Supplementary Materials 2

Pipoly et al., "The genetic sex determination system predicts adult sex ratios in tetrapods"

This Supplementary Materials presents population genetic models of the effect that genetic sex determination systems may have on the adult sex ratio. Section 1 develops results for deleterious mutations, and Section 2 for sex-antagonistic selection.

All the models assume that populations are sufficiently large that the effects of drift can be neglected and the loci evolve independently. We expect the results will give good approximations for loci where the magnitude of the selection coefficient s is larger than $1/N_e$, where N_e is the effective population size of the sex chromosome under consideration.

These models do not capture the effects of several stochastic processes thought to be important to sex chromosomes because of their reduced effective population sizes[32]. One is Muller's ratchet, in which deleterious mutations drift to fixation on nonrecombining sex chromosomes. A second is the fixation of deleterious mutations that hitchhike with beneficial mutations that sweep to fixation at linked loci. While those processes could contribute to biased adult sex ratios, they are complex, and an adequate analysis of their effects on the ASR is beyond what is possible here. We leave that as a future research goal.

1. Deleterious mutations

This section develops a simple model to estimate the impact that deleterious mutation may have on the adults sex ratio (ASR), which we define as the proportion of males in the adult population. If the sex ratio is unbiased at conception, the adult sex ratio will be

$$\mathrm{ASR} \;=\; \frac{\overline{W}_m}{\overline{W}_f \;+\; \overline{W}_m} \tag{1}$$

where $\overline{W}_m$ and $\overline{W}_f$ are the relative rates of survival to adulthood of males and females. For concreteness, we develop the model assuming XY sex determination, and at the end we generalize the results to ZW systems. For simplicity, the model assumes the loci are completely sex-linked, and that loci carried on one type of sex chromosome (e.g. the X) have no homologue on the other type (e.g. the Y) that might mask the fitness effects of deleterious mutations. Intuitively, we expect that loci in the pseudoautosomal region will have a smaller impact on the ASR.

Begin by considering X-linked loci. We assume that fitness effects are multiplicative across loci. The mean fitnesses of females and males are approximately

$$\overline{W}_f \;\approx\; \prod_i \left(1 - h_i\, s_i^f\, p_i\right) \;\approx\; \exp\left\{-\sum_i h_i\, s_i^f\, p_i\right\} \tag{2}$$

$$\overline{W}_m \;\approx\; \prod_i (1 - s_i^m\, p_i) \;\approx\; \exp\left\{-\sum_i s_i^m\, p_i\right\} \tag{3}$$

where s_i^f and s_i^f are the selection coefficients for the deleterious allele at locus i, p_i is that allele's frequency, and h_i is the dominance coefficient in females. These approximations hold when linkage disequilibrium is weak, mutation is weak relative to selection, and $s_i^m,\ h_i\, s_i^f \;<<\; 1$. At a mutation-selection equilibrium,

$$p_i \;\approx\; \mu_i \Big/ \left(\frac{2}{3} h_i\, s_i^f \;+\; \frac{1}{3} s_i^m\right). \tag{4}$$

where μ_i is the mutation rate to the deleterious allele at locus i. The form of the denominator is a result of the fact that deleterious mutations spend 2/3 of their evolutionary time in females and 1/3 in males. So we have

$$\overline{W}_f \;\approx\; \exp\left\{-3 \sum_i \left(\frac{\mu_i\, h_i\, s_i^f}{2\, h_i\, s_i^f \;+\; s_i^m}\right)\right\} \tag{5}$$

$$\overline{W}_m \;\approx\; \exp\left\{-3 \sum_i \left(\frac{\mu_i\, s_i^m}{2\, h_i\, s_i^f \;+\; s_i^m}\right)\right\} \tag{6}$$

Now assume that deleterous mutations are nearly or completely recessive in females ($h_i \;<<\; 1$). Then

$$\overline{W}_f \approx 1 \tag{7}$$

$$\overline{W}_m \approx \exp\{-3\,U_X\} \tag{8}$$

where U_X is the total mutation rate for X-linked genes (that is, the sum across loci of the mutation rates to deleterious alleles per gamete per generation).

These results are consistent with the well-known result that the genetic load (that is, the loss in population mean fitness) from deleterious mutation is simply equal to the mutation rate and is independent of selection coefficient[103]. The factor of 3 appears because recessive mutations at X-linked loci experience selection in males in only one of every three generations.

The second class of loci we consider are genes carried on the Y but absent from the X. The genetic load principal applies directly to this case, and so

$$\overline{W}_f \approx 1 \tag{9}$$

$$\overline{W}_m \approx \exp\{-U_Y\} \tag{10}$$

where U_Y is the total rate of deleterious mutation for loci in this first class.

Combining the effects of X-linked and Y-linked genes (Eqs. (7) - (9)), we have

$$\overline{W}_f \approx 1 \tag{11}$$

$$\overline{W}_m \approx \exp\{-3\,U_X - U_Y\}. \tag{12}$$

If the total mutation rates are small (U_X, $U_Y << 1$), the fitness of males relative to the fitness of females is:

$$\overline{W}_m \approx 1 - 3\,U_X - U_Y. \tag{13}$$

We can now find the ASR resulting from deleterious mutation by multiplying the fitness effects of X-linked and Y-linked genes (Eqs. (9) - (12)), which gives:

$$\text{ASR} \approx \frac{\exp\{-3\,U_X - U_Y\}}{1 + \exp\{-3\,U_X - U_Y\}}. \tag{14}$$

This result simplifies further when the total mutation rates, U_X and U_Y, are much smaller than 1:

$$\text{ASR} \approx \frac{1}{2} - \frac{3}{4}U_X - \frac{1}{4}U_Y. \tag{15}$$

A parallel argument for ZW sex determination systems gives

$$\overline{W}_f \approx \exp\{-3\,U_Z - U_W\}. \tag{16}$$

$$\overline{W}_m \approx 1 \tag{17}$$

$$\text{ASR} \approx \frac{1}{1 + \exp\{-3\,U_Z - U_W\}} \tag{18}$$

$$\approx \frac{1}{2} + \frac{3}{4}U_Z + \frac{1}{4}U_W \tag{19}$$

where in Eq. (19) we again assume that the total mutation rates are much smaller than 1.

Sex chromosomes show bewildering variation across animals and plants[23], which makes it difficult to make general statements about what the empirical implications of these calculations might be. To get some sense, consider the following crude estimates for U_X and U_Y in

humans. The human X carries about 5% of the genes in the genome[104], and the Y carries about 0.3 % of the genes[105]. The genome-wide rate of mutation to deleterious alleles is estimated to be about 1 per haploid genome per generation[106], suggesting $U_X \approx 0.05$ and $U_Y \approx 0.003$. Using those values and Eq. (13), the equilibrium adult sex ratio is ASR = 0.46.

This calculation is very rough. The parameter estimates are crude and they neglect important factors such as sex-biased mutation. Further, we have made restrictive assumptions (e.g. that deleterious mutations are fully recessive). It seems unlikely, however, that refining the parameter estimates and generalizing the assumptions would lead to a sex ratio that deviates from 1/2 by more than a few percent for humans (and likely other eutherian mammals). The conclusion could be very different in other species, however, particularly if values for U_X and U_Y are much larger.

2. Sex-antagonistic selection

Sex-antagonistic selection occurs when alleles have opposing fitness effects on females and males. When this type of selection acts on sex-linked loci (on X or Z chromosomes), either fixation or polymorphism can result.

Fixation

Fixation is the typical outcome when dominance effects are weak and the relative fitness effects of the alleles within males are approximately equal in magnitude but opposite in sign to their relative fitnesses in females. In that case, the allele that is favored in the homogametic sex fixes because it experiences selection in the homogametic sex twice as often as in the heterogametic sex.

This outcome, however, does not automatically lead to a prediction about which sex will have higher mortality. That is because it is the evolutionary outcome depends on the relative fitnesses *within* each sex, and is independent of how much each allele affects females versus males. (We are very grateful to a reviewer for pointing this out.) This point may become clearer with a simple numerical example. Consider an X-linked locus in an XY sex determination system with two alleles, a and A. First consider the case where the viabilities are

	Allele		
	a	*A*	
Males:	0.9	1	
	aa	*Aa*	*AA*
Females:	1	0.9	0.8

The female-beneficial allele a will fix, which leads to a female-biased sex ratio. Now consider a second case in which the viabilities are

	Allele		
	a	*A*	
Males:	0.9	1	
	aa	*Aa*	*AA*
Females:	0.8	0.7	0.6

In this case, the female-beneficial allele again fixes, but the outcome is a male-biased sex ratio. These two examples illustrate the basic point that fixation of the allele that is favored in the homogametic sex does not necessarily lead to higher viability for that sex.

We are, however, able to make a general statement by introducing an additional assumption. Again assuming approximately equal relative allelic effects within each sex and weak or no dominance, and assume further that the optimal genotype for males has the same viability as the optimal genotype for females. (The first case above is an example.) The outcome is that female-favorable alleles fix in XY systems, causing the ASR to decrease. Conversely, male-favorable alleles will tend to fix in ZW systems, leading to an increase in the ASR.

When selection is stronger in the hemizygous sex, the allele favorable to that sex can fix. That would increase the ASR in XY systems and decrease it in ZW systems.

In sum, there are limited situations in which we can predict how fixation of alleles under sex-antagonistic selection will impact the ASR.

Stable polymorphism

Another possible outcome of sex-antagonistic selection is a stable polymorphism. In this case, there does not seem to be any simple generalization that can be made the direction in which the ASR will be biased. The range of parameters that support a stable polymorphism is fairly limited[107], however, so this may not often be an important factor in the evolution of the ASR.

To make these statements more quantitative, we consider a model for sex-antagonistic selection analyzed by Bennett[107]. There are two alleles, A and a, that are X-linked. The relative viability scheme that we use here is:

Males:	*a*	*A*

	1	$1 + s_m$	
Females:	*aa*	*Aa*	*AA*
	$1 + s_{aa}$	1	$1 - s_{AA}$

For concreteness here we assume all the $s \geq 0$, which means allele *A* is favored in males and allele *a* in females, and that heterozygotes have intermediate fitness in females.

Bennett found that a stable polymorphism occurs if and only if:

$$s_{aa} > \frac{s_m}{2} \text{ and } s_{AA} < \frac{s_m}{2\,(1 + s_m)} \tag{20}$$

When those conditions are met, the equilibrium frequency of *A* in eggs is

$$\hat{p}_f = \frac{2\,s_{aa} - s_m}{2\,(s_{aa} - s_{AA}\,(1 + s_m))} \tag{21}$$

and in sperm.

$$\hat{p}_m = \frac{(1 + s_m)\,(s_m - 2\,s_{aa})}{s_m^2 - 2\,s_{aa}\,(1 + s_m) + 2\,s_{AA}\,(1 + s_m)}. \tag{22}$$

When there is no dominance in females ($s_{aa} = s_{AA}$), one can show that the female favorable allele *a* will fix if:

$$\frac{s_m}{2} \leq s_{aa} = s_{AA}\,. \tag{23}$$

That result is the basis of the earlier statement that the female-favorable allele will generally fix when fitness effects in the two sexes are of comparable magnitude and opposite in sign, and heterozygotes have intermediate viability. The conclusion is reversed for ZW systems: there Z chromosomes spend more of their evolutionary histories in males, and so male-favorable alleles will tend to fix.

When there is a stable polymorphism, we can calculate the ratio of female to male fitness:

$$R_W = \frac{(s_{AA}\,(1 + s_m) - s_{aa})\,(1 + (2 - 4\,(1 + s_{aa})\,(1 - s_{AA}))\,(1 + s_m) + (1 + s_m)^2)}{(1 - 2\,(1 + s_{aa} - s_{AA})\,(1 + s_m) + (1 + s_m)^2)^2} \tag{24}$$

Here are two numerical examples. In the first, females have higher viability than males ($R_W > 1$), while in the second example the males have higher viability ($R_W < 1$):

s_m	s_{aa}	s_{AA}	$\hat{p}_f$	$\hat{p}_m$	R_W
0.205	0.1	0.1	0.12	0.14	1.09
0.22	0.1	0.1	0.45	0.50	0.91

These examples illustrate the point made earlier that there are no robust generalizations about which sex will have higher viability when sex-antagonism results in a polymorphism.

Supplementary Materials 2 References

103. Haldane, J.M.S. The effect of variation on fitness. *American Naturalist* **71**: 337-349 (1937).

104. Ross, M.T., *et al*. The DNA sequence of the human X chromosome. *Nature* **434**: 325-337 (2005).

105. Skaletsky, H., *et al*. The male-specific region of the human Y chromosome is a mosaic of discrete sequence classes. *Nature* **423**: 825-837 (2003).

106. Keightley, P.D. Rates and fitness consequences of new mutations in humans. *Genetics* **190**: 295-304 (2012).

107. Bennett, J.H. Selectively balanced polymorphism at a sex-linked locus. *Nature* **180**: 1363-1364 (1957).