FITNESS CONSEQUENCES OF SEX-SPECIFIC SELECTION

Tim Connallon,[1,2,3] Robert M. Cox,[4,5] and Ryan Calsbeek[4,6]

[1]University of Michigan, Department of Ecology & Evolutionary Biology and Museum of Zoology, Ann Arbor, Michigan 48109

[2]E-mail: tmc233@cornell.edu

[4]Dartmouth College, Department of Biological Sciences, Hanover, New Hampshire 03755

[5]E-mail: robert.m.cox@dartmouth.edu

[6]E-mail: ryan.calsbeek@dartmouth.edu

Theory suggests that sex-specific selection can facilitate adaptation in sexually reproducing populations. However, sexual conflict theory and recent experiments indicate that sex-specific selection is potentially costly due to sexual antagonism: alleles harmful to one sex can accumulate within a population because they are favored in the other sex. Whether sex-specific selection provides a net fitness benefit or cost depends, in part, on the relative frequency and strength of sexually concordant versus sexually antagonistic selection throughout a species' genome. Here, we model the net fitness consequences of sex-specific selection while explicitly considering both sexually concordant and sexually antagonistic selection. The model shows that, even when sexual antagonism is rare, the fitness costs that it imposes will generally overwhelm fitness benefits of sexually concordant selection. Furthermore, the cost of sexual antagonism is, at best, only partially resolved by the evolution of sex-limited gene expression. To evaluate the key parameters of the model, we analyze an extensive dataset of sex-specific selection gradients from wild populations, along with data from the experimental evolution literature. The model and data imply that sex-specific selection may likely impose a net cost on sexually reproducing species, although additional research will be required to confirm this conclusion.

KEY WORDS: Evolution of sex, good genes, intralocus sexual conflict, sexual antagonism.

One feature that distinguishes sexual populations from their asexual counterparts is the potential for natural and sexual selection to differ in strength and/or direction between the sexes. Such sex-specific selection has been proposed to enhance the rate of adaptation to a changing environment (Lorch et al. 2003; Candolin and Heuschele 2008), facilitate fixation of beneficial mutations (Whitlock 2000), increase purifying selection against deleterious mutations (Kondrashov 1988; Whitlock and Agrawal 2009), and provide a resolution to the paradox of sex (Manning 1984; Koeslag and Koeslag 1994; Agrawal 2001; Siller 2001; Hadany and Beker 2007). Mathematical theory shows that sex-specific selection increases the fitness of a population when it acts in the same direction on males and females, but is relatively stronger in males (Whitlock and Agrawal 2009). This occurs because selection on males does not affect the reproductive rate of a population, which depends only on the survival and fecundity of females. However, strong selection on males can provide a benefit by purging deleterious mutations from the population. Thus, a sexual population can experience strong purifying selection without suffering extreme reductions in its reproductive rate via increased mortality or variable fecundity of females. The benefits of this mechanism can theoretically arise from sex differences in selection arising from differential survival, fecundity, and/or mating success.

For sex-specific selection to provide a benefit, selection must favor the same alleles in each sex and differ only in its relative strength. Whether selection has this sexually concordant effect is difficult to assess at the genotypic level, but it is increasingly

[3]Current address: Cornell University, Biotechnology Building (room 227), Ithaca, NY 14853-2703.

recognized that many phenotypic traits are subject to opposing selection pressures in each sex (Rice and Chippindale 2001; Cox and Calsbeek 2009). This sexual antagonism can lead to the accumulation of mutations that are beneficial to males, but detrimental to females, thereby reducing the fitness of sexual populations (Prasad et al. 2007; Bonduriansky and Chenoweth 2009). Under such a scenario, sex-specific selection can generate an additional cost of sexual reproduction.

Given these two highly divergent outcomes, it remains unclear whether sex-specific selection typically reduces or increases the fitness of sexually reproducing populations. This uncertainty stems from two major limitations of existing theory and data. First, theoretical models have yet to consider the effects of sexual antagonism when assessing the benefits of sexual selection. Second, the paucity of sex-specific selection estimates has precluded rigorous empirical tests of these models (for discussion, see Hollis et al. 2009; Whitlock and Agrawal 2009). Here, we extend the theoretical and empirical scope of previous studies by incorporating both sexually concordant and sexually antagonistic selection pressures into a new model that contrasts fitness between sexual and asexual populations. We then discuss empirical data from experimental evolution and field-based studies of sex-specific selection with respect to the key parameters of this model. By combining a new mathematical model with several independent lines of empirical data, we show that sex-specific selection is likely to impose additional costs on sexual species, contrary to the conclusions of several previous theoretical studies.

Model

Consider a diploid species with L loci and the same strength and form of selection acting on males and females. At each locus, the input of deleterious mutations reduces fitness, and selection against these mutations opposes their accumulation within the population. The balance between mutation and selection leads to an equilibrium frequency of deleterious alleles $\hat{p} \approx \mu/sh$, where μ is the mutation rate per locus/gamete/generation, s is the selection coefficient and h is the dominance coefficient (μ, s, $h >$ 0). Haldane (1937) showed how mutations reduce mean population fitness below a fitness optimum: mean fitness per locus is $w = 1 - \hat{p}s[2h + \hat{p}(1 - 2h)] \approx e^{-2\mu}$, representing a difference of approximately 2μ, otherwise known as the mutational load (Whitlock and Agrawal 2009). Although the impact of a single locus on this load will be small (because μ is small), mutations at many loci can have more substantial effects on fitness. Considering the L loci within the genome, and assuming independence between mutations (no epistasis) and between loci (no linkage disequilibrium), mean population fitness is

$$\bar{W} = \prod_{i=1}^{L} w_i = \exp\left(\sum_{i=1}^{L} \log_e(w_i)\right) = e^{-2L\mu} \quad (1)$$

(e.g., Chasnov 2000; Agrawal and Chasnov 2001; Gillespie 2004; Haag and Roze 2007), a result that applies even more generally to asexually reproducing populations (Kimura and Maruyama 1966; Kondrashov and Crow 1988).

Sex-specific selection introduces two consequences for adaptation throughout the genome. Mutations arising at a proportion (hereafter ζ) of L loci may no longer be subject to purifying selection in both sexes, and instead give rise to sexually antagonistic selection. That is, alleles that were formerly deleterious to all individuals become beneficial to males and remain deleterious to females. Mutations at the other $L(1 - \zeta)$ loci remain deleterious to all individuals and are subject to sexually concordant selection, although the strength of purifying selection may differ between the sexes. Thus, we use the term "sexually antagonistic" to refer to sex-specific selection in which the direction of selection differs between the sexes, and "sexually concordant" to refer to sex-specific selection in which the direction of selection is the same in both sexes, despite differences in its relative strength. Below, we separately address the population genetic consequences of sexually concordant and sexually antagonistic selection, and then consider how both processes jointly contribute to genome-wide fitness.

EVOLUTION AT SEXUALLY CONCORDANT LOCI
For the case of sexually concordant selection at a locus with two alleles, A_1 and A_2, sex-specific fitness follows the scheme:

Genotype:	A_1A_1	A_1A_2	A_2A_2
Female fitness (w_f):	$1 - s_f$	$1 - s_f h$	1
Male fitness (w_m):	$1 - s_m$	$1 - s_m h$	1

where the selection coefficients s_m and s_f, and the dominance coefficient h, are all positive. Here, the A_1 allele is disfavored in both sexes, but will persist at low frequency due to mutations from A_2 to A_1. Under sexually concordant selection, the deleterious allele A_1 evolves to a single equilibrium, at mutation–selection balance

$$\hat{p}_C \approx \frac{2\mu}{s_f h(1 + a_C)} \quad (2)$$

(Whitlock and Agrawal 2009), where $\alpha_C = s_m/s_f$ and μ refers to the mutation rate from A_2 to A_1 (backmutation is assumed to be negligible because A_1 is rare). Mean female fitness per sexually concordant locus is

$$w_C = 1 - \hat{p}_C s_f[2h + \hat{p}_C(1 - 2h)] \approx \exp\left(-\frac{4u}{1 + \alpha_C}\right) \quad (3)$$

which assumes that s_f, s_m, and $\hat{p}_C$ are small, as seems reasonable.

EVOLUTION AT SEXUALLY ANTAGONISTIC LOCI

For the case of sexual antagonism at a locus with two alleles, sex-specific fitness follows the scheme:

Genotype:	A_1A_1	A_1A_2	A_2A_2
Female fitness (w_f):	$1 - s_f$	$1 - h_f s_f$	1
Male fitness (w_m):	1	$1 - h_m t_m$	$1 - t_m$

where sexually antagonistic selection coefficients s_f and t_m, and dominance coefficients h_f and h_m, are all positive. Here, the A_1 allele (at frequency p_A) increases male fitness, thereby generating conflicting selection pressures between the sexes. At equilibrium, mean female fitness at a sexually antagonistic locus is

$$w_A = 1 - \hat{p}_A s_f [2h_f + \hat{p}_A(1 - 2h_f)]$$
$$\approx \exp\left(-\hat{p}_A s_f [2h_f + \hat{p}_A(1 - 2h_f)]\right) \quad (4)$$

assuming that s_f is small and the frequency of A_1 is approximately equal in males and females. In the context of genetic load—the disparity between mean fitness and fitness of the best genotype—the fitness effect of deleterious mutations, per sexually concordant locus, is on the order of the mutation rate, μ. The genetic load caused by sexually antagonistic alleles, per sexually antagonistic locus, approaches s_f as $\hat{p}_A$ approaches one. Because s_f can be orders of magnitude greater than the mutation rate, it is clear that sexual antagonism potentially represents a profound constraint on adaptation.

Sexual antagonism generates three possible equilibria for the female-detrimental allele. These equilibria depend upon the strength of selection in males relative to females (Kidwell et al. 1977; Appendix S1). When selection is stronger in females than in males, the male-beneficial allele, A_1, evolves to a low-frequency equilibrium at mutation–selection balance. This condition specifically occurs when

$$s_f > \frac{t_m(1 - h_m)}{h_f(1 - t_m)}. \quad (5)$$

When selection is stronger in males than in females, the female beneficial allele, A_2, occurs at low frequency at mutation–selection balance. This condition occurs when

$$s_f < \frac{t_m h_m}{1 - h_f + t_m h_m}. \quad (6)$$

When selection in males and females is similar in strength, sexual antagonism can maintain a stable polymorphism, under the condition

$$\frac{t_m h_m}{1 - h_f + t_m h_m} < s_f < \frac{t_m(1 - h_m)}{h_f(1 - t_m)}. \quad (7)$$

When A_1 is equally dominant in males and females (i.e., $h_f = 1 - h_m$) and selection coefficients are relatively small ($t_m, s_f < 0.1$), the conditions favoring a balanced polymorphism

are quite restrictive (Kidwell et al. 1977; Prout 1999; Fry 2009; Appendix S1), and there are essentially two equilibria: one in which selection on females dominates and A_1 remains at low frequency (condition 5; hereafter "female-biased" sexual antagonism), and one in which selection on males dominates and A_1 approaches fixation (condition 6; hereafter "male-biased" sexual antagonism). Note that under the model parameterization given above, the condition $h_f = h_m \neq 0.5$ yields a dominance reversal, where the allele that is dominant in males is recessive in females. Although we do not analytically address dominance reversal scenarios, we show by simulation that they are likely to strengthen our conclusions (see below and Supporting information for details).

Under "female-biased" sexual antagonism, the female-detrimental allele (A_1) evolves to the equilibrium

$$\hat{p}_{\alpha_A < 1} \approx \frac{2\mu}{s_f h_f(1 - \alpha_A)}, \quad (8)$$

where α_A is the relative strength of sexual antagonism, defined as $\alpha_A = t_m/s_f$ (see Appendix S2). Substitution into equation (4) and ignoring terms of p^2, mean female fitness at the sexually antagonistic locus is

$$w_{\alpha_A < 1} \approx \exp\left(-\frac{4\mu}{1 - \alpha_A}\right). \quad (9)$$

For "male-biased" sexual antagonism ($\alpha_A > 1$), female-detrimental alleles are nearly fixed within the population (Kidwell et al. 1977). At mutation–selection equilibrium, the frequency of a female-detrimental allele is

$$\hat{p}_{\alpha_A > 1} \approx 1 - \frac{2\mu}{s_f(\alpha_A - 1)(1 - h_f)} \quad (10)$$

(see Appendix S2), and mean fitness at the locus is

$$w_{\alpha_A > 1} \approx \exp\left(-\frac{s_f(\alpha_A - 1) - 4\mu}{(\alpha_A - 1)}\right). \quad (11)$$

GENOME-WIDE FEMALE FITNESS UNDER SEX-SPECIFIC SELECTION

Assuming independence between loci (no epistasis and no linkage disequilibrium), female fitness across the entire genome is the product of fitness at the $L(1 - \zeta)$ sexually concordant and $L\zeta$ sexually antagonistic loci (e.g., Chasnov 2000; Agrawal and Chasnov 2001; Gillespie 2004; Haag and Roze 2007). Although sexually antagonistic alleles can hypothetically equilibrate at any frequency between zero and one, it is worth focusing on the two extreme conditions: (1) female-biased sexual antagonism, where all female-detrimental alleles are rare (condition 5; $\alpha_A < 1$), and (2) male-biased sexual antagonism, where all female-detrimental alleles are nearly fixed within the population (condition 6; $\alpha_A > 1$). These scenarios represent lower and upper bounds on the fitness costs of sexual antagonism, Fitness costs arising from

balanced polymorphisms and combinations of female-biased and male-biased sexual antagonism will necessarily fall between these extremes. For mutation and selection parameters μ, α_C and α_A are fixed across sexually concordant and antagonistic loci, respectively, net female fitness under female-biased sexual antagonism is

$$\bar{W}_f = \exp\{L(1 - \zeta)\log_e(w_C) + L\zeta \log_e(w_A)\}$$
$$= \exp\left(-\frac{4L(1 - \zeta)\mu}{1 + \alpha_C} - \frac{4L\zeta\mu}{1 - \alpha_A}\right). \quad (12)$$

Under the male-biased sexual antagonism scenario, net female fitness is

$$\bar{W}_f = \exp\left(-\frac{4L(1 - \zeta)\mu}{1 + \alpha_C} - L\zeta s_f - \frac{4L\zeta\mu}{1 - \alpha_A}\right). \quad (13)$$

FEMALE FITNESS FOLLOWING SEX-LIMITATION OF SEXUALLY ANTAGONISTIC LOCI

Fitness costs associated with sexually antagonistic alleles can be mitigated by the evolution of loci with sex-limited fitness effects. Nevertheless, the evolution of sex-limitation is unlikely to fully resolve sexually antagonistic costs if there is a temporal lag between the evolutionary invasion of sexually antagonistic alleles and the evolution of sex limitation (Lande 1980), or if sex-limitation itself carries a cost (Bonduriansky and Chenoweth 2009). To consider this second possibility, suppose that sexually antagonistic loci become sex-limited when: (A) the ζL antagonistic loci become duplicated, and (B) one copy of each duplicate pair evolves male- or female-specific expression and function, thereby eliminating the past sexual antagonism. The differentiated elements could potentially represent entire genes, alternatively spliced exons, or sex-specific regulatory sequences. Although the sexual lineage has now transitioned from L to $L + \zeta L$ loci, female fitness remains a function of genetic variation at L loci, with sex-limited mutations at mutation–selection balance evolving to the equilibrium

$$\hat{p}_{SL} \approx \frac{2\mu}{s_f h_f}. \quad (14)$$

Sex-limited mutations occur during every generation, yet selection is limited to 50% of generations (i.e., each mutation has a 0.5 probability of occurring in a male or a female genome during each generation). These loci therefore harbor at least twice as much deleterious variation as loci that are under sexually concordant selection (where $\alpha_C \geq 1$). Net female fitness, including both sex-limited and sexually concordant loci, will be

$$\bar{W}_f = \exp\left\{-4L\mu\left(\frac{1 + \zeta\alpha_C}{1 + \alpha_C}\right)\right\}. \quad (15)$$

Evolution of DNA sequences with sex-specific expression may be a common mechanism to resolve sexually antagonistic

selection, as indicated by ubiquitous sex-biased gene expression (Ellegren and Parsch 2007), sex-specific splicing of protein coding loci (McIntyre et al. 2006; Telonis-Scott et al. 2009), and genomic associations between gene duplication and sex-specific expression (Gnad and Parsch 2006; Bonduriansky and Chenoweth 2009). Yet it should be noted that additional, nongenetic mechanisms might also mitigate costs of sexual antagonism. Processes of genomic imprinting (Day and Bonduransky 2004), maternal effects/differential allocation (Foerster et al. 2007; Bonduriansky and Chenoweth 2009), and biased sperm use by mothers (Calsbeek and Bonneaud 2008) can theoretically reduce the cost of inheriting sexually antagonistic alleles, though the relative frequency with which they operate is currently unknown (see Bonduriansky and Chenoweth 2009 for a recent review). These intriguing possibilities are beyond the scope of this article, though they represent future opportunities for theory as new data arise. However, it is worth pointing out that these alternative mechanisms are not expected to completely eliminate adaptive constraints arising from sexual antagonism and would not overturn our conclusions, were they to typically occur. Genomic imprinting, offspring-specific maternal effects, and biased sperm use can be adaptive if they reduce the cross-sex heritability of sexually antagonistic traits (or fitness), yet none of these models predict that male- or female-beneficial variants will necessarily become fixed. Rather, sexually antagonistic loci are expected to remain polymorphic. Thus, females will continue to transmit male-beneficial/female-detrimental alleles to daughters, and these maternally inherited alleles will evade imprinting or sperm-sorting mechanisms. Likewise, increased maternal investment can partially overcome fitness costs to offspring incurred by the inheritance of harmful sexually antagonistic alleles. However, parental investment is energetically costly, and maternal effects shift costs of sexual antagonism to the parent, thereby reducing female fecundity in a cross-generational pattern.

Finally, although we focus our analysis and discussion on autosomal inheritance, which characterizes the majority of genes in animal genomes, sexually antagonistic selection can also occur on sex chromosomes that spend portions of their evolutionary history within both male and female genomes (such as X or Z chromosomes). Theory suggests that X- or Z-linkage potentially promotes the maintenance of sexually antagonistic variation via balancing selection (e.g., Rice 1984; Fry 2009; Patten and Haig 2009). In our model (see simulations below and in the Supporting information), we find that balanced sexually antagonistic variation severely reduces mean fitness relative to a sex-specific optimum. An extreme fitness reduction caused by intermediate-frequency, female-detrimental alleles will have much more of an impact on female fitness than the relatively small fitness increase caused by enhanced purifying selection via males. Therefore, sex linkage will (if anything) enhance fitness costs of sexual antagonism,

and would generally strengthen our theoretical conclusions (see below).

SIMULATIONS

The analytical solutions presented here rely on two important assumptions about sexually antagonistic variation. Selection co-efficients are assumed to be relatively small and dominance is assumed to be identical between the sexes (i.e., A_1 is equally dominant in males and females, which requires that $h_f = 1 - h_m$). Under these assumptions, conditions favoring a stable polymorphism are extremely restrictive (see above), sexually antagonistic alleles have approximately equal frequencies in male and female gametes, and the analytical results are expected to be quite accurate. However, as selection increases in strength, or as dominance becomes sex-specific (particularly for the case of dominance reversal; Kidwell et al. 1977; Fry 2009), approximations for sex-specific allele and genotype frequencies, and for female fitness, can break down, and conclusions based on the analytical models become less reliable. We therefore performed a series of simulations to account for strong genic-selection and sex-specific dominance. These simulations show that equations (12) and (13) represent lower and upper limits for the costs of sexual antagonism, respectively (see Supporting information for details). As the strength of selection increases ($t_m, s_f \to 1$) or under dominance reversal conditions (e.g., $h_f, h_m < 0.5$) the parameter space where sexual selection provides a net benefit becomes reduced relative to analytical approximations. Nevertheless, the approximations are very close to the exact results generated by simulation (see Fig. 1), and are particularly accurate for plausible parameter values of s_f and μ. Our main conclusion below, that even a small proportion of sexually antagonistic selection will generate a cost to females that overwhelms benefits of sexually concordant selection, is therefore robust.

Results

The average fitness of an asexual individual, where sex-specific selection is absent, is

$$\bar{W}_{asex} = e^{-U}, \tag{16}$$

where $U = 2L\mu$ is the genomic mutation rate (e.g., Kimura and Maruyama 1966; Maynard Smith 1978; Kondrashov and Crow 1988). Sex-specific selection can substantially alter mean fitness of females in a sexually reproducing population. Consistent with previous work (Agrawal 2001; Siller 2001), we find that sex-specific selection will increase female fitness, in the absence of sexual antagonism ($\zeta = 0$) and when deleterious mutations are more harmful to males than to females ($\alpha_C > 1$; Fig. 1).

When there is sexual antagonism ($\zeta > 0$), sex-specific selection can also generate a net fitness benefit for females, but only
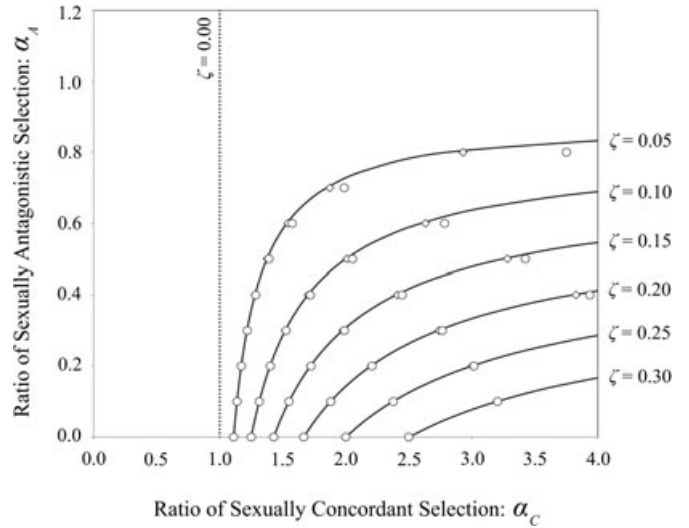

Figure 1. Benefits of sex-specific selection are severely constrained by sexual antagonism. The parameters α_A and α_C refer (respectively) to the strength of sexually antagonistic and sexually concordant selection in males relative to females (details provided within the text). Space below each curve corresponds to conditions under which sex-specific selection provides a net benefit of sex. When all genes evolve under sexually concordant selection ($\zeta = 0$), mean female fitness increases when selection is stronger in males, as indicated by the dotted line at $\alpha_C = 1$. ζ indicates the proportion of the genome that experiences sexual antagonism. Solid lines are based on the approximation from equation (17) in the text. Exact results based on simulations are represented as diamonds (for $s_f = 0.01$; $\mu = 10^{-8}$; $h_f, h_m = 0.5$) and circles (for $s_f = 0.05$; $\mu = 10^{-8}$; $h_f, h_m = 0.5$).

when α_C increases much more rapidly than α_A. If "female-biased" sexual antagonism predominates, such that female-detrimental alleles remain at low frequencies ($\alpha_A < 1$; with unresolved sexual antagonism, this represents the best possible scenario for female fitness), sex-specific selection improves the fitness of females under the condition

$$1 > \frac{2(1 - \zeta)(1 - \alpha_A) + 2\zeta(1 + \alpha_C)}{(1 + \alpha_C)(1 - \alpha_A)}. \tag{17}$$

Otherwise, sex-specific selection generates a cost of sexual reproduction. An analysis of condition (17) shows that, even under this best-case scenario, sex-specific selection generates a reduction in the net fitness of females when even a small fraction of the genome is exposed to sexually antagonistic selection (Fig. 1).

When "male-biased" antagonism predominates (i.e., $\alpha_A > 1$; a worst-case scenario for females), the costs of sexual antagonism generally overwhelm any benefits generated by sexually concordant selection. Sex-specific selection improves female fitness under the condition

$$1 > \frac{2(1 - \zeta)}{1 + a_C} - \frac{2\zeta}{a_A - 1} + \frac{\zeta s_f}{2\mu}, \tag{18}$$

where the mutation rate per locus (μ) and female selection coefficient (s_f) no longer drop out of the analysis (as they do under female-biased sexual antagonism). Estimates of μ from the literature indicate that it is on the order of 10^{-8} (e.g., Haag-Liautard et al. 2007). Although estimates of s are less clear, it is likely within a range between $s = 10^{-5}$ (based on analysis of segregating polymorphism; Loewe et al. 2006; Andolfatto 2007) and $s = 10^{-2}$ (based on mutation-accumulation; Shabalina et al. 1997). Given a rough estimate of s_f/μ between 10^3 and 10^6, the term $\zeta s_f/2\mu$ will often severely inflate the right side of condition (18), even when sexual antagonism is rare ($\zeta \ll 1$) and sexually concordant selection is strong (α_C goes to infinity). In other words, male-biased sexually antagonistic selection produces a cost that is so severe that it is unlikely to be offset by benefits of enhanced purifying selection in males.

The transition points that define whether sex-specific selection improves or reduces female fitness are independent of the genomic mutation rate, $U = 2L\mu$. However, the magnitude of the net costs or benefits of sex-specific selection is closely tied to U. Within the parameter space producing a net cost of sex-specific selection, high values of U, which previous models suggest should increase the benefits of sex (Kondrashov 1982; Charlesworth 1990; Agrawal 2001; Siller 2001; Keightley and Otto 2006), can have the opposite effect, and actually increase the net cost of sex.

Lastly, we can ask how the evolution of sex-limited expression, as a long-term consequence of sexual antagonism, will influence the adaptation of females. Under the assumption that sexually antagonistic selection is completely resolved by the evolution of sex-limited loci, sex-specific selection produces a net benefit when

$$\alpha_C > \frac{1}{1 - 2\zeta} \qquad (19)$$

(here, ζ refers to proportion of loci that are female-limited in expression). This result suggests that fitness costs of sexual antagonism cannot be completely resolved by the evolution of sex-limitation. Rather, sex-limitation can generate a net cost of sex-specific selection, despite strong sexually concordant selection at loci expressed in both sexes (Fig. 2).

Discussion

Our model derives the costs and benefits of sex-specific selection with respect to three key parameters: the relative strength of sexually concordant selection in males and females ($\alpha_C = s_m/s_f$), the relative strength of sexually antagonistic selection in males and females ($\alpha_A = t_m/s_f$), and the proportion of the genome exposed to sexual antagonism (ζ). To empirically test whether sexual selection provides a long-term benefit or a fitness cost, we would
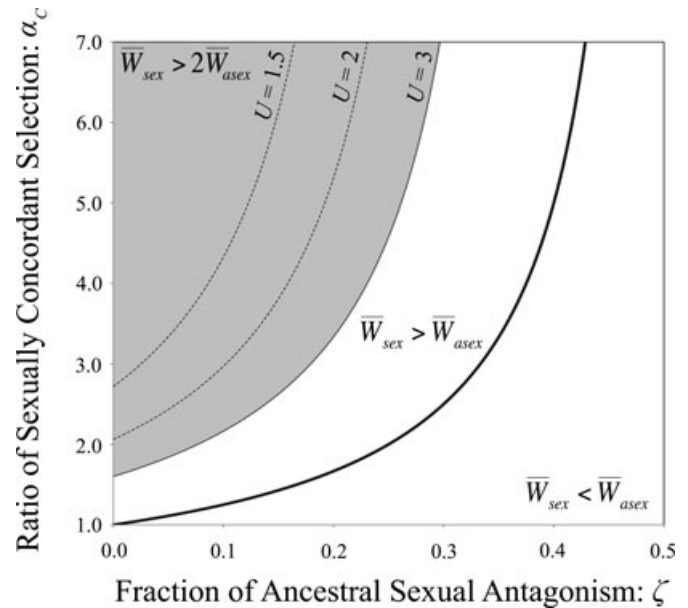

Figure 2. Sex-limitation reduces opportunities for benefits of sex-specific selection. The thick, solid line delineates the region of parameter space where sex-specific selection provides a net fitness benefit to females (where $\bar{W}_{sex} > \bar{W}_{asex}$); these results were obtained with equation (19), under the assumption that sexual antagonism is completely resolved by sex-limitation. The addition of unresolved sexual antagonism further reduces the parameter space where sex-specific selection is beneficial. The gray, shaded region represents the parameter conditions in which sex-specific selection yields a twofold fitness advantage to females (i.e., $\bar{W}_{sex} > 2\bar{W}_{asex}$; note that these results are not independent of the genomic mutation rate, U); results are obtained using equations (15) and (16).

ideally analyze sex-specific fitness estimates for a large number of mutations throughout the genome. At present, such data do not exist (Whitlock and Agrawal 2009). However, several other lines of evidence have strong implications for this issue. Below, we analyze three independent empirical approaches, discuss their current implications and limitations with respect to quantifying net benefits and costs of sex-specific selection, and propose additional experiments that might shed further light on the subject.

SEX-SPECIFIC SELECTION COEFFICIENTS FROM VISIBLE MUTATIONS IN *DROSOPHILA*

Experiments using the fruit fly *Drosophila melanogaster* indicate that visible mutations typically produce different fitness consequences in males relative to females (Whitlock and Bourguet 2000; Pischedda and Chippindale 2005; Sharp and Agrawal 2008). These mutations have effects ranging from sexual concordance to sexual antagonism (Table 1). When selection is sexually concordant, it tends to be stronger in males relative to females (with mean α_C between 2.3 and 2.4, approximately).

Table 1. Point estimates of sex-specific selection on visible mutations in *Drosophila*. Single estimates of selection are shown when fitness is measured in a single environment. Ranges are reported when selection was estimated in multiple environments. [1] Selection coefficients based on data from Whitlock and Bourguet (2000; their Table 1); productivity (fecundity and offspring survival) is the measure of female fitness; competitive mating success is the measure of male fitness. [2] Selection coefficients based on total sex-specific fitness estimates reported by Pischedda and Chippindale (2005). [3] Selection coefficients based on data from Sharp and Agrawal (2008; their Table 3); total fitness assumes juvenile viability and adult reproductive success interact multiplicatively.

Concordantly Selected mutations

Mutation	s_f	s_m	α_C	Source
B	0.08	0.34	4.43	[1]
Dr	0.13	0.75–0.80	5.79–6.15	[3]
e/sr	0.46	0.76	1.65	[1]
Frd	0.22	0.20–0.22	0.92–1.00	[3]
Gla	0.53	0.78–0.84	1.46–1.58	[3]
L	0.26	0.62–0.68	2.39–2.63	[3]
Ly	0.53	0.80–0.88	1.51–1.67	[3]
Nub[1]	0.38	0.74	1.95	[2]
Pin	0.22	0.04–0.06	0.18–0.26	[3]
Sb	0.19	0.48–0.52	2.50–2.73	[3]

Antagonistically Selected mutations

Mutation	s_f	t_m	α_A	Source
Ca	0.018	0.38	21.37	[1]
H	0.52	0.12	0.23	[1]
px/sp	0.46	0.61	1.33	[1]
U	0.20	0.12–0.19	0.59–0.97	[3]

However, sexually antagonistic selection is commonly observed in these experiments (mutations had opposing fitness effects—positive in one sex and negative in the other—for approximately 30% of cases). Such a combination of sex-specific fitness effects is expected to generate a net fitness cost of sex-specific selection.

However, it is unlikely that these data can be interpreted in such a straightforward manner. Not only is this sample size of 14 mutations small and limited to a single species, but these mutations are also potentially not representative of most spontaneous mutations within *Drosophila*. Each mutation produces a marked phenotypic and fitness effect, with selection coefficient estimates that are considerably larger than those estimated from mutation-accumulation experiments (e.g., Shabalina et al. 1997). Because most of the mutations affect eyes, wings, or body pigmentation, they are likely to directly influence male mating success. This could upwardly bias estimates of the deleterious fitness effect of these mutations in males, thus upwardly biasing estimates of the

intensity of concordant selection in males relative to females (for discussion, see Hollis et al. 2009). Furthermore, mutations with large fitness effects are expected to be deleterious to both sexes (i.e., as an extension of Fisher's Geometric Model; Fisher 1930). Thus, visible mutations might have a higher incidence of sexually concordant selection, relative to a random collection of mutations with smaller phenotypic and fitness effects. On the other hand, selection coefficient estimates are often associated with substantial standard errors, which might cause selection coefficients to, by chance, have different signs. This factor could artificially inflate the observations of sexually antagonistic selection.

Although visible-mutation data imply that sex-specific selection might generate a net fitness cost for females, the caveats listed above currently preclude any definitive conclusions. Future studies in *Drosophila* could greatly improve upon the strength of our inferences by selecting larger samples of random mutations for analysis. This could be accomplished via gene knockout-deficiency genotypes (readily available through *Drosophila* stock centers; Presgraves 2003), or by using RNA interference libraries to silence random sets of genes (Dietzl et al. 2007). Detecting sex-specific fitness effects of individual mutations might also be approached indirectly via experimental evolution within population cages, as shown in two recent studies (Stewart et al. 2005; Hollis et al. 2009).

MUTATION ACCUMULATION AND SEX-SPECIFIC FITNESS

A recent study using *D. melanogaster* took a novel and promising approach toward quantifying the sex-specific effects of individual mutations (Morrow et al. 2008). Adopting a sex-limited "Middle Class Neighborhood" design, the authors were able to limit selection to either males or to females. The Middle Class Neighborhood design experimentally eliminates fitness variance (i.e., every individual has the same fitness) by ensuring that each individual contributes a fixed number of offspring to the following generation. The method can also be applied sex-specifically by holding the fitness of one sex constant (the "unselected sex") and permitting fitness of the other sex to vary (the "selected sex"). This sex-limitation can have three potential consequences: (1) the strength of sexually concordant selection will be reduced, with accumulating mutations reducing fitness of both sexes; (2) selection against sex-limited mutations is only possible when they affect the selected sex, causing a fitness decline in the unselected sex (no change to the selected sex); and (3) sexually antagonistic alleles that are beneficial to the selected sex can accumulate, increasing fitness of the selected sex and decreasing that of the unselected sex.

Following sex-limited selection for 26 generations, Morrow et al. (2008) measured the relative fitness of both sexes in experimental lineages exposed to female-limited selection or to

male-limited selection, and observed a net fitness decline in both sexes. In other words, elimination of selection in one sex had an overall negative impact on fitness for the other sex. However, the fitness decline was sex-specific, with a faster rate of decline in the unselected sex. This pattern was symmetric: the rate of fitness decline in females was twice as high when they were the unselected sex relative to when they were the selected sex. Likewise, fitness of males declined at a twofold higher rate when they were the unselected sex relative to when they were the selected sex.

These results have three major implications for inferring sex-specific fitness effects. First, the net fitness decline in males and females suggests that most mutations are deleterious to both sexes (i.e., they are sexually concordant). Second, a faster rate of fitness decline for the unselected sex indicates that a nontrivial proportion of the genome has sex-limited and/or sexually antagonistic effects on fitness. Third, the pattern of symmetry (i.e., that fitness declines about twice as fast for the unselected sex, whether male or female) suggests that strength of purifying selection does not generally differ between the sexes (i.e., $\alpha_C \approx 1$).

This final point can be illustrated with a simple model. Consider a scenario of sexually concordant selection with sex-specific selection coefficients: $s_f \alpha_C = s_m$. When selection is experimentally limited to males, the rate of fitness decline in sex i (where $i = f$ in the case of females; $i = m$ in males) is expected to be

$$\Delta w_i(\text{selection in males}) = \frac{2s_i h\mu \left(1 - \dfrac{\alpha_C}{1 + \alpha_C}\right)}{1 - 2\hat{p}s_i h} \quad (20)$$

(see Appendix S3 for details). Similarly, when selection is limited to females, the fitness decline in each sex occurs at the rate

$$\Delta w_i(\text{selection in females}) = \frac{2s_i h\mu \left(1 - \dfrac{1}{1 + \alpha_C}\right)}{1 - 2\hat{p}s_i h}. \quad (21)$$

The rate of fitness decline when selection is limited to males relative to the case in which selection is limited to females is therefore equal to

$$\frac{\Delta w_i(\text{selection in males})}{\Delta w_i(\text{selection in females})} = \frac{1}{\alpha_C}. \quad (22)$$

If $\alpha_C > 1$, females will benefit by being the unselected sex, whereas males will suffer a cost of being the unselected sex. In females, this should at least partially offset fitness costs arising from the accumulation of female-deleterious variation at sexually antagonistic and sex-limited loci. In males, the cost of being the unselected sex will be enhanced by sexually antagonistic and sex-limited loci. The results of Morrow et al. (2008) clearly show that both males and females suffer nearly identical, twofold costs of being the unselected sex. This pattern suggests that the fitness consequences of sexually concordant mutations are approximately equal between males and females. Fitness benefits to females of strong purifying selection in males do not appear to offset costs of sex-specific selection.

The mutation accumulation approach provides a nice complement to studies of individual mutations of large effect in *Drosophila*. An added benefit of the approach is that it can be applied to nonmodel species. To date, only two additional studies have examined whether sex-specific selection reduces the fitness costs of mutation accumulation. These studies (both using the bulb mite, *Rhizoglyphus robini*) yield conflicting evidence: one reports a benefit to embryo viability (Radwan 2004), whereas the other reports no effect on female fecundity (Radwan et al. 2004). Future studies, using spontaneous and induced mutation accumulation in a wider variety of animal populations, could further illuminate patterns of sex-specific selection across the genome.

SEX-SPECIFIC SELECTION GRADIENTS ESTIMATED WITHIN NATURAL POPULATIONS

The *Drosophila* data discussed above indicate that benefits of sex-specific selection are unlikely to offset its costs. However, this inference is drawn solely from laboratory-adapted populations of a single insect species. Although the genetic resources available for *Drosophila* are generally lacking in nonmodel organisms, studies of selection in the field have produced a large dataset of sex-specific selection estimates from a wide variety of natural animal populations. Below, we use this extensive dataset and present an analysis of sex-specific selection in the wild. The resulting analyses are tentatively used as a proxy for inferring patterns of sex-specific selection throughout nonmodel animal genomes.

We used a large dataset of 423 sex-specific measures of selection acting on 90 traits from 34 animal species (the full dataset is presented by Cox and Calsbeek 2009) to estimate model parameters α_C and α_A from several different subsets of these data. Cases of sexually concordant selection are those where the signs of the sex-specific selection gradients are the same (i.e., both positive or both negative); opposing signs were defined as cases of sexual antagonism. First, we treated each reported selection gradient or differential as an independent observation (Appendix A of Cox and Calsbeek 2009). This approach maximized the inclusion of available data (423 estimates), but many of these estimates comprise spatial or temporal replicates of the same traits measured in the same species, and therefore cannot be considered independent observations. Thus, we repeated our estimates of model parameters using a smaller dataset in which a single mean value of selection was derived for any replicated measures (Appendix B of Cox and Calsbeek 2009). This yielded a smaller dataset (203 estimates), but one free from multiple counting due to replicated measures. This dataset also includes estimates of net selection obtained by treating gradients and differentials from individual fitness components (i.e., viability, fecundity, mating success)

Table 2. Parameter estimates (means and 95% confidence intervals) based on sex-specific selection gradient data from natural animal populations.

	n	α_C[1]	α_A[1]	Proportion of sexual antagonism[2]
Traits Analyzed[3]				
All	423	1.20 (1.05, 1.37)	0.98 (0.83, 1.15)	0.41 (0.36, 0.46)
Statistically Sig.	33	1.28 (1.04, 1.58)	0.87 (0.66, 1.14)	0.39 (0.25, 0.56)
Fitness Component[4]				
Net Selection	47	1.03 (0.69, 1.55)	1.02 (0.62, 1.69)	0.47 (0.33, 0.61)
Fecundity	39	0.97 (0.66, 1.42)	0.86 (0.45, 1.57)	0.26 (0.15, 0.41)
Mating Success	28	1.34 (0.86, 2.13)	1.06 (0.57, 1.99)	0.54 (0.36, 0.71)
Viability	71	0.81 (0.57, 1.14)	1.21 (0.72, 2.07)	0.34 (0.24, 0.45)

[1]Averages and 95% confidence intervals were calculated for the variable $x=S_m/(S_m+S_f)$, where S_m and S_f are the male and female selection gradients, respectively. Means and 95% confidence intervals for x were used to calculate equivalent statistics for S_m/S_f by substituting $S_f\alpha_C$ for S_m, which leads to the relationship: $\alpha_C=S_m/S_f=x/(1-x)$. The same approach was applied to cases of sexually antagonistic selection, with absolute values of selection gradients.
[2]Represents the proportion of traits where male and female selection gradients had opposite signs (i.e., $S_m/S_f<0$); confidence intervals were obtained by hand, using the chi-square distribution.
[3]Data are from "dataset A," as described in Cox and Calsbeek (2009); the "significant" category refers to traits with statistically significant selection gradients in both sexes.
[4]Data are from "dataset B", as described in Cox and Calsbeek (2009).

as additive (see Cox and Calsbeek 2009 for details and further justification).

Our selection gradient analysis yields two interesting results. First, the strength of selection in males is approximately equal to the strength of selection in females for both sexually concordant and antagonistically selected traits (Table 2). This pattern is consistent across different classes of traits, and under different types of selection (e.g., viability, fecundity, mating success, and total "net" fitness). Furthermore, the relative strength of concordant and antagonistic selection remains approximately the same for traits exposed to statistically significant directional selection in both sexes (i.e., those with selection gradient estimates that are significantly different than zero; Table 2).

Secondly, sexually antagonistic selection is common relative to sexually concordant selection, with the proportion of traits subject to sexual antagonism ranging between 25 and 55% (Table 2). Given the nature of the data and obvious difficulty of inferring genotypic selection from phenotypic data, it is not possible to estimate the proportion of underlying loci that are evolving via sexual antagonism. However, the data do suggest that ongoing, unresolved sexual antagonism is at least common enough to be observable, which implies that sexually antagonistic constraints to female adaptation are unlikely to be trivial. This result is also compatible with observations of sexual antagonistic genetic variation for fitness from both wild and laboratory populations (Chippindale et al. 2001; Brommer et al. 2007; Foerster et al. 2007).

Patterns of sex-specific selection in the wild are generally consistent with the idea that benefits of strong sexually concordant selection are relatively weak. The presence of unresolved sexual antagonism is therefore expected to generate a net cost of sex-specific selection. This conclusion comes with the caveat that selection gradients are based on quantitative traits, which have complicated polygenic and environmental developmental bases, and therefore limit our ability to make direct connections between genotype and phenotype. Nevertheless, these selection gradient data exhibit similar patterns of sex-specific selection as do genetic data from *Drosophila* (see above), and should be considered as complimentary to genotype-based estimates of fitness. Both lines of evidence implicate a net cost of sex-specific selection.

Conclusion

Our mathematical results show that a relatively small proportion of unresolved sexual antagonism will typically overwhelm any fitness benefits arising from strong sexually concordant selection. Furthermore, the resolution of sexual antagonism via sex-limited gene expression is likely to generate long-term fitness costs for sexually reproducing populations. This suggests that sex-specific selection should generally reduce the fitness of females, compared to a hypothetical population in which sex-specific selection is absent. Whether this is actually true of most populations is currently unclear. However, a growing body of research suggests that sexually antagonistic selection is ongoing and detectable within animal genomes (see above; Chippindale et al. 2001; Rice and Chippindale 2001; Brommer et al. 2007; Foerster et al. 2007; Prasad et al. 2007; Bonduriansky and Chenoweth 2009; Cox and Calsbeek 2009). Unresolved sexual antagonism is clearly costly and should represent an adaptive constraint for sexually reproducing species. Evidence demonstrating benefits

of stronger sexually concordant selection in males than females is substantially weaker. Such benefits have been found in some cases (e.g., Promislow et al. 1998; Dolgin et al. 2006; Hollis et al. 2009; Whitlock and Agrawal 2009), but most evidence suggests that these benefits are relatively small (see above; Holland 2002; Rundle et al. 2006; Fricke and Arnqvist 2007; Candolin and Heuschele 2008; Maklakov et al. 2009). In line with predictions from our model and the current lack of support for strong fitness benefits of sexually concordant selection, we conclude that sex-specific selection is unlikely to yield a large, net benefit to most sexual species, and is relatively likely to induce a cost.

These results also have implications for the paradox of sex—the puzzling observation that sex is ubiquitous despite several costs, most notably the "twofold cost" to population growth (Maynard Smith 1978). Our study shows that the decoupling of male and female fitness, which leads to sexually antagonistic and/or sex-limited selection pressures, is likely to exacerbate costs of sexual reproduction. This does not imply that sexual reproduction is incapable of providing benefits that balance multiple severe costs. Indeed, several possible evolutionary mechanisms, including the Red Queen (Hamilton 1980; Agrawal 2006) or interactions between recombination and purifying selection (Kimura and Maruyama 1966; Felsenstein 1974; Kondrashov 1982; Keightley and Otto 2006), can provide long-term benefits to sexual populations. Nevertheless, benefits derived from these possible mechanisms must be substantial to outweigh high costs associated with sexual reproduction.

Finally, the balance of benefits and costs of sex-specific selection can potentially differ among sexually reproducing species. Opportunities for sexually antagonistic selection might vary between species in which the sexes have similar strategies for maximizing fitness, relative to species with fitness landscapes that are highly discordant between males and females. Most studies emphasize sex-specific selection related to mating success, with males selected to maximize their number of mates, and females selected to increase mate quality (Trivers 1972), or decrease mating frequency (Holland and Rice 1998). Sex differences in selection can also arise from ecological differences in species where males and females systematically inhabit different environments (e.g., Trivers and Willard 1973; Bull and Charnov 1977), encounter different sources of mortality (Magnhagen 1991), or exploit different foraging strategies (Shine 1989). Although previous authors have speculated that such ecological differentiation might promote population growth by reducing intraspecific competition (e.g., Selander 1966), ecological differences between males and females might instead exacerbate sexually antagonistic selection or promote genomic expansion of sex-limited loci. From the perspective of population genetics, these consequences of sex-specific selection can constrain adaptation, and potentially reduce population productivity.

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Supporting Information

The following supporting information is available for this article:

Appendix S1. Equilibrium conditions for sexually antagonistic alleles.

Appendix S2. Sexually antagonistic mutation-selection equilibria under weak selection (s_f, t_m) < 0.1) and equal dominance for A_1 between the sexes ($h_f = 1 - h_m$).

Appendix S3. Sex-specific fitness consequences of sex-limited mutation accumulation.

Figure S1. Comparison of exact simulated equilibrium conditions with analytical approximations of the frequency ($\hat{p}$) of a male-beneficial/female-deleterious allele under additive sexually antagonistic selection.

Figure S2. Representative equilibrium conditions for sexually antagonistic selection with dominance reversals between the sexes.

Supporting Information may be found in the online version of this article.

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