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THE EFFECTS OF SELECTION AND GENETIC DRIFT ON THE GENOMIC DISTRIBUTION OF SEXUALLY ANTAGONISTIC ALLELES

Charles Mullon,[1,2] Andrew Pomiankowski,[1,2] and Max Reuter[2,3]

[1]*CoMPLEX, University College London, London WC1E 6BT, United Kingdom*

[2]*Department of Genetics, Evolution and Environment, University College London, London WC1E 6BT, United Kingdom*

[3]*E-mail: m.reuter@ucl.ac.uk*

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Sexual antagonism (SA) occurs when an allele that is beneficial to one sex, is detrimental to the other. This conflict can result in balancing, directional, or disruptive selection acting on SA alleles. A body of theory predicts the conditions under which sexually antagonistic mutants will invade and be maintained in stable polymorphism under balancing selection. There remains, however, considerable debate over the distribution of SA genetic variation across autosomes and sex chromosomes, with contradictory evidence coming from data and theory. In this article, we investigate how the interplay between selection and genetic drift will affect the genomic distribution of sexually antagonistic alleles. The effective population sizes can differ between the autosomes and the sex chromosomes due to a number of ecological factors and, consequently, the distribution of SA genetic variation in genomes. In general, we predict the interplay of SA selection and genetic drift should lead to the accumulation of SA alleles on the X in male heterogametic (XY) species and, on the autosomes in female heterogametic (ZW) species, especially when sexual competition is strong among males.

KEY WORDS: **Genetic drift, genetic variation, population genetics, sexual antagonism.**

Male and female reproductive roles differ and accordingly, many phenotypic traits are selected in different directions in the two sexes. Responding to divergent selection pressures, however, is not straightforward. Because the sexes share a large part of their genomes and traits are determined by the same genes, homologous traits in males and females are expected to show strong genetic correlations. Opposing selection pressures on the two sexes therefore lead to a tug-of-war, which has been coined "sexual antagonism" (SA) or "intra-locus sexual conflict" (Parker 1979; Rice 1984; Bonduriansky and Chenoweth 2009; Van Doorn 2009).

At the allelic level, SA means selection on one sex favors the fixation of one allele, whereas selection on the other sex favors fixation of another allele. A number of population genetic models have been developed to identify the conditions under which sexually antagonistic mutants invade and are maintained in stable polymorphism. There has been considerable interest in comparing autosome and sex chromosome linkage. An influential theoretical analysis (Rice 1984) and a later follow-up (Gavrilets and Rice 2006) concluded that the conditions for invasion and maintenance of SA alleles were more stringent on the autosomes than on the X and Z sex chromosomes, in male and female heterogametic systems, respectively. Fry (2010) argued that this conclusion was a consequence of the way these models constrained the dominance relationships between antagonistic alleles. Building on a previous model with arbitrary dominance (Kidwell et al. 1977), Fry (2010) showed that sex-specific dominance leads to an enrichment of SA genetic variation on the autosomes.

Empirical data has been demonstrating the presence of sexually antagonistic genetic variation in a variety of organisms (Chippindale et al. 2001; Brommer et al. 2007; Foerster et al. 2007;

Mainguy et al. 2009; Svensson et al. 2009) (see Cox and Calsbeek 2009, for a review). But if early empirical data from *Drosophila melanogaster* supported the prediction of X enrichment (Gibson et al. 2002), no clear picture has emerged from subsequent studies (Fry 2010). In addition, virtually nothing is currently known about the properties of alleles segregating at antagonistic loci, including their fitness effects, dominance, or patterns of epistatic interactions. Part of the problem stems from the difficulty in mapping SA to single genes. If a large number of genes have sexually antagonistic expression patterns in *D. melanogaster* (Innocenti and Morrow 2010), it is not clear to what extent this pattern is due to true differences in gene expression, or simply reflects the different ways in which expression is associated with fitness in the two sexes. Even if true expression differences are present, it remains open to what extent these represent many antagonistic loci or many regulatory targets of transcription factors encoded by a few loci.

The vast majority of sexually antagonistic theory has ignored genetic drift (Owen 1953; Kidwell et al. 1977; Rice 1984; Gavrilets and Rice 2006; Fry 2010; Jordan and Charlesworth 2011). But recently Connallon and Clark (2012) showed that genetic drift can have important consequences for the level of antagonistic polymorphism observed in natural populations. The random sampling of alleles causes fluctuations of gene frequencies, and eventually leads to the fixation of one allele and the loss of genetic variation. Genetic drift will therefore oppose balancing selection generated by sexually antagonistic fitness effects. Similarly, genetic drift can slow down the fixation of sexually antagonistic alleles that are under directional or disruptive selection, and hence contribute to SA genetic variation. The amount and nature of genetic variation we observe in natural populations will thus depend on the relative intensity of genetic drift and its interplay with sexually antagonistic selection.

Taking into account the effect of drift is particularly important when considering the genomic location of SA variation. In species with an XY sex determining system, the X, which is hemizygous in males, has a smaller population size, and so is a priori subject to a greater intensity of genetic drift than the autosomes (Charlesworth et al. 1987; Caballero 1995; Vicoso and Charlesworth 2009). In a large, randomly mating population with an even sex ratio, the ratio of the effective population sizes of the X to the autosomes has the baseline value of $N_{eX}/N_{eA} = 3/4$. This ratio, however, is significantly influenced by departures from the idealized assumptions on which it relies. If, as is often the case (Clutton-Brock 2007), males have higher variance in reproductive success than females, the lower uncertainty in the transmission of maternal genes compensates for the lower copy number of X chromosomes and $N_{eX}/N_{eA} > 3/4$ (Caballero 1995; Vicoso and Charlesworth 2009). Similar arguments apply to species with ZW sex determination; here, increased male reproductive variance in this case exacerbates the difference in genetic drift affecting the autosomes and the Z chromosome, so that $N_{eZ}/N_{eA} < 3/4$. To predict the genomic distribution of SA variation, it is therefore important to not only take into account the effect selection, but also the intensity of genetic drift across the genome, which erodes genetic variation.

Table 1. Fitness scheme (following Kidwell et al. 1977).

Genotype	$\Lambda_f\ \Lambda_f$	$\Lambda_f\ \Lambda_m$	$\Lambda_m\ \Lambda_m$
Female	1	1-h_f s_f	1-s_f
Male	1-s_m	1–h_m s_m	1

In this article, we present a population genetic model of SA evolution that incorporates genetic drift and allows variation in its intensity on the autosomes and the X chromosome (our model equally applies to the Z chromosome). The model is used to calculate the relative predisposition of autosomes and sex chromosomes to harbor SA genetic variation. We first present a biallelic model of SA evolution. We deduce the expected heterozygosity at mutation-selection-drift balance for a single locus, and compare the properties of selection and drift for an X-linked and autosomal locus. We use this to make predictions on the effects of SA selection and genetic drift on heterozygosity according to genomic location. Finally, we test these predictions and measure the effect of N_{eX}/N_{eA} on the distribution of SA genetic variation across chromosomal compartments. We use two measures of polymorphism to do this, expected heterozygosity and time to fixation, and calculate their X-to-autosome ratio as a function of chromosomal effective population sizes and selection parameters. We interpret our results to provide an intuitive understanding of the distribution of SA genetic variation in the genome.

Model

The segregation of two alleles, Λ_f and Λ_m, is modeled for an X-linked and an autosomal (written A) locus. We consider a finite population with constant numbers of males and females, and nonoverlapping generations. We assume a Wright–Fisher process with the following life cycle. Male and female adults produce large numbers of gametes, which mutate at a rate μ. This rate is identical in the two sexes and equal in both directions ($\Lambda_f \rightarrow \Lambda_m$ and $\Lambda_m \rightarrow \Lambda_f$). Gametes are randomly paired to produce zygotes. The zygotes are then sampled with replacement and with a selective bias to form the males and females of the next generation. The allele frequencies in males and females are tracked separately, so the process is a Markov chain in two dimensions. The fitness scheme (Table 1) is equivalent to that used by Kidwell et al. (1977)

and constructed so that the locus is a priori sexually antagonistic. We use sex-specific dominance parameters (Kidwell et al. 1977; Fry 2010), allowing for the possibility that both male and female heterozygotes bear little of the fitness cost due to SA. Fixation of Λ_f is assumed to be beneficial to females and detrimental to males, and the opposite is true of Λ_m.

We use the diffusion approximation to derive properties of the gene frequency dynamics. This method is well established and is known to be a good approximation of the Wright–Fisher process, even in complicated selection scenarios (Ewens and Thomson 1970). When selection and the mutation rate are weak (roughly $<$ 0.1), and the population is large, the two-dimensional Wright–Fisher process can be approximated as a single diffusion variable (Norman 1975; Ethier and Nagylaki 1988). The variable corresponds to the average of the male and female frequencies, weighted by the reproductive values of each sex, so that in the absence of selection and mutation ($\mu = s_m = s_f = 0$), the expected frequency change of the averaged variable is zero. If p_m and p_f are the frequencies of allele Λ_m in males and females, respectively, the averaged variable is $p = 1/2(p_m + p_f)$ for an autosomal locus and $p = 1/3$, $p_m + 2/3$, p_f for an X-linked locus in an XY heterogametic species.

The probability distribution function of the average gene frequency p at generation t, $\phi(p;t)$, satisfies the Fokker–Planck equation

$$\frac{\partial \phi}{\partial t} = a(p)\frac{\partial \phi}{\partial p} + \frac{1}{2}b(p)\frac{\partial^2 \phi}{\partial p^2}, \tag{1}$$

where the advection term $a(p) \equiv \mathrm{E}[\Delta p]$ is the expected allelic frequency change over one generation, and the diffusion term $b(p) \equiv \mathrm{Var}[\Delta p]$ is the variance in allele frequency change (Norman 1975; Ethier and Nagylaki 1988).

The advection term, $a(p)$, determines the effect of selection and describes the expected gene frequency change. Because we define p to be the frequency of the male-beneficial allele Λ_m, positive value of $a(p)$ indicate that Λ_m is selectively favored at frequency p (while Λ_f is selected against). Equivalently, selection is negative on Λ_m (and positive on Λ_f) when $a(p)$ is negative. The advection terms for autosomal (A) and X-linked loci are

$$\begin{aligned} a_A(p) &= \frac{1}{2}p(1-p)\Big(s_f\big(p(2h_f-1)-h_f\big) \\ &\quad + s_m\big(p(2h_m-1)+1-h_m\big)\Big) \\ &\quad + (1-2p)\mu + O\big(\mu^2, s_m^2, s_f^2\big), \\ a_X(p) &= \frac{1}{3}p(1-p)\Big(2s_f\big(p(2h_f-1)-h_f\big) + s_m\Big) \\ &\quad + (1-2p)\mu + O\big(\mu^2, s_m^2, s_f^2\big). \end{aligned} \tag{2}$$

These expressions are identical to those derived by Connallon and Clark (2012). The rate of change of the allele frequency density function ϕ in equation (1) also depends on the strength of genetic drift and it is this effect that is expressed by the diffusion term $b(p)$. The variance in allele frequency change is written as

$$b_{A,X} = \frac{p(1-p)}{2N_{eA,X}} + O(1/N_{eA,X}), \tag{3}$$

for an A- and X-linked locus, respectively. The effective population sizes for A (N_{eA}) and X (N_{eX}) loci are related to the number of males and females (Ewens 2004, p. 124). However, the notation N_{eA} and N_{eX} is used to highlight that differences in effective population sizes may be due to other factors than the sex ratio (Caballero 1995).

Table 2. Values of α and ρ^* for SA loci according to chromosomal location and fitness scheme.

	$p^* \leq 0$	$0 < p^* < 1$	$p^* \geq 1$
$\alpha > 0$	Negative	Balancing	Positive
$\alpha = 0$	Neutral	Neutral	Neutral
$\alpha < 0$	Positive	Disruptive	Negative

Results

EFFECTS OF SELECTION ON HETEROZYGOSITY IN FINITE POPULATIONS

Before comparing explicitly the level of SA genetic variation across the genome, we make general observations on how the combined effects of selection and genetic drift impact variation at a single locus. We will do so using expected heterozygosity as a measure of standing genetic variation (we will later verify and generalize our results by using time to fixation). At mutation-selection-drift balance, expected heterozygosity is $\mathrm{E}[H] = \mathrm{E}[2p(1-p)] = \lim_{t\to\infty}\int_0^1 2p(1-p)\phi(p,t)dp$. The effect of selection on heterozygosity depends on whether selection is balancing, directional or disruptive. This can be better seen if the advection term is written as

$$a(p) = \alpha(p^* - p)p(1-p) + (1-2p)\mu, \tag{4}$$

(Ewens and Thomson 1970; Connallon and Clark 2012). The three possible selection regimes can then be inferred from the values of α and p^* (see Table 2). If $p^* \leq 0$ or $p^* \geq 1$, then selection is directional. In this case, selection is negative (for smaller values of p) when $\alpha(p^* - p) < 0$ and positive (for larger values of p) when $\alpha(p^* - p) > 0$, whereby the strength of selection is modulated by the absolute value α. If $0 < p^* < 1$, there is a selective equilibrium at frequency p^*. The sign of α then determines whether selection is balancing ($\alpha > 0$) or disruptive ($\alpha < 0$), and the absolute value of α determines the strength with which p is pulled toward or away from $0 < p^* < 1$.

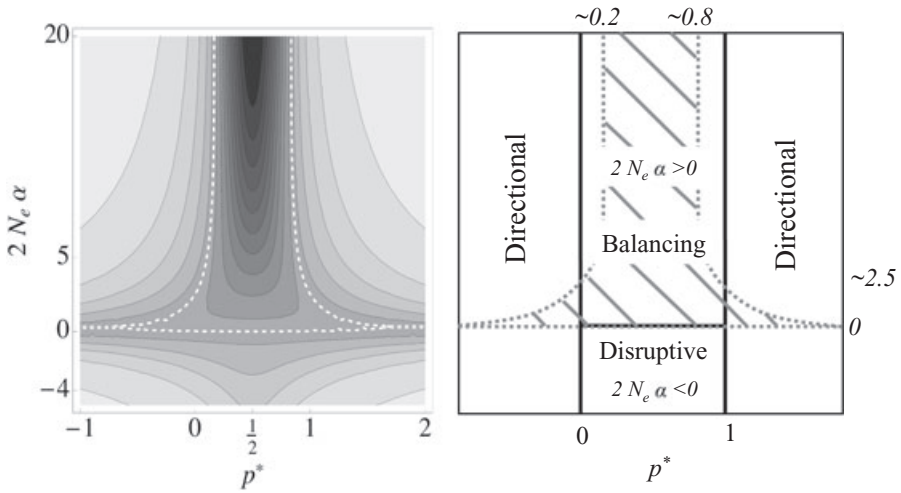

Figure 1. Expected heterozygosity at a single locus as a function of relative strength of selection, $2N_e\alpha$, and the equilibrium allele frequency, p^*. Darker regions represent higher levels of heterozygosity. The striped region within the dashed white line represents levels of heterozygosity greater than neutral heterozygosity undergoing the same mutation rate (fixed at $2N_e\mu = 0.1$ here), whereas the region outside represents levels of heterozygosity lower than neutral heterozygosity.

For an arbitrary locus, expected heterozygosity depends on the relative strength of selection $2N_e\alpha$, the parameter p^* and the scaled mutation rate $2N_e\mu$ (see Appendix for details on calculating expected heterozygosity). To investigate the effect of these parameters, we compare the region under which selection generates a level of heterozygosity greater or less than a locus that evolves neutrally (see Fig. 1, region delimited by the dashed contour). This shows that in general, heterozygosity is elevated beyond the neutral expectation when selection is balancing, and more so when selection is strong ($2N_e\alpha$ large) and favors an equilibrium frequency in the proximity of $p^* = 1/2$ (Fig. 1).

In addition to these expected patterns, there are three points worth noting. First, if selection is weak ($2N_e\,\alpha \lesssim 2.5$), then a locus under directional selection ($p^* < 0$ or $p^* > 1$) may cause greater levels of heterozygosity than a neutral locus. Such an effect could arise due to new mutations slowly traversing the frequency spectrum under weak selection until they reach fixation. Second, a locus under strong balancing selection may generate lower levels of heterozygosity than a neutral locus. This occurs when the favored equilibrium under balancing selection is close to the boundaries ($p^* \lesssim 0.2$ or $p^* \gtrsim 0.8$). Intuitively, as balancing selection generates a force that tends to maintain allele frequencies close to the boundaries, it increases the chances of an allele being lost or fixed due to random genetic drift. This echoes numerical results obtained for the number of generations taken for a heterotic polymorphism to be lost (Robertson 1962; Ewens and Thomson 1970). Finally, we note that the mutation rate has no effect here. Mutation increases the level of heterozygosity, but has the same effect on neutral heterozygosity. So the level of heterozygosity of a locus under selection relative to neutral remains unaffected by the mutation rate.

Table 3. Type of selection according to parameters α and ρ*.

Locus	α	p^*
Autosomal	$\frac{1}{2}(s_f(1-2h_f)+s_m(1-2h_m))$	$\frac{h_f s_f - s_m(1-h_m)}{s_f(2h_f-1)+s_m(2h_m-1)}$
X	$\frac{2}{3}s_f(1-2h_f)$	$\frac{2h_f s_f - s_m}{2s_f(2h_f-1)}$

COMPARISON OF AUTOSOMAL AND X-LINKAGE

To generate predictions on how genomic location affects SA selection and heterozygosity, we first rearrange the advection terms of equation (2) in the form of equation (4). This allows us to express α and p^* in terms of selection and dominance parameters for A- and X-linked loci (Table 3). The three factors that contribute to expected heterozygosity (as above) can then be synthesized as ratios of the relative effect of X-linkage to A-linkage

$$2N_{eA}\alpha_A = \frac{3(1+s\theta)}{4N_{eX}/N_{eA}}2N_{eX}\alpha_X \tag{5a}$$

$$p_A^* = \frac{p_X^* - 1/2}{1+s\theta} + 1/2 \tag{5b}$$

$$2N_{eA}\mu = \frac{1}{N_{eX}/N_{eA}}2N_{eX}\mu. \tag{5c}$$

The value of $s\theta = s_m(1-2h_m)/(s_f(1-2h_f))$ measures the difference in fitness cost in males and females of a sexually antagonistic allele. The effects of sex-specific selection can be isolated from those of dominance. The selection term $s = s_m/s_f > 0$ measures the relative selection differential between homozygotes in males and females (Table 1). The parameter $\theta = (1-2h_m)/(1-2h_f)$ compares the cost of SA in male and

female heterozygotes for an autosomal locus, where $\theta = 1$ indicates equal relative cost in the sexes ($h_m = h_f$) and $\theta = -1$ implies that dominance of Λ_m is equal across the sexes ($h_m = 1 - h_f$, as in Rice (1984)).

Because heterozygosity increases with $2N_e\alpha$ and the proximity of p^* to 1/2, genetic variation on the autosomes is greater relative to the X if $|s\theta|$ is large and $s\theta$ is the same sign as α_X in equations (5a) and (5b). These conditions are met if selection in males is stronger than in females ($s_m >> s_f$) and the SA cost in males is recessive ($h_m < 1/2$). Conversely, dominant SA costs in males ($h_m > 1/2$) favor the accumulation of SA genetic variation on the X. This is intuitive as dominant SA costs in males are only apparent to selection when they are autosomally expressed, hence reducing genetic variation on this chromosomal compartment only. These results and their interpretation generalizes those of deterministic models. Deterministic model find that recessive cost of SA in males increases the likelihood that the SA locus is under balancing selection on the X (Kidwell et al. 1977; Fry 2010). We find that this condition promotes higher levels of heterozygosity on the X, irrespective of the selective regime undergone by the locus. Equation (5) also highlights the effect of differences in genetic drift on A and X chromosomes. Because heterozygosity increases with $2N_e\alpha$ and $2N_e\mu$, equations (5a) and (5c) suggest that genetic variation will be favored on autosomes relative to the X if the ratio of effective population sizes N_{eX}/N_{eA} is small, that is, if genetic drift is stronger on the X than on the autosomes.

X-TO-A HETEROZYGOSITY UNDER SELECTION AND DRIFT

To understand these general patterns in a more detailed manner, we numerically compute the ratio of expected heterozygosity for A- and X-linked SA polymorphism at selection-mutation-drift balance, $E[H_X]/E[H_A]$. As a baseline, we can use classical results on gene frequency distributions for neutral loci, $\lim_{t\to\infty} \phi(p, t)$ (Ewens 2004, p. 174). For the ratio of X-to-A heterozygosity, this is a function of the ratio of the effective population sizes and the mutation rates scaled with respect to drift $E[H_X]/E[H_A] = (N_{eX}/N_{eA} + 4N_{eX}\mu_X)/(1 + 4N_{eX}\mu_X)$. A neutral locus then, generates greater heterozygosity on the X if $N_{eX}/N_{eA} > 1$.

To incorporate the effect of SA selection, we use the X-linked locus as a reference. For this locus, we fix values for the relative strength of selection $2N_e\alpha$, equilibrium frequency p^*, and relative mutation rate $2N_e\mu$. The corresponding values for an autosomal locus are then found using equation (5) and varying the selection $s\theta$ and drift N_{eX}/N_{eA} parameters. A sensitivity analysis was performed on reasonable ranges for the parameters (see Appendix for details), concentrating on the empirically estimated values of N_{eX}/N_{eA} between 0.5 and 1.1 (Mank et al. 2010). As suggested by Figure 1 and equation (5b), results were symmetric with respect to p_X^* about 1/2. For simplicity, we only present results for $p^* > 1/2$.

Figure 2 shows how the relative enrichment of X and A for SA polymorphism varies with the intensity of selection and drift. Two general patterns emerge here. First, and as might be expected, the effect of N_{eX}/N_{eA} on the ratio of expected heterozygosity declines with increasing strength of selection. When selection is very weak with respect to drift ($2N_{eX}\alpha_X \approx 2N_{eA}\alpha_A \approx 0$), levels of heterozygosity are determined by drift alone. In this case, $E[H_X]/E[H_A]$ is proportional to N_{eX}/N_{eA} (Fig. 2a, b). When selection is strong, in contrast, $E[H_X]/E[H_A]$ is almost invariable with respect to N_{eX}/N_{eA} (Fig. 2g, h). The second general pattern concerns the direction of chromosomal enrichment for SA polymorphism. Whether heterozygosity is greater on the X than the A ($E[H_X]/E[H_A] > 1$) or greater on the A than the X ($E[H_X]/E[H_A] < 1$) is determined by the signs of $s\theta$ and $2N_{eX}\alpha_X$. For $2N_{eX}\alpha_X > 0$, negative values of $s\theta$ favor the accumulation of variation on the X if, whereas positive values favor accumulation of variation on the A (Fig. 2c, e). The opposite is true if $2N_{eX}\alpha_X < 0$ (Fig. 2d, f). The combinations of $s\theta < 0$ with $2N_{eX}\alpha_X > 0$ and of $s\theta > 0$ with $2N_{eX}\alpha_X < 0$ are both equivalent to a dominant cost of the female beneficial allele in males ($h_m > 1/2$), and their effect on $E[H_X]/E[H_A]$ is in line with the argument in the previous section.

In addition to these general patterns, our numerical analysis also reveals more nuanced effects. One is the interplay between N_{eX}/N_{eA} and the equilibrium frequency p^*, most pronounced for intermediate intensities of selection (Fig. 2e, f). Here, we observe that effective population size has the strongest impact on heterozygosity when equilibrium frequencies are close to 1/2, but become less relevant as selection becomes more strongly directional ($p^* > 1$ in Fig. 2). This can be understood as follows. With intermediate intensity of selection and $p_X^* = p_A^* = 1/2$, SA generates balancing selection of similar, limited, magnitude ($s\theta$ small, equation (5a)) and the absolute levels of heterozygosity are maximal on both the X and A (Fig. 1). In this case, differences between N_{eX} and N_{eA} alter the likelihood that random variation leads to fixation of allelic variation and the N_{eX}/N_{eA} ratio has a large effect on $E[H_X]/E[H_A]$. But as the value of p^* departs from 1/2, and selection on the X and A becomes increasingly directional (i.e., $p_X^* > 1$ and $s\theta$ small, Fig. 2e), the impact of N_{eX}/N_{eA} on $E[H_X]/E[H_A]$ diminishes. Thus, differences in effective population size between X and A then have little impact on allelic variation when selection is directional. Variation in N_{eX}/N_{eA} likewise has significant consequences when SA generates limited disruptive selection (i.e., $p_X^* = 1/2$ and $2N_{eX}\alpha_X < 0$; Fig. 2f), but less impact as selection becomes directional.

We also observe interesting changes in $E[H_X]/E[H_A]$ under strong selection. First, we find that chromosomal enrichment for SA variation is determined by the interaction between p^* and $s\theta$

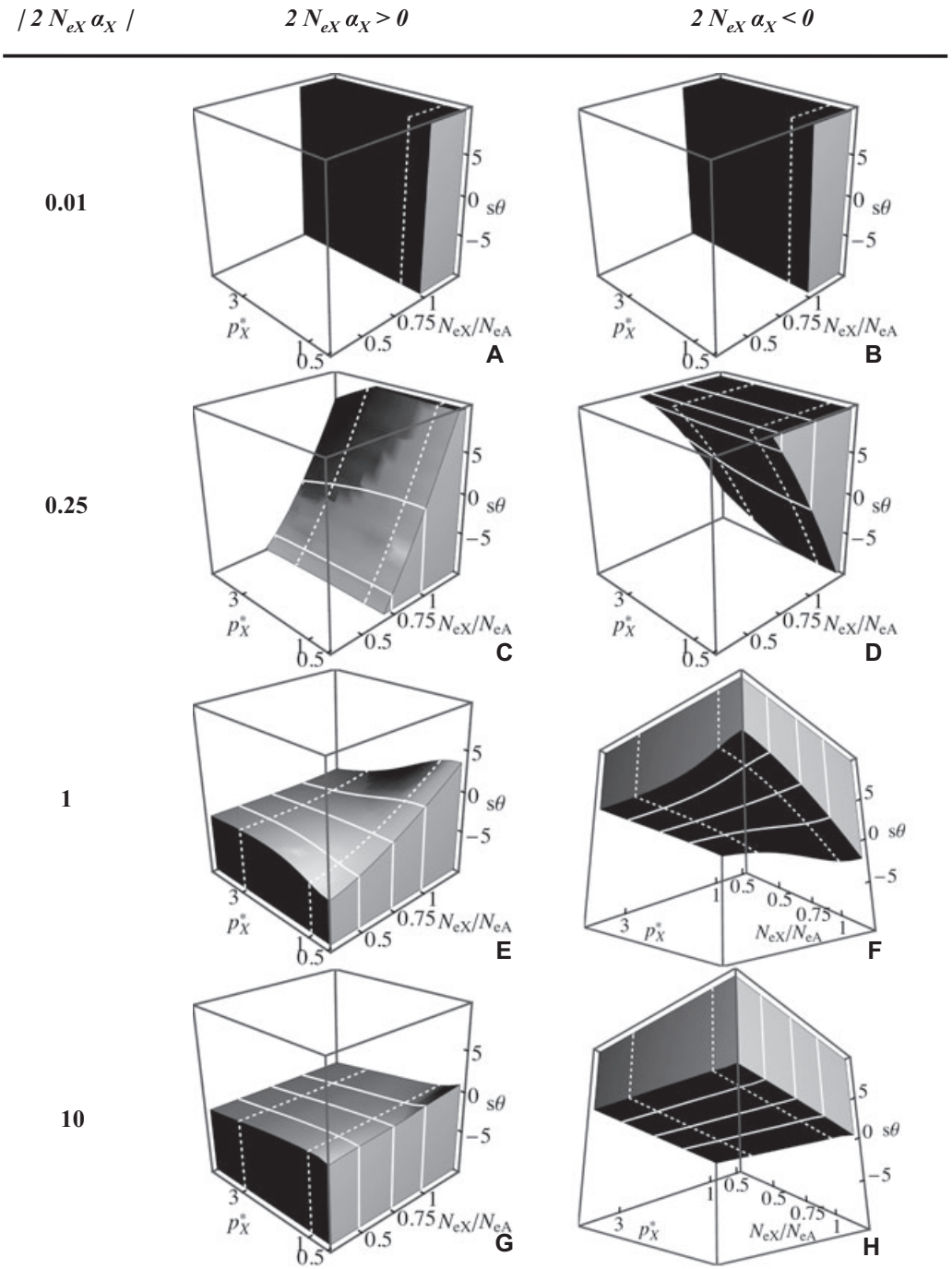

Figure 2. Parameter space for greater SA heterozygosity on the X. Three-dimensional plot in the p_X^*, $s\theta$, N_{eX}/N_{eA} space. The gray volume corresponds to the combination of parameters for which $E[H]_X > E[H]_A$. The values of $2N_{eX}\alpha_X$ are (A) 0.01, (B) –0.01, (C) 0.25, (D) –0.25, (E) 1, (F) –1, (G) 10, and (H) –10. The mutation rate is fixed at $2N_{eX}\mu_X = 0.1$. The space in panels (F) and (H) is rotated upwards to show the shape of the lower surface.

(Fig. 3). Because heterozygosity is maximized when the equilibrium frequency $p^* = 1/2$, values of p_X^* close to 1/2 promote heterozygosity on the X relative to A. Therefore, as p_X^* deviates from 1/2 and rises to one, greater heterozygosity on the X than the A can only be maintained by making $s\theta$ increasingly negative for $2N_{eX}\alpha_X > 0$ (Fig. 3a) or increasingly positive for $2N_{eX}\alpha_X < 0$ (Fig. 3b), making selection on the autosomes either strongly directional or strongly disruptive (equation (5)).

Furthermore, differences in genetic drift (N_{eX}/N_{eA}) may also influence the ratio of expected levels of heterozygosity, even under strong selection (Fig. 3a). This is the case whenever $2N_{eX}\alpha_X > 0$, $p_X^* \approx 1/2$ and $s\theta \approx 0$. These conditions are equivalent to

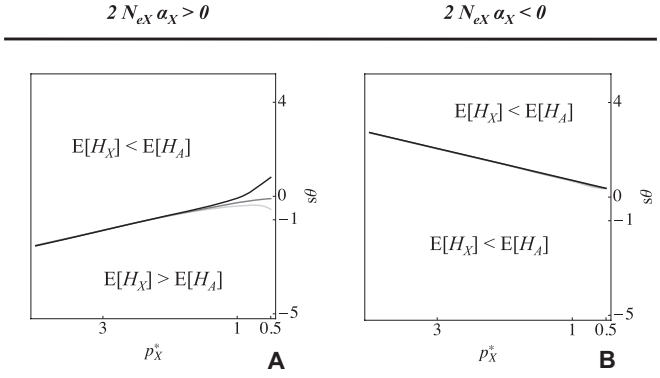

Figure 3. Parameter space for greater SA heterozygosity on the X when selection is strong relative to drift. Two-dimensional plot in the p^*_X, $s\theta$ plane for different N_{eX}/N_{eA} values with (A) $2N_{eX}\alpha_X = 10$ and (B) $2N_{eX}\alpha_X = -10$. Each curve is for a different value of N_{eX}/N_{eA}, with 0.5 in light gray, 3/4 in dark gray, and 1 in black. The mutation rate is fixed at $2N_{eX}\mu_X = 0.1$.

balancing selection acting on both the autosomal and the X-linked locus, with favored polymorphism close to 1/2. They further imply very similar selection gradients in males and females ($s_f = s_m$) and additive allelic effects in males ($h_m = 1/2$). In this case, differences in the strength of selection protecting polymorphism, $2N_e\alpha$, on the X and A become very sensitive to changes in N_{eX}/N_{eA} (equation (5a)).

EXPECTED HETEROZYGOSITY UNDER MUTATION PRESSURE

The effect of mutation on the ratio of expected heterozygosity is restricted to the extremes of the spectrum of mutation rate. At low rates, mutational input exaggerates differences in heterozygosity across the genome that arise due to other parameters. With high rates, recurrent mutations become the chief cause for genetic variation and differences in selection and effective population sizes cause less quantitative changes in the $E[H_X]/E[H_A]$ ratio. For most intermediate values, however, the scaled mutation rate has no qualitative effect on $E[H_X]/E[H_A]$ and heterozygosity are dominated by the other parameters ($2N_{eX}\alpha_X$, p^*_X, $s\theta$, and N_{eX}/N_{eA}).

TIMES TO FIXATION OF AUTOSOMAL AND X-LINKED POLYMORPHISM

In the analyses presented so far, we measured polymorphism based on the expected heterozygosity $E[H]$ at SA loci. To assess the generality of our inferences, we now generate predictions based on another measure of polymorphism—the expected time to fixation $E[T]$. This allows us to compare the stability of polymorphism on the X and the autosomes by calculating the ratio of times to fixation $E[T_X]/E[T_A]$. When $E[T_X]/E[T_A] > 1$, a locus on the X is expected to remain polymorphic for longer than a locus on the autosome and vice versa. Based on classical results (Ewens 2004, p. 160), the ratio for neutral loci is a function of the ratio of effective population sizes, $E[T_X]/E[T_A] \approx 4N_{eX}/(3N_{eA})$. As for $E[H_X]/E[H_A]$, we investigated how $E[T_X]/E[T_A]$ varies with effective population sizes and selection parameters by using the X-linked locus as a reference for $2N_e\alpha$ and p^*. We then determine the corresponding values for autosomes using equation (5a) and calculate $E[T_X]/E[T_A]$ (see Appendix).

We find that $E[T_X]/E[T_A]$ increases for larger values of N_{eX}/N_{eA}, implying that a relatively larger effective population size on the X leads to relatively longer lived polymorphism on the X (Fig. 4). Furthermore, $E[T_X]/E[T_A]$ (and in particular whether its value is above or below 1) is more sensitive to changes in N_{eX}/N_{eA} when selection is relatively weak (Fig. 4a, b vs. Fig. 4c, d). Finally, the distribution of polymorphism is affected by the relative strength of selection on the X and the autosomes. Polymorphism is longer lived on the X chromosome than the autosomes when $2N_{eX}\alpha_X > 0$ and $s\theta > 0$ or when $2N_{eX}\alpha_X < 0$ and $s\theta < 0$. As discussed previously, these conditions are equivalent to a dominant cost of SA in males ($h_m < 1/2$).

These results are the same as those obtained with the heterozygosity ratio $E[H_X]/E[H_A]$. However, we also find some interesting differences. Specifically, $E[T_X]/E[T_A]$ is more strongly affected by changes in N_{eX}/N_{eA} than $E[H_X]/E[H_A]$, and the impact of effective population sizes is not conditional on equilibrium allele frequencies being close to $1/2$ (compare Fig. 4c, d). As a consequence, the ratio of times to fixation varies with effective population sizes under both balancing and directional selection, both under weak selection (Fig. 4a, b) and strong selection (Fig. 4c, d).

Discussion

Population genetic models show that SA is able to generate balancing selection and hence contribute to the maintenance of genetic polymorphism (Owen 1953; Kidwell et al. 1977). By using these models to predict the relative abundance of sexually antagonistic polymorphism on the autosomes and the X chromosome (Rice 1984; Fry 2010; Connallon and Clark 2011), it has been possible to gain a thorough understanding of how selection affects the distribution of sexually antagonistic variation across the genome. However, these previous analyses have omitted genetic drift and therefore ignored a major factor determining the balance of polymorphism between the X and the autosomes. Genetic drift significantly hinders the ability of antagonism to generate genetic diversity (Connallon and Clark 2012), and the impact of genetic drift may differ in magnitude across the genome (Caballero 1995). To address this shortcoming, we have analyzed a model of sexually antagonistic evolution at autosomal and X-linked loci in a finite, dioecious population. This model takes into account the

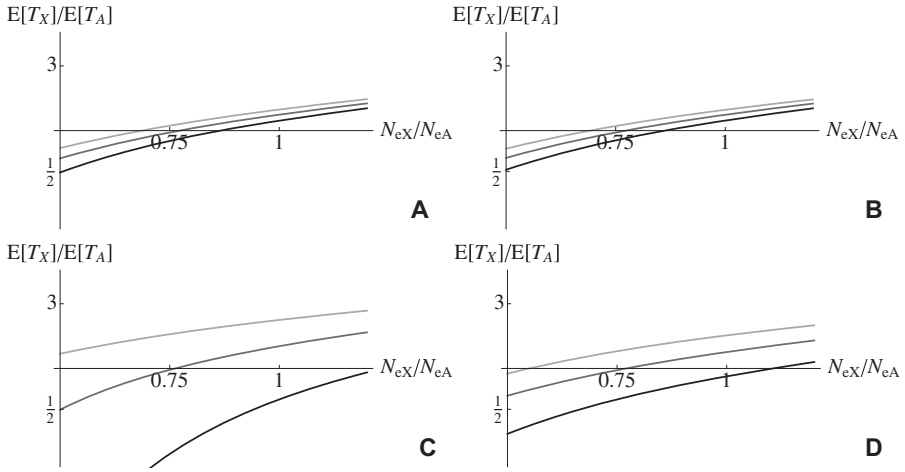

Figure 4. The E[T_X]/E[T_A] ratio versus N_{eX}/N_{eA}. The different lines in represent different values of $s\theta$: –2 (light gray), 0 (gray), and 2 (black). The rows represent different strength of selection and the columns different values of p_X^*. (A) and (B) correspond to weak selection ($2N_{eX}\alpha_X = 1$) and, (C) and (D) to stronger selection ($2N_{eX}\alpha_X = 5$). In (A) and (C), $p_X^* = 1/2$, and $p_X^* = 1.5$ in (B) and (D). The origin is set at E[T_X]/E[T_A] = 1.

effect of genetic drift and how its intensity relative to selection, differs between the autosomes and the X chromosome.

The model analyzed here not only incorporates drift, it also widens the scope of understanding of the interaction of drift with different types of selection. Previous analyses have focused on balancing selection. But as sexually antagonistic alleles may also be under directional or disruptive selection regimes, the contribution of these other forms of selection needs to be taken into account. The model predicts that generally, genetic variation is maintained when polymorphism is stabilized by balancing selection that is strong relative to drift (measured in this article by $2N_e\alpha$, Fig. 1 and see Connallon and Clark (2012)). However, there is not a simple correspondence between the presence of balancing selection and excess polymorphism. For example, the equilibrium frequency p^* is an important determinant of how well balancing selection will maintain polymorphism. Although polymorphisms with intermediate values of p^* are stable, balancing selection for equilibria close to 0 or 1 will tend to drive allele frequencies toward the boundaries and thereby precipitate the loss or fixation through genetic drift. As a consequence, we expect to see lower levels of polymorphism than expected under neutrality in these cases (Fig. 1). We also find interesting effects of drift on directional selection. While strong directional and disruptive selection (defined by $2N_e\alpha$ and p^*, see Table 2) lead to the rapid loss of genetic variation, weak directional selection can lead to polymorphism in excess of the level expected at neutral loci (Fig. 1).

To understand how the interaction between genetic drift and sexually antagonistic selection differs between the X and the autosomes, we compared $2N_e\alpha$ and p^* for the two types of chromosome. To do this, we agglomerated all selection and dominance terms in the quantity $s\theta = (s_m(1 - 2h_m))/(s_f(1 - 2h_f))$, and used the ratio of effective population sizes of the X to the autosomes, N_{eX}/N_{eA} (equation (5)). Comparing $2N_e\alpha$ and p^* for autosomal and X-linked loci (equation (5)), we found that the relative strength of genetic drift will affect the levels of polymorphism on the two chromosomal compartments, with greater values of N_{eX}/N_{eA} favoring the accumulation of sexually antagonistic variation on the X chromosome. We also found greater X-linked relative to autosomal polymorphism if the cost of SA is dominant in males ($h_m > 1/2$), because they are then only apparent to selection when autosomally expressed. This result is in line with previous predictions from deterministic systems (Kidwell et al. 1977; Fry 2010). Interestingly, this correspondence occurs despite the fact that these models concentrated on the case of balancing selection, whereas we have generalized the analysis to all types of selection. Even if the bulk of standing SA variation within a population is expected to be due to loci under strong balancing selection, alleles that are under other selection regimes will also contribute to sexually antagonistic variation, especially if the effective population size is small.

To investigate with greater precision how the combined effect of sexually antagonistic selection and genetic drift play out, we calculated the ratio of sexually antagonistic heterozygosity on the X compared to autosomes, E[H_X]/E[H_A]. As expected, N_{eX}/N_{eA} is the critical factor when the strength of selection is weak with respect to drift ($|2N_e\alpha|$ small) or if N_e is small (Fig. 2a– d). Accordingly, we expect X-enrichment for SA variation with higher values of N_{eX}/N_{eA} and autosomal enrichment for lower values of N_{eX}/N_{eA}. This is true irrespective of the selection regime (directional, disruptive, as well as balancing) undergone by the alleles.

As the relative strength of selection increases ($|2N_e\alpha|$), we found that the main causes of difference in expected heterozygosity across the genome are the selection parameters, scaled by $s\theta$ and p_X^* (Fig. 3). This means that the dominant SA cost in males ($h_m > 1/2$) privileges the accumulation of SA genetic variation on the X. However, even when relative strength of selection is strong, the N_{eX}/N_{eA} ratio within reasonable range is able to alter predictions made on the basis of selection parameters alone. For values of $s\theta$ close to zero and p^* close to 1/2, differences in genetic drift (N_{eX}/N_{eA}) are able to alter the predictions generated by selection (Fig. 3c). So the contribution of the N_{eX}/N_{eA} ratio will be important when alleles have equal fitness gradients in males and females ($s_f = s_m$), with additive effects in males ($h_m = 1/2$) and recessive cost in females ($h_f < 1/2$).

Similar conclusions emerge for a related measure of polymorphism, the time to fixation (E[T], Fig. 4). The N_{eX}/N_{eA} ratio has a stronger effect and the selection parameters a weaker effect on effect on expected time to fixation than on expected heterozygosity. This difference in behavior arises because whereas E[T] simply requires that allelic variation is present, E[H] also explicitly relies on the time spent at specific allelic frequencies, and is more sensitive to whether the allele frequencies are held close to 1/2 by selection (as E[H] = E[$2p(1-p)$]). So expected heterozygosity exaggerates the effect of the value of p^*. When interpreting the predictions of our model it is therefore important to consider which facet of polymorphism is most interesting, population allele frequencies (i.e., E[H]) or simply the presence of allelic variation (i.e., E[T]).

Like previous studies, our model predicts that the location of sexually antagonistic genetic variation will in part depend on the values of the selection and dominance coefficients. However, the interpretation of these predictions is problematic in several ways. First, as noted by Fry (2010) and Jordan and Charlesworth (2011), there is little hope of being able to map sexually antagonistic traits to single genes and estimate their sex specific selection coefficients and dominance relationships. So attempts to validate theoretical results based on estimations of selection parameters seem implausible. Second, it seems unlikely that the distribution of selection parameters is significantly different from one population to another, and hence this is not an obvious general explanation for the diversity of sexually antagonistic genetic variation (Fry 2010).

An alternative, and more feasible approach to address the question of the location of SA variation in the genome, is to consider explanations based on the N_{eX}/N_{eA} ratio. It can be calculated from levels of neutral polymorphism on the X and autosomes. And such estimates have been obtained and vary significantly across species and even across populations (e.g., Mank et al. 2010). The N_{eX}/N_{eA} ratio synthesizes many genetic, ecological, and behavioral processes (Caballero 1995; Laporte and Charlesworth 2002; Hutter et al. 2007; Vicoso and Charlesworth 2009) and thereby is apt in explaining population level variation in the distribution of sexually antagonistic polymorphism. It will be interesting to confront our predicted correlation between N_{eX}/N_{eA} and enrichment of antagonistic variation with empirical data. The estimates for N_{eX}/N_{eA} show moderate deviations from the baseline value of 3/4, with $N_{eX}/N_{eA} > 3/4$ and $N_{eZ}/N_{eA} < 3/4$ that are compatible with observed variation in male reproductive success (Mank et al. 2010). We thus predict a higher level of X enrichment in species with XY sex determination, such as mammals and many groups of insects, compared to species with ZW sex determination, such as birds and butterflies.

In addition, if precise experimental estimation of selection parameters is today unlikely, our model provides a way to obtain coarse estimates. For instance, observing X enrichment of sexually antagonistic variation in a population with $N_{eX}/N_{eA} << 1$ would imply that most sexually antagonistic mutations have a dominant cost in heterozygotic males, whereas autosomal enrichment with $N_{eX}/N_{eA} >> 1$ would hint toward recessive cost. It is unfortunate that the most detailed empirical results on SA variation to date, from a *Drosophila* laboratory population that showed almost exclusive X-linkage of sexually antagonistic variation, are inconclusive on that front (Gibson et al. 2002). So this result cannot be used to comment on the selection parameters of antagonistic alleles.

In conclusion, we have shown how selection and drift can affect sexually antagonistic variation differently at autosomal and sex-linked loci. Our model makes predictions about the extent and nature of genetic variation expected under different scenarios, and opens the possibility of combining quantitative with population genetic data to gain information on the characteristics of antagonistic mutations segregating in wild populations.

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Appendix

CALCULATING EXPECTED HETEROZYGOSITY

To obtain expected heterozygosity at mutation-selection-drift balance, we first compute the stationary distribution $\hat{\phi}(p)$, for a locus with advection term $a(p)$ and diffusion term $b(p)$

$$\hat{\phi}(p) = \frac{C}{b(p)} \exp\left(2 \int \frac{a(p)}{b(p)} dp\right), \tag{A1}$$

where the constant of integration C is calculated so that $\int_0^1 \hat{\phi}(p)dp = 1$ (Ewens 2004, p. 146). Then the expected heterozygosity is given by $\int_0^1 2p(1-p)\hat{\phi}(p)dp$. Although $\int a(p)/b(p)dp$ can be computed exactly, the integrals to compute C and the expected heterozygosity do not have a general solution. We evaluated those integrals numerically, using an adaptive Monte Carlo scheme with Mathematica version 7.0.1.0. Expected heterozygosity was first evaluated for the X-linked locus with arbitrary values of $2N_{eX}\alpha_X$, p_X^*, and $2N_{eX}\mu_X$, and then varied parameters $s\theta$ and N_{eX}/N_{eA} to obtain expected heterozygosity for an autosomal locus using equation (5). This had the advantages of reducing the number of parameters from seven to five, and provide an intuitive understanding of the effects of selection schemes on the $\mathrm{E}[H_X]/\mathrm{E}[H_A]$ ratio. We explored the following parameter ranges $-20 < 2N_e\alpha < 20$, $-10 < p^* < 10$, $0.01 < 2N_e\mu < 0.2$, $-10 < s\theta < 10$, and $0.3 < N_{eX}/N_{eA} < 1.5$, with at least 100 sampling points for each range.

CALCULATING THE NUMBER OF GENERATIONS TILL LOSS OF POLYMORPHISM

Briefly, we calculated $t(p_0)$, the expected time taken for an allele to be lost or fixed, given its initial frequency p_0 at each locus. Time to fixation is measured in units of effective population size, so that the expected number of generations until fixation is given by $\mathrm{E}[T] = 2N_e t(p_0)$. For a given pair of alleles, the value of t is found by (in our case numerically) solving the differential equation

$$1 + a_S(p)\frac{dt}{dp} + \frac{1}{2}b_S(p)\frac{d^2t}{dp^2} = 0, \tag{A2}$$

with boundary conditions $t(0) = t(1) = 0$ (Ewens 2004, p. 141), and where $a_S(p) = 2N_e\alpha(p^* - p)p(1-p)$ and $b_S(p) = p(1-p)$ are the scaled (with respect to N_e) advection and

diffusion terms. When calculating E[T], we assumed that polymorphism arose by mutation and that the mutant was initially present in a single copy in a randomly sampled individual (which may be male or female). The population was assumed to be composed of $N = 10^3$ individuals with equal number of males and females. Accordingly, the initial frequencies of new A- and X-linked mutants, averaged over the sexes, are given by

$$p_{0A} = \frac{1}{2N} \text{ and } p_{0X} = \frac{2}{3N}. \tag{A3}$$

We assumed that male- and female-beneficial mutations are equally likely and averaged their times until loss of polymorphism to calculate E[T]. The ratio E[T_X]/E[T_A] is then given by

$$\frac{\mathrm{E}[T_X]}{\mathrm{E}[T_A]} = \frac{N_{eX}}{N_{eA}} \left(\frac{t_X(p_{0X}) + t_X(1 - p_{0X})}{t_A(p_{0A}) + t_A(1 - p_{0A})} \right). \tag{A4}$$

The numerical integration to solve for t is significantly more sensitive to rounding errors than the one used to calculate expected heterozygosity. To ensure the accuracy of our results, we rejected results for which integration converged with a numerical error greater than 10^{-12}. This procedure constrained the results we could generate and meant that the parameter range explored for E[T_X]/E[T_A] was not as large as for E[H_X]/E[H_A]. Nevertheless, we were able to generate results that allow us to verify the predictions made based on E[H_X]/E[H_A], as well as explore how the properties of the two measures of polymorphism differ.