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The Role of Recombination in the Modifier Theory of Autosomal Segregation Distortion[1]

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The effects of recombination on the equilibrium structures of two-locus systems of autosomal segregation distortion are studied. Exact conditions pertaining to the stability of polymorphic equilibria maintaining multiple distorters at the segregation–determination locus as well as their resistance to the invasion of mutant distorters are given. Evolutionary patterns of autosomal meiotic drive and the status of Mendelian segregation are reexamined. © 1985 Academic Press, Inc.

1. INTRODUCTION

Non-Mendelian segregation ratios of genes are not unusual in diploid populations. As a result of a direct alteration of the normal mechanism of meiosis or a subsequent selective process among gametes, a heterozygous parent can transmit two gametic alternatives to its progeny with a bias in favor of one type.

Distinction between meiotic drive and gametic selection at a later stage (due, e.g., to competition of sperm to fertilize ova) may be delicate, requiring cytological studies, since the effects on the genetic composition of the population are similar. Moreover, departures from Mendelian segregation ratios are often sex dependent, are associated with fertility differences, and involve multiple alleles and/or loci.

Examples of segregation distortion and/or sex-ratio distortion in natural populations include chromosome K10 in maize which exhibits preferential segregaton over the nonknobbed chromosome k10; persistent supernumerary B-chromosomes in a variety of plants and animals in spite of deleterious effects when present in large number; the sex-linked factor *D* in the mosquito, *Aedes aegypti*, causing sex-ratio distortion in favor of males

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which are heterozygous at an autosomal locus; the sr system in *Drosophila obscura* and *pseudoobscura* with X_rY males transmitting mainly X_r chromosomes; *t*-alleles (tailless alleles) in the house mouse that are lethal in homozygous males but preferentially transmitted by heterozygous males; and the SD system in *Drosophila melanogaster* involving two major factors flanking the centromere of chromosome 2 with a segregation distorter Sd on the right arm causing a responder Rsp located on the left arm to be recovered in excess over its homologue Rsp^+ in the progeny of heterozygous males Rsp/Rsp^+ but leading to sperm dysfunction (and reduced fertility) in homozygous males Rsp/Rsp (see, e.g., Sandler and Novitski, 1957; Gluecksohn–Waelsch and Erickson, 1970; Zimmering *et al.*, 1970; Hartl and Hiraizumi, 1976; and references therein).

Following some analyses of one-locus population genetics models for meiotic drive (Prout, 1953; Hiraizumi *et al.*, 1960; Hamilton, 1967; Lewontin, 1968; Hartl, 1970a,b), the theory of modifiers of segregation distortion has been developed. A two-locus model for autosomal modifiers of autosomal segregation ratios was introduced by Prout *et al.* (1973) and generalized in Thomson and Feldman (1976). A primary locus subject to meiotic drive and zygotic selection displays the genotypes *DD*, *Dd*, and *dd* whose respective fitnesses are $w_0 = 1$, w_1, and w_2. A secondary locus with possible alleles *M*, *m* controls the intensity of the drive at the primary locus such that the heterozygotes *Dd* that are *MM*, *Mm*, and *mm* at the secondary locus transmit *d* gametes to their progeny with probabilities k_1, k_2, and $\frac{1}{2}$, respectively. Prout *et al.* (1973) studied the case $w_1 = 1$, $k_1 = k_2 = 1$ and exhibited a stable polymorphic equilibrium when the recombination fraction r between the two loci satisfies $w_2 < 2r < 1$. Thomson and Feldman (1976) determined that up to three allelic polymorphisms can exist in the general case, one showing linkage equilibrium and two others showing linkage disequilibrium. The former can be stable for relatively tight linkage above some minimum threshold whereas the latter generally require loose linkage to exist and be stable. Charlesworth and Hartl (1978) combined segregation distortion with fertility differences in males and recombination only in females to conform more closely to the SD system in *D. melanogaster*. With tight linkage, they found a stable polymorphic equilibrium point approached cyclically. Maffi and Jayakar (1981), partly analytically and partly numerically, studied the effects of the recombination fraction on the equilibrium configuration for a two-locus model of sex-linked meiotic drive without selection (a first locus responsible for sex determination, males being heterozygous and females homozygous, and a second locus modifying sex-ratio distortion in the progeny of males) with possible applications to *A. aegypti* populations. Their conclusions are qualitatively similar to those of Thomson and Feldman (1976) for autosomal meiotic drive with limit cycles also occurring in the case of tight

linkage. With dominance at the segregation modifier locus, the analysis in Maffi and Jayakar (1981) is complemented by the exhibition of a polymorphism if there is sufficient recombination (Lessard and Karlin, 1982). Wu (1983) extended the analysis to many cases found in *Drosophila* by incorporating fitness differences to autosomal modifiers influencing meiotic drive in X_rY males.

It is a well-known fact that X-linked or Y-linked modifiers of sex ratio distortion in the heterogametic sex increase in frequency until fixation is reached if they promote their own representation in the next generations and no other selective forces counteract their invasion (e.g., Hamilton, 1967). Edwards (1961) introduced viability differences in an attempt to explain observed polymorphisms in *D. pseudoobscura*. Thomson and Feldman (1975) differentiated the gametic production of the heterogametic sex as occurs in *D. pseudoobscura* and deduced conditions for the maintenance of an allele modifying fertilify and drive intensity located on X or Y chromosomes [see also Bengtsson (1977) for the wood lemming and Feldman and Krakauer (1976) for autosomal modifiers]. Two-locus models provide alternative and/or more elaborated mechanisms for explaining the maintenance of polymorphic equilibria.

Autosomal (unliked) modifiers of sex-ratio determination were considered in Speith (1974), Uyenoyama and Bengtsson (1979), Eshel and Feldman (1982), and Karlin and Lessard (1983) among others. In these cases, the distortion of sex-ratio outcomes may be caused by a drive during meiosis, spermatic competition, and/or a maternal selective control of X- or Y-bearing sperm (and/or sex allocation differentials in the case of hermaphrodites). Optimality principles pertaining to the evolution of the sex ratio were the main concern in these studies.

In the same vein, the two-locus model of Prout *et al.* (1973) has been used to predict evolutionary patterns of segregation distortion and/or address theoretical questions concerning the evolution of Mendelian segregation. Hartl (1975) studied the evolutionary fate of rare modifiers of recessive lethal segregation distorters. Liberman (1976) observed that Mendelian segregation, when fixed in the population, is never stable against the introduction of a segregation distorter if there is some linkage, and that any fixed segregation ratio is rendered unstable by a mutant modifier if the recombination rate between the drive modifier locus and the driven locus is sufficiently small. Eshel (1985) was mainly concerned with the evolutionary stability of Mendelian segregation when there is free recombination. In this case, it can be shown that a polymorphic non-Mendelian segregation equilibrium is initially invaded by a mutant segregation distorter if and only if the mutant average segregation ratio is on the side of Mendelian segregation with respect to the common average segregation ratio in the population. Moreover, Eshel and Liberman (personal communication)

proved that fixation of Mendelian segregation is always stable in this context.

This paper focuses on polymorphic equilibria maintaining multiple alleles at an autosomal locus controlling segregation distortion at another autosomal locus involving two alleles and undergoing overdominance. (A companion paper will deal exclusively with sex-ratio distortion.) With any degree of linkage between the two loci, exact conditions ascertaining stability within the resident allelic systems and resistance to the invasion of new segregation distorters for all equilibria exhibiting no linkage disequilibrium (also called symmetric) are given. The precise effects of the recombination rate are analyzed. In the case of free recombination, a further stability analysis makes possible a complete description of the equilibrium structure. Evolutionary schemes of autosomal meiotic drive and the status of Mendelian segregation are examined in the light of our findings.

2. A Segregation–Determination Model

Consider three possible genotypes DD, Dd, and dd at a primary locus subject to positive fitness values w_0, $w_1 = 1$, and w_2, respectively. Overdominance is assumed, i.e., $w_1 > w_0$ and $w_1 > w_2$ (otherwise, the heterozygous genotype Dd would go extinct). A neutral secondary locus with possible alleles $A_1, \ldots, A_n$ determines the segregation ratio at the primary locus as follows: A_iD/A_jd genotypes segregate gametes carrying allele d with probability k_{ij} without affecting fertility. The *segregation-determination matrix* $K = \|k_{ij}\|$ is assumed to be positive, symmetric, and nonsingular. A recombination event between the segregation-determination locus and the locus subject to zygotic viability selection takes place prior to the meiotic drive effects with probability r $(0 \leqslant r \leqslant \frac{1}{2})$.

Let p_i be the frequency of A_iD gametes among all D gametes whose own frequency is denoted by x_1. The quantities q_i and $x_2 = 1 - x_1$ are defined analogously for A_id gametes and d gametes. Assuming random mating (i.e., random union of gametes) and an infinite population, the zygotes are of genotypes DD, Dd, and dd at the primary locus with relative frequencies x_1^2, $2x_1x_2$, and x_2^2. Following zygotic selection, these frequencies become $w_0x_1^2/w$, $2w_1x_1x_2/w$, and $w_2x_2^2/w$, respectively, where w is the mean fitness in the population, i.e.,

$$w = w_0x_1^2 + 2w_1x_1x_2 + w_2x_2^2. \tag{2.1}$$

Among all DD genotypes, the frequency of A_iD gametes produced is p_i while among all dd genotyes the frequency of A_id gametes is q_i. Among all Dd genotypes, the frequency of A_iD/A_jd genotypes is p_iq_j. These produce

the gametes A_iD, A_jD, A_id, and A_jd with the probabilities $(1-k_{ij})(1-r)$, $(1-k_{ij})r$, $k_{ij}r$, and $k_{ij}(1-r)$, respectively. In particular, the frequency of d gametes compared to D gametes produced by all Dd genotypes in the population is

$$k = \sum_{i,j=1}^{n} k_{ij} p_i q_j. \tag{2.2}$$

The quantity k represents an average segregation rate over all heterozygotes at the primary locus in the population.

From the above remarks, the recurrence relations over two successive generations can be described by the following system of equations:

$$p_i' = \frac{w_0 x_1^2 p_i + 2w_1 x_1 x_2 [(1-r) p_i \sum_{j=1}^{n} (1-k_{ij}) q_j + r q_i \sum_{j=1}^{n} (1-k_{ij}) p_j]}{w_0 x_1^2 + 2w_1 x_1 x_2 (1-k)},$$

$$i = 1,..., n,$$

$$q_i' = \frac{w_2 x_2^2 q_i + 2w_1 x_1 x_2 [r p_i \sum_{j=1}^{n} k_{ij} q_j + (1-r) q_i \sum_{j=1}^{n} k_{ij} p_j]}{w_2 x_2^2 + 2w_1 x_1 x_2 k},$$

$$i = 1,..., n,$$

$$x_2' = \frac{w_2 x_2^2 + 2w_1 x_1 x_2 k}{w}, \qquad \text{where} \quad x_1 = 1 - x_2. \tag{2.3}$$

Introducing the notation $\mathbf{y} \circ \mathbf{z} = (y_1 z_1,..., y_n z_n)$ for the product component by component and $\langle \mathbf{y}, \mathbf{z} \rangle = \sum_{i=1}^{n} y_i z_i$ for the scalar product of two vectors $\mathbf{y} = (y_1,..., y_n)$ and $\mathbf{z} = (z_1,..., z_n)$, the recurrence system (2.3) can be written in the form

$$\mathbf{p}' = \frac{w_0 x_1 \mathbf{p} + 2w_1 x_2 [(1-r)\, \mathbf{p} \circ (U-K)\, \mathbf{q} + r \mathbf{q} \circ (U-K)\mathbf{p}]}{w_0 x_1 + 2w_1 x_2 (1-k)}, \tag{2.4a}$$

$$\mathbf{q}' = \frac{w_2 x_2 \mathbf{q} + 2w_1 x_1 [r \mathbf{p} \circ K\mathbf{q} + (1-r)\mathbf{q} \circ K\mathbf{p}]}{w_2 x_2 + 2w_1 x_1 k}, \tag{2.4b}$$

$$x_2' = \frac{w_2 x_2^2 + 2w_1 x_1 x_2 k}{w}, \tag{2.4c}$$

where U denotes the matrix with all unit entries and $x_1 = 1 - x_2$, $w = w_0 x_1^2 + 2w_1 x_1 x_2 + w_2^2 x_2^2$, and $k = \langle \mathbf{p}, K\mathbf{q} \rangle$. The system of equations (2.4) is equivalent to the system introduced in Eshel (1985) and studied in the case $r = \frac{1}{2}$.

3. Symmetric Equilibria and Their Stability

A special class of equilibrium $\{\hat{\mathbf{p}}, \hat{\mathbf{q}}, \hat{x}\}$ of (2.4) has $\hat{\mathbf{p}} = \hat{\mathbf{q}}$, i.e., the equilibrium allelic frequencies at the secondary locus are independent of the allele present at the primary locus or, equivalently, there is linkage equilibrium. Such equilibria will be called *symmetric* (Eshel, 1985). At a symmetric equilibrium $\{\hat{\mathbf{p}}, \hat{\mathbf{p}}, \hat{x}\}$, the equations (2.4a), (2.4b) are equivalent to

$$\hat{\mathbf{p}} = \frac{\hat{\mathbf{p}} \circ K\hat{\mathbf{p}}}{\hat{k}}, \tag{3.1}$$

where $\hat{k} = \langle \hat{\mathbf{p}}, K\hat{\mathbf{p}} \rangle$. The equilibrium frequency $\hat{x}$ of allele d deduced from (2.4c) is

$$\hat{x} = \frac{2w_1\hat{k} - w_0}{2w_1 - w_0 - w_2}. \tag{3.2}$$

The equilibrium is *admissible* if $0 < \hat{x} < 1$, i.e.,

$$\frac{w_0}{2w_1} < \hat{k} < 1 - \frac{w_2}{2w_1}. \tag{3.3}$$

The admissibility condition (3.3) will be hereafter assumed.

If $\{\hat{\mathbf{p}}, \hat{\mathbf{p}}, \hat{x}\}$ is a polymorphic symmetric equilibrium, i.e., with $\hat{\mathbf{p}} = (\hat{p}_1, \ldots, \hat{p}_n)$ such that $\hat{p}_i > 0$ for all i, the matrix

$$K(\hat{\mathbf{p}}) = \frac{\hat{\mathbf{p}} \circ K}{\hat{k}} \tag{3.4}$$

whose ith row is the ith row of the positive matrix K multiplied by $\hat{p}_i/\hat{k}$ is a positive matrix. Since $K(\hat{\mathbf{p}})\,\hat{\mathbf{p}} = \hat{\mathbf{p}}$, the Perron–Frobenius theory (see, e.g., Gantmacher, 1959; Lancaster, 1969) asserts that one is a simple eigenvalue of $K(\hat{\mathbf{p}})$ which strictly dominates all the other eigenvalues in magnitude. These are all real since $K(\hat{\mathbf{p}})$ is similar to a symmetric matrix. Note also that $K(\hat{\mathbf{p}})$ is nonsingular since K has been assumed nonsingular. For the same reason, there exists at most one polymorphic symmetric equilibrium $\{\hat{\mathbf{p}}, \hat{\mathbf{p}}, \hat{x}\}$ of (2.4) since then $\hat{\mathbf{p}}$ must be the unique positive frequency vector solving $K\hat{\mathbf{p}} = \hat{k}\mathbf{u}$ where $\mathbf{u}$ is the vector with all unit components [see (3.1)]. Our results will be set forth for the case $\hat{k} = \langle \hat{\mathbf{p}}, K\hat{\mathbf{p}} \rangle \leqslant \frac{1}{2}$. The case $\hat{k} \geqslant \frac{1}{2}$ is analogous by symmetry (it suffices to replace $K = \|k_{ij}\|$ by $U - K = \|1 - k_{ij}\|$). All proofs are relegated to the Appendix.

Result I. *Let* $0 < r < \frac{1}{2}$. *A polymorphic symmetric equilibrium* $\{\hat{\mathbf{p}}, \hat{\mathbf{p}}, \hat{x}\}$

of (2.4) *with* $\hat{k} = \langle \hat{\mathbf{p}}, K\hat{\mathbf{p}} \rangle < \frac{1}{2}$ *is stable if every eigenvalue* $\lambda \neq 1$ *of* $K(\hat{\mathbf{p}}) = \hat{\mathbf{p}} \circ K/\hat{k}$ *satisfies*

$$\lambda^- < \lambda < 0 \qquad or \qquad \frac{r(1-2\hat{k})}{\hat{k}(1-2r)} < \lambda < \lambda^+, \tag{3.5}$$

where λ^- *and* λ^+ *are the roots of*

$$P(\lambda) = 2w_1\hat{x}_1\hat{x}_2\hat{k}\lambda\{\lambda\hat{k}(1-2r) - r(1-2\hat{k})\} - \hat{w}r\{\hat{x}_2(1-\hat{k}+\lambda\hat{k}) + \hat{x}_1\hat{k}(1-\lambda)\} \tag{3.6}$$

using the notation $\hat{w} = w_0\hat{x}_1^2 + 2w_1\hat{x}_1\hat{x}_2 + w_2\hat{x}_2^2$ *with* $\hat{x}_2 = \hat{x}$ *and* $\hat{x}_1 = 1 - \hat{x}$. *If any one of the inequalities* (3.5) *is reversed, then the equilibrium is unstable.*

Remark. The quantities λ^+ and λ^- are greater than one in absolute value [and in that case do not play any role in (3.5) since necessarily $|\lambda| < 1$] if the recombination fraction r is not too small. Actually it is sufficient that $r > \frac{1}{4}$. [The exact lower bounds are given in (A.15) and (A.16) in the Appendix.] As r decreases, λ^+ and λ^- come closer to zero and vanish at $r = 0$. Moreover, an eigenvalue $\lambda \neq 1$ of $K(\hat{\mathbf{p}})$ such that $\lambda \leqslant \lambda^-$ or $\lambda \geqslant \lambda^+$ corresponds to a conjugate pair of complex eigenvalues of magnitude $\geqslant 1$ for the linear approximation of (2.4) near $\{\hat{\mathbf{p}}, \hat{\mathbf{p}}, \hat{x}\}$ (see Appendix). This ensures the appearance of a periodic orbit by Hopf bifurcation in the vicinity of that equilibrium each time λ^+ or λ^- crosses an eigenvalue $\lambda \neq 1$ of $K(\hat{\mathbf{p}})$ as the recombination rate r diminishes (see, e.g., Marsden and McCraken, 1976). On the other hand, there is bifurcation to nearby equilibrium points when $(r(1-2\hat{k}))/(\hat{k}(1-2r))$ crosses a positive eigenvalue $\lambda \neq 1$ of $K(\hat{\mathbf{p}})$ as r increases. These observations are in agreement with the studies of Thomson and Feldman (1976) in the case of two segregation distorters.

Consider next a mutant allele A_{n+1} at the segregation modifier locus. Let $k_{i,n+1}$ be the segregation ratio in favor of gametes carrying allele d produced by $A_iD/A_{n+1}d$ and $A_{n+1}D/A_id$ genotypes for $i = 1,..., n+1$. At a symmetric equilibrium $\{\hat{\mathbf{p}}, \hat{\mathbf{p}}, \hat{x}\}$ for the system (2.4) not involving allele A_{n+1}, the quantity

$$\hat{k}_{n+1} = \sum_{i=1}^{n} k_{i,n+1}\hat{p}_i \tag{3.7}$$

measures the average segregation rate in favor of d gametes over all heterozygotes Dd carrying the mutant allele A_{n+1} at the segregation modifier locus. Only mutations with $\hat{k}_{n+1} \neq \hat{k} = \langle \hat{\mathbf{p}}, K\hat{\mathbf{p}} \rangle$ are considered throughout.

Our second result highlights necessary and sufficient conditions for the initial increase in frequency of such mutant alleles.

RESULT II. *Let* $0<r<1/2$. *A polymorphic symmetric equilibrium* $\{\hat{\mathbf{p}}, \hat{\mathbf{p}}, \hat{x}\}$ *of* (2.4) *associated with an average segregation rate* $\hat{k}=\langle \hat{\mathbf{p}}, \hat{K}\hat{\mathbf{p}}\rangle < 1/2$ *is stable against a mutant allele* A_{n+1} *at the segregation modifier locus if the average mutant segregation rate* $\hat{k}_{n+1}$ *defined in* (3.7) *satisfies*

$$\frac{\hat{k}-r}{1-2r} < \hat{k}_{n+1} < \hat{k}. \tag{3.8}$$

The allele A_{n+1} *cannot go extinct (actually increases in frequency after some generations) near* $\{\hat{\mathbf{p}}, \hat{\mathbf{p}}, \hat{x}\}$ *if any one of the inequalities* (3.8) *is reversed.*

Result II is in agreement with Liberman (1976) and Hartl (1975) when the symmetric equilibrium corresponds to a fixation state at the segregation determination locus. The proofs of Results I and II are set forth in the Appendix. Result I deals with necessary and sufficient conditions for *internal stability* with respect only to the positive components of a symmetric equilibrium while Result II is about *external stability* when a new allele is introduced in small quantity at the segregation modifier locus. Note that all the inequalities involved in the conditions for stability-instability in both results [see (3.5) and (3.8)] are strict. Equalities which would require special relationships among the parameters $\{k_{ij}\}$ represent nongeneric cases that have been ignored in the above statements.

The stability conditions (3.5) and (3.8) for a symmetric equilibrium with average segregation rate $\hat{k}<1/2$ reveal that the constraints to ensure internal stability are less stringent with $\hat{k}$ closer to 1/2 (at least for $r>1/4$ by the remark following Result I) while those for external stability become more restrictive (assuming $r\neq 1/2$). The paradox is extreme at the critical value $\hat{k}=1/2$ that reflects a Mendelian average segregation rate in the population at equilibrium. In this case, with sufficient recombination, no further conditions are required to decide about internal stability and external stability which become totally incompatible as highlighted in the following statement.

RESULT III. *At least for* $1/4<r<1/2$, *any symmetric equilibrium* $\{\hat{\mathbf{p}}, \hat{\mathbf{p}}, \hat{x}\}$ *of* (2.4) *that is Mendelian, i.e., with* $\hat{k}=\langle \hat{\mathbf{p}}, K\hat{\mathbf{p}}\rangle = 1/2$, *is internally stable and externally unstable.*

Remark. The exact range for r is $1/6<r_2\leqslant r<1/2$ where

$$r_2=\max\left\{\frac{1-w_2}{4-2w_2(1+w_0)}, \frac{1-w_0}{4-2w_0(1+w_2)}\right\},$$

assuming $w_1=1$.

In general, as r decreases beyond 1/4, the critical regions in (3.5) and (3.8) for internal and external stability, respectively, narrow to vanish com-

pletely at $r=0$. Moreover, when the segregation-determination locus is tightly linked to the locus subject to segregation (i.e., r almost zero), it is easy to check that only symmetric equilibria can occur in (2.4). Consequently, we have:

RESULT IV. *In case of tight linkage, every equilibrium point of* (2.4) *is unstable, internally and externally.*

Actually, it can be shown from the analysis in the Appendix that the relevant eigenvalues of the linear approximation of (2.4) near any equilibrium $\{\hat{\mathbf{p}}, \hat{\mathbf{p}}, \hat{x}\}$ are all larger than one in magnitude if r is small enough. In such a case every equilibrium point is repelling in the sense that it is impossible to have convergence to it. Of course this does not preclude limit cycles.

4. MENDELIAN SEGREGATION EQUILIBRIA IN THE CASE OF FREE RECOMBINATION ($r=1/2$)

The segregation-determination model (2.4) in the case where the segregation modifier locus is unlinked (i.e., $r=1/2$) was studied in Eshel (1985). This author dealt mainly with conditions for the initial spread of a mutant allele at the segregation modifier locus near a symmetric equilibrium. In addition to symmetric equilibria, a second class of equilibrium associated with a Mendelian population segregation rate (i.e., $k=1/2$) was pointed out although its existence was not investigated. In this section, we propose a complete description of the equilibrium structure and a further analysis of stability properties in the case of free recombination.

For a symmetric equilibrium, Results I and II extend to the following necessary and sufficient conditons for stability in the case $r=1/2$.

RESULT V. *If* $r=1/2$, *a polymorphic symmetric equilibrium* $\{\hat{\mathbf{p}}, \hat{\mathbf{p}}, \hat{x}\}$ *of* (2.4) *with* $\hat{k}=\langle \hat{\mathbf{p}}, K\hat{\mathbf{p}}\rangle < 1/2$ *is internally stable if and only if the eigenvalues of* $K(\hat{\mathbf{p}})=\hat{\mathbf{p}}\circ K/\hat{k}$ *different from one are all negative. It is externally stable against the introduction of a new allele* A_{n+1} *at the segregation modifier locus if and only if* $\hat{k}_{n+1}$ *of* (3.7) *is less than* $\hat{k}$.

The external stability condition $\hat{k}_{n+1}<\hat{k}$ is in Eshel (1985). We now examine the possibility of nonsymmetric equilibria. When $r=1/2$, the equilibrium relations $\mathbf{p}'=\mathbf{p}$ and $\mathbf{q}'=\mathbf{q}$ in (2.4a, b) are equivalent to

$$2(1-k)\,\mathbf{p}=\mathbf{p}\circ(U-K)\,\mathbf{q}+\mathbf{q}\circ(U-K)\,\mathbf{p}, \tag{4.1a}$$

$$2k\mathbf{q}=\mathbf{p}\circ K\mathbf{q}+\mathbf{q}\circ K\mathbf{p}. \tag{4.1b}$$

Summing (4.1a) and (4.1b) yields the necessary equilibrium condition

$$(1-2k)\,\mathbf{p} = (1-2k)\,\mathbf{q}. \tag{4.2}$$

Therefore a nonsymmetric equilibrium $\{\tilde{\mathbf{p}}, \tilde{\mathbf{q}}, \tilde{x}\}$ of (2.4) must have $\tilde{k} = \langle \tilde{\mathbf{p}}, K\tilde{\mathbf{q}} \rangle = 1/2$. Such an equilibrium will be called a *Mendelian segregation equilibrium.* In this event, a necessary and sufficient condition for equilibrium in (2.4a), (2.4b) is

$$\tilde{\mathbf{q}} = \tilde{\mathbf{p}} \circ K\tilde{\mathbf{q}} + \tilde{\mathbf{q}} \circ K\tilde{\mathbf{p}}. \tag{4.3}$$

From (2.4c), the equilibrium frequency $\tilde{x}$ is

$$\tilde{x} = \frac{w_1 - w_0}{2w_1 - w_0 - w_2}, \tag{4.4}$$

i.e., the equilibrium frequency $\tilde{x}$ of allele d corresponds to the polymorphic equilibrium at the primary locus for zygotic viability selection with standard Mendelian segregation.

The equilibrium relation (4.3) also arose in sex-ratio-determination models (see Karlin and Lessard, 1983, 1984). It can be interpreted in the following manner. Let

$$B(\mathbf{p}) = \operatorname{diag}(\mathbf{p})\,K + \operatorname{diag}(K\mathbf{p}), \tag{4.5}$$

where $\operatorname{diag}(\mathbf{p})$ is the diagonal matrix with the components of $\mathbf{p}$ on the main diagonal. If all the components of $\mathbf{p}$ are positive, then the matrix $B(\mathbf{p})$ is positive and the Perron–Frobenius theory (see, e.g., Gantmacher, 1959; Lancaster 1969) affirms that the eigenvalue of largest magnitude of $B(\mathbf{p})$, denoted by $\rho(B(\mathbf{p}))$, is real and positive admitting a unique frequency vector $\mathbf{q}$ as a positive right eigenvector, i.e., such that

$$B(\mathbf{p})\,\mathbf{q} = \rho(B(\mathbf{p}))\,\mathbf{q}. \tag{4.6}$$

Moreover, $\mathbf{q} = \mathbf{q}(\mathbf{p})$ and $\rho(\mathbf{p}) = \rho(B(\mathbf{p}))$ vary continously as functions of the frequency vector $\mathbf{p}$. Comparing with (4.3), we note that a polymorphic Mendelian segregation equilibrium $\{\tilde{\mathbf{p}}, \tilde{\mathbf{q}}, \tilde{x}\}$ is characterized by the equation

$$\rho(B(\tilde{\mathbf{p}})) = 1, \tag{4.7}$$

and then the corresponding $\mathbf{q}(\tilde{\mathbf{p}})$ is $\tilde{\mathbf{q}}$ while $\tilde{x}$ is given by (4.4). This observation in conjunction with Result V allows one to apply directly the results of Karlin and Lessard (1983, 1984) for sex-ratio-determination models to the segregation-determination model (2.4) in the case of free recombination.

RESULT VI. *Let any equilibrium* $\{\mathbf{p}^*, \mathbf{q}^*, x^*\}$ *of the segregation-determination model* (2.4) *with* $r = 1/2$ *be represented by the frequency vector* $\mathbf{p}^*$.

(i) *A Mendelian segregation equilibrium* $\tilde{\mathbf{p}}$ *cannot coexist with a stable polymorphic equilibrium* $\hat{\mathbf{p}}$ *that is non-Mendelian.*

(ii) *Two symmetric equilibria* $\hat{\mathbf{p}}_\alpha$ *and* $\hat{\mathbf{p}}_\beta$ *with associated average segregation ratios* $\hat{k}_\alpha = \langle \hat{\mathbf{p}}_\alpha, K\hat{\mathbf{p}}_\alpha \rangle < 1/2$ *and* $\hat{k}_\beta = \langle \hat{\mathbf{p}}_\beta, K\hat{\mathbf{p}}_\beta \rangle > 1/2$ *are completely separated by at least one Mendelian segregation equilibrium surface.* (Every continuous curve of frequency vectors joining $\hat{\mathbf{p}}_\alpha$ and $\hat{\mathbf{p}}_\beta$ intersects at least one Mendelian segregation equilibrium $\tilde{\mathbf{p}}$.)

(iii) *If* $\hat{\mathbf{p}}$ *is a stable polymorphic symmetric equilibrium with average segregation ratio* $\hat{k} = \langle \hat{\mathbf{p}}, K\hat{\mathbf{p}} \rangle < 1/2$ *that becomes unstable following the introduction of a new allele* A_{n+1} (*see Result* V), *then for the augmented allelic system, either* (a) *there exists a unique stable equilibrium whose average segregation ratio is closer to* 1/2 *compared to* $\hat{k}$ *and that does not coexist with any Mendelian segregation equilibrium, or* (b) $\hat{\mathbf{p}}$ *is enclosed by a Mendelian segregation equilibrium surface containing no stable non-Mendelian equilibria.* (See *loc cit* for more details.)

5. DISCUSSION

Thomson and Feldman (1976), extending Prout *et al.* (1973), exhibited up to three polymorphic equilibria but at most one symmetric by linkage equilibrium for autosomal two-locus segregation distortion models involving two modifiers of meiotic drive. Stability conditions supported by simulations were discussed. We have shown that with any number of modifiers there generally exists at most one polymorphic symmetric equilibrium whose stability conditions can be analytically determined (Result I). Such an equilibrium can be stable if there is sufficient recombination between the drive modifier locus and the driven locus and, more precisely, for an intermediate range of values of the recombination fraction. For lower values, limit cycles can surround the symmetric equilibrium while for upper values nearby equilibrium points associated with linkage disequilibrium can become stable.

Many authors (e.g., Hartl, 1975; Liberman, 1976; Eshel, 1985) pursuing mainly evolutionary interests, focussed on conditions for the initial increase in frequency of mutant modifiers of autosomal segregation distortion. If the resident equilibrium is symmetric (not only a fixation state) and given any recombination fraction, the exact conditions for external stability following the introduction of a new segregation distorter can be ascertained (Result II). With tight linkage, there is departure from any symmetric equilibrium and limit cycles are predicted (Result IV).

With sufficiently loose linkage, the likelihood of invasion by a mutant segregation distorter increases as the population equilibrium segregation ratio comes closer to 1/2, while the conditions for internal stability become less stringent. With an average Mendelian segregation ratio, a symmetric equilibrium is necessarily internally stable and externally unstable (Result III). This exhibits a case where a general evolutionary tendency *cannot* be based on initial increase properties. The hitchhiking effects of linkage between the segregation modifier locus and the locus subject to zygotic viability selection indiscriminately promote more polymorphism at the segregation-modifier locus while the segregation modifiers themselves tend to favor the occurrence of Mendelian segregation in the population. With free recombination, the counterforce is inoperant and the evolutionary tendency toward an average Mendelian segregation ratio cannot be stopped (Results V and III) as predicted in Eshel (1985).

The model studied in this paper assumes that A_iD/A_jd and A_jD/A_id genotypes (male and female) produce the same proportion $k_{ij}=k_{ji}$ of D gametes. More realistic and/or general models would not impose these assumptions of symmetry. Sex-dependent recombination fractions would have also to be allowed.

APPENDIX: Stability Analysis of the Symmetric Equilibria of (2.4)

A1. *Internal Stability*

Consider a polymorphic symmetric equilibrium $\{\hat{\mathbf{p}}, \hat{\mathbf{p}}, \hat{x}\}$ of (2.4) with $\hat{k}=\langle\hat{\mathbf{p}}, \hat{K}\hat{\mathbf{p}}\rangle<1/2$. Taking $w_1=1$ and writing $\mathbf{p}=\hat{\mathbf{p}}+\boldsymbol{\xi}$, $\mathbf{q}=\hat{\mathbf{p}}+\boldsymbol{\eta}$, $x_2=\hat{x}+\delta$ where $\boldsymbol{\xi}=(\xi_1,\ldots,\xi_n)$ and $\boldsymbol{\eta}=(\eta_1,\ldots,\eta_n)$ satisfy $\sum_{i=1}^n \xi_i=\sum_{i=1}^n \eta_i=0$, the linear approximation of the transformation for the variables $\{\boldsymbol{\xi}, \boldsymbol{\eta}, \delta\}$ when these are small in modulus is described by the matrix

$$L=\frac{1}{\hat{w}}\begin{bmatrix} L_{11} & L_{12} & 0 \\ L_{21} & L_{22} & 0 \\ 0 & 0 & \beta \end{bmatrix} \tag{A.1}$$

where 0 designates a matrix with all zero entries and

$$\begin{aligned}
L_{11} &= [w_0\hat{x}_1+2(1-r)\,\hat{x}_2(1-\hat{k})]\,I+2r\hat{x}_2\hat{\mathbf{p}}\circ(U-K),\\
L_{12} &= 2r\hat{x}_2(1-\hat{k})\,I+2(1-r)\,\hat{x}_2\hat{\mathbf{p}}\circ(U-K),\\
L_{21} &= 2r\hat{x}_1\hat{k}I+2(1-r)\,\hat{x}_1\hat{\mathbf{p}}\circ K,\\
L_{22} &= [w_2\hat{x}_2+2(1-r)\,\hat{x}_1\hat{k}]\,I+2r\hat{x}_1\hat{\mathbf{p}}\circ K,\\
\beta &= 2\hat{x}_1\hat{k}+2\hat{x}_2(1-\hat{k})-2(2-w_0-w_2)\,\hat{x}_1\hat{x}_2,\\
\hat{w} &= w_0\hat{x}_1+2\hat{x}_2(1-\hat{k})=w_2\hat{x}_2+2\hat{x}_1\hat{k},
\end{aligned} \tag{A.2}$$

with I denoting the identity matrix and

$$\hat{x}_2 = \frac{2\hat{k} - w_0}{2 - w_0 - w_2}, \qquad \hat{x}_1 = \frac{2(1-\hat{k}) - w_2}{2 - w_0 - w_2}. \tag{A.3}$$

Using these formulas, we find

$$\begin{aligned} \beta &= w_0\hat{x}_1 + w_2\hat{x}_2 \\ &= [w_0\hat{x}_1 + w_2\hat{x}_2][\hat{x}_1 + \hat{x}_2] \\ &= w_0\hat{x}_1^2 + (w_0 + w_2)\,\hat{x}_1\hat{x}_2 + w_2\hat{x}_2^2 \\ &< w_0\hat{x}_1^2 + 2\hat{x}_1\hat{x}_2 + w_2\hat{x}_2^2 = \hat{w} \end{aligned} \tag{A.4}$$

since we have assumed overdominance, i.e., $w_0 < 1$ and $w_2 < 1$, while the quantities $\hat{x}_2$ and $\hat{x}_1 = 1 - \hat{x}_2$ are positive by the assumption (3.3). We conclude that the eigenvalue $\beta/\hat{w}$ of L is always positive and less than one.

To find the other eigenvalues of L, we try eigenvectors in the form $\{a\xi, b\xi, 0\}$, where $\langle \xi, \mathbf{u} \rangle = \sum_{i=1}^{n} \xi_i = 0$ and

$$k(\hat{\mathbf{p}})\,\xi = \frac{\hat{\mathbf{p}} \circ K}{\hat{k}}\,\xi = \lambda\xi. \tag{A.5}$$

Necessarily, $|\lambda| < 1$ since the matrix $K(\hat{\mathbf{p}})$ is positive and $K(\hat{\mathbf{p}})\,\hat{\mathbf{p}} = \hat{\mathbf{p}}$ (see, e.g., Gantmacher, 1959; Lancaster, 1969). Note also that $K(\hat{\mathbf{p}})$ has only real eigenvalues and a complete set of eigenvectors since it is a product of a positive diagonal matrix with a symmetric matrix. Moreover, every right eigenvector ξ of $K(\hat{\mathbf{p}})$ associated with an eigenvalue $\lambda \neq 1$ must be perpendicular to the left eigenvector $\mathbf{u}$ associated with the eigenvalue one because

$$\langle \xi, \mathbf{u} \rangle = \langle \xi, \mathbf{u}K(\hat{\mathbf{p}}) \rangle = \langle K(\hat{\mathbf{p}})\,\xi, \mathbf{u} \rangle = \lambda \langle \xi, \mathbf{u} \rangle \tag{A.6}$$

which is compatible only if $\langle \xi, \mathbf{u} \rangle = 0$.

We find that $\{a\xi, b\xi, 0\}$ with ξ satisfying (A.5) is an eigenvector of L if and only if (a, b) is an eigenvector corresponding to the same eigenvalue for the two-dimensional matrix $B = \|b_{kl}\|_{k,l=1}^{2}$, where

$$\begin{aligned} \hat{w}b_{11} &= w_0\hat{x}_1 + 2\hat{x}_2[(1-r)(1-\hat{k}) - r\lambda\hat{k}], \\ \hat{w}b_{12} &= 2\hat{x}_2[r(1-\hat{k}) - (1-r)\,\lambda\hat{k}], \\ \hat{w}b_{21} &= 2\hat{x}_1[r\hat{k} + (1-r)\,\lambda\hat{k}], \\ \hat{w}b_{22} &= w_2\hat{x}_2 + 2\hat{x}_1[(1-r)\,\hat{k} + r\lambda\hat{k}]. \end{aligned} \tag{A.7}$$

The eigenvalues of B are

$$\mu^{\pm}=\frac{(b_{11}+b_{22})\pm\sqrt{(b_{11}+b_{22})^2-4(b_{11}b_{22}-b_{12}b_{21})}}{2}. \tag{A.8}$$

Using the inequalities $0<r<1/2$, $0<\hat{k}<1/2$, and $-1<\lambda<1$, it can be checked that

$$1>b_{11}>|b_{12}| \qquad \text{and} \qquad 1>b_{22}>|b_{21}|. \tag{A.9}$$

Defining $Q(\mu)=\det[B-\mu I]$, we find

$$Q(1)=\frac{4\hat{x}_1\hat{x}_2\hat{k}}{\hat{w}^2}\lambda\{\lambda\hat{k}(1-2r)-r(1-2\hat{k})\}. \tag{A.10}$$

Therefore $0<\mu^-<1<\mu^+$ if and only if $Q(1)<0$ or, equivalently,

$$0<\lambda<\frac{r(1-2\hat{k})}{\hat{k}(1-2r)}. \tag{A.11}$$

Otherwise the possibility of a conjugate pair of complex eigenvalues emerges.

These are of magnitude less than one if and only if

$$\mu^-\mu^+=b_{11}b_{22}-b_{12}b_{21}=Q(1)+b_{11}+b_{22}-1<1, \tag{A.12}$$

or equivalently

$$\begin{aligned}P(\lambda)=&\,2\hat{x}_1\hat{x}_2\hat{k}\lambda\{\lambda\hat{k}(1-2r)-r(1-2\hat{k})\}\\&-r\hat{w}\hat{x}_2(1-\hat{k}+\lambda\hat{k})-r\hat{w}\hat{x}_1\hat{k}(1-\lambda)<0.\end{aligned} \tag{A.13}$$

This occurs for $\lambda^-<\lambda<\lambda^+$ where λ^- and λ^+ are the roots of $P(\lambda)$. It is easy to check that λ^- and λ^+ are zero at $r=0$ and are pushed away from zero as r increases, since

$$\begin{aligned}\frac{\partial P(\lambda)}{\partial r}=&-\hat{x}_2(1-\hat{k}+\lambda\hat{k})[w_2\hat{x}_2+2\hat{x}_1\hat{k}(1+\lambda)]\\&-\hat{x}_1\hat{k}(1-\lambda)[w_0\hat{x}_1+2\hat{x}_2(1-\hat{k}-\lambda\hat{k})]<0\end{aligned} \tag{A.14}$$

for $-1<\lambda<1$ and $\hat{k}<1/2$. In particular, $\lambda^+\geqslant 1$ if and only if

$$r\geqslant\frac{2\hat{x}_1\hat{k}^2}{4\hat{x}_1\hat{k}+w_2\hat{x}_2}=r_0 \tag{A.15}$$

while $\lambda^- \leqslant -1$ if and only if

$$r \geqslant \frac{2\hat{x}_1\hat{x}_2\hat{k}^2}{4\hat{x}_1\hat{x}_2\hat{k} + 2w_0\hat{x}_1^2\hat{k} + w_2\hat{x}_2^2(1-2\hat{k})} = r_1. \tag{A.16}$$

For $\hat{k} < 1/2$, we always have $r_0, r_1 < 1/4$. For $\hat{k} = 1/2$, the conditions (A.15) and (A.16) are simultaneously satisfied if and only if

$$r \geqslant \max\left\{\frac{1-w_2}{4-2w_2(1+w_0)}, \frac{1-w_0}{4-2w_0(1+w_2)}\right\} = r_2. \tag{A.17}$$

It is easy to check that $1/6 < r_2 < 1/4$. The lower bound $1/6$ is approached when selection is weak, i.e., when w_0 and w_2 are close to one.

The above procedure discloses all the eigenvalues of L (since it discloses a complete set of eigenvectors). The conclusions about the stability of $\{\hat{\mathbf{p}}, \hat{\mathbf{p}}, \hat{\mathbf{x}}\}$ are summarized in Result I with a general value for w_1.

A.2. *External Stability*

Consider a mutant allele A_{n+1} introduced at a polymorphic symmetric equilibrium $\{\hat{\mathbf{p}}, \hat{\mathbf{p}}, \hat{x}\}$ of (2.4). Denoting the frequencies of the new gametes $A_{n+1}D$ and $A_{n+1}d$ by p_{n+1} and q_{n+1}, respectively, a first-order approximation for these frequencies over two successive generations near the equilibrium $\{\hat{\mathbf{p}}, \hat{\mathbf{p}}, \hat{x}\}$ gives

$$\begin{bmatrix} p'_{n+1} \\ q'_{n+1} \end{bmatrix} \approx \begin{bmatrix} \dfrac{w_0\hat{x}_1 + 2(1-r)\,\hat{x}_2(1-\hat{k}_{n+1})}{\hat{w}} & \dfrac{2r\hat{x}_2(1-\hat{k}_{n+1})}{\hat{w}} \\ \dfrac{2r\hat{x}_1\hat{k}_{n+1}}{\hat{w}} & \dfrac{w_2\hat{x}_2 + 2(1-r)\,\hat{x}_1\hat{k}_{n+1}}{\hat{w}} \end{bmatrix} \begin{bmatrix} p_{n+1} \\ q_{n+1} \end{bmatrix} \tag{A.18}$$

where $\hat{k}_{n+1}$ is the average mutant segregation rate defined in (3.7) and $\hat{x}_1, \hat{x}_2, \hat{w}$ are the quantities given in (A.2) and (A.3).

Denoting the matrix in (A.17) by $M = \|m_{kl}\|_{k,l=1}^2$ and its characteristic polynomial of degree two by $R(\mu) = \det[M - \mu I]$, we find

$$R(1) = -\frac{4\hat{x}_1\hat{x}_2}{\hat{w}^2}(\hat{k} - \hat{k}_{n+1})[(\hat{k} - r) - \hat{k}_{n+1}(1-2r)]. \tag{A.19}$$

In the case $\hat{k} < 1/2$, $R(1) > 0$ if and only if

$$\frac{\hat{k} - r}{1-2r} < \hat{k}_{n+1} < \hat{k}. \tag{A.20}$$

[Compare with Hartl (1975) and Liberman (1976).] In this range of values, the positive matrix $M = \|m_{kl}\|$ has $m_{11}, m_{22} < 1$, compelling $R'(1) = 2 - m_{11} - m_{22} > 0$ and therefore two (real) eigenvalues less than one in absolute value by appeal to the Perron–Frobenius theory. The proof of Result II is complete. Results III, IV, and V are limit cases of Results I and II.

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