The ecology and evolutionary dynamics of meiotic drive

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- Both naturally occurring and synthetic “meiotic drivers” violate Mendel’s law of equal segregation and can rapidly spread through populations even when they reduce the fitness of individuals carrying them.
- Synthetic drivers are being developed to spread desirable genes in natural populations of target species. How ecology influences the population dynamics of meiotic drivers is important for predicting the success of synthetic drive elements.
- An enduring puzzle concerns why some meiotic drivers persist at stable, intermediate frequencies rather than sweeping to fixation.
- Drivers can have a wide range of consequences from extinction to changes in mating system.

Abstract

Meiotic drivers are genetic variants that selfishly manipulate the production of gametes to increase their own rate of transmission, often to the detriment of the rest of the genome and the individual that carries them. This genomic conflict potentially occurs whenever a diploid organism produces a haploid stage, and can have profound evolutionary impacts on gametogenesis, fertility, individual behaviour, mating system, population survival, and reproductive isolation. Multiple research teams are developing artificial drive systems for pest control, utilizing the transmission advantage of drive to alter or exterminate target species. Here, we review current knowledge of how natural drive systems function, how drivers spread through natural populations, and the factors that limit their invasion.

The battle for transmission

One of the few rules in biology is Mendel's law of equal segregation: the two copies of each gene and/or chromosome in a diploid organism are transmitted with equal probability to its offspring. Although often taken for granted, it is increasingly clear that equal segregation is a fragile détente in a world of constant intra-genomic competition (see Glossary) for passage to the next generation. Such conflict plays out in the arenas of meiosis and gametogenesis, and results in meiotic drive [1], the biased transmission of a gene or chromosome against its alternative (Box 1). Because selection on meiotic drive elements operates at a level below that of the individual, drivers can spread through populations even if they reduce organism fitness [2]. By the same process, recently developed synthetic drive elements, which are currently still confined to laboratories, have the potential to rapidly modify genomes in wild populations [3]. Both natural and synthetic drive systems can have profound ecological, evolutionary, and genomic consequences.

Meiotic drive systems in nature

In this review we explore the ecological and evolutionary dynamics of natural meiotic drive systems. We focus on three kinds of drive: female meiotic drive, male meiotic drive (sperm killers), and drive in haploid spores (spore killers, Box 1). However, meiotic drive can encompass a broad range of systems we do not discuss, including supernumerary B chromosomes, zygote killers and paternal genome eliminators.

Female meiotic drive occurs when homologous chromosomes are differentially transmitted to the egg during meiosis. In plants and animals, female meiosis is asymmetric, with only one of the four meiotic products becoming an egg or, in plants, a megagametophyte ([4],

Box 1). Any chromosomal variant that biases its own segregation (for example, by preferentially associating with and moving toward the egg pole at Meiosis I) will be transmitted to more than half of the maturing eggs. Although this bias does not necessarily reduce the production of eggs (as only one egg matures per meiosis), the fitness of other alleles at the same locus, that do not bias transmission, and alleles linked to them, is reduced. Such meiotic drivers could reduce the fitness of individuals that carry them, if the driving variant is genetically linked to deleterious mutations or has deleterious pleiotropic effects.

Male meiotic drive takes multiple forms – some at least partially meiotic, some entirely post-meiotic – but all involve a driving element that prevents maturation or function of sperm that do not contain it. Because haploid sperm within a single ejaculate compete to fertilize the same pool of eggs, disabling non-carrier sperm results in transmission of the driving element to more than half of the functional gametes and resulting offspring ([5], Box 1). However, disabling non-carrier sperm often reduces fertility [6].

Spore drive in fungi, in which the products of meiosis are packaged together in an ascus, operates via similar mechanisms. Spores with one haploid genotype will kill or disable spores of the alternative haplotype ([7], Box 1). If spores disperse long distances sibling spores are unlikely to compete and killing them will not increase the killer's fitness. However, spore killing can be beneficial if there is local resource competition.

Exciting progress has been made in dissecting the genetic and cellular mechanisms of multiple drive systems that span eukaryotic diversity (Box 1). However, we are still in the early stages of understanding how these genetic systems interact with ecology to shape the dynamics of drivers in natural populations. The fate of a meiotic driver depends on the costs

of transmission bias and the mating system, environmental factors, and population and geographic structure that affect the fitness of its carriers. These interactions might then affect how drivers contribute to genetic and phenotypic variation within and among populations, potentially contributing to speciation [8]. On a larger time-scale, coevolution between drive elements and suppressors might also shape fundamental aspects of eukaryotic biology, including meiosis, gametogenesis, and genome structure [9-11]. Finally, understanding how ecology influences the population dynamics of meiotic drivers is important for predicting the success of synthetic drive elements, which are currently being engineered and applied to the management of vector populations of important human diseases ([12], Box 2 and Box 3). In this review, we consider the impacts drivers can have on the genomes, individuals and populations that harbour them, then discuss the factors that influence the dynamics of drivers in natural populations.

Consequences of drive

Genomic conflict

Meiotic drivers can pose a significant cost to the rest of the genome, which is then under selection for unlinked alleles that suppress drive and restore equal segregation. Consider a driving allele that resides on an X-chromosome in a species with heterogametic (XY) males. The driving X causes Y-bearing sperm to die, such that the driving X is transmitted to all offspring, who become daughters. The spread of the driving X makes the population sex ratio increasingly female-biased, until lack of males causes population collapse and extinction [13]. It is easy to imagine that any Y-chromosome that resists drive will be favoured by selection [14], even if the driver is rare. Once the population sex ratio has become female-biased, classical Fisherian sex ratio selection will favour any autosomal

mutation that suppresses drive [13, 15]. Interestingly, a recent comparative study on tetrapods suggests that sex chromosome drive could account for the evolutionary pattern of species with male heterogamety exhibiting more female-biased adult sex ratios than species with female heterogamety [16].

Many drive systems consist of multiple drivers and suppressors, with several loci being involved with drive expression [17]. These systems suggest that the conflict does not end once a suppressor of drive has evolved. Instead, enhancers linked to the original drive locus could evolve to restore drive, resuming the conflict. In this way, a drive system can cycle through periods of apparent drive and lack of drive resembling a co-evolutionary arms race [18], resulting in a complex genetic drive system. Recurrent coevolution between drivers and suppressors can contribute to the rapid evolution of genes, satellite DNA, and pathways whose functions might otherwise be expected to be conserved.

Rapid divergence in sequences, genome organisation and populations

Drive can contribute to DNA sequence evolution via selfish, driving nucleotide substitutions. For example, the meiotic drive gene *Overdrive* (Genbank: GA19777) of the fruit-fly, *Drosophila pseudoobscura bogatana*, differs from the non-driving wildtype allele of its close relative, *D. pseudoobscura pseudoobscura*, by seven nucleotide changes [19]. More often, drive seems to involve copy number variants: the *Segregation Distorter* system of *Drosophila melanogaster* involves a partial duplication of a protein-coding gene [20]; the *t* haplotype distorter system of the house mouse (*Mus musculus*) involves four tandemly-duplicated genes [21]; copy number gain of the *R2d* distorter locus in house mice is associated with drive [22]; and the tandemly-repeated, rapidly evolving, testis-expressed ampliconic genes of mammalian sex chromosomes are thought to result from recurrent

arms races over gene dosage [23]. Such arms races do not necessarily occur between a driver and suppressors: different allelic variants of a meiotic driver can also compete against one another [24, 25]. The rapid evolution of centromeres and centromeric proteins is particularly striking because these essential proteins are otherwise expected to be highly conserved [26]. Early speculation that female meiotic drive might be responsible for this rapid centromeric change is now supported by evidence in *Mimulus* monkeyflowers [27]. Finally, testis-expressed de novo genes often arise and spread to fixation but then, once fixed, degenerate into non-functional pseudogenes—a pattern suggestive of drive [28]. The recent identification of a young, rapidly evolving heterochromatin protein gene involved in a case of X chromosome drive in *Drosophila simulans* strongly supports this idea [29].

Drive can also have large-scale impacts on genome organization and chromosome structure. Sperm killing meiotic drive elements often begin with just two loci — a driver and a target sequence, tightly linked to prevent the production of a suicide chromosome — but subsequently become elaborated via the recruitment of genetically linked enhancers. Such linked, co-adapted gene complexes are expected to evolve in regions of low recombination and can become further protected from recombination by chromosomal inversions [30]. Reduced recombination associated with male drive has been found in *Segregation Distorter* [31], the *t* haplotype [32], *Spore killer* [33] and *Drosophila recens Sex-Ratio* [34]. Female drive can involve dramatic changes in the quantity and sequence content of centromeric satellite DNA and proteins, as centromeres evolve to compete for access to primary oocytes and avoid relegation to the polar bodies, losing their chance for transmission (Box 1; [11, 35, 36]). Female drive can also favour the evolution of chromosome fusions or fissions, in which two fused centromeres experience a transmission rate different from that of non-fused

ones, thus fuelling karyotype evolution [4]. As drive is usually exclusive to one sex, it accentuates intralocus sexual conflict [37]. Hence a drive locus is expected to acquire genetically linked sexually antagonistic loci [38], potentially explaining the origin of sex chromosomes [39]

The combined effects of drive on DNA, genome, and karyotype evolution can lead to rapid divergence between populations and ultimately to speciation. For example, the fixation of alternative chromosome fusions in different populations can result in incompatible karyotypes that cause meiotic segregation problems in heterozygous individuals [36, 40]. Recurrent drive and suppression can lead to cryptic drive systems, where fair meiosis has been restored within a species, but in a hybrid individual the dormant or suppressed drive elements can then spring into action [5, 41, 42]. Due to reduced recombination and lack of homology, well-differentiated sex chromosomes are more susceptible to the invasion of drive elements. The recurrent fixation of cryptic drive systems on sex chromosomes might explain the prominent role of the X chromosome in the evolution of hybrid sterility in a wide range of species [42-44]. Cryptic drive systems appear to contribute to reproductive isolation between populations and species of *Drosophila* [19, 45], stalk-eyed flies [46] and yeasts [47].

Growth and persistence of populations

Drive can also have ecological consequences. Female-biased populations are expected to have higher per capita growth rates [13, 48]. Although individuals carrying X-linked drivers might leave fewer descendants than other members of their subpopulation that lack drivers, subpopulations containing an intermediate frequency of drivers might have faster population growth relative to driver-free subpopulations [48] and competing species [49].

Finally, a significant consequence of distorted sex ratios is the potential for population extinction due to the lack of one sex [13, 50, 51], though definite evidence for such extinctions is almost entirely limited to lab populations [52-54].

Dynamics of drive

Stability of driver frequencies in natural populations

All else being equal, drivers are predicted to increase in frequency due to biased transmission, and go to fixation. However, the spread of a driver can be limited by genetic suppressors, as well as fitness costs to carriers such as decreased fertility or viability [50]. Most of the known drive elements impose fitness costs on their carriers [6, 31, 55], either due to direct pleiotropic effects of the driver on survival or reproductive success, production of a biased sex ratio (in the case of sex-linked drivers), or via deleterious mutations linked to the driver. The latter are expected to build up in drive systems located in genomic regions with reduced recombination (e.g., inversions). Genetic studies suggest that some well-studied drive systems apparently have persisted for considerable time (estimated ages: *t* haplotype in mice circa 2 MYA [56], *D. pseudoobscura Sex-Ratio* circa 1 MYA [57]). This long-term stability is surprising: a drive polymorphism is characterised by powerful selection on drivers and suppressors, and simple models suggest even a small change in drive or suppression strength can potentially lead rapidly to extinction or fixation. However, well-studied drivers in stable polymorphisms may represent a biased sample, if most drivers rapidly reach fixation or extinction, thereby becoming almost impossible to detect.

Fitness costs to individuals homozygous for the drive allele might help explain the persistence of some polymorphisms [51, 58, 59]. As autosomal drivers only benefit from

transmission bias when in heterozygotes, they are most likely to be able to drive when rare. At higher frequencies, driver homozygotes become common, unmasking any recessive deleterious mutations linked to the drive allele. Processes that increase homozygote frequency, such as inbreeding, are predicted to reduce autosomal driver frequency [58]. The general prediction of an intermediate equilibrium for drivers with homozygous costs is borne out in some cases; for example, in yellow monkeyflowers, male and female fitness costs measured in the field together predict the observed frequency of a centromere-associated driver [59]. However, driver frequency in natural populations is often substantially lower than predicted by simple models based on homozygote fitness effects [17, 60].

Field studies of driver dynamics are rare, as few wild populations harbouring meiotic drivers have been repeatedly sampled [24, 54, 61, 62]. Long-term studies of driver frequencies within populations are even rarer [60]. Several species show apparently stable clines in driver frequency [54, 62], e.g. the frequencies in *Drosophila pseudoobscura* populations across North America have remained unchanged for 70 years. In contrast, a strong decline of the house mouse *t* haplotype frequency within one population was seen over six years [60]. There are also examples of rapidly spreading drivers. In *D. simulans*, a young X driver originating in Africa has spread in the Middle East within the last two decades [62] while simultaneously decreasing in East Africa due to genetic suppression. The reasons for the stability of some drive systems, and the rapid spread and decline of others, are poorly understood and a major focus of drive research.

Sexual selection against driver-carrying individuals

Male and female mating behaviour are predicted to influence driver dynamics. The costs associated with drive create a benefit to avoiding mating with individuals carrying a driver, and so preferences against driver-carriers are expected to evolve [63]. In stalk-eyed flies (*Teleopsis dalmanni*) females prefer to mate with males with larger eyespans, and driver-carrying males tend to have smaller eyespans [64, 65]. In some house mouse populations, females carrying the *t* haplotype discriminate against driver males in choice tests, though wildtype females show no preference [66, 67]. However, as recombination is expected to break linkage between drive elements and traits that allow mate choice [63], with undetectable drivers predicted to rapidly outcompete detectable forms, premating discrimination against driver males might be uncommon [6]. Alternatively, as many sperm killers significantly reduce sperm numbers, females could potentially avoid drivers by preferentially discarding sperm from males transferring small ejaculates, as hinted by a study in *D. simulans* [68]. The production of driver-carrying progeny can also be avoided through sperm competition when females mate with multiple males, assuming driver-carrying males are poor sperm competitors [69]. Both theoretical models [51, 60, 70] and empirical studies [54, 55, 61, 71-73] support the idea that gamete competition can reduce driver frequencies and limit the spread of male drivers under some conditions (see [51]). Indeed, the presence of drive elements can select for and lead to an increase in female mating frequency. If female mating rates are density dependent [73], this could make drivers rare in denser populations.

Spatial heterogeneity

Driver distribution varies across space and between habitats, and this aspect of natural drive systems might be important for the successful application of artificial drivers (see Box 2 and

Box 3). Drivers in mice and monkeyflowers vary in abundance between populations [59, 74]. *Segregation Distorter* is typically found at very low frequencies in *D. melanogaster* [31], while two other *Drosophila* species show latitudinal clines in driver frequency across North America [54, 61]. Driver frequency correlates negatively with the frequency of polyandry in these populations, supporting the hypothesis that polyandry impacts the success of drivers in nature. However, in *D. neotestacea*, the environmental factor that best predicts the frequency of drivers is winter temperature [75], implying that drivers might be limited by elevated susceptibility to cold in driver carriers. Frequency of drivers in *D. pseudoobscura* can cycle yearly [76], suggesting more complex ecological interactions control driver abundance. Sperm killers can interact with other environmental factors that affect male fertility, such as high temperature [77]. It seems that variation in driver fitness between populations can result from interactions between environmental factors and the characteristics of populations harbouring drivers, potentially including differences between populations in deleterious genes linked to drive elements.

Fixation and extinction of drivers

Stable drive systems might be the exception, not the rule, with most drivers rapidly reaching fixation or extinction and becoming undetectable [50]. Population extinction is frequently predicted by simple models of sex chromosome drive [13, 50, 51]. It is difficult to measure the frequency of drive-mediated extinction because extinct populations leave no trace: while sampling wild *D. neotestacea*, Pinzone and Dyer [54] collected 175 flies from an isolated population, 91% of which were female; the following year only three flies were found at the same site, all driver-carrying females, and only one was inseminated. Laboratory experiments suggest that local extinctions are likely [52, 53]. Local extinctions

might allow drive to persist in a spatial mosaic where drive-related local extinctions are followed by rapid recolonisation from nearby sites [78]. Finding definitive evidence for such processes is very difficult, and the frequency at which such extinctions occur cannot typically be gauged.

Autosomal male meiotic drivers, as well as chromosomal variants driving through female meiosis, might often fix without causing extinction. Thus models predict a large number of cryptic drive systems, that could potentially be revealed by crosses between populations (see Box 4). However, population studies of autosomal drivers are so rare that the evidence is extremely limited. Moreover, the best studied autosomal sperm killing meiotic driver [31] and female meiotic drivers [59] are polymorphic within species, not fixed. Consequently we do not know how common autosomal and female drive systems are, nor how often they reach fixation.

Poorly understood dynamics in many systems

The ecological dynamics of spore killers in fungi are little known. Although the system is increasingly understood at the genetic level [32, 77], the rarity of local resource competition makes the advantage they gain from drive obscure [78]. Ecological understanding of the dynamics of female drivers is also poor, with the exception of *Mimulus* monkeyflowers [59]. Finally, some documented sperm killer systems are more complex than any existing theoretical models. For example, *Drosophila paramelanica* has two driving X chromosomes, a Y that is susceptible to both, another Y that is resistant to one of the drivers, and latitudinal differences between populations in the co-occurrence of drivers and Y chromosomes [79]. Currently, little is known about how multiple drivers and resistance chromosomes coexist. Understanding factors that influence natural drive system dynamics

is likely to be important to ensure the successful application of synthetic drive systems (see Box 2 and Box 3).

Summary and conclusions

The potential for meiotic drive is probably high in all sexual organisms with a diploid phase, because the conflict over the transmission of homologous chromosomes in haploid gametes is nearly universal. Our understanding of the ecological and evolutionary dynamics of drive is surprisingly poor, even in well-studied systems. Nevertheless, some consistent themes stand out. Genetic suppression can evolve to neutralize drivers to the extent that the driver becomes undetectable, and this suppression can evolve and spread extremely rapidly [62]. Yet suppression is not universal, and some ancient systems seem to have never evolved resistance or suppression. All well-studied extant drivers have costs, either intrinsic to the mechanism they use to gain their transmission advantage, or resulting from the reduced recombination that commonly associates with drive. Repeated discoveries of such associations suggest that extant drive systems are often complex, using multiple genes, perhaps indicating that successful drivers need modifiers that help them avoid suppression. Active drive systems vary in frequency between populations, and sometimes over seasons and years, suggesting that the fitness of drivers depends on their local environmental conditions, in ways that are currently not well understood.

Novel synthetic drive techniques (see Box 2) have the potential to fundamentally alter natural populations in ways analogous to meiotic drive. These synthetic drive systems have enormous potential for biocontrol, but if they are used without understanding how drive behaves in natural systems, there are serious risks of synthetic drive both failing to achieve its aims and having unintended negative consequences. Work on natural drive systems

shows that the consequences of drive are manifold, from speciation to genome organisation, gametogenesis, competition between species, mate choice and mating systems. Once synthetic drivers are released into nature, the potential for long-term evolutionary changes in the target species and its community are profound.

New natural drive systems will be discovered in coming years (see Box 4), e.g. by the discovery of non-Mendelian patterns of inheritance in sequence data. Detecting new drivers should help answer many of the outstanding questions in the field (Box 5), and without doubt will uncover new mechanisms of drive, as well as unexpected genomic consequences of drive.

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Box 1. Definition, mechanisms and species

Meiotic drive occurs when alleles, haplotypes, or chromosomes subvert mechanisms of fair segregation to obtain greater than Mendelian transmission at the expense of homologues. Sandler & Novitski [1] first used the term "meiotic drive" to describe biased transmission that results as "a consequence of the mechanics of the meiotic divisions". For instance, in taxa with asymmetric female meiosis, structural elements of chromosomes— *e.g.*, centromeres, telomeres and heterochromatic neo-centromeres ("knobs")— can compete for inclusion in the gamete and hence transmission to subsequent generations, with failing chromosomes discarded into the polar bodies. Examples of drive through female meiosis have been observed in mice [22, 36], maize [80], and monkeyflowers ([35], Figure 1A). However, "meiotic drive" is often used in a broader sense to include biased transmission resulting from a variety of premeiotic, meiotic and postmeiotic events during gametogenesis [17]. In males, for instance, drive elements can achieve biased transmission by killing sperm that lack the element (Figure 1B). These gametic drivers typically involve a drive locus and a target locus. They can occur on autosomes— as in the mouse *t* haplotype [56] and the fruitfly *Segregation Distorter* [31]— or on sex chromosomes, causing distorted sex ratios among progeny— as in *Silene* flowering plants [81], stalk-eyed flies [82], mosquitoes [17], and many *Drosophila* species [17]. Finally, in fungi a heterozygous cross between strains carrying a spore killer allele and a sensitive allele results in elimination of haploid ascospores that lack the spore killer allele ([7], Figure 1C). Spore killer genetics can involve a single locus [83], or be complex, involving multiple loci [33]. Even this brief summary highlights that selfish drive elements gain transmission advantages through diverse genetic mechanisms across the eukaryotes.

383 FIGURE 1 HERE

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Box 2. Synthetic drive

Disease-transmitting insects impose a massive burden on human populations. There are an estimated 198 million cases of malaria each year, resulting in 580 thousand deaths, and 390 million people infected with dengue. Control of insect vectors using pesticides is expensive and can damage both ecosystems and people [84]. There is an urgent need for inexpensive, targeted pest control techniques. In recent years, researchers have turned to genetic engineering tools to control vectors of human disease with one of two goals: 1) to modify target populations to carry anti-pathogen genes that limit their capacity to spread disease, and 2) to reduce or collapse target population sizes [13, 85]. Various drive systems can be exploited to create synthetic drive systems (also known as gene drive) that can quickly spread through populations [85]. Transposable elements, homing endonucleases , *Medea* elements*, Wolbachia*, CRISPR-Cas9, as well as meiotic drivers each have potential use in synthetic drive methods to modify or collapse disease vector populations [1, 53, 85-87].

Several groups have engineered synthetic drive systems in mosquitoes [88] and *Drosophila* [87, 89, 90]. Extreme sex ratio distortion offers one method of population extermination [13, 53]. Galizi *et al.* [88] recently developed a homing endonuclease-based synthetic drive system capable of eliminating experimental populations of *Anopheles gambiae* mosquitoes (Box Figure 2) within six generations by targeting X chromosomes during meiosis. Alternative strategies for population modification or collapse involve synthetic toxin-antidote systems [85, 87, 91]. Many of these systems are modelled after *Medea*, a female gamete killing driver originally discovered in *Tribolium castaneum* that kills embryos that fail to inherit the element [87, 91].

Homing endonucleases have been used to create an artificial sperm killing meiotic drive system [85, 88]. The new CRISPR-Cas9 genome editing technology targets specific sites in the genome and could prove to be a powerful source of synthetic drive systems, even in non-model pest species [86].

Synthetic drive systems have applications far beyond insect population control [92], including in agriculture [93], controlling invasive species and pests, or even conservation [92]. We discuss the significant challenges and risks involved in the release of any such drive system in Box 3.

FIGURE 2 HERE

Box 3. Synthetic drive: Lessons from natural drive systems

Genetic engineering of synthetic drive systems (Box 2) for release in natural populations has provoked controversy. If a synthetic driver spreads successfully, will it spread to non-target populations or species? Will the drive mechanism interfere with key molecular pathways, resulting in unexpected phenotypic changes? Progress toward a synthetic drive system in a target disease vector has been slow owing to challenges in genetic engineering in non-model organisms. However, genome editing using the CRISPR-Cas9 system has the potential to rapidly accelerate the field. Several groups have suggested policy or protocols for releasing drive systems, but with these recent advances, additional discussion and regulation is urgently needed [12, 92, 94, 95]. Below we outline several key challenges and concerns.

1. Adverse effects of synthetic drive: Before a synthetic drive system can be used in a natural population, extensive testing for unintended consequences and side effects (*e.g*. it does not transmit other pathogens, lead to higher bite rates from insect disease vectors, or have unanticipated effects on local ecology) is needed. Adverse phenotypic effects might be ameliorated by introducing another driver to reverse the effects of the initial driver [92, 95].
2. Risk of cross-contamination: This risk is presumably low for homing endonuclease genes [85] or CRISPR-Cas9-based drive systems or other site-specific synthetic drivers, and could be reduced further by targeting specific sites limited to the intended species [92].

3. Suppressors: Any drive system must spread rapidly enough to be relevant to human disease, and before the system has time to evolve suppressors [85]. Multiple drivers with multiple targets is one possible solution to combat suppression [85].
4. Environmental heterogeneity: many natural drive systems show patchy or clinal distributions, indicating that costs of drivers vary between locations. Even strong synthetic drivers might be unable to penetrate all areas a target inhabits, potentially leaving reservoirs where suppression can evolve.

The parallels between synthetic and natural drivers make it likely that synthetic drive can be usefully informed by understanding the function and regulation of natural drive systems. In particular, suppressors are common in natural drive systems and can evolve rapidly [62]. Modified natural drive systems in both *Drosophila* [53] and mosquito species [96] faced difficulties from the rapid response of segregating suppressors in the population.

Box 4 Discovering drive

Initial detection -- Meiotic drive, both apparent and cryptic, affects patterns of phenotypic, genetic, and genomic variation. Although these patterns are generally not exclusive to drive, and thus are not definitive signatures, they provide valuable clues that drive might be present in a population or species. Polymorphic spore killer and sex-chromosome sperm killer systems might even be detectable in natural populations, as they visibly affect spores within an ascus and sex ratios in progeny, respectively. Similarly, high genetic variance in fertility that is incompatible with mutation-selection balance models might suggest the presence of either autosomal sperm killers or costs associated with other balanced drive polymorphisms [97]. All forms of drive discussed here could be revealed as genetically-localized transmission ratio distortion (TRD) in mapping populations or pedigrees, and, with sufficient sample sizes, gametic distortion might be statistically distinguishable from post-zygotic (non-drive) distortion mechanisms [98]. Indeed, cryptic drive systems, in which a driver and suppressor have both gone to local fixation, are primarily detectable as aberrant phenomena (sterility, sex ratio, TRD, chromosomal abnormalities) in experimental hybrids between distinct populations or species. As genomic scans of variation become increasingly common, there will also undoubtedly be cases where selective sweeps or balanced inversion polymorphisms reflect natural selection via meiotic drive rather than via individual fitness [99].

Validation -- Of course, none of these possible indications of meiotic drive are exclusively (or even most plausibly) explained by drive rather than other processes. Thus, the characterization of new drive systems ideally includes both exclusion of alternative processes that can generate TRD, infertility, or other suggestive phenomena, and positive

476 validation of a given drive mechanism. Validation can be quite difficult for some systems
477 and forms of drive, but is relatively accessible in others. New genomic technologies are likely
478 to accelerate both validation and detection of drive. For example, deep-sequencing of
479 pooled sperm of F1 hybrids can directly determine gamete frequency prior to the
480 confounding effects of fertilization, and thus holds great promise as a tool for the detection
481 and validation of autosomal sperm killer systems [100]. Broad application of such
482 approaches will be the key to addressing general questions about the relative frequency of
483 different kinds of drive in nature.

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Box. 5 Outstanding questions

Despite involving key processes of life, our understanding of meiotic drive remains rudimentary. Here we outline some key unresolved questions.

How common is drive?

Drive is the result of a fundamental conflict and potentially occurs in any diploid organism. Yet known drivers come from a limited range of species. Is it simply that drivers are rare? If so, why? Or do drivers usually persist for a very short time before reaching fixation or going extinct? Alternatively, are some taxa particularly susceptible to drive? Indeed, we have little understanding of how often novel mutations create drive. Why are so many of the detected drivers so strong, when theory suggests weak drive should be common? Is it simply that weak drive is difficult to detect?

Drivers across space and time

Despite decades of research, we lack data on how drivers varies across time and space. Consequently, we do not know if drive is stable or cycles. We also do not know if drivers require a metapopulation for survival, nor what limits the spread of drivers between populations. Moreover, do drivers spread between hybridizing species?

Molecular mechanisms of drive

We understand the genetic basis of very few drive systems. Are there general themes in the mechanisms? Do all gametic drive systems target similar pathways, or is each unique? Is the preponderance of drive systems in the Diptera (flies) due to some shared weakness in spermatogenesis that drive can exploit? Why is genetic suppression apparently absent in

some ancient drive systems? Do these drive systems target something fundamental that cannot be defended, or are these drivers simply evolving faster than their targets?

Contrasting synthetic and natural drive

How similar are the mechanisms of natural drive to synthetic drive systems? As the survivors of generations of counter selection, are natural drivers more robust than synthetic ones? Or are they limited by mutations where the designers of synthetic drivers are not?

Evolutionary impacts of drive

Theory suggests drive has major impacts on meiosis and gametogenesis, and may be a major reason for recombination itself. Has drive really had this much impact? Drive has also been proposed as a mechanism for promoting speciation by rapidly generating idiosyncratic differences between populations in reproductive genes, but the evidence is not yet conclusive. Finally, does drive really cause population or even species extinctions, and if so has this species-level selection impacted traits in extant organisms?

Glossary

Ascus: The sexual cell in fungi that undergoes meiosis to produce spores, typically eight

Autosomal drivers: Transmission distorters located on autosomal chromosomes

Centromere: The part of the chromosome attached to the spindle during cell division that allows chromosomes to separate during meiosis

CRISPR-Cas9: A genome editing technique involving a Cas9 nuclease, originally isolated from bacteria, that cuts target sites in the genome specified by complementary guide RNAs.

Drive suppressors: Factors that reduce the transmission rate of a driver

Enhancers: Genes that increase the transmission rate of a driver

Female meiotic drive: Biased transmission that arises during asymmetric female meiosis

Fisherian sex ratio selection: Theory predicting 1:1 male:female sex ratios because the fitness of the rarer sex is higher, all else being equal

Homing endonuclease genes: Transmission distorters that insert themselves onto the homologous chromosome during DNA repair, converting a heterozgyote into a homozygote for the element

Intra-genomic competition and conflict: The conflict between elements of the genome when the action of one reduces the transmission of the other, encompassing meiotic drive, selfish endosymbionts, transposable elements, homing-endonucleases and many others.

Karyotype: The number and large-scale structure of chromosomes of an individual

Male meiotic drive: Biased transmission that arises during male gamete production

Meiotic drive: Allelic variants that manipulate gamete production to ensure they are transmitted to more than a fair Mendelian proportion of gametes

Polyandry: Female mating with multiple males

Post-zygotic (non-drive) distortion mechanisms: Selection on zygotes, for example the natural death of low fitness zygotes

Segregation Distorter: An autosomal male driver in *Drosophila melanogaster* that kills sperm that do not carry a copy of it

Segregation distortion: Biased transmission to the next generation by the selfish action of a genetic element

X (or Y)-linked driver: Meiotic drive system located on a sex chromosome

Sperm killer: A male meiotic driver that impairs development of sperm that do not carry it

Spore killer: A meiotic driver in fungi that kills spores that do not carry a copy of it

Synthetic drive systems: Drivers that have been artificially engineered in the laboratory

Target sequence: Specific DNA sequence that is acted upon by another factor such as a driver or nuclease

***t* haplotype distorter**: an autosomal driver acting in the house mouse male that harms sperm that do not carry a copy of it

Telomere: A region of repetitive DNA that caps the ends of chromosomes

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Figure Legends

Figure 1. Meiotic drive. The first column shows schematics of three types of meiotic drive, with the second column showing a species that carries that drive system. (A) Female gametogenesis: driving chromosomes relegate rival chromosomes to the polar bodies. The polar bodies are lost, while the drive chromosome enters the egg. (B) Female drive occurs in monkeyflowers (C) Male gametogenesis: driving chromosomes ("D") cause sperm that carry the rival chromosome ("d") to die. (D) Sperm-killing segregation distortion in stalk-eyed flies. (E) Fungal spore production. Similar to male drivers, spore killers cause the death of spores that carry rival chromosomes. (F) A spore-killing system found in *Neurospora* fungi.

Images: (B) Lila Fishman (D) Gerald Wilkinson (F) Hanna Johannesson

Figure 2. *Anopheles gambiae* female. This is the primary species responsible for the transmission of *Plasmodium falciparum*—the parasite that causes malaria—to humans.