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Conflict between heterozygote advantage and hybrid incompatibility in haplodiploids (and sex chromosomes)

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Heterosis *versus* hybrid breakdown

Abstract

In many diploid species the sex chromosomes play a special role in mediating reproductive isolation. In haplodiploids (i.e., females are diploid and males haploid), the whole genome behaves similar to the X/Z chromosomes of diploids, and thus haplodiploid systems can serve as a model for the role of sex chromosomes in speciation and hybridization. A previously described population of Finnish *Formica* wood ants displays genome-wide signs of ploidally and sexually antagonistic selection resulting from hybridization. Here, hybrid diploid females have increased survivorship but hybrid haploid males are inviable. In order to understand how this unusual natural population may sustain this antagonistic selection for hybrid status, we developed a mathematical model with hybrid incompatibility, female heterozygote advantage,

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recombination, and assortative mating. The rugged fitness landscape resulting from the conflict between heterozygote advantage and hybrid incompatibility results in sexual conflict in haplodiploids, which is absent in diploids. Thus, whereas heterozygote advantage always promotes long-term polymorphism in diploids, we find various outcomes in haplodiploids in which the conflict can be resolved either in favor of males, females, or via maximizing the number of introgressed individuals. We fit our model to data from the Finnish wood ant population in order to discuss its potential long-term fate. We highlight the general implications of our results for speciation and hybridization in haplodiploids versus diploids, and how such fitness conflicts could contribute to the outstanding role of sex chromosomes as hotspots of sexual conflict and genes involved in speciation.

Introduction

Haplodiploids are an emerging system for speciation genetics (Koevoets and Beukeboom, 2009; Kulmuni and Pamilo, 2014; Lohse and Ross, 2015; Knegt et al., 2017). Although $\approx 20\%$ of animal species are haplodiploid (comprising most *Hymenopterans*, some arthropods, thrips and *Hemipterans*, and several clades of beetles and mites; Crozier and Pamilo, 1996; Evans et al., 2004; de la Filia et al., 2015), little evolutionary theory has been developed specifically for speciation in haplodiploids (Koevoets and Beukeboom, 2009). Under haplodiploidy with arrhenotoky (hereafter simply haplodiploidy; Suomalainen et al., 1987), males develop from the mother's unfertilized eggs and are haploid, whereas eggs fertilized by fathers result in diploid females. Since this mode of inheritance is from a theoretical viewpoint similar to that of the X/Z chromosome, most work on speciation of haplodiploids comes from the rich literature of sex chromosome evolution (Jablonka and Lamb, 1991; Presgraves, 2008; Johnson and Lachance, 2012; Lohse and Ross, 2015). An important similarity between haplodiploids and X/Z chromosomes is that recessive mutations in the haploid sex are exposed to selection, but they are masked in diploids. This is expected to lead to faster evolution in the sex chromosomes (Charlesworth et al., 1987) that may partly underlie the large-X effect (Presgraves, 2008). The large-X effect refers to the observation that the sex chromosomes seem to play a special role in speciation by acting as the strongest barrier for gene flow between hybridizing lineages across different species (Höllinger and Hermisson, 2017). Similarly, haplodiploid species have been suggested to acquire reproductive isolation earlier and speciate faster than diploid species (Lohse and Ross, 2015; Lima, 2014). Although the factors influencing haplodiploid and X/Z chromosome evolution are not expected to be exactly the same (e.g. movement of sexually antagonistic genes to the sex chromosomes, dosage compensation between the sex chromosomes and autosomes, and turnover of sex chromosomes cannot occur in haplodiploids; Abbott et al., 2017), by studying haplodiploid models we can both improve our understanding of how speciation happens in the large subgroup of the animal kingdom that is haplodiploid, and gain new insights into the role of X/Z chromosomes in speciation for diploid species.

Recent studies have shown that hybridization and resulting gene flow between diverging populations may be important players in the speciation process since signs of hybridization and introgression are being observed ubiquitously in natural populations (Mallet, 2005; Dieckmann and Doebeli, 1999; Schluter, 2009; Schluter and Conte, 2009; Seehausen et al., 2014). When a hybrid population is formed, various selective forces may act simultaneously to either increase or decrease hybrid fitness, thus dictating the fate of the metapopulation. One commonly documented finding is hybrid incompatibility (Presgraves, 2008; Fraïsse et al., 2014; Chen et al., 2016), where combinations of alleles at different loci interact to confer poor fitness when homozygous in a hybrid individual (Bateson, 1909; Dobzhansky, 1936; Muller,

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1942; Orr, 1995). In a hybrid population, the existence of hybrid incompatibility reduces the mean fitness of the metapopulation. This deficit can be resolved either through reinforcement (evolution of increased premating isolation to avoid production of unfit hybrids; Servedio and Noor, 2003), or by purging (demographic swamping leading to extinction of one of the local populations/species; Wolf et al., 2001). On the other hand, hybridization can transfer adaptive genetic variation from one lineage to another (Heliconius Genome Consortium, 2012; Song et al., 2011; Whitney et al., 2010) and may result in overall heterosis (also known as hybrid vigor): a higher fitness of hybrids as compared to their parents (Schwarz et al., 2005; Chen, 2013; Bernardes et al., 2017). Heterosis can stabilize polymorphisms by conferring a fitness advantage to hybrids, and thus favors the maintenance of hybridization either through the improved exploitation of novel ecological niches or the masking of recessive deleterious mutations. Therefore hybrid incompatibility acts to avert ongoing hybridization while heterosis favors the maintenance of hybrids.

One example of the simultaneous action of hybridization-averse and hybridization-favoring forces is found in a hybrid population of *Formica polyctena* and *F. aquilonia* wood ants in Finland (Kulmuni et al., 2010; Kulmuni and Pamilo, 2014; Beresford et al., 2017). Here, it has been reported that hybrid (haploid) males do not survive to adulthood, whereas (diploid) females have higher survivorship when they carry many introgressed alleles as heterozygotes (i.e., heterozygous for alleles originating from one of the parental species in a genomic background otherwise from the other parental species). Thus, a combination of hybrid incompatibility and heterosis seems to dictate the dynamics of the population, in both ploidy- and sex-specific manner: hybrid haploid males suffer a fitness cost while diploid hybrid females can have a selective advantage over parental ones. Here, the differences in ploidy create a sexual conflict which would be absent if the same rugged fitness landscape (i.e., the complex relationship between genotypes and fitness created via hybrid incompatibility and heterozygote advantage) occurred on diploid autosomes.

When both hybridization-averse and hybridization-favoring forces are acting, the long-term resolution of a hybridizing population is difficult to foresee: will hybridization eventually result in either complete speciation or extinction of one of the populations involved? Alternatively, can it represent an equilibrium maintained stably on an evolutionary time scale? Furthermore, will the probability of these outcomes depend on ploidy? In other words, is one of these outcomes more probable when interacting genes are found on a "haplodiploid" X/Z chromosome than when they exist on a "diploid" autosome?

We here develop and analyze a population-genetic model of an isolated hybrid population in which both hybridization-averse and hybridization-favoring forces are acting, and we study the evolutionary outcomes in both haplodiploid and (fully) diploid genetic systems. The rich dynamics of the haplodiploid model can result in four possible evolutionary stable states depending on the strength of heterozygote advantage *versus* hybrid incompatibility, the strength of recombination, and the degree of assortative mating. This includes a case of symmetric coexistence (where all diversity is maintained) where both alleles can be maintained despite the ongoing genetic conflict, and thus long-term hybridization is favored. We find that the dynamics differ between haplodiploid and diploid systems, and that unlike in previous models of sexual conflict in haplodiploid populations (Kraaijeveld, 2009; Albert and Otto, 2005), sexual conflict is not necessarily resolved in favor of the females. Indeed, a compromise may be reached at which the average fitness of females is decreased to rescue part of the fitness of males. Moreover, fitting of the data from the natural hybrid population suggests that, under the assumption of an equilibrium, the Finnish ant population may represent an example of compromise between male costs and female benefits through asymmetric coexistence. We discuss our findings with respect to the long-term effects of hybridization, the potential for

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Table 1: List of model parameters.

Symbol	Parameter	Limits
σ, ω	**Strength of heterozygote advantage**, resulting in fitness $\omega = (1+\sigma)$ or $\omega^2 = (1+\sigma)^2$ of introgressed or double heterozygous diploid hybrids, respectively.	$\omega - 1 = \sigma > 0$
γ_1, γ_2	**Strength of fully recessive negative epistasis**, resulting in fitness $(1-\gamma_1)$ for A_+B_- homozygous diploid hybrids and A_+B_- hybrid haploid males, and $(1-\gamma_2)$ for A_-B_+ homozygous diploid hybrids and A_-B_+ hybrid haploid males.	$0 \leq \gamma_1, \gamma_2 \leq 1$
ρ	**Recombination rate** between locus **A** and **B**.	$0 \leq \rho \leq 0.5$
α	**Strength of assortment** via genotype matching, where $\alpha = 0$ represents random mating, $\alpha > 0$ represents assortative mating among conspecifics, and $\alpha < 0$ represents assortative mating between heterospecifics.	$-1 \leq \alpha \leq 1$

speciation in haplodiploid versus diploid species, and with respect to their relevance for X- or Z-linked alleles in diploid individuals.

Materials and Methods

The model

We model an isolated haplodiploid or diploid hybrid population with individuals from two founder populations P_+ and P_-. Note that throughout the manuscript, we preferentially refer to (sub-) populations rather than species; in those instances in which we use the term 'species' it is in order to emphasize that the two populations have diverged sufficiently for (potentially strong) hybrid incompatibilities to exist. We assume discrete generations and consider two loci, **A** and **B**. Each locus has two alleles, the '+' allele (A_+ or B_+) inherited from population P_+ or the '−' allele (A_- or B_-) inherited from population P_-. We refer to 'hybrids' as individuals that carry two alleles from each of the two parental populations and cannot be assigned to either parental background. We refer to 'introgressed' individuals as those genotypes for which three of the four alleles are from the same parental population; these genotypes are identical to those produced by hybridization followed by backcrossing. We assume an equal sex ratio, and ignore new or recurrent mutation and genetic drift (i.e., we assume an effectively infinite population size). The life cycle is as follows (Fig. S1; see also Table 1 for a list of model parameters):

1. viability (or survival) selection, where heterosis is modeled as a heterozygote advantage, σ, and hybrid incompatibility is modeled as a fully recessive negative epistasis, γ_1 and γ_2 (further details are provided below and in Figure 1);

2. mating, either randomly or via genotype matching with assortment strength α as detailed below;

3. recombination at rate ρ.

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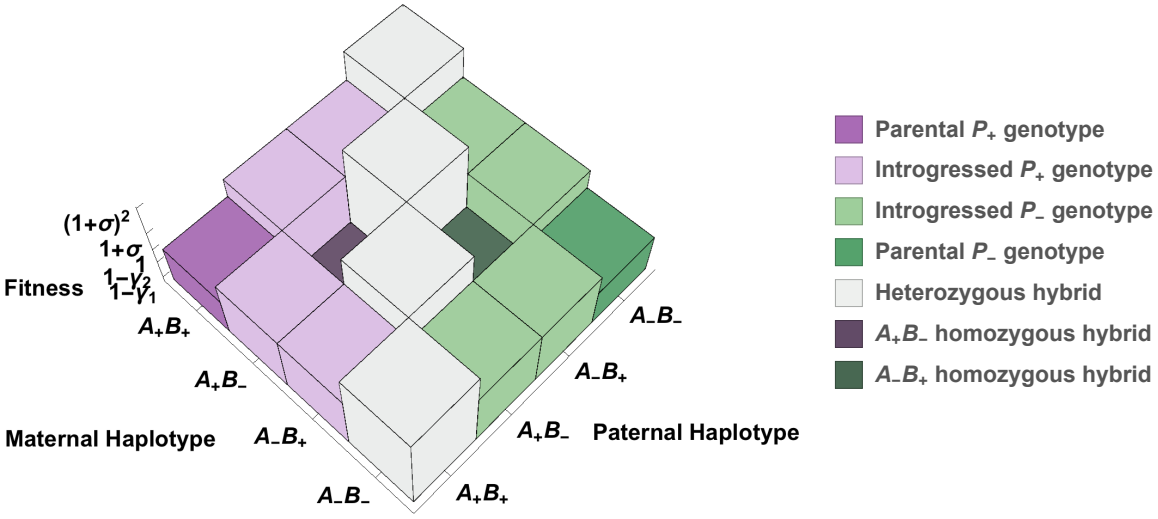
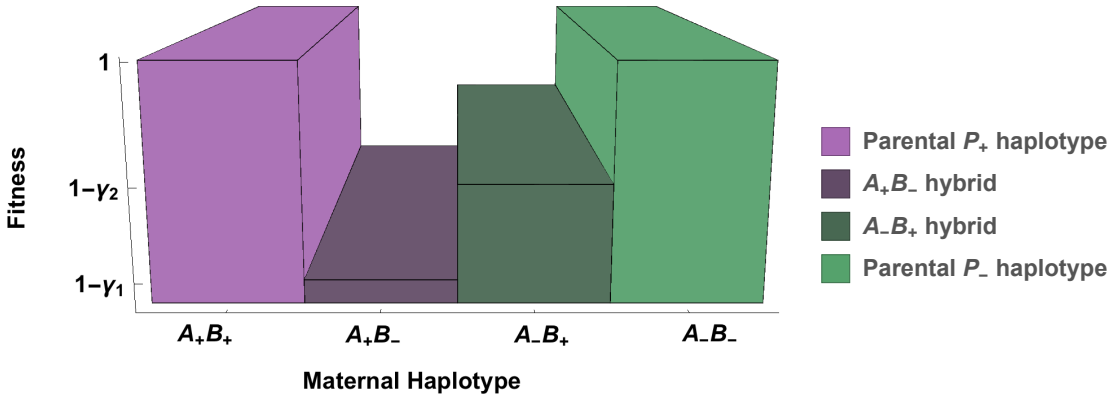


(a) Fitness Landscape for Diploid Individuals



(b) Fitness Landscape for Haploid Males

Figure 1: Three-dimensional fitness landscapes for the (a) diploid and (b) haploid genotypes. Panel a) corresponds to females in the haplodiploid model and all individuals in the diploid model. Individuals heterozygous at both loci (heterozygous hybrids) reside on a high fitness ridge (in white), whereas individuals homozygous at both loci (homozygous hybrids) suffer from reduced fitness due to negative epistasis. Panel b) shows the fitness landscape for haploid individuals (i.e. males) in the haplodiploid model. This landscape is identical to a transect from Panel a) for genotypes homozygous at both loci.

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Viability selection

The fitness landscape described here (Fig. 1) is inspired by the situation observed in Finnish *Formica* ants (Kulmuni et al., 2010; Kulmuni and Pamilo, 2014; Beresford et al., 2017). There, the authors discovered heterosis in the diploid females but recessive incompatibilities expressed in the haploid males. This creates a genomic conflict where the same alleles that are favored in heterozygote females are selected against in hybrid haploid males. In the haplodiploid genetic system, males possess only one copy of each locus so they cannot be heterozygous and, thus, cannot experience heterozygote advantage (Fig. 1(b)). Therefore, a fitness scheme with heterozygote advantage and recessive incompatibilities expresses itself as a sexual conflict in haplodiploids.

In our model, selection for heterozygous individuals is multiplicative with respect to the number of heterozygous loci: introgressed individuals with one heterozygous locus have fitness $1 + \sigma$, whereas heterozygous hybrid individuals are heterozygous at both loci and have survivorship $(1 + \sigma)^2$ (Fig. 1(a)). Note that when $\gamma_1 = \gamma_2 = 1$, haploid hybrid males and homozygous hybrid zygotes are produced but do not survive to adulthood. Finally, the recessive epistatic incompatibility parameter γ_1 acts on individuals homozygous or haploid for the A_+B_- haplotype, and γ_2 acts on individuals homozygous or haploid for the A_-B_+ haplotype (without loss of generality, we assume $\gamma_1 \geq \gamma_2$). Thus, epistasis in this model can be asymmetric, reflecting, for example, two Dobzhansky-Muller incompatibilities of different strength that have accumulated in a negligible recombination distance between the same chromosome pairs. Note that the classical case of a single Dobzhansky-Muller incompatibility is recovered when $\gamma_2 = 0$.

Assortative mating

Prezygotic isolation via assortative mating is an important mechanism that could mediate the conflict between heterozygote advantage and epistasis modeled here. In the Finnish wood ant population that inspired our model (Kulmuni and Pamilo, 2014), almost all egg-laying queens collected had been inseminated by males of the same genetic group, indicating that prezygotic isolation mechanisms are likely operating to result in assortative mating. In this case, assortative mating could arise both via choosiness of mating partners, via genotype-dependent development times, or via other post-mating prezygotic mechanisms. We implemented assortment via genotype matching (reviewed in Kopp et al., in press), where the proportion of matings depends on the genetic distance between two mating partners (and their respective frequencies in the population). We use quadratic assortment (e.g., De Cara et al., 2008), which results in assortative mating without costs of choosiness but with sexual selection. The mating probability of a pair of male and female genotypes, $\{g_f, g_m\}$, is $\frac{1}{2}(1-\alpha)d_{g_f,g_m}\chi_{g_f}\chi_{g_m}$, where d_{g_f,g_m} is the Hamming distance between the female and male genotypes (where the male haplotype is doubled in the haplodiploid model) and χ_{g_f}, χ_{g_m} are the respective genotype frequencies.

Simulations

Derivations, simulations, and data fitting were performed in *Mathematica* (v 10.4.1.0; Wolfram Research, Inc., 2016), and are supplied as Online Supplement. Equilibrium genotype frequencies were obtained numerically when possible, or based on simulations until the difference between genotype frequencies between two consecutive generations was smaller than 10^{-8} (or stopped after 10^5 generations without convergence).

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Estimating genotype frequencies from a natural ant population

In order to compare our model with data from the natural, hybridizing Finnish ant population, we estimated the different genotype frequencies of parental *F. polyctena*-like and *F. aquilonia*-like individuals at pre-selection and post-selection life stages for males and females (Fig. S1(a)). We did not estimate the frequencies of introgressed or hybrid individuals. We used the genotype frequencies at different life-stages estimated in Kulmuni and Pamilo (2014) from nine microsatellite loci. For males, eggs were used to estimate pre-selection frequencies; the sum of adults and reproductive fathers was used to estimate post-selection frequencies. For females, eggs were used for pre-selection frequencies and the sum of young and old queens was used for post-selection frequencies. We used two different estimates for the number of parental females: individuals with exactly zero loci heterozygous for an introgressed allele, and individuals with one or more loci homozygous for the parental allele (i.e., the "diagnostic allele" in Kulmuni and Pamilo, 2014). In order to make these data comparable to our model, we rescaled the genotype frequencies such that 10.3% of the population is from the *F. polyctena*-like sub-population and 89.7% from the *F. aquilonia*-like sub-population, as estimated from the observed abundances of *F. polyctena*-like and *F. aquilonia*-like individuals from nests in the hybrid population collected between 1996-2012 (Table S1). Assuming that the natural population is at equilibrium, we fit the data (Table S2) to the model by calculating the sum of squared differences between the observed data and predicted equilibrium frequencies from 40600 parameter combinations.

Results

In this section, we describe the dynamics of a hybrid population under our model, with a particular focus on quantifying the differences between the haplodiploid and the diploid model. Two parameter ranges are of particular interest:

1. The case of free recombination and strong epistasis (i.e., large γ_1, γ_2) most likely resembles that of the natural ant hybrid population that inspired the model. Here, hybrid incompatibilities are found between chromosomes, and they are strong enough to erase a large fraction of male zygotes during development.

2. The case of low recombination is most relevant for the effects of a fitness landscape with epistasis (i.e., a "rugged" landscape) in X or Z chromosomes. Here, epistasis could arise, for example, through interactions between regulatory regions and their respective genes.

Evolutionary scenarios

Below, we describe four different types of evolutionary stable states (i.e., equilibrium scenarios) of the model, which represent long-term solutions to the conflict between the hybridization-averse force of recessive negative epistasis and the hybridization-favoring heterozygote advantage. The population will attain these equilibria if no further pre- or post-zygotic mechanisms or other functional mutations appear. Next, we provide various necessary and sufficient analytical conditions for these scenarios. Figure 2 illustrates the potential equilibria by means of phase diagrams.

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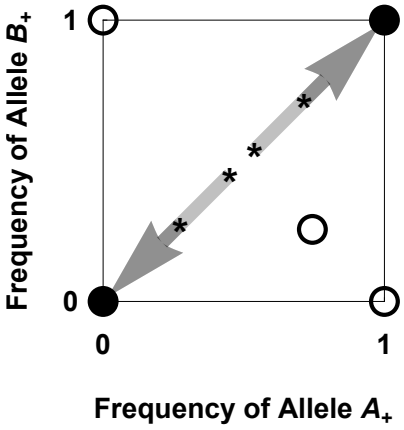
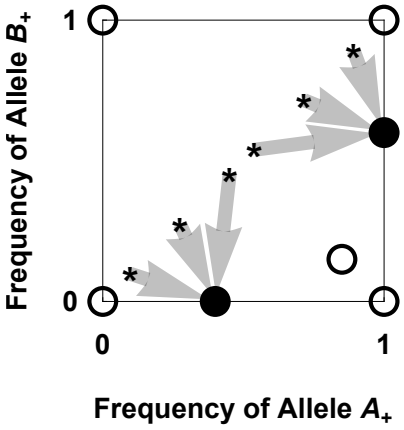
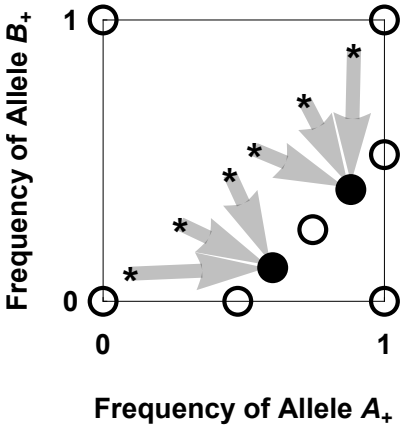


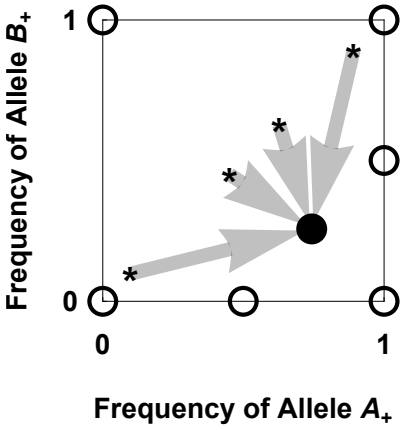
(a) Exclusion



(b) Single-Locus Polymorphism



(c) Asymmetric Coexistence



(d) Symmetric Coexistence

Figure 2: Phase-plane diagrams illustrating possible evolutionary scenarios in the haplodiploid model. The filled black dots show locally stable equilibria and the empty dots show unstable ones. The gray arrows show the basin of attraction starting from secondary contact scenarios (black crosses on the line at $p_{B_+} = p_{A_+}$). Panel (a) illustrates exclusion: There are 2 external locally stable equilibria, each corresponding to the fixation of a parental population haplotype. (Here, $\sigma = 0.02$, $\gamma_1 = 0.9$, $\gamma_2 = 0.11$, $\rho = 0.5$, and $\alpha = 0$.) Panel (b) represents a single-locus polymorphism. Only one locus is polymorphic, leading to the maintenance of the weaker of the two incompatibilities (the A_-B_+ interaction). (Here, $\sigma = 0.009$, $\gamma_1 = 0.11$, $\gamma_2 = 0.002$, $\rho = 0.5$, and $\alpha = 0$.) Panel (c) corresponds to asymmetric coexistence. Two internal equilibria are locally stable, with one allele close to fixation. This scenario minimize the expression of the strongest interaction A_+B_-. (Here, $\sigma = 0.03$, $\gamma_1 = 0.11$, $\gamma_2 = 0.0013$, $\rho = 0.5$, and $\alpha = 0$.) Panel (d) shows symmetric coexistence. Frequencies of alleles A_- and B_- are symmetric around 0.5, with $p_{B_+} = 1 - p_{A_+}$. This scenario maximizes the formation of female heterozygous hybrids. (Here, $\sigma = 0.09$, $\gamma_1 = 0.3$, $\gamma_2 = 10^{-4}$, $\rho = 0.5$, and $\alpha = 0$.)

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Exclusion

The *exclusion* scenario corresponds to the hybrid population becoming identical to one of the two parental populations, either P_+ or P_-, and the other parental population being therefore excluded. It occurs when both alleles from one of the founder subpopulations are purged, leading to a monomorphic stable state of the population (Fig. 2(a)). In this case, the initial frequency of A_+B_+ versus A_-B_- individuals mainly determines the outcome (i.e., the population is swamped by the majority subpopulation). As a rule of thumb, this outcome is observed when recombination is frequent and when the hybridization-averse force of negative epistasis is strong as compared with the hybridization-favoring heterozygote advantage ($\gamma_1, \gamma_2 \gg \sigma$).

With regard to sexual conflict in the haplodiploid model, exclusion can be interpreted as a victory of the males because all polymorphism is lost and no low-fitness hybrid males are produced. Conversely, since all polymorphism is lost, females "lose" in this case and neither high-fitness introgressed (i.e., those individuals carrying only one 'foreign' allele) nor highest-fitness heterozygous hybrid females are produced.

Single-locus polymorphism

A *single-locus polymorphism* occurs when one allele is purged from the population but the other locus remains polymorphic at equilibrium (Fig. 2(b)). Because this is possible for either of the two loci, two such equilibria exist simultaneously, which are reached depending on the initial haplotype frequencies. This outcome is observed when recombination is frequent, epistasis is asymmetric ($\gamma_1 \neq \gamma_2$), and heterozygote advantage is small ($\gamma_1 \gg \sigma$). Like asymmetric coexistence below, this case represents a compromise between the hybridization-averse and hybridization-favoring forces of negative epistasis and heterozygote advantage, and is reached by maximizing the number of introgressed individuals of one founder subpopulation.

In the haplodiploid model, this can be seen as a male-dominated compromise because, since one locus is fixed, one epistatic interaction has disappeared and few low-fitness hybrid males are produced. In females, high-fitness introgressed female frequencies are maximized but, since one locus is fixed, the highest-fitness heterozygous hybrid females are not produced at all. This scenario represents a male-dominated compromise because male costs are mitigated but females cannot reap the highest fitness of the heterozygote advantage.

Single-locus polymorphism is never stable in the diploid model because it can always be invaded by the asymmetric coexistence scenario described below. In a diploid population transiently at single-locus polymorphism, a rare mutant at the second locus will always begin as heterozygote and therefore reap the advantage of being a heterozygote hybrid long before it suffers the epistatic cost of being a homozygote hybrid.

Asymmetric coexistence

"Asymmetric" coexistence occurs when all four haplotypes remain in the population and the frequency of introgressed individuals of one founder subpopulation is maximized (Fig. 2(c)). Because this can be achieved in two ways, two possible equilibria reside off the diagonal line $p_B = 1 - p_A$ (where p_A and p_B denote the allele frequencies of the '$-$' allele at the respective locus), and the initial contribution of different haplotypes determines which equilibrium will be attained. Like the single-locus polymorphism, this equilibrium represents a compromise between hybridization-averse and hybridization-favoring forces that is reached by maximizing the number of introgressed individuals. Our simulations demonstrate that this scenario is rarely present in haplodiploids, and it generally involves asymmetric epistasis and intermediate-strength heterozygote advantage.

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In the haplodiploid model, asymmetric coexistence can be seen as a female-dominated compromise. Unlike the single-locus polymorphism scenario, both loci are polymorphic and some double-heterozygous hybrid females are produced. But, unlike the symmetric coexistence scenario described below, females are not victorious over males because such high-fitness hybrid females are produced only at low frequencies.

Symmetric coexistence

Symmetric coexistence occurs when a locally stable equilibrium exists on the diagonal $p_B = 1 - p_A$, such that the number of heterozygous hybrids is maximized (Fig. 2(d)). Our notion of "symmetric" refers to the total fraction of alleles from the P_+ and P_- founder populations segregating at equilibrium, which is equal in this case. Here, prolonged hybridization is a mutual best-case scenario for both populations. This equilibrium is most likely when recombination is weak or when the hybridization-favoring force of heterozygote advantage is strong as compared with the hybridization-averse negative epistasis ($\sigma \geq \gamma_1, \gamma_2$). In the haplodiploid model, symmetric coexistence represents a victory for the females, because they maximize their own fitness without regard to the production of unfit hybrid males.

The four evolutionary stable states described above usually result in either a single, globally stable (in the case of symmetric coexistence) or a bistable system, in which two locally stable equilibria exist. In rare cases and close to bifurcation points, we observe cases of tristability, which are further described in Figure S2.

Stability analysis of the model

Although the model dynamics are too complex to derive general analytical solutions, we were able to perform stability analyses for specific cases, which yield information about the general behavior of the model. In the following, our use of '$>$' and '$<$' does not necessarily imply strict inequalities; we merely did not explicitly study the limiting cases. For ease of notation, we refer to heterozygote advantage in terms of ω below; recall that $\omega = 1 + \sigma$.

Conditions for symmetric coexistence when epistasis is lethal

We begin by describing the equilibrium structure when epistasis is lethal, i.e. $\gamma_1 = \gamma_2 = 1$; this case may resemble that in the natural ant population, in which most hybrid males do not survive to reproduce. For the haplodiploid model, we obtain a full analytic solution of the identity, existence and stability of equilibria. Here, only two outcomes are possible: symmetric coexistence and exclusion (Fig. 3(a)). As necessary and sufficient criterion for exclusion, we obtain

$$\rho > \frac{\omega^2 - 1}{\omega^2}. \tag{1}$$

Thus, exclusion is only possible if heterozygote advantage is not too strong, and if recombination is breaking up gametes sufficiently often to significantly harm the males.

For the diploid model, we can show that no boundary equilibrium is ever stable; asymmetric and symmetric coexistence are the only two possible outcomes. Although it was not possible to perform a stability analysis on the internal equilibria, we were able to propose a condition for asymmetric coexistence, which has been evaluated numerically:

$$\rho > \frac{(\omega^2-1)(2\omega^4 - 6\omega^3 + \omega^2 + 6\omega - 2)}{\omega^2\,(2\omega^2 - 4\omega + 1)\,(2\omega^2 - 3)} + 2\sqrt{\frac{(\omega-1)^5(\omega+1)^2(\omega^3 - \omega^2 - 3\omega + 1)}{\omega^4\,(2\omega^2 - 4\omega + 1)^2\,(2\omega^2 - 3)^2}}. \tag{2}$$

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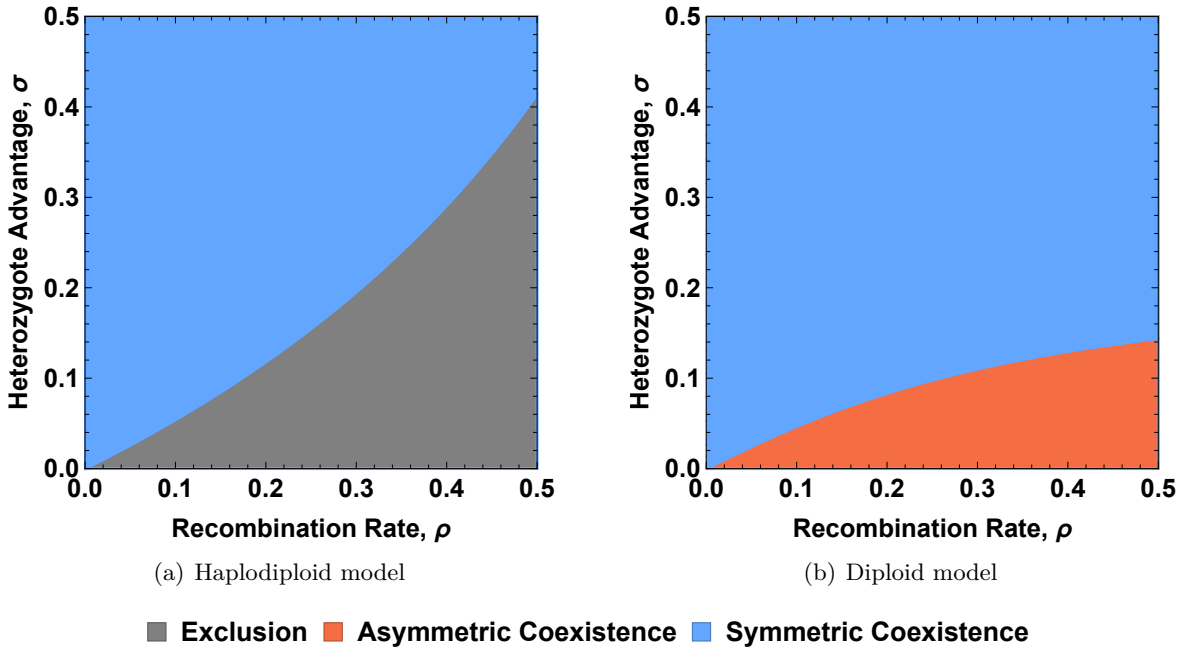

(a) Haplodiploid model

(b) Diploid model

Figure 3: Symmetric coexistence can be locally stable if the heterozygote advantage, σ, is strong enough to compensate for recombination breaking up the parental haplotypes. Here we assume that epistasis is symmetric and lethal ($\gamma_1 = \gamma_2 = 1$). Panel (a) is an illustration of the condition for haplodiploids given in equation (1) and panel (b) of equation (2) for diploids.

Although this expression is not very telling, its illustration in Figure 3(b) demonstrates how different this criterion is from that of the haplodiploid model. Because in the diploid model males benefit from the heterozygote advantage too, asymmetric coexistence is very unlikely. Indeed, a heterozygote advantage of $\omega - 1 = \sigma > \approx 0.14$ is sufficient to ensure symmetric coexistence for all recombination rates, whereas in the haplodiploid model, $\sigma > \sqrt{2} - 1 \approx 0.41$ is necessary for symmetric coexistence independent of the recombination rate.

General stability conditions in the haplodiploid model

Using the results derived for the case of lethal epistasis, and by means of critical examination of the existence and stability conditions that we were able to compute analytically, we arrived at several illustrative conjectures delimiting the evolutionary outcomes in the haplodiploid model when epistasis is not lethal ($\gamma_1, \gamma_2 \neq 1$). These were all confirmed by extensive numerical simulations (see Mathematica Online Supplement). Note that assortative mating was not considered here.

Firstly, strong heterozygote advantage can always override the effect of epistasis. Specifically, if

$$\omega > \sqrt{2}, \tag{3}$$

the evolutionary outcome is always symmetric coexistence, regardless of the values of γ_1 and γ_2. This is true not only for a single pair of interacting loci, but also for an arbitrary number of independent incompatibility pairs, because the conflict at each incompatibility pair is eventually resolved independently (see also the section on multiple loci below).

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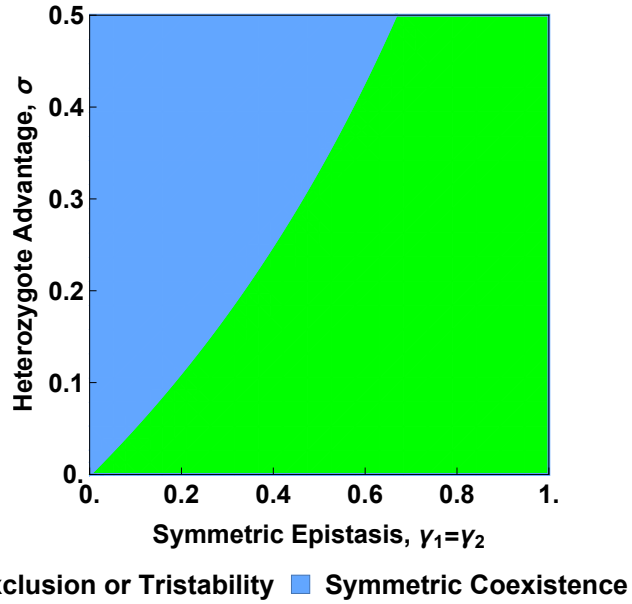

Figure 4: In haplodiploids, symmetric coexistence requires that heterozygote advantage, σ, is strong enough to both compensate for recombination such that the condition in equation 4 is fulfilled (see also Fig. 3(a)), and to overcome the deleterious effects of epistasis, as expressed by condition 5 for symmetric epistasis.

Secondly, recombination is a key player to determine whether compromise or exclusion can occur. In particular,

$$\rho < \frac{\omega^2 - 1}{\omega^2} \tag{4}$$

is a sufficient condition for the observation of symmetric coexistence, independent of the strength and symmetry of epistasis. This makes intuitive sense, because the conflict between heterozygote advantage and hybrid incompatibility only occurs if gametes are broken up by recombination.

Thirdly, for symmetric epistasis ($\gamma_1 = \gamma_2$), there are three possible equilibrium patterns: symmetric coexistence, exclusion, and tristability of the two former types of equilibria. A necessary and sufficient condition for observation of anything but symmetric coexistence is

$$\omega < \sqrt{2} \quad \text{and} \quad \rho > \frac{\omega^2 - 1}{\omega^2} \quad \text{and} \quad \gamma_1 = \gamma_2 > \frac{2(\omega - 1)}{\omega}. \tag{5}$$

If the recombination rate ρ and the epistatic effects γ_1, γ_2 are very close to this limit, there is tristability; if they are far away, there is exclusion (cf. Fig. 4).

Finally, for asymmetric epistasis ($\gamma_1 \neq \gamma_2$), the dynamics display the whole range of possible evolutionary outcomes: symmetric coexistence, asymmetric coexistence, single-locus polymorphism, exclusion, as well as tristability of exclusion *and* symmetric coexistence, and single-locus polymorphism *and* symmetric coexistence. The local stability criterion for the stability of the monomorphic equilibria (i.e., the criterion for exclusion, or tristability of exclusion and symmetric coexistence) is

$$\omega < \sqrt{2} \quad \text{and} \quad \rho > \frac{\omega^2 - 1}{\omega^2} \quad \text{and} \quad \gamma_2 > \frac{2(\omega - 1)}{\omega}. \tag{6}$$

Thus, if epistasis is strong as compared with heterozygote advantage, no degree of asymmetry is sufficient to promote a compromise between males and females (i.e., single-locus

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polymorphism or asymmetric coexistence). In fact, we observe the following necessary (but not sufficient) condition for a single-locus polymorphism:

$$\omega < \sqrt{2} \quad \text{and} \quad \rho > \frac{\omega^2 - 1}{\omega^2} \quad \text{and} \quad \gamma_1 > \frac{2(\omega - 1)}{\omega} \quad \text{and} \quad \gamma_2 < \frac{2(\omega - 1)}{\omega}. \tag{7}$$

Hence, only a tight balance between the selective pressures of epistasis and heterozygote advantage in combination with asymmetry of the hybrid incompatibility promotes a long-term equilibrium with compromise.

An extension to multiple loci

Incompatibilities involving four loci

Above, we have demonstrated that recombination is an essential player when determining whether exclusion or coexistence is the long-term outcome in the haplodiploid dynamics. In order to see how our results change in the (biologically relevant) case of multiple hybrid incompatibilities, we implemented the dynamics for four loci. Given the complexity of the system, we considered only lethal incompatibilities, i.e. $\gamma_i = 1$ for all interactions i. With this extension, we consider two scenarios. Firstly, in the *"pairwise"* case we consider pairs of independent hybrid incompatibilities, where we assume that the incompatible loci are located next to each other (locus **A** interacts with locus **B** at recombination distance ρ_{12}, and locus **C** with locus **D** at recombination distance ρ_{34}), which leaves four viable male haplotypes ($A_+B_+C_+D_+$, $A_+B_+C_-D_-$, $A_-B_-C_+D_+$ and $A_-B_-C_-D_-$). Secondly, in the *"network"* case we assume that all loci interact such that only two viable male haplotypes exist $A_+B_+C_+D_+$ and $A_-B_-C_-D_-$. In both cases, heterozygote advantage is defined as before, now acting on all four loci multiplicatively.

Under this model, we derived the conditions under which exclusion (the purging of all foreign alleles resulting in a monomorphic equilibrium) is locally stable (cf. Mathematica Online Supplement). For the pairwise case, exclusion is stable only if heterozygote advantage is relatively weak:

$$\omega < \min\left[\frac{1}{\sqrt{1-\rho_{12}}}, \frac{1}{\sqrt{1-\rho_{34}}}\right], \tag{8}$$

where ρ_{ij} is the recombination rate between neighboring loci i and j. Note that this is independent of the recombination rate between non-interacting loci, here ρ_{23}. If $\rho_{12} = \rho_{34}$, this expression is equivalent to equation 1 (Fig. 3(a)). Overall, this condition indicates that exclusion (defined as the fixation of one of the parental haplotypes) is less likely with four interacting loci than with two.

For the network case, the condition for stability of exclusion (see also Fig. S3) is

$$\omega < ((1-\rho_{12})(1-\rho_{23})(1-\rho_{34}))^{-\frac{1}{4}}. \tag{9}$$

In this scenario, exclusion is a more likely outcome with two incompatibilities than with one.

Incompatibilities involving an arbitrary number of loci

From the results for two and four loci, we derived a conjecture that generalizes to an arbitrary number of loci. For the pairwise case, equation 8 can be generalized to

$$\omega < \min\left[\frac{1}{\sqrt{1-\rho_{ij}}}\right], \tag{10}$$

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with i and j representing neighboring interacting loci. Note that this result holds only if interacting loci are next to each other on the same chromosome, or if all loci are unlinked (in which case it simplifies to $\omega < \sqrt{2}$).

For the network case, equation (9) generalizes to

$$\omega < \left(\prod_{\substack{i=1 \\ j=i+1}}^{n-1} 1 - \rho_{ij} \right)^{-\frac{1}{n}}, \tag{11}$$

with i and j neighboring loci and n the total number of loci in the network. Unlike in the pairwise case, the results for the network case do not depend on the genetic architecture (here, the ordering of loci along the genome).

We can therefore deduce that, for the pairwise case, exclusion becomes increasingly unlikely as the number of pairs of independent hybrid incompatibilities involved in the genetic barrier increases. Conversely, the opposite result is observed for the network case: more loci make exclusion a more likely outcome, but each additional interaction contributes less (cf. Fig. S3).

Increased assortative mating counteracts recombination and heterozygote advantage

Increasing the strength of assortative mating, $\alpha > 0$, counteracts the hybridization-favoring effect of heterozygote advantage, because matings between individuals with the same genotype are more common under stronger, positive assortment. Under sufficiently large positive α, exclusion is unavoidable. In general, increasing α leads to less maintenance of polymorphism in the population (Fig. S4). Conversely, when $\alpha < 0$, which means that individuals prefer to mate with those whose genotype is most different from their own, polymorphism is more likely to be maintained in the population.

Also with assortative mating, recombination remains a key player in determining the evolutionary outcome. When $\alpha < 0$ and recombination is small, symmetric coexistence is possible even in the absence of heterozygote advantage (i.e., $\sigma = 0$; Fig. S4). Indeed, under these conditions and assuming epistasis is very strong, (almost) all hybrid males are dead and only parental males survive. This 'disassortative' mating ($\alpha < 0$) creates a bias for the rare male haplotype. For example, if one female genotype increases in frequency, it will seek mainly the males of the other parental haplotype to reproduce with (which are currently rare, as their frequency is directly tied to the frequency of the female at the previous generation. This will increases their reproductive success leading to an increase of this haplotype frequency. Therefore, under this mate choice regime, we observe a stable population composed almost exclusively of the A_+B_+ and A_-B_- haplotypes.

Differences between the haplodiploid and the diploid systems

As described above and illustrated in Figure 5, the resulting haplodiploid dynamics display a wider range of possible evolutionary outcomes than the diploid dynamics. Because both males and females profit from heterozygote advantage in the diploid model, polymorphism is always maintained; in other words, even the smallest amount of heterozygote advantage promotes the creation or maintenance of diversity in diploids (Table S3). Conversely, in the haplodiploid model, polymorphism can be lost either at one or both loci, resulting in a single-locus polymorphism or exclusion. Thus, alleles responsible for incompatibilities are more effectively purged in the haplodiploid model.

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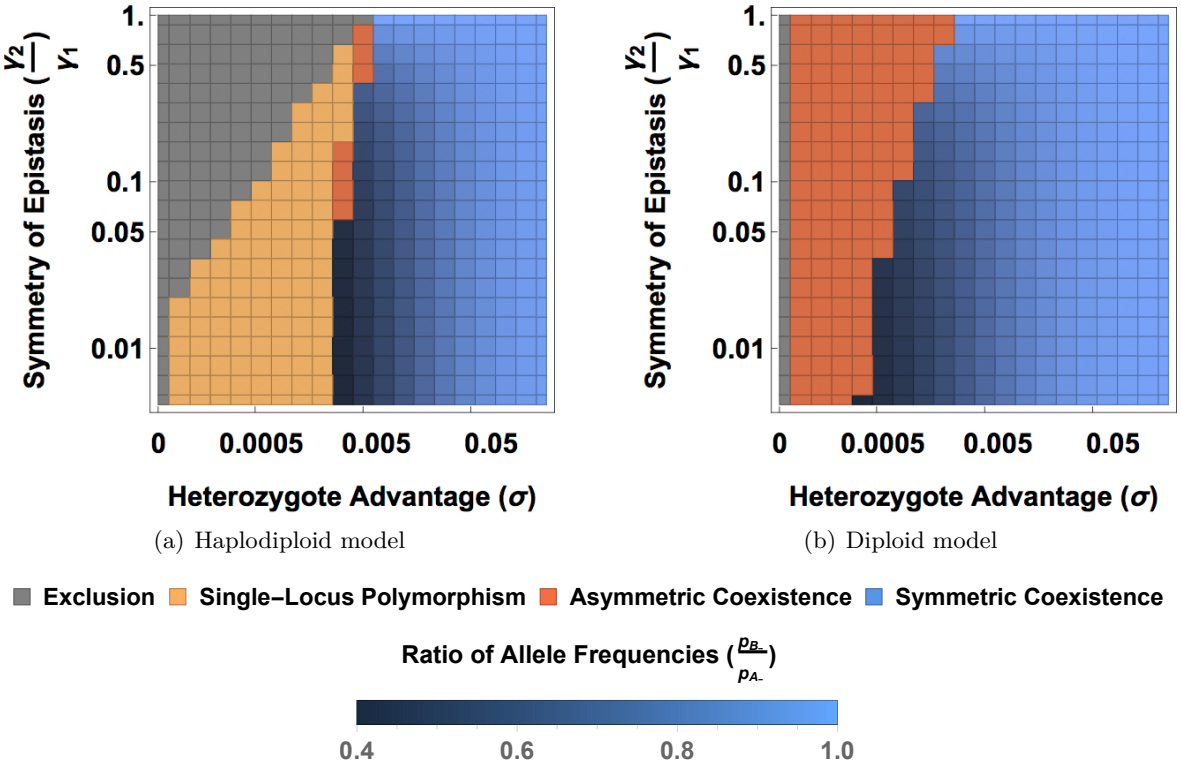

(a) Haplodiploid model

(b) Diploid model

Figure 5: More evolutionary outcomes are possible in (a) the haplodiploid than (b) the diploid model. The y-axis shows the ratio of the two epistasis parameters ($\frac{\gamma_2}{\gamma_1}$) for a constant value of $\gamma_1 = 0.01$, thus it represents the degree of asymmetry of epistasis. For symmetric coexistence, the locally stable equilibrium can be at any point on the diagonal $p_{B_-} = 1 - p_{A_-}$, where p_{A_-} and p_{B_-} denote the allele frequencies of the $-$ allele at the respective locus. Blue shading illustrates the location of the equilibrium at symmetric coexistence: darker shades correspond to a bigger disparity in allele frequencies. This is the case when the asymmetry of the two epistasis parameters is large (i.e. smaller values on the y-axis) because smaller values of γ_2 favor the A_-B_+ haplotype over the A_+B_- haplotype. (Here, $\gamma_1 = 0.01, \rho = 0.5, \alpha = 0$.)

In the diploid model, a single-locus polymorphism is never stable: Assume locus A is polymorphic and locus B is fixed for allele B_+. Then, a new mutant carrying allele B_- will always have a selective advantage regardless of the genotype in which it first appears (Table S3). In contrast, in the haplodiploid model, this is no longer true as the mutant carrying allele B_- will have a much lower fitness in males when associated to allele A_+. Therefore, if the cost of generating this unfit haplotype in males overrides the advantage in females, and allele A_+ is at high frequency, then invasion of the B_+ mutant may be prevented, leading to the stability of the single-locus polymorphism.

When polymorphism is maintained at both loci at equilibrium (i.e., asymmetric and symmetric coexistence), epistasis creates associations between the compatible alleles which results in elevated linkage disequilibrium (LD). Recombination breaks the association between alleles, thus high recombination decreases normalized LD (D', where $D' = \frac{LD}{D_{max}}$; Fig. S5). D' increases with the strength of heterozygote advantage at low recombination rates, because it maximizes the discrepancy between highly fit double-heterozygote females that can, under low recombination rate still produce many fit male offspring, and introgressed females, who

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are less fit and produce many unfit hybrid males.

In Figure S6, we compare the normalized LD (i.e. D') between the haplodiploid and diploid models. When polymorphism is maintained at both loci in both the haplodiploid and diploid model, normalized LD is always larger in haplodiploids than diploids. The difference in normalized LD between haplodiploids and diploids is maximized for intermediate recombination rates, where recombination is strong enough to induce the conflict between heterozygote advantage and hybrid incompatibility, but not efficient enough to break the arising associations. Due to the increased selection against hybrid incompatibility in haploid males in the haplodiploid model, the normalized LD is usually 2-3 times higher in the haplodiploid as compared with the diploid model.

Thus, the hybrid incompatibility leaves a statistical signature in a population, even if the population finds itself at an equilibrium. The increased association across the genome, exhibited if the interacting loci are on the same chromosome, may also result in an underestimate of the recombination rate. Although both the diploid and the haplodiploid models display the elevated LD signal, it is much more pronounced in the haplodiploid scenario. This is because only an eighth of the possible diploid male genotypes suffer the cost of the incompatibility as compared to half of the possible haploid male genotypes.

Fitting the model to natural population frequencies

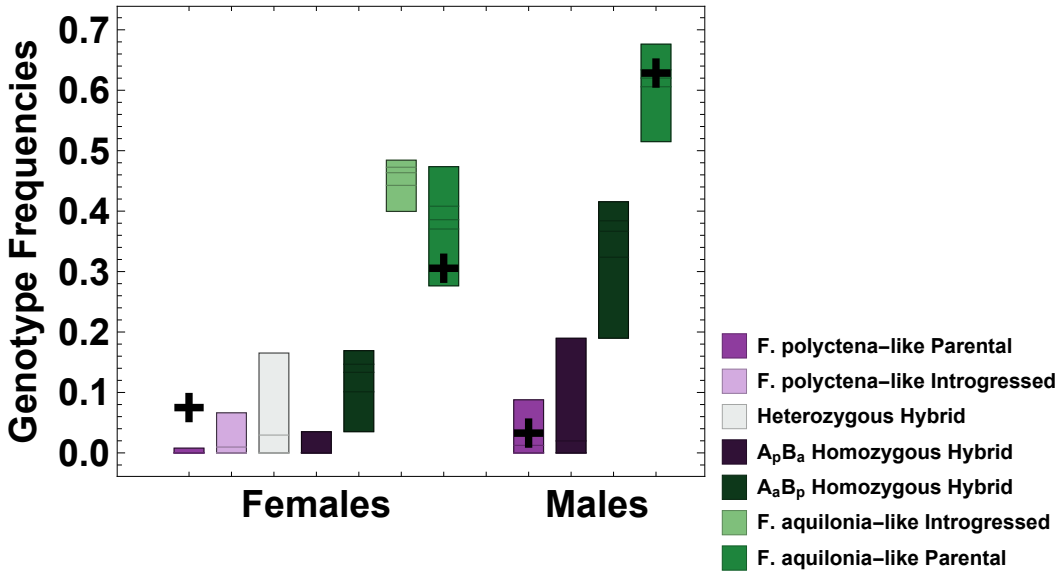

Figure 6: Comparison of model predictions (boxplots) to the data used for fitting the model (+) shows that the model is able to capture the high frequency of *F. aquilona*-like alleles (green shades) in the population. Boxplots show the genotype frequencies for females and males before selection that are predicted from the distribution of the best fitting models. In this case parental genotype frequencies (shown on plot as +) are estimated using individuals with one or more loci homozygous for the parental allele.

We compared the pre- and post-selection haplodiploid model (Fig. S1(a)) predictions with the estimated genotype frequencies of the natural, hybridizing *Formica* wood ant population for eggs and reproductive life-stages of males and females (Table S2). The model predictions from the best-fit models are shown in Figures 6, S7, and S8. The best-fit models had parameter values corresponding to single-locus polymorphism or asymmetric coexistence, regardless

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of how the female frequencies were estimated (Fig. S9). Since these outcomes can occur at a variety of parameter combinations, we were not able to infer any specific parameter estimates other than that large values appear to be preferred for γ_1 and recombination (Fig. S10-S13), consistent with the genomic architecture of the natural population, where multiple incompatibilities are likely to be spread across chromosomes (Kulmuni and Pamilo, 2014). Our model predicts less change in the genotype frequencies before vs. after selection as compared to the differential observed in the data for eggs vs. reproductive adults (Fig. S7(c) and S8(b)).

Discussion

Multiple recent studies have highlighted the pervasive nature of hybridization and its potential consequences for diversification and speciation (Abbott et al., 2013; Runemark et al., 2017; Montecinos et al., 2017). We here modeled the fate of a hybrid population in a scenario in which hybridization is simultaneously favored and selected against, inspired by a natural population of hybrid ants that simultaneously displays heterosis and hybrid incompatibility. In addition, both adaptive introgression and hybrid incompatibilities have been identified in natural systems (Heliconius Genome Consortium, 2012; Whitney et al., 2015; Corbett-Detig et al., 2013) and thus it is likely that both processes may occur simultaneously during a single hybridization event resulting in a 'genomic conflict'. Furthermore, we were interested in comparing the long-term resolutions to this genomic conflict under different ploidies (haplodiploid versus diploid), since it has been argued that haplodiploids might speciate more easily that diploids (Lohse and Ross, 2015). Finally, the comparison of ploidies can also be transferred to the case of diploid species, in which the genomic conflict appears on the X/Z chromosome as compared with the autosomes.

Our model considers a population in which heterozygote advantage and hybrid incompatibility act simultaneously on the same pair of loci, creating a rugged fitness landscape with a ridge of high-fitness heterozygote genotypes, adjacent to which there are holes of incompatible double homozygotes (Fig. 1(a)). Fundamentally, in haplodploids, where females are diploid and males are haploid, this creates a situation in which males cannot profit from heterozygote advantage but suffer strongly from hybrid incompatibility (Fig. 1(b)). Thus, the studied fitness landscape, which creates a genomic conflict in diploids of both sexes, creates a sexual conflict in haplodiploids, where males survive best if diversity is purged whereas females profit from maximum heterozygosity.

We found that in the haplodiploid model, there exist four different stable outcomes for sexual conflict over hybrid status (Fig. 2): exclusion, where "males win"; symmetric coexistence, where "females win"; and two outcomes, single-locus polymorphism and asymmetric coexistence, where a compromise between male costs and female benefits is mediated by high frequencies of introgressed females. In fact, since low-frequency heterozygotes are favored both in males and in females in the diploid model, while only suffering the hybrid cost if introgressed alleles rise to high frequencies, exclusion and single-locus polymorphism never occur in the diploid model, reducing the number of possible outcomes to asymmetric and symmetric coexistence. Thus, consistent with Pamilo (1979); Pamilo and Crozier (1981); Patten et al. (2015), we found that introgression and maintenance of polymorphism, and thus long-term hybridization, are less likely in haplodiploids as compared to diploids.

Prior work has found that in haplodiploid species sexual conflict tends to be resolved in favor of females because genes spend two thirds of their time in females (Albert and Otto, 2005). For several scenarios, we here derived the conditions for either type of solution. We find, that in addition to the strength of selection, recombination is a major player (cf. Fig. 3 and equation 6); the conflict is only expressed in the first place, if recombination breaks

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up gametes and causes the incompatibilities to be expressed. With free recombination, i.e., if the interacting genes are found on separate chromosomes, heterozygote advantage has to be very strong to counteract the hybrid incompatibility. We find that it has to be on the same order of magnitude than the strength of the incompatibility, but can be slightly lower in its absolute value. For example, heterozygote advantage of strength 41% is sufficient to result in symmetric coexistence even if the incompatibility is lethal (Fig. 3B). Thus, under consideration of absolute magnitude, our results are consistent with prior work. However, reported cases and potential mechanisms of hybrid incompatibility indicate that large effects are feasible, whereas observed cases of heterozygote advantage or heterosis of large effect are relatively rare (Hedrick, 2012). Thus, it may well be that under natural circumstances, the conflict modeled here may indeed be likely to be resolved via purging of at least one incompatible allele and thus in favor of males.

As expected in the presence of epistasis, we observed that linkage disequilibrium (LD) is elevated at all polymorphic stable states (i.e., for symmetric and asymmetric coexistence) both in the diploid and haplodiploid models, especially at intermediate recombination rates. This is particularly true for haplodiploids, which display about 2-3 times the LD of the diploid model with the same parameters. Transferred to the context of X/Z chromosomes, this is consistent with observations of larger LD on the X chromosome as compared with autosomes. It has been argued that this is because selection is more effective on X-linked loci: recessive deleterious mutations are more visible to selection in haploid individuals (Charlesworth et al., 1987). However, a hybrid incompatibility accompanied by heterosis/heterozygote advantage as in our model may not be purged, but create a continuous high-LD signal in an equilibrium population, thus potentially resulting in less efficient recombination and in underestimates of recombination rates on X chromosomes (because recombined individuals are not observed).

Exclusion remains a stable solution when we extend the model to multiple loci and incompatibilities. We describe an interesting difference between multiple independent pairs of incompatibilities, and multiple loci that all interact with each other: in the latter case, exclusion becomes increasingly probable because the number of viable males decreases. This scenario of higher-order epistasis has recently received attention with regards to speciation (Paixão et al., 2014; Fraïsse et al., 2014), and it will be interesting to identify molecular scenarios (for example, involving biological pathways) that could result in such incompatibilities in the future. In contrast, exclusion becomes less likely in the case of independent incompatibility pairs, where each incompatibility has to be purged independently in the same direction for exclusion to occur. Here, mechanisms that reduce the recombination rate, such as inversions, could potentially invade and tilt the balance towards coexistence and thus maintenance of polymorphism in the hybrid population. It is important to not that the independent purging of incompatibilities is only true in effectively infinite-sized populations. Thus, we expect that exclusion becomes a more likely scenario in small populations, especially if lethal incompatibility pairs are present.

Model assumptions

We chose a classical population-genetic modeling approach (Bürger, 2000; Nagylaki et al., 1992) to study how a specific type of genomic conflict between heterozygote advantage and hybrid incompatibility can be resolved in a hybrid population. By treating the problem in a deterministic framework and considering only two loci throughout most of the manuscript, we vastly oversimplify the situation in the natural population that our model was inspired by. However, at the same time this allowed us to gain a general insight in how the genomic (and, in haplodiploids, sexual) conflict may be resolved, often expressed by means of analytical expressions. In addition to some obvious mechanisms at play in natural popu-

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lations, which we ignore in our model (e.g., random genetic drift), some extensions of the model could be interesting to elaborate on in the future. For example, the ant populations represent networks of interacting nests with many queens per nest, but potentially different hatching/development times depending on sun exposure in the spring. In addition, males are the sex that is in greater abundance and that tends to migrate between nests. Thus, for the purpose of population-genetic inference of the evolutionary history (and potential evolutionary fate) of the hybrid ant population in Finland, it would be desirable to incorporate population structure, uneven sex rations, and sex-biased dispersal into the model, and obtain population-genomic data to infer evolutionary parameters.

Is the natural population at an equilibrium of asymmetric coexistence?

Model fitting results to the data from Table S2 are inconclusive about the fate of the natural ant population that inspired our model. Our results suggest that it might be approaching an evolutionary outcome that allows a compromise between male and female interests; either as single-locus polymorphism or via asymmetric coexistence.

However, we fitted our model to the data from the natural ant population described in Kulmuni and Pamilo (2014) and Table S1 in a rather crude approach. In the fitting procedure, we ignored that the data contain information from marker loci rather than the selected alleles, and we summarized the data in categories to resemble our case of a two-locus interaction. Our model fitting results indicate that the unequal ratio of *F. polyctena*-like and *F. aquilona*-like types that is observed in the natural population could represent a stable equilibrium of asymmetric coexistence. In fact, the high recombination rates among diagnostic alleles and strong prezygotic mechanisms producing within-group zygotes exhibited in the natural population Kulmuni et al. (2010); Kulmuni and Pamilo (2014) correspond with an area in the parameter space where asymmetric coexistence can be stably maintained over a wide range of values for female hybrid advantage.

Our model fit does not perform well at predicting the number of introgressed and hybrid females in the population. We were not able to estimate the population frequencies for introgressed and hybrid females with data from Kulmuni and Pamilo (2014), but we know from Kulmuni et al. (2010) that the vast majority of both *F. polyctena*-like and *F. aquilonia*-like females exhibit some introgression. Contrary to this observation in the natural population, our model fit predicts that introgressed *F. polyctena*-like females should be rare ($< 15\%$) and that pure *F. aquilona*-like females should be only slightly less common than the introgressed *F. polyctena*-like females (Fig. 6). More complex models, for example including more than two incompatibility loci, may be better able to explain the high frequencies of introgressed females observed in the natural hybrid population. As argued in the Results, interactions at or between multiple loci should result in steeper differences of introgressed-allele frequencies across life stages than our model is able to produce.

Implications for hybrid speciation

Our model illustrates how a genomic conflict between heterozygote advantage and hybrid incompatibility is resolved in haplodiploid and diploid populations. We can hypothesize how these different outcomes may provide an engine to hybrid speciation, or which other long-term evolutionary scenarios we expect to arise. The case of exclusion, which is possible only in the haplodiploid model, will lead to loss of diversity in the hybrid population, and, in the two-locus case, should result in the reversion of the hybrid population into one of its parental species. However, if multiple pairs of interacting loci are resolved independently, they may be purged randomly towards either parent, which could result in a true hybrid species that is

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isolated from both its parental species (Buerkle et al., 2000; Butlin and Ritchie, 2013; Schumer et al., 2015). In fact, our finding that exclusion is less likely to occur in populations with multiple pairs of interacting loci may result from exactly this mechanism, but it is beyond the scope of this manuscript to explore this further.

The long-term fate of the population is less straightforward to anticipate in the case of polymorphic stable equilibria. For any of these, heterozygote advantage is strong enough to stabilize the polymorphism either at one or both loci. Thus, without further occurrence of functional mutations, males (in the haplodiploid model) and double-homozygotes for the incompatible alleles will continue to suffer a potentially large fitness cost. Mechanisms that could reduce this cost would be increased assortative mating or decreased recombination. However, none of these would necessarily cause isolation from the parental species, unless they involved additional hybrid incompatibilities which isolate the hybrid population from its parental species. Alternatively, mutations that lower the hybrid fitness cost could invade, which will result in a weakening of species barriers and promote further introgression from the parental species. This indicates that any scenario in which polymorphic equilibria are stable may indeed be an unlikely candidate for hybrid speciation. Considering that such stable polymorphism (either as symmetric or asymmetric coexistence) is the only possible outcome in the diploid model, this results in the prediction that hybrid speciation would be more likely in a haplodiploid scenario. This is an interesting observation that is in line with other predictions that haplodiploids speciate more easily, that X/Z chromosomes are engines of speciation (Lima, 2014), and that hybrid speciation is rare (Schumer et al., 2014).

Relevance of the model for sex chromosomes

Haplodiploids and X/Z chromosomes have a similar mode of inheritance, where one sex carries a single copy of the chromosome, and the other carries two copies. Therefore, our results apply equally to cases of X-to-X or Z-to-Z hybrid incompatibilities (Lohse and Ross, 2015). Although haplodiploid systems do not include all of the unique evolutionary phenomena exhibited by sex chromosomes (Abbott et al., 2017), our results for haplodiploids are relevant for sex chromosomes. Our model predicts how a conflict between heterozygote advantage and hybrid incompatibilities will be resolved, and indicates the signatures that this type of fitness landscape could leave depending on whether it finds itself on an X chromosome or an autosome.

Firstly, as argued above, what is a genomic conflict between heterozygote advantage and hybrid incompatibility on autosomes/in diploids becomes a sexual conflict on the X chromosome/in haplodiploids. Thus, the same fitness landscape that would be well masked on an autosome and result in a stable polymorphism, would create a signal of sexually antagonistic selection on an X chromosome. Most importantly, this signal is created without the need for direct sexually antagonistic selection on single functional genes that have a sex-specific antagonistic effect. Thus, our model proposes an additional mechanism by which sex chromosomes can appear as hot spot of sexual conflict (e.g., Gibson et al., 2002; Pischedda and Chippindale, 2006).

Secondly, we find that purging of incompatibilities is more likely in the haplodiploid model, and thus on X/W chromosomes. This is consistent with the faster-X theory (Charlesworth et al., 1987). However, we only if recombination is strong enough, incompatibilities will become visible to selection and purged in the presence of heterozygote advantage. If they are not purged, they may persist in a long-term polymorphism, invisible to most empirical approaches, and confound population-genetic inference by creating signals of elevated linkage disequilibrium.

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Conclusion

Hybridization is observed frequently in natural populations, and can have both deleterious and advantageous effects. We here showed how diverse outcomes are produced even under a rather simple model of a single hybrid population, in which heterozygote advantage and hybrid incompatibility are occurring at the same time. Consistent with previous theory on haplodiploids and X/Z chromosomes, we found that incompatible alleles are more likely to be purged in a haplodiploid than in a diploid model. Nevertheless, our results suggest that long-term hybridization can occur even in the presence of hybrid incompatibility, and if there are many incompatibility pairs or many loci involved in the incompatibility. The evolutionary fate of the Finnish hybrid population that our model was inspired by is difficult to predict; further population-genetic analysis will be necessary to gain a more complete picture of its structure and evolutionary history.

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Data Accessibility

The complete documentation of all steps of the analysis is available as a Mathematica Online Supplement. Ant colony data is provided as Supplementary Table S1; genotype frequency data were obtained from Kulmuni and Pamilo (2014).

Author Contributions

CB, JK, and RB designed research, AB and CB developed the models, AHG performed simulations and data analysis, all authors interpreted the results and wrote the manuscript.

Bibliography

Abbott, J., Nordén, A., and Hansson, B. (2017). Sex chromosome evolution: Historical insights and future perspectives. *Proceedings of the Royal Society of London B: Biological Sciences*, 284(1854):20162806.

Abbott, R., Albach, D., Ansell, S., Arntzen, J. W., Baird, S. J. E., Bierne, N., Boughman, J., Brelsford, A., Buerkle, C. A., Buggs, R., Butlin, R. K., Dieckmann, U., Eroukhmanoff, F., Grill, A., Cahan, S. H., Hermansen, J. S., Hewitt, G., Hudson, A. G., Jiggins, C., Jones, J., Keller, B., Marczewski, T., Mallet, J., Martinez-Rodriguez, P., Möst, M., Mullen, S., Nichols, R., Nolte, A. W., Parisod, C., Pfennig, K., Rice, A. M., Ritchie, M. G., Seifert, B., Smadja, C. M., Stelkens, R., Szymura, J. M., Väinölä, R., Wolf, J. B. W., and Zinner, D. (2013). Hybridization and speciation. *Journal of Evolutionary Biology*, 26(2):229–246.

Albert, A. and Otto, S. (2005). Sexual selection can resolve sex-linked sexual antagonism. *Science*, 310(5745):119–121.

bioRxiv preprint doi: https://doi.org/10.1101/196469; this version posted September 30, 2017. The copyright holder for this preprint (which was not certified by peer review) is the author/funder, who has granted bioRxiv a license to display the preprint in perpetuity. It is made available under aCC-BY-NC 4.0 International license.

Bateson, W. (1909). Heredity and variation in modern lights. *Darwin and modern science*, pages 85–101.

Beresford, J., Elias, M., Pluckrose, L., Sundström, L., Butlin, R., Pamilo, P., and Kulmuni, J. (2017). Widespread hybridization within mound-building wood ants in Southern Finland results in cytonuclear mismatches and potential for sex-specific hybrid breakdown. *Molecular Ecology*, 26(15):4013–26.

Bernardes, J., Stelkens, R., and Greig, D. (2017). Heterosis in hybrids within and between yeast species. *Journal of Evolutionary Biology*, 30(3):538–548.

Buerkle, C. A., Morris, R. J., Asmussen, M. A., and Rieseberg, L. H. (2000). The likelihood of homoploid hybrid speciation. *Heredity*, 84(4):441–451.

Bürger, R. (2000). *The mathematical theory of selection, recombination, and mutation*, volume 228. Wiley Chichester.

Butlin, R. K. and Ritchie, M. G. (2013). Pulling together or pulling apart: hybridization in theory and practice. *Journal of Evolutionary Biology*, 26(2):294–298.

Charlesworth, B., Coyne, J., and Barton, N. (1987). The relative rates of evolution of sex chromosomes and autosomes. *The American Naturalist*, 130(1):113–146.

Chen, C., Zhiguo, E., and Lin, H.-X. (2016). Evolution and molecular control of hybrid incompatibility in plants. *Frontiers in Plant Science*, 7:1208.

Chen, Z. (2013). Genomic and epigenetic insights into the molecular bases of heterosis. *Nature Review Genetics*, 14(7):471–482.

Corbett-Detig, R. B., Zhou, J., Clark, A. G., Hartl, D. L., and Ayroles, J. F. (2013). Genetic incompatibilities are widespread within species. *Nature*, 504(7478):135–7.

Crozier, R. and Pamilo, P. (1996). *Evolution of social insect colonies: Sex allocation and kin selection*. Oxford University Press, Oxford, UK.

De Cara, M., Barton, N., and Kirkpatrick, M. (2008). A model for the evolution of assortative mating. *The American Naturalist*, 171(5):580–596.

de la Filia, A., Bain, S., and Ross, L. (2015). Haplodiploidy and the reproductive ecology of arthropods. *Current Opinion in Insect Science*, 9:36–43.

Dieckmann, U. and Doebeli, M. (1999). On the origin of species by sympatric speciation. *Nature*, 400(6742):354–357.

Dobzhansky, T. (1936). Studies on hybrid sterility. II. Localization of sterility factors in *Drosophila pseudoobscura* hybrids. *Genetics*, 21(2):113.

Evans, J., Shearman, D., and Oldroyd, B. (2004). Molecular basis of sex determination in haplodiploids. *Trends in Ecology and Evolution*, 19(1):1–3.

Fraïsse, C., Elderfield, J., and Welch, J. (2014). The genetics of speciation: are complex incompatibilities easier to evolve? *Journal of Evolutionary Biology*, 27(4):688–99.

Gibson, J., Chippindale, A., and Rice, W. (2002). The X chromosome is a hot spot for sexually antagonistic fitness variation. *Proceedings of the Royal Society of London B: Biological Sciences*, 269(1490):499–505.

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Hedrick, P. W. (2012). What is the evidence for heterozygote advantage selection? *Trends in Ecology & Evolution*, 27(12):698–704.

Heliconius Genome Consortium (2012). Butterfly genome reveals promiscuous exchange of mimicry adaptations among species. *Nature*, 487(7405):94.

Höllinger, I. and Hermisson, J. (2017). Bounds to parapatric speciation: A Dobzhansky–Muller incompatibility model involving autosomes, X chromosomes, and mitochondria. *Evolution*, 71(5):1366–1380.

Jablonka, E. and Lamb, M. J. (1991). Sex Chromosomes and Speciation. *Proceedings of the Royal Society B: Biological Sciences*, 243(1308):203–208.

Johnson, N. A. and Lachance, J. (2012). The genetics of sex chromosomes: evolution and implications for hybrid incompatibility. *Annals of the New York Academy of Sciences*, 1256(1):E1–E22.

Knegt, B., Potter, T., Pearson, N., Sato, Y., Staudacher, H., Schimmel, B., Kiers, E., and Egas, M. (2017). Detection of genetic incompatibilities in non-model systems using simple genetic markers: hybrid breakdown in the haplodiploid spider mite tetranychus evansi. *Heredity*, 118(4):311.

Koevoets, T. and Beukeboom, L. (2009). Genetics of postzygotic isolation and Haldane's rule in haplodiploids. *Heredity*, 102(1):16–23.

Kopp, M., Servedio, M. S., Mendelson, T. C., Safran, R. J., Rodríguez, R. L., Scordato, E. C., Symes, L. B., Balakrishnan, C. N., Hauber, M. E., Zonana, D. M., and van Doorn, G. S. Mechanisms of assortative mating in speciation: connecting theory and empirical research. *The American Naturalist*.

Kraaijeveld, K. (2009). Male genes with nowhere to hide; sexual conflict in haplodiploids. *Animal Biology*, 59(4):403–415.

Kulmuni, J. and Pamilo, P. (2014). Introgression in hybrid ants is favored in females but selected against in males. *Proceedings of the National Academy of Sciences*, 111(35):12805–10.

Kulmuni, J., Seifert, B., and Pamilo, P. (2010). Segregation distortion causes large-scale differences between male and female genomes in hybrid ants. *Proceedings of the National Academy of Sciences*, 107(16):7371–6.

Lima, T. G. (2014). Higher levels of sex chromosome heteromorphism are associated with markedly stronger reproductive isolation. *Nature Communications*, 5:4743.

Lohse, K. and Ross, L. (2015). What haplodiploids can teach us about hybridization and speciation. *Molecular Ecology*, 24(20):5075–5077.

Mallet, J. (2005). Hybridization as an invasion of the genome. *Trends in Ecology and Evoluion*, 20(5):229–237.

Montecinos, A. E., Guillemin, M.-L., Couceiro, L., Peters, A. F., Stoeckel, S., and Valero, M. (2017). Hybridization between two cryptic filamentous brown seaweeds along the shore: analysing pre- and postzygotic barriers in populations of individuals with varying ploidy levels. *Molecular Ecology*, 26(13):3497–3512.

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Muller, H. (1942). Isolating mechanisms, evolution and temperature. In *Biology Symposium*, volume 6, pages 71–125.

Nagylaki, T. et al. (1992). *Introduction to theoretical population genetics*, volume 142. Springer-Verlag Berlin.

Orr, H. (1995). The population genetics of speciation: The evolution of hybrid incompatibilities. *Genetics*, 139(4):1805–1813.

Paixão, T., Bassler, K. E., and Azevedo, R. B. R. (2014). Emergent speciation by multiple Dobzhansky-Muller incompatibilities. *bioRxiv*, page 8268.

Pamilo, P. (1979). Genic variation at sex-linked loci: Quantification of regular selection models. *Hereditas*, 91(1):129–133.

Pamilo, P. and Crozier, R. H. (1981). Genic variation in male haploids under deterministic selection. *Genetics*, 98(1):199–214.

Patten, M., Carioscia, S., and Linnen, C. (2015). Biased introgression of mitochondrial and nuclear genes: A comparison of diploid and haplodiploid systems. *Molecular Ecology*, 24(20):5200–5210.

Pischedda, A. and Chippindale, A. K. (2006). Intralocus sexual conflict diminishes the benefits of sexual selection. *PLoS biology*, 4(11):e356.

Presgraves, D. (2008). Sex chromosomes and speciation in *Drosophila*. *Trends in Genetics*, 24(7):336–343.

Runemark, A., Trier, C. N., Eroukhmanoff, F., Hermansen, J. S., Matschiner, M., Ravinet, M., Elgvin, T. O., and Saetre, G.-P. (2017). Variation and constraints in hybrid genome formation. *bioRxiv*, page 107508.

Schluter, D. (2009). Evidence for ecological speciation and its alternative. *Science*, 323(5915):737–741.

Schluter, D. and Conte, G. (2009). Genetics and ecological speciation. *Proceedings of the National Academy of Sciences*, 106(Supplement 1):9955–9962.

Schumer, M., Cui, R., Rosenthal, G. G., and Andolfatto, P. (2015). Reproductive isolation of hybrid populations driven by genetic incompatibilities. *PLOS Genetics*, 11(3):1–21.

Schumer, M., Rosenthal, G., and Andolfatto, P. (2014). How common is homoploid hybrid speciation? *Evolution*, 68(6):1553–1560.

Schwarz, D., Matta, B., Shakir-Botteri, N., and McPheron, B. (2005). Host shift to an invasive plant triggers rapid animal hybrid speciation. *Nature*, 436(7050):546–9.

Seehausen, O., Butlin, R., Keller, I., Wagner, C., Boughman, J., Hohenlohe, P., Peichel, C., Saetre, G.-P., Bank, C., Brännström, Å., Brelsford, A., Clarkson, C., Eroukhmanoff, F., Feder, J., Fischer, M., Foote, A., Franchini, P., et al. (2014). Genomics and the origin of species. *Nature Reviews Genetics*, 15(3):176–192.

Servedio, M. and Noor, M. (2003). The role of reinforcement in speciation: theory and data. *Annual Review of Ecology, Evolution, and Systematics*, 34(1):339–364.

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Song, Y., Endepols, S., Klemann, N., Richter, D., Matuschka, F.-R., Shih, C.-H., Nachman, M., and Kohn, M. (2011). Adaptive introgression of anticoagulant rodent poison resistance by hybridization between old world mice. *Current Biology*, 21(15):1296–1301.

Suomalainen, E., Saura, A., and Lokki, J. (1987). *Cytology and evolution in parthenogenesis*. CRC Press, Boca Raton, Florida.

Whitney, K., Randell, R., and Rieseberg, L. (2010). Adaptive introgression of abiotic tolerance traits in the sunflower *Helianthus annuus*. *New Phytologist*, 187(1):230–239.

Whitney, K. D., Broman, K. W., Kane, N. C., Hovick, S. M., Randell, R. A., and Rieseberg, L. H. (2015). Quantitative trait locus mapping identifies candidate alleles involved in adaptive introgression and range expansion in a wild sunflower. *Molecular Ecology*, 24(9):2194–2211.

Wolf, D., Takebayashi, N., and Rieseberg, L. (2001). Predicting the risk of extinction through hybridization. *Conservation Biology*, 15(4):1039–1053.

Wolfram Research, Inc. (2016). Mathematica v. 10.4.1.0. Champaign, Illinois, USA. https://www.wolfram.com.