# Transitions in sex determination mechanisms through parental and sexual antagonism

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# Abstract (247/250 words)

Sex chromosomes carry the sex-determining locus, causing them to be differently transmitted to and from females and males. These differences lead them to be selected upon in different ways, and hence they are predicted to become enriched for sexually- and parentally-antagonistic genes. Sexually-antagonistic genes have opposing fitness effects in females versus in males; parentally-antagonistic genes have opposing fitness effects when inherited maternally versus paternally. Sexually-antagonistic selection can drive sex determination transitions, whereby an autosome pair becomes a sex chromosome pair in lieu of the ancestral sex chromosomes. Whether parentally-antagonistic selection can similarly drive sex determination transitions remains unknown. I present a model to investigate the potential for transitions in sex determination through parentally-antagonistic selection as compared to sexually-antagonistic selection. This model assumes an ancestral sex-chromosomal sex-determining locus linked to a parentally- or sexually-antagonistic gene, and an autosomal parentally- or sexually-antagonistic gene in whose vicinity a novel sex-determining gene arises. I find that parentally-antagonistic selection can promote the spread of novel sex-determining genes as well as maintain ancestral sex-determining genes when the invasion of the novel sex-determining gene would involve transitions from male to female heterogamety (or vice versa), similar to sexually-antagonistic selection. Transitions between male and female heterogamety are, however, more likely when the ancestral sex-determining locus is linked to a parentally-antagonistic locus. Consequently, parentally-antagonistic selection can enable some highly unusual evolutionary patterns not encountered in other evolutionary models of sex determination. These results provide novel insights into why some sex-determining mechanisms may be so evolutionary labile.

# Article summary (76/80 words):

Sex chromosomes carry the sex-determining genes, and are therefore differently transmitted to and from females and males. Theory therefore predicts that sex chromosomes become enriched for sexually- and parentally-antagonistic alleles. Sexually-antagonistic selection has been shown to enable transitions between different sex determination mechanisms, but this is not yet known for parentally-antagonistic selection. Here, I show that parentally-antagonistic selection can also enable such transitions, and can lead to complex patterns in the evolution of sex determination mechanisms.

# Keywords:

female heterogamety; male heterogamety; parent-of-origin effects; parentally-antagonistic selection; sex chromosomes; sexually-antagonistic selection.

# Introduction

Sex determination directs individual development into a female or male, which must be properly executed to ensure the individual will be able to reproduce. Despite this pivotal role, the mechanisms controlling sex determination are astonishingly diverse (Bachtrog *et al.*, 2014; Beukeboom and Perrin, 2014). In some groups, sex-determining mechanisms exhibit high rates of evolutionary change, suggesting these are liable to turnover. Identifying and understanding the processes underlying the evolution of sex determination has been a major question in evolutionary biology. Theoretical models of sex determination evolution have identified numerous factors that can drive transitions in sex determination (reviewed in van Doorn, 2014). These transitions occur through the invasion of a novel sex-determining gene, typically on a different chromosome pair so that a former autosome turns into a novel sex chromosome pair (though novel sex-determining genes may also evolve on existing sex chromosomes). They may occur neutrally, e.g. through genetic drift (Bull and Charnov, 1977; Veller *et al.*, 2017), or may be driven by one of numerous selective processes including segregation distortion (Kozielska *et al.*, 2010; Úbeda *et al.*, 2014), sex ratio selection (Werren and Beukeboom, 1998; Kozielska *et al.*, 2006; Uller *et al.*, 2007), and sexually-antagonistic selection (van Doorn and Kirkpatrick, 2007, 2010; Muralidhar and Veller, 2018). Furthermore, environmental effects may cause variation in the expression of sex determination genes, thus interfering with sex determination, and thereby help shape its evolutionary trajectory (e.g. Pen et al. 2010; Schenkel et al. 2023). Sex determination mechanisms are thus incredibly malleable, and transitions between different systems can occur readily.

As noted above, transitions in sex determination often results in the establishment of a novel sex chromosome pair. Sex chromosomes represent a special component of the genome owing to the presence of the master sex-determining gene, which causes the sex chromosomes to segregate to and from females and males in biased patterns (Rice, 1984; Hurst, 1994; Haig *et al.*, 2014; Schenkel and Beukeboom, 2016; Figure 1A). Consequently, genes that differently affect fitness depending on the carrier’s sex, or the origin of the allele, may evolve differently on these chromosomes as compared to when they occur on autosomes (Rice, 1984; Patten and Haig, 2009; Jordan and Charlesworth, 2012; Mank, 2017a). Genes that have opposing fitness effects in females and males (i.e. fitness costs in one sex versus benefits in the other) are known as sexually-antagonistic genes, or are said to be involved in intralocus sexual conflict (Bonduriansky and Chenoweth, 2009; Schenkel *et al.*, 2018); similarly, genes with different effects depending on their parent of origin are known as parentally-antagonistic genes (Haig, 1997).

The evolutionary significance of sexually-antagonistic genes has been extensively explored (e.g., Charlesworth *et al.* 2014; Mank 2017b; a; Muralidhar and Coop 2024), but the dynamics of parentally-antagonistic genes has received far less attention. One part of the explanation here may be that parental antagonism has predominantly been studied in isolation. For example, theoretical models have been developed to determine when parentally-antagonistic loci might be stably polymorphic, thus contributing to the maintenance of genetic variation for fitness (Patten and Haig, 2009; Patten *et al.*, 2013), but little has been done to determine how this intersects with other evolutionary phenomena. A second part lies in the difficulty of identifying parentally-antagonistic genes, though examples have been identified in the context of human disease (Kong *et al.*, 2009) and through parent-of-origin effects on selfish genetic elements (Pliota *et al.*, 2024). Identifying parentally-antagonistic selection requires a fitness contrast between reciprocal heterozygotes, and identifying parentally-antagonistic fitness effects may be further complicated by further confounding effects (Lawson *et al.*, 2013). More formally, parentally-antagonistic genes can be considered to have opposing fitness effects in a matrigenic versus in a patrigenic context (Haig, 1997; Haig *et al.*, 2014).

An example of how this works is found in genes that exhibit genomic imprinting, where one allele (e.g. the maternally-inherited copy) is silenced and the other (e.g. the paternally-inherited one) is expressed (Moore and Haig, 1991; Haig, 1997). Genomic imprinting may have evolved due to the different relatedness maternally- and paternally-inherited genes experience between e.g. halfsiblings (Haig, 1997, 2000), and often affect traits related to parental investment (Moore and Haig, 1991). Consider, for example, a female who has mated with several males. Each of these males sires one single offspring, so that each of the offspring produced by these females are related maternally but not paternally. The fitness (e.g. survival) of each offspring next depends on the amount of resources that are maternally provided; resource provisioning is controlled by a gene in the offspring, where enhanced expression of said gene induces higher resource provisioning by the mother. Patrilineal genes in each offspring, which have no inclusive fitness stake in any of the other offspring, would optimize their fitness (odds of transmission to future offspring) by ensuring that their bearer is allocated more resources. The matrilineal genes, on the other hand, may seek to reduce allocation, freeing up resources which could be used to foster additional halfsiblings by whom they could also be transmitted. The organism as a whole would optimize its inclusive fitness for some intermediate allocation. Genomic imprinting can then evolve where expression of an allele is suppressed in matrigenic context (e.g. via epigenetic marks such as methylation), which should help reduce overall gene expression so that the matrilineal allele would experience a fitness benefit. In contrast, it continues to be expressed in its patrigenic context, and its expression level may increase over evolutionary times, thus its enhancing fitness through the patrigenic niche (Haig *et al.*, 2014). Eventually, this would result in the maternal copy being completely silenced, and the paternal copy being transcribed at its own optimum (per the loudest-voice-prevails theory; Haig 1996).

The genomic imprinting example above highlights how a gene may have different evolutionary optima depending on their parental origin. While genomic imprinting has been described in mammals and plants (Patten *et al.* 2014; but see Queller 2003; da Silva 2023), the scope for such conflicting selection pressures to occur is vastly larger. Haig *et al.* (2014) describe how this hinges on the occurrence of relatedness asymmetries; patrigenes and matrigenes with different relatedness to social partners (e.g. maternal halfsiblings) experience different inclusive fitness optima, possibly affecting a wealth of social traits (e.g., resource allocation among offspring). One need only look at non-monogamous birds (in whom imprinting has not been detected; reviewed in John *et al.* 2023) for examples of such asymmetries combined with e.g. parental care of offspring to identify potential conflicts. Combined with parent-of-origin effects in such species (e.g., Tuiskula-Haavisto and Vilkki 2007), the potential impact of parental antagonism may be much larger than currently considered.

Parental antagonism and associated phenomena such as genomic imprinting generally revolve around gene-level selection (Ågren and Patten, 2022). Translating these effects to the level of the individual requires knowledge (or assumptions) on the underlying mechanisms of e.g. resource provisioning, mating systems, and/or relatedness among social partners (e.g., Meunier & Kölliker, 2012). Circumventing this issue, Patten & Haig (2009) developed a population genetic approach that generalizes parentally-antagonistic selection as a specialized case of bipolar dominance effects on fitness (Wolf *et al.* 2008; Lawson *et al.* 2013; for further details, see “Parentally-antagonistic selection” under Methods). Through this, they are able to compare the evolutionary dynamics of loci under sexually-antagonistic selection versus parentally-antagonistic selection.

Mathematical modeling suggest that sexually-antagonistic selection can enable transitions in sex determination (Rice 1986; van Doorn and Kirkpatrick 2007, 2010; van Doorn 2014; Muralidhar and Veller 2018). Here, selection may favor the evolution of linkage disequilibrium between an allele with male-beneficial/female-detrimental effects to an allele that causes maleness, i.e. a male-determiner on a Y-chromosome. Such a supergene would more often end up in males, in whom it enhances fitness, and less often in females, in whom it decreases fitness. Selection similarly favors its X-chromosomal counterpart, comprising a recessive female-determining allele and an allele with female-beneficial/male-detrimental effects, reflecting that the X-chromosome spends more time in females than in males (assuming equal sex ratios; see also Mank, 2009). Possibly, parentally-antagonistic selection may favor similar supergenes as a male-determining allele, which is always inherited paternally, becomes associated with an allele that enhances fitness when paternally-inherited to form a Y-chromosomal complex; inversely, the X-chromosome would become associated with genes that confer fitness benefits when maternally-inherited (Patten and Haig, 2009). Haig et al. (2014) speculate on the selective benefit of sex-biased segregation of parentally-antagonistic genes, but the capacity for such benefits to facilitate transitions in sex determination has not yet been investigated formally.

Here, I present a model of sex determination transitions through linkage between parentally-antagonistic and sex-determining genes. In line with the van Doorn and Kirkpatrick (2007, 2010) models for transitions through sexually-antagonistic selection, I hypothesized that the scope for invasion of a novel sex determination gene would be affected by the strength of selection acting on both parentally-antagonistic loci, and by the degree of linkage between the sex-determining and parentally-antagonistic loci. The effect of selection here depends on the fitness effect of the parentally-antagonistic locus in homozygotes, as well as the different dominance parameters that determine the relative fitness of the heterozygotes in which the focal allele is maternally- versus paternally-inherited. I additionally consider the role of linkage between sex-determining genes and paternally-antagonistic genes in shaping the scope for turnover. Finally, I extend this model to allow for sexually-antagonistic, rather than parentally-antagonistic, selection to affect either the ancestral sex chromosome or the novel sex chromosome. Through this, I compare the potential for sexually-antagonistic versus parentally-antagonistic selection to retain the ancestral sex chromosome c.q. drive the invasion of a novel sex chromosome.

# Methods

## Model overview

I provide here a general description of the model; the detailed, mathematical model is included in the Supplementary Material; an overview of all model parameters including standard values is included in Supplementary Table 1. The model is a modified version of the one presented in Schenkel et al. (2021). I present a two-locus, two-allele model per linkage group, with a genome consisting of two linkage groups (1 and 2) so that the full model features four loci (Figure 1B). Linkage group 1 represents the ancestral sex chromosome pair, whereas linkage group 2 represents the initially-autosomal pair carrying the newly-evolving sex-determining locus. All individuals are diploid; all genotypes in the model are represented with the maternally-inherited allele first, and the paternally-inherited allele second. Each linkage group carries an ancestral ( or novel () sex-determining locus with alleles and and locus with alleles and ; each locus is under either parentally-antagonistic or sexually-antagonistic selection (see below for details). Fitness effects of and are multiplicative, i.e. the fitness of a genotype is given by . Selection occurs based on viability, and takes place during maturation from the juvenile to the adult stage, so that survival is proportional to relative fitness. Recombination between and occurs at a rate in both sexes. The sex determination system is assumed to be male heterogametic (females , males ). The locus is initially fixed for the non-sex-determining allele (males and females both ); sex determination transitions occur by the invasion of a novel SD allele on , denoted . If has a male-determining effect, its invasion would cause a transition between two different male heterogamety systems (Figure 1C, Supplementary Figure 1A); females would retain an genotype, but males would be instead of . If has a female-determining effect, I assume it to be dominant over . Under these conditions, its invasion would lead to fixation of in all individuals and on the maternal copy in females (females , males ; Figure 1D, Supplementary Figure 1B). Note that terms such as ‘female’ and ‘male’, and similarly ‘maternal’ and ‘paternal’ can be swapped so that different sex determination transitions are accounted for in my model (e.g., one might label a female-determiner, so that the original sex determination system is female heterogametic instead of male heterogametic (females , males ).

## Parentally-antagonistic selection

Constructing a formal model that integrates conflicts between matrigenes and patrigenes requires making mechanistic assumptions about e.g., the mating system, parental care, and asymmetric relatedness of siblings. While such an approach would be interesting in its own right (particularly in comparison to models of e.g. parent-offspring conflict in relation to sex ratios, e.g. Pen, 2006), such approaches may be overly complex for the matter at hand (Ågren and Patten, 2022), and preclude a straightforward comparison to existing models of sexually-antagonistic selection (e.g. van Doorn & Kirkpatrick, 2007, 2010). Instead, I adopt a population genetic framework for modelling parentally-antagonistic selection adapted from Patten & Haig (2009) and Patten *et al.* (2013) where specific alleles are beneficial to the bearer’s fitness when maternally-inherited, but detrimental when paternally-inherited (or vice versa), much like how specific sexually-antagonistic alleles may be beneficial in females but deleterious in males (or vice versa). Specifically, alleles are beneficial when maternally-inherited, but detrimental when paternally-inherited and vice versa for , so that the optimal genotype for each locus is whereas the least optimal genotype is (i.e. bipolar dominance; Wolf *et al.*, 2008; Lawson *et al.*, 2013). The fitnes of a genotype is determined as follows:

(1a)

(1b)

(1c)

(1d)

Here, indicates the fitness effect of the allele, and and represent dominance parameters for heterozygous genotypes when is maternally- () or paternally-inherited (). For simplicity, I assume selection on is positive (i.e. has a higher fitness than ), so that . Because I assume that is detrimental when maternally-inherited but beneficial when paternally-inherited, this means that and .

## Sexually-antagonistic selection

Under sexually-antagonistic selection, alleles are beneficial in females, but detrimental in males, and vice versa for ; the optimal genotype in females for either locus is then , whereas in males the genotype is optimal; this methodology matches the one used by van Doorn and Kirkpatrick (2007, 2010). The fitness of females with a genotype is determined as follows:

In males, the fitness is given by:

Here, ( indicates the fitness benefit conferred by ( in females (males), and () is the dominance of (in female (male) heterozygotes.

## Simulation procedure

I initialize an infinitely large population with non-overlapping generations to obtain a deterministic model. The initial population has a sex ratio equal to one, where all females have a genotype and males . Both loci start with a frequency of 0.5 regardless of the parameter values for and (under parentally-antagonistic selection), or and (sexually-antagonistic selection), and (either selection scenario). Parameter values were varied in different sets of simulations in which some were kept at constant values and others were varied by random sampling from uniform distributions (i.e. shotgun sampling; for details, see Results). This generates a unique, randomly-selected set of parameter values (for those that were varied) for each simulation. The combined set of simulation results can be used to fit a statistical model (details under “Statistical analysis”) with a relatively small number of simulations while minimizing the loss of generality.

I restrict my analysis to cases where both loci would remain polymorphic when autosomal, i.e. both alleles and have a non-zero frequency even when not linked to a sex-determining gene. This is necessary for both loci to cause fitness variation, and hence selection to act on both the ancestral and the novel sex chromosome pair. If is fixed, then selection cannot act to maintain the ancestral sex chromosome when a new sex-determining gene evolves. If is fixed, selection cannot drive the invasion of the novel sex-determining allele A; if both loci are fixed, invasion of the novel sex-determining allele occurs via neutral processes. Variation at each locus is maintained when the average heterozygote fitness exceeds the fitness of the two homozygous genotypes (for sexually-antagonistic selection, the average fitness across both sexes) (Pearce and Spencer, 1992; Úbeda and Haig, 2004), i.e.:

(2a)

(2b)

(2c)

For parentally-antagonistic selection, assuming , inequalities 2a-c are satisfied when:

(3)

For sexually-antagonistic selection, inequalities 2a-c are satisfied when:

(4a)

(4b)

I standardize with for parentally-antagonistic selection, where is s scaling parameter that describes how beneficial a genotype is relative to the genotype. For sexually antagonistic selection, I assume the selection coefficient in males and females are identical, i.e. , and represent their shared value with . I standardize and for sexually-antagonistic selection so that inequalities 3 and 4a,b are satisfied. Note that outside of the parameter range investigated here, mutation-selection equilibria at either locus might also yield sufficient genetic variation to enable transitions between sex-determining systems. Here, a locus would be fixed for a specific allele, and the alternative allele would be recurrently formed through mutation. However, selection on this alternative allele is such that despite its selective benefit in one condition (in males or females for sexually-antagonistic genes, or maternally- or paternally-inherited for parentally-antagonistic selection) is insufficient to offset the selective costs in the other condition so that newly-mutated alleles of this type are constantly being purged.

I perform different sets of simulations where I vary the values of (under parentally-antagonistic selection), and and,(sexually-antagonistic selection) and (both scenarios) in different combinations to explore how they affect the scope for invasion. I allow both *P* loci to evolve towards equilibrium during 10,000 generations; I then introduce the allele once by mutating a small proportion () of the loci from to , proportionally distributed among all haplotypes with non-zero frequencies in the gamete pool to prevent linkage disequilibrium. Subsequently, I allow for at least 40,000 more generations before I determine the final frequency of the allele and thereby whether a sex determination transition has occurred. I consider scenarios where represents (1) a male-determining gene that functions similarly to so that invasion of entails a transition between homologous male heterogametic systems, and (2) a female-determining gene that is dominant over so that invasion of entails a transition from male heterogamety to female heterogamety. I additionally vary whether the loci are under sexually-antagonistic or parentally-antagonistic selection. The scenario in which both and loci are under sexually-antagonistic selection is described in Van Doorn & Kirkpatrick ( 2007, 2010); I therefore focus primarily on cases where (1) is under parentally-antagonistic selection, but is under sexually-antagonistic selection; and (3) is under sexually-antagonistic selection, but is under parentally-antagonistic selection.

## Statistical analysis

All simulations, data analyses, and data visualization were performed in R (v.4.2.1; R Development Core Team 2023) and RStudio (v.2023.06.01; RStudio Team 2023) using the ‘tidyverse’ (Wickham *et al.*, 2019), ‘mgcv’ (Wood, 2017), and ‘viridis’ (Garnier, 2018) packages. All simulations are scored based on the final frequency of . I determine whether this exceeds 0.1 and 0.9, which are taken as arbitrary cutoffs to determine whether invades and whether it is fixed, respectively; intermediate values mean that invades but is not fixed, so that a polymorphism with and is established. I fitted generalized additive models with binomial distributions to these scores to interpolate between sampled parameter values. For transitions with as a male-determiner, I used the frequencies of on the paternal copy in males, whereas if functioned as a female-determiner, I used the frequencies on the maternal copy in females because only for these copies can achieve a non-zero frequency under these conditions. I used full tensor smooths between different parameter combinations as the predictor variable (Wood, 2017; Pedersen *et al.*, 2019), depending on which parameters were varied in a set of simulations. Thin plate regression splines with extra shrinkage were used as the base functions.

# Results

## Sex determination transitions through parentally-antagonistic selection

When represents a male-determining gene that is functionally homologous to , its invasion means that the ancestral male heterogamety system is replaced by a similar male heterogamety system (Figures 1E, Supplementary Figure 1A). I find that the scope for such transitions depends both on the selection regimes acting on as well as and the degree of recombination between the and *P* loci on both chromosomes (Figure 2A; Supplementary Figure 2). When is strongly disfavored when maternally-inherited and/or strongly favored when paternally-inherited, linkage disequilibrium between and , where is associated primarily with , may protect from being replaced by . However, if is sufficiently deleterious when maternally-inherited (e.g. ), then invasion of may be favored. The scope for invasion of is also increased when has stronger benefits when paternally-inherited, i.e. for higher values of .

Varying the selective effects , and the recombination rates revealed that can invade when recombination between and is sufficiently low and/or selection on is sufficiently higher than on (Figure 2A). In contrast, lower recombination between and or stronger selection on decreases the scope for invasion by . Polymorphic sex determination systems, where and coexist in the population, can also occur, particularly when recombination between and and between and is relatively high and selection on both loci is sufficiently weak.

When represents a female-determining gene that is dominant over , its invasion means that the ancestral male heterogamety system is replaced by a female heterogamety system (Figure 1F, Supplementary Figure 2B), which also features fixation of in both sexes. Unlike when represents a male-determining gene, I find that the spread of a female-determining can spread even if selection on is weak provided that recombination between and is sufficiently low (Figure 2B; Supplementary Figure 3). Only when recombination is high and selection on is sufficiently weak can be maintained as the sole sex-determining gene.

One explanation for the broad range of conditions under which may spread is that the dominant feminizing invades through two processes. Initially, linkage disequilibrium has been built up between and , resulting in a paternally-adapted, male-limited haplotype (the *de facto* Y-chromosome) and a more maternally-adapted haplotype (the *de facto* X-chromosome) being relatively overrepresented, whereas a and are relatively underrepresented. Although remains polymorphic, meaning and are present in the population, transmission of from fathers to daughters will be reduced because males have higher fitness than males. This generates a genetic load in females as they typically inherit an haplotype paternally, resulting in lower fitness in these females. In contrast, females bearing can inherit the paternally-adapted haplotype, thus experiencing a higher fitness than non--bearing females. This drives the initial invasion of . At some point during its invasion, becomes associated with which is beneficial when maternally-inherited, driving to fixation. This rationale is further supported for the wide scope for which both and may co-occur (Figure 3B, dark blue area); can invade under wide range of parameter values, but can only be fixed if the recombination rate between and is sufficiently low. When recombination is too high, might invade by resolving the genetic load, but is unable to build up a sufficiently stable association with to become fixed.

Invasion of however induces a genetic load in males for similar reasons as applied to females under male heterogamety. Given that the initial genetic load enabled the invasion of , we might expect that this newly-established load could, through similar mechanisms, enable the secondary invasion of another sex-determining allele. One possible scenario is that a novel male-determining variant of, denoted , that is dominant over the newly-invaded feminizing should be able to invade. To test this, I determined whether (1) a dominant female-determining could invade in a population with male heterogamety with as the male-determining gene, and (2) an even more dominant male-determiner could invade in a population where had previously invaded as the female-determining gene. Such reciprocal invasions are indeed possible (Figure 3). Given that can invade under an extremely broad range of parameter values when linkage is sufficiently strong (Figures 2B, Supplementary Figure 3), the scope for reciprocal invasions is also likely to be broad.

## Sexually-antagonistic versus parentally-antagonistic selection as drivers of sex determination transitions

To compare the influence of parentally-antagonistic and sexually-antagonistic selection on sex determination transitions, I considered situations where either or was under sexually-antagonistic selection, and retained parentally-antagonistic selection at the other locus. When is sexually-antagonistic, this determines whether parentally-antagonistic can be strong enough to drive the invasion of a novel sex-determining allele , whereas if is sexually-antagonistic, this determines if parentally-antagonistic selection can help retain the ancestral sex-determining locus and the associated sex chromosome pair. When is under parentally-antagonistic selection and under sexually-antagonistic selection, the scope for invasion of is reduced relative to that when both loci experience parentally-antagonistic selection (Figures 4A and C). However, the same principles appear to apply, in that a female-determining allele invades more readily when selection on is stronger, further suggesting that parentally-antagonistic selection establishes a genetic load on the sex chromosomes which favors their replacement. Whether a female-determining is fixed or only reaches an intermediate frequency (and hence results in a polymorphic system with both and ) depends on the strength of sexually-antagonistic selection acting on , with the scope for fixation being substantially higher when selection is stronger. These results underline how parentally-antagonistic selection on the ancestral sex-chromosomal pair promotes the invasion of a novel sex-determining gene, rather than any linked selection acting on this sex-determining gene itself (in stark contrast to other models of transitions in sex determination, such as those involving sexually-antagonistic selection; van Doorn & Kirkpatrick, 2007, 2010).

When is under sexually-antagonistic selection and under parentally-antagonistic selection, invasion of is determined in a more straightforward manner (Figures 4B and D), and does not differ substantially depending on whether has a male-determining or a female-determining function. Stronger selection on increases the scope for invasion, whereas stronger selection on reduces it. Similarly, higher recombination between and relaxes the degree of linkage between and that is required for to invade. However, increased recombination between and may lead to only spread to intermediate levels rather than to fixation, so that when recombination between and as well as between and is high, a polymorphic system with both and is established. Altogether, the ability for parentally-antagonistic selection to favor novel sex-determining alleles appears to be sufficient to drive their invasion, both when the ancestral sex-determining allele is linked to a locus under parentally-antagonistic or sexually-antagonistic selection.

# Discussion

Here, I presented a model to study transitions between sex determination mechanisms due to linkage between sex-determining loci and loci with parentally- or sexually-antagonistic effects. In this model, a novel sex determination gene is linked to a gene under parentally- or sexually-antagonistic selection. This formerly-autosomal, now-sex chromosome pair invades and replaces the pre-existing sex chromosome pair (which similarly carries a sex determination gene and a parentally- or sexually-antagonistic gene), establishing a novel sex chromosome system. Transitions between different chromosomes can occur through invasion of a sex determination gene with a homologous function, in which case the homogametic and heterogametic sex do not change (e.g. male heterogamety to male heterogamety), or through the invasion of a dominant gene that overrules the function of the ancestral sex determination gene, so that the homogametic and heterogametic sex switch (e.g. male heterogamety to female heterogamety).

Both types of sex determination turnovers can readily take place when both chromosomes carry parentally-antagonistic genes, though the scope for invasion of a novel sex determination gene differs substantially. For a transition to a homologous sex determination gene, I find that the novel male-determining can invade and fix provided that theselective effects involved with are sufficiently stronger than those of , and/or the linkage to between and is tighter than that between and (Figure 2; Supplementary Figure 2). Transitions between different male heterogamety systems may be constrained, because invasion of the novel male-determining requires that the co-adapted gene complex is broken down. That is, the sex-specific inheritance patterns of the sex chromosome pair (linkage group 1) promote differentiation between the X- and the Y-chromosome. Here, the Y-chromosome (bearing the allele) comes to be enriched for paternal-benefit alleles () and the X-chromosome (bearing ) becomes enriched for maternal-benefit alleles ().Males bearing may lack the beneficial haplotype, instead carrying two haplotypes at linkage group 1. This leads to reduced fitness, and invasion of is thus only favored if the initial benefit of inheriting an haplotype is sufficiently strong and/or reliable (i.e., unlikely to be broken down by recombination).

In contrast, transitions where the novel sex determination gene is dominant over the ancestral gene (and hence a change in heterogametic sex occurs) are much more readily observed within the parameter space considered here. One possible explanation (see also Results) is that evolution of the ancestral Y-chromosome leads to linkage disequilibrium between and the paternal-benefit allele . This establishes a co-adapted gene complex in males, particularly when paired with an X-chromosome with the maternal-benefit allele as the genotype has optimal fitness. Daughters from such males experience a genetic load, as paternal inheritance of is disfavored. When a dominant feminizing allele evolves, this genetic load can be resolved as daughters can now inherit the complex. The possibility to inherit the co-adapted gene complex means that -bearing females tend to have higher average fitness than non--bearing females, promoting the initial spread of in the population. Note that while these females may transmit the co-adapted complex maternally, the average fitness of their -bearing daughters exceeds that of non--bearing females. This is because while is rare, the genetic load on the locus remains unresolved, and the benefit of inheriting the complex paternally outweighs the cost of inheriting the complex maternally. As becomes more prevalent during the transition to female heterogamety, selection tends to favor the haplotypes over haplotypes. This differentiation can now occur, as is a female-limited gene. Consequently, spreads through the effect of two different selective processes. In contrast to parentally-antagonistic selection, this genetic load effect does not hold for sexually-antagonistic selection on . Instead, association between the male-determining allele and the male-beneficial allele under this model would actually inhibit the spread of a feminizing allele, as females that inherit this gene complex would actually experience lower fitness than their non--bearing counterparts.

Note that in my model, I assume the novel sex-determining allele to be dominant over its partner allele . Alternatively, new sex-determining alleles may evolve that act recessively, or that exhibit incomplete penetrance (as considered in e.g. Bull and Charnov, 1977). Such sex-determining alleles are expected to be less likely to spread through the patterns described above. This is because building up linkage disequilibrium between the sex-determining locus and the parentally-antagonistic locus may be slower, or the severity of this disequilibrium reduced, both of which may be due to the less strict sex-biased inheritance of such sex-determining genes. Other variations to the model presented here may involve the transition from hermaphroditism to separate sexes, or from environmental sex determination to genetic sex determination (Muralidhar and Veller, 2018; Olito and Connallon, 2019). In the second scenario, genes experiencing sexually-antagonistic selection become linked to genes that skew the threshold for female versus male development. Successive bouts of this pattern generates a complex of linked genes that confers a strong sex-specific fitness benefit while extending the range of conditions under which an individual will develop into the sex that experiences said benefit. Ultimately, this leads to a *de facto* sex-determining chromosome, e.g. a male-determining Y-chromosome associated with increased male fitness, where its bearer develops as a male regardless of the further environmental conditions. For parentally-antagonistic selection, a similar coevolutionary pattern could hold where e.g. paternal-benefit genes come to be associated with male-biasing mutations.

One consequence of the spread of is that males, rather than females, are now subject to a genetic load. Under these conditions they more often inherit the allele through their mothers, as females have higher fitness than females. The presence of this genetic load in males is similar to the previous genetic load in females which enabled the evolution of ; we could similarly expect a novel sex-determining allele to evolve to resolve this newly-established genetic load. One interesting possibility is that the ancestral sex-determining locus evolves a male-determining allele that is dominant over . To explore this possibility, I considered a novel mutation at the locus, denoted , which functions as a male-determining allele that overrules (Figure 3). The spread of this gene reverts the genetic load to again occur in females, effectively returning to the ancestral state altogether. This can lead to dynamics where and take turns as the dominant sex determination gene, as each invasion at one chromosome begets a new invasion at the other chromosome, with increasing levels of dominance of each newly-invading sex determination gene. This establishes a ‘sex chromosome ping pong’ where continuous switchovers occur between sex chromosome pairs and male versus female heterogamety (Figure 3C). This could lead to continuous evolution of both sex determination genes, and may help explain why some sex determination genes exhibit such high evolutionary rates, without invoking any conflict between them. That said, sex determination mechanisms are typically assumed to evolve by stepwise additions of novel genes to form a serial cascade (Wilkins, 1995; Pomiankowski *et al.*, 2004). Genes that have previously been incorporated and are now in the middle of the cascade are then thought to be constrained in their evolution because they have previously-selected functions within the cascade, e.g. to control other more downstream genes, which would diminish the possibility for these dynamics to occur. In turn, however, this restriction has been drawn into question given that some downstream genes have in fact been found to evolve, such as in medaka fish (Herpin *et al.*, 2013; Herpin and Schartl, 2015) and houseflies (Hediger *et al.*, 2010; Schenkel *et al.*, 2023). While such cases may represent single instances of a reversion to a prior sex-determining locus and not the back-and-forth dynamic described above, they do provide evidence that the underlying assumptions need not be implausible.

The observation that sex determination genes linked to parentally-antagonistic genes are in effect destabilized is particularly interesting in light of the expected accumulation of parentally-antagonistic genes on sex chromosomes (Patten and Haig, 2009; Haig *et al.*, 2014). As sex chromosomes develop from small sex-linked regions into genetically-distinct, non-recombining chromosomes, the genetic contents of the X- and Y-chromosomes (or Z- and W-chromosomes in female heterogametic systems) are expected to diverge substantially (Rice, 1987). This could include the accumulation of parentally-antagonistic genes (Hurst, 1994; Patten *et al.*, 2013). If so, the divergence of these sex chromosomes does not render them more stable against turnover, but rather primes them for replacement. These evolutionary dynamics differ markedly from other models of sex chromosome evolution, e.g. those invoking sexually-antagonistic selection, where differentiation between the X- and Y-chromosomes tends to stabilize them against turnovers. That said, the “hot potato” model (Blaser *et al.*, 2014) of sex chromosome turnover does share some similarities to the model presented here, in that the evolution of sex chromosomes eventually causes selection to favor them to be replaced. Importantly, however, the “hot potato” model invokes the accumulation of deleterious mutation after recombination has halted, and predicts that transitions should occur primarily between different male or female heterogamety systems. In contrast, my model does not invoke such deleterious mutations, and emphasizes that transitions should more easily occur between male and female heterogamety systems (or vice versa). These differences could be useful to empirical approaches to evaluating both of these models.

In addition to the situation where both the ancestral and novel sex chromosome pair carry parentally-antagonistic loci, I considered situations where one of these instead carried a sexually-antagonistic locus to compare it to previous models by Van Doorn and Kirkpatrick (2007, 2010). When the novel sex chromosome pair carries a sexually-antagonistic locus, I found that the scope for turnover was quite similar to when both carry parentally-antagonistic loci (Figures 4A and C), i.e. a male-determining allele can invade if selection on is sufficiently strong and/or recombination between and is sufficiently low. A female-determining , however, spreads much more readily, consistent with the genetic load scenario described above. When the ancestral sex chromosome pair carries a sexually-antagonistic locus, the scope for turnover is again quite simple, and follows the same logic as described above for the male-determining where stronger selection on and lower recombination between and promotes turnover. Altogether, for conditions where selection pressures on both chromosomes are of comparable magnitude, parentally-antagonistic selection (1) is just as effective at driving transitions in sex determination as is sexually-antagonistic selection; (2) can favor the ancestral sex-determining allele over a novel sex-determining allele with identical function; and (3) favors replacement of the ancestral sex-determining allele by the invasion of a dominant allele that triggers a transition from male to female heterogamety (or vice versa).

Altogether, these results further enhance our understanding of the malleability of sex determination. In comparison to other models, sex determination transitions mediated by parental antagonism exhibit some very unusual dynamics, most striking of which is the possibility for different chromosome pairs to take turns as the sex chromosome pair. This phenomenon can help explain why some sex determination mechanisms have genes that exhibit high evolutionary rates, such as in amphibians and teleost fish (reviewed in Miura, 2018; Kitano *et al.*, 2024). As parental antagonism is only poorly understood, the prevalence of sex determination transitions that are driven by this phenomenon is still unclear. However, as between-parent conflict is nearly ubiquitous, the scope for parental antagonism to occur may also be broad, and therefore parental antagonism may be a previously unconsidered factor in shaping sex determination mechanisms. As parental antagonism may act alongside other selective processes affecting sex determination genes, the peculiar dynamics described here may help understand why some sex chromosomes systems are so easily displaced.

# Author contributions

MAS conceived the study; developed the model; analyzed the data; and wrote the manuscript.

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# Conflict of interest

I declare no conflict of interest.

# Data availability

Model source code, secondary data, analysis scripts, and output files are freely available through GitHub (<https://github.com/MartijnSchenkel/SexDeterminationParentalAntagonism>) and will be stored in Dryad upon acceptance.

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# Figure captions

**Figure 1:** Sex chromosome inheritance, model setup, and transitions in sex determination. (A) Autosomal inheritance (left) allows for all chromosomes to freely segregate from and to females and males (indicated by arrows). Sex chromosomal inheritance (right) leads to biased patterns: the Y-chromosome (dark blue) is always transmitted paternally from fathers to sons; the X-chromosome in such fathers (light blue) is always transmitted to daughters. X-chromosomes in mothers (pink) are transmitted to daughters and sons alike. (B) In my model, I consider two linkage groups , each of which carries a (potential) sex determination locus , with alleles and and a parentally-antagonistic locus with alleles and ; recombination between and occurs at a rate . (C) Fitness effects of parentally-antagonistic loci depend on maternal versus paternal inheritance of and alleles. (D) Fitness effects of sexually-antagonistic loci depend on the sex and the genotype. An individual’s fitness depends on the genotype at each locus . The partial fitness scores of and are multiplied to obtain the individual’s total fitness. The parameter constraints are set so that each locus will be polymorphic regardless of whether it experiences sexually- or parentally-antagonistic selection. (E) If has a male-determining function, transitions in sex determination occur via the loss of (and fixation of ) as invades on the paternal copy in males. (F) If has a female-determining function, transitions in sex determination occur via the fixation of in both sexes, and the invasion of on the maternal copy in females. Grey chromosomes indicate autosomes; white chromosomes indicate sex chromosome complements that lack a dominant sex-determining allele or .

**Figure 2:** Invasion of a novel sex-determining allele under different selection effect sizes and recombination rates. Invasion of a male-determining (top row) or a female-determining allele (bottom row). Left column: and are under parentally-antagonistic selection. Right column: and are under sexually-antagonistic selection. Different colors indicate whether can invade and replace as the sex-determining gene (pink) or not (orange), or whether a polymorphism occurs (dark blue). polymorphism is said to occur when both and have a frequency of at least 10% on the paternal allele of males (top row) or has a frequency between 10% and 90% on the maternal copy of females (bottom row). Values in horizontal strips denote the selective effect associated with ; values in vertical strips denote the selective effect associated with . Parameter values: Fitted GAMs used and as predictor variables; separate GAMs were fitted for each panel (i.e. combination of and ).

**Figure 3:** Sex chromosome ping pong through recurrent reciprocal turnover. (A) Invasion of a female-determining that is dominant to . Fixation of is expected to take place over an extended period of time (not shown). (B) Invasion of a male-determining variant that is dominant over the female-determining allele that invaded in (A). The regular is presumed to be fixed prior to invasion of (not shown). Dashed vertical lines denote introduction of (in (A)) and (in (B)). Parameter values: . (C) Reciprocal invasibility leads to continuous alternations between and as the most-dominant sex-determining gene. Arrows indicate transitions between male and female heterogamety and vice versa. From an initial population with male heterogamety ( shown in dark blue), invasion of a feminizing (orange) can occur which causes a transition from male to female heterogamety as is fixed in both sexes (similar to (A)). Subsequent invasion of a (light blue) that is dominant over re-establishes male heterogamety (similar to (B)), after which a secondary feminizing (red) that is yet again dominant over can again yield female heterogamety (not shown). Such patterns can in principle repeat indefinitely, establishing a ping pong pattern where the different chromosome pairs take turns as the sex chromosome pair.

**Figure 4:** Comparing parentally-antagonistic versus sexually-antagonistic selection in sex determination transitions. Invasion of a male-determining (top row) or a female-determining allele (bottom row). Left column: locus is under parentally-antagonistic selection whereas is under sexually-antagonistic selection to determine the capacity for parentally-antagonistic selection to retain the ancestral sex chromosome pair. Right column: is under sexually-antagonistic selection and is under parentally-antagonistic selection to determine the capacity for parentally-antagonistic selection to drive transitions to a novel sex chromosome pair. Parameter values: . Fitted GAMs used and as predictor variables. Separate GAMs were fitted for each panel (i.e. each combination of and ).