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Even more extreme fertility insurance and the sex ratios of protozoan blood parasites

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Abstract

Theory developed for malaria and other protozoan parasites predicts that the evolutionarily stable gametocyte sex ratio (z^*; proportion of gametocytes that are male) should be related to the inbreeding rate (f) by the equation $z^* = (1-f)/2$. Although this equation has been applied with some success, it has been suggested that in some cases a less female biased sex ratio can be favoured to ensure female gametes are fertilized. Such fertility insurance can arise in response to two factors: (i) low numbers of gametes produced per gametocyte and (ii) the gametes of only a limited number of gametocytes being able to interact. However, previous theoretical studies have considered the influence of these two forms of fertility insurance separately. We use a stochastic analytical model to address this problem, and examine the consequences of when these two types of fertility insurance are allowed to occur simultaneously. Our results show that interactions between the two types of fertility insurance reduce the extent of female bias predicted in the sex ratio, suggesting that fertility insurance may be more important than has previously been assumed.

Keywords: Fertility insurance; Local mate competition; Malaria; Sex allocation; Stochastic model

1. Introduction

One of the many successful applications of sex allocation theory has been the study of how competition for mates between related males can favour the evolution of female biased sex ratios (Charnov, 1982; Godfray, 1994; Hamilton, 1967; West et al., 2000a, b). Recent years have seen an increasing interest in applying this theory (local mate competition; LMC) to malaria and related protozoan parasites (Read et al., 2002; West et al., 2001). Here, the appropriate prediction is that the evolutionarily stable (ES; Maynard Smith, 1982) gametocyte sex ratio (z^*; proportion of gametocytes that are male) should be related to the inbreeding rate (f) by the equation $z^* = (1-f)/2$ (Hamilton, 1967; Nee et al., 2002; Read et al., 1992). When there is complete inbreeding ($f = 1$; i.e. a single lineage or clone is selfing), the ES strategy is to produce the minimum number of males required to fertilize the available female gametes and thus, maximize the number of zygotes. Conversely, when gametes in the mating pool are of a mixture of lineages, f decreases and the sex ratio increases in order for each lineage to maximize its genetic representation in the zygote population. The relationship between the inbreeding rate and sex ratio has been able to explain a number of sex ratio patterns in Apicomplexan parasite populations (reviewed by West et al., 2001; Read et al., 2002). However, there are a number of observations that cannot be explained by this equation. In particular: (1) across *Haemoproteus* populations in birds the sex ratio does not correlate with an expected correlate of the inbreeding rate (prevalance; Shutler et al., 1995; Shutler and Read, 1998); (2) in malaria parasites, sex ratios within and between infections can be extremely variable (Osgood et al., 2002; Paul et al., 1999, 2000, 2002; Pickering et al. 2000; Schall, 1989; Taylor, 1997), and less female biased sex ratios can lead to greater transmission success (Robert et al., 1996).

A potential explanation for these contradictory observations is "fertility insurance"—the production of a less female biased sex ratio to ensure that all female gametes are fertilized (West et al., 2002). Before describing how fertility insurance can influence the ES sex ratio it is necessary to describe the background

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biology. In malaria and related Haemospororin parasites, haploid sexual stages (gametocytes) are taken up from the host in the blood meal of a vector. Once inside the midgut, the haploid gametocytes differentiate into haploid gametes and fuse to form zygotes. These resulting diploid zygotes undergo meiosis and asexual proliferation before migrating to the vector's salivary glands where they wait to enter a new vertebrate host. Each female gametocyte (macro-gametocyte) will differentiate into 1 female gamete, whereas each male gametocyte (micro-gametocyte) will produce several motile male gametes. The number of viable gametes produced per male gametocyte varies enormously across species—4–8 in mammalian malaria parasites (Read et al., 1992); ~ 2 in some lizard malarias (Schall, 2000); 5–>1000 in *Eimeriorin* intestinal parasites (West et al., 2000a, b).

Fertility insurance can occur for two broad reasons—which are summarized here but discussed more fully in West et al. (2002). First, the number of male gametes produced per gametocyte (c) may be a limiting factor (Read et al., 1992). If the mean number of viable gametes produced per male gametocyte is c, then the ES sex ratio must be $z^* \geqslant 1/(c+1)$, otherwise there will not be enough male gametes to fertilize the female gametes (Fig. 1A; Read et al., 1992). Second, the ability of gametes to interact may be a limiting factor. West et al. (2002) investigated this possibility by assuming that the number of gametocytes whose gametes can interact (q) is restricted. In this case a less female biased sex ratio is favoured to avoid the stochastic absence of males in a mating group of q gametocytes (Fig. 1B; West et al., 2002). A low q could occur for a number of reasons including low male gamete motility, high gametocyte or gamete mortality, low gametocyte density, or small blood meals (Shutler and Read, 1998; Paul et al., 1999, 2000, 2002; Reece and Read, 2000; West et al., 2001, 2002). Recent attention has focused on how the host immune response may influence and vary the importance of these factors (Paul et al., 1999, 2000, 2002; Reece and Read, 2000).

In order to make their analyses mathematically tractable, previous studies have considered the influence of these two forms of fertility insurance separately. When examining the influence of male gametocyte fecundity (c), Read et al. (1992) assumed that the gametes from an infinite pool of gametocytes can interact ($q = \infty$), and when examining the influence of the number of gametocytes whose gametes can interact (q), West et al. (2002) assumed that male gamete fecundity was not a limiting factor ($c = \infty$; i.e. one male gametocyte is able to provide enough gametes to fertilize all of the female gametes in its mating group arising from q gametocytes). It has subsequently been assumed that the overall effect of these two factors can be examined by seeing which is more constraining, and

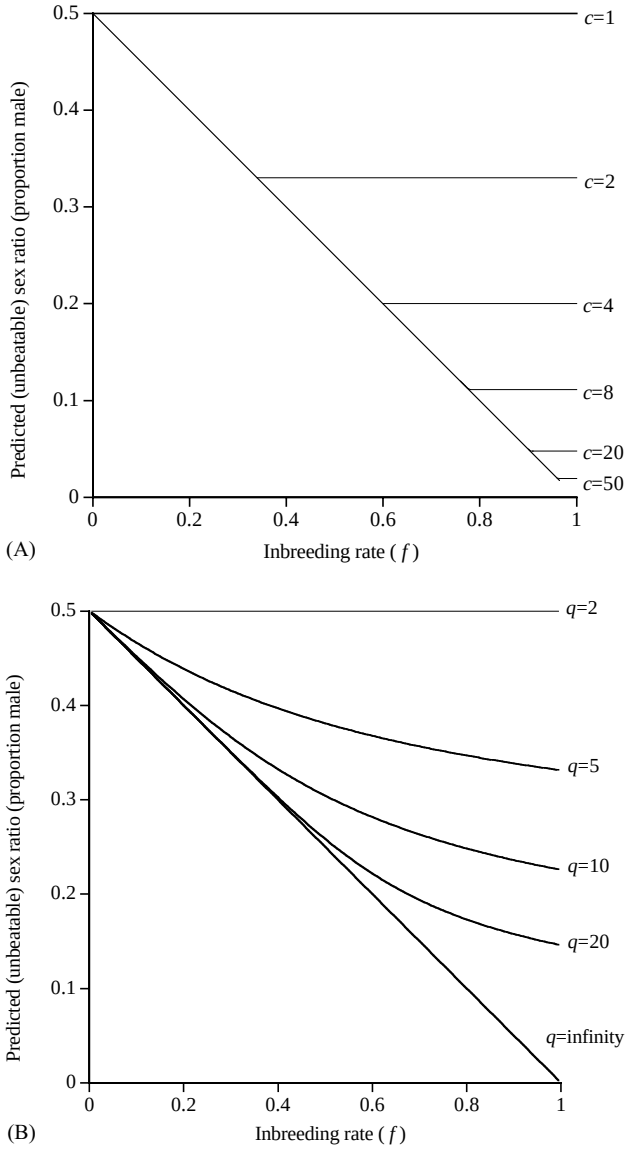

Fig. 1. The relationship between the predicted unbeatable sex ratio (proportion of gametocytes that are male; z^*) and the inbreeding rate (f). (A) Unbeatable sex ratio when the number of gametes produced by each male gametocyte (c) varies and gametes from all gametocytes in a very large group can interact ($q \to \infty$; Read et al. 1992). (B) Unbeatable sex ratio when the number of gametocytes whose gametes can interact (q) is limited and the number of gametes produced by each male gametocyte (c) is not limiting (West et al., 2002).

favours the least female biased sex ratio (West et al., 2002). However, there is the possibility that these factors may interact—when both c and q are low, even if there are males in a mating group, these males may not be able to provide enough gametes to fertilize all the female gametes. Although this scenario could logically occur, it is not clear whether this interaction will significantly influence the ES sex ratio. We use a stochastic analytical model to address this problem and consider how the unbeatable sex ratio is influenced by the interaction of finite values for both c and q. We use life history

terminology associated with malaria parasites, but our results are applicable to any Apicomplexan parasite with dimorphic sexual stages.

2. Methods

We consider an infinite population of vertebrates harbouring malaria parasites and supporting an infinite number of blood-feeding dipteran vectors (effects due to finite numbers of vertebrate hosts is negligible unless the number of hosts are extremely small; Taylor and Bulmer, 1980). Every host contains an infinite pool of haploid gametocytes circulating in the peripheral blood, comprising n independent lineages (all notation is given in Table 1). Within a lineage, all gametocytes are clonally derived from a single sporozoite founder individual. Each lineage produces a proportion z of male gametocytes and $1-z$ of female gametocytes, where z is determined by a single biallelic nuclear gene. A common 'Null' allele exists at frequency $1-m$ and has $z=z_N$, and an infinitely rare 'Mutant' allele exists at frequency m and has $z=z_M$. We may assign each infected host individual to one of $n+1$ classes on the basis of the number of Mutant lineages carried. Each host is fed upon by a large number of vectors, transmitting q gametocytes to each vector in the process. Once in the midgut of the vector, each male gametocyte gives rise to c male gametes and female gametocytes each give rise to a single female gamete. Random syngamy ensues, and the resulting next generation of zygotes are, following Read et al. (1992), assumed to reflect the genetic composition of the next generation of infections. It is worth noting that although each vector contains a single mating group of size q the predictions of this analysis will hold for any number of such groups, provided that there is no exchange of gametes between mating groups.

Table 1
Definition of each parameter/variable referred to in the methods and appendix

Symbol	Definition
$Bi(k,\pi)$	Binomial distribution: k trials and probability of success π
C	Number of viable male gametes per male gametocyte
F	Inbreeding coefficient; $f=n^{-1}$
g_X	Number of X-allele male gametes remaining viable
$HypGeo(\alpha,\beta,\gamma)$	Hypergeometric distribution: α trials, and β potential successes out of γ
M	The Mutant allele
M	Population frequency of the mutant
N	The Null allele
N	Number of independent lineages per vertebrate host
P	Probability of male gamete survival
Q	Number of gametocytes whose gametes can interact in the vector
$S_{X,y}$	Success of the X-allele in a host containing y Mutant infections
w_X	Absolute fitness of the X-allele
Z	Sex ratio (proportion male gametocytes per lineage)
z^*	Evolutionarily stable (ES) sex ratio
z_X	Sex ratio employed by the X-allele
χ	Species-specific number of gametes released per male gametocyte
ϕ_X	Number of X-allele females in a mating group
μ_X	Number of X-allele males in a mating group
τ_X	Total number of X-allele gametocytes in a mating group
$\varpi_{X,y}$	Frequency of X-alleles in successful male ($y=1$) or female ($y=0$) gametes
ω	Relative fitness of the Null, w_N/w_M; Mutant invades if $\omega<1$
ζ	Number of zygotes produced by the mating group

The fitness of the Null is the mean success of a Null lineage from each host-class weighted by the number of Null lineages in the host-class and the frequency of that host-class. As the mutant is infinitely rare, so that $m\to 0$, the fitness of the Null is dominated by its success in vectors feeding upon hosts containing no Mutant lineages

$$w_N \approx \frac{1}{n} S_{N,0} = f\, S_{N,0}, \tag{1}$$

where $S_{N,0}$ is the mean number of zygotic Null alleles produced per vector feeding on a host harbouring zero Mutant lineages, and f is the degree of inbreeding. The Mutant never occurs in such hosts, and almost never occurs in hosts with other Mutant lineages, so its fitness is dominated by its success in vectors feeding upon hosts with 1 Mutant lineage and $n-1$ Null lineages

$$w_M \approx S_{M,1}, \tag{2}$$

where $S_{M,1}$ is the mean number of zygotic Mutant alleles derived from a vector feeding on a host containing one Mutant infection only. The Mutant invades if $w_M > w_N$ and so the ES sex ratio z^* is the value of z_N, such that $\omega = w_N/w_M$ is not less than unity for all $0\leqslant z_M \leqslant 1$. Exact solutions for $S_{N,0}$ and $S_{M,1}$ will be determined, so that for known q, c and f pairs of sex ratio strategies may be compared.

A vector feeding on a Null-only host is assured of obtaining q Null gametocytes in its bloodmeal. $\mu_N \sim Bi(q, z_N,)$ are male, and the remaining $\phi_N = q-\mu_N$ are female, so that there are $c\mu_N$ male gametes and ϕ_N female gametes able to interact in the midgut. The number of zygotes, ζ, is the smaller of these two values, and since zygotes are diploid the number of Null alleles formed in that vector is 2ζ:

$$S_{N,0} = \sum_{\mu_N=0}^{q} \binom{q}{\mu_N} z_N^{\mu_N}(1-z_N)^{q-\mu_N} 2\min\{c\mu_N, q-\mu_N\}. \tag{3}$$

A vector feeding on a host containing 1 Mutant and $n-1$ Null lineages will obtain q gametocytes of which $\tau_M \sim Bi(q,f)$ are Mutant and $\tau_N = q - \tau_M$ are Null. These will comprise $\mu_M \sim Bi(\tau_M, z_M)$ Mutant males and $\phi_M = \tau_M - \mu_M$ Mutant females, and $\mu_N \sim Bi(\tau_N, z_N)$ Null males and $\phi_N = \tau_N - \mu_N$ Null females. The number of zygotes, ζ, is then the lower of the two values $c(\mu_M + \mu_N)$ and $\phi_M + \phi_N$, meaning that there are ζ successful male gametes and ζ successful female gametes. Of the former, a proportion $\varpi_{M,1} \sim HypGeo(\zeta, c\mu_M, c(\mu_M + \mu_N))/\zeta$ will be Mutant, and of the latter a proportion $\varpi_{M,0} \sim HypGeo(\zeta, \phi_M, \phi_M + \phi_N)/\zeta$ will be Mutant. The success of the Mutant is simply $\zeta(\varpi_{M,1} + \varpi_{M,0})$ (Taylor, 1981; Charnov, 1982), i.e.:

$$S_{M,1} = \sum_{\tau_M=0}^{q} \sum_{\mu_M=0}^{\tau_M} \sum_{\mu_N=0}^{q-\tau_M} \binom{q}{\tau_M} f^{\tau_M} (1-f)^{q-\tau_M} \binom{\tau_M}{\mu_M} z_M^{\mu_M} (1-z_M)^{\tau_M-\mu_M} \binom{q-\tau_M}{\mu_N} z_N^{\mu_N} (1-z_N)^{q-\tau_M-\mu_N} \min\{c(\mu_M+\mu_N), q-\mu_M-\mu_N\} (E[\varpi_{M,1}] + E[\varpi_{M,0}]), \quad (4a)$$

where

$$E[\varpi_{M,1}] = \begin{cases} \dfrac{\mu_M}{\mu_M+\mu_N} & \text{if} \quad \mu_M+\mu_N > 0, \\ 0 & \mu_M+\mu_N = 0, \end{cases} \quad (4b)$$

$$E[\varpi_{M,0}] = \begin{cases} \dfrac{\tau_M-\mu_M}{q-\mu_M-\mu_N} & \text{if} \quad q-\mu_M-\mu_N > 0, \\ 0 & q-\mu_M-\mu_N = 0. \end{cases} \quad (4c)$$

These expressions reveal whether the Mutant allele can invade a population fixed for the Null. We determined the ES sex ratio iteratively, such that the value of z_N in each round is the sex ratio of the successfully invading Mutant or successfully defending Null of the previous round, and z_M is a randomly assigned value. After an indefinite number of rounds the Null will assume and subsequently retain the value of z^*, so that at any time the currently unbeaten z can be tested for evolutionary stability by plotting ω for z_N equal to the putative z^* against all $0 \leqslant z_M \leqslant 1$ and rejecting if $\omega < 1$ for any z_M.

To check our expressions, we derived Eqs. (3) and (4) for the special cases where q or c are infinite, i.e. corresponding to the analyses of Read et al. (1992) and West et al. (2002). These equations are presented in the appendix, and in all cases gave the same results as the previous analyses.

3. Results and discussion

We have discriminated between two types of fertility insurance, in response to: (i) low male gamete fertility (low c), and (ii) the ability of gametes to interact (low q). Previous theoretical work has examined the effect of these two types of fertility insurance separately. Specifically, West et al. (2002) assumed that when both of these factors are operating, the effect for sex ratio evolution can be determined by seeing which leads to a greater reduction in the predicted female bias (i.e. which of Figs. 1A and B predicts the least female biased sex ratio). In contrast, our model explicitly allows for both types of fertility insurance to act simultaneously, and hence allows for any interactions. In Figs. 2–4 we give

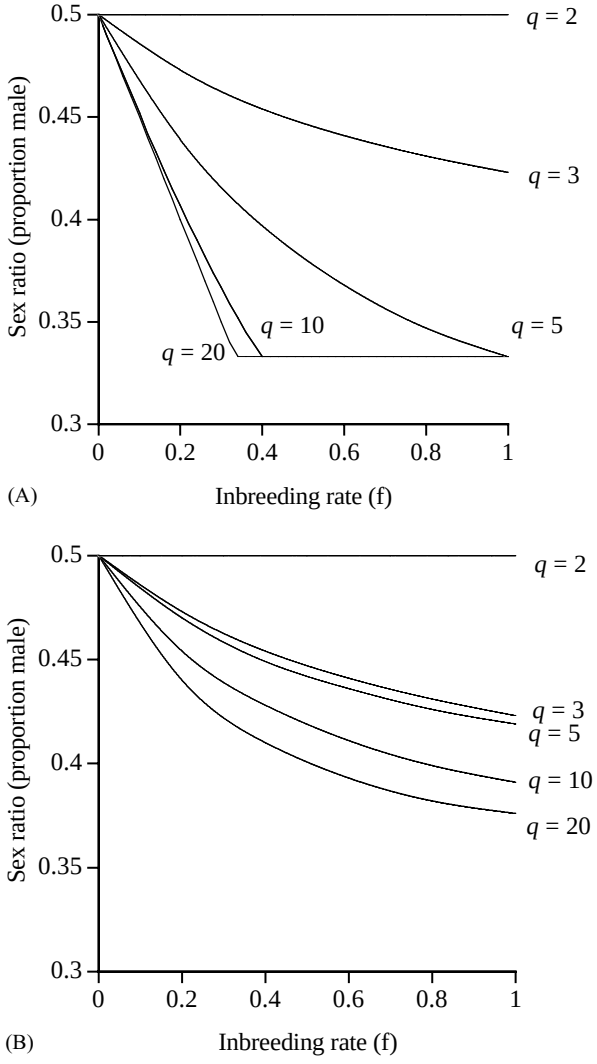

Fig. 2. (A) Relationship between predicted sex ratio and inbreeding rate, for given values of q when $c = 2$ assuming no interaction between the two types of fertility insurance and (B) relationship between ES sex ratio and inbreeding rate arising from Eqs. (1)–(4), for given values of q when $c = 2$.

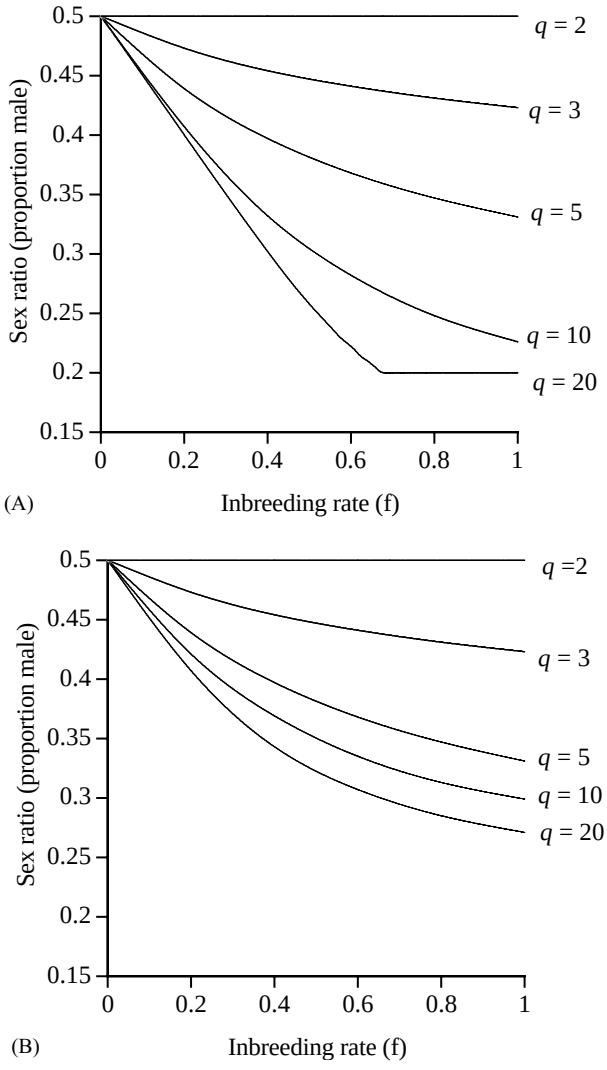

Fig. 3. (A) Relationship between predicted sex ratio and inbreeding rate, for given values of q when $c = 4$ assuming no interaction between the two types of fertility insurance and (B) Relationship between ES sex ratio and inbreeding rate arising from Eqs. (1)–(4), for given values of q when $c = 4$.

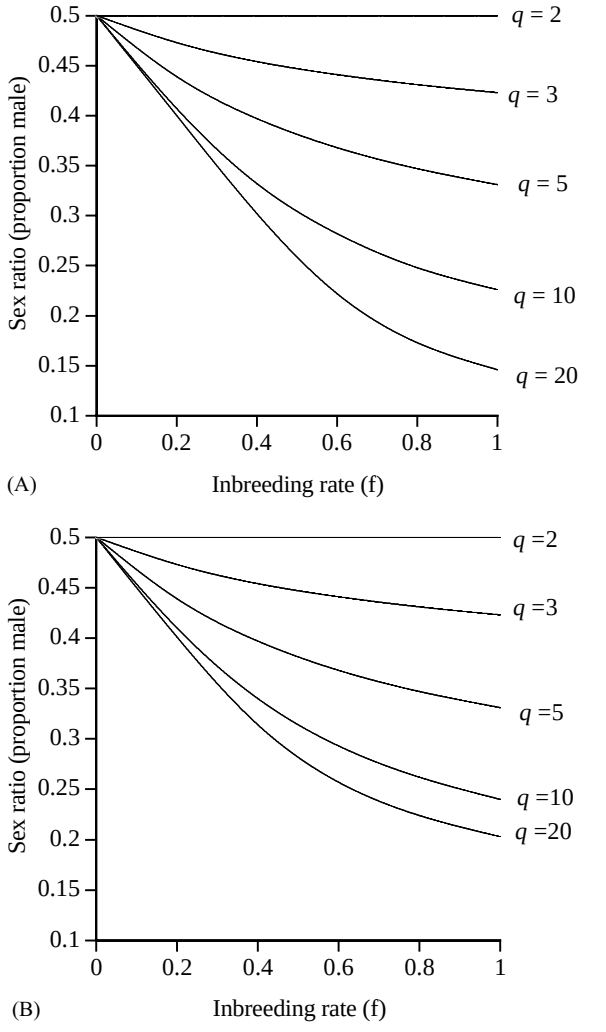

Fig. 4. (A) Relationship between predicted sex ratio and inbreeding rate, for given values of q when $c = 8$ assuming no interaction between the two types of fertility insurance and (B) relationship between ES sex ratio and inbreeding rate arising from Eqs. (1)–(4), for given values of q when $c = 8$.

example predictions when the two types of fertility insurance are allowed to act separately as previously assumed by West et al. (2002) (part A of the figures) or simultaneously in our model (part B of the figures). Our results show that when both c and q are low, the ES sex ratio may be higher than predicted when considering these two effects separately.

Why does our model predict a less female biased sex ratio? It has been assumed that one male gametocyte will be able to provide enough gametes to fertilize all the female gametes in the mating group that arises from q gametocytes. This is not the case if $(q-1) > c$. More generally, the male gametocytes will not be able to fertilize all the female gametes when $(q-\mu) > c\mu$, where μ is the number of male gametocytes in a mating group. This risk of not having enough males to fertilize the females in the group leads to less female biased sex ratios being favoured. Another way of conceptualising this is that a finite q increases the potential for low c to be a problem—when gametes can not interact as successfully (finite q), a mating group may contain only a single or small number of male gametocytes, and so the gamete fecundity (c) of these males is more likely to be a limiting factor.

Our model shows that the interaction between the two types of fertility insurance can have a surprisingly large influence on the ES sex ratio. In the examples that we give, the predicted sex ratio can be up to 0.1 higher (Fig. 2, when $c = 2$, $q = 10$ and $f = 0.3$). In this instance the sex ratio deviates from equality (0.5) by approximately half the amount inferred by West et al. (2002). Although increasing c proportionally reduces the degree of female bias, the complex interplay between male fecundity and

size of mating groups makes it difficult to relate the magnitude of this effect to q. In the limit, as q increases towards infinity, the effect dissipates as the predictions converge with those of Read et al. (1992). However, as q rises it increases the propensity for c to become limiting. The effect is therefore a dome-shaped function of q, although the exact relationship crucially depends upon the particular parameter values.

We also extended our model to allow stochastic variability in the number of viable gametes per gametocyte (c); see appendix, Eqs. (A.5) and (A.6). This could occur through variation in the number of gametes produced per gametocyte, or through mortality. Adding in this stochasticity (for invariant $E[c]$) gives further reduction in the female bias predicted, although this effect is negligible in all but the smallest of mating groups. However, a novel prediction arises from this form of stochasticity, as it allows the investigation of the mean value of $c<1$, so that male fecundity is lower than that of females. In this case, a male biased sex ratio is favoured. For the case of $q\to\infty$ Eqs. (A.3) and (A.4) remain valid even for $c<1$, and male biased ES sex ratios are easily demonstrated. Switching the roles of males and females in the classic LMC relation, the result of Read et al. (1992) can be extended so that, as before, for $c\geqslant 1$ $z^*=\max\{(1-f)/2, 1/(c+1)\}$, yet now for $c\leqslant 1$ $z^*=\min\{(1+f)/2, 1/(c+1)\}$. This prediction contrasts with standard LMC models constructed for insects (e.g. Nagelkerke and Hardy, 1994; West and Herre, 1998), where male biased sex ratios are never predicted, due to the assumption that one male can mate any number of females (analogous to assuming $c=\infty$). Male biased sex ratios have been observed in some samples of lizard malaria (Paperna and Landau, 1991), although the necessarily small sample sizes mean that these observations should be treated with caution.

To conclude, our analysis has revealed that fertility insurance can be a more potent evolutionary buffer to female biased sex ratios in malaria and related parasites than previously suggested. Clearly, the outstanding problem is to obtain empirical estimates of c and q, and how their values are influenced by factors such as host immune responses. We have recently reviewed the existing literature on this (West et al., 2002), and sadly very little is known.

Acknowledgements

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Appendix

In West et al. (2002) the implications of finite mating group size for fertility insurance were made amenable for mathematical treatment by assuming infinite male fecundity. This represents a special case of our model, such that $c=\infty$ and Eqs. (3) and (4) reduce to

$$S_{N,0}=\sum_{\mu_N=0}^{q}\binom{q}{\mu_N}z_N^{\mu_N}(1-z_N)^{q-\mu_N}2\zeta, \tag{A.1a}$$

where

$$\zeta=\begin{cases} q-\mu_N & \text{if} \quad \mu_N>0,\\ 0 & \mu_N=0\end{cases} \tag{A.1b}$$

and

$$S_{M,0}=\sum_{\tau_M=0}^{q}\sum_{\mu_M=0}^{\tau_M}\sum_{\mu_N=0}^{q-\tau_M}\binom{q}{\tau_M}f^{\tau_M}(1-f)^{q-\tau_M}\binom{\tau_M}{\mu_M} z_M^{\mu_M}(1-z_M)^{\tau_M-\mu_M}\binom{q-\tau_M}{\mu_N}z_N^{\mu_N}(1-z_N)^{q-\tau_M-\mu_N}\zeta (E[\varpi_{M,1}]+E[\varpi_{M,0}]), \tag{A.2a}$$

where

$$\zeta=\begin{cases} q-\mu_M-\mu_N & \text{if} \quad \mu_M+\mu_N>0,\\ 0 & \mu_M+\mu_N=0,\end{cases} \tag{A.2b}$$

$$E[\varpi_{M,1}]=\begin{cases}\dfrac{\mu_M}{\mu_M+\mu_N} & \text{if} \quad \mu_M+\mu_N>0,\\ 0 & \mu_M+\mu_N=0,\end{cases} \tag{A.2c}$$

$$E[\varpi_{M,0}]=\begin{cases}\dfrac{\tau_M-\mu_M}{q-\mu_M-\mu_N} & \text{if} \quad q-\mu_M-\mu_N>0,\\ 0 & q-\mu_M-\mu_N=0.\end{cases} \tag{A.2d}$$

Conversely, in the deterministic analysis of Read et al. (1992), the fertility insurance consequences of limited male fecundity were investigated under the assumption of infinite mating group size. This special case, $q=\infty$, reduces Eqs. (3) and (4) to give

$$S_{N,0}=2q\min\{cz_N,(1-z_N)\} \tag{A.3}$$

and

$$S_{M,1}=q\min\{c(z_Mf+z_N(1-f)), (1-z_M)f+(1-z_N)(1-f)\}\times\left(\frac{z_Mf}{z_Mf+z_N(1-f)}+\frac{(1-z_M)f}{(1-z_M)f+(1-z_N)(1-f)}\right). \tag{A.4}$$

Although both $S_{N,0}$ and $S_{M,1}$ are linear functions of q, and therefore have infinite solutions, the relative fitness of the Null allele may still be evaluated as ω is the ratio of the two and hence is finite. The predictions converge with those of Read et al. (1992) for $c\geqslant 1$, but being more

general, are able to predict the male biased ES sex ratio when males fecundity is more limiting than that of females, so that $c<1$.

We considered the possibility of stochastic male fecundity, specifically, how accurately do expressions (3) and (4) predict the ES sex ratio when the value of c represents the expectation of a random variable? Assuming that males all produce the same species-specific number (χ) of gametes, each with independent probability p of being viable for fertilization, Eqs. (3) and (4) become

$$S_{N,0}=\sum_{\mu_N=0}^{q}\sum_{g_N=0}^{\chi\ \mu_N}\binom{q}{\mu_N}z_N^{\mu_N}(1-z_N)^{q-\mu_N}\binom{\chi\mu_N}{g_N} p^{g_N}(1-p)^{\chi\mu_N-g_N}2\min\{g_N,q-\mu_N\} \tag{A.5}$$

and

$$S_{M,1}=\sum_{\tau_M=0}^{q}\sum_{\mu_M=0}^{\tau_M}\sum_{\mu_N=0}^{q-\mu_M}\sum_{g_M=0}^{\chi\mu_M}\sum_{g_N=0}^{\chi\mu_N}\binom{q}{\tau_M}f^{\tau_M}(1-f)^{q-\tau_M}\binom{\tau_M}{\mu_M} z_M^{\mu_M}(1-z_M)^{\tau_M-\mu_M}\binom{q-\tau_M}{\mu_N}z_N^{\mu_N}(1-z_N)^{q-\tau_M-\mu_N} \binom{\chi\mu_M}{g_M}\binom{\chi\mu_N}{g_N}p^{g_M+g_N}(1-p)^{\chi(\mu_M+\mu_N)-g_M-g_N} \min\{g_M+g_N,q-\mu_M-\mu_N\}(E[\varpi_{M,1}]+E[\varpi_{M,0}]), \tag{A.6a}$$

where

$$E[\varpi_{M,1}]=\begin{cases}\dfrac{g_M}{g_M+g_N} & \text{if}\quad g_M+g_N>0,\\ 0 & g_M+g_N=0,\end{cases} \tag{A.6b}$$

$$E[\varpi_{M,0}]=\begin{cases}\dfrac{\tau_M-\mu_M}{q-\mu_M-\mu_N} & \text{if}\quad q-\mu_M-\mu_N>0,\\ 0 & q-\mu_M-\mu_N=0.\end{cases} \tag{A.6c}$$

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