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Evolutionary implications for the determination of gametocyte sex ratios under fecundity variation for the malaria parasite

Miranda I. Teboh-Ewungkem [a,*], Thomas Yuster [b]

[a] Department of Mathematics, Lehigh University, Bethlehem, PA 18015, USA
[b] Department of Mathematics, Lafayette College, Easton, PA 18042, USA

HIGHLIGHTS

- We investigate sex ratio determination based on putative changes in male fecundity.
- We investigate how sex ratio choice strategies might have evolved.
- Changes are investigated over the lifetime of a malaria infection.
- The Self-Knowledge Model (SKM) yields a unique ESS that was unbeatable.
- The Dual Knowledge Model (DKM) yields a unique ESS, but not every ESS was unbeatable.

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ABSTRACT

We investigate sex ratio determination strategies for the Malaria parasite based on putative changes in its male fecundity over the lifetime of an infection, and how such strategies might have evolved. We model fitness using the incomplete fertilization limit developed in Teboh-Ewungkem and Yuster (2010). We divide the infection lifetime of a strain into two periods, assume each human is infected by two different strains, and assume that there are two different strategies present among the many strains in the general malaria parasite population. A unique parameter dependent ESS exists for all parameter values in both of our main models, with many such strategies unbeatable. These strategies produce both male and female biased population sex ratios with female bias predominating over most of the parameter space. The first model (SKM) suggests that strains without the ability to detect characteristics of other strains present could still have evolved strategies to vary sex ratio over their lifetimes, and the second model (DKM) suggests strains with detection abilities might have evolved after that. Our analysis suggests that once the ability to detect the population sizes and fecundities of other strains has developed, detection of their sex ratio choices confers no additional selective advantage in that a DKM ESS is still an ESS among sex ratio detecting strategies. The sex ratio choices for each DKM ESS are given by the equilibrium values of the parameter equivalent sex ratio detecting strategy described in Teboh-Ewungkem and Wang (2012), in the case where two strains employing that strategy encounter each other.

1. Introduction

Malaria is still a major burden in many regions in the world, and especially in Africa. According to the recent WHO report (2014 data), there were an estimated 198 million malaria cases worldwide, resulting in an estimated 584,000 malaria deaths (World Health Organization, 2015) in 2013. With increased research and measures applied towards malaria prevention and control, the malaria burden has been declining over the years (World Health Organization, 2015). The *Plasmodium* parasite, the agent that causes malaria, has developed mechanisms to ensure its success over many generations. It relies on both a human host and a mosquito vector to successfully complete its life cycle, in the process killing far too many humans, especially children (World Health Organization, 2015). The ability of the parasite to succeed in spreading from one human to another over its long history can in part be attributed to the parasite's sophisticated reproductive mechanism that can adapt when conditions warrant (Reece et al., 2008; Teboh-Ewungkem and Wang, 2012).

Plasmodium parasites replicate asexually as haploid cells within the vertebrate host (humans). Developing through an intriguing

* Corresponding author.
E-mail addresses: mit703@lehigh.edu (M.I. Teboh-Ewungkem), yustert@lafayette.edu (T. Yuster).

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process, gametocytogenesis, a single haploid cell eventually produces both male and female gametocytes through a cyclic process that occurs multiple times over the course of an infection (Baker, 2010; Talman et al., 2004). These sexual forms, the male and female gametocytes, are the transmissible forms of the parasite from humans to mosquitoes (Baton and Ranford-Cartwright, 2005; Carter et al., 1988). In a mosquito's gut, ingested gametocytes undergo gametogenesis, whereby a female gametocyte gives rise to a single female gamete while a male gametocyte can release up to eight viable male gametes. Random mating is assumed to occur rapidly between male and female gametes, leading to the formation of diploid zygotes. Zygotes transform to eventually become oocysts, and oocysts mature undergoing the process of sporogony, leading to the release of haploid sporozoites that migrate to the mosquito's salivary glands (Baton and Ranford-Cartwright, 2005; Teboh-Ewungkem and Yuster, 2010). Salivary glands sporozoites are the transmissible forms of the parasite from mosquitoes to humans.

A way that *Plasmodium* parasites can increase their chances of successfully being transmitted from a mosquito to a human is through optimizing the fertilization process. Fertilization may lead to the production of many zygotes which increases the chances of the production of at least one oocyst. A crucial factor in the mechanism of fertilization and thus the ultimate success of the malaria parasite is the ratio of male and female gametocytes, known as the gametocyte sex ratio. Therefore, understanding how gametocyte sex ratios are modulated in a malaria parasite population is important.

Variation in gametocyte sex ratios for the human malaria parasite has been a topic of interest to researchers, both in the past and currently (Gardner et al., 2003; Read et al., 1992; Reece et al., 2008; Schall, 2009; Teboh-Ewungkem and Wang, 2012; West et al., 2002). Studies have reported sex ratios for the human malaria parasite ranging from highly female-bias to a slight male-bias (Gardner et al., 2003; Read et al., 1992; Reece et al., 2008; Schall, 2009; Teboh-Ewungkem and Yuster, 2010; Teboh-Ewungkem and Wang, 2012; West et al., 2002). The observed female-bias sex ratios have been explained using classical sex ratio strategies under complete fertilization (Godfray and Werren, 1996; Nee et al., 2002; Paul et al., 2000; Read et al., 1992), and extended to explain the less female-biased sex ratios when gametocyte density and male gametocyte fecundity are low (Gardner et al., 2003; West et al., 2002). Teboh-Ewungkem and Yuster (2010) showed that incomplete fertilization (indicating that most gametocytes, and thus gametes, are not involved in the successfully production of zygotes) had implications for sex ratio determination. Their model predicted a one-to-one sex ratio ($m=0.5$) in the incomplete fertilization limit when competing gametocyte populations had equal male fecundity. The effect of fecundity variation on sex ratio was later investigated in Teboh-Ewungkem and Wang (2012) under the incomplete fertilization limit. Using a two strain, single encounter model based on maximizing the numbers of genes in the next generation, Teboh-Ewungkem and Wang (2012) calculated optimal sex ratios for the two plasmodia strains during this encounter, based on the relative male fecundities and populations sizes of those strains. The resulting total population sex ratios were calculated over a large range of relative fecundities and population sizes, producing population sex ratios that varied from highly female-bias to a slight male-bias. It was suggested in Teboh-Ewungkem and Wang (2012), that the single encounter optimal sex ratio choices given by their model might comprise an optimal strategy when extended to the entirety of an infection, i.e. the strain lifetime. In this paper, that claim is investigated. Specifically, the questions of what optimal lifetime sex ratio strategies are and of how such strategies might have evolved are addressed.

In Teboh-Ewungkem and Wang (2012), sex ratio determination was based on a single fixed time encounter between two strains with no consideration of optimization over the lifetime of a strain. A strain chose a sex ratio based on knowledge of the relative sizes and fecundities of the two strains, as well as knowledge of the sex ratio choice of the other strain. In this paper, we construct relatively simple models that contain some of the basic elements necessary to understand sex ratio optimization over a strain's lifetime. The models, termed the Self-Knowledge Model (SKM) and Dual-Knowledge Model (DKM), split parasite lifetime into two stages based on the age of the parasite, and restrict the information the parasite has when determining its sex ratio. The stages are referred to as the early period and the late period, and we assume that early period gametocytes are more fecund than late period gametocytes. We determine optimal strategies under those model assumptions, and use those results to consider the evolution of sex ratio strategies. Our results suggest that the claim by Teboh-Ewungkem and Wang (2012) was correct in a limited context and that there is a plausible path for strains to evolve strategies very similar to those they described.

The paper is subdivided as follows: in Section 2, we define terminologies and state the model assumptions, while in Section 3, we present the mathematical models, describing the Self-Knowledge Model and the Dual-Knowledge Model. We then discuss general sex ratio dependent strategies in Section 4. Section 5 contains the discussion and the conclusions. Many technical detail can be found in the appendices.

2. Definitions and assumptions

In this paper, we will study possible strategies for sex ratio determination that strains of plasmodia may employ over their lifetimes and the relative fitnesses of those strategies. To do so, we need to be precise concerning our definitions and model assumptions.

Definition 1. A *strain* of plasmodia is a collection of genetically identical members.

Definition 2. The *fecundity* of a strain is the average number of viable male gametes produced by a male gametocyte of that strain. Fecundity can vary for a strain over the lifetime of an infection.

Definition 3. The *relative fecundity* of two populations of gametocytes is the ratio of the fecundities for each. Relative fecundity can be calculated for a single strain at two different points in its lifetime.

Definition 4. The *sex ratio* of a strain is the ratio of male gametocytes to all gametocytes for the strain, and can vary over the lifetime of an infection.

Definition 5. The *fitness* of a strain is the average number of sets of genes per gametocyte that make it into the next generation. We will calculate this number under the assumptions of the incomplete fertilization limit model developed in Teboh-Ewungkem and Wang (2012). The fitness of a strain is calculated over the lifetimes of all infections involving that strain.

Definition 6. A *strategy* is a time dependent sex ratio choice employed by a gametocyte strain over its lifetime. The sex ratio choice may vary over the lifetime of a strain and is dependent on the strain's characteristics and the characteristics of other strains present, such as relative sizes, fecundities, and the sex ratio choices of the other strains encountered. Although a strategy is constant across a strain, different strains may employ the same strategy.

Definition 7. An *unbeatable strategy* is an evolutionary stable strategy (ESS) that cannot be successfully invaded by any other