

Segregation distortion in a deme-structured population: opposing demands of gene, individual and group selection

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Abstract

The evolution of segregation distortion is governed by the interplay of selection at different levels. Despite their systematic advantage at the gamete level, none of the well-known segregation distorters spreads to fixation since they induce severe negative fitness effects at the individual level. In a deme-structured population, selection at the population level also plays a role. By means of a population genetical model, we analyse the various factors that determine the success of a segregation distorter in a metapopulation. Our focus is on the question of how the success of a distorter allele is affected by its segregation ratio and its fitness effects at the individual level. The analysis reveals that distorter alleles with high segregation ratios are the best invaders and reach the highest frequencies within single demes. However, the productivity of a deme harbouring a distorter with a high segregation ratio may be significantly reduced. As a consequence, an efficient distorter will be underrepresented in the migrant pool and, moreover, it may increase the probability of deme extinction. In other words, efficient distorters with high segregation ratios may well succumb to their own success. Therefore, distorters with intermediate segregation ratios may reach the highest frequency in the metapopulation as a result of the opposing forces of gamete, individual and group selection. We discuss the implications of this conclusion for the *t* complex of the house mouse.

Introduction

The phenomenon of segregation distortion has long fascinated evolutionary biologists because it exemplifies that selection at a lower level can lead to maladaptive features at a higher level. By disturbing Mendelian segregation in their favour, segregation distorters obtain a systematic advantage at the gamete level. In all examples of segregation distortion (reviewed by Lyttle, 1991), this advantage is counterbalanced by negative fitness effects at the individual level. In a deme-structured population, selection at the population level also plays a role (Lewontin, 1962). In fact, demes that contain a high proportion of individuals of low fitness will

typically perform less well than demes without such individuals.

The opposing forces of gamete, individual and inter-deme selection will often lead to a stable polymorphism. Such a polymorphism is the result of an intricate interplay between selection at different levels, and it is difficult to ascertain the relative importance of each level. To gain a better understanding of the various forces and their interaction, we analyse, by means of a population genetical metapopulation model, the most important determinants for the success of a segregation distorter. In particular, we consider (1) the ability of a distorter to invade a wildtype deme, (2) the frequency that it reaches in a deme once established, (3) the time it is able to persist in a deme, (4) its effect on the productivity of a deme and (5) its representation in the migrant pool. The analysis of these factors will shed some light on the question of how the overall success of a segregation distorter depends on its basic characteristics.

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Our model is motivated by the *t* complex of the house mouse, the standard example for segregation distortion in a deme-structured population (Williams, 1966; see Silver, 1993, for a review). Certain variants at this gene complex, the so-called *t* haplotypes, strongly distort segregation in their favour in males heterozygous for the wildtype and a *t* haplotype. Segregation ratios as high as 0.95 are not uncommon. However, there is considerable variation in the degree of distortion (Petras, 1967; Bennett *et al.*, 1983; Gummere *et al.*, 1986; Lenington *et al.*, 1988; Ardlie & Silver, 1996). At the individual level, *t* haplotypes have severe negative fitness effects. In homozygous condition, all *t* haplotypes induce male sterility (at least all 'complete' *t* haplotypes; Lyon, 1991; Johnson *et al.*, 1995). Moreover, many *t* haplotypes carry recessive lethals, leading to the death and abortion of both female and male embryos. Up to now no less than 16 different recessive lethals, located at different positions within the *t* complex, have been found (Klein *et al.*, 1984). Evolution at the *t* complex is probably also affected by interdeme selection (Lewontin, 1962). In fact, house mouse populations are generally thought to be subdivided into small, relatively isolated breeding clusters (e.g. Singleton & Hay, 1983; Lidicker & Patton, 1987), and *t*-bearing demes may have a much higher probability of extinction.

A large number of models have been analysed to study the evolutionary dynamics of *t* haplotypes, both in the context of a large well-mixed population (e.g. Bruck, 1957; Dunn & Levene, 1961) and in the context of a deme-structured metapopulation (e.g. Lewontin & Dunn, 1960; Lewontin, 1962; Levin *et al.*, 1969; Petras & Topping, 1983; Nunney & Baker, 1993; Durand *et al.*, 1997). The deterministic models for large, well-mixed populations generally predict unrealistically high distorter frequencies (but see Petras, 1967; Lewontin, 1968). Most metapopulation models have focused on this problem: they consider one specific distorter allele and address the question of whether a satisfying fit between empirical estimates and theoretical expectation is obtained if population structure is taken into account. We are less interested in such realistic predictions for a specific distorter allele. Instead, we consider a broad spectrum of distorter alleles which we compare with respect to their frequency in the metapopulation. This allows us, in the spirit of Lewontin's (1962) seminal paper, to investigate how the success of a distorter is affected by its segregation ratio and its fitness effects.

We present a metapopulation model which captures the most important features of sex-specific segregation distortion in a deme-structured population. First, we show how the frequency of a distorter allele depends on its basic characteristics (i.e. segregation ratio, fitness effects), and on structural aspects of the population (e.g. deme size, migration rate, sex ratio). We then try to gain a better understanding of the factors that determine the success of a distorter (invasion efficiency, typical

frequency, persistence ability, deme productivity, migrant production). To this end, we analyse a simple Markov model, which describes the dynamics of segregation distortion in a single deme. Compared to the individual-based simulation model, the state-based Markov model has the advantage of analytical tractability.

Let us stress from the beginning that we strive more for conceptual clarification than for the most adequate representation of a particular system. Although the model structure and parameters resemble the situation at the *t* complex, we have not tried to capture all aspects of house mouse populations in the most realistic way. In our opinion, a realistic model is hardly achievable since population structure is not known in sufficient detail, and probably varies considerably. We show, however, that our conclusions are rather robust and that they also apply to Nunney & Baker's (1993) model that was specifically tailored to the *t* complex.

Models and methods

Motivated by the *t* complex of the house mouse and other prominent examples of segregation distortion, we consider segregation distorters which have strong negative fitness effects in homozygous condition, and which distort Mendelian segregation in heterozygous males. More specifically, we focus on segregation distorters which lead to sterility of males homozygous for the distorter allele ('sterile' distorters) and on distorter alleles that induce lethality of both female and male zygotes when homozygous ('lethal' distorters). A single autosomal gene locus is considered with a wildtype allele and a distorter allele *t*. The segregation ratio or fraction of distorter alleles contributed by heterozygous *+t* males is denoted by σ . Hence, $\sigma = 0.50$ means that segregation is Mendelian. We will first present our basic simulation model which describes the dynamics of segregation distortion in a deme-structured population. To analyse the dynamics of segregation distortion in small, isolated populations (i.e. in the absence of migration), we also consider a Markov model. This model closely resembles the simulation model for the case of no migration.

The simulation model

Consider a metapopulation which consists of a large number of demes that are connected by migration. Within each deme there is a fixed maximum number of $N^{\text{♀}}$ adult females and $N^{\text{♂}}$ adult males. Generations are nonoverlapping, mating occurs at random, and each female is able to produce a maximum of z zygotes. As a result, a deme may produce $N^{\text{♀}}z$ offspring per generation. However, the actual number of offspring produced will be lower if a deme contains sterile males, or if zygotes happen to be homozygous for a lethal distorter allele. Per female gamete, a male gamete is chosen from a randomly chosen male. In case of a sterile distorter, we assume that

no zygote is produced if the male is sterile. Hence, the reduction in the actual number of zygotes produced is proportional to the number of sterile males. In case of a lethal distorter, no zygote is produced if both the female and the male contribute a gamete carrying a lethal distorter allele. The sex of the offspring is determined at random: with probability $\frac{1}{2}$ it is a female, and with probability $\frac{1}{2}$ it is a male. From the offspring a number of N^{\square} females and N^{δ} males is chosen at random to make up the next generation of adults. The supernumerary offspring that do not succeed in acquiring a position in their local deme enter a common pool of migrants. In case that less than N^{\square} female offspring or less than N^{δ} male offspring are produced, deme size is reduced accordingly, and such a deme does not produce female or male migrants.

Migration operates via the replacement of deme members by randomly chosen individuals from the migrant pool. With probability m , a resident individual is replaced by a migrant. Moreover, if a deme does not contain any female or male, an individual from the missing sex is added from the migrant pool. In this way, recolonization by a founding individual from the missing sex prevents extinction of a deme.

Model parameters

The metapopulation model was analysed by means of computer simulations. In all simulations the number of demes was $n = 1000$, so that the effects of population-wide genetic drift are minimized. We focused on metapopulations with small deme size ($N = 6$), intermediate deme size ($N = 10$) and large deme size ($N = 20$), where $N = N^{\square} + N^{\delta}$. Throughout the sex ratio is 1:1, unless otherwise stated. The number of offspring per female in the absence of segregation distortion is set at $z = 6$. This corresponds, roughly, to empirical estimates for the house mouse (Pelikan, 1981; Sage, 1981). Immigration rates varied from $m = 0.025$ to $m = 0.1$. All simulations shown here were started with one randomly assigned copy of the distorter allele per deme. However, the initial composition of the metapopulation did not seem to affect the results, since regardless of the initial composition populations quickly (within 200 generations, say) reached a characteristic composition. All simulations were run for 1000 generations. The frequency of the distorter allele in the migrants, and the distorter frequency in the metapopulation were determined by taking the metapopulation average over the last 500 generations.

The Markov model

In the Markov model we consider a single deme with a fixed number of N^{\square} adult females and N^{δ} adult males. The unordered genotype frequencies at the adult stage are denoted by P_{++}^{\square} , P_{+t}^{\square} and P_{tt}^{\square} in the females, and P_{++}^{δ} ,

P_{+t}^{δ} and P_{tt}^{δ} in the males. Let us first consider g_t^{\square} and g_t^{δ} , the relative frequencies of t -bearing gametes produced by females and males, respectively. In case of a lethal distorter, tt adults are absent ($P_{tt}^{\square} = P_{tt}^{\delta} = 0$). As a consequence, the gamete frequencies are given by

$$\begin{aligned} g_t^{\square} &= \frac{1}{2} P_{+t}^{\square} \\ g_t^{\delta} &= \sigma P_{+t}^{\delta}. \end{aligned} \quad (1a)$$

In case of a sterile distorter, homozygous tt individuals are viable, but the males are sterile. Hence a fraction P_{tt}^{δ} of males does not contribute gametes to the next generation. Therefore, the relative gamete frequencies are given by

$$\begin{aligned} g_t^{\square} &= \frac{1}{2} P_{+t}^{\square} + P_{tt}^{\square} \\ g_t^{\delta} &= \sigma \frac{P_{+t}^{\delta}}{1 - P_{tt}^{\delta}}. \end{aligned} \quad (1b)$$

To avoid unnecessary complexity, we assume random union of gametes rather than random mating. Hence, the probabilities of forming a $++$, $+t$, or tt zygote are given by

$$\begin{aligned} P_{tt}^* &= g_t^{\square} g_t^{\delta} \\ P_{+t}^* &= g_{+}^{\square} g_t^{\delta} + g_t^{\square} g_{+}^{\delta} \\ P_{++}^* &= g_{+}^{\square} g_{+}^{\delta}, \end{aligned} \quad (2)$$

where $g_{+}^{\square} = 1 - g_t^{\square}$ and $g_{+}^{\delta} = 1 - g_t^{\delta}$ are the relative frequencies of wildtype gametes. To make up the new generation of adults, N^{\square} females and N^{δ} males are formed by randomly assigning genotypes according to the probability distribution specified by eqs (1) and (2).

In the Markov model, extinction of a population is modelled as follows. The females of a deme are able to produce a number of $N^{\square}z$ potential zygotes, where z is a fixed fertility parameter. If φ denotes the probability that a female gamete is fertilized and viable, $N_z = N^{\square}z\varphi$ viable zygotes will be produced on average. We assume that a population will go extinct if the number of viable zygotes is smaller than a certain critical number N_0 . The probability of population extinction is therefore

$$\text{Prob}(N_z < N_0) = \sum_{n < N_0} \binom{N^{\square}z}{n} \varphi^n (1 - \varphi)^{N^{\square}z - n}. \quad (3)$$

Typically, we have taken $N_0 = N^{\square} + N^{\delta}$, which means that extinction occurs if not enough viable zygotes are formed to make up a next generation of $N^{\square} + N^{\delta}$ individuals.

The probability φ that a female gamete is fertilized and that the resulting zygote is viable depends on the availability of fertile males in case of a sterile distorter and on the production of viable zygotes in case of a lethal distorter. For a sterile distorter we assume, in accordance with the metapopulation model, that each female mates with a single, randomly chosen male. Hence, φ should be proportional to the fraction of fertile males:

$$\varphi_{\text{sterile}} = 1 - P_{tt}^{\delta} \quad (4a)$$

The consequences of this assumption will be discussed below. In case of a lethal distorter, all zygotes are fertilized and φ is given by the probability that a zygote is viable, i.e. that it is not of the lethal genotype tt :

$$\varphi_{\text{lethal}} = 1 - P_{tt}^* = 1 - g_i^{\circ} g_i^{\delta} \quad (4b)$$

For any choice of φ , the Markov model can now easily be specified: the states of the model are given by all possible distributions of the three genotypes over N° females and N^{δ} males plus one state corresponding to extinction. The number of states may be quite large, and is given by $1/4(N^{\circ} + 1)(N^{\delta} + 1)(N^{\delta} + 2) + 1$. For a given state, the corresponding genotype distributions P_{\dots}° and P_{\dots}^{δ} are readily calculated. The probability distribution over the states in the next generation is then given by eqs (1) and (2) in case of deme survival, while the probability of deme extinction is given by eqs (3) and (4). This process can be characterized by a matrix M of transition probabilities, where m_{ij} denotes the probability that a population in state j enters state i in the next generation (e.g. Kemeny & Snell, 1960).

An advantage of the Markov model over the metapopulation model is that the expected fate of an allele can be obtained directly and analytically from the transition matrix M (see below). On the other hand, some simplifying assumptions had to be made. For instance, extinction is modelled as an all or nothing event, rather than being the result of gradual population decline. Accordingly, the genetic composition of a population has no effect on population size until a certain threshold is crossed. Furthermore, we assumed random union of gametes instead of random mating. However, these discrepancies between the Markov model and the metapopulation model are apparently of marginal importance. With respect to all but one of the measures considered in this study, the Markov model produces virtually identical results as the metapopulation model in the absence of migration ($m = 0$). Only with respect to persistence ability there are some quantitative (but no qualitative) differences between both models, as will be discussed below. Regardless, our simplifying assumptions do not really pose a problem since the Markov model mainly serves a conceptual purpose.

Analysis of the Markov model

We use the Markov model to investigate various determinants of the success of a distorter allele within an isolated deme. In particular, we consider the invasion success of a rare distorter allele in a wildtype deme, the persistence ability of a distorter allele once established in a deme, the typical frequency that an established distorter reaches, and the productivity of a deme as a function of its distorter frequency.

Invasion efficiency

The success of a segregation distorter in a metapopulation depends crucially on its ability to become established in a wildtype deme. Let us operationally define the invasion efficiency of a rare distorter by the probability that it ever reaches a certain critical frequency p_{crit} . This probability was obtained from the Markov model in the following manner: starting with a given initial genotype distribution, the Markov process is iterated, thereby killing those paths where the distorter has reached the critical frequency. An alternative method is to replace those states of the Markov model that correspond to distorter frequencies equal or above the critical frequency by a single absorbing state. The invasion efficiency then corresponds to the probability that the absorbing state is reached and can be obtained directly from the fundamental matrix of the corresponding reduced Markov model (e.g. Kemeny & Snell, 1960).

Persistence ability

The time that a distorter is able to persist in a deme is another important determinant of its success. Quite generally, the rate at which polymorphism is lost will be higher in a small deme than in a large deme. In order to compensate for this general effect, we will compare the rate at which a distorter allele is lost with the rate at which a neutral allele is lost in a deme of size $N = N^{\circ} + N^{\delta}$. To this end, we apply Robertson's (1962) concept of a 'retardation factor'. In our context, the retardation factor is defined as

$$R = \frac{1 - \lambda_n}{1 - \lambda_s}, \quad (5)$$

where $1 - \lambda_n$ and $1 - \lambda_s$ represent the rate at which polymorphism is lost in case of neutral and distorter alleles, respectively.

Technically, λ_n and λ_s correspond to the largest nonunit eigenvalue of the Markov chains describing genetic drift acting on a neutral and a distorter locus, respectively (e.g. Gale, 1990). In case of segregation distortion, λ_s can be calculated numerically from the Markov matrix M . In case of neutral alleles, it is well known that in a haploid, asexual population of size $2N$ polymorphism is lost at a rate $\lambda_n = 1 - [1/(2N)]$. For a dioecious population consisting of N° females and N^{δ} males, λ_n is slightly larger (Li, 1976; p.337) and given by

$$\lambda_n = 1 - \frac{1}{2N_e} + \frac{1}{2} \left(\sqrt{1 + \frac{1}{N_e^2}} - 1 \right), \quad (6)$$

where $N_e = \frac{4N^{\circ}N^{\delta}}{N^{\circ} + N^{\delta}}$.

Typical frequency

In an infinite population, a sterile or lethal distorter reaches a stable equilibrium where its frequency is positively related to its segregation ratio (see eqn 7

below). In a finite population, a stable polymorphic equilibrium does not exist since the ultimate fate of every deme is either extinction or fixation of the wildtype allele. We may, however, focus on the frequency that a distorter 'typically' reaches in a polymorphic deme. The typical frequency is of importance since it determines the productivity of a deme and the representation of the distorter allele in the migrants. This frequency is determined from the eigenvector of genotype frequencies that belongs to λ_s , the first nonunit eigenvalue of the Markov matrix M (e.g. Gale, 1990).

Deme productivity

The Markov model was also used to determine the productivity of a deme as a function of the distorter frequency. A deme without any distorter allele produces exactly N^2z offspring, of which $N = N^2 + N^3$ stay in their natal deme. Hence, such a deme produces an excess of $N^2z - N$ migrant individuals. In case of segregation distortion, the number of viable zygotes is reduced by a fraction ϕ (see eqn 4), and the number of emigrants is reduced accordingly. To determine the number of emigrants produced by a deme with a certain distorter frequency, we calculated the expected number of migrants for all possible genotype combinations, and weighted the output of emigrants by their probability of occurrence (given by the eigenvector corresponding to the first nonunit eigenvalue λ_s).

Results

Distorter frequency as a function of the segregation ratio

In an infinite, well-mixed population a sterile or a lethal distorter reaches a stable equilibrium which depends on its segregation ratio σ . It is well known (Bruck, 1957; Dunn & Levene, 1961) that the equilibrium frequency of the distorter in adults is given by

$$\begin{aligned} p_{\text{sterile}}^* &= 2\sigma - 1 \\ p_{\text{lethal}}^* &= \frac{1}{2} - \frac{1}{2} \sqrt{\frac{1-\sigma}{\sigma}} \end{aligned} \quad (7)$$

Figure 1 shows that, in the metapopulation context, the frequency of a distorter allele is always smaller. In fact, the frequency of a distorter decreases with decreasing deme size or immigration rate. This is not surprising since a small deme size and/or a low immigration rate enhance the efficiency of selection at the population level. Notice that very weak distorters with only a slight segregation advantage (e.g. $\sigma = 0.55$) cannot persist at all in the metapopulation. Again, this is especially so if deme size is small or if the immigration rate is low.

Lethal distorters (right-hand panels), generally profit from a high segregation ratio. In fact, their frequency in the metapopulation is positively related to the segrega-

tion ratio (but see Fig. 9B below). In case of a sterile distorter, the relation between segregation ratio and frequency is less straightforward. Typically, a sterile distorter reaches the highest frequency at an intermediate segregation ratio. This 'optimal' segregation ratio decreases as deme size gets smaller and/or as the immigration rate is reduced. For instance, in a metapopulation with deme size $N = 20$, the segregation ratio where a distorter reaches the highest frequency increases from $\sigma_{\text{opt}} = 0.80$ if $m = 0.025$, to $\sigma_{\text{opt}} = 0.90$ if $m = 0.1$. Notice furthermore, that very efficient sterile distorters with high segregation ratios may not be able to persist at all if deme size is too small or if the immigration rate is too low.

To obtain a better understanding of these results, we used the Markov model to study the fate of various sterile distorters after being introduced in a single copy into a wildtype deme. As shown in Fig. 2(A), the short-term success of a distorter does not necessarily coincide with its success in the longer run. During the first few generations, the distorter with the highest segregation ratio has the highest probability to remain in the population. Later on, however, this distorter is lost at a much higher rate than those with a lower segregation ratio. As a result, the distorter with the intermediate segregation ratio has the highest probability to be still present after 25 generations. Figure 2(B) illustrates how this can be explained. In the first generations, where the distorter frequency is low, genetic drift is the main cause of loss of the distorter. Apparently, a higher segregation ratio buffers a distorter against loss in this critical phase. In later generations, where the distorter frequency is high, deme productivity is significantly impaired. Now, loss of the distorter due to population extinction becomes paramount. Accordingly, especially efficient distorters are endangered since they attain the highest frequencies.

Hence, the segregation ratio may affect the invasion efficiency and the persistence ability of a distorter in a different way. We will now use the Markov model to investigate these and other determinants of success more systematically.

Invasion efficiency

Figure 3 shows that the invasion success of a rare distorter is always positively related to its segregation ratio. This is not surprising, since the risk of getting lost due to genetic drift is reduced for efficient distorters which are transmitted at a high rate by heterozygous males. The negative fitness effects at the individual level (sterility or lethality) do not matter in the initial phase of invasion. In fact, these effects only occur in homozygous condition, and homozygotes are very rare as long as the distorter frequency is low. As a consequence, the invasion prospects of sterile and lethal distorters are almost identical. Notice, however, that even the most efficient

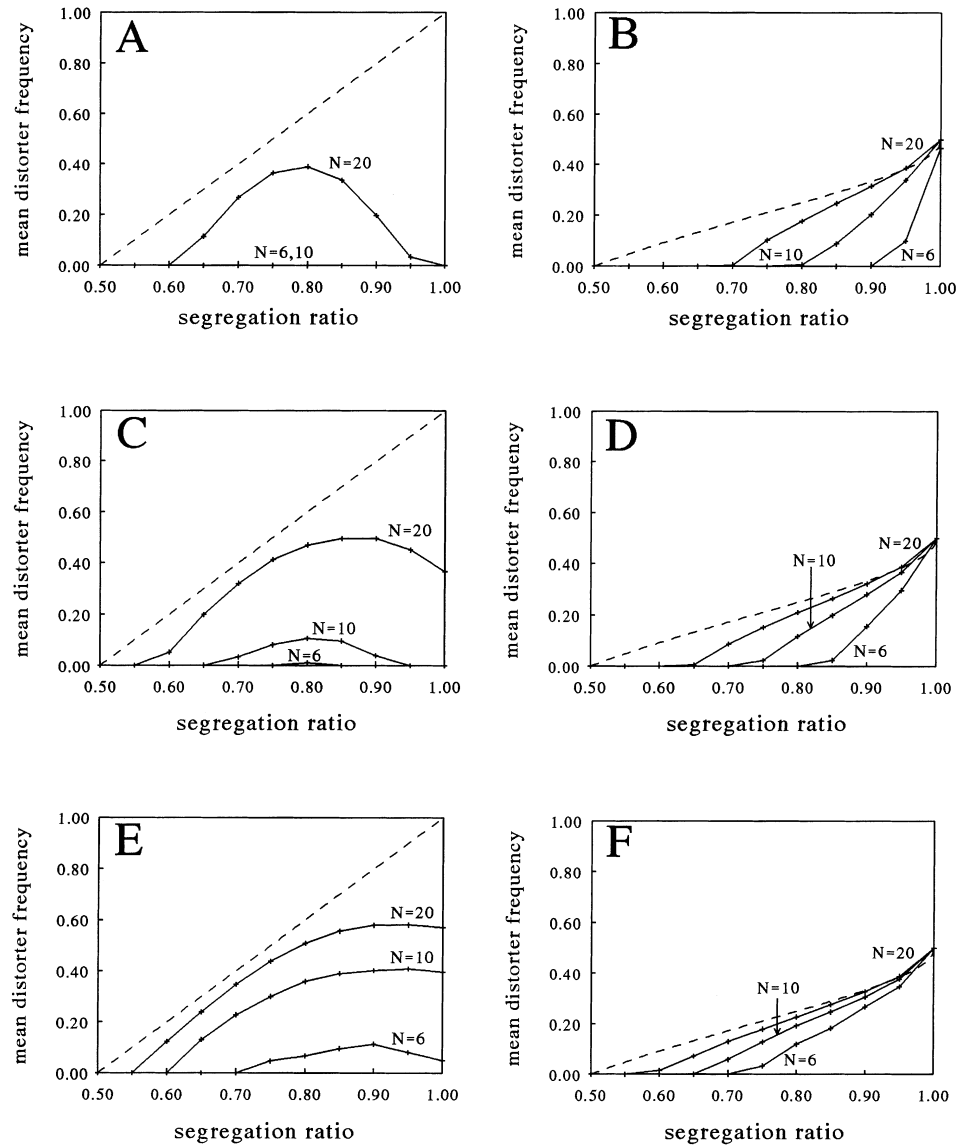


Fig. 1 Distorter frequency in a metapopulation as a function of the segregation ratio. The left-hand panels (A), (C) and (E) consider sterile distorters, while the right-hand panels (B), (D) and (F) consider lethal distorters. In (A) and (B) the immigration rate is low ($m = 0.025$), in (C) and (D) it is intermediate ($m = 0.05$), and in (E) and (F) it is high ($m = 0.1$). The metapopulation consists of demes of maximal size, $N = 6, 10$ and 20 , respectively. The dashed lines give the equilibrium frequency in an unstructured, infinitely large population (eqn 7).

segregation distorters ($\sigma = 1.0$) are not always successful in invading a wildtype deme, and may well be lost by chance.

The fact that the invasion success of a rare distorter is highest in the smallest populations is to a certain extent an artefact of our definition of invasion efficiency. In fact, in a small population a distorter allele starts with a higher frequency ($= 1/(2N)$), and less copies of the distorter are required to reach the critical frequency p_{crit} (here $p_{\text{crit}} = 0.25$).

Frequency in a polymorphic deme

Figure 4 shows that the 'typical' frequency of a distorter allele in an isolated polymorphic deme is generally positively related to the segregation ratio. However, in

case of a sterile distorter (Fig. 4A) the typical frequency is not always maximal for $\sigma = 1$, but for slightly lower segregation ratios.

Compared to the equilibrium frequency in an infinite population (dashed lines), the typical frequency of a sterile distorter (Fig. 4A) is higher than the deterministic equilibrium frequency for low segregation ratios (< 0.75) and lower for high segregation ratios (> 0.75). For a lethal distorter (Fig. 4B) the typical frequency in a small deme is always higher than the deterministic equilibrium frequency. The deviations between the typical frequency and the deterministic equilibrium frequency are largest if the latter is close to 0 or 1 and if deme size is small. As expected, the conformity between typical frequency and deterministic equilibrium frequency gets better with increasing population size.

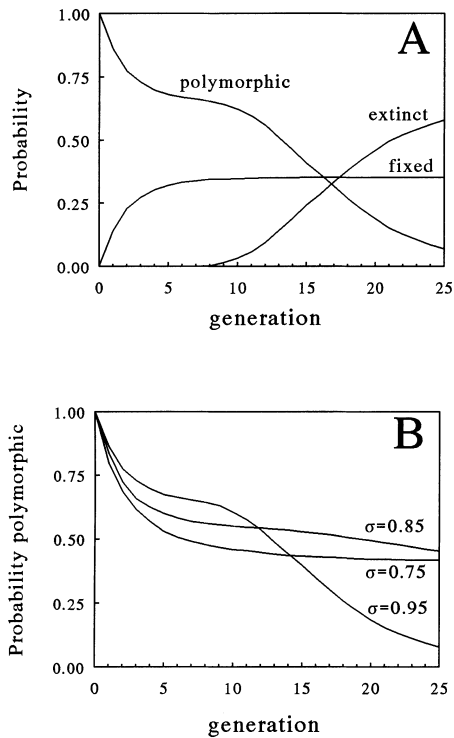


Fig. 2 The fate of a sterile segregation distorter after being introduced in a single copy (a heterozygous male) into a wildtype deme ($N^{\text{f}} = N^{\text{s}} = 10$): (A) gives for three segregation ratios the probability that the population remains polymorphic, while (B) shows for $\sigma = 0.95$ the probability that the population is either fixed for the wildtype allele, extinct, or still polymorphic as a function of time.

Compared to the frequency in the metapopulation as a whole (Fig. 1), the typical frequency of a distorter allele in an isolated polymorphic deme is considerably higher. This phenomenon is of some practical relevance for the *t* complex of the house mouse, since the distorter frequency in polymorphic units is sometimes used to estimate the distorter frequency in the total population. The discrepancy between the ‘local’ and ‘global’ distorter frequency is explained by the fact that the typical frequency in a deme only refers to *polymorphic* demes,

while *all* demes contribute to the mean frequency in the metapopulation. Demes with extreme distorter frequencies (i.e. with frequencies close to 0 or 1) are most prone to fixation or extinction. As a consequence, intermediate allele frequencies (closer to 0.50) are overrepresented in polymorphic demes. This explains why for both types of distorters the typical frequency in a polymorphic deme (Fig. 4) lies somewhere between 0.50 and the equilibrium frequency in an infinite population.

Persistence ability

The time that a segregation distorter is able to persist in a deme is another important determinant of its success (Lewontin, 1962). Here we quantify the persistence ability of a distorter allele by the retardation factor *R* (see eqn 5). *R* has a clear-cut interpretation: if *R* = 10, polymorphism is lost at a rate 10 times more slowly than for neutral alleles, while if *R* = 0.1 it is lost 10 times faster.

Figures 5(A) and (B) show the results for the default parameter setting (*z* = 6). Clearly, sterile as well as lethal distorters persist for the longest times if the segregation ratio is intermediate. However, it is also clear that with respect to persistence the optimal segregation ratio is much smaller for sterile distorters than for lethal distorters ($0.60 < \sigma_{\text{opt}} < 0.70$ for a sterile distorter vs. $0.85 < \sigma_{\text{opt}} < 0.95$ for a lethal distorter). Moreover, the optimal segregation ratio also depends on deme size: in small demes the optimal segregation ratio is somewhat lower than in large demes. It is further interesting to note that in small demes (*N* = 6, 10) a sterile segregation distorter, its segregation advantage notwithstanding, is always lost at a higher rate than a neutral allele.

These phenomena can be explained as follows. A distorter allele with a low segregation ratio typically reaches a low frequency in a deme. Therefore, it is easily lost by genetic drift. If, on the other hand, the segregation ratio is high, a distorter will typically be present in high frequency. Demes with a high frequency of a distorter allele are easily driven to extinction. In this way, a segregation distorter may rapidly be lost from a poly-

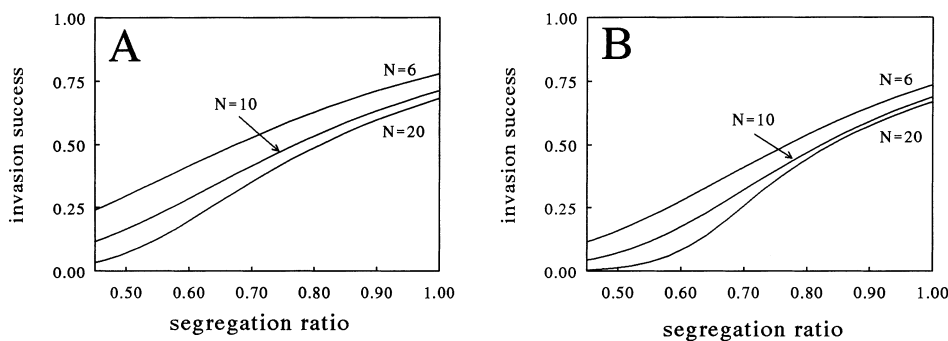
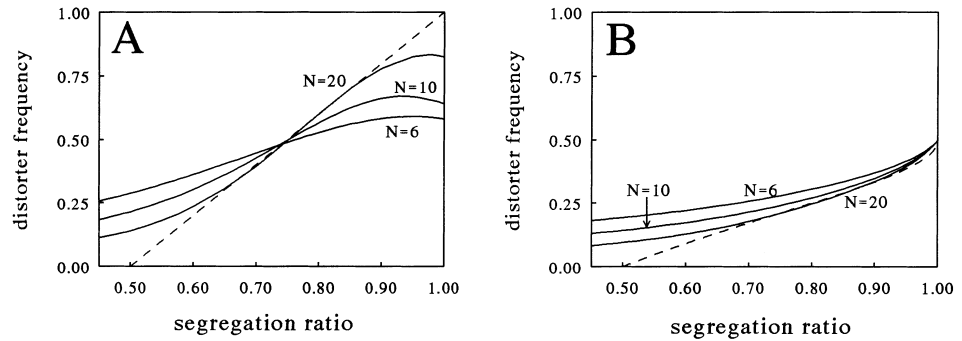


Fig. 3 Invasion efficiency of a sterile (A) or a lethal (B) segregation distorter after being introduced into a wildtype deme. In all cases, one heterozygous +*t* male was introduced into a wildtype deme of maximal size, *N* = 6, 10 and 20, respectively. Invasion efficiency is operationally defined by the probability that the distorter allele ever reaches a critical frequency 0.25.

Fig. 4 Typical frequency of a sterile (A) and a lethal (B) segregation distorter in an isolated deme as a function of its segregation ratio. The dashed lines represent the equilibrium frequency in an infinite population (eqn 7).



morphic deme if it has a low segregation ratio *and* if it has a high segregation ratio.

The probability of population extinction is strongly affected by the productivity of a deme. In Figs 5(C) and (D) the potential number of zygotes per female is reduced from $z = 6$ to $z = 3$. In comparison with Figs 5(A) and (B), the optimal segregation ratio is decreased considerably ($0.50 < \sigma_{opt} < 0.60$ for a sterile distorter and $0.60 < \sigma_{opt} < 0.75$ for a lethal distorter). Moreover, for most segregation ratios and population sizes, a distorter is now lost much more rapidly than a neutral allele.

We based our judgement of the persistence ability on the Markov model which differs in one important aspect from the metapopulation model: deme extinction is an all or nothing event and not the result of gradual

population decline. It is therefore not surprising that the loss of distorter alleles is somewhat slower in the metapopulation context than in the Markov model. Despite these quantitative differences, the two models lead to qualitatively the same conclusions. In fact, the dependence of the retardation factor on the segregation ratio has the same shape in both contexts. Moreover, the retardation factor is similarly affected by the other characteristics of the distorter (male sterility vs. lethality in both sexes), or by structural aspects such as deme size, female productivity and the sex-ratio.

Summarizing, the rate at which a segregation distorter is lost from a small population depends in a complicated way on the type of distorter, on the segregation ratio and on the potential productivity of a deme. For most parameter settings segregation distorters with intermedi-

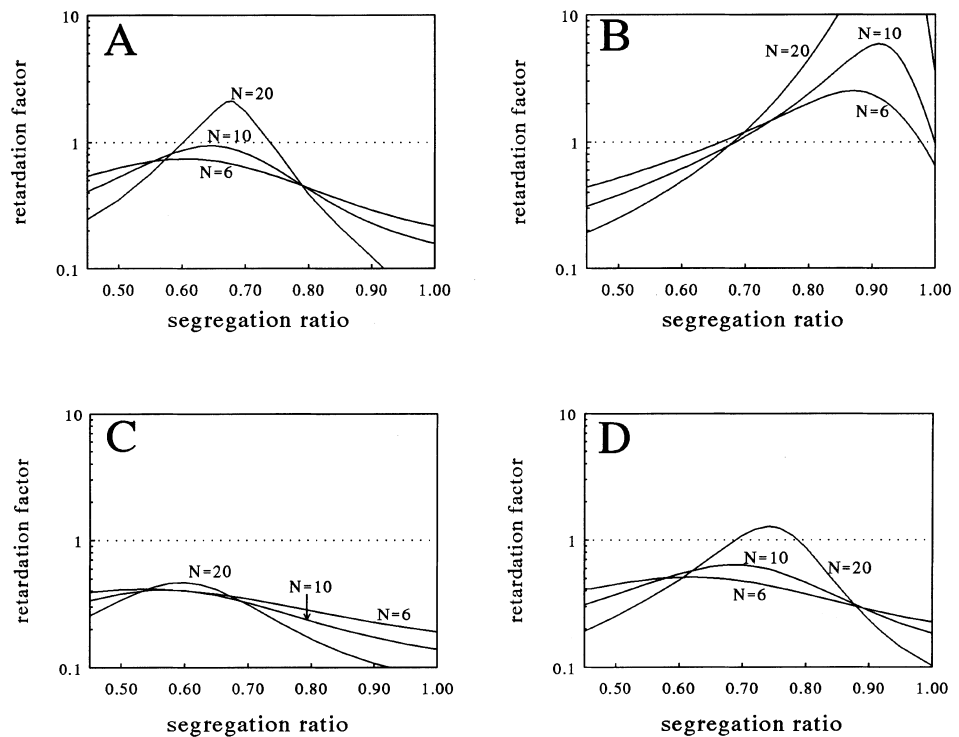


Fig. 5 Retardation of the rate at which polymorphism is lost for sterile distorters (left-hand side panels), and lethal distorters (right-hand side panels): (A) and (B) give the results for the standard configuration where the maximal number of zygotes per female is $z = 6$. Panels (C) and (D) show the results when female productivity is decreased to $z = 3$.

ate segregation ratios provide the best persistence ability. Moreover, the optimal segregation ratio with respect to persistence is typically lower for sterile than for lethal distorters.

Deme productivity

Interdeme selection operates if demes differ in productivity and/or if there is differential extinction and colonization of demes (e.g. Williams, 1966). Obviously, the total production of emigrants will be negatively related to the distorter frequency. This is illustrated in Fig. 6 for a sterile (left-hand panel) and a lethal (right-hand panel) distorter allele with segregation ratio $\sigma = 0.85$. From the point of view of the distorter, however, the total emigrant production is less important than the production of *t*-bearing emigrants. In this respect, the production of emigrants is highest for those demes in which the distorter frequency is intermediate. This results from the fact that although the absolute production of migrants is negatively related to the distorter frequency, the fraction of distorter-bearing individuals in the migrants increases with the distorter frequency. Note furthermore that adults homozygous for

a lethal distorter (*tt*, right-hand panel) do not exist. Therefore, the frequency of a lethal distorter can never be higher than 0.50.

Figure 6 gives an illustration for a specific example ($\sigma = 0.85$, $N = 20$). However, the phenomenon that the production of emigrants which carry a distorter allele is highest for intermediate distorter frequencies is quite general (data not shown).

As shown above, the productivity of a deme strongly depends on the distorter frequency, which fluctuates in time. As a consequence, the average productivity of a deme reflects the distribution of distorter frequencies in the deme over time. Since this distribution is strongly affected by migration, it is not useful to study the productivity of a deme in isolation (i.e. on basis of the Markov model). Therefore, we will now use the metapopulation model to study the distribution of distorter frequencies, and its implications for deme productivity.

Distribution of distorter frequencies in the metapopulation

Figure 7 shows for several distorter alleles the distribution of distorter frequencies in the demes of the meta-

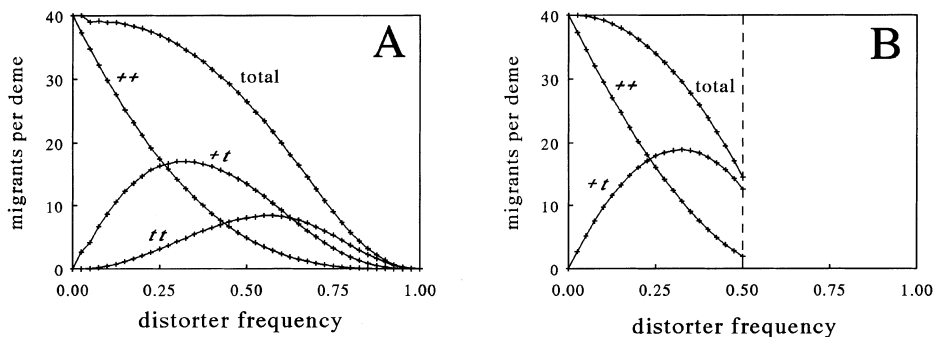


Fig. 6 Productivity of a deme as a function of the distorter frequency in case of a sterile distorter (A), and a lethal distorter (B). In both panels deme size is $N = 20$, and the segregation ratio is $\sigma = 0.85$. Given are the total number of emigrants, the number of wildtype emigrants (*++*), the number of heterozygous emigrants (*+t*), and the number of emigrants homozygous for the distorter allele (*tt*). In case of a lethal distorter *tt* individuals are absent, and, as a consequence, the distorter frequency cannot exceed 0.50.

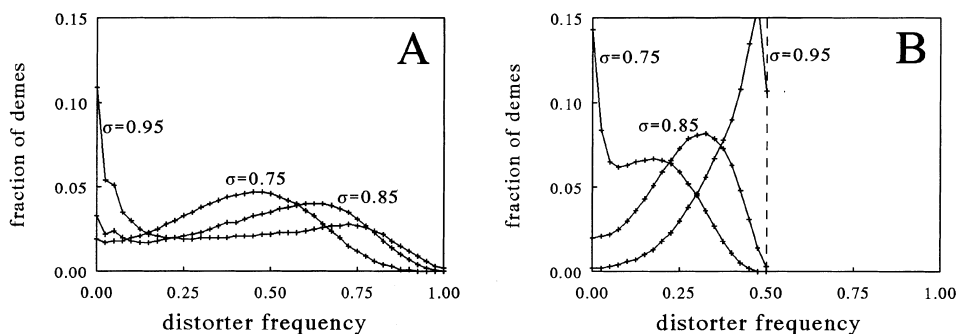
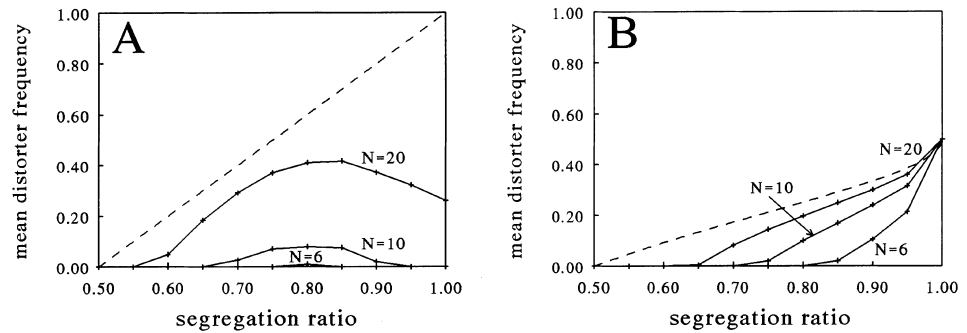


Fig. 7 Distribution of distorter frequencies in a metapopulation for three sterile (A), and three lethal (B) distorters. Segregation ratios are set at $\sigma = 0.75$, 0.85 and 0.95 , maximal deme size is $N = 20$ and the immigration rate is $m = 0.05$.

Fig. 8 Frequency of sterile (A), and lethal (B) segregation distorters in the migrant pool as a function of the segregation ratio. The metapopulations consist of $n = 1000$ demes, deme size is $N = 20$, the maximal number of zygotes per female is $z = 6$ and the immigration rate is $m = 0.05$, so that the figure should be compared with Figs 1(C) and (D).



population. Deme size is $N = 20$ and the immigration rate is $m = 0.05$. Typically, the distribution of distorter frequencies is bimodal, with a peak at a zero distorter frequency and a second one at an intermediate distorter frequency. For both sterile and lethal distorters the latter peak shifts to the right as the segregation ratio increases. This is a reflection of the fact that efficient distorters tend to reach high frequencies within single demes. However, a high distorter frequency brings along a risk of population extinction. If deme extinction occurs, a new deme is founded by a pair of individuals from the migrant pool. A newly founded deme may coincidentally not contain any distorter allele. But even if it does contain a distorter allele, such an allele may be lost in the initial phase by chance. Hence, due to a higher rate of extinction and recolonization, a metapopulation with an efficient distorter may have a very high fraction of demes where the distorter allele is absent. This is exemplified in Fig. 7(A) which shows that the metapopulation with the most efficient sterile distorter actually has the highest fraction of wildtype demes. Since population extinction generally occurs much less easily for lethal distorters (Fig. 5), this phenomenon does not occur for the efficient lethal distorter of Fig. 7(B). Instead, the frequency distribution has a single high peak at a distorter frequency of 0.475 at which most individuals are heterozygous for the wildtype and the distorter allele.

The fact that the distribution of distorter frequencies is not narrowly centred around its average value may have practical implications. Take, for example, the most

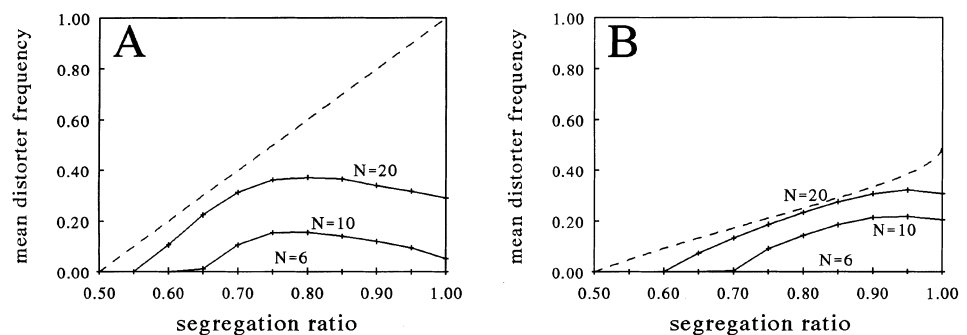
efficient sterile distorter ($\sigma = 0.95$) of Fig. 7(A). For this distorter a large fraction of demes (0.11) does not contain the distorter allele at all. In case that a deme is polymorphic, the distorter frequency may be anywhere between 0 and 1. In other words, the variance of distorter frequencies within demes is considerable, and a large number of samples from different demes is needed to obtain an accurate estimate of the average distorter frequency. In practice, however, this is often not feasible, and estimates of t haplotype frequencies are usually derived from a relatively small number of samples (reviewed by Lenington *et al.*, 1988).

We have now derived the deme productivity given a certain distorter frequency (Fig. 6) and the distribution of distorter frequencies in the metapopulation (Fig. 7). Together, they determine the average productivity of demes and the representation of a distorter allele in the migrant pool. Figure 8 shows how the distorter frequency in migrants depends on the segregation ratio. For the parameters shown ($m = 0.05$), Fig. 8 corresponds to Figs 1(C) and (D) which give the distorter frequency within demes. Both figures are strikingly similar. Notice, however, that the frequency of the segregation distorter is consistently lower in the migrant pool than it is within demes.

Effect of parameters and model structure

In order to investigate the robustness of our conclusions, we will now analyse how the results are affected by the

Fig. 9 Female productivity and the frequency of a sterile (left-hand panel) and lethal (right-hand panel) distorter in the metapopulation. The maximal productivity of a female is reduced from the default value of $z = 6$ (Fig. 1) to $z = 3$. The immigration rate is $m = 0.1$.



productivity of females, the sex ratio, the mating system and other structural assumptions of our model.

Figure 9 shows how the distorter frequency in the metapopulation changes when female productivity is decreased from $z = 6$ to $z = 3$. Both sterile and lethal distorters now reach considerably lower frequencies (cf. Figs 1E and F). Moreover, lethal distorters now also reach the highest frequency at an intermediate segregation ratio: for a high segregation ratio the reduced productivity of demes and the loss of lethal distorters by population extinction apparently outweigh their effectiveness in invading new populations. This shows that if productivity is low, lethal distorters may also benefit from an intermediate segregation ratio.

Throughout, we focused on populations with an equal number of females and males. Since the roles of females and males are asymmetric with respect to the segregation advantage, the selection regime, and the extinction criterion, it is not obvious how a bias in the sex ratio affects the results. On the one hand, a biased sex ratio increases the relative importance of genetic drift. Therefore, a skewed sex ratio tends to decrease the frequency of a distorter allele. On the other hand, a female-biased sex ratio increases the potential productivity of a deme (N^2z), and may therefore also increase the persistence ability of a segregation distorter. This is indeed so for a lethal distorter, for which the actual productivity of a deme is positively related to the number of females. For a sterile distorter, however, the actual productivity of a deme may not only depend on the number of females, but also on the number of males: a deme with a small number of males is more likely to accidentally contain only sterile males than is a deme with more males. As a result, a sterile distorter generally profits from a relatively even sex ratio, while for a lethal distorter a female-biased sex ratio is favourable (data not shown).

Up to now we have assumed that each female mates with a single, randomly chosen male. As a consequence, the reduction in the number of offspring is proportional to the number of sterile males. However, other assumptions on the mating system may be equally plausible. If, for instance, a sterile male cannot withhold a female from mating with other males, one fertile male could already be sufficient to fertilize all females. In this case deme productivity is only impaired and deme extinction only occurs if *all* males are sterile (cf. Lewontin, 1962). As a consequence, deme extinction is a rare event, and the distorter frequency is higher, especially at high segregation ratios (Fig. 10A, which should be compared with Fig. 1E). Still, distorters with intermediate segregation ratios reach the highest frequencies. However, in comparison with Fig. 1(E) the segregation ratio for which a distorter reaches the highest frequency is increased.

Males compete equally for access to females in our basic metapopulation model. However, it may be more realistic to assume that males compete for dominance, and that only a small number of 'dominant' males

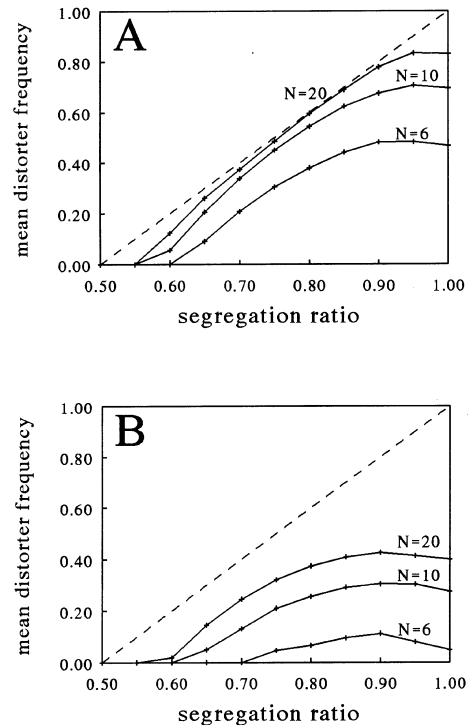


Fig. 10 Effect of the mating system on the frequency of a sterile distorter in the metapopulation. In the upper panel one fertile male suffices to guarantee maximal deme productivity. In the bottom panel three randomly chosen dominant males produce all offspring. In both panels the immigration rate is $m = 0.1$.

produce all offspring ('dominance polygyny', Nunney, 1993). Figure 10(B) shows the results if three randomly chosen males are dominant per deme. Under this mating system the variance in male reproductive success is increased. As a result, genetic drift becomes more important, and the distorter frequency is lowered (cf. Fig. 1E). Notice that, again, distorters with intermediate segregation ratios yield the highest distorter frequencies.

Obviously, our metapopulation model is still quite simplistic. The size of a deme is related to its productivity in a very simple manner, generations do not overlap and migration operates through a common pool of migrants. These assumptions were made intentionally, to be able to focus on the impact of population structure *per se*. To see to what extent our results apply in a model that is more specifically tailored to the *t* complex of the house mouse, we used Nunney & Baker's (1993) metapopulation model. In this model generations do overlap (every adult has a probability of $p_{\text{surv}} = 0.67$ to survive to the next breeding cycle), deme size varies from generation to generation (the number of females and males is essentially Poisson distributed with means N^2 and N^3), and the breeding system is modelled in a more realistic manner. Moreover, migration operates by assigning some of the vacant positions to juvenile immigrants. Hence, in this

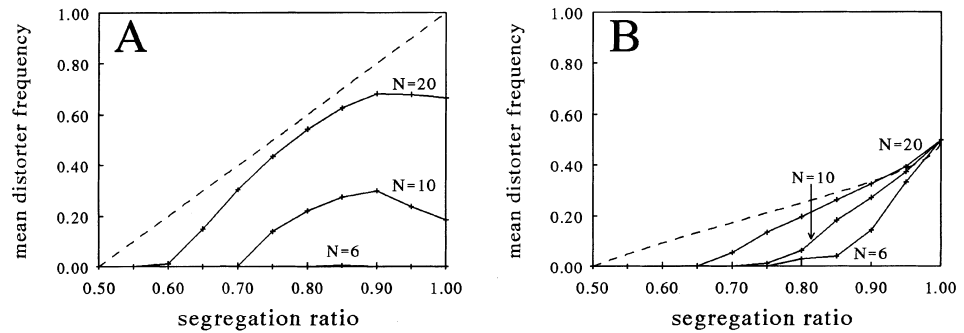


Fig. 11 Mean distorter frequency in Nunney & Baker's (1993) metapopulation model (see text). The immigration rate is $m = 0.05$, and all adults breed continuously.

model the immigration parameter m refers to the probability that a migrant captures a vacant position that would otherwise be assigned to a resident juvenile, while in our metapopulation model it refers to the probability that a resident adult is replaced. As a consequence, it is difficult to compare simulations that are based on the same numerical value of m . On average, Nm immigrants enter a deme per generation in our model, while in Nunney and Baker's model $(1 - p_{\text{surv}})N$ positions are open to juveniles and immigrants on average. Hence, for a given value of m there is less immigration in Nunney and Baker's model ($(1 - p_{\text{surv}})Nm$) than in our model. On the other hand, extinction also occurs less often in Nunney and Baker's model. This is due to the fact that not all individuals are replaced each breeding cycle (generation). Nevertheless, an efficient distorter with a high segregation ratio may still reach a lower frequency than a less efficient distorter allele. Moreover, the segregation ratio for which a distorter reaches the highest frequency is also typically lower for sterile than for lethal distorters. This is illustrated in Fig. 11, which shows for $m = 0.05$ that a lethal distorter reaches the highest frequency when the segregation ratio is maximal, while a sterile distorter profits from a lower segregation ratio. We may conclude that our results are quite robust, at least qualitatively.

Discussion

Intermediate segregation ratios as a compromise

In this paper we have focused on the question of how the success (i.e. the frequency) of a segregation distorter in a metapopulation context is affected by its segregation advantage and its negative fitness effects at the individual level. To dissect what makes a segregation distorter successful, we singled out various determinants of success: a successful distorter should be an efficient invader, reach a high frequency in an isolated deme, be able to persist for a long time in a deme and be well represented in the migrant pool.

Efficient distorters with a high segregation ratio are the best invaders, and typically reach the highest frequency within single demes. However, such distorters also impair

the productivity of demes. As a result, segregation distorters with intermediate segregation ratios persist for the longest times (see also Lewontin, 1962), and are expected to produce the most emigrants carrying a distorter allele. As a result, segregation distorters with intermediate segregation ratios may reach the highest frequency.

Our results also indicate that the optimal segregation ratio is typically lower for a sterile than for a lethal distorter (e.g. Fig. 1). Model parameters such as female productivity or the operational sex ratio affect lethal and sterile distorters differently. For example, a female-biased sex ratio is advantageous for a lethal distorter, while a sterile distorter may profit from a male-biased sex ratio. This difference reflects the fact that deme productivity is limited by female productivity in case of a lethal distorter, while in case of a sterile distorter the number of fertile males may become limiting.

Relevance for the *t* complex

To keep things as simple as possible, and to be able to focus on the effects of population structure *per se*, a variety of factors that play a role at the *t* complex were left out of the model. For instance, we did not take into account inbreeding (Petras, 1967), fitness effects in heterozygous condition (Johnston & Brown, 1969), sexual selection (Lenington & Heisler, 1991), reproductive compensation or kin selection (Charlesworth, 1994), and the genetically complex nature of the *t* complex (Lyon, 1991; van Boven & Weissing, unpublished observation). Moreover, some of our model assumptions are rather *ad hoc*, and motivated mainly by considerations of simplicity. For instance, we assumed a fixed maximal deme size, nonoverlapping generations, and a very simple coupling between the genetic and demographic processes. However, our basic metapopulation model, the even simpler Markov model, and the more realistic model of Nunney & Baker (1993) give qualitatively the same results. This gives some confidence in the robustness of our results, and in their relevance for the *t* complex.

There is an ongoing discussion on the question of which *t* haplotype frequencies are typical in natural

populations (Lenington *et al.*, 1988; K. Ardlie, personal communication), and how to reconcile the empirically found values with those predicted by models on the *t* complex (e.g. Petras & Topping, 1983; Nunney & Baker, 1993; Durand *et al.*, 1997). Our models clearly show that a large variation in distorter frequencies is to be expected in a metapopulation. In fact, all feasible distorter frequencies are expected to occur, and a sizeable fraction of demes will not contain a distorter at all. This has important practical implications, since estimates of *t* haplotype frequencies will have to be based on a large number of samples. Moreover, reliable estimates of the "typical" *t* haplotype frequencies should not only be based on polymorphic demes, but should include wild-type demes as well.

One of the most striking aspects of *t* haplotypes is their high diversity. Some *t* haplotypes lead to lethality in homozygous condition, some lead to sterility and some combinations of *t* haplotypes may be partially fertile (e.g. Lyon, 1991). Segregation ratios also show considerable variation. In the laboratory segregation ratios vary from as low as 0.20 to as high as 1.0 (Gummere *et al.*, 1986; Lyon, 1991). In closed laboratory populations, however, segregation ratios tend to decline over generations (Bennett *et al.*, 1983). Data from field populations, on the other hand, indicate that segregation ratios are typically high, but not maximal (Petras, 1967; Gummere *et al.*, 1986; Ardlie & Silver, 1996). Petras found the average segregation ratio from wild caught house mice carrying a sterile distorter to be $\sigma = 0.80$, and of those carrying a lethal distorter to be $\sigma = 0.89$ (but see Ardlie & Silver, 1996). The finding that segregation ratios in natural populations are high but not maximal is not too surprising in view of our results which suggest that distorters with an intermediate segregation ratio are most easily able to reach appreciable frequencies in a metapopulation. The observation that lethal *t* haplotypes usually have higher segregation ratios than sterile *t* haplotypes is compatible with our finding that a lethal distorter requires a higher segregation ratio than a sterile distorter in order to obtain a similar frequency. Finally, the finding that segregation ratios tend to decline in closed laboratory populations might be attributed to the fact that such populations tend to be relatively small and isolated.

Several authors (e.g. Lewontin, 1962; Silver, 1993) have suggested that the prevalence of lethal *t* haplotypes in natural house mouse populations (e.g. Lenington *et al.*, 1988) can be explained by interdeme selection. In our model, lethal distorters only reach higher frequencies than sterile distorters if the sex-ratio is female biased, if deme size is extremely small and/or if migration rates are very low. Accordingly, our results do not immediately lead to the conclusion that lethal distorters have a systematic advantage due to interdeme selection. On the other hand, our results do suggest that selection at the group level may have played a major role in

moulding the segregation ratios present in natural populations.

Evolution of segregation distortion

The result that a segregation distorter which confers only a slight segregation advantage cannot maintain itself in a deme-structured population (e.g. Fig. 1) is of some relevance for the discussion on the evolutionary stability of 'honest' Mendelian segregation. Typically, this subject has been considered in the context of large unstructured populations (e.g. Crow, 1991). In such a population, any allele that manages to increase its segregation ratio above 0.50 will succeed in destabilizing Mendelian segregation, regardless of its negative fitness effects in homozygous condition. Our results show that this is no longer true in a deme-structured population. In this context a certain critical segregation ratio σ_{crit} substantially higher than 0.50 is needed for a distorter to be able to persist stably. Moreover, a very efficient distorter may also be lost due to interdeme selection. In other words, only a relatively small spectrum of distorters is able to persist in a metapopulation context, and the evolutionary stability of Mendelian segregation is less of a problem than in the context of a large, unstructured population.

Let us stress, however, that the evolutionary conclusions that can be drawn from our models (and most other models considered in the literature) may be limited. By focusing on the frequency that a distorter allele reaches in a metapopulation, we have combined our five determinants of success into a single composite measure. This measure is obviously related to the 'success' of a distorter with respect to its interaction with the wildtype allele. Ultimately, however, the evolutionary fate of a distorter will depend on its ability to outcompete other distorter alleles. It is well conceivable that a distorter that is highly successful in competition with the wildtype allele, is less successful in the competition with other distorter alleles. In fact, we have shown before that no single distorter allele is competitively superior if the fitness of individuals heterozygous for two distorter alleles is relatively high (van Boven & Weissing, 1996, 1998; van Boven *et al.*, 1996). Such complementation between distorter alleles is well documented in some systems (e.g. the mouse *t* complex; Lyon, 1991), but it remains to be seen whether it is commonplace in natural systems. It is therefore an open question as to whether the frequency that a single distorter reaches in a metapopulation is a reliable predictor for the outcome of evolution.

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