Gametic Selection, Sex Ratio Bias, and Transitions Between Sex Determination Systems

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Contributions:

Abstract

Sex determination systems are remarkably dynamic; many studied taxa display transitions between sex-determining genes across chromosomes or the evolution of new sex-determining systems. Here, we utilize population genetic models to study the spread of novel sex-determiners in systems with haploid gametic selection, e.g., pollen or sperm competition. Haploid selected loci experience a form of sex-specific selection when gametic competition occurs predominantly among haploids produced by one sex (e.g., pollen competition). This can cause sex ratios at birth to become biased as sex ratios are determined by the fertilization success of X- versus Y-bearing pollen/sperm (or Z- versus W-bearing eggs). Notably, we find that the spread of new genetic sex determination systems is not affected by sex ratio biases that are caused by gametic selection because sex ratios become biased after parental provisioning has occurred, even if pollen/sperm competition occurs within the mother (e.g., pollen competition in stigma). In addition, we find that linkage of an ancestral sex chromosome to a locus under haploid selection can favour transitions between male and female heterogamety (e.g., XY to ZW), which is not the case for any forms of diploid sex specific selection (e.g., sexually antagonistic selection). During these transitions, new sex-determining alleles spread despite breaking up favourable associations that build up between ancestral sex-determining loci and selected loci, reducing population mean fitness. Furthermore, a period of selection among haploids can favour the stable maintenance of polymorphic sex determination systems. Thus, our models offer several new insights to be explored as information about sex determination in non-model taxa accumulates.

Introduction

Animals and angiosperms exhibit extremely diverse sex determination systems (reviewed in Bull 1983, Charlesworth and Mank 2010, Beukeboom and Perrin 2014, Bachtrog et al. 2014). Among species with genetic sex determination of diploid sexes, some taxa have heterogametic males (XY) and homogametic females (XX), including mammals and most dioecious plants (Ming et al. 2011); 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 (Li et al. 2011, Yano et al. 2012), Diptera (Vicoso and Bachtrog 2015), and *Oryzias* (Myosho et al. 2012). In addition, many gonochoric/dioecious clades with genetic sex determination exhibit transitions between male (XY) and female (ZW) heterogamety, including lizards (Ezaz et al. 2009), eight of 26 teleost fish families (Mank et al. 2006), true fruit flies (Tephritids, Vicoso and Bachtrog 2015), amphibians (Hillis and Green 1990), the angiosperm genus *Silene* (Slancarova et al. 2013), Coleoptera and Hemiptera (Beukeboom and Perrin 2014, plate 2). Indeed, in some cases, both male and female heterogametic sex determination systems can be found in the same species, as exhibited by some cichlid species (Ser et al. 2010) and *Rana rugosa* (Ogata et al. 2007). In addition, multiple transitions have occurred between genetic and environmental sex determination systems, e.g., in reptiles and fishes (Conover and Heins 1987, Mank et al. 2006, Pokorná and Kratochvíl 2009, Ezaz et al. 2009, Pen et al. 2010, Holleley et al. 2015).

Predominant theories in which new sex determination systems are favoured by selection involve fitness differences between sexes (e.g., sexually antagonistic selection) or sex ratio selection. van Doorn and Kirkpatrick (2007; 2010) show that new sex determination loci can be favoured if they arise in close linkage with a locus that experiences sexual antagonism. For ex-

ample, linkage allows favourable associations to build up between a male-beneficial allele and a neo-Y chromosome. Such associations can favour a new master sex-determining gene on a new chromosome (van Doorn and Kirkpatrick 2007) and can also favour a transition between male and female heterogamety (e.g., a ZW to XY transition, van Doorn and Kirkpatrick 2010). However, any sexually-antagonistic loci that are linked to the ancestral sex-determination locus will develop similar, favourable associations and select against the spread of a new sex-determination system.

It has been suggested that sex ratio selection could be a particularly important force driving transitions between sex-determining systems (Beukeboom and Perrin 2014, Chapter 7). For example, flexible sex determination systems may be favoured in order to exploit local environmental conditions that are optimal for males or females, which creates locally biased sex ratios (Charnov and Bull 1977, Werren and Taylor 1984, Pen et al. 2010). In addition, feminizing mutations may invade when female biased sex ratios are favoured due to selection among demes (Wilson and Colwell 1981, Vuillleumier et al. 2007). In other situations, sex ratio selection may favour transitions in order to restore equal sex ratios. For example, Kozielska et al. (2010) 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 (Hamilton 1967). They find that new, unlinked sex-determining loci (masculinizing or feminizing mutations, i.e., neo-Y or neo-W loci) can then spread, restoring an even sex ratio.

Here, we use mathematical models to find the conditions under which new sex determination systems are favoured by selection when there is a period of selection among haploid gametes/gametophytes. Selection among haploid genotypes is thought to occur primarily among pollen/sperm, which can compete whenever there are more pollen/sperm than required for fertilization (Mulcahy et al. 1996, Joseph and Kirkpatrick 2004). Haploid selection

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 (Borg et al. 2009, Arunkumar et al. 2013, Gossmann et al. 2014). In addition, artificial selection pressures applied to male gametophytes cause the frequency of resistant alleles to increase (e.g., Hormaza and Herrero 1996, Ravikumar et al. 2003, Hedhly et al. 2004, Clarke et al. 2004). A smaller (but non-negligible) proportion of genes are thought to be expressed and selected in animal sperm, although precise estimates are uncertain (Zheng et al. 2001, Joseph and Kirkpatrick 2004, Vibranovski et al. 2010).

There are various ways in which a period of haploid selection could influence transitions between sex determination systems. Firstly, if we assume that haploid selection at any particular locus predominantly occurs in one sex (e.g., pollen/sperm competition), then such loci experience a form of sex-specific selection. In this respect, we might expect that haploid selection might affect transitions between sex determination systems in a similar manner to sex-specific diploid selection (as explored by van Doorn and Kirkpatrick 2007; 2010). That is, new masculizing mutations (neo-Y chromosomes) could be favoured via linkage associations with alleles that are beneficial in pollen/sperm. However, sex ratios can also become biased if there is linkage between the sex-determining region and a locus that harbours genetic variation in haploid fitness. For example, differences in fitness between X- and Y-bearing pollen tubes can cause the sex ratio among seeds to become biased when there is pollen competition (Lloyd 1974, Conn and Blum 1981, Stehlik and Barrett 2005; 2006, Field et al. 2012; 2013). It is not immediately clear how the spread of new sex determination systems would be influenced by the combination of sex ratio biases and favourable associations between haploid selected loci and sex-determining regions.

Surprisingly, our models show that haploid selection influences the evolution of new sex determination systems in a way that is distinct from both

diploid sex-specific selection and sex ratio selection. We find that new genetic sex determination systems are not affected by any sex ratio biases caused by associations between sex-determining regions and haploid selected loci. In addition, we find that associations that build up between an ancestral sex-determining locus and a haploid-selected locus can favour transitions between male and female heterogamety (e.g., a neo-W allele arising at a previously autosomal locus spreads in an ancestrally XY system), despite the fact that these ancestral associations were built up by selection. This does not occur in models that do not include haploid selection.

NOTE RE: DRIVE. I expect drive (that occurs specifically in one sex, e.g., during spermatogenesis) to behave almost exactly like haploid selection. That is, I think that a XY-linked driver that is maintained by selection (e.g., because it causes sterility when homozygous, which is common in known drive systems) will only favour invasion of a more tightly linked neo-Y (worsening sex ratio biases) and could favour invasion of a neo-W. This may run counter to generic expectations from new sex chromosome systems evolving to balance the sex ratio. So, do you think it would significantly enhance the paper to model drive explicitly or just discuss it as being similar???

FOR RESULTS?

FROM PREVIOUS PAPER: The maintenance of polymorphism at loci that experience sex specific selection in both haploid and diploid phases was considered by Immler et al. Immler et al. (2012), demonstrating that polymorphisms can be maintained by sexually antagonistic selection or overdominance as well as by conflicting selection pressures in haploids and diploids (haploid-diploid conflict or ploidally antagonistic selection) or a combination of these selective regimes.

Model

We consider the transition between ancestral and novel sex determination systems using a three locus model. 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 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 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, the m allele confers environmental sex determination such that zygotes develop as females in a proportion (k) of the environments they experience. Finally, we also analyze a model of maternally-controlled environmental sex-determination (ESD), where mothers with at least one m allele produce daughters with probability k.

In each generation, we census the genotype frequencies in male and female gametes/gametophytes (hereafter gametes) before haploid competition (see Sup. Mat. for recursion equations). First, competition occurs among male gametes (sperm/pollen competition) and among female gametes (egg/ovule competition). Selection during haploid competition depends on the **A** locus genotype, fitnesses are w_A^m and w_a^m for male gametes and w_A^f and w_a^f for female gametes, see table 1. Random mating then occurs between male and female gametes. The resulting zygotes develop as males or females, depending on their genotypes at the **X** and **M** loci (and the **M** genotype of their mother in the case of maternal control) as described above. Diploid males

and females then experience selection, male fitness is given by w_h^m and female fitness by w_h^f, where h is the genotype at the **A** locus ($h \in AA, Aa, aa$). The next generation of gametes are then produced by meiosis, during which recombination and sex-specific meiotic drive can occur. Recombination 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 χ. Therefore, any order of the loci can be modelled with appropriate choices of r, R, and χ (see Table S.1). Males/females that are heterozygous at the **A** locus experience meiotic drive; Aa heterozgotes of sex d produce gametes bearing allele A with probability α^d. Thus, the **A** locus can experience sex-specific haploid competition, diploid selection and/or meiotic drive.

Table 1: Fitness of different genotypes in sex d

Genotype	Fitness during haploid competition
A	$w_A^d = 1 + t^d$
a	$w_a^d = 1$
Genotype	Fitness during diploid selection
AA	$w_{AA}^d = 1 + s^d$
Aa	$w_{Aa}^d = 1 + h^k s^d$
aa	$w_{aa}^d = 1$
Genotype	Tranmission during meiosis in Aa heterozygotes
A	$\alpha^d = 1/2 + \alpha_\Delta^d/2$
a	$(1 - \alpha^d) = 1/2 - \alpha_\Delta^d/2$

Results

The only asymmetry between males and females in our model is that, under the ancestral sex determination system, males develop with genotype XY (or ZZ) and females with genotype XX (or ZW). Therefore, without loss of generality, we primarily present results for ancestral XY sex determination.

Ancestral ZW sex determination can be considered by changing the notation such that X becomes Z, Y becomes W and the labelling of male and female selection terms are reversed.

Resident equilibrium and stability

In the resident population (allele M fixed), we follow the frequency of A in female gametes (eggs) from an XX female, p_X^f, and in X-bearing, p_X^m, and Y-bearing, p_Y^m, male gametes (sperm). We also track the total frequency of Y-bearing male gametes, q, which may deviate from $1/2$ due to meiotic drive in males.

Various forms of selection can maintain a polymorphism at the **A** locus, including sexually antagonistic selection, overdominance and conflicts between diploid selection and selection upon haploid genotypes (ploidally antagonistic selection, Immler et al. 2012) or a combination of these selective regimes. In particular special cases, e.g., no sex-differences in selection or meiotic drive ($s^m = s^f$, $h^m = h^f$, and $\alpha^m = \alpha^f = 1/2$), equilibrium allele frequency and stability can be calculated analytically without assuming weak selection. Here, we assume that selection and meiotic drive are weak relative to recombination (s^k, t^k, α_Δ^k of order ϵ). The maintenance of a polymorphism at the **A** locus then requires that

$$\begin{aligned} 0 &< -((1-h^f)s^f + (1-h^m)s^m + t^f + t^m + \alpha_\Delta^f + \alpha_\Delta^m) \\ 0 &< (h^f s^f + h^m s^m + t^f + t^m + \alpha_\Delta^f + \alpha_\Delta^m). \end{aligned} \tag{1}$$

which indicates that a polymorphism is maintained under various selective regimes.

Given that a polymorphism is maintained at the **A** locus by selection, with weak selection and drive, to leading order, the frequencies of A in each type of gamete are the same ($\hat{p}_X^f = \hat{p}_X^m = \hat{p}_Y^m = \bar{p}$) and given by

$$\bar{p} = \frac{h^f s^f + h^m s^m + t^f + t^m + \alpha^f_\Delta + \alpha^m_\Delta}{(2h^f - 1)s^f + (2h^m - 1)s^m} + O(\epsilon). \tag{2}$$

Differences in frequency between gamete types are of order ϵ to leading order and given by

$$\begin{aligned}
\hat{p}^m_X - \hat{p}^f_X &= V_A\big(D^m - D^f + \alpha^m_\Delta - \alpha^f_\Delta\big) + O(\epsilon^2) \\
\hat{p}^m_Y - \hat{p}^f_X &= V_A\big(D^m - D^f + \alpha^m_\Delta - \alpha^f_\Delta + (1-2r)(t^m - t^f)\big)/2r + O(\epsilon^2) \\
\hat{p}^m_Y - \hat{p}^m_X &= V_A\big(D^m - D^f + \alpha^m_\Delta - \alpha^f_\Delta + t^m - t^f\big)(1-2r)/2r + O(\epsilon^2)
\end{aligned} \tag{3}$$

where $V_A = \bar{p}(1-\bar{p})$ is the variance in the frequency of A and $D^d = \big(\bar{p}s^d + (1-\bar{p})h^d s^d\big) - \big(\bar{p}h^d s^d + (1-\bar{p})\big)$ corresponds to the difference in fitness between A and a alleles in diploids of sex d ($\bar{p}$ is the leading-order probability of mating with an A-bearing gamete from the opposite sex). The frequency of Y among male gametes depends upon the difference in A allele frequency on X- and Y-bearing male gametes and the strength of meiotic drive in favour of the A allele, $q = 1/2 + \alpha^m_\Delta(\hat{p}^m_Y - \hat{p}^m_X)/2 + O(\epsilon^3)$. Without haploid competition or drive ($\alpha^d_\Delta = t^d = 0$), these results reduce to those of van Doorn and Kirkpatrick (2007).

Sex chromosome turnover

The evolution of a new sex determination system requires that a rare mutant, m, at the novel sex-determining locus 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 described by the next generation frequency of eggs and sperm carrying the mutation, (S.1c), (S.1d), (S.1g), (S.1h), which is an eight equation system. Dominant neo-Y chromosomes (when $k = 0$) or neo-W chromosomes (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 (for a neo-Y) or by females (for a neo-W). Furthermore, if the m allele is fully dominant over the ancestral sex-determining system, phenotypes are not affected by the genotype at the ancestral sex-determining region (**X** locus). Therefore, the invasion of rare mutant neo-Y or neo-W chromosomes can be simplified and given by the largest eigenvalue that solves the quadratic characteristic polynomial

$$\lambda^2 + b\lambda + c = 0 \tag{4}$$

where b is the average of the growth rates of the two haplotypes that carry the m allele (mA and ma), $b = (\lambda^m_{mA} + \lambda^m_{ma})/2$, and c also involves the fitness of m alleles when they recombine onto the other **A** background in a heterozygote, $c = \lambda_{mA}\lambda_{ma} + \rho_{mA}\rho_{ma}$, see table 2.

Table 2: Parameters determining invasion (equation 4) for neo-Y or neo-W chromosomes

neo-Y ($k = 0$)
$\lambda_{mA} = \{p^f_X w^f_A w^m_A w^m_{AA} + (1 - p^f_X) w^f_a w^m_A w^m_{Aa} \alpha^m (1 - R)\}/\bar{w}^f_H \bar{w}^m_H \bar{w}^m$
$\lambda_{ma} = \{(1 - p^f_X) w^f_a w^m_a w^m_{aa} + p^f_X w^f_A w^m_a w^m_{Aa} (1 - \alpha^m)(1 - R)\}/\bar{w}^f_H \bar{w}^m_H \bar{w}^m$
$\rho_{mA} = R\{(1 - p^f_X) w^f_a w^m_A w^m_{Aa} (1 - \alpha_m)\}/\bar{w}^f_H \bar{w}^m_H \bar{w}^m$
$\rho_{ma} = R\{p^f_X w^f_A w^m_a w^m_{Aa} \alpha_m\}/\bar{w}^f_H \bar{w}^m_H \bar{w}^m$
neo-W ($k = 1$) *
$\lambda_{mA} = \{\bar{p}^m w^m_A w^f_A w^f_{AA} + (1 - \bar{p}^m) w^m_a w^f_A w^f_{Aa} \alpha^f (1 - R)\}/\bar{w}^f_H \bar{w}^m_H \bar{w}^f$
$\lambda_{ma} = \{(1 - \bar{p}^m) w^m_a w^f_a w^f_{aa} + \bar{p}^m w^m_A w^f_a w^f_{Aa} (1 - \alpha^f)(1 - R)\}/\bar{w}^f_H \bar{w}^m_H \bar{w}^f$
$\rho_{mA} = R\{(1 - \bar{p}^m) w^m_a w^f_A w^f_{Aa} (1 - \alpha_f)\}/\bar{w}^f_H \bar{w}^m_H \bar{w}^f$
$\rho_{ma} = R\{\bar{p}^m w^m_A w^f_a w^f_{Aa} \alpha_f\}/\bar{w}^f_H \bar{w}^m_H \bar{w}^f$

* $\bar{p}^m = p^m_Y q + p^m_X (1 - q)$ is the average frequency of the A allele among X- and Y-bearing male gametes (pollen/sperm).

Equation (4) and table 2 illustrate a number of key points about the invasion of neo-Y and neo-W mutations. For a neo-Y, invasion depends on the relative (is this right, is relative fitness divided by mean fitness or difference from 1???) fitness of A-bearing and a-bearing male gametes (i.e., in sperm only, not eggs). The fitness of male gametes partly depends on the allele carried by the female gamete that they mate with (e.g., A with probability $p_X^f w_A^f/\bar{w}_H^f$). Similarly, invasion of a neo-W depends on the relative fitness of A-bearing and a-bearing female gametes. However, in the case of a neo-W, the allele carried by the male gamete that they mate with can come from either an X-bearing or a Y-bearing sperm (e.g., A with probability $\bar{p}^m w_A^m/\bar{w}_H^m$, where $\bar{p}^m = p_Y^m q + p_X^m(1-q)$). In either case, the zygote will then develop as a female due to the presence of a neo-W. By contrast, females that do not carry the neo-W, only result from matings with X-bearing sperm (e.g., matings with A-bearing sperm occur with probability $\bar{p}_X^m w_A^m/\bar{w}_H^m$). If the **A** locus is initially linked to the ancestral sex-determining locus, **X**, (i.e., $r < 1/2$) the frequency of the A allele among X- and Y-bearing sperm can differ (equation 3). Thus, eggs with and without a neo-W differ in the frequency of A alleles they obtain from mating with male gametes.

We are particularly concerned with whether or not a rare neo-sex-determining region increases in frequency, which occurs when the largest eigenvalue, λ, that solves (4) is greater than one. If the average change in frequency of the two haplotypes that carry the m allele (Am and am) is positive, invasion will always occur (if $\{(\lambda_{mA}-1)+(\lambda_{ma}-1)\}/2 > 0$, $\lambda > 1$). If neither haplotype increases in frequency ($\lambda_{mA}, \lambda_{ma} < 1$ is this notation valid?), the m allele will not invade. Otherwise, the new sex-determining allele increases in frequency on one **A** background and declines on the other, and invasion requires

$$R\left[\frac{p_X^f w_a^m(1-\alpha^m)}{(\lambda_{mA}-1)\bar{w}_H^m} + \frac{(1-p_X^f)w_A^m\alpha^m\bar{w}_H^m}{(\lambda_{ma}-1)\bar{w}_H^m}\right]\frac{w_{Aa}^m}{\bar{w}^m} < 1, \tag{5}$$

for the neo-Y, and

$$R\left[\frac{(1-\bar{p}^m)w_a^m}{(\lambda_{mA}-1)\bar{w}_H^m}+\frac{\bar{p}^m w_A^m}{(\lambda_{ma}-1)\bar{w}_H^m}\right]\frac{w_{Aa}^f}{\bar{w}^f}<1 \tag{6}$$

FIX THESE EQUATIONS... for the neo-W. Equations (5) and (6) show that the new sex-determining allele, m, is expected to invade for any recombination rate, R, when the net flow of recombinants is from the less fit (smaller λ_{mi}) to the more fit **A** background (making the terms inside the square brackets in Equations 5 and 6 negative). Q: is it definitely possible to have negative square brackets for a equilibria maintained by selection? When the net flow of recombinants is from the more fit to the less fit haplotype, the new sex-determining allele can still invade when the rate of recombination between it and the selected locus, R, is small enough. Q:Is it the case that sometimes the square brackets are positive and invasion occurs for $R = 1/2$? In which case it might be better to have slightly different phrasing here.

We can explicitly determine the conditions under which invasion occurs if we assume that the A allele reaches an equilibrium frequency under the ancestral sex-determination system before the neo-sex-determination system (m) arises. The equilibrium frequency of A on different ancestral backgrounds ($\hat{p}_Y^m$, $\hat{p}_X^m$, and $\hat{p}_X^f$) is given by equations (2) and (3) where we assume selection and meiotic drive are weak relative to recombination (s^k, t^k, α_Δ^k of order ϵ). Under weak selection, we denote the leading eigenvalue describing the invasion of a neo-Y ($k = 0$) and a neo-W ($k = 0$) into an ancestrally XY system by $\lambda_{Y',XY}$ and $\lambda_{W',XY}$, respectively, which are given by

$$\lambda_{Y',XY} = 1 + \frac{V_A\,(r-R)\,(S_A)^2}{rR} + O\left(\epsilon^3\right) \tag{7}$$

and

$$\lambda_{W',XY} = \lambda_{Y',XY} + \left(2\alpha_\Delta^m - 2\alpha_\Delta^f + t^m - t^f\right)(\hat{p}_Y^m - \hat{p}_X^m) + O\left(\epsilon^3\right) \tag{8}$$

where $V_A = \bar{p}(1-\bar{p})$ is the variance in the frequency of A and $S_A = (D^m + \alpha_\Delta^m + t^m) - (D^f + \alpha_\Delta^f + t^f)$ is the difference in fitness in males versus females for the A allele against the a allele across diploid selection, haploid competition, and meiosis.

It may seem counterintuitive that, if the A allele is more common on the ancestral-Y than the ancestral-X, and only favoured during haploid selection in males

although our predictions also perform well when recombination is small, see figure 1. We would have to add a line showing what invasion fitness the weak selection approximation would give and add dots to this figure (dots that are currently connected by a line), as in (vD&K, 2010)

Add figure w/ drive that explains this. Previous research suggests, 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 can invade in order to restore equal sex ratios (Kozielska et al. 2010). Our model provides a good opportunity to determine whether Fisherian sex ratio selection provides a useful explanation for the evolution of new sex-determining loci in other contexts. 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 (e.g., during spermatogenesis but not during oogenesis, $\alpha^m \neq 1/2$, $\alpha^f = 1/2$). We will also disregard haploid competition ($t^f = t^m = 0$) such that zygotic sex ratios can only be biased by meiotic drive in males. In this case, the zygotic sex ratio can be initially biased only if the ancestral sex-determining system is XY. If the ancestral sex-determining system is ZW, the zygotic sex ratio will be 1:1 because diploid sex is determined by the proportion of Z-bearing versus W-bearing eggs (and meiosis in females is fair). Thus, if the zygotic sex ratio is crucial to the evolution of new genetic sex-determining systems, invasion into ZW and XY systems will be distinct. However, we find that invasion of new homogametic systems (XY to XY, or ZW to ZW) and heterogametic systems (XY to ZW or ZY to XY) occur

under the same conditions. That is, $\lambda_{Y',XY} = \lambda_{W',ZW}$ and $\lambda_{Y',ZW} = \lambda_{W',XY}$.

Offspring-controlled neo-ESD

The growth rate of a rare, dominant offspring-controlled neo-ESD region that produces males or females with equal probability ($k = 1/2$) is

$$\lambda_{ESD,XY} \approx 1 + \frac{1}{2}\frac{(\lambda_{Y,XY} - 1) + (\lambda_{W,XY} - 1)}{2}\Big|_{R=1/2} \tag{9}$$

Thus with $k = 1/2$ the neo-ESD gets half of the advantages of a neo-W and half that of a 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). Recombination between the selected locus and the novel sex-determining locus, R, doesn't enter into the $k = 1/2$ results because sex is essentially randomized each generation, preventing associations from building up between allele A and sex.

Depends 50% on its fitness relative to non-mutant males and 50% on its fitness relative to non-mutant females.

Maternally-controlled neo-ESD

One might think that when the sex of zygotes is under the control of mothers, there would be strong selection to balance the sex ratio among zygotes. However, we find that, as with offspring control, under weak selection the invasion fitness of a sex-determiner that is maternally controlled can be written

$$\lambda_{k,XY} \approx 1 + V_A S_A C_k, \tag{10}$$

where C_k is a term that depends on k. Of particular interest is $k = 1/2$ (i.e., when the mother perfectly balances the sex ratio of her offspring). When both recombination rates are small we have $C_{1/2} \approx R(s^m - s^f)/8 = \lim_{r\to 0} C_1/4$. This implies that, at least under tight linkage, the invasion of maternally-

controlled ESD is independent of R (because $S_A \propto R^{-1}$) and can invade whenever a neo-W can (which can invade even when it biases the sex ratio further; Figures 1 – 2).

Discussion

Brief results summary.

Fisherian sex ratio selection follows from the fact that, for an autosomal locus, half of the genetic material is inherited from a male, and half from a female. Thus, if the population sex ratio is biased towards females, the average per-individual contribution of genetic material to the next generation from males is greater than the contribution from females (and vice versa for male-biased sex ratios). Therefore, a mutant that increases investment in males will spread via the higher per-individual contributions made by males. That is, under Fisherian sex ratio selection, the success of a mutant relative to the non-mutant depends, in equal parts, on the contributions made by males and females to the next generation. An implicit assumption of Fisherian sex ratio selection is that the mutant allele is autosomal and has the same inheritance pattern as the non-mutant allele. The mutations we consider here, neo-sex-determining alleles, break this assumption. For example, the success of neo-Y mutations depends only on the number of alleles contributed by males (equation 4 and Table 2). Even mutants that are equally likely to be found in males or females, such as an environmental sex determination mutation (equation 9), are not strictly autosomal if they determine sex. Thus, despite the fact that sex ratio biases caused by haploid competition or meiotic drive have been shown to exert selection on various modifiers (Stalker 1961, Smith 1975, Frank 1989, Hough et al. 2013, Úbeda et al. 2015, Otto et al. 2015), we do not find evidence that Fisherian sex ratio selection acting upon neo-sex-determination systems (e.g., see figure REF).

DRAFT (improve): In Úbeda et al. (2015), the new sex determining locus

spreads because it arises in linkage with a locus that experiences drive. They assume that drive occurs predominantly in one sex, e.g., during spermatogenesis or a 'killer' sperm. A driving allele is maintained at an intermediate frequency by selection, e.g., because it causes male sterility when homozygous (because all male sperm are killed). Y chromosomes that arise in linkage with the driving allele spread because they allow drive to occur more often, thus genetic sex determination with a sex ratio bias evolves. Thus Úbeda et al. (2015) also find that genetic sex determiners can invade, despite causing sex ratios to become biased. Finally, they show that autosomal 'restorers' that negate the effects of meiotic drive can invade and restore an equal sex ratio.

We only consider selection at the **A** locus, the sex-determining regions do not experience direct selection except via their associations with sex and **A** locus alleles. However, in some cases, there may be significant degeneration around the sex-limited allele (Y or W) in the ancestral sex determining region. That is, recessive deleterious mutations and/or deletions may fix around the Y or W allele **????**). Degenerated Y could prevent fixation, this was studied by vD&K 2010, which is why we didn't do it. They note that YY lethality can prevent neo-W (and Y) fixing but that even very small amounts of recombination between X and Y can complete the process.

Discuss patterns that might be looked for:

Taken at face value, our results indicate that transitions in heterogametey (XY to ZW or vice versa) are more likely to be favoured by selection if there is selection upon both haploid and diploid genotypes rather than diploid selection alone.

In broadcast spawning animal species (e.g., corals, many fish) and species where sperm typically requires greater longevity, haploid selection may be stronger because transcripts shared during spermatogenesis may become depleted (Immler et al. 2014). also, mating systems (e.g., fewer alleles are available during haploid competition in monogamous species), selfing rates, and estimates of pollen limitation could be used as indicators of the intensity

of haploid selection

We have results where polygenic sex determination is sometimes stable, may be worth mentioning:

"Polygenic sex determination has been reported in many plants (e.g. Shannon & Holsinger 2007), fishes (Vandeputte et al. 2007; Ser et al. 2010; Liew et al. 2012), crustaceans (e.g. Battaglia 1958; Battaglia & Malesani 1959; Voordouw & Anholt 2002), bivalves (Haley 1977; Saavedra et al. 1997), gastropods (Yusa 2007a,b), and polychaetes (Bacci 1965, 1978; Premoli et al. 1996)." From Vuilleumier et al. 2007: "Polymorphism for sex-determining genes within or among populations has been reported in many species including houseflies, midges, woodlice, platyfish, cichlid fish, and frogs (Gordon, 1944; Kallman, 1970; Thomp-son, 1971; Macdonald, 1978; Bull, 1983; Rigaud et al., 1997; Caubet et al., 2000; Lande et al., 2001; Ogataet al., 2003; Lee et al., 2004; Mank et al., 2006)."

We caution that our model of meiotic drive is very simple, involving a single locus with two alleles. Many meiotic drive systems involve an interaction with another locus at which alleles may 'suppress' the action of meiotic drive. Furthermore, in some cases, a driving allele may act by killing any gametes that carry a 'target' allele at another locus, in which case the total number of gametes produced will be reduced (here, we assume total gamete number is not affected by drive).

Mix pollen competition and sex-ratio affects in here? Kokko paper addresses some of these issues, but not related to sex-determination. These feedbacks between population densities and meiotic drive or haploid competition for different sexual/mating systems deserve further attention.

Here, we have not considered any population size dynamics

(Check with Jim Bull that it's ok before including this speculation:) Finally, Hamilton (1967) pointed out that biased sex ratios can affect population size because the number of offspring in each generation is typically determined by the number of females. Population density can, in turn, af-

fect the intensity of pollen/sperm competition in future generations because fewer males are available to donate pollen/sperm in a particular area. Thus, a feedback could occur between population densities and haploid selection, which has not yet been investigated.

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Figures

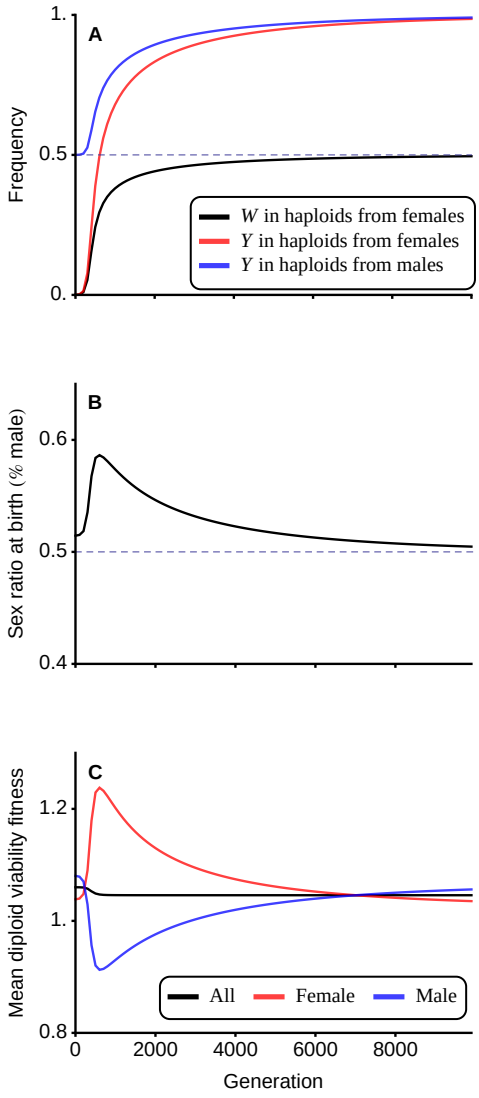

Figure 1: Haploid selection allows a neo-W to invade an ancestral XY system and fix (**A**) despite temporarily biasing the sex ratio further (**B**) and decreasing mean diploid viability fitness (**C**). Complete turnover between genetic sex-determination systems occurs despite the neo-W being less tightly linked to the selected locus than the ancestral sex-determining locus is, $R > r$. Parameters: $k = 1$, $s^f = 0.05$, $s^m = 0.15$, $h^f = h^m = 0.7$, $t^f = 0$, $t^m = -0.1$, $\alpha^m = \alpha^f = 1/2$, $r = 0.01$, $R = 0.05$.

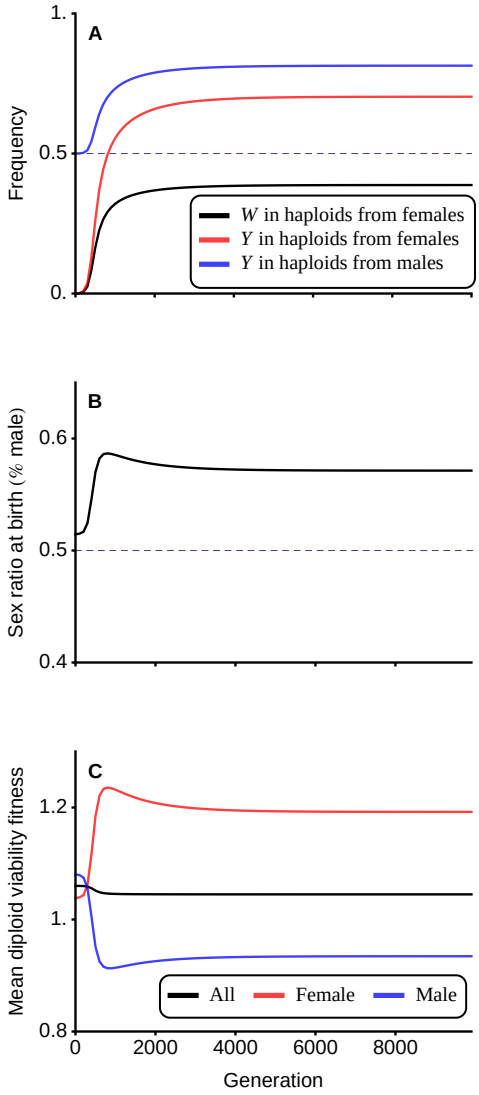

Figure 2: Haploid selection allows a completely unlinked neo-W to invade an ancestral XY system (**A**) despite further biasing the sex ratio (**B**) and decreasing mean diploid viability fitness (**C**). The neo-W does not fix (although variation at the **A** locus is maintained, $V_A > 0$), resulting in a polymorphic sex-determination system. Parameters as in Figure 1 but with $R = 0.5$.

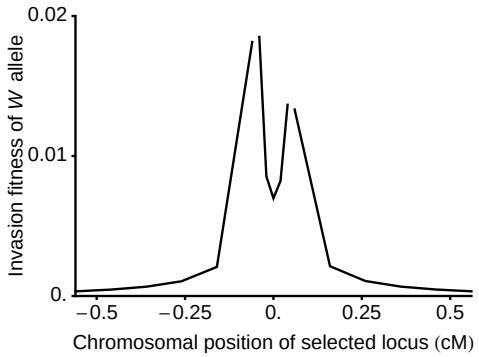

Figure 3: Haploid selection allows a neo-W to invade an ancestral XY system regardless of how tightly it and the ancestral sex-determining locus are linked to the selected locus. The ancestral sex-determining locus is located at -0.05 and the novel sex-determining locus is located at 0.05 (corresponding to the peaks of invasion fitness), such that the probability of a cross-over between them is ≈ 0.1. The x-axis gives the position of the locus under haploid selection. We used Haldane's map function (Equation 3 in **?**) to convert from map distance (centiMorgans) to the probability of a cross-over event. Parameters as in Figure 1.

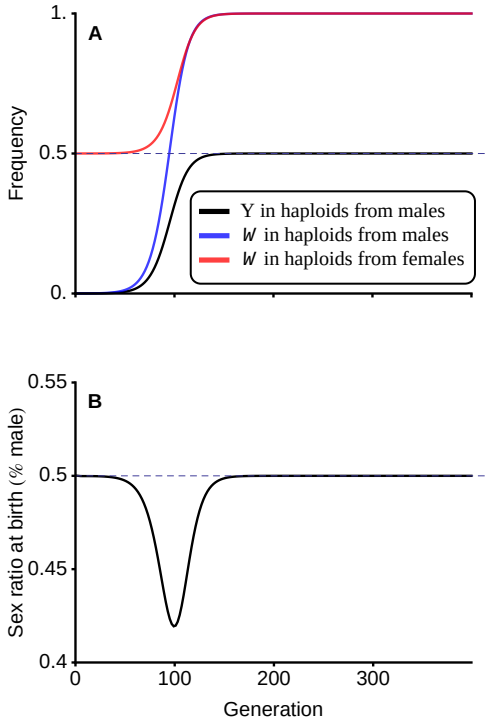

Figure 4: Meiotic drive allows a neo-Y to invade an ancestral ZW system and fix (**A**) despite temporarily biasing the sex ratio (**B**). Parameters: $k = 0$, $s^f = s^m = t^f = t^m = 0$, $\alpha^m = 0.4$, $\alpha^f = 1/2$, $r = 0$, $R = 0$.

Appendix

Recursion Equations

In each generation we census the genotype frequencies in male and female gametes/gametophytes (hereafter, gametes) before haploid competition. Before haploid competition, the frequencies of X-bearing male and female gametes are given by X_i^m and X_i^f and the frequencies of Y-bearing gametes are given by Y_i^m and Y_i^f where the index i specifies genotypes $MA = 1$, $Ma = 2$, $mA = 3$, and $ma = 4$. Competition then occurs among gametes of the same sex (e.g., among eggs and among sperm separately) according to the **A** locus allele, g ($g \in A$, a, see Table 1), carried by individuals with genotype i. The genotype frequencies after haploid competition are $X_i^{d,s} = w_g X_i^d / \bar{w}_H^d$ and $Y_i^{d,s} = w_g Y_i^d / \bar{w}_H^d$, where $\bar{w}_H^d = \sum_{i=1}^4 w_g X_i^d + w_g Y_i^d$ is the mean fitness of male ($d = m$) or female ($d = f$) gametes. Random mating then occurs between gametes to produce diploid zygotes with genotype ij at the **A** and **M** loci, such that XX zygotes are denoted xx_{ij}, XY zygotes are xy_{ij}, and YY zygotes are yy_{ij}. In XX and YY zygotes, individuals with genotype ij are equivalent to those with genotype ji. For simplicity, we denote the frequency of genotype ij in XX and YY zygotes to the average of these frequencies, $xx_{ij} = (X_i^{f,s} X_j^{m,s} + X_j^{f,s} X_i^{m,s})/2$ and $yy_{ij} = (Y_i^{f,s} Y_j^{m,s} + Y_j^{f,s} Y_i^{m,s})/2$.

Denoting the **M** locus genotype by b ($b \in MM$, Mm, mm) and the **X** locus genotype by c ($c \in XX$, XY, YY), zygotes develop as females with probability k_{bc}. Therefore, the frequencies of XX females are given by $xx_{ij}^f = k_{bc} xx_{ij}$, XY females are given by $xy_{ij}^f = k_{bc} xy_{ij}$, and YY females are given by $yy_{ij}^f = k_{bc} xy_{ij}$. Similarly, XX male frequencies are $xx_{ij}^m = (1 - k_{bc}) xx_{ij}$, XY male frequencies are $xy_{ij}^m = (1 - k_{bc}) xy_{ij}$, and YY males frequencies are $yy_{ij}^m = (1 - k_{bc}) xy_{ij}$. This notation allows both the ancestral and novel sex-determining regions to determine zygotic sex according to an XY system, a ZW system, or an environmental sex-determining system. In addition, we can consider any dominance relationship between the two sex-determining

loci. Typically, we assume that the ancestral sex-determining system (**X** locus) is XY ($k_{MMXX} = 1$ and $k_{MMXY} = k_{MMYY} = 0$) and recessive to a dominant novel sex-determining locus, **M** ($k_{Mmc} = k_{mmc} = k$).

Selection among diploids then occurs according to the diploid genotype at the **A** locus, h, for an individual of type ij ($h \in AA$, Aa, aa, see Table 1). The diploid frequencies after selection in sex d are given by $xx_{ij}^{d,s} = w_h^d xx_{ij}/\bar{w}^d$, $xy_{ij}^{d,s} = w_h^d xy_{ij}/\bar{w}^d$, and $yy_{ij}^{d,s} = w_h^d yy_{ij}/\bar{w}^d$, where $\bar{w}^d = \sum_{i=1}^{4}\sum_{j=1}^{4} w_h^d xx_{ij} + w_h^d xy_{ij} + w_h^d yy_{ij}$ is the mean fitness of individuals of sex d.

Finally, these diploids undergo meiosis to produce the next generation of gametes. Recombination and sex-specific meiotic drive occur during meiosis. Here, we allow the relative locations of the SDR, **A**, and **M** loci to be generic by using three parameters to describe the recombination rates between them. R is the recombination rate between the **A** locus and the **M** locus, χ is the recombination rate between the **M** locus and the **X** locus, and r is the recombination rate between the **A** locus and the **X** locus. Table S.1 gives substitutions for χ for defined relative locations of these loci. During meiosis in sex d, meiotic drive occurs such that, in Aa heterozygotes, a fraction α_d of gametes produced carry the A allele and $(1 - \alpha^d)$ carry the a allele.

Table S.1: χ substitutions for different loci orders (assuming no interference)

Order of loci	
SDR-A-M	$\chi = R(1-r) + r(1-R)$
SDR-M-A	$\chi = (r-R)/(1-2R)$
A-SDR-M	$\chi = (R-r)/(1-2r)$

Among gametes from sex d (sperm/pollen when $d = m$, eggs/ovules when $d = f$), the frequency of haplotypes (before haploid competition) in the next generation are given by

$$
\begin{aligned}
X_{MA}^{d'} =& xx_{11}^{d,s} + xx_{13}^{d,s}/2 + (xx_{12}^{d,s} + xx_{14}^{d,s})\alpha^d \\
& - R(xx_{14}^{d,s} - xx_{23}^{d,s})\alpha^d \\
& + (xy_{11}^{d,s} + xy_{13}^{d,s})/2 + (xy_{12}^{d,s} + xy_{14}^{d,s})\alpha^d \\
& - r(xy_{12}^{d,s} - xy_{21}^{d,s})\alpha^d - \chi(xy_{13}^{d,s} - xy_{31}^{d,s})/2 \\
& + \big\{ - (R + r + \chi)xy_{14}^{d,s} + (r + \chi - R)xy_{41}^{d,s} \\
& + (R + r - \chi)xy_{23}^{d,s} + (R + \chi - r)xy_{32}^{d,s} \big\}\alpha^d/2
\end{aligned}
\tag{S.1a}
$$

$$
\begin{aligned}
X_{Ma}^{d'} =& xx_{22}^{d,s} + xx_{24}^{d,s}/2 + (xx_{12}^{d,s} + xx_{23}^{d,s})\alpha^d \\
& - R(xx_{23}^{d,s} - xx_{14}^{d,s})\alpha^d \\
& (xy_{22}^{d,s} + xy_{24}^{d,s})/2 + (xy_{21}^{d,s} + xy_{23}^{d,s})(1 - \alpha^d) \\
& - r(xy_{21}^{d,s} - xy_{12}^{d,s})(1 - \alpha^d) - \chi(xy_{24}^{d,s} - xy_{42}^{d,s})/2 \\
& + \big\{ - (R + r + \chi)xy_{23}^{d,s} + (r + \chi - R)xy_{32}^{d,s} \\
& + (R + r - \chi)xy_{14}^{d,s} + (R + \chi - r)xy_{41}^{d,s} \big\}(1 - \alpha^d)/2
\end{aligned}
\tag{S.1b}
$$

$$
\begin{aligned}
X_{mA}^{d'} =& xx_{33}^{d,s} + xx_{13}^{d,s}/2 + (xx_{23}^{d,s} + xx_{34}^{d,s})\alpha^d \\
& - R(xx_{23}^{d,s} - xx_{14}^{d,s})\alpha^d \\
& (xy_{33}^{d,s} + xy_{31}^{d,s})/2 + (xy_{32}^{d,s} + xy_{34}^{d,s})\alpha^d \\
& - r(xy_{34}^{d,s} - xy_{43}^{d,s})\alpha^d - \chi(xy_{31}^{d,s} - xy_{13}^{d,s})/2 \\
& + \big\{ - (R + r + \chi)xy_{32}^{d,s} + (r + \chi - R)xy_{23}^{d,s} \\
& + (R + r - \chi)xy_{41}^{d,s} + (R + \chi - r)xy_{14}^{d,s} \big\}\alpha^d/2
\end{aligned}
\tag{S.1c}
$$

$$
\begin{aligned}
X_{ma}^{d'} =& xx_{44}^{d,s} + xx_{34}^{d,s}/2 + (xx_{14}^{d,s} + xx_{24}^{d,s})\alpha^d \\
& - R(xx_{14}^{d,s} - xx_{23}^{d,s})\alpha^d \\
& (xy_{44}^{d,s} + xy_{42}^{d,s})/2 + (xy_{41}^{d,s} + xy_{43}^{d,s})(1 - \alpha^d) \\
& - r(xy_{43}^{d,s} - xy_{34}^{d,s})(1 - \alpha^d) - \chi(xy_{42}^{d,s} - xy_{24}^{d,s})/2 \\
& + \big\{ - (R + r + \chi)xy_{41}^{d,s} + (r + \chi - R)xy_{14}^{d,s} \\
& + (R + r - \chi)xy_{32}^{d,s} + (R + \chi - r)xy_{23}^{d,s} \big\}(1 - \alpha^d)/2
\end{aligned}
\tag{S.1d}
$$

$$
\begin{aligned}
Y_{MA}^{d'} =& yy_{11}^{d,s} + yy_{13}^{d,s}/2 + (yy_{12}^{d,s} + yy_{14}^{d,s})\alpha^d \\
& - R(yy_{14}^{d,s} - yy_{23}^{d,s})\alpha^d \\
& (xy_{11}^{d,s} + xy_{31}^{d,s})/2 + (xy_{21}^{d,s} + xy_{41}^{d,s})\alpha^d \\
& - r(xy_{21}^{d,s} - xy_{12}^{d,s})\alpha^d - \chi(xy_{31}^{d,s} - xy_{13}^{d,s})/2 \\
& + \big\{ - (R + r + \chi)xy_{41}^{d,s} + (r + \chi - R)xy_{14}^{d,s} \\
& + (R + r - \chi)xy_{32}^{d,s} + (R + \chi - r)xy_{23}^{d,s} \big\}\alpha^d/2
\end{aligned}
\tag{S.1e}
$$

$$
\begin{aligned}
Y_{Ma}^{d'} =& yy_{22}^{d,s} + yy_{24}^{d,s}/2 + (yy_{12}^{d,s} + yy_{23}^{d,s})\alpha^d \\
& - R(yy_{23}^{d,s} - yy_{14}^{d,s})\alpha^d \\
& (xy_{22}^{d,s} + xy_{42}^{d,s})/2 + (xy_{12}^{d,s} + xy_{32}^{d,s})(1 - \alpha^d) \\
& - r(xy_{12}^{d,s} - xy_{21}^{d,s})(1 - \alpha^d) - \chi(xy_{42}^{d,s} - xy_{24}^{d,s})/2 \\
& + \big\{ - (R + r + \chi)xy_{32}^{d,s} + (r + \chi - R)xy_{23}^{d,s} \\
& + (R + r - \chi)xy_{41}^{d,s} + (R + \chi - r)xy_{14}^{d,s} \big\}(1 - \alpha^d)/2
\end{aligned}
\tag{S.1f}
$$

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$$
\begin{aligned}
Y_{mA}^{d'} =& yy_{33}^{d,s} + yy_{13}^{d,s}/2 + (yy_{23}^{d,s} + yy_{34}^{d,s})\alpha^d \\
& - R(yy_{23}^{d,s} - yy_{14}^{d,s})\alpha^d \\
& (xy_{33}^{d,s} + xy_{13}^{d,s})/2 + (xy_{23}^{d,s} + xy_{43}^{d,s})\alpha^d \\
& - r(xy_{43}^{d,s} - xy_{34}^{d,s})\alpha^d - \chi(xy_{13}^{d,s} - xy_{31}^{d,s})/2 \\
& + \big\{ - (R + r + \chi)xy_{23}^{d,s} + (r + \chi - R)xy_{32}^{d,s} \\
& + (R + r - \chi)xy_{14}^{d,s} + (R + \chi - r)xy_{41}^{d,s} \big\}\alpha^d/2
\end{aligned}
\tag{S.1g}
$$

$$
\begin{aligned}
Y_{ma}^{d'} =& yy_{44}^{d,s} + yy_{34}^{d,s}/2 + (yy_{14}^{d,s} + yy_{24}^{d,s})\alpha^d \\
& - R(yy_{14}^{d,s} - yy_{23}^{d,s})\alpha^d \\
& (xy_{44}^{d,s} + xy_{24}^{d,s})/2 + (xy_{14}^{d,s} + xy_{34}^{d,s})(1 - \alpha^d) \\
& - r(xy_{34}^{d,s} - xy_{43}^{d,s})(1 - \alpha^d) - \chi(xy_{24}^{d,s} - xy_{42}^{d,s})/2 \\
& + \big\{ - (R + r + \chi)xy_{14}^{d,s} + (r + \chi - R)xy_{41}^{d,s} \\
& + (R + r - \chi)xy_{23}^{d,s} + (R + \chi - r)xy_{32}^{d,s} \big\}(1 - \alpha^d)/2
\end{aligned}
\tag{S.1h}
$$

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The full system is therefore described by 16 recurrence equations (three loci,

each with two alleles, and two gamete sexes yields 16 combinations). However, some diploid types are not produced under a given sex determination system. For example, with the M allele fixed and ancestral XY sex determination, there are no XX males, XY females, or YY females (xx^m_{11}, xx^m_{12}, xx^m_{22}, xy^f_{11}, xy^f_{12}, xy^f_{22}, yy^f_{11}, yy^f_{12}, and yy^f_{22} are all 0). In this case, the system only involves six recursion equations because there is only one **M** locus allele and no Y-bearing female gametes. This six-equation system yields equilibrium (2). Within this resident population (when m is absent) we describe frequencies among different gamete types, which are given by $X^f_{MA} = p_{Xf}$, $X^f_{Ma} = (1-p_{Xf})$, $X^m_{MA} = (1-q)p_{Xm}$, $X^m_{Ma} = (1-q)(1-p_{Xm})$, $Y^m_{MA} = qp_{Ym}$, and $Y^m_{Ma} = q(1-p_{Ym})$.