MINI REVIEW

Intersexual ontogenetic conflict

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Introduction

Evolutionary conflict can occur at many levels (Fig. 1). At the interspecific level, conflict arises during the Red Queen process of antagonistic coevolution between a species and its enemies (Van Valen, 1973). At the intraspecific level, there are three major types of evolutionary conflict. Intragenomic conflict occurs between genes located in the same individual, such as ultraselfish nuclear genes or cytoplasmic genes that increase in frequency at the expense of other, nonallelic genes. For example, some cytoplasmic genes that are only transmitted through the matrilineage will feminize, sterilize or kill sons to promote reproduction through daughters (e.g. Hurst, 1992; Werren & Beukeboom, 1998). Intergenomic conflict involves genes, generally located at different loci, that mediate contests (e.g. competition) between different individuals (Trivers, 1974; Parker, 1979; West-Eberhard, 1984; Rice & Holland, 1997). For example, seminal fluid proteins are known to increase a male’s fertilization success although simultaneously reducing his mate’s fitness by increasing her mortality (Chapman et al., 1995; Rice, 1996; Holland & Rice, 1998). When a new mutation evolves at a seminal fluid locus that increases male fitness at the expense of his mate, this selects for counter-adaptation by females at a second locus (e.g. a locus coding for a female receptor that interacts with the seminal fluid protein), which can lead to self-reinforcing, open-ended cycles of interlocus contest evolution (i.e. ICE, Rice & Holland, 1997).

Here we focus on intersexual ontogenetic conflict as a third type of intraspecific evolutionary conflict. This form of conflict has received far less attention than the types described above. It arises when alleles are expressed in both sexes but are selected diametrically between the sexes (i.e. sexually antagonistic alleles). We first introduce this form of conflict with an illustrative example and assess conditions for maintaining polymorphism for alleles underlying the conflict. We then summarize evidence from our own experiments with Drosophila melanogaster that show substantial genome-wide sexually antagonistic fitness variation. Finally we discuss evidence from other organisms and some of the ramifications of widespread polymorphism for sexually antagonistic fitness variation.

Keywords:
- genomic conflict
- intersexual conflict
- ontogenetic conflict
- ontogeny
- sexual dimorphism

Abstract

Evolutionary conflict has been investigated at many levels of organization, from interactions between loci within a genome to the coevolution of species. Here we review evidence for intersexual ontogenetic conflict, a type of conflict that has received relatively little attention both theoretically and empirically. It is manifest during development when expression of the same allele, on average, moves one sex towards, and the other sex away from, its phenotypic optimum. We first introduce this type of conflict with an illustrative example and assess conditions for maintaining polymorphism for alleles underlying the conflict. We then summarize evidence from our own experiments with Drosophila melanogaster that show substantial genome-wide sexually antagonistic fitness variation. Finally we discuss evidence from other organisms and some of the ramifications of widespread polymorphism for sexually antagonistic fitness variation.

Fitness and the human hip

Consider the hip of Homo sapiens. Comparison with other primates indicates that hip width was far less sexually dimorphic in our ancestors than it is today (Ridley, 1995). The increased sexual dimorphism in hip width presumably evolved to accommodate the increased head width of the foetus at the time of parturition (Lavelle, 1995). For the purpose of illustration, here we assume that (i) hip width was controlled polygenically and that
many of the contributing loci were expressed in both sexes, (ii) at some time in the past there was disruptive selection on hip size, with wider hips being favoured in females compared with males, and (iii) selection on hip width can be described by simple linear fitness functions, with male and female optima on opposite sides of the extant phenotypic distribution of hip sizes (Fig. 2, top-left). To make the fitness model more realistic, the male and female fitness functions were assumed to differ in shape, with the female fitness function being twice as steep as that for males. The higher slope in females reflects the strong selection associated with the risk of injury to the mother during childbirth.

**An intersexual tug-of-war**

Consider an arbitrary quantitative trait locus (QTL) influencing hip width in primitive humans, i.e. the
A-locus. To begin, we assume that this locus was initially fixed for a sexually monomorphic allele \((A_0)\) that produced a proportionately similar sized hip in both sexes. Next consider a new mutation \((A_1)\), assumed here for simplicity to be dominant, but the same logic applies irrespective of dominance of alleles) that increased hip width substantially in both sexes and that pleiotropically reduced locomotor performance to a lesser degree. The \(A_1\) allele would be favoured in females when the benefit during parturition more than outweighs the cost to locomotor performance. But in males, the \(A_1\) allele would always be selected against because this sex experiences the locomotor cost but not the benefit during parturition. The \(A_1\) allele is therefore sexually antagonistic, and if it accumulated in the gene pool it would lead to developmental conflict because its expression during ontogeny would move females closer to their optimal phenotype and moving males further from theirs.

In general an autosomal allele that is sexually antagonistic will accumulate to fixation whenever it has a net selective advantage when averaged across the sexes (Rice, 1984). This can be expressed graphically (Fig. 2) by plotting the phenotype of the mutant allele \(A_1\) when expressed in males \((Y\text{-axis})\) vs. females \((X\text{-axis})\). Because the linear fitness function of females is assumed to be twice as steep as that of males, a line of slope \(\hat{2}\) drawn through the phenotype of the established \(A_0\) allele (scaled to be zero in both sexes, Fig. 2) defines all possible neutral alleles. Any allele mapping to the right (left) of this line has a net selective advantage (disadvantage) when averaged across the two sexes.

An \(A_1\) mutation that mapped to the bottom-right quadrant of Fig. 2 will be favoured in both sexes, rapidly fix, and would not contribute to intersexual developmental conflict. However, these mutations require the same allele to have effects of opposite direction when expressed in the two sexes. Although it is common for alleles influencing polygenic traits to have different degrees of effect in each sex, we would expect the direction of the effect to be the same. For this reason an \(A_1\) allele mapping to the bottom-right quadrant in Fig. 2 will generally require the additional evolution of gender-specific modifiers (that reverse the direction of the allelic effect between the sexes), or a gene duplication followed by the evolution of gender-specific expression of each locus. Because both of these scenarios require co-ordinated mutations at different loci, they are likely to evolve more slowly than single mutations, so we consider first only those mutations having the same direction of effect in both sexes.

In Fig. 2 we plot the phenotype of the \(A_1\) allele assuming a consistent direction of effect in both sexes but sex-specific magnitude, i.e. \(A_1\) increases hip size in both sexes but more so in females. The \(A_1\) allele maps to the right of the line of neutrality so the allele has a net selective advantage despite its harm to males, and fixation is expected (Rice, 1984). But the \(A_1\) allele, like the \(A_0\) allele, can be invaded by new mutations. Any new mutation whose phenotype maps to the right of the neutrality line of slope \(\hat{2}\) (that passes through the joint male vs. female phenotype produced by the \(A_1\) allele, e.g. the plotted point of mutation \(A_2\) in Fig. 2) would have a net selective advantage and would replace an established \(A_1\) allele. In finite populations chance determines the order in which new mutations are introduced.

In Fig. 2 we assumed that the next allele that was introduced by mutation, and not lost early via sampling error, was the \(A_2\) allele that reduced hip size in both sexes, but to a substantially greater extent in males. The \(A_2\) allele has a net selective advantage and is expected to replace the \(A_1\) allele (Figs 2 & 3).

A succession of allelic replacements (i.e. a tug-of-war between the sexes) would be expected to continue (Fig. 2, alleles 3–6; Fig. 3a–c) until a modifier gene evolves that reverses the direction of effect of the same \(A\)-allele in the two sexes, thereby permitting each sex to independently evolve towards its own gender-specific optimum (Fig. 2, alleles 7–8). A gene duplication

![Figure 3](image-url)
followed by gender-specific gene expression at the duplicated loci is an alternative way to permit each sex to move to its own optimum. Until one of these events occurs, however, recurrent allelic replacement will lead to transient polymorphisms for sexually antagonistic alleles. If the number of loci in the genome that are capable of mutating to sexually antagonistic alleles is large (see below), this transient polymorphism would lead to substantial standing sexually antagonistic variation and promote intersexual ontogenetic conflict.

**Equilibrium polymorphism for sexually antagonistic alleles**

One way that chronic polymorphism can be achieved involves alleles of large effect. In Fig. 4a, the allele is assumed to have a large effect size, and for simplicity, to be codominant and to increase hip size to the same degree in both sexes. In an outbred population the allele will be expressed predominantly in the heterozygous state when rare, and in this case the allele increases female fitness more than it reduces male fitness (Fig. 4a) so the allele begins to spread. But as it accumulates it will be increasingly expressed in the homozygous state. In this case females overshoot their optimum, so the homozygous allele hurts males more than it helps females. This generates heterozygote advantage and leads to stable polymorphism.

An alternative way to maintain stable polymorphism is to replace the simplifying assumptions of linear fitness functions with quadratic functions (Fig. 4b). Next consider the case where the allele is codominant and has the same small effect in both sexes. In the heterozygous state the allele helps females more than it hurts males and would therefore begin to accumulate in outbred populations. But as it accumulates it will be expressed more in the homozygous state where, because of the curvilinear fitness functions, it hurts males more than it helps females. This generates heterozygote advantage and leads to stable polymorphism. These two examples are meant to illustrate how equilibrium polymorphism might be achieved, rather than representing a full range of possibilities.

**Data from a *D. melanogaster* model system**

Evidence for the common occurrence of sexually antagonistic variation comes from four experiments. In the first experiment, synthetic female-determining genes (dominant alleles that produce visible eye colour variants, see Fig. 5a) were introduced into experimental populations (Rice, 1992). If female-benefit sexually antagonistic alleles were present in the genome at low frequency because of mutation-selection balance (i.e. alleles which did not have a net selective advantage when averaged across the sexes), then they should be able to accumulate when in tight linkage with a new female-determining allele. Tight linkage promotes the accumulation of female-benefit sexually antagonistic alleles because these alleles would, more often than not, co-segregate with the female-determining allele and therefore be expressed predominantly in the sex where they were favoured.

![Fig. 4](a) An additive mutation of large effect can be favoured in the heterozygous state but disfavoured in the homozygous state, leading to overdominance and equilibrium polymorphism. (b) Nonlinear fitness functions also can generate over-dominance and lead to stable polymorphism. Filled histograms denote the effect of the allele on female fitness, striped histograms the effect on male fitness, and open histograms denote the average fitness effect of the allele when summed across the sexes.
To increase experimental power, two synthetic female-determining genes on different autosomes were utilized simultaneously. These were placed in centromere-proximate euchromatic regions where the density of genes per map unit is high, which increased the number of loci in tight linkage with the female-determining genes. After 29 generations the female-determining markers (and tightly linked loci) were expressed in both males and females and fitness was measured. Males were found to have markedly reduced fitness compared with controls but a parallel increase in female fitness was not statistically significant. This asymmetry indicates that the variation that accumulated near the synthetic female-determining loci had a larger disadvantage to males compared with any benefit to females. The asymmetry was not unanticipated because the type of variation that would accumulate would be expected to harm males more than it helped females; the tighter the linkage the greater the potential disparity in the effect sizes of male-loss vs. female gain in fitness (Rice, 1984, 1987). Because genetic drift was unlikely to cause such a rapid reduction in male fitness after only 29 generations, and because reduced male fitness was not observed in the controls, these experiments provided evidence for the accumulation of female-benefit/male-detriment sexually antagonistic variation in regions that were proximate to the synthetic female determining genes.

In the second experiment, a sample of 774 whole genomic haplotypes [X + major autosomes (excluding the dot fourth chromosome) = 99% of genome, hereafter referred to as genomes] was made to be male-limited for 41 generations (Fig. 5b), and then fitness was measured when the evolved genomes were placed into both males and females. If genome-wide male-benefit
sexually antagonistic variation was common, despite being rare at individual loci, then male-limited transmis-
sion would prevent counter-selection in females and permit this variation to accumulate. As a result, the evolved genomes should increase fitness when expressed in males and decrease fitness when expressed in females. This pattern was observed (Rice, 1998) in the two replicates of male-limited experimental genomes but not in the two replicates of control genomes that were expressed in both sexes over the course of the experiment.

In the third experiment, cytogenetic techniques were used to clone a random sample of 40 haploid genomes from a large laboratory population that had adapted to the lab environment for over 200 generations (Fig. 5b; Chippindale et al., 2001). Each genome was expressed in both males and females, and in each sex the genomes were expressed in an average of 75 different heterozy-
gous genetic backgrounds. Lifetime fitness was measured in each sex under competitive conditions and decom-
posed into its two sequential components: juvenile fitness (egg-to-adult viability) and adult fitness (male reproductive success or female fecundity).

Substantial heritable variation for total, juvenile, and adult fitness was found in both sexes. In the juvenile stage, where gender roles are most similar, a strong positive genetic correlation was observed when the same genomes were expressed in males and females (principal axis slope = 0.83; intersexual genetic correlation = 0.49; P < 0.001, Fig. 6a). The plot of male vs. female juvenile fitness had a slope that was statistically indistinguishable from unity, so there was no measurable evidence for sexually antagonistic variation at this life-history stage. But in the adult stage, where gender roles diverge substantially, a negative correlation for fitness was observed (principal axis slope = -0.28; intersexual genetic correlation = -0.30; P = 0.03, Fig. 6a). Although gender-specific expression of part of the genome would be expected to reduce the intersexual correlation for fitness towards a value of zero, only sexually antagonistic variation would be expected to reduce the correlation to a negative value. As many of the genes that led to a positive intersexual correlation for fitness during the juvenile stage were likely to carry over and be expressed in the adult stage, the reversal of the sign of the correlation between life-history stages is the strongest evidence to date for substantial, genome-wide sexually antagonistic variation.

When fitness for the two life-history stages was combined to estimate net fitness, there was no significant intersexual correlation (Fig. 6a, the point estimate of the slope is negative but it is far from statistical significance, P = 0.37). This indicated that, on average, the positive juvenile correlation and the negative adult correlation for fitness were counterbalancing. Although on average there was no significant intersexual correlation for net fitness, there was a strong intersexual interaction (i.e. frequent reversals in net fitness when the same genomes were expressed in males vs. females, leading to a crossing interaction pattern) for net fitness among individual genomes (Fig. 6b). It was common for genomes that produced the best males to produce the worst females, and vice versa.

As an independent check on the intersexual-interac-
tion for total fitness reported in Chippindale et al. (2001), we recently screened a new sample of 119 genomes for total fitness in males. Each genome was assayed for total fitness eight times independently (as described in Chippindale et al., 2001) and from this sample we selected those genomes that consistently displayed: (i) the highest male fitness (seven ‘Casanova’ genomes), (ii) the lowest male fitness (seven ‘Quasimodo’ genomes), and (iii) average fitness (four ‘Joe-average’ genomes).

Fig. 6 (a) The intersexual regression for juvenile, adult and total fitness from a study of 40 genomic haplotypes (from D. melanogaster) that were cytogenetically cloned and then expressed in both sexes. (b) An interaction plot for total fitness of these 40 genomes. Fitness values of the same expressed genome in males vs. females are connected by lines.
specifies a specific genomic haplotype. Forsman, 1995) demonstrate that traits such as colour-studies of animals (e.g. Sherman, 1977; Endler, 1980; other than D. melanogaster in independent fashion. mutations were favoured or disfavoured in a gender-seen in the juvenile stage) that would be expected if the pool of sexually antagonistic variation was substantial and strong enough to reverse the positive correlation total fitness variation) indicated that the relative size of adult stage (which accounts for approximately 75% of fitness of the same sets of genes when expressed in males vs. females. The net negative correlation for fitness in the adult stage (which accounts for approximately 75% of fitness variation) indicated that the relative size of the pool of sexually antagonistic variation was substantial and strong enough to reverse the positive correlation (seen in the juvenile stage) that would be expected if mutations were favoured or disfavoured in a gender-independent fashion.

Sexually antagonistic genes may be common in species other than D. melanogaster. For example, ecological studies of animals (e.g. Sherman, 1977; Endler, 1980; Forsman, 1995) demonstrate that traits such as colour-ation and behaviour can be selected discordantly in the two sexes. Data from dioecious plants suggest a trade-off between male and female reproductive function mediated by vegetative and floral morphology. For example, Kohorn (1994) identified distinct ‘female-like’ and ‘male-like’ morphologies in the dioecious shrub jojoba. Males with more male-like vegetative morphology tended to have greater reproductive success than those with female-like attributes, and the reciprocal was true in females. The trait-suites described were analogous to those found to be strongly negatively correlated by Meagher (1992) in a quantitative genetic study of Silene.

If sexually antagonistic fitness variation is as common in other species as it appears to be in Drosophila, then why have so few studies documented its prevalence? We think that the answer lies in the experimental protocols and tools that are available only with the Drosophila model system. Experimental power is substantially increased in Drosophila because it is possible to: (i) adapt large populations for hundreds of generations to tractable laboratory environments, (ii) randomly sample entire genomic haplotypes (i.e. full set of genes, hereafter referred to as genomes), (iii) clonally amplify genomes, (iv) express genomes in a large number of heterozygous genetic backgrounds in both males and females, and (v) obtain replicate measures for the life-time fitness of individual genomes and their juvenile and adult components. In principle, quantitative genetic analysis could be used to assess the level of sexually antagonistic fitness variation in any species. The simplest design would be to produce paternal half-sib families (to reduce maternal effects) and then determine the covariance for fitness within and between the sexes. A finding of negative intersexual covariance for fitness would demonstrate abundant genome-wide sexually antagonistic fitness variation.

Sexually antagonistic fitness variation can be viewed as an example of an evolutionary trade-off, but only in the context of genic, as opposed to individual, selection. Consider again the example of hip width in humans. If wide hips facilitate childbirth but reduce locomotor capacity in females, then this would be an example of a classical, functional trade-off. But when the same trait is selectively favoured in one sex and disfavoured in the other, then the trade-off occurs between individuals and between generations. Rather than occurring within individuals as a result of negative pleiotropy, trade-offs involving sexual antagonism occur at the level of the gene because this is the evolutionary unit that moves between the two sexual environments in different generations.

The common occurrence of sexually antagonistic variation has major implications for evolutionary models that explicitly separate the sexes, such as models of sexual selection. These models must incorporate the fact that a substantial proportion of total fitness variation can be diametrically selected between the sexes, i.e. alleles

These 18 genomes were then assayed eight times independently for total fitness in females (as described in Chippindale et al., 2001). As expected from the prior screening of 40 genomic haplotypes, most Casanova and Quasimodo genomes produced strong reversals in fitness when expressed in females (Fig. 7; conditional binomial exact test, $P = 0.0007$), whereas the fitness of the Joe-average genomes was similar between the sexes (Fig. 7).

**Implications of intersexual ontogenetic conflict**

Taken collectively, these four experiments suggest that the genome of D. melanogaster is a mixture of sexually concordant and discordant fitness variation. On average, these two pools of fitness variation combined to form a net zero correlation between the sexes, but individual genomes frequently produced strong reversal in the net fitness of the same sets of genes when expressed in males vs. females. The net negative correlation for fitness in the adult stage (which accounts for approximately 75% of total fitness variation) indicated that the relative size of the pool of sexually antagonistic variation was substantial and strong enough to reverse the positive correlation (seen in the juvenile stage) that would be expected if mutations were favoured or disfavoured in a gender-independent fashion.

Sexually antagonistic genes may be common in species other than D. melanogaster. For example, ecological studies of animals (e.g. Sherman, 1977; Endler, 1980; Forsman, 1995) demonstrate that traits such as colour-
that produce high fitness sons will frequently contribute to low fitness daughters, and vice versa. ‘Good genes’ models of sexual selection must account for this gender-specific tension within the genome. For example, some tests of ‘good genes’ have found a correlation between male display characters and the viability of their offspring (reviewed in Andersson, 1994). Our data from *Drosophila* (discussed earlier) suggest that egg-to-adult viability may be a poor measure for testing the ‘good genes’ model because it does not incorporate potential negative covariance between the sexes for adult fitness. If sexually antagonistic fitness variation is common in most species, then in general (i) females will need to choose different males to optimize the fitness of the their sons and daughters, and (ii) sons and daughters from the same family should have negative covariance for adult reproductive success (where gender roles diverge) and positive covariance for juvenile survival (where gender roles are most similar). It may be possible to reanalyse the data from past studies of the ‘good genes’ model to evaluate these predictions.

The effect of sexually antagonistic variation on models of sexual selection will be especially pronounced if, as predicted by theory (Rice, 1984) and our recent unpublished results (J.R. Gibson, A.K. Chippindale & W.R. Rice, unpublished data), the X chromosome is especially enriched with sexually antagonistic variation. This prediction presumes differentiated X and Y chromosomes, with the nonrecombining portion of the Y having a reduced number of functional genes. In species with male heterogamety, males never pass their X to their sons (so sire-son X-linked heritability is zero) and always pass it to their daughters, whereas females pass their X to both sons and daughters. X-linked sexually antagonistic variation will therefore contribute to a negative intersexual heritability for fitness, with high-fitness males producing low-fitness daughters, and high fitness females producing low-fitness sons. The influence of this process should increase with the proportion of the genome that is sex-linked, so the karyotype of a species may influence (i) its load of sexually antagonistic fitness variation and (ii) the degree to which sexually antagonistic fitness variation interferes with the ‘good genes’ model of sexual selection. Interestingly, when males are the homogametic sex, as occurs in birds, some fish, and Lepidoptera, then males do pass their X chromosome to their sons. This father-to-son transmission of the X will increase the heritability of X-linked traits and, as a consequence, sexual selection may be intrinsically more effective with this form of sex determination. A comparative study of the relative influence of sexual selection (e.g. degree of sexual dimorphism, relative importance of fitness components associated with sexual vs. nonsexual selection, etc.) in relation to the mode of sex determination would be informative in this regard.

The widespread occurrence of sexually antagonistic fitness variation suggests that it may be common for females to be ‘masculinized’, in the currency of fitness, to varying degrees based on the amount of male-benefit sexually antagonistic variation present within their genomes. A parallel level of ‘feminization’ of males is also indicated. At the level of the gonad and genitalia, sexual dimorphism is highly discrete (Fig. 8), e.g. gonadal/genitalic intersexual flies are rare in *D. melanogaster*. But at the level of the entire organism when measured in the currency of fitness, our data suggest a more continuous transition between the sexes (Fig. 8), so that most males and females deviate substantially from the optimal sex-specific phenotype as a result of the expression of extensive, sexually antagonistic genetic variation. As a result, much of the phenotypic variation observed within each sex may be a manifestation of intersexual ontogenetic conflict, i.e. as a result of the expression of sexually antagonistic alleles. This idea can be evaluated in any species in which it is possible to test for negative intersexual covariance for fitness among related individuals.

The existence of sexually antagonistic variation indicates that optimality models of adaptive evolution should be interpreted with caution. Many traits observed in each sex may not be adaptive within that sex, but instead persist in populations as a consequence both fixed and segregating sexually antagonistic variation within the gene pool. The observation of non-adaptive traits within each sex produces an apparent paradox from the perspective of individual selection that is readily understood from the perspective of genic selection. In this case the sexes are viewed as different environments for gene expression, rather than explicit evolutionary units.

Because the extent of intersexual ontogenetic conflict was not appreciated in past studies, there may be an opportunity for substantial re-evaluation of existing datasets, particularly those concerning sexual dimorphism, relative importance of fitness components associated with sexual vs. nonsexual selection, etc.) in relation to the mode of sex determination would be informative in this regard.

![Fig. 8 A graphical model of intersexual developmental conflict.](image-url)
dimorphism. Remarkably few quantitative genetic studies have considered the genetic correlation between the sexes, although many have measured both sexes. Where estimated, the intersexual genetic correlation tends to be high (typically >0.8), especially for morphological traits (reviewed in Roff, 1997; Lynch & Walsh, 1998). In order to relate such intersexual genetic correlations to ontogenetic conflict, the correlation between the dimorphic trait and gender-specific fitness must also be measured. Much of the sexual dimorphism seen in present species may be the result of an evolutionary resolution, either complete or in progress, of intersexual ontogenetic conflict.

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References


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