

Dedicated to the memory of William Donald Hamilton

Antigenic diversity and the selective value of sex in parasites

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We employ a stochastic model of helminth transmission to explore the persistence properties of sexual versus asexual parasites in the face of a host population that develops immunity. We assume that this immunity is specific to the parasite strain, such that different parasite strains express unique antigens which in turn elicit specific host immune responses. Sexual parasites are inherently disadvantaged by a fecundity that is only half that of asexual parasites, given that males do not produce offspring. However, we demonstrate that sexual parasites benefit from the greater production and maintenance of antigenic genotypes than mutation alone in asexuals. The ability of sexual parasites to produce antigenic diversity enhances population persistence of the parasites, given that enhanced antigenic diversity permits evasion of host immunity. Therefore, we argue that sexual reproduction for parasites under intense negative frequency dependent selection induced by host immunity is associated with advantages that may be sufficient to compensate for lower intrinsic reproductive potential.

Introduction

The widespread existence of sexual reproduction in the natural world despite substantial fitness costs has been a long-standing enigma in

evolutionary biology (Maynard Smith 1971). The major cost for sexual parasites arises because males do not produce offspring directly, giving rise to what has been known as the twofold cost of sex (Williams 1975). In addi-

tion, females have no certainty of finding a mate, particularly in a number of parasite species (MacDonald 1965). Consequently, there must be a significant advantage associated with sex to compensate for its costs.

Hamilton developed one of the first models to investigate potential evolutionary advantages of sex for organisms evolving under intense negative frequency dependent selection (Hamilton 1980). He proposed that continuous parasitic attack may fuel selection favouring the evolution of sex in vertebrate hosts. Hamilton argued that parasites have a much shorter generation time than their hosts and therefore a more rapid rate of evolution. Consequently, the immune system of hosts will be subject to selection to keep up with the ever-changing antigenic nature of parasites. Hamilton suggested that sexual reproduction made this possible for hosts.

Here we explore this coevolutionary arms race from the perspective of the parasite by considering the impact of host immunity on the selective value of sexual versus asexual reproduction for helminth parasites [as has Lythgoe (2000)]. Empirical research has demonstrated that hosts develop immune responses that are specific to the antigens of different helminth strains (Currie *et al.* 1998). This strain-specific immunity will drive frequency-dependent selection of individual strains and thus favours antigenic diversity in parasites. In other words, given that immunity imposes selection against a given parasite strain, a rare strain will be favoured as only a small proportion of the host population will have encountered it. Thus, the host population will be largely susceptible to a new strain. However, as a strain becomes increasingly common, the immunity against it mounts, and it is selected against relative to less common strains. We show that sex enhances the production and maintenance of antigenic diversity through Mendelian segregation of alleles. In turn, sex can generate superior population persistence relative to asexual reproduction.

Theoretical studies that consider the selective value of sex from the perspective of helminth parasites are sparse [notable exception is Lythgoe (2000)]. For example, Hamilton's assumptions were appropriate for microparasites, such as viruses and bacteria (Hamilton 1980), but not

for helminths. The lack of attention that this issue has drawn is by no means a reflection of its importance. Reproductive strategy is clearly a fundamental aspect of the biology of any organism. Furthermore, helminths, such as the whipworm *Trichuris trichiura*, infect a third of the world's population (Hall 1993, Chan *et al.* 1994, Nokes & Bundy 1994). They also constitute a severe public health burden, particularly given that even moderate intensity infections can have a major impact on the cognitive (Nokes *et al.* 1992) and physical growth (Hall 1993) of children.

In previous models, the biological reality of a number of central assumptions has been compromised to handle limitations in computational power. One of the essential assumptions of Hamilton's models and those that followed involved extreme genotypic specificity of host-parasite interactions (Hamilton 1980, Hamilton *et al.* 1990). This assumption had been required to give sufficiently strong frequency-dependent selection to fuel sustained cycling of host genotypes. Hamilton found that these dynamics were necessary to give a selective advantage to sexual reproduction in hosts. However, such extreme genotypic specificity is not consistent with empirical data suggesting that parasites are much more broadly infective (Parker 1994), a limitation that Hamilton himself recognised (Hamilton 1980, Hamilton *et al.* 1990).

A number of models have been developed to explore the adaptive value of sexual recombination within host populations (Bell & Maynard Smith 1987, Charlesworth 1993a, Charlesworth 1993b, Howard & Lively 1994, Lively & Howard 1994, Barton 1995, Burger *et al.* 1995, Lande & Shannon 1996, Burger 1999, Waxman & Peck 1999). In these studies the adaptive value of recombination arose primarily from its ability to unlink beneficial mutations from less-fit genotypes by breaking down linkage disequilibrium. It was found that the adaptive value of this feature of recombination depends on the selective regime. For example, if a trait that had already reached its optimum was subject to stabilising selection, recombination resulted in a maladaptive 'genetic load' (Burger 1999). On the other hand, if a trait was subject to directional selection, recombination accelerates the rate

of adaptation (Burger *et al.* 1995, Burger 1999). By contrast, Lythgoe (2000) found that the advantage to recombination disappears when selection is directional. The discrepancy between these studies may arise because the response to directional selection in Lythgoe's model was hampered anyway because she did not allow for mutation, while Burger does. Finally, many studies have demonstrated an adaptive value for recombination when selection fluctuates epistatically (Charlesworth 1993a, Charlesworth 1993b, Burger *et al.* 1995, Lande & Shannon 1996), as could arise from host-parasite interactions (Nee 1989). Bell and Maynard Smith (1987) looked at the success of recombination in populations of both parasites and hosts. They found that a rare recombination allele is favoured in the parasite but not in the host.

The recent analysis of Lythgoe (2000) explored the evolution of recombination in helminth parasites under selection by the host immune system. She showed that sexual invaders were not able to drive asexuals extinct, even in the absence of a cost to sex, though asexuals and sexuals were able to coexist in some parameter regimes. Furthermore, coexistence depended on fluctuating epistasis to drive linkage disequilibrium, and intermediate levels of cross-immunity were required to give the greatest degree of fluctuating epistasis and hence the largest advantage to sex. However, unlike the work we present here, Lythgoe used a deterministic model which did not incorporate sex (or mutation) directly, and instead assumed parasites were identical reproductively, with 'sexual' parasites recombining randomly. The model used also only described four parasite genotypes, which may have further limited the advantages to sex observed (May & Anderson 1983, Hamilton *et al.* 1990).

Overall, the previous studies outlined above have focused principally on the evolution of recombination while not necessarily addressing the twofold cost of sex. By contrast, we look at the evolution of sex with Mendelian segregation at a single antigenic locus. Also, the fitness benefit we find for sex does not rely on fluctuating epistasis, linkage disequilibrium or cross-immunity, but the generation and maintenance of diversity.

Model description and assumptions

We developed a stochastic simulation model that integrates population genetics and the dynamics of helminth epidemiology. The model was written in Delphi 4 (Borland Corporation, Scotts Valley, California), a dialect of the Pascal programming language. The model is based on a discrete time step of about nine days. We verified that reducing the time step from nine days to one day made no detectable difference to our results, suggesting that the nine day time step is an accurate approximation to a continuous time model.

Using a micro-simulation enabled the properties of distinct individuals of parasites and hosts to be tracked through time. The stochastic nature of the model allowed extinction dynamics to be explored, given that real populations are finite and often spatially isolated, and that we are specifically interested in examining the establishment dynamics of new, low-frequency parasite strains.

The model assumed a single antigenic locus at which the number of alleles can be varied up to ten, giving a maximum of 55 possible strains. Empirical studies have revealed highly protective strain specific responses in a number of helminth species (Nadler 1987, Dobson & Jian-Ming 1991, Fraser & Kennedy 1991, Goyal & Wakelin 1993, Zvelebil *et al.* 1993, Bellaby *et al.* 1995, Tang *et al.* 1995, Currie *et al.* 1998, Wassom *et al.* 1988), including *Trichuris trichiura* specifically (Currie *et al.* 1998). Parasite strains are defined by genetic polymorphism at the antigenic locus. When a parasite strain infects a host, the host acquires immunity specific to the antigens of that strain. This immunity then prevents reinfection of the host by the same strain.

The model captures the life cycle of a directly transmitted helminth, such as the clinically important whipworm *Trichuris trichiura* (Fig. 1). Directly transmitted parasites do not pass through an intermediate host. There is a reproductive phase in the human host and a free-living infective larval stage. Immediately upon infection, parasites reach reproductive maturity. Adult parasites complete the lifecycle by pro-

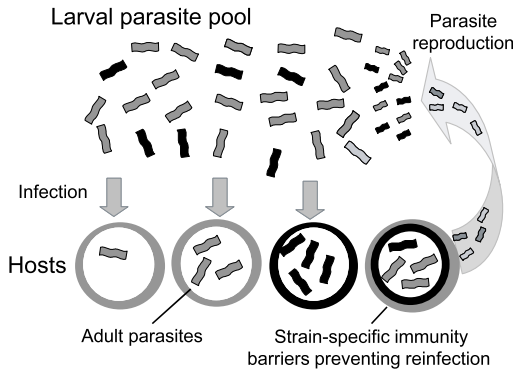


Fig. 1. Schematic representation of our model. The rings around hosts represent immunity barriers to further infection, resulting from previous or current exposure to parasites. The different shades of the parasites illustrate multiple strains (up to 55 in our actual model). Hosts infected by different strains of parasites acquire immunity against each, depicted here by double rings.

ducing offspring which are then released into the larval pool in the environment. We assume that a female (or asexual) *T. trichiura* parasite produces a maximum of 3500 eggs, in correspondence with empirical data (Bundy & Cooper 1989), and that all females in a host are equally fecund. However, parasite fecundity within a single host is subject to density dependent competition between parasites such for space and/or nutrients (Keymer 1982, Keymer & Slater 1987). This is represented by assuming fecundity to be a negative exponential function of parasite burden (Croll *et al.* 1982, Anderson & Schad 1985, Medley & Anderson 1985), $e^{-(n-1)/a}$, where n is the parasite burden of an individual host and a characterises the inverse of the intensity of competition. Here $a = 100$ parasites was assumed (Anderson & May 1985).

Parasite mortality within the host is modelled as a Poisson process, resulting in an exponential distribution of parasite lifespan with a mean of three years, in line with empirical estimates (Anderson & May 1985). Larval mortality was also modelled as a Poisson process with a mean of about ten days.

The per capita mortality rate of hosts is assumed to be $5.5 \times 10^{-5} \text{ day}^{-1}$, giving an average lifespan of 50 years. Infection does not affect the survival of the hosts. We assumed that

the size of the human host population is stable, such that each host death coincided with the birth of an immunologically naive and uninfected host.

The infection process is also modelled stochastically, with the number of total infections occurring in the host population per unit time being Poisson distributed with a mean proportional to the production rate of larvae, such that the force of infection (Λ) was proportional to the total rate of production of larvae across all hosts at a given time.

As in most past work, we assumed that immunity generates a reduced host susceptibility to reinfection (reviewed in Mitchell 1979). Immediately upon infection, hosts were assumed to develop life-long, strain-specific immunity which prevented reinfection by the same parasite strain (so $I = 1$), though the model allowed simultaneous infection by multiple parasites with the same strain.

We considered two modes of sexual reproduction: mating outside the host and mating within the host. In both cases, the mating system is panmictic and polygamous with a one to one sex ratio, as is true for the vast majority of helminth species (Anderson & May 1991). In both sexual mating systems, the genotypes of the offspring are produced in accordance with Mendelian segregation, resulting in Hardy-Weinberg ratios. Mutation of antigenic alleles occurs at an average rate of one in a million offspring. We assume that there is no deleterious mutation. Therefore, all mutations are beneficial in terms of evasion of pre-existing immunity.

When parasites mate within hosts, for example in *T. trichiura*, every female is randomly fertilised by a coinfecting male in the same host. A male may fertilise a potentially unlimited number of females. If there are no males present in a host, none of the females in that host produce offspring, giving rise to what is known as the mating probability (MacDonald 1965). The mating probability can result in a further reduction to the fitness of sexual parasites.

We also modelled sexual parasites that mate outside the host, as occurs in the intestinal rat nematode *Strongyloides ratti*. The unique feature of mating outside is that females are randomly fertilized by any male that is present in

the environment. In other words, all females will mate provided that there is at least one male present in the parasite population. Consequently, these parasites will not suffer from mating probability suppression which has been argued to be unimportant in practice anyway (May 1977). Comparison of these two sexual strategies helps us to unravel the influence of the two-fold cost of sex and the uncertainty of finding a mate.

To represent asexual reproduction, all adult parasites produce offspring irrespective of whether another parasite is present in the same host. Therefore, the fecundity of an asexual population will be twice that of a sexual population, everything else being equal. Parental and offspring genotypes are identical unless there is mutation. These occur at the same rate as in the sexual population.

As our measure of selective value for the respective reproductive strategies, we compared the ability of populations to persist for at least a thousand years under different reproductive strategies. For each set of parameters, 200 realisations were performed and the average of these plotted.

Deterministic representation of the model

The deterministic equivalent of our stochastic model is defined by the following equation for the dynamics of the numbers of parasites of a given genotype j of gender s in an individual host i , n_{ijs} :

$$\frac{dn_{ijs}}{dt} = \Lambda_{ij} - \mu n_{ijs}$$

Here μ is the mortality rate of adult parasites, and the force of infection of strain j on host i , Λ_{ij} , is defined by:

$$\Lambda_{ij} = \beta c_i \lambda p (1 - I_{ij}) \times \sum_{k,l,m} \frac{n_{kl0} n_{kml}}{\sum_j n_{kq0}} \left[(1 - \delta) M_{ilm} + \sum_j \Omega_{jl} M_{j'lm} \right] \exp \left[- \left(\sum_{q,s} n_{kqs} - 1 \right) / \alpha \right]$$

where β is the transmissibility of the parasite, or

the probability that a susceptible host exposed to a parasite larvae will become infected. We assume that all strains are equally transmissible. Parameter c_i is the susceptibility of host i (drawn from a negative binomial distribution with mean = 6 and parameter $k = 0.25$), λ is the maximal output of larvae by adult females, p is the proportion of larvae surviving to encounter hosts, I_{ij} is the acquired immunity of host i against parasite strain j , M_{jlm} is the proportion of offspring of matings between genotypes l and m that produce genotype j , δ is the proportion of offspring with antigenic mutations, $\Omega_{j'}$ is the proportion of antigenic mutations of parasites with genotype j' that generate genotype j , and α represents the intensity of frequency-dependent suppression of fecundity, as outlined earlier.

This expression is slightly changed if sexual parasites mate externally:

$$\Lambda_{ij} = \beta c_i \lambda p (1 - I_{ij}) \times \frac{\sum_{k,k',l,m} n_{k'l0} n_{kml}}{\sum_{k,q} n_{k'q0}} \left[(1 - \delta) M_{jlm} + \delta \sum_{j'} \Omega_{j'j} M_{j'lm} \right] \exp \left[- \left(\sum_{q,s} n_{kqs} - 1 \right) / \alpha \right]$$

For asexual parasites, sex is not relevant, so the dynamics are given by

$$\frac{dn_{ij}}{dt} = \Lambda_{ij} - \mu n_{ij}$$

where:

$$\Lambda_{ij} = \beta c_i \lambda p (1 - I_{ij}) \times \sum_k \left[(1 - \delta) n_{kj} + \delta \sum_{j'} \Omega_{j'j} n_{kj'} \right] \times \exp \left[- \left(\sum_{q,s} n_{kqs} - 1 \right) / \alpha \right]$$

Results

We looked at the effect of increasing antigenic diversity on total parasite abundance when infections are in equilibrium in the host population. Parasite abundance has epidemiological significance, as the severity of symptoms correlates directly with the parasite abundance in the

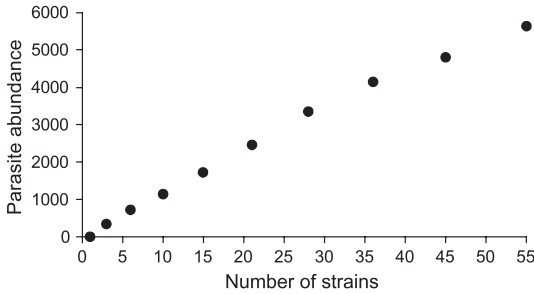


Fig. 2. The increase in total parasite abundance within a host population of 2000 individuals, as a function of increasing numbers of sexual parasite strains circulating.

host population (Watkins & Pollitt 1997, Raj & Naing 1998). We found that total parasite abundance increases almost linearly with the number of strains circulating (Fig. 2). The levelling out of the slope arises from mounting density dependent suppression of parasite fecundity with increasing numbers of coinfecting parasites.

Enhanced antigenic diversity achieves evasion of host immunity and thus effectively widens the niche of host susceptibility for the parasite population. In other words, strain-specific immunity generates negative frequency-dependent selection against individual antigenic genotypes. A rare mutant is initially favoured but is then selected against as it becomes increasingly common and the host population becomes immune to it. Consequently, the production of a diversity of novel antigenic genotypes permits the expansion of the parasite population.

We compared the probability of persistence of sexual versus asexual populations when they circulated independently under different levels of initial antigenic diversity (Fig. 3). Here initial antigenic diversity refers to the initial number of different homozygous strains. At low levels of antigenic diversity, asexual populations have a higher probability of persistence than sexual populations. There are more asexual parasites present at equilibrium than in an equivalent sexual population because every asexual adult reproduces. Greater numbers of parasites also mean more targets for mutation, resulting in further diversity.

The selective dynamics change as the level of initial antigenic diversity increases. One con-

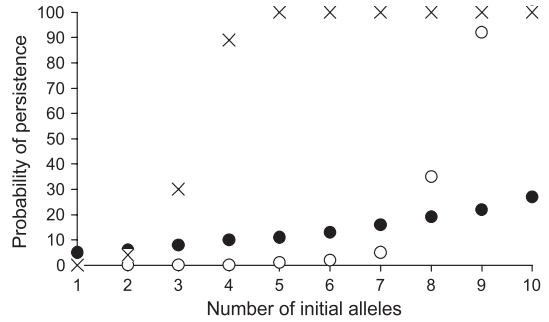


Fig. 3. Probability of parasite population persistence after at least 1000 years as a function of the number of initial antigenic alleles. Here $\beta = 0.04$. It compares asexual parasites (black circles) with sexual parasites mating within hosts (white circles) and outside hosts (crosses). Each realisation was initiated with homozygous parasites only. 200 realisations were performed to calculate each point.

sequence of Mendelian segregation is that a single mutation in a system that already has n alleles will produce a further $n + 1$ strains (n new heterozygotes and one new homozygote). In other words, when an additional allele is introduced into the system, combining this allele with n pre-existing alleles will generate n new heterozygous strains and the combination of the new allele with itself will generate a new homozygous strain. Therefore, the number of additional strains that can be produced through sexual reproduction rises exponentially with the initial level of antigenic diversity. By contrast, production of each additional strain is limited by the rate of mutation in an asexual system. Moreover, sexual genotypes are less vulnerable to permanent extinction. A sexual genotype that is lost can be immediately recreated in the next generation by persisting related strains.

These results are consistent with previous studies suggesting that sexual recombination is selected for its ability to produce genetic diversity. In particular (Howard & Lively 1994) make the point that parasites do not select for sex *per se* in their hosts, but for genetic diversity.

In our model, all mutations at the antigenic locus are beneficial for parasites in terms of evading pre-existing immunity. Therefore we did not take into account that in nature the vast majority of mutations are deleterious. We would

predict that the advantage of sexual reproduction relative to asexual reproduction would increase further with the incorporation of deleterious mutations. For instance, the models of Howard and Lively (1994), and Lively and Howard (1994) have explored the interplay between the accumulation of deleterious mutations (Muller 1964, Kondrashov 1988) and host-parasite coevolution. They found that parasites elevate the accumulation of deleterious mutations by periodically depressing the asexual lineage. Over time, the combination of these effects sent the asexual parasite population extinct. In fact, they found that deleterious mutation was necessary to prevent the rapid extinction of sexuals in the face of asexual invasion. By contrast, our advantage to sex did not require the accumulation of deleterious mutation. Lively and Howard (1994) only consider four immunological genotypes which may explain why parasite-host coevolution in their models was not sufficient to overcome the twofold cost of sex.

We also see that a greater level of sexual population persistence relative to asexual persistence is achieved much more rapidly when parasites mate outside the host than when they mate within the host, the threshold occurring at three versus eight antigenic alleles (Fig. 3). This demonstrates the theoretical importance of the mating probability to the persistence of sexual parasites. When parasite abundance is already suppressed, females may have a low probability of finding a mate.

As defined earlier, parasite transmissibility (β) is the probability that a susceptible host exposed to a parasite larvae will become infected. As outlined earlier, transmissibility correlates directly with the force of infection (A) and is therefore of epidemiological significance in determining the prevalence of parasites in a host population. We found that the level of transmissibility alters the relative persistence properties of sexual versus asexual reproduction (Fig. 4). As the level of transmissibility increases from 0.04 to 0.05, the level of antigenic complexity in a system required to give sex a persistence advantage over asexual reproduction decreased from eight initial homozygotes to seven. In other words, although persistence increases for all parasites as transmissibility rises, it increases

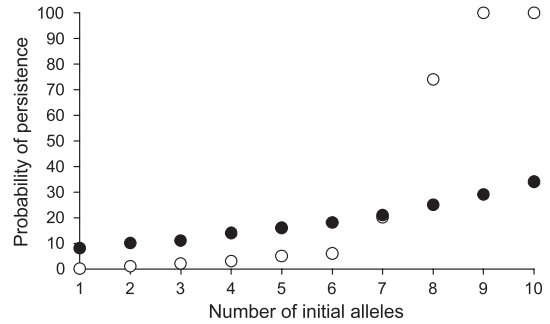


Fig. 4. Probability of parasite population persistence under the same parameter regime as in Fig. 3, except that β has been increased to 0.05. Here we compare asexual parasites (black circles) with sexual parasites mating within hosts (white circles).

more quickly for sexual parasites than for asexual parasites.

Transmissibility will have two important repercussions on the dynamics of the system, given that as transmissibility rises, the size of the parasite burden also increases within a host population of fixed size. Firstly, the mating probability rises with increasing transmissibility. Secondly, higher transmissibility and the associated increased parasite abundance results in more intense immunity. The parameters we employed for transmissibility were conservative, given that it has been estimated that between 5% and 22% of *T. trichiura* eggs that are ingested by humans develop into reproductively mature parasites (Wong *et al.* 1988). Our results suggest that increasing the level of transmissibility within this range of empirical estimates will benefit the persistence of sex relative to asexual reproduction further.

Conclusions

Achieving antigenic diversity by means of a high mutation rate is a viable strategy for retroviruses which have relatively simple genomes and huge population sizes within individual hosts. Decreasing generation time is one mechanism by which parasites can increase the net mutation rate. However, assuming that the transmission capacity of a parasite is limited, a reduction in generation time will result in a

reduction in the duration of infectiousness and thus a lower prevalence of infection. Consequently, a reduction in generation time could be expected to result in higher rates of extinction and poorer persistence of parasite populations. Furthermore, the cost of a high mutation rate in terms of the accumulation of deleterious mutations is exorbitant for relatively complex eukaryotes such as helminths, particularly due to their small population sizes within hosts. These smaller populations are more likely to suffer from the accumulation of deleterious mutations (Howard & Lively 1994, Lively & Howard 1994). In addition, Burger (1999) found that recombination is much more effective at enhancing genetic diversity than increasing the reproductive rate by an equivalent amount.

To compete in the parasitic niche, helminths require a different mechanism to generate antigenic diversity. Our results suggest that this mechanism may be sexual reproduction. We have shown that in a stochastic environment, the advantage that adaptive immunity gives to antigenic diversity can be expected to select for sexual reproduction in helminth parasites, despite the twofold cost. Furthermore, we assumed that all mutations were beneficial in terms of generating diversity. The advantage to sex is likely to become more pronounced if it is taken into account that many mutations will be deleterious [as did Howard and Lively (1994), and Lively and Howard (1994)].

Lythgoe (2000) concluded that the interactions between parasites and host immunity did not impose a sufficient selection pressure to overcome the twofold cost of sex. By contrast, our model suggests that these interactions can be strong enough to compensate for the twofold cost. In addition, May and Anderson (1983) had speculated that theoretical frameworks integrating the population dynamics, epidemiology and genetics are less likely to favour sexual reproduction than those that consider the dynamics of allele frequencies only. However, we have been able to demonstrate a selective advantage for sexual reproduction using a model that incorporates the processes outlined by May and Anderson (1983).

Our results are consistent with empirical observations. For example, helminth species that

are not parasitic are less likely to be sexual than parasitic species (Levin 1975, Glesener & Tilman 1978, Maynard Smith & Szathmari 1995). The facultatively sexual rat nematode *Strongyloides ratti* is more likely to reproduce sexually in hosts expressing a strong immune response than these parasites are in immunocompromised hosts (Gemmill *et al.* 1997). Likewise, helminth parasites of host species with a poor immune response are less likely to be sexual than those that mount a highly protective response (Poinar & Hansen 1983). Similarly, there tends to be more genetic exchange in parasitic nematodes of mammals than of plants (Anderson *et al.* 1998).

The model presented here could be developed in a number of different directions. It would be interesting to compare obligately and facultatively sexual strategies (Green & Noakes 1995). One could also introduce multiple loci to look at the effects of heterozygosity and linkage disequilibrium. Finally, one could incorporate spatially explicit dynamics of parasite transmission. We would predict that this would further elevate the selective value of sexual reproduction relative to asexual reproduction. The production of antigenically diverse offspring will be particularly adaptive if local pockets of immunity develop and offspring are more likely to be transmitted to surrounding hosts than to the wider community.

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