# 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 sexually-antagonistic locus. We use population genetic models to extend these theories in two ways: (1) We explicitly consider selection on 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 unlinked) to the locus under selection, which is not predicted by previous theory. (2) We consider selection upon haploid genotypes either during gametic competition (e.g., pollen/sperm competition involving multiple males) or meiosis (i.e., non-Mendelian segregation), which can cause the zygotic sex ratio to become biased. We find that associations with haploid selected loci can drive transitions between sex-determining systems, without requiring sexually-antagonistic selection in diploids. Unexpectedly, with haploid selection, transitions between male and female heterogamety can also evolve where linkage with the sex-determining locus is weakened. Furthermore, sex-ratio biases may increase or decrease with the spread of new sex chromosomes. Thus, we find 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. These results predict conditions under which sex-determining systems are likely to be labile and draw connections with sex-ratio evolution.

## 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 extend these theories to include selection upon haploid genotypes (meiotic drive or gametic competition), which causes sex-ratio biases and occurs differently in males and females. Surprisingly, we find the two forces (sex-ratio selection and associations with genes that have sex-specific effects) will often be equally strong, and thus neither dominates the spread of new sex-determining systems alone. Even more unexpectedly, we find that new sex-determining alleles can spread despite being less closely linked to selected loci under a wide range of conditions. 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 [1–4]). Among species with genetic sex determination (GSD), some taxa have heterogametic males (XY) and homogametic females (XX), including mammals and most dioecious plants [5]; 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 [6, 7], Diptera [8], and *Oryzias* [9]. In addition, many clades exhibit transitions between male and female heterogamety (XY↔ZW, hereafter 'trans-GSD transitions'), including snakes [10], lizards [11], eight of 26 teleost fish families [12], true fruit flies (Tephritids, [8]), amphibians [13], the angiosperm genus *Silene* [14], the angiosperm family *Salicaceae* [15, 16] 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 [17], midges [18], frogs [19], cichlid fish [20], tilapia [21], sea bass [22], and lab-strains of Zebrafish [23, 24]. In addition, multiple transitions have occurred between genetic and environmental sex-determining systems (GSD↔ESD), e.g., in reptiles and fishes [11, 12, 25–28]. In sum, accumulating evidence indicates that transitions between sex-determining systems are common [4].

Predominant theories accounting for transitions between GSD systems by selection involve sex-ratio selection or fitness differences between sexes (e.g., sexually antagonistic selection) [3, 29, 30]. 'Fisherian' sex-ratio selection favours a 1:1 zygotic sex ratio when assuming that males and females are equally costly to produce [34, 35]. 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 [36]. 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. Because the sex ratio is directly determined by the sex-determining system, it has been suggested that sex-ratio selection is a particularly dominant force in the evolution of sex determination (e.g., Bull, 1983, p 66-67 [1]; Buekeboom and Perrin, 2014, Chapter 7 [3]).

New genetic sex-determining alleles have been shown to be favoured in they arise in close linkage with a locus that experiences sexual antagonism [31–33]. Tighter 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 [31], trans-GSD transitions [32], and new partially-masculinizing or partially-feminizing alleles [33]. However, any sexually-antagonistic loci that are more closely linked to the ancestral sex-determining locus will develop similar, favourable associations and are expected to hinder the spread of a new sex-determining system [31, 32].

One novel feature of the models developed here is that we explicitly (is this wording fair to vD&K?) consider loci in very tight linkage with the ancestral sex-determining locus (e.g., within

the non-recombining region of a sex chromosome). Our analysis shows that, under various forms of selection, the ancestral-X can carry suboptimal alleles for females and/or the ancestral-Y can carry female-beneficial alleles. This, in turn, can favour a new ZW sex-determining locus that has weaker linkage with loci under selection, which has not been predicted by previous theory. That is, very tight linkage with the ancestral GSD locus can favour trans-GSD transitions in which associations with selected loci are actually weakened.

Furthermore, we include haploid selection in models describing cis-GSD, trans-GSD, and GSD to ESD transitions. Haploid selection (gametic competition or meiotic drive) is typically sex-specific in that it usually occurs among gametes produced by one sex only [37, 38, 45, 46]. Therefore, one might expect new sex-determining systems to benefit from close linkage with haploid selected loci, as found for sex-specific diploid selection [31–33]. On the other hand, associations between sex-determining loci and haploid selected loci generate biased zygotic sex ratios. Nevertheless, numerical simulations by Ubeda et al. (2015) [58] suggest that, starting from GSD, new masculinizing mutations (neo-Y alleles) spread via associations with alleles that are beneficial in the male haploid stage (e.g., [58]), leading to male-biased sex ratios.

But Kozielska uses numerical simulations to show that ancestral sex ratio biases caused by haploid selection...

move to discussion somewhere: Even in animal and plant species that have much larger and more conspicuous diploid phases than haploid phases, many loci experience significant haploid selection through gamete competition and/or meiotic drive [37, 38].

move to results somewhere: We use the term ‘meiotic drive’ to refer to the biased (non-Mendelian) segregation of genotypes during gamete production (from one parent only) and the term ‘gametic competition’ to refer to selection upon haploid genotypes within a gamete/gametophyte pool (from many parents); the term ‘haploid selection’ encompasses both processes.

move to discussion somewhere: Segregation distortion provides putative evidence of haploid selection and can sometimes be attributed to meiotic drive and/or gametic competition [39–44]. Where it has been characterized, individual cases of meiotic drive are generally sex-limited, exclusively affecting male or female gametes [45, 46]. Gametic competition is also typically sex-limited, occurring primarily among male gametes, because there are typically many more pollen/sperm than required for fertilization. Gametic competition may be particularly common in plants, in which 60-70% of all genes are expressed in the male gametophyte, and these genes exhibit stronger signatures of selection than randomly-chosen genes [47–49]. In addition, artificial selection pressures applied to male gametophytes are known to cause a response to selection (e.g., [50–53]). A smaller proportion of genes are thought to be expressed and selected during competition in animal sperm, although precise estimates are uncertain [38, 54, 55]. Nevertheless, recent studies have demonstrated that sperm competition in animals, even within a single ejaculate, can alter haploid allele frequencies and increase offspring fitness [56, 57].

There are various ways by which haploid selection could influence transitions between sex-determining systems. If we assume that haploid selection at any particular locus predominantly occurs in one sex (e.g., meiotic drive during spermatogenesis), then such loci experience a form of sex-specific selection. In this respect, we might expect that haploid selection would affect transitions between sex-determining systems in a similar manner to sex-specific diploid selection (as explored in [31, 32]). That is, new masculinizing mutations (neo-Y alleles) could be favoured via associations with alleles that are beneficial in the male haploid stage (e.g., [58]). Kozielska et al. (2010) [59] have shown this to be theoretically possible for the special case of perfect linkage between the new sex-determining locus and a locus that experiences meiotic drive in one sex, under a limited number of forms of diploid selection. Similarly, Ubeda et al. (2015) [58] numerically show that sex-specific meiotic drive can allow masculinizing and feminizing mutations to spread in an ancestrally environmental-sex-determination system, again under a limited number of forms of diploid selection. On the other hand, sex ratios can also become biased by linkage between the

sex-determining locus and a locus that harbours genetic variation in haploid fitness, as indeed occurs in the two examples above. There are also several known empirical cases of sex-ratio bias caused by sex-linked meiotic drive alleles (Burt and Trivers, 2006, Chapter 6 [60]) or selection among X- and Y-bearing pollen [61–66]. Sex-ratio selection can thus select against the spread of linked sex-determining alleles and favour the invasion of alternative, unlinked sex-determination systems [58, 59]. It is not yet clear when new sex-determining alleles are favoured by associations with haploid selected alleles vs. sex-ratio bias, especially under a wide range of possible diploid selection regimes (e.g., sex-antagonism, overdominance).

We consider both selected loci that are loosely linked to the sex-determining region (e.g., on an autosome) and selected loci that are in very tight linkage with the ancestral sex-determining locus (e.g., within the non-recombining sex-determining region). Our main findings are three: (1) transitions between sex-determining systems can decrease or increase sex-ratio bias, and with sufficiently loose linkage between the selected locus and the sex-determining locus, the selective force exerted by sex-ratio selection and favourable associations with haploid-selected alleles are exactly equivalent; (2) ancestrally-tight sex-linkage and haploid selection allow trans-GSD transitions that weaken sex-linkage; and (3) haploid selection removes the need for sex-antagonism, increasing the range of scenarios that select for 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). 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 invasion, fixation, maintenance, and/or loss of a novel sex-determining allele ($m$) at the **M** locus. 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.

A full description of our model, including recursion equations, is given in S1 Appendix. In each generation, we census the genotype frequencies in male and female gametes/gametophytes (hereafter gametes) before gametic competition. First, competition occurs among male gametes (sperm/pollen competition) and among female gametes (egg/ovule competition) separately. Selection during gametic competition depends on the **A** locus genotype; relative fitnesses are given by $w^{\circ}_{A}$ and $w^{\circ}_{a}$ ($\circ \in \{♀, ♂\}$; see table 1). We assume that all gametes compete for fertilization during gametic competition, which implies a polygamous mating system. Gametic competition in monogamous mating systems is, however, equivalent to meiotic drive in our model (described below), as either only alters the frequency of gametes produced by heterozygotes. 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(?) selection, with relative fitnesses $w^{\circ}_{AA}$, $w^{\circ}_{Aa}$, and $w^{\circ}_{aa}$. We do not consider fertility(?) 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 $\rho$. Any linear order of the loci can be modelled with appropriate choices of $r$,

**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 past recombination 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 occur 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.

$R$, and $\rho$ (see Fig 1A and S1 Table). Individuals that are heterozygous at the **A** locus may experience meiotic drive; a gamete produced by $Aa$ heterozgotes of sex $\circ$ bears allele $A$ with probability $\alpha^\circ$. Thus, the **A** locus can experience sex-specific gametic competition, diploid selection, and/or meiotic drive. ‘

**Table 1. Relative fitness of different genotypes in sex $\circ \in \{♀, ♂\}$**

| 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 |
| $A$ | $\alpha^\circ = 1/2 + \alpha^\circ_\Delta/2$ |
| $a$ | $1 - \alpha^\circ = 1/2 - \alpha^\circ_\Delta/2$ |

# Results

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 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.

## Generic invasion by a neo-Y or neo-W

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 a 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 "haplotypic recombination rate"(?)), 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. $\zeta$ 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 ($w_i^{\circ}$, $\alpha_\Delta^{\circ}$) 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 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 $R = 0$ ($\Lambda_{ma}^{(XY)} < 1 < \Lambda_{mA}^{(XY)}$) the first term on the left-hand side of (1) is negative and invasion requires that rate of growth of $mA$ haplotypes ($\Lambda_{mA}^{(i)} - 1 > 0$) and the rate at which $mA$ haplotypes are produced by recombination in $ma$ haplotypes ($\chi_{ma}^{(i)}$) are sufficiently large relative to the rate of decline of $ma$ haplotypes ($1 - \Lambda_{ma}^{(i)} > 0$) and the rate of loss of $mA$ haplotypes due to 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). That is,

*Conclusion 1: neither sex-ratio selection or selection on associated alleles dominates the invasion dynamics of a new sex-determining allele, allowing the sex ratio to become more or less biased during a transition.* [as suspected from Kozielska and Ubeda special cases]

And thirdly, Table 2 also shows that

*Conclusion 2: cis- and trans-GSD transitions are qualitatively different.* [already known from van Doorn and Kirkpatrick?]

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 rare 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. Since only the **A** locus experiences selection directly, any deterministic evolution requires that there is a polymorphism at the **A** locus. Polymorphisms can be maintained by mutation-selection balance or transiently present during the spread of beneficial alleles. However, polymorphisms maintained by selection can maintain alleles at intermediate allele frequencies for longer periods. Here, we focus on polymorphisms maintained by selection, where the $A$ allele reaches a stable intermediate equilibrium frequency under the ancestral sex-determining system before the new sex-determining allele ($m$) arises. Such polymorphisms can be maintained by heterozygote advantage, sexually-antagonistic selection, ploidally-antagonistic selection, or a

combination [67]. We can analytically calculate the allele frequency of the $A$ allele using two alternative simplifying assumptions: (1) the **A** locus is within (or tightly linked to) the non-recombining region around the ancestral sex-determining locus ($r \approx 0$) or (2) selection is weak relative to recombination ($s^\circ$, $t^\circ$, $\alpha_\Delta^\circ << r$).

## 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). When $R = 0$, a neo-Y haplotype with the same allele as the ancestral Y is neutral ($\Lambda_{Y'a}^{(XY)} = 1$) and does not change in frequency. The other neo-Y haplotype will not spread ($\Lambda_{Y'A}^{(XY)} < 1$) given that the initial equilibrium is stable. Therefore, a neo-Y mutation cannot spread in an ancestral XY system ($\lambda_{Y'}^{(XY)} \leq 1$, regardless of $R$) where selected loci are within or very near the non-recombining region around the sex-determining locus. 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. Given that the ancestral Y is at this equilibrium, it is not possible for a neo-Y to create males that have higher fitness than the ancestral Y.

Neo-W alleles, on the other hand, can invade an ancestral XY system under some conditions (the full invasion conditions are given in S3 Appendix; equations S3.1 and S3.2). In particular,

*Conclusion 3: selection on loci within the non-recombining region around the sex-determining locus ($r \approx 0$) allows the invasion of less closely linked sex-determining alleles ($r < R \leq 1/2$) during a trans-GSD transition*. [new result for sex-antagonism and overdominance, but already shown by Kozielska for ploidy-antagonism]

This 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 but is not possible with only sexually-antagonistic selection if selection is directional in each diploid sex (see S1 File).

To develop an intuition for how less closely linked neo-W alleles invade ($R > r$), we here focus on cases where there is no haploid selection and discuss the additional effect of haploid selection in S3 Appendix. If we categorise the $a$ allele as being ancestrally 'male-beneficial' via the fact that it is fixed on Y backgrounds, then $\Lambda_{W'A}^{(XY)} > 1$ indicates that the neo-W spreads when found with the ancestrally 'female-beneficial' allele. Broadly, this is possible because ancestral X alleles are sometimes in males and are therefore unable to perfectly specialise on the 'female-beneficial' allele. For example, when the $a$ allele is favoured on ancestral X backgrounds in males, a polymorphism of $A$ and $a$ alleles can be maintained on the X background despite selection for the $A$ allele in females ($s^{\female} > 0$, $0 < h^{\female} < 1$), see outlined region in Fig 3A. When the $a$ allele is strongly favoured on the X background in males ($w_{aa}^{\male}$

**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 (even without haploid selection).** In panel A, 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 B, linkage is tight enough relative to selection that the analytical results assuming weak selection do not hold, and a neo-W can invade even when it is less tightly linked with the selected locus ($r < R$; unshaded region around *). 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 (neo-W which are too loosely linked (blue and green) do not invade). 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: $w^{\varphi}_{AA} = 1.05$, $w^{\sigma}_{aa} = 1.2$, $w^{\varphi}_{aa} = w^{\sigma}_{AA} = 0.85$, $w^{\circ}_{Aa} = 1$, $t^{\circ} = \alpha^{\circ}_{\Delta} = 0$.

sufficiently large relative to $w^{\sigma}_{Aa}$), neo-W-$A$ haplotypes can spread ($\Lambda^{(XY)}_{W'A} > 1$, see grey region in Fig 3A) because they produce higher fitness females ($AA$ or $Aa$ genotypes) and are unleashed from counterselection in males.

**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.** 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 Y backgrounds, 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. Here, there is no haploid selection $t^{\circ} = \alpha^{\circ}_{\Delta} = 0$.

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

Given that the $a$ allele can be considered ancestrally 'male-beneficial' because it is fixed on Y backgrounds, it is surprising that neo-W-$a$ haplotypes can sometimes be favoured by selection in females ($\Lambda^{(XY)}_{W'a} > 1$). Again, this occurs because ancestral X alleles also experience selection in males, where they are ancestrally always paired with a Y-$a$ gamete. 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 [68, 69]). 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).

Assuming selection is weak relative to recombination, van Doorn and Kirkpatrick [32] showed that invasion by a neo-W allele occurs under the same conditions as 'pseudo-fixation' (at pseudo-fixation the neo-W reaches its maximum frequency among eggs, which is usually 1/2, but can deviate from 1/2 when there is haploid selection before censusing). An equivalent analysis is not possible where recombination rates are low. However, numerical simulations demonstrate that, with tight sex linkage, new sex-determining alleles do not necessarily reach pseudo-fixation, 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).

## Loose linkage with the ancestral sex-determining region

Here we assume that selection is weak ($s^\circ$, $t^\circ$, $\alpha_\Delta^\circ$ of order $\epsilon$, where $\epsilon$ is some number much less than one) and thus implicitly assume that all recombination rates ($r$, $R$ and $\rho$) 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

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

where $V_A = \bar{p}(1-\bar{p})$ is the variance in the equilibrium frequency of $A$ and $S_A = (D^{\male} + \alpha_\Delta^{\male} + t^{\male}) - (D^{\female} + \alpha_\Delta^{\female} + t^{\female})$ describes sex differences in selection for the $A$ versus $a$ allele across diploid selection, meiosis, and gametic competition. The diploid selection term, $D^\circ = \left[\bar{p}s^\circ + (1-\bar{p})h^\circ s^\circ\right] - \left[\bar{p}h^\circ s^\circ + (1-\bar{p})\right]$, 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). The difference in $A$-allele-frequency among Y-bearing sperm versus X-bearing sperm is given by $\hat{p}_Y^{\male} - \hat{p}_X^{\male} = V_A\left(D^{\male} - D^{\female} + \alpha_\Delta^{\male} - \alpha_\Delta^{\female} + t^{\male} - t^{\female}\right)(1-2r)/(2r)$.

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 $\mathbf{A}$ 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 [31], 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.

With weak selection and no haploid selection ($t^\circ = \alpha_\Delta^\circ = 0$), the spread of a neo-W is equivalent to the spread of a neo-Y ($\lambda_{W'}^{(XY)} = \lambda_{Y'}^{(XY)}$), 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 [32]. 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 $\mathbf{A}$ locus is unlinked to the ancestral sex-determining locus ($r = 1/2$), a more closely linked neo-W ($R < 1/2$) can always invade. In this case, there is no ancestral association between $\mathbf{A}$ alleles and sex chromosomes in males, $\left(\hat{p}_Y^{\male} - \hat{p}_X^{\male}\right) = 0$, see Eq (S2.4). The second term in Eq (3) therefore disappears and invasion depends only on the sign of $(r - R)$.

However, with haploid selection and $r < 1/2$, the additional term in Eq (3) can be positive. This implies,

**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 which case the new sex-determining allele can invade regardless of its linkage with the selected locus ($R$). 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 which case the new sex-determining allele can once again invade regardless of $R$.

*Conclusion 4: when there is an intermediate rate of recombination between the ancestral sex-determining allele and a selected locus ($0 < r < 1/2$), haploid selection allows less closely linked sex-determining alleles ($r < R$) to invade during trans-GSD transitions ($\lambda_{W'}^{(XY)} > 1$).* [new result because Kozielska had tight linkage and Ubeda had ESD]

To clarify the parameter space under which invasion occurs despite looser sex-linkage ($\lambda_{W'}^{(XY)} > 1$ despite $R > r$), 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, $h^{\female} = h^{\male}$. When there is no gametic competition and meiotic drive is in one sex only, an unlinked neo-W can invade as long as the same allele is favoured during diploid selection in males and females ($s^{\female}s^{\male} > 0$, see Fig 4A and Fig 5B). When there is no meiotic drive and gametic competition occurs in one sex only, an unlinked neo-W can invade as long as the same allele is favoured in male and female diploid selection and there are sex differences in selection of one type (e.g., $s^{\female}(s^{\male} - s^{\female}) > 0$, see Fig 4B). These special cases indicate that neo-W invasion occurs for a relatively large fraction of the parameter space, even if the neo-W uncouples the sex-determining locus from a locus under selection.

**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 one 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 | $h^{\male} = h^{\female}$, $t^{\male} = \alpha_{\Delta}^{\female} = \alpha_{\Delta}^{\male} = 0$ | $s^{\male}(s^{\female} - s^{\male}) > 0$ |

**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 among female gametes, reaching pseudo-fixation), 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 among male gametes, reaching pseudo-fixation). Parameters: $s^{\female} = s^{\male} = 0.2$, $h^{\female} = h^{\male} = 0.7$, $t^{\female} = t^{\male} = \alpha_{\Delta}^{\female} = 0$, $\alpha_{\Delta}^{\male} = -0.1$, $r = 0.02$.

Previous research has shown that when the ancestral sex-determining locus is linked to a locus that experiences haploid selection (e.g., meiotic drive), alleles at a new, unlinked sex-determining locus can invade and restore equal sex ratios [58, 59]. Consider, for example, the case where the **A** locus is linked to the ancestral sex-determining locus ($r < 1/2$) and experiences meiotic drive in males only ($\alpha_\Delta^\male \neq 0$, $\alpha_\Delta^\female = 0$), without gametic competition ($t^\female = t^\male = 0$). In this case, the zygotic sex ratio can be initially biased only if the ancestral sex-determining system is XY (Fig 1A and 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 $\epsilon^2$). For example, in Fig 5A neo-W alleles invade an ancestral-XY system where females are initially rare, equalizing the sex ratio. 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 in the scenarios considered in [58, 59]). 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).

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 diploids bearing it more often carry the non-driven allele $A$, which is found at high frequency on the W background and has higher average diploid fitness.

## 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 is exactly $k$, even when $m$ is rare (exploring the effect of the variance induced by ESD would also be interesting). Here, we do not assume that the environmental conditions that determine sex also 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, 35, 36]).

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

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

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 ESD 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 $\lambda^{(XY)}_{Y'|R=1/2}$ and $\lambda^{(XY)}_{W'|R=1/2}$ represent $\lambda^{(XY)}_{Y'}$ and $\lambda^{(XY)}_{W'}$ 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, $\lambda^{(XY)}_{Y'|R=1/2}$ is necessarily less than one, but $\lambda^{(XY)}_{W'|R=1/2}$ can be greater than one if there is haploid selection. That is:

*Conclusion 5: 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 a neo-Y can).* [I imagine this is a new result as it requires the evolution of effectively looser linkage from a weak recombination ancestor, which requires haploid selection, and neither Kozielska or Ubeda had GSD to ESD.]

Significantly, Eq (5) is the same whether ESD is invading an ancestrally XY or ZW system (because $\lambda^{(XY)}_{Y'} = \lambda^{(ZW)}_{W'}$ and $\lambda^{(XY)}_{W'} = \lambda^{(ZW)}_{Y'}$). Thus, Fisherian sex-ratio selection alone does not easily explain GSD to ESD transitions. For example, when the ancestral sex-determining system is XY, but not ZW, the sex ratio is biased by male haploid selection. Nevertheless, ESD is equally likely to invade when it equalizes the zygotic sex ratio (through $\lambda^{(XY)}_{W'}$) as when it doesn't (through $\lambda^{(ZW)}_{Y'}$). In addition, we note that ESD may not invade, even if the sex ratio is initially biased (e.g., with drive in males only, $r < 1/2$, $h^{♀} = h^{♂}$, and $s^{♀}s^{♂} < 0$, then $\lambda^{(XY)}_{W'} < 1$, see Table 3). We conclude that, as with neo-W and neo-Y loci, associations with selected loci mean that the evolution of ESD is not straightforwardly predicted by selection to balance the zygotic sex ratio when haploid selection is present.

Somehow need to add two further conclusions suggested by review 2:

*Conclusion 6: sex-antagonism and tighter sex linkage not required for transitions.*

*Conclusion 7: haploid selection makes conditions for transitions permissive.*

Or are these evident from the first 5 conclusions?

## Discussion

Two predominant theories explaining the remarkably high frequency of transitions between genetic sex-determining systems are sexually-antagonistic selection and sex-ratio selection (reviewed in [29, 30]). The former predicts that new sex-determining alleles can invade when they arise in closer linkage with a sexually-antagonistic locus ($r < R$, [31–33]). The latter predicts that new sex-determining systems are generally favoured if they result in more equal sex ratios than the ancestral system. In contrast to these prevailing views, we show that selection (including sexually-antagonistic selection, overdominance, and/or ploidally-antagonistic selection) on loci tightly linked to the ancestral sex-determining locus can favour trans-GSD transitions (XY↔ ZW) to new sex-determining systems that are less closely linked to the selected loci (e.g., see Fig 2). Similarly, even when linkage is weak relative to selection, we show that trans-GSD transitions can occur where the new sex-determining locus is less closely linked to the locus under selection if there is haploid selection (e.g., Figs 4 and 5).

We find that the spread of new sex-determining systems cannot be simply predicted from their effect on the sex ratio. On one hand, sex-ratio biases caused by haploid selection can facilitate trans-GSD transitions or transitions from genetic to environmental sex determination. For instance, alleles favoured by haploid selection in males often become associated with the Y allele, which leads to a male-biased zygotic sex ratio. This male bias increases the potential for a neo-W allele to invade (Table 2), which can equalize the sex ratio (e.g., see Fig 5B, for related examples see [59]). 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 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 [58]). Significantly, with weak selection, we find that there is no difference in conditions allowing XY to ZW and ZW to XY transitions, indicating that sex chromosome transitions 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.

We have shown that the spread of new sex-determining systems can be driven by loci experiencing haploid selection. In agreement with this hypothesis, 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 (Sandler et al., 2018, personal communication). 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 (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, which are thought to experience more selection during their multicellular haploid stage.

If haploid selection is strong but selective differences between male and female diploids are weak, we find 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 $\lambda_{W'}^{(XY)} > \lambda_{Y'}^{(XY)}$; Eqs 3 and S2.4). Among the relatively few dioecious clades in which multiple species have well characterized sex chromosomes [5], trans-GSD transitions have been inferred in *Silene* subsection *Otites* [14] and in *Salicaceae* [15, 16]. 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 [70, 71]. To further examine this link, future investigations could examine the combined effects of haploid pollen competition, selfing, and inbreeding depression in allowing transitions between dioecy and hermaphroditism.

In support of their role in sex chromosome turnover, genes expected to be under sexually-antagonistic selection (e.g., those causing bright male colouration) have been found on recently derived sex chromosomes [20, 72, 73]. Our results show, however, that tight ancestral-linkage of polymorphic loci, maintained by sexually-antagonistic selection or otherwise, can also drive 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 [32]. For example, our results suggest a potential mechanism maintaining multiple sex determining alleles in the platyfish (*Xiphophorus maculatus*), in which

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 [74–77]. Several rodent species also maintain feminizing alleles along with the ancestral X and Y sex-determination alleles (reviewed in [78]). For example, in nine *Akadon* species, it appears that male-determining-*sry* expression is suppressed by an autosomal feminizing allele, creating XY females [79, 80], which have increased fitness relative to XX females [81]. In *Mus microtoides*, females can have XX, XX* or X*Y genotypes [82]. 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 [83–85]. 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 is a parsimonious explanation for the spread of feminizing alleles in these rodent species.

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 this non-recombining regions [86–89]. 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) [32], 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 [8].

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 [33]. These results echo those for large-effect neo-Y/neo-W alleles [31, 32]. 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 cause trans-GSD transitions [90]. Finally, while we have considered cis-GSD, trans-GSD, and GSD to ESD transitions, we have not explicitly considered ESD to GSD transitions. Recent models of ESD to GSD transitions [33, 58] show that that neo-Y/neo-W alleles can be favoured when they arise near to haploid and/or diploid selected loci, which also occurs in our model.

## 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. In addition, haploid selection can cause transitions analogous to those caused by purely sexually-antagonistic selection, eliminating the need for differences in selection between male and female diploids. 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. 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, $s^\female = s^\male$, and the x-axes show sex-specific drive, $\alpha_\Delta^\circ$, or haploid competition, $t^\circ$. 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, $h^\female = h^\male = 3/4$. 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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