On the evolution of sex and its consequences

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Abstract

This dissertation is an empirical and theoretical examination of the evolution of sex, sex-determining mechanisms, and sexual selection. Chapter 1 surveys adult sex ratios across species and populations of Anolis lizards to determine whether increased sexual selection—as proxied by sexual dimorphism—is associated with skewed adult sex ratios. Chapter 2 develops an evolutionary model to explain the simultaneous evolution of asexuality and increased ploidy in angiosperms, based on the biology of the well-studied asexual genus *Taraxacum* (dandelions). Chapter 3 analyzes the stochastic evolutionary dynamics of transitions between male and female heterogamety (XX/XY and ZW/ZZ), and discovers that evolution along the paths of (deterministic) equilibria that link these two systems is non-neutral, even when all genotypes are equally fit. Instead, an emergent 'drift-induced' selective force biases substitution rates in favor of dominant sex-determining mutations. Chapter 4 proposes a theoretical explanation for the prevalence of genetic versus environmental sex determination. Under environmental sex determination, a gene that increases the probability that its bearers develop as one of the sexes couples with a sexually antagonistic gene that is beneficial in that sex but detrimental in the other. The coupled haplotype invades, and recruits more sex biasing and sexually antagonistic alleles, eventuating in a sex chromosome, i.e., genetic sex determination. Chapter 5 proposes a novel explanation for the evolution of female preferences for costly male traits, based on the selfish genetic interests of sex chromosomes within the genome. Female-biased genetic elements, such as the W and X sex chromosomes, evolve mating preferences for males displaying traits that reduce those males' fitness (or that

of their male offspring) but increase the fitness of female offspring. This process may explain differences in costly ornamentation and behavior across species with divergent sex-determining mechanisms. Chapter 6 reanalyzes the logic underlying another theory for the evolution of female mating preferences for costly male traits, Fisherian runaway selection, and identifies two distinct channels through which it operates in diploids.

Contents

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Listing of figures

Dedicated to my parents, Krishnamurty Muralidhar and Radhika Santhanam.

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Introduction

I was initially attracted to evolutionary biology by the clear logic underlying evolution by natural selection. To slightly reformulate Lewontin's statement from 1970, there are four requirements for evolution by natural selection: (i) there exists phenotypic variation in a population; (ii) this variation is heritable; (iii) there is differential success in survival or reproduction among members of a population; (iv) this differential success in survival or reproduction is correlated with the phenotypic variation [128]. If these requirements are fulfilled, natural selection will operate. These conditions can be applied to scenarios as diverse as determining the properties of universes that proliferate in a hypothetical multiverse, to calculating which zebra will evade predators and survive to produce offspring, to predicting which viral strain will succeed in infecting a particular cell. The contribution of modern population genetics, with its well-defined rules of Mendelian assortment and segregation, has only strengthened our ability to understand and predict how evolution by natural selection occurs. Evolutionary genetics has been a remarkably fruitful branch of scientific inquiry owing to this combination of a well-grounded theoretical foundation and the empirical clarity of Mendelian genetics.

During the early stages of my PhD in evolutionary biology, I became fascinated

by phenotypic diversity between the sexes across taxa. The evolution of sexual reproduction, and the subsequent evolution of separate sexes, have resulted in a dazzling array of differences between males and females of the same species, in phenotypes ranging from morphology to physiology to behavior. Understanding the evolutionary forces that drive and constrain the evolution of these differences has formed the core of my research program.

I have focused on three key phenomena that drive this diversity between the sexes. The first of these, sexual antagonism, arises because males and females have different fitness optima for many traits, but are hindered in evolving to these optima because they share most of the genome. This form of intragenomic conflict is widespread—indeed, it is predicted to manifest in all species with separate males and females. The long-term resolution of sexual antagonism is sex-specific limitation of a trait, which leads to the evolution of sexual dimorphism—quantitative and qualitative differences between the sexes. However, sexual dimorphism that arises through independent mechanisms may in turn enhance ongoing sexually antagonistic conflict. Finally, sex-determining systems often play a key role in modulating sexually antagonistic selection through, for example, the evolution of sex chromosomes, which are regions of the genome not shared equally between the sexes. Sex chromosomes can increase levels of sexual dimorphism, while sexually dimorphic traits are often the critical factors driving turnovers in sex-determining systems.

Using a combination of theoretical and empirical approaches, I have investigated the interactions between these key evolutionary forces, and their downstream consequences on processes such as sexual selection, mating systems, and sex ratio evolution. I have also investigated more upstream questions, such as the evolution and maintenance of sexual versus asexual reproduction. This integrative approach to un-

derstanding the evolutionary consequences of sex can provide powerful explanations for the observed diversity between males and females across the tree of life.

1

Sexual selection and sex ratios in *Anolis* lizards

1.1 Abstract

Biased sex ratios, or unequal numbers of males and females in a population, can alter the intensity of sexual selection by enhancing competition for mates, and thus may affect the evolution of reproductive strategies. Studies of sex-ratio variation across a clade provide an opportunity to examine the morphological or behavioral consequences of different levels of sexual selection. We examined sex-ratio variation, using phylogenetic comparative methods, across a diverse clade of terrestrial

vertebrates, the *Anolis* lizards. Across a sample of 14 species in 21 localities, we found remarkable bidirectional variation in sex ratios across the *Anolis* clade: males are more common in some populations, and females in others. However, we find no evidence that sex-ratio bias is associated with sexual size dimorphism, a proxy for sexual selection. Nor do we find an association of sex-ratio bias with ecological niches (i.e., ecomorphs), which vary in sexual selection pressures and mating systems. The observed inter-specific variation in sex ratio suggests that a balance of different, possibly opposing, factors, including sex-specific dispersal and mortality rates, may play a role in determining population sex ratio.

1.2 Introduction

The population sex ratio reflects both the distribution and availability of potential mates, and thus affects sexual selection within a species [58, 122]. Skew in adult sex ratio often corresponds with differences in the variation in average reproductive success within each sex [55, 58]. If the sexes differ in their variance in reproductive success, divergent mating strategies for each sex are favored; this phenomenon is exemplified by polygynous mating systems, in which females discriminate between possible mates, while males compete for access to mating opportunities [58, 116, 230].

Variation in adult sex ratio can be observed across geographically distinct populations within a single species, while the sex ratio of a single population can also change across multiple generations. If such changes in sex ratio are persistent across multiple generations in their bias toward a single sex, they can lead to alterations in patterns of sexual selection within a population, modifying the intensity of both intersexual and intrasexual selection. This phenomenon of increased sexual selection due to sex-ratio bias has been observed across multiple taxa in both natural

populations and experimental manipulations: within-sex competition and mate selection strategies respond to changes in sex-ratio skew in plants [204], insects [130], amphibians [103, 184], fish [82, 151], birds [185], and mammals [152]. Studying the causes and consequences of biased sex ratios may therefore uncover a framework for the evolution of mating systems, and by extension, reflect the strength of sexual selection in different species [58, 177]. Specifically, if one sex is limited in a population, the other, more common, sex is expected to compete more for mating opportunities and thus be under stronger sexual selection [58, 103, 116, 122]. Despite the important role that sex ratio may play in mating systems and patterns of sexual selection, the consequences of variation in sex ratio among diverse members of a clade remain unclear [177].

Here we report variation in sex ratios across and within species using a diverse clade of reptiles: lizards in the genus *Anolis*. Anoles are well known for their ecological niche diversification, and species vary in territoriality, sexual dimorphism, and mating systems (reviewed in [131]). Greater Antillean anole species are grouped into six main ecological niches, or ecomorphs (trunk-crown, trunk-ground, trunk, grass-bush, twig, and crown-giant), that have independently evolved multiple times on different islands [132, 260]. These ecomorphs are also characterized by different degrees of sexual size dimorphism [29, 30], a measure that often corresponds to the degree of sexual selection in a lineage [2, 152]. We would therefore expect that a population will exhibit a bias in sexual size dimorphism toward the more common sex, as a result of increased sexual selection pressure. In addition, as both sexual size dimorphism and mating systems diverge between ecomorphs, we expect an association between biased sex ratios and ecomorph class. To date this hypothesis has not been examined, and few comparative data are available on anole sex ratios.

Understanding these correlations between sex ratio and sexual selection provides additional information on whether biased sex ratios, and the opportunity they provide for sexual selection, can influence the evolution and divergence of anole species.

We examined sex ratios of 14 species of *Anolis* lizards in 21 localities. These species occupy four different islands and four ecomorph types in the Caribbean, with one species in mainland North America. For six of these species, we also examined the sex ratio in multiple localities to determine the extent of intra-specific variation in sex ratio. Our aims were (1) to quantify sex ratios in species across the *Anolis* clade and determine if these ratios varied across species, (2) to test the hypothesis that sex ratios converge by ecomorph class or level of sexual dimorphism, and (3) to examine the level of sex-ratio variation within a species.

1.3 Materials and Methods

We chose four sites on Jamaica, Puerto Rico, Dominican Republic, and South Bimini, Bahamas, with each study site containing multiple anole species. We also chose a site in southeast Texas to sample multiple localities of the North American mainland anole, *Anolis carolinensis*, as a comparison to the island populations. All anole species have male heterogametic sex determination and so their sex ratios will not be directly affected by different environments [75]. At each site, we set up two or three 500-1000 m^2 plots and captured every individual found within each plot. In cases where we set up paired plots to determine variation in sex ratios within a species (Dominican Republic and Jamaica), we chose two localities that were similar in species richness, population density, habitat availability, and levels of direct sunlight to minimize environmental variation between the plots. In this way, we determined the level of sex-ratio variation between localities without confounding

habitat differences. At our mainland site, we sampled three localities from a single forested area that differed in microhabitat type. Additional details on the study plots are available in [54, 102].

Every individual within a plot was captured and permanently tagged with beads sewn into the tail [67] or temporarily marked with bee marking tags [100]. We recorded snout-vent length (SVL) and sex for each individual, and released it at its site of capture for subsequent behavioral observations over the next several weeks. The sex of each individual was determined by a combination of everting the hemipenes of males, palpating large eggs in the abdomens of females, and visual inspections of dewlap size in species with sexually dimorphic dewlaps. We tagged any new anoles entering the plots during the observation period to include all available individuals of each sex within our observed area. By continuously observing each plot for multiple weeks, we censused the entire anole population within a given area, and accurately estimated the sex ratio of a population [206]. We calculated sex ratios as the proportion of males among adults in the population, where 0.5 indicated an equal sex ratio. All plots were observed at approximately the same time of year (May-early July) in summer, during the height of the mating season [102, 131].

Because we had two or three localities for six species in our data set, we performed all analyses including both localities, and included each locality from the species individually (i.e., without its paired population) to determine whether the duplicate locality had an effect on our results. No results changed significantly under this treatment, and so all results are reported with both localities of each species included for analysis.

We performed chi-squared tests on each species or locality to determine whether

they deviated significantly from our null expectation of a 1:1 (i.e., 0.5) sex ratio (Table 1.4.1). We used Fisher's test of combined probabilities on these results to determine whether the overall sex ratios of all of the anole species differed from 1:1. We also tested for significant differences between our paired localities using Welsh's two-sample t test. Across all populations, the mean number of males was 28 (range = 12–58) and the mean number of females was 30 (range = 15–65).

We sampled lizards from four ecomorphs: trunk-ground, trunk-crown, grass-bush, and twig anole species. We tested for association between ecomorph class and sex ratio with phylogenetic ANOVA using the geiger package [88] in R. We determined whether there was phylogenetic signal in sex ratio using Blomberg's K and Pagel's lambda, calculated using the phytools package [193] in R. Because anole ecomorph classes fall into two categories of sexual size dimorphism (trunk-ground and trunk-crown species are highly sexually size dimorphic, whereas grass-bush and twig species are not [29]), we grouped species into high and low sexual dimorphism categories to examine the association between sex ratio and sexual selection, using phylogenetic ANOVA. We also tested for effects of locality and island on population sex ratio using phylogenetic ANOVA. We calculated the specific sexual size dimorphism of each species or locality by dividing the average SVL of the larger sex by the average SVL of the smaller sex, and subtracting 1 [134], although males were the larger sex in all our populations. We conducted a regression using a phylogenetic generalized least squares (PGLS) regression analysis, using the caper package [72] in R, to determine whether the sexual size dimorphism of a population was associated with the sex ratio of that population [29]. All phylogenetic analyses were performed with average sex ratios for each species, and using the squamate phylogeny in [186] pruned to include only the species in this study.

1.4 Results

We found a range of sex ratios across species and localities (Fig. 1.4.1, from a female bias of 0.32 (*Anolis krugi*) to a male bias of 0.61 (*Anolis smaragdinus*), with an average sex ratio of 0.48 (Table 1.4.1). While sex ratios varied substantially among species, only two populations diverged significantly ($p < 0.05$) from an expected 1:1 sex ratio (Table 1.4.1; *Anolis valencienni* and *Anolis krugi* (2), $p = 0.01$), both with an excess of females relative to males. Fisher's test of combined probabilities was significant when we included all of our populations ($p = 0.016$), suggesting that females are more common than males in anole populations, but not when we removed the *Anolis valencienni* and the second *Anolis krugi* locality ($p = 0.18$). We also tested for differences in sex ratio between our paired anole localities within a single species, but found no significant differences. We found no relationship between population size and the degree of sex ratio bias in that population ($R^2 = 0.04$).

We found no evidence that ecomorph categories varied in sex ratio (phylogenetic ANOVA, $F_{3,10} = 0.09$, $p = 0.96$), or that sex ratio differed between the high and low sexual size dimorphism ecomorph classes (phylogenetic ANOVA: $F_{1,12} = 0.23$, $p = 0.60$). We also found no evidence that the sexual size dimorphism of a species, based on male to female SVL measurements, was related to its sex ratio (PGLS: adjusted $R^2 = -0.08$, $p = 0.86$). Finally, there was no effect of locality (phylogenetic ANOVA: $F_{6,7} = 2.2$, $p = 0.31$) or island (phylogenetic ANOVA: $F_{4,9} = 3.5$, $p = 0.19$) on sex ratio, and no phylogenetic signal in sex ratio (lambda $= 6.61e-05$; $K = 0.66$, $p = 0.71$).

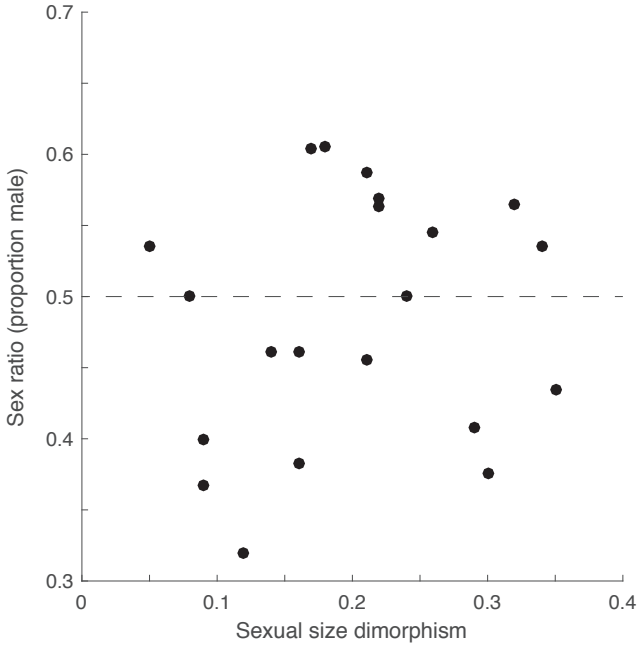

Figure 1.4.1: Sex ratio is represented as the proportion of males among adults in the population, while sexual size dimorphism was calculated dividing the average SVL of the larger sex by the average SVL of the smaller sex, and subtracting 1, for each population. Each circle represents one of the 21 localities sampled in this study. The dashed line represents an equal sex ratio of 0.5. We found no relationship between sexual size dimorphism and sex ratio across the 21 localities (PGLS: adjusted $R^2 = -0.08$, $p = 0.86$).

Table 1.4.1: Sex ratios across *Anolis*. All sex ratios reported from a survey of 21 *Anolis* localities. Ecomorph categories have been abbreviated as follows: TW (twig), TG (trunk-ground), TC (trunk-crown), GB (grass-bush). Sex ratios are the proportion of males among adults in the population. SSD indicates sexual size dimorphism; SSD category classifications are taken from Butler et al. (2000), while ♂/♀ SVL is the ratio of average male snout-vent length to average female snout-vent length within each study locality. P values reported are the results of a chi-squared test against a null hypothesis of an equal number of males and females in the population (see Materials and Methods).

	Ecomorph	Pop. size	Males	Females	Sex ratio	*P*-value	SSD	♂/♀ SVL
Jamaica								
A. valencienni	TW	87	32	55	0.37	0.01	low	0.09
A. lineatopus (1)	TG	103	58	45	0.56	0.20	high	0.22
A. lineatopus (2)	TG	72	41	31	0.57	0.24	high	0.22
A. grahami (1)	TC	79	36	43	0.46	0.43	high	0.21
A. grahami (2)	TC	54	27	27	0.50	1.00	high	0.24
Bimini								
A. angusticeps	TW	48	29	19	0.60	0.15	low	0.17
A. sagrei	TG	43	23	20	0.53	0.65	high	0.34
A. smargadinus	TC	38	23	15	0.61	0.19	high	0.18
Dominican republic								
A. baharucoensis	GB	52	24	28	0.46	0.58	low	0.16
A. olssoni	GB	43	23	20	0.53	0.65	low	0.05
A. cybotes (1)	TG	46	27	19	0.59	0.24	high	0.21
A. cybotes (2)	TG	44	24	20	0.55	0.55	high	0.26
A. coelestinus (1)	TC	32	12	20	0.38	0.16	high	0.30
A. coelestinus (2)	TC	46	26	20	0.57	0.38	high	0.32
Puerto Rico								
A. krugi (1)	GB	36	18	18	0.50	1.00	low	0.08
A. krugi (2)	GB	50	16	34	0.32	0.01	low	0.12
A. cristatellus	TG	81	33	48	0.41	0.10	high	0.29
A. gundlachi	TG	115	50	65	0.43	0.16	high	0.35
USA								
A. carolinensis (1)	TC	39	18	21	0.46	0.63	high	0.14
A. carolinensis (2)	TC	50	20	30	0.40	0.16	high	0.09
A. carolinensis (3)	TC	60	23	37	0.38	0.07	high	0.16

1.5 Discussion

We find a range of both male and female biased sex ratios across anole species, from 0.32 (about one male to every two females) to 0.61 (about three males to every two

females). Our results fall within those of previous studies on adult sex ratios in anoles, which have reported values as low as 0.31 and as high as 0.76 (*Anolis sagrei* [206]). If stable over time, this level of variation is likely to have a large impact on intrasexual competition for mates and the selection strategies of the rare sex, which could lead to the establishment of different mating systems [55, 58].

Despite the variation in sex ratio that we observed among species, only two of 21 sex ratios significantly diverged from our null expectations of an equal number of males and females. The extremely female-skewed sex ratio of *Anolis valencienni* (0.37) is surprising, as it is a twig anole species with very low sexual dimorphism [29, 92]. This species is cryptic and arboreal, which can make detection and capture of individuals difficult; female *A. valencienni* also perch lower in trees than males on average [101], and so our ability to detect males (from the ground) may have been compromised if they were using the highest available perches. However, our extended behavioral observations of our study population and our success at capturing every individual we saw, regardless of sex, does provide support for our reported sex ratio. In addition, the other cryptic and arboreal twig anole species in our data set, *Anolis angusticeps*, has a male-biased sex ratio, suggesting that any capture bias in these species was limited.

Remarkably, previous behavioral work on *Anolis valencienni* reported almost no territoriality or sex-specific resource competition, a rare observation in anoles [92]. This behavioral information suggests that males should not undergo increased mortality compared to females within this species, as they likely suffer no additional costs of territory or resource defense. Because the costs of survival and reproduction should be more similar for both sexes in this species compared to species with a higher degree of polygyny, we would predict an approximately equal adult sex ratio

in this species [2, 92]. Our results may indicate greater variability in mating pattern or reproductive costs than previously inferred in this species, or the presence of sex-specific effects on dispersal or mortality.

Anolis krugi, the other species with a significantly biased sex ratio (0.32) in one of the two studied localities, also has an extremely female-biased sex ratio and low sexual size dimorphism, yet we have no reason to believe that our detection and capture of this species was sex-biased as the result of their habitat use. However, the paired *Anolis krugi* locality does not show any skew in sex ratio. This may indicate that sex ratio is primarily influenced by highly localized population dynamics, rather than species-level factors. In general, the highly skewed sex ratios we observed may indicate that the factors influencing sex ratio in anole populations are more complex than simple sex-specific differential mortality. This conclusion is further supported by the lack of a relationship across species between sex ratio and both the degree of sexual size dimorphism or ecomorph.

While we find variation in sex ratio between and within anole species, this variation could be attributed to random fluctuations around a true population sex ratio of 1:1 [261]. Although we did obtain large sample sizes for some species, the sample size for most species is relatively low and so we may lack power to detect statistically significant skew in sex ratio. The variance of the binomial distribution of our statistical tests is greatest at the mean, and therefore skew from an equal sex ratio is intrinsically difficult to detect. Assuming a true underlying sex ratio of 0.4 (or 0.6), we would need population sizes of approximately 780 lizards to detect a significant skew away from equality 80% of the time. Population sizes this large will be difficult to find for many anole species, and may simply not exist for many others. Thus, the differences in sex ratio we report may have biological meaning,

even though this dataset cannot show statistically significant sex-ratio skew. Indeed, detecting significant sex-ratio skew may not be possible for a wide range of vertebrates with low population sizes, if the sex-ratio bias is not extreme. The biological meaning of biased sex ratios should therefore be assessed separately from whether this skew is statistically significant [55]. This issue is especially critical in threatened or declining populations, where high levels of sex-ratio bias may have dire effects on conservation efforts [55].

If sex-ratio variation is real and maintained over time, the number of available mates for males and females is dramatically different, favoring different reproductive strategies for each sex [58]. In anoles, this variation could promote migration between populations, especially sex-biased dispersal of individuals between populations in search of potential mates. In addition, anoles may be able to bias the sex of their offspring; strong sex-ratio skew may provide a selective advantage to individuals who can produce offspring of the less frequent sex [68]. Ideally, further observations of sex ratio in anoles with large sample sizes across multiple years will clarify whether this pattern of variation has a biological basis. Our intra-specific sex ratio comparisons also illustrate potential flaws in the use of adult sex ratios as representative of species, given the high level of variation in sex ratio we observe between nearly identical localities [177]; measurements of adult sex ratios between and within anole species may indicate whether species in this clade can be accurately characterized by a single sex ratio. We present the strengths and limitations of our study of sex ratios here to demonstrate the potential power of our approach for future studies of sex ratios of species in highly variable environments; this is especially true when strong intra-population sex ratio differences are suspected. Sex ratios across populations and clades may provide more information on sex-specific

causes of mortality or dispersal, along with suggesting the potential for divergence in mating systems within and between species and confirming theoretical predictions on the prevalence of sex-ratio skew.

2

Sexy males and sexless females: the origin of triploid apomicts

2.1 Abstract

Apomixis and polyploidy are closely associated in angiosperms, but the evolutionary reason for this association is unknown. *Taraxacum officinale*, the common dandelion, exists both as diploid sexuals and triploid apomicts. Here, in the context of *T. officinale*, we provide a model of the evolution of triploid apomicts from diploid

sexuals. We posit an apomictic allele that arrests female meiosis in diploids, so that the plant produces diploid egg cells that can develop without fertilization, but haploid pollen. We propose occasional fertilization of diploid egg cells by haploid pollen, resulting in triploid apomicts that produce triploid egg cells but largely non-functional pollen. The irreversibility of this process renders diploid partial apomicts evolutionarily short-lived, and results in fixation of triploid apomicts except when they suffer extreme selective disadvantages. Our model can account for the high genetic diversity found in *T. officinale* triploid populations, because recombinant haploid pollen produced by diploids allows the apomictic allele to spread onto many genetic backgrounds. This leads to multiple clonal lineages in the newly apomictic population, and thereby alleviates some of the usual pitfalls of asexual reproduction.

2.2 Introduction

Asexual reproduction via seeds (apomixis) has evolved many times in flowering plants [95, 200, 237, 258] and is commonly associated with increased ploidy [14, 258]. Obligately asexual species are often claimed to enjoy an initial advantage over their sexual relatives owing to greater reproductive efficiency (the "two-fold cost of sex") and assurance (no need for mate-finding via pollination), followed by a long-term evolutionary disadvantage from lack of adaptability [51, 142]. However, in hermaphroditic plants, the two-fold increase in genetic representation in apomictic seeds, relative to sexual seeds, would seem to be balanced by the loss of reproduction via male (pollen) function, for no net advantage [155]. The initial advantage of apomixis seems more likely to be the preservation of high-quality genotypes by the suppression of sexual recombination. Consistent with this, apomictic lineages occupy more extensive geographic ranges than their sexual relatives, especially at

higher latitudes [14, 237]. Consistent with a long-term disadvantage, apomictic plants tend to occupy the 'twigs' of phylogenetic trees, nested within sexual clades [237].

The geographical supremacy of apomictic lineages, given that they are usually polyploid, could also be explained by advantages of polyploidy itself, which can confer a physiological advantage in harsh environments [127, 227], increase the rate of a population's adaptation [170], and act as a buffer against deleterious mutations, at least in the short term [109, 156, 203, 214, 219]. But aside from any general advantages and disadvantages of sex and polyploidy, the ability to reproduce asexually is clearly advantageous to polyploid individuals that are unable to produce viable haploid spores by conventional meiosis. However, there is no obvious reason why polyploidy should directly induce apomixis, and so the repeated association of the two phenomena remains a mystery.

Taraxacum officinale, the common dandelion, is a model system for studying the evolution of apomixis [200]. Sexual dandelions are hermaphroditic, with individual plants producing both pollen and egg cells [84, 237]. In Europe, *T. officinale* exists as both diploid sexual populations and triploid apomictic clones that produce little, if any, functional pollen [156, 237, 238]. By contrast, all *T. officinale* in North America are apomictic triploids [135]. Triploid *T. officinale* are autonomous gametophytic apomicts, meaning that embryo sacs develop from unreduced megaspores and both endosperm and embryo are produced without fertilization [84]. *T. officinale* in Europe and Asia exhibits the common pattern of geographical parthenogenesis in which apomicts are more widely distributed than sexual forms [156, 237]. The well-studied natural history of this species, along with the stable existence of both apomictic triploid and sexual diploid populations, make it an ideal taxon on which

to base a model of the concomitant evolution of apomixis and polyploidy.

Populations of apomictic dandelions are clonally diverse, contrary to the intuitive expectation that asexual populations should be genetically homogenous [137, 236, 237]. While mutational divergence will eventually result in clonal diversity, this process is likely to occur over long periods of evolutionary time. High clonal diversity of triploid apomicts could result from the rare recruitment of new apomictic clones through the occasional fertilization of haploid egg cells in sexual diploids with diploid pollen from triploid apomicts. Alternatively, this diversity could arise from many origins of apomicts from an original sexual population with multiple lineages maintained over evolutionary time.

Here, we propose a model of the origin and spread of apomixis in *T. officinale* in which apomictic seed production originates in diploid individuals that reproduce sexually via pollen, thus spreading the apomictic trait onto diverse genetic backgrounds. Occasional fertilization of apomictic diploid egg cells by haploid pollen of any genotype generates new triploid apomicts that no longer produce functional pollen. We explore the model's dynamics under a variety of selection regimes. We find that one equilibrium state of the system is a diverse population of triploid apomicts without diploid individuals. This provides an explanation of clonal diversity among apomicts that does not require rare function of pollen from triploid apomicts [225]. The equilibrium states of our model are unchanged if multiple loci form the genetic basis of apomixis, although the rate of the spread of apomixis is slowed due to recombination and segregation in pollen production. This is because the entire genome functions as a single locus in apomictic reproduction. Although our model is based on the biology of *T. officinale*, it can provide insight into transitions in ploidy and sexuality across the tree of life [7, 162].

For simplicity, our model assumes that triploid apomicts produce no viable pollen. Most pollen produced by *T. officinale* triploid apomicts is aneuploid and inviable, but experimental crosses between diploid sexual dandelions and triploid apomictic dandelions show that triploid apomicts produce a small proportion of viable euploid pollen (haploid, diploid, or triploid) [225]. This rare euploid pollen could serve as a vector for the transmission of apomixis into a diploid sexual population in the presence of triploid apomicts. We would expect to observe relatively more functional diploid, than haploid pollen in lineages that have been apomictic for many generations because of the gradual accumulation of deleterious recessive mutations that would be exposed and selected against in haploid pollen, but masked in diploid pollen [225, 237].

Our model is the first theoretical explanation of the dual origin of apomixis and triploidy in *T. officinale*, and can also explain the high clonal diversity in newly apomictic populations. Previous models have suggested that triploid diversity in this species is generated by the fertilization of haploid egg cells of sexual females by diploid pollen produced by previously apomictic males [237]. In the model we propose here, triploid diversity is initially generated by the fertilization of diploid egg cells of apomictic females by haploid pollen of sexual males. However, these two models of gene flow – the hybridization of apomictic populations with sexual populations or the origin and spread of an apomictic allele within a population- are reciprocal. Both processes may have contributed to the current observed diversity of established populations of triploids in *T. officinale*.

2.3 Materials and Methods

We assume a single dominant locus that allows the production of apomictic seeds, akin to the *Diplosporous* genomic region identified in *T. officinale* [13, 200, 238, 252]. However, this locus may also represent a set of tightly linked genes associated in function, such as a gene controlling apomeiosis (meiotic arrest resulting in unreduced gametes) linked with a gene controlling parthenogenesis (development of an unfertilized egg cell) [238]. This locus has two alleles, an original recessive a and a dominant allele A causing the production of diploid egg cells with identical Aa genotype of the parent plant. This allele may function on a genomic background that includes other alleles that enable apomixis, rather than being solely responsible for the trait [258]. The production of diploid egg cells would likely occur by some form of arrest in female meiosis, but does not apply to pollen production [238]. Individuals with Aa genotypes will therefore produce egg cells with Aa genotypes, but normal haploid pollen with an A or a genotype in equal proportions (diploid aa individuals produce both haploid a egg cells and haploid a pollen).

We allow the Aa egg cells of the diploid apomicts to be fertilized at some frequency u, which then results in triploid Aaa or AAa individuals, depending on the genotype of the haploid pollen [225]. This parameter can vary according to the difficulty of fertilizing an unreduced egg cell. Triploid individuals can only reproduce apomictically, and therefore only produce triploid seeds of identical genotypes and almost no functional pollen; we do not consider the production of rare euploid pollen by triploids in our model [225, 238]. Rare tetraploid individuals are sometimes detected in natural populations [249] but, for simplicity, we do not consider the fertilization of triploid (or higher ploid) apomicts or the fertilization of haploid egg cells by triploid pollen. Our model also includes viability selection against both

triploid apomicts, Aaa and AAa, and diploid apomicts (denoted by the variables t, f, and s respectively), reflecting a situation in which reduced genetic variation among an individual's offspring may lead to increased susceptibility to pathogens or predators [119] (Table2.3.1). We assume random mixing of pollen and egg cells in order to determine frequencies in the next generation.

If P and Q are the respective population frequencies of sexual and apomictic diploids in a given generation, and s is the viability disadvantage of the diploid apomicts relative to the sexual diploids, then the proportions of A and a pollen in the next generation are:

$$p_A = (1-s)(Q/2)/[P + (1-s)Q], \tag{2.1}$$

$$p_a = 1 - P_A = [P + (1-s)(Q/2)]/[P + (1-s)Q]. \tag{2.2}$$

If, further, R and K are the respective frequencies of Aaa and AAa triploid apomicts (so that $P + Q + R + K = 1$), whose viability disadvantages relative to sexual diploids are t and f respectively, then seeds of genotypes a, Aa, Aaa, and AAa are produced in proportions:

$$q_a = P/[P + (1-s)Q + (1-t)R + (1-f)K], \tag{2.3}$$

$$q_{Aa} = (1-s)Q/[P + (1-s)Q + (1-t)R + (1-f)K], \tag{2.4}$$

$$q_{Aaa} = (1-t)R/[P + (1-s)Q + (1-t)R + (1-f)K], \tag{2.5}$$

$$q_{AAa} = (1-f)K/[P + (1-s)Q + (1-t)R + (1-f)K]. \tag{2.6}$$

A proportion u of the diploid egg cells is fertilized by pollen, and so the population

Table 2.3.1: The genotypes and associated phenotypes used in our model of apomixis, along with the variables representing each genotype in our Equations. The selection coefficients used in our model are listed under viability and are expressed as the selective disadvantage of each genotype from a maximum fitness of 1 (see Materials and Methods for more detail).

Genotype	Phenotype	Frequency	Viability
aa	Diploid sexual	P	1
Aa	Diploid partial apomict	Q	$1-s$
Aaa	Triploid apomict	R	$1-t$
AAa	Triploid apomict	K	$1-f$

frequencies of plants of the various genotypes in the next generation are:

$$P' = p_a q_a, \tag{2.7}$$

$$Q' = p_A q_a + (1-u) q_{Aa}, \tag{2.8}$$

$$R' = q_{Aaa} + u p_a q_{Aa}, \tag{2.9}$$

$$K' = q_{AAa} + u p_A q_{Aa}. \tag{2.10}$$

We ran our model under several different selective regimes in order to determine the evolutionary dynamics of the apomictic allele, A, when introduced at low frequency (0.01%) into a population of diploid sexuals. These selective regimes included selection against apomicts (Aa, Aaa, and AAa individuals; $s = t = f > 0$); selection due to the apomictic allele (Aa, Aaa, and AAa individuals; $s = t = f/2 > 0$); selection against triploids (Aaa and AAa individuals; $s = 0, t = f > 0$); and selection against diploid apomicts (Aa individuals; $s > 0, t = f = 0$). Under each scenario, we assigned different values to the selective coefficients against each genotype class (Table 2.3.1), and observed the equilibrium frequency of the genotypes in the population. All simulations described in this paper were run in Matlab (Version R2016a).

2.4 Results

Selection against apomicts

We begin with a case in which equal selective disadvantages were assigned to all of the apomicts ($s = t = f > 0$). For selection coefficients from 0 to 1/3 (where selection is expressed as $1 - s$), the triploid apomicts take over the population (Figure 2.4.1). This transition occurred rapidly, with partially apomictic diploids present for only a transient phrase in the population, rising in frequency rapidly as the A allele is introduced into the population and then steadily declining (Figure 2.4.1). When $s > 1/3$, diploid apomicts do not become established in the population and sexual diploids remain the only genotype. Overall, high selective disadvantages are needed to prevent the rise in frequency of diploid partial apomicts and the subsequent rise in frequency of triploid apomicts. While the rate of fertilization (u in Table 2.3.1) of diploid apomicts determines the length of time in which they exist in the population, it does not qualitatively change our results; triploid apomicts still take over the population.

Logically, if diploid and triploid apomicts share the same selective disadvantage, the diploid apomicts will be converted to triploid apomicts at a constant frequency u, which is the fertilization rate of diploid egg cells in our model. Since the triploid apomicts are an absorbing state in this model, they will inevitably rise in frequency holding all other factors constant. Any selective advantage in favor of the apomicts will only enhance this path to fixation. Separating the triploid apomicts into two categories (Aaa and AAa) reveals that triploids with two recessive alleles will rise in frequency before triploids with two dominant alleles, because of the initially high frequency of a in the pollen population. As diploid apomicts replace diploid sexuals

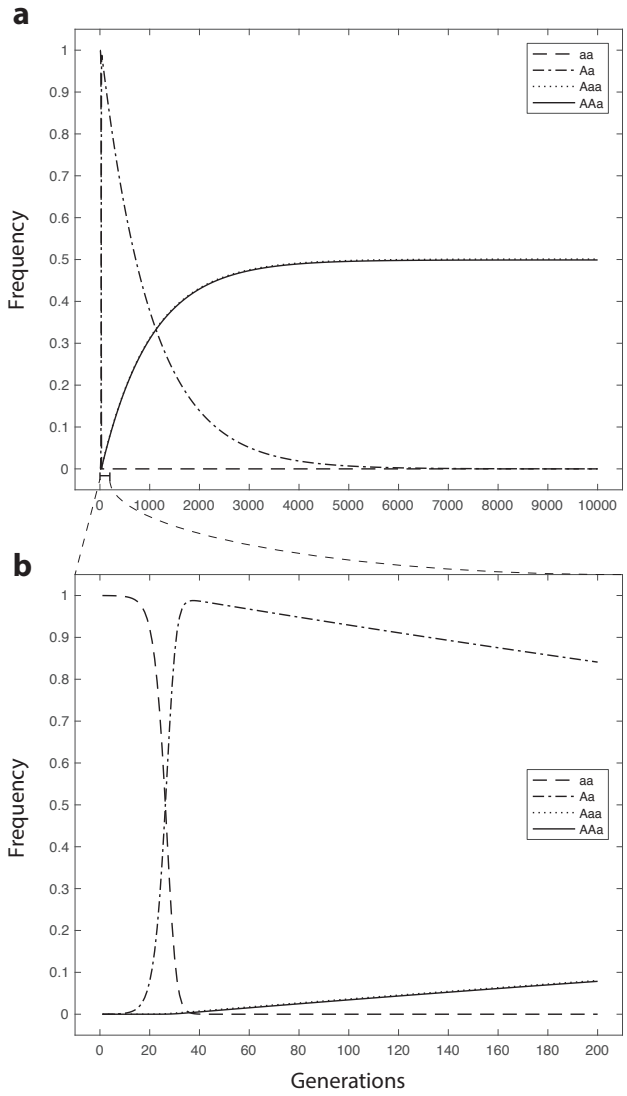

Figure 2.4.1: The Aa genotype was introduced into the population at initial frequency 0.0001, with a proportion u=0.001 of diploid egg cells fertilized each generation. Using the notation from Table 2.3.1, the selective coefficients against the three apomictic genotypes were equal at 0.05. a, the dynamics of this selection regime across 10000 generations, which reach an equilibrium state with only the triploid genotypes; b, focusing on the first 200 generations allows it more clearly to be seen that diploid sexuals are rapidly replaced by diploid partial apomicts, which are in turn converted into triploid apomicts.

in the population of haploid pollen-producers, however, new *Aaa* and *AAa* triploids will be generated in equal frequencies.

Selective disadvantage due to the apomictic allele

In the next scenario, we ran the model assuming that the A apomictic allele carries an additive selective disadvantage, possibly due to pleiotropic effects in other aspects of reproduction [104]. In this scenario, *AAa* has twice the selective disadvantage of *Aa* and *Aaa* ($s = t = f/2 > 0$). As expected, *Aaa* eventually reaches fixation after the transitory appearance of *AAa* individuals (Figure 2.4.2). Extending this result to non-additive cases, *AAa* will be lost in any case where its selective disadvantage is greater than that of the *Aaa* triploid. This scenario is not qualitatively different for the diploid apomict, which follows a pattern of briefly reaching high frequencies, but then gradually disappearing. This pattern of a single triploid genotype resembles empirical observations of the gene *Diplosporous* [238]. The *Diplosporous* allele occurs in single dose in triploid apomictic dandelions [238]. Triploids have the genotype *Ddd* where D is a dominant allele controlling the production of unreduced megaspores and thus disrupting traditional meiosis [238]. Furthermore, no genotypes of the form *AAa* have been found in any previously studied apomictic plant [172].

Selection against triploids

We then examined a scenario in which triploidy carried a selective disadvantage, while *Aa* diploid apomicts suffered no selective disadvantage ($s = 0$, $t = f > 0$). This resulted in the stable co-existence of *Aa*, *Aaa*, and *AAa* apomicts. The relative frequencies of the three genotypes at selective equilibrium depended on s, t, and f.

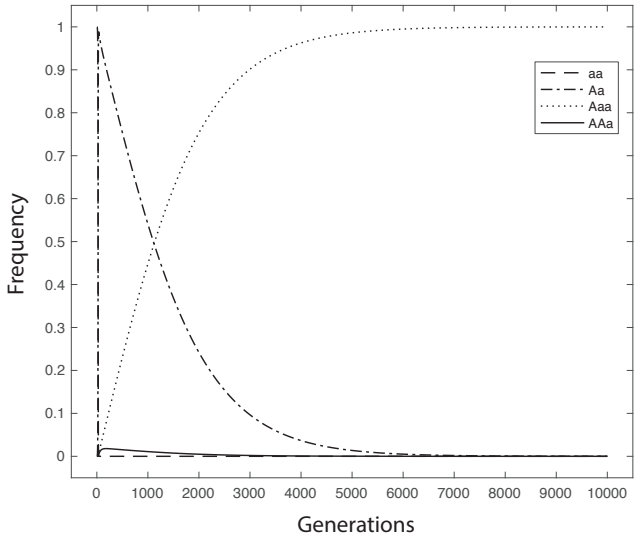

Figure 2.4.2: The Aa genotype was introduced into the population at initial frequency 0.0001, with a proportion u=0.001 of diploid egg cells fertilized each generation. The selective coefficients against the Aa and Aaa genotypes were 0.025, while that against the AAa genotype was 0.05.

Figure 2.4.3 illustrates an example with realistic selective coefficients where the three genotypes approach similar frequencies. With very high selection against triploids, diploid apomicts predominate.

This scenario can be thought of in terms of a heterozygote advantage; the diploid apomicts are constantly transforming into triploids at the fertilization rate u, but their relative selective advantage prevents them from vanishing as they did in the previous scenario. Diploid apomictic dandelions have not been reported in natural populations. In terms of our model, this suggests that triploid apomicts cannot have experienced a major selective disadvantage relative to diploids.

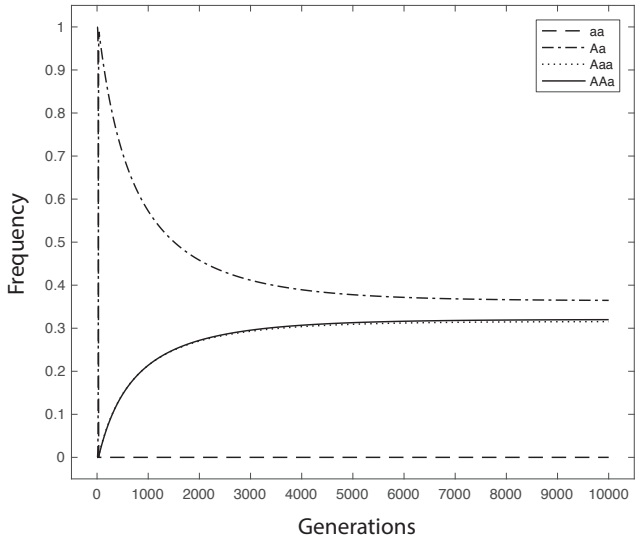

Figure 2.4.3: The Aa genotype was introduced into the population at initial frequency 0.0001, with a proportion u=0.001 of diploid egg cells fertilized each generation. The selective coefficients against the AAa and Aaa genotypes were 0.05, and that against the Aa genotype was 0.0485 (97% of the selection against triploids).

Selection against diploid apomicts

Finally, we consider the scenario in which diploid apomicts have a selective disadvantage relative to both the sexual diploids and the triploid apomicts ($s > 0$, $t = f = 0$). This scenario seems the least biologically relevant, but might occur if there is an intrinsic conflict between apomictic and sexual reproduction in the same plant that results in an overall fitness loss for the individual. If the previous selection against triploids resembled a heterozygote advantage case, this scenario resembles a heterozygote disadvantage situation. In this case, the population eventually consists of triploids only as long as selection against diploid apomicts is less than 1/3. However, if there is no selective disadvantage against either triploid, the population will have a higher frequency of the Aaa genotype than the AAa genotype (Figure 2.4.4). This is explained by the relative lack of A pollen in the population due to the se-

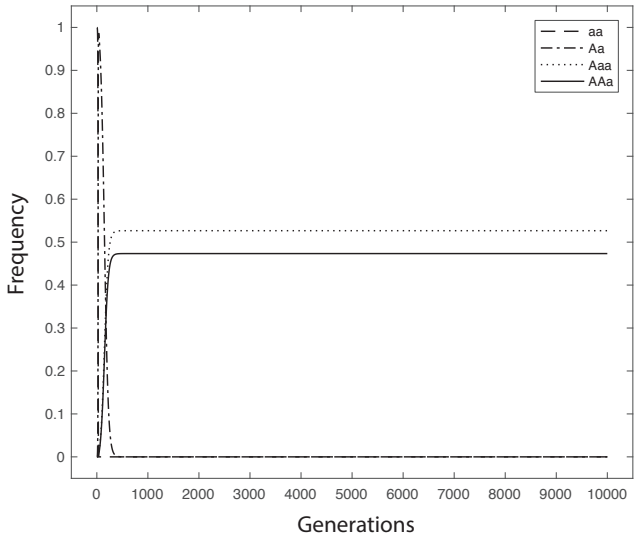

Figure 2.4.4: The Aa genotype was introduced into the population at initial frequency 0.0001, with a proportion u=0.001 of diploid egg cells fertilized each generation. The selective coefficients for the AAa and Aaa genotypes were 0, and the selective coefficient against the Aa genotype was 0.025.

lective disadvantage of the diploids, resulting in the fixation of the more common Aaa genotype (which only depends on a pollen). Again, this pattern mimics empirical evidence from the *Diplosporous* gene, suggesting another possibility for the fixation of a single triploid Ddd genotype at that locus [238]. As selection against triploids increases, this scenario approaches general selection against apomicts, and both triploid genotypes reach equal frequencies in the population.

Relaxing the conditions for success of apomixis by adding complexity

Our model assumes fixed selection coefficients for the apomictic genotypes relative to sexual diploids. However, in a more realistic model, the average fitness of the apomictic population as a whole would increase over time with the generation of new apomictic lineages from the sexual population. The fitness of an allele in a

sexual population is averaged across genetic backgrounds because multilocus genotypes are being continually recombined. Thus, alleles in sexual populations change in frequency according to their average effect on fitness (narrow-sense heritability of fitness). By contrast, each apomictic lineage perpetuates itself indefinitely and changes in frequency according to the fitness of its unique multilocus genotype (broad-sense heritability of fitness). Given the sexual spread of the gene for apomixis onto new genetic backgrounds via pollen, the population of apomicts will come to be dominated by elite non-recombining genotypes.

Apomictic reproduction in dandelions requires the formation of unreduced egg cells (apomeiosis) and the development of embryos from these egg cells without fertilization (parthenogenesis). Our model treats both these traits as residing in a single allele A at a single locus. The absence of recombination in apomictic reproduction relaxes the requirement for a supergene that determines both apomictic characters. Assume that diploid apomixis occurs in $AaBb$ genotypes, where A represents an allele causing female apomeiosis and B represents an allele allowing parthenogenesis. Given the origin of the first such genotype, perhaps by the chance co-occurrence of two separate mutations in the same individual, apomixis would spread through the population by fertilization of diploid sexuals by AB pollen. If the two loci were unlinked, this would comprise a quarter of the pollen produced by $AaBb$ diploid apomicts. The rate of spread of apomixis into the sexual population would be slowed, relative to the single-locus model, but the basic dynamics of the spread of apomixis and the conversion of diploid apomicts to male-sterile triploid apomicts would be unchanged.

Our model also assumes that triploid apomicts produce no viable pollen. Most pollen produced by triploid apomicts is aneuploid and inviable, but experimental

crosses between diploid sexual dandelions and triploid apomictic dandelions show that triploid apomicts produce a small proportion of viable euploid pollen [225]. This rare euploid pollen could serve as a transmission mechanism of apomixis into a diploid sexual population in the presence of triploid apomicts. We would expect to observe a greater frequency of functional diploid, rather than haploid, pollen in lineages that have been apomictic for many generations because of the gradual accumulation of deleterious recessive mutations that would be exposed and selected against in haploid pollen, but masked in diploid pollen [225, 237].

2.5 Discussion

In the scenarios we examined, triploid apomicts invade a mixed population of sexual and apomictic diploids in almost every case, barring a strong selective disadvantage of triploidy. Surprisingly, diploid apomicts that are able to reproduce both sexually and asexually are usually unable to persist in the population unless they have substantially higher survival than triploids that cannot reproduce sexually. The ability of diploid apomicts to reproduce by both means is cancelled out by their irreversible conversion to triploids by occasional fertilization of diploid egg cells by haploid pollen. In our model, this conversion occurs at the constant rate u. In reality, the rate of fertilization of diploid egg cells would decline as the proportion of diploid pollen-producers declined. This may indicate a selective advantage to sexual diploids in natural populations of *T. officinale*, which enables them to overcome a constant conversion into triploid apomicts, or a reciprocal return to sexual reproduction in apomictic populations [220].

Our model provides a path for the evolution of triploid apomicts that does not require a causal role for triploidy in apomixis. Given the rapid conversion of diploid

apomicts to triploids determined by the rate of diploid fertilization, we also do not expect prolonged persistence of diploid apomicts within a population. Further investigation into the structure of mixed *T. officinale* populations in Central Europe may provide evidence for this transitional state [240]. Though our model has two possible triploid genotypes (*AAa* and *Aaa*), any selective differences between them would result in one eventually outcompeting the other. A cost to the extra apomictic allele in *AAa* apomicts, and therefore the relative dominance of the *Aaa* genotype, is consistent with the observation that triploid apomictic dandelions carry only one copy of the *Diplosporous* allele [238]. The existence, albeit rare, of viable tetraploids lends support to our model, suggesting that occasional fertilization of triploid egg cells by haploid pollen, or of haploid egg cells by triploid pollen, may be possible.

Previous explanations of clonal diversity among apomictic Taraxacum have focused on the fertilization of haploid sexual egg cell by diploid pollen derived from apomicts, which provides a mechanism for gene flow from sexual diploids into the population of apomicts [237]. However, this process does not explain the origin of apomictic triploids. Our model suggests that apomictic triploids could initially have been produced by the fertilization of unreduced diploid egg cells by haploid sperm. Because our model describes the initial evolution of apomixis, recessive deleterious mutations would not have had time to accumulate and haploid pollen containing the apomictic allele would still be viable. While the combination of pollen production by a triploid individual and the transmission of this pollen to a new population is likely infrequent, there is some evidence to suggest that apomictic polyploid plants may occasionally act as viable pollen donors and enable the spread of apomixis across populations [149, 158, 240].

Instead of the spread of a single apomictic allele through multiple populations,

the representative locus in our model could be a gene with recurrent mutations that result in apomictic seed production. This could occur in a gene controlling meiosis in the embryo sac, in which a disrupting mutation against the correct genetic background could result in an unreduced apomictic egg cell. This apomeiotic allele must occur against a parthenogenetic background to result in an apomictic phenotype. This scenario is partially supported by experiments to isolate the locus controlling apomixis in Taraxacum; the *Diplosporous* locus appears to be large, and mutations in this region may be associated with meiotic arrest and provide the initial step in the path to apomictic reproduction [238, 245, 252].

In either case, our model provides an explanation for the clonal diversity found among apomictic lines, as they could originate from multiple diploid apomicts with different recessive haplotypes. This overcomes some of the evolutionary cost of Darlington's "blind alley" of apomixis, making these species partially robust to environmental perturbations selecting for phenotypic diversity and suggesting a novel explanation for their wide distribution across multiple continents [51, 237].

We recognize the oddity of invoking a phenotype (diploid male-fertile apomicts) that has not been observed in natural populations of dandelions to explain the origin of triploid apomicts, although diploid apomicts have been observed in other taxa such as *Hieracium* [12] and *Boechera* [133]. But our model also explains why we should fail to observe this phenotype, as their presence in a population is predicted to be ephemeral. If diploid male-fertile apomicts were to arise within a population, then their initial success is predicted to be terminated by their replacement by their own triploid apomictic progeny. In addition, while we have focused on the transition to sexual diploids to apomictic triploids in *T. officinale*, our model can be applied to a range of organisms with similar transitions from sexual to asexual reproduction

associated with higher ploidy levels [7, 162].

3

Drift-induced selection between male and female heterogamety

3.1 Abstract

Evolutionary transitions between male and female heterogamety are common in both vertebrates and invertebrates. Theoretical studies of these transitions have found that, when all genotypes are equally fit, continuous paths of intermediate equilibria link the two sex chromosome systems. This observation has led to a belief that

neutral evolution along these paths can drive transitions, and that arbitrarily small fitness differences among sex chromosome genotypes can determine the system to which evolution leads. Here, we study stochastic evolutionary dynamics along these equilibrium paths. We find non-neutrality, both in transitions retaining the ancestral pair of sex chromosomes and in those creating a new pair. In fact, substitution rates are biased in favor of dominant sex determining chromosomes, which fix with higher probabilities than mutations of no effect. Using diffusion approximations, we show that this non-neutrality is a result of 'drift-induced selection' operating at every point along the equilibrium paths: stochastic jumps off the paths return, on average, with a directional bias in favor of the dominant segregating sex chromosome. Our results offer a novel explanation for the observed preponderance of dominant sex determining genes, and hint that drift-induced selection may be a common force in standard population genetic systems.

3.2 Introduction

In most animals, sex is determined genetically [19]. Among those animals with genetic sex determination, the majority exhibit heterogametic sex determination: the presence or absence of a sex-specific chromosome triggers sexual differentiation [10, 19]. Depending on whether the sex-specific chromosome is in males or in females, the system is, respectively, male heterogamety (XX females, XY males) or female heterogamety (ZW females, ZZ males).

The system of heterogamety is a fundamental genetic property of a species. It is therefore surprising that it is evolutionarily very labile, with transitions between male and female heterogamety having occurred frequently in amphibians [93], reptiles [62, 179], and fishes [61, 138, 140], as well as in invertebrates [8, 105, 251]. A

striking example of a recent transition is found in the frog *Rana rugosa*: populations in northern Japan exhibit female heterogamety while populations in southern Japan exhibit male heterogamety [154, 164].

In a classic theoretical study, Bull and Charnov [23] showed that continuous paths of population genetic equilibria exist between male and female heterogamety. States along these paths are equilibria in the sense that the evolutionary dynamics of an infinite, randomly mating population are stationary at them when all genotypes are equally fit. Intermediate states along the paths involve the presence of multiple genotypes for each sex, a situation observed in several species, e.g., the platyfish *Xiphophorus maculatus* [106, 107], the blue tilapia *Oreochromis aureus* [126], a Lake Malawi cichlid *Metriaclima pyrsonotus* [215], the western clawed frog *Xenopus tropicalis* [202], and the housefly *Musca domestica* [65, 71, 148].

Two of these equilibrium paths are of particular interest. The first, which we shall refer to as 'model 1', governs those transitions between male and female heterogamety that involve the same pair of sex chromosomes [23] (see Figures 3.3.1 and 3.3.3A). The second, which we shall refer to as 'model 2', governs those transitions between male and female heterogamety that involve different pairs of sex chromosomes, i.e., where the sex chromosome pair in one system is autosomal in the other, and vice versa [23, 210, 211] (see Figures 3.3.2 and 3.3.3B).

The existence of these deterministic equilibrium paths has led to a belief that neutral drift along them in finite populations could be responsible for transitions between male and female heterogamety [19, 20, 242], an important baseline model for such transitions [242]. Moreover, arbitrarily small fitness differences between the sexual genotypes can eliminate the equilibrium paths under deterministic evolutionary dynamics, and render one of the heterogametic systems stable and the

other unstable [23]. This has led to a belief that small fitness differences alone can determine which transitions are possible [19, 20, 242].

Here, we examine these claims in the context of finite-population evolutionary dynamics. Using both stochastic simulations and analytical approximations based on the removal of fast variables, we estimate the fixation probabilities of the various sex determining mutations along the two equilibrium paths, starting from a state of simple heterogamety. We find that evolution along these 'neutral' equilibrium paths is in fact not neutral, instead showing a clear bias in favor of dominant sex determining mutations. Selection for otherwise deterministically neutral genotypes has previously been recognized in other settings [43, 45, 79, 115, 129, 174, 226, 250]. Perhaps the most prominent example is Gillespie's criterion [79], which states that if the reproductive rates of two genotypes have equal arithmetic mean but different variance, then the genotype with lower variance will be selected for, owing to higher geometric mean fitness. A key difference is that, in the neutral models we study, we assume no *a priori* differences in the reproductive rates of the various genotypes; these instead emerge naturally in our analysis of the dynamics along and around the equilibrium paths.

When all genotypes are equally fit, we find in both models that the substitution rates of the dominant sex determining mutations (in directions a and c in Figure 3.3.3) are higher than the substitution rates of recessive mutations (in directions b and d in Figure 3.3.3). Thus, in finite populations, stochastic evolutionary dynamics have a clear directionality along the equilibrium paths, owing to a drift-induced selective force. However, this selective force is a weak one—its effect on fixation probabilities in the neutral case is of order $1/N$—and therefore can be dominated by direct selective forces such as viability, fecundity, or fertility differences between

genotypes.

We also study the case where the sex-specific chromosome (the Y or the W) has accumulated deleterious recessive mutations, as it is expected to do over time in its non-recombining region [32, 34]. When the sex-specific chromosome is so degraded that homozygosity for it is lethal (as in mammals and birds), most heterogametic transitions are impossible [19]. However, in many other taxa, the sex-specific chromosome has accumulated only few recessive deleterious mutations—this state is common, for example, in amphibians, reptiles, and fish [4]. In such cases, homozygosity for the sex-specific chromosome is not expected to be lethal, and in fact can be associated with only a small fitness cost, if any at all. When taking into account these natural selective forces, we find in model 1 that the drift-induced selective bias in favor of dominant sex determining mutations is amplified, though the overall substitution rates in both directions are reduced. In model 2, the drift-induced bias in favor of dominant sex determining mutations is reduced when these selective forces are taken into account. Thus, in model 2, when selection is weak and the population is small, dominant sex determining mutations substitute at a higher rate; when selection is strong and the population is large, recessive sex determining mutations substitute at a higher rate.

The potential for drift-induced selection in transitions between sex determining systems has previously been noted by Vuilleumier et al. [253], who use simulations to investigate the stochastic dynamics of model 1, focusing predominantly on the effects of population structure. Our work overlaps with theirs in one particular case, that of a single deme, with no viability differences between the various genotypes. In that case, they too find non-neutral fixation probabilities for new dominant and recessive sex determining mutations, but find fixation probabilities substantially

above the neutral expectation for both classes of mutation. In contrast, we find in this case that dominant sex determining mutations fix with probability above the neutral expectation, but recessive mutations fix with probability lower than the neutral expectation. The fixation probabilities that they report are also orders of magnitude different from those we report, especially for large populations [compare, for example, their Figure 1(a) with our Figure 4A]. They also find mean conditional fixation times that are invariant, and in some cases even decrease, as population size increases; we find mean conditional fixation times that increase linearly with population size, consistent with drift-like dynamics. We have independently simulated their population model for the case that overlaps with ours, and obtain results consistent with ours, but different from those they report. The validity of our results is supported by mathematical analysis, which also allows us to explain them in analytical detail. In addition, we also consider transitions between sex determining systems in model 2, where the sex chromosome locus is changed in the course of a transition; empirically, this scenario is possibly even more common than model 1 [61]. Our results thus suggest that biases favoring dominant sex determining mutations may be general to transitions between male and female heterogamety.

3.3 Characterization of the equilibrium paths

3.3.1 Model 1

Consider an initial male-heterogametic system, XX/XY. Suppose now that a mutation occurs on an X chromosome that renders the feminizing tendency of the resulting chromosome—call the new chromosome X′—dominant to the masculinizing tendency of the Y (so that X′Y individuals are female). Allowing all possible

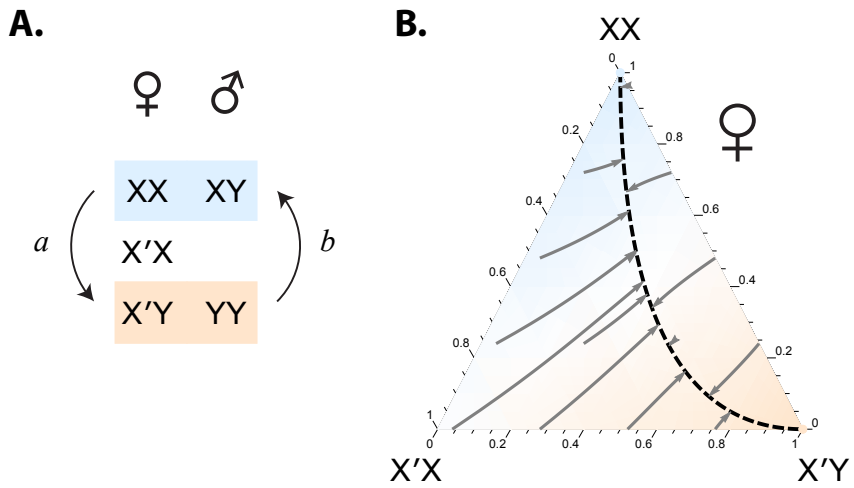

Figure 3.3.1: Transitions between male and female heterogamety without a change in the sex determining locus (model 1). (A) In model 1, heterogametic transitions involve intermediate systems of five sexual genotypes. In the system depicted here, there are three female and two male genotypes. Transition *a* is from male to female heterogamety, and involves fixation of the dominant feminizing X′ chromosome (mutated from an X). The reverse transition, *b*, is from female to male heterogamety, and involves fixation of the recessive feminizing X chromosome (mutated from an X′). A symmetric path, with two female and three male genotypes, also exists (see Figure 3.3.3A). (B) The equilibrium path (dashed line) governing transitions *a* and *b*. For ease of visualization, attention is restricted to the frequencies of the three female genotypes when the sex ratio is $1/2$ (as it is at every point on the equilibrium path). These frequencies are displayed in a de Finetti diagram, where, for example, the relative frequency of XX females at a point is given by the height of that point along a perpendicular line dropped from the XX corner to its opposing side. Some deterministic trajectories to the equilibrium path are displayed with arrowed grey lines. Color shading indicates frequency of XX females (blue) relative to X′Y females (orange). The equation for the equilibrium path is given in Eq. (3.1).

male-female matings between the genotypes results in a closed system of five sexual genotypes: females can be XX, X′X, or X′Y, while males can be XY or YY (Figure 3.3.1A, system arises in direction *a*). Clearly, this system could also arise in the reverse direction: starting from a female-heterogametic system, X′Y/YY, an X′ chromosome can mutate to an X chromosome with recessive feminizing tendency (Figure 3.3.1A, direction *b*). (It should of course be noted that the usual sex chromosome labels—X, Y, Z, and W—are arbitrary, so that we could just as validly label those in a female-heterogametic system X′ and Y. We also note that 'sex chromosomes' are defined simply by the presence of a locus at which genes of major sex determining effect segregate—it is possible, for example, that X and Y chromosomes are identical along their entire length, and recombine along their entire length, except at the major sex determining locus.)

Assuming the genotypes all to have equal fitness (i.e., that the system is neutral), enumerating them in the above order (XX, X′X, X′Y, XY, YY), and letting p_i be the population frequency of genotype i, Bull and Charnov [23] showed that, for any value $0 \leq q \leq 1$, the population state

$$p_1 = \frac{(1-q)^2}{2(1+q)^2}, \quad p_2 = \frac{q(1-q)}{(1+q)^2}, \quad p_3 = \frac{q}{1+q},$$
$$p_4 = (1-q)/2, \quad p_5 = q/2, \tag{3.1}$$

is an equilibrium in an infinite, randomly-mating population (Figure 3.3.1B). When $q = 0$, all males are XY and all females XX, so that a system of male heterogamety operates; when $q = 1$, males are YY and females X′Y, and the system is female heterogamety. For intermediate values $0 < q < 1$, all five genotypes are present at positive frequency.

A symmetric, though distinct, path exists where, from an initial female-heterogametic system ZW/ZZ, a dominant masculinizing Z′ arises from a mutated Z, and, if it reaches high enough frequency, establishes a male-heterogametic WW/WZ′ system. The reverse transition along the same path involves fixation of the recessive Z chromosome from an initial WW/WZ′ system. Intermediate states along this path involve two female and three male genotypes.

These symmetric paths, one with three female and two male genotypes (as illustrated in Figure 3.3.1), and the other with two female and three male genotypes (described in the previous paragraph), are illustrated in a general format in Figure 3.3.3A. There, among the transitions involving fixation of dominant sex determining mutations, those from male to female heterogamety are labeled a (as in Figure 3.3.1A), while those from female to male heterogamety are labeled c. Among the transitions involving fixation of recessive sex determining mutations, those from female to male heterogamety are labeled b (as in Figure 3.3.1A), while those from male to female heterogamety are labeled d. We shall use this labeling throughout for model 1 transitions.

Notice that, if there are no demographic differences between males and females, then the dynamics in directions c and d are identical to those in directions a and b, respectively, up to a relabeling of males and females.

For the non-neutral case, the equilibrium path connecting systems of male and female heterogamety no longer exists [23]. The resultant dynamics in this scenario depend on the selective forces acting on each of the genotypes. Transitions in either direction involve the production of individuals homozygous for a previously sex-specific chromosome (the Y for transitions in direction a and the X′ and X for those in direction b). Sex-specific chromosomes are expected to accumulate reces-

sive deleterious mutations in a heterogametic system [32, 34], causing individuals homozygous for them to be selected against weakly in young heterogametic systems (as in many reptiles, amphibians, and fishes) and to be inviable in old systems (as in mammals and birds). In the latter case, model 1 transitions are impossible. In the former case, we expect YY genotypes to be selected against in transitions in direction a, and X′X and XX genotypes to be selected against in transitions in direction b (in direction b, the X chromosome is created simply by mutation at a major sex determining locus on the X′ chromosome; the X is therefore expected to carry the same deleterious mutations that the X′ does).

3.3.2 Model 2

Begin with a male-heterogametic system XX,AA/XY,AA, where A is initially autosomal. Now suppose that a mutation occurs on an A chromosome that confers on the resultant chromosome, A′, a feminizing tendency dominant to the masculinizing tendency of the Y (so that XY,AA′ and YY,AA′ individuals are female). All possible matings then yield a closed system of six sexual genotypes, females being XX,AA, XX,AA′, XY,AA′, or YY,AA′, and males being XY,AA or YY,AA (Figure 3.3.2, direction a). Again, this system could arise in the reverse direction as well, starting from the female-heterogametic system YY,AA′/YY,AA and introducing, as a mutated Y chromosome, a recessive feminizing X (Figure 3.3.2, direction b).

Scudo [210, 211] and Bull and Charnov [23] showed that, when all genotypes are equally fit (i.e. when the system is neutral), enumerating them in the above order (XX,AA, XX,AA′, XY,AA′, YY,AA′, XY,AA, YY,AA), and writing p_i for

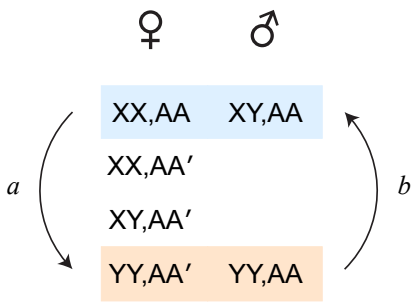

Figure 3.3.2: Transitions between male and female heterogamety with a change in the sex determining locus to a previous autosome (model 2). Model 2 transitional systems involve six sexual genotypes. In the system illustrated here, there are four female and two male genotypes. Transition *a* involves fixation of the dominant feminizing A′ chromosome (mutated from an A), and causes the previous sex chromosome Y to become an autosome. Transition *b* involves fixation of the recessive feminizing X (mutated from a Y), and causes the previous sex chromosome A to become an autosome. The equilibrium path of this system is given in Eq. (3.2). A symmetric path, with two female and four male genotypes, also exists (see Figure 3.3.3B).

the frequency of genotype i, a continuous path of equilibria,

$$p_1 = \frac{(1-q)^2}{2(1+q)^2}, \quad p_2 = \frac{q(1-q)^2}{2(1+q)^2}, \quad p_3 = \frac{q(1-q)}{1+q}, \quad p_4 = q/2,$$
$$p_5 = (1-q)/2, \quad p_6 = q/2, \tag{3.2}$$

connects male heterogamety at one end (XX,AA/XY,AA; $q = 0$) with female heterogamety at the other (YY,AA′/YY,AA; $q = 1$), with intermediate equilibria ($0 < q < 1$) involving all six genotypes.

Notice that, if the former system transitions to the latter (Figure 3.3.2, direction *a*), the Y chromosome becomes autosomal, and the previous autosome A becomes a sex chromosome. Notice too that this transition involves the production of YY individuals. On the other hand, the reverse transition (Figure 3.3.2, direction *b*) does not involve the production of individuals homozygous for the previously sex-specific chromosome (here, the A′ chromosome), an important difference.

Again, a symmetric, though distinct, equilibrium path exists that connects a female-heterogametic system AA,ZW/AA,ZZ with a male-heterogametic system AA′,WW/AA,WW via an intermediate system with two female and four male genotypes. Transitions from female to male heterogamety along this path involve production of WW individuals, the W having been female-specific in the original system of female heterogamety. But transitions from male to female heterogamety along this path do not involve the production of A′A′ individuals, the A′ having been male-specific under male heterogamety. That heterogametic transitions along standard equilibrium paths are possible without the production of WW or YY individuals (using the standard labeling) is an important fact often forgotten in the literature on evolutionary transitions between sex determining mechanisms.

These symmetric equilibrium paths, one with four female and two male genotypes (as in Figure 3.3.2), and the other with two female and four male genotypes (as described in the previous paragraph), are illustrated in a general way in Figure 3.3.3B. There, among model 2 transitions involving fixation of dominant sex determining mutations, those from male to female heterogamety are labeled a, while those from female to male heterogamety are labeled c. Among the reverse transitions involving fixation of recessive sex determining mutations, those from female to male heterogamety are labeled b, while those from male to female heterogamety are labeled d. We shall use this labeling throughout for model 2 transitions. Transitions b and d do not involve the production of individuals homozygous for a previously sex-specific chromosome, while transitions a and c do.

Again, notice that, if there are no demographic differences between males and females, then the dynamics in directions c and d are respectively identical to those in directions a and b up to a relabeling of males and females.

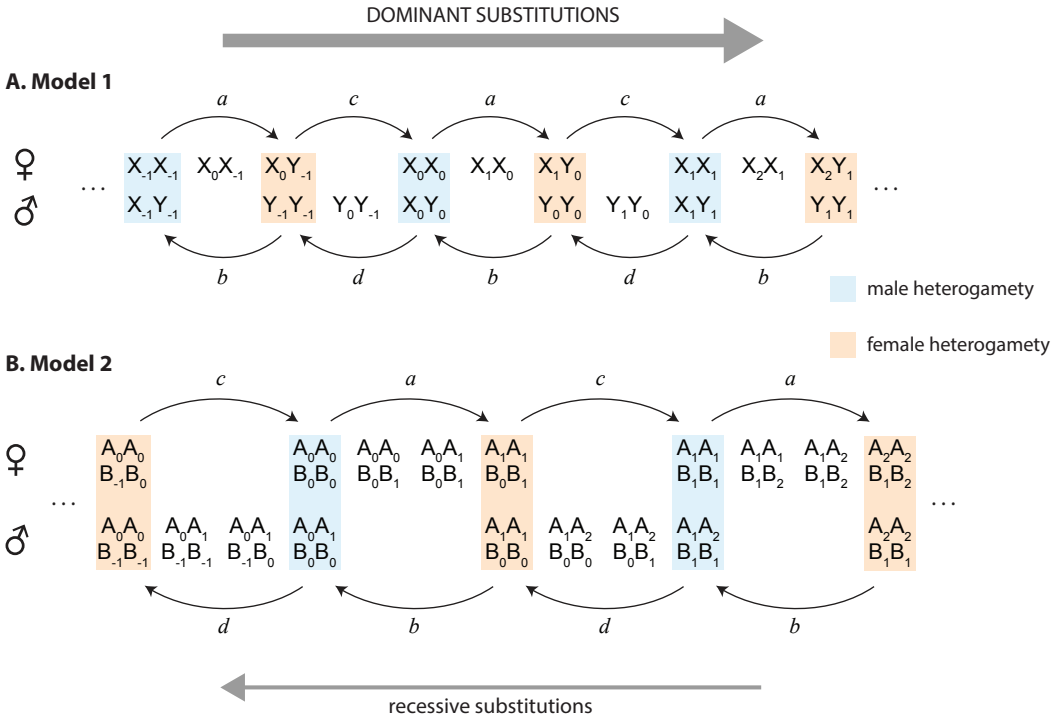

Figure 3.3.3: A general representation of the substitutions involved in changing the heterogametic system, both for model 1 transitions (A) and for model 2 transitions (B). Transitions between heterogametic systems that involve the arrival and fixation ('substitution') of new dominant sex determining mutations are labeled *a* and *c*. Transitions that involve the substitution of new recessive sex determining mutations are labeled *b* and *d*. For model 2 (B), we have used the arbitrary letters A and B to denote the two separate chromosomes/unlinked loci: one switches to a sex chromosome, and the other switches to an autosome, each time the heterogametic system changes.

3.4 Methods

The equilibrium paths described in the previous section arise under deterministic evolutionary dynamics. Our aim is to study stochastic evolution along and around these paths. To do so, we employ Monte Carlo simulations to estimate the substitution rates of the various mutations along the paths, and approximation techniques to analytically investigate the results of these simulations.

For computational efficiency, our simulations are of a non-overlapping generations Wright-Fisher process [68, 89, 262]. For mathematical tractability, on the other hand, our analytical treatment considers models of the overlapping generations Moran type [157]; mapping between these processes in the diffusion limit simply requires rescaling the rate of genetic drift [60]. The agreement of the results under the two processes will demonstrate their robustness to the consideration of overlapping or non-overlapping generations.

3.4.1 Monte Carlo simulations

For both model 1 and model 2, we simulate a population of constant size N, which comprises males and females, and evolves according to a sexual Wright-Fisher process [68, 89, 262]. Each generation, males and females form mating pairs, N in total. An individual can be in more than one pair, and the probability that an individual is in a given pair is proportional to that individual's fitness relative to other members of its sex (and is independent across pairs). Each mating pair produces a single offspring, whose sexual genotype (and therefore sex) is determined by randomly choosing a gamete from each of its parents. The sex chromosomes of heterogametic individuals are assumed to segregate in a Mendelian fashion. After offspring production, all individuals in the parental generation die. (This model is equivalent to

one in which each male contributes a large number of sperm, proportional to his fitness, to a common sperm pool, each female contributes a large number of eggs, proportional to her fitness, to a common egg pool, and each of N offspring is then formed by drawing a random sperm and a random egg from the respective pools.)

As a baseline for both models, we consider the case where each genotype is equally fit (the 'neutral' case), i.e., where each individual within a sex is equally likely to be chosen to be in a given mating pair. Thereafter, we focus on cases where individuals that are homozygous for a previously sex-specific chromosome suffer a selective disadvantage: each such individual is a fraction $1 - s$ as likely as other members of its sex to be chosen to be in a given mating pair.

In all cases, we assume no population structure (mating is random), and no demographic differences between males and females in our simulations. Relaxing these assumptions is an important direction of future work, and would be aided by parallel theoretical developments in the general study of drift-induced selection. In [246, Section S1.3], we give some numerical picture of how demographic differences between males and female (viz. greater variance in male reproductive success) affect our results (also see Discussion section).

3.4.2 Diffusion approximations

In the Moran formulation, we likewise consider a discrete population of N individuals. Males and females of each genotype encounter each other with a probability per unit time proportional to their frequency in the population. On encountering each other, a pair produces a single offspring, which inherits its sexual genotype from its parents in a Mendelian fashion. In order to keep the population size constant at N, another individual is chosen to die. In the neutral case, each individual in

the population is equally likely to be chosen to die. In the case with selection, the probability that an individual is chosen to die is weighted by a normalized death probability, the inverse of that genotype's fitness. This implementation of selection will give similar dynamics to the Wright-Fisher model to leading order in the selection strength (see In [246, Section S2.1].

In order to simplify the probabilistic model, we make use of a diffusion approximation [48]. Denoting the frequency of each genotype by p_i and assuming N to be large but finite, the evolution of the pdf for the system $\phi(\boldsymbol{p}, t)$ is approximately governed by

$$\begin{aligned}\frac{\partial \phi(\boldsymbol{p}, \tau)}{\partial \tau} = &- \sum_i \frac{\partial}{\partial p_i} \left[A_i(\boldsymbol{p}) \phi(\boldsymbol{p}, \tau)\right] \\ &+ \frac{1}{2N} \sum_{i,j} \frac{\partial^2}{\partial p_i \partial p_j} \left[B_{ij}(\boldsymbol{p}) \phi(\boldsymbol{p}, \tau)\right] \end{aligned} \tag{3.3}$$

[76, 147], where the forms of the vector $\boldsymbol{A}(\boldsymbol{p})$ and the matrix $B(\boldsymbol{p})$ can be directly calculated for both models 1 and 2 from their respective probability transition rates (see [246, Section S2.1]. The term $\boldsymbol{A}(\boldsymbol{p})$ primarily controls the time-evolution of the mean of $\phi(\boldsymbol{p}, t)$, and can thus be interpreted as a deterministic selective term. Indeed, in the deterministic limit ($N \to \infty$), the dynamics of the system are described by the ordinary differential equations $\dot{\boldsymbol{p}} = \boldsymbol{A}(\boldsymbol{p})$. Meanwhile, the term $B(\boldsymbol{p})$ controls the diffusion of $\phi(\boldsymbol{p}, t)$, thus capturing the effect of genetic drift.

In comparing this diffusion equation with one for the analogous Wright-Fisher process, we must take account of two scalings. First, genetic drift is larger by a factor of two in the Moran formulation than in the Wright-Fisher formulation [60, 66]. This leads to an additional pre-factor of $1/2$ appearing before the $B(\boldsymbol{P})$ in the Wright-Fisher formulation of Eq. (3.3). Second, reproduction occurs $4N$ times faster in

the Wright-Fisher model. This is because individual reproduction events in the sexual Moran model occur at an average rate proportional to the product of the frequency of males and females in the population (which is 1/4 at equilibrium sex ratios), whereas, in the Wright-Fisher model, N reproduction events occur every time-step. Since we have already taken into account a factor N in timescale in obtaining Eq. (3.3) ($\tau = t/N$), the Wright-Fisher formulation of Eq. (3.3) contains an additional factor of 4 preceding all terms on the right-hand side of Eq. (3.3).

We wish to determine the probabilities of transitions from male to female heterogamety, and vice-versa. The calculation of these quantities is not straightforward; the diffusion equation (3.3) governing the dynamics is non-linear in either four or five variables (for models 1 and 2, respectively). However, analytical progress can be made by exploiting a separation of timescales that is present in both models. Such methods have long been successfully employed in population genetics to solve a wide range of problems [59, 163, 222]. The key to progress is in noting that, in the deterministic neutral systems, a trajectory starting from any initial point will quickly collapse to a point on the equilibrium path of the system, Eq. (3.1) for model 1 (Figure 3.3.1B) and Eq. (3.2) for model 2, where it will then stay. In the current notation, this line is the set of solutions $\boldsymbol{p}$ to the equation $\boldsymbol{A}(\boldsymbol{p}) = 0$. When genetic drift and selection are taken into account, the system will no longer reach and subsequently remain at a position on this line. However, if selection is weak and N is large (such that the rate of genetic drift, $1/N$, is small), then the system will quickly collapse to a subspace in the vicinity of this line; it will then slowly move along this 'slow subspace' until the system fixes in a state of either male or female heterogamety. We exploit this separation of timescales by removing the fast transient dynamics to obtain an approximation for the system dynamics

in the slow subspace. Since this approximate description in the slow subspace is in terms of a single variable, q [see Eqs. (3.1) and (3.2)], fixation probabilities are then straightforward to calculate.

There is no unique way to mathematically implement the approach outlined conceptually above. While methods similar to the projection operator formalism described in [76] have historically found most favor in the population genetics literature (e.g., [59, 222]), in this paper we implement the approach described in [173], which is more intuitive in the present case. The full calculation is provided in the [246, Section S2.2]. Here we simply state the key results. On removing the fast-variables, the dynamics of Eq. (3.3) can be approximated by

$$\begin{aligned}\frac{\partial \psi(q,\tau)}{\partial \tau} = &- \frac{\partial}{\partial q}\left\{\left[\mathcal{D}(q)+\mathcal{S}(q)\right]\psi(q,\tau)\right\} \\ &+ \frac{1}{2N}\frac{\partial^2}{\partial^2 q}\left\{\mathcal{B}(q)\psi(q,\tau)\right\} . \end{aligned} \tag{3.4}$$

Here, $\psi(q,t)$ is the probability density function for q along the slow subspace. In a similar fashion to Eq. (3.3), the terms $\mathcal{D}(q)$ and $\mathcal{S}(q)$ control the time-evolution of the mean of $\psi(q,t)$ and can thus be interpreted as selective terms for q along the slow subspace. Likewise, the term $\mathcal{B}(q)$ controls the diffusion of $\phi(\boldsymbol{p},t)$, and can thus be interpreted as capturing the effect of genetic drift along the slow subspace.

The equation for the slow subspace itself can be approximated by the equation for the equilibrium line, since they lie close to each other in the weak selection limit, and coincide when selection is absent. The equations for $\mathcal{D}(q)$, $\mathcal{S}(q)$, and $\mathcal{B}(q)$ can be determined from $\boldsymbol{A}(\boldsymbol{p})$ and $B(\boldsymbol{p})$ along with the equation for the slow subspace. The terms $\mathcal{D}(q)$ and $\mathcal{B}(q)$ are simply the components of $\boldsymbol{A}(\boldsymbol{p})$ and $B(\boldsymbol{p})$ along the slow subspace (i.e., respectively, the components of deterministic selection and genetic

drift in the subspace). More interesting is the term $\mathcal{S}(q)$, which is a selective term induced by genetic drift. Its origin can be interpreted in various ways. First, it can be graphically understood as resulting from a bias in how fluctuations taking the system off the slow subspace return to the slow subspace (i.e., fluctuations do not return, on average, to the point from which they originated on the slow subspace) [45, 173]. Second, it can be mathematically understood as the result of making a non-linear change of stochastic variables [201] into the system's slow variable. Finally, it can be understood as the result of a selective pressure favoring genotypes with a lower variance in their reproductive output—Gillespie's Criterion [78, 87, 174]. In Eq. (3.4), differences in the variance of the reproductive output of the genotypes emerge naturally from the confinement of the system to the slow subspace.

3.5 Results

3.5.1 Model 1: Transitions using the same chromosomes

In this section, we study transitions between male and female heterogamety where the sex chromosome locus is the same under both systems (Figures 3.3.1 and 3.3.3A).

Monte Carlo simulations

We begin with a male-heterogametic system, XX/XY, in a population of constant size N, initially with $N/2$ females (all XX) and $N/2$ males (all XY). We consider a mutation to one of the X chromosomes, rendering it an X′ chromosome, X′Y and X′X bearers of which are female. YY individuals are male. If the X′ chromosome 'fixes' in the population, a female-heterogametic system, X′Y/YY, is established (direction a in Figures 3.3.1A and 3.3.3A).

Influenced by whether the original X′ mutation occurs in oogenesis or spermato-

genesis, the X′ could initially find itself in an X′X or an X′Y female. We consider both cases in our simulations, and in both begin with a population that is $N/2$ females (one of which carries an X′ chromosome) and $N/2$ males.

Initially assuming all five sexual genotypes to be equally fit, what is a reasonable null expectation for the fixation probability of this X′ chromosome? The fixation probability of a mutation on the X chromosome of no effect is simply the inverse of the initial census count of the X chromosome, i.e., $1/(3N/2)$. This we take to be the neutral expectation for $\rho_{\mathrm{X}'}^{\mathrm{null}}$, the fixation probability of the X′ chromosome, so that $N\rho_{\mathrm{X}'}^{\mathrm{null}} = 2/3$.

Instead, we find in our simulations that the fixation probability of the X′ chromosome is higher than this neutral expectation, with $N\rho_{\mathrm{X}'} \approx 1.12$ (Figure 3.5.1A). This is irrespective of the background on which the initial X′ chromosome finds itself [246, Figure S1A]. The average conditional fixation time of the X′ chromosome is close to $2.4N$ for each N considered in our simulations, and again, this is irrespective of the mutation's initial background [246, Figure S1B]. A fixation time that scales linearly with N is strongly suggestive of drift-like evolutionary dynamics.

We now consider evolution in the other direction along the path (direction b in Figures 3.3.1A and 3.3.3A). We begin with an established X′Y/YY female-heterogametic system, and consider a mutation to one of the X′ chromosome that renders it an X. If this X chromosome subsequently fixes in the population of X and X′ chromosomes, an XX/XY male-heterogametic system would be established. Here, the X mutation must occur in oogenesis, since it derives from an X′ chromosome which must have been borne by a female. Therefore, the first individual to carry the new X chromosome must be an XY male. For consistency, we begin our simulations with $N/2$ females and $N/2$ males (one of which carries the X

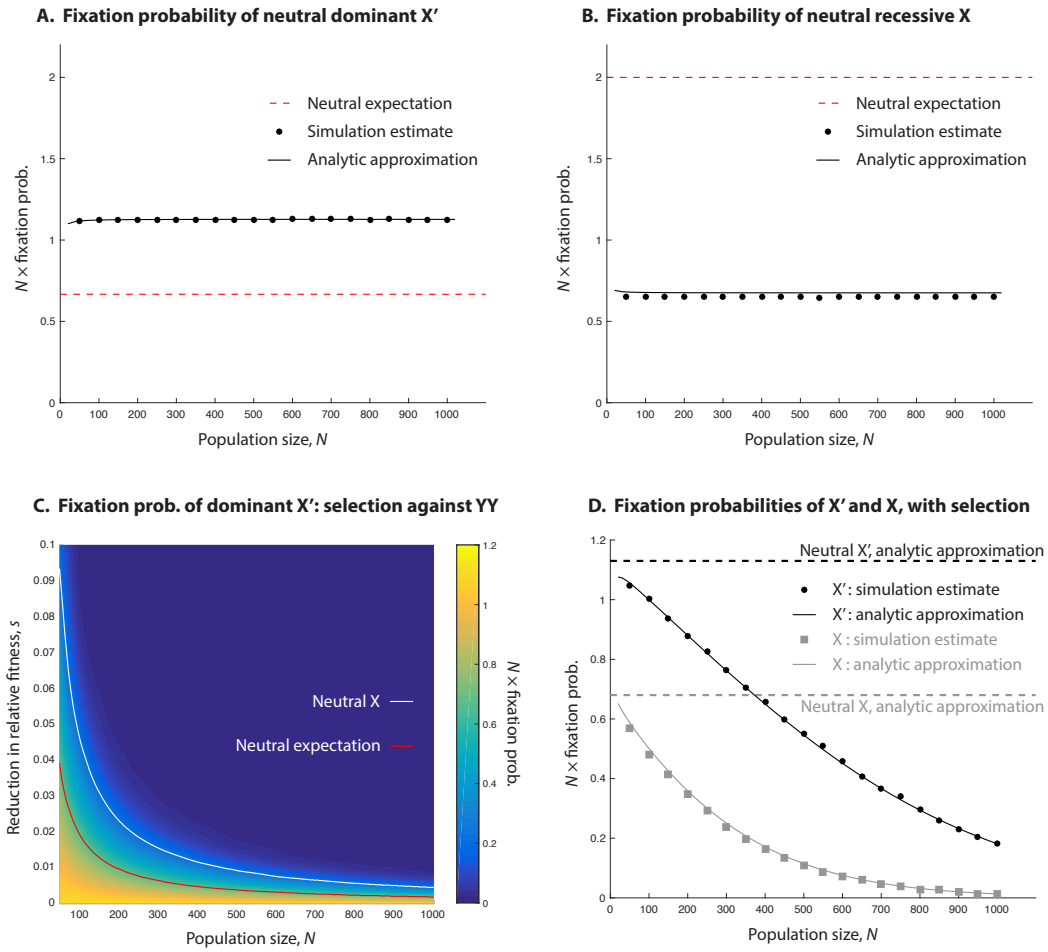

Figure 3.5.1: Fixation probabilities in Model 1 heterogametic transitions. (A, B) The fixation probability of a neutral dominant feminizing X′ arising in an XX/XY system is significantly higher than the neutral expectation (A), while the reverse fixation probability of a neutral recessive feminizing X chromosome arising in an X′Y/YY system is lower than the neutral expectation (B). (C) If YY individuals are selected against in the transition from XX/XY to X′Y/YY, the substitution rate of the X′ chromosome causing this transition is reduced. Still, selection needs to be sufficiently strong to reduce the substitution rate below the neutral expectation (above red line), and even stronger to reduce the substitution rate below that of the neutral X chromosome in the reverse transition (above white line). This is especially true in smaller populations. (D) Fixation probabilities of the X′ and X chromosomes, in directions *a* and *b* of Figure 3.3.1A respectively, when individuals homozygous for a previously sex-specific chromosome have relative fitness reduced by $s = 0.5\%$. Though the fixation probabilities of the two chromosomes decrease when this selection operates, the relative advantage in substitution rates enjoyed by the dominant X′ over the recessive X is exacerbated.

chromosome).

Similar to before, our neutral expectation for the fixation probability of the X is just the inverse of the number of X′ chromosomes initially in the population, i.e., $\rho_{\mathrm{X}}^{\mathrm{null}} = 1/(N/2)$, so that $N\rho_{\mathrm{X}}^{\mathrm{null}} = 2$. Instead, in our simulations we find the fixation probability of the X chromosome to be much lower than this neutral expectation, with $\rho_{\mathrm{X}} \approx 0.65$ (Figure 3.5.1B). The average conditional fixation time of the X chromosome is, like that of the X′, close to $2.4N$ for each N considered [246, Figure S2B].

Thus, the fixation probability of the X′, starting from an initial XX/XY system, is almost twice as great as the fixation probability of the X, starting from an initial X′Y/YY system. However, to properly determine whether evolution along the equilibrium path is biased in favor of the X′ chromosome, we must consider the *substitution rates* of the two chromosomes. In doing so, we assume symmetric mutation rates in the two directions, i.e., that the probability of an X chromosome mutating to an X′ is the same as the probability of an X′ chromosome mutating to an X. We also assume this mutation rate to be sufficiently small that at most one mutation segregates in the population at any given time (a common assumption [143]).

Suppose this mutation rate to be u per chromosome per generation. An XX/XY population with even sex ratio produces X′ mutations at a rate of $\mu_{\mathrm{X}'} = (3N/2)u$ per generation, while an X′Y/YY population produces X mutations at a third of this rate, $\mu_{\mathrm{X}} = (N/2)u$ per generation. Under our naive neutral expectations, the substitution rates of the X and X′ chromosomes should both be u ($= \mu_{\mathrm{X}'}\rho_{\mathrm{X}'}^{\mathrm{null}} = \mu_{\mathrm{X}}\rho_{\mathrm{X}}^{\mathrm{null}}$). Instead, the substitution rate $\mu_{\mathrm{X}'}\rho_{\mathrm{X}'}$ from an XX/XY to an X′Y/YY system (in direction a of Figures 3.3.1A, 3.3.3A) is about $(3N/2)u \times 1.12/N = 1.68u$, while the substitution rate $\mu_{\mathrm{X}}\rho_{\mathrm{X}}$ from an X′Y/YY to an XX/XY system (direction

b of Figures 3.3.1A, 3.3.3A) is about $(N/2)u \times 0.65/N = 0.325u$. That is, the substitution rate of the X′ is more than *five times higher* than that of the X.

Since, in the population model we have simulated, there are no demographic differences between males and females, the transitions symmetric to those above (i.e., in directions c and d in Figure 3.3.3) occur with fixation probabilities and substitution rates equivalent to those we have estimated above (i.e., with reference to Figure 3.3.3, the fixation probabilities in directions a and b match those in directions c and d respectively).

Therefore, the most likely trajectory that the neutral dynamical system will follow in the long term is the recurrent invasion and fixation of successive *dominant* sex determining mutations, flipping the system repeatedly between male and female heterogamety. This corresponds to a bias in favor of rightward transitions in Figure 3.3.3.

We now consider the possibility that some genotypes are fitter than others. In particular, we study the case where individuals homozygous for a previously sex-specific chromosome (including mutated versions of it) are of lower fitness.

The transition from a male-heterogametic XX/XY system to a female-heterogametic X′Y/YY system, via fixation of the dominant X′ chromosome and displacement of the X, involves the production of YY males. Assume that YY males have relative fitness $1 - s$, while all other sexual genotypes are of equal fitness 1. Figure 3.5.1C gives the fixation probability of the X′ chromosome for various values of s and N. As expected, the fixation probability decreases as selection against the YY genotype increases. Nonetheless, it is clear that the YY genotype can suffer appreciable fitness reductions with the X′ chromosome still fixing with probability higher than the neutral expectation. This is especially true in small populations, in which se-

lection acts less efficiently [124]; we would expect this to carry over to structured populations of larger size, e.g., those that are subdivided into many small demes in which drift is an important force [125, 257].

The reverse transition, from the X′Y/YY to the XX/XY system, involves the production of X′X and XX females. The substitution rate of the X, in direction b of Figure 3.3.1A, was very low even when no genotypes were of reduced fitness; selection against the XX and X′X genotypes (recall that the X′ chromosome is just an X mutated at the sex-determining locus) severely exacerbates this disadvantage (Figures 3.5.1D and S4). Again, given the symmetry between transitions in directions a and c in Figure 3.3.3, and between transitions in directions b and d, the above results imply a bias towards c transitions over d transitions, with this bias exacerbated by selection. That is, selection generally exacerbates the bias in favor of rightward (dominant) transitions in Figure 3.3.3.

Analytical results

To better understand these simulation results, we now study the system analytically in the diffusion limit. We first consider the neutral case. Applying the fast-variable elimination described in *Methods* and detailed in full in [246, Section S2], we find for the model 1 system described in Eq. (3.1) that the system dynamics can be approximated by Eq. (3.4) with $\mathcal{D}(q) = 0$ and

$$\begin{aligned}\mathcal{S}(q) &= \frac{1}{4N}\frac{q(1-q)(1+q)^3(1+q^2)\{1+(2-q)q[4+q(6+q)]\}}{[1+q(2+3q)]^3}\\ \mathcal{B}(q) &= \frac{1}{4}\frac{q(1+q)^3\{1+q\,[1+q(6-q(6+(3-q)q))]\}}{[1+q(2+3q)]^2}\end{aligned} \tag{3.5}$$

(calculations in [246, Section S2.2.1]). As we expect in this neutral scenario, there are no deterministic contributions to selection along the equilibrium path [$\mathcal{D}(q) = 0$]. However, there is a drift-induced selection term [$\mathcal{S}(q) \neq 0$]. The strength of the drift-induced selection is of order $1/N$, generated as it is by demographic fluctuations. Recalling that $q = 0$ corresponds to male heterogamety [XX/XY; $p_1 = 1/2$, $p_4 = 1/2$ in Eq. (3.1)], while $q = 1$ corresponds to female heterogamety [X′Y/YY; $p_3 = 1/2$, $p_5 = 1/2$ in Eq. (3.1)], we find that the drift-induced selection selects for the fixation of the dominant sex determining mutation *at every point* on the equilibrium path [$\mathcal{S}(q) > 0$ for all $q \in (0, 1)$].

How does this drift-induced selection emerge? Essentially, in this 'neutral' stochastic system, demographic fluctuations continually perturb the system away from the equilibrium path (to which the deterministic system is constrained). There is then a selective pressure for the system to return to the equilibrium path. However, the nonlinear trajectories along which these fluctuations return, combined with the curvature of the equilibrium path, give rise to a bias in the average position to which fluctuations return. In other words, fluctuations arising at a point q return on average to a point $q + \delta(q)$ on the equilibrium path.

Mathematically quantifying this bias requires taking account of the probability distribution of fluctuations in each genotype, the form of trajectories back to the equilibrium path, and the curvature of the equilibrium path itself, each of which varies as q is varied. However, further intuition can be gained by decomposing $\mathcal{S}(q)$ into two components: $\mathcal{S}(q) = \mathcal{S}^{\mathrm{NL}}(q) + \mathcal{S}^{\mathrm{C}}(q)$. The first term, $\mathcal{S}^{\mathrm{NL}}(q)$, quantifies contributions to $\mathcal{S}(q)$ arising from the non-linearity of trajectories that take the system back to the equilibrium path. The second term, $\mathcal{S}^{\mathrm{C}}(q)$, quantifies contributions to $\mathcal{S}(q)$ arising from the curvature of the equilibrium path itself. Plotting these

terms together in Figure 3.5.2A, we see that it is the curvature of the equilibrium path that contributes most to the observed drift-induced selection.

Standard methods can be used to numerically calculate the fixation probability of either male or female heterogamety for any initial condition q_0 on the slow subspace (see [76, 201]; and [246, Section S2.3]). Our final task is to calculate how the initial conditions described in the previous section, those of single mutants invading a resident population, map onto initial conditions on the equilibrium path. That is, for a given $\boldsymbol{p}_0$, we wish to determine q_0. This calculation is given in [246, Section S2.3.1]; with it, the neutral fixation probabilities can be calculated.

The results for the fixation probabilities of the mutants are given in Figure 3.5.1A, in which we see excellent agreement between theory and simulations. In particular we find that the fixation probability of the X′ chromosome under the diffusion approximation is $N\rho_{\mathrm{X}'} \approx 1.13$ (Figure 3.5.1A). This is irrespective of the background on which the initial X′ chromosome finds itself, as both of these initial conditions lead to the same initial condition q_0 on the equilibrium path [246, Section S2.3.1]. We may also compute the mean conditional fixation time of the X, which agrees well with our simulation estimates when the differences in variance between the Wright-Fisher and Moran processes are taken into account [246, Figure S1B]. Meanwhile the fixation probability of an X chromosome is $N\rho_{\mathrm{X}} \approx 0.68$, again in close agreement with our simulation results (Figure 3.5.1B), as is the computed mean conditional fixation time [246, Figure S2B].

We now consider the possibility that some genotypes are fitter than others. For transition direction a, assume that YY males (with frequency p_5) have relative death rate $\Delta_5 = 1+s$, while all other sexual genotypes have death rate 1. When s is small, we can still utilize fast-variable elimination to arrive at the approximate description

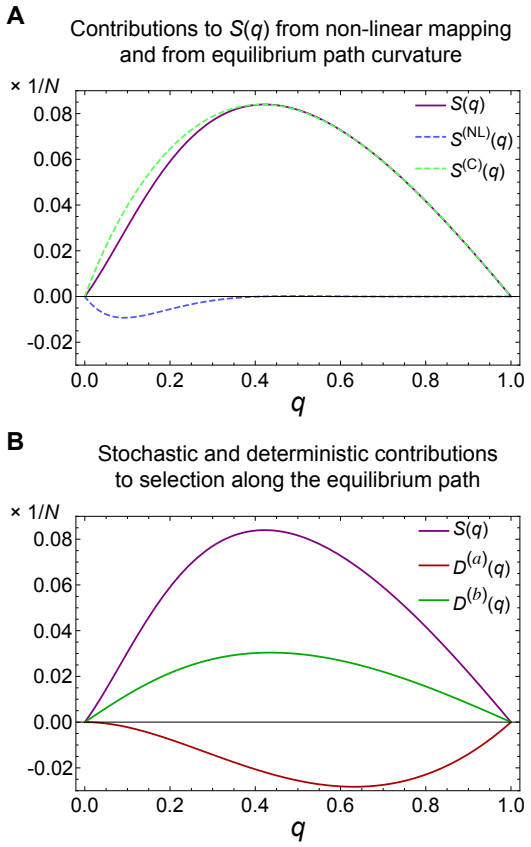

Figure 3.5.2: (A) In model 1, random demographic fluctuations induce a selective gradient $\mathcal{S}(q)$ along the equilibrium path in favor of the dominant sex determining chromosome, i.e., causing q to increase on average [see Eqs. (3.4) and (3.5)]. $\mathcal{S}(q)$ can be divided into two components. The first, $\mathcal{S}^{(\mathsf{NL})}$, is from non-linear components of the mapping of fluctuations back to the equilibrium path; the second, $\mathcal{S}^{(\mathsf{C})}$, is from the curvature of the equilibrium path. In this case, it can be seen that the primary contribution to the drift-induced bias $\mathcal{S}(q)$ is from curvature of the equilibrium path. (B) Contributions to average dynamics along the equilibrium path arising from drift-induced selection, $\mathcal{S}(q)$, and deterministic selection against individuals homozygous for a previously sex-specific chromosome, $\mathcal{D}(q)$ [see Eq. (3.4)]. Note that the form of $\mathcal{D}(q)$ is expected to change depending on whether the initial population exhibits XX/XY male heterogamety [$\mathcal{D}^{(a)}(q)$] or X′Y/YY female heterogamety [$\mathcal{D}^{(b)}(q)$] [Eqs. (3.6) and (3.7)], i.e., whether the transition is in direction *a* or direction *b* of Figure 3.3.1A. In both plots the parameters have been scaled such that $N\delta = 1$ in order to facilitate the comparison of contributions to selection along the slow subspace.

of the system dynamics given by Eq. (3.4). The functions $\mathcal{S}(q)$ and $\mathcal{B}(q)$ retain the forms given in Eq. (3.5), but now $\mathcal{D}(q) = \mathcal{D}^{(a)}(q)$, where

$$\mathcal{D}^{(a)}(q) = -\frac{s}{4}\frac{q^2(1-q)(1+q)^2}{1+2q+3q^2} \tag{3.6}$$

and the superscript '(a)' denotes that this is $\mathcal{D}(q)$ evaluated for transitions in direction a (Figure 3.5.2B; calculations in [246, Section S2.2.1]). This term is of order s as this is the deterministic contribution to the dynamics along the slow subspace.

For the reverse transition b, assume that XX and X′X females (with frequencies p_1 and p_2) have relative death rates $\Delta_1 = 1+s$ and $\Delta_2 = 1+s$ respectively, while all other sexual genotypes have death rate 1. Again utilizing fast variable elimination, we find $\mathcal{D}(q) = \mathcal{D}^{(b)}(q)$, where

$$\mathcal{D}^{(b)}(q) = -\frac{s}{8}\frac{q(1+2q-q^2)(1-q^2)}{1+2q+3q^2} \tag{3.7}$$

and the superscript '(b)' denotes that this is $\mathcal{D}(q)$ evaluated for transitions in direction b (Figure 3.5.2B; calculations in [246, Section S2.2.1]).

We are now in a position to calculate the respective fixation probabilities of mutations arising in directions a and b. We find that, while the fixation probability of X′ in direction a is of course lower than in the neutral case (since YY is selected against), the relative reduction of the fixation probability of X in direction b is even higher (Figure 3.5.1D).

3.5.2 Model 2: Transitions that change the sex chromosome pair

In this section, we study transitions between male and female heterogamety where, in the course of the transitions, a pair of chromosomes that are initially autosomal

are co-opted as new sex chromosomes, while one of the old sex chromosomes becomes autosomal (Figures 3.3.2 and 3.3.3B).

Monte Carlo simulations

Beginning with an XX,AA/XY,AA male-heterogametic system (where X and Y are sex chromosomes and A is an autosome), assume that a mutation appears on an A chromosome, rendering it an A′ such that XX,AA, XX,AA′, XY,AA′, and YY,AA′ individuals are female, while XY,AA and YY,AA individuals are male (Figure 3.3.2). If the A′ chromosome reaches sufficiently high frequency in the population, the X chromosome is eliminated, and a YY,AA′/YY,AA female-heterogametic system establishes (direction a in Figures 3.3.2 and 3.3.3B).

We initially assume all six sexual genotypes to be equally fit. Unlike for the case of transitions involving the same chromosome pair, we do not propose a null *expectation* for the fixation probability of the A′ mutation. This is because, if it fixes, it displaces the unlinked X chromosome from the population: this is not the 'population' in which the A′ arises, being a mutated A chromosome. (In contrast, in model 1, the X′ chromosome for example is a mutated X chromosome, and if it fixes, it displaces the X chromosome.) Therefore, we shall focus predominantly on comparing the substitution rates of the A′ and X chromosomes (i.e., the substitution rates, respectively, in directions a and b of Figure 3.3.2). We may, however, take as a *reference* neutral fixation probability for both mutations, ρ^{ref}, that of a mutation of no effect occurring on an autosome: $N\rho^{\text{ref}} = 1/2$.

In our simulations, we find the fixation probability of the A′ chromosome to be $N\rho_{\text{A}'} \approx 1.07$ (Figure 3.5.3A), substantially higher than our reference value of 1/2. This value is insensitive to the genetic background of the initial mutation [246,

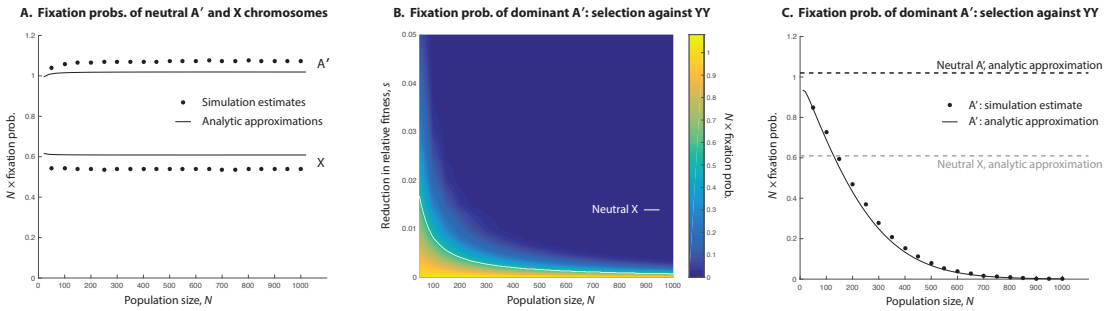

Figure 3.5.3: Fixation probabilities in Model 2 heterogametic transitions. (A) The fixation probability of a neutral dominant feminizing A′ arising in an XX,AA/XY,AA system is substantially higher than the reverse fixation probability, that of a neutral recessive feminizing X chromosome arising in an YY,AA′/YY,AA system. (B) If YY individuals are selected against in the transition from XX,AA/XY,AA male heterogamety to YY,AA′/YY,AA female heterogamety (direction *a* in Figure 3.3.2), the substitution rate of the A′ chromosome causing this transition is reduced. But selection needs to be sufficiently strong to reduce the substitution rate below that of the neutral X chromosome in the reverse transition (above white line), especially in smaller populations. (C) Fixation probability of the A′ chromosome when YY individuals have relative fitness reduction $s = 0.5\%$. Since the reverse transition (direction *b* in Figure 3.3.2) does not involve the production of individuals homozygous for the previously sex specific chromosome (the A′), the substitution rates in the two directions are equal where the declining fixation probability of the A′ intersects the flat neutral fixation probability of the X, here at a population size of only about 150 individuals. For larger populations, the recessive X substitutes at a higher rate than the dominant A′.

Figure S5A]. The average conditional fixation time of the A′ in our simulations is approximately $2.65N$ for each N considered, again regardless of the initial background of the mutation [246, Figure S5B], and again suggestive of drift-like dynamics.

Turning our attention to transitions in the other direction along the equilibrium path (direction *b* in Figures 3.3.2 and 3.3.3B), we begin with a female-heterogametic YY,AA′/YY,AA system, and assume that a mutation on a Y chromosome occurs, rendering the chromosome a recessive feminizing X. If this mutation reaches sufficient frequency, the male-heterogametic system XX,AA/XY,AA establishes.

We estimate in our simulations that the fixation probability of the X is $N\rho_X \approx 0.54$ (Figure 3.5.3A), which is fractionally higher than the reference value of 1/2.

The background on which the mutation arises has no effect on its fixation probability [246, Figure S6A]. The average conditional fixation time of the X chromosome is also close to $2.65N$ for all values of N considered [246, Figure S6B].

To see if there is a directional bias in one direction or the other along the equilibrium path, we assume that these mutations occur at the same rate, u per chromosome per generation, and calculate the substitution rates of the two transitions.

The male-heterogametic system XX,AA/XY,AA generates A′ mutations at rate $\mu_{A'} = 2Nu$, so that the substitution rate from an XX,AA/XY,AA system to a YY,AA′/YY,AA system (in direction a of Figures 3.3.2, 3.3.3B) is about $\mu_{A'}\rho_{A'} = 2Nu \times 1.07/N = 2.14u$. Similarly, the female-heterogametic system YY,AA′/YY,AA generates X mutations at rate $\mu_X = 2Nu$, and so the substitution rate from a YY,AA′/YY,AA system to an XX,AA/XY,AA system (direction b of Figures 3.3.2, 3.3.3B) is about $\mu_X\rho_X = 2Nu \times 0.54/N = 1.08u$, or about half that of the reverse transition.

Again, with no demographic differences between males and females, the transitions symmetric to those above (i.e., in directions c and d in Figure 3.3.3B) occur with fixation probabilities and substitution rates equivalent to those we have estimated above (i.e., the fixation probabilities in directions a and b match those in directions c and d respectively).

We now consider the role of selective differences between the genotypes. This is an especially important question here because, unlike in model 1 heterogametic transitions, model 2 transitions are possible without the production of individuals homozygous for a previously sex-specific chromosome. In particular, the transitions in directions b and d of Figure 3.3.3B change the heterogametic system, but do not involve the production of individuals homozygous for the previously sex-specific

chromosome. In contrast, the reverse transitions (in directions a and c) do involve the production of individuals homozygous for previously sex-specific chromosomes. Since we have found these latter transitions to have higher substitution rates than the reverse transitions in the neutral case, we should expect selection to reduce, and when strong enough to overturn, this bias.

We focus on the transition from the male-heterogametic XX,AA/XY,AA system to the female-heterogametic YY,AA′/YY,AA system (direction a in Figures 3.3.2 and 3.3.3B), involving the substitution of a dominant female-determining A′ chromosome as a mutated A. The Y chromosome is sex-specific in the original XX,AA/XY,AA system, and we assume that it has accumulated deleterious recessive mutations such that the two YY genotypes are of fitness $1 - s$, relative to all other genotypes' fitness of 1. Figure 3.5.3B gives the fixation probability of the A′ chromosome for various values of s and N. Naturally, the fixation probability decreases as selection against the YY genotypes increases, and this effect is stronger in larger populations (in which selection acts more efficiently [124]). Indeed, in large populations, even very small degrees of selection against the YY genotypes are enough to overturn the substitution rate bias in favor of dominant sex determining mutations.

Analytical results

We begin by considering the dynamics of the neutral model. Once again, fast-variable elimination can be used to calculate the effective dynamics of the system along the equilibrium path [see Eq. (3.4)]. For model 2 (as with model 1), $\mathcal{D}(q) = 0$ (that is, there is no deterministic contribution to the dynamics along the equilibrium

path), but there is a drift-induced selection term, which now takes the form

$$\mathcal{S}(q) = \frac{q(1-q)(1+q)^3\left[1+(2-q)q\right]\left\{1+q\left[6-q\left(2-q(10+q)\right)\right]\right\}}{4N\left[1+q(2+5q)\right]^3}, \tag{3.8}$$

which, along with the expression for diffusion along the equilibrium path,

$$\mathcal{B}(q) = \frac{1}{4}\frac{q(1+q)^3\left\{1+q\left[1+q\left(10-q(2+q)(5-q)\right)\right]\right\}}{\left[1+q(2+5q)\right]^2}, \tag{3.9}$$

approximates the stochastic dynamics (calculations in [246, Section S2.2.2]). Recalling that $q = 0$ corresponds to male heterogamety [XX,AA/XY,AA; $p_1 = 1/2$, $p_5 = 1/2$ in Eq. (3.2)], while $q = 1$ corresponds to female heterogamety [YY,AA′/YY,AA; $p_4 = 1/2$, $p_6 = 1/2$ in Eq. (3.2)], we find that the drift-induced selection selects for the fixation of the dominant sex determining mutation *at every point* on the equilibrium path [$\mathcal{S}(q) > 0$ for all $q \in (0,1)$].

As in model 1, we find that demographic fluctuations away from the equilibrium path return to the equilibrium path on average with a bias, described by the drift-induced selection term $\mathcal{S}(q)$. Once again, $\mathcal{S}(q)$ can be split into two components, $\mathcal{S}^{\mathrm{NL}}(q)$ and $\mathcal{S}^{\mathrm{C}}(q)$, that respectively capture the contribution to $\mathcal{S}(q)$ arising from the non-linearity of trajectories taking the system back to the equilibrium path and the curvature of the equilibrium path itself. These terms are plotted in Figure 3.5.4A, in which we see that, as with model 1, it is the curvature of the equilibrium path that contributes most to drift-induced selection in model 2.

Using this single-variable description of the dynamics, the fixation probability for any initial condition q_0 on the equilibrium path can be calculated. In order to determine the fixation probability of mutants in the system starting from a single copy, we need to calculate the mapping, for each initial mutation scenario, from $\boldsymbol{p}_0$

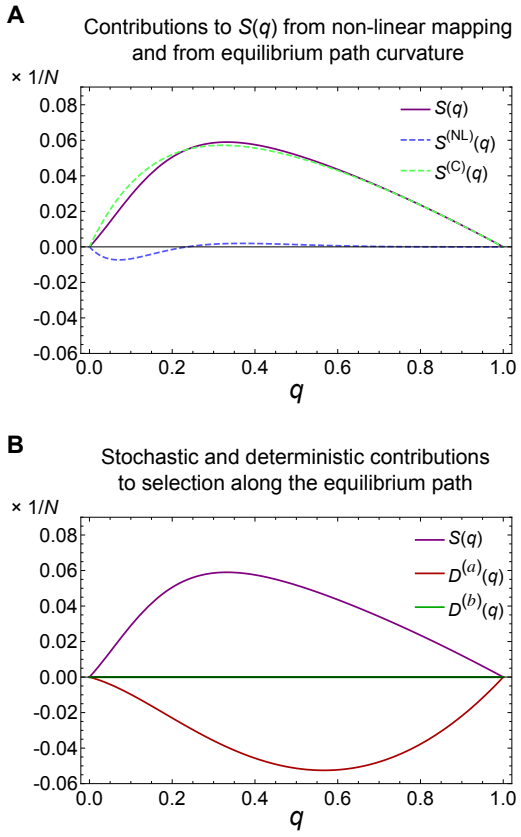

Figure 3.5.4: (A) In model 2, as in model 1, random demographic fluctuations induce a selective gradient $\mathcal{S}(q)$ along the equilibrium path in favor of the dominant sex determining chromosome, i.e., causing q to increase on average [see Eqs. (3.4) and (3.8)]. Again, $\mathcal{S}(q)$ can be divided into two components: $\mathcal{S}^{(\mathsf{NL})}$, from non-linear components of the mapping of fluctuations back to the equilibrium path, and $\mathcal{S}^{(\mathsf{C})}$, from the curvature of the equilibrium path. As in model 1, curvature of the equilibrium path is the primary contributor to drift-induced selection in favor of increasing q. (B) Contributions to average dynamics along the equilibrium path arising from drift-induced selection, $\mathcal{S}(q)$, and deterministic selection against individuals homozygous for a previously sex-specific chromosome, $\mathcal{D}(q)$ [see Eq. (3.4)]. Such individuals are only produced in transitions in direction *a* of Figure 3.3.2, where the initial population is XX,AA/XY,AA male heterogametic, so that $\mathcal{D}^{(a)}(q) < 0$ for all $q \in (0,1)$ [see Eq. (3.10)]. In transitions in direction *b* of Figure 3.3.2, where the initial population is YY,AA′/YY,AA female-heterogametic, no A′A′ individuals are produced, and so $\mathcal{D}^{(b)}(q) = 0$ for all q. In both plots the parameters have been scaled such that $N\delta = 1$ in order to facilitate the comparison of contributions to selection along the slow subspace.

to q_0. This calculation is given in [246, Section S2.3.2]. We can now evaluate our numerical expression for the neutral fixation probability at these initial conditions. Recall that simulations of the Wright-Fisher process showed the fixation probability of the A′ chromosome to be $N\rho_{\mathrm{A}'} \approx 1.07$, higher than our reference value of $1/2$. Our analytical prediction slightly underestimates this fixation probability ($N\rho_{\mathrm{X}} \approx 1.02$; Figure 3.5.3A). The background on which the mutation arises has no effect on its fixation probability, because the two scenarios initially have an identical component q_0 along the slow manifold [246, Section S2.3.2]. The computed mean conditional fixation time of the A′ agrees well with our simulation estimates [246, Figure S5B].

We next consider the fixation probability of an X mutation occurring on an initially autosomal Y. Our Wright-Fisher simulations returned an estimated fixation probability of $N\rho_{\mathrm{A}'} \approx 0.54$. Once again, there is a small discrepancy with our analytical results, which overestimate this value ($N\rho_{\mathrm{X}} \approx 0.61$; Figure 3.5.3A). The fixation probability is again the same irrespective of the background on which the X mutation occurs, because the initial conditions on the equilibrium path are the same [246, Section S2.3.2]. Again, we may compute the mean conditional fixation time of the X, and find good agreement with our simulation estimates when the variance difference between the Wright-Fisher and Moran processes is taken into account [246, Figure S6B].

We now consider the role of selective differences between the genotypes. As we have noted, comparing transitions in directions a and b, only those in direction a involve the production of individuals homozygous for a previously sex-specific chromosome, and so we focus here on transitions in direction a. We assume that the two YY genotypes (with frequencies p_4 and p_6) have elevated death rates $\Delta_4 = 1+s$ and $\Delta_6 = 1+s$ relative to all other genotypes' death rates of 1. The term $\mathcal{D}(q)$ in

Eq. (3.4) now becomes $\mathcal{D}(q) = \mathcal{D}^{(a)}(q)$, where

$$\mathcal{D}^{(a)}(q) = -\frac{s}{16}\frac{q(1-q)(1+q)^2\left[1+(8-q)q\right]}{1+q(2+5q)}. \tag{3.10}$$

$\mathcal{D}^{(a)}(q) < 0$ for all $q \in (0,1)$, and so this term acts in the opposite direction to $\mathcal{S}(q) > 0$ (Figure 3.5.4B; calculations in [246, Section S2.2.2]). There is thus an antagonism between the deterministic contribution to selection $\mathcal{D}^{(a)}(q)$ (favoring transitions in direction b) and the drift-induced selection (favoring transitions in direction a). Which of these dominates depends on the strength of selection and the population size: $\mathcal{D}^{(a)}(q)$ increases with s, while $\mathcal{S}(q)$ decreases with N.

In contrast, since transitions in direction b do not produce individuals homozygous for a previously sex-specific chromosome, none of the genotypes is selected against. Therefore, $\mathcal{D}(q)$ in direction b is $\mathcal{D}^{(b)}(q) = 0$.

Whereas in model 1 selection exacerbated the directionality of switching between sex determining systems (while decreasing the overall switching rate), in model 2 we see that deterministic selection and drift-induced selection work in opposite directions. Thus, for small populations with weak selection, transitions in directions a and c in Figure 3.3.3B occur more often than transitions in directions b and d, while for large populations with strong selection, transitions in b and d occur more often than transitions in directions a and c.

3.6 Discussion

We have studied stochastic evolution along two 'neutral' equilibrium paths connecting male and female heterogamety. We have shown that, even when all genotypes are equally fit, evolution along these paths is not neutral. Instead, it shows significant

substitution rate biases in particular directions, specifically in favor of dominant sex determining mutations. We have demonstrated these biases to be the result of drift-induced selection: random perturbations off the equilibrium path—inevitable in finite populations—return to the equilibrium path with an average directional bias in favor of the dominant segregating sex chromosome. The substitution rates of dominant sex determining mutations that switch the system of heterogamety are, in both of the cases we have studied, higher than those of truly neutral mutations occurring on the same chromosomes.

Evolutionary transitions between male and female heterogamety have been common in the evolutionary history of animals [4, 61, 62, 93, 105, 138, 140, 179], despite the fact that, in any given heterogametic system, the sex-specific chromosome should degrade over time by the operation of Muller's ratchet [32, 34]. To counter this 'evolutionary trap' [24, 199], mechanisms based on direct selective forces have been invoked to explain the frequency of heterogametic transitions (e.g., the operation of sex-specific selection [244]). Our demonstration of drift-induced selection in transitions between male and female heterogamety suggests that mechanisms based on direct selective differences between the sex chromosome genotypes may be unnecessary to explain empirical transitions. We have shown that small fitness reductions to individuals homozygous for previously sex-specific chromosomes are not enough to overturn the biases caused by drift-induced selection (Figures 3.5.1C and 3.5.3B). Large fitness reductions to such individuals (and in the limit, their inviability) render most transitions impossible—the exception being the recessive transitions b and d in model 2.

The influence of drift-induced selection in heterogametic transitions is therefore best understood in terms of evolutionary timescale. From an initial heterogametic

system with homomorphic sex chromosomes, the sex-specific chromosome gradually accumulates recessive deleterious mutations that would reduce the fitness of individuals homozygous for this chromosome. At some threshold period of time of accumulation of these mutations, the fitness reduction of the homozygote reduces the fixation probability of a dominant sex reversal mutation exactly enough to cancel this mutation's drift-induced selective advantage (Figures 3.5.1C and 3.5.3B). Prior to this time threshold, a transition via a dominant sex reversal mutation is likely—it becomes less likely as the threshold is neared. However, progress towards the threshold is reset every time a transition occurs, because each transition creates a new sex-specific chromosome from a chromosome that was previously not sex-specific.

A notable prediction of our findings is that heterogametic transitions should typically involve dominant sex determining mutations. That is, we should expect transitions usually to occur in directions *a* and *c* in Figures 3.3.3A and 3.3.3B, and not in directions *b* and *d*. This general prediction is not unique to our theory. For example, under the theory that heterogametic transitions are driven by linkage between novel sex determining genes and genes with sex-specific fitness effects [244], dominance of the sex determining mutation is either required for a transition, or substantially increases the parameter range over which a transition may occur. However, our analysis does reveal that this prediction can be recapitulated with a minimal number of biological assumptions.

Evidence in favor of this prediction comes from intermediate 'multi-factorial' systems [3]. In the platyfish *Xiphophorus maculatus*, females are XX, WX, or WY, while males are XY or YY [106, 107]. In principle, such a system could have arisen either in directions *a* or *b* of Figure 3.3.3A, depending on the ancestral heteroga-

metic system. Mapping known systems of heterogamety in the genus *Xiphophorus* [229] onto a phylogeny of the clade [49] suggests this ancestral system to be male heterogamety, in which case the intermediate system of *X. maculatus* has arisen in direction *a* of Figure 3.3.3A, via a dominant sex reversal mutation, consistent with our prediction. The western clawed frog, *Xenopus tropicalis*, also has an intermediate system: females are ZW or WW, and males are ZZ, ZY, or WY [202]. This system could have arisen in direction *c* or *d* in Figure 3.3.3A, depending on the ancestral system. The mechanism of sex determination has yet to be determined for most members of the genus *Xenopus* [202, 229], but the well-studied *X. laevis* is female-heterogametic [31], as is *X. borealis* [74]. If female heterogamety is ancestral to the intermediate system of *X. tropicalis*, then this intermediate system would have arisen in direction *c* of Figure 3.3.3A, again consistent with our prediction. Though it is possible that balancing selection operates to stabilize these observed instances of multi-factorial systems (e.g., [167])—with the important suggestion that, because observed instances are rare, most intermediate multi-factorial systems are transitional—the drift-induced selection that we have discovered operating at all points on the slow subspace near the line of equilibria will, even in this case, act so as to make invasion of dominant sex determining mutations more likely.

The prediction that heterogametic transitions should usually involve dominant sex determining mutations can also be tested by reciprocal crosses of species or populations on either side of a recent heterogametic transition, provided the ancestral system is known. In the frog *Rana rugosa*, populations in northern Japan are female-heterogametic, while those in southern Japan are male-heterogametic [154, 164]. The sex chromosomes in these populations are all homologous [234], and so a model 1 transition appears to have occurred. Because the ancestral system

is male heterogamety [165], the candidate directions in Figure 3.3.3A are *a* and *d*. These two directions can be distinguished by crossing a homogametic male (from the north) with a homogametic female (from the south). If the transition occurred in direction *a*, all the offspring from this cross should be male, but if it occurred instead in direction *d*, all the offspring should be female. This test has been carried out using homogametic males from Hirosaki (in the north) and homogametic females from Kumano (in the south), the reciprocal cross of which yielded almost all male offspring [164]. Again, this is consistent with our prediction. [Crossing heterogametic males and females yielded a sex ratio of 1/2 [164], consistent with the model 1 transitions we have studied, though not informative of which direction the transition was in.]

The bias we have found in favor of substitution of dominant sex determining mutations also carries predictions for how the genetic pathways underlying sex determination should look. We have referred throughout to 'sex chromosomes', but in reality we are talking about genes of major sex determining effect, the presence or absence of which acts as a switch to direct development down separate molecular pathways, or sex determining 'cascades', which then produce males and females. The downstream components of these cascades tend to be widely conserved [10], but there is significant lability in the upstream components—through the addition of new sex determining genes to the top of the cascade [259] and the shuffling of genes already in a cascade [205]—suggesting that these cascades evolve 'from the bottom up'. This is consistent with our findings: our model predicts successive transitions involving dominant sex determining mutations, with comparatively few reversals involving fixation of recessive sex determining mutations, and so we expect either the expansion of sex determining cascades, or their shuffling, but seldom their

contraction.

The drift-induced selective force that we have identified is a weak one: when all genotypes are equally fit, it shifts fixation probabilities away from the values expected under neutrality by amounts of order $1/N$. This raises two questions. First, are neutral transitions, even in the direction of the drift-induced bias, empirically relevant, given that they involve fixation probabilities of order $1/N$? Second, would direct selective forces, such as viability differences among genotypes, not overwhelm the drift-induced bias?

On the first question, as with the study of neutral substitutions elsewhere in the genome, this depends on how often the relevant mutations are produced. The extended sex-determining cascades discussed above present a large mutational target: mutations of major sex determining effect can occur at many points along them. These mutations can also occur in many ways, in addition to standard sequence-mutation events: (i) translocation of a gene in a sex determining pathway and a resulting shift in expression or function [36, 228], (ii) duplication and subsequent neo-functionalization of such a gene [11, 205], and (iii) mutation of a major sex determining gene's regulatory elements, such as transcription factors [10, 223]. The frequency of these mutations is evidenced by the heterogeneity of major sex determining genes observed between and within clades [10].

On the second question, it is true that the drift-induced bias we have found becomes very weak as population size increases, while direct selective forces do not. When such selective forces operate—for example, when there is selection against individuals homozygous for a previously sex-specific chromosome—we have argued that drift-induced biases are most likely to be relevant in populations with small effective sizes. One way in which effective population size can be reduced is through

demographic differences between the sexes, for example if males exhibit higher variance in reproductive success. Notice that demographic differences between the sexes also eliminate the symmetry between dominant transitions from male to female heterogamety and from female to male heterogamety, and the same for recessive transitions, so that they also allow the possibility that male or female heterogamety may be favored. In [246, Section S1.3], we have introduced greater variance in male reproductive success for the case of model 1 transitions by altering our baseline population model so that, each generation, a reduced subset of males is randomly chosen to be candidate mates, with the other males denied the possibility of mating. In the neutral case, we find that dominant transitions from male to female heterogamety exhibit a substantially higher substitution rate than in the case with no demographic differences between the sexes [246, Figure S8A], while dominant transitions from female to male heterogamety have a slightly reduced substitution rate [246, Figure S8B]. The substitution rate of recessive transitions from female to male heterogamety is increased marginally relative to the case of no sex differences [246, Figure S8D], while recessive transitions from male to female heterogamety have a significantly reduced substitution rate [246, Figure S8D]. Therefore, the general effect of greater variance in male reproductive success in the neutral case is to exacerbate the bias in favor of dominant sex determining mutations, and to bias evolution towards female heterogamety. When selection against individuals homozygous for a previously sex specific chromosome is taken into account, we expect the results to differ from those under no sex differences for two reasons: because drift-induced selection operates differently in this regime, as for the neutral results just described, and because reducing the number of males eligible to mate reduces the effective population size, rendering the deterministic selection against individuals homozygous

for a previously sex specific chromosome less effective. To illustrate these effects, Figure S10 in [246] displays the fixation probabilities of a dominant X′ chromosome in an initially XX/XY system, with varying strengths of selection against YY males. Compared with the case of no sex differences (Figure 3.5.1C, [246, Figure S10C]), the fixation probabilities of the X′ are greatly increased when males have greater variance in reproductive success [246, Figure S10A,B], so that, even for substantial degrees of selection against YY individuals, the X′ fixes with non-negligible probability. Another effect of the reduced effective population size is that conditional fixation times are substantially smaller than in the case of no sex differences [246, Figure S9].

In comparing the substitution rates of dominant and recessive sex determining mutations, we have assumed that their respective mutation rates, i.e., the rates at which they are generated, are equal. It is possible that this is not the case, and that one class of sex determining mutations is generated more rapidly than the other [3, 93]. If this were the case, it would simply be a distinct mechanism by which we expect one class of sex determining gene to be more prevalent than the other. We should note that this is not as simple as comparing the rates of generation of gain-of-function and loss-of-function mutations. Suppose, for example, that a system is initially XX/XY male heterogametic, and consider a transition in direction a of Figure 3.3.1A, involving fixation of a dominant feminizing X′ mutation. Depending on the molecular functioning of the initial XX/XY system, this dominant X′ could be gain-of-function or loss-of-function. If the Y is initially dominant male-determining (as, e.g., in mammals [10, 118]), then a mutation on the X chromosome that blocks the Y's activity (a gain-of-function mutation) would be dominant feminizing, as we require. If, however, the initial system depends on the ratio of some gene (or

genes) on the X chromosome with respect to autosomes (as in *Drosophila* [10, 15]), then a loss-of-function mutation to a relevant gene on the X chromosome could be dominant feminizing.

We have studied direct transitions between male and female heterogamety. These appear to have been common, at least in vertebrates [61]. However, transitions are also possible between heterogametic and environmental sex determination [18, 19, 94, 188], so that transitions between heterogametic systems could also occur via an intermediate system of environmental sex determination.

We have identified the force driving our results to be drift-induced selection operating along the equilibrium path (in the neutral case) or in its near vicinity (in the case with selection). While drift-induced selection as a force in natural selection has analogs that have been known for some time (e.g., Gillespie's criterion [78, 79], and selection in favor of reduced variance in offspring sex ratios [226, 250]), the demonstration that it acts endogenously in systems of biological interest is relatively recent [43, 45, 115, 129, 174]. We suspect that drift-induced selection will come to be recognized as an important force in many dynamical systems in population biology.

4

Sexual antagonism and the instability of environmental sex determination

4.1 Abstract

The sex of an organism can be determined by its genetics or by its early environment. Across the animal kingdom, genetic sex determination (GSD) is far more common than environmental sex determination (ESD). Here, we propose an explanation for this pattern: the coupling of genes that bias offspring sex ratios toward one sex with

genes that are beneficial in that sex but costly in the other. Gradual strengthening of the sex-specific tendency of this association eventuates in a neo-sex chromosome, i.e., GSD. Our model predicts to which system of heterogamety ESD will evolve when nesting behavior is an important determinant of brood sex ratios. It explains the puzzling observation in some GSD species of sex reversal induced by extreme environments. The model also suggests an approach to discovering sex determining genes in ESD species.

4.2 Introduction

The dominance of GSD over ESD across the animal kingdom is well illustrated in vertebrates (Fig. 4.2.1), where the most prevalent form of GSD, heterogamety, is far more common than the most prevalent form of ESD, temperature-dependent sex determination (TSD) [4, 10, 19]. A similar preponderance of GSD, and heterogamety in particular, is found in invertebrates [4, 10, 19].

This pattern is unexpected, because ESD allows a species to take advantage of environmental variation that differentially affects the fitness of sons and daughters—the Charnov-Bull effect [17, 39, 218, 254, 255]—while GSD does not. For example, it could be that developing at warmer temperatures is beneficial for offspring of both sexes, owing to more rapid development, but that the benefit to female offspring is greater than that to male offspring (Fig. 4.2.2). In this case, a system of TSD where offspring incubated above some threshold temperature develop as female, while those incubated below the threshold temperature develop as male, is evolutionarily stable, including against invasion of GSD [17, 38] (Fig. 4.2.2 and [161, Section S1, S2]). This system—'females high, males low'—is common in reptiles with TSD, especially turtles [16, 98]. If, instead, males benefit more from developing at higher tempera-

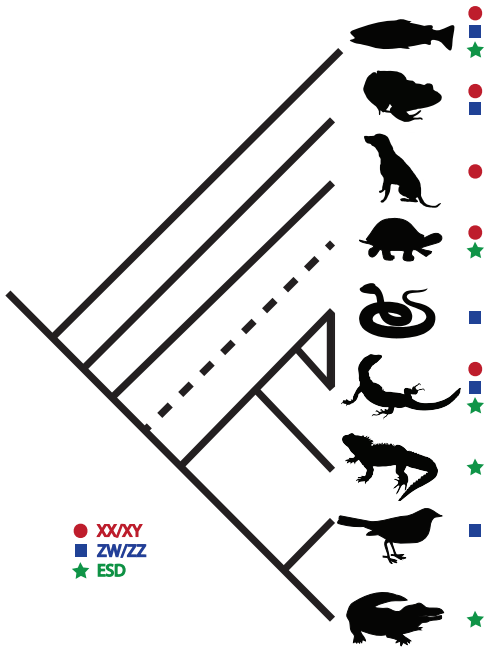

Figure 4.2.1: Genetic sex determination dominates environmental sex determination in vertebrates. Cladogram of vertebrates illustrating the sex determination mechanisms found in all major groups. Genetic sex determination (GSD) has been split into male heterogamety (XX female, XY males) and female heterogamety (ZW females, ZZ males). For fish, only gonochoric species (species with separate males and females) have been included. While information for many species is not available, it is clear that GSD is far more common than environmental sex determination (ESD) across all clades. The ancestral sex determining mechanism for all vertebrates is probably GSD [99], but phylogenetic reconstructions of clades within vertebrates, such as squamates (for whom ESD is probably ancestral [179]), indicate multiple independent transitions from ESD to GSD within each group, with many fewer transitions in the reverse direction, suggesting an inherent instability of ESD [166].

tures, then the stable TSD system is reversed: offspring above a certain threshold temperature develop as male, and those below as female—this 'males high, females low' system is observed in all known fish species with TSD [168].

Explanations for why GSD dominates, despite this advantage to ESD, have focused on sex ratio fluctuations under ESD caused by environmental perturbations [16, 17, 19, 56, 209]; these fluctuations are avoided under GSD. But this selective disadvantage of ESD can be mitigated by responsive maternal nesting behavior [16, 25, 27, 153, 159, 192] and long lifespans [22, 209]. A more robust explanation for the observed instability of ESD is lacking. Here, we propose an explanation based on factors that are expected to operate in all ESD populations, whether or not they can mitigate the problems associated with fluctuating sex ratios in variable environments.

4.3 Results and discussion

Our model is set in a population initially with TSD. We assume underlying fitness effects that lead to a 'females high, males low' system, as described above (Fig. 4.2.2), although our model also applies, with appropriate modifications, to fitness effects that result in the other forms of TSD. Each embryo has a specific 'threshold' temperature θ; if incubated above this temperature, it develops as female, and if below, as male. An embryo's threshold temperature is determined by multiple genes [25, 27, 144, 146]. Allelic variation at these 'threshold loci' results in shifted thresholds: some individuals will develop as female at a slightly lower temperature or a slightly higher temperature than the population average [25, 97, 98]. We shall refer to alleles that decrease their bearers' thresholds as 'female biasing', and those that increase their bearers' thresholds as 'male biasing'. This genetic

variation in thresholds makes our model of a form described as being between GSD and TSD in recent mechanistic models of sex determination [85, 188, 208], though we do not model the mechanistic basis of the genotype-to-phenotype mapping, as these models do [85, 176, 188, 208]; our model is also consistent with more classical models of TSD [27]. In deriving the analytical results below, we assume that almost every individual in the population initially exhibits a threshold close to the evolutionarily stable threshold, θ^* (Fig. 4.2.2b). We later relax this assumption in numerical simulations of our model, to verify that our analytical results are robust to the existence of appreciable initial threshold variation in the population. Environmental temperature varies across the population's range, so that some patches produce mostly males or mostly females (Figs.4.2.2a, 4.3.1a). Under the assumed fitness effects, the population sex ratio associated with the stable average threshold θ^* is expected to be slightly male biased (the proportion of males $m > 1/2$) [17, 38].

We now assume that, at a distinct locus, a new allele arises that does not affect the threshold but confers a fitness benefit s_f when expressed in females, and a fitness cost s_m when expressed in males. We assume this allele to be dominant to the wild-type allele, and $s_m > s_f$, so that the allele is, averaged across the sexes, costly to bear. Such 'sexually antagonistic' alleles are common throughout the genomes of sexual organisms [86, 194, 198], and have been invoked elsewhere in the evolution of sex determining mechanisms to explain why GSD species typically have only one major sex determining gene [196] and to explain transitions within and between heterogametic GSD systems [243, 244]. For brevity, we shall refer to the allele as a 'female-beneficial' allele. If the female-beneficial allele arises on the same chromosome as a threshold locus with a rare dominant female-biasing allele—i.e., one that codes for a lower-than-average threshold $\theta' < \theta^*$, producing a proportion

$m' < m$ of males (Figs. 4.2.2, 4.3.1b)—then the initial TSD system is unstable with respect to invasion of the female-beneficial, female-biasing haplotype if the following condition holds (all mathematical details in [161, Methods and Section S1-3]):

$$\frac{s_f}{2}\left(1-m'\right)\overline{W'_{\female}} - \frac{s_m}{2}m'\overline{W'_{\male}} - s_T > \frac{r}{1-r}. \tag{4.1}$$

Here, r is the rate of recombination of the two loci—the right hand side of Eq. (4.1) is an increasing function of r, ranging from 0 (when $r = 0$) to 1 (when $r = 1/2$). s_T is the marginal fitness cost of bearing the female-biasing threshold allele, ignoring the presence of the female-biasing allele. This cost stems from the fact that the mutant threshold allele systematically causes its bearers to develop as female in some environments where male development would be optimal (Fig. 4.2.2). The general form of s_T is given in Fig. 4.2.2, and derived in [161, Methods]. It depends on various factors, including the size of the difference between the two thresholds θ^* and θ', the nature of the underlying Charnov-Bull fitness functions, and the temperature distribution. Some numerical examples of s_T are given in [161, Figure S3]. $\overline{W'_{\female}}$ and $\overline{W'_{\male}}$ are the average fitnesses of, respectively, female and male bearers of the female-biasing threshold allele who do not bear the female-beneficial sexually antagonistic allele. Therefore, $s_f\left(1-m'\right)\overline{W'_{\female}}/2 - s_m m'\overline{W'_{\male}}/2$ is the marginal benefit of having the mutant female-beneficial allele, conditional on also having the female-biasing threshold allele.

Condition (4.1) is easier to satisfy when the fitness cost to males of the sexually antagonistic allele is not much larger than its fitness benefit to females ($s_m \approx s_f$), and when the female-biasing and female-beneficial alleles are tightly linked (r is small) so that their haplotype is seldom disrupted by recombination. Some numerical examples of values of r for which the haplotype can invade, under reasonable

specifications of the temperature distribution and fitness functions, are given in Fig. 4.3.2. These examples show that the haplotype can invade even when the two loci recombine at an appreciable rate (above 4% in some cases).

We note two caveats to the invasion analysis above. First, we have assumed that almost every individual in the population initially exhibits a threshold close to the evolutionarily stable threshold, θ^*. This assumption was made for the purpose of deriving the simple analytical form of condition (4.1), but ESD populations in fact exhibit considerable threshold variation [25, 97, 98]. To investigate whether condition (4.1) accurately predicts the invasion of the female-biasing, female-beneficial haplotype arising in a population with substantial threshold variation, we turn to simulations of our model. Specifically, we include three or four 'regular' threshold loci along a single chromosome, each segregating for two alleles, one male-biasing and one female-biasing. These regular threshold alleles influence their bearer's threshold in an additive fashion (the model is described in detail in [161, Section S7]). Imposing a normal distribution of temperature across patches and Charnov-Bull fitness effects as described above, we allow the population to evolve for 1000 generations, by which time a stable distribution of genotypes is attained, with an expected male-biased sex ratio (Fig. 4.3.3, Table S1), but with substantial threshold variation (Table S1). We introduce into this population a rare female-biasing, female-beneficial haplotype, and observe if it goes on to attain appreciable frequency (i.e., if it invades). The results are presented in Figs. S5-12, and demonstrate that condition (4.1) is a good predictor of the conditions for invasion when there is initial threshold variation in the population.

Second, we have assumed that both the female-biasing and female-beneficial (and

male-costly) alleles are initially present at low frequency in the population. This could occur if one of the alleles is initially present at a low-frequency mutation-selection balance when the other is introduced into the population by mutation, or if both are initially at mutation-selection balance. It could also occur if the alleles recurrently appear by mutation—though each will usually appear in isolation of the other, and therefore will often go extinct by drift or selection, at some point in evolutionary time the two mutations are expected to co-occur in the same population. This second possibility would imply much less frequent invasion of the haplotype than the first. It is also possible that one of the mutations is initially at a medium-frequency mutation selection balance, instead of the low initial frequency we have assumed in our analysis—this would be expected simply to improve the prospects for invasion of the female-biasing, female-beneficial haplotype.

Our model, and the invasion condition (4.1), bear similarities to W.R. Rice's classic model of, and condition for, the instability of polygenic sex determination with respect to genes of major sex-determining effect [196]. There are key conceptual and biological differences between the models, however. We have directly modelled the Charnov-Bull fitness effects that are thought to be the underlying evolutionary reason for ESD; Rice's model does not, and therefore better applies to other polygenic systems. In addition, Rice's model invokes the spontaneous appearance in the population of a mutation of major sex determining effect (e.g., the *SRY* gene in mammals), while our model invokes already-existing polygenic variation in thresholds, known to be present in populations with TSD [25, 27]. A major sex determining genetic complex is expected eventually to evolve in our model (see below), but it does so gradually, instead of appearing spontaneously as a single, large-effect mutation. We shall demonstrate that this gradual evolution of a sex chromosome

has novel empirical implications, distinct from the implications of Rice's model.

The initial invasion of the female-biasing, female-beneficial haplotype causes the population sex ratio to become more female-biased, which selects for male-biasing threshold alleles in the genome (Figs. 4.3.1c, 4.3.3). Importantly, this selection for male-biasing alleles does not apply to regions tightly linked and in phase with the female-biasing, female-beneficial haplotype, because of the strong selective disadvantage of the haplotype in males. The increase in frequency of male-biasing alleles evens the population sex ratio, relaxing the Fisherian sex ratio selection acting against the female-biasing, female-beneficial haplotype, which can therefore increase further in frequency (Figs. 4.3.1c, 4.3.3). The simulation results that we described previously verify this, showing that the haplotype goes on to attain appreciable frequency after initial invasion (5-25% [161, Figure S5-12]). This is despite our model of multiple threshold loci being highly restrictive, involving, for computational reasons, only a single chromosome with four or fewer threshold loci in addition to the focal locus.

As the haplotype increases in frequency, selection simultaneously acts to reduce recombination between its two loci, because of the average deleterious effect of the female-beneficial allele when uncoupled from the female-biasing allele. If recombination is shut down between the loci (for example, via an inversion), the haplotype becomes, in effect, a single female-biasing, female-beneficial allele [19, 33, 35, 69, 197]. Then, by the same logic as that described above, further female-biasing or female-beneficial alleles that arise near the haplotype will couple with it, creating a larger and larger haplotype that is successively more female-biasing and female-beneficial. This further selects for male-biasing alleles elsewhere in the genome. The end result of this process is a haplotype whose bearers develop as females and whose non-

bearers develop as males under all experienced environmental conditions—that is, a major sex determining factor1 on a neo-W chromosome (Fig. 4.3.1d). We have investigated this process using the simulation model described above. Technical details are in [161, Methods and Section S8]. An example of the gradual evolution of a W chromosome in our simulations is displayed Fig. 4.3.3. There, it can also be seen that the population sex ratio gradually shifts from the male-biased sex ratio expected under ESD with the Charnov-Bull fitness functions we have assumed to the even sex ratio expected under heterogamety. Moreover, mutations that weaken either the female-biasing or female-beneficial tendencies of the haplotype on its way to defining a W chromosome fail to invade [161, Fig. S13], suggesting that the process is irreversible.

The process described above involves the coupling of female-biasing threshold alleles and female-beneficial sexually antagonistic alleles, which leads to a neo-W chromosome and female heterogamety. The symmetric alternative, also possible, is the successive coupling of male-biasing and male-beneficial alleles, leading to a neo-Y chromosome and male heterogamety. A condition similar to Eq. (4.1) can be derived for the invasion of male-biasing, male-beneficial haplotypes [161, Section S4]. These haplotypes can invade if they do not reduce female fitness too much relative to their benefit to male fitness, and if their two loci do not recombine too often. Examples of recombination rates for which male-biasing, male-beneficial haplotype can invade are given in Fig. 4.3.2, and, like for the invasion of female-biasing, female-beneficial haplotypes studied above, can be appreciable.

Despite these similarities, genetic or demographic differences between the sexes might render the invasion of a male-biasing, male-beneficial haplotype more or less likely than a female-biasing, female-beneficial haplotype. For example, a lower

rate of recombination in males relative to females, as observed in many species [232], would allow male-biasing and male-beneficial alleles to couple more tightly—their average rate of recombination being lower because they are more often found in males—promoting the invasion of male-biasing, male-beneficial haplotypes over female-biasing, female-beneficial haplotypes (this is formalized mathematically in [161, Section S5] and displayed in [161, Fig. S4]). This would bias evolution towards male heterogamety, an argument that has previously been given by Trivers for genes of major sex-determining effect [232]. The argument presented here is made especially relevant by the finding of extremely reduced male recombination in a species with TSD, the saltwater crocodile [150].

We have thus far invoked threshold alleles, expressed in zygotes, as a source of heritable sex ratio bias. An alternative and common source of heritable variation in offspring sex ratios is maternal nesting behavior [16, 25, 27, 144, 145, 153, 159, 192]. Applied to our model, the coupling of female-beneficial sexually antagonistic alleles with alleles that cause mothers to nest, for example, in warmer patches (and therefore to produce predominantly female offspring) will eventuate in a neo-W chromosome and female heterogamety. Importantly, male heterogamety is a much less likely result in this 'maternal behavior' scenario, because it would require the repeated expression of male-beneficial (and female-costly) alleles in mothers (this argument is formalized mathematically in [161, Section S6], for the case where Charnov-Bull fitness effects are absent; a similar logic has been given by Tanaka and Iwasa [224] for the different potentials for spread of a Japanese superstition under matrilineal and patrilineal transmission). Sex ratio biases from maternal nesting behavior can arise in many ways, including nest-site choice, nest construction, nesting timing, and the duration of incubation [25, 153, 159], so this route to heterogamety might not be

infrequent relative to that involving threshold alleles acting in embryos. If so, transitions from ESD to female heterogamety should be more common than from ESD to male heterogamety, a pattern that has been observed within reptiles (including birds) [166]. The observed preponderance of male over female heterogamety [19, 93] would then seem to have to be explained by biased transitions between these two systems [93, 242, 244, 246].

Searching for threshold genes in TSD species is an area of active research [141, 207], but is extremely difficult, as males and females have identical genomes, and large-scale gene expression assays at multiple points in development are required. Our model predicts that, in a species that has recently evolved GSD from ancestral TSD (examples in Table 4.3.1), the sex chromosomes will contain ancestral threshold genes (possibly including genes that have translocated from other chromosomes), and moreover, are likely to be enriched for them, relative to other chromosomes. If so, examining the sex chromosomes of species with newly evolved GSD, or their homologs in closely related TSD species (Table 4.3.1), will more readily uncover candidate loci for threshold genes—these can then be studied more closely by measuring expression during development. The jacky dragon, *Amphibolurus muricatus*, is already a model organism for the study of TSD [254, 255], and so, together with the closely related *A. norrisi* (GSD), represents an especially promising species in which to apply this method of search for TSD genes.

Recent evidence suggests that some species previously thought to exhibit exclusively genetic sex determination in fact also exhibit an environmental component at extreme temperatures [10, 94, 187, 189, 235]. Our model for transitions from TSD to GSD can explain this 'environmental override' phenomenon in two ways. First, it could be a late intermediate stage in the gradual transition to true GSD, when

Table 4.3.1: Species in which to search for threshold genes. Closely-related squamate species in clades with ancestral temperature sex determination (TSD), one with the ancestral TSD, and one with recently evolved genetic sex determination (GSD) [179]. Our model predicts that the new sex chromosomes in the GSD species, or their homologs in the TSD species, will be a fruitful place to search for TSD genes.

Genus with ancestral ESD	ESD species	GSD species
Amphibolurus (Agamidae)	*A. muricatus*	*A. norrisi*
Ctenophorus (Agamidae)	*C. pictus*	*C. fordi*
Phelsuma (Gekkonidae)	*P. ornata*	*P. guimbeaui*
Furcifer (Chamaelionidae)	*F. pardalis*	*F. lateralis*

thresholds in the population are shifted towards the extremes of the environmental temperature distribution (Fig 3c,d), so that TSD still operates at these extreme temperatures. Second, our model predicts that thresholds will diverge until, but not further than the point where some genotypes develop as females at all commonly experienced temperatures, while the rest develop as males at all commonly experienced temperatures. The selection we have modelled acts only weakly outside of the range of commonly experienced temperatures. TSD would therefore be expected still to operate at uncommon temperatures, until a gene of major sex determining effect evolves.

For clarity, we summarize the predictions of our model: (1) Transitions from ESD to female heterogamety should be more common in clades with intensive maternal nesting behaviour. This prediction could be tested in a comparative phylogenetic framework. (2) In GSD systems that have recently evolved from ESD, the sex chromosomes should be enriched for genes that were involved in the ancestral ESD system, e.g., genes affecting thresholds if the ancestral system was TSD. Such genes could be identified by sequencing the sex chromosomes of the GSD species or their homolog in a closely related ESD species; candidates identified in this fashion could then be experimentally verified using gene expression assays in the related ESD

species. We have listed some promising candidate species for such testing in Table 4.3.1. (3) 'Mixed' ESD-GSD systems, where at most temperatures sex is determined by the presence or absence of a particular chromosome, but with sex reversal at extreme temperatures, are a natural expectation under our model. Moreover, the pattern of sex reversal is expected to respect the ancestral ESD system. For example, since all known TSD fish species exhibit a 'males high, females low' system, we expect any transitions from TSD to GSD in fishes to be from this particular TSD system. If sex reversal occurs in a derived GSD species, then our model predicts that it should take the form of reversal to male development at very high temperatures, or reversal to female development at very low temperatures. Indeed, all clear cases of sex reversal in GSD fishes involve male development at very high temperatures [168, 175]. We should note that this final prediction, concerning the precise patterns of environmental override in derived GSD species, is unlikely to be unique to our model.

Our arguments can also explain transitions from hermaphroditism (simultaneous or sequential) to dioecy/gonochorism, as a result of the coupling of alleles that increase or prolong female function with alleles that improve female function and worsen male function (or, of course, coupled alleles with the opposite effect). The timing of the transition between sexes in simultaneous hermaphrodites, and the allocation of reproductive expenditure on female and male function in simultaneous hermaphrodites, are both theoretically analogous to the threshold temperature in species with temperature sex determination [37, 39, 77]. Both sequential and simultaneous hermaphroditism are rare among animals, the latter especially so when considering only non-selfing organisms [4, 77, 108]. This rarity of hermaphroditism is in spite of its plausible advantages [40, 77, 108, 108], and, we propose, may be

the result of sexual antagonism coupled with genetic variation for allocation of reproductive expenditure to each sex.

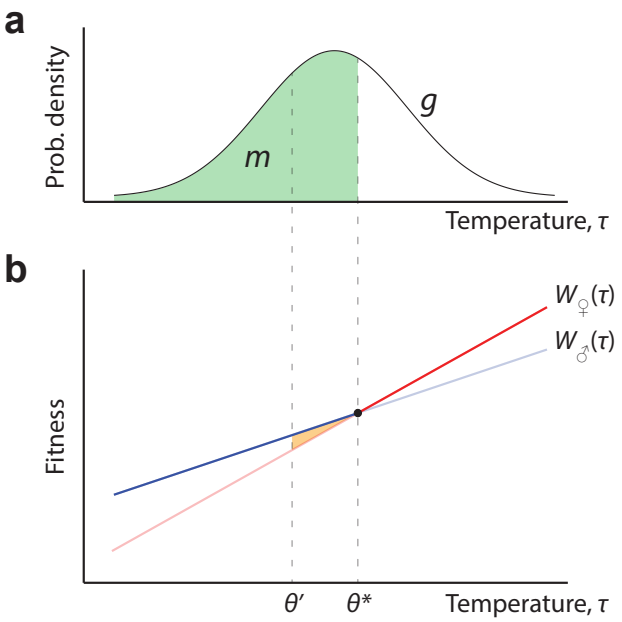

Figure 4.2.2: The advantage of environmental sex determination: exploiting sex-specific benefits of different environments. An example of Charnov-Bull fitness functions [39] that lead, in the absence of other forces, to an evolutionarily stable system of temperature sex determination. a, Temperature τ is distributed across regions in the environment according to the distribution g. b, Offspring of both sexes benefit from developing at higher temperatures, but female offspring benefit more: Female fitness as a function of temperature, $W_{♀}(\tau)$, is steeper than male fitness, $W_{♂}(\tau)$. These fitness functions are derived from underlying male and female viabilities (or fertilities or fecundities); the calculations for this derivation are given in [161, Methods and Section S2]. With these fitness functions, there is a threshold temperature θ^* such that the following system of temperature sex determination is evolutionarily stable: offspring develop as female when incubated at temperatures above θ^*, and as male when incubated below θ^*. The stable threshold θ^* satisfies $W_{♀}(\theta^*) = W_{♂}(\theta^*)$, and in this case is associated with a male-biased sex ratio (proportion of males $m > 1/2$) [21, 37]. When almost all members of the population have thresholds close to θ^*, a rare mutant with a deviant threshold $\theta' < \theta^*$ suffers, all else equal, a fitness cost $s_T = \frac{1}{2}\int_{\theta'}^{\theta^*} \left[W_{♂}(\tau) - W_{♀}(\tau)\right] g(\tau) d\tau > 0$ (see [161, Methods] for details of this calculation). Graphically, this fitness cost is half the area of the orange shaded triangle in b, weighted according to g.

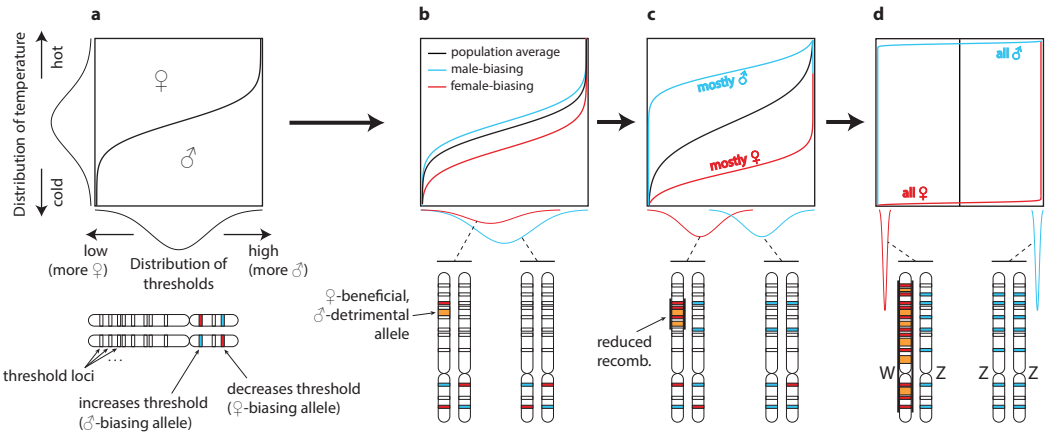

Figure 4.3.1: Genetic sex determination evolves from temperature sex determination via sexually antagonistic genes. An illustration of our general model. a, The population initially exhibits temperature sex determination, with embryos becoming female at high temperatures and male at low. There is variation in threshold temperatures (x axis), owing to male-biasing and female-biasing threshold alleles segregating in the population, but the average embryo has an approximately even chance of developing as male or female given the prevailing distribution of environmental temperatures (y axis). b, A female-beneficial sexually antagonistic allele arises near a female-biasing threshold allele. If they are sufficiently tightly linked [Condition (4.1)], this female-biasing, female-beneficial haplotype increases in frequency, shifting the population sex ratio towards a slight female bias. c, As the female-biasing, female-beneficial haplotype increases in frequency, male-biasing alleles are selected for elsewhere in the genome, to compensate for the population's female bias. Simultaneously, there is selection for reduced recombination between the female-biasing and female-beneficial alleles in the haplotype. The effect of these two selection pressures is to allow the haplotype to increase further in frequency. Those embryos that bear it have low threshold temperatures, and therefore develop as female under most temperatures; non-bearers have high threshold temperatures, and therefore develop as male under most temperatures. d, The female tendency of the haplotype attracts further linked female-biasing and female-beneficial alleles, which in turn selects for reduced recombination within the growing haplotype, as well as more male-biasing alleles elsewhere in the genome. Eventually, embryos that bear the haplotype develop as female at all experienced temperatures, while non-bearers develop as male at all experienced temperatures. Sex in the population is then genetically determined, with the haplotype on a neo-W chromosome.

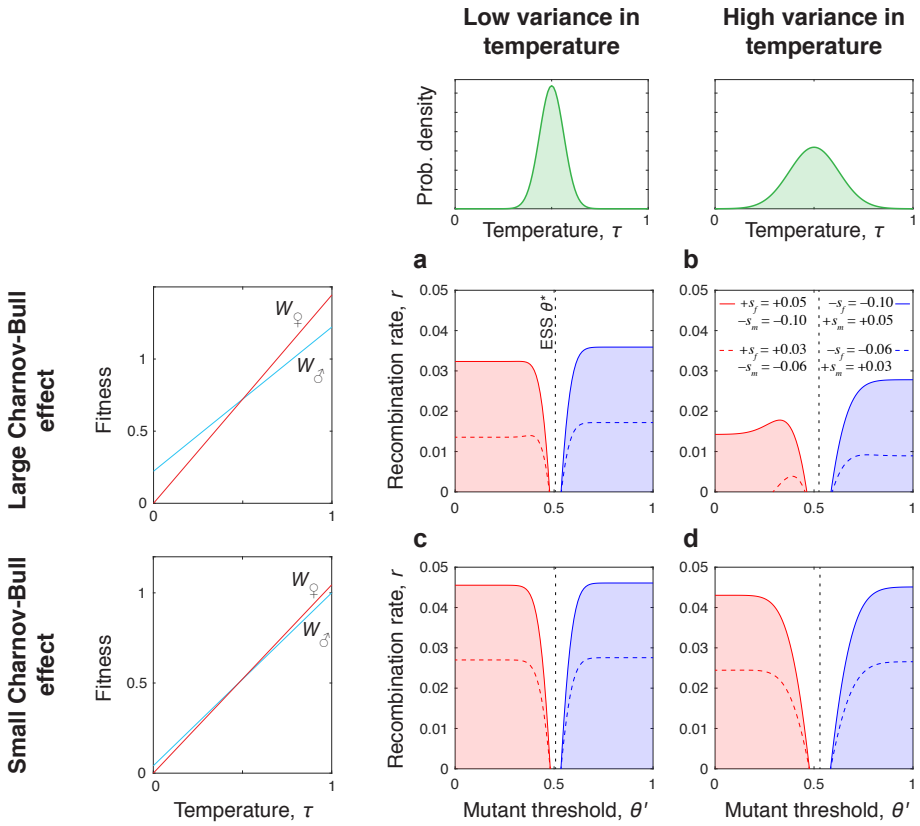

Figure 4.3.2: For sensible empirical specifications of the temperature distribution (normal) and of male and female fitness functions (linear), the figure shows the maximum recombination rates below which female-biasing, female-beneficial (red shading) and male-biasing, male-beneficial (blue shading) haplotypes can invade a population with temperature sex determination. Recombination rates are the same in both sexes. In general, both female-beneficial, female-biasing haplotypes and male-biasing, male-beneficial haplotypes can invade even with appreciable recombination of their constituent alleles. Their invasion is more likely when Charnov-Bull fitness effects are minor (c, d) and the temperature distribution exhibits lower variance (a, c). Invasion is least likely under conditions of high temperature variance and large Charnov-Bull effects (b), but even then, is possible for reasonable recombination rates (up to about 2.5% for the parameters considered here). Details: Temperature is distributed normally with mean $1/2$ and standard deviation $1/16$ ('low variance') or $1/8$ ('high variance'). Individuals homozygous for the wild-type allele a that develop at temperature have viability $V_{♂}(\tau) = k + \tau$ if male and $V_{♀}(\tau) = \lambda\tau$ if female, with $= 1 + 2$k. For 'large Charnov-Bull effect', $k = 2/9$; for 'small Charnov-Bull effect', $k = 2/90$.

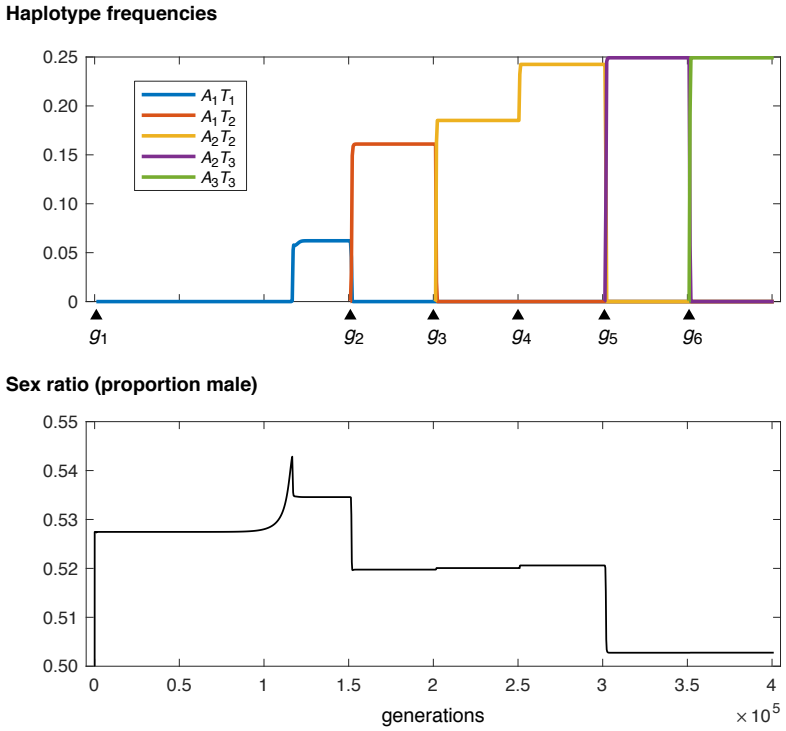

Figure 4.3.3: Gradual evolution of GSD from TSD. After the initial invasion of a female-biasing, female-beneficial haplotype A_1T_1 (in generation g_1), mutations that successively strengthen the female-biasing tendency (T_2 and T_3) and female-beneficial tendency (A_2 and A_3) of the haplotype, as well as the shutting down of recombination between its constituent loci in generation g_4, lead it to attain higher and higher frequency. Eventually, the haplotype is at 25% frequency, and causes almost all its bearers to develop as female. At this point, the haplotype essentially defines a W chromosome, and sex is determined genetically according to a system of female heterogamety. In the gradual transition from TSD to GSD, the sex ratio of the population moves from the male-biased sex ratio that is stable under TSD with the Charnov-Bull fitness effects we have assumed to an almost even sex ratio, as expected under GSD. Simulation details: Model as described in [161, Section S8]. Initial recombination rate between the focal viability and threshold loci: 1%. Temperature distribution and Charnov-Bull effects as in Fig. 4.3.2a. An individual's baseline threshold is determined additively by the number of male-biasing alleles at four regular threshold loci (those in addition to the focal threshold locus): threshold 0.20 if 0/8 male-biasing alleles, threshold 0.50 if 4/8 male-biasing alleles, threshold 0.80 if 8/8 male-biasing alleles. Threshold reductions caused by (dominant) alleles T_1, T_2, and T_3 are 0.1, 0.2, and 0.3 respectively. Fitness effects of sexually antagonistic alleles: A_1: $s_f = +0.04$, $-s_m = -0.08$; A_2: $s_f = +0.06$, $-s_m = -0.12$; A_3: $s_f = +0.08$, $-s_m = -0.16$.

5

Mating preferences of selfish sex chromosomes

5.1 Abstract

The evolution of female mating preferences for harmful male traits is a central paradox of sexual selection [1, 2, 68, 81, 110, 123, 183, 231, 264]. Two dominant explanations of this paradox [117, 183] are Fisher's runaway process, based on genetic correlations between preference and trait [68, 110, 123], and Zahavi's handicap principle, where the trait is an honest costly signal of male quality [81, 182, 183, 264]. However, both require exogenous initial spread of female preferences before harmful

male traits can evolve [68, 81, 110, 123, 182, 183, 264]. Here, I present a novel mechanism for the evolution of female preferences for harmful male traits, based on the selfish evolutionary interests of sex chromosomes. I demonstrate that female-biased genetic elements, such as the W and X sex chromosomes, will evolve mating preferences for males who display traits that reduce fitness in males but increase fitness in female offspring. W-linked preferences, in particular, can cause nearly-lethal male traits to sweep to fixation. Sex-linked preferences can drive the evolution of traits such as ornamental handicaps and male parental care, and can explain variation in ornamentation and behaviour across taxa with divergent sex-determining mechanisms.

5.2 Introduction and Results

Females' mating preferences should evolve to maximize total offspring fitness [2]. Intra-genomic conflict complicates this picture, because females can carry multiple genetic elements with sex-biased transmission [28, 86]. This is clearest for the W chromosome in female-heterogametic (ZW) species such as birds: while autosomes spend as many generations in males as in females, the W is only ever carried by females [4, 28, 86]. A preference encoded on the W should therefore evolve to maximize the total fitness of daughters, with no regard for the fitness of sons (to whom it is not transmitted).

Traits that increase daughters' fitness at the expense of the fitness of fathers or sons can take many forms. One major category is sexually antagonistic traits, which increase fitness in one sex but reduce it in the other [86, 195]. Such traits are common in natural populations [41, 46, 96, 241]. Usually, to avoid elimination by natural selection, a sexually antagonistic trait must confer a fitness advantage when

averaged across the sexes, or it must be sex-linked [86, 195]. In all previously studied scenarios, these conditions limit the fitness cost that can be imposed on the sex for which the trait is deleterious. Here, I show that this is no longer true when mating preferences for sexually antagonistic traits are encoded on a sex chromosome.

Previous theoretical work has separately considered the roles of sexual antagonism [1, 213], sex-linkage [113], sex determination [90, 190], and reinforcing female preferences [213, 231] in sexual selection. However, no previous model has examined the co-evolution of sex-linked female preferences for autosomal, sexually antagonistic traits.

To examine this process, consider a two-locus population genetic model of a ZW species, with an autosomal 'trait' locus and a W-linked 'preference' locus (full details in [160, Methods]). Z-linked and X-linked preferences will be considered later. Two alleles segregate at the trait locus: a wild-type allele t, and a mutant allele T that increases female viability (by a factor $1+s_f$ for TT homozygotes and $1+h_T s_f$ for Tt heterozygotes) but reduces male viability (by $1-s_m$ for TT and $1-h_T s_m$ for Tt). The alleles mutate to one another at a symmetric rate u per replication. I assume that $s_m > s_f$, so that T is selected against in the absence of other forces. Two alleles segregate at the W-linked preference locus: the wild-type p, and the mutant P, bearers of which (always female) have a greater propensity to mate with trait-expressing males, by a factor $\alpha > 1$ for TT males and α^{h_T} for Tt males. I assume $h_T = 1/2$ (co-dominance) for the main results, though their qualitative features do not depend on this [160, Extended Data Fig. 1].

It can be proven that, as long as the trait locus is polymorphic, the preference allele P increases in frequency [160, SI]. Therefore, given a source of persistent trait polymorphism (e.g., recurrent mutation, or migration from a population with

reduced selection against the trait), P will fix (Fig. 5.2.1). This positive selection arises indirectly. By inducing its bearers to preferentially mate with T-bearing males, P generates a positive genetic correlation between itself and T. Because T increases fitness in females, and P is present only in females, this positive association causes P to rise in frequency.

The strength of positive selection acting on P depends on several factors. For example, it increases with the strength of the preference induced by P, and with the fitness advantage of the trait in females. To investigate the strength of selection in favour of P, I compared the strengths observed in several configurations of the model to those observed in the standard two-locus autosomal model of Fisherian sexual selection [110]. Selection for low-frequency W-linked preferences is consistently stronger—often by orders of magnitude—than selection for analogous autosomal preferences, even when the latter start at the high frequencies required for the trait to spread [160, SI].

Selection on T depends on its cost in males, its benefit in females, and the proportion of females carrying P. If the strength of the preference, α, is sufficiently large ($\gtrsim 1/[(1-s_m)(1+s_f)]$; [160, SI]), there is a frequency of P above which selection favours T. Because P inevitably rises to fixation, this threshold is eventually exceeded, and T spreads. This equilibrium is one where many males exhibit a trait that severely impairs their survival, and all females exhibit a strong mating preference for these low-viability males (Fig. 5.2.1; [160, Extended Data Fig. 2b]). This can occur even for traits that are nearly lethal to males while conferring only a small advantage to females (Fig. 5.2.1d). If, instead, $\alpha \lesssim 1/[(1-s_m)(1+s_f)]$, T remains at low frequency, even after P has fixed. In this equilibrium, all females prefer low-viability males, despite those males being nearly absent (Fig. 5.2.1; [160,

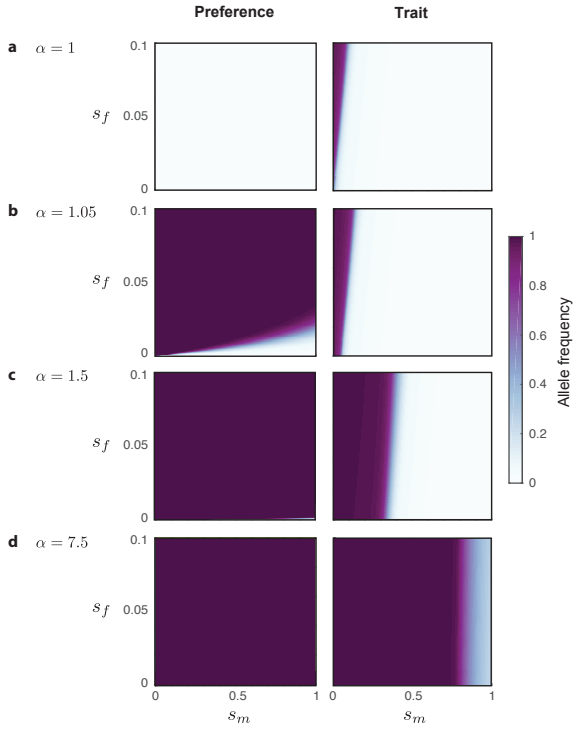

Figure 5.2.1: Long-run frequencies of the W-linked preference allele, P, and the autosomal sexually-antagonistic allele, T, after 5×10^6 generations, each having started at 1% frequency. T and its wild-type allele t mutate to one another at rate 10^{-3}/replication. a. When P induces no preference ($\alpha = 1$), the sexually antagonistic trait allele T reaches high frequency only when it increases viability on average across the sexes, i.e., when $(1 + s_f)(1 - s_m) > 1$. b. Even when the preference it encodes is weak ($\alpha = 1.05$), P is positively selected, and fixes in a large region of the parameter space where the sex-averaged viability effect of T is negative, i.e., where $(1+s_f)(1-s_m) < 1$. Fixation of P pushes T to high frequency over a small region of parameter space, where the trait's cost to males, s_m, is not too large compared to its benefit to females, s_f. c. For slightly higher strengths of the preference ($\alpha = 1.5$), P always fixes, and T attains high frequency in very male-costly regions of parameter space. d. When the preference is strong ($\alpha = 7.5$), T attains high frequency even when it is nearly lethal in homozygous male bearers, imposing an 80% survival cost on them.

Extended Data Fig. 2a]).

Spread of the harmful male trait in this model does not require initial neutral drift of, or exogenous selection for, the mutant preference, unlike in analogous two-locus models of Fisher's runaway process [110, 183] and Zahavi's handicap model [81, 182, 183]. By extension, preferences that impose fitness costs on females (e.g., by reducing their probability of finding a mate) can invade from low frequency in this model, unlike in comparable major-effect runaway and handicap models (which are very sensitive to costs of female preferences [183]).

One way to resolve sexual antagonism is to restrict expression of a trait to the sex it benefits [41, 86, 195]. Counterintuitively, this is not necessarily the expected outcome for sexually antagonistic traits when they are subject to sex-linked mating preferences. For instance, the presence at high frequency of the W-linked preference allele P can select against modifiers that restrict expression of the trait allele T to females, because female-specific expression increases the viability but decreases the mating success of T-bearing males. Sex-linked preferences can thus impede the evolution of sex-specific expression and, by extension, sexual dimorphism [195].

I have thus far limited the discussion to classical sexually antagonistic traits. The model applies more generally, though, to three categories of costly male-specific traits: those that (i) increase the fitness of daughters, (ii) have no effect on the fitness of daughters, or (iii) indicate "good genes" (e.g., classic handicap traits). On (i), costly male traits that increase offspring fitness are functionally identical to sexually antagonistic traits in this model. Such traits include male parental care [44], which is more common in ZW than XY species [191]. On (ii), W-linked preferences for traits with no effect on females ($s_f = 0$) but large costs in males ($s_m \gg 0$) evolve neutrally. Such preferences can therefore drift to high frequency, possibly driving

the evolution of exaggerated male-specific phenotypes previously assumed to be the result of Fisherian runaway processes [2, 81, 264].

On (iii), if a male-specific handicap signals intrinsic, sex-independent quality [81, 264], then a W-linked mating preference for handicapped males is favoured, irrespective of the costs of the handicap, because daughters enjoy higher quality without suffering the handicap [90]. An analogous autosomal preference is transmitted to sons half the time, so the higher quality of its bearers' offspring must be offset by fitness costs in their handicapped sons. If the handicap is too costly, an autosomal mating preference for it will not spread, though a W-linked preference will. The handicap then signals a "sexually antagonistic genome": good in females (because high quality) but bad in sons (because of the severe cost of the handicap). Formal modelling of this process [160, SI Section S5] reveals: (i) the W-linked preference is always favoured under the standard "Spence condition" [81, 221] that the viability cost of the handicap is proportionately lower in higher-quality males; (ii) more stringent conditions are required for the analogous autosomal preference to be favoured; (iii) the handicap must be heritable for these differences to hold.

In the above model, the selfish W-linked preference allele P, by driving to high frequency a trait that severely impairs male survival, might create selection for autosomal suppression of its activity. In an augmented model with a third locus, autosomal but unlinked to the trait locus, with a mutant allele S that suppresses the effect of P so that its female bearers are indiscriminate in mate choice [160, Methods], simulations reveal that S in fact invades only when the strength of the preference it suppresses is weak and when the trait carries a high net cost [160, Extended Data Figs. 3, 4]. Thus, strong W-linked preferences appear to be robust to suppression.

Sex-specific chromosomes (the W or Y) are often stereotyped as degraded and gene-poor. This would seem to diminish the possibility of their carrying preference genes. However, while the sex-specific chromosomes of therian mammals and neognath birds are indeed gene-poor, in other clades they vary widely in size and gene-content [4, 9]. In addition, sex-specific chromosomes usually contain a non-degraded 'pseudoautosomal region' (PAR) that recombines in the heterogametic sex [171]. Simulations reveal that preferences like those modelled above can fix in the PAR, though only if they arise close to the PAR's border with the sex-determining region [160, Extended Data Fig. 5].

The logic articulated above for the W chromosome applies to other genetic elements with exclusive or predominant maternal transmission. These include mitochondria and other cytoplasmic factors [28, 86], intracellular parasites such as Wolbachia [256], as well as microbiota, which often show vertical maternal transmission [73] and are known to influence behaviour—including mate choice—in a number of taxa [63].

While the W chromosome is sex-specific, the Z and the X are only partially sex-biased, being borne twice as often by one sex (males for the Z, females for the X). These transmission biases, together with recent discoveries of X- and Z-linked genes that influence mate choice [160, SI Section S7], raise the possibility that the Z and X can evolve preferences for sexually antagonistic traits—the Z for male-beneficial, female-costly traits, and the X for male-costly, female-beneficial traits. (The evolution of X- and Z-linked preferences for costly male-limited traits has previously been considered [113].)

Modifying the model for X- and Z-linked preferences [160, Methods], I find in both cases that preference and trait can co-evolve to high frequency (Fig. 5.2.2). This

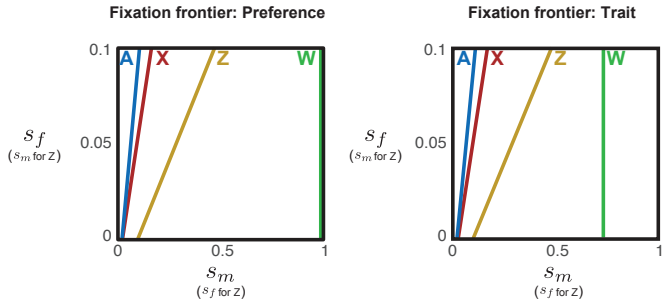

Figure 5.2.2: The preference strength is $\alpha = 5$ in all cases. Each line is a frontier between parameter regions where the preference (left panel) or trait (right panel) allele attains high frequency (region to the left of the line) or not (region to the right of the line). The frontier for autosomes (labeled 'A') is displayed for reference. Note that Z-linked preferences are for male-beneficial, female-costly traits, contrary to the W and X, so the axes are reversed for the Z. W-linked preferences for males displaying female-beneficial, male-costly traits fix for any degree of sexual antagonism. Z-linked preferences for males displaying male-beneficial, female-costly traits fix even with substantially female-costly traits, though the parameter range over which they fix is smaller than for W-linked preferences. X-linked preferences for female-beneficial, male-costly traits fix only when the degree of sexual antagonism is relatively small, though they nonetheless fix in regions where autosomal preferences cannot. Note that, unlike W-linked preferences, Z- and X-linked preferences fix only when they also drive their preferred traits to high frequency.

effect is stronger for the Z, despite the 'biases' of the X and Z being symmetric. To understand this, consider sex chromosome transmission from ZW and XX females to offspring. A Z-linked allele encoding a mating preference for a male-beneficial trait is passed on by a mother only to her sons, thus gaining an immediate advantage. In contrast, an X-linked preference allele is transmitted equally to sons and daughters, thus immediately experiencing both cost and benefit of the trait. In fact, the pedigree transmission profiles of X- and Z-linked preference alleles are symmetric, except for the initial sons-only generation of the Z [160, SI Section S6], explaining why Z-linked mating preferences for sexually antagonistic traits evolve more readily. For both the Z and X, as expected, the effect is weaker than for the W (Fig. 5.2.2).

While I have considered a population in which mate choice is practised exclusively

by females, the model also applies to male mate choice, which recent work has suggested to be more common than previously recognized [57].

To investigate the empirical possibility of sex-linked preferences, I have collected a list of known genomic locations of mate preference genes [160, SI Section S7]. Across a variety of heterogametic species, sex chromosomes are substantially over-enriched for preference genes (relative to their karyotypic representation). Sex-specific chromosomes do not feature prominently, probably because they are highly degenerate in the majority of species in the list. Indeed, one of the major goals of the theoretical work presented here is to point genomic research on mate preferences towards species with gene-rich sex-specific chromosomes.

The model above predicts different outcomes for XY and ZW systems when mate choice is practised predominantly by females. In ZW species, the female-specific W is a very strong attractor of preferences for male-costly, female-beneficial traits, while the male-biased Z attracts preferences for male-beneficial, female-costly traits. In contrast, XY species have no female-specific chromosome, and the X attracts preferences more weakly than the Z (Fig. 5.2.2). Therefore, ZW species are particularly prone to the evolution of sex-linked preferences for sexually antagonistic traits. This concurs with the phylogenetic association between ZW heterogamety and greater male ornamentation in vertebrates [190], although this relationship is ambiguous within certain clades [139]. Further comparative research, especially in clades with rapid heterogametic transitions, would be useful in clarifying this relationship [4].

6

On the logic of Fisherian sexual selection

6.1 Abstract

In Fisher's model of sexual selection, a female preference for a male trait spreads together with the trait because their genetic bases become correlated. This can be interpreted as a 'greenbeard' system: a preference gene, by inducing a female to mate with a trait-bearing male, favors itself because the male is disproportionately likely also to carry the preference gene. Here, we use this logic to argue that Fisherian sexual selection in diploids proceeds via two channels: (i) trait-bearing males

are disproportionately the product of matings between preference-bearing mothers and trait-bearing fathers, and thus trait and preference genes are correlated 'in trans'; (ii) trait and preference genes come into gametic phase disequilibrium, and thus are correlated 'in cis'. Gametic phase disequilibrium is generated by three distinct mechanisms that we identify. The trans channel does not operate when sexual selection is restricted to the haploid phase, and therefore represents a fundamental difference between haploid and diploid models of sexual selection. We show that the cis and trans channels contribute equally to the spread of the preference when recombination between the preference and trait loci is free, but that the trans channel becomes substantially more important when linkage is tight.

6.2 Introduction

It is an evolutionary paradox that males often display costly ornaments or behaviors and females often prefer such males in mate choice. In The Genetical Theory of Natural Selection, Fisher [68] outlined a theory for how such a state might evolve. In Fisher's theory of sexual selection, (i) if the female mate preference becomes sufficiently common, the sexual advantage it confers on the male ornament/behavior (the male 'trait') outweighs the male trait's survival cost, and (ii) the resulting positive selection of the male trait causes indirect positive selection of the female preference, as their genetic bases become correlated because of non-random mating. Thus, both trait and preference spread together.

Half a century later, the possibility of Fisherian sexual selection was demonstrated mathematically by Lande [123], assuming a quantitative genetic basis of preference and trait, and by Kirkpatrick [110], assuming a haploid population genetics model where preference and trait are each encoded at single loci. A major advantage of the

population genetics approach is that the dynamics can be analyzed in full generality [121], whereas analysis of quantitative genetic models such as Lande's typically requires simplifying assumptions, for example a pre-existing, constant genetic correlation between preference and trait.

Since we are usually interested in mate choice and sexual selection in diploid organisms, an important question is whether the population dynamics differs between the two-locus haploid model—studied by Kirkpatrick [110] for its mathematical tractability—and the diploid analog. Previous work has uncovered differences, particularly in the structure of sets of equilibria possible under the two models [80, 83, 91, 169]. For example, stable lines of equilibria involving polymorphism at both loci are characteristic of the haploid model, but are not observed for most configurations of the diploid model [91]. In addition, intermediate dominances of the trait allele in its negative viability effect and its positive effect on attractiveness can combine to produce overall fitness overdominance [50]. This phenomenon, which is obviously not possible in the haploid model, promotes long-term polymorphism at the trait locus. In general, however, it has been argued that many of the differences between the diploid and haploid models are due to the greater complexity of the diploid model—both in the number of parameters and the number of possible genotypes—rather than sexual selection occurring in the diploid phase per se [5].

Here, we make use of the greenbeard interpretation of Fisherian sexual selection [53, 64, 178] to compare the haploid and diploid models, and to gain a greater conceptual understanding of the general operation of Fisher's process. A greenbeard gene [52] causes its bearer both to grow a green beard and to behave so as to preferentially benefit others with green beards. The gene in a potential benefactor uses the green beard of potential beneficiaries as information that they also carry

the gene; this allows the gene to favor copies of itself in other individuals, and thus to spread. In Fisherian sexual selection, a preference allele causes its female bearers to benefit males who display the trait—by favoring them in mating. If males displaying the trait are disproportionately likely to carry the preference allele, then, by conferring a mating advantage on such males, the preference allele confers a mating advantage on copies of itself. In this way, the trait acts as a green beard, providing information that its bearers likely carry the preference allele.

The greenbeard interpretation thus directs attention to the key question underlying Fisher's theory of sexual selection: Why are trait-displaying males disproportionately likely to carry the preference allele? That is, what is the nature of the association between the preference and trait alleles? When sexual selection occurs in the haploid phase, as in the model of Kirkpatrick [110], the only possible association between the trait and preference alleles in males is one of gametic phase disequilibrium, or cis-linkage disequilibrium. However, if sexual selection occurs in the diploid phase, there are two possible associations between the trait and preference alleles: they can be in cis-linkage disequilibrium and/or in trans-linkage disequilibrium (Fig. 6.2.1). Trans-linkage disequilibrium is a direct consequence of the action of the mate preference, which causes a disproportionate number of offspring to inherit the preference allele from their mothers and the trait allele from their fathers. Cis-linkage disequilibrium is generated by a network of interacting mechanisms that we explore below.

These two genetic associations between the trait and preference represent two channels by which Fisherian sexual selection can operate in diploids. In this paper, we demonstrate the independent operation of the trans channel in diploid sexual selection, and investigate what factors influence the relative importance of the trans

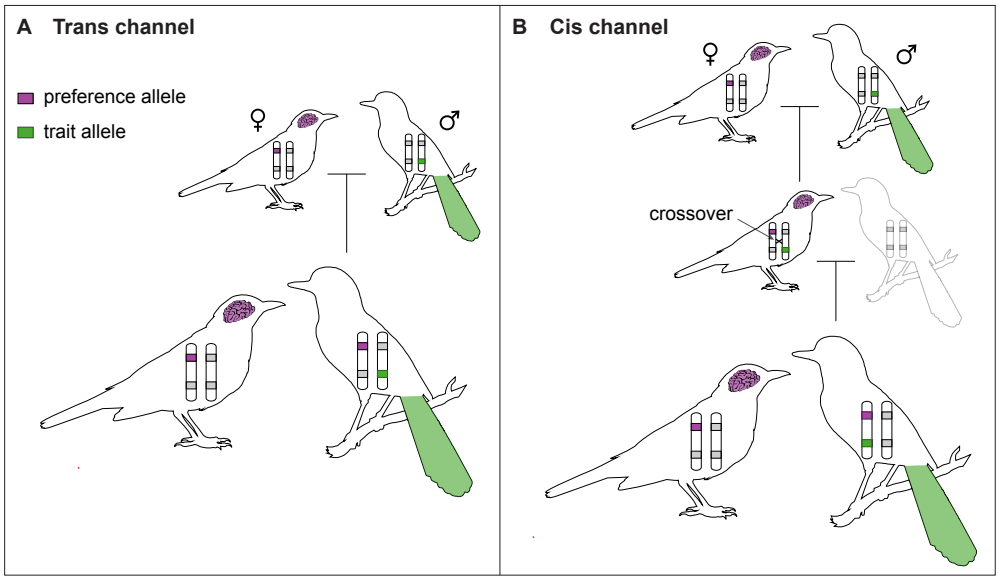

Figure 6.2.1: Under the greenbeard interpretation of Fisherian sexual selection, a preference allele acting in a female uses a male's display of the preferred trait (here, a green tail) as information that he probably carries the preference allele. This requires a statistical association between the trait allele and the preference allele. Two such associations exist. **A.** Because a trait-displaying male is disproportionately likely to be the product of a mating between a preference-bearing mother and a trait-displaying father, he is disproportionately likely to carry the preference and trait alleles in a trans association. These trans associations are the basis for the trans channel of Fisherian sexual selection in diploids. **B.** By the action of the mate preference in the grandparental generation, individuals in the parental generation are disproportionately likely to carry the preference and trait alleles in a trans association. This gives the alleles disproportionate opportunities to recombine into the same gamete, and thus to be carried in a cis association in males in the current generation. Two other mechanisms, discussed in the text, also generate cis associations between the preference and trait alleles. These cis associations are the basis for the cis channel of Fisherian sexual selection in diploids. The two loci are displayed as being on the same chromosome here, but could also be on separate chromosomes.

and cis channels to the spread of the preference. Our aim is to gain a conceptual understanding of the phenomena we discuss, and for this reason we first develop the logic of our arguments and then illustrate this logic with a few instructive simulations, rather than constructing the arguments on the basis of a simulation scan over the entire parameter space. Our primary focus is on the non-equilibrium dynamics of sexual selection, for several reasons: (i) the equilibria of the haploid and diploid models are well studied [80, 91, 110], (ii) in many configurations of these models, the dynamics are sufficiently slow that non-equilibrium dynamics are important even on long timescales (e.g., [91], [83], and below), and (iii) as we show, the non-equilibrium dynamics are often more revealing of the mechanisms underlying Fisherian sexual selection.

6.3 The model

The model we employ is the diploid version of the canonical two-locus model of Fisherian sexual selection [110], as studied, for instance, by Gomulkiewicz & Hastings [80], Heisler & Curtsinger [91], Otto [169], and Greenspoon & Otto [83]. The organism is sexual, and both natural and sexual selection are restricted to the diploid phase of its life cycle. Generations are non-overlapping, and the population is large enough that dynamics can be assumed to be deterministic.

There are two autosomal loci, the 'trait locus' and the 'preference locus', which recombine with rate r. Two alleles segregate at the trait locus: the wild-type t and the 'trait allele' T. T encodes a male-specific trait which reduces the viability of its bearers by a factor $1 - h_T s_T$ for Tt males and $1 - s_T$ for TT males, where h_T is the dominance of T with respect to t. Two alleles segregate at the preference locus: the wild-type p and the 'preference allele' P. P encodes a female mate

preference for the male trait, according to the usual 'fixed relative preference' model [212]. A PP female is more likely to mate with a given TT male or a given Tt male than with a given tt male by factors α and α^{h_T} respectively, where α is the strength of the preference. The analogous factors for a Pp female are α^{h_P} and $\alpha^{h_P h_T}$, where h_P is the dominance of P with respect to p. For our main results, we assume co-dominance at both loci ($h_T = h_P = 1/2$), though we also examine the effects of different dominance values of T. For an explanation of the exponential functional relationship between preference strength and dominance coefficients, see [160]. Alleles at the preference locus have no direct influence on viability, fertility, or fecundity, although we briefly consider the effect of intrinsically costly preferences in the Discussion. The alleles at the trait locus mutate to each other with symmetric rate μ per replication.

Each generation, viability selection acts on juveniles, after which mating occurs subject to the preferences described above. This leads to a standard set of recursions describing the population dynamics (e.g., [80]). Our results derive from computer simulations of these recursions. Unless otherwise stated, we begin each simulation with the two loci in Hardy-Weinberg and linkage equilibrium.

The canonical two-locus haploid model of Fisherian sexual selection [110] is the same as that described above, except that natural and sexual selection are restricted to the haploid phase of the life cycle (which makes the dominance coefficients h_T and h_P irrelevant).

6.4 Selection on the preference allele

Several general features can be observed from frequency trajectories of the preference allele P and the trait allele T in the standard diploid model of Fisherian sexual

selection (Fig. 6.4.1A). First, P increases in frequency only when T also increases in frequency. This is because selection on P is indirect, being a result of selection on T and the fact that P and T become associated. Second, when the trait reduces the viability of its male bearers, the preference must initially be sufficiently common for T (and thus, indirectly, P) to be positively selected. Third, increases in frequency of P tend to be of short duration, and therefore small, as T is rapidly driven to fixation.

Mutation at the trait locus permits long-term spread of the preference. This third feature, the transience of the period during which the preference increases in frequency, limits analysis of the long-run dynamics of Fisherian sexual selection in two-locus models. Fortunately, there is a simple (and realistic) modification of the model that leads to longer term increases of the preference: mutation at the trait locus. When the two alleles at the trait locus, t and T, are allowed to mutate to one another, persistent polymorphism at the trait locus is generated, which makes long-term spread (or elimination) of P possible (Fig. 6.4.1B). We include mutation at the trait locus for all further results, and discuss its role in more detail in the Discussion section.

6.5 Two channels of Fisherian selection in diploids

Spread of P is an indirect consequence of its being positively associated with T—that is, individuals carrying T are disproportionately likely also to carry P. If mate choice occurs among diploids, two positive associations between T and P can be used as information by P: a male carrying T could be disproportionately likely to carry P on the haploid set of chromosomes inherited from the same parent or from the other parent (Fig. 6.2.1). That is, T and P can be in positive cis-linkage disequilibrium

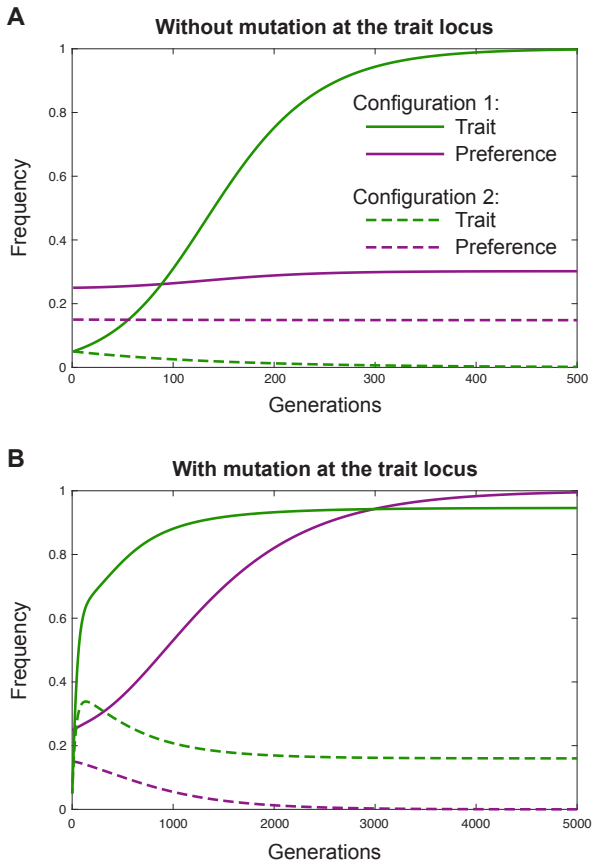

Figure 6.4.1: Frequency trajectories of the trait and preference alleles, for two initial starting frequencies of the preference allele. In configuration 1, the preference is initially common enough that the trait is positively selected and rises in frequency. In configuration 2, the preference is initially too rare for the trait to be positively selected, and so the trait allele decreases in frequency. **A.** Without mutation at the trait locus, the trait rapidly rises to fixation in configuration 1, and decreases to extinction in configuration 2. As a correlated response, the preference allele rises in frequency in configuration 1 and decreases in frequency in configuration 2, but the elimination of trait variation among males causes the preference to then stagnate in both cases. **B.** With mutation at the trait locus, variation for the trait is never eliminated, and persistent frequency change of the preference—including to fixation or extinction—becomes possible. Parameters: $\alpha = 3$, $s_T = 0.2$, $h_T = h_P = 1/2$, $r = 0.1$, $\mu = 0$ (**A**) or $\mu = 0.01$ (**B**). Starting frequencies: T: 5%, P: 25% (configuration 1) or 15% (configuration 2), in Hardy-Weinberg and linkage equilibrium.

(c-LD; gametic phase disequilibrium) and/or positive trans-linkage disequilibrium (t-LD). These two sources of information represent two channels of Fisherian sexual selection in diploids.

The 'trans channel' is based on positive t-LD between the P and T alleles, which arises each generation because of the action of the mate preference in the previous generation—a disproportionate number of offspring are produced from matings between preference-bearing females and trait-bearing males. The 'cis channel' operates because of positive c-LD between P and T, which builds up by several mechanisms that we discuss later. Importantly, the generation of t-LD is a simple consequence of the action of the mate preference each generation, and thus does not depend on prior c-LD; in contrast, the generation of c-LD does, in part, depend on prior t-LD between the alleles (below).

Artificial removal of the cis channel demonstrates independent operation of the trans channel. This asymmetry of the causal relationship between c-LD and t-LD allows us to artificially eliminate the cis channel in simulations while keeping the trans channel intact. We achieve this by eliminating c-LD each generation, by manipulating the relative frequencies of the two double heterozygotes, Pt/pT and PT/pt—this procedure alters haplotype frequencies but not diploid genotype frequencies. Note that it does not matter whether we remove c-LD before or after viability selection has acted, because, without epistatic selection, c-LD does not build up within generations. (Note too that, because the c-LD underlying the cis channel relies in part on prior t-LD, we cannot permanently eliminate the trans channel without affecting the cis channel.)

When we carry out this procedure in our simulations, several points become apparent (Fig. 6.5.1A). First, P can increase in frequency even in the absence of

c-LD. This demonstrates independent operation of Fisherian sexual selection via the trans channel. Second, when P is positively selected, it spreads more slowly than it would were the cis channel intact. As a check, we apply the same procedure to the haploid model, artificially eliminating c-LD each generation. As expected, P does not increase in frequency in this case (Fig. 6.5.1B), since selection on P in the haploid model operates only through the cis channel.

The trans channel allows the preference allele to spread with the trait allele even when they are in negative cis-linkage disequilibrium. The presence of an always-positive trans channel in the diploid model implies, in principle, that P can spread together with T even when they are in negative c-LD, provided the positive trans association is stronger than the negative cis association. While the configurations of the model that we have studied so far lead to positive c-LD, there are some configurations of the model, particularly when the trait allele is fully dominant, that can lead to negative c-LD (discussed below). An example of such a configuration is given in [248, Fig. S1A], where P and T both increase in frequency despite negative c-LD between them. The spread of the preference here must be due to the trans channel.

An experimental demonstration that P can spread despite being in negative c-LD with T can also be achieved in our baseline case of co-dominance of both alleles ($h_T = h_P = 1/2$), by beginning simulations without the PT haplotype. We further assume that there is no recombination between the two loci, so that the PT haplotype can only be restored slowly by mutation. (Note that restoration of the PT haplotype is required because, were it permanently absent, P could never increase in frequency along with T. This is because, in the absence of the PT haplotype, the only favorable genotype that involves P [Pt/pT] also involves p, but there are favorable genotypes

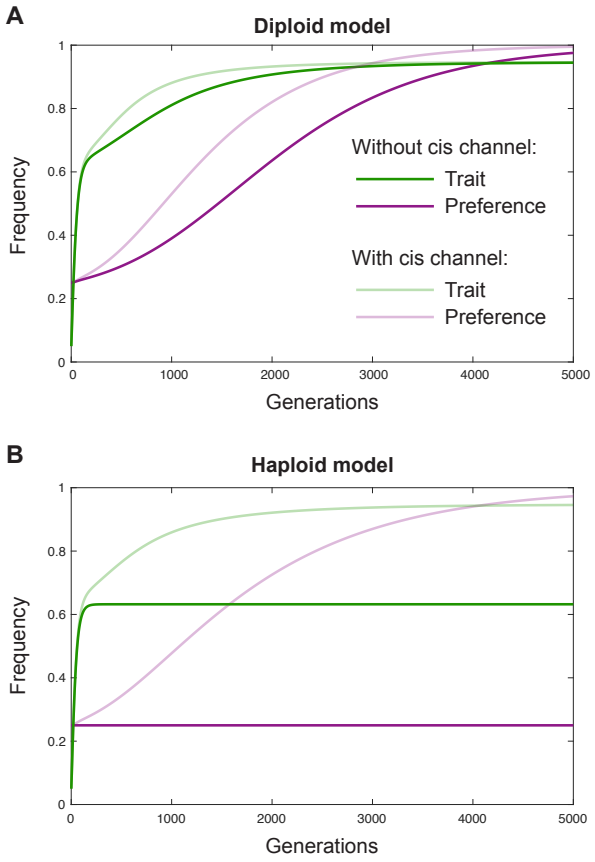

Figure 6.5.1: In the text, we describe a procedure to experimentally eliminate cis associations between the preference and trait alleles without changing genotype frequencies. Here, the faint lines indicate allele trajectories when this procedure has not been carried out. **A.** Eliminating the cis channel in the diploid model, we find that the preference can nonetheless spread, indicating that another channel—the trans channel—is operating. Spread of the preference is, however, slower in the absence of the cis channel. **B.** The haploid model, in contrast, depends on cis associations for the spread of the preference, and so the preference cannot spread when we experimentally eliminate these cis associations. Parameters in **A** are the same as in Fig. 6.4.1B, configuration 1. Parameters in **B** are the haploid analog of those in **A**: $\alpha = \sqrt{3}$, $s_T = 0.1$, $r = 0.1$, $\mu = 0.01$, starting frequencies: T: 5%, P: 25% in linkage equilibrium.

that involve p but not P [pT/pt and pT/pT].) c-LD is thus forced initially to be negative (with $q_{PT} \approx 0$, c-LD $= q_{PT}q_{pt} - q_{Pt}q_{pT} \approx -q_{Pt}q_{pT} < 0$, where $q_{(\cdot)}$ is the frequency of the subscripted haplotype among diploids). [248, Fig. S1B] displays an example in this case where P spreads during a period when c-LD is still negative. The spread of the preference while c-LD is negative must be due to the trans channel.

6.6 Relative importance of the trans and cis channels

Trans associations of trait and preference are more informative when linkage is tight. The results above demonstrate that sexual selection on female mate preferences in diploids operates through two channels, the trans channel and the cis channel. Under the greenbeard interpretation of Fisherian sexual selection, these constitute, for a copy of P acting in a female, two channels of information about the likelihood that a trait-displaying male carries P too. Therefore, a natural way to compare the relative importance of the two channels is to compare how informative they are in this regard. That is, considering a given copy of T in a male, what are the (conditional) probabilities that he carries P in trans, and in cis, with respect to the focal trait allele? With no association, this probability would simply be the frequency of P, and so we are interested in how much the two conditional probabilities exceed this baseline value. The ratio of the excess of these two probabilities over the baseline value gives the relative importance of the trans channel over the cis channel, and is in fact equal to the ratio of t-LD and c-LD.

In calculating the trajectory of this ratio for a variety of recombination rates, we make several observations (Fig. 6.6.1A). First, the trans channel is always at least as important as the cis channel (among the configurations we have tested). Second, the relative importance of the trans channel over the cis channel increases as the

recombination rate between the preference and trait loci decreases. When recombination is free, the cis and trans channels are of approximately equal importance, consistent with analytical results that c-LD and t-LD are equal in the quasi-linkage equilibrium (QLE) limit of the diploid model, where recombination is strong and selection is weak ([114, Eq. 56]; [83, Eq. 6]). When linkage is tight, the trans channel becomes much more important than the cis channel—e.g., as much as 300 times more important for the parameters used in Fig. 6.6.1.

The trans channel contributes more to the spread of the preference when linkage is tight. A second way to assay the relative importance of the trans and cis channels is to ask how much of the selective advantage of the preference is due to each—that is, to decompose frequency increases of P into a component due to the trans channel and a component due to the cis channel. We achieve this in our simulations in the following way. Each generation g, we construct two populations of zygotes: a true population taking into account the action of the mate preference in generation $g-1$, and a hypothetical population assuming random mating in $g-1$. We then calculate the frequency change of P from zygotes in g to zygotes in $g+1$ for both populations, taking into account the action of the mate preference among adults in g. Because the hypothetical population in g has no trans association between P and T (its parents mated randomly), any increase of P between g and $g+1$ must be due solely to the cis channel. Therefore, the difference between the frequency increases of P in the true and hypothetical populations identifies the contribution of the trans channel. (Note that this procedure does not permanently remove the trans channel—as pointed out earlier, this would permanently affect the cis channel as well. Instead, this procedure temporarily removes the trans channel

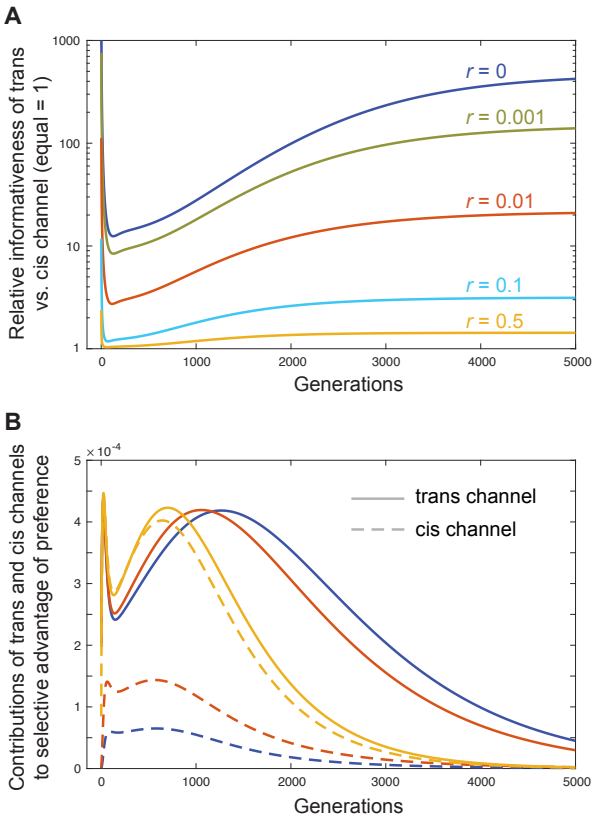

Figure 6.6.1: A. The ratio of t-LD to c-LD, for various recombination rates. In the language of the greenbeard interpretation, this is the ratio of the two channels' informativeness to a preference allele in a female that a trait-displaying male is likely to carry the preference allele. **B.** By temporarily disabling the trans channel each generation (procedure described in text), we can observe how much of the frequency increase of the preference allele is due to the cis channel, and therefore also how much is due to the trans channel. These contributions are plotted for selected recombination rates from **A**. Both **A** and **B** reveal that the relative importance of the trans channel increases as the recombination fraction between the two loci decreases. Parameters: As in Fig. 6.4.1B, configuration 1, except for variable r.

each generation, but restores it for the production of true genotype frequencies in the next generation.)

Consistent with the conditional probability results (Fig. 6.6.1A), we find in our simulations that the trans channel always contributes at least as much to the selective advantage of the preference as the cis channel does, and that the relative contribution of the trans channel increases as the recombination rate between the preference and trait loci decreases (Fig. 6.6.1B). Thus, when recombination is free, the contributions of the trans and cis channels are approximately equal, consistent with previous analytical results in the QLE limit [83, 114], but when recombination is rare, the trans channel's contribution dominates.

6.7 Multiple mechanisms for the generation of cis-linkage disequilibrium

The recombination mechanism. The simplest mechanism by which c-LD is generated in Fisherian sexual selection is by recombination. The mate preference acting in one generation causes the P and T alleles to be disproportionately associated in trans in the next generation, thus giving them disproportionate opportunities to recombine onto the same background in gametogenesis. When recombination occurs at a higher rate, this 'recombination mechanism' is stronger, and thus positive c-LD can build up faster. The recombination mechanism promotes positive c-LD quite generally in models of Fisherian sexual selection, e.g., across different dominance values of the trait and preference alleles in the diploid model.

In the haploid model, positive c-LD cannot be generated in the absence of recombination if P and T start in initial linkage equilibrium, and so the preference cannot co-spread with the trait in this case [248, Fig. S2]. This can be seen in Kirkpatrick's

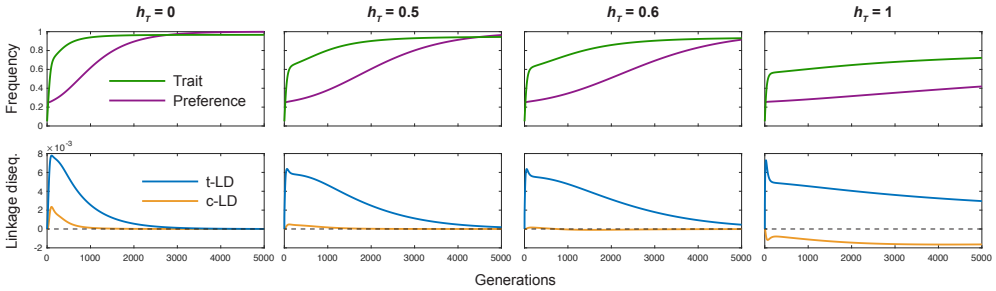

Figure 6.7.1: Here, recombination is assumed to be absent, so that the only sources of c-LD in the diploid model are the 'dominance mechanism' and, reinforcing this, the 'syngamic admixture mechanism'. c-LD is positive when the trait is recessive, weakly positive when the trait is co-dominant, approximately zero for an intermediate value of dominance of the trait ($h_T = 0.6$), and negative when the trait is fully dominant (although note that the preference nonetheless spreads in this case, because of the operation of the trans channel). Parameters: As in Fig. 6.4.1B, configuration 1, except for h_T.

[110] analytical treatment of the haploid model by setting D and R to zero in his Eq. (1c)—the result is not altered by the inclusion of mutation at the trait locus (e.g., [248, Fig. S2]).

However, a surprising finding in the above analyses is that, in the diploid model, positive c-LD is generated in the absence of recombination when the trait is co-dominant, starting from a state of linkage equilibrium (Fig. 6.7.1). This explains why the trans channel is only finitely more important than the cis channel when recombination is absent in the diploid model (Fig. 6.6.1), and points to mechanisms other than recombination for the generation of c-LD.

The dominance mechanism. A second mechanism for the generation of c-LD is exclusive to the diploid model, and can operate even in the absence of recombination. It arises from differences in the transmission rates of the various haplotypes, caused by an interaction between (i) their non-random association with other haplotypes

in diploid males, and (ii) the dominance of the trait allele T.

The operation of this 'dominance mechanism' is easiest to see in the case where recombination is absent, the system begins in linkage equilibrium, and the preference allele P starts at a sufficiently high frequency that trait-bearing males are positively selected. In this case, there is no LD in the gametes of first-generation males or females, nor is there c-LD in second-generation zygotes. However, a consequence of the mate preference in the first generation is that madumnal (maternally-derived) PT and Pt haplotypes in second-generation males are disproportionately associated with padumnal (paternally-derived) T alleles, while madumnal pT and pt haplotypes are not.

If T is fully recessive, these associations give PT haplotypes in second-generation males (which disproportionately reside in TT males) a transmission advantage over pT haplotypes, but give Pt haplotypes (which disproportionately reside in Tt males) no advantage over pt haplotypes. Thus, while haplotype frequencies in second-generation males obey (no c-LD), haplotype frequencies in the successful sperm of these males obey (positive c-LD). On the other hand, if T is fully dominant, then the haplotype associations in males give PT haplotypes no advantage over pT haplotypes (since there is no advantage to being associated with another T allele), but give Pt haplotypes an advantage over pt haplotypes, so that among sperm (negative c-LD). For some intermediate level of dominance, among sperm (no c-LD generated by the dominance mechanism). An extreme case is where T is overdominant, so that Tt males are fittest. In this case, madumnal Pt haplotypes benefit, and PT haplotypes suffer, from their preferential association with padumnal T alleles. This generates negative c-LD between the P and T alleles. Nonetheless, as shown by Otto [169], a rare P allele invades in this case when $r = 0$, which invasion must therefore be due

to the trans channel.

Thus, the 'dominance channel' generates positive c-LD when T is recessive, negative c-LD when T is dominant (or overdominant), and no c-LD when T has a certain intermediate dominance (Fig. 6.7.1). Though we have focused, for clarity, on the first few generations in the case where recombination is absent, the logic above relies only on the fact that madumnal PT and Pt haplotypes associate disproportionately with padumnal T alleles—the dominance of T then governs the transmission advantages these associations confer on the PT and Pt haplotypes relative to the pT and pt haplotypes, respectively, and thus the effect on c-LD.

It is clear that the dominance mechanism cannot operate in the haploid model, because haploid PT and pT males are equally fit, and so these haplotypes have equal transmission rates in sperm; the same holds for the Pt and pt haplotypes.

The syngamic admixture mechanism. A third mechanism for the generation of c-LD derives from sex-specific selection at both loci. Viability and sexual selection on T in males causes the frequency of T to differ between the sperm and eggs that produce the next generation. If there is an association between T and P in males (either cis or trans), then, as a correlated response to male-specific selection on T, the frequency of P will also differ between sperm and eggs. Allele frequency differences at multiple loci in sperm and eggs create c-LD upon syngamy [233]. If, for example, there is positive selection on T and a positive association between T and P in males, then T and P will be at higher frequency in sperm and eggs, increasing c-LD upon syngamy.

This argument applies equally to the haploid and diploid models, so why is c-LD generated in the absence of recombination in the diploid model but not the haploid model? The 'syngamic admixture mechanism' for generating c-LD requires

a prior association between P and T, so that male-specific selection on the trait changes the frequencies of both alleles in sperm relative to eggs. In the haploid model, the only possible prior association is c-LD, and so syngamic admixture cannot generate c-LD without initial c-LD [248, Fig. S2]. In the diploid model, even in the absence of recombination, P and T immediately come into a trans association by the action of the mate preference. Thus, selection on the trait in males causes the frequencies of both alleles to differ between sperm and eggs, leading to c-LD by syngamic admixture.

In the haploid model, if c-LD is initially generated for other reasons (e.g., by the recombination mechanism, or by random drift), then the syngamic admixture mechanism does operate. Eq. (1c) in Kirkpatrick [110] provides a general expression for the total change in c-LD from one generation to the next in the haploid model. In [248, SI File S1], we isolate from this expression the component due to syngamic admixture, in the case where $r = 0$.

Notice that the effect of syngamic admixture on c-LD depends on the sign of the pre-existing association between P and T. If there is a net positive association between the alleles (e.g., if t-LD and c-LD are both positive, or if negative c-LD arising from the dominance mechanism is outweighed by positive t-LD arising directly by the action of the mate preference), then they will change in frequency in the same direction in sperm, and so syngamic admixture makes a positive contribution to c-LD in the next generation [233]. If there is a net negative association between the alleles (e.g., if negative c-LD arising from the dominance mechanism outweighs the positive t-LD generated by non-random mating), then they will change in frequency in opposite directions in sperm, and so syngamic admixture makes a negative contribution to c-LD. Thus, syngamic admixture only reinforces pre-existing associations

between the alleles.

6.8 Discussion

The life cycle of all sexual organisms involves alternation between haploid and diploid phases [136]. Sexual selection can operate in either phase, leading to separate haploid and diploid models of Fisherian sexual selection. Classical work characterized the population dynamics of the two-locus haploid model [110]; later work identified differences in the dynamics of diploid models, particularly relating to the structure of stable equilibrium sets (e.g., [80, 91]). However, as noted by Barton & Turelli [5], many of these differences are due not to the action of sexual selection in the diploid phase *per se*, but rather to the additional parametric complexity of the diploid model. Here, we have identified a fundamental conceptual difference between haploid and diploid models of Fisherian sexual selection.

In doing so, we have drawn intuition from the greenbeard interpretation of Fisherian sexual selection [53, 64, 178]. Under this interpretation, the trait displayed by a male is used by a preference allele in a female as information that the male probably carries the preference allele. The preference allele in the female induces her to mate with the male, thus likely conferring a mating advantage on a copy of itself in the male. This interpretation directs attention to the question: What is the mechanism by which a male's display of the trait is informative that he likely carries the preference allele? That is, what is the nature of the association between the trait and preference alleles?

If sexual selection operates in the haploid phase, there is only one way in which the trait and preference alleles can be associated in males: they must be in cis-linkage disequilibrium (c-LD; gametic phase disequilibrium). However, if sexual selection

occurs in the diploid phase, there are two ways in which the trait and preference alleles can be associated: they can be in c-LD or in trans-linkage disequilibrium (t-LD). These represent two distinct ways in which the trait displayed by a diploid male is informative that he carries the preference allele, and they thus represent two distinct channels of Fisherian sexual selection in diploids. We have named these two channels the 'trans channel' and the 'cis channel'.

We have demonstrated the independent action of the trans channel in the diploid model by comparing, in simulations, the population dynamics of the trait and preference alleles when the cis channel is kept open and when it is switched off (by the artificial removal of c-LD each generation). When the cis channel is switched off in the haploid model, the preference is unable to increase in frequency (Fig. 6.5.1B). In contrast, in the diploid channel, the preference can still increase in frequency when the cis channel is switched off (Fig. 6.5.1A). This increase in frequency in the diploid model is due to the independent operation of the trans channel.

A subtlety is that, in both the haploid and diploid models of Fisherian sexual selection, the generation of c-LD (and thus the operation of the cis channel) depends on repeated trans associations of the preference and trait alleles in the diploid phase of the lifecycle. The key difference between the haploid and diploid models, in terms of operation of the trans channel, is that sexual selection acts in the diploid phase in the 'diploid model' but not in the 'haploid model'. Therefore, in the language of the greenbeard interpretation, the trans association is itself informative to the preference in the diploid model, in addition to its fundamental role in generating c-LD; this is not the case in the haploid model.

Recombination has played an important role in our findings. When the recombination rate between preference and trait loci is low, c-LD builds up more slowly,

and to a lower level, than when the recombination rate is high. As a result, the trans channel—which is insensitive to the recombination rate, being a direct consequence of the action of the mate preference in the previous generation—is more important than the cis channel when the recombination rate is low (Fig. 6.6.1). An implication of this result is that lowering the recombination rate between the trait and preference loci severely slows down Fisherian sexual selection in the haploid model, where cis-linkage disequilibrium is the only mechanism by which the preference can increase in frequency, but has a less severe effect in the diploid model, with its ever-present trans channel [248, Fig. S3].

This finding is a consequence of our focus on the non-equilibrium dynamics of sexual selection. Indeed, the sets of stable equilibria that are possible in two-locus models of Fisherian sexual selection are generally insensitive to the degree of linkage between the preference and trait loci ([26, 80, 110]; for an exception, see [169]). Therefore, recombination typically does not affect what long-run equilibrium outcomes are possible in models of sexual selection. Instead, through its positive effect on the rate and eventual degree of buildup of linkage disequilibrium between the preference and trait alleles, recombination can affect which of these equilibrium outcomes is reached from a particular initial state, and/or how rapidly equilibrium is reached. This latter effect, recombination's positive influence on the rate of approach of equilibrium, is particularly important in cases where equilibrium is expected to be reached only after many generations [248, Fig. S3], because in such cases the non-equilibrium dynamics are of primary importance.

The above considerations, together with the combinatorial fact that, in most species, the vast majority of locus pairs lie on separate chromosomes [47, 247], suggest that two-locus Fisherian systems should usually involve unlinked loci. There

are relatively few instances of mate choice for which the genetic bases of both preference and trait have been localized [42]. However, in some of these, loci contributing to variation in preference and trait have been found to be tightly linked (e.g., [6, 120, 217, 263]). In these cases, our results suggest that the operation of the trans channel was vital for the establishment of these preference-trait gene pairs (the examples all involve sexual selection in diploids), unless the preference and trait alleles are sufficiently tightly linked and appeared already at high cis-linkage disequilibrium and at a sufficient frequency to initiate the Fisherian process.

Interestingly, the examples of tightly linked preference and trait genes cited above are all in clades with recent species radiations and ongoing hybridization. In such cases, tight linkage of preference and trait genes (or pleiotropy of a single gene) might be beneficial in preventing their dissociation in the face of introgression [263]. If so, this would be an instance of a more general evolutionary phenomenon where introgression favors tight linkage of co-adapted gene complexes [112]. From a theoretical perspective, there are two scenarios: (i) Sexual selection on the preference gene is weaker when it is tightly linked to the trait gene, so that such complexes fix more slowly and less frequently (consistent with our results); however, when they do, they are more robust in the face of introgression and therefore persist while complexes with looser linkage do not; (ii) Ongoing introgression in fact causes sexual selection on a preference gene to be stronger when it is tightly linked to the trait gene, so that tightly linked complexes fix more rapidly and more frequently. More modelling of Fisherian sexual selection with introgression (e.g., [216]) is required to understand the relative likelihood of these two possibilities. Note that the results of such models are likely to be sensitive to whether sexual selection occurs in the haploid or the diploid phase, since, as we have found, the trans channel dominates

in diploid sexual selection when linkage is tight, but does not exist in haploid sexual selection.

We have started all of our simulations with the preference and trait alleles in Hardy-Weinberg and cis-linkage equilibrium. From such an initial state, when recombination between the loci is absent, only weak c-LD between the alleles can build up (and in the haploid model, none at all). Thus, the trans channel, driven directly by assortative mating, dominates. However, there are instances where we expect Fisherian sexual selection within a population to begin from a state where the preference and trait alleles are already in strong c-LD. For example, if the preference and trait loci lie within a chromosomal segment that is inverted in one population relative to the other, then introgression of preference and trait alleles from a population where they are fixed into the other where they are absent would constitute an injection of preference and trait alleles in perfect c-LD. Because they reside in an inversion in the recipient population, recombination cannot dissociate them, and their c-LD is maintained. Notice, however, that the preference-trait haplotype must be introgressed at a sufficiently high frequency that the mating advantage conferred on the introgressed trait outweighs its viability disadvantage. If so, the cis-channel would dominate in the resulting positive Fisherian sexual selection of the introgressed preference. This is in sharp contrast to our results concerning the importance of the cis and trans channels when recombination is absent and the preference and trait alleles start in linkage equilibrium, and thus highlights the role of initial linkage in how the Fisherian process plays out.

Although we have focused on autosomally encoded preferences and traits in diploids, our conceptual distinction between the cis and trans channels generalizes easily to other systems. Note first that the greenbeard interpretation of Fishe-

rian sexual selection, where a preference allele in a female uses a male's display of the trait to infer that he is disproportionately likely to carry the preference allele, makes clear that it is only genetic correlations between preference and trait in males that directly matter. Now consider X-linked preference and trait alleles in a male-heterogametic (XX/XY) species. In this case, although females are diploid at the preference and trait loci, males are effectively haploid. Therefore, only cis associations of the preference and trait alleles are possible in males, and so only the cis channel of Fisherian sexual selection operates in this case. In contrast, Z-linked traits in female-heterogametic (ZW/ZZ) species are informative to Z-linked preferences via both the cis and trans channels, because males are diploid for the Z. This suggests (i) that Fisherian preference and trait allele pairs should be more common on Z chromosomes than on X chromosomes, all else equal, and (ii) Z chromosomes should be especially enriched for tightly-linked preference and trait alleles relative to X chromosomes, because tight linkage will severely slow down the co-spread of these alleles in XX/XY species (where only the recombination-sensitive cis channel is operating) but not in ZW/ZZ species (where the recombination-insensitive trans channel operates too). Implication (i) is consistent with analytical results in the QLE limit of weak selection and strong recombination [113].

The situation is slightly more complicated when only the trait locus is sex-linked. An X-linked trait allele carried by a male was necessarily inherited from his mother. Thus, even though a trans association between the preference and trait alleles is technically possible in this case (because of diploidy at the preference locus in males), the trans channel, which functions in the autosomal diploid model because trait-bearing males are disproportionately likely to have inherited the trait allele from their fathers and the preference allele from their mothers, in fact does not operate

here. In contrast, both the cis and trans channels operate when the trait is Z-linked and the preference is autosomal, because each male inherits a Z from both his mother and his father. Therefore, we expect Z-linked preferences for autosomally-encoded traits to be more common than X-linked preferences for autosomally encoded traits, all else equal—this is consistent with analytical results in the weak selection limit [113].

The situation for haplodiploid species is the same as the case where both the preference and trait are X-linked, with the additional point that the preference and trait loci can lie on separate chromosomes in haplodiploids—an important point, given that only the cis channel operates in this case, so that free recombination between the preference and trait loci (in females) is very helpful. Finally, we have considered the case of female mating preferences for male traits, but all of our results apply, *mutatis mutandis*, to male mating preferences for female traits, which are now recognized to play an important role in many systems [57, 70]. The results for autosomal traits and preferences are the same as those for female choice, while the statements above for XX/XY and ZW/ZZ species reverse.

When the only forces affecting the frequencies of the preference and trait alleles are viability selection and the mate preference, frequency changes of the preference allele are typically small, as the trait is rapidly driven either to fixation or extinction (Fig. 6.4.1A). A simple augmentation of the model that allows for longer-term frequency changes of the preference allele, either to fixation or extinction, is mutation at the trait locus (Fig. 6.4.1B). This result—that fixation or elimination of the preference is generic in the presence of trait mutation—can be deduced from Bulmer's [26] mathematical analysis of the equilibria of the haploid model [by setting $v_1 = v_2 = 0$ in Eq. (10c) of [26]]. It has also been observed in simulations of the

haploid model in the context of one-way mutation away from the trait [64]. The effect of mutation can be understood from the case where the preference is initially sufficiently common that the trait allele T is positively selected. T rapidly spreads to a mutation-selection balance near its fixation boundary. At this mutation-selection balance, the fitness advantage of T (owing to the common mate preference) is a force pushing it up in frequency, while mutation is a force pushing it down in frequency (since T is much more common than t). Because the preference allele P is in a positive association with T, it benefits indirectly from T's overall fitness advantage without suffering from the net mutational loss of T alleles. P thus increases in frequency as long as polymorphism is maintained at the trait locus.

We have focused on the 'Fisherian' case where the only selection acting on the mate preference is indirect, as a correlated response to direct selection on the trait. However, discriminatory mate choice is often associated with direct fitness costs, reducing the number of offspring that choosy females have [180, 239]. The persistent indirect selective advantage to P that is generated by mutation at the trait locus allows P to spread even when it carries a direct fitness cost, provided that this cost is not too large [248, Fig. S4]. This is impossible in models without trait mutation—either two-locus or quantitative—where direct costs of the preference lead to its eventual extinction [111, 180, 181]. Importantly, in the two-locus model, mutation at the trait locus can lead to persistent spread of an intrinsically costly preference no matter the relative mutation rates from $t \to T$ and $T \to t$ (as long as the latter is not zero). In particular, a costly preference can spread even when there is a substantial bias in favor of $t \to T$ mutations [248, Fig. S4]. This is in contrast to quantitative genetic models of Fisher's process, where a costly preference can spread in the long term only if there is a mutational bias away from the preferred trait [181].

References

[1] A. Y. K. Albert and S. P. Otto. Sexual selection can resolve sex-linked sexual antagonism. *Science*, 310(5745):119–121, 2005.

[2] M. Andersson. *Sexual Selection*. Princeton University Press, Princeton, 1994.

[3] D. Bachtrog, M. Kirkpatrick, J. E. Mank, S. F. McDaniel, J. C. Pires, W. Rice, and N. Valenzuela. Are all sex chromosomes created equal? *Trends in Genetics*, 27(9):350–357, 2011.

[4] D. Bachtrog, J. E. Mank, C. L. Peichel, M. Kirkpatrick, S. P. Otto, T.-L. Ashman, M. W. Hahn, J. Kitano, I. Mayrose, R. Ming, et al. Sex determination: why so many ways of doing it? *PLoS Biology*, 12(7):e1001899, 2014.

[5] N. H. Barton and M. Turelli. Natural and sexual selection on many loci. *Genetics*, 127(1):229–255, 1991.

[6] R. A. Bay, M. E. Arnegard, G. L. Conte, J. Best, N. L. Bedford, S. R. McCann, M. E. Dubin, Y. F. Chan, F. C. Jones, D. M. Kingsley, et al. Genetic coupling of female mate choice with polygenic ecological divergence facilitates stickleback speciation. *Current Biology*, 27(21):3344–3349, 2017.

[7] M. J. Beaton and P. D. Hebert. Geographical parthenogenesis and polyploidy in *Daphnia pulex*. *The American Naturalist*, 132(6):837–845, 1988.

[8] T. Becking, I. Giraud, M. Raimond, B. Moumen, C. Chandler, R. Cordaux, and G. Clément. Diversity and evolution of sex determination systems in terrestrial isopods. *Scientific Reports*, 7:1084, 2017.

[9] L. Berset-Brändli, J. Jaquiéry, T. Broquet, Y. Ulrich, and N. Perrin. Extreme heterochiasmy and nascent sex chromosomes in european tree frogs. *Proceedings of the Royal Society B: Biological Sciences*, 275(1642):1577–1585, 2008.

[10] L. W. Beukeboom and N. Perrin. *The evolution of sex determination*. Oxford University Press, 2014.

[11] A. J. Bewick, D. W. Anderson, and B. J. Evans. Evolution of the closely related, sex-related genes DM-W and DMRT1 in African Clawed Frogs (*Xenopus*). *Evolution*, 65(3):698–712, 2011.

[12] R. Bicknell. Isolation of a diploid, apomictic plant of *Hieracium aurantiacum*. *Sexual Plant Reproduction*, 10(3):168–172, 1997.

[13] R. Bicknell, N. Borst, and A. Koltunow. Monogenic inheritance of apomixis in two *Hieracium* species with distinct developmental mechanisms. *Heredity*, 84(2):228–237, 2000.

[14] P. Bierzychudek. Patterns in plant parthenogenesis. *Experientia*, 41(10):1255–1264, 1985.

[15] C. B. Bridges. Triploid intersexes in *Drosophila melanogaster*. *Science*, 54: 252–254, 1921.

[16] J. J. Bull. Sex determination in reptiles. *Quarterly Review of Biology*, 55(1): 3–21, 1980.

[17] J. J. Bull. Sex ratio evolution when fitness varies. *Heredity*, 46(1):9, 1981.

[18] J. J. Bull. Evolution of environmental sex determination from genotypic sex determination. *Heredity*, 47(2):173–184, 1981.

[19] J. J. Bull. *The evolution of sex determining mechanisms*. Benjamin Cummings, 1983.

[20] J. J. Bull. Sex determining mechanisms: an evolutionary perspective. In S. C. Stearns, editor, *The Evolution of Sex and its Consequences*, pages 93–115. Springer, 1987.

[21] J. J. Bull and M. G. Bulmer. The evolution of XY females in mammals. *Heredity*, 47(3):347–365, 1981.

[22] J. J. Bull and M. G. Bulmer. Longevity enhances selection of environmental sex determination. *Heredity*, 63(3):315, 1989.

[23] J. J. Bull and E. L. Charnov. Changes in the heterogametic mechanism of sex determination. *Heredity*, 39(1):1–14, 1977.

[24] J. J. Bull and E. L. Charnov. On irreversible evolution. *Evolution*, 39(5): 1149–1155, 1985.

[25] J. J. Bull, R. C. Vogt, and M. G. Bulmer. Heritability of sex ratio in turtles with environmental sex determination. *Evolution*, 36(2):333–341, 1982.

[26] M. G. Bulmer. Structural instability of models of sexual selection. *Theoretical population biology*, 35(2):195–206, 1989.

[27] M. G. Bulmer and J. J. Bull. Models of polygenic sex determination and sex ratio control. *Evolution*, 36(1):13–26, 1982.

[28] A. Burt and R. L. Trivers. *Genes in conflict*. Belknap Press, 2006.

[29] M. A. Butler, T. W. Schoener, and J. B. Losos. The relationship between sexual size dimorphism and habitat use in Greater Antillean *Anolis* lizards. *Evolution*, 54(1):259–272, 2000.

[30] M. A. Butler, S. A. Sawyer, and J. B. Losos. Sexual dimorphism and adaptive radiation in *Anolis* lizards. *Nature*, 447(7141):202–205, 2007.

[31] C. Y. Chang and E. Witschi. Genic control and hormonal reversal of sex differentiation in *Xenopus*. *Proceedings of the Society for Experimental Biology and Medicine*, 93(1):140–144, 1956.

[32] B. Charlesworth. Model for evolution of Y chromosomes and dosage compensation. *Proceedings of the National Academy of Sciences USA*, 75(11): 5618–5622, 1978.

[33] B. Charlesworth. The evolution of sex chromosomes. *Science*, 251(4997): 1030–1033, 1991.

[34] B. Charlesworth and D. Charlesworth. The degeneration of Y chromosomes. *Philosophical Transactions of the Royal Society of London B: Biological Sciences*, 355(1403):1563, 2000.

[35] D. Charlesworth and B. Charlesworth. Sex differences in fitness and selection for centric fusions between sex-chromosomes and autosomes. *Genetics Research*, 35(2):205–214, 1980.

[36] D. Charlesworth, B. Charlesworth, and G. Marais. Steps in the evolution of heteromorphic sex chromosomes. *Heredity*, 95(2):118–128, 2005.

[37] E. L. Charnov. *The Theory of Sex Allocation*. Princeton University Press, 1982.

[38] E. L. Charnov and J. Bull. Non-fisherian sex ratios with sex change and environmental sex determination. *Nature*, 338(6211):148, 1989.

[39] E. L. Charnov and J. J. Bull. When is sex environmentally determined? *Nature*, 266(5605):828, 1977.

[40] E. L. Charnov, J. J. Bull, and J. M. Smith. Why be an hermaphrodite? *Nature*, 263(5573):125, 1976.

[41] C. Cheng and M. Kirkpatrick. Sex-specific selection and sex-biased gene expression in humans and flies. *PLoS Genetics*, 12(9), 2016.

[42] S. F. Chenoweth and M. W. Blows. Dissecting the complex genetic basis of mate choice. *Nature Reviews Genetics*, 7(9):681–692, 2006.

[43] T. Chotibut and D. R. Nelson. Population genetics with fluctuating population sizes. *Journal of Statistical Physics*, 167(3-4):777–791, 2017.

[44] T. H. Clutton-Brock. *The Evolution of Parental Care*. Princeton University Press, 1991.

[45] G. W. A. Constable, T. Rogers, A. J. McKane, and C. E. Tarnita. Demographic noise can reverse the direction of deterministic selection. *Proceedings of the National Academy of Sciences USA*, 113(32):E4745–E4754, 2016.

[46] R. M. Cox and R. Calsbeek. Sexually antagonistic selection, sexual dimorphism, and the resolution of intralocus sexual conflict. *The American Naturalist*, 173(2):176–187, 2009.

[47] J. F. Crow. The importance of recombination. In R. E. Michod and B. R. Levin, editors, *The evolution of sex: an examination of current ideas*. Sinauer, 1988.

[48] J. F. Crow and M. Kimura. *An Introduction to Population Genetics Theory*. Harper & Row, 1970.

[49] R. Cui, M. Schumer, K. Kruesi, R. Walter, P. Andolfatto, and G. G. Rosenthal. Phylogenomics reveals extensive reticulate evolution in *Xiphophorus* fishes. *Evolution*, 67(8):2166–2179, 2013.

[50] J. W. Curtsinger and I. L. Heisler. A diploid "sexy son" model. *The American Naturalist*, 132(3):437–453, 1988.

[51] C. D. Darlington. *The Evolution of Genetic Systems*. Cambridge University Press, 1939.

[52] R. Dawkins. *The selfish gene*. Oxford University Press, Oxford, 1976.

[53] R. Dawkins. *The blind watchmaker*. W. W. Norton & Company, New York, 1986.

[54] A. Dill, T. Sanger, A. C. Battles, and M. A. Johnson. Sexual dimorphisms in habitat-specific morphology and behavior in the green anole lizard. *Journal of Zoology*, 290(2):135–142, 2013.

[55] P. F. Donald. Adult sex ratios in wild bird populations. *Ibis*, 149(4):671–692, 2007.

[56] T. J. V. Dooren and O. Leimar. The evolution of environmental and genetic sex determination in fluctuating environments. *Evolution*, 57(12):2667–2677, 2003.

[57] D. A. Edward and T. Chapman. The evolution and significance of male mate choice. *Trends in Ecology & Evolution*, 26(12):647–654, 2011.

[58] S. T. Emlen and L. W. Oring. Ecology, sexual selection, and the evolution of mating systems. *Science*, 197(4300):215–223, 1977.

[59] S. N. Ethier and T. Nagylaki. Diffusion approximations of Markov chains with two time scales and applications to population genetics. *Advances in Applied Probability*, 12:14–49, 1980.

[60] W. J. Ewens. *Mathematical Population Genetics 1. Theoretical Introduction*. Springer-Verlag, 2004.

[61] T. Ezaz, R. Stiglec, F. Veyrunes, and J. A. M. Graves. Relationships between vertebrate ZW and XY sex chromosome systems. *Current Biology*, 16(17): R736–R743, 2006.

[62] T. Ezaz, S. Sarre, D. O'Meally, J. Marshall Graves, and A. Georges. Sex chromosome evolution in lizards: independent origins and rapid transitions. *Cytogenetic and Genome Research*, 127(2-4):249–260, 2009.

[63] V. O. Ezenwa, N. M. Gerardo, D. W. Inouye, M. Medina, and J. B. Xavier. Animal behavior and the microbiome. *Science*, 338(6104):198–199, 2012.

[64] G. S. Faria, S. A. Varela, and A. Gardner. The relation between RA Fisher's sexy-son hypothesis and WD Hamilton's greenbeard effect. *Evolution Letters*, 2(3):190–200, 2018.

[65] B. Feldmeyer, M. Kozielska, B. Kuijper, F. J. Weissing, L. W. Beukeboom, and I. Pen. Climatic variation and the geographical distribution of sex-determining mechanisms in the housefly. *Evolutionary Ecology Research*, 10(6):797–809, 2008.

[66] J. Felsenstein. Inbreeding and variance effective numbers in populations with overlapping generations. *Genetics*, 68:581–597, 1971.

[67] M. Fisher and A. Muth. A technique for permanently marking lizards. *Herpetological Review*, 20(2):45–46, 1989.

[68] R. A. Fisher. *The Genetical Theory of Natural Selection*. Clarendon Press, 1930.

[69] R. A. Fisher. The evolution of dominance. *Biological reviews*, 6(4):345–368, 1931.

[70] C. L. Fitzpatrick and M. R. Servedio. The evolution of male mate choice and female ornamentation: a review of mathematical models. *Current zoology*, 64 (3):323–333, 2018.

[71] M. Franco, P. Rubini, and M. Vecchi. Sex-determinants and their distribution in various populations of *Musca domestica* L. of Western Europe. *Genetical Research*, 40(03):279–293, 1982.

[72] R. P. Freckleton, P. H. Harvey, and M. Pagel. Phylogenetic analysis and comparative data: a test and review of evidence. *The American Naturalist*, 160(6):712–726, 2002.

[73] L. J. Funkhouser and S. R. Bordenstein. Mom knows best: the universality of maternal microbial transmission. *PLoS biology*, 11(8), 2013.

[74] B. L. Furman and B. J. Evans. Sequential turnovers of sex chromosomes in African clawed frogs (*Xenopus*) suggest some genomic regions are good at sex determination. *G3: Genes | Genomes | Genetics*, 6(11):3625–3633, 2016.

[75] T. Gamble, A. J. Geneva, R. E. Glor, and D. Zarkower. *Anolis* sex chromosomes are derived from a single ancestral pair. *Evolution*, 68(4):1027–1041, 2014.

[76] C. W. Gardiner. *Handbook of Stochastic Methods*. Springer, Berlin, 2009.

[77] M. T. Ghiselin. The evolution of hermaphroditism among animals. *Quarterly Review of Biology*, 44(2):189–208, 1969.

[78] J. H. Gillespie. Natural selection for within-generation variance in offspring number. *Genetics*, 76(3):601–606, 1974.

[79] J. H. Gillespie. Natural selection for variances in offspring numbers: a new evolutionary principle. *American Naturalist*, 111(981):1010–1014, 1977.

[80] R. S. Gomulkiewicz and A. Hastings. Ploidy and evolution by sexual selection: a comparison of haploid and diploid female choice models near fixation equilibria. *Evolution*, 44(4):757–770, 1990.

[81] A. Grafen. Biological signals as handicaps. *Journal of Theoretical Biology*, 144(4):517–546, 1990.

[82] J. W. Grant, M. J. Bryant, and C. E. Soos. Operational sex ratio, mediated by synchrony of female arrival, alters the variance of male mating success in Japanese medaka. *Animal Behaviour*, 49(2):367–375, 1995.

[83] P. B. Greenspoon and S. P. Otto. Evolution by Fisherian sexual selection in diploids. *Evolution*, 63(4):1076–1083, 2009.

[84] D. Grimanelli, O. Leblanc, E. Perotti, and U. Grossniklaus. Developmental genetics of gametophytic apomixis. *Trends in Genetics*, 17(10):597–604, 2001.

[85] C. Grossen, S. Neuenschwander, and N. Perrin. Temperature-dependent turnovers in sex-determination mechanisms: a quantitative model. *Evolution*, 65(1):64–78, 2011.

[86] D. Haig, F. Úbeda, and M. M. Patten. Specialists and generalists: the sexual ecology of the genome. *Cold Spring Harbor perspectives in biology*, 6(9): a017525, 2014.

[87] T. F. Hansen. On the definition and measurement of fitness in finite populations. *Journal of Theoretical Biology*, 419:36–43, 2017.

[88] L. J. Harmon, J. T. Weir, C. D. Brock, R. E. Glor, and W. Challenger. GEIGER: investigating evolutionary radiations. *Bioinformatics*, 24(1):129–131, 2008.

[89] D. L. Hartl and A. G. Clark. *Principles of population genetics*. Sinauer, 4th edition, 2007.

[90] I. M. Hastings. Manifestations of sexual selection may depend on the genetic basis of sex determination. *Proceedings of the Royal Society of London. Series B: Biological Sciences*, 258(1351):83–87, 1994.

[91] I. L. Heisler and J. W. Curtsinger. Dynamics of sexual selection in diploid populations. *Evolution*, 44(5):1164–1176, 1990.

[92] R. Hicks and R. Trivers. The social behavior of *Anolis valencienni*. In A. G. J. Rhodin and K. Mivata, editors, *Advances in herpetology and evolutionary biology*, pages 570–595. Museum of Comparative Zoology, Harvard University, Cambridge, MA, 1983.

[93] D. M. Hillis and D. M. Green. Evolutionary changes of heterogametic sex in the phylogenetic history of amphibians. *Journal of Evolutionary Biology*, 3 (1-2):49–64, 1990.

[94] C. E. Holleley, D. O'Meally, S. D. Sarre, J. A. M. Graves, T. Ezaz, K. Matsubara, B. Azad, X. Zhang, and A. Georges. Sex reversal triggers the rapid transition from genetic to temperature-dependent sex. *Nature*, 523(7558):79–82, 2015.

[95] E. Hörandl and D. Hojsgaard. The evolution of apomixis in angiosperms: a reappraisal. *Plant Biosystems*, 146(3):681–693, 2012.

[96] P. Innocenti and E. H. Morrow. The sexually antagonistic genes of *Drosophila melanogaster*. *PLoS biology*, 8(3), 2010.

[97] F. J. Janzen. Heritable variation for sex ratio under environmental sex determination in the common snapping turtle (*Chelydra serpentina*). *Genetics*, 131 (1):155–161, 1992.

[98] F. J. Janzen and G. L. Paukstis. Environmental sex determination in reptiles: ecology, evolution, and experimental design. *Quarterly Review of Biology*, 66 (2):149–179, 1991.

[99] F. J. Janzen and P. C. Phillips. Exploring the evolution of environmental sex determination, especially in reptiles. *Journal of Evolutionary Biology*, 19(6): 1775–1784, 2006.

[100] M. A. Johnson. A new method of temporarily marking lizards. *Herpetological Review*, 36(3):277–278, 2005.

[101] M. A. Johnson. *Behavioral ecology of Caribbean Anolis lizards: a comparative approach*. PhD thesis, Washington University, St. Louis, 2007.

[102] M. A. Johnson, L. J. Revell, and J. B. Losos. Behavioral convergence and adaptive radiation: effects of habitat use on territorial behavior in *Anolis* lizards. *Evolution*, 64(4):1151–1159, 2010.

[103] A. G. Jones, J. R. Arguello, and S. J. Arnold. Molecular parentage analysis in experimental newt populations: the response of mating system measures to variation in the operational sex ratio. *The American Naturalist*, 164(4): 444–456, 2004.

[104] A. Joshi and M. E. Moody. The cost of sex revisited: effects of male gamete output of hermaphrodites that are asexual in their female capacity. *Journal of theoretical biology*, 195(4):533–542, 1998.

[105] V. B. Kaiser and D. Bachtrog. Evolution of sex chromosomes in insects. *Annual Review of Genetics*, 44:91–112, 2010.

[106] K. D. Kallman. Genetics and geography of sex determination in the poeciliid fish, *Xiphophorus maculatus*. *Zoologica*, 50(1):151–190, 1965.

[107] K. D. Kallman. Evidence for the existence of transformer genes for sex in the teleost *Xiphophorus maculatus*. *Genetics*, 60(4):811, 1968.

[108] E. Kazancıoğlu and S. H. Alonzo. A comparative analysis of sex change in Labridae supports the size advantage hypothesis. *Evolution*, 64(8):2254–2264, 2010.

[109] K. King, O. Seppälä, and M. Neiman. Is more better? Polyploidy and parasite resistance. *Biology letters*, 8(4):598–600, 2012.

[110] M. Kirkpatrick. Sexual selection and the evolution of female choice. *Evolution*, 36(1):1–12, 1982.

[111] M. Kirkpatrick. Evolution of female choice and male parental investment in polygynous species: The demise of the "sexy son". *The American Naturalist*, 125(6):788–810, 1985.

[112] M. Kirkpatrick and N. H. Barton. Chromosome inversions, local adaptation and speciation. *Genetics*, 173(1):419–434, 2006.

[113] M. Kirkpatrick and D. W. Hall. Sexual selection and sex linkage. *Evolution*, 58(4):683–691, 2004.

[114] M. Kirkpatrick, T. Johnson, and N. H. Barton. General models of multilocus evolution. *Genetics*, 161(4):1727–1750, 2002.

[115] O. Kogan, M. Khasin, B. Meerson, D. Schneider, and C. R. Myers. Two-strain competition in quasi-neutral stochastic disease dynamics. *Phys. Rev. E*, 90: 042149, 2014.

[116] H. Kokko and M. D. Jennions. Parental investment, sexual selection and sex ratios. *Journal of evolutionary biology*, 21(4):919–948, 2008.

[117] H. Kokko, R. Brooks, J. M. McNamara, and A. I. Houston. The sexual selection continuum. *Proceedings of the Royal Society of London. Series B: Biological Sciences*, 269(1498):1331–1340, 2002.

[118] P. Koopman, J. Gubbay, N. Vivian, P. Goodfellow, and R. Lovell-Badge. Male development of chromosomally female mice transgenic for *Sry*. *Nature*, 351 (6322):117, 1991.

[119] D. Kovel and D. Jong. Selection on apomictic lineages of *Taraxacum* at establishment in a mixed sexual–apomictic population. *Journal of Evolutionary Biology*, 13(4):561–568, 2000.

[120] M. R. Kronforst, L. G. Young, D. D. Kapan, C. McNeely, R. J. O'Neill, and L. E. Gilbert. Linkage of butterfly mate preference and wing color preference cue at the genomic location of *wingless*. *Proceedings of the National Academy of Sciences*, 103(17):6575–6580, 2006.

[121] B. Kuijper, I. Pen, and F. J. Weissing. A guide to sexual selection theory. *Annual Review of Ecology, Evolution, and Systematics*, 43:287–311, 2012.

[122] C. Kvarnemo and I. Ahnesjo. The dynamics of operational sex ratios and competition for mates. *Trends in Ecology & Evolution*, 11(10):404–408, 1996.

[123] R. Lande. Models of speciation by sexual selection on polygenic traits. *Proceedings of the National Academy of Sciences*, 78(6):3721–3725, 1981.

[124] R. Lanfear, H. Kokko, and A. Eyre-Walker. Population size and the rate of evolution. *Trends in Ecology & Evolution*, 29(1):33–41, 2014.

[125] V. Laporte and B. Charlesworth. Effective population size and population subdivision in demographically structured populations. *Genetics*, 162(1):501–519, 2002.

[126] B. Y. Lee, G. Hulata, and T. D. Kocher. Two unlinked loci controlling the sex of blue tilapia (*Oreochromis aureus*). *Heredity*, 92(6):543–549, 2004.

[127] D. A. Levin. Polyploidy and novelty in flowering plants. *The American Naturalist*, 122(1):1–25, 1983.

[128] R. C. Lewontin. The units of selection. *Annual review of ecology and systematics*, 1(1):1–18, 1970.

[129] Y. T. Lin, H. Kim, and C. R. Doering. Features of fast living: On the weak selection for longevity in degenerate birth-death processes. *J. Stat. Phys.*, 148: 646–662, 2012.

[130] J. R. Linklater, B. Wertheim, S. Wigby, and T. Chapman. Ejaculate depletion patterns evolve in response to experimental manipulation of sex ratio in *Drosophila melanogaster*. *Evolution*, 61(8):2027–2034, 2007.

[131] J. B. Losos. *Lizards in an evolutionary tree: ecology and adaptive radiation of anoles*. University of California Press, Berkeley, 2009.

[132] J. B. Losos, T. R. Jackman, A. Larson, K. de Queiroz, and L. Rodríguez-Schettino. Contingency and determinism in replicated adaptive radiations of island lizards. *Science*, 279(5359):2115–2118, 1998.

[133] J. T. Lovell, O. M. Aliyu, M. Mau, M. E. Schranz, M. Koch, C. Kiefer, B.-H. Song, T. Mitchell-Olds, and T. F. Sharbel. On the origin and evolution of apomixis in *Boechera*. *Plant reproduction*, 26(4):309–315, 2013.

[134] J. E. Lovich and J. W. Gibbons. A review of techniques for quantifying sexual size dimorphism. *Growth Development and Aging*, 56:269–269, 1992.

[135] J. C. Lyman and N. C. Ellstrand. Relative contribution of breeding system and endemism to genotypic diversity: the outcrossing endemic *Taraxacum californicum* vs. the widespread apomict *T. officinale* (sensu lato). *Madrono*, pages 283–289, 1998.

[136] B. K. Mable and S. P. Otto. The evolution of life cycles with haploid and diploid phases. *BioEssays*, 20(6):453–462, 1998.

[137] L. Majeskỳ, R. J. Vašut, M. Kitner, and B. Trávníček. The pattern of genetic variability in apomictic clones of *Taraxacum officinale* indicates the alternation of asexual and sexual histories of apomicts. *PLoS One*, 7(8), 2012.

[138] J. E. Mank and J. C. Avise. Evolutionary diversity and turn-over of sex determination in teleost fishes. *Sexual Development*, 3(2-3):60–67, 2009.

[139] J. E. Mank, D. W. Hall, M. Kirkpatrick, and J. C. Avise. Sex chromosomes and male ornaments: a comparative evaluation in ray-finned fishes. *Proceedings of the Royal Society B: Biological Sciences*, 273(1583):233–236, 2006.

[140] J. E. Mank, D. E. L. Promislow, and J. C. Avise. Evolution of alternative sex-determining mechanisms in teleost fishes. *Biological Journal of the Linnean Society*, 87(1):83–93, 2006.

[141] Y. Matsumoto and D. Crews. Molecular mechanisms of temperature-dependent sex determination in the context of ecological developmental biology. *Molecular and Cellular Endocrinology*, 354(1-2):103–110, 2012.

[142] J. Maynard Smith. *The evolution of sex*. Cambridge University Press, 1978.

[143] D. M. McCandlish and A. Stoltzfus. Modeling evolution using the probability of fixation: History and implications. *Quarterly Review of Biology*, 89(3): 225–252, 2014.

[144] S. McGaugh and F. Janzen. Effective heritability of targets of sex-ratio selection under environmental sex determination. *Journal of Evolutionary Biology*, 24(4):784–794, 2011.

[145] S. E. McGaugh, L. E. Schwanz, R. M. Bowden, J. E. Gonzalez, and F. J. Janzen. Inheritance of nesting behaviour across natural environmental variation in a turtle with temperature-dependent sex determination. *Proceedings of the Royal Society of London B: Biological Sciences*, 277(1685):1219–1226, 2009.

[146] S. E. McGaugh, R. M. Bowden, C.-H. Kuo, and F. J. Janzen. Field-measured heritability of the threshold for sex determination in a turtle with temperature-dependent sex determination. *Evolutionary Ecology Research*, 13:75, 2011.

[147] A. McKane, T. Biancalani, and T. Rogers. Stochastic pattern formation and spontaneous polarisation: The linear noise approximation and beyond. *Bulletin of Mathematical Biology*, 76:895, 2014.

[148] R. P. Meisel, T. Davey, J. H. Son, A. C. Gerry, T. Shono, and J. G. Scott. Is multifactorial sex determination in the house fly, *Musca domestica* (L.), stable over time? *Journal of Heredity*, 107(7):615–625, 2016.

[149] S. B. J. Menken, E. Smit, and J. C. M. den Nijs. Genetical population structure in plants: gene flow between diploid sexual and triploid asexual dandelions (*Taraxacum section Ruderalia*). *Evolution*, 49(6):1108–1118, 1995.

[150] L. G. Miles, S. R. Isberg, T. C. Glenn, S. L. Lance, P. Dalzell, P. C. Thomson, and C. Moran. A genetic linkage map for the saltwater crocodile (*Crocodylus porosus*). *Bmc Genomics*, 10(1):339, 2009.

[151] S. C. Mills and J. D. Reynolds. Operational sex ratio and alternative reproductive behaviours in the European bitterling, *Rhodeus sericeus*. *Behavioral Ecology and Sociobiology*, 54(2):98–104, 2003.

[152] J. C. Mitani, J. Gros-Louis, and A. F. Richards. Sexual dimorphism, the operational sex ratio, and the intensity of male competition in polygynous primates. *The American Naturalist*, 147(6):966–980, 1996.

[153] T. S. Mitchell, J. A. Maciel, and F. J. Janzen. Does sex-ratio selection influence nest-site choice in a reptile with temperature-dependent sex determination? *Proceedings of the Royal Society of London B: Biological Sciences*, 280(1772): 20132460, 2013.

[154] I. Miura, H. Ohtani, M. Nakamura, Y. Ichikawa, and K. Saitoh. The origin and differentiation of the heteromorphic sex chromosomes Z, W, X, and Y in the frog *Rana rugosa*, inferred from the sequences of a sex-linked gene, ADP/ATP translocase. *Molecular biology and evolution*, 15(12):1612–1619, 1998.

[155] M. Mogie. Is there a cost of sex in hermaphrodites? *Naturwissenschaften*, 83: 225–226, 1996.

[156] M. Mogie and H. Ford. Sexual and asexual *Taraxacum* species. *Biological Journal of the Linnean Society*, 35(2):155–168, 1988.

[157] P. A. P. Moran. Random processes in genetics. *Proceedings of the Cambridge Philosophical Society*, 54(01):60–71, 1958.

[158] T. Morita, A. A. Sterk, and J. C. M. den Nijs. The significance of agamospermous triploid pollen donors in the sexual relationships between diploids and triploids in *Taraxacum* (Compositae). *Plant Species Biology*, 5(1):167–176, 1990.

[159] C. L. Morjan. How rapidly can maternal behavior affecting primary sex ratio evolve in a reptile with environmental sex determination? *American Naturalist*, 162(2):205–219, 2003.

[160] P. Muralidhar. Mating preferences of selfish sex chromosomes. *Nature*, 570 (7761):376–379, 2019.

[161] P. Muralidhar and C. Veller. Sexual antagonism and the instability of environmental sex determination. *Nature Ecology & Evolution*, 2:343–351, 2018.

[162] M. Neiman, D. Paczesniak, D. M. Soper, A. T. Baldwin, and G. Hehman. Wide variation in ploidy level and genome size in a new zealand freshwater snail with coexisting sexual and asexual lineages. *Evolution*, 65(11):3202–3216, 2011.

[163] M. G. Newberry, D. M. McCandlish, and J. B. Plotkin. Assortative mating can impede or facilitate fixation of underdominant alleles. *Theoretical Population Biology*, 112:14–21, 2016.

[164] M. Nishioka, I. Miura, and K. Saitoh. Sex chromosomes of *Rana rugosa* with special reference to local differences in sex-determining mechanism. *Scientific report of the Laboratory for Amphibian Biology, Hiroshima University*, 12: 55–81, 1993.

[165] M. Ogata, H. Ohtani, T. Igarashi, Y. Hasegawa, Y. Ichikawa, and I. Miura. Change of the heterogametic sex from male to female in the frog. *Genetics*, 164(2):613–620, 2003.

[166] C. L. Organ and D. E. Janes. Evolution of sex chromosomes in Sauropsida. *Integrative and Comparative Biology*, 48(4):512–519, 2008.

[167] S. H. Orzack, J. J. Sohn, K. D. Kallman, S. A. Levin, and R. Johnston. Maintenance of the three sex chromosome polymorphism in the platyfish, *Xiphophorus maculatus*. *Evolution*, 34(4):663–672, 1980.

[168] N. Ospina-Alvarez and F. Piferrer. Temperature-dependent sex determination in fish revisited: prevalence, a single sex ratio response pattern, and possible effects of climate change. *PloS one*, 3(7):e2837, 2008.

[169] S. P. Otto. On evolution under sexual and viability selection: a two-locus diploid model. *Evolution*, 45(6):1443–1457, 1991.

[170] S. P. Otto. The evolutionary consequences of polyploidy. *Cell*, 131(3):452–462, 2007.

[171] S. P. Otto, J. R. Pannell, C. L. Peichel, T.-L. Ashman, D. Charlesworth, A. K. Chippindale, L. F. Delph, R. F. Guerrero, S. V. Scarpino, and B. F. McAllister. About PAR: the distinct evolutionary dynamics of the pseudoautosomal region. *Trends in Genetics*, 27(9):358–367, 2011.

[172] P. Ozias-Akins and P. J. van Dijk. Mendelian genetics of apomixis in plants. *Annual Review of Genetics*, 41:509–537, 2007.

[173] T. L. Parsons and T. Rogers. Dimension reduction via timescale separation in stochastic dynamical systems. *arXiv:1510.07031*, 2015.

[174] T. L. Parsons, C. Quince, and J. B. Plotkin. Some consequences of demographic stochasticity in population genetics. *Genetics*, 185(4):1345–1354, 2010.

[175] N. Perrin. Sex reversal: a fountain of youth for sex chromosomes? *Evolution*, 63(12):3043–3049, 2009.

[176] N. Pezaro, J. S. Doody, and M. B. Thompson. The ecology and evolution of temperature-dependent reaction norms for sex determination in reptiles: a mechanistic conceptual model. *Biological Reviews*, 92(3):1348–1364, 2017.

[177] I. Pipoly, V. Bókony, M. Kirkpatrick, P. F. Donald, T. Székely, and A. Liker. The genetic sex-determination system predicts adult sex ratios in tetrapods. *Nature*, 527(7576):91–94, 2015.

[178] T. Pizzari and A. Gardner. The sociobiology of sex: inclusive fitness consequences of inter-sexual interactions. *Philosophical Transactions of the Royal Society B: Biological Sciences*, 367(1600):2314–2323, 2012.

[179] M. Pokorna and L. Kratochvíl. Phylogeny of sex-determining mechanisms in squamate reptiles: are sex chromosomes an evolutionary trap? *Zoological Journal of the Linnean Society*, 156(1):168–183, 2009.

[180] A. Pomiankowski. The costs of choice in sexual selection. *Journal of Theoretical Biology*, 128(2):195–218, 1987.

[181] A. Pomiankowski, Y. Iwasa, and S. Nee. The evolution of costly mate preferences I. Fisher and biased mutation. *Evolution*, 45(6):1422–1430, 1991.

[182] A. N. Pomiankowski. Sexual selection: the handicap principle does work–sometimes. *Proceedings of the Royal society of London. Series B. Biological sciences*, 231(1262):123–145, 1987.

[183] A. N. Pomiankowski. The evolution of female mate preference for male genetic quality. *Oxford surveys in evolutionary biology*, 1988.

[184] H. Pröhl. Population differences in female resource abundance, adult sex ratio, and male mating success in *Dendrobates pumilio*. *Behavioral Ecology*, 13(2): 175–181, 2002.

[185] S. Pruett-Jones and M. Lewis. Sex ratio and habitat limitation promote delayed dispersal in superb fairy-wrens. *Nature*, 348(6301):541–542, 1990.

[186] R. A. Pyron, F. T. Burbrink, and J. J. Wiens. A phylogeny and revised classification of Squamata, including 4161 species of lizards and snakes. *BMC evolutionary biology*, 13(1):93, 2013.

[187] A. E. Quinn, A. Georges, S. D. Sarre, F. Guarino, T. Ezaz, and J. A. M. Graves. Temperature sex reversal implies sex gene dosage in a reptile. *Science*, 316(5823):411–411, 2007.

[188] A. E. Quinn, S. D. Sarre, T. Ezaz, J. A. Marshall Graves, and A. Georges. Evolutionary transitions between mechanisms of sex determination in vertebrates. *Biology Letters*, 7(3):443–448, 2011.

[189] R. S. Radder, A. E. Quinn, A. Georges, S. D. Sarre, and R. Shine. Genetic evidence for co-occurrence of chromosomal and thermal sex-determining systems in a lizard. *Biology Letters*, 4(2):176–178, 2007.

[190] H. K. Reeve and D. W. Pfennig. Genetic biases for showy males: Are some genetic systems especially conducive to sexual selection? *Proceedings of the National Academy of Sciences*, 100(3):1089–1094, 2003.

[191] H. K. Reeve and J. S. Shellman-Reeve. The general protected invasion theory: sex biases in parental and alloparental care. *Evolutionary Ecology*, 11(3):357–370, 1997.

[192] J. M. Refsnider, C. Milne-Zelman, D. A. Warner, and F. J. Janzen. Population sex ratios under differing local climates in a reptile with environmental sex determination. *Evolutionary ecology*, 28(5):977–989, 2014.

[193] L. J. Revell. phytools: an R package for phylogenetic comparative biology (and other things). *Methods in ecology and evolution*, 3(2):217–223, 2012.

[194] W. Rice and A. Chippindale. Intersexual ontogenetic conflict. *Journal of Evolutionary Biology*, 14(5):685–693, 2001.

[195] W. R. Rice. Sex chromosomes and the evolution of sexual dimorphism. *Evolution*, 38(4):735–742, 1984.

[196] W. R. Rice. On the instability of polygenic sex determination: the effect of sex-specific selection. *Evolution*, 40(3):633–639, 1986.

[197] W. R. Rice. The accumulation of sexually antagonistic genes as a selective agent promoting the evolution of reduced recombination between primitive sex chromosomes. *Evolution*, 41(4):911–914, 1987.

[198] W. R. Rice. Sexually antagonistic genes: experimental evidence. *Science*, 256 (5062):1436–1439, 1992.

[199] W. R. Rice. Male fitness increases when females are eliminated from gene pool: implications for the Y chromosome. *Proceedings of the National Academy of Sciences USA*, 95(11):6217–6221, 1998.

[200] A. J. Richards. Apomixis in flowering plants: an overview. *Philosophical Transactions of the Royal Society of London. Series B: Biological Sciences*, 358(1434):1085–1093, 2003.

[201] H. Risken. *The Fokker-Planck Equation*. Springer, Berlin, 1989.

[202] Á. S. Roco, A. W. Olmstead, S. J. Degitz, T. Amano, L. B. Zimmerman, and M. Bullejos. Coexistence of Y, W, and Z sex chromosomes in *Xenopus tropicalis*. *Proceedings of the National Academy of Sciences USA*, 112(34): E4752–E4761, 2015.

[203] M. Saccucci, R. Denton, M. Holding, and H. Gibbs. Polyploid unisexual salamanders have higher tissue regeneration rates than diploid sexual relatives. *Journal of Zoology*, 300(2):77–81, 2016.

[204] B. J. Sanderson, M. E. Augat, D. R. Taylor, and E. D. Brodie III. Scale dependence of sex ratio in wild plant populations: implications for social selection. *Ecology and evolution*, 6(5):1411–1419, 2016.

[205] M. Schartl. Sex chromosome evolution in non-mammalian vertebrates. *Current opinion in genetics & development*, 14(6):634–641, 2004.

[206] T. W. Schoener and A. Schoener. Densities, sex ratios, and population structure in four species of Bahamian *Anolis* lizards. *The Journal of Animal Ecology*, pages 19–53, 1980.

[207] A. L. Schroeder, K. J. Metzger, A. Miller, and T. Rhen. A novel candidate gene for temperature-dependent sex determination in the common snapping turtle. *Genetics*, 203(1):557–571, 2016.

[208] L. Schwanz, T. Ezaz, B. Gruber, and A. Georges. Novel evolutionary pathways of sex-determining mechanisms. *Journal of Evolutionary Biology*, 26(12):2544–2557, 2013.

[209] L. E. Schwanz and S. R. Proulx. Mutual information reveals variation in temperature-dependent sex determination in response to environmental fluctuation, lifespan and selection. *Proceedings of the Royal Society of London B: Biological Sciences*, 275(1650):2441–2448, 2008.

[210] F. M. Scudo. Sex population genetics. *La Ricerca Scientifica, Anno 34, Serie 2, II-B*, 5(2):93–143, 1964.

[211] F. M. Scudo. Criteria for the analysis of multifactorial sex determination. *Monitore Zoologico Italiano*, 1:1–21, 1967.

[212] J. Seger. Unifying genetic models for the evolution of female choice. *Evolution*, 39(6):1185–1193, 1985.

[213] J. Seger and R. Trivers. Asymmetry in the evolution of female mating preferences. *Nature*, 319(6056):771–773, 1986.

[214] A. M. Selmecki, Y. E. Maruvka, P. A. Richmond, M. Guillet, N. Shoresh, A. L. Sorenson, S. De, R. Kishony, F. Michor, R. Dowell, et al. Polyploidy can drive rapid adaptation in yeast. *Nature*, 519(7543):349–352, 2015.

[215] J. R. Ser, R. B. Roberts, and T. D. Kocher. Multiple interacting loci control sex determination in Lake Malawi cichlid fish. *Evolution*, 64(2):486–501, 2010.

[216] M. R. Servedio and R. Bürger. The effects on parapatric divergence of linkage between preference and trait loci versus pleiotropy. *Genes*, 9(4):217, 2018.

[217] K. L. Shaw and S. C. Lesnick. Genomic linkage of male song and female acoustic preference QTL underlying a rapid species radiation. *Proceedings of the National Academy of Sciences*, 106(24):9737–9742, 2009.

[218] R. Shine. Why is sex determined by nest temperature in many reptiles? *Trends in Ecology & Evolution*, 14(5):186–189, 1999.

[219] D. E. Soltis, C. J. Visger, and P. S. Soltis. The polyploidy revolution then... and now: Stebbins revisited. *American journal of botany*, 101(7):1057–1078, 2014.

[220] T. Sorensen. Sexual chromosome-aberrants in triploid apomictic *Taraxaca*. *Bot. Tidsskr.*, 54:1–22, 1958.

[221] A. M. Spence. Job market signaling. *The Quarterly Journal of Economics*, 87 (3):355–374, 1973.

[222] W. Stephan, B. Charlesworth, and G. McVean. The effect of background selection at a single locus on weakly selected, partially linked variants. *Genet. Res., Camb.*, 73:133–146, 1999.

[223] Y. Takehana, M. Matsuda, T. Myosho, M. L. Suster, K. Kawakami, T. Shin, Y. Kohara, Y. Kuroki, A. Toyoda, A. Fujiyama, et al. Co-option of *Sox3* as the male-determining factor on the Y chromosome in the fish *Oryzias dancena*. *Nature communications*, 5, 2014.

[224] C. M. Tanaka and Y. Iwasa. Cultural evolution of a belief controlling human mate choice: Dynamic modeling of the hinoeuma superstition in Japan. *Journal of Theoretical Biology*, 309:20–28, 2012.

[225] I. C. Q. Tas and P. J. Van Dijk. Crosses between sexual and apomictic dandelions (*Taraxacum*). I. The inheritance of apomixis. *Heredity*, 83(6):707–714, 1999.

[226] P. D. Taylor and A. Sauer. The selective advantage of sex-ratio homeostasis. *American Naturalist*, 116(2):305–310, 1980.

[227] M. Te Beest, J. J. Le Roux, D. M. Richardson, A. K. Brysting, J. Suda, M. Kubešová, and P. Pyšek. The more the better? The role of polyploidy in facilitating plant invasions. *Annals of botany*, 109(1):19–45, 2012.

[228] W. Traut and U. Willhoeft. A jumping sex determining factor in the fly *Megaselia scalaris*. *Chromosoma*, 99(6):407–412, 1990.

[229] Tree of Sex Consortium. Tree of Sex: A database of sexual systems. *Scientific Data*, 1, 2014.

[230] R. Trivers. Parental investment and sexual selection. In B. Campbell, editor, *Sexual selection and the descent of man*, pages 136–179. Aldine, Chicago, 1972.

[231] R. Trivers. *Social evolution*. Benjamin Cummings, Menlo Park, 1985.

[232] R. L. Trivers. Sex differences in rates of recombination and sexual selection. In R. E. Michod and B. R. Levin, editors, *The evolution of sex: an examination of current ideas*. Sinauer, 1988.

[233] F. Úbeda, D. Haig, and M. M. Patten. Stable linkage disequilibrium owing to sexual antagonism. *Proceedings of the Royal Society B: Biological Sciences*, 278(1707):855–862, 2011.

[234] Y. Uno, C. Nishida, Y. Oshima, S. Yokoyama, I. Miura, Y. Matsuda, and M. Nakamura. Comparative chromosome mapping of sex-linked genes and identification of sex chromosomal rearrangements in the Japanese wrinkled frog (*Rana rugosa*, Ranidae) with ZW and XY sex chromosome systems. *Chromosome Research*, 16(4):637–647, 2008.

[235] N. Valenzuela, D. C. Adams, and F. J. Janzen. Pattern does not equal process: exactly when is sex environmentally determined? *American Naturalist*, 161 (4):676–683, 2003.

[236] R. Van der Hulst, T. H. Mes, M. Falque, P. Stam, J. Den Nijs, and K. Bachmann. Genetic structure of a population sample of apomictic dandelions. *Heredity*, 90(4):326–335, 2003.

[237] P. J. van Dijk. Ecological and evolutionary opportunities of apomixis: insights from *Taraxacum* and *Chondrilla*. *Philosophical Transactions of the Royal Society of London. Series B: Biological Sciences*, 358(1434):1113–1121, 2003.

[238] P. J. van Dijk and J. M. T. Bakx-Schotman. Formation of unreduced megaspores (diplospory) in apomictic dandelions (*Taraxacum officinale*, sl) is controlled by a sex-specific dominant locus. *Genetics*, 166(1):483–492, 2004.

[239] van Dijk P J, H. de Jong, K. Vijverberg, and B. A. The evolutionary forces acting on female mating preferences in polygynous animals. In I. Schön, K. Martens, and P. J. van Dijk, editors, *Lost Sex*, pages 475–493. Springer, Netherlands, 2009.

[240] van Dijk P J, H. de Jong, K. Vijverberg, and B. A. An apomixis-gene's view on dandelions. In I. Schön, K. Martens, and P. J. van Dijk, editors, *Lost Sex*, pages 475–493. Springer, Netherlands, 2009.

[241] G. S. van Doorn. Intralocus sexual conflict. *Annals of the New York Academy of Sciences*, 1168(1):52–71, 2009.

[242] G. S. van Doorn. Evolutionary transitions between sex-determining mechanisms: a review of theory. *Sexual Development*, 8(1-3):7–19, 2014.

[243] G. S. van Doorn and M. Kirkpatrick. Turnover of sex chromosomes induced by sexual conflict. *Nature*, 449:909–912, 2007.

[244] G. S. van Doorn and M. Kirkpatrick. Transitions between male and female heterogamety caused by sex-antagonistic selection. *Genetics*, 186(2):629–645, 2010.

[245] R. J. Vašut, K. Vijverberg, P. J. van Dijk, and H. de Jong. Fluorescent in situ hybridization shows *DIPLOSPOROUS* located on one of the NOR chromosomes in apomictic dandelions (*Taraxacum*) in the absence of a large hemizygous chromosomal region. *Genome*, 57(11/12):609–620, 2014.

[246] C. Veller, P. Muralidhar, G. W. Constable, and M. A. Nowak. Drift-induced selection between male and female heterogamety. *Genetics*, 207(2):711–727, 2017.

[247] C. Veller, N. Kleckner, and M. A. Nowak. A rigorous measure of genome-wide genetic shuffling that takes into account crossover positions and Mendel's second law. *Proceedings of the National Academy of Sciences USA*, 116(5): 1659–1668, 2019.

[248] C. Veller, P. Muralidhar, and H. D. On the logic of fisherian sexual selection. *Evolution*, 2020.

[249] M. H. Verduijn, P. J. Van Dijk, and J. M. M. Van Damme. The role of tetraploids in the sexual–asexual cycle in dandelions (*Taraxacum*). *Heredity*, 93(4):390–398, 2004.

[250] J. Verner. Selection for sex ratio. *American Naturalist*, 99(908):419–421, 1965.

[251] B. Vicoso and D. Bachtrog. Numerous transitions of sex chromosomes in Diptera. *PLoS Biology*, 13(4):e1002078, 2015.

[252] K. Vijverberg, S. Milanovic-Ivanovic, T. Bakx-Schotman, and P. J. van Dijk. Genetic fine-mapping of *DIPLOSPOROUS* in *Taraxacum* (dandelion; Asteraceae) indicates a duplicated *DIP*-gene. *BMC Plant Biology*, 10(1):154, 2010.

[253] S. Vuilleumier, R. Lande, J. Van Alphen, and O. Seehausen. Invasion and fixation of sex-reversal genes. *Journal of Evolutionary Biology*, 20(3):913–920, 2007.

[254] D. Warner and R. Shine. The adaptive significance of temperature-dependent sex determination in a reptile. *Nature*, 451(7178):566, 2008.

[255] D. A. Warner and R. Shine. The adaptive significance of temperature-dependent sex determination: experimental tests with a short-lived lizard. *Evolution*, 59(10):2209–2221, 2005.

[256] J. H. Werren, L. Baldo, and M. E. Clark. Wolbachia: master manipulators of invertebrate biology. *Nature Reviews Microbiology*, 6(10):741–751, 2008.

[257] M. C. Whitlock. Fixation probability and time in subdivided populations. *Genetics*, 164(2):767–779, 2003.

[258] J. Whitton, C. J. Sears, E. J. Baack, and S. P. Otto. The dynamic nature of apomixis in the angiosperms. *International Journal of Plant Sciences*, 169(1): 169–182, 2008.

[259] A. S. Wilkins. Moving up the hierarchy: a hypothesis on the evolution of a genetic sex determination pathway. *BioEssays*, 17(1):71–77, 1995.

[260] E. E. Williams. The origin of faunas. Evolution of lizard congeners in a complex island fauna: a trial analysis. In *Evolutionary biology*, pages 47–89. Springer, 1972.

[261] G. C. Williams. The question of adaptive sex ratio in outcrossed vertebrates. *Proceedings of the Royal Society of London B: Biological Sciences*, 205(1161): 567–580, 1979.

[262] S. Wright. Evolution in Mendelian populations. *Genetics*, 16(2):97–159, 1931.

[263] M. Xu and K. L. Shaw. Genetic coupling of signal and preference facilitates sexual isolation during rapid speciation. *Proceedings of the Royal Society B*, 286(1913):20191607, 2019.

[264] A. Zahavi. Mate selection—a selection for a handicap. *Journal of theoretical Biology*, 53(1):205–214, 1975.