

COMPETITION BETWEEN SEGREGATION DISTORTERS: COEXISTENCE OF “SUPERIOR” AND “INFERIOR” HAPLOTYPES AT THE *t* COMPLEX

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Abstract.—By means of population genetical models, we investigate the competition between sex-specific segregation distorters. Although the models are quite general, they are motivated by a specific example, the *t* complex of the house mouse. Some variants at this gene complex, the *t* haplotypes, distort Mendelian segregation in heterozygous males in their favor. The selective advantage at the gamete level is counterbalanced by strong negative fitness effects at the individual level (male sterility or even lethality in both sexes). A plethora of different *t* haplotypes has been found, both in the field and in the lab. Up to now, however, models have focused on the equilibrium frequency of a single *t* haplotype. In contrast, we explicitly model the competition between several *t* haplotypes. A deterministic model for a large, well-mixed population predicts a surprisingly high degree of polymorphism. Haplotypes with seemingly inferior fitness characteristics may easily coexist with “superior” haplotypes. For instance, a lethal haplotype with a low segregation ratio may stably coexist with a sterile haplotype with a high segregation ratio. Stable coexistence is even possible for haplotypes with a segregation disadvantage. A simple stochastic model shows that the same principles apply in the context of a structured metapopulation. Although counterintuitive at first sight, all our results can be explained by the fact that segregation distorters have an inherent advantage when they are rare. We conclude that fitness comparisons are not sufficient to predict the outcome of competition when selective forces are acting at different levels.

Key words.—Complementation, house mouse, mathematical model, meiotic drive, polymorphism, population genetics, *t* haplotypes.

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The *t* complex of the house mouse is a large complex of closely linked genes on chromosome 17. Variants of this gene complex, the so-called *t* haplotypes, lead to reduced viability and complete male sterility in homozygous condition. Nevertheless, *t* haplotypes reach appreciable frequencies (10%–25%) in most feral house-mouse populations (Lenington et al. 1988). This polymorphism results from the fact that the negative fitness effects of *t* haplotypes at the individual level are counterbalanced by a fitness advantage at the gamete level. In heterozygous males, Mendelian segregation is strongly distorted in favor of *t* haplotypes. In fact, segregation ratios greater than 0.95 are not uncommon.

By now, a large number of different *t* haplotypes has been found. All *t* haplotypes lead to male sterility in homozygous condition, but they vary in their effects on viability. Some haplotypes are completely viable, some have a reduced viability, whereas still others induce complete lethality in homozygous condition (Klein et al. 1984). Although a large variety of fitness effects has been described, most *t* haplotypes in feral house-mouse populations lead to embryonic lethality both in males and in females (Silver 1993).

The segregation ratio is also subject to considerable variation: segregation ratios vary from as low as 0.20 to as high as 1.00 (Bennett et al. 1983; Gummere et al. 1986; Lenington and Heisler 1991). Besides “complete” haplotypes with high segregation ratios, a large number of “partial” *t* haplotypes with much lower segregation ratios has been characterized. However, most of these haplotypes are found only under lab conditions. In the field, segregation ratios also vary, but *t* haplotypes with high segregation ratios are clearly overrepresented (Petras 1967; Bennett et al. 1983; Lenington and Heisler 1991).

The question arises why lethal *t* haplotypes can stably coexist with haplotypes that cause only male sterility, and why efficient haplotypes with a high segregation ratio prevail in natural populations. In this paper, we show that the “standard” explanations given in the literature are not fully convincing. Many researchers of the *t* complex have argued that factors such as interdeme selection (Lewontin and Dunn 1960; Lewontin 1962) or kin selection (Charlesworth 1994) are required to explain the stable persistence (and even prevalence) of lethal *t* haplotypes. The prevalence of *t* haplotypes with a high segregation ratio is explained by the seemingly obvious idea that efficient *t* haplotypes will outcompete less efficient ones. For instance, Hartl and Clark (1989, p. 192) argued that “. . . partial haplotypes are exceedingly rare in nature, because there is strong viability selection against them, and they have no meiotic advantage.” Or, in the words of Silver (1993, p. 254): “This suggests that as the *t* haplotype evolved over millions of years, new improved versions—with higher effective levels of transmission ratio—may frequently have swept through the population, eliminating all previous versions of *t*.” These arguments sound plausible, but intuition can be misleading when selection is acting at different levels.

The competition between several sex-specific segregation distorters has never been modeled explicitly (but see Hartl 1970; Liberman 1991). Here we take a first step in this direction. To keep things as simple as possible, we focus on a single autosomal distorter locus. Fitness and segregation parameters are chosen so as to reflect the *t* haplotypes. As we are mainly interested in the competition effects per se, we first consider a large, unstructured, randomly mating population. To show that the results of the model are also relevant in the context of a structured population, we then present a

simple metapopulation model in which local demes are connected by migration.

The analysis will reveal that the competition between segregation distorters has a number of surprising aspects. In particular, distorters that are superior at the gamete and individual level will only under specific circumstances outcompete apparently "inferior" distorters. Although our models are motivated by the *t* complex of the house mouse, we want to stress from the beginning that we do not intend to give a specific treatment of the *t* haplotype dynamics in the field. Rather, we want to illustrate the general principle that segregation distorters are inherently favored when they are rare.

MATERIALS AND METHODS

Segregation Distortion in a Large, Unstructured Population

In our basic model, we consider an infinite diploid population with two sexes. Generations are discrete and non-overlapping, and mating occurs at random. We focus on a single autosomal distorter locus with a wild-type allele, $+$, and two distorter alleles t_1 and t_2 . Segregation distortion takes place in heterozygous $+t_i$ males only. The segregation ratio or fraction of t_i gametes contributed by such males is denoted by σ_i . Hence, segregation is Mendelian if $\sigma_i = 1/2$. In line with empirical evidence (Lyon 1991, but see Lyon and Zenithon 1987), we assume that segregation is not distorted in compound t_1t_2 heterozygotes.

The segregation advantage of a distorter in combination with a wild-type allele is typically counterbalanced by negative fitness effects in homozygous t_it_i individuals. As is the case at the *t* complex, we assume that the fertility of males and the viability of the males and females may be impaired. The relative fertility of $++$, $+t_i$, and t_it_j males will be denoted by f_{++}^s , f_{+i}^s , and f_{ij}^s , respectively. We assume that the fertility of male individuals carrying at least one wild-type allele is maximal ($f_{++}^s = 1$, where the dot denotes any allele) and that males homozygous for a distorter allele are completely sterile ($f_{11}^s = f_{22}^s = 0$). Heterozygous t_1t_2 males may be sterile ($f_{12}^s = 0$), fully fertile ($f_{12}^s = 1$), or partially fertile ($0 < f_{12}^s < 1$). In case of the *t* complex, there is clear evidence (Lyon 1991; Johnson et al. 1995) that a certain degree of "complementation with respect to male fertility" (i.e., $f_{12}^s > 0$, whereas $f_{11}^s = f_{22}^s = 0$) does indeed occur.

The relative viability of $++$, $+t_i$, and t_it_j individuals is denoted by v_{++} , v_{+i} , and v_{ij} and is assumed to be independent of sex. Individuals that carry at least one wild-type allele are fully viable ($v_{++} = 1$), whereas homozygosity for a distorter allele may lead to a reduced viability ($0 \leq v_{ii} \leq 1$). Here we focus on two extreme types of distorters, "sterile" distorters, which are fully viable ($v_{ii} = 1$), and "lethal" distorters ($v_{ii} = 0$). At the *t* complex, lethality of homozygous individuals is caused by closely linked recessive lethals, which are often different for different *t* haplotypes (Klein et al. 1984). Hence, t_1t_2 heterozygotes for two lethal haplotypes may be fully viable ($v_{12} = 1$) if t_1 and t_2 belong to different "complementation groups." In this case (i.e., if $v_{12} > 0$ whereas $v_{11} = v_{22} = 0$), we say that there is "complementation with respect to viability."

In the context of a large, well-mixed population, it is standard practice to translate these assumptions into a system of

recurrence equations. Although empiricists mainly consider the allele frequencies in adults (e.g., Lenington et al. 1988), the selection dynamics is more easily formulated in terms of the genotype frequencies at the zygote stage (Nagyaki 1992) or in terms of allele frequencies in male and female gametes (Lessard 1989). We focus on the allele frequencies in zygotes, because at that stage the frequencies do not differ between the sexes.

The resulting selection dynamics (see Appendix) was studied by means of extensive computer simulations. For a given combination of lethal and sterile distorters, the model is fully specified by the segregation ratios σ_1 and σ_2 , and the complementation parameters v_{12} and f_{12}^s . We usually assume full complementation with respect to viability ($v_{12} = 1$), and we focus on the cases of full ($f_{12}^s = 1$), intermediate ($f_{12}^s = 0.2$), and no ($f_{12}^s = 0$) complementation with respect to male fertility. For all combinations of fitness parameters, the segregation parameters σ_1 and σ_2 were systematically varied from 0 to 1 with a step size of 0.002.

In all our simulations, the allele frequencies converged rapidly (in fewer than 100 generations, say) and irrespective of the starting conditions to an equilibrium. Without loss of generality, we therefore present only the outcome of simulations that were run for 1000 generations, and where each distorter allele had an initial frequency of 0.05.

Segregation Distortion in a Structured Metapopulation

Because house-mouse populations are generally thought to be structured into relatively small, local breeding units (e.g., Lidicker and Patton 1987), we also consider a model for a structured metapopulation. Despite extensive research efforts, the structure of feral mouse populations is still not well understood, and a large variety of potentially realistic deme-structured models is conceivable (e.g., Nunney and Baker 1993). Here we are less interested in the most realistic and complete representation of a deme-structured population. Our metapopulation model serves mainly to illustrate that the results of the deterministic model are no artifacts of the assumption of infinite population size. For this reason, we have kept the model as simple as possible.

As in the previous model, we assume that generations are discrete and nonoverlapping. A fixed number of n local demes is considered, which are connected by migration. Within each deme, there is a maximum number of N^s adult males and N^f adult females. A male is either fertile or completely sterile. The probability that a t_it_j male is fertile is given by f_{ij}^s . As before, we assume that t_1t_1 and t_2t_2 males are completely sterile ($f_{11}^s = f_{22}^s = 0$), whereas t_1t_2 males are fertile with positive probability ($f_{12}^s > 0$) if there is complementation with respect to male fertility. Each female is able to produce z zygotes, such that a total of $N^f z$ offspring can be produced in each deme. Per zygote a potential father is chosen at random from the males in the local population. No offspring is produced if the potential father is sterile. Even if the potential father is fertile, the resulting zygote may still be inviable. A t_it_j zygote is completely viable with probability v_{ij} , and not viable at all with probability $1 - v_{ij}$. Again, in case of a "sterile" distorter t_i , homozygous t_it_i individuals are always viable ($v_{ii} = 1$), whereas in case of a lethal distorter t_i , ho-

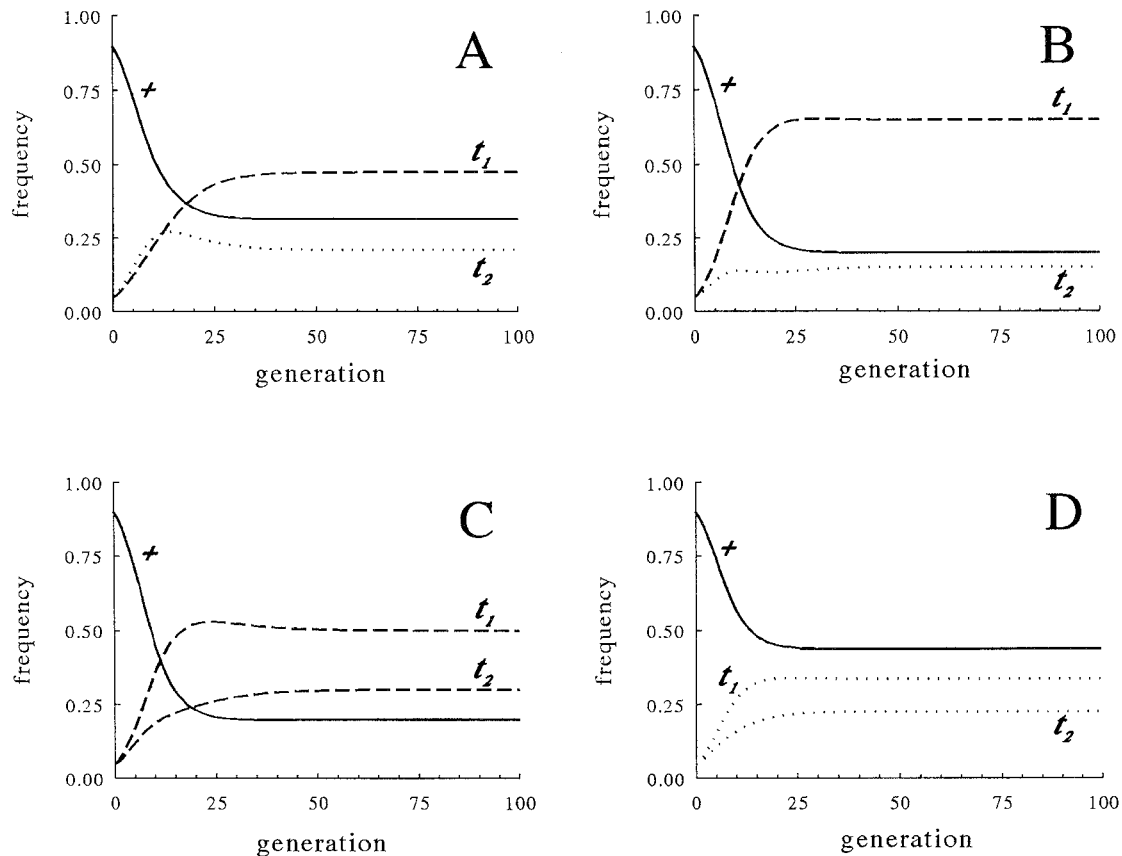


FIG. 1. Stable coexistence of two distorters. In each panel, the fate of two rare distorters after introduction into a wild-type population is shown. Wild-type alleles are indicated by solid lines, sterile distorters ($f_{ii}^s = 0$) by dashed lines, and lethal distorters ($v_{ii} = 0$) by dotted lines. In all cases, there is full complementation with respect to viability ($v_{12} = 1$), and partial complementation with respect to male fertility ($f_{12}^s = 0.2$). In (A) $\sigma_1 = 0.80$ and $\sigma_2 = 0.90$, and in (B), (C), (D) $\sigma_1 = 0.90$ and $\sigma_2 = 0.80$.

mozygous $t_1 t_1$ individuals are never viable ($v_{ii} = 0$). Individuals heterozygous for two different lethal distorter alleles t_1 and t_2 are viable with positive probability ($v_{12} > 0$) if t_1 and t_2 belong to different complementation groups.

After reproduction has taken place, all adult individuals die and are replaced by individuals from the local offspring pools for each parameter setting. The excess of offspring that does not succeed in acquiring a position in their local deme enters a pool of migrants. Some of the migrants manage to supersede resident individuals: with probability m , a resident is replaced by a randomly chosen individual from the migrant pool. Moreover, if a deme does not contain males or females at all, a male or a female is chosen at random from the migrant pool.

In all simulations, the number of demes was $n = 100$, and the migration rate was $m = 0.05$. We studied the model for the deme sizes $N = 10$ ($N^\sigma = 5$ and $N^\delta = 5$) and $N = 20$ ($N^\sigma = 10$ and $N^\delta = 10$). The number of zygotes that a female is able to produce was taken to be $z = 6$. For simplicity, we consider only the case of full complementation with respect to male fertility ($f_{12}^s = 1$). In case of $N = 10$, each deme initially contained one randomly assigned copy of each distorter allele, whereas in case of $N = 20$ each deme initially contained two copies of each distorter allele. In this way, the initial frequency of the distorters was 0.05 in all demes.

As in the deterministic model, we analyzed the effect of the

segregation ratios σ_1 and σ_2 on the ability of the wild type and the two distorter alleles to persist in the population. To this end, the segregation ratios σ_1 and σ_2 were systematically varied from 0 to 1 with a step size of 0.025. Because of the stochastic nature of the process, five replicates were considered for each parameter setting. Each replicate was run for 1000 generations, after which we classified which alleles did still persist in the metapopulation. The most frequent outcome was taken as representative for a given set of parameters.

RESULTS

Coexistence of "Superior" and "Inferior" Distorters

Let us first focus on the deterministic model for a large, unstructured population. In Figure 1, some aspects of the competition between a wild type and two distorter alleles are illustrated by means of four examples. Figure 1A shows the outcome of selection between the wild-type allele, a sterile distorter with a relatively low segregation ratio ($\sigma_{\text{sterile}} = 0.80$), and a lethal distorter with a high segregation ratio ($\sigma_{\text{lethal}} = 0.90$). The fertility of $t_1 t_2$ males is severely impaired, but not equal to 0. Such segregation and fitness parameters are not unrealistic for "partial" t haplotypes (e.g., Lyon 1991). Note that both distorters reach appreciable frequencies and coexist stably with the wild-type allele. One may be

tempted to explain the coexistence of the two distorters from the fact that the lethal distorter is superior at the gamete level (i.e., $\sigma_{\text{lethal}} > \sigma_{\text{sterile}}$) but inferior at the individual level (lethality in both sexes versus male sterility). Figure 1B shows, however, that coexistence is even possible for a distorter that is inferior both with respect to segregation and with respect to fitness ($\sigma_{\text{lethal}} = 0.80$ versus $\sigma_{\text{sterile}} = 0.90$). Moreover, stable coexistence is also possible for two distorters that differ only in their segregation ratios (Fig. 1C, two sterile distorters; Fig. 1D, two lethal distorters). Apparently, distorters that are inferior in some or all of their fitness characteristics are not always competitively excluded by superior ones.

Figure 2 shows more systematically for which segregation distorters stable coexistence is possible. Consider Figure 2A, which illustrates the outcome of competition between the wild-type allele and two sterile distorters as a function of the segregation ratios σ_1 and σ_2 . One might have expected that only the wild type persists if none of the distorters has a segregation advantage ($\sigma_1 \leq 1/2$, $\sigma_2 \leq 1/2$) and that in all other cases the distorter with the highest segregation ratio outcompetes the other one. In contrast, Figure 2A shows that there is a broad range of parameter combinations (indicated by $+t_1t_2$ and t_1t_2) for which both distorters stably coexist. Note that stable coexistence is easily achieved if the segregation ratios are close to another ($\sigma_1 \approx \sigma_2$). Interestingly, however, stable coexistence is also possible for extremely asymmetric segregation configurations (e.g., $\sigma_1 = 0.99$, $\sigma_2 = 0.01$). In fact, a high segregation ratio of one distorter facilitates the persistence of the other. Surprisingly, *any* second distorter will persist if the segregation ratio of the first distorter is high enough ($\sigma_1 > 0.95$ in Fig. 2A). Hence, a distorter with a segregation disadvantage ($\sigma_2 < 1/2$) may stably coexist with a distorter with a strong segregation advantage!

Figure 2B shows that the situation is similar in case of competition of two lethal distorters with the wild-type allele. Unlike the case of two sterile distorters, coexistence of two lethal distorters requires the presence of the wild-type allele. Again, two lethal distorters may stably coexist if their segregation ratios are similar. Here, coexistence is even more easily achieved than in the case of two sterile distorters. However, coexistence is more difficult to achieve for a highly asymmetric configuration of segregation ratios. But again, persistence of the second distorter is facilitated if the first distorter has a high segregation ratio, and a distorter with a segregation disadvantage (e.g., $\sigma_2 = 0.25$) may stably coexist with a distorter with a strong segregation advantage (e.g., $\sigma_1 = 0.99$).

The equilibrium diagram for the competition of the wild-type allele with a sterile and a lethal distorter (Fig. 2C) is similar to the previous ones. In fact, Figure 2C combines the features of Figure 2A and B. The curves that separate the regions $+t_1$ and $+t_1t_2$ are identical in Figure 2A and C. The same is true for the curves separating the regions of $+t_2$ and $+t_1t_2$ in Figure 2B and C. Apparently, the fitness consequences in homozygous condition (male sterility versus complete lethality) are not important for the ability of a second distorter to coexist with an already present first distorter.

Figure 3 shows that the allele frequencies at equilibrium depend on the parameters in a nonobvious way. For three values of σ_1 , Figures 3A, B, and C give the equilibrium

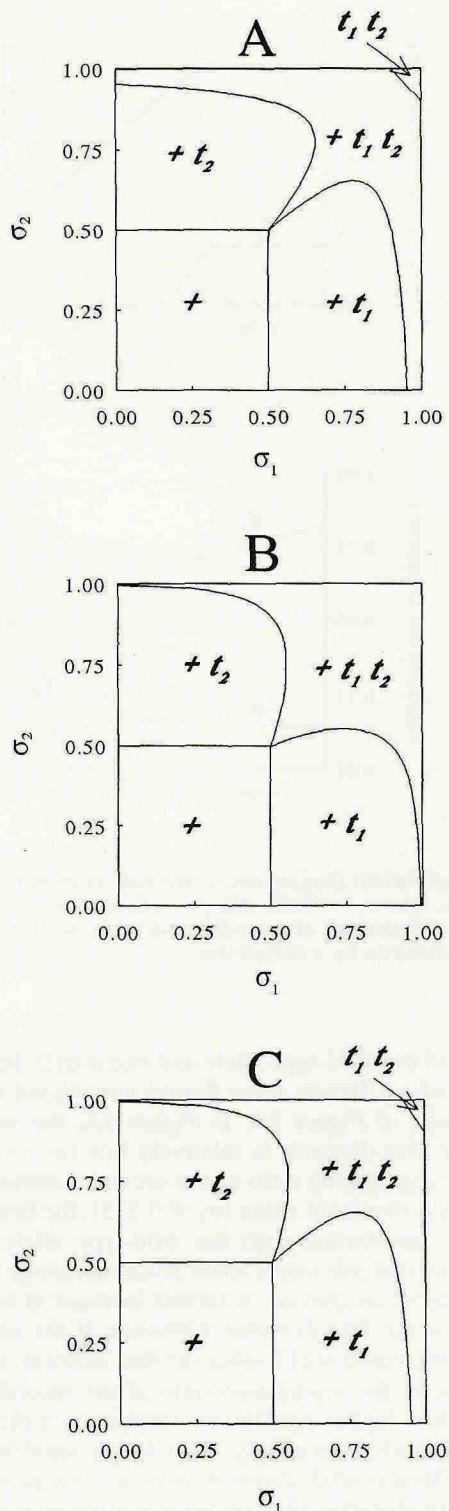


FIG. 2. Outcome of competition between wild type and two distorters as a function of the segregation ratios σ_1 and σ_2 . In all cases, we found global convergence to a stable equilibrium. Depending on the parameters, five equilibrium outcomes are possible: only the wild type survives (+), the wild type survives with only one distorter ($+t_1$ and $+t_2$), the wild type survives with both distorters ($+t_1t_2$), or both distorters survive without the wild-type allele (t_1t_2). (A) Two sterile distorters, (B) two lethal distorters, and (C) a sterile (t_1) and a lethal (t_2) distorter. Fitness parameters are as in Figure 1, that is, $v_{12} = 1$ and $f_{12}^0 = 0.2$.

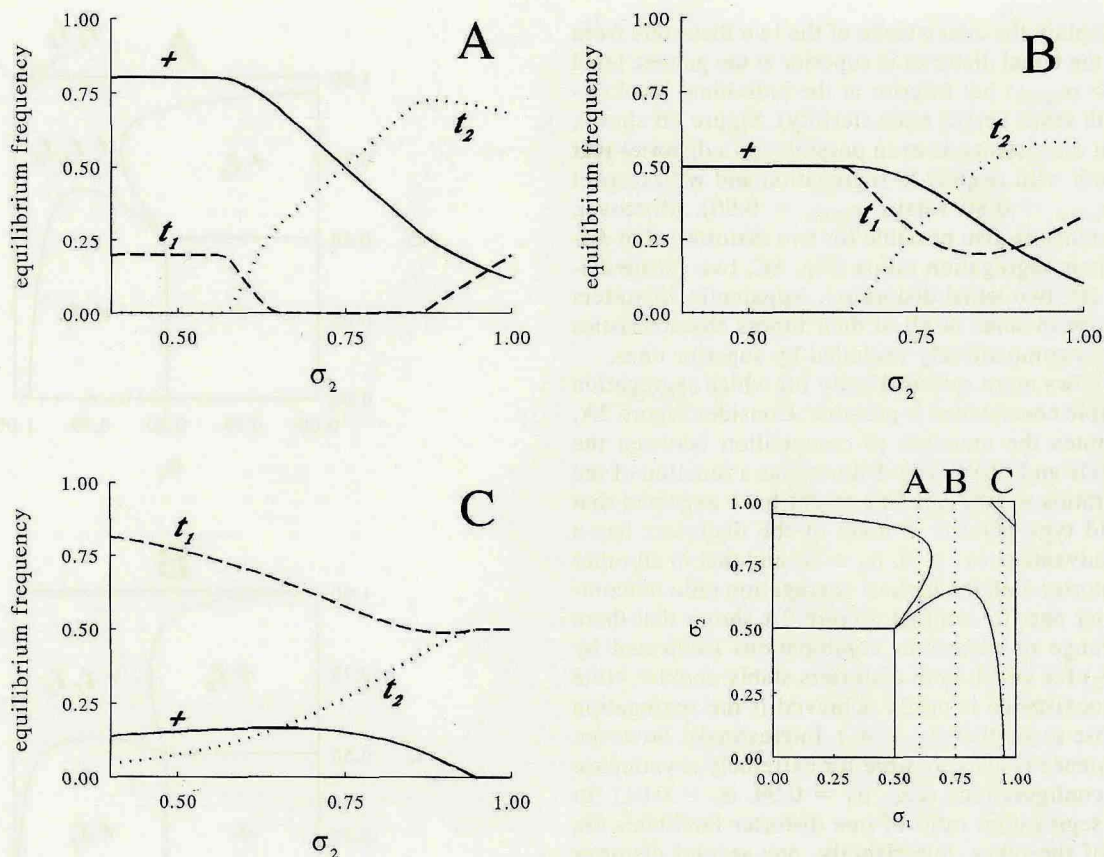


FIG. 3. Equilibrium frequencies of the wild type and two sterile distorters as a function of the segregation ratio σ_2 . σ_1 is kept fixed at three values: (A) $\sigma_1 = 0.60$, (B) $\sigma_1 = 0.75$, (C) $\sigma_1 = 0.95$, corresponding with three cross sections of Figure 2A (see inset). The equilibrium frequencies of the wild-type allele are indicated by a solid line, those of the first distorter by a dashed line, and those of the second distorter by a dotted line.

frequency of the wild-type allele and two sterile distorters as a function of σ_2 . Hence, these figures correspond with three cross sections of Figure 2A. In Figure 3A, the segregation ratio of the first distorter is relatively low ($\sigma_1 = 0.60$). As long as the segregation ratio of the second distorter is lower than a certain threshold value ($\sigma_2 < 0.575$), the first distorter reaches an equilibrium with the wild-type allele. If σ_2 is increased beyond this value, there is a small range for which both distorters can coexist. A further increase in σ_2 leads to exclusion of the first distorter. However, if the segregation ratio σ_2 is increased still further the first distorter reappears. An increase in the segregation ratio of the second distorter now leads to a higher equilibrium frequency of the first distorter and, quite surprisingly, to a lower equilibrium frequency of the second distorter. Hence, at some point it is the less efficient distorter that profits from an increase in the segregation ratio of the more efficient one.

If the segregation ratio of the first distorter is somewhat higher ($\sigma_1 = 0.75$ in Fig. 3B), the first distorter again reaches an equilibrium with the wild-type allele for low values of σ_2 . At some point ($\sigma_2 > 0.65$), however, all three alleles again coexist. Note that the second distorter needs a higher segregation ratio than in Figure 3A to be able to persist with the first distorter. If σ_2 is increased, there is again a point

beyond which it is the first distorter that profits from a further increase in σ_2 .

If σ_1 is very high ($\sigma_1 = 0.95$ in Fig. 3C), a second distorter may hike along with the first distorter, even if it has a segregation disadvantage. For high values of σ_2 , the wild-type allele reaches a very low frequency, and it may even be outcompeted by the joint action of the distorters.

Inherent Advantage of Rare Distorters

All the above results seemed counterintuitive to us at first sight, but they can be explained on the basis of the following argument. Consider a newly arising distorter t_2 that is introduced into the population in small frequency. As long as the distorter is rare, it will hardly occur in homozygous condition, and hence it will not be affected by its negative fitness effects at the individual level (homozygous sterility and lethality). If the wild-type allele (+) is prevalent in the population, the rare distorter will most often occur in $+t_2$ individuals. In these individuals, the distorter is favored if it has a segregation advantage. If, on the other hand, another distorter t_1 is already present in high frequency, the rare distorter t_2 will often be associated with t_1 . In t_1t_2 individuals, the segregation ratios of t_1 and t_2 with the wild-type allele are irrelevant. Here the prospects of t_2 mainly depend on the fitness of t_1t_2

individuals when compared with that of t_1t_1 individuals. Thus, t_2 will be favored with respect to t_1 as soon as some complementation does occur.

As a consequence, rare distorters have a systematic advantage. On the one hand, they do not (yet) experience the negative fitness effects that they induce in homozygous condition. On the other hand, they are favored in heterozygotes because of (1) their segregation advantage in combination with the wild-type allele, and (2) the occurrence of complementation in combination with another distorter. In view of this inherent rareness advantage, it is conceivable that a large variety of newly arising distorters is able to spread, irrespective of the population composition. Accordingly, a high degree of polymorphism is to be expected.

Complementation as a Prerequisite for Coexistence

Let us now investigate more systematically the importance of complementation for the ability of different distorter alleles to coexist. In Figures 1 to 3, we assumed that there was full complementation with respect to viability ($v_{12} = 1$) and partial complementation with respect to male fertility ($f_{12}^s = 0.2$). Figure 4 illustrates the outcome of competition in the absence of complementation with respect to male fertility ($f_{12}^s = 0$). In case of sterile distorters (Fig. 4A), the distorter with the highest segregation ratio now always competitively excludes the other one. Hence, in this case the results coincide with our original expectation that the most efficient distorters should outcompete all other ones. In contrast, two lethal distorters are still able to persist (Fig. 4B). Note, however, that coexistence is more difficult to achieve than in Figure 2B. In particular, persistence of distorters with a segregation disadvantage is not possible any more. Figure 4C shows the outcome of competition between a sterile and a lethal distorter. As in Figure 2, this figure combines features of the competition between two sterile and two lethal distorters. Here coexistence is possible only if the lethal distorter has a segregation advantage over the sterile distorter.

The quantitative effect of complementation with respect to male fertility (f_{12}^s) is illustrated by Figure 5. This figure shows the outcome of competition as a function of f_{12}^s and σ_2 . The segregation ratio of the first distorter is kept fixed at $\sigma_1 = 0.80$. The figure clearly shows that complementation facilitates the coexistence of two distorters. Note that if the degree of complementation is low, a relatively high segregation ratio σ_2 is needed for two sterile distorters to coexist (Fig. 5A), whereas for two lethal distorters coexistence is achieved more easily (Fig. 5B). In contrast, the situation is reversed if the degree of complementation is high: two sterile distorters may coexist for almost all values of σ_2 , whereas for two lethal distorters coexistence is not possible if σ_2 is too small.

If there is no complementation with respect to viability, that is, if we consider lethal distorters belonging to the same "complementation group" ($v_{12} = 0$), the picture is identical to Figure 4A. Hence, lethal distorters that do not complement each other with respect to viability cannot coexist, and the distorter with the highest segregation ratio outcompetes all other ones. We conclude that complementation is a potent force enhancing the coexistence of segregation distorters and

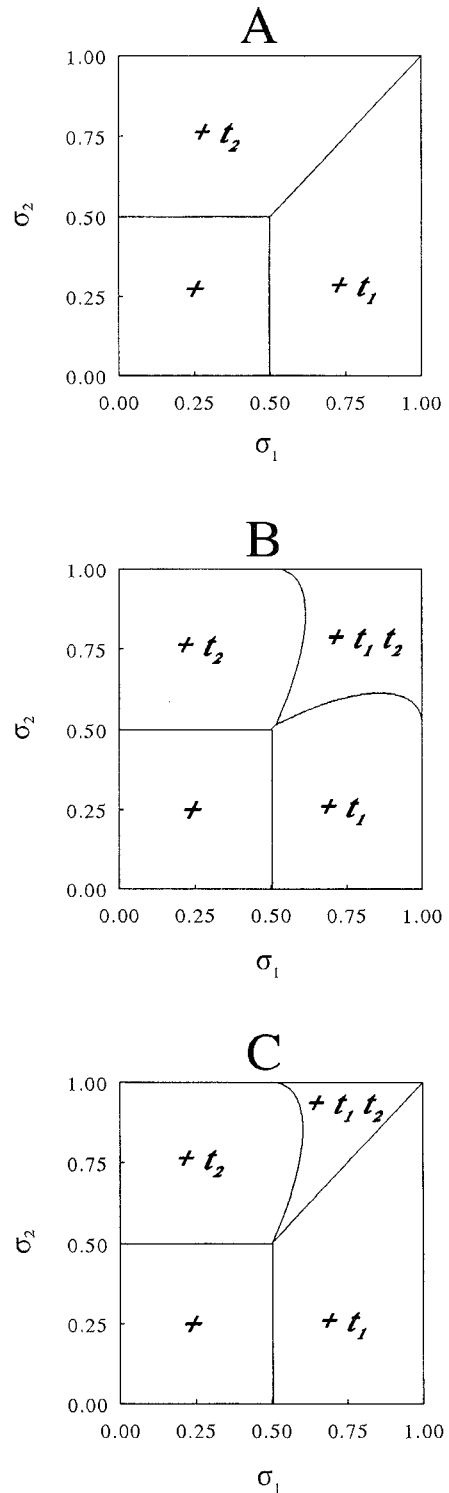


FIG. 4. Outcome of competition between wild type and two distorters in the absence of complementation with respect to male fertility ($f_{12}^s = 0$). In case of two sterile distorters, (A) the distorter with the highest segregation ratio competitively excludes the other. In contrast, stable coexistence is possible in case of two lethal distorters (B), or in case of a sterile (t_1) and a lethal (t_2) distorter (C).

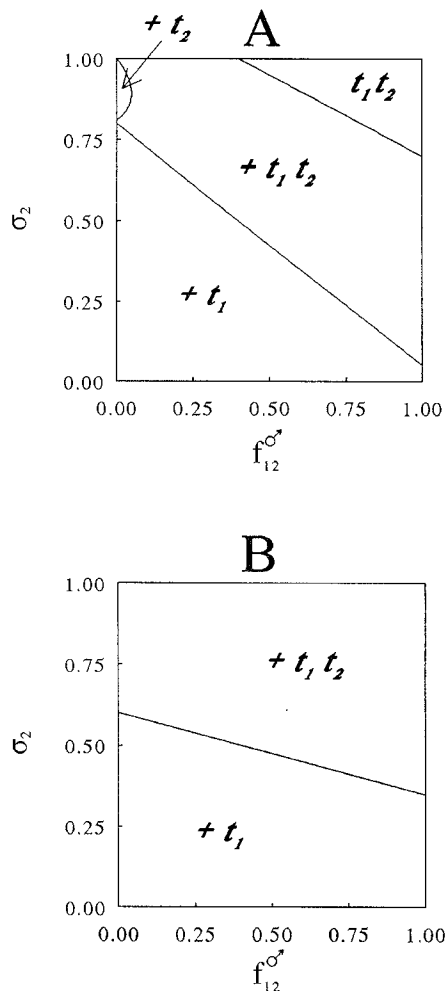


FIG. 5. Coexistence as function of complementation with respect to male fertility (f_{12}^{σ}). (A) two sterile distorters, and (B) two lethal distorters. The segregation ratio of the second distorter varies, while that of the first distorter is kept fixed at $\sigma_1 = 0.80$. Note that for low degrees of complementation (f_{12}^{σ} small), coexistence is more easily achieved for two lethal distorters, whereas for high degrees of complementation coexistence is more easily achieved for two sterile ones.

that coexistence of two distorters is only precluded if there is no complementation at all.

Trade-off between Segregation Distortion and Male Fertility

Up to now, we assumed that segregation distortion and complementation with respect to male fertility are independent of one another. For t haplotypes, however, this is not the case. Segregation distortion at the t complex results from the action of several distorter genes on a responder locus. The distorters have a harmful effect on the wild-type form of the responder, whereas the t form of the responder provides at least a partial protection against the action of the distorter alleles. This protection breaks down when the number of distorter alleles is too high. As a consequence, fertility may be impaired if a male happens to be homozygous at one or several of the distorter loci (Lyon 1991; Johnson et al. 1995). Therefore, a complete t haplotype with distorter alleles at all

distorter loci usually has a high segregation ratio, but at the same time it will very likely induce male sterility in combination with another haplotype. Partial haplotypes that carry distorters alleles at only one or two distorter loci may not have such a high segregation ratio in combination with the wild type, but they are more likely to be fertile when coupled to another haplotype.

The details of the interaction between segregation distortion and male fertility are not yet well understood. Let us therefore consider a simple model for the trade-off between segregation distortion and male fertility. We assume that the fertility f_{12}^{σ} of a $t_1 t_2$ male is negatively related to the segregation ratios σ_1 and σ_2 and that the effect of segregation distortion on fertility is represented by a function $\phi(\sigma)$. For simplicity, we assume that fertility is affected only by positive distorters (i.e., distorters with $\sigma_i > 1/2$) and that the reduction in fertility by such a distorter is linearly related to the segregation ratio σ_i :

$$\phi(\sigma_i) = \begin{cases} 0 & \text{if } \sigma_i \leq \frac{1}{2} \\ 2\sigma_i - 1 & \text{if } \sigma_i > \frac{1}{2} \end{cases} \quad (1)$$

We consider two different assumptions on the interaction of two distorters t_1 and t_2 :

$$f_{12}^{\sigma} = [1 - \phi(\sigma_1)][1 - \phi(\sigma_2)], \quad (2)$$

and

$$f_{12}^{\sigma} = 1 - \phi(\sigma_1)\phi(\sigma_2). \quad (3)$$

The resulting models will be called the “multiplicative fertility model” (2) and the “epistatic fertility model” (3), respectively. In (2), the two distorters have a separate, “multiplicative” effect on fertility, whereas model (3) assumes an “epistatic” interaction because male fertility is only reduced if *both* distorters have a tendency to impair fertility [i.e., $\phi(\sigma_1) > 0$ and $\phi(\sigma_2) > 0$]. The outcome of competition may differ between the two models, because complementation with respect to fertility is always lower in the multiplicative model than in the epistatic model.

The simulation results are presented in Figure 6. As in the previous sections, a distorter that is inferior with respect to its segregation ratio may well coexist with a superior distorter. However, in case of the multiplicative model (Fig. 6A), persistence of distorters with a segregation disadvantage ($\sigma_i < 1/2$) is not possible anymore. In contrast, in case of the epistatic model coexistence is possible for a broad range of parameters.

Let us stress once more that the models considered here are rather ad hoc. In fact, the mechanisms of fertility impairment are not known well enough to give an accurate description for the trade-off between segregation distortion and male fertility at the t complex. Nevertheless, our simple models illustrate that the outcome of competition may strongly depend on the details of the interaction between selection at the gamete level, and selection at the individual level. As shown here, the existence of a trade-off between the two levels does not per se eliminate the possibility that “inferior” distorters may stably persist. This implies that the claim that

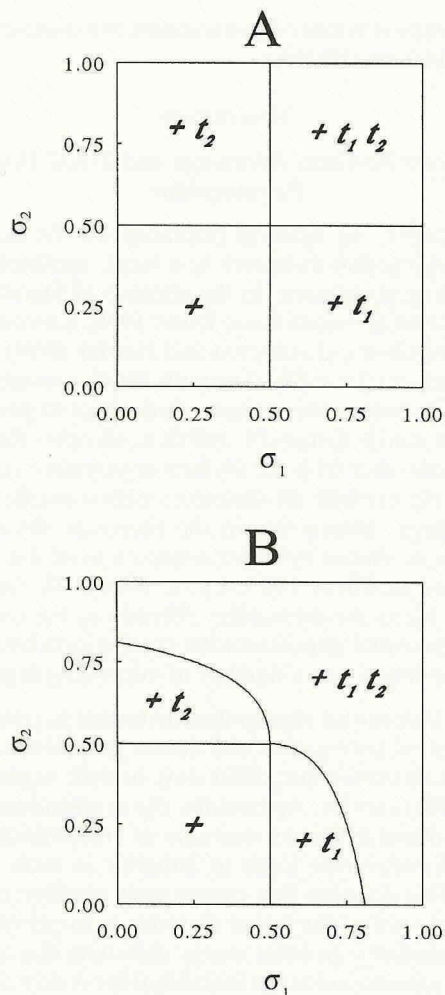


FIG. 6. Outcome of competition between sterile distorters when there is a trade-off between male fertility (f_{12}^s) and the segregation ratios σ_1 and σ_2 . (A) Multiplicative fertility model, and (B) epistatic fertility model. Note that the outcome of competition may crucially depend on the details of the trade-off between segregation distortion and male fertility.

less efficient partial t haplotypes will be competitively excluded by complete haplotypes (e.g., Hartl and Clark 1989) is premature. The reduced ability of partial t haplotypes to distort Mendelian segregation will typically be compensated by an increased ability to complement other t haplotypes. Whether in practice such compensation is strong enough to make stable coexistence of segregation distorters possible is still an open question.

Competition between Segregation Distorters in a Structured Metapopulation

Up to now, we have considered a deterministic model for a large, unstructured population. One might therefore question the relevance of our results for the t complex, because house-mouse populations are thought to be structured into small, relatively isolated breeding units. To investigate whether stable coexistence of "inferior" and "superior" distorter alleles is still possible in a structured population, we

used our simple metapopulation model to classify the outcome of competition between two segregation distorters as a function of their segregation ratios.

Figure 7 shows that our earlier conclusions extend to the metapopulation context. For instance, a sterile distorter with a high segregation ratio does not necessarily outcompete a lethal distorter with a much lower segregation ratio. Conversely, a sterile distorter with a low segregation ratio may persist in the presence of a lethal distorter with a high segregation ratio. Moreover, the persistence of negative distorters (i.e., $\sigma < 1/2$) is not only feasible in an infinite population, but also in a deme-structured population.

It is, however, also clear from Figure 7 that the persistence of a single distorter as well as the coexistence of two distorters is more difficult to achieve in the context of a metapopulation. In particular, the persistence of a single weak distorter (i.e., σ only slightly larger than $1/2$) or the coexistence of a very inefficient distorter ($\sigma \approx 0$) with a highly efficient one is now ruled out. It is easy to conceive why such weak distorters have difficulties to persist in a structured population. In fact, the frequency of a weak distorter will typically be low in all demes where it is present. In small demes, any allele may be lost due to random genetic drift, but the risk of getting lost is much higher for alleles that systematically occur in low frequency (e.g., Robertson 1962). Therefore, a distorter allele can only persist for appreciable amounts of time if its segregation ratio and, hence, its typical frequency is not too low. Figure 7 shows that the minimal segregation ratio allowing persistence of a single distorter allele is closely related to deme size and, accordingly, to the relative importance of genetic drift ($\sigma > 1/2$ if $N = \infty$; $\sigma > 0.65$, say, if $N = 20$; and $\sigma > 0.75$, say, if $N = 10$).

Not only weak distorters, but also highly efficient distorters may have difficulties to persist in a metapopulation. Figure 7C illustrates that a very efficient sterile distorter ($\sigma > 0.9375$) cannot coexist with the wild type if deme size is too small. Within single demes, an efficient distorter fares quite well, because it has the tendency to reach a high frequency. However, the productivity of demes with a high distorter frequency is substantially impaired. As a consequence, such demes will, on average, contribute less than other demes to the migrant pool. Moreover, deme extinction becomes a real possibility if most males are sterile and/or too many inviable offspring are produced. At the metapopulation level, the frequency of a highly efficient distorter may therefore decrease due to a higher local extinction rate and a lower colonization rate. In extreme cases, such efficient distorters may even get lost from the metapopulation.

Summarizing, Figure 7 demonstrates that the coexistence of a lethal and a sterile distorter under a relatively broad range of segregation ratios is not an artifact of our earlier deterministic model. Similarly, the coexistence of two lethal or two sterile distorters is also easily achieved in a metapopulation context (results not shown). Admittedly, our metapopulation model is overly simplistic, and a more thorough, systematic study is required to investigate how population structure affects the competitive abilities of different distorter alleles (van Boven and Weissing, unpubl. manuscript). We are confident, however, that our argument of an inherent rare-

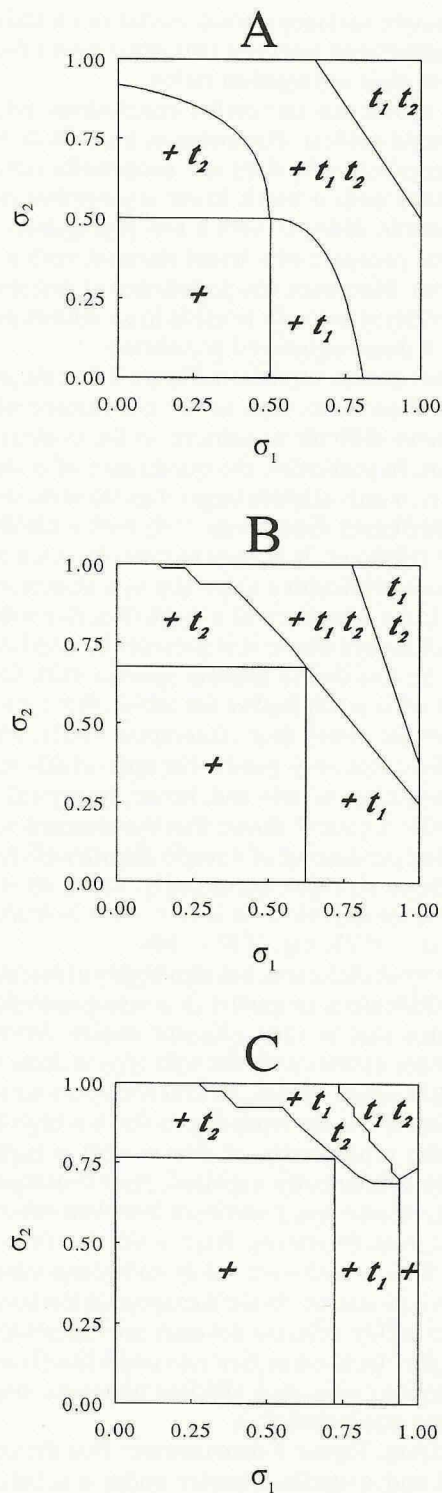


FIG. 7. Outcome of competition between wildtype, a sterile (t_1) and a lethal (t_2) distorter after 1000 generations. (A) Deterministic model for an unstructured population, (B) stochastic model with deme size $N = 20$, and (C) stochastic model with deme size $N = 10$. In (B) and (C), $n = 100$ demes are considered, and the migration rate is $m = 0.05$. In all panels, there is full complementation with respect to male fertility ($f_{12}^c = 1$).

ness advantage is rather robust and does not depend on details of the population structure.

DISCUSSION

Inherent Rareness Advantage and Trend Toward Polymorphism

In this paper, we focused primarily on the competition between segregation distorters in a large, unstructured, randomly mating population. In the absence of factors as inter-deme selection (Lewontin and Dunn 1960; Lewontin 1962), female mate choice (Lenington and Heisler 1991), or reproductive compensation (Charlesworth 1994), one might expect that lethal distorters should have difficulties to persist in the presence of sterile distorters, and that, all other things being equal, the distorter with the highest segregation ratio should competitively exclude all distorters with a smaller segregation advantage. Statements in the literature show that this expectation is shared by many researchers of the t complex (see reviews in Silver 1985; Lyttle 1991). We have shown that such claims are premature. Already in the context of a large, unstructured population the competition between segregation distorters has a number of surprising aspects:

- (1) Coexistence of segregation distorters is possible for a broad range of segregation and fitness parameters.
- (2) Two distorters that differ only in their segregation ratios will often coexist. Apparently, the segregation ratios per se are not decisive for the outcome of competition.
- (3) A distorter that leads to lethality in both sexes can coexist with a distorter that causes male sterility, even if the segregation ratio of the lethal distorter is lower than that of the sterile distorter. In other words, distorters that are inferior both at the gamete and at the individual level may well persist in a population.
- (4) A distorter with a segregation disadvantage ($\sigma < 1/2$) can sometimes stably persist in a population. Actually, the most efficient distorters pave the way for the persistence of the least efficient ones.

These phenomena do not only occur in a large, unstructured population. They can also be observed in the context of a deme-structured metapopulation.

Our results can easily be understood if one realizes that the adverse fitness effects of a distorter at the individual level (lethality or male sterility) are restricted to homozygous individuals. As long as a distorter is rare, it will almost exclusively occur in heterozygous condition. In heterozygotes, segregation distorters are systematically favored. As a result, most newly arising distorters will increase in frequency. This verbal argument is not only plausible, but it can be validated analytically (Weissing and van Boven, unpubl. manuscript).

As a result of the inherent advantage of rare distorter alleles, a high degree of polymorphism is to be expected. It is indeed easy to construct examples in which large numbers of distorters coexist (results not shown). However, the stable coexistence of distorters is possible only if the fitness (viability times fertility) of heterozygotes carrying two different distorter alleles is not too low. All the results mentioned above require at least a minimal amount of complementation ($v_{12} > 0$ and/or $f_{12}^c > 0$). Therefore, the number of coexisting

distorters will be limited by the number of complementation groups.

Although coexistence of several distorter alleles is also easily achieved in a metapopulation, the potential for polymorphism is lower due to the loss of alleles by genetic drift. The risk of getting lost from a small deme is highest for those alleles that systematically attain low frequencies. Such a rareness disadvantage applies to weak distorters, and it may compensate for their inherent rareness advantage. As a consequence, a higher segregation advantage is required in a structured population to offset a severe fitness disadvantage as male sterility or lethality.

Empirical Relevance

This paper mainly has a conceptual purpose. However, the attributes of the distorters considered here reflect those of the *t* haplotypes. For instance, we typically assumed that there was some complementation in individuals heterozygous for two distorter alleles. The occurrence of complementation, for viability as well as for male fertility, is well documented at the *t* complex of the house mouse. As a matter of fact, until recently *t* haplotypes could be classified only as being different if they belonged to different complementation groups. No fewer than 16 complementation groups for viability have been described (Klein et al. 1984). Complementation with respect to male fertility is also amply documented (e.g., Lyon 1991; Johnson et al. 1995). Although complete *t* haplotypes do not show complementation for male fertility, many partial *t* haplotypes do. In fact, some combinations of partial haplotypes do not seem to impair male fertility at all (e.g., t^{h49} and t^{h6} , Lyon 1991).

Although the characteristics of the distorters considered here appear to be quite realistic, our model is certainly too simplistic to really represent the dynamics of *t* haplotypes in the field. Other factors such as inbreeding (Petras 1967), interdeme selection (Lewontin 1962; Nunney and Baker 1993), reproductive compensation (Charlesworth 1994), heterozygote disadvantage (Johnston and Brown 1969), or behavioral reduction in the transmission of *t* haplotypes (Lenington and Heisler 1991) may also play an important role. In particular, there is a striking difference between the equilibrium frequencies predicted by our deterministic model (Fig. 1 and 3), and the much lower frequencies of *t* haplotypes in the field (Lenington et al. 1988; Ruvinsky et al. 1991). This is a general problem shared by most deterministic models of segregation distortion. Our stochastic model produces more realistic distorter frequencies (data not shown), but it is difficult to relate the parameters of this model to the features of specific house-mouse populations. Irrespective of the exact distorter frequencies, however, our argument of an inherent rareness advantage appears to be quite robust, and we expect it to apply not only to model systems, but also to natural populations.

Our study was motivated by the question which factors account for the distribution of *t* haplotypes in the field. In view of our results, it is no surprise that there is variation in the segregation ratios of *t* haplotypes. Moreover, the stable coexistence of lethal and sterile *t* haplotypes is easily explained by our model. In fact, factors as interdeme selection

are not required to explain this phenomenon. On the other hand, population structure seems to be essential to explain why lethal *t* haplotypes are prevalent, and why segregation distorters with low segregation ratios are hardly ever found.

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APPENDIX

Here we present an elementary derivation of the dynamics of our deterministic model. A more general derivation is given elsewhere (Weissing and van Boven, unpubl. manuscript). The model dynamics is characterized by recurrence equations for the (ordered) genotype frequencies P_{ij} at the zygote stage. Let P_{ii} denote the relative frequency of homozygous $t_i t_i$ zygotes, whereas $2P_{ij}$ denotes the relative frequency of heterozygous $t_i t_j$ zygotes ($i \neq j$). For notational convenience, the wild-type allele is denoted by t_0 (such that, for instance, P_{00} represents the relative frequency of zygotes homozygous for the wild-type allele). We assume an infinite population, discrete nonoverlapping generations, and random mating. As viability selection is not sex specific in our model, the genotype frequencies after viability selection, \tilde{P}_{ij} , are the same in males and females, and are given by (e.g., Nagylaki 1992)

$$\tilde{P}_{ij} = P_{ij} \frac{v_{ij}}{\bar{v}}. \quad (\text{A1})$$

Here v_{ij} is the viability of $t_i t_j$ individuals, and $\bar{v} = \sum_{ij} P_{ij} v_{ij}$ represents the mean viability of the population.

There is no segregation distortion or fertility selection in females. Therefore, the frequency q_i of allele t_i in female gametes is given by

$$q_i = \sum_j \tilde{P}_{ij}. \quad (\text{A2})$$

In contrast, the frequency p_i of t_i in male gametes is affected by fertility selection and segregation distortion. Let f_{ij}^s denote the fertility of $t_i t_j$ males, and let s_{ij}^s denote the fraction of t_i gametes contributed by a male of genotype $t_i t_j$. Then p_i is of the form

$$p_i = \sum_j \tilde{P}_{ij} \frac{s_{ij}^s f_{ij}^s}{\bar{s}^s \bar{f}^s} \quad (\text{A3})$$

where $\bar{f}^s = \sum_{i,j} \tilde{P}_{ij} f_{ij}^s$ and $\bar{s}^s = 1/2$ represent the mean male fertility and the mean segregation ratio. The segregation ratios s_{ij}^s of our model correspond to the parameters σ_i in the following manner

$$s_{ij}^s = \begin{cases} \sigma_i & \text{if } i \neq 0 \text{ and } j = 0 \\ 1 - \sigma_j & \text{if } i = 0 \text{ and } j \neq 0 \\ 1/2 & \text{otherwise.} \end{cases} \quad (\text{A4})$$

In other words, $t_0 t_i$ males (i.e., males heterozygous for a wild type and a distorter allele) segregate t_i and t_0 in the ratio $\sigma_i : 1 - \sigma_i$ and segregation is Mendelian in all other cases.

Finally, because we assumed random mating (which is in our case equivalent to random union of gametes; Nagylaki 1992), the genotype frequencies in the zygotes of the new generation are given by

$$P_{ij} = 1/2 (p_i q_j + q_i p_j). \quad (\text{A5})$$

This completes the model.