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The Evolution of Sex-Specific Dominance in Response to Sexually Antagonistic Selection

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ABSTRACT: Arguments about the evolutionary modification of genetic dominance have a long history in genetics, dating back more than 100 years. Mathematical investigations have shown that modifiers of the level of dominance at the locus of interest can spread at a reasonable rate only if heterozygotes at that locus are common. One hitherto neglected scenario is that of sexually antagonistic selection, which not only is ubiquitous in sexual species but also can generate stable high frequencies of heterozygotes that would appear to facilitate the spread of such modifiers. Here we present a mathematical model that shows that sexually specific dominance modification is a potential outcome of sexually antagonistic selection. Our model predicts that loci with higher levels of sexual conflict should exhibit greater differentiation between males and females in levels of dominance and that the strength of antagonistic selection experienced by one sex should be proportional to the level of dominance modification. We show that evidence from the literature is consistent with these predictions but suggest that empiricists should be alert to the possibility of there being numerous cases of sex-specific dominance. Further, in order to determine the significance of sexual conflict in the evolution of dominance, we need improved measures of sexual conflict and better characterization of loci that modify dominance of genes with sexually antagonistic fitness effects.

Keywords: genetic dominance, modification of dominance, Fisher, Wright, sexual conflict, mathematical model.

For much of the past century, the selective modification of genetic dominance was considered to have played only a minor role in the evolutionary process (Bourguet 1999; Bagheri 2006). Though championed by Ronald Fisher (1928a, 1928b), the view that selection acted directly to modify genetic dominance was criticized by Sewall Wright (1929), who argued that the strength of selection for modification of dominance was proportional to the frequency of heterozygotes (in which dominance could be observed). Alleles at the frequency of the classical mutation-selection balance are rare, and hence so also are the heterozygotes. Thus, selection would be too weak to modify the degree of dominance manifested in these heterozygotes. (For an overview of the sometimes fiery debate, see Provine 1985 and Otto and Bourguet 1999, although we note that the first suggestions about how dominance may have evolved date from significantly earlier than these reviews imply. The biometricians Karl Pearson and Ethel Elderton, who were strongly critical of Mendelian theory, speculated on the subject as early as 1907 [Elderton and Pearson 1907] and in more detail 4 years later [Elderton 1911].)

Feldman and Karlin (1971; see also Bürger 1983) formalized Wright's verbal outline in a mathematical model in which alleles at a second, modifier locus determined the degree of dominance at the locus of interest and effectively confirmed his view. Subsequently, Charlesworth (1979) and, later, Orr (1991) reported that mutations had characteristics (e.g., a negative correlation between homozygous fitness effect and dominance coefficient) that were consistent with Wright's ideas. Finally, the development of metabolic control theory provided evidence that supported Wright's notion that recessivity, not dominance, is an intrinsic feature of physiologically constrained systems (Kacser and Burns 1981; Keightley 1996; Agutter 2008; but see Savageau and Sorribas 1989; Bourguet 1999; Bagheri and Wagner 2004; Bagheri 2006).

Nevertheless, as Wright (1929) himself noted, his arguments required heterozygotes to be rare, and so it was possible that Fisher's theory applied when this condition was not met. Indeed, Otto and Bourguet (1999) showed that dominance modifiers could evolve when environmental heterogeneity maintains heterozygotes at high frequencies. This finding is consistent with empirical evidence from experiments in which dominance coefficients were successfully selected to change (reviewed in Otto and Bourguet 1999). Thus, if heterozygotes are common, Fisher's theory may obtain.

One such scenario is that of sexually antagonistic selection, in which different alleles at one locus are favored in males and females. Population-genetic theory shows that this form

of selection can maintain diallelic polymorphisms in which both alleles are common (Owen 1953; Kidwell et al. 1977; Rice 1984; Patten and Haig 2009; Connallon and Clark 2012). Importantly, different selective pressures on males and females are likely to be widespread in natural populations of sexually reproducing species (Arnqvist and Rowe 2005; Connallon and Clark 2014), and so this scenario seems reasonable. Critically, the sexual conflict inherent in sexually antagonistic selection means that neither sex can attain its selective optimum (Bonduriansky and Chenoweth 2009; Cox and Calsbeek 2009; Connallon and Clark 2011*b*). Such sexual conflict may be resolved (or at least reduced) in a number of ways, depending on the genetic architecture of the species concerned (Rhen 2000, 2007; Bonduriansky 2007).

Intralocus sexual conflict could be ameliorated by the evolution of sex-specific modification of genetic dominance, so that the favored allele in each sex is dominant in that sex. Indeed, Fisher (1931) suggested that sex-linked genes subject to different selection pressures in males and females should evolve to be dominant in one sex and recessive (and eventually unexpressed) in the other. Rice (1984) modeled the evolution of sex-specific expression as a response to sexually antagonistic selection and found that sex linkage of the loci in question facilitated such an outcome. Genomic imprinting, too, is a possible response to intralocus genetic conflict (Day and Bonduriansky 2004), which is interesting, given the parallels between imprinting and genetic dominance (Anderson and Spencer 1999). Nevertheless, the conditions under which sex-specific modification of dominance might evolve are not clear.

Here we present a mathematical model that examines how sexually antagonistic selection influences the evolution of modifiers of dominance. The model is a classical "neutral modifier model"; this sort of model has been used previously to examine the evolution of several aspects of genetic architecture, such as recombination rates (reviewed in Feldman et al. 1996), migration rates (Balkau and Feldman 1973), genomic imprinting (Spencer and Williams 1997), and epistasis (Liberman and Feldman 2006), as well as dominance (reviewed in Otto and Bourguet 1999). In contrast to previous models for the evolution of dominance, we also allow dominance parameters to differ in males and females. We note that models of differential selection on males and females are conceptually similar to Levene's (1953) model of soft selection acting differentially in two environments with complete mixing (i.e., free migration) each generation (Kidwell et al. 1977; Seger and Brockmann 1987; Star et al. 2008), even though they differ in their disassortative mating structure, which generates greater heterozygosity. (A little algebra shows that, compared to a simple model with no sex differences in allele frequencies, heterozygosity in a two-sex model with male and female allele frequencies of p_m and p_f, respectively, is inflated by an amount $(p_m - p_f)^2/2$.) In addition, our models differ from

the "large-scale patch" models used by Otto and Bourguet (1999) to investigate the evolution of dominance modifiers when genetic variation is maintained by environmental heterogeneity, in that these authors focused on conditions with low migration rates.

Model

We consider a single autosomal locus, A, targeted by selection with two alleles, *A* and *a*. The fitnesses of males and females of the three possible genotypes are shown in table 1. In brief, *A* is favored in males and *a* in females, and the heterozygotes have some intermediate fitness, depending on the dominance parameters for each sex. Clearly, for any given allele frequencies, if *A* were dominant over *a* in males ($k_\alpha = 0$) and *a* dominant over *A* in females ($h_\alpha = 0$), the mean fitness of each sex would be maximized.

Consider now a second diallelic locus, M, at a recombination distance *r* from A, which modifies the degree of dominance at A. We assume that, initially, allele *m* is fixed and that male *Aa* heterozygotes have fitness $1 - k_{mm}t$ and corresponding females fitness $1 - h_{mm}s$. The second allele at this modifier locus, M, changes these values, depending on the number of *M* alleles present (table 1). We are interested in the conditions under which *M* can invade a population fixed for *m* and the conditions (possibly the same ones) under which it fixes, driving *m* to extinction. Note that there is no selection directly on the M locus; changes in the frequency of alleles at this locus are driven solely by the effect they have on the variation present at the A locus.

If the four possible haplotypes in the population, *AM*, *aM*, *Am*, and *am*, have respective frequencies x_1, x_2, x_3, and x_4 ($= 1 - x_1 - x_2 - x_3$) in females and y_1, y_2, y_3, and y_4 ($= 1 - y_1 - y_2 - y_3$) in males, we can then adapt the equations of the standard two-locus, two-allele selection model (see, e.g., Bürger 2000) to obtain the iterations for our model of these frequencies after a single generation of selection and random mating (ignoring genetic drift), which are, for $i = 1$, 2, 3, and 4,

$$x_i' = \frac{x_i^s}{\bar{x}},$$
$$y_i' = \frac{y_i^s}{\bar{y}}, \qquad (1)$$

Table 1: Male and female fitnesses

Genotype	*AA*	*Aa*	*aa*
Fitness of females	$1 - s$	$1 - h_\alpha s$	1
Fitness of males	1	$1 - k_\alpha t$	$1 - t$

Note: $\alpha \in \{MM, Mm, mm\}$.

in which

$$
x_1^s = x_1 y_1 (1 - s) + \frac{1}{2}(x_1 y_2 + x_2 y_1)(1 - h_{MM}s)
$$
$$
+ \frac{1}{2}(x_1 y_3 + x_3 y_1)(1 - s)
$$
$$
+ \frac{1}{2}(x_1 y_4 + x_4 y_1)(1 - h_{Mm}s) - r \cdot \tilde{d}(1 - h_{Mm}s),
$$
$$
x_2^s = \frac{1}{2}(x_2 y_1 + x_1 y_2)(1 - h_{MM}s) + x_2 y_2 \cdot 1
$$
$$
+ \frac{1}{2}(x_2 y_3 + x_3 y_2)(1 - h_{Mm}s)
$$
$$
+ \frac{1}{2}(x_2 y_4 + x_4 y_2) \cdot 1 + r \cdot \tilde{d}(1 - h_{Mm}s),
$$
$$
x_3^s = \frac{1}{2}(x_3 y_1 + x_1 y_3)(1 - s) + (x_3 y_2 + x_2 y_3)(1 - h_{Mm}s)
$$
$$
+ x_3 y_3 (1 - s) + \frac{1}{2}(x_3 y_4 + x_4 y_3)(1 - h_{mm}s)
$$
$$
+ r \cdot \tilde{d}(1 - h_{Mm}s),
$$
$$
x_4^s = \frac{1}{2}(x_4 y_1 + x_1 y_4)(1 - h_{Mm}s) + \frac{1}{2}(x_4 y_2 + x_2 y_4) \cdot 1
$$
$$
+ \frac{1}{2}(x_4 y_3 + x_3 y_4)(1 - h_{mm}s) + x_4 y_4 \cdot 1
$$
$$
- r \cdot \tilde{d}(1 - h_{Mm}s),
$$
$$
\bar{x} = x_1^s + x_2^s + x_3^s + x_4^s
$$

(2)

describe the iterations in females,

$$
y_1^s = x_1 y_1 \cdot 1 + \frac{1}{2}(x_1 y_2 + x_2 y_1)(1 - k_{MM}t)
$$
$$
+ \frac{1}{2}(x_1 y_3 + x_3 y_1) \cdot 1 + \frac{1}{2}(x_1 y_4 + x_4 y_1)(1 - k_{Mm}t)
$$
$$
- r \cdot \tilde{d}(1 - k_{Mm}t),
$$
$$
y_2^s = \frac{1}{2}(x_2 y_1 + x_1 y_2)(1 - k_{MM}t) + x_2 y_2 (1 - t)
$$
$$
+ \frac{1}{2}(x_2 y_3 + x_3 y_2)(1 - k_{Mm}t)
$$
$$
+ \frac{1}{2}(x_2 y_4 + x_4 y_2)(1 - t) + r \cdot \tilde{d}(1 - k_{Mm}t),
$$
$$
y_3^s = \frac{1}{2}(x_3 y_1 + x_1 y_3) \cdot 1 + (x_3 y_2 + x_2 y_3)(1 - k_{Mm}t)
$$
$$
+ x_3 y_3 \cdot 1 + \frac{1}{2}(x_3 y_4 + x_4 y_3)(1 - k_{mm}t)
$$
$$
+ r \cdot \tilde{d}(1 - k_{Mm}t),
$$
$$
y_4^s = \frac{1}{2}(x_4 y_1 + x_1 y_4)(1 - k_{Mm}t) + \frac{1}{2}(x_4 y_2 + x_2 y_4)(1 - t)
$$
$$
+ \frac{1}{2}(x_4 y_3 + x_3 y_4)(1 - k_{mm}t) + x_4 y_4 (1 - t)
$$
$$
- r \cdot \tilde{d}(1 - k_{Mm}t),
$$
$$
\bar{y} = y_1^s + y_2^s + y_3^s + y_4^s
$$

(3)

those in males, and

$$
\tilde{d} = \frac{1}{2}(x_1 y_4 + x_4 y_1 - x_2 y_3 - x_3 y_2) \tag{4}
$$

is the modified linkage disequilibrium.

When m is fixed, $x_1 = x_2 = y_1 = y_2 = 0$ and remain so, whereas the iterations for x_3 and y_3 are equivalent to those of Owen's (1953) model of differential viability selection on females and males (see also Kidwell et al. 1977).

Results and Analysis

Let us first consider the special case in which $h_\alpha + k_\alpha = 1$ for all $\alpha \in \{MM, Mm, mm\}$. This complementarity means that there is a trade-off in the levels of dominance between males and females, so that any benefit to one sex of any modification of dominance is offset against a detriment to the other. This assumption is not essential for our overall analysis—we relax it below—but it provides a convenient place to start. Nevertheless, it can also be argued that using this special case also makes biological sense. Complementarity covers the case in which the phenotypes under this differential selection pressure are identical in males and females and the fitnesses in both sexes are linear functions of the phenotype on some suitable scale. For example, suppose the mean phenotypes of AA, Aa, and aa genotypes are 0, φ, and 1, respectively, for both males and females (with $0 < \varphi < 1$). If the phenotypic value 0 is favored in males and the phenotypic value 1 in females, then the closer φ is to 1, the smaller h_{mm} and the larger k_{mm} are. Moreover, $k_{mm} = \varphi$ and $h_{mm} = 1 - \varphi$. It seems plausible, therefore, that when differential selection first arises, perhaps in response to some environmental change differentially affecting the sexes, $h_{mm} + k_{mm} = 1$.

When m is fixed, Kidwell et al. (1977) have shown that the equivalent one-locus model has a single globally stable polymorphic equilibrium, $(\hat{x}_3, \hat{x}_4, \hat{y}_3, \hat{y}_4)$, provided that

$$
\frac{s}{1 + s} < t < \frac{s}{1 - s}. \tag{5}
$$

Outside these bounds, either A or a fixes. It is noteworthy that the existence of this equilibrium does not depend on h_{mm} (although its haplotype-frequency values do). It is also important to realize that condition (5) is quite restrictive, allowing only a small range of similar-sized parameter values, especially for weak selection (small s and t; fig. 1; see also Kidwell et al. 1977).

In order to determine the fate of an M allele attempting to invade such a population fixed for m and following the method in Feldman and Karlin (1971), we examine the leading eigenvalue of the reduced system in x_1', x_2', y_1',
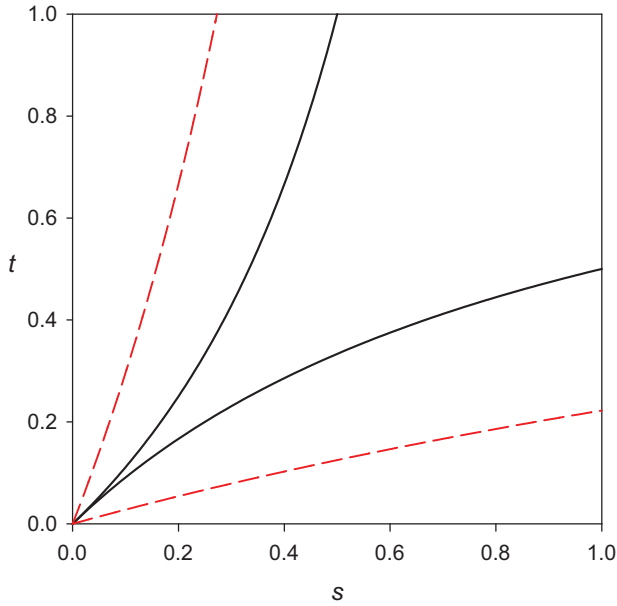
Figure 1: Region of parameter space under sexually antagonistic selection affording a unique, stable, polymorphic equilibrium at the A locus, assuming (1) $h_\alpha + k_\alpha = 1$, in which case it lies between the two solid black curves (after Kidwell et al. 1977), or (2) $h_\alpha = 0.2$ and $k_\alpha = 0.3$ (so $h_\alpha + k_\alpha < 1$), in which case it lies between the dashed red curves. As shown in table 1, s is the selection coefficient against AA females and t that against aa males; h_α and k_α are the dominance parameters for females and males, respectively. Note that when $h_\alpha + k_\alpha = 1$ for weak selection (small s and/or t), the region is also small, requiring $s \approx t$, whereas for $h_\alpha + k_\alpha < 1$, the region is unconditionally larger.

and y_2' linearized around $(x_3, x_4, y_3, y_4) = (\hat{x}_3, \hat{x}_4, \hat{y}_3, \hat{y}_4)$. A Mathematica script (see supplementary zip file, available online)[1] shows that this leading eigenvalue is exactly 1, which means that, to a first approximation at least, the invasion of M is neither favored nor prevented by selection. Extensive numerical analysis found no counterexamples, which suggests that our linear approximation is accurate. This result is, perhaps, not surprising, because the average of the mean fitnesses of males and females at $(x_3, x_4, y_3, y_4) = (\hat{x}_3, \hat{x}_4, \hat{y}_3, \hat{y}_4)$ is given by

$$\frac{1}{2}(\hat{\bar{x}} + \hat{\bar{y}}) = \frac{1-s}{4} + \frac{1-t}{4} + \frac{s^2 + t^2}{4st}, \quad (6)$$

independent of h_{mm}. Consequently, the population's fitness is not affected by the alleles at the M locus.

We can use this result in a first step to elucidate the general conditions under which M will invade. First, we keep the assumption that $h_{mm} + k_{mm} = 1$ but remove the previ-

ous complementarity constraints on the other dominance parameters. Extensive numerical exploration reveals that, given the accuracy of our linearization approximation, M will invade if and only if $h_{Mm} + k_{Mm} < 1$, which means that it is alleviating some of the conflict. Critically, we find that the modifier can invade even if it makes things worse for one sex (i.e., it increases the dominance parameter for that sex), provided that the benefit to the other sex (i.e., the decrease in its dominance parameter) is sufficiently large. In these cases, a trade-off is evident between the fitnesses of the heterozygotes of each sex, although decreases in fitness are of lower magnitude than the increases, which means that the population may gain overall.

An example is shown in figure 2A, where a modifier (M) that reduces the fitness of Aa females ($h_{Mm} > h_{mm}$) but increases that of Aa males ($k_{Mm} < k_{mm}$) successfully invades but the frequency of A, favored in males but not females, declines. Interestingly, in this example, the mean fitness of females increases monotonically, whereas the mean fitness of males increases at first and then decreases, although the overall change is positive. Moreover, we note that arguments using initial changes in mean fitness, often used in game-theoretic or adaptive-dynamic approaches (see Spencer and Feldman 2005), do not make the correct prediction, either: the modifier can invade even if one of the male and female mean fitnesses decreases; an example is shown in figure 2B. We note, too, that, in these examples, the increase in frequency of M is initially very slow: no perceptible increase occurs for the first 400 generations, even though the reduction in the sum of the dominance parameters (0.1) is not negligible.

When $h_\alpha + k_\alpha < 1$, Kidwell et al. (1977) showed that at most one stable polymorphic equilibrium was possible and that such an outcome occurred, provided that

$$\frac{h_\alpha s}{1 - k_\alpha + h_\alpha s} < t < \frac{(1 - h_\alpha)s}{k_\alpha(1 - s)}. \quad (7)$$

An example of such a region is shown in figure 1. Note that this part of parameter space is a superset of that affording a stable polymorphic equilibrium at A when $h_\alpha + k_\alpha = 1$. Thus, if there exists a stable polymorphism at A for $h_{mm} + k_{mm} = 1$, any successful invasion of M will preserve this polymorphism, since $h_{Mm} + k_{Mm} < 1$.

We now examine the case when $h_{mm} + k_{mm} < 1$. Our numerical explorations show that the conditions for the invasion of M are not simple. For example, it is neither sufficient nor necessary that $h_{Mm} + k_{Mm} < h_{mm} + k_{mm}$. Figure 3 shows, for a representative set of parameters $(r, s, t, h_{mm}, k_{mm})$ that result in a stable polymorphism at A when m is fixed, the regions of (h_{Mm}, k_{Mm}) parameter space that favor the invasion of M. The insufficiency of the $h_{Mm} + k_{Mm} < h_{mm} + k_{mm}$ condition is exemplified by the parts of parameter space be-
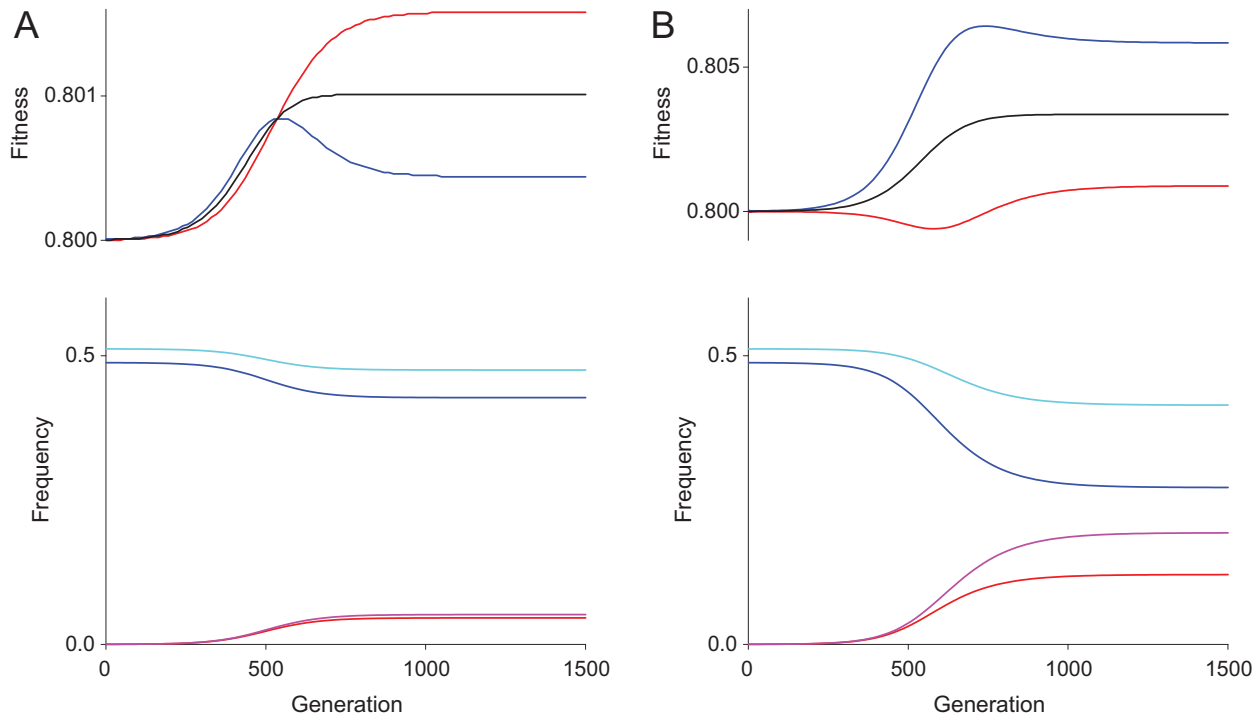
Figure 2: Trajectories of haplotype frequencies and mean fitnesses showing that (*A*) modifiers deleterious to one sex (in this case females) can invade ($r = 0.2$, $s = t = 0.4$, $h_{MM} = k_{MM} = 0.9$, $h_{Mm} = 0.5$, $k_{Mm} = 0.4$, $h_{mm} = 0.4$, and $k_{mm} = 0.6$) and (*B*) the female mean fitnesses need not increase ($r = 0.2$, $s = t = 0.4$, $h_{MM} = 0.9$, $k_{MM} = 0.2$, $h_{Mm} = 0.7$, $k_{Mm} = 0.2$, $h_{mm} = 0.4$, and $k_{mm} = 0.6$). In both panels, in the lower graph, the frequencies of the four haplotypes, *AM*, *aM*, *Am*, and *am*, respectively x_1, x_2, x_3, and x_4, are depicted by red, pink, dark blue, and light blue, respectively; in the upper graph, the female mean fitness is shown in red, the male in blue, and the average in black. Initial haplotype frequencies for x_3, x_4, y_3, and y_4 were given by the equilibria under Owen's (1953) model minus 0.0001; those for x_1, x_2, y_1, and y_2 were all 0.0001.

low the light blue line but above the dark blue line and its unnecessity by the regions below the dark blue line but above the light blue line. Nevertheless, the trend is certainly that selection favors modifiers that reduce the sum of the dominance parameters; the exceptions (below the dark blue line but above the light blue one) arise when the differences are small. In the numerical example of figure 3, invasion of M requires a reduction in h more than a decrease in k, because $s > t$. Figure 3 also shows the more restricted part of parameter space satisfying the more stringent requirement for M to invade at a reasonably rapid rate (in the case of the figure, requiring the leading eigenvalue to be greater than 1.01, implying an initial increase of more than 1% in frequency each generation). In brief, the change in dominance parameters must be substantive and suggests that the exceptions to $h_{Mm} + k_{Mm} < h_{mm} + k_{mm}$ will be rare.

Finally, we turn to the case in which $h_{mm} + k_{mm} > 1$. Although it seems that such a condition is unlikely either initially, when differential selection on males and females first arises, or subsequently (indeed especially), after the invasion and fixation of a new modifier, we do so for the sake

of completeness. Kidwell et al. (1977) showed that at most one stable polymorphic equilibrium at A was possible, although its stability may not be global because fixation of either *A* or *a* (depending on the parameters) may also be locally stable. For our purposes, however, we are interested in when variation is maintained at A, because that is when genetic conflict arises; we note that this condition implies large values of s and t, which may also be considered unlikely. In the event, numerical analyses suggest that the general trend described above still pertains: a modifier M will invade if, in general, it reduces the sum of the dominance parameters, although exceptions do occur if the dominance parameter of one sex would be altered by some small amount. A numerical example is shown in figure 4.

We also investigated the effect of the recombination parameter, r. In contrast to two-locus models of differential selection on males and females in which the magnitude of r has significant consequences (Patten et al. 2010), changing r rarely altered the outcome in our model, presumably because the modifier locus was selectively neutral. Extensive simulations revealed that, on the rare occasions in
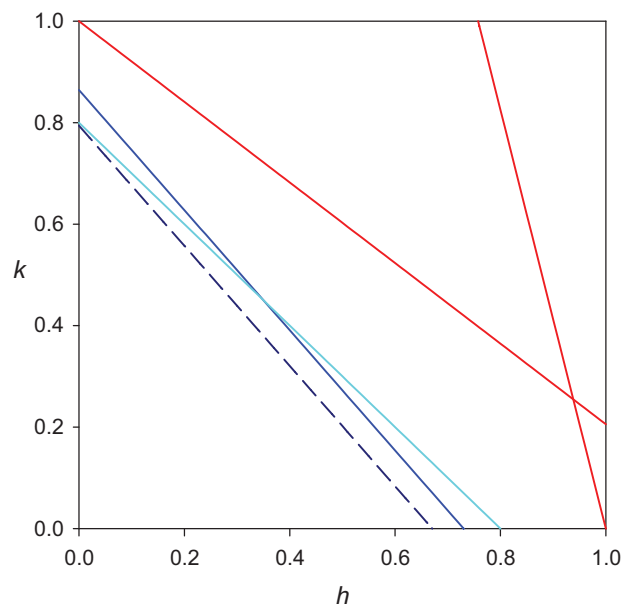
Figure 3: The (h_{Mm}, k_{Mm}) parameter space when $(r, s, t, h_{mm}, k_{mm}) = (0.1, 0.65, 0.45, 0.35, 0.45)$. The modifier allele, M, will invade a population fixed for m provided that the heterozygotes' dominance parameters (h_{Mm}, k_{Mm}) are to the left of (below) the solid dark blue line. The light blue line represents $h_{Mm} + k_{Mm} = h_{mm} + k_{mm} = 0.8$. A globally stable polymorphism at A is possible only for h_{mm} and k_{mm} values below both red lines. Note that the two solid blue lines intersect when $h_{mm} = h_{Mm}$ and $k_{mm} = k_{Mm}$. The parts of the parameter space below the dashed blue line have a leading eigenvalue greater than 1.01.

which there was an effect, smaller r values favored the invasion of M whereas larger values caused the fixation of m to be stable. In other words, the leading eigenvalue was a decreasing function of r.

The conditions under which M continues to fixation can be deduced from the above results: they are effectively the same conditions required for m to repel an invasion by M, but with the allele names swapped. For example, assuming that M has invaded successfully in the first place, if we also have $h_{MM} + k_{MM} < h_{Mm} + k_{Mm}$, then it is almost certain that it will fix, the exceptions arising when the difference in these two sums is small.

Discussion

Our analytical and numerical investigations show that sexually antagonistic selection maintaining a polymorphism provides the opportunity for the evolution of dominance in accordance with Fisher's theory. Thus, this form of selection can be added to the list of heterozygote advantage and spatially variable selection (Otto and Bourguet 1999), as well as frequency-dependent selection (Peischl and Schneider

2010), under which there are sufficient heterozygotes in the population for selective modification of dominance to take place. Our finding is important because there is abundant evidence that sexually antagonistic selection is ubiquitous in natural populations (Arnqvist and Rowe 2005; Connallon and Clark 2014)—certainly it is far more frequent than heterozygote advantage, for example—and so dominance is likely to have been subject to selective change significantly more often than currently thought.

The evolution of dominance continues to be a central question in evolutionary biology, not only because it was the topic that led to the falling out of two of the most important historical figures in the field, Ronald Fisher and Sewall Wright (Provine 1985), but also because it has basic implications for sexual antagonism, the nature of inheritance, and the evolution of genetic diseases (Wilkie 1994; Rhen 2000; Bagheri 2006; Connallon and Clark 2014). It had long been held that modifiers of dominance were unlikely to contribute to genetic architecture, both because direct selection had to be unreasonably strong to modify dominance of new mutations and because it was thought that dominance was an emergent property of metabolic networks (Kacser and Burns 1981; Keightley 1996; Agutter 2008). Our modeling shows that sexual conflict can plausibly drive the evolution of dominance modifiers at reason-
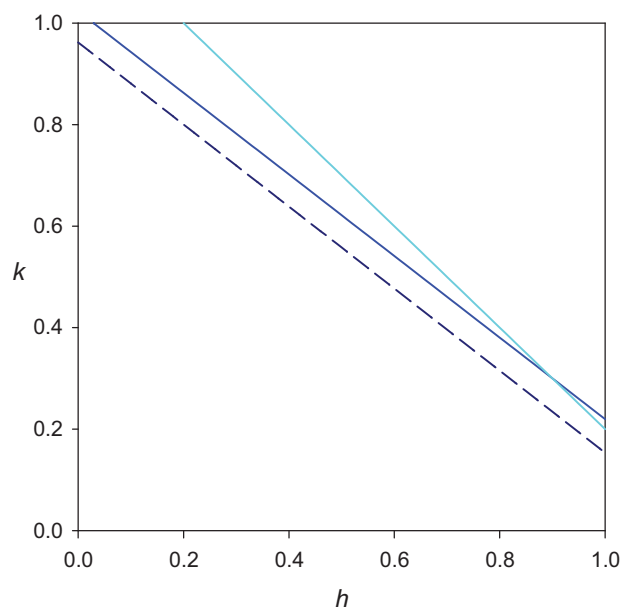

Figure 4: The (h_{Mm}, k_{Mm}) parameter space when $(r, s, t, h_{mm}, k_{mm}) = (0.1, 0.8, 0.6, 0.9, 0.3)$. The modifier allele, M, will invade a population fixed for m, provided that (h_{Mm}, k_{Mm}) is to the left of (below) the solid dark blue line. The light blue line represents $h_{Mm} + k_{Mm} = h_{mm} + k_{mm} = 1.2$. Note that the two solid blue lines intersect when $h_{mm} = h_{Mm}$ and $k_{mm} = k_{Mm}$. Parts of parameter space below the dashed line have a leading eigenvalue of greater than 1.01.

able rates, adding to the increasing number of studies questioning this orthodoxy.

Moreover, our models predict that at loci subject to sexually antagonistic selection, males and females are likely to evolve different dominance parameters. Indeed, there are a number of genetic phenomena that are consistent with this prediction, including sex-specific epistasis (Long et al. 1995), molecular mechanisms underlying sex-limited gene expression (Hodgkin 1990), dominance in sex determination (Rhen et al. 2011), sex-specific nonadditivity of gene expression (Gibson 2004), sex-specific modification of disease pathologies (Weydt et al. 2014), different dominance hierarchies of self-incompatibility alleles in the pollen and stigma of a number of plants (Llaurens et al. 2009; Schoen and Busch 2009), and evidence for the modification of dominance of genes with sex-specific functions (Montgomery et al. 1996).

It is important to note that modification of sex-specific dominance can lessen the degree of sexual conflict but may not resolve it completely. In our model, for example, selectively disadvantageous *AA* females and *aa* males will still be produced every generation. Full resolution of this conflict would require further changes in genetic architecture, such as gene duplication followed by sex-specific expression of each locus (Connallon and Clark 2011*b*). If examples of sex-specific dominance turn out to be rare, it may be because the remaining sexual conflict has been resolved in a way that obliterates any such dominance or renders any selection for it unnecessary. Alternatively, the conflict may have been resolved through some other genetic change (see Bonduriansky and Chenoweth 2009 for a number of possibilities). Such alternative resolutions might be considered more general in their effects (and thus more likely) if, unlike modifiers of dominance, which act on particular alleles, they can act on many alleles at one locus or even several loci simultaneously. Finally, the rapid evolution at sexually antagonistic loci predicted by coevolutionary models may be considerably faster than any changes in dominance (Bonduriansky and Chenoweth 2009).

Sexually antagonistic selection can occur when fitness optima are balanced between the sexes or when there is asymmetry in the antagonistic selection, such that benefits to one sex outweigh the costs to the other. Our model shows that the modification of dominance can evolve under either condition, though with different predicted patterns of the evolution of dominance. When sexual conflict affects both sexes equally, modifiers of dominance on new recessive mutations will tend to ameliorate the conflict by making the heterozygotes of each sex more like the favored homozygote of that sex. This finding leads to a general prediction that species with higher levels of sexual conflict should exhibit higher levels of sex-specific dominance. When there is asymmetry in the antagonistic selection, we find that selec-

tion will favor modifiers of dominance that alter expression more in the sex that exhibits the greater fitness costs. This result leads to the prediction that the sex that experiences greater levels of antagonistic selection should exhibit greater levels of dominance.

Although we cannot distinguish between other possible hypotheses, there is some evidence from the literature that is consistent with both of these predictions. High degrees of dominance in fitness traits are evident in species, such as the fruit fly, the seed beetle, and water striders, in which females exhibit substantial costs of mating (Mukai et al. 1972; Bilde et al. 2008; Wolak 2013). In addition, in each of these species females exhibit higher levels of dominance in adult fitness traits than do males (Fox et al. 2004; Gibson et al. 2004; Wolak 2013). In seed beetles, females exhibit substantially more dominance variance in longevity, a trait that is governed largely by male mating behavior, but not in development time or weight, which are not directly affected by antagonistic behaviors of males (Fox et al. 2004; Hallsson and Björklund 2011). But we need more research on the loci underlying sexual conflict to understand the source of these patterns.

When they have been identified, loci underlying intralocus sexual conflict often exhibit large sex-specific differences in dominance. Perhaps the best example is that of the vestigial-like family member 3 gene (*VGLL3*) in Atlantic salmon, for which sex-dependent dominance leads to earlier maturation of males than of females, a difference strongly favored by selection (Barson et al. 2015). And, in mice, between-sex differences in dominance are greater for loci underlying sexually dimorphic traits, such as body size, than for traits in which there is no evidence of dimorphism, such as liver and spleen mass at adulthood (Hager et al. 2008).

The mouse example is particularly interesting because it provides evidence that sex-specific modification of dominance can be altered though development (Hager et al. 2008). Although both body size and dominance are equivalent between the sexes at birth, the loci associated with body size exhibit increased dominance in males but not in females, who become proportionally bigger than males during development. Although it is tempting to suggest that male body size must, therefore, be under intense sexually antagonistic selection, it is important to note that the mouse strains in question result from an artificial-selection experiment on sex-corrected body size (Hager et al. 2008), which we would not expect to generate sexual conflict. This example highlights the problem that we need better data to distinguish between possible sources and potential evolutionary consequences of sexual antagonism.

We also need to be able to identify the loci that modify dominance. One of the critical assumptions of our model is that modifier alleles act on genes with substantial genotype-

and sex-dependent influences on fitness. As we argue above, when sexually antagonistic selection first arises, it is reasonable to assume that the male and female dominance parameters are complementary ($h_{mm} + k_{mm} = 1$). Our models imply that a modifier, M, will invade, provided that this complementarity can be broken ($h_{Mm} + k_{Mm} < 1$). There is evidence that such noncomplementary parameters do exist in nature. In fruit flies, there is evidence for the types of genes required for dominance modification to succeed, as it has been shown that alleles with sex-biased expression often have fitness effects in the sex in which the expression is biased (Connallon and Clark 2011a). In sheep, loci have been characterized that modify sex-limited alleles at the horn-development locus, *Ho* (Montgomery et al. 1996).

One final point is on the nature of how these alleles evolve with respect to the average fitness of a population. We find that the mean fitness of one sex can, at least initially, decrease in the course of a successful invasion by a novel dominance modifier. Many studies of sexually antagonistic selection, including artificial-selection experiments, have argued that reduced population fitness is characteristic of sexual antagonism. Our findings indicate that fitness can be decreased even when alleles that tend to resolve conflict are rapidly increasing in frequency. This model behavior suggests that arguments based on changes in a population's mean fitness must be viewed with caution (Spencer and Feldman 2005).

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