Two Locus Autosomal Sex Determination I. On the Evolutionary Genetic Stability of the Even Sex Ratio

Uri Liberman, Marcus W. Feldman, Ilan Eshel, Sarah P. Otto

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Uri Liberman
Ilan Eshel
Department of Statistics
Tel Aviv University
Tel Aviv, Israel

Marcus W. Feldman
Sarah P. Otto
Department of Biological Sciences
Stanford University
Stanford, CA 94305-5020

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Abstract.

In two locus models of sex determination, there are three kinds of interior (polymorphic) equilibria. One class has the even sex ratio, one has equal allele frequencies in the sexes and one, with linkage disequilibrium, has neither of the first two properties. The condition for external stability of these equilibria to invasion by a new allele is that the appropriately averaged sex ratio near the equilibrium be moved closer to even than the average among the resident genotypes. Invasion by a new *chromosome*, however, 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 (1930) argued that, if the costs involved in producing male and female offspring were equal, a sex ratio of one–to–one 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 (Nur, 1974; Eshel, 1975; Uyenoyama and Bengtsson 1979, 1981, 1982). Sex determination by a single sex–linked locus produces a different conclusion (Hamilton, 1967; Bengtsson, 1977; Uyenoyama and Bengtsson 1981, 1982), although Eshel (1986a,b) 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 (1982a) 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 (1967) *unbeatable* strategy or of Maynard Smith and Price's (1973) Evolutionary Stable Strategy (ESS). 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 one–to–one, then a new autosomal mutation introduced near that equilibrium will initially increase provided that it render the sex ratio closer to one–to–one. Eshel and Feldman called properties (i) and (ii) Evolutionary Genetic Stability (EGS) of the even sex ratio. It was proved by Karlin and Lessard (1983, 1984) that, following 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 which may recombine. We show that with respect to 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 $m_{ab,cd} = m_{ba,cd} = m_{ab,dc} = m_{ba,dc}$. Some special cases in which certain $m_{ab,cd}$ took the value 1 and others the value 0 were examined by Karlin and Lessard (1986, ch 5). 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 A_iB_j/A_kB_ℓ, where $i \neq k$ or $j \neq \ell$ is $x_{ij}y_{k\ell} + x_{k\ell}y_{ij}$. The total frequency of males among these offspring is then

$$M = \sum_i \sum_j \sum_k \sum_\ell x_{ij}y_{k\ell}m_{ij,k\ell} \tag{1}$$

and of females is $1 - M$.

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

$$x'_{ij} = \frac{1}{2M} \sum_k \sum_\ell \{(1-R)[x_{ij}y_{k\ell} + x_{k\ell}y_{ij}] + R[x_{i\ell}y_{kj} + x_{kj}y_{i\ell}]\}\, m_{ij,k\ell} \tag{2}$$

$$= \frac{1}{2M}\Big\{\sum_k \sum_\ell (x_{ij}y_{k\ell} + x_{k\ell}y_{ij})m_{ij,k\ell} - R\Delta^*_{ij}\Big\}. \tag{3}$$

In gametes transmitted by females we have

$$y'_{ij} = \frac{1}{2(1-M)} \sum_k \sum_\ell \{(1-R)[x_{ij}y_{k\ell} + x_{k\ell}y_{ij}] + R[x_{i\ell}y_{kj} + x_{kj}y_{i\ell}]\}\,(1 - m_{ij,k\ell}) \tag{4}$$

$$= \frac{1}{2(1-M)}\left\{x_{ij} + y_{ij} - R\Delta_{ij} - 2Mx'_{ij}\right\}, \tag{5}$$

where

$$\Delta^*_{ij} = \sum_{k\neq i} \sum_{\ell\neq j} m_{ij,k\ell}[x_{ij}y_{k\ell} + x_{k\ell}y_{ij} - x_{i\ell}y_{kj} - x_{kj}y_{i\ell}] \tag{6}$$

and

$$\Delta_{ij} = \sum_{k\neq i} \sum_{\ell\neq j} [x_{ij}y_{k\ell} + x_{k\ell}y_{ij} - x_{i\ell}y_{kj} - x_{kj}y_{i\ell}]. \tag{7}$$

From (5) at equilibrium we have

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

Simple manipulation of (7) reveals that

$$\sum_i \Delta_{ij} = \sum_j \Delta_{ij} = 0, \tag{9}$$

so that, at equilibrium, for all i and j

$$(1-2M)(x_i-y_i) = (1-2M)(u_j-v_j) = 0, \tag{10}$$

where

$$\begin{aligned} x_i &= \sum_j x_{ij}, \quad y_i = \sum_j y_{ij}, \\ u_j &= \sum_i x_{ij}, \quad v_j = \sum_i y_{ij}, \end{aligned} \tag{11}$$

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. At equilibrium either the sex ratio is one–to–one or the allele frequencies at each locus are equal in males and females; in (10) either $\hat{M} = \frac{1}{2}$ or $\hat{x}_i = \hat{y}_i$ and $\hat{u}_j = \hat{v}_j$. The frequencies of the chromosomes may not be equal in the two sexes. (The caret ˆ will be used to denote equilibrium values).

Remark 1. The quantities Δ_{ij} are two–sex linkage disequilibrium values and if any of them vanish at equilibrium, then either $\hat{M} = \frac{1}{2}$ 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 $\hat{M} \neq \frac{1}{2}$ then it is obvious from (37) that the equilibrium chromosome frequencies are identical to those of a one–locus multiple allele selection model with viability matrix $\|m_{ij}\|$. Further, since $\hat{\Delta}_{ij} = 0$, these equilibrium chromosome frequencies must be products of the constituent allele frequencies at the two loci.

Remark 2. Result 1 has a generalization to the multilocus situation with an arbitrary number of alleles. In the Appendix we show, using the representation of Karlin (1978) and Karlin and Liberman (1979a,b), that at equilibrium either the sex ratio is even or the allele frequencies at each locus are equal in males and females. Further, the chromosome frequencies at equilibrium with $\hat{M} \neq \frac{1}{2}$ are products of the allele frequencies at each of the multiple loci.

Suppose that $\hat{M} \neq \frac{1}{2}$ so that $\hat{x}_i = \hat{y}_i$ and $\hat{u}_j = \hat{v}_j$. Then we may write

$$\hat{x}_{ij} = \hat{x}_i \hat{u}_j + \hat{\Delta}^x_{ij}, \quad \hat{y}_{ij} = \hat{x}_i \hat{u}_j + \hat{\Delta}^y_{ij} \tag{12}$$

where

$$\hat{\Delta}^x_{ij} = \sum_{k \neq i} \sum_{\ell \neq j} (\hat{x}_{ij}\hat{x}_{k\ell} - \hat{x}_{i\ell}\hat{x}_{kj}) \tag{13a}$$

and

$$\hat{\Delta}^y_{ij} = \sum_{k \neq i} \sum_{\ell \neq j} (\hat{y}_{ij}\hat{y}_{k\ell} - \hat{y}_{i\ell}\hat{y}_{kj}). \tag{13b}$$

Now write (7) in the form

$$\begin{aligned}\hat{\Delta}_{ij} = 2\hat{\Delta}^x_{ij} + \sum_{k \neq i} \sum_{\ell \neq j} \{ & (\hat{x}_i \hat{u}_j + \hat{\Delta}^x_{ij})[-R\hat{\Delta}_{k\ell}/(1-2M)] \\ & + (\hat{x}_k \hat{u}_\ell + \hat{\Delta}^x_{k\ell})[-R\hat{\Delta}_{ij}/(1-2M)] \\ & + (\hat{x}_i u_\ell + \hat{\Delta}^x_{i\ell})[R\hat{\Delta}_{kj}/(1-2M)] \\ & + (\hat{x}_k u_j + \hat{\Delta}^x_{kj})[R\hat{\Delta}_{i\ell}/(1-2M)] \},\end{aligned} \tag{14}$$

where we have repeatedly used (8) and (12). Major simplification of (14) is possible because, by (9)

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

This produces the result

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

or

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

In the same way

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

so that

Result 2. At equilibrium with $\hat{M} \neq \frac{1}{2}$

$$\hat{\Delta}_{ij} = \hat{\Delta}^x_{ij} + \hat{\Delta}^y_{ij},$$

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 average of those in the single sexes.

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} which 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 $\epsilon_1, \epsilon_2, \ldots, \epsilon_L$ in males and $\eta_1, \eta_2, \ldots, \eta_L$ in females. Primes denote frequencies in the next generation and quadratic and higher order terms in ϵ's and η's may be ignored. Recursions (2) and (4) reduce under these conditions to the linear system

$$\begin{aligned} 2\hat{M}\epsilon'_j &= \epsilon_j \hat{M}^y_{K+1,j\cdot} + \eta_j \hat{M}^x_{K+1,j\cdot} \\ &\quad - R \sum_{\substack{s \neq K+1 \\ t \neq j}} m_{K+1,j,st}(\epsilon_j \hat{y}_{st} + \eta_j \hat{x}_{st} - \epsilon_t \hat{y}_{sj} - \eta_t \hat{x}_{sj}), \end{aligned} \tag{17a}$$

$$\begin{aligned} 2(1-\hat{M})\eta'_j &= \epsilon_j(1 - \hat{M}^y_{K+1,j\cdot}) + \eta_j(1 - \hat{M}^x_{K+1,j\cdot}) \\ &\quad - R \sum_{\substack{s \neq K+1 \\ t \neq j}} (1 - m_{K+1,j,st})(\epsilon_j \hat{y}_{st} + \eta_j \hat{x}_{st} - \epsilon_t \hat{y}_{sj} - \eta_t \hat{x}_{sj}), \end{aligned} \tag{17b}$$

where

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

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

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

For $R = 0$ the problem reduces to that studied by Eshel and Feldman (1982) with multiple alleles at one locus. The system (17) has a strictly positive matrix when $R > 0$.

Hence, there is a unique largest eigenvalue which 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

$$(\underline{\tilde{\varepsilon}}, \underline{\tilde{\eta}}) = (\tilde{\varepsilon}_1, \tilde{\varepsilon}_2, \ldots, \tilde{\varepsilon}_L, \tilde{\eta}_1, \tilde{\eta}_2, \ldots, \tilde{\eta}_L). \tag{18}$$

Then of course

$$\tilde{\varepsilon}'_j = \lambda_0 \tilde{\varepsilon}_j, \quad \tilde{\eta}'_j = \lambda_0 \tilde{\eta}_j. \tag{19}$$

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

$$\tilde{\varepsilon}' + \tilde{\eta}' = \lambda_0(\tilde{\varepsilon} + \tilde{\eta}). \tag{20}$$

Set $w_j = \tilde{\varepsilon}_j/(\tilde{\varepsilon}+\tilde{\eta})$ and $z_j = \tilde{\eta}_j/(\tilde{\varepsilon}+\tilde{\eta})$ so that $\sum_{j=1}^{L}(w_j + z_j) = 1$. Our choice of $(\underline{\tilde{\varepsilon}}, \underline{\tilde{\eta}})$ as the right eigenvector associated with λ_0 ensures that, to quadratic orders, $w'_j = w_j$ and $z'_j = z_j$.

From (17a) and (17b) we have

$$\tilde{\varepsilon}' = \sum_{j=1}^{L} \tilde{\varepsilon}'_j = (\tilde{\varepsilon}+\tilde{\eta})\Big[\sum_j w_j \hat{M}^y_{K+1,j\cdot} + \sum_j z_j \hat{M}^x_{K+1,j\cdot}\Big]/2\hat{M} \tag{21}$$

$$\tilde{\eta}' = \sum_{j=1}^{L} \tilde{\eta}'_j = (\tilde{\varepsilon}+\tilde{\eta})\Big[\sum_j w_j (1-\hat{M}^y_{K+1,j\cdot}) + \sum_j z_j (1-\hat{M}^x_{K+1,j\cdot})\Big]/2(1-\hat{M}) \tag{22}$$

In view of the fact that $w'_j = w_j$ and $z'_j = z_j$ to linear order, the square–bracketed terms on the right of (21) and (22) are constant to the order of the linear approximation. Combining (21) and (22) we have

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

Comparison of (23) and (20) reveals that

$$\lambda_0 = \sum_j \left\{ w_j \left[1 + \frac{(\frac{1}{2} - \hat{M})(\hat{M}^y_{K+1,j\cdot} - \hat{M})}{\hat{M}(1-\hat{M})} \right] + z_j \left[1 + \frac{(\frac{1}{2} - \hat{M})(\hat{M}^x_{K+1,j\cdot} - \hat{M})}{\hat{M}(1-\hat{M})} \right] \right\} \tag{24}$$

$$= 1 + \frac{(\frac{1}{2} - \hat{M})}{\hat{M}(1-\hat{M})} \left\{ \sum_j \left(w_j \hat{M}^y_{K+1,j\cdot} + z_j \hat{M}^x_{K+1,j\cdot} \right) - \hat{M} \right\} \tag{25}$$

$$= 1 + \frac{(\frac{1}{2} - \hat{M})(\hat{M}_{K+1} - \hat{M})}{\hat{M}(1-\hat{M})}, \tag{26}$$

say, where

$$\hat{M}_{K+1} = \sum_j (w_j \hat{M}^y_{K+1,j\cdot} + z_j \hat{M}^x_{K+1,j\cdot}). \tag{27}$$

Thus $\lambda_0 > 1$ if either $\hat{M} < \frac{1}{2}$ and $\hat{M}_{K+1} > \hat{M}$ or $\hat{M} > \frac{1}{2}$ and $\hat{M}_{K+1} < \hat{M}$. The expression M_{K+1} in (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 (17) that governs the external stability to invasion by A_{K+1}. Note that if $\hat{M} = \frac{1}{2}$ the leading eigenvalue is unity and linear analysis is uninformative about the fate of A_{k+1}. We summarize with:

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 one–to–one, 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 (1984) 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 (1988) and Lessard (1989). (See also Karlin and Lessard, 1986). 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.

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 (Mueller and Feldman, 1985; Uyenoyama, 1989). 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 $0 \le x_i, y_i \le 1$ for $i = 1,2,3,4$ and $\sum_{i=1}^4 x_i = 1$, $\sum_{i=1}^4 y_i = 1$. Write $\epsilon_2, \epsilon_3, \epsilon_4$ 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 (3) and (4), neglecting terms of quadratic or higher order we have

$$\epsilon_2' + \eta_2' = (\epsilon_2 + \eta_2)m_{12}^* + (\epsilon_4 + \eta_4)m_{14}^* R \tag{28a}$$

$$\epsilon_3' + \eta_3' = (\epsilon_3 + \eta_3)m_{13}^* + (\epsilon_4 + \eta_4)m_{14}^* R \tag{28b}$$

$$\epsilon_4' + \eta_4' = (\epsilon_4 + \eta_4)m_{14}^*(1 - R), \tag{28c}$$

where for $j = 2,3,4$

$$m_{ij}^* = \frac{m_{ij}}{2m_{11}} + \frac{1 - m_{ij}}{2(1 - m_{11})} = 1 + \frac{(\frac{1}{2} - m_{11})(m_{ij} - m_{11})}{m_{11}(1 - m_{11})} \tag{29}$$

Suppose $m_{12} < m_{11} < \frac{1}{2}$ and, to make the algebra a little simpler, set $m_{13} = m_{12}$. Then from (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

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

which entails from (29) that $m_{14} > m_{11}$. For sufficiently small ϵ's and η's, the relative values of

$$(\epsilon_2 + \eta_2),\ (\epsilon_3 + \eta_3),\ (\epsilon_4 + \eta_4).$$

are

$$k \ : \ k \ : \ 1$$

where

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

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

$$M' - M = (\epsilon_2 + \eta_2 + \epsilon_3 + \eta_3)\frac{(m_{12} - m_{11})^2(1-2m_{11})}{2m_{11}(1-m_{11})} + (\epsilon_4 + \eta_4)\left\{\frac{(m_{14} - m_{11})^2(1-2m_{11})}{2m_{11}(1-m_{11})} - \frac{R(m_{11} + m_{14} - 2m_{12})(m_{11} + m_{14} - 2m_{11}m_{14})}{2m_{11}(1-m_{11})}\right\}. \tag{32}$$

Substitute (31) into (32) and reorganize to obtain

$$M' - M = \frac{(\epsilon_4 + \eta_4)[m^*_{14}(1-R) - 1]}{m^*_{14}(1-R) - m^*_{12}}\{2Rm^*_{14}(m_{12} - m_{11}) + (m_{14} - m_{11})[m^*_{14}(1-R) - m^*_{12}]\}. \tag{33}$$

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

$$(m_{14} - m_{11})(m^*_{14} - m^*_{12}) - Rm^*_{14}E \tag{34}$$

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

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

But for instability of $\hat{x}=1, \hat{y}=1$ (30) holds, namely

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

For (35) and (36) to be compatible we require

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

which is guaranteed by our assumptions.

To summarize we have

Result 4. Under the conditions (35) and (36) with $m_{12} < m_{11} < m_{14}$ and $m_{11} < \frac{1}{2}$, 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 $M' < M$ 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 determination we addressed the question of the ultimate value of the sex ratio after invasion. Recall the result of Karlin and Lessard (1983, 1984) 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 $0 < R^* < \frac{1}{2}$, 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 $|\hat{M} - \frac{1}{2}| > |m_{11} - \frac{1}{2}|$. 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 $\hat{M} \neq \frac{1}{2}$ by new alleles at each locus would produce the same result.

It seems reasonable to conjecture that invasion of a two locus *polymorphic* equilibrium with $\hat{M} \neq \frac{1}{2}$ 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 ($\hat{M} = \frac{1}{2}$) or the allelic frequencies at each locus are equal in the two sexes ($\hat{x}_i = \hat{y}_i$), although the chromosomal frequencies need not be equal ($\hat{x}_{ij} \neq \hat{y}_{ij}$). These results hold for multiple loci as well.

In order to analyze the long–term evolution of the system, we continued the approach of Eshel and Feldman (1982a) 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. The even sex ratio does not, however, 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.

Appendix. Multilocus–Multiallele Model of Sex Determination.

The model.

Suppose that sex is determined at n loci with $A_1^k, A_2^k, \ldots, A_{\nu_k}^k$ the possible alleles at the k–th locus ($k = 1, 2, \ldots, n$). Then a typical gamete is represented by an n-tuple

$$\underline{i_0} = (i_0^1, i_0^2, \ldots, i_0^n), \tag{A1}$$

where i_0^k is one of $A_1^k, \ldots, A_{\nu_k}^k$. A typical genotype composed of two chromosomes is displayed in the form

$$\left(\frac{\underline{i_0}}{\underline{i_1}}\right) = \left(\frac{i_0^1, i_0^2, \ldots, i_0^n}{i_1^1, i_1^2, \ldots, i_1^n}\right), \tag{A2}$$

where at locus k the alleles i_0^k and i_1^k are present. The probability of this genotype being male is

$$m\left(\frac{\underline{i_0}}{\underline{i_1}}\right) = m\left(\frac{i_0^1, \ldots, i_0^n}{i_1^1, \ldots, i_1^n}\right) = m(\underline{i_0}, \underline{i_1}) \tag{A3}$$

and of being a female is $1 - m(\underline{i_0}, \underline{i_1})$. The array of these values over all genotypes generates the sex determination matrix $\boldsymbol{M}$ of order $(\Pi_{k=1}^n \nu_k) \times (\Pi_{k=1}^n \nu_k)$.

The recombination–segregation frequencies are the same in the two sexes and are summarized by the array $\boldsymbol{R} = \{R(\underline{\varepsilon})\}_{\underline{\varepsilon}}$ of non–negative quantities

$$R(\underline{\varepsilon}) = R(\varepsilon_1, \varepsilon_2, \ldots, \varepsilon_n), \tag{A4}$$

where the n-tuples $\underline{\varepsilon} = (\varepsilon_1, \varepsilon_2, \ldots, \varepsilon_n)$ satisfy $\varepsilon_i = 0$ or $\varepsilon_i = 1$ for $i = 1, 2, \ldots, n$. Thus with probability $R(\underline{\varepsilon})$ the genotype $\left(\frac{\underline{i_0}}{\underline{i_1}}\right)$ produces the gamete $\underline{i_\varepsilon} = \left(i_{\varepsilon_1}^1, i_{\varepsilon_2}^2, \ldots, i_{\varepsilon_n}^n\right)$ as a result of recombination and Mendelian segregation.

Equivalently with probability $R(\underline{\varepsilon})$ the genotype $\left(\frac{\underline{i_\varepsilon}}{\underline{i_{1-\varepsilon}}}\right)$ produces the gamete $\left(i_0^1, i_0^2, \ldots, i_0^n\right)$. The recombination frequencies $\{R(\underline{\varepsilon})\}_{\underline{\varepsilon}}$ satisfy the two relations

$$\begin{aligned} &R(\underline{\varepsilon}) = R(\underline{1} - \underline{\varepsilon}) \quad \text{for all} \quad \underline{\varepsilon} \\ &\sum_{\underline{\varepsilon}} R(\underline{\varepsilon}) = 1. \end{aligned} \tag{A5}$$

Let $x(\underline{i}_0)$ and $y(\underline{i}_0)$ be the frequencies of the gamete $\underline{i}_0$ in males and females, respectively at the present generation and $x'(\underline{i}_0)$ and $y'(\underline{i}_0)$ the corresponding frequencies at the next generation. The transformation equations connecting the gamete frequencies over successive generations are described as follows (see Karlin and Liberman, 1979)

$$
\begin{aligned}
m(\underline{x},\underline{y})x'(\underline{i}_0) &= \sum_{\underline{i}_1}\sum_{\underline{\varepsilon}} R(\underline{\varepsilon}) m\left(\frac{\underline{i}_\varepsilon}{\underline{i}_{1-\varepsilon}}\right) x(\underline{i}_\varepsilon) y(\underline{i}_{1-\varepsilon}) \\
[1-m(\underline{x},\underline{y})]y'(\underline{i}_0) &= \sum_{\underline{i}_1}\sum_{\underline{\varepsilon}} R(\varepsilon)\left[1-m\left(\frac{\underline{i}_\varepsilon}{\underline{i}_{1-\varepsilon}}\right)\right] x(i_\varepsilon) y(\underline{i}_1-\underline{\varepsilon}),
\end{aligned} \tag{A6}
$$

where $m(\underline{x},\underline{y})$ is the (male) sex–ratio at the population state $(\underline{x},\underline{y})$ given by

$$
m(x,y) = \sum_{\underline{i}_0,\underline{i}_1} m(\underline{i}_0,\underline{i}_1)x(\underline{i}_0)y(\underline{i}_1). \tag{A7}
$$

Equilibrium structure.

Let $\{\underline{x}^*,\underline{y}^*\}$ be an equilibrium point with $m^* = m(\underline{x}^*,\underline{y}^*)$ its associated sex–ratio. We will prove

Result A1.

At equilibrium either the sex–ratio is $\frac{1}{2}$ or the allelic frequencies at the two sexes are the same. That is $m^* = \frac{1}{2}$ or $x^*(i_0^k) = y^*(i_0^k)$ for all i_0^k and all $k = 1,2,\ldots,n$.

Proof.

At equilibrium (A6) gives

$$
(1-m^*)y^*(\underline{i}_0) = \sum_{\underline{i}_1}\sum_{\underline{\varepsilon}} R(\underline{\varepsilon})x^*(\underline{i}_\varepsilon)y^*(\underline{i}_{1-\varepsilon}) - m^*x(\underline{i}_0). \tag{A8}
$$

We will show, for example, that the equilibrium frequencies at the n-th locus coincide at the two sexes at equilibrium, namely $x^*(i_0^n) = y^*(i_0^n)$. Note that

$$x^*(i_0^n) = \sum_{(i_0^1,\ldots,i_0^{n-1})} x^*\left(i_0^1,\ldots,i_0^{n-1},i_0^n\right)$$

$$y^*(i_0^n) = \sum_{(i_0^1,\ldots,i_0^{n-1})} y^*\left(i_0^1,\ldots,i_0^{n-1},i_0^n\right). \qquad (A9)$$

Then by summing both sides of (A8) over $(i_0^1,\ldots,i_0^{n-1})$ we get that

$$(1-m^*)y^*(i_0^n) = \sum_{(i_0^1,\ldots,i_0^{n-1})}\sum_{(i_1^1,\ldots,i_1^n)}\sum_{\underline{\varepsilon}} R(\underline{\varepsilon})x^*(\underline{i}_{\underline{\varepsilon}})y^*(\underline{i}_{\underline{1}-\underline{\varepsilon}}) - m^*x^*(i_0^n). \qquad (A10)$$

We concentrate on the first term on the right–hand side of (A10) and break it into two sums with respect to $\underline{\varepsilon}$, namely

$$\sum_{(\varepsilon_1,\ldots,\varepsilon_n)} = \sum_{(\varepsilon_1,\ldots,\varepsilon_{n-1},0)} + \sum_{(\varepsilon_1,\ldots,\varepsilon_{n-1},1)}. \qquad (A11)$$

Now

$$\sum_{(\varepsilon_1,\ldots,\varepsilon_{n-1},0)} = \sum_{(\varepsilon_1,\ldots,\varepsilon_{n-1})}\sum_{i_1^n} R(\varepsilon_1,\ldots,\varepsilon_{n-1},0)\sum_{(i_0^1,\ldots,i_0^{n-1})}$$

$$\sum_{(i_1^1,\ldots,i_1^{n-1})} x^*\left(i_{\varepsilon_1}^1,\ldots,i_{\varepsilon_{n-1}}^{n-1},i_0^n\right) y^*\left(i_{1-\varepsilon_1}^1,\ldots,i_{1-\varepsilon_{n-1}}^{n-1},i_1^n\right). \qquad (A12)$$

But for all $(\varepsilon_1,\varepsilon_2,\ldots,\varepsilon_{n-1})$ we have

$$\sum_{(i_0^1,\ldots,i_0^{n-1})}\sum_{(i_1^1,\ldots,i_1^{n-1})} x^*\left(i_{\varepsilon_1}^1,\ldots,i_{\varepsilon_{n-1}}^{n-1},i_0^n\right) y^*\left(i_{1-\varepsilon_1}^1,\ldots,i_{1-\varepsilon_{n-1}}^{n-1},i_1^n\right) =$$

$$= \sum_{(i_0^1,\ldots,i_0^{n-1})}\sum_{(i_1^1,\ldots,i_1^{n-1})} x^*(i_0^1,\ldots,i_0^{n-1},i_0^n)y^*(i_1^1,\ldots,i_1^{n-1},i_1^n) \qquad (A13)$$

$$= x^*(i_0^n)y^*(i_1^n).$$

Since $\sum_{i_1^n} y(i_1^n) = 1$ and $\sum_{(\varepsilon_1,\ldots,\varepsilon_{n-1})} R(\varepsilon_1,\ldots,\varepsilon_{n-1},0) = \frac{1}{2}$, we have

$$\sum_{(\varepsilon_1,\ldots,\varepsilon_{n-1},0)} = \frac{1}{2}x^*(i_0^n). \qquad (A14)$$

Similarly

$$\sum_{(\epsilon_1,\ldots,\epsilon_{n-1},1)} = \frac{1}{2}y^*(i_0^n). \tag{A15}$$

Therefore

$$\sum_{(\epsilon_1,\ldots,\epsilon_n)} = \frac{1}{2}x^*(i_0^n) + \frac{1}{2}y^*(i_0^n).$$

and the equilibrium equation (A10) reads

$$(1-m^*)y^*(i_0^n) = \frac{1}{2}x^*(i_0^n) + \frac{1}{2}y^*(i_0^n) - m^*x^*(i_0^n). \tag{A16}$$

In other words,

$$\left(\frac{1}{2} - m^*\right)[y^*(i_0^n) - x^*(i_0^n)] = 0. \tag{A17}$$

Thus either $m^* = \frac{1}{2}$ or $x^*(i_0^n) = y(i_0^n)$ as desired.

In the case $m^* = \frac{1}{2}$ we get a curve of equilibrium points $\{\underline{x}^*, \underline{y}^*\}$ all satisfying the sex–ratio equation

$$m^* = \sum_{\underline{i}_0,\underline{i}_1} m(\underline{i}_0,\underline{i}_1)x^*(\underline{i}_0)y^*(\underline{i}_1) = \frac{1}{2}. \tag{A18}$$

When $m^* \neq \frac{1}{2}$, the allelic frequencies show sex symmetry, namely $x^*(i_0^k) = y^*(i_0^k)$ for all alleles i_0^k and all loci $k = 1, 2, 3, \ldots, n$, but the chromosome frequencies are not necessarily equal in the sexes. The following result extends that described in Remark 2 following Result 1 of the main text.

Result A2.

Suppose $\{\underline{x}^*, \underline{y}^*\}$ is a sex–symmetric equilibrium point such that $\underline{x}^* = \underline{y}^*$, then when there is positive recombination.

(i) *$\underline{x}^*$ solves the equilibrium equations*

$$m^*x^*(\underline{i}_0) = \sum_{\underline{i}_1} m(\underline{i}_0,\underline{i}_1)x^*(\underline{i}_0)x^*(\underline{i}_1), \tag{A19}$$

and

(ii) *$\underline{x}^*$ is a multilocus Hardy–Weinberg equilibrium, i.e.*

$$x^*(\underline{i}_0) = x^*(i_0^1)x^*(i_0^2)\dots x^*(i_0^n). \tag{A20}$$

Proof.

If $\{\underline{x}^*, \underline{y}^*\}$ is an equilibrium point with $\underline{x}^* = \underline{y}^*$ then it solves the set of equilibrium equations (see (A6))

$$m^* x^*(\underline{i}_0) = \sum_{\underline{i}_1} \sum_{\underline{\varepsilon}} R(\underline{\varepsilon}) m(\underline{i}_{\underline{\varepsilon}}, \underline{i}_{\underline{1}-\underline{\varepsilon}}) x^*(\underline{i}_{\underline{\varepsilon}}) x^*(\underline{i}_{\underline{1}-\underline{\varepsilon}}) \tag{A21a}$$

$$x^*(\underline{i}_0) = \sum_{\underline{i}_1} \sum_{\underline{\varepsilon}} R(\underline{\varepsilon}) x^*(\underline{i}_{\underline{\varepsilon}}) x^*(\underline{i}_{\underline{1}-\underline{\varepsilon}}). \tag{A21b}$$

It is easily seen, by summing over all alleles on the complementary set of a given set of loci, that equations (A21b) hold also for any given subset of loci where $\boldsymbol{R}$ is replaced by the marginal recombination distribution associated with the given set of loci. Thus, e.g. for the first two loci (1 and 2) we have from (A21b) that

$$x^*(i_0^1, i_0^2) = [R(0,0) + R(1,1)]x^*(i_0^1, i_0^2) + [R(0,1) + R(1,0)]x^*(i_0^1)x^*(i_0^2). \tag{A22}$$

Hence, if there is recombination between the loci such that $R(0,1) + R(1,0) > 0$ then

$$x^*(i_0^1, i_0^2) = x^*(i_0^1)x^*(i_0^2). \tag{A23}$$

Similarly for any two loci k and ℓ we have

$$x^*(i_0^k, i_0^\ell) = x^*(i_0^k)x^*(i_0^\ell). \tag{A24}$$

Continuing like this to the first three loci (1, 2, and 3) we have from (A21b) that

$$\begin{aligned} x^*(i_0^1, i_0^2, i_0^3) = {} & [R(0,0,0) + R(1,1,1)]x^*(i_0^1, i_0^2, i_0^3) \\ & + [R(0,0,1) + R(1,1,0)]x^*(i_0^1, i_0^2)x^*(i_0^3) \\ & + [R(1,0,0) + R(0,1,1)]x^*(i_0^2, i_0^3)x^*(i_0^1) \\ & + [R(0,1,0) + R(1,0,1)]x^*(i_0^1, i_0^3)x^*(i_0^2). \end{aligned} \tag{A25}$$

Using (A24) and the assumption that there is recombination between the three loci, i.e. $R(0,0,0) + R(1,1,1) < 1$ we conclude that $x^*(i_0^1, i_0^2, x_0^3) = x^*(i_0^1)x^*(i_0^2)x^*(i_0^3)$. Thus for any three loci k, ℓ, $\imath$ we have

$$x^*(i_0^k, i_0^\ell, i_0^\imath) = x^*(i_0^k)x^*(i_0^\ell)x^*(i_0^\imath). \qquad (A26)$$

Continuing by induction we conclude that

$$x^*(\underline{i_0}) = x^*(i_0^1)x^*(i_0^2)\ldots x(i_0^n), \qquad (A27)$$

and $\underline{x}^*$ is a multilocus Hardy–Weinberg equilibrium. Substituting (A27) in (A21a) we have

$$m^* x^*(\underline{i_0}) = \sum_{\underline{\varepsilon}} R(\underline{\varepsilon}) \sum_{\underline{i_1}} m(\underline{i_0}, \underline{i_1}) x^*(\underline{i_0}) x^*(\underline{i_1}) \qquad (A28)$$

and as $\sum_{\underline{\varepsilon}} R(\underline{\varepsilon}) = 1$ we conclude that (A19) holds.

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