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EVOLUTION AT THE MOUSE *t* COMPLEX: WHY IS THE *t* HAPLOTYPE PRESERVED AS AN INTEGRAL UNIT?

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Abstract.—Segregation distorters are selfish genetic elements that bias Mendelian segregation in their favor. All well-known segregation distortion systems consist of one or more ''distorter'' loci that act upon a ''responder'' locus. At the *t* complex of the house mouse, segregation distortion is brought about by the harmful effect of *t* alleles at a number of distorter loci on the wild-type variant of the responder locus. The responder and distorter alleles are closely linked by a number of inversions, thus forming a coherent *t* haplotype. It has been conjectured that the close integration of the various components into a ''complete'' *t* haplotype has been crucial for the evolutionary success of these selfish genetic elements. By means of a population genetical metapopulation model, we show that this intuition may be unfounded. In fact, under most circumstances an ''insensitive'' *t* haplotype retaining only the responder did invade and reach a high frequency, despite the fact that this haplotype has a strong segregation disadvantage. For certain population structures, the complete *t* haplotype was even competitively excluded by partial *t* haplotypes with lower segregation ratios. Moreover, *t* haplotypes carrying one or more recessive lethals only prevailed over their nonlethal counterparts if the product of local population size and migration rate (*Nm*) was not much smaller or larger than one. These phenomena occurred for rather realistic fitness, segregation, and recombination values. It is therefore quite puzzling that partial *t* haplotypes are absent from natural house mousepopulations, and that *t* haplotypes carrying recessive lethals prevail over nonlethal *t* haplotypes.

Key words.—Distorter, meiotic drive, metapopulation model, responder, segregation distortion, Tcd, Tcr.

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The evolution of segregation distortion is governed by selection at different levels. At the gamete level, segregation distorters manage to obtain a strong segregation advantage in combination with the wild type. At the individual level, these selfish elements induce severe negative fitness effects, such as sterility or lethality. The opposing forces of gamete and individual selection typically lead to a stable polymorphism of the wild-type and distorter allele.

The *t* complex of the house mouse is one of the best studied examples of segregation distortion. The so-called *t* haplotypes are variants of the proximal third of chromosome 17 that are present in most natural house mouse populations (Lenington et al. 1988; Ruvinsky et al. 1991; Ardlie and Silver 1996a; Ardlie 1998). Males heterozygous for a *t* haplotype and the wild-type form of the *t* complex typically produce more than 90% *t*-bearing functional gametes. On the other hand, homozygosity for the *t* haplotype leads to male sterility, and often even to embryonic lethality in both sexes.

Mechanistically, segregation distortion results from the interaction of a number of distorter genes with a responder locus (Lyon 1984, 1986, 1991; Herrmann et al. 1999; see Fig. 1). The distorter alleles at the distorter loci have a harmful effect on the wild-type form of the responder, whereas the *t* form of the responder provides some protection against the action of the distorter alleles. This protection, however, breaks down when the number of distorter alleles is too high, and the fitness of individuals that carry too many distorter alleles is severely impaired. In particular, males that are heterozygous for the wild-type form of the *t* complex and a ''complete'' *t* haplotype with *t* alleles at all loci invariably have a high segregation ratio, but at the same time homozygosity of the complete *t* haplotype induces unconditional male sterility.

In a short time perspective, the complete *t* haplotype is kept together as an integral unit due to recombination suppression by a number of inversions (Artzt et al. 1982; Herrmann et al. 1986; Hammer et al. 1989; see Fig. 1). However, rare recombination events between the complete *t* haplotype and the wild type do occur once in every 200 to 1000 offspring (e.g., Bennett et al. 1976; Sarvetnick et al. 1986). The ''partial'' *t* haplotypes that are so generated retain a subset of the characteristics of the complete *t* haplotype (e.g., Lyon 1991). In the laboratory, more than a dozen genetically different partial *t* haplotypes have been constructed. In the field, however, partial *t* haplotypes seem to be virtually absent (e.g., Silver 1993; Ardlie 1998; Ardlie and Silver 1998).

It is not obvious why the complete *t* haplotype is preserved as an integral unit on a longer, evolutionary time scale. Until now, this question has never seriously been scrutinized. It has been conjectured that partial *t* haplotypes cannot persist in natural populations because they lose some or even all of their distorting ability (e.g., Hartl and Clark 1989, p. 192; Silver 1993; Forejt 1996). This is not obvious, however, for two reasons. First, a reduction in distortion efficiency is typically accompanied by an increase in fitness at the individual level. Second, even if two distorters differ only in their segregation ratios, the less efficient distorter is often not outcompeted by the more efficient one (van Boven and Weissing 1996, 1998; van Boven et al. 1996; van Boven 1997).

Furthermore, most *t* haplotypes in natural house mouse populations carry one or more recessive lethals (e.g., Klein et al. 1984; Ardlie and Silver 1998). The ubiquity of these lethals has led to the suggestion that they may be favored by kin selection through reproductive compensation (Charlesworth 1994) or by group selection (Lewontin 1962; Silver

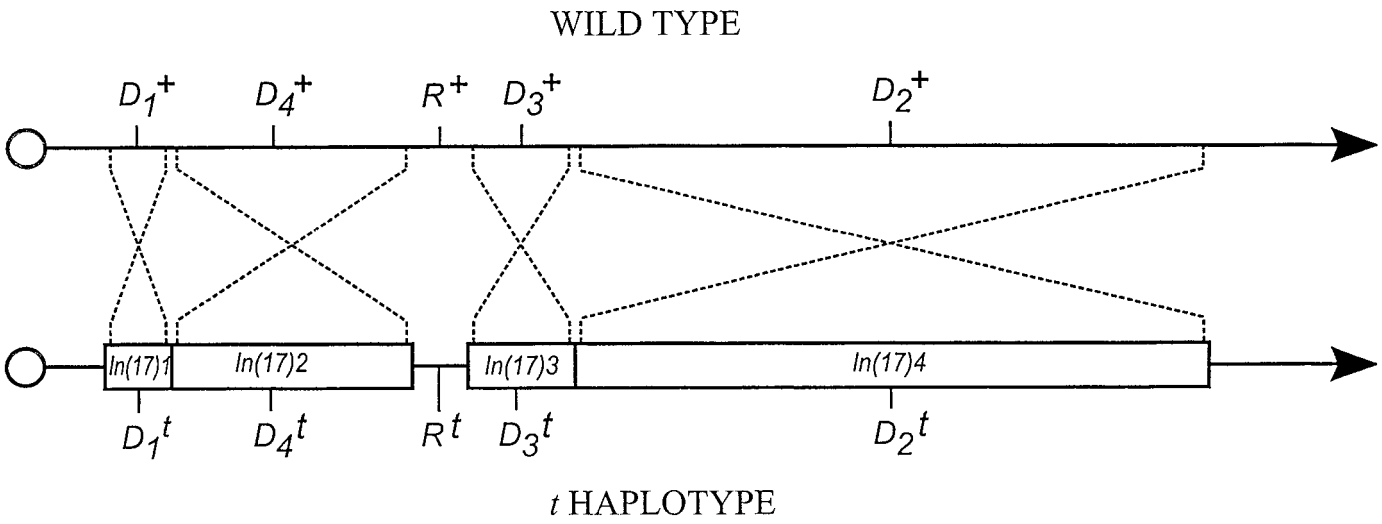

FIG. 1. Schematic structure of the *t* complex (after Silver 1993). Segregation distortion results from the action of the distorter alleles D^t_1, D^t_2, D^t_3 and D^t_4 on the wild-type form of the responder, R^+. In homozygous condition, the distorter alleles impair male fertility. Recombination between the complete *t* haplotype and the wild-type form of the *t* complex is suppressed by four inversions. See text for details.

1993; van Boven and Weissing 1999). It is, however, not at all clear whether the number of recessive lethal loci at the *t* complex is unusually high (Lyon 1986, p. 362), although the frequency of the lethal alleles is much too high to be explained purely on the basis of mutation-selection balance.

In this paper we investigate why the complete *t* haplotype has in the course of evolution not been decomposed into its components and why most naturally occurring *t* haplotypes carry recessive lethals. We tackle these questions by means of a population genetical model that takes the details of the genetic structure of the *t* complex into account. Fitness, segregation, and recombination values are based on estimates from empirical studies. Because house mouse populations are generally thought to be structured into small and relatively isolated breeding units (e.g., Lidicker and Patton 1987), we will throughout assume that the population is structured into a large number of demes with limited migration between the demes. To see how the results depend on population structure, we systematically vary deme size and migration rate. In this manner, we are able to analyze how the genetic structure of the *t* complex is molded by population structure.

Although we did our best to properly represent current knowledge of the *t* complex, the model predictions are strikingly different from what is found in nature. Whereas partial *t* haplotypes are regularly observed in the lab, natural house mouse populations seem to harbor only two types: the wild type and the complete *t* haplotype. In contrast, our analysis suggests that such a population composition consisting of wild type and complete *t* haplotype only is inherently unstable for almost all parameter combinations: In a highly structured population no *t* haplotype is able to persist, whereas in less structured populations a partial *t* haplotype, the ''insensitive'' *t* haplotype, is expected to invade. Furthermore, the complete *t* haplotype may even be outcompeted by less efficient partial *t* haplotypes that lack *t* alleles at one or more of their distorter loci. These results hold for ''nonlethal'' *t* haplotypes that induce male sterility in homozygous condition as well as for ''lethal'' *t* haplotypes that lead to embryonic lethality in both sexes when homozygous. The model predictions seem to be rather robust, because various versions of the model lead to virtually identical conclusions. Apparently, some of the established facts concerning population structure of house mouse populations, transmission and fitness consequences of the *t* haplotypes, or the genetic structure of the *t* complex will have to be re-evaluated.

THE MODEL

All well-known segregation distortion systems consist of a number of distorter loci that act upon a responder locus (Lyon 1991; Lyttle 1991). Inspired by the *t* complex, we consider a responder locus R with a wild-type allele R^+ and a *t* allele R^t, and four distorter loci D_1 D_2, D_3, and D_4, with wild-type alleles D^+_1, D^+_2, D^+_3, D^+_4 and *t* alleles D^t_1, D^t_2, D^t_3, D^t_4. The loci are ordered as at the *t* complex (see Fig. 1). D_1 is the most proximaldistorter and D_2 is the most distal distorter, and the responder is located between D_4 and D_3.

The *t* complex is defined by a number of inversions In(17)1–In(17)4. In line with empirical evidence we assume that the distorter alleles D^t_1, D^t_2, D^t_3 and D^t_4 are always located on $In(17)1^t$, $In(17)4^t$, $In(17)3^t$, and $In(17)2^t$, whereas the wild-type alleles D^+_1, D^+_2, D^+_3, and D^+_4 are always located on $In(17)1^+$ $In(17)4^+$, $In(17)3^+$, and $In(17)2^+$, respectively (see Fig. 1). In other words, the distorter alleles never occur on the wild-type variants of the inversions, and the wild-type alleles never occur on the distorter variants of the inversions.

Evidence for the existence of the distorters D_1, D_2, and D_3, and their effectiveness on transmission ratio distortion is undisputed. This is not (yet) the case for the distorter D_4 (Silver and Remis 1987; but see Lyon 1990). In addition, there is some evidence for a fifth distorter locus located on In(17)2 (Silver 1989; Silver and Buck 1993).

Formally, a complete *t* haplotype with all inversions and *t* alleles and recessive lethals on $In(17)1^t$ and $In(17)2^t$ should

TABLE 1. Transmission ratios of males heterozygous for the responder (R). Data are after Lyon (1991). The inversion In(17)2 with the putative distorter D_4 is omitted because it is assumed to have no effect on the level of segregation distortion. Numbers in parentheses represent educated guesses.

Number of distorter alleles	Genotype	Transmission ratio of R^t
No distorter	$+R++/++++$	0.20
One distorter	$+RD_3+/++++$	(0.30)
	$D_1R++/++++$	0.40
	$+R+D_2/++++$	0.50
Two distorters	$D_1RD_3+/++++$	0.50
	$+RD_3D_2/++++$	0.60
	$D_1R+D_2/++++$	0.90
Three distorters	$D_1RD_3D_2/++++$	0.99
One distorter homozygous	$+RD_3+/++D_3+$	(0.90)

TABLE 2. Fertility of males carrying one or more distorter alleles. Data are after Lyon (1991). The inversion In(17)2 with the putative distorter D_4 is omitted because it is assumed to have no effect on male fertility. Numbers in parentheses represent educated guesses.

Number of distorter alleles	Genotype	Male fertility
No distorter homozygous	$D_1RD_3D_2/++++$	1.0
One distorter homozygous	$+RD_3+/++D_3+$	(0.9)
	D_1R++/D_1+++	(0.8)
	$+R+D_2/+++D_2$	(0.7)
One distorter homozygous and one heterozygous	$D_1RD_3+/++D_3+$	(0.4)
	$+RD_3D_2/++D_3+$	(0.3)
	D_1RD_3+/D_1+++	0.2
	D_1R+D_2/D_1+++	0.0
	$+RD_3D_2/+++D_2$	0.0
	$D_1R+D_2/+++D_2$	0.0
One distorter homozygous and two heterozygous	$D_1RD_3D_2/++D_3+$	0.0

be represented by something like $D_1^tD_4^t\ R^tD_3^tD_2^t$, whereas the partial *t* haplotype with *t* alleles at R, D_1, and D_4 and a lethal on *In*(17)1^t would be denoted by $D_1^tD_4^tR^tD_3^+D_2^+$. To avoid proliferation of indices, wild-type alleles will in the following be denoted by +, and *t* alleles by *R*, D_1, D_2, etcetera, so that haplotypesare represented by combinations such as $D_1^tD_4RD_3D_2^t$ or $D_1^tD_4+++$.

Segregation distortion only occurs in males heterozygous at the responder locus (Lyon 1984, 1991; for complications see Lyon and Zenthon 1987). Table 1 shows the default segregation values for the various male genotype combinations as estimated by Lyon (1991). In the absence of any distorter allele, the responder is transmitted in low frequency. As the number of distorter alleles increases, the segregation ratio of the chromosome carrying the responder also increases. Note that the distorter alleles are not equally potent: D_3 is the weakest distorter and D_2 is the strongest. D_1 is of intermediate strength. For simplicity and because no explicit fitness estimates for the putative distorter D_4 are available, we here mainly consider scenarios where D_4 has no direct effect on transmission ratio distortion or male fertility. We refer to van Boven (1997) for scenarios where *In*(17)2^t does carry an effective distorter.

Males that are homozygous for one distorter allele and heterozygous for at least one other distorter allele suffer from a severely reduced fertility (Lyon 1986, 1987, 1991). Table 2 summarizes the default parameter setting (data after Lyon 1991). Although there is evidence that the responder R^t provides some protection against the reduction in male fertility (Lyon 1991), for simplicity we will assume that male fertility is not affected by the genetic constitution at the responder locus.

For a variety of reasons, the distorter alleles have additional negative fitness effects in heterozygous condition (e.g., Johnston and Brown 1969; Ardlie and Silver 1996a; Ardlie 1998 and references therein). This is especially so for heterozygous males. Thus, Lyon's fitness values may actually overestimate the fitness of males carrying distorter alleles. Therefore, we will consider a number of additional scenarios in which the fertility of males carrying distorter alleles is decreased more strongly than in Table 2. In particular, we focus on scenarios in which the extra reduction in male fertility is equal to $(1 - s)^d$, where *s* is the per distorter reduction in fertility and *d* denotes the number of distorter alleles per individual. Typically, we take $s = 0.05$ or $s = 0.1$. Consider, for example, a $D_1D_4RD_3+/+++D_3+$ male. According to Table 2, the fertility of such a male would be 0.4. In our additional scenarios the fertility of such a male is decreased further to $0.4(1 - s)^4$, leading to a $0.4(1 - 0.05)^4 = 0.33$ or $0.4(1 - 0.1)^4 = 0.26$ relative fertility of our $D_1D_4RD_3+/+++D_3+$ male. In the same manner, the relative fertility of a fully heterozygous $D_1D_4RD_3D_2/++++$ male would be 0.66 or 0.81, instead of 1.0. These numbers are not incompatible with the studies of Johnston and Brown (1969) and Ardlie and Silver (1996a).

We may now classify haplotypes into five categories: (1) wild type; (2) complete; (3) partial; (4) insensitive; and (5) self-mutilating. The wildtype $++++$ and the complete *t* haplotype $D_1D_4RD_3D_2$ carry none and all of the *t* alleles, respectively. Partial *t* haplotypes carry the *t* allele of the responder, and *t* alleles at some but not all of the distorter loci (e.g., $++RD_3D_2$). The insensitive *t* haplotype $++R++$ carries the *t* allele of the responder but wild-type alleles at all distorter loci. It is called insensitive because it cannot be exploited by the complete *t* haplotype or by any partial *t* haplotype, while the fertility of males that carry a copy of this haplotype is maximal. Finally, self-mutilating haplotypes carry *t* alleles at one or more of the distorter loci, but the wild-type allele at the responder locus. Such haplotypes are called self-mutilating because they suffer from the negative fertility effects of the distorter allele(s), without gaining from an increased segregation ratio in combination with other haplotypes. Note that haplotypes from different categories do not always differ fundamentally. For instance, the insensitive *t* haplotype $++R++$ and the partial *t* haplotype $++RD_3+$ (or $+D_4R++$) are alike in some of their effects. The former haplotype has a very low segregation ratio in combination with the wild type (0.20; Table 1) and no negative fitness effects in homozygous condition, whereas the latter have a somewhat higher segregation ratio in combination with the wild type (0.30; Table 1), and only a slightly reduced male fertility when homozygous (0.9; Table 2).

Recombination between the wild type and the complete *t* haplotype is strongly suppressed by a number of inversions. However, rare recombinants are found at a rate of 1–5 $\times$

10^{-3} (e.g., Bennett et al. 1976; Sarvetnick et al. 1986). Most of these recombination events occur between the inversions breakpoints. In particular, the majority of these recombination events seem to occur at the breakpoint between In(17)2 and In(17)3. For simplicity and because no reliable quantitative estimates are available, we assume that the recombination probability is identical between all inversions. The default probability of recombination for a pair of gametes is $r_{bp} = 2 \times 10^{-3}$, so that the probability of recombination per inversion breakpoint is $2/3 \times 10^{-3} = 6.6 \times 10^{-4}$. The location of the responder gene relative to the breakpoints of the adjacent inversions In(17)2 and In(17)3, and its precise nature has long remained enigmatic (e.g., Ewulonu et al. 1996; Kispert et al. 1999; Schimenti 1999; but see Herrmann et al. 1999). Here we assume that, in case of recombination between In(17)2 and In(17)3, the alleles at the responder locus segregate with In(17)2 or with In(17)3 with equal probability.

Apart from rare recombination events between inversion breakpoints, recombination occurs at a normal rate within regions homozygous for an inversion. The default recombination probability in individuals homozygous for In(17)2 or homozygous for In(17)3 is $r_{In(17)2} = 0.041$ and $r_{In(17)3} = 0.017$, respectively (Forejt 1996). Because new haplotypes can only be generated by recombination events in the middle inversions In(17)2 and In(17)3, for our purposes we may neglect recombination in In(17)1 and In(17)4 when homozygous.

Genes located within the *t* complex may mutate and lose their function. For simplicity, we assume that there is a fixed probability μ that an inversion mutates to a state of recessive lethality. Because there is really no evidence on the rate at which inversions mutate into their recessive lethal counterparts, we will simply assume that the mutation probability is the same for all inversions. Whenever mutation to recessive lethality is taken into account, we take $\mu = 10^{-5}$.

Together with a specification of the mating and population structure, the above assumptions on the segregation ratios, fitness effects, and the recombination and mutation probabilities translate into a selection model. Here, mating and population structure are represented by a simple stochastic model that has been described in detail elsewhere (van Boven 1997; van Boven and Weissing 1999). In short, we consider a metapopulation with a fixed number of n demes of maximal size N that are connected by migration. The total size of the metapopulation is fixed at $nN = 10{,}000$ individuals. Generations are discrete and nonoverlapping, and mating occurs at random. Per generation, each female is able to produce a fixed number of l offspring. Typically, we take $l = 6$. However, the actual number of offspring produced per female may be lower than l if a female mated with a sterile male or if some of the zygotes happen to be inviable. Per deme, N juveniles are chosen at random to form the next generation of adults. In cases when not enough juveniles are available to make up a new generation of N adults, the actual deme size is reduced. In cases when more than N juveniles are produced, the extra individuals enter a common pool of migrants. Migration operates through replacement of deme members by individuals from the migrant pool. In particular, each deme member is replaced by a randomly chosen individual from the migrant pool with probability m. Thus, m refers to the immigration rather than emigration probability. Throughout, the immigration rate per deme is systematically varied from $Nm = 0.25$ to $Nm = 4$. These values are not unreasonable in view of the results of Dallas et al. (1995), whose estimates of Nm varied from $Nm = 1$ to $Nm = 5$. However, the total amount of migration may be highly specific for a given population. For example, the migration rate may differ systematically with deme size, N. In fact, there is some evidence that m is negatively related to N, because large populations typically arise in relatively stable environments, thereby impeding migration (Ardlie and Silver 1998). It is even possible that the total number of immigrants, Nm, is negatively related to deme size, N.

In an earlier study (van Boven 1997), we considered two models that differ from the simple metapopulation model described above: A deterministic model for an infinitely large population, and the stochastic metapopulation model of Nunney and Baker (1993; van Boven and Weissing 1999). In the deterministic model generations are discrete and nonoverlapping, and the evolutionary dynamics is described by recurrence equations. Nunney and Baker's model is specifically tailored to the house mouse: Generations overlap, and potential deme size varies between breeding cycles. As in the present model, demes are connected by juvenile migration through a common migrant pool, but the models differ in many details. To illustrate the robustness of our conclusions, we will at several points in this paper indicate how our results relate to the two other models.

Results

Evolution of Nonlethal t Haplotypes

Let us first consider a scenario in which there is no mutation to recessive lethals (i.e., $\mu = 0$). In this case, the deleterious effects of the *t* haplotypes on fitness are only through a reduction of male fertility (Table 2). Although this scenario is perhaps not the most realistic, it already shows some the intricacies of what may happen. Moreover, it provides a baseline against which the more realistic scenarios considered later may be compared. The results are summarized in Table 3 and in Figures 2 and 3. For clarity, we will group the results by the amount of immigration per deme, which is represented by the product of deme size, N, and immigration rate, m.

Low level of migration ($Nm < 1$).—For these parameter combinations, genetic drift is the dominating force in the population. As the results in the upper left corner of Table 3 ($N = 10$ or $m = 0.025$; $N = 10$ and $m = 0.05$; $N = 20$ and $m = 0.025$) show, *t* haplotypes are in the long run (usually within 1000 generations) ousted from the metapopulation. This is not only true for the default initial conditions where we introduced one complete *t* haplotype per deme in an otherwise wild-type population, but also for a whole variety of other initial conditions (data not shown). Apparently, the negative fitness effects of the *t* haplotypes on the demes in which they reside outweigh their advantage upon introduction in wild-type demes, so that stable persistence of *t* haplotypes in the metapopulation is not possible. In other words, group selection is the dominating force in the metapopulation for small values of deme size, N, and immigration rate, m (cf.

TABLE 3. Summary of the simulation results for the default parameter setting: $\mu = 0$ (no mutation to recessive lethals), $r_{bp} = 0.002$ (recombination probability between inversion breakpoints), $r_{In(17)2} = 0.041$ and $r_{In(17)3} = 0.017$ (recombination probabilities within In17(4) and In17(3) when homozygous), $s = 0$ (no extra reduction of male fertility by the inversion), and $l = 6$ (six offspring per female per generation). Maximal deme size varies from $N = 10$ to $N = 40$, and the migration rate varies from $m = 0.025$ to $m = 0.1$. All simulations are started with one copy of the complete *t* haplotype per deme ($D_1D_4RD_3D_2$) and are run for 50,000 generations. The numbers in parentheses represent average frequencies of five replicate runs over the last 1000 generations. No qualitative differences between replicate runs were observed. Only haplotypes that reach a frequency of 1% or more are given.

	$N = 10$	$N = 20$	$N = 40$
$m = 0.025$	+++++(1.0)	+++++(1.0)	++*R*++(0.40) +++++(0.30) $D_1D_4RD_3D_2$(0.29)
$m = 0.05$	+++++(1.0)	+++++(0.68) $D_1D_4R+D_2$(0.28) D_1D_4R++(0.03) ++++D_2(0.01)	++*R*++(0.41) $D_1D_4RD_3D_2$(0.32) +++++(0.26)
$m = 0.1$	+++++(0.76) $D_1D_4RD_3D_2$(0.24)	++*R*++(0.36) $D_1D_4RD_3D_2$(0.33) +++++(0.31)	++*R*++(0.69) $D_1D_4RD_3D_2$(0.35) +++++(0.25)

van Boven and Weissing 1999). The same phenomenon is observed in Nunney and Baker's metapopulation model (Nunney and Baker 1993; van Boven 1997; van Boven and Weissing 1999).

Intermediate level of migration ($Nm \approx 1$).—For these parameter combinations, the forces of segregation distortion, selection, and genetic drift are of comparable strength. As Table 3 shows, there is considerable variation in the outcome of the simulations for different combinations of deme size and migration rate.

For relatively small deme size and relatively high migration rate ($N = 10$ and $m = 0.1$), the population eventually ends up in a state where only the wild type and the complete *t* haplotype (frequency = 0.24) are present. However, in comparison with predictions of deterministic models for large randomly mixing populations, the frequency of the complete *t* haplotype is considerably lower. For instance, the classical one-locus deterministic model of Dunn and Levene (1961) predicts an equilibrium *t* haplotype frequency of $2\sigma - 1$, where σ is the segregation ratio of the complete *t* haplotype

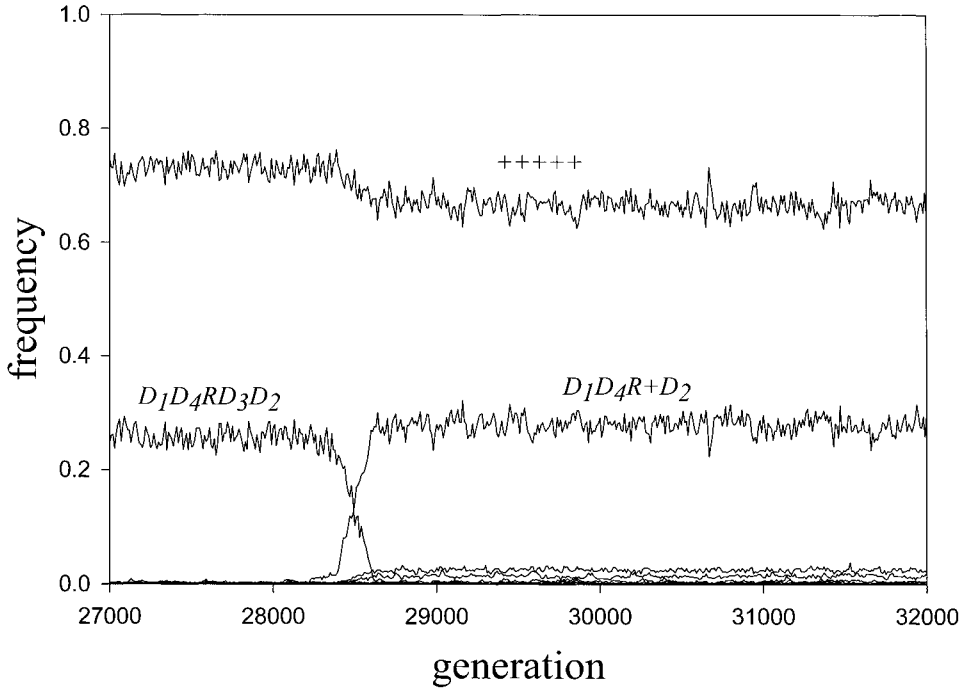

FIG. 2. Dynamics of the haplotype frequencies in a moderately structured metapopulation ($Nm = 1$). Maximal deme size is $N = 20$, the immigration probability is $m = 0.05$, and there is no mutation to recessive lethals ($\mu = 0$; cf. Table 3). In the long run, the complete *t* haplotype is wiped out of the population by the partial *t* haplotype $D_1D_4R+D_2$. This partial *t* haplotype has a smaller segregation advantage in combination with the wild type (0.90 versus 0.99), but it nevertheless outcompetes the complete *t* haplotype because it does not put a large burden on demes in which it is present.

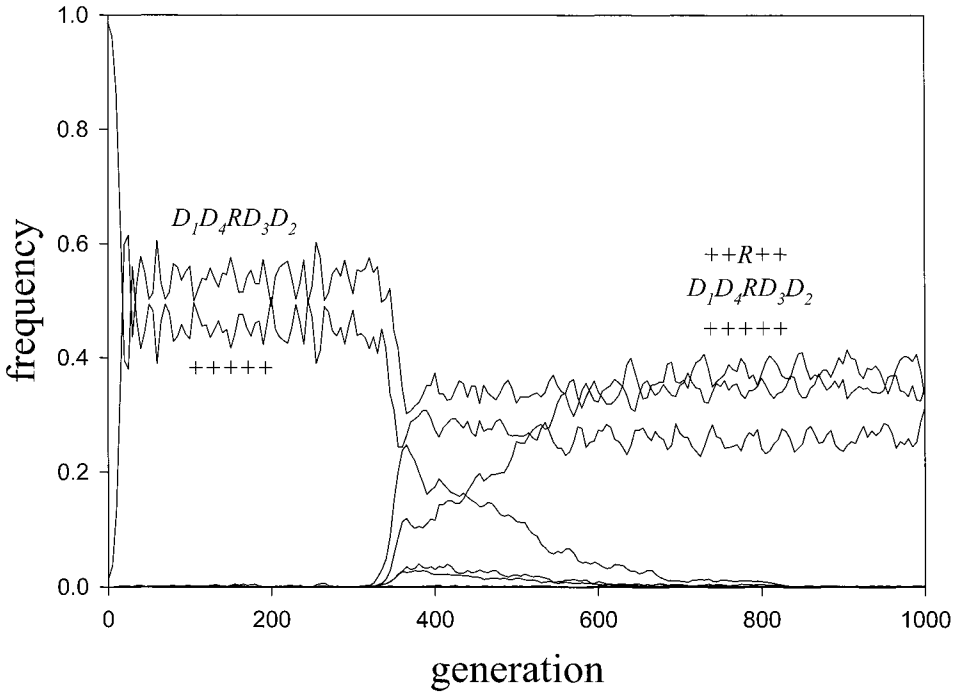

FIG. 3. Dynamics of the haplotype frequencies in a relatively unstructured metapopulation ($Nm = 4$). Maximal deme size is $N = 40$, the immigration probability is $m = 0.1$, and there is no mutation to recessive lethals ($\mu = 0$; cf. Table 3). All demes are initialized with one randomly assigned copy of the complete *t* haplotype ($D_1D_4RD_3D_2$). The complete *t* haplotype quickly increases to reach a frequency, thereby paving the way for insensitive *t* haplotypes. In the long run the population reaches a composition that is characterized by the wild type, the complete *t* haplotype ($D_1D_4RD_3D_2$), and the insensitive *t* haplotype $++R++$.

in combination with the wild type. Because $\sigma = 0.99$ (Table 1), this would lead to an equilibrium *t* haplotype frequency of 0.98, as opposed to 0.24. Apparently, the dominance of the complete *t* haplotype over the wild type in an unstructured population is reduced considerably by selection at the level of local demes against the complete *t* haplotype. This is in line with the conclusions of previous one-locus models for segregation distortion in a metapopulation context (Lewontin 1962; van Boven and Weissing 1999).

Although the frequency of the complete *t* haplotype is rather low if $N = 10$ and $m = 0.1$, the complete *t* haplotype is not decomposed in to its components, and no other partial *t* haplotype is able to remain in the population for prolonged periods of time. Thus, the outcome of the simulations corresponds to the common intuition that partial *t* haplotypes cannot persist in the population because they have a smaller segregation ratio than the complete *t* haplotype in combination with the wild type (Hartl and Clark 1989; Silver 1993). However, as we will show in the following, this outcome is not very typical. On the one hand, a slight decrease in deme size or migration rate suffices to make persistence of any *t* haplotype impossible. On the other hand, a slight increase in deme size or migration rate is enough to destabilize the equilibrium consisting of wild-type and complete *t* haplotype, and a variety of partial *t* haplotypes may invade.

If deme size is increased to $N = 20$ and the migration is decreased to $m = 0.05$, the outcome of evolution is rather different. In this case, the population is in the long run dominated by the wild-type and the partial *t* haplotype $D_1D_4R+D_2$. The partial *t* haplotypes D_1D_4R++ and $++++D_2$ that result from recombination within $In(17)3^+$ in $D_1D_4R+D_2/+++++$ individuals are present in low frequency. Figure 2 shows an illustrative simulation run. Upon its introduction, the complete *t* haplotype quickly increases to reach a frequency of about 0.40. This situation appears to be stable for many thousands of generations. In the long run, however, the partial *t* haplotype $D_1D_4R+D_2$ turns up in the population by a double recombination event, at the breakpoints between R and In(17)3 and In(17)3 and In(17)4. Although this partial *t* haplotype has a lower segregation ratio than the complete *t* haplotype in combination with the wild type (0.90 vs. 0.99), it steadily starts to increase at the expense of the complete *t* haplotype. In the long run, the complete *t* haplotype is wiped out of the population.

This phenomenon can be understood as follows. Within single demes, the complete *t* haplotype fares quite well and reaches a very high frequency. As a result, demes where the complete *t* haplotype is present typically contain many sterile males. Such demes have a two fold disadvantage. First, the effective contribution of these demes to the migrant pool is lower than that of demes where the complete *t* haplotype is absent. Second, demes where the complete *t* haplotype is present run a high risk of extinction. The less efficient partial *t* haplotype $D_1D_4R+D_2$ does not reach a very high frequency within demes, and it therefore impairs deme productivity to a much lesser extent. As a result of this, the partial *t* haplotype $D_1D_4R+ D_2$ is at an overall advantage in the metapopulation. We conclude that the partial *t* haplotype $D_1D_4R+D_2$ with its modest segregation advantage is favored over the complete *t* haplotype by selection at the level of the demes.

TABLE 4. Summary of the simulation results in the presence of mutation of the inversions to a state of recessive lethality. The per inversion mutation frequency is $\mu = 10^{-5}$. Other parameter values are as in Table 3. Simulations are started with one copy of the complete *t* haplotype that carries a recessive lethal per deme ($D_1D_4RD_3D_2^l$). Frequencies of haplotypes that carry lethals (e.g., $D_1D_4RD_3D_2$ and $D_1D_4RD_3D_2^l$) are pooled and denoted in boldface.

	$N = 10$	$N = 20$	$N = 40$
$m = 0.025$	$+++++$(0.70) $\boldsymbol{D_1D_4RD_3D_2}$(0.20) $++R++$(0.09)	$+++++$(0.58) $\boldsymbol{D_1D_4RD_3D_2}$(0.20) $++R++$(0.12) $+++D_3+$(0.08)	$+++++$(0.49) $\boldsymbol{D_1D_4RD_3D_2}$(0.25) $++R++$(0.24)
$m = 0.05$	$+++++$(0.63) $\boldsymbol{D_1D_4RD_3D_2}$(0.21) $++R++$(0.16)	$+++++$(0.52) $++R++$(0.24) $\boldsymbol{D_1D_4RD_3D_2}$(0.23)	$++R++$(0.41) $D_1D_4RD_3D_2$(0.32) $+++++$(0.26)
$m = 0.1$	$+++++$(0.56) $\boldsymbol{D_1D_4RD_3D_2}$(0.22) $++R++$(0.21)	$++R++$(0.36) $D_1D_4RD_3D_2$(0.33) $+++++$(0.31)	$++R++$(0.39) $D_1D_4RD_3D_2$(0.35) $+++++$(0.25)

For $N = 40$ and $m = 0.025$, the population is in the long run dominated by the wild type (0.30), the complete *t* haplotype (0.29), and the insensitive *t* haplotype $++R++$ (0.40). Conditions leading to this population composition are discussed below.

High level of migration ($Nm > 1$).—For these parameter combinations, selection and segregation distortion dominate genetic drift. The results are summarized in the bottom right corner of Table 3 ($N = 20$ and $m = 0.1$; $N = 40$ and $m = 0.05$; $N = 40$ and $m = 0.1$). Figure 3 shows an illustrative simulation run. In the initial phase, the complete *t* haplotype quickly increases in frequency at the expense of the wild type. After 50 generations, it reaches an equilibrium of approximately 0.55 with the wild type. As a result, the mean fitness of the population is strongly depressed. In fact, the fraction of sterile males in the population is well above 0.25, and there is selection in favor of types that cannot be exploited by the complete *t* haplotype and that have less drastic fitness consequences. The insensitive *t* haplotype $++R++$ and the partial *t* haplotype $+D_4R++$ satisfy these criteria: Segregation is Mendelian in combination with the complete *t* haplotype, and male fertility is not impaired in combination with any other haplotype. Thus, as soon as these insensitive *t* haplotypes are formed by recombination, they start to increase in frequency. In the long run, the insensitive *t* haplotype $++R++$ outcompetes $+D_4R++$ because it is not broken up by recombination in $+D_4R++/D_1D_4RD_3D_2$ individuals within $In(17)2^t$. The insensitive *t* haplotype $++R++$ does not spread to fixation, but is kept in check by the wild type because it has a strong segregation disadvantage in $+++++/++R++$ males (Table 1).

Apart from our standard initial configuration where we introduced one copy of the complete *t* haplotype per deme, we also considered a whole variety of other initial conditions. It appears that in the long run the population always ends up in a state where, apart from the wild type, the complete and the insensitive *t* haplotype are present or the wild type and the partial *t* haplotypes $D_1D_4R+D_2$ and $++RD_3+$ or $D_1+RD_3D_2$ and $+D_4R++$. Because heterozygous $D_1D_4R+D_2/++RD_3+$, $D_1+RD_3D_2/+D_4R++$, and $D_1D_4RD_3D_2/++R++$ males are fully fertile, we will say that the *t* haplotypes $D_1D_4R+D_2$ and $++RD_3+$, $D_1+RD_3D_2$ and $+D_4R++$, or $D_1D_4RD_3D_2$ and $++R++$ complement another with respect to male fertility. The present results corroborate our previous conclusion from a suite of deterministic models that complementation is a potent force enhancing coexistence of *t* haplotypes (van Boven et al. 1996; van Boven 1997; van Boven and Weissing 1998).

Summarizing, our model predicts that in an unstructured population with a relatively high migration rate and large deme size the complete *t* haplotype is not able to resist invasion by other *t* haplotypes. Under all circumstances, an insensitive partial *t* haplotype that has a severe segregation disadvantage in combination with the wild type but that cannot be exploited by the complete *t* haplotype will invade and persist stably. Moreover, depending on the initial conditions, the complete *t* haplotype may even be competitively excluded by a combination of less efficient but complementing partial *t* haplotypes.

Competition between Lethal and Nonlethal t Haplotypes

Until now, we assumed that *t* haplotypes impair male fertility, but have no effect on viability. Now we turn to our main scenario, where the inversions may mutate to a state of recessive lethality. The results are summarized in Table 4 and in Figures 4 and 5. Again, the results are grouped by the amount of migration in the metapopulation, which is represented by the product of deme size and migration rate (Nm).

Low to intermediate level of migration ($Nm \leq 1$).—For these parameter combinations ($N = 10$ and $m = 0.025$; or $N = 20$ and $m = 0.05$ in Table 4) the complete *t* haplotype that does not carry any recessive lethal is in the long run always outcompeted by complete *t* haplotypes that carry one or more recessive lethals. Upon its introduction, the complete *t* haplotype that carries a recessive lethal on the inversion $In(17)4^t$ (i.e., $D_1D_4RD_3D_2^l$) quickly increases to reach an appreciable frequency (e.g., 0.35 in case that $N = 20$ and $m = 0.025$). As in our previous scenario with no mutation to a state of recessive lethality and a high level of migration, there is strong selection in favor of *t* haplotypes that cannot be exploited by the complete *t* haplotype and that have less drastic fitness consequences when homozygous. Consequently, the insensitive *t* haplotype $++R++$ starts to increase. Ultimately, the population ends up in a state where the wild type, the insensitive *t* haplotype, and a number of lethal complete *t* haplotypes are present.

How can the competitive superiority of lethal *t* haplotypes over nonlethal *t* haplotypes be understood? The clue to the

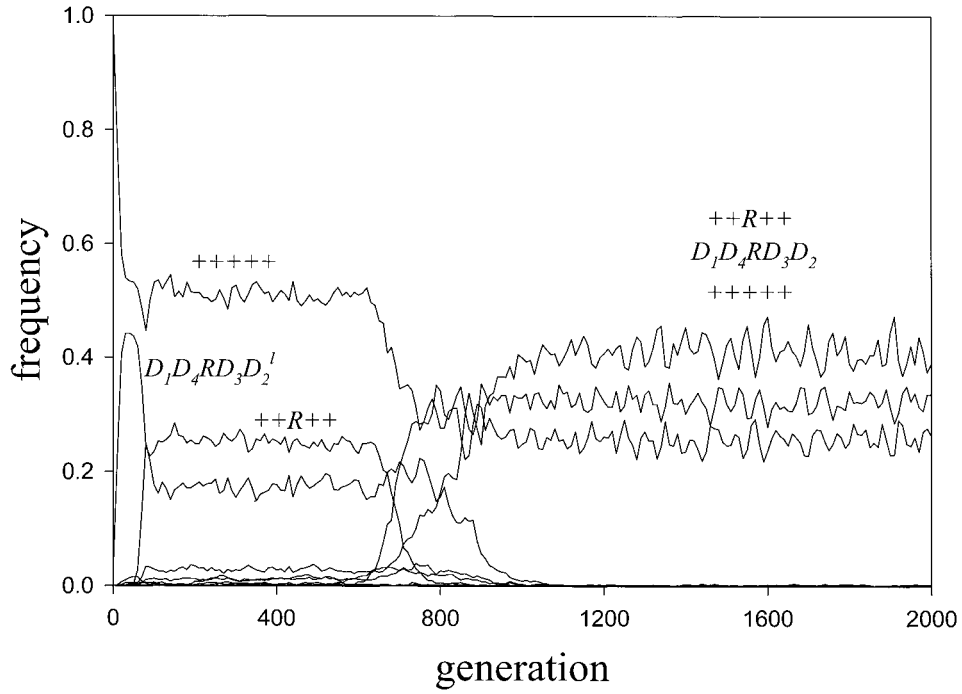

FIG. 4. Dynamics of the haplotype frequencies in a relatively unstructured metapopulation ($Nm = 4$). Maximal deme size is $N = 40$, the immigration probability is $m = 0.1$, and the mutation rate is $\mu = 10^{-5}$ (cf. Table 4). All demes are initialized with one randomly assigned copy of the complete *t* haplotype that carries a recessive lethal ($D_1D_4RD_3D_2^l$). In the long run, the complete *t* haplotype that does not carry recessive any lethal outcompetes all lethal *t* haplotypes because it has a fitness advantage in homozygous condition.

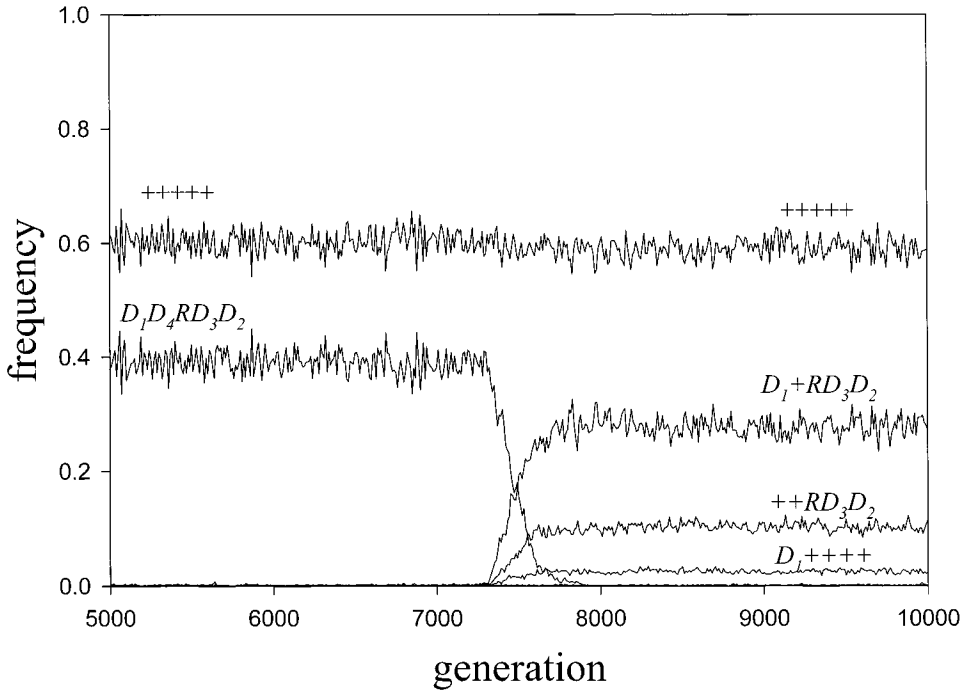

FIG. 5. Dynamics of the haplotype frequencies in a relatively unstructured metapopulation ($Nm = 4$). Maximal deme size is $N = 40$, the immigration probability is $m = 0.1$, and the mutation rate is $\mu = 10^{-5}$. The fertility of males carrying the inversions $In(17)1^t$ − $In(17)4^t$ is strongly reduced ($s = 0.1$; cf. Table 6). The inversion $In(17)2^t$ with the putative distorter D_4^t is excised from the complete *t* haplotype because it decreases male fertility considerably and is only of limited value by decreasing recombination with the wild type. In the long run the wild type and the partial *t* haplotype $D_1+RD_3D_2$ prevail, while the recombination products $D_1+RD_3D_2$ and D_1++++ are present with low frequency.

answer lies in the observation that lethal *t* haplotypes may be favored over their nonlethal counterparts by group selection (cf. Lewontin 1962). Within single demes, a nonlethal *t* haplotype typically reaches a higher frequency than the corresponding *t* haplotype that induces lethality in both males and females. As a result, demes carrying a nonlethal *t* haplotype are at a higher risk of extinction. Moreover, the production of emigrants by demes carrying a nonlethal *t* haplotype is typically also smaller than the production of demes carrying a lethal *t* haplotype. Together, these two advantages of lethal *t* haplotypes over their nonlethal counterpart at the level of local populations more than offset their fitness disadvantage at the individual level. A detailed comparison of lethal and nonlethal *t* haplotypes in a metapopulation context is given by van Boven and Weissing (1999).

Although the wild type, a complete *t* haplotype carrying one or more recessive lethals (henceforth called $D_1^{\chi}D_4^{\chi}RD_3^{\chi}D_2^{\chi}$), and the insensitive *t* haplotype are the predominant haplotypes most of the time for an intermediate level of migration, there are also intermittent outbreaks of other *t* haplotypes. Moreover, some partial *t* haplotypes may remain present for long periods of time. One of these is the self-mutilating *t* haplotype $+++D_3+$. This *t* haplotype carries a weak distorter allele D_3^t but not the responder R^t. As Table 4 shows $+++D_3+$ can reach an appreciable frequency for specific values of *N* and *m* ($N = 20$ and $m = 0.025$).

The phenomenon of the stable presence of the self-mutilating *t* haplotype $+++D_3+$ is quite puzzling. How can a haplotype that has a fitness disadvantage both at the gamete and at the individual level increase to a frequency that can hardly be accounted for by genetic drift? The clue to the answer again lies in the observation that group selection may operate to favor $+++D_3+$ over the wild type at the level of the demes. Consider a deme that consists of $+++D_3+$ individuals only. Such a deme is favored in two ways over a typical deme where $+++++$, $D_1^{\chi}D_4^{\chi}RD_3^{\chi}D_2^{\chi}$, and $++R++$ are present. First, ademe where all individuals carry the distorter allele D_3^t has become effectively uninvadable for the complete *t* haplotype, because $+++D_3+/D_1^{\chi}D_4^{\chi}RD_3^{\chi}D_2^{\chi}$ males are sterile. Second, the effective contribution of such a $+++D_3+$ deme to the migrant pool is higher than that of a typical deme, even though all males in a $+++D_3+$ deme suffer from a slightly reduced fertility (0.9). This is due to the fact that in a typical deme a sizeable fraction of the offspring is not viable (the homozygous $D_1^{\chi}D_4^{\chi}RD_3^{\chi}D_2^{\chi}/D_1^{\chi}D_4^{\chi}RD_3^{\chi}D_2^{\chi}$ individuals). For the parameter setting $N = 20$ and $m = 0.025$, a stable equilibrium of wild type, complete *t* haplotype, insensitive *t* haplotype, and the self-mutilating *t* haplotype $+++D_3+$ results in the long run.

For other parameter combinations, we observe intermittent outbreaks of the self-mutilating *t* haplotype $+++D_3+$, instead of stable persistence (see also van Boven 1997). Here, the self-mutilating *t* haplotype $+++D_3+$ may reach a considerable frequency during an outbreak (> 0.20). However, stable persistence of $+++D_3+$ over long periods of time is prevented by the partial *t* haplotype $D_1D_4R+D_2$. In contrast to the complete *t* haplotype, this partial *t* haplotype is very effective in exploiting $+++D_3+$: $D_1D_4R+D_2/+++D_3+$ males are fully fertile and the segregation ratio of $D_1D_4R+D_2$ is increased from 0.90 in combination with the wild type to 0.99 in combination with $+++D_3+$. In the long run, $D_1D_4R+D_2$ is in turn wiped out of the population or brought to a very low frequency by competition with the complete *t* haplotype.

We may conclude that self-mutilating haplotypes, which are usually (and safely) discarded from consideration in an unstructured population (Charlesworth and Hartl 1978; Wu and Hammer 1991; Nauta and Hoekstra 1993; Stadler 1996), can play an important role in the context of a deme-structured population, especially when the costs at the individual level are small and the benefits at the group level are large.

High level of migration ($Nm > 1$).—If the level of migration is high or if local deme size is large, the advantage of lethal *t* haplotypes over nonlethal *t* haplotypes by group selection vanishes ($N = 40$ and $m = 0.05$; $N = 40$ and $m = 0.1$; $N = 20$ and $m = 0.1$ in Table 4). This is illustrated by Figure 4, where a complete *t* haplotype carrying a recessive lethal at $In(17)4^t$ (i.e., D_2^l) is introduced at $t = 0$ in a wild-type population. Initially, $D_1D_4RD_3D_2^l$ quickly increases and reaches a frequency of more than 0.40. As a result, the fitness of the population is reduced and there is selection for haplotypes that cannot be exploited and that do not suffer from severe negative fitness effects. Consequently, the insensitive *t* haplotype $++R++$increases in frequency once it is discovered by recombination. For several hundreds of generations the composition of wild type (frequency = 0.54), complete *t* haplotype $D_1D_4RD_3D_2^l$ (0.18), and insensitive *t* haplotype (0.27) appears to be stable. In the long run, however, lethal complete *t* haplotypes are outcompeted by the nonlethal complete *t* haplotype, and the population ends up in a state where the insensitive *t* haplotype (frequency = 0.39), the nonlethal complete *t* haplotype (0.35), and the wild type (0.25) prevail. Note that for a high level of migration the outcome of evolution is the same whether mutation toward recessive lethals is taken into account or not (Table 4 vs. Table 3). We conclude that the apparent prevalence of lethal *t* haplotypes in natural house mouse populations can only be explained by group selection if house mouse breeding units are relatively small and isolated.

Male Fertility and the Evolution of t Haplotypes

Until now, we assumed that the reduction in male fertility by the distorter genes is given by the estimates of Lyon (1991; Table 2). These estimates imply that the distorter genes have no effect on male fertility in fully heterozygous individuals. This may not be realistic (see above). Therefore, we will now consider additional scenarios where male fertility is reduced by a factor $(1 - s)^d$, where *d* is the number of distorter alleles per male and *s* is the per distorter reduction in male fertility. In the following, we take $s = 0.05$ or $s = 0.1$. In both scenarios, mutation to recessive lethals is taken into account.

Moderate reduction in male fertility ($s = 0.05$).—In this scenario, the relative fertility of fully heterozygous $+++++/D_1D_4RD_3D_2$ males is $(1 - 0.05)^4 = 0.81$ as compared to 1.0 in wild-type males. The results of this scenario are given in Table 5. In comparison with Table 4, there are some distinct differences. First, if the product of deme size, *N*, and migration rate, *m*, is small ($N = 10$ and $m = 0.025$ in Table 5), no *t* haplotype can persist. For these parameter

TABLE 5. Summary of the simulation results in case that the reduction of male fertility by the inversions is moderately increased ($s = 0.05$). Simulations are started with one copy of the complete *t* haplotype that carries a recessive lethal per deme ($D_1D_4RD_3D_2^l$). Haplotype combinations that carry recessive lethals are denoted in boldface.

	$N = 10$	$N = 20$	$N = 40$
$m = 0.025$	+++++(1.0)	+++++(0.70) **$D_1D_4RD_3D_2$**(0.25) ++R++(0.04)	+++++(0.63) **$D_1D_4RD_3D_2$**(0.28) ++R++(0.09)
$m = 0.05$	+++++(0.88) **$D_1D_4RD_3D_2$**(0.12)	+++++(0.67) **$D_1D_4RD_3D_2$**(0.25) ++R++(0.08)	+++++(0.42) $D_1D_4RD_3D_2$(0.36) ++R++(0.22)
$m = 0.1$	+++++(0.73) **$D_1D_4RD_3D_2$**(0.25) ++R++(0.02)	+++++(0.64) $D_1D_4RD_3D_2$(0.35)	$D_1D_4RD_3D_2$(0.38) +++++(0.37) ++R++(0.24)

combinations, the segregation advantage of (partial and complete) *t* haplotypes in combination with the wild type is not enough to compensate for its negative fitness effects at the individual and group level.

Second, for all parameter values the wild type now reaches a considerably higher frequency than in Table 4. However, this does not imply that the frequency of the complete *t* haplotype is decreased in comparison with Table 4. On the contrary, for most parameter combinations the frequency of the complete *t* haplotype even increases somewhat. Typically, the insensitive *t* haplotype ++R++ suffers most from the decrease in the male fertility by the distorter alleles. This is somewhat surprising in view of the fact that it does not carry a single distorter allele. This phenomenon can be explained by the negative fitness effects in $D_1D_4RD_3D_2$/++R++ males and by the fact that the complete *t* haplotype does not reach a very high frequency in demes anymore. Still, the insensitive *t* haplotype is able to persist for most parameter combinations, albeit at a rather low frequency.

Strong reduction in male fertility ($s = 0.1$).—In this scenario, the relative fertility of fully heterozygous +++++/$D_1D_4RD_3D_2$ males is $(1 - 0.1)^4 = 0.66$ as opposed to 1.0. Thus, +++++/$D_1D_4RD_3D_2$ males have a 34% reduction in fertility as compared to wild-type males. The results of this scenario are given in Table 6 and Figure 5.

In view of the results of our previous scenario, where the extra reduction in male fertility was rather modest, we might have anticipated that the frequency of the complete *t* haplotype is increased still further in comparison with Tables 4 and 5. This is, however, not the case. It appears that for $s = 0.1$ the decrease in the fertility of male individuals carrying distorter alleles is such that *t* haplotypes have serious difficulties in persisting in the metapopulation. In particular, if the level of migration is low to intermediate ($Nm \leq 1$), no *t* haplotype is able to persist, regardless of its segregation ratio in combination with the wild type (data not shown). If the level of migration is high ($Nm > 1$), some partial *t* haplotypes can persist, but the complete *t* haplotype cannot. In this case, the weak distorter alleles D_3^t and D_4^t are of limited value because they increase the segregation advantage of the complete *t* haplotype in combination with the wild type only slightly, while they decrease the fertility of males considerably. As a result, the weak distorter alleles D_3^t and D_4^t are in the long run excised from the complete *t* haplotype by recombination. For parameter combinations with $Nm = 2$ in Table 6 ($N = 40$ and $m = 0.05$; $N = 20$ and $m = 0.1$), in the long run both the distorter D_4^t, which has no effect on segregation distortion, and the distorter D_3^t, which has a comparatively small effect, are lost from the complete *t* haplotype. Thus, D_1+R+D_2 is the prevailing *t* haplotype in the population. The recombinational ''waste products'' ++R+D_2, D_1++++, ++++D_2, D_1+R++, and ++R++ are present with low frequency. For $Nm = 4$, only D_4^t is excised from the complete *t* haplotype (Fig. 5). In this case the recombi-

TABLE 6. Summary of the simulation results in case that the reduction of male fertility by the inversions is strongly increased ($s = 0.1$). All simulations are started with one copy of the complete *t* haplotype that carries a recessive lethal per deme ($D_1D_4RD_3D_2^l$). Haplotype combinations that carry recessive lethals are denoted in boldface.

	$N = 10$	$N = 20$	$N = 40$
$m = 0.025$	+++++(1.0)	+++++(1.0)	+++++(1.0) +++++(0.73) D_1+R+D_2(0.13) ++R+D_2(0.07)
$m = 0.05$	+++++(1.0)	+++++(1.0)	D_1++++(0.02) ++++D_2(0.02) D_1+R++(0.02) ++R++(0.01)
$m = 0.1$	++++(1.0)	++++(0.79) D_1+R+D_2(0.11) ++R+D_2(0.05) D_1++++(0.02) ++++D_2(0.02) D_1+R++(0.01)	+++++(0.60) D_1+RD_3D_2(0.27) ++RD_3D_2(0.10) D_1++++(0.03)

national products $++RD_3D_2$ and D_1++++ are present with low frequency. For all parameter combinations, *t* haplotypes carrying recessive lethals cannot persist.

Taken together, the results of Table 6 indicate that as the reduction in male fertility increases, it becomes increasingly less likely that the complete *t* haplotype remains intact as an integral unit, and it is either decomposed into its components or not able to persist at all. Moreover, lethal *t* haplotypes that were in earlier scenarios sometimes able to persist are in the present scenario always wiped out of the population.

Discussion

On the basis of a suite of population genetical models, we have argued earlier that the dominance of the complete *t* haplotype in natural house mouse populations is quite puzzling. For instance, we have shown that two segregation distorters can easily coexist if they differ *only* in their segregation ratios (van Boven et al. 1996; van Boven 1997; van Boven and Weissing 1998). It is therefore not obvious a priori why partial *t* haplotypes are absent from natural populations, and how the complete *t* haplotype has succeeded in preserving its genetic integrity. However, our previous models were highly simplified, and therefore do not apply directly to the *t* complex. To investigate to what extent the results of our earlier one-locus models still hold in a more realistic setting, we here incorporated the genetic structure of the *t* complex and many features characteristic for house mouse populations.

Our previous models indicated that a high degree of polymorphism is to be expected if the various distorter alleles complement another, i.e., if the fitness of individuals heterozygous for two distorter alleles is higher than the fitness of individuals homozygous for one of the distorter alleles (van Boven et al. 1996; van Boven 1997; van Boven and Weissing 1998). Complementation, both with respect to viability (which define the so-called complementation groups) and with respect to male fertility is commonplace at the *t* complex (Table 2), may well be typical for segregation distortion systems (for the *SD* complex of *Drosophila melanogaster*, see Temin et al. 1991). Nevertheless, our present analysis predicts a much more limited amount of polymorphism at the *t* complex than our earlier, more abstract models suggested. In almost all simulations, at least two *t* haplotypes did coexist, but coexistence of three or more *t* haplotypes was the exception, rather than the rule.

Still, the simulation results are neither in line with empirical evidence nor with the standard verbal arguments mentioned above. In a relatively unstructured population with small deme size and low migration rate ($Nm < 1$), no *t* haplotype was able to persist. In a moderately structured population ($Nm \approx 1$), combinations of moderately efficient but complementing partial *t* haplotypes often dominated. Finally, in a relatively unstructured population ($Nm > 1$), the complete *t* haplotype was not able to exclude all other haplotypes. In particular, the complete *t* haplotype could not prevent invasion of the insensitive *t* haplotype, which cannot be exploited by the complete *t* haplotype and which does not suffer from negative effects on male fertility.

Although the complete *t* haplotype was almost always unable to resist invasion by other *t* haplotypes, the complete *t* haplotype was often not wiped out of the population. To a certain extent this can be regarded as an artifact of our initial conditions, which systematically favored the complete *t* haplotype. Indeed, when the level of migration was high ($Nm > 1$), the outcome of the simulations depended strongly on the initial conditions. For these parameter combinations, a combination of the complementing partial *t* haplotypes $D_1+RD_3D_2$ and $+D_4R++$, or $D_1D_4R+D_2$ and $++RD_3+$ was usually just as stable as the combination of complete and insensitive *t* haplotype. In some cases, the complete *t* haplotype was in the long run outcompeted by partial *t* haplotypes even when it was initially the only *t* haplotype present. This occurred when the level of migration was intermediate ($Nm \approx 1$). For these parameter combinations, the complete *t* haplotype could be outcompeted by the partial *t* haplotype $D_1D_4R+D_2$ by group selection (Table 3, Fig. 3). Finally, when the negative fitness consequences of the distorter alleles were severe, the partial *t* haplotypes $D_1+RD_3D_2$ or D_1+R+D_2 outcompeted the complete *t* haplotype by selection at the individual level (Table 6).

Our finding that the complete *t* haplotype cannot be expected to play a dominant role is in striking contrast to suggestions in the literature (e.g., Silver 1993) that other *t* haplotypes are virtually absent from natural house mouse populations. How strong, then, is the evidence that insensitive, partial, or self-mutilating *t* haplotypes do not occur in the field? Traditionally, the presence of a *t* haplotype is revealed by breeding wild-caught mice to laboratory animals that carry the Brachyury (*T*) allele (*T*/*t* offspring are born tailless). However, some partial *t* haplotypes are not uncovered in this manner, and the method does not distinguish between the complete *t* haplotype and a number of partial *t* haplotypes. More recent studies using molecular techniques often focus on a single *t* locus only (e.g., Ardlie and Silver 1996b) and are also not indicative for the presence of partial *t* haplotypes. It is therefore possible that partial *t* haplotypes have been systematically overlooked in field studies. There have only been a few reports of partial *t* haplotypes, in the Mediterranean region (Silver et al. 1987; Figueroa et al. 1988) and in North America (Erhart et al. 1989). Figueroa et al. did indeed find a number of partial *t* haplotypes with reduced segregation ratios (but not the insensitive *t* haplotype). The results of Erhart, however, are probably best explained by genetic exchange at a relatively small scale between wild-type and *t* haplotype DNA that does not significantly affect the genetic structure of the *t* haplotype (Hammer et al. 1991; K. Ardlie, pers. comm.). In any case, the fact that segregation ratios in litters from wild-caught mice are invariably high (Ardlie and Silver 1996a) strongly contradicts a very widespread occurrence of partial *t* haplotypes.

In addition to the presence of partial and insensitive *t* haplotypes, two other aspects of our simulations are also not in line with empirical evidence. First, the equilibrium frequency of the complete *t* haplotype differs significantly from that observed in the field. Due to the presence of other *t* haplotypes, our model does predict a lower frequency than earlier models that considered only the wild type and the complete *t* haplotype (Bruck 1957; Dunn and Levene 1961; Nunney and Baker 1993; Durand et al. 1997; but see Petras 1967;

Lewontin 1968). Still, even in our model this frequency (usually > 0.20) is considerably higher than recent estimates from natural house mouse populations (0.05; Ardlie and Silver 1998). This discrepancy apparently does not result from the fact that we underestimated the reduction in individual fitness by the distorter alleles. In fact, the scenarios where male fertility was more strongly depressed than estimated by Lyon (1991) did, surprisingly, not result in a stable low frequency of the complete *t* haplotype. On the contrary, if the extra decrease in male fitness was moderate (Table 5), the complete *t* haplotype actually increased in frequency in comparison with our standard scenario (Table 4). If the extra decrease in male fertility was strong (Table 6), the complete *t* haplotype could not persist at all.

As earlier models, our model predicts an increase of the frequency of *t* haplotypes with the number of immigrants, *Nm*. Surprisingly, Ardlie and Silver (1998) found that *t* haplotypes were at a relatively high overall frequency in small populations (0.12 in populations of $N \leq 60$) and at relatively low frequency in large populations (0.04 in populations of $N > 60$). Ardlie and Silver hypothesize that this somewhat counterintuitive finding can be explained by the fact that large populations occur more often in stable environments and that these populations are more persistent. In other words, the total number of immigrants per deme, *Nm*, may actually be negatively related to *N*. This is consistent with Selander's (1970) results from allozyme analysis, which showed that the deficit in heterozygotes was systematically larger in large populations than in small populations.

Our simulations do not lead to the conclusion that, in general, lethal *t* haplotypes are favored over their nonlethal counterparts. In fact, this was only the case when the level of migration was intermediate ($Nm \approx 1$), and when the fitness reduction by the distorter alleles was not too strong. These conditions are rather restrictive. Nevertheless, lethal *t* haplotypes prevail in natural populations, especially in North America, where populations are dominated by the lethal *t* haplotypes t^{w5} and t^{w1} (e.g., Lenington et al. 1988). However, there are also populations, especially in the Middle East, that are dominated by nonlethal *t* haplotypes. Perhaps this difference in the prevalence of lethal *t* haplotypes reflects systematic differences in population structure. But, of course, other factors, not included in the model might also play a role. For instance, lethal *t* haplotypes may to a certain extent be favored over their nonlethal counterparts by reproductive compensation. However, this factor alone cannot explain the complete absence of nonlethal *t* haplotypes in many feral house mouse populations (Charlesworth 1994).

In this study, we found a number of conspicuous discrepancies between model predictions and empirical findings. Instead of rendering a model useless, such discrepancies may be highly valuable, because they point out gaps in our knowledge. Apparently, one or several aspects of our model are not realistic but, to us at least, it is far from obvious which factors are responsible for the discrepancy between data and predictions. One might argue that our metapopulation model with fixed maximal deme size and a single level of population subdivision is too simplistic. In field populations deme size is likely to vary considerably, and population subdivision will occur at several levels (e.g., demes, farms, villages, and geographic regions; Ardlie and Silver 1998 and references therein). However, we are confident that our conclusions are not an artifact of oversimplified structural assumptions. In fact, all our results are also observed in the structurally different metapopulation model of Nunney and Baker (1993; see also van Boven 1997). Moreover, the fact that the findings of the present paper are in line with those of more abstract and general models (van Boven et al. 1996; van Boven 1997; van Boven and Weissing 1998) indicates that our conclusions are robust.

Two of the discrepancies between model predictions and empirical data may be closely related. Perhaps, the partial *t* haplotypes could only spread in our model populations because the frequency of the complete *t* haplotype was considerably higher than in natural populations. Therefore, all factors that reduce the frequency of the complete *t* haplotype might also reduce the chances for invasion of the insensitive or other partial *t* haplotypes. Several such factors come to mind. For instance, the transmission ratios may have been overestimated. In fact, there is evidence that the transmission ratio of the complete *t* haplotype is somewhat lower in natural house mouse populations than Lyon's (1991) laboratory-based estimate suggests (0.90 instead of 0.99; Ardlie and Silver 1996b). Moreover, transmission ratios may vary depending on the timing of mating. In particular, the segregation ratios in litters conceived from postpartum estrus may be lower than those in litters conceived from cycling estrus (Lenington and Heisler 1991; but see Ardlie and Silver 1996a). Other factors that are likely to reduce the frequency of the complete *t* haplotype are female preferences for non-*t* males as mates (e.g., Lenington and Heisler 1991), inbreeding (e.g., Petras 1967), and strong seasonal or spatial fluctuations in population size.

In this paper, we mainly focused on the question why the complete *t* haplotype, once being common, remains intact as an integral unit, rather than decaying into its components. A very different question would be: How did the complete *t* haplotype arise in the first place? It is probably no coincidence that all well-known segregation distortion systems consist of several closely linked loci. Wu and Hammer (1991, p. 185) argued that this is due to the complexity of the process involved: ''It is highly unlikely that a true single-locus drive could exist; the locus would have to encode a product that not only recognizes itself, but also selectively interacts with one allelic form but not the other.'' It is, however, not at all clear that the evolution of a segregation distortion system by stepwise addition of basic components should lead to the appearance of a strong segregation distorter: Even newly arising distorter alleles at loci that are already tightly linked to other distorter loci need not be incorporated into a preexisting segregation distorter. Instead, such newly arising alleles may just as well be incorporated into insensitive types. Thus, the evolution of a strong segregation distorter may depend on specific conditions, such as a rare interspecies exchange of genetic material (Silver 1993). This may be a major reason that more autosomal segregation distorters do not occur in the real world.

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