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The Maintenance of Genetic Variability in Two-Locus Models of Stabilizing Selection

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ABSTRACT

The maintenance of genetic variability at two diallelic loci under stabilizing selection is investigated. Generations are discrete and nonoverlapping; mating is random; mutation and random genetic drift are absent; selection operates only through viability differences. The determination of the genotypic values is purely additive. The fitness function has its optimum at the value of the double heterozygote and decreases monotonically and symmetrically from its optimum, but is otherwise arbitrary. The resulting fitness scheme is identical to the symmetric viability model. Linkage disequilibrium is neglected, but the results are otherwise exact. Explicit formulas are found for all the equilibria, and explicit conditions are derived for their existence and stability. A complete classification of the six possible global convergence patterns is presented. In addition to the symmetric equilibrium (with gene frequency 1/2 at both loci), a pair of unsymmetric equilibria may exist; the latter are usually, but not always, unstable. If the ratio of the effect of the major locus to that of the minor one exceeds a critical value, both loci will be stably polymorphic. If selection is weak at the minor locus, the more rapidly the fitness function decreases near the optimum, the lower is this critical value; for rapidly decreasing fitness functions, the critical value is close to one. If the fitness function is smooth at the optimum, then a stable polymorphism exists at both loci only if selection is strong at the major locus.

THE maintenance of genetic variability in quantitative characters is of fundamental evolutionary importance. The mechanism proposed most widely in studies of this question is the balance between mutation and stabilizing selection. Consult BARTON (1986), BARTON and TURELLI (1987), BÜRGER (1986, 1988, 1989), NARAIN and CHAKRABORTY (1987), SLATKIN (1987), and TACHIDA and COCKERHAM (1988) for recent investigations and references to the earlier work of BULMER, FLEMING, KIMURA, LANDE, LATTER, and TURELLI.

Stabilizing selection toward an intermediate phenotypic optimum has been established for many quantitative characters in natural populations (ENDLER 1986, Ch. 7). Mutation is incorporated because several analyses suggest that stabilizing selection tends to reduce genetic variability in polygenic traits. This view is supported by approximations that focus on a single locus at a time (FISHER 1930, Ch. 5; ROBERTSON 1956; BULMER 1971; KIMURA 1981; NAGYLAKI 1984). WRIGHT's (1935) study of the quadratic optimum model for diallelic loci without epistasis in the determination of the character provides additional support. He neglected linkage disequilibrium and found that at most one locus could be in stable polymorphic equilibrium if dominance was either absent or complete. For two loci with equal effects, complete additivity, arbitrary recombination rate, and an arbitrary symmetric fitness function with optimum at the value of the double heterozygote, HASTINGS (1987) proved that both loci are ultimately fixed.

Stable multilocus polymorphisms can occur in the quadratic optimum model even with equal contributions if there is partial dominance (KOJIMA 1959; LEWONTIN 1964; SINGH and LEWONTIN 1966), epistasis (A. GIMELFARB, unpublished manuscript), or pleiotropy for two characters (GIMELFARB 1986). The combination of stabilizing selection and viability overdominance can also maintain genetic variation (BULMER 1973; GILLESPIE 1984).

In all the investigations of mutation-selection balance cited above, it is assumed that the trait is determined without dominance or epistasis. Therefore, numerical work of GALE and KEARSEY (1968), and KEARSEY and GALE (1968) on completely additive two- and three-locus models of pure stabilizing selection is of particular interest. In contrast to the commonly posited quadratic or Gaussian fitness functions, these authors used a triangular one (*i.e.*, one that decreases linearly from its optimum). They found that all the loci can be stably polymorphic if their effects are sufficiently unequal, and that the amount of disparity required decreases as linkage becomes tighter. However, they did not incorporate a parameter to control the intensity of selection. Since selection is strong in all their examples, even the ones with loose linkage exhibit considerable linkage disequilibrium.

The results of WRIGHT (1935) and GALE and KEAR-

SEY (1968) still leave open the questions of the dependence of the possibility of stable multilocus polymorphism on the intensity of stabilizing selection and on the form of the fitness function. These questions will be answered for two loci in this paper.

We shall see that our fitness scheme is identical to the symmetric viability model. By neglecting linkage disequilibrium, we shall obtain a complete global analysis, which complements the exact, local results of BODMER and FELSENSTEIN (1967) and KARLIN and FELDMAN (1970) on this model.

In the next section, we formulate our model and establish some preliminary results. In the following section, we present explicit formulas for all the equilibria and explicit conditions for their existence and stability. These results provide a complete classification of the six possible global convergence patterns and are proved in the APPENDIX. In the succeeding section, we examine how the amount of disparity between loci and the form of the fitness function affect the maintenance of genetic diversity. Then we treat some specific fitness functions. In the final section, we summarize our main results and discuss extensions and further applications.

FORMULATION

We assume that generations are discrete and nonoverlapping, mating is random, mutation and random genetic drift are absent, and selection operates only through viability differences.

Our sole approximation is to neglect linkage disequilibrium. Suppose that the genotypic fitnesses are constant and there is no position effect; there are arbitrarily many alleles at each of n loci. Let $p_j^{(i)}$ and $w_{i_1j_1,\cdots,i_nj_n}$ denote the frequency of the allele $A_j^{(i)}$ at locus i and the fitness of the genotype $A_{i_1}^{(1)}A_{j_1}^{(1)}\cdots A_{i_n}^{(n)}A_{j_n}^{(n)}$. Then the mean fitness reads

$$\bar{w} = \sum_{i_1,j_1,\cdots,i_n,j_n} w_{i_1j_1,\cdots,i_nj_n} \prod_k p_{i_k}^{(k)} p_{j_k}^{(k)}, \tag{1}$$

which is a polynomial of degree $2n$. The gene frequencies in the next generation are given by

$$p_j^{(i)\prime} = p_j^{(i)} \frac{\partial \bar{w}}{\partial p_j^{(i)}} \Big/ \sum_k p_k^{(i)} \frac{\partial \bar{w}}{\partial p_k^{(i)}}, \tag{2}$$

where all allelic frequencies are treated as independent in the partial differentiation. From the inequality of BAUM and EAGON (1967) we conclude immediately that the mean fitness is nondecreasing: $\bar{w}' \geq \bar{w}$, with equality only at equilibrium. Hence, in this approximation, locating all the stationary points of $\bar{w}$ and determining whether they are maxima provides a global analysis of the evolution of the population.

We specialize now to two diallelic loci. The linkage-equilibrium approximation is accurate for the situation of most biological interest, weak selection (NAGYLAKI 1976; 1977a, pp. 167–177; 1977b). The computations of SINGH and LEWONTIN (1966) and GIMELFARB (1986, unpublished manuscript) and comparison of our results with those of GALE and KEARSEY (1968) suggest that the inclusion of linkage disequilibrium would relax the conditions for the existence of stable two-locus polymorphism without changing them qualitatively.

TABLE 1

The genotypic values

	BB	*Bb*	*bb*
AA	$d+c$	c	$-d+c$
Aa	d	0	$-d$
aa	$d-c$	$-c$	$-d-c$

$d \geq c > 0$.

TABLE 2

The genotypic fitnesses

	BB	*Bb*	*bb*
AA	$1-\delta$	$1-\beta$	$1-\alpha$
Aa	$1-\gamma$	1	$1-\gamma$
aa	$1-\alpha$	$1-\beta$	$1-\delta$

$0 \leq \alpha, \beta \leq \gamma < \delta \leq 1$.

Simplifying the notation, we call the alleles A and a at the first locus and B and b at the second. Let p_1, q_1, p_2, and q_2 designate the frequencies of A, a, B, and b, respectively. The alleles determine the genotypic value, z, purely additively; without loss of generality, we parametrize the contributions of A, a, B, and b to z as $\frac{1}{2}c$, $-\frac{1}{2}c$, $\frac{1}{2}d$, and $-\frac{1}{2}d$ and take $d \geq c > 0$. Thus, we obtain the genotypic values shown in Table 1. We call c and d the effects of the minor and major loci, respectively.

We assume that the genotypic fitnesses depend only on the genotypic value and write them as $w(z)$. We posit that the fitness function $w(z)$ has its optimum at zero, the genotypic value of the double heterozygote; we scale $w(z)$ so that $w(0) = 1$. We suppose that $w(z)$ decreases monotonically from its optimum and is even, $w(-z) = w(z)$. Henceforth, we shall write $w(z)$ only for $z \geq 0$; replacing z by $|z|$ would always produce expressions valid for $-\infty < z < \infty$. With these hypotheses, the genotypic values in Table 1 yield the fitness scheme in Table 2, where

$$\alpha = 1 - w(d-c), \quad \beta = 1 - w(c), \tag{3a}$$

$$\gamma = 1 - w(d), \quad \delta = 1 - w(d+c); \tag{3b}$$

$$0 \leq \alpha, \beta \leq \gamma < \delta \leq 1. \tag{4}$$

We shall repeatedly utilize the simple fact that $\alpha > \beta$ ($\alpha < \beta$) if and only if $d > 2c$ ($d < 2c$). Furthermore, $\beta > 0$ and $\gamma > \alpha$.

The fitness scheme in Table 2 is identical to the symmetric viability model (BODMER and FELSENSTEIN 1967; KARLIN and FELDMAN 1970). Given c and d such that $d \geq c > 0$ and α, β, γ, and δ satisfying (4), there exist infinitely many nonnegative, nonincreasing $w(z)$ that pass through the points $(0, 1)$, $(d - c, 1 - \alpha)$, $(c, 1 - \beta)$, $(d, 1 - \gamma)$, and $(d + c, 1 - \delta)$.

Our fitness scheme is symmetric under the simultaneous interchanges $A \leftrightarrow a$ and $B \leftrightarrow b$, which correspond to $p_1 \leftrightarrow q_1$ and $p_2 \leftrightarrow q_2$, respectively. Therefore, every convergence pattern in the p_1p_2-plane is symmetric under reflection in the point $(\frac{1}{2}, \frac{1}{2})$. In particular, excluding the equilibrium $(\frac{1}{2}, \frac{1}{2})$, the equilibria must occur in pairs (p_1, p_2) and (q_1, q_2).

We shall see that if selection is weak at the minor locus, the possible convergence patterns depend on the behavior of $w(z)$ near the origin. This behavior, in turn, depends on what smoothness hypotheses, if any, we impose on $w(z)$. Although we shall impose none, it is important to see that $w(z)$ must be smooth (*i.e.*, have infinitely many continuous derivatives) under the following set of conditions. Suppose the phenotypic value is the sum of the genotypic value and a stochastically independent environmental contribution. Then the genotypic fitness function can be written as

$$w(z) = \int_{-\infty}^{\infty} W(z + \zeta)\phi(\zeta)d\zeta, \tag{5}$$

where W and ϕ represent, respectively, the phenotypic fitness function and the probability density of the environmental value. If $W(z)$ decreases sufficiently rapidly as $|z| \to \infty$ to be integrable from $-\infty$ to ∞ and ϕ is smooth (*e.g.*, Gaussian), then w is smooth (APOSTOL 1974, p. 328). Thus, smooth $w(z)$ are of particular biological interest.

GENERAL RESULTS

In this section, we locate all the equilibria and present conditions for their stability. This enables us to classify the six possible global convergence patterns, as shown in Table 3 and Figure 1 below. We state our major results as theorems and prove them in the APPENDIX.

We define first some parameter combinations that greatly simplify our formulas:

$$l = \delta + \alpha, \qquad m = \delta - \alpha, \tag{6a}$$

$$\lambda = l - 2\beta, \qquad \rho = 2(\gamma - \beta), \tag{6b}$$

$$\epsilon = l\left(\frac{\lambda^2 - m^2}{\lambda^2 + m^2}\right), \quad \mu = l^2 - 4m^2, \tag{6c}$$

$$f = \tfrac{1}{2}(l - \rho), \qquad h = \tfrac{1}{2}(l + \rho), \tag{7a}$$

$$g = 2(2\gamma - \lambda). \tag{7b}$$

[In BODMER and FELSENSTEIN (1967) and KARLIN and FELDMAN (1970), l denotes $2\gamma - \lambda$, not $\delta + \alpha$.] These parameters satisfy some useful inequalities. Subtracting β from (4) and employing (6a) and (6b), we find

$$\max(0, \lambda - m) \leq \rho < \lambda + m; \tag{8a}$$

in particular,

$$\lambda > -m. \tag{8b}$$

From (6) and (8b) we deduce the bidirectional implications

$$\alpha > \beta \Leftrightarrow \lambda > m \Leftrightarrow \epsilon > 0. \tag{8c}$$

If $\lambda > 0$, we can establish

$$\epsilon^2 > \mu \Leftrightarrow \lambda - 2\beta > \epsilon \tag{8d}$$

by using (6) to prove that both inequalities in (8d) are equivalent to $m^2 > 2\beta\lambda$.

Clearly, the four vertices $(0, 0)$, $(1, 1)$, $(1, 0)$, and $(0, 1)$ of the unit square in the p_1p_2-plane are equilibria. We define

$$P_1 = \{(0, 0), (1, 1)\}, \quad P_2 = \{(1, 0), (0, 1)\}. \tag{9}$$

A glance at Table 2 informs us that there exist no edge equilibria if $\alpha \leq \beta$, whereas there exist the two overdominant ones,

$$p_1 = 0, \quad p_2 = \frac{1}{2} + \frac{m}{2\lambda} > \frac{1}{2}, \tag{10a}$$

$$p_1 = 1, \quad p_2 = \frac{1}{2} - \frac{m}{2\lambda} < \frac{1}{2}, \tag{10b}$$

if $\alpha > \beta$; we call these P_e. Note that (10) satisfies the reflection symmetry $(p_1, p_2) \leftrightarrow (q_1, q_2)$, as it must. By the same symmetry, the point $P_0 = (\frac{1}{2}, \frac{1}{2})$ is an equilibrium. To specify the unsymmetric internal equilibria, set

$$p_1 = \tfrac{1}{2} + x, \quad q_1 = \tfrac{1}{2} - x, \tag{11a}$$

$$p_2 = \tfrac{1}{2} + y, \quad q_2 = \tfrac{1}{2} - y, \tag{11b}$$

so that $-\frac{1}{2} \leq x, y \leq \frac{1}{2}$.

Theorem 1: *(i) Suppose $g \neq 0$. A pair of unsymmetric internal equilibria, $P_\pm$, given by*

$$x = \pm\left[\frac{1}{g}\left(h - m\sqrt{\frac{h}{f}}\right)\right]^{1/2}, \qquad y = -\sqrt{\frac{f}{h}}\,x, \tag{12}$$

exists in Cases a, b, and c in Table 3, but not otherwise. (ii) Suppose $g = 0$. The line of equilibria

$$y = -\frac{m}{h}x \tag{13}$$

TABLE 3

Classification of the convergence patterns and the existence and stability of the equilibria

Case	Conditions			Equilibria P_1	P_2	P_e	P_0	$P_\pm$
a	$\epsilon > \rho$	$\mu < \rho^2$		U	U	U	U	S
b	$\epsilon < \rho$	$\mu > \rho^2$	$\alpha \le \beta$	U	S	—	S	U
c	$\epsilon < \rho$	$\mu > \rho^2$	$\alpha > \beta$	U	U	S	S	U
d	$\epsilon < \rho$	$\mu < \rho^2$	$\alpha \le \beta$	U	S	—	U	—
e	$\epsilon < \rho$	$\mu < \rho^2$	$\alpha > \beta$	U	U	S	U	—
f	$\epsilon > \rho$	$\mu > \rho^2$		U	U	U	S	—

The parameters are defined in Equation 6. P_1, P_2, P_e, P_0, and $P_\pm$ designate the vertices (0, 0) and (1, 1), the vertices (1, 0) and (0, 1), the two edge equilibria (10), the symmetric equilibrium (½, ½), and the two unsymmetric equilibria (12), respectively. The dash, S, and U signify nonexistence, stability, and instability of an equilibrium, respectively. Figure 1 shows the global convergence patterns for the six cases.

exists if and only if $\mu = \rho^2$, *which is equivalent to*

$$\alpha = \beta + \gamma - \sqrt{\beta\gamma}, \quad \delta = \beta + \gamma + \sqrt{\beta\gamma}. \tag{14}$$

In Table 3, Cases d, e, and f complement Cases a, b, and c, excluding the degenerate cases of equality $\epsilon = \rho$ and $\mu = \rho^2$. Notice that, by (8a) and (8c), in Cases a and f $\alpha > \beta$, which is equivalent to $d > 2c$. The full significance of our classification follows from the conditions for stability of the equilibria, which we proceed to consider. We abbreviate *asymptotic stability* as *stability*. Let t designate time in generations.

Table 2 and (4) inform us that, as $t \to \infty$, $p_1(t) \to 1$ along $p_2 = 0$ and $p_1(t) \to 0$ along $p_2 = 1$. Similarly, if $\alpha \le \beta$, $p_2(t) \to 1$ along $p_1 = 0$ and $p_2(t) \to 0$ along $p_1 = 1$. If $\alpha > \beta$, $p_2(t)$ converges along $p_1 = 0$ to the edge equilibrium (10a) and along $p_1 = 1$ to (10b). We conclude that the equilibria (0, 0) and (1, 1) are always unstable, whereas (1, 0) and (0, 1) are stable if $\alpha \le \beta$ and unstable if $\alpha > \beta$.

Our next theorem concerns the stability of the edge equilibria (10), which exist if and only if $\alpha > \beta$.

Theorem 2: *Suppose* $\alpha > \beta$. *The edge equilibria (10) are stable if* $\epsilon < \rho$ *and unstable if* $\epsilon > \rho$. *In the degenerate case* $\epsilon = \rho$, *they are stable if* $g < 0$ *and unstable if* $g > 0$.

The stability of the symmetry point (½, ½), at which the genetic variance is maximized, is of particular interest.

Theorem 3: *The symmetric equilibrium (½, ½) is stable if* $\mu > \rho^2$ *and unstable if* $\mu < \rho^2$.

Thus, each of the three conditions in Table 3 has an immediate meaning. As we proved below (2), the mean fitness is nondecreasing. Therefore, in nondegenerate cases, the gene frequencies must converge to some equilibrium point from all initial conditions, and this enables us to determine the stability of the unsymmetric interior equilibria (12) from that of the other equilibria. In this manner, we obtain the six global convergence patterns shown in Figure 1, corresponding to the six cases in Table 3.

Several features of Table 3 and Figure 1 are interesting. If there is a stable internal equilibrium, it is either P_0, the symmetric one (Cases b, c, and f), or $P_\pm$, the pair of unsymmetric ones (Case a). If $P_\pm$ exists, its stability is opposite to that of P_0. There exists at least one stable internal equilibrium in Cases a, b, c, and f, but the two-locus polymorphism is protected only in Cases a and f. Thus, protection is sufficient, but not necessary, for the existence of a stable internal equilibrium. Moreover, in Cases a and f, as we noted below (14), $d > 2c$, which means that a substantial disparity between the effects of the major and minor loci is necessary, but not sufficient, for protection. Finally, observe that stable internal equilibria are maxima of the mean fitness $\bar{w}$, unstable internal equilibria are saddle points, and internal minima do not exist.

MORAN (1963) proved for two independent diallelic loci with arbitrary fitnesses that, excluding degenerate cases, there exist at most five internal equilibria, of which at most three are stable, and he offered examples in which these bounds are attained. KARLIN and FELDMAN (1970) demonstrated that as many as seven internal equilibria can exist simultaneously in the exact symmetric viability model, and HASTINGS (1985) proved that four of these can be simultaneously stable. Figure 1 establishes that with independent loci, at least under the restriction (4), the generic number of internal equilibria in the symmetric viability model is either one or three, and the number of stable internal equilibria is 0, 1, or 2.

We shall see that Case a seems to occur very rarely. When can it be excluded analytically? In the course of proving Theorem 1, we shall demonstrate that Case a cannot occur if $g > 0$. If several fitness functions $w_i(z)$ satisfy our restrictions (normalization, monotonicity, and symmetry), then so does the fitness function

$$w(z) = \sum_i a_i w_i(z), \quad \sum_i a_i = 1, \tag{15}$$

where the a_i represent positive constants. For each i, we define our parameters by subscripting (3), (6), and (7). Then we calculate α, β, γ, and δ by averaging as in (15); since (6a) and (7b) are linear, we get

$$g = \sum_i a_i g_i. \tag{16}$$

Consequently, if $g_i > 0$ for every i, then $g > 0$. This result helps to exclude Case a for some fitness functions.

Let us prove next that $g > 0$, and hence Case a cannot occur, if $w(z)$ is convex for $z \ge 0$. For all $z_1 \ge 0$ and $z_2 \ge 0$ we have

$$w[\tfrac{1}{2}(z_1 + z_2)] \le \tfrac{1}{2}[w(z_1) + w(z_2)]. \tag{17}$$

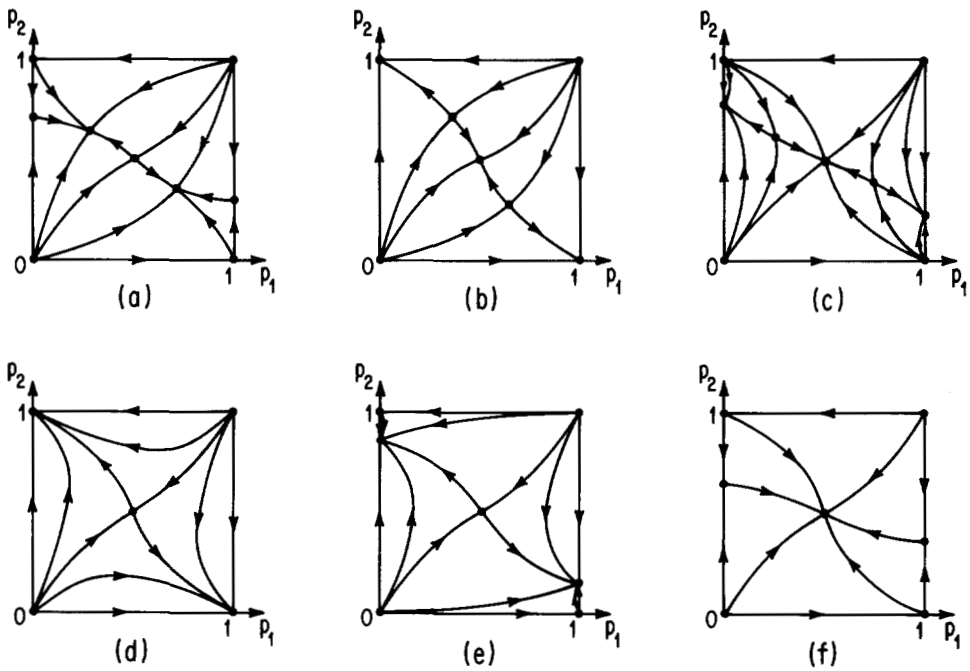

FIGURE 1.—The six possible convergence patterns for the symmetric viability model with independent loci. The coordinates are the gene frequencies at the two loci.

Taking $z_1 = d + c$ and $z_2 = d - c$ in (17) and recalling (3) and (6a), we find $l \leq 2\gamma$; in view of (6b) and (7b), this implies that $g \geq 4\beta > 0$.

We summarize the conclusions of the last two paragraphs in the following proposition. We shall demonstrate by example below (55) that the conditions of Proposition 1 are not necessary.

Proposition 1: *(i) If $g > 0$, Case a cannot occur. (ii) If $w(z)$ is given by (15) and $g_i > 0$ for each i, then $g > 0$. (iii) If $w(z)$ is convex for $z \geq 0$, then $g > 0$.*

We devote the next two sections to extracting the implications of the above general results.

ASYMPTOTIC RESULTS

For each fitness function $w(z)$, the line $d = 2c$ and the boundary curves $\epsilon = \rho$ and $\mu = \rho^2$ divide the wedge $d \geq c > 0$ into at most six regions, each of which corresponds to one of the cases in Table 3. In the next section, we shall exhibit such case maps for some particular fitness functions. Here, we derive general features of case maps in proximate and distal regions of the wedge $d \geq c > 0$ by treating successively (i) equal effects ($c = d$), (ii) strong selection at the major locus ($d \to \infty$ with c fixed), (iii) weak selection at the minor locus ($c \to 0$ with d fixed), (iv) weak selection at both loci ($0 < c \leq d \to 0$), and (v) strong selection at both loci ($d \geq c \to \infty$). If we scale z so that $w(z) \approx 1$ for $|z| \ll 1$ and $w(z) \ll 1$ for $|z| \gg 1$, then we can approximate the limits (ii), (iii), (iv), and (v) by $d \gg 1$, $c \ll 1$, $0 < c \leq d \ll 1$, and $d \geq c \gg 1$, respectively.

Equal effects: If the two loci contribute equally to the character, *i.e.*, $c = d$, then (3) yields $\alpha = 0$ and $\beta = \gamma$. Hence, (6) and (8c) give $l = m = \delta$, $\rho = 0$, $\mu < 0$, and $\epsilon < 0$. We infer from Table 3 that Case d and Figure 1d apply. Consequently, on account of the biological ubiquity of small perturbations, the population converges to either (1, 0) or (0, 1), *i.e.*, ultimately the sole genotype in the population is either *AAbb* or *aaBB*.

HASTINGS (1987) proved this result in the exact model with linkage.

Strong selection at the major locus: We assume that $w(z) \to 0$ as $z \to \infty$ and let $d \to \infty$ with c fixed. From (3), (6), and (7b), we get $\alpha, \gamma, \delta \to 1$, $l \to 2$, $m \to 0$, $\rho \to 2(1 - \beta)$, $\mu \to 4$, and $\epsilon \to 2$. Therefore, Table 3 tells us that Case f applies in this limit. Thus, P_0 is globally stable if selection at the major locus is sufficiently strong. This result is intuitively reasonable: in the limit, all the fitnesses in the first and third columns of Table 2 are zero, so (½, ½) is the globally stable equilibrium.

Our conclusion here seems to disagree with WRIGHT's (1935) result that at most one locus can be in stable polymorphic equilibrium for the quadratic fitness function. The apparent discrepancy is resolved by noting that for the quadratic fitness function (which we shall examine in the next section), the nonnegativity of $w(z)$ imposes an upper bound on d, so one cannot let $d \to \infty$.

Weak selection at the minor locus: We let $c \to 0$ with d fixed. Assume that $w(z)$ has at least three continuous derivatives for $z > 0$ and

$$w(z) = 1 - kz^{\kappa} + o(z^{\kappa}) \tag{18}$$

as $z \to 0+$, where $k > 0$ and $\kappa > 0$ designate constants. By the argument below (5), fitness functions that are smooth even at the origin are especially important. For such $w(z)$, κ must be an even integer, so we usually

TABLE 4

Classification of the convergence patterns for small minor-locus effect

Conditions		Case
$\kappa < 2$		f
$\kappa = 2$	$\eta < k$	f
$\kappa = 2$	$\eta > k$	e
$\kappa > 2$	$\eta \leq 0$	f
$\kappa > 2$	$\eta > 0$	e

The parameters are defined in (18), (20), and (22).

expect $\kappa = 2$, as for the Gaussian fitness function. Employing (18) and Taylor's theorem in (3), we deduce

$$\alpha = \gamma - \sigma c - \tau c^2 + O(c^3), \tag{19a}$$

$$\beta = kc^\kappa + o(c^\kappa), \tag{19b}$$

$$\delta = \gamma + \sigma c - \tau c^2 + O(c^3) \tag{19c}$$

as $c \to 0$, in which σ and τ represent the first and second derivatives

$$\sigma = -w'(d) > 0, \quad \tau = \tfrac{1}{2}w''(d). \tag{20}$$

Inserting (19) into (6) leads to

$$\rho = 2(\gamma - kc^\kappa) + o(c^\kappa), \tag{21a}$$

$$\rho^2 = 4\gamma(\gamma - 2kc^\kappa) + o(c^\kappa), \tag{21b}$$

$$\mu = 4\gamma(\gamma - 2\eta c^2) + O(c^3), \tag{21c}$$

$$\epsilon = 2(\gamma - \eta c^2) + O(c^3) + o(c^\kappa) \tag{21d}$$

as $c \to 0$, where

$$\eta = \tau + 2\gamma^{-1}\sigma^2. \tag{22}$$

From (19a) and (19b) we see that $\alpha > \beta$ for sufficiently small c. Table 3 and (21) inform us that as $c \to 0$ with d fixed, either Case e or Case f applies, as shown in Table 4. According to Table 4, if $w(z)$ decreases rapidly near the optimum ($\kappa < 2$), the symmetric equilibrium (P_0) is globally stable for sufficiently weak selection at the minor locus. This has the important consequence that P_0 is globally stable with arbitrarily weak selection, provided d/c is sufficiently large. If $w(z)$ decreases more slowly near the optimum ($\kappa \geq 2$), the existence of a stable internal equilibrium depends on the major-locus effect (d) and details of the fitness function.

We can obtain more insight for $\kappa \geq 2$ by studying the limits $d \to 0$ and $d \to \infty$ (after taking the limit $c \to 0$). From (18), (20), and (22), we find

$$\eta(d) \sim \tfrac{1}{2}k\kappa(3\kappa + 1)d^{\kappa-2} \tag{23}$$

as $d \to 0$. Hence, Table 4 reveals that Case e holds for sufficiently small d. For most simple fitness functions, $w''(z) > 0$ for sufficiently large z, and $w'(z)$, $w''(z) \to 0$ as $z \to \infty$. Under these conditions, $\eta(d) \to 0+$ as $d \to \infty$, whence Table 4 implies for sufficiently large d that Cases f and e apply for $\kappa = 2$ and $\kappa > 2$, respectively. Thus, if $\kappa \geq 2$, the existence of a stable internal equilibrium requires strong selection at the major locus. These observations further support the conclusion of the previous paragraph that rapid decrease of $w(z)$ near the origin enhances the opportunity for stable polymorphism.

Weak selection at both loci: We have already proved that Case f applies as $d \to \infty$ with c fixed. By Table 4, if $\kappa < 2$ in (18), then Case f also applies as $c \to 0$ with d fixed. We conclude that if $\kappa < 2$, the boundary curves $\epsilon = \rho$ and $\mu = \rho^2$ must emanate from the origin. Therefore, we assume that $\kappa < 2$ and seek their slopes at the origin. These will yield the classification of the convergence patterns in the weak-selection limit ($0 < c \leq d \to 0$) for fitness functions that decrease rapidly near the optimum ($\kappa < 2$).

We put

$$\xi = d/c \tag{24}$$

and assume ξ remains bounded as $c \to 0$. Appealing to (3) and (18), we derive

$$\alpha = kc^\kappa(\xi - 1)^\kappa + o(c^\kappa), \tag{25a}$$

$$\beta = kc^\kappa + o(c^\kappa), \tag{25b}$$

$$\gamma = kc^\kappa\xi^\kappa + o(c^\kappa), \tag{25c}$$

$$\delta = kc^\kappa(\xi + 1)^\kappa + o(c^\kappa) \tag{25d}$$

as $c \to 0$ with ξ bounded. In the limit $c \to 0$, we obtain the slopes ξ_ϵ and ξ_μ of $\epsilon = \rho$ and $\mu = \rho^2$, respectively, at the origin.

Consider first $\epsilon = \rho$. Inserting (25) into (6) and letting $c \to 0$ lead to

$$(\lambda_0 + 2)(\lambda_0^2 - m_0^2) = 2(\xi_\epsilon^\kappa - 1)(\lambda_0^2 + m_0^2), \tag{26a}$$

where

$$\lambda_0 = (\xi_\epsilon + 1)^\kappa + (\xi_\epsilon - 1)^\kappa - 2, \tag{26b}$$

$$m_0 = (\xi_\epsilon + 1)^\kappa - (\xi_\epsilon - 1)^\kappa. \tag{26c}$$

By (8c) and (24), $\epsilon < 0 < \rho$ if $\xi < 2$, so we investigate (26) only in $[2, \infty)$; assertions of uniqueness refer only to this interval. If $\kappa = 1$, it is easy to see that (26) has the unique root $\xi_\epsilon = 2 + \sqrt{2}$. We offer some numerical examples in Table 5; the roots appear to be unique.

Intuition and Table 5 suggest that $\xi_\epsilon \to 2+$ as $\kappa \to 0+$. This observation enables us to approximate ξ_ϵ for $\kappa \ll 1$. We substitute

$$\xi_\epsilon = 2 + \omega_\epsilon \tag{27}$$

into (26) and expand as $\kappa \to 0+$ and $\omega_\epsilon \to 0+$; we find

$$\begin{aligned}\omega_\epsilon &= [\tfrac{1}{2}(\ln 2)(\ln 3)]\,\kappa + O(\omega_\epsilon^2 + \kappa\omega_\epsilon) \\ &= [\tfrac{1}{2}(\ln 2)(\ln 3)]\,\kappa + O(\kappa^2)\end{aligned} \tag{28}$$

TABLE 5

The slopes of the boundary curves $\epsilon = \rho$ and $\mu = \rho^2$ at the origin

κ	ξ_ϵ	ξ_μ
0.25	2.122	1.025
0.50	2.322	1.255
0.75	2.678	1.688
1.00	3.414	2.500
1.25	5.492	4.694
1.50	17.70	17.24
1.75	894.5	894.5

The parameters are defined in (6), (18), and (24).

as $\kappa \to 0$. The constant in brackets is about 0.3808. Equation 28 is fairly accurate even for κ as large as 0.25, in which case the relative error is 1.2%.

Intuition and Table 5 also indicate that $\xi_\epsilon \to \infty$ as $\kappa \to 2-$. Therefore, we set

$$\nu_\epsilon = 1/\xi_\epsilon \tag{29}$$

and rewrite (26) as

$$(\lambda_1 + 2\nu_\epsilon^\kappa)(\lambda_1^2 - m_1^2) = 2(1 - \nu_\epsilon^\kappa)(\lambda_1^2 + m_1^2), \tag{30a}$$

where

$$\lambda_1 = (1 + \nu_\epsilon)^\kappa + (1 - \nu_\epsilon)^\kappa - 2\nu_\epsilon^\kappa, \tag{30b}$$

$$m_1 = (1 + \nu_\epsilon)^\kappa - (1 - \nu_\epsilon)^\kappa. \tag{30c}$$

Expanding (30) as $\nu_\epsilon \to 0$, we deduce

$$\nu_\epsilon^s = \theta^{-1} + O(\nu_\epsilon^\kappa) = \theta^{-1}[1 + O(\nu_\epsilon^\kappa)], \tag{31a}$$

where

$$s = 2 - \kappa, \quad \theta = \tfrac{1}{2}\kappa(3\kappa + 1). \tag{31b}$$

From (31a) we get

$$\begin{aligned}\xi_\epsilon &= \theta^{1/s}[1 + O(s^{-1}\xi_\epsilon^{-\kappa})] \\ &= \theta^{1/s}[1 + O(s^{-1}\theta^{-\kappa/s})]\end{aligned} \tag{32}$$

as $s \to 0+$. This approximation has an error of 3.9% for $\kappa = 1.50$, but only about 0.01% for $\kappa = 1.75$. The expansion

$$\theta^{1/s} = e^{-13/14}7^{1/s}[1 + O(s)] \tag{33}$$

exhibits the extremely rapid divergence of ξ_ϵ as $s \to 0$.

We turn now to $\mu = \rho^2$. Substituting (6a) into (6c), we have

$$\mu = (3\delta - \alpha)(3\alpha - \delta). \tag{34}$$

Consequently, in the limit $c \to 0$, (6b), (25), and (34) yield

$$\begin{aligned}[3(\xi_\mu + 1)^\kappa - (\xi_\mu - 1)^\kappa][3(\xi_\mu - 1)^\kappa - (\xi_\mu + 1)^\kappa] \\ = 4(\xi_\mu^\kappa - 1)^2.\end{aligned} \tag{35}$$

Since $d \geq c$, we examine (35) only in $[1, \infty)$; all assertions of uniqueness are confined to this interval. If $\kappa = 1$, we can see easily that (35) has the unique solution $\xi_\mu = 5/2$. The roots in Table 5 appear to be unique. Observe that, as the case maps in the next section suggest, $\xi_\epsilon > \xi_\mu$ in Table 5.

TABLE 6

Classification of the convergence patterns for weak selection with $0 < \kappa < 2$

Condition	Case
$1 \leq \xi < \min(2,\xi_\mu)$	d
$\min(2,\xi_\mu) < \xi < \max(2,\xi_\mu)$	b or e
$\max(2,\xi_\mu) < \xi < \xi_\epsilon$	c
$\xi > \xi_\epsilon$	f

The parameters are defined in (18), (24), and Table 5. In the second line, Case b applies if $\xi_\mu < 2$ and Case e does if $\xi_\mu > 2$. The inequality $\xi_\mu < 2$ holds if and only if $\kappa \lesssim 0.8690$.

Evidently, $\xi_\mu \to 1+$ as $\kappa \to 0+$. We insert

$$\xi_\mu = 1 + \omega_\mu \tag{36}$$

into (35) and rearrange it in the form

$$3\omega_\mu^\kappa - (2 + \omega_\mu)^\kappa = \frac{4[(1 + \omega_\mu)^\kappa - 1]^2}{3(2 + \omega_\mu)^\kappa - \omega_\mu^\kappa}. \tag{37}$$

Since the denominator on the right side of (37) exceeds 2 for $0 < \omega_\mu < 1$, therefore, as $\kappa \to 0+$ and $\omega_\mu \to 0+$, (37) becomes

$$3\omega_\mu^\kappa - (2 + \omega_\mu)^\kappa = O(\kappa^2\omega_\mu^2). \tag{38}$$

Hence,

$$3^{1/\kappa}\omega_\mu = (2 + \omega_\mu)[1 + O(\kappa\omega_\mu^2)], \tag{39}$$

which has the solution

$$\begin{aligned}\omega_\mu &= \frac{2}{3^{1/\kappa} - 1}[1 + O(\kappa\omega_\mu^2)] \\ &= \frac{2}{3^{1/\kappa} - 1}[1 + O(\kappa/3^{2/\kappa})]\end{aligned} \tag{40}$$

as $\kappa \to 0$. Equation 40 is accurate even if κ is as large as 0.25: then the error is 0.44%. According to (40), $\omega_\mu \to 0$ extremely rapidly as $\kappa \to 0$; *e.g.*, $\omega_\mu \approx 3.387 \times 10^{-5}$ if $\kappa = 0.10$.

Manifestly, $\xi_\mu \to \infty$ as $\kappa \to 2-$. Setting $\nu_\mu = 1/\xi_\mu$ as in (29) and expanding (35) as $\nu_\mu \to 0$, we find that ν_μ satisfies (31). We conclude that ξ_μ is also given by (32). Thus, $\xi_\epsilon/\xi_\mu \to 1$ as $\kappa \to 2$. Equation 32 is fairly accurate even for κ as small as 1.50: then the error is 1.3%; if $\kappa = 1.75$, the error is only about 0.01%.

Invoking Table 3, we obtain the classification of the convergence patterns in Table 6. In the second line, Case b applies if $\xi_\mu < 2$ and Case e does if $\xi_\mu > 2$. By setting $\xi_\mu = 2$ and solving for κ in (35), we deduce that $\xi_\mu < 2$ if and only if $\kappa \lesssim 0.8690$. Tables 5 and 6 demonstrate that, in the weak-selection limit, the more rapidly the fitness function decreases near the

optimum, the less stringent are the conditions for locally ($\xi > \xi_\mu$) and globally ($\xi > \xi_\epsilon$) stable two-locus polymorphism. If the decrease is fairly rapid ($\kappa \lesssim 0.25$), only a very slight disparity between the effects of the major and minor loci is required for local stability. This disparity must be substantial, however, for $\kappa \gtrsim 1$, and it increases extremely fast as $\kappa \to 2$. The condition for global stability is more restrictive: $\xi > 2$ is necessary but not sufficient.

Strong selection at both loci: In this subsection, we assume that $w(z) \to 0$ as $z \to \infty$ and investigate the boundary curves $\epsilon = \rho$ and $\mu = \rho^2$ in the limit $d \geq c \to \infty$.

As $c \to \infty$, (3) yields $\beta, \gamma, \delta \to 1$, whence (6b) gives $\rho \to 0$. Therefore, $\epsilon \to 0$ along $\epsilon = \rho$ and $\mu \to 0$ along $\mu = \rho^2$. Since $d = 2c$ and $\epsilon = 0$ are equivalent by (8c), we expect $\epsilon = \rho$ to be asymptotic to $d = 2c$.

On account of (34), $\mu = 0$ is equivalent to $\delta = 3\alpha$. Thus, we expect $\mu = \rho^2$ to be asymptotic to

$$1 - w(d + c) = 3[1 - w(d - c)]. \tag{41}$$

As $c \to \infty$, the left side of (41) converges to one, so

$$w(d - c) \to 2/3. \tag{42}$$

Consequently, we expect $\mu = \rho^2$ to be asymptotic to the line

$$d = c + r, \quad w(r) = 2/3. \tag{43}$$

Since $w(z)$ decreases monotonically from 1 to 0 as z increases from 0 to ∞, there exists a unique constant r in $(0, \infty)$.

EXAMPLES

Here we illustrate the results of the last two sections by classifying the convergence patterns for some specific fitness functions.

The quadratic fitness function: Scaling c and d in terms of the selection intensity allows us to take

$$w(z) = 1 - z^2, \quad 0 \leq z \leq 1, \tag{44}$$

without loss of generality. From (3), (6), and (44), we find

$$\rho = 2(d^2 - c^2), \tag{45a}$$

$$\mu = 4(d^4 - 14c^2d^2 + c^4), \tag{45b}$$

$$\epsilon = 2(d^2 + c^2)\frac{d^2 - 4c^2}{d^2 + 4c^2}. \tag{45c}$$

Trivial manipulation of (45) yields $\epsilon < \rho$ and $\mu < \rho^2$, so Table 3 gives Case d for $d \leq 2c$ and Case e for $d > 2c$. Thus, in agreement with WRIGHT (1935), at most one locus can segregate stably. This was discussed further in the last section.

The triangular fitness function: On the appropriate scale, we have

$$w(z) = 1 - z, \quad 0 \leq z \leq 1. \tag{46}$$

Employing (3), (6), (24), and (46) leads to

$$\rho = 2c(\xi - 1), \tag{47a}$$

$$\mu = 4c^2(\xi^2 - 4), \tag{47b}$$

$$\epsilon = \frac{2c\xi^2(\xi - 2)}{\xi^2 - 2\xi + 2}, \tag{47c}$$

whence we see easily that $\epsilon > \rho$ and $\mu > \rho^2$ are equivalent to $\xi > 2 + \sqrt{2}$ and $\xi > 5/2$, in agreement with (26) and (35), respectively. Table 3 then yields Table 7, excluding $\xi = 5/2$ and $\xi = 2 + \sqrt{2}$. To classify these two values, note first that $g = 4c > 0$, so the line of equilibria (13) does not exist. If $\xi = 5/2$, then $\epsilon < \rho$, so the edge equilibria P_e are stable by Theorem 2, and hence P_0 is unstable. Therefore, Figure 1e applies. If $\xi = 2 + \sqrt{2}$, then $\mu > \rho^2$, so P_0 is stable by Theorem 3, and hence the pair P_e is unstable. Therefore, Figure 1f applies.

TABLE 7

Classification of the convergence patterns for the triangular fitness function

Condition	Case
$1 \leq \xi \leq 2$	d
$2 < \xi \leq 5/2$	e
$5/2 < \xi < 2 + \sqrt{2}$	c
$\xi \geq 2 + \sqrt{2}$	f

$\xi = d/c$.

The fitness function (46) generalizes that of GALE and KEARSEY (1968) to arbitrary selection intensity (their $1 + k$ is our ξ). We have found that there exists a stable internal equilibrium if and only if the ratio of the effects of the major and minor loci, ξ, exceeds 5/2; the stability is global if and only if $\xi \geq 2 + \sqrt{2}$. GALE and KEARSEY (1968) incorporate linkage and find numerically that, for a fixed, large selection coefficient, the critical value of ξ increases from about 1.2 to about 2.0 as the recombination frequency increases from 0.05 to 0.50. Since all their examples exhibit considerable linkage disequilibrium, it is not surprising that their critical values do not approach 5/2, as they would for weak selection. By neglecting linkage disequilibrium, we have obtained critical values that are independent of the selection intensity and higher than the exact ones.

The Gaussian fitness function: Our most important example is

$$w(z) = e^{-z^2}. \tag{48}$$

Let us prove first that $g > 0$; by Proposition 1, this implies that Case a does not occur. Appealing to (3), (6a), (6b), (7b), and (48), we obtain

$$g = 2[2(1 - e^{-c^2} - e^{-d^2}) + u], \tag{49a}$$

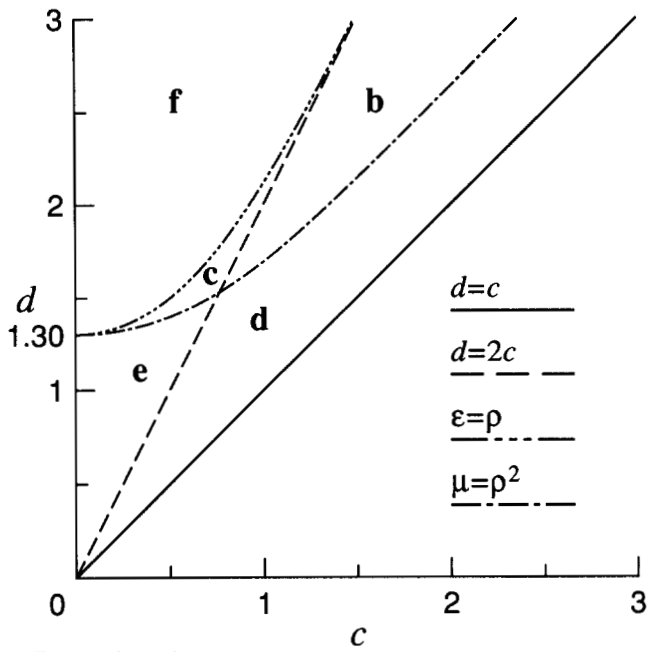

FIGURE 2.—The case map for the Gaussian fitness function (31). The boldface letters refer to the cases in Table 3 and Figure 1. The coordinate c designates the effect of the minor locus; d is that of the major one. The other parameters are defined in Equations 3 and 6.

where

$$u = e^{-(d+c)^2} + e^{-(d-c)^2}$$
$$= 2e^{-c^2-d^2}\cosh(2cd) > 2e^{-c^2-d^2}. \qquad (50)$$

Substituting (50) into (49a) produces

$$g > 4(1 - e^{-c^2})(1 - e^{-d^2}) > 0. \qquad (51)$$

Second, from (18), (20), (22), and (48), we find that $\eta < k$ if and only if

$$e^{2v} - 2ve^{v} - 6v - 1 > 0, \qquad (52)$$

where $v = d^2$. It is easy to see that the equation associated with the inequality (52) has a unique positive root. Evaluating it numerically, we infer from Table 4 (since $\kappa = 2$ here) that, as $c \to 0$, Case e applies for $d < d_0 \approx 1.301$, whereas Case f applies for $d > d_0$.

Third, the asymptotic parameter in (43) is $r = (\ln 3/2)^{1/2} \approx 0.6368$.

The case map exhibited in Figure 2 agrees with the above analytic results. As expected, it shows that for weak selection one may use the quadratic fitness function (44). The symmetric equilibrium (P_0) is stable above the curve $\mu = \rho^2$; the unsymmetric equilibria ($P_\pm$) are unstable when they exist (Cases b and c), and then the stability of P_0 is not global. The most important conclusion from Figure 2 is that, even for arbitrarily weak selection at the minor locus, strong selection at the major locus ($d > d_0$) is necessary for the maintenance of genetic variability at both loci.

The case map for

$$w(z) = 1/(1 + z^2) \qquad (53)$$

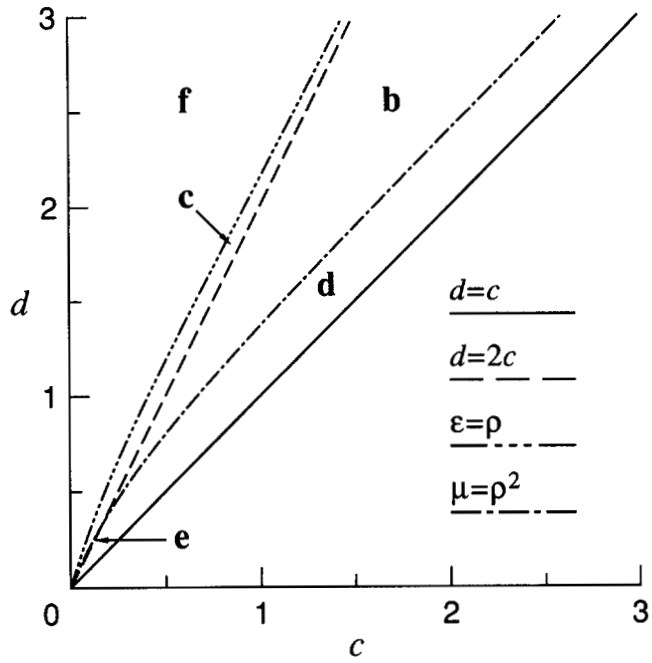

FIGURE 3.—The case map for the double-exponential fitness function (37).

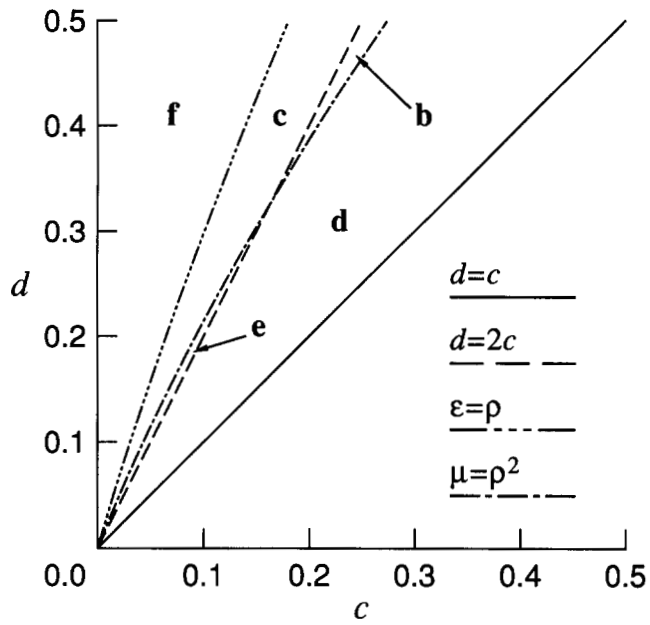

FIGURE 4.—The case map for the double-exponential fitness function (37) near the origin.

is qualitatively identical to Figure 2. Direct algebra establishes that $g > 0$. Now $d_0 \approx 1.094$ and $r = 1/\sqrt{2} \approx 0.7071$.

The double-exponential fitness function: For

$$w(z) = e^{-z}, \quad z \geq 0, \qquad (54)$$

by Proposition 1, convexity implies that $g > 0$ and thus excludes Case a. Since $\kappa = 1 < 2$, Table 4 tells us that Case f applies if c is sufficiently small. In (43), we have $r = \ln 3/2 \approx 0.4055$. The case map in Figure 3

displays these features. Near the optimum ($|z| \ll 1$), (46) approximates (54). Therefore, as expected and shown in Figure 4, for weak selection ($d \ll 1$) the case map for (54) agrees with Table 7. Thus, the discussion below (47) is pertinent here.

Slow decrease near the optimum: In Figure 5, we exhibit the case map for

$$w(z) = e^{-z^4}. \tag{55}$$

Here, $\kappa = 4 > 2$. Although Figure 5 shows that Case a does not occur, a Taylor series establishes that $g < 0$ if d is sufficiently small. Thus, the conditions in Proposition 1 are not necessary. It is not difficult to prove, however, that $\eta > 0$. Hence, in agreement with Figure 5, in which the boundary curves are asymptotic to, but do not reach, the ordinate, Table 4 demonstrates that Case e applies as $c \to 0$. Figure 5 exemplifies the fact that if $w(z)$ decreases slowly near the optimum, then strong selection (here, $d \gtrsim 1.719$; the minimum occurs at $c \approx 0.4287$) is required for stable polymorphism at both loci. Furthermore, if selection is very weak at the minor locus ($c \ll 1$), then it must be very strong at the major locus ($d \gg 1$).

The case map is similar for

$$w(z) = 1/(1 + z^4), \tag{56}$$

except that the rate of convergence of the boundary curves to their asymptotes is much slower. Again, one can prove that $\eta > 0$, thereby confirming analytically the most interesting feature of the case map.

An example with Case a: The attentive reader may have noticed that Case a (the only one with stable unsymmetric equilibria) occurs neither in any of the limits in the previous section nor in any of the above examples. In fact, despite an extensive numerical search, no smooth fitness function for which Case a occurs has been found. The fitness function

$$w(z) = \begin{cases} e^{-b_1 z}, & 0 \le z \le 1, \\ e^{-b_1 - b_2 z^*} \sum_{n=0}^{3} \dfrac{(b_3 z^*)^n}{n!}, & z > 1, \end{cases} \tag{57a}$$

$$b_3 = b_2 - b_1, \quad z^* = z - 1 \tag{57b}$$

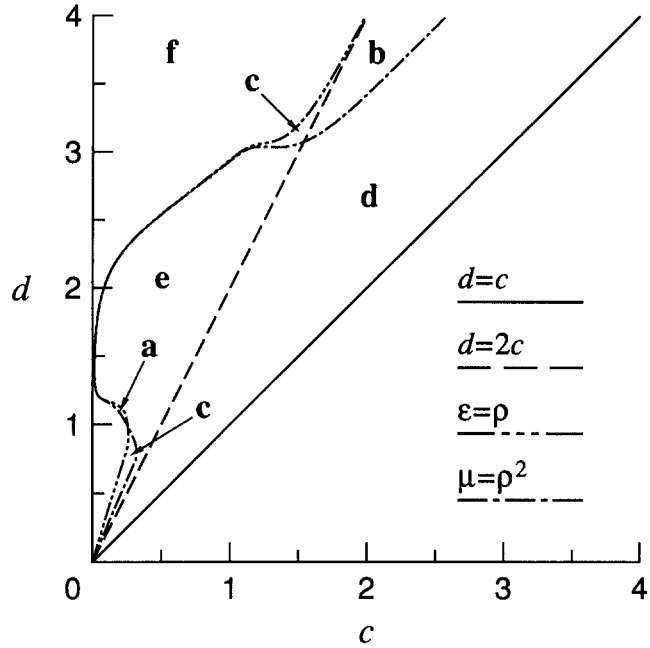

FIGURE 6.—The case map for the fitness function (57). The boundary curves approach the ordinate very closely, but do not touch it.

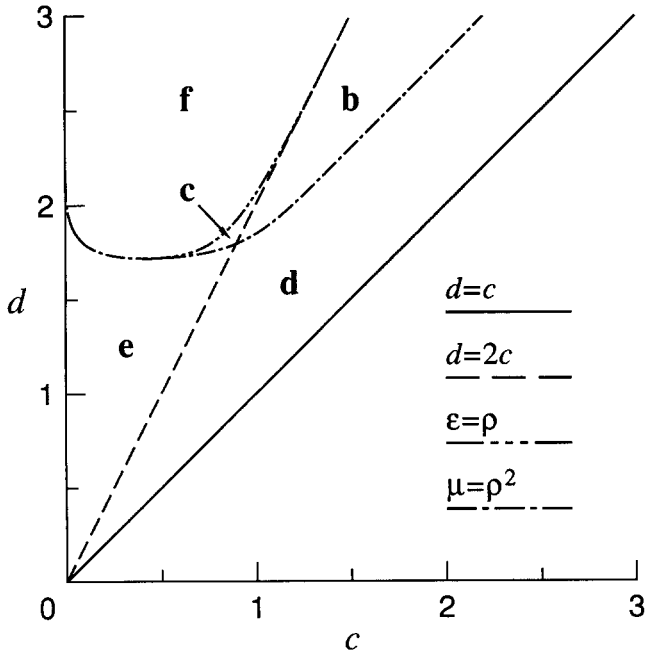

FIGURE 5.—The case map for $w(z) = e^{-z^4}$. The boundary curves are asymptotic to, but do not reach, the ordinate.

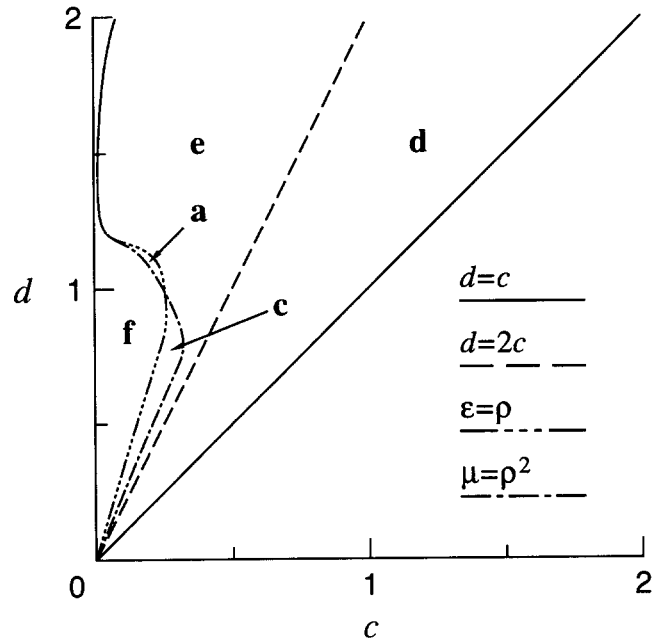

FIGURE 7.—The case map for the fitness function (57) near the origin.

has exactly three continuous derivatives if $b_1 \neq b_2$. Choosing $b_1 = 0.1$ and $b_2 = 6.0$, we obtain the case map in Figures 6 and 7, of which Case a occupies a small region. Note that the relative rate of decrease of $w(z)$ is much greater for $z > 1$ than for $0 < z \leq 1$. Although the boundary curves approach the ordinate very closely, by Table 4 (since $\kappa = 1$ here) they cannot touch it for $d > 0$.

DISCUSSION

Here we recapitulate our main results and discuss extensions and further applications. Our sole approximation was to neglect linkage disequilibrium. Therefore, our results are most accurate for weak selection. As explained below (2), we expect the inclusion of linkage disequilibrium to relax the conditions for the existence of stable two-locus polymorphism without changing them qualitatively.

Our two-locus model of stabilizing selection is identical to the symmetric viability model in Table 2, with the restriction (4) on the selection coefficients. In addition to the four vertex equilibria P_1 and P_2, given by (9), the two edge equilibria P_e, given by (10), and the symmetric equilibrium P_0: (½, ½), there may be (generically) two unsymmetric equilibria $P_\pm$, as specified in Theorem 1. Theorems 2 and 3 give conditions for the stability of P_e and P_0. A complete classification of the six possible global convergence patterns is presented in Table 3 and Figure 1. The unsymmetric equilibria are stable only in Case a, and, as discussed at the end of the last section, this does not seem to occur for most simple, smooth fitness functions $w(z)$.

If selection at the major locus is sufficiently strong, Case f applies, *i.e.*, the symmetric polymorphism P_0 (where the genetic variance is maximal) is globally stable. As shown in Table 4, if $w(z)$ decreases rapidly near the optimum [$\kappa < 2$ in (18)], P_0 is globally stable for sufficiently weak selection at the minor locus. Tables 4, 5, and 6 and Equations 26, 28, 32, 35, and 40 reveal that, at least for weak selection at the minor locus, the more rapid the decrease of $w(z)$ near the optimum, the greater is the opportunity for stable polymorphism. For weak selection at both loci, if this decrease is fairly rapid ($\kappa \lesssim 0.25$), even a very slight disparity between the effects of the major and minor loci produces local stability of P_0. This disparity must be substantial, however, for $\kappa \gtrsim 1$, and it increases extremely fast as $\kappa \to 2$. The condition for global stability of P_0 is more stringent: it is necessary, but not sufficient, that the disparity $d/c > 2$.

Figure 2 demonstrates that for the Gaussian fitness function (which has $\kappa = 2$), strong selection at the major locus ($d \gtrsim 1.301$) is necessary for the maintenance of genetic variability at both loci. This conclusion holds for all fitness functions that are smooth at the optimum. As Figure 5 exemplifies, if $w(z)$ decreases slowly near the optimum ($\kappa > 2$) and selection is weak at the minor locus, then selection must be very strong at the major locus.

Despite the biological simplicity of the model treated here, its analysis requires considerable algebra. Therefore, the study of the model's natural extensions is likely to be more numerical than analytic and much less complete than our investigation. The incorporation of linkage disequilibrium would determine the accuracy of our approximation for various parameter combinations. Would moving the optimum to an arbitrary point affect our results qualitatively? The importance of generalizing to multiple loci is obvious. Yet settling even the simplest question appears to be nontrivial: If we neglect linkage disequilibrium and posit equal effects, we expect instability of the symmetric polymorphism (with gene frequency

TABLE 8

Classification of the convergence patterns for GIMELFARB's (1986) pleiotropic model

Case	Condition
A	$s_2 \leq s_1/(3 + s_1)$
B	$s_1/(3 + s_1) < s_2 < \frac{1}{3}s_1$
C	$\frac{1}{3}s_1 \leq s_2 \leq s_1$

The parameters are defined in (58); $0 < s_2 \leq s_1 \leq \frac{1}{4}$. Figure 8 shows the global convergence patterns in the three cases.

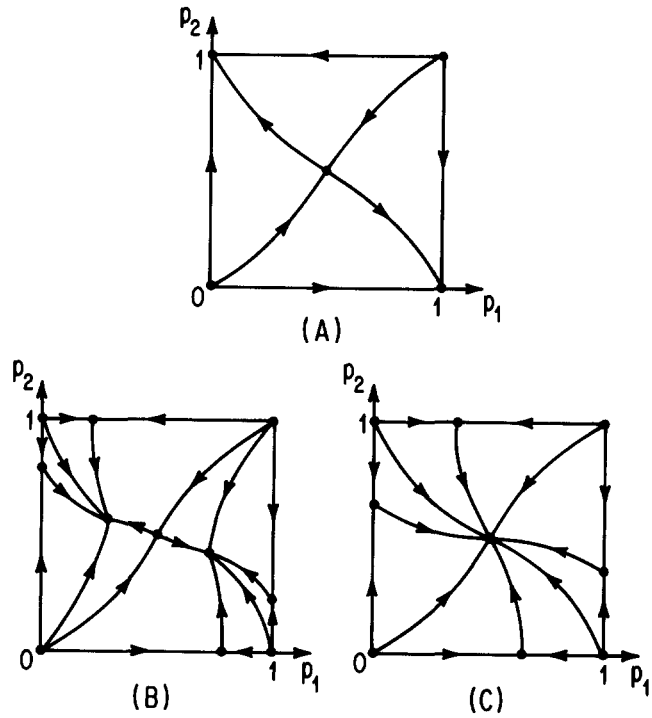

FIGURE 8.—The three possible convergence patterns for GIMELFARB's (1986) pleiotropic model. The coordinates are the gene frequencies at the two loci.

1/2 at each locus) for any symmetric, monotone decreasing fitness function. Instability for two loci suggests, but does not prove, multilocus instability.

Our results and approach have other, closely related applications. GIMELFARB (1986) noted that his two-locus model of pleiotropy for two quantitative characters is a special case of the symmetric viability model:

$$\alpha = 4s_2, \quad \delta = 4s_1, \tag{58a}$$

$$\beta = \gamma = s_1 + s_2 - s_1 s_2, \tag{58b}$$

where s_1 and s_2, $0 < s_2 \leq s_1 \leq 1/4$, denote the intensities of quadratic stabilizing selection on the two characters. Since $\beta = \gamma$ here, this model is much easier to analyze than the general one in Table 2, Nevertheless, slight modifications of our results are required because $\gamma < \alpha$ is possible, so that (4) may not hold. The four edge equilibria

$$x = \mp 1/2, \quad y = \pm(s_1 - s_2)/(s_1 + s_2 + s_1 s_2), \tag{59a}$$

$$x = \pm(s_1 - s_2)/(s_1 + s_2 + s_1 s_2), \quad y = \mp 1/2 \tag{59b}$$

exist if and only if $s_1/(3 + s_1) < s_2 \leq s_1$. The pair of unsymmetric internal equilibria

$$x = \pm[(s_1 - 3s_2)/(4s_1 s_2)]^{1/2}, \quad y = -x \tag{60}$$

exists if and only if $s_1/(3 + s_1) < s_2 < 1/3 s_1$.

In Table 8, we classify the three possible convergence patterns exhibited in Figure 8. If selection on one character is considerably stronger than on the other, Case A applies and both loci are ultimately fixed. In a narrow range of appreciable disparity between the two selection intensities, Case B applies and the gene frequencies converge to one of the two unsymmetric polymorphisms. If the disparity is at most a factor of three, there is global convergence to the symmetric polymorphism (Case C).

These approximate analytic results agree completely with GIMELFARB's (1986) numerical examples. For various combinations of s_1 and s_2, he computed for the exact model the maximum value of the recombination frequency, r^*, for which a stable symmetric polymorphism exists. He found that $r^* < 1/2$ for $s_1/s_2 \geq 4$ and $r^* = 1/2$ for $s_1/s_2 \leq 3$; he did not study the unsymmetric equilibria.

A. GIMELFARB's (unpublished manuscript) two-locus epistatic model is invariant under the interchange of the gene frequencies at the two loci ($p_1 \leftrightarrow p_2$), unlike the symmetric viability model, which is invariant under the simultaneous interchange of each gene frequency and its complement ($p_1 \leftrightarrow q_1$ and $p_2 \leftrightarrow q_2$). Therefore, this model requires a new analysis.

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APPENDIX

Here we prove Theorems 1, 2, and 3. Let $w_{1,11}$, $w_{1,12}$, $w_{1,22}$, $w_{2,11}$, $w_{2,12}$, and $w_{2,22}$ represent the marginal fitnesses of AA, Aa, aa, BB, Bb, and bb individuals, respectively. Then we can express the mean fitness in the two convenient forms ($i = 1, 2$)

$$\bar{w} = w_{i,11}p_i^2 + 2w_{i,12}p_iq_i + w_{i,22}q_i^2, \tag{A1}$$

and Table 2 yields

$$w_{1,11} = 1 - \delta p_2^2 - 2\beta p_2q_2 - \alpha q_2^2, \tag{A2a}$$

$$w_{1,12} = 1 - \gamma(p_2^2 + q_2^2), \tag{A2b}$$

$$w_{1,22} = 1 - \alpha p_2^2 - 2\beta p_2q_2 - \delta q_2^2; \tag{A2c}$$

$$w_{2,11} = 1 - \delta p_1^2 - 2\gamma p_1q_1 - \alpha q_1^2, \tag{A3a}$$

$$w_{2,12} = 1 - \beta(p_1^2 + q_1^2), \tag{A3b}$$

$$w_{2,22} = 1 - \alpha p_1^2 - 2\gamma p_1q_1 - \delta q_1^2. \tag{A3c}$$

We need the first two partial derivatives of $\bar{w}$; when calculating these [in contradistinction to the definition in (2)], we always set $q_i = 1 - p_i$ ($i = 1, 2$). From (A1), (A2), (A3), (6), (7), and (11), we obtain

$$\frac{1}{2}\frac{\partial \bar{w}}{\partial p_i} = w_{i,12} - w_{i,22} + (w_{i,11} - 2w_{i,12} + w_{i,22})p_i; \tag{A4}$$

$$-\frac{1}{2}\frac{\partial \bar{w}}{\partial p_1} = my + (f - gy^2)x, \tag{A5a}$$

$$-\frac{1}{2}\frac{\partial \bar{w}}{\partial p_2} = mx + (h - gx^2)y; \tag{A5b}$$

$$\frac{1}{2}\frac{\partial^2 \bar{w}}{\partial p_1^2} = \rho - \lambda - gp_2q_2 \tag{A6a}$$

$$= \tfrac{1}{2}(\rho - \lambda) - \beta + gy^2, \tag{A6b}$$

$$\frac{1}{2}\frac{\partial^2 \bar{w}}{\partial p_2^2} = -\lambda - gp_1q_1 \tag{A7a}$$

$$= -\tfrac{1}{2}(\rho + \lambda) - \beta + gx^2, \tag{A7b}$$

$$\frac{1}{2}\frac{\partial^2 \bar{w}}{\partial p_1\partial p_2} = -m + \tfrac{1}{2}g(p_1 - q_1)(p_2 - q_2) \tag{A8a}$$

$$= -m + 2gxy. \tag{A8b}$$

Proof of Theorem 1: To locate the unsymmetric internal equilibria, we assume that $x \neq 0$ or $y \neq 0$, and set (A5) equal to zero. By (A5), $x = 0$ if and only if $y = 0$, so we assume $xy \neq 0$, which implies

$$(f - gy^2)(h - gx^2) \neq 0. \tag{A9}$$

Therefore, (A5) gives

$$x = -\frac{my}{f - gy^2}, \quad y = -\frac{mx}{h - gx^2}. \tag{A10}$$

Multiplying these equations, dividing by $xy \neq 0$, and eliminating y lead to

$$m^2h = f(h - gx^2)^2. \tag{A11}$$

Since, by (7a), $h > 0$, therefore (A11) has a solution only if $f > 0$, which is equivalent to

$$\rho < l, \tag{A12}$$

and then (A11) gives

$$gx^2 = h \mp m\sqrt{h/f}. \tag{A13}$$

Substituting (A13) into (A10), we get

$$y = \mp \sqrt{f/h}\, x. \tag{A14}$$

In view of (11), roots are acceptable if and only if $0 < x^2, y^2 < \tfrac{1}{4}$. But (7a) informs us that $f \leq h$, whence (A14) implies that $y^2 \leq x^2$. We conclude that $0 < x^2 < \tfrac{1}{4}$ is necessary and sufficient for acceptability of unsymmetric internal equilibria.

Let us prove first that the *plus sign* in (A13) yields no acceptable equilibria. Since $m > 0$ and $h > 0$ by (6a) and (7a), we infer from (A13) that $x^2 > 0$ if and only if $g > 0$ (*i.e.*, $\lambda < 2\gamma$). Straightforward manipulation of (A13) then reveals that $x^2 < \tfrac{1}{4}$ if and only if both left-hand inequalities in (A15) hold; we can easily demonstrate their equivalence to the inequalities on the right by employing (6) and (7):

$$\tfrac{1}{4}g - h > 0 \Leftrightarrow \lambda < 0, \tag{A15a}$$

$$m^2h < f(\tfrac{1}{4}g - h)^2 \Leftrightarrow \epsilon > \rho. \tag{A15b}$$

By (8c), the right-hand inequalities in (A15) are inconsistent, which establishes our assertion.

Hereafter we confine our analysis to the *minus sign* in (A13). There are three cases: (i) $g = 0$, (ii) $g < 0$, and (iii) $g > 0$. In the last two, (A13) and (A14) give (12).

(i) $g = 0$: The homogeneous linear system (A5) has a nontrivial solution if and only if $m^2 = fh$; by (6c) and (7a), this is equivalent to $\mu = \rho^2$. Since $h > 0$, (13) follows from (A5b). Invoking (6), we can demonstrate that $\lambda = 2\gamma$ (*i.e.*, $g = 0$) and $\mu = \rho^2$ both hold if and only if (14) does. Observe that the condition $m^2 = fh$ follows directly from (A11) and therefore implies (A12).

(ii) $g < 0$: Here we have

$$\lambda > 2\gamma, \tag{A16}$$

which implies (A12). From (A13) we see that $x^2 > 0$ if and only if the first inequality below holds; by (6b) and (7a), it is equivalent to the second inequality:

$$h < m\sqrt{h/f} \Leftrightarrow \mu < \rho^2. \tag{A17}$$

Rearranging (A13) and recalling (A15b), we can show that $x^2 < \tfrac{1}{4}$ if and only if $\epsilon > \rho$.

To prove that this is Case a in Table 3, we must demonstrate that $\epsilon > \rho$ and $\mu < \rho^2$ jointly imply (A16). Observe first that, by (8c), $\epsilon > \rho$ implies $\lambda > 0$, so (8d) holds. Since $\mu < \rho^2 < \epsilon^2$, (8d)

yields (A16):

$$\lambda > 2\beta + \epsilon > 2\beta + \rho = 2\gamma.$$

(iii) $g > 0$: Here we have

$$\lambda < 2\gamma. \tag{A18}$$

From (A13) we now infer that $x^2 > 0$ if and only if the inequalities in (A17) are reversed. Invoking (6c), we see immediately that $\mu > \rho^2$ implies (A12). Employing (A13) and (A15), we deduce that $x^2 < 1/4$ if and only if either $\lambda \leq 0$, or $\lambda > 0$ and $\epsilon < \rho$. Since, by (8c), $\lambda \leq 0$ implies that $\epsilon < 0 \leq \rho$, we can simplify our conditions to $\epsilon < \rho$ and $\mu > \rho^2$, in addition to (A18).

To prove that we have Cases b and c here, we must demonstrate that $\epsilon < \rho$ and $\mu > \rho^2$ jointly imply (A18). If $\lambda \leq m$, we note first that $\mu > \rho^2$ implies that $l > 2m$, whence

$$m \geq \lambda > 2m - 2\beta,$$

which gives

$$\lambda \leq m < 2\beta \leq 2\gamma.$$

This is Case b. If $\lambda > m$, then $\epsilon > 0$ by (8c), and consequently $\mu > \rho^2 > \epsilon^2$, so (8d) yields

$$\lambda - 2\beta < \epsilon < \rho,$$

which is precisely (A18). This is Case c.

Proof of Theorem 2: We posit that $\alpha > \beta$, which is necessary and sufficient for the existence of the equilibria (10). By symmetry, it suffices to test the stability of (10a). Since (10a) is an overdominant equilibrium, $\bar{w}$ must be maximized along $p_1 = 0$, so

$$\frac{\partial^2 \bar{w}}{\partial p_2^2} < 0 \tag{A19a}$$

at (10a). A Taylor expansion then shows at once that (10a) is stable if

$$\frac{\partial \bar{w}}{\partial p_1} < 0 \tag{A19b}$$

at (10a) and unstable if the inequality (A19b) is reversed. Appealing to (A5a), (10a), (11), (6), and (7), by direct calculation we find

$$\frac{\partial \bar{w}}{\partial p_1} = \left(\frac{\lambda^2 + m^2}{2\lambda^2}\right)(\epsilon - \rho) \tag{A20}$$

at (10a), which proves the first part of Theorem 2.

If $\epsilon = \rho$, the above analysis is inconclusive, but we may test stability as if (10a) were an internal equilibrium: (10a) is stable if (Apostol 1974, p. 379)

$$D_1 = \frac{\partial^2 \bar{w}}{\partial p_1^2} < 0 \tag{A21a}$$

and

$$D_2 = \left(\frac{\partial^2 \bar{w}}{\partial p_1^2}\right)\left(\frac{\partial^2 \bar{w}}{\partial p_2^2}\right) - \left(\frac{\partial^2 \bar{w}}{\partial p_1 \partial p_2}\right)^2 > 0 \tag{A21b}$$

at (10a); it is unstable if either of the inequalities (A21) is reversed. From (A6b), (A7a), (A8b), (10a), (11), (6), (7), $\epsilon = \rho$, and (8c), we derive

$$D_1 = -2m^2/\lambda < 0, \tag{A22a}$$

$$D_2 = -4m^2 gh/\lambda^2, \tag{A22b}$$

which proves the second part of Theorem 2.

Proof of Theorem 3: At the symmetric equilibrium (P_0), $x = y = 0$. Appealing to (A6b), (A7b), (A8b), (6b), and (6c), we deduce at once

$$D_1 = \rho - l, \quad D_2 = \mu - \rho^2. \tag{A23}$$

If $\mu > \rho^2$, then $D_2 > 0$ and (6c) gives $l > \rho$, so $D_1 < 0$, and therefore P_0 is stable. If $\mu < \rho^2$, then $D_2 < 0$, so P_0 is unstable.