SIMULTANEOUS STABILITY OF D=0 AND D≠0 FOR MULTIPLICATIVE VIABILITIES AT TWO LOCI*

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ABSTRACT

The two-locus, two-allele multiplicative viability model is investigated. It is shown that the well-known region of recombination values for which $D = 0$ is locally stable does not preclude the local stability of an equilibrium with $D \neq 0$. This is shown numerically and is true for every case investigated in which both loci are overdominant and the viabilities not symmetric.

THE extent to which linkage disequilibrium exists in natural populations has been a focus of interest for experimental population genetics. The interpretation of the results in terms of possible modes of selection (including none at all) has been rather vague. In some loose sense, the absence of linkage disequilibrium between a pair of loci has been taken to indicate lack of epistasis. In this note we demonstrate a surprising complexity in the case where the selection regimes at each of two loci are independent and overdominant. For a range of recombination values, both $D = 0$ and $D \neq 0$ are stable.

BACKGROUND

Suppose that two gene loci have alleles A and a at the first, and B and b at the second. The frequencies of the four chromosomes AB, Ab, aB and ab will be written x_1, x_2, x_3 and x_4, respectively, with $\sum_{i=1}^{4} x_i = 1$. The recombination fraction between the two loci is R with $0 \leq R \leq 1/2$. The effect of natural selection on the system is described in terms of a 4 × 4 fitness matrix, W, whose entries are the relative viabilities of the genotypes as follows:

$$W = \begin{array}{c|cccc} & AB & Ab & aB & ab \\ AB & w_{11} & w_{12} & w_{13} & w_{14} \\ Ab & w_{12} & w_{22} & w_{23} & w_{24} \\ aB & w_{13} & w_{23} & w_{33} & w_{34} \\ ab & w_{14} & w_{24} & w_{34} & w_{44} \end{array} \qquad (1)$$

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Usually the fitnesses of the double heterozygotes, w_{23} and w_{14} are assumed to be equal, in which case W can be written in locus-by-locus form:

$$\begin{array}{cccc} & BB & Bb & bb \\ AA & w_{11} & w_{12} & w_{22} \\ Aa & w_{13} & w_{14} & w_{24} \\ aa & w_{33} & w_{34} & w_{44} \end{array} \tag{2}$$

The frequencies of the four chromosomes in the next generation can then be written in terms of those in the present according to the recursion system

$$\overline{W}\, x_i' = x_i\, W_{i.} + \varepsilon_i\, \mathrm{RD}\, w_{14} \ , \tag{3}$$

where

$$W_{i.} = \sum_j w_{ij}\, x_j, \quad \overline{W} = \sum_i W_{i.}\, x_i \ , \tag{4}$$

$\varepsilon_i = -1$ for $i = 1, 4$ and $\varepsilon_i = +1$ for $i = 2, 3$, and

$$D = x_1 x_4 - x_2 x_3 \ . \tag{5}$$

A coordinate system equivalent to the chromosome frequencies includes the gene frequencies

$$p_A = x_1 + x_2, \quad p_B = x_1 + x_3 \tag{6}$$

of alleles A and B together with D in (5). Thus, using (6) we have for example

$$x_1 = p_A p_B + D \tag{7}$$

with similar relations holding for x_2, x_3 and x_4. From (7) we see that D measures the departure from independence of the gene frequencies at the separate loci in determining the four chromosome frequencies. D also has an interpretation as a covariance between the state variables of the separate loci.

When $R = 0$, the recursion system (3) can be analyzed in terms of the stability of the various equilibria (KINGMAN 1961). When $R \neq 0$, the equilibrium behavior for the general viability matrix is not known, although certain features of the equilibrium structure, especially for tight linkage (R small), have been demonstrated (KARLIN 1975). More detailed results are available for three special classes of viability matrices, the additive viability system

$$\begin{array}{cccc} & BB & Bb & bb \\ AA & \alpha_1+\beta_1 & \alpha_1+\beta_2 & \alpha_1+\beta_3 \\ Aa & \alpha_2+\beta_1 & \alpha_2+\beta_2 & \alpha_2+\beta_3 \\ aa & \alpha_3+\beta_1 & \alpha_3+\beta_2 & \alpha_3+\beta_3 \ , \end{array} \tag{8}$$

the symmetric viability system

$$\begin{array}{cccc} & BB & Bb & bb \\ AA & \gamma_0 & \gamma_1 & \gamma_2 \\ Aa & \gamma_3 & \gamma_2 & \gamma_3 \\ aa & \gamma_2 & \gamma_1 & \gamma_0 \ , \end{array} \tag{9}$$

and the multiplicative viability system

$$\begin{array}{cccc} & BB & Bb & bb \\ AA & \alpha_1\beta_1 & \alpha_1\beta_2 & \alpha_1\beta_3 \\ Aa & \alpha_2\beta_1 & \alpha_2\beta_2 & \alpha_2\beta_3 \\ aa & \alpha_3\beta_1 & \alpha_3\beta_2 & \alpha_3\beta_3 \end{array} \; . \qquad (10)$$

With additive viabilities (8), as long as $0 < R \leq 1/2$ the system (3) converges from any nontrivial starting condition to the equilibrium point

$\mathbf{x}^* = (x_1^*, x_2^*, x_3^*, x_4^*)$ with

$$x_1^* = p_A^* p_B^*,\ x_2^* = p_A^* (1-p_B^*),\ x_3^* = (1-p_A^*)\ p_B^*,\ x_4^* = (1-p_A^*)(1-p_B^*), \qquad (11)$$

where

$$p_A^* = (\alpha_2 - \alpha_3)/(2\alpha_2 - \alpha_1 - \alpha_3),\ p_B^* = (\beta_2 - \beta_3)/(2\beta_2 - \beta_1 - \beta_3), \qquad (12)$$

provided that there is overdominance at each locus, that is

$$\alpha_2 > \max\,(\alpha_1, \alpha_3),\quad \beta_2 > \max\,(\beta_1, \beta_3)\ . \qquad (13)$$

The point (11) is usually called the *Hardy-Weinberg equilibrium* of the system (3).

For the symmetric viability system (9) in (3), an equilibrium of the form (11), *i.e.*, with $D^* = 0$, exists with $p_A^* = p_B^* = 1/2$ for all $R \geq 0$. However, it is locally stable if, and only if

$$\gamma_2 - \gamma_0 > |\ \gamma_1 - \gamma_3\ |\ \text{ and }\ R > (\gamma_2 - \gamma_1 - \gamma_3 + \gamma_0)/4\gamma_2 \qquad (14)$$

For $0 \leq \mathrm{R} < (\gamma_2 - \gamma_1 - \gamma_3 + \gamma_0)/4$, this Hardy-Weinberg equilibrium is not stable. In this region, two other equilibria with $p_A^* = p_B^* = 1/2$ and

$$D^* = \pm\ (0.25)\sqrt{1 - 4R\gamma_2/(\gamma_2 - \gamma_1 - \gamma_3 + \gamma_0)} \qquad (15)$$

exist. These equilibria can be stable only when the Hardy-Weinberg equilibrium is not, but the conditions within this range can be quite complicated (EWENS 1968; KARLIN and FELDMAN 1970). KARLIN and FELDMAN (1970) discuss generalizations of (9) that can exhibit up to seven interior equilibria. The details of the results reviewed above can be found in LEWONTIN and KOJIMA (1960), BODMER and FELSENSTEIN (1967) and KARLIN and FELDMAN (1970).

Multiplicative viabilities in system (3) have been studied by BODMER and FELSENSTEIN (1967), MORAN (1968) and KARLIN (1975). When there is overdominance at both loci [*i.e.*, (13) holds] BODMER and FELSENSTEIN (1967) showed that $\mathbf{x}^*$ in (11) is locally stable, provided that‡

$$R > R_0 = \frac{(\alpha_2 - \alpha_1)\ (\alpha_2 - \alpha_3)\ (\beta_2 - \beta_1)\ (\beta_2 - \beta_3)}{\alpha_2\beta_2\ (2\alpha_2 - \alpha_2 - \alpha_3)\ (2\beta_2 - \beta_1 - \beta_3)}\ . \qquad (16)$$

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‡ We take this opportunity to correct the formula for R_0 printed incorrectly on the top of page 376 of KARLIN (1975). The correct formula is as in (16).

It is assumed throughout this discussion that $R \leq 1/2$. Oscillatory behavior of the population about $\mathbf{x}^*$ is possible if $R > 3/4$.

MORAN (1968) established that $\mathbf{x}^*$ in (11) is globally stable if

$$R > \tilde{R} = 1/2 - \min (A,B) \tag{17}$$

where

$$A = \frac{(\alpha_2-\alpha_1)(\alpha_2-\alpha_3)}{6\alpha_2(2\alpha_2-\alpha_1-\alpha_3)}, \quad B = \frac{(\beta_2-\beta_1)(\beta_2-\beta_3)}{6\beta_2(2\beta_2-\beta_1-\beta_3)}. \tag{18}$$

Thus, under the condition (17), the population evolves to $\mathbf{x}^*$ from any initial gamete frequency array.

In addition to these facts concerning the Hardy-Weinberg equilibrium, the following properties of the multiplicative viability model are true. The gamete frequency domain $\{\mathbf{x} = (x_1, x_2, x_3, x_4): x_i \geq 0, \sum_{i=1}^{4} x_i = 1\}$ is divided by the surface $D(\mathbf{x}) = 0$ into two disjoint parts $\mathcal{R}^+$ and $\mathcal{R}^-$ with

$$\mathcal{R}^+ = \{\mathbf{x}\colon\ D(x) > 0\}$$
$$\mathcal{R}^- = \{\mathbf{x}\colon\ D(x) < 0\}$$

$\mathcal{R}^+$ and $\mathcal{R}^-$ are invariant regions under the transformation (3), so that if $\mathbf{x}$ is such that $D > 0$ (< 0), then the frequency vector $\mathbf{x}'$ of the next generation has $D > 0$ (< 0). The sign of the disequilibrium function is preserved in successive generations (KARLIN 1975). The surface separating $\mathcal{R}^+$ and $\mathcal{R}^-$ is also preserved for all R. That is, $D(\mathbf{x}) = 0$ entails $D(\mathbf{x}') = 0$ (MORAN 1967; BODMER and FELSENSTEIN 1967).

When linkage is tight to the extent that $R < R_0$, and if the overdominance conditions (13) hold, there are two locally stable polymorphic equilibria, one in $\mathcal{R}^+$ and the other in $\mathcal{R}^-$. If $R = 0$ these locally stable equilibria can be explicitly determined; the nine mutually exclusive configurations possible when (13) holds are detailed in Table 1 of KARLIN (1975, p. 378).

As a final introductory remark we note that if the viabilities are simultaneously multiplicative and symmetric, so that $\alpha_1 = \alpha_3$, $\beta_1 = \beta_3$, then, under the condition (13), $R = 0$ entails the local stability of the two equilibria at which the gamete arrays are the complementary pairs [(1/2) *AB*, (1/2) *ab*] and [(1/2) *Ab*, (1/2) *aB*] respectively. For R positive, but small, two stable polymorphic equilibria involving mostly these complementary pairs must exist. These two equilibria simultaneously become locally unstable at the value $R = R_0$ given by (16). The value of R_0 is equal to the value given in (14) in this symmetric case, and for $R > R_0$ only the Hardy-Weinberg point is stable.

It has generally been assumed that in the general (asymmetric) multiplicative viability model results similar to those of the previous paragraph hold, namely, that as the value of R increases to R_0, both of the equilibria stable for R small coalesce into the Hardy-Weinberg point. It has been assumed, therefore, that for $R > R_0$ only the Hardy-Weinberg equilibrium (11) is locally stable. This note is addressed to the demonstration that this assumption is false and that, over a suitable range of recombination values, the Hardy-Weinberg equilibrium with $D^* = 0$ can be simultaneously stable with an equilibrium having $D^* \neq 0$. The finding of FRANKLIN and FELDMAN (1977) is therefore extended to the multiplicative viability system.

RESULTS

One-hundred multiplicative viability regimes were constructed by choosing $\alpha_1,\alpha_2,\alpha_3,\beta_1,\beta_2,\beta_3$ at random from a uniform distribution on [0,1] and multiplying the numbers as in (10). None of these matrices turned out to be symmetric. Ten initial gametic frequency arrays were chosen randomly in a similar way. For each matrix and an array of recombination fractions, the system (3) was iterated from each of the ten starting conditions. Of the 100 matrices, 13 satisfied the overdominance conditions. In all other cases convergence occurred to a chromosome or gene fixation state ($x_1^* + x_2^* = 1, x_1^* + x_3^* = 1, x_3^* + x_4^* = 1, x_2^* + x_4^* = 1$). This is in good agreement with KARLIN and CARMELLI (1975), who found seven out of 50 matrices gave overdominance at both loci. The exact breakdown of the stable configurations for $R=0$ from the 100 matrices is shown in Table 1A. The terminology used in the table is the following: A "corner" equilibrium is a chromosome fixation state; A "g.f. edge" is a state of gene fixation; a two-boundary equilibrium stands for a gamete array composed of either *AB* and *ab* or *Ab* and *aB* (*i.e.*, complementary gamete pairs); a three-boundary equilibrium denotes one in which one of the four possible sets of three gametes is stable. In Table 1B the stable configurations for 100 matrices constructed at random, but restricted to satisfy the overdominance criteria (13), are shown.

For each of the 13 matrices satisfying conditions (13), the transformation (3) was iterated numerically for values of *R* increasing from zero to 0.5. Our obser-

TABLE 1A

Stable configurations from 100 randomly chosen multiplicative viability matrices (R=0)

Corners	g.f. edges	Two 2-boundary equilibria	One 2-boundary and one 3-boundary equilibrium	Two 3-boundary equilibria
44	43	5	4	4

TABLE 1B

Stable configurations for 100 randomly chosen overdominant multiplicative viability matrices

Two 2-boundary equilibria	One 2-boundary and one 3-boundary equilibrium	Two 3-boundary equilibria
31	47	22

Note that more than 2/3 of the equilibria at $R=0$ do not occur on edges, *i.e.*, are not of the high complementarity type. The preponderance of asymmetry suggests that high complementarity would not be the usual polymorphism to be expected of two loci on which selection acts independently, *i.e.*, multiplicatively.

vations on these iterations led us to select a further ten matrices with heterozygote advantage at each of the loci. The same procedure was carried through; equilibria were obtained at $R=0$ and the value of R increased with iteration to equilibrium for each R value. The results were as for the previous 13 cases. In order to understand the implications, it is worthwhile to describe the results and then present the numerical evidence that our description is indeed quite general. We shall assume throughout what follows that the multiplicative viability array satisfies (13).

Define R^* as the critical recombination value such that if $R > R^*$ the Hardy-Weinberg equilibrium (11) is globally stable, whereas if $R < R^*$, it is not. The exact value of R^* is not known, although in view of (16) and (17) we must always have

$$R_0 \leq R^* < \tilde{R} \tag{19}$$

What is demonstrated by our numerical work is that, in fact,

$$R_0 < R^* \tag{20}$$

unless the viability system is symmetric as well as multiplicative *i.e.*, $\alpha_1 = \alpha_3$, $\beta_1 = \beta_3$. Thus, the Hardy-Weinberg equilibrium becomes locally stable at a smaller recombination fraction (R_0) than that at which it becomes globally stable (R^*). This is contrary to the commonly accepted description of the equilibrium behavior of the multiplicative viability model. The way in which this comes about is as follows.

At $R=0$, the stable equilibria are composed of the gametes (AB, ab) or (AB, aB, ab) or (AB, Ab, ab) in $\mathscr{R}^+$ and (Ab, aB) or (AB, Ab, aB) or (Ab, aB, ab) in $\mathscr{R}^-$, one from each of $\mathscr{R}^+$ and $\mathscr{R}^-$. Now, over the ranges $0 < R < R_0$ and $R_0 < R < R^*$ denote the two stable equilibria as

$$\hat{\mathbf{x}}(R) \text{ and } \hat{\hat{\mathbf{x}}}(R) \tag{21}$$

to emphasize their dependence on R. For definiteness, in $0 \leq R < R_0$, choose these such that $D(\hat{\mathbf{x}}) > 0$ and $D(\hat{\hat{\mathbf{x}}}) < 0$. Since for $R < R_0$ the Hardy-Weinberg point (11) is unstable, with this range of recombination values the domain of attraction to $\hat{\mathbf{x}}$ is $\mathscr{R}^+$ and to $\hat{\hat{\mathbf{x}}}$ is $\mathscr{R}^-$. The continuity theory (KARLIN and MCGREGOR 1972) implies that $\hat{\mathbf{x}}(R)$ and $\hat{\hat{\mathbf{x}}}(R)$ vary continuously with R in $0 \leq R < R_0$. From the numerical studies, it is clear that as R increases to R_0, except in the symmetric case $\alpha_1 = \alpha_3$, $\beta_1 = \beta_3$, one, but not both of $\hat{\mathbf{x}}$ and $\hat{\hat{\mathbf{x}}}$ merges with the Hardy-Weinberg point $\mathbf{x}^*$. Suppose for definiteness that this one is $\hat{\mathbf{x}}$. Then $\hat{\hat{\mathbf{x}}}(R)$ remains distinct from $\mathbf{x}^*$ for the additional recombination range $R_0 \leq R < R^*$. For R satisfying $R_0 < R < R^*$, $\hat{\mathbf{x}}(R) = \mathbf{x}^*$ so that

$$D[\hat{\mathbf{x}}(R)] = D(\mathbf{x}^*) = 0 \ ,$$

while $D[\hat{\hat{\mathbf{x}}}(R)] < 0$. It should be noted that for $R_0 < R < R^*$ the domain of attraction to $\mathbf{x}^*$ properly contains $\mathscr{R}^+$ while that to $\hat{\hat{\mathbf{x}}}(R)$ is a reduced part of $\mathscr{R}^-$. As R increases to R^*, $\hat{\hat{\mathbf{x}}}(R)$ approaches $\mathbf{x}^*$ as well, and for $R > R^*$ the Hardy-

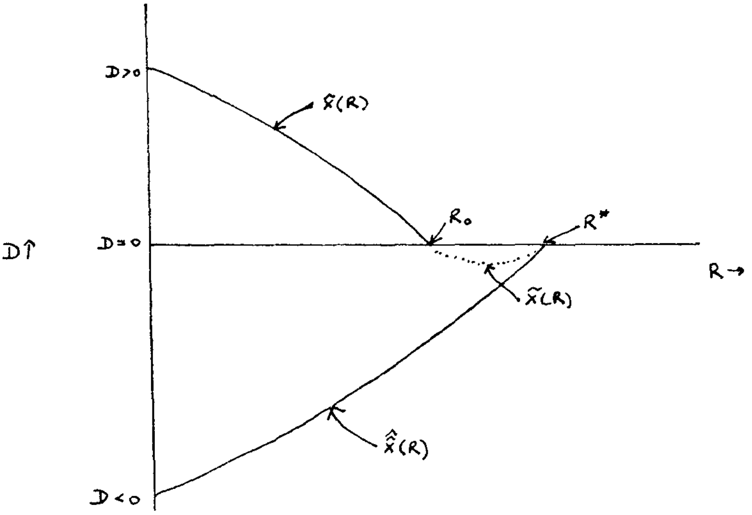

FIGURE 1.—$\hat{\mathbf{x}}(R)$ and $\hat{\hat{\mathbf{x}}}(R)$ as functions of R as represented by the disequilibrium. The drawing is schematic and not to scale.

Weinberg equilibrium is globally stable. These movements of $\hat{\mathbf{x}}(R)$ and $\hat{\hat{\mathbf{x}}}(R)$ as functions of R are depicted in Figure 1. At the point R_0, the equilibrium, $\hat{\mathbf{x}}(R)$, previously stable, changes its role and is represented by the curve $\tilde{\mathbf{x}}(R)$ of unstable equilibria that persists until $R=R^*$, when all the equilibria coalesce.

These remarks are essentially interpretations of the numerical findings. Table 2 lists the ten fitness matrices whose detailed properties with respect to R follow.

TABLE 2

Ten randomly generated overdominant fitness matrices of the form (10)

	Fitness matrix 1	Fitness matrix 2	Fitness matrix 3	Fitness matrix 4	Fitness matrix 5
α_1	0.37788	0.58472	0.22677	0.62671	0.35488
α_2	0.61941	0.85739	0.67275	0.82654	0.87748
α_3	0.43919	0.51495	0.33016	0.69473	0.40923
β_1	0.33845	0.12073	0.13951	0.24875	0.01092
β_2	0.77882	0.80629	0.92846	0.37554	0.79654
β_3	0.54932	0.47801	0.18424	0.15911	0.11282
	Fitness matrix 6	Fitness matrix 7	Fitness matrix 8	Fitness matrix 9	Fitness matrix 10
α_1	0.75577	0.26775	0.63871	0.06077	0.59953
α_2	0.99053	0.48721	0.72554	0.63215	0.75542
α_3	0.92211	0.38483	0.01532	0.18273	0.12276
β_1	0.34715	0.13207	0.20407	0.58386	0.81754
β_2	0.99135	0.73914	0.59292	0.94149	0.94925
β_3	0.94099	0.38276	0.12289	0.43520	0.12866

In matrices #3, 5, 9 the equilibria for $R=0$ are of category 2–2. Matrices 6 and 8 are both 3–3, while 1, 2, 4, 7, 10 have 2–3 (or 3–2) configurations. The two critical recombination values R_0 [from (16)] and $\tilde{R}$ [from (17)] are listed together with our estimate of R^* from the numerical results. The values of $D[\hat{x}(R)]$ and $D[\hat{\hat{x}}(R)]$ for the ten multiplicative viability matrices mentioned earlier, chosen such that (13) holds, are listed in Table 3. In each case a judicious choice of recombination values is reported. In particular, the choices of R are refined in the neighborhood of R_0, and a close approximation to R^* can also be extracted. In the third column the values of the mean fitness $W[\hat{x}(R)]$ and $W[\hat{\hat{x}}(R)]$ are recorded. Of the ten cases, using the terminology of Table 1, three were of the two 2-boundary type, five were of the one 2-boundary, one 3-boundary type and two were of the two 3-boundary type. The type of two-equilibrium configuration is listed at the top of each data set.

TABLE 3

Numerical results for the ten matrices of Table 2

Fitness matrix #1 (2–3)

R	$D(\hat{x}(R))$	$D(\hat{\hat{x}}(R))$	$W(\hat{x}(R))$	$W(\hat{\hat{x}}(R))$
0.0	0.241	—0.207	0.338886	0.332493
0.025	0.116	—0.079	0.327875	0.325847
0.030	0.073	—0.040	0.325639	0.324565
0.03226	0.034	—0.7E-3	0.324466	0.324148
0.03227	0.034	—0.6E-3	0.324459	0.324148
0.03228	0.034	—0.17E-4	0.324452	0.324148
0.03229	0.034	—0.96E-8	0.324445	0.324148
0.035	0.25E-12	—0.26E-12	0.324148	0.324148
0.04	0.86E-13	—0.88E-13	0.324148	0.324148

$R_0 = 0.03227950$ $R^* = 0.034$ $\tilde{R} = 0.48535221$

Fitness matrix #2 (3–2)

R	$D(\hat{x}(R))$	$D(\hat{\hat{x}}(R))$	$W(\hat{x}(R))$	$W(\hat{\hat{x}}(R))$
0.0	0.233	—0.239	0.432150	0.442418
0.04	0.069	—0.098	0.415190	0.418243
0.045	0.042	—0.069	0.413335	0.415276
0.04873	0.4E-3	—0.027	0.412284	0.412762
0.04874	0.1E-4	—0.027	0.412284	0.412752
0.04875	0.12E-7	—0.027	0.412284	0.412743
0.04876	0.6E-10	—0.027	0.412284	0.412733
0.05	0.49E-12	—0.47E-12	0.412284	0.412284
0.075	0.22E-13	—0.23E-13	0.412284	0.412284

$R_0 = 0.04874439$ $R^* = 0.050$ $\tilde{R} = 0.48487203$

Fitness matrix #3 (2–2)

R	$D(\hat{x}(R))$	$D(\hat{\hat{x}}(R))$	$W(\hat{x}(R))$	$W(\hat{\hat{x}}(R))$
0.0	0.2498	—0.2499	0.335609	0.334272
0.075	0.152	—0.149	0.288822	0.287684
0.1	0.099	—0.096	0.273230	0.272404
0.11878	0.005	—0.001	0.261319	0.261290

0.11879	0.004	—0.82E-3	0.261308	0.261289
0.11880	0.53E-7	—0.56E-10	0.261289	0.261289
0.11881	0.2E-10	—0.2E-10	0.261289	0.261289
0.125	0.65E-13	—0.66E-13	0.261289	0.261289
0.15	0.13E-13	—0.13E-13	0.261289	0.261289

$R_o = 0.11879223$ $R^* = 0.11881$ $\tilde{R} = 0.46272062$

Fitness matrix #4 (3–2)

R	$D(\hat{x}(R))$	$D(\hat{\hat{x}}(R))$	$W(\hat{x}(R))$	$W(\hat{\hat{x}}(R))$
0.0	0.193	—0.239	0.224018	0.227166
0.019	0.039	—0.081	0.220995	0.221541
0.02	0.016	—0.058	0.220867	0.221200
0.02044	0.9E-3	—0.040	0.220837	0.221023
0.02045	0.4E-3	—0.040	0.220837	0.221019
0.02046	0.67E-5	—0.039	0.220837	0.221014
0.02047	0.2E-7	—0.039	0.220837	0.221009
0.025	0.15E-12	—0.15E-12	0.220837	0.220837
0.03	0.73E-13	—0.75E-13	0.220837	0.220837

$R_o = 0.02045804$ $R^* = 0.024$ $\tilde{R} = 0.49445779$

Fitness matrix #5 (2–2)

R	$D(\hat{x}(R))$	$D(\hat{\hat{x}}(R))$	$W(\hat{x}(R))$	$W(\hat{\hat{x}}(R))$
0.0	0.2479	—0.2498	0.362315	0.360833
0.1	0.120	—0.116	0.292469	0.291362
0.125	0.046	—0.043	0.274856	0.274381
0.12916	0.004	—0.001	0.271765	0.271733
0.12917	0.004	—0.91E-4	0.271753	0.271732
0.12918	0.43E-10	—0.44E-10	0.271732	0.271732
0.12919	0.2E-10	—0.2E-10	0.271732	0.271732
0.15	0.18E-13	—0.18E-13	0.271732	0.271732
0.16	0.12E-13	—0.12E-13	0.271732	0.271732

$R_o = 0.12917058$ $R^* = 0.12918$ $\tilde{R} = 0.46546190$

Fitness matrix #6 (3–3)

R	$D(\hat{x}(R))$	$D(\hat{\hat{x}}(R))$	$W(\hat{x}(R))$	$W(\hat{\hat{x}}(R))$
0.0	0.070	—0.017	0.886473	0.885703
0.001	0.062	—0.011	0.886325	0.885673
0.002	0.052	—0.005	0.886153	0.885650
0.00251	0.046	—0.99E-4	0.886054	0.885646
0.00252	0.046	—0.1E-4	0.886052	0.885646
0.00253	0.046	—0.15E-9	0.886050	0.885646
0.00254	0.046	—0.3E-9	0.886048	0.885646
0.003	0.039	—0.29E-11	0.885945	0.885646
0.004	0.61E-12	—0.61E-12	0.885646	0.885646

$R_o = 0.00252002$ $R^* = 0.004$ $\tilde{R} = 0.49744785$

Fitness matrix #7 (2–3)

R	$D(\hat{x}(R))$	$D(\hat{\hat{x}}(R))$	$W(\hat{x}(R))$	$W(\hat{\hat{x}}(R))$
0.0	0.239	—0.182	0.231549	0.221234
0.035	0.124	—0.055	0.219373	0.215693
0.04	0.095	—0.029	0.217502	0.215047

TABLE 3—Continued

0.04352	0.064	—0.1E-3	0.216001	0.214786
0.04353	0.064	—0.2E-4	0.215996	0.214786
0.04354	0.064	—0.68E-10	0.215991	0.214786
0.04355	0.064	—0.3E-10	0.215986	0.241786
0.05	0.93E-13	—0.92E-13	0.214786	0.214786
0.075	0.18E-13	—0.18E-13	0.214786	0.214786

$R_0 = 0.04353096$ $R^* = 0.049$ $\tilde{R} = 0.48696445$

Fitness matrix #8 (3–3)

R	$D(\hat{x}(R))$	$D(\hat{\hat{x}}(R))$	$W(\hat{x}(R))$	$W(\hat{\hat{x}}(R))$
0.0	0.199	—0.096	0.254262	0.249568
0.03	0.061	—0.030	0.248240	0.246925
0.035	0.040	—0.016	0.247320	0.246542
0.03826	0.021	—0.1E-3	0.246663	0.246380
0.03827	0.021	—0.2E-4	0.246661	0.246380
0.03828	0.021	—0.84E-9	0.246658	0.246380
0.03829	0.021	—0.4E-10	0.246656	0.246380
0.04	0.33E-12	—0.33E-12	0.246380	0.246380
0.045	0.83E-13	—0.84E-13	0.246380	0.246380

$R_0 = 0.03827367$ $R^* = 0.040$ $\tilde{R} = 0.49013333$

Fitness matrix #9 (2–2)

R	$D(\hat{x}(R))$	$D(\hat{\hat{x}}(R))$	$W(\hat{x}(R))$	$W(\hat{\hat{x}}(R))$
0.0	0.2496	—0.2486	0.326784	0.332388
0.05	0.153	—0.166	0.298003	0.302759
0.075	0.084	—0.102	0.284717	0.287756
0.08857	0.5E-3	—0.020	0.278557	0.278892
0.08858	0.20E-3	—0.018	0.278557	0.278881
0.08859	0.43E-7	—0.018	0.278557	0.278870
0.08860	0.4E-10	—0.018	0.278557	0.278859
0.1	0.41E-13	—0.39E-13	0.278557	0.278557
0.125	0.13E-13	—0.13E-13	0.278557	0.278557

$R_0 = 0.08858629$ $R^* = 0.098$ $\tilde{R} = 0.47786037$

Fitness matrix #10 (2–3)

R	$D(\hat{x}(R))$	$D(\hat{\hat{x}}(R))$	$W(\hat{x}(R))$	$W(\hat{\hat{x}}(R))$
0.0	0.185	—0.029	0.545625	0.527422
0.018	0.126	—0.004	0.536153	0.526828
0.019	0.121	—0.001	0.535618	0.526820
0.01978	0.119	—0.3E-4	0.535198	0.526818
0.01979	0.119	—0.1E-4	0.535193	0.526818
0.01980	0.119	—0.89E-8	0.535188	0.526818
0.01981	0.119	—0.1E-9	0.535182	0.526818
0.02	0.118	—0.36E-11	0.535080	0.526818
0.025	0.093	—0.1E-12	0.532259	0.526818

$R_0 = 0.01979474$ $R^* = 0.040$ $\tilde{R} = 0.48927793$

DISCUSSION

Although no formal stability analysis of the equilibria in $\mathcal{R}^+$ and $\mathcal{R}^-$ has ever been performed, it has previously been assumed that the interval of recombination in which these two equilibria were locally stable was $R < R_0$. We now know that this is not the case. The fact that $D = 0$ and $D \neq 0$ can be simultaneously locally stable was determined by FRANKLIN and FELDMAN (1977) for a class of viability matrices involving five parameters. The classical multiplicative viability model involves four parameters after each locus is normalized to the heterozygote and is endowed with the same property. The phenomenon has occurred in every example chosen, except those in the symmetric case $\alpha_1 = \alpha_3$, $\beta_1 = \beta_3$, and for which the local stability conditions of $D = 0$ and $D \neq 0$ are known not to overlap. It therefore appears that the result can be attributed to *asymmetries* in the viability system producing disequilibria in $\mathcal{R}^+$ and $\mathcal{R}^-$ of different magnitudes. In the FRANKLIN-FELDMAN (1977) model, the two equilibria initially (*i.e.*, at $R = 0$) had disequilibria of the same sign, but different magnitudes. Further, after one of the $D \neq 0$ equilibria had emerged with the $D = 0$ point, the other $D \neq 0$ equilibrium remained stable for all R values to $R = 1/2$. In the present multiplicative case, at $R = R^*$ all three equilibria coalesce into x^*.

Certain observations on the equilibria in $\mathcal{R}^+$ and $\mathcal{R}^-$ are worth making. At $R = 0$, a stable equilibrium in a 3-boundary tends to have a smaller D magnitude than one in a 2-boundary. In all of our runs in which at $R = 0$, there was one stable 3-boundary equilibrium together with a stable 2-boundary equilibrium; the former had the smaller D magnitude and also was the equilibrium that merged at $R = R_0$ with the Hardy-Weinberg point. It is tempting to conjecture that this is a general phenomenon, *i.e.*, that the point with the smaller $|D|$ at $R = 0$ is that which meets $\mathbf{x}^*$ first. However, with two 2-boundary equilibria, this is not necessarily the case (examples 3, 5, 9). Always in our runs that point with the smaller $W(\mathbf{x})$ at $R = 0$ met $\mathbf{x}^*$ first.

The interval of overlap of stability of a $D \neq 0$ with the $D = 0$ equilibrium is generally largest when at $R = 0$ the stable equilibrium configuration is one 3-boundary and one 2-boundary. In our examples the interval $[R_0, R^*]$ was smallest with two 2-boundaries as the initial configuration. The difference in magnitudes of the initial D values is a good gauge to the relative size of the interval of overlap.

The value R_0 where the central equilibrium first becomes stable depends on the initial $(R = 0)$ equilibrium configuration. Thus, when the stable points at $R = 0$ are in the 3–3 or 3–2 configuration, R_0 is in the small to moderate range, usually between 0.005 and 0.05. When the stable equilibria at $R = 0$ are in the 2–2 configuration, R_0 is in the moderate range, usually between 0.05 and 0.15. Obviously the strength of selection is important in determining R_0.

Along each curve $\hat{\mathbf{x}}(R)$ and $\hat{\hat{\mathbf{x}}}(R)$, $|D[\hat{\mathbf{x}}(R)]|$ and $|D[\hat{\hat{\mathbf{x}}}(R)]|$ are invariably strictly decreasing to zero. Similarly, the mean fitness $W[\hat{\mathbf{x}}(R)]$ and $W[\hat{\hat{\mathbf{x}}}(R)]$ are decreasing functions of R. The fact that for general two-locus viability

TABLE 4

Comparison of multiplicative and symmetric viability models

	Multiplicative viabilities (10) with (13)	Symmetric viabilities (9)
Existence of Hardy-Weinberg polymorphism	Equilibrium (11) always exists	$\mathbf{x} = (1/4, 1/4, 1/4, 1/4)$. equilibrium always exists
Tight linkage Stability of the Hardy Weinberg equilibrium	Never stable for $R = 0$, therefore not stable for R small and positive	Can be stable for $R = 0$. If so, then stable for all $0 \leq R \leq 0.5$.
Loose linkage	Always stable for moderate to free recombination ($R > R_0$). Globally stable for $R > R^*$.	Usually stable for free recombination but, depending on fitness values, may not be stable for any R.
Existence of equilibria with $D^* \neq 0$	Always two distinct stable equilibria for $0 < R < R_0$. One is stable also for $R_0 < R < R^*$.	If the Hardy-Weinberg equilibrium for $R = 0$, then usually two stable equilibria with $D \neq 0$ exist for R small. These are not necessarily stable throughout their range of existence, which is complementary to the range of stability of $D = 0$.
Comments		Symmetric viabilities The nonHardy-Weinberg equilibria can, for some fitness arrangements, be stable over two disjoint segments $0 < R < R_1$, $R_2 < R < R_0 = R^*$ (see EWENS 1968; KARLIN and FELDMAN 1970).

models the mean fitness $W[\hat{\mathbf{x}}(R)]$ at a stable curve is not always decreasing as R increases is noted in KARLIN and CARMELLI (1975), although $W[\hat{\mathbf{x}}(R)]$ must decrease for R sufficiently small.

It is interesting to compare properties of the stable equilibria in the general two-locus, two-allele multiplicative viability model (10) with those of the symmetric viability system (9). This is facilitated by Table 4.

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