{1 + \frac{16r^2_3}{k^2}}, \; \hat{x}_6 = \hat{x}_7 = \tfrac{1}{2} - \hat{x}_5 \quad \text{(4b)}$$

when only m is present, with $\hat{x}_1 = \hat{x}_2 = \hat{x}_3 = \hat{x}_4 = 0$.

Basically, the stability condition* for (3)a is that the quantities under the square roots be positive, i.e. $r_1 < (l/8)$. If $r_1 > (l/8)$, (3)b is stable and $r_3 > (l/8)$ makes (3)d stable. For the equilibria (4)a and (4)b the condition for stability is that r_1 and r_3 be smaller than a certain constant, expressible in terms of the selection coefficients and given by KARLIN and FELDMAN (1970). These facts do not give the whole story; with strong single-locus underdominance, for example, (3)a and (3)c may not be stable in the whole interval while in both models unsymmetric equilibria may exist. We shall not consider these here as they are unstable.

3. *Recombination Balance: Interior Three-Locus Equilibria*

The result of FELDMAN (1972) for the cases of the previous section are that when either of (3)a or (4)a is stable in the two-locus sense it is unstable in the three-locus sense provided $r_2 < r_1$. Similarly when either of (3)c or (4)b is stable in the two-locus sense it is unstable in the three-locus sense provided $r_2 < r_3$. Insofar as (3)b and (3)d are concerned, in the seven-dimensional frequency simplex there is a curve of equilibria joining these two points and parameterized by p_M, the frequency of M. It appears that when (3)a and (3)c are unstable (in the three-locus sense) there is convergence to this curve, the precise point depending on the starting conditions. Throughout the rest of this paper we assume that $r_1 = r_3$ and that, when $\alpha = \delta$, $r_1 < (l/8)$ so that (3)a and (3)c are stable as two-locus equilibria in the LEWONTIN-KOJIMA case. In the WRIGHT model, when $l = 0$, (4)a and (4)b are assumed stable as two-locus equilibria. Finally, considered as three-locus equilibria, we assume that all of these are unstable, i.e. $r_2 < r_1$. We are now interested in the behavior of the system (1) as a bona fide three-locus system.

Consider first the case, $\alpha = \delta$. Since MM and mm produce the same recombination fraction r_1 between A/a and B/b it might be expected that the population would move towards a stable equilibrium at which the frequencies of chromosomes MAB, MAb, MaB and Mab are, respectively, equal to mAB, mAb, maB and mab; i.e., $x_1 = x_5$, $x_2 = x_6$, $x_3 = x_7$, $x_4 = x_8$. Indeed it is quickly seen that two

---

* Stability in this paper means local stability.

such equilibria exist and, as expected, are of the form (3)a but with recombination fraction $\frac{r_1+r_2}{2}$, namely,

$$\hat{x}_1 = \hat{x}_5 = \hat{x}_4 = \hat{x}_8 = 1/8 \pm 1/8 \sqrt{1 - 8\left(\frac{r_1+r_2}{2}\right)/l}$$

$$\hat{x}_2 = \hat{x}_6 = \hat{x}_3 = \hat{x}_7 = 1/8 \mp 1/8 \sqrt{1 - 8\left(\frac{r_1+r_2}{2}\right)/l}\,. \tag{5}$$

Similarly in the WRIGHT case $l = 2(\beta+\gamma) - (\alpha+\delta) = 0$ the same reasoning produces the equilibrium, with $k = \delta - \alpha > 0$.

$$\hat{x}_1 = \hat{x}_5 = \hat{x}_4 = \hat{x}_8 = 1/8 + \frac{(r_1+r_2)/2}{2k} - 1/8 \sqrt{1 + \frac{16\left(\frac{r_1+r_2}{2}\right)^2}{k^2}}$$

$$\hat{x}_2 = \hat{x}_6 = \hat{x}_3 = \hat{x}_7 = 1/4 - \hat{x}_1\,. \tag{6}$$

With $\alpha = \delta$ and $r_1 = r_3 > (l/8)$, equilibria (3)b and (3)d are stable in the two-locus sense. From (1) with (2) it is easy to seen that these two boundary equilibria are joined by the curve of equilibria specified by

$$x_1 = \frac{p_M}{4} = x_2 = x_3 = x_4\,; \quad x_5 = \frac{p_m}{4} = x_6 = x_7 = x_8 \tag{7}$$

where $p_M = 1 - p_m$ is the frequency of M.

This approach is of limited usefulness and in order to discover whether these are the only equilibria we make use of the transformation used by FELDMAN, FRANKLIN and THOMSON (1973) for the study of the three-locus symmetric viability model. We change the coordinates from x_i to u_i where

$$\begin{aligned}
u_1 &= x_1 + x_2 + x_3 + x_4 - x_5 - x_6 - x_7 - x_8 \\
u_2 &= x_1 + x_2 + x_5 + x_6 - x_3 - x_4 - x_7 - x_8 \\
u_3 &= x_1 + x_3 + x_5 + x_7 - x_2 - x_4 - x_6 - x_8 \\
u_4 &= x_1 + x_4 + x_6 + x_7 - x_2 - x_3 - x_5 - x_8 \\
u_5 &= x_1 + x_2 + x_7 + x_8 - x_3 - x_4 - x_5 - x_6 \\
u_6 &= x_1 + x_3 + x_6 + x_8 - x_2 - x_4 - x_5 - x_7 \\
u_7 &= x_1 + x_4 + x_5 + x_8 - x_2 - x_3 - x_6 - x_7\ .
\end{aligned} \tag{8}$$

From (7) we can write the x's as functions of u's as follows:

$$\begin{aligned}
x_1 &= (1 + u_1 + u_2 + u_3 + u_4 + u_5 + u_6 + u_7)/8 \\
x_2 &= (1 + u_1 + u_2 - u_3 - u_4 + u_5 - u_6 - u_7)/8 \\
x_3 &= (1 + u_1 - u_2 + u_3 - u_4 - u_5 + u_6 - u_7)/8 \\
x_4 &= (1 + u_1 - u_2 - u_3 + u_4 - u_5 - u_6 + u_7)/8 \\
x_5 &= (1 - u_1 + u_2 + u_3 - u_4 - u_5 - u_6 + u_7)/8 \\
x_6 &= (1 - u_1 + u_2 - u_3 + u_4 - u_5 + u_6 - u_7)/8 \\
x_7 &= (1 - u_1 - u_2 + u_3 + u_4 + u_5 - u_6 - u_7)/8 \\
x_8 &= (1 - u_1 - u_2 - u_3 - u_4 + u_5 + u_6 + u_7)/8\ .
\end{aligned} \tag{9}$$

(This transformation is seen to be an extension of that used by KARLIN and FELDMAN [1970] for their study of the two-locus symmetric viability model.)

It is easy to see that the three-locus viability model given by four blocks identical to (2) is a particular case of the symmetric viability three-locus model. In the present case, however, an additional recombination parameter is involved. Even so, it is natural to ask whether there are symmetric equilibria in the present setup, i.e. equilibria with $\hat{x}_1 = \hat{x}_8$, $\hat{x}_2 = \hat{x}_7$, $\hat{x}_3 = \hat{x}_6$, $\hat{x}_4 = \hat{x}_5$. These are the type of equilibria to which the study of FELDMAN, FRANKLIN and THOMSON (1973) is devoted. In terms of the u's these are of the form $\hat{u}_1 = \hat{u}_2 = \hat{u}_3 = \hat{u}_4 = 0$. It will be seen that the search for such symmetric equilibria in the linkage modification context produces a great deal of useful information about the equilibrium behavior of the model.

3A. LEWONTIN-KOJIMA *System* $\alpha = \delta$; $r_1 < \frac{l}{8} = \frac{\beta+\gamma-\delta}{4}$.

Rewrite the recursion system in terms of the u variables. To obtain the symmetric solutions set the variables u_1, u_2, u_3 and u_4 equal to zero. We are left with three simultaneous cubics in u_5, u_6 and u_7 as follows

$$\text{(a)}\quad w^* u_5 = u_5\left[1 - \frac{\delta}{4} - \frac{\beta}{4} - \frac{\gamma}{4} - r\left(1 - \frac{\gamma}{2}\right)\right] + u_6 u_7\left[\frac{l}{8} - \frac{r\gamma}{2}\right]$$

$$\text{(b)}\quad w^* u_6 = u_6\left[1 - \frac{\delta}{4} - \frac{\beta}{4} - \frac{\gamma}{4} - (r + r_2 - 2rr_2)\left(1 - \frac{\beta}{2}\right)\right] + u_5 u_7\left[\frac{l}{8} - \beta\left(\frac{r + r_2 - 2rr_2}{2}\right)\right]$$

$$\text{(c)}\quad w^* u_7 = u_7\left[1 - \frac{\delta}{2} - \frac{r_1 + r_2}{2}\right] + u_5 u_6\left(\frac{r_1 - r_2}{2}\right) \qquad (10)$$

where $w^* = 1 - \frac{\delta}{4} - \frac{\beta}{4} - \frac{\gamma}{4} + \frac{l}{8} u_7^2$ is written for $\bar{w}$ with $u_1 = u_2 = u_3 = u_4 = 0$.

Clearly one solution of (10) is $\hat{u}_5 = \hat{u}_6 = \hat{u}_7 = 0$, or

$$\hat{x}_1 = \hat{x}_2 = \hat{x}_3 = \hat{x}_4 = \hat{x}_5 = \hat{x}_6 = \hat{x}_7 = \hat{x}_8 = 1/8\,, \qquad (11)$$

which lies on the curve (7). There cannot exist solutions of the form $\hat{u}_5 \neq 0$; $\hat{u}_6 = \hat{u}_7 = 0$ unless, from (10)a, $r = 0$. Similarly, unless $r_1 + r_2 - 2rr_2 = 0$ there are no solutions with $\hat{u}_6 \neq 0$ and $\hat{u}_5 = \hat{u}_7 = 0$. From (10)c, however, there are solutions of the form $\hat{u}_5 = \hat{u}_6 = 0$; $\hat{u}_7 \neq 0$, and these are given by

$$u_7 = \pm\sqrt{1 - 8(r_1 + r_2)/2)/l} \qquad (12)$$

which from (9) are seen to be the points (5) obtained previously.

It is obvious that unless special relations hold among the parameters in (10) no solutions with exactly two of u_5, u_6, u_7 non-zero are possible. It remains to determine those solutions, if any, with all three variables non-zero. To this end make the further transformation

$$\xi_1 = u_6 u_7 / u_5\,, \quad \xi_2 = u_5 u_7 / u_6\,, \quad \xi_3 = u_5 u_6 / u_7\,. \qquad (13)$$

Then, since $u_7^2 = \xi_1\xi_2$, from (10)a we have

$$\xi_2 = \frac{-r(1-\gamma/2) + \xi_1[l/8 - r\gamma/2]}{l\xi_1/8} \tag{14}$$

and from (10)c we have

$$\begin{aligned}\xi_3 &= \frac{l/8 - (r_1+r_2)/2 - l\xi_1\xi_2/8}{(r_2-r_1)/2} \\ &= \frac{l/8 - (r_1+r_2)/2 + r(1-\gamma/2) - \xi_1[l/8 - r\gamma/2]}{(r_2-r_1)/2}\end{aligned} \tag{15}$$

Finally, using (14) in (10)b we obtain the quadratic equation in ξ_1

$$\begin{aligned}&l(l/8 - r\gamma/2)\xi_1^2/8 + \\ &\xi_1\Big\{ l[(r+r_2-2rr_2)(1-\beta/2) - r(1-\gamma/2)]/8 - [l/8 - r\gamma/2] \\ &[l/8 - \frac{(r+r_2+2rr_2)\beta}{2}]\Big\} + r(1-\gamma/2)\Big[l/8 - \frac{(r+r_2-2rr_2)\beta}{2}\Big] .\end{aligned} \tag{16}$$

For fixed $r_2 > 0$, this quadratic is seen to have real roots in an interval of r values including $r = 0$. Now given any real root of (16) we determine $\hat{\xi}_2$ and $\hat{\xi}_3$ from (14) and (15) and then $\hat{u}_5$, $\hat{u}_6$, $\hat{u}_7$ from the fact that $\hat{u}_5^2 = \hat{\xi}_2\hat{\xi}_3$, $\hat{u}_6^2 = \hat{\xi}_1\hat{\xi}_3$ and $\hat{u}_7^2 = \hat{\xi}_1\hat{\xi}_2$. Therefore the valid roots must have $\hat{\xi}_1$, $\hat{\xi}_2$ and $\hat{\xi}_3$ all with the same sign. We now discuss the case $r = 0$ since from this case we learn quite a bit about the case where r is small and positive.

Special Case $r = 0$.

Clearly, when $r = 0$, from (10)a there is a continuum of equilibria with $u_6 = u_7 = 0$, $u_5 \neq 0$. They are of the form

$$\begin{aligned}x_1 = x_2 = x_7 = x_8 &= \tfrac{1}{8}(1+u_5) \\ x_3 = x_6 = x_4 = x_5 &= \tfrac{1}{8}(1-u_5)\end{aligned} \tag{17}$$

with $-1 \leq u_5 \leq 1$. In addition to this curve, the curve (7) and the points (12) there are boundary equilibria given by

$$\hat{\xi}_1 = 1 - \frac{8r_2}{l}\,, \quad \hat{\xi}_2 = 1\,, \quad \hat{\xi}_3 = 1\,. \tag{18}$$

or

$$\hat{x}_1 = \hat{x}_8 = \tfrac{1}{2} - \hat{x}_2 = \tfrac{1}{2} - \hat{x}_7 = \tfrac{1}{4}\left(1 \pm \sqrt{1 - \frac{8r_2}{l}}\right) \tag{19a}$$

$$\hat{x}_3 = \hat{x}_4 = \hat{x}_5 = \hat{x}_6 = 0$$

and

$$\hat{x}_3 = \hat{x}_6 = \tfrac{1}{2} - \hat{x}_4 = \tfrac{1}{2} - \hat{x}_5 = \tfrac{1}{4}\left(1 \pm \sqrt{1 - \frac{8r_2}{l}}\right) \tag{19b}$$

$$\hat{x}_1 = \hat{x}_2 = \hat{x}_7 = \hat{x}_8 = 0\,.$$

Points (19)a and (19)b are to be expected since when $r = 0$, the *M/m* and *A/a* loci are superimposed, and in effect we have a two-locus situation. Thus we might write A^* for MA and a^* for ma in which case (19)a represents the usual LEWONTIN-KOJIMA equilibria for the two-locus model having chromosomes A^*B, A^*b, a^*B and a^*b. Similar considerations apply to (19)b.

We shall have more to say about (19)a and (19)b in Section 4, but at this stage we point out that when r is positive and sufficiently small these boundary equilibria move into the interior of the simplex producing four non-trivial polymorphic equilibria.

For very small r it can be seen that (16) has one root, $\hat{\xi}_1$ very close to zero, but positive, and the other, $\hat{\xi}^*_1$, substantially positive. Now under our hypothesis $r_2 < r_1$ and $l/8 > \frac{r_1+r_2}{2}$. Therefore, for r small enough, from (15) the value of $\hat{\xi}_3$ corresponding to $\hat{\xi}_1$ is negative. This is inadmissable since all $\hat{\xi}$'s must have the same sign. Thus there may exist a maximum of four additional equilibria with $\hat{u}_5 \neq 0$, $\hat{u}_6 \neq 0$, $\hat{u}_7 \neq 0$ when r is small, and this maximum is attained. (It is interesting to compare this with the three-locus symmetric viability model where eight such equilibria exist.)

It is possible to present a more detailed analysis of the existence conditions for the equilibria from the roots of (16) in terms of (10)a, (10)b and (10)c or (14) and (15), as well as all of the parameters. An analysis of this type is presented elsewhere by FELDMAN, FRANKLIN and THOMSON (1973) for the fifteen symmetric equilibria of the three-locus symmetric viability model, so we do not present such detailed arguments here. Some elementary facts are worth noting, however. The first is that the condition for stability of the central points (5) is (see section 4)

$$l\hat{D}^2[4r-4rr_2+r_2-r_1] + r(r+r_2-2rr_2)[(1-\gamma/2)(1-\beta/2)-4\beta\gamma\hat{D}^2] > 0 \quad (20)$$

where $\hat{D}^2 = 1/16\,[1-4(r_1+r_2)/l]$. Now if $(r+r_2-2rr_2)\beta/2 > l/8 > r\gamma/2$ or if $r\gamma/2 > l/8 > (r+r_2-2rr_2)\beta/2$, then from (16), (14) and (15), it is quickly seen that no roots of (16) can be valid. On the other hand if $l/8 > r\gamma/2$ and $l/8 > (r+r_2-2rr_2)\beta/2$ and (20) is violated, there are two positive roots of (16), the larger of which $\hat{\xi}^*_1$ is valid from (14) and (15) and the smaller one invalid.* The larger root produces four valid symmetric equilibria which exist when the central points (5) are unstable, namely when r is small. For values of r slightly larger than that allowing stability of (5) there are no valid symmetric equilibria except (5), and when $r\gamma/2$ and $(r+r_2-2rr_2)\beta/2$ are both greater than $l/8$, neither of the resulting negative roots of (16) is valid. To summarize, for the modifier tightly linked to the modified loci, four symmetric equilibria and the central points (5) coexist, with the latter unstable. These four extra symmetric points cease to exist as r increases and (5) become stable.

3B. WRIGHT'S *Model* $2(\beta+\gamma) = \alpha+\delta$, $k = \delta-\alpha > 0$.

We have already remarked that (4)a and (4)b are the equilibria in this case corresponding to the boundaries where M and m, respectively, are fixed. With $r_1 > r_2$ these are unstable in the three-locus sense. In addition there is the interior

---

* A valid $\hat{\xi}^*_1$ is one for which the corresponding x-values are between zero and 1.

equilibrium (6). In the same way as before we proceed to seek the symmetric equilibria. Using (9) we rewrite (1) and set $u_1 = u_2 = u_3 = u_4 = 0$ to obtain the symmetric equilibria. We obtain

$$(a) \quad \tilde{w}u_5 = u_5[1 - \frac{\alpha+\delta}{8} - \frac{\beta+\gamma}{4} - r(1-\gamma/2)] - u_6u_7\frac{r\gamma}{2} - \frac{k}{8}[u_6+u_5u_7]$$

$$(b) \quad \tilde{w}u_6 = u_6[1 - \frac{\alpha+\delta}{8} - \frac{\beta+\gamma}{4} - (r+r_2-2rr_2)(1-\beta/2)] - u_5u_7\frac{(r+r_2-2rr_2)\beta}{2} - \frac{k}{8}[u_5+u_6u_7]$$

$$(c) \quad \tilde{w}u_7 = u_7\left[1 - \frac{\alpha+\delta}{4} - \frac{r_1+r_2}{2}\right] - \frac{k}{8}u^2 - \frac{k}{8} + u_5u_6\left(\frac{r_1-r_2}{2}\right) \tag{21}$$

with

$$\tilde{w} = 1 - \frac{\alpha+\delta}{8} - \frac{\beta+\gamma}{4} - \frac{ku_7}{4}.$$

Note that these are no longer cubics and have a somewhat different structure from that in the Lewontin-Kojima case. From (21)c there is no solution with $\hat{u}_5 = \hat{u}_6 = \hat{u}_7 = 0$. Also there are no solutions with $\hat{u}_5 \neq 0$ and $\hat{u}_6 = \hat{u}_7 = 0$ or with $\hat{u}_6 \neq 0$ and $u_5 = u_7 = 0$. From (21)c, however, there is a solution with $\hat{u}_7 \neq 0$ and $\hat{u}_5 = \hat{u}_6 = 0$. In fact, there are two such solutions but the admissable one is

$$\hat{u}_7 = 4\left\{\frac{(r_1+r_2)/2}{k}\right\} - \sqrt{1 + 16[(r_1+r_2)/2]^2/k^2} < 0 \tag{22}$$

which is precisely the same as (6). Finally we look for solutions of the form $\hat{u}_5 \neq 0$, $\hat{u}_6 \neq 0$, $\hat{u}_7 \neq 0$. Some elementary algebra on (21)a and (21)b, respectively, produces the relations

$$\frac{u_5}{u_6} = \frac{k/8 + r\gamma u_7/2}{ku_7/8 - r(1-\gamma/2)} \tag{23}$$

and

$$\frac{u_5}{u_6} = \frac{ku_7/8 - (r+r_2-2rr_2)(1-\beta/2)}{k/8 + (r+r_2-2rr_2)u_7/2} \tag{24}$$

Combining these we have the quadratic in u_7

$$u_7^2\left[\frac{r(r+r_2-2rr_2)\gamma\beta}{4} - \frac{k^2}{64}\right] + u_7\left[\frac{k(2r+r_2-2rr_2}{8}\right] + \frac{k^2}{64} - r(r+r_2-2rr_2)\left(1-\frac{\beta}{2}\right)\left(1-\frac{\gamma}{2}\right) = 0. \tag{25}$$

For r small the roots are clearly real and the negative one is admissible while the positive is not. Substituting the admissible root, $\hat{u}_7$, into (21)c we obtain an equation of the form

$$u_6 = \frac{g(\hat{u}_7)}{u_5(r_1-r_2)/2} \tag{26}$$

with $g(\hat{u}_7) = \frac{k(1-\hat{u}^2{}_7)}{8} + \left(\frac{r_1+r_2}{2}\right)\hat{u}_7$. Substituting back into (23), say, we find

$$\hat{u}_5^2 = \frac{g(\hat{u}_7)\left[k/8 + \frac{\hat{u}_7 r\gamma}{2}\right]}{\frac{(r_1-r_2)}{2}\left[\frac{k\hat{u}_7}{8} - r\left(1-\frac{\gamma}{2}\right)\right]}\,. \tag{27}$$

It is not difficult to show that $g(\hat{u}_7)$ is negative near $r = 0$, so that this is a valid expression for $\hat{u}_5^2$. For the admissible $\hat{u}_7$ value we therefore have two additional symmetric equilibria in a range of r values including $r = 0$.

Remark 1: In the same way as for the LEWONTIN-KOJIMA model when $r = 0$, the admissible roots are on the boundaries and are functions of r_2 only. When $r_2 = 0$ as well these boundary equilibria have the form

$$\text{(a) } \hat{x}_1 = \hat{x}_8 = \tfrac{1}{2}, \quad \text{(b) } \hat{x}_2 = \hat{x}_7 = \tfrac{1}{2}, \quad \text{(c) } \hat{x}_4 = \hat{x}_5 = \tfrac{1}{2}, \quad \text{(d) } \hat{x}_3 = \hat{x}_6 = \tfrac{1}{2}. \tag{28}$$

Remark 2: For both models 3A and 3B it is conceivable that additional unsymmetric equilibria exist (apart from those already mentioned in the analysis of 3A). We have not analyzed these here.

4. *Stability of the Interior Polymorphisms*

FELDMAN (1972) showed that if $r_1 = r_3$ equilibria (3)a, (3)c, (4)a, and (4)b are unstable in the three-locus sense if and only if $r_2 < r_1$. We assume, of course, that these exist and are stable in the two-locus sense on their respective boundaries. In the LEWONTIN-KOJIMA case this also entails that (3)b and (3)d are unstable in the two-locus sense and we assume that, in this case, the curve (7) is unstable. It remains to establish the stability properties of the equilibria (5) and (16) for the LEWONTIN-KOJIMA case and (6) and (25) for the WRIGHT model. We discuss mainly the former since the arguments are the same for the latter.

Stability is taken locally by linearizing (1) in the neighborhood of the appropriate equilibrium and evaluating the eigenvalues of the resulting matrix. First consider the more central equilibria (5) for the LEWONTIN-KOJIMA case, (6) for the WRIGHT model. The 7 × 7 local stability determinant breaks into a quartic and a cubic. The eigenvalues from the latter are simply those for the stability, in the two-locus symmetric viability sense, of these equilibria but with $r^* = (r_1+r_2)/2$ as recombination fraction. Since $\frac{r_1+r_2}{2} < r_1$, all three eigenvalues in both models will be less than unity.

The remaining quartic breaks into two quadratics, one of which has both roots less than unity if and only if $r_2 < r_1$. The remaining quadratic produces an interesting finding. In the LEWONTIN-KOJIMA case the larger eigenvalue is less than unity and hence the equilibrium is stable if inequality (20) holds. In the Wright model the corresponding condition is, with $k = \delta - \alpha > 0$,

$$\frac{-k\hat{D}}{4}\,[4r-4rr_2+r_2-r_1] + r[r+r_2-2rr_2]\left[1-\frac{\beta+\gamma}{2}-\frac{4\beta\gamma(r_1+r_2)\hat{D}}{k}\right] > 0 \quad (29)$$

where

$$\hat{D} = \frac{(r_1+r_2)/2}{k} - \tfrac{1}{4}\sqrt{1+\frac{16[(r_1+r_2)/2]^2}{k^2}}\,.$$

Clearly when $r = 0$ these conditions reduce to the condition $r_2 > r_1$. Hence when $r = 0$ then (5) and (6) are unstable for their respective models. Further, when $r = 0$ it is easy to show that the condition $r_1 > r_2$ ensures that the boundary equilibria (19)a and (19)b are stable in the Lewontin-Kojima case and similarly in the Wright model. It is clearly necessary for the instability of (5) and (6) that $r < \frac{r - r}{4(1-r_2)}$ (since the last terms in (20) and (29) are positive).

The other symmetric equilibria (16) and (25) are more complicated to analyze but we believe the main properties have been uncovered. We report only the Lewontin-Kojima case here although the Wright case can be done in a similar way. The stability determinant factors into a cubic and two quadratics. The cubic has not been shown to have real roots although for r small it does, since when $r = 0$ it factors producing the stability conditions $l > 0$, $r_2 < l/8$, $r_1 > r_2$, all of which were assumed anyway. In fact, if the cubic has real roots they are all less than unity in absolute value if and only if the derivative of the quadratic (16) evaluated at the equilibrium is positive. This is certainly the case for the larger positive root of (16) in its range of validity, namely when (5) are unstable.

One of the remaining two quadratics can be shown to produce real eigenvalues less than unity in modulus if $r_1 > r_2$. The other quadratic produces the stability condition

$$\delta^2 - \frac{(\beta+\gamma)^2}{16} + \frac{\hat{\xi}_1\hat{\xi}_2}{4}\left[\frac{\delta(\beta+\gamma-\delta)}{2} + \frac{(\beta+\gamma-\delta)^2}{4}\hat{\xi}_1\hat{\xi}_2 - (\beta-\delta)(\gamma-\delta)\right] > 0\,. \quad (30)$$

This condition is completely analogous to, and when $r = 0$, is identical to condition (4.2) of Karlin and Feldman (1970) for the non-existence of the "gap" of instability originally discovered by Ewens (1968). As was the case in that study, overdominance at each of the A/a and B/b loci is sufficient to ensure the truth of (30). In summary, when $l/8 > r_1 > r_2$, and there is overdominance at the separate modified loci, the symmetric equilibria resulting from (16) are stable for r small. These equilibria are each characterized by high frequencies of the two complementary pairs of chromosomes. When r is larger, the central symmetric points with effective recombination fraction $\frac{r_1+r_2}{2}$ are stable.

DISCUSSION

The existence of the stable interior polymorphism in the models treated here confirms predictions based on the instability of the boundary equilibria previously proved by FELDMAN (1972). The instability of the boundary equilibria does not depend on the degree of linkage of the modifier to the modified loci, but, as has been shown here, the polymorphism attained does. When the modifier is tightly linked to the modified genes, the polymorphisms are characterized by two pairs of complementary chromosomes in high frequencies, with the others in low frequencies. This might have been predicted from the standard two-locus theory of KARLIN and FELDMAN (1970), for when r is zero the model essentially is a two-locus symmetric viability model. When r is large a more evenly distributed polymorphism results.

Polymorphisms for genes which affect the *fitness* of other genes have been studied in connection with epistatic two-locus theory, evolution of dominance and a number of other situations. The linkage modifiers we have discussed have no effect on the fitness of their carriers—they are selectively neutral—yet through their effect on the linkage disequilibrium at the modified loci they are *effectively* selected. We propose to call this type of selection *secondary selection*, as opposed to primary selection which occurs for genes affecting the fitness of their carriers. Secondary selection might just as well be called *induced selection*, as the changes in frequency of the genes at the modifier locus are induced by the selection going on at the primary loci. This stands in contrast to the situation of evolution of dominance in which the selection is imposed by the modifier locus on the modified locus. As discussed by KARLIN and McGREGOR (1974) this really makes it impossible to distinguish the primary from the secondary locus in the evolution of dominance situation. In the cases discussed in this paper the recombination fraction is lower with a heterozygous modifier than with either homozygote. We could describe this as *induced* or *secondary* overdominance.

It is not necessary that secondary overdominance always involves a parametric reduction by the modifier heterozygote compared to the modifying homozygotes. It occurs in the models we have examined but we conjecture that this is because the basic two-locus polymorphisms are such that stable linkage disequilibrium exists only for tight linkage between the selected loci. Now, except for the unsymmetric equilibria of KARLIN and FELDMAN (1970), there are no examples in the literature of stable linkage disequilibrium for relatively loose linkage. If such an equilibrium came from some asymmetric selection model it is conceivable that "overdominance" would have the opposite meaning to the above. Thus looser linkage in the heterozygote than homozygotes at the modifier locus might produce the polymorphism. An example of this is discussed by THOMSON and FELDMAN (1974) in connection with a model of segregation distortion due to PROUT, BUNGAARD and BRYANT (1973). The meaning of the term "overdominance" in this context will depend on the selection regime, degree of recombination and type of equilibrium considered at the modified loci.

In the case of evolution of dominance the order of magnitude of selection is the mutation rate at the beginning and the square root of the mutation rate at the conclusion (unless the latter is algebraic). On the other hand, with secondary selection the order of magnitude of the selection depends on the magnitude of the parametric changes caused by the modifier locus. These are probably characteristic of the parameter. Thus one might expect smaller changes in mutation modification than, say, in migration or recombination modification. (The first two have been studied by BALKAU and FELDMAN [1973] and by KARLIN and MCGREGOR [1973].)

One interesting corollary of the arguments presented in this paper pertains to speculations on the origin of inversion polymorphisms, such as the discussions by HALDANE (1957) and DOBZHANSKY (1970, p. 145). HALDANE's condition for the existence of such polymorphisms was that "heterozygosis at any locus concerned in the genetical polymorphism should have a greater effect in raising fitness when the other loci concerned are heterozygous than when they are homozygous." In terms of the two-locus LEWONTIN-KOJIMA model, for example, this would seem to mean that the difference in fitness between *AaBb* and *AABb* should be greater than the difference in fitness between *AaBB* and *AABB*. When $\alpha = \delta$, $\beta = \gamma$, HALDANE's condition merely entails that $2\beta > \delta$, or in the terminology above $l > 0$.

Now $l > 0$ is the condition that the original equilibria with $\hat{D} \neq 0$ exist. We have shown here that when these equilibria are stable a recombination balance can be set up if the recombination between heterozygotes (measured by r_2) is less frequent than between homozygotes (measured by r_1). This balance is, we believe, completely analogous to the polymorphism between inversion and standard chromosome forms. In other words HALDANE's argument is not complete. Indeed, it is conceivable under his condition that an equilibrium with $\hat{D} = 0$ be stable (for loose linkage) in which case linkage modification would not proceed.

The completion of these arguments of HALDANE is a quantitative expression of the qualitative arguments expressed by LEWONTIN (1967) and discussed by DOBZHANSKY (1970, p. 145) that the relevant dimension in the dynamics of change of inversion frequency is the extent of disequilibrium, not necessarily the extent of heterosis.

In the study of KARLIN and MCGREGOR (1973) of the models discussed here, and of a number of others, it has been shown that the properties of the mean fitness at equilibrium in fact determine the fate of modifying genes. The recombination examples studied by FELDMAN (1972) had the property that $\partial\hat{\bar{w}}/\partial r > 0$ at the stable equilibria where modification occurred. Thus, although the modifier did not alter the fitness of its carrier, for it to increase, it had to increase the mean fitness of the population. In this sense, then, we may even conceive of a gene which decreased the fitness of its carriers but still increased by virtue of secondary selection, i.e. its effect on population fitness. This would seem to provide an example of the "altruistic" gene discussed by HALDANE (1966). Although his discussion was mainly in terms of "social" animals, secondary selection may provide a more basic framework in which to view this idea.

The above-mentioned new modifying principle enunciated by KARLIN and MCGREGOR (1974) has been shown by them to apply to many more models than the original linkage modification cases. In these cases, any mutation which decreases the fitness of its carrier but which sufficiently increases the mean equilibrium fitness of the population we presume will increase, and such a mutant gene could well be called "altruistic." We are currently investigating the details of this phenomenon.

The authors are grateful to PROFESSORS S. KARLIN and J. MCGREGOR for a number of stimulating discussions, and for permission to see their unpublished manuscript.

LITERATURE CITED

BALKAU, B. and M. W. FFLDMAN, 1973 Selection for migration modification. Genetics. **74**: 171–174.

BODMER, W. F. and J. FELSENSTEIN, 1967 Linkage and selection: Theoretical analysis of the deterministic two locus random model. Genetics **57**: 237–265.

DOBZHANSKY, T., 1970 *Genetics of the Evolutionary Process* Columbia University Press, New York.

EWENS, W. J., 1968 A genetic model having complex linkage behaviour. Theor. Appl. Genet, **1**: 140–143.

FELDMAN, M. W., 1972 Selection for linkage modification I: Random mating populations. Theor. Pop. Bio. **3**: 324–346.

FELDMAN, M. W. and B. BALKAU, 1972 Some results in the theory of three gen eloci. *Proceedings of the Symposium on Population Dynamics*, Madison, Wisconsin. Academic Press, New York.

FELDMAN, M. W., I. FRANKLIN and G. J. THOMSON, 1973 Selection on complex genetic systems. I. The symmetric equilibria of the three locus symmetric viability model. Submitted for publication.

FELDMAN, M. W. and S. KARLIN, 1971 The evolution of dominance: a direct approach through the theory of linkage and selection. Theoret. Pop. Biol. **2**: 482–492.

HALDANE, J. B. S., 1957 The conditions for co-adaptation in polymorphism for inversions. J. Genet. **55**: 218–225. ——, 1966 *The Causes of Evolution.* Cornell University Press, Ithaca, New York.

KARLIN, S. and M. W. FELDMAN, 1970 Linkage and selection: Two locus symmetric viability model. Theor. Pop. Bio. **1**: 39–71.

KARLIN, S. and J. L. MCGREGOR, 1972 The evolutionary development of modifier genes. Proc. Nat. Acad. Sci. U.S. **69**: 3611–3614. ——, 1974 Towards a theory of the evolution of modifier genes. (In preparation).

LEWONTIN, R. C., 1967 The genetics of complex systems. Proc. 5th Berkeley Symp. Math. Stat. Prob. **4**: 439–455.

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

NEI, M., 1967 Modification of linkage intensity by natural selection. Genetics **57**: 681–699. ——, 1969 Linkage modification and sex difference in recombination. Genetics **63**: 681–699.

PROUT, T., J. BUNGAARD and S. BRYANT, 1973 Population genetics of modifiers of meiotic drive. I. The solution of a special case and some general implications. Theoret. Pop. Biol. (In press).

THOMSON, G. J. and M. W. FELDMAN, 1974 Population genetics of modifiers of meiotic drive. II. Linkage modification. Theor. Pop. Biol. (In press).

WRIGHT, S., 1952. The genetics of quantitative variability. In: *Quantitative Inheritance.* Edited by K. MATHER. London, Her Majesty's Stationary Office, 5–41.