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Host–parasite interactions and the evolution of nonrandom mating

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Some species mate nonrandomly with respect to alleles underlying immunity. One hypothesis proposes that this is advantageous because nonrandom mating can lead to offspring with superior parasite resistance. We investigate this hypothesis, generalizing previous models in four ways: First, rather than only examining invasibility of modifiers of nonrandom mating, we identify evolutionarily stable strategies. Second, we study coevolution of both haploid and diploid hosts and parasites. Third, we allow for maternal parasite transmission. Fourth, we allow for many alleles at the interaction locus. We find that evolutionarily stable rates of assortative or disassortative mating are usually near zero or one. However, for one case, in which assumptions most closely match the major histocompatibility complex (MHC) system, intermediate rates of disassortative mating can evolve. Across all cases, with haploid hosts, evolution proceeds toward complete disassortative mating, whereas with diploid hosts either assortative or disassortative mating can evolve. Evolution of nonrandom mating is much less affected by the ploidy of parasites. For the MHC case, maternal transmission of parasites, because it creates an advantage to producing offspring that differ from their parents, leads to higher evolutionarily stable rates of disassortative mating. Lastly, with more alleles at the interaction locus, disassortative mating evolves to higher levels.

KEY WORDS: **Assortative mating, coevolution, disassortative mating, maternal effects, modifier model, parasites.**

Rather than mate randomly, many organisms choose mates using specific cues. In some cases, individuals select mates that are similar to themselves (assortative mating), whereas in other cases, individuals select mates that are different (disassortative mating). Both types of nonrandom mating affect the organization of genetic diversity within a species. For example, in a diploid species, disassortative mating typically leads to an excess of heterozygotes, whereas assortative mating leads to an excess of homozygotes. Thus, to understand why assortative versus disassortative mating evolves, we must identify processes that induce selection on heterozygosity.

Nonrandom mating on the basis of alleles at the major histocompatibility complex (MHC) has been observed across many vertebrate taxa including birds (Løvlie et al. 2013), mammals (Huchard et al. 2013), and fish (Matthews et al. 2010; Evans et al. 2012). One explanation for why nonrandom mating might evolve with regard to MHC genotype is that higher MHC diversity provides superior immunity. The first theoretical studies on this topic supported this claim, showing that disassortative mating is expected to evolve in a haploid host population that is coevolving with parasites (Howard and Lively 2003, 2004). Recently, however, a theoretical model that considered a range of possible assumptions for the genetics of mating and infection in diploids showed that both assortative and disassortative mating can evolve, depending on which model is considered (Nuismer et al. 2008). Disassortative mating still tend to evolve under an MHC-like infection model, as long as there were no costs associated with mate selection.

Work on this topic typically treats hosts and parasites as pools of randomly mixing individuals. However, encounters with parasites are often not random. The most common mode of nonrandom parasite transmission is likely infection by one's mother.

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Table 1. Model parameters and variables.

Variables and parameters	Definitions
v	Fitness cost in hosts of being infected.
$\mathbf{X}$ ($\mathbf{Y}$)	The genotype vector of a female (male).
$f(\mathbf{X^I})$ ($f(\mathbf{Y^I})$)	The frequency of females (males) with infection status $\mathbf{I}$ and genotype $\mathbf{X}$ ($\mathbf{Y}$).
$G_k(\mathbf{X})$ ($G_k(\mathbf{Y})$)	The probability that a female (male) of genotype $\mathbf{X}$ ($\mathbf{Y}$) joins group k.
$F(\mathbf{Y^I}, \mathbf{X^I})$	The probability of a female of genotype $\mathbf{X^I}$ mating with a male of genotype $\mathbf{Y^I}$.
$\bar{F}$	The mean fertility of the female population.
$R(\mathbf{Y^I}, \mathbf{X^I})$	The relative preference of a female of genotype $\mathbf{X^I}$ for males of genotype $\mathbf{Y^I}$.
λ	The probability that an encounter with a compatible parasite causes an infection.
μ_i	Mutation rate of individuals of species i (i = H for host and i = P for parasite).
$\rho(\mathbf{X^I})$	The level of assortative/disassortative mating exhibited by a female of genotype $\mathbf{X^I}$.
ϕ	The probability that the parasite a host individual encounters is maternally transmitted.
ω	Indicator parameter that equals 0 when the **M**-locus adjusts the level of disassortative mating and 1 when it adjusts the level of assortative mating.

Such maternal transmission occurs in parasites infecting plants (e.g., Agarwal and Sinclair 1997; Pearce 1998) and animals (e.g., Fowler et al. 2000; Knell and Webberley 2004; Carlier et al. 2012). Recent theoretical work has shown that maternal transmission of parasites changes predictions about the evolution of sex (Agrawal 2006) and mutation rate (Greenspoon and M'Gonigle 2013). Maternally transmitted parasites tend to be genetically well targeted to offspring by virtue of the genetic similarity between mother and offspring. Hence, sex and mutation, both processes that cause offspring to differ genetically from their mothers, can be advantageous.

Here, we use a general simulation-based framework to investigate how antagonistic coevolutionary interactions affect the evolution of nonrandom mating across a range of host–parasite ploidy combinations, genetic infection models, mating preference models, and modes of parasite transmission. Specifically, we build on previous models in four important ways. First, rather than only investigate invasion of modifiers of nonrandom mating, we identify evolutionarily stable rates. Second, we consider the coevolution of haploid and diploid hosts with haploid and diploid parasites in all combinations. Third, we include maternal transmission of parasites, and investigate its impact relative to global transmission on the evolution of nonrandom mating. Fourth, we consider the effect of population-wide allelic diversity at the interaction locus on evolutionary outcomes.

When hosts are diploid, we can generally predict whether assortative or disassortative mating will evolve based on the relative fitness of heterozygotes. When hosts are haploid, however, whether nonrandom mating evolves depends on the action of negative frequency-dependent selection. For most cases, extreme rates of nonrandom mating evolve (i.e., rates near zero or one). Intermediate levels of nonrandom mating only evolve under a single combination of mating and infection schemes. For this case, we find that maternal transmission of parasites increases the strength of selection for disassortative mating because disassortative mating, like sex and mutation, decreases the similarity between mother and offspring. We also find here that increasing the number of alleles at the interaction locus, increases the level of disassortative mating that evolves.

Table 2. Models of infection for diploid hosts and diploid parasites.

	Host genotype		
Parasite genotype	AA	Aa	aa
BB	{R,I}	{R,I}	{I,R}
Bb	{R,R}	{R,I}	{R,R}
bb	{I,R}	{R,I}	{R,I}

The first entry is for the IMA model and the second for the MA model. Host resistance occurs in cells labeled "R" and infection occurs in cells labeled "I." Table reproduced from Nuismer et al. (2008). For models of infection in haploid hosts and/or parasites see Tables S1– S3.

Model

We study the evolution of a host species interacting with a parasite species. Model parameters and variables are summarized in Table 1. Each species can be either haploid or diploid. Both species possess an interaction locus with potentially many alleles, the **A**-locus in hosts and the **B**-locus in parasites, which mediates infection according to one of two standard models: inverse matching alleles (IMAs) or matching alleles (MAs; see Tables 2 and S1–S3 for the case where there are only two alleles at the interaction locus). The IMA model represents a scenario like that which occurs with MHC immunity, in which a parasite can infect a host that lacks complementary recognition alleles (Frank 2002); the MA model represents a scenario in which a parasite can infect

if it mimics host factors involved in self/nonself-recognition (e.g., Drayman et al. 2013).

The host has a second, biallelic, modifier locus (denoted here as the **M**-locus), which determines the strength of assortative or disassortative mating exhibited by females. Mating occurs according to one of three standard models: the animal model, plant model, or grouping model. For a full description of these mating models, see Otto et al. (2008). Briefly, the animal and plant models both assume that females choose their mates with relative preferences based on phenotype. In the animal model, all females have equal fecundities, whereas in the plant model, females suffer a fitness cost for being choosy. The animal model thus applies to cases where females are the limiting sex, such as in lekking species, whereas the plant model applies to cases where males are limiting, such as in pollen-limited plant species. In the grouping model, mating takes place within groups, membership to which is based on phenotype, and females either mate within their own group or at random across all groups. For example, the grouping model applies to species that exhibit genetically based habitat choice.

Our model and notation are based on those of Nuismer et al. (2008). Unlike their model, we explicitly track which host individuals are infected and, if infected, by which parasite genotype. Hence, in a model of diploid hosts infected by diploid parasites, there are a total of 80 types to track. This approach allows us to investigate nonrandom parasite transmission. Similar approaches have been used to evaluate the effect of maternal transmission on the evolution of sex (Agrawal 2006) and the evolution of mutation rate (Greenspoon and M'Gonigle 2013).

We define $f(\mathbf{X^I})$ (or $f(\mathbf{Y^I})$) as the frequency of individuals of genotype $\mathbf{X}$ (or $\mathbf{Y}$) that are female (or male) in infection class $\mathbf{I}$, where $\mathbf{I}$ is either the genotype of the infecting parasite or the empty set, $\emptyset$, for uninfected individuals. We refer to $\mathbf{X^I}$ and $\mathbf{Y^I}$ as immunogenotypes. Because host individuals are assumed to be infected by only one parasite strain prior to mutation, we do not include sexual reproduction in parasites, as it would have a negligible effect. Hence, we only study the evolution of assortative/disassortative mating in hosts.

MATING

Mate choice occurs according to one of the three models described above, namely the plant, animal, and grouping models. For the grouping model, only the evolution of assortative mating is applicable (Nuismer et al. 2008), as groups are not typically thought to form based on trait dissimilarity. For the animal and plant models, on the other hand, we study the evolution of assortative mating and disassortative mating separately. The value of the indicator parameter ω indicates whether we are investigating the evolution of disassortative mating ($\omega = 0$) or assortative mating ($\omega = 1$) (Tables 3 and S4 for two-allele case).

The following is based on the model presented in Nuismer et al. (2008), but with modifications to allow us to track individual infection histories.

Plant model

In this model, a female's fertility is lower if she is choosy, because choosy females run the risk of not mating. The probability that a female of immunogenotype $\mathbf{X^I}$ chooses to mate with a male of immunogenotype $\mathbf{Y^I}$ is

$$F(\mathbf{Y^I}, \mathbf{X^I}) = R(\mathbf{Y^I}, \mathbf{X^I}) , \tag{1}$$

where $R(\mathbf{Y^I}, \mathbf{X^I})$ is the relative preference of a female of immunogenotype $\mathbf{X^I}$ for a male of immunogenotype $\mathbf{Y^I}$ (Tables 3 and S4 for two-allele case).

The frequency of matings between males of immunogenotype $\mathbf{Y^I}$ and females of immunogenotype $\mathbf{X^I}$ is then

$$f(\mathbf{Y^I}, \mathbf{X^I}) = \frac{f(\mathbf{Y^I}) f(\mathbf{X^I}) F(\mathbf{Y^I}, \mathbf{X^I})}{\bar{F}} , \tag{2}$$

where $\bar{F}$ denotes the mean fertility of the population and is given by

$$\bar{F} = \sum_{\mathbf{Y^I}, \mathbf{X^I}} f(\mathbf{Y^I}) f(\mathbf{X^I}) F(\mathbf{Y^I}, \mathbf{X^I}) . \tag{3}$$

Animal model

In the animal model, unlike in the plant model, all females are assumed to have equal fertility (i.e., are guaranteed to mate). The probability that a female of immunogenotype $\mathbf{X^I}$ chooses to mate with a male of immunogenotype $\mathbf{Y^I}$ is

$$F(\mathbf{Y^I}, \mathbf{X^I}) = \frac{R(\mathbf{Y^I}, \mathbf{X^I})}{\sum_{\mathbf{Y^I}} f(\mathbf{Y^I}) R(\mathbf{Y^I}, \mathbf{X^I})} . \tag{4}$$

The frequency of matings between males of immunogenotype $\mathbf{Y^I}$ and females of immunogenotype $\mathbf{X^I}$ is then

$$f(\mathbf{Y^I}, \mathbf{X^I}) = f(\mathbf{Y^I}) f(\mathbf{X^I}) F(\mathbf{Y^I}, \mathbf{X^I}) . \tag{5}$$

Grouping model

In the grouping model, all males reside within groups, which we assume are sorted according to genotype at the **A**-locus (Tables 4 and S5 for two-allele case). A female can choose either to mate within her group (with a probability determined by the **M**-locus), or to mate randomly. The frequency of matings between a male of immunogenotype $\mathbf{Y^I}$ and a female of immunogenotype $\mathbf{X^I}$ is

$$f(\mathbf{Y^I}, \mathbf{X^I}) = f(\mathbf{Y^I}) f(\mathbf{X^I}) \times \left(\rho(\mathbf{X^I}) \sum_{k=1}^{N} \frac{G_k(\mathbf{Y^I}) G_k(\mathbf{X^I})}{g_k} + [1 - \rho(\mathbf{X^I})] \right) , \tag{6}$$

Table 3. Relative preferences of females for males under assortative ($\omega = 1$) or disassortative ($\omega = 0$) mating in plant and animal models when hosts are diploids.

	Male genotype		
Female genotype	AA	Aa	aa
AA	$1 - (1 - \omega) * \rho(\mathbf{X})$	$1 - \omega * \rho(\mathbf{X})$	$1 - \omega * \rho(\mathbf{X})$
Aa	$1 - \omega * \rho(\mathbf{X})$	$1 - (1 - \omega) * \rho(\mathbf{X})$	$1 - \omega * \rho(\mathbf{X})$
aa	$1 - \omega * \rho(\mathbf{X})$	$1 - \omega * \rho(\mathbf{X})$	$1 - (1 - \omega) * \rho(\mathbf{X})$

Table reproduced from Nuismer et al. (2008). For relative preferences in haploid hosts, see Table S4.

Table 4. Grouping model probabilities in diploids.

	Genotype		
Group	AA	Aa	aa
AA	1	0	0
Aa	0	1	0
aa	0	0	1

Each cell gives the probability that an individual of a given genotype would join a given group. Table reproduced from Nuismer et al. (2008). For grouping model probabilities in haploid hosts, see Table S5.

where $\rho(\mathbf{X^I})$ is the probability that a female of immunogenotype $\mathbf{X^I}$ chooses to mate within her group, $G_k(\mathbf{Y^I})$ is the probability that a male of immunogenotype $\mathbf{Y^I}$ resides in group k, which we assume equals $G_k(\mathbf{X^I})$ for females of the same immunogenotype (Tables 4 and S5 for two-allele case), and g_k denotes the frequency of males residing in group k and is given by

$$g_k = \sum_{\mathbf{Y^I}} f(\mathbf{Y^I}) G_k(\mathbf{Y^I}) \,. \tag{7}$$

SEX

Gametes are produced according to standard Mendelian segregation with recombination between the interaction and modifier locus occurring at rate r and mutation at the **A**-locus occurring at rate μ_H. Sexual reproduction takes place within mating pairs through random union of gametes.

PARASITE MUTATION

We assume that parasites undergo a single round of mutation at the **B**-locus with mutation rate μ_P. Mutation occurs within hosts and prior to transmission, so each infected host contains a small fraction of mutant parasites. Throughout, we fix mutation rates in both species at 10^{-5}.

INFECTION

During transmission, each host individual encounters a single parasite. Those individuals with infected mothers encounter one of their mother's parasites with probability ϕ, and a parasite drawn from the population at random with probability $(1 - \phi)$. We call this latter population of parasites the "global population" and refer to infection via these parasites as "global infection." Individuals with uninfected mothers encounter a single parasite, drawn at random, from this global pool. If the encountered parasite is genetically compatible (Tables 2 and S1–S3 for two-allele cases) with the host, it will cause a new infection with probability λ. Because ϕ determines the relative importance of maternal transmission, we refer to it as the "strength" of maternal transmission.

We note that the above-described process of infection differs from that implemented in previous modifier models that examined maternal parasite transmission (Agrawal 2006; Greenspoon and M'Gonigle 2013). In contrast to our one-step infection, these models considered a two-step process in which parasites were first transmitted maternally and then transmitted globally. The advantage to our implementation is that the number of host–parasite encounters does not depend on the rate of maternal transmission. This allows us to isolate the effect of maternal transmission from the potentially confounding effect of number of parasite encounters. Although both models are potentially plausible, we consider the former here to facilitate comparison to previous work on the evolution of nonrandom mating that did not contain a maternal transmission step (Nuismer et al. 2008).

SELECTION

Infected individuals have a reduced probability of surviving until reproduction. In particular, infected hosts have fitness $(1 - v)$ compared to uninfected individuals that have fitness 1. We refer to v as the "virulence" of infection.

Results

We investigated evolution at the modifier locus across a range of conditions and parameter values. We did this by tracking

evolution to identify evolutionarily stable rates of assortative or disassortative mating. To simplify presentation of the results from our large collection of models, we summarize our data by partitioning evolutionary outcomes into three categories: random mating (nonrandom mating does not evolve), an intermediate rate of nonrandom mating, or complete nonrandom mating. Interestingly, intermediate levels of nonrandom mating only occur in one case, which happens to correspond to the example of the MHC. To provide additional insight, we then focus more closely on this case.

EVOLUTIONARILY STABLE STRATEGIES

We conducted an analysis of evolutionarily stable strategies (ESSs). At every iteration of our algorithm, we began with a resident population fixed for an allele that codes for some strength of nonrandom mating, which we denote as ρ_{res}. We then introduced, at a frequency of 10^{-4}, a mutant that encoded for a different strength of nonrandom mating, specifically $\rho_{mut} = \rho_{res} + \delta$. After 100 generations, we determined if the modifier had successfully invaded by assessing whether it had increased in frequency. If invasion was successful, we set $\rho'_{res} = \rho_{mut}$ for the next iteration of the algorithm. Otherwise, if invasion failed, we set $\rho'_{res} = \rho_{res}$ and $\delta' = -\frac{\delta}{2}$ for the next iteration of the algorithm. By halving and reversing the sign of δ whenever invasion failed, we found the evolutionarily stable value of ρ. We initiated with $\rho_{res} = 0$ and $\delta = 0.1$. This algorithm can be thought of as exploring a pairwise invasibility plot to identify the ESS. A small sample of algorithm outputs was validated against pairwise invasibility plots (not shown).

The combinations of parameter values used in this analysis can be found in Table S6, and we consider cases with between two and five alleles at the interaction locus. As mentioned earlier, we classify the ESS rates of nonrandom mating into one of three categories: near zero (i.e., nonrandom mating does not evolve), intermediate, and near one (i.e., complete nonrandom mating evolves). Cases in which nonrandom mating does not evolve (ρ remains near zero when initiated at zero) are denoted "random mating." Cases in which complete disassortative (assortative) mating evolves (ρ evolves to its largest possible value) are described as "complete disassortative mating" ("complete assortative mating"). Cases in which an intermediate level of nonrandom mating evolves are described as "intermediate."

Evolution of nonrandom mating depends on the strength and direction of both parasite-induced selection and sexual selection (Nuismer et al. 2008; Otto et al. 2008). For diploid hosts, parasite-induced selection is expected to promote the evolution of higher disassortative (assortative) mating when the infection scheme used tends to favor heterozygotes (homozygotes). Sexual selection, on the other hand, is expected to favor modifiers that promote the production of offspring that are preferred during mate selection. For instance, in a population with a high level of disassortative mating, there will be an excess of heterozygotes, which may favor modifiers that weaken disassortative mating because the heterozygotes that are produced by disassortative mating are sexually disfavored as their type is common.

In what follows, we first provide a summary of how mating and infection scheme, and host and parasite ploidy affect the evolution of nonrandom mating (presented in Tables 5 and 6 for two and five alleles at the interaction locus, respectively). For simplicity, in this section, we pool across values of ϕ. Then, in the next section, we quantitatively examine the impact of the strength of maternal transmission, number of interaction locus alleles, and other parameters on the ESS values for the case when ESSs are intermediate, which is the case that corresponds to the MHC system.

Under the plant mating model (case 1, Tables 5 and 6), nonrandom mating of either kind is predicted not to evolve. As was also found by Nuismer et al. (2008), the cost of choosiness in this case is too severe for nonrandom mating to evolve.

Interestingly, across all of our model combinations, the only case in which an intermediate ESS occurs is the scenario that represents the MHC system. Specifically, under the animal model with IMA infection, when hosts are diploid and parasites are haploid or diploid (case 3, Tables 5 and 6), only disassortative mating evolves ($\omega = 0$), and to either an intermediate or complete level. With more alleles at the interaction locus, the fraction of model combinations associated with the evolution of complete (as opposed to intermediate) disassortative mating increases (compare case 3 between Tables 5 and 6 that show outcomes when there are two and five alleles at the interaction locus, respectively). This can be understood as follows: Under the IMA model, heterozygotes are favored by parasite-induced selection that favors disassortative mating. As the level of disassortative mating rises, heterozygotes become more common, which reduces their mating fitness. Frequency-dependent selection, in which an allele's relative fitness changes as the genetic composition of the parasite population changes will also promote the evolution of disassortative mating, because it can create associations between modifier alleles that increase the rate of disassortative mating and rare advantageous interaction locus alleles (see Fig. S1 for sample runs showing frequency-dependent coevolutionary dynamics). With more than two alleles, and more than one type of heterozygote, frequency-dependent selection becomes an increasingly important factor in explaining the evolution of disassortative mating, as different heterozygote genotypes vary over time in their relative fitnesses. Because heterozygotes are favored under the IMA model, assortative mating fails to evolve under the grouping model (case 5, Tables 5 and 6).

For diploid hosts and parasites of either ploidy in the MA model, complete assortative mating is predicted to evolve

Table 5. Summary of evolutionary outcomes with two alleles at the interaction locus.

Case	Infection model	Mating model	Host ploidy	Parasite ploidy	Predominant result (%)
1	IMA, MA	Plant	1, 2	1, 2	Random mating (100)
2	IMA, MA	Animal	1	1, 2	Complete disassortative mating (100)
3 (MHC)	IMA	Animal	2	1, 2	Intermediate disassortative mating (99)
4	IMA, MA	Grouping	1	1, 2	Random mating (100)*
5	IMA	Grouping	2	1, 2	Random mating (100)*
6	MA	Animal	2	1	Complete assortative mating (93)
7	MA	Animal	2	2	Complete assortative mating (96)
8	MA	Grouping	2	1, 2	Complete assortative mating (100)*

We classify an ESS as "random mating," "intermediate," or "complete" if it lies, respectively, in the interval [0, 0.05], [0.05, 0.95], or [0.95, 1]. For each scenario, we only report the predominant outcome, with numbers in parentheses indicating the percentage of parameter combinations that led to that particular outcome. Because maternal transmission did not impact these results, we pooled our data across values of maternal transmission. As discussed in the main text, in cases under the grouping model (indicated with symbol "∗"), only the evolution of assortative mating (and not disassortative mating) is applicable.

Table 6. Summary of evolutionary outcomes with five alleles at the interaction locus.

Case	Infection model	Mating model	Host ploidy	Parasite ploidy	Predominant result (%)
1	IMA, MA	Plant	1, 2	1, 2	Random mating (100)
2	IMA, MA	Animal	1	1, 2	Complete disassortative mating (100)
3 (MHC)	IMA	Animal	2	1, 2	Intermediate disassortative mating (25) Complete disassortative mating (75)
4	IMA, MA	Grouping	1	1, 2	Random mating (100)*
5	IMA	Grouping	2	1, 2	Random mating (100)*
6	MA	Animal	2	1	Complete assortative mating (98)
7	MA	Animal	2	2	Complete assortative mating (98)
8	MA	Grouping	2	1, 2	Complete assortative mating (100) *

See Table 5 caption for other details.

for both the animal and grouping mating models (cases 6–8, Tables 5 and 6). In this case, parasite-induced selection favors homozygotes, which confers an advantage to assortative mating. As homozygotes and assortative mating become more common, sexual selection also favors homozygotes. These findings are also generally consistent with those of Nuismer et al. (2008) who used invasion analyses to study the evolution of nonrandom mating in diploids only.

For haploid hosts and parasites of either ploidy, complete disassortative mating is generally predicted to evolve, except in the grouping model in which disassortative mating is not applicable (cases 2 and 4, Tables 5 and 6). As is true in host–parasite models for the evolution of mutation rate (M'Gonigle et al. 2009; Greenspoon and M'Gonigle 2013), evolution of disassortative mating in haploid models occurs as a result of negative frequency-dependent selection (see Fig. S1 for sample runs showing frequency-dependent coevolutionary dynamics). Host–parasite coevolutionary models exhibit cyclical allele-frequency dynamics because rare alleles tend to be advantageous (Nee 1989). It follows, then, that females who select mates with rare alleles (by mating disassortatively) will produce higher fitness offspring, because those offspring will tend to inherit that advantageous allele. It is noteworthy that this process requires at least some recombination in order that the modifier can become associated with the beneficial rare allele.

In our above analyses, we have tracked the fitness of successive modifiers of nonrandom mating, each of which is introduced into a population whose allele frequencies at the antigen locus have not been given time to reach equilibrium dynamics (e.g., see sample cycle dynamics in Fig. S1). This could be problematic when considering the evolution of disassortative mating for cases that lack cycles at equilibrium, because disassortative mating should be more advantageous when there is coevolutionary cycling. Thus, for cases in which there are no cycles at equilibrium, with our analysis we could find positive selection on modifiers even if no selection would occur at equilibrium (Howard and Lively 2004). Unfortunately, with infinite population sizes, as considered here, no length of burn in will sufficiently allow for dynamics at the antigen locus to equilibrate and even the smallest deviation from this equilibrium may be enough to favor a

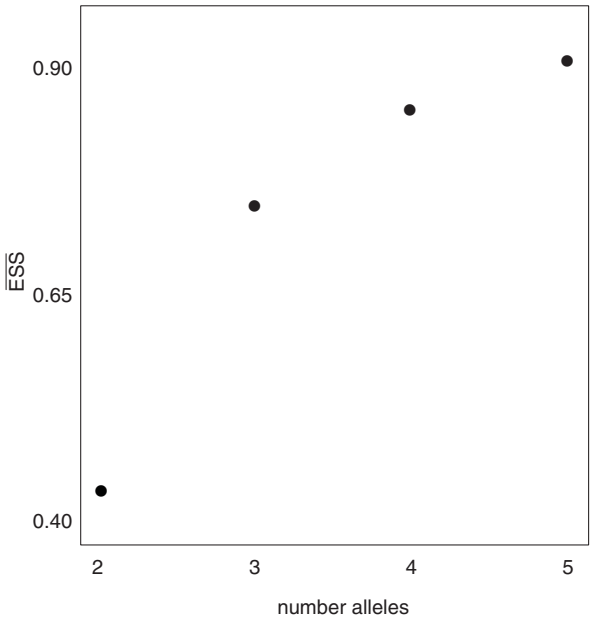

Figure 1. The $\overline{ESS}$ level of disassortative mating in diploids as a function of the number of alleles at the interaction locus for the case that corresponds to the MHC. $\overline{ESS}$ is defined as the mean ESS taken over the range of combinations of the parameters (see Table S6).

modifier allele. Furthermore, initializing model runs exactly at the potential noncycling equilibrium (e.g., with each antigen at exactly equal frequency) is not interesting from a biological perspective. Thus, we conducted an additional set of model runs where allele frequencies were initialized close to, but not identically at the noncycling equilibrium (with two alleles at frequencies of 0.49 and 0.51). We found that, for the evolution of disassortative mating under the animal mating model, these results were qualitatively the same as those discussed above. Thus, our findings should apply to any population that is not precisely at the noncycling equilibrium.

MHC EXAMPLE

We now focus our attention to the scenario described above that represents the MHC system, as this is the only case that exhibits intermediate ESSs (case 3, Tables 5 and 6). Specifically, we aim to provide additional insight into how the number of alleles at the interaction locus and maternal transmission affect the evolution of nonrandom mating. To do this, we examined how the mean ESS, $\overline{ESS}$ (defined in more detail in the captions of Figs. 1, 2), varies with the number of alleles and ϕ. Additionally, we looked at the effects of virulence, v; probability of successful infection, λ; and recombination rate, r. As contour plots revealed no notable qualitative interactions between the parameters (e.g., there are no changes in direction of the effect of one parameter depending on the value of the other; Fig. S2), we conducted our analyses by varying each parameter on its own.

As discussed above and confirmed here, the main effect of increasing the number of alleles is to increase the mean level of disassortative mating that evolves (Fig. 1). The value of $\overline{ESS}$ increases as the strength of maternal transmission, ϕ, increases, although the effect is weak (Figs. 2A, 3A). This is consistent with the finding that maternal transmission can select for higher rates of sex (Agrawal 2006) and mutation (Greenspoon and M'Gonigle 2013). In genetically diverse populations, offspring are more similar to their mothers. Consequently, parasites that are well targeted to an individual's mother will also tend to be well targeted to that individual. Disassortative mating thus becomes more advantageous with higher rates of maternal transmission of parasites, because it tends to make offspring less similar to their mothers.

Nuismer et al. (2008) only considered interaction loci with two alleles. However, the MHC is known for having much larger population-wide allelic diversity. Allowing for more alleles, we find that the value of $\overline{ESS}$ increases with the number of alleles at the interaction locus. In the two-allele case, there is one type of heterozygote and it is always the superior genotype with respect to interactions with the parasite. With more alleles, a heterozygote could still benefit from disassortative mating, because disassortative mating may lead to the production of a heterozygote bearing different alleles that are more favorable within the current parasite population.

The value of $\overline{ESS}$ also increases with the virulence of parasites, v (Figs. 2B, 3B). Higher virulence increases the strength of parasite-induced selection, which tends to select for stronger disassortative mating (Table 2). On the other hand, sexual selection increasingly selects against disassortative mating as the rate of disassortative mating, and thus the frequency of heterozygotes, increases. The evolutionarily stable level of disassortative mating reflects a balance between these two processes and thus more virulent parasites select for higher levels of disassortative mating. For a similar reason, the value of $\overline{ESS}$ also increases with the probability of successful infection, λ (Figs. 2C, 3C).

Lastly, the value of $\overline{ESS}$ decreases with recombination rate, r, with two alleles (Fig. 2D), but, at low values of r, increases with r with more than two alleles (Figs. S3D , 3D). As noted above, with more alleles the importance of frequency-dependent selection, as opposed to heterozygote advantage, increases. Recombination should only impact the ability of the former to induce selection on disassortative mating, because recombination may enable a modifier allele to recombine into the background of a different interaction locus allele. Recombination has a complex role because, while it can promote the evolution of disassortative mating by enabling modifiers that code for high levels of disassortative mating to become associated with currently favorable interaction locus alleles, it can also hamper the

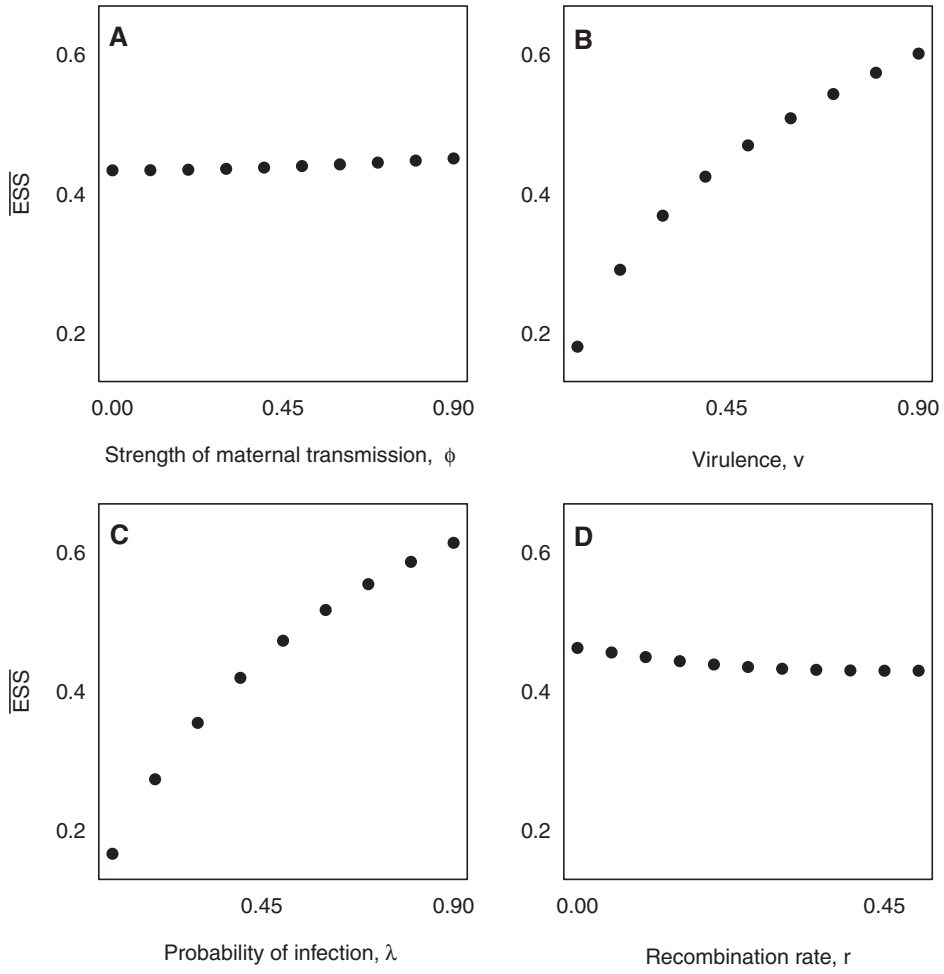

Figure 2. The $\overline{ESS}$ level of disassortative mating in diploids as a function of the rate of maternal transmission (A), virulence (B), the probability of infection (C), and the rate of recombination (D) with two alleles at the interaction locus for the case that corresponds to the MHC. For each of the parameters, $\overline{ESS}$ is defined as the mean ESS taken over the range of combinations of the other parameters (see Table S6) with the focal parameter fixed at the corresponding value on the horizontal axis.

evolution of disassortative mating by disassociating the alleles. For more than two alleles, when frequency dependence becomes more important, low levels of recombination become more critical for building associations between the modifiers that code for high rates of disassortative mating and the currently favorable, rare interaction locus alleles.

Our modeling framework in which results are summarized across a range of models and parameter combinations has previously been used to study the evolution of nonrandom mating in response to host–parasite coevolution for diploid hosts with diploid parasites and complete global infection (Nuismer et al. 2008). The strength of this approach is that it allows us to identify general trends across a broad range of models and parameter values. The main downside (compared to an analytical model or more focused simulation model) is that it is difficult to identify the mechanisms that underlie some of the trends observed here. Thus, the explanations given above should be interpreted with some caution until further work investigates them in a more focused modeling framework.

Discussion

Nonrandom mating is common. But why should species evolve to be picky? One possibility is that the genetic consequences of nonrandom mating (e.g., heterozygosity) are selectively advantageous in the face of parasite-induced selection. The MHC is known to play a role in both immune function and mate choice (Milinski 2006). An intriguing hypothesis is that disassortative mating with respect to the MHC could be an adaptation to increase diversity at MHC loci, thus conferring superior protection against disease. Previous theoretical work in haploids (Howard and Lively 2003, 2004) and diploids (Nuismer et al. 2008) has shown that disassortative mating could evolve in response to parasite-induced selection, while in diploids assortative mating could also evolve

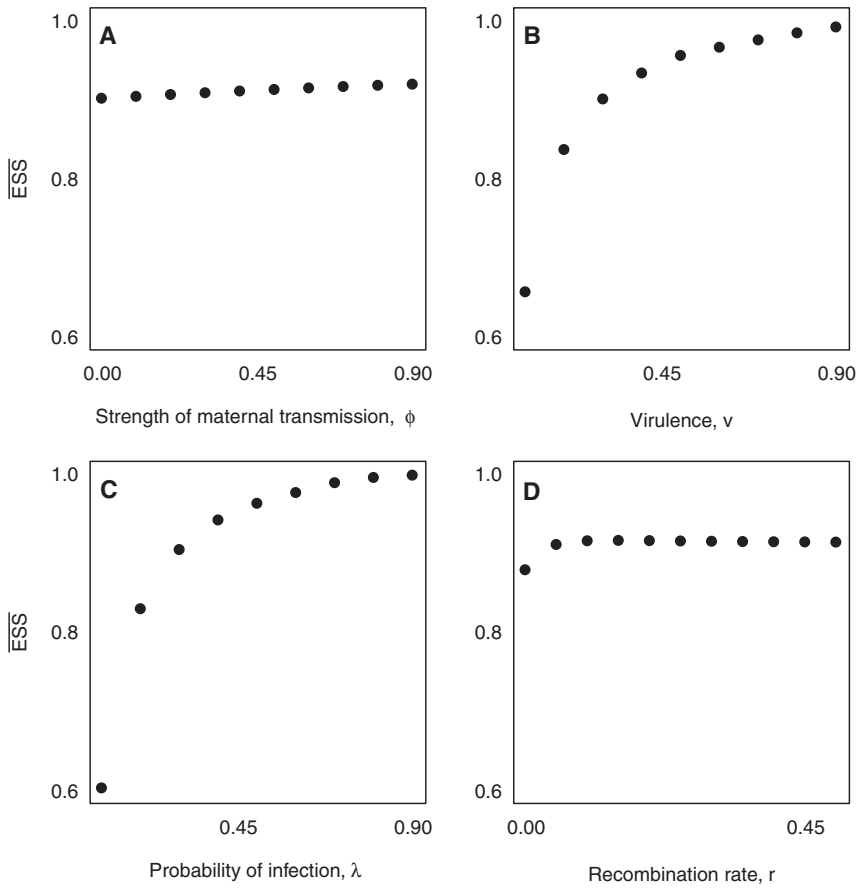

Figure 3. The $\overline{ESS}$ as a function of the rate of maternal transmission (A), virulence (B), the probability of infection (C), and the rate of recombination (D) with five alleles at the interaction locus. All else is as described in Figure 2.

depending on how infection and mate choice occur. Here, we have studied the evolution of nonrandom mating in an antagonistic coevolutionary model, and built on previous work in four specific ways: First, we looked at evolutionarily stable strategies rather than simply invasion as has been done previously. Second, we presented results for both haploid and diploid hosts and parasites within a common modeling framework. Third, we examined how maternal transmission of parasites affects evolution of nonrandom mating. Fourth, we investigated the effect of the number of interaction locus alleles on the evolution of nonrandom mating.

The findings of our analysis of ESSs are consistent with previous work that focused only on whether modifiers of assortative mating could invade randomly mating populations. Here, we have gone one step further by investigating evolutionarily stable rates of nonrandom mating. Particularly interesting is the finding that intermediate levels of disassortative mating evolve for diploid hosts under the IMA infection model when choosiness is not costly, a model that corresponds to the MHC system. Previous analytical studies of simpler models have shown that parasite-induced selection and sexual selection impact the evolution of modifiers of nonrandom mating. Our finding that intermediate rates are stable reveals that there can be a balance between these two forces. On the one hand, parasite-induced selection confers an advantage to heterozygotes under the IMA model, thus favoring disassortative mating that produces more heterozygotes. On the other hand, as the strength of disassortative mating evolves to higher levels and the frequency of heterozygotes increases, heterozygotes become, on average, less successful at procuring mates. As our results suggest, at some intermediate level of disassortative mating these factors balance out.

Our finding with haploid hosts that complete disassortative mating evolves differs from the results of Howard and Lively (2003, 2004) who showed that although an allele causing disassortative mating always invades a randomly mating population, it only rises to an intermediate frequency. As they discussed, at this intermediate frequency coevolutionary cycles at the interaction locus cease, and thus selection for increased disassortative mating also ceases. The algorithm we used to locate an ESS sequentially introduces novel alleles at the modifier locus and determines whether they increase in frequency. Even if the resident modifier might code for a level of disassortative mating that would not exhibit cyclical dynamics at the interaction locus

at equilibrium, there may be nonequilibrial cycles at the start of invasion when interaction locus allele frequencies are not exactly even (e.g., 50:50 for the two-allele case; see Fig. S1). This initial bout of frequency-dependent selection can be sufficient to promote the invasion of a modifier coding for a higher level of disassortative mating. Thus our analysis here applies to situations where allele frequencies are perturbed from equilibrium, such that transient cycles occur. It is also worth mentioning that, in contrast to Howard and Lively's stochastic model, we used a deterministic model that has a greater ability to detect slight changes at the modifier locus. Thus we might have reported an increase in frequency in a case when they would not have.

Although previous models focused only on single ploidy combinations (either both hosts and parasites haploid [Howard and Lively 2003, 2004], or both diploid [Nuismer et al. 2008]), here we examined all combinations of host and parasite ploidy. It is worth mentioning, however, that although we compared haploidy to diploidy, a comparison between one interaction locus haploids and two interaction locus haploids, would likely yield similar conclusions, provided an analogous infection scheme were implemented.

We found that the ploidy of hosts dramatically affects whether nonrandom mating evolves, whereas ploidy of parasites does not. For simplicity, there has been a tendency in the past to develop primarily haploid modifier models under the assumption that their behavior approximates that of diploids. However, care must be taken in applying the results from haploid models to diploids. For example, the predictions of diploid Red Queen models of the evolution of sex differ importantly from haploid models because they incorporate the effects of both segregation and recombination rather than only recombination (Agrawal and Otto 2006).

For the scenario that corresponds to the MHC model, we found that increasing the strength of maternal transmission led to stronger selection for modifiers that increase the level of disassortative mating, although this effect was weak. This finding is consistent with previous work that has shown that maternal transmission can also strengthen selection for modifiers that increase the rate of sex (Agrawal 2006) and mutation (Greenspoon and M'Gonigle 2013). In all three cases, maternal transmission promotes the spread of a modifier that decreases genetic similarity between a mother and her offspring. This is advantageous when parasites are maternally transmitted because maternally transmitted parasites tend to be the most likely to cause a successful infection. We found that, as the number of alleles at the interaction locus increases, so does the level of disassortative mating that evolves, a result that had been missed by the previous two-allele diploid model of Nuismer et al. (2008). We would predict, therefore, that populations with more MHC variants should exhibit stronger levels of disassortative mating. We also found that higher virulence and/or probability of successful infection led to higher ESS rates of nonrandom mating, because both increase the strength of parasite-induced selection.

There is a vast literature investigating the relationship between MHC genotype and resistance to infection (Kubinak et al. 2012). Although some studies have supported the view that maximum MHC heterozygosity is optimal, an alternative hypothesis that has received support—known as the optimality hypothesis—is that intermediate, rather than maximal MHC heterozygosity is optimal (e.g., Wegner et al. 2003; Kurtz et al. 2004; Milinski 2006; Woelfing et al. 2009; Kubinak et al. 2012). This pattern can be explained by the existence of a trade-off between higher intraindividual MHC variation, which confers resistance against more parasites, and the various costs associated with high MHC heterozygosity, such as autoimmunity (Kubinak et al. 2012). Our MHC model, which simply assumes that more MHC diversity is better, thus tells just one part of the story. A more complete, and consequently more complex, model could attempt to incorporate immunological details, such as risk of autoimmunity, as well.

The optimality hypothesis predicts that mates would be chosen such that intermediately MHC-variable offspring would be produced, and intermediately MHC-variable individuals would exhibit the highest fitness (Kubinak et al. 2012). There has been some support for this. For example, in sticklebacks intermediate intraindividual MHC-diversity has been shown to be optimal due to selection imposed by parasites (Wegner et al. 2003) and females have been shown to prefer males whose MHC-diversity complements theirs in such a way that their offspring are intermediately heterozygous (Aeschlimann et al. 2003; Kubinak et al. 2012). Although our MHC model does predict the evolution of intermediate rates of disassortative mating, this is not equivalent to predicting the evolution of a preference for mates of intermediate MHC differences. For the sake of simplicity, we did not investigate whether more nuanced mating schemes could evolve. The main value of doing so would, again, occur in the context of a model that incorporated the costs to heightened MHC heterozygosity. In such a model, heightened costs of MHC heterozygosity would likely induce the evolution of preferences for intermediately differentiated mates.

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Supporting Information

Additional Supporting Information may be found in the online version of this article at the publisher's website:

Figure S1. Allele frequency dynamics at the interaction locus in the host (black) and parasite (blue) populations during coevolution under the IMA infection model and animal mating model.

Figure S2. Contour plots of the ESS level of disassortative mating in diploids as a function of strength of maternal transmission, f; virulence, v; probability of infection, l, recombination rate, r, and the number of alleles at the interaction locus in all pairwise combinations for the case that corresponds to the MHC.

Figure S3. The ESS as a function of the rate of maternal transmission (A), virulence (B), the probability of infection (C), and the rate of recombination (D) with three alleles at the interaction locus.

Table S1. Models of infection in haploid hosts and haploid parasites.

Table S2. Models of infection in diploid hosts with haploid parasites.

Table S3. Models of infection in haploid hosts and diploid parasites.

Table S4. Relative preferences of females for males under assortative ($w = 1$) or disassortative ($w = 0$) mating in plant and animal models when hosts are haploids.

Table S5. Grouping model probabilities in haploids.

Table S6. Parameter values used for generating Table 5 and Figure 1.