*LINKAGE AND SELECTION: NEW EQUILIBRIUM PROPERTIES OF THE TWO-LOCUS SYMMETRIC VIABILITY MODEL**

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Abstract and Summary.—In the two-locus symmetric viability model with recombination, conditions for the existence and stability of a new class of polymorphic equilibria are given. These "unsymmetric" equilibria, which exist for relatively loose linkage, can be explicitly obtained, in contrast to the previously known symmetric equilibria which are generally given by the solutions of a cubic equation.

For sufficiently tight linkage, there is always at least one stable symmetric equilibrium. Seven is the precise maximum for the number of interior equilibria. The qualitative consequences of these results are briefly examined. In particular it is pointed out that since for some linkage values no stable polymorphic equilibria exist, there is no "overdominance theorem" comparable to the single-locus case.

Lewontin and Kojima,[1] Bodmer and Parsons,[2] and Bodmer and Felsenstein[3] have used the term "symmetric viability" model to describe the situation when the selection values for the genotypes in the two-locus model have the matrix representation

$$\begin{array}{cccc} & AA & Aa & aa \\ \text{BB} & 1\text{-}\delta & 1\text{-}\beta & 1\text{-}\alpha \\ \text{Bb} & 1\text{-}\gamma & 1 & 1\text{-}\gamma \\ \text{bb} & 1\text{-}\alpha & 1\text{-}\beta & 1\text{-}\delta \end{array} \tag{1}$$

Wright[4] has considered the case $\beta = \gamma$ and especially the case $2(\beta + \gamma) = \alpha + \delta$. The model examined by Kimura[5] can be set in the form (1) taking $\delta = (-s + t)/(1 + t)$, $\alpha = (s + t)/(1 + t)$, $\beta = t/(1 + t)$, $\gamma = 0$. Lewontin and Kojima, in their analysis, assumed $\alpha = \delta$, whereas Bodmer and Parsons dealt principally with the case $\beta = \gamma$.

Let x_1, x_2, x_3, and x_4 be the frequencies of the chromosomes AB, Ab, aB, and ab, respectively, and r the recombination fraction. Then corresponding to (1), the recursion relations relating the frequencies x_1', x_2', x_3', and x_4' in the next generation to x_1, x_2, x_3, and x_4 have been shown to be[5, 1, 3]

$$\begin{aligned} \overline{w}x_1' &= x_1 - \delta x_1^2 - \beta x_1x_2 - \gamma x_1x_3 - rD \\ \overline{w}x_2' &= x_2 - \beta x_1x_2 - \alpha x_2^2 - \gamma x_2x_4 + rD \\ \overline{w}x_3' &= x_3 - \gamma x_1x_3 - \alpha x_3^2 - \beta x_3x_4 + rD \\ \overline{w}x_4' &= x_4 - \gamma x_2x_4 - \beta x_3x_4 - \delta x_4^2 - rD, \end{aligned} \tag{2}$$

where $\overline{w} = 1 - \delta(x_1^2 + x_4^2) - \alpha(x_2^2 + x_3^2) - 2\beta(x_3x_4 + x_1x_2) - 2\gamma(x_1x_3 + x_2x_4)$ and $D = x_1x_4 - x_2x_3$ is usually called the linkage disequilibrium value.[1]

Most of the authors mentioned above have assumed that, since there is symmetry in the viability pattern, all polymorphic equilibria (i.e., interior equilibrium solutions of (2)) must be of the form $\hat{x}_1 = \hat{x}_4$ and $x_2 = \hat{x}_3$; that is, at any polymorphic equilibrium the chromosomes AB and ab have equal frequencies and so do Ab and aB. Equilibria of this form, which we shall call *symmetric equilibria*, are given by $\hat{x}_1 = \hat{x}_4 = {}^1/_4 + \hat{D}$ and $\hat{x}_2 = \hat{x}_3 = {}^1/_4 - \hat{D}$, where the value of $\hat{D}$ is a solution of the cubic equation[2, 3]

$$64\, lD^3 - 16\, mD^2 - 4(l - 8r)\, D + m = 0, \tag{3}$$

satisfying $|\hat{D}| \leq {}^1/_4$. Here, $l = 2(\beta + \gamma) - (\alpha + \delta)$ and $m = \delta - \alpha$.

Our purpose in this note is to describe some rather surprising results obtained from a more complete mathematical analysis of the system (2) than has previously been made. Specifically we have found classes of *stable* polymorphic equilibria in which the chromosomes AB and ab or the chromosomes Ab and aB have unequal frequencies. Proofs of these assertions, further discussion of the properties of the symmetric equilibria, and more numerical details will appear elsewhere.[6]

Results.—Assume that α, β, γ, and δ are all positive. For tight linkage, the following can be concluded.

THEOREM 1. *For linkage sufficiently tight and any set of selection coefficients there always exists a locally stable symmetric equilibrium.*

This fact can be deduced to a large extent by suitably combining results obtained by previous authors. Thus, for instance, it is easily established[3] that if $\beta + \gamma > \alpha$, then for r small enough there is a locally stable equilibrium near $\hat{x}_1 = \hat{x}_4 = 0$, $\hat{x}_2 = \hat{x}_3 = {}^1/_2$. Similarly if $\beta + \gamma > \delta$, there is a locally stable equilibrium near $\hat{x}_1 = \hat{x}_4 = {}^1/_2$, $\hat{x}_2 = \hat{x}_3 = 0$, when r is small enough. When $r = 0$, (2) reduces to the equations for the dynamics of a four-allele system at a single locus. If in addition $\alpha > \beta + \gamma$, $\delta > \beta + \gamma$ and r is sufficiently small, the well-known properties[7] of multiallelic systems can be readily exploited to prove global convergence to a unique interior equilibrium.

There have been a number of analytical studies of the stability of the symmetric equilibria.[1, 3, 5, 8] A complete study of the stability of the symmetric equilibria will appear later.[6] For loose linkage only numerical results have so far been obtained[9, 10] except in special cases. The next two theorems which are relevant when linkage is loose demonstrate the surprising properties of the unsymmetric equilibria.

Assume that $\beta = \gamma$ (see below for $\beta \neq \gamma$). We then have the following theorem.

THEOREM 2. *Let*

$$\hat{Z} = \left\{\beta - \frac{\alpha}{2} + \frac{\delta r}{2(r - \delta)}\right\} \Bigg/ \left\{2\beta - \frac{\alpha}{2} - \delta + \frac{\delta r}{2(r - \delta)}\right\} \tag{4}$$

and

$$\hat{R} = \hat{Z}^2 - r(1 - \hat{Z})^2/(r - \delta). \tag{5}$$

Assume that $r > \delta$ *and* $\alpha/2 - \delta r/2(r - \delta) > \delta > \beta = \gamma$. *Then two unsymmetric equilibria exist and are locally stable if and only if* $\hat{R} > 0$. *These equilibria are given by*

$$\hat{x}_1 = {}^1/_2(\hat{Z} + \sqrt{\hat{R}}),\ \hat{x}_2 = \hat{x}_3 = {}^1/_2(1 - \hat{Z}),\ \hat{x}_4 = {}^1/_2(\hat{Z} - \sqrt{\hat{R}}) \tag{6}$$

and

$$\hat{x}_1 = {}^1/_2(\hat{Z} - \sqrt{\hat{R}}),\ \hat{x}_2 = \hat{x}_3 = {}^1/_2(1 - \hat{Z}),\ \hat{x}_4 = {}^1/_2(\hat{Z} + \sqrt{\hat{R}}). \tag{7}$$

Examples of parameter sets for which Theorem 2 holds, and the corresponding equilibrium values, are:

$\alpha = 0.03,\quad \beta = 0.004,\quad \delta = 0.005,\quad r = 0.05$

$x_1 = 0.8878\quad x_2 = 0.0542\quad x_3 = 0.0542\quad x_4 = 0.0038$

$x_1 = 0.0038\quad x_2 = 0.0542\quad x_3 = 0.0542\quad x_4 = 0.8878$

and

$\alpha = 0.1,\quad \beta = 0.005,\quad \delta = 0.01,\quad r = 0.02$

$x_1 = 0.866\quad x_2 = 0.0625\quad x_3 = 0.0625\quad x_4 = 0.009$

$x_1 = 0.009\quad x_2 = 0.0625\quad x_3 = 0.0625\quad x_4 = 0.866.$

Theorem 2 remains true if we interchange δ and α, provided that in both (6) and (7) $\hat{x}_1$ and $\hat{x}_2$ are interchanged and also $\hat{x}_3$ and $\hat{x}_4$.

THEOREM 3. *Let* $\hat{Z}$ *and* $\hat{R}$ *be as in Theorem 2 and let* Z^* *and* R^* *be the corresponding quantities obtained by interchanging* δ *and* α *in (4) and (5). Assume that* $r > \delta$ *and* $r > \alpha$ *and*

$$\beta > \delta > \frac{\alpha}{2} - \frac{\delta r}{2(r - \delta)},\quad \beta > \alpha > \frac{\delta}{2} - \frac{\alpha r}{2(r - \alpha)}. \tag{8}$$

Then four unsymmetric equilibria exist, provided that $\hat{R} > 0$ *and* $R^* > 0$. *The equilibria are given by (6) and (7) and*

$$\hat{x}_1 = \hat{x}_4 = {}^1/_2(1 - Z^*),\ \hat{x}_2 = {}^1/_2(Z^* + \sqrt{R^*}),\ \hat{x}_3 = {}^1/_2(Z^* - \sqrt{R^*}) \tag{9}$$

and

$$\hat{x}_1 = \hat{x}_4 = {}^1/_2(1 - Z^*),\ \hat{x}_2 = {}^1/_2(Z^* - \sqrt{R^*}),\ \hat{x}_3 = {}^1/_2(Z^* + \sqrt{R^*}). \tag{10}$$

These four unsymmetric equilibria are locally unstable.

Examples of parameter sets for which Theorem 3 holds, and the corresponding equilibrium values, are:

$\alpha = 0.02,\quad \beta = 0.04,\quad \delta = 0.03,\quad r = 0.04$

$x_1 = 0.1539\quad x_2 = 0.6562\quad x_3 = 0.0360\quad x_4 = 0.1539$

$x_1 = 0.1539\quad x_2 = 0.0360\quad x_3 = 0.6562\quad x_4 = 0.1539$

$x_1 = 0.8888\quad x_2 = 0.05\quad x_3 = 0.05\quad x_4 = 0.0112$

$x_1 = 0.0112\quad x_2 = 0.05\quad x_3 = 0.05\quad x_4 = 0.8888$

and

$$\begin{array}{llll} \alpha = 0.05, & \beta = 0.07, & \delta = 0.06, & r = 0.1 \\ x_1 = 0.9191 & x_2 = 0.0385 & x_3 = 0.0385 & x_4 = 0.0039 \\ x_1 = 0.0039 & x_2 = 0.0385 & x_3 = 0.0385 & x_4 = 0.9191 \\ x_1 = 0.0909 & x_2 = 0.8131 & x_3 = 0.0051 & x_4 = 0.0909 \\ x_1 = 0.0909 & x_2 = 0.0050 & x_3 = 0.8130 & x_4 = 0.0909. \end{array}$$

For $\beta \neq \gamma$ there may exist four unsymmetric equilibria of the form $\hat{x}_1 \neq \hat{x}_4$, $\hat{x}_2 \neq \hat{x}_3$. In this case a complete description of the equilibria has been obtained but in terms of some very cumbersome algebraic expressions. For certain special relations between the selection parameters, theorems similar to the above are available.

In view of the fact that there may be three symmetric equilibria, from Theorem 3 we infer that there may be as many as seven interior equilibrium solutions of (2). Moran[11] conjectured that five was the maximum number possible in the general two-locus model. For the symmetric viability model, the precise maximum is seven, and an example where this occurs is $\alpha = \delta = 0.1$, $\beta = \gamma = 0.8$, $r = 0.3735$ (see also Ewens[8]). For these parameter values there are three symmetric equilibria (of which two are stable) and four unsymmetric equilibria.

Discussion.—If a recombination reducing mechanism is introduced into a population such as that represented by the model treated here, the fate of the mechanism will depend largely on the state of the population prior to its introduction. Indeed, any theory for the evolution of supergenes or tightly linked clusters of loci must take into account the equilibrium properties of the model.

Theorems 1, 2, and 3 show that theory based on the knowledge of the symmetric equilibria alone (see, e.g., Turner,[12] page 211) applies in general for relatively tight linkage. For looser linkage we must contend with the possible existence of stable unsymmetric equilibria. Theorem 1 asserts the intuitive fact that for tight linkage the behavior of the system is governed by the properties of the corresponding four-allele model. When linkage is looser, the effects of the separate genes become more pronounced so that the individual selection parameters are decisive in determining which of a possible seven equilibrium states will be reached. Theorems 2 and 3 indicate to some extent how this determination is made. They also provide some insight into the domains of attraction to the various equilibria.

If we combine Theorems 2 and 3 with the known properties of the symmetric equilibria, the stability patterns are seen to be quite complicated. Ewens[8] has given an example of the complications which can arise for moderate linkage values. When $\alpha = \delta$, he showed that, although for tight and loose linkage stable symmetric polymorphisms exist, there may be an interval of moderate recombination values for which no symmetric equilibrium is stable. It is possible to show further that for this interval the unsymmetric equilibria do not exist.

Theorems 2 and 3 and the anomaly discovered by Ewens demonstrate that in the symmetric viability model there is no "overdominance theorem" comparable to the single-locus case. Even though the double heterozygotes are most fit, there may exist a region of moderate linkage values allowing no stable interior equilibrium. A more detailed discussion of this point is warranted.[6]

The fact that unsymmetric equilibria exist in one of the simplest two-locus models indicates that in multilocus models with selection and several recombination parameters, unsymmetric equilibria will also exist. Further, if such models are analyzed solely in terms of some average disequilibrium function, these equilibria will not be found.

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[1] Lewontin, R. C., and Ken-ichi Kojima, *Evolution*, **14**, 458–472 (1960).

[2] Bodmer, W. F., and P. A. Parsons, *Advan. Genet.*, **11**, 1–87 (1962).

[3] Bodmer, W. F., and J. Felsenstein, *Genetics*, **57**, 237–265 (1967).

[4] Wright, S., in *Quantitative Inheritance*, ed. E. C. R. Reeve and C. H. Waddington (London: Her Majesty's Stationery Office (1952)).

[5] Kimura, M., *Evolution*, **10**, 278–287 (1956).

[6] Karlin, S. and M. W. Feldman, manuscript in preparation.

[7] Mandel, S. P. H., *Heredity*, **13**, 289–302 (1959).

[8] Ewens, W. J., *Theoret. and Appl. Genet.*, **38**, 140–144 (1968).

[9] Lewontin, R. C., *Genetics*, **49**, 49–67 (1964).

[10] Jain, S. K., and R. W. Allard, *Genetics*, **53**, 633–659 (1966).

[11] Moran, P. A. P., *Proc. Fifth Berkeley Symp. Math. Stat. Prob.*, **4**, 457–480 (1967).

[12] Turner, J. R. G., *Am. Naturalist*, **101**, 195–221 (1967).