Parasitic castration promotes coevolutionary cycling but also imposes a cost on sex

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Antagonistic coevolution between hosts and parasites is thought to drive a range of biological phenomena including the maintenance of sexual reproduction. Of particular interest are conditions that produce persistent fluctuations in the frequencies of genes governing host-parasite specificity (coevolutionary cycling), as sex may be more beneficial than asexual reproduction in a constantly changing environment. While many studies have shown that coevolutionary cycling can lead to the maintenance of sex, the effects of ecological feedbacks on the persistence of these fluctuations in gene frequencies are not well understood. Here, we use a simple deterministic model that incorporates ecological feedbacks to explore how parasitic reductions in host fecundity affect the maintenance of coevolutionary cycling. We demonstrate that parasitic castration is inherently destabilizing and may be necessary for coevolutionary cycling to persist indefinitely, but also reduces the likelihood that sexually-reproducing individuals will find a fertile partner, which may select against sex. These findings suggest that castrators can play an important role in shaping host evolution and are likely to be good targets for observing fluctuations in gene frequencies that govern specificity in host-parasite interactions.

Introduction

Parasites are near-ubiquitous in nature, sometimes causing severe damage to their hosts and creating strong selection for resistance (Dybdahl and Lively 1998; Buckling and Rainey 2002; Thrall and Burdon 2003; Decaestecker et al. 2007) or other disease-avoidance mechanisms (Simms and Triplett 1994; Hamilton and Poulin 1997). Some host-parasite systems are characterized by directional selection for increasingly sophisticated means of defense and counter-defense (Buckling and Rainey 2002; Thrall and Burdon 2003), but others are prone to negative frequency-dependent selection where genotypes fluctuate in prevalence through time (Dybdahl and Lively 1998; Decaestecker et al. 2007; Gomez and Buckling 2011). Persistent fluctuations in host and parasite gene frequencies, often referred to as 'coevolutionary cycling', are of special interest to evolutionary biologists as they may help to resolve prominent questions such as why certain genes are highly polymorphic (e.g. those involved in the Major Histocompatibility Complex; Penman et al. 2013) and why many organisms reproduce sexually. The evolution of sex has received considerable attention from both theoreticians and empiricists in the context of the Red Queen Hypothesis (RQH), which posits that costs associated with sex (e.g. the twofold cost of males, sexual conflict, etc) may be offset by more rapid adaptation to coevolving antagonists (Jaenike 1978; Maynard Smith 1978; Hamilton 1980; Bell 1982). Specifically, the RQH predicts that sex should be the dominant mode of reproduction if segregation and recombination lead to an increase in the frequency of rare gene combinations that confer resistance to contemporaneous parasites (Peters and Lively 1999; Gandon and Otto 2007). Directional selection may also contribute to the maintenance of sex, as recombination breaks up linkage disequilibria that reduce additive genetic variance, allowing sexual populations to adapt at a faster rate (Barton 1995; Peters and Lively 1999).

Although many studies have explored conditions that sustain selection for novel gene combinations due to coevolutionary cycling, most have used traditional population genetics approaches that lack ecological feedbacks (Hamilton 1980; Hamilton et al. 1990; Sasaki 2000; Agrawal and Lively 2002, 2003; Otto and Nuismer 2004; Agrawal 2009; Fenton et al. 2012). Ecological feedbacks such as time

delays in the life cycle of the parasite, parasitic reductions in host fecundity and seasonal forcing are known to have a destabilizing effect on population dynamics that can lead to sustained epidemic cycles (May and Anderson 1978; Hudson et al. 1998; Boots and Norman 2000; Smith et al. 2008; but see also White and Grenfell 1997; Lively 2006); improving our understanding of how these processes influence coevolutionary dynamics is central to determining the generality of the RQH (May and Anderson 1983; Gandon and Day 2009; Lively 2010; Gokhale et al. 2013). The present study explores how parasitic reductions in host fecundity affect the propensity for epidemiological systems to exhibit coevolutionary cycling.

Parasites may indirectly reduce the fecundity of their host by limiting an individual's ability to find or compete for suitable mates (Hamilton and Zuk 1982; Boyce 1990; Hamilton and Poulin 1997). However, parasites that directly target host reproductive tissues or hormone pathways have a much greater inhibitory effect on host fecundity (Baudoin 1975). This infection strategy, which has been observed across a variety of taxa (Blower and Roughgarden 1989; Crews and Yoshino 1989; Lockhart et al. 1996; Agrios 1997; Hudson et al. 1998; Ebert et al. 2004; Sarasa et al. 2011), can lead to different pathological outcomes for the host (e.g. gigantism; Ebert et al. 2004) and evolutionary outcomes for the parasite (e.g. runaway virulence (full castration); O'Keefe and Antonovics 2002) that are not normally observed for other parasites. By definition, castrators target reproductive mechanisms, but it is important to note that many castrators also increase the mortality rate of their host. For example, several microparasites that infect the waterflea *Daphnia magna* are capable of both castrating and killing their host (e.g. *Pasteuria ramosa;* Ebert et al. 2000) and parasitic trematodes (*Microphallus* sp.) are known to affect the foraging behavior of water snails (*Potamopyrgus antipodarum)*, which increases predation by waterfowl (Levri 1995). Theoretical models that have explicitly incorporated parasitic reductions in host fecundity have tended to focus on epidemiological outcomes or predictions for the evolution of virulence, rather than coevolutionary dynamics (May and Anderson 1978; Boots and Norman 2000; O'Keefe and Antonovics 2002; Smith et al. 2008; Ashby and Gupta 2013; although see Lively 2010). Yet, much of the empirical work surrounding the issue of

coevolutionary cycling and the RQH has involved castrators (Lively 1987; Dybdahl and Lively 1998; Decaestecker et al. 2007; King et al. 2009).

Castrators may target both sexual and asexual members of a population, but a crucial difference exists between the two. Asexuals do not need to find mates and so are unaffected by the fertility of other individuals, but sexual reproduction is only successful if both individuals in a pair are fertile. Hence, we should expect parasitic castration to have a more severe effect on sexual than asexual populations. Despite this notable difference between the two modes of reproduction in the presence of castrators, theoretical studies of the RQH have yet to account for this additional cost of sex (Lively 2010). Here, we analyze a simple epidemiological model to determine how parasitic reductions in host fecundity affect coevolutionary dynamics and assess whether sexual reproduction is likely to be maintained when castration restricts the availability of fertile mates.

Model description

We use a deterministic model, where parasites are haploid with two biallelic loci (00, 01, 10 and 11) and hosts are diploid with two biallelic loci per haplotype (haplotypes: 00, 01, 10 and 11). The infectivity of parasite genotype j on host genotype i, Q_{ij}, is equal to the proportion of host haplotypes that are matched by the parasite at both loci. Consequently, homozygotes are only susceptible to one type of parasite $\left(Q_{ij}=1\right)$ and heterozygotes are susceptible to two, but with lesser infectivity ($Q_{ij}=1/2$ for each parasite), which ensures there is no underdominance for the host on average. This type of framework is normally referred to as 'matching alleles' (MA) specificity and has traditionally been used to represent self/non-self recognition mechanisms among animals (Hamilton 1980; Penn and Potts 1999). In essence, the MA framework is akin to a lock and key mechanism, where parasites are only able to specialize on narrow subsets of the host population, which typically leads to coevolutionary cycling in traditional population genetics models due to negative frequency-dependent selection (Hamilton 1980; Hamilton et al. 1990; Agrawal and Lively 2002; Agrawal 2009).

We split the population into susceptible $\left(S_i^g\right)$ and infectious $\left(I_{ij}^g\right)$ classes, where subscripts correspond to different host $\left(i\right)$ and parasite $\left(j\right)$ genotypes and superscripts denote asexual $\left(g = A\right)$ and hermaphroditic sexual $\left(g = S\right)$ members of the population. We assume that the population mixes randomly and all parasites have a transmission rate of β, so that the force of infection for parasite j is $\lambda_j = \beta \sum_i \left(I_{ij}^S + I_{ij}^A\right)$. For simplicity, we also assume coinfection does not occur and hosts are unable to recover once infected. All hosts have a maximum per-capita birth rate of $r > 0$ and a natural mortality rate of $\mu > 0$, but infected individuals may also experience a disease-associated mortality rate of $\alpha \geq 0$ and a reduction in fertility, f $\left(0 \leq f \leq 1\right)$. When $f = 1$ the parasite has no effect on fertility $\left(rf = r\right)$, whereas $f = 0$ represents full castration of the host $\left(rf = 0\right)$. Newborn hosts of genotype i are produced at the following rates for asexual

$$b_i^A = r\left(S_i^A + f\sum_j I_{ij}^A\right) \tag{1}$$

and sexual

$$b_i^S = \frac{r\left(1+\delta_i\right)F_p F_q z}{2\sum_k F_k} \tag{2}$$

members of the population, respectively, where $\delta_i = 1$ if i is heterozygous and $\delta_i = 0$ if i is homozygous, z is the probability of a sexual individual finding at least one fertile partner and F_p and F_q are the densities of haplotypes p and q that together form host genotype i, modified by the fertility of hosts with these haplotypes. In other words, if following recombination (which occurs at a rate ρ) there are u copies of haplotype k in susceptible individuals and v copies in infected individuals, then $F_k = u + fv$. We set $b_i^S = 0$ if $\sum_k F_k = 0$. We assume that sexual members of the population can mate multiply to increase their chances of finding a fertile partner. Each individual engages in m independent mating attempts per unit time, but is limited to bearing at most r offspring during this period. Biologically, this could be interpreted as a restriction on the rate at which

hermaphrodites can produce eggs (r per unit time), with no limitation on the rate at which sperm are produced. Thus, individuals can continue to fertilize other members of the population even if they have temporarily exhausted their supply of eggs. The probability of finding a fertile mate in any attempt is therefore $\sum_k F_k / 2N_S$, where $N_S = \sum_i \left(S_i^S + \sum_j I_{ij}^S \right)$ is the size of the sexual population. It follows that z is given by:

$$z = 1 - \left(1 - \frac{\sum_k F_k}{2N_S} \right)^m \tag{3}$$

(see figure 1). Note that the birth rates of sexual and asexual individuals are equal when parasites do not inhibit reproduction ($f = 1 \Rightarrow z = 1$, so $\sum_i b_i^S = \sum_i b_i^A = r$) and that $z \to 1$ as $m \to \infty$ provided some members of the sexual population have not been fully castrated $\left(\sum_k F_k > 0 \right)$. If parasites do inhibit reproduction $\left(f < 1 \right)$, then the overall birth rates of the two populations may still differ even when sexual individuals undergo an infinite number of mating attempts per unit time $\left(z = 1 \right)$, as certain haplotypes may be more prone to infection than others (e.g. $b_i^S = 0$ if $F_p = 0$ or $F_q = 0$, even if $z = 1$).

We implement our model using the following set of ordinary differential equations:

$$\frac{dS_i^g}{dt} = b_i^g - S_i^g \left(\sum_j Q_{ij} \lambda_j + \mu \right) \tag{4a}$$

$$\frac{dI_{ij}^g}{dt} = S_i^g Q_{ij} \lambda_j - \left(\alpha + \mu \right) I_{ij}^g \tag{4b}$$

which is simply a generalization of the standard SI epidemiological framework (see e.g. Anderson and May, 1991) to incorporate MA infection genetics. The infectious period is equal to $1/\left(\alpha + \mu \right)$ and the average number of secondary infections produced per infectious individual is given by

$R_{EFF}^{j} = \beta \sum_i Q_{ij} \left(S_i^A + S_i^S \right) / \left(\alpha + \mu \right)$, which must exceed unity for the parasite j to increase in prevalence.

We take a similar approach to Otto and Nuismer (2004) in not including an explicit cost of sex in our model other than the cost of finding a mate as described above, as this allows us to determine the extent to which castrators disproportionately harm the sexual population by directly comparing sexual and asexual populations, all else being equal. In other words, if asexual reproduction is favored under certain conditions in our model, then this outcome can be entirely attributed to differential effects of parasitism on sexual and asexual populations rather than to intrinsic costs of sex.

Results

Castration promotes persistent coevolutionary cycling

We begin by analyzing the case where only homozygous asexual hosts are present, as this allows us to derive straightforward conditions under which coevolutionary cycling persists by simplifying the stability analysis of the system (homozygotes can only be infected by one type of parasite and asexual populations do not exhibit segregation and recombination). The reduced system can be represented by the following set of equations:

$$\frac{dS_i^A}{dt} = r\left(S_i^A + f \sum_j \eta_{ij} I_{ij}^A \right) - S_i^A \left(\beta \sum_j \eta_{ij} I_{ij}^A + \mu \right) \tag{5a}$$

$$\frac{dI_{ij}^A}{dt} = \left(\beta \eta_{ij} S_i^A - \alpha - \mu \right) I_{ij}^A \tag{5b}$$

where $\eta_{ij} = 1$ if the parasite matches the (repeated) host haplotype at both loci and is otherwise equal to 0. The non-trivial fixed point ($S_i^{A*}, I_{ij}^{A*} > 0$, for i and j such that $\eta_{ij} = 1$) is given by:

$$S_i^{A*} = S^* = \frac{\alpha + \mu}{\beta} \tag{6a}$$

$$I_{ij}^{A*} = I^* = \frac{(r-\mu)(\alpha+\mu)}{\beta(\alpha+\mu-rf)} \tag{6b}$$

which only exists provided $r > \mu$ (the birth rate is greater than the death rate) and $\alpha + \mu > rf$ (the parasite controls the population size). At this fixed point, the system has two repeated eigenvalues (Λ):

$$\Lambda = \frac{1}{2}\left(\frac{-rf(r-\mu)}{\alpha+\mu-rf} \pm \sqrt{\left(\frac{rf(r-\mu)}{\alpha+\mu-rf}\right)^2 - 4(r-\mu)(\alpha+\mu)} \right) \tag{7}$$

which must be complex for oscillations to occur. Oscillations will be damped if the real part of equation 7 is less than zero $\left(\mathrm{Re}(\Lambda) = -rf(r-\mu)/2(\alpha+\mu-rf)\right)$, but will persist if $\mathrm{Re}(\Lambda) = 0$. Thus, only parasites that fully castrate their hosts $(f = 0)$ are able to maintain coevolutionary cycling indefinitely. Although non-castrators $(f > 0)$ still produce transient coevolutionary cycling provided $(rf/(\alpha+\mu-rf))^2 < 4(\alpha+\mu)/(r-\mu)$, these oscillations are damped because the supply of new susceptible hosts is less restricted, allowing the system to tend towards a stable equilibrium (e.g. figure 2b). Note that $\mathrm{Re}(\Lambda) \to 0$ as $f \to 0$, $\alpha \to \infty$ or $\mu \to r$, which means that partial reductions in host fertility or high mortality rates will slow the decay of oscillations, but will not allow these dynamics to persist indefinitely. The transmission rate, β, is absent from equation 7, so does not have any effect on the stability of the fixed point. The period of oscillations, T, is approximately equal to 2π multiplied by the reciprocal of the imaginary part of λ. When $f = 0$, $T \approx 2\pi/\sqrt{\bar{r}\bar{\alpha}}$, where $\bar{r} = r - \mu$ and $\bar{\alpha} = \alpha + \mu$, so the period of oscillations will increase as $\bar{\alpha} \to 0$ or $\mu \to r$.

The reason why castrators cause this fundamental shift in the long-term behavior of the system becomes clear if we set $f = 0$ and rewrite equation 5 as:

$$\frac{dS_i^A}{dt} = S_i^A\left(\bar{r} - \beta\eta_{ij}I_{ij}^A\right) \tag{8a}$$

$$\frac{dI_{ij}^A}{dt} = -I_{ij}^A\left(\bar{\alpha} - \beta\eta_{ij}S_i^A\right) \tag{8b}$$

for i and j such that $\eta_{ij} = 1$. From a mathematical point of view, castrators create a perfect correspondence with a classical Lotka-Volterra predator-prey system, which is known to produce persistent oscillations (May 1973). This is because infected individuals only contribute to the reproductive success of the parasite and cannot themselves reproduce in the presence of a castrator, which causes the host and parasite populations to suffer precipitous declines. In the context of the present study, hosts that are able to avoid contemporaneous parasites have the highest per-capita growth rate, but this will not last for long as parasites that target the most abundant host genotypes will be fittest, leading to coevolutionary cycling. The same principle allows non-castrators to produce transient oscillatory dynamics, but infected individuals still contribute to the reproductive success of the host $(f > 0)$, which has a damping effect due to weaker selection against currently disadvantageous genotypes. Higher mortality rates allow transient oscillations to persist for longer, but also reduce the infectious period, $1/(\alpha + \mu)$, limiting the size of an epidemic and hence the strength of selection on the host.

The stability analysis presented here only applies to asexual populations, but a numerical exploration of the parameter space indicates that patterns of coevolutionary cycling are qualitatively similar when hosts reproduce sexually, with full castration required for coevolutionary cycling to persist indefinitely. Oscillations tend to experience slower decay rates for small values of f, large values of α and as $\mu \to r$, as observed in asexual populations (figure 3). Higher recombination rates have a relatively minor negative impact on the persistence of oscillations, but the effects of the transmission rate are negligible (log-log regression, $R^2<0.27$ and $R^2\leq0.04$, respectively; table 1).

As part of our numerical analysis, we also measured the average period of oscillations when coevolutionary cycling persists (i.e. when $f = 0$), as previous studies have shown that the frequency

of oscillations can be crucial in determining whether sex is maintained (Barton 1995; Gandon and Otto 2007). We found that low disease-associated mortality rates and very high natural mortality rates are associated with lower frequency oscillations, as observed with asexual populations (figure 4). Again, the recombination rate has a very minor negative influence on the period of oscillations and the effects of the transmission rate are negligible (log-normal regression, R^2=0.106 and R^2<0.001, respectively; table 1).

Castration disproportionately harms sexual populations

The previous section demonstrated that persistent coevolutionary cycling is only likely to be maintained in the presence of a castrating parasite. This finding is particularly relevant to the maintenance of sex according to the RQH, which requires a continually changing environment for sexual populations to outcompete their asexual counterparts. A naive interpretation of our model would therefore be that castrating parasites are more likely to select for sex than non-castrators, as only they are able to induce persistent coevolutionary cycling. However, this neglects a fundamental difference between sexual and asexual reproduction; a sexually-reproducing female is only able to produce offspring if both she and her partner are fertile, whereas asexual individuals are unaffected by the fertility of other members of the population. We capture this asymmetry in reproductive success using the term z in equation 3, which gives the probability that a sexually-reproducing individual will find a fertile mate, given m mating attempts per unit time. Figure 1 shows how z depends on both m and the average fertility of potential mates. Even when average fertility is reasonably high, a large number of mating attempts is required before the probability of finding a fertile mate approaches certainty.

Figure 5 demonstrates the typical behavior of our model in the presence of castrating parasites. When the number of mating attempts for sexuals is relatively low, asexual reproduction tends to dominate. Yet, if the number of mating attempts is sufficiently high, the implicit costs of castration are less severe, so sexual members of the population are not driven extinct. Instead, better avoidance of contemporaneous parasites by sexual individuals leads to the suppression of asexual reproduction.

Hence, the number of mating attempts is crucial in determining whether sexual reproduction is maintained. Other model parameters were also found to have an impact on the maintenance of sex, with high mortality (disease and natural), intermediate transmission, and high recombination rates increasing selection for sex (figures 6 and S1). Unlike previous studies (Barton 1995; Peters and Lively 1999; Gandon and Otto 2007), we found that the period of oscillations had no discernible impact on the maintenance of sexual reproduction (figures 4, 6a, c). This is most likely attributable to ecological feedbacks in our model, as higher mortality rates reduce the average proportion of the population that is infected (equation 6), making it easier to find a fertile partner (z increases). Thus, it is the availability of fertile mates, rather than the period of oscillations that appears to be the dominant force in our model. High rates of recombination increase the likelihood that offspring will avoid infection by contemporaneous parasites, which reduces the number of mating attempts required for sexual populations to dominate (figure 6d), but the effects are less profound than for changes in mortality rates. The influence of the transmission rate on the maintenance of sex is less clear (figure 6b), but it appears that extreme values of β lead to high amplitude fluctuations in the proportion of the population that is infected, which periodically restricts the availability of fertile mates and consequently selects against sex.

Discussion

Fluctuations in gene frequencies caused by host-parasite interactions are thought to play a pivotal role in several biological phenomena, so it is important to understand conditions that promote or inhibit these dynamics. Using a deterministic epidemiological model with overlapping generations, we have demonstrated that coevolutionary cycling will only persist in the presence of parasites that fully castrate their hosts. Even extremely lethal parasites are unable to sustain cycles indefinitely in the absence of castration (although they do allow oscillations to persist for longer), as high disease-associated mortality rates cause a reduction in the average infectious period, which limits the size of an epidemic and consequently the overall strength of selection. Castration does not reduce the infectious period so a larger proportion of the population can be infected during an epidemic, leading

to greater population crashes and inducing stronger selection for resistance, which are both more conducive to persistent oscillatory dynamics (May and Anderson 1978; Otto and Nuismer 2004).

Although castrators promote coevolutionary cycling, they also have a disproportionately harmful effect on sexual populations, as both members of a sexual partnership must be fertile for offspring to be produced. By contrast, the production of each asexual offspring is only dependent on the fertility of a single female. Taking this fundamental difference between the two modes of reproduction into account, we found that sex will only outcompete asexual reproduction provided multiple mating is very common. We did not include an explicit cost of sex in our model apart from the cost of finding a fertile mate, so that we could ascertain the severity of implicit costs of sex caused by castration, all else being equal. Still, we struggled to find conditions where sex is likely to outcompete asexual reproduction, either due to these implicit costs or a lack of coevolutionary cycling; thus conditions for sex to dominate could be even stricter than described herein.

A large number of mathematical models have been developed since the RQH was first proposed as a possible mechanism for the maintenance of sex (Hamilton 1980; May and Anderson 1983; Hamilton et al. 1990; Doebeli 1996; Otto and Nuismer 2004; Kouyos et al. 2007; Agrawal 2009; Lively 2010; Gokhale et al. 2013), but our results differ from previous studies in a number of important ways. First, the MA framework has previously been shown to persistently oscillate under a broad range of conditions, whereas our model only maintains coevolutionary cycling in the presence of castrators. This difference is partially due to our inclusion of density-dependent processes, which are typically omitted from traditional population genetics models (Hamilton 1980; Hamilton et al. 1990; Agrawal and Lively 2002; Agrawal 2009). Cycling is easier to maintain in the absence of density-dependence, as an increase in the prevalence of one allele must be exactly offset by decreases in alleles with below average fitness. In our model, castrators cause sudden population crashes for currently disadvantageous haplotypes, which then take a relatively long time to recover to sufficient levels for a new epidemic to occur $\left(R_{EFF}^{j} > 1\right)$. Parasites that only partially reduce host fecundity have less of an impact on the supply of new susceptible hosts, so oscillations decay due to this ecological feedback. Crucially, an increase in the absolute prevalence of one allele does not need to be offset by changes in

another, so cycling is not as readily maintained. The other reason that coevolutionary cycling is more common in previous models is due to their tendency to use discrete rather than overlapping generations (Hamilton 1980; Hamilton et al. 1990; Doebeli 1996; Otto and Nuismer 2004; Agrawal 2009; Lively 2010). Discretised generations synchronize various ecological and epidemiological processes, leading to persistent oscillations that would otherwise be damped if generations were to overlap. Had our model employed discrete generations, oscillations would have persisted over a much broader set of conditions (May 1973). It is vital to establish whether oscillations in theoretical models are being propagated by fundamental aspects of a host-parasite relationship or are simply arising due to the method of implementation. This question was explored by Kouyos et al. (2007), who found that moving from discrete to continuous time led to the loss of persistent oscillations of linkage disequilibria. Models that lack ecological feedbacks or overlapping generations may therefore be overestimating conditions that favor coevolutionary cycling, and hence sex. This point is particularly important, as much of the debate over the generality of the RQH may be fuelled by fundamental differences in modeling approaches (i.e. presence/lack of ecological feedbacks, continuous versus discrete time, diploid versus haploid hosts (see below)).

Second, Lively (2010) has shown that sex can be maintained in the presence of a castrating parasite with or without coevolutionary cycling, but our model will only select for sex if cycling occurs. The contrasting outcomes are due to different initial conditions, as here we have assumed that sexual and asexual populations start with all genotypes present, but Lively (2010) challenged established sexual populations with invasion by a single clonal lineage, which increased the benefits of sex. Our model has the additional requirement that sex will only be maintained in the presence of a castrator if individuals mate with a sufficient number of partners, as we explicitly account for a limited number of sexual contacts per individual rather than basing birth rates on the average fertility of the sexual population. Lively (2010) took the latter approach, which again increases selection for sex.

Third, sexual populations are most successful in our model when recombination rates are high, but Otto and Nuismer (2004) have suggested that this is only likely to be true when selection is strong. However, the two findings are not directly comparable as Otto and Nuismer (2004) used a population

genetics approach that did not include ecological feedbacks. Additionally, Otto and Nuismer (2004) modeled haploid hosts (as have most studies), whereas we have focused on diploids. Selection for sex will depend on the effects of both segregation and recombination, but the former cannot be accounted for in haploids (Agrawal 2009). It is important to note that our model assumes there is no underdominance or overdominance, but previous studies have shown that either can select against sex as segregation breaks up beneficial combinations of alleles (Otto 2003; Agrawal and Otto 2006). In addition, the period of oscillations appeared to have little impact on the maintenance of sex in our model, but others have shown that the period of fluctuating epistasis can be crucial, with sex only likely to be maintained for a narrow range of frequencies (Barton 1995; Peters and Lively 1999; Gandon and Otto 2007). Again, this discrepancy is attributable to ecological feedbacks that were absent in other models; sex is maintained in our model even when the period of oscillations is very high, because these conditions are associated with a relatively low prevalence of infection, which reduces the cost of sex by increasing the probability of finding a fertile mate (figures 4, 6).

Although we have made our model as general as possible, it is likely that real host-parasite systems may differ in a number of aspects, some of which may alter selection for sex. For example, any synchronization in ecological or epidemiological processes (e.g. annual populations or seasonal epidemics) could increase the likelihood of coevolutionary cycling being maintained indefinitely, as could other environmental effects (Wolinska and King 2009). It is also possible that stochasticity in natural populations may be sufficient to counteract the damping effects caused by deterministic attractors or may lead to random linkage disequilibria (i.e. the Hill-Robertson effect), allowing coevolutionary cycling (and potentially sex) to persist under a wider range of conditions than observed here (Rohani et al. 1999; Kouyos et al. 2007). However, it has recently been demonstrated that stochasticity may have the opposite effect, increasing the likelihood that certain alleles will reach fixation rather than persistently oscillate (Gokhale et al. 2013). Finally, sexual populations may have access to regions of genotype space that are unavailable to asexuals, which may allow them to survive invasion by clonal lineages, even in the absence of coevolutionary cycling (Lively 2010).

Some of these caveats may help to explain why empirical observations of certain host-parasite systems provide support for the RQH, most notably in the freshwater snail *Potamopyrgus antipodarum* (Lively 1987; King et al. 2009). These snails are no doubt host to a variety of parasites, but it is the presence or absence of the parasitic trematode *Microphallus* that determines whether sex is maintained. Crucially, this parasite differs from others in that it fully castrates its host; our model suggests that it is this feature of the host-parasite relationship that induces persistent coevolutionary cycling, which is a prerequisite for sex to be maintained according to the RQH. These snails are also known to exhibit multiple mating (Soper et al. 2012), which will reduce the disproportional impact of castration on sexual populations, as demonstrated by our model. Note however that multiple mating could incur an opportunity cost, as individuals will have less time and energy available for foraging. Other factors such as spatial structure (offspring are more likely to experience the same parasites as their hosts if dispersal is limited), the complex life cycle of the parasite (synchronization of ecological processes) or the accumulation of deleterious mutations were not captured by our model, but could conceivably contribute to the maintenance of sex (Howard and Lively 1994; Keeling and Rand 1995; West et al. 1999).

We are aware of only one other experimental system where recombination (sex) has been selected for in the presence of parasites, but this involved a highly virulent pathogen that killed its host within 24 hours (*Caenorhabditis elegans*-*Serratia marcescens*; Morran et al. 2011). We have shown that high disease-associated mortality rates allow coevolutionary cycling to persist for longer (figure 3), but our findings suggest that selection for recombination may not continue indefinitely in this system. Empirical tests of the RQH are generally difficult, as we are limited by the need for comparable sexual and asexual populations. Similarly, coevolutionary cycling is often hard to detect in real host-parasite systems, but has been observed among invertebrates (Dybdahl and Lively 1998; Decaestecker et al. 2007). It is interesting to note that the bacterium *Pasteuria Ramosa*, which undergoes coevolutionary cycling with its host *Daphnia magna*, is also a castrator (Decaestecker et al. 2007). In the absence of evidence from a more diverse set of systems, it is difficult to draw conclusions about the generality of the RQH from these observations alone. In a review of the RQH in the context of

plant-parasite interactions, Clay and Kover (1996) came to the conclusion that "parasites that kill or sterilize [castrate] their hosts are the most likely players in the coevolutionary scenario envisioned by the RQH. Many lesion-forming parasites are unlikely to exert selection on hosts of a magnitude strong enough to generate cycles of gene frequencies". In light of our results, it appears that parasitic castrators are a much more likely candidate for producing these dynamics, but the implicit costs imposed on sexually-reproducing individuals means that asexual populations may still win the evolutionary battle.

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Table 1

Coefficient of determination, R^2 (regression)

	f=0.001	f=0.01	f=0.1
Persistence of oscillations, figure 3 (log-log)			
Disease-associated mortality rate, α	0.934	0.945	0.971
Transmission rate, β[1]	0.002	0.04	0.039
Natural mortality rate, μ	0.650	0.665	0.625
Recombination rate, ρ[1]	0.268	0.203	0.001
		f=0	
Period of oscillations, figure 4 (log-normal)			
Disease-associated mortality rate, α		0.909	
Transmission rate, β[1]		<0.001	
Natural mortality rate, μ		0.282	
Recombination rate, ρ[1]		0.106	

[1]The recombination rate had a relatively minor negative impact on both the persistence and period of oscillations, but the effects of the transmission rate were negligible.

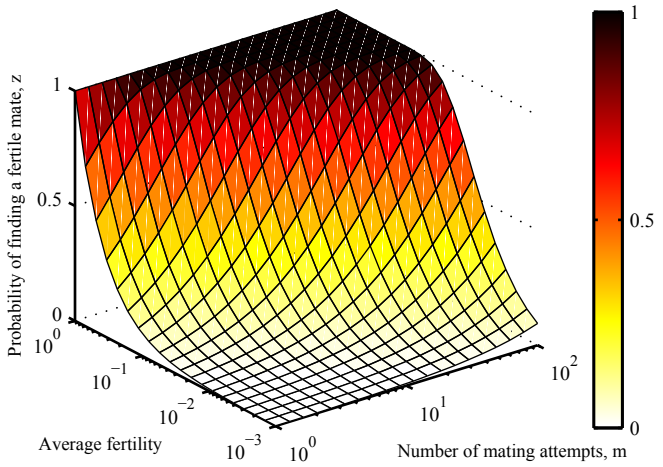

Figure 1 – Probability of finding at least one fertile mate (z; equation 3) as a function of the number of mating attempts (m) and average fertility ($\Sigma_k F_k/2N_s$).

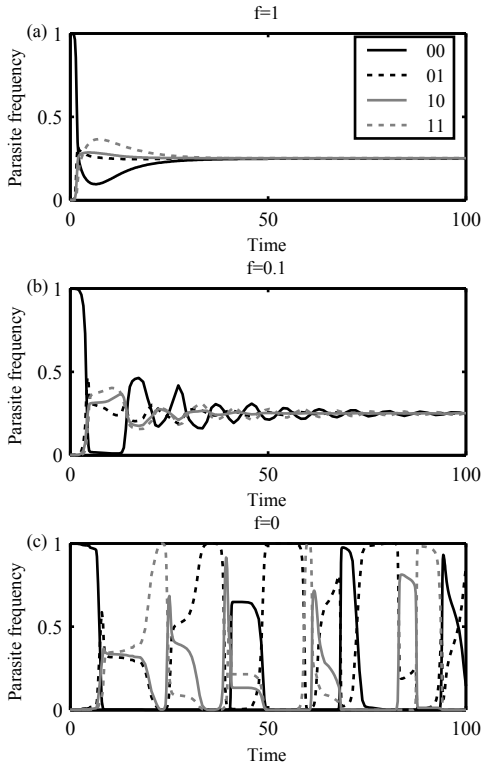

Figure 2 - Example dynamics in an asexual population, with (a) f=1 (no disease effects on reproduction); (b) f=0.1 (partial reproduction inhibition); (c) f=0 (full castration). Coevolutionary cycling is only able to persist in the presence of a castrator (equation 7). The dynamics for sexual and mixed populations are qualitatively similar. Parameters: α=1, β=0.05, μ=0.1, r=1.

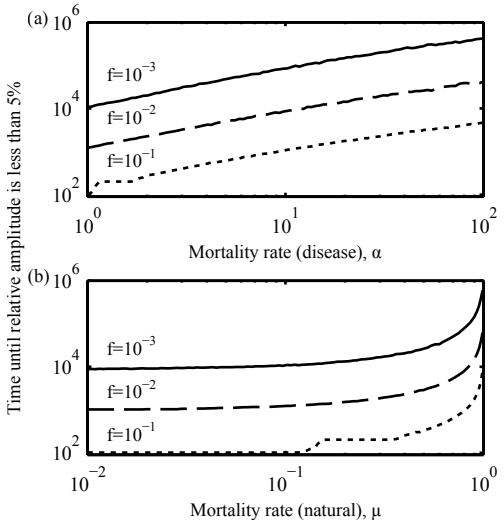

Figure 3 – The effects of the disease-associated (α) and natural (μ) mortality rates on the decay of oscillations in sexual populations when $f=10^{-3}$ (solid), $f=10^{-2}$ (dashed) and $f=10^{-1}$ (dotted). Simulations were terminated when fluctuations in the abundance of haplotypes were within 2.5% of the mean (i.e. relative amplitudes were less than 5%). Coevolutionary cycling persisted for longer for high values of α and μ, and low values of f. Higher recombination rates, ρ, have a relatively minor negative impact on the persistence of oscillations (log-log regression, $R^2<0.27$; table 1), but the effects of the transmission rate are negligible (log-log regression, $R^2\leq0.04$; table 1). Fixed parameters as specified in figure 2, with $\rho=0.1$ and z held constant at 1 (i.e. $m\rightarrow\infty$).

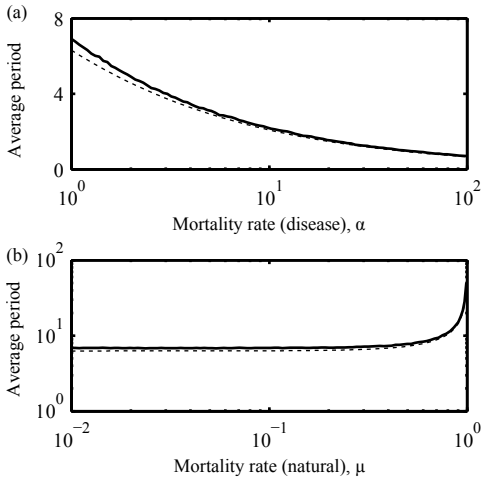

Figure 4 – The effects of the disease-associated (α) and natural (μ) mortality rates on the period of oscillations in sexual (solid) populations when f=0. Low values of α and high values of μ are associated with lower frequency oscillations. The recombination rate has a very minor negative influence on the period of oscillations (R^2=0.106), but the effects of the transmission rate are negligible (R^2<0.001). Dotted lines show the period of oscillations in homozygous asexual populations. Parameters as specified in figure 3.

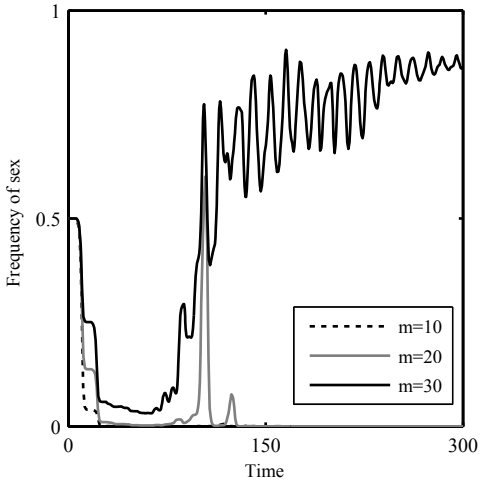

Figure 5 – Example dynamics showing the frequency of sexually-reproducing individuals in the presence of castrating parasites (f=0), for different values of m (mating attempts): m=10 (dotted); (b) m=20 (gray); (c) m=30 (black). Although castrators induce coevolutionary cycling (figure 2), they also reduce the chances of sexually-reproducing individuals finding a fertile mate (equation 3). Mating multiply can counteract this implicit cost of sex, but may require a large number of sexual partners. Fixed parameters as specified in figure 2, with ρ=0.1.

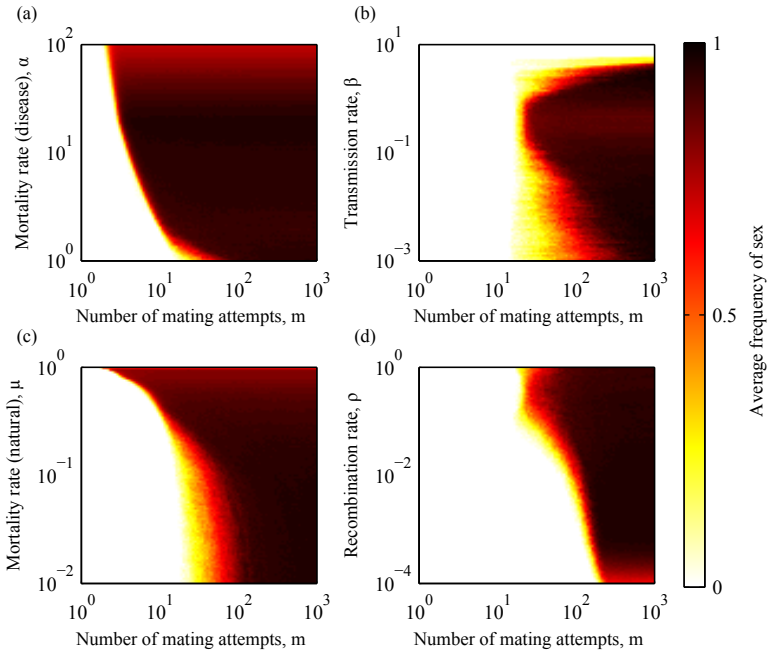

Figure 6 - The effects of the number of mating attempts (m) and other model parameters on the maintenance of sex in the presence of castrating parasites (f=0). Heatmaps show the average frequency of sex at equilibrium over 100 randomly chosen sets of initial conditions. Asexual populations dominate in the white areas and sex dominates in the dark areas. Both populations may coexist in the boundary between these two regions, but evolutionary outcomes are often highly dependent on initial conditions (see figure S1 for standard deviations), with sexual populations more likely to displace asexual populations in red areas (and vice versa in yellow areas). Fixed parameters as specified in figure 2, with ρ=0.1 in (a)-(c).

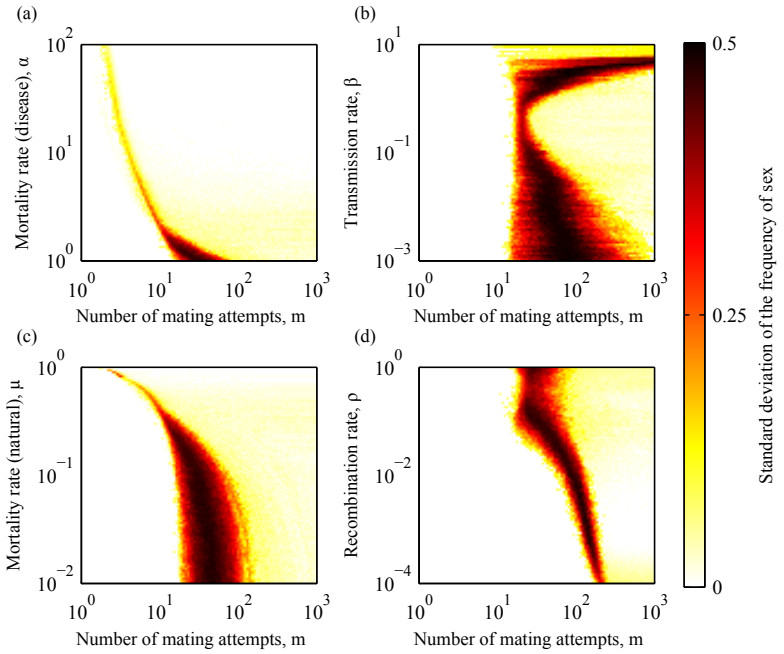

Figure S1 - The effects of the number of mating attempts (m) and other model parameters on the maintenance of sex in the presence of castrating parasites (f=0). Heat maps show the standard deviation of the frequency of sex at equilibrium over 100 randomly chosen sets of initial conditions (see figure 6 for average values). Dark regions correspond to evolutionary outcomes that are highly dependent on initial conditions. Fixed parameters as specified in figure 2, with ρ=0.1 in (a)-(c).