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Competition at the Mouse *t* Complex: Rare Alleles Are Inherently Favored

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We investigate the competition between alleles at a segregation distorter locus. The focus is on the invasion prospects of rare mutant distorter alleles in a population in which a wildtype and a resident distorter allele are present. The parameters are chosen to reflect the situation at the *t* complex of the house mouse, one of the best-studied examples of segregation distortion. By analyzing the invasion chances of rare alleles, we provide an analytical justification of earlier simulation results. We show that a new distorter allele can successfully invade even if it is inferior both at the gamete and at the individual level. In fact, newly arising distorter alleles have an inherent rareness advantage if their negative fitness consequences are restricted to homozygous condition. Likewise, rare mutant wildtype alleles may often invade even if their viability or fertility is reduced. As a consequence, the competition between alleles at a segregation distorter locus should lead to a high degree of polymorphism. We discuss the implications of this conclusion for the *t* complex of the house mouse and for the evolutionary stability of ''honest'' Mendelian segregation.

Key Words: **segregation distortion; meiotic drive; Shaw–Mohler equation; invadability; rareness advantage; *t* complex; *SD* complex; *Drosophila melanogaster*; Mendelian segregation; mathematical model.**

INTRODUCTION

Segregation distorters are genetic elements that disturb Mendelian segregation in their favor. In well-known examples such as the *SD* complex of *Drosophila melanogaster* (Temin *et al.*, 1991) and the *t* complex of the house mouse (Silver, 1993), the distorter alleles manage to be present in more than 90% of the gametes of heterozygous males. Nevertheless, these selfish genetic elements do not spread to fixation since they typically induce severe negative fitness effects at the individual level.

Ever since their detection, segregation distorters have fascinated evolutionary biologists because they exemplify selection at a lower level leading to maladaptive features at a higher level. The outcome of evolution in systems in which selection operates at different levels is, however, still poorly understood. For example, one might expect that, all other things being equal, the most ''efficient'' distorter with the highest transmission ratio should outcompete less efficient distorters. This expectation is, however, not justified, as was shown in an earlier simulation study (van Boven *et al.*, 1996). In fact, the

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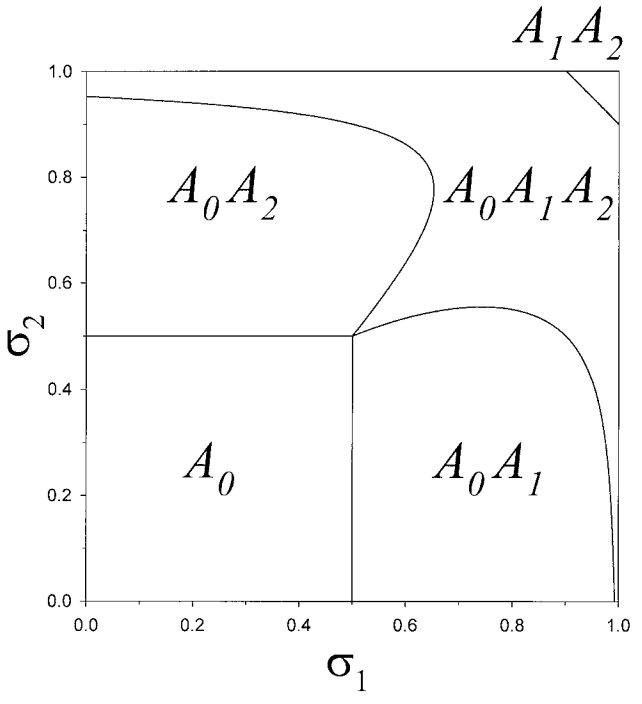

FIG. 1. Outcome of the competition between a wildtype allele A_0 and two segregation distorters A_1 and A_2 as a function of their transmission ratios σ_1 and σ_2 (van Boven *et al.*, 1996). When homozygous, A_1 induces lethality in both males and females, while A_2 only leads to male sterility in homozygous condition. Heterozygous A_1A_2 males are to some extent viable and fertile, so that the product of relative viability and relative fertility is 0.1. Heterozygous A_1A_2 females are fully viable and fertile. Segregation distortion occurs only in males. Five equilibrium outcomes are possible: (1) only the wildtype A_0 persists, (2) the wildtype persists with the first distorter A_1, (3) the wildtype persists with the second distorter A_2, (4) the wildtype persists with both distorter alleles, or (5) both distorter alleles persist without the wildtype.

competition between segregation distorters has a number of surprising aspects, some of which are exemplified by Fig. 1:

- A segregation distorter that causes lethality in both sexes when homozygous can stably coexist with a distorter that induces only male sterility in homozygous condition, even if the "lethal" distorter has a smaller segregation advantage than the "sterile" distorter.
- Even "negative" segregation distorters with a segregation disadvantage ($\sigma < \frac{1}{2}$ in Fig. 1) can stably persist in a population. Actually, the most efficient distorters pave the way for the persistence of the least efficient distorters.
- Coexistence of a second segregation distorter with an already present first distorter is most difficult to achieve if the transmission ratio σ of the first distorter is intermediate (say $0.70 < \sigma < 0.90$).

In this paper we complement our previous simulation study by a systematic analytical investigation of the competition between segregation distorters. This question is of empirical relevance, because a variety of distorter alleles are found in well-studied systems (e.g., the *t* complex of the house mouse and the *SD* complex of *Drosophila melanogaster*), both in the lab and in the field. The standard models for the evolution of segregation distortion (see Feldman and Otto (1991) and references therein) are not directly applicable to this situation since they focus on the interaction of the wildtype with a single distorter allele. For instance, the classical models of Bruck (1957) and Dunn and Levene (1961) are designed to describe the interaction of a single lethal or sterile *t* haplotype (*t* allele) with the wildtype. The few models on the interaction of several distorter alleles (e.g., Hartl, 1970) make the unrealistic assumption that both sexes are equally affected by selection and segregation distortion. In a companion paper (Weissing and van Boven, 2001) we have therefore developed some new theory for the interaction of several distorter alleles in a sex-differentiated population. Here the theory is applied to the *t* complex of the house mouse, thereby illustrating how the general results can be put into practice.

The paper is organized as follows. We start by a characterization of the interaction of a wildtype allele A_0 with a segregation distorter allele A_1. Then we move on to consider invasion attempts of a rare distorter allele A_2 and ask how large the transmission ratio of the second distorter has to be for successful invasion. Technically, this amounts to determining whether the resident population consisting of the wildtype A_0 and the first distorter A_1 is unstable with respect to invasion attempts by A_2. Similarly, we can study the conditions under which A_1, when rare, can invade in a population in which A_0 and A_2 are present. It is likely that all three alleles will stably coexist if they are able to invade when rare. In fact, we will show that the invasion analysis of the present paper provides a complete analytical characterization of Fig. 1 and all other equilibrium diagrams of van Boven *et al.* (1996) and van Boven and Weissing (1996).

THE MODEL

Fitness

We focus on a single autosomal locus A with three alleles A_0, A_1, and A_2. A_0 represents the wildtype allele, while the distorter alleles are labeled A_1 and A_2. The sex-specific viabilities of A_iA_j males and females ($i, j = 0, 1, 2$) are denoted by v_{ij}^m and v_{ij}^f. Likewise, the sex-specific

fertilities of A_iA_j males and females are given by φ_{ij}^m and φ_{ij}^f. The transmission ratio of A_i in A_iA_j males and females (i.e., the fraction of functional A_i gametes produced by an A_iA_j individual) is denoted by σ_{ij}^m and σ_{ij}^f, respectively.

The viability, fertility, and segregation parameters are combined into a single male and female set of fitness parameters m_{ij} and f_{ij} as follows:

$$m_{ij} = v_{ij}^m \varphi_{ij}^m \sigma_{ij}^m \qquad \text{and} \qquad f_{ij} = v_{ij}^f \varphi_{ij}^f \sigma_{ij}^f. \tag{1}$$

The m_{ij} and f_{ij} represent the male and female fitness of genotype A_iA_j viewed from the perspective of allele A_i. Hence, our model explicitly takes the point of view of the gene (or rather the allele) rather than that of the individual (or, more precisely, the genotype).

Throughout, the fitness parameters are assumed to be nonnegative. Moreover, the viability and fertility parameters v_{ij} and φ_{ij} are normalized so that the genotype A_iA_j with highest viability or fertility has $v_{ij} = 1$ or $\varphi_{ij} = 1$. In the complete absence of viability or fertility selection this implies that $v_{ij} = 1$ or $\varphi_{ij} = 1$ for all i and j. The viability and fertility parameters are assumed to be symmetric; i.e., they satisfy $v_{ij} = v_{ji}$ and $\varphi_{ij} = \varphi_{ji}$ for all i and j. The segregation parameters σ_{ij}, on the other hand, are not symmetric but satisfy $\sigma_{ij} = 1 - \sigma_{ji}$. This reflects the fact that an individual of genotype A_iA_j will always transmit one of the alleles A_i or A_j to its offspring. In the case of Mendelian segregation, the segregation parameters are given by $\sigma_{ij} = \sigma_{ji} = \frac{1}{2}$. In the complete absence of viability selection, fertility selection, and segregation distortion, (1) implies $m_{ij} = f_{ij} = \frac{1}{2}$; the fitness of an allele in an individual is $\frac{1}{2}$.

Dynamics

Consider an infinitely large population. Mating occurs at random, and generations are discrete and nonoverlapping. The allele frequency dynamics is given by the following set of recurrence equations for the allele frequencies in male and female gametes, p_i and q_i:

$$\begin{aligned} p_i' &= \frac{M_i}{\bar{m}} \\ q_i' &= \frac{F_i}{\bar{f}}. \end{aligned} \tag{2}$$

The numerators are given by $M_i = \frac{1}{2} p_i \sum_l m_{il} q_l + \frac{1}{2} q_i \sum_l m_{il} p_l$ and $F_i = \frac{1}{2} p_i \sum_l f_{il} q_l + \frac{1}{2} q_i \sum_l f_{il} p_l$, respectively. The denominators $\bar{m} = \sum_k M_k$ and $\bar{f} = \sum_k F_k$ represent the mean fitness of the male and female subpopulations, respectively. A derivation of the model is presented in the companion paper (Weissing and van Boven, 2001; see also Karlin, 1978; Karlin and Lessard, 1986; Nagylaki, 1992).

In the special case of no differences between the sexes ($m_{ij} = f_{ij} = w_{ij}$), the allele frequencies in males and females are equal after one generation ($p_i' = q_i'$). From then on the dynamics is given by the following set of recurrence equations:

$$p_i' = \frac{p_i w_i}{\bar{w}}. \tag{3}$$

Here $w_i = \sum_l w_{il} p_l$ represents the marginal fitness of allele A_i, while $\bar{w} = \sum_{k,l} p_k w_{kl} p_l$ is the mean fitness of the population.

Equilibria and Their Stability

The equilibria of the simplified model (3) are found by putting $p_i' = p_i = p_i^*$. Hence, at equilibrium either the frequency of an allele is zero ($p_i^* = 0$) or its marginal fitness equals the fitness of the population ($w_i^* = \bar{w}^*$). Hence, the marginal fitnesses of all alleles present at equilibrium are identical ($w_i^* = w_j^*$ for all i and j). The equilibria are readily calculated, even if a large number of alleles are involved, since they are given by a set of linear equations (see the companion paper).

The equilibria of the more general model (2) are given by the relations $p_i^* \bar{m}^* = M_i^*$ and $q_i^* \bar{f}^* = F_i^*$, unless $p_i^* = q_i^* = 0$. In contrast to the model given by (3), determination of the equilibria is a formidable task, even in those cases where only a small number of alleles are involved (see Lewontin (1968) for a specific example). In the special case of a so-called symmetric equilibrium, i.e., an equilibrium where the allele frequencies are identical in male and female gametes, the analysis is greatly simplified. In this case $q_i^* = p_i^*$, and the equilibrium conditions are given by the relations $\sum_l m_{il} p_l^* = \bar{m}^*$ unless $p_i^* = 0$, again leading to a set of linear equations for p_i^* (see the companion paper).

The stability of an equilibrium is determined by the linear approximation of the allele frequency dynamics at the equilibrium. An equilibrium is stable if the eigenvalues of the Jacobian are smaller than one in absolute value. To facilitate the stability analysis, we will distinguish between two types of stability: internal stability and external stability. Internal stability refers to stability with respect to perturbations of the alleles that are present at equilibrium. In contrast, external stability refers to stability with respect to invasion attempts by alleles that are not yet present. Often, determination of the internal stability of an equilibrium is a formidable task. In contrast, determination of the external stability of an equilibrium is usually feasible.

In the case of a symmetric equilibrium (i.e., $q_i^* = p_i^*$ for all i), the invasion prospects of a newly arising allele are particularly easy to determine. Symmetric equilibria occur whenever selection and segregation distortion are the same in both sexes or whenever selection and segregation distortion are restricted to one of the sexes. In case of a symmetric equilibrium, invasion of a rare allele can be judged on the basis of a Shaw–Mohler criterion (Shaw and Mohler, 1953). A symmetric equilibrium where the alleles A_0 and A_1 are present can be invaded by a rare allele A_2 if

$$\frac{1}{2}\left(\frac{\sum_l m_{2l} p_l^*}{\sum_l m_{il} p_l^*} + \frac{\sum_l f_{2l} p_l^*}{\sum_l f_{il} p_l^*}\right) > 1 \qquad (4)$$

for either of the resident alleles $i = 0$ or $i = 1$. In other words, allele A_2 will spread if it has a higher fitness in males and females than the resident alleles. Examples 1, 2, and 3 below provide examples of an invasion analysis based on the Shaw–Mohler criterion (4). In the case of an asymmetric equilibrium ($q_i^* \neq p_i^*$), determination of the invasion prospects of a rare allele is more difficult but still possible (Example 4).

THE *t* COMPLEX OF THE HOUSE MOUSE

Motivated by the *t* complex of the house mouse, we are particularly interested in the interaction of a wildtype A_0 with two distorter alleles A_1 and A_2 in a situation where the male and female fitness matrices $\mathbf{M} = (m_{ij})$ and $\mathbf{F} = (f_{ij})$ are of the form

$$\mathbf{M} = \begin{array}{c} \\ A_0 \\ A_1 \\ A_2 \end{array} \begin{array}{c} \begin{array}{ccc} A_0 & A_1 & A_2 \end{array} \\ \begin{pmatrix} \frac{1}{2} & 1-\sigma_1 & 1-\sigma_2 \\ \sigma_1 & \delta_1 & \alpha \\ \sigma_2 & \alpha & \delta_2 \end{pmatrix} \end{array}, \qquad (5)$$

$$\mathbf{F} = \begin{array}{c} \\ A_0 \\ A_1 \\ A_2 \end{array} \begin{array}{c} \begin{array}{ccc} A_0 & A_1 & A_2 \end{array} \\ \begin{pmatrix} \frac{1}{2} & \frac{1}{2} & \frac{1}{2} \\ \frac{1}{2} & \varepsilon_1 & \beta \\ \frac{1}{2} & \beta & \varepsilon_2 \end{pmatrix} \end{array}.$$

The interpretation of these matrices is as follows (see van Boven *et al.* (1996), van Boven (1997), and van Boven and Weissing (2000) for a biological justification). Individuals bearing the wild-type allele A_0 have the highest product of viability and fertility, which is normalized to 1. In the absence of segregation distortion, this value is multiplied by $\frac{1}{2}$, the ratio of Mendelian segregation. Segregation distortion occurs in heterozygous A_0A_1 and A_0A_2 males only. The transmission ratios of A_1 and A_2 in combination with the wildtype are denoted by σ_1 and σ_2, respectively ($0 \leqslant \sigma_1, \sigma_2 \leqslant 1$).

In the case of the *t* complex, males homozygous for a distorter allele suffer from severely impaired viability or fertility. Specifically, homozygous A_1A_1 or A_2A_2 males are (nearly) always sterile, leading to $\delta_1 = \delta_2 = 0$. Males that are heterozygous for two different distorter alleles may be at least partially fertile ($0 \leqslant \alpha < \frac{1}{2}$) if the distorter alleles complement each other with respect to fertility, i.e., if the fitness of a A_1A_2 heterozygote is higher than the fitness of A_1A_1 and A_2A_2 homozygotes. Formally, A_1 and A_2 are said to complement each other if $\alpha > \max(\delta_1, \delta_2)$. Complementation with respect to male fertility is well documented (Lyon, 1991).

The distorter alleles at the *t* complex (the *t* haplotypes) may have no effect on female fitness ("male sterile" *t* haplotypes or simply "sterile" *t* haplotypes) or they may lead to lethality in the homozygous condition in both females and males ("lethal" *t* haplotypes). In case of two lethal *t* haplotypes, we have, in addition to $\delta_1 = \delta_2 = 0$, $\varepsilon_1 = \varepsilon_2 = 0$. Lethal *t* haplotypes are said to complement each other if $\beta > 0$ or $\alpha > 0$, i.e., if the fitness of females or males heterozygous for two different distorter alleles is higher than the fitness of one of the homozygotes. Complementation with respect to viability is also well documented (Klein *et al.*, 1984). In fact, at the *t* complex there are at least 16 so-called "complementation groups" which are defined by the occurrence of complementation with respect to viability.

THE WILDTYPE AND A SINGLE DISTORTER ALLELE

Dynamics

Let us first consider the interaction of the wildtype A_0 with a single distorter allele A_1. In this case, the fitness matrices (5) reduce to

$$\mathbf{M} = \begin{pmatrix} \frac{1}{2} & 1-\sigma_1 \\ \sigma_1 & \delta_1 \end{pmatrix}, \qquad \mathbf{F} = \begin{pmatrix} \frac{1}{2} & \frac{1}{2} \\ \frac{1}{2} & \varepsilon_1 \end{pmatrix}. \qquad (6)$$

The dynamics of the system is essentially determined by the recurrence equations for p_1 and q_1, the allele frequencies of A_1 in males and females, respectively. A

straightforward calculation shows that the numerators M_1 and F_1 in (2) are given by

$$M_1 = \tfrac{1}{2}\sigma_1(p_1+q_1-2p_1q_1)+\delta_1 p_1 q_1$$
$$F_1 = \tfrac{1}{4}(p_1+p_1-2p_1q_1)+\varepsilon_1 p_1 q_1,$$

while the mean fitnesses in males and females take the form

$$\bar{m} = \tfrac{1}{2}(1-p_1q_1)+\delta_1 p_1 q_1$$
$$\bar{f} = \tfrac{1}{2}(1-p_1q_1)+\varepsilon_1 p_1 q_1.$$

As a consequence, the allele frequency dynamics is characterized by

$$p_1' = \frac{\sigma_1(p_1+q_1-2p_1q_1)+2\delta_1 p_1 q_1}{1-p_1q_1+2\delta_1 p_1 q_1}$$
$$q_1' = \frac{\tfrac{1}{2}(p_1+q_1-2p_1q_1)+2\varepsilon_1 p_1 q_1}{1-p_1q_1+2\varepsilon_1 p_1 q_1}. \qquad (7)$$

Equilibria

In addition to the border equilibria $p_1^* = q_1^* = 0$ and $p_1^* = q_1^* = 1$, the A_0A_1 system admits potentially an interior equilibrium $0 < p_1^*, q_1^* < 1$ that is characterized by $p_1' = p_1 = p_1^*$ and $q_1' = q_1 = q_1^*$. Solving these equilibrium equations boils down to finding the roots of a third-order polynomial. It is therefore not surprising that—even in this simple scenario—an explicit calculation of the equilibrium frequencies is only feasible for some special cases.

In the special case that selection and segregation distortion occur in males only ($\varepsilon_1 = \frac{1}{2}$), the equilibrium frequencies are the same in males and females. The equilibrium frequency of A_1 in males and females is given by

$$p_1^* = q_1^* = \frac{2\sigma_1 - 1}{1-2\delta_1}, \qquad (8)$$

while $q_0^* = p_0^* = 1-p_1^*$. In the case of a male sterile distorter ($\delta_1 = 0$), the equilibrium frequencies reduce to those of the classical model of Dunn and Levene (1961).

In the case of a lethal distorter ($\delta_1 = \varepsilon_1 = 0$), a straightforward calculation shows that the equilibrium frequency of A_1 in males and females is given by

$$p_1^* = \sigma_1\left(1-\sqrt{\frac{1-\sigma_1}{\sigma_1}}\right)$$
$$q_1^* = \frac{1}{2}\left(1-\sqrt{\frac{1-\sigma_1}{\sigma_1}}\right), \qquad (9)$$

while the mean fitness in males equals the mean fitness in females:

$$\bar{m}^* = \bar{f}^* = \tfrac{1}{4}+\tfrac{1}{2}\sqrt{\sigma_1(1-\sigma_1)}.$$

It is not difficult to check that p_1^* and q_1^* correspond with the equilibrium frequency of a lethal t haplotype predicted by the model of Bruck (1957). Bruck, however, focused on the allele frequencies in adults, before segregation distortion has taken place.

Instability of the Border Equilibria

The border equilibrium $p_1^* = q_1^* = 0$, where only the wildtype is present, is stable if and only if the distorter allele A_1 cannot invade when rare. According to a Shaw–Mohler criterion analogous to (4), A_1 will spread when rare if

$$\frac{1}{2}\left(\frac{m_{10}}{m_{00}}+\frac{f_{10}}{f_{00}}\right) = \frac{1}{2}(2\sigma_1+1) > 1.$$

Obviously, this is equivalent to

$$\sigma_1 > \tfrac{1}{2};$$

i.e., A_1 will invade whenever it has a segregation advantage.

The border equilibrium $p_1^* = q_1^* = 1$, in which only the distorter allele is present, is stable if and only if the wildtype allele A_0 cannot invade when rare. A_0 will invade when rare if

$$\frac{1}{2}\left(\frac{m_{01}}{m_{11}}+\frac{f_{01}}{f_{11}}\right) = \frac{1}{2}\left(\frac{1-\sigma_1}{\delta_1}+\frac{\frac{1}{2}}{\varepsilon_1}\right) > 1$$

or, equivalently, if

$$\sigma_1 < 1-\delta_1\left(2-\frac{1}{2\varepsilon_1}\right).$$

Accordingly, fixation of the distorter A_1 is stable only if

$$\sigma_1 > 1-\delta_1\left(2-\frac{1}{2\varepsilon_1}\right);$$

i.e., if the segregation advantage outweighs the negative fitness effects at the individual level.

Existence and Stability of the A_0A_1 Equilibrium

It is easy to see that the border equilibria $p_1^* = q_1^* = 0$ and $p_1^* = q_1^* = 1$ cannot both be stable. If one of the border equilibria is stable while the other is unstable, the system converges to the stable equilibrium. If both border equilibria are unstable it is plausible that the system converges to a polymorphic equilibrium in which both alleles are present. In Appendix A we show that the polymorphic equilibrium—if it exists—is stable:

Result 1 (Stable Coexistence of the Wildtype and a Single Distorter). A polymorphic equilibrium $0 < p_1^*, q_1^* < 1$ of the dynamics given by (7), where both alleles are present, exists if and only if the inequalities

$$\frac{1}{2} < \sigma_1 < 1 - \delta_1 \left(2 - \frac{1}{2\varepsilon_1}\right) \tag{10}$$

are satisfied. Whenever a polymorphic equilibrium exists, it is stable.

INVASION OF A RARE DISTORTER ALLELE

With a characterization of the interaction of the wildtype with a single distorter allele at hand, we move on to consider the interaction between three alleles. In particular, we focus on the question under which conditions a rare second distorter allele can invade in a population in which a wildtype allele A_0 and a resident distorter allele A_1 are present. We consider four examples of increasing complexity.

Example 1 (No Differences between the Sexes). Let us start with the simplest case of no sex differences. In this case the male and female fitness matrices are identical,

$$\mathbf{M} = \mathbf{F} = \mathbf{W} = \begin{pmatrix} \frac{1}{2} & 1-\sigma_1 & 1-\sigma_2 \\ \sigma_1 & \delta_1 & \alpha \\ \sigma_2 & \alpha & \delta_2 \end{pmatrix} \tag{11}$$

(i.e., $m_{ij} = f_{ij} = w_{ij}$ for all i and j). After one generation the allele frequencies in males and females are equal ($q_i' = p_i'$ for all i) and the allele frequency dynamics is given by (3).

First, we focus on the A_0A_1 system. A polymorphic equilibrium (p_0^*, p_1^*) exists if $\frac{1}{2} < \sigma_1 < 1 - \delta_1$. The polymorphic equilibrium is given by (8) Analogously to Result 1, it can be shown that the polymorphic equilibrium is stable whenever it exists.

The invasion prospects of the rare distorter allele A_2 are given by the Shaw–Mohler criterion (4). Since the allele frequencies in males and females are identical, the Shaw–Mohler criterion reduces to

$$\sum_l w_{2l} p_l^* > \sum_l w_{il} p_l^*$$

for $i = 0$ or $i = 1$. In other words, the rare allele A_2 will invade if its marginal fitness $w_2^* = \sum_l w_{2l} p_l^*$ exceeds the marginal fitness $w_i^* = \sum_l w_{il} p_l^*$ of the resident alleles. Insertion of the fitness parameters (11) in the above inequality shows that the rare distorter A_2 will spread whenever

$$\sigma_2 p_0^* + \alpha p_1^* > \sigma_1 p_0^* + \delta_1 p_1^*.$$

Rearrangement and insertion of the equilibrium frequencies (8) yields:

Result 2a (No Differences between the Sexes). In a population with no differences between the sexes, a rare distorter allele A_2 will successfully invade an internally stable equilibrium consisting of a wildtype A_0 and a resident distorter A_1 if and only if

$$\sigma_2 > \sigma_1 - \left(\sigma_1 - \frac{1}{2}\right) \frac{\alpha - \delta_1}{1 - \sigma_1 - \delta_1}. \tag{12}$$

Result 2a is illustrated by Fig. 2. Notice that for $\alpha = \delta_1$ invasion is possible if and only if A_2 has a higher transmission ratio than A_1 in combination with the wild-type allele (i.e., $\sigma_2 > \sigma_1$). If, however, α is larger than δ_1 (i.e., A_1 and A_2 complement one another), A_2 may spread despite $\sigma_2 < \sigma_1$. In fact, if σ_1 is large enough ($\sigma_1 > \frac{1}{2}(1 - \alpha + \sqrt{(1-\alpha)^2 + 2(\alpha - \delta_1)})$), A_2 will spread irrespective of its transmission ratio σ_2!

Example 2 (Two Sterile t Haplotypes). Now consider the case in which selection and segregation distortion are restricted to one sex, the males. In this case, the fitness matrices $\mathbf{M}$ and $\mathbf{F}$ are given by

$$\mathbf{M} = \begin{pmatrix} \frac{1}{2} & 1-\sigma_1 & 1-\sigma_2 \\ \sigma_1 & \delta_1 & \alpha \\ \sigma_2 & \alpha & \delta_2 \end{pmatrix}, \quad \mathbf{F} = \begin{pmatrix} \frac{1}{2} & \frac{1}{2} & \frac{1}{2} \\ \frac{1}{2} & \frac{1}{2} & \frac{1}{2} \\ \frac{1}{2} & \frac{1}{2} & \frac{1}{2} \end{pmatrix}. \tag{13}$$

If $\delta_1 = 0$, the resident distorter A_1 corresponds to a sterile t haplotype. If both $\delta_1 = 0$ and $\delta_2 = 0$, this scenario corresponds to the competition between two sterile t haplotypes.

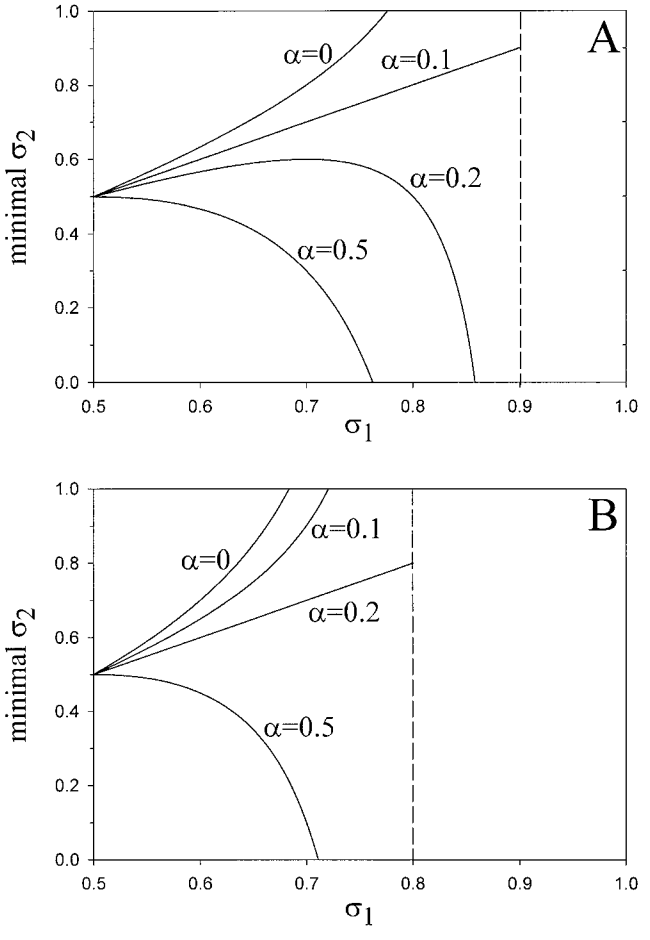

FIG. 2. Minimal transmission ratio required for succesful invasion of a rare second distorter in a population without sex differentiation. The fitness of individuals homozygous for the resident distorter allele is $\delta_1 = 0.1$ in (A) and $\delta_2 = 0.2$ in (B). A polymorphic equilibrium of the wild type and the resident distorter exist only if $\sigma_1 < 1-\delta_1$. As soon as there is some complementation (i.e., $\alpha > \delta_1$) it is possible to find a second distorter which is inferior with respect to its transmission ratio ($\sigma_2 < \sigma_1$) but is nevertheless able to invade the population (Result 2a). The same applies to a population where selection and segregation distortion are restricted to one of the sexes, as in the case of two sterile *t* haplotypes (Result 2b).

The analysis of the A_0A_1 system is relatively easy: The polymorphic equilibrium given by (8) exists if $\frac{1}{2} < \sigma_1 < 1-\delta_1$. Result 1 guarantees that the equilibrium is stable. The invasion prospects of A_2 are found by insertion of the fitness parameters and equilibrium frequencies into the Shaw–Mohler criterion (4). A simple calculation shows that the invasion prospects of the rare distorter A_2 are identical to the invasion prospects in a population where there are no differences between the sexes (Result 2a):

Result 2b (Competition between Sterile t Haplotypes). In a population where selection and segregation distortion are restricted to one of the sexes, the invasion prospects of a rare distorter allele A_2 in a population consisting of a wild type A_0 and a resident distorter A_1 are determined by the invasion criterion (12).

The fact that the invasion prospects of A_2 are identical in a population with no sex differentiation and in a population with selection and segregation distortion acting in one sex only is derived more generally in the companion paper. In fact, Result 10 of the companion paper shows that results of Scenario 1 (no differences between the sexes) are directly applicable to Scenario 2 (selection and segregation distortion in one sex only) and vice versa.

EXAMPLE 3 (A Sterile Resident *t* Haplotype). Consider now the case in which selection and segregation distortion in the resident population are restricted to one sex. The male and female fitness matrices take the form

$$\mathbf{M} = \begin{pmatrix} \frac{1}{2} & 1-\sigma_1 & 1-\sigma_2 \\ \sigma_1 & \delta_1 & \alpha \\ \sigma_2 & \alpha & \delta_2 \end{pmatrix}, \quad \mathbf{F} = \begin{pmatrix} \frac{1}{2} & \frac{1}{2} & \frac{1}{2} \\ \frac{1}{2} & \frac{1}{2} & \beta \\ \frac{1}{2} & \beta & \varepsilon_2 \end{pmatrix} \quad (14)$$

(i.e., $\varepsilon_1 = \frac{1}{2}$). In other words, the rare distorter allele A_2 may have fitness effects in females, but the resident distorter allele A_1 does not. Hence, if we choose $\delta_1 = 0$, A_1 corresponds to a sterile *t* haplotype, while A_2 is an as yet unspecified distorter since no specific values are assigned to δ_2 and ε_2.

With respect to the A_0A_1 system, nothing has changed. The only nontrivial equilibrium is symmetric ($q_i^* = p_i^*$) and given by (8). The equilibrium is stable whenever $\frac{1}{2} < \sigma_1 < 1-\delta_1$.

The external stability of (p_0^*, p_1^*) is again judged on the basis of the Shaw–Mohler criterion (4). A rare allele A_2 will invade whenever the arithmetic average of the marginal fitness of A_2 in males and females as compared to the marginal fitness of the resident alleles is larger than 1. A comparison of the marginal fitness of the invading distorter with the marginal fitness of the resident distorter (4) shows that the rare distorter will invade if

$$\frac{1}{2}\left(\frac{\sigma_2 p_0^* + \alpha p_1^*}{\sigma_1 p_0^* + \delta_1 p_1^*} + \frac{\frac{1}{2} p_0^* + \beta p_1^*}{\frac{1}{2}}\right) > 1.$$

After insertion of the equilibrium frequencies p_0^* and p_1^* (8), a simple calculation yields:

Result 3 (A Sterile Resident t Haplotype). In the system defined by (14), a rare distorter allele A_2 will successfully invade an internally stable equilibrium

consisting of a wildtype A_0 and a resident distorter allele A_1 if and only if

$$\sigma_2 > \sigma_1 - \left(\sigma_1 - \frac{1}{2}\right)\left(\frac{\alpha - \delta_1}{1-\sigma_1-\delta_1} - \frac{(1-2\beta)(2\sigma_1(1-\sigma_1)-\delta_1)}{(1-2\delta_1)(1-\sigma_1-\delta_1)}\right). \quad (15)$$

Notice that for $\beta = \frac{1}{2}$ (15) reduces to (12). In the case of a sterile resident t haplotype, we may safely assume that $\delta - 1 = 0$. Under this assumption, (15) simplifies to

$$\sigma_2 > \sigma_1 - \left(\sigma_1 - \frac{1}{2}\right)\left(\frac{\alpha}{1-\sigma_1} - 2\sigma_1(1-2\beta)\right). \quad (16)$$

Figure 3 illustrates (16) for $\beta = \frac{1}{2}$ (Fig. 3A) and $\beta = 0$ (Fig. 3B). Again, a less efficient distorter A_2 (i.e., $\sigma_2 < \sigma_1$) can easily invade the population if its fitness effects in females are not too drastic (β not too small) and if at least some complementation between A_1 and A_2 occurs in males ($\alpha > \delta_1$).

EXAMPLE 4 (A Lethal Resident t Haplotype). Let us now turn to the general case of selection and segregation distortion differing in both sexes, but let us for simplicity assume that $\delta_1 = \varepsilon_1 = 0$. In this case the resident distorter corresponds to a lethal t haplotype. The male and female fitness matrices look as follows:

$$\mathbf{M} = \begin{pmatrix} \frac{1}{2} & 1-\sigma_1 & 1-\sigma_2 \\ \sigma_1 & 0 & \alpha \\ \sigma_2 & \alpha & \delta_2 \end{pmatrix}, \quad \mathbf{F} = \begin{pmatrix} \frac{1}{2} & \frac{1}{2} & \frac{1}{2} \\ \frac{1}{2} & 0 & \beta \\ \frac{1}{2} & \beta & \varepsilon_2 \end{pmatrix}. \quad (17)$$

The fact that selection in the resident population is not restricted to one of the sexes complicates the analysis, as the frequencies of the alleles now differ between the sexes. In particular, the equilibria are not symmetric any more ($q_i^* \neq p_i^*$). In fact, the polymorphic equilibrium $0 < p_1^*, q_1^* < 1$ is given by (9). Result 1 guarantees that the equilibrium is stable.

With respect to the invasion prospects of a rare second distorter allele, the analysis is also more intricate than in the earlier examples. However, in Appendix B we show that it is still possible to derive an explicit invasion criterion:

Result 4 (A Lethal Resident t Haplotype). In the system defined by (17) with $\beta = \frac{1}{2}$, a rare distorter allele A_2 will successfully invade an internally stable equilibrium consisting of a wildtype A_0 and a resident distorter A_1 if and only if

$$\sigma_2 > \sigma_1 - \left(\sigma_1 - \frac{1}{2}\right)\frac{\alpha + \sqrt{\sigma_1(1-\sigma_1)}}{1-\sigma_1+\sqrt{\sigma_1(1-\sigma_1)}}. \quad (18)$$

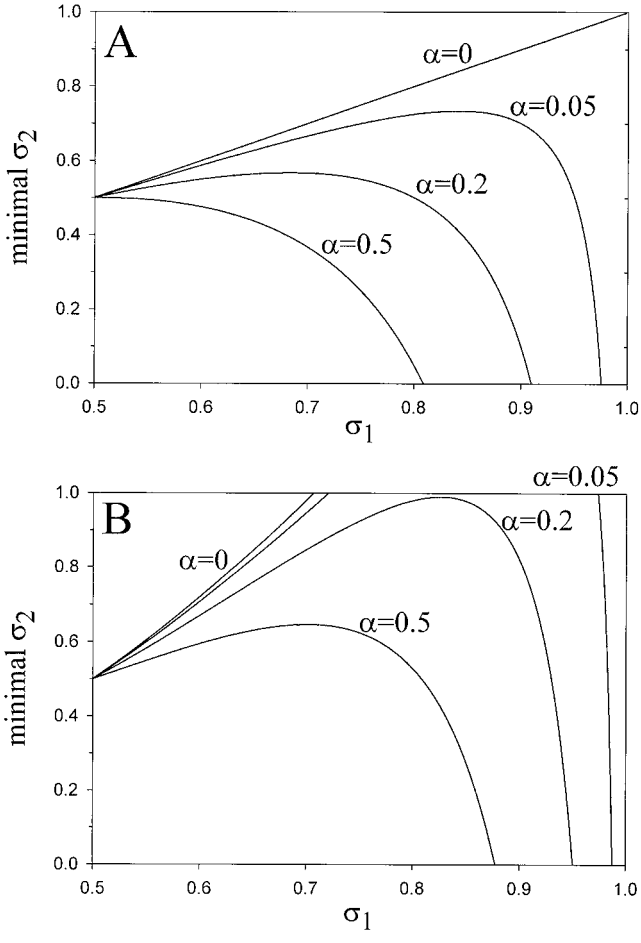

FIG. 3. Invasion of a rare second distorter in a population in which the resident distorter affects only males (Result 3). Hence, the resident distorter corresponds to a sterile t haplotype. As in Fig. 2, it is possible to find an "inferior" second distorter (i.e., $\sigma_2 < \sigma_1$) which is nevertheless able to invade the population if there is some complementation (i.e., $\alpha > 0$). In (A) heterozygous A_1A_2 females are fully viable and fertile ($\beta = \frac{1}{2}$), while in (B) A_1A_2 females have zero fitness ($\beta = 0$).

Result 4 is illustrated by Fig. 4. As before, a weaker distorter ($\sigma_2 < \sigma_1$) can easily invade if there is at least some complementation (i.e., $\alpha > 0$ or $\beta > 0$). Notice that in the special case $\alpha = 0$ and $\beta = \frac{1}{2}$ (no complementation in males and full complementation in females), a second distorter A_2 can always invade if $\sigma_2 > 0.61$. In the more plausible scenario $\alpha = \frac{1}{2}$ and $\beta = \frac{1}{2}$ (full complementation in both males and females), a second distorter can always invade if it confers the slightest segregation advantage

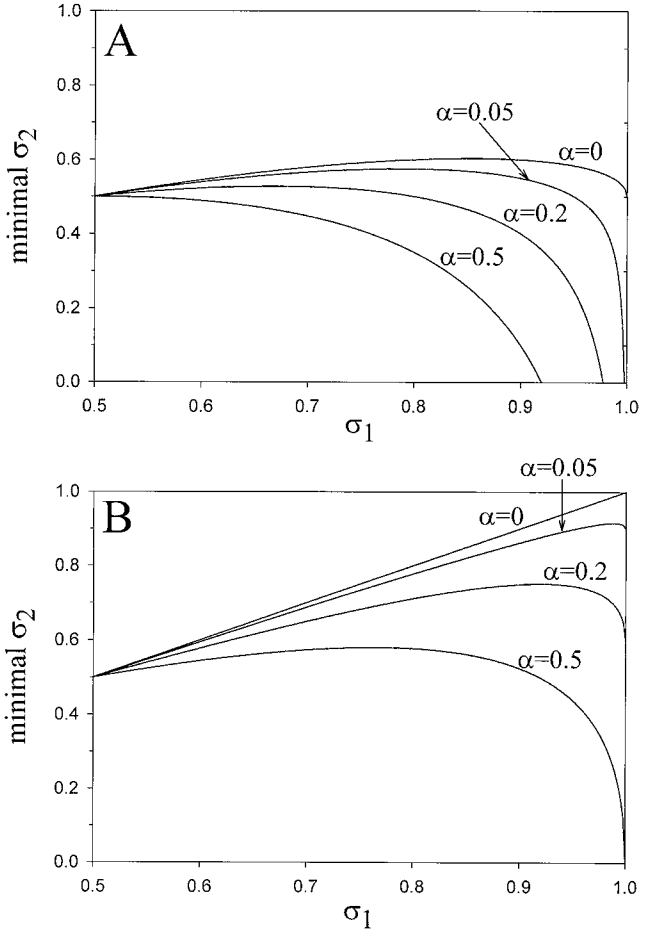

FIG. 4. Invasion of a rare second distorter in a population in which the resident distorter has zero fitness in homozygous males and females. Hence, the resident distorter corresponds to a lethal *t* haplotype. In (A) heterozygous A_1A_2 females are fully viable and fertile ($\beta = \frac{1}{2}$, Result 4), while in (B) A_1A_2 females have zero fitness ($\beta = 0$, invasion criterion not shown).

($\sigma_2 > \frac{1}{2}$) and often even if it has a segregation disadvantage ($\sigma_2 < \frac{1}{2}$). Such a scenario applies to the competition between lethal *t* haplotypes that belong to different complementation groups, i.e., that carry recessive lethal alleles at two different loci within the *t* complex (e.g., Klein *et al.*, 1984).

Notice that this example represents the most general case with selection in both sexes and segregation distortion differing between the sexes. In general, the analysis of such a model is a forbidding task, even in the simplest case of two alleles (cf. Hartl, 1970). That it is still possible in this particular case to find a simple expression for the equilibrium frequencies and a pleasant-looking invasion criterion hinges on the fact that selection does not differ between the sexes (i.e., $\varphi_{ij}^m v_{ij}^m = \varphi_{ij}^f v_{ij}^f$ for all i and j). As a result, the mean fitness in males equals the mean fitness in females.

STERILE VERSUS LETHAL *t* HAPLOTYPES: A COMPARISON

All the invasion criteria for a rare mutant distorter share a number of features. First, for a given σ_1, the threshold for invasion functions is negatively related to α and β. In other words, the invasion chances of a rare second distorter are always enhanced by a higher degree of complementation. Second, none of the invasion criteria depend on the fitness that the rare distorter has in homozygous condition (δ_2 and ε_2). This is not surprising since a rare distorter A_2 will almost never occur in the homozygous condition. Hence, in the case of the *t* complex the invasion prospects of rare sterile and rare lethal *t* haplotypes should be identical.

For a more specific comparison of the invasion criteria let us confine ourselves to the case $\delta_1 = 0$ (sterility or lethality of resident A_1A_1 males) and $\beta = \frac{1}{2}$ (full complementation of A_1 and A_2 in females). If A_1 corresponds to a sterile *t* haplotype ($\varepsilon_1 = \frac{1}{2}$), the threshold function for the spread of A_2 is (Result 3)

$$T_{sterile}(\sigma_1, \alpha) = \sigma_1 - \left(\sigma_1 - \frac{1}{2}\right)\frac{\alpha}{1-\sigma_1}. \qquad (19)$$

If, on the other hand, A_1 corresponds to a lethal *t* haplotype ($\varepsilon_1 = 0$), the threshold function is given by Result 4:

$$T_{lethal}(\sigma_1, \alpha) = \sigma_1 - \left(\sigma_1 - \frac{1}{2}\right)\frac{\alpha + \sqrt{\sigma_1(1-\sigma_1)}}{1-\sigma_1+\sqrt{\sigma_1(1-\sigma_1)}}. \qquad (20)$$

The threshold functions $T_{sterile}(\sigma_1, \alpha)$ and $T_{lethal}(\sigma_1, \alpha)$ are illustrated in Fig. 5.

First, notice that both $T_{sterile}$ and T_{lethal} satisfy

$$T(\sigma_1, \alpha) < \sigma_1 \qquad \text{for} \quad \alpha > 0.$$

In other words, in the presence of the slightest amount of complementation ($\alpha > 0$), there always exist distorters which can successfully invade the population despite $\sigma_2 < \sigma_1$. This shows that the intuitive explanation that more efficient distorters will outcompete less efficient ones is not justified.

Second, it is easy to see that both $T_{sterile}$ and T_{lethal} have the property

$$T(\sigma_1, \alpha) > \tfrac{1}{2} \qquad \text{if} \quad \sigma_1 < 1-\alpha$$
$$T(\sigma_1, \alpha) < \tfrac{1}{2} \qquad \text{if} \quad \sigma_1 > 1-\alpha.$$

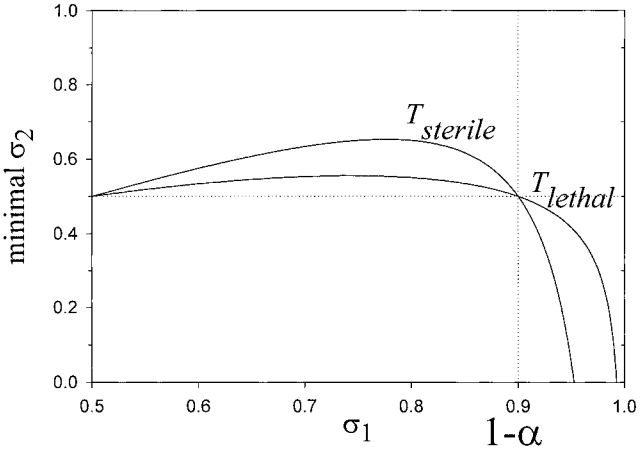

FIG. 5. A comparison of the invasion functions $T_{sterile}$ and T_{lethal}. If the transmission ratio of the resident distorter is low ($\sigma_1 < 1-\alpha$), invasion is more difficult to achieve in case of a sterile resident distorter, while if the transmission ratio is high ($\sigma_1 < 1-\alpha$), invasion is harder to achieve in case of a lethal resident distorter. Notice, moreover, that if the transmission ratio of the resident distorter is high ($\sigma_1 > 1-\alpha$), invasion is possible even for distorters with a segregation disadvantage ($\sigma_2 < \frac{1}{2}$).

Hence, if the transmission ratio of the resident distorter is high enough ($\sigma_1 > 1-\alpha$) then *all* positive distorters (i.e., $\sigma_2 > \frac{1}{2}$) can invade the population. Moreover, for $\sigma_1 > 1-\alpha$ there always exist some distorters which can invade even if they confer a segregation disadvantage ($\sigma_2 < \frac{1}{2}$).

Third, both invasion functions attain a single maximum at an intermediate transmission ratio. Consequently, segregation distorters with intermediate transmission ratios provide the best protection against invasion attempts of novel distorters (see also van Boven and Weissing, 1999). It is interesting to notice that transmission ratios of wild-caught mice carrying a *t* haplotype typically lie between 0.70 and 0.90 (Petras, 1967; Bennet *et al.*, 1983; Lenington *et al.*, 1988; Ardlie and Silver, 1996), which is lower than the segregation ratios of some *t* haplotypes in the laboratory (≈ 0.99; e.g., Lyon, 1991).

On the other hand, there is also a quantitative difference between the threshold functions $T_{sterile}$ and T_{lethal}:

$$T_{sterile}(\sigma_1, \alpha) > T_{lethal}(\sigma_1, \alpha) > \tfrac{1}{2} \quad \text{if} \quad \sigma_1 < 1-\alpha$$
$$T_{sterile}(\sigma_1, \alpha) < T_{lethal}(\sigma_1, \alpha) < \tfrac{1}{2} \quad \text{if} \quad \sigma_1 > 1-\alpha.$$

Hence, for relatively low transmission ratios ($\sigma_1 < 1-\alpha$) invasion is easier if the resident distorter induces homozygous lethality in both sexes, while for high transmission ratios ($\sigma_1 > 1-\alpha$) invasion is easier if the resident distorter leads to male sterility. It is tempting to speculate that the reported higher transmission ratios of lethal *t* haplotypes (0.89 versus 0.80, Petras, 1967; but see Ardlie and Silver, 1996) might be related to this difference.

INVASION OF A RARE WILDTYPE ALLELE

Up to now, the analysis was concerned with the invasion prospects of a rare distorter allele. The obvious next thing to do is to shift the focus of attention from competition between distorter alleles to competition between wildtype alleles and ask whether a rare mutant wildtype that is less prone to exploitation by the resident distorter can invade. The transmission ratio of the mutant wildtype in combination with the distorter is denote by τ_1 ($\tau_1 < \sigma_1$).

Differential sensitivity of wildtype alleles to segregation distortion is well documented at the *t* complex (e.g., Gummere *et al.*, 1986) and in particular at the *SD* complex of *D. melanogaster* (e.g., Temin *et al.*, 1991). However, resistant wildtype alleles usually do pay a cost, in terms of a reduction in fertility (e.g., Temin *et al.*, 1991) or in terms of a segregation disadvantage in combination with the resident wildtype (e.g., Lyon and Zenthon, 1987). Since the precise molecular mechanism of segregation distortion at the *t* complex is still not unraveled (although considerable progress has recently been made; Herrmann *et al.*, 1999; see also Schimenti, 2000; Lyon, 2000), we will here consider a simple scenario in which the relative fitness of individuals heterozygous for the two wildtype alleles is γ ($0 \leqslant \gamma \leqslant \frac{1}{2}$). If $\gamma = \frac{1}{2}$, the invading wildtype has maximal fitness, while if $\gamma = 0$, the invading wildtype induces complete lethality or sterility in combination with the resident wildtype.

For simplicity, we consider a population in which only males are affected by selection and segregation distortion. The fitness matrices of the males and females are given by

$$\mathbf{M} = \begin{pmatrix} \frac{1}{2} & 1-\sigma_1 & \gamma \\ \sigma_1 & \delta_1 & \tau_1 \\ \gamma & 1-\tau_1 & \delta_2 \end{pmatrix}, \qquad \mathbf{F} = \begin{pmatrix} \frac{1}{2} & \frac{1}{2} & \frac{1}{2} \\ \frac{1}{2} & \frac{1}{2} & \frac{1}{2} \\ \frac{1}{2} & \frac{1}{2} & \frac{1}{2} \end{pmatrix}. \quad (21)$$

The analysis proceeds along the same lines as in Scenario 1. The stable equilibrium (p_0^*, p_1^*) of the A_0A_1 system is given by (8). Insertion of the fitness parameters (21) into the Shaw–Mohler criterion (4) shows that A_2 will successfully invade if

$$\gamma p_0^* + (1-\tau_1)\, p_1^* > \tfrac{1}{2} p_0^* + (1-\sigma_1)\, p_1^*.$$

After inserting the equilibrium frequencies p_0^* and p_1^* (8), we are led to the following result:

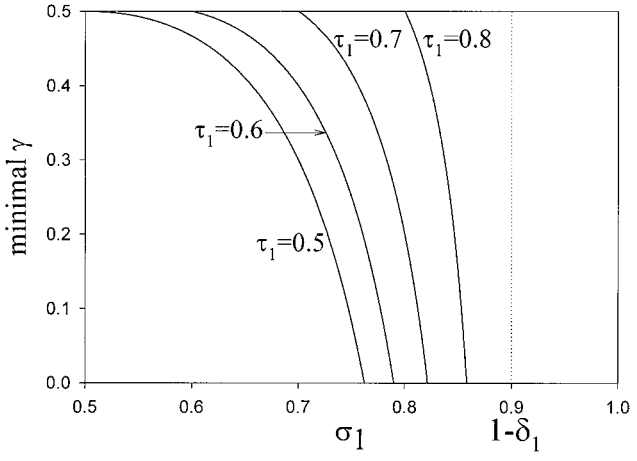

FIG. 6. Minimal fitness γ of heterozygous wildtype individuals needed for successful invasion of a rare wildtype allele (Result 5). The fitness of individuals homozygous for the resident distorter allele is fixed at $\delta_1 = 0.1$, while the segregation advantage of the distorter in combination with the rare wildtype is given by γ_1 ($0 \leqslant \gamma_1 \leqslant \sigma_1$).

Result 5 (Invasion of a Rare Wildtype). In the system defined by (21), a rare wildtype allele A_2 will successfully invade an equilibrium population consisting of a resident wildtype allele A_0 and a segregation distorter A_1 if and only if

$$\gamma > \frac{1}{2} - \frac{1}{2}(\sigma_1 - \tau_1)\frac{2\sigma_1 - 1}{2(1-\sigma_1-\delta_1)}. \qquad (22)$$

Result 5 is illustrated by Fig. 6. The figure shows that a rare mutant wildtype may successfully invade even if the fitness of individuals carrying two different wildtype alleles is reduced ($\gamma < \frac{1}{2}$). Invasion attempts of a rare wild type allele are especially likely to be successful if the transmission ratio σ_1 of the distorter in combination with the resident wildtype is high. Moreover, if the difference between the transmission ratios of the resident and the mutant wildtype, $\sigma_1 - \tau_1$, is large enough, the mutant wildtype can invade even if its fitness in combination with the resident wildtype is zero! This will happen whenever $\sigma_1 - \tau_1 > \frac{2(1-\sigma_1-\delta_1)}{2\sigma_1 - 1}$.

DISCUSSION

Mutual Invadability and Stable Equilibrium Coexistence

The most direct approach to studying the competition between three alleles at a segregation distorter locus would be to characterize all equilibrium points and to investigate their stability. Unfortunately, this approach is only possible in the specific cases where selection and segregation distortion are restricted to one sex or where selection and segregation distortion are the same in both sexes. If selection and segregation distortion differ between the sexes, the space of perturbations is already four-dimensional. Moreover, the coordinates of the equilibria depend on the parameters in a complicated way. Accordingly, we have little hope that a full analytical characterization of the equilibrium where all three alleles are present can be accomplished.

Therefore we followed a different strategy. We characterized the conditions under which an allele, when rare, can successfully invade a population in which two other alleles are present. It is plausible to assume that a protected polymorphism of all three alleles will occur when each of the alleles is able to spread when rare. In the context of a population without differences between the sexes or with selection and segregation distortion in one sex only, this claim can be justified in general: The external instability of all three border equilibria where two alleles are present is in fact equivalent to the existence and stability of a polymorphic equilibrium where all three alleles are present (F. J. Weissing and M. van Boven, unpublished). In general, however, this claim need not hold true. Convergence to a so-called heteroclinic cycle or more complex attractor may also occur (see the companion paper).

For the examples considered in this paper (i.e, for the dynamics induced by the fitness matrices (5)), such complications do not arise. In fact, the internal stability and external instability of the border equilibria where only two alleles are present precludes the possibility of an allele that is able to invade when rare but that nevertheless reaches an infinitesimally small frequency in the long run. Therefore, the invasion criteria in the present paper provide a complete analytical characterization of the equilibrium diagrams of van Boven *et al.* (1996). In particular, the equilibrium diagram of Fig. 1 corresponds to the invasion functions $T_{sterile}$ (19) and T_{lethal} (20) derived above.

Inherent Advantage of Rare Alleles

Our study was motivated by the simulation results of van Boven *et al.* (1996) and van Boven and Weissing (1998), which suggested that a high degree of polymorphism is to be expected if several complementing distorters arise in the same population. To explain this result, we have here considered a class of examples that resemble well-studied empirical systems such as the *t*

complex of the house mouse (e.g., Lyon, 1991) or the *SD* complex of *D. melanogaster* (e.g., Temin *et al.*, 1991).We focused on the invasion prospects of rare alleles in (internally stable) equilibrium populations consisting of a single wildtype and a single segregation distorter. In line with the simulation results, our invasion analysis shows that rare segregation distorters are inherently favored (Results 2–4, Figs 2–5). Invasion by a rare distorter is often possible even if it has inferior fitness characteristics (lower transmission ratio, lower fitness in homozygous condition) compared with both the wildtype and the resident distorter.

Intuitively, this rareness advantage can be explained as follows. As long as a distorter is rare, it will hardly ever occur in the homozygous condition. Accordingly, its fitness disadvantages when homozygous do not matter. When heterozygous with the wildtype allele, the rare distorter is favored if it has a segregation advantage: $\sigma_2 > \frac{1}{2}$. When heterozygous with the resident distorter, it is favored if complementation occurs. Hence a positive distorter will spread if the wildtype allele is present in high frequency, and a complementing distorter will spread if the resident distorter is prevalent.

It is conceivable that in view of their rareness advantage, inferior distorters may persist with superior distorters. However, this is only possible if complementation occurs, i.e., if the fitness (viability times fertility) of individuals heterozygous for two distorter alleles is higher than that of individuals homozygous for the resident distorter. Complementation is well documented for the *t* complex of the house mouse (Lyon, 1991) and for the *SD* complex of *D. melanogaster* (Temin *et al.*, 1991). In both systems, the mechanisms leading to segregation distortion and male sterility are closely intertwined (cf. van Boven and Weissing, 1998). In fact, there seems to be a negative relation between distorting ability on the one hand and complementing ability on the other (Lyon, 1991; Johnson *et al.*, 1995). We suspect that such a trade-off can play an important role in the evolution of segregation distorters. Anyhow, a one-sided focus on the transmission ratio is certainly too simplistic.

In addition, rare wildtype alleles are also inherently favored: A rare wildtype allele that is less prone to exploitation can successfully invade even if its viability or fertility in combination with the resident wildtype is reduced (Result 5, Fig. 6). Invasion by such a rare wildtype allele is especially likely to be successful if the transmission ratio of the distorter with the resident wildtype is high, i.e., if the resident wildtype is efficiently exploited. On the other hand, a rare wildtype that has higher fitness in combination with the resident wildtype can also easily invade, even if it is more efficiently exploited by a segregation distorter (results not shown). This is especially likely to happen if the resident wildtype has a small segregation disadvantage in combination with the distorter.

These phenomena can be understood as follows. If the resident wildtype is efficiently exploited, a segregation distorter will typically reach a high frequency in the population. As a result, the interaction of a rare mutant wildtype with the distorter is more important than its interaction with the resident wildtype, and the rare wildtype will invade if it is less easily exploited by the distorter. If, on the other hand, the resident wildtype is not efficiently exploited (i.e., the transmission ratio of the distorter with the resident wildtype is low), the resident wildtype will be the predominant allele in the population. As a consequence, a rare mutant wildtype allele will successfully invade if it does well in combination with the resident wildtype, i.e. if the fitness of heterozygous individuals carrying the resident and mutant wildtype is high.

Implications for the t Complex

How do the above predictions relate to the situation in the field and in particular to the *t* complex of the house mouse? There is one notable difference between our deterministic models and the empirical data that needs closer scrutiny: The distorter frequencies predicted by our models (e.g., (8) or (9)) are invariably much higher than those observed in the field. For instance, the models predict an equilibrium frequency in adults of 0.80 for a sterile distorter and 0.33 for a lethal distorter if the transmission ratio is 0.90, while recent evidence suggests that the overall frequency of *t* haplotypes in the field may be as low as 0.05 (Ardlie and Silver, 1998). This problem is shared by many deterministic models of segregation distortion (e.g., Bruck, 1957; Dunn and Levene, 1961; see van Boven and Weissing, 2000, for a discussion of possible explanations).

On the one hand, the fact that the *t* haplotype frequencies in the field are low implies that the invasion prospects of rare mutant *t* haplotypes that complement the resident *t* haplotype are in fact rather bleak. In particular, our prediction that even negative segregation distorters can invade if they complement a highly efficient resident distorter may not hold true, as it rests on the assumption that an efficient resident distorter will reach a high frequency in the population. On the other hand, the fact that the frequency of the wildtype is much higher than predicted by the models implies that there should be ample opportunities for mutant *t* haplotypes with a segregation advantage to invade. Likewise, the invasion prospects of rare mutant wildtype alleles will be

determined more by their interaction with the resident wildtype than by their interaction with the distorter.

In short, the main selection pressure on rare mutant alleles will be to do well in combination with the resident wildtype, as this is by far the predominant allele in the population ($\approx 95\%$). Hence, mutant *t* haplotypes will predominantly be selected to efficiently exploit the wildtype, while mutant wildtype alleles will be selected to have high fitness in combination with the resident wildtype. One may therefore argue that the selection pressure on mutant wildtype alleles to be resistant against exploitation by *t* haplotypes is of secondary importance. Even a rare mutant wildtype that is considerably more resistant against exploitation and that has only a slightly reduced fitness may not be able to invade.

Stability of Mendelian Segregation

We have seen that highly efficient distorters do not necessarily outcompete less efficient ones. On the contrary, all alternative distorter alleles with a certain complementing ability can invade if they face a very efficient resident distorter. In this sense, efficient distorters open invasion opportunities for less efficient ones. As a consequence, it is not at all obvious that an evolutionary trend toward increasing transmission ratios is to be expected. In other words, the stability of "honest" Mendelian segregation might be less difficult to explain than appears at first sight (Haig and Grafen, 1991).

Of course, a coherent theory of the evolution and stability of Mendelian segregation has to take modifiers of segregation into account. Current modifier theory (Eshel, 1985; Lessard, 1985) explains the apparent ubiquity of Mendelian segregation by the fact that modifiers that are not linked to the distorter will increase in frequency only if they shift the transmission ratio closer to $\frac{1}{2}$. In other words, the "parliament of genes" is expected to act to keep segregation honest. However, the situation is different for modifiers that are linked to a distorter allele. One might expect that such a modifier could spread only if it enhanced the expression of segregation distortion. In line with the conclusions of Liberman (1976), our model shows that this is not necessarily the case. Strictly speaking, our model applies only to the one-locus context. Still, it may also shed some light on the evolution at closely linked modifier loci, since perfectly linked modifiers may be viewed as mutant alleles at the distorter locus. Viewed this way, our results imply that a modifier allele at a modifier locus that is closely linked to a distorter locus may spread not only if it increases the transmission ratio but also if it decreases the transmission ratio. However, the latter will occur only if the modifier-induced reduction in distortion ability is associated with a certain degree of complementation.

Evolutionary Trends toward Polymorphism

In recent years, long-term evolution has often been imagined as a sequence of allele substitution events (e.g., Eshel, 1996; Hammerstein, 1996; Weissing, 1996). According to this view, a monomorphic population is challenged by single, newly arising mutants. Only mutants which confer a fitness advantage will successfully invade. Implicitly, it is typically assumed that successful mutants will spread to fixation, thereby leading to a new, monomorphic resident population.

In the case of segregation distortion, such a scenario is unrealistic and it might actually be misleading. If rareness is advantageous per se, it is conceivable that a resident population can be invaded by mutants with adverse fitness effects. Moreover, no single population is evolutionarily stable against invasion by all possible mutant alleles (van Boven and Weissing, 1998).

Examples of a systematic minority advantage are by no means uncommon. In addition to segregation distortion, they include phenomena such as marginal overdominance due to pleiotropy or spatiotemporal variability (e.g., Lewontin, 1974), genetic incompatibility (e.g., Uyenoyama, 1993), negative assortative mating and preference for rare mates (e.g., Partridge, 1988), competition avoidance due to deviation from the population standard (e.g., Chesson, 1985), apostatic selection mediated by predators (e.g., Allen, 1988), or the arms race between infectious agents their hosts (e.g., May, 1985). In all these systems fitness considerations alone are not sufficient to predict the outcome of evolution, and a high degree of polymorphism is to be expected.

APPENDIX A

Stability of the A_0A_1 Equilibrium

The internal stability of the equilibrium (p_1^*, q_1^*) generated by (7) is determined by the Jacobian matrix **A** at equilibrium. **A** is given by the matrix of partial derivatives of (7):

$$\mathbf{A} = \left(\begin{array}{cc} \frac{\partial p_1'}{\partial p_1} & \frac{\partial p_1'}{\partial q_1} \\ \frac{\partial q_1'}{\partial p_1} & \frac{\partial q_1'}{\partial q_1} \end{array} \right) \Bigg|_{(p_1^*, q_1^*)} .$$

The equilibrium (p_1^*, q_1^*) is (hyperbolically) internally stable if and only if $|\mathrm{tr}(\mathbf{A}))| < 1 + \det(\mathbf{A}) < 2$ (e.g., Edelstein-Keshet, 1988). After insertion of the fitness parameters (6), it can be shown that these conditions are always satisfied (F. J. Weissing and M. van Boven, unpublished). The calculations, however, are unwieldy. Therefore we here focus on the special case of a lethal distorter (i.e, $\delta_1 = \varepsilon_1 = 0$).

In the case of a lethal distorter, a simple calculation shows that the Jacobian $\mathbf{A}$ is given by

$$\mathbf{A} = \frac{1}{(1-p_1^*q_1^*)^2}\begin{pmatrix} \sigma_1(1-q_1^*)^2 & \sigma_1(1-p_1^*)^2 \\ \frac{1}{2}(1-q_1^*)^2 & \frac{1}{2}(1-p_1^*)^2 \end{pmatrix}.$$

It is obvious that $\det(\mathbf{A}) = 0$. Hence, only we have to show that $\mathrm{tr}(\mathbf{A}) < 1$. This is equivalent to

$$\sigma_1(1-q_1^*)^2 + \tfrac{1}{2}(1-p_1^*)^2 < (1-p_1^*q_1^*)^2. \qquad \text{(A1)}$$

If we insert the equilibrium frequencies (9) into (A1), we get the following condition for σ_1:

$$1 + 2\sigma_1^2 < 3\sigma_1 + (2\sigma_1 - 1)\sqrt{\sigma_1(1-\sigma_1)}.$$

If the condition for a polymorphic equilibrium, $\frac{1}{2} < \sigma_1 < 1$, is satisfied, the second term on the righthand side is positive and $1 + 2\sigma_1^2 < 3\sigma_1$. Hence, $\mathrm{tr}(\mathbf{A}) < 1$, and the polymorphic equilibrium is internally stable.

APPENDIX B

External Instability of the Equilibrium (9)

The invasion prospects of a rare mutant allele A_2 in an equilibrium population where A_0 and A_1 are present is determined by the linearized dynamics of the rare allele A_2 near the equilibrium (9). As shown in the companion paper, the fate of the mutant allele is determined by an "invasion matrix" $\mathbf{C}$:

$$\mathbf{C} = \begin{pmatrix} \dfrac{\sum_l m_{2l}q_l^*}{2\bar{m}^*} & \dfrac{\sum_l m_{2l}p_l^*}{2\bar{m}^*} \\ \dfrac{\sum_l f_{2l}q_l^*}{2\bar{f}^*} & \dfrac{\sum_l f_{2l}p_l^*}{2\bar{f}^*} \end{pmatrix}. \qquad \text{(B1)}$$

The rare allele A_2 will invade whenever the largest eigenvalue in absolute value of $\mathbf{C}$ exceeds one. Since the trace of $\mathbf{C}$ is positive, this implies that either $\det(\mathbf{C}) > 1$ or $\mathrm{tr}(\mathbf{C}) > 1 + \det(\mathbf{C})$. In the case of a wildtype A_0 and a resident lethal t haplotype A_1, insertion of (p_1^*, q_1^*) (9) into $\mathbf{C}$ yields

$$\mathbf{C} = \frac{1}{1-p_1^*q_1^*}\begin{pmatrix} \sigma_2 q_0^* + \alpha q_1^* & \sigma_2 p_0^* + \alpha p_1^* \\ \frac{1}{2}q_0^* + \beta q_1^* & \frac{1}{2}p_0^* + \beta p_1^* \end{pmatrix}.$$

We will first shows that the determinant of $\mathbf{C}$ is always smaller than 1 in absolute value. Then we will show that the second inequality yields the invasion criterion (18). To reduce the calculations, we focus on the special case $\beta = \frac{1}{2}$. The trace and determinant of $\mathbf{C}$ are given by

$$\begin{aligned} \mathrm{tr}(\mathbf{C}) &= \frac{1}{2\bar{m}^*}\left(\frac{1}{2} + \sigma_2 + (\alpha - \sigma_2)\, q_1^*\right) \\ \det(\mathbf{C}) &= \left(\frac{1}{2\bar{m}^*}\right)^2 \frac{1}{2}(\sigma_2 - \alpha)(p_1^* - q_1^*). \end{aligned} \qquad \text{(B2)}$$

Notice that, since $\frac{1}{2} < \sigma_1 < 1$

$$0 < p_1^* - q_1^* = \left(\sigma_1 - \frac{1}{2}\right)\left(1 - \sqrt{\frac{1-\sigma_1}{\sigma_1}}\right) < \frac{1}{2}.$$

Since $|\sigma_2 - \alpha| < 1$ we get

$$\tfrac{1}{2}|\sigma_2 - \alpha|\,(p_1^* - q_1^*) < \tfrac{1}{4}. \qquad \text{(B3)}$$

Moreover, $2\bar{m}^* > \frac{1}{2}$ and therefore

$$\left(\frac{1}{2\bar{m}^*}\right)^2 < 4. \qquad \text{(B4)}$$

Together, (B3) and (B4) imply

$$|\det(\mathbf{C})| < 1.$$

On the other hand, $\mathrm{tr}(\mathbf{C}) > 1 + \det(\mathbf{C})$ is equivalent to

$$2\bar{m}^*(\tfrac{1}{2} + \alpha q_1^* + \sigma_2(1-q_1^*)) > (2\bar{m}^*)^2 + \tfrac{1}{2}(\sigma_2 - \alpha)(p_1^* - q_1^*).$$

If we take terms with σ_2 to the lefthand side, we get

$$\begin{aligned} &\sigma_2(2\bar{m}^*(1-q_1^*) - \tfrac{1}{2}(p_1^* - q_1^*)) \\ &\quad > (2\bar{m}^*)^2 - (2\alpha q_1^* + 1)\,\bar{m}^* - \tfrac{1}{2}\alpha(p_1^* - q_1^*). \end{aligned}$$

Insertion of p_1^*, q_1^*, and $\bar{m}^*$ yields

$$\begin{aligned} &\sigma_2(1 - \sigma_1 + \sqrt{\sigma_1(1-\sigma_1)}) \\ &\quad > \sigma_1(1-\sigma_2) - \tfrac{1}{2}\alpha + \tfrac{1}{2}\sqrt{\sigma_1(1-\sigma_1)}, \end{aligned}$$

which leads to the invasion criterion (18)

$$\sigma_2 > \sigma_1 - \left(\sigma_1 - \frac{1}{2}\right)\frac{\alpha + \sqrt{\sigma_1(1-\sigma_1)}}{1-\sigma_1+\sqrt{\sigma_1(1-\sigma_1)}}. \qquad \text{(B5)}$$

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