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Short Review

Are *Drosophila* SR drive chromosomes always balanced?

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SR chromosomes are the best-known case of sex chromosome meiotic drive. These X chromosomes cause the production of female-biased progenies in several *Drosophila* species. Due to their meiotic drive advantage, they are expected to spread and become fixed, resulting in population extinction due to the lack of males. However, this apparently does not occur: SR chromosomes are maintained in balanced polymorphisms, resulting from the equilibrium between their meiotic drive advantage and deleterious fitness effects. In this paper we review the current explanations for their deleterious effects and we argue that it is highly improbable that all newly emerged SR are sufficiently deleterious to avoid fixation. Unbalanced SR almost certainly arise and go unnoticed because of three possible outcomes: (i) fixation followed by extinction of the population or species; (ii) fixation followed by the emergence and fixation of drive suppressors, restoring the normal 1:1 sexual proportion; or (iii) transformation into balanced SR due to partial suppression. If these outcomes really occur, then extant cases of sex-chromosome meiotic drive such as SR, causing small deviations on the population sexual proportion, are only the tip of the iceberg and strong sexual proportion shifts (possibly followed by extinction) are a more common feature of species evolution than is usually assumed.

Keywords: *Drosophila*, meiotic drive, sex chromosomes, sex-ratio, suppressors, unisexual extinctions

Introduction

Sex-chromosome meiotic drive seems to be a rather common trait, for it is known in a variety of organisms such as plants (Taylor, 1999), stalk-eyed flies (Presgraves *et al*., 1997), mosquitoes, *Drosophila* and mammals, and most cases were accidentally discovered (see Hurst & Pomiankowski, 1991 for a list of species). The best studied case is the sex-ratio trait of *Drosophila*: in 12 species of this genus males carrying certain X chromosomes (called 'SR') produce female-biased progenies due to the degeneration of Y-bearing sperm (Gershenson, 1928; Montchamp-Moreau & Joly, 1997). In most of these species SR chromosomes carry specific chromosomal inversions.

As a consequence of their meiotic drive advantage, SR chromosomes are expected to spread and become fixed causing population extinction due to the lack of males (Hamilton, 1967). This perturbing property of SR chromosomes is shared by all meiotically driven sex chromosomes and was noted at the time of their initial discovery (Gershenson, 1928). However, SR polymorphisms are stable in natural populations (with SR frequency usually below 20%), and SR chromosomes are typically lost in experimental populations of *D. pseudoobscura* (Wallace, 1948; Curtsinger & Feldman, 1980; Beckenbach, 1996). These results imply some form of natural selection against SR, which in fact has been found in *D. pseudoobscura*, *D. quinaria*, *D. recens* and *D. simulans*, the only species investigated in this respect (Wallace, 1948; Beckenbach, 1996; Jaenike, 1996; Capillon & Atlan, 1999). Data for other species are scarce or absent but the persistence of SR polymorphisms in natural populations strongly suggests that SR chromosomes are also deleterious in these cases. For example, the frequency of SR in a natural population of *D. mediopunctata* did not change in 10 years (1987: 13.2% 1997: 14.0%; Varandas *et al*., 1997; A. B. Carvalho & S. C. Vaz, in prep.), in spite of a rather strong meiotic drive advantage. Thus, at least 12 *Drosophila* species bear a dangerous genetic element (the SR chromosome) whose destructive properties are maintained under control by counter selection. But are meiotic drive advantage and counter selection inextricably linked? Curtsinger & Feldman (1980) suggested that 'it may not be reasonable to propose that new drive mutants are always associated with deleterious alleles that prevent their fixation'. In the absence of this general, obligatory relationship between meiotic drive and fitness loss, it is highly probable that some (perhaps many) species have dealt with an unbalanced SR chromosome that approached fixation.

In this paper we review the current explanations for the deleterious effects of SR, and we find that there is no such obligatory relationship. The current explanations may account for the deleterious effects of SR in some species, but not all. We then examine the possible fates of unbalanced SR, and we find that they most likely go unnoticed because: (i) their fixation is

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followed by extinction of the population or species (Gershenson, 1928; Beckenbach, 1996); (ii) their fixation is followed by the emergence and fixation of drive suppressors, restoring the normal 1:1 sexual proportion (Policansky & Dempsey, 1978); or (iii) they are transformed into balanced SR due to partial suppression (Varandas *et al*., 1997; this paper). In particular, we show that suppressors of SR expression almost always run to fixation (and hence, make SR virtually undetectable) unless SR is deleterious. Thus, SR deleterious effects are a necessary condition for the evolutionary persistence of SR expression. We also show that at least one extant balanced SR most likely was unbalanced when it first appeared, before being partially suppressed. If unbalanced SR does arise sometimes, then *Drosophila* species (and possibly most species with sex-chromosomes) may periodically experience very skewed sexual proportions due to their invasion; the few known cases of sex-chromosome meiotic drive (e.g. extant SR chromosomes in *Drosophila*) would be just the tip of the iceberg. Although this review is concentrated on the sex-ratio trait of *Drosophila* (for it is the best studied case), the above conclusions are likely to be valid for all species with chromosomal sex-determination.

Current explanations for SR deleterious effect

Pleiotropic deleterious effects of the sex-ratio gene itself

This hypothesis is appealing because it would give a general explanation for the stability of SR polymorphisms. It has been proposed that selection against SR/SR females may stabilize the polymorphism (Wallace, 1948; Beckenbach, 1996). But why would a male-acting gene have obligatory deleterious effects in females? Male fitness is a more likely candidate for pleiotropic effects: it is conceivable that a gene that causes sperm loss reduces male fertility. However, Curtsinger & Feldman (1980) showed that under constant fitness it is not possible to stabilize SR polymorphism with selection restricted to males. This limitation was overcome by Jaenike (1996), who proposed that the male fertility loss is frequency dependent: the spread of SR increases the proportion of females and hence the opportunity to mate. The greater frequency of matings decreases the relative fitness of SR males because they are more readily sperm depleted than non-SR males (Beckenbach, 1978; Wu, 1983a).

The main limitation of this stabilizing mechanism is its requirement that under repeated copulations the fertility of SR/Y males falls to **less** than half that of wild-type ones (Jaenike, 1996). This certainly is a restrictive requirement because in principle one would expect at most a half loss (corresponding to the loss of Y sperm), but there are several possible biological explanations for it (Wu, 1983a; Jaenike, 1996). This requirement is met under some experimental conditions in two species (*D. pseudoobscura* and *D. recens*), but not in *D. quinaria* and *D. subobscura* (Hauschteck-Jungen *et al*., 1987; Jaenike, 1996). Indeed, *D. subobscura* SR/Y males do not suffer any fertility loss at all.

In short, the robustness of the pleiotropy hypothesis requires strong frequency-dependent selection against SR/Y males. Though there is a likely mechanism for it, not all species have the necessary 'number of matings vs. SR/Y fertility loss' relationship. Thus it seems that the pleiotropy hypothesis may explain some cases (e.g. *D. recens*) but it can hardly be a general explanation for either the deleterious effects of SR or for the stability of SR polymorphisms.

Chromosomal homozygosity

Many studies in diverse *Drosophila* species show that flies homozygous for whole autosomal chromosomes (collected from natural populations) suffer severe fitness losses ranging from lethality and sterility to less severe viability and fertility reductions (see Lewontin, 1974 for a review). This genetic load is thought to result from recessive deleterious alleles which are in mutation-selection equilibrium. Chromosomal inversions such as SR have a single origin (Babcock & Anderson, 1996; but see Caccone *et al*., 1998). Homozygosity for SR should, then, cause deleterious effects proportionally similar to those observed when wild-caught chromosomes are made homozygous. As noted by Curtsinger & Feldman (1980), this may explain the detrimental effects of SR. Female and male fitness loss would be caused by deleterious alleles in accidental linkage to the meiotic drive gene(s), and this linkage will persist almost indefinitely because meiotic recombination is blocked by the SR inversion. This hypothesis may be tested by comparison of the homozygosity effects of SR and a random sample of X chromosomes, from which SR presumably originated. It is important to use X chromosomes, instead of autosomes, because their genetic loads are different (below). These data became available some years later (virtually all previous studies on inbreeding depression were done with autosomes), and does not support the homozygosity hypothesis: Eanes *et al*. (1985) examined 140 wild-caught X chromosomes from *D. melanogaster*, and found very small viability effects in males and homozygous females. This fitness pattern is very different from the SR chromosomes of *D. pseudoobscura* (the sole species investigated in detail), which have strong deleterious viability effects in males and homozygous females (Wallace, 1948; Curtsinger & Feldman, 1980; Beckenbach, 1996). Thus, whatever the reason, SR homozygosity seems to result in much greater fitness loss than homozygosity for typical X chromosomes, which contradicts the 'chromosomal homozygosity' hypothesis. It should be noted that the results of Eanes *et al*. (1985) probably occur in all species, rather then being a specific feature of *D. melanogaster*: recessive viability-reducing alleles have a very low equilibrium frequency on X chromosomes due to male hemizygosity; the observed deleterious effects of X homozygosity are explained by recessive mutations affecting female fertility (Wilton & Sved, 1979).

Another limitation of the homozygosity hypothesis is that it does not apply to at least two *Drosophila* species (*D. neotestacea* and *D. simulans*; James & Jaenike, 1990; Merçot *et al*., 1995) because their SR chromosomes do not carry chromosomal inversions. Thus, we conclude that the homozygosity hypothesis is not a general explanation for the deleterious effects of SR.

The 'tip of the iceberg' hypothesis

In the previous section we examined the possible explanations for SR deleterious effects and we found that although they may apply to some cases, they do not warrant that all newly emerged SR are sufficiently deleterious to be balanced. Unbalanced SR must occasionally arise. In the present section we examine their three possible fates: extinction of the host population (Gershenson, 1928; Beckenbach, 1996), total neutralization by suppressor fixation (Policansky & Dempsey, 1978), and transformation into a balanced SR by partial suppression (Varandas *et al*., 1997). The first and second fates result in the disappearance or nondetection of unbalanced SR, leading to an observational bias: on average extant SR would be more deleterious than newly emerged ones. In the third fate, formerly unbalanced SR would still be detected, as a partially suppressed, and now balanced, SR. Under this view extant SR chromosomes are just the tip of the iceberg, and their unharmful appearance (deleterious and balanced drivers maintained at rather low frequencies, causing slight female excess) hides a past of strong shifts in the population sexual proportion.

Population extinction as a source of bias

It is not known how a SR chromosome originates, but once it happens, its fate will be governed by the balance between its meiotic drive advantage and its viability and fertility effects. As shown in Fig. 1, very low fitness SR chromosomes are lost, because their meiotic drive advantage is insufficient to equilibrate the strong counter-selection (region 1 of the parameter space). In region 2, SR is still very deleterious, but its meiotic drive advantage suffices to maintain it in polymorphic state. The conditions for the stability of this polymorphism are well known (Edwards, 1961). In region 3 SR will quickly run to fixation, which may cause population extinction (Gershenson, 1928; Hamilton, 1967). Bearing in mind the previous arguments, this seems to be a rather plausible outcome: there is no general mechanism ensuring that all newly emerged SR chromosomes must necessarily have a fitness lower than, say, 0.81 (the boundary between regions 2 and 3). The likelihood of SR fixation increases if we take into account that depending on the pattern of selection, the 'fixation boundary' may be as low as 0.5 (Table 1). Thus, SR chromosomes with fitness greater than the fixation boundary are likely to arise in nature. Their absence from the extant collection of cases is likely to be an 'observational bias' and suggests that some populations (or species) became extinct due to their spread (Beckenbach, 1996; a similar suggestion was made by Hurst (1993) for the case of cytoplasmic distorters).

Table 1 Minimal values of SR fitness required for SR fixation (fixation boundary) under different patterns of selection

Pattern of selection	Fixation boundary (fitness of SR)
Only against SR/Y males	0.50*
Only against SR/SR females	0.75
Against SR/Y males and SR/SR females; $W_{SR/ST} = 1.0$	0.81†
Against SR/Y males and SR/SR females; $W_{SR/ST} = 1.2$	0.92

*In this case there is no stable SR/ST polymorphism (Edwards, 1961; Curtsinger & Feldman, 1980) and the boundary is between SR loss and SR fixation.
†This is the pattern showed in Fig. 1.

Is there any evidence that unbalanced meiotically driven sex-chromosomes cause population extinction? Lyttle (1979) directly demonstrated this: he generated a meiotically driven Y chromosome in *D. melanogaster* that caused extinction in population cages in ~7 generations. This is even more significant when we take into account that the Y driver was generated from a naturally occurring meiotic drive gene (Lyttle translocated the autosomal *Segregation Distorter* to the Y chromosome). Thus, meiotic drive genes can cause population extinction, though male excess (as is the case of Lyttle's populations) is probably more threatening than female excess (as caused by SR). It is perhaps not surprising that no one has witnessed a natural example of SR spread and fixation: this will depend on the lucky observation of a process that lasts few generations.

Fixation of suppressors of SR as a second source of bias

The spread of SR chromosomes is expected to elicit the evolution of suppressors of their expression, on the autosomes

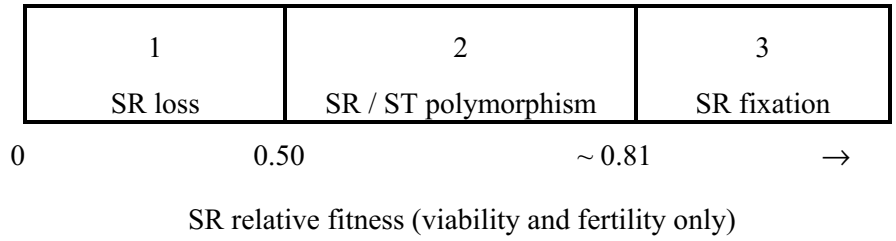

Fig. 1 The fate of SR chromosomes as a function of their fitness (without suppressors). The boundaries are given by Edwards's (1961) constant fitness model. SR chromosomes with relative fitness lower than 0.50 will be lost and those with fitness higher than 0.81 will become fixed. For the sake of simplicity we assume full meiotic drive and that $W_{SR/Y} = W_{SR/SR} =$ 'SR relative fitness'. The fitness of ST/ST, ST/SR, and ST/Y genotypes are set to 1.0. Different assumptions merely change the boundary positions, as shown in Table 1.

and on the Y chromosome (Stalker, 1961; Hamilton, 1967). This has been demonstrated in experimental populations (Carvalho *et al*., 1998; Capillon & Atlan, 1999). In fact, both autosomal and Y-linked suppressors of SR have been found in natural populations of almost all SR-bearing species that have been well studied (*D. paramelanica*, *D. affinis*, *D. mediopunctata*, *D. simulans* and *D. quinaria*; Stalker, 1961; Voelker, 1972; Atlan *et al*., 1997; Carvalho *et al*., 1997, 1998; Jaenike, 1999), though their absence in *D. pseudoobscura* remains a puzzle (Policansky & Dempsey, 1978; Wu, 1983b).

These suppressors may cause a serious observational bias: almost all SR chromosomes were accidentally discovered by the observation of female-biased progenies of wild-caught flies during other types of studies (e.g. Presgraves *et al*., 1997). Policansky & Dempsey (1978) suggested that 'the few cases of SR reported … may represent those rare cases where modifiers [suppressors] have not yet become fixed'. Here we investigate when suppressor fixation is expected to occur. We found that the likelihood of this outcome depends in a curious way on the fitness of SR: the less deleterious they are, the more likely they will be 'neutralized' by their suppressors. We will consider here only Y-linked suppressors; the same qualitative conclusions are obtained with autosomal suppression (S. C. Vaz & A. B. Carvalho, in prep.). The properties of Y-linked suppressors are shown in Fig. 2 (see Carvalho *et al*., 1997 for a full analysis). The main point is that if SR is not deleterious then it runs to fixation and the same occurs with $Y^{suppressor}$ (unless $Y^{suppressor}$ is exceedingly deleterious, almost a lethal). In this case female-biased progenies disappear and SR chromosomes become undetectable. Thus, the nonfixation of $Y^{suppressor}$ requires SR to be deleterious. It also requires that $Y^{suppressor}$ be slightly deleterious; neutral $Y^{suppressor}$ will spread until fixation or until SR is lost, whereas advantageous $Y^{suppressor}$ will always spread (Carvalho *et al*., 1997). In short, only deleterious SR are not always neutralized by $Y^{suppressor}$ because suppressor polymorphism is possible only if SR is deleterious. This property follows almost directly from the theoretical population genetics of Y chromosomes: stable Y polymorphisms require X polymorphism (Clark, 1987; Carvalho *et al*., 1997), a condition that can only be met in the case of SR if its meiotic drive advantage is counter-acted by natural selection.

Is there any evidence of fixation of a SR and its suppressors? *D. simulans* provides a nearly complete example, though in this case SR and suppressors have attained very high frequencies in natural populations but are not fixed (see next paragraph). There is also a suspected case precisely in *D. melanogaster*: Hurst (1996) argued that the Y-linked *Suppressor of Stellate* locus is in fact a suppressor of X chromosome meiotic drive, and that the X-linked *Stellate* locus is the driver (but see Robbins *et al*., 1996); the genotype of wild-type flies would be $SR/Y^{suppressor}$.

The possible relationship between *Stellate* and meiotic drive could only be suspected because *D. melanogaster* has been so heavily studied, and even then its discovery took a long time. *Stellate* was found after many studies, starting with classical genetics (more than 30 years ago), and ending with DNA sequencing. Totally suppressed SR will indeed be hard to find. Even partially suppressed SR may escape detection, as dramatically illustrated by the *D. simulans* case: despite more than 70 years of research with this species, it was discovered only recently that many of its populations have a high frequency of a SR chromosome (up to 60%; Atlan *et al*., 1997). In most of these populations SR is almost totally neutralized by Y-linked and autosomal suppressors; it was accidentally uncovered when crosses between strains from different populations resulted in female-biased progenies (Merçot *et al*., 1995). The examples of *D. simulans* and *Stellate* suggest how it would be possible to detect suppressed SR. However, it should be noted that even these more sophisticated methods that do not rely on the observation of female-biased progenies of wild-caught flies may fail: a totally suppressed SR has no advantage over ST and may be lost by random drift or may lose its meiotic drive genes by accumulation of mutations.

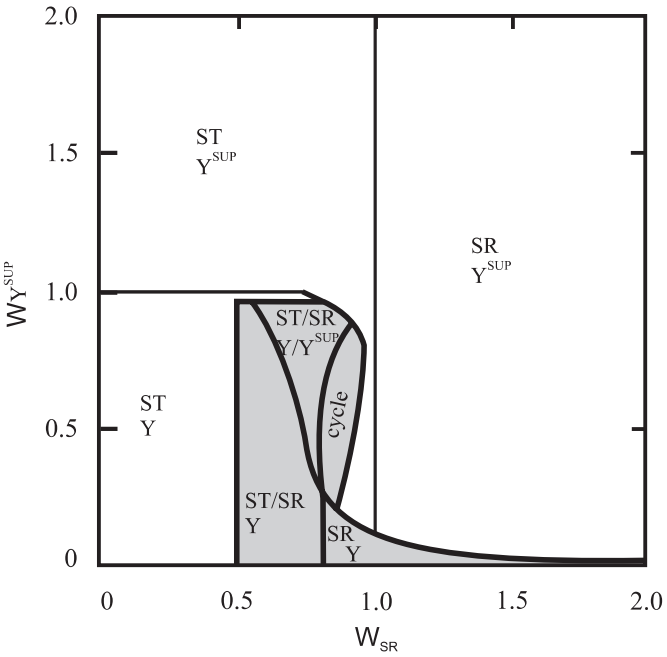

Fig. 2 Numerical simulations of the fate of a Y-linked suppressor and SR. The figure summarizes the outcomes of 200 000 simulations, each using different numerical values for the two parameters, fitness of SR (W_{SR}) and fitness of $Y^{suppressor}$ ($W_Y{}^{sup}$). In each simulation the frequencies of ST, SR, Y and $Y^{suppressor}$ were iterated for 40 000 generations or until an equilibrium was attained. See Carvalho *et al*. (1997) for a complete description of the model and the recurrence equations. The darkened areas represent the regions of the parameter space that result in detectable SR chromosomes (i.e. SR is present and is not totally suppressed). Different combinations of W_{SR} and $W_Y{}^{sup}$ lead to 7 different outcomes ('ST Y^{sup}' means fixation of ST and Y^{sup} alleles, 'ST/SR Y' means X polymorphism and Y fixation, 'ST/SR Y/Y^{sup}' means X and Y polymorphisms, etc.). 'Cycle' is an X and Y polymorphism in which the allele frequencies oscillate in a limit cycle. Note that detectable SR chromosomes are practically restricted to the deleterious SR region ($W_{SR} < 1$).

Perhaps this explains the negative results of Coyne & Orr (1993) and Johnson & Wu (1992), who searched for fixed SR and suppressors of SR with interspecific crosses (they tested four species pairs). Interestingly, one of these species pairs (*D. simulans*/*D. sechellia*) has recently been found to produce female-biased progenies, using a different cross scheme and strains (E. Dermitzakis & A. G. Clark, pers. comm.). It would be very desirable to test more species pairs, using different crosses and strains.

The third possible fate of unbalanced SR: transformation into balanced SR through partial suppression

As noted in the previous section, partial suppression of SR expression is very common. Partial suppression lowers the equilibrium frequency of SR (Varandas *et al*., 1997) and is caused by polymorphic Y-linked or autosomal suppressors that most likely evolved in response to the spread of SR. Hence, the conclusion is almost inescapable: before suppressors originated by mutation and spread, these SR chromosomes attained higher frequencies and caused a much stronger female bias. The spread of suppressors may even have transformed an unbalanced SR into a balanced one.

Varandas *et al*. (1997) showed that it is possible to estimate the past frequency of SR, before the spread of suppressors. The basis of the method is that SR equilibrium frequency results from the balance between its meiotic drive advantage and the counter-acting selection; if we know two of the parameters (present SR frequency and present drive strength) we may calculate the third (selection against SR), using Edward's (1961) equilibrium equation. Now, using the calculated selection against SR, and setting drive strength to 100% (which is its presumed value before the spread of suppressors, and is the value in *D. pseudoobscura*, which has no suppressors), we may estimate the past SR frequency. Varandas *et al*. (1997) applied this procedure to the *D. mediopunctata* data and found that the past frequency of SR ranged from 29% to 100%, depending on the assumed pattern of selection. Thus, the presently balanced SR chromosome of *D. mediopunctata*, whose low frequency did not change in 10 years (see Introduction), may quite well have been a dangerous unbalanced chromosome that approached fixation before the origin and spread of its suppressors. The case of *D. simulans* SR is particularly interesting in this context because, as noted by Atlan *et al*. (1997), its high frequency even under strong suppression implies that it is only slightly deleterious in natural conditions. We applied the procedure of Varandas *et al*. (1997) to the *D. simulans* data of the Bellemene population (Atlan *et al*., 1997), where the present SR frequency is 55% and the present strength of drive results in 54% of females in the progenies (in the absence of drive progenies contain ~50% of females, whereas full drive leads to 100% of females). Selection coefficients compatible with these data are shown in Fig. 3. When we set the drive strength to 100%, as probably occurred when SR first appeared, we find that the SR chromosome should run to fixation in 70% of the compatible selection coefficients and approach fixation in the remaining 30% (average SR frequency in polymorphic cases: 80%). Thus, *D. simulans* SR most likely is an unbalanced SR that became balanced by partial suppression. One would expect that SR will run to fixation in SR/ST population cages with a suppressor-free background, assuming that the fitness in nature and laboratory are similar. Rather surprisingly, SR is quickly lost in these populations which indicates either that in nature there is an interaction with suppressors that rescue its deleterious effects (Capillon & Atlan, 1999), or that SR is much more deleterious in the laboratory environment (as occurs with *D. pseudoobscura*). It will be very interesting to study the *D. simulans* case more thoroughly, as well as other species with partial suppression. Although fitness in nature is what matters, these studies may provide a support to the 'tip of the iceberg' hypothesis, by showing that SR can really spread and cause strong female bias in populations.

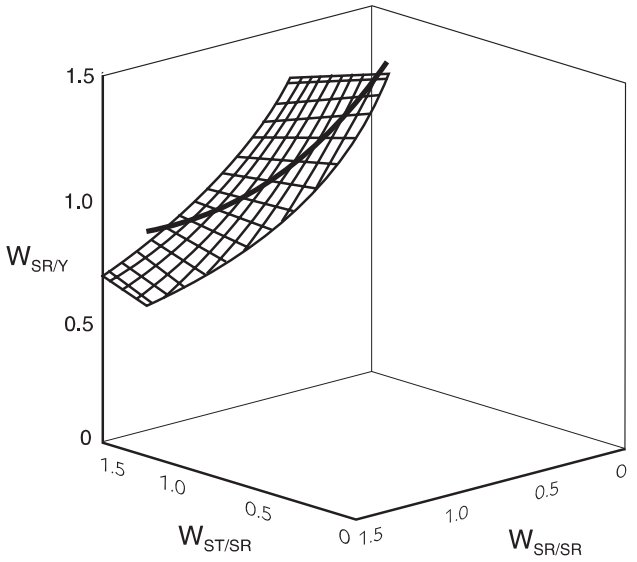

Fig. 3 Fate of *D. simulans* SR in the absence of suppressors. The whole surface contains every combination of fitness of ST/SR, SR/SR and SR/Y compatible with the data from Bellemene population (Atlan *et al*., 1997). The true parameter values for this population correspond to a single point somewhere on the surface. The thick curve divides the surface into two areas, according to the expected behaviour of SR chromosomes in the absence of suppressors. SR fixation would occur at all points below the thick line (~70% of the surface), whereas in the remaining 30% of the surface (points above the thick line) SR would remain polymorphic but at very high frequencies (80% on average).

Partial suppression of SR is expected on theoretical grounds (Carvalho *et al*., 1997) and seems to be the rule. This should be taken into consideration before accepting the view that SR chromosomes are dangerous in theory, but in practice cause little harm to populations: all partially suppressed SR may have approached fixation in the past.

Sizing the risk

A key question on the likelihood of SR fixation is: how frequently does a new SR chromosome with fitness higher than

the fixation boundary arise? A full answer would require data on the fitness distribution and on the exact pattern of selection of newly emerged SR. Neither is available. A rough approximation can be obtained by examining the fitness distribution of normal X chromosomes (from which SR presumably originated) and assuming some arbitrary patterns of selection. As far as we know, the only study on net fitness of X chromosomes is Wilton & Sved (1979), who analysed a sample of 31 wild-caught X chromosomes of *D. melanogaster*. They found that the net fitness of X chromosomes as homozygotes ranged from 0.14 to 0.91 (values obtained from Wilton & Sved, 1979; Fig. 3, setting the fitness of heterozygotes to 1.0). If these fitness values are used in Fig. 1, then 4 out of 31 (13%) newly emerged SR would be fixed (region 3 of the parameter space). Of the remaining 27, 15 (48%) would be maintained in a polymorphic state (region 2 of the parameter space), and 12 (39%) would be lost (region 1). The above estimates assume equal selection against SR/Y males and SR/SR females (which is possibly a conservative estimate, since X chromosome genetic load is restricted to females; Eanes *et al*., 1985) and no selection in SR/ST females. Thus, the probability of fixation of newly emerged SR seems far from being negligible. We may take our crude calculations one step further and estimate the number of *Drosophila* species that might have dealt with an unbalanced SR. There are 1677 known *Drosophila* species (Ashburner, 1989). The majority of them have not yet been studied, but five out of nine species in a random sample show SR/ST polymorphisms (Jaenike, 1996). Assuming that this is an unbiased estimate (which is uncertain, because researchers tend to not report negative results), we may expect that there are 930 cases of SR polymorphisms. The expected ratio of SR fixation/SR polymorphism is 4/15 (see above). Thus, perhaps 250 *Drosophila* species have faced an unbalanced SR chromosome! Though the above numbers should be viewed cautiously (since they rely on several simplifying assumptions), they strongly suggest that several new SR attained fixation or dangerously approached this point.

Figure 4 summarizes the three possible fates of an unbalanced SR. Once it appears and approaches fixation, which factors determine its final fate? Chance probably plays an important role since the outcome depends mostly on a mutation originating an autosomal or Y-linked suppressor allele. Once a suppressor allele arises, it should spread quickly, and population extinction would not occur. Lyttle (1979) showed that the origin of suppressors may require too long for population survival, and that extinction is a likely outcome; however, it should be taken into account that the relatively small size of his experimental populations probably reduced the opportunity for suppressors to arise by mutation. Besides chance, the tolerance of the species to skewed sexual proportions and the fitness of SR are also likely to play an important role (Lyttle, 1979; A. B. Carvalho & S. C. Vaz, in prep.).

Some limitations of the 'tip of iceberg' hypothesis

Our conclusion that all partially suppressed SR may have approached fixation in the past assumes that a full driver evolved before the spread of suppressors. Alternatively, it is possible that both driver and suppressors gradually increase their strengths. For example, *Stellate* and *Suppressor of Stellate* are both repetitive genes with variable copy number, and Hurst (1996) proposed that their copy numbers gradually

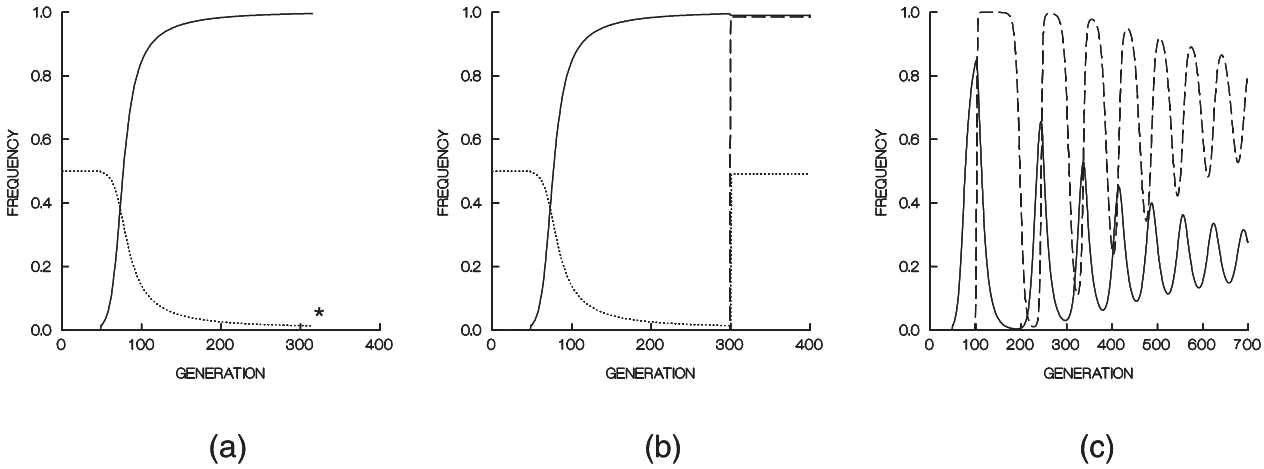

Fig. 4 Fates of unbalanced SR chromosomes. Abscissa: number of generations; ordinate: frequency of SR (solid line), $Y^{suppressor}$ (dashed line) and proportion of males (dotted line). The unbalanced SR chromosome ($W_{SR} = 0.82$) was introduced at an initial frequency of 0.01 in generation 50. (a) Population extinction (indicated by the asterisk) may occur if no suppressors arise; (b) Fixation of SR and suppressor may occur (among other possibilities) if suppressor arises shortly after SR fixation; (c) Transformation into balanced SR may occur if suppressor arises before SR fixation; the damped oscillations eventually attain a stable equilibrium (at generation ~2000) with SR = 23% and $Y^{suppressor} = 71\%$. The suppressor was introduced at an initial frequency of 0.01 in generation 300, and 100 in cases 4B and 4C, respectively. $Y^{suppressor}$ fitness is set to 0.83, and unsuppressed SR/Y males are assumed to produce 0.1% of sons. For additional assumptions see Fig. 1. Note that the unbalanced SR would not be detected as such in any of the three outcomes.

increased with a stronger driver (an X with increased copy number of *Stellate*) eliciting the evolution of a stronger suppressor (a Y with increased copy number of *Suppressor of Stellate*). In this case even a strong driver may not have caused a strong female bias. Even though we cannot prove (or disprove) this gradual pathway for all SR chromosomes, the case of *D. pseudoobscura* shows that it is at least not obligatory, for this species has a full driver and no suppressors.

An interesting criticism arises from the comparison of SR with *Wolbachia*, a bacterium that also has an 'evolutionary interest' in females (they have cytoplasmic transmission in many arthropods). These bacteria are widespread, and the fact that it has been possible to detect them as the cause of female-bias in many species (Hurst, 1993) may suggest that SR chromosomes are not common. We are now trying to address this point by direct search of skewed sexual proportions in poorly studied *Drosophila* species.

Capillon & Atlan (1999) suggested that in *D. simulans* the spread of suppressors reduces the deleterious effects of SR. If this effect turns out to be relevant for natural populations then our conclusions about the past frequency of SR in this species (Fig. 3) will be incorrect.

We assumed throughout this work that sperm is not a limiting factor, and this is likely to be valid for most species. However, in some *Drosophila* species sperm is very large (up to 58 mm!), and males may transmit as few as 50 gametes in each copulation (Pitnick *et al*., 1995). Meiotic drive genes have not been described in these species, but since their sperm is so costly, the selection against drivers and in favour of suppressors is expected to be much stronger than in 'normal' species.

Conclusions

There is a sharp contrast between theoretical predictions about sex-chromosome meiotic drive and observational data. Whereas simple theory predicts highly skewed sexual proportions, increasing SR frequency to eventual fixation and population extinction, observations show stable, low-frequency SR polymorphisms with a slight female excess. A possible explanation for this paradox is that the theoretical predictions do not ever materialize, due to SR deleterious effects. This seems to be the usual interpretation: most papers on SR comment on their potentially destructive properties and then readily note their reassuring deleterious effects (e.g. Varandas *et al*., 1997). An alternative interpretation is that these invariable deleterious effects are not reassuring at all: they point to the disappearance of several (perhaps many) neutral or quasi-neutral unbalanced SR chromosomes, extinct with their populations (by the skewed sexual proportions), silenced by suppressor fixation, or attenuated by partial suppression. Thus, the paradox would be explained by extant SR being very unrepresentative of the whole evolutionary history of SR chromosomes. If this is correct, then strong shifts in sexual proportion (possibly followed by extinction) are a more common feature of species evolution than it is usually assumed. Support for this hypothesis may come from finding more cases of silenced meiotically driven sex-chromosomes (as in *D. simulans* and possibly *D. melanogaster*), or from the direct (and lucky!) observation of unisexual extinction events. If meiotic drive genes prove to have some constant molecular feature (which seems unlikely, given the differences between *Segregation Distortion*, *Stellate* and *t*-haplotype; Robbins *et al*., 1996; Harrison *et al*., 1998; Merrill *et al*., 1999), then their traces may also be detected by DNA studies. Finally, support for the existence of unbalanced SR chromosomes may come from population cage experiments in species with partial suppression. Although the ultimate answer to this hypothesis may prove hard to find, it should be kept in mind that otherwise merely curious phenomena such as slightly skewed sexual proportions and meiotic drive suppressors may be the traces of very important biological processes such as strong sexual proportion shifts and unisexual extinctions.

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