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Title: Fitness decline in species with small populations and biased sex ratios

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**Abstract:** The abstract should be 100-125 words, and organized in this structure: An opening sentence that sets the question that you address and is comprehensible to the general reader, background content specific to this study, results, and a concluding sentence. It should be a single paragraph.

In both captive and natural conditions, many species face small population sizes and an imbalance between the number of males and females reproducing. How do these characteristics impact the fitness of each sex and the species? These characteristics ultimately determine the strength of selection and random genetic drift in the species and within each sex. This balance between selection and drift can impact the fate of alleles that are under different selection pressure in males and females. Using simulations, we show that under certain conditions, species will fix alleles that benefit the common sex and harm the rarer sex. Our results provide insights into how small population sizes and how biased sex ratios can be before one sex is likely to experience a fitness collapse.

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If population size is small and the ratio of males to females is unequal the rarer sex is destined to become unfit.

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**Introduction**

**Many species have small population sizes and biased sex ratio**

Many species are naturally rare and likely characterized by small population sizes (cite). Other species that were once present in large numbers are now isolated in small populations due to climate change and habitat destruction (cite). The population size of a species determines the degree to which natural selection controls the fate of mutations. When population sizes are large natural selection can dominate the change in allele frequency such that beneficial mutations are more likely to increase in frequency and deleterious mutations are more likely to decrease in frequency. But, if population sizes are small genetic drift can be the dominant force in allele frequency change such that beneficial and deleterious mutations have equal likelihood of increasing or decreasing in frequency. Thus, these species with small population size are at risk of accumulating more mildly deleterious alleles and being unable to fix new adaptive mutations. This balance between selection and drift has been well explored in both empirical and theoretical frameworks (lots of cites). However, in theoretical studies it has been customary to treat populations as being of roughly equal sex ratio (cite). Yet in many species there are strong biases in the OSR (operational sex ratio). OSR is the ratio of the rarer sex to the more common sex. Strong bias in OSR has been well documented in insects, birds, fish, and mammals (Elmberg 1990; Gwynne 1990; Mitani *et al.* 1996; Jirotkul 1999). These imbalances in the number of males and females that are able to reproduce can originate from a skewed ratio of males and females at birth, may develop due to differences among sexes in survival to reproductive maturity, or may be a product of the ability of a few individuals of one sex to dominate all mating opportunities. In these cases of strong OSR does the balance of selection and drift then extend to the sexes? Can the fate of mutations be dominated by drift in one sex but by selection in the other?

If this balance between selection and drift extends to the sexes within a species it could have a striking impact on the fate of genetic variation. Many mutations have different selection coefficients in males and females. The evolution of separate sexes often leads to a cascading effect where the adaptive landscape of males and females is strikingly different. These differences in selection pressure experienced by the sexes can lead to fundamental differences in the benefits and costs associated with mutations. The classic example is the case where an allele benefits one sex but harms the other, this pattern is known as sexually antagonistic selection. Empirical studies have identified several examples of loci that have differential fitness effects in males and females. In 12 species of African cichlid in the genera *Labeotropheus*, *Matriaclima* and *Tropheops* the OB locus has an allele that causes the orange-blotch color pattern and provides crypsis for females but disrupts the male color cues used for mate recognition. This sexually antagonistic variation has been largely resolved by the tight linkage of the OB locus to a dominant female sex determining allele (Roberts, Ser & Kocher 2009). Similarly, among sympatric populations of sticklebacks in Japan, it appears that sexually antagonistic variation has driven a fusion between an autosome and sex chromosome, and may have contributed to a speciation event (Kitano *et al.* 2009). More broadly, work in Drosophila has shown that some haplotypes provide strikingly different fitness depending on the sex in which they are carried (Innocenti & Morrow 2010). Even in the human genome, evidence has been found for the footprint of sexual antagonism. At birth, allele frequencies should be equal between males and females. However, some genes show a divergence in allele frequency among adults. This divergence is strongest in genes that are slightly sex-biased (Cheng & Kirkpatrick 2016; but see Kasimatis, Ralph & Phillips 2019). Even in cases where a mutation is either beneficial or deleterious in both sexes the selection coefficient that is measured in the sexes may be strikingly different (Sharp & Agrawal 2013). At an extreme are those genes that have sex specific expression where a mutation regardless of its selection coefficient is only selected on in a single sex. Understanding the way that population size and sex bias interact to determine the fate of genetic variation is key to make informed decisions in captive breeding programs, domestic animal production, and even maintenance of laboratory colonies of model organisms.

**Results and Discussion**

**Model**

We used diploid biallelic forward-time population genetic simulations to investigate the fate of mutations with different selection coefficients in males and females. These simulations spanned population sizes 50 to 2000 individuals, four dominance factors (0, 0.5, 1, and sex specific dominance), four selection coefficients (.1 - .9), and eight levels of operational sex ratio (OSR) bias (0.01 to 1.0). All dominance factors describe the allele benefiting the male. All simulations began with alleles at equal frequency and were run till a single allele fixed or 1000 generations had elapsed. For each set of possible parameters we performed 1000 simulations. The primary results discussed are for a locus that exhibits symmetric sexual antagonism where the benefit to one sex is the same as the cost to the other sex. In some cases, the results are best understood by considering Ne, the effective population size, for this we use the standard formula for variance effective population size with unequal sex ratio (supplementary file 1 equation 1). Results for a model of sex-limited selection, linkage to a sex determining locus and a complete description of methods are available in the supplementary file 1.

**H and maintenance & Fitness is balanced between sexes**

Consistent with previous research our model shows that when populations have equal sex ratio and large size (greater than XXX of each sex) both alleles are maintained and the dominance factor of the alleles determines the allele frequency at equilibrium (figure XXX). In these cases, since both alleles are maintained both sexes exhibit intermediate mean fitness. At the opposite end of the spectrum is the case where population size is small (Ne less than XXX). Under these conditions drift becomes the dominant force in both sexes and one allele will normally fix. If the genetic architecture includes a recessive and dominant allele the recessive allele would normally be maintained at a higher frequency and is thus often the allele that fixes (figure XXXX). For cases of additive architecture or sex specific dominance (the allele that benefits a sex is dominant in that sex) both alleles are equally likely to fix. Our simulations show that when OSR is not considered sexually antagonistic alleles will be maintained or fixed randomly such that fitness of the sexes will remain on average equal.

**Intro to results a single example of how it can collapse**

In contrast to the results with equal sex ratio, our results reveal that there is a combination of population sizes and OSRs that will lead to consistent biases in the alleles that fix in a population. Specifically, we find that when the combination of OSR and population size lead to an Ne of XXX to XXXX alleles benefiting the common sex are more likely to fix. For instance, when common sex is represented by XXXX individuals and OSR is XXXX the Ne is XXXX. For the case of strong selection (s=0.9) we find that the allele benefiting the common sex fixes in W, X, Y, Z, percent of simulations for recessive, additive, dominant and sex specific dominance respectively. These can be compared to the frequency of fixation where the common sex is held constant at XXXX but OSR is 1.0. This shows that the increase in frequency of fixing the allele benfitting the common sex is W, X, Y, and Z for the same four cases. This bias in allele fixation leads to an average increase in fitness for the common sex and a collapse of fitness in the rarer sex.

**The impact of selection strength**

The selection coefficient of a mutation determines the population size that is required for natural selection to determine the fate of an allele. As such we see that the Ne required for a bias in fixation probabilities varies with the selection coefficient of the mutation being investigated. For the case of strong selection it is XXX described above. For mutations with a lower selection coefficient of XXXX the same results are achieved when Ne is somewhat higher at XXX. For the weakest selection coefficient we find that a common sex of XXX and an OSR of XXXX is required for a substantial bias in fixation probabilities to occur.

**Sex chromosomes**

Sex chromosomes are a particularly interesting portion of the genome to investigate because even when the sex ratio is equal X and Y chromosome linked alleles are selected in the sexes at different frequencies. In our simulations of a locus that is loosely linked to a sex determining locus we find that strong OSR can lead to either a feminized or masculinized X or Y chromosome. This pattern is most extreme when the chromosome and the more common sex match for instance when males are more common the Y chromosome becomes hyper masculinized. However, this pattern can extend to the X chromosome as well. In the case of populations with XXXXX males and and OSR of XXX (XXXX females) the X and Y will fix the allele benefitting the male in XXXX percent of cases.

Our results show a clear pattern that strong imbalances between the number of males and females in a population can lead to the fate of an allele being driven by the selection coefficient of a single sex. When the selection coefficient among the sexes is opposite this will lead to an inevitable decline in fitness of the rare sex. For this reason, managers of captive populations (in conservation or domestic production arenas) should strive to insure a roughly equal contribution of males and females in reproduction. Further, we recognize that these results reveal a method that could be used in model organisms to effectively query the genome through an evolve and resequence approach to determine the relative frequency and nature of differences in male and female selection coefficients across the genome.

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**Acknowledgments:** We thank members of the Blackmon lab and J.N. Dulin for feedback as this project progressed **Funding:** Texas A&M University HB startup funds; **Author contributions:** All authors contributed to analysis, HB designed the study, RDG and AS wrote the initial draft of the manuscript; **Competing interests:** Authors declare no competing interests. **Data and materials availability:** Code necessary for running all simulations and producing all figures is avaialbe via the GitHub repository: XXXXXXX.

Supplementary Materials:

Materials and Methods

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