Meiotic drive influences the outcome of sexually antagonistic selection at a linked locus

M. M. PATTEN
Department of Biology, Georgetown University, Washington, DC, USA

Keywords:
genetic conflict; genome architecture; meiotic drive; sexual antagonism.

Abstract
Most meiotic drivers, such as the t-haplotype in Mus and the segregation distorter (SD) in Drosophila, act in a sex-specific manner, gaining a transmission advantage through one sex although suffering only the fitness costs associated with the driver in the other. Their inheritance is thus more likely through one of the two sexes, a property they share with sexually antagonistic alleles. Previous theory has shown that pairs of linked loci segregating for sexually antagonistic alleles are more likely to remain polymorphic and that linkage disequilibrium accrues between them. I probe this similarity between drive and sexual antagonism and examine the evolution of chromosomes experiencing these selection pressures simultaneously. Reminiscent of previous theory, I find that: the opportunity for polymorphism increases for a sexually antagonistic locus that is physically linked to a driving locus; the opportunity for polymorphism at a driving locus also increases when linked to a sexually antagonistic locus; and stable linkage disequilibrium accompanies any polymorphic equilibrium. Additionally, I find that drive at a linked locus favours the fixation of sexually antagonistic alleles that benefit the sex in which drive occurs. Further, I show that under certain conditions reduced recombination between these two loci is selectively favoured. These theoretical results provide clear, testable predictions about the nature of sexually antagonistic variation on driving chromosomes and have implications for the evolution of genomic architecture.

Introduction
In sexually reproducing populations, there are two halves to the gene pool – a male half and a female half. Likewise, there are two halves to the diploid individual that results from sexual reproduction – the two genomes inherited from its two parents. Selection on these halves may run in opposite directions. In such instances, we have genetic conflicts, which can promote rapid evolutionary change and mould the design of genetic systems (Burt & Trivers, 2006). In this study, I consider two genetic conflicts and investigate how they combine to affect patterns of genetic variation within a population.

The first genetic conflict I consider, meiotic drive, disrupts what is a mostly cooperative interaction between the two genomes within a diploid individual. A driving allele or haplotype will pass to >50% of the haploid products (spores or gametes) of a heterozygote, thus gaining more than its ‘fair’ share (Queller & Strassman, 2013). The phenomenon was first recognized almost a century ago (Gershenson, 1928), but despite earlier attention (Sandler & Novitski, 1957), it has only recently come to be recognized as a potent force in evolutionary genetics (Burt & Trivers, 2006; Werren, 2011; Rice, 2013). Meiotic drive is known from only a handful of well-studied systems (e.g. Larracuente & Presgraves, 2012; Kanizay et al., 2013; Grogn et al., 2014; Schimenti, 2014), and although this paucity makes drive seem rare, our inability to detect it in many cases may obscure how taxonomically widespread it is (Burt & Trivers, 2006; Presgraves, 2012). Detecting drive requires that the driving locus be polymorphic in the population. But any driver that
is unopposed by countervailing selection should spread rapidly to fixation, making polymorphism fleeting. Consequently, most systems of drive that have been studied are maintained in a polymorphic state by either recessive lethality or strong negative frequency-dependent selection.

The second genetic conflict I consider, intralocus sexual conflict, arises when males and females share a genetic architecture for a trait but differ in their phenotypic optimum for it (Bonduriansky & Chenoweth, 2009; van Doorn, 2009; Pennell & Morrow, 2013). Intralocus sexual conflict, which can be thought of as a form of antagonistic pleiotropy (and which is why the term ‘sexual antagonism’ will be used hereafter), is not to be confused with interlocus sexual conflict, which typically involves behavioural interactions between individual males and females (reviewed by Arnqvist & Rowe, 2005). Sexual antagonism can theoretically maintain genetic variation within populations, but additional theory suggests that its ability to achieve this end and our ability to recover its signal are limited (Prout, 2000; Connallon & Clark, 2012, 2013). Despite this, studies of laboratory populations (e.g. Chippindale et al., 2001; Prasad et al., 2007; Delcourt et al., 2009; Innocenti & Morrow, 2010) and natural populations (e.g. Fedorka & Mousseau, 2004; Brommer et al., 2007; Foerster et al., 2007) have found extensive sexually antagonistic genetic variance. Since Haldane (1926), theoretical studies have shown how various genetic properties, such as dominance and transmission patterns, of sexually antagonistic loci influence the pattern of variation (e.g. Rice, 1984), and much recent theoretical work has attempted to define more clearly our expectations for patterns of genetic variation under sexual antagonism (Prout, 2000; Patten & Haig, 2009; Blackburn et al., 2010; Fry, 2010; Patten et al., 2010; Arnqvist, 2011; Connallon & Clark, 2011, 2012; Jordan & Charlesworth, 2012; Arnqvist et al., 2014).

Below, I add to this recent work by examining how the presence of meiotic drive affects the predicted pattern of genetic variation at a linked sexually antagonistic locus. The motivation for this analysis stems from a superficial similarity between these two forms of natural selection: both cause a disparity in the allele frequencies transmitted through eggs and sperm. Previous theory has shown that pairs of linked sexually antagonistic loci, which also generate these disparities, can influence each other’s ability to maintain polymorphism (Patten et al., 2010) and can develop stable linkage disequilibrium (Ubeda et al., 2011). I ask here whether meiotic drive interacts with sexual antagonism in an analogous fashion and brings about similar effects and associations. Burt & Trivers (2006) have previously hypothesized that driving haplotypes would be enriched for male- or female-beneficial effects. The model I present here also offers a direct theoretical test of this idea.

Model

I use a slight modification of a standard two-locus population genetic model (Bodmer & Felsenstein, 1967; Karlin, 1975). I consider a randomly mating, diploid, dioecious population with discrete generations. The first locus has alleles $A_1$ and $A_2$ and the second has alleles $B_1$ and $B_2$. Recombination between loci during meiosis occurs at sex-specific rates: $r_m$ in males; $r_f$ in females. The frequencies of haplotypes $A_1B_1$, $A_1B_2$, $A_2B_1$ and $A_2B_2$ are $x_1$, $x_2$, $x_3$ and $x_4$ in eggs and $y_1$, $y_2$, $y_3$ and $y_4$ in sperm. The fitness of a zygote formed from the union of the $i$th egg haplotype and the $j$th sperm haplotype is $w_{ijm}$ for males and $w_{ijf}$ for females. I assign a relative fitness of 1 to the $A_1A_2$ (and $A_2A_1$) and $A_2A_2$ genotypes, but I assume that the driving $A_1$ allele is a recessive lethal. This closely approximates several familiar examples of drive, for example the $t$-haplotype (Silver, 1993) and SD polymorphism (Larracuente & Pregarves, 2012). The $B$ locus experiences sexually antagonistic selection. Genotypes $B_1B_1$, $B_1B_2$ and $B_2B_2$ have fitnesses of 1, $1-\frac{1}{2}t_m$ and $1-\frac{1}{2}t_f$, respectively. In females, these genotypes have fitnesses of $1-\frac{1}{2}t_f$, $1-\frac{1}{2}t_f$ and 1, respectively. The ‘$\frac{1}{2}$’ in these fitness terms represents an assumption, made for ease of presentation, that the fitness effects are additive within loci. The fitness of a two-locus genotype, $w_{ij}$ (where $\chi \in \{m,f\}$), is obtained by multiplying together the fitnesses of its single-locus genotypes. This reflects an assumption that the fitness effects conferred by the two loci are independent of each other (Wade et al., 2001).

I initiate the recursions (see Appendix 1) with the $B$ locus fixed for $B_1$ and the $A$ locus at its polymorphic equilibrium frequency (Hartl, 1970). I then introduce $B_2$ into a population fixed for $B_1$ by mutation and assess whether invasion is permitted. (I alternately introduced $B_1$ into a population fixed for $B_2$, but found that the eventual outcome was the same, regardless of the starting frequencies at $B_1$.) In the absence of a drive locus, the invasion conditions can be obtained analytically and are as follows:

$$\frac{t_f}{1+t_f} < t_m < \frac{t_f}{1-t_f}$$

(Owen, 1953; Kidwell et al., 1977; Prout, 2000; Connallon & Clark, 2012). In the two-locus model with sex-specific fitness and drive, however, a simple, analytical solution for the invasion conditions did not readily yield, so these conditions were determined numerically instead, by testing 10 000 pairs of $(t_m, t_f)$ values. Equilibrium haplotype frequencies were obtained by iterating the recursions for 10 000 generations, which was sufficient time to reach stability even for the weakest selection coefficients considered. All analyses were performed in Mathworks, Inc (2014). The code has been deposited in Dryad (doi:10.5061/dryad.7q577).
At the eventual population genetic equilibrium for both loci, linkage disequilibrium was measured in diploid zygotes. The zygotic linkage disequilibrium is calculated as

\[ D_z = \frac{1}{2} (x_1 y_4 + x_4 y_1 - (x_2 y_3 + x_3 y_2)). \]

I also examined the fate of a neutral modifier of recombination at a third locus. I followed a standard modifier-locus modelling approach (Nei, 1967; Feldman, 1972; Karlin & McGregor, 1974). The modifier locus has two alleles, \( M_1 \), which leaves recombination rate unaffected, and \( M_2 \), which reduces the recombination rate by some fraction. I explored numerically the conditions under which a rare \( M_2 \) allele introduced on an \( A_1-B_1 \) haplotype could invade a population fixed for \( M_1 \). A description of the model for this three-locus system is given in the Appendix 1.

**Results**

Linkage to the driving locus relaxes the invasion conditions for a sexually antagonistic allele and therefore expands the parameter space that permits a polymorphism (Figs 1 and 2). This effect on the opportunity for polymorphism at a sexually antagonistic locus is greater with tighter linkage to the driving locus (i.e. lower \( r \)) and stronger drive at the driving locus (i.e. higher \( k \); Figs 1 and 2).

I also examined the reverse order of evolutionary events: first, I ran the sexually antagonistic locus to equilibrium, and then, I let the meiotic drive allele invade. The opportunity for polymorphism at the \( B \) locus in this case was the same for all recombination distances between \( A \) and \( B \) for a trivial reason: with this order of events, the region of polymorphism is given by eqn (1) each time. The equilibrium allele frequencies within the region of polymorphism were the same as under the original order of mutational events.

The opportunity for polymorphism at a drive locus with a lethal driver is also affected by the linked locus. When the driver is a purely recessive lethal, any amount of drive (i.e. any \( k > 0.5 \)) is sufficient to allow invasion of a rare driver. If the fitness of drive heterozygotes is \( w \) relative to the fitness of \( A_2A_2 \) homozygotes, then the condition for invasion in a one-locus model is

\[ k > \frac{2 - w}{2w} \]

(Hartl, 1970; Feldman & Otto, 1991). With linkage, this condition is relaxed (Fig. 3). In other words, there are values of \( k \) that would not permit invasion in the absence of linkage that lead to polymorphism when the driving locus is linked to a sexually antagonistic locus.

Linkage to the driving locus also biases the direction of fixation at the sexually antagonistic locus. In the absence of linked drivers, the regions of parameter space that lead to the fixation of the male- or female-beneficial allele at a sexually antagonistic locus are of equal size (Owen, 1953; Kidwell et al., 1977). When linked to the driving locus, however, this symmetry is lost. In populations where one sex is achiasmate, this asymmetry is especially pronounced. In male-achiasmate species, there are parameterizations that lead to fixation of the male-beneficial allele despite there being stronger selection on females at the sexually antagonis-
tic locus (i.e. cases in which $t_f > t_m$) and vice versa for female-achiasmate species (as can be seen in Figs 1, 2 and 4). The influence of drive can be felt all along a chromosome in species with sex-limited achiasmy of this sort.

Positive linkage disequilibrium accompanies all polymorphic equilibria (Fig. 4), even with free recombination between loci. Haplotypes that couple spermatogenic drivers with male-beneficial alleles and haplotypes that couple drive-sensitive to female-beneficial alleles are overrepresented.

I compared the allele frequency that is predicted for a driving allele in a one-locus model (Hardl, 1970) with the eventual frequency it reaches when linked to a locus segregating for sexually antagonistic alleles. In all cases, except for when recombination is perfectly free in both sexes, the frequency of the driver is increased by linkage to a sexually antagonistic polymorphism (Fig. 5).

In the few parameterizations that I considered, a linked recombination modifier could invade and fix when it reduced recombination between $A$ and $B$, but an unlinked modifier could not (Fig. 6). The three-locus recursions can even be tuned to capture the effect of introducing an inversion (i.e. if the modifier eliminates recombination between $A$ and $B$ altogether and is itself perfectly linked to the $A-B$ locus). In this event, an inversion that ties together $A_1$ and $B_1$ can invade and spread. This haplotype will not fix, however, because $A_1$ is a recessive lethal (Fig. 6).

In all of the above results, I have assumed a spermatogenic driver. The results for female drive are attainable by an appropriate swapping of labels.

**Discussion**

Before turning attention to the implications of the above results, I offer a brief intuitive explanation for how they arise. The stable linkage disequilibrium that results stems from admixture of unlike gene pools, which has long been known to produce associations between loci (Nei & Li, 1973; Li & Nei, 1974). Every generation sperm will be enriched for the driving allele
(A₁) and the male-beneficial allele (B₁) relative to eggs, which will be enriched for the drive-sensitive allele (A₂) and female-beneficial allele (B₂). The allele frequencies at the two loci measured in sperm and eggs positively covary, which accounts for the positive sign of the linkage disequilibrium. Meiotic drive and sexual antagonism are akin to previous pairings of selection pressures that have been shown to produce stable linkage disequilibrium in that they entail correlations between the histories of pairs of loci (Ubeda et al., 2011; Haig et al., 2014). Haplotypes inherited from fathers are more likely to have been present in paternal grandfathers than paternal grandmothers because of sex-specific selection (and vice versa for haplotypes...

![Graphical representation of positive linkage disequilibrium between sexually antagonistic loci and meiotic drive loci.](image1)

**Fig. 4** Positive linkage disequilibrium accumulates between sexually antagonistic loci and meiotic drive loci. Here, linkage disequilibrium (Dz) is measured in zygotes; the value of Dz is plotted in colour as a function of the strength of sexually antagonistic selection. Recombination rates in males and females are rm = 0.01 or 0.5 unless indicated otherwise. Dz is always positive; haplotypes that pair male-beneficial with driving alleles and female-beneficial with drive-sensitive alleles are overrepresented at equilibrium. This result holds regardless of recombination rates. In the absence of drive, the trumpet-shaped region that permits polymorphism (bounded by the black curves) is symmetric. Drive eliminates this symmetry. Achiasmate meiosis in one of the sexes further enhances the asymmetry.

![Graphical representation of the difference in equilibrium allele frequency in sperm of the driver before and after the introduction of sexually antagonistic variation at a linked locus.](image2)

**Fig. 5** The difference in equilibrium allele frequency in sperm of the driver before and after the introduction of sexually antagonistic variation at a linked locus. The colour depicts the change in allele frequency of A₁, the driving allele from before the introduction of variation at the linked sexually antagonistic locus to after the two loci reach their new equilibrium frequencies. The drive strength was k = 0.95 in the simulations shown. Notice how the presence of a linked sexually antagonistic locus cause an increase in the equilibrium frequency of the driver in all cases.
inherited from mothers). This correlation between their histories also helps to explain the expansion of the opportunity for polymorphism. On its own, without any linked influences on fitness, a male-beneficial allele faces sex-specific selection pressures – it gains an advantage in males but experiences a cost in females – and male-beneficial alleles are therefore expected to have spent more of their ancestry in male bodies. Linkage to a spermatogenic drive locus distorts the ancestry of male-beneficial alleles still further towards males because spermatogenic drivers are also more often inherited from males. By virtue of being co-inherited with driving alleles, male-beneficial alleles will have spent fewer previous generations in female bodies, thus avoiding their selective disadvantage more often than the 50% of time that is expected for neutral alleles. The same argument applies to female-beneficial alleles on drive-sensitive haplotypes. By virtue of being co-inherited with the drive-sensitive allele, they avoid the fitness costs associated with the driving allele and thus are more often inherited from mothers. Because alleles spend less of their ancestry in the sex in which they are selectively disfavoured, selection is ineffective in removing them from the population. The result is polymorphism.

Burt & Trivers (2006) suggested that driving haplotypes would be enriched for sexually antagonistic effects because of the distortion to the ancestry described above (see also Úbeda & Haig, 2005 for a similar thought pertaining to permanently heterozygous drive systems). Under their hypothesis, the drivers themselves would not evolve these sexually antagonistic effects, but rather they would recruit linked loci that produce such effects. The results of the model above agree with their notion: spermatogenic drivers will be a magnet for male-beneficial but female-costly effects. (An appropriate swapping of labels in the model above will also show that female meiotic drivers will recruit female-beneficial effects.) We might therefore predict, for instance, that females heterozygous for the Mus c-haplotype, a spermatogenic driver, will suffer reduced fitness relative to females that are homozygous for the drive-sensitive haplotype. Likewise, we might predict that heterozygous males will show higher fitness than males homozygous for the drive-sensitive haplotype. Tests of these two predictions run into a serious problem: driving haplotypes are often found in areas of reduced recombination and are therefore predicted to accumulate mutations detrimental to both sexes. Consequently, heterozygotes of both sexes might be less fit than homozygotes (e.g. Carroll et al., 2004). In that case, the signal of a sexually antagonistic effect from one linked locus might be swamped by the deleterious effect of other linked loci.

Despite this possible complication, there is evidence that driving haplotypes have sexually antagonistic
effects (Burt & Trivers, 2006). In mice, +/t heterozygotes demonstrated behaviour consistent with these types of opposing effects (Lenington, 1991; Lenington et al., 1996), and certain components of fitness showed antagonistic effects in the direction predicted by the model above (Dunn & Suckling, 1956; Dunn et al., 1958). Ab10, an abnormal version of chromosome 10 in maize that possesses a heterochromatric knob at its distal end and drives during megasporogenesis (which is analogous for these purposes to female meiotic drive), shows reduced success in pollen (Rhoades, 1942). More recently, Fishman & Saunders (2008) measured a reduction in fitness through male function in plants heterozygous for a haplotype that drives in megasporogenesis. It is unclear whether any of these fitness effects are caused by pleiotropy of the driving locus itself or whether they are instead caused by linked loci with sex-specific effects (Fishman, 2013).

Perhaps the biggest difficulty lurking in the empirical study of meiotic drive is that too often the observed frequency of a driving allele is considerably less than what is expected from the theoretical predictions (Lyttle, 1991; Ardlie & Silver, 1998; Jaenike, 2001; Burt & Trivers, 2006). Countervailing pressures that limit the spread of driving alleles have been sought, both theoretically (e.g. Charlesworth & Hartl, 1978; Haig & Bergstrom, 1995) and empirically (e.g. Wilkinson et al., 2006; Price et al., 2014). I find that the frequency of a driving allele is theoretically increased whenever it is linked to a sexually antagonistic polymorphism. This finding only magnifies the problem of accounting for the allele frequencies in nature.

Had I incorporated into the model any forces that lessen the equilibrium frequency of drivers, the results I found would have changed quantitatively. However, the results would not change qualitatively; one would still expect to find an increased opportunity for polymorphism owing to linkage, linkage disequilibrium between A and B when both were polymorphic at equilibrium, selection favouring reduced recombination, and a boost to the driver’s frequency by being linked to the sexually antagonistic polymorphism.

Many driving haplotypes are tied up in one or more inversions, and additional inversions are often found at nearby loci on driving chromosomes (Hammer et al., 1989; Lyttle, 1991; Silver, 1993; Jaenike, 2001; Dyer et al., 2007). Their existence has previously been explained by their ability to trap enhancers of drive together with the driving loci – that is to promote good epistatic pairings – and several examples of these modifier loci have been characterized (Ganetzky, 1977; Lyttle, 1991). However, the results from the model above suggest another possibility for what favours inversions around drive haplotypes. If selection produces positive linkage disequilibrium between driving loci and sexually antagonistic loci, then one might predict that modifiers of the recombination rate will be selected to reduce the frequency of recombination between them (Karlin & McGregor, 1974; Feldman et al., 1996). In this way, drivers would be similar to sex-determining loci in their ability to accumulate sexually antagonistic loci nearby and then evolve reduced recombination (Rice, 1987).

I tested this prediction by considering the evolution of a neutral modifier locus, M, next to the B locus. After A and B had run to their polymorphic equilibrium, I introduced a rare, dominant allele, M2, that lowers recombination between A and B. I found that such a modifier allele could invade provided there was linkage between it and the other two loci (Fig. 6). This was by no means an exhaustive investigation of the possibility of linkage modification, but it suggests that meiotic drive and sexual antagonism can in principle cause congealment along a chromosome. At least from this preliminary sketch, it would appear that intralocus conflicts (sexual antagonism and meiotic drive) prompt the opposite effect on recombination from interlocus conflict (Roze & Otto, 2012; Dapper & Lively, 2014). The full analysis of this three-locus system, which lies beyond the scope of this study, awaits further investigation.

Perhaps the most intriguing result found above is the demonstration of the influence of drive on unlinked sexually antagonistic loci, particularly in those species in which one sex undergoes achiasmate meiosis. For example, despite their being ≥50 cM from driving loci in females, sexually antagonistic loci can be biased to resolve in favour of male-beneficial effects in male-achiasmate species. If we consider the SD polymorphism of Drosophila, this would mean that all of chromosome 2, or ~30% of the genome, is biased in favour of male-beneficial effects. The magnitude of this predicted effect should be tempered by the recognition that the allele frequencies for drivers used in the model reflect the theoretical predictions, which, as mentioned previously, are generally much higher than the observed frequencies in nature (Lyttle, 1991; Ardlie & Silver, 1998; Jaenike, 2001; Burt & Trivers, 2006).

The final implication of the results above is for conflict resolutions. If these results on meiotic drive and sexual antagonism are combined with previous work on sexual antagonism (Patten et al., 2010; Úbeda et al., 2011), we should expect to find haplotypes in nature that are enriched for sexually antagonistic effects. Rice (1986) and, more recently, van Doorn & Kirkpatrick (2007, 2010) have modelled the evolution of genetic sex determination as a resolution to such sexually antagonistic fitness variation. In the light of the prediction of increasingly antagonistic haplotypes with drivers and sexually antagonistic effects, one appreciates that the selection pressure favouring the origin of new sex-determining alleles is even greater than might have been previously envisioned. Meiotic drive is particularly strong in its sex-specific fitness effects and may favour
the establishment of new sex-determining alleles (Haig, 1997). One possible resolution to the polymorphic equilibria found above for driving loci and sexually antagonistic loci is for a dominant sex-determining allele to arise at another linked locus. If the mutant allele arises on the drive-sensitive haplotype and initiates the development of the sex in which drive does not occur, then it should be favoured by natural selection. Drive is well known on sex chromosomes (Jaenike, 2001), but its potential for a role in their origin is, by comparison, relatively unexamined (but see Kozielska et al., 2010).

There are several reasons that future attention should be given to the interplay of drive and sexual antagonism on sex chromosomes: one, drive is thought to be easier to attain on the X than on an autosome (Hurst & Pomiankowski, 1991; Jaenike, 2001); two, the X differs from autosomes with respect to expectations of sexually antagonistic variation (Rice, 1984; Patten & Haig, 2009); and three, a sex difference in recombination rate, which was found here to produce marked asymmetries in the outcome of sexually antagonistic selection, is characteristic of the sex chromosomes.

The lesson that comes from unifying the results of this study with that of previous theoretical work on sexual antagonism, genetic sex determination and meiotic drive is that if any one of these three features is present in a population, the other two are expected to eventually accompany. Each one invites the others. For example, sex chromosomes have been shown to attract meiotic drive (Jaenike, 2001) and sexual antagonism (Rice, 1992); sexual antagonism has been shown to attract genetic sex determination (Rice, 1986; van Doorn & Kirkpatrick, 2007, 2010) and further sexual antagonism (Patten et al., 2010; Ubeda et al., 2011); and now, in the current study, I have shown how meiotic drive attracts sexual antagonism. The current work adds to the view that conflicting selection pressures play a major role in shaping the pattern of polymorphism in populations and the architecture of genomes (Rice, 2013).

Acknowledgments

I am grateful to two anonymous reviewers for their helpful suggestions on the original draft of this manuscript.

References


Meiotic drive and sexual antagonism


Roze, D. & Otto, S.P. 2012. Differential selection between the recursions for haplotype frequencies in sperm are as follows:

\[
x_1' = \frac{1}{w_1} \left[ x_1 y_1 w_{11f} + \frac{1}{2} x_1 y_2 w_{21f} + \frac{1}{2} x_2 y_1 w_{12f} + \frac{1}{2} x_2 y_2 w_{22f} + \frac{1}{2} x_3 y_1 w_{13f} + \frac{1}{2} x_3 y_2 w_{23f} + \frac{1}{2} (1 - r_f) x_1 y_4 w_{14f} + \frac{1}{2} r_f x_2 y_3 w_{23f} \right]
\]

\[
x_2' = \frac{1}{w_2} \left[ x_2 y_2 w_{22f} + \frac{1}{2} x_1 y_2 w_{12f} + \frac{1}{2} x_2 y_1 w_{21f} + \frac{1}{2} x_3 y_2 w_{32f} + \frac{1}{2} x_4 y_2 w_{42f} + \frac{1}{2} r_f x_1 y_4 w_{14f} + \frac{1}{2} (1 - r_f) x_2 y_1 w_{21f} \right]
\]

\[
x_3' = \frac{1}{w_3} \left[ x_3 y_3 w_{33f} + \frac{1}{2} x_1 y_3 w_{13f} + \frac{1}{2} x_3 y_1 w_{31f} + \frac{1}{2} x_4 y_3 w_{43f} + \frac{1}{2} x_4 y_4 w_{44f} + \frac{1}{2} r_f x_1 y_4 w_{14f} + \frac{1}{2} (1 - r_f) x_3 y_2 w_{32f} \right]
\]

\[
x_4' = \frac{1}{w_4} \left[ x_4 y_4 w_{44f} + \frac{1}{2} x_4 y_5 w_{43f} + \frac{1}{2} x_5 y_4 w_{54f} + \frac{1}{2} x_2 y_4 w_{24f} + \frac{1}{2} x_4 y_2 w_{42f} + \frac{1}{2} (1 - r_f) x_4 y_1 w_{41f} \right]
\]

The above recursions assume Mendelian segregation during meiosis in *A₁A₂* (and *A₂A₁*) females. For males, let *k* be the proportion of functional sperm produced by heterozygotes that carry an *A₁* allele and let \( \frac{1}{2} < k \leq 1 \). The recursions for haplotype frequencies in sperm are as follows:

\[
y_1' = \frac{1}{w_m} \left[ x_1 y_1 w_{11m} + \frac{1}{2} x_1 y_2 w_{12m} + \frac{1}{2} x_2 y_1 w_{21m} + k x_3 y_1 w_{31m} + k x_3 y_1 w_{31m} + k (1 - r_m) x_1 y_4 w_{14m} + k r_f x_2 y_3 w_{23m} \right]
\]

\[
y_2' = \frac{1}{w_m} \left[ x_2 y_2 w_{22m} + k x_1 y_2 w_{12m} + \frac{1}{2} x_2 y_1 w_{21m} + k x_3 y_2 w_{32m} + k (1 - r_m) x_1 y_4 w_{14m} + k r_f x_2 y_3 w_{23m} \right]
\]
\[ y'_2 = \frac{1}{w_m} \left[ x_2 y_2 w_{22m} + \frac{1}{2} x_1 y_2 w_{12m} + \frac{1}{2} x_2 y_1 w_{21m} + k x_2 y_4 w_{24m} + k x_4 y_2 w_{42m} + k r_m x_1 y_4 w_{14m} + k(1 - r_m) x_2 y_3 w_{23m} \right. \\
+ k(1 - r_m) x_3 y_2 w_{32m} + k r_m x_4 y_1 w_{41m} \right] \\

\[ y'_3 = \frac{1}{w_m} \left[ x_1 y_3 w_{31m} + (1 - k) x_1 y_1 w_{13m} + (1 - k) x_3 y_1 w_{31m} + \frac{1}{2} x_3 y_4 w_{34m} + \frac{1}{2} x_4 y_3 w_{43m} + (1 - k) r_m x_1 y_4 w_{14m} \right. \\
+ (1 - k)(1 - r_m) x_2 y_3 w_{23m} + (1 - k)(1 - r_m) x_3 y_2 w_{32m} + (1 - k)(1 - r_m) r_m x_4 y_1 w_{41m} \right] \\

\[ y'_4 = \frac{1}{w_m} \left[ x_4 y_3 w_{43m} + \frac{1}{2} x_4 y_1 w_{14m} + \frac{1}{2} x_3 y_4 w_{34m} + (1 - k) x_2 y_4 w_{24m} + (1 - k) x_4 y_2 w_{42m} + (1 - k)(1 - r_m) x_1 y_4 w_{14m} \right. \\
+ (1 - k) r_m x_2 y_3 w_{23m} + (1 - k) r_m x_3 y_2 w_{32m} + (1 - k)(1 - r_m) x_4 y_1 w_{41m} \right] \quad (A1b) \\

In the model and results section, I refer to male meiotic drive only, but results for female meiotic drive can be obtained by the appropriate swapping of labels. The mean fitness in a particular sex is as follows:

\[ \overline{w_x} = \sum_i \sum_j x_i y_j w_{ij} \quad (A1c) \]

where \( x \in f.m. \).

The three-locus model makes similar assumptions of random union of gametes, no mutation, no migration and no drift. The third locus, \( M \), is selectively neutral, so the fitness of a diploid genotype is determined as before, from the genotypes at the \( A \) and \( B \) loci. Recombination between \( B \) and \( M \) is governed by the parameter \( c_l \) in females and \( c_m \) in males. I assume there is no crossover interference. The \( M_2 \) allele is a dominant modifier of the recombination rate. Individuals heterozygous or homozygous for \( M_2 \) have reduced recombination between \( A \) and \( B \), equal to \( m \) times \( r_l \) or \( r_m \), respectively, \((m \leq 0)\). The full recursions, which comprise sixteen equations (eight haplotype frequencies each for eggs and sperm) and 64 terms (one for each diploid genotype frequency) each, are too expansive for the page here but can be found in the code, which has been deposited in Dryad (doi:10.5061/dryad.7q577).

Received 12 June 2014; revised 1 August 2014; accepted 14 August 2014