Genet. Res., Camb. (1973), **22**, *pp.* 195–200
Printed in Great Britain

The three locus model with multiplicative fitness values

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(*Received* 10 *May* 1973)

SUMMARY

The necessary and sufficient conditions for the stability of the equilibrium point with no linkage disequilibrium are obtained for the three locus model with multiplicative fitnesses. It is shown that there are six inequalities that must be satisfied in order for this equilibrium to be stable. Three of the inequalities require that there be heterozygotic superiority at all loci. The other three are exactly those inequalities which are required for each pair of loci to be stable with linkage equilibrium if they are considered to be an isolated two locus system. Thus, all the information needed to determine the stability of this equilibrium with three loci is contained in one and two locus theory.

1. INTRODUCTION

One of the simplifying assumptions made in classical population genetics is that there is only one locus. In recent years this assumption has been somewhat relaxed by the development of two locus theory (Lewontin & Kojima, 1960; Bodmer & Parsons, 1962). Two models of fitness values have been studied extensively, the symmetric selection model (Karlin & Feldman, 1970) and the multiplicative fitness model (Bodmer & Felsenstein, 1967).

The multiplicative model arises naturally if loci which affect the viability act at different times in the life cycle. For this reason the multiplicative fitness model has been used in computer studies with more than two loci (Lewontin, 1964; Franklin & Lewontin, 1970; Slatkin, 1972). For the two locus model with arbitrary multiplicative fitness values only the conditions for the stability of the equilibrium with no linkage disequilibrium have been obtained. The other equilibrium points and their stability properties can be determined if the fitness values are symmetric (Karlin & Feldman, 1970).

In this paper the necessary and sufficient conditions for the stability of the equilibrium with no linkage disequilibrium are obtained for the three locus model with multiplicative fitnesses. From these results some insight is gained into the n locus problem.

2. THEORY

The model which will be developed is a three locus model with two alleles at each locus. The two alleles at the three loci will be denoted by A_1 and A_0, B_1 and B_0, and C_1 and C_0. Let X_{ijk} $(i, j, k = 0, 1)$ be the frequency of the gamete $A_iB_jC_k$ in the population. The relative fitness of the genotype $A_iA_jB_kB_lC_mC_n$ will be denoted by $a_{i+j,\,k+l,\,m+n}$ and will be taken to equal $w^A_{i+j}w^B_{k+l}w^C_{m+n}$, where, for instance w^B_2 is the relative fitness of the genotype B_1B_1. For all loci w_1 is assumed equal to 1.

The recombination value between the first and second loci will be defined to be r_1 and between the second and third loci, r_2. If there is no interference, the recombination between the first and third loci is $r_1+r_2-2r_1r_2$ and the frequency of double cross-overs is r_1r_2.

With these definitions the recurrence equations for the eight gametic types are given in Table 1.

Instead of using the gametic frequencies, which are subject to the constraint that they must add to one, as variables; it will be convenient to define the following seven independent variables:

$$\left.\begin{aligned}
p_1 &= X_{111}+X_{110}+X_{101}+X_{100},\\
p_2 &= \frac{X_{111}+X_{110}}{X_{111}+X_{110}+X_{101}+X_{100}},\\
p_3 &= \frac{X_{011}+X_{010}}{X_{011}+X_{010}+X_{001}+X_{000}},\\
p_4 &= \frac{X_{111}}{X_{111}+X_{110}},\\
p_5 &= \frac{X_{101}}{X_{101}+X_{100}},\\
p_6 &= \frac{X_{011}}{X_{011}+X_{010}},\\
p_7 &= \frac{X_{001}}{X_{001}+X_{000}}.
\end{aligned}\right\} \tag{1}$$

In these variables the gametic frequencies are:

$$\left.\begin{aligned}
X_{111} &= p_1p_2p_4, & X_{011} &= (1-p_1)p_3p_6,\\
X_{110} &= p_1p_2(1-p_4), & X_{010} &= (1-p_1)p_3(1-p_6),\\
X_{101} &= p_1(1-p_2)p_5, & X_{001} &= (1-p_1)(1-p_3)p_7,\\
X_{100} &= p_1(1-p_2)(1-p_5), & X_{000} &= (1-p_1)(1-p_3)(1-p_7)
\end{aligned}\right\} \tag{2}$$

The recurrence equations for the p_i can be obtained by substituting equations (2) into the equations given in Table 1 and using the relationships between the gametic frequencies and the variables p_i given in (1).

The equilibrium point with linkage equilibrium is given by

$$\left.\begin{aligned}
\hat{p}_1 &= \frac{b_1}{a_1+b_1},\\
\hat{p}_2 &= \hat{p}_3 = \frac{b_2}{a_2+b_2},\\
\hat{p}_4 &= \hat{p}_5 = \hat{p}_6 = \hat{p}_7 = \frac{b_3}{a_3+b_3},
\end{aligned}\right\} \tag{3}$$

where $a_1 = w^A_2-w^A_1$ and $b_1 = w^A_0-w^A_1$ and similarly for the second and third loci.

Table 1. *Equations for selection with three loci*

$$\begin{aligned}
\overline{W}X'_{111} &= X_{111}\overline{W}_{111} - a_{112}r_1D^1_{12} - a_{111}r_1H_1 - a_{211}r_2D^1_{23} - a_{111}r_2H_2 - a_{121}(r_1+r_2-2r_1r_2)D^1_{13} + a_{111}r_1r_2H\\
\overline{W}X'_{110} &= X_{110}\overline{W}_{110} - a_{110}r_1D^0_{12} + a_{111}r_1H_3 + a_{211}r_2D^1_{23} + a_{111}r_2H_2 + a_{121}(r_1+r_2-2r_1r_2)D^1_{13} - a_{111}r_1r_2H\\
\overline{W}X'_{101} &= X_{101}\overline{W}_{101} + a_{112}r_1D^1_{12} - a_{111}r_1H_3 + a_{211}r_2D^1_{23} - a_{111}r_2H_4 - a_{101}(r_1+r_2-2r_1r_2)D^0_{13} + a_{111}r_1r_2H\\
\overline{W}X'_{100} &= X_{100}\overline{W}_{100} + a_{110}r_1D^0_{12} + a_{111}r_1H_1 - a_{211}r_2D^1_{23} + a_{111}r_2H_4 + a_{101}(r_1+r_2-2r_1r_2)D^0_{13} - a_{111}r_1r_2H\\
\overline{W}X'_{011} &= X_{011}\overline{W}_{011} + a_{112}r_1D^1_{12} + a_{111}r_1H_1 - a_{011}r_2D^0_{23} + a_{111}r_2H_4 + a_{121}(r_1+r_2-2r_1r_2)D^1_{13} - a_{111}r_1r_2H\\
\overline{W}X'_{010} &= X_{010}\overline{W}_{010} + a_{110}r_1D^0_{12} - a_{111}r_1H_3 + a_{011}r_2D^0_{23} - a_{111}r_2H_4 - a_{121}(r_1+r_2-2r_1r_2)D^1_{13} + a_{111}r_1r_2H\\
\overline{W}X'_{001} &= X_{001}\overline{W}_{001} - a_{112}r_1D^1_{12} + a_{111}r_1H_3 + a_{011}r_2D^0_{23} + a_{111}r_2H_2 + a_{101}(r_1+r_2-2r_1r_2)D^0_{13} - a_{111}r_1r_2H\\
\overline{W}X'_{000} &= X_{000}\overline{W}_{000} - a_{110}r_1D^0_{12} - a_{111}r_1H_1 - a_{011}r_2D^0_{23} - a_{111}r_2H_2 - a_{101}(r_1+r_2-2r_1r_2)D^0_{13} + a_{111}r_1r_2H
\end{aligned}$$

$$\begin{aligned}
D^1_{12} &= X_{111}X_{001} - X_{101}X_{011} & D^0_{12} &= X_{110}X_{000} - X_{100}X_{010}\\
D^1_{23} &= X_{111}X_{100} - X_{110}X_{101} & D^0_{23} &= X_{011}X_{000} - X_{010}X_{001}\\
D^1_{13} &= X_{111}X_{010} - X_{110}X_{011} & D^0_{13} &= X_{101}X_{000} - X_{100}X_{001}\\
H_1 &= X_{111}X_{000} - X_{011}X_{100} & H_2 &= X_{111}X_{000} - X_{110}X_{001}\\
H_3 &= X_{101}X_{010} - X_{110}X_{001} & H_4 &= X_{101}X_{010} - X_{011}X_{100}
\end{aligned}$$

$$H = X_{111}X_{000} + X_{101}X_{010} - X_{110}X_{001} - X_{011}X_{100}$$

$$\overline{W}_{lmn} = \sum_i\sum_j\sum_k a_{l+i,\,m+j,\,n+k}X_{ijk}$$

$$\overline{W} = \sum_i\sum_j\sum_k X_{ijk}\overline{W}_{ijk}$$

The criterion for the stability of this equilibrium point can be obtained from the eigenvalues of the Jacobian

$$\mathbf{J} = \left(\frac{\partial p'_i}{\partial p_j}\right)$$

evaluated at this equilibrium point. This is the matrix

$$\mathbf{J} = \begin{pmatrix}\mathbf{A} & 0 & 0\\ 0 & \mathbf{B} & 0\\ 0 & 0 & \mathbf{C}\end{pmatrix}$$

where

$$\mathbf{A} = \left(1+\frac{K_1}{1+K_1}\right)$$

$$\mathbf{B} = \begin{pmatrix} 1+\dfrac{(K_1+\hat{p}_1)K_2-r_1\hat{q}_1}{(1+K_1)(1+K_2)}, & \dfrac{\hat{q}_1K_2+r_1\hat{q}_1}{(1+K_1)(1+K_2)},\\ \dfrac{\hat{p}_1K_2+r_1\hat{p}_1}{(1+K_1)(1+K_2)}, & 1+\dfrac{(K_1+\hat{q}_1)K_2-r_1\hat{p}_1}{(1+K_1)(1+K_2)}\end{pmatrix}$$

and $\mathbf{C}$ is a 4×4 matrix with the elements given in Table 2. In these matrices $\hat{q}_i = 1-\hat{p}_i$ and

$$K_i = \frac{a_ib_i}{a_i+b_i}$$

which is negative if the heterozygote is fitter than both homozygotes.

The eigenvalues of $\mathbf{B}$ and $\mathbf{C}$ can be found by noting that

$$\xi_1 = \begin{pmatrix}1\\1\end{pmatrix} \quad\text{and}\quad \xi_2 = \begin{pmatrix}a_1\\-b_1\end{pmatrix}$$

are the eigenvectors of **B** and

$$\xi_3 = \begin{pmatrix} 1 \\ 1 \\ 1 \\ 1 \end{pmatrix}, \quad \xi_4 = \begin{pmatrix} a_1 \\ a_1 \\ -b_1 \\ -b_1 \end{pmatrix}, \quad \xi_5 = \begin{pmatrix} a_2 \\ -b_2 \\ a_2 \\ -b_2 \end{pmatrix}, \quad \xi_6 = \begin{pmatrix} a_1 a_2 \\ -a_1 b_2 \\ -b_1 a_2 \\ b_1 b_2 \end{pmatrix}$$

are the eigenvectors of **C**.

Table 2. *Elements of the matrix* **C**

$$c_{11} = 1 + \frac{(K_1+\hat{p}_1)(K_2+\hat{p}_2)K_3 - r_1\hat{q}_1\hat{q}_2(1+K_3) - r_2(1+K_1)\hat{q}_2 - (r_1+r_2-2r_1r_2)\hat{q}_1(K_2+\hat{p}_2) + r_1r_2\hat{q}_1\hat{q}_2}{(1+K_1)(1+K_2)(1+K_3)}$$

$$c_{12} = \frac{(K_1+\hat{p}_1)\hat{q}_2K_3 + r_1\hat{q}_1\hat{q}_2K_3 + r_2(K_1+\hat{p}_1)\hat{q}_2 + r_1r_2\hat{q}_1\hat{q}_2}{(1+K_1)(1+K_2)(1+K_3)}$$

$$c_{13} = \frac{\hat{q}_1(K_2+\hat{p}_2)K_3 + r_1\hat{q}_1\hat{q}_2(1+K_3) + (r_1+r_2-2r_1r_2)\hat{q}_1(K_2+\hat{p}_2) - r_1r_2\hat{q}_1\hat{q}_2}{(1+K_1)(1+K_2)(1+K_3)}$$

$$c_{14} = \frac{\hat{q}_1\hat{q}_2K_3 - r_1\hat{q}_1\hat{q}_2K_3 + r_2\hat{q}_1\hat{q}_2 - r_1r_2\hat{q}_1\hat{q}_2}{(1+K_1)(1+K_2)(1+K_3)}$$

$$c_{21} = \frac{(K_1+\hat{p}_1)\hat{p}_2K_3 + r_1\hat{q}_1\hat{p}_2K_3 + r_2(K_1+\hat{p}_1)\hat{p}_2 + r_1r_2\hat{q}_1\hat{p}_2}{(1+K_1)(1+K_2)(1+K_3)}$$

$$c_{22} = 1 + \frac{(K_1+\hat{p}_1)(K_2+\hat{q}_2)K_3 - r_1\hat{q}_1\hat{p}_2(1+K_3) - r_2(1+K_1)\hat{p}_2 - (r_1+r_2-2r_1r_2)\hat{q}_1(K_2+\hat{q}_2) + r_1r_2\hat{q}_1\hat{p}_2}{(1+K_1)(1+K_2)(1+K_3)}$$

$$c_{23} = \frac{\hat{q}_1\hat{p}_2K_3 - r_1\hat{q}_1\hat{p}_2K_3 + r_2\hat{q}_1\hat{p}_2 - r_1r_2\hat{q}_1\hat{p}_2}{(1+K_1)(1+K_2)(1+K_3)}$$

$$c_{24} = \frac{\hat{q}_1(K_2+\hat{q}_2)K_3 + r_1\hat{q}_1\hat{p}_2(1+K_3) + (r_1+r_2-2r_1r_2)\hat{q}_1(K_2+\hat{q}_2) - r_1r_2\hat{q}_1\hat{p}_2}{(1+K_1)(1+K_2)(1+K_3)}$$

$$c_{31} = \frac{\hat{p}_1(K_2+\hat{p}_2)K_3 + r_1\hat{p}_1\hat{q}_2(1+K_3) + (r_1+r_2-2r_1r_2)\hat{p}_1(K_2+\hat{p}_2) - r_1r_2\hat{p}_1\hat{q}_2}{(1+K_1)(1+K_2)(1+K_3)}$$

$$c_{32} = \frac{\hat{p}_1\hat{q}_2K_3 - r_1\hat{p}_1\hat{q}_2K_3 + r_2\hat{p}_1\hat{q}_2 - r_1r_2\hat{p}_1\hat{q}_2}{(1+K_1)(1+K_2)(1+K_3)}$$

$$c_{33} = 1 + \frac{(K_1+\hat{q}_1)(K_2+\hat{p}_2)K_3 - r_1\hat{p}_1\hat{q}_2(1+K_3) - r_2(1+K_1)\hat{q}_2 - (r_1+r_2-2r_1r_2)\hat{p}_1(K_2+\hat{p}_2) + r_1r_2\hat{p}_1\hat{q}_2}{(1+K_1)(1+K_2)(1+K_3)}$$

$$c_{34} = \frac{(K_1+\hat{q}_1)\hat{q}_2K_3 + r_1\hat{p}_1\hat{q}_2K_3 + r_2(K_1+\hat{q}_1)\hat{q}_2 + r_1r_2\hat{p}_1\hat{q}_2}{(1+K_1)(1+K_2)(1+K_3)}$$

$$c_{41} = \frac{\hat{p}_1\hat{p}_2K_3 - r_1\hat{p}_1\hat{p}_2K_3 + r_2\hat{p}_1\hat{p}_2 - r_1r_2\hat{p}_1\hat{p}_2}{(1+K_1)(1+K_2)(1+K_3)}$$

$$c_{42} = \frac{\hat{p}_1(K_2+\hat{q}_2)K_3 + r_1\hat{p}_1\hat{p}_2(1+K_3) + (r_1+r_2-2r_1r_2)\hat{p}_1(K_2+\hat{q}_2) - r_1r_2\hat{p}_1\hat{p}_2}{(1+K_1)(1+K_2)(1+K_3)}$$

$$c_{43} = \frac{(K_1+\hat{q}_1)\hat{p}_2K_3 + r_1\hat{p}_1\hat{p}_2K_3 + r_2(K_1+\hat{q}_1)\hat{p}_2 + r_1r_2\hat{p}_1\hat{p}_2}{(1+K_1)(1+K_2)(1+K_3)}$$

$$c_{44} = 1 + \frac{(K_1+\hat{q}_1)(K_2+\hat{q}_2)K_3 - r_1\hat{p}_1\hat{p}_2(1+K_3) - r_2(1+K_1)\hat{p}_2 - (r_1+r_2-2r_1r_2)\hat{p}_1(K_2+\hat{q}_2) + r_1r_2\hat{p}_1\hat{p}_2}{(1+K_1)(1+K_2)(1+K_3)}$$

The eigenvalues of $\mathbf{J}$, arranged in a natural order, are therefore

$$\lambda_1 = 1+\frac{K_1}{1+K_1},$$

$$\lambda_2 = 1+\frac{K_2}{1+K_2},$$

$$\lambda_3 = 1+\frac{K_3}{1+K_3},$$

$$\lambda_4 = 1+\frac{K_1K_2-r_1}{(1+K_1)(1+K_2)},$$

$$\lambda_5 = 1+\frac{K_2K_3-r_2}{(1+K_2)(1+K_3)},$$

$$\lambda_6 = 1+\frac{K_1K_3-(r_1+r_2-2r_1r_2)}{(1+K_1)(1+K_3)},$$

$$\lambda_7 = 1+\frac{K_1K_2K_3-r_1(\frac{1}{2}+K_3)-r_2(\frac{1}{2}+K_1)-(r_1+r_2-2r_1r_2)(\frac{1}{2}+K_2)}{(1+K_1)(1+K_2)(1+K_3)}.$$

For the equilibrium point given in (3) to be stable all of the eigenvalues must be less than one in absolute value.

The first three eigenvalues λ_1, λ_2, and λ_3 lead to the conditions

$$K_1 < 0, \quad K_2 < 0 \quad \text{and} \quad K_3 < 0$$

which must be satisfied if the equilibrium point is to be stable. These conditions are satisfied if there is heterozygotic superiority at each locus and are not satisfied if there is heterozygotic inferiority.

The eigenvalues λ_4, λ_5, and λ_6 lead to the conditions

$$r_1 > K_1K_2,$$
$$r_2 > K_2K_3,$$
$$r_1+r_2-2r_1r_2 > K_1K_3,$$

which must be satisfied if the equilibrium is to be stable. These conditions result from the two loci interactions. They are exactly the same inequalities which would result if each pair of loci were considered as an isolated two locus system (Bodmer & Felsenstein, 1967).

The last eigenvalue λ_7 can be shown to always be less than one in absolute value if there is heterozygotic superiority at each locus. This follows from the fact that $-\frac{1}{2} < K_i < 0$ if there is a heterozygotic advantage at each locus. From this it can easily be seen the λ_7 must be less than one. In order to show that $\lambda_7 > -1$ we must show that

$$2+\frac{K_1K_2K_3-r_1(\frac{1}{2}+K_3)-r_2(\frac{1}{2}+K_1)-(r_1+r_2-2r_1r_2)(\frac{1}{2}+K_2)}{(1+K_1)(1+K_2)(1+K_3)} > 0.$$

Upon multiplying through by the denominator and rearranging, the left-hand side of the inequality becomes

$$\tfrac{1}{4}+K_1K_2K_3+(\tfrac{1}{2}-r_1)(\tfrac{1}{2}+K_3)+(\tfrac{1}{2}-r_2)(\tfrac{1}{2}+K_1)+(\tfrac{1}{2}-r_1-r_2+2r_1r_2)(\tfrac{1}{2}+K_2)$$
$$+(\tfrac{1}{2}+K_1)(\tfrac{1}{2}+K_2)+(\tfrac{1}{2}+K_1)(\tfrac{1}{2}+K_3)+(\tfrac{1}{2}+K_2)(\tfrac{1}{2}+K_3)+2(\tfrac{1}{2}+K_1)(\tfrac{1}{2}+K_2)(\tfrac{1}{2}+K_3).$$

This can be seen to be always positive since $-\frac{1}{2} < K_i < 0$ and $r_i < \frac{1}{2}$. Thus λ_7 does not lead to any new condition which must be satisfied in order for the equilibrium to be stable.

It has therefore been shown that, for the three locus model with multiplicative fitnesses, the conditions for stability of the equilibrium with no linkage disequilibrium are (*a*) three conditions which require heterozygotic superiority at each of the three loci, and (*b*) three conditions resulting from the three pairs of two loci interactions which are exactly the same as if each pair is considered as an isolated two locus system. There is no new condition resulting from the three loci interactions.

It therefore seems likely that for the n locus model with multiplicative fitnesses the conditions for stability of the equilibrium with no linkage disequilibrium will be (*a*) n conditions requiring there to be heterozygotic superiority at each of the n loci, and (*b*) $\binom{n}{2}$ conditions for each pair of loci which are exactly the same as if each pair is considered an isolated two locus system.

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