Sperm should evolve to make female meiosis fair.

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Abstract: Genomic conflicts arise when an allele gains an evolutionary advantage at a cost to organismal fitness. Oögenesis is inherently susceptible to such conflicts because alleles compete to be the product of female meiosis transmitted to the egg. Alleles that distort meiosis in their favor (i.e. meiotic drivers) often decrease organismal fitness, and therefore indirectly favor the evolution of mechanisms to suppress meiotic drive. In this light, many facets of oögenesis and gametogenesis have been interpreted as mechanisms of protection against genomic outlaws. Why then is female meiosis often left uncompleted until after fertilization in many animals – potentially providing an opportunity for sperm alleles to meddle with its outcome and help like-alleles drive in heterozygous females? The population genetic theory presented herein suggests that sperm nearly always evolve to increase the fairness of female meiosis in the face of genomic conflicts. These results are consistent with current knowledge of sperm-dependent meiotic drivers (loci whose distortion of female meiosis depends on sperm genotype), and suggest that the requirement of fertilization for the completion of female meiosis potentially represents a mechanism employed by females to ensure a fair meiosis.

Introduction

Despite the apparent unity of the organism, 'selfish' alleles can gain an evolutionary advantage at a cost to individual fitness [6], often by exploiting meiosis and gametogenesis. Because only one of the four products of female meiosis is transmitted to the egg, female meiosis is particularly vulnerable to such exploitation [26, 20]. An allele that biases female meiosis in its favor (i.e. a meiotic driver), may increase in frequency even if it entails a pleiotropic fitness cost [24], generating a genetic conflict between the success of the driver and organismal fitness. Meiotic drivers observed in both plants [5, 10, 9], and animals [1, 29, 21] highlight this conflict – the selfish benefits and the associated pleiotropic fitness costs of drive sustain a balanced polymorphism [24], and often generate ongoing evolutionary escalations of drive suppressors and enhancers [8, 9]. The threat of meiotic drive to organismal fitness is potentially so severe that many basic properties of meiosis and oögenesis, including the initial genome doubling in meiosis I [13], arrested female meiosis [19], the structure of centromere machinery [15, 16], and sex differences in the recombination rate [12, 4] have perhaps evolved to enforce fairness by disrupting meiotic drive [25].

It is therefore somewhat surprising that despite the intense evolutionary pressure on female meiosis to prevent meiotic drive, it is potentially open to sabotage by a virtual stranger – a haploid sperm genome. That is, in many animal species, female meiosis is completed only after fertilization [17], creating ample opportunity for interaction between the sperm and female meiotic machinery (note that the alternation of generations in likely precludes this interaction in plants). Therefore, a 'green-bearded' [11] sperm-acting allele that recognizes and facilitates the meiotic drive of a genetically equivalent allele in heterozygous females could presumably rapidly spread through a population. At first sight, female meiosis appears primed for exploitation by such selfish systems. Why then is the requirement of fertilization to complete female meiosis so ubiquitous?

It is certainly not the case that animals are mechanistically incapable of circumventing

this requirement. The stage at which female meiosis requires fertilization varies widely across taxa, and in a few animals female meiosis is complete upon ovulation (that is, fertilization is not required for female meiosis [e.g. Table 1 in 17]).

It is also not the case that sperm is mechanistically incapable of influencing female meiosis. In *C. elegans*, premature deployment of the aster – a vital component of mitotic machinery provided by the sperm, disrupts MII meiotic segregation in the egg, leading to a triploid zygote [18]. Thus, there is direct mechanistic evidence that sperm can influence female meiosis. Additionally, genetic evidence from the *In* and *Om* drive systems in mice suggests that the transmission of alternate alleles in heterozygous females can depend on sperm haplotype. While ruling out the alternative hypothesis of early selection on zygotes in these cases is challenging [see pages 52-54 in 6], it appears that the extent to which *In* and *Om* distort the second female meiotic division partially depends on the genotype of the fertilizing sperm [2, 29].

We develop population genetic models exploring the evolution of sperm influence on female meiotic drive. We first focus on models in which 'self-promoting' alleles in sperm facilitate drive of like alleles during gametogenesis in heterozygous females. These models show that such sperm-acting alleles have more difficulty invading a population than do traditional meiotic drivers, and under most circumstances, cannot be maintained as a balanced polymorphism. Because self-promoting drivers are unlikely to create a sustained genomic conflict, female meiosis will have little incentive to evolve resistance to them. We then examine models in which a novel sperm-acting allele modifies the efficacy of a polymorphic meiotic driver. Such models universally reveal that sperm-acting drive modifiers are favored only if they suppress drive. These results highlight the fact that the interests of sperm and maternal genomes' are often aligned, as both are invested in the fate of the resultant zygote (as was speculated for the *In* locus [23]). Therefore, there is little selective benefit to females in preventing sperm to influence female meioses. Rather, features of oögenesis may evolve to facilitate an interaction with sperm as yet another mechanism to enforce an equitable

transfer of genetic material.

Results

Invasion of the population by a driving allele that promotes itself.

In the standard single-locus, biallelic model of female meiotic drive, the driving allele is transmitted to the egg in heterozygotes with probability $d > 1/2$, regardless of sperm genotype [e.g. 28, and see Model 1 in the Appendix for more details]. To depict a case of a self-promoting meiotic driver, we modify this standard model such that the driver is only effective when fertilized by a sperm carrying that allele (see Figure 1A and Model 2 in the Appendix and Supplementary Worksheet). We then identify the conditions allowing for the spread of this self-promoting driver, and evaluate whether a driver of this form could generate a sustained conflict favoring the evolution of suppressors. We conclude our single locus results with an analysis of a related model (Model 3) - in which drivers influence their transmission in females via paternal genotype, rather than sperm haplotype.

For comparative purposes, we first briefly present the standard drive model [see e.g. 24, 28, for additional results]. Assuming that the driving allele is deleterious in both sexes, but fully recessive (i.e. the fitness of drive homozygotes equals $w_{BB} = 1 - s$ and other genotypic fitnesses equal $w_{AA} = w_{AB} = 1$), it always invades because, when rare it occurs predominantly in heterozygotes and therefore drives without a fitness cost. However, when s is large ($s > (2d - 1)/(2)$, solid black line in Figure 1B) a driver cannot fix and will be maintained as a protected polymorphism [24]. The parameter space where the allele can invade but not fix is shown in white in Figure 1B. When the allele is maintained as a polymorphism, it provides an opportunity for the evolution of drive suppressors, corresponding well to empirical examples of female meiotic drive [reviewed in 6].

In contrast to a traditional driver, which drives but pays effectively no fitness cost when

rare, a self-promoting driver specifically creates low fitness drive homozygotes by uniting driving female gametes with sperm enabling that drive. It must therefore overcome a drive-associated homozygous fitness cost simply to spread when rare. The conditions allowing the invasion of a self-promoting driver are consequently far more restrictive than those for a standard meiotic driver. When rare, a fully recessive, self-promoting driver can only invade when s is less than approximately $(2d-1)/(4d)$ – see dashed black line in Figure 1B. This analytical approximation, derived from Equation (1) assuming Hardy-Weinberg, closely matches results obtained by exact numerical iteration (Figure 1B).

When a self-promoting driver does spread it spends much of its time at low frequency, because the paucity of complimentary sperm compromises its ability to drive. However, once relatively common, it rapidly achieves fixation due to its positive frequency dependent behavior (Figure 1B.1). This positive frequency dependence can induce bistability in its spread – some values of s allow the fixation of this driver when common, but preclude its invasion when rare (Equation 2 and Figure 1B). In this case, the driver will be fixed if its frequency exceeds some threshold (approximated in Equation 3 and presented exactly in Figure S1) and lost otherwise. For most parameters, this threshold is likely too high to be reached by drift, and therefore the fate of a self-promoting driver is determined by the more restrictive invasion criteria rather than the fixation criteria.

Inclusion of a heterozygous fitness cost (i.e. $w_{AB} = 1-s_h$) further constrains the evolution of a self-promoting driver. In fact, with any heterozygous fitness cost, a rare self-promoting driver is always selected against. However, this case also displays bistability – when s is sufficiently small (Equation 4) this allele fixes deterministically if its frequency exceeds some threshold (Equation 5, exact results in Figure S2). This bistability prevents self-promoting drivers from invading reasonably sized populations, and assures that if they do invade, they will rapidly fix. Our model therefore predicts that self-promoting drivers will not be observed as stable polymorphisms in natural populations. This lack of a balanced polymorphism precludes the evolution of an allele that suppresses this form of meiotic drive in females.

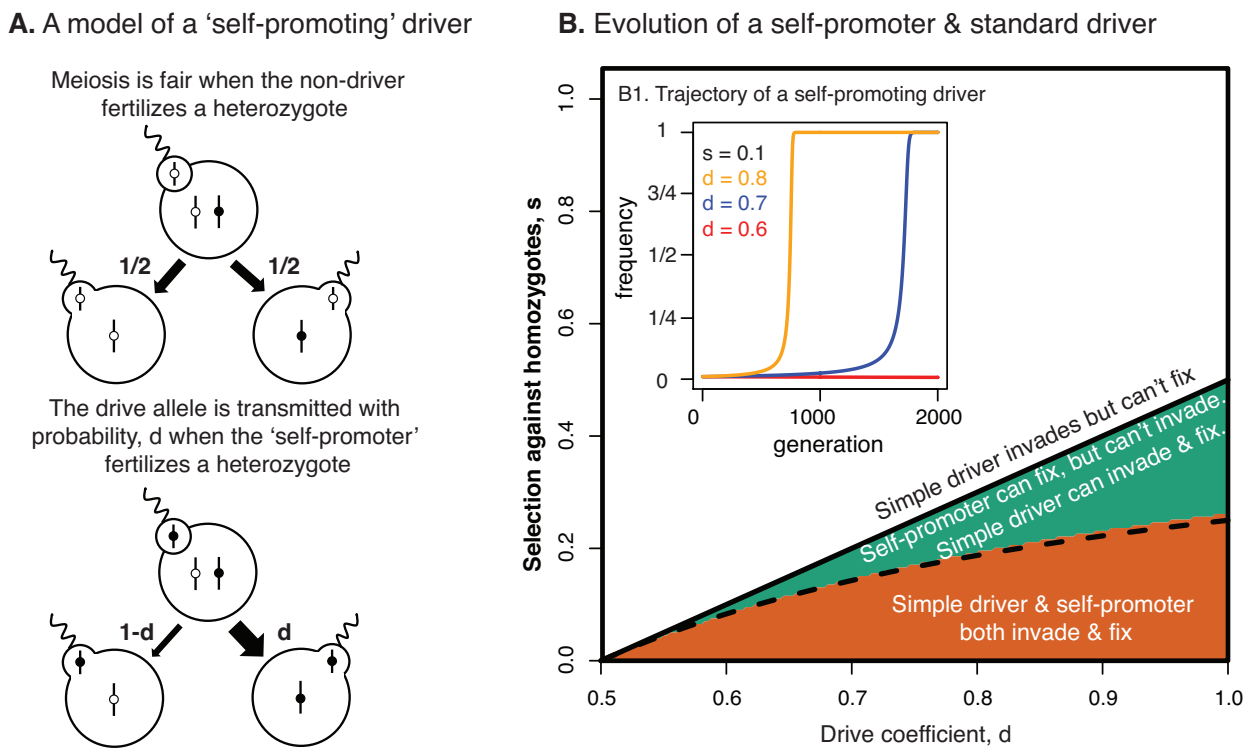

Figure 1: **A.** A visual depiction of our model of 'self-promoting' driver. Transmission probabilities for alleles through female meiosis depend on sperm genotype. The non-driving A-allele, and self-promoting B-allele are represented by unfilled and filled circles, respectively. **B.** Evolution of a self-promoter and standard driver. Assuming that the fitnesses of drive homozygotes and heterozygotes are $1 - s$ and 1, respectively. *Main figure:* Boundary conditions for the invasion and fixation of self-promoting and standard meiotic drivers, with drive coefficient, d. Colored regions depict exact results, while lines represent analytical approximations. *B1:* Trajectories of sperm-dependent female drive each allele has $s = 0.1$ against the homozygotes. The drive coefficient is denoted by color.

Although the allelic identity of sperm could plausibly influence the outcome of female meiosis, limited gene expression in sperm [e.g. 14] suggests a model where sperm influence female meiosis via expression of the fertilizing male's diploid genotype (perhaps due to proteins and RNAs packaged into the sperm), rather than sperm haplotype. This paternal-genotype dependent model (Model 3 in the Appendix) requires one additional parameter, as we exchange d in the sperm dependent case for d_{het} and d_{hom} which describe the transmission of the drive allele in a heterozygous female mating with males heterozygous and homozygous for the self-promoting drive allele, respectively. Here, a rare driver invades when s is less than $(d_{het} - 1/2)/d_{het}$, and usually fixes when it invades. However, when the distorting effect of genotype displays strong dominance in its effect on female meiosis (d_{het} is close to d_{hom}), a narrow sliver of parameter space sustains a polymorphism when the cost of the drive is recessive (see Figure S3, and Equation 6). While mathematically interesting, it does not seem particularly realistic to think that the effect of the drive allele would be dominant in its action through the male genotype, while the cost would be recessive. Therefore, although Model 3 can sustain a polymorphism, the lack of biological reality underlying the small portion of parameter values required for this polymorphism make us doubt its general applicability.

Given the difficulty that self-promoting meiotic drivers have entering the population, the speed at which they fix if they do, and the narrow parameter range permitting balanced polymorphisms at such loci, it seems very unlikely that such alleles could drive the evolution of female suppressors of sperm-enabled female meiotic drive.

Two locus models of sperm-dependent female drive

Models 2 and 3, above, explored the dynamics of an allele that drove in females when signaled by a complementary signal in sperm. We complement this single-locus approach with alternative models of two loci - one a female driver, and the other, a sperm-acting allele

which modifies the effect of drive upon fertilization. In this model, a female meiotic driver with no sperm-dependency initially reaches drive-viability equilibrium (with two alleles A and B are the ancestral non-driver and driver alleles, Figure 2A1). Subsequently, a sperm-acting modifier of female meiotic drive arises at another locus.

We first assume that the modifier is tightly linked to the drive locus (effectively creating a third allele/haplotype at this locus) and arises on the drive-background. Tight linkage offers the best chance for a collaboration to evolve between a driver and a sperm-acting drive enhancer, as recombination breaks up drive haplotypes [27, 7, 13]. Additionally, tight linkage between female driver and sperm modifier is consistent with the nature of well characterized drive systems which are often maintained as polymorphic inversions with numerous linked modifiers [6]. We conclude by analyzing models with alternative linkage relationship between driver and drive modifier - in Model 5 the modifier arises tightly linked to the non-driving allele, and in Model 6 it is unlinked to the driver.

When the modifier of drive arises on the drive background (i.e. in coupling phase), is tightly linked to the driver, and enhances drive we label this non-recombining drive/modifier haplotype as the B^+ allele. The B^+ allele acts in sperm to increase the effectiveness of drive for both the B and B^+ alleles in AB and AB^+ heterozygotes (see Figure 2A2, and Model 4 in the Appendix and Supplementary Worksheet). Naively, B^+ may spread by capitalizing on the additional drive it causes; however, this is not the case for a few simple reasons. First, the novel B^+ haplotype arises when the ancestral driver is at drive-selection balance, and therefore immediately suffers a homozygous fitness cost. Worse yet, a novel B^+ haplotype most often helps the B allele drive (B^+ sperm meeting AB eggs), because B is initially more common than B^+. Therefore, sperm-acting drive facilitator alleles experience a profound disadvantage in this scenario, even more so than under the previous two allele model. We have found no parameter range of this three allele system that allows the sperm-acting drive facilitator B^+ to invade the population (Appendix Model 4, eqn. (8), and Mathematical Supplement).

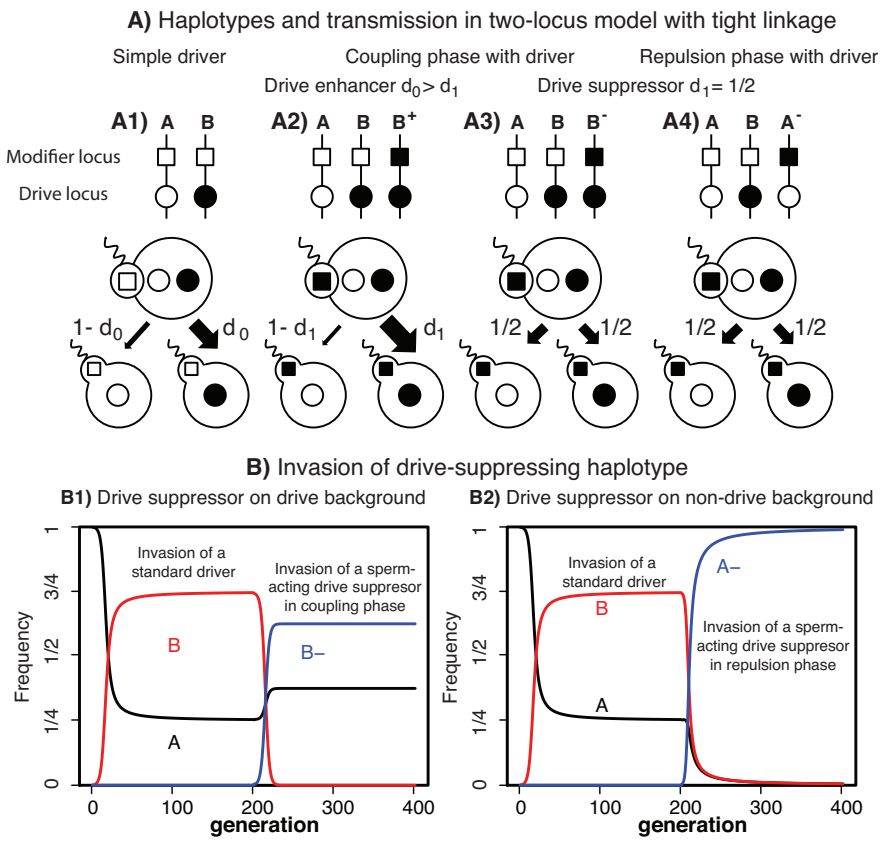

Figure 2: Models of a sperm-acting drive modifier tightly linked to a meiotic driver. **(A)** Sperm carrying the derived allele at the modifier locus (filled squares) alters transmission at the driving allele (filled circles) during female meiosis. Alleles at these two tightly linked loci form three haplotypes (top of A). **A1)** In the standard model of drive there is no variation at the modifier, and the driver is transmitted to the egg with probability d_0. **A2)** The modifier allele increases the transmission of the drive allele ($d_1 > d_0$), and due to their shared genetic background, also increases its drive. **A3 & A4)** The sperm-acting modifier acts to decrease drive ($d_1 = 1/2$ in A3 & A4, or more generally, $d_1 < d_0$) and arises on the same or opposite background from the driver (A3 & A4 respectively). **(B)** Invasion of a sperm-acting drive suppressor linked to a driver. After the driver (B haplotype) reaches drive selection equilibrium, we introduce a sperm acting drive modifier. We assume full drive ($D_0 = 1$), a recessive lethal fitness cost to drive ($h_s = 0$, $s = 1$) and that the sperm-acting modifier results in a fair meiosis. **B1)** The B^- allele replaces the ancestral drive haplotype, but segregates at a lower equilibrium frequency. **B2)** The A^- allele replaces the ancestral non-driving haplotype, and in this case, removes the driver from the population.

While sperm enhancement of a female drive cannot displace a polymorphic female driver, sperm based drive suppressors can. Imagine a sperm-acting allele that restores fairness to female meiosis arises on the drive background, creating a third allele B^- (Figure 2A3, Model 4 in Appendix). This new allele still experiences female drive when fertilized by A or B sperm, but is does not drive when fertilized by another B^- so it avoid the excess formation of low fitness homozygotes. This allows the B^- to displace the ancestral driver (Figure 2B1, Equation 8), and often returns to a lower equilibrium frequency than the the B allele, further decreasing the extent of drive in the population. If this sperm-acting drive suppressor arises on the non-driving A background (i.e. in repulsion phase, creating a third allele A^-, Figure 2A4, Model 5), or is unlinked to the drive locus (Model 6), it readily invades a population segregating for the drive system (Equations 9 and 10). This allele lowers the frequency of the original driver (perhaps to zero), and spreads to fixation if it does not carry strong fitness costs (Figure 2B2). This result is consistent with previous work showing that drive suppressors unlinked to, or in repulsion phase with drivers usually invade polymorphic drive systems [e.g. 4]. Therefore, all two-locus models of sperm influence on female drive suggest that sperm will evolve to oppose female meiotic drive.

Discussion

Sexual reproduction is a high-stakes event that determines what gets transmitted to the next generation. As a consequence of this intense competition, alleles that gain a transmission advantage during reproduction can succeed evolutionarily even if they lower organismal fitness. This generates numerous conflicts [6] including sexual conflicts between mates [3], and conflicts between alleles that are over-transmitted in meiosis and the organisms they injure while doing so. Such conflicts and their resolution likely play a major role in the structure and evolution of many basic biological processes [25].

It seems that allowing sperm to influence the outcome of female meiosis would generate

a confluence of these potential conflicts – sperm could actually assist an allele that distorts female meiosis. However, this is not the case. We find that an allele which acts through sperm to distort female meiosis in its favor can rarely spread through a population if it bears any cost. Additionally, when this self-promoting driver can spread, it can only rarely be maintained as a protected polymorphism, and due to its positive frequency dependence, it spends very little time at intermediate frequency. As such, this type of exploitation cannot generate a sustained genetic conflict. It is therefore unlikely that female oogenesis and meiosis will evolve to prevent their effect. This likely explains why females can delay the completion of meiosis until after fertilization without risking exploitation by collaborations between female drivers and sperm alleles.

Why is it that an allele that biases female meiosis in its favor can generate a genetic conflict, but an allele in sperm that assists this female driver cannot? So long as the transmission advantage of female meiotic drive outweigh the organismal fitness cost to heterozygotes, the female driver can spread when rare, and it increases in frequency until the fitness cost to homozygotes balances the transmission advantage. By contrast, a sperm promoter of female drive is only effective when matched with a heterozygote female – meaning that, when rare, this allele rarely enhances female drive. Even worse, when it does so it will preferentially find itself in a low fitness drive homozygote. Not only are drive-promoting sperm alleles unable to create a sustained genetic conflict, but alleles in sperm with the opposite effect - that is those that prevent their own drive through female meiosis do maintain a polymorphism and provide evolution with time and opportunity to further minimize drive. This is because such drive suppressing alleles reduced their chances of forming low fitness homozygotes. More generally, natural selection favors alleles that act through sperm to reduce the opportunity of female meiotic drive regardless of linkage or phase.

Our theory offers a novel interpretation of a baffling idiosyncrasy of female meiosis in many animals – the requirement of fertilization before fertilization is complete. We argue that females do not complete meiosis until after fertilization as a mechanism to encourage

meiotic fairness. In addition to providing a new interpretation of a basic biological process, our theory provides numerous testable predictions. We predict that female drive, at a stage influenceable by sperm, should be reduced when fertilized by complimentary sperm. Therefore, for example, MII female drive should be exceptionally severe in interspecific crosses between animals which complete the second meiotic division after fertilization, as heterospecific sperm will not specifically evolve to resists a female driver in another species. Our theory also encourages phylogenetic hypotheses concerning the relationship between the opportunity for female meiotic drive and the requirement of fertilization for the completion of female meiosis. For example, we predict that a lower opportunity for female meiotic drive, e.g. an animal lineage with a long history of high inbreeding or selfing, would often be accompanied by a relaxation of the requirement of fertilization for the completion of female meiosis.

Our results highlight potentially counterintuitive results of complex genetic conflicts. Despite much opportunity for conflict between sperm and females over fertilization [22], the interests of fertilizing sperm and female are quite well aligned during syngamy. While conflict between mother and her alternative chromosomes ensue, fertilizing sperm decidedly side with mom, as both have a shared interest in producing a viable and potentially fit offspring.

Appendix

We highlight simple analytical results from: the standard model of female meiotic drive (Model 1); a sperm-dependent model of female meiotic drive (Model 2); a male-genotype-dependent model of female meiotic drive (Model 3); and more complex two-locus sperm-dependent drive models (Models 4-6). All models include a biallelic locus (A/B) with non-driving and driving alleles in frequencies f_A and f_B, respectively, while more complex models include more loci and/or alleles. Transmission rules describing the outcomes of all matings in each model are presented in a Supplementary Worksheet. The fitness of genotype, g is sex-independent and equals 1, $1-h_s$, and $1-s$ for genotypes AA, AB, and BB, respectively.

Genotypic frequencies equal f_g for adults in the current generation, f'_g in the next generation of zygotes (i.e. after recombination, random mating, drive, and syngamy, but before selection) and f''_g in adults after selection. After a complete generation $f''_g = f'_g w_g/\bar{w}$, where $\bar{w}$ is the population mean fitness and equals $\Sigma w_g f'_g$. Because many of our analyses assume genotype frequencies expected under Hardy Weinberg Equilibrium (HWE), we note which analytical results are approximations. We verify these approximations with exact numerical iterations in Supplementary Figures and Supplementary Scripts, and detail the derivation of these approximations in our Mathematical Supplement.

Models 1-3. Single-locus drive

Model 1. Traditional driver

In the standard female drive model, meiosis in males is fair such that A/B heterozygotes contribute A and B alleles with equal probabilities; however, A/B females transmit the B allele with probability $d > 1/2$. We note that the timing of fertilization relative to female meiosis places another constraint on d, for example, if fertilization (and therefore, sperm dependent drive) takes place at MII (as in mammals), female drive requires an uneven number of crossovers between the centromere and the drive locus, so d is bounded to be < 0.83 [see 5, for discussion]. After drive and random mating, genotype frequencies are $f'_{AA} = f_A(f_{AA} + f_{AB}(1-d))$, $f'_{AB} = f_A(f_{BB} + f_{AB}d) + f_B(f_{AA} + f_{AB}(1-d))$, and $f'_{BB} = f_B(f_{AB}d + f_{BB})$. As detailed above, exact frequencies after drive, random mating and selection are $f''_g = f'_g w_g/\bar{w}$. Assuming HWE, a rare driver will spread when $s_h \lessapprox (2d-1)/(1+2d)$, and will fix when $s \lessapprox d - 1/2 + 3s_h/2 - ds_h$. This later inequality reduces to $s \lessapprox (2d-1)/2$ when the cost of drive is fully recessive.

Model 2. Single locus, sperm-dependent drive.

Our single-locus model of sperm-dependent drive resembles the traditional driver, with the caveat that the B allele drives in heterozygous females only when fertilized by B-bearing sperm. Therefore, genotype frequencies after drive are $f'_{AA} = f_A^2$, $f'_{AB} = f_A f_B + f_B(f_{AA} + f_{AB}(1-d))$, and $f'_{BB} = f_B(f_{AB}d + f_{BB})$. We iterate exact genotype frequency recursions ($f''_g = f'_g w_g/\bar{w}$) over generations to produce the frequency trajectories shown in the inset of Figure 1B by plotting $f_B = f_{BB} + \frac{1}{2}f_{AB}$ over time. To assess invasion or fixation criteria, as well as bistability points, we iterate this system and test whether f_B increases over a grid of parameters.

Recessive fitness cost of self-promoting driver: When fully recessive, the change in frequency of the self-promoting driver across generations equals

$$\Delta f_B = f_A f_B^2 \left([1-F][d(1-2f_A s) - f_B s - 1/2] - sF\right)/\bar{w} \tag{1}$$

where F is the deviation from genotypic frequencies expected under Hardy-Weinberg. Assuming HWE ($F = 0$) a common, recessive, self-promoting driver invades if $s \lessapprox (2d-1)/(4d)$, and fixes if $s \lessapprox (2d-1)/2$. Therefore, when

$$(2d-1)/(4d) \lessapprox s \lessapprox (2d-1)/2 \tag{2}$$

a recessive, self-promoting driver will deterministically fix if drift, mutation, or migration pressure bring its frequency above

$$f^*_{B\ \text{recessive}} \approx (1-2d+4ds)/(2s(2d-1)) \tag{3}$$

but it will be lost when introduced below this frequency. Compared to exact results (Supplementary Figure S1), Equations (2) and (3) offer reasonable, but imperfect approximations.

Cost of driver in heterozygotes: When the fitness of drive heterozygotes is compromised ($s_h > 0$), a self-promoting driver cannot invade when rare. This results from the fact that,

when rare, B-bearing sperm and heterozygous eggs will rarely encounter one another ($\sim f_B^2$) but the allele still pays a cost in heterozygous individuals ($\sim f_B$). However, this system too, is bistable – as the driver increases in frequency it is more often fertilized by a driving sperm and therefore drives more effectively. Therefore, assuming HWE, if

$$s \lessapprox d - 1/2 + s_h(3 - 2d)/2 \tag{4}$$

this self-promoting driver deterministically fixes when its frequency is greater than

$$f_B^* \approx \frac{a_1 + \sqrt{a_1^2 + 8s_h a_2}}{2a_2} \tag{5}$$

where, $a_1 = 1 - 2ds_h + 4ds - 2d - 3s_h$ and $a_2 = 2(s - s_h)(2d - 1)$. Comparison of Equation 5 to exact results obtained by a simple parameter search (Supplementary Figure S2) show that this approximation is reasonably correct for small parameter values; however, it underestimates f_B^* for large parameter values, presumably because they result in strong departures from HWE.

Model 3. Single locus, paternal genotype dependent drive:

In the case when female meiotic drive depends on paternal genotype, a heterozygous female will transmit the B allele with probabilities $\frac{1}{2}$, $d_{het} \geqslant 1/2$ or $d_{hom} \geqslant d_{het}$, when mated with to AA, AB, or BB males, respectively. In this model, genotype frequencies after drive, random mating, and selection are $f''_{AA} = w_{AA}\left(f_{AA}[2f_A + f_{AB}] + f_{AB}^2[1 - d_{het}]\right)/(2\bar{w})$, $f''_{AB} = w_{AB}(f_{AA}[f_B + f_{AB}/2] + f_{AB}f_B + f_{BB}[f_A - f_{AB}d_{hom}])/\bar{w}$, and $f''_{BB} = w_{BB}(f_{AB}(f_{AB}d_{het}/2 + f_{BB}d_{hom}) + f_{BB}f_B)/\bar{w}$.

If the cost of drive is fully recessive (i.e. $s_h = 0$), assuming HWE, a rare paternal-genotype-dependent driver invades when $s \lessapprox (d_{het} - 1/2)/(d_{het})$, and when common, this driver fixes if $s \lessapprox d_{hom} - 1/2$, approximations well supported by exact results (Supplementary Figure S3). Specifically, when drive in heterozygotes is large relative to that in homozygotes,

$$d_{het} \gtrapprox 1/(3 - 2d_{hom}) \tag{6}$$

fixation criteria are more stringent than invasion criteria, and therefore some values of s can maintain a stable polymorphism. Under these parameter values, a rare paternal-genotype-dependent driver can increase in frequency because it gains a transmission advantage and suffers no fitness cost when heterozygous eggs are fertilized by A-bearing sperm of heterozygous males. As the frequency of the B allele increases, it will be unable to avoid producing unfit homozygous offspring, leaving it trapped in the population at frequency $f^*_{B\ \mathrm{pat}}$. Assuming HWE, a recessive fitness cost ($h_s = 0$), and dominance of driver ($d_{het} = d_{hom}$) this equilibrium frequency is

$$f^*_{B\ \mathrm{pat}} \approx 2(1 + 2d_{hom}[s-1])/([2s-1][2d_{hom}-1]) \tag{7}$$

By contrast, when $d_{het} \lessapprox 1/(3 - 2d_{hom})$ the case is reversed, and the model is bistable.

Models 4-6. Two-locus, sperm-dependent drive.

Assuming that a traditional driver segregates at its equilibrium frequency (Model 1), we investigate the evolution of tightly linked (Models 4 and 5), and unlinked (Model 6) sperm-dependent modifiers of drive. In Models 4 and 5, we treat this two-locus system as if it consists of a single locus with three alleles: A, B and C, corresponding to the case when the sperm-modifier arises once, tightly linked to one or other of the alleles at the drive locus (such that recombination is unexpected). In all cases, we assume that fitness is independent of the drive modifier. We assume the traditional driver is transmitted to d_0 of gametes from female heterozygotes when fertilized by wild-type sperm, and $d_1 = d_0 + \epsilon$ when fertilized by a sperm-acting drive-modifier.

Model 4. Drive-modifier in coupling phase:

When the C allele is tightly linked to the driver allele, genotypic fitnesses equal $w_{AC} = w_{AB} = 1 - s_h$, and $w_{BC} = w_{CC} = w_{BB} = 1 - s$. Assuming HWE, a recessive fitness cost to drive, and assuming that the A/B locus is at its equilibrium frequency, the change in

frequency of a rare drive modifier is

$$\Delta C \approx -\epsilon f_C \frac{1 - 2d_0(-2d_0 + s + 2) + \sqrt{2}\sqrt{s(2d_0(d_0(s-2)+2)-1)}}{2\bar{w}(1-2d_0)^2} \tag{8}$$

For all parameters sustaining a polymorphism at the drive locus ($s > d_0 - 1/2$), this corresponds to a decrease in frequency of the C allele when it enhances drive ($\epsilon > 0$ – the B^+ model, above), and an increase in frequency of the C allele when it suppresses drive ($\epsilon < 0$ – the B^- model, above). More generally, even when the cost of drive is not fully recessive, the B^- allele will invade and fix under all parameters sustaining a previous polymorphism at the drive locus (see Mathematical Supplement).

Model 5. Drive-modifier in repulsion phase:

When the C allele is tightly linked to the non-driver, genotypic fitnesses equal $w_{CC} = w_{AC} = w_{AA} = 1$, and $w_{BC} = w_{AB} = 1 - s_h$. Assuming HWE, a recessive fitness cost to drive, and assuming that the A/B locus is at its equilibrium frequency, the change in frequency of a rare drive modifier is

$$\Delta C \approx -\epsilon f_{C^-}^2 \frac{\left(2d_0 s - \sqrt{2}\sqrt{s(2d_0(d_0(s-2)+2)-1)}\right)}{2\bar{w}s(2d_0-1)}. \tag{9}$$

For all values of interest ($0 < s < 1$, $0.5 < d_0 < 1$), the change in frequency a rare C allele is positive when it decreases drive (i.e. $\epsilon < 0$, corresponding to the A^- model, above), a result which holds qualitatively for a common C allele, as well (Mathematical Supplement). Somewhat counterintuitively, the spread of the A^- allele is substantially slower than that of the B^- allele (it is on the order of C^2 rather than C). This is because the A^- allele will never occur in drive-homozygotes and therefore only spreads by preventing itself from the cheating of the driver.

Model 6. Unlinked drive-modifier:

For the unlinked model, we introduce another locus where drive is modified in A/B females fertilized by M allele, while the wild-type L allele does not influence drive. Assuming HWE

and linkage equilibrium, the change in frequency of a rare unlinked, sperm-acting drive modifier is

$$\Delta M = -\epsilon f_A f_B (f_B s + s_h (f_A - f_B)) \frac{f_M}{\bar{w}} \tag{10}$$

Thus, a rare drive suppressor ($\epsilon < 0$) will spread so long as the fitness cost of the driver does not display over- or under-dominance. Notably, this result holds while assuming complete linkage equilibrium, and therefore sperm suppression of female meiotic drive is likely more powerful than more direct female-enforced drive suppressors which usually spread due to the indirect benefit of avoiding drive haplotypes [e.g. 4].

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Supplementary Material

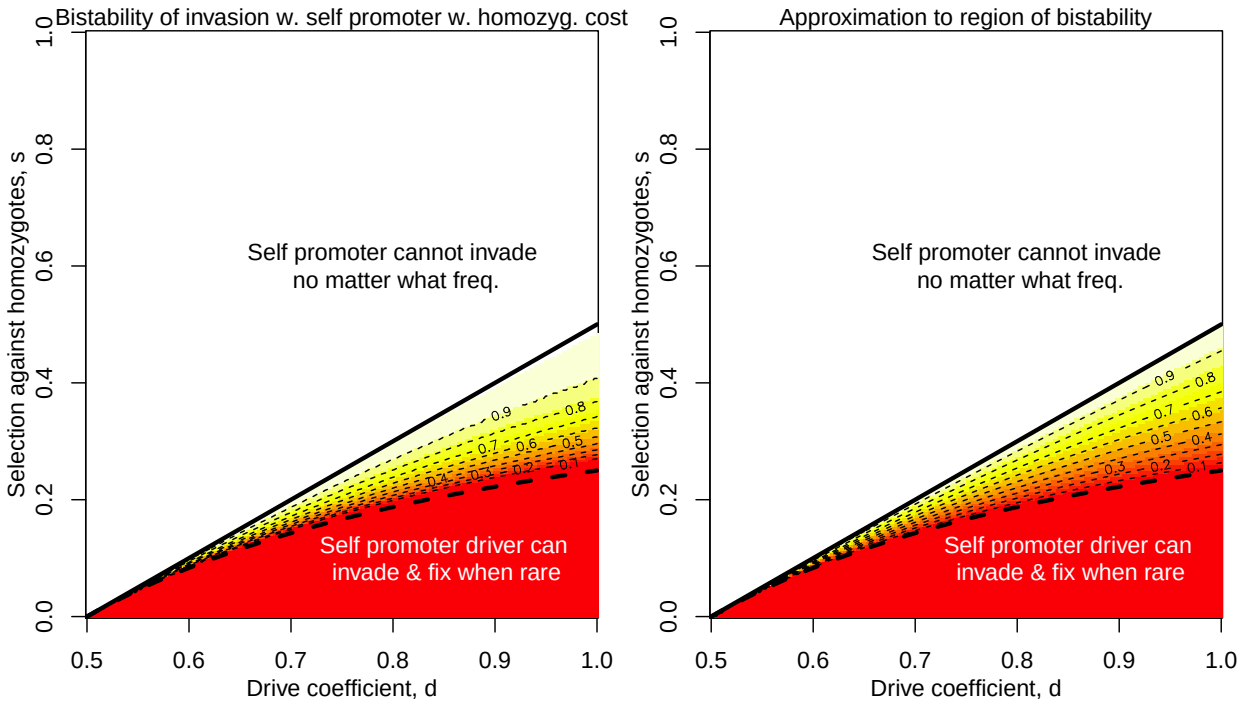

Figure S1: Invasion analysis for a self-promoting female meiotic drive allele with recessive costs (selection coefficient s), showing the region of bistability. The colors, and the thin dashed contours, indicate the frequency the allele must be above to invade the population (note that these alleles reach fixation conditional on invading). In the white area the allele cannot invade ($x \geqslant 1$), in the solid red area the allele can invade and fix when rare. In the left panel we show the results obtained by a grid search using the recursion, on the right we show the approximation obtained assuming that HWE holds.

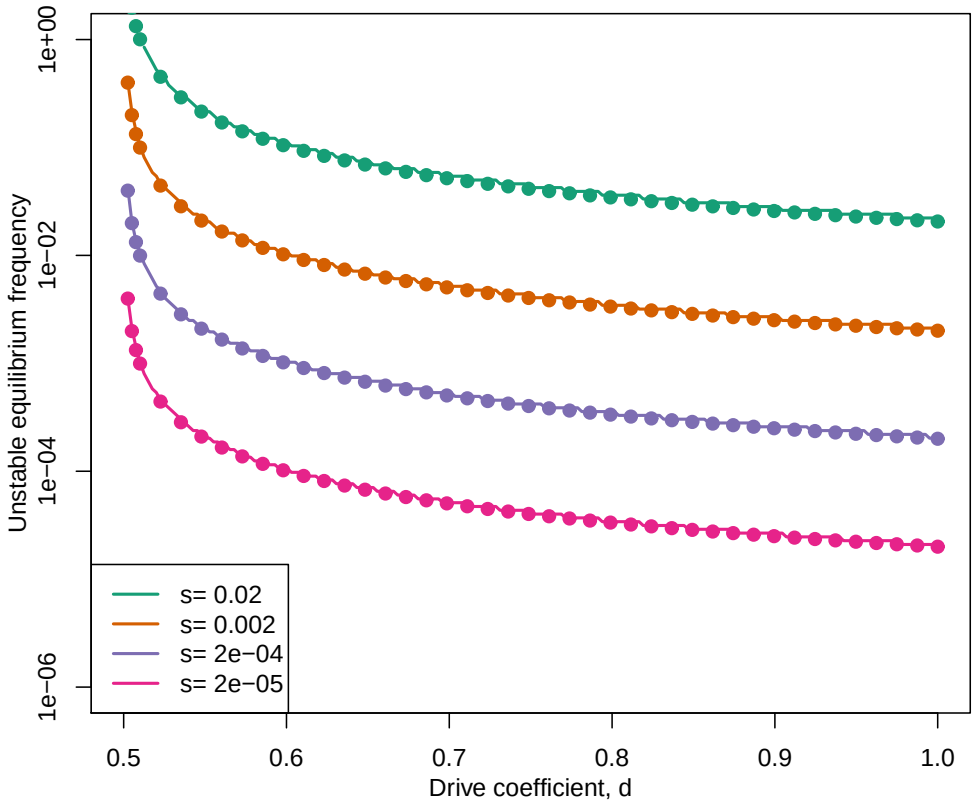

Figure S2: The unstable equilibrium frequency for a self-promoting female meiotic drive allele with an additive cost ($s_h = s/2$) as a function of the drive parameter. The solid line shows results obtained using the recursion, the dots our approximation given by Equation (5)

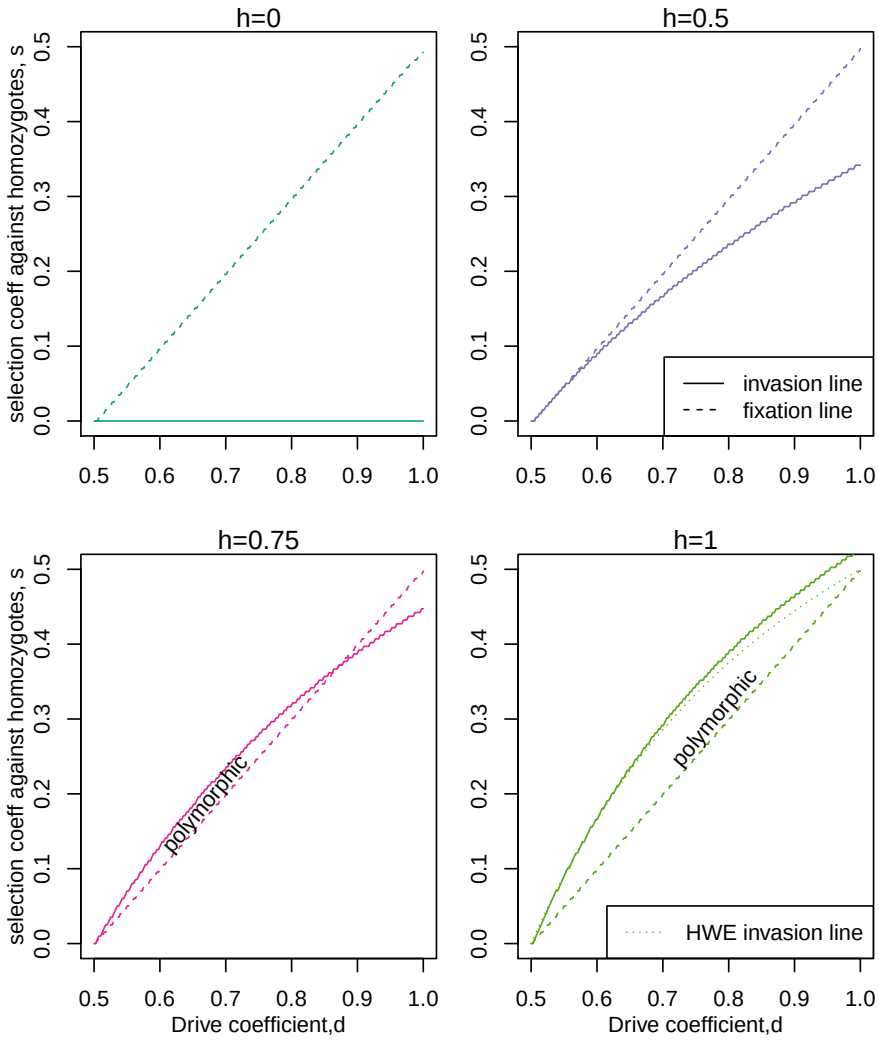

Figure S3: Exact results of invasion analysis of an allele whose effect on female meiosis is mediated by the genotype of the fertilizing male. A heterozygous female transmits the B allele with probabilities $\frac{1}{2}$, $d_{het} = \frac{1}{2} + h(d_{hom} - \frac{1}{2})$ or d_{hom}, if she mated with a n AA, AB, or BB male, respectively. The allele suffers a recessive fitness cost s. The four panels correspond to different dominance relationships. In the parameter space below the invasion (solid) line the self-promoter driver can invade. In the parameter space below the fixation (long dash) line the self-promoter can fix. In the last two panels the invasion line is above the fixation line and so the allele can be maintained as a polymorphism in that thin slice of parameter space between the two lines. In the final panel we show the fixation line (small dashes) as predicted by our HWE approximation ($(d_{het} - 1/2)/d_{het}$) see the appendix for more details.