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Malaria Parasites and Sex Ratios

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I've been much delayed, since I am starting to work seriously on my dissertation. This sucks up an amazing amount of brainpower. Initially I was planning on delaying this post another day, but have now been fortified with a BLT (heavy on the bacon) and am ready to tackle the topic. It is one that interests me because it combines two fascinating topics, malaria and sex ratios.

Malaria is a disease caused by protozoan parasites in the genus *Plasmodium*. They are unusual in possessing an organelle called the apicoplast, a degenerated plastid captured from some point in the past from a plant cell, probably a dinoflagellate. This is interesting because plastids themselves probably originated from cyanobacteria that were captured by a eukaryote ancestral to the plants sometime in the Precambrian. The apicoplast could prove a useful drug target, since it is derived from plants, and selectively targeting its biosynthetic routes should interfere little with host cell processes.

Plasmodium parasites complete part of their lifecyle in a vertebrate host, but require an insect vector to complete the lifecycle. Asexual reproduction takes place in the vertebrate host, with an initial round of replication in the liver cells immediately following infection. Schizonts in the liver cells divide into multiple merozoites, which are released and infect red blood cells. Here the organism passes through a trophozoite stage, degrading the host erythrocyte's hemoglobin to harvest valuable amino acids. The reactive heme core is trapped in polymeric hemozoin to prevent oxidative damage to the parasite. Once it has grown enough, the trophozoite matures to a schizont, divides multiple times to produce merozoite offspring, and the erythrocyte ruptures. The maturation of the parasites in red blood cells is often coordinated and periodic, and leads to the cyclical fevers of malaria when high loads of merozoites are repeatedly dumped into the bloodstream.

The asexual lifecycle is a good mechanism for building up large numbers of the parasites in the host, but in order to travel to a new host, the parasite needs to undergo sexual reproduction. At the trophozoite stage many parasites go on to the asexual lifecycle, but some differentiate to gametocytes, which are infective to the mosquito host when ingested (unlike the asexual stages). The sex of these gametocytes is determined by environmental cues, and the sex ratio can vary widely. If the gametocyte

is female, it produces a single gamete, but the male gametocytes can produce up to eight gametes. If the usual 50/50 sex ratio that we are most familiar with is preserved, this would lead to a huge excess of male gametes! Instead, the sex ratio tends to be biased towards females.

Sex ratios are a popular topic in evolutionary biology, and are generally well understood. While *Plasmodium* and other apicomplexan parasites often behave as predicted by theory, there are many examples of unusual findings. For instance, Hamilton's theory of local mate competition says that when multiple unrelated strains are present, there should be selection for a higher proportion of males. Each male can fertilize multiple females, so producing males preferentially should propagate that genotype most efficiently at the expense of the unrelated genotypes. However, when only one genotype is present, the genotype would be competing with itself and selection for a more balanced sex ratio should result. Using local mate competition theory we can calculate the ideal sex ratio for a population of malaria parasites.

In their new *Nature* paper, Reece, Drew, and Gardner point out several observations from *Plasmodium* and other apicomplexans that are contrary to theory:

1. In some related avian apicomplexan parasites, sex ratios do not correlate with genetic diversity of an infection, and the ratio of females is consistently less than expected.
2. Over the course of an infection sex ratio can vary dramatically, and local mate competition theory does not explain this.
3. The ability of *Plasmodium* to alter sex ratios in response to host anemia shows local mate competition theory does not completely explain sex ratio.
4. A clonal line's sex ratio does not appear to influence success in transmitting to the insect host.

In light of these observations, they decided to directly test the influence of sex ratio upon breeding success, and the influence of different variables upon sex ratio. The first experiment was a rather nifty assay involving two genetically modified *Plasmodium berghei* strains. One was incapable of producing viable female gametes, the other incapable of producing viable male gametes. By combining the two strains in different proportions they could directly control the male to female sex ratio of the population. The ookinetes produced could then be counted to determine reproductive success. They discovered that sex ratio was indeed female-biased, as predicted by theory, but that the males did not maximize their potential reproductive fitness. While capable of producing eight gametes, most males only produced two gametes, perhaps due to host immune response. This helps to explain why the sex ratio is not as female-biased as would be expected.

The next experiments used several clonal lines of *Plasmodium chabaudi* in mice. Six clonal lines were isolated and cultured, and the authors discovered that sex ratio varied over the course of infection for all. Three followed a similar pattern, but the other three showed their own unique time-course of sex ratios. This demonstrates genetic influence upon sex ratio in different strains, possibly adaptive variation. They discovered also that sex ratio is related to the level of anemia in the host. This is consistent with previous observations and with predictions. A female-biased sex ratio in combination with anemia in the host could lead to too few males being ingested by the insect vector to fertilize all of the females ingested. Thus, selection should favor tilting the sex ratio towards more males in the presence of host anemia. This was consistently shown to be true.

The high point of the paper is probably the studies of coinfection of mice with multiple *Plasmodium* strains. This is where local mate competition theory was directly tested. When strains were studied individually in a host, the sex ratio should be heavily female-skewed. However, when multiple strains are present, local mate competition theory predicts that more males will be produced. Exactly this pattern was observed, with a single-genotype infection sex ratio of about 15% males compared to a

six-genotype infection sex ratio of about 44% males just before parasite load peak. Reece and coworkers also did a similar study with only two competing strains. With two out of three combinations a significant difference in sex ratio was observed, but it is not clear why the third strain did not modify sex ratio in response to co-infection. This strain was the least virulent, so there may be factors related to virulence and reproductive strategies that remain to be examined.

The pattern of sex ratios in apicomplexan parasites has been often confounding, and this paper helps to illuminate some of the reasons for apparent contradictions. While following the same general trends, sex ratio in different clonal lines is subject to genetic variation. Environmental factors such as anemia and host immune response can also influence sex ratio. When these factors are taken into account, the response of *Plasmodium* parasites to clonal and mixed infection is consistent with local mate competition theory. It is still unknown how the parasites determine their level of relatedness to other malaria parasites in the bloodstream, and this is an intriguing direction for future research.

Reece, S.E., Drew, D.R., Gardner, A. (2008). Sex ratio adjustment and kin discrimination in malaria parasites. *Nature, 453*(7195), 609-614. DOI: 10.1038/nature06954

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