

UNEXPECTED BEHAVIOR IN TWO LOCUS GENETIC SYSTEMS: AN ANALYSIS OF MARGINAL UNDERDOMINANCE AT A STABLE EQUILIBRIUM

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Manuscript received February 19, 1982

Revised copy accepted May 10, 1982

ABSTRACT

The phenomenon of marginal underdominance at a stable equilibrium in a two-locus-two-allele deterministic selection model is studied analytically using bifurcation theory. This technique and additional numerical studies indicate several new aspects of the phenomenon that are of biological importance. Marginal underdominance can occur at both loci simultaneously and can be present in a model with small fitness differentials. This can occur for a fitness scheme that is a one parameter generalization of the classical symmetric fitness model.

MOST of the deterministic theory of selection in Mendelian populations has concentrated on models of one or two loci, in part for reasons of mathematical simplicity. Underlying this research strategy has been the tacit assumption (or hope) that much of the behavior of one- or two-locus systems imbedded in truly multilocus systems could be understood by examining one- or two-locus models. One example of such an assumption was the conjecture that at a stable equilibrium in a multilocus model the marginal fitnesses at subsystems must appear as though the subsystems are at a stable equilibrium. In particular, one-locus subsystems must exhibit overdominance. If this conjecture had been true, apparent examples of underdominance at one-locus genetic systems at a stable equilibrium (LEWONTIN and WHITE 1960; CHRISTIANSEN *et al.* 1974; MITTON and KOEHN 1975) could not be explained by appealing to unseen loci.

In a recent paper (HASTINGS 1981a), numerical examples of marginal underdominance at a stable equilibrium of a two-locus-two-allele model were presented. This settled the conjecture of KARLIN and CARMELLI (1975) but left open the question of the forms of the fitness matrices that lead to marginal underdominance, since the results were strictly numerical. Thus, an assessment of the possible biological import of the phenomenon was difficult. In the present paper, I will present an analytical characterization of a class of fitness matrices that lead to marginal underdominance for a range of recombination values. This characterization will be produced using bifurcation theory in a fashion similar to that used in HASTINGS (1981b) to study a different problem in two-locus-two-allele models.

Additional numerical results will also be reported here, showing that there are ways other than those deduced by bifurcation theory in which marginal underdominance can arise. I will also present examples of ways in which

marginal underdominance can appear simultaneously at both loci in a two-locus-two-allele model.

The results of this paper will thus allow an assessment of the biological import of the phenomenon of marginal underdominance. A knowledge of the form of the fitness matrix permits a judgment of the likelihood of fitness patterns leading to underdominance occurring in nature, and the nature of the equilibria at which marginal underdominance occurs. Additionally, one can determine the most likely form for the other equilibria present in situations in which underdominance is possible. However, the results in this paper must also be viewed with caution, since multilocus systems may behave differently from two-locus systems with respect to marginal underdominance.

BACKGROUND

The model used here is the standard two-locus-two-allele discrete time deterministic model reviewed in KARLIN (1975). Let A and a be the alleles at the A locus, and B and b be the alleles at the B locus. The frequencies (and "names") of the four chromosomal types AB , Ab , aB , and ab are x_1 , x_2 , x_3 and x_4 , respectively. Let w_{ij} (with $w_{ij} = w_{ji}$ and $w_{14} = w_{23}$) be the fitness of an individual with chromosomes x_i and x_j .

Let D be the disequilibrium,

$$D = x_1x_4 - x_2x_3, \quad (1)$$

p_A be the frequency of allele A , p_B that of allele B , so

$$p_A = x_1 + x_2, \quad p_B = x_1 + x_3. \quad (2)$$

Finally let r be the recombination rate between the two loci.

The evolution of this system is described by

$$x'_i = \bar{w}^{-1}(x_i w_i \pm rD) \quad \text{for } i = 1 \text{ to } 4, \quad (3)$$

where the sign is minus for $i = 1$ and 4 and is plus for $i = 2$ or 3 . The marginal mean fitness of x_i is

$$w_i = \sum_{j=1}^4 w_{ij} x_j \quad (4)$$

and the mean fitness of the population is

$$\bar{w} = \sum_{i=1}^4 w_i x_i. \quad (5)$$

The marginal fitnesses at the A locus are the quantities that would be observed if only that locus were studied. They are computed as (e.g., BODMER and FELSENSTEIN 1967; KARLIN 1975; EWENS and THOMSON 1977):

$$w_{AA} = (w_{11}x_1^2 + 2w_{12}x_1x_2 + w_{22}x_2^2)/(x_1 + x_2)^2 \quad (6a)$$

$$w_{Aa} = (w_{13}x_1x_3 + w_{14}x_1x_4 + w_{23}x_2x_3 + w_{24}x_2x_4)/[(x_1 + x_2)(x_3 + x_4)] \quad (6b)$$

$$w_{aa} = (w_{33}x_3^2 + 2w_{34}x_3x_4 + 2w_{44}x_4^2)/(x_3 + x_4)^2. \quad (6c)$$

Similar definitions apply to the *B* locus.

Marginal underdominance will hold at the *A* locus if the inequalities

$$w_{Aa} < w_{aa} \quad (7a)$$

and

$$w_{Aa} < w_{AA} \quad (7b)$$

hold. EWENS and THOMSON (1977) showed that for any full system at equilibrium, any marginal subsystem must have marginal fitnesses which satisfy the conditions for equilibrium. Hence, in a one locus subsystem, at equilibrium the quantities $w_{AA} - w_{Aa}$ and $w_{aa} - w_{Aa}$ must have the same sign. Consequently, the inequalities (7) are seen to be equivalent to:

$$w_{Aa}^2 < w_{aa}w_{AA}, \quad (8)$$

a form more useful below.

ANALYSIS OF THE MODEL USING BIFURCATION THEORY

The analysis in the present section will concentrate on a bifurcation analysis of a two-locus-two-allele system in the vicinity of a corner equilibrium (e.g., $p_A = p_B = 0$ or $x_1 = x_2 = x_3 = 0, x_4 = 1$) for those values of the recombination parameter r slightly smaller than the critical value r_c which makes the corner equilibrium stable. This will allow the approximate determination (in powers of $r_c - r$) of a stable polymorphic (internal) equilibrium for these special values of r . The possibility of marginal underdominance at this stable equilibrium can then be assessed using the inequality (8).

The necessary preliminary calculations of the stability of a corner equilibrium are in BODMER and FELSENSTEIN (1967) and are summarized next. In what follows I have normalized the fitnesses so that $w_{14} = w_{23} = 1$. The linearization of the system (3) about the corner equilibrium

$$p_A = p_B = 0 \quad (9)$$

takes the form:

$$x' = Jx \quad (10)$$

where the matrix J is:

$$\begin{pmatrix} (1-r)/w_{44} & 0 & 0 \\ r/w_{44} & w_{24}/w_{44} & 0 \\ r/w_{44} & 0 & w_{34}/w_{44} \end{pmatrix}. \quad (11)$$

The vector x is the three-dimensional vector with entries x_1, x_2, x_3 . (Note that it is sufficient to use the three variables above since the four frequencies x_i sum to one. The choice of these coordinates is indicated by the fact that at the corner equilibrium the vector x is zero.) Hence, if

$$1 > w_{44} > w_{24}, w_{34} \quad (12)$$

the equilibrium (9) is (locally asymptotically) stable if $r > r_c$ and unstable if $r < r_c$ where

$$r_c = (1 - w_{44}). \quad (13)$$

In what follows I will assume that (12) holds and that w_{44} is greater than $\frac{1}{2}$ so that r_c is less than $\frac{1}{2}$.

If it were the case that w_{44} were larger than 1 as well as w_{24} and w_{34} , then the corner equilibrium would be stable for any value of the recombination parameter r . Instead, I will examine the case in which (12) holds, which implies that the stability of the corner equilibrium changes as r is varied through r_c . Bifurcation theory implies that this change in stability occurs when a second equilibrium whose value depends on r passes through the fixed (corner) equilibrium. Bifurcation theory provides a means to compute the stability and approximate location of this new equilibrium. The procedure will be to find this new curve of equilibria, and determine when this curve consists of stable equilibria exhibiting marginal underdominance.

The necessary theoretical background for the bifurcation calculations that follow is in HASTINGS (1981b), which also treats a two-locus population genetics problem, although dealing with a different set of variables. The first step is to change variables so that the linearization matrix (11) takes the form

$$\begin{pmatrix} 1 & 0 & 0 \\ 0 & & H \\ 0 & & \end{pmatrix} \quad (14)$$

at the point where $r = r_c$ and the 2×2 matrix H has both eigenvalues less than 1. An appropriate change of variables is

$$y = Px \quad (15)$$

and

$$x = P^{-1}y \quad (16)$$

where the symbols x and y represent three-dimensional vectors and the matrices P and P^{-1} , with the eigenvectors of (11) as the columns of P^{-1} , are:

$$P = \begin{pmatrix} 1 & 0 & 0 \\ -(1 - w_{44})/(w_{44} - w_{24}) & 1 & 0 \\ -(1 - w_{44})/(w_{44} - w_{34}) & 0 & 1 \end{pmatrix} \quad (17)$$

and

$$P^{-1} = \begin{pmatrix} 1 & 0 & 0 \\ (1 - w_{44})/(w_{44} - w_{24}) & 1 & 0 \\ (1 - w_{44})/(w_{44} - w_{34}) & 0 & 1 \end{pmatrix}. \quad (18)$$

The goal now is to find the coefficient f_{11} of y_1^2 in the equation for y_1' to use in the bifurcation calculations. Bifurcation theory (see HASTINGS 1981b; HASSARD, KAZARINOFF and WAN 1981) says that to lowest order the dynamics of the system (3) are governed by the equation for y_1' in the neighborhood of the equilibrium (9) and the parameter value $r = r_c$. [At the new bifurcating equilibrium determined by the equation for y_1' , to lowest order, the equilibrium values of y_2 and y_3 do not change from their values at the equilibrium (9).] Note that negative values of y_1 are not biologically meaningful because then x_i for i from 1 to 3 would be negative. Positive values of y_1 are biologically meaningful since from (18) all the x_i would be positive if y_1 were positive and y_2 and y_3 were 0. Specifically, the equation for y_1' , as determined from (11), (17) and (18) is

$$y_1' = [1 + (r_c - r)/w_{44}]y_1 + f_{11}y_1^2 + \text{higher order terms.} \quad (19)$$

More precisely, the theory used in HASTINGS (1981b) (*cf.* HASSARD, KAZARINOFF and WAN 1981) says that the system (3), for λ sufficiently small, will have an equilibrium given by:

$$\begin{aligned} y_1 &= -\lambda/(f_{11}w_{44}) + \mathcal{O}(\lambda^2) \\ y_2 &= \mathcal{O}(\lambda^2) \\ y_3 &= \mathcal{O}(\lambda^2) \end{aligned} \quad (20)$$

where

$$\lambda = r_c - r. \quad (21)$$

Hence, the biologically meaningful positive polymorphic equilibrium solutions to the equations (3) occur for $r < r_c$ and are stable if $f_{11} < 0$. If $f_{11} > 0$, the positive solutions occur for $r > r_c$ and are unstable, so the case of interest is when $f_{11} < 0$. In terms of the original variables x_i , the gamete frequencies, the new equilibrium is [using (18) and (20)]:

$$\begin{aligned} x_1 &= -\lambda/(f_{11}w_{44}) + \mathcal{O}(\lambda^2) \\ x_2 &= -\lambda(1 - w_{44})/[(f_{11}w_{44})(w_{44} - w_{24})] + \mathcal{O}(\lambda^2) \\ x_3 &= -\lambda(1 - w_{44})/[(f_{11}w_{44})(w_{44} - w_{34})] + \mathcal{O}(\lambda^2) \\ x_4 &= 1 + \lambda[1 + (1 - w_{44})[1/(w_{44} - w_{24}) + \\ &\quad 1/(w_{44} - w_{34})]]/(f_{11}w_{44}) + \mathcal{O}(\lambda^2) \end{aligned} \quad (22)$$

With the aid of a symbol manipulation routine, the quantity f_{11} (which depends on all the second partial derivatives of x'_1 evaluated at (9) and is calculated from (3), (18) and (20) using the fact that all the x_i sum to one) is found to be:

$$\begin{aligned} [(w_{44} - w_{24})(w_{44} - w_{34})(w_{11} - 2 + w_{44}) + (1 - w_{44})(w_{44} - w_{34})(w_{12} - 2w_{24} + \\ w_{44}) + (1 - w_{44})(w_{44} - w_{24})(w_{13} - 2w_{34} + w_{44}) + \\ (1 - w_{44})^3]/[w_{44}(w_{44} - w_{24})(w_{44} - w_{34})] \end{aligned} \quad (23)$$

The meaning of this quantity will be explored below.

To determine whether marginal underdominance holds at the bifurcating equilibrium, simply substitute the quantities (22) in the inequality (8) and consider the lowest order (in λ) nonzero term. This turns out to be the λ^2 term, so underdominance holds at the A locus if:

$$\begin{aligned} w_{11}(w_{44} - w_{24})^2 + 2w_{12}(1 - w_{44})(w_{44} - w_{24}) + \\ w_{22}(1 - w_{44})^2 - w_{44}(1 - w_{24})^2 > 0. \end{aligned} \quad (24a)$$

An analogous condition holds at the B locus, namely underdominance holds if:

$$\begin{aligned} w_{11}(w_{44} - w_{34})^2 + 2w_{13}(1 - w_{44})(w_{44} - w_{34}) + \\ w_{33}(1 - w_{44})^2 - w_{44}(1 - w_{34})^2 > 0. \end{aligned} \quad (24b)$$

INTERPRETATION OF THE ANALYTICAL RESULTS

The first step in the interpretation of the conditions (23) and (24) is to notice that not all of the entries in the fitness matrix appear in all the conditions. Specifically the stability (and direction) of the bifurcation does not depend on

w_{22} and w_{33} . The condition for underdominance at the A locus does not depend on w_{13} and w_{33} and similarly the condition for underdominance at the B locus does not depend on w_{12} and w_{22} . This information makes it simple to generate examples at which marginal underdominance holds at one or both loci at a stable equilibrium.

The first step is to choose all the entries in the fitness matrix except w_{22} and w_{33} so that the bifurcation is to a stable equilibrium, i.e., f_{11} as defined in (23) is negative. Note that decreasing w_{11} , w_{12} and w_{13} always decreases the quantity (23), making f_{11} smaller. Hence, the first step in choosing fitnesses that lead to a stable bifurcation is to examine the form (23) takes when w_{11} , w_{12} , and w_{13} are all zero. Then, after simplifying, the inequality $f_{11} < 0$ derived from (23) becomes:

$$(w_{44} - w_{24})(w_{44} - w_{34})(-2 + w_{44}) + (1 - w_{44})(w_{44} - w_{34})(-2w_{24} + w_{44}) + (1 - w_{44})(w_{44} - w_{24})(-2w_{34} + w_{44}) + (1 - w_{44})^3 < 0. \quad (25)$$

If

$$w_{44}/2 < w_{24} \quad (26a)$$

and

$$w_{44}/2 < w_{34} \quad (26b)$$

only the last term on the left side of (25) is positive. If $w_{44} = w_{23} = w_{24}$, then the left side of (25) is positive. However, if $1 - w_{44}$ is very small, and the difference between w_{44} and w_{23} , w_{24} is larger but not so large that (26a) or (26b) is close to being violated, then (25) clearly holds. In particular, sufficient conditions for inequality (25) to be satisfied are:

$$\begin{aligned} w_{44} - w_{34} &\geq 1 - w_{44} \\ w_{44} - w_{24} &\geq 1 - w_{44} \\ w_{34} &> 1/2 \\ w_{24} &> 1/2. \end{aligned} \quad (27)$$

If inequality (25) is satisfied, then for sufficiently small values of w_{11} , w_{12} and w_{13} the inequality (23) will hold and the bifurcation will be to a stable equilibrium. The condition that w_{11} , w_{12} and w_{13} be sufficiently small is not at all extreme, as demonstrated in an example below.

Now that a fitness matrix producing a bifurcation to a stable equilibrium has been produced, the quantities w_{22} and w_{33} , which have yet to be determined, can be chosen so that marginal underdominance holds at both loci at the bifurcating equilibrium. Note from inequalities (24) that simply by choosing w_{22} and w_{33} sufficiently large the condition that marginal underdominance hold can be satisfied. As above, the condition that w_{22} and w_{33} be sufficiently large is not extreme, as will be shown below.

It is important to note that the sufficient conditions for marginal underdominance to occur that have just been derived do not preclude a certain kind of symmetry in the fitness matrix, namely that the effects of the A and the B locus are identical. Hence, assume that the A and B loci are identical in their effects, so let:

$$\begin{aligned}
 c &= w_{24} = w_{34}, \\
 d &= w_{12} = w_{13}, \\
 k &= w_{22} = w_{33}.
 \end{aligned}
 \tag{28}$$

In fact the parameters c and d can be chosen to be the same, and have the inequalities (24) and $f_{11} < 0$ satisfied. Thus, a fitness matrix that differs from the classical symmetric model (reviewed in KARLIN 1975 and EWENS 1979) only in having $w_{11} \neq w_{44}$ can lead to stable marginal underdominance at both loci.

Such an example of marginal underdominance, with small fitness differentials, will now be constructed. If we choose $c = d = 0.98$, and $w_{44} = 0.99$, the condition derived from (23) that the bifurcation be to a stable equilibrium is satisfied if $w_{11} < 0.98$. If we choose w_{11} to be 0.97, then the conditions (24) that marginal underdominance hold are satisfied if $k > 1.03$. Hence, the following fitness matrix (displayed in 3×3 form, as all examples will be shown) leads to marginal underdominance at both loci, for the quantity $(0.01 - r)$ sufficiently small and positive:

$$\begin{array}{ccc}
 & BB & Bb & bb \\
 AA & \left(\begin{array}{ccc} 0.97 & 0.98 & 1.04 \\ 0.98 & 1.0 & 0.98 \\ 1.04 & 0.98 & 0.99 \end{array} \right) & & \\
 Aa & & & \\
 aa & & &
 \end{array}
 \tag{29}$$

At the equilibrium p_A and p_B are very small. Numerically, the equilibrium is found to exist for $r^* < r < 0.01$ where r^* lies between 0.0090 and 0.0095.

NUMERICAL RESULTS

Even with the analytical characterization of the previous section, numerical work is still useful as a supplement to answer two important questions. The bifurcation analysis is an accurate descriptor of the dynamics only for values of r sufficiently close to r_c . What is the behavior for other values of r ? Can one find all instances of marginal underdominance in two locus systems using the bifurcation analysis described above?

I have followed the dynamics, as r is varied, of two-locus models with fitness matrices leading to marginal underdominance that arise from the bifurcation analyzed above. In all cases the qualitative picture of the behavior is similar—for some value of r less than r_c the equilibrium coalesces with an unstable equilibrium and disappears. I have not been able to deduce a simple measure of the length of the interval over which the equilibrium exists, although if r_c is small the interval must be small since KARLIN (1978) showed that underdominance cannot occur for r sufficiently small.

However, it appears that if fitness differentials are larger than in (29), and underdominance holds at only one locus, the range of r values over which marginal underdominance holds can be much larger. For example, if the fitnesses are:

$$\begin{array}{ccc}
 & \left(\begin{array}{ccc} 0.33 & 0.31 & 0.56 \\ 1.20 & 1.0 & 0.85 \\ 1.20 & 0.84 & 0.92 \end{array} \right) & \\
 & &
 \end{array}
 \tag{30}$$

there is a stable equilibrium with marginal underdominance at the B locus for

$r^* < r < 0.08$, where r^* lies between 0.061 and 0.062. When $r = 0.062$, the equilibrium is approximately $p_A = 0.0495$, $p_B = 0.0622$, $D = 0.0265$. The marginal fitnesses at the B locus are $w_{BB} = 1.016$, $w_{Bb} = 0.908$, $w_{bb} = 0.917$. These certainly represent differences that could be detected. Note that the fitness matrix (30) does satisfy the conditions for bifurcation to a stable equilibrium with marginal underdominance at the B locus as determined in this paper.

To answer the question concerning whether the bifurcation described above can find all cases of marginal underdominance, cases of marginal underdominance derived using the numerical methods described in HASTINGS (1981a) were studied in detail. Two other ways in which underdominance can arise as r is varied were determined. One way is through bifurcation from a "face" equilibrium, where one locus is polymorphic and the other is not. A fitness matrix where this occurs is:

$$\begin{pmatrix} 0.636380 & 0.786382 & 0.077030 \\ 0.433378 & 1.0 & 0.138740 \\ 1.440334 & 0.417419 & 0.042957 \end{pmatrix}. \quad (31)$$

The face equilibrium with $p_A = 1$, $p_B = 0.8245$ (approximately) is stable if $r > 0.328$, and unstable otherwise. If $0.290 < r < 0.328$ there is a stable polymorphic equilibrium at which marginal underdominance holds at the A locus. This equilibrium approaches the boundary equilibrium as r approaches 0.328 from below. In principle, an analysis analogous to that of the present paper could be applied to this case, although the algebra is much more complex. The preliminary calculations of the stability of the equilibrium are in BODMER and FELSENSTEIN (1967).

Another interesting way in which marginal underdominance can arise is for the character of a particular equilibrium to change from one with marginal overdominance to one with marginal underdominance as r is varied. Of necessity, according to the results of EWENS and THOMSON (1977) there must be a value of r at which all the marginal fitnesses are identical for this to happen. A fitness matrix for which this occurs is:

$$\begin{pmatrix} 0.625220 & 0.109520 & 1.243060 \\ 0.405000 & 1.0 & 0.480030 \\ 0.919330 & 0.002090 & 0.323730 \end{pmatrix}. \quad (32)$$

For a value of r approximately 0.357 all the marginal fitnesses at the B locus are the same at a stable equilibrium with p_A approximately 0.85 and p_B approximately 0.91. For larger values of r there is marginal overdominance at this equilibrium and for smaller values of r (but greater than 0.34) there is marginal underdominance.

DISCUSSION

Several new features and qualitative properties related to the phenomenon of marginal underdominance have emerged from the analysis here. The most important is that marginal underdominance can appear in cases in which the fitness differences among differing genotypes are small, as in the fitness matrix (29). This in itself suggests that the phenomenon may have more biological importance than was apparent from the previous numerical work. A second important biological feature is the possibility of marginal underdominance

appearing simultaneously at both loci in a two-locus model. Additionally, the form of epistasis required to generate marginal underdominance is not nearly as unreasonable as that indicated by the numerical studies in HASTINGS (1981a), as evidenced by the fitness matrices (29)–(31). The general conclusions drawn from the study here coincide with the viewpoint emerging from the experimental work reported in MITTON and KOEHN (1975). They report that several isozyme loci in *Eundulus heteroclitus* exhibit heterozygote deficiency and none exhibit heterozygote excess. Perhaps an extension of the work reported here to multi-locus models would demonstrate that marginal underdominance is even easier to obtain.

Another feature that is of interest is the range of values of the recombination rate, r , over which the phenomenon of marginal underdominance occurs. In the analysis here, if fitness differentials are small, r_c is small, so marginal underdominance holds at small values of the recombination parameter, r . This is perhaps surprising in light of KARLIN's (1978) earlier analysis that marginal overdominance must hold for r sufficiently small. The analysis in the present paper shows that KARLIN's analysis can only hold if r/s is small where s is a measure of fitness differences.

The nature of the equilibria at which marginal underdominance holds is of interest. In the examples generated by the analysis of the paper, if A is the locus at which underdominance holds, p_A will be small, with w_{AA} much larger than w_{Aa} whereas w_{Aa} and w_{aa} are nearly equal. Such an observation would certainly appear curious to an experimenter. In fact, in the examples generated here, since w_{22} would have been chosen large, the equilibrium with $p_A = 1$ would also be stable.

The work reported here and elsewhere (HASTINGS 1981a and 1981c) indicates that there are many surprises in the equilibrium and dynamic behavior of multilocus population genetic models. To the extent that phenotypes are determined by many loci with epistasis playing an important role, some of the intuition gained from the analysis of models with few and especially one locus must be viewed with caution. This caveat applies as well to the results in this paper itself (a metacaveat). Marginal properties of systems with more than two loci may be much more complex and surprising than those of systems with two loci.

I thank ELAINE FINGERETT, JOHN GILLESPIE and MIKE TURELLI for helpful discussions. The exposition was greatly improved as a result of the good advice of two conscientious referees. This research was supported in part by National Science Foundation Grant DEB 8002593.

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