UNIVERSITY COLLEGE LONDON

Investigating the evolution of sex-specific phenotypes

A Thesis submitted for the degree of Doctor of Philosophy

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I, Charles Dominique Léon Mullon, confirm that the work presented in this thesis is my own. Where information has been derived from other sources, I confirm that this has been indicated in the thesis.

Thesis abstract

This thesis uses theoretical models to investigate a diverse set of questions that revolve around the evolution sex-specific phenotypes. Chapter 1 studies the evolution of sex-determining mechanisms. It investigates the evolutionary change in the coding sequences of sex determining genes associated with the recruitment of a top regulatory gene in *Drosophila*. We find that this recruitment coincided with changes in the evolution of all the genes of the sex determining pathway. We discuss how these changes are tied with the genes' molecular functions, and highlight the limits of inference from DNA sequence change only. Chapter 2 investigates the genomic distribution of sexually antagonistic alleles. Our study predicts that the interplay of sexually antagonistic selection and genetic drift leads to the accumulation of sexually antagonistic alleles on the X in XY species and, on the autosomes in ZW species, especially when sexual competition is strong among males. Chapter 3 studies the evolution and consequences of sex-specific reproductive variance by constructing a population genetic model that is based on an explicit representation of sexual reproduction. In particular, we derive the probability of fixation for mutations affecting male and female reproductive traits in different ways and find that sex-specific reproductive variance may have profound consequences for the evolution of sex-specific phenotypes. Finally, chapter 4 adapts this latter model to investigate the evolution of developmental instability in the presence of female choice. Developmental instability can be selected for by female choice. But it can have very dire consequences for other aspects of the phenotype, notably in female fecundity and offspring survival. We discuss the effects of reproductive variance on whether these detrimental effects are capable of preventing developmental instability. Overall, this thesis highlights how not only sex-specific selection, but also sex-specific variance in gene transmission contribute to variation in sex-specific phenotypes.

Acknowledgements

I thank my supervisors, Max Reuter and Andrew Pomiankowski for their guidance, support and patience, which have made writing this thesis almost always pleasurable. Their rigour and interest in science will remain a model to me. I would also like to thank my collaborator Laurent Lehmann whose encouragements and enthusiasm have been invaluable.

To those I have shared an office with from GEE, thank you for your assistance, entertainment and for putting up with me. Andy, thanks for being willing to stay out very late in horrible bars. Thanks to those of CoMPLEX who have been around uni these last five (or even six) years, Gwenan, Dot, Lisa, Max, Kevin, Johannes, and Sam, meeting you all has been as enriching as entertaining. And especially to Lorette, who was there when I couldn't speak and every time I needed a break. Also to Alex, sadly far away, still big. To you from home, Anne, Thomas and Tanguy, I have missed you.

Finally, thanks to my parents, Dominique and Christian, who manage to remain awesome after all these years.

for Rachel and Justine, who never cease to amaze me, with all my love

and for Pierre, the coolest, who's had to deal with so much more than writing a thesis these last four years

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General introduction

Sexual reproduction is the fusion of two gametes. More often than not, one gamete is much larger than the other. This difference in gamete size, or anisogamy, divides a population into two sexes. Large gamete producers are females, while small gamete producers are males. Since the appearance of anisogamy, evolution has produced remarkable sex-specific attributes that extend far beyond the requirements of producing different gametes. Males and females of the same species can exhibit differences in phenotype so spectacular that it is sometimes startling that they share the vast majority of their genomes. So much so that eminent taxonomists have famously mistaken males and females as species (Andersson, 1994). Examples of sex-specific differences encompass all levels of the organism, from subtle gene expression to intricate ornaments and complex behaviour. Phenotypic traits that are expressed differently in the sexes are said to be sexually dimorphic. This thesis explores various questions that revolve around the evolution of sexual dimorphism using theoretical models. It spans multiple stages of its evolution as well as different scales of measurements. In this section, the main topics that are studied in this thesis are introduced, together with the questions we set out to answer. Relevant reviews of the literature are found in each chapter.

At the root of sexual dimorphism lies a chemical signal that tells whether an organism is male or female. In most invertebrates, this signal is set up cell-autonomously early in development and installs a life-long signature of sex. Sex determination systems describe the mechanisms behind the implementation of this developmental decision, and how cellular memory is maintained. Sex determination is primordial for the development of sexual dimorphism, and its evolution is investigated in chapter 1.

In contrast to other fundamental developmental processes, the molecular mechanisms that underlie sex determination have not been conserved (Marin and Baker, 1998). And even closely related species can exhibit significant differences in sex determination mechanisms, suggesting fast evolutionary turnover (Sánchez, 2008; Gempe and Beye, 2011). Despite this rapid divergence, the architecture of the gene pathway connecting sex determining genes is relatively well

conserved (Sánchez, 2008). The genes involved in sex determination tend to interact with one another linearly. To be more specific, after an initial signal, genes are activated in a cascade, one after the other and one by the other, including an auto-regulatory gene which preserves the cellular memory of the sex. Eventually, the cascade activates the final male and female differentiation genes, defined experimentally as those genes lowest in the cascade that can reverse the whole implementation of sex decision.

The bottom differentiation genes are shared by a large number of taxa, but as one moves up the sex determining cascade, the genes involved at each step are shared by smaller and smaller phylogenetic groups and increasingly diverse (Marin and Baker, 1998). This has led to the interesting hypothesis that sex determination cascades evolve from the bottom up, constructed by the successive recruitment of top regulators (Pomiankowski et al., 2004). It is unclear what general principle underlies this bottom-up evolution, or even whether such a general principle exists (Wilkins, 2002), but testable hypotheses on the repercussions of bottom-up evolution can be formulated. In chapter 1, we test some of these hypotheses. By combining the idea that sex-determining cascades evolve from the bottom-up, with the substantial knowledge of the molecular interactions between the *Drosophila* sex-determining genes, we formulate predictions about the evolution of the amino-acid sequences of the genes involved. We test these using DNA sequence data and a computational model of sequence evolution. The degree of agreement between predictions and results are then used to suggest refinements to the evolutionary scenario that led to the *Drosophila* sex determining cascade.

Once the sex determination signal is established, a cell has a number of sex-specific regulators at its disposal. It is then able to fine-tune gene expression according to the sex of the individual it resides in, and in coordination with other cells, produce complex sexually dimorphic phenotypes. But the path from sex determination to sexual dimorphism is not necessarily straightforward. Some of the obstacles in the evolution of sexual dimorphism and their consequences are investigated in chapter 2.

In an adaptive scenario, a sexually dimorphic trait reflects the adaptation to sex-specific fitness peaks. It is the result of a long history of selection that pushed the trait in different directions, depending on the sex it is expressed in. But males and females of the same species share a common gene pool and, in all likelihood, a homologous trait is the product of the same genes irrespective of sex. So until the development of a trait is independent in males and females, its value differs by very little across the sexes, and reflects some average of the selection pressures it is subject

to in both sexes (Van Doorn, 2009; Bonduriansky and Chenoweth, 2009). This tug-of-war has been coined as “sexual antagonism" (Parker, 1979; Rice, 1984). At the level of the gene, sexual antagonism means that while selection on one sex favors the fixation of one allele, selection on the other sex favors fixation of another allele. A possible evolutionary outcome of this tug-of-war is that neither allele fixes (Owen, 1953; Kidwell et al., 1977), and sexually antagonistic genetic variation persists in the gene pool. Thus, sexual antagonism may contribute to the maintenance of genetic variation for fitness in the face of selection, a central problem of evolutionary genetics.

A question of long-standing interest has been where sexually antagonistic genetic variation resides within the genome. The imbalance of sexually antagonistic variation across the genome may have important consequences. For instance, the presence of this type of variation on the X-chromosome would significantly hamper the sexual selection of good genes (Pischedda and Chippindale, 2006). Since males only transmit their X chromosome to their female offspring, daughters of high-fitness males necessarily inherit genes that are detrimental to female fitness, and simultaneously, sons of high-fitness male do not inherit any of the X-linked male-beneficial genes. Nonetheless, the traditionally held view is that the X chromosome (or the Z in a ZW species) is a hotspot for sexually antagonistic variation (Rice, 1984; Gavrilets and Rice, 2006). As it has recently been pointed out, the theoretical and empirical grounds to support this view are not unequivocal (Fry, 2010).

In chapter 2, we argue that there has been a crucial omission in the discussion of the genomic location of sexually antagonistic variation. Previous theoretical approaches have concentrated on how the difference in ploidy and sexual antagonistic selection interact (Owen, 1953; Kidwell et al., 1977; Rice, 1984; Gavrilets and Rice, 2006; Fry, 2010; Jordan and Charlesworth, 2011). They have ignored the role genetic drift. But this latter may be a deciding ingredient. Indeed, if sexually antagonistic promotes variation, genetic drift destroys it. Thus, everything else being equal, the chromosome harbouring the most variation is the one suffering the weakest intensity of genetic drift. Since there are always fewer copies of the X (or Z) than of an autosome, the sex chromosome is expected to be subject to a greater intensity of genetic drift. But this baseline disadvantage for the sex chromosome may either be compensated, if the homogametic sex has lower reproductive variance, or be amplified, if it has higher reproductive variance (Charlesworth et al., 1987; Caballero, 1995; Vicoso and Charlesworth, 2009). For instance, since males tend to have higher variance in reproductive success than females, the lower uncertainty in the transmission of maternal genes compensates for the lower copy number of X chromosomes, and so the difference

in intensity of genetic drift between the X and autosomes is smaller than under baseline conditions. But in a ZW species, higher male reproductive variance exacerbates the difference in genetic drift affecting the autosomes and the Z chromosome.

The interaction between sexually antagonistic selection, genetic drift, and genomic location then is not straightforward. In an effort to understand this interaction better, we adapt a well-known population genetic model in chapter 2 to incorporate all three factors, and use it to predict the conditions that lead to elevated levels of difference in sexually antagonistic variation between the autosome and sex chromosome. Our results suggest that differences between the reproductive variances of males and females may be crucial in answering where sexually antagonistic variation preferentially resides in the genome.

Reproductive variance in the model of chapter 2's model is a static parameter, incorporated into the variance effective population size. In this case, the link between reproductive variance with the mechanics of reproduction, from mating to parental care strategies, is difficult to see. Thus, predicting the evolution of reproductive variance in this set-up is not simple. In chapter 3, we develop a general population genetic model that is able to predict not only its evolution, but also its effect on the evolution of other traits. This is not straightforward because it requires the incorporation of the selection undergone by reproductive variance. Models have shown that reproductive variance is also under selection (Gillespie, 1974, 1975, 1977). In particular, theory predicts that selection favors genes that minimize the variance in the number of offspring produced, and thus reduce reproductive variance. But previous models incorporating reproductive variance have either been confined to asexual populations or have simplified sexual reproduction to the point of clouding sex-specificities in reproductive variance (Taylor, 2009).

In chapter 3, we clarify the link between reproductive variance and the reproductive biology of dioecious species, and ensure that the model is able to take into account sex-specificities of reproductive variance. In order to infer on long term evolutionary dynamics, we derive the probability of fixation of mutant genes, which is in turn used to find evolutionary stable sex-specific phenotypes. We use our results to discuss the feedback mechanisms between reproductive traits of each sex and the efficacy of selection that shapes them. We also argue how the model may provide a general framework to study a large class of evolutionary problems for sexual species.

Finally, the general model developed in chapter 3 is applied to study sexual selection and some of its potential side-effects in the 4^{th} chapter. Sexual selection is an important driver in the evolution of sexual dimorphism, and the most striking and popular examples of sexual dimor-

phism are results of sexual selection (Andersson, 1994). Whether through female choice or direct male-to-male competition, the males of some species have evolved phenotypes so extravagant that they seem maladapted to their ecological environment. In contrast, the somewhat austere look of females suggest better adaptation. To produce phenotypic traits so exaggerated, it has been suggested that female preference amplifies the perceived signal strengths of male traits (Lande, 1981; Kirkpatrick, 1987; Mead and Arnold, 2004; Procter et al., 2012). This means that females disproportionately advantage males with greater than average trait values, resulting in a female preference curve which increases greater than linearly with the size of the male trait. But greater than linear selection also promotes the release of phenotypic variation in trait size (Lande, 1980a; Shnol and Kondrashov, 1993). This occurs because if by chance a male produces a trait slightly bigger than a given average, the improvement in its mating rate compensates completely the depreciation suffered were the trait slightly smaller than average. So increasing the variance in the production of the trait is worth the risk. One way to achieve this is by making the development of the trait unstable (Pomiankowski and Møller, 1995). But if the trait is genetically correlated with female traits, and in particular female fertility, then increasing developmental instability may also increase female fertility variance. In addition, if developmental instability of the male ornament carries over to vital traits, then its increase may have harmful effects to the progeny of an unstable male.

In order to study these pleiotropic effects taking into account their sex-specific effects on phenotypic variance, we adapt the model developed in chapter 3. We use it to investigate the conditions that lead to the evolution of developmental instability of male secondary sexual trait and discuss why it is rarely observed in nature, concluding this thesis.

Chapter 1

Molecular evolution of *Drosophila Sex-lethal* and related sex determining genes

This study was conducted in collaboration with Max Reuter and Andrew Pomiankowski, and has been published in *BMC Evolutionary Biology* (Mullon et al., 2012a).

Abstract

Sex determining mechanisms are evolutionarily labile and related species often use different primary signals and gene regulatory networks. This is well illustrated by the sex determining cascade of *Drosophila* fruitflies, which have recruited *Sex-lethal* as the master switch and cellular memory of sexual identity, a role performed in other insects by the gene *transformer*. Here we investigate the evolutionary change in the coding sequences of sex determining genes associated with the recruitment of *Sex-lethal*. We analyze sequences of *Sex-lethal* itself, its *Drosophila* paralogue *sister-or-Sex-lethal* and downstream targets *transformer* and *doublesex*.We find that the recruitment of *sister-or-Sex-lethal* was associated with a number of adaptive amino acid substitutions, followed by a tightening of purifying selection within the *Drosophila* clade. Sequences of the paralogue *sister-or-Sex-lethal*, in contrast, show a signature of rampant positive selection and relaxation of purifying selection. The recruitment of *Sex-lethal* as top regulator and memory gene is associated with a significant release from purifying selection in *transformer* throughout the *Drosophila* clade. In addition, *doublesex* shows a signature of positive selection and relaxation of purifying selection in the *Drosophila* clade. A similar pattern is seen in sequences from the sister Tephritidae clade.The pattern of molecular evolution we observe for *Sex-lethal* and its paralogue *sister-or-Sex-lethal* is not characteristic of a duplication followed by neo-functionalization. Rather, evidence suggests a sub-functionalization scenario achieved through the evolution of sophisticated splicing. As expected, we find that *transformer* evolves under relaxed purifying selection after the recruitment of *Sex-lethal* in *Drosophila*. Finally, the observation of *doublesex* adaptation in both *Drosophila* and Tephritidae suggests that these changes are due to ongoing adaptation of downstream sex-specific regulation, rather than being associated the recruitment of *Sex-lethal* and the resulting change in the topology of the sex determining cascade.

1.1 Introduction

Sex determination is the process by which an individual makes the developmental decision to become male or female. Unlike other fundamental processes in development, such as body patterning by *Hox* genes (Lappin et al., 2006), the molecular mechanisms responsible for sex determination have not been conserved (Marin and Baker, 1998). Instead, a plethora of sex determining strategies exist, varying greatly in the primary signal used in sex determination. This diversity can be seen across the Diptera alone, where the initial signal is genetic in *Drosophila melanogaster*, environmental in *Sciara ocellaris* and maternal in *Chrysomya rufifacies* (Sánchez, 2008; Gempe and Beye, 2011, for reviews). Variation and fast turnover also occur in the genetic implementation of sex determining mechanisms. The housefly *Musca domestica* provides a striking example for evolutionary lability at this level. In some populations, male development is triggered by the presence of masculinizing alleles with varying genomic location in some populations, whereas in other populations these factors are fixed and sex is based on the presence of a dominant feminizing allele at another locus (Dubendorfer et al., 2002).

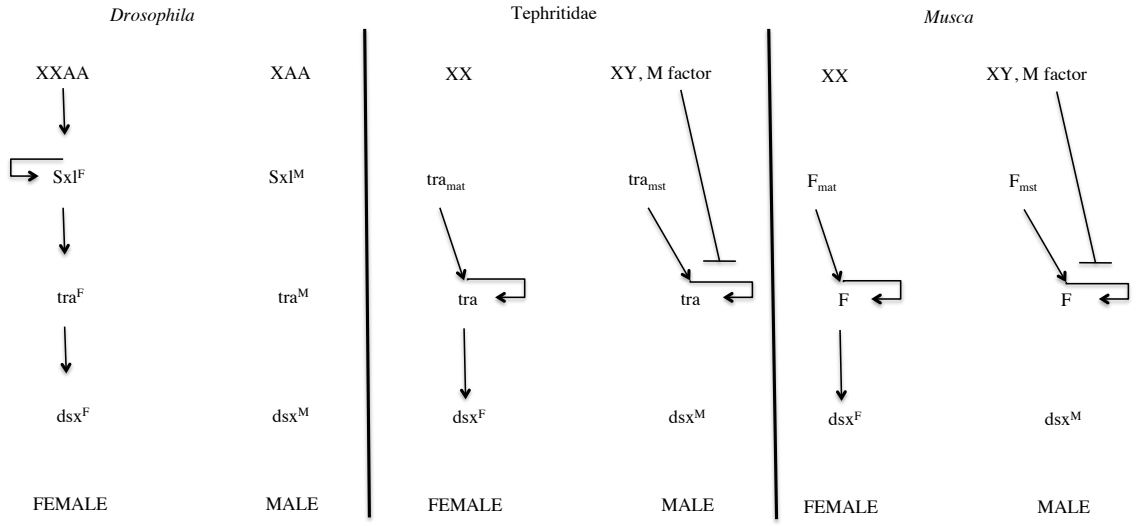

Figure 1.1: Sex determination networks in flies - A comparison between the sex determination networks in the *Drosophila*, Tephritidae and *Musca domestica* (after Sánchez (2008))

Dipteran sex determination probably provides the best studied model for understanding the evolution of sex determining mechanisms. Particularly well described is the genetic cascade of *D. melanogaster*, in which sex is determined by a primary signal that is transmitted through a short cascade of regulatory genes and translated into sexual phenotypes via downstream transcription factors (see Figure 1.1, and Salz and Erickson, 2010, for a most recent review). In

D. melanogaster, the primary signal is provided by a gene counting mechanism sensing the number of X chromosomes (2 in females, 1 in males). This primary input is translated into differential expression of splice forms of the switch gene *Sex-lethal* (*Sxl*). Female embryos express a fully functional SXL protein while males produce a shorter peptide that lacks an RNA-binding domain. The female protein SXLF maintains the master signal through an auto-regulatory self-splicing loop. At the same time, SXLF transmits the female signal further down the cascade by ensuring that *transformer* (*tra*) transcripts are spliced into a female-specific, functional, form. The female TRAF protein, in turn, forms a heterodimer with TRA2 protein to regulate the splicing of the transcription factor *doublesex* (*dsx*) mRNA. The resulting female variant DSXF regulates female differentiation of somatic tissue. In males, the truncated SXLM has no regulatory effect, leading to the production of an equally inactive default splice variant of *tra*. The presence of TRAM (i.e., absence of TRAF), results in the production of default male forms of the downstream target *dsx*, DSXM. *tra* also regulates the splicing of another transcription factor *fruitless*. A sex-specific mRNA of this gene is produced in males that contributes to differentiation of male nervous tissue.

A comparison between the *Drosophila* sex determining cascade and those of the closely related families Tephritidae and *Muscidae* (Figure 1.1) illustrates how sex determining cascades evolved from the bottom up (Wilkins, 1995). The downstream genes *tra* and *dsx* are used by all three groups. Only *Drosophila* uses the switch gene *Sxl* which appears to have been recruited recently to the top of the cascade. The ancestral condition is present in the Tephritidae and *Muscidae*, which uses *tra* and a *tra*-orthologue, respectively, as the switch gene (Hediger et al., 2004, 2010; Salvemini et al., 2009). The *tra* gene in these species maintains its signal through a self-splicing loop operated by the TRA/TRA2 heterodimer. This mechanism is common among the Diptera (Hediger et al., 2004) and might be an ancestral element of the sex determining cascade across the insects (Verhulst et al., 2010), as indicated by the discovery in honeybees of a conserved gene with homology to *tra* (Hasselmann et al., 2008). Outside the insects, there is no evidence for *tra* involvement in sex determination. Homologues of the downstream target *dsx*, however, have been identified not only in other insects (Ohbayashi et al., 2001; Dubendorfer et al., 2002) but also in worms and mammals (Raymond et al., 2000; Hodgkin, 2002). This suggests that *dsx* has been involved in sex determination for a very long time (Pomiankowski et al., 2004).

It is unclear what general principles underlie the bottom-up evolution of sex determining mechanisms or whether indeed such general principles exist (Wilkins, 2002; MacCarthy et al., 2010). However, adaptive scenarios have been proposed for the the recruitment of *Sxl* to the

Drosophila cascade (Pomiankowski et al., 2004). Here, we investigate the molecular changes to
226 the *Drosophila* sex determining cascade due to the recruitment of *Sxl*. We use sequences from twelve *Drosophila* species, a sample of species from the Tephritidae, as well as *Musca domestica*
228 to infer patterns of selection on the coding regions of sex determining genes. Thanks to the detailed molecular knowledge of sex determination in *D. melanogaster* and the simple structure of
230 the genetic cascade, we are able to formulate clear hypotheses for the consequences of recruitment of *Sxl* on the molecular evolution of *Sxl* itself and its downstream targets.

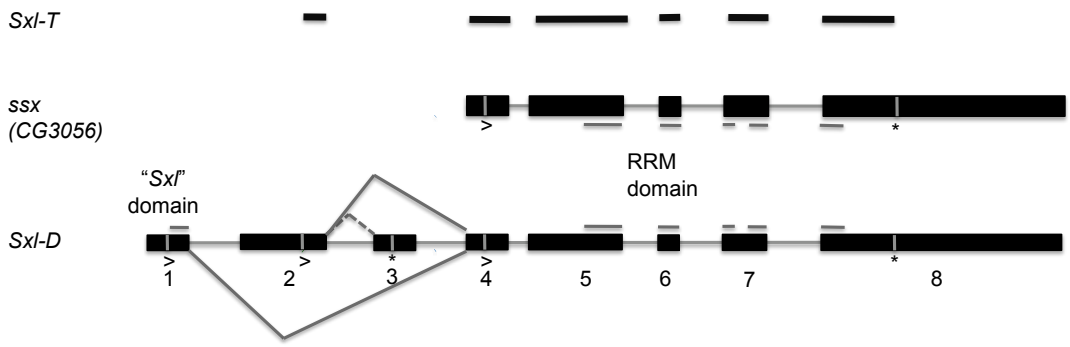

Figure 1.2: Structure of *Drosophila* and tephritid *Sex-lethal* (*Sxl-D* and *Sxl-T* in the Figure) and the *Drosophila* paralogue *ssx* - the figure shows splice variants of *Sxl-D*, the position of translation start sites (>) and stop codons (*) as well as the position of the *Sxl*-specific and RRM protein domains following (Lee et al., 2004). The gene structure for *Sxl-T* is for indicative purposes only, as only exonic sequences are available and the exact position of introns is unknown.

232 Hypotheses about the patterns of molecular evolution in *Drosophila Sxl* can be derived from the evolutionary origin of the gene. Evidence suggests that the recruitment of *Sxl* coincided with a
234 gene duplication event (Traut et al., 2006; Cline et al., 2010) that gave rise to *Sxl* and its paralogue *CG3056*, now named *sister-of-Sex-lethal* (*ssx*) (Cline et al., 2010). Both *Drosophila* genes and
236 their orthologue in the Tephritidae contain two RNA recognition motifs (RRM domains) (Traut et al., 2006, see also Figure 1.2). *Drosophila Sxl* encodes an additional N-terminal protein do-
238 main, the '*Sxl*-specific domain' (Figure 1.2). Truncated proteins lacking this domain show the same binding affinity as the full *Sxl* protein, but fail to induce female-specific self-splicing of *Sxl*
240 transcripts (Bopp et al., 1996). The presence of the *Sxl*-specific domain in *Drosophila*, together with the fact that neither *ssx* in *Drosophila* nor the *Sxl* orthologue in the Tephritidae and *Muscidae*
242 show sex-specific expression or splicing (Saccone et al., 1998; Lagos et al., 2005; Traut et al., 2006; Meise et al., 1998; Gabrieli et al., 2010) suggest neo-functionalization of the *Drosophila Sxl*
244 duplicate (Traut et al., 2006). According to this hypothesis, the common ancestor of Drosophilidae and Tephritidae would have employed a sex determining mechanism similar to that used by the

Tephritidae today (Pomiankowski et al., 2004); following duplication in the *Drosophila* lineage, *Sxl* then adapted to its new role in sex determination while the paralogue *ssx* retained the ancestral, non-sex specific function. Based on this scenario, we would expect a signature of adaptation under positive selection in *Drosophila Sxl* but comparable levels of purifying selection on tephritid *Sxl* and *Drosophila ssx*.

A recent study has put forward an alternative scenario for the evolution of *Sxl* and *ssx* (Cline et al., 2010), whereby *Sxl* would have acquired a new role in sex determination while retaining its ancestral, sex-independent function, whereas *ssx* would have neo-functionalized to take on roles not previously performed by *Sxl*. This scenario is based on the observations that loss of *ssx* had no significant negative effect in fly viability or fertility combined with the discovery of a conserved, non-sex-specific splice variant of *Sxl*. Under this scenario, we would expect signals of positive selection in both *ssx* and *Drosophila-Sxl*, while tephritid *Sxl* would have evolved under purifying selection.

We also predict an effect of *Sxl* recruitment on the evolution of the downstream genes in the sex determining cascade. In *Drosophila*, *Sxl* took over the memory function previously held by *tra*. This should have led to evolutionary change at two levels. First, we expect relaxation of selection on amino acids involved in the now obsolete self-splicing of *tra*. Whether this will result in changes in the *tra* coding sequence depends on the degree to which the self-splicing mechanism differs from the interaction of TRA/TRA2 with its regulatory targets *dsx* and *fru*. The high degree of similarity between TRA/TRA2 binding sites in the intronic sequences of *tra* outside of *Drosophila* (the target of self-splicing) (Pane et al., 2002; Lagos et al., 2007; Ruiz et al., 2007) and in *dsx* (Hoshijima et al., 1991) and *fru* (Heinrichs et al., 1998) within and outside of *Drosophila* (the targets of allo-splicing) suggest similar splicing mechanism. The evolutionary loss of *tra* self-splicing in *Drosophila* then might not have resulted in changes in its amino acid sequence. However, there is also evidence that the self-splicing mechanism involves a protein complex including not only TRA/TRA2 and RBP1 but also an as yet unknown factor (Ruiz et al., 2007, named X-SR). TRA coding regions involved in the interactions with these proteins would then be free to erode after *Sxl* recruitment rendered *tra* self-splicing redundant. Second, we expect adaptive change to accommodate the new splicing regulation of *tra* through *Sxl*. As this regulation in *Drosophila* occurs via the binding of SXL to a non-coding region of *tra* transcripts, adaptation of *tra* is expected to have occurred at the level of non-coding (intronic) rather than coding sequences. Adaptive evolution in response to the recruitment of *Drosophila Sxl* is not expected at the bottom

gene of the cascade, as *dsx* does not directly interact with *Sxl* and the functional link between *tra* and *dsx* is unaffected by *Sxl* recruitment. If at all, the recruitment of *Sxl* might have allowed fine-tuning of the sex-specific signal of *dsx* in *Drosophila* (Pomiankowski et al., 2004), which would be evident in its relative expression in males and females rather than in changes in the coding sequence.

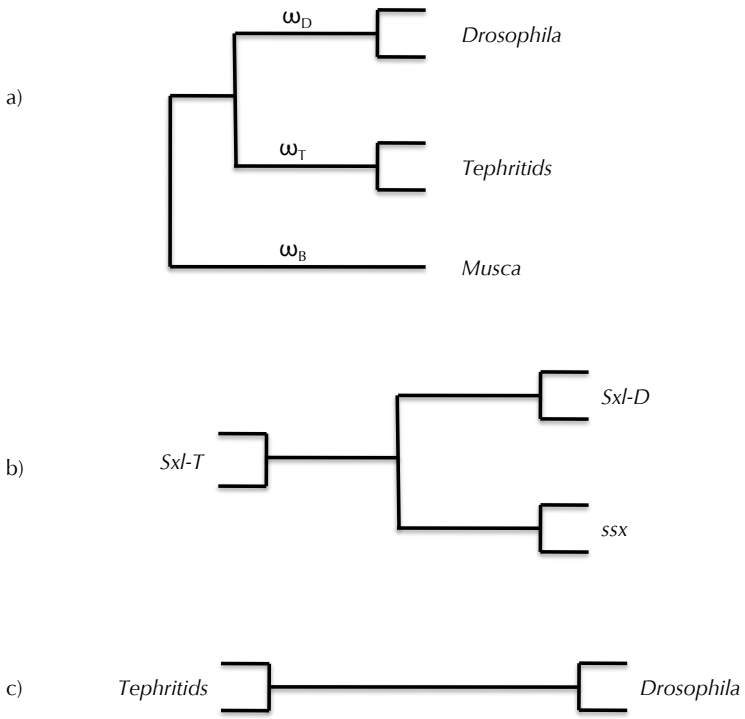

Figure 1.3: Illustration of the phylogenetic trees used for analyses of molecular evolution - a) analyses including sequences from *Drosophila*, the Tephritidae and *M. domestica*, b) the Tephritidae and a *Drosophila* paralogue, as used for *Sxl* and *ssx*, and c) analyses including sequences from *Drosophila* and the Tephritidae.

1.2 Methods

We analyze patterns of molecular evolution by applying phylogenetic maximum likelihood models to sequence alignments of sex determining genes. The mode of selection acting on coding sequences (purifying, neutral or positive) was inferred by estimating the $\omega = dN/dS$ ratio that compares the rates of non-synonymous and synonymous mutations. An ω ratio smaller than one indicates that sequences are under purifying selection, where non-synonymous mutations are eliminated from the gene-pool and hence fixed at a lower rate than synonymous mutations; an ω ratio equal to one occurs in neutrally evolving sequences where drift affects synonymous and non-synonymous mutations to the same extent; finally, an ω ratio greater than one occurs in sequences

under positive selection, where non-synonymous mutations have a greater chance of reaching fixation than synonymous mutations.

1.2.1 Sequence Data

For the genus *Drosophila*, our analyses were based on the genome sequence and annotation of *D. melanogaster* (Flybase, 1999) and genome assemblies for eleven additional species, *D. simulans*, *D. sechelia*, *D. yakuba*, *D. erecta*, *D. ananassae*, *D. pseudoobscura*, *D. persimilis*, *D. willistoni*, *D. virilis* and *D. grimshawi*. Starting from the *D. melanogaster* annotation, we identified orthologous sequences of *Sxl*, *ssx*, *tra*, and *dsx* in the eleven other species by querying their genomic scaffolds with exonic sequences of *D. melanogaster* using the BLAST program (v8.11.0) (Altschul et al., 1997).

Orthologues of the genes in the Tephritidae were obtained from the NCBI sequence repository. In these searches, we used the female splice variants of *Sxl* and *tra* in *D. melanogaster* and concatenated the early and late variants of *Sxl*. For *dsx*, the male and female variants were also concatenated. Using this approach, we obtained orthologues of *Sxl* from one *Ceratitis* and one *Bactrocera* species, and orthologues of *tra* and *dsx* from eight *Anastrepha*, one *Ceratitis* and three *Bactrocera* species. The accession numbers of these sequences can be found in Table 1.A.1. For the gene *fruitless*, alignments of available sequences produced only a moderate number of overlapping sites. This gene was therefore excluded form our analyses.

Sequences were aligned with the Mafft software (v6.624 beta) (Katoh et al., 2005) using the E-INS-i option with default parameters. Exon boundaries were checked for the *Drosophila* species using the Jalview visualization software (v11) (Clamp et al., 2004) and the DEDB database (Lee et al., 2004). Before proceeding with selection analyses, all positions containing indels were removed from the alignment. Complete alignments are provided in the supplementary files of Mullon et al. (2012a).

1.2.2 Maximum Likelihood Tests of Positive Selection

Estimations of the selection pressure on coding sequences were based on the $\omega = dN/dS$ ratio, comparing the rates of non-synonymous and synonymous mutations. We estimated ω ratios using PAML software (v4.4b) (Yang, 2007). Several different types of maximum likelihood tests of positive selection were performed.

Test 1 aims to detect amino acids that are under positive selection on all branches. It assumes

that codons are under identical selection pressures on all branches of the tree ($\omega^T = \omega^B = \omega^D$ for each codon, see Figure 1.3a for a tree with branch labels). Test 1 is based on the three "sites" models (Yang, 2007): the "one ratio" model (Yang, 2007) estimates a single ω_0 value for all codons, the "nearly neutral" model ("M1a") classifies codons into those under purifying selection (for which it estimates an $\omega_0 < 1$) and those evolving neutrally (for which it fixes $\omega_1 = 1$), and finally the "positive selection" model ("M2a") adds a third category of codons under positive selection (for which an $\omega_2 > 1$ is estimated). Likelihood ratio tests were used to detect relaxation of purifying selection (comparing the likelihood of the nearly neutral model to that of the one-ratio model) and positive selection (comparing the positive selection to the nearly neutral model). These tests compare the difference in likelihood between two nested models (as $2\Delta L$) to a χ^2 distribution with degrees of freedom equal to the difference in the number of parameters used by the two models compared.

Tests 2 and 3 are based on "branch-site" models (Yang et al., 2005) and are aimed at detecting differences in the selective pressures that affect particular codons on particular branches of the tree. Test 2 allows us to detect selective pressures on the basal branch between the *Drosophila* and tephritid clades, coinciding with the recruitment of *Sxl* to the *Drosophila* sex determining cascade. It identifies amino acids that either evolve neutrally on the basal branch but are under purifying selection in both the *Drosophila* and tephritid clades ($\omega^T = \omega^D < 1$, $\omega^B = 1$) or those that evolve under positive selection on the basal branch while being under purifying or no selection within the clades ($\omega^T = \omega^D \leq 1$, $\omega^B > 1$). Test 3 detects general changes in the mode of selection following the recruitment of *Sxl*. It allows us to detect amino acids that are under purifying selection in one clade but evolve neutrally in the rest of the tree, or those that evolve neutrally in one clade but are under positive selection on the rest of the tree. Each of these tests are specified by three models. The null model ("uniform selection") does not include differences between branches and considers two classes of sites, those evolving under purifying selection ($\omega_0 < 1$) and those evolving neutrally ($\omega_1 = 1$) across the whole tree. This model is identical to the "nearly neutral model" of test 1 ("M1a"). The first alternative model ("local relaxation") assumes relaxed selection on the branch(es) to be tested. It includes a third class of sites that are evolving neutrally (with $\omega_1 = 1$) on the tested branch(es) while being under purifying selection (with $\omega_0 < 1$) on the remainder of the tree. The second alternative model ("local selection") omits the class of branch-specific neutral evolution of the "local relaxation" model and replaces it by two additional classes in which sites are under positive selection (with $\omega_2 > 1$) on the tested branch(es) but are either under purifying

selection (with $\omega_0 < 1$) or evolve neutrally (with $\omega_1 = 1$) on the rest of tree. Again, likelihood ratio tests are used to assess the improvement of fit between increasingly more parameter-rich models. Whenever likelihood ratio tests provided evidence for significant positive selection, a bayesian procedure (Yang et al., 2005) implemented in PAML was used to identify the individual sites that most likely were the targets of that selection. All tests were performed according to PAML guidance (Yang, 2007).

To check that saturation of synonymous substitutions was not spuriously inflating the dN/dS ratio, we performed a simulation analysis following the approach of (Studer et al., 2008). Artificial alignments were produced with EVOLVER (Yang, 2007) under the null model of "local relaxation". All parameters were set at values equal to the maximum likelihood estimates obtained by fitting the "local relaxation" model to the original data, except the length of the tested branch (defined as number of substitutions per codon in EVOLVER) which was multiplied by a factor of 1.5. The resulting alignments were tested for positive selection by applying test 2. The log-likelihood difference ($2\Delta L$) of these tests was recorded. As the sequences were generated in the absence of true positive selection but with longer branch lengths, this procedure provided a null distribution of $2\Delta L$ for sequences with exaggerated divergence against which we tested the value observed in the analysis of the original data. Due to the artificially increased branch lengths in the simulated data, this approach provides an extremely conservative test for positive selection. If the test on the original sequences was prone to type I error due to saturation in the estimated rate of synonymous substitutions, then tests on the even more divergent produced alignments should be even more so, and the original $2\Delta L$ value would be unlikely to fall within the extremes of the null distribution.

1.3 Results

1.3.1 Molecular evolution of *Sxl*

We first inferred selection on *Sxl* associated with its recruitment to the sex determining pathway of *Drosophila* by analyzing an alignment of *Sxl* sequences from the *Drosophila* species, the Tephritidae and *M. domestica* (Figures 1.3a). Before analyzing evolutionary patterns specifically associated with *Sxl* recruitment, we tested for global patterns of neutral evolution and positive selection along all branches of the tree (Test 1, see Methods). We detected a proportion of amino acids that evolve neutrally (Table 1.1, line a), but there was no evidence for the evolution of amino

384 acids under positive selection across all taxa studied ($P = 1$, Table 1.A.2).

Test	Line	Alternative M[a]	Null M[a]	$2\Delta L$	df	P[b]	Sites[c]
1	a	Nearly Neutral	One ratio	112.53	1	< 0.0001	21
2-D	b	Local selection	Local relaxation	9.16	1	0.0024	17
2-T	c	Local relaxation	Uniform Selection	262.18	2	< 0.0001	1
2-T	*d*	*Local selection*	*Local relaxation*	*5.46*	*1*	*0.019*	*0*
3-D	*e*	*Local relaxation*	*Uniform Selection*	*248.25*	*2*	< 0.0001	*0*
3-R[d]	f	Local relaxation	Uniform Selection	208.30	2	< 0.0001	43

Table 1.1: Significant likelihood ratio tests of selection on *Sxl* in *Drosophila*, the *Tephritidae* and *M. domestica* - [a] Alternative and null models, see Table 1.A.2 for more information on models and Log-likelihood values, [b] P value calculated from a χ^2 distribution, [c] number of sites significant in Bayesian post-hoc tests ($P < 0.05$), [d] clade consisting of all species excluding *Drosophila*. The alignment, after deleting gaps, was composed of 298 codons. Tests that we deemed weakly significant because Bayesian post-hoc tests did not detect relevant AA are shown in italics.

We then looked for signatures of selection during *Sxl*'s recruitment to the sex determining cas-
386 cade. We tested for a signal of relaxed selection on the basal branch leading to the *Drosophila* clade, i.e., identifying amino acids that evolve neutrally on the basal branch but are under purify-
388 ing selection on the rest of the tree. This test was significant ($P < 0.0001$, Table 1.A.2) revealing an evolutionary shift from purifying selection to neutral evolution on the branch leading to the
390 *Drosophila* clade. Given the signature of relaxed purifying selection, we then tested for the signal of positive selection on the basal *Drosophila* branch, seeking to identify sites that are under posi-
392 tive selection on that branch but evolve neutrally or are under purifying selection on the rest of the tree. We found significant evidence of positive selection ($P = 0.0024$, Table 1.1, line b). Further-
394 more, posterior Bayesian analysis provided evidence for adaptive fixation of 17 amino acids (with $P \geq 95\%$) (Table 1.1, line b). Taken together, these tests indicate that the recruitment of *Sxl* to the
396 *Drosophila* sex determining cascade coincided with release from selective constraint and adaptive changes in the protein sequence.

398 As a comparison, the same tests were applied to assess selection specific to the basal branch of the tephritid clade. The test for positive selection was significant (Table 1.1, line d), but Bayesian
400 analysis did not identify any site under positive selection (Table 1.1, line d). The failure to identify selected codons by Bayesian estimation does not provide reliable evidence for positive selection on
402 the branch leading to the Tephritidae. Inconsistent results of this type can occur whenever codons

cannot be unambiguously allocated to a particular class of sites (Z. Yang, pers. comm.). Our data therefore provide, at best, weak evidence for positive selection at the root of the Tephritidae, in contrast to strong evidence for positive selection at the root of the *Drosophila* clade.

Test	Line	Alternative M[a]	Null M[a]	$2\Delta L$	df	P[b]	Sites[c]
1	a	Nearly Neutral	One ratio	189.21	1	< 0.0001	24
2-*ssx*	b	Local selection	Local relaxation	7.94	1	0.019	18
3-*ssx*	c	Local relaxation	Uniform Selection	193.70	2	< 0.0001	31

Table 1.2: Significant likelihood ratio tests for selection on *Drosophila* and tephritid *Sxl* and *Drosophila ssx* - [a] Alternative and null models, see Table 1.A.3 for more information on models and Log-likelihood values, [b] P value calculated from a χ^2 distribution, [c] number of sites significant in Bayesian post-hoc tests ($P < 0.05$). The alignment, after deleting gaps, was composed of 265 codons.

The previous tests investigated the selective signatures of substitutions along the branch coinciding with *Sxl*'s recruitment to the sex determining cascade. We also performed tests to investigate patterns of evolutionary change following the recruitment to sex determination. A first test sought to identify sites that are under relaxed selection along all branches of the *Drosophila* clade but under purifying selection elsewhere in the tree. This test was significant ($P < 0.0001$, Table 1.1, line e), but again no individual amino acid was identified by site-specific Bayesian tests. Evidence for relaxed selection of *Sxl* in the *Drosophila* clade is therefore inconclusive. In contrast to this, we obtained highly significant results for the mirror model, which identified amino acids that are under purifying selection in *Drosophila* but evolve neutrally across the rest of the clade. Moreover, Bayesian posterior tests provided robust evidence for relaxation of purifying selection affecting 43 sites (Table 1.1, line f). Tests for positive selection either along the internal branches of the *Drosophila* clade or the rest of the tree were non-significant. Together this evidence suggests that the main evolutionary change to *Sxl* after its recruitment to *Drosophila* sex determination was a relative strengthening of purifying selection. The absence of recurrent positive adaption within the *Drosophila* clade indicates that adaptive change of *Sxl* to its new role in sex determination occurred prior to the divergence of the *Drosophila* species.

1.3.2 Molecular evolution of the *Sxl* paralogue *ssx*

We investigated selection pressures associated with the duplication of *Sxl* in *Drosophila* by analysing an alignment including *Drosophila Sxl* and *ssx* as well as their orthologue *Sxl* in the

Tephritidae (Figure 1.3b). Analysis of selection on specific sites along all branches provided evidence for neutrally evolving sites over the whole tree (Table 1.2, line a) but the test for tree-wide positive selection was not significant ($P = 1$, Table 1.A.3). Branch-site models on the branch leading from the *Sxl*/*ssx* split to the *ssx* clade in *Drosophila* provided evidence for the adaptive fixation of 18 amino acids on the ancestral branch (Table 1.2, line b). In addition, the test for local relaxation across the *ssx* clade, rather than the basal branch only, was significant (Table 1.2, line c) and identified 31 codons that evolve under purifying selection in *Sxl*, but neutrally in *ssx*. So we find evidence from two different tests: adaptive fixation of some amino acids on the ancestral branch of *ssx* (from the first test) which is followed by neutral evolution of some amino acids in the clade (from the second test). Because nine of the 18 amino acids that were inferred by Bayesian analysis to have been positively fixed at the *Sxl* / *ssx* split were also found to evolve neutrally once fixed in the *ssx* clade, they are likely characteristic of *Sxl* evolution rather than *ssx* evolution. There remains consistent evidence of nine amino acids fixing under positive selection for *ssx*. Our results suggest that adaptive evolution following the gene duplication in *Drosophila* was not restricted to *Sxl*, as extensive ancestral adaptive evolution was observed for amino acids of the paralogue *ssx*.

1.3.3 Molecular evolution of downstream sex determining genes

We performed analyses designed to detect changes in the pattern of molecular evolution of the downstream sex determining genes *tra* and *dsx*, coinciding with the recruitment of *Sxl* in *Drosophila*. For *tra*, we analyzed an alignment of *Drosophila* and tephritid sequences (Figure 1.3c). We found evidence for site-specific neutral evolution (Table 1.3, line a). The likelihood ratio test for local relaxation on the basal branch (separating the *Drosophila* clade and the Tephritidae) was significant, but no amino acid was found to have evolved neutrally on that branch (Table 1.3, line b), so the overall evidence for relaxation on the basal branch alone is weak. Tests of local relaxation of selective constraint were significant for both clades (Table 1.3, lines c and d). The effect was quantitatively stronger in the *Drosophila* clade than in the Tephritidae (Table 1.A.4); 16 sites were inferred to evolve neutrally in *Drosophila*, but only 1 in the Tephritidae. Taken together, these results show that the recruitment of *Sxl* to the sex determining cascade coincided with a significant loosening of selective constraint in the *Drosophila* clade.

The evidence for a relaxed purifying selection in *Drosophila tra* is corroborated by the pattern of insertions and deletions (indels) for *tra* that is not taken into account by PAML's analysis of coding sequences. First, the coding sequence of the *tra* protein is on average much shorter in

Test	Line	Alternative M[a]	Null M[a]	$2\Delta L$	df	P[b]	Sites[c]
1	a	Nearly Neutral	One ratio	13.75	1	0.0002	4
2	*b*	*Local relaxation*	*Uniform Selection*	*5.39*	*2*	*0.02*	*0*
3-D	c	Local relaxation	Uniform Selection	64.89	2	< 0.0001	16
3-T	d	Local relaxation	Uniform Selection	15.79	2	< 0.0001	1

Table 1.3: Significant likelihood ratio tests of selection on *transformer* in *Drosophila* and the *Tephritidae* - [a] Alternative and null models, see Table 1.A.4 for more information on models and Log-likelihood values, [b] P value calculated from a χ^2 distribution, [c] number of sites significant in Bayesian post-hoc tests ($P < 0.05$). The alignment, after deleting gaps, was composed of 122 codons. Tests that we deemed weakly significant because Bayesian post-hoc tests did not detect relevant AA are shown in italics.

Drosophila than in the tephritids (Table 1.4). Whilst some indels appear to be species-specific, we observe four substantial domains (length greater than 30 nucleotides, with a total of 469 nucleotides) that are conserved in all tephritid species but absent in all *Drosophila* species (see Fig. S4 in Mullon et al., 2012a). These represent indel events that have most likely taken place on the ancestral branch dividing the two clades. The difference in mean coding length between the two clades is 652 nucleotides, so the 469 ancestral indels make up a significant share of this length difference. These important structural changes in the protein provide further evidence for the relaxation of purifying selection on *tra* coinciding with the recruitment of *Sxl* in the sex determination network.

In addition to a general shortening, we observe much greater variance in the length of the *tra* protein between *Drosophila* than between tephritid species (see Table 1.4). This again suggests weaker purifying selection against indels, or less consistent selection across *Drosophila* species. The comparison between *Drosophila* and the Tephritidae is potentially confounded by differences in branch length (i.e., divergence time) between the clades. To control for this effect, pairwise comparisons were made within each clade, and the number of indels per site was scaled by the branch lengths separating each pair of species. Based on these data, we found that the rate of indels is higher in the *Drosophila* than the tephritid clade (Wilcoxon test, $W = 1092$, $P = 0.017$). In addition, the variance in the indel rate was much higher in the *Drosophila* than the tephritid clade (Bartlett test for homogeneity of variances, $K^2 = 28.6$, $P < 0.0001$). From a statistical point of view these tests are not entirely rigorous, as they do not take into account the inter-dependence between the data points derived from overlapping pairs of species. However, the large difference observed, in particular in the variance in indel rates, suggests that the evolutionary processes are

not identical in the two clades, with lower evolutionary constraint in the *Drosophila* clade.

Clade	**CDS Length**		**Indel rate**[a]	
	Mean	Variance	Mean	Variance
Drosophila	603	4412	0.409	0.397
Tephritids	1255	132	0.258	0.062
P Value	< 0.0001	< 0.0001	0.017	< 0.0001

Table 1.4: Coding sequence (CDS) length and indel rate within the Drosophila and tephritid clades for transformer - [a] Indel rate was calculated for each pair of species within a clade by dividing the number of indel sites by the number of nucleotides in the pairwise alignment, then further dividing by the branch length between the two species estimated using the *dsx* gene.

We finally analyzed patterns of molecular evolution in the *dsx* gene. The lower rate of change in *dsx* allowed us to include the gene sequence from *M. domestica* in our analysis, without removing an excess of amino acids due to alignment gaps (Figures 1.3a). As with *Sxl* and *tra*, analyses based on site models revealed that some sites evolve neutrally across the entire tree (Table 1.5, line a), but there was no evidence for consistent positive selection ($P = 1$, Table 1.A.5). Including the sequences from *M. domestica* allowed us to root the split between the *Drosophila* and tephritid clades. Applying tests to infer changes in selection on the basal branches leading to the *Drosophila* and tephritid clades, we detected evidence for positive selection along both branches (Table 1.5, lines b and c), with 6 and 4 sites being identified as targets in *Drosophila* and the Tephritidae, respectively. Comparing the evolution of the gene within and outside of *Drosophila*, we found evidence for relaxation of purifying selection at a small proportion of sites within *Drosophila* (4 sites, Table 1.5, line d) and in the outgroup (8 sites in the Tephritidae and *M. domestica*, Table 1.5, line e).

1.3.4 Type I error in the inference of positive selection

Although our analyses provide evidence for adaptation at some point in the phylogeny of every gene except *tra*, caution is required when inferring past selection from DNA sequences. When sequences are very divergent, the occurrence of multiple substitutions at a site (saturation) can cause the rate of synonymous substitutions (dS) to be under-estimated. This, in turn, results in an inflated dN/dS ratio and the inference of spurious positive selection. Problems of this kind are unlikely to affect our results because the MLE methods used here estimate the most likely dN/dS

ratio based on patterns of substitutions along all branches of a tree and have been shown to be significantly more powerful and reliable for inferring ancestral positive selection than counting methods comparing pairs of sequences (Zhang and Parsch, 2005; Yang and dos Reis, 2011; Studer et al., 2008).

Test	Line	Alternative M[a]	Null M[a]	$2\Delta L$	df	P[b]	Sites[c]
1	a	Nearly Neutral	One ratio	183.62	1	0.0001	17
2-D	b	Local selection	Local relaxation	10.52	1	0.005	6
2-T	c	Local selection	Local relaxation	8.34	1	0.015	4
3-D	d	Local relaxation	Uniform Selection	36.64	2	< 0.0001	4
3-R[d]	e	Local relaxation	Uniform Selection	70.17	2	< 0.0001	8

Table 1.5: Significant likelihood ratio tests of selection on *doublesex* in *Drosophila*, the *Tephritidae* and *M. domestica* - [a] Alternative and null models, see Table 1.A.5 for more information on models and Log-likelihood values, [b] P value calculated from a χ^2 distribution, [c] number of sites significant in Bayesian post-hoc tests ($P < 0.05$). The alignment, after deleting gaps, was composed of 364 codons.

In order to formally rule out effects of saturation on our results, we performed extensive simulations in an approach previously taken by Studer et al. (Studer et al., 2008, see also Methods). These simulations seek to estimate the type I error in a conservative scenario. We generated artificial alignments by simulating sequence evolution along the tree of the original sequences using the parameters of the null models (in the absence of positive selection) for all genes. To make the test conservative, the risk of saturation was artificially increased by multiplying the number of substitutions per codon on the tested branch by a factor of 1.5. For each gene, a set of 200 simulated alignments was analyzed for positive selection using the same tests as in the original analyses. The highest rate of false positives observed in our conservative approach was 1% (for *Sxl*), indicating that our inferences of positive selection are extremely unlikely to be due to type I error.

1.4 Discussion

We investigated the changes in the patterns of molecular evolution evolution of sex determining genes associated with the recruitment of *Sxl* to the top of the *Drosophila* sex determining cascade. We analyzed the evolution of *Sxl* itself, its *Drosophila* paralogue *ssx*, and the downstream targets *tra* and *dsx*, using sequences from species of *Drosophila* and their sister clade the Tephritidae, as

well as *M. domestica*.

Drosophila Sxl is thought to have originated through duplication on the branch leading to the *Drosophila* clade (Traut et al., 2006; Cline et al., 2010). The ancestral function of *Sxl*, and its current function in the Diptera outside *Drosophila* are not known to be associated with sex determination (Saccone et al., 1998; Meise et al., 1998). Two hypotheses have been put forward as to how new and ancestral functions were shared between the two *Drosophila* paralogues *Sxl* and *ssx*. Traut et al. (2006) proposed that *Sxl* neo-functionalized to its sex determining role whereas the paralogue *ssx* would have maintained the ancestral functions. Alternatively, Cline et al. (2010) suggested *Sxl* would take on a new sex determining function while simultaneously both *Sxl* and *ssx* would sub-functionalize to share non sex-specific functions ancestrally performed by *Sxl*.

Based on our analyses and including previous findings, it is now possible to weigh up the relative merits of these two evolutionary scenarios. The fact that *Sxl* has undergone significant changes is not contentious. It is clear that the gene has adapted to its new sex determining role by the addition of a new domain and the evolution of sophisticated RNA splicing. Our analyses have shown that *Sxl* has undergone adaptive evolution in its coding sequence at a limited number of amino acids, followed by a tightening of purifying selection on the protein sequence. It seems furthermore likely that *Sxl* has retained an ancestral function, an interpretation that is supported by the fact that one of the *Sxl* transcripts in *Drosophila* lacks the *Sxl*-specific domain and is expressed in both sexes (Cline et al., 2010). But in the light of our findings it is now also clear that *ssx* has undergone adaptive evolution. Thus, we have shown that the gene shows a signature of adaptive change as well as a release from purifying selection on its coding sequence, resulting in a protein that differs significantly from both its paralogue in *Drosophila* and its orthologue in the Tephritidae. This finding is in line with Cline *et al.*'s (Cline et al., 2010) hypothesis of sub-functionalization. Adaptation in both genes could further indicate that the duplication of *Sxl* allowed for the alleviation of 'adaptive conflict' (Hughes, 1994) previously imposed by the double function of the ancestral gene. Establishing whether this is the case, however, will require more detailed information on the non sex-specific functions of *Drosophila Sxl* and *ssx* and their orthologue in other dipteran species.

Our analyses were also able to shed some light on the repercussions of *Sxl* recruitment in the patterns of molecular evolution of genes further down the sex determining cascade. The protein evolution observed in *Drosophila tra* is characterized by extensive neutral evolution and high rates of indels. These results echo those found by a previous study using a smaller number of species

(Kulathinal et al., 2003). The evidence for sequence degradation adds to the inferred loss of the putative auto-regulation domain in *Drosophila tra* (Ruiz et al., 2007; Verhulst et al., 2010), and corroborates the view that the recruitment of *Sxl* as the main sex switch gene relieved the pressure of purifying selection on *tra*. Whether the relaxation of selection on *Drosophila tra* outside the specific auto-regulatory domain is due to the loss of the sexual memory function is difficult to ascertain. The TRA/TRA2 binding sites in *Drosophila dsx* and *fru* are well conserved (Pane et al., 2002; Lagos et al., 2007; Ruiz et al., 2007; Hoshijima et al., 1991; Heinrichs et al., 1998), implying that TRA's regulatory function is still required. There are, however, suggestions that the auto-regulation of *tra* is more complicated than its regulation of *dsx* (Ruiz et al., 2007; Ruiz and Sánchez, 2010); rather than forming an enhancing complex with TRA2 as for *dsx* pre-mRNA, the TRA protein silences expression in *tra* pre-mRNA. Regions of the protein only involved in these specific auto-regulatory mechanisms would be free to erode after recruitment of *Sxl* in *Drosophila*.

There is also the additional (and non-exclusive) possibility that the relaxation of purifying selection on *tra* sequence is the result of *Sxl* taking over other sex-specific regulatory functions. Over thirty potential functional binding sites for *Sxl* have been found in *Drosophila* (Samuels et al., 1994; Robida et al., 2007), some of these may have been ancestrally regulated by *tra*. The loss of these functional links from *tra* could have relieved it from selection pressure. Since *Drosophila Sxl* was sex specifically spliced by *tra* before it was promoted to top regulator in the sex determining cascade (Siera and Cline, 2008), there has been a relatively long evolutionary time for *Sxl* and *tra* to exchange various functions, potentially selected for their effectiveness of specific target splicing. In that light it would be interesting to compare the putative targets of *Sxl* in *Drosophila* with those of *tra* outside of *Drosophila*. Overlap between these two sets would support this hypothesis.

Taken together, our results indicate that the adaption of *tra* to its new regulatory role in somatic sex determination (loss of self-regulation, and potential targets, interaction with *Sxl*), did not require positively selected amino acid substitutions, but rather the degradation of redundant parts of the protein-coding sequence. This partial erosion was complemented with selective changes elsewhere in the gene sequence. Thus, we observe changes in the non-coding sequence, where we see the emergence and conservation of a *Sxl* binding site in intronic sequences of *Drosophila tra* (see figure 1.4).

The evolution of *Sxl* and *tra* in *Drosophila* can be compared with a different change in the top regulator in honeybees. In this group, female development is driven *complementary sex determiner* (*csd*), a switch gene specific to the genus *Apis*. Sex determination in honeybees is haplodiploid,

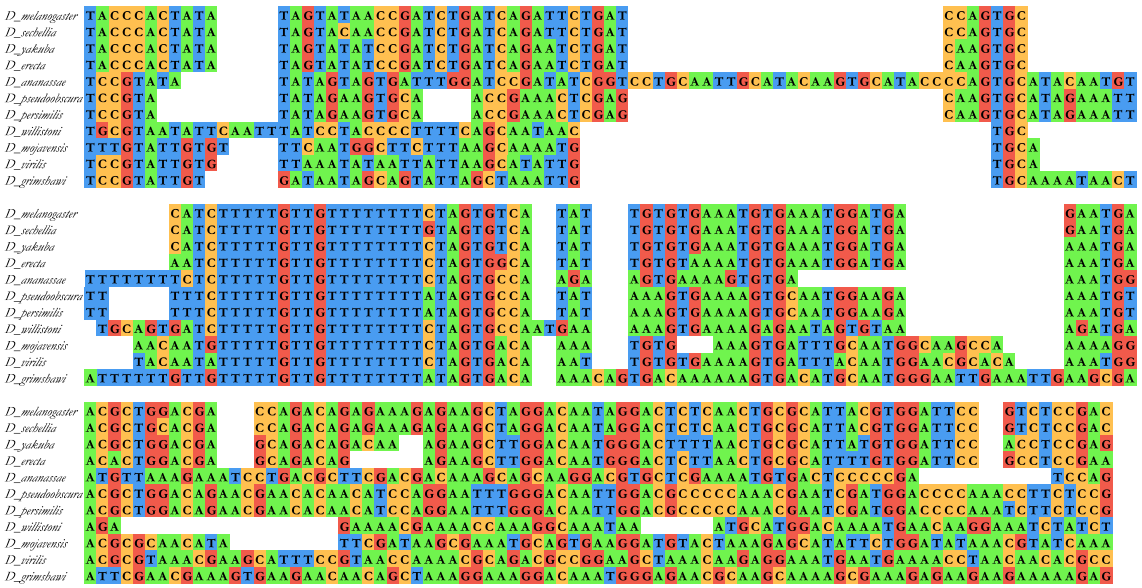

Figure 1.4: Alignment of intronic sequence of *tra* in *Drosophila* species - The nucleotide sequence corresponds to the intron upstream of exon 2. In females, SXL binds to the highly conserved polypyrimidine tract and prevents splicing at this site. Auxiliary splicing factor then promotes splicing at the weaker downstream splice site, thus obtaining an open reading frame.

with females heterozygous and males hemizygous at the *csd* locus. Similar to *Drosophila Sxl*, *csd* arose by duplication of *feminizer* (*fem*), the ancestral top regulator and orthologue of *tra* (Hasselmann et al., 2008, 2010). In contrast to *Drosophila*, where *Sxl* underwent a short bout of adaptation on its recruitment and *tra* shows evidence of relaxed selection, *csd* in honeybees has undergone continued positive selection since its creation by duplication, whereas *fem* has experienced tightening purifying selection. Presumably, it is the requirement for heterozygosity in females that drives continued change in the amino acid sequence of *csd* (Hasselmann et al., 2010). The strong purifying selection on *fem* has been attributed to potentially deleterious effects of unspecific protein-protein interactions that could arise from amino acid changes (Hasselmann et al., 2010). Our results suggest that such deleterious effects either play a lesser role in *Drosophila* or are compensated by the benefit of mutations degrading *tra* functions that have become redundant since the recruitment of *Sxl*.

We also found evidence for positive selection and relaxed purifying selection in *dsx*, the transcription factor translating the sex determining signal into sex-specific gene expression and differentiation. This was detected both in the *Drosophila* and in the Tephritidae (albeit in different amino acids). The evidence for widespread adaptive evolution in the downstream target genes of sex determination in *Drosophila* is surprising *dsx* does not interact with *Sxl* and should therefore

be unaffected by the recruitment of *Sxl*. In the Tephritidae, adaptive change is even more surprising, as it occurs in the absence of any (known) topological change in the sex determining cascade. The results therefore suggest that although *dsx* is conserved in function and sequence across a large part of the animal tree (Raymond et al., 1998), continuous evolutionary change occurs independent of topological changes in the network. It is unclear what forces might generate positive selection on downstream sex determining genes (Pomiankowski et al., 2004).

We have shown that the recruitment of *Sxl* to the *Drosophila* sex determining cascade has coincided with changes in the evolution of the *Sxl* gene itself, its paralogue *ssx* and the downstream genes involved in sex determination, *tra*, and *dsx*. Studying a well-known and relatively simple gene cascade has enabled us to relate and confront the evolution of a network structure with the direction of selection on the amino acids of the genes participating in that network. Patterns of molecular evolution of amino acids in relation to network changes (or indeed their absence) in *Drosophila* emerge from our analysis, notably the sub-functionalization of *Sxl* and *ssx*, and the degeneration of *tra*, along with the ongoing evolution of *dsx* in *Drosophila* and the Tephritidae. Future experimental work will hopefully shed more light on this issue, notably by investigating the molecular function of *Sxl* splice forms that are produced equally in both sexes and so may perform one the of the ancestral function of the gene.

1.A Appendix

Gene	Numbers
Sxl	2981304, 52075415.
tra	157930032, 157930030, 157930028, 157930026, 157930024, 157930022, 157930020, 157930012, 157930010, 52075411, 22003420.
dsx	2827982, 2827984, 46019686, 46019688, 62999442, 62999444, 95044935, 95044937, 95044939, 95044941, 95044943, 95044945, 56384904, 56384902, 165934579, 165934086, 95044979, 165934086, 95044979, 95044977, 95044975, 95044973, 95044971, 95044969, 95044929, 95044981, 38564770, 38564768.

Table 1.A.1: GI Accession numbers for sequences.

Branch(es)	Model	N of parameters	Log-likelihood
-	One ratio	1	-4540.06
-	Nearly neutral	2	-4483.80
-	Positive selection	4	-4483.80
Basal-*Drosophila*	Local relaxation	4	-4321.44
	Local selection	5	-4316.86
Basal-Tephritidae	Local relaxation	4	-4352.71
	Local selection	5	-4349.98
Drosophila	Local relaxation	4	-4359.67
	Local selection	5	-4359.67
Remainder	Local relaxation	4	-4379.65
	Local selection	5	-4379.65

Table 1.A.2: Maximum likelihood models of selection on *Sxl* in *Drosophila*, the Tephritidae and *M. domestica* sequences

Branch(es)	Model	N of parameters	Log-likelihood
-	One ratio	1	-7041.53
-	Nearly neutral	2	-6946.92
-	Positive selection	4	-6946.92
Basal-*ssx*	Local relaxation	4	-6917.04
	Local selection	5	-6913.07
Clade-*ssx*	Local relaxation	4	-6850.07
	Local selection	5	-6850.07

Table 1.A.3: Maximum likelihood ratio models for selection on *Drosophila* and tephritid *Sxl* and *Drosophila ssx*

Branch(es)	Model	N of parameters	Log-likelihood
-	One ratio	1	-4136.36
-	Nearly neutral	2	-4129.49
-	Positive selection	4	-4129.49
Basal	Local relaxation	4	-4126.80
	Local selection	5	-4124.17
Drosophila	Local relaxation	4	-4097.05
	Local selection	5	-4097.05
Tephritidae	Local relaxation	4	-4121.60
	Local selection	5	-4121.60

Table 1.A.4: Maximum likelihood models of selection on *transformer* in *Drosophila* and the Tephritidae.

Branch(es)	Model	N of parameters	Log-likelihood
-	One ratio	1	-8211.64
-	Nearly neutral	2	-8119.83
-	Positive selection	4	-8119.83
Basal-*Drosophila*	Local relaxation	4	-8110.65
	Local selection	5	-8105.39
Basal-Tephritidae	Local relaxation	4	-8111.28
	Local selection	5	-8107.11
Drosophila	Local relaxation	4	-8101.51
	Local selection	5	-8101.51
Remainder	Local relaxation	4	-8084.74
	Local selection	5	-8084.74

Table 1.A.5: Maximum likelihood models of selection on *doublesex* in *Drosophila*, the Tephritidae and *M. domestica*.

Chapter 2

The effects of selection and genetic drift on the genomic distribution of sexually antagonistic alleles

This study was conducted in collaboration with Max Reuter and Andrew Pomiankowski, and is in press (Mullon et al., 2012b).

Abstract

Sexual antagonism (SA) occurs when an allele that is beneficial to one sex, is detrimental to the other. This conflict can result in balancing, directional or disruptive selection acting on SA alleles. A body of theory predicts the conditions under which sexually antagonistic mutants will invade and be maintained in stable polymorphism under balancing selection. There remains however considerable debate over the distribution of SA genetic variation across autosomes and sex chromosomes, with contradictory evidence coming from data and theory. In this chapter, we investigate how the interplay between selection and genetic drift will affect the genomic distribution of sexually antagonistic alleles. The effective population sizes can differ between the autosomes and the sex chromosomes due to a number of ecological factors and, consequently, the distribution of SA genetic variation in genomes. In general, we predict the interplay of SA selection and genetic drift should lead to the accumulation of SA alleles on the X in male heterogametic (XY) species and, on the autosomes in female heterogametic (ZW) species, especially when sexual competition is strong among males.

2.1 Introduction

Male and female reproductive roles differ and accordingly, many phenotypic traits are selected in different directions in the two sexes. Responding to divergent selection pressures, however, is not straightforward. Because the sexes share a large part of their genomes and traits are determined by the same genes, homologous traits in males and females are expected to show strong genetic correlations. Opposing selection pressures on the two sexes therefore lead to a tug-of-war, which has been coined 'sexual antagonism' (SA) or 'intra-locus sexual conflict' (Parker, 1979; Rice, 1984; Van Doorn, 2009; Bonduriansky and Chenoweth, 2009).

At the allelic level, SA means selection on one sex favors the fixation of one allele, while selection on the other sex favors fixation of another allele. A number of population genetic models have been developed to identify the conditions under which sexually antagonistic mutants invade and are maintained in stable polymorphism. There has been considerable interest in comparing autosome and sex chromosome linkage. An influential theoretical analysis (Rice, 1984) and a later follow-up (Gavrilets and Rice, 2006) concluded that the conditions for invasion and maintenance of SA alleles were more stringent on the autosomes than on the X and Z sex chromosomes, in male and female heterogametic systems respectively. Fry (2010) argued that this conclusion was a consequence of the way these models constrained the dominance relationships between antagonistic alleles. Building on a previous model with arbitrary dominance (Kidwell et al., 1977), Fry (2010) showed that sex-specific dominance leads to an enrichment of SA genetic variation on the autosomes.

Empirical data has been demonstrating the presence of sexually antagonistic genetic variation in a variety of organisms (Chippindale et al., 2001; Foerster et al., 2007; Brommer et al., 2007; Mainguy et al., 2009; Svensson et al., 2009) (see Cox and Calsbeek, 2009, for a review). But if early empirical data from *Drosophila melanogaster* supported the prediction of X enrichment (Gibson et al., 2002), no clear picture has emerged from subsequent studies (Fry, 2010). In addition, virtually nothing is currently known about the properties of alleles segregating at antagonistic loci, including their fitness effects, dominance or patterns of epistatic interactions. Part of the problem stems from the difficulty in mapping sexual antagonism to single genes. If a large number of genes have sexually antagonistic expression patterns in *D. melanogaster* (Innocenti and Morrow, 2010), it is not clear to what extent this pattern is due to true differences in gene expression, or simply reflects the different ways in which expression is associated with fitness in the two sexes.

Even if true expression differences are present, it remains open to what extent these represent many antagonistic loci or many regulatory targets of transcription factors encoded by a few loci.

Despite the considerable effort invested in predicting antagonistic polymorphism and its genomic location (Owen, 1953; Kidwell et al., 1977; Rice, 1984; Gavrilets and Rice, 2006; Fry, 2010; Jordan and Charlesworth, 2011), a major element is missing from our current knowledge. Built exclusively on deterministic models, the existing body of SA theory ignores the effect of genetic drift. The random sampling of alleles causes fluctuations of gene frequencies, and eventually leads to the fixation of one allele and the loss of genetic variation. Genetic drift will therefore oppose balancing selection generated by sexually antagonistic fitness effects. Similarly, genetic drift can slow down the fixation of sexually antagonistic alleles that are under directional or disruptive selection, and hence contribute to SA genetic variation. The amount and nature of genetic variation we observe in natural populations will thus depend on the relative intensity of genetic drift and its interplay with sexually antagonistic selection.

Taking into account the effect of drift is particularly important when considering the genomic location of SA variation. In species with an XY sex determining system, the X, which is hemizygous in males, has a smaller population size, and so is *a priori* subject to a greater intensity of genetic drift than the autosomes (Charlesworth et al., 1987; Caballero, 1995; Vicoso and Charlesworth, 2009). In a large, randomly mating population with an even sex ratio, the ratio of the effective population sizes of the X to the autosomes has the baseline value of $N_{eX}/N_{eA} = 3/4$. This ratio however is significantly influenced by departures from the idealized assumptions on which it relies. If, as is often the case (Clutton-Brock, 2007), males have higher variance in reproductive success than females, the lower uncertainty in the transmission of maternal genes compensates for the lower copy number of X chromosomes and $N_{eX}/N_{eA} > 3/4$ (Caballero, 1995; Vicoso and Charlesworth, 2009). Similar arguments apply to species with ZW sex determination; here, increased male reproductive variance in this case exacerbates the difference in genetic drift affecting the autosomes and the Z chromosome, so that $N_{eZ}/N_{eA} < 3/4$. In order to predict the genomic distribution of SA variation, it is therefore important to not only take into account the effect selection, but also the intensity of genetic drift across the genome, which erodes genetic variation.

In this chapter, we present a population genetic model of SA evolution that incorporates genetic drift and allows variation in its intensity on the autosomes and the X chromosome (our model equally applies to the Z chromosome). The model is used to calculate the relative predisposition of autosomes and sex chromosomes to harbor SA genetic variation. We first present a bi-allelic

model of SA evolution. We deduce the expected heterozygosity at mutation-selection-drift balance for a single locus, and compare the properties of selection and drift for an X-linked and autosomal locus. We use this to make predictions on the effects of SA selection and genetic drift on heterozygosity according to genomic location. Finally, we test these predictions and measure the effect of N_{eX}/N_{eA} on the distribution of SA genetic variation across chromosomal compartments. We use two measures of polymorphism to do this, expected heterozygosity and time to fixation, and calculate their X-to-autosome ratio as a function of chromosomal effective population sizes and selection parameters. We interpret our results to provide an intuitive understanding of the distribution of SA genetic variation in the genome.

2.2 Model

The segregation of two alleles, Λ_f and Λ_m, is modeled for an X-linked and an autosomal (written A) locus. We consider a finite population with constant numbers of males and females, and non-overlapping generations. We assume a Wright-Fisher process with the following life cycle. Male and female adults produce large numbers of gametes, which mutate at a rate μ. This rate is identical in the two sexes and equal in both directions ($\Lambda_f \rightarrow \Lambda_m$ and $\Lambda_m \rightarrow \Lambda_f$). Gametes are randomly paired to produce zygotes. The zygotes are then sampled with replacement and with a selective bias to form the males and females of the next generation. The allele frequencies in males and females are tracked separately, so the process is a Markov chain in two dimensions. The fitness scheme (Table 2.1) is equivalent to that used by Kidwell et al. (1977) and constructed so that the locus is *a priori* sexually antagonistic. We use sex-specific dominance parameters (Kidwell et al., 1977; Fry, 2010), allowing for the possibility that both male and female heterozygotes bear little of the fitness cost due to SA. Fixation of Λ_f is assumed to be beneficial to females and detrimental to males, and the opposite is true of Λ_m.

Genotype	$\Lambda_f\Lambda_f$	$\Lambda_f\Lambda_m$	$\Lambda_m\Lambda_m$
Female fitness	1	$1-h_f s_f$	$1-s_f$
Male fitness	$1-s_m$	$1-h_m s_m$	1

Table 2.1: Fitness scheme - following Kidwell et al. 1977.

We use the diffusion approximation to derive properties of the gene frequency dynamics. This method is well established and is known to be a good approximation of the Wright-Fisher process,

even in complicated selection scenarios (Ewens and Thomson, 1970). When selection and the mutation rate are weak (roughly < 0.1), and the population is large, the two-dimensional Wright-Fisher process can be approximated as a single diffusion variable (Norman, 1975; Ethier and Nagylaki, 1988). The variable corresponds to the average of the male and female frequencies, weighted by the reproductive values of each sex, so that in the absence of selection and mutation ($\mu = s_\mathrm{m} = s_\mathrm{f} = 0$), the expected frequency change of the averaged variable is zero. If p_m and p_f are the frequencies of allele Λ_m in males and females respectively, the averaged variable is $p = 1/2(p_\mathrm{m} + p_\mathrm{f})$ for an autosomal locus and $p = 1/3\,p_\mathrm{m} + 2/3\,p_\mathrm{f}$ for an X-linked locus in an XY heterogametic species.

The probability distribution function of the average gene frequency p at generation t, $\phi(p;t)$, satisfies the Fokker-Planck equation

$$\frac{\partial \phi}{\partial t} = a(p)\frac{\partial \phi}{\partial p} + \frac{1}{2}b(p)\frac{\partial^2 \phi}{\partial p^2}, \tag{2.1}$$

where the advection term $a(p) \equiv \mathrm{E}[\Delta p]$ is the expected allelic frequency change over one generation, and the diffusion term $b(p) \equiv \mathrm{Var}[\Delta p]$ is the variance in allele frequency change (Norman, 1975; Ethier and Nagylaki, 1988).

The advection term, $a(p)$, determines the effect of selection and describes the expected gene frequency change. Because we define p to be the frequency of the male-beneficial allele Λ_m, positive value of $a(p)$ indicate that Λ_m is selectively favored at frequency p (while Λ_f is selected against). Equivalently, selection is negative on Λ_m (and positive on Λ_f) when $a(p)$ is negative. The advection terms for autosomal (A) and X-linked loci are

$$\begin{aligned} a_A(p) &= \frac{1}{2}p(1-p)\Big(s_\mathrm{f}\big(p(2h_\mathrm{f}-1)-h_\mathrm{f}\big) + s_\mathrm{m}\big(p(2h_\mathrm{m}-1)+1-h_\mathrm{m}\big)\Big) \\ &\quad + (1-2p)\mu + O(\mu^2, s_\mathrm{m}^2, s_\mathrm{f}^2), \\ a_X(p) &= \frac{1}{3}p(1-p)\Big(2s_\mathrm{f}\big(p(2h_\mathrm{f}-1)-h_\mathrm{f}\big) + s_\mathrm{m}\Big) + (1-2p)\mu + O(\mu^2, s_\mathrm{m}^2, s_\mathrm{f}^2). \end{aligned} \tag{2.2}$$

The rate of change of the allele frequency density function ϕ in equation (2.1) also depends on the strength of genetic drift and it is this effect that is expressed by the diffusion term $b(p)$. The variance in allele frequency change is written as

$$b_{A,X} = \frac{p(1-p)}{2N_{eA,X}} + O(1/N_{eA,X}), \tag{2.3}$$

for an A- and X-linked locus respectively. The effective population sizes for A (N_{eA}) and X (N_{eX}) loci are related to the number of males and females (Ewens, 2004, p. 124). However, the notation N_{eA} and N_{eX} is used to highlight that differences in effective population sizes may be due to other factors than the sex ratio (Caballero, 1995).

2.3 Results

2.3.1 Effects of selection on heterozygosity in finite populations

Before comparing explicitly the level of SA genetic variation across the genome, we make general observations on how the combined effects of selection and genetic drift impact variation at a single locus. We will do so using expected heterozygosity as a measure of standing genetic variation (we will later verify and generalize our results by using time to fixation). At mutation-selection-drift balance, expected heterozygosity is $\mathrm{E}[H] = \mathrm{E}[2p(1-p)] = \lim_{t\to\infty} \int_0^1 2p(1-p)\phi(p,t)dp$. The effect of selection on heterozygosity depends on whether selection is balancing, directional or disruptive. This can be better seen if the advection term is written as

$$a(p) = \alpha(p^* - p)p(1-p) + (1-2p)\mu, \tag{2.4}$$

(Ewens and Thomson, 1970). The three possible selection regimes can then be inferred from the values of α and p^* (see Table 2.2). If $p^* < 0$ or $p^* > 1$, then selection is directional. In this case, selection is negative (for smaller values of p) when $\alpha(p^* - p) < 0$ and positive (for larger values of p) when $\alpha(p^* - p) > 0$, whereby the strength of selection is modulated by the absolute value α. If $0 < p^* < 1$, there is a selective equilibrium at frequency p^*. The sign of α then determines whether selection is balancing ($\alpha > 0$) or disruptive ($\alpha < 0$), and the absolute value of α determines the strength with which p is pulled towards or away from $0 < p^* < 1$.

	$p^* \leq 1$	$0 < p^* < 1$	$p^* > 1$
$\alpha < 0$	Negative	Balancing	Positive
$\alpha = 0$	Neutral	Neutral	Neutral
$\alpha > 0$	Positive	Disruptive	Negative

Table 2.2: Type of selection according to parameters α and p^*.

For an arbitrary locus, expected heterozygosity depends on the relative strength of selection

$2N_e\alpha$, the parameter p^* and the scaled mutation rate $2N_e\mu$ (see Appendix 2.A for details on calculating expected heterozygosity). To investigate the effect of these parameters, we compare the region under which selection generates a level of heterozygosity greater or less than a locus that evolves neutrally (see Figure 2.1, region delimited by the dashed contour). This shows that in general, heterozygosity is elevated beyond the neutral expectation when selection is balancing, and more so when selection is strong ($2N_e\alpha$ large) and favors an equilibrium frequency in the proximity of $p^* = 1/2$ (Figure 2.1).

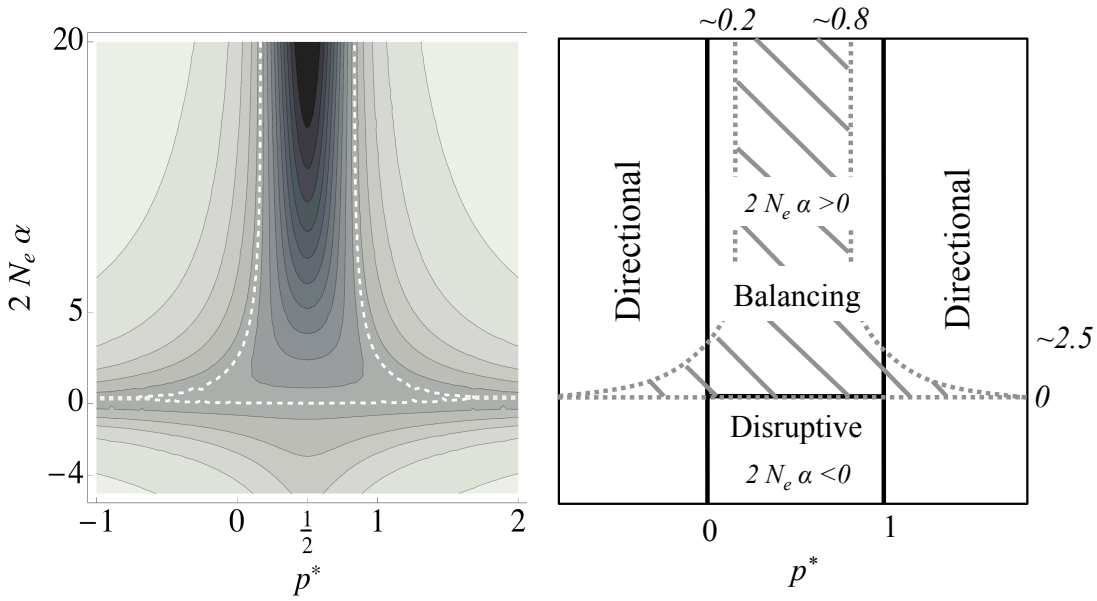

Figure 2.1: Expected heterozygosity at a single locus as a function of relative strength of selection, $2N_e\alpha$, and the equilibrium allele frequency, p^* - Darker regions represent higher levels of heterozygosity. The striped region within the dashed white line represents levels of heterozygosity greater than neutral heterozygosity undergoing the same mutation rate (fixed at $2N_e\mu = 0.1$ here), whilst the region outside represents levels of heterozygosity lower than neutral heterozygosity.

In addition to these expected patterns, there are three points worth noting. First, if selection is weak ($2N_e\alpha \lesssim 2.5$), then a locus under directional selection ($p^* < 0$ or $p^* > 1$) may cause greater levels of heterozygosity than a neutral locus. Such an effect could arise due to new mutations slowly traversing the frequency spectrum under weak selection until they reach fixation. Second, a locus under strong balancing selection may generate lower levels of heterozygosity than a neutral locus. This occurs when the favored equilibrium under balancing selection is close to the boundaries ($p^* \lesssim 0.2$ or $p^* \gtrsim 0.8$). Intuitively, as balancing selection generates a force that tends to maintain allele frequencies close to the boundaries, it increases the chances of an allele being lost or fixed due to random genetic drift. This echoes numerical results obtained for the number of

generations taken for a heterotic polymorphism to be lost (Robertson, 1962; Ewens and Thomson, 1970). Finally we note that the mutation rate has no effect here. Mutation increases the level of heterozygosity, but has the same effect on neutral heterozygosity. So the level of heterozygosity of a locus under selection relative to neutral remains unaffected by the mutation rate.

2.3.2 Comparison of autosomal and X-linkage

In order to generate predictions on how genomic location affects SA selection and heterozygosity, we first re-arrange the advection terms of equations (2.2) in the form of equation (2.4). This allows us to express α and p^* in terms of selection and dominance parameters for A- and X-linked loci (Table 2.3). The three factors that contribute to expected heterozygosity (as above) can then be synthesized as ratios of the relative effect of X-linkage to A-linkage

$$2N_{eA}\alpha_A = \frac{3(1+s\theta)}{4N_{eX}/N_{eA}} 2N_{eX}\alpha_X \tag{2.5a}$$

$$p_A^* = \frac{p_X^* - 1/2}{1+s\theta} + 1/2 \tag{2.5b}$$

$$2N_{eA}\mu = \frac{1}{N_{eX}/N_{eA}} 2N_{eX}\mu. \tag{2.5c}$$

The value of $s\theta = s_{\mathrm{m}}(1-2h_{\mathrm{m}})/(s_{\mathrm{f}}(1-2h_{\mathrm{f}}))$ measures the difference in fitness cost in males and females of a sexually antagonistic allele. The effects of sex-specific selection can be isolated from those of dominance. The selection term $s = s_{\mathrm{m}}/s_{\mathrm{f}} > 0$ measures the relative selection differential between homozygotes in males and females (Table 2.1). The parameter $\theta = (1-2h_{\mathrm{m}})/(1-2h_{\mathrm{f}})$ compares the cost of SA in male and female heterozygotes for an autosomal locus, where $\theta = 1$ indicates equal relative cost in the sexes ($h_{\mathrm{m}} = h_{\mathrm{f}}$) and $\theta = -1$ implies that dominance of Λ_{m} is equal across the sexes ($h_{\mathrm{m}} = 1 - h_{\mathrm{f}}$, as in Rice (1984)).

Locus	α	p^*
Autosomal	$\frac{1}{2}(s_{\mathrm{f}}(1-2h_{\mathrm{f}}) + s_{\mathrm{m}}(1-2h_{\mathrm{m}}))$	$\frac{h_{\mathrm{f}}s_{\mathrm{f}} - s_{\mathrm{m}}(1-h_{\mathrm{m}})}{s_{\mathrm{f}}(2h_{\mathrm{f}}-1) + s_{\mathrm{m}}(2h_{\mathrm{m}}-1)}$
X	$\frac{2}{3}s_{\mathrm{f}}(1-2h_{\mathrm{f}})$	$\frac{2h_{\mathrm{f}}s_{\mathrm{f}} - s_{\mathrm{m}}}{2s_{\mathrm{f}}(2h_{\mathrm{f}}-1)}$

Table 2.3: Values of α and p^* for SA loci according to chromosomal location and fitness scheme.

Since heterozygosity increases with $2N_e\alpha$ and the proximity of p^* to $1/2$, genetic variation

on the autosomes is greater relative to the X if $|s\theta|$ is large and $s\theta$ is the same sign as α_X in equations (2.5a) and (2.5b). These conditions are met if selection in males is stronger than in females ($s_{\mathrm{m}} >> s_{\mathrm{f}}$) and the SA cost in males is recessive ($h_{\mathrm{m}} < 1/2$). Conversely, dominant SA costs in males ($h_{\mathrm{m}} > 1/2$) favor the accumulation of SA genetic variation on the X. This is intuitive as dominant SA costs in males are only apparent to selection when they are autosomally expressed, hence reducing genetic variation on this chromosomal compartment only. Equation (2.5) also highlights the effect of differences in genetic drift on A and X chromosomes. Since heterozygosity increases with $2N_e\alpha$ and $2N_e\mu$, equations (2.5a) and (2.5c) suggest that genetic variation will be favored on autosomes relative to the X if the ratio of effective population sizes N_{eX}/N_{eA} is small, that is, if genetic drift is stronger on the X than on the autosomes.

2.3.3 X-to-A heterozygosity under selection and drift

To understand these general patterns in a more detailed manner, we numerically compute the ratio of expected heterozygosity for A- and X-linked SA polymorphism at selection-mutation-drift balance, $\mathrm{E}[H_X]/\mathrm{E}[H_A]$. As a baseline, we can use classical results on gene frequency distributions for neutral loci, $\lim_{t\to\infty}\phi(p,t)$ (Ewens, 2004, p. 174). For the ratio of X-to-A heterozygosity, this is a function of the ratio of the effective population sizes and the mutation rates scaled with respect to drift $\mathrm{E}[H_X]/\mathrm{E}[H_A] = (N_{eX}/N_{eA} + 4N_{eX}\mu_X)/(1+4N_{eX}\mu_X)$. A neutral locus then, generates greater heterozygosity on the X if $N_{eX}/N_{eA} > 1$.

To incorporate the effect of SA selection, we use the X-linked locus as a reference. For this locus, we fix values for the relative strength of selection $2N_e\alpha$, equilibrium frequency p^*, and relative mutation rate $2N_e\mu$. The corresponding values for an autosomal locus are then found using equation (2.5) and varying the selection $s\theta$ and drift N_{eX}/N_{eA} parameters. A sensitivity analysis was performed on reasonable ranges for the parameters (see Appendix 2.A for details), concentrating on the empirically estimated values of N_{eX}/N_{eA} between 0.5 and 1.1 (Mank et al., 2010). As suggested by Figure 2.1 and equation (2.5b), results were symmetric with respect to p_X^* about $1/2$. For simplicity, we only present results for $p^* > 1/2$.

Figure 2.2 shows how the relative enrichment of X and A for SA polymorphism varies with the intensity of selection and drift. Two general patterns emerge here. First, and as might be expected, the effect of N_{eX}/N_{eA} on the ratio of expected heterozygosity declines with increasing strength of selection. When selection is very weak with respect to drift ($2N_{eX}\alpha_X \approx 2N_{eA}\alpha_A \approx 0$), levels of heterozygosity are determined by drift alone. In this case, $\mathrm{E}[H_X]/\mathrm{E}[H_A]$ is proportional to N_{eX}/N_{eA}

(Figures 2.2a and 2.2b). When selection is strong, in contrast, $\mathrm{E}[H_X]/\mathrm{E}[H_A]$ is almost invariable with respect to N_{eX}/N_{eA} (Figures 2.2g and 2.2h). The second general pattern concerns the direction of chromosomal enrichment for SA polymorphism. Whether heterozygosity is greater on the X than the A ($\mathrm{E}[H_X]/\mathrm{E}[H_A] > 1$) or greater on the A than the X ($\mathrm{E}[H_X]/\mathrm{E}[H_A] < 1$) is determined by the signs of $s\theta$ and $2N_{eX}\alpha_X$. For $2N_{eX}\alpha_X > 0$, negative values of $s\theta$ favor the accumulation of variation on the X if, whereas positive values favor accumulation of variation on the A (Figures 2.2c and 2.2e). The opposite is true if $2N_{eX}\alpha_X < 0$ (Figures 2.2d and 2.2f). The combinations of $s\theta < 0$ with $2N_{eX}\alpha_X > 0$ and of $s\theta > 0$ with $2N_{eX}\alpha_X < 0$ are both equivalent to a dominant cost of the female beneficial allele in males ($h_\mathrm{m} > 1/2$), and their effect on $\mathrm{E}[H_X]/\mathrm{E}[H_A]$ is in line with the argument in the previous section.

In addition to these general patterns, our numerical analysis also reveals more nuanced effects. One is the interplay between N_{eX}/N_{eA} and the equilibrium frequency p^*, most pronounced for intermediate intensities of selection (Figures 2.2e and 2.2f). Here, we observe that effective population size has the strongest impact on heterozygosity when equilibrium frequencies are close to 1/2, but become less relevant as selection becomes more strongly directional ($p^* > 1$ in Figure 2.2). This can be understood as follows. With intermediate intensity of selection and $p_X^* = p_A^* = 1/2$, SA generates balancing selection of similar, limited, magnitude ($s\theta$ small, equation (2.5a)) and the absolute levels of heterozygosity are maximal on both the X and A (Figure 2.1). In this case, differences between N_{eX} and N_{eA} alter the likelihood that random variation leads to fixation of allelic variation and the N_{eX}/N_{eA} ratio has a large effect on $\mathrm{E}[H_X]/\mathrm{E}[H_A]$. But as the value of p^* departs from 1/2, and selection on the X and A becomes increasingly directional (i.e., $p_X^* > 1$ and $s\theta$ small, Figure 2.2e), the impact of N_{eX}/N_{eA} on $\mathrm{E}[H_X]/\mathrm{E}[H_A]$ diminishes. Thus, differences in effective population size between X and A then have little impact on allelic variation when selection is directional. Variation in N_{eX}/N_{eA} likewise has significant consequences when SA generates limited disruptive selection (i.e., $p_X^* = 1/2$ and $2N_{eX}\alpha_X < 0$; Figure 2.2f), but less impact as selection becomes directional.

We also observe interesting changes in $\mathrm{E}[H_X]/\mathrm{E}[H_A]$ under strong selection. First, we find that chromosomal enrichment for SA variation is determined by the interaction between p^* and $s\theta$ (Figure 2.3). Since heterozygosity is maximized when the equilibrium frequency $p^* = 1/2$, values of p_X^* close to $1/2$ promote heterozygosity on the X relative to A. Therefore, as p_X^* deviates from 1/2 and rises to one, greater heterozygosity on the X than the A can only be maintained by making $s\theta$ increasingly negative for $2N_{eX}\alpha_X > 0$ (Figure 2.3a) or increasingly positive for $2N_{eX}\alpha_X < 0$

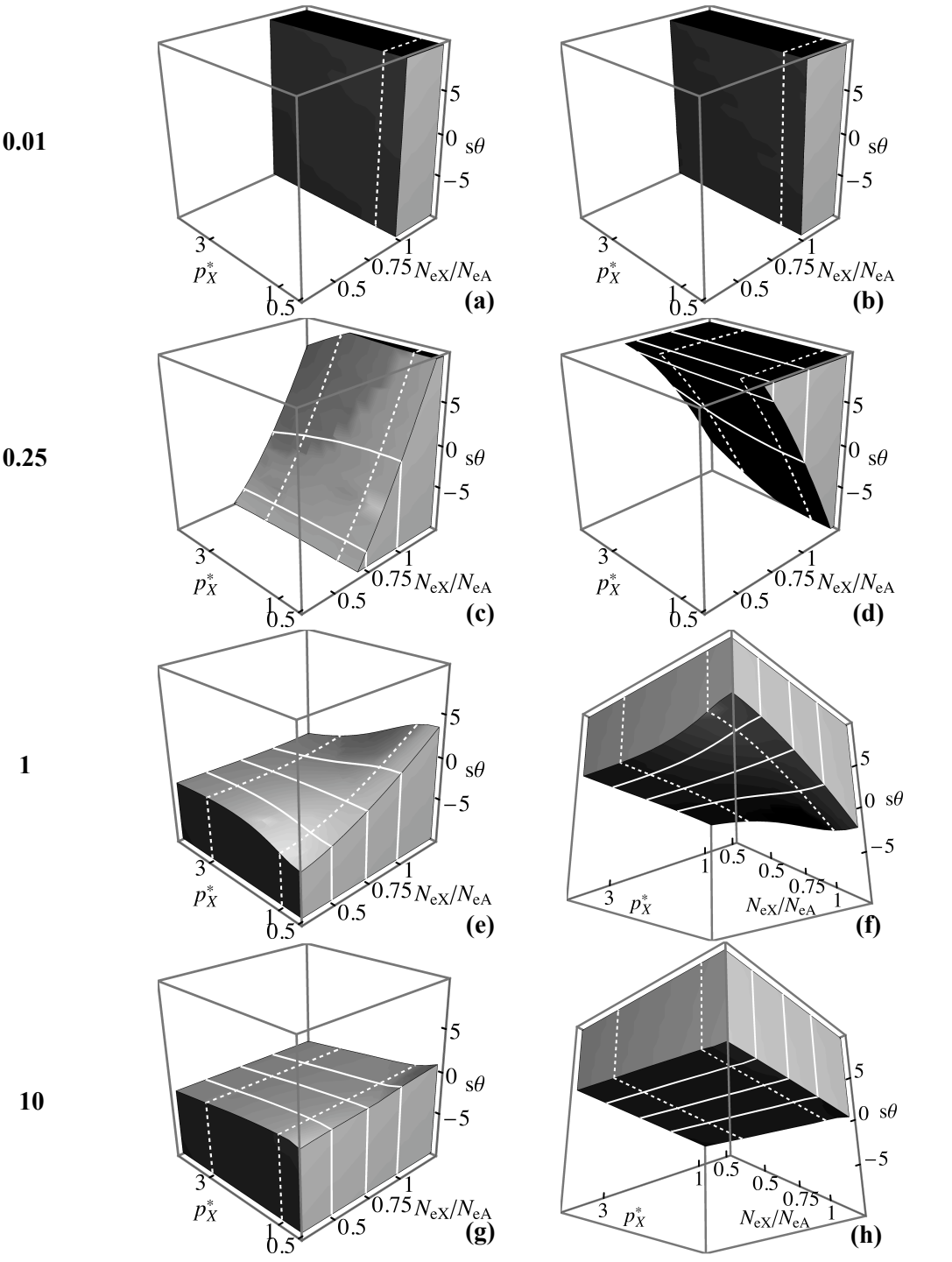

Figure 2.2: Parameter space for greater SA heterozygosity on the X - Three-dimensional plot in the p_X^*, $s\theta$, N_{eX}/N_{eA} space. The grey volume corresponds to the combination of parameters for which $\mathrm{E}[H]_X > \mathrm{E}[H]_A$. The values of $2N_{eX}\alpha_X$ are (a) 0.01, (b) -0.01, (c) 0.25, (d) -0.25, (e) 1, (f) -1, (g) 10, and (h) -10. The mutation rate is fixed at $2N_{eX}\mu_X = 0.1$. The space in panels (f) and (h) is rotated upwards to show the shape of the lower surface.

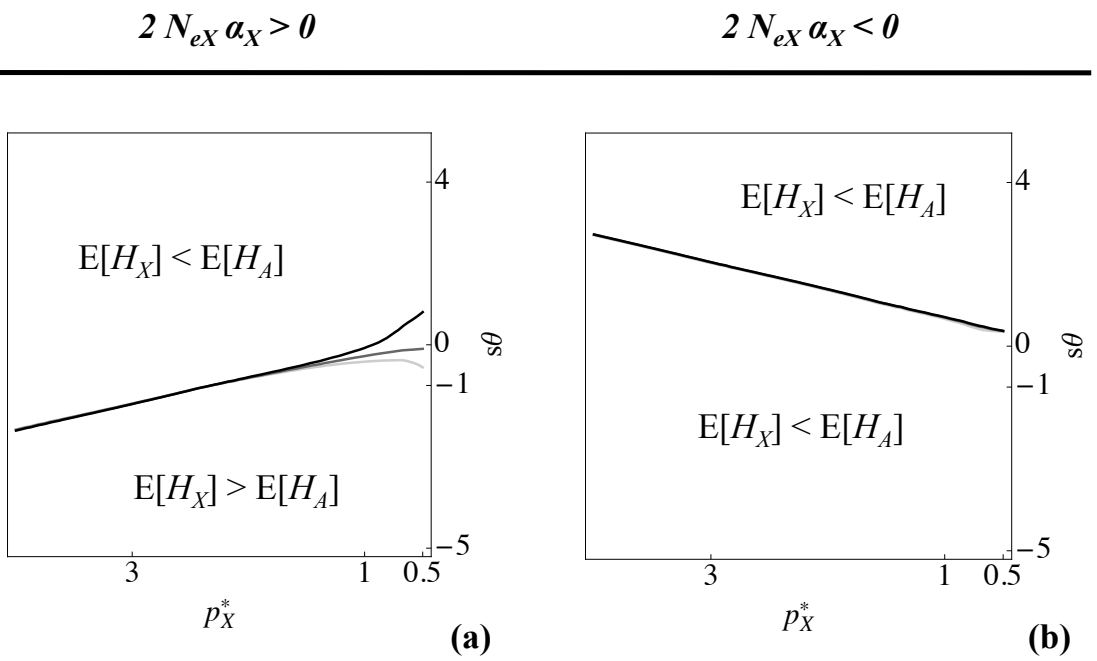

Figure 2.3: Parameter space for greater SA heterozygosity on the X when selection is strong relative to drift - Two-dimensional plot in the p_X^*, $s\theta$ plane for different N_{eX}/N_{eA} values with (a) $2N_{eX}\alpha_X = 10$ and (b) $2N_{eX}\alpha_X = -10$. Each curve is for a different value of N_{eX}/N_{eA}, with 0.5 in light grey, 3/4 in dark grey, and 1 in black. The mutation rate is fixed at $2N_{eX}\mu_X = 0.1$.

(Figure 2.3b), making selection on the autosomes either strongly directional or strongly disruptive (equation (2.5)).

Furthermore, differences in genetic drift (N_{eX}/N_{eA}) may also influence the ratio of expected levels of heterozygosity, even under strong selection (Figure 2.3a). This is the case whenever $2N_{eX}\alpha_X > 0$, $p_X^* \approx 1/2$ and $s\theta \approx 0$. These conditions are equivalent to balancing selection acting on both the autosomal and the X-linked locus, with favored polymorphism close to 1/2. They further imply very similar selection gradients in males and females ($s_\mathrm{f} = s_\mathrm{m}$) and additive allelic effects in males ($h_\mathrm{m} = 1/2$). In this case, differences in the strength of selection protecting polymorphism, $2N_e\alpha$, on the X and A become very sensitive to changes in N_{eX}/N_{eA} (equation (2.5a)).

2.3.4 Expected heterozygosity under mutation pressure

The effect of mutation on the ratio of expected heterozygosity is restricted to the extremes of the spectrum of mutation rate. At low rates, mutational input exaggerates differences in heterozygosity across the genome that arise due to other parameters. With high rates, recurrent mutations become the chief cause for genetic variation and differences in selection and effective population sizes cause less quantitative changes in the $\mathrm{E}[H_X]/\mathrm{E}[H_A]$ ratio. For most intermediate values,

however, the scaled mutation rate has no qualitative effect on $\mathrm{E}[H_X]/\mathrm{E}[H_A]$ and heterozygosity are dominated by the other parameters ($2N_{eX}\alpha_X$, p_X^*, $s\theta$ and N_{eX}/N_{eA}).

2.3.5 Times to fixation of autosomal and X-linked polymorphism

In the analyses presented so far, we measured polymorphism based on the expected heterozygosity $\mathrm{E}[H]$ at SA loci. In order to assess the generality of our inferences, we now generate predictions based on another measure of polymorphism – the expected time to fixation $\mathrm{E}[T]$. This allows us to compare the stability of polymorphism on the X and the autosomes by calculating the ratio of times to fixation $\mathrm{E}[T_X]/\mathrm{E}[T_A]$. When $\mathrm{E}[T_X]/\mathrm{E}[T_A] > 1$, a locus on the X is expected to remain polymorphic for longer than a locus on the autosome and vice versa. Based on classical results (Ewens, 2004, p. 160), the ratio for neutral loci is a function of the ratio of effective population sizes, $\mathrm{E}[T_X]/\mathrm{E}[T_A] \approx 4N_{eX}/(3N_{eA})$. As for $\mathrm{E}[H_X]/\mathrm{E}[H_A]$, we investigated how $\mathrm{E}[T_X]/\mathrm{E}[T_A]$ varies with effective population sizes and selection parameters by using the X-linked locus as a reference for $2N_e\alpha$ and p^*. We then determine the corresponding values for autosomes using equation (2.5a) and calculate $\mathrm{E}[T_X]/\mathrm{E}[T_A]$ (see Appendix 2.B).

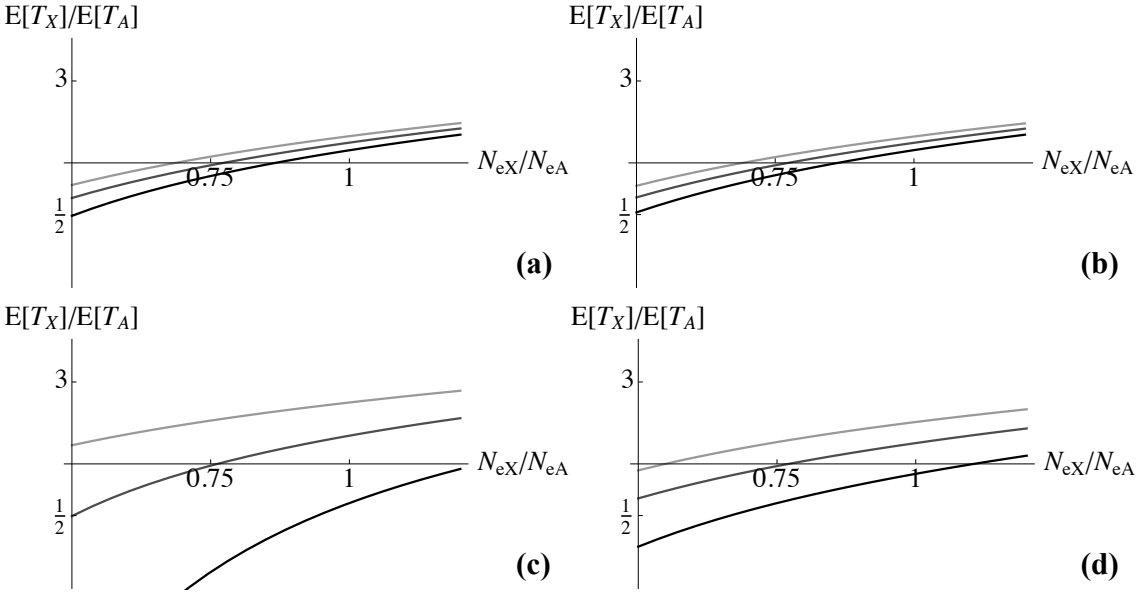

Figure 2.4: The $\mathrm{E}[T_X]/\mathrm{E}[T_A]$ ratio vs N_{eX}/N_{eA} - The different lines in represent different values of $s\theta$: -2 (light grey), 0 (grey) and 2 (black). The rows represent different strength of selection and the columns different values of p_X^*. (a) and (b) correspond to weak selection ($2N_{eX}\alpha_X = 1$) and, (c) and (d) to stronger selection ($2N_{eX}\alpha_X = 5$). In (a) and (c), $p_X^* = 1/2$, and $p_X^* = 1.5$ in (b) and (d). The origin is set at $\mathrm{E}[T_X]/\mathrm{E}[T_A] = 1$.

We find that $\mathrm{E}[T_X]/\mathrm{E}[T_A]$ increases for larger values of N_{eX}/N_{eA}, implying that a relatively larger effective population size on the X leads to relatively longer lived polymorphism on the X

(Figure 2.4). Furthermore, $\mathrm{E}[T_X]/\mathrm{E}[T_A]$ (and in particular whether its value is above or below 1) is more sensitive to changes in N_{eX}/N_{eA} when selection is relatively weak (Figures 2.4a,b vs. Figures 2.4c,d). Finally, the distribution of polymorphism is affected by the relative strength of selection on the X and the autosomes. Polymorphism is longer lived on the X chromosome than the autosomes when $2N_{eX}\alpha_X > 0$ and $s\theta > 0$ or when $2N_{eX}\alpha_X < 0$ and $s\theta < 0$. As discussed previously, these conditions are equivalent to a dominant cost of SA in males ($h_\mathrm{m} < 1/2$).

These results are the same as those obtained with the heterozygosity ratio $\mathrm{E}[H_X]/\mathrm{E}[H_A]$. However, we also find some interesting differences. Specifically, $\mathrm{E}[T_X]/\mathrm{E}[T_A]$ is more strongly affected by changes in N_{eX}/N_{eA} than $\mathrm{E}[H_X]/\mathrm{E}[H_A]$, and the impact of effective population sizes is not conditional on equilibrium allele frequencies being close to $1/2$ (compare Fig 2.4c and d). As a consequence, the ratio of times to fixation varies with effective population sizes under both balancing and directional selection, both under weak selection (Figures 2.4a and b) and strong selection (Figures 2.4c and d).

2.4 Discussion

Population genetic models show that sexual antagonism is able to generate balancing selection and hence contribute to the maintenance of genetic polymorphism (Owen, 1953; Kidwell et al., 1977). By using these models to predict the relative abundance of sexually antagonistic polymorphism on the autosomes and the X chromosome (Rice, 1984; Fry, 2010; Connallon and Clark, 2011), they have provided a thorough understanding of how selection affects the distribution of sexually antagonistic variation across the genome. However, because all natural populations are finite, and the impact of genetic drift may differ in magnitude across the genome (Caballero, 1995), these previous analyses are lacking a crucial factor by omitting genetic drift. To address this shortcoming, we have analyzed a model of sexually antagonistic evolution at autosomal and X-linked loci in a finite, dioecious population. This model takes into account the effect of genetic drift and how its intensity relative to selection, differs between the autosomes and the X chromosome.

In addition to incorporating drift, our model also widens the scope of selection analysis. Previous analyses have focused on determining whether the location of novel SA mutations alters the probability that they are subject to balancing selection. Since sexually antagonistic alleles may also be under directional or disruptive selection regimes, the contribution of these other forms of selection to sexually antagonistic variation needs to be taken into account. Furthermore, there has

been no consideration of the extent of heterozygosity generated by sexually antagonistic selection, nor its persistence through time. In this study we have rectified this situation through a full analysis of the interaction between genetic drift and selection to the generation of sexually antagonistic heterozygosity.

Our model predicts that generally (and unsurprisingly), genetic variation is maintained when polymorphism is stabilized by balancing selection that is strong relative to drift (measured here by $2N_e\alpha$, Figure 2.1). However, we also show that there is not an immediate correspondence between presence of balancing selection and excess polymorphism. For example, the equilibrium frequency p^* is an important determinant of how well balancing selection will maintain polymorphism. While polymorphisms with intermediate values of p^* are stable, balancing selection for equilibria close to 0 or 1 will tend to drive allele frequency towards the boundaries and thereby precipitate the loss or fixation through genetic drift. As a consequence, we expect to see lower levels of polymorphism in these cases than expected under neutrality (Figure 2.1). We also find interesting effects of directional selection. While strong directional and disruptive selection (defined by $2N_e\alpha$ and p^*, see Table 2.2) lead to the rapid loss of genetic variation, weak directional selection can lead to polymorphism in excess of the level expected at neutral loci (Figure 2.1).

In order to understand how the interaction between genetic drift and sexually antagonistic selection differs between the X and the autosomes, we compared $2N_e\alpha$ and p^* for the two types of chromosome. To do this, we agglomerated all selection and dominance terms in the quantity $s\theta = (s_{\mathrm{m}}(1-2h_{\mathrm{m}}))/(s_{\mathrm{f}}(1-2h_{\mathrm{f}}))$, and used the ratio of effective population sizes of the X to the autosomes, N_{eX}/N_{eA} (equation (2.5)). Comparing $2N_e\alpha$ and p^* for autosomal and X-linked loci (equation (2.5)), we found that the relative strength of genetic drift will affect the levels of polymorphism on the two chromosomal compartments, with greater values of N_{eX}/N_{eA} favoring the accumulation of sexually antagonistic variation on the X chromosome. We also found greater X-linked relative to autosomal polymorphism if the cost of sexual antagonism is dominant in males ($h_{\mathrm{m}} > 1/2$), because they are then only apparent to selection when autosomally expressed. This result is in line with previous predictions from deterministic systems (Kidwell et al., 1977; Fry, 2010). Interestingly, this correspondence occurs despite the fact that these models concentrated on the case of balancing selection, whereas we have generalized the analysis to all types of selection. Even if the bulk of standing SA variation within a population is expected to be due to loci under strong balancing selection, alleles that are under other selection regimes will also contribute to sexually antagonistic variation, especially if the effective population size is small.

To investigate with greater precision how the combined effect of sexually antagonistic selection and genetic drift play out, we calculated the ratio of sexually antagonistic heterozygosity on the X compared to autosomes, $\mathrm{E}[H_X]/\mathrm{E}[H_A]$. As expected, N_{eX}/N_{eA} is the critical factor when the strength of selection is weak with respect to drift ($|2N_e\alpha|$ small) or if N_e is small (Figures 2.2a-d). Accordingly, we expect X-enrichment for SA variation with higher values of N_{eX}/N_{eA} and autosomal enrichment for lower values of N_{eX}/N_{eA}. This is true irrespective of the selection regime (directional, disruptive as well as balancing) undergone by the alleles.

As the relative strength of selection increases ($|2N_e\alpha|$), we found that the main causes of difference in expected heterozygosity across the genome are the selection parameters, scaled by $s\theta$ and p_X^* (Figure 2.3). This means that the dominant SA cost in males ($h_\mathrm{m} > 1/2$) privileges the accumulation of SA genetic variation on the X. However, even when relative strength of selection is strong, the N_{eX}/N_{eA} ratio within reasonable range is able to alter predictions made on the basis of selection parameters alone. For values of $s\theta$ close to zero and p^* close to 1/2, differences in genetic drift (N_{eX}/N_{eA}) are able to alter the predictions generated by selection (Figure 2.3c). So the contribution of the N_{eX}/N_{eA} ratio will be important when alleles have equal fitness gradients in males and females ($s_\mathrm{f} = s_\mathrm{m}$), with additive effects in males ($h_\mathrm{m} = 1/2$) and recessive cost in females ($h_\mathrm{f} < 1/2$).

Similar conclusions emerge for a related measure of polymorphism, the time to fixation ($\mathrm{E}[T]$, Figure 2.4). The N_{eX}/N_{eA} ratio has a stronger effect and the selection parameters a weaker effect on effect on expected time to fixation than on expected heterozygosity. This difference in behavior arises because whereas $\mathrm{E}[T]$ simply requires that allelic variation is present, $\mathrm{E}[H]$ also explicitly relies on the time spent at specific allelic frequencies, and is more sensitive to whether the allele frequencies are held close to $1/2$ by selection (as $\mathrm{E}[H] = \mathrm{E}[2p(1-p)]$). So expected heterozygosity exaggerates the effect of the value of p^*. When interpreting the predictions of our model it is therefore important to consider which facet of polymorphism is most interesting, population allele frequencies (i.e., $\mathrm{E}[H]$) or simply the presence of allelic variation (i.e., $\mathrm{E}[T]$).

Like previous studies, our model predicts that the location of sexually antagonistic genetic variation will in part depend on the values of the selection and dominance coefficients. However, the interpretation of these predictions seems currently difficult. First, as noted by Fry (2010) and Jordan and Charlesworth (2011), there is little hope of being able to map sexually antagonistic traits to single genes and estimate their sex specific selection coefficients and dominance relationships. So attempts to validate theoretical results based on estimations of selection parameters

seem implausible. Secondly, it seems unlikely that the distribution of selection parameters is significantly different from one population to another, and hence this is not an obvious explanation of the diversity of sexually antagonistic genetic variation (Fry, 2010).

An alternative, and more feasible approach to address the question of the location of SA variation in the genome, is to consider explanations based on the N_{eX}/N_{eA} ratio. It can be calculated from levels of neutral polymorphism on the X and autosomes. And such estimates have been obtained and vary significantly across species and even across populations (e.g., Mank et al., 2010). The N_{eX}/N_{eA} ratio synthesizes many genetic, ecological and behavioral processes (Caballero, 1995; Laporte and Charlesworth, 2002; Hutter et al., 2007; Vicoso and Charlesworth, 2009) and thereby is apt in explaining population level variation in the distribution of sexually antagonistic polymorphism. It will be interesting to confront our predicted correlation between N_{eX}/N_{eA} and enrichment of antagonistic variation with empirical data. The estimates for N_{eX}/N_{eA} show moderate deviations from the baseline value of 3/4, with $N_{eX}/N_{eA} > 3/4$ and $N_{eZ}/N_{eA} < 3/4$ that are compatible with observed variation in male reproductive success (Mank et al., 2010). We thus predict a higher level of X-enrichment in species with XY sex determination, such as mammals and many groups of insects, compared to species with ZW sex determination, such as birds and butterflies.

In addition, if precise experimental estimation of selection parameters is today unlikely, our model provides a way to obtain coarse estimates. For instance, observing X enrichment of sexually antagonistic variation in a population with $N_{eX}/N_{eA} << 1$ would imply that most sexually antagonistic mutations have a dominant cost in heterozygotic males, whereas autosomal enrichment with $N_{eX}/N_{eA} >> 1$ would hint towards recessive cost. It is unfortunate that the most detailed empirical results on SA variation to date, from a *Drosophila* lab population that showed almost exclusive X-linkage of sexually antagonistic variation, are inconclusive on that front (Gibson et al., 2002). So this result cannot be used to comment on the selection parameters of antagonistic alleles.

In conclusion, we have shown how selection and drift can affect sexually antagonistic variation differently at autosomal and sex-linked loci. Our model makes predictions about the extent and nature of genetic variation expected under different scenarios, and opens the possibility of combining quantitative with population genetic data in order to gain information on the characteristics of antagonistic mutations segregating in wild populations.

Appendix

2.A Calculating expected heterozygosity

To obtain expected heterozygosity at mutation-selection-drift balance, we first compute the stationary distribution $\hat{\phi}(p)$, for a locus with advection term $a(p)$ and diffusion term $b(p)$

$$\hat{\phi}(p) = \frac{C}{b(p)} \exp\left(2 \int \frac{a(p)}{b(p)} dp\right), \tag{2.A.1}$$

where the constant of integration C is calculated so that $\int_0^1 \hat{\phi}(p)dp = 1$ (Ewens, 2004, p. 146). Then the expected heterozygosity is given by $\int_0^1 2p(1-p)\hat{\phi}(p)dp$. Whilst $\int a(p)/b(p)dp$ can be computed exactly, the integrals to compute C and the expected heterozygosity do not have a general solution. We evaluated those integrals numerically, using an adaptive Monte Carlo scheme with Mathematica v7.0.1.0. Expected heterozygosity was first evaluated for the X-linked locus with arbitrary values of $2N_{eX}\alpha_X$, p_X^* and $2N_{eX}\mu_X$, and then varied parameters $s\theta$ and N_{eX}/N_{eA} to obtain expected heterozygosity for an autosomal locus using equation (2.5). This had the advantages of reducing the number of parameters from seven to five, and provide an intuitive understanding of the effects of selection schemes on the $\mathrm{E}[H_X]/\mathrm{E}[H_A]$ ratio. We explored the following parameter ranges $-20 < 2N_e\alpha < 20$, $-10 < p^* < 10$, $0.01 < 2N_e\mu < 0.2$, $-10 < s\theta < 10$ and $0.3 < N_{eX}/N_{eA} < 1.5$, with at least 100 sampling points for each range.

2.B Calculating the number of generations till loss of polymorphism

Briefly, we calculated $t(p_0)$, the expected time taken for an allele to be lost or fixed, given its initial frequency p_0 at each locus. Time to fixation is measured in units of effective population size, so that the expected number of generations until fixation is given by $\mathrm{E}[T] = 2N_e t(p_0)$. For a given pair of alleles, the value of t is found by (in our case numerically) solving the differential equation

$$1 + a_S(p)\frac{dt}{dp} + \frac{1}{2}b_S(p)\frac{d^2t}{dp^2} = 0, \tag{2.B.1}$$

with boundary conditions $t(0) = t(1) = 0$ (Ewens, 2004, p. 141), and where $a_S(p) = 2N_e\alpha(p^* - p)p(1-p)$ and $b_S(p) = p(1-p)$ are the scaled (with respect to N_e) advection and diffusion terms.

When calculating $\mathrm{E}[T]$, we assumed that polymorphism arose by mutation and that the mutant was initially present in a single copy in a randomly sampled individual (which may be male or female). The population was assumed to be composed of $N = 10^3$ individuals with equal number of males and females. Accordingly, the initial frequencies of new A- and X-linked mutants, averaged over the sexes, are given by

$$p_{0A} = \frac{1}{2N} \text{ and } p_{0X} = \frac{2}{3N}, \tag{2.B.2}$$

We assumed that male- and female-beneficial mutations are equally likely and averaged their times until loss of polymorphism to calculate $\mathrm{E}[T]$. The ratio $\mathrm{E}[T_X]/\mathrm{E}[T_A]$ is then given by

$$\frac{\mathrm{E}[T_X]}{\mathrm{E}[T_A]} = \frac{N_{eX}}{N_{eA}} \left(\frac{t_X(p_{0X}) + t_X(1-p_{0X})}{t_A(p_{0A}) + t_A(1-p_{0A})} \right). \tag{2.B.3}$$

The numerical integration to solve for t is significantly more sensitive to rounding errors than the one used to calculate expected heterozygosity. In order to ensure the accuracy of our results, we rejected results for which integration converged with a numerical error greater than 10^{-12}. This procedure constrained the results we could generate and meant that the parameter range explored for $\mathrm{E}[T_X]/\mathrm{E}[T_A]$ was not as large as for $\mathrm{E}[H_X]/\mathrm{E}[H_A]$. Nevertheless, we were able to generate results that allow us to verify the predictions made based on $\mathrm{E}[H_X]/\mathrm{E}[H_A]$, as well as explore how the properties of the two measures of polymorphism differ.

Chapter 3

The evolution and consequences of sex-specific reproductive variance

This study was conducted in collaboration with Max Reuter and Laurent Lehmann, and is being prepared for submission to *Genetics*.

Abstract

Natural selection favors genes that increase the number of offspring produced by their carriers. Natural selection has thus mostly been investigated by looking at how genes maximize the expected number of offspring of their carriers. But theory predicts that selection also favors genes that reduce the variance in the number of offspring produced. If previous models have established this principle, they have not incorporated fundamental aspects of sexual reproduction, and how different traits affect reproductive variance. Since the causes and intensity of this variance are thought to differ across the sexes, it is relevant to decompose the contributions of various traits to reproductive variance in sexual species. To study the evolution and consequences of sex-specific reproductive variance, we present here a population genetic model that is based on an explicit representation of sexual reproduction, and which incorporates variance-minimizing selection. In particular, we derive the probability of fixation for mutations affecting any male and/or female reproductive traits. Our modeling framework is used to calculate the selection gradient along which general reproductive traits evolve. We interpret their evolution in terms of the selective pressures that act on the mean and variance of sex-specific reproductive success. Beyond these generalities, the model can be adapted to model very specific reproductive systems. It thus opens the possibility for more detailed analyses, enabling a better picture of the evolution of reproductive biology.

3.1 Introduction

In the absence of mutation, the change in gene frequency is the result of natural selection and genetic drift. Natural selection favors genes that maximize their representation within the gene pool of future generations. A large body of work has investigated how genes achieve this by increasing the expected number of offspring produced by their carriers. Genetic drift arises from randomness in the reproduction of gene carriers and reduces the efficacy of natural selection. If reproduction is highly variable compared to genetic differences in mean offspring production, genetic drift may even prevent adaptation altogether.

While many studies have investigated how selection maximizes the mean number of offspring in the face of genetic drift, less attention has been given to the degree to which selection acts on the variance in offspring number, and in turn, to how the evolution of this variance contributes to the intensity of genetic drift. Gillespie (1974; 1975; 1977) investigated how natural selection can dampen randomness in within-generation fertility in a haploid population. He demonstrated that between two genotypes that on average produce the same number of offspring, natural selection favors the genotype that produces a number of offspring with smaller variance. His model also revealed that the level of genetic drift affecting the segregation of the two genotypes increases with their variance in offspring production. As a consequence, fixation of the allele coding for lower fertility variance potentially reduces the intensity of genetic drift for future segregation processes.

The variance in fertility considered by Gillespie (1974; 1975; 1977) had arbitrary causes, and could have stemmed from randomness at any stage of an individual's life history, such as its development, its fertility or the survival of its offspring. Extensions of Gillespie's models have since investigated the manifestation of variance-minimizing selection under more specific life histories, and how it affects their evolution. For instance, Shpak (2007) investigated the evolution of the variance in offspring number in an age-structured population, and showed that selection favors genotypes with lower stochasticity in age-specific survival and fertility. Meanwhile, Taylor (2009) extended Gillespie's (1974) model to investigate the effect of sex-specific variance in gamete production on coalescent times. Furthermore, despite variance-minimizing selection being inversely proportional to population size, it was found that it could still be significant for the evolution of large but structured populations. And variance-minimizing selection has been demonstrated to affect selection on traits like sex allocation (Proulx, 2000), dispersal (Shpak, 2005; Shpak and Proulx, 2007; Lehmann and Balloux, 2007), and helping behaviors (Lehmann and Balloux, 2007;

Beckerman et al., 2011).

The aforementioned models have highlighted that variance-minimizing selection may be a subtle yet significant force in the evolution of many different traits in natural populations. It remains unclear however how the biology of organisms is shaped by the operation of variance-minimizing selection on reproductive traits, and in turn, how these traits affect the intensity of genetic drift. The main reason for this is that models so far have either omitted sex altogether, or neglected to give a realistic account of the reproduction episode. For instance, by articulating mating as a random union of gametes, and by assuming the absence of covariances between individual gametic production, Taylor (2009) ignored important effects that stem from mating patterns. The breeding system, or how males and females organize themselves into reproductive units, have significant consequences for variance in offspring number (e.g. Bateman, 1948; Wade, 1979), and thus for the evolution of the reproductive traits that generate this variance.

A legitimate starting point to improve on current models would be to consider mating and fertilization as two separate processes. There are at least three reasons to do this. First, variations in both mating and fertilization success may be a major source of reproductive variance (as explored in the sexual selection literature, for eg. Andersson, 1994; Eberhard, 1996; Birkhead and Moller, 1998). So distinguishing between mating and fertilization would enable looking into how variance-minimizing acts upon on the variance of either and also on their covariance. Secondly, separating mating and fertilization would explicitly take into account the covariance between the juvenile productions of different individuals that is created by the mating system. For example, if two males mate with the same female, their offspring production become immediately negatively correlated if the female has a finite number of eggs. Finally, sex-specificities in reproductive variance are thought to stem from differences in variation at these two episodes. Males are often described as suffering greater reproductive variance due to limited access to mates, whilst variance in females is thought to be mainly due to differences in fertility (Bateman, 1948; Wade, 1979; Clutton-Brock, 2007). Isolating mating and fertility would then allow the precise capturing of sex-specific reproductive variance.

In this chapter, we construct a population genetic model that incorporates an explicit representation of sexual reproduction. Our model is capable of accounting for complex interactions between males and females, whether they occur at the stage of mating or gamete fusion. The model is used to characterize the co-evolutionary stable states of multiple reproductive traits, taking into account their effects on sex-specific reproductive variance. In addition to the general insights pro-

vided by the traits we investigate, the model lays the foundation for more precise descriptions of the reproductive episode. This framework will hopefully help gaining a better understanding, not only of how natural selection shapes the reproductive biology of individuals, but also of the feedback mechanism between reproductive traits and the efficacy of selection that shapes them.

3.2 The model

3.2.1 Biological scenario

We model a dioecious population with constant, finite numbers of N_{m} adult males and N_{f} females. Generations are non-overlapping and the life-cycle followed by the organism comprises four steps: mating, birth, viability selection, and regulation. Males and females are assumed to produce a sufficiently large number of juveniles for the population to maintain its constant size. Our aim is to evaluate the evolution of a quantitative phenotypic trait z in this population. This phenotype is expressed in females and males and may affect all events in the life cycle (e.g., mating, resource competition, birth, viability). This phenotype may in addition be subject to frequency-dependent selection, taking into account selection pressures arising from social interactions.

3.2.2 Genotypes and Phenotypes

The evolving phenotype z is determined by an autosomal locus, where two alleles segregate: a resident allele denoted a and a mutant allele denoted A. The frequency of the mutant in a focal male $i \in \{1,\dots,N_{\mathrm{m}}\}$ is written as $p_{\mathrm{m}i} \in \{0,1/2,1\}$, whilst the frequency in a focal female $j \in \{1,\dots,N_{\mathrm{f}}\}$ is written $p_{\mathrm{f}j} \in \{0,1/2,1\}$. In order to include dominance effects, we define indicator variables $\mathbb{1}_{\male i}$ and $\mathbb{1}_{\female i}$ for each individual i (whether it is male or female), which take the value one if the paternally and maternally inherited alleles are mutant, zero otherwise. The mutant frequency in male i and female j may then be written as

$$p_{\mathrm{m}i} = \frac{\mathbb{1}_{\male i} + \mathbb{1}_{\female i}}{2} \quad \text{and} \quad p_{\mathrm{f}j} = \frac{\mathbb{1}_{\male j} + \mathbb{1}_{\female j}}{2}. \tag{3.1}$$

We write the phenotypic value of the three genotypes aa, Aa, and AA in males as z_{m}, $z_{\mathrm{m}}^{Aa} = z_{\mathrm{m}} + h\delta_{\mathrm{m}}$, and $z_{\mathrm{m}}^{AA} = z_{\mathrm{m}} + \delta_{\mathrm{m}}$, where h is the dominance coefficient of A in heterozygotes, and δ_{m} measures the difference between the phenotype of the two types of homozygote. Similarly, the phenotypic value of the three genotypes in females are written as z_{f}, $z_{\mathrm{f}}^{Aa} = z_{\mathrm{f}} + h\delta_{\mathrm{f}}$, and $z_{\mathrm{f}}^{AA} =$

$z_f + \delta_f$. For simplicity, dominance h is written as being the same in males and females throughout, but our main results of section 3.5 only require that dominance is the same on average (over all possible mutants).

Combining the expressions for the phenotypic values of the genotypes with the frequency of mutant alleles within individuals, we obtain for the phenotypes of a focal male i and female j

$$\begin{aligned} z_{mi} &= z_m + \delta_m(2hp_{mi} + (1-2h)\mathbb{1}_{\male i}\mathbb{1}_{\female i}) \\ z_{fj} &= z_f + \delta_f(2hp_{fj} + (1-2h)\mathbb{1}_{\male j}\mathbb{1}_{\female j}). \end{aligned} \tag{3.2}$$

Throughout this chapter we consider phenotypes that evolve by small steps, where the differences δ_m and δ_f between the phenotypes of a mutant and a resident homozygote are small. We also note here that although it is the phenotypic trait value z, such as height or weight, that is evolving, we can and will use this as a modeling device to infer on the evolution of any (differentiable) function $f(z)$ of that phenotype, like mating success or offspring survival. Because of the direct link between the phenotypic trait and the higher-level life history strategies we are ultimately interested in, we interchangeably speak of the evolution of the phenotypic trait or of the more general functions of that trait, without re-iterating that these functions are assumed to depend on the trait.

3.2.3 Life Cycle

The life cycle followed by the population is detailed below (see also fig. 3.1). It is articulated as a stochastic process determined by the evolving phenotypes.

3.2.3.1 Juvenile Production

In order to reproduce, a male i and a female j must first pair up to mate. This pairing event is captured by the random indicator variables $\mathbb{1}_{P_{ij}}$, which take the value one if male i and female j mate and zero otherwise. If pairing takes place, the female then produces a finite random number $B_{ij} \in \{0,1,\ldots\}$ of offspring. This number is specific to her mating with male i, thereby allowing the model to take into account the case in which a female produces a collection of broods of varying size with different males (for example B_{1j}, B_{2j} if she has mated with the two males indexed 1, 2). An offspring, indexed by $n \in \{0,1,\ldots,B_{ij}\}$, either becomes male, in which case the indicator variable $\mathbb{1}_{R_n}$ takes the value 1, or a female, where $\mathbb{1}_{R_n} = 0$. The offspring are then subject to sex-

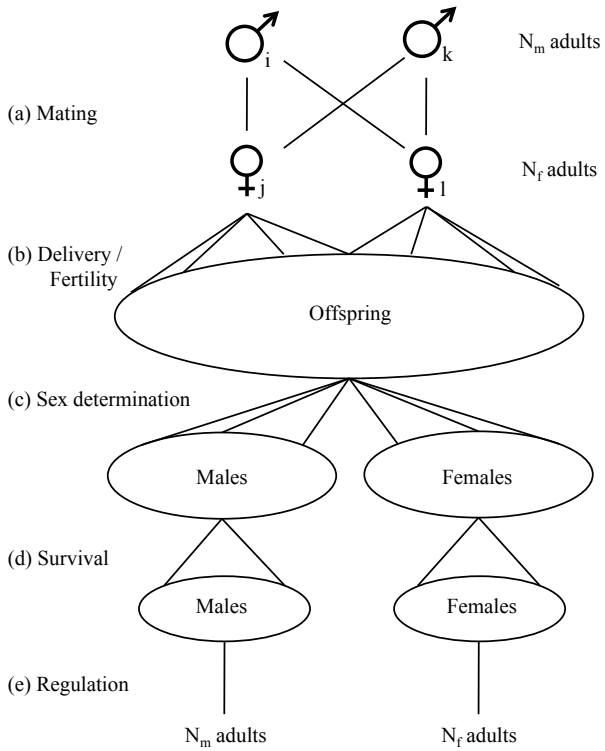

Figure 3.1: Outline of the life cycle - See text for details. Tables 3.1 and 3.2 give the list of the underlying random variables that define the life cycle, and the moments of their corresponding distribution.

specific viability selection. We define an indicator random variable $\mathbb{1}_{S_n^u}$, which takes the value 1 if offspring n of sex $u \in \{\mathrm{m},\mathrm{f}\}$ survives and 0 otherwise. The total number of juveniles of sex u produced by a male i and a female j respectively are then given by a set of random variables $J^u_{\mathrm{m}i}$ and $J^u_{\mathrm{f}j}$

$$\begin{array}{cc} & \text{Parent} \\ & \begin{array}{cc} \text{male } i & \text{female } j \end{array} \\ \text{Offspring} \begin{array}{c} \text{male} \\ \text{female} \end{array} & \begin{array}{cc} J^{\mathrm{m}}_{\mathrm{m}i} = \sum_j \mathbb{1}_{P_{ij}} \sum_n^{B_{ij}} \mathbb{1}_{R_n} \mathbb{1}_{S_n^{\mathrm{m}}} & J^{\mathrm{m}}_{\mathrm{f}j} = \sum_i \mathbb{1}_{P_{ij}} \sum_n^{B_{ij}} \mathbb{1}_{R_n} \mathbb{1}_{S_n^{\mathrm{m}}} \\ J^{\mathrm{f}}_{\mathrm{m}i} = \sum_j \mathbb{1}_{P_{ij}} \sum_n^{B_{ij}} (1-\mathbb{1}_{R_n}) \mathbb{1}_{S_n^{\mathrm{f}}} & J^{\mathrm{f}}_{\mathrm{f}j} = \sum_i \mathbb{1}_{P_{ij}} \sum_n^{B_{ij}} (1-\mathbb{1}_{R_n}) \mathbb{1}_{S_n^{\mathrm{f}}} \end{array} \end{array} \tag{3.3}$$

where the columns give the sex of the parent and the rows give the sex of the offspring.

3.2.3.2 Density-dependent regulation, culling

A new generation of reproductive individuals is established by sampling N_{m} males and N_{f} females from the pool of surviving offspring. We assume that the pools of male and female offspring are greater than N_{m} and N_{f}, which is reasonable for moderately large fertility and/or survival. Males

and females are sampled independently. Within a sex, sampling is random and unbiased with respect to phenotype. As a consequence, the expected numbers of sons and daughters that a parent will contribute to the next generation are proportional to the frequencies of the parent's offspring among the male and female sampling pools. So the expected number of breeders of sex u of individual i who is of sex v, w^u_{vi}, conditional on the realized offspring production of all parents in the population, $\mathbf{J}^u_v = (J^u_{v1}, J^u_{v2}, \ldots, J^u_{vN_v})^T$ and non-extinction ($\sum_k J^u_{vk} > 0$) is

$$w^u_{vi} \mid \mathbf{J}^u_v = N_u \frac{J^u_{vi}}{\sum_k J^u_{vk}}. \tag{3.4}$$

3.3 Individual fitness

3.3.1 Expansion of fitness in terms of reproductive variance and population size

We define the expected number of breeders produced by individual i as its fitness (Hamilton, 1964). Eq. (3.4) then gives the fitness of i through its offspring of sex u. To obtain unconditional fitness, expectation of eq. (3.4) is taken over the distribution of $\mathbf{J}^u_v$. We see from the equation that fitness depends on the measure of relative success $F(\mathbf{J}^u_v) = J^u_{vi}/\sum_k J^u_{vk}$, the expectation of which generally cannot be evaluated analytically. As in previous work (Gillespie, 1975; Proulx, 2000; Shpak and Proulx, 2007; Lehmann and Balloux, 2007), we approximate $\mathrm{E}[F(\mathbf{J}^u_v)]$ using the delta method (Oehlert, 1992). For this purpose, F is Taylor-expanded about the mean of $\mathbf{J}^u_v$, $\mathrm{E}[\mathbf{J}^u_v] = \boldsymbol{\mu}^u_v = (\mu_1, \mu_2, \ldots, \mu_N)$ up to second order: $F(\mathbf{J}^u_v) \approx F(\boldsymbol{\mu}^u_v) + (\mathbf{J}^u_v - \boldsymbol{\mu}^u_v)^T DF(\boldsymbol{\mu}^u_v) + (1/2)(\mathbf{J}^u_v - \boldsymbol{\mu}^u_v)^T D^2F(\boldsymbol{\mu}^u_v)(\mathbf{J}^u_v - \boldsymbol{\mu}^u_v) + \cdots$, where $DF(\boldsymbol{\mu}^u_v)$ is the gradient of F, evaluated at the mean offspring production $\boldsymbol{\mu}^u_v$ and $D^2F(\boldsymbol{\mu}^u_v)$ is the Hessian matrix of F, which estimates the curvature of the measure of relative success at $\boldsymbol{\mu}^u_v$. Then, applying the expectation operator over $\mathbf{J}^u_v$ to F, the first order terms $(\mathbf{J}^u_v - \boldsymbol{\mu}^u_v)^T DF(\boldsymbol{\mu}^u_v)$ disappear, as for each i, $E[J^u_{vi} - \mu^u_{vi}] = 0$. The second order terms $(\mathbf{J}^u_v - \boldsymbol{\mu}^u_v)^T D^2F(\boldsymbol{\mu}^u_v)(\mathbf{J}^u_v - \boldsymbol{\mu}^u_v)$ consists of the variance $E[(J^u_{vi} - \mu^u_{vi})^2]$ and covariance terms $E[(J^u_{vi} - \mu^u_{vi})(J^u_{vk} - \mu^u_{vk})]_{i \neq k}$. Substituting $F(\mathbf{J}^u_v) = J^u_{vi}/\sum_k J^u_{vk}$ into the Taylor expansion, the component of sex u of individual i's fitness becomes

$$w^u_{vi} = N_u \left(\frac{\mu^u_{vi}}{\mu^u_T} - \frac{\mu^u_T - \mu^u_{vi}}{{\mu^u_T}^3} \sigma^u_{vii} - \frac{\mu^u_T - 2\mu^u_{vi}}{{\mu^u_T}^3} \sum_{k \neq i} \sigma^u_{vik} + \frac{\mu^u_{vi}}{{\mu^u_T}^3} \sum_{k \neq i} \sum_{l \neq i} \sigma^u_{vkl} \right) + R, \tag{3.5}$$

where $\mu^u_T = \sum_k \mu^u_{vk}$ is the expected total number of juveniles produced in the population, σ^u_{vii} is the variance of the number of offspring of individual i ($\sigma^u_{vii} = \mathrm{V}[J^u_{vi}]$) and σ^u_{vik} is the covariance

between the number of offspring of individuals i and k ($\sigma^u_{vik} = \mathrm{C}[J^u_{vi}, J^u_{vk}]$). The remainder R is composed of central cross moments of $\mathbf{J}^u_v$ of order three and higher.

Eq. (3.5) shows that individual fitness can be summarized by four terms. Fitness increases with the relative expected number of offspring produced (μ^u_{vi}/μ^u_T), decreases with the variance of offspring it produces (σ^u_{vii}), decreases with the covariance between the number of its offspring and that of the remaining individuals in the population ($\sum_{k\neq i}\sigma^u_{vik}$), and increases with the variance in the number of offspring produced by the remaining individuals in the population ($\sum_{k\neq i}\sum_{l\neq i}\sigma^u_{vkl}$). The positive effect of increased expected number of offspring on fitness is obvious. The fitness effects of the variance terms stem from the non-linearity between fitness

$$w^u_{vi} \mid \mathbf{J}^u_v = N_u \frac{J^u_{vi}}{J^u_{vi} + \sum_{k\neq i} J^u_{vk}}. \tag{3.6}$$

and the offspring production of both the focal (J^u_{vi}, see fig. 3.2a), and that of the rest of the population ($\sum_{k\neq i} J^u_{vk}$, see fig. 3.2b). For a given offspring production by the rest of the population, the fitness benefit for the focal of producing more offspring due to variance is on average less than the cost of producing fewer, resulting in a net negative effect of variance in the reproductive output of the focal on its fitness (σ^u_{vii} in eq. 3.5 and see fig. 3.2a for graphical explanation). Conversely, for a given production by the focal individual, the advantage of competing within a less productive population due to variance is on average greater than the disadvantage of competing in a more productive one, leading to a net positive effect of population variance on the focal individual's fitness ($\sum_{k\neq i}\sum_{l\neq i}\sigma^u_{vkl}$ in eq. 3.5 and see fig. 3.2b for graphical explanation). Finally, using a similar graphical arguments as those presented in fig. 3.2, one can see that the benefit of over-performing in a less competitive population is on average greater than the cost of under-performing in a more competitive population. As a consequence, the covariance between the offspring productions of the focal individual and the rest of the population has a negative impact on focal fitness ($\sum_{k\neq i}\sigma^u_{vik}$ in eq. 3.5).

By assuming the distribution of $\mathbf{J}^u_v$ is well behaved as the population size N gets large, we can relate the effect of the different terms of eq. (3.5) on fitness to population size. It is also ensured that the remainder terms R have weak effects and can justifiably be discarded from the approximation of fitness. Previous models of variance-minimizing selection used the central limit theorem to justify that the remainder terms rapidly vanished with N, at a rate $1/N^2$ (as in eq. (A6) of Lehmann and Balloux, 2007). Since the offspring productions of different individuals are not independent

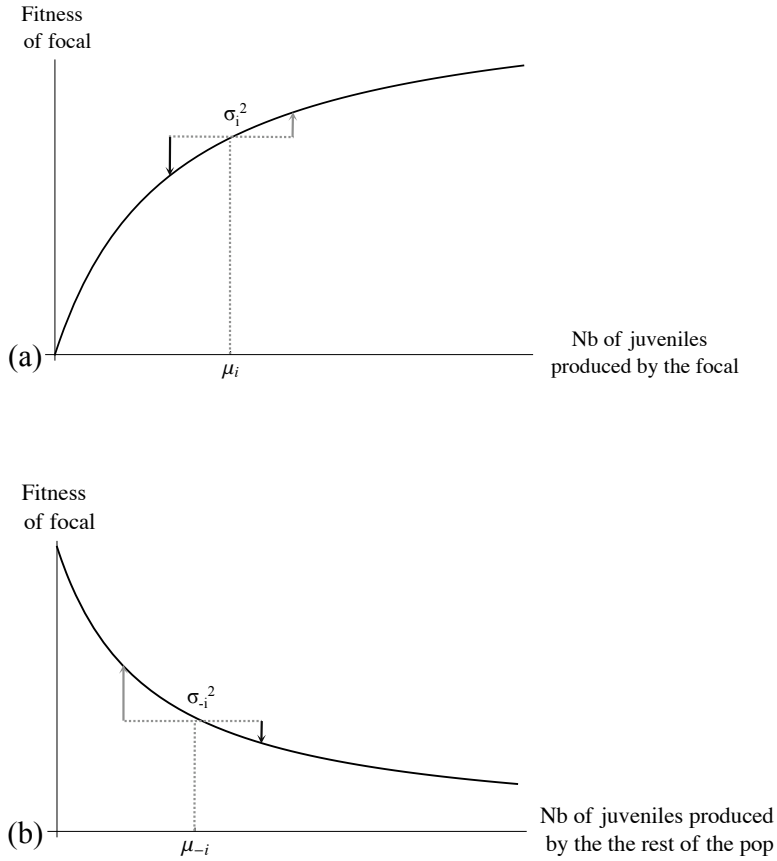

Figure 3.2: Effects of variance on focal fitness. - (a) Fitness of a focal individual graphed against the random number of offspring it produces and holding the rest of the population constant. Ignoring the sex of parent and offspring, the focal produces on average μ_i offspring with variance σ_i^2. It is then equally likely to produce more or less than μ_i offspring. But fitness is a relative measure of reproductive success (see eq. 3.4). Even if it is always better to produce more offspring, the advantage of producing more offspring depreciates with the number of offspring produced because sibs also compete against each other. Graphically, this means that the fitness function is concave with respect to the number of offspring produced by the focal. Then, as shown on the graph, the benefits reaped when it produces more offspring than his average (gray arrow) are outweighed by the cost when it producing less (black arrow). Overall, the variance in offspring number production is then detrimental to individual fitness. (b) Fitness of a focal individual graphed against the random number of offspring produced by the rest of the population and by holding the number of offspring of the focal constant. The rest of the population produces on average μ_{-i} offspring with variance σ_{-i}^2. The fitness function of a focal individual is convex with respect to the reproductive output of the rest of the population, which means that the benefits it reaps when they produce less (gray arrow) outweighs the cost paid when they produce more (black arrow). So overall, the variance in offspring production by the rest of the population is beneficial to the focal.

here, straightforward arguments based on the central limit theorem are not available to us. For the sake of simplicity, it is however assumed that offspring productions are close to independence, and that the "total" covariance between a given set of individuals decreases as the number of individuals in that set increases. Mathematical details are left in appendix 3.A (see eq. 3.A.1), but according to our assumption, the expected number of juveniles produced by an individual is of order N ($\mu^u_{vi} \sim O(N)$), in which case the total number of juveniles in the population is of order $\mu^u_T \sim O(N^2)$. The covariance between the number of juveniles of two individuals $\sigma^u_{vik} \sim O(N)$ term is weaker than the marginal variance $\sigma^u_{vii} \sim O(N^2)$. Summing appropriately over individuals in eq. (3.5), the leading order term $N_u \mu^u_{vi}/\mu^u_T$ is of order $O(1)$, and the remaining variance terms are of order $O(1/N)$. Hence, with condition (3.A.1), the effects of (co)variances on individual fitness vanish as $N \to \infty$ (as in Gillespie, 1975; Proulx, 2000; Shpak and Proulx, 2007; Lehmann and Balloux, 2007).

3.3.2 Expression of fitness in terms of life history traits and phenotype

Eq. (3.5) shows that fitness depends on the means and (co)variances of the distribution of the juvenile production vector $\mathbf{J}^u_v$; namely μ^u_{vi}, μ^u_T, and σ^u_{vik}. In the following, we show how μ^u_{vi}, μ^u_T, and σ^u_{vik} can be expressed in terms of the vital parameters of the model, defined here as the first and second moments of the distributions of the random variables that characterize the life cycle (i.e. all the random variables that appear in eq. 3.3). We will use the fitness $w^{\mathrm{m}}_{\mathrm{m}i}$ that male i gains through the production of male offspring as an example, but all the arguments presented below apply equally to the other components of fitness $w^{\mathrm{f}}_{\mathrm{m}i}$, $w^{\mathrm{m}}_{\mathrm{f}j}$, and $w^{\mathrm{m}}_{\mathrm{f}j}$.

3.3.2.1 Expected numbers of juveniles, $\mu^{\mathrm{m}}_{\mathrm{m}i}$ and μ^{m}_T

The number of male juveniles produced by the focal male i is given by the sum of his reproduction over all females. From eq. (3.3), this is

$$J^{\mathrm{m}}_{\mathrm{m}i} = \sum_j \mathbb{1}_{P_{ij}} Y_{ij} \text{ , where } Y_{ij} = \sum_n^{B_{ij}} \mathbb{1}_{R_n} \mathbb{1}_{S^{\mathrm{m}}_n} \tag{3.7}$$

is the number of male offspring he produces with female j, given that they have mated. We assume that the sex and the survival of an offspring are independent of the sex and survival of other offspring. Then, because $\mathbb{1}_{P_{ij}}$, B_{ij}, $\mathbb{1}_{R_n}$ and $\mathbb{1}_{S^{\mathrm{m}}_n}$ are uncorrelated with one another, taking

expectations of $J^{\mathrm{m}}_{\mathrm{m}i}$ yields

$$\mu^{\mathrm{m}}_{\mathrm{m}i} = \mathrm{E}[J^{\mathrm{m}}_{\mathrm{m}i}] = \sum_j \mathrm{E}[\mathbb{1}_{P_{ij}} Y_{ij}] = \sum_j \phi_{z_{\mathrm{m}i},z_{\mathrm{f}j}} \alpha_{z_{\mathrm{m}i},z_{\mathrm{f}j}} r_{z_{\mathrm{m}i},z_{\mathrm{f}j}} s^{\mathrm{m}}_{z_{\mathrm{m}i},z_{\mathrm{f}j}}. \tag{3.8}$$

The right-hand sum in this equation is over vital parameters, where $\phi_{z_{\mathrm{m}i},z_{\mathrm{f}j}} = \mathrm{E}[\mathbb{1}_{P_{ij}}]$ is the probability that a mating between male i and female j takes place, $r_{z_{\mathrm{m}i},z_{\mathrm{f}j}} = \mathrm{E}[\mathbb{1}_{R_n}]$ is the probability that the sex of an offspring of that mating is male, $s^{\mathrm{m}}_{z_{\mathrm{m}i},z_{\mathrm{f}j}} = \mathrm{E}[\mathbb{1}_{S^{\mathrm{m}}_n}]$ is the probability that this male offspring survives and $\alpha_{z_{\mathrm{m}i},z_{\mathrm{f}j}} = \mathrm{E}[B_{ij}]$ is the expected total number of offspring for a mating between male i and female j. All vital parameters are summarized in tables 3.1 and 3.2.

All vital parameters in eq. (3.8) depend on the phenotypes of the focal male and of the interacting female, as indicated by the subscripts $z_{\mathrm{m}i}, z_{\mathrm{f}j}$. However, because the difference between the phenotype of mutants and residents is small, we can re-write the vital parameters, and hence $\mu^{\mathrm{m}}_{\mathrm{m}i}$, to depend only on the phenotype of male i, $z_{\mathrm{m}i}$, and the population average female phenotypic value $\bar{z}_{\mathrm{f}} = \sum_j z_{\mathrm{f}j}/N_{\mathrm{f}}$. For a function g, writing $g(z_{\mathrm{f}j}) = g(\bar{z}_{\mathrm{f}} - (\bar{z}_{\mathrm{f}} - z_{\mathrm{f}j}))$ and Taylor-expanding g about $\bar{z}_{\mathrm{f}}$, we get

$$\sum_j g(z_{\mathrm{f}j}) = N_{\mathrm{f}} g(\bar{z}_{\mathrm{f}}) + g'(\bar{z}_{\mathrm{f}}) \sum_j (\bar{z}_{\mathrm{f}} - z_{\mathrm{f}j}) + O(\delta^2_{\mathrm{f}}) = N_{\mathrm{f}} g(\bar{z}_{\mathrm{f}}) + O(\delta^2_{\mathrm{f}}), \tag{3.9}$$

since $\sum_j (\bar{z}_{\mathrm{f}} - z_{\mathrm{f}j}) = 0$ and $(\bar{z}_{\mathrm{f}} - z_{\mathrm{f}j}) \sim O(\delta_{\mathrm{f}})$. It is assumed that phenotypic effects in males and females are of the same of order $\delta_{\mathrm{f}} \sim \delta_{\mathrm{m}} \sim O(\delta)$. So applying eq. (3.9) to eq. (3.8) we obtain that the expected number of male juveniles of a focal male i is

$$\mu^{\mathrm{m}}_{\mathrm{m}i} = N_{\mathrm{f}} \phi_{z_{\mathrm{m}i},\bar{z}_{\mathrm{f}}} \alpha_{z_{\mathrm{m}i},\bar{z}_{\mathrm{f}}} r_{z_{\mathrm{m}i},\bar{z}_{\mathrm{f}}} s^{\mathrm{m}}_{z_{\mathrm{m}i},\bar{z}_{\mathrm{f}}} + O(\delta^2), \tag{3.10}$$

which depends only on its phenotype $z_{\mathrm{m}i}$ and the average female phenotypic value $\bar{z}_{\mathrm{f}}$ in the population. Eq. (3.10) shows that the average reproductive output of a focal male i is approximately the product of the expected number of females he mates with ($N_{\mathrm{f}} \phi_{z_{\mathrm{m}i},\bar{z}_{\mathrm{f}}}$) and the expected number of surviving males that he produces in a mating with an average female in the population ($\alpha_{z_{\mathrm{m}i},\bar{z}_{\mathrm{f}}} r_{z_{\mathrm{m}i},\bar{z}_{\mathrm{f}}} s^{\mathrm{m}}_{z_{\mathrm{m}i},\bar{z}_{\mathrm{f}}}$).

The total expected number of male juveniles μ^{m}_T is approximated similarly by expanding about the average male phenotype $\bar{z}_{\mathrm{m}} = \sum_j z_{\mathrm{f}j}/N_{\mathrm{m}}$ as

$$\mu^{\mathrm{m}}_T = N_{\mathrm{f}} N_{\mathrm{m}} \phi_{\bar{z}_{\mathrm{m}},\bar{z}_{\mathrm{f}}} \alpha_{\bar{z}_{\mathrm{m}},\bar{z}_{\mathrm{f}}} r_{\bar{z}_{\mathrm{m}},\bar{z}_{\mathrm{f}}} s^{\mathrm{m}}_{\bar{z}_{\mathrm{m}},\bar{z}_{\mathrm{f}}} + O(\delta^2). \tag{3.11}$$

Stage	Symbol	Definition	Description
	$\phi_{z_{\mathrm{m}i},z_{\mathrm{f}j}}$	$\mathrm{E}[\mathbb{1}_{P_{ij}}]$	Probability that a male with phenotype $z_{\mathrm{m}i}$ and a female with phenotype $z_{\mathrm{f}j}$ mate.
(a) Mating	$\phi^{\mathrm{m}}_{z_{\mathrm{m}i},z_{\mathrm{f}j},z_{\mathrm{f}l}}$	$\mathrm{E}[\mathbb{1}_{P_{ij}}\mathbb{1}_{P_{il}}]$	Probability that a male with phenotype $z_{\mathrm{m}i}$ mates with females with phenotypes $z_{\mathrm{f}j}$ and $z_{\mathrm{f}l}$.
	$\phi^{\mathrm{f}}_{z_{\mathrm{m}i},z_{\mathrm{f}j},z_{\mathrm{m}k}}$	$\mathrm{E}[\mathbb{1}_{P_{ij}}\mathbb{1}_{P_{kj}}]$	Probability that a female with phenotype $z_{\mathrm{f}j}$ mates with males with phenotypes $z_{\mathrm{m}i}$ and $z_{\mathrm{m}k}$.
	$\alpha_{z_{\mathrm{m}i},z_{\mathrm{f}j}}$	$\mathrm{E}[B_{ij}]$	Expected number of offspring produced by the mating of a male with phenotype $z_{\mathrm{m}i}$ and of a male with phenotype $z_{\mathrm{f}j}$.
	$\beta_{z_{\mathrm{m}i},z_{\mathrm{f}j}}$	$\mathrm{V}[B_{ij}]$	Variance in the number of offspring produced by the mating of a male with phenotype $z_{\mathrm{m}i}$ and of a male with phenotype $z_{\mathrm{f}j}$.
(b) Fertility	$\gamma^{\mathrm{m}}_{z_{\mathrm{m}i},z_{\mathrm{f}j},z_{\mathrm{f}l}}$	$\mathrm{E}[B_{ij}B_{il}]$	Expected product of the fertilities of two matings of a male with phenotype $z_{\mathrm{m}i}$, one with a female with phenotype $z_{\mathrm{f}j}$ and the other $z_{\mathrm{f}l}$.
	$\gamma^{\mathrm{f}}_{z_{\mathrm{m}i},z_{\mathrm{f}j},z_{\mathrm{m}k}}$	$\mathrm{E}[B_{ij}B_{kj}]$	Expected product of the fertilities of two matings of a female with phenotype $z_{\mathrm{f}j}$, one with a male with phenotype $z_{\mathrm{f}j}$ and the other $z_{\mathrm{m}k}$.

Table 3.1: Parameters of reproductive strategies.

3.3.2.2 Variances and covariances between juvenile numbers

We can express $\sigma^{\mathrm{m}}_{\mathrm{m}ik}$, the covariance between the number of male juveniles produced by males i and k, or the variance for a single male i if $i=k$, as the sum of the covariances between the number of juveniles produced by these males in two mating events, summed over all possible mating pairs

$$\sigma^{\mathrm{m}}_{\mathrm{m}ik}=\mathrm{C}[J_{\mathrm{mm}i},J_{\mathrm{mm}k}]=\mathrm{C}[\sum_j \mathbb{1}_{P_{ij}}Y_{ij},\sum_l \mathbb{1}_{P_{kl}}Y_{kl}]=\sum_{j,l}\mathrm{C}[\mathbb{1}_{P_{ij}}Y_{ij},\mathbb{1}_{P_{kl}}Y_{kl}]. \tag{3.12}$$

When considering the covariance terms on the right-hand side of eq. (3.12), we can distinguish between four cases. First, if the males and females of both matings are the same, $i=k$ and $j=l$, then the covariance collapses to the variance in the number of male juveniles produced by male i and female j. We write this quantity as $\mathrm{C}[\mathbb{1}_{P_{ij}}Y_{ij},\mathbb{1}_{P_{ij}}Y_{ij}]=\Upsilon_{z_{\mathrm{m}i},z_{\mathrm{f}j}}$, with subscripts indicating the

fact that the value of the variance depends on the phenotypes of the male and the female involved. Second, in the case where the male is the same ($i = k$) but the two females are different ($j \neq l$), we write $\mathrm{C}[\mathbb{1}_{P_{ij}} Y_{ij}, \mathbb{1}_{P_{il}} Y_{il}] = \Upsilon^{\mathrm{m}}_{z_{\mathrm{m}i}, z_{\mathrm{f}j}, z_{\mathrm{f}l}}$ for the covariance between the number of male juveniles produced through two matings of the same male i. Third, in the case where the female is the same ($j = l$) but the two males are different ($i \neq k$), we write $\mathrm{C}[\mathbb{1}_{P_{ij}} Y_{ij}, \mathbb{1}_{P_{kj}} Y_{kj}] = \Upsilon^{\mathrm{f}}_{z_{\mathrm{m}i}, z_{\mathrm{f}j}, z_{\mathrm{m}k}}$ for the covariance between the number of male juveniles produced through two matings of the same female j. Fourth and finally, we have the case where neither a male nor a female is shared between two mating pairs ($i \neq k$ and $j \neq l$), in which case we assume that the covariance in the number of male juveniles produced by the two pairs to be zero (or, more precisely, of order $O(1/N^2)$ or less). In summary, we have

$$\mathrm{C}[\mathbb{1}_{P_{ij}} Y_{ij}, \mathbb{1}_{P_{kl}} Y_{kl}] = \begin{cases} \Upsilon_{z_{\mathrm{m}i}, z_{\mathrm{f}j}} & \text{if } i = k \text{ and } j = l \\ \Upsilon^{\mathrm{m}}_{z_{\mathrm{m}i}, z_{\mathrm{f}j}, z_{\mathrm{f}l}} & \text{if } i = k \text{ and } j \neq l \\ \Upsilon^{\mathrm{f}}_{z_{\mathrm{m}i}, z_{\mathrm{f}j}, z_{\mathrm{m}k}} & \text{if } i \neq k \text{ and } j = l \\ 0 & \text{if } i \neq k \text{ and } j \neq l. \end{cases} \tag{3.13}$$

Each covariance is expanded in detail and expressed in terms of vital parameters in appendix 3.B. Here, we only state how the covariances affect fitness as described by eq. (3.5).

The variance in the number of male juveniles produced by male i, $\sigma^{\mathrm{m}}_{\mathrm{m}ii}$, is composed of the variance in male production in matings with an individual female and the covariance between matings with different females. Using eqs. (3.12) and (3.13) and expanding each relevant sum around phenotypic averages using the argument of eq. (3.9), the total variance is

$$\sigma^{\mathrm{m}}_{\mathrm{m}ii} = N_{\mathrm{f}} \Upsilon_{z_{\mathrm{m}i}, \bar{z}_{\mathrm{f}}} + N_{\mathrm{f}}(N_{\mathrm{f}} - 1) \Upsilon^{\mathrm{m}}_{z_{\mathrm{m}i}, \bar{z}_{\mathrm{f}}, \bar{z}_{\mathrm{f}}} + O(\delta^2). \tag{3.14}$$

As shown in appendix 3.B, the variance in reproductive output of a mating pair is

$$\begin{aligned} \Upsilon_{z_{\mathrm{m}i}, z_{\mathrm{f}j}} = & \phi_{z_{\mathrm{m}i}, z_{\mathrm{f}j}} r_{z_{\mathrm{m}i}, z_{\mathrm{f}j}} s^{\mathrm{m}}_{z_{\mathrm{m}i}, z_{\mathrm{f}j}} \Big(\alpha_{z_{\mathrm{m}i}, z_{\mathrm{f}j}} (1 - r_{z_{\mathrm{m}i}, z_{\mathrm{f}j}} s^{\mathrm{m}}_{z_{\mathrm{m}i}, z_{\mathrm{f}j}}) \\ & + r_{z_{\mathrm{m}i}, z_{\mathrm{f}j}} s^{\mathrm{m}}_{z_{\mathrm{m}i}, z_{\mathrm{f}j}} \left(\beta_{z_{\mathrm{m}i}, z_{\mathrm{f}j}} + \alpha^2_{z_{\mathrm{m}i}, z_{\mathrm{f}j}} (1 - \phi_{z_{\mathrm{m}i}, z_{\mathrm{f}j}}) \right) \Big). \end{aligned} \tag{3.15}$$

This quantity, and hence also σ^u_{vii}, increases with the variance $\beta_{z_{\mathrm{m}i}, z_{\mathrm{f}j}} = \mathrm{V}[B_{ij}]$ in fertility of a

mating between a male i and a female j, given that the mating event has occurred. Further,

$$\Upsilon^{\mathrm{m}}_{z_{\mathrm{m}i},z_{\mathrm{f}j},z_{\mathrm{f}l}} = r_{z_{\mathrm{m}i},z_{\mathrm{f}j}} s^{\mathrm{m}}_{z_{\mathrm{m}i},z_{\mathrm{f}j}} r_{z_{\mathrm{m}i},z_{\mathrm{f}l}} s^{\mathrm{m}}_{z_{\mathrm{m}i},z_{\mathrm{f}l}} (\phi^{\mathrm{m}}_{z_{\mathrm{m}i},z_{\mathrm{f}j},z_{\mathrm{f}l}} \gamma^{\mathrm{m}}_{z_{\mathrm{m}i},z_{\mathrm{f}j},z_{\mathrm{f}l}} - \phi_{z_{\mathrm{m}i},z_{\mathrm{f}j}} \alpha_{z_{\mathrm{m}i},z_{\mathrm{f}l}} \phi_{z_{\mathrm{m}i},z_{\mathrm{f}l}} \alpha_{z_{\mathrm{m}i},z_{\mathrm{f}j}}), \tag{3.16}$$

where $\phi^{\mathrm{m}}_{z_{\mathrm{m}i},z_{\mathrm{f}j},z_{\mathrm{f}l}} = E[\mathbb{1}_{P_{ij}} \mathbb{1}_{P_{il}}]$ is the probability that male i mates with females j and l, and $\gamma^{\mathrm{m}}_{z_{\mathrm{m}i},z_{\mathrm{f}j},z_{\mathrm{f}l}} = \mathrm{E}[B_{ij}B_{il}]$ is the expected product of the fertilities of these matings. Both $\phi^{\mathrm{m}}_{z_{\mathrm{m}i},z_{\mathrm{f}j},z_{\mathrm{f}l}}$ and $\gamma^{\mathrm{m}}_{z_{\mathrm{m}i},z_{\mathrm{f}j},z_{\mathrm{f}l}}$ increase the covariance between the matings of a male with different females, and thus $\sigma^{\mathrm{m}}_{\mathrm{m}ii}$. They can be thought of measures of covariance in the reproductive traits. In particular, the bracketed difference of eq. (3.16) measures the difference between the expected product of offspring a male produces through two matings ($\phi^{\mathrm{m}}_{z_{\mathrm{m}i},z_{\mathrm{f}j},z_{\mathrm{f}l}} \gamma^{\mathrm{m}}_{z_{\mathrm{m}i},z_{\mathrm{f}j},z_{\mathrm{f}l}}$), and the product of the marginal expectations of male i's offspring production in the two matings ($\phi_{z_{\mathrm{m}i},z_{\mathrm{f}j}} \alpha_{z_{\mathrm{m}i},z_{\mathrm{f}l}} \phi_{z_{\mathrm{m}i},z_{\mathrm{f}l}} \alpha_{z_{\mathrm{m}i},z_{\mathrm{f}j}}$). If the occurrence and outcome of each mating are independent, the difference, and the covariance between two matings of a male, is zero. But deviations from independence in either mating or fertility generate a non-zero difference, and so a non-zero covariance $\Upsilon^{\mathrm{m}}_{z_{\mathrm{m}i},z_{\mathrm{f}j},z_{\mathrm{f}l}}$.

Stage	Symbol	Definition	Description
(c) Sex-determination	$r_{z_{\mathrm{m}i},z_{\mathrm{f}j}}$	$\mathrm{E}[\mathbb{1}_{R_n}]$	Probability that an offspring (indexed n) of a male with phenotype $z_{\mathrm{m}i}$ and a female with phenotype $z_{\mathrm{f}j}$ is male.
(d) Survival	$s^{\mathrm{m}}_{z_{\mathrm{m}i},z_{\mathrm{f}j}}$	$\mathrm{E}[\mathbb{1}_{S^{\mathrm{m}}_n}]$	Probability that a male offspring (indexed n) of a male with phenotype $z_{\mathrm{m}i}$ and a female with phenotype $z_{\mathrm{f}j}$ survives.
	$s^{\mathrm{f}}_{z_{\mathrm{m}i},z_{\mathrm{f}j}}$	$\mathrm{E}[\mathbb{1}_{S^{\mathrm{f}}_n}]$	Probability that a female offspring (indexed n) of a male with phenotype $z_{\mathrm{m}i}$ and a female with phenotype $z_{\mathrm{f}j}$ survives.

Table 3.2: Parameters of parenting strategies.

To express the covariance between the number of offspring of a male i and that of the remaining males in the population, $\sigma^{\mathrm{m}}_{\mathrm{m}ik}$ (with $k \neq i$), we first define $\bar{z}_{-\mathrm{m}i} = 1/(N_{\mathrm{m}}-1)\sum_{k\neq i} z_{\mathrm{m}k} = (N_{\mathrm{m}}\bar{z}_{\mathrm{m}} - z_{\mathrm{m}i})/(N_{\mathrm{m}}-1)$, as the average male phenotype when male i is excluded from the population. Then, using eqs. (3.12) and (3.13), and an argument similar to that used in eq. (3.9), we can approximate

the covariance term by

$$\sum_{k\neq i}\sigma^{\mathrm{m}}_{\mathrm{m}ik} = (N_{\mathrm{m}}-1)N_{\mathrm{f}}\Upsilon^{\mathrm{f}}_{z_{\mathrm{m}i},\bar{z}_{\mathrm{f}},\bar{z}_{-\mathrm{m}i}} + O(\delta^2). \tag{3.17}$$

As shown in appendix 3.B, the covariance between the number of offspring produced through two matings of the same female is given by

$$\Upsilon^{\mathrm{f}}_{z_{\mathrm{m}i},z_{\mathrm{f}j},z_{\mathrm{m}k}} = r_{z_{\mathrm{m}i},z_{\mathrm{f}j}}s^{\mathrm{m}}_{z_{\mathrm{m}i},z_{\mathrm{f}j}}r_{z_{\mathrm{m}k},z_{\mathrm{f}j}}s^{\mathrm{m}}_{z_{\mathrm{m}k},z_{\mathrm{f}j}}(\phi^{\mathrm{f}}_{z_{\mathrm{m}i},z_{\mathrm{f}j},z_{\mathrm{m}k}}\gamma^{\mathrm{f}}_{z_{\mathrm{m}i},z_{\mathrm{f}j},z_{\mathrm{m}k}} - \phi_{z_{\mathrm{m}i},z_{\mathrm{f}j}}\alpha_{z_{\mathrm{m}k},z_{\mathrm{f}j}}\phi_{z_{\mathrm{m}k},z_{\mathrm{f}j}}\alpha_{z_{\mathrm{m}i},z_{\mathrm{f}j}}). \tag{3.18}$$

Here, the measures of covariance in the reproductive traits are $\phi^{\mathrm{f}}_{z_{\mathrm{m}i},z_{\mathrm{f}j},z_{\mathrm{m}k}} = E[\mathbb{1}_{P_{ij}}\mathbb{1}_{P_{kj}}]$, which is the probability that female j mates with males i and k, and $\gamma^{\mathrm{f}}_{z_{\mathrm{m}i},z_{\mathrm{f}j},z_{\mathrm{m}k}} = \mathrm{E}[B_{ij}B_{kj}]$, which is the expected product of the fertilities of these two matings (given they have occurred). Both increase the covariance $\Upsilon^{\mathrm{f}}_{z_{\mathrm{m}i},z_{\mathrm{f}j},z_{\mathrm{m}k}}$.

The final variance term of the fitness eq. (3.5), is given by previous definitions as

$$\sum_{k\neq i}\sum_{l\neq i}\sigma^{\mathrm{m}}_{\mathrm{m}kl} = (N_{\mathrm{m}}-1)N_{\mathrm{f}}\left(\Upsilon_{\bar{z}_{-\mathrm{m}i},\bar{z}_{\mathrm{f}}} + (N_{\mathrm{f}}-1)\Upsilon^{\mathrm{m}}_{\bar{z}_{-\mathrm{m}i},\bar{z}_{\mathrm{f}},\bar{z}_{\mathrm{f}}} + (N_{\mathrm{m}}-2)\Upsilon^{\mathrm{f}}_{\bar{z}_{-\mathrm{m}i},\bar{z}_{\mathrm{f}},\bar{z}_{-\mathrm{m}i}}\right) + O(\delta^2). \tag{3.19}$$

3.3.2.3 Specifying the fitness function

We now have all the elements necessary to describe the fitness of male i through the production of male offspring in terms of vital parameters ($w^{\mathrm{m}}_{\mathrm{m}i}$, eq. 3.5). To obtain an explicit expression for $w^{\mathrm{m}}_{\mathrm{m}i}$, we first substitute eqs. (3.15), (3.18) and (3.16) into eqs. (3.17), (3.14) and (3.19). Then, substituting eqs. (3.10), (3.11), (3.17), (3.14) and (3.19) into eq. (3.5) gives $w^{\mathrm{m}}_{\mathrm{m}i}$ in terms of vital parameters. The female component $w^{\mathrm{f}}_{\mathrm{m}i}$ of the fitness of male i is obtained from $w^{\mathrm{m}}_{\mathrm{m}i}$ by replacing the sex determination rate function r by $1-r$, to account for the production of daughters rather than sons, and by substituting the sex-specific survival rate s^{f} of females for that of males, s^{m}. The fitness components $w^{\mathrm{m}}_{\mathrm{f}j}$ and $w^{\mathrm{f}}_{\mathrm{f}j}$ of a female j are found using a similar methods and no other definition is required. They are given in appendix 3.C.

We would like to stress that the expression of male and female fitness w_{ui} and w_{uj} are entirely characterized by the phenotype of the focal individual (male i or female j) and the average male and female phenotypes in the population, $\bar{z}_{\mathrm{m}}$ and $\bar{z}_{\mathrm{f}}$ (as $\bar{z}_{-\mathrm{m}i} = (N_{\mathrm{m}}\bar{z}_{\mathrm{m}} - z_{\mathrm{m}i})/(N_{\mathrm{m}}-1)$). It is then only necessary to consider the interaction between the focal with an “average" male and an “average" female, rather than each specific individual present in the population. As we will see in the next section, this greatly simplifies the calculations for the evolution of genotypes that code for phenotypes.

It is also worth noting that to satisfy the order condition (3.A.1), the vital parameters are related to the size of the population. First, the probability of two individuals mating ($\phi_{z_{\mathrm{m}i},z_{\mathrm{f}j}}$) is of order $1/N$, which ensures that the expected total number of mates of an individual remains bounded and non-zero as population size gets large. Similarly, for the variance in total mating partners to remain bounded, the probabilities of double matings ϕ^{f} and ϕ^{m} are of order $1/N^2$. Then, for condition (3.A.1) to be satisfied, the expected fertility of a mating α, is of order N and the variance in fertility of a mating β, as well as expected product of the fertilities of two matings γ^{m} and γ^{f}, are all of order N^2.

3.4 Allele frequency change

3.4.1 Conditional allele frequency change

The change of mutant frequency in males and females over one generation is derived in this section using a weak selection perturbation approach for finite populations (Rousset, 2003; Rousset and Ronce, 2004; Lessard and Ladret, 2007; Lehmann and Rousset, 2009). For this purpose, we introduce some additional notation. We denote by $\mathbb{P}_t$ the distribution of paternally and maternally inherited mutants $\mathbb{1}_{\male i}$ and $\mathbb{1}_{\female i}$ across all males and females in the population at generation t, and by $\mathscr{P}_t$ a realization of this distribution. Also, we write $\overline{p}_{\mathrm{m},t}=\sum_{i=1}^{N_{\mathrm{m}}} p_{\mathrm{m}i,t}/N_{\mathrm{m}}$ and $\overline{p}_{\mathrm{f},t}=\sum_{j=1}^{N_{\mathrm{f}}} p_{\mathrm{f}j,t}/N_{\mathrm{f}}$ for the realized average mutant frequencies in males and females under the realization $\mathscr{P}_t$. Conditional on this realization and following Price (1970), the expected average male and female mutant frequencies in the next generation is

$$\begin{aligned}\mathrm{E}[\overline{p}_{\mathrm{m},t+1}|\mathscr{P}_t]&=\frac{1}{2N_{\mathrm{m}}}\left(\sum_{i=1}^{N_{\mathrm{m}}} p_{\mathrm{m}i,t}w^{\mathrm{m}}_{\mathrm{m}i}+\sum_{j=1}^{N_{\mathrm{f}}} p_{\mathrm{f}j,t}w^{\mathrm{m}}_{\mathrm{f}j}\right)\\ \mathrm{E}[\overline{p}_{\mathrm{f},t+1}|\mathscr{P}_t]&=\frac{1}{2N_{\mathrm{f}}}\left(\sum_{i=1}^{N_{\mathrm{m}}} p_{\mathrm{m}i,t}w^{\mathrm{f}}_{\mathrm{m}j}+\sum_{j=1}^{N_{\mathrm{f}}} p_{\mathrm{f}j,t}w^{\mathrm{f}}_{\mathrm{f}j}\right).\end{aligned} \tag{3.20}$$

Since selection is weak, it is sufficient to approximate allele frequency change to the first order of phenotypic effect in males and females δ_{m} and δ_{f}. Fitness is approximated as $w^u_{vi}=w^u_{vi}+\delta_{\mathrm{m}}(\partial w^u_{vi}/\partial\delta_{\mathrm{m}})+\delta_{\mathrm{f}}(\partial w^u_{vi}/\partial\delta_{\mathrm{f}})+O(\delta^2)$ evaluated at $\delta_{\mathrm{m}}=\delta_{\mathrm{f}}=0$. We make two observations before substituting for w^u_{vi} into eq. (3.20). First, in the absence of phenotypic differences ($\delta_{\mathrm{m}}=\delta_{\mathrm{f}}=0$) each individual is expected to contribute equally to the next generation and we have $w^u_{vi}|_{\delta_{\mathrm{m}}=\delta_{\mathrm{f}}=0}=N_u/N_v$. Secondly, the partial derivatives of an individual's fitness with respect to

phenotypic effect in the other sex is zero so that only the partial derivatives of the form $\partial w_{vi}^{u}/\partial\delta_v$ are non zero. Substituting for w_{vi}^{u} in eq. (3.20) then gives

$$\begin{aligned}
\mathrm{E}[\overline{p}_{\mathrm{m},t+1}|\mathscr{P}_t] &= \frac{1}{2}(\overline{p}_{\mathrm{m},t}+\overline{p}_{\mathrm{f},t})+\frac{1}{2N_{\mathrm{m}}}\left(\delta_{\mathrm{m}}\sum_{i=1}^{N_{\mathrm{m}}}p_{\mathrm{m}i,t}\frac{\partial w_{\mathrm{m}i}^{\mathrm{m}}}{\partial\delta_{\mathrm{m}}}+\delta_{\mathrm{f}}\sum_{j=1}^{N_{\mathrm{f}}}p_{\mathrm{f}j,t}\frac{\partial w_{\mathrm{f}j}^{\mathrm{m}}}{\partial\delta_{\mathrm{f}}}\right)_{\delta_{\mathrm{m}}=\delta_{\mathrm{f}}=0}+O(\delta^2)\\
\mathrm{E}[\overline{p}_{\mathrm{f},t+1}|\mathscr{P}_t] &= \frac{1}{2}(\overline{p}_{\mathrm{m},t}+\overline{p}_{\mathrm{f},t})+\frac{1}{2N_{\mathrm{f}}}\left(\delta_{\mathrm{m}}\sum_{i=1}^{N_{\mathrm{m}}}p_{\mathrm{m}i,t}\frac{\partial w_{\mathrm{m}i}^{\mathrm{f}}}{\partial\delta_{\mathrm{m}}}+\delta_{\mathrm{f}}\sum_{j=1}^{N_{\mathrm{f}}}p_{\mathrm{f}j,t}\frac{\partial w_{\mathrm{f}j}^{\mathrm{f}}}{\partial\delta_{\mathrm{f}}}\right)_{\delta_{\mathrm{m}}=\delta_{\mathrm{f}}=0}+O(\delta^2).
\end{aligned} \tag{3.21}$$

3.4.2 Unconditional allele frequency change

Eq. (3.21) is conditional on a particular realization of gene frequencies $\mathscr{P}_t$. We can obtain the unconditional expectations of mutant frequencies in males and females at generation $t+1$ as $p_{\mathrm{m},t+1}=\mathrm{E}[\mathrm{E}[\overline{p}_{\mathrm{m},t+1}|\mathscr{P}_t]]=\sum\mathrm{E}[\overline{p}_{\mathrm{m},t+1}|\mathscr{P}_t]\Pr(\mathbb{P}_t=\mathscr{P}_t)$ and $p_{\mathrm{f},t+1}=\mathrm{E}[\mathrm{E}[\overline{p}_{\mathrm{f},t+1}|\mathscr{P}_t]]=\sum\mathrm{E}[\overline{p}_{\mathrm{f},t+1}|\mathscr{P}_t]\Pr(\mathbb{P}_t=\mathscr{P}_t)$. Since only the first-order effects of selection are considered, it is sufficient to marginalize $\mathrm{E}[\overline{p}_{\mathrm{m},t+1}|\mathscr{P}_t]$ and $\mathrm{E}[\overline{p}_{\mathrm{f},t+1}|\mathscr{P}_t]$ over the distribution of $\mathbb{P}_t$ in the absence of phenotypic differences ($\delta_{\mathrm{m}}=\delta_{\mathrm{f}}=0$). We denote this by using the expectation operator $\overset{\circ}{\mathrm{E}}$. The unconditional expected mutant frequencies in males and females of the next generation are then approximately $p_{\mathrm{m},t+1}=\overset{\circ}{\mathrm{E}}[\mathrm{E}[\overline{p}_{\mathrm{m},t+1}|\mathscr{P}_t]]+O(\delta^2)$ and $p_{\mathrm{f},t+1}=\overset{\circ}{\mathrm{E}}[\mathrm{E}[\overline{p}_{\mathrm{f},t+1}|\mathscr{P}_t]]+O(\delta^2)$, respectively. Marginalization, even in the absence of phenotypic differences, is relatively cumbersome algebraically but calculations can be found in 3.D. In short, we find that the unconditional expected allele frequencies in the next generation are given by

$$\begin{aligned}
p_{\mathrm{m},t+1} &= \frac{1}{2}(p_{\mathrm{m},t}+p_{\mathrm{f},t})+\frac{1}{2}\left(\delta_{\mathrm{m}}K_{\mathrm{m},t}\frac{dw_{\mathrm{m}i}^{\mathrm{m}}}{dz_{\mathrm{m}i}}+\delta_{\mathrm{f}}\frac{N_{\mathrm{f}}}{N_{\mathrm{m}}}K_{\mathrm{f},t}\frac{dw_{\mathrm{f}j}^{\mathrm{m}}}{dz_{\mathrm{f}j}}\right)_{\delta_{\mathrm{m}}=\delta_{\mathrm{f}}=0}+O(\delta^2)\\
p_{\mathrm{f},t+1} &= \frac{1}{2}(p_{\mathrm{m},t}+p_{\mathrm{f},t})+\frac{1}{2}\left(\delta_{\mathrm{m}}\frac{N_{\mathrm{m}}}{N_{\mathrm{f}}}K_{\mathrm{m},t}\frac{dw_{\mathrm{m}i}^{\mathrm{f}}}{dz_{\mathrm{m}i}}+\delta_{\mathrm{f}}K_{\mathrm{f},t}\frac{dw_{\mathrm{f}j}^{\mathrm{f}}}{dz_{\mathrm{f}j}}\right)_{\delta_{\mathrm{m}}=\delta_{\mathrm{f}}=0}+O(\delta^2),
\end{aligned} \tag{3.22}$$

where $dw_{\mathrm{m}i}^{\mathrm{m}}/dz_{\mathrm{m}i}=(\partial/\partial z_{\mathrm{m}i}+(1/N_{\mathrm{m}})\partial/\partial\overline{z}_{\mathrm{m}})w_{\mathrm{m}i}^{\mathrm{m}}$ is the total derivative of the fitness a male obtains through its sons with respect to the focal male phenotype (since $d/dz_{\mathrm{m}i}=\partial/\partial z_{\mathrm{m}i}+(d\overline{z}_{\mathrm{m}}/dz_{\mathrm{m}i})\partial/\partial\overline{z}_{\mathrm{m}}=\partial/\partial z_{\mathrm{m}i}+(1/N_{\mathrm{m}})\partial/\partial\overline{z}_{\mathrm{m}}$). Similarly, $dw_{\mathrm{f}j}^{\mathrm{m}}/dz_{\mathrm{f}j}=(\partial/\partial z_{\mathrm{f}j}+(1/N_{\mathrm{f}})\partial/\partial\overline{z}_{\mathrm{f}})w_{\mathrm{f}j}^{\mathrm{m}}$ is the total derivative of the fitness of a focal female receives trough its sons with respect to her phenotype. The remaining derivatives with superscript $.^{\mathrm{f}}$ represent the fitness received through daughters.

The derivatives of fitness with respect to the different phenotypes in eq. (3.22) are weighted

by the coefficients

$$K_{\mathrm{m},t} = h\left(p_{\mathrm{m},t} - \frac{\kappa_t^{\male} + \kappa_t^{\female}}{2}\right) + (1-2h)\left(\eta_t - \frac{\rho_t^{\male} + \rho_t^{\female}}{2}\right)$$
$$K_{\mathrm{f},t} = h\left(p_{\mathrm{f},t} - \frac{\kappa_t^{\male} + \kappa_t^{\female}}{2}\right) + (1-2h)\left(\eta_t - \frac{\rho_t^{\male} + \rho_t^{\female}}{2}\right). \tag{3.23}$$

These coefficients are non-negative provided $0 \leq h \leq 1$ and scale the effects of selection on gene frequency according to the dominance of the mutant h and the frequency distribution in the population at generation t. The latter is captured by the average gene frequencies $p_{\mathrm{m},t}$ and $p_{\mathrm{f},t}$ at generation t, as well as the following additional moments:

- $\eta_t = \overset{\circ}{\mathrm{E}}[\mathbb{1}_{\male}\mathbb{1}_{\female}]$: probability that an individual's paternal and maternal alleles are both mutant
- $\kappa_t^{\male} = \overset{\circ}{\mathrm{E}}[\mathbb{1}_{\male}\mathbb{1}_{\male}]$: probability that two randomly sampled paternal alleles are mutant
- $\kappa_t^{\female} = \overset{\circ}{\mathrm{E}}[\mathbb{1}_{\female}\mathbb{1}_{\female}]$: probability that two randomly sampled maternal alleles are mutant
- $\rho_t^{\male} = \overset{\circ}{\mathrm{E}}[\mathbb{1}_{\male}\mathbb{1}_{\male}\mathbb{1}_{\female}]$: probability that one random maternal and two random paternal alleles are mutant
- $\rho_t^{\female} = \overset{\circ}{\mathrm{E}}[\mathbb{1}_{\female}\mathbb{1}_{\male}\mathbb{1}_{\female}]$: probability that one random paternal and two random maternal alleles are mutant

For all these probabilities, alleles are sampled without replacement from the adults of generation t.

The moments η_t, $\kappa_t^{\male}$, $\kappa_t^{\female}$, $\rho_t^{\male}$, and $\rho_t^{\female}$ also change from one generation to the next under the effect of genetic drift (we evaluate them in the absence of phenotypic differences and can therefore ignore changes due to selection) and we need to specify these changes in order to predict the expected change of $p_{\mathrm{m},t}$ and $p_{\mathrm{f},t}$ over many generations. The calculations specifying the change in moments of gene frequency are presented in 3.E and 3.F. These include recursions for η_t, $\kappa_t^{\male}$, $\kappa_t^{\female}$, $\rho_t^{\male}$, and $\rho_t^{\female}$, as well as higher moments of the distribution of the mutant in the population $\mathbb{P}_t$, denoted as ς, which are required to predict the change of the lower moments listed above.

Since all recursions are linear (see 3.E and 3.F for details), we can express the expected change in average male and female frequencies p_{m} and p_{f}, and all relevant moments of the frequency distribution, as a matrix operation. To do so, all the necessary moments of $\mathbb{P}_t$ are collected in the vector $\mathbf{p}_t$=(p_{m}, p_{f}, η, $\kappa^{\male}$, $\kappa^{\female}$, $\rho^{\male}$, $\rho^{\female}$, ς). We then write

$$\mathbf{p}_{t+1} = \mathbf{A}\mathbf{p}_t \quad \text{with} \quad \mathbf{A} = \mathbf{A}^{\circ} + \delta_{\mathrm{m}}\dot{\mathbf{A}}_{\mathrm{m}} + \delta_{\mathrm{f}}\dot{\mathbf{A}}_{\mathrm{f}} + O(\delta^2), \tag{3.24}$$

where the matrix $\mathbf{A}^{\circ}$ describes the neutral change in moments (see 3.G), while the matrices $\dot{\mathbf{A}}_{\mathrm{m}}$ and $\dot{\mathbf{A}}_{\mathrm{f}}$ describes the first order perturbation of average frequency change due to mutant effect in males and females respectively (see 3.H).

3.5 Evolutionary asymptotics

3.5.1 Probability of fixation

In the preceding section, we characterized the short-term evolution of the mutant, measuring its expected change over one generation. Its long-term fate is evaluated by deriving its fixation probability. The fixation probability in males and females is the asymptotic average frequency of the mutant in each class: $\pi_{\mathrm{m}} = \lim_{t\to\infty} p_{\mathrm{m},t}$ and $\pi_{\mathrm{f}} = \lim_{t\to\infty} p_{\mathrm{f},t}$. Because the mutant allele is either eliminated or goes to fixation in the population, the fixation probability in males and females is the same $\pi_{\mathrm{m}} = \pi_{\mathrm{f}} = \pi$. Using the vector iteration (eq. 3.24), it is then convenient to compute the fixation probability of the mutant as the average $\pi = \pi_{\mathrm{m}}/2 + \pi_{\mathrm{f}}/2$ (see 3.I), which can be expressed in terms of arbitrary initial frequencies in males and females as

$$\pi = \frac{1}{2}(p_{\mathrm{m},0} + p_{\mathrm{f},0}) + \delta_{\mathrm{m}}\tilde{\pi}'_{\mathrm{m}} + \delta_{\mathrm{f}}\tilde{\pi}'_{\mathrm{f}} + O(\delta^2), \tag{3.25}$$

where $\tilde{\pi}'_{\mathrm{m}} = \partial\pi/\partial\delta_{\mathrm{m}}$ and $\tilde{\pi}'_{\mathrm{f}} = \partial\pi/\partial\delta_{\mathrm{f}}$ are the perturbations of the fixation probability due to selection in males and females respectively, evaluated at $\delta_{\mathrm{m}} = \delta_{\mathrm{f}} = 0$.

Furthermore, if the mutation rate is the same in male and female genes, the initial mutant frequency is on average the same $p_0 = p_{\mathrm{m},0} = p_{\mathrm{f},0}$. In this case, we show in 3.I.3 that the effect of selection on the fixation probability can be expressed as the product

$$\delta_{\mathrm{m}}\tilde{\pi}'_{\mathrm{m}} + \delta_{\mathrm{f}}\tilde{\pi}'_{\mathrm{f}} = K(z_{\mathrm{m}}, z_{\mathrm{f}})\Big(\delta_{\mathrm{m}}G_{\mathrm{m}}(z_{\mathrm{m}}, z_{\mathrm{f}}) + \delta_{\mathrm{f}}G_{\mathrm{f}}(z_{\mathrm{m}}, z_{\mathrm{f}})\Big), \tag{3.26}$$

where

$$\begin{aligned} G_{\mathrm{m}}(z_{\mathrm{m}}, z_{\mathrm{f}}) &= \frac{1}{4}\left[\frac{\partial w^{\mathrm{m}}_{\mathrm{m}i}}{\partial z_{\mathrm{m}i}} + \frac{1}{N_{\mathrm{m}}}\frac{\partial w^{\mathrm{m}}_{\mathrm{m}i}}{\partial \bar{z}_{\mathrm{m}}} + \frac{N_{\mathrm{m}}}{N_{\mathrm{f}}}\left(\frac{\partial w^{\mathrm{f}}_{\mathrm{m}i}}{\partial z_{\mathrm{m}i}} + \frac{1}{N_{\mathrm{m}}}\frac{\partial w^{\mathrm{f}}_{\mathrm{m}i}}{\partial \bar{z}_{\mathrm{m}}}\right)\right]\Bigg|_{z_{\mathrm{m}i}=\bar{z}_{\mathrm{m}}=z_{\mathrm{m}}} \\ G_{\mathrm{f}}(z_{\mathrm{m}}, z_{\mathrm{f}}) &= \frac{1}{4}\left[\frac{\partial w^{\mathrm{f}}_{\mathrm{f}j}}{\partial z_{\mathrm{f}j}} + \frac{1}{N_{\mathrm{f}}}\frac{\partial w^{\mathrm{f}}_{\mathrm{f}j}}{\partial \bar{z}_{\mathrm{f}}} + \frac{N_{\mathrm{f}}}{N_{\mathrm{m}}}\left(\frac{\partial w^{\mathrm{m}}_{\mathrm{f}j}}{\partial z_{\mathrm{f}j}} + \frac{1}{N_{\mathrm{f}}}\frac{\partial w^{\mathrm{m}}_{\mathrm{f}j}}{\partial \bar{z}_{\mathrm{f}}}\right)\right]\Bigg|_{z_{\mathrm{f}j}=\bar{z}_{\mathrm{f}}=z_{\mathrm{f}}} \end{aligned} \tag{3.27}$$

can be thought of as a the gradients of selection on male and female phenotypes, respectively,

and where all male phenotypes are evaluated at the resident phenotypic values (z_{m} for male and z_{f} for females, which is equivalent to the condition $\delta_{\mathrm{m}} = \delta_{\mathrm{f}} = 0$). The factor $K > 0$ in eq. (3.31) is a measure of how well the population adapts in response to selection. Its value depends on dominance (h), the initial frequencies of the mutant, and population size. In the hypothetical case of $K = 0$, selection cannot act on the population at all but as K increases, the fixation probability of the mutant is increasingly reflects the selection pressure given by G. Although the general solution for K with arbitrary dominance is complicated (eq. 3.I.12, 3.I.3), it can be expressed in terms of coalescent times (eq. 3.I.13). If the mutant is additive ($h = 1/2$), K simplifies to

$$K(z_{\mathrm{m}}, z_{\mathrm{f}}) = \frac{4p_0}{\Theta^{\male} + \Theta^{\female}}, \tag{3.28}$$

where $\Theta^{\male}$ and $\Theta^{\female}$ depend on resident phenotypes $(z_{\mathrm{m}}, z_{\mathrm{f}})$, and are what we refer to as "probabilities of sibship", in this case the probabilities that two randomly sampled adults have the same father and mother, respectively. We describe these probabilities in greater detail the next paragraph.

Symbol	Definition	Description
C_v^2	$\beta_{z_{\mathrm{m}},z_{\mathrm{f}}}/\alpha^2_{z_{\mathrm{m}},z_{\mathrm{f}}}$	is the coefficient of variation of a couples' fertility given mating.
C_{m}	$\phi^{\mathrm{m}}_{z_{\mathrm{m}},z_{\mathrm{f}},z_{\mathrm{m}}}\gamma^{\mathrm{m}}_{z_{\mathrm{m}},z_{\mathrm{f}},z_{\mathrm{m}}}/(\phi_{z_{\mathrm{m}},z_{\mathrm{f}}}\alpha_{z_{\mathrm{m}},z_{\mathrm{f}}})^2$	measures the relative covariance between the offspring production a male has with two random females.
C_{f}	$\phi^{\mathrm{f}}_{z_{\mathrm{m}},z_{\mathrm{f}},z_{\mathrm{f}}}\gamma^{\mathrm{f}}_{z_{\mathrm{m}},z_{\mathrm{f}},z_{\mathrm{f}}}/(\phi_{z_{\mathrm{m}},z_{\mathrm{f}}}\alpha_{z_{\mathrm{m}},z_{\mathrm{f}}})^2$	measures the relative covariance between the offspring production a female has with two random males.

Table 3.3: Parameters for probabilities of sibship

The probabilities of sibship are given by

$$\begin{aligned}\Theta^{\male} &= \frac{1+C_v^2}{N_{\mathrm{m}}N_{\mathrm{f}}\phi} + \frac{C_{\mathrm{m}}}{N_{\mathrm{m}}}\\ \Theta^{\female} &= \frac{1+C_v^2}{N_{\mathrm{m}}N_{\mathrm{f}}\phi} + \frac{C_{\mathrm{f}}}{N_{\mathrm{f}}},\end{aligned} \tag{3.29}$$

where $\phi = \phi(z_{\mathrm{m}}, z_{\mathrm{f}})$ and the other parameters are given in Table 3.3. Eq. (3.29) shows that $\Theta^{\male}$ and $\Theta^{\female}$ are inversely related to the probability ϕ that an average male and an average female mate. Then, as expected, the more promiscuous the population is, the lower the probability that two individuals are sibs. Probabilities of sibship increase with the population compounds C_v^2, C_{m}

and C_{f} which measure the level of variance and covariance in offspring production in the population. Specifically, C_v^2 is the ratio of the variance to the squared mean (coefficient of variation) of a couple's fertility. The sex-specific parameters C_{m} and C_{f} describe the covariances between the reproductive outputs of a male and a female, respectively, over two matings with different partners (see Table 3.3). For instance, $C_{\mathrm{f}} = 1$ means that two matings of a female, along with their subsequent offspring production, are uncorrelated. If $C_{\mathrm{f}} < 1$ then they are negatively correlated. Biologically, $C_{\mathrm{f}} < 1$ could capture the effects of females having a finite number of eggs. Similarly, $C_{\mathrm{m}} < 1$ could stand for sperm depletion or costly mating in the presence of finite resources. By taking these correlation effects into account, $\Theta^{\male}$ and $\Theta^{\female}$ can be used as measures of reproductive variance within each sex, and the higher these probabilities are, the more offspring production is monopolized by few individuals in the population. In addition, since $\Theta^{\male}$ and $\Theta^{\female}$ are sex-specific, so are the reproductive variances they describe. For example, $\Theta^{\male} > \Theta^{\female}$, indicate that there is higher reproductive variance in males than in females.

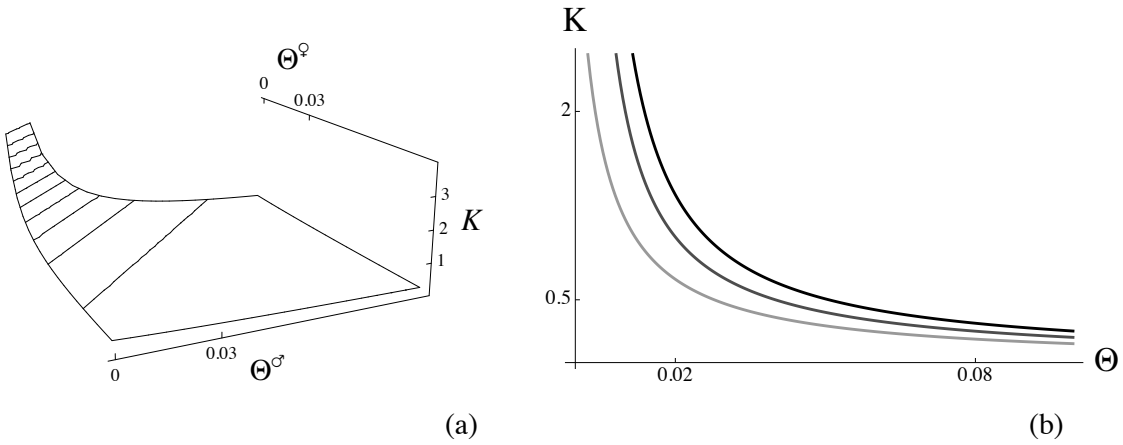

Figure 3.3: Population adaptability and dominance - (a) Three-dimensional plot of K in terms of probabilities of sibship $\Theta^{\male}$ and $\Theta^{\female}$. Dominance is fixed at $h = 0.6$ and initial value is $p_0 = 1/100$. (b) K versus $\Theta = \Theta^{\male} = \Theta^{\female}$ for recessive ($h = 0$, light gray), additive ($h = 0.5$, gray), and dominant mutants ($h = 1$, black). Initial value is $p_0 = 1/100$. For comparison, in the classical Wright-Fisher model with N males and N females, $\Theta^{\male} = 1/N$ and $\Theta^{\female} = 1/N$, a single copy mutant has an initial frequency of $p_0 = 1/(4N)$ and we find that $K = 1/2$.

Returning to K for an additive mutant (eq. 3.28), we see that K increases with initial mutant frequency p_0, and decreases with both probabilities of sibship. Thus, male and female reproductive variance reduces the efficacy of selection, decreasing the probability of fixation of a positively selected mutant and increasing the probability of fixation of a negatively selected mutant. This is a consequence of the offspring production being monopolized by a subset of individuals: the

likelihood that a randomly sampled individual transmits its genes is reduced, and so is the likelihood that the mutant stays apparent to selection. If the mutant is non-additive ($h \neq 1/2$) and K is solved numerically, we observe the same negative effects of reproductive variance (see fig. 3.3a). These calculations also show that K increases with dominance (see fig. 3.3b), indicating that selection acts more efficiently on dominant than recessive mutants. Since any mutant is initially expressed mostly in heterozygotes, the more dominant mutants they are, the more apparent they are to selection at the initial phase of segregation.

3.5.2 Evolutionary stable phenotypes and phenotypic distributions

The factorized probability π that a mutation will reach fixation (eqs. 3.25 and 3.26) can be used to infer the expected evolutionary trajectory of phenotypic traits and their evolutionary stable values. To do so, we assume that the locus under consideration mutates at rate ν independently of the resident phenotypic value and that the mutation rate is small enough with respect to the fixation process so that the population undergoes a monomorphic traits substitution sequence (Metz et al., 1995; Champagnat and Lambert, 2007). In order to evaluate the dynamics of male and female phenotype under this separation of time scales, we call $k(\delta_\mathrm{m}, \delta_\mathrm{f}, z_\mathrm{m}, z_\mathrm{f})$ the substitution rate of a population monomorphic for trait values $(z_\mathrm{m}, z_\mathrm{f})$ by a population monomorphic with trait values $(z_\mathrm{m} + \delta_\mathrm{m}, z_\mathrm{f} + \delta_\mathrm{f})$. The substitution rate can be written as in Lehmann (2012)

$$k(\delta_\mathrm{m}, \delta_\mathrm{f}, z_\mathrm{m}, z_\mathrm{f}) = \bar{N}\nu\, u(\delta_\mathrm{m}, \delta_\mathrm{f}) \left(\frac{1}{\bar{N}} + K(z_\mathrm{m}, z_\mathrm{f}) \big(\delta_\mathrm{m} G_\mathrm{m}(z_\mathrm{m}, z_\mathrm{f}) + \delta_\mathrm{f} G_\mathrm{f}(z_\mathrm{m}, z_\mathrm{f}) \big) \right) \tag{3.30}$$

where $\bar{N} = 2N_\mathrm{m} + 2N_\mathrm{f}$ is the number of gene copies in the adult population; μ is the mutation rate; $u(\delta_\mathrm{m}, \delta_\mathrm{f})$ is the distribution of the mutation step size distribution, conditional on a mutation arising, and the last term in eq. (3.30) is the fixation probability of a mutant with phenotypic values $(z_\mathrm{m} + \delta_\mathrm{m}, z_\mathrm{f} + \delta_\mathrm{f})$ in a $(z_\mathrm{m}, z_\mathrm{f})$ resident population.

The substitution rate $k(\delta_\mathrm{m}, \delta_\mathrm{f}, z_\mathrm{m}, z_\mathrm{f})$ allows us to evaluate the infinitesimal change in mean and variance of the evolving phenotypes, which characterizes a diffusion process on the phenotypic state space. For instance, the expected change in phenotype in sex v, conditional on the population being in state $(z_\mathrm{m}, z_\mathrm{f})$, is $a_v(z_\mathrm{m}, z_\mathrm{f}) = \mathrm{E}[\Delta z_v | z_\mathrm{m}, z_\mathrm{f}] = \int \delta_v k(\delta_\mathrm{m}, \delta_\mathrm{f}, z_\mathrm{m}, z_\mathrm{f})\, \mathrm{d}\delta_\mathrm{m}\, \mathrm{d}\delta_\mathrm{f}$. From eq. (3.30),

we obtain the infinitesimal conditional change in male and female phenotype as

$$\begin{aligned} a_{\mathrm{m}}(z_{\mathrm{m}},z_{\mathrm{f}}) &= \bar{N}\nu K(z_{\mathrm{m}},z_{\mathrm{f}})\Big(\varphi_{\mathrm{mm}}G_{\mathrm{m}}(z_{\mathrm{m}},z_{\mathrm{f}})+\varphi_{\mathrm{mf}}G_{\mathrm{f}}(z_{\mathrm{m}},z_{\mathrm{f}})\Big) \\ a_{\mathrm{f}}(z_{\mathrm{m}},z_{\mathrm{f}}) &= \bar{N}\nu K(z_{\mathrm{m}},z_{\mathrm{f}})\Big(\varphi_{\mathrm{mf}}G_{\mathrm{m}}(z_{\mathrm{m}},z_{\mathrm{f}})+\varphi_{\mathrm{ff}}G_{\mathrm{f}}(z_{\mathrm{m}},z_{\mathrm{f}})\Big), \end{aligned} \tag{3.31}$$

where φ_{mm} (σ_{ff}) is the variance in mutation step-size in males (females), and φ_{mf} is the covariance between the mutation step-size in males and females (e.g., $\varphi_{\mathrm{mf}} = \int \delta_{\mathrm{f}}\delta_{\mathrm{m}}u(\delta_{\mathrm{m}},\delta_{\mathrm{f}})\,\mathrm{d}\delta_{\mathrm{m}}\,\mathrm{d}\delta_{\mathrm{f}}$). These quantities play the same role as the genetic variance and covariances in standard models of sex-specific phenotypic evolution (Lande, 1980b).

A candidate evolutionary stable phenotypic equilibrium (z_{m}^*, z_{f}^*) can be defined as a point where the evolutionary dynamics will not induce any systematic change in male and female phenotype given that all individuals in the population express the phenotypic values (z_{m}^*, z_{f}^*). From eq. (3.31), this is a point where the infinitesimal change in phenotypes are zero: $a_{\mathrm{m}}(z_{\mathrm{m}}^*,z_{\mathrm{f}}^*) = a_{\mathrm{f}}(z_{\mathrm{m}}^*,z_{\mathrm{f}}^*) = 0$. Since $K(z_{\mathrm{m}},z_{\mathrm{f}}) > 0$, the candidate optimal male and female phenotype satisfy

$$\begin{aligned} \varphi_{\mathrm{mm}}G_{\mathrm{m}}(z_{\mathrm{m}}^*,z_{\mathrm{f}}^*)+\varphi_{\mathrm{mf}}G_{\mathrm{f}}(z_{\mathrm{m}}^*,z_{\mathrm{f}}^*) &= 0 \\ \varphi_{\mathrm{mf}}G_{\mathrm{m}}(z_{\mathrm{m}}^*,z_{\mathrm{f}}^*)+\varphi_{\mathrm{ff}}G_{\mathrm{f}}(z_{\mathrm{m}}^*,z_{\mathrm{f}}^*) &= 0, \end{aligned} \tag{3.32}$$

and can thus be computed from the gradients alone. Finally, we note that $(z_{\mathrm{m}}^*,z_{\mathrm{f}}^*)$, as defined by eq. (3.32), correspond to candidate evolutionary stable resident strategy, not the mean phenotypic values in the population at steady state. To compute these would require first characterizing the stability of $(z_{\mathrm{m}}^*,z_{\mathrm{f}}^*)$, which is done using higher order derivatives of $a_{\mathrm{m}}(z_{\mathrm{m}},z_{\mathrm{f}})$ and $a_{\mathrm{f}}(z_{\mathrm{m}},z_{\mathrm{f}})$ evaluated at $(z_{\mathrm{m}}^*,z_{\mathrm{f}}^*)$. The stationary distribution of phenotypes in the population can then be inferred using the method of Lehmann (2012).

3.6 Selection on vital parameters

The selection gradient can be used to investigate the long-term evolution of a phenotypic trait that affects one, several or all vital parameters simultaneously. For illustration, we now present an analysis of selection on a few such phenotypes. For simplicity we consider the case where mutations have the same step size in males and females, i.e. $\delta_{\mathrm{f}} = \delta_{\mathrm{m}}$, so that $\varphi_{\mathrm{mm}} = \varphi_{\mathrm{mf}} = \varphi_{\mathrm{ff}}$ and the total selection gradient is the added selection gradients in males and females $G(z_{\mathrm{m}},z_{\mathrm{f}}) = G_{\mathrm{m}}(z_{\mathrm{m}},z_{\mathrm{f}}) + G_{\mathrm{f}}(z_{\mathrm{m}},z_{\mathrm{f}})$. In addition, for the sake of clarity, but rather arbitrarily, we explore sep-

arately phenotypes that each affect one of the four aspects of the life cycle, fertility, mating, offspring survival, and sex ratio. This is done by evaluating the selection gradient G in the case where (eq. 3.31), and holding at zero the derivatives of the parameters that are assumed to be unaffected by the evolving trait.

3.6.1 Fertility

Although the life cycle begins by mating, we begin with selection on fertility, to illustrate the approach and compare the results with previous work investigating this vital parameter (Gillespie, 1975; Lehmann and Balloux, 2007). We thus calculate the selection gradient on a phenotype that only affects the vital parameters reflecting the distribution of the fertility of mated pairs, α, β, γ^{m}, and γ^{f} (see table 3.1b). From eq. (3.31), by setting to zero all derivatives of parameters that do not pertain to fertility, we obtain

$$\begin{aligned} G(z_{\mathrm{m}}, z_{\mathrm{f}}) = \frac{1}{2}\left[1 + \frac{C_{\mathrm{m}}}{N_{\mathrm{m}}} + \frac{C_{\mathrm{f}}}{N_{\mathrm{f}}} + \frac{C_v^2}{N_{\mathrm{m}}N_{\mathrm{f}}\phi} - \frac{1}{N_{\mathrm{m}}N_{\mathrm{f}}\phi}\right](\hat{\alpha}_{\mathrm{m}} + \hat{\alpha}_{\mathrm{f}}) \\ - \frac{1}{2}\frac{C_v^2}{N_{\mathrm{m}}N_{\mathrm{f}}\phi}(\hat{\beta}_{\mathrm{m}} + \hat{\beta}_{\mathrm{f}}) - \frac{1}{2}\frac{C_{\mathrm{m}}}{N_{\mathrm{m}}}(\hat{\gamma}^{\mathrm{m}}_{\mathrm{m}} + \hat{\gamma}^{\mathrm{m}}_{\mathrm{f}}) - \frac{1}{2}\frac{C_{\mathrm{f}}}{N_{\mathrm{f}}}(\hat{\gamma}^{\mathrm{f}}_{\mathrm{m}} + \hat{\gamma}^{\mathrm{f}}_{\mathrm{f}}), \end{aligned} \tag{3.33}$$

where the over-hat symbols combined with a subscript m or f ($\hat{x}_{\mathrm{m,f}}$) denote the relative rate of change of quantities due to the presence of the mutant in a male or a female respectively,

$$\hat{x}_{\mathrm{m}} = \left.\frac{\frac{\partial x}{\partial z_{\mathrm{m}i}}}{x}\right|_{z_{\mathrm{m}i}=\bar{z}_{\mathrm{m}}=z_{\mathrm{m}}, z_{\mathrm{f}j}=\bar{z}_{\mathrm{f}}=z_{\mathrm{f}}}, \quad \hat{x}_{\mathrm{f}} = \left.\frac{\frac{\partial x}{\partial z_{\mathrm{f}j}}}{x}\right|_{z_{\mathrm{m}i}=\bar{z}_{\mathrm{m}}=z_{\mathrm{m}}, z_{\mathrm{f}j}=\bar{z}_{\mathrm{f}}=z_{\mathrm{f}}}, \tag{3.34}$$

evaluated at the resident phenotypic values z_{m} and z_{f}.

Eq. (3.33) allows us to separate and interpret the different selective forces acting on traits affecting the distribution of fertility. The first term describes the directional selection pressure on changing the expected fertility per mating. This selection pressure reflects both the benefits of increasing offspring production (captured in the positive terms in the square bracket), but also the cost that stems from the resulting increased competition between the offspring of the same parent (the last negative term in the square bracket). It is also worth mentioning that since our model allows for fertility to be jointly determined by the phenotypes of both the male and the female mating partner, selection acts on the average effect of male and female effects on fertility $(\hat{\alpha}_{\mathrm{m}} + \hat{\alpha}_{\mathrm{f}})/2$. If the phenotypic effect of a mutation is limited to one sex (for example the female), selection on fertility is proportional to the change of fertility due to an altered phenotype in that

sex only and the derivative for the other sex vanishes (e.g., $\hat{\alpha}_{\mathrm{m}} = 0$).

The remaining terms of eq. (3.33) express the selection pressures which act through and on the variance in an individual's offspring production and its covariance with the rest of the population. To illustrate how selection acts on (co)variances, we consider the effects of a male-limited mutation (this may not be the most biologically relevant case for fertility, but allows us to refer to the detailed development of male fitness above). With male limitation of the phenotype, all hatted terms with subscripts $_{\mathrm{f}}$ in eq. (3.33) vanish. The variance in a male's reproductive output comprises two components, the variance in his output across different matings, and the covariance between his own offspring production and that of other individuals in the population. As shown in eq. (3.14), the variance in the male's own reproduction can yet again be separated in the variance in fertility of a single mating (β, see eq. 3.15), and the covariance between the number of offspring the male produces with two different mating partners (as measured by γ^{m}, see eq. 3.16). The selection gradient on fertility (eq. 3.33, second and third term) shows that a mutation that increases either of these variance components has a negative impact on its fitness and be selected against (see eq. 3.5). The variance in a male's fitness that arises due to the covariance between its own offspring production and that of the rest of the population (as measured by γ^{f}) increases with the covariance between the number of offspring females have with the focal male other males in the population (see eqs. 3.17 and 3.18). Since the covariance of the focal male with the rest of the population decreases his fitness (see eq. 3.5), mutations that increase γ^{f} are also under negative selection, as shown by the last term of eq. (3.33).

Eq. (3.33) is in agreement with previous haploid models of fertility evolution. Under the assumption that individuals do not mate more than once ($\phi^{\mathrm{m}} = \phi^{\mathrm{f}} = 0$), we have $C_{\mathrm{m}} = C_{\mathrm{f}} = 0$ and the selection gradient of eq. (3.33) reduces to

$$G(z_{\mathrm{m}}, z_{\mathrm{f}}) = \frac{1}{2}\left[1 - \frac{1 - C_v^2}{N_{\mathrm{m}} N_{\mathrm{f}} \phi}\right](\hat{\alpha}_{\mathrm{m}} + \hat{\alpha}_{\mathrm{f}}) - \frac{1}{2}\frac{C_v^2}{N_{\mathrm{m}} N_{\mathrm{f}} \phi}(\hat{\beta}_{\mathrm{m}} + \hat{\beta}_{\mathrm{f}}). \tag{3.35}$$

This expression only differs from eq. (A37) of Lehmann and Balloux (2007) in that the effect of, and selection on, reproductive variance is inversely proportional to $N_{\mathrm{m}} N_{\mathrm{f}} \phi$, instead of the total haploid population size. This difference is consistent with our consideration of mating events. In our case, $N_{\mathrm{m}} N_{\mathrm{f}} \phi \sim O(N)$ represents the expected total number of mating pairs, and hence the number of reproductive units in the populations. This could be interpreted as equivalent to the number of individuals in a haploid population. Eq. (3.35) also reflects the fact that in our dioecious

model both males and females contribute to the mean and variance fertility of a mating. Selection therefore acts on the averaged male and female effects $(1/2)(\hat{x}_\mathrm{m}+\hat{x}_\mathrm{f})$, $x \in \{\alpha,\beta\}$.

Eq. (3.35) can be further reduced to a two sex version of the selection gradient presented by Gillespie (1975, eq. 11a). His analysis uses the diffusion approximation and requires that the difference between the mean fertilities of the resident and mutant phenotypes tend to zero as the population size tends to infinity ($\hat{\alpha}_\mathrm{m} \sim O(1/N)$, $\hat{\alpha}_\mathrm{f} \sim O(1/N)$). Applying this assumption to eq. (3.35), the equation simplifies to

$$G(z_\mathrm{m},z_\mathrm{f}) = \frac{1}{2}(\hat{\alpha}_\mathrm{m}+\hat{\alpha}_\mathrm{f}) - \frac{1}{2}\frac{C_v^2}{N_\mathrm{m}N_\mathrm{f}\phi}(\hat{\beta}_\mathrm{m}+\hat{\beta}_\mathrm{f}). \tag{3.36}$$

In this expression, the deleterious effects of sib competition appear as a negative selection pressure acting on fertility variance (cf. fig. 3.2a). However, the effects of sib competition term on expected fecundity (the term $(\hat{\alpha}_\mathrm{m}+\hat{\alpha}_\mathrm{f})/(2N_\mathrm{m}N_\mathrm{f}\phi)$ in eq. 3.35) that are captured by the method we use to derive the probability of fixation, fall victim to the order condition required by the diffusion approach (Gillespie, 1975; Taylor, 2009).

3.6.2 Mating

By assuming the effect of the mutation is limited to a phenotype that affects the mating parameters ϕ, ϕ^m, and ϕ^f (see table 3.1a), the selection gradient reduces to

$$G(z_\mathrm{m},z_\mathrm{f}) = \frac{1}{2}\left[1+\frac{C_\mathrm{m}}{N_\mathrm{m}}+\frac{C_\mathrm{f}}{N_\mathrm{f}}\right](\hat{\phi}_\mathrm{m}+\hat{\phi}_\mathrm{f}) - \frac{1}{2}\frac{C_\mathrm{m}}{N_\mathrm{m}}(\hat{\phi}_\mathrm{m}^\mathrm{m}+\hat{\phi}_\mathrm{f}^\mathrm{m}) - \frac{1}{2}\frac{C_\mathrm{f}}{N_\mathrm{f}}(\hat{\phi}_\mathrm{m}^\mathrm{f}+\hat{\phi}_\mathrm{f}^\mathrm{f}). \tag{3.37}$$

This expression appears simpler than the equivalent for fertility (eq. 3.33), with fewer terms weighting the relative marginal change in average mating probability $(\hat{\phi}_\mathrm{m}+\hat{\phi}_\mathrm{f})/2$, and variance terms missing. The apparent simplicity stems from the fact that mating between a male i and a female j is an all or nothing event, and hence a Bernoulli random variable with parameter $\phi_{z_{\mathrm{m}i},z_{\mathrm{f}j}}$. In this case, the mean and variance a mating event are both functions of a single same parameter $\phi_{z_{\mathrm{m}i},z_{\mathrm{f}j}}$. The terms $\hat{\phi}_\mathrm{m}$ and $\hat{\phi}_\mathrm{f}$ in (3.37) therefore capture the net fitness effect of changes in mating rate on the distribution of mating success, rather than separating effects of mean and variance as in the first and second term of eq. (3.33).

To see the equivalence of eqs. (3.37) and (3.33) based on the argument presented above, consider a female-limited mutant in a population in which each mating event results in the production of a fixed number of B offspring. Then, the expected number of offspring produced

by a male i and female j is $B\phi_{z_{\mathrm{m}i},z_{\mathrm{f}j}}$. So the relative effect of the mutant on the mean number of offspring, $\hat{\alpha}_{\mathrm{f}} = \hat{\phi}_{\mathrm{f}}$, depends on $\hat{\phi}_{\mathrm{f}}$. But with the variance in the number of offspring as $\beta = B^2\mathrm{V}\left[\mathbb{1}_{P_{ij}}\right] = B^2\phi_{z_{\mathrm{m}i},z_{\mathrm{f}j}}(1-\phi_{z_{\mathrm{m}i},z_{\mathrm{f}j}})$, the relative effect of the mutant on this variance also depends on $\hat{\phi}_{\mathrm{f}}$: $\hat{\beta}_{\mathrm{f}} = \hat{\phi}_{\mathrm{f}}(1-2\phi)/(1-\phi)$. So here, any mutant that disrupts $\phi_{z_{\mathrm{m}i},z_{\mathrm{f}j}}$ simultaneously disrupts the mean and variance in offspring production. Note that we also have $C_v^2 = (1-\phi)/\phi$, and $\hat{\gamma}_{\mathrm{f}}^{\mathrm{m}} = \hat{\phi}_{\mathrm{f}}^{\mathrm{m}}$ and $\hat{\gamma}_{\mathrm{f}}^{\mathrm{f}} = \hat{\phi}_{\mathrm{f}}^{\mathrm{f}}$, and substituting for all these terms in eq. (3.33), and for C_v^2 in eq. (3.37) yields the same expression, which highlights that selection on the variance operates in the same way on mating and fertility but depend on how the contribution to the variance in reproductive success is split across mating and fertility.

3.6.3 Survival selection

We now turn our attention to the evolution of phenotype that affects the survival rates of male and female offspring, s^{m} and s^{f}. The survival of an offspring is assumed to depend on the phenotypic values of its two parents and its own sex. Then, from eq (3.31) and table 3.2b, we obtain

$$G(z_{\mathrm{m}},z_{\mathrm{f}}) = \frac{1}{2}(1-\Theta^{\male})\left(\hat{s}_{\mathrm{m}}^{\mathrm{m}}+\hat{s}_{\mathrm{m}}^{\mathrm{f}}\right)+\frac{1}{2}(1-\Theta^{\female})\left(\hat{s}_{\mathrm{f}}^{\mathrm{m}}+\hat{s}_{\mathrm{f}}^{\mathrm{f}}\right), \tag{3.38}$$

where $\hat{s}_u^v$ denotes the relative rate of change of the probability of survival of an offspring of sex v due to the presence of the mutant in a parent of sex u (eq. 3.34). The probabilities of sibship $\Theta^{\male}$ and $\Theta^{\female}$ are of order $O(1/N)$, and given by eq. (3.29).

Since the weights $(1-\Theta^{\male})$ and $(1-\Theta^{\female})$ are positive, the direction of selection on a mutant is determined by its effects on survival, i.e., the $\hat{s}_u^v$ terms. Thus, a mutation that improves the likelihood of survival of sons and daughters for both fathers ($\hat{s}_{\mathrm{m}}^{\mathrm{m}} > 0$ and $\hat{s}_{\mathrm{m}}^{\mathrm{f}} > 0$) and mothers ($\hat{s}_{\mathrm{f}}^{\mathrm{m}} > 0$ and $\hat{s}_{\mathrm{f}}^{\mathrm{f}} > 0$) undergoes positive selection. Furthermore, mutations that benefit the survival of one sex at the expense of the other sex are selected positively as long as the overall benefit exceeds the overall cost, $\hat{s}^{\mathrm{m}} + \hat{s}^{\mathrm{f}} > 0$. The weights $(1-\Theta^{\male})$ and $(1-\Theta^{\female})$ express how the beneficial effect of improving offspring survival decreases with increasing probability of sibship. This depreciation reflects the fitness consequences of increased sibling competition. Furthermore, and along the lines of a similar argument as made previously for mating rate, it incorporates the effect of increased variance in the total number of surviving offspring that is associated with an increased offspring survival rate. As for mating rates (eq. 3.37), this can be seen by showing the equivalence between eq. (3.38) and the selection gradient for fertility effects, eq. (3.33). For

simplicity, we again show the parallel for a mutation with female-limited expression that affects the survival of male offspring, i.e., for $\hat{s}_{\mathrm{f}}^{\mathrm{m}}$ only. The number of offspring produced by a mating may be interpreted as the total number of surviving male offspring, in which case

$$\alpha = \mathrm{E}\left[\sum_{n}^{B_{ij}} \mathbb{1}_{R_n} \mathbb{1}_{S_n^{\mathrm{m}}}\right] \text{ and } \beta = \mathrm{V}\left[\sum_{n}^{B_{ij}} \mathbb{1}_{R_n} \mathbb{1}_{S_n^{\mathrm{m}}}\right]. \tag{3.39}$$

Then, assuming the phenotype does not affect the total number offspring produced nor the sex ratio, the effect of the mutation on the mean number of offspring is measured as $\hat{\alpha}_{\mathrm{f}} = \hat{s}_{\mathrm{f}}^{\mathrm{m}}$, that on the variance as $\hat{\beta}_{\mathrm{f}} \approx 2\hat{s}_{\mathrm{f}}^{\mathrm{m}}$ (which is approximated to the order $O(1/N)$, since $\hat{\beta}_{\mathrm{m}}$ is factored by $C_v^2/(N_{\mathrm{m}}N_{\mathrm{f}}\phi) \sim O(1/N)$ in eq. (3.33)). Thus, a mutation that improves mean survival contributes twice as much to the relative change of variance in the number of offspring. Again, the immediate relationship between mean and variance arises because survival is modeled as a Bernoulli trial for each offspring, and the survival rate s contributes to both the mean in and the variance of the number of offspring entering competition. The independence between the survival of different offspring also entails that the covariance between the offspring number of two matings is always zero, and $\hat{\gamma}_{\mathrm{f}}^{\mathrm{f}} = \hat{\gamma}_{\mathrm{m}}^{\mathrm{f}} = 0$. Substituting for all these into eq. (3.33) yields eq. (3.38), supporting our interpretation that the weights $-\Theta^{\male} < 0$ and $-\Theta^{\female} < 0$ in eq. (3.38) reflect both the costs associated with increasing the expected number of offspring entering competition and those of increasing the variance in their number.

The expression of eq. (3.38) in terms $\Theta^{\male}$ and $\Theta^{\female}$ has the advantage of highlighting the effects of sex-specific reproductive variance. As mentioned in section 3.5, the probabilities of sibship $\Theta^{\male}$ and $\Theta^{\female}$ are a measure of reproductive variance within each sex. Higher reproductive variance implies greater relatedness among the individuals of the offspring generation and eq. (3.38) thus shows that the benefits of increasing offspring survival decreases with offspring relatedness. In addition, with $\Theta^{\male}$ weighing the male-limited effects of the mutant, and $\Theta^{\female}$ the female-limited ones, the effect of reproductive variance on the strength of selection is specific to the sex in which the mutant is expressed. If, for example, reproductive variance is higher in males ($1 - \Theta^{\male} < 1 - \Theta^{\female}$), then a mutant which improves offspring survival through its effect on the paternal phenotype has a weaker chance of fixing than a mutant which acts through the maternal phenotype. An asymmetry in sex-specific reproductive variance would then be particularly relevant for the fixation of parental care strategies. If parental care improves offspring survival, then it is under stronger selection in the sex with lowest reproductive variance.

3.6.4 Sex ratio evolution

Finally, we investigate the evolution of a phenotype that affects sex allocation. The probability $r(z_{\mathrm{m}i}, z_{\mathrm{f}j})$ that an offspring is male is assumed to be determined by the phenotypes of both its parents (see table 3.2c), and its selection gradient is given by

$$G(z_{\mathrm{m}}, z_{\mathrm{f}}) = \frac{1}{4}\frac{1-2r}{(1-r)}\left[(1-\Theta^{\male})\hat{r}_{\mathrm{m}} + (1-\Theta^{\female\!\!\!\male})\hat{r}_{\mathrm{f}}\right]. \tag{3.40}$$

where $r = r(z_{\mathrm{m}}, z_{\mathrm{f}})$ is the average sex ratio at birth in the population, measured as the proportion of males. The selection gradient for sex allocation is similar to that for survival rates (eq. 3.38). In contrast to that latter, however, eq. (3.40) is factored by $(1-2r)/(1-r)$. This factor reflects the standard frequency-dependence of sex allocation (e.g. Bulmer, 1994; Frank, 1998). It is positive when $r < 1/2$, negative when $r > 1/2$, and vanishes at an even population sex ratio ($r = 1/2$). Individual sex allocation strategies which lead to $r = 1/2$ are favored by natural selection. As for eq. (3.38), the weights $(1-\Theta^{\male})$ and $(1-\Theta^{\male})$ capture the balance between the cost and benefits from changing the expected value of, and variance in, the number of male or female offspring entering sex-specific competition. Again, they imply that selection on sex allocation is stronger in the sex with the lower reproductive variance.

3.7 Discussion

In this chapter, we have constructed a framework to investigate the evolution of male and female reproductive traits within a biologically realistic context of sexual reproduction. While building on an established population genetic foundation, the model takes into account the stochastic effects arising from mating interactions, finite fertility, sex allocation and offspring survival. We have illustrated its usefulness by discussing the evolution of some general traits, and opened the door for the analysis of more specific reproductive phenotypes, taking into account not only their effects on average sex-specific reproductive success, but also on its variance.

Reflecting the more realistic representation of sexual reproduction, our measure of fitness (eq. 3.5) includes previously ignored relationships between the reproductive output of different individuals across the population. Thus, individual fitness depends not only on the relative value of expected offspring number (μ^u_{vi}/μ^u_T), but also a number of (co)variance terms. These include the variance in the reproductive output of the focal individual (σ^u_{vii}), which decreases fitness (fig.

2(a)), and the variance in the total reproductive output of the rest of the population ($\sum_{k\neq i}\sigma_{kk}$), which increases fitness (fig. 3.2(b)). The role of these variances on fitness had been accounted for in previous variance-sensitive models (e.g. Gillespie, 1975; Taylor, 2009). However, our model also takes into account the covariance between the numbers of juveniles produced by different individuals (σ^u_{vik}, $i \neq k$), which had been ignored so far. This covariance is generated by finite number of matings and fecundity. These properties represent a biological reality across a wide range of organisms, and the selective forces they generate cannot be ignored when trying to predict the evolution of reproductive traits.

To infer on the long-term evolution of reproductive traits, we derived the probability of fixation for a mutant that alters a phenotypic trait affecting any number of these traits. We have shown that if the mutation rate is equal in both sexes, the probability of fixation of a mutant can be expressed in a succinct and manageable form as the product of two factors, K and G (eq. 3.26). The parameter $K > 0$ is a measure of the efficacy of selection. It incorporates not only the level of standing genetic variation in the population and, through the dominance coefficient h, the extent to which genetic variation translates into phenotypic variation visible to selection (see eq. 3.23 and fig. 3.3), but also of the degree of genetic drift due to reproductive variance (eq. 3.28 and fig. 3.3). As the value of K increases, the probability of fixation of a mutant increasingly reflects the selection pressure acting on it. We found that K is greatest when alleles are dominant and reproductive variance in a population is minimal (eq. 3.28 and fig. 3.3), maximizing the probability of fixation of a beneficial mutation and the loss of a deleterious one.

The probability of fixation also depends on the selection gradient G, which expresses the direction and intensity of selection on a mutant. The general equation for the gradient G that we have derived (eq. 3.31) can be used to predict short-term frequency change as well as the evolutionary stable states in male and female traits (eq. 3.32). In both cases, predictions take into account the effects of a finite population size, but also those arising from sex-specific reproductive variance. In addition, the model can be used to analyze the evolution of social interactions between individuals under frequency-dependent selection. Possible traits of interest here could include those involved in interactions between the male and female of a mating pair, or those affecting interactions between individuals of the same sex, for example in male-male competition for mating and fertilization success. Using our model to study social aspects of reproductive evolution is made simple because all vital parameters in G (tables 3.1 and 3.2) are functions of the phenotype of the focal individual and the average male and female population phenotype only.

To illustrate how reproductive traits are shaped by natural selection and sex-specific reproductive variance, we analyzed the selection gradients of four general traits, the fertility of mated pairs (eq. 3.33), mating (eq. 3.37), sex-specific offspring survival (eq. 3.38), and sex allocation (eq. 3.40). In line with the description of fitness in our model, these gradients demonstrate that traits are under selection for their effects on the expected number of offspring they produce, as well as on the different components of variance. The prediction that reproductive variance can be a target of selection is in agreement with previous models (Gillespie, 1974; Proulx, 2000; Shpak, 2007; Lehmann and Balloux, 2007; Taylor, 2009), and is a consequence of competition between the offspring produced by an individual. Variance in fertility is deleterious to an individual's fitness because the occasional benefits of increased reproduction are reduced by increased kin competition and therefore cannot outweigh the occasional costs of reduced reproduction (see fig. 3.2(a)). While these concepts have been described before, our dioecious model allows us to investigate how the balance between selection on expected offspring production and on reproductive variance differs between the sexes. These differences are particularly apparent in traits that have simpler selection gradient, survival and sex-ratio (eqs. 3.38 and 3.38). Here it is obvious that reproductive variance, reflected in the probabilities of sibship, decrease the intensity of selection in a sex-specific manner. As a consequence, traits that improve offspring survival or promote an even sex-ratio are under stronger selection in the sex with the lower reproductive variance.

The interaction between sex specific reproductive variance and selection can be used to make predictions on the existence of sex-specific strategies, and their co-evolution with mating systems in natural populations. For example, we expect that parental care strategies that improve offspring survival to evolve more readily in species with low reproductive variance in both sexes, and to be present more often in the sex with the lower reproductive variance. Since males often suffer greater reproductive variance than females (Bateman, 1948; Clutton-Brock, 2007), the latter part of this prediction is borne out in the predominance of maternal care compared to paternal care. But the model also predicts an association between the mating system and parental care provided by males. Paternal care is less likely to evolve when male reproductive variance is high, such as in the situation of a polygynous mating system. Rather, it is expected that paternal care should be exhibited in populations with mating systems with low male reproductive variance, such as monogamy, in accordance with previous models and data (see Kokko and Jennions, 2008, for a review).

The model not only considers the effects of reproductive variance on evolution, but can also

be used to understand the evolution of reproductive variance itself. We find that the reproductive parameters that define the probabilities of sibship (table 3.3) are under negative selection (eqs. 3.33 and 3.37). The intensity of this negative selection is proportional to the reproductive variance in the population, and so vanishes as the latter approaches zero. But if reproductive variance decreases, then efficacy of selection K increases, and with it the efficacy of the negative selection acting on reproductive variance. We then find that, ignoring trade-offs with the evolution of other vital parameters, selection is expected to drive reproductive variance towards zero. However, as observed in previous variance-sensitive models, any mutant that improves mean reproductive success at the expense of increasing the variance is likely to be under positive selection as selection on the variance is inversely proportional to the population size and thus weaker. We also note here that if selection on reproductive variance vanishes as the population size gets very large, our model and observations remain valid for large but structured population as long as selection is soft, in which case variance-minimizing selection is inversely proportional to patch size (Proulx, 2000; Shpak, 2005; Shpak and Proulx, 2007; Lehmann and Balloux, 2007; Beckerman et al., 2011).

The analysis of selection in the present chapter has put the emphasis on understanding how selection acts on traits through their combined effects on the expected number of offspring and on the components of reproductive variance. But the model and analytical approach can easily be adapted to study the selection on very specific reproductive traits, such as an exaggerated male trait which makes it more attractive to females but decreases its sperm count in a monandrous population. To use and extend the model to investigate the evolution of specific traits in a more precise mating system we make two suggestions. First, it would be informative to underpin the mating system by a stochastic process amenable to simulations, and relate it to the parameters of reproductive traits (see table 3.1 for definitions). These relations will highlight the constraints the parameters impose on another, which have been ignored here but are expected to be significant. Indeed, since the parameters we use to capture the mating system depend on the same set of underlying events, they are not free to evolve independently. For instance, the marginal probability of a single mating ϕ is necessarily functionally related to the probabilities of double matings, ϕ^{m} and ϕ^{f}. Secondly, it would also be interesting to incorporate genetic covariance between traits. It is conceivable that mutations affect more than one vital parameter, and are therefore subject to selection that combines elements of the examples presented in this chapter. Once a model has been defined in such way, it is straightforward to use our model to generate predictions about the evolutionary trajectory, stable states and even the stationary distribution of the reproductive traits

considered.

To conclude, we have provided a general framework to study the co-evolution of reproductive traits in sexual populations, taking into account sex-specific variance in reproductive success. We have derived a selection gradient that can be used to infer on evolutionary stable phenotypes and discussed the general features of selection on four episodes of the life cycle. While more detailed analyses are beyond the scope of this article, it is important to note that our model is easily adaptable to more refined reproductive systems, and is ready to study their evolution. If specific phenotypic traits are identified, and their effect on the variables given in tables 3.1 and 3.2 are characterized, the evolution of these traits can be analyzed by substituting the derived variables into the selection gradient G (eq. 3.31). By summing selection gradients for different traits, it is then possible to model the co-evolution of multiple traits. So this model provides a methodology to study the evolutionary feedback between the evolution of reproductive traits, their effects on sex-specific reproductive variance, and how, in turn, reproductive variance impacts on the transmission of these traits and on the level of genetic drift that affects their evolution.

Appendix

3.A Assumption on distribution of juveniles

Given an index set of individuals $\mathscr{I} \ni i$, and a corresponding set of powers defined by a mapping $\zeta : \mathscr{I} \to \mathbb{Z}^+$, the following holds

$$\mathrm{E}\left[\Pi_{i\in\mathscr{I}}(J^u_{vi} - \mu^u_{vi})^{\zeta(i)}\right] \sim O\left(N^{\Sigma_{i\in\mathscr{I}}\,\zeta(i)+1-|\mathscr{I}|}\right), \tag{3.A.1}$$

where $|\mathscr{I}|$ is the number of individuals in set $\mathscr{I}$. The remainder terms that appear in R, given by the higher order terms of the Taylor expansion of F, are thus of order $1/N^2$.

3.B Covariances between the number of offspring of two couples

3.B.1 Variance for a single couple, $\Upsilon_{z_{\mathrm{m}i},z_{\mathrm{f}j}}$

The variance in the number of male offspring from a mating, between male i and female j can be developed as $\Upsilon_{1z_{\mathrm{m}i},z_{\mathrm{f}j}} = \mathrm{V}[\mathbb{1}_{P_{ij}}Y_{ij}] = \mathrm{E}[\mathbb{1}_{P_{ij}}Y_{ij}^2] - \mathrm{E}[\mathbb{1}_{P_{ij}}Y_{ij}]^2$, where the second term is given in eq. (3.8) of the main text. For the first term, since $Y_{ij} > 0$ is conditional on the mating

event, we have $\mathrm{E}[\mathbb{1}_{P_{ij}} Y_{ij}^2] = \phi_{z_{\mathrm{m}i},z_{\mathrm{f}j}} \mathrm{E}[Y_{ij}^2]$ and therefore $\Upsilon_{1 z_{\mathrm{m}i},z_{\mathrm{f}j}} = \phi_{z_{\mathrm{m}i},z_{\mathrm{f}j}} (\mathrm{E}[Y_{ij}^2] - \phi_{z_{\mathrm{m}i},z_{\mathrm{f}j}} \mathrm{E}[Y_{ij}]^2) = \phi_{z_{\mathrm{m}i},z_{\mathrm{f}j}} (\mathrm{V}[Y_{ij}] + (1 - \phi_{z_{\mathrm{m}i},z_{\mathrm{f}j}}) \mathrm{E}[Y_{ij}]^2)$. Because sex determination and survival of each offspring are assumed to be independent, we may expand the sums $Y_{ij} = \sum_n^{B_{ij}} \mathbb{1}_{R_n} \mathbb{1}_{S_n^{\mathrm{m}}}$ over the random number of offspring as $\mathrm{V}[Y_{ij}] = \alpha_{z_{\mathrm{m}i},z_{\mathrm{f}j}} \mathrm{V}[\mathbb{1}_{R_n} \mathbb{1}_{S_n^{\mathrm{m}}}] + \mathrm{V}[B_{ij}] (r_{z_{\mathrm{m}i},z_{\mathrm{f}j}} s^{\mathrm{m}}_{z_{\mathrm{m}i},z_{\mathrm{f}j}})^2$, where $\mathrm{V}[\mathbb{1}_{R_n} \mathbb{1}_{S_n^{\mathrm{m}}}] = r_{z_{\mathrm{m}i},z_{\mathrm{f}j}} s^{\mathrm{m}}_{z_{\mathrm{m}i},z_{\mathrm{f}j}} (1 - r_{z_{\mathrm{m}i},z_{\mathrm{f}j}} s^{\mathrm{m}}_{z_{\mathrm{m}i},z_{\mathrm{f}j}})$. Writing the variance in fertility of a mating between a male i and a female j, given that the mating event has occurred, as $\beta_{z_{\mathrm{m}i},z_{\mathrm{f}j}} = \mathrm{V}[B_{ij}]$ yields eq. (3.15) of the main text.

3.B.2 Covariance between two matings, $\Upsilon^{\mathrm{m}}_{z_{\mathrm{m}i},z_{\mathrm{f}j},z_{\mathrm{f}l}}$ and $\Upsilon^{\mathrm{f}}_{z_{\mathrm{m}i},z_{\mathrm{f}j},z_{\mathrm{m}k}}$

The covariance between the number of male juveniles produced by a male i in two matings, with females j and l, is given by $\Upsilon^{\mathrm{m}}_{z_{\mathrm{m}i},z_{\mathrm{f}j},z_{\mathrm{m}k}} = \mathrm{C}[\mathbb{1}_{P_{ij}} Y_{ij} \mathbb{1}_{P_{il}} Y_{il}] = \mathrm{E}[\mathbb{1}_{P_{ij}} Y_{ij} \mathbb{1}_{P_{il}} Y_{il}] - \mathrm{E}[\mathbb{1}_{P_{ij}} Y_{ij}] \mathrm{E}[\mathbb{1}_{P_{il}} Y_{il}]$. The second term is found using eq. (3.8) of the main text. To evaluate the first term, we only need to consider the event when $\mathbb{1}_{P_{ij}} Y_{ij} \mathbb{1}_{P_{il}} Y_{il}$ is non-zero, since it is the only one to contribute to its mean. A necessary condition is that both mating events occur: $\mathbb{1}_{P_{ij}} = \mathbb{1}_{P_{il}} = 1$. We write the probability of both matings occurring as $\mathrm{P}[\mathbb{1}_{P_{ij}} = \mathbb{1}_{P_{il}} = 1] = \phi^{\mathrm{m}}_{z_{\mathrm{m}i},z_{\mathrm{f}j},z_{\mathrm{f}l}}$, which depends on the phenotypes male i and that of the two females j and l. The expectation $\mathrm{E}[\mathbb{1}_{P_{ij}} Y_{ij} \mathbb{1}_{P_{il}} Y_{il}]$ may then be expressed as $\phi^{\mathrm{m}}_{z_{\mathrm{m}i},z_{\mathrm{f}j},z_{\mathrm{f}l}} \mathrm{E}[Y_{ij} Y_{il}]$, where $\mathrm{E}[Y_{ij} Y_{il}] = \mathrm{E}[B_{ij} B_{il}] r_{z_{\mathrm{m}i},z_{\mathrm{f}j}} s^{\mathrm{m}}_{z_{\mathrm{m}i},z_{\mathrm{f}j}} r_{z_{\mathrm{m}i},z_{\mathrm{f}l}} s^{\mathrm{m}}_{z_{\mathrm{m}i},z_{\mathrm{f}l}}$ is conditional on both mating events. Writing the expected product of fertilities of two matings of the same male as $\gamma^{\mathrm{m}}_{z_{\mathrm{m}i},z_{\mathrm{f}j},z_{\mathrm{f}l}} = \mathrm{E}[B_{ij} B_{il}]$, yields eq. (3.16) of the main text.

The covariance between the number of male juveniles produced by a female j in matings with males i and k, $\Upsilon^{\mathrm{f}}_{z_{\mathrm{m}i},z_{\mathrm{f}j},z_{\mathrm{m}k}}$, is found with a similar argument. Defining $\phi^{\mathrm{f}}_{z_{\mathrm{m}i},z_{\mathrm{f}j},z_{\mathrm{m}k}} = E[\mathbb{1}_{P_{ij}} \mathbb{1}_{P_{kj}}]$ as the probability that female j mates with males i and k, and $\gamma^{\mathrm{f}}_{z_{\mathrm{m}i},z_{\mathrm{f}j},z_{\mathrm{m}k}} = \mathrm{E}[B_{ij} B_{kj}]$ as the expected product of fertilities of two matings of the same female, given the two matings have occurred, gives eq. (3.18) of the main text.

3.C Individual female fitness components

The expected number $w^{\mathrm{m}}_{\mathrm{f}j}$ of male breeders produced by a focal female j is given by eq. (3.5). In addition to relying on μ^{m}_T (given by eq. 3.11), $w^{\mathrm{m}}_{\mathrm{f}j}$ also depends on $\mu^{\mathrm{m}}_{\mathrm{f}j}$, $\sum_{l \neq j} \sigma^{\mathrm{m}}_{\mathrm{f}jl}$ and $\sigma^{\mathrm{m}}_{\mathrm{f}jj}$, which we define now. The expected number of offspring of female j is given by the sum of her interactions with every male and approximated by expanding about the average male phenotype, which yields

$$\mu^{\mathrm{m}}_{\mathrm{f}j} = N_{\mathrm{m}} \phi_{\bar{z}_{\mathrm{m}},z_j} \alpha_{\bar{z}_{\mathrm{m}},z_{\mathrm{f}j}} r_{\bar{z}_{\mathrm{m}},z_{\mathrm{f}j}} s^{\mathrm{m}}_{\bar{z}_{\mathrm{m}},z_{\mathrm{f}j}} + O(\delta^2). \tag{3.C.1}$$

The sum of the covariances between the offspring production of focal female j and all other females, $\sum_{l\neq j}\sigma^{\mathrm{m}}_{\mathrm{f}jl}$, is the sum of their interactions (given by $\Upsilon^{\mathrm{m}}_{z_{\mathrm{m}i},z_{\mathrm{f}j},z_{\mathrm{f}l}}$) over every male. Approximated by expanding about average male phenotype and female phenotypes excluding female j ($\bar{z}_{-\mathrm{f}j}=\sum_{l\neq j}z_{\mathrm{f}l}/(N_{\mathrm{f}}-1)$), this gives

$$\sum_{l\neq j}\sigma^{\mathrm{m}}_{\mathrm{f}jl}=(N_{\mathrm{f}}-1)N_{\mathrm{m}}\Upsilon^{\mathrm{m}}_{\bar{z}_{\mathrm{m}},z_{\mathrm{f}j},\bar{z}_{-\mathrm{f}j}}+O(\delta^2). \tag{3.C.2}$$

The variance $\sigma^{\mathrm{m}}_{\mathrm{f}jj}$ in offspring production of focal female j approximated about average male phenotype is

$$\sigma^{\mathrm{m}}_{\mathrm{f}jj}=N_{\mathrm{m}}\Upsilon_{1\bar{z}_{\mathrm{m}},z_{\mathrm{f}j}}+N_{\mathrm{m}}(N_{\mathrm{m}}-1)\Upsilon^{\mathrm{f}}_{\bar{z}_{\mathrm{m}},z_{\mathrm{f}j},\bar{z}_{\mathrm{m}}}+O(\delta^2). \tag{3.C.3}$$

Finally, the sum of variance/covariances over every females different to j is given by

$$\sum_{k\neq j}\sum_{l\neq j}\sigma^{\mathrm{m}}_{\mathrm{f}kl}=(N_{\mathrm{f}}-1)N_{\mathrm{m}}\left(\Upsilon_{\bar{z}_{\mathrm{m}},\bar{z}_{-\mathrm{f}j}}+(N_{\mathrm{m}}-1)\Upsilon^{\mathrm{f}}_{\bar{z}_{\mathrm{m}},\bar{z}_{-\mathrm{f}j},\bar{z}_{\mathrm{m}}}+(N_{\mathrm{f}}-2)\Upsilon^{\mathrm{m}}_{\bar{z}_{\mathrm{m}},\bar{z}_{-\mathrm{f}j},\bar{z}_{-\mathrm{f}j}}\right)+O(\delta^2). \tag{3.C.4}$$

3.D Unconditional expected mutant frequency

Here the conditional expectations $\mathrm{E}[\overline{p}_{\mathrm{m},t+1}|\mathscr{P}_t]$ and $\mathrm{E}[\overline{p}_{\mathrm{f},t+1}|\mathscr{P}_t]$ are integrated over the probability distribution $\mathbb{P}_t$ of the realization $\mathscr{P}_t$, and we deduce eqs. (3.22) and (3.23) of the main text. In order to isolate the summary statistics of the realized frequency distribution of the mutant $\mathscr{P}_t$ required to evaluate the mutant allele frequency change, the sums over individuals in eq. (3.21) are Taylor-expanded about $\delta_{\mathrm{m}}=\delta_{\mathrm{f}}=0$ to the first order, and expressed in terms of population averages. To do so, we use two observations. First, the fitness function w^u_{vi} depends on three variables: the phenotype of the focal individual $z_{\mathrm{m}i}$ and the average male and female phenotypes in the population, $\bar{z}_{\mathrm{m}}$ and $\bar{z}_{\mathrm{f}}$. The derivatives of fitness in (3.21) with respect to δ_y is then found by using the chain rule over these variables $\partial w^u_{vi}/\partial\delta_y=(\partial w^u_{vi}/\partial z_{vi})dz_{vi}+(\partial w^u_{vi}/\partial\bar{z}_{\mathrm{m}})d\bar{z}_{\mathrm{m}}+(\partial w^u_{vi}/\partial\bar{z}_{\mathrm{f}})d\bar{z}_{\mathrm{f}}$, where the shorthand notation dx denotes the derivative $dx/d\delta_y$ of x with respect to δ. Second, because the derivatives of an individual's fitness with respect to phenotypic values ($\partial w^u_{vi}/\partial z$ with $z\in\{z_{vi},\bar{z}_{\mathrm{f}},\bar{z}_{\mathrm{m}}\}$) are not independent from one another, one of the derivatives may be expressed in terms of the other two. With the number of adults of either sex held constant at each generation, we must have $\partial w_{ui}/\partial z_{\mathrm{m}i}=-\partial w^u_{vi}/\partial\bar{z}_{\mathrm{m}}-\partial w^u_{vi}/\partial\bar{z}_{\mathrm{f}}$ (Rousset, 2004, p. 96). Using the latter to substitute for $\partial w^{\mathrm{m}}_{\mathrm{m}i}/\partial\bar{z}_{\mathrm{f}}$, $\partial w^{\mathrm{f}}_{\mathrm{m}i}/\partial\bar{z}_{\mathrm{f}}$, $\partial w^{\mathrm{f}}_{\mathrm{f}j}/\partial\bar{z}_{\mathrm{m}}$ and $\partial w_{\mathrm{m}j}/\partial\bar{z}_{\mathrm{m}}$, we obtain by way of a Taylor

expansion of (3.21) about $\delta_{\mathrm{m}} = \delta_{\mathrm{f}} = 0$:

$$\begin{aligned} \mathrm{E}[\overline{p}_{\mathrm{m},t+1}|\mathscr{P}_t] &= \frac{1}{2}(\overline{p}_{\mathrm{m},t} + \overline{p}_{\mathrm{f},t}) + \frac{1}{2}D_{\mathrm{m},t} + O(\delta^2) \\ \mathrm{E}[\overline{p}_{\mathrm{f},t+1}|\mathscr{P}_t] &= \frac{1}{2}(\overline{p}_{\mathrm{m},t} + \overline{p}_{\mathrm{f},t}) + \frac{1}{2}D_{\mathrm{f},t} + O(\delta^2) \end{aligned} \tag{3.D.5}$$

where

$$\begin{aligned} D_{\mathrm{m},t} =& \delta_{\mathrm{m}} \left(\frac{\partial w^{\mathrm{m}}_{\mathrm{m}i}}{\partial z_{\mathrm{m}i}} (\overline{p_{\mathrm{m}i} dz_{\mathrm{m}i}} - \overline{p}_{\mathrm{m}} d\overline{z}_{\mathrm{f}})_t + \frac{\partial w^{\mathrm{m}}_{\mathrm{m}i}}{\partial \overline{z}_{\mathrm{m}}} (\overline{p}_{\mathrm{m}} d\overline{z}_{\mathrm{m}} - \overline{p}_{\mathrm{m}} d\overline{z}_{\mathrm{f}})_t \right) \\ &+ \delta_{\mathrm{f}} \frac{N_{\mathrm{f}}}{N_{\mathrm{m}}} \left(\frac{\partial w^{\mathrm{m}}_{\mathrm{f}j}}{\partial z_{\mathrm{f}j}} (\overline{p_{\mathrm{f}j} dz_{\mathrm{f}j}} - p_{\mathrm{f}} d\overline{z}_{\mathrm{m}})_t + \frac{\partial w^{\mathrm{m}}_{\mathrm{f}j}}{\partial \overline{z}_{\mathrm{f}}} (\overline{p}_{\mathrm{f}} d\overline{z}_{\mathrm{f}} - \overline{p}_{\mathrm{f}} d\overline{z}_{\mathrm{m}})_t \right) \\ D_{\mathrm{f},t} =& \delta_{\mathrm{m}} \frac{N_{\mathrm{m}}}{N_{\mathrm{f}}} \left(\frac{\partial w^{\mathrm{f}}_{\mathrm{m}i}}{\partial z_{\mathrm{m}i}} (\overline{p_{\mathrm{m}i} dz_{\mathrm{m}i}} - \overline{p}_{\mathrm{m}} d\overline{z}_{\mathrm{f}})_t + \frac{\partial w^{\mathrm{f}}_{\mathrm{m}i}}{\partial \overline{z}_{\mathrm{m}}} (\overline{p}_{\mathrm{m}} d\overline{z}_{\mathrm{m}} - \overline{p}_{\mathrm{m}} d\overline{z}_{\mathrm{f}})_t \right) \\ &+ \delta_{\mathrm{f}} \left(\frac{\partial w^{\mathrm{f}}_{\mathrm{f}j}}{\partial z_{\mathrm{f}j}} (\overline{p_{\mathrm{f}j} dz_{\mathrm{f}j}} - \overline{p}_{\mathrm{f}} d\overline{z}_{\mathrm{m}})_t + \frac{\partial w^{\mathrm{f}}_{\mathrm{f}j}}{\partial \overline{z}_{\mathrm{f}}} (\overline{p}_{\mathrm{f}} d\overline{z}_{\mathrm{f}} - \overline{p}_{\mathrm{f}} d\overline{z}_{\mathrm{m}})_t \right) \end{aligned} \tag{3.D.6}$$

are the perturbations of mutant frequencies from the neutral trajectory induced by selection.

The effect of selection on expected allele frequency in the next generation, as seen in eqs. (3.D.5) and (3.D.6), is a sum of effects of the different phenotypes on fitness, weighted by statistics of $\mathscr{P}_t$ ($\overline{p_{\mathrm{m}i} dz_{\mathrm{m}i}}, \overline{p}_{\mathrm{m}} d\overline{z}_{\mathrm{f}}$, etc.). These statistics, once marginalized over the probability distribution $\mathbb{P}_t$ of $\mathscr{P}_t$, will provide the moments of the probability distribution $\mathbb{P}_t$ required to calculate the expected allele frequency change. Because expected allele frequency is approximated with δ close to 0, it is sufficient to evaluate all moments in $D_{\mathrm{m},t}$ and $D_{\mathrm{f},t}$ in the absence of phenotypic differences ($\delta_{\mathrm{m}} = \delta_{\mathrm{f}} = 0$). So it is sufficient to marginalize $\mathrm{E}[\overline{p}_{\mathrm{m},t+1}|\mathscr{P}_t]$ and $\mathrm{E}[\overline{p}_{\mathrm{f},t+1}|\mathscr{P}_t]$ for a neutral process ($\delta_{\mathrm{m}} = \delta_{\mathrm{f}} = 0$), and the expectation operator for this case is written $\overset{\circ}{\mathrm{E}}[\cdot]$. The unconditional expected mutant frequencies in males and females of the next generation are then given by $\mathrm{E}[\overline{p}_{\mathrm{m},t+1}] = \overset{\circ}{\mathrm{E}}[\mathrm{E}[\overline{p}_{\mathrm{m},t+1}|\mathscr{P}_t]] + O(\delta^2)$ and $\mathrm{E}[\overline{p}_{\mathrm{f},t+1}] = \overset{\circ}{\mathrm{E}}[\mathrm{E}[\overline{p}_{\mathrm{f},t+1}|\mathscr{P}_t]] + O(\delta^2)$, respectively. Eqs. (3.D.5) and (3.D.6) then indicate that we need to characterize the moments $\overset{\circ}{\mathrm{E}}[\overline{p_{\mathrm{m}i} dz_{\mathrm{m}i}}]$, $\overset{\circ}{\mathrm{E}}[\overline{p_{\mathrm{f}j} dz_{\mathrm{f}j}}]$, $\overset{\circ}{\mathrm{E}}[\overline{p}_{\mathrm{m}} d\overline{z}_{\mathrm{f}}]$, $\overset{\circ}{\mathrm{E}}[\overline{p}_{\mathrm{f}} d\overline{z}_{\mathrm{m}}]$, $\overset{\circ}{\mathrm{E}}[\overline{p}_{\mathrm{m}} d\overline{z}_{\mathrm{m}}]$, and $\overset{\circ}{\mathrm{E}}[\overline{p}_{\mathrm{f}} d\overline{z}_{\mathrm{f}}]$ in order to evaluate $\mathrm{E}[\overline{p}_{\mathrm{m},t+1}]$ and $\mathrm{E}[\overline{p}_{\mathrm{f},t+1}]$. To do this, we first use eq. (3.2) to write the average male and female phenotypic values as $\overline{z}_{\mathrm{m}} = \sum_i z_{\mathrm{m}i}/N_{\mathrm{m}} = z_{aa} + \delta(2h\overline{p}_{\mathrm{m},t} + (1-2h)\overline{\mathbb{1}_{\male i}\mathbb{1}_{\female i_t}})$ and $\overline{z}_{\mathrm{f}} = \sum_j z_{\mathrm{f}j}/N_{\mathrm{f}} = z_{aa} + \delta(2h\overline{p}_{\mathrm{f},t} + (1-2h)\overline{\mathbb{1}_{\male j}\mathbb{1}_{\female j t}})$. We can then obtain the derivatives with respect to δ of these

averages and the phenotype of male i, which are needed for the population statistics, as

$$dz_{\mathrm{m}i} = 2hp_{\mathrm{m}i} + (1-2h)\mathbb{1}_{\male i}\mathbb{1}_{\female i},\ d\bar{z}_{\mathrm{m}} = 2h\bar{p}_{\mathrm{m},t} + (1-2h)\overline{\mathbb{1}_{\male i}\mathbb{1}_{\female i}}_t,\ d\bar{z}_{\mathrm{f}} = 2h\bar{p}_{\mathrm{f},t} + (1-2h)\overline{\mathbb{1}_{\male j}\mathbb{1}_{\female j}}_t. \tag{3.D.7}$$

3.D.1 $\overset{\circ}{\mathrm{E}}[\overline{p_{\mathrm{m}i}dz_{\mathrm{m}i}}]$ and $\overset{\circ}{\mathrm{E}}[\overline{p_{\mathrm{f}j}dz_{\mathrm{f}j}}]$

We first consider the two expectations: $\overset{\circ}{\mathrm{E}}[\overline{p_{\mathrm{m}i}dz_{\mathrm{m}i}}]$ and $\overset{\circ}{\mathrm{E}}[\overline{p_{\mathrm{f}j}dz_{\mathrm{f}j}}]$ at generation t. Expanding the mutant frequency in terms of indicator variables for paternally and maternally inherited alleles, using eq. (3.1) together with eq. (3.D.7), we have

$$\begin{aligned}
\overset{\circ}{\mathrm{E}}[\overline{p_{\mathrm{m}i}dz_{\mathrm{m}i}}]_t &= \overset{\circ}{\mathrm{E}}\left[\overline{\frac{\mathbb{1}_{\male i}+\mathbb{1}_{\female i}}{2}\left(h(\mathbb{1}_{\male i}+\mathbb{1}_{\female i})+(1-2h)\mathbb{1}_{\male i}\mathbb{1}_{\female i}\right)}\right]_t \\
\overset{\circ}{\mathrm{E}}[\overline{p_{\mathrm{f}j}dz_{\mathrm{f}j}}]_t &= \overset{\circ}{\mathrm{E}}\left[\overline{\frac{\mathbb{1}_{\male j}+\mathbb{1}_{\female j}}{2}\left(h(\mathbb{1}_{\male j}+\mathbb{1}_{\female j})+(1-2h)\mathbb{1}_{\male j}\mathbb{1}_{\female j}\right)}\right]_t,
\end{aligned}$$

where in the first equation, the averaging is over the males and in the second over the females. Expanding, we have $\overset{\circ}{\mathrm{E}}[\overline{p_{\mathrm{m}i}dz_{\mathrm{m}i}}]_t = \overset{\circ}{\mathrm{E}}[h/2(\mathbb{1}_{\male i}+2\mathbb{1}_{\male i}\mathbb{1}_{\female i}+\mathbb{1}_{\female i})+(1-2h)\mathbb{1}_{\male i}\mathbb{1}_{\female i}]_t$, or more succinctly

$$\begin{aligned}
\overset{\circ}{\mathrm{E}}[\overline{p_{\mathrm{m}i}dz_{\mathrm{m}i}}]_t &= h(p_{\mathrm{m},t}+\eta_t^H)+(1-2h)\eta_t^H \\
\overset{\circ}{\mathrm{E}}[\overline{p_{\mathrm{f}j}dz_{\mathrm{f}j}}] &= h(p_{\mathrm{f},t}+\eta_t^H)+(1-2h)\eta_t^H,
\end{aligned} \tag{3.D.8}$$

where $\eta^H = \overset{\circ}{\mathrm{E}}[\mathbb{1}_{\male i}\mathbb{1}_{\female i}]$ is the probability that both the paternal and maternal alleles of an individual are mutants. In the absence of phenotypic differences, this probability is equal for all individuals $\overset{\circ}{\mathrm{E}}[\mathbb{1}_{\male i}\mathbb{1}_{\female i}] = \overset{\circ}{\mathrm{E}}[\mathbb{1}_{\male k}\mathbb{1}_{\female k}]$ for all i and k and irrespective of the sexes of the individuals. To see this, consider the recurrence for η^H over one generation: $\eta_{t+1}^H = \overset{\circ}{\mathrm{E}}[\mathbb{1}_{\male i}\mathbb{1}_{\female i}]_{t+1}$. Assuming individual i of generation $t+1$ has father indexed a and mother indexed c at generation t, we may write

$$\eta_{t+1}^H = \frac{1}{4}\overset{\circ}{\mathrm{E}}[(\mathbb{1}_{\male a}+\mathbb{1}_{\female a})(\mathbb{1}_{\male c}+\mathbb{1}_{\female c})]_t, \tag{3.D.9}$$

since the paternally inherited mutant of i is equally likely the paternally or the maternally inherited mutant of its father a, and the maternally inherited mutant of i is equally likely the paternally or the maternally inherited mutant of its mother c. This argument holds whatever the sex of i, so $\eta^H = \overset{\circ}{\mathrm{E}}[\mathbb{1}_{\male i}\mathbb{1}_{\female i}]$ does not depend on the sex of individual i.

3.D.2 $\overset{\circ}{\mathrm{E}}[\overline{p}_{\mathrm{m}} d\overline{z}_{\mathrm{f}}]$ and $\overset{\circ}{\mathrm{E}}[\overline{p}_{\mathrm{f}} d\overline{z}_{\mathrm{m}}]$

We now develop $\overset{\circ}{\mathrm{E}}[\overline{p}_{\mathrm{m}} d\overline{z}_{\mathrm{f}}]$ and $\overset{\circ}{\mathrm{E}}[\overline{p}_{\mathrm{f}} d\overline{z}_{\mathrm{m}}]$. Substituting for $\overline{p}_{\mathrm{m}} d\overline{z}_{\mathrm{f}}$ and $\overline{p}_{\mathrm{f}} d\overline{z}_{\mathrm{m}}$ using eqs. (3.1) and (3.D.7), we have

$$\begin{aligned}
\overset{\circ}{\mathrm{E}}[p_{\mathrm{m}} d\overline{z}_{\mathrm{f}}]_t &= \overset{\circ}{\mathrm{E}}\left[\frac{\overline{\mathbb{1}_{\male i} + \mathbb{1}_{\female i}}}{2}\left(h(\overline{\mathbb{1}_{\male j} + \mathbb{1}_{\female j}}) + (1-2h)\overline{\mathbb{1}_{\male j}\mathbb{1}_{\female j}}\right)\right]_t \\
\overset{\circ}{\mathrm{E}}[p_{\mathrm{f}} d\overline{z}_{\mathrm{m}}]_t &= \overset{\circ}{\mathrm{E}}\left[\frac{\overline{\mathbb{1}_{\male j} + \mathbb{1}_{\female j}}}{2}\left(h(\overline{\mathbb{1}_{\male i} + \mathbb{1}_{\female i}}) + (1-2h)\overline{\mathbb{1}_{\male i}\mathbb{1}_{\female i}}\right)\right]_t,
\end{aligned}$$

where the averaging of terms with subscript i is over males ($\overline{x_i} = \sum_{i=1}^{N_{\mathrm{m}}} x_i$) and the averaging of terms with subscript j is over females ($\overline{x_j} = \sum_{j=1}^{N_{\mathrm{f}}} x_j$). Expanding the sums as $\overset{\circ}{\mathrm{E}}[\overline{p}_{\mathrm{m}} d\overline{z}_{\mathrm{f}}]_t = \sum_i \sum_j \overset{\circ}{\mathrm{E}}[h/2(\mathbb{1}_{\male i}\mathbb{1}_{\female j} + \mathbb{1}_{\male i}\mathbb{1}_{\male j} + \mathbb{1}_{\female i}\mathbb{1}_{\male j} + \mathbb{1}_{\female i}\mathbb{1}_{\female j}) + (1-2h)/2(\mathbb{1}_{\male i}\mathbb{1}_{\male j}\mathbb{1}_{\female j} + \mathbb{1}_{\male j}\mathbb{1}_{\female j}\mathbb{1}_{\female i})]_t$, we obtain an expression of the form

$$\overset{\circ}{\mathrm{E}}[\overline{p}_{\mathrm{m}} d\overline{z}_{\mathrm{f}}]_t = \overset{\circ}{\mathrm{E}}[\overline{p}_{\mathrm{f}} d\overline{z}_{\mathrm{m}}]_t = h\left(\eta_t + \frac{\kappa_t^{\male} + \kappa_t^{\female}}{2}\right) + (1-2h)\frac{\rho_t^{\male} + \rho_t^{\female}}{2}. \tag{3.D.10}$$

Here, $\eta = \overset{\circ}{\mathrm{E}}[\mathbb{1}_{\male i}\mathbb{1}_{\female j}] = \overset{\circ}{\mathrm{E}}[\mathbb{1}_{\male j}\mathbb{1}_{\female i}]$ is the probability that a paternally inherited allele and a maternally inherited allele of two different, randomly sampled individuals are mutants. Further, $\kappa^{\male} = \overset{\circ}{\mathrm{E}}[\mathbb{1}_{\male i}\mathbb{1}_{\male j}]$ is the probability that a randomly sampled male i and a randomly sampled female j both have inherited the mutant alleles from their fathers, and $\kappa^{\female} = \overset{\circ}{\mathrm{E}}[\mathbb{1}_{\female i}\mathbb{1}_{\female j}]$ is the probability that randomly sampled male i and female j both have inherited the mutant alleles from their mothers. Finally, $\rho^{\male} = \overset{\circ}{\mathrm{E}}[\mathbb{1}_{\male i}\mathbb{1}_{\male j}\mathbb{1}_{\female j}]$ is the probability that randomly sampled male i has inherited the mutant from its father and that randomly sampled female j is homozygous for the mutant, and $\rho^{\female} = \overset{\circ}{\mathrm{E}}[\mathbb{1}_{\female j}\mathbb{1}_{\male j}\mathbb{1}_{\female i}]$ is the probability that randomly sampled male i has inherited the mutant from its mother and that randomly sampled female j is homozygous for the mutant.

Following the same argument used above to show that the probability that the two genes of an individual are mutants (η^H) is equal for males and female at every generation (eq. 3.D.9), we find that η^H is equal to the probability η that the maternal gene of one individual and the paternal gene of another individual are both mutants, $\eta = \eta^H$. So, for ease of presentation in subsequent calculations and in the main text, we drop the superscript H and only use η. In addition, by using a similar argument as in eq. (3.D.9), one can show that the other probabilities ($\kappa^{\male}, \kappa^{\female}, \rho^{\male}$ and $\rho^{\female}$) are also independent of the sex of the individuals considered at every generation (see appendices 3.E and 3.F). For instance, the probability $\kappa^{\male} = \overset{\circ}{\mathrm{E}}[\mathbb{1}_{\male i}\mathbb{1}_{\male j}]$ that a randomly sampled individual

i and a randomly sampled individual j both have inherited the mutant alleles from their fathers is the same, independently of whether i and j are both males, both females, or one male and one female.

3.D.3 $\overset{\circ}{\mathrm{E}}[\overline{p}_{\mathrm{m}} d\overline{z}_{\mathrm{m}}]$ and $\overset{\circ}{\mathrm{E}}[\overline{p}_{\mathrm{f}} d\overline{z}_{\mathrm{f}}]$

The other expectations we need to evaluate are $\overset{\circ}{\mathrm{E}}[\overline{p}_{\mathrm{m}} d\overline{z}_{\mathrm{m}}]$ and $\overset{\circ}{\mathrm{E}}[\overline{p}_{\mathrm{f}} d\overline{z}_{\mathrm{f}}]$. Using eq. (3.D.7) and rearranging to collect the terms that involve the same male i, and those that involve two different males i and k, we have $\overset{\circ}{\mathrm{E}}[\overline{p}_{\mathrm{m}} d\overline{z}_{\mathrm{m}}]_t = \overset{\circ}{\mathrm{E}}[2h/N_{\mathrm{m}}^2(\sum_i p_{\mathrm{m}i}^2 + \sum_{i,k,i\neq k} p_{\mathrm{m}i}p_k) + (1-2h)/(N_{\mathrm{m}}^2)(\sum_i p_{\mathrm{m}i}\mathbb{1}_{\male i}\mathbb{1}_{\female i} + \sum_{i,k,i\neq k} p_{\mathrm{m}i}\mathbb{1}_{\male k}\mathbb{1}_{\female k})]_t$. Letting expectation run through gives $2h/N_{\mathrm{m}}(\overset{\circ}{\mathrm{E}}[\overline{p_{\mathrm{m}i}^2}]_t + (N_{\mathrm{m}}-1)\overset{\circ}{\mathrm{E}}[\overline{p_{\mathrm{m}i}p_k}]_t) + (1-2h)/N_{\mathrm{m}}(\overset{\circ}{\mathrm{E}}[\overline{p_{\mathrm{m}i}\mathbb{1}_{\male i}\mathbb{1}_{\female i}}]_t + (N_{\mathrm{m}}-1)\overset{\circ}{\mathrm{E}}[\overline{p_{\mathrm{m}i}\mathbb{1}_{\male k}\mathbb{1}_{\female k}}]_t)$ where $i \neq k$. Finally, factoring by $1/N_{\mathrm{m}}$ yields

$$\begin{aligned}\overset{\circ}{\mathrm{E}}[\overline{p}_{\mathrm{m}} d\overline{z}_{\mathrm{m}}]_t = \frac{1}{N_{\mathrm{m}}}\Bigg(&2h\left(\overset{\circ}{\mathrm{E}}[\overline{p_{\mathrm{m}i}^2}]_t - \overset{\circ}{\mathrm{E}}[\overline{p_{\mathrm{m}i}p_k}]_t\right) + (1-2h)\left(\overset{\circ}{\mathrm{E}}[\overline{p_{\mathrm{m}i}\mathbb{1}_{\male i}\mathbb{1}_{\female i}}]_t - \overset{\circ}{\mathrm{E}}[\overline{p_{\mathrm{m}i}\mathbb{1}_{\male k}\mathbb{1}_{\female k}}]_t\right)\Bigg)\\ &+ 2h\,\overset{\circ}{\mathrm{E}}[\overline{p_{\mathrm{m}i}p_k}]_t + (1-2h)\,\overset{\circ}{\mathrm{E}}[\overline{p_{\mathrm{m}i}\mathbb{1}_{\male k}\mathbb{1}_{\female k}}]_t.\end{aligned} \tag{3.D.11}$$

Expanding in terms of indicator variables for paternally and maternally inherited alleles, we have for each term $\overset{\circ}{\mathrm{E}}[p_{\mathrm{m}i}^2] = \overset{\circ}{\mathrm{E}}[(\mathbb{1}_{\male i} + \mathbb{1}_{\female i} + 2\mathbb{1}_{\male i}\mathbb{1}_{\female i})/4] = (p_{\mathrm{m}} + \eta)/2$; $\overset{\circ}{\mathrm{E}}[p_{\mathrm{m}i}p_k] = (2\eta + \kappa^{\male} + \kappa^{\female})/4$, $\overset{\circ}{\mathrm{E}}[p_{\mathrm{m}i}\mathbb{1}_{\male i}\mathbb{1}_{\female i}] = \eta$, and finally $\overset{\circ}{\mathrm{E}}[p_{\mathrm{m}i}\mathbb{1}_{\male k}\mathbb{1}_{\female k}] = (\rho^{\male} + \rho^{\female})/2$. So that after using the similar argument for $\overset{\circ}{\mathrm{E}}[p_{\mathrm{f}} d\overline{z}_{\mathrm{f}}]$, we find that at generation t

$$\begin{aligned}\overset{\circ}{\mathrm{E}}[\overline{p}_{\mathrm{m}} d\overline{z}_{\mathrm{m}}]_t &= \frac{1}{N_{\mathrm{m}}}\left\{h\left(p_{\mathrm{m},t} - \frac{\kappa_t^{\male} + \kappa_t^{\female}}{2}\right) + (1-2h)\left(\eta_t - \frac{\rho_t^{\male} + \rho_t^{\female}}{2}\right)\right\}\\ &\quad + h\left(\eta_t + \frac{\kappa_t^{\male} + \kappa_t^{\female}}{2}\right) + (1-2h)\left(\frac{\rho_t^{\male} + \rho_t^{\female}}{2}\right),\\ \overset{\circ}{\mathrm{E}}[\overline{p}_{\mathrm{f}} d\overline{z}_{\mathrm{f}}]_t &= \frac{1}{N_{\mathrm{f}}}\left\{h\left(p_{\mathrm{f},t} - \frac{\kappa_t^{\male} + \kappa_t^{\female}}{2}\right) + (1-2h)\left(\eta_t - \frac{\rho_t^{\male} + \rho_t^{\female}}{2}\right)\right\}\\ &\quad + h\left(\eta_t + \frac{\kappa_t^{\male} + \kappa_t^{\female}}{2}\right) + (1-2h)\left(\frac{\rho_t^{\male} + \rho_t^{\female}}{2}\right).\end{aligned} \tag{3.D.12}$$

We now have all elements to express $\mathrm{E}[\overline{p}_{\mathrm{m},t+1}]$ and $\mathrm{E}[\overline{p}_{\mathrm{f},t+1}]$ in terms of neutral moments, all of which can be defined iteratively (i.e. from one generation to the next). Substituting eqs. (3.D.8), (3.D.10), (3.D.12) into the conditional expected frequency change eq. (3.D.5) (3.D.6) then yields the unconditional expected mutant frequency eqs. (3.22) and (3.23) of the main text.

3.E Recursions for the moments of allelic state

The moments η_t^H, $\kappa_t^{\male}$, $\kappa_t^{\female}$, $\rho_t^{\male}$, and $\rho_t^{\female}$ of the population genetic state, which appear in the expected mutant frequency change (eq. 3.23), are related to one another through their expected change from one generation to the next (Karlin, 1968). The resulting linear recurrences allow us to construct the matrix of neutral allelic frequency change $\mathbf{A}^\circ$ appearing in eq. (3.24). We now consider the recurrences of each of these moments, and define a further eight moments in order to close the recurrences.

3.E.1 p_{m} and p_{f}

In the absence of phenotypic differences, a randomly sampled gene in an individual at $t+1$ comes with equal probability from its father or its mother, so it is mutant with probability

$$p_{\mathrm{m},t+1} = p_{\mathrm{f},t+1} = \frac{1}{2}\left(\overset{\circ}{\mathrm{E}}\left[\mathbb{1}_{\male i} + \mathbb{1}_{\male i}\right]_t\right) = \frac{1}{2}(p_{\mathrm{m},t} + p_{\mathrm{f},t}). \tag{3.E.13}$$

3.E.2 η

The probability that the paternally and the maternally inherited allele of individual i at time $t+1$ are both mutant, η_{t+1}, is given in terms of neutral moments of gene frequency at generation t in eq. (3.D.9) which, if expanded and using previous definitions, gives

$$\eta_{t+1} = \frac{1}{4}(2\eta_t + \kappa_t^{\male} + \kappa_t^{\female}). \tag{3.E.14}$$

3.E.3 κ

Wether two paternally inherited alleles randomly sampled in two different individuals are both mutants at generation $t+1$, $\kappa_{t+1}^{\male}$, depends on wether the two individuals have the same father, which occurs with a probability denoted $\Theta^{\male}$ or not (which occurs with probability $1-\Theta^{\male}$). If two individuals have the same father, which we index a, then their paternal alleles can be either both copies of the paternal gene of a (with probability $1/4$), both copies of the maternal gene of a (with probability $1/4$), or one is a paternal copy and one is a maternal copy (with probability $1/2$). So, if two individuals have the same father, their two paternally sampled genes are mutants with probability $(1/4)\overset{\circ}{\mathrm{E}}\left[(\mathbb{1}_{\male a} + \mathbb{1}_{\female a})^2\right]_t$. If they have different fathers, indexed a and b, then the paternal copy of the first individual may be the paternal or maternal copy of a (each with

probability $1/2$) and the paternal copy of the second individual may be the paternal or maternal copy of b (also each with probability $1/2$). In this case, the two individuals' paternal alleles are both mutants with probability $(1/4)\overset{\circ}{\mathrm{E}}[(\mathbb{1}_{\male a}+\mathbb{1}_{\female a})(\mathbb{1}_{\male b}+\mathbb{1}_{\female b})]_t$. Combining these two cases, the probability that to randomly sampled paternal alleles at generation $t+1$ are mutants is $\kappa^{\male}_{t+1}=\Theta^{\male}(1/4)\overset{\circ}{\mathrm{E}}[(\mathbb{1}_{\male a}+\mathbb{1}_{\female a})^2]_t+(1-\Theta^{\male})(1/4)\overset{\circ}{\mathrm{E}}[(\mathbb{1}_{\male a}+\mathbb{1}_{\female a})(\mathbb{1}_{\male b}+\mathbb{1}_{\female b})]_t$ which, after letting expectation $\overset{\circ}{\mathrm{E}}[.]$ run through and using previous definitions, gives

$$\kappa^{\male}_{t+1}=\frac{\Theta^{\male}}{4}(p_{\mathrm{m},t}+p_{\mathrm{f},t}+2\eta_t)+\frac{1-\Theta^{\male}}{4}(\kappa^{\male}_t+\kappa^{\female}_t+2\eta_t). \tag{3.E.15}$$

This probability depends on the sexes of the individuals form which alleles are sampled only if the probabilities of having the same father ($\Theta^{\male}$) differ between males and females. However, we show in 3.F.1 that the probability of having a same parent is independent of sex, implying that $\kappa^{\male}_{t+1}$ is valid for paternally genes sampled in pairs of individual of any sex. Using a similar argument for the probability that two maternal alleles randomly sampled in two different individuals are both mutants, we find

$$\kappa^{\female}_{t+1}=\frac{\Theta^{\female}}{4}(p_{\mathrm{m},t}+p_{\mathrm{f},t}+2\eta_t)+\frac{1-\Theta^{\female}}{4}(\kappa^{\male}_t+\kappa^{\female}_t+2\eta_t), \tag{3.E.16}$$

where $\Theta^{\female}$ is the probability that two individuals have the same mother.

3.E.4 ρ

The probability $\rho^{\male}_{t+1}=\overset{\circ}{\mathrm{E}}[\mathbb{1}_{\male i}\mathbb{1}_{\male j}\mathbb{1}_{\female k}]_{t+1}$ that two (different) paternally inherited alleles and one maternally inherited allele at generation $t+1$ are mutants depends on whether individuals i and j from which the paternal alleles are sampled have the same father (indexed a) or different fathers (a and b). Using a similar argument as in the preceding section, and indexing by c the mother of the individual who holds the maternal allele, we have $\rho^{\male}_{t+1}=\Theta^{\male}(1/8)\overset{\circ}{\mathrm{E}}[(\mathbb{1}_{\male a}+\mathbb{1}_{\female a})^2(\mathbb{1}_{\male c}+\mathbb{1}_{\female c})]_t+(1-\Theta^{\male})(1/8)\overset{\circ}{\mathrm{E}}[(\mathbb{1}_{\male a}+\mathbb{1}_{\female a})(\mathbb{1}_{\male b}+\mathbb{1}_{\female b})(\mathbb{1}_{\male c}+\mathbb{1}_{\female c})]_t$. Then, expanding and letting expectation run through, we have:

$$\rho^{\male}_{t+1}=\frac{\Theta^{\male}}{8}\left(2\eta_t+\kappa^{\male}_t+\kappa^{\female}_t+2\rho^{\male}_t+2\rho^{\female}_t\right)+\frac{1-\Theta^{\male}_x}{8}\left(\varsigma^{\male}_{2\mathrm{m},t}+\varsigma^{\female}_{2\mathrm{m},t}+3\rho^{\male}_t+3\rho^{\female}_t\right) \tag{3.E.17}$$

where $\varsigma^{\male}_{2\mathrm{m},t}=\overset{\circ}{\mathrm{E}}[\mathbb{1}_{\male a}\mathbb{1}_{\male b}\mathbb{1}_{\male c}]_t$ and $\varsigma^{\female}_{2\mathrm{m},t}=\overset{\circ}{\mathrm{E}}[\mathbb{1}_{\female a}\mathbb{1}_{\female b}\mathbb{1}_{\female c}]_t$ are the probabilities that the paternal and maternal alleles, respectively, of two randomly sampled (without replacement) males a and b

and a female c at generation t are all mutants.

Similarly, the probability that two (different) maternally inherited alleles and one paternally inherited allele from two individuals are mutants at generation $t+1$, $\rho^{\female}_{t+1} = \mathring{\mathrm{E}}\left[\mathbb{1}_{\female i}\mathbb{1}_{\female j}\mathbb{1}_{\male k}\right]_{t+1}$, depends on whether individuals i and j from which maternal genes are sampled have the same mother (indexed c) or different mothers (c and d), $\rho^{\female}_{t+1} = \Theta^{\female}(1/8)\,\mathring{\mathrm{E}}\left[(\mathbb{1}_{\male c}+\mathbb{1}_{\female c})^2(\mathbb{1}_{\male a}+\mathbb{1}_{\female a})\right]_t + (1-\Theta^{\female})(1/8)\,\mathring{\mathrm{E}}\left[(\mathbb{1}_{\male c}+\mathbb{1}_{\female c})(\mathbb{1}_{\male d}+\mathbb{1}_{\female d})(\mathbb{1}_{\male a}+\mathbb{1}_{\female a})\right]_t$, where a is the father of the individual whose paternal gene is sampled. Then

$$\rho^{\female}_{t+1} = \frac{\Theta^{\female}}{8}\left(2\eta_t + \kappa^{\male}_t + \kappa^{\female}_t + 2\rho^{\male}_t + 2\rho^{\female}_t\right) + \frac{1-\Theta^{\female}}{8}\left(\varsigma^{\male}_{2\mathrm{f},t} + \varsigma^{\female}_{2\mathrm{f},t} + 3\rho^{\male}_t + 3\rho^{\female}_t\right), \quad (3.E.18)$$

where $\varsigma^{\male}_{2\mathrm{f},t} = \mathring{\mathrm{E}}\left[\mathbb{1}_{\male a}\mathbb{1}_{\male c}\mathbb{1}_{\male d}\right]_t$ and $\varsigma^{\female}_{2\mathrm{f},t} = \mathring{\mathrm{E}}\left[\mathbb{1}_{\female a}\mathbb{1}_{\female c}\mathbb{1}_{\female d}\right]_t$ are the probabilities that the paternal and maternal alleles, respectively, of a male a and of two different females c and d at generation t are all mutants.

3.E.5 ς

The moments presented so far (p, η, κ, ρ) all appear in eq. (3.23) for the expected mutant allele frequency. In order to characterize their recurrence over a generation, four additional moments $\varsigma^{\male}_{2\mathrm{m},t}$, $\varsigma^{\female}_{2\mathrm{m},t}$, $\varsigma^{\male}_{2\mathrm{f},t}$, and $\varsigma^{\female}_{2\mathrm{f},t}$ were defined. We now consider the recurrences of these terms and find that a further four moments are needed to close the recurrence system.

The recurrence of the probability that three alleles sampled from different individuals are mutants depends on the probabilities of sibship of three individuals. Unlike the probabilities of sibship of two individuals ($\Theta^{\male}$ and $\Theta^{\female}$), the probabilities of sibship of three individuals depend on the sexes of the carriers, as is shown in appendix 3.F.2. So to consider the iteration of the probability $\varsigma^{\male}_x$ that three randomly chosen paternally inherited genes are mutants, we need to separate the cases where all three individuals are males (subscript $x = 3\mathrm{m}$), all three are females ($x = 3\mathrm{f}$), two are males and one is female ($x = 2\mathrm{m}$), or two are females and one is male ($x = 2\mathrm{f}$). The probabilities that three paternal alleles are mutants then depend on wether all three individuals have the same father, which occurs with a probability we write as $\Xi 3^{\male}_x$, whether only two have a same father (with probability $\Xi 2^{\male}_x$), or if none of the three have the same father (with probability $1 - \Xi 3^{\male}_x - \Xi 2^{\male}_x$). If they all have the same father (indexed a), then they are all mutants if they have inherited the mutant gene from the maternal or paternal locus from a. And similar arguments apply for the case when only two have the same father (indexed a, and the other father is indexed

b) or if they have three different fathers (indexed a, b and c) to give

$$\begin{aligned}\varsigma^{\male}_{x,t+1} = \frac{\Xi 3^{\male}_x}{8} \overset{\circ}{\mathrm{E}}\left[(\mathbb{1}_{\male a} + \mathbb{1}_{\female a})^3\right]_t + \frac{\Xi 2^{\male}_x}{8} \overset{\circ}{\mathrm{E}}\left[(\mathbb{1}_{\male a} + \mathbb{1}_{\female a})^2(\mathbb{1}_{\male b} + \mathbb{1}_{\female b})\right]_t \\ + \frac{1 - \Xi 3^{\male}_x - \Xi 2^{\male}_x}{8} \overset{\circ}{\mathrm{E}}\left[(\mathbb{1}_{\male a} + \mathbb{1}_{\female a})(\mathbb{1}_{\male b} + \mathbb{1}_{\female b})(\mathbb{1}_{\male c} + \mathbb{1}_{\female c})\right]_t\end{aligned} \tag{3.E.19}$$

which, expanding and letting expectation run through, results in

$$\begin{aligned}\varsigma^{\male}_{x,t+1} = \frac{\Xi 3^{\male}_x}{8}(p_{\mathrm{m},t} + p_{\mathrm{f},t} + 6\eta_t) + \frac{\Xi 2^{\male}_x}{8}(2\eta_t + \kappa^{\male}_t + \kappa^{\female}_t + 2\rho^{\male}_t + 2\rho^{\female}_t) \\ + \frac{1 - \Xi 3^{\male}_x - \Xi 2^{\male}_x}{8}(\varsigma^{\male}_{3\mathrm{m},t} + \varsigma^{\female}_{3\mathrm{m},t} + 3\rho^{\male}_t + 3\rho^{\female}_t).\end{aligned} \tag{3.E.20}$$

Similarly, the probability that three randomly chosen maternally inherited genes $\varsigma^{\female}_x$ are mutants can be expressed in terms of the probabilities that the individuals have the same mother,

$$\begin{aligned}\varsigma^{\female}_{x,t+1} = \frac{\Xi 3^{\female}_x}{8}(p_{\mathrm{m},t} + p_{\mathrm{f},t} + 6\eta_t) + \frac{\Xi 2^{\female}_x}{8}(2\eta_t + \kappa^{\male}_t + \kappa^{\female}_t + 2\rho^{\male}_t + 2\rho^{\female}_t) \\ + \frac{1 - \Xi 3^{\female}_x - \Xi 2^{\female}_x}{8}(\varsigma^{\male}_{3\mathrm{f},t} + \varsigma^{\female}_{3\mathrm{f},t} + 3\rho^{\male}_t + 3\rho^{\female}_t)\end{aligned} \tag{3.E.21}$$

where $\Xi 3^{\female}_x$ is the probability that the three holders (whose sexes are given by $x \in \{3\mathrm{m}, 3\mathrm{f}, 2\mathrm{m}, 2\mathrm{f}\}$) have the same mother, and $\Xi 2^{\female}_x$ is the probability that out of the three individuals, two have the same mother. The moments $\varsigma^{\male}_{x,t+1}$ and $\varsigma^{\female}_{x,t+1}$ ($x \in \{3\mathrm{m}, 3\mathrm{f}, 2\mathrm{m}, 2\mathrm{f}\}$) complete the necessary moments to close the system of neutral allelic frequency change over one generation. The full system of recurrence equations determines the matrix $\mathbf{A}^\circ$ of eq. (3.24). The matrix $\mathbf{A}^\circ$ is given in terms of probabilities of sibship in appendix 3.G.

3.F Probabilities of sibship

Here, we calculate the probabilities that two or three adults have the same parent, which appear in the neutral transition matrix $\mathbf{A}^\circ$ of the main text. We show that that when approximated to the order $1/N$, the probabilities that two individuals have the same father or the same mother are independent of the sexes of the individuals considered.

3.F.1 Probabilities that two individuals are sibs

3.F.1.1 Probability that two males have the same father

The probability that two randomly sampled adult males have the same father, $\Theta_{\mathrm{m}}^{\male}$, is given by the expected value of the ratio of the number of ways two individuals may be sampled from the number of adult males produced by each male, to the number of ways of sampling two males out of the entire male population. That is, $\Theta_{\mathrm{m}}^{\male} = \overset{\circ}{\mathrm{E}}\left[\sum_{i=1}^{N_{\mathrm{m}}} \binom{W_{\mathrm{m}i}^{\mathrm{m}}}{2} / \binom{N_{\mathrm{m}}}{2}\right]$, where $W_{\mathrm{m}i}^{\mathrm{m}}$ is the random variable for the number of male breeders produced by male i. In the absence of phenotypic differences, each male has the same distribution for their reproductive output, so the sum may be taken out in $\Theta_{\mathrm{m}}^{\male}$, and the subscript i now denotes a randomly sampled male: $1/(N_{\mathrm{m}}-1)\left[\overset{\circ}{\mathrm{V}}[W_{\mathrm{m}i}^{\mathrm{m}}] + \overset{\circ}{\mathrm{E}}[W_{\mathrm{m}i}^{\mathrm{m}}](\overset{\circ}{\mathrm{E}}[W_{\mathrm{m}i}^{\mathrm{m}}]-1)\right]$. The expected number of male adults produced by a male in the absence of phenotypic differences, $\overset{\circ}{\mathrm{E}}[W_{\mathrm{m}i}^{\mathrm{m}}] = 1$, so the probability that two randomly sampled adult males have the same father reduces to $\Theta_{\mathrm{m}}^{\male} = \overset{\circ}{\mathrm{V}}[W_{\mathrm{m}i}^{\mathrm{m}}]/(N_{\mathrm{m}}-1)$.

Conditioning on the number of male juveniles produced in the population, and using the law of total variance, we find that

$$\Theta_{\mathrm{m}}^{\male} = 1/(N_{\mathrm{m}}-1)(N_{\mathrm{m}}^2 \overset{\circ}{\mathrm{V}}[J_{\mathrm{m}i}^{\mathrm{m}}/J_{\mathrm{m}}] + \overset{\circ}{\mathrm{E}}[\overset{\circ}{\mathrm{V}}[W_{\mathrm{m}i}^{\mathrm{m}}|J_{\mathrm{m}i}^{\mathrm{m}}, J_{\mathrm{m}}]]). \tag{3.F.1}$$

The second variance term in this eq. (3.F.1) depends on how culling or regulation is assumed to take place. We assume here that culling occurs by sampling without replacement. In this case, $W_{\mathrm{m}i}^{\mathrm{m}}$ follows a hypergeometric distribution with N_{m} draws and parameters given by the realization of $\mathbf{J}_{\mathrm{m}}^{\mathrm{m}}$, with initial probability of success $J_{\mathrm{m}i}^{\mathrm{m}}/J_{\mathrm{m}}$ and a total population size of J_{m}. Then, $\overset{\circ}{\mathrm{E}}[\overset{\circ}{\mathrm{V}}[W_{\mathrm{m}i}^{\mathrm{m}}|J_{\mathrm{m}i}^{\mathrm{m}}, J_{\mathrm{m}}]] = \overset{\circ}{\mathrm{E}}[N_{\mathrm{m}} J_{\mathrm{m}i}^{\mathrm{m}}(J_{\mathrm{m}} - J_{\mathrm{m}i}^{\mathrm{m}})(J_{\mathrm{m}} - N_{\mathrm{m}})/(J_{\mathrm{m}}^2(J_{\mathrm{m}}-1))]$. Since we discard terms of order $1/N^2$ in the the probabilities of sibship, we can approximate both variance terms in eq. (3.F.1) using the delta method (Taylor expansion). With our assumption on the relation between the moments and the population size (eq. 3.A.1), the second variance term can be approximated as

$$\frac{1}{N_{\mathrm{m}}-1} \overset{\circ}{\mathrm{E}}\left[\frac{N_{\mathrm{m}} J_{\mathrm{m}i}^{\mathrm{m}}(J_{\mathrm{m}} - J_{\mathrm{m}i}^{\mathrm{m}})(J_{\mathrm{m}} - N_{\mathrm{m}})}{J_{\mathrm{m}}^2(J_{\mathrm{m}}-1)}\right] = \frac{1}{N_{\mathrm{m}}-1} \frac{\overset{\circ}{\mathrm{E}}[J_{\mathrm{m}i}^{\mathrm{m}}]}{\overset{\circ}{\mathrm{E}}[J_{\mathrm{m}}]} + O(1/N^2) = \frac{1}{N_{\mathrm{m}}-1} \frac{\mu_{\mathrm{m}i}^{\mathrm{m}}}{\mu_T^{\mathrm{m}}} + O(1/N^2) \tag{3.F.2}$$

where μ_{vi}^{u} and μ_T^{u} are given in eqs. (3.10) and (3.11) and evaluated in the absence of phenotypic differences, so male phenotype $z_{\mathrm{m}i}$ is equal to average male phenotype $\bar{z}_{\mathrm{m}}$ and the resident phenotype z_{m}. Using the delta method with the variance operator, the first variance term in eq. (3.F.1)

is

$$\frac{N_{\mathrm{m}}^2}{N_{\mathrm{m}}-1}\overset{\circ}{\mathrm{V}}\left[\frac{J_{\mathrm{m}i}^{\mathrm{m}}}{J_{\mathrm{m}}}\right]=N_{\mathrm{m}}\frac{\overset{\circ}{\mathrm{V}}\left[J_{\mathrm{m}i}^{\mathrm{m}}\right]}{\overset{\circ}{\mathrm{E}}\left[J_{\mathrm{m}}\right]^2}+O(1/N^2)=N_{\mathrm{m}}\frac{\sigma_{\mathrm{m}ii}^{\mathrm{m}}}{\mu_T^{\mathrm{m}2}}+O(1/N^2) \tag{3.F.3}$$

where $\sigma_{\mathrm{m}ii}^{\mathrm{m}}$ is given by eq. (3.14). Substituting for $\mu_{\mathrm{m}ii}^{\mathrm{m}}$, μ_T^{m} and $\sigma_{\mathrm{m}ii}^{\mathrm{m}}$, we find that the probability that two males have the same father is as in eq. (3.29) of the main text.

3.F.1.2 Probability that two females have the same father

Using a similar argument as above, and the means and variances/covariances of male fitness, it is found that the probability that two females have the father $\Theta_{\mathrm{f}}^{\male}$ is equal to that of two males $\Theta_{\mathrm{f}}^{\male}=\Theta_{\mathrm{m}}^{\male}$.

3.F.1.3 Probability that a male and a female have the same father

The probability that a male and a female have the same father $\Theta_c^{\male}$ is given by $\overset{\circ}{\mathrm{E}}\left[\sum_{i=1}^{N_{\mathrm{m}}}W_{\mathrm{m}i}^{\mathrm{m}}W_{\mathrm{m}i}^{\mathrm{f}}/(N_{\mathrm{m}}N_{\mathrm{f}})\right]$, where $W_{\mathrm{m}i}^{\mathrm{f}}$ is the random variable for the number of female breeders produced by male i. By conditioning on the juvenile production of every individual and using the assumption that male and female offspring are culled independently, we have $\Theta_c^{\male}=N_{\mathrm{m}}N_{\mathrm{f}}\overset{\circ}{\mathrm{E}}\left[J_{\mathrm{m}i}^{\mathrm{m}}J_{\mathrm{m}i}^{\mathrm{f}}/(J_{\mathrm{m}}J_{\mathrm{f}})\right]$. To approximate this, we again use the delta method and, expanding about the means of $J_{\mathrm{m}i}^{\mathrm{m}},J_{\mathrm{m}i}^{\mathrm{f}},J_{\mathrm{m}}$ and J_{f} and using the order condition (3.A.1), find that

$$\begin{aligned}\overset{\circ}{\mathrm{E}}\left[\frac{J_{\mathrm{m}i}^{\mathrm{m}}}{J_{\mathrm{m}}}\frac{J_{\mathrm{m}i}^{\mathrm{f}}}{J_{\mathrm{f}}}\right]=\frac{1}{\overset{\circ}{\mathrm{E}}\left[J_{\mathrm{m}}\right]\overset{\circ}{\mathrm{E}}\left[J_{\mathrm{f}}\right]}\Bigg(&\overset{\circ}{\mathrm{C}}\left[J_{\mathrm{m}i}^{\mathrm{m}},J_{\mathrm{m}i}^{\mathrm{f}}\right]-\frac{\overset{\circ}{\mathrm{C}}\left[J_{\mathrm{m}i}^{\mathrm{f}},J_{\mathrm{m}}\right]\overset{\circ}{\mathrm{E}}\left[J_{\mathrm{m}i}^{\mathrm{m}}\right]}{\overset{\circ}{\mathrm{E}}\left[J_{\mathrm{m}}\right]}+\overset{\circ}{\mathrm{E}}\left[J_{\mathrm{m}i}^{\mathrm{m}}\right]\overset{\circ}{\mathrm{E}}\left[J_{\mathrm{m}i}^{\mathrm{f}}\right]\\&-\frac{\overset{\circ}{\mathrm{C}}\left[J_{\mathrm{m}i}^{\mathrm{m}},J_{\mathrm{m}}\right]\overset{\circ}{\mathrm{E}}\left[J_{\mathrm{m}i}^{\mathrm{f}}\right]}{\overset{\circ}{\mathrm{E}}\left[J_{\mathrm{m}}\right]}-\frac{\overset{\circ}{\mathrm{C}}\left[J_{\mathrm{m}i}^{\mathrm{f}},J_{\mathrm{f}}\right]\overset{\circ}{\mathrm{E}}\left[J_{\mathrm{m}i}^{\mathrm{m}}\right]}{\overset{\circ}{\mathrm{E}}\left[J_{\mathrm{f}}\right]}-\frac{\overset{\circ}{\mathrm{C}}\left[J_{\mathrm{m}i}^{\mathrm{m}},J_{\mathrm{f}}\right]\overset{\circ}{\mathrm{E}}\left[J_{\mathrm{m}i}^{\mathrm{f}}\right]}{\overset{\circ}{\mathrm{E}}\left[J_{\mathrm{f}}\right]}\\&+\frac{\overset{\circ}{\mathrm{C}}\left[J_{\mathrm{m}},J_{\mathrm{f}}\right]\overset{\circ}{\mathrm{E}}\left[J_{\mathrm{m}i}^{\mathrm{m}}\right]\overset{\circ}{\mathrm{E}}\left[J_{\mathrm{m}i}^{\mathrm{f}}\right]}{\overset{\circ}{\mathrm{E}}\left[J_{\mathrm{m}}\right]\overset{\circ}{\mathrm{E}}\left[J_{\mathrm{f}}\right]}+\frac{\overset{\circ}{\mathrm{E}}\left[J_{\mathrm{m}i}^{\mathrm{m}}\right]\overset{\circ}{\mathrm{E}}\left[J_{\mathrm{m}i}^{\mathrm{f}}\right]\overset{\circ}{\mathrm{V}}\left[J_{\mathrm{m}}\right]}{\overset{\circ}{\mathrm{E}}\left[J_{\mathrm{m}}\right]^2}+\frac{\overset{\circ}{\mathrm{E}}\left[J_{\mathrm{m}i}^{\mathrm{m}}\right]\overset{\circ}{\mathrm{E}}\left[J_{\mathrm{m}i}^{\mathrm{f}}\right]\overset{\circ}{\mathrm{V}}\left[J_{\mathrm{f}}\right]}{\overset{\circ}{\mathrm{E}}\left[J_{\mathrm{f}}\right]^2}\Bigg)\\&+O(1/N^3).\end{aligned} \tag{3.F.4}$$

Covariances between the number of juveniles of a particular sex produced by a focal individual and the total number of juveniles of the same sex produced in the total population are derived in eq. (3.13) of the main text. We now develop the covariances between the number of female and male produced by two matings in order to compute eq. (3.F.4).

We write $Z_{ij}=\sum_n^{B_{ij}}(1-\mathbb{1}_{R_n})\mathbb{1}_{S_n^{\mathrm{f}}}$ for the random variable of the number of female juveniles produced by the couple i and j, given that they have mated. The covariance terms

$\overset{\circ}{\mathrm{C}}[J^{\mathrm{m}}_{\mathrm{m}i}, J^{\mathrm{f}}_{\mathrm{m}i}], \overset{\circ}{\mathrm{C}}[J^{\mathrm{f}}_{\mathrm{m}i}, J_{\mathrm{m}}], \overset{\circ}{\mathrm{C}}[J^{\mathrm{m}}_{\mathrm{m}i}, J_{\mathrm{f}}]$ and $\overset{\circ}{\mathrm{C}}[J_{\mathrm{m}}, J_{\mathrm{f}}]$ of eq. (3.F.4) may be expressed as sums of the covariance $\overset{\circ}{\mathrm{C}}[\mathbb{1}_{P_{ij}} Y_{ij}, \mathbb{1}_{P_{kl}} Z_{kl}]$. We define the following covariance functions between different pairs of individuals, assuming that the covariance between pairs that share no individual is zero,

$$\mathrm{C}[\mathbb{1}_{P_{ij}} Y_{ij}, \mathbb{1}_{P_{kl}} Z_{kl}] = \begin{cases} \Psi_{z_{\mathrm{m}i}, z_{\mathrm{f}j}} & \text{if } i = k \text{ and } j = l \\ \Psi^{\mathrm{m}}_{z_{\mathrm{m}i}, z_{\mathrm{f}j}, z_{\mathrm{f}l}} & \text{if } i = k \text{ and } j \neq l \\ \Psi^{\mathrm{f}}_{z_{\mathrm{m}i}, z_{\mathrm{f}j}, z_{\mathrm{m}k}} & \text{if } i \neq k \text{ and } j = l \\ 0 & \text{if } i \neq k \text{ and } j \neq l. \end{cases} \tag{3.F.5}$$

In the absence of phenotypic differences (where all males have the same phenotype $\bar{z}_{\mathrm{m}}$ and all females the same phenotype $\bar{z}_{\mathrm{f}}$), we then obtain

$$\begin{aligned} \overset{\circ}{\mathrm{C}}[J^{\mathrm{m}}_{\mathrm{m}i}, J^{\mathrm{f}}_{\mathrm{m}i}] &= N_{\mathrm{f}} \Psi_{\bar{z}_{\mathrm{m}}, \bar{z}_{\mathrm{f}}} + N_{\mathrm{f}}(N_{\mathrm{f}} - 1) \Psi^{\mathrm{m}}_{\bar{z}_{\mathrm{m}}, \bar{z}_{\mathrm{f}}, \bar{z}_{\mathrm{f}}} \\ \overset{\circ}{\mathrm{C}}[J^{\mathrm{m}}_{\mathrm{m}i}, J_{\mathrm{f}}] = \overset{\circ}{\mathrm{C}}[J^{\mathrm{f}}_{\mathrm{m}i}, J_{\mathrm{m}}] &= N_{\mathrm{f}} \Psi_{\bar{z}_{\mathrm{m}}, \bar{z}_{\mathrm{f}}} + N_{\mathrm{f}}(N_{\mathrm{m}} - 1) \Psi^{\mathrm{f}}_{\bar{z}_{\mathrm{m}}, \bar{z}_{\mathrm{f}}, \bar{z}_{\mathrm{m}}} + N_{\mathrm{f}}(N_{\mathrm{f}} - 1) \Psi^{\mathrm{m}}_{\bar{z}_{\mathrm{m}}, \bar{z}_{\mathrm{f}}, \bar{z}_{\mathrm{f}}} \\ \overset{\circ}{\mathrm{C}}[J_{\mathrm{m}}, J_{\mathrm{f}}] &= N_{\mathrm{m}} N_{\mathrm{f}} \Psi_{\bar{z}_{\mathrm{m}}, \bar{z}_{\mathrm{f}}} + N_{\mathrm{f}} N_{\mathrm{m}}(N_{\mathrm{m}} - 1) \Psi^{\mathrm{f}}_{\bar{z}_{\mathrm{m}}, \bar{z}_{\mathrm{f}}, \bar{z}_{\mathrm{m}}} + N_{\mathrm{m}} N_{\mathrm{f}}(N_{\mathrm{f}} - 1) \Psi^{\mathrm{m}}_{\bar{z}_{\mathrm{m}}, \bar{z}_{\mathrm{f}}, \bar{z}_{\mathrm{f}}}. \end{aligned} \tag{3.F.6}$$

Each Ψ is now developed in terms of the life cycle.

Covariance between the number of males and the number of females produced by the same couple The covariance between the number of males and the number of females produced by a pair $\{i, j\}$ is $\mathrm{C}[\mathbb{1}_{P_{ij}} Y_{ij}, \mathbb{1}_{P_{ij}} Z_{ij}] = \mathrm{E}[\mathbb{1}_{P_{ij}} Y_{ij} Z_{ij}] - E[\mathbb{1}_{P_{ij}} Y_{ij}] E[\mathbb{1}_{P_{ij}} Z_{ij}]$. The first term can be written as $\mathrm{E}[\mathbb{1}_{P_{ij}} Y_{ij} Z_{ij}] = \phi_{z_{\mathrm{m}i}, z_{\mathrm{f}j}} E[Y_{ij} Z_{ij}]$ by conditioning on the mating event. Then, by definition, the product of the number of males and females produced by the mating is $Y_{ij} Z_{ij} = \sum_n^{B_{ij}} \mathbb{1}_{R_n} \mathbb{1}_{S^{\mathrm{m}}_n} \sum_l^{B_{ij}} (1 - \mathbb{1}_{R_l}) \mathbb{1}_{S^{\mathrm{f}}_l}$. Because we sum over the same set of offspring, realizations of the sex determination are no longer independent: an individual cannot simultaneously be male and female. To take this into account, we write $Y_{ij} Z_{ij} = \sum_n^{B_{ij}} \mathbb{1}_{R_n} \mathbb{1}_{S^{\mathrm{m}}_n} (1 - \mathbb{1}_{R_n}) \mathbb{1}_{S^{\mathrm{f}}_n} + \sum_{l,n,l \neq n}^{B_{ij}} \mathbb{1}_{R_n} \mathbb{1}_{S^{\mathrm{m}}_n} (1 - \mathbb{1}_{R_l}) \mathbb{1}_{S^{\mathrm{f}}_l}$. Because of the non-independence of the sex of offspring n, the expected value of the first sum is zero: $\mathrm{E}[\sum_n^{B_{ij}} \mathbb{1}_{R_n} \mathbb{1}_{S^{\mathrm{m}}_n} (1 - \mathbb{1}_{R_n}) \mathbb{1}_{S^{\mathrm{f}}_n}] = 0$. For the second term, since different offspring are considered, they are independent of one another, so that $\mathrm{E}[\sum_{l,n,l \neq n}^{B_{ij}} \mathbb{1}_{R_n} \mathbb{1}_{S^{\mathrm{m}}_n} (1 - r_{ijl}) s^{\mathrm{f}}_{ijl}] = E[B_{ij}(B_{ij} - 1)] r_{z_{\mathrm{m}i}, z_{\mathrm{f}j}} s^{\mathrm{m}}_{z_{\mathrm{m}i}, z_{\mathrm{f}j}} (1 - r_{z_{\mathrm{m}i}, z_{\mathrm{f}j}}) s^{\mathrm{f}}_{z_{\mathrm{m}i}, z_{\mathrm{f}j}}$. The covariance between the number of males and

the number of females produced by a male i and a female j is then

$$\Psi_{1z_{\mathrm{m}i},z_{\mathrm{f}j}} = \phi_{z_{\mathrm{m}i},z_{\mathrm{f}j}} r_{z_{\mathrm{m}i},z_{\mathrm{f}j}} s^{\mathrm{m}}_{z_{\mathrm{m}i},z_{\mathrm{f}j}} (1 - r_{z_{\mathrm{m}i},z_{\mathrm{f}j}}) s^{\mathrm{f}}_{z_{\mathrm{m}i},z_{\mathrm{f}j}} (\beta_{z_{\mathrm{m}i},z_{\mathrm{f}j}} + \alpha_{z_{\mathrm{m}i},z_{\mathrm{f}j}} (\alpha_{z_{\mathrm{m}i},z_{\mathrm{f}j}} - 1) - \phi_{z_{\mathrm{m}i},z_{\mathrm{f}j}} \alpha^2_{z_{\mathrm{m}i},z_{\mathrm{f}j}}). \tag{3.F.7}$$

Covariance between the number of males produced by a pair, and the number of females produced by another pair, when both pairs share one parent For this covariance, we consider two different sets of offspring. This allows us to use a similar argument as the one used in section 3.3.1 in the main text, and we find

$$\begin{aligned}
\Psi^{\mathrm{m}}_{z_{\mathrm{m}i},z_{\mathrm{f}j},z_{\mathrm{f}l}} =& r_{z_{\mathrm{m}i},z_{\mathrm{f}j}} s^{\mathrm{m}}_{z_{\mathrm{m}i},z_{\mathrm{f}j}} (1 - r_{z_{\mathrm{m}i},z_{\mathrm{f}l}}) s^{\mathrm{f}}_{z_{\mathrm{m}i},z_{\mathrm{f}l}} (\phi^{\mathrm{m}}_{z_{\mathrm{m}i},z_{\mathrm{f}j},z_{\mathrm{f}l}} \gamma^{\mathrm{m}}_{z_{\mathrm{m}i},z_{\mathrm{f}j},z_{\mathrm{f}l}} - \phi_{z_{\mathrm{m}i},z_{\mathrm{f}j}} \alpha_{z_{\mathrm{m}i},z_{\mathrm{f}l}} \phi_{z_{\mathrm{m}i},z_{\mathrm{f}l}} \alpha_{z_{\mathrm{m}i},z_{\mathrm{f}j}}) \\
\Psi^{\mathrm{f}}_{z_{\mathrm{m}i},z_{\mathrm{f}j},z_{\mathrm{m}k}} =& r_{z_{\mathrm{m}i},z_{\mathrm{f}j}} s^{\mathrm{m}}_{z_{\mathrm{m}k},z_{\mathrm{f}j}} (1 - r_{z_{\mathrm{m}k},z_{\mathrm{f}j}}) s^{\mathrm{f}}_{z_{\mathrm{m}k},z_{\mathrm{f}j}} (\phi^{\mathrm{f}}_{z_{\mathrm{m}i},z_{\mathrm{f}j},z_{\mathrm{m}k}} \gamma^{\mathrm{f}}_{z_{\mathrm{m}i},z_{\mathrm{f}j},z_{\mathrm{m}k}} - \phi_{z_{\mathrm{m}i},z_{\mathrm{f}j}} \alpha_{z_{\mathrm{m}k},z_{\mathrm{f}j}} \phi_{z_{\mathrm{m}k},z_{\mathrm{f}j}} \alpha_{z_{\mathrm{m}i},z_{\mathrm{f}j}}).
\end{aligned} \tag{3.F.8}$$

3.F.1.4 Probability that two individuals have the same father or mother

After substituting the covariances Ψ into eq. (3.F.4), we find the probability that a son and a daughter have the same father is the same as the probability of two males or two females sharing a same father, so to the order $1/N$, the probability that two individuals have the same father is independent of their sex and $\Theta^{\male}_{c} = \Theta^{\male}_{\mathrm{m}} = \Theta^{\male}_{\mathrm{f}} = \Theta^{\male}$. Using a similar argument, we find that the probability that two individuals have the same mother is given by eq. (3.29) of the main text.

3.F.2 Probabilities of sibship among three individuals

We find that the probabilities of sibship of three individuals can be expressed in terms of the probabilities of sibship of two individuals $\Theta^{\male}$ and $\Theta^{\female}$ to the order $1/N$.

3.F.2.1 Probability that three individuals have the same parent

As for the probability of two males having the same a father, we can calculate the probability that three randomly sampled adult males have the same father as $\Xi 3^{\male}_{3\mathrm{m}} = \overset{\circ}{\mathrm{E}}\left[\sum_i^{N_{\mathrm{m}}} \binom{W^{\mathrm{m}}_{\mathrm{m}i}}{3} / \binom{N_{\mathrm{m}}}{3}\right]$. In the absence of phenotypic differences, each male has the same distribution of reproductive output and $\Xi 3^{\male}_{3\mathrm{m}} = 1/((N_{\mathrm{m}}-1)(N_{\mathrm{m}}-2)) \overset{\circ}{\mathrm{E}}\left[W^{\mathrm{m}3}_{\mathrm{m}i} - 3W^{\mathrm{m}2}_{\mathrm{m}i} + 2W^{\mathrm{m}}_{\mathrm{m}i}\right]$. By conditioning on juvenile production and using the order condition (3.A.1), we find that none of the terms in $\Xi 3^{\male}_{3\mathrm{m}}$ are of order $1/N$ or more, so the probability that three randomly sampled adult males have the same father can be

approximated to being zero. Similarly, we find that all probabilities of sibship three genes in the same individual are approximately zero and $\Xi 3_x^{\male} = \Xi 3_x^{\female} = 0 + O(1/N^2)$ for $x \in \{3\mathrm{m}, 3\mathrm{f}, 2\mathrm{m}, 2\mathrm{f}\}$.

3.F.2.2 Probability that two of three individuals have the same parent

Rather than calculating $\Xi 2_{3\mathrm{m}}^{\male}$ the probability that out of three males only two have the same father directly, it is easier to consider the probability that out of three males, none have the same father. These two probabilities are related by $1 - \Xi 3_{3\mathrm{m}}^{\male} - \Xi 2_{3\mathrm{m}}^{\male} = 1 - \Xi 2_{3\mathrm{m}}^{\male}$ (since $\Xi 3_{3\mathrm{m}}^{\male} = 0 + O(1/N^2)$). The probability that out of three males, none have the same father is given by the expected value of the ratio of the number of ways three individuals may be sampled from the male offspring of three different adult males to the number of ways of sampling three males out of the entire male population $1 - \Xi 2_{3\mathrm{m}}^{\male} = [\sum_i^{N_\mathrm{m}} \sum_{j<i}^{N_\mathrm{m}} \sum_{k<j}^{N_\mathrm{m}} W_{\mathrm{m}i}^{\mathrm{m}} W_{\mathrm{m}j}^{\mathrm{m}} W_{\mathrm{m}k}^{\mathrm{m}} / \binom{N_\mathrm{m}}{3}]$, which after taking the sum and denominator outside reduces to $\overset{\circ}{\mathrm{E}}[W_{\mathrm{m}i}^{\mathrm{m}} W_{\mathrm{m}j}^{\mathrm{m}} W_{\mathrm{m}k}^{\mathrm{m}}]_{i\neq j\neq k\neq i}$. Using the delta method and approximating to the order of $1/N^2$ results in $1 - \Xi 2_{3\mathrm{m}}^{\male} = 1 + 3\,\overset{\circ}{\mathrm{C}}\left[W_{\mathrm{m}i}^{\mathrm{m}}, W_{\mathrm{m}j}^{\mathrm{m}}\right]_{i\neq j} + O(1/N^2)$.

The covariance term $\overset{\circ}{\mathrm{C}}\left[W_{\mathrm{m}i}^{\mathrm{m}}, W_{\mathrm{m}j}^{\mathrm{m}}\right]_{i\neq j}$ may be expressed in terms of $\Theta^{\male}$. The probability that two individuals do not have the same father is, by definition, $1 - \Theta^{\male}$, but it is also given by $\overset{\circ}{\mathrm{E}}[\sum_i \sum_{j<i} W_{\mathrm{m}i}^{\mathrm{m}} W_{\mathrm{m}j}^{\mathrm{m}} / \binom{N_\mathrm{m}}{2}] = \overset{\circ}{\mathrm{E}}[W_{\mathrm{m}i}^{\mathrm{m}}, W_{\mathrm{m}j}^{\mathrm{m}}]_{i\neq j} = \overset{\circ}{\mathrm{C}}[W_{\mathrm{m}i}^{\mathrm{m}} W_{\mathrm{m}j}^{\mathrm{m}}]_{i\neq j} + 1$, so that $\overset{\circ}{\mathrm{C}}\left[W_{\mathrm{m}i}^{\mathrm{m}}, W_{\mathrm{m}j}^{\mathrm{m}}\right]_{i\neq j} = -\Theta^{\male}$. Hence substituting back into the probability that out of three males none have the same father, and solving for $\Xi 2_{3\mathrm{m}}^{\male}$, we obtain that the probability that out of three males only two have the same father is

$$\Xi 2_{3\mathrm{m}}^{\male} = 3\Theta^{\male} + O(1/N^2). \tag{3.F.9}$$

The remaining probabilities can be derived in terms of $\Theta^{\male}$ by using the same argument, which produces

$$\begin{aligned}
\Xi 2_{3\mathrm{f}}^{\male} &= 3\Theta^{\male} + O(1/N^2) \\
\Xi 2_{2\mathrm{m}}^{\male} &= \frac{2}{3N_\mathrm{m}} + \frac{5}{3}\Theta^{\male} + O(1/N^2) \\
\Xi 2_{2\mathrm{f}}^{\male} &= \frac{2}{3}\left(\frac{2}{N_\mathrm{m}} - \frac{1}{N_\mathrm{f}}\right) + \frac{5}{3}\Theta^{\male} + O(1/N^2).
\end{aligned} \tag{3.F.10}$$

By symmetry, we find that the probabilities of sibship of three maternal genes are given to the

order $O(1/N)$ by

$$\begin{aligned}
\Xi 2^{\varsigma\!\!\!\!\!\!\varsigma}_{3\mathrm{m}} &= \Xi 2^{\varsigma\!\!\!\!\!\!\varsigma}_{3\mathrm{f}} = 3\Theta^{\varsigma\!\!\!\!\!\!\varsigma} + O(1/N^2) \\
\Xi 2^{\varsigma\!\!\!\!\!\!\varsigma}_{2\mathrm{m}} &= \frac{2}{3}\left(\frac{2}{N_\mathrm{f}} - \frac{1}{N_\mathrm{m}}\right) + \frac{5}{3}\Theta^{\varsigma\!\!\!\!\!\!\varsigma} + O(1/N^2) \\
\Xi 2^{\varsigma\!\!\!\!\!\!\varsigma}_{2\mathrm{f}} &= \frac{2}{3N_\mathrm{f}} + \frac{5}{3}\Theta^{\varsigma\!\!\!\!\!\!\varsigma} + O(1/N^2).
\end{aligned} \tag{3.F.11}$$

3.G Matrix of neutral change

In the absence of selection ($\delta_\mathrm{m} = \delta_\mathrm{f} = 0$), the moments of allelic state collected in the vector $\mathbf{p}_t^\circ = (p_{\mathrm{m},t}, p_{\mathrm{f},t}, \eta_t, \kappa_t^{\male}, \kappa_t^{\female}, \rho_t^{\male}, \rho_t^{\female}, \varsigma_{3\mathrm{m}}^{\male}, \varsigma_{3\mathrm{f}}^{\male}, \varsigma_{2\mathrm{m}}^{\male}, \varsigma_{2\mathrm{f}}^{\male}, \varsigma_{3\mathrm{m}}^{\female}, \varsigma_{3\mathrm{f}}^{\female}, \varsigma_{2\mathrm{m}}^{\female}, \varsigma_{2\mathrm{f}}^{\female})^T$ are related from one generation to another by linear recurrences given in appendix 3.E, so that together they satisfy the iteration $\mathbf{p}_{t+1}^\circ = \mathbf{A}^\circ \mathbf{p}_t^\circ$ with

$$\mathbf{A}^\circ = \begin{pmatrix}
\frac{1}{2} & \frac{1}{2} & 0 & & & & & & & & & & & & 0 \\
\frac{1}{2} & \frac{1}{2} & 0 & & & & & & & & & & & & 0 \\
0 & 0 & \frac{1}{2} & \frac{1}{4} & \frac{1}{4} & 0 & & & & & & & & & 0 \\
\frac{\Theta^{\male}}{4} & \frac{\Theta^{\male}}{4} & \frac{1}{2} & \frac{1-\Theta^{\male}}{4} & \frac{1-\Theta^{\male}}{4} & 0 & & & & & & & & & 0 \\
\frac{\Theta^{\female}}{4} & \frac{\Theta^{\female}}{4} & \frac{1}{2} & \frac{1-\Theta^{\female}}{4} & \frac{1-\Theta^{\female}}{4} & 0 & & & & & & & & & 0 \\
0 & 0 & \frac{\Theta^{\male}}{4} & \frac{\Theta^{\male}}{8} & \frac{\Theta^{\male}}{8} & \frac{3-\Theta^{\male}}{8} & \frac{3-\Theta^{\male}}{8} & 0 & 0 & \frac{1-\Theta^{\male}}{8} & 0 & 0 & 0 & \frac{1-\Theta^{\male}}{8} & 0 \\
0 & 0 & \frac{\Theta^{\female}}{4} & \frac{\Theta^{\female}}{8} & \frac{\Theta^{\female}}{8} & \frac{3-\Theta^{\female}}{8} & \frac{3-\Theta^{\female}}{8} & 0 & 0 & 0 & \frac{1-\Theta^{\female}}{8} & 0 & 0 & 0 & \frac{1-\Theta^{\female}}{8} \\
\frac{\Xi 3_{3\mathrm{m}}^{\male}}{8} & \frac{\Xi 3_{3\mathrm{m}}^{\male}}{8} & \frac{3\Xi 3_{3\mathrm{m}}^{\male}+\Xi 2_{3\mathrm{m}}^{\male}}{4} & \frac{\Xi 2_{3\mathrm{m}}^{\male}}{8} & \frac{\Xi 2_{3\mathrm{m}}^{\male}}{8} & \frac{3-3\Xi 3_{3\mathrm{m}}^{\male}-\Xi 2_{3\mathrm{m}}^{\male}}{8} & \frac{3-3\Xi 3_{3\mathrm{m}}^{\male}-\Xi 2_{3\mathrm{m}}^{\male}}{8} & \frac{1-\Xi 3_{3\mathrm{m}}^{\male}-\Xi 2_{3\mathrm{m}}^{\male}}{8} & 0 & 0 & 0 & \frac{1-\Xi 3_{3\mathrm{m}}^{\male}-\Xi 2_{3\mathrm{m}}^{\male}}{8} & 0 & 0 & 0 \\
\frac{\Xi 3_{3\mathrm{f}}^{\male}}{8} & \frac{\Xi 3_{3\mathrm{f}}^{\male}}{8} & \frac{3\Xi 3_{3\mathrm{f}}^{\male}+\Xi 2_{3\mathrm{f}}^{\male}}{4} & \frac{\Xi 2_{3\mathrm{f}}^{\male}}{8} & \frac{\Xi 2_{3\mathrm{f}}^{\male}}{8} & \frac{3-3\Xi 3_{3\mathrm{f}}^{\male}-\Xi 2_{3\mathrm{f}}^{\male}}{8} & \frac{3-3\Xi 3_{3\mathrm{f}}^{\male}-\Xi 2_{3\mathrm{f}}^{\male}}{8} & \frac{1-\Xi 3_{3\mathrm{f}}^{\male}-\Xi 2_{3\mathrm{f}}^{\male}}{8} & 0 & 0 & 0 & \frac{1-\Xi 3_{3\mathrm{f}}^{\male}-\Xi 2_{3\mathrm{f}}^{\male}}{8} & 0 & 0 & 0 \\
\frac{\Xi 3_{2\mathrm{m}}^{\male}}{8} & \frac{\Xi 3_{2\mathrm{m}}^{\male}}{8} & \frac{3\Xi 3_{2\mathrm{m}}^{\male}+\Xi 2_{2\mathrm{m}}^{\male}}{4} & \frac{\Xi 2_{2\mathrm{m}}^{\male}}{8} & \frac{\Xi 2_{2\mathrm{m}}^{\male}}{8} & \frac{3-3\Xi 3_{2\mathrm{m}}^{\male}-\Xi 2_{2\mathrm{m}}^{\male}}{8} & \frac{3-3\Xi 3_{2\mathrm{m}}^{\male}-\Xi 2_{2\mathrm{m}}^{\male}}{8} & \frac{1-\Xi 3_{2\mathrm{m}}^{\male}-\Xi 2_{2\mathrm{m}}^{\male}}{8} & 0 & 0 & 0 & \frac{1-\Xi 3_{2\mathrm{m}}^{\male}-\Xi 2_{2\mathrm{m}}^{\male}}{8} & 0 & 0 & 0 \\
\frac{\Xi 3_{2\mathrm{f}}^{\male}}{8} & \frac{\Xi 3_{2\mathrm{f}}^{\male}}{8} & \frac{3\Xi 3_{2\mathrm{f}}^{\male}+\Xi 2_{2\mathrm{f}}^{\male}}{4} & \frac{\Xi 2_{2\mathrm{f}}^{\male}}{8} & \frac{\Xi 2_{2\mathrm{f}}^{\male}}{8} & \frac{3-3\Xi 3_{2\mathrm{f}}^{\male}-\Xi 2_{2\mathrm{f}}^{\male}}{8} & \frac{3-3\Xi 3_{2\mathrm{f}}^{\male}-\Xi 2_{2\mathrm{f}}^{\male}}{8} & \frac{1-\Xi 3_{2\mathrm{f}}^{\male}-\Xi 2_{2\mathrm{f}}^{\male}}{8} & 0 & 0 & 0 & \frac{1-\Xi 3_{2\mathrm{f}}^{\male}-\Xi 2_{2\mathrm{f}}^{\male}}{8} & 0 & 0 & 0 \\
\frac{\Xi 3_{3\mathrm{m}}^{\female}}{8} & \frac{\Xi 3_{3\mathrm{m}}^{\female}}{8} & \frac{3\Xi 3_{3\mathrm{m}}^{\female}+\Xi 2_{3\mathrm{m}}^{\female}}{4} & \frac{\Xi 2_{3\mathrm{m}}^{\female}}{8} & \frac{\Xi 2_{3\mathrm{m}}^{\female}}{8} & \frac{3-3\Xi 3_{3\mathrm{m}}^{\female}-\Xi 2_{3\mathrm{m}}^{\female}}{8} & \frac{3-3\Xi 3_{3\mathrm{m}}^{\female}-\Xi 2_{3\mathrm{m}}^{\female}}{8} & 0 & \frac{1-\Xi 3_{3\mathrm{m}}^{\female}-\Xi 2_{3\mathrm{m}}^{\female}}{8} & 0 & 0 & 0 & \frac{1-\Xi 3_{3\mathrm{m}}^{\female}-\Xi 2_{3\mathrm{m}}^{\female}}{8} & 0 & 0 \\
\frac{\Xi 3_{3\mathrm{f}}^{\female}}{8} & \frac{\Xi 3_{3\mathrm{f}}^{\female}}{8} & \frac{3\Xi 3_{3\mathrm{f}}^{\female}+\Xi 2_{3\mathrm{f}}^{\female}}{4} & \frac{\Xi 2_{3\mathrm{f}}^{\female}}{8} & \frac{\Xi 2_{3\mathrm{f}}^{\female}}{8} & \frac{3-3\Xi 3_{3\mathrm{f}}^{\female}-\Xi 2_{3\mathrm{f}}^{\female}}{8} & \frac{3-3\Xi 3_{3\mathrm{f}}^{\female}-\Xi 2_{3\mathrm{f}}^{\female}}{8} & 0 & \frac{1-\Xi 3_{3\mathrm{f}}^{\female}-\Xi 2_{3\mathrm{f}}^{\female}}{8} & 0 & 0 & 0 & \frac{1-\Xi 3_{3\mathrm{f}}^{\female}-\Xi 2_{3\mathrm{f}}^{\female}}{8} & 0 & 0 \\
\frac{\Xi 3_{2\mathrm{m}}^{\female}}{8} & \frac{\Xi 3_{2\mathrm{m}}^{\female}}{8} & \frac{3\Xi 3_{2\mathrm{m}}^{\female}+\Xi 2_{2\mathrm{m}}^{\female}}{4} & \frac{\Xi 2_{2\mathrm{m}}^{\female}}{8} & \frac{\Xi 2_{2\mathrm{m}}^{\female}}{8} & \frac{3-3\Xi 3_{2\mathrm{m}}^{\female}-\Xi 2_{2\mathrm{m}}^{\female}}{8} & \frac{3-3\Xi 3_{2\mathrm{m}}^{\female}-\Xi 2_{2\mathrm{m}}^{\female}}{8} & 0 & \frac{1-\Xi 3_{2\mathrm{m}}^{\female}-\Xi 2_{2\mathrm{m}}^{\female}}{8} & 0 & 0 & 0 & \frac{1-\Xi 3_{2\mathrm{m}}^{\female}-\Xi 2_{2\mathrm{m}}^{\female}}{8} & 0 & 0 \\
\frac{\Xi 3_{2\mathrm{f}}^{\female}}{8} & \frac{\Xi 3_{2\mathrm{f}}^{\female}}{8} & \frac{3\Xi 3_{2\mathrm{f}}^{\female}+\Xi 2_{2\mathrm{f}}^{\female}}{4} & \frac{\Xi 2_{2\mathrm{f}}^{\female}}{8} & \frac{\Xi 2_{2\mathrm{f}}^{\female}}{8} & \frac{3-3\Xi 3_{2\mathrm{f}}^{\female}-\Xi 2_{2\mathrm{f}}^{\female}}{8} & \frac{3-3\Xi 3_{2\mathrm{f}}^{\female}-\Xi 2_{2\mathrm{f}}^{\female}}{8} & 0 & \frac{1-\Xi 3_{2\mathrm{f}}^{\female}-\Xi 2_{2\mathrm{f}}^{\female}}{8} & 0 & 0 & 0 & \frac{1-\Xi 3_{2\mathrm{f}}^{\female}-\Xi 2_{2\mathrm{f}}^{\female}}{8} & 0 & 0
\end{pmatrix},$$

where the functions Θ and Ξ correspond to sibship probabilities given in appendix 3.F.

3.H Selection matrix

To the first order effect of selection, the change in male and female average mutant frequency are respectively given by $K_{\mathrm{m},t}dw^{\mathrm{m}}_{\mathrm{m}i}/dz_{\mathrm{m}i} + (N_{\mathrm{f}}/N_{\mathrm{m}})K_{\mathrm{f},t}dw^{\mathrm{m}}_{\mathrm{f}j}/dz_{\mathrm{f}j}$ and $(N_{\mathrm{m}}/N_{\mathrm{f}})K_{\mathrm{m},t}dw^{\mathrm{f}}_{\mathrm{m}i}/dz_{\mathrm{m}i} + K_{\mathrm{f},t}dw^{\mathrm{f}}_{\mathrm{f}j}/dz_{\mathrm{f}j}$ (eq. (3.22)). Then, we have $\mathbf{p}_{t+1} = (\mathbf{A}^{\circ} + \delta_{\mathrm{m}}\dot{\mathbf{A}}_{\mathrm{m}} + \delta_{\mathrm{f}}\dot{\mathbf{A}}_{\mathrm{f}})\mathbf{p}_t + O(\delta^2)$ with

$$\dot{\mathbf{A}}_{\mathrm{m}} = \frac{1}{2}\begin{pmatrix} h\frac{dw^{\mathrm{m}}_{\mathrm{m}i}}{dz_{\mathrm{m}i}} & 0 & (1-2h)\frac{dw^{\mathrm{m}}_{\mathrm{m}i}}{dz_{\mathrm{m}i}} & -\frac{h}{2}\frac{dw^{\mathrm{m}}_{\mathrm{m}i}}{dz_{\mathrm{m}i}} & -\frac{h}{2}\frac{dw^{\mathrm{m}}_{\mathrm{m}i}}{dz_{\mathrm{m}i}} & -\frac{1-2h}{2}\frac{dw^{\mathrm{m}}_{\mathrm{m}i}}{dz_{\mathrm{m}i}} & -\frac{1-2h}{2}\frac{dw^{\mathrm{m}}_{\mathrm{m}i}}{dz_{\mathrm{m}i}} & 0 & \cdots & 0 \\ h\frac{N_{\mathrm{m}}}{N_{\mathrm{f}}}\frac{dw^{\mathrm{f}}_{\mathrm{m}i}}{dz_{\mathrm{m}i}} & 0 & (1-2h)\frac{N_{\mathrm{m}}}{N_{\mathrm{f}}}\frac{dw^{\mathrm{f}}_{\mathrm{m}i}}{dz_{\mathrm{m}i}} & -\frac{h}{2}\frac{N_{\mathrm{m}}}{N_{\mathrm{f}}}\frac{dw^{\mathrm{f}}_{\mathrm{m}i}}{dz_{\mathrm{m}i}} & -\frac{h}{2}\frac{N_{\mathrm{m}}}{N_{\mathrm{f}}}\frac{dw^{\mathrm{f}}_{\mathrm{m}i}}{dz_{\mathrm{m}i}} & -\frac{1-2h}{2}\frac{N_{\mathrm{m}}}{N_{\mathrm{f}}}\frac{dw^{\mathrm{f}}_{\mathrm{m}i}}{dz_{\mathrm{m}i}} & -\frac{1-2h}{2}\frac{N_{\mathrm{m}}}{N_{\mathrm{f}}}\frac{dw^{\mathrm{f}}_{\mathrm{m}i}}{dz_{\mathrm{m}i}} & 0 & \cdots & 0 \\ 0 & & & & & & & & & \vdots \\ \vdots & & & & & & & & & \vdots \\ 0 & & \cdots & & \cdots & & \cdots & & & 0 \end{pmatrix},$$

$$\dot{\mathbf{A}}_{\mathrm{f}} = \frac{1}{2}\begin{pmatrix} 0 & h\frac{N_{\mathrm{f}}}{N_{\mathrm{m}}}\frac{dw^{\mathrm{m}}_{\mathrm{f}j}}{dz_{\mathrm{f}j}} & (1-2h)\frac{N_{\mathrm{f}}}{N_{\mathrm{m}}}\frac{dw^{\mathrm{m}}_{\mathrm{f}j}}{dz_{\mathrm{f}j}} & -\frac{h}{2}\frac{N_{\mathrm{f}}}{N_{\mathrm{m}}}\frac{dw^{\mathrm{m}}_{\mathrm{f}j}}{dz_{\mathrm{f}j}} & -\frac{h}{2}\frac{N_{\mathrm{f}}}{N_{\mathrm{m}}}\frac{dw^{\mathrm{m}}_{\mathrm{f}j}}{dz_{\mathrm{f}j}} & -\frac{1-2h}{2}\frac{N_{\mathrm{f}}}{N_{\mathrm{m}}}\frac{dw^{\mathrm{m}}_{\mathrm{f}j}}{dz_{\mathrm{f}j}} & -\frac{1-2h}{2}\frac{N_{\mathrm{f}}}{N_{\mathrm{m}}}\frac{dw^{\mathrm{m}}_{\mathrm{f}j}}{dz_{\mathrm{f}j}} & 0 & \cdots & 0 \\ 0 & h\frac{dw^{\mathrm{f}}_{\mathrm{f}j}}{dz_{\mathrm{f}j}} & (1-2h)\frac{dw^{\mathrm{f}}_{\mathrm{f}j}}{dz_{\mathrm{f}j}} & -\frac{h}{2}\frac{dw^{\mathrm{f}}_{\mathrm{f}j}}{dz_{\mathrm{f}j}} & -\frac{h}{2}\frac{dw^{\mathrm{f}}_{\mathrm{f}j}}{dz_{\mathrm{f}j}} & -\frac{1-2h}{2}\frac{dw^{\mathrm{f}}_{\mathrm{f}j}}{dz_{\mathrm{f}j}} & -\frac{1-2h}{2}\frac{dw^{\mathrm{f}}_{\mathrm{f}j}}{dz_{\mathrm{f}j}} & 0 & \cdots & 0 \\ 0 & & & & & & & & & \vdots \\ \vdots & & & & & & & & & \vdots \\ 0 & & \cdots & & \cdots & & \cdots & & & 0 \end{pmatrix},$$

where $dw^{\mathrm{m}}_{\mathrm{m}i}/dz_{\mathrm{m}i}$, $dw^{\mathrm{f}}_{\mathrm{m}i}/dz_{\mathrm{m}i}$, $dw^{\mathrm{m}}_{\mathrm{f}j}/dz_{\mathrm{f}j}$, $dw^{\mathrm{f}}_{\mathrm{f}j}/dz_{\mathrm{f}j}$ are the total derivatives of fitness with respect to phenotypic values in males and females (see section 3.4.2).

3.I Probability of fixation

3.I.1 Average probability of fixation

Here, we derive the expression for the fixation probability π of the mutant. Because the mutant allele is either eliminated or goes to fixation in the whole population, we have $\pi = \pi_{\mathrm{m}} = \pi_{\mathrm{f}}$. Although the fixation probabilities in males and females could be obtained from the asymptotic vector $\lim_{t\to\infty} \mathbf{A}^t \mathbf{p}_0$, this is difficult to evaluate in practice as it requires the calculation of $\mathbf{A}$'s eigenvectors. We thus rely on an alternative scheme to obtain π using only matrix inversion. To that aim it is convenient to express the fixation probability of the mutant as the average

$$\pi = \alpha\pi_{\mathrm{m}} + (1-\alpha)\pi_{\mathrm{f}}, \tag{3.I.1}$$

where the weight α is chosen such that the expected frequency change of a neutral mutant in any generation t is zero: $(1-\alpha)\mathrm{E}[\Delta p_{\mathrm{m},t}] + \alpha\mathrm{E}[\Delta p_{\mathrm{f},t}] = 0$. With this, the weighs α and $(1-\alpha)$ are the class reproductive values of males and females, and for our diploid, autosomal genetic system this is $\alpha = 1/2$.

3.I.2 Solving for the probability of fixation

Eq. (3.I.1) can be written as a sum of gene frequency change from the appearance to the eventual fixation of the mutant

$$\pi = \alpha p_{\mathrm{m},0} + (1-\alpha)p_{\mathrm{f},0} + \sum_{t=0}^{\infty}\Big(\alpha\mathrm{E}[\Delta p_{\mathrm{m},t}] + (1-\alpha)\mathrm{E}[\Delta p_{\mathrm{f},t}]\Big). \tag{3.I.2}$$

We begin by considering the first order effects of male phenotype on π, i.e. $\tilde{\pi}'_{\mathrm{m}}$ (see eq. 3.25). Using eq. (3.I.2), it is

$$\tilde{\pi}'_{\mathrm{m}} = \frac{\partial}{\partial\delta_{\mathrm{m}}}\sum_{t=0}^{\infty}\Big(\alpha\mathrm{E}[\Delta p_{\mathrm{m},t}] + (1-\alpha)\mathrm{E}[\Delta p_{\mathrm{f},t}]\Big)\Big|_{\delta_{\mathrm{m}}=\delta_{\mathrm{f}}=0}, \tag{3.I.3}$$

which in matrix notation may be written as

$$\tilde{\pi}'_{\mathrm{m}} = \boldsymbol{\alpha}\cdot\sum_{t=0}^{\infty}\frac{\partial}{\partial\delta_{\mathrm{m}}}(\mathbf{p}_{t+1}-\mathbf{p}_t)\Big|_{\delta_{\mathrm{m}}=\delta_{\mathrm{f}}=0} \tag{3.I.4}$$

where $\boldsymbol{\alpha} = (\alpha, 1-\alpha, 0, \ldots, 0)$ is such that when dot multiplied with $\mathbf{p}_t$, it collects and sums $p_{\mathrm{m},t}$ and $p_{\mathrm{f},t}$ weighted by the reproductive values. Then, using eqs. (3.24), we have $\partial(\mathbf{p}_{t+1}-\mathbf{p}_t)/\partial\delta_{\mathrm{m}} =$

$\dot{\mathbf{A}}_{\mathrm{m}}\mathbf{p}_t$. So the male perturbation of the probability of fixation may be written as

$$\tilde{\pi}'_{\mathrm{m}} = \boldsymbol{\alpha} \cdot \sum_{t=0}^{\infty} \dot{\mathbf{A}}_{\mathrm{m}}\mathbf{p}_t \Big|_{\delta_{\mathrm{m}}=\delta_{\mathrm{f}}=0}. \tag{3.I.5}$$

Now, the sum $\sum_{t=0}^{\infty}\mathbf{p}_t|_{\delta_{\mathrm{m}}=\delta_{\mathrm{f}}=0}$, which we write as $\sum_{t=0}^{\infty}\mathbf{p}_t^{\circ}$ where $\mathbf{p}_{t+1}^{\circ} = \mathbf{A}^{\circ}\mathbf{p}_t^{\circ}$, does not converge as $\mathbf{A}^{\circ}$ is not regular. This means $\dot{\mathbf{A}}$ cannot be factored out of the sum in eq. (3.I.5). To circumvent this problem we construct an iteration around a centered variable using the zero row-sum property of matrix $\dot{\mathbf{A}}_{\mathrm{m}}$ (Lehmann and Rousset, 2009), and define a vector $\mathbf{q}_t^{\circ}$ and a matrix $\mathbf{Q}^{\circ}$ such that

1. $\sum_{t=0}^{\infty}\dot{\mathbf{A}}_{\mathrm{m}}\mathbf{p}_t = \sum_{t=0}^{\infty}\dot{\mathbf{A}}_{\mathrm{m}}(\mathbf{p}_t^{\circ} - \mathbf{q}_t^{\circ})$,
2. $\mathbf{p}_{t+1}^{\circ} - \mathbf{q}_{t+1}^{\circ} = (\mathbf{A}^{\circ} - \mathbf{Q}^{\circ})(\mathbf{p}_t^{\circ} - \mathbf{q}_t^{\circ})$, and
3. $\lim_{t\to\infty}\mathbf{p}_t^{\circ} - \mathbf{q}_t^{\circ} = 0$.

The choice of $\mathbf{q}_t^{\circ}$ with all vector elements being equal to $\alpha p_{\mathrm{f},t} + (1-\alpha)p_{\mathrm{m},t}$, which acts as a reference variable, and $\mathbf{Q}^{\circ} = (q_{ij})$ with all elements of column 1 being equal to α, all elements of column 2 being equal to $1-\alpha$, and zero otherwise satisfies all three conditions. In effect, this choice of the vector $\mathbf{q}_t^{\circ}$ centers the iteration around the mutant frequency averaged across the sexes according to their reproductive class (this average is the reference variable), while $\mathbf{Q}^{\circ}$ provides the iteration of the reference variable.

Using properties 1-3 above, we can now factorize $\sum_{t=0}^{\infty}\dot{\mathbf{A}}_{\mathrm{m}}\mathbf{p}_t = \dot{\mathbf{A}}_{\mathrm{m}}\sum_{t=0}^{\infty}(\mathbf{p}_t^{\circ} - \mathbf{q}_t^{\circ}) = \dot{\mathbf{A}}_{\mathrm{m}}\sum_{t=0}^{\infty}(\mathbf{A}^{\circ} - \mathbf{Q}^{\circ})^t(\mathbf{p}_0 - \mathbf{q}_0^{\circ})$. With all eigenvalues of $(\mathbf{A}^{\circ} - \mathbf{Q}^{\circ})$ being less than 1 in absolute value (Lehmann and Rousset, 2009), the sum $\mathbf{d}^{\circ} = \sum_{t=0}^{\infty}(\mathbf{A}^{\circ} - \mathbf{Q}^{\circ})^t(\mathbf{p}_0 - \mathbf{q}_0^{\circ})$ can be evaluated as $[\mathbf{I} - \mathbf{A}^{\circ} + \mathbf{Q}^{\circ}]^{-1}$, where $\mathbf{I}$ is the identity matrix, so we have

$$\tilde{\pi}'_{\mathrm{m}} = \boldsymbol{\alpha} \cdot \dot{\mathbf{A}}_{\mathrm{m}}\mathbf{d}^{\circ}, \tag{3.I.6}$$

where

$$\mathbf{d}^{\circ} = [\mathbf{I} - \mathbf{A}^{\circ} + \mathbf{Q}^{\circ}]^{-1}(\mathbf{p}_0 - \mathbf{q}_0). \tag{3.I.7}$$

All the arguments used to derive eq. (3.I.6) can be used for $\tilde{\pi}'_{\mathrm{f}}$ (see eq. 3.25), and we find

$$\tilde{\pi}'_{\mathrm{f}} = \boldsymbol{\alpha} \cdot \dot{\mathbf{A}}_{\mathrm{f}}\mathbf{d}^{\circ}. \tag{3.I.8}$$

Hence, the fixation probability to the first order in selection intensity can be calculated as

$$\pi = \alpha p_{\mathrm{m},0} + (1-\alpha)p_{\mathrm{f},0} + \delta_{\mathrm{m}}\boldsymbol{\alpha}\cdot\dot{\mathbf{A}}_{\mathrm{m}}\mathbf{d}^{\circ} + \delta_{\mathrm{f}}\boldsymbol{\alpha}\cdot\dot{\mathbf{A}}_{\mathrm{f}}\mathbf{d}^{\circ} + O(\delta^2). \tag{3.I.9}$$

2190 The entries of $\mathbf{d}^{\circ}$ can be interpreted in terms of mean coalescent times in the resident population. To see this, we first note that if the expected initial frequency of the mutant is the same
2192 in males and females, then$p_{\mathrm{m},0} = p_{\mathrm{f},0} = p_0$, which is equivalent to assuming that mutation rate is the same in males and females. Then, if the mutant arose as a single copy, $p_0 = 1/(2N)$, where
2194 $N = N_{\mathrm{m}} + N_{\mathrm{f}}$, and we have $\mathbf{p}_0 - \mathbf{q}_0 = (0, 0, -1/(2N), -1/(2N), \ldots, -1/(2N))^T$. In this case, as shown by Lehmann and Rousset (2009, eqs. A-28–A-29), element d_i° for $i \geq 3$ of $\mathbf{d}^{\circ}$ is

$$d_i^{\circ} = -T_{(i)}/(2N), \tag{3.I.10}$$

2196 where $T_{(i)}$ is the mean coalescent time into a single individual of a set of gene lineages initially residing in state i. State here refers to the configuration of the sampled gene lineages, which are
2198 given by the entries of $\mathbf{p}_t$, e.g., for $i = 3$, the third entry of $\mathbf{p}_t$ corresponds to η_t, the probability that an individual's paternal and maternal alleles are both mutant, so $d_3^{\circ} = -T_{(3)}/(2N)$, where $T_{(3)}$
2200 is the expected number of generations taken for the paternal and maternal genes of an individual to coalesce, which we write as T_2^H.

2202 3.I.3 Factoring the probability of fixation

Substituting for $\alpha = 1/2$ (for an autosomal gene) and for matrices $\dot{\mathbf{A}}_{\mathrm{m}}$ and $\dot{\mathbf{A}}_{\mathrm{f}}$ from 3.H into
2204 eq. (3.I.9), we find that we can express the probability of fixation

$$\pi = \frac{1}{2}(p_{\mathrm{m},0} + p_{\mathrm{f},0}) + K\left(\delta_{\mathrm{m}}G_{\mathrm{m}}(z_{\mathrm{m}}, z_{\mathrm{f}}) + \delta_{\mathrm{f}}G_{\mathrm{f}}(z_{\mathrm{m}}, z_{\mathrm{f}})\right) + O(\delta^2), \tag{3.I.11}$$

where G_{m} and G_{m} are given in eq. (3.31) and correspond to the selection gradients of the mutant
2206 due to its effect on male fitness and female fitness respectively. The coefficient K is

$$K = -h\left(\frac{d_4^{\circ} + d_5^{\circ}}{2}\right) - (1-2h)\left(\frac{d_6^{\circ} + d_7^{\circ}}{2} - d_3^{\circ}\right) \tag{3.I.12}$$

where d_i is the ith entry of the vector $\mathbf{d}^{\circ}$ defined in eq. (3.I.7). So, as shown in the preceding
2208 section using the relation to coalescent times (eq. 3.I.10) and $p_0 = 1/(2N)$ where N is the total

population size, $N = N_{\mathrm{m}} + N_{\mathrm{f}}$, we have

$$K = \frac{h}{2N}\left(\frac{T_2^{\female} + T_2^{\male}}{2}\right) + \frac{1-2h}{2N}\left(\frac{T_3^{\female} - T_2^{H}}{2} + \frac{T_3^{\male} - T_2^{H}}{2}\right), \tag{3.I.13}$$

where $T_2^{\male}$ ($T_2^{\female}$) is the expected number of generations taken for two paternal (maternal) genes sampled without replacement to coalesce, $T_3^{\female}$ is the expected number of generations taken for two maternal genes and one paternal gene sampled without replacement to coalesce and finally, and $T_3^{\male}$ is the expected number of generations taken for two paternal genes and one maternal gene sampled without replacement to coalesce.

Solving explicitly for K requires inverting a 13x13 matrix, $(\mathbf{I} - \mathbf{A}^{\circ} + \mathbf{Q}^{\circ})^{-1}$, which is computationally expensive, but can be done numerically. However if the mutant effect is additive ($h = 1/2$), then we can obtain the exact expression for K. If $h = 1/2$, then only the first 5 entries of $\mathbf{p}_t$ are required to solve for $K = -(d_4 + d_5)/4$. So $\mathbf{A}^{\circ}$ can be reduced to

$$\mathbf{A}^{\circ} = \begin{pmatrix} \frac{1}{2} & \frac{1}{2} & 0 & 0 & 0 \\ \frac{1}{2} & \frac{1}{2} & 0 & 0 & 0 \\ 0 & 0 & \frac{1}{2} & \frac{1}{4} & \frac{1}{4} \\ \frac{\Theta^{\male}}{4} & \frac{\Theta^{\male}}{4} & \frac{1}{2} & \frac{1-\Theta^{\male}}{4} & \frac{1-\Theta^{\male}}{4} \\ \frac{\Theta^{\female}}{4} & \frac{\Theta^{\female}}{4} & \frac{1}{2} & \frac{1-\Theta^{\female}}{4} & \frac{1-\Theta^{\female}}{4} \end{pmatrix} \tag{3.I.14}$$

and using eq. (3.I.7) with $\mathbf{A}^{\circ}$ as above, we find that K satisfies eq. (3.28), as required.

Chapter 4

Evolution of canalization in the presence of female choice

This study was conducted in collaboration with Max Reuter and Andrew Pomiankowski.

Abstract

Robustness describes the ability of a phenotype to be buffered against perturbations. It is an essential feature of many biological systems and understanding its evolution has raised considerable interest. But many questions concerning the causes and mechanisms by which robustness evolves remain open. In particular, the evolution of robustness and the presence of sexual selection have been related by two hypotheses with orthogonal outcomes. On one hand, there are claims that sexual selection favours the evolution of robustness of male secondary sexual trait, using morphological symmetry and homogeneity as a signal for good genes. On the other hand, the strong directional selection exercised on male ornaments by female choice may promote ornament phenotypic diversification, and thus disfavours its robustness by a process called decanalization. In this chapter, we present a population genetics model to investigate the conditions in which decanalization is favoured by selection (and thus robustness is disfavoured). In addition, we accomodate for negative pleiotropic effects of decanalization on female and offspring fitness. In accordance with previous claims, we find that greater than linear female preference for male trait favours the invasion of mutants that destabilize the development. But we find that this is conditional on infinite population size and the absence of significant deleterious effects on offspring survival. As the population size decreases, decanalization is increasingly compromised.

4.1 Introduction

A biological system is robust if it is phenotypically invariant in the face of genetic or environmental perturbations. Robustness is exhibited at many levels of biological an organism, from gene expression (Kaern et al., 2005) and metabolic pathways (eg. Shinar and Feinberg, 2010), all the way to organismal fitness, with behavior and phenotypic plasticity shielding fitness from a temperamental environment (de Visser et al., 2003). Mechanisms that create robust biological systems are said to be “canalizing" (Flatt, 2005). Given the variety of components of an organism that may be described as robust, it is not surprising that no general canalization process exists. But evidence suggests at least some correspondence between the mechanisms that protect the integrity of a phenotype from genetic disruptions, and those that protect it from environmental ones (Masel and Siegal, 2009).

The causes behind the evolution of robustness remain unclear, and are probably specific to the system under scrutiny. But two general hypotheses have been laid out (Siegal and Bergman, 2002; de Visser et al., 2003; Kitano, 2004; Masel and Siegal, 2009). First, phenotypic canalization could be intrinsic to the system that produces that phenotype. For example, populations evolving over neutral networks of genotypes, where two genotypes are connected if one can mutate from the other, tend to concentrate at highly connected genotypes (van Nimwegen et al., 1999), that is, mutationally robust genotypes. Secondly, canalization could evolve as an adaptive traits in its own right. This can occur in response to a long history of stabilizing selection. Once a population has reached its fitness optimum, any deviation from this optimum is counter-selected; in this situation, any heritable trait that stabilizes phenotypic expression ate the optimum will be positively selected (Lande, 1980a). Alternatively (or in addition) robustness could also evolve directly in response to sexual selection (Møller, 1990; Møller and Pomiankowski, 1993; Møller, 1997). The idea behind this hypothesis is that developmental stability provides a signal of genetic quality. Symmetry and lack of morphological abnormalities in male secondary sexual traits would then form the basis of female choice. Although the evidence across species is not entirely consistent (Polak, 2008), this paradigm seems to apply to at least some populations with female choice.

On the other hand, it has been suggested that sexual selection can favor decanalization of male secondary sexual traits. If females disproportionately advantage males with greater than average trait values, it effectively leads to the selection for greater phenotypic variance in that trait (Pomiankowski and Møller, 1995). This type of preference has been coined as “open-ended" because

it keeps increasing with trait size (Kirkpatrick, 1987), and there have been suggestions that they are the result of sensory bias exaggerating differences between large ornaments (Lande, 1981). Then, if this results in the probability of mating for a male increasing more than linearly with the size of some ornament, each decrease in fitness due to random perturbations, provoking a smaller ornament, is more than compensated by the fitness benefit reaped when random perturbations provoke a larger ornament. Thereby phenotypic variance in trait size expression is favored by female choice. Experimental support for this scenario is still wanting but there is some evidence of greater than linear female preference for trait size (eg. Mead and Arnold, 2004; Procter et al., 2012). Also, the general observation that sexual traits exhibit greater phenotypic variation than non-sexual trait suggests at minima that canalization for sexual traits is under weaker selection (Pomiankowski and Møller, 1995).

The hypothesis that it is open-ended female preference which results in heightened genetic (and thus phenotypic) variation in sexual traits has been met with criticism, notably on the premise that the overall selection on the trait is stabilizing (Rowe and Houle, 1996). This would be because overall selection reflects a trade-off between sexual selection, which exerts positive directional selection on the trait, and viability selection, which exerts negative directional selection. The following comments highlight that not only is this argument subject to caution, but also that important gaps in the current analyses discussing the relationship between female choice and canalization of male secondary sexual trait. First, whether the combined selective episodes result in stabilizing selection will depend on the fitness curve at each stage, even if they are in opposite directions (McGlothlin, 2010). An open-ended female preference, which results in a highly nonlinear fitness curve, may be difficult to counterbalance. Secondly, even if overall selection pressure on the trait is stabilizing, minimization of trait variance is selected only once the mean trait value has reached the fitness peak, but to attain this maximum may be difficult (Kingsolver et al., 2012), in which case trait variance may still be under positive selection.

In addition, previous accounts have focused on the viability and sexual selection on male traits size only. But canalization itself may be under selection, and thus affect the evolution of the trait it canalizes. And individual reproductive variance, which undergoes negative directional selection that is inversely proportional to population size (Gillespie, 1975; Lehmann and Balloux, 2007; Rice, 2008, and chapter 3), has been largely left out of the equation. But if developmental instability affects the chances of reproduction of a male, then a model taking reproductive variance into account should be used. Also, if decanalization of the male ornament disrupts the development of

other vital traits, this could have harmful effects for offspring survival. The pleiotropic effects of developmental instability of the male trait may extend beyond the balance of positive and negative fitness effects of the trait size at different stage of the male's life-cycle (Delcourt et al., 2012). Indeed, unless the development of the male secondary sexual trait is completely decoupled from that of females, decanalizing its development may have knock-on effects on female fecundity variance. The total selection would then reflect some average of these effects in each sex. Combined with the incorporation of reproductive variance, this average would be subject to sex-specific weightings (see chapter 3) complicating further the intuition that trade-offs between fitness effects of a trait results in negative directional selection on decanalization.

The relationship between canalization of male secondary sexual trait, sexual selection, and other selection pressures arising from pleiotropic effects of canalization remains unclear. In this chapter, we adapt the population genetic model of chapter 3, which is able to incorporate sex-specific variance in fertility, to disentangle the various fitness effects, and investigate the conditions under which of sexual selection is able to select for decanalizing in the face of pleiotropic effects.

4.2 Model & analysis

4.2.1 Set-up

We model the evolution of the degree of developmental instability, which is denoted by z_k for an individual indexed k. The greater z_k is, the greater the effect random perturbations have on the development of k's traits. The value of z_k is determined by an autosomal locus and the population is initially monomorphic for a resident allele, with male and female resident trait value at $z_k = z_R$ for all k. A mutant modifier causes a perturbation in z_k, and the trait value in mutant homozygotes shifts to $z_k = z_R + \delta$. The mutant has an additive effect so that the trait value in heterozygotes is $z_k = z_R + \delta/2$.

We use the method described in chapter 3 to derive the probability of fixation of the mutant. The population is composed of a finite number of adult males N_m and females N_f, and a sufficiently large number of juveniles is produced for the population to be maintained at a constant size. Generations are non-overlapping, and the life-cycle followed by the organism comprises four broad steps: mating, offspring production, viability selection, and culling which are given in greater details below.

4.2.2 Life-cycle

Male ornament Males express a secondary sexual trait that is under sexual selection from female choice. All males have the same expected ornament size $\mu_X > 0$, However, the expression of the trait is subject to random developmental variation and the realized trait size of male i is a random variable $X_i > 0$. The variation of X_i around the expectation μ_X is an increasing function of i's degree of decanalization z_i, $\sigma_X^2(z_i)$.

Mating Females mate once and choose their mates independently of one another. Female choose mating partners based on the size of the male ornament. This dependency is reflected by writing attraction as a function of X_i

$$A_i = u\big(X_i\big), \tag{4.1}$$

where the function $u(x) > 0$ models female choosiness. In the absence of female choice, $u(x)$ is a positive constant and $p_i = 1/N_\mathrm{m}$ (see eq. 4.2).

The probability p_i of a male indexed i mating with a given female k depends on female attraction to male i, written as the random variable $A_i > 0$, relative to her attraction to all males in the population

$$p_i|\mathbf{X} = \frac{A_i}{A_i + \sum_{k\neq i} A_k} = \frac{u\big(X_i\big)}{u\big(X_i\big) + \sum_{k\neq i} u\big(X_k\big)}, \tag{4.2}$$

where $\mathbf{X}$ is the collection of the X_i's for all males, and $\sum_{k\neq i} u\big(X_k\big)$ is the total attraction a female has to all males other than i. The probability p_i is approximated by first Taylor expanding eq. (4.2) about $\mu_X = \mathrm{E}[X_i] = \mathrm{E}[X_k]$, and marginalizing over the distribution of $\mathbf{X}$. Then, we substitute for the dependency for the degree of decanalization of trait variance $\sigma_X^2(z_k)$, and assume that the difference between the levels of decanalization z_k of different individuals are small, that is, of the order δ. Finally, to the first order of δ, we obtain

$$p_i(z_i, \bar{z}_{-\mathrm{m}i}) \approx \frac{1}{N_\mathrm{m}} + \frac{N_\mathrm{m}-1}{N_\mathrm{m}^2}\big(\sigma_X^2(z_i) - \sigma_X^2(\bar{z}_{-\mathrm{m}i})\big)\left(\frac{1}{2}\frac{u''(\mu_X)}{u(\mu_X)} - \frac{1}{N_\mathrm{m}}\frac{u'(\mu_X)^2}{u(\mu_X)^2}\right), \tag{4.3}$$

where z_{-i} denotes the average male degree of decanalization omitting the focal: $z_{-i} = \sum_{a\neq i} z_a/(N_\mathrm{m}-1)$. The first term of eq. (4.3), $1/N_\mathrm{m}$, is the baseline probability that male i mates with the focal female. So $p_i = 1/N_\mathrm{m}$ when the second term is zero, which occurs either in the absence of female choice, i.e. with $u(x)$ constant, or in the absence of differences between males, i.e. $z_i = \bar{z}_{-\mathrm{m}i}$. The second term of eq. (4.3) expresses the effect of differences in canalization and

is composed of three elements. The first one reflects the number of males in the competition to obtain a mating with a female and expresses the fact that selection on trait variability increases as the number of competing males decreases. The second one measures the difference between the trait variance of the focal ($\sigma^2_X(z_i)$) and that of the rest of the population ($\sigma^2_X(\bar{z}_{-\mathrm{m}i})$). The third one, finally, depends on the shape of female preference (given by the derivatives of u) and determines whether greater trait variance augments mating probability or not. When this term is positive, mutants that increase their bearers' trait variance ($\sigma^2_X(z_i) > \sigma^2_X(\bar{z}_{-\mathrm{m}i})$) increases the probability of mating.

Inspection of the last term of eq. (4.3) confirms that the effect of developmental stability on mating success depends on the shape of the female preference function u. However, it also shows that for variance to increase mating success, it is not sufficient for the preference function to show a positive curvature ($u''(\mu_X) > 0$). Rather the function must satisfy

$$u''(\mu_X) > \frac{2}{N_\mathrm{m}} \frac{u'(\mu_X)^2}{u(\mu_X)} \geq 0. \tag{4.4}$$

The offset occurs because our model takes into account the competition for matings that occurs between males. Specifically, it takes into account the balance of two effects, the net fitness effect of variation in the trait of the focal given a constant size for competitors, and the net fitness effects of variation in the trait size of competing males given a constant size of the focal individual (for a graphical illustration, see fig. 3.2 of chapter 3). The net effect of variation in the trait of the focal trait is negative. Because males compete for mating with a female, the mating probability of the focal male is a saturating function of the focal attractiveness (see eq. 4.2) and the cost of reduced mating probability when expressing a small trait is greater than the benefit of increased mating when expressing a big trait. The net effect of variation in the trait size of competitors is positive, because mating success decreases exponentially with the competitors' trait size, meaning that the benefits from competing against other males expressing a small trait more than compensate the cost of competing against males with large ornaments (fig. 3.2 of chapter 3). Both effects are inversely proportional to the number of males in the competition, N_m.

Offspring production Once the jth female has mated, she produces a total number of Y_j offspring. Y_j is a random variable with an expected value of μ_Y, the mean number of offspring for all females in the population. Because decanalization may also affect female fecundity, Y_j has a variance $\sigma^2_Y(z_j)$ that increases with the degree of decanalization z_j. Each offspring becomes male

or female independently of one another with equal probability 1/2.

Viability selection and population regulation Each offspring undergoes sex-specific viability selection where survival rate depends on the level of paternal and maternal decanalization z_i and z_j. To reflect this, we write $s^{\mathrm{m}}(z_i, z_j)$ and $s^{\mathrm{f}}(z_i, z_j)$ for male and female survival rate, respectively. A new generation of reproductive individuals is established by sampling N_{m} males and N_{f} females from the pool of surviving offspring without replacement. Males and females are sampled independently, and within a sex, sampling is unbiased with respect to the individuals' phenotypes.

4.2.3 Probability of fixation

Following the model of chapter 3, the probability of fixation π of a mutant that perturbs the degree of decanalization can be written as

$$\pi = p_0 + \delta G(\bar{z}_{\mathrm{m}}, \bar{z}_{\mathrm{f}})K + O(\delta^2), \tag{4.5}$$

where $G(\bar{z}_{\mathrm{m}}, \bar{z}_{\mathrm{f}})$ denotes the selection gradient acting on a decanalizing mutant in a population with average male and female phenotypes $\bar{z}_{\mathrm{m}} = (1/N_{\mathrm{f}})\sum_j z_j$ and $\bar{z}_{\mathrm{f}} = (1/N_{\mathrm{f}})\sum_j z_j$. If $G > 0$, then selection on the mutant is positive, and vice versa. The gradient G is weighted by a measure of adaptability $K > 0$ which integrates population genetic processes (see chapter 3). It measures the efficiency of transmission and the level of genetic drift in the population. When K is large, then the probability of selection will largely reflect the selection pressure acting on it, whereas if K is small, then π depends only weakly on selection. So K can be thought of a measure of how well the population is able to respond to selection and is thus referred as adaptability. We derived the selection gradient G and weight K for our population. The selection gradient G is found by calculating the effect of a small increase of decanalization on male and female fitness separately in an homogenous population. The two effects are averaged to give the total selection on a mutant that codes for such an increase in decanalization. the term K consists of the geometric mean of male and female reproductive variances (for details on calculating $G(\bar{z}_{\mathrm{m}}, \bar{z}_{\mathrm{f}})$ and K see chapter 3).

4.2.4 Selection gradient

In the following section we present selection gradients that measure the intensity of selection acting on a decanalizing mutant through its effects on different aspects of male and female fitness, i.e., effects on mating success through the size of the male ornament ($G_{\sigma_x^2}(\bar{z}_{\mathrm{m}})$), effects on female

fertility ($G_{\sigma_Y^2}(\bar{z}_\mathrm{f})$) and effects on offspring survival ($G_s(\bar{z}_\mathrm{m},\bar{z}_\mathrm{f})$). The total selection gradient of a pleiotropic mutant that decanalizes all of these traits is then found by adding up the individual contributions $G(\bar{z}_\mathrm{m},\bar{z}_\mathrm{f}) = G_{\sigma_X^2}(\bar{z}_\mathrm{m}) + G_{\sigma_Y^2}(\bar{z}_\mathrm{f}) + G_s(\bar{z}_\mathrm{m},\bar{z}_\mathrm{f})$.

4.2.4.1 Decanalization of male secondary sexual trait

The strength of selection on a decanalizing mutant due to its effect on variance in the expression of male ornaments, σ_X^2, is given by

$$G_{\sigma_X^2}(\bar{z}_\mathrm{m}) = \frac{1}{2}\sigma_X^{2\prime}(\bar{z}_\mathrm{m})\left(\frac{u''(\mu_X)}{u(\mu_X)}\left(\frac{1}{2}-\frac{1}{N_\mathrm{m}}\right)-\frac{1}{N_\mathrm{m}}\frac{u'(\mu_X)^2}{u(\mu_X)^2}\right). \tag{4.6}$$

The term $\sigma_X^{2\prime}(\bar{z}_\mathrm{m})$ measures the impact of decanalization on the variance of the male secondary sexual trait. Since variance of the male secondary sexual trait increases with decanalization, $\sigma_X^{2\prime}(\bar{z}_\mathrm{m}) > 0$. The second term of eq. (4.6) then captures the direction of selection on the decanalizing gene. If it is positive, then the contribution to the selection gradient of the mutant due to its effects on the male ornament is positive and decanalization is selected for. If it is negative, decanalization is selected against.

Eq. (4.6) is similar in form to eq. (4.3) and can be understood when considering the factors determining mating success. The only additional element is the negative term $-u''(\mu_X)/(N_\mathrm{m}u(\mu_X))$. This term expresses the fact that the benefit of increased mating success is partially cancelled out by increased competition with (mutant) siblings as the population size decreases (Lehmann and Balloux, 2007, chapter 3).

4.2.4.2 Decanalization of female fecundity

Females produce a number Y_j of offspring, with an expected value of μ_Y and a variance $\sigma_Y^2(z_j)$. The strength of selection on a decanalizing mutant due to its effect on this variance of fertility is given by

$$G_{\sigma_Y^2}(\bar{z}_\mathrm{f}) = -\frac{1}{2}\sigma_Y^{2\prime}(\bar{z}_\mathrm{f})\frac{1}{N_\mathrm{f}\mu_Y^2}, \tag{4.7}$$

where $\sigma_Y^{2\prime}(\bar{z}_\mathrm{f}) > 0$ measures the impact of decanalization on the variance of female offspring number. Eq. (4.7) shows that decanalization is always selected against in females. This is in line with previous results indicating that selection acts as to minimise variance in female fertility (Gillespie, 1975; Lehmann and Balloux, 2007). Weighted by the inverse of $N_\mathrm{f}\mu_Y^2$, this selection pressure only vanishes when the number of females and/or the square of the mean offspring number become

very large and reproduction approximatively deterministic (as in Gillespie, 1975; Lehmann and Balloux, 2007).

4.2.4.3 Sex-specific survival

The strength of selection on a decanalizing mutant due to its effect on offspring survival, $s(\bar{z}_\mathrm{m}, \bar{z}_\mathrm{f})$, is given by

$$\begin{aligned} G_s(\bar{z}_\mathrm{m}, \bar{z}_\mathrm{f}) = &\left(1 - \frac{1+\overline{C_Y^2}}{N_\mathrm{f}}\right) \frac{\partial \mathscr{S}(z_i, z_j)}{\partial z_j}\bigg|_{z_i=\bar{z}_\mathrm{m}, z_j=\bar{z}_\mathrm{f}} \\ &+ \left(1 - \frac{1+\overline{C_Y^2}}{N_\mathrm{f}} - \frac{1}{N_\mathrm{m}}\right) \frac{\partial \mathscr{S}(z_i, z_j)}{\partial z_i}\bigg|_{z_i=\bar{z}_\mathrm{m}, z_j=\bar{z}_\mathrm{f}} \end{aligned} \tag{4.8}$$

where $\overline{C_Y^2} = \sigma_Y^2(\bar{z}_\mathrm{f})/\mu_Y^2$ is the coefficient of variation in fecundity of a female with population average degree of decanalization $\bar{z}_\mathrm{f}$, and

$$\mathscr{S}(z_i, z_j) = \frac{1}{2}\left(\frac{s^\mathrm{f}(z_i, z_j)}{s^\mathrm{f}(\bar{z}_\mathrm{m}, \bar{z}_\mathrm{f})} + \frac{s^\mathrm{m}(z_i, z_j)}{s^\mathrm{m}(\bar{z}_\mathrm{m}, \bar{z}_\mathrm{f})}\right) \tag{4.9}$$

is the relative survival rate of the offspring of the focal couple, averaged across male and female offspring. The first line of eq. (4.8) then measures the maternal effect (with the partial differential $\partial/\partial z_j$) on the survival rate of the offspring of the focal couple, whilst the second line measures the paternal effect (with the partial differential $\partial/\partial z_i$). If decanalization decreases offspring survival, partial differentials with respect to z_i and z_j are all negative.

The paternal and maternal effects on survival $\partial\mathscr{S}/\partial z$ in eq. (4.8) are both weighted by terms in parentheses that capture how selection changes with population genetic structure. These terms are of the form $1-\alpha$, where the α terms are inversely proportional to male and female population sizes N_m and N_f and hence vanish when population sizes become large. The leading "1" term reflects the reduction in fitness associated with decreased offspring survival. In a large population ($1/N_{\mathrm{m,f}} \to 0$) this will select against decanalization. The intensity of this counter-selection, however, weakens with decreasing population size, as expressed by the negative $-\alpha$ term. In small populations, the benefits of increased reproductive output are partially cancelled by competition between siblings (Lehmann and Balloux, 2007, chapter 3). Accordingly, a reduction in offspring survival is less deleterious under these conditions.

The cost $\alpha = (1+\overline{C_Y^2})/N_\mathrm{f}$ on maternal strategies reflect that if, on average, female variance in fecundity is high, it is more likely that a subset of female monopolizes the reproduc-

tive effort, and thus increase the probability that two individuals are sibs through their mothers. This cost due to female variance in fecundity carries over to selection for paternal strategies ($\alpha = (1+\overline{C_Y^2})/N_\mathrm{f} + 1/N_\mathrm{m}$), since male fertility is constrained by females. In addition males may mate multiply, thus increasing the likelihood that some males monopolize offspring production. In a genetically homogenous population, that increase in likelihood is simply $1/N_\mathrm{m}$.

4.2.5 Adaptability

The probability of fixation of a decanalizing mutant also depends on adaptability $K > 0$ which weights the selection gradient (eq. 4.5). And for an additive ($h = 1/2$) mutant that arises with initial frequency p_0, we have

$$K = \frac{4p_0}{\frac{1}{N_\mathrm{m}} + \frac{2}{N_\mathrm{f}}\left(1+\overline{C_Y^2}\right)}. \tag{4.10}$$

So K increases with p_0. This is because mutants that have greater initial frequency p_0 are initially more apparent to selection, and so their probability of fixation is a better reflection of the selection pressure acting upon them. In addition, eq. (4.10) shows that K increases with population size and decreases with the average coefficient of variation $\overline{C_Y^2}$. In accordance with previous work (Caballero, 1995), we find that small populations in which females produce a more variable number of offspring have a smaller effective population size and respond less well to selection.

4.3 Discussion

The relationship between the evolution of robustness and sexual selection is not straightforward. It has been argued that the strong directional selection on male ornaments that sexual selection generates may promote the release of phenotypic variation for ornament size (Pomiankowski and Møller, 1995), and thus the decanalization of the trait. If previous studies have accounted for the effect that decanalization has on the production of a mean number of offspring for a male (Lande, 1980a; Shnol and Kondrashov, 1993; Pomiankowski and Møller, 1995), they have not integrated its effect on the variance in its offspring production. More importantly, little consideration has been given to pleiotropic effects of altering developmental instability. Unless the control mechanisms of male and female development have evolved to be independent, selection for decanalization of the male trait may also increase variance in female fertility. Similarly, higher levels of developmental instability might have deleterious effects on offspring survival.

In this chapter, we aimed to clarify the evolution of developmental instability under female

choice sexual selection. To do so, we derived the probability of fixation of a mutant which decanalizes the expression of a male secondary sexual trait using the model developed in chapter 3. Through its effect on the expression of the ornament, the mutant affects male mating rate (eq. 4.6) according to female preference. In addition, we include possible pleiotropic effects by assumed tht the mutant increases variance in female fertility (eq. 4.7), and decreases offspring survival (eq. 4.8).

The effect of decanalization on the male mating rate depends on its effect on the male ornament, and female preference for that ornament. We modelled the attraction of a female for a male with trait size x with a general function $u(x) > 0$ and derived the mating probability (eq. 4.3). Previous arguments (Pomiankowski and Møller, 1995) have suggested that an open-ended preference function ($u''(\mu_X) > 0$) is sufficient for the release of phenotypic variation, but we find that this is not enough, even in the absence of pleiotropic effects. If indeed the mating probability of a male with an arbitrary female does increase with $u''(\mu_X)$ (eq. 4.3), the conditions for a decanalized male to have a higher mating probability than a canalized male are more stringent (eq. 4.4). The reason for this is that the mating probability saturates with the attractiveness of the focal male (eq. 4.2), which means that there is an intrinsic diminution in mating probability from attractiveness variance. This reduction is inversely proportional to the number of males and the more males there are, the less significant the effect of variance in attractiveness is on mating probability (eq. 4.3). To compensate for this diminution due to variance, attractiveness has to accelerate even more with respect to male trait size (according to the inequality in eq. 4.4), and this compensation diminishes with the number of males. The effect of reproductive variance further diminishes the selection pressure that may promote decanalization (eq. 4.6). As in chapter 3, this is due to the increase in sibling competition reducing the impact of beneficial mutations in small populations. So the conditions for female preference to select for decanalization, irrespective of pleiotropic effects, may be more stringent than previously suggested, particularly in populations with few males.

By construction, we assumed that decanalization of the male trait had the knock-on effect of increasing variance in female fertility and decreasing offspring survival. So unless the selection gradient due to its effect on male mating rate (eq. 4.6) is positive, selection will necessarily aim to drive down developmental instability. Assuming eq. (4.6) is positive, then the total selection gradient for a mutant reflects the balance between its positive effect on male mating rate and its deleterious pleiotropic effects.

Our model predicts that this balance, and hence the net selection on the mutant, depends to a

large degree on population size and variation in female fertility. As we saw in chapter 3, selection on fertility variance is inversely proportional to population size, so the deleterious effects of decanalization on female fitness vanishes with population size (eq. 4.7). In an infinite population, the mutant will then be positively selected if the positive effects of male mating rate are greater than the cost due to the reduction in offspring survival

$$\frac{1}{4}\sigma_X^{2\prime}(\bar{z}_\mathrm{m})\frac{u''(\mu_X)}{u(\mu_X)} > -\left(\frac{\partial \mathscr{S}(z_i,z_j)}{\partial z_j}+\frac{\partial \mathscr{S}(z_i,z_j)}{\partial z_i}\right)\Bigg|_{z_i=\bar{z}_\mathrm{m},z_j=\bar{z}_\mathrm{f}}. \tag{4.11}$$

But as the population size gets smaller, selection acting against variance in female fertility intensifies and increasingly affects the total selection gradient (eq. 4.7). The increased sibling competition also abates the intensity of purifying selection stemming from diminished offspring survival (eq. 4.8). This may or may not be counterbalanced by the parallel effects that reduce the positive selection due to male mating rate (see two paragraphs above). And whether it does will depend, at least partly, on the coefficient of variation of female fertility $\overline{C_Y^2}$. If this is very large, then the diminution in negative selection on the mutant may be much larger than diminution in negative selection due to a reduction in population size (compare eqs. 4.6 and 4.8). Together, these results suggest that in small populations in which female fertility is very stable, decanalization will have a much harder time invading.

In contrast, our selection analysis suggests that if the coefficient of variation of female fertility $\overline{C_Y^2}$ is very large, then a decanalizing mutant that was positively selected in an infinite population may still be under positive selection when the population is small. However, while selection remains positive, it will tend to be inefficient, because a small population size coupled with significant coefficient of variation of female fertility $\overline{C_Y^2}$ results in a small adaptability term K (eq 4.10). As a consequence, the likelihood that a positively selected mutant will reach fixation is diminished. So even if small population sizes and highly variable female fertility favour the invasion of decanalizing mutants, their fixation is less certain under these conditions than their purge in the reverse scenario (small $\overline{C_Y^2}$).

The conditions for the invasion of decanalizing mutants then appear significantly compromised compared to those suggested by Pomiankowski and Møller (1995). This stems not only from previously omitted competition terms that weaken the positive selection on the decanalization of the male secondary sexual trait, but also from the negative selection generated by detrimental pleiotropic effects and ecological factors such as smaller population size and stable female fertility.

This corroborates with the metadata analysis, also by Pomiankowski and Møller (1995), which showed that male secondary sexual traits do not have any more residual (i.e. environmental) variance than non-sexual trait, thereby suggesting that decanalization of male ornaments is rare.

To conclude, it is undisputed that pleiotropic fitness effects of decanalization are very important in determining the balance of selection forces acting upon it, but demography and ecology also play a vital part. In particular, by showing that in small population size in which females reproduce with little variance, the invasion of decanalizing mutants is severely compromised, we have highlighted how demographical and ecological factors may even shift the balance of selective forces. This study also serves as an example for the type of argument that can be studied with the model of chapter 3, and of how the inclusion of selection on reproductive variance and correct calibration of genetic drift may change standard results.

General conclusion

Despite sharing the vast majority of their genes, males and females of the same species can exhibit striking phenotypic differences. To understand the evolution and mechanisms leading to sexual dimorphism is of great interest. Answering why, and how, such a level of phenotypic differences can arise when relatively little genetic variation is available, not only satisfies scientific curiosity, it also provides key insight into how a genome achieves phenotypic plasticity. Sexual dimorphism can apply to the many scales of measurements of a phenotype, and its study is a huge field of research. This thesis necessarily had to brush over some details, but nonetheless covered a wide range of topics about the evolution and mechanisms of sexual dimorphism. In this final section, we first summarize the results of the four chapters of this thesis, and then discuss how they tie in together in the study of the evolution of sex-specific phenotypes.

In chapter 1, we started by answering some questions revolving around the evolution of sex determination cascades, which establish the chemical background necessary to sexual dimorphism. Specifically, we investigated the correlation between the evolution of the gene pathway in *Drosophila* and the evolution of the DNA sequences of the genes that compose it. The main hypothesis about the evolution of sex determination cascades is that they evolve from the bottom-up, that is, by the successive recruitment of top regulators. Simplistically, this would suggest that the DNA sequence of the bottom gene has changed very little, as it has a common function in many species, but that the higher up the genes are in the cascade, their DNA sequence is increasingly variable. In addition, we could expect to see the recent prints of positive selection for recently recruited genes. However, this is not exactly what we observed. Rather, we found that the molecular functions of, and interactions between, the different genes to be of primordial importance in understanding the changes at the level of DNA. This highlights the limitations of corroborating evolutionary changes separated by more than one scale of measurement directly, here DNA with gene-networks. We were able to find a high degree of correspondence between the changes at these two scales only once we had combined the hypothesis of bottom-up evolution with the in-

depth molecular knowledge of the sex determining genes of the *Drosophila* cascade. This allowed us to tentatively suggest some direction for future molecular research.

Once sex determination is set-up, the cell has an array of sex-specific regulators at its disposal, but evolving sexual dimorphism is not necessarily straightforward due to genetic correlations between males and females. In chapter 2, we investigated the evolution of sexually antagonistic genes, which are the precursors to the appearance of adaptive sexual dimorphism. Genes are sexually antagonistic if they are beneficial to one sex and detrimental to the other. The tension between selection on one sex promoting fixation of one allele, and selection on the other sex promoting fixation of another, can end up in stable polymorphism. Until the gene is sex-specifically regulated, which results in sexual dimorphism, sexually antagonistic variation is maintained indefinitely in the gene pool. Indefinitely, that is, in the absence of genetic drift. Random perturbations to gene frequencies can drive an allele to fixation resulting in the loss of genetic variation. In chapter 2, we measured the impact of genetic drift on the genomic distribution of sexually antagonistic distribution. The intensity of genetic drift can change throughout the genome, notably because there are fewer copies of the X chromosome than autosomes. But this baseline difference can be compensated if males have stronger reproductive variance as the transmission of female genomes becomes on average more reliable. We found that differences in genetic drift, synthesized by the N_{eX}/N_{eA} ratio, can significantly alter predictions based on selection only about where sexually antagonistic variation lies in the genome. Further, we argued that since the N_{eX}/N_{eA} ratio is a population based parameter, it is more apt in explaining variation of distribution across populations than systematic differences in selection parameters. Finally, we used our results to predict that the interplay of sexually antagonistic selection and genetic drift should lead to the broad brush pattern of accumulation of sexually antagonistic alleles on the X in male heterogametic (XY) species and, on the autosomes in female heterogametic (ZW) species. This should be especially so when reproductive variance is stronger in males than in females, which is often the case in non-monogmaous species.

In chapter 3, the importance of sex-specific reproductive variance became the focus of research. The chief objectives of that chapter were to characterize and model the evolution of sex-specific reproductive variance. Given the widespread existence of sex-specific reproductive skew, we aimed to predict the fate of alleles which are able control the reproductive variance of males and females. To that end, we constructed a population genetic framework with a biologically realistic account of sexual reproduction. Variance in sex-specific fertility had so far been modelled as variance in the production of gametes, which then mixed randomly to form zygotes. Individuals

produced gametes independently of one another, so there was no covariance between the gamete production of two individuals. We relaxed that assumption, and by implementing an explicit mating system, we studied at how mating structures these (co)variances. We then investigated how the reproductive (co)variances evolve, and in turn affect the evolution of reproductive traits. In agreement with previous studies, we found that the different components of the total variance in fertility were under negative selection, albeit with an intensity inversely proportional to population size. So variance-minimizing selection vanishes as the population size gets very large. But if the population is spatially structured, and there is at least some local competition, variance-minimizing selection is inversely proportional to patch size and may thus still be effectual in large populations.

We also looked at the impact of reproductive variance on the evolution of other traits and we observed two interrelated effects. First, we saw that elevated reproductive variance, in either sex, abates the efficacy of selection for any trait. This reduction in adaptation was paralleled to the effect of genetic drift. By reducing the efficacy of transmission, reproductive variance reduces the efficacy of selection. Secondly, we found that because reproductive variance and the level of kinship in the population are positively correlated, reproductive variance reduced some of the selection pressure on beneficial traits due to sib competition. Also, since the probability that two offspring are sibs through their mother or through their father may be different, sex-specific reproductive variance could weigh differently on male and female traits. Notably, we could show that if reproductive variance is higher in males, a paternal strategy that improves offspring survival has a weaker chance of fixing in the population than a maternal strategy that improves offspring survival by the same amount. The effect of sex-specific reproductive variance on traits related to mating and fertility distribution were not as clear-cut, partly due to the intricacy of the problem. We suggested directions for future implementations of the model to alleviate some of the complexity.

Finally, chapter 4 provides an example of how to apply the model. We used it to study the relationship between sexual selection and developmental instability. Sexual selection through female choice applies a strong directional selective force on male traits. This consistently selects males with larger traits. But when female preference is open-ended, this has the interesting effect of selecting for increased phenotypic variance in males. Under these circumstances, the probability of mating for a male increases more than linearly with the size of some ornament, so that each decrease in fitness due to perturbations provoking a smaller ornament, is more than compensated by the fitness benefit reaped when perturbations provoke a larger ornament. Phenotypic variance can be released by increasing developmental instability of the male ornament. Intuitively, dis-

rupting phenotypic variance will also affect reproductive variance of a male, and thereby either reduce or magnify potential benefits of increasing phenotypic variance which has not previously been taken into account. Not only that but increasing developmental instability of the male may have pleiotropic sex-specific effects on the development of females as well, for example increasing their variance in fecundity. In addition, if decanalization of the male ornament disrupts the development of other vital traits, this could have harmful effects for offspring survival. We adapted the model of chapter 3 to study these pleiotropic interactions, and how they affect the evolution of developmental stability in the presence of female choice. In contrast to previous studies, we found that open-ended preference was not a sufficient condition to select for developmental instability, particularly in small populations, and irrespectively of pleiotropic detrimental effects of developmental instability. We saw that whether these latter effects inhibited the invasion of decanalizing mutants depended on their strength, but also on the population size, and reproductive variance. This showed how the inclusion of selection on reproductive variance and correct calibration of genetic drift may change standard results, and highlighted the importance of incorporating ecological knowledge into evolutionary arguments.

This thesis has investigated the evolution of sex-specific phenotypes with theoretical models, and in particular, looked at the modelling of sexually antagonistic traits. We discuss in the following how the model of chapter 3 may prove useful in studying the evolution of sexually antagonistic traits. First, we discuss how this model can take sex-specific selection into account more appropriately. This could be important as the consequences of sexually antagonistic selection have been suggested to reach far beyond the evolution of sexual dimorphism. It would not only compromise the efficacy of sexual selection (Pischedda and Chippindale, 2006) and maintain genetic variation in the face of selection (Kidwell et al., 1977), but would also to able to change sex determining loci (van Doorn and Kirkpatrick, 2010) and population sex ratio (Blackburn et al., 2010). The standard Wright-Fisher model, on which chapter 2 and previous studies are based, was a good starting point to investigate sexually antagonistic selection, but has limitations. Selection in the Wright-Fisher model is best interpreted as survival selection, filtering the juveniles that will reproduce. But experiments have shown that there is little conflict over what makes a good juvenile, as juvenile fitness is positively correlated inter-sexually, and genomes that are sexually antagonistic are negatively correlated across the sexes for reproductive success (Chippindale et al., 2001). In particular, the antagonism affects male mating rate and female fertility. To specifically tackle reproductive success was made possible in chapter 3. The population genetic model of chapter 3 is

fully capable of integrating antagonistic selection at the correct level of life-histories.

Antagonistic selection is not the only factor to affect the evolution of antagonistic traits. As it was underlined in chapter 2, the impact of genetic drift may also have important consequences for the presence and genomic distribution of sexually antagonistic alleles. Given that genetic drift synthesises many population-wide and ecological parameters, like population size, sex ratio and sex-specific reproductive variance (Caballero, 1995), it is fit to explain variation across populations. The theoretical machinery used in chapter 2 however synthesizes all these population and ecological information into a single parameter, and necessarily loses some details about the initial information. Differences in reproductive variance across the sexes in chapter 2 are limited to inflate or deflate the variance effective population size. But as showed in the model of chapter 3, and as illustrated in chapter 4, greater levels of reproductive variance not only increase the overall level of genetic drift, but also influence the strength of selection on sex-specific traits in a sex-specific manner. The model of chapter 3 then offers a more in-depth view of the effects of asymmetries across the sexes of reproductive variance. But chapter 2 also highlighted the importance of the location of sexually antagonistic genes. That X-linked genes are not apparent to selection in male heterozygotes has profound consequences for the overall selection scheme that sexually antagonistic genes undergo. To understand even further the interaction between genomic location, reproductive variance and sex-specific selection, we have begun, with Max Reuter and Laurent Lehmann, to modify our model of chapter 3 to encompass X-linked genes.

As illustrated by chapter 4, applying the model of chapter 3 to previously established evolutionary results may reveal some interesting effects of the population structure and ecology of dioecious populations. We have discussed how it could be interesting to use it to study sexual antagonism. This echoes Gillespie (1977)'s insight, who foresaw that polymorphism for fertility variance in haploids would change the game. Since then, haploid models have been used to show that fertility variance has important consequences for the evolution of traits as diverse as dispersal (Shpak, 2005; Shpak and Proulx, 2007; Lehmann and Balloux, 2007), and helping behaviors (Lehmann and Balloux, 2007; Beckerman et al., 2011). The model of chapter 3 extends Gillespie (1974)'s framework to dioecious populations. And unlike previous applications (Taylor, 2009), it enables the inclusion of the deleterious effects of sib competition and establishes a clear link with the reproductive biology of populations. Further, we note that the capabilities of the model extend beyond the investigation performed in chapter 4, that is calculation of mutant fixation probability. We gave recipes on how the model can be used to derive the stationary distributions of phenotypic

traits in males and females separately. Making statistical comparisons between these predictions and distributions observed in experimental or wild populations then opens the way for making more detailed and realistic inferences of the forces driving the the evolution of sex-specific phenotypes.

To conclude, our exploration of the evolution of sexual dimorphism has highlighted that investigating the sex-specific fitness of traits is not enough in order to understand the evolution of sex-specific phenotypes. The genetic architecture supporting that trait, how the trait is transmitted, and whether this transmission exhibits sex-specificities are all significant factors in the evolution of sexual dimorphism. In particular, we mentioned not only genetic effects, like the architecture of the gene pathway underlying a trait and, the location of genes in the genome, but also ecological effects, such as sex ratio, population size and the way the sexes arrange themselves to reproduce. In turn, these genetic and ecological factors may evolve in response to sexual dimorphism, and the feedback mechanism quickly becomes intractable, suggesting a bright future for theoretical models in the study of the evolution of sex-specific phenotypes.

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