When do opposites attract? A model uncovering the evolution of disassortative mating

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Abstract

Disassortative mating is a rare form of mate preference that promotes the persistence of polymorphism. While the evolution of assortative mating, and its consequences on trait variation and speciation have been extensively studied, the conditions enabling the evolution of disassortative mating are still poorly understood. Mate preferences reduce the number of available partners, a cost that can be compensated by a greater fitness of offspring. Heterozygote advantage should therefore promote the evolution of disassortative mating, which maximizes the number of heterozygous offspring. From the analysis of a two-locus diploid model, with one locus controlling the mating cue under natural selection and the other locus coding for the level of disassortative preference, we show that heterozygote advantage and negative frequency dependent selection acting at the cue locus promote the fixation of disassortative preferences. Interestingly, we show that disassortative mating generates a negative frequency-dependent sexual selection, which in turn disadvantages heterozygotes at the cue locus, limiting the evolution of disassortative preferences. This negative feedback loop could explain why this behavior is rare in natural populations. Yet, the conditions enabling the evolution of disassortative mating in our model match the selection regimes acting on traits subject to disassortative mating behavior in the wild.

Introduction

The evolution of mate preferences is puzzling because preferences reduce the number of available sexual partners, which may incur an opportunity cost. The evolution of disassortative mating, i.e. of preference towards individuals displaying a different trait is all the more surprising, because it also requests the persistence of traits variation within populations. While the evolution of assortative mating has been reported in many species, disassortative mating is more scarcely observed (Jiang et al., 2013), suggesting that the conditions enabling its evolution could be more restrictive. Here we aim at investigating the selection regimes allowing the evolution of disassortative mating using a mathematical approach.

The multiple types of cost associated with mate choice (such as increased investment in mate searching and courtship, for instance) tend to generate direct selection against the evolution of mate preferences (see (Pomiankowski, 1987) for a review), and may further limit the evolution of disassortative mating. Furthermore, choosy individuals can pay a fitness cost because they refuse mating opportunities (that strongly limits the evolution of preference in theoretical studies Kopp and Hermisson (2008); Schneider and Bürger (2006)). Moreover the mechanisms underlying mate choice may require specialized morphological, physiological and cognitive changes (see Rosenthal (2017) for a review), that may induce specific metabolic costs. For example, in the self-incompatibility system in the genus *Brassica*, mate choice involves a specialized receptor-ligang association Hiscock and McInnis (2003), so that the evolution of self-incompatibility is associated with metabolic costs induced by the production of the specific proteins. Mate choice can also increase the investment in mate searching, because an individual needs to sample several

mates to find a suitable one. This increased sampling effort can be costly in time Kruijt and Hogan (1967), in energy (as empirically estimated in antilopes Byers et al. (2005)) and may increase predation risk, for instance in patrolling animals Hughes et al. (2012). In addition, the evolution of mate preferences can involve supplementary costs associated with the rebuttal. In the fly species *Musca domestica*, males jump on females' back to initiate mating and choosy females have to kick unpreferred males to avoid mating Sacca (1964).

Despite these costs, mate choice is ubiquitous in nature (Backwell and Passmore, 1996; Barrett, 1990; Cisar, 1999; Hiscock and McInnis, 2003; Jiggins et al., 2001; Merrill et al., 2014; Savolainen et al., 2006) indicating that mate preference evolves readily and that choosy individuals enjoy benefits compensating those costs. Choosy individuals may enjoy direct benefits (Wagner, 2011) (for instance through beneficial sexually transmitted infections (Smith and Mueller, 2015), or by decreasing risk of pre-copulatory cannibalism (Pruitt and Riechert, 2009)), as well as indirect benefits associated with mate preferences through an enhanced quality of their offspring (Byers and Waits, 2006; Drickamer et al., 2000; Jiggins et al., 2001; Petrie, 1994; Sheldon et al., 1997; Welch et al., 1998).

Natural selection acting on mating cues, by generating indirect selection on preferences, may thus promote their evolution (Fisher, 1930). The effect of natural selection on mating cues on the evolution of mate preferences, first identified by Fisher, has now been confirmed in many theoretical studies (Heisler, 1984, 1985; Kirkpatrick, 1982; O'Donald, 1980a). A growing number of empirical evidence showing that female choice does improve offspring fitness is also reported (Byers and Waits, 2006; Drickamer et al., 2000; Petrie, 1994; Sheldon et al., 1997; Welch et al., 1998). The indirect selection through offspring fitness may thus be a major driver of the evolution of mate choice.

Once mate preferences are established in the population, they generate sexual selection on the traits exhibited by individuals during courtship, that may drive the evolution of extravagant traits in males, following a fisherian runaway (Fisher, 1930; Lande, 1981; O'Donald, 1980b). The evolution of mate preferences thus involves complex evolutionary processes where preferences co-evolve with the cues displayed by the chosen individuals. This co-evolution has been observed in natural populations (Grace and Shaw, 2011; Higginson et al., 2012) and in experimental studies (Brooks and Couldridge, 1999; Miller and Pitnick, 2002), underpinning the importance of sexual selection feedbacks on the evolution of mate preferences.

The different selection regimes acting on mating cues can therefore drive the evolution of different types of mate preferences, through indirect selection. Disruptive selection whereby different mating cues are favored in different habitats for instance, has been demonstrated to promote assortative preferences that improves local adaptation in the offspring (Bank et al., 2012; de Cara et al., 2008; Dieckmann, 2004; Dieckmann and Doebeli, 1999; Gavrilets, 2004; Kirkpatrick, 2000; Kirkpatrick and Ravigné, 2002; Otto et al., 2008). By contrast, selection conferring fitness advantages to intermediate phenotypes is often thought to promote disassortative mating (Kirkpatrick and Nuismer, 2004; Kondrashov and Shpak, 1998). Nevertheless, the selection regimes enabling the evolution of disassortative mating are much less studied than the selective pressures involved in the evolution of assortative mating, extensively investigated in the context of speciation (Gavrilets, 2004).

Disassortative mating has been documented only in a few cases, as for instance the MHC locus in humans and mice, where females prefer males with a genotype different from their own (Wedekind et al., 1995), the plumage coloration in the white throated

sparrow (Throneycroft, 1975), or the wing color pattern in the mimetic butterfly *Heliconius numata* (Chouteau et al., 2017). In those cases, empirical evidences of heterozygote advantage have been reported (Jay et al., 2019), so that disassortative mating may increase the offspring fitness. In a model focusing in evolution of disassortative mating on polymorphic mimetic colour patterns, Maisonneuve et al. (2019) shows that heterozygote advantage at the locus controlling colour pattern variation may promote the emergence of disassortative mating, highlighting the effect of indirect selection acting on offspring's fitness. Ihara and Feldman (2003) also showed that disassortative mating can be promoted when matings of pairs with different phenotypes are more fertile. Other theoretical studies have focused on the effect of disassortative mating on the persistence of variations at the cue locus, illustrating that this mate preference may limit the purging of maladaptive cue alleles, and therefore promotes higher levels of polymorphism at the cue locus (Falk and Li, 1969; Ihara and Feldman, 2003; Karlin and Feldman, 1968), and in turn, maintains conditions favoring this mate preference. These results suggest that the evolution of disassortative preferences is likely to depend on the natural selection acting at the cue locus but also on complex feedbacks between cue polymorphism and mate choice. This is now calling for a mathematical framework providing general predictions on the selection regimes enabling the evolution of disassortative mating.

To this end, we develop a mathematical model assuming a population of diploid individuals with two key loci: the first locus C controls variation in a single mating cue, that may be subject to natural selection. The second locus P controls mate preference towards the cues encoded by locus C. We take into account fixed and relative costs associated with choosiness. Building on a previous model of evolution of assortative mating developed by Otto et al. (2008), we first analyze the model under a Quasi-linkage Equi-

librium (QLE). We thus derive analytic expressions of changes in genetic frequency at both the cue and preference loci, providing general expectations on the conditions enabling the emergence and persistence of disassortative mating. We then use numerical simulations to explore the evolution of disassortative preferences under strong overdominant selection acting at the cue locus, that does not match the QLE assumptions. We finally compare our theoretical predictions with the few documented cases of disassortative mating and discuss why the evolution of disassortative mating may be limited in natural populations.

Methods

We assume a two-sex diploid species, and two loci C and P. The locus C controls for a trait used as a mating cue and the locus P for the mate preference. Locus C can be under different selection regimes. The two loci recombine with probability r at each birth event. We consider a discrete time model and follow the genotypes frequencies over time.

Mating cue locus under natural selection

We have two different alleles at locus C, a and b, and $\mathcal{G}_C = \{aa, ab, bb\}$ is the set of possible genotypes at this locus. Dominance between alleles a and b is controlled by the *dominance coefficient* at locus C, h_C. If $h_C = 1/2$ alleles a and b are codominant. If $h_C = 0$ (resp. 1) a is dominant (resp. recessive) to b. If $0 < h_C < 1/2$ (resp. $1/2 < h_C < 1$) allele a is incompletely dominant (resp. recessive) to b.

The cue induced by the genotype at locus C determines mating success but can also be under different selection regimes, favoring the persistence of polymorphism. Con-

trary to assortative mating, which is favored when the mating cue is under positive selection, disassortative mating implies some polymorphism of mating cue. We explore the evolution of disassortative mating under any selective regime acting on the mating cues, and specifically focus on the case when natural selection promotes polymorphism at locus C.

Let $f^t(i,k)$ be the frequency of genotype $(i,k) \in \mathcal{G}_C \times \mathcal{G}_P$ at time t with $\mathcal{G}_P$ being the set of genotypes at the preference locus. We introduce a selection coefficient $S_i(f, h_C)$ acting on genotype $i \in \mathcal{G}_C$, which may vary depending on genotypic frequencies at locus C and dominance between alleles a and b. This allows exploring different regimes of balancing selection, including negative frequency-dependent selection, that can favor polymorphism at locus C. Let w_i^t be the fitness of genotype i at time t resulting from natural selection acting at the locus C

$$w_i^t := 1 + S_i(f^t, h_C).$$

We assume that natural selection generating changes in genotype frequencies at locus C acts before reproduction. As a consequence, the changes in frequencies due to sexual selection depend on the frequencies at locus C after natural selection, described below. For $(i,k) \in \mathcal{G}_C \times \mathcal{G}_P$:

$$f_{i,k}^{t+\frac{1}{2}} = \frac{w_i^t}{\overline{w}^t} f_{i,k}^t,$$

with

$$\overline{w}^t = \sum_{i \in \mathcal{G}_C} w_i^t \left(\sum_{k \in \mathcal{G}_P} f_{i,k}^t \right)$$

being the average fitness of the females. The exponent $t + 1/2$ emphasizes the asynchronous steps between mating and natural selection frequencies updates.

Mate choice and reproduction

Reproduction depends on the mating cues controlled by locus C, but also on mate preferences. At the mating preference locus P, we assume two alleles: a resident allele M and a mutant one m. The set of possible genotypes at this locus is thus $\mathcal{G}_P = \{MM, Mm, mm\}$. Each genotype $k \in \mathcal{G}_P$ is associated with a coefficient ρ_k, which quantifies how much a female of genotype k tends to reject males with the same cue as her own (i.e. the disassortative preference of females). The values of ρ_{MM} and ρ_{mm} are fixed. For the genotype Mm, we introduce a dominance coefficient h_P at locus P, similarly as the dominance at locus C. We have the following relation:

$$\rho_{Mm} = (1 - h_P)\rho_{MM} + h_P\rho_{mm}.$$

We assume females to be the choosy sex (de Cara et al., 2008; Gavrilets and Boake, 1998; Kopp and Hermisson, 2008; Lande, 1981; Otto et al., 2008), so that males can mate with any accepting females. We assume a balanced sex-ratio and consider that the frequencies of females and males with genotype i are equal (de Cara et al., 2008; Gavrilets and Boake, 1998; Otto et al., 2008).

To quantify the mating probability between two individuals we introduce the preference matrix $Pref(\rho_k), k \in \mathcal{G}_P$. For $(i, j) \in \mathcal{G}_C^2, k \in \mathcal{G}_P$, $Pref_{ij}(\rho_k)$ measures the strength of preference of female i with genotype k at locus P for male j.

$$Pref(\rho_k) = \begin{array}{cc} & \begin{array}{ccc} aa & ab & bb \end{array} \\ & \begin{pmatrix} 1-\rho_k & 1-(1-h_C)\rho_k & 1 \\ 1-(1-h_C)\rho_k & 1-\rho_k & 1-h_C\,\rho_k \\ 1 & 1-h_C\,\rho_k & 1-\rho_k \end{pmatrix} \begin{array}{c} aa \\ ab \\ bb \end{array} \end{array}. \tag{1}$$

For $(i,k) \in \mathcal{G}_C \times \mathcal{G}_P$, we define $T^t_{i,k}$ as the probability that a female of genotype (i,k) accepts a male during a mating encounter:

$$T^{t+\frac{1}{2}}_{i,k} = \sum_{j \in \mathcal{G}_C} Pref_{ij}(\rho_k) p^{t+\frac{1}{2}}_j,$$

with

$$p^{t+\frac{1}{2}}_j := \sum_{l \in \mathcal{G}_P} f^{t+\frac{1}{2}}_{j,l}$$

being the proportion of genotype j at the cue locus C among males (and females).

Choosy females of genotype k at locus P are assumed to pay a fixed cost $c_f \rho_k$ for their choosiness (the more a female is choosy the higher this cost is), that accounts for a greater investment in the search or rejection of mates. Mating behavior is indeed thought to be more costly for choosy females than for females mating with the first male encountered, regardless of displayed cue.

Furthermore, choosy females also pay a relative cost of choosiness, depending on the proportion of preferred males and on a coefficient $c_r \in [0,1]$. A choosy female pays a small relative cost of choosiness if the preferred mates are abundant in the population. When a female rejects a given male because he displays an unpreferred cue, she can still accept another mate with probability $1 - c_r$.

We define the fertility of a female of genotype $(i,k) \in \mathcal{G}_C \times \mathcal{G}_P$ as

$$F^{t+\frac{1}{2}}_{i,k} = (1 - c_r + c_r T^{t+\frac{1}{2}}_{i,k})(1 - c_f \rho_k).$$

The average fertility in the population is thus:

$$\overline{F}^{t+\frac{1}{2}} = \sum_{(i,k) \in \mathcal{G}_C \times \mathcal{G}_P} f^{t+\frac{1}{2}}_{i,k} F^{t+\frac{1}{2}}_{i,k}.$$

Then changes in genotypes frequencies are as follows. For $(i', k') \in \mathcal{G}_C \times \mathcal{G}_P$:

$$f_{i',k'}^{t+1} = \sum_{(i,k)\in\mathcal{G}_C\times\mathcal{G}_P} \left(f_{i,k}^{t+\frac{1}{2}} \frac{F_{i,k}^{t+\frac{1}{2}}}{\overline{F}^{t+\frac{1}{2}}} \sum_{(j,l)\in\mathcal{G}_C\times\mathcal{G}_P} coef_{i',k',i,k,j,l,r} \frac{Pref_{ij}(\rho_k)) f_{j,l}^{t+\frac{1}{2}}}{T_{i,k}^{t+\frac{1}{2}}} \right),$$

where *coef* controls the Mendelian segregation of alleles during reproduction between the choosing individual of genotype i at locus C and k at locus P and a chosen individual of genotype j at locus C and l at locus P, determining his displayed cue. The Mendelian segregation also depends on the recombination probability r between the cue locus C and the preference locus P. All variables and parameters used in the model are summed up in Table 1.

Model exploration

QLE approximation exploring the evolution of weak disassortative preference

We use the QLE analysis results presented in a previous model of evolution of assortative mating (see Appendix B in (Otto et al., 2008)). This approach is valid when the selection coefficients, the strength of choosiness as well as costs of assortment are small; namely, for all $(i, f, h_C) \in \mathcal{G}_C \times \mathcal{F}_{C,P} \times [0, 1]$ (where $\mathcal{F}_{C,P}$ denotes the space of frequencies on $\mathcal{G}_C \times \mathcal{G}_P$) and k in $\mathcal{G}_P$, $S_i(f, h_C), \rho_k, c_r$ and c_f are of order ϵ with ϵ small. Under this hypothesis the genetic association (linkage desequilibria and departures from Hardy-Weinberg) are small (of order ϵ). This approach allows to obtain mathematical expressions of allele frequency changes at the cue and preference loci from the Hardy-Weinberg equilibrium. This method highlights the key evolutionary mechanisms shaping the evolution of allele frequencies at these loci. The QLE approximation assumes a weak natural selection at the cue locus C and is mostly relevant to explore the evolution of weak tendency to disassortative mating (low values of ρ).

Abbreviation	Description
$\mathcal{G}_C$	Set of possible genotypes at locus C: $\mathcal{G}_C = \{aa, ab, bb\}$
$\mathcal{G}_P$	Set of possible genotypes at locus P: $\mathcal{G}_P = \{MM, Mm, mm\}$
$f_{i,k}$	Frequency of genotype (i,k) in the population, $(i,k) \in \mathcal{G}_C \times \in \mathcal{G}_P$
p_a	Proportion of allele a at locus C in the population.
p_b	Proportion of allele b at locus C in the population.
p_M	Proportion of allele M at locus P in the population.
p_m	Proportion of allele m at locus P in the population.
r	Recombination probability between the loci C and P.
ρ_k	Strength of disassortative mating within a female of genotype $k \in \mathcal{G}_P$ at locus P as described in the preference matrix (1).
h_C	Dominance coefficient at locus C.
h_P	Dominance coefficient at locus P.
$S_i(f, h_C)$	Natural selection coefficient when the allele frequencies are f and the dominance coefficient at locus C is h_C.
c_f	Fixed cost of choosiness.
c_r	Relative cost of choosiness.
D_C	Genetic diversity at locus C, $D_C = p_a p_b$.
D_P	Genetic diversity at locus P, $D_P = p_m p_M$.
P_{he}^{HW}	Proportion of heterozygotes at the Hardy-Weinberg equilibrium, $P_{he}^{HW} = 2p_a p_b$
P_{ho}^{HW}	Proportion of homozygotes at the Hardy-Weinberg equilibrium, $P_{ho}^{HW} = p_a^2 + p_b^2$
H_{ns}	Heterozygote advantage due to natural selection.
H_{ss}	Heterozygote advantage due to sexual selection.
H	Heterozygote advantage.
$\overline{\rho}$	Average strength of disassortative mating in the population.
Δ_ρ	Effect of allele m on the level of disassortative mating in the population.
D_{am}	Linkage disequilibrium between alleles a and m within chromosome (cis). $D_{am} = p_{am} - p_a p_m$, where p_{am} is the proportion of the association between alleles a and m within the chromosome.
$D_{a,m}$	Linkage disequilibrium between alleles a and m between homologous chromosomes (trans). $D_{a,m} = p_{a,m} - p_a p_m$, where $p_{a,m}$ is the proportion of the association between alleles a and m between homologous chromosomes.
D_{he}	Excess of heterozygotes at locus C, $D_{he} = 1 - p_{aa}^2 - p_{bb}^2$.
$D_{he,m}$	Trigenic disequilibrium measuring the association between allele m and the excess of heterozygotes at locus C.

Table 1: Description of variables and parameters used in the model.

Numerical simulations

We then use numerical simulations to explore the evolutionary stable level of strength of disassortative mating acting on loci where natural selection has a significant effect. We specifically focus on a realistic case of natural selection promoting polymorphism at the cue locus, assuming overdominance. We explore the effect of variations in some parameters in range where the QLE analysis is not relevant.

To explore the evolution of disassortative mating acting on the cue locus submitted to overdominance, we model a natural selection regime favoring heterozygotes. We thus set the selection coefficients associated with the different genotypes at the cue locus as:

$$S_{aa} = -(1-\mu)\delta, \quad S_{ab} = 0 \quad \text{and} \quad S_{bb} = -\mu\delta,$$

where δ is the fitness reduction in homozygotes and μ is the asymmetry in natural selection acting on the two homozygous genotypes. If $\mu = 0$ (resp. 1), the disadvantage is applied to genotype aa (resp. bb) only, and if $\mu = 1/2$ the disadvantage is the same for both homozygotes.

To study the evolutionary stable level of strength of disassortative mating, we numerically compute the invasion gradient. First we consider a population without mutant ($p_m = 0$), for each value of the strength of disassortative mating of the resident ρ_{MM}, we let the initial population evolve until the genotype frequencies at the cue locus C reach equilibrium. At equilibrium, we introduce the mutant allele m with an initial 0.01 frequency. We call $\Delta^{100} p_m$ the change in the mutant frequency after hundred generations. We then numerically estimate

$$D(\rho_{MM}) = \frac{\partial \Delta^{100} p_m}{\partial \rho_{mm}}.$$

The evolutionary stable level of strength of disassortative mating p_m is the value for which $D = 0$.

We explore the effect of variations of each of the key parameters (δ, h_P, r, h_C, μ, c_f and c_r) using independent simulations. We use the following default values for the remaining parameters: $\rho_{MM} = 0$, $\rho_{mm} = 0.9$, $h_C = 1/2$, $h_P = 1/2$, $r = 0$, $\delta = 1$, $\mu = 1/2$ and $c_f = c_r = 0.005$.

Results

Sexual selection at the cue locus generated by disassortative mating

Following the QLE approach (*i.e.* assuming that terms of the form $S_i(f, h_C)$, ρ_k, c_r and c_f are of order ϵ and ϵ is small (see Section Methods)), the change in frequency of allele a at the locus C controlling mating cue is (see Eq. (B2a) in (Otto et al., 2008)):

$$\begin{aligned}\Delta p_a = &\overbrace{D_C(p_a(S_{aa}(f,h_C) - S_{ab}(f,h_C)) + p_b(S_{ab}(f,h_C) - S_{bb}(f,h_C)))}^{\text{Effect of natural selection}} \\ &\underbrace{+\overline{\rho}(1+c_r)D_C((p_b^4 - p_a^4)/4 + (h_C - 1/2)(2P_{he}^{HW} - P_{ho}^{HW}))}_{\text{Effect of sexual selection}} + O(\epsilon^2), \qquad (2)\end{aligned}$$

where $D_C = p_a p_b$ is the genetic diversity at locus C,

$$\overline{\rho} = p_M^2 \rho_{MM} + 2p_M p_m \rho_{Mm} + p_m^2 \rho_{mm},$$

is the average disassortative mate preference at locus P,

$$P_{he}^{HW} = 2p_a p_b \quad \text{and} \quad P_{ho}^{HW} = p_a^2 + p_b^2 \qquad (3)$$

are respectively the proportion of heterozygotes and homozygotes at the Hardy-Weinberg equilibrium. Under the QLE assumption the departure from the Hardy-Weinberg equilibrium is small, hence the proportions of heterozygotes and homozygotes are close to

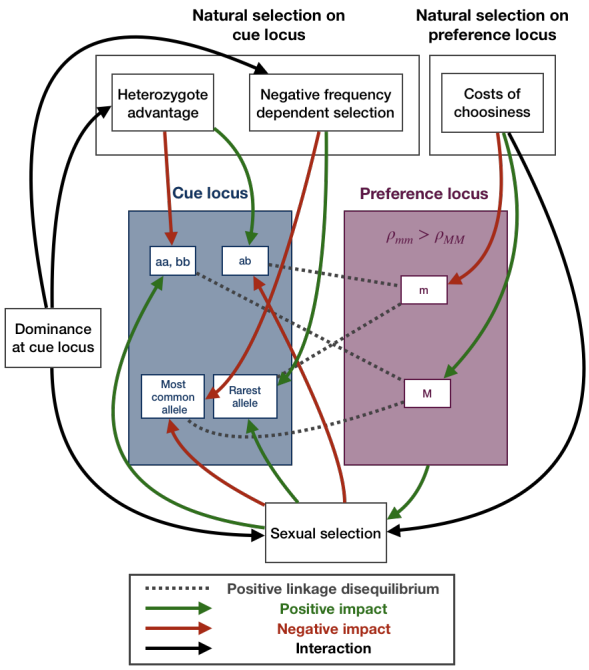

Figure 1: **Selective forces acting on cue and preference loci.** Dashed lines represent positive linkage disequilibrium between cue genotype and preference genotype. Green and red arrows represent the positive and negative impact respectively. Black arrows represent an unspecified impact (see manuscript for details).

P_{he}^{HW} and P_{ho}^{HW}.

Eq. (2) highlights that the dynamics of the mating cue allele a can be affected by both natural and sexual selections. Disassortative preferences generate negative frequency dependent sexual selection (see green and red arrows Fig. 1). The strength of sexual selection then depends on the average strength of disassortative preference ($\overline{\rho}$) but is also amplified by the relative cost of choosiness (c_r) (see black arrow in Fig. 1). Sexual selection also tightly depends on dominance at the cue locus C. When $h_C \neq 1/2$, the

evolutionary fate of alleles is strongly influenced by their dominance. When heterozygotes are frequent at locus C ($P_{he}^{HW} > 1/3$), allele a is favored when recessive ($h_C < 1/2$), because aa homozygotes then display the rarest phenotype and therefore benefit from an improved reproductive success. By contrast, when heterozygotes are rare at locus C ($P_{he}^{HW} < 1/3$ *i.e.* when $2P_{he}^{HW} - P_{ho}^{HW} < 0$), alleles at the cue locus are favored when dominant ($h_C > 1/2$). Indeed when allele a is rare ($p_a < 0.21$, see details in SI Appendix), $bb \times bb$ crosses are the most common, followed by $ab \times bb$ crosses. The increase in frequency of allele a is then favored when a is dominant because the $ab \times bb$ crosses are more successful, due to disassortative mate preferences. When cue allele a is common ($p_a > 0.79$), the dominance of allele a limits the reproductive success of the few remaining heterozygotes ab displaying the frequent phenotype shared with homozygotes aa, which leads to the gradual elimination of the alternative allele b.

These conclusions are drawn from the QLE approximation, and are relevant for moderate levels of disassortative mating (low values of ρ). Stronger levels of disassortative mating may lead to contrasted outcomes, because some crosses (e.g. $aa \times aa$) will no longer occur.

Evolutionary fate of disassortative mating mutants

To understand the conditions enabling the evolution of disassortative mating, we now approximate the change in frequency of the mutant allele m at the preference locus P. QLE analysis highlights that the evolution of disassortative mating depends on (1) the heterozygote advantage, (2) the genetic variation at the cue locus C, and (3) the costs of choosiness, described by the terms $\Delta^{he} p_m$, $\Delta^{C} p_m$ and $\Delta^{cost} p_m$ respectively. Assuming that

ϵ is small we obtain (see Eq. (B3a) in (Otto et al., 2008)):

$$\Delta p_m = \Delta^{he} p_m + \Delta^{C} p_m + \Delta^{cost} p_m + O(\epsilon^3). \tag{4}$$

In the following sections we define these three terms and dissect the evolutionary mechanisms acting on preference alleles.

Disassortative mating is promoted by heterozygote advantage at the cue locus

The impact of heterozygote advantage on the frequency of the mate choice allele m is given by:

$$\Delta^{he} p_m = D_{he,m} H, \tag{5}$$

where $D_{he,m}$ (see (7)) is the trigenic disequilibrium describing the association between the mutant m at the mate choice locus P and heterozygotes at the cue locus C and H is the heterozygote advantage at the cue locus C (see (6)). The fitness of heterozygotes H can be influenced by both natural and sexual selections, as detailed below:

$$H = \overbrace{2S_{ab}(f) - S_{aa}(f) - S_{bb}(f)}^{\text{Natural selection acting on cues } (H_{ns})} + \overbrace{\frac{1}{2}(p_a^2 H_{aa} + 2p_a p_b H_{ab} + p_b^2 H_{bb})}^{\text{Sexual selection acting on cues } (H_{ss})}. \tag{6}$$

The sexual selection promoting heterozygotes at the cue locus C depends on mate preferences associated with the different genotypes $i \in \mathcal{G}_C$ at locus C (H_{i}):

$$H_{\mathrm{i}} = 2Pref(\overline{\rho})_{i,ab} - Pref(\overline{\rho})_{i,aa} - Pref(\overline{\rho})_{i,bb}.$$

The effect of heterozygote advantage at the cue locus C on the disassortative mating allele m is then modulated by the association between the mutant m and heterozygotes at the cue locus (i.e. the trigenic disequilibrium $D_{he,m}$), as described by Eq. (5). At QLE, the trigenic disequilibrium satisfies:

$$D_{he,m} = \frac{1}{2} D_P \Delta D_{he} + O(\epsilon^2), \tag{7}$$

where D_{he} is the excess of heterozygotes at locus C due to allele m and $D_P = p_M p_m$ is the genetic diversity at locus P.

The trigenic disequilibrium depends on the change in the excess of heterozygotes due to allele m following a single round of mating. This change depends on (1) the fraction of homozygotes at the cue locus C, determined by allele frequencies (p_a and p_b) and dominance relationships (h_C) and (2) the increase in disassortative preferences in the population Δ_ρ (Eq. (8)).

$$\Delta D_{he} = D_C^2 \Delta_\rho (P_{ho}^{HW} + (h_C - \frac{1}{2})2(p_a - p_b)) + O(\epsilon^2). \tag{8}$$

The increase in disassortative preferences Δ_ρ depends on the effect of the mutant m at the preference locus P and its frequency (Eq. (9)).

$$\Delta_\rho = p_m(\rho_{mm} - \rho_{Mm}) + p_M(\rho_{Mm} - \rho_{MM}). \tag{9}$$

When mutant m increases disassortative preferences (*i.e.* $\rho_{mm} > \rho_{MM}$), $\Delta D_{he} > 0$ (see Appendix A for details), meaning that individuals with disassortative preferences tend to produce more heterozygotes at locus C. As a consequence, mutant alleles m, increasing disassortative preferences, are preferentially associated with heterozygotes at the cue locus C (see dashed lines in Fig. 1). The disassortative mutant m is thus promoted when natural and sexual selections both favor heterozygotes at the mating cue locus C.

Dominance relationships affect the change in the frequency of heterozygotes. For instance when a rare cue allele is dominant, a round of moderate disassortative mating (*i.e.* ρ_{MM} and ρ_{mm} are small) produces more heterozygotes than when the cue allele is recessive, because the expression of the rare mating cue in heterozygotes is promoted by disassortative mate preferences.

Sexual selection produced by disassortative mating generates a heterozygote disadvantage limiting the evolution of such a behavior

As described above, the disassortative alleles m tend to be preferentially associated with heterozygotes at locus C. Because ab heterozygotes with disassortative preferences (*i.e.* carrying a m allele) mate preferentially with either of the aa or bb homozygotes (depending on the direction of dominance h_C), the evolution of disassortative preferences generates a sexual selection disfavoring heterozygotes at locus C (see red arrows in Fig. 1). This mechanism is likely to hamper the fixation of allele m and restrict the emergence of disassortative mating in natural populations. This effect is determined by the mating success of heterozygotes at locus C. From Eq. (6), the sexual selection term can be written as:

$$H_{\text{ss}} = \overline{\rho}\left(-\frac{P_{he}^{HW}}{2} + (h_C - \frac{1}{2})(p_a - p_b)\right). \tag{10}$$

Sexual selection on heterozygotes depends on the strength of disassortative mating ($\overline{\rho}$), the allele frequencies at locus C (p_a and p_b) and the dominance relationship (h_C). Heterozygote advantage due to sexual selection decreases when the dominant allele becomes common: when allele a is dominant ($h_C = 0$), disassortative mating favors the $aa \times bb$ and $ab \times bb$ crosses. The frequency of the $aa \times bb$ crosses is higher when allele a is common, favoring reproductive success of homozygotes. Then disassortative alleles, which tend to be associated with heterozygoty at cue locus, are disfavored by sexual selection. Indeed alleles with reduced disassortative preference tend to be preferentially associated with homozygotes and are then promoted by sexual selection. Moderate levels of disassortative mating (as assumed under QLE) associated with heterozygoty excess at locus C therefore tend to decrease heterozygote advantage due to sexual selection at locus C.

The more common disassortative preferences are in the population, the more this sexual selection acting against heterozygotes is high. The spread of disassortative alleles is limited by this negative feedback.

Disassortative preferences are favored when the rarest allele is promoted

The change in the frequency of cue alleles impacts the evolution of preference alleles. This impact is described by the term:

$$\Delta^C p_m = (D_{am} + D_{a,m}) \frac{\Delta p_a}{D_C}. \tag{11}$$

As highlighted in the second term of Eq. (11), the invasion of a disassortative mutant m depends on its linkage with the cue allele a (either in *cis* or in *trans*, described by D_{am} and $D_{a,m}$ respectively) and on the variation in the frequency of allele a (Δp_a). If allele m is associated with allele a and the frequency of allele a increases then the frequency of allele m increases. The QLE approximates the *cis* and *trans* linkage desequilibria between the mutant allele m and the cue allele a as:

$$D_{am} = D_{a,m} + O(\epsilon^2) = \frac{D_P D_C}{2} \Delta\rho((p_b^4 - p_a^4) + (h_C - \frac{1}{2})(P_{he}^{HW} - P_{ho}^{HW})) + O(\epsilon^2). \tag{12}$$

When cue alleles are codominant (*i.e.* $h_C = 1/2$), D_{am} is positive (resp. negative) when allele a is the rarest (resp. most common). Thus Eq. (12) indicates that the disassortative mating allele m tends to be linked with the rarest allele at locus C (see dashed line Fig.1). This predicts that disassortative mating is likely to emerge when natural selection on the cue provides fitness benefit to rare alleles. Allele m also tends to be linked with the dominant allele when the frequency of homozygotes is high or with the recessive allele when the frequency of heterozygotes is high (*i.e* when $(h_C - 1/2)(P_{he}^{HW} - P_{ho}^{HW}) \geq 0$),

increasing the association between alleles a and m). Allele m is thus predicted to be linked with the cue allele it will favor through sexual selection.

In natural populations, the rareness of alleles can stem from their poor fitness, therefore limiting the emergence of disassortative mating alleles that tend to be linked with these rare deleterious cue alleles. This may explain why disassortative mating is so rare, except for cue loci where natural selection promotes rare alleles.

The costs of choosiness limit the fixation of disassortative mating

The evolution of mate preferences is generally limited by the costs associated with choosiness. Eq. (13) shows that both fixed and relative costs of choosiness indeed limit the fixation of the disassortative mutant m:

$$\Delta^{cost} p_m = -\frac{\Delta_\rho}{2} D_P \Big(c_f + c_r \left(mate_0 + \frac{1}{2} mate_1 + (h_C - \frac{1}{2})(mate_1^a - mate_1^b) \right) \Big) \tag{13}$$

where $mate_i$, $i \in \{0,1\}$ and $mate_1^\alpha$, $\alpha \in \{a,b\}$ decribing the proportion of mating partners sharing different numbers of alleles (see Eq. (14) and (16)). Indeed, the costs of choosiness disfavor preference alleles increasing disassortative choices (i.e. when $\rho_{mm} > \rho_{MM}$) (see Appendix A for details). The relative cost of choosiness then crucially depends on the proportion of preferred mates. This effect can be captured by the parameters $mate_k, k \in \{0,1\}$ representing the probability that a female encounters a male differing by k allele at locus C at the Hardy-Weinberg equilibrium:

$$mate_0 = p_a^2 p_a^2 + 2p_a p_b 2p_a p_b + p_b^2 p_b^2, \tag{14}$$

$$mate_1 = p_a^2 (2p_a p_b) + 2p_a p_b (p_a^2 + p_b^2) + p_b^2 (2p_a p_b). \tag{15}$$

The mating between individuals differing by zero ($mate_0$) or one cue allele ($mate_1$) may be partially avoided when individuals have a disassortative preference, resulting in

a cost c_r for the choosy female that may fail to find a suitable male. The term $mate_0 + \frac{1}{2}mate_1$ is minimal when $p_a = p_b$, so that the impact of the relative cost of choosiness is weaker when the cue alleles are in similar proportions in the population, maximizing the opportunities for females to find a male displaying the preferred cue. The dominance at the cue locus C then modulates the crosses at the Hardy-Weinberg equilibrium between individuals carrying at least one allele a ($mate_1^a$) and between individuals carrying at least one allele b ($mate_1^b$)

$$mate_1^a = p_a^2(2p_ap_b) + 2p_ap_b(p_a^2), \tag{16}$$

$$mate_1^b = p_b^2(2p_ap_b) + 2p_ap_b(p_b^2). \tag{17}$$

When a is dominant ($h_C < 1/2$), the relative cost of choosiness is limited when allele a is rare, because bb homozygotes will frequently meet ab heterozygotes displaying their preferred cue. Symmetrically, the cost of choosiness acting on the mutant allele m is higher when the most common cue allele is dominant.

Evolution of disassortative mating assuming overdominance at the cue locus

The QLE approximation highlights that the evolution of disassortative mating is challenging but can be promoted when natural selection favors heterozygotes. We thus focus on the evolution of disassortative mating acting on a cue locus where overdominance is operating. As detailed in the *Materials and Methods* Section we ran numerical simulations to cover the cases where the QLE analysis is not relevant, *i.e.* cases where natural selection at the cue locus can be strong and/or marked mate preferences lead to high rate of disassortative mating. The results are summarized in Fig. 2.

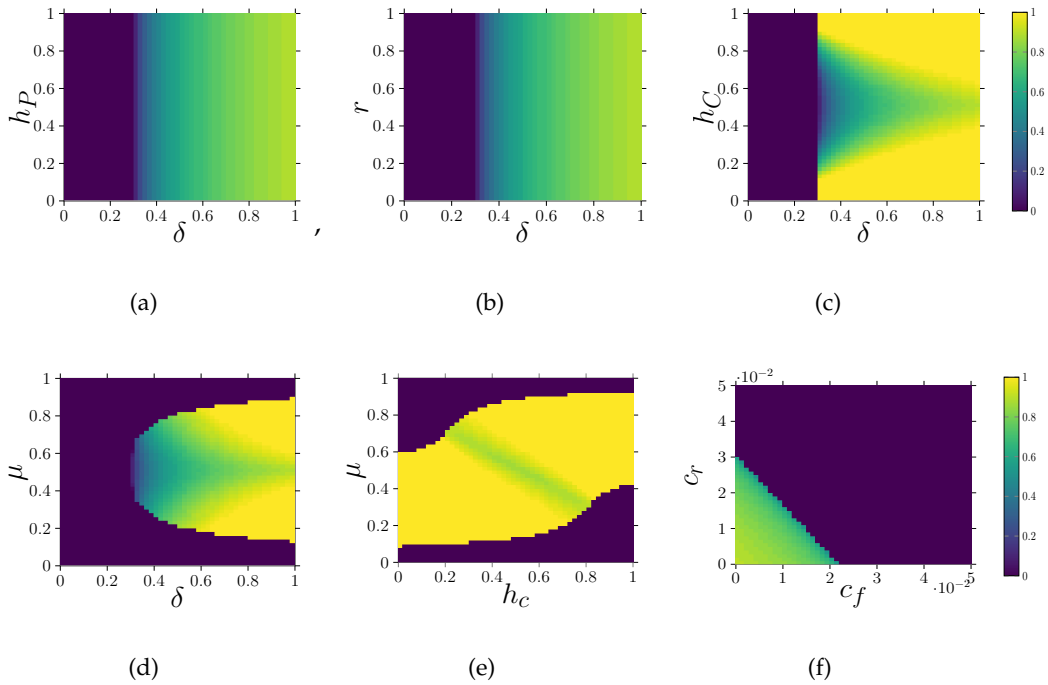

Figure 2: **Evolutionary stable level of strength of disassortative mating ρ acting on a cue locus submitted to overdominance.** We plotted the evolutionnary stable level of strength of disassortative mating ρ. The effect of key parameters on the evolution of the disassortative mating acting on the cue loci submitted to overdominance are explored in the different panels: (a) Effect of fitness reduction in homozygotes δ and of dominance coefficient at the preference locus P h_P, (b) Effect of fitness reduction in homozygotes δ and of recombination rate r between locus C and P, (c) Effect of fitness reduction in homozygotes δ and of dominance coefficient at the cue locus C h_C, (d) Effect of fitness reduction in homozygotes δ and asymmetry in this reduction on the two homozygotes μ, (e) Effect of dominance coefficient at the cue locus C h_C and asymmetry in the fitness reduction on the two homozygotes μ and (f) Effect of fixed cost of choosiness (c_f) and relative cost of choosiness (c_r). The default parameters values are as follows: $\rho_{MM} = 0$, $\rho_{mm} = 0.9$, $h_C = \frac{1}{2}$, $h_P = \frac{1}{2}$, $r = 0$, $\delta = 0.9$, $\mu = \frac{1}{2}$ and $c_r = c_f = 0.005$.

Genetic architecture of mate preferences does not impact the evolution of disassortative mating

The recombination probability between cue and preferences alleles has no impact on the evolutionary stable level of the disassortative mating mutant (Fig. 2(b)), consistent with the QLE prediction (Eq. (4)). Disassortative mate choice is based on phenotypic dissimilarity of mates, thus the preference of the choosy individual does not depend on linkage between cue and preference alleles. Dominance at the mate choice locus h_P does not impact the evolution of disassortative mating either (Fig. 2(a)), so that the genetic architecture of mate preference does not modify the evolution of disassortative mating in our model. The difference between heterozygotes and homozygotes fitness, on the contrary, has a strong effect on the evolution of disassortative mate preferences (Fig. 2(b) and 2(a)).

Disassortative mating is favored by asymmetrical overdominance

Higher levels of disassortative mating are favored when heterozygotes at the cue locus are advantaged by natural selection (i.e. when homozygotes suffers from a significant genetic load δ, Fig. 2(a)-2(d)), consistent with the predictions brought by the QLE approximation. Interestingly, higher levels of disassortative mating are favored when there is a moderate asymmetry (μ) in the negative selection acting on homozygotes at the cue locus, *i.e.* when one out of the two cue alleles is associated with a stronger genetic load (Fig. 2(d)). But when this asymmetry is too high, high levels of disassortative mating are no longer favored: selection indirectly acting on mating preference indeed crucially depends on genotypic frequencies at the cue locus C, which become unbalanced under asymmetrical selection. Unbalanced cue allele frequencies tend to increase

the frequency of homozygotes compared to the frequency of heterozygotes, increasing the relative advantage of heterozygotes. As disassortative preference tends to be linked with heterozygotes, high levels of disassortative mating are advantaged by the unbalanced cue allele frequencies. Furthermore, when allele frequencies are unbalanced at the cue locus, disassortative preferences are preferentially associated with the rarer cue allele, which suffers from a poor fitness when homozygous. Asymmetrical overdominance therefore promotes the evolution of disassortative mating preference, but only when the asymmetry in the genetic load associated with cue alleles is not too high.

Interactions between dominance and fitness of cue alleles determine the evolution of disassortative mate preferences

High levels of disassortative mating are favored when dominance relationships at the cue locus are strict (i.e. when allele a (resp. b) is fully dominant to b ($h_C = 0$) (resp. a ($h_C = 1$)) as highlighted on Fig. 2(c). The dominant allele is disfavored by sexual selection generated by disassortative mating. When the dominant allele is rare the association of disassortative preference and cue heterozygosity increases, promoting high levels of disassortative mating. Moreover when the dominant allele is rare, the impact of the costs of choosiness on frequency changes is lower, further promoting high levels of disassortative mating.

When combining both effects leading to unbalanced cue allele frequencies (i.e. dominance and asymmetrical negative selection on cue alleles), we show that high levels of disassortative mating are strongly favored when the fitness reduction in homozygotes is associated with the dominant cue allele (Fig. 2(e)). This numerical result is consistent with the prediction drawn from the QLE approximation, because in this case, the

dominant allele is in low frequency (because of both natural and sexual selection).

The challenging emergence of disassortative mating

Numerical simulations confirm that the evolution of disassortative mating is challenging, even when overdominance (enhancing the fitness of heterozygotes) is at play at the cue locus. In most cases, strict disassortative mating is not favored. The higher the disassortative preferences, the more sexual selection acts against heterozygotes. When heterozygote advantage is not strong enough, sexual selection caused by mating preferences can overcome heterozygote advantage, favoring intermediate level of disassortative mating (see green areas on Fig. 2(a)-2(d)). By contrast, when natural selection produces strong heterozygote advantage (δ is high) that can compensate sexual selection, complete disassortative preferences can be fixed (see Fig. 2(c) and 2(d)).

The costs of choosiness may further limit the evolution of the disassortative mutant. Fig. 2(f) shows that disassortative mating is under positive selection only when the costs of choosiness are limited (at least inferior to 0.03).

Discussion

Sexual selection generated by disassortative mating limits its propagation

Our results show that the evolution of disassortative preferences is promoted by heterozygote advantage at the locus controlling the mating cue, especially when the fitness of one homozygote is lower than the other one. Nevertheless, our analyses show that the sexual selection generated by such disassortative preferences triggers a negative feedback limiting the fixation of disassortative mating. The commoner disassortative mating

in a population the more sexual selection acts against heterozygotes, indirectly disfavoring disassortative preferences. This negative feedback loop can limit the invasion of disassortative preferences under favorable conditions. This effect has been reported in a theoretical study focusing on the evolution of preference driven by host-parasite interactions (Nuismer et al., 2008).

By contrast, assortative preferences are associated with an excess of homozygotes at the cue locus and with the most common allele (Otto et al., 2008). The conditions promoting assortative mating (homozygote advantage or a selection promoting the most common allele) favor a low level of heterozygotes. Because assortative mating usually produces more homozygotes that random mating, a decrease in the level of heterozygosity at the cue locus is expected when assortative preferences are spreading within a population. There is thus a positive feedback loop due to sexual selection promoting the evolution of assortative mating, in sharp contrast with the negative feedback loop in the evolution of disassortative mating.

The strength of the negative feedback generated by sexual selection crucially depends on the stringency of mate preferences. Under conditions favoring disassortative mating, choosy individuals are favored by the indirect effects of natural selection (*i.e.* they produce less homozygous offspring with poor fitness). However, sexual selection limiting the evolution of the choosy mutant is more important. Hence, favorable conditions for disassortative preferences may result in intermediate values of choosiness in the population.

The level of choosiness can be estimated empirically, using mate choice experiments, and is generally found to be loose (in the tetrad experiment of (Chouteau et al., 2017) for example, 3/4 of crosses were involving disassortative pairs). In a meta-analysis covering

1,116 published empirical studies, (Jiang et al., 2013) computed the strength of negative assortment (corresponding to the level of disassortative choosiness) and found values ranging from -0.5 to 0 suggesting that intermediate values of strength of disassortative mating are frequently observed.

Dominance relationships at the cue locus interfere with sexual selection

Our simulations show that higher levels of disassortative mating are promoted when one cue allele is dominant. The dominance relationship can indeed decrease the negative feedback loop limiting the evolution of disassortative preferences by favoring either the recessive or the dominant cue allele depending on their respective frequencies, and therefore providing a persistent advantage to disassortative mating.

Simulations also highlight that higher levels of disassortative mating are promoted when the dominant allele is disfavored when homozygous. This effect is consistent with the observed cases of disassortative mating. For instance the butterfly *H. numata* displays disassortative mating based on wing-pattern phenotype (Chouteau et al., 2017). In this species, the variation in wing-pattern morphs is controlled by a supergene with three main haplotypes (H_{n0}, H_{n1} and H_{n123}) (Joron et al., 2011). The haplotypes H_{n1} and H_{n123} are dominant to H_{n0} and are also associated with a low larval survival rate of homozygotes (Jay et al., 2019). This case of disassortative mating seems to gather the conditions pinpointed by our model to enable the emergence of disassortative mating. Similarly, in the white-throated sparrow *Zonotrichia albicollis* disassortative preferences are based on plumage morphs (*white* or *tan*) (Tuttle et al., 2016). Two supergene haplotypes ZAL2 and ZLA2^m control this variation in plumage coloration. Individuals with ZAL2/2 genotype have a *tan* coloration whereas individuals carrying ZAL2/2^m and ZAL2^m/2^m geno-

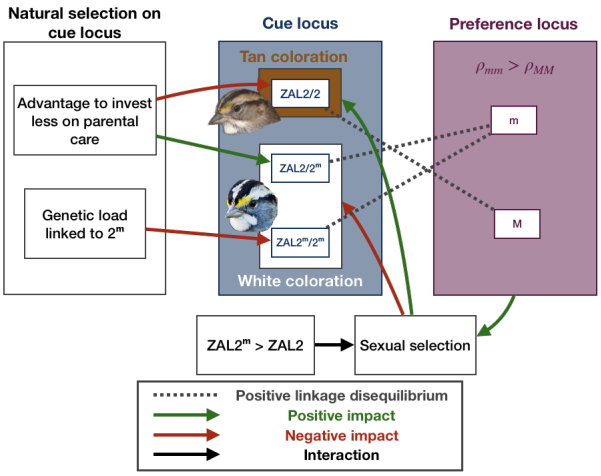

Figure 3: **Selective forces acting on cue loci in the example of the white-throated sparrow.** Dashed lines represent positive linkage disequilibrium between cue genotype and preference genotype. Green and red arrows represent the positive and negative impact respectively. Black arrows represent an unspecified impact, this impact is described more precisely in the text. Credits to Flickr (tan) and Shenandoah National Park from Virginia (white).

type have a *white* coloration. However the dominant haplotype ZAL2^m is associated with strong homozygote disadvantage (Tuttle et al., 2016). Individuals with *white* coloration may be advantaged over *tan* individuals because they invest less into parental care (Knapton and Falls, 1983), generating an advantage of heterozygotes ZAL2/2^m under homozygotes ZAL2/2. Here the dominant cue allele is again associated with a strong disadvantage when homozygous, which, according to our results, strongly favors the emergence of disassortative preferences (see Fig 3).

How can negative frequency dependent selection promote disassortative mating ?

Our results show that disassortative mating is associated with the rarest allele in the population. It could thus be favored when rarer alleles are promoted by natural selection, as observed under negative frequency-dependent selection regimes. This is supported by several examples. For instance mate preference based on dissimilarity at the major histocompatibility complex (MHC) locus has been reported in fish (Agbali et al., 2010), junglefowl (Løvlie et al., 2013), mouse (Yamazaki et al., 1976) and human (Dandine-Roulland et al., 2019; Ober et al., 1997; Wedekind et al., 1995). MHC alleles are involved in immune response regulation by producing proteins that detect foreign proteins (Janeway et al., 2001), and a high diversity observed at MHC locus is supposed to be maintained by a pathogen-driven balancing selection (Doherty and Zinkernagel, 1975; Hedrick et al., 2001).

It is still unclear whether negative frequency dependent selection (the Red Queen hypothesis), heterozygote advantage (overdominance hypothesis) or both are the main driver of balancing selection at MHC locus (Penn and Potts, 1999; Slade and McCallum, 1992) but rare MHC alleles recognizing emerging pathogens are likely to be promoted by natural selection. Moreover (Apanius et al., 1997; Piertney and Oliver, 2006) argue that negative frequency dependent selection cannot be separated from heterozygote advantage. Indeed rare alleles occur disproportionately in heterozygous genotypes. Then under negative frequency dependent selection the average fitness of heterozygotes is higher than homozygotes', generating heterozygote advantage.

Some studies have been conducted to understand how pathogen driven selection can

promote preference for MHC-dissimilar individuals. (Penn and Potts, 1999) hypothesized that MHC-based disassortative mating is favored because this preference provides host a moving target against parasites. Disassortative mating enhances the production of offspring with rare phenotypes to which parasites are not adapted. Using numerical simulations (Howard and Lively, 2003) shows that alleles increasing preference toward mate with dissimilar MHC genotype spread when rare in host population. However this result cannot be generalized because the authors describe an haploid MHC locus in which all choosy individuals are guaranteed to mate. Along the same line (Nuismer et al., 2008) shows that generally host-parasite interactions promote MHC dissimilar preferences.

These studies have been done to understand the evolution of MHC based mate choice. More generally our results could help to understand how negative frequency dependent selection can promote disassortative mating. The coevolutionary arm race between hosts and parasites generates cycles where the frequency of different types of hosts and parasites oscillate (called Red Queen dynamics) (Bell, 1982; May and Anderson, 1990; Rabajante et al., 2015). Negative frequency dependent selection is known to produce oscillations of the proportions of phenotypes/genotypes (Hori, 1993; Sinervo et al., 2000; Turner, 1980). If these oscillations are small, as for the frequency of left- or right-handed in scale-eating cichlid fish studied by (Hori, 1993), the advantage to rare phenotypes should be negligible. Conversely when the oscillations are high this advantage becomes stronger. Disassortative preferences, which are associated with rare alleles, should be promoted.

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Appendix A: Details of analytic results

We study the evolution of alleles frequencies in a two locus diploid model. One locus controls the mating cue (with two alleles a and b) and the other controls mate preference (with two alleles M and m). The model is described in the main file. We used a QLE analysis in order to approximate the changes in frequency of the cue allele a and of the preference allele m (see main file for more details). Here, we detail how our analytic results pinpoint some mechanisms explained in the main file.

The dominance relationship at cue locus impacts the action of sexual selection in a way depending on the proportion of heterozygotes

The approximation of the change in frequency of the cue allele a using QLE analysis is given by:

$$\begin{aligned}\Delta p_a =& D_C\left(p_a(S_{aa}(f,h_C)-S_{ab}(f,h_C))+p_b(S_{ab}(f,h_C)-S_{bb}(f,h_C))\right)\\ &+\overline{\rho}(1+c_r)D_C\left(\frac{p_b^4-p_a^4}{4}+(h_C-\frac{1}{2})(2P_{he}^{HW}-P_{ho}^{HW})\right)+O(\epsilon^2),\end{aligned}$$

where we recall that under the QLE approximation, ϵ is a small quantity.

Here we aim to study the impact of the dominance relationship on the variation of allele a frequency. We therefore study the sign of the term

$$A := (h_C-\frac{1}{2})(2P_{he}^{HW}-P_{ho}^{HW}),$$

describing the effect of the dominance relationship. As $P_{he}^{HW}+P_{ho}^{HW}=1$ by definition we have:

$$A = (h_C-\frac{1}{2})(3P_{he}^{HW}-1).$$

Thus $A > 0$ when a is partially dominant ($h_C < 1/2$) (resp. recessive ($h_C > 1/2$)) and the proportion of heterozygotes is lower (resp. higher) than $1/3$. This entails that that when the proportion of heterozygotes is low (resp. high), the dominant (resp. recessive) cue allele is favored.

The condition on P_{he}^{HW} translates in a condition on p_a as follows:

$$\begin{aligned} P_{he}^{HW} > 1/3 &\iff 2p_a p_b > 1/3 \\ &\iff 6p_a(1-p_a) - 1 > 0 \\ &\iff -6p_a^2 + 6p_a - 1 > 0 \\ &\iff p_a \in (\frac{3-\sqrt{3}}{6}, \frac{3+\sqrt{3}}{6}). \end{aligned}$$

For greater simplicity in the manuscript we use the approximation $\frac{3-\sqrt{3}}{6} = 0.21$ and $\frac{3+\sqrt{3}}{6} = 0.79$.

Disassortative preference promotes heterozygote excess at cue locus

We develop the expression of the change of excess of heterozygotes at cue locus due to the preference allele m, ΔD_{he}:

$$\Delta D_{he} = D_C^2 \Delta\rho(p_a^2 + p_b^2 + (h_C - \frac{1}{2})2(p_a - p_b)) + O(\epsilon^2).$$

Thus ΔD_{he} depends on the sign of the term $p_a^2 + p_b^2 + (h_C - \frac{1}{2})2(p_a - p_b)$. But the latter can be written as follows:

$$\begin{aligned} p_a^2 + p_b^2 + (h_C - \frac{1}{2})2(p_a - p_b) &= p_a^2 + (1-p_a)^2 + (h_C - \frac{1}{2})2(p_a - (1-p_a)), \\ &= 2p_a^2 + 4(h_C - 1)p_a + 2 - 2h. \end{aligned}$$

This term is a quadratic function in p_a. The value of its discriminant is:

$$\Delta = -16h_C(1-h_C) < 0,$$

which entails that this quadratic function is always positive, and that ΔD_{he} has the same sign as $\Delta\rho$. Hence, when allele m is associated with higher disassortative preference ($\Delta\rho$) it promotes heterozygoty excess.

Costs of choosiness penalize the preference allele associated with higher levels of disassortative mating

Here we study the impact of the costs of choosiness on frequencies of preference alleles. We recall that the impact of the costs of choosiness on allele m frequency is given by:

$$-\frac{\Delta\rho}{2}D_P\Big(c_f + c_r\left(mate_0 + \frac{1}{2}mate_1 + (h_C - \frac{1}{2})(mate_1^a - mate_1^b)\right)\Big).$$

We are interested in the sign of the term B defined by:

$$\begin{aligned} B &:= mate_0 + \frac{1}{2}mate_1 + (h_C - \frac{1}{2})(mate_1^a - mate_1^b) \\ &= mate_0 + 4p_a(1-p_a)(p_a^2 + 2(h_C-1)p_a + 1 - h_C). \end{aligned}$$

As

$$\begin{aligned} p_a^2 + 2(h_C-1)p_a + 1 - h_C &\geq p_a^2 - 2(1-h_C)p_a + (1-h_C)^2 \\ &\geq (p_a - (1-h_C))^2 \geq 0, \end{aligned}$$

we conclude that B is positive when $\Delta\rho$ is positive (*i.e.* when $\rho_{mm} > \rho_{MM}$). The costs of choosiness thus penalize the preference allele associated with higher disassortative preferences.

Appendix B: Comparison of QLE analysis results with numerical simulations

We used a QLE analysis in order to draw analytic approximations for the changes in frequencies at the cue and preference loci (Δp_a and Δp_m). The results of the QLE analysis are only relevant when for all $(i, f, h_C) \in \mathcal{G}_C \times \mathcal{F}_{C,P} \times [0,1]$ (where $\mathcal{F}_{C,P}$ denotes the space of frequencies on $\mathcal{G}_C \times \mathcal{G}_P$), $S_i(f, h_C) = O(\epsilon)$; for all k in $\mathcal{G}_P$, $\rho_k = O(\epsilon)$, $c_r = O(\epsilon)$ and $c_f = O(\epsilon)$ with ϵ small.

To illustrate that the QLE results provide a good approximation under the QLE hypothesis, we then compare the values of the frequency changes predicted by the QLE analysis ($\Delta^{QLE} p_a$ and $\Delta^{QLE} p_m$) with values from numerical simulations ($\Delta^{num} p_a$ and $\Delta^{num} p_m$). We define $Err\Delta p_a = |\frac{\Delta^{QLE} p_a - \Delta^{num} p_a}{\Delta^{num} p_a}|$ and $Err\Delta p_m = |\frac{\Delta^{QLE} p_m - \Delta^{num} p_m}{\Delta^{num} p_m}|$ to quantify the error of the QLE approximation. We assume that the natural selection does not depend on the frequencies distribution and of the dominance at cue locus . Then for all $i \in \mathcal{G}_C, S_i(f, h_C) = S_i$. The results are plotted in Figures B1 and B2 and show that the error of the QLE approximations are low when the hypotheses of the QLE are satisfied *i.e.* the parameters S_{aa}, S_{ab}, S_{bb}, ρ_{MM}, ρ_{mM}, ρ_{mm}, c_r and c_f are small.

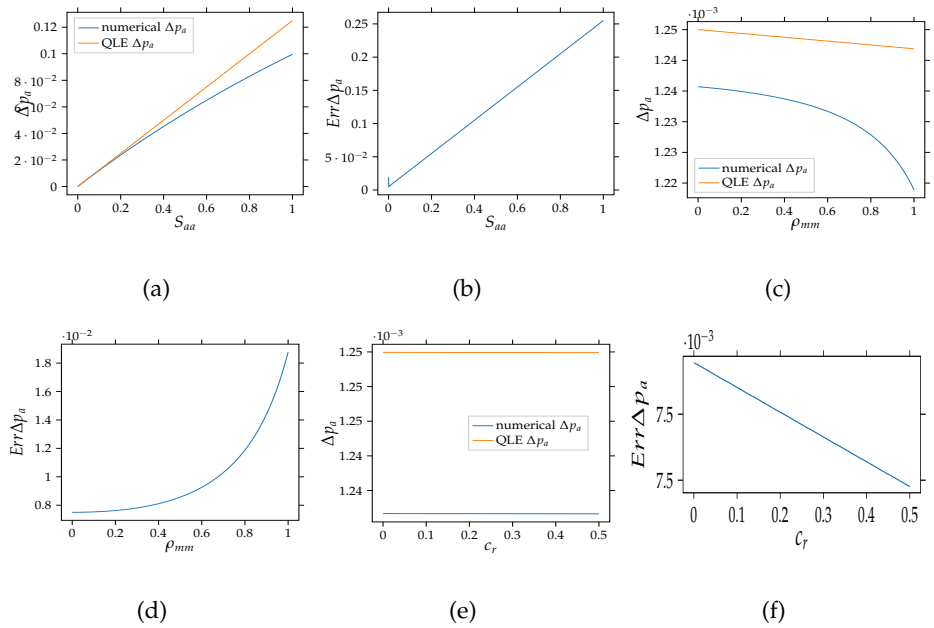

Figure B1: **Change of allele *a* frequency at cue locus (Δ) after the introduction of mutant predicted by the QLE analysis (orange lines) and by numerical simulations (blue lines).** The effect of key parameters on the evolution of the disassortative mating is explored in the different panels: (a)(b) Effect of the natural selection acting on homozygote *aa* at cue locus (S_{aa}), (c)(d) Effect of the strength of disassortative mating within an individual of genotype *mm* at preference locus (ρ_{mm}), (e)(f) Effect of the relative cost of choosiness (c_r). The default parameters values are as follows: $\rho_{MM} = 0$, $\rho_{mm} = 0.01$, $h_C = 0$, $h_P = 0$, $r = 0.1$, $c_r = 0$, $c_f = 0$, $S_{aa} = 0$, $S_{ab} = 0.01$ and $S_{bb} = 0$.

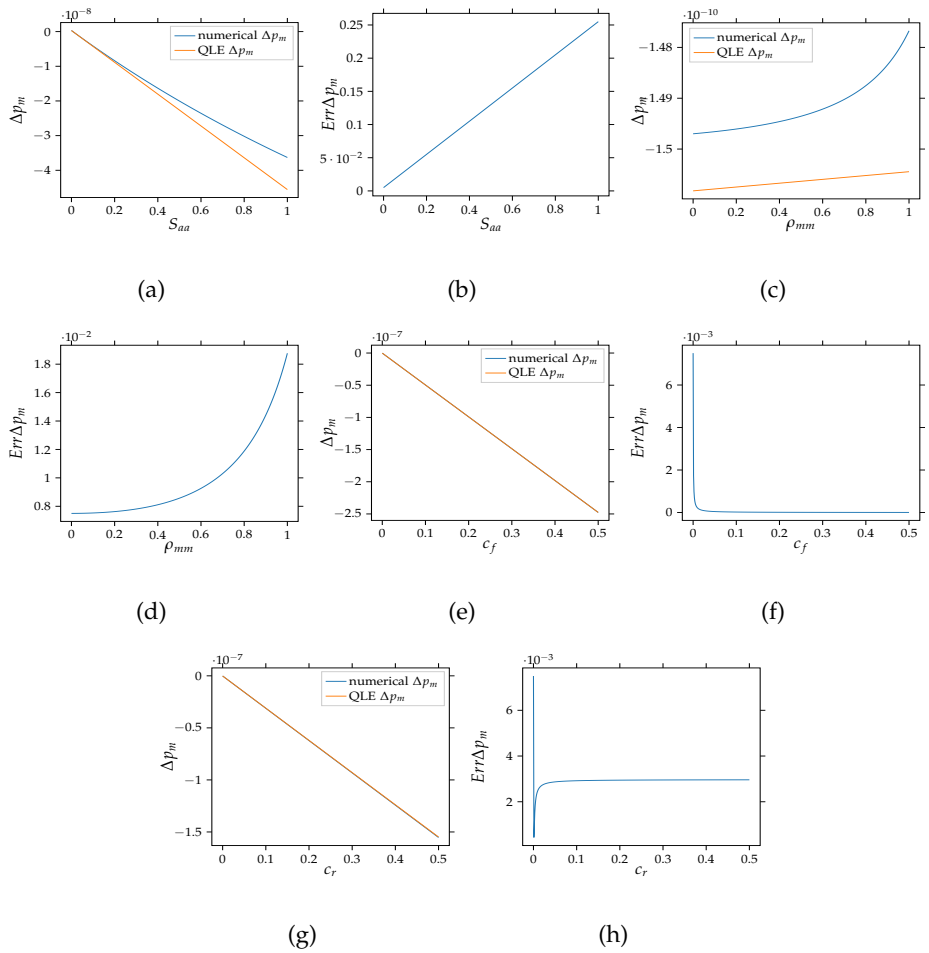

Figure B2: **Change of allele m frequency at preference locus (Δp_m) after the introduction of the mutant predicted by the QLE analysis (orange lines) and by numerical simulations (blue lines).** The effect of key parameters on the evolution of the disassortative mating is explored in the different panels: (a)(b) Effect of the natural selection acting on homozygote *aa* at cue locus (S_{aa}), (c)(d) Effect of the strength of disassortative mating within an individual of genotype *mm* at preference locus (ρ_{mm}), (e)(f) Effect of the fixed cost of choosiness (c_f), (g)(h) Effect of the relative cost of choosiness (c_r). The default parameters values are as follows: $\rho_{MM} = 0$, $\rho_{mm} = 0.01$, $h_C = 0$, $h_P = 0$, $r = 0.1$, $c_r = 0$, $c_f = 0$, $S_{aa} = 0$, $S_{ab} = 0.01$ and $S_{bb} = 0$.