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Evolution

Two-locus autosomal sex determination: On the evolutionary genetic stability of the even sex ratio

(linkage/population–genetic models/classes of polymorphisms/long-term evaluation)

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ABSTRACT **In two-locus models of sex determination, there are two kinds of interior (polymorphic) equilibria. One class has the even sex ratio, and the other has equal allele frequencies in the two sexes. Equilibria of the second class may exhibit linkage disequilibrium. The condition for external stability of these second-class equilibria to invasion by a new allele is that the appropriately averaged sex ratio near the equilibrium be moved closer to the even sex ratio than the average among the resident genotypes. However, invasion by a new chromosome depends on the recombination fraction in a way that appears to preclude general results about the evolutionary genetic stability of the even sex ratio in this situation.**

1. Introduction

Fisher (1) argued that if the costs involved in producing male and female offspring were equal, a sex ratio of 1:1 would maximize the number of "grandoffspring" attributable to any individual. Models of autosomal sex determination by a single gene with two alleles in which an individual's genotype determined its sex or that of its offspring have supported Fisher's prediction (except under certain well-defined restrictions) that there should be evolution toward the even sex ratio (2–6). Sex determination by a single sex-linked locus produces a different conclusion (5–8), although Eshel (9, 10) has suggested that Fisher's argument can be replaced by one in which the number of one's genes carried by grandoffspring is maximized.

Eshel and Feldman (11) suggested an approach to the long-term evolution at a locus controlling sex determination by considering the fate of new mutations that arise near a multiallelic polymorphic equilibrium. This approach may be regarded as an extension of Hamilton's (7) "unbeatable strategy" or of Maynard Smith and Price's (12) "evolutionary stable strategy." Eshel and Feldman showed (*i*) that no matter how many alleles exist at the sex-determining locus, an equilibrium with the even sex ratio is the only one that can be stable to the introduction of any new mutation that affects sex determination, and (*ii*) that if the sex ratio at equilibrium is not 1:1, then a new autosomal mutation introduced near that equilibrium will initially increase provided that it renders the sex ratio closer to 1:1. Eshel and Feldman called properties *i* and *ii* evolutionary genetic stability (EGS) of the even sex ratio. It was proved by Karlin and Lessard (13, 14) that after the initial invasion, the new interior equilibrium attained produced an average sex ratio closer to even than that prior to the invasion.

In the present note we extend considerations of long-term evolution to the situation where sex is determined by two autosomal loci that may recombine. We show that with respect to a new mutation at each of the loci separately, there is a reasonable extension of the property of EGS, although invasion by new chromosomes presents interesting difficulties.

2. Interior Equilibria in the Two-Locus Model

In an infinite, diploid, random-mating population, we consider alleles $A_1, A_2, \ldots, A_K$ at the first locus and alleles $B_1, B_2, \ldots, B_L$ at the second. There are KL chromosomes (A_iB_j). The probability that genotype A_aB_b/A_cB_d is male is $m_{ab,cd}$ with $0 \leq m_{ab,cd} \leq 1$ and $m_{ab,cd} = m_{cd,ab} = m_{ad,cb} = m_{cb,ad}$. Some special cases in which certain $m_{ab,cd}$ took the value 1 and others the value 0 were examined by Karlin and Lessard (chap. 5 in ref. 15). Denote by x_{ij} and y_{ij} the relative frequencies of the chromosome A_iB_j transmitted to offspring by adult males and females, respectively, after recombination in a given generation. Then among these offspring, the relative frequency of double homozygotes A_iB_j/A_iB_j is $x_{ij}y_{ij}$ and that of heterozygotes is A_iB_j/A_kB_l, where $i \neq k$ or $j \neq l$ is $x_{ij}y_{kl} + x_{kl}y_{ij}$. The total frequency of males among these offspring is then

$$M = \sum_i \sum_j \sum_k \sum_l x_{ij}y_{kl}m_{ij,kl} \qquad [1]$$

and of females is $1 - M$.

These offspring develop into adults in whom recombination occurs at meiosis at the rate R, $0 \leq R \leq 1/2$. The relative frequency of A_iB_j transmitted by these males is then

$$x'_{ij} = \frac{1}{2M} \sum_k \sum_l \{(1 - R)[x_{ij}y_{kl} + x_{kl}y_{ij}] + R[x_{il}y_{kj} + x_{kj}y_{il}]\}m_{ij,kl} \qquad [2]$$

$$= \frac{1}{2M}\left\{\sum_k \sum_l (x_{ij}y_{kl} + x_{kl}y_{ij})m_{ij,kl} - R\Delta^*_{ij}\right\}. \qquad [3]$$

In gametes transmitted by females we have

$$y'_{ij} = \frac{1}{2(1 - M)} \sum_k \sum_l \{(1 - R)[x_{ij}y_{kl} + x_{kl}y_{ij}] + R[x_{il}y_{kj} + x_{kj}y_{il}]\}(1 - m_{ij,kl}) \qquad [4]$$

$$= \frac{1}{2(1 - M)}\{x_{ij} + y_{ij} - R\Delta_{ij} - 2Mx'_{ij}\}, \qquad [5]$$

where

$$\Delta^*_{ij} = \sum_k \sum_l m_{ij,kl}[x_{ij}y_{kl} + x_{kl}y_{ij} - x_{il}y_{kj} - x_{kj}y_{il}] \qquad [6]$$

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Abbreviation: EGS, evolutionary genetic stability.

and

$$\Delta_{ij} = \sum_{k} \sum_{l} [x_{ij}y_{kl} + x_{kl}y_{ij} - x_{il}y_{kj} - x_{kj}y_{il}]. \qquad [7]$$

From Eq. **5** at equilibrium we have

$$(1 - 2M)(x_{ij} - y_{ij}) = R\Delta_{ij}. \qquad [8]$$

Simple manipulation of Eq. **7** reveals that

$$\sum_{i} \Delta_{ij} = \sum_{j} \Delta_{ij} = 0, \qquad [9]$$

so that at equilibrium, for all i and j,

$$(1 - 2M)(x_{i\cdot} - y_{i\cdot}) = (1 - 2M)(x_{\cdot j} - y_{\cdot j}) = 0, \qquad [10]$$

where

$$x_{i\cdot} = \sum_{j} x_{ij},\ y_{i\cdot} = \sum_{j} y_{ij}$$

and

$$x_{\cdot j} = \sum_{i} x_{ij},\ y_{\cdot j} = \sum_{i} y_{ij} \qquad [11]$$

are the frequencies of A_i in males and females and the frequencies of B_j in males and females, respectively. Thus, we have *Result 1.*

RESULT 1. *At equilibrium either the sex ratio is* 1:1 *or the allele frequencies at each locus are equal in males and females; in Eq.* **10** *either* $\hat{M} = 1/2$ *or* $\hat{x}_{i\cdot} = \hat{y}_{i\cdot}$ *and* $\hat{x}_{\cdot j} = \hat{y}_{\cdot j}$. *The frequencies of the chromosomes may not be equal in the two sexes. (The caret will be used to denote equilibrium values.)*

Suppose that $\hat{M} \neq 1/2$ so that $\hat{x}_{i\cdot} = \hat{y}_{i\cdot}$ and $\hat{x}_{\cdot j} = \hat{y}_{\cdot j}$ for all i, j. Then we may write

$$\hat{x}_{ij} = \hat{x}_{i\cdot}\, \hat{x}_{\cdot j} + \hat{\Delta}^{x}_{ij},\ \hat{y}_{ij} = \hat{x}_{i\cdot}\, \hat{x}_{\cdot j} + \hat{\Delta}^{y}_{ij} \qquad [12]$$

where

$$\hat{\Delta}^{x}_{ij} = \sum_{k} \sum_{l} (\hat{x}_{ij}\hat{x}_{kl} - \hat{x}_{il}\hat{x}_{kj}) \qquad [13a]$$

and

$$\hat{\Delta}^{y}_{ij} = \sum_{k} \sum_{l} (\hat{y}_{ij}\hat{y}_{kl} - \hat{y}_{il}\hat{y}_{kj}). \qquad [13b]$$

Now write Eq. **7** in the form

$$\begin{aligned}\hat{\Delta}_{ij} = 2\hat{\Delta}^{x}_{ij} + \sum_{k} \sum_{l} \{&(\hat{x}_{i\cdot}\, \hat{x}_{\cdot j} + \hat{\Delta}^{x}_{ij})[-R\hat{\Delta}_{kl}/(1 - 2M)]\\ &+ (\hat{x}_{k\cdot}\, \hat{x}_{\cdot l} + \hat{\Delta}^{x}_{kl})[-R\hat{\Delta}_{ij}/(1 - 2M)]\\ &+ (\hat{x}_{i\cdot}\, x_{\cdot l} + \hat{\Delta}^{x}_{il})[R\Delta_{kj}/(1 - 2M)]\\ &+ (\hat{x}_{k\cdot}\, x_{\cdot j} + \hat{\Delta}^{x}_{kj})[R\hat{\Delta}_{il}/(1 - 2M)]\},\end{aligned} \qquad [14]$$

where we repeatedly have used Eqs. **8** and **12**. Major simplification of Eq. **14** is possible because by Eq. **9**

$$\Delta_{ij} = -\sum_{k \neq i} \Delta_{kj} = -\sum_{l \neq j} \Delta_{il}.$$

This produces the result

$$\hat{\Delta}_{ij} = 2\hat{\Delta}^{x}_{ij} - \frac{R}{1 - 2M}\hat{\Delta}_{ij}$$

or

$$\hat{\Delta}^{x}_{ij} = \hat{\Delta}_{ij}[1 - 2\hat{M} + R]/2(1 - 2\hat{M}). \qquad [15]$$

In the same way

$$\hat{\Delta}^{y}_{ij} = \hat{\Delta}_{ij}[1 - 2\hat{M} - R]/2(1 - 2\hat{M}), \qquad [16]$$

so that we get *Result 2.*

RESULT 2. *At equilibrium with* $\hat{M} \neq 1/2$,

$$\hat{\Delta}_{ij} = \hat{\Delta}^{x}_{ij} + \hat{\Delta}^{y}_{ij},$$

and if $\hat{\Delta}_{ij} = 0$, *then* $\hat{\Delta}^{x}_{ij} = \hat{\Delta}^{y}_{ij} = 0$ *also. In other words, the "two-sex disequilibrium"* Δ_{ij} *is the sum of those in the single sexes.*

Remark 1: The quantities Δ_{ij} are two-sex linkage disequilibrium values, and if any of them vanishes at equilibrium, then either $\hat{M} = 1/2$ or the chromosome frequencies corresponding to the vanishing Δ_{ij} are equal in the sexes. If $\hat{\Delta}_{ij} = 0$ for all i and j and $\hat{M} \neq 1/2$, then it is obvious from Eqs. **3**, **5**, **15**, and **16** that the equilibrium chromosome frequencies are identical to those of a one-locus multiple allele selection model with viability matrix $\| m_{ij,kl} \|$. Further, since $\hat{\Delta}_{ij} = 0$, these equilibrium chromosome frequencies must be products of the constituent allele frequencies at the two loci. Karlin and Lessard (chap. 5 in ref. 15) discuss stability properties of some special sex-determination models that allow equilibria of this kind.

Remark 2: Result 1 and *Remark 1* have generalizations to the multilocus situation with an arbitrary number of alleles. Elsewhere we show, using the representation of Karlin (16) and Karlin and Liberman (17, 18), that at equilibrium either the sex ratio is even or the allele frequencies at each locus are equal in males and females. Further, if the chromosome frequencies at equilibrium with $\hat{M} \neq 1/2$ are sex symmetric, then they are products of the allele frequencies at each of the multiple loci.

3. External Stability and EGS

Suppose that an equilibrium solution $(\hat{x}_{ij}, \hat{y}_{ij})$ with $i = 1, 2, \ldots, K$; $j = 1, 2, \ldots, L$ exists and is stable with respect to perturbations among these KL chromosomes. Consider a new allele A_{K+1} that arises in the neighborhood of this equilibrium. The frequencies of chromosomes $A_{K+1}B_1$, $A_{K+1}B_2, \ldots, A_{K+1}B_L$ are $\varepsilon_1, \varepsilon_2, \ldots, \varepsilon_L$ in males and $\eta_1, \eta_2, \ldots, \eta_L$ in females. Primes denote frequencies in the next generation, and quadratic and higher order ε and η terms may be ignored. Recursions **2** and **4** reduce under these conditions to the linear system

$$\begin{aligned}2\hat{M}\varepsilon'_j = {}&\varepsilon_j\hat{M}^{y}_{K+1,j\cdot} + \eta_j\hat{M}^{x}_{K+1,j\cdot}\\ &- R \sum_{\substack{s \neq K+1\\ t \neq j}} m_{K+1,j,st}(\varepsilon_j\hat{y}_{st} + \eta_j\hat{x}_{st} - \varepsilon_t\hat{y}_{sj} - \eta_t\hat{x}_{sj}),\end{aligned} \qquad [17a]$$

$$\begin{aligned}2(1 - \hat{M})\eta'_j = {}&\varepsilon_j(1 - \hat{M}^{y}_{K+1,j\cdot}) + \eta_j(1 - \hat{M}^{x}_{K+1,j\cdot})\\ &- R \sum_{\substack{s \neq K+1\\ t \neq j}} (1 - m_{K+1,j,st})\\ &\times (\varepsilon_j\hat{y}_{st} + \eta_j\hat{x}_{st} - \varepsilon_t\hat{y}_{sj} - \eta_t\hat{x}_{sj}),\end{aligned} \qquad [17b]$$

where

$$\hat{M} = \sum_{a=1}^{K} \sum_{b=1}^{L} \sum_{c=1}^{K} \sum_{d=1}^{L} m_{ab,cd}\hat{x}_{ab}\hat{y}_{cd}, \qquad [17c]$$

$$\hat{M}^{x}_{K+1,j\cdot} = \sum_{s=1}^{K} \sum_{t=1}^{L} m_{K+1,j,st}\hat{x}_{st}, \qquad [17d]$$

$$\hat{M}^{y}_{K+1,j\cdot} = \sum_{s=1}^{K} \sum_{t=1}^{L} m_{K+1,j,st}\hat{y}_{st}. \qquad [17e]$$

For $R = 0$, the problem reduces to that studied by Eshel and Feldman (19) with multiple alleles at one locus. The system **17** has a strictly positive matrix when $R > 0$. Hence, there is a unique largest eigenvalue that has an associated strictly positive right eigenvector. Denote this eigenvalue by λ_0, and restrict attention to perturbations in the direction of this main eigenvector, which we write as

$$(\tilde{\boldsymbol{\varepsilon}}, \tilde{\boldsymbol{\eta}}) = (\tilde{\varepsilon}_1, \tilde{\varepsilon}_2, \ldots, \tilde{\varepsilon}_L, \tilde{\eta}_1, \tilde{\eta}_2, \ldots, \tilde{\eta}_L). \qquad [18]$$

Then of course

$$\tilde{\varepsilon}_j' = \lambda_0 \tilde{\varepsilon}_j, \; \tilde{\eta}_j' = \lambda_0 \tilde{\eta}_j \qquad [19]$$

and, if we write $\tilde{\varepsilon} = \Sigma_j \tilde{\varepsilon}_j$, $\tilde{\eta} = \Sigma_j \tilde{\eta}_j$,

$$\tilde{\varepsilon}' + \tilde{\eta}' = \lambda_0(\tilde{\varepsilon} + \tilde{\eta}). \qquad [20]$$

Set $w_j = \tilde{\varepsilon}_j/(\tilde{\varepsilon} + \tilde{\eta})$ and $z_j = \tilde{\eta}_j/(\tilde{\varepsilon} + \tilde{\eta})$ so that $\Sigma_{j=1}^{L} (w_j + z_j) = 1$.

From Eqs. **17a** and **17b** we have

$$\tilde{\varepsilon}' = \sum_{j=1}^{L} \tilde{\varepsilon}_j' = (\tilde{\varepsilon} + \tilde{\eta})\left[\sum_j w_j \hat{M}^{y}_{K+1,j\cdot} + \sum_j z_j \hat{M}^{x}_{K+1,j\cdot}\right]\Big/2\hat{M} \qquad [21]$$

$$\tilde{\eta}' = \sum_{j=1}^{L} \tilde{\eta}_j' = (\tilde{\varepsilon} + \tilde{\eta})\left[\sum_j w_j(1 - \hat{M}^{y}_{K+1,j\cdot}) + \sum_j z_j(1 - \hat{M}^{x}_{K+1,j\cdot})\right]\Big/2(1 - \hat{M}). \qquad [22]$$

Combining Eqs. **21** and **22** we have

$$(\tilde{\varepsilon}' + \tilde{\eta}') = (\tilde{\varepsilon} + \tilde{\eta})\left\{\sum_j w_j\left[\frac{\hat{M}^{y}_{K+1,j\cdot}}{2\hat{M}} + \frac{1 - \hat{M}^{y}_{K+1,j\cdot}}{2(1 - \hat{M})}\right] + \sum_j z_j\left[\frac{\hat{M}^{x}_{K+1,j\cdot}}{2\hat{M}} + \frac{1 - \hat{M}^{x}_{K+1,j\cdot}}{2(1 - \hat{M})}\right]\right\}. \qquad [23]$$

Comparison of Eqs. **23** and **20** reveals that

$$\lambda_0 = \sum_j \left\{ w_j\left[1 + \frac{(\tfrac{1}{2} - \hat{M})(\hat{M}^{y}_{K+1,j\cdot} - \hat{M})}{\hat{M}(1 - \hat{M})}\right] + z_j\left[1 + \frac{(\tfrac{1}{2} - \hat{M})(\hat{M}^{x}_{K+1,j\cdot} - \hat{M})}{\hat{M}(1 - \hat{M})}\right]\right\} \qquad [24]$$

$$= 1 + \frac{(\tfrac{1}{2} - \hat{M})}{\hat{M}(1 - \hat{M})}\left\{\sum_j (w_j \hat{M}^{y}_{K+1,j\cdot} + z_j \hat{M}^{x}_{K+1,j\cdot}) - \hat{M}\right\} \qquad [25]$$

$$= 1 + \frac{(\tfrac{1}{2} - \hat{M})(\hat{M}_{K+1} - \hat{M})}{\hat{M}(1 - \hat{M})}, \qquad [26]$$

say, where

$$\hat{M}_{K+1} = \sum_j (w_j \hat{M}^{y}_{K+1,j\cdot} + z_j \hat{M}^{x}_{K+1,j\cdot}). \qquad [27]$$

Thus, $\lambda_0 > 1$ if either $\hat{M} < \tfrac{1}{2}$ and $\hat{M}_{K+1} > \hat{M}$ or $\hat{M} > \tfrac{1}{2}$ and $\hat{M}_{K+1} < \hat{M}$. The expression M_{K+1} in Eq. **27** may be regarded as the marginal average sex ratio induced by A_{K+1} in the direction of the leading eigenvector of the local linear transformation Eq. **17** that governs the external stability to invasion by A_{K+1}. Note that if $\hat{M} = \tfrac{1}{2}$, the leading eigenvalue is unity, and linear analysis is uninformative about the fate of A_{K+1}. We summarize with *Result 3.*

RESULT 3. *In a two-locus random-mating system of autosomal sex determination, if a new mutation at one of the loci appears near an equilibrium where the sex ratio is not* 1:1, *the mutation will invade if it initially renders the sex ratio closer to even in the direction of the leading eigenvector of the local linear transformation.*

Remark 1: If at equilibrium prior to the introduction of A_{K+1} we had $\hat{x}_{ij} = \hat{y}_{ij}$ for all i, j (so that $\hat{\Delta}_{ij} = 0$ also), then $\hat{M}^{x}_{K+1,j\cdot} = \hat{M}^{y}_{K+1,j\cdot}$ and the local stability analysis reduces to exactly that used by Eshel and Feldman (20) to study external stability in the two-locus multiallele model.

Remark 2: The case of sex determination studied here can be viewed as a special case of the two-sex viability model studied by Liberman (21) and Lessard (22). [See also Karlin and Lessard (15).] Liberman and Lessard independently obtained an external stability condition similar to that obtained here—namely, that the marginal average fitness of the new allele should be greater than the mean fitness of the residents. The averages must be taken over the sexes and in the direction of the leading eigenvector for the local linear transformation. It is of interest that this class of results for initial increase of alleles does not apply to initial increase of chromosomes, as we shall now see.

4. Invasion by a New Chromosome and Failure of EGS

In the previous section, a new allele arose at one of the two loci in the system. The fate of a new chromosome that appears in the population has also been a focus of interest in studies of evolution at linked loci. The dependence of the invasion on the extent of recombination has had interesting qualitative ramifications, for example in the case of kin selection (23, 24). The same is true in the case of two-locus models of sex determination, as we now proceed to show.

It will be sufficient to consider the special case $K = L = 2$ of the model in *Section 2*, in which case sex determination is described by a 4 × 4 symmetric, nonnegative matrix. For convenience, in this matrix and for the chromosome frequencies we use the identification 1, 2, 3, 4 for chromosomes previously denoted [11], [12], [21], and [22], respectively. Consider the case where A_1B_1 is initially fixed—i.e., $\hat{x}_1 = \hat{y}_1 = 1$ prior to the introduction of both A_2 and B_2. We seek the local stability properties of $\hat{x}_1 = 1$, $\hat{y}_1 = 1$ in the six-dimensional simplex $0 \leq x_i, y_i \leq 1$ for $i = 1, 2, 3, 4$ and $\Sigma_{i=1}^{4} x_i = 1$, $\Sigma_{i=1}^{4} y_i = 1$. Write $\varepsilon_2, \varepsilon_3, \varepsilon_4$ and η_2, η_3, η_4 for the small frequencies of A_1B_2, A_2B_1, A_2B_2 in males and females, respectively, near $\hat{x}_1 = 1$, $\hat{y}_1 = 1$. Then from Eqs. **3** and **4**, neglecting terms of quadratic or higher order, we have

$$\varepsilon_2' + \eta_2' = (\varepsilon_2 + \eta_2)m^{*}_{12} + (\varepsilon_4 + \eta_4)m^{*}_{14}R \qquad [28a]$$

$$\varepsilon_3' + \eta_3' = (\varepsilon_3 + \eta_3)m^{*}_{13} + (\varepsilon_4 + \eta_4)m^{*}_{14}R \qquad [28b]$$

$$\varepsilon_4' + \eta_4' = (\varepsilon_4 + \eta_4)m^{*}_{14}(1 - R), \qquad [28c]$$

where for $j = 2, 3$, and 4

$$m^{*}_{ij} = \frac{m_{ij}}{2m_{11}} + \frac{1 - m_{ij}}{2(1 - m_{11})} = 1 + \frac{(\tfrac{1}{2} - m_{11})(m_{ij} - m_{11})}{m_{11}(1 - m_{11})} \qquad [29]$$

Suppose $m_{12} < m_{11} < \tfrac{1}{2}$ and, to make the algebra a little simpler, set $m_{13} = m_{12}$. Then from Eqs. **28** and **29** neither A_2 nor B_2 separately could invade A_1B_1. Assume that in addition $\hat{x}_1 = 1$, $\hat{y}_1 = 1$ is locally unstable so that

$$(1 - R)m^{*}_{14} > 1, \qquad [30]$$

which entails from Eq. **29** that $m_{14} > m_{11}$. For sufficiently small ε and η values, the leading eigenvector of the matrix (Eq. **28**) is of the form $(k, k, 1)$, where

$$k = Rm^{*}_{14}/[m^{*}_{14}(1 - R) - m^{*}_{12}]. \qquad [31]$$

Near $\hat{x}_1 = \hat{y}_1 = 1$, it is possible to express the difference $M' - M$ in terms of the $(\varepsilon_j + \eta_j)$—namely,

$$M' - M = (\varepsilon_2 + \eta_2 + \varepsilon_3 + \eta_3)\,\frac{(m_{12} - m_{11})^2(1 - 2m_{11})}{2m_{11}(1 - m_{11})} + (\varepsilon_4 + \eta_4)\left[\frac{(m_{14} - m_{11})^2(1 - 2m_{11})}{2m_{11}(1 - m_{11})} - \frac{R(m_{11} + m_{14} - 2m_{12})(m_{11} + m_{14} - 2m_{11}m_{14})}{2m_{11}(1 - m_{11})}\right]. \quad [32]$$

Substitute Eq. **31** into **32** and reorganize to obtain

$$M' - M = \frac{(\varepsilon_4 + \eta_4)[m_{14}^*(1 - R) - 1]}{m_{14}^*(1 - R) - m_{12}^*}\{2Rm_{14}^*(m_{12} - m_{11}) + (m_{14} - m_{11})[m_{14}^*(1 - R) - m_{12}^*]\}. \quad [33]$$

The sign of $M' - M$ is therefore the same as that of

$$(m_{14} - m_{11})(m_{14}^* - m_{12}^*) - Rm_{14}^*E, \quad [34]$$

where E is the additive epistasis: $E = m_{14} + m_{11} - 2m_{12}$. Under our assumptions, $E > 0$. We conclude that $M' < M$ if

$$R > \frac{(m_{14} - m_{11})(m_{14} - m_{12})(1 - 2m_{11})}{(m_{11} + m_{14} - 2m_{11}m_{14})(m_{11} + m_{14} - 2m_{12})}. \quad [35]$$

But for instability of $\hat{x} = 1$, $\hat{y} = 1$, Eq. **30** holds—namely,

$$R < (m_{14}^* - 1)/m_{14}^* = \frac{(1 - 2m_{11})(m_{14} - m_{11})}{m_{11} + m_{14} - 2m_{11}m_{14}}. \quad [36]$$

For Eqs. **35** and **36** to be compatible, we require

$$1 > (m_{14} - m_{12})/(m_{14} + m_{11} - 2m_{12}) \quad [37]$$

which is guaranteed by our assumptions.

To summarize we have

RESULT 4. *Under the conditions* **35** *and* **36** *with* $\mathrm{m}_{12} < \mathrm{m}_{11} < \mathrm{m}_{14}$ *and with* $\mathrm{m}_{11} < ½$, A_2 *and* B_2 *invade* $\hat{x}_1 = 1$, $\hat{y}_1 = 1$, *but in the direction of the leading eigenvector of the local stability matrix, we have* $\mathrm{M}' < \mathrm{M}$ *locally. In other words, invasion can produce a sex ratio further from even than it was originally.*

As part of a larger numerical study of two-locus sex determinations, we addressed the question of the ultimate value of the sex ratio after invasion. Recall the result of Karlin and Lessard (13, 14) for the one-locus case—that after invasion the sex ratio at equilibrium is closer to even than it was prior to invasion.

We considered 21 numerical examples of two loci with two alleles each in which m_{11}, $m_{12} = m_{13}$, m_{14} were chosen at random uniformly on [0, 1]. The choice was made so that for $R > R^*$, *with* $0 < R^* < ½$, the fixation state $\hat{x}_1 = 1$, $\hat{y}_1 = 1$($\hat{M} = m_{11}$) was locally stable, while for $0 < R < R^*$ it was locally unstable. Of these 21 cases, 8 exhibited the result that for an interval of R values in which $\hat{x}_1 = 1$, $\hat{y}_1 = 1$ was locally unstable, the ultimate equilibrium attained was an isolated interior polymorphism at which the sex ratio $\hat{M}$ satisfied $|\hat{M} - ½| > |m_{11} - ½|$. In other words, the departure of the local stability from the one-locus result we saw in *Result 4* can be accompanied by violation of the Karlin–Lessard result for the ultimate equilibrium:

RESULT 5. *Invasion of a chromosomal fixation state by a new allele at each locus may produce an ultimate sex ratio further from even than it was originally. The dynamics in such cases depend on the recombination fraction.*

It seems reasonable to conjecture that invasion of a two locus polymorphic equilibrium with $\hat{M} \neq ½$ by new alleles at each locus would produce the same result.

5. Concluding Remarks

In this paper we have extended a previous model of autosomal sex determination to two loci with multiple alleles. Such an analysis aims at a better approximation of natural systems as well as a better understanding of the generality of conclusions based on one-locus models.

We demonstrate that two types of equilibria exist. Either the sex ratio at equilibrium is even ($\hat{M} = ½$) or the allelic frequencies at each locus are equal in the two sexes ($\hat{x}_{i\cdot} = \hat{y}_{i\cdot}$, $\hat{x}_{\cdot j} = \hat{y}_{\cdot j}$), although the chromosomal frequencies need not be equal ($\hat{x}_{ij} \neq \hat{y}_{ij}$). These results hold for multiple loci as well.

To analyze the long-term evolution of the system, we continued the approach of Eshel and Feldman (11) by examining the stability of equilibria to invasion by new genotypes such as might occur by mutation or migration. This approach provides insight into the long-term dynamics of the sex ratio in that it indicates whether, in the long run, the even sex ratio tends to be approached as a consequence of successive genetic changes at the loci. This is our concept of EGS.

As in the one-locus case, only the even sex ratio has EGS in the sense of being stable to the introduction of any new mutation at a single locus. In fact, a newly introduced allele will increase when rare if it initially renders the sex ratio closer to even, at least along the direction of the leading eigenvector of the local linear transformation. It has been pointed out by M. K. Uyenoyama (personal communication) that condition **26** for invasion by a new allele is equivalent to the inequality $(\alpha_1 - \alpha_2)(½ - \hat{M}) < 0$, where $(\alpha_1 - \alpha_2)$ is the average effect of substituting the new allele relative to the average of the resident alleles on the character of male production. Inequalities of this form appear in invasion criteria for new alleles in many evolutionary contexts (24). However, the even sex ratio does not have EGS with respect to all genetic changes in the two-locus system. Thus, we find that simultaneous invasion by new alleles at each of two loci may occur despite the fact that the departure of the sex ratio from one-to-one initially increases. Further, the sex ratio may achieve ultimate equilibrium at a value further from 1:1 than it was originally. These violations of EGS for the even sex ratio depend on the extent of recombination between the two loci.

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