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Sex-Specific Meiotic Drive and Selection at an Imprinted Locus

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ABSTRACT

We present a one-locus model that breaks two symmetries of Mendelian genetics. Whereas symmetry of transmission is breached by allowing sex-specific segregation distortion, symmetry of expression is breached by allowing genomic imprinting. Simple conditions for the existence of at least one polymorphic stable equilibrium are provided. In general, population mean fitness is not maximized at polymorphic equilibria. However, mean fitness at a polymorphic equilibrium with segregation distortion may be higher than mean fitness at the corresponding equilibrium with Mendelian segregation if one (or both) of the heterozygote classes has higher fitness than both homozygote classes. In this case, mean fitness is maximized by complete, but opposite, drive in the two sexes. We undertook an extensive numerical analysis of the parameter space, finding, for the first time in this class of models, parameter sets yielding two stable polymorphic equilibria. Multiple equilibria exist both with and without genomic imprinting, although they occurred in a greater proportion of parameter sets with genomic imprinting.

THE two alleles at a locus of a diploid individual are equally represented in its gametes. Segregation distorters, however, violate fair meiosis by ensuring their own presence in >50% of the functional gametes of heterozygotes (Crow 1979). Meiotic drive, in its extended sense, refers to "any alteration of meiosis or gametogenesis that results in preferential transmission of a particular allele or chromosome" (Ganetzky 1999, p. 3). A segregation distorter that reduces the viability of heterozygotes can persist in a population as long as its transmission advantage outweighs the decline in viability. Such a distorter reduces the fitness of most of the genes with which it is temporarily associated because unlinked genes gain none of the benefits of segregation distortion but experience the full viability cost. Thus, segregation distorters have been considered paradigmatic examples of ultraselfish genes (Crow 1988).

All known systems of meiotic drive involve segregation ratios that differ between the sexes. The mouse *t*-haplotype and the fruit fly *SD* system are examples of meiotic drive restricted to male meiosis. These haplotypes are transmitted to >90% of the functional sperm of heterozygous males but to only half of the ova of heterozygous females (Lyttle 1991). Meiotic drive may also be limited to female meiosis: mouse *In* haplotype is present in 80–90% of the ova of heterozygous females (Agulnik *et al.* 1990, 1993) while maize *Ab10*-knob is present in 70% of the functional megaspores of heterozygous plants (Rhoades 1942); both are transmitted to half of the gametes of heterozygous males. Finally, in systems of permanent translocation heterozygosity (*e.g.*, *Oenothera* spp.) all individuals are heterozygous for two chromosome complexes; one complex is transmitted to all functional microspores, and the other to all functional megaspores (Holsinger and Ellstrand 1984). In addition to the evidence provided, the fundamental differences in the mechanisms of male and female meiosis make it highly unlikely that any genetic agent would cause identical segregation distortion in the two sexes.

Putting mathematical tractability before empirical evidence, models of meiotic drive frequently assumed identical segregation ratios in males and females (Feldman and Otto 1991). More realistic ones allowed sex-limited segregation distortion, but often imposed significant constraints on the viability parameters. Bruck (1957) introduced the first of these models. Segregation distortion was restricted to males, whereas females showed Mendelian segregation. Heterozygotes had the same viability as homozygotes for the nondriving allele whereas homozygotes for the driving allele were lethal. Dunn and Levene (1961) elaborated a similar model in which viability selection was replaced by fertility selection in males. Lewontin (1968) combined these features in a model with male-limited segregation distortion and fertility selection, but allowing viability selection in both sexes. Homozygotes for the driving allele were sterile. These early models were tailored to explain a classic example of meiotic drive, the mouse *t*-haplotype system.

Wright (1969) and Hartl (1970) formulated a general model of segregation distortion with identical viability parameters in males and females but, otherwise, unconstrained. It was Hartl (1970) who provided an analytical and numerical analysis of the equilibria, finding examples of parameter sets with two polymorphic

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equilibria (one stable). In his analysis, however, Hartl did not find parameter sets with three polymorphic equilibria (two stable), nor did he consider segregation schemes like those in permanent translocation heterozygotes. Another assumption of Hartl's (1970) model was that of identical viability of reciprocal heterozygotes. Symmetric expression is a classic assumption of population genetics models that has started to be relaxed after evidence of genomic imprinting was found.

Genomic imprinting refers to a differential expression of genes depending on their parental origin (Reik and Walter 2001). Consider an imprinted locus in which the expression of genes with paternal origin is upregulated while the expression of genes with maternal origin is downregulated. Thus, the expression of *A* relative to *B* is greater in genotype *AB* than in genotype *BA* (where the allele with paternal origin is mentioned first). Such differential expression can cause reciprocal heterozygotes to have distinguishable phenotypes and different viabilities (Pearce and Spencer 1992). Most theoretical work on the population genetics of genomic imprinting has been undertaken by Spencer and colleagues (see Spencer 2000 for a review). Their models have considered the effects of selection at autosomal loci (Pearce and Spencer 1992) and the interaction between mutation and selection (Spencer 1997). The interaction between genomic imprinting and the segregation distortion, however, has yet to be considered.

In this article, we extend Wright's (1969) model by assigning separate viabilities to reciprocal heterozygotes, as might occur at an imprinted locus. This extension is justified by Pearce and Spencer's (1992) conclusion that systems with genomic imprinting may show qualitatively different behavior from otherwise identical systems without imprinting. Its biological motivation, however, lies in the work of Naumova *et al.* (2001) on transmission ratio distortion at imprinted loci in the human genome. This work finds evidence of a deviation from Mendelian transmission of paternal and maternal imprinted regions linked to embryo viability. Thus, from both theoretical and empirical perspectives, the extension of Hartl's (1970) model to allow the interaction of segregation distortion and genomic imprinting seems justified.

If reciprocal heterozygotes have the same viability, our model reduces to Hartl's (1970). We complete his analysis, however, by explicitly considering perfect transmission of one allele in one sex and the other allele in the opposite sex as occurs in *Oenothera* spp. or *Isotoma petraea* (Holsinger and Ellstrand 1984). Such a segregation scheme is relevant not only because it is exhibited in nature by permanent translocation heterozygotes but also because it maximizes the population mean fitness of our model given heterozygote advantage. In addition, we carry out a thorough exploration of the parameter space in search of parameter sets yielding three polymorphic equilibria. The aim is to investigate the existence of two stable polymorphic equilibria, similar to what occurs in selection models with differential viability between the sexes (Owen 1953).

MODEL

Consider an infinite, panmictic diploid population. Let the viability of genotypes A_1A_1, A_1A_2, A_2A_1, and A_2A_2 be v_{11}, v_{12}, v_{21}, and v_{22}, where the autosomal allele written first has paternal origin while the one written second has maternal origin. Let the segregation ratio of A_1 be k in male meiosis and κ in female meiosis while the corresponding ratios for A_2 are $1 - k$ and $1 - \kappa$ ($0 < k, \kappa < 1$). Values of k and κ less than one-half can be interpreted as segregation distortion in favor of A_2 or negative segregation distortion of A_1 (Hiraizumi 1989, 1990).

Let the frequency of gametes A_1, A_2 be x_1, x_2 in sperm and y_1, y_2 in eggs ($0 < x_i, y_i < 1$, and $\Sigma_i x_i = \Sigma_i y_i = 1$). The interaction between viability selection and segregation distortion determines the frequency of allele A_1 one generation later,

$$\overline{w}x_1' = v_{11}x_1y_1 + k(v_{12}x_1y_2 + v_{21}x_2y_1) \quad (1a)$$

$$\overline{w}y_1' = v_{11}x_1y_1 + \kappa(v_{12}x_1y_2 + v_{21}x_2y_1) \quad (1b)$$

$$\overline{w} = v_{11}x_1y_1 + v_{12}x_1y_2 + v_{21}x_2y_1 + v_{22}x_2y_2, \quad (2)$$

where the normalizing factor $\overline{w}$ is known as the mean fitness of the population.

Subtracting (1b) from (1a) yields: $\overline{w}(x_1' - y_1') = (k - \kappa)(v_{12}x_1y_2 + v_{21}x_2y_1)$. After one generation, $x_1 - y_1$ takes the same sign as $k - \kappa$. That is, A_1 will be more frequent in sperm than in eggs if segregation favors A_1 more strongly in spermatogenesis than in oogenesis, and as a consequence A_1A_2 heterozygotes will be more frequent than A_2A_1 heterozygotes.

The change in allele frequencies from one generation to the next, *i.e.*, $x_1' - x_1 = \Delta x_1$ and $y_1' - y_1 = \Delta y_1$, are

$$\overline{w}\Delta x_1 = \frac{\partial \overline{w}}{\partial x_1}x_1x_2 - (1 - k)v_{12}x_1y_2 + kv_{21}x_2y_1 \quad (3a)$$

$$\overline{w}\Delta y_1 = \frac{\partial \overline{w}}{\partial y_1}y_1y_2 - (1 - \kappa)v_{21}y_1x_2 + \kappa v_{12}y_2x_1. \quad (3b)$$

Given that $0 < x_1, x_2 < 1$, and $x_2 = 1 - x_1$, variable $x = x_1$ alone characterizes the frequency of alleles A_1 and A_2 in sperm. Similarly, variable $y = y_1$ alone characterizes the frequency of alleles A_1 and A_2 in eggs. Henceforth, we eliminate the subscripts in variables x_i and y_i. Any point (x, y) in the unit square Ω describes the state of our system without losing information. Ω is the region of space with biological meaning.

EQUILIBRIA

An equilibrium $(\hat{x}, \hat{y})$ is characterized by the lack of change of allele frequency over time, *i.e.*, $\Delta x = 0$ and

$\Delta y = 0$. We use the label *trivial* to designate an equilibrium in which either A_1 or A_2 is absent, while *nontrivial* refers to all other cases.

Close form solution: Consider the case $\Delta x = 0$. From (3a), $\hat{y}$ can be written as a function of $\hat{x}$,

$$\hat{y} = -\hat{x}\,\frac{a_2\hat{x} + a_1}{a_5\hat{x}^2 + a_4\hat{x} + a_3}, \tag{4}$$

where $a_1 = kv_{12} - v_{22}$, $a_2 = v_{22} - v_{12}$, $a_3 = kv_{21}$, $a_4 = v_{11} + v_{22} - kv_{12} - (1 + k)v_{21}$, and $a_5 = v_{12} + v_{21} - v_{11} - v_{22}$.

Consider the case $\Delta y = 0$. From (3b), $\hat{x}$ can be written as a function of $\hat{y}$,

$$\hat{x} = -\hat{y}\,\frac{b_2\hat{y} + b_1}{b_5\hat{y}^2 + b_4\hat{y} + b_3}, \tag{5}$$

where $b_1 = \kappa v_{21} - v_{22}$, $b_2 = v_{22} - v_{21}$, $b_3 = \kappa v_{12}$, $b_4 = v_{11} + v_{22} - (1 + \kappa)v_{12} - \kappa v_{21}$, and $b_5 = a_5$.

Substituting (4) into (5) yields a quintic polynomial with one root at $\hat{x} = 0$. This root corresponds to trivial equilibrium $(0, 0) = \mathbf{0}$,

$$\hat{x}[c_4\hat{x}^4 + c_3\hat{x}^3 + c_2\hat{x}^2 + c_1\hat{x} + c_0] = 0, \tag{6}$$

where $c_0 = a_3^2b_3 - a_1a_3b_1$, $c_1 = a_1^2b_2 + 2a_3a_4b_3 - a_2a_3b_1 - a_1a_4b_1 - a_1a_3b_4$, $c_2 = a_1^2a_5 + a_4^2b_3 + 2a_1a_2b_2 + 2a_3a_5b_3 - a_2a_4b_1 - a_1a_5b_1 - a_2a_3b_4 - a_1a_4b_4$, $c_3 = a_2^2b_2 + 2a_1a_2a_5 + 2a_4a_5b_3 - a_2a_5b_1 - a_2a_4b_4 - a_1a_5b_4$, and $c_4 = a_2^2a_5 + a_5^2b_3 - a_2a_5b_4$.

Root $\hat{x} = 1$, corresponding to trivial equilibrium $(1, 1) = \mathbf{1}$, can be factored out of the last equation,

$$\hat{x}(1 - \hat{x})[d_3\hat{x}^3 + d_2\hat{x}^2 + d_1\hat{x} + d_0] = 0, \tag{7}$$

where $d_0 = c_1 + c_2 + c_3 + c_4$, $d_1 = c_2 + c_3 + c_4$, $d_2 = c_3 + c_4$, and $d_3 = c_4$.

Dividing the previous equation by d_3 yields

$$\hat{x}(1 - \hat{x})[\hat{x}^3 + e_2\hat{x}^2 + e_1\hat{x} + e_0] = 0, \tag{8}$$

where $e_2 = d_2/d_3$, $e_1 = d_1/d_3$, and $e_0 = d_0/d_3$.

The cubic polynomial in (8), $p(x)$, contributes up to three equilibria, ϕ_1, ϕ_2, and ϕ_3, that might be nontrivial. The close form of the roots in $p(\hat{x}) = 0$ can be written using Cardano's formulas (Weisstein 2002),

$$\hat{x}_{\phi_1} = -\frac{1}{3}e_2 + r_1 + r_2 \tag{9a}$$

$$\hat{x}_{\phi_2} = -\frac{1}{3}e_2 - \frac{1}{2}(r_1 + r_2) + \frac{1}{2}i\sqrt{3}(r_1 - r_2) \tag{9b}$$

$$\hat{x}_{\phi_3} = -\frac{1}{3}e_2 - \frac{1}{2}(r_1 + r_2) - \frac{1}{2}i\sqrt{3}(r_1 - r_2), \tag{9c}$$

where $r_1 = \sqrt[3]{t + \sqrt{\Delta}}$ and $r_2 = \sqrt[3]{t - \sqrt{\Delta}}$.

Variable Δ represents the discriminant of the cubic polynomial,

$$\Delta = s^3 + t^2, \tag{10}$$

where $s = \frac{1}{9}(3e_1 - e_2^2)$ and $t = \frac{1}{54}(9e_1e_2 - 27e_0 - 2e_2^3)$.

To summarize, system (3) has at least two trivial equilibria ($\mathbf{0}$ and $\mathbf{1}$) but no more than three nontrivial equilibria (ϕ_1, ϕ_2, and ϕ_3). The algebraic expressions of roots in $p(\hat{x}) = 0$ are sufficiently complicated as to convey little biological insight. Their existence depends not only on the sign of Δ but also on the biological constraint that requires ϕ to belong to Ω.

Existence and stability: The instabilities of both trivial equilibria are sufficient and necessary conditions to have precisely one stable polymorphic equilibrium or three polymorphic equilibria (two of them stable and the other unstable; Prout 1968). This is true only if we assume, as we do, that there are no stable cycles in our model (Cannings 1969). Ruling out the possibility of having stable cycles is beyond the scope of this article.

If one of the trivial equilibria is stable and the other unstable, system (3) may have zero or two nontrivial equilibria (one of them stable and the other unstable). If both trivial equilibria are stable, system (3) may have one unstable nontrivial equilibrium or three equilibria (one of them stable and the other two unstable). Therefore, the instability of $\mathbf{0}$ and $\mathbf{1}$ is a sufficient but not necessary condition for the existence of at least one stable nontrivial equilibrium.

The condition for instability of $\mathbf{0}$ (see appendix a) can be written as

$$\left[kv_{12} - \frac{1}{2}v_{22}\right] + \left[\kappa v_{21} - \frac{1}{2}v_{22}\right] > 0. \tag{11}$$

This has a simple biological interpretation. In the vicinity of $\mathbf{0}$ allele A_1 is rare. On one hand, A_1 will be present mostly in heterozygotes and will be transmitted to a fraction k of its bearers' sperm and a fraction κ of its bearers' eggs. A_1 sperm will fertilize A_2 eggs, producing offspring with viability v_{12}, whereas A_1 eggs will be fertilized by A_2 sperm, producing offspring with viability v_{21}. On the other hand, A_2 will be present mostly in homozygotes and a particular allele will be transmitted to half of its bearers' gametes, producing offspring with viability v_{22}. Thus, the two terms within brackets in (11) refer to the relative fitness advantage of A_1 over A_2 via sperm and via eggs, respectively. A_1 can invade a gene pool near fixation for A_2 if the sum of these terms is positive.

Similarly, the condition for instability of $\mathbf{1}$ can be written as

$$\left[(1 - k)v_{21} - \frac{1}{2}v_{11}\right] + \left[(1 - \kappa)v_{12} - \frac{1}{2}v_{11}\right] > 0. \tag{12}$$

In the vicinity of $\mathbf{1}$ allele A_2 is rare. On one hand, A_2 will be present mostly in heterozygotes and will be transmitted to a fraction $(1 - k)$ of its bearers' sperm and a fraction $(1 - \kappa)$ of its bearers' eggs. A_2 sperm will fertilize A_1 eggs, producing offspring with viability v_{21}, whereas A_2 eggs will be fertilized by A_1 sperm, producing offspring with viability v_{12}. On the other hand, A_1 will be present mostly in homozygotes and a particular allele will be transmitted to half of its bearers' gametes,

TABLE 1

Summary of conditions for existence and stability of at least one polymorphic equilibrium

	$v_{12} = v_{21}$	$v_{12} \neq v_{21}$
Mendelian segregation	$v_{12} > v_{22}$ $v_{12} > v_{11}$ $v_{11} + v_{22} - 2v_{12} < 0$	$\frac{1}{2}(v_{12} + v_{21}) > v_{22}$ $\frac{1}{2}(v_{12} + v_{21}) > v_{11}$ $v_{11} + v_{22} - v_{12} - v_{21} < 0$
Segregation distortion		
$k = \kappa$	$2kv_{12} > v_{22}$ $2(1 - k)v_{12} > v_{11}$ $v_{11} + v_{22} - 2v_{12} < 0$	$k(v_{12} + v_{21}) > v_{22}$ $(1 - k)\ (v_{12} + v_{21}) > v_{11}$ $v_{11} + v_{22} - v_{12} - v_{21} < 0$
$k \neq \kappa$	$(k + \kappa)v_{12} > v_{22}$ $(2 - k - \kappa)v_{12} > v_{11}$ $v_{11} + v_{22} - 2v_{12} < 0$	$kv_{12} + \kappa v_{21} > v_{22}$ $(1 - \kappa)v_{12} + (1 - k)v_{21} > v_{11}$ $v_{11} + v_{22} - v_{12} - v_{21} < (k - \kappa)\ (v_{12} - v_{21})$

In each of the models considered, the conditions for instability of **0** and **1** are provided first. The last condition results from adding up the previous two and it is a necessary condition for their satisfaction.

producing offspring with viability v_{11}. Thus, the two terms within brackets in (12) refer to the relative fitness advantage of A_2 over A_1 via sperm and via eggs, respectively. A_2 can invade a gene pool near fixation for A_1 if the sum of these terms is positive.

The equivalent set of conditions in models in which either segregation distortion or genomic imprinting is missing is summarized in Table 1. In particular, the comparison between our model and a model without imprinting, but otherwise equal, reveals that in the latter the width of the (k, κ) region in which there is at least one polymorphic equilibrium is independent of the sex bias in segregation ratios, $k - \kappa$ (see Figure 1a).

Further comparison reveals that a necessary condition for the existence and stability of a polymorphic equilibrium encompassing all models in Table 1, except ours, is that the average viability of heterozygotes has to be greater than the average viability of homozygotes. This requirement is further relaxed in our model, which is replaced by

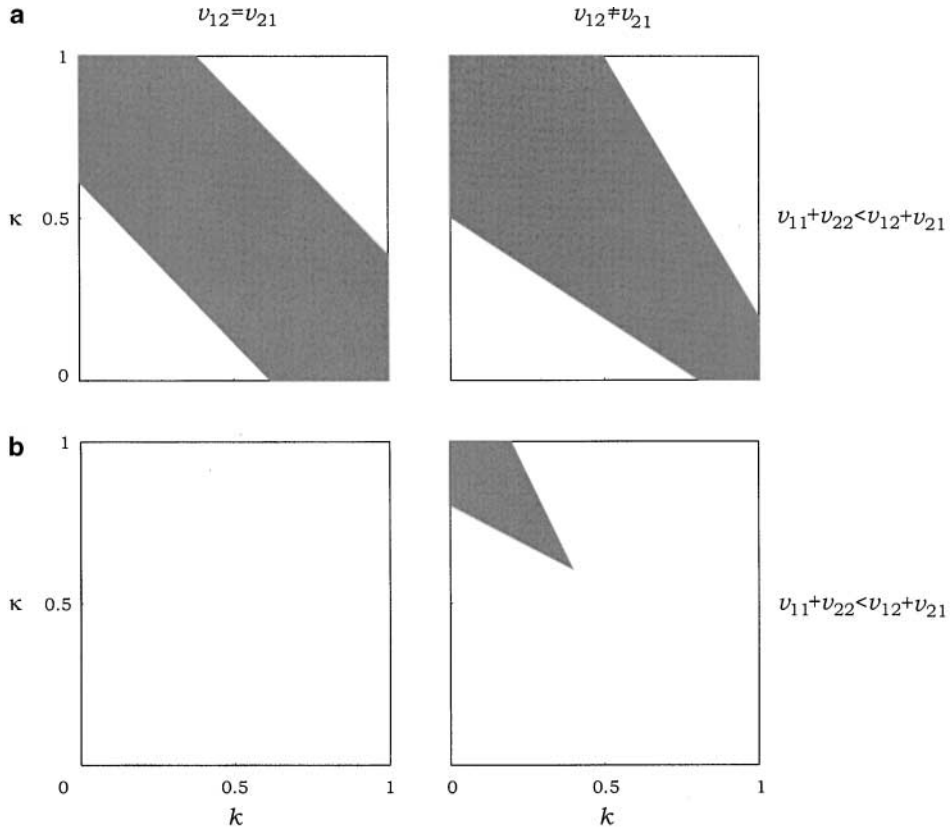

FIGURE 1.—Comparison of existence and stability conditions. We consider four viability sets: (1.6, 2.6, 2.6, 1.6), (1.6, 1.5, 1.5, 1.6), (1.6, 2, 3.2, 1.6), and (1.6, 1, 2, 1.6). These are arranged as a table; columns show absence or presence of genomic imprinting while rows show average heterozygote advantage (a) and average heterozygote disadvantage (b). To facilitate the comparison, the viability of heterozygotes in the absence of imprinting corresponds to the average viability of heterozygotes in its presence. To further simplify, the viability of homozygotes is the same within and across examples. The shaded area represents the region of the parameter space (k, κ) in which existence and stability conditions are satisfied, thus yielding at least one stable equilibrium.

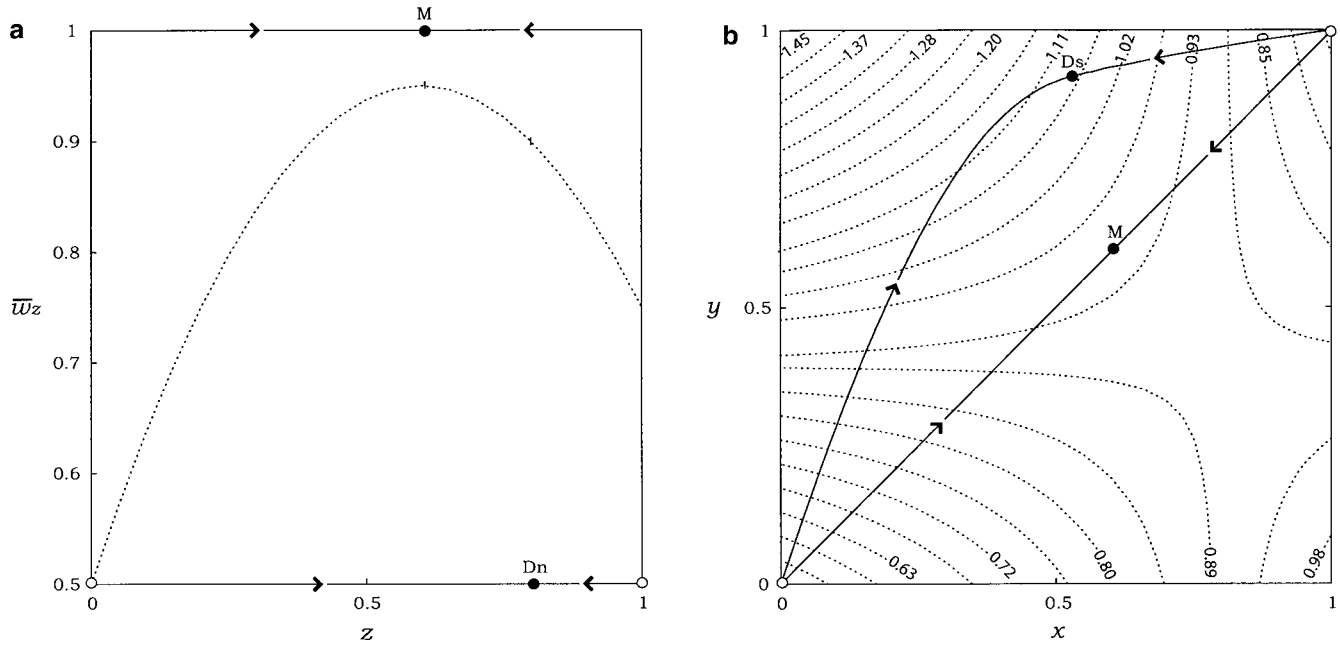

FIGURE 2.—Comparison of population mean fitness. Consider the viability set (0.75, 1, 1.5, 0.5). With Mendelian segregation and sex-independent segregation distortion (a) the frequency of alleles in males and females is the same (z), and the population mean fitness ($\overline{w}_z$) is a function of one variable. The stable equilibrium with Mendelian segregation, M, maximizes $\overline{w}_z$ but the introduction of sex-independent segregation distortion ($k_n = \kappa_n = 0.6$) results in a stable equilibrium, D_n, with lower $\overline{w}$ value. This is true for any k_n value. With sex-specific segregation distortion (b) the frequency of alleles can differ in males (x) and females (y), and $\overline{w}$ is a function of two variables. To facilitate the comparison we consider a segregation scheme (k_s, κ_s) such that $\frac{1}{2}(k_s + \kappa_s) = k_n$. In particular, segregation scheme (0.3, 0.9) results in a stable equilibrium, D_s, with a $\overline{w}$ value higher than the one corresponding to M. This is true for some (k_s, κ_s) only. Solid circles indicate locally stable equilibria; open circles indicate unstable equilibria. Solid lines represent allele frequency trajectories with arrows indicating the direction of temporal change. Dashed lines represent population mean fitness values.

$$(k + 1 - \kappa)v_{12} + (1 - k + \kappa)v_{21} > v_{11} + v_{22}. \quad (13)$$

Figure 1b illustrates this singularity of our model. There, we provide a particular set of viabilities (v_{11}, v_{12}, v_{21}, v_{22}) such that $v_{12} + v_{21} < v_{11} + v_{22}$. In the absence of imprinting, $v_{12} = v_{21} = a$, the set of conditions for existence and stability cannot be satisfied for any (k, κ) while in the presence of imprinting with $\frac{1}{2}(v_{12} + v_{21}) = a$ the equivalent set of conditions is satisfied by some (k, κ).

The special cases in which one or both of the existence and stability conditions are met with strict equality are considered in APPENDIX A.

Population mean fitness: Another singularity of our model lies in the value taken by the population mean fitness at equilibrium. While it is a maximum with Mendelian segregation, the introduction of sex-independent segregation distortion results in its reduction. However, sex-specific segregation distortion may increase the mean fitness at equilibrium compared to the corresponding value with Mendelian segregation.

The allele frequencies in eggs and sperm given Mendelian segregation ($k = \kappa = \frac{1}{2}$) are the same ($x = y = z$) after one generation. System (3) reduces to

$$\overline{w}_z \Delta z = \frac{1}{2}\frac{d\overline{w}_z}{dz} z(1 - z), \quad (14)$$

where $\overline{w}_z = v_{11}z^2 + (v_{12} + v_{21})z(1 - z) + v_{22}(1 - z)^2$. A polymorphic equilibrium ($\Delta z = 0$ with $z \neq 0, 1$) corresponds to a critical point of the mean fitness function ($d\overline{w}_z/dz = 0$). Furthermore, this equilibrium is stable if the critical point satisfies the conditions for a maximum, that is, $\frac{1}{2}(v_{12} + v_{21}) > v_{11}, v_{22}$ (see Figure 2a).

Sex-independent segregation distortion ($k = \kappa$), however, sends the equilibrium away from the mean fitness maximum (see Figure 2a; ESHEL 1985). System (3) reduces to

$$\overline{w}_z \Delta z = \left[\frac{1}{2}\frac{d\overline{w}_z}{dz} - \left(\frac{1}{2} - k\right)(v_{12} + v_{21})\right] z(1 - z). \quad (15)$$

Term $(\frac{1}{2} - k)(v_{12} + v_{21})$ prevents the equivalence between polymorphic equilibrium and critical point.

Sex-specific segregation distortion may or may not result in an increase of the population mean fitness at equilibrium compared to its corresponding value given Mendelian segregation (see Figure 2b). The equivalence between polymorphic equilibrium and critical point is possible as long as the necessary condition $k + \kappa = 1$ is satisfied. All critical points, however, are saddle points (see APPENDIX B). The population mean fitness maxima are confined to the corners of Ω; in any of these corners all individuals carry and give birth to the highest viability genotype.

TABLE 2

Classification of parameter sets according to the number of nontrivial equilibria they produce and their stability

		No. of polymorphic equilibria				
0	**1**	0	1	2	3	Total
			$v_{12} = v_{21}$			
−	−	—	1,076,203	—	12	1,706,215
		—	(0.2510)	—	(3×10^{-6})	(0.2510)
−	+	1,863,947	—	4,749	—	1,868,696
+	−	(0.4348)	—	(0.0011)	—	(0.4359)
+	+	—	1,314,369	—	0	1,314,369
		—	(0.3066)	—	(0.0000)	(0.3066)
Indeterminate		26,957	634	4	0	27,595
		(0.0063)	(0.0001)	(10^{-6})	(0.0000)	(0.0064)
Total		1,890,904	2,391,206	4,753	12	4,286,875
		(0.4411)	(0.5578)	(0.0011)	(3×10^{-6})	
			$v_{12} \neq v_{21}$			
−	−	—	18,184,520	—	1,192	18,185,712
		—	(0.2357)	—	(1.5×10^{-6})	(0.2357)
−	+	38,445,946	—	184,966	—	38,630,912
+	−	(0.4982)	—	(0.0024)	—	(0.5006)
+	+	—	20,197,168	—	0	20,197,168
		—	(0.2617)	—	(0.0000)	(0.2617)
Indeterminate		137,620	12,053	285	0	149,958
		(0.0018)	(0.0002)	(4×10^{-6})	(0.0000)	(0.0020)
Total		38,583,566	38,393,741	185,251	1,192	77,163,750
		(0.5000)	(0.4976)	(0.0024)	(1.5×10^{-6})	

The parameter sets investigated were all combinations of the viabilities v_{ij} in the range (0, 2) at intervals of 0.1 and segregation ratios (k, κ) in the range (0, 1) at intervals of 0.04. Sets are classified by the number of nontrivial equilibria and the stability (+) or not (−) of the trivial equilibria (**0** and **1**). First-order conditions, however, fail to characterize the stability of the trivial equilibria for those sets labeled "indeterminate." Each cell contains the number of parameter sets observed; its proportion with respect to the total is given in parentheses. Em dashes refer to impossible cases.

Polymorphic corners, *i.e.*, (0, 1) and (1, 0), are unattainable with sex-independent segregation ratios, Mendelian or not. However, a population fixed for heterozygote A_1A_2 results from the segregation scheme (k, κ) = (1, 0). This equilibrium is stable and a local $\bar{w}$ maximum when $v_{12} > v_{11}, v_{22}$. Similarly, a population fixed for heterozygote A_2A_1 results from the segregation scheme (k, κ) = (0, 1). This equilibrium is stable and a local $\bar{w}$ maximum when $v_{21} > v_{11}, v_{22}$ (see APPENDIX C).

NUMERICAL RESULTS

The complex algebraic expression of ϕ_i requires the use of numerical methods to identify sets of parameter values $\mathbf{v} = (v_{11}, v_{12}, v_{21}, v_{22})$ and $\mathbf{s} = (k, \kappa)$ yielding multiple polymorphic equilibria. Describing the parameter space in terms of number of polymorphic equilibria produced is the purpose of this section.

Each $\{\bar{\mathbf{v}}, \bar{\mathbf{s}}\}$ depicts a specific instance of (1) that might have up to three polymorphic equilibria. We have calculated the equilibria for >81 million $\{\bar{\mathbf{v}}, \bar{\mathbf{s}}\}$ sets consisting of all combinations of values in **v** taken at intervals 0.1 within the range [0.1, 1.9] and values in **s** taken at intervals 0.04 within the range [0.02, 0.98]. Special cases (0, 1) and (1, 0) were considered above and in APPENDIX B.

This analysis (see Table 2 for results) shows that with imprinting, 50% of all {**v**, **s**} sets produce only trivial equilibria while the other 50% bear at least one polymorphic equilibrium (48% of the polymorphic equilibria are stable). Without imprinting, 44% of all {**v**, **s**} sets produce only trivial equilibria while the remaining 56% bear at least one polymorphic equilibrium (50% of the polymorphic equilibria are stable).

Multiple equilibria: Our numerical analysis confirmed the existence of parameter values yielding two polymorphic equilibria (HARTL 1970) and found, for the first time, parameter values yielding three polymorphic equilibria. The frequency of the former is small (≈2.4 in 10^3) while the frequency of the latter is very small (≈1.5 in 10^5). Multiple polymorphic equilibria were found both with and without imprinting. The fraction of such

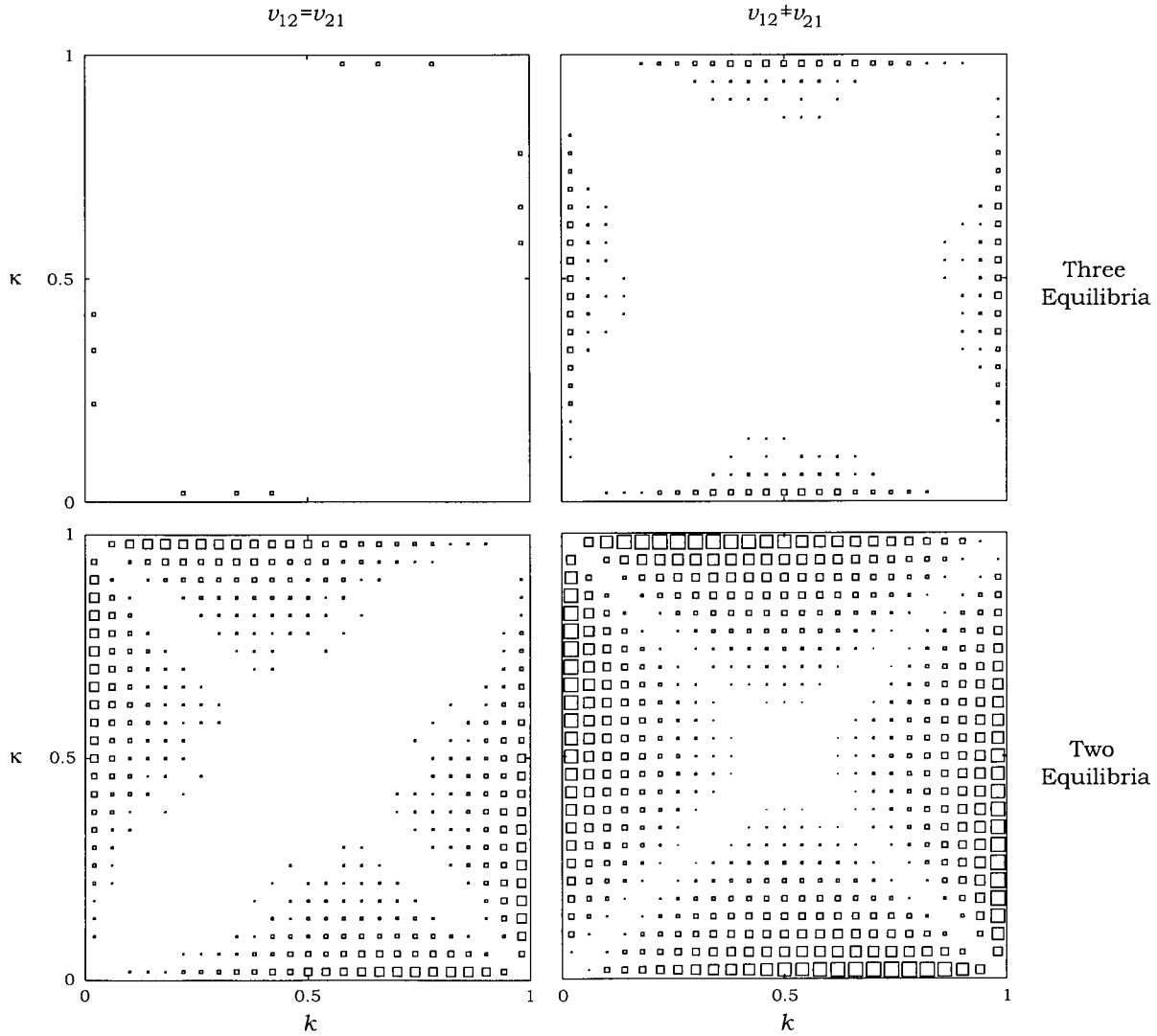

FIGURE 3.—Multiple equilibria in parameter subspace (k, κ). We separate parameter sets yielding two equilibria from those yielding three equilibria in columns. Also we separate parameter sets with genomic imprinting from parameter sets without genomic imprinting in rows. The area of each square is proportional to the number of parameter sets yielding multiple equilibria for a pair (k, κ). Given the difference in magnitude between two and three equilibria, the scale used for the latter is 10 times larger than the one used for the former.

cases, however, was substantially greater in the presence of imprinting. In particular, the fraction of cases producing two equilibria was increased by a factor of two while the fraction producing three equilibria was increased by a factor of five.

In an attempt to characterize the parameter space where there are multiple equilibria, the number of $\bar{\mathbf{v}}$ sets yielding two or three equilibria was plotted against $\mathbf{s}$ (see Figure 3). The parameter subspace $\{(k, \kappa) | 0 \leq k, \kappa \leq 1\}$ has two diagonals: the main diagonal ($k = \kappa$) and the secondary diagonal ($k + \kappa = 1$), which are axes of mirror symmetry. The main diagonal reflects interchangeability of the sexes while the secondary one reflects interchangeability of alleles A_1 and A_2. The most prominent features of these plots are the absence of multiple equilibria on the diagonals and a higher probability of observing multiple equilibria in the proximity of Mendelian segregation in one sex but perfect drive in the other.

The lack of multiple equilibria with equal segregation distortion in the two sexes is a well-known result. The lack of multiple equilibria when drive in one sex is perfectly compensated by drag in the opposite sex is a novel observation. The detail of our numerical analysis provides strong evidence for the validity of this observation but we have no mathematical proof. It is also interesting that the probability of having multiple equilibria increases with the distortion strength of one allele in one sex while the other sex shows Mendelian segregation or slight segregation distortion against the same allele.

Three equilibria: In this section we focus on parameter values yielding three equilibria. Table 3 presents some examples while Figures 4 and 5 make a detailed

TABLE 3

Examples of {v, s} sets yielding three equilibria

	Viability:	Segregation:	Equilibria		
	$(v_{11}, v_{12}, v_{21}, v_{22})$	(k, κ)	(x_1, y_1)	(x_2, y_2)	(x_3, y_3)
$(k-\kappa)(v_{12}-v_{21})$					
<0	(0.4, 1.0, 1.3, 1.6)	(0.98, 0.50)	(0.9353, 0.6629)	(0.8488, 0.5492)	(0.4280, 0.2342)
	(0.5, 1.5, 0.7, 1.0)	(0.22, 0.98)	(0.5075, 0.9477)	(0.2603, 0.7341)	(0.1326, 0.4688)
	(0.6, 0.9, 1.5, 1.4)	(0.94, 0.38)	(0.9324, 0.6796)	(0.6432, 0.3351)	(0.4497, 0.2111)
	(0.6, 1.0, 1.7, 1.7)	(0.94, 0.46)	(0.9261, 0.7074)	(0.8867, 0.6365)	(0.2873, 0.1495)
	(0.7, 1.5, 1.0, 1.6)	(0.50, 0.86)	(0.7870, 0.9152)	(0.6154, 0.8000)	(0.2049, 0.3278)
	(0.7, 1.9, 1.3, 1.9)	(0.34, 0.98)	(0.5427, 0.9274)	(0.3548, 0.7507)	(0.1301, 0.3401)
	(0.8, 1.8, 1.2, 1.9)	(0.46, 0.90)	(0.7880, 0.9397)	(0.4216, 0.6620)	(0.1245, 0.2308)
	(1.0, 1.1, 0.7, 0.4)	(0.02, 0.70)	(0.5132, 0.8223)	(0.2000, 0.6364)	(0.1212, 0.5590)
$=0$	(0.2, 1.1, 1.1, 1.9)	(0.78, 0.98)	(0.8252, 0.9398)	(0.7592, 0.8869)	(0.5601, 0.6812)
	(1.4, 0.9, 0.9, 0.3)	(0.02, 0.42)	(0.7266, 0.8334)	(0.5610, 0.7259)	(0.0300, 0.2194)
	(0.3, 1.1, 1.1, 1.8)	(0.66, 0.98)	(0.8154, 0.9679)	(0.5476, 0.7438)	(0.0832, 0.1226)
>0	(1.5, 1.0, 0.9, 0.3)	(0.42, 0.02)	(0.9488, 0.9142)	(0.5200, 0.2769)	(0.3093, 0.0713)

These examples are classified according to the sign of the product $(k-\kappa)(v_{12}-v_{21})$. In the absence of imprinting the product is null.

exploration of two of them. Figure 4 provides a large-scale picture of equilibria considering the whole range of values that k may take. Figures 5 and 6, however, zoom in the window of (k, κ) values where three polymorphic equilibria exist.

Figure 4 considers $\bar{\mathbf{v}} = (0.3, 1.7, 0.5, 1)$ and explores the continuum $0 \le k \le 1$ in the proximity of $\kappa = 0.98$. Starting with $\kappa = 0.7$, for $k > 0.5$ fixation of A_2 is the only stable equilibrium. As the value of k decreases past 0.5, a polymorphic equilibrium steals the stability from fixation of A_2. This polymorphic equilibrium vanishes for a further decrease in k past 0.3. Past 0.11 two imaginary roots become real. For $k < 0.11$ fixation of A_1 and a polymorphic equilibrium are simultaneously locally stable, whereas fixation of A_2 and a second polymorphic equilibrium are both unstable (see Figure 4a).

With $\kappa = 0.7$ we get a maximum of two simultaneous polymorphic equilibria. An increase in κ to 0.9 keeps a similar scenario but brings about three simultaneous polymorphic equilibria as inflection points I_1 and I_2 come closer. In window $0.36 \le k \le 0.41$ two polymorphic equilibria are simultaneously locally stable, whereas fixation of A_1, A_2, and another polymorphic equilibrium are all unstable. Before and after this window, there is a single polymorphic stable equilibrium (see Figure 4b). Finally, with perfect drive in oogenesis inflection points I_1 and I_2 merge. In window $0.29 \le k \le 0.38$ there are three polymorphic equilibria, two of them simultaneously stable, while in window $0 \le k \le 0.29$ there are two polymorphic equilibria, one of them stable. In $k = 0.25$ the stability of the two simultaneous equilibria reverses (see Figure 4c).

Figure 5 considers $\bar{\mathbf{v}} = (1, 0.5, 1.3, 0.3)$ and explores the continuum $\{0.4 \le k \le 0.6\} \times \{0 \le \kappa \le 0.1\}$. Equation $p_{\bar{\mathbf{v}}}(\hat{x}) = 0$ [where the subscript denotes that $p(\hat{x})$ has been evaluated in $\bar{\mathbf{v}}$] implicitly defines a surface for the equilibrium frequency of A_1 as a function of k and κ. This surface is known in nonlinear dynamics as the catastrophe surface (Poston and Stewart 1978). In the region studied, the surface folds over itself, allowing a vertical line to intersect it at three points. Points on the upper and lower sheets of the pleat are locally stable equilibria whereas points on the middle sheet are locally unstable (see Figure 5a).

The projection of the fold onto the (k, κ) plane is known as the cusp curve (Poston and Stewart 1978). Sudden changes in the number of equilibria, from one to three and back again, take place at this curve. The cusp curve has two branches diverging from a point (see Figure 5b); at this point all three equilibria coincide while on either of the branches two of the three equilibrium frequencies coincide because $\Delta_{\bar{\mathbf{v}}} = 0$. Between the branches, $\Delta_{\bar{\mathbf{v}}} < 0$ and $p_{\bar{\mathbf{v}}}(\hat{x})$ has three real roots while outside the branches $\Delta_{\bar{\mathbf{v}}} > 0$ and $p_{\bar{\mathbf{v}}}(\hat{x})$ has a single real root.

On one hand, if the curve resulting from taking a vertical slice of the catastrophe surface at $\kappa = 0.03$ is walked from right to left, there is a gradual decrease in the value of $\hat{x}$ until $k = 0.53$, beyond which point $\hat{x}$ suddenly drops to a lower value and so does $\bar{w}$ (see Figure 6). This sudden change in the value of $\hat{x}$ is the "catastrophe" that gives the surface its name. On the other hand, if the curve is walked from left to right, there is a gradual increase in the value of $\hat{x}$ until $k = 0.56$, beyond which point $\hat{x}$ suddenly jumps to a higher value and so does $\bar{w}$. In the window $0.53 \le k \le 0.56$

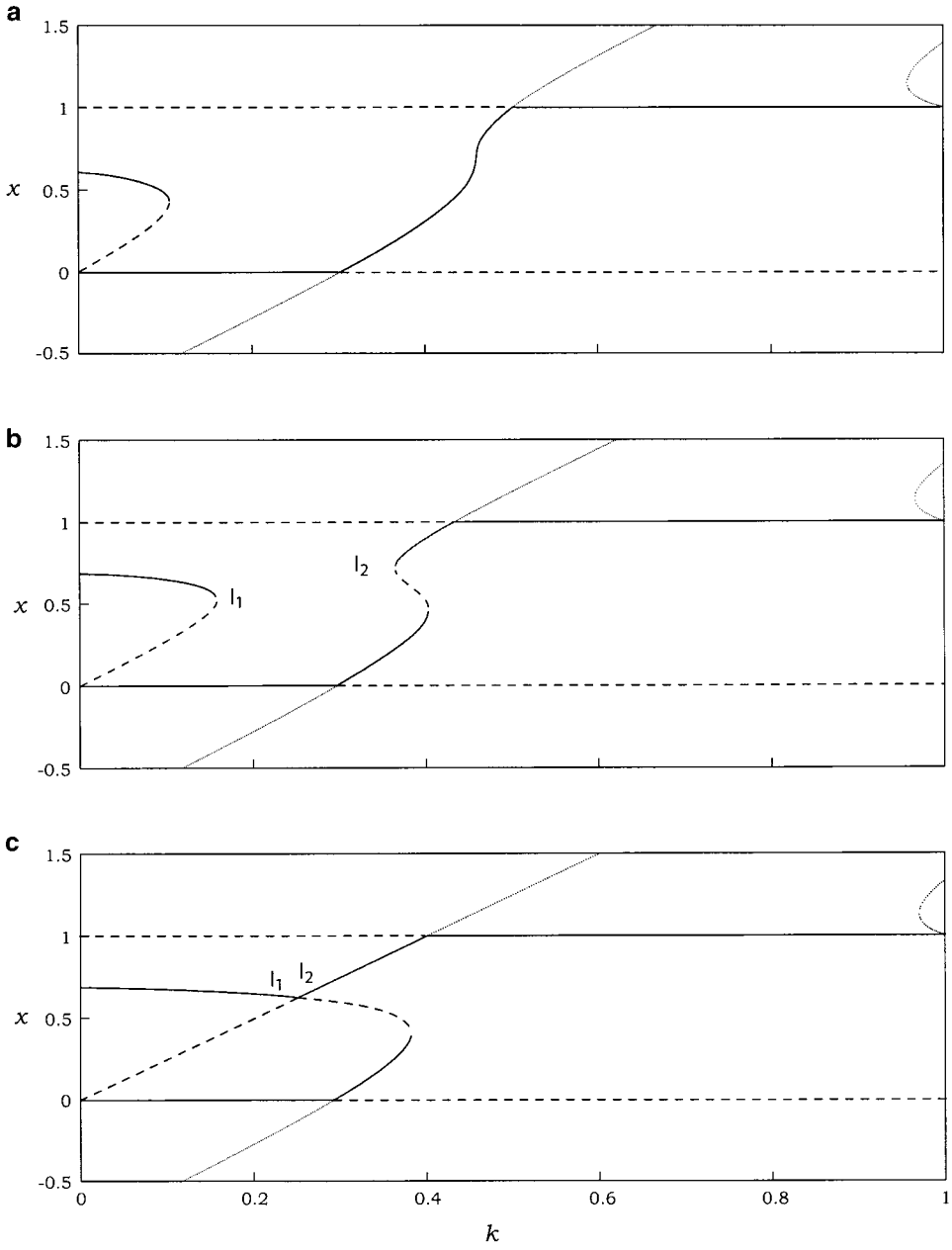

FIGURE 4.—Roots of our system as a function of k. Consider the viability set (0.3, 1.7, 0.5, 1). The x component of the equilibrium value is drawn as a function of k. Solid lines denote locally stable equilibria; dashed lines, unstable equilibria; and dotted lines, unfeasible equilibria (values of $x < 0$ or > 1 are devoid of biological meaning). These roots are drawn for three values of κ: (a) 0.7, showing a maximum of two polymorphic equilibria; (b) 0.9, showing a maximum of three polymorphic equilibria; (c) 1, where regions with two and three polymorphic equilibria fuse.

there are three polymorphic equilibria, the middle of which delimits the basins of attraction of the other two polymorphic equilibria.

In all cases of parameter values yielding three polymorphic equilibria, two of them are stable and one is unstable. Although we suspect that the system precludes cases of one stable and two unstable equilibria we cannot reject the possibility that these exist in exceedingly rare numbers. Otherwise, $\{\mathbf{v}, \mathbf{s}\}$ sets producing three polymorphic equilibria do not have obvious common features. It would be reasonable to think that they require two pairs of opposing forces. These forces could be provided on the one hand by average heterozygote advantage, $v_{12} + v_{21} > v_{11} + v_{22}$, and on the other hand by a segregation bias toward formation of the least viable of the two heterozygotes, $(k - \kappa)(v_{12} - v_{21}) < 0$. While the first selective force favors the formation of a polymorphic equilibrium, the second force becomes relevant in a polymorphic population and favors the fixation of one allele. This pair of antagonistic forces exists in all but one of the three equilibria under a viability scheme with imprinting but fails to explain all cases in the absence of imprinting (see Table 3).

DISCUSSION

The one-locus model we present in this article further generalizes earlier models of sex-specific meiotic drive (WRIGHT 1969; HARTL 1970) by allowing nonequivalence of the viabilities of reciprocal heterozygotes, as might occur at an imprinted locus. It also extends the analysis of HARTL (1970), considering the case of per-

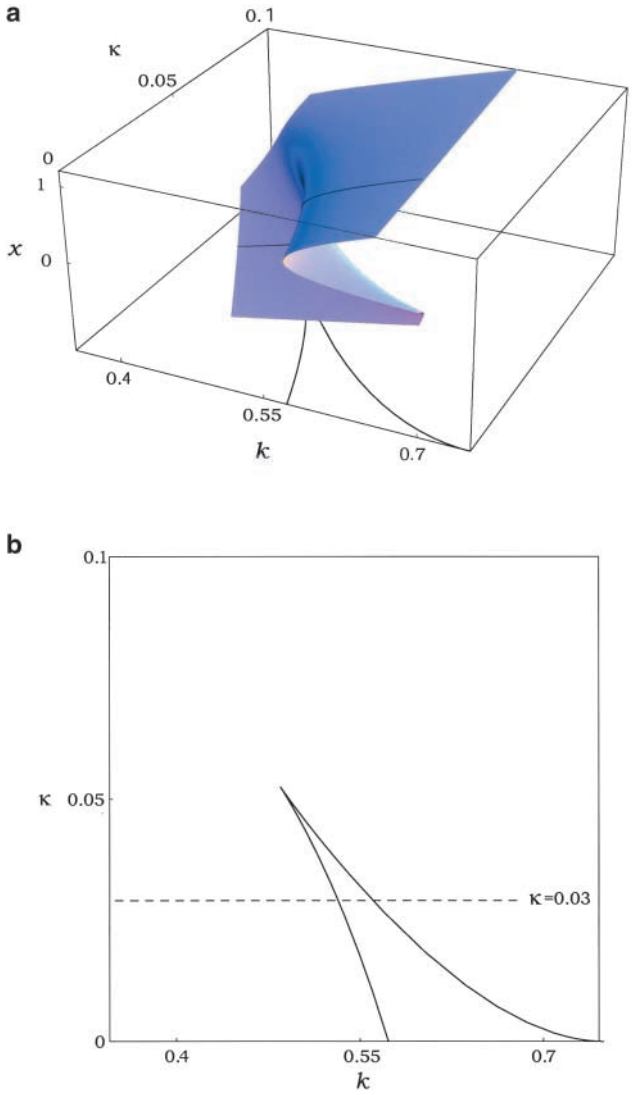

FIGURE 5.—Roots of $p(x)$ as a function of k and κ. Consider the viability set (1, 0.5, 1.3, 0.3). The catastrophe surface (a) is drawn in the window $[0.35, 0.75] \times [0.0, 0.1]$ where it folds over itself. The projection of the boundary of the fold onto the (k, κ) plane is known as a catastrophe curve (b). Outside the fold, the system has none or one polymorphic equilibrium, whereas it has three polymorphic equilibria within the fold. The line along the catastrophe surface and across the catastrophe curve corresponds to the section used to draw Figure 6.

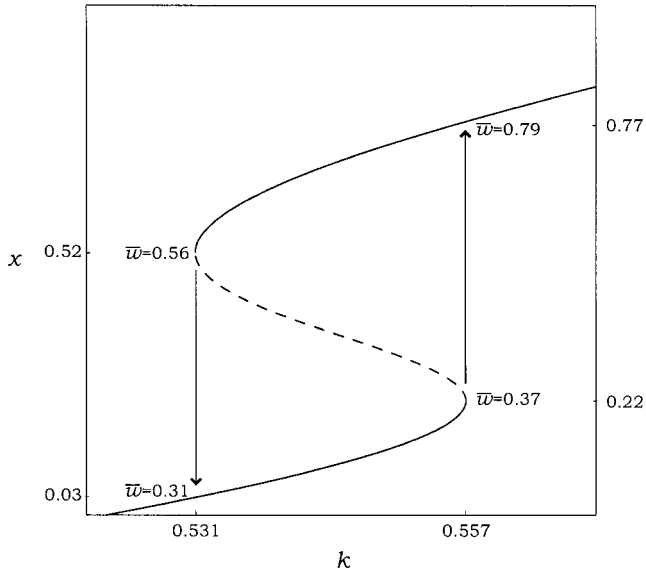

FIGURE 6.—Section of Figure 5 at κ = 0.03. Solid portions of the curve represent locally stable equilibria whereas dashed portions of the curve represent unstable equilibria. Polynomial $p(x)$ has three roots in the interval 0.531–0.557. The arrows represent sudden ("catastrophic") changes in the equilibrium of the system due to small variations in k. The change in population mean fitness that accompanies these jumps is also indicated.

fect drive in favor of one allele in one sex and against the same allele in the other sex, and exploring the parameter space in search of parameter sets yielding two stable polymorphic equilibria.

Stable polymorphic equilibria in single-locus models of viability selection maximize population mean fitness under the constraint of Mendelian segregation. A segregation ratio other than Mendelian but equal for both sexes drives this equilibrium away from the optimal population mean fitness, however. We have shown that the latter result does not need to be true if the segregation ratio is allowed to differ between the sexes. For example, if one of the heterozygote classes has higher fitness than both homozygote classes, mean fitness is maximized by a system of permanent translocation heterozygotes (*e.g.*, *Oenothera* spp. and *I. petraea*) in which perfect meiotic drive of one allele in one sex is balanced by perfect drag of the same allele in the other sex (HOLSINGER and ELLSTRAND 1984). This observation does not rely on the differential viability of reciprocal heterozygotes.

ESHEL (1985) contends that selection on unlinked modifiers favors Mendelian segregation at a polymorphic locus because mean viability is increased by modifiers that reduce the strength of segregation distortion. However, his model assumed equal segregation distortion in the two sexes, and his elegant solution of a major evolutionary puzzle is unlikely to apply (at least in unmodified form) if segregation ratios are allowed to differ between the sexes. This is because unlinked modifiers will sometimes favor enhanced segregation distortion if one of the heterozygous classes is the most fit genotype. Eshel's solution to the puzzle of Mendelian segregation could be rescued if it were assumed that most balanced polymorphisms involve heterozygotes with lower viability than one of the homozygous classes. This might be the case if most polymorphisms were maintained by segregation distortion, or by analogous intragenomic conflicts, rather than by classical heterozygote advantage.

Using numerical analysis, we have shown that our model can have multiple polymorphic equilibria. While parameter sets yielding two equilibria are rare (≈2.4 in 10^3), parameter sets yielding three equilibria are even rarer (≈1.5 in 10^5). Cases of multiple equilibria are not

restricted to differential viability of reciprocal heterozygotes. Without genomic imprinting, however, the proportions of parameter sets yielding two and three polymorphic equilibria experience a twofold and fivefold decrease, respectively. Hartl (1970) finds sets yielding two polymorphic equilibria with frequency ≈ 2.1 in 10^3. This result is not comparable to ours because Hartl surveys a nonsymmetric subset of our parameter space. Multiple equilibria occur more often when segregation distortion is strong in one sex and mild (or absent) in the other sex. In the absence of imprinting, this is the region of the parameter space where the classic examples of segregation distortion, the *SD* system in Drosophila and *t*-haplotype in mouse, lie.

Owen (1953) was the first to describe a genetic model with two stable polymorphic equilibria. In his model, segregation was Mendelian but the same genotype had different viabilities in males and females. A sufficient condition to have two stable polymorphic equilibria in these kinds of models is heterozygote superiority in one sex but heterozygote inferiority in the other (Karlin 1972). Even though our model and Owen's (1953) model have a component of sex specificity, Owen's results cannot be extrapolated to our model because they are not formally equivalent. An interesting but daunting task would be incorporating sex-specific viability to our model.

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APPENDIX A

Conditions for existence of a nontrivial equilibrium: Polynomial $p(x)$ is a continuous function. Therefore, if $p(0)$ and $p(1)$ have opposite sign, $p(x)$ must equal zero for at least one point in $(0, 1)$. Hence, $p(x)$ has at least one root in the $(0, 1)$ interval if

$$\frac{p(0)}{p(1)} = \frac{kv_{21}v_{22}}{(1-k)v_{11}v_{12}} \cdot \frac{v_{22} - (kv_{12} + \kappa v_{21})}{(1-\kappa)v_{12} + (1-k)v_{21} - v_{11}} < 0. \tag{A1}$$

The satisfaction of this inequality depends solely on the sign of the second fraction and translates into two alternative sets of conditions,

$$kv_{12} + \kappa v_{21} - v_{22} > 0 \tag{A2a}$$

$$(1-\kappa)v_{12} + (1-k)v_{21} - v_{11} > 0 \tag{A2b}$$

or

$$kv_{12} + \kappa v_{21} - v_{22} < 0 \tag{A3a}$$

$$(1-\kappa)v_{12} + (1-k)v_{21} - v_{11} < 0. \tag{A3b}$$

If we assume that there is at most one nontrivial equilibrium, these conditions are sufficient and necessary.

However, they are sufficient but not necessary if multiple equilibria are taken into consideration.

Conditions for stability of a nontrivial equilibrium: The first-order approximation of system (1) evaluated in the proximity of equilibrium $(\hat{x}, \hat{y})$ is

$$\begin{bmatrix} x' \\ y' \end{bmatrix} = \begin{bmatrix} \partial x'/\partial x|_{(\hat{x},\hat{y})} & \partial x'/\partial y|_{(\hat{x},\hat{y})} \\ \partial y'/\partial x|_{(\hat{x},\hat{y})} & \partial y'/\partial y|_{(\hat{x},\hat{y})} \end{bmatrix} \begin{bmatrix} x \\ y \end{bmatrix}, \tag{A4}$$

where

$$\bar{w}\frac{\partial x'}{\partial x}\bigg|_{(\hat{x},\hat{y})} = v_{11}\hat{y}(1-\hat{x}) + v_{22}\hat{x}(1-\hat{y}) + (k-\hat{x})(v_{12}(1-\hat{y}) - v_{21}\hat{y}) \tag{A5a}$$

$$\bar{w}\frac{\partial x'}{\partial y}\bigg|_{(\hat{x},\hat{y})} = (v_{11}+v_{22})\hat{x}(1-\hat{x}) + (k-\hat{x})(v_{21}(1-\hat{x}) - v_{12}\hat{x}) \tag{A5b}$$

$$\bar{w}\frac{\partial y'}{\partial x}\bigg|_{(\hat{x},\hat{y})} = (v_{11}+v_{22})\hat{y}(1-\hat{y}) + (\kappa-\hat{y})(v_{12}(1-\hat{y}) - v_{21}\hat{y}) \tag{A5c}$$

$$\bar{w}\frac{\partial y'}{\partial y}\bigg|_{(\hat{x},\hat{y})} = v_{11}\hat{x}(1-\hat{y}) + v_{22}\hat{y}(1-\hat{x}) + (\kappa-\hat{y})(v_{21}(1-\hat{x}) - v_{12}\hat{x}). \tag{A5d}$$

Let $\mathbf{G}$ be the gradient matrix in (A4) and $g(\lambda) = \lambda^2 - \mathrm{tr}(\mathbf{G})\lambda + \det(\mathbf{G})$ be the characteristic polynomial associated with the linearized system, where $\mathrm{tr}(\mathbf{G})$ stands for the trace of $\mathbf{G}$ and $\det(\mathbf{G})$ refers to its determinant. The necessary and sufficient conditions for local stability of $(\hat{x}, \hat{y})$ are $g|_{\lambda=1} > 0$ and $\partial g/\partial\lambda|_{\lambda=1} > 0$.

Let $\mathbf{G_0}$ ($\mathbf{G_1}$) be matrix $\mathbf{G}$ evaluated in $\mathbf{0}$ ($\mathbf{1}$). Assuming the system does not present stable cycles, at least one nontrivial equilibrium is stable whenever both trivial equilibria are locally unstable. $\mathbf{0}$ is locally unstable if $g|_{\mathbf{G_0},\lambda=1} < 0$ and $\partial g/\partial\lambda|_{\mathbf{G_0},\lambda=1} < 0$, which yields $kv_{12} + \kappa v_{21} > v_{22}$. $\mathbf{1}$ is locally unstable if $g|_{\mathbf{G_1},\lambda=1} < 0$ and $\partial g/\partial\lambda|_{\mathbf{G_1},\lambda=1} < 0$, which yields $(1-k)v_{21} + (1-\kappa)v_{12} > v_{11}$.

Note that the first set of conditions for the existence of at least one nontrivial equilibrium corresponds to the instability of both $\mathbf{0}$ and $\mathbf{1}$ while the second set of conditions corresponds to the stability of $\mathbf{0}$ and $\mathbf{1}$. To summarize, the stability conditions are sufficient but not necessary conditions for the existence and stability of at least one trivial equilibrium.

Strict equality: If $v_{22} = kv_{12} + \kappa v_{21}$, $\mathbf{0}$ is a double equilibrium and the leading eigenvalue of $\mathbf{G_0}$, $\rho(\mathbf{G_0})$, takes the unit value. Thus we need to recur to second-order conditions to characterize the stability of $\mathbf{0}$. Following the general solution of Lessard and Karlin (1982), for eigenvalue 1 problems we can conclude that $\mathbf{0}$ is unstable whenever

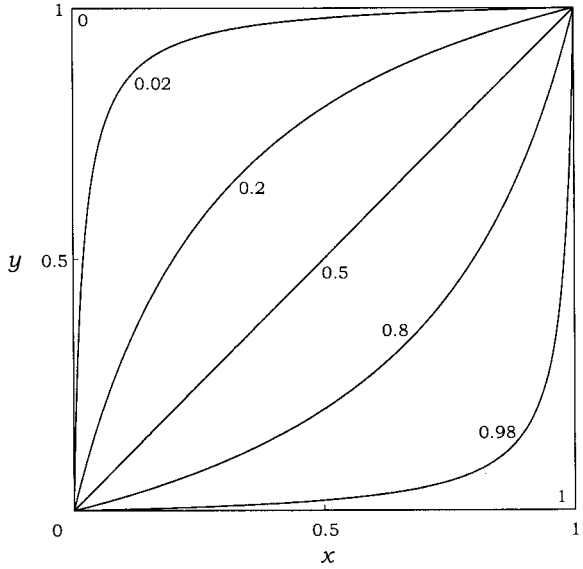

Figure A1.—Family of neutral equilibria when $k = 1 - \kappa$. This family is drawn in Ω for the values of k indicated beside each curve.

$$\frac{v_{11}}{v_{22}} > \frac{1-k}{\kappa}\frac{v_{12}}{v_{12}+v_{21}} + \frac{1-\kappa}{k}\frac{v_{21}}{v_{12}+v_{21}}. \tag{A6}$$

If $v_{11} = (1-k)v_{21} + (1-\kappa)v_{12}$, $\mathbf{1}$ is a double equilibrium and $\rho(\mathbf{G_1}) = 1$. Thus $\mathbf{1}$ is unstable whenever

$$\frac{v_{22}}{v_{11}} < \frac{k}{1-\kappa}\frac{v_{21}}{v_{12}+v_{21}} + \frac{\kappa}{1-k}\frac{v_{12}}{v_{12}+v_{21}}. \tag{A7}$$

If $v_{22} = kv_{12} + \kappa v_{21}$ and $v_{11} = (1-k)v_{21} + (1-\kappa)v_{12}$, both $\mathbf{0}$ and $\mathbf{1}$ are double equilibria, and (7) can be fully factored,

$$\hat{x}^2(1-\hat{x})^2(k-\kappa)(1-k-\kappa)(\hat{x} + (e_2+1)) = 0. \tag{A8}$$

From the last expression it is obvious that whenever $k = \kappa$ or $k + \kappa = 1$ the identity is true for any $\hat{x}$. Thus, a first family of neutral equilibria results from substituting $k = \kappa$ in (4),

$$\hat{x} = \hat{y}. \tag{A9}$$

A second family of neutral equilibria results from substituting $k + \kappa = 1$ in (4),

$$\hat{x} = \frac{(1-\kappa)\hat{y}}{\kappa + (1-2\kappa)\hat{y}}. \tag{A10}$$

These families of equilibria (see Figure A1) are stable in the sense that deviations from a particular equilibrium yield a succession of states closer to the family of equilibria although not necessarily closer to the initial equilibrium. Changes from one equilibrium to another within a family are governed by random gametic drift.

Instability conditions (A6) and (A7) reduce to

$$(k - \kappa)(1 - k - \kappa)(\kappa v_{21}^2 - k v_{12}^2) > 0 \quad \text{(A11a)}$$

$$(k - \kappa)(1 - k - \kappa)((1 - k) v_{21}^2 - (1 - \kappa) v_{12}^2) > 0. \quad \text{(A11b)}$$

APPENDIX B

Assuming equal segregation ratio in both sexes the mean fitness function takes the form

$$\overline{w}_z = v_{11} z^2 + (v_{12} + v_{21}) z(1 - z) + v_{22}(1 - z)^2. \quad \text{(B1)}$$

This function is defined for values of z in the interval [0, 1].Given that this interval is closed and bounded and that $\overline{w}$ is a continuous function, Weierstrass's theorem guarantees the existence of a global maximum. The first-order condition $\partial\overline{w}/\partial z = 0$ defines a critical point $\tilde{z}$ that corresponds to a maximum only if the second-order condition $\partial^2\overline{w}/\partial z^2 \leq 0$ is satisfied. Straight differentiation from (B1) yields $\partial^2\overline{w}/\partial z^2 = 2(v_{11} + v_{22} - v_{12} - v_{21})$. Thus, $\tilde{z}$ is a maximum whenever $v_{12} + v_{21} \geq v_{11} + v_{22}$.

Allowing a different segregation ratio in each sex, the mean fitness function takes the form

$$\overline{w} = v_{11} xy + v_{12} x(1 - y) + v_{21}(1 - x) y + v_{22}(1 - x)(1 - y). \quad \text{(B2)}$$

This function is defined in Ω. Once again, Weierstrass's theorem guarantees the existence of a global maximum. Now, first- and second-order conditions are those corresponding to multivariate optimization. Let $\mathbf{H}$ be the matrix of second derivatives (a.k.a. the Hessian matrix),

$$\mathbf{H} = \begin{bmatrix} \partial^2\overline{w}/\partial x^2 & \partial^2\overline{w}/\partial x \partial y \\ \partial^2\overline{w}/\partial y \partial x & \partial^2\overline{w}/\partial y^2 \end{bmatrix}. \quad \text{(B3)}$$

The first-order condition $\partial\overline{w}/\partial x = \partial\overline{w}/\partial y = 0$ defines a critical point $(\tilde{x}, \tilde{y})$ that corresponds to a maximum only if the Hessian matrix is negative semidefinite; *i.e.*, $\mathbf{h}^T\mathbf{H}\mathbf{h} \leq 0$ for any column vector $\mathbf{h} = (h_1, h_2)$. Matrix $\mathbf{H}$ satisfies the second-order condition if and only if $|\mathbf{H}_1| \leq 0$ and $|\mathbf{H}_2| \geq 0$, where $\mathbf{H}_n$ is a submatrix formed by the n first rows and columns of matrix $\mathbf{H}$ (minor of order n of matrix $\mathbf{H}$). Straight differentiation from (B2) yields

$$\mathbf{H} = \begin{bmatrix} 0 & v_{11} + v_{22} - v_{12} - v_{21} \\ v_{11} + v_{22} - v_{12} - v_{21} & 0 \end{bmatrix}. \quad \text{(B4)}$$

Consequently, $|\mathbf{H}_1| = 0$, $|\mathbf{H}_2| = -(v_{11} + v_{22} - v_{12} - v_{21})^2$ and unless $v_{11} + v_{22} = v_{12} + v_{21}$ the critical point does not satisfy the condition for maximum. Instead, the fact that $|\mathbf{H}_2| < 0$ for any (x, y) indicates that $(\tilde{x}, \tilde{y})$ is always a saddle point. This result reduces the potential maxima to the borders of Ω. Even more, the derivatives of $\overline{w}$ along the borders take constant values and, therefore, candidates for maxima are restricted to one of the four corners of Ω.

APPENDIX C

When $k = 1$ and $\kappa = 0$, Equations 3 simplify to

$$\overline{w}\Delta x = \frac{\partial\overline{w}}{\partial x} x(1 - x) + v_{21}(1 - x) y \quad \text{(C1a)}$$

$$\overline{w}\Delta y = \frac{\partial\overline{w}}{\partial y} y(1 - y) - v_{21}(1 - x) y. \quad \text{(C1b)}$$

And the equilibria result from solving the system

$$(1 - \hat{x})\left[\frac{\partial\overline{w}}{\partial x}\hat{x} + v_{21}\hat{y}\right] = 0 \quad \text{(C2a)}$$

$$\hat{y}\left[\frac{\partial\overline{w}}{\partial y_1}(1 - \hat{y}) - v_{21}(1 - \hat{x})\right] = 0. \quad \text{(C2b)}$$

Equation C2a is satisfied when $\hat{x} = 1$, in which case (C2b) implies $(v_{11} - v_{12})\hat{y}(1 - \hat{y}) = 0$. The latter is true whenever $\hat{y} = 0$, $\hat{y} = 1$, or $v_{12} = v_{11}$. Similarly, Equation C2b is satisfied when $\hat{y} = 0$, in which case Equation C2a requires that $(v_{12} - v_{22})\hat{x}(1 - \hat{x}) = 0$. The latter is true whenever $\hat{x} = 0$, $\hat{x} = 1$, or $v_{12} = v_{22}$.

Simple inspection provides three equilibria: the trivial ones at $\mathbf{0}$ and $\mathbf{1}$ and the polymorphic corner (1, 0). The corner equilibrium is stable whenever $v_{12} > v_{11}, v_{22}$. There is one other polymorphic equilibrium in Ω but this is always unstable. Boundary $x = 1$ comprises a family of equilibria when $v_{12} = v_{11}$ while boundary $y = 1$ comprises a family of equilibria when $v_{12} = v_{22}$.

When $\kappa = 1$ and $k = 0$ we reach analogous results with the roles of A_1 and A_2 reversed. To summarize, corner (0, 1) is a stable equilibrium whenever $v_{21} > v_{11}, v_{22}$. Boundaries $x = 0$ and $y = 1$ comprise families of equilibria when $v_{21} = v_{22}$ and $v_{21} = v_{11}$, respectively.