SELECTION IN COMPLEX GENETIC SYSTEMS I. THE SYMMETRIC EQUILIBRIA OF THE THREE-LOCUS SYMMETRIC VIABILITY MODEL

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ABSTRACT

The symmetric equilibria of the three-locus symmetric viability model are determined and their stability analyzed. For tight linkage there may be four stable equilibria, each characterized by having one pair of complementary chromosomes in high frequencies, with all others low. For looser linkage the only stable symmetric equilibrium is that with complete linkage equilibrium. For intermediate recombination values both types of equilibria may be stable. A new class of equilibria with all pairwise linkage disequilibria zero, but with third order linkage disequilibrium, has been discovered. It may be stable for tight linkage.

THE equilibrium theory of selection on two recombining loci has been developed primarily with respect to three types of selection schemes. When the contributions of the loci to the viabilities are additive, it is known that there is a single interior polymorphism which is globally stable for all non-zero recombination values when both loci are heterotic (BODMER and FELSENSTEIN 1967; MORAN 1968; KARLIN and FELDMAN 1970a). The equilibrium population is in linkage equilibrium. When the viabilities are multiplicative, it is known that for loose linkage, heterozygote advantage at the separate loci is sufficient for global stability of the equilibrium having linkage equilibrium (MORAN 1968; BODMER and FELSENSTEIN 1967). With these viabilities, however, the equilibrium behavior for tighter linkage is not known, although for sufficiently small recombination values, KARLIN and MCGREGOR (1971) have shown the existence of two stable equilibria in linkage disequilibrium.

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A special case of multiplicative viabilities is included in the general symmetric viability model (LEWONTIN and KOJIMA 1960; BODMER and FELSENSTEIN 1967; KARLIN and FELDMAN 1970; and EWENS 1968). For this model it has been shown (KARLIN and FELDMAN 1970b) that there is a maximum of seven interior equilibria with possibly two stable simultaneously. Combined with the eight boundary equilibria possible for non-zero recombination, this makes a total of fifteen in the symmetric viability model.

The theory developed by the above authors has produced certain conclusions of a qualitative nature which are biologically interesting. Tight linkage usually produces a stable symmetric equilibrium, and this is always (except for the additive case) in linkage disequilibrium. Loose linkage usually produces a stable linkage equilibrium state although certain unsymmetric equilibria may exist and be stable for moderate and loose linkage under strong selection. A selective advantage to the double heterozygote does not ensure polymorphism if the single loci have strong enough underdominance (EWENS 1968). The mean fitness cannot be used to produce information on equilibria and their stability especially for tight linkage. A final conclusion is that in the above models it is not possible for two equilibria, one in linkage equilibrium and one in linkage disequilibrium, to co-exist and be stable for the same value of the recombination fraction.

Recently FRANKLIN and LEWONTIN (1970) have made a numerical study, considerably extending those studies of LEWONTIN (1964a and b), concerning interactions between selection and linkage in 2-, 5-, 18-, 36-, and 360-locus models with multiplicative symmetric viabilities and equal (pairwise) recombination fractions. Looking at the symmetric equilibria, these authors determined (among other things) that the range of recombination values can be partitioned into three intervals: for small recombination values a single class of equilibria with relatively high pairwise linkage disequilibrium values is stable; for large recombination fractions linkage disequilibrium is zero at the stable polymorphism while in the intermediate range it is possible to have two stable situations for the same recombination value, one with zero disequilibrium and one with high disequilibrium.

In this paper we report primarily our results for the symmetric equilibria of the three-locus symmetric viability model (which includes the simplest multiplicative model as a special case). In large part our findings for the symmetric equilibria corroborate those which FRANKLIN and LEWONTIN (1970) obtained numerically. The stability analysis for one class of symmetric equilibria, as reported here, is not quite complete; but the analytic conclusions we make for the stability of these are in agreement with the findings from a series of numerical examples analyzed by computer. We also report a result for the simplest class of unsymmetric equilibria. This result indicates a major difference between the two- and multi-locus models.

The major conclusions of our analysis are the following:

1) For multiplicative symmetric viabilities and equally spaced loci, the conclusions of FRANKLIN and LEWONTIN (1970) hold: namely, for tight linkage the stable equilibria exhibit high complementarity (i.e., high disequilibrium); for

loose linkage there is stable linkage equilibrium; and in between there is a region where both types of equilibria are simultaneously stable.
2) When linkage is tight but the loci are unequally spaced, two stable equilibria exhibiting reduced disequilibrium can be stable simultaneously with the high complementarity equilibria above.
3) For tight linkage but non-multiplicative symmetric viabilities, two new stable unsymmetric equilibria exist simultaneously, but with the high complementarity equilibria above. These exhibit pairwise linkage equilibrium but have third-order linkage disequilibrium.

1. THREE-LOCUS MODEL

We consider three loci with two alleles at each. At the first, the alleles are A and a, at the second B and b and at the third C and c. The frequencies in a given generation of the eight chromosomes ABC, ABc, AbC, Abc, aBC, aBc, abC and abc are, respectively, $x_1, x_2, x_3, x_4, x_5, x_6, x_7$ and x_8. Random mating is assumed. The viability matrix we shall consider is detailed in (1.1) below.

	Frequency	ABC x_1	ABc x_2	AbC x_3	Abc x_4	aBC x_5	aBc x_6	abC x_7	abc x_8
	ABC	$1-\delta$	$1-\beta_1$	$1-\beta_3$	$1-\eta_2$	$1-\beta_2$	$1-\eta_3$	$1-\eta_1$	1
	ABc	$1-\beta_1$	$1-\delta$	$1-\eta_2$	$1-\beta_3$	$1-\eta_3$	$1-\beta_2$	1	$1-\eta_1$
	AbC	$1-\beta_3$	$1-\eta_2$	$1-\delta$	$1-\beta_1$	$1-\eta_1$	1	$1-\beta_2$	$1-\eta_3$
(1.1)	Abc	$1-\eta_2$	$1-\beta_3$	$1-\beta_1$	$1-\delta$	1	$1-\eta_1$	$1-\eta_3$	$1-\beta_2$
	aBC	$1-\beta_2$	$1-\eta_3$	$1-\eta_1$	1	$1-\delta$	$1-\beta_1$	$1-\beta_3$	$1-\eta_2$
	aBc	$1-\eta_3$	$1-\beta_2$	1	$1-\eta_1$	$1-\beta_1$	$1-\delta$	$1-\eta_2$	$1-\beta_3$
	abC	$1-\eta_1$	1	$1-\beta_2$	$1-\eta_3$	$1-\beta_3$	$1-\eta_2$	$1-\delta$	$1-\beta_1$
	abc	1	$1-\eta_1$	$1-\eta_3$	$1-\beta_2$	$1-\eta_2$	$1-\beta_3$	$1-\beta_1$	$1-\delta$

Thus the fitness of Abc/ABc is $1-\beta_3$, etc. All triple homozygotes are assumed to be equally fit. Some of our analysis is restricted to the $\beta_1 = \beta_2 = \beta_3$; $\eta_1 = \eta_2 = \eta_3$ case for simplicity. The simplest symmetric viability fitness model would have the viabilities multiplicative also, so that $(1-\delta) = W^3$, $1-\beta_1 = 1-\beta_2 = 1-\beta_3 = W^2$ and $1-\eta_1 = 1-\eta_2 = 1-\eta_3 = W$.

To complete the specification of the model, suppose that the recombination fraction between the A-a locus and the B-b locus is r_1, that between the B-b locus and the C-c locus is r_2 and that between the A-a and C-c loci is r_3. If we assume that there is no interference as in much of our analysis, then $r_3 = r_1 + r_2 - 2r_1r_2$. Under the above assumptions the recursion system relating the frequencies $x'_1, x'_2, \ldots, x'_8$ in the next generation to $x_1, x_2, \ldots, x_8$, those in the present, is given by Table 1.

2. TRANSFORMATIONS

In KARLIN and FELDMAN (1970) the recursion system involving the chromosome frequencies was transformed to a simpler more symmetric system which allowed the extraction of the unsymmetric equilibria and the determination of their stability. The same technique is used here. The appropriate coordinate system appears to be u_i, $i = 1, \ldots, 7$ with

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

TABLE 1

Recursion equations for the three-locus, symmetric viability model

$$\bar{w}x_1' = w_1x_1 - r_1\{(1-\eta_1)(x_1x_7-x_3x_5) + \tfrac{1}{2}\Delta_1\} - r_2\{(1-\eta_2)(x_1x_4-x_2x_3) + \tfrac{1}{2}\Delta_2\} - r_3\{(1-\eta_3)(x_1x_6-x_2x_5) + \tfrac{1}{2}\Delta_3\}$$

$$\bar{w}x_2' = w_2x_2 - r_1\{(1-\eta_1)(x_2x_8-x_4x_6) + \tfrac{1}{2}\Delta_1\} + r_2\{(1-\eta_2)(x_1x_4-x_2x_3) + \tfrac{1}{2}\Delta_2\} + r_3\{(1-\eta_3)(x_1x_6-x_2x_5) + \tfrac{1}{2}\Delta_3\}$$

$$\bar{w}x_3' = w_3x_3 + r_1\{(1-\eta_1)(x_1x_7-x_3x_5) + \tfrac{1}{2}\Delta_1\} + r_2\{(1-\eta_2)(x_1x_4-x_2x_3) + \tfrac{1}{2}\Delta_2\} - r_3\{(1-\eta_3)(x_3x_8-x_4x_7) + \tfrac{1}{2}\Delta_3\}$$

$$\bar{w}x_4' = w_4x_4 + r_1\{(1-\eta_1)(x_2x_8-x_4x_6) + \tfrac{1}{2}\Delta_1\} - r_2\{(1-\eta_2)(x_1x_4-x_2x_3) + \tfrac{1}{2}\Delta_2\} + r_3\{(1-\eta_3)(x_3x_8-x_4x_7) + \tfrac{1}{2}\Delta_3\}$$

$$\bar{w}x_5' = w_5x_5 + r_1\{(1-\eta_1)(x_1x_7-x_3x_5) + \tfrac{1}{2}\Delta_1\} - r_2\{(1-\eta_2)(x_5x_8-x_6x_7) + \tfrac{1}{2}\Delta_2\} + r_3\{(1-\eta_3)(x_1x_6-x_2x_5) + \tfrac{1}{2}\Delta_3\}$$

$$\bar{w}x_6' = w_6x_6 + r_1\{(1-\eta_1)(x_2x_8-x_4x_6) + \tfrac{1}{2}\Delta_1\} + r_2\{(1-\eta_2)(x_5x_8-x_6x_7) + \tfrac{1}{2}\Delta_2\} - r_3\{(1-\eta_3)(x_1x_6-x_2x_5) + \tfrac{1}{2}\Delta_3\}$$

$$\bar{w}x_7' = w_7x_7 - r_1\{(1-\eta_1)(x_1x_7-x_3x_5) + \tfrac{1}{2}\Delta_1\} + r_2\{(1-\eta_2)(x_5x_8-x_6x_7) + \tfrac{1}{2}\Delta_2\} + r_3\{(1-\eta_3)(x_3x_8-x_4x_7) + \tfrac{1}{2}\Delta_3\}$$

$$\bar{w}x_8' = w_8x_8 - r_1\{(1-\eta_1)(x_2x_8-x_4x_6) + \tfrac{1}{2}\Delta_1\} - r_2\{(1-\eta_2)(x_5x_8-x_6x_7) + \tfrac{1}{2}\Delta_2\} - r_3\{(1-\eta_3)(x_3x_8-x_4x_7) + \tfrac{1}{2}\Delta_3\}$$

where

w_i = marginal fitness of the i^{th} gamete

eg. $w_1 = (1-\delta x_1-\beta_1x_2-\beta_3x_3-\eta_2x_4-\beta_2x_5-\eta_3x_6-\eta_1x_7)$

$\Delta_1 = x_1x_8 + x_2x_7 - x_3x_6 - x_4x_5$, $\Delta_2 = x_1x_8 - x_2x_7 - x_3x_6 + x_4x_5$, $\Delta_3 = x_1x_8 - x_2x_7 + x_3x_6 - x_4x_5$

and

$$\bar{w} = \sum_{i=1}^{8} x_iw_i$$

From (2.1) we can write the x's as functions of u's as follows:

$$\begin{aligned}
x_1 &= (1 + u_1 + u_2 + u_3 + u_4 + u_5 + u_6 + u_7)/8\\
x_2 &= (1 + u_1 + u_2 - u_3 - u_4 + u_5 - u_6 - u_7)/8\\
x_3 &= (1 + u_1 - u_2 + u_3 - u_4 - u_5 + u_6 - u_7)/8\\
x_4 &= (1 + u_1 - u_2 - u_3 + u_4 - u_5 - u_6 + u_7)/8\\
x_5 &= (1 - u_1 + u_2 + u_3 - u_4 - u_5 - u_6 + u_7)/8\\
x_6 &= (1 - u_1 + u_2 - u_3 + u_4 - u_5 + u_6 - u_7)/8\\
x_7 &= (1 - u_1 - u_2 + u_3 + u_4 + u_5 - u_6 - u_7)/8\\
x_8 &= (1 - u_1 - u_2 - u_3 - u_4 + u_5 + u_6 + u_7)/8 .
\end{aligned} \tag{2.2}$$

When (2.1) and (2.2) are applied to Table 1 the recursion system simplifies substantially. We shall deal primarily with the transformed system (2.3) in what follows.

$$\bar{w}\,u'_1 = u_1(1 - \frac{\delta}{4} - \frac{\beta_1+\beta}{4} - \frac{\eta_2}{4}) + \frac{u_2u_5}{4}(\beta_3-\beta_1+\eta_2-\delta) + \frac{u_3u_6}{4}(\beta_1-\beta_3+\eta_2-\delta) + \frac{u_4u_7}{4}(\beta_1+\beta_3-\eta_2-\delta)$$

$$\bar{w}\,u'_2 = u_2(1 - \frac{\delta}{4} - \frac{\beta_1+\beta_2}{4} - \frac{\eta_3}{4}) + \frac{u_1u_5}{4}(\beta_2-\beta_1+\eta_3-\delta) + \frac{u_3u_7}{4}(\beta_1-\beta_2+\eta_3-\delta)$$

$$+\frac{u_4u_6}{4}(\beta_1+\beta_2-\eta_3-\delta)$$

$$\bar{w}\,u'_3=u_3(1-\frac{\delta}{4}-\frac{\beta_2+\beta_3}{4}-\frac{\eta_1}{4})+\frac{u_1u_6}{4}(\beta_2-\beta_3+\eta_1-\delta)+\frac{u_2u_7}{4}(\beta_3-\beta_2+\eta_1-\delta)$$
$$+\frac{u_4u_5}{4}(\beta_2+\beta_3-\eta_1-\delta)$$

$$\bar{w}\,u'_4=u_4(1-\frac{\delta}{4}-\frac{\eta_1}{4}-\frac{\eta_2}{4}-\frac{\eta_3}{4})+\frac{u_1u_7}{4}(\eta_1-\eta_2+\eta_3-\delta)+\frac{u_2u_6}{4}(\eta_1+\eta_2-\eta_3-\delta)$$

(2.3)
$$+\frac{u_3u_5}{4}(\eta_2-\eta_1+\eta_3-\delta)-\frac{r_1(1-\eta_1)}{2}(u_4+u_3u_5-u_1u_7-u_2u_6)$$
$$-\frac{r_2(1-\eta_2)}{2}(u_4+u_1u_7-u_2u_6-u_3u_5)-\frac{r_3(1-\eta_3)}{2}(u_4+u_2u_6-u_1u_7-u_3u_5)$$

$$\bar{w}\,u'_5=u_5(1-\frac{\delta}{4}-\frac{\beta_1}{4}-\frac{\eta_1}{4})+\frac{u_1u_2}{4}(\eta_1-\beta_1-\delta)+\frac{u_3u_4}{4}(\beta_1-\eta_1-\delta)+\frac{u_6u_7}{4}(\beta_1+\eta_1-\delta)$$
$$-\frac{r_1}{2}\{(1-\eta_1)(u_5-u_1u_2+u_3u_4-u_6u_7)+u_5-u_1u_2-u_3u_4+u_6u_7\}$$

$$\bar{w}\,u'_6=u_6(1-\frac{\delta}{4}-\frac{\beta_3}{4}-\frac{\eta_3}{4})+\frac{u_1u_3}{4}(\eta_3-\beta_3-\delta)+\frac{u_2u_4}{4}(\beta_3-\eta_3-\delta)+\frac{u_5u_7}{4}(\beta_3+\eta_3-\delta)$$
$$-\frac{r_3}{2}\{(1-\eta_3)(u_6-u_1u_3+u_2u_4-u_5u_7)+u_6-u_1u_3-u_2u_4+u_5u_7\}$$

$$\bar{w}\,u'_7=u_7(1-\frac{\delta}{4}-\frac{\beta_2}{4}-\frac{\eta_2}{4})+\frac{u_1u_4}{4}(\beta_2-\eta_2-\delta)+\frac{u_2u_3}{4}(\eta_2-\beta_2-\delta)+\frac{u_5u_6}{4}(\beta_2+\eta_2-\delta)$$
$$-\frac{r_2}{2}\{(1-\eta_2)(u_7+u_1u_4-u_2u_3-u_5u_6)+u_7-u_1u_4-u_2u_3+u_5u_6\}$$

where

$$\bar{w}=1-\frac{\delta}{8}-\frac{\beta_1+\beta_2+\beta_3+\eta_1+\eta_2+\eta_3}{8}+\sum_{i=1}^{7}u_i^2c_i$$

with

(2.4)
$$\begin{aligned}
c_1 &= (-\beta_1+\beta_2-\beta_3+\eta_1-\eta_2+\eta_3-\delta)/8\\
c_2 &= (-\beta_1-\beta_2+\beta_3+\eta_1+\eta_2-\eta_3-\delta)/8\\
c_3 &= (\beta_1-\beta_2-\beta_3-\eta_1+\eta_2+\eta_3-\delta)/8\\
c_4 &= (\beta_1+\beta_2+\beta_3-\eta_1-\eta_2-\eta_3-\delta)/8\\
c_5 &= (-\beta_1+\beta_2+\beta_3-\eta_1+\eta_2+\eta_3-\delta)/8\\
c_6 &= (\beta_1+\beta_2-\beta_3+\eta_1+\eta_2-\eta_3-\delta)/8\\
c_7 &= (\beta_1-\beta_2+\beta_3+\eta_1-\eta_2+\eta_3-\delta)/8
\end{aligned}$$

Equations (2.3) are analogous to the system (2.7) in KARLIN and FELDMAN (1970). We shall use them in the next two sections to determine the equilibria of the original system (Table 1).

It has been common practice in discussions of two-locus models with two alleles at each locus to transform the gametic frequencies into two gene frequencies and a coefficient of linkage disequilibrium, i.e. the frequency of the gamete AB can be written

$$p_{AB}=p_Ap_B-D$$

where p_A and p_B are the frequencies of the alleles A and B and where D, the linkage disequilibrium between the A and B loci, equals $p_{AB}p_{ab}-p_{Ab}p_{aB}$.

Similarly for the three-locus model the gametic frequencies can be completely specified with three gene frequencies and four disequilibrium parameters. If we let p_1, p_2 and p_3 be the gene frequencies of the alleles A, B and C, respectively, and let D_{12} be the coefficient of linkage disequilibrium between locus 1 and 2, etc., we can also define a fourth coefficient of disequilibrium

(2.5)
$$D_{123}=x_1-p_1D_{23}-p_2D_{13}-p_3D_{12}-p_1p_2p_3\,;$$

see BENNETT (1954). In terms of the above transformation we have

$$(2.6)\qquad \begin{aligned} p_i &= \frac{1}{2}(1+u_i), \quad i = 1, 2, 3 \\ D_{12} &= \frac{1}{4}(u_5-u_1u_2) \\ D_{13} &= \frac{1}{4}(u_6-u_1u_3) \\ D_{23} &= \frac{1}{4}(u_7-u_2u_3) \\ D_{123} &= \frac{1}{8}(u_4-u_3u_5-u_2u_6-u_1u_7+2u_1u_2u_3)\,. \end{aligned}$$

3. DETERMINATION OF THE SYMMETRIC EQUILIBRIA

(A) *General parameters:* In accordance with the terminology of the two-locus symmetric viability model we term those equilibria (i.e., solutions of (2.3) with primes deleted from the left-hand side) which have

$$(3.1)\,(a)\qquad x_1 = x_8,\ x_2 = x_7,\ x_3 = x_6,\ x_4 = x_5\,,$$

symmetric equilibria. This is the same as

$$(3.1)\,(b)\qquad u_1 = u_2 = u_3 = u_4 = 0\,.$$

Also, from (2.6) we have

$$(3.1)\,(c)\qquad p_1 = p_2 = p_3 = 0.5\,, \qquad D_{123} = 0$$

and u_5, u_6, u_7 are measures of linkage disequilibrium between loci 1 and 2, 1 and 3, and 2 and 3, respectively.

The equilibrium version of (2.3) can be more concisely written as follows:

$$\begin{aligned}
&(3.2)\,(\mathrm{i}) && w^*\, u_1 = c_1u_1 + u_4u_7(c_4+c_7) + u_2u_5(c_2+c_5) + u_3u_6(c_3+c_6) \\
&(\mathrm{ii}) && w^*\, u_2 = c_2u_2 + u_4u_6(c_4+c_6) + u_1u_5(c_1+c_5) + u_3u_7(c_3+c_7) \\
&(\mathrm{iii}) && w^*\, u_3 = c_3u_3 + u_1u_6(c_1+c_6) + u_2u_7(c_2+c_7) + u_4u_5(c_4+c_5) \\
&(\mathrm{iv}) && w^*\, u_4 = c_4u_4 + u_1u_7(c_1+c_7) + u_2u_6(c_2+c_6) + u_3u_5(c_3+c_5) \\
& && \quad -\frac{r_1(1-\eta_1)}{2}(u_4+u_3u_5-u_1u_7-u_2u_6) - \frac{r_2(1-\eta_2)}{2}(u_4+u_1u_7-u_2u_6-u_3u_5) \\
& && \quad -\frac{r_3(1-\eta_3)}{2}(u_4+u_2u_6-u_1u_7-u_3u_5) \\
&(\mathrm{v}) && w^*\, u_5 = c_5u_5 + u_1u_2(c_1+c_2) + u_3u_4(c_3+c_4) + u_6u_7(c_6+c_7) \\
& && \quad -\frac{r_1}{2}\{(1-\eta_1)(u\ -u_1u_2+u_3u_4-u_6u_7) + u_5 - u_1u_2 - u_3u_4 + u_6u_7\} \\
&(\mathrm{vi}) && w^*\, u_6 = c_6u_6 + u_1u_3(c_1+c_3) + u_2u_4(c_2+c_4) + u_5u_7(c_5+c_7) \\
& && \quad -\frac{r_3}{2}\{(1-\eta_3)(u_6-u_1u_3+u_2u_4-u_5u_7) + u_6 - u_1u_3 - u_2u_4 + u_5u_7\} \\
&(\mathrm{vii}) && w^*\, u_7 = c_7u_7 + u_1u_4(c_1+c_4) + u_2u_3(c_2+c_3) + u_5u_6(c_5+c_6) \\
& && \quad -\frac{r_2}{2}\{(1-\eta_2)(u_7+u_1u_4-u_2u_3-u_5u_6) + u_7 - u_1u_4 - u_2u_3 + u_5u_6\}
\end{aligned}$$

where $w^* = \Sigma^7{}_{i=1}\, u^2{}_i\, c_i$ and the c_i are given by (2.4).

Substituting (3.1) (b) into (3.2) the symmetric equilibria are seen to be the solutions of the three simultaneous cubic equations

$$(3.3)\,(\mathrm{i})\qquad (\sum_{i=5}^{7} u^2{}_ic_i)u_5 = c_5u_5 + u_6u_7(c_6+c_7) - r_1\{(1-\frac{\eta_1}{2})u_5 + \frac{\eta_1}{2}u_6u_7\}$$

(ii) $\quad (\sum_{i=5}^{7} u^2{}_i c_i)u_6 = c_6u_6 + u_5u_7(c_5+c_7) - r_3\{(1-\frac{\eta_3}{2})u_6 + \frac{\eta_3}{2}u_5u_7\}$

(iii) $\quad (\sum_{i=5}^{7} u^2{}_i c_i)u_7 = c_6u_7 + u_5u_6(c_5+c_6) - r_2\{(1-\frac{\eta_2}{2})u_7 + \frac{\eta_2}{2}u_5u_6\}$

There are three classes of solutions to (4.3) depending on how many of u_5, u_6 and u_7 are zero. The first solution is obviously that given by $\hat{u}_5 = \hat{u}_6 = \hat{u}_7 = 0$, namely

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

(We use hats to denote equilibrium values). This could be termed the "central solution," not only because of its obvious evenness property but also as it is the only interior (i.e., all chromosomes present) solution when $r_1 = r_2 = r_3 = 0$.

The second class of three symmetric solutions is given by

(3.5) (a) $\quad u_5 \neq 0, \quad u_6 = u_7 = 0$

(b) $\quad u_6 \neq 0, \quad u_5 = u_7 = 0$

(c) $\quad u_7 \neq 0, \quad u_5 = u_6 = 0.$

If $u_5 \neq 0$ and $u_6 = u_7 = 0$ then from (3.3) (i)

(3.6) (a) $$\hat{u}_5 = \pm\sqrt{1 - \frac{r_1(1-\frac{1}{2}\eta_1)}{c_5}}, \quad \hat{u}_6 = \hat{u}_7 = 0$$

so that

(3.6) (b) $$\begin{aligned} \hat{x}_1 = \hat{x}_8 = \hat{x}_2 = \hat{x}_7 &= \tfrac{1}{8}(1 \pm \hat{u}_5) \\ \hat{x}_3 = \hat{x}_6 = \hat{x}_4 = \hat{x}_5 &= \tfrac{1}{8}(1 \mp \hat{u}_5) \end{aligned} \quad .$$

If $u_6 \neq 0$ and $\hat{u}_5 = \hat{u}_7 = 0$ then from (3.3) (ii)

(3.7) (a) $$\hat{u}_6 = \pm\sqrt{1 - \frac{r_3(1-\frac{1}{2}\eta_3)}{c_6}}, \quad \hat{u}_5 = \hat{u}_7 = 0$$

so that

(3.7) (b) $$\begin{aligned} \hat{x}_1 = \hat{x}_8 = \hat{x}_3 = \hat{x}_6 &= \tfrac{1}{8}(1 \pm \hat{u}_6) \\ \hat{x}_2 = \hat{x}_7 = \hat{x}_4 = \hat{x}_5 &= \tfrac{1}{8}(1 \mp \hat{u}_6) \end{aligned} \quad .$$

If $u_7 \neq 0$ and $\hat{u}_5 = \hat{u}_6 = 0$ then from (3.3) (iii)

(3.8) (a) $$\hat{u}_7 = \pm\sqrt{1 - \frac{r_2(1-\frac{1}{2}\eta_2)}{c_7}}, \quad \hat{u}_5 = \hat{u}_6 = 0$$

so that

(3.8) (b) $$\begin{aligned} \hat{x}_1 = \hat{x}_8 = \hat{x}_4 = \hat{x}_5 &= \tfrac{1}{8}(1 \pm \hat{u}_7) \\ \hat{x}_2 = \hat{x}_7 = \hat{x}_3 = \hat{x}_6 &= \tfrac{1}{8}(1 \mp \hat{u}_7) \end{aligned} \quad .$$

It is obvious from (3.3) that two of $\hat{u}_5$, $\hat{u}_6$ and $\hat{u}_7$ cannot be nonzero with the third zero. Therefore, the final class of symmetric equilibria is of the form $\hat{u}_5 \neq 0$, $\hat{u}_6 \neq 0$, $\hat{u}_7 \neq 0$. From (3.3), writing $\omega^* = \sum_{i=5}^{7} u^2{}_i c_i$

We have

(3.9) (a) $$w^* = c_5 + \frac{u_6u_7}{u_5}(c_6+c_7) - r_1\{(1-\frac{\eta_1}{2}) + \frac{\eta_1}{2}(\frac{u_6u_7}{u_5})\}$$

(b) $$= c_6 + \frac{u_5u_7}{u_6}(c_5+c_7) - r_3\{(1-\frac{\eta_3}{2}) + \frac{\eta_3}{2}(\frac{u_5u_7}{u_6})\}$$

(c) $$= c_7 + \frac{u_5u_6}{u_7}(c_5+c_6) - r_2\{(1-\frac{\eta_2}{2}) + \frac{\eta_2}{2}(\frac{u_5u_6}{u_7})\}$$

Now define

(3.10) $$\xi_1 = \frac{u_6u_7}{u_5}, \quad \xi_2 = \frac{u_5u_7}{u_6}, \quad \xi_3 = \frac{u_5u_6}{u_7}.$$

Then from (3.9)(a) and (b) we have

$$\xi_1 = \frac{c_6 - c_5 + r_1(1-\eta_1/2) - r_3(1-\eta_3/2) + \xi_2(c_5+c_7-r_3\eta_3/2)}{c_6+c_7 - r_1\eta_1/2}. \tag{3.11}$$

while from (3.9)(b) and (c)

$$\xi_3 = \frac{c_6 - c_7 + r_2(1-\eta_2/2) - r_3(1-\eta/2) + \xi_2(c_5+c_7-r_3\eta_3/2)}{c_5+c_6 - r_2\eta_2/2}. \tag{3.12}$$

Now treating (3.9)(b) alone and using (3.10) we have

$$c_5\xi_2\xi_3 + c_6\xi_1\xi_3 + c_7\xi_1\xi_2 = c_6 + \xi_2(c_5+c_7-r_3\eta_3/2) - r_3(1-\eta_3/2). \tag{3.13}$$

Substituting from (3.11) and (3.12) for ξ_1 and ξ_3 (3.13) reduces to a quadratic equation in ξ_2 alone. This can be written as

$$K_2\xi^2_2 + K_1\xi_2 + K_0 = 0 \tag{3.14}$$

where

$$\begin{aligned} K_2 &= B_6(c_5B_5 + c_6B_6 + c_7B_7) \\ K_1 &= c_7B_7(A_6-A_5) + c_5B_5(A_6-A_7) + c_6B_6[2A_6-A_5-A_7] - B_5B_6B_7 \\ K_0 &= c_6(A_6-A_5)(A_6-A_7) - A_6B_5B_7 \end{aligned}$$

with

$$\begin{aligned} A_5 &= c_5 - r_1(1-\frac{\eta_1}{2}) \\ A_6 &= c_6 - r_3(1-\frac{\eta_3}{2}) \\ A_7 &= c_7 - r_2(1-\frac{\eta_2}{2}) \\ B_5 &= c_6 + c_7 - \frac{r_1\eta_1}{2} \\ B_6 &= c_5 + c_7 - \frac{r_3\eta_3}{2} \\ B_7 &= c_5 + c_6 - \frac{r_2\eta_2}{2} \end{aligned}$$

Now (3.14) produces two equilibrium solutions for ξ_2, namely $\xi_2^{(1)}$ and $\xi_2^{(2)}$. We therefore have, from (3.11) and (3.12) the two solutions (in terms of ξ's) $(\xi_1^{(1)}, \xi_2^{(1)}, \xi_3^{(1)})$ and $(\xi_1^{(2)}, \xi_2^{(2)}, \xi_3^{(2)})$. Now, for these we have, possibly

$$\hat{u}_5^{(1)} = \pm\sqrt{\xi_2^{(1)}\xi_3^{(1)}}, \quad \hat{u}_6^{(1)} = \pm\sqrt{\xi_1^{(1)}\xi_3^{(1)}}, \quad \hat{u}_7^{(1)} = \pm\sqrt{\xi_1^{(1)}\xi_2^{(1)}} \tag{3.15}$$

and

$$\hat{u}_5^{(2)} = \pm\sqrt{\xi_2^{(2)}\xi_3^{(2)}}, \quad \hat{u}_6^{(2)} = \pm\sqrt{\xi_1^{(2)}\xi_3^{(2)}}, \quad \hat{u}_7^{(2)} = \pm\sqrt{\xi_1^{(2)}\xi_2^{(2)}}. \tag{3.16}$$

There are real solutions for $\hat{u}_5$, $\hat{u}_6$ and $\hat{u}_7$ if ξ_1, ξ_2 and ξ_3 are all of the same sign. If, for example $\xi_2^{(1)} > 0$, the possible sign configurations are

$$\begin{aligned} &\hat{u}_5 > 0,\ \hat{u}_6 > 0,\ \hat{u}_7 > 0 \\ &\hat{u}_5 > 0,\ \hat{u}_6 < 0,\ \hat{u}_7 < 0 \\ &\hat{u}_5 < 0,\ \hat{u}_6 < 0,\ \hat{u}_7 > 0 \\ &\hat{u}_5 < 0,\ \hat{u}_6 > 0,\ \hat{u}_7 < 0 \end{aligned}$$

with the other four possibilities invalid. If $\hat{\xi}_2^{(1)} < 0$ similar considerations dictate that only four valid equilibria exist. Identical arguments for $\hat{\xi}_2^{(2)}$ produce a maximum of four further valid equilibria. In total, therefore, a maximum of eight symmetric equilibria with $\hat{u}_5 \neq 0$, $\hat{u}_6 \neq 0$, $\hat{u}_7 \neq 0$ are possible. The solutions are specified by (3.10), (3.14), (3.11), (3.12) with the appropriate sign considerations.

(B) *A Simpler Parameter Set.* For stability analysis the equilibria treated last in §3A are rather complicated unless some additional assumptions are made about the parameters. For the analysis to be carried out in §5 and §6 this is seen to be most important for the $u_5 \neq 0$, $u_6 \neq 0$, $u_7 \neq 0$ equilibria. Suppose therefore that $r_1 = r_2 = r$, so that assuming no interference, $r_3 = 2r(1-r)$ which we now write as R, and that for the selection matrix, $\beta_1 = \beta_2 = \beta_3 = \beta$; $\eta_1 = \eta_2 = \eta_3 = \eta$. The system now involves the four parameters β, δ, η and r, one more than the simple Lewontin-Kojima two locus model. Equilibria (3.6), (3.7) and (3.8) do not simplify any further except that $c_5 = c_6 = c_7$. In fact we have now

$$(3.17) \qquad c_5 = c_6 = c_7 = \frac{\beta+\eta-\delta}{8}, \; c_4 = \frac{3\beta-3\eta-\delta}{8}, \; c_1 = c_2 = c_3 = \frac{\eta-\beta-\delta}{8}.$$

Clearly for (3.6), (3.7), (3.8) to be valid $\beta + \eta - \delta$ must be positive. This will be assumed unless specifically mentioned.

Let us reexamine the case $\hat{u}_5 \neq 0$, $\hat{u}_6 \neq 0$, $\hat{u}_7 \neq 0$ with the simpler parameters. From (3.3)(i) and (3.3)(iii) it is easy to verify that we must have

$$(3.18) \qquad \text{(a)} \quad \hat{u}_5 = \hat{u}_7 \qquad \text{or} \quad \text{(b)} \quad \hat{u}_5 = -\hat{u}_7 .$$

Consider first $\hat{u}_5 = \hat{u}_7$ and (3.3)(i). We have, dividing by u_5,

$$(3.19) \qquad \frac{\beta+\eta-\delta}{8}(2u_5^2+u_6^2-1) = -r(1-\eta/2) + u_6\left(\frac{\beta+\eta-\delta}{4} - r\eta/2\right).$$

Replacing the term in parentheses on the left side of (3.3)(ii) by the right side of (3.19), (3.3)(ii) is seen to reduce to

$$(3.20)\,\text{(a)} \qquad u_5^2 = \frac{-(r-R)(1-\eta/2)u_6 + u_6^2\left(\frac{\beta+\eta-\delta}{4} - r\eta/2\right)}{\left(\frac{\beta+\eta-\delta}{4} - R\eta/2\right)}$$

Substituting (3.20)(a) back into (3.19) produces the quadratic equation in u_6.

$$\begin{aligned}
&u_6^2\left\{\frac{\beta+\eta-\delta}{4}\left(\frac{\beta+\eta-\delta}{4} - r\eta/2\right) + \frac{\beta+\eta-\delta}{8}\left(\frac{\beta+\eta-\delta}{4} - R\eta/2\right)\right\}\\
(3.21)\,\text{(a)} \quad &-u_6\left\{\frac{\beta+\eta-\delta}{4}(r-R)(1-\eta/2) + \left(\frac{\beta+\eta-\delta}{4} - r\eta/2\right)\left(\frac{\beta+\eta-\delta}{4} - R\eta/2\right)\right\}\\
&-\left(\frac{\beta+\eta-\delta}{8} - r(1-\eta/2)\right)\left(\frac{\beta+\eta-\delta}{4} - R\eta/2\right) = 0.
\end{aligned}$$

For each of the two possible roots of (3.21)(a) we have two possible $\hat{u}_5$ values given by (3.20)(a). When $\hat{u}_5 = \hat{u}_7$ there are therefore four possible equilibria of the form $\hat{u}_5 = \hat{u}_7 \neq 0$, $\hat{u}_6 \neq 0$.

For solutions of the form $u_5 = -u_7$ the same procedure produces

$$(3.20)\,\text{(b)} \qquad u_5^2 = \frac{(r-R)(1-\eta/2)u_6 + u_6^2\left(\frac{\beta+\eta-\delta}{4} - r\eta/2\right)}{\frac{\beta+\eta-\delta}{4} - R\eta/2}$$

and (3.21)(a) becomes

$$\begin{aligned}
&u_6^2\left[\frac{\beta+\eta-\delta}{4}\left(\frac{\beta+\eta-\delta}{4} - r\eta/2\right) + \frac{\beta+\eta-\delta}{8}\left(\frac{\beta+\eta-\delta}{4} - R\eta/2\right)\right]\\
(3.21)\,\text{(b)} \quad &+u_6\left\{\frac{\beta+\eta-\delta}{4}(r-R)(1-\eta/2) + \left(\frac{\beta+\eta-\delta}{4} - r\eta/2\right)\left(\frac{\beta+\eta-\delta}{4} - R\eta/2\right)\right\}\\
&-\left(\frac{\beta+\eta-\delta}{8} - r(1-\eta/2)\right)\left(\frac{\beta+\eta-\delta}{4} - R\eta/2\right) = 0 .
\end{aligned}$$

So there are four possible solutions of the form $\hat{u}_5 = -\hat{u}_7 \neq 0$, $\hat{u}_6 \neq 0$. Thus the total possible number of equilibria in the third class is eight.

4. EXISTENCE CONDITIONS FOR THE SYMMETRIC EQUILIBRIA

We have divided the symmetric equilibria into three classes.
Class 1. The central solution given by (3.4), that is, $\hat{u}_5 = \hat{u}_6 = \hat{u}_7 = 0$ or $x_i = 1/8$, $i = 1, \ldots, 8$.
Class 2. The solutions (3.6), (3.7) and (3.8) obtained by equating two of u_5, u_6, u_7 to zero.

2(a) $\hat{x}_1 = \hat{x}_2 = \hat{x}_7 = \hat{x}_8 = 1/8(1 \pm \hat{u}_5)$, $\hat{x}_3 = \hat{x}_4 = \hat{x}_5 = \hat{x}_6 = 1/8(1 \mp \hat{u}_5)$

2(b) $\hat{x}_1 = \hat{x}_3 = \hat{x}_6 = \hat{x}_8 = 1/8(1 \pm \hat{u}_6)$, $\hat{x}_2 = \hat{x}_4 = \hat{x}_5 = \hat{x}_7 = 1/8(1 \mp \hat{u}_6)$

2(c) $\hat{x}_1 = \hat{x}_4 = \hat{x}_5 = \hat{x}_8 = 1/8(1 \pm \hat{u}_7)$, $\hat{x}_2 = \hat{x}_3 = \hat{x}_6 = \hat{x}_7 = 1/8(1 \mp \hat{u}_7)$

Class 3. The solutions in which $\hat{u}_5 \neq 0$, $\hat{u}_6 \neq 0$, $\hat{u}_7 \neq 0$.
(A) *Equilibrium Class 1.* The solution $x_i = 1/8$, $i = 1, \ldots, 8$ exists for all recombination and selection parameters.
(B) *Equilibrium Class 2.* Note that if the gametic frequencies are to be in the correct range it is necessary that $\hat{u}_5$, $\hat{u}_6$ and $\hat{u}_7$ are each less than 1 in absolute value. Hence the existence conditions for equilibria 2a, 2b and 2c are

(4.1)(a) $c_5 > 0$ and $c_5 > r_1(1 - 1/2\, \eta_1)$

(4.1)(b) $c_6 > 0$ and $c_6 > r_3(1 - 1/2\, \eta_3)$

(4.1)(c) $c_7 > 0$ and $c_7 > r_2(1 - 1/2\, \eta_2)$.

(C) *Equilibria Class 3.* (Existence of the $\hat{u}_5 \neq 0$, $\hat{u}_6 \neq 0$, $\hat{u}_7 \neq 0$ equilibria)

For simplicity consider only the parameter set described in 3(B). As shown in that section, there may be eight equilibria of this form, four with $\hat{u}_5 = \hat{u}_7$ and four with $\hat{u}_5 = -\hat{u}_7$. The former are given by (3.20)(a) and (3.21)(a) and the latter by (3.20)(b) and (3.21)(b). The analysis is rather tedious but we have included some of it, for the case $\hat{u}_5 = \hat{u}_7$, as an appendix. The main points to make are that over the range $0 < r < \dfrac{\beta+\eta-\delta}{8(1-\eta/2)}$, four valid equilibria always exist and an additional four exist for r near 0. For $r > \dfrac{\beta+\eta-\delta}{8(1-\eta/2)}$ either eight or no valid solutions exist. For larger r no valid solutions exist until near $r = 1/2$ where eight valid solutions exist, depending on the selection parameters.

Thus the class 3 equilibria may exist simultaneously with the "central solution" (class 1) and with the class 2 equilibria.

5. STABILITY OF THE SYMMETRIC EQUILIBRIA *(Classes 1 and 2)*

We shall now consider the local stability of the symmetric solutions determined in 3(A). Suppose that each u_i differs from its equilibrium value $\hat{u}_i$ by a small amount δ_i, and by an amount δ_i' in the next generation. Ignoring small order terms gives

(5.1) $$\delta' = M\delta/w$$

where M and w are given in Table 2. The equilibrium is locally stable if all eigenvalues λ_i, $i = 1, \ldots, 7$ of M/w are less than unity in absolute value.
Solution (3.4). $\hat{x}_1 = \hat{x}_2 = \hat{x}_3 = \hat{x}_4 = \hat{x}_5 = \hat{x}_6 = \hat{x}_7 = \hat{x}_8 = 1/8$.
Substituting $u_i = 0$, $i = 1, \ldots, 7$ in (4.1) produces a diagonal matrix for M. The requirement that the seven eigenvalues of M/w be less than 1 in absolute value gives the following stability conditions for the "central solution."

(5.2)
(a) $c_1 < 0$
(b) $c_2 < 0$
(c) $c_3 < 0$
(d) $c_4 < 1/2 \sum_{i=1}^{3} r_i(1-\eta_i)$
(e) $c_5 < r_1(1 - 1/2\, \eta_1)$
(f) $c_6 < r_3(1 - 1/2\, \eta_3)$
(g) $c_7 < r_2(1 - 1/2\, \eta_2)$.

TABLE 2

Local stability matrix M, where $\delta' = \frac{1}{w} M\delta$ *(see text)*

$$w = 1 - \frac{\Sigma\eta_i + \Sigma\beta_i + \delta}{8} + \Sigma c_i u_i^2$$
$$= K + \sum_{i=1}^{7} c_i u_i^2$$

$K + c_1(1-2u_1^2)$	$c_2(u_5-2u_1u_2) + c_5u_5$	$c_3(u_6-2u_1u_3) + c_6u_6$	$c_4(u_7-2u_1u_4) + c_7u_7$	$c_5(u_2-2u_1u_5) + c_2u_2$	$c_6(u_3-2u_1u_6) + c_3u_3$	$c_7(u_4-2u_1u_7) + c_4u_4$
$c_1(u_5-2u_1u_2) + c_5u_5$	$K + c_2(1-2u_2^2)$	$c_3(u_7-2u_2u_3) + c_7u_7$	$c_4(u_6-2u_2u_4) + c_6u_6$	$c_5(u_1-2u_2u_5) + c_1u_1$	$c_6(u_4-2u_2u_6) + c_4u_4$	$c_7(u_3-2u_2u_7) + c_3u_3$
$c_1(u_6-2u_1u_3) + c_6u_6$	$c_2(u_7-2u_2u_3) + c_7u_7$	$K + c_3(1-2u_3^2)$	$c_4(u_5-2u_3u_4) + c_5u_5$	$c_5(u_4-2u_3u_5) + c_4u_4$	$c_6(u_1-2u_3u_6) + c_1u_1$	$c_7(u_2-2u_3u_7) + c_2u_2$
$c_1(u_7-2u_1u_4) + c_7u_7$ $+ (R_1-R_2+R_3)u_7$	$c_2(u_6-2u_2u_4) + c_6u_6$ $+ (R_1+R_2-R_3)u_6$	$c_3(u_5-2u_3u_4) + c_5u_5$ $+ (-R_1+R_2+R_3)u_5$	$K + c_4(1-2u_4^2)$ $- (R_1+R_2+R_3)$	$c_5(u_3-2u_4u_5) + c_3u_3$ $+ (-R_1+R_2+R_3)u_3$	$c_6(u_2-2u_4u_6) + c_2u_2$ $+ (R_1+R_2-R_3)u_2$	$c_7(u_1-2u_4u_7) + c_1u_1$ $+ (R_1-R_2+R_3)u_1$
$c_1(u_2-2u_1u_5) + c_2u_2$ $+ r_1(1-\frac{1}{2}\eta_1)u_2$	$c_2(u_1-2u_2u_5) + c_1u_1$ $+ r_1(1-\frac{1}{2}\eta_1)u_1$	$c_3(u_4-2u_3u_5) + c_4u_4$ $+ r_1\frac{1}{2}\eta_1u_4$	$c_4(u_3-2u_4u_5) + c_3u_3$ $+ r_1\frac{1}{2}\eta_1u_3$	$K + c_5(1-2u_5^2)$ $- r_1(1-\frac{1}{2}\eta_1)$	$c_6(u_7-2u_5u_6) + c_7u_7$ $- r_1\frac{1}{2}\eta_1u_7$	$c_7(u_6-2u_5u_7) + c_6u_6$ $- r_1\frac{1}{2}\eta_1u_6$
$c_1(u_3-2u_1u_6) + c_3u_3$ $+ r_3(1-\frac{1}{2}\eta_3)u_3$	$c_2(u_4-2u_2u_6) + c_4u_4$ $+ r_3\frac{1}{2}\eta_3u_4$	$c_3(u_1-2u_3u_6) + c_1u_1$ $+ r_3(1-\frac{1}{2}\eta_3)u_1$	$c_4(u_2-2u_4u_6) + c_2u_2$ $+ r_3\frac{1}{2}\eta_3u_2$	$c_5(u_7-2u_5u_6) + c_7u_7$ $- r_3\frac{1}{2}\eta_3u_7$	$K + c_6(1-2u_6^2)$ $- r_3(1-\frac{1}{2}\eta_3)$	$c_7(u_5-2u_6u_7) + c_5u_5$ $- r_3\frac{1}{2}\eta_3 u_5$
$c_1(u_4-2u_1u_7) + c_4u_4$ $+ r_2\frac{1}{2}\eta_2u_4$	$c_2(u_3-2u_2u_7) + c_3u_3$ $+ r_2(1-\frac{1}{2}\eta_2)u_3$	$c_3(u_2-2u_3u_7) + c_2u_2$ $+ r_2(1-\frac{1}{2}\eta_2)u_2$	$c_4(u_1-2u_4u_7) + c_1u_1$ $+ r_2\frac{1}{2}\eta_2u_1$	$c_5(u_6\,2u_5u_7) + c_6u_6$ $- r_2\frac{1}{2}\eta_2u_6$	$c_6(u_5-2u_6u_7) + c_5u_5$ $- r_2\frac{1}{2}\eta_2u_5$	$K + c_7(1-2u_7^2)$ $- r_2(1-\frac{1}{2}\eta_2)$

$K = 1 - \delta - \Sigma c_i$

$R_i = \frac{1}{2} r_i(1-\eta_i)\ , \quad i = 1, 2, 3\ .$

Obviously conditions (5.2)(e), (f) and (g) preclude the existence of the class 2 equilibria (3.6), (3.7) and (3.8), a situation which should be compared to that for loose linkage in the two-locus model. Condition (5.2)(d) precludes the existence of an unsymmetric equilibrium which we shall discuss later. Conditions (5.2)(a), (b), (c) have no obvious analog in the two-locus model but, if fitnesses are multiplicative, (5.2)(a), (b), (c) are automatically true, as is (5.2)(d).

If the three loci have the same viabilities, i.e. $\eta_1 = \eta_2 = \eta_3 = \eta$, and $\beta_1 = \beta_2 = \beta_3 = \beta$, then $c_1 = c_2 = c_3 = \frac{\eta-\beta-\delta}{8}$, $c_4 = \frac{3\beta-3\eta-\delta}{8}$, $c_5 = c_6 = c_7 = \frac{\beta+\eta-\delta}{8}$, and (5.2) becomes

(5.2)′

$$\text{(a)}\quad \beta - \eta + \delta > 0$$

$$\text{(b)}\quad r_1 + r_2 + r_3 > \frac{3\beta-3\eta-\delta}{4(1-\eta)}$$

$$\text{(c)}\quad r_1, r_2, r_3 > \frac{\beta+\eta-\delta}{8(1-\tfrac{1}{2}\eta)}.$$

The stability of equilibrium (3.6) is discussed in Appendix B using this simplified selection scheme and assuming no interference so that $r_3 = r_1 + r_2 - 2r_1r_2$. Appendix C contains a similar stability analysis for the equilibrium with $\hat{u}_5 \neq 0$, $\hat{u}_6 \neq 0$ and $\hat{u}_7 \neq 0$ specified by (3.21)(a).

6. TWO SIMPLE UNSYMMETRIC EQUILIBRIA

In the two-locus symmetric viability model, KARLIN and FELDMAN (1970b) proved the existence of four and the stability of, at most, two unsymmetric equilibria for moderate to loose linkage. The region of stability of these apparently does not overlap the stability region of any symmetric equilibria.

Now return to (3.2) and assume $u_1 = u_2 = u_3 = u_5 = u_6 = u_7 = 0$, but $u_4 \neq 0$. Then from (3.1)(b) any solutions will be unsymmetric. Using the simpler parameter set (3.17) we solve the quadratic to find

$$\hat{u}_4 = \pm\sqrt{1 - \frac{\sum_{i=1}^{3} r_i(1-\eta_i)}{2c_4}} \tag{6.1}$$

The existence conditions for (6.1) are clearly

$$c_4 > 0 \tag{6.2}$$

and

$$0 < \tfrac{1}{2}\sum_{i=1}^{3} r_i(1-\eta_i) < c_4\,. \tag{6.3}$$

It is important to note from (4.2)(b) that (6.3) precludes the stability of the central equilibrium (3.4). Thus these unsymmetric equilibria cannot exist when the central equilibrium is stable. Note also that when the viabilities are of the simple multiplicative form condition (6.2) is not satisfied and the unsymmetric equilibria cannot exist. These unsymmetric equilibria are of the form

$$\hat{x}_1 = \hat{x}_4 = \hat{x}_6 = \hat{x}_7 = \tfrac{1}{8}\,(1 \pm \hat{u}_4)$$
$$\hat{x}_2 = \hat{x}_3 = \hat{x}_5 = \hat{x}_8 = \tfrac{1}{8}\,(1 \mp \hat{u}_4)$$

and from (2.6) we see that each of the gene frequencies is 0.5, that all pairwise disequilibrium ccefficients are zero but the third order interaction D_{123} is not zero and is equal to $\tfrac{1}{8}\,\hat{u}_4$. The type of linkage disequilibrium exhibited by this solution could not be detected by measuring correlations between pairs of loci.

When r_1, r_2 and r_3 tend to zero these unsymmetric equilibria are of the form (¼ *ABC*, ¼ *aBc*, ¼ *Abc*, ¼ *abC*) and (¼ *ABc*, ¼ *aBC*, ¼ *AbC*, ¼ *abc*). It is not difficult to prove that when the r's are zero the latter two equilibria are *stable* if $\eta > \delta$ and $3\beta - 3\eta - \delta > 0$. For tight linkage, these unsymmetric equilibria (6.1) may be stable. The precise conditions for stability are given by the roots of three quadratic equations. A more detailed analysis is presented in a forthcoming paper on the unsymmetric equilibria. It is important that these two unsymmetric equilibria may be stable simultaneously with four of the symmetric equilibria. Example 6 of §7 is a numerical case where this happens.

7. NUMERICAL EXAMPLES

In the following eight examples we shall discuss three models to illustrate the existence and stability conditions for the symmetric equilibria. For simplicity we shall consider only models in which all loci have equal selective values, hence $\eta_1 = \eta_2 = \eta_3 = \eta$, and $\beta_1 = \beta_2 = \beta_3 = \beta$. The selective values η, β, δ are shown in (7.1).

(7.1)

	η	β	δ	$c_1 = c_2 = c_3$	c_4	$c_5 = c_6 = c_7$
Model 1	0.2	0.36	0.488	−0.081	−0.001	+0.009
Model 2	0.2	0.37	0.45	−0.0775	+0.0075	+0.015
Model 3	−0.2	−0.44	−0.728	+0.121	+0.001	+0.011

Model 1 assumes overdominance at each locus and multiplicative interaction. Note that $(1-\beta) = (1-\eta)^2$ and $(1-\delta) = (1-\eta)^3$. The first five examples illustrate the symmetric equilibria for these selective values, and in the first four of these it is further assumed that $r_1 = r_2 = r$ and $r_3 = r_1 + r_2 - 2r_1r_2 = R$ (i.e., no interference). In this case $r^* = 0.0050253$, $\dfrac{\beta+\eta-\delta}{8(1-\eta/2)} = 0.01$ and $r^{**} = 0.1$ (see Appendix C) and the equilibria divide r_1 into five regions shown in 7.2.

(7.2)

	Number of equilibria: Class 1	2	3	Total	Number stable
$0.0 < r_1 < .0047327$	1	6	8	15	4
$.0047327 < r_1 < .0050253$	1	6	4	11	4
$.0050253 < r_1 < .0100000$	1	4	4	9	4
$.0100000 < r_1 < .0104272$	1	0	8	9	5
$.0104272 < r_1 < 0.5$	1	0	0	1	1

Example 5, in which $r_1 \neq r_2$, shows a situation in which six symmetric equilibria are simultaneously stable.

Examples 6 and 7 illustrate equilibria for model 2, in which all loci are overdominant but do not interact multiplicatively. The symmetric equilibria for model 2 are similar to those for model 1, but the existence and stability of the unsymmetric equilibria are very different in the two models. Model 3 is a symmetric underdominance model, with multiplicative interaction. Again all equilibria exist for small recombination values but none are stable (Example 8).

The Class 1 equilibria are given by (3.4), Class 2 equilibria by (3.6), (3.7) and (3.8), and the Class 3 equilibria are those with $\hat{u}_5 \neq 0$, $\hat{u}_6 \neq 0$ and $\hat{u}_7 \neq 0$ and are given by (3.18), (3.20) and (3.21) when $r_1 = r_2$ and by (3.10), (3.14), (3.11) and (3.12) when $r_1 \neq r_2$. The appropriate eigenvalues have been found from the matrix $\dfrac{1}{\bar{w}}M$ (see Table 2) at the equilibrium values.

EXAMPLE 1

Class 1. From (5.2) this equilibrium is unstable as $r < \dfrac{\beta+\eta-\delta}{8(1-\frac{\eta}{2})}$.

Class 2. The three classes of equilibria exist. Class 2b equilibria are always unstable. From (B.7) 2a and 2c equilibria are unstable since $r_1 = r_2$.

Class 3. The range is $0 < r < r^*$, so for r near zero there are eight valid solutions. From (C.2), $|\lambda_5| < 1$ for $\hat{u}_6 > 0$ with $\hat{u}_5 = \hat{u}_7$ and for $\hat{u}_6 < 0$ with $\hat{u}_5 = -\hat{u}_7$. These four solutions also satisfy (C.4) and (C.6), so we would predict stability. The other four solutions do not satisfy (C.2) and are unstable.

Selection coefficients: $\eta = 0.2$, $\beta = 0.36$, $\delta = 0.488$
Recombination: $r_1 = .004$, $r_2 = .004$, $r_3 = .007968$

Equilibrium	$\hat{u}_5$	$\hat{u}_6$	$\hat{u}_7$	Gamete Frequencies $x_1 = x_8$	$x_2 = x_7$	$x_3 = x_6$	$x_4 = x_5$	
1	.0000000	.0000000	.0000000	.1250000	.1250000	.1250000	.1250000	Unstable
2a	.7745967	.0000000	.0000000	.2218246	.2218246	.0281754	.0281754	Unstable
	-.7745967	.0000000	.0000000	.0281754	.0281754	.2218246	.2218246	
2b	.0000000	.4507771	.0000000	.1813471	.0686529	.1813471	.0686529	Unstable
	.0000000	-.4507771	.0000000	.0686529	.1813471	.0686529	.1813471	
2c	.0000000	.0000000	.7745967	.2218246	.0281754	.0281754	.2218246	Unstable
	.0000000	..0000000	-.7745967	.0281754	.2218246	.2218246	.0281754	
3ai	.8689615	.7636253	.8689615	.4376935	.0295468	.0032128	.0295468	Stable
	.8689615	-.7636253	-.8689615	.0295468	.4376935	.0295468	.0032128	
	-.8689615	-.7636253	.8689615	.0295468	.0032128	.0295468	.4376935	
	-.8689615	.7636253	-.8689615	.0032128	.0295468	.4376935	.0295468	
3aii	.1205105	-.2579422	.1205105	.1228849	.1572428	.0626296	.1572428	Unstable
	.1205105	.2579422	-.1205105	.1572428	.1228849	.1572428	.0626296	
	-.1205105	.2579422	.1205105	.1572428	.0626296	.1572428	.1228849	
	-.1205105	-.2579422	-.1205105	.0626296	.1572428	.1228849	.1572428	

Eigenvalues

1	1.0074074	1.0074074	1.0025086	0.9898667	0.8888889	0.8888889	0.8888889
2a,2c	1.0160818	0.9852941	0.9790554	0.9760523	0.9582938	0.8888889	0.8064121
2b	1.0157422	0.9949953	0.9940308	0.9851653	0.9310744	0.8888889	0.8522548
3ai	0.9694377	0.9640507	0.9574309	0.9551389	0.9551389	0.9400155	0.7141235
3aii	1.0124401	1.0046362	0.9943337	0.9873055	0.9228028	0.8797199	0.8623955

EXAMPLE 2

Class 1. Unstable as $r = \dfrac{\beta+\eta-\delta}{8(1-\frac{\eta}{2})}$.

Class 2. Solutions 2a and 2c are unstable since $r_1 = r_2$.

Class 3. The range is $0 < r < r^*$, but with r very close to r^*, so there are four valid solutions. From (C.2), $|\lambda_5| < 1$ for $\hat{u}_6 > 0$ with $\hat{u}_5 = \hat{u}_7$ and for $\hat{u}_6 < 0$ with $\hat{u}_5 = -\hat{u}_7$, and these solutions also satisfy (C.4) and (C.6) so we predict stability.

Selection coefficients: $\eta = 0.2$, $\beta = 0.36$, $\delta = 0.488$
Recombination: $r_1 = .005$, $r_2 = .005$, $r_3 = .00995$

Equilibrium	$\hat{u}_5$	$\hat{u}_6$	$\hat{u}_7$	Gamete Frequencies $x_1 = x_8$	$x_2 = x_7$	$x_3 = x_6$	$x_4 = x_5$	
1	.0000000	.0000000	.0000000	.1250000	.1250000	.1250000	.1250000	Unstable
2a	.7071068	.0000000	.0000000	.2133833	.2133833	.0366117	.0366117	Unstable
	-.7071068	.0000000	.0000000	.0366117	.0366117	.2133833	.2133833	
2b	.0000000	.0707107	.0000000	.1338388	.1161612	.1338388	.1161612	Unstable
	.0000000	-.0707107	.0000000	.1161612	.1338388	.1161612	.1338388	
2c	.0000000	.0000000	.7071068	.2133833	.0366117	.0366117	.2133833	Unstable
	.0000000	.0000000	-.7071068	.0366117	.2133833	.2133833	.0366117	
3ai	.8277410	.6985331	.8277410	.4192519	.0376834	.0053814	.0376834	Stable
	.8277410	-.6985331	-.8277410	.0376834	.4192519	.0376834	.0053814	
	-.8277410	-.6985331	.8277510	.0376834	.0053814	.0376834	.4192519	
	-.8277410	.6985331	-.8277510	.0053814	.0376834	.4192519	.0376834	
3aii	No Solutions Exist							

Eigenvalues

1	1.0061728	1.0061728	1.0000617	0.9876818	0.8888889	0.8888889	0.8888889
2a,2c	1.0138682	0.9877306	0.9800582	0.9761691	0.9528448	0.8888889	0.8140263
2b	1.0078081	1.0044134	0.9998766	0.9875659	0.8958174	0.8888889	0.8818507
3ai	0.9737436	0.9672149	0.9590359	0.9555496	0.9555496	0.9363980	0.7248958

EXAMPLE 3

Class 1. R is greater than $\frac{\beta+\eta-\delta}{8(1-\frac{\eta}{2})}$ although $r < \frac{\beta+\eta-\delta}{8(1-\frac{\eta}{2})}$. Hence the central solution is still unstable.

Class 2. Since $r_1 = r_2$ solutions 2a and 2c are unstable.

Class 3. The range under consideration is $r^* < r < \frac{\beta+\eta-\delta}{8(1-\frac{\eta}{2})}$ so a total of four valid solutions exist. Those four satisfy (C.2), (C.4) and (C.6). Thus we predict stability.

Selection coefficients: $\eta = 0.2$, $\beta = 0.36$, $\delta = 0.488$
Recombination: $r_1 = 0.006$, $r_2 = 0.006$, $r_3 = 0.011928$

Equilibrium	$\hat{u}_5$	$\hat{u}_6$	$\hat{u}_7$	Gamete Frequencies $x_1 = x_8$	$x_2 = x_7$	$x_3 = x_6$	$x_4 = x_5$	
1	.0000000	.0000000	.0000000	.1250000	.1250000	.0250000	.1250000	Unstable
2a	.6324555	.0000000	.0000000	.2040569	.2040569	.0459431	.0459431	Unstable
	-.6324555	.0000000	.0000000	.0459431	.0459431	.2040569	.2040569	
2b	No Solutions Exist							
2c	.0000000	.0000000	.6324555	.2040569	.0459431	.0459431	.2040569	Unstable
	.0000000	.0000000	-.6324555	.0459431	.2040569	.2040569	.0459431	
3ai	.7813211	.6297407	.7813211	.3990479	.0462824	.0083873	.0462824	Stable
	.7813211	-.6297407	-.7813211	.0462824	.3990479	.0462824	.0083873	
	-.7813211	-.6297407	.7813211	.0462824	.0083873	.0462824	.3990479	
	-.7813211	.6297407	-.7813211	.0083873	.0462824	.3990479	.0462824	
3aii	No Solutions Exist							

Eigenvalues

1	1.0049383	1.0049383	0.9976198	0.9854990	0.8888889	0.8888889	0.8888889
2a, 2c	1.0115645	0.9901720	0.9811529	0.9762883	0.9466787	0.8888889	0.8223631
3ai	0.9780822	0.9705269	0.9608497	0.9557872	0.9557872	0.9324650	0.7366237

EXAMPLE 4

Class 1. The five conditions in (4.2) are satisfied so this equilibrium is stable.

Class 2. No equilibria exist as $r > \frac{\beta-\eta-\delta}{8(1-\frac{\eta}{2})}$.

Class 3. The appropriate range is $\frac{\beta+\eta-\delta}{8(1-\frac{\eta}{2})} < r < r^{**}$. The coefficient of the u_6 term in (3.21)

(a) is negative so when $\hat{u}_5 = \hat{u}_7$ there are two positive $\hat{u}_6$ solutions, when $\hat{u}_5 = -\hat{u}_7$ there are two negative $\hat{u}_6$ solutions. Together there will be eight valid solutions. All will satisfy the condition (C.2). From (C.4) $|\lambda_2|$, $|\lambda_3|$ are less than 1 for the largest $\hat{u}_6$ solution when $\hat{u}_5 = \hat{u}_7$ and for the most negative $\hat{u}_6$ solution when $\hat{u}_5 = -\hat{u}_7$. These four solutions also satisfy (C.6). The other four solutions do not satisfy (C.4) and so are unstable.

Selection coefficients: $\eta = 0.2$, $\beta = 0.36$, $\delta = 0.488$
Recombination: $r_1 = .0104$, $r_2 = .0104$, $r_3 = .020584$

Equilibrium	$\hat{u}_5$	$\hat{u}_6$	$\hat{u}_7$	Gamete Frequencies $x_1 = x_8$	$x_2 = x_7$	$x_3 = x_6$	$x_4 = x_5$	
1	.0000000	.0000000	.0000000	.1250000	.1250000	.1250000	.1250000	Stable
2	No Solutions Exist							
3ai	.3306752	.1490700	.3306752	.2263026	.1063663	.0609649	.1063663	Stable
	.3306752	-.1490700	-.3306752	.1063663	.2263026	.1063663	.0609649	
	-.3306752	-.1490700	.3306752	.1063663	.0609649	.1063663	.2263026	
	-.3306752	.1490700	-.3306752	.0609649	.1063663	.2263026	.1063663	
3aii	.2390673	.0857899	.2390673	.1954906	.1142763	.0759569	.1142763	Unstable
	.2390673	-.0857899	-.2390673	.1142763	.1954906	.1142763	.0759569	
	-.2390673	.0857899	-.2390673	.1142763	.0759569	.1142763	.1954906	
	-.2390673	-.8857899	.2390673	.0759569	.1142763	.1954906	.1142763	

Eigenvalues

1	0.9995062	0.9995062	0.9869337	0.9759211	0.8888889	0.8888889	0.8888889
3ai	0.9994567	0.9930844	0.9786195	0.9708758	0.9262588	0.9909323	0.8337191
3aii	1.0003405	0.9960142	0.9821135	0.9732860	0.9173472	0.8960161	0.8504754

EXAMPLE 5

Class 1. Unstable as $r_1 < \dfrac{\beta+\eta-\delta}{8(1-\frac{\eta}{2})}$.

Class 2. Only the class 2a solutions exist. The value of the quadratic $ar^2_2 + br_2 + c$ in (B.7) is $+0.00000056$, implying that λ_6 is just slightly less than 1. In fact, from the numerical work, $\lambda_6 = 0.9999188$. Note that with the above selection values and $r_1 = .0099$ but $r_2 = .0102$, then λ_6 is just slightly larger than 1.

Class 3. Consider the existence and stability behavior for $r_1 = r_2 = 0.01$, $R = 0.0198$. This is the point $r_1 = \dfrac{\beta+\eta-\delta}{8(1-\frac{\eta}{2})}$. The coefficient of the u_6 term in (3.21)(a) is negative so for r_1 slightly less than $\dfrac{\beta+\eta-\delta}{8(1-\frac{\eta}{2})}$ there is one valid $\hat{u}_6$ solution producing two equilibria of the form $\hat{u}_5 = \hat{u}_7$. Similarly (3.21)(b) gives rise to two valid equilibria of the form $\hat{u}_6 < 0$, $\hat{u}_5 = -\hat{u}_7$. These solutions will satisfy (C.2), (C.4) and (C.6). We cannot *a priori* predict whether the remaining four should exist here due to the difference between r_1 and r_2.

Selection coefficients: $\eta = 0.2$, $\beta = 0.36$, $\delta = 0.488$
Recombination: $r_1 = .0099$, $r_2 = .0103$, $r_3 = .019996$

				Gamete Frequencies				
Equilibrium	$\hat{u}_5$	$\hat{u}_6$	$\hat{u}_7$	$x_1 = x_8$	$x_2 = x_7$	$x_3 = x_6$	$x_4 = x_5$	
1	.0000000	.0000000	.0000000	.1250000	.1250000	.1250000	.1250000	Unstable
2a	.1000000	.0000000	.0000000	.1375000	.1375000	.1125000	.1125000	Stable
	-.1000000	.0000000	.0000000	.1125000	.1125000	.1375000	.1375000	
2b, 2c	No Solutions Exist							
3ai	.4445181	.2341716	.4243619	.2628815	.0982481	.0456614	.0932090	Stable
	.4445181	-.2341716	-.4243619	.0982481	.2628815	.0932090	.0456614	
	-.4445181	-.2341716	.4243619	.0932090	.0456614	.0982481	.2628815	
	-.4445181	.2341716	-.4243619	.0456614	.0932090	.2628815	.0982481	
3aii	.1174182	.0084034	.0408655	.1458359	.1335187	.1062650	.1143805	Unstable
	.1174182	-.0084034	-.0408655	.1335187	.1458359	.1143805	.1062650	
	-.1174182	-.0084034	.0408655	.1143805	.1062650	.1335187	.1458359	
	-.1174182	.0084034	-.0408655	.1062650	.1143805	.1458359	.1335187	

Eigenvalues

1	1.0001235	0.9996296	0.9876592	0.9765728	0.8888889	0.8888889	0.8888889
2a	0.9999188	0.9997531	0.9871247	0.9763425	0.8986545	0.8888889	0.8789038
3ai	0.9972622	0.9891364	0.9745238	0.9678262	0.9352954	0.9071496	0.8136178
3aii	1.0001069	0.9995003	0.9868492	0.9762168	0.9007831	0.8893363	0.8762050

EXAMPLE 6a

Selection: coefficients: $\eta = 0.2$, $\beta = 0.37$, $\delta = 0.45$
Recombination: $r_1 = .001$, $r_2 = .001$, $r_3 = .001998$

				Gamete Frequencies				
Equilibrium	$\hat{u}_5$	$\hat{u}_6$	$\hat{u}_7$	$x_1 = x_8$	$x_2 = x_7$	$x_3 = x_6$	$x_4 = x_5$	
1	.0000000	.0000000	.0000000	.1250000	.1250000	.1250000	.1250000	Unstable
2a	.8717798	.0000000	.0000000	.2339725	.2339725	.0160275	.0160275	Unstable
	-.8717798	.0000000	.0000000	.0160275	.0160275	.2339725	.2339725	
2b	.0000000	.7224403	.0000000	.2153050	.0346950	.2153050	.0346950	Unstable
	.0000000	-.7224403	.0000000	.0346950	.2153050	.0346950	.2153050	
2c	.0000000	.0000000	.8717798	.2339725	.0160275	.0160275	.2339725	Unstable
	.0000000	.0000000	.8717798	.0160275	.2339725	.2339725	.0160275	
3ai	.9268309	.8622477	.9268309	.4644887	.0172190	.0010732	.0172190	Stable
	.9268309	-.8622477	-.9268309	.0172190	.4644887	.0172190	.0010732	
	-.9268309	-.8622477	.9268309	.0172190	.0010732	.0172190	.4644887	
	-.9268309	.8622477	-.9268309	.0010732	.0172190	.4644887	.0172190	
3aii	.2243313	-.2911683	.2243313	.1446868	.1613960	.0325212	.1613960	Unstable
	.2243313	.2911683	-.2243313	.1613960	.1446868	.1613960	.0325212	
	-.2243313	.2911683	.2253313	.1613960	.0325212	.1613960	.1446868	
	-.2243313	-.2911683	-.2243313	.0325212	.1613960	.1446868	.1613960	

Eigenvalues

1	1.0156164	1.0156164	1.0107244	1.0015244	0.8938356	0.8938356	0.8938356
2a, 2c	1.0322466	0.9692474	0.9641817	0.9629365	0.9535827	0.9020347	0.8066007
2b	1.0338228	0.9787788	0.9762263	0.9758575	0.9455480	0.8990228	0.8231550
3ai	0.9389198	0.9334417	0.9281059	0.9281059	0.9268570	0.9210715	0.7284330
3aii	1.0235229	1.0165837	0.9895749	0.9827128	0.9406593	0.8732087	0.8656087

EXAMPLE 6b. Simple Unsymmetric Equilibria
Selection: coefficients: $\eta = 0.2$, $\beta = 0.37$, $\delta = 0.45$
Recombination: $r_1 = r_2 = r$

r	$\hat{u}_4^2$	Eigenvalues							
.000	1.00000	0.97966	0.97966	0.97966	0.97966	0.91525	0.91525	0.91525	Stable
.001	0.78677	0.98876	0.98723	0.98876	0.98396	0.90905	0.90936	0.90905	Stable
.002	0.57376	0.99665	0.99384	0.99665	0.98828	0.90406	0.90443	0.90406	Stable
.003	0.36096	1.00378	0.99982	1.00378	0.99261	0.89984	0.90014	0.89984	Unstable
.004	0.14837	1.01038	1.00536	1.01038	0.99696	0.89616	0.89630	0.89616	Unstable
.00468	0.00393	1.01464	1.00892	1.01464	0.99992	0.89390	0.89390	0.89390	Unstable

EXAMPLE 7

Selection: coefficients: $\eta = 0.2$, $\beta = 0.37$, $\delta = 0.45$
Recombination: $r_1 = .004$, $r_2 = .004$, $r_3 = .007968$

Equilibrium	$\hat{u}_5$	$\hat{u}_6$	$\hat{u}_7$	Gamete Frequencies $\hat{x}_1 = \hat{x}_8$	$\hat{x}_2 = \hat{x}_7$	$\hat{x}_3 = \hat{x}_6$	$\hat{x}_4 = \hat{x}_5$	
1	.000000	.000000	.000000	.125000	.125000	.125000	.125000	Unstable
2a	.969536	.000000	.000000	.246192	.246192	.003808	.003808	Unstable
	-.969536	.000000	.000000	.003808	.003808	.246192	.246192	
2b	.000000	.938147	.000000	.242268	.007732	.242268	.007732	Unstable
	.000000	-.938147	.000000	.007732	.242268	.007732	.242268	
2c	.000000	.000000	.969536	.246192	.003808	.003808	.246192	Unstable
	.000000	.000000	-.969536	.003808	.246192	.246192	.003808	
3ai	.982962	.966415	.982962	.491542	.004198	.000061	.004198	Stable
	.982962	-.966415	-.982962	.004198	.491542	.004198	.000061	
	-.982962	-.966415	.982962	.004198	.000061	.004198	.491542	
	-.982962	.966415	-.982962	.000061	.004198	.491542	.004198	
3aii	.308630	-.323500	.308630	.161720	.165438	.007405	.165438	Unstable
	.308630	.323500	-.308630	.165438	.161720	.165438	.007405	
	-.308630	.323500	.308630	.165438	.007405	.165438	.161720	
	-.308630	-.323500	-.308630	.007405	.165438	.161720	.165438	

Eigenvalues

1	1.019315	1.019315	1.018085	1.008083	0.893836	0.893836	0.893836
2a,2b	1.038295	0.962102	0.960935	0.960498	0.958334	0.904944	0.795463
2b	1.038951	0.964473	0.964192	0.963466	0.956852	0.903942	0.799064
3ai	0.926649	0.925237	0.923968	0.923968	0.923563	0.922257	0.714173
3aii	1.026341	1.024690	0.983867	0.975200	0.959958	0.862606	0.860917

EXAMPLE 8

Selection coefficients: $\eta = -0.2$, $\beta = -0.44$, $\delta = -0.728$
Recombination: $r_1 = .004$, $r_2 = .004$, $r_3 = .007968$

Equilibrium	$\hat{u}_5$	$\hat{u}_6$	$\hat{u}_7$	Gamete Frequencies $x_1 = x_8$	$x_2 = x_7$	$x_3 = x_6$	$x_4 = x_5$	
1	.0000000	.0000000	.0000000	.1250000	.1250000	.1250000	.1250000	Unstable
2a	.7745967 -.7745967	.0000000 .0000000	.0000000 .0000000	.2218246 .0281754	.2218246 .0281754	.0281754 .2218246	.0281754 .2218246	Unstable
2b	.0000000 .0000000	.4507771 -.4507771	.0000000 .0000000	.1813471 .0686529	.0686529 .1813471	.1813471 .0686529	.0686529 .1813471	Unstable
2c	.0000000 .0000000	.0000000 .0000000	.7745967 -.7745967	.2218246 .0281754	.0281754 .2218246	.0281754 .2218246	.2218246 .0281754	Unstable
3ai	.8923375 .8923375 -.8923375 -.8923375	.8080347 -.8080347 -.8080347 .8080347	.8923375 -.8923375 .8923375 -.8923375	.4490887 .0239957 .0239957 .0029200	.0239957 .4490887 .0029200 .0239957	.0029200 .0239957 .0239957 .4490887	.0239957 .0029200 .4490887 .0239957	Unstable
3aii	.1169267 .1169267 -.1169267 -.1169267	-.2504200 .2504200 .2504200 -.2504200	.1169267 -.1169267 .1169267 -.1169267	.1229292 .1563025 .1563025 .0644658	.1563025 .1229292 .0644658 .1563025	.0644658 .1563025 .1563025 .1229292	.1563025 .0644658 .1229292 .1563025	Unstable

Eigenvalues

1	1.0049587	1.0049587	1.0016793	1.0909091	1.0909091	1.0909091	0.9935531
2a	0.9901316	0.9851810	1.0115558	0.9832679	1.0909091	1.0090859	1.1619668
2b	0.9957002	1.0108475	0.9966470	1.0444499	1.1337104	0.9900585	1.0909091
2c	0.9851810	1.0115558	0.9901316	1.0090859	1.1619668	0.9832679	1.0909091
3ai	0.9780283	0.9689624	0.9732980	0.9675129	1.2466726	0.9820082	0.9923578
3aii	0.9962298	1.0084226	1.0032172	0.9916894	1.0580683	1.1149144	1.0984355

The range under consideration is $0 < r < r^*$. Obviously Class 1 and 2 equilibria are unstable. Four of the solutions from Class 3 satisfy (C.2), (C.4) and (C.6). Numerical studies indicate that in this case one of the eigenvalues from (C.8) is greater than 1. The other four solutions are also unstable from (C.2).

DISCUSSION

The increased complexity of the three-locus system over two-locus models is evident. For two loci (each with two alleles) there are three internal, symmetric equilibria, and at most two of these may be stable. In the three-locus symmetric viability model discussed in this paper we have shown that there may be fifteen symmetric equilibria, and as many as six of these can be stable for a given set of recombination values. These fifteen equilibria all exist, if linkage is sufficiently tight, for a number of selection models, including symmetric overdominance (Examples 1, 6 and 7), and symmetric underdominance (Example 8).

Examples 1, 6 and 7 show overdominance models in which four of the fifteen equilibria are stable. In symmetric equilibria each gamete, and its complement (obtained by substituting one allele for another at all loci), have the same frequency, and each of the four stable equilibria have one of the four pairs predominating in frequency. Example 4 shows a feature of three-locus models not found in studies of two loci, namely the simultaneous stability of solutions in which there is no linkage disequilibrium (Class 1) and the four described above (Class 3ai), making five stable equilibria in all. In this example the region of simultaneous stability is very small ($r = 0.01 - 0.010427$), but for a different stability regime or if there are many loci the region may be large (FRANKLIN and LEWONTIN 1970). There can be six stable symmetric equilibria if recombination between loci 1 and 2 is not equal to that between 2 and 3 (Example 5).

When six symmetric equilibria are stable for the same recombination fractions they comprise four of Class 3 and two of Class 2 with the classes characterized by different nonzero values of the linkage disequilibrium. This possibility was not uncovered by FRANKLIN and LEWONTIN. We have proved for the three-locus case that the number of equilibria in such a situation is five. In addition, we pointed out in Section 8 that there may exist two unsymmetric equilibria which may be stable for tight linkage simultaneously with the four stable Class 3 equilibria. The implications of this are discussed in our work in preparation.

How much of the behavior of the three-locus system might have been predicted from the extensive analyses of two-locus models? For tight linkage it is known that in a suitably interacting two-locus model the equilibrium with $D = 0$ is unstable, and it would have been reasonable to assume that the three-locus analog of the two-locus model would also show that the central solution (i.e., all $D_{ij} = 0$) would be unstable for small recombination. In addition, for loose linkage the central solution is the only symmetric equilibrium which exists, and is stable. The three-locus model shows a similar behavior. Similarly, if one pair of loci is tightly linked, and the other pairs are loosely linked, we could predict that there would be stable disequilibrium between the tightly linked pair and no disequilibrium between the remaining pairs. Further we might predict some of the behavior shown in Examples 1–4. Here the loci have equal effect, and are equally spaced. If linkage is tight enough so that the disequilibrium between locus 1 and 2 is stable (as judged by the criteria established for the two-locus model), then zero disequilibrium between 2 and 3 would be unstable, hence Class 2a equilibria in which $D_{12} \neq 0$, $D_{23} = 0$ would be unstable. Similarly 2b and 2c are predictably unstable. Hence we would assume that the stable equilibria, if they exist, would have $D_{12} \neq 0$, $D_{23} \neq 0$.

Ignoring the effect of the third locus, there will exist an equilibrium with $D_{12} \neq 0$ if $r_1 < 0.1$ in Examples 1–4. (This is based on the two-locus theory of LEWONTIN and KOJIMA (1960)). Using the above argument equilibrium 2a will be stable if $r_2 > .01$ and unstable if $r_2 < .01$. This prediction is in agreement with the findings in § 4.

This is about as far as one can go using two-locus theory. The number of equilibria with nonzero disequilibrium between all pairs could not be predicted easily *a priori*, nor the conditions for existence and stability. (From symmetry considerations we might say that there are at least four such equilibria, and we have shown that there are in fact eight). The region of simultaneous stability is a feature of the three-locus model which does not follow from two-locus analyses.

Perhaps the relevant question for multilocus models should not be how much can be generalized from the two-locus model. Instead, we might ask how much can be inferred from the multiallele model with the number of alleles corresponding to the number of gametic types in the multilocus model. In fact, when there is no recombination the models are identical. Since the multiallele theory is completely known the multilocus theory for tight linkage should be deducible. Thus with three loci and the symmetric viabilities of this paper, we would predict that for r small and $\beta, \delta, \eta > 0$ four symmetric equilibria should be stable, the central point unstable, and for general symmetric viabilities two unsymmetric equilibria could also be stable. KARLIN and McGREGOR (1971) have presented similar arguments in the context of a general small parameter theory.

Similarly we might consider the Class 2 equilibria (4.6) as r_1 tends to zero. These equilibria approach the central equilibria of the appropriate two-locus model, which are stable for r_2 large. We therefore infer that for Class 2 equilibria to be stable, there must be asymmetry with respect to the way the loci lie on the chromosome. In other words, although we cannot tell for what recombination values the various equilibria come and go, we can obtain a great deal of useful information on which equilibria govern the evolution for tight linkage by considering the appropriate multiallele case.

The body of this paper has been concerned only with symmetric equilibria. One of the key distinguishing features of this three-locus work over the two-locus work is that two unsymmetric equilibria may exist for tight linkage, and be stable. Again this may be inferred from the multiallele theory. This would make a total of six stable equilibria for tight linkage. The question of unsymmetric equilibria in the three-locus model is an interesting problem, and in our subsequent paper we shall explore the interaction of these with the symmetric equilibria discussed above.

Thus there are two points of generalization from the work of FRANKLIN and LEWONTIN which are worth noting. First, if the three loci are not equally spaced (as we would expect in more realistic models) there can be, in addition to the stable solutions with all $D \neq 0$, equilibria in which one of the adjacent pairs has $D \neq 0$ and the other is in linkage equilibrium. This will undoubtedly generalize to more loci in a complicated manner. Second, unsymmetric equilibria stable for tight linkage may exist simultaneously with symmetric equilibria.

In general, however, our analysis supports the numerical conclusions of FRANKLIN and LEWONTIN (1970), who found a class of stable symmetric equilibria comprising 2^{n-1} solutions, where n is the number of loci. These equilibria are characterized by a high degree of linkage disequilibrium between all pairs of loci and correspond in the three-locus model to equilibria 3ai. Our analysis has proven the existence of a region of simultaneous stability of the central point and the stable Class 3 equilibria which they originally discovered.

The unsymmetric equilibria for the three-locus model add considerably to the complexity of the situation. In a preliminary analysis of Model 2, with small recombination values, we have found thirty internal, unsymmetric equilibria, some of which, as mentioned above, are stable.

The method of analysis used in § 2 and § 3 to obtain the symmetric equilibria is based on a transformation similar to that used by KARLIN and FELDMAN (1970). The method used here can be applied to the two-locus symmetric viability model to obtain the unsymmetric equilibria more simply. In principle the system of gametic frequencies for more than three loci can be transformed in the same way.

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APPENDIX A

Existence of the class 3 symmetric equilibria: ($\hat{u}_5 \neq 0$, $\hat{u}_6 \neq 0$ and $\hat{u}_7 \neq 0$) with $r_1 = r_2 = r$ and $R = 2r(1-r)$.

(i) Consider first values of r such that $R(1-\frac{\eta}{2}) < \frac{\beta+\eta-\delta}{8}$. This implies that $r\frac{\eta}{2}$, $R\frac{\eta}{2}$ and $r(1-\frac{\eta}{2})$ are all less than $\frac{\beta+\eta-\delta}{8}$. Define r^* as the smaller root of $R(1-\frac{\eta}{2}) = \frac{\beta+\eta-\delta}{8}$ (note $r^* < \frac{1}{2}$) so that in this first range $r < r^*$. (In Model 1, §7, $r^* = .0050253$.) From (3.21) (a) there are two valid roots $\hat{u}_6$, one positive and one negative. The positive one also validates (3.20) (a) and therefore produces two valid equilibria. For the negative root to be valid in (3.20) (a) we require

$$\hat{u}_6 < \frac{(r-R)(1-\frac{\eta}{2})}{(\frac{\beta+\eta-\delta}{4} - \frac{r\eta}{2})} < 0. \tag{A.1}$$

This is not automatically satisfied. In fact from (3.21) (a) for (A.1) to hold we need

$$(\frac{\beta+\eta-\delta}{4} - \frac{R\eta}{2}) \left[\frac{r^2(1-2r)^2(1-\frac{\eta}{2})^2}{(\frac{\beta+\eta-\delta}{4} - \frac{r\eta}{2})^2} (\frac{\beta+\eta-\delta}{8}) - (\frac{\beta+\eta-\delta}{8} - R(1-\frac{\eta}{2})) \right] < 0 \tag{A.2}$$

(note that (A.2) holds near $r = 0$). Hence, $r < r^*$ always produces two equilibria from (3.20) (a) and (3.21) (a) with $\hat{u}_6 > 0$, $\hat{u}_5 = \hat{u}_7$, and in the same way there will be two from (3.20) (b) and (3.21) (b) with $\hat{u}_6 < 0$, $\hat{u}_5 = -\hat{u}_7$. In addition if (A.2) holds four more will exist. However, for r very close to r^*, (A.2) is obviously violated.

(ii) Next consider the range $r^* \leq r < \frac{\beta+\eta-\delta}{8(1-\frac{\eta}{2})}$ so that in addition

$$\frac{\beta+\eta-\delta}{4} > 2r(1-\frac{\eta}{2}) > 2r(1-r)(1-\frac{\eta}{2}) > 2r(1-r)\frac{\eta}{2} = \frac{R\eta}{2}.$$

Thus from (3.21) (a) two valid $\hat{u}_6$ solutions exist. From (3.20(a) the positive one is valid. However, using the same argument as before, since $r \geq r^*$ the negative $\hat{u}_6$ solution is invalid. Thus in this range, two solutions of the form $\hat{u}_6 > 0$, $\hat{u}_5 = \hat{u}_7$ exist. In the same way from (3.20) (b) and (3.21) (b) two solutions of the form $\hat{u}_6 < 0$, $\hat{u}_5 = -\hat{u}_7$ are valid, so that the total cannot exceed four here.

(iii) Now consider $(\beta+\eta-\delta)/8(1-\frac{\eta}{2}) < r < r^{**}$ where r^{**} is the smaller root of $\frac{\beta+\eta-\delta}{4} = \frac{R\eta}{2}$. (In Model 1, § 7, $r^{**} = 0.1$.) Clearly in this range the constant term of (3.21) (a) and (3.21) (b) is positive (note that if $\beta > \delta$ [single heterozygotes less fit than triple homozygotes] $r^{**} > \frac{1}{2}$ so this complete the range of r values). This case is difficult to analyze completely so we are content to consider what happens near the limits of the range.

When $r = (\beta+\eta-\delta)/8(1-\frac{\eta}{2})$, $\hat{u}_6 = 0$ is a valid solution although, since it entails $\hat{u}_5 = \hat{u}_7 = 0$, it is in fact the "central solution." The validity of the non-zero solution will then depend on the slope of (3.21) (a) at $u_6 = 0$ for this value of r. If the slope is negative this solution will be positive and will be valid from (3.20) (a). When r is slightly greater than $(\beta+\eta-\delta)/8(1-\frac{\eta}{2})$ the slope of (3.21) (a) at $u_6 = 0$ will still be negative but since the value at the origin is now positive there will be two positive $\hat{u}_6$ solutions both of which will be valid from (3.20) (a) and four valid equilibria will result. Similarly, under these same conditions, four valid equilibria with $\hat{u}_6 < 0$ will result from (3.20) (b) and (3.21) (b). If, however, the slope of (3.21) (a) at $u_6 = 0$ is positive for $r = (\beta+\eta-\delta)/8(1-\frac{\eta}{2})$ the solutions for r slightly greater will both be negative and invalid. What we expect therefore depends on the slope of (3.21) (a) at $u_6 = 0$ for $r = (\beta+\eta-\delta)/8(1-\frac{\eta}{2})$. This seems to depend critically on the selection parameters in such a way that when η is small this slope is negative and all eight equilibria exist. (It is important for the stability analysis to note that at the smaller positive root of (3.21) (a), in this case the slope, is negative.)

As r increases to r^{**} the constant term of (3.21) (a) again vanishes. When r is slightly less than r^{**} no positive $\hat{u}_6$ roots exist (nor negative roots of (3.21) (b)) so that no valid equilibria are possible. At $r = r^{**}$ is is clear that no valid roots are possible. To summarize, in the range $(\beta+\eta-\delta)/8(1-\frac{\eta}{2}) < r < r^{**}$ there may be eight solutions in the smaller part of the range but these disappear as r increases to r^{**}.

(iv) If $\delta > \beta$ then consider the range $r^{**} < r < \frac{\beta+\eta-\delta}{2\eta}$. We have to split this range further because the coefficient of $u_6{}^2$ in (3.21) (a) has a root l_1, say, which it is easy to see lies in this interval and at which it changes sign from positive to negative. Let us first treat r values with $r^{**} < r < l_1$ so that the coefficient of $u_6{}^2$ is positive, while the constant term is negative. In this range, then, there is a positive and a negative root of (3.21) (a). But the denominator on the right side of (3.20) (a) is negative. Hence the positive root is invalid. For the negative root to be valid in (3.20) (a) we must have

$$0 > \hat{u}_6 > \frac{(r-R)(1-\frac{\eta}{2})}{(\frac{\beta+\eta-\delta}{4} - \frac{r\eta}{2})}.$$

On substitution into (3.21)(a) it is seen that the reverse of condition (A.2) must hold for this negative root to be valid. This is clearly impossible. Hence in $r^{**} < r < l_1$ no valid roots are possible.

To complete case iv we examine $l_1 \leq r < \frac{\beta+\eta-\delta}{2\eta}$. Note that the coefficient of u_6 in (3.21)(a) is a cubic in r. It has three positive roots $m_1 < m_2 < m_3$, and it is easy to see that

$$r^* < m_1 < r^{**}, \quad \frac{\beta+\eta-\delta}{2\eta} < m_2 < ½, \quad m_3 > ½ .$$

Therefore, when $r = l_1$ and (3.21)(a) is linear, the root is positive, and as above, is invalid. For r close to l_1 the roots of (3.21)(a) are real. Any roots in this range must be positive and again from (3.20)(a) cannot be valid.

In the range $r^{**} < r < \frac{\beta+\eta-\delta}{2\eta}$, therefore, there are no valid roots.

(v) $\frac{\beta+\eta-\delta}{2\eta} < r < ½$. Again this breaks naturally into the regions $\frac{\beta+\eta-\delta}{2\eta} < r < m_2$ and $m_2 \leq r < ½$ where m_2 is the second root of the coefficient of u_6 in (3.21)(a). In the first sub-region all real roots of (3.21)(a) must be positive. From (3.20)(a) where r is close to $(\beta+\eta-\delta)/2\eta$ the roots are invalid. Also, from (3.21)(a) when r is close to m_2 no real $\hat{u}_6$ roots exist. In between, for a valid positive $\hat{u}_6$ we need

$$u_6 > \frac{(r-R)(1-\frac{\eta}{2})}{[(\beta+\eta-\delta)/4-\frac{r\eta}{2}]} .$$

The slope of (3.21)(a) when $\hat{u}_6 = (r-R)(1-\frac{\eta}{2})/[(\beta+\eta-\delta)/4-\frac{r\eta}{2}]$ is clearly negative so so the inequality is violated and no roots can be valid in the range $(\beta+\eta-\delta)/2\eta < r < m_2$.

It remains to treat the case $m_2 \leq r < ½$. Again near $r = m_2$ (3.21)(a) has imaginary roots. In this region any real roots must be negative and, if they exist, will certainly satisfy (3.20)(a). At $r = ½$ the reality of the roots of (3.21)(a) depends on the selection values. If $(2(\beta-\delta)+3\eta)^2 - 12(\beta+\eta-\delta) > 0$ eight valid solutions will exist at $r = ½$. This condition is clearly satisfied if η is small and $\delta > \beta$ and, of course, $\beta + \eta - \delta < 0$.

(vi) $\beta + \eta - \delta < 0$. Equilibria (3.6), (3.7) and (3.8) cannot exist. From (3.21)(a) one positive and one negative $\hat{u}_6$ root exist. The negative root always satisfies (3.20)(a) and from (4.3) the positive root will also be valid in (3.20)(a). Therefore, eight valid roots always exist.

APPENDIX B

Solution (3.6): $\hat{x}_1 = \hat{x}_2 = \hat{x}_7 = \hat{x}_8 = ⅛\,(1 \pm \hat{u}_5)$, $\hat{x}_3 = \hat{x}_4 + \hat{x}_5 = \hat{x}_6 = ⅛\,(1 \mp u_5)$ where $u_5{}^2 = 1 - 8r_1(1-\eta/2)(\beta+\eta-\delta)^{-1}$.

The local stability determinant partitions into a linear term and three quadratics. From the linear term the condition that the first eigenvalue be less than 1 is the existence condition for (3.6), namely, $\lambda_1 < 1$ if

(B.1) $$r_1 < \frac{\beta+\eta-\delta}{8(1-\eta/2)} .$$

The roots of the first quadratic λ_2 and λ_3, say, are less than unity (in modulus) if, respectively,

(B.2) $$\frac{\beta+\eta-\delta}{8}\hat{u}_5{}^2 + \frac{\delta-\eta}{4}\hat{u}_5 + \frac{\beta-\eta+\delta}{8} > 0$$

and

(B.3) $$\frac{\beta+\eta-\delta}{8}\hat{u}_5{}^2 - \frac{\delta-\eta}{4}\hat{u}_5 + \frac{\beta-\eta+\delta}{8} > 0$$

hold.

From (B.2) and (B.3) when $\delta > \eta$ no new conditions are required. When $\eta > \delta$ and $\beta - \eta + \delta < 0$, we have $\lambda_2 > 1$ so that for stability we do require $\beta - \eta + \delta > 0$. In summary the conditions that λ_2 and λ_3 both be less than unity in absolute value are:

(B.4) (a) $\quad \delta > \eta$ implies $|\lambda_2|, |\lambda_3| < 1$ for all r_1

or

(B.4) (b) $\quad \eta > \delta,\ \beta > \sqrt{2(\eta-\delta)}$ imply $|\lambda_2|, |\lambda_3| < 1$ for all r_1.

(B.4) (c) $\quad \eta > \delta,\ \eta - \delta < \beta < \sqrt{2(\eta-\delta)}$ implies

$$|\lambda_2|,\ |\lambda_3| < 1 \text{ if } 0 < r_1 < C \text{ or } D < r_1 < \frac{\beta+\eta-\delta}{8(1-\eta/2)}$$

where

$$C = \frac{\beta^2 - (\eta-\delta)^2 + \beta(\eta-\delta) - (\eta-\delta)\sqrt{[2(\eta-\delta)^2 - \beta^2]}}{4(1-\eta/2)(\beta+\eta-\delta)}$$

$$D = \frac{\beta^2 - (\eta-\delta)^2 + \beta(\eta-\delta) + (\eta-\delta)\sqrt{[2(\eta-\delta)^2 - \beta^2]}}{4(1-\eta/2)(\beta+\eta-\delta)}$$

It should be noted that (B.4) (c) allows a gap, $C < r_1 < D$, of instability analogous to that discovered by EWENS (1968) (see also KARLIN and FELDMAN (1970b)).

The remaining four eigenvalues are quite complicated to analyze. They are the roots λ_4 and λ_5 of the quadratic

$$\begin{aligned}(\text{B.5})\qquad & \bar{w}^2\lambda^2 - \bar{w}\lambda[2 - \frac{\delta}{2} - \frac{\beta}{2} - \eta - \frac{(1-\eta)}{2}(r_1+r_2+r_3)] \\ & + (1 - \frac{\delta}{4} - \frac{\beta}{2} - \frac{\eta}{4})[1 - \frac{\delta}{4} - \frac{3\eta}{4} - \frac{(1-\eta)}{2}(r_1+r_2+r_3)] \\ & - [\frac{2\beta-\eta-\delta}{4}][\frac{\eta-\delta}{4} + (r_3-r_1+r_2)(1-\eta)/2]\hat{u}_5^2 = 0.\end{aligned}$$

and the roots λ_6 and λ_7 of the quadratic

$$\begin{aligned}(\text{B.6})\qquad & \bar{w}^2\lambda^2 - \bar{w}\lambda[2 - \frac{\beta+\eta+\delta}{2} - (r_3+r_2)(1-\eta/2)] \\ & + (1 - \frac{\beta+\eta+\delta}{4} - r_3(1-\eta/2))(1 - \frac{\beta+\eta+\delta}{4} - r_2(1-\eta/2)) \\ & - [\frac{\beta+\eta-\delta}{4} - r_2\eta/2][\frac{\beta+\eta-\delta}{4} - r_3\eta/2]\hat{u}_5^2 = 0\end{aligned}$$

where

$$\bar{w} = 1 - \frac{\delta}{8} - \frac{3(\beta+\eta)}{8} + \frac{(\beta+\eta-\delta)}{8}\hat{u}_5^2.$$

It is easy to see that λ_6 and λ_7 are real. After some algebra the condition that they both be less than 1 in absolute value turns out to be

$$(\text{B.7})\qquad ar_2^2 + br_2 + c > 0$$

where a, b and c are the functions (of r_1)

$$\begin{aligned}(\text{B.8})\qquad & a = \frac{(1-2r_1)}{4}[4(1-\eta) + (1-\hat{u}_5^2)\eta^2] \\ & b = -(1-\eta/2)^2 r_1(1-2r_1) - \hat{u}_5^2[r_1\frac{\eta^2}{4} - (1-r_1)(\frac{\beta+\eta-\delta}{4})\eta] \\ & c = -\hat{u}_5^2(\frac{\beta+\eta-\delta}{8})[\frac{\beta+\eta-\delta}{2} - r_1\eta].\end{aligned}$$

The most important property of (B.7) is that the inequality is false if $r_2 \leq r_1$. The symmetry of the model therefore implies that (3.6) and (3.8) cannot be stable together. In particular, if $r_1 = r_2$ neither can be stable.

The roots of (B.5) are more difficult to analyze in a qualitative way. If the viabilities are multiplicative it is easy to see that λ_4 and λ_5 are real and less than unity in modulus. When the more general fitness scheme is in force we can see that for r_1 close to zero or near its maximum

$(\beta+\eta-\delta)/8(1-\eta/2)$ the roots are real. Near $r_1=0$ the condition that they be less than unity is

(B.9) $$\beta-\eta-\delta<0$$

while near $r_1=(\beta+\eta-\delta)/8(1-\eta/2)$ the conditions are the same as (5.2)′(a) and (5.2)′(b), namely

(B.10) $$\beta-\eta+\delta>0, \quad (r_1+r_2-r_1r_2)>(3\beta-3\eta-\delta)/8(1-\eta).$$

The general conditions on the roots of (B.5) seem complicated to write down. We can say that if the selection coefficients do not depart greatly from multiplicative by continuity we expect these two roots to be less than unity for very tight linkage.

(C) *Solution (3.7):* $\hat{x}_1=\hat{x}_3=\hat{x}_6=\hat{x}_8=\frac{1}{8}(1\pm\hat{u}_6)$, $\hat{x}_2=\hat{x}_4=\hat{x}_5=\hat{x}_7=\frac{1}{8}(1\mp\hat{u}_6)$ where $\hat{u}_6^2=1-8r_3(1-\eta/2)(\beta+\eta-\delta)^{-1}$ (all other $\hat{u}_i=0$). The first condition for the stability of (3.7) is seen to be the existence condition, namely

(B.11) $$0<r_3<(\beta+\eta-\delta)/8(1-\eta/2).$$

Now corresponding to (B.6) with r_3 and r_1 interchanged we obtain the eigenvalues λ_6 and λ_7 as

$$(\bar{w})^{-1}\{[1-\frac{\beta+\eta+\delta}{4}-\frac{r_1+r_2}{2}(1-\frac{\eta}{2})]$$
$$\pm\frac{1}{2}\sqrt{[(r_1-r_2)^2(1-\frac{\eta}{2})^2+4u_6^2(\frac{\beta+\eta-\delta}{4}-\frac{r_1\eta}{2})(\frac{\beta+\eta-\delta}{4}-\frac{r_2\eta}{2})]}\}$$

which are real. Substituting $\bar{w}=1-\dfrac{\beta+\eta+\delta}{4}-r_3(1-\eta/2)$ we have λ_6 (the larger) <1 if

(B.12) $$(r_1+r_2-4r_1r_2)(1-\eta/2)$$
$$+\sqrt{(r_1-r_2)^2(1-\eta/2)^2+4\hat{u}_6^2[\frac{\beta+\eta-\delta}{4}-\frac{r_1\eta}{2}][\frac{\beta+\eta-\delta}{4}-\frac{r_2\eta}{2}]}$$

is negative. But since $r_1, r_2<\frac{1}{2}$ this is impossible and therefore λ_6 is always greater than unity. Thus (3.7) can never be stable.

(D) *Solution (3.8):* $\hat{x}_1=\hat{x}_4=\hat{x}_5=\hat{x}_8=\frac{1}{8}(1\pm\hat{u}_7)$, $\hat{x}_2=\hat{x}_7=\hat{x}_3=\hat{x}_6=\frac{1}{8}(1\mp\hat{u}_7)$ where $\hat{u}_7^2=1-8r_2(1-\eta/2)(\beta+\eta-\delta)^{-1}$ all other $\hat{u}_i=0$. The conditions for stability are as for (3.6) with r_1 and r_2 interchanged. Again, it should be emphasized that (3.8) and (3.6) cannot be stable simultaneously. In fact of the seven solutions so far analyzed, for tight linkage only (3.6) or (3.8) (not both) may be stable, while for looser linkage (3.4) may be stable. In fact, if r_2 is sufficiently great relative to r_1 we predict (3.6) will be stable. A case is given by Example 5 of §7. The stability of this class of equilibria was not considered by FRANKLIN and LEWONTIN (1970).

APPENDIX C

Stability of the $\hat{u}_5\neq0$, $\hat{u}_6\neq0$, $\hat{u}_7\neq0$ solution when $\beta+\eta-\delta>0$.

The stability determinant splits into a cubic and a quartic. From the cubic we have been able to obtain the three eigenvalues, and these three appear to give us most of the information we need on stability for tight linkage. In other words, the numerical examples in §7 can be predicted from these eigenvalues alone, although with less simple selection parameters there may be difficulties involving the other four eigenvalues.

We shall refer to solutions $\hat{u}_6$ from (3.21)(a) and the relevant remarks for (3.21)(b) are easily inferred.

The first eigenvalue from the cubic is λ_5, given by

(C.1) $$\bar{w}\lambda_5=1-\frac{\beta+\eta+\delta}{4}-r(1-\frac{\eta}{2})-\frac{\beta+\eta-\delta}{4}\hat{u}_6+\frac{r\eta}{2}\hat{u}_6,$$

where $\bar{w}=1-\dfrac{\delta}{4}(1+\hat{u}_6)-\dfrac{\beta}{4}(1-\hat{u}_6)-\dfrac{\eta}{4}(1-\hat{u}_6)-r(1-\dfrac{\eta}{2})-\dfrac{r\eta}{2}\hat{u}_6$.

Clearly $\lambda_5>0$ and is less than 1 if

(C.2) $$\hat{u}_6(\frac{\beta+\eta-\delta}{4}-\frac{r\eta}{2})>0.$$

That is, if $r<\dfrac{\beta+\eta-\delta}{2\eta}$, for stability $\hat{u}_6$ must be positive, while if $r>\dfrac{\beta+\eta-\delta}{2\eta}$, $\hat{u}_6$ must be negative. From Appendix A this condition already eliminates four of the eight equilibria which may exist when $r < r^*$, where r^* is the smaller root of $R(1-\frac{\eta}{2}) = \frac{\beta+\eta-\delta}{8}$. For $r > r^*$ all the possible equilibria which exist satisfy this first stability condition.

The remaining two eigenvalues from the cubic are the solutions λ_2 and λ_3 of

(C.3) $$g(\lambda) = \lambda^2\bar{w}^2 - \lambda\bar{w}(J+N+L) + N(J+L) - 2KM = 0$$

where

$$J = 1 - \frac{\beta+\eta+\delta}{4} - r(1-\frac{\eta}{2}) - \frac{\beta+\eta-\delta}{4}\hat{u}_5^2$$

$$K = -(\frac{\beta+\eta-\delta}{4})\hat{u}_5\hat{u}_6 + (\frac{\beta+\eta-\delta}{4} - \frac{r\eta}{2})\hat{u}_5$$

$$L = -(\frac{\beta+\eta-\delta}{4})\hat{u}_5^2 + (\frac{\beta+\eta-\delta}{4} - \frac{r\eta}{2})\hat{u}_6$$

$$M = -(\frac{\beta+\eta-\delta}{4})\hat{u}_5\hat{u}_6 + (\frac{\beta+\eta-\delta}{4} - \frac{R\eta}{2})\hat{u}_5$$

$$N = 1 - \frac{\beta+\eta+\delta}{4} - \mathrm{R}(1-\frac{\eta}{2}) - \frac{\beta+\eta-\delta}{4}\hat{u}_6^2.$$

It can be shown that $J + N + L > 0$. It is important to note that in the region $R > \frac{\beta+\eta-\delta}{2\eta} > r$ (or equivalently $r^{**} < r < \frac{\beta+\eta-\delta}{2\eta}$, where r^{**} is the smaller root of $\frac{\beta+\eta-\delta}{2\eta} = R$) if $\delta > \beta$ no valid roots exist. Therefore in considering the reality of λ_2 and λ_3 we may assume either

(C.4) (a) $$\frac{\beta+\eta-\delta}{2\eta} > R$$

or

(C.4) (b) $$r > \frac{\beta+\eta-\delta}{2\eta}.$$

In both of these cases it is not difficult to show that $KM > 0$ so that λ_2 and λ_3 are real. The condition that $|\lambda_2|$, $|\lambda_3|$ be less than 1 is therefore that $g(1) > 0$, namely

(C.5) $$\hat{u}_5^2\Big\{\hat{u}_6[\frac{\beta+\eta-\delta}{2}\{(\frac{\beta+\eta-\delta}{4} - \frac{r\eta}{2}) + (\frac{\beta+\eta-\delta}{4} - \frac{R\eta}{2})/2\}] + (\frac{\beta+\eta-\delta}{4})(R-r)(1-\frac{\eta}{2}) - [\frac{\beta+\eta-\delta}{4} - \frac{r\eta}{2}][\frac{\beta+\eta-\delta}{4} - \frac{R\eta}{2}]\Big\} > 0.$$

But condition (C.4) is precisely the condition that the derivative of (3.21)(a) be positive at $\hat{u}_6$. This, therefore, tells us in cases (iii) and (v) of Appendix A which $\hat{u}_6$ roots could be stable. In the range $\frac{\beta+\eta-\delta}{8(1-(\eta/2))} < r < r^{**}$ this condition informs us that the smaller positive root is unstable while, when $\frac{\beta+\eta-\delta}{2\eta} < r < ½$ the smaller (in absolute value) negative root is unstable.

The conditions, taken jointly, imply that whenever eight equilibria exist, only four can be stable. When only four exist the first three eigenvalues are always less than unity. As can be seen from 7 these three eigenvalues seem to be very good predictors for the complete stability, at least in the case where the viabilities are multiplicative and linkage tight.

The fourth-degree determinant factors into a linear and a cubic. From the linear part we have

(C.6) $$\lambda_4 = (\bar{w})^{-1}[1 - \frac{\delta}{4} - \frac{\beta}{2} - \frac{\eta}{4} + (\delta - \eta)\hat{u}_6/4] < 1$$

if

(C.7) $$[\frac{\beta+2\eta-2\delta}{4} - \frac{r\eta}{2}]\hat{u}_6 > [r(1-\frac{\eta}{2}) - \frac{\beta}{4}]\,.$$

This is a somewhat strange condition. But for r very small so that $\hat{u}_6$ is close to $+1$ (note that by the above the equilibrium $\hat{u}_6 = -\frac{1}{3}$ cannot be stable), the condition reduces to $\beta + \eta - \delta > 0$. For sufficiently tight linkage this eigenvalue imposes no additional restrains. However, at $r = \frac{1}{2}$ (C.7) can never be true so that for very loose linkage equilibria of the form $u_5 \neq 0$, $u_6 \neq 0$, $u_7 \neq 0$ cannot be stable.

The remaining stability eigenvalues are the roots of the equation

(C.8) $$\begin{vmatrix} A - \lambda\bar{w} & 2B & E \\ B & A + C - \lambda\bar{w} & D \\ C + G & 2(B+F) & H - \lambda\bar{w} \end{vmatrix} = 0$$

where

$$A = 1 - \frac{\delta}{4} - \frac{\beta}{2} - \frac{\eta}{4}, \qquad B = \frac{(\eta-\delta)}{4}\hat{u}_5$$

$$C = \frac{(\eta-\delta)}{4}\hat{u}_6 \qquad , \qquad D = \frac{(2\beta-\eta-\delta)}{4}\hat{u}_5$$

$$E = \frac{(2\beta-\eta-\delta)}{4}\hat{u}_6 \quad , \quad F = \frac{R(1-\eta)}{2}\hat{u}_5$$

$$G = r^2\frac{(1-\eta)}{2}\hat{u}_6 \qquad , \quad H = 1 - \frac{\delta}{4} - \frac{3\eta}{4} - \frac{(1-\eta)}{2}(R+2r).$$

When r is sufficiently small the condition that all three roots of this determinant be less than unity reduces to $\beta + \eta - \delta > 0$. When $r = \frac{1}{2}$ the cubic factors to produce a second eigenvalue equal to λ_4 in (C.6). No further analysis of the cubic has been made. It appears that such an extended analysis would have to be made numerically. From § 7, however, it seems that for relatively tight linkage, the first three eigenvalues do a good job of predicting stability, while for loose linkage $\lambda_4 > 1$ allows us to infer that the equilibria are unstable.