Title: The fitness of a the rare sex is destined to decline

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**Abstract:**

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.

**One Sentence Summary**:

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

The joint action of natural selection and genetic drift determine the fate of genetic variation. The population size of a species determines the balance between these forces. When population sizes are large natural selection will dominate 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. However, if population sizes are small genetic drift will be the dominant force in allele frequency change such that beneficial and deleterious mutations can have similar probability of increasing or decreasing in frequency. Indeed many species are naturally rare and likely characterized by small population sizes (cite). Simultaneously climate change and habitat loss are leading to the fragmentation and isolation of ranges of once common species (cite). Thus, these species with small population sizes are at greater 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).

Species don’t just vary in their population sizes, they also vary in the balance between the number of males and females that are able to reproduce. We know that in many species, there are strong biases in the OSR (operational sex ratio). OSR is the ratio of the number of the rarer sex to the more common sex that participate in reproduction. 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. It is unclear how strong OSR bias will impact the balance of selection and drift. 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 particularly when that variation has 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 selection coefficients when a genotype is expressed in a male versus a female. The classic example of this 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 (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 suggesting differential viability selection among the sexes in a single generation. (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). A more extreme example are those genes that have sex-specific expression where a mutation can only be selected on in one sex.

To explore the impact of OSR on genetic variation, we used forward time population genetic simulations. This paper demonstrates that OSR can have profound impacts on the fate of alleles with different selection coefficients among males and females. We describe a range of population characteristics that can lead to a collapse of fitness in the rarer sex in a population. These results are key to making informed decisions in captive breeding programs, animal production, and maintenance of laboratory colonies of model organisms.

**Results and Discussion**

**Model**

We used diploid biallelic two-locus forward-time population genetic simulations to investigate the fate of mutations with different selection coefficients in males and females. The first locus is a sex-determining locus with alleles X and Y. Individuals that are homozygous for the X allele are females, while heterozygous individuals are males. The second locus (the sexually antagonistic locus) has alleles A1 and A2 where the A1 allele is male beneficial, and allele A2 is female beneficial. The two loci were separated by a recombination distance of either 20 or 50 centimorgans to represent either a site linked to the sex-determining locus or an autosomal site. Population size was defined by the number of the common sex (four levels varying from 50 to 1000 individuals) and the operational sex ratio (OSR) bias (eight levels varying from 0.05 to 1.0), which determines the number of the rare sex. For example, if the common sex is represented by 500 individuals and OSR is 0.6 then the rare sex would be represented by 300 individuals. For each set of population size parameters, four dominance factors (0.0, 0.5, 1.0) were analyzed and describe the allele benefitting males. We repeated each simulation using four selection coefficients (varying from 0.1 to 0.9). These combinations lead to 768 model scenarios. For each of these scenarios, the model was initialized with the frequency of the A1 allele set to 50% in both males and females and were run till a single allele fixed or 1000 generations had elapsed. For each scenario, 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.



**Figure 1 Impact of variation in operational sex ratio on genetic variation.** Columns represents models with 50, 100, 500, or 1000 individuals of the common sex. Rows represents models with dominance factors of 0.0, 0.5, or 1.0. The horizontal axis indicates the operational sex ratio–number of the rare sex divided by the number of the common sex. The vertical axis indicates the mean frequency of the allele benefitting the common sex in yellow or the proportion of simulations where this allele fixed in purple.

Our results reveal distinct danger zones where the concentration of selection in the common sex leads to fixation of alleles beneficial to that sex and the collapse of fitness in the rare sex. In each set of scenarios, genetic architecture leads to variation in fixation rates. Rates are highest when the allele beneficial to the common sex is recessive and lowest when the allele beneficial to the common sex is dominant. In scenarios with 1000 individuals of the common sex and an OSR of 0.05, the allele beneficial to the common sex will fix in 2-26% of simulations (Fig. 1A). When OSR is higher, both alleles are maintained in almost all simulations. In scenarios with 500 individuals of the common sex and an OSR of 0.10 or 0.05, the allele beneficial to the common sex will fix in approximately 2-27% and 40-98% of simulations, respectively (Fig. 1A). Scenarios with 100 individuals of the common sex provide the most striking examples of fitness collapse in the rare sex. In these scenarios, we find many genetic architectures and OSR values will lead to high fixation rates of alleles benefitting the common sex. The most compelling of these is when OSR is either 0.10 or 0.20. In these cases, the fixation rates for alleles beneficial to the common sex often approach 100% (Fig. 1A). In scenarios with just 50 individuals of the common sex drift is a much more powerful force. The combination of equilibrium frequencies and drift lead to high fixation rates even with equal sex ratio. When sex ratio is equal and the genetic architecture is additive, 25% simulations will fix one of the alleles. In the scenario where the allele benefitting the common sex is recessive, it will fix in approximately 60% of simulations, and likewise, in the case where the allele benefitting the rare sex is recessive, it will fix in 60% of simulations. In fact, this is the one scenario (recessive allele benefitting the rare sex and common sex number of 50 individuals) that we see a consistent pattern of higher fitness in the rare sex (Fig. S1). However, it should be noted that this would be expected to be balanced by an equal number of mutations with the opposite genetic architecture leading to no net gain in fitness in the rare sex. Even under these conditions of strong drift with a common number of just 50 if the OSR is reduced below 1.0 we begin to see a bias towards favoring alleles benefitting the common sex.

There is no apriori reason to believe that mutations benefitting one sex should be biased towards a particular genetic architecture, and as such, we can marginalize across architectures and evaluate the mean difference in fitness of the common sex and the rare sex. In figure 2 we see that when the common sex is represented by either 50 or 100 individuals, any OSR less than 1 will lead to a decrease in fitness of the rare sex relative to the common sex. This fitness collapse is most extreme for OSR levels of 0.2. In contrast, with larger populations, the level of OSR required to force a collapse of fitness in the rarer sex is higher (0.05-0.10). However, we note this is also the scenario where this effect is most extreme, and the rarer sex's fitness collapses most dramatically.



Figure 2 Fitness divergence among sexes. The vertical axis is the absolute fitness of the common sex minus the fitness of the rare sex. The horizontal axis represents the operational sex ratio and the color of each line denotes the number of the common sex. Higher values indicate increased fitness in the common sex and reduced fitness in the rarer sex.

The results presented here are for an autosomal locus in a system with an XY sex-determination system. However, these results would apply equally to any autosomal locus in a ZW sex-determination system and to all loci in a system with environmental sex-determination. The application of these results to species with environmental sex determination could be particularly concerning in light of rising temperatures which could lead to a consistent strong bias in sex ratio and the potential collapse of fitness in the rarer sex.

Together these results demonstrate that the balance between drift and selection does extend below the species level and that strong OSR can lead to a concentration of drift in one sex and selection in the other. Captive breeding programs are becoming an essential tool in the conservation of species in danger of extinction. In captive breeding programs having more females offers the opportunity to maximize the number of offspring that can be produced. However, based on these findings, we suggest that any captive propagation should make every attempt to maintain relatively equal numbers of males and females in captivity. This route may extend the time course for recovery. However, ultimately the species that emerges will maintain fitness in both sexes unlike one produced with a highly skewed sex ratio during an extended captive phase.

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Supplementary Materials:

Materials and Methods

Figures S1-S#

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Cheng, C. & Kirkpatrick, M. (2016) Sex-specific selection and sex-biased gene expression in humans and flies. *PLoS Genet,* **12,** e1006170.

Innocenti, P. & Morrow, E.H. (2010) The sexually antagonistic genes of Drosophila melanogaster. *PLoS biology,* **8,** e1000335.

Kasimatis, K.R., Ralph, P.L. & Phillips, P.C. (2019) Limits to Genomic Divergence Under Sexually Antagonistic Selection. *bioRxiv***,** 591610.

Kitano, J., Ross, J.A., Mori, S., Kume, M., Jones, F.C., Chan, Y.F., Absher, D.M., Grimwood, J., Schmutz, J. & Myers, R.M. (2009) A role for a neo-sex chromosome in stickleback speciation. *Nature,* **461,** 1079-1083.

Roberts, R.B., Ser, J.R. & Kocher, T.D. (2009) Sexual conflict resolved by invasion of a novel sex determiner in Lake Malawi cichlid fishes. *Science,* **326,** 998-1001.

Sharp, N.P. & Agrawal, A.F. (2013) Male‐biased fitness effects of spontaneous mutations in Drosophila melanogaster. *Evolution: International Journal of Organic Evolution,* **67,** 1189-1195.