The evolution of sex ratios and sex-determining systems

Tobias Uller[1], Ido Pen[2], Erik Wapstra[3], Leo W. Beukeboom[4] and Jan Komdeur[5]

[1] School of Biological Sciences, University of Wollongong, Wollongong, NSW 2522, Australia
[2] Theoretical Biology, Centre for Ecological and Evolutionary Studies, University of Groningen, PO Box 14, 9750 AA Haren, the Netherlands
[3] School of Zoology, Locked Bag 5, University of Tasmania, Hobart 7001, Tasmania, Australia
[4] Evolutionary Genetics, Centre for Ecological and Evolutionary Studies, University of Groningen, PO Box 14, 9750 AA Haren, the Netherlands
[5] Animal Ecology, Centre for Ecological and Evolutionary Studies, University of Groningen, PO Box 14, 9750 AA Haren, the Netherlands

Sex determination is a fundamental process governed by diverse mechanisms. Sex ratio selection is commonly implicated in the evolution of sex-determining systems, although formal models are rare. Here, we argue that, although sex ratio selection can induce shifts in sex determination, genomic conflicts between parents and offspring can explain why single-factor systems (e.g. XY/XX or ZW/ZZ) are common even in species that experience selection for biased sex ratios. Importantly, evolutionary shifts in sex determination do not always result in the biased production of sons and daughters *sensu* sex ratio theory. Thus, equal sex ratios might be an emergent character of sex-determining systems even when biased sex ratios are favored by selection.

Introduction

Sex determination (see Glossary) is a fundamental process in all sexual organisms. However, the mechanisms behind it are diverse, ranging from homo- or heterogametic genotypic sex determination (GSD) to environmental sex determination (ESD) [1–3]. Furthermore, the underlying molecular mechanisms of superficially similar sex-determining systems (such as male heterogamety, XY/XX) can also show large interspecific variation [4]. This evolutionary lability of sex-determining mechanisms is surprising given that fundamental developmental processes should be subject to strong selection, thereby reducing genetic variation and, consequently, limiting the potential for evolutionary shifts. Thus, the intuitive rigidity of sex-determining systems does not correspond to factual patterns observed in natural populations and warrants further explanation.

Sex determination can have consequences for the primary sex ratio and, therefore, selection for biased sex ratios might induce evolutionary shifts in sex-determining mechanisms [1]. Here, we review recent models of sex determination and argue that a better understanding of its evolution requires a more extensive use of mechanistic models that reflect the levels at which a response to selection can occur. Furthermore, we emphasize that even when

sex ratio selection induces a shift in sex determination, the proportion of sons at equilibrium often does not deviate substantially from 50%, suggesting that there are fundamental constraints on the production of biased sex ratios.

Sex ratio selection and the evolution of genotypic sex determination

Early work by Darwin, Düsing and Fisher (see Refs [5,6] for an historical overview) showed that an even primary sex ratio is usually evolutionarily stable because of frequency-dependent selection against the most common sex. Consequently, selection should favor sex-determining mechanisms that ensure equal proportions of sons and

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Glossary

Antagonistic pleiotropy: one gene has positive effects on overall fitness through its impact on one trait but negative effects on overall fitness through its impact on another trait.

Environmental sex determination (ESD): the process by which sex differentiation is determined by external environmental factors (e.g. temperature or pH) during offspring development.

Frequency dependence: selection in which the fitness of a genotype or phenotype is not constant but varies according to the frequency of that genotype or phenotype relative to others. Typically, when rare, the particular genotype is at an advantage compared with the other possible genotypes (or phenotypes), but, when common, is at a disadvantage.

Genotypic sex determination (GSD): the process by which sex differentiation is determined primarily by genetic factors, most commonly on the sex chromosomes.

Haplodiploidy: a sex-determinating system where sex is determined by ploidy level. Males are haploid and develop from unfertilized eggs, whereas females are diploid and develop from fertilized eggs. Females typically have control over fertilization.

Heterogamety: the sex with a pair of non-homologous sex chromosomes (e.g. male XY in mammals; female ZW in birds). The heterogametic sex produces two different types of gamete, one with one type of sex chromosome and one with the other.

Homogamety: the sex with a pair of homologous sex chromosomes (e.g. female XX in mammals; male ZZ in birds) and, therefore, producing gametes with one type of sex chromosome.

Genomic conflict: conflict that occurs when genes affecting the same trait experience different selection pressures because they follow different transmission rules or experience opposing selection at different levels, such as in parents versus offspring.

Sex determination: any of various mechanisms in which the sex of the individual animal (or plant) is determined.

Sex differentiation: differentiation of undifferentiated gonads into male and female.

Temperature-dependent sex determination (TSD): the process by which sex differentiation is determined by temperature during offspring development.

Corresponding author: Komdeur, J. (j.komdeur@rug.nl).
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daughters. This result readily explains the commonly observed single-factor genotypic sex determination system where offspring sex is determined by the presence or absence of an allele on a single gene locus and, thus, by random segregation of genes in meiosis. Heteromorphic sex chromosomes (e.g. XX/XY) can subsequently evolve via chromosome degeneration [7,8], under which one of the chromosomes loses most of its functional genomic material.

However, selection for equal sex ratios is not universal. For example, if one of the sexes is more costly to produce in terms of parental energetic expenditure, selection favors a sex ratio that is biased towards the cheaper sex [9,10]. Consequently, it would appear that a sex-determining system with equal probability of inheritance of the male or female factor will no longer be favored by selection. To address the evolutionary dynamics of sex determination under such circumstances, it is necessary to understand the levels at which a genetic response to selection can occur [11].

There are four main categories of genes that can be the focus of selection on sex determination (Figure 1): (i) sex-determining genes expressed within the offspring, affecting the probability of developing into male or female, such as the sex-determining region Y (SRY) present on the mammalian Y chromosome [12]; (ii) genes acting in the parents and biasing the distribution of genetic sex-determining factors among the offspring; for example, genes controlling sex chromosome segregation [13]; (iii) parental effects genes, that is, genes expressed in the parents but where the gene product (e.g. mRNA or yolk hormones) acts as a sex-determining factor in the offspring, [11,14]; and (iv) genes acting in the parents and biasing the distribution of external environmental sex-determining factors among the offspring; for example, via choice of oviposition sites in

Figure 1. Interacting components of the sex-determining system. Sex determination can be viewed as the outcome of interactions among genetic factors in the offspring genome, parentally transmitted gene products and environmental conditions experienced during development. These factors, and their relative contribution to sex determination, can respond to direct or indirect selection via changes in: **(a)** genes expressed within the offspring that affect the probability of developing into a male or female; **(b)** segregation of genetic sex-determining factors (either under parental control or as intra- and extranuclear sex ratio distorters); **(c)** parentally produced sex-determining factors (e.g. transfer of mRNA); and **(d)** parental transmission of environmental sex-determining factors (e.g. via behavioral choice of oviposition site). The evolutionary response to selection depends upon the level of variation in genetic components of offspring or parental control and upon the intra- and intergenomic conflicts that arise from conflicting selection pressures within and between generations.

species with ESD [15,16]. In theory, all these gene categories could respond to selection, and the evolution of sex determination will depend, to some extent, on the level of genetic variation for each category and on potential constraints on an evolutionary response owing to, for example, antagonistic pleiotropy or genomic conflict.

GSD under zygotic influence
Perhaps the simplest scenario of sex ratio selection driving the evolution of sex determination is when all sex-determining genes are expressed in the offspring and there is no environmental sensitivity or fitness difference among genotypes other than that arising from sex ratio variation. Building on early insights by Bull [1], Kozielska and co-workers [17] addressed the evolution of multi-factor sex determination by modeling a three-locus system with each locus having two alleles, similar to the system found in the housefly *Musca domestica* (Box 1). Selection for biased sex ratios was assumed to act via differential costs of producing sons and daughters. The model generated several outcomes that are important for the evolution of sex determination. First, multi-factor sex-determining systems can be stable both with and without selection for biased sex ratios. Second, even under sex ratio selection, one of the sex-determining factors can go to fixation, ultimately reducing sex determination to a two-locus system. Third, selection for biased sex ratios alone is insufficient to induce a complete shift in heterogamety, but the strength of selection influences the final genotype frequencies. Thus, sex ratio selection alone seems incapable of explaining the observed multi-factor sex determination system in houseflies.

GSD under both parental and zygotic influence
The emergence of new sex-determining factors acting in the offspring might interfere with normal sexual development (e.g. via antagonistic pleiotropy) and, therefore, might be initially selected against [4]. An alternative evolutionary response to selection for biased sex ratios would therefore be maternal control over offspring sex, for example, by female control over sex chromosome segregation [13,18]. However, as first identified by Trivers [19], parents and offspring can have different 'optima' for sex ratios, with the parental genome usually favoring a more biased sex ratio than does the offspring genome ([19] but see Ref. [20]). Thus, when expression of sex-determining genes occurs in both generations, intergenomic conflicts might affect the evolutionary outcome of sex determination (Box 2).

Building on these insights, Werren and co-workers [21,22] showed that, when the brood sex ratio affects offspring or parental fitness, conflict between genes expressed in the parent and those expressed in the offspring can result in the evolution of a dominant single sex-determining locus expressed in the offspring. If male offspring reduce the fitness of the overall brood or the fitness of its parents (the 'family' fitness), a dominant *Mm* male–*mm* female system evolves. However, if female offspring reduce family fitness, a dominant *Ff* female–*ff* male system evolves [22]. Eventually, the presence of dominant sex determination is likely to result in heteromorphic sex chromosomes, with
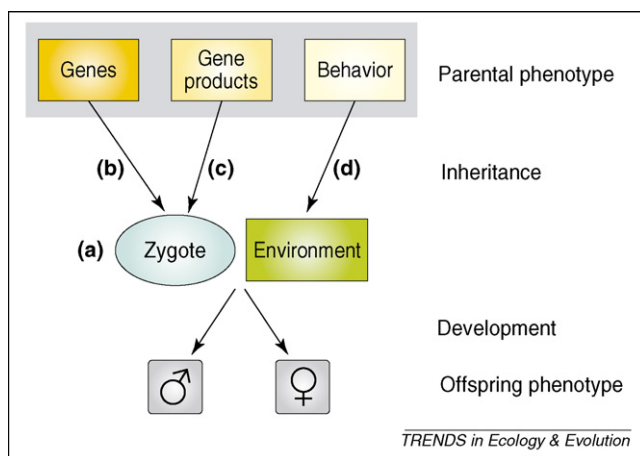
Box 1. Mixed sex-determining systems in flies and lizards

Species in which multiple factors combine to determine the sex of offspring occur in both invertebrates and vertebrates and provide outstanding opportunities for addressing the role of selection for sex ratio bias in the evolution of sex determination.

Sex determination in houseflies

The multi-factor sex-determining system of houseflies *Musca domestica* (Figure Ia; reproduced with permission from Peter Koomen) is well established ([17,44] and references therein). Most abundant is male heterogamety, with a dominant male determiner (*M*) on the Y chromosome. The *M* factor can also be found on one or more of the five autosomes (autosomal *M*) or even on the X chromosome, rendering these the sex-determination chromosomes. In addition, female heterogamety occurs with a dominant female determiner (F^D) on chromosome IV. There is a clinal pattern in the distribution of these mechanisms in North America, Europe, Southern Africa and Japan. The male heterogamety system prevails at high latitudes, whereas populations consist entirely of autosomal *M* individuals at lower latitudes. The selective forces responsible for the observed clines are still unknown. The F^D system occurs only in populations with autosomal *M*. Several populations are polymorphic for *M* factors located on the Y-chromosomes or on one or more autosomes. The *M* factor has yet to be cloned and characterized and, therefore, it is unknown whether it is a transposing element or whether multiple genes can execute the *M* function.

Sex determination in lizards

Equally intriguing, but with less information available about the underlying mechanisms, is the sex-determining system of the lizard *Bassiana duperreyi* (Figure Ib; reproduced with permission from Geoff Swan), which has heteromorphic XX/XY sex chromosomes. However, chromosomal sex is overridden by temperature under naturally cool incubation conditions [38], with an overproduction of male offspring. Consequently, the population will consist of XY males, XX males and XX females. This unidirected effect of incubation temperature avoids the production of inferior YY individuals [4] and, consequently, the invasion of temperature-sensitive sex-determination genes might not be selected against for developmental reasons. Furthermore, an overproduction of males at relatively cool conditions might be adaptive, as there is some evidence for sex-specific effects of

incubation temperature on offspring performance [49]. *Bassiana duperreyi* might, therefore, represent a first step in the evolution from genetic to environmental sex determination. Interestingly, there is also some evidence that egg size is related to offspring sex [38], suggesting that maternally produced sex-determining factors also have a role.
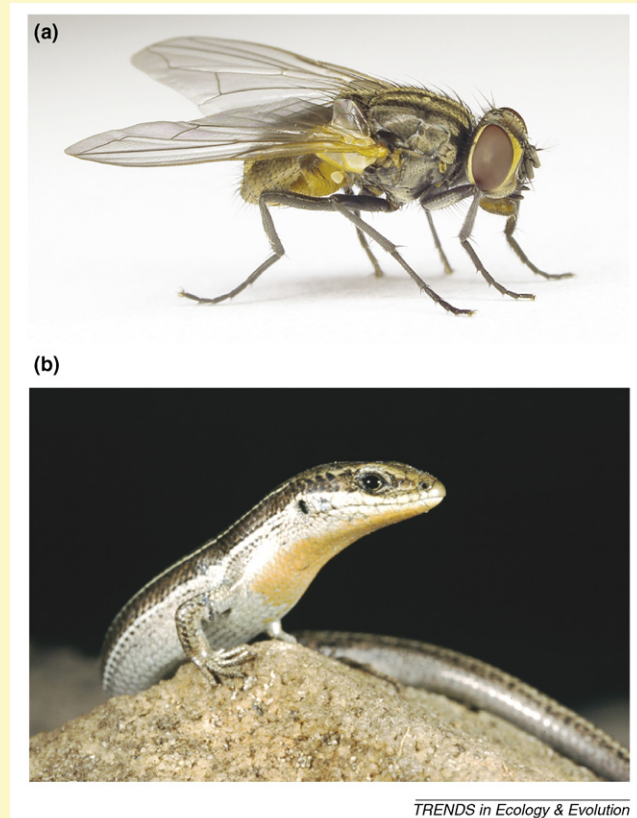
(a)

(b)

TRENDS in Ecology & Evolution

Figure I.

dominant male *Mm* leading to a XY/XX system and dominant female *Ff* leading to ZW/ZZ system. Thus, even when sex-determining factors can act in both the parental and offspring generation, the evolutionary outcome is a relatively simple system of offspring control over sex determination.

Although the models by Werren *et al.* require that brood sex ratio affects family fitness, this will occur whenever: (i) there is partial inbreeding or local mate competition; (ii) males and females have different costs of production; (iii) brood sex ratio affects the fitness of individual offspring within the brood; or (iv) brood sex ratio affects the lifetime fitness of the parents. One or more of these four criteria are fulfilled in several animals (e.g. many vertebrates [23,24] and parasitoid wasps [25]) and the models might thus be of importance for the evolution of sex determination in a range of taxa. Genomic conflict has also recently been argued to be the reason for the evolution of haplodiploidy, a flexible sex determination system in which females control the sex of their offspring through fertilization (Box 3). Thus, genomic conflict might be able to generate simple sex-determining systems with either parental or offspring control; however, the conditions that favor one outcome over the other have not yet been addressed.

GSD and sex ratios at equilibrium

Although the models described above were primarily developed to address the potential for sex ratio selection to cause evolutionary shifts in sex determination, they have also generated another important insight. In models with exclusive expression of sex-determining factors in the offspring and in models that enable dual action of parental and offspring genes, the evolutionarily stable sex ratio deviates only marginally from 50:50, even when selection favors highly biased sex ratios [1,17,22]. In other words, selection for biased sex ratios yields evolutionary shifts in sex determination but does not result in the sex ratio predicted by standard theory. For example, in the housefly three-locus sex-determining model (Box 1), male-biased sex ratios are impossible and the female-biased sex ratios that evolve when sons are more costly to produce are smaller than predicted under perfect maternal or offspring control [17]. The reason for this result is that mixtures between genotypes that create biased sex ratios are not evolutionarily stable. Thus, these analyses suggest the presence of real genetic constraints on sex ratio evolution that could explain why adaptive sex ratio adjustment is documented so rarely for species with GSD despite selection for biased sex ratios ([26] but see e.g. Refs [27,28]).

Box 2. Kin selection, parent–offspring conflict and sex determination

Trivers [19] was the first to show that the direction of selection on sex-determining genes can depend on whether the genes are expressed in the mother or in the offspring. The logic underlying this parent–offspring conflict is most easily appreciated from a kin selection perspective. Generally, whenever relatives compete over limiting resources, selection favors genes that bias the sex ratio towards the sex least interfering with relatives [19,20,50,51]. For example, in a deme-structured population with sex-specific dispersal, a sex ratio biased towards the most dispersive sex is expected because this sex is least likely to compete with relatives [20,51,52]. Indeed, if females disperse from their natal deme with rate d_f and males with rate d_m, then the equilibrium primary sex ratio is given by Equation I:

$$\frac{\text{sons}}{\text{daughters}} = \frac{r - \left(1 - d_m\right)^2 R}{r - \left(1 - d_f\right)^2 R} \qquad \text{[Eqn I]}$$

where r and R are coefficients of relatedness, the values of which depend on whether maternal genes or offspring genes control the sex ratio [20]. In the case of maternal control, r is her relatedness to her own offspring ($1/2 \leq r \leq 1$) and, in the case of offspring control, r is the relatedness of the offspring to itself ($r = 1$). R is the average relatedness of the controlling individual to all offspring born in the same deme.

It can be seen from Equation I that, regardless of who is in control, the sex ratio is biased towards the sex with the greater dispersal rate. However, relatedness asymmetries typically cause maternal genes and offspring genes to favor quantitatively different sex ratios. For monogamous and polyandrous mating systems, the R of the offspring is equal to or smaller than that of the mother and Equation I predicts that maternal genes will favor a more biased sex ratio than will offspring genes. By contrast, for polygynous mating systems, offspring from different mothers can be related through their father and thus might prefer a more biased sex ratio than does their mother [20].

Using a combination of population genetic and individual-based models, Werren *et al.* [22] and Pen [20] showed that, when the sex ratio is at the equilibrium favored by maternal genes, dominant sex-determining genes that act in the offspring can invade and reach fixation. For example, if maternal genes favor female-biased sex ratios and offspring genes favor less female-biased sex ratios, then dominant male-determining genes (e.g. proto-Y chromosomes) can invade. By contrast, if offspring genes favor a more female-biased sex ratio, then dominant female-determining genes (e.g. proto-W chromosomes) can invade.

Box 3. Haplodiploidy

Haplodiploidy is a form of sex determination where offspring sex is determined by ploidy level in the absence of heteromorphic sex chromosomes. Males develop from unfertilized eggs and are haploid, whereas females develop from fertilized eggs and are diploid. Haplodiploidy has evolved multiple times and occurs in all Hymenoptera (ants, bees, wasps and sawflies) and several other invertebrate taxa, including beetles, thrips, scale insects and mites [53].

Sex determination in honey bees and many other hymenopterans depends on the allelic composition of a single locus, although alternative molecular mechanisms also exist [54,55]. Females typically manipulate the fertilization process, which makes haplodiploidy flexible for sex ratio adaptations under maternal control. Sex ratio selection has therefore been the traditional explanation for the evolution of haplodiploidy [25]; however, recent evidence suggests that genomic conflict is a more probable explanation [56]. Haplodiploidy has arisen in organisms with highly gregarious kin groups [53,56] that, in addition to favoring biased sex ratios, often creates conflicts of interest between maternally and paternally derived alleles within the offspring ([56,57] see also Box 2). Most notably, haplodiploidy will select for paternal alleles that favor fitness of individual offspring despite compromising the fitness of the mother and the brood as a whole. Haplodiploidy might evolve as a means to reduce this conflict via the evolution of maternal control over transmission genetics and, hence, elimination of 'greedy' paternal alleles [56]. This process can be further facilitated by the presence of maternally inherited male-killing cytoplasmic elements [56,58,59].

However, the constraining role of sex-determining mechanisms must be empirically evaluated, using a comparative approach, in taxa that differ in sex determination, but experience similar selection pressures [28–30].

Sex ratio selection and evolutionary transitions between GSD and ESD

Although ESD might be ancestral in some lineages and, thus, has been retained without positive selection [31], sex ratio selection can both cause and maintain ESD [1,29,32–34]. As originally outlined by Charnov and Bull [33], their model makes three fundamental assumptions: (i) environmental conditions experienced during sexual differentiation have sex-specific fitness consequences; (ii) mating is random with respect to these developmental conditions; and (iii) both parents and offspring have limited control over the environmental conditions that the offspring will experience. Because of the third assumption,

an evolutionary response via maternal manipulation of environmental conditions experienced by the offspring is constrained. The expected outcome is that the offspring genome evolves to channel development into a male phenotype under conditions where males have higher fitness than do females, and a female phenotype under conditions where females have higher fitness than do males [32–34]. Relaxation of the third assumption of no parental choice of environmental conditions (e.g. thermal characteristics of nests in reptiles) can influence both the primary sex ratio and the rate of evolution of the population [1,15].

Environmental sex determination can lead to large spatial or temporal fluctuations in population sex ratios, which reduces the benefits of matching offspring sex to environmental conditions ([35] but see Ref. [36]). This can lead to disruptive selection on sex determination and enables genes of major effects to invade, causing an evolutionary shift from ESD to GSD [35,37]. However, an alternative response is the evolution of decreased accuracy in the mapping of environmental conditions onto sex determination, as this dampens the magnitude of sex ratio variation in relation to fluctuating environmental conditions [37]. Thus, when environmental variation is large, selection might favor increased randomness (i.e. reduced canalization) of sex determination, thereby reducing the likelihood of an evolutionary transition from ESD to GSD.

The transition between GSD and ESD is predicted to occur rapidly and the intermediate stage, where both genetic and environmental factors influence sex determination, should therefore be brief. Nevertheless, mixtures between GSD and ESD have been shown to exist within populations ([2,38], Box 1); however, the extent to which multi-factor sex-determining systems with both genetic factors and environmental sensitivity are evolutionarily stable remains to be explored theoretically.

Integrating theory and empirical research on sex ratios and sex determination

Although theoretical models have shown that sex ratio selection can cause evolutionary shifts in sex determination, the analyses also emphasize that the evolutionary outcome of sex determination is sensitive to the particulars of the system, especially the level at which a genetic response to selection can occur (Figure 1). Progress in this field would therefore be facilitated by incorporation of mechanistic details of sex determination and documented sex ratio selection pressures into theoretical models [9]. This requires a detailed understanding of proximate mechanisms of sex-determining systems, as well as empirical tests of sex ratio selection pressures in natural populations. Empirical work, however, relies on model systems that enable researchers to test hypotheses in a comparative framework or to conduct controlled experiments. Birds and mammals, taxa that figure prominently in the sex ratio literature [30], have been considered to be relatively uninformative with respect to the evolution of sex determination because of their invariant genotypic sex-determining systems. However, some species of birds and mammals show non-random sex ratios at conception (e.g. Refs [39–41]), suggesting maternal control over chromosome segregation or maternal or offspring production of a sex-determining factor that override chromosomal sex in the developing fetus [13,18]. Nevertheless, the most promising model systems for investigating the relationships between sex ratio selection and sex determination will be those in which different sex-determining systems occur within or between closely related populations or species. Such systems exist in both animals and plants, such as houseflies, lizards and sorrels [2,29,42–44].

Unfortunately, in comparison to mammals, our understanding of the mechanisms of sex determination is limited in many of the taxa that show evolutionary lability of sex-determining mechanisms or presence of multiple sex-determining factors within a single population. For example, although the male heterogametic system of the scincid lizard *Bassiana duperreyi* is known to be overridden at low incubation temperatures ([38], Box 1), the mechanisms behind sex determination in this species are poorly understood. Consequently, empirical studies of proximate mechanisms in taxa not traditionally used as model organisms (such as lizards) might not only lead to a better understanding of sex determination itself [45,46], but will also increase our understanding of its evolution.

Correspondingly, theoretical models of systems that are relatively well understood from a proximate perspective (such as houseflies) are likely to capture the evolutionary dynamics of sex ratio selection and sex determination to a larger extent than are less mechanistic models. The value of a mechanistic approach is shown by a recent reconstruction of the evolution of the regulatory cascade of sex determination in *Drosophila* that explicitly inferred sex-specific fitness consequences of gene expression as the underlying selective force behind evolutionary change [47]. A similar approach could be taken for species where selection for biased sex ratios is established or implied. Furthermore, many invertebrates also lend themselves readily to laboratory experiments and artificial selection, which enables explicit tests of theory [48].

Evolution of sex determination and constraints on sex ratio bias

One of the most important results from recent models of sex determination is that even when selection for sex ratio bias causes changes in sex-determining mechanisms, the resulting sex ratio at equilibrium might not show the expected deviation from 50:50 [17,22]. This adds a novel perspective on the role of genetic constraints on sex ratio adjustment as it suggests that constraints evolve from a system that is free to vary, rather than *a priori* postulating constraints based on the 'difficulty' by which the appropriate mechanism can evolve (see also Ref. [26]). However, whether this can explain the scant and conflicting evidence for sex ratio adjustment in particular taxa remains to be shown. A complicating factor is that most theoretical models, in particular the genomic conflict models, attempt to address how selection for a particular population-wide sex ratio bias (i.e. a deviation from 50:50) affect the evolution of sex-determining mechanisms, whereas empirical work is often based on an implicit assumption of individual plasticity in sex determination (e.g. in relation to maternal condition; reviewed in Ref. [27]) rather than a fixed bias. Conditional sex ratio strategies might be subject to lower intergenomic conflict than are fixed strategies, as parents and offspring are more likely to converge on which sex yields the highest fitness returns under given conditions. Thus, genomic conflict models especially need to take into account the possibility of individual plasticity. The inevitably more complex models that this requires will probably entail a greater reliance on individual-based simulations as a modeling tool [20,37]. Although such simulations sacrifice generality to some extent, they are easily tailored to the biology of specific organisms and, hence, can be valuable tools in forging a further integration of theory and empirical research.

Conclusions

Recent theoretical models have shown that sex ratio selection can generate complex sex-determining systems similar to those that have been described in animals and plants. Nevertheless, these multi-factor systems are frequently unstable, owing partly to intergenomic conflicts between parents and offspring, leading to the evolution of familiar single-factor systems, such as the XY/XX system seen in most mammals. Thus, genomic conflicts might not only explain why multi-factor systems are relatively rare, but the nature of these conflicts might also dictate the conditions that are necessary for the evolution and maintenance of multi-factor systems.

Finally, perhaps the most surprising result from theoretical models is that even when sex ratio selection does induce evolutionary shifts in sex determination, the sex ratio at equilibrium does not correspond to that predicted by game-theory or optimality models. This suggests that equal sex ratios might be an emergent character of sex-determining systems even when biased sex ratios are favored by selection. Further progress in the field requires a better integration of theoretical and empirical research to enable the development and testing of mechanistic models within an evolutionary framework.

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