X-linked meiotic drive can boost population size and persistence

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ABSTRACT X-linked meiotic drivers cause X-bearing sperm to be produced in excess by male carriers, leading to female-biased sex ratios. Here, we find general conditions for the spread and fixation of X-linked alleles. Our conditions show that the spread of X-linked alleles depends on sex-specific selection and the way they are transmitted rather than the time spent in each sex. Applying this logic to meiotic drive, we show that polymorphism is heavily dependent on sperm competition induced both by female and male mating behaviour and the degree of compensation to gamete loss in the ejaculate size of drive males. We extend these evolutionary models to investigate the demographic consequences of biased sex ratios. Our results suggest driving X-alleles that invade and reach polymorphism (or fix and do not bias segregation excessively) will boost population size and persistence time by increasing population productivity, demonstrating the potential for selfish genetic elements to move sex ratios closer to the population-level optimum. However, when the spread of drive causes strong sex ratio bias, it can lead to populations with so few males that females remain unmated, cannot produce offspring and go extinct. This outcome is exacerbated when the male mating rate is low. We suggest that researchers should consider the potential for ecologically beneficial side effects of selfish genetic elements, especially in light of proposals to use meiotic drive for biological control.

KEYWORDS sex ratio; selfish genetic elements; sex chromosome; levels of selection; polyandry; segregation distortion; eco-evolutionary model

Introduction

Meiotic drivers violate Mendel's law of equal segregation by ensuring that they are transmitted to more than half of a carrier's progeny (Burt and Trivers 2006). While beneficial at the chromosome-level, this transmission benefit usually comes at a cost to carrier survival or fecundity (Werren 2011). Meiotic drive has been observed across a wide variety of animal and plant taxa (Sandler *et al.* 1959; Turner and Perkins 1979; Jaenike 1996; Ardlie 1998; Taylor *et al.* 1999; Fishman and Willis 2005; Tao *et al.* 2007; Lindholm *et al.* 2016), particularly in flies and rodents (Helleu *et al.* 2015). Many of the described systems are sex-specific (Úbeda and Haig 2005; Lindholm *et al.* 2016), arising due to activity in either female (e.g., Fishman and Willis (2005)) or male meiosis (e.g., Sandler *et al.* (1959)). When meiotic drivers arise on sex chromosomes, they change the relative frequencies of gametes carrying the sex-determining alleles, resulting in brood sex ratio bias (Burt and Trivers 2006). In particular, where X-linked meiotic drivers bias segregation in males, X-bearing sperm outnumber Y-bearing sperm and the sex ratio among offspring is female-biased. Hamilton (1967) noted that extreme sex ratios caused by X-linked meiotic drivers could lead to population extinction, as eventually the almost entirely female population will go unmated and be unable to produce offspring.

Substantial theoretical work since Hamilton's pioneering study (Hamilton 1967) has investigated the spread of meiotic drive, and the conditions that lead to its polymorphism and prevent population extinction. Polymorphism and population persistence are most directly achieved via suppression systems that evolve at other loci to negate meiotic drive (Hamilton 1967; Charlesworth and Hartl 1978; Frank 1991). In the absence of suppression, fixation of autosomal (Ardlie 1998; Larracuente and Presgraves 2012) or X-linked (Taylor and Jaenike 2002, 2003; Price *et al.* 2014) meiotic drive can be prevented by direct fitness costs associated with carrying the driving allele. Meiotic drive systems often occur within inversions that link together the required drive and enhancer loci (Pomiankowski and Hurst 1999).

doi: 10.1534/genetics.XXX.XXXXXX
Manuscript compiled: Thursday 12th November, 2020
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These inversions may also capture deleterious alleles and/or allow deleterious mutations to accumulate through Muller's ratchet, potentially explaining the fitness costs associated with meiotic drivers (Edwards 1961; Curtsinger and Feldman 1980; Dyer *et al.* 2007; Kirkpatrick 2010). Such effects have been demonstrated empirically, with female carriers of X-linked meiotic drive observed to have reduced survival or fecundity, especially when homozygous (Larner *et al.* 2019; Dyer and Hall 2019; Keais *et al.* 2020). However, these fitness costs are not necessarily sex-specific or recessive (Finnegan *et al.* 2019b).

Meiotic drive can also have deleterious effects by reducing male fertility, most obviously because sperm/spores that do not carry the driving element are rendered dysfunctional or killed (Price *et al.* 2008). This effect may be negligible when females mate with a single male, but drive can alter competition between the ejaculates of different males in a polyandrous mating system. Not only do drive-carrying males deliver fewer sperm per ejaculate, but drive-carrying sperm can also perform more poorly in sperm competition with sperm from wild-type males (Price *et al.* 2008; Manser *et al.* 2017; Dyer and Hall 2019; Manser *et al.* 2020). Offspring sired by drive males have lower fitness which may favour the evolution of increased sperm competition through female polyandry, an argument for which there is some theoretical and experimental evidence (Price *et al.* 2008; Wedell 2013; Price *et al.* 2014; Holman *et al.* 2015; Manser *et al.* 2017), but see (Sutter *et al.* 2019). The fertility cost to drive males, and associated selection for female polyandry, becomes less important as male frequency declines leading to lower competition for mates and fertilisation (Taylor and Jaenike 2002, 2003). In line with this, modelling has shown that polyandry can limit the spread of meiotic drive alleles, but the evolution of polyandry is not sufficient to stop meiotic drive alleles fixing (Holman *et al.* 2015).

The above models have focused on the evolutionary dynamics of meiotic drive but ignored its demographic consequences. This is surprising as in one of the foundational models of the field, Hamilton (1967) showed that sex-linked drive causes transient population expansion before extinction. Population decline occurs when the sex ratio is pushed beyond the point where females can find sufficient mates. This model did not include density-dependent population regulation or fertility/viability costs associated with meiotic drive. Nevertheless, it suggests that X-linked meiotic drivers will increase population size when they cause sex ratios to be biased, but not extremely biased. Some subsequent analyses support this hypothesis, but it has not been examined directly. Unckless and Clark (2014) showed that species with X-linked meiotic drivers can have an advantage during interspecific competition, shifting the community competition in their favour (James and Jaenike 1990). Similar effects can occur with other systems that cause female-biased sex ratios. For example, feminisation caused by *Wolbachia* can increase population size until females go unmated due to a lack of males (Hatcher *et al.* 1999; Dyson and Hurst 2004). Finally, under temperature-dependent sex determination, shifts in climate can bias the sex ratio towards females (West 2009), which is predicted to increase population sizes providing males are not limiting (Boyle *et al.* 2014).

First, we derive new general analytical expressions for the invasion and maintenance of X chromosome variants. The results define the relative weighting of selection in males/females and maternal/paternal transmission, refining the heuristic that X-linked alleles weight their fitness effects twice as strongly in females because they spend twice as much time in females (Patten 2019; Hitchcock and Gardner 2020). We use these results and a simulation-based model to investigate the interplay between female mating rate (polyandry), male mating rate (limits to the number of females each male can mate with) and male sperm compensation (for losses caused by meiotic drive) in the maintenance of X-drive polymorphism. Having established the evolutionary dynamics, we investigate the demographic consequences of meiotic drive and show that drive can cause population sizes to be larger than wild-type populations, enabling them to persist for longer and with lower intrinsic birth rates.

Materials and Methods

We model a well-mixed population with XY sex-determination where generations are discrete and non-overlapping. There are two types of X chromosome segregating in the population, a standard X chromosome and a drive X_d chromosome. There are three female genotypes XX, X_dX and X_dX_d, and two male genotypes XY and X_dY, which we describe as wild-type and drive males respectively. In XY males, meiosis is fair. The X_d chromosome biases segregation such the ratio of X_d to Y chromosomes among their sperm is $(1+\delta)/2 : (1-\delta)/2$. When $\delta = 0$, meiosis is fair and sex chromosomes are transmitted with equal probability; when $\delta = 1$ drive males produce only X_d sperm.

We assume males (whether drive or wild-type) produce sufficient sperm in an ejaculate to fertilise all a female's eggs. Drive males have reduced ejaculate size because Y-bearing sperm are rendered dysfunctional, reducing their success in sperm competition. The ejaculate size of X_dY drive males is determined by the degree of compensation c ($c \in [0,1]$). When $c = 1/(1+\delta)$, there is no compensation for dysfunctional Y sperm. When $c > 1/(1+\delta)$, drive males produce extra sperm in their ejaculate to compensate for those lost through meiotic drive. In the extreme when $c = 1$, drive male ejaculates contain the same number of viable sperm as wild-type males. Compensation affects the success of drive males in sperm competition which is assumed to follow a fair raffle (Parker 1990). In this paper, we refer to c in the context of ejaculate size, however it can also be interpreted as the competitive ability of drive male sperm. This could apply to cases where sperm have reduced motility, for example.

We track the genotypes of adults, who experience density dependent competition for resources and mate at random before producing offspring. We assume that fertilization follows sperm competition among the ejaculates of all males a female mates with. The resulting offspring experience selection according to their genotype before they become the adults of the next generation. The fitness of each genotype is given by w_i^f and w_i^m, allelic fitness effects in males and females are given by s_f, $s_m \in [0,1]$ and $h \in [0,1]$ determines dominance in females (Table 1).

Analytical model

The total number of adults in the population is given by $N = \sum_i F_i + \sum_j M_j$, where F_i and M_j represent female and male population densities respectively and $i \in \{XX, XX_d, X_dX_d\}$ and $j \in \{XY, X_dY\}$. We assume that competition for resources among adults linearly reduces the fecundity of females. Specifically, each adult female gives birth to $B_N = b(1-\alpha N)$ offspring, where b is the intrinsic female fecundity in the absence of competition and α is the per-individual competitive effect on fecundity. In the absence of meiotic drive or other genotypic

female genotype i	w_i^f	$E_{X,i}$	$E_{X_d,i}$	
$i = XX$	1	1	0	
$i = X_dX$	$1 - hs_f$	1/2	1/2	
$i = X_dX_d$	$1 - s_f$	0	1	
male genotype j	w_j^m	$S_{X,j}$	$S_{X_d,j}$	$S_{Y,j}$
$j = XY$	1	1/2	0	1/2
$j = X_dY$	$1 - s_m$	0	$c(1+\delta)/2$	$c(1-\delta)/2$

Table 1 Relative fitness and transmission parameters for different male and female genotypes

effects on fitness, the population size in the next generation is $N' = (b/2)(1 - \alpha N)N$ and the equilibrium population size is $\hat{N} = (b-2)/b\alpha$. This form of density dependence can equally apply to intra-specific competition that reduces female survival probability before reproduction. We consider cases where the strength of density dependence is a function of the birth rate in the Supplementary Information.

In this model, we consider various degrees of polyandry determined by a fixed integer λ_f: females mate λ_f times, with a male mate chosen uniformly at random. When each female mates once ($\lambda_f = 1$), the adult female densities of genotype ab in the next generation, summed across matings between all possible female i and male j parents, are given by

$$F'_{ab} = \left(\sum_{i \text{ female}} B_N F_i E_{a,i} \right) \left(\sum_{j \text{ male}} \frac{m_j S_{b,j}}{\sum_k S_{k,j}} \right) w_{ab}^f, \qquad (1)$$

and the male densities of gentotype aY are given by

$$M'_{aY} = \left(\sum_{i \text{ female}} B_N F_i E_{a,i} \right) \left(\sum_{j \text{ male}} \frac{m_j S_{Y,j}}{\sum_k S_{k,j}} \right) w_{aY}^m, \qquad (2)$$

where $E_{a,i}$ is the proportion of eggs with haploid genotype a produced by females with diploid genotype i, $m_j = M_j / \sum_k M_k$ is the frequency of males with genotype j, and $S_{b,j}$ is the proportion of sperm with haploid genotype b contributed by males with genotype j (Table 1). That is, diploid parental genotypes are denoted by subscripts i and j for males and females, while subscripts a and b represent haploid chromosomes inherited maternally and paternally, respectively. As there are no parent-of-origin effects, the sum of F'_{X_dX} and F'_{XX_d} is represented simply as F'_{X_dX}.

When each female mates twice ($\lambda_f = 2$), female densities in the next generations are given by

$$F'_{ab} = \left(\sum_{i \text{ female}} B_N F_i E_{a,i} \right) \left(\sum_{j,k \text{ male}} \frac{m_j m_k \left(S_{b,j} + S_{b,k} \right)}{\sum_l \left(S_{l,j} + S_{l,k} \right)} \right) w_{ab}^f, \qquad (3)$$

where there is competition for fertilization of each egg among the sperm contributed by two males, firstly with genotype j and then with genotype k. When each female mates many times (λ_f large), the female densities in the next generation approach

Term	Definition
M_i	Density of males with genotype i
F_i	Density of females with genotype i
m_i	Within-sex frequency of males with genotype i
λ_f	Number of matings before laying eggs in a females' lifetime
$E_{a.i}$	Proportion of eggs of genotype a produced by a female of genotype i
$S_{b,i}$	Units of sperm of type b produced by a male of genotype i relative to wild-type
N	Total density of males and females
α	Per-adult cost to average female fecundity
b	Intrinsic female fecundity (in the absence of competition)
B_N	Female fecundity in a population of size N
c	Ejaculate size of a drive male compared to a wild-type male
δ	Strength of drive

Table 2 Table of terms

$$F'_{ab} = \left(\sum_{i \text{ female}} B_N F_i E_{a,i} \right) \left(\sum_j m_j \frac{M_j S_{b,j}}{M_{XY} + cM_{X_dY}} \right) w_{ab}^f, \qquad (4)$$

where females effectively sample sperm randomly from the total pool of gametes produced by all males in the population. Recursion equations for male densities follow similarly, replacing $S_{b,i}$ with $S_{Y,i}$ and w_{ab}^f with w_{aY}^m in equations Eq(3) and Eq(4).

Simulation model

The previous model assumes that male matings are not limiting. Population extinction can only occur when the birth rate is low and/or no males remain. In the simulation model, we allow limitations on the mating rate in both female and male matings which are capped by λ_f and λ_m respectively. When an individual reaches the maximum number of matings they cannot mate again. This constraint precludes the possibility that a small number of males can fertilise a large number of females, which is possible in the analytical model. Under these more realistic conditions, it is possible for a population to become extinct because the sex ratio is female biased and there are insufficient males to sustain the population.

As in the analytical model, adult females experience density-dependent competition for resources. In the absence of any competition, females lay b eggs each. In the case where b is non-integer, females lay a mean of b eggs by laying a minimum of $\lfloor b \rfloor$ eggs with a $100(b - \lfloor b \rfloor)\%$ chance of laying one more. Whether or not a birth occurs depends on the competitive influence of other adults, with birth probability $1 - \alpha N$.

The first generation comprises N_0 wild-type individuals at an equal sex ratio, and the driving X_d chromosome is introduced into the population at a proportion q in Hardy-Weinberg equilibrium. Generations then proceed similarly to the previous model. Adults mate randomly until there are either no females

or no males available to mate. Assuming they are able to mate, every individual is picked with equal probability. We track the sperm carried by each female as a 3-tuple (x, y, z), representing the quantity of X, X_d, and Y bearing sperm respectively. When a male mates with a female, he adds to the sperm that the female carries. XY males add $(0.5, 0, 0.5)$, and X_dY males add $(0, c(1+\delta/2), c(1-\delta)/2)$. Once mating is complete, each egg is fertilised by a sperm sampled randomly, weighted by the probability distribution (x, y, z) after normalisation. The juveniles then undergo viability selection according to their genotypic fitness, with survival probabilities given in Table 1.

There are three main sources of stochasticity present within the simulation model but not in the analytical model. First, the exact sperm that fertilises an egg is sampled at random. Second, juvenile survival to adulthood and the realisation of births is probabilistic. And finally, mating is at random. These three sources can result in fluctuations in genotype frequencies, which can affect the population sex ratio and population size.

Data availability.

Mathematica notebooks for the main text and supplementary information can be found in Files S1 and S2, and the Python script used to simulate data can be found in File S3 at (figshare link).

Results

Invasion of a rare X chromosome

We first give general conditions for the spread of a rare X chromosome. A rare X-linked allele increases in frequency if

$$\frac{1}{2}w^f_{mat} + \frac{1}{2}w^m_{mat} * w^f_{pat} > 1, \tag{5}$$

where w^i_j is the relative fitness of the mutant X chromosome in sex i when inherited maternally ($j = mat$) or paternally ($j = pat$). These relative fitnesses include any transmission biases that arise during gamete production or competition, relative to the transmission of the resident chromosome in the same sex. This is a general expression that covers classical models of sex-specific selection on the X chromosome without sperm competition or meiotic drive (e.g. Curtsinger and Feldman (1980); Rice (1984)).

A widespread heuristic posits that X-linked alleles weight female fitness components twice as much as male fitness effects because X chromosomes spend twice as much time in females as in males (Patten 2019; Hitchcock and Gardner 2020). This two-thirds to one third weighting is a linear weak selection approximation of Eq (5), in which all the terms become additive. The more-accurate full expression Eq(5) has two parts, reflecting the two pathways via which a rare X chromosome can increase in frequency in females, which are equally weighted (Figure 1). First, X chromosomes can be inherited from mother to daughter (w^f_{mat}). Second, X chromosomes in males are always inherited from the mother and will always then be passed to a daughter ($w^m_{mat} * w^f_{pat}$). If, averaged over these two pathways, the frequency of female carriers increases, then a rare chromosome type will spread in the population. This condition (Eq(5)) shows that the spread of X-linked alleles depends on sex-specific selection and their transmission through the generations rather than the time spent in each sex.

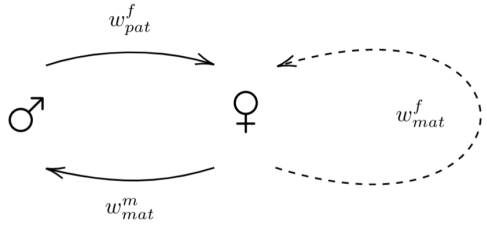

Figure 1 For a rare X chromosome variant to spread in a population, it must increase in frequency in females, which may occur via either of the paths shown. Females transmit X chromosomes (maternally) to either sons or daughters. Sons transmit all X chromosomes (paternally) to females in the next generation

Maintenance of drive polymorphism We now apply this general condition to a driving X_d chromosome. To remain polymorphic, a rare X_d chromosome must increase in frequency when rare but not fix in the population. That is, $w^f_{mat} = 1 - hs_f$ is the viability of the heterozygous female; $w^m_{mat} = 1 - s_m$ is the viability of the drive male; and $w^f_{pat} = (1+\delta)[c\lambda_f/(c+\lambda_f-1)](1-hs_f)$ is the transmission of meiotic drive alleles through sperm competition and then their viability in female heterozygotes. Combining these terms, the driving X_d chromosome spreads if

$$\frac{(1-hs_f)}{2}\left(1+\left[\frac{c\lambda_f}{c+(\lambda_f-1)}\right](1+\delta)(1-s_m)\right) - 1 > 0. \tag{6}$$

The success of a rare drive allele in sperm competition is $c/(c+(\lambda_f-1))$, given that a female mates with a single drive male and $\lambda_f - 1$ wild-type males. Across all matings, the relative success of rare drive alleles during sperm competition is given by the term in square brackets.

Using the same logic, the driving X_d chromosomes will not fix in the population if

$$\frac{(1-hs_f)}{2(1-s_f)}\left(1+\left[\frac{\lambda_f}{1+c(\lambda_f-1)}\right]\frac{1}{(1+\delta)(1-s_m)}\right) - 1 > 0. \tag{7}$$

As X chromosome meiotic drive (X_d) becomes common, the transmission and fitness advantage/disadvantage of X_d chromosomes in males is unchanged (terms involving δ and s_m). The sperm competition term (in square brackets) now reflects the relative competitiveness of sperm from non-drive males.

Importantly, close to fixation, most females are either heterozygous or homozygous for meiotic drive and, unlike Eq(6), Eq(7) depends on these relative female fitnesses. The maintenance of polymorphism (satisfying inequalities in both Eq(6, 7)) occurs when meiotic drive causes low fitness cost in female heterozygotes (hs_f) relative to the cost in female homozygotes (s_f), which allows invasion but prevents fixation. For example, meiotic drive alleles are less likely to reach fixation when the negative fitness effects of drive are recessive ($h = 0$, Figure 2).

Sperm competition affects the dynamics of rare X-alleles through a combination of polyandry (λ_f) and any reduction in ejaculate size caused by drive (c) (Figure 2). If females mate with only one male ($\lambda_f = 1$) then sperm competition has no effect. The same holds if drive males produce the same amount of sperm as wild-type males ($c = 1$) (Figure 2). In both cases, the sperm competition term in the square brackets of Eqs(6-7) is

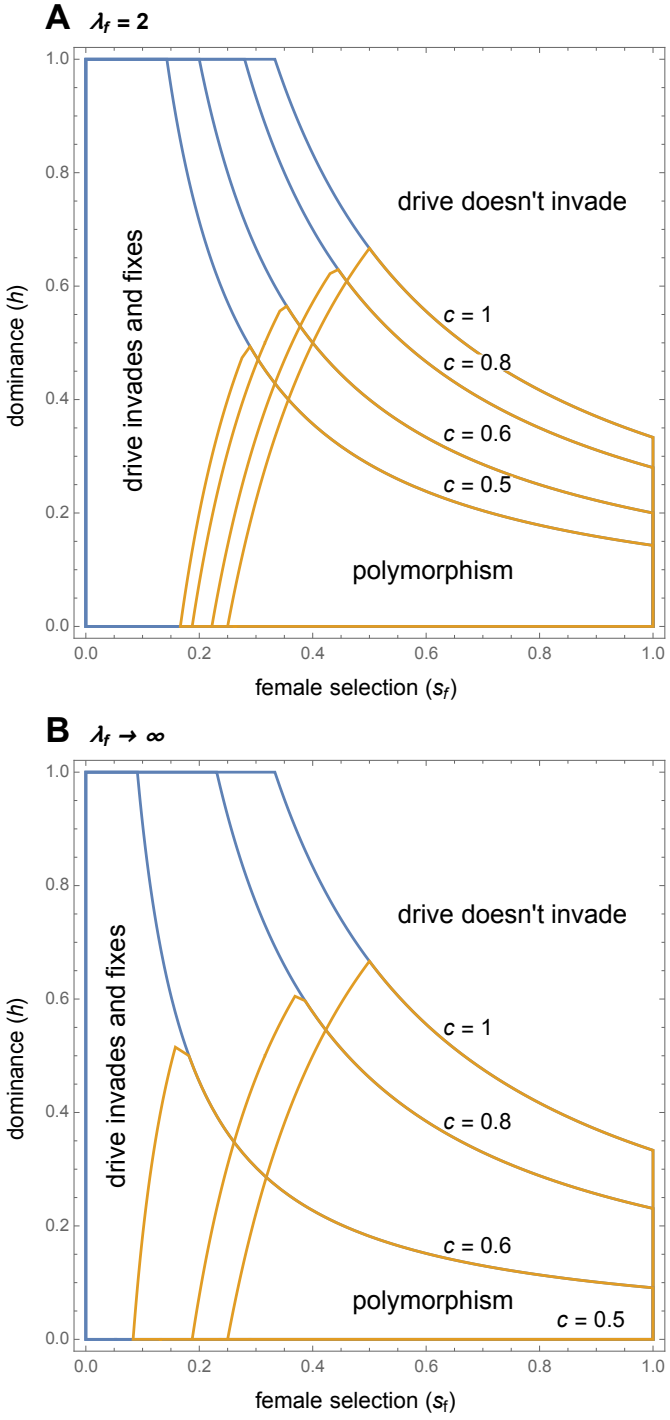

Figure 2 Fitness parameters under which X chromosome meiotic drive invades, reaches polymorphism (orange border), or fixes (blue border), given different levels of sperm compensation (c). Boundaries at $c = 1$ (full compensation) are equivalent to the condition of a single female mating ($\lambda_f = 1$). In A), females mate twice ($\lambda_f = 2$), in B) females mate many times, effectively sampling at random from all male sperm produced. If females mate many times and there is no sperm compensation ($c = 0.5$), then polymorphism is not possible. Other parameter values: no fitness effects in drive males ($s_m = 0$) who only produce X_d-bearing sperm ($\delta = 1$).

equal to 1. At the other extreme, where females mate many times ($\lambda_f \to \infty$) the sperm competition term becomes c - the relative ejaculate size of drive males. If there is also no compensation for Y-bearing sperm killed by meiotic drive alleles ($c = 1/(1+\delta)$), meiotic drive cannot invade (Figure 2B). Between these extremes, increases in polyandry (larger λ_f) and decreases in compensation in drive males (smaller c) hinder both invasion and fixation of meiotic drive alleles (Figure 2). Sperm competition is most important when there is both extensive polyandry and a large reduction in ejaculate size caused by meiotic drive (Figure 2).

Limiting male matings narrows the polymorphism space In the results presented above, we assume that there is no sperm limitation, so even a small number of males is capable of fertilizing a large female population. In this case, extinction by meiotic drive only occurs when there are no males left in the population.

Here, we use the simulation model to consider limitations on the number of matings that a male can perform. First, we compare the proportion of numerical simulations that result in drive polymorphism to the predictions from the analytical model, where there are no limits to male mating. With male mating set at $\lambda_m = 20$ (Figure 3A), the region of polymorphism shrinks (the orange tiles do not completely fill the theoretical polymorphism space). On the upper boundary, this represents conditions where the polymorphism is unstable because meiotic drive alleles have only a slight advantage and remain at low frequencies where they are exposed to loss by genetic drift. The leftmost boundary is where drive is strong enough to reach a high frequency and the sex ratio is heavily female biased, so many females go unmated due to male mating limitation, and the population can go extinct. When the maximum number of matings per male was reduced to $\lambda_m = 2$ (Figure 3B), just as many lose drive stochastically (on the upper boundary). But the problem of females remaining unmated is exacerbated. More populations go extinct close to the fixation boundary, with fewer simulations resulting in polymorphism. Thus, we predict that population extinction is likely when male mating rates are low and strong meiotic drive alleles reach high frequencies.

Population size in the presence of drive

By creating female biased sex ratios, meiotic drive can influence population size. Figure 4 illustrates two different outcomes when drive spreads (extinction and polymorphism). As a base for comparison, parameter values are chosen under which a wild-type population is stably maintained (Figure 4A). When a driving X allele is introduced into the population it rapidly increases in frequency. This can skew the sex ratio further and further towards females until extinction ensues because there are insufficient males to fertilise all the females (Figure 4B). When the fitness costs of drive in females are higher, drive can be stably maintained. The resulting population is female-biased and larger than it would be in the absence of drive because the higher proportion of females increases the productivity of the population (Figure 4C).

In the absence of meiotic drive ($p = 0$), the population reaches an equilibrium population size ($\hat{N}$) given by the intrinsic birth rate (b) and the density-dependent reduction in female fecundity caused by competition among individuals (α):

$$\hat{N}|_{p=0} = \frac{b-2}{b\alpha}, \tag{8}$$

which is a standard result for logistic population growth with non-overlapping generations (Edelstein-Keshet 1987, pp.44-46

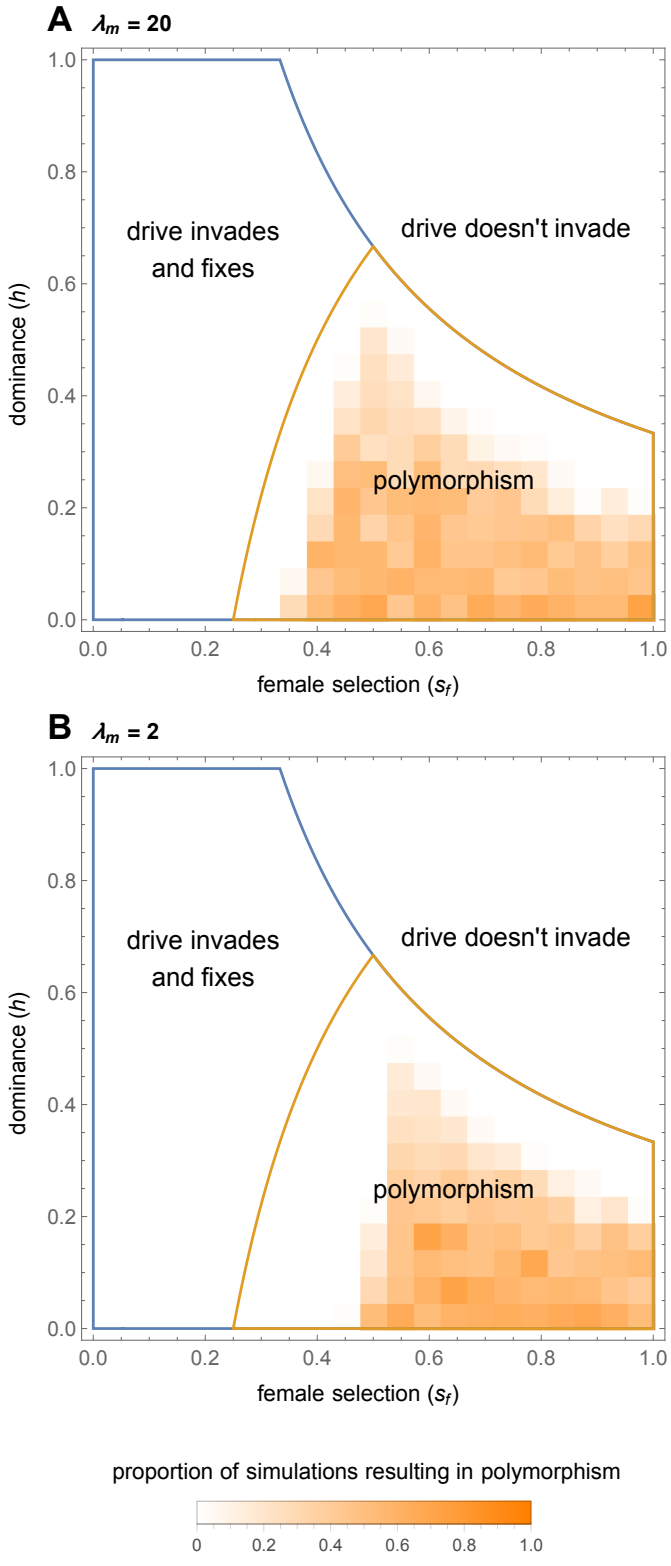

Figure 3 The effect of the male mating rate. Numerical simulation data showing the proportion of times (out of 50 simulations) that a polymorphism was maintained for 2000 generations when A) males mate 20 times ($\lambda_m = 20$) and B) males mate twice ($\lambda_m = 2$). The region of polymorphism is demarcated on the assumption that there are no constraints on male mating (area within orange line). The simulation parameters used were $\delta = 1, c = 1, \lambda_f = 1, q = 0.01, N_0 = 200, b = 2.4, \alpha = 0.001$.

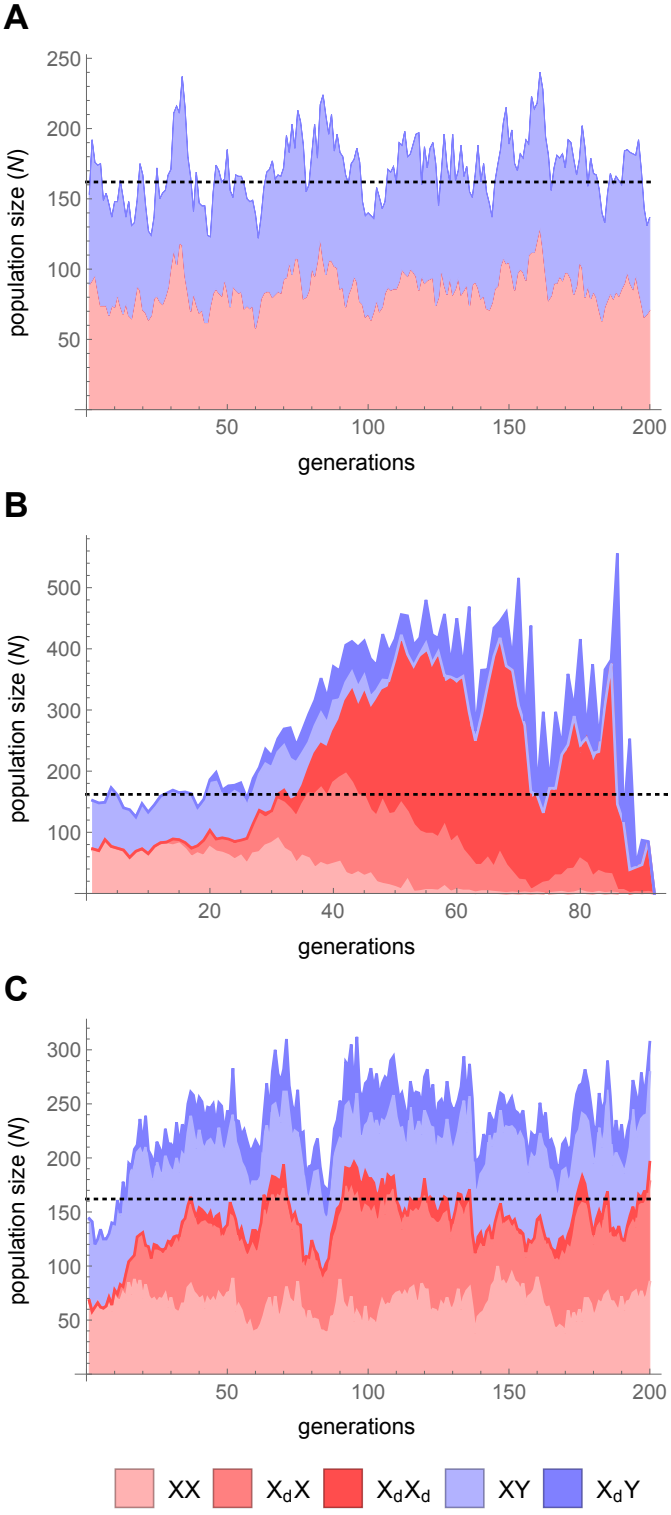

Figure 4 Illustrative examples of population dynamics with and without drive. A) the wild-type population without drive, B) the addition of drive causing rapid population extinction ($h = 0.4, s_f = 0.2$), C) the addition of drive subject to stronger counter selection leading to a population polymorphic for drive ($h = 0.2, s_f = 0.55$). Female genotypes are shown in red, and male in blue. The mean wild-type population size was 161 and is shown by the dotted line (analytical model predicts approximately 167). Other parameters used were $c = 0.75, \delta = 1, b = 2.4, \alpha = 10^{-3}, \lambda_f = 2, \lambda_m = 20, q = 0.01$, and the initial population size was 150.

with $r = b/2$ and $d = b\alpha$). The equilibrium population size is larger when the intrinsic birth rate (b) is higher or the competitive effect of other individuals (α) is weaker. For the population to persist, each female must produce at least two offspring ($b_{min}|_{p=0} = 2$).

To derive the population size with meiotic drive, we focus on the case where females mate only once, excluding the effects of sperm competition. First, we define ϕ and ψ as the LHS of Eq(6) and Eq(7) respectively, with $\lambda_f = 1$; ϕ gives the selective advantage of drive alleles when rare and ψ is the advantage of wild-type alleles in a population fixed for drive. If an X chromosome meiotic driver invades (i.e. $\phi > 0$, Eq(6)) and reaches a polymorphic equilibrium (i.e. $\psi > 0$, Eq(7)) then its frequency in females and males is given by

$$\hat{p}_f = \frac{\phi}{\phi + \psi}, \tag{9}$$

$$\hat{p}_m = \frac{(1 - s_m)\phi}{(1 - s_m)\phi + \psi}. \tag{10}$$

At the polymorphic equilibrium, the sex ratio will be female-biased and this in turn affects the ecological equilibrium population size

$$\hat{N}|_{p=\hat{p}} = \frac{b^* - 2}{b^*\alpha}, \tag{11}$$

where

$$b^* = b(1 + \phi p_f/2)\frac{1 - p_m}{1 - p_f} > b. \tag{12}$$

b^* is the effective birth rate given the change in the sex ratio caused by meiotic drive. The effective birth rate with drive is higher, $b^* > b$, because ϕ and p_f are non-negative and $p_m \leq p_f$ (from Eq(10)). The effective birth rate is increased by a factor equal to the number of females surviving to reproductive age (given the equilibrium frequency of drive) relative to the number of females in a wildtype population (see File S1). As $b^* > b$, the population size with drive is always larger than it would have been without drive (Figure 5A). Drive populations effectively behave like wild-type populations with a higher birth rate, as a result of the sex ratio bias.

A similar outcome holds when a drive allele fixes. The total population size is

$$\hat{N}|_{p=\hat{p}} = \frac{\tilde{b} - 2}{\tilde{b}\alpha}, \tag{13}$$

where

$$\tilde{b} = b(1 + \delta)(1 - s_f). \tag{14}$$

For drive alleles that reach fixation, $\tilde{b} > b$. Again, by biasing the sex ratio towards females, fixed drive increases the population birth rate and thereby increases the overall population size (Figure 5A). However, this result may be most relevant for weak meiotic drivers ($\delta < 1$) because there will be no males in the population when strong meiotic drivers ($\delta \approx 1$) reach fixation.

By increasing population productivity, meiotic drive alleles also help to protect populations from extinction. With strong drive at an intermediate equilibrium frequency, the minimum intrinsic birth rate required for population persistence is $b_{min}|_{p=\hat{p}} = 2/(1 + \hat{p}_f\phi)$, while for weak drive at fixation this is $b_{min}|_{p=\hat{p}} = 2/(1 - s_f)(1 + \delta)$. Both of these values are less than two, the cut-off value for a population to go extinct in the absence of drive. Populations with drive can persist with a lower average number of offspring per female than those without, because a higher proportion of the population are female. The

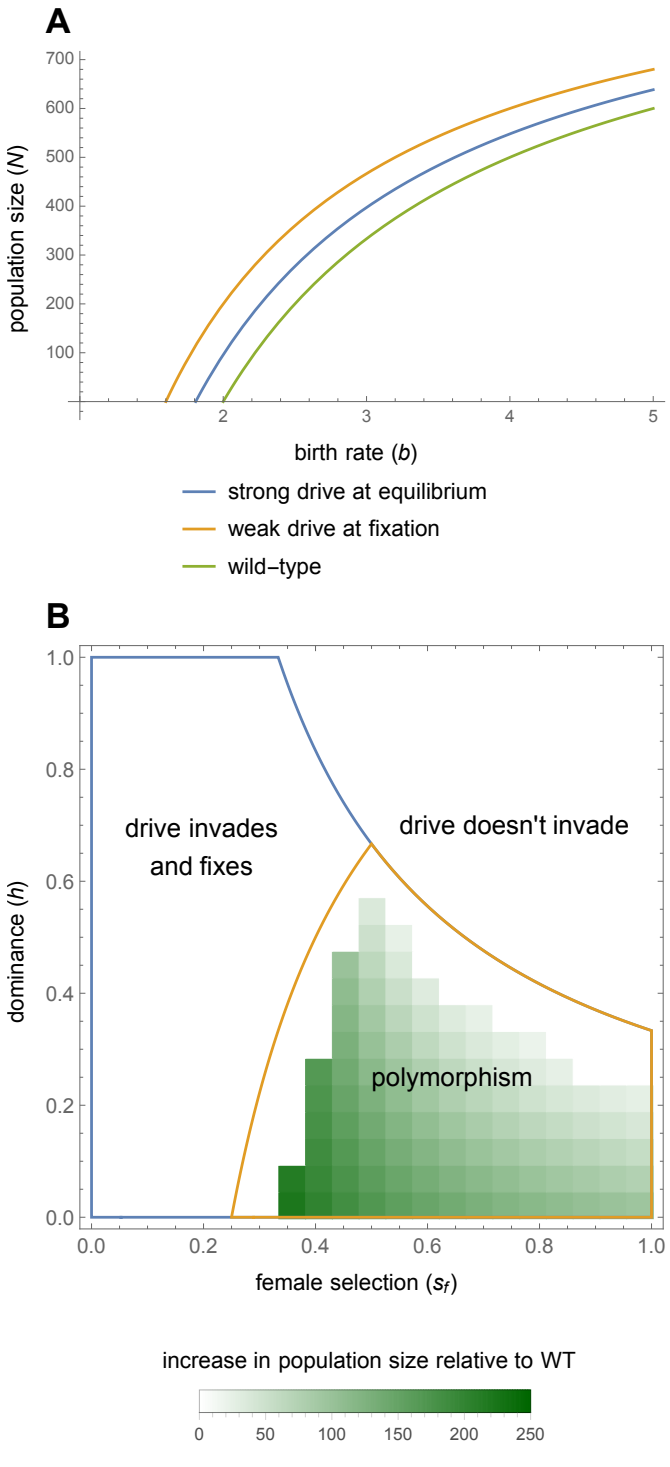

Figure 5 Population size is increased with meiotic drive. A) Two examples where populations with meiotic drive have higher population size and persist with lower intrinsic growth rates ($b < 2$). The first when drive is weak and at fixation ($\delta = 0.25$) and the second when drive is strong and at equilibrium ($\delta = 1$). Other parameter values: $s_f = 0$ for weak drive, $s_f = 0.8, h = 0.1$ for strong drive, $s_m = 0, c = 1, \alpha = 10^{-3}$. B) The average increase in population size compared to a wild-type population without meiotic drive for the data in Figure 3A. The population size for each simulation was taken to be the mean size after a 100 generation burn in period, and the value for each tile in the plot is the mean of those simulations that resulted in polymorphism from a sample of 50.

results of the simulation model align with the analytic model. Whenever a polymorphism is reached, the resulting population size is bigger than in the absence of drive (Figure 5B). The extent of the boost in population size depends on the viability cost associated with drive. As the cost decreases (either h or s_f decreases), the equilibrium frequency of drive increases, the sex ratio becomes more female biased, and the increase in population size becomes larger. Overall, these simulations confirm that meiotic drive can boost population size even when males can only fertilize a limited number of females.

Population persistence time

Populations that are relatively small are liable to go extinct within a reasonable time due to demographic stochasticity. To examine the effect of drive on persistence times simulations were run in small populations with a low intrinsic birth rate ($b = 2.4$, $\alpha = 10^{-2.4}$), reflecting for example a small patch in a suboptimal or marginal environment. In these simulations, the mean population size without meiotic drive was $\bar{N} \pm s.d. = 36.3 \pm 12.7$ (consistent with the expected population size from Eq(8), which is $\hat{N} = 41.9$) and the persistence time was mean $\pm s.d. = 1088 \pm 1001$ generations). The approximate alignment of the mean and standard deviation is expected because the persistence times of stochastic logistic growth models are exponentially distributed (Ovaskainen and Meerson 2010).

First, we consider the case where meiotic drive has no fitness costs ($s_f = s_m = 0$) and either spreads to fixation or is lost by drift (Figure 6A). With $\delta = 0$ (i.e. no transmission distortion), the X_d allele is completely neutral and the population persists as if it were wild-type (Figure 6A). For increasingly strong meiotic drivers (increasing δ), the probability of invasion increases and meiotic drive alleles are present at the end of more simulations, causing populations to persist for longer. In this example (Figure 6A), the male mating rate is high ($\lambda_m = 20$), so there are sufficient males to maintain female fecundity and resist extinction, even with strong drive (Figure 6A). However, when drive is very strong ($\delta \geq 0.8$), the sex ratio can become excessively female biased and population extinction becomes more likely.

Population persistence was also evaluated for strong meiotic drivers ($\delta = 1$). For simplicity, the dominance coefficient in females was set to $h = 0$, limiting viability reduction to homozygous female carriers (Figure 6B). When drive incurs no or small fitness costs ($s_f < 0.2$), it spreads to fixation and causes rapid extinction through extreme sex ratios. As the cost increases ($0.2 < s_f \leq 0.5$), meiotic drive spreads more slowly and the persistence time increases back towards that found in wild-type populations. Eventually, with higher cost ($s_f > 0.5$), drive does not fix. Here, the sex ratio is skewed towards females but there are sufficient males, leading to longer population persistence than wild-type populations. Where the cost is very high ($s_f > 0.7$), drive is maintained at a low frequency and may itself be stochastically lost. However, the transient presence of drive still increases the overall longevity of the population.

These two examples demonstrate how drive increases population persistence until sex ratio biases are so strong that the males cannot fertilise all the females. The effect of drive on population persistence depends on its frequency and thus the sex ratio bias created. As outlined in our evolutionary analysis above, other parameters affect the frequency of meiotic drive alleles (dominance, male fitness effects, polyandry, ejaculate size compensation) and have corresponding effects on population persistence.

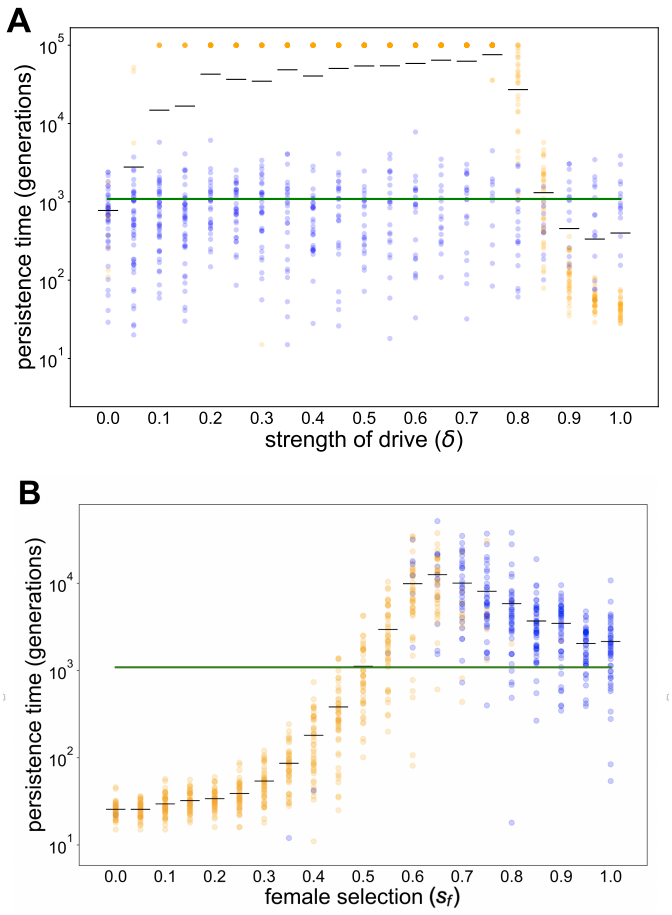

Figure 6 Persistence times for populations as A) the strength of drive increases (δ), and B) the strength of selection in females increases (s_f). Orange points denote populations where drive was present and blue points where drive was absent at the time of extinction or at the maximum simulation duration of 10^5 generations. The green line represents the mean persistence time of wild-type populations without meiotic drive and the black lines show mean persistence times. Populations began with an initial drive frequency of $q = 0.1$. Female adults had a mean birth rate of $b = 2.4$ with a high cost of competition, $\alpha = 10^{-2.4}$. In A) $s_f = 0$, drive acts by killing a fraction of Y sperm with no compensation ($c = 1/(1+\delta)$) and in B) viability costs were in homozygotes only ($h = 0$), males produced only X_d sperm and had full compensation ($\delta = c = 1$). Other parameter values $s_m = 0, \lambda_f = 2, \lambda_m = 20$.

Discussion

This paper sets out a general condition for the spread, polymorphism and fixation of X-linked alleles,Eq(5), which we apply to the study of the evolutionary dynamics of meiotic drive. There are two equally important pathways by which X-alleles spread: either from mother to daughters, or from mother to sons and then into granddaughters (Figure 1). Our condition shows that the success of X-linked alleles depends on sex-specific selection as well as the asymmetric transmission through the sexes. If selection is weak, female fitness effects are twice as influential, as X chromosomes spend twice as much time in females as in males (Patten 2019; Hitchcock and Gardner 2020). But this 2:1 rule does not apply when selection is strong, as is likely to be the case in meiotic drive.

A central finding is that X-linked meiotic drivers generally increase population size. By biasing the sex ratio towards females, meiotic drive effectively boosts the population birth rate which is typically limited by the number of females (Eq(12,14)). This increases the expected population size beyond the level in wild-type populations (Figures 4 and 5). In small populations at risk of stochastic population extinction, the increase in population size through meiotic drive can dramatically increase population persistence time (Figure 6). This should enable populations to persist in marginal environments where they would otherwise go extinct. The population-level benefit of drive breaks down when males become limiting and are no longer able to mate often enough for females to achieve full fecundity (Figure 6).

Previous work (Pomiankowski and Hurst 1999; Taylor and Jaenike 2002, 2003; Dyer and Hall 2019; Larner *et al.* 2019) has shown that female fitness in drive heterozygotes and homozygotes affects the frequency of meiotic drive alleles. We show the additional dependence on the female (Figure 2) and male mating rate (Figure 3), and how this then impacts the sex ratio bias, population size and persistence time of populations invaded by meiotic drive alleles (Figures 4, 5, 6). We find that the male mating rate (λ_m) is key to determining whether meiotic drive cause population extinction. When males can mate repeatedly, their rarity does not cause sperm limitation amongst females and the distortion in the sex ratio is beneficial to population persistence. Limits on the number of females each male can mate with cause some females to go unmated resulting in population extinction as meiotic drive spreads and skews the sex ratio. This higher likelihood of extinction narrows the space in which meiotic drive is likely to occur as a polymorphism in natural populations (Figure 3).

Most previous work has concentrated on the consequences of female rather than male mating rates, that is polyandry (λ_f), as this is a cause of sperm competition that hinders the spread of meiotic drive alleles (Price *et al.* 2010, 2014; Holman *et al.* 2015). Our work shows that this is only the case when ejaculate size is significantly reduced in male meiotic drive carriers (Figure 2). Generally, as compensation increases (i.e. $c \to 1$), so does the likelihood of polymorphism, because drive male success in sperm competition reaches towards that of wild-type males. In the modelling, we consider drive males to have lower fertility because of reductions in ejaculate size (proportional to the strength of drive δ). The same logic applies to other mechanisms that might disadvantage the success of drive males in sperm competition, like slower sperm swimming speeds or reduced sperm longevity (Olds-Clarke and Johnson 1993; Kruger *et al.* 2019; Rathje *et al.* 2019).

Although there are few empirically obtained estimates for the fitness costs of X-linked drive, many of them are compatible with polymorphism according to our model. Female viability costs in *Drosophila* are often recessive but strong ($h = 0 - 0.11, s_f = 0.56 - 1$, see Table 1 in (Unckless and Clark 2014) and (Larner *et al.* 2019; Dyer and Hall 2019)). A counterfactual is the estimate from the stalk-eyed fly *Teleopsis dalmanni* (Finnegan *et al.* 2019a) which found additivity and weaker viability loss in egg-to-adult viability, though the range on the dominance estimate is large. A limitation of attempts to measure fitness is that they are based on laboratory conditions that may distort the pressures that exist in natural populations. They also typically measure one component of fitness, for example survival over a particular life stage, neglecting others such as reproductive success. Furthermore, we note that these empirical estimates may be biased towards systems with strong meiotic drive ($\delta \approx 1$) because weak meiotic drivers are less easy to detect (Burt and Trivers 2006).

Population persistence is predicted to increase exponentially with population size (Ovaskainen and Meerson 2010) (Figure 6). Therefore, we predict that populations with meiotic drive are more likely to be observed in marginal habitats where wild-type populations may go extinct. In natural populations, tests of this prediction may be confounded by a range of other factors associated with marginal habitats. For instance the rate of polyandry is likely to be lower in poor quality environments and this will favour the spread of drive (Pinzone and Dyer 2013; Finnegan 2020). A viable first experimental step may be to use lab populations to evaluate whether X-linked meiotic drive can increase population birth rates and/or rescue declining populations from extinction.

A relationship between sex ratios and population size/persistence is also not yet clearly established in species with temperature-dependent sex determination, despite similar predictions (Boyle *et al.* 2014; Hays *et al.* 2017). As predicted previously (Hamilton 1967), severely male limited populations should be quickly driven to extinction, which can occur in lab populations (Price *et al.* 2010) and may have been observed in a natural population (Pinzone and Dyer 2013). However, high male mating rates can facilitate population persistence in the face of extremely biased sex ratios. A *Wolbachia* infection in butterflies resulted in a sex ratio of 100 females per male, but these populations persisted perhaps because males can mate more than 50 times in a lifetime (Dyson and Hurst 2004).

The population dynamics of sex ratio distorting elements are thought to be influenced by their propensity to colonise new patches and drive them to extinction, i.e., metapopulation dynamics (Hatcher 2000). When drive is strong and confers little fitness cost in females, new populations cannot be established by drive genotypes because of the deficit in the numbers of males and resulting weak population growth. This could lead to cycling dynamics where colonisation by non-drive genotypes is needed to establish populations, which can then be invaded by drive genotypes whose spread is followed by extinction (Taylor and Jaenike 2003). These population level costs can decrease the overall frequency of selfish genetic elements across the metapopulation (Boven and Weissing 1999). Our results emphasise the potential for X-linked meiotic drivers to boost population sizes and persistence times, which we expect would increase the proportion of patches expected to have drive. It has also been suggested that individuals carrying selfish genetic elements may show a greater propensity to migrate between populations, increasing their fitness by reaching patches with lower numbers of heterozygotes and less polyandry (Runge and

Lindholm 2018). However, the full metapopulation dynamics where local population sizes are affected by drive frequency remains to be investigated.

We generally predict population size to be increased when the sex ratio is biased towards females. Thus we expect our results to hold in species with ZW sex determination when meiotic drive favours W chromosomes (Kern *et al.* 2015) but not when meiotic drivers favours Y chromosomes or Z chromosomes (Hickey and Craig 1966; Gileva 1987). A general constraint on our conclusions is that they hold for competition models where an increase in birth rate increases population size (Supplementary Information). If the population is limited by the availability of resources regardless of the birth rate, boosts in population size are not expected. Likewise, where males contribute to parental care either through direct care or via control of resources used by females, sex ratio distortion will not have such a profound effect because the expected change in the number of offspring produced will be reduced and have a lesser effect on population size and persistence (West 2009). A further caveat of these results is that they assume density dependent selection is contributed to equally by both sexes. Where males contribute less than females the sex-ratio skew will have a lesser impact on population size. There may also be cases where increased birth rates cause competition to become increasingly intense and reduce population size. An example is given in the Supplementary Information, where drive counter-intuitively decreases population size by increasing the effective birth rate beyond a critical level (see Figure S1). Although this pattern of density dependence seems likely to be atypical, it points to the need for the biological details of particular species to be taken into account.

Our results are also pertinent to the design of synthetic gene drive systems. Gene drive systems have been proposed as a method of controlling pest populations through altering the sex ratio so that one sex becomes limiting. Many of these proposals are analogous to Y-linked meiotic drive, for example "X-shredders" (Windbichler *et al.* 2008; Galizi *et al.* 2014; Burt and Deredec 2018) that limit the reproductive output of the population by biasing segregation towards Y-bearing sperm. We expect systems that cause male sex ratio bias to be effective. X-drive has also been recently suggested as a tool for biological control (Prowse *et al.* 2019). As observed in some simulations, as long as males are not limiting, the population may benefit from the introduction of an X-drive that increases the population productivity and carrying capacity (Prowse *et al.* 2019). That is, less efficient synthetic X-drivers may fix and result in larger populations without causing populations to crash (Prowse *et al.* 2019); this is analogous to fixation of weak meiotic drive in our model. Another possibility is that the driving allele does not fix but is maintained at a polymorphic equilibrium by the evolution of suppressors or associated fitness costs, for example. The resulting population will have a female-biased sex ratio, which our results suggest could increase population size and persistence. Thus, we urge caution when considering the use of X-linked gene drive for population control.

At the population level, the optimal sex ratio is likely to be female biased because relatively few males are required for complete fertilization. In some circumstances, such as local mate competition, individual-level and group-level selection can align, and female-biased sex ratios can evolve (West 2009; Hardy and Boulton 2019). Here, we show that selfish genetic elements (specifically, X-linked meiotic drivers) can move populations towards their population-level optimum and benefit population-level traits (such as population size and persistence time), a possibility that has probably been under-emphasised relative to their detrimental effects on populations.

Acknowledgements

The authors would like to thank two anonymous reviewers and the Genetics editors, along with Max Reuter and Ewan Flintham for their insights and helpful comments on the manuscript. CM is supported by a CoMPLEX EPSRC studentship (EP/N509577/1). AP is supported by EPSRC grants (EP/F500351/1, EP/I017909/1) and a NERC grant (NE/R010579/1). MFS is supported by BBSRC grants (BB/M011585/1, BB/P024726/1) and a Leverhulme Early Career Fellowship (ECF-2020-095).

Author contributions.

The research project was conceived, carried out and the paper written by all authors. CM and MFS carried out the modelling work.

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Supplementary Information

Alternative form of density dependence

In the main text, we assumed that competition for resources among adults is a source of density dependent selection by reducing the survival or fecundity of adult females. The assumption is that the density dependence is generated by the population size (αN), but not by the birth rate (b). Here, we explore an alternative form of density dependence in which competition for resources can cause the population size to be depressed as population birth rate increases. For instance, if the density dependence is defined by

$$(1 - b\alpha N), \tag{S1}$$

then increasing the birth rate does not always increase population size (Figure S1). Without meiotic drive, the equilibrium population size is

$$\hat{N}|_{p=0} = \frac{b-2}{b^2\alpha}, \tag{S2}$$

which now includes a quadratic term in b not present in (Eq(8)). Thus, when birth rates are very high, the equilibrium population size decreases because competition becomes more intense. For example, if competition is a function of the number of juveniles $J = bN$, then high birth rates both increase the number of juveniles, J, and increase the strength of competition among them.

As in our main results, we find that the intrinsic birth rate must be at least two for wild-type populations to persist whereas populations with drive can persist with a lower intrinsic birth rate (Figure S1). However, meiotic drive does not always increase population size in this scenario because increasing the effective birth rate by biasing the sex ratio towards females does not always lead to larger populations. Thus, some forms of density dependence could mean that increased birth rates do not increase population size, in which case the effect of meiotic drive on boosting the effective birth rate may change. However, we expect that increased birth rates will increase population size in most models of intraspecific competition.

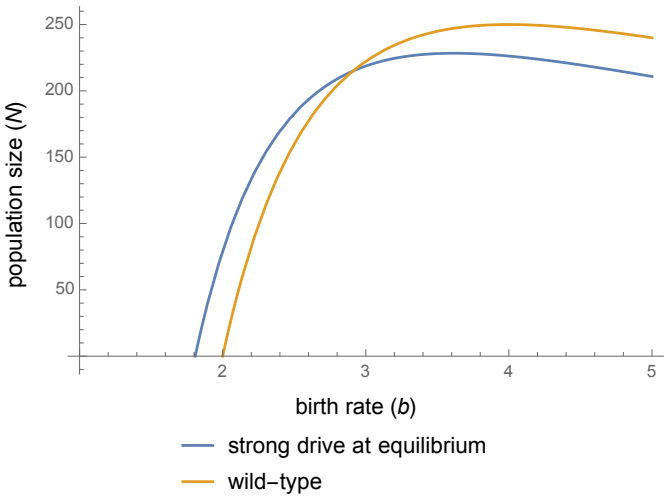

Figure S1 Equilbrium population size given density dependence is based on the the intrinsic birth rate (b). As before, meiotic drive allows the population to persist with lower birth rates ($b < 2$). But with higher values of the birth rate ($b > 3$), meiotic drive reduces population size. Parameter values: $s_m = 0, c = 1, h = 0.1, s_f = 0.8, \lambda_f = 1, \alpha = 10^{-3}$.