Haploid selection, sex-ratio bias, and transitions between sex-determining systems

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Abstract

Sex determination is remarkably dynamic; many taxa display shifts in the location of sex-determining loci or the evolution of entirely new sex-determining systems. Predominant theories for why we observe such transitions generally conclude that novel sex-determining systems are favoured by selection if they equalise the sex ratio or increase linkage with a locus that experiences different selection in males vs. females. We use population genetic models to extend these theories in two ways: (1) We consider the dynamics of loci very tightly linked to the ancestral sex-determining loci, e.g., within the non-recombining region of the ancestral sex chromosomes. Variation at such loci can favour the spread of new sex-determining systems in which the heterogametic sex changes (XY to ZW or ZW to XY) and the new sex-determining region is less closely linked (or even unlinked) to the locus under selection, which is not expected from previous theory. (2) We consider selection upon haploid genotypes either during gametic competition (e.g., pollen competition) or meiosis (i.e., non-Mendelian segregation), which can cause the zygotic sex ratio to become biased. Haploid selection can drive transitions between sex-determining systems without requiring selection to act differently in diploid males vs. females. With haploid selection, we find that transitions between male and female heterogamety can evolve where linkage with the sex-determining locus is either strengthened or weakened. Furthermore, we find that the selective forces to equalize the sex ratio are equally important to selective forces that generate skewed sex ratios when accounting for the spread of new sex chromosomes. This allows sex-ratio biases to increase or decrease with the spread of new sex chromosomes and implies that transitions between sex-determining systems cannot be simply predicted by selection to equalise the sex ratio. Overall, our models reveal that transitions between sex-determining systems, particularly transitions where the heterogametic sex changes, can be driven by loci in previously unpredicted genomic locations that experience selection during diploid and/or haploid phases.

Author summary

Systems of sex determination are strikingly diverse and labile in many clades. This poses the question: what drives transitions between sex-determining systems? Here, we use models to derive conditions under which new sex-determining systems spread. Prevailing views suggest that new sex-determining systems are favoured when they equalize the sex ratio and/or when they are more closely linked to genes that experience differential selection in males and females.

Our models include selection upon haploid genotypes (meiotic drive or gametic competition), which causes sex-ratio biases and occurs differently in male and female gametes. Surprisingly, we find the two forces (selection to equalize the sex ratio and the benefits of hitchhiking with driven alleles that distort the sex ratio) will often be equally strong, and thus neither is sufficient to explain the spread of new sex-determining systems in every case. Even more unexpectedly, we find that new sex-determining alleles can spread despite being less closely linked to selected loci. Therefore, our models predict loci in previously unexpected genomic locations and/or experiencing various types of selection (including haploid selection) can now be implicated as drivers of transitions between sex-determining systems.

Introduction

Animals and angiosperms exhibit extremely diverse sex-determining systems (reviewed in [1–5]). Among species with genetic sex determination (GSD), some taxa have heterogametic males (XY) and homogametic females (XX), including mammals and most dioecious plants [6]; whereas other taxa have homogametic males (ZZ) and heterogametic females (ZW), including Lepidoptera and birds. Within several taxa, the chromosome that harbours the master sex-determining locus changes. For example, transitions of the master sex-determining locus between chromosomes or the evolution of new master sex-determining loci where the heterogametic sex does not change (hereafter 'cis-GSD transitions') have occurred in Salmonids [7, 8], Diptera [9], and *Oryzias* [10]. In addition, many clades exhibit transitions between male and female heterogamety (XY↔ZW, hereafter 'trans-GSD transitions'), including snakes [11], lizards [12], eight of 26 teleost fish families [13], true fruit flies (Tephritids, [9]), amphibians [14], the angiosperm genus *Silene* [15], the angiosperm family *Salicaceae* [16, 17] and Coleoptera and Hemiptera (plate 2 [3]). Indeed, in some cases, both male and female heterogametic sex-determining systems can be found in the same species, as reported in houseflies [18], midges [19], frogs [20], cichlid fish [21], tilapia [22], sea bass [23], and lab-strains of Zebrafish [24, 25]. In addition, multiple transitions have occurred between genetic and environmental sex-determining systems (GSD↔ESD), e.g., in reptiles and fishes [5, 12, 13, 26–29]. In sum, accumulating evidence indicates that transitions between sex-determining systems are common [4].

It has been suggested that sex-ratio selection is a particularly dominant force in the evolution of sex determination because the sex ratio is directly determined by the sex-determining system (e.g., Bull, 1983, p 66-67 [1]; Buekeboom and Perrin, 2014, Chapter 7 [3]). Classic 'Fisherian' sex-ratio selection favours a 1:1 zygotic sex ratio when assuming that males and females are equally costly to produce [30, 31]. This follows from the fact that, for an autosomal locus, half of the genetic material is inherited from a male and half from a female [32]. Thus, if the sex ratio is biased, an individual of the rarer sex will, on average, contribute more genetic material to the next generation. Selection therefore typically favours mutants that increase investment in the rarer sex.

The evolution of sex determination is also thought to be strongly influenced by differences in selection between the sexes [3, 33, 34]. For example, loci experiencing sexual antagonism have been shown to favour the spread of new genetic sex-determining alleles that are closely linked [35–37]. Linkage allows a stronger favourable association to build up between a male-beneficial allele and a neo-Y allele, for example. Such associations can favour cis-GSD transitions [35], trans-GSD transitions [36], and new partially-masculinizing or partially-feminizing alleles in a population with ESD [37]. By similar logic, however, existing sexually-antagonistic alleles associated with the current sex-determining locus are expected to hinder the spread of a new sex-determining system [35, 36].

One novel feature of the models developed here is that we explicitly consider the maintenance of genetic variation around the ancestral sex-determining locus (e.g., within the non-recombining region of a sex chromosome). Counterintuitively, when linkage is tight

between the sex-determining locus and a selected locus, an allele good for females can be at higher frequency on the ancestral-Y than on the ancestral-X under a variety of forms of selection. This, in turn, can favour a new ZW sex-determining locus that has weaker linkage with loci under selection (a similar argument applies to ZW→XY transitions), which was not considered in previous theory [36]. That is, we show that selected loci in very tight linkage with the ancestral GSD locus can favour trans-GSD transitions during which linkage associations are actually weakened.

Most significantly, we include haploid selection (gametic competition or meiotic drive) in models describing cis-GSD, trans-GSD, and GSD to ESD transitions, which poses an apparent evolutionary problem. On one hand, haploid selection is typically sex-specific in that it usually occurs among gametes produced by one sex only [38–41]. Therefore, one might expect new sex-determining systems to benefit from close linkage with haploid selected loci, as found for sex-differences in diploid selection [35–37]. On the other hand, associations between sex-determining loci and haploid selected loci generate biased zygotic sex ratios, which should generally hinder the spread of new sex-determining systems.

Two previous studies have considered the spread of GSD with sex-specific meiotic drive [42, 43] under a limited number of possible genetic architectures and diploid selective regimes. Ubeda et al. (2015) [43] considers ancestral-ESD (with no sex-ratio bias) and numerically show that new GSD alleles can spread if they arise in linkage with meiotic drive loci. For example, a masculinizing allele spreads in association with an allele that is favoured during male meiosis, causing sex ratios to become male-biased and thereby suggesting that such beneficial associations overwhelm selection to balance the sex ratio. However, Kozielska et al. (2010) [42] consider meiotic drive on an ancestral GSD sex chromosome (creating a sex ratio bias). They find that new, completely unlinked, GSD systems can spread if they generate the rarer sex, creating a balanced sex ratio. That is, they conclude that Fisherian sex-ratio selection caused by haploid selection favours new GSD systems.

Here, we analytically find the conditions under which new GSD or ESD systems spread with generic linkage between the loci involved (and generic sex-specific haploid and diploid selection). Strikingly, we reconcile the results of Kozielska et al. (2010) [42] and Ubeda et al. (2015) [43] by showing when new GSD systems that increase *or* decrease linkage with loci spread. This result is qualitatively distinct from those for diploid selection alone [35, 36] and suggests that haploid selection is more likely to promote transitions between sex-determination systems. We also show that transitions involving haploid selection cannot be simply explained by invoking sex-ratio selection. In particular, under a wide range of conditions, we show that transitions in sex-determining system are favoured *equally strongly* in situations where sex-ratio biases increase or decrease (and in situations where sex-ratio biases are ancestrally present or absent). Finally, we show that ESD may not evolve, even if the sex ratio is initially biased by haploid selection, which would not be predicted by previous theories for transitions to ESD [1, 31, 32]. Together, our results suggest that selection to equalize the sex ratio is not an overwhelming force driving transitions between sex-determining systems.

Model

We consider transitions between ancestral and novel sex-determining systems using a three-locus model, each locus having two alleles (Fig 1). A full description of our model, including recursion equations, is given in S1 Appendix. Locus **X** is the ancestral sex-determining region, with alleles X and Y (or Z and W). Locus **A** is a locus under selection, with alleles *A* and *a*. Locus **M** is a novel sex-determining region, at which the null allele (*M*) is initially fixed in the population such that sex of zygotes is determined by the genotype at the ancestral sex-determining region, **X**; XX genotypes become females and XY become males (or ZW become females and ZZ become males). To evaluate the evolution of new sex-determining systems, we consider the spread of a novel sex-determining allele (*m*) at the **M** locus.

Here, we assume that the **M** locus is 'epistatically dominant' over the **X** locus such that zygotes with at least one m allele develop as females with probability k and as males with probability $1-k$, regardless of the **X** locus genotype. With $k=0$, the m allele is a masculinizer (a neo-Y allele) and with $k=1$ the m allele is a feminizer (a neo-W allele). With intermediate k, we can interpret m as an environmental sex-determination (ESD) allele, such that zygotes develop as females in a proportion (k) of the environments they experience. The assumption that derived sex-determining loci are epistatically dominant is motivated by empirical systems in which multiple sex determining alleles segregate (i.e., X, Y, Z, and W alleles present), such as, cichlid fish [21], platyfish (*Xiphophorus maculatus* [44]), houseflies (*Musca domestica* [45]), western clawed frogs (*Xenopus tropicalis* [46]) and *Rana rugosa* [20]. Nevertheless, our supplementary analysis file (S1 File) allows other dominance relationships between loci to be specified (see also [35] supplementary material for a numerical analysis).

We consider two forms of selection upon haploid genotypes, 'gametic competition' and 'meiotic drive'. During gametic competition, we assume that a representative sample of all gametes/gametophytes (hereafter gametes) compete for fertilization, which implies a polygamous mating system. Relative fitnesses during gametic competition are given by w°_{A} and w°_{a} ($\circ \in \{\female, \male\}$; see table 1). On the other hand, meiotic drive in our model only affects the segregation of gametes produced by heterozgotes. Specifically, gametes produced by Aa heterozgotes of sex $\circ$ bear allele A with probability α°. We note that competition between sperm produced by a single male (e.g. in a monogamous mating system) would be appropriately modelled as male meiotic drive, as only the frequency of gametes produced by heterozygotes would be affected. However, we do not consider scenarios in which there is competition among gametes produced by a small number of males/females (e.g., [47]).

In each generation, we census the genotype frequencies in male and female gametes before gametic competition. After gametic competition, conjugation between male and female gametes occurs at random. The resulting zygotes develop as males or females, depending on their genotypes at the **X** and **M** loci. Diploid males and females then experience viability and/or individual-based fertility selection, with relative fitnesses w°_{AA}, w°_{Aa}, and w°_{aa}. We do not consider fertility selection based on the mating pair or sexual selection. The next generation of gametes is produced by meiosis, during which recombination and sex-specific meiotic drive can occur. Recombination (i.e., an odd number of cross-overs) occurs between loci **X** and **A** with probability r, between loci **A** and **M** with probability R, and between loci **X** and **M** with probability ρ. Any linear order of the loci can be modelled with appropriate choices of r, R, and ρ (see Fig 1A and S1 Table). Our model is entirely deterministic and hence ignores chance fluctuations in allele frequencies due to genetic drift.

Table 1. Relative fitness of different genotypes in sex $\circ \in \{\female, \male\}$

Genotype	Relative fitness during gametic competition
A	$w^{\circ}_{A} = 1 + t^{\circ}$
a	$w^{\circ}_{a} = 1$
Genotype	Relative fitness during diploid selection
AA	$w^{\circ}_{AA} = 1 + s^{\circ}$
Aa	$w^{\circ}_{Aa} = 1 + h^{\circ}s^{\circ}$
aa	$w^{\circ}_{aa} = 1$
Genotype	Transmission during meiosis in Aa heterozygotes
A	$\alpha^{\circ} = 1/2 + \alpha^{\circ}_{\Delta}/2$
a	$1 - \alpha^{\circ} = 1/2 - \alpha^{\circ}_{\Delta}/2$

The model outlined above describes both ancestral XY and ZW sex-determining systems. Without loss of generality, we refer to the ancestrally heterogametic sex as male and the

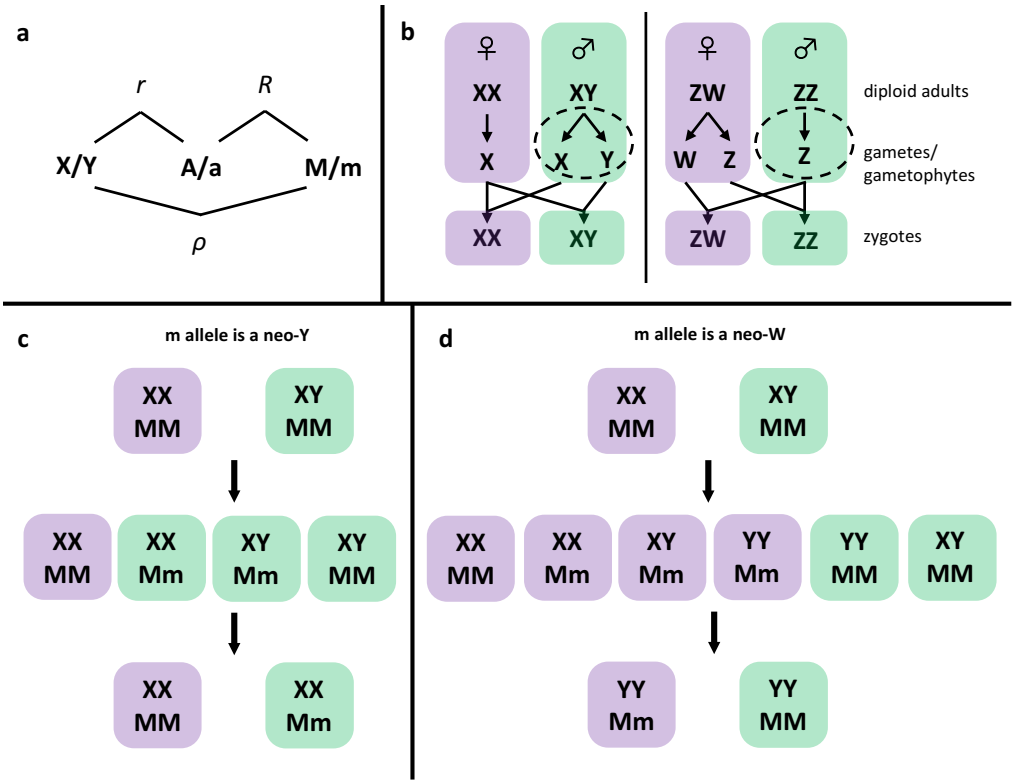

Fig 1. Outline of model features. Panel A: Recombination rate parameters between the ancestral-sex-determining locus (**X**, here assumed to have alleles X and Y), a locus under selection (**A**, with alleles *A* and *a*), and a new sex-determining locus (**M**, with alleles *M* and *m*). If $r < 1/2$, then associations between ancestral sex-determining alleles and selected alleles can be maintained in males. Panel B: Haploid selection is often sex-specific, occurring during haploid production or competition in either males or females. For example, haploid selection in males only is represented by the dashed circle. If X or Y alleles remain associated with alleles that experience haploid selection in males ($r < 1/2$), then zygotic sex ratios can become biased because either X- or Y-bearing male gametes/gametophytes will be more abundant after haploid selection. However, the zygotic sex ratio is not biased by male haploid selection in ZW sex-determining systems. Similarly, zygotic sex-ratio biases can arise if haploid selected alleles are associated with new sex-determining alleles ($R < 1/2$). Panel C: During cis-GSD transitions (XY to XY or ZW to ZW), a neo-Y allele spreads to pseudo-fixation (its maximum frequency among male gametes) and the ancestral Y allele is lost. Panel D: During trans-GSD transitions (XY to ZW or ZW to XY), a neo-W allele spreads to pseudo-fixation (its maximum frequency among female gametes) and the ancestral X allele is lost. Neo-W alleles allow Y-associated alleles into females, which may impede or aid their spread.

ancestrally homogametic sex as female. That is, we primarily describe an ancestral XY sex-determining system but our model is equally applicable to an ancestral ZW sex-determining system (relabelling the ancestrally heterogametic sex as female and the ancestrally homogametic sex as male and switching the labels of males and females throughout). We use a superscript to specify the ancestral sex-determining system described, e.g., $^{(XY)}$ for ancestral XY sex-determination.

Results

Generic invasion by a neo-Y or neo-W

We begin by describing the precise conditions under which new sex determining alleles can spread within a population. These general conditions then allow us to consider several special cases of interest in subsequent sections.

The evolution of a new sex-determining system requires that a rare mutant allele, m, at the novel sex-determining locus, **M**, increases in frequency when rare. This is determined by the leading eigenvalue ($\lambda_m^{(XY)}$) of the system of eight equations describing the frequency of eggs and sperm carrying the m allele in the next generation (equations S1.1). This system simplifies substantially for an epistatically dominant neo-Y ($k = 0$) or neo-W ($k = 1$), see S3 Appendix. The leading eigenvalue for a rare neo-Y or neo-W allele, $m \in \{Y', W'\}$, is the largest value of x that solves $x^2 + bx + c = 0$. The coefficients are $b = -(\Lambda_{mA}^{(XY)} + \Lambda_{ma}^{(XY)}) + (\chi_{mA}^{(XY)} + \chi_{ma}^{(XY)})$ and $c = (\Lambda_{mA}^{(XY)} - \chi_{mA}^{(XY)})(\Lambda_{ma}^{(XY)} - \chi_{ma}^{(XY)}) - \chi_{mA}^{(XY)}\chi_{ma}^{(XY)}$, where $\Lambda_{mi}^{(XY)} > 0$ is the multiplicative growth rate (which we will call the "haplotypic growth rate") of the neo-sex determination allele m on background $i \in \{A, a\}$ without accounting for loss due to recombination ($R = 0$), and $\chi_{mi}^{(XY)} > 0$ is the rate at which mutant haplotypes on background $i \in \{A, a\}$ recombine onto the other **A** locus background in heterozygotes (proportional to R; we call this the "dissociative force" as it breaks down linkage disequilibrium), see Table 2. In the ancestral population, it is convenient to follow the frequency of the A allele among female gametes (eggs), $p_X^{\female}$, and among X-bearing, $p_X^{\male}$, and among Y-bearing, $p_Y^{\male}$, male gametes (sperm/pollen). We also track the fraction of male gametes that are Y-bearing, q, which may deviate from $1/2$ due to meiotic drive in males. We will consider only equilibrium frequencies of alleles, $\hat{p}_i^{\circ}$, and Y-bearing male gametes, $\hat{q}$, when calculating the eigenvalues.

Table 2. Parameters determining invasion of mutant neo-Y and neo-W alleles into an ancestrally XY system

m is a neo-Y ($k = 0$)
$\Lambda_{Y'A}^{(XY)} = (2\zeta)^{-1}\left[\hat{p}_X^{\female} w_A^{\female} w_A^{\male} w_{AA}^{\male} + (1-\hat{p}_X^{\female}) w_a^{\female} w_A^{\male} w_{Aa}^{\male}(1+\alpha_\Delta^{\male})\right] / \left(\bar{w}_H^{\female}\bar{w}_H^{\male}\bar{w}_D^{\male}\right)$
$\Lambda_{Y'a}^{(XY)} = (2\zeta)^{-1}\left[(1-\hat{p}_X^{\female}) w_a^{\female} w_a^{\male} w_{aa}^{\male} + \hat{p}_X^{\female} w_A^{\female} w_a^{\male} w_{Aa}^{\male}(1-\alpha_\Delta^{\male})\right] / \left(\bar{w}_H^{\female}\bar{w}_H^{\male}\bar{w}_D^{\male}\right)$
$\chi_{Y'A}^{(XY)} = R(2\zeta)^{-1}\left[(1-\hat{p}_X^{\female}) w_a^{\female} w_A^{\male} w_{Aa}^{\male}(1+\alpha_\Delta^{\male})\right] / \left(\bar{w}_H^{\female}\bar{w}_H^{\male}\bar{w}_D^{\male}\right)$
$\chi_{Y'a}^{(XY)} = R(2\zeta)^{-1}\left[\hat{p}_X^{\female} w_A^{\female} w_a^{\male} w_{Aa}^{\male}(1-\alpha_\Delta^{\male})\right] / \left(\bar{w}_H^{\female}\bar{w}_H^{\male}\bar{w}_D^{\male}\right)$
m is a neo-W ($k = 1$)
$\Lambda_{W'A}^{(XY)} = [2(1-\zeta)]^{-1}\left[\bar{p}^{\male} w_A^{\male} w_A^{\female} w_{AA}^{\female} + (1-\bar{p}^{\male}) w_a^{\male} w_A^{\female} w_{Aa}^{\female}(1+\alpha_\Delta^{\female})\right] / \left(\bar{w}_H^{\female}\bar{w}_H^{\male}\bar{w}_D^{\female}\right)$
$\Lambda_{W'a}^{(XY)} = [2(1-\zeta)]^{-1}\left[(1-\bar{p}^{\male}) w_a^{\male} w_a^{\female} w_{aa}^{\female} + \bar{p}^{\male} w_A^{\male} w_a^{\female} w_{Aa}^{\female}(1-\alpha_\Delta^{\female})\right] / \left(\bar{w}_H^{\female}\bar{w}_H^{\male}\bar{w}_D^{\female}\right)$
$\chi_{W'A}^{(XY)} = R[2(1-\zeta)]^{-1}\left[(1-\bar{p}^{\male}) w_a^{\male} w_A^{\female} w_{Aa}^{\female}(1+\alpha_\Delta^{\female})\right] / \left(\bar{w}_H^{\female}\bar{w}_H^{\male}\bar{w}_D^{\female}\right)$
$\chi_{W'a}^{(XY)} = R[2(1-\zeta)]^{-1}\left[\bar{p}^{\male} w_A^{\male} w_a^{\female} w_{Aa}^{\female}(1-\alpha_\Delta^{\female})\right] / \left(\bar{w}_H^{\female}\bar{w}_H^{\male}\bar{w}_D^{\female}\right)$

$\hat{p}_X^{\female}$ is the frequency of A among female gametes. $\bar{p}^{\male} = (1-\hat{q})\hat{p}_X^{\male} + \hat{q}\hat{p}_Y^{\male}$ is the average frequency of the A allele among X- and Y-bearing male gametes. ζ is the zygotic sex ratio (fraction male). $\bar{w}_D^{\circ}$ is the mean fitness of diploids of sex $\circ \in \{\female, \male\}$. $\bar{w}_H^{\circ}$ is the mean fitness of haploids from sex $\circ$, see S2 Table. R is the rate of recombination between the neo-sex-determiner and the selected locus. Selection terms (w_i°, α_Δ°) are described in Table 1.

The new sex-determining allele increases in frequency when rare when the largest eigenvalue is greater than one ($\lambda_m^{(XY)} > 1$). If both haplotypic growth rates are greater than one ($\Lambda_{mA}^{(XY)}, \Lambda_{ma}^{(XY)} > 1$), then the new sex-determining allele invades regardless of the rate of recombination between the new sex-determining locus and the selected locus (R), see S3 Appendix for details. Conversely, if both haplotypic growth rates are less than one ($\Lambda_{mA}^{(XY)}, \Lambda_{ma}^{(XY)} < 1$), then invasion can never occur. Finally, if only one haplotypic growth rate is greater than one, the new sex-determining allele can always invade when arising at a locus that is tightly linked to the selected locus ($R \approx 0$). Furthermore, it can be shown that the leading eigenvalue declines with R, and invasion requires that R is sufficiently small such that:

$$\chi_{ma}^{(XY)} / \left(\Lambda_{ma}^{(XY)} - 1\right) + \chi_{mA}^{(XY)} / \left(\Lambda_{mA}^{(XY)} - 1\right) < 1. \quad (1)$$

This condition may or may not be satisfied for the full range of locations of the new sex-determining locus, including $R = 1/2$, depending on the nature of selection. Interpreting this condition, if we assume that only the mA haplotype would increase in frequency when $R = 0$ ($\Lambda_{ma}^{(XY)} < 1 < \Lambda_{mA}^{(XY)}$) then the first term on the left-hand side of (1) is negative and invasion requires that growth rate of mA haplotypes ($\Lambda_{mA}^{(i)} - 1 > 0$) and the rate at which they are produced by recombination ($\chi_{ma}^{(i)}$) are sufficiently large relative to the rate of decline of ma haplotypes ($1 - \Lambda_{ma}^{(i)} > 0$) and the rate at which m and A are dissociated by recombination ($\chi_{mA}^{(i)}$).

We draw three main points about the generic invasion of neo-Y and neo-W mutations from Table 2. First, invasion by a neo-Y (neo-W) does not directly depend on the fitness of female (male) diploids. This is because a dominant neo-Y (neo-W) is always found in males (females), and therefore the frequency of the neo-Y (neo-W), m, only changes in males (females), Fig 1C,D. Second, Fisherian sex-ratio selection will favour the spread of a neo-W and inhibit the spread of a neo-Y if the ancestral zygotic sex ratio is biased towards males (i.e., the first factor of the $\Lambda_{mi}^{(XY)}$ is greater than one for a neo-W and less than one for a neo-Y when $\zeta > 1/2$), as might occur when the ancestral sex-determining locus is linked to a locus experiencing meiotic drive in males, for example. However, the spread of a neo-Y (neo-W) also depends on the male (female) fitness of associated alleles (see terms involving equilibrium allele frequencies, $\hat{p}$'s), including haploid selection that additionally biases the sex ratio. This implies that both Fisherian selection to equalize the sex-ratio and selection favoring sex-linked drivers that distort the sex ratio play roles in the invasion dynamics of a new sex-determining allele, allowing the sex ratio to become more or less biased during a transition (as previously shown in two special cases; [42, 43]). And thirdly, Table 2 also shows that cis- and trans-GSD transitions are qualitatively different. This is because, in an ancestrally XY system, a gamete with the neo-Y always pairs with a female gamete containing an X, Fig 1C. By contrast, a gamete with a neo-W can pair with an X- or Y-bearing male gamete, Fig 1D. Consequently, neo-W-bearing females obtain a different frequency of A alleles from mating (when $\hat{p}_X^{\male} \neq \hat{p}_Y^{\male}$) compared to ancestral (MM) females, which can inhibit or favour its spread.

In order to explicitly determine the conditions under which a new sex-determining allele spreads, we must calculate the equilibrium frequency of the A allele (i.e., $\hat{p}_X^{\female}$, $\hat{p}_X^{\male}$, and $\hat{p}_Y^{\male}$) and Y-bearing male gametes ($\hat{q}$) in the ancestral population. Because only the **A** locus experiences selection directly, any deterministic evolution requires that there be a polymorphism at the **A** locus. Polymorphisms can be maintained by mutation-selection balance or transiently present during the spread of beneficial alleles. Here, however, we focus on polymorphisms maintained by selection, which can maintain alleles at intermediate frequencies for longer periods. Such polymorphisms can be maintained by heterozygote advantage, sexually-antagonistic selection, ploidally-antagonistic selection, or a combination [48]. We can analytically calculate the allele frequency of the A allele using two alternative simplifying assumptions: (1) the **A** locus is tightly linked to the non-recombining region around the ancestral sex-determining locus ($r \approx 0$) or (2) selection is weak relative to recombination (s°, t°, $\alpha_\Delta^\circ << r$).

Tight linkage with the ancestral sex-determining locus ($r \approx 0$)

The ancestral equilibrium allele frequencies and their stability conditions are given in S2 Appendix. When there is complete linkage between the ancestral sex-determining locus and the **A** locus ($r = 0$), either the A allele or the a allele must be fixed in gametes containing a Y allele. Because the labelling of alleles is arbitrary, we will assume that the a locus is fixed in gametes with a Y ($p_Y^{\male} = 0$), without loss of generality. If there are two alleles maintained at the **A** locus, the A allele can be fixed ($\hat{p}_X^{\female} = \hat{p}_X^{\male} = 1$) or segregating at an intermediate frequency ($0 < \hat{p}_X^{\female}, \hat{p}_X^{\male} < 1$) in gametes with an X.

We find that a neo-Y allele can never invade an ancestral XY system that already has tight linkage with the locus under selection ($\lambda_{Y'}^{(XY)} \leq 1$ when $r = 0$, for details see S1 File). In essence, through tight linkage with the **A** locus, the ancestral Y becomes strongly specialized on the allele that has the highest fitness across male haploid and diploid phases. It is thus not possible for a neo-Y to create males that have higher fitness than the ancestral Y, and cis-GSD transitions are never favoured.

Neo-W alleles, on the other hand, can invade an ancestral XY system because, under some conditions the W can become more strongly specialized for females (the full invasion conditions are given in S3 Appendix; equations S3.1 and S3.2). Thus,

Conclusion 1A: **Selection on loci in or near the non-recombining region around the sex-determining locus ($r \approx 0$) prevents cis-GSD transitions (XY ↔ XY, ZW ↔ ZW) but can spur trans-GSD transitions (XY ↔ ZW).**

Conclusion 1A does not depend on the form of selection maintaining a polymorphism (sexually-antagonistic selection, overdominance, ploidally-antagonistic selection, or some combination, Fig 2, S2 Fig, S8 Fig, and S3 Fig). The conditions become more restrictive, however, with increasing recombination (R) between the new sex-determining locus and the selected locus. The invasion of completely unlinked neo-W alleles ($R = 1/2$) can occur with overdominance in males or with haploid selection (e.g., a case with male drive opposed by diploid selection in [42]) but is not possible with only sexually-antagonistic selection where selection is directional in each diploid sex (see S1 File). Here, we focus on cases where there is no haploid selection (Fig 2A) and discuss the additional effect of haploid selection in S3 Appendix.

add to Appendix: In absence of haploid selection Conclusion 1A can also be reached from Equation 7 in [36]; for example, with no polymorphism on the Y ($V_Y = 0$) and an allelic substitution favoured in females ($\alpha^f, \alpha_X^f > 0$) a loosely linked neo-W can invade given the allelic substitution is sufficiently disfavoured on the X in males ($\alpha_X^m < -2\alpha_X^f$), although it is unclear from their implicit equation if and when such an equilibrium is stable.

The reason that neo-W-A haplotypes can spread ($\Lambda_{W'A}^{(XY)} > 1$) is because they can sometimes produce higher fitness females that are unleashed from counterselection in males. Broadly, this is possible because ancestral X alleles are found in both males and females and are therefore unable to perfectly specialize on the 'female-beneficial' allele. For example, when A is female beneficial and a is male beneficial, a polymorphism can be maintained on the X when the A allele is strongly counterselected in males ($w_{Aa}^{\male}$ sufficiently small relative to $w_{aa}^{\male}$). Neo-Ws, however, spend no time in males and can build stronger associations with the female-beneficial allele (see gray region in Fig 3A).

When only one neo-W haplotype has growth rate greater than one (see Fig 3), a neo-W allele can invade as long as Eq (1) is satisfied, which may require that the recombination rate, R, is small enough. Nevertheless, because we assume here that r is small, these results indicate that a more loosely linked sex-determining region ($r < R$) can spread. For example, tightly sex-linked loci that experience sexually-antagonistic selection can drive trans-GSD transitions in which the

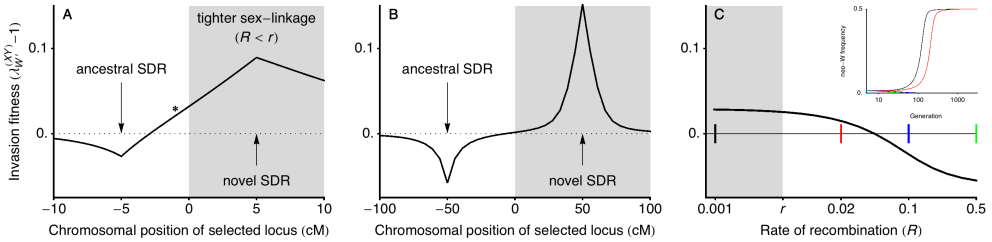

Fig 2. Transitions between XY and ZW systems can occur even when the new sex-determining locus is less tightly linked to a locus under sexually-antagonistic selection (no haploid selection). In panel A, linkage is initially tight relative to selection and a neo-W can invade even when it is less tightly linked with the selected locus ($r < R$; unshaded region around *). In panel B, linkage is loose enough relative to selection that the analytical results assuming weak selection hold, and a neo-W allele can only invade when it arises at a locus more tightly linked with the selected locus ($R < r$; shaded region). In panel C we vary the recombination rate between the neo-W and the selected locus (R) for a fixed recombination rate between the ancestral sex-determining locus and the selected locus ($r = 0.005$). Coloured markers show recombination rates for which the temporal dynamics of invasion are plotted in the inset, demonstrating that neo-W alleles can reach pseudo-fixation if they are more (black) or less (red) closely linked to a locus experiencing sexually-antagonistic selection. A very loosely linked neo-W does not spread in this case (blue and green lines overlap and go to 0 in inset). Fitness parameters are: $w^{\varphi}_{AA} = 1.05$, $w^{\sigma}_{aa} = 1.2$, $w^{\varphi}_{aa} = w^{\sigma}_{AA} = 0.85$, $w^{\circ}_{Aa} = 1$.

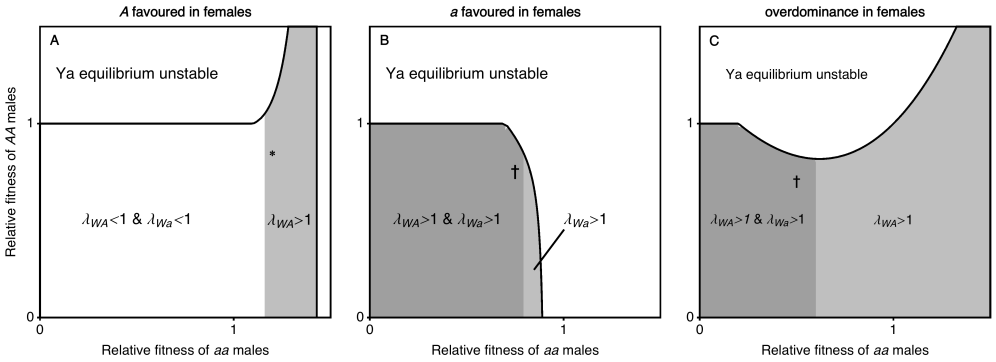

Fig 3. When the ancestral XY locus is tightly linked to a locus under selection ($r = 0$), one or both neo-W haplotypes can spread (no haploid selection). We vary the fitness of male homozygotes relative to heterozygotes ($w^{\circ}_{Aa} = 1$) and only consider stable equilibria at which both **A** locus alleles are maintained and the *a* allele is initially fixed on the Y (region outlined). Here, selection in females can favour the *A* allele (panel A, $w^{\varphi}_{aa} = 0.85$, $w^{\varphi}_{AA} = 1.05$), favour the *a* allele (panel B, $w^{\varphi}_{aa} = 1.05$, $w^{\varphi}_{AA} = 0.85$), or be overdominant (panel C, $w^{\varphi}_{aa} = w^{\varphi}_{AA} = 0.6$). If either haplotypic growth rate ($\Lambda^{(XY)}_{W'A}$ or $\Lambda^{(XY)}_{W'a}$) is greater than one, then a rare neo-W allele can spread for, at least, some values of $R > r$. The parameter values marked with an asterisk correspond to the fitnesses used in Fig 2C. Where both haplotypic growth rates are greater than one, a neo-W will spread when rare, regardless of linkage with the selected locus (for any R). S1 Fig shows the dynamics arising with the parameters marked with a dagger.

new sex-determining locus is less closely linked to the locus under selection (Fig 2).

Given that the *a* allele is fixed on the Y and can be considered ancestrally 'male-beneficial', it is surprising that neo-W-*a* haplotypes can sometimes be favoured by selection in females

($\Lambda_{W'a}^{(XY)} > 1$). Again, this occurs because ancestral X alleles experience selection in both males and females, and conditions can arise where increases in the *a* allele would be favored in females too. For example, if there is overdominance in males, X-*A* Y-*a* males have high fitness and the *A* allele is favoured by selection on the X background in males. Therefore, the *A* allele can be polymorphic or even fixed on the X background despite selection favouring the *a* allele in females (e.g., see outlined region in Fig 3B and [49, 50]). In such cases, neo-W-*a* haplotypes can spread because they create more *Aa* and *aa* females when pairing with an X-bearing gamete from males and because they bring Y-*a* haplotypes into females, where it has higher fitness (Fig 1D).

In some cases, both W-*A* and W-*a* haplotypes can spread. For example, when *AA* individuals have low fitness in females yet the *A* is polymorphic or fixed on the X background due to overdominance in males (Fig 3B and 3C), both neo-W-*A* and neo-W-*a* haplotypes produce fewer unfit *AA* females. This is true for the neo-W-*A* haplotype because it can pair with a Y-*a* haplotype and still be female. Wherever both haplotypic growth rates are greater than one, invasion by a neo-W is expected regardless of its linkage with the selected locus (i.e., for any R, see S1 Fig and S2 Fig for examples). As a consequence, evolution can favor a new sex determination system on a different chromosome, despite the fact that this unlinks the sex determination locus from the selected locus.

Assuming selection is weak relative to recombination, van Doorn and Kirkpatrick [36] showed that invasion by a neo-W allele occurs under the same conditions as its fixation in females. An equivalent analysis is not possible where recombination rates are low. However, numerical simulations demonstrate that, with tight sex linkage, neo-Y or neo-W alleles do not necessarily reach fixation in males or females, respectively, which can lead to the stable maintenance of a mixed sex-determining system, in which X, Y, Z, and W alleles all segregate (e.g., S9 FigB,C).

From the arguments above we conclude that

Conclusion 1B: **With tight linkage between a selected locus and the ancestral sex determination system ($r \approx 0$), selection to better specialize on the ancestrally-non-heterogametic sex can drive trans-GSD transitions (XY $\leftrightarrow$ ZW) that weaken sex-linkage ($r < R \leq 1/2$; potentially even shifting sex determination to a different chromosome) and/or lead to polymorphic sex-determination systems.**

Adding haploid selection (S3 Appendix) we also conclude that

Conclusion 1C: **Haploid selection allows trans-GSD transitions that weaken sex-linkage ($r < R \leq 1/2$; potentially even shifting sex determination to a different chromosome) even when selection is sexually-antagonistic with directional selection in each diploid sex. With initially tight linkage, these transitions equalize the sex ratio by reducing linkage to alleles under haploid selection.**

Loose linkage with the ancestral sex-determining region

Here we assume that selection is weak (s°, t°, α_Δ° of order ϵ, where ϵ is some number much less than one) and thus implicitly assume that all recombination rates (r, R and ρ) are large relative to selection. To leading order in selection,

$$\lambda_{Y'}^{(XY)} = 1 + \frac{1}{4} V_A S_A^2 \frac{(r-R)}{rR} + O\left(\epsilon^3\right) \tag{2}$$

and

$$\lambda_{W'}^{(XY)} = \lambda_{Y'}^{(XY)} + \left[\left(2\alpha_\Delta^{\male} - 2\alpha_\Delta^{\female} + t^{\male} - t^{\female}\right)\left(\hat{p}_Y^{\male} - \hat{p}_X^{\male}\right)/2\right] + O\left(\epsilon^3\right) \tag{3}$$

where $V_A = \bar{p}(1-\bar{p})$ is the variance in the equilibrium frequency of A and $S_A = (\bar{s}^{\male} + \alpha_\Delta^{\male} + t^{\male}) - (\bar{s}^{\female} + \alpha_\Delta^{\female} + t^{\female})$ describes sex differences in selection for the A versus a allele across diploid selection, meiosis, and gametic competition. The diploid selection term, $\bar{s}^\circ = \left[\bar{p}s^\circ + (1-\bar{p})h^\circ s^\circ\right] - \left[\bar{p}h^\circ s^\circ + (1-\bar{p})\right]$, is the difference in fitness between A and a alleles in diploids of sex $\circ \in \{\female, \male\}$, where $\bar{p}$ is the leading-order probability of mating with an A-bearing gamete from the opposite sex (equation S2.3) and the difference in A-allele-frequency among Y-bearing sperm versus X-bearing sperm is, at equilibrium, $\hat{p}_Y^{\male} - \hat{p}_X^{\male} = V_A S_A (1-2r)/(2r)$.

Eq (2) demonstrates that, under weak selection, a neo-Y allele will invade an XY system ($\lambda_{Y'}^{(XY)} > 1$) if and only if it is more closely linked to the selected locus than the ancestral sex-determining locus (i.e., if $R < r$; note that $V_A S_A^2$ is strictly positive as long as **A** is polymorphic). This echoes our results above where a neo-Y could never invade if $r \approx 0$. It is also consistent with the results of [35], who considered diploid selection only and also found that cis-GSD transitions can only occur when the new sex-determining locus is more closely linked to a locus under sexually-antagonistic selection.

Without haploid selection ($t^\circ = \alpha_\Delta^\circ = 0$), the spread of a neo-W is equivalent to the spread of a neo-Y ($\lambda_{W'}^{(XY)} = \lambda_{Y'}^{(XY)}$), when selection is weak relative to recombination, such that trans-GSD transitions can also occur only if the new sex-determining locus is more closely linked to a locus under selection ($R < r$), as found by [36]. When there is haploid selection, invasion also typically occurs when the neo-W is more closely linked to the selected locus than the ancestral sex-determining region (Fig 4). For example, if the **A** locus is unlinked to the ancestral sex-determining locus ($r = 1/2$, which implies that $\hat{p}_Y^{\male} - \hat{p}_X^{\male} = 0$), a more closely linked neo-W ($R < 1/2$) can always invade. However, with haploid selection and some ancestral sex-linkage ($r < 1/2$; allowing allele frequency differences on the X and Y), the term in square brackets in Eq (3) can be positive. This implies the following two conclusions:

Conclusion 2A: **New sex-determining alleles (causing cis- *or* trans-GSD transitions) can spread if they arise in closer linkage with a locus that experiences selection than the ancestral-sex-determining locus ($R < r$).**

Conclusion 2B: **New sex-determining alleles (causing trans-GSD transitions) can spread if they arise in looser linkage with a locus that experiences selection than the ancestral-sex-determining locus ($r < R$), requiring haploid selection and some initial sex-linkage ($r < 1/2$) as necessary conditions.**

To clarify the parameter space under which invasion occurs despite looser sex-linkage ($\lambda_{W'}^{(XY)} > 1$ despite $R > r$; Conclusion 2B), we focus on the special case where $R = 1/2$ and $r < 1/2$ (e.g., the selected locus is on the ancestral sex chromosome and the novel sex-determining locus arises on an autosome). In Table 3 we give the conditions where invasion occurs when we further assume that haploid selection only occurs in one sex (e.g., during male meiosis only) and dominance coefficients are equal in the two sexes, $h^{\female} = h^{\male}$. These special cases indicate that neo-W invasion occurs for a large fraction of the parameter space, even if the neo-W uncouples the sex-determining locus from a locus under selection. Surprisingly, neo-W alleles can spread when they are more closely *or* more loosely linked to a locus that experiences haploid selection, as shown in Fig 4 (c.f., Fig 2A for diploid sexually-antagonistic selection alone). In Fig 5, we also show examples of trans-GSD transitions in sex determination during which linkage with a haploid selected locus increases *or* decreases, increasing or decreasing sex-ratio bias. When sex-linkage decreases ($R > r$), neo-W alleles can benefit from Y-associated alleles that have higher fitness in the female diploid phase but then dissociate from these alleles through recombination before any subsequent haploid selection.

Our model allows us to analytically compare transitions in genetic sex-determination where

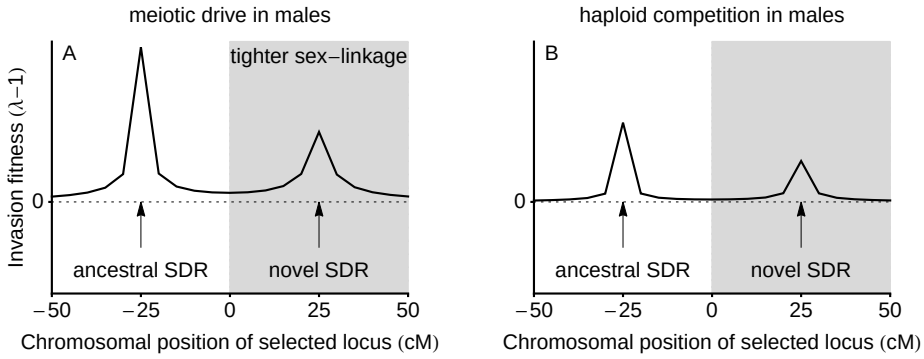

Fig 4. Ploidally-antagonistic selection allows a less tightly linked neo-W allele to invade. In panel A, male drive ($\alpha_{\Delta}^{\male} = -1/20$, $t^{\circ} = \alpha_{\Delta}^{\female} = 0$) opposes selection in diploids (no sex-differences: $s^{\circ} = 1/10$, $h^{\circ} = 7/10$). In panel B, gametic competition in males ($t^{\male} = -1/10$, $t^{\female} = \alpha_{\Delta}^{\circ} = 0$) opposes selection in diploids (sex-differences: $s^{\male} = 3/20$, $s^{\female} = 1/20$, $h^{\circ} = 7/10$). In either case the new sex-determining allele can invade regardless of R.

Table 3. Invasion conditions for a neo-W allele at an unlinked locus ($R = 1/2$) into an ancestral XY system with linkage ($r < 1/2$) and a single form of haploid selection

Scenario	Assumptions	neo-W spreads ($\lambda_{W'}^{(XY)} > 1$) if
male drive only	$h^{\male} = h^{\female}$, $t^{\female} = t^{\male} = \alpha_{\Delta}^{\female} = 0$	$s^{\female} s^{\male} > 0$
female drive only	$h^{\male} = h^{\female}$, $t^{\female} = t^{\male} = \alpha_{\Delta}^{\male} = 0$	$s^{\female} s^{\male} > 0$
male gametic competition only	$h^{\male} = h^{\female}$, $t^{\female} = \alpha_{\Delta}^{\female} = \alpha_{\Delta}^{\male} = 0$	$s^{\female}(s^{\male} - s^{\female}) > 0$
female gametic competition only	$h^{\male} = h^{\female}$, $t^{\male} = \alpha_{\Delta}^{\female} = \alpha_{\Delta}^{\male} = 0$	$s^{\male}(s^{\female} - s^{\male}) > 0$

sex-ratio bias increases, decreases, or remains equal. For example, if there is meiotic drive in males only ($\alpha_{\Delta}^{\male} \neq 0$, $\alpha_{\Delta}^{\female} = 0$), without gametic competition ($t^{\female} = t^{\male} = 0$) the zygotic sex ratio is initially biased only when the ancestral sex-determining system is XY (Fig 1A and Fig 5A) and not ZW (Fig 5B). If Fisherian sex-ratio selection were dominant, we would thus expect a difference in the potential for XY to ZW and ZW to XY transitions. However, invasion by a neo-W allele into an XY system and invasion by a neo-Y allele into a ZW system occur under the same conditions ($\lambda_{Y'}^{(XY)} = \lambda_{W'}^{(ZW)}$ and $\lambda_{W'}^{(XY)} = \lambda_{Y'}^{(ZW)}$, at least to order ϵ^2), implying that,

Conclusion 3: **When selection is weak relative to recombination, the presence of haploid selection equally favors the spread of a new sex chromosome that reduces sex-ratio bias (benefiting from Fisherian sex ratio selection) as a new sex chromosome that generates a sex-ratio bias (benefiting from drive)"**

For example, in Fig 5A neo-W alleles invade an ancestral-XY system where females are initially rare, equalizing the sex ratio (as occurs in [42]). However, Fig 5B shows that a neo-Y can invade the resulting ZW system under the same conditions. When $R < 1/2$, the invading neo-Y becomes associated with the male meiotic drive allele and the zygotic sex ratio actually evolves to become male-biased (as occurs in [43], beginning from ESD). In this case, the neo-Y spreads because it is often found in males and can, if it carries the driven allele a, benefit from haploid selection in males (Fig 5B).

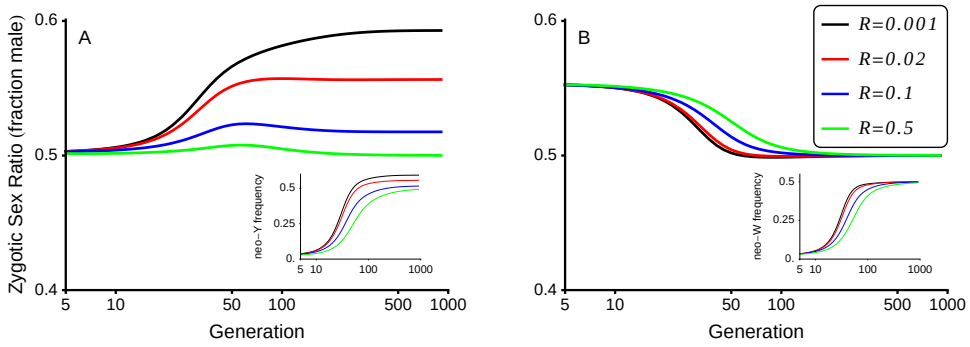

Fig 5. Fisherian sex-ratio selection alone is not a good predictor of turnover between sex-determining systems. In this figure, selection is ploidally antagonistic with haploid selection favouring the a allele during male meiosis. In panel A, male meiotic drive in an ancestral XY system causes a male bias (see Fig 1B), allowing a neo-W to invade and replace the ancestral sex-determining system (inset shows neo-W frequency rising to fixation among female gametes), which balances the zygotic sex ratio. In panel B, male drive in an ancestral ZW system has no effect on the zygotic sex ratio yet a neo-Y can invade and replace the ancestral sex-determining system (inset shows neo-Y frequency rising to fixation among male gametes). Parameters: $s^{\varphi} = s^{\sigma} = 0.2$, $h^{\varphi} = h^{\sigma} = 0.7$, $t^{\varphi} = t^{\sigma} = \alpha_{\Delta}^{\varphi} = 0$, $\alpha_{\Delta}^{\sigma} = -0.1$, $r = 0.02$.

While equalizing the sex ratio and benefiting from drive are two primary reasons why haploid selection spurs sex chromosome transitions, more complex situations also arise. For example with $R = 1/2$ in Fig 5B (green curve), the neo-Y allele spreads despite the fact that it cannot benefit from drive because free recombination moves it randomly between driven and non-driven backgrounds. Nevertheless, the unlinked neo-Y can spread because males bearing it more often carry the non-driven allele A and have higher average diploid fitness compared to ZZ males, which bear a high frequency of the driven allele (since $r < R$).

Environmental sex determination

We next consider the case where the new sex-determining mutation, m, causes sex to be determined probabilistically or by heterogeneous environmental conditions (environmental sex determination, ESD), with individuals carrying allele m developing as females with probability k. In our deterministic model this means the fraction female in the subpopulation containing m is exactly k, even when m is rare (i.e., ESD does not introduce any additional variance in sex determination). Here, we assume that the environmental conditions that determine sex does not differentially affect the fitness of males versus females. Such correlations can favour environmental sex-determining systems by allowing each sex to be produced in the environment in which it has highest fitness; in the absence of these correlations, previous theory would predict that ESD is favoured when it produces more equal sex ratios than the ancestral system (see reviews by [1, 31, 32]).

The characteristic polynomial determining the leading eigenvalue (equations S1.1) does not factor for ESD ($0 < k < 1$) as it does for a neo-Y ($k = 0$) or neo-W ($k = 1$) allele. We therefore focus on weak selection here, where the leading eigenvalue is

$$\begin{aligned}\lambda_{ESD'}^{(XY)} =& 1 + \frac{(1-2k)^2}{4} V_A {S_A}^2 \frac{r-R}{rR} \\ &+ \frac{k(\hat{p}_Y^{\sigma} - \hat{p}_X^{\sigma})}{2} \left[k\left(2\alpha_{\Delta}^{\sigma} - 2\alpha_{\Delta}^{\varphi} + t^{\sigma} - t^{\varphi}\right) - 2(1-k)S_A\right] + O\left(\epsilon^3\right).\end{aligned} \tag{4}$$

This reduces to $\lambda_{Y'}^{(XY)}$ when $k = 0$ and $\lambda_{W'}^{(XY)}$ when $k = 1$.

Of particular interest are ESD mutations that cause half of their carriers to develop as females and half as males ($k = 1/2$), creating equal sex ratios. The spread of such mutations is determined by

$$\lambda_{ESD'}^{(XY)} = 1 + \frac{1}{2}\frac{(\lambda_{Y'|R=1/2}^{(XY)} - 1) + (\lambda_{W'|R=1/2}^{(XY)} - 1)}{2} + O\left(\epsilon^3\right), \tag{5}$$

where $\lambda_{Y'|R=1/2}^{(XY)}$ and $\lambda_{W'|R=1/2}^{(XY)}$ represent $\lambda_{Y'}^{(XY)}$ and $\lambda_{W'}^{(XY)}$ when evaluated at $R = 1/2$ (Equations 2 and 3). That is, recombination between the selected locus and the novel sex-determining locus, R, does not enter into the $k = 1/2$ results. This is because sex is essentially randomized each generation, preventing associations from building up between alleles at locus **A** and sex. Eq (5) shows that the ESD mutation gets half of the fitness of a feminizing mutation (neo-W) and half of the fitness of a masculinizing mutation (neo-Y), but only has an effect one half of the time (the other half of the time it produces the same sex as the ancestral system would have). As discussed above, $\lambda_{Y'|R=1/2}^{(XY)}$ is necessarily less than one (cis-GSD transition), but $\lambda_{W'|R=1/2}^{(XY)}$ (trans-GSD transition) can be greater than one if there is haploid selection (see Conclusion 2B). That is, with haploid selection, an allele causing environmental-sex-determination can invade an ancestrally-XY system because it generates females that are either rare or have high fitness, in the same manner as a neo-W (likewise, ESD invades a ZW system for the same reasons as a neo-Y can).

Significantly, Eq (5) is the same whether ESD is invading an ancestrally XY or ZW system (because $\lambda_{Y'}^{(XY)} = \lambda_{W'}^{(ZW)}$ and $\lambda_{W'}^{(XY)} = \lambda_{Y'}^{(ZW)}$). Thus, focusing solely on Fisherian selection to equalize the sex-ratio does not fully explain GSD to ESD transitions. For example, when the ancestral sex-determining system is XY the sex ratio is biased by male haploid selection. When the ancestral sex-determining system is ZW the sex ratio is not biased. Nevertheless, ESD is equally likely to invade both XY and ZW systems, equalizing the zygotic sex ratio in the former case (through $\lambda_{W'}^{(XY)}$) but not in the latter (through $\lambda_{Y'}^{(ZW)}$). In addition, we note that ESD may not invade, even if the sex ratio is initially biased (e.g., with drive in males only, $r < 1/2$, $h^{\text{♀}} = h^{\text{♂}}$, and $s^{\text{♀}}s^{\text{♂}} < 0$, then $\lambda_{W'}^{(XY)} < 1$, see Table 3). We conclude that, as with neo-W and neo-Y loci:

Conclusion 4: **Transitions from genetic to environmental sex-determination are not straightforwardly predicted by selection to balance the zygotic sex ratio when haploid selection is present.**

Discussion

New sex determination systems are typically expected to spread when they equalise the sex ratio and/or when they increase linkage with loci that experience sex-differences in selection [33, 34] (including sex-differences at the haploid stage, Conclusion 2A and [43]). However, we find that trans-GSD transitions can be favoured in cases where linkage with the sex-determining locus is actually weakened (Conclusions 1 & 2B, Fig 2), especially when there is haploid selection (Conclusion 2B, Figs 4 & 5). Furthermore, we show that the spread of new sex-determination systems is not dominated by selection to balance the sex ratio (Conclusions 3 & 4, Fig 5).

On one hand, sex-ratio biases caused by haploid selection can facilitate trans-GSD transitions or transitions from genetic to environmental sex determination [42]. For instance, alleles favoured by haploid selection in males often become associated with the Y allele, which leads to an ancestral male-biased zygotic sex ratio. This male bias increases the potential for a neo-W or ESD allele to invade (Table 2), which can equalize the sex ratio (e.g., see Fig 5B, for related examples see [42]). On the other hand, sex-ratio selection can be overwhelmed by additional

selective effects, preventing a neo-W or ESD allele from invading, even if it would balance the sex ratio (e.g., when selection also acts in opposite directions in male and female diploids, Table 3). Indeed, transitions between sex-determining systems can generate stronger sex-ratio biases (e.g., Fig 5A and step 1 in [43]). Significantly, with weak selection, we find that there is no difference in conditions allowing XY to ZW and ZW to XY transitions (Conclusion 3), indicating that transitions in sex determination are not predominantly predicted by their effect on the sex ratio (i.e., the sex-ratio bias created by male haploid selection facilitates the spread of a neo-W allele into an XY system to the same degree that male haploid selection drives the spread of a neo-Y into a ZW system with a 1:1 sex ratio). Thus, haploid selection can favour trans-GSD transitions both via sex-ratio selection and via selection on alleles associated with the new sex-determining allele, and these selective pressures are often predicted to be of equal magnitude.

Our results indicate that haploid selection could be an important factor driving the evolution of new sex-determining systems. Even in animal and plant species that have much larger and more conspicuous diploid phases than haploid phases, many loci have been shown to experience haploid selection through gamete competition and/or meiotic drive [38–41, 51–56]. In some cases, meiotic drive (Burt and Trivers, 2006, Chapter 6 [57]) or gametic competition [58–63] among X- and Y-bearing gametes is known to cause sex ratio biases. In animals, recent studies have demonstrated that sperm competition, even within a single ejaculate, can alter haploid allele frequencies and increase offspring fitness [64, 65]. Nevertheless, although precise estimates are uncertain, a relatively small proportion of all genes are thought to be expressed and selected during competition in animal sperm [39, 66, 67]. In plants, however, haploid selection may be particularly important due to the presence of a multicellular haploid stage. For example, 60-70% of all genes are expressed in the male gametophyte, and these genes exhibit stronger signatures of selection than randomly-chosen genes [68–70]. Furthermore, artificial selection pressures applied to male gametophytes are known to cause a response to selection (e.g., [71–74]).

Linking haploid expression with the evolution of sex-determination, a recent transcriptome analysis in *Rumex* shows that pollen-biased expression (relative to expression in flower buds or leaves) is enhanced among XY-linked genes compared to autosomal genes or compared to hemizygous genes that are only linked to the X [75]. In addition, Y-linked genes are over-expressed relative to X-linked genes in pollen (but not in flower buds or leaves). This suggests that the spread of neo-Y chromosomes in this clade could have been favoured through linkage with haploid selected genes.

In general, we predict that haploid selection increases lability of sex-determining systems, particularly because haploid selection can cause transitions that increase or decrease sex-linkage (Conclusion 2A & 2B, e.g., the final state of the red line in Fig 5B is the starting state in Fig 5A). Frequent turnovers driven by haploid selection may help to explain the relative rarity of heteromorphic sex chromosomes in plants. If haploid selection is strong but selective differences between male and female diploids are weak, we specifically predict that trans-GSD transitions are favoured more strongly than cis-GSD transitions, with transitions to ESD intermediate (e.g., with $|D^{\male} - D^{\female}| << |\alpha_{\Delta}^{\male} - \alpha_{\Delta}^{\female} + t^{\male} - t^{\female}|$ we have $\lambda_{W'}^{(XY)} > \lambda_{Y'}^{(XY)}$; Eq 3). Among the relatively few dioecious clades in which multiple species have well characterized sex chromosomes [6], trans-GSD transitions have been inferred in *Silene* subsection *Otites* [15] and in *Salicaceae* [16, 17]. Assuming that transitions from dioecy to hermaphroditism (equal parental investment in male and female gametes) are favoured in a similar manner to the ESD examined here (equal probability of zygotes developing as males or females), our results suggest that competition among haploid pollen could drive transitions between dioecy and hermaphroditism, which are frequent in plants [76, 77]. To further examine this link, future theoretical investigations could also include selfing and inbreeding depression during transitions between dioecy and hermaphroditism. Future empirical investigations could look for evidence of haploid selection acting on former sex chromosomes in hermaphroditic species (e.g., a study such as [75] on ancestral, rather than derived, sex chromosomes).

New sex-determining alleles have previously be shown to spread when they arise in linkage

with loci that experience sex differences in selection because beneficial associations build up between alleles that determine sex and alleles that are favoured in that sex [35–37, 43]. In support of this hypothesis, researchers have identified genes on recently derived sex chromosomes that might be under sexually-antagonistic selection [21, 78, 79]. However, we show that, if selected loci are tightly linked to the ancestral sex-determining locus, they can drive trans-GSD transitions during which sex-linkage is reduced (Conclusion 1), thus widening the genomic locations that could be driving trans-GSD transitions. In addition, we find that polymorphic sex determining systems (X, Y, W, and Z alleles all present) can be maintained when a selected locus is tightly linked to the ancestral sex-determining system (e.g., S9 FigB and S9 FigC), which is not possible with loose linkage [36]. These conclusions apply in cases with or without haploid selection.

Our tight linkage results are consistent with empirical data from species in which new feminizing mutations are found alongside ancestral XY loci. For example, in the platyfish (*Xiphophorus maculatus*), X,Y, and W alleles segregate at one locus (or two closely-linked loci) near to potentially sexually-antagonistic genes for pigmentation and sexual maturity [44, 80–82]. Furthermore, several rodent species maintain feminizing alleles along with the ancestral X and Y sex-determination alleles (reviewed in [83]). In nine *Akadon* rodent species, it appears that male-determining-*sry* expression is suppressed by an autosomal feminizing allele, creating XY females [84, 85]. XY females have increased fitness relative to XX females [86]. However, it is not yet clear whether loci linked to the feminizing factor or the ancestral Y cause this effect. Most convincingly, in *Mus microtoides*, females can have XX, XX* or X*Y genotypes [87]. Previous theory would predict that the X* chromosome (or the autosome it is fused to) harbours female beneficial alleles, driving its spread. However, XX and XX* females have similar fitness, whereas X*Y female fitness is enhanced [88–90]. Although Y-linkage of female-beneficial alleles is counterintuitive, our model suggests that it can be stably maintained and then favour new feminizing mutations, which would be a parsimonious explanation for the spread of feminizing alleles in this case.

We note that we assume that sex-determining alleles do not experience direct selection except via their associations with sex and selected alleles. However, in some cases, there may be significant degeneration around the sex-limited allele (Y or W) in the ancestral sex-determining region because recessive deleterious mutations and/or deletions accumulate in the surrounding non-recombining regions [91–94]. During trans-GSD transitions, but not cis-GSD transitions, any recessive deleterious alleles linked to the Y or W are revealed to selection in YY or WW individuals [4]. This phenomenon was studied by van Doorn and Kirkpatrick (2010) [36], who found that degeneration can prevent fixation of a neo-W or a neo-Y allele, leading to a mixed sex-determining system where the ancestral and new sex-determining loci are both segregating. However, they noted that very rare recombination events around the ancestral sex-determining locus can allow these trans-GSD transitions to complete. Degeneration around the Y or W could explain why trans-GSD transitions are not observed to be much more common than cis-GSD transitions despite the fact that our models demonstrate that they are favoured under a wider range of conditions, especially with haploid selection. For example, there are a dozen sex chromosome configurations among Dipteran species but only one transition between male and female heterogamety [9].

In this study, we have only considered new sex-determining alleles of large effect. However, we expect similar selective forces to act on masculinizing/feminizing alleles of weaker effect. For example, small effect masculinizing/feminizing alleles within a threshold model of sex determination can be favoured when linked to loci that experience sexually-antagonistic selection [37]. These results echo those for large-effect neo-Y/neo-W alleles [35, 36]. It should be noted, however, that the dynamics of sex-determining alleles with very weak effect will be influenced by genetic drift, which itself has been shown to bias transitions towards epistatically-dominant sex-determining systems when there is no selection [95].

Conclusion

We have shown that tight sex-linkage and haploid selection can drive previously unexpected transitions between sex-determining systems. In particular, both can select for new sex-determining loci that are more loosely linked to loci under selection (Conclusions 1 & 2B). In addition, haploid selection can cause transitions in GSD analogous to those caused by purely sexually-antagonistic selection, eliminating the need for differences in selection between male and female diploids (Conclusion 2A). We conclude that haploid selection should be considered as a pivotal factor driving transitions between sex-determining systems. Further, transitions involving haploid selection can be driven by sex-ratio selection or cause sex-ratio biases to evolve; Fisherian sex-ratio selection is not an overwhelming force (Conclusions 3 & 4). Overall, our results suggest several new scenarios under which new sex-determining systems are favoured, which could help to explain why the evolution of sex-determining systems is so dynamic.

Supporting information

S1 File. Supplementary *Mathematica* file. This file can be used to re-derive our results and generate figures.

S1 Table Substitutions for different loci orders assuming no interference.

S2 Table Mean fitnesses and zygotic sex ratio in the resident population (M fixed, XY sex determination).

S1 Appendix. Recursion equations and complete model description.

S2 Appendix. Equilibria and stability conditions when M allele is fixed.

S3 Appendix. Invasion conditions for the m allele.

S1 Fig. With overdominance, loci near to the ancestral sex-determining locus ($r \approx 0$) can favour neo-W alleles that are less tightly linked ($R > r$). In panels A and B, the a allele is favoured in females ($w^{\varphi}_{aa} = 1.05$, $w^{\circ}_{Aa} = 1$, $w^{\varphi}_{AA} = 0.85$) and selection in males is overdominant ($w^{\sigma}_{aa} = w^{\sigma}_{AA} = 0.75$). In panels C and D, selection in males and females is overdominant ($w^{\varphi}_{aa} = w^{\varphi}_{AA} = 0.6$, $w^{\sigma}_{aa} = 0.5$, $w^{\sigma}_{AA} = 0.7$, $w^{\circ}_{Aa} = 1$). There is no haploid selection $t^{\circ} = \alpha^{\circ}_{\Delta} = 0$. These parameters are marked by daggers in Fig 3B and C, which show that neo-W invasion is expected for any R ($\Lambda^{(XY)}_{W'A}, \Lambda^{(XY)}_{W'a} > 1$) if the a allele is nearly fixed on the Y (black lines in this figure; not stable for $r >> 0$). Equilibria where the A allele is more common among Y-bearing male gametes can also be stable and allow neo-W invasion for these parameters (blue lines).

S2 Fig. Following invasion by a neo-W allele, there can be a complete transition to a new sex-determining system, maintenance of both ancestral-XY and neo-ZW sex determining systems, or loss of the new sex-determining allele. Here, we plot the frequency of the neo-W allele among female gametes. Panels A, C and D show cases where a steady state is reached with the neo-W at a frequency below 0.5, in which case ancestral-X and Y alleles also both segregate. In all cases, we assume that the a allele is initially more common than the A allele on the Y background (Y-a is fixed when $r = 0$). When $r > 0$ (panels B and D), Y-A haplotypes created by recombination can become more common than Y-a haplotypes as the neo-W spreads. In B, this leads to loss of the neo-W and the system goes to an equilibrium with X-a and Y-A haplotypes

fixed (equilibrium A'), such that all females have the high fitness genotype aa and all males are Aa. For the parameters in B, neo-W alleles have negative invasion fitness when the Y-A haplotype is ancestrally more common than Y-a (compare blue to black curves in S1 FigA and S1 FigB near the ancestral sex-determining locus). In contrast, the neo-W is not lost in panel D as it is favoured regardless of whether Y-A or Y-a haplotypes predominate (again, compare blue to black curves in S1 FigC and S1 FigD).

S3 Fig. When there is sexually-antagonistic selection and haploid selection, a neo-W allele may invade for any R. Panel A shows that the invasion fitness of a neo-W is positive, even when $r < R$ (unshaded region). In panel B, we vary the recombination rate between the neo-W and the selected locus (R) for a fixed recombination rate between the ancestral sex-determining locus and the selected locus ($r = 0.005$). Coloured markers show recombination rates for which the temporal dynamics of neo-W invasion are plotted in panel C (black $R = 0.001$, red $R = 0.02$, blue $R = 0.1$, green $R = 0.5$). The diploid selection parameters used in this plot are the same as in Fig 2. There is also meiotic drive in males favouring a ($\alpha_\Delta^\male = -0.08$), this full set of parameters is marked by an asterisk in S4 FigA. When $R = 0.5$ (green curve), the neo-W does not reach fixation and X, Y, Z, and W alleles are all maintained in the population, see S9 FigC.

S4 Fig. Parameters for which neo-W-A and neo-W-a haplotypes spread when there is male meiotic drive at a locus that is tightly linked to the ancestral XY locus ($r = 0$). This figure is equivalent to Fig 3 but with meiotic drive in males. In panels A-C, meiotic drive in males favours the a allele ($\alpha_\Delta^\male = -0.16$), creating male-biased sex ratios and generally increasing $\Lambda_{W'A}^{(XY)}$ and $\Lambda_{W'a}^{(XY)}$. By contrast, $\Lambda_{W'A}^{(XY)}$ and $\Lambda_{W'a}^{(XY)}$ tend to be reduced when meiotic drive in males favours the A allele ($\alpha_\Delta^\male = 0.16$), panels D-F.

S5 Fig. Parameters for which neo-W-A and neo-W-a haplotypes spread when there is male gametic competition at a locus that is tightly linked to the ancestral XY locus ($r = 0$). This figure is equivalent to Fig 3 but with gametic competition in males. The a allele is favoured during male gametic competition in Panels A-C ($w_a^\male = 1.16$, $w_A^\male = 1$), which creates male biased sex ratios and increases $\Lambda_{W'A}^{(XY)}$ and $\Lambda_{W'a}^{(XY)}$. By contrast, $\Lambda_{W'A}^{(XY)}$ and $\Lambda_{W'a}^{(XY)}$ tend to be reduced when the A allele is favoured during male gametic competition, panels D-F. Compared to the meiotic drive parameters in S4 Fig, the effect of these male gametic competition parameters on the sex ratio is smaller. For example, in S4 FigA-C, the ancestral sex ratio is $\alpha^\male = 0.58$ at equilibrium (B) and in panels A-C of this plot, the ancestral sex ratio is $w_a^\male/(w_A^\male + w_a^\male) = 0.537$ at equilibrium (B).

S6 Fig. Parameters for which neo-W-A and neo-W-a haplotypes spread when there is female meiotic drive at a locus that is tightly linked to the ancestral XY locus ($r = 0$). This figure is equivalent to Fig 3 but with meiotic drive in females. The a allele is favoured by meiotic drive in females in Panels A-C ($\alpha_\Delta^\female = -0.16$), which increases $\Lambda_{W'a}^{(XY)}$ and decreases $\Lambda_{W'A}^{(XY)}$. Female meiotic drive in favour of the A allele (panels D-F, $\alpha_\Delta^\female = -0.16$) has the opposite effect.

S7 Fig. Parameters for which neo-W-A and neo-W-a haplotypes spread when there is female gametic competition at a locus that is tightly linked to the ancestral XY locus ($r = 0$). This figure is equivalent to Fig 3 but with gametic competition in females. The a allele is favoured during female gametic competition in females in Panels A-C ($w_a^\female = 1.16$, $w_A^\female = 1$), which increases $\Lambda_{W'a}^{(XY)}$ and decreases $\Lambda_{W'A}^{(XY)}$. The A allele is favoured during gametic competition in panels D-F ($w_a^\female = 1$, $w_A^\female = 1.16$), giving the opposite effect on $\Lambda_{W'a}^{(XY)}$ and $\Lambda_{W'A}^{(XY)}$.

S8 Fig. Ploidally-antagonistic selection can drive the spread of neo-W alleles. A-D show when each of the neo-W haplotypes invades an internally stable equilibrium with a fixed on the Y (found by setting $r = 0$). The y-axis shows directional selection in diploids of both sexes, $s^{\varphi} = s^{\sigma}$, and the x-axes show sex-specific drive, α°_{Δ}, or haploid competition, t°. The top left and bottom right quadrants therefore imply ploidally-antagonistic selection (and these are the only places where neo-W haplotypes can invade). Dominance is equal in both sexes, $h^{\varphi} = h^{\sigma} = 3/4$. E-F show the temporal dynamics of neo-W frequency in females with parameters given by the asterisks in the corresponding A-D plot, with $r = 1/200$, for four different R. Black $R = 1/1000$, Red $R = 2/100$, Blue $R = 1/10$, Green $R = 1/2$.

S9 Fig. Pseudo-fixation of neo-W or maintenance of multiple sex-determining alleles. The curves show the frequencies of the neo-W (red), ancestral Y (blue), and A allele (black) among female gametes (solid curves) and among male gametes (dashed curves). In panel A, there is a complete transition from XY sex determination (XX-ZZ females and XY-ZZ males) to ZW sex determination (YY-ZW females and YY-ZZ males). In panels B and C a polymorphism is maintained at both the ancestral XY locus and the new ZW locus, such that there are males with genotypes XY-ZZ and YY-ZZ and females with genotypes XX-ZZ, XX-ZW, XY-ZW, and YY-ZW. In panel A, selection is ploidally-antagonistic with drive in males (parameters as in the green curve in Fig 5B). In panel B, there is overdominance in both sexes and no haploid selection (parameters as in the green curve in S2 FigC). In panel C, there is sexually-antagonistic selection in diploids with drive in males (parameters as in the green curve in S4 FigC). In all cases, the initial equilibrium frequency has a near fixation on the Y.

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