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

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Abstract

Sex-determination systems are 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-determination 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 also consider selection upon haploid genotypes either during gametic competition (e.g., pollen/sperm competition) or meiosis (i.e., non-Mendelian segregation); selective processes that typically occur in one sex or the other. We find that associations with haploid selected loci can drive transitions between sex determination 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, haploid selection in the heterogametic sex can cause sex ratio biases, which may increase or decrease with the spread of new sex chromosomes. Thus, we find that transitions between sex-determination systems cannot be simply predicted by selection to equalise the sex ratio. Overall, our models reveal that transitions between sex-determination 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-determination systems are likely to be labile and draw novel connections with sex ratio evolution

Author summary

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Introduction

Animals and angiosperms exhibit extremely diverse sex-determination systems (reviewed in [1–4]). Among species with genetic sex determination of diploid sexes (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 region changes. For example, transitions of the master sex-determining gene between chromosomes or the evolution of new master sex-determining genes have occurred in Salmonids [6, 7], Diptera [8], and *Oryzias* [9]. In addition, many clades exhibit transitions between male (XY) and female (ZW) heterogamety, 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-determination 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 (GSD) and environmental sex-determination (ESD) systems, e.g., in reptiles and fishes [11, 12, 25–28].

Predominant theories accounting for the spread of new sex-determination systems by selection involve fitness differences between sexes (e.g., sexually antagonistic selection) or sex ratio selection [3, 29, 30]. van Doorn and Kirkpatrick [31, 32] and Muralidhar and Veller [33] have shown that new sex-determining loci can be favoured if they arise in close linkage with a locus that experiences sexual antagonism. Tighter linkage allows a stronger favourable association to build up between a male-beneficial allele, and a neo-Y chromosome, for example. Such associations can favour a new partially-masculinizing or partially-feminizing allele [33], a new master sex-determining gene [31], and transitions between male and female heterogamety (trans-GSD transitions, ZW to XY or XY to ZW [32]). However, any sexually-antagonistic loci that are more closely linked to the ancestral sex-determination locus will develop similar, favourable associations and are expected to hinder the spread of a new sex-determination system.

The sex ratio is directly determined by the sex-determination system, and it has therefore been suggested that sex ratio selection is a dominant force in the evolution of sex determination (e.g., Bull, 1983, p 66-67 [1]; Buekeboom and Perrin, 2014, Chapter 7 [3]). '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 population sex ratio is biased towards one sex, the average per-individual contribution of genetic material to the next generation from the opposite sex is greater. Therefore, a mutant that increases investment in the rarer sex will spread via the higher per-individual contributions made by that sex. In the case of sex-chromosome evolution, Kozielska et al. (2014) [37] consider systems in which the ancestral sex chromosomes experience meiotic drive (e.g., where driving X or Y chromosomes are inherited disproportionately often), which causes sex ratios to become biased [38]. They find that new, unlinked sex-determining loci (masculinizing or feminizing mutations, i.e., neo-Y or neo-W loci) can then spread, which restore an even sex ratio.

Here we use mathematical models to find the conditions under which new sex-determination systems spread when individuals experience selection at both diploid and haploid stages. 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 [39, 40]. We use the term 'meiotic drive' to refer to the biased (non-Mendelian) segregation of genotypes during gamete production (from one parent) and the term 'gametic competition' to refer to selection upon haploid genotypes within a gamete/gametophyte pool (potentially from multiple parents); the term 'haploid selection' encompasses both processes.

Segregation distortion provides putative evidence of haploid selection and can sometimes be

attributed to meiotic drive and/or gametic competition [41–46]. Where it has been characterized, meiotic drive generally occurs either during the production of male or female gametes only [47, 48]. Gametic competition is also typically sex specific, 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 random genes [49–51]. In addition, artificial selection pressures applied to male gametophytes are known to cause a response to selection (e.g., [52–55]. A smaller proportion of genes are thought to be expressed and selected during competition in animal sperm, although precise estimates are uncertain [40, 56, 57]. Nevertheless, recent studies have demonstrated that sperm competition in animals can alter haploid allele frequencies and increase offspring fitness [58, 59].

There are various ways by which genes experiencing haploid selection could influence transitions between sex-determination 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-determination systems in a similar manner to sex-specific diploid selection (as explored in [31, 32]). That is, new masculinizing mutations (neo-Y chromosomes) could be favoured via associations with alleles that are beneficial in the male haploid stage. On the other hand, sex ratios can also become biased by linkage between the sex-determining region and a locus that harbours genetic variation in haploid fitness. For example, there are several known cases of sex ratio bias caused by sex-linked meiotic drive alleles (Burt, 2006, Chapter 6 [60]) or selection among X- and Y-bearing pollen [61–66]. It is not immediately clear how the spread of new sex-determination systems would be influenced by the combination of sex ratio biases and associations between haploid selected loci and sex-determining regions.

We find that the spread of novel sex-determiners is influenced by both Fisherian sex ratio selection and by selection on genetically-associated alleles. Surprisingly, Fisherian sex ratio selection does not dominate; it is possible for selection on linked alleles to drive turnover between sex-determining systems despite causing increasingly biased sex ratios. In addition to considering haploid selection, another novel development in our model is that we consider loci that are in very tight linkage with the ancestral sex-determining region. Because sex-determining loci are often found within a region of suppressed recombination, there can be a significant number of tightly linked loci. We find that loci linked with the ancestral sex-determining region can drive transitions in which the heterogametic sex changes, even when the neo-sex-determining locus is less closely linked to loci under selection (either including haploid selection or not).

Model

We consider transitions between ancestral and novel sex-determining systems using a three-locus model, each locus having two alleles (Figure 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-determination systems, we consider the invasion, fixation, maintenance, and/or loss of novel sex-determining alleles (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 (i.e., a neo-Y) and with $k = 1$ the m allele is a feminizer (i.e., a neo-W). 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.

Fig 1. Outline of model features. Panel A: Recombination rate parameters between the ancestral-sex-determining locus (here, assumed to have X or Y alleles), a locus under selection (**A**, with alleles *A* and *a*), and a neo-sex-determining locus (**M**, with alleles *M* and *m*). If $r < 1/2$, then associations between ancestral-sex-determining alleles (X and Y) and **A** locus 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 male gametes/gametophytes will be abundant after haploid selection. However, the zygotic sex ratio is not biased by male haploid selection in ZW sex-determination systems. Similarly, zygotic sex ratio biases can occur if haploid selected alleles are associated with neo-sex-determining alleles (*M* and *m*, i.e., if $R < 1/2$). Panel C: During cis-GSD transitions (XY to XY or ZW to ZW, without loss of generality we assume ancestral XY sex determination here), a neo-Y allele spreads to pseudo-fixation (its maximum frequency among male gametes) and the 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 mutations allow Y-associated alleles into females, which may impede or aid their spread.

In each generation, we census the genotype frequencies in male and female gametes/gametophytes (hereafter gametes) before gametic competition. A full description of our model, including recursion equations, is given in the Appendix. 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 $w_A^{\male}$ and $w_a^{\male}$ ($\male \in \{\female, \male\}$; see table 1). We assume that all gametes compete for fertilization during gametic competition, which assumes 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, random mating occurs between male and female gametes. The resulting zygotes develop as males or females, depending on their genotypes at the **X** and **M** loci. Diploid males and females then experience selection, with relative fitnesses $w_{AA}^{\male}$, $w_{Aa}^{\male}$, and $w_{aa}^{\male}$. 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 Figure 1A and Table). Individuals that are heterozygous at the **A** locus may experience meiotic drive; a gamete produced by *Aa* heterozgotes of sex $\male$ bears allele *A* with probability $\alpha^{\male}$. Thus, the **A** locus can experience sex-specific gametic competition, diploid selection, and/or meiotic drive.

Results

The model outlined above describes both ancestrally-XY and ancestrally-ZW sex-determination systems if we relabel the two sexes as being ancestrally 'heterogametic' or ancestrally 'homogametic'. Without loss of generality, we primarily refer to the ancestrally heterogametic sex as male and the ancestrally homogametic sex as female. That is, we describe an ancestral XY sex-determination system but our model is equally applicable to an ancestral ZW sex-determination system (relabelling the ancestrally-heterogametic sex as female and the ancestrally-homogametic sex as male and switching the labels of males and females throughout).

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

Genotype	Relative fitness during gametic competition
A	$w_A^{\male\female} = 1 + t^{\male\female}$
a	$w_a^{\male\female} = 1$
Genotype	**Relative fitness during diploid selection**
AA	$w_{AA}^{\male\female} = 1 + s^{\male\female}$
Aa	$w_{Aa}^{\male\female} = 1 + h^{\male\female} s^{\male\female}$
aa	$w_{aa}^{\male\female} = 1$
Genotype	**Transmission during meiosis in *Aa* heterozygotes**
A	$\alpha^{\male\female} = 1/2 + \alpha_\Delta^{\male\female}/2$
a	$1 - \alpha^{\male\female} = 1/2 - \alpha_\Delta^{\male\female}/2$

Generic invasion by a neo-Y or neo-W

The evolution of a new sex-determination system requires that a rare mutant allele at the novel sex-determining locus, m, increases in frequency when rare. The spread of a rare mutant m at the **M** locus is determined by the leading eigenvalue, λ, of the system of eight equations describing the frequency of eggs and sperm carrying the m allele in the next generation (equations **??**). This system simplifies substantially in a number of cases of interest. Dominant neo-Y (when $k = 0$) or neo-W alleles (when $k = 1$) are only found in male diploids (neo-Y) or female diploids (neo-W) such that their growth rate ultimately depends only on the change in frequency of m-bearing gametes produced by males or by females, respectively. Furthermore, if the m allele is fully epistatically dominant over the ancestral sex-determining system, phenotypes are not affected by the genotype at the ancestral sex-determining region (**X** locus). Thus, the invasion of rare dominant neo-Y or neo-W alleles is determined by the largest eigenvalue that solves the quadratic, $\lambda^2 + b\lambda + c = 0$ (see Appendix for a discussion of other roots - or Sally's proof!). Here, $b = -(\lambda_{mA} + \lambda_{ma}) + (\chi_{mA} + \chi_{ma})$ and $c = (\lambda_{mA} - \chi_{mA})(\lambda_{ma} - \chi_{ma}) - \chi_{mA}\chi_{ma}$, where λ_{mi} is the multiplicative growth rate (which we will call the "haplotypic growth rate") of the neo-sex determination allele m on background i without accounting for loss due to recombination, and χ_{mi} is the rate at which mutant haplotypes on background $i \in \{A, a\}$ recombine onto the other **A** locus background in heterozygotes (see Table 2). The λ_{mi} and χ_{mi}, and thus the spread of the mutant m allele, depend on the frequency of alleles at the **A** and **X** loci in the ancestral population. 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, $\hat{p}_i^{\male\female}$, and Y-bearing male gametes, $\hat{q}$, when calculating the eigenvalues.

We are particularly concerned with the conditions under which a rare neo-sex-determining allele increases in frequency, which occurs when the largest eigenvalue, λ, is greater than one. The leading eigenvalue solves $f(\lambda) = \lambda^2 + b\lambda + c = 0$ and the Perron-Frobenius theorem guarantees that the leading eigenvalue is positive, unique, and real. Since $f(\lambda_{mA})$ and $f(\lambda_{ma})$ are of opposite signs, the leading eigenvalue must fall between these two quantities and is the larger of them when $R = 0$ (see supplementary Mathematica file). Consequently, if both λ_{mA} and λ_{ma} are greater than one, then the leading eigenvalue will always be greater than one, regardless of the linkage between the neo-sex determination factor and the selected locus (R). In particular, having $\lambda_{mA} > 1$ and $\lambda_{ma} > 1$ thus guarantees that an unlinked sex determining factor can invade ($R = 1/2$). Conversely, if both λ_{mA} and λ_{ma} are smaller than one, then invasion can

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

m is a neo-Y ($k = 0$)
$\lambda_{YA} = (2\zeta)^{-1}\left[\hat{p}_X^{\varphi} w_A^{\varphi} w_A^{\sigma} w_{AA}^{\sigma} + (1-\hat{p}_X^{\varphi}) w_a^{\varphi} w_A^{\sigma} w_{Aa}^{\sigma}(1+\alpha_\Delta^{\sigma})\right] / \left(\bar{w}_H^{\varphi}\bar{w}_H^{\sigma}\bar{w}^{\sigma}\right)$
$\lambda_{Ya} = (2\zeta)^{-1}\left[(1-\hat{p}_X^{\varphi}) w_a^{\varphi} w_a^{\sigma} w_{aa}^{\sigma} + \hat{p}_X^{\varphi} w_A^{\varphi} w_a^{\sigma} w_{Aa}^{\sigma}(1-\alpha_\Delta^{\sigma})\right] / \left(\bar{w}_H^{\varphi}\bar{w}_H^{\sigma}\bar{w}^{\sigma}\right)$
$\chi_{YA} = R\,(2\zeta)^{-1}\left[(1-\hat{p}_X^{\varphi}) w_a^{\varphi} w_A^{\sigma} w_{Aa}^{\sigma}(1+\alpha_\Delta^{\sigma})\right] / \left(\bar{w}_H^{\varphi}\bar{w}_H^{\sigma}\bar{w}^{\sigma}\right)$
$\chi_{Ya} = R\,(2\zeta)^{-1}\left[\hat{p}_X^{\varphi} w_A^{\varphi} w_a^{\sigma} w_{Aa}^{\sigma}(1-\alpha_\Delta^{\sigma})\right] / \left(\bar{w}_H^{\varphi}\bar{w}_H^{\sigma}\bar{w}^{\sigma}\right)$
m is a neo-W ($k = 1$)
$\lambda_{WA} = [2(1-\zeta)]^{-1}\left[\bar{p}^{\sigma} w_A^{\sigma} w_A^{\varphi} w_{AA}^{\varphi} + (1-\bar{p}^{\sigma}) w_a^{\sigma} w_A^{\varphi} w_{Aa}^{\varphi}(1+\alpha_\Delta^{\varphi})\right] / \left(\bar{w}_H^{\varphi}\bar{w}_H^{\sigma}\bar{w}^{\varphi}\right)$
$\lambda_{Wa} = [2(1-\zeta)]^{-1}\left[(1-\bar{p}^{\sigma}) w_a^{\sigma} w_a^{\varphi} w_{aa}^{\varphi} + \bar{p}^{\sigma} w_A^{\sigma} w_a^{\varphi} w_{Aa}^{\varphi}(1-\alpha_\Delta^{\varphi})\right] / \left(\bar{w}_H^{\varphi}\bar{w}_H^{\sigma}\bar{w}^{\varphi}\right)$
$\chi_{WA} = R\,[2(1-\zeta)]^{-1}\left[(1-\bar{p}^{\sigma}) w_a^{\sigma} w_A^{\varphi} w_{Aa}^{\varphi}(1+\alpha_\Delta^{\varphi})\right] / \left(\bar{w}_H^{\varphi}\bar{w}_H^{\sigma}\bar{w}^{\varphi}\right)$
$\chi_{Wa} = R\,[2(1-\zeta)]^{-1}\left[\bar{p}^{\sigma} w_A^{\sigma} w_a^{\varphi} w_{Aa}^{\varphi}(1-\alpha_\Delta^{\varphi})\right] / \left(\bar{w}_H^{\varphi}\bar{w}_H^{\sigma}\bar{w}^{\varphi}\right)$

$\bar{p}^{\sigma} = (1-\hat{q})\hat{p}_X^{\sigma} + \hat{q}\hat{p}_Y^{\sigma}$ is the average frequency of the A allele among X- and Y-bearing male gametes. ζ is the zygotic sex ratio (fraction male). $\bar{w}^{\varphi}$ is the mean fitness of diploids of sex φ, see Table . $\bar{w}_H^{\varphi}$ is the mean fitness of haploids from sex φ, see Table .

never occur. Finally, if only one of λ_{mA} and λ_{ma} is greater than one, the new sex determining factor can always invade when tightly linked to the selected locus (R near 0). Furthermore, it can be shown that the leading eigenvalue declines with R, and invasion requires that R is sufficiently small that the following condition holds:

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

This condition may or may not be satisfied for the full range of locations of the new sex determining factor, including $R = 1/2$, depending on the nature of selection. Interpreting this condition, if we assume that only the mA haplotype has a positive growth rate when $R = 0$, $\lambda_{ma} < 1 < \lambda_{mA}$, the first term on the left-hand side of (1) is negative and invasion requires that the mA haplotype growth rate ($\lambda_{mA} - 1$) and the rate at which they are produced by recombination in ma haplotypes (χ_{ma}) are sufficiently large relative to the ma haplotype rate of decline ($1 - \lambda_{ma}$) and the rate of loss of mA haplotypes due to recombination (χ_{mA}).

We can draw a number of key points about the invasion of neo-Y and neo-W mutations from Table 2. First, Fisherian sex ratio selection will favour the spread of a neo-Y if the ancestral zygotic sex ratio is biased towards females, $\zeta < 1/2$ (i.e., the first factor of the λ_{mi} is greater than one for a neo-Y and less than one for a neo-W). 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). Second, invasion by a neo-Y (neo-W) allele 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) allele, m, only changes in males (females), Figure 1C,D. Finally, invasions by a neo-Y and a neo-W are qualitatively different. This is because a gamete with the neo-Y always pairs with a female gamete containing an X, and develop into males, Figure 1C. By contrast, a gamete with a neo-W can pair with an X or Y male gamete, developing into a female, Figure 1D. Consequently, neo-W bearing females obtain a differerent frequency of A alleles from mating (when $\hat{p}_X^{\sigma} \neq \hat{p}_Y^{\sigma}$) compared to ancestral (MM) females.

In order to explicitly determine the conditions under which a rare neo-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-determination system before the neo-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 SDR ($r \approx 0$) or (2) selection is weak relative to recombination ($s^{\female}$, $t^{\female}$, $\alpha_{\Delta}^{\female}$ of order $\epsilon << 1$).

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

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

We find that a neo-Y can never invade an ancestral XY system that already has tight linkage with the locus under selection ($r = 0$, for details see supplementary *Mathematica* file). When $R = 0$, a neo-Y haplotype with the same allele as the ancestral Y is neutral ($\lambda_{Ya} = 1$) and does not change in frequency. The other neo-Y haplotype will not spread ($\lambda_{YA} < 1$) given that the initial equilibrium is stable. Therefore, a neo-Y mutation cannot spread ($\lambda \leq 1$, regardless of R) in an ancestral XY system where selected loci are within or very near the non-recombining region around the SDR. 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 the appendix; equations **??** and **??**). Counterintuitively, selection on loci within the non-recombining region of the SDR can favour the invasion of a less closely linked neo-W, whatever the form of selection maintaining a polymorphism (sexually-antagonistic selection, overdominance, ploidally-antagonistic selection, or some combination, Figures 2, S2 Fig, S8 Fig, and S3 Fig). The conditions become more restrictive, however, with increasing recombination (R) between the new sex determining region 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 Supplementary *Mathematica* file). To develop an intuition for how less closely linked neo-W alleles invade ($R > r$), we first focus on cases where there is no haploid selection and discuss the additional effect of haploid selection in the appendix.

If we categorise the a allele as being ancestrally 'male-beneficial' via the fact that it is fixed on the Y, then $\lambda_{WA} > 1$ indicates that the neo-W spreads when found with the ancestrally 'female-beneficial' allele. Broadly, this is possible because the ancestral X chromosome is sometimes found in males and is therefore unable to perfectly specialise on the 'female-beneficial' allele. For example, when the a allele is favoured on the ancestral X in males, a polymorphism of A and a alleles can be maintained on the X despite directional selection in

Fig 2. Transitions between XY and ZW systems can occur even when the neo-SDR is less tightly linked to a locus under sexually-antagonistic selection (here, 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 can only invade when it is 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 marked by *). 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-SDR 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). Fitness parameters are: $w^{\female}_{AA} = 1.05$, $w^{\male}_{aa} = 1.2$, $w^{\female}_{aa} = w^{\male}_{AA} = 0.85$, $w^{\female\male}_{Aa} = 1$, $t^{\female\male} = \alpha^{\female\male}_{\Delta} = 0$.

favour of the A allele in females ($s^{\female} > 0$, $0 < h^{\female} < 1$), see outlined region in Figure 3A. When the a allele is strongly favoured on X chromosomes in males ($w^{\male}_{aa}$ sufficiently large relative to $w^{\male}_{Aa}$), neo-W-A haplotypes can spread ($\lambda_{WA} > 1$, see grey region in Figure 3A) because they produce hgher 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 ($w^{\female\male}_{Aa} = 1$) 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, $w^{\female}_{aa} = 0.85$, $w^{\female}_{AA} = 1.05$), favour the a allele (panel B, $w^{\female}_{aa} = 1.05$, $w^{\female}_{AA} = 0.85$), or be overdominant (panel C, $w^{\female}_{aa} = w^{\female}_{AA} = 0.6$). If λ_{wA} or λ_{wa} is greater than one, then a rare neo-W can spread for, at least, some values of $R > r$. The parameter values marked with an asterisk correspond to the fitnesses used in Figure 2C. Where both λ_{wA} and λ_{wa} are greater than one, a neo-W will spread when rare, regardless of linkage with the selected locus (for any R). Figure S1 Fig shows the dynamics using the parameters marked with a dagger. Here, there is no haploid selection $t^{\female\male} = \alpha^{\female\male}_{\Delta} = 0$.

When only one neo-W haplotype has a positive growth rate (see Figure 3), a neo-W can invade as long as equation (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. Therefore, tightly sex-linked loci that experience sexually-antagonistic selection can drive trans-GSD transitions in which the neo-SDR is less closely linked to the locus under selection (Figure 2).

Given that the a allele can be considered ancestrally 'male-beneficial' because it is fixed on the Y, it is surprising that neo-W-a haplotypes can sometimes be favoured by selection in females ($\lambda_{Wa} > 1$). Again, this occurs because ancestral X's also experience selection in males, in which they will always be paired with a Y-a. 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 in males. Therefore, the X can be polymorphic or even fixed for the A allele despite favouring the a allele during selection in females (e.g., see outlined region in Figure 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 from males and because they bring Y-a haplotypes into females, where it has higher fitness (Figure 1D).

In some cases, both W-A and W-a haplotypes can spread, e.g., when AA individuals have low fitness in females yet the A is polymorphic or fixed on the X due to overdominance in males (Figure 3B and 3C). Both neo-W-A and neo-W-a haplotypes then 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 haplotypes have positive growth rates, invasion by a neo-W is expected regardless of its linkage with the selected locus (i.e., even unlinked neo-W alleles can invade, see Figures S1 Fig and S2 Fig for examples).

Assuming that linkage is not tight, van Doorn and Kirkpatrick (2010) [32] showed that invasion by a neo-W occurs under the same conditions as 'pseudo-fixation' (at pseudo-fixation the neo-W reaches its maximum frequency among eggs, which is 1/2). An equivalent analysis is not possible where we assume that linkage is tight. However, numerical simulations with tight linkage demonstrate that the neo-SDR does not necessarily reach pseudo-fixation, leading to the stable maintenance of a mixed sex-determining system, in which X, Y, Z, and W alleles all segregate (e.g., Figure S9 FigB,C).

Loose linkage with the ancestral sex-determining region

Assuming that selection is weak ($s^{\mathfrak{gd}}$, $t^{\mathfrak{gd}}$, $\alpha_\Delta^{\mathfrak{gd}}$ of order $\epsilon << 1$) and thus implicitly assuming that all recombination rates (r, R and ρ) are large relative to selection, we denote the leading eigenvalues describing the invasion of a neo-Y ($k = 0$) and a neo-W ($k = 1$) into an ancestrally XY system by $\lambda_{Y',XY}$ and $\lambda_{W',XY}$, respectively. To leading order in selection, these are:

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

and

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

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

The neo-sex-determining allele, m, will spread if $\lambda_{m,XY} > 1$. Equation (2) demonstrates that, under weak selection, a neo-Y will invade an XY system if and only if it is more closely linked to the selected locus than the ancestral sex-determining region (i.e., if $R < r$; note that $V_A S_A^2$ is strictly positive as long as **A** is polymorphic). This echoes our tight linkage 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 (XY to XY or ZW to ZW) can only occur when the neo-sex-determining locus is more closely linked to a locus under sexually-antagonistic selection.

With weak selection and no haploid selection ($t^{\mathfrak{gd}} = \alpha_\Delta^{\mathfrak{gd}} = 0$), 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 (XY to ZW or ZW to XY) can also occur only if the neo-sex-determining region is more closely linked to a locus under selection ($R < r$), as found by [32]. With haploid selection, however, the additional term in equation (3) can be positive, which can allow, for example, neo-W invasion ($\lambda_{W',XY} > 1$) even when the neo-sex-determining region is less closely linked to the selected locus ($R > r$).

Equation (3) shows that, with weak selection, neo-W alleles can invade an XY system for a large number of selective regimes. To clarify the parameter space under which $\lambda_{W',XY} > 1$, we consider several special cases. Firstly, if the **A** locus is unlinked to the ancestral sex-determining region ($r = 1/2$), a more closely linked neo-W ($R < 1/2$) can always invade because there is no ancestral association between A alleles and sex chromosomes in males, $\left(\hat{p}_Y^{\mathfrak{d}} - \hat{p}_X^{\mathfrak{d}}\right) = 0$, see

equation (**??**). The second term in equation (3) therefore disappears and invasion depends only on the sign of $(r - R)$, as in the case of the neo-Y. Indeed, invasion typically occurs when the neo-W is more closely linked to the selected locus than the ancestral sex-determining region (Figure 4).

Fig 4. Ploidally-antagonistic selection allows a less tightly linked neo-W to invade. In panel A, male drive ($\alpha_\Delta^\male = -1/20$, $t^\male = \alpha_\Delta^\female = 0$) opposes selection in diploids (no sex-differences: $s^\male = 1/10$, $h^\male = 7/10$), in which case the neo-sex-determining allele can invade regardless of linkage. In panel B, gametic competition in males ($t^\male = -1/10$, $t^\female = \alpha_\Delta^\male = 0$) opposes selection in diploids (sex-differences: $s^\male = 3/20$, $s^\female = 1/20$, $h^\male = 7/10$), in which case the neo-sex-determining allele can once again invade regardless of linkage. We use Haldane's map function (Equation 3 in [70]) to convert from map distance (centiMorgans, cM) to the probability of recombination (an odd number of cross-over events).

Secondly, we can simplify the discussion of cases where invasion occurs despite looser sex-linkage, $R > r$, by focusing 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 Figure 4A and Figure 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 Figure 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 unlinked neo-W ($R = 1/2$, $r < 1/2$) into ancestral XY with 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	$h^\male = h^\female$, $t^\female = t^\male = \alpha_\Delta^\male = 0$	$s^\female s^\male > 0$
sperm competition only	$h^\male = h^\female$, $t^\female = \alpha_\Delta^\female = \alpha_\Delta^\male = 0$	$s^\female(s^\male - s^\female) > 0$
egg competition only	$h^\male = h^\female$, $t^\male = \alpha_\Delta^\female = \alpha_\Delta^\male = 0$	$s^\male(s^\female - s^\male) > 0$

Previous research suggests that when the ancestral sex-determining locus is linked to a locus that experiences haploid selection (e.g., meiotic drive), a new, unlinked sex-determining locus invades in order to restore equal sex ratios [37]. Consider, for example, the case where the **A** locus is linked to the ancestral-SDR ($r < 1/2$) 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 (Figure 1B and Figure 5B). If Fisherian sex ratio selection were dominant, we would expect a difference in the potential for XY to ZW and ZW to XY transitions. However, invasion by a neo-W into an XY system and invasion by a neo-Y into a ZW system occur under the same conditions ($\lambda_{Y',XY} = \lambda_{W',ZW}$ and $\lambda_{Y',ZW} = \lambda_{W',XY}$, at least to order ϵ^2). For example, in Figure 5A neo-W alleles invade an ancestral-XY system where females are initially rare. However, Figure 5B shows that a neo-Y can invade an ancestral-ZW system under the same conditions. As a consequence, whenever

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 drive in an ancestral XY system causes a male bias (see Figure 1B), allowing a neo-W to invade and replace the ancestral sex-determination system (inset shows neo-W frequency among female gametes), which balances the zygotic sex ratio. In panel B, male drive in an ancestral ZW system has no affect on the zygotic sex ratio (see Figure 1B) yet a neo-Y can invade and replace the ancestral sex-determination system (inset shows neo-Y frequency among male gametes, the ancestral W also goes to fixation during this transition). When $R < 1/2$, the neo-Y becomes associated with the allele favoured by drive, causing the zygotic sex ratio to become biased, hence the frequency of the neo-Y at pseudo-fixation can be higher than 0.5 (inset). Parameters: $s^{\text{♀}} = s^{\text{♂}} = 0.2$, $h^{\text{♀}} = h^{\text{♂}} = 0.7$, $t^{\text{♀}} = t^{\text{♂}} = \alpha_{\Delta}^{\text{♀}} = 0$, $\alpha_{\Delta}^{\text{♂}} = -0.1$, $r = 0.02$.

$R < 1/2$, the neo-Y becomes associated with the male meiotic drive allele such that the zygotic sex ratio actually evolves to become biased towards males.

Why can new sex-determining regions invade when more loosely linked to selected loci ($R > r$)? Consider first the case where both loci are linked to the selected locus ($r < R < 1/2$). In an XY system, haploid selection in males can facilitate the spread of a neo-W because the zygotic sex ratio is ancestrally biased and the W helps to equalize the sex ratio (Figure 5A). A new sex determining region can also, however, benefit from becoming more associated with drive. For example in a ZW system with the same selection regime (haploid selection in males), a neo-Y can spread despite the fact that the zygotic sex is initially even; 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 (Figure 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 Figure 5B (green curve), the neo-Y 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* found at high frequency on the W background, which has higher average diploid fitness to balance the haploid advantage of the *a* allele at equilibrium.

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. 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-determination systems that allow 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 eigenvalues (equations **??**) does not factor for ESD mutants as it does for $k = 0$ or $k = 1$. We therefore focus on weak selection here. Assuming weak selection, the spread of the new sex-determining region is given by

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

which 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 which is given by

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

where $\lambda_{Y',XY|R=1/2}$ and $\lambda_{W',XY|R=1/2}$ 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, doesn't enter into the $k = 1/2$ results. This is because sex is essentially randomized each generation, preventing associations from building up between allele A and sex. Equation (5) shows that the neo-ESD 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, $\lambda_{Y',XY|R=1/2}$ is necessarily less than one, but $\lambda_{W',XY|R=1/2}$ can be greater than one if there is haploid selection. That is, when there is haploid selection, ESD mutations can invade an ancestrally-XY system because they generate females that are either rare or have high fitness, in the same manner as a neo-W.

Significantly, equation (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, Fisherian sex ratio selection alone does not easily explain the invasion of ESD. For example, when the ancestral sex-determination 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 $\lambda_{W',XY}$) and when it doesn't (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, $r < 1/2$, $h^{♀} = h^{♂}$, and $s^{♀}s^{♂} < 0$, then $\lambda_{W',XY} < 1$, see Table 3). We conclude that, as with neo-W and neo-Y loci, associations with selected loci mean that the evolution of neo-ESD systems is not straightforwardly predicted by selection to balance the zygotic sex ratio when haploid selection is present.

Discussion

Two predominant theories explaining the remarkably high frequency of transitions between sex-determination systems are sexually-antagonistic selection and sex ratio selection (reviewed in [29, 30]). The former predicts that neo-sex-determining alleles can invade when they arise in closer linkage with a sexually-antagonistic locus [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 region can favour trans-GSD transitions (XY to ZW or ZW to XY) to new sex-determining systems that are less closely linked to the selected loci (e.g., see Figure 2). Similarly, even when linkage is weak relative to selection, we show that trans-GSD transitions (XY to ZW or ZW to XY) can occur where the new sex-determining region is less closely linked to the locus under selection if there is haploid selection (e.g., Figures 4 and 5).

We find that the spread of neo-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 GSD-ESD transitions between sex-determining systems. For instance, alleles favoured by haploid selection in males often become associated with the Y, which leads to a male-biased zygotic sex ratio. This male bias increases the potential for a neo-W to invade (Table 2), which can equalize the sex ratio (e.g., see Figure 5B, for related examples see [37]). 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., Figure 5A and step 1 in [71]). 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 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 neo-sex-determining allele, and these selective pressures are often predicted to be of equal magnitude.

We have shown that the spread of new sex determination systems can be driven by loci experiencing haploid selection. In agreement with this hypothesis, a recent transcriptome analysis in *Rumex* shows that Y-linked genes have higher expression in haploid pollen than autosomal genes (check this is accurate). Interestingly, haploid-expression is also more common on the autosome that is orthologous to the sex chromosomes in closely related species suggesting that new sex chromosomes may have been favoured through their association with haploid selected alleles on these chromosomes (Sandler et al., 2018, Personal Communication). In general, we predict that haploid selection increases lability of sex-determination systems, particularly because haploid selection can cause transitions that increase or decrease sex-linkage (e.g., the final state of the red line in Figure 5B is the starting state in Figure 5A). 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 (XY to ZW or ZW to XY) 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 $\lambda_{W',XY} > \lambda_{Y',XY}$; Equations 3 and **??**). 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 during the haploid stage could also drive transitions between dioecy and hermaphroditism, which are frequent in plants [72, 73].

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, 74, 75]. Our results show, however, that tight ancestral-linkage of polymorphic loci 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., Figures 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 [76–79]. Several rodent species also maintain feminizing alleles along with the ancestral X and Y sex-determination alleles (reviewed in [80]). For example, in nine *Akadon* species, it appears that male-determining-*sry* expression is suppressed by an autosomal feminizing allele, creating XY females [81, 82], which have increased fitness relative to XX females [83]. In *Mus microtoides*, females can have XX, XX* or X*Y genotypes [84]. 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 [85–87]. Although Y-linkage of female-beneficial alleles is counterintuitive, our tight linkage 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 around the Y or W sex-determining regions [88–91]. During trans-GSD transitions (XY to ZW or ZW to XY), but not cis-GSD transitions (XY to XY or ZW to ZW), 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-determination 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 region 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, [8] found a dozen sex chromosome configurations among Dipteran species but only one transition between male and female heterogamety.

In this study, we have only considered neo-sex-determining alleles of large effect. However, we expect similar selective forces to act on masculinizing/feminizing alleles of weaker effect. For example, [33] consider small effect masculinizing/feminizing alleles within a threshold model of sex determination, finding that they can be favoured when linked to loci that experience sexually-antagonistic selection. These results echo those for large-effect neo-Y/neo-W alleles [31, 32]. 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, 71] 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-determination systems. In particular, both can select for neo-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-determination systems. Perhaps counterintuitively, transitions involving haploid selection can be driven by sex ratio selection or cause sex ratio biases to evolve; we do not find Fisherian sex ratio selection to be an overwhelming force. Overall, our results suggest several new scenarios under which new sex-determination systems are favoured, which could help to explain why the evolution of sex-determination 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. Neo-W alleles can spread when loci under diploid selection are tightly linked to the ancestral sex determining locus ($r \approx 0$). In panels A and B, the a allele is favoured in females ($w^{\female}_{aa} = 1.05$, $w^{\female}_{Aa} = 1$, $w^{\female}_{AA} = 0.85$) and selection in males is overdominant ($w^{\male}_{aa} = w^{\male}_{AA} = 0.75$). In panels C and D, selection in males and females is overdominant ($w^{\female}_{aa} = w^{\female}_{AA} = 0.6$, $w^{\male}_{aa} = 0.5$, $w^{\male}_{AA} = 0.7$, $w^{\female\male}_{Aa} = 1$). There is no haploid selection $t^{\female\male} = \alpha^{\female\male}_{\Delta} = 0$. These parameters are marked by daggers in Figure 3B and C, which show that neo-W invasion is expected for any R ($\lambda_{WA}, \lambda_{Wa} > 1$) when 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). The weak selection approximation holds when all recombination rates are large relative to selection (around 0 in panels A and C), in which case, in the absence of haploid selection, neo-W alleles should spread if and only if they are more tightly linked to the selected locus (positive invasion fitness if and only if the selected locus is in the grey region). However, when linkage is tight (panels B and D and when the selected locus is near the SDRs in all panels), this weak selection prediction can break down.

S2 Fig. Following invasion by a neo-W allele, there can be a complete transition to a new sex-determination system, maintenance of polymorphism at both ancestral-XY and neo-ZW sex determining regions, or loss of the new sex-determining allele. Here we plot the frequency of the neo-W allele among female gametes; as the neo-W reaches frequency 0.5, polymorphism at the ancestral XY locus is lost with Y becoming fixed such that sex is determined only be the ZW allele carried by a female gamete. 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 (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 (see blue lines in Figure S1 FigA and S1 FigB near the ancestral SDR). In contrast, the neo-W is not lost in panel D as it is favoured near $r \approx 0$ (see blue lines in Figure S1 FigC and S1 FigD near the ancestral SDR). Fitness parameters are the same as in Figure S1 Fig; in panels A and B the a allele is favoured in females ($w^{\female}_{aa} = 1.05$, $w^{\female}_{Aa} = 1$, $w^{\female}_{AA} = 0.85$) while there is overdominance in males ($w^{\male}_{aa} = w^{\male}_{AA} = 0.75$) and in panels C and D, there is overdominance in both sexes ($w^{\female}_{aa} = w^{\female}_{AA} = 0.6$, $w^{\male}_{aa} = 0.5$, $w^{\male}_{AA} = 0.7$, $w^{\female\male}_{Aa} = 1$). These parameters are marked by a dagger in Figure 3. Here, there is no haploid selection $t^{\female\male} = \alpha^{\female\male}_{\Delta} = 0$.

S3 Fig. When there is sexually-antagonistic selection and haploid selection, a neo-W may invade for any R. Panel A shows that the invasion fitness of a neo-W is positive where linkage is tight, 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-SDR 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 Figure 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 Figure 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 Figure S9 FigC.

S4 Fig. Meiotic drive in males affects whether neo-W-*A* and neo-W-*a* haplotypes spread when the ancestral-XY locus is tightly linked to a locus under selection ($r = 0$). We vary the fitness of male homozygotes relative to heterozygotes ($w_{Aa}^{\male\female} = 1$) and only consider stable equilibria at which both **A** locus allele are maintained and the a allele is initially fixed on the Y, region outlined. 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 λ_{WA} and λ_{Wa}. By contrast, λ_{WA} and λ_{Wa} tend to be reduced when meiotic drive in males favours the A allele ($\alpha_\Delta^\male = 0.16$), panels D-F. We consider three forms of selection in females: directional selection in favour of the A allele (panels A and D, $w_{aa}^\female = 0.85$, $w_{AA}^\female = 1.05$), direction selection in favour of the a allele (panels B and E, $w_{aa}^\female = 1.05$, $w_{AA}^\female = 0.85$), and overdominance (panels C and F, $w_{aa}^\female = w_{AA}^\female = 0.6$).

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. Diploid selection parameters ($w_{ij}^{\male\female}$) are the same as those in Figure S4 Fig. 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 λ_{WA} and λ_{Wa}. On the other hand, the A allele is favoured during male gametic competition in Panels D-F ($w_a^\male = 1$, $w_A^\male = 1.16$) and λ_{WA} and λ_{Wa} tend to be reduced. Compared to the meiotic drive parameters in Figure S4 Fig, the effect of these male gametic competition parameters on the sex ratio is smaller. For example, in Figure 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. Diploid selection parameters ($w_{ij}^{\male\female}$) are the same as those in Figure S4 Fig and S5 Fig. The a allele is favoured by meiotic drive in females in Panels A-C ($\alpha_\Delta^\female = -0.16$), which increases λ_{Wa} and decreases λ_{WA}. 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. Diploid selection parameters ($w_{ij}^{\male\female}$) are the same as those in Figure S4 Fig, S5 Fig, and S6 Fig. 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 λ_{Wa} and decreases λ_{WA}. 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 λ_{Wa} and λ_{WA}.

S8 Fig. A-D show when each of the neo-W haplotypes invade 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, $\alpha_\Delta^{\male\female}$, or haploid competition, $t^{\male\female}$. 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. Fixation of neo-W or maintenance of multiple sex-determining systems. 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 neo-ZW locus, such that there are males with genotypes XY-ZZ or YY-ZZ and females with genotypes XX-ZZ, XX-ZW, XY-ZW, or YY-ZW. In panel A, selection is ploidally antagonistic with drive in males (parameters as in the green curve in Figure 5B). In panel B, there is overdominance in both sexes and no haploid selection (parameters as in the green curve in Figure S2 FigC). In panel C, there is sexually-antagonistic selection in diploids with drive in males (parameters as in the green curve in Figure S4 FigC). In all cases, the initial equilibrium frequency has a near fixation on the Y.

Acknowledgments

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