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

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Running title:
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 ploidal 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,
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; Knekt 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 (Hollinger 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; Fraisè 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, 1932).
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...
Table 1: List of model parameters.

<table>
<thead>
<tr>
<th>Symbol</th>
<th>Parameter</th>
<th>Limits</th>
</tr>
</thead>
<tbody>
<tr>
<td>σ,ω</td>
<td><strong>Strength of heterozygote advantage</strong>, resulting in fitness ω = (1 + σ) or ω² = (1 + σ)² of introgressed or double heterozygous diploid hybrids, respectively.</td>
<td>ω − 1 = σ &gt; 0</td>
</tr>
<tr>
<td>γ₁, γ₂</td>
<td><strong>Strength of fully recessive negative epistasis</strong>, resulting in fitness (1 − γ₁) for A⁺B⁻ homozgyous diploid hybrids and A⁺B⁻ hybrid haploid males, and (1 − γ₂) for A⁻B⁺ homozgyous diploid hybrids and A⁻B⁺ hybrid haploid males.</td>
<td>0 ≤ γ₁, γ₂ ≤ 1</td>
</tr>
<tr>
<td>ρ</td>
<td><strong>Recombination rate</strong> between locus A and B.</td>
<td>0 ≤ ρ ≤ 0.5</td>
</tr>
<tr>
<td>α</td>
<td><strong>Strength of assortment</strong> via genotype matching, where α = 0 represents random mating, α &gt; 0 represents assortative mating among conspecifics, and α &lt; 0 represents assortative mating between heterospecifics.</td>
<td>−1 ≤ α ≤ 1</td>
</tr>
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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, γ₁ and γ₂ (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.
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.
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 $\gamma_1$ acts on individuals homozygous or haploid for the $A_+B_-$ haplotype, and $\gamma_2$ 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 $\frac{1}{2}(1 - \alpha)d_{g_fg_m}\chi_{g_f}\chi_{g_m}$, where $d_{g_fg_m}$ is the Hamming distance between the female and male genotypes (where the male haplotype is doubled in the haplodiploid model) and $\chi_{g_f}, \chi_{g_m}$ 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).
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 $\gamma_1, \gamma_2$) 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.
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 $\alpha = 0$.)
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 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 $1^−1$ 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.
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 \( \omega \) 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

\[
\rho > \frac{\omega^2 - 1}{\omega^2}.
\]

(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:

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

(2)
Figure 3: Symmetric coexistence can be locally stable if the heterozygote advantage, $\sigma$, 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

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

the evolutionary outcome is always symmetric coexistence, regardless of the values of $\gamma_1$ and $\gamma_2$. 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).
Figure 4: In haplodiploids, symmetric coexistence requires that heterozygote advantage, $\sigma$, 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,

$$\rho < \frac{\omega^2 - 1}{\omega^2} \quad (4)$$

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

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

If the recombination rate $\rho$ and the epistatic effects $\gamma_1, \gamma_2$ 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

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

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

$$\omega < \sqrt{2} \text{ and } \rho > \frac{\omega^2 - 1}{\omega^2} \text{ and } \gamma_1 > \frac{2(\omega - 1)}{\omega} \text{ and } \gamma_2 < \frac{2(\omega - 1)}{\omega}.$$  \hfill (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 $$\rho_{12}$$, and locus $$C$$ with locus $$D$$ at recombination distance $$\rho_{34}$$), 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:

$$\omega < \min \left[ \frac{1}{\sqrt{1 - \rho_{ij}}} \frac{1}{\sqrt{1 - \rho_{23}}} \right],$$  \hfill (8)

where $$\rho_{ij}$$ is the recombination rate between neighboring loci $$i$$ and $$j$$. Note that this is independent of the recombination rate between non-interacting loci, here $$\rho_{23}$$. 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

$$\omega < (1 - \rho_{12})(1 - \rho_{23})(1 - \rho_{34})^{-\frac{1}{2}}.$$  \hfill (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

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

\[
\omega < \left( \prod_{i=1}^{n-1} \left( 1 - \rho_{ij} \right) \right)^{-\frac{1}{n}},
\]

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 \(\alpha\), exclusion is unavoidable. In general, increasing \(\alpha\) leads to less maintenance of polymorphism in the population (Fig. S1). 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. S1). 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 increase 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 S5, 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.
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 \( \gamma_2 / \gamma_1 \) 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 \( \gamma_2 \) 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
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**

![Genotype Frequencies](image)

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. aquilonia*-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 S6 and S7. The best-fit models had parameter values corresponding to single-locus polymorphism or asymmetric coexistence, regardless
of how the female frequencies were estimated (Fig. 9). 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 $\gamma_1$ 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 than 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 haplodiploids, 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. 3): 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 3); the conflict is only expressed in the first place, if recombination breaks
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 in-
compatibilities. 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 Fraisse et al. 2014], and it will be interesting to identify molecular
scenarios (for example, involving biological pathways) that could result in such incompat-
ibilities 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 in-
dependent 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 choose 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 ge-
nomic (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-
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. aquilonia*-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. aquilonia*-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
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.
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


