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Evolutionary inevitability of sexual antagonism

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Sexual antagonism, whereby mutations are favourable in one sex and dis-favourable in the other, is common in natural populations, yet the root causes of sexual antagonism are rarely considered in evolutionary theories of adaptation. Here, we explore the evolutionary consequences of sex-differential selection and genotype-by-sex interactions for adaptation in species with separate sexes. We show that sexual antagonism emerges naturally from sex differences in the direction of selection on phenotypes expressed by both sexes *or* from sex-by-genotype interactions affecting the expression of such phenotypes. Moreover, modest sex differences in selection or genotype-by-sex effects profoundly influence the long-term evolutionary trajectories of populations with separate sexes, as these conditions trigger the evolution of strong sexual antagonism as a by-product of adaptively driven evolutionary change. The theory demonstrates that sexual antagonism is an inescapable by-product of adaptation in species with separate sexes, whether or not selection favours evolutionary divergence between males and females.

1. Introduction

Species with separate sexes face two important evolutionary challenges that can limit their abilities to adapt to a changing environment. First, discrete sexes are common among complex organisms, in which pleiotropic effects can constrain adaptation [1–3]. Second, patterns of selection and the phenotypic effects of mutations each differ between the sexes [4–6], which can decouple the genetic basis of male versus female fitness. When male and female fitness is decoupled, mutations benefitting one sex will sometimes be deleterious to the other (i.e. their fitness effects are ‘sexually antagonistic’ [7]), which diminishes a population’s ability to respond to selection through fixation of beneficial mutations.

An emerging body of data implies that sexual antagonism is an important feature of animal and plant populations [8–11]. Nevertheless, several fundamental questions regarding sexual antagonism remain unaddressed. For example, how often does sexual antagonism arise owing to sex differences in the direction of selection? How severely does sexual antagonism limit the rate of adaptation in each sex, and how do such constraints evolve over time? How does environmental change mediate opportunities for sexual antagonism, including differences between poorly versus well-adapted populations?

These questions can be addressed with theoretical models that effectively bridge the divide between empirically measurable properties of mutation and selection, and the evolutionary genetic patterns and processes that we seek to understand. Quantitative genetics theory has proved extremely useful for quantifying short-term constraints to sex-specific adaptive evolution [12], yet we currently lack clear theoretical predictions about the underlying population genetics of sexual antagonism, including the fraction of mutations that has sexually antagonistic fitness effects, and the role of sexual antagonism in shaping the long-term evolutionary trajectories of males and females in adaptively evolving populations. With these issues in mind, we developed a two-sex extension of Fisher’s geometric model [13], and used it to characterize the sex-specific distribution of mutant fitness effects, and the population genetic dynamics of adaptation in species with separate sexes.

2. Fisher's geometric model in species with separate sexes

Fisher's original model provides a simplified mapping between genotype, phenotype and fitness that captures the basic biological details of adaptation within a complex organism: (i) mutations cause random changes within multi-dimensional trait space; (ii) selection favours those mutations that move the system of traits closer to an optimal phenotypic value that maximizes fitness; and (iii) a population approaches its fitness optimum by successively fixing beneficial mutations [14,15]. Although alternative modes of evolutionary change—e.g. polygenic adaptation involving modest allele frequency shifts at many loci—may also contribute to adaptation over short evolutionary time-scales, such short-term responses may be weak when pleiotropic constraints—including sexual antagonism—are severe [16–18]. In such cases, adaptation is likely to be dominated by the fixation of beneficial mutations, provided directional selection is sustained over time [19,20]. Fisher's model also makes simplifying assumptions about the mutational architecture of traits, yet its original assumptions can be relaxed without greatly altering the model's basic predictions [21–23] and these predictions are adept at explaining a variety of interesting empirical patterns that emerge from the study of real organisms (e.g. [24–28]).

In extending Fisher's model to a two-sex system, we characterize the evolution of n traits that are each expressed, but not necessarily equally, in males and females (see the electronic supplementary material). Sets of trait values are depicted using Cartesian coordinates, with each set of coordinates representing an individual's genetically determined position in n -dimensional phenotypic space. Following prior work, we assume that fitness depends on the Euclidean distance of each sex to its optimum, and mutational effects are unbiased in direction (uniformly oriented in n -dimensional space [13,29,30]). These assumptions are not restrictive as long as we interpret n as the 'effective complexity' of a species (i.e. the effective number of traits can be less than the actual number [21–23]). To simplify the presentation, we model mutation and evolution in a haploid population; our results also apply to diploids, with the caveat that mutations contributing to adaptation in diploids will sometimes involve a transient, balanced polymorphic state [30]. Finally, although we focus on evolution in dioecious (gonochoristic) species with distinct sexes, sexual antagonism may also manifest within hermaphrodites, by way of allocation trade-offs between male and female reproductive structures in simultaneous hermaphrodites, or antagonistic pleiotropy between male and female stages in sequential hermaphrodites [31]. Our results may imperfectly characterize adaptation in hermaphrodites, yet our underlying mathematical framework is sufficiently flexible to permit future theoretical extensions to mating systems that we do not specifically consider here.

Patterns of selection depend on the distance and orientation of each sex to its phenotypic optimum. Let z_m and z_f represent the Euclidean distance between the optimal phenotype and the actual phenotype expressed by each sex (subscripts, m and f, hereafter refer to 'male' and 'female'). Fitness functions for each sex are Gaussian, with $w_m = \exp(-\omega_m z_m^2)$ and $w_f = \exp(-\omega_f z_f^2)$, and ω_m and ω_f are positive constants specifying the strength of the fitness decline with increased distance from the optimum. The relative orientation of each sex to its optimum—the *direction* of

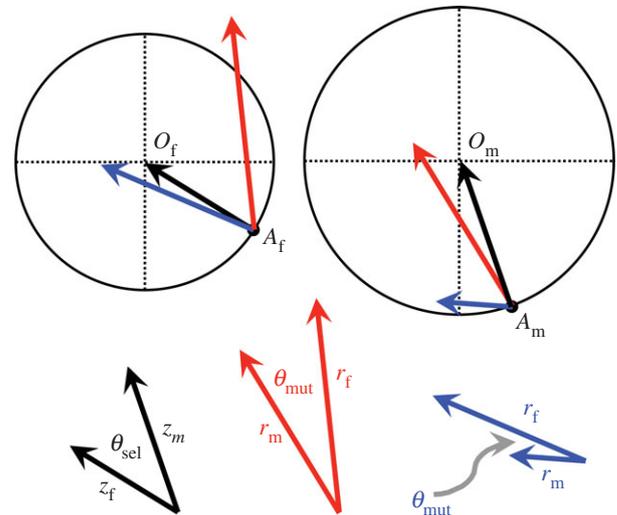


Figure 1. Fisher's geometric model in two dimensions and with two sexes. Trait values are represented by the x - and y -axes, with each of the traits expressed by both sexes. A_f and A_m depict the trait values expressed by females and males in the population, and O_f and O_m are the female and male trait optima. Black arrows represent the sex-specific selection vectors that reflect the distance of each sex to its optimum (vector lengths, z_f and z_m). Sex differences in directional selection are described by the angle between selection vectors (θ_{sel}). The fitness effects of each mutation depend on its phenotypic effect in each sex: its size (vector length, r_m and r_f) and orientation in phenotypic space. Sex differences in a mutation's orientation are described by the angle between mutation vectors (θ_{mut}). Mutations that bring a given sex closer to its optimum (i.e. within the relevant circle) are beneficial to that sex, whereas those causing movement away from the optimum will be deleterious (i.e. outside the relevant circle). Two mutations are shown: one that is beneficial to both sexes (blue), and the other that is sexually antagonistic (red).

selection—can be described by a pair of vectors that extend from the current locations of each sex within phenotypic space to the location of its optimum (figure 1). The *strength* of selection is defined as $\beta_m = |\partial \ln(w_m) / \partial z_m| = 2\omega_m z_m$ and $\beta_f = |\partial \ln(w_f) / \partial z_f| = 2\omega_f z_f$, which parallel the definition of the selection gradient from quantitative genetics (see [32, pp. 122–123]). θ_{sel} represents the angle between male and female selection vectors, with $\rho_{\text{sel}} = \cos(\theta_{\text{sel}})$ representing the correlation between male and female orientations of directional selection ($-1 < \cos(\theta_{\text{sel}}) < 1$, with $\rho_{\text{sel}} = 1$ representing identical directions of selection; see [33]).

Phenotypic effects of mutations are similarly described using paired vectors, with each mutation having a unique magnitude (r_m and r_f) and orientation within each sex (figure 1). For each mutation, θ_{mut} is a random variable, which represents the angle between male and female orientations of phenotypic change caused by the mutation. For mutations with specified magnitude r_m and r_f , the phenotypic correlation between the sexes for each trait axis is given by ρ_{mut} . In the two-sex extension of Fisher's model, there is a geometric relationship between ρ_{mut} and the angle between mutation vectors: $\rho_{\text{mut}} = \langle \cos(\theta_{\text{mut}}) \rangle$, where the angle brackets denote the mean among random mutations (see the electronic supplementary material).

Unique mutations arise randomly within a population that is initially fixed at each locus for a resident (wild-type) allele. For a given mutation, its sex-specific fitness effect

in the j th sex is $s_j = (w_j(z_{j*})/w_j(z_{j+}) - 1)$, where z_{j+} and z_{j*} represent distances to the optimum for wild-type and mutant individuals, respectively. Letting $t_j = \ln(1+s_j)$ represent the logarithm of relative fitness, $f(t_m, t_f; r_m, r_f)$ is the bivariate distribution of t_m and t_f among mutations with arbitrary magnitude, r_m and r_f ($r_m, r_f > 0$). In many dimensions ($n \gg 1$), this distribution converges to a bivariate normal distribution, with marginal mean and variance $\langle t_j \rangle = -\omega_j r_j^2$ and $\text{var}(t_j) = (2\omega_j r_j^2)^2/n$, respectively, and between-sex correlation coefficient of $\rho_{mf} = \cos(\theta_{sel})\langle \cos(\theta_{mut}) \rangle = \rho_{sel}\rho_{mut}$ (see the electronic supplementary material, noting that s_m, s_f will also be bivariate normal in the limit: $s_m, s_f \rightarrow 0$). This simple identity for ρ_{mf} implies that genotype-by-sex interactions and sex-differential selection contribute multiplicatively to the fitness effect correlation between the sexes. Moreover, either factor is sufficient to generate an imperfect genetic correlation between male and female fitness.

Adaptive evolutionary change involves the sequential fixation of mutations with sex-averaged beneficial fitness effects ($s_{avg} = s_m/2 + s_f/2 > 0$). Similar to previous work in Fisher's geometric model (e.g. [29]), we characterize evolutionary change in a large population where beneficial mutations are rare, selection coefficients of beneficial alleles are small ($s_m, s_f \ll 1$; see [34]), and therefore each mutation's probability of fixation depends only on its net fitness effect. Provided the sex-averaged fitness effect is positive ($s_{avg} > 0$), a mutation's probability of fixation is $1 - \exp(-2s_{avg})$, and otherwise its fixation probability is zero. Mutations that are successfully fixed trigger a change in the location of males and females within phenotypic space. Following each substitution, new distances and relative orientations of males and females to their optima may be calculated (i.e. new values of z_m, z_f, θ_{sel}), and the next step of adaptation can proceed from this new population state (see the electronic supplementary material).

Because substitutions in Fisher's model are discrete (see above and [29]), each time point during evolution is associated with specific values for z_m, z_f and θ_{sel} and these terms may therefore be treated as population parameters appropriate for a given time point. We assume throughout that the phenotypic distributions of mutations remain constant during evolution (distributions of r_m, r_f and θ_{mut} remain constant). Therefore, ρ_{mf} can be treated as a population parameter, albeit one that can evolve over the course of an adaptive walk. Accordingly, we first consider the sex-specific fitness effects of new mutations and the rate of adaptation, for an arbitrary population with parameters z_m, z_f and θ_{sel} . We then characterize the long-term evolution of such populations as they adapt, with each sex approaching its fitness optimum.

3. Results and discussion

Adaptation requires beneficial genetic variation, which serves as the fuel for evolutionary change. In populations with separate sexes, random mutations can be deleterious to both sexes, beneficial to both, or beneficial to one sex and deleterious to the other ('sexually antagonistic'). Among mutations that are beneficial to at least one sex ($s_m > 0$ and/or $s_f > 0$), the fraction that is sexually antagonistic is:

$$f_{SA} = \frac{\Pr(s_m/s_f < 0)}{1 - \Pr(s_m < 0; s_f < 0)}, \quad (3.1a)$$

which, in the limit of small mutation size, reduces to a simple function of the fitness effect correlation (ρ_{mf}):

$$\lim_{r_f, r_m \rightarrow 0} f_{SA} = \frac{2\pi - 4 \sin^{-1}(\rho_{mf})}{3\pi - 2 \sin^{-1}(\rho_{mf})}. \quad (3.1b)$$

Equation (3.1b) approximates the minimum proportion of beneficial mutations that are sexually antagonistic (see the electronic supplementary material). Numerical evaluation of equation (3.1), along with exact computer simulations across a distribution of r_m and r_f values, shows that f_{SA} increases with dimensionality and mutation size—factors that also increase the 'scaled size' of mutations in Fisher's geometric model (i.e. the scaled mutation size in sex j is defined as $x_j = r_j \sqrt{(n)/(2z_j)}$; see [13,29]). Overall, sexual antagonism is pervasive, and is a dominant feature of beneficial mutations, across the entire range of ρ_{mf} (figure 2).

Adaptation represents a compromise between fitness benefits and costs to males and females, with selection favouring mutations with positive, sex-averaged fitness effects (i.e. $s_{avg} = s_m/2 + s_f/2 > 0$). Rates of adaptation in each sex can be approximated by taking into account both the mutation rate to positively selected alleles and the fixation probabilities of individual mutations [1]. To quantify the effect of an imperfect fitness correlation on the rate of adaptation, constraint is expressed as the ratio of the expected rate of adaptation in a population with imperfectly correlated male and female fitness effects ($\rho_{mf} < 1$) to the rate of adaptation in an ideal population with perfectly correlated fitness effects ($\rho_{mf} = 1$). We formally define this constraint as $C_j = (dz_j/dt | \rho_{mf} < 1)/(dz_j/dt | \rho_{mf} = 1)$, where dz_j/dt is the rate of evolutionary change of sex j towards its optimum (see the electronic supplementary material; $C_j = 1$ in the absence of sexually antagonistic constraints, and otherwise, $C_j < 1$). In the limit of small mutation size ($r_f, r_m \rightarrow 0$), these ratios in males and females are approximately:

$$C_m = 1 - (1 - \rho_{mf}) \frac{r_f \beta_f}{r_f \beta_f + r_m \beta_m} \quad \text{and} \quad C_f = 1 - (1 - \rho_{mf}) \frac{r_m \beta_m}{r_m \beta_m + r_f \beta_f}, \quad (3.2)$$

which compares well with exact computer simulations of small to moderately sized mutations, and it underestimates the true magnitude of constraint, particularly when scaled mutation sizes are large (figure 2, where $x_j = r_j \sqrt{(n)/(2z_j)}$ is the scaled size). An imperfect fitness correlation between the sexes significantly decreases the rate of adaptation (C_m and C_f can be substantially lower than one), with the relative magnitude of constraint dependent upon mutation and selection asymmetries between the sexes. With equally strong directional selection in each sex and similar-sized mutations ($r_m \beta_m = r_f \beta_f$), males and females experience equal degrees of constraint: $C_m = C_f = 1 - (1 - \rho_{mf})/2$. Asymmetries between the sexes ($r_m \beta_m \neq r_f \beta_f$) shift the burden of constraint to the sex that experiences weaker selection or mutation (figure 2).

The results above describe features of selection and adaptation at single time points during evolution, and consequently they treat fitness effect distributions and sex-specific rates of adaptation and constraint as static rather than evolutionarily labile population properties. However, each mutation that is fixed during adaptation will carry the population to a new location in phenotypic space and will alter the distance and orientation of each sex to its optimum. Fitness effect distributions and subsequent opportunities

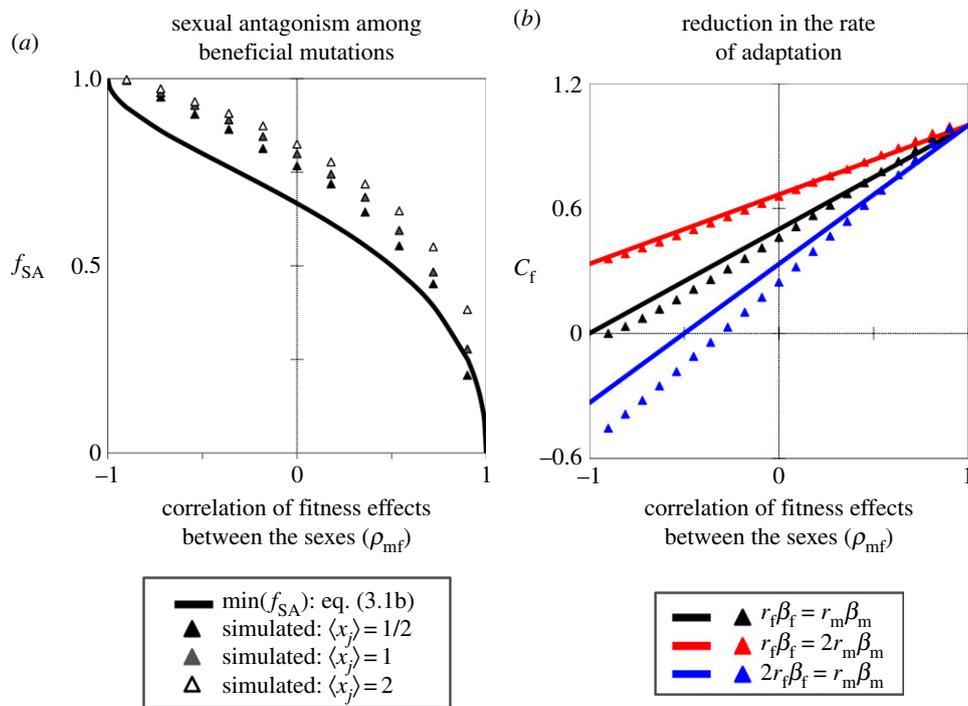


Figure 2. The fitness effect correlation between sexes (ρ_{mf}) predicts the fraction of sexually antagonistic mutations, and the severity of constraints to sex-specific adaptation. The minimum fraction of beneficial mutations that are sexually antagonistic (f_{SA} ; (a)) is based on the approximation in equation (3.1b) (solid curve), and from exact simulation results, using three different mutation size distributions (triangles). Shown are results using a bivariate exponential distribution for r_m and r_f , with $\text{corr}(r_m, r_f) = 0.9$ and equal marginal distributions for r_m and r_f [35]. The mean scaled mutation size is $\langle x_j \rangle = \langle r_j \rangle \sqrt{(n)/(2z_j)}$, with $n = 25$ dimensions, and $z_j = 1/2$; $j = \{m, f\}$. Each simulation result is based on 10 000 randomly generated beneficial mutations (e.g. beneficial to at least one sex). The relative reduction in the rate of adaptation in females (C_f ; (b)) is based on the small mutation approximation in equation (3.2) (solid lines). Exact simulation results are depicted by triangles, based on the parameters: $r_m = r_f = 0.05$, $z_m = z_f = 1/2$, $n = 25$ ($x_j = 0.25$) and $\beta_m/\beta_f = \omega_m/\omega_f$. Additional details of the simulation procedure can be found in the electronic supplementary material.

for adaptation will therefore change following each genetic substitution. To characterize such changes during the course of adaptive evolution, we analysed adaptive walks of populations towards stationary male and female fitness optima (see the electronic supplementary material; figure 3). We focused on the strength and orientation of sex-specific directional selection (β_m , β_f and ρ_{sel})—quantities that directly impact the distribution of mutant fitness effects.

Despite an enormous range of possible initial conditions and sex-specific mutation and selection parametrizations, two general patterns emerge from the analysis. First, as long as mutant phenotypic effects are positively but imperfectly correlated between the sexes, as appears likely [6,36,37] (see below), the genetically coupled evolution of male and female phenotypes will inevitably generate sex-specific selection in opposing directions in phenotypic space (figure 3; i.e. adaptation eventually causes $\rho_{sel} < 0$, and thus, $\rho_{mf} < 0$ and $f_{SA} > 2/3$; see the electronic supplementary material). In other words, adaptation generates opposing selection on traits expressed by males and females, and widespread sexual antagonism among mutations that are individually beneficial to males or females. This outcome includes cases where directional selection is initially identical between the sexes (figure 3 and electronic supplementary material, figure S2). Second, initial differences in the strength of directional selection decrease during adaptation ($\beta_m/\beta_f \rightarrow 1$), which causes the severity of sex-specific adaptive constraints to converge over time (figure 3 and electronic supplementary material, figure S3). Given that ρ_{mf} eventually evolves to be negative, sexual antagonism is expected to ultimately reduce the subsequent rate of

adaptation in each sex by at least twofold ($C_f, C_m < 1/2$), with a strong majority of beneficial mutations having sexually antagonistic fitness effects ($f_{SA} > 2/3$).

Our model yields two general insights into the evolution of species with separate sexes. First, conditions for sexual antagonism among beneficial mutations are extremely permissive and readily emerge when directional selection *or* the phenotypic effects of mutations differ between the sexes. Indeed, the correlation of mutant fitness effects is equally sensitive to both factors, as reflected in the identity: $\rho_{mf} = \rho_{sel} \rho_{mut} = \cos(\theta_{sel}) \cos(\theta_{mut})$. Second, decoupling the male and female fitness effects of random mutations significantly reduces the rate of adaptation of both sexes, with sexual antagonism and the magnitude of adaptive constraints increasing during the process of adaptation. Evolution of sexual antagonism occurs whether or not selection favours phenotypic divergence between the sexes (figure 3 and electronic supplementary material, figure S2). Opposing selection between the sexes—for homologous traits expressed by both sexes and mutations affecting these traits—is therefore an inescapable by-product of adaptation in populations with separate sexes.

The model is parametrized using measurable properties of mutation and selection and should therefore be useful for inferring the extent of sexual antagonism in populations conducive to such measures. Although sex-specific phenotypic properties of spontaneous mutations have yet to receive much attention, current data on genetic correlations between the sexes (based on quantitative genetic data [36,37], and mutation-accumulation experiments in *Drosophila* [6]) suggest that mutations are likely to have strong, positively correlated effects

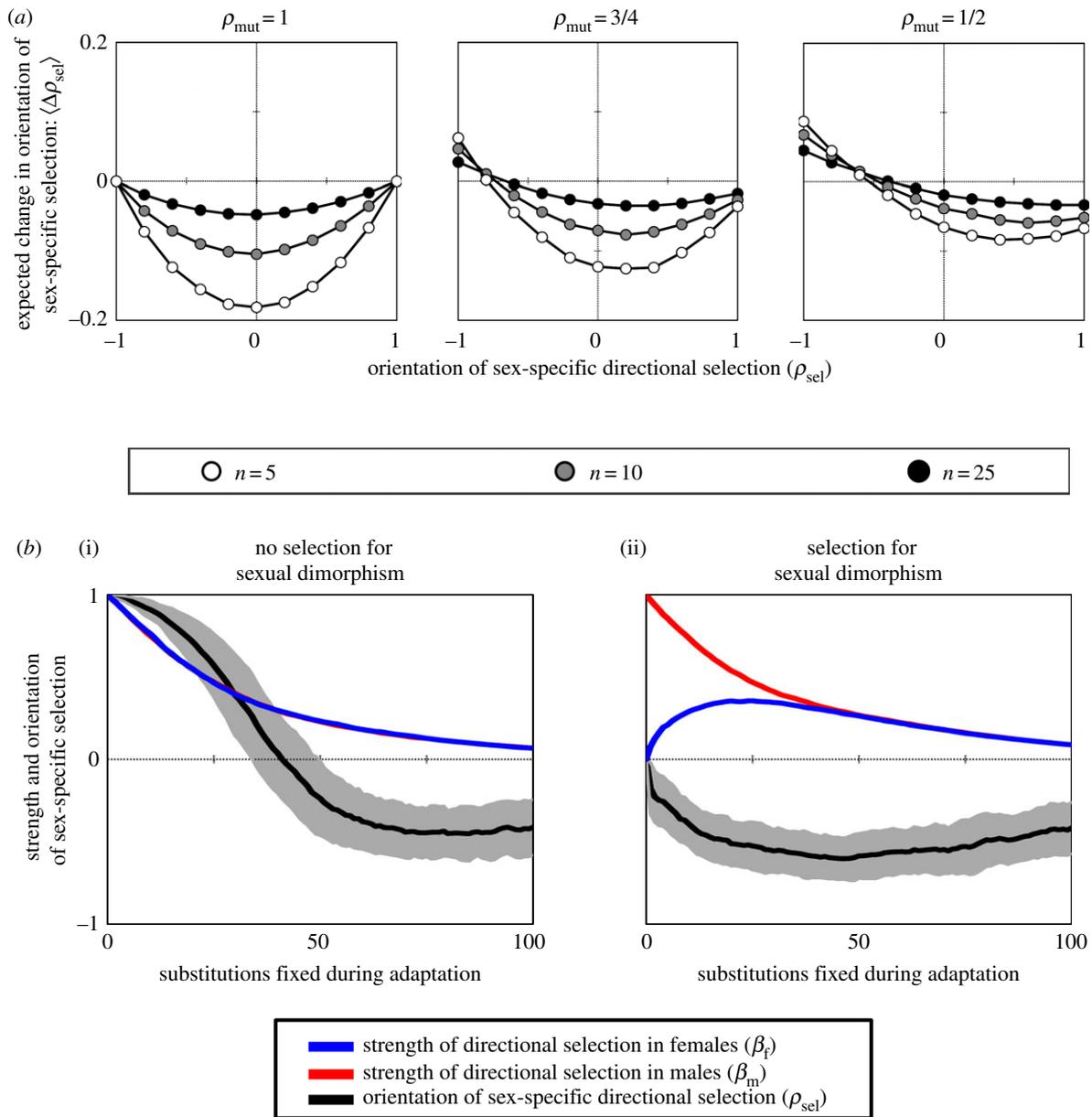


Figure 3. Adaptation generates opposing directional selection between the sexes. (a) The average change in the orientation of directional selection in males and females during adaptation: $\langle \Delta \rho_{\text{sel}} \rangle$. Each data point represents the average change for 10 000 simulated substitutions, with simulation parameters $z_m = z_f = 1/2$, $\omega_m = \omega_f = 1$, and mutation sizes drawn from a bivariate exponential distribution with marginal mean of $\langle r_m \rangle = \langle r_f \rangle = 0.1$ and between-sex correlation of $\text{corr}(r_m, r_f) = \langle \cos(\theta_{\text{mut}}) \rangle = \rho_{\text{mut}}$. (b) The strength of directional selection in males and females (β_m and β_f) and the relative orientation of directional selection between the sexes (represented by ρ_{sel}), during adaptive walks. Each step of adaptation coincides with fixation of a positively selected mutation (with $s_{\text{avg}} > 0$), and the solid lines show averages over 100 simulated adaptive walks (shaded area shows \pm one standard deviation for ρ_{sel}). Two extreme initial conditions of the population are shown: (b(i)) directional selection is initially identical in both sexes and phenotypic divergence between the sexes is not favoured (initial conditions: $z_m = z_f = 1/2$; $\theta_{\text{sel}} = 0$; $\rho_{\text{sel}} = 1$); and (b(ii)) selection favours phenotypic divergence between males and females (males are initially displaced from their optimum but females are not; initial conditions: $z_m = 1/2$; $z_f = 0$). Mutation sizes were drawn from a bivariate exponential distribution with marginal means $\langle r_m \rangle = \langle r_f \rangle = 0.05$, and $\text{corr}(r_m, r_f) = \langle \cos(\theta_{\text{mut}}) \rangle = \rho_{\text{mut}} = 0.75$. Additional parameters include $\omega_m = \omega_f = 1$. Additional results, and details of the simulation procedure, can be found in the electronic supplementary material.

between the sexes. Estimates of selection on single traits suggest that opposing directional selection is common, and often of similar magnitude between the sexes [5,38]. Of the few studies estimating the angle between male and female directional selection on multiple traits, two support the general prediction that opposing selection readily evolves ($\rho_{\text{sel}} \approx -0.61$ and -0.73 in a moth and fly population, respectively [39,40]), whereas a third reveals a positive correlation between male and female directional selection, albeit in a modern human population that has had little time to adapt to its current environment

($\rho_{\text{sel}} \approx 0.22$ [41]). To systematically test whether opposing selection between the sexes evolves during adaptation, future studies could contrast patterns of sex-specific directional selection in poorly versus well-adapted populations, with the latter expected to exhibit more strongly opposing selection between males and females (for a similar prediction, see [42]).

We have identified general conditions yielding sexually antagonistic selection, and although such antagonism does not require that selection favour evolutionary divergence between the sexes, the pervasiveness and intensity of

antagonism is expected to increase when selection does favour sexual dimorphism. Discordance between the fitness landscapes of males and females—the root cause of selection for dimorphism—emerges from the unique interactions between each sex and its environment [8–11], which can lead to sex-differential opportunities for niche partitioning, reproductive investment, competition for mates or their susceptibilities to predation and parasitism. We emphasize the population genetic consequences of distinct male and female fitness landscapes, while placing no special emphasis on the specific ecological causes for divergent male and female optima. The ubiquity of sexually dimorphic phenotypes [43], including conspicuous differences between

closely related species [44], attests to the biological fact of fitness landscape dimorphism and implies a central role for antagonistic selection during the process of adaptation within lineages and speciation between them.

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References

- Orr HA. 2000 Adaptation and the cost of complexity. *Evolution* **54**, 13–20. (doi:10.1111/j.0014-3820.2000.tb00002.x)
- Welch JJ, Waxman D. 2003 Modularity and the cost of complexity. *Evolution* **57**, 1723–1734.
- Wang Z, Liao BY, Zhang J. 2010 Genomic patterns of pleiotropy and the evolution of complexity. *Proc. Natl Acad. Sci. USA* **107**, 18 034–18 039. (doi:10.1073/pnas.0914711107)
- Mackay TAF. 2001 The genetic architecture of quantitative traits. *Ann. Rev. Genet.* **35**, 303–339. (doi:10.1146/annurev.genet.35.102401.090633)
- Cox RM, Calsbeek R. 2009 Sexually antagonistic selection, sexual dimorphism, and the resolution of intralocus sexual conflict. *Am. Nat.* **173**, 176–187. (doi:10.1086/595841)
- Houle D, Fierst J. 2012 Properties of spontaneous mutational variance and covariance for wing size and shape in *Drosophila melanogaster*. *Evolution* **67**, 1116–1130. (doi:10.1111/j.1558-5646.2012.01838.x)
- Rice WR. 1992 Sexually antagonistic genes: experimental evidence. *Science* **256**, 1436–1439. (doi:10.1126/science.1604317)
- Bonduriansky R, Chenoweth SF. 2009 Intralocus sexual conflict. *Trends Ecol. Evol.* **24**, 280–288. (doi:10.1016/j.tree.2008.12.005)
- van Doorn GS. 2009 Intralocus sexual conflict. *Ann. N. Y. Acad. Sci.* **1168**, 52–71. (doi:10.1111/j.1749-6632.2009.04573.x)
- Pennell TM, Morrow EH. 2013 Two sexes, one genome: the evolutionary dynamics of intralocus sexual conflict. *Ecol. Evol.* **3**, 1819–1834. (doi:10.1002/ece3.540)
- Maklakov AA, Lummaa V. 2013 Evolution of sex differences in lifespan and aging: causes and constraints. *BioEssays* **35**, 717–724. (doi:10.1002/bies.201300021)
- Lande R. 1980 Sexual dimorphism, sexual selection, and adaptation in polygenic characters. *Evolution* **34**, 292–305. (doi:10.2307/2407393)
- Fisher RA. 1930 *The genetical theory of natural selection*. Oxford, UK: The Clarendon Press.
- Orr HA. 2005 The genetic theory of adaptation: a brief history. *Nat. Rev. Genet.* **6**, 119–127. (doi:10.1038/nrg1523)
- Orr HA. 2005 Theories of adaptation: what they do and don't say. *Genetica* **123**, 3–13. (doi:10.1007/s10709-004-2702-3)
- Blows M, Walsh B. 2009 Spherical cows grazing on flatland: constraints to selection and adaptation. In *Adaptation and fitness in animal populations* (eds J van der Werf, HU Graser, R Frankham, C Gondro), pp. 83–101. Dordrecht, The Netherlands: Springer Science+Business Media B.V.
- Walsh B, Blows M. 2009 Abundant genetic variation+strong selection=multivariate genetic constraints: a geometric view of adaptation. *Annu. Rev. Ecol. Evol. Syst.* **40**, 41–59. (doi:10.1146/annurev.ecolsys.110308.120232)
- Kirkpatrick M. 2009 Patterns of quantitative genetic variation in multiple dimensions. *Genetica* **136**, 271–284. (doi:10.1007/s10709-008-9302-6)
- Hill WG. 1982 Rates of change in quantitative traits from fixation of new mutations. *Proc. Natl Acad. Sci. USA* **79**, 142–145. (doi:10.1073/pnas.79.1.142)
- Hill WG. 1982 Predictions of response to artificial selection from new mutations. *Genet. Res. Camb.* **40**, 255–278. (doi:10.1017/S0016672300019145)
- Rice SH. 1990 A geometric model for the evolution of development. *J. Theor. Biol.* **143**, 319–342. (doi:10.1016/S0022-5193(05)80033-5)
- Waxman D, Welch JJ. 2005 Fisher's microscope and Haldane's ellipse. *Am. Nat.* **166**, 447–457. (doi:10.1086/444404)
- Martin G, Lenormand T. 2006 A general multivariate extension of Fisher's geometrical model and the distribution of mutation fitness effects across species. *Evolution* **60**, 893–907.
- Martin G, Elena SF, Lenormand T. 2007 Distributions of epistasis in microbes fit predictions from a fitness landscape model. *Nat. Genet.* **39**, 555–560. (doi:10.1038/ng1998)
- Gordo I, Campos PRA. 2013 Evolution of clonal populations approaching a fitness peak. *Biol. Lett.* **9**, 20120239. (doi:10.1098/rsbl.2012.0239)
- Hietpas RT, Bank C, Jensen JD, Bolon DNA. In press. Shifting fitness landscapes in response to altered environments. *Evolution*. (doi:10.1111/evo.12207)
- Perfeito L, Sousa A, Bataillon T, Gordo I. In press. Rates of fitness decline and rebound suggest pervasive epistasis. *Evolution*. (doi:10.1111/evo.12234)
- Caudle SB, Miller CR, Rokyta DR. In press. Environment determines epistatic patterns for a ssDNA virus. *Genetics*. (doi:10.1534/genetics.113.158154)
- Orr HA. 1998 The population genetics of adaptation; the distribution of factors fixed during adaptive evolution. *Evolution* **52**, 935–949. (doi:10.2307/2411226)
- Sellis D, Callahan BJ, Petrov DA, Messer PW. 2011 Heterozygote advantage as a natural consequence of adaptation in diploids. *Proc. Natl Acad. Sci. USA* **108**, 20 666–20 671. (doi:10.1073/pnas.1114573108)
- Abbott JK. 2011 Intra-locus sexual conflict and sexually antagonistic genetic variation in hermaphroditic animals. *Proc. R. Soc. B* **178**, 161–169. (doi:10.1098/rspb.2010.1401)
- Charlesworth B, Charlesworth D. 2010 *Elements of evolutionary genetics*. Greenwood Village: Roberts and Company Publishers.
- Rodgers JL, Nicewander WA. 1988 Thirteen ways to look at the correlation coefficient. *Am. Stat.* **42**, 59–66. (doi:10.2307/2685263)
- Nagylaki T. 1979 Selection in dioecious populations. *Ann. Hum. Genet.* **14**, 143–150. (doi:10.1111/j.1469-1809.1979.tb02007.x)
- Michael JR, Schucany WR. 2002 The mixture approach for simulating bivariate distributions with specified correlations. *Am. Stat.* **56**, 48–54. (doi:10.1198/00031300275361367)
- Poissant J, Wilson AJ, Coltman DW. 2010 Sex-specific genetic variance and the evolution of sexual dimorphism: a systematic review of cross-sex genetic correlations. *Evolution* **64**, 97–107. (doi:10.1111/j.1558-5646.2009.00793.x)
- Griffin RM, Dean R, Grace JL, Rydén P, Friberg U. 2013 The shared genome is a pervasive constraint on the evolution of sex-biased gene expression.

- Mol. Biol. Evol.* **30**, 2168–2176. (doi:10.1093/molbev/mst121)
38. Connallon T, Cox RM, Calsbeek R. 2010 Fitness consequences of sex-specific selection. *Evolution* **64**, 1671–1682. (doi:10.1111/j.1558-5646.2009.00934.x)
39. Lewis Z, Wedell N, Hunt J. 2011 Evidence for strong intralocus sexual conflict in the Indian meal moth, *Plodia interpunctella*. *Evolution* **65**, 2085–2097. (doi:10.1111/j.1558-5646.2011.01267.x)
40. Gosden TP, Shastri KL, Innocenti P, Chenoweth SF. 2012 The B-matrix harbors significant and sex-specific constraints on the evolution of multicharacter sexual dimorphism. *Evolution* **66**, 2106–2116. (doi:10.1111/j.1558-5646.2012.01579.x)
41. Stearns SC, Govindaraju DR, Ewbank D, Byars SG. 2012 Constraints on the coevolution of contemporary human males and females. *Proc. R. Soc. B* **279**, 4836–4844. (doi:10.1098/rspb.2012.2024)
42. Long TAF, Agrawal AF, Rowe L. 2012 The effect of sexual selection on offspring fitness depends on the nature of genetic variation. *Curr Biol.* **22**, 204–208. (doi:10.1016/j.cub.2011.12.020)
43. Darwin C. 1871 *The descent of man, and selection in relation to sex*. London, UK: John Murray.
44. Panhuis TM, Butlin R, Zuk M, Tregenza T. 2001 Sexual selection and speciation. *Trends Ecol. Evol.* **16**, 364–371. (doi:10.1016/S0169-5347(01)02160-7)