Recent developments in sex ratio studies

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The allocation of resources to male and female progeny is a major component of the reproductive strategies of all sexual plants and animals. Over the past 30 years there has been intensive theoretical and experimental investigation of how natural selection moulds the sex ratio. Here, we discuss recent exciting developments and new applications of sex allocation theory and highlight some unresolved issues.

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In a famous remark, Darwin left to his successors the problem of explaining how natural selection influenced the sex ratio, a challenge taken up by Fisher[1] who in 1930 showed how an equal sex ratio (or, more precisely, an equal investment ratio) could evolve through individual-based frequency-dependent selection. The modern era of research into sex ratios began with Hamilton's[2] observation that many insects and mites have highly female-biased sex ratios and that this trait is associated with high levels of brother-sister mating. Hamilton explained this result by his theory of local mate competition (LMC), which has been extended to other cases of interactions between siblings. Briefly, if one sex suffers a greater reduction in fitness through competition with siblings of the same sex, the mother is selected to bias the sex ratio towards the sex that suffers less competition. Fisher's frequency-dependent argument is thus modified in populations where relatives compete.

A second major development was Trivers and Willard's[3] insight that the fitness of sons and daughters might vary depending on their mothers' condition or circumstance. Thus, in mammal societies with dominance hierarchies, if son or daughter rank is correlated with that of their mother, a high-ranking female should produce offspring of the sex that benefits most from her position. Charnov[4] generalized this theory to any circumstance where the reproductive value of sons and daughters differs among parents. For example, if female parasitoid wasps gain a greater increment of fitness than males from developing in large, good-quality hosts, an ovipositing mother confronted with such a host should lay a female eggs. That sex ratio was correlated with host size had long been known to occur in many parasitoids, and theoretical advances in sex ratio helped to place these in an evolutionary context.

A third major development in sex ratio theory was the increasing realization of the importance of genetic conflict. A number of authors[2,6-9] pointed out that the inheritance pattern of genetic elements determines how they will be selected to influence the sex ratio. For example, cytoplasmically inherited factors, which are passed on through females but not through males, are generally selected to produce 100% females, whereas nuclear genes (specifically autosomal genes) are selected to produce offspring of both sexes, the exact sex ratio depending on the factors mentioned above. There is thus the potential for conflicting selection pressures when different genetic factors are able to influence investment in sons and daughters, and the resultant `intragenomic' or `genetic conflict' has significant implications for both sex ratio and sex determination.

Charnov's[10] important 1982 book provided the subject with a more unified conceptual framework by showing that the principles of sex ratio theory can be generalized to any circumstance in which organisms invest in male and in female function (what Charnov called sex allocation; see also his more recent discussion of sex ratio invariants[11]). For example, in hermaphroditic plants, selection acts upon the relative allocation of resources to pollen versus ovules, and in hermaphroditic animals upon the allocation to sperm versus eggs. Similarly, sequential hermaphrodites must `decide' when to shift from one sex to the other. Stimulated by these advances in theory, the past 15 years have seen an explosion of laboratory and field studies and the qualitative and often quantitative contamination of many of the predictions of theory (for an altogether more jaundiced view, see Ref. 12). There has also been a flowering of sex allocation studies with plants. Another development was the formulation of a formal population-genetic theory of sex allocation[13], although this approach has yet to inspire a large body of experimental work.

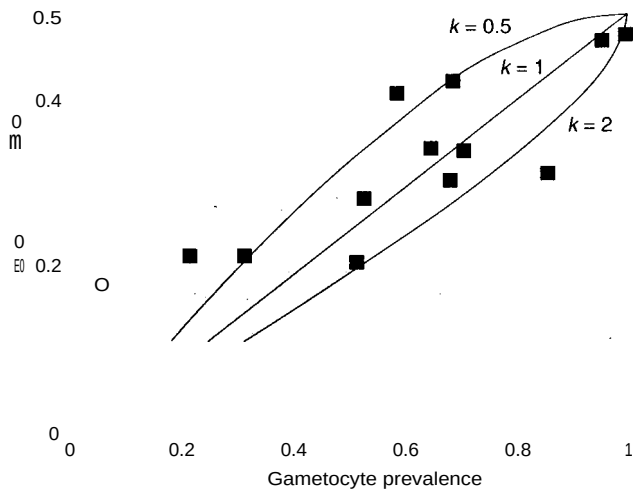
In this article, we make no attempt to review comprehensively the field of sex allocation (see Refs 10,14-17). Instead, we will focus on recent applications of sex ratio theory to interesting problems.

Malaria and local mate competition

Since Hamilton's pioneering work, the effects of subdivided population structure on sex allocation have been studied in a number of organisms, notably parasitoid wasps and fig wasps, and general patterns are consistent with LMC theory[18]. Recent work has involved previously little-studied animals and also the development of LMC theory as a tool for studying population structure. A good example concerns the protozoan parasites in **Plasmodium** and related genera, the agents that cause human and animal malaria.

First, a brief reminder of the life cycle of **Plasmodium.** Malaria is transmitted by female mosquitoes that suck up blood containing red blood cells infected by either male or female haploid gametocytes. The sex ratio of **Plasmodium is** measured by counting the ratio of gametocytes in blood samples taken from infected people. Once in the mosquito, the gametocytes rupture - females releasing a single macrogamete, and males up to eight microgametes. The gametes fuse, and the meiotic products of the resulting diploid zygote eventually form numerous sporozoites that migrate to the salivary glands. When the mosquito feeds again, the sporozoites infect the host and give rise to one or more clones of cells that undergo a complex cycle of cell divisions that ultimately leads to the production of gametocytes.

Malarial sex ratios are often female biased and several workers have suggested that LMC may be responsible[19]. The extent of LMC clearly depends upon how many different genotypes are circulating in the blood of an infected host. If an individual is infected by many **Plasmodium** genotypes, then the blood meal ingested by a mosquito can result in outbred mating. LMC theory predicts that the greater the number of multiple infections within hosts, the less female biased the male/female gametocyte ratio should be.



Flg.1. The relationship between gametocyte sex ratio and gametocyte prevalence in 12 populations of birds (filled squares; for species names and sources see Ref. 20). The predicted sex ratio from LMC theory depends on the degree of clumping of parasites across hosts. Read et al.[20] modelled this aggregation using the negative binomial distribution with parameter k and predicted sex ratios for three levels of aggregation are shown as solid lines. As explained in the text, a minimum sex ratio is set by the number of microgametes produced by each male gametocyte. This is thought to he in the range 4-8, which gives rise to a region of sex ratio uncertainty that is shaded in the figure. The unfilled square is the data from human populations in New Guinea[24].

A recent comparative study[20] supports the contention that malarial sex ratios reflect population structure. Prevalence of infection was plotted against sex ratio (for different levels of parasite overdispersion - see legend to Fig. 1) for 12 populations of avian malaria *(Leucocytozoon). As* expected, in populations where malarial prevalence is low (and presumably multiple infections are also low and inbreeding common), more female-biased sex ratios occur. However, a similar study with a different genus of avian malaria *(Haemo*proteus) failed to find a relationship between prevalence and sex ration. Understanding why the two genera differ is an interesting challenge; possibly it may have something to do with their different insect vectors[20].

There is controversy concerning the population structure of human malaria agents. Some workers have suggested that low levels of linkage disequilibrium indicate mostly outbred mating, while other workers have argued for effective clonality[22]. *Plasmodium* population structure has direct implications for human health: panmictic and inbred populations will differ in their ability to evolve resistance to chemotherapy or to future vaccines[23]. Population structure can be explored directly using the tools of molecular biology, but an attractive alternative is to use sex ratio theory to infer levels of inbreeding.

Read and colleagues[24,25] applied standard LMC theory for malaria and found the pleasing and robust result that the mean rate of mating between identical gametocytes (or, equivalently, Wright's coefficient of inbreeding) is simply 1-2(observed sex ratio). In their study of *Plasmodium falciparum* in New Guinea, the observed sex ratio was 0.18 and they estimated the selling rate to be between 0.55 and 0.71. There is one complication. Suppose the population was completely inbred: sufficient male gametocytes should be produced such that all female gametocytes can find a partner. If each male gametocyte produces eight healthy gametes then the inbred population should have a sex ratio of 1/(1 + 8) = 0.11. If the numbers of microgametes that survive fall below an average of about 5.5, then the observed sex ratio is consistent with a selfing rate of 1.0. The break-up of the male gametocyte seems to be a rather chancy business and the survival of as few as five male gametes is quite likely. The sex ratio argument thus predicts selling rates of between 0.55 and 1.0, not ruling out effective clonality, but strongly suggesting that the population is a long way from panmixis. Very recent work by Paul, Day and colleagues[23] has confirmed the prediction from sex ratio theory. Using PCR techniques, they surveyed the genetic heterogeneity of individual oocysts and estimated a selling rate of 0.915 (99%> confidence interval: 0.835-0.966). *A* similar study in Tanzania[27], where transmission intensity is much higher, estimated a much lower selfing rate of about 0.33. This great variability in selling rates suggests that, in the absence of direct molecular data, consideration of the sex ratio may be a valuable means of obtaining information on *Plasmodium* population structure.

Mammals and birds

Studying sex allocation in birds and mammals presents a number of special problems. Fitness returns from investment in sons and daughters are commonly non-linear and unequal. This arises because (1) fecundities are generally low; (2) the period of parental care is normally extended (both pre-natally and post-natally); and (3) the costs of investing in sons and daughters may not be the same. In an important review of sex allocation theory as applied to birds and mammals, Franks has argued that although the potential importance of non-linearities in fitness returns has been recognized since the work of Trivers and Willard[3], its full ramifications are seldom appreciated. For example, there had been a tendency to use Trivers and Willard's theory to predict the sex allocation strategy of individuals, but to rely on Fisher's argument to predict an overall population sex allocation strategy of equality. In fact, if Trivers and Willard's ideas apply, then the assumptions implicit in Fisher's argument are automatically violated. The population sex ratio with non-linear fitness returns can be calculated, and is usually biased towards the sex produced under poor conditions[5,28,29].

The chromosomal mechanism of sex determination found in most birds and mammals severely constrains the feasible range of sex allocation strategies that they can employ. Sex ratios at conception are often fixed at equality although the extended period of pre- and post-natal parental care provides an opportunity for mammals to manipulate sexual allocation by differential elimination of, or investment in, the two sexes. However, studying such complex investment patterns and assessing their fitness costs and benefits is exceedingly difficult, and requires a detailed understanding of the organism's life history and physiology.

Our knowledge of how sex ratio adjustment occurs in birds and mammals is still rather rudimentary, although growing rapidly[30]. Despite the problems mentioned above, it is widely believed that local resource competition among the philopatric sex (normally daughters) and the Trivers and Willard mechanism described in the introduction are the most important factors leading to biased sex ratios in a number of mammals"[32]. *As* an example of the complexities that can arise, consider Cockburn'sX; recent work on *Antechinus stuartii,* a brown marsupial carnivore that resembles (at least to northern hemisphere eyes) a large mouse. Males live for just under a year, expiring after the annual rut. Females live for either one (semelparous) or two (biparous) breeding seasons, producing broods of about eight to ten young, one for each teat. Unlike placental mammals, relatively little investment takes place before birth and so selective brood reduction is an efficient means of sex ratio adjustment.

Captive *Antechinus* have been observed to kill and eat certain of their offspring and similar behaviour probably

occurs in the wild. Cockburn documented the sex ratio produced by three categories of *Antechinus* over a number of years: semelparous females; biparous females in their first year; and biparous females in their second year. Nearly all females reduced the size of their brood but they almost always ensured that at least one daughter survived. However, there was a bimodal distribution of sons with some females rearing nearly all their sons and others, particular biparous females in their second breeding season, rearing no sons. The interpretation of these data is not completely clear and different explanations are discussed by Cockburn. What seems to be happening is that mothers try to rear one or possibly two daughters, but not more. Females are philopatric while males disperse widely and thus local resource competition favours a male-biased sex ratio. However, there seem to be special costs associated with rearing sons, especially for old (biparous second season) females, and possibly other females of low quality. Attempting to rear too many sons may lead to the mother's death before weaning, and hence the loss of the whole brood. Poor quality females who risk this fate are selected to destroy the males in their brood. Moreover, the sons produced by poor quality females may themselves be of very poor quality. Maternal reproductive status was found to have a very large influence on the reproductive success of daughters, but because sons disperse so widely it was not possible to see whether sons were also affected and hence to explore if a Trivers and Willard mechanism might operate. Despite all these complexities, population-wide sex ratios at birth and after brood reduction were not distinguishable from equality.

Genetic conflict

Most sex allocation theories implicitly assume that sex allocation is determined by autosomal nuclear genes expressed in the mother. Frequency dependent selection for sex allocation is a direct result of the fact that nuclear genes are inherited equally through both sexes. In contrast, some genetic elements have asymmetric inheritance, being transmitted through one sex but not the other. Asymmetries in the inheritance of genetic elements have two important consequences: (1) such elements are selected to skew the sex ratio toward the `transmitting sex'; and (2) genetic conflict occurs between different elements in a genome over sex allocation.

Genetic conflict is most easily visualized by considering cytoplasmically inherited elements. Mitochondria and a wide range of inherited microorganisms are typically transmitted via the egg cytoplasm and therefore are inherited through females but not through males. As a result, mitochondria and cytoplasmic microorganisms are selected to skew sex allocation towards females, the sex that transmits them to future generations. Cytoplasmically inherited factors that skew sex allocation towards females are known for a wide range of plants and animals. Examples include mitochondrial male sterility factors in plants, and microorganisms that cause selective male lethality, feminization, parthenogenesis or primary sex ratio shifts in animals.

Genetic conflict occurs between cytoplasmic sex ratio distorters and nuclear genes (particularly those residing on autosomal chromosomes) because cytoplasmic distorters are selected to produce only females, whereas autosomal genes are selected to produce a more balanced sex ratio. These conflicting selective pressures will lead to the evolution of autosomal suppressors of the cytoplasmic sex ratio distorters.

An evolutionary `arms race' between these different genetic elements could be important in shaping the evolution of sex-determining mechanisms. Just such a case may have occurred in the woodlouse, *Armadillidium uulgare*, a small isopod that has been studied extensively by Juchault, Rigaud and colleagues[34-37]. *Armadillidium uulgare* females typically have heterogametic sex chromosomes (ZW) whereas males are homogametic (ZZ). However, many populations also carry a cytoplasmically inherited bacterium (F) that causes feminization of genetic males by suppression of the male determining gland. These females are completely fertile and transmit the bacterium to their progeny. Although the story is not completely resolved, the Fbacterium appears to have cascading effects on sex ratio selection in host populations. Some populations have extremely female-biased sex ratios and in these the *F* bacterium is at high frequency and the female-determining W chromosome has been effectively driven to extinction (nearly all females are genetic males with *F* bacteria). The extreme scarcity of males, and their consequent high fitness, imparts an intense selective advantage on any genotype that is able to produce males. As expected, autosomal suppressors of the *F* bacterium have arisen, thus modifying the sex determination system.

There is a second female-determining factor (f) that is predominantly (although not exclusively) inherited cytoplasmically. Dominant autosomal suppressors of ***f*** occur in some populations and where these are present, males are effectively heterogametic (one copy of suppressor), whereas females are effectively homogametic (no suppressor). There has thus been a shift from female to male heterogamety, illustrating further how sex ratio distorters can destabilize and change the sex determination system.

In addition to conflict between cytoplasmic and autosomal genes, there are other forms of genetic conflict over sex allocation. Genes on the sex chromosomes can be selected for meiotic drive, resulting in sex ratios skewed toward females (Xdrivers) or males (Ydrivers), with subsequent selection for suppressors at unlinked loci[2]. Although it remains to be proven, genetic conflict between sex chromosomes may also be an important force influencing the evolution of sex determination.

Social insects

Conflict over sex allocation can occur not only within the genome, but also between individuals in a society when more than one individual has an influence over sex allocation. In 1976, Trivers and Hare[33] identified an area of conflict at the heart of sex allocation in eusocial ants, bees and wasps. Their haplodiploidy means that the queen and her workers have different levels of genetic relatedness to females and males produced in the colony, which leads to differences in their optimal sex ratios. For example, consider a colony with a single queen who has mated only once, in a species with population-wide mating. If the queen controls the sex ratio, then Fisher's argument applies and investment in the two sexes should be equal. But if workers control the sex ratio, they should bias allocation towards females rather, than males (that is, towards sisters rather than brothers). The workers' optimal sex ratio is 3/1, reflecting their greater genetic stake in sisters (coefficient of relatedness 3/4) than brothers (relatedness 1/4).

This clear prediction of sex allocation theory would seem to offer an excellent opportunity for discovering whether queens or workers control sex ratio. However, the intricate biology of social insects complicates this simple prediction. Queens and workers may have different opportunities for controlling sex ratio, and workers are not always sterile. Questions of sex ratio are influenced by the related issue of allocation to workers versus reproductives. The optimum sex ratio for one or both parties is influenced by the number of times the queen has mated, the number of queens per colony and, if it occurs, by local mate competition. Furthermore, it is technically very difficult to measure colony sex

allocation because it depends on primary sex ratio, differential investment in male and female progeny, and differential mortality. Finally, the sex ratio in many species is overdispersed with colonies concentrating on the production of one sex, a situation referred to as `split sex ratios'.

Boomsma and Grafen[37,39] have shown that split sex ratios are compatible with worker but not queen control of the sex ratio. Consider again a species with single-queen colonies, and population-wide mating, but now assume that some queens are single-mated but others have mated more than once. If workers control the sex ratio then those in colonies with single-mated queens will have a greater incentive to bias the sex ratio towards females than those in colonies with multiple-mated queens. However, the ESS sex ratio depends on the relative abundance of single- and multiple-mated queens within the total population. In general, selection will favour workers with single-mated queens producing wholly or largely females, and those with multiple-mated queens producing wholly or largely males.

Several experimental studies support Boomsma and Grafen's ideas, the most impressive to date being Sundstrom's[40,41] four-year study of the ant Formica *6uncomm* in Finland. In one population, nests contain one queen (monogyne colonies) but the queen may be mated once, twice or three times (determined by allozyme studies). Colonies with single-mated queens produced all female or female-biased sex ratios, while those whose queens had mated more often produced all males or male-biased sex ratios. In a second population, nests contained several queens (polygyne colonies). Queens in the same nest were normally related and mated more than once, and there was little variation in relatedness across colonies. As expected, split sex ratios were not found in this population. Polygyne colonies did tend to have a male-biased sex ratio, which Sundstrom argues is probably caused by local resource competition among females. Sundstrom's work provides evidence for worker control and the ability of workers to assess the genetic makeup of the colony. How the latter is achieved has yet to be determined.

Is it possible that multiple mating by queens may be a reproductive strategy to favour worker production of more balanced sex ratios? A few social insects, honeybees in particular, mate a large number of times and Queller[42] has argued that this might be the end point of an arms race in which queens and workers successively adjust their mating frequency and sex allocation strategies. Recent theoretical studies also suggest that the two traits may coevolve[43].

Other mechanisms could lead to split sex ratios in social insects, among them the occurrence of cytoplasmic sex ratio microorganisms. This possibility has not been widely investigated in the social Hymenoptera, although it is known to occur in other hymenopterans[9]. Another aspect of hymenopteran biology that may influence sex allocation is the production of diploid males[44]. Although males are typically haploid, many hymenopterans have a single sex-determining locus, in which homozygous or hemizygous (i.e. haploid) individuals develop into males, whereas heterozygous individuals develop into females. Diploid males are typically sterile and occur when an egg and a sperm carrying the same sex allele fuse. The fire ant *(Solenopsis inuicta)* has both multi-queen colony and single-queen colony races. Ross and colleagues[45,46] have shown that diploid males occur during incipient colony formation in both types. Colonies with single queens that produce diploid males (in place of female workers) fail to survive. However, in multi-queen colonies, the production of diploid males by some queens is not always fatal for the colony. Therefore, avoidance of diploid male production may be another factor selecting for multiple mating by queens.

Conclusion

Studies of sex allocation in animals and plants (which as zoologists we have shamefully ignored) provide a compelling argument for the value of modern evolutionary ecology in explaining complex adaptations. We suspect that the near future will see a continuing expansion of the subject into the investigation of sex allocation in previous unstudied groups of organisms, as well as further interest in conflict over the sex ratio. At the moment, most studies of sex ratio involve the qualitative testing of the predictions of rather general theory with specific organisms. An exciting prospect is that our growing understanding of the physiology and genetics underlying sex allocation and sex determination will allow us to build more specific models that are tailored to individual species, and to test their predictions quantitatively.

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Sex-determining mechanisms in animals

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Biological mechanisms leading to the development of males and females are extremely varied. In the XX/XY system, the male has an unequal pair of chromosomes, while in the_ZZ/ZW system, the unequal pair is in the female. Sex can also be determined by the temperature of incubation. Recent research has focused on the identification of sex-determining genes, culminating in the demonstration that the *Sry* gene on the Y chromosome of mice can induce male development in genetically female XX mouse embryos. Nevertheless, the occurrence of phenotypes in apparent contrast to the genotype suggests that the genetic male/female switch is not simple, and there may be common features linking different sex-determining mechanisms. There is increasing evidence that such a link may be provided by the induction of growth differences, and that the primary sex difference may result from the distinction between fast versus slow growth.

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The process of sexual reproduction in all multicellular animals begins with the coming together of two specialized germ cells - a large immotile egg (formed in the ovary), and a small germ cell capable of movement, the sperm or spermatozoon (formed in the testis). In most animals, ovaries and testes develop in separate individuals, known, respectively, as females and males.

Since the division of the sexes is fundamentally so similar throughout the animal kingdom, one might have thought that the mechanism that causes their divergence would have been stabilized at an early stage of evolution. In fact, the opposite has occurred, so that we are confronted with an almost embarrassing variety of sex-determining mechanisms (Table 1).

In mammals, males have an unequal pair of sex chromosomes, a larger X and a smaller Y chromosome, but in birds, the unequal pair is present in females and is referred to as ZW, whereas male birds have two Z chromosomes. In the other vertebrate taxa, both XY and ZW mechanisms are found. Also, there are some other species of reptiles that do not have sex chromosomes at all; instead, sex is determined by the temperature of incubationl[2]. In the fruitfly *(Drosophila melanogaster),* males are XY and females XX, but the mechanism of sex determination differs in detail from that of mammals[2], while in Lepidoptera, females are ZW and males ZZ.

Because of its historical importance as well as its. present-day interest, I shall begin by taking a brief look at the system operating in *Drosophila.*

Sex determination in *Drosophila*

The foundations of our present-day understanding of sex determination were firmly laid in the first quarter of the present century, with *Drosophila melanogaster* playing a leading role. The phenotype of the first mutant - a male with white eyes - was found to be due to a gene on the X chromosome, of which females have two and males only one[3]. Further breeding and cytological results revealed that XXY flies are fertile females, while so-called `XO' flies, with a single X and no Y chromosome, are male, albeit sterile[4], ruling out the possibility that the Y chromosome in *Drosophila* might have a male-determining function. Bridges[5] proposed that the sex of flies is determined by the ratio of the number of X chromosomes to that of autosomes, and