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On the origin of sex chromosomes from meiotic drive

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Most animals and many plants make use of specialized chromosomes (sex chromosomes) to determine an individual's sex. Best known are the XY and ZW sex-determination systems. Despite having evolved numerous times, sex chromosomes present something of an evolutionary puzzle. At their origin, alleles that dictate development as one sex or the other (primitive sex chromosomes) face a selective penalty, as they will be found more often in the more abundant sex. How is it possible that primitive sex chromosomes overcome this disadvantage? Any theory for the origin of sex chromosomes must identify the benefit that outweighs this cost and enables a sex-determining mutation to establish in the population. Here we show that a new sex-determining allele succeeds when linked to a sex-specific meiotic driver. The new sex-determining allele benefits from confining the driving allele to the sex in which it gains the benefit of drive. Our model requires few special assumptions and is sufficiently general to apply to the evolution of sex chromosomes in outbreeding cosexual or dioecious species. We highlight predictions of the model that can discriminate between this and previous theories of sex-chromosome origins.

1. Introduction

The mechanisms to determine whether an animal will develop as male or female are diverse. Some species rely on environmental cues (environmental sex determination)—as is the case in some fishes and reptiles—and others rely on specialized chromosomes (genetic sex determination)—as is the case in most mammals, birds, beetles and butterflies [1,2]. Sex chromosomes are chromosomes involved in sex determination characterized by reduced recombination, specialized gene content and dosage compensation. They have evolved numerous times in multicellular organisms [1,2] and are the most common form of sex determination in animals [1,2]. When sex is determined by the inheritance of sex chromosomes, the particulars can vary: in some species individuals inheriting two different sex chromosomes develop as males (XY male heterogametic sex determination); in other species, individuals inheriting two different sex chromosomes develop as females (ZW female heterogametic sex determination) [1,2]. Here, we use the term proto-sex chromosome to refer to an autosome carrying a sex-determining allele that may or may not exhibit all other characteristics of a sex chromosome—e.g. reduced recombination, dosage compensation and the acquisition of a specialized gene content. While there is much theoretical literature to explain the differentiation that occurs along a proto-sex chromosome once it has been established in a population [3,4] there has been much less theoretical attention paid to the initial event that sets this subsequent evolution in motion. Here, we focus on the origin of sex chromosomes by studying the invasion and establishment of a proto-sex chromosome.

A rare sex-determining allele is, all other things equal, initially at a disadvantage in a population where sex is determined by another cue. In a well-mixed population, the fitness of individuals of a given sex depends on the population sex ratio [5]. The rarer sex is always at an advantage, and an evolutionary equilibrium is reached when sexes are equally abundant [5–7]. It follows that any sex-determining allele that might arise in a well-mixed population is

self-defeating, as its spread will enrich the population for the sex that it determines [8]. That said, some sex-determining alleles do achieve high frequencies. What makes these alleles different? What benefits do they receive that others may not?

Two previous theories for the origin of sex chromosomes have, respectively, sought to answer these questions. First, Charlesworth & Charlesworth [9] show that in self-fertilizing, cosexual populations, genetic sex determination can be favoured when there are high levels of inbreeding and strong inbreeding depression. In their model, sex-determination functions as an instrument of self-incompatibility. The sex-determining allele precludes selfing and will become associated with reduced inbreeding coefficients, thereby providing a benefit to its bearers. Second, Rice [10] and van Doorn & Kirkpatrick [11,12] show that in dioecious populations, sexually antagonistic viability selection can favour newly arising sex-determining alleles providing linkage between the viability and sex-determining loci. The benefit in this case is best attributed to the sex-determining allele itself rather than the individual who possesses it. The new sex-determining allele fares better than the resident allele, which leaves sex determination to environmental cues and suffers the viability costs associated with its linked allele half of the time. By contrast, the sex-determining allele guarantees that it will be assigned to the sex that experiences the benefit associated with its linked allele.

Here, we provide an alternative explanation for the origin of sex chromosomes that relies on a sex-determining allele benefiting from meiotic drive. Meiotic drive refers to any alteration of meiosis or gametogenesis that causes preferential transmission of a particular allele or chromosome [13,14]. Although originally considered a genetic oddity, meiotic drive has since been found on autosomes and sex chromosomes in a wide range of taxa [15,16], and it has come to be appreciated as a potent force in the evolution of various traits [17–19], including sex determination [20–24]. Still, despite much previous work that examines meiotic drive's influence on sex determination, its potential role in the origin of genetic sex determination and sex chromosomes has not, to our knowledge, ever been explored.

In the following sections, we demonstrate how linkage to a meiotic driver favours the spread of a novel sex-determining allele in a dioecious population using environmental cues for sex determination (the model also applies to an initially outbreeding cosexual population). Once this allele is established in the population, it causes a biased sex ratio. We then show that an unlinked gene is selected to suppress drive in the heterogametic sex, thus restoring fair segregation and an even sex ratio and giving rise to chromosomes that behave like standard X and Y (or Z and W) chromosomes. In our theory, the actions of 'genetic outlaws' [25] and the 'parliament of genes' [26] combine to produce the sex chromosomes of a new heterogametic system.

2. Model and results

We formulate a population genetics model consisting of three loci with an arbitrary number of alleles at each locus. The first locus A influences sex determination and may carry alleles $A_1, A_2, \ldots, A_I$. The probability that an individual with genotype A_iA_l develops into a male is s_{il}; with $0 \leq s_{il} \leq 1$ and $s_{il} = s_{li}$. The second locus B may carry alleles $B_1, B_2, \ldots, B_J$ controlling the rate of segregation during meiosis (drive locus). We assume that driving alleles are perfectly linked to alleles that have viability effects on their carriers, effects that are independent of the sex they are expressed in [16]. Therefore, the relative probability that a male or female with genotype B_jB_m survives to adulthood is v_{jm}; with $v_{jm} \geq 0$ and $v_{jm} = v_{mj}$. The third locus C may carry alleles $C_1, C_2, \ldots, C_K$ modifying segregation of alleles at the previous locus (drive modifier). We assume that modifying alleles are neutral with respect to fitness as is usually the case with modifiers [27]. An individual with genotype B_jC_k/B_mC_n segregates allele B_j with probability $d^{\male}_{jm,kn}$ and $d^{\female}_{jm,kn}$ in sperm and eggs; with $0 \leq d^{\circ}_{jm,kn} \leq 1$ and $d^{\circ}_{jm,kn} = d^{\circ}_{jm,nk}$ (where $^{\circ} = \{\male, \female\}$).

Denote the frequency of haplotype $A_iB_jC_k$ in sperm and eggs by x_{ijk} and y_{ijk}, respectively. We assume that zygotes result from the random union of gametes. A zygote with genotype $A_iB_jCk/A_lB_mC_n$ develops into a male with probability s_{il} and into a female with probability $1 - s_{il}$. This individual reaches adulthood with relative probability v_{jm}. The total production of sperm and eggs in the population is proportional to $\bar{m}$ and $\bar{f}$, respectively, where $\bar{m} = \sum_{i,j,k} \sum_{l,m,n} x_{ijk}y_{lmn}s_{il}v_{jm}$ and $\bar{f} = \sum_{i,j,k} \sum_{l,m,n} x_{ijk}y_{lmn}(1 - s_{il})v_{jm}$. Because the constant of proportionality is the same for each of the previous quantities, we can assert that total production of gametes in the population is proportional to the population mean fitness $\bar{w}$ where $\bar{w} = \sum_{i,j,k} \sum_{l,m,n} x_{ijk}y_{lmn}v_{jm} = \bar{m} + \bar{f}$. Recombination takes place during meiosis at a rate r_1 between locus A and B and r_2 between locus B and C with $0 \leq r_1, r_2 \leq 1/2$. After recombination takes place, allele B_j is transmitted with probability $d^{\male}_{jm,kn}$ and $d^{\female}_{jm,kn}$ in males and females, and B_m is transmitted with probability $d^{\male}_{mj,kn} = 1 - d^{\male}_{jm,kn}$ and $d^{\female}_{mj,kn} = 1 - d^{\female}_{jm,kn}$ in males and females. This brings us back to the beginning of our census, and so the frequency of haplotype $A_iB_jC_k$ in sperm and eggs in the next generation is:

$$\begin{aligned} x'_{ijk} = \frac{1}{\bar{m}} \sum_{lmn} [&(1 - r_1)(1 - r_2)(x_{ijk}y_{lmn} + x_{lmn}y_{ijk}) \\ &+ r_1(1 - r_2)(x_{ljk}y_{imn} + x_{imn}y_{ljk}) \\ &+ (1 - r_1)r_2(x_{ijn}y_{lmk} + x_{lmk}y_{ijn}) \\ &+ r_1r_2(x_{imk}y_{ljn} + x_{ljn}y_{imk})]s_{il}v_{jm}d^{\male}_{jm,kn} \end{aligned}$$

and

$$\begin{aligned} y'_{ijk} = \frac{1}{\bar{f}} \sum_{lmn} [&(1 - r_1)(1 - r_2)(x_{ijk}y_{lmn} + x_{lmn}y_{ijk}) \\ &+ r_1(1 - r_2)(x_{ljk}y_{imn} + x_{imn}y_{ljk}) \\ &+ (1 - r_1)r_2(x_{ijn}y_{lmk} + x_{lmk}y_{ijn}) \\ &+ r_1r_2(x_{imk}y_{ljn} + x_{ljn}y_{imk})](1 - s_{il})v_{jm}d^{\female}_{jm,kn}, \end{aligned}$$

where the frequency of males and females in the adult population is M and F, respectively, where $M = \bar{m}/\bar{w}$ and $F = \bar{f}/\bar{w}$ and $M + F = 1$. We use this system of recursive equations to carry out an analysis of the initial conditions and the mutational steps leading from these to XY or ZW sex-determination systems.

(a) Initial conditions

We assume that all loci are initially monomorphic. The A locus is fixed for A_1, which has no influence on the probability of developing into one sex or the other. In particular, we assume offspring use environmental cues to develop as male

or female (environmental sex determination) with equal probability (equal sex ratio), i.e. $s_{11} = 1/2$. The B locus is fixed for B_1, which does not distort segregation. The C is fixed for C_1, which does not modify segregation at the B locus.

(b) An initial sex-specific drive polymorphism

Consider a mutation at the B locus. Mutant allele B_2 can distort segregation differently in males and females and comes accompanied by viability effects in both sexes. These assumptions are informed by the known effects of natural drivers: all known drivers have differential drive in males and females [16] and are often found in inversions that trap deleterious alleles with similar effects on male and female carriers [13,15]; for example, the t-haplotype [28].

We derive the conditions that maintain a polymorphism at B (see the electronic supplementary material), namely

$$1 - \frac{1}{2}\frac{v_{22}}{v_{12}} > d_{21,11} > \frac{1}{2}\frac{v_{11}}{v_{12}},$$

where $d_{21,11} = \frac{1}{2}d^{\male}_{21,11} + \frac{1}{2}d^{\female}_{21,11}$ is the average segregation probability of allele B_2 across males and females. In order to maintain polymorphism at the B locus, it must be true that: (i) the probability that a rare B_2 is transmitted ($d_{21,11}v_{12}$) is greater than the probability that a single common B_1 allele is transmitted ($v_{11}/2$); and (ii) the probability that a rare B_1 is transmitted $(1 - d_{21,11})v_{12}$ is greater than the probability that a single common B_2 is transmitted ($v_{22}/2$). In graphical terms, this corresponds to the region below the brown line ($d_{21,11} < 1 - 1/2(v_{22}/v_{12})$) and above the orange line ($d_{21,11} > 1/2(v_{11}/v_{12})$), see the electronic supplementary material, figure S1.

Note that a variety of combinations of drive and viability regimes can maintain polymorphism at the B locus. In particular, three forms of drive: (i) sex-limited drive when B_2 is over-transmitted in one sex but fairly segregated in the other, that is $d^{\male}_{21,11} > \frac{1}{2}$ but $d^{\female}_{21,11} = \frac{1}{2}$ (male limited) or $d^{\female}_{21,11} > \frac{1}{2}$ but $d^{\male}_{21,11} = \frac{1}{2}$ (female limited); (ii) sex-synergistic drive when B_2 is over-transmitted or under-transmitted in both sexes, that is $d^{\male}_{21,11}$, $d^{\female}_{21,11} > \frac{1}{2}$ or $d^{\male}_{21,11}$, $d^{\female}_{21,11} < \frac{1}{2}$; and (iii) sex-antagonistic drive when B_2 is over-transmitted in one sex but under-transmitted in the other, that is $d^{\male}_{21,11} > \frac{1}{2}$ but $d^{\female}_{21,11} < \frac{1}{2}$ or $d^{\female}_{21,11} > \frac{1}{2}$ but $d^{\male}_{21,11} < \frac{1}{2}$ (see the electronic supplementary material, figure S1). Also, three viability regimes: (i) heterozygote advantage when the viability of the heterozygote is greater than the viability of both homozygotes, that is $v_{12} > v_{11}$, v_{22}; (ii) the viability of the heterozygote is equal to the viability of one homozygote and greater than the other, that is either $v_{12} = v_{11} > v_{22}$ or $v_{12} = v_{22} > v_{11}$; and (iii) homozygote advantage when the viability of one homozygote is greater than the viability of the heterozygote and the other homozygote, that is either $v_{11} > v_{12}$, v_{22} or $v_{22} > v_{12}$, v_{11} (see the electronic supplementary material, figure S1).

For simplicity, we henceforth focus on the case when allele B_2 drives in males only, that is, $d^{\male}_{21,11} > \frac{1}{2}$ but $d^{\female}_{21,11} = \frac{1}{2}$, and is deleterious recessive relative to B_1, that is, $v_{22} < v_{12} = v_{11}$.

(c) Mutational step 1: a male-determining allele invades and the population departs from an even sex ratio

The population is at a polymorphic equilibrium between the non-driving allele B_1 and the driving allele B_2 with an even sex ratio. We are interested in finding whether the presence of a driving allele at equilibrium enables the invasion of a sex-determining allele even though such an allele will bring the population away from an even sex ratio. Consider a male-determining mutant at locus A. Assume this rare male-determining allele A_2 is dominant to A_1 and results in carriers developing as males only ($s_{12} = s_{22} = 1$).

Numerical analysis shows that A_2 invades when there is drive in males ($d^{\male}_{21,11} > \frac{1}{2}$), and recombination between the sex-determining locus A and the drive locus B is less than free ($r_1 < 1/2$; figure 1). Therefore, a population with male-limited drive does not exhibit evolutionary genetic stability [29] against male-determining alleles. A male-determining mutant A_2 invades when in linkage disequilibrium with the male-driving allele B_2 (figure 2). When recombination is free ($r_1 = 1/2$), these alleles remain unlinked and a male-determining mutant A_2 cannot enter the population (figures 1 and 3). The spread of the male-determining allele produces a male-biased adult sex ratio at equilibrium ($\hat{M} > \frac{1}{2}$; figure 2).

Note that A_2 is absent from eggs because it is a dominant male-determining allele (figure 2). The lower the recombination rate, the greater the frequency of the male-determining allele A_2 at equilibrium and the more male biased the adult sex ratio (figure 3). The greater the drive in males, the greater the frequency of the male-determining allele A_2 and the male bias of the adult sex ratio at equilibrium (figure 3).

The population at equilibrium is a mixture of males whose sex is determined by the presence of allele A_2 and homozygous A_1 males and females whose sex is environmentally determined.

(d) Mutational step 2: a female-determining allele invades and the male-biased sex ratio is maintained

Consider a female-determining mutant at locus A. Assume this rare female-determining allele A_3 is dominant to A_1 and results in carriers developing as females only ($s_{13} = s_{33} = 0$). However, assume A_3 is recessive to A_2 ($s_{23} = 1$).

Numerical analysis shows that A_3 invades when there is drive in males ($d^{\male}_{21,11} > \frac{1}{2}$) and the recombination between the sex-determining locus A and the drive locus B is less than free ($r_1 < 1/2$; figures 2 and 3). A female-determining mutant A_3 invades when in linkage disequilibrium with the non-driving allele B_1, which is under-transmitted through sperm (figure 3). When recombination is free ($r_1 = 1/2$), these alleles remain unlinked and a female-determining mutant A_3 cannot enter the population (figure 3). The spread of the female-determining allele A_3 has three effects: (i) it furthers the spread of the male-determining allele A_2 (even in regions of the parameter space where the male-determining allele was rare); (ii) together with A_2 it drives A_1 to extinction; and (iii) together with A_2 it further skews the adult sex ratio towards males ($\hat{M} > \frac{1}{2}$; figures 2 and 3).

The lower the recombination rate, the lower the frequency of the female-determining allele A_3 at equilibrium and the greater the male bias of the adult sex ratio (figure 3). The greater the drive in males, the lower the frequency of the female-determining allele A_3 and the greater the male bias of the adult sex ratio at equilibrium (figure 3).

The population at equilibrium is a mixture of heterogametic (A_2A_3) males and homogametic (A_3A_3) females. At

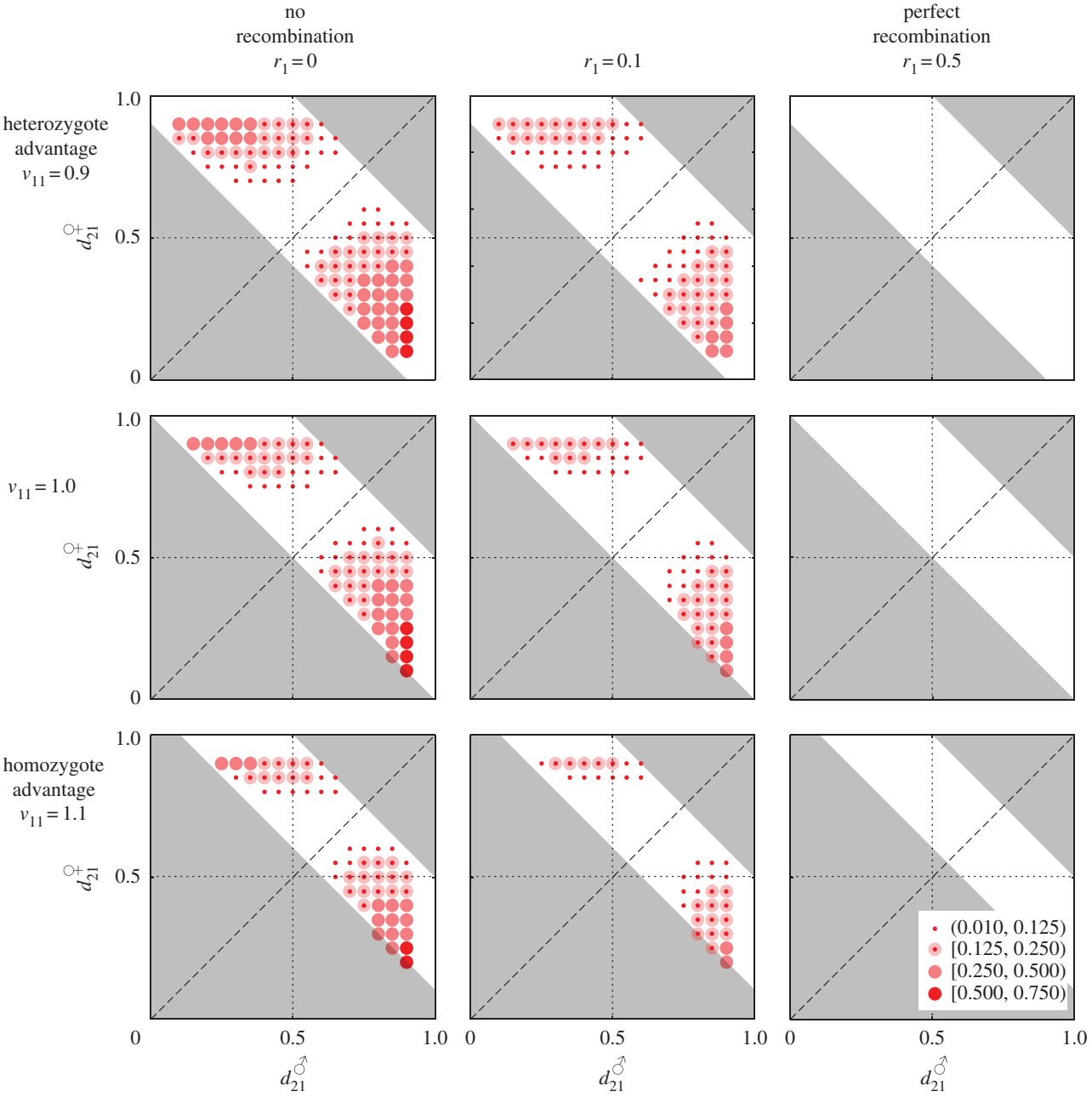

Figure 1. Invasion of a male-determining gene. Plots are organized on a grid corresponding to increasing values of recombination, r_1, from left to right and increasing values of the viability of the homozygote for allele B_1, v_{11}, from top to bottom. Within each plot the horizontal and vertical axis depict the segregation probability of allele B_2 in males and females respectively, $d_{21}^{\male}$, $d_{21}^{\female}$. The region in white represents the existence of a polymorphism at the drive locus B. For each combination of parameter values, red dots indicate that a male-determining allele increases in frequency when rare and becomes established in the population at the frequency indicated in the legend.

this equilibrium, the heterogametic males preferentially transmit the male-determining allele, thus maintaining a male-biased sex ratio.

(e) Mutational step 3: an unlinked drive modifier restores an even sex ratio

Finally, consider a mutant at locus C that prevents the driving allele from driving. Assume this rare modifier of drive C_2 acts additively, i.e. $d_{21,12}^{\male} = \frac{1}{2}(d_{21,11}^{\male} + d_{21,22}^{\male})$, bringing segregation closer to Mendelian expectations during spermatogenesis ($d_{21,22}^{\male} = \frac{1}{2}$). Henceforth, we will refer to this modifier as a Mendelian modifier. Finally, assume there is free recombination between C and the other two loci A and B, i.e. $r_2 = 1/2$.

Numerical analysis shows that C_2 invades when there is drive in males ($d_{21,11}^{\male} > \frac{1}{2}$) irrespective of the recombination rate between the sex-determining and drive loci (figures 2 and 3). Modifier theory shows that an unlinked locus is under selective pressure to increase population mean fitness [27]. In the case considered, this would be achieved by either reducing the bias in sex ratio or by reducing the genetic load [30]. The genetic load of a population, L, is defined as 'the proportion by which the population mean fitness is decreased in comparison with an optimum genotype' [30]:

$$L = \frac{\max(v_{ij}) - \bar{w}}{\max(v_{ij})}.$$

In agreement, our Mendelian modifier invades not only when the sex ratio of the population is male biased ($\hat{M} > \frac{1}{2}$) but also

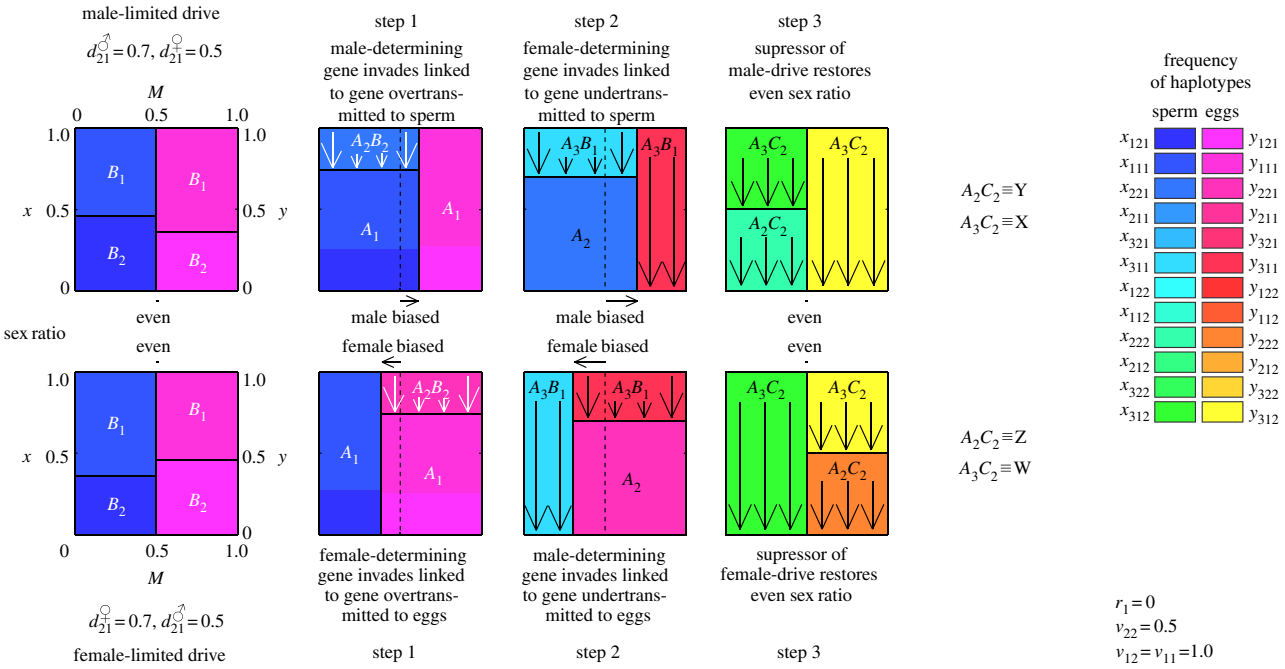

Figure 2. Steps leading to the formation of sex chromosomes (either XY or ZW). Within each plot the frequency of adult males in the population is depicted on the horizontal axis. The vertical axis shows the frequency of haplotypes in sperm, x, to the left, and the frequency of haplotypes in eggs, y, to the right. Each plot consists of two stacked bars depicting the composition of the pool of sperm (left bar) and the pool of eggs (right bar). The width of each bar indicates the proportion of adult males and females, respectively. The identity of each of 12 haplotypes within each pool is indicated by a colour code in the legend. The first plot in the top row depicts a polymorphic population at equilibrium (with male-limited drive, $d_{21}^{\male}=0.7$ and $d_{21}^{\female}=0.5$, and viability regime $v_{11}=v_{12}=1.0$, $v_{22}=0.5$). In step 1, a rare male-determining allele, A_2, is introduced at a locus that is completely linked ($r_1=0$) to the drive locus. In step 2, a rare female-determining allele, A_3, which is recessive to the male-determining allele A_2, is introduced. The male- and female-determining alleles force A_1 to extinction. In step 3, a rare suppressor of male drive, C_2, is introduced at a locus that freely recombines with the drive locus. The modifier allele, C_2, forces the non-modifying allele, C_1, to extinction. An XY sex-determination system evolves with haplotype $A_2B_2C_2$ acting as a Y-chromosome and haplotype $A_3B_1C_2$ acting as an X-chromosome. In the bottom row, the plots depict how analogous steps lead to the evolution of a ZW sex-determination system when the initial polymorphism involves a female-limited driver.

when viability selection against the driving allele maintains a polymorphism at the drive locus, thus maintaining a genetic load (figures 3 and 4).

The spread of the unlinked Mendelian modifier C_2 has two effects: (i) it restores an even adult sex ratio ($\hat{M}=\frac{1}{2}$); and (ii) when there is some recombination ($r_1>0$) between A and B, it eliminates the polymorphism at B by fixing allele B_1 at the drive locus (figures 2 and 3).

(f) Summary of results

In general, the haplotype containing the dominant male-determining allele A_2 becomes established exhibiting fair segregation in the heterogametic sex—characteristics that define a proto-Y chromosome. The haplotype containing the recessive female-determining allele A_3 becomes established and also exhibits fair segregation in the heterogametic sex—characteristics that define a proto-X chromosome. The population ends up with a mixture of heterogametic ($A_3A_2 \equiv$ XY) males and homogametic ($A_3A_3 \equiv$ XX) females with equal segregation of male and female proto-sex chromosomes in the heterogametic sex. Note that an XY sex-determination system evolves for any initial strength of drive—i.e. provided $d_{21,11}^{\male}>\frac{1}{2}$—and any degree of linkage between A and B —i.e. provided $r_1<0.5$.

The recombination rate between the sex-determining locus A and the drive locus B influences the fate of alleles at the B locus. When recombination between A and B is absent ($r_1=0$), a polymorphism is maintained at B: the $A_2B_2C_2$ haplotype acts as a Y-chromosome; the $A_3B_1C_2$ haplotype acts as an X-chromosome (figures 2 and 3). When there is some recombination between these two loci ($0<r_1<1/2$), the B_1 allele reaches fixation: the $A_2B_1C_2$ haplotype acts as a Y-chromosome; the $A_3B_1C_2$ haplotype acts as an X-chromosome (figures 2 and 3).

With the appropriate swapping of labels, analogous results could be derived from the model above for a system in which allele B_2 drives in females ($d_{21,11}^{\female}>\frac{1}{2}$) and allele A_2 determines development as a female. The population would end up at equilibrium with a mixture of heterogametic ($A_3A_2 \equiv$ ZW) females and homogametic ($A_3A_3 \equiv$ ZZ) males with equal segregation of male and female-determining chromosomes in female meiosis. Additionally, it is possible for the above model to produce heterogamety in the opposite sex from where drive originally occurs. To achieve this one needs only to change the dominance relation of alleles at the A locus. If A_3 is dominant to A_2, then the driving sex will go on to be homozygous (homogametic) for A_2 (not shown).

3. Discussion

The intuition behind our model of sex-chromosome evolution is simple. In the initial population, the segregating polymorphism involves one allele (the driving allele, B_2) that drives in spermatogenesis against B_1. Although the B_2 allele confers lower viability in both sexes, it can at least gain a segregation advantage in males. The B_2 allele would therefore

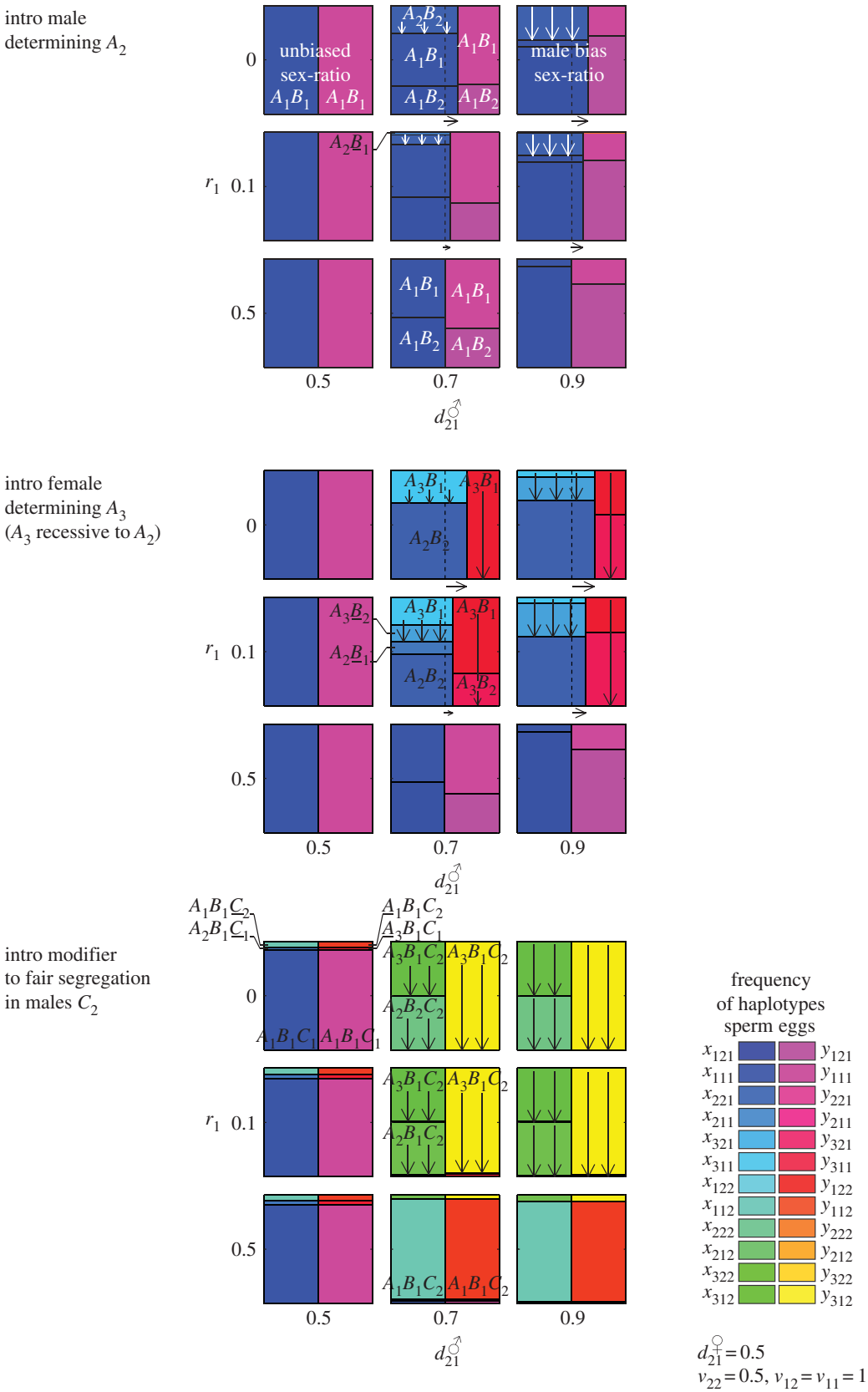

Figure 3. Steps leading to the evolution of sex chromosomes. This figure extends figure 2 by providing a range of values for the strength of male drive and the recombination frequency. Drive remains male limited ($d_{21}^{\female} = 0.5$), and the viability regime remains the same: $v_{11} = v_{12} = 1.0$, $v_{22} = 0.5$. For each of the three steps leading to the formation of sex chromosomes, every row of a plot corresponds to a different value of recombination between the sex-determining locus *A* and the meiotic drive locus *B* ranging from no recombination, $r_1 = 0$, to free recombination $r_1 = 0.5$. Every column corresponds to a different value of drive in males ranging from fair segregation, $d_{21}^{\male} = 0.5$, to strong drive, $d_{21}^{\male} = 0.9$.

benefit from finding itself in males more often than females. The benefit of a new, linked sex-determining allele is found in how it spares B_2 the disadvantage of being in the wrong sex. It is as though the driving allele acquires the ability to specify which sex it will heretofore belong to. The sex-determining allele at the linked locus likewise benefits from this arrangement. The alternative allele, which leaves sex determination to environmental cues, will experience the costs of the

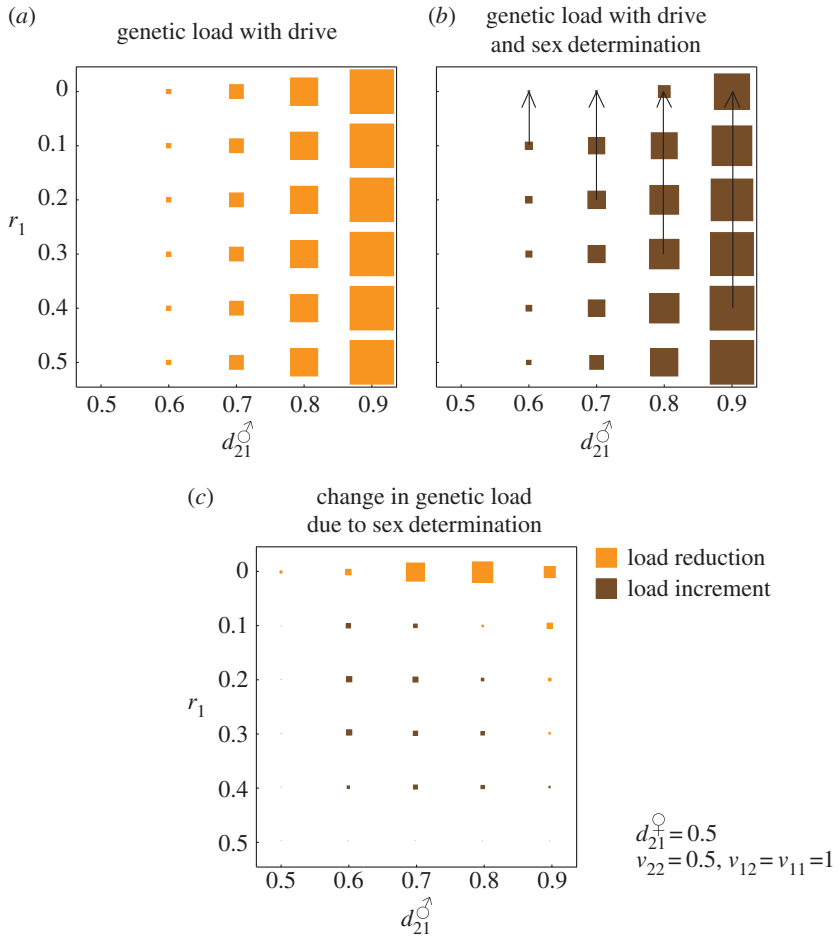

Figure 4. Genetic load, drive and sex determination. Within each plot, the horizontal axis corresponds to the segregation probability of allele B_2 in males, $d_{21}^{\male}$, and the vertical axis corresponds to recombination between the drive and the sex-determining loci. Segregation is fair in females, $d_{21}^{\female} = 0.5$, and the viability regime is $v_{11} = v_{12} = 1.0$, $v_{22} = 0.5$. The genetic load accrued by males and females is presented in separate plots and is depicted by the area of the squares within each. (*a*) The genetic load in a population at equilibrium when there is drive but no sex-determining alleles. With stronger drive in males, $d_{21}^{\male}$, the driving allele is more common and the genetic load is greater. (*b*) The genetic load in a population at equilibrium when there is a drive polymorphism and sex-determining alleles (A_2 and A_3). The stronger the drive, $d_{21}^{\male}$, the greater is the genetic load. Increases in recombination have opposing effects on load depending on whether the initial condition is low or high recombination. Arrows indicate the region of the parameter space where an increase in recombination reduces genetic load. (*c*) The net effect of introducing sex-determining alleles. Sex-determining alleles reduce genetic load when drive is sufficiently strong or recombination is sufficiently weak.

driving allele just as often in males as it does in females, in which sex it misses out on the advantage of drive. Thus, the sex-determining allele will spread when rare, but will only spread so far as the advantage of this linkage arrangement exceeds the costs owing to the sex ratio bias that its increased frequency brings. From that point on, the model we outline follows the familiar logic of models of sex ratio and genetic load.

As with any model of a complex process, ours entails several simplifying assumptions that merit closer examination. First, we assume random union of gametes. This is a reasonable assumption for an already dioecious species and for a cosexual species where self-fertilization is rare, but less so for cosexual species where self-fertilization is abundant. A full analysis of the influence of inbreeding on the evolution of genetic sex determination from drive would be an interesting avenue for future research but is beyond the scope of this paper. It is interesting, however, to speculate that inbreeding may not prevent drivers from successfully mediating the evolution of genetic sex determination. While it is true that inbreeding would increase homozygosity at the *B* locus, thus eroding the effect of a driver (as drivers gain an advantage in heterozygotes only), inbreeding often brings inbreeding depression, which increases heterozygosis through heterozygote advantage at the *B* locus, thus strengthening the effect of a driver. These opposing forces may balance each other out in terms of their effect on a driver. In cosexual species where self-fertilization is abundant, sex chromosomes can evolve when there is strong inbreeding depression [9]. We speculate that a sex-specific driver in such a population may further facilitate the evolution of sex chromosomes by relaxing the requirement of strong inbreeding depression.

Second, we assume that a driving allele comes along with viability effects that do not differ between the sexes. This assumption was informed by the known effects of natural drivers—for example, the *t*-haplotype [28]—and recognizes that driving haplotypes are often found within large inversions that trap deleterious alleles which are rarely sex-specific [13,15]. The model we present cannot tell us how sex-specific viabilities will influence the likelihood of evolving genetic sex determination, and its modification to accommodate sex-specific viabilities would be another interesting avenue for future research. An informed guess indicates that sex-specific viabilities are unlikely to reverse any of the results we found. With sex-independent viability a polymorphism at the *B* locus is maintained when the driving allele is linked to another allele causing a viability disadvantage in both sexes. With sex-specific viability a polymorphism at the *B*

locus would be maintained when the driving allele is linked to another allele causing a fitness disadvantage either in males or in females. When the fitness effect is in the same sex as the driving effect, a sex-determining gene will still invade but only when there is heterozygote advantage, as the sex-determining allele increases heterozygosity. When the viability effect is in the opposite sex as the driving effect, a sex-determining gene will still invade by virtue of confining the driving allele to the sex where it gains a transmission advantage and the non-driving allele to the sex where it gains a viability advantage.

Finally, we assume that the effects of the sex-determining alleles and the drive-suppressor alleles are all-or-none. These are customary assumptions in sex-determining models [9] and modifier theory [27]. If we were to reduce the penetrance of any of these alleles, selection would still be oriented in the same direction, but the speed with which fixation occurs would probably be less.

We also assume that there are three mutational steps in the process from a drive polymorphism to a proto-sex chromosome, and, given the way we portray it, it might seem that proto-sex chromosomes automatically follow from drive. But other mutational trajectories are possible, and not all will lead to proto-sex chromosomes. For example, in our model, the drive suppressor arrives late, only after the sex-determining alleles have spread through the population. If the suppressor were to arise earlier, then there would be no way for a later-arising sex-determining allele to use the driver to ride to high frequency. Whether linked sex-determining mutations or drive-suppressor mutations are more likely to arise by mutation is an empirical question. However, drivers and suppressors are often engaged in antagonistic coevolution with drivers evolving to evade the effects of suppressors. Thus, one would expect multiple opportunities for a sex-determining gene to arise while the same driving allele is waiting for a suppressor to arise.

Although we do not explicitly model the evolution of recombination, we find that the birth of proto-sex chromosomes is accompanied by linkage disequilibrium between the sex-determining and driving locus. Interestingly, drivers often carry inversions that tie up epistatically interacting loci [15,18], thus drivers may come along with the kind of genetic architecture (reduced recombination over a fraction of the chromosome) that favours the evolution of a proto-sex chromosomes. Furthermore, our model suggests that for a given level of segregation distortion, once the sex-determining allele has reached a stable equilibrium, a further reduction in recombination between the driving and sex-determining components of the proto-sex chromosomes reduces the genetic load (figure 4). Our model provides an additional explanation for why recombination on proto-sex chromosomes will be diminished. Previous theory [3,31] and ample empirical evidence [32] shows that sex chromosomes evolve reduced recombination around the regions that harbour sex-determining alleles.

Our meiotic drive model makes several testable predictions. Similar to Charlesworth & Charlesworth [9], we suggest that plants which evolve sex chromosomes will pass through a transitional stage of gynodioecy or androdioecy. Under our drive hypothesis, we predict that the unisexual plants in these populations will produce more than 50% unisexual broods, because the unisexual plants are heterozygous for a driving sex-determining allele (on their proto-W or proto-Y) and a drive-sensitive allele on the other chromosome. Crosses between sister species pairs also provide tests of the drive hypothesis. If the species with sex chromosomes carries a driving, male-determining Y, an unlinked, fixed suppressor of drive, and a female-determining X, then hybrid females, which will be heterozygous for a female-determining X should produce 50% daughters and 50% cosexual offspring when backcrossed to the cosexual species. Repeated backcrossing of hybrid males to the cosexual species should produce male-biased broods in later generations because the suppressor of Y-chromosome drive may be unlinked from the driving Y chromosome itself and therefore not transmitted along with the Y.

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