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On the Evolutionary Stability of Mendelian Segregation

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ABSTRACT

We present a model of a primary locus subject to viability selection and an unlinked locus that causes sex-specific modification of the segregation ratio at the primary locus. If there is a balanced polymorphism at the primary locus, a population undergoing Mendelian segregation can be invaded by modifier alleles that cause sex-specific biases in the segregation ratio. Even though this effect is particularly strong if reciprocal heterozygotes at the primary locus have distinct viabilities, as might occur with genomic imprinting, it also applies if reciprocal heterozygotes have equal viabilities. The expected outcome of the evolution of sex-specific segregation distorters is all-and-none segregation schemes in which one allele at the primary locus undergoes complete drive in spermatogenesis and the other allele undergoes complete drive in oogenesis. All-and-none segregation results in a population in which all individuals are maximally fit heterozygotes. Unlinked modifiers that alter the segregation ratio are unable to invade such a population. These results raise questions about the reasons for the ubiquity of Mendelian segregation.

THE two alleles at a heterozygous locus are equally represented among the functional products of meiosis. This expectation was formalized at the origin of modern genetics as the first of Mendel's laws. The rule is not absolute, however. Mendelian segregation is violated by genes known as segregation distorters (Crow 1979). Given the strong selective forces associated with biased transmission a question arises, Why is Mendelian segregation the rule and segregation distortion the exception rather than the other way around?

Models addressing the evolution of fair segregation have considered a primary locus (with alleles A_1 and A_2) undergoing viability selection and a modifier locus that determines the segregation ratio at the primary locus. If the two loci are linked, modifiers that change the segregation ratio at the primary locus are able to invade a population undergoing Mendelian segregation (Prout *et al*. 1973; Hartl 1975; Liberman 1976). The intuitive reason for this result is that a modifier that confers a segregation advantage on allele A_1 will be favored by natural selection because it comes to be preferentially associated with A_1 and thus shares in that allele's segregation advantage. By contrast, a modifier that confers a segregation disadvantage on A_1 (*i.e*., segregation advantage on A_2) will become preferentially associated with A_2. The introduction of either kind of modifier by itself would destabilize Mendelian segregation.

Eshel (1985) proposed an elegant solution to this conundrum. He showed that if the modifier locus is unlinked to the primary locus, then natural selection disfavors modifier alleles that take the segregation ratio away from Mendelian expectations but favors alleles that bring the segregation ratio closer to Mendelian expectations. Therefore, Mendelian segregation has the property of evolutionary genetic stability (Eshel 1996) with respect to unlinked modifiers. Furthermore, an increase in recombination between the main and modifier locus would be favored by natural selection until they become unlinked and segregation distortion is eliminated (Haig and Grafen 1991). Taken together, these results seem to explain the ubiquity of fair segregation in diploid organisms with multiple chromosomes by invoking mutual policing between genes over deviations from fair segregation. Fair segregation is maintained because most loci in the genome, and hence the majority of potential modifiers of the segregation ratio, are unlinked to any particular locus. The intuitive explanation for Eshel's (1985) result is that an unlinked modifier conferring a segregation advantage on A_1 is not preferentially associated with this allele, thus sharing in A_1 segregation advantage as much as in A_2 segregation disadvantage. Alleles at an unlinked modifier locus can gain no direct advantage from segregation distortion at the primary locus. Therefore, such alleles should favor whatever segregation ratio maximizes population mean fitness, which in Eshel's model is Mendelian segregation.

Brief reflection, however, reveals that Mendelian segregation does not maximize mean fitness at a locus subject to heterozygote advantage because this segregation scheme always produces some offspring with the less-fit homozygous genotypes. Rather, mean fitness is maximized by what we call an *all-and-none* segregation

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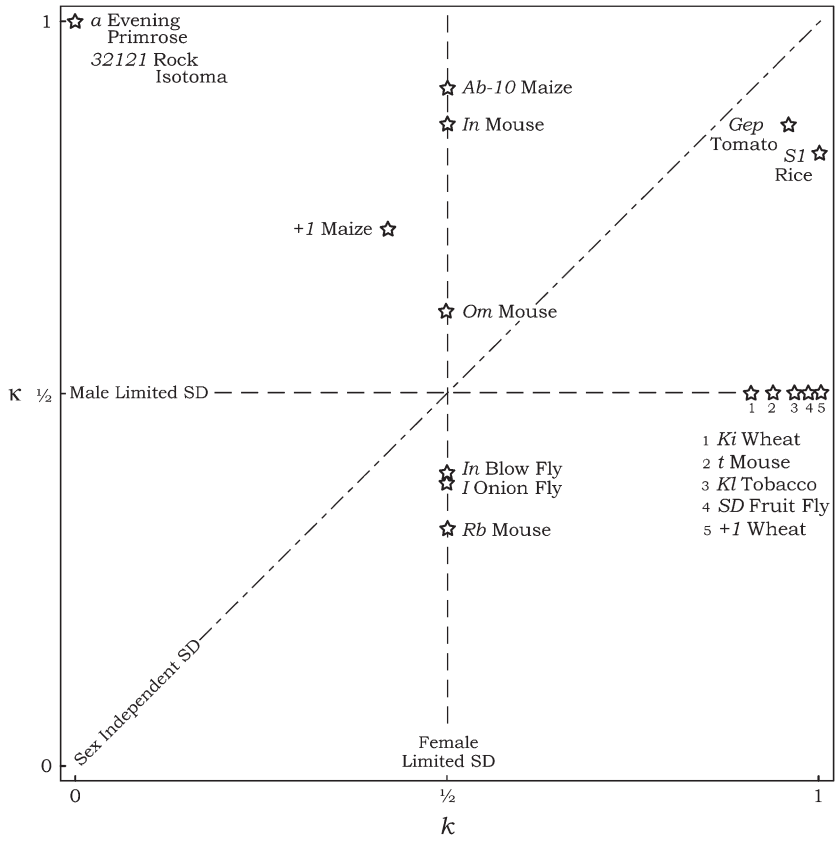

FIGURE 1.—Sex-specific segregation distortion. This chart summarizes a detailed review of genetic systems in which segregation distortion in autosomes has been reported (RHOADES 1942; CAMERON and MOAV 1957; LOEGERING and SEARS 1963; MAGUIRE 1963; RICK 1966; MAAN 1975; VAN HEERMERT 1977; GROPP and WINKING 1981; SANDLER and GOLIC 1985; SILVER 1985; LAVERY and JAMES 1987; AGULNIK *et al*. 1990; SANO 1990; FOSTER and WHITTEN 1991; LYTTLE 1991; PARDO-MANUEL DE VILLENA *et al*. 2000). Each star corresponds to a particular haplotype (in italics) and its host organism. Its coordinates indicate the segregation proportion in favor of that particular haplotype in males and females. The main diagonal corresponds to sex-independent segregation distortion. This is the assumption in previous work on the evolution of Mendelian segregation. The vertical axis in $k = ½$ corresponds to female-limited segregation distortion while the horizontal axis in $\kappa = ½$ corresponds to male-limited segregation distortion.

scheme in which one of the alleles is transmitted to all sperm (or microspores) and no eggs (or megaspores) or vice versa (ÚBEDA and HAIG 2004). Under such a segregation scheme, all adults will be maximally fit heterozygotes. This possibility was considered neither by ESHEL (1985) nor by earlier models of the evolution of the segregation ratio because these models made the simplifying assumption that segregation was the same in males and females. Assuming that a modifier of segregation has equal effects in spermatogenesis (or microsporogenesis) and oogenesis (or macrosporogenesis) is far from being realistic, however. A detailed review of genetic systems in which segregation distortion has been reported fails to provide a single case with identical segregation in males and females (see Figure 1 and references therein). This comes as no surprise since mechanisms underlying male and female gametogenesis are extremely different (PARDO-MANUEL DE VILLENA and SAPIENZA 2001). Thus, it is difficult to posit a modifier of segregation having identical effects in the two processes.

We extend previous analyses by considering modifiers of the segregation acting in a sex-specific manner. In addition, we allow for nonequivalent fitness of reciprocal heterozygotes (*i.e.*, individuals with the same genotype but with the parental origins of their two alleles reversed) as might arise, for example, from genomic imprinting (PEARCE and SPENCER 1992; REIK and WALTER 2001). We show that the equivalence *vs.* nonequivalence of reciprocal heterozygotes has important consequences for the evolutionary stability of Mendelian segregation.

First we introduce a two-locus model for the interaction between viability selection and segregation distortion. Then, we carry out stability analysis of the parameter space for sex-specific segregation with a focus on Mendelian and all-and-none segregation. Finally, we analyze the particular case of permanent translocation heterozygotes and discuss some possible explanations for the scarcity of all-and-none segregation and the ubiquity of Mendelian segregation.

MODEL

Consider two autosomal loci, A and M, carried by diploid individuals mating randomly within an infinite population.

Alleles A_1 and A_2 determine the viability of their carrier. Let the viability parameters corresponding to genotypes A_1A_1, A_1A_2, A_2A_1, A_2A_2 be v_{11}, v_{12}, v_{21}, v_{22}, where paternally inherited alleles are listed first. Viability parameters are arranged in a four-by-four matrix, $\mathbf{V}$, with elements $\mathbf{V}_{ij}$ that are matrices themselves,

$$\mathbf{V}_{ij} = \begin{bmatrix} v_{11} & v_{12} \\ v_{21} & v_{22} \end{bmatrix}. \quad (1)$$

Boldface lowercase and uppercase letters denote vectors

and matrices, respectively. Superscript T represents the transposed of a vector or matrix.

Alleles M_1 and M_2 determine the segregation ratio of alleles at the A locus. Let the segregation ratio of A_1 corresponding to genotypes M_1M_1, M_1M_2, M_2M_1, M_2M_2 be k_{11}, k_{12}, k_{21}, k_{22} in males and κ_{11}, κ_{12}, κ_{21}, κ_{22} in females, with $k_{ij} = k_{ji}$, $\kappa_{ij} = \kappa_{ji}$, and $0 \le k_{ij}, \kappa_{ij} \le 1$. The segregation ratio of A_2 corresponding to genotype M_iM_j is $1 - k_{ij}$ in males and $1 - \kappa_{ij}$ in females. Segregation ratios in males are arranged in a matrix, $\mathbf{S}^{\mathrm{m}}$, with elements $\mathbf{S}^{\mathrm{m}}_{ij}$ that are matrices themselves,

$$\mathbf{S}^{\mathrm{m}}_{ij} = \begin{bmatrix} \tfrac{1}{2} & k_{ij} \\ 1 - k_{ij} & \tfrac{1}{2} \end{bmatrix}. \tag{2}$$

Its equivalent for females is matrix $\mathbf{S}^{\mathrm{f}}$ with elements

$$\mathbf{S}^{\mathrm{f}}_{ij} = \begin{bmatrix} \tfrac{1}{2} & \kappa_{ij} \\ 1 - \kappa_{ij} & \tfrac{1}{2} \end{bmatrix}. \tag{3}$$

In a single generation, there are four possible transmission paths for one haplotype: from male to male, from male to female, from female to male, and from female to female. Each path relates to a fitness matrix that results from multiplying the viability of the transmitting individual and the segregation ratio of that particular haplotype: $\mathbf{W}^{\mathrm{mm}} = \mathbf{V} \circ \mathbf{S}^{\mathrm{m}}$, $\mathbf{W}^{\mathrm{mf}} = \mathbf{V} \circ \mathbf{S}^{\mathrm{f}}$, $\mathbf{W}^{\mathrm{fm}} = \mathbf{V}^{\mathrm{T}} \circ \mathbf{S}^{\mathrm{m}}$, $\mathbf{W}^{\mathrm{ff}} = \mathbf{V}^{\mathrm{T}} \circ \mathbf{S}^{\mathrm{f}}$. The symbol $\circ$ represents the Schur product of two matrices, which is another matrix with elements $\mathbf{V} \circ \mathbf{S} = \mathbf{V}_{ij} \circ \mathbf{S}_{ij} = v_{mn}s_{mn}$. Following Prout *et al.* (1973), Liberman (1976), and Eshel (1985) we assume no pleiotropic effect of the modifier locus over the fitness locus. Let the frequency of haplotypes A_1M_1, A_2M_1, A_1M_2, A_2M_2 be x_1, x_2, x_3, x_4 in sperm and y_1, y_2, y_3, y_4 in eggs, with $0 \le x_i, y_j \le 1$, and $\Sigma_i x_i = \Sigma_j y_j = 1$. Given an initial distribution of haplotype frequencies, random union of gametes results in individuals whose chances of reproducing are determined by the viability of each genotype. Prior to the formation of a new gamete pool, recombination and segregation take place. We assume independent assortment between A and M because this is the most favorable case for Mendelian segregation (Eshel 1985).The frequency of each haplotype in the next generation is

$$x_i' = \frac{x_i(\mathbf{W}^{\mathrm{mm}}\mathbf{y})_i + y_i(\mathbf{W}^{\mathrm{fm}}\mathbf{x})_i - \tfrac{1}{2}\delta_i^{\mathrm{m}}}{\mathbf{x} \cdot (\mathbf{W}^{\mathrm{mm}}\mathbf{y}) + \mathbf{y} \cdot (\mathbf{W}^{\mathrm{fm}}\mathbf{x})} \tag{4a}$$

$$y_i' = \frac{x_i(\mathbf{W}^{\mathrm{mf}}\mathbf{y})_i + y_i(\mathbf{W}^{\mathrm{ff}}\mathbf{x})_i - \tfrac{1}{2}\delta_i^{\mathrm{f}}}{\mathbf{x} \cdot (\mathbf{W}^{\mathrm{mf}}\mathbf{y}) + \mathbf{y} \cdot (\mathbf{W}^{\mathrm{ff}}\mathbf{x})}, \tag{4b}$$

where δ_i^{m} and δ_i^{f} represent the linkage disequilibrium function for haplotype i in males and females, respectively. These are $\delta_1^{\mathrm{m}} = \delta_3^{\mathrm{m}} = k_{12}d$, $\delta_2^{\mathrm{m}} = \delta_4^{\mathrm{m}} = (k_{12} - 1)d$ and $\delta_1^{\mathrm{f}} = \delta_3^{\mathrm{f}} = \kappa_{12}d$, $\delta_2^{\mathrm{f}} = \delta_4^{\mathrm{f}} = (\kappa_{12} - 1)d$, with $d = v_{12}(x_1y_4 - x_3y_2) + v_{21}(x_4y_1 - x_2y_3)$. The symbol $\cdot$ represents the inner product of two vectors, which is the number $x \cdot y = \Sigma_i x_i y_i$. The normalizing factor in (4) is the population mean fitness, which is equal in the two sexes,

$$\bar{w} = \mathbf{x} \cdot (\mathbf{W}^{\mathrm{mm}}\mathbf{y}) + \mathbf{y} \cdot (\mathbf{W}^{\mathrm{fm}}\mathbf{x}) = \mathbf{x} \cdot (\mathbf{W}^{\mathrm{mf}}\mathbf{y}) + \mathbf{y} \cdot (\mathbf{W}^{\mathrm{ff}}\mathbf{x}). \tag{5}$$

STABILITY ANALYSIS

We consider a scenario in which there is a balanced polymorphism of A_1 and A_2 at the viability locus and contemplate the fate of a rare allele M_2 introduced into a population fixed for M_1 at the modifier locus. We assume that the initial frequency of alleles A_1 and A_2 corresponds to a stable equilibrium $(\hat{\mathbf{x}}, \hat{\mathbf{y}})$ given fixation of M_1 at the modifier locus. This equilibrium is stable in the sense that it remains unaltered over small perturbations of the frequency of A_1 and A_2 (short-term stability) with M_1 fixed but it may not be stable to the introduction of new alleles (long-term stability) (Eshel 1996). To explore the long-term stability of equilibrium $(\hat{\mathbf{x}}, \hat{\mathbf{y}})$ to the introduction of M_2 we simplify our notation by using (k, κ) to refer to the segregation scheme (k_{11}, κ_{11}) of the common M_1M_1 homozygotes, and (k_{+1}, κ_{+1}) to refer to the segregation scheme (k_{12}, κ_{12}) of rare M_1M_2 heterozygotes.

Methods: To study the long-term stability of a particular segregation scheme it is necessary to have a polymorphic equilibrium at the main locus; otherwise modifiers have no effect over segregation and their fate is determined by drift instead of selection. For this reason, we start by considering a short-term stable equilibrium $(\hat{\mathbf{x}}, \hat{\mathbf{y}})$ polymorphic at the main locus. Hence inequalities $kv_{12} + \kappa v_{21} > v_{22}$ and $(1 - \kappa)v_{12} + (1 - k)v_{21} > v_{11}$ derived in Úbeda and Haig (2004) must be satisfied.

Let matrix $\mathbf{G}$ be the gradient matrix of system (4) evaluated at equilibrium $(\hat{\mathbf{x}}, \hat{\mathbf{y}})$. Matrix $\mathbf{G}$ is a block matrix that contains submatrix $\mathbf{L}$ (see appendix a). If the leading eigenvalue of matrix $\mathbf{L} > 1$, $\rho(\mathbf{L}) > 1$, modifier M_2 introduced in a population at equilibrium $(\hat{\mathbf{x}}, \hat{\mathbf{y}})$ increases in frequency at a geometric rate. However, if $\rho(\mathbf{L}) = 1$ nothing can be concluded about the long-term stability of $(\hat{\mathbf{x}}, \hat{\mathbf{y}})$. We deal with this problem using the method suggested by Lessard (1989). In his work Lessard (1989) defines the term Q from a generic gradient matrix and its second derivatives, concluding that a particular equilibrium shows long-term instability when Q is positive. Therefore, if the term Q derived from our gradient matrix $\mathbf{G}$ (see appendix a) is positive, $Q(\mathbf{G}) > 0$, modifier M_2 introduced in a population at equilibrium $(\hat{\mathbf{x}}, \hat{\mathbf{y}})$ increases at an arithmetic rate. To summarize, allele M_2 will be favored by natural selection when rare whenever $\rho(\mathbf{L}) > 1$ or whenever $\rho(\mathbf{L}) = 1$ and $Q(\mathbf{G}) > 0$. If this is the case, segregation scheme (k, κ) does not show evolutionary genetic stability (EGS) and can be invaded by segregation scheme (k_{+1}, κ_{+1}).

We used analytical expressions for $\rho(\mathbf{L})$ when we were able to derive these, but used numerical analysis to draw conclusions when we were unable to derive an analytical solution. In our numerical analyses, for each combination of k and κ considered we explored all combinations

of v_{11}, v_{12}, v_{21}, v_{22} in the range [0.1, 1.9] separated at intervals 0.225. For each set of viability parameters yielding a short-term stable polymorphic equilibrium we explore all combinations of k_{+1} and κ_{+1} in the range [0.02, 0.98] separated at intervals 0.08. We then calculated $\rho(\mathbf{L})$ and use this value to classify the parameter sets. This routine was implemented in Matlab 5.3 (MATHWORKS 1991).

Results: *Mendelian segregation:* Consider a population undergoing Mendelian segregation $(k, \kappa) = (\frac{1}{2}, \frac{1}{2})$. Whenever $\frac{1}{2}(v_{12} + v_{21}) > v_{11}, v_{22}$ the corresponding equilibrium $(\hat{\mathbf{x}}, \hat{\mathbf{y}})_{(\frac{1}{2},\frac{1}{2})}$ shows short-term stability. The simplifying assumption $v_{11} = v_{22}$ allows us to get a tractable expression for $\rho(\mathbf{L})$ and $Q(\mathbf{G})$.

The leading eigenvalue of $\mathbf{L}$ evaluated at equilibrium $(\hat{\mathbf{x}}, \hat{\mathbf{y}})_{(\frac{1}{2},\frac{1}{2})}$ is

$$\rho(\mathbf{L}_{(\frac{1}{2},\frac{1}{2})}) = 1 + (2f_2)^{-1}\left(f_1 - f_2 + \sqrt{(f_1 + f_2)^2 - 8v_{11}f_1}\right), \tag{6}$$

where $f_1 = (k_{+1} - \kappa_{+1})(v_{12} - v_{21})$ and $f_2 = v_{11} + v_{12} + v_{21} + v_{22}$. Simple algebra (see APPENDIX B) shows that $\rho(\mathbf{L}_{(\frac{1}{2},\frac{1}{2})}) > 1$ when

$$(k_{+1} - \kappa_{+1})(v_{12} - v_{21}) > 0. \tag{7}$$

Whenever reciprocal heterozygotes have the same fitness $f_1 = 0$ and $\rho(\mathbf{L}_{(\frac{1}{2},\frac{1}{2})}) = 1$. Term $Q(\mathbf{G})$ evaluated at equilibrium $(\hat{\mathbf{x}}, \hat{\mathbf{y}})_{(\frac{1}{2},\frac{1}{2})}$ is

$$Q(\mathbf{G}_{(\frac{1}{2},\frac{1}{2})}) = g_1(v_{11}/v_{12})^2 + (2g_1 + g_2)(v_{11}/v_{12}) + g_3, \tag{8}$$

where $g_1 = 2(1 - k_{+1} - \kappa_{+1})$, $g_2 = 2(k_{+1} - \kappa_{+1})$, and $g_3 = (1 - 2k_{+1})(1 - 2\kappa_{+1})$.

The sign of $Q(\mathbf{G})$ depends on the relative viabilities of homozygotes and heterozygotes. The two extreme cases are lethal homozygotes ($v_{11}/v_{12} = 0$) and equal viability of both homozygote and heterozygote classes ($v_{11}/v_{12} = 1$). Taking limits in $Q(\mathbf{G})$ for each of these cases we get

$$\lim_{v_{11}/v_{12}\to 0} Q(\mathbf{G}_{(\frac{1}{2},\frac{1}{2})}) = (1 - 2k_{+1})(1 - 2\kappa_{+1}) \tag{9a}$$

$$\lim_{v_{11}/v_{12}\to 1} Q(\mathbf{G}_{(\frac{1}{2},\frac{1}{2})}) = 4(1 - k_{+1} - \kappa_{+1})^2. \tag{9b}$$

These analytical results rely on the simplifying assumption of equal viability of homozygote classes. We do not expect this assumption often to be true and use numerical analysis to find out whether our analytical results can be extended to the more general case of differential viability of homozygote classes.

In our systematic exploration of the parameter space we find 293,384 combinations of v_{11}, v_{12}, v_{21}, v_{22} yielding a short-term stable polymorphic equilibrium. In the 119,496 cases in which $(k_{+1} - \kappa_{+1})(v_{12} - v_{21}) < 0$, eigenvalue $\rho(\mathbf{L}_{(\frac{1}{2},\frac{1}{2})}) > 1$. In the 119,496 cases in which $(k_{+1} - \kappa_{+1})(v_{12} - v_{21}) > 0$, eigenvalue $\rho(\mathbf{L}_{(\frac{1}{2},\frac{1}{2})}) < 1$. Finally, in the 54,392 cases in which $(k_{+1} - \kappa_{+1})(v_{12} - v_{21}) = 0$ (due to either $k_{+1} = \kappa_{+1}$ or $v_{12} = v_{21}$), $\rho(\mathbf{L}_{(\frac{1}{2},\frac{1}{2})})$ takes the unit value. Hence, in principle, our analytical results can be extended to the case of differential viability of homozygote classes.

All-and-none segregation: Consider a population with segregation $(k, \kappa) = (1, 0)$, one of the two possible forms of all-and-none segregation. Whenever $v_{12} > v_{11}, v_{22}$ the corresponding equilibrium $(\hat{\mathbf{x}}, \hat{\mathbf{y}})_{(1,0)}$ shows short-term stability. The simplifying assumption $v_{11} = v_{22}$ allows us to get a tractable expression for $\rho(\mathbf{L})$.

The leading eigenvalue of $\mathbf{L}$ evaluated at equilibrium $(\hat{\mathbf{x}}, \hat{\mathbf{y}})_{(1,0)}$ is

$$\rho(\mathbf{L}_{(1,0)}) = 1 + (4v_{12})^{-1}\left(f_3 + f_4 - 4v_{12} + \sqrt{(f_3 + f_4)^2 - 8v_{11}f_3}\right), \tag{10}$$

where $f_3 = (k_{+1} - \kappa_{+1})v_{12}$ and $f_4 = v_{11} + v_{12}$. Simple algebra (see APPENDIX B) shows that $\rho(\mathbf{L}_{(1,0)}) > 1$ when

$$v_{12} > v_{11}, v_{22}. \tag{11}$$

Note that the short-term stability of equilibrium $(\hat{\mathbf{x}}, \hat{\mathbf{y}})_{(1,0)}$ is a sufficient condition for its long-term stability. Whether the reciprocal heterozygotes take the same or a different value does not affect the value of $\rho(\mathbf{L}_{(1,0)})$.

Again we resort to numerical analysis to determine whether our analytical results can be extended to the more general case of differential viability of homozygote classes. In our systematic exploration of the parameter space we find 310,284 combinations of v_{11}, v_{12}, v_{21}, v_{22} yielding a short-term stable polymorphic equilibrium. We failed to find a single case in which $\rho(\mathbf{L}_{(1,0)}) < 1$. This allows us to extend our analytical results to the case of differential viability of homozygote classes.

Other segregation schemes: We used numerical analysis to investigate the long-term stability of all combinations of k and κ in the range [0.02, 0.98] separated at intervals 0.08. We failed to find a single case in which (k, κ) could not be invaded by some (k_{+1}, κ_{+1}).

Conclusion: Our results are simplest when there is a balanced polymorphism at the primary locus for a fitness scheme in which reciprocal heterozygotes have distinct fitnesses ($v_{12} \neq v_{21}$). In this case, a rare modifier coding for a segregation scheme (k_{+1}, κ_{+1}) such that $(k_{+1} - \kappa_{+1})(v_{12} - v_{21}) > 0$ can invade a population fixed for Mendelian segregation. Suppose that $v_{12} > v_{21}$; then the population can be invaded by any segregation scheme such that A_1 is transmitted in greater proportion to sperm than to eggs, *i.e.*, $k_{+1} > \kappa_{+1}$ (Figure 2a.2). The reason for this instability is straightforward. At the Mendelian equilibrium, A_1 has higher fitness when transmitted via sperm than via eggs and A_2 has higher fitness when transmitted via eggs than via sperm. Therefore, heterozygotes would gain a reproductive advantage by increasing the frequency of A_1 among their sperm or by increasing the frequency of A_2 among their eggs. Of particular significance, Mendelian segregation can

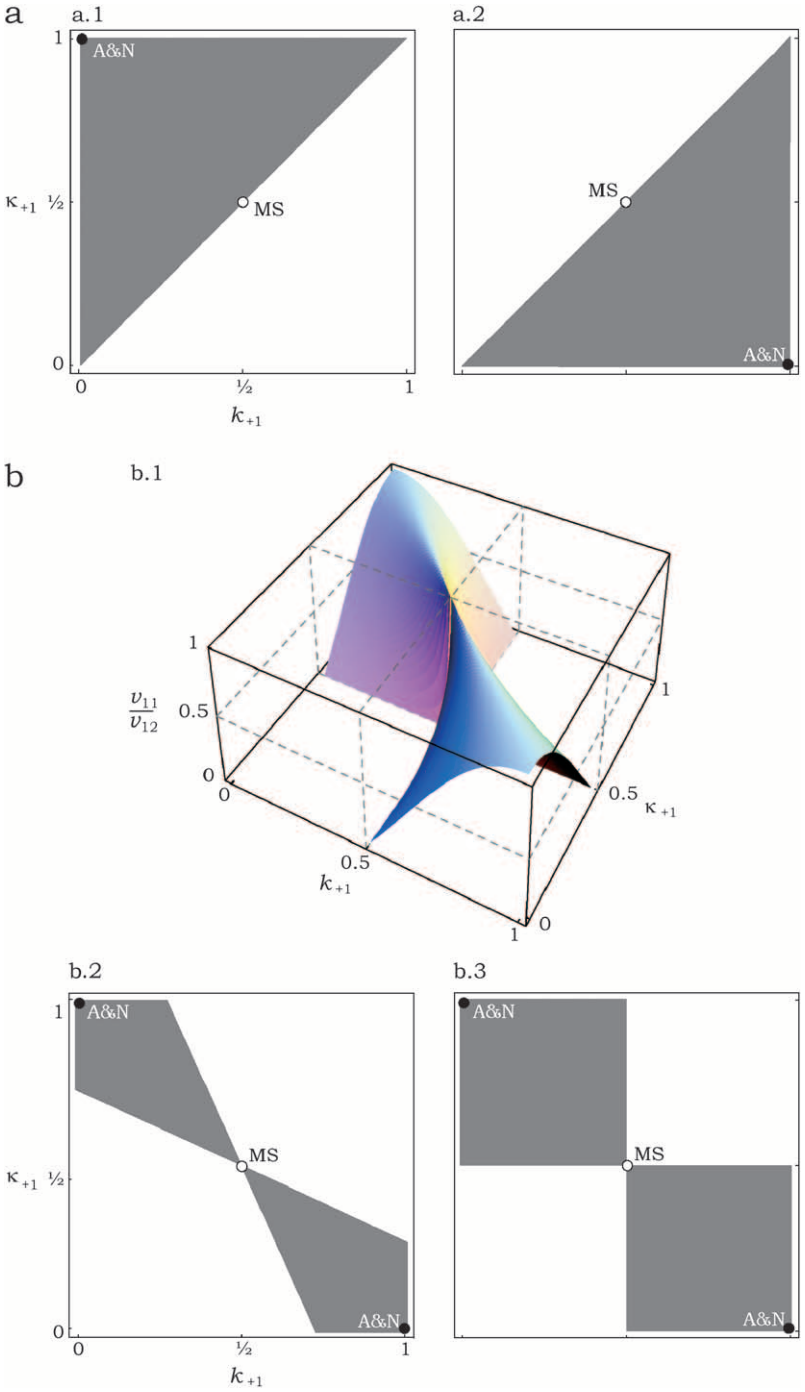

FIGURE 2.—Stability of Mendelian segregation. (a) Differential fitness of reciprocal heterozygotes ($v_{12} \neq v_{21}$). Mendelian segregation (MS) is susceptible to invasion by (k_{+1}, κ_{+1}) when this segregation scheme maps onto the shaded area. (a.1) $v_{21} > v_{12}$ requires $\kappa_{+1} > k_{+1}$. (a.2) $v_{12} > v_{21}$ requires $k_{+1} > \kappa_{+1}$. Open circles represent segregation schemes showing evolutionary genetic instability. However, all-and-none segregation (A&N) cannot be invaded by any other segregation scheme. Solid circles represent segregation schemes showing evolutionary genetic stability. (b) Identical fitness of reciprocal heterozygotes ($v_{12} = v_{21}$). Invading segregation schemes are confined beneath the surface in b.1. Slices of this surface at $v_{11}/v_{12} = 5/8$ (b.2) and $v_{11}/v_{12} = 0$ (b.3) provide graphics with the same interpretation as the ones in a.

be invaded by segregation schemes $(k_{+1}, \frac{1}{2})$, where $k_{+1} > \frac{1}{2}$ or $(\frac{1}{2}, \kappa_{+1})$, where $\kappa_{+1} < \frac{1}{2}$. That is, changes in segregation ratio do not need to be coordinated between the sexes: a successful modifier can change the segregation ratio in spermatogenesis without a change in oogenesis, or the reverse.

Mendelian segregation also lacks evolutionary stability if reciprocal heterozygotes have identical viability ($v_{12} = v_{21}$), but in this case the selective forces acting on modifiers of the segregation ratio are weaker. Specifically, successful modifiers initially increase at a geometric rate when reciprocal heterozygotes have different viabilities, but at an arithmetic rate when reciprocal heterozygotes have identical viability. A rare modifier coding for segregation scheme (k_{+1}, κ_{+1}) located below the surface $Q(\mathbf{G}) = 0$ will be favored by natural selection over a modifier coding for Mendelian segregation and fixed in the population (Figure 2b.1). Simple observation of surface $Q(\mathbf{G}) = 0$ reveals that successful modifiers must code for a segregation scheme with opposite effects in spermatogenesis and oogenesis. Moreover, the precision with which the segregation advantage in one

sex is complemented by a segregation disadvantage in the opposite sex becomes increasingly stringent as there is a progressively smaller advantage of A_1A_2 heterozygotes over homozygous genotypes.

Under the simplifying assumption that $v_{11} = v_{22}$, the two extreme cases are minimum heterozygote advantage, $v_{11}/v_{12} \approx 1$, and maximum heterozygote advantage, $v_{11}/v_{12} \approx 0$. In the first scenario, it is only modifiers with equal, but opposite, effects in males and females, *i.e.*, $k_{+1} + \kappa_{+1} = 1$, that can invade a population in which Mendelian segregation is the norm. In the second scenario, it is enough that the modifier has opposite effects in males and females, *i.e.*, $(k_{+1} - \frac{1}{2})(\kappa_{+1} - \frac{1}{2}) < 0$, to be favored by natural selection (Figure 2b.3). For example, consider $v_{12} = v_{21}$ and $v_{11} = v_{22} = 0$; a Mendelian population can be invaded by a modifier that increases the transmission of A_1 to sperm ($k_{+1} > \frac{1}{2}$) but reduces its transmission to eggs ($\kappa_{+1} < \frac{1}{2}$). The same population can be invaded by a modifier that reduces the transmission of A_1 to sperm ($k_{+1} < \frac{1}{2}$) but increases its transmission to eggs ($\kappa_{+1} > \frac{1}{2}$) (Figure 2b.3).

If reciprocal heterozygotes have identical viability, the modifiers that can invade a population fixed for Mendelian segregation must cause coordinated changes in spermatogenesis and oogenesis. This is because A_1 and A_2 have the same fitness whether transmitted via eggs or sperm when allele frequencies are at the equilibrium determined by Mendelian segregation. Selection is initially weak because, in a panmictic population, the rare eggs produced by the modified segregation scheme gain a fitness advantage only from their even rarer unions with the rare sperm produced by the modified segregation scheme. Modifications need to be coordinated between oogenesis and spermatogenesis because these unions need to produce an increased frequency of heterozygotes whereas some combinations of changes, including unilateral changes in one sex but not in the other, will result in increased production of the less-fit homozygous genotypes.

The intuitive reason why fair segregation shows evolutionary instability is that this segregation scheme does not maximize population mean fitness when sex-specific segregation is allowed (Úbeda and Haig 2004). Hence, those segregation schemes able to bias the offspring production in favor of the fittest heterozygote will be favored by natural selection. The link between fitness and segregation can be clarified by using the concept of genetic load. Crow (1970) defined genetic load as the fraction by which the population mean fitness at equilibrium differs from the fitness of the most viable genotype,

$$L = \frac{\max\{v_{ij}\} - \overline{w}}{\max\{v_{ij}\}}. \qquad (12)$$

Crow differentiated two kinds of genetic load that are relevant to our argument. *Segregation load* is the reduction in mean fitness due to the production of homozygous progeny in sexual populations with heterozygote advantage (Crow 1970). *Drive load* is the reduction in mean fitness due to the production of progeny less fit than other zygotic combinations in populations with meiotic drive (Crow 1970).

While the enforcement of Mendelian segregation eliminates drive load it does not affect segregation load (Figure 3). However, if sex-specific segregation is allowed, distorters can modify both types of load (Figure 3). If the net result is a reduction of load, distorters are beneficial to their host genotype and we would expect them to invade a Mendelian population. That is, distorters of Mendelian segregation can be beneficial to their host genotype if they reduce segregation load. This might call into question the use of the adjective "ultraselfish" (Crow 1988) to describe segregation distorters.

Following this intuitive reasoning, we would expect to find that any segregation scheme other than all-and-none segregation shows evolutionary instability, the rationale being that even when alternative segregation schemes are reducing the genetic load there will always be room for further reduction until all-and-none segregation is reached. All-and-none is the only segregation scheme that gets rid of both genetic loads (Figure 3).

Our results back this intuition. For example, consider the case $v_{12} > v_{21}$ in which fair segregation can be invaded by any segregation scheme (k_{+1}, κ_{+1}) such that $k_{+1} > \kappa_{+1}$. Numerical evidence suggests that none of these segregation schemes except all-and-none segregation of the type (1, 0) show evolutionary stability (see Figure 4). For another example, consider the case $v_{12} = v_{21}$ and $v_{11} = v_{22} = 0$ in which fair segregation can be invaded by any segregation scheme (k_{+1}, κ_{+1}) such that $(k_{+1} - \frac{1}{2})(\kappa_{+1} - \frac{1}{2}) < 0$. Numerical evidence suggests that none of these segregation schemes except all-and-none segregation show evolutionary stability. Furthermore, analytical results demonstrate that all-and-none segregation of the type (1, 0) shows evolutionary stability when $v_{12} > v_{11}, v_{22}$ while its symmetric segregation (0, 1) shows evolutionary stability when $v_{21} > v_{11}, v_{22}$.

Making use of local stability analysis we showed that Mendelian segregation is unstable while all-and-none segregation is stable. This suggests, but does not guarantee, that a population undergoing fair segregation would be replaced by another undergoing all-and-none segregation. However, iterating equations in (4) we found out that under the same conditions derived from local stability analysis, all-and-none segregation is able to replace Mendelian segregation. The full dynamics of a rare all-and-none modifier on a Mendelian population are presented in Figure 5. They were generated making use of a script written in Matlab (Mathworks 1991).

DISCUSSION

Eshel (1985) analyzed the fate of new mutations at a modifier locus that governed the segregation ratio at an unlinked locus. He showed that for any configuration

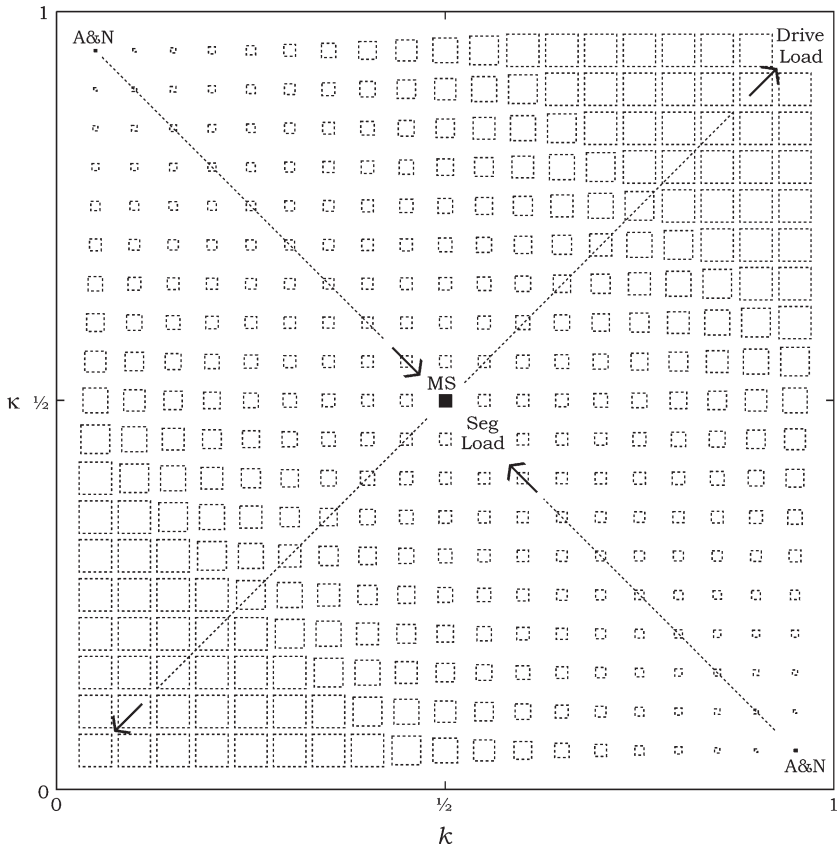

FIGURE 3.—Genetic load in terms of fitness. The area of each square represents the genetic load corresponding to segregation scheme (k, κ). The ordering of the viability parameters considered is $v_{12} = v_{21} > v_{11} = v_{22}$. The genetic load has two components, drive load and segregation load. With sex-independent segregation ($k = \kappa$) we consider the drive load component only. Any segregation away from Mendelian expectations increases the genetic load. With perfect compensation between drive and drag in the two sexes ($k + \kappa = 1$) we consider the segregation load component only. Any segregation away from all-and-none expectations increases the genetic load. All-and-none segregation is the only segregation scheme that gets rid off both types of load.

of alleles at the modifier locus, mutant alleles that initially reduce meiotic drive always increase in frequency, whereas mutant alleles that initially increase meiotic drive decrease in frequency. His model assumed equal segregation ratios in the two sexes. We have shown that Eshel's conclusion does not hold when sex-specific modifiers of segregation are considered. Instead, we have shown that if there is a balanced polymorphism at a locus determining viability, then unlinked modifiers will favor an all-and-none segregation scheme in which one allele drives completely in oogenesis and the other allele drives completely in spermatogenesis. Further, we have shown that this segregation scheme has properties of long-term evolutionary stability, given the assumptions of our model.

All-and-none segregation is not a theoretical caprice: it is the segregation scheme employed by at least 57 species of flowering plants (in seven genera) that exist as permanent translocation heterozygotes (HOLSINGER and ELLSTRAND 1984). For example, some species of Oenothera are permanent structural heterozygotes for two chromosome complexes, with one set of chromosomes (the α-complex) transmitted to all megaspores ($\kappa = 1$), and the other set (the β-complex) transmitted to all microspores ($k = 0$) (CLELAND 1972).

CHARLESWORTH (1979) proposed that systems of permanent translocation heterozygosity evolved to fix a beneficial heterozygous genotype in inbred populations. His model assumed heterozygote advantage and obligate self-fertilization. Under these assumptions, any modifier of Mendelian segregation in one sex is neutral, but once there is a bias in segregation of one of the "alleles" to one class of gametes/spores, there is positive selection for modifiers that established the opposite bias in segregation to the other class of gametes/spores.

Our model suggests an alternative path to permanent heterozygosity. If there is differential viability of reciprocal heterozygotes, one allele will have higher fitness at the Mendelian equilibrium when transmitted by sperm/microspores and the other allele will have higher fitness when transmitted by eggs/megaspores. Therefore, modifiers of the segregation ratio in one sex will be favored by selection, even without an opposite bias of the segregation ratio in the other sex (VON WANGENHEIM 1962 provides evidence of genomic imprinting in Oenothera; see interpretation of his results in HAIG and WESTOBY 1991). Unlike Charlesworth's model, our model does not require initial inbreeding. The natural history of permanent translocation heterozygosity does not strongly favor one model or the other, because these species are usually self-fertilizing but with outcrossing relatives (*e.g.*, GRANT 1975, p. 407).

It has not escaped our notice that Mendelian segregation is the rule and all-and-none segregation the rare exception. What processes then could account for the ubiquity of Mendelian segregation? We make four suggestions. There may well be others.

1. We have shown that there is strong selection on unlinked modifiers to favor departures from Mendelian

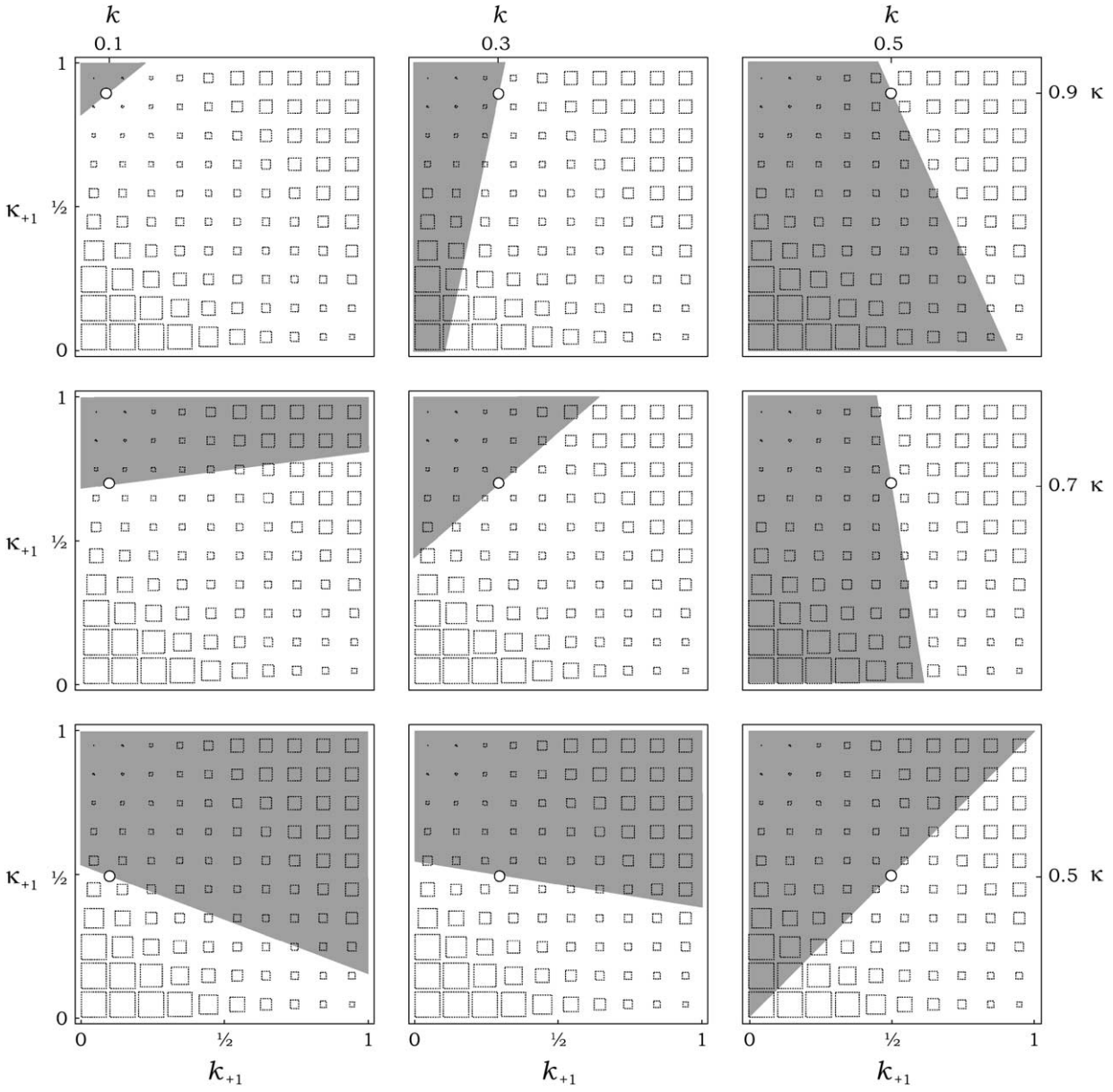

FIGURE 4.—Evolutionary stability of segregation schemes other than Mendelian. Let $v_{11} = 1$, $v_{12} = 1.5$, $v_{21} = 2$, $v_{22} = 0.6$. For each combination of k in {0.1, 0.3, 0.5} and κ in {0.5, 0.7, 0.9} we draw a map of the genetic load (dotted squares) in the (k_{+1}, κ_{+1}) plane. Which combination of k and κ corresponds to each window is indicated by a number above and to the right of the graphic and is represented by a circle in the (k_{+1}, κ_{+1}) plane. Segregation scheme (k, κ) is susceptible to invasion by any other segregation scheme (k_{+1}, κ_{+1}) mapping onto the shaded area. In particular, all-and-none segregation of the type (0, 1) can invade any (k, κ) and, considering local deviations from (k, κ), the ones that can invade always reduce the genetic load.

segregation for a balanced polymorphism at which reciprocal heterozygotes have different fitness ($v_{12} \neq v_{21}$). However, such balanced polymorphisms may be rare. In the simplest form of genomic imprinting, an allele is silent when inherited from one parent, but expressed when inherited from the other. If so, the allele inherited from one parent does not affect fitness and each heterozygous genotype has a fitness equal to one of the homozygous genotypes (either $v_{12} = v_{11}$ and $v_{21} = v_{22}$ or $v_{12} = v_{22}$ and $v_{21} = v_{11}$). No balanced polymorphism is possible for such fitness schemes (PEARCE and SPENCER 1992).

The possibility of balanced polymorphisms with $v_{12} \neq v_{21}$ cannot be rejected so simply, however. Imprinted genes are often clustered, with maternally expressed genes tightly linked to paternally expressed genes. Moreover, some imprinted genes are expressed biallelically in most tissues, but have monoallelic expression in some cell types. In such cases, an imprinted haplotype will have effects when it is both maternally and paternally inherited. Thus, the heterozygous genotypes need not be phenotypically equivalent to the homozygous genotypes. The model of this article also assumes that fitnesses are fixed

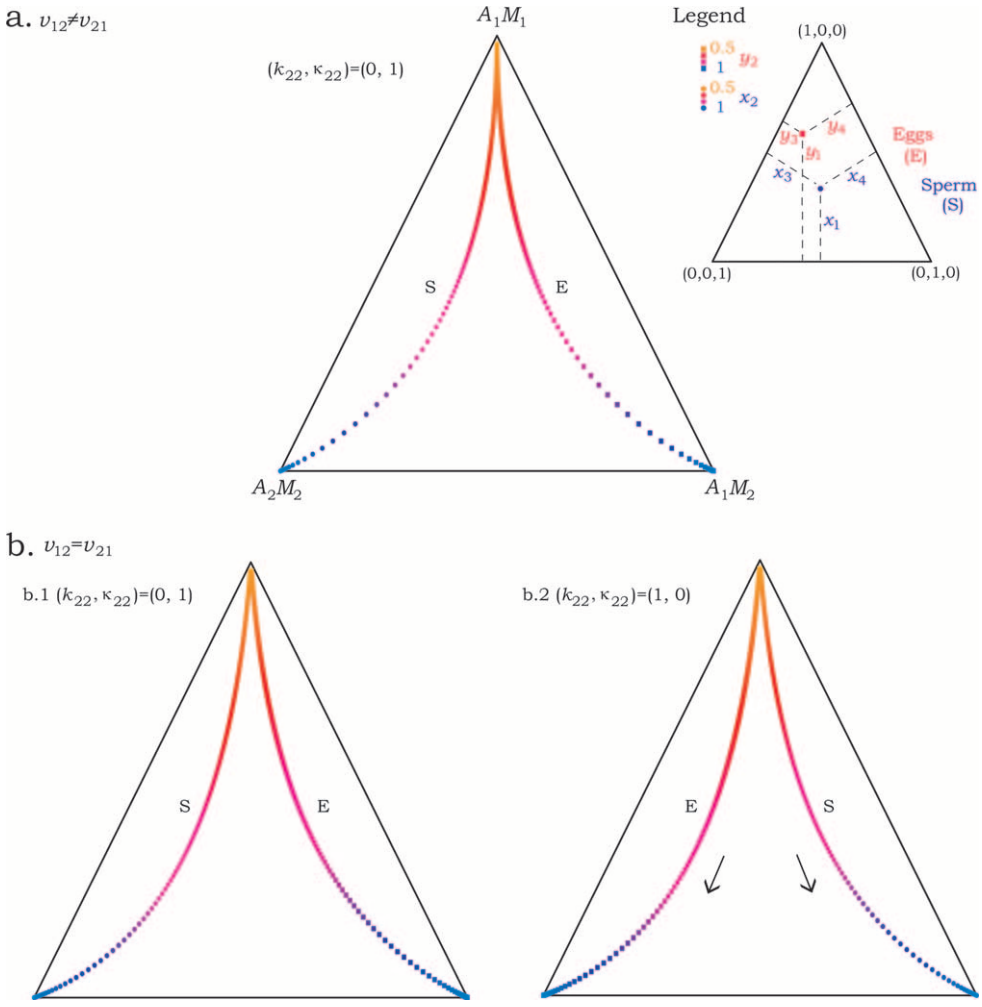

FIGURE 5.—Haplotype dynamics. We represent the change in frequency of all haplotypes after a rare modifier of segregation arises. The perpendicular distance from the bottom of the triangle to a particular point is the frequency of A_1M_1, from the left it is that of A_1M_2, and from the right it is that of A_2M_2. We use a color code to represent the frequency of A_2M_1. Vertex (1, 0, 0) corresponds to extinction of haplotypes A_2M_2 and A_1M_2; (0, 1, 0), to extinction of A_1M_1 and A_2M_2; and (0, 0, 1), to extinction of A_1M_1 and A_1M_2. Consider a population at a polymorphic short-term stable equilibrium at the main locus but fixed for allele M_1 coding for Mendelian segregation ($k = \kappa = \frac{1}{2}$). A mutant modifier M_2 is introduced in proportion $\varepsilon = 5 \times 10^{-3}$. (a) Nonsymmetric viability of reciprocal heterozygotes. Let $v_{11} = 0.8$, $v_{12} = 1.6$, $v_{21} = 2$, and $v_{22} = 0.8$. Our results show that allele M_2 coding for segregation scheme (0, 1) in homozygotes fully replaces allele M_1. Specifically, haplotypes A_2M_2 and A_1M_2 become fixed in sperm and eggs, respectively. (b) Symmetric viability of reciprocal heterozygotes. Let $v_{11} = 0.8$, $v_{12} = v_{21} = 1.8$, and $v_{22} = 0.8$. Our results show that both (b.1) an allele M_2 coding for segregation scheme (0, 1) in homozygotes and (b.2) an allele M_2 coding for segregation scheme (1, 0) in homozygotes fully replace allele M_1. While in the former case haplotypes A_2M_2 and A_1M_2 become fixed in sperm and eggs, in the latter case they become fixed in eggs and sperm, respectively. In the absence of imprinting the number of generations represented is four times larger than that in its presence. Arrows indicate the sense in which time increases.

properties of an individual's genotype. However, if an individual's fitness is influenced by the genotypes of other family members, the fitnesses of the different genotypes are frequency dependent. A_1A_2 heterozygotes may exist in family environments different from those of A_2A_1 heterozygotes and from that of either homozygous genotype (*e.g.*, in models of sib competition with multiple paternity within litters). In such models, A_1A_2 and A_2A_1 heterozygotes may have different fitnesses even at an unimprinted locus.

2. Selection on unlinked modifiers to favor departures from Mendelian segregation is weak for balanced polymorphisms at which reciprocal heterozygotes have the same fitness ($v_{12} = v_{21}$). To a first-order approximation, both alleles confer the same average fitness when transmitted via eggs or sperm. The effects of rare modifiers on fitness are of the second order in a panmictic population. Moreover, for a rare modifier to increase in frequency at the Mendelian equilibrium it must simultaneously increase the segregation ratio in one sex and decrease the segregation ratio in the other sex (or two modifiers must both be present with these opposite effects). A modifier that causes exactly opposite changes in the segregation ratios of the two sexes can always increase in frequency, albeit slowly, if there is heterozygous advantage. Whether a modifier that causes an increase in one sex but an unequal decrease in the other sex can increase in frequency depends on the precise relations between homozygous and heterozygous viabilities. This requirement for coordinated changes in spermatogenesis and oogenesis is possibly a major constraint on the evolution of non-Mendelian segregation schemes. Our model assumes a single locus determining the segregation ratio that must have effects in both oogenesis and spermatogenesis. The extent to which this constraint would persist in a model with sex-specific modifiers of segregation at multiple loci is a question for future study.
3. Systems of permanent heterozygosity maintained by

non-Mendelian segregation will have "pathological" features that may increase the risk of extinction and prevent the long-term persistence of such systems. If one allele exists on a haplotype that is never transmitted via sperm and the other allele exists on a haplotype that is never transmitted via eggs, then the first haplotype can accumulate fitness modifiers that are beneficial for female function even if these effects are greatly outweighed by costs for male function and the reverse happens for the second haplotype. This problem disappears in systems of self-fertilization because each haplotype depends on the maintenance of male and female functions in a single individual. This may be one reason why known systems of permanent translocation heterozygosity are associated with self-fertilization, even though they have been derived from outcrossed ancestors.

4. Our model assumes that modification of the segregation ratio does not have direct effects on individual fitness, but only indirect effects due to changes in the genotype frequencies at the primary locus. However, segregation distortion in spermatogenesis/microsporogenesis is usually associated with a reduction in the number of functional male gametes. This may reduce male fertility in situations of sperm competition (Haig and Bergstrom 1995). Unlinked modifiers that maintain Mendelian segregation in male meiosis may be selectively favored because they are associated with maximal male fertility.

To conclude, the prevailing solution to the evolutionary puzzle of Mendelian segregation (Eshel 1985) does not apply when sex-specific segregation is allowed. In our model, fair segregation does not show evolutionary genetic stability while all-and-none segregation does. Clearly, the selective forces that maintain Mendelian segregation in most organisms are not fully understood.

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APPENDIX A

Gradient matrix and first derivatives: Gradient matrix **G** is a matrix with elements that are matrices themselves:

$$\mathbf{G}_{ij} = \begin{bmatrix} \partial x_i'/\partial x_j & \partial x_i'/\partial y_j \\ \partial y_i'/\partial x_j & \partial y_i'/\partial y_j \end{bmatrix}\Bigg|_{(\hat{\mathbf{x}},\hat{\mathbf{y}})}. \tag{A1}$$

Straight differentiation in (4) yields the first-order derivatives

$$\frac{\partial x_i'}{\partial x_j}\Big|_{(\hat{\mathbf{x}},\hat{\mathbf{y}})} = \overline{w}\Big|^{-1}_{(\hat{\mathbf{x}},\hat{\mathbf{y}})}\left[\delta_{ij}(\mathbf{W}^{\mathrm{mm}}\mathbf{y})_i + y_i w_{ij}^{\mathrm{fm}} - \tfrac{1}{2}\frac{\partial \delta_i^{\mathrm{m}}}{\partial x_j} - x_i\frac{\partial \overline{w}}{\partial x_j}\right]\Bigg|_{(\hat{\mathbf{x}},\hat{\mathbf{y}})} \tag{A2a}$$

$$\frac{\partial x_i'}{\partial y_j}\Big|_{(\hat{\mathbf{x}},\hat{\mathbf{y}})} = \overline{w}\Big|^{-1}_{(\hat{\mathbf{x}},\hat{\mathbf{y}})}\left[x_i w_{ij}^{\mathrm{mm}} + \delta_{ij}(\mathbf{W}^{\mathrm{fm}}\mathbf{x})_i - \tfrac{1}{2}\frac{\partial \delta_i^{\mathrm{m}}}{\partial y_j} - x_i\frac{\partial \overline{w}}{\partial y_j}\right]\Bigg|_{(\hat{\mathbf{x}},\hat{\mathbf{y}})} \tag{A2b}$$

$$\frac{\partial y_i'}{\partial x_j}\Big|_{(\hat{\mathbf{x}},\hat{\mathbf{y}})} = \overline{w}\Big|^{-1}_{(\hat{\mathbf{x}},\hat{\mathbf{y}})}\left[\delta_{ij}(\mathbf{W}^{\mathrm{mf}}\mathbf{y})_i + y_i w_{ij}^{\mathrm{ff}} - \tfrac{1}{2}\frac{\partial \delta_i^{\mathrm{f}}}{\partial x_j} - y_i\frac{\partial \overline{w}}{\partial x_j}\right]\Bigg|_{(\hat{\mathbf{x}},\hat{\mathbf{y}})} \tag{A2c}$$

$$\frac{\partial y_i'}{\partial y_j}\Big|_{(\hat{\mathbf{x}},\hat{\mathbf{y}})} = \overline{w}\Big|^{-1}_{(\hat{\mathbf{x}},\hat{\mathbf{y}})}\left[x_i w_{ij}^{\mathrm{mf}} + \delta_{ij}(\mathbf{W}^{\mathrm{ff}}\mathbf{x})_i - \tfrac{1}{2}\frac{\partial \delta_i^{\mathrm{f}}}{\partial y_j} - y_i\frac{\partial \overline{w}}{\partial y_j}\right]\Bigg|_{(\hat{\mathbf{x}},\hat{\mathbf{y}})}, \tag{A2d}$$

where

$$\frac{\partial \overline{w}}{\partial x_j}\Big|_{(\hat{\mathbf{x}},\hat{\mathbf{y}})} = (\mathbf{W}^{\mathrm{mm}}\hat{\mathbf{y}})_j + (\mathbf{W}^{\mathrm{fm}^{\mathrm{T}}}\hat{\mathbf{y}})_j = (\mathbf{W}^{\mathrm{mf}}\hat{\mathbf{y}})_j + (\mathbf{W}^{\mathrm{ff}^{\mathrm{T}}}\hat{\mathbf{y}})_j \tag{A3a}$$

$$\frac{\partial \overline{w}}{\partial y_j}\Big|_{(\hat{\mathbf{x}},\hat{\mathbf{y}})} = (\mathbf{W}^{\mathrm{mm}^{\mathrm{T}}}\hat{\mathbf{x}})_j + (\mathbf{W}^{\mathrm{fm}}\hat{\mathbf{x}})_j = (\mathbf{W}^{\mathrm{mf}^{\mathrm{T}}}\hat{\mathbf{x}})_j + (\mathbf{W}^{\mathrm{ff}}\hat{\mathbf{x}})_j \tag{A3b}$$

and δ_{ij} is the Kronecker delta; that is, $\delta_{ij} = 1$ if $i = j$, and $\delta_{ij} = 0$ otherwise.

Let $\mathbf{S} = \mathbf{G}_{ij} i, j \in \{1, 2\}$; $\mathbf{R} = \mathbf{G}_{ij} i \in \{1, 2\}, j \in \{3, 4\}$; and $\mathbf{L} = \mathbf{G}_{ij} i, j \in \{3, 4\}$. Matrix **G** has the structure

$$\mathbf{G} = \begin{bmatrix} \mathbf{S} & \mathbf{R} \\ \mathbf{0} & \mathbf{L} \end{bmatrix}, \tag{A4}$$

where **0** is a four-by-four matrix of zeros. Such a structure simplifies our calculations concerning the spectral radius of matrix **G**.

The leading eigenvalue of **G** is greater than one if either the leading eigenvalue of **S** or the leading eigenvalue of **L** is greater than one. Furthermore, the leading eigenvalue of **S** must be less than one given the short-term stability of $(\hat{\mathbf{x}}, \hat{\mathbf{y}})$. Hence, the long-term stability of equilibrium $(\hat{\mathbf{x}}, \hat{\mathbf{y}})$ is characterized by the leading eigenvalue of **L**, $\rho(\mathbf{L})$. The full expression of **L** is

$$\mathbf{L}_{(k_{11},\kappa_{11})} = \frac{1}{2\overline{w}}\begin{bmatrix} v_{11}y_1 + k_{12}v_{12}y_2 & v_{11}x_1 + k_{12}v_{21}x_2 & k_{12}v_{21}y_1 & k_{12}v_{12}x_1 \\ v_{11}y_1 + \kappa_{12}v_{12}y_2 & v_{11}x_1 + \kappa_{12}v_{21}x_2 & \kappa_{12}v_{21}y_1 & \kappa_{12}v_{12}x_1 \\ (1 - k_{12})v_{12}y_2 & (1 - k_{12})v_{21}x_2 & v_{22}y_2 + (1 - k_{12})v_{21}y_1 & v_{22}x_2 + (1 - k_{12})v_{12}x_1 \\ (1 - \kappa_{12})v_{12}y_2 & (1 - \kappa_{12})v_{21}x_2 & v_{22}y_2 + (1 - \kappa_{12})v_{21}y_1 & v_{22}x_2 + (1 - \kappa_{12})v_{12}x_1 \end{bmatrix}\Bigg|_{(\hat{\mathbf{x}},\hat{\mathbf{y}})_{(k_{11},\kappa_{11})}}, \tag{A5}$$

where

$$\overline{w} = v_{11}x_1y_1 + v_{12}x_1y_2 + v_{21}x_2y_1 + v_{22}x_2y_2. \tag{A6}$$

Hessian matrix and second derivatives: Hessian matrix **H** is a matrix with elements that are matrices themselves:

$$\mathbf{H}^{x}_{ijl} = \left[\begin{matrix} \partial^2 x_i'/\partial x_j \partial x_l & \partial^2 x_i'/\partial y_j \partial x_l \\ \partial^2 y_i'/\partial x_j \partial x_l & \partial^2 y_i'/\partial y_j \partial x_l \end{matrix}\right]\Bigg|_{(\hat{\mathbf{x}},\hat{\mathbf{y}})} \tag{A7a}$$

$$\mathbf{H}^{y}_{ijl} = \left[\begin{matrix} \partial^2 x_i'/\partial x_j \partial y_l & \partial^2 x_i'/\partial y_j \partial y_l \\ \partial^2 y_i'/\partial x_j \partial y_l & \partial^2 y_i'/\partial y_j \partial y_l \end{matrix}\right]\Bigg|_{(\hat{\mathbf{x}},\hat{\mathbf{y}})}. \tag{A7b}$$

Straight differentiation in (A2) yields the second-order derivatives with respect to x_l,

$$\left.\frac{\partial^2 x_i'}{\partial x_j \partial x_l}\right|_{(\hat{\mathbf{x}},\hat{\mathbf{y}})} = -\overline{w}\big|^{-1}_{(\hat{\mathbf{x}},\hat{\mathbf{y}})}\left[\frac{\partial x_i'}{\partial x_j}\frac{\partial \overline{w}}{\partial x_l} + \delta_{il}\frac{\partial \overline{w}}{\partial x_j}\right]\Bigg|_{(\hat{\mathbf{x}},\hat{\mathbf{y}})} \tag{A8a}$$

$$\left.\frac{\partial^2 x_i'}{\partial y_j \partial x_l}\right|_{(\hat{\mathbf{x}},\hat{\mathbf{y}})} = -\overline{w}\big|^{-1}_{(\hat{\mathbf{x}},\hat{\mathbf{y}})}\left[\frac{\partial x_i'}{\partial y_j}\frac{\partial \overline{w}}{\partial x_l} - \delta_{il}\left(w_{ij}^{\mathrm{mm}} - \frac{\partial \overline{w}}{\partial y_j}\right) - \delta_{ij} w_{il}^{\mathrm{fm}} + \tfrac{1}{2}\frac{\partial \delta_i^{\mathrm{m}}}{\partial y_j \partial x_l}\right]\Bigg|_{(\hat{\mathbf{x}},\hat{\mathbf{y}})} \tag{A8b}$$

$$\left.\frac{\partial^2 y_i'}{\partial x_j \partial x_l}\right|_{(\hat{\mathbf{x}},\hat{\mathbf{y}})} = -\overline{w}\big|^{-1}_{(\hat{\mathbf{x}},\hat{\mathbf{y}})}\left[\frac{\partial y_i'}{\partial x_j}\frac{\partial \overline{w}}{\partial x_l}\right]\Bigg|_{(\hat{\mathbf{x}},\hat{\mathbf{y}})} \tag{A8c}$$

$$\left.\frac{\partial^2 y_i'}{\partial y_j \partial x_l}\right|_{(\hat{\mathbf{x}},\hat{\mathbf{y}})} = -\overline{w}\big|^{-1}_{(\hat{\mathbf{x}},\hat{\mathbf{y}})}\left[\frac{\partial y_i'}{\partial y_j}\frac{\partial \overline{w}}{\partial x_l} - \delta_{il} w_{ij}^{\mathrm{mf}} - \delta_{ij} w_{il}^{\mathrm{ff}} + \tfrac{1}{2}\frac{\partial \delta_i^{\mathrm{f}}}{\partial y_j \partial x_l}\right]\Bigg|_{(\hat{\mathbf{x}},\hat{\mathbf{y}})}, \tag{A8d}$$

and with respect to y_l,

$$\left.\frac{\partial^2 x_i'}{\partial x_j \partial y_k}\right|_{(\hat{\mathbf{x}},\hat{\mathbf{y}})} = -\overline{w}\big|^{-1}_{(\hat{\mathbf{x}},\hat{\mathbf{y}})}\left[\frac{\partial x_i'}{\partial x_j}\frac{\partial \overline{w}}{\partial y_l} - \delta_{ij} w_{il}^{\mathrm{mm}} - \delta_{il} w_{ij}^{\mathrm{fm}} + \tfrac{1}{2}\frac{\partial \delta_i^{\mathrm{m}}}{\partial x_j \partial y_l}\right]\Bigg|_{(\hat{\mathbf{x}},\hat{\mathbf{y}})} \tag{A9a}$$

$$\left.\frac{\partial^2 x_i'}{\partial y_j \partial y_l}\right|_{(\hat{\mathbf{x}},\hat{\mathbf{y}})} = -\overline{w}\big|^{-1}_{(\hat{\mathbf{x}},\hat{\mathbf{y}})}\left[\frac{\partial x_i'}{\partial y_j}\frac{\partial \overline{w}}{\partial y_l}\right]\Bigg|_{(\hat{\mathbf{x}},\hat{\mathbf{y}})} \tag{A9b}$$

$$\left.\frac{\partial^2 y_i'}{\partial y_j \partial x_l}\right|_{(\hat{\mathbf{x}},\hat{\mathbf{y}})} = -\overline{w}\big|^{-1}_{(\hat{\mathbf{x}},\hat{\mathbf{y}})}\left[\frac{\partial y_i'}{\partial x_j}\frac{\partial \overline{w}}{\partial y_l} - \delta_{ij} w_{il}^{\mathrm{mf}} - \delta_{il}\left(w_{ij}^{\mathrm{ff}} - \frac{\partial \overline{w}}{\partial x_j}\right) + \tfrac{1}{2}\frac{\partial \delta_i^{\mathrm{f}}}{\partial x_j \partial y_k}\right]\Bigg|_{(\hat{\mathbf{x}},\hat{\mathbf{y}})} \tag{A9c}$$

$$\left.\frac{\partial^2 y_i'}{\partial y_j \partial y_l}\right|_{(\hat{\mathbf{x}},\hat{\mathbf{y}})} = -\overline{w}\big|^{-1}_{(\hat{\mathbf{x}},\hat{\mathbf{y}})}\left[\frac{\partial y_i'}{\partial y_j}\frac{\partial \overline{w}}{\partial y_l} + \delta_{il}\frac{\partial \overline{w}}{\partial y_j}\right]\Bigg|_{(\hat{\mathbf{x}},\hat{\mathbf{y}})}. \tag{A9d}$$

The term $Q(\mathbf{G})$ results from multiplying the left eigenvector of $\mathbf{L}$, elements of $\mathbf{H}$, and pairs of values of the right eigenvector of $\mathbf{G}$ as specified in Lessard (1989).

APPENDIX B

Spectral radius of $\mathbf{L}_{(\frac{1}{2},\frac{1}{2})} > 1$: The leading eigenvalue of $\mathbf{L}_{(\frac{1}{2},\frac{1}{2})}$ is

$$\rho(\mathbf{L}_{(\frac{1}{2},\frac{1}{2})}) = 1 + (2f_2)^{-1}\left(f_1 - f_2 + \sqrt{(f_1+f_2)^2 - 8v_{11}f_1}\right), \tag{B1}$$

where $f_1 = (k_{12} - \kappa_{12})(v_{12} - v_{21})$ and $f_2 = 2v_{11} + v_{12} + v_{21}$. Hence $\rho(\mathbf{L}_{(\frac{1}{2},\frac{1}{2})}) > 1$ whenever

$$(2f_2)^{-1}\left(f_1 - f_2 + \sqrt{(f_1+f_2)^2 - 8v_{11}f_1}\right) > 0. \tag{B2}$$

Given that $f_2 > 0$ the above inequality simplifies to

$$\sqrt{(f_1+f_2)^2 - 8v_{11}f_1} > f_2 - f_1. \tag{B3}$$

Given that $f_2 - f_1 > 0$ we can square both sides of the above inequality keeping its sense:

$$\begin{aligned}(f_1+f_2)^2 - 8v_{11}f_1 &> (f_2-f_1)^2 \\ f_1 f_2 &> 2v_{11}f_1.\end{aligned} \tag{B4}$$

There are two alternatives $f_1 > 0$ and $f_1 < 0$. If $f_1 > 0$ inequality (B4) reduces to $f_2 > 2v_{11}$. Substituting f_2 for its expression and simplifying the latter inequality reads $v_{12} + v_{21} > 0$, which is always true. If $f_1 < 0$ inequality (B4) reduces to $f_2 > 2v_{11}$, which is always false.

Consequently, the necessary and sufficient condition for the long-term instability of Mendelian segregation is $f_1 > 0$. Substituting f_1 for its expression and simplifying, this inequality reads

$$(k_{12} - \kappa_{12})(v_{12} - v_{21}) > 0. \tag{B5}$$

Spectral radius of $\mathbf{L}_{(1,0)} < 1$: The leading eigenvalue of $\mathbf{L}_{(1,0)}$ is

$$\rho(\mathbf{L}_{(1,0)}) = 1 + (4v_{12})^{-1}\left(f_3 + f_4 - 4v_{12} + \sqrt{(f_3 + f_4)^2 - 8v_{11}f_3}\right), \tag{B6}$$

where $f_3 = (k_{12} - \kappa_{12})v_{12}$ and $f_4 = v_{11} + v_{12}$. Hence $\mathbf{L}_{(1,0)} < 1$ whenever

$$\sqrt{(f_3 + f_4)^2 - 8v_{11}f_3} < 4v_{12} - (f_3 + f_4). \tag{B7}$$

There are two alternatives $4v_{12} > f_3 + f_4$ and $4v_{12} < f_3 + f_4$. If $4v_{12} > f_3 + f_4$, we can square both sides of inequality (B7), keeping its sense:

$$v_{12}(f_3 + f_4 - 2v_{12}) < v_{11}f_3. \tag{B8}$$

Substituting f_3 and f_4 for their expression and simplifying, we get the pair of conditions $(3 + \kappa_{12} - k_{12})v_{12} > v_{11}$ and $v_{12} > v_{11}$. Given that $3 + \kappa_{12} - k_{12} > 1$, inequality $v_{12} > v_{11}$ is the more restrictive of the two conditions and, therefore, the only one that is relevant. The latter condition is always true if equilibrium $(\hat{\mathbf{x}}, \hat{\mathbf{y}})_{(1,0)}$ is short-term stable.

If $4v_{12} < f_3 + f_4$, we have to reverse the sense of inequality (B7) when squaring:

$$v_{12}(f_3 + f_4 - 2v_{12}) > v_{11}f_3. \tag{B9}$$

Substituting f_3 and f_4 for their expression and simplifying, we get condition $v_{12} < v_{11}$, which is always false if equilibrium $(\hat{\mathbf{x}}, \hat{\mathbf{y}})_{(1,0)}$ is short-term stable.

To summarize, condition $v_{12} > v_{11}$, v_{22} is necessary and sufficient to guarantee the long-term stability of the segregation scheme (1, 0). This is the same condition required for the short-term stability of equilibrium $(\hat{\mathbf{x}}, \hat{\mathbf{y}})_{(1,0)}$.

Spectral radius of $\mathbf{L}_{(0,1)} < 1$: Similarly, the leading eigenvalue of $\mathbf{L}_{(0,1)}$ is

$$\rho(\mathbf{L}_{(0,1)}) = 1 + (4v_{21})^{-1}\left(f_5 + f_6 - 4v_{21} + \sqrt{(f_5 + f_6)^2 - 8v_{11}f_5}\right), \tag{B10}$$

where $f_5 = (\kappa_{+1} - k_{+1})v_{21}$ and $f_6 = v_{11} + v_{21}$.

Hence $\mathbf{L}_{(0,1)} < 1$ whenever

$$\sqrt{(f_5 + f_6)^2 - 8v_{11}f_5} < 4v_{21} - (f_5 + f_6). \tag{B11}$$

If $4v_{12} > f_5 + f_6$, we can square both sides of inequality (B7), keeping its sense:

$$v_{21}(f_5 + f_6 - 2v_{21}) < v_{11}f_5. \tag{B12}$$

Substituting f_5 and f_6 for their expression and simplifying, we get condition $v_{21} > v_{11}$, which is always true if equilibrium $(\hat{\mathbf{x}}, \hat{\mathbf{y}})_{(1,0)}$ is short-term stable.