

1 **The genomic and ecological context of hybridization affect the**
2 **probability that symmetrical incompatibilities drive hybrid speciation.**

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9

10 **Abstract**

11

12 Despite examples of homoploid hybrid species, theoretical work describing when,
13 where, and how we expect homoploid hybrid speciation to occur remains relatively rare.
14 Here I explore the probability of homoploid hybrid speciation due to “symmetrical
15 incompatibilities” under different selective and genetic scenarios. Through simulation, I
16 test how genetic architecture and selection acting on traits that do not themselves
17 generate incompatibilities interact to affect the probability that hybrids evolve
18 symmetrical incompatibilities with their parent species. Unsurprisingly, selection against
19 admixture at ‘adaptive’ loci that are linked to loci that generate incompatibilities tends to
20 reduce the probability of evolving symmetrical incompatibilities. By contrast, selection
21 that favors admixed genotypes at adaptive loci can promote the evolution of symmetrical
22 incompatibilities. The magnitude of these outcomes is affected by the strength of
23 selection, aspects of genetic architecture such as linkage relationships and the linear
24 arrangement of loci along a chromosome, and the amount of hybridization following the
25 formation of a hybrid zone. These results highlight how understanding the nature of
26 selection, aspects of the genetics of traits affecting fitness, and the strength of
27 reproductive isolation between hybridizing taxa can all be used to inform when we expect
28 to observe homoploid hybrid speciation due to symmetrical incompatibilities.

29 Introduction

30
31 Modern genomic data and analyses are revealing that naturally occurring
32 hybridization and admixture between divergent lineages is not rare (Maqbool *et al.* 2015;
33 Racimo *et al.* 2015; Pease *et al.* 2016; Wallbank *et al.* 2016). The evolutionary
34 consequences of hybridization are however diverse. On one hand, hybridization has
35 been described as “the grossest blunder in sexual preference which we can conceive of
36 an animal making” (Fisher 1930). On the other, hybridization can be a generative force,
37 facilitating adaptive evolution via adaptive introgression (Song *et al.* 2011;
38 Dasmahapatra *et al.* 2012) or promoting diversification through hybrid speciation
39 (Anderson & Stebbins 1954; Buerkle *et al.* 2000; Gross & Rieseberg 2005; Mallet 2007).
40 Cases of hybrid speciation exist (Rieseberg *et al.* 2003; Gompert *et al.* 2006; Duenez-
41 Guzman *et al.* 2009; Salazar *et al.* 2010; Nice *et al.* 2013; Hermansen *et al.* 2014;
42 Lamichhaney *et al.* 2017), and some have suggested that hybridization may be
43 responsible for a larger fraction of species diversity than previously appreciated (Mallet
44 2007; Mavarez & Linares 2008). However, linking the specific mechanism(s) through
45 which hybridization causally leads to the evolution of reproductive isolation (RI) between
46 hybrids and their parents, in many putative cases, remains a major challenge (Schumer
47 *et al.* 2014).

48 Hybrid speciation can occur either with or without a change in ploidy between
49 hybrid lineages and their parents (Stebbins 1959; Rieseberg *et al.* 1995; Hegarty &
50 Hiscock 2005; Mallet 2007). Polyploid hybrid speciation is rare in animals, but relatively
51 common in plants (see Stebbins 1959; Hegarty & Hiscock 2005), because, relative to
52 plants, incidence of polyploidy are rare in most groups of animals (Orr 1990; Otto &
53 Whitton 2000; Mable 2004). By contrast, homoploid hybrid speciation (HHS) has been
54 shown to occur in plants (e.g. *Helianthus anomalus*; (Rieseberg *et al.* 1995, 2003;
55 Ungerer *et al.* 1998), animals (e.g. *Heliconius heurippa*; (Jiggins *et al.* 2008; Melo *et al.*
56 2009; Salazar *et al.* 2010), and fungi (Leducq *et al.* 2016). Additional examples of
57 putative homoploid hybrid species are becoming more common (reviewed in Gross &

58 Rieseberg 2005; Mavarez & Linares 2008). For details of specific examples of hybrid
59 species, I refer the reader to citations presented throughout this manuscript; hereafter I
60 focus specifically on the processes generating RI during HHS.

61 At least four studies have quantitatively explored conditions that can lead to HHS.
62 These studies demonstrate that admixed populations are more likely to stabilize, and
63 evolve RI from their parental species, when they display a high rate of selfing (in plants;
64 McCarthy *et al.* 1995) or assortative mating (in animals; Duenez-Guzman *et al.* 2009),
65 show transgressive segregation at traits influencing fitness in a novel environment
66 (Buerkle *et al.* 2000), and/or are geographically isolated from their parental species
67 (McCarthy *et al.* 1995; Buerkle *et al.* 2000; Schumer *et al.* 2015). Each of these factors
68 can promote reproductive isolation between admixed and parental lineages and allow
69 for genomic stabilization and independent evolution to occur within admixed populations.
70 In addition to cohesion through geographic, ecological, or sexual isolation, hybrid
71 populations can display intrinsic incompatibilities with their parental species (Rieseberg
72 *et al.* 1995; Hermansen *et al.* 2014). These intrinsic incompatibilities can help maintain
73 stable hybrid populations despite the opportunity for ongoing gene flow with their
74 parental species. In order to better appreciate when hybridization is most likely to drive
75 speciation, it is therefore important to understand the conditions and mechanisms that
76 result in genomic stabilization within hybrid lineages, and the evolution of RI between
77 hybrid lineages and their parents.

78 One such mechanism is when two or more independently acting genetic
79 incompatibilities fix for alternate parental genotypes in a hybrid population. This
80 ‘balancing’ of incompatibilities results in admixed genomes (or more specifically,
81 haplotypes) that are compatible with each other, but will manifest at least one
82 incompatibility with either of their parental species (herein referred to as “symmetrical
83 incompatibilities”). Loci that can generate symmetrical incompatibilities include
84 chromosomal rearrangements (McCarthy *et al.* 1995; Buerkle *et al.* 2000) or epistatic
85 pairs of loci that affect fitness as a result of inter-allelic interactions (e.g. Dobzhansky-
86 Muller Incompatibilities) (Schumer *et al.* 2015). For example, consider a pair of loci that

87 interact through epistasis and are segregating for both parental ancestries at equal
88 frequencies. Under the assumptions that selection favors interactions between alleles
89 sharing the same ancestry within each pair symmetrically (e.g. Table 2) and that the
90 strength of selection is greater than drift (i.e. greater than $\sim 1/(2N_e)$), both parental
91 ancestries have an equal probability of fixing within each of the two pairs of interacting
92 loci. Extending this example to multiple independent pairs of ‘epistatic loci’, the
93 probability of fixing for either parent 1 or parent 2 alleles across all epistatic pairs is
94 2×0.5^n , where n is the number of epistatic pairs. Conversely, the probability of evolving
95 mixed ancestry and some amount of RI due to symmetrical incompatibilities across the n
96 epistatic pairs is $1 - (2 \times 0.5^n)$. All-else being equal (e.g. independent assortment of loci
97 and no selection acting on additional traits), symmetrical incompatibilities may therefore
98 readily evolve in sufficiently admixed populations (Schumer *et al.* 2015).

99 McCarthy *et al.* (1995) and Buerkle *et al.* (2000) tested the probability that
100 symmetrical incompatibilities would evolve between admixed populations and their
101 parents as a result of novel “chromosomally balanced” genotypes with respect to two
102 rearrangements that differed between the parental species. Their simulations show that
103 admixed populations can evolve RI under this mechanism, and that the probability of
104 evolving RI increases both as hybrid fitness in a novel environment and geographic
105 isolation from parental populations increases. Taken with the results presented by
106 Schumer *et al.* (2015), these analyses describe (1) how symmetrical incompatibilities
107 can evolve in admixed populations and generate RI between admixed and parental
108 populations and (2) suggest that the probability of evolving symmetrical incompatibilities
109 is contingent upon the nature of selection acting on hybrid individuals.

110 In nature, the fitness of naturally occurring hybrids in different environments
111 relative to their parents is seldom known; however, it is likely to vary depending on
112 multiple factors. In some cases, such as in *Helianthus* sunflowers, hybrids may be more
113 fit than their parental species in certain environments (Rieseberg *et al.* 1995, 2003). In
114 others, hybrids may be less fit than their parents, and this may (or may not) depend on
115 the environment that a hybrid finds itself in (Vamosi & Schluter 1999; Linn *et al.* 2004;

116 Bridle *et al.* 2006; Delmore & Irwin 2014; Turissini *et al.* 2017). It is therefore likely that
117 the evolution of symmetrical incompatibilities will be affected by the specific fitness
118 function acting on admixed genotypes. By extension, selection acting at linked sites will
119 also affect the probability of evolving symmetrical incompatibilities. Understanding the
120 genetic architecture of traits, and the form of selection acting on those traits, is therefore
121 important to fully appreciate the scenarios that either permit or constrain the evolution of
122 symmetrical incompatibilities in admixed populations.

123 In this manuscript I use forward-time individual-based simulations to illustrate how
124 the nature of selection acting on, and the linkage relationships between, loci that
125 generate incompatibilities (hereafter “epistatic” loci) and those that affect an additional
126 trait under selection (hereafter “adaptive” loci) affect the probability that admixed
127 populations evolve symmetrical incompatibilities. To accomplish this, I simulate three
128 different types of selection acting on adaptive loci and varied (1) the strength of selection
129 acting on both adaptive and epistatic loci, (2) the order of loci along a chromosome, and
130 (3) recombination rates between adjacent loci. Each of these parameters were varied in
131 a ‘hybridizing deme’ experiencing gene flow from demes containing their parental
132 species. Consistent with previous work, these simulations show how selection favoring
133 admixed genotypes at adaptive loci tends to increase the probability of evolving
134 symmetrical incompatibilities, while selection favoring alleles from one or both parental
135 species at adaptive loci tends to decrease the probability of evolving symmetrical
136 incompatibilities. Both the strength of selection acting on the different types of loci and
137 their genetic architecture affect the probability that a hybrid population will evolve
138 symmetrical incompatibilities. Below I summarize these effects and highlight how
139 understanding how selection acts on hybrids, along with knowledge of the genetic basis
140 of traits that are subject to selection and underlie reproductive isolation between
141 parental species, can be used to predict when we expect to observe homoploid hybrid
142 species evolve.

143

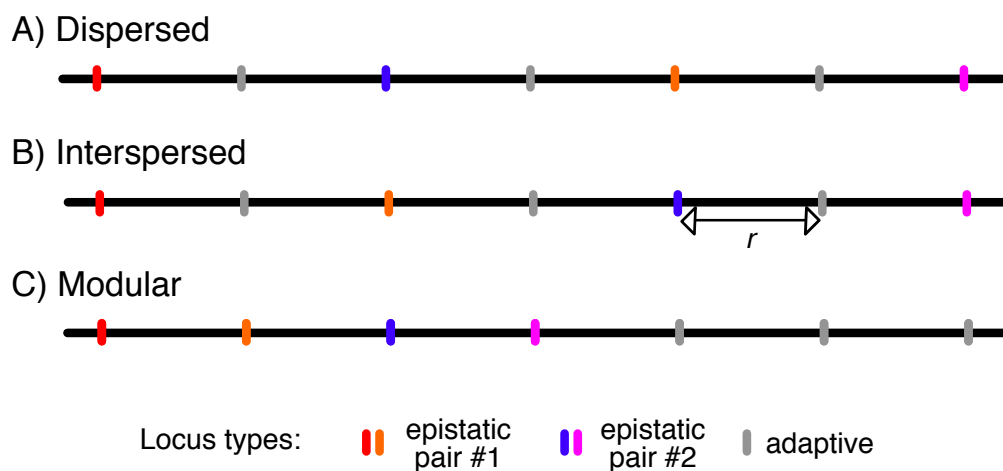
144 **Materials and Methods**

145

146 *General Description of Model*

147 I carried out forward-time simulations of demes composed of 1,000, diploid
148 individuals. Hybrid populations in nature seldom evolve without some level of ongoing
149 hybridization with parental populations; therefore, I simulated structured populations that
150 consisted of two 'parental demes' and a central 'hybrid deme'. Hybridization occurred in
151 the hybrid deme that experienced immigrants from the two parental demes at rate m ,
152 per parental deme. I simulated three different rates of m : 0.0001, 0.001, and 0.1,
153 corresponding to an average of 0.1, 1, and 10 immigrant individuals from each parental
154 deme per generation, respectively. Simulations were initiated under each of two different
155 conditions: (1) the hybrid deme was composed of equal proportions of randomly mating
156 parental genotypes or (2) the hybrid deme was composed of an equal number of males
157 and females that were heterozygous with respect to ancestry across all loci (i.e. all
158 individuals were F_1 hybrids).

159



160

161 Figure 1. Illustration of the three genetic architectures simulated in this study. Each
162 horizontal black line represents a haploid chromosome and vertical lines indicate the
163 position of loci. Recombination occurs along the chromosome at a rate of r between
164 adjacent loci.

165

166 Each individual's genome consisted of a single chromosome with seven equally-
167 spaced loci (Figure 1). Two pairs of loci were subject to selection due to epistasis. (Two
168 is the minimum number of pairs required to allow for symmetrical incompatibilities to
169 evolve.) The remaining three loci additively affected an individual's fitness in the
170 environment (e.g. ecological, social, or sexual environment). The relative fitness of an
171 individual was a function of their genotype at these loci (see "Selection" below; Tables 2
172 and 3). I tracked allele frequencies at each locus, within each population, for 1,000
173 generations, recording allele frequencies every 10 generations. Mating was
174 accomplished by randomly sampling individuals, with replacement, with the probability of
175 sampling an individual being proportional to their fitness. All simulations were carried out
176 using Python scripts (available at <https://github.com/comeaultresearch/simuHybrid>) that
177 utilize objects and functions contained within the simuPOP environment (Peng & Kimmel
178 2005).

179

180 *Genetic Architecture*

181 Loci were equally spaced along each individual's chromosomes. The two pairs of
182 loci that contain epistatically-interacting loci (i.e. "epistatic" loci) affected the fitness of an
183 individual as described in Table 1. The effect that these loci have on fitness is solely due
184 to epistasis. Epistatic loci may represent incompatibilities that, for example, cause
185 sterility, but may also underlie any trait that depends on the interaction between multiple
186 loci to function properly. The three other loci additively affect the fitness of an individual
187 as described in Table 2 (i.e. "adaptive" loci). These loci can be thought of as affecting
188 any trait that is controlled by additively acting genetic effects. Adjacent loci recombined
189 at a rate of 0.1, 0.2, or 0.5 per generation. The recombination rates of 0.1 and 0.2
190 allowed me to test the effect of linkage on the evolution of symmetrical incompatibilities.
191 The maximum rate of recombination (0.5) allowed for random assortment of loci and is
192 equivalent to each locus being located on its own chromosome.

193 In addition to varying recombination rates, I tested how the physical arrangement
194 of loci along a chromosome affects the probability of evolving symmetrical

195 incompatibilities. I either positioned loci such that the distance between similar types of
 196 loci was maximized (“dispersed” genetic architecture; Figure 1A), the two epistatic pairs
 197 were on opposite ends of the chromosome, but were interspersed by the adaptive loci
 198 (“interspersed” genetic architecture; Figure 1B), or loci were grouped by type such that
 199 epistatic loci and pairs were adjacent to each other and were not interspersed by an
 200 adaptive locus (“modular” genetic architecture; Figure 1C).

201
 202 Table 1. List of variables and parameters used for simulating evolution within hybrid
 203 swarms.

Variable / Parameter	Description	Values used
N	Total number of diploid individuals within each population.	1,000
n -loci	Number of diploid loci: two pairs of epistatic loci; three loci additively affecting fitness.	7
generations	Number of generations populations were monitored.	1,000
$S_{epistatic}$	Selection coefficient acting against mismatched alleles at epistatic loci.	0.000, 0.001, 0.01, 0.05, 0.10
$S_{adaptive}$	Selection coefficient acting against parent #2 alleles at loci additively affecting fitness in the environment.	0.00, 0.01, 0.02, 0.03, 0.04, 0.05, 0.06, 0.07, 0.08, 0.09, 0.10
r	Recombination rate between adjacent loci.	0.1, 0.2, 0.5
m	Probability of migration into from parental populations into hybrid zone.	0, 0.0001, 0.001, 0.01
genetic architecture	Arrangement of epistatic and adaptive loci along a chromosome.	3 different architectures (see Methods and Figure 1).

205

206

207 Table 2. The strength of selection as a function of genotype at a pair of ‘epistatic’ loci.
 208 Alleles have ancestry from either parent 1 (P_1 alleles) or parent 2 (P_2 alleles). Total
 209 selection due to maladaptive epistatic interactions ($s_{epistatic}$) was summed across the two
 210 epistatic pairs considered during simulations. The dominance coefficient (h) was held
 211 constant at 0.5 in all simulations.
 212

		genotype at locus 1		
		P_1P_1	P_1P_2	P_2P_2
genotype at locus 2	P_1P_1	0	$h^*s_{epistatic}$	$2^*s_{epistatic}$
	P_1P_2	$h^*s_{epistatic}$	$2^*h^*s_{epistatic}$	$h^*s_{epistatic}$
	P_2P_2	$2^*s_{epistatic}$	$h^*s_{epistatic}$	0

213
 214 Table 3. Descriptions of the three fitness schemes imposed on ‘adaptive’ loci. The total
 215 strength of selection against possible genotypes across the three adaptive loci is shown
 216 ($s_{adaptive}$) along with a description of the different genotypes. Total $s_{adaptive}$ was subtracted
 217 from 1 when determining the relative fitness of an individual during simulation.
 218

Total $s_{adaptive}$	Genotype Description
A) ‘directional selection’	
$n_{ALT}(s_{adaptive})$	Where n_{ALT} is the number of alleles with ancestry from the ‘unfit’ parent.
B) ‘disruptive selection’	
$n_{MINOR}(s_{adaptive})$	Where n_{MINOR} is the number of minor ancestry alleles if the number of minor ancestry alleles is less than 3 or all adaptive loci are heterozygous.
$5(s_{adaptive})$	If two loci are homozygous with different ancestry and the third is heterozygous.
C) ‘selection-for-admixture’	
$6(s_{adaptive})$	If homozygous for the same ancestry across all adaptive loci.
$5(s_{adaptive})$	If two loci are homozygous for the same ancestry and the third is heterozygous.
$n_{HET}(s_{adaptive})$	Where n_{HET} is the number of heterozygous loci if > 1 locus is heterozygous.
$1(s_{adaptive})$	If two loci are homozygous with different ancestry and the third is heterozygous.
$0(s_{adaptive})$	If two loci are homozygous with ancestry from the same parent and the third is homozygous with ancestry from the other parent.

219 *Selection*

220 During simulations, an individual produced offspring proportional to their relative
221 fitness. An individual's fitness was a function of selection acting against alleles subject to
222 either epistatic ($s_{\text{epistatic}}$) or 'adaptive' selection (s_{adaptive}) such that $\omega = 1 - (s_{\text{epistatic pair 1}}) -$
223 $(s_{\text{epistatic pair 2}}) - (s_{\text{adaptive}})$. Selection acted independently on each epistatic pair, and the
224 number of 'mismatched' alleles within a given pair determined fitness (Table 2).

225 I simulated three different models of selection on adaptive loci. First I simulated
226 'directional selection', where selection on the three adaptive loci acted additively and
227 alleles with ancestry from one of the parents (hereafter referred to as "P1") were always
228 favored over alleles with ancestry from the other parent (hereafter "P2"), except in the
229 case where there was no selection acting on these loci (Table 3A). My rationale for
230 simulating this scenario is to expand on treatments of hybrid speciation where hybrids
231 are afforded a fitness advantage in a certain environment (Buerkle *et al.* 2000) or where
232 their fitness is independent of the environment (Schumer *et al.* 2015). The particular
233 parent that I deem selectively favored is arbitrary and represents a scenario where
234 ancestry from one parental species at adaptive loci is favored over the second, while
235 hybrids have intermediate fitness. Second, I simulated 'diversifying selection', where
236 selection acted such that homozygous parental genotypes across all three adaptive loci
237 were favored over heterozygous or admixed parental genotypes (Table 3B). This
238 scenario reflects one where hybrid genotypes are at a fitness disadvantage relative to
239 parental genotypes, and parental genotypes are equally fit. Third, I simulated 'selection-
240 for-admixture', where selection favored admixed genotypes across the three adaptive
241 loci over parental and heterozygous genotypes (Table 3C). This scenario represents
242 one where hybrids have a selective advantage, such as simulated by Buerkle *et al.*
243 (2000). The difference between the scenario modeled by Buerkle *et al.* and that
244 presented here is that the 'ecological' locus in Buerkle *et al.* (2000) segregated
245 independently of the inversions that caused symmetrical incompatibilities, while in this
246 study I explicitly model different scenarios of linkage between adaptive and epistatic loci.

247 This allows me to compare the probability that selection-for-admixture will promote the
248 evolution of symmetrical incompatibilities under different genetic scenarios.

249 For epistatic loci, I simulated selection strengths ($s_{\text{epistatic}}$) of 0, 0.001, 0.01, 0.05,
250 or 0.1. For adaptive loci, selection (s_{adaptive}) ranged from 0 to 0.1, in increments of 0.01.
251 The maximum total strength of selection I consider is when $s_{\text{epistatic}} = 0.1$ and $s_{\text{adaptive}} =$
252 0.1. At this maximum strength of selection, F_1 hybrids have a relative fitness of 0.3 under
253 each model of selection. Parental genotypes have respective fitness of 1 (P1) and 0.4
254 (P2), 1, or 0.4 under the directional selection, diversifying selection, and selection-for-
255 admixture models, respectively. The weakest combination of non-zero selection
256 strengths I consider is $s_{\text{epistatic}} = 0.001$ and $s_{\text{adaptive}} = 0.01$, corresponding to an F_1 hybrid
257 fitness of 0.966 under each model of selection. At this minimum strength of selection,
258 parental genotypes have a fitness of 1 and 0.94, 1, or 0.94, under the directional
259 selection, diversifying selection, and selection-for-admixture models, respectively. The
260 models of selection and strengths of selection I simulate were chosen to represent
261 biologically plausible scenarios. For example, hybridizations that produce a large
262 fraction of sterile F_1 offspring (Coyne & Orr 1989; Coyne *et al.* 2004), to those where
263 hybrids show more subtle deficits in traits that affect their ability to survive or procure
264 resources such as food or mates (Blows & Allan 1998; Bolnick & Lau 2008; Delmore &
265 Irwin 2014; Rennison *et al.* 2015; Turissini *et al.* 2017), to those where admixed
266 genotypes are afforded a fitness advantage over their parental species (Rieseberg *et al.*
267 2003).

268

269 *Gene flow*

270 Migration (m) was independent of genotype, and individuals from the parental
271 demes moved into the hybrid deme with probability 0.0001, 0.001, or 0.01, for all
272 combinations of $s_{\text{epistatic}}$, s_{adaptive} , r , and genetic architecture described in Table 1.

273

274 *The effect of initial conditions on the evolution of symmetrical incompatibilities*

275 To test how the amount of hybridization occurring in a hybrid zone affects the
276 probability of evolving symmetrical incompatibilities, I initiated simulations either with a
277 hybrid deme containing an equal number of P₁ and P₂ individuals that mated at random
278 or a hybrid deme containing all F₁ hybrids. Under both of these starting conditions, I
279 simulated three rates of migration ($m = 0.0001, 0.001, \text{ and } 0.01$) for all combinations of
280 $s_{\text{epistatic}}, s_{\text{adaptive}}, r,$ and genetic architecture described in Table 1. I quantified the effect
281 that a forced bout of hybridization (i.e. all individuals initiated as F₁ hybrids) had on the
282 evolution of symmetrical incompatibilities by calculating the proportional change in the
283 number of hybrid populations evolving symmetrical incompatibilities under the ‘all F₁s’
284 relative to the ‘randomly mating parents’ starting condition.

285

286 *Definition of evolving reproductive isolation*

287 I considered a population of hybrids to have evolved RI from their parental
288 species, due to symmetrical incompatibilities, when the difference in mean allele
289 frequency (AF) at the two epistatic pairs of loci was greater than 0.9. This condition
290 represents a scenario where the population is nearly fixed for alleles coming from one
291 parental species at one epistatic pair (e.g. mean P₁ allele frequency > 95%) and nearly
292 fixed for alleles coming from the second parental species at the second epistatic pair
293 (e.g. mean P₂ allele frequency > 95%). I use 90% AF difference as a threshold defining
294 the evolution of RI because the majority of haplotypes within a population that has a
295 difference in parental allele frequency at the two epistatic pairs > 0.9 will be fertile with
296 other hybrids from that population, but manifest incompatibilities with either parental
297 species (the strength being proportion to $s_{\text{epistatic}}$).

298 Hybrid speciation differs from ‘classical’ speciation in that barriers to gene flow do
299 not need to evolve *de novo*, potentially leading to rapid speciation. As such, for each
300 population that showed evidence of evolving RI, I recorded the time it took for allele
301 frequencies at the two epistatic pairs to differ by > 0.9, to the nearest 10 generations.

302

303 **Results and Discussion**

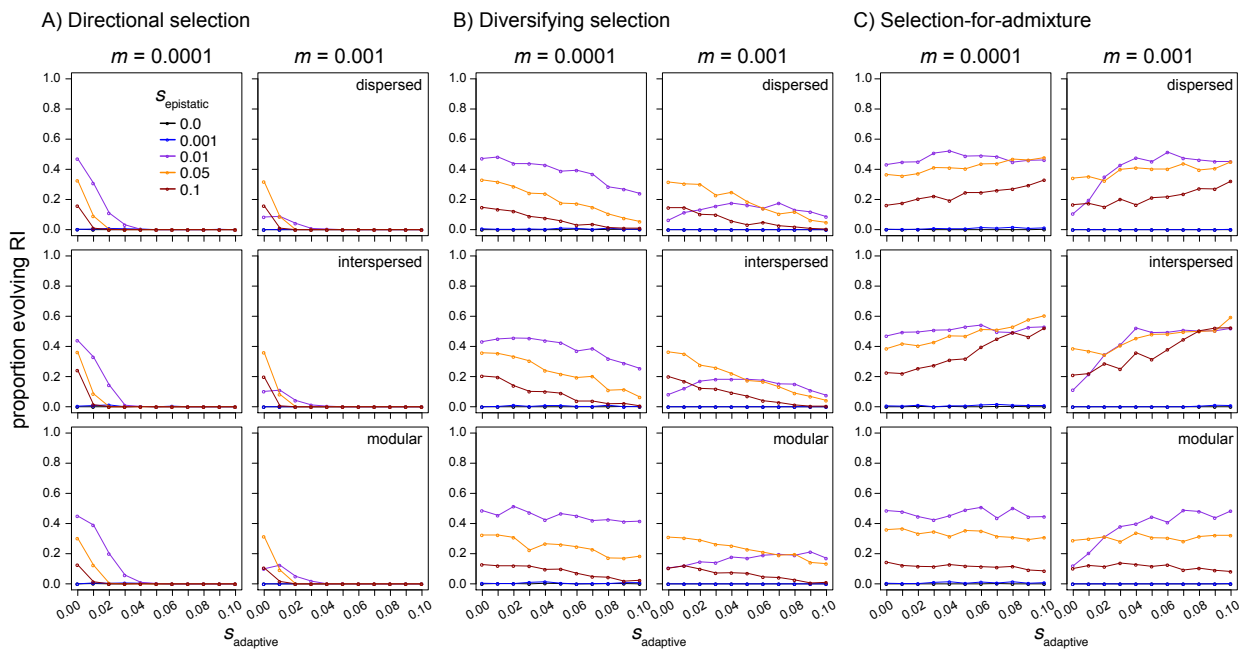
304

305 *Selection on epistatic interactions and the evolution of symmetrical incompatibilities*

306 An important parameter that affects the evolution of symmetrical incompatibilities
307 is the strength of selection acting to maintain functional epistatic interactions within
308 independent epistatic pairs ($s_{\text{epistatic}}$). When I simulated populations initiated with 1000
309 randomly mating parental individuals (equal proportions) subject to weak (0.001) or
310 nonexistent (0) $s_{\text{epistatic}}$, little gene flow from parental populations ($m = 0.0001$), moderate
311 linkage between adjacent loci ($r = 0.2$), and no selection on adaptive loci (i.e. $s_{\text{adaptive}} =$
312 0), a maximum of 3 of 500 simulated populations evolved symmetrical incompatibilities,
313 across all three genetic architectures (blue and black points in Figure 2). This is because
314 populations tended to maintain parental diversity at epistatic loci when $s_{\text{epistatic}}$ was weak
315 (less-than or equal-to 0.001 for the simulations summarized in this manuscript). More
316 generally, when epistatic interactions are subject to weak selection and symmetrical
317 incompatibilities do evolve, the magnitude of RI will also be weak. For example, the
318 reduction in fitness of an offspring produced by a mating between an individual from an
319 admixed population that evolved symmetrical incompatibilities and either parent species
320 would be 0.1% when $s_{\text{epistatic}} = 0.001$. The same scenario for $s_{\text{epistatic}} = 0.05$ or $s_{\text{epistatic}} =$
321 0.1 would result in a 5 or 10% decrease in fitness, respectively. Therefore, meaningful
322 RI is unlikely to evolve through symmetrical incompatibilities unless parental species
323 have accumulated genetic differences that result in at least moderately strong
324 incompatibilities.

325 The strength of $s_{\text{epistatic}}$ also affects the probability that recombinant haplotypes
326 will persist in a population. When $s_{\text{epistatic}}$ is strong, recombinant haplotypes are less
327 likely to be maintained in the population and symmetrical incompatibilities are less likely
328 to evolve. For example, when I simulated hybridization in populations experiencing little
329 gene flow from parental populations ($m = 0.0001$) and no selection on additional
330 adaptive loci ($s_{\text{adaptive}} = 0$), the greatest proportion of populations evolved RI when
331 $s_{\text{epistatic}}$ was moderate (0.01; see purple line in left column of panels in Figure 2A-C), with
332 the proportion evolving RI decreasing as the strength of $s_{\text{epistatic}}$ increased (gold and red

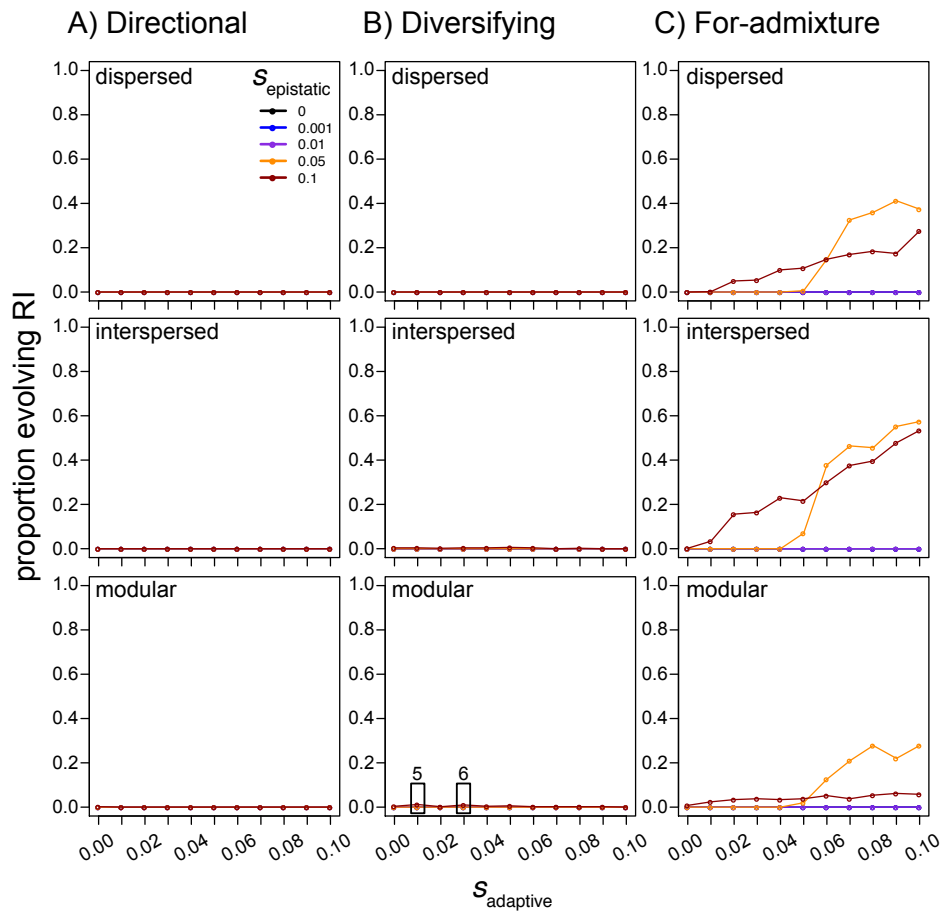
333 lines in left column of panels of Figure 2A-C). This result illustrates how the total
 334 strength of selection acting to maintain functional epistatic interactions can reduce the
 335 ability of admixed haplotypes to form when species come into secondary contact and
 336 hybridize. As such, symmetrical incompatibilities that will contribute to meaningful
 337 isolation between admixed and parental lineages are most likely to evolve when $s_{\text{epistatic}}$
 338 is moderate (relative to m ; see following section), because weak $s_{\text{epistatic}}$ will result in
 339 variation being maintained within epistatic pairs or generate proportionally weak
 340 incompatibilities, while strong $s_{\text{epistatic}}$ will limit the opportunity for recombinant haplotypes
 341 to form.



342
 343 Figure 2. The frequency of hybrid speciation (proportion of 500 simulated hybrid swarms
 344 evolving reproductive isolation; y-axis) as a function of the strength of selection acting
 345 on epistatic loci ($s_{\text{epistatic}}$; colored points and lines) and selection acting on additional
 346 'adaptive' loci subject to selection (s_{adaptive} ; x-axis; A: directional selection model; B:
 347 diversifying selection [i.e. parental genotypes equally favored]; C: selection-for-
 348 admixture). Results are shown for hybrid populations simulated with an inter-locus
 349 recombination rate of 0.2, migration rates of 0.0001 and 0.001 (panel columns), and with
 350 different linear arrangements of loci along the chromosome (i.e. genetic architectures;
 351 panel rows).

352

353



354

355

356 Figure 3. The proportion of hybrid populations evolving symmetrical incompatibilities (y-
 357 axis) at high levels of gene flow ($m = 0.01$). Under the directional and diversifying
 358 selection models, symmetrical incompatibilities only evolved when $s_{\text{epistatic}} = 0.1$, and
 359 even then, was rare (less than 1%). Two exceptions are highlighted by black rectangles
 360 in the bottom panel of B, with the number of simulated populations that evolved
 361 symmetrical incompatibilities given above the rectangles. Panels in C show how
 362 symmetrical incompatibilities are most likely to evolve when there is selection-for-
 363 admixture and both s_{adaptive} and $s_{\text{epistatic}}$ are strong. Results are shown for hybrid
 364 populations simulated with an inter-locus recombination rate of 0.2 and with different
 365 linear arrangements of loci along the chromosome (i.e. genetic architectures; panel
 366 rows).

367

368 *Gene flow*

369 As expected, gene flow from parental species generally tends to limit the
370 probability that symmetrical incompatibilities evolve. Specifically, because gene flow can
371 swamp locally adapted epistatic interactions, higher rates of gene flow tend to increase
372 the threshold strength of $s_{\text{epistatic}}$ required for symmetrical incompatibilities to evolve. For
373 example, consider the purple points between the left and right columns of figure 2A, B,
374 and C: when $s_{\text{epistatic}} = 0.01$, fewer populations evolve RI when $m = 0.001$ compared to
375 when $m = 0.0001$. By contrast, for $s_{\text{epistatic}} > 0.01$, a similar proportion of populations
376 evolve RI when $m = 0.0001$ or $m = 0.001$ because the relative strength of $s_{\text{epistatic}}$ is
377 greater than rates of gene flow from parental populations.

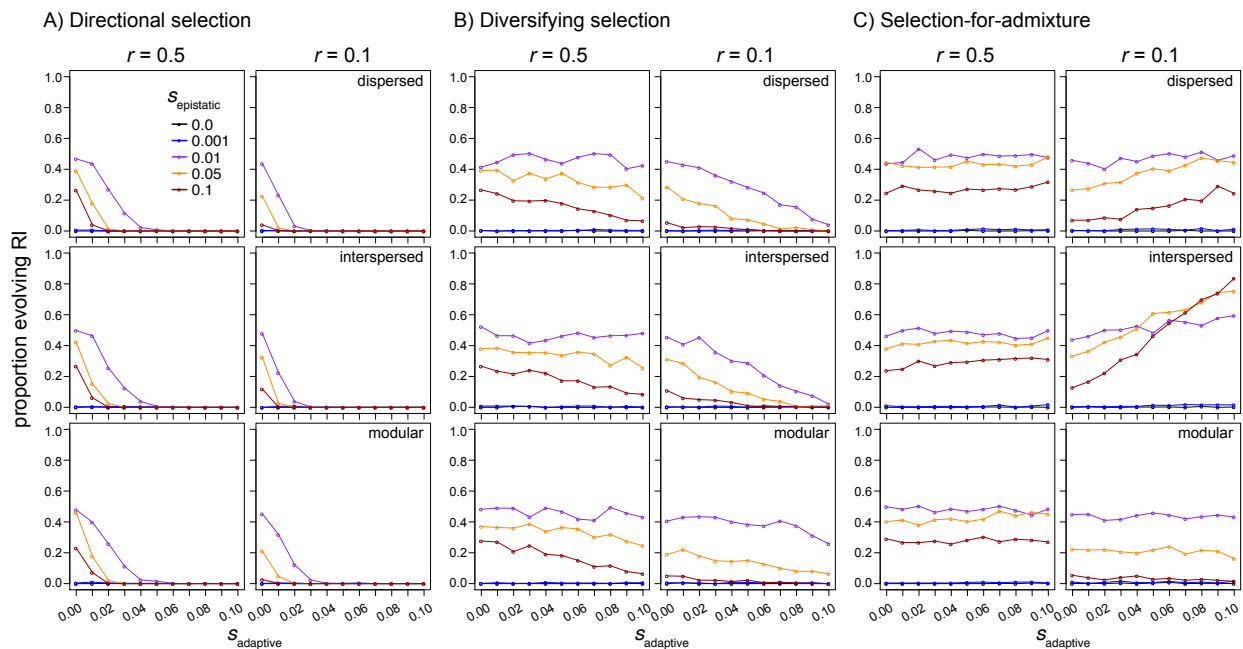
378 Interestingly, with modest gene flow ($m = 0.001$), symmetrical incompatibilities
379 were able to evolve under all three models of s_{adaptive} I simulated, as long as selection
380 against hybrids was not too strong (increasing values on the x-axes of Figure 2A and B).
381 This result also depended on the strength of linkage between epistatic and adaptive loci,
382 with tighter linkage further reducing the proportion of populations evolving symmetrical
383 incompatibilities (Figures 4 and S1). By contrast, at high rates of gene flow ($m = 0.01$, or
384 the equivalent of 10 immigrants from each parental population each generation),
385 symmetrically compatibilities were only able to evolve under the directional and
386 diversifying selection models with moderate linkage between loci ($r = 0.2$) when $s_{\text{epistatic}}$
387 was strong (0.1; red lines in Figure 3A and B); and even then, the probability they
388 evolved was low (less than 1% of populations). The only exception was that symmetrical
389 incompatibilities evolved with appreciable frequency ($> \sim 20\%$) in the face of high gene
390 flow when there was selection for admixture and $s_{\text{epistatic}}$ was strong (i.e. 0.05 or 0.1; gold
391 and red points in Figure 3C). These dynamics illustrate how the probability of evolving
392 symmetrical incompatibilities can remain relatively high ($> \sim 20\%$), even under high rates
393 of gene flow (i.e. 10 immigrants from both parental species every generation) when
394 selection-for-admixture and $s_{\text{epistatic}}$ are also strong.

395

396 *Selection on adaptive loci and the evolution of symmetrical incompatibilities*

397 In addition to the strength of epistatic selection and rates of gene flow, changes in
 398 allele frequencies at epistatic loci can be influenced by selection at linked sites (Maynard
 399 Smith & Haigh 1974; Barton 2000). Below I explore the effect of three different models
 400 of selection acting on ‘adaptive’ loci linked to the epistatic loci responsible for generating
 401 symmetrical incompatibilities. I first present results from simulations initiated with a
 402 hybrid deme composed of randomly mating parental species, and then discuss the
 403 consequences of a forced bout of admixture in the section “*The effect of initial conditions*
 404 *on the evolution of symmetrical incompatibilities*”.

405



406

407 Figure 4. Selection at linked sites and the evolution of symmetrical incompatibilities.
 408 Linkage between epistatic and adaptive loci tends to decrease the probability of evolving
 409 symmetrical incompatibilities when adaptive loci are subject to directional or diversifying
 410 selection (panels in A and B, respectively), but increase the probability of evolving
 411 symmetrical incompatibilities when selection favors admixture (C). Results are shown for
 412 populations simulated with inter-locus recombination rates of 0.5 (i.e. no linkage; left
 413 column of panels) or 0.1 (moderate linkage; right column of panels), $m = 0.0001$, and
 414 with different linear arrangements of loci along the chromosome (i.e. genetic
 415 architectures; panel rows). Note that genetic architecture is only relevant when r is less
 416 than 0.5. Refer to Figure S1 for results with $m = 0.001$.

417 Selection acting on sites subject to s_{adaptive} either decreased or increased the
418 probability that symmetrical incompatibilities evolved, and the direction of this effect
419 depended on the form of s_{adaptive} . Directional selection that favored ancestry from one
420 parental species over the other at adaptive loci always reduced the probability that
421 populations of hybrids evolved incompatibilities (Figure 2A). When there is no linkage
422 between epistatic and adaptive loci ($r = 0.5$), this reduction occurs because selection
423 favors ancestry from one parent over the other and limits the opportunity for
424 recombinant haplotypes to form (left column of panels in Figure 4A). Specifically,
425 selection favoring ancestry from one parent over the other at the adaptive loci biases
426 epistatic loci to evolve toward the fitter parent's ancestry (Figures S2 – S4). This effect
427 was consistent at low, moderate, and high levels of gene flow (Figures 2A and 3A).
428 Under the directional selection model, we therefore expect that as s_{adaptive} increases,
429 ancestry within admixed populations will evolve towards the fitter parent and the
430 evolution of symmetrical incompatibilities will be less likely. For the parameter values I
431 simulated, this resulted in no symmetrical incompatibilities evolving when s_{adaptive} was
432 greater than 0.03 and there was at least some linkage between adaptive and epistatic
433 loci (Figure 2A and 4A).

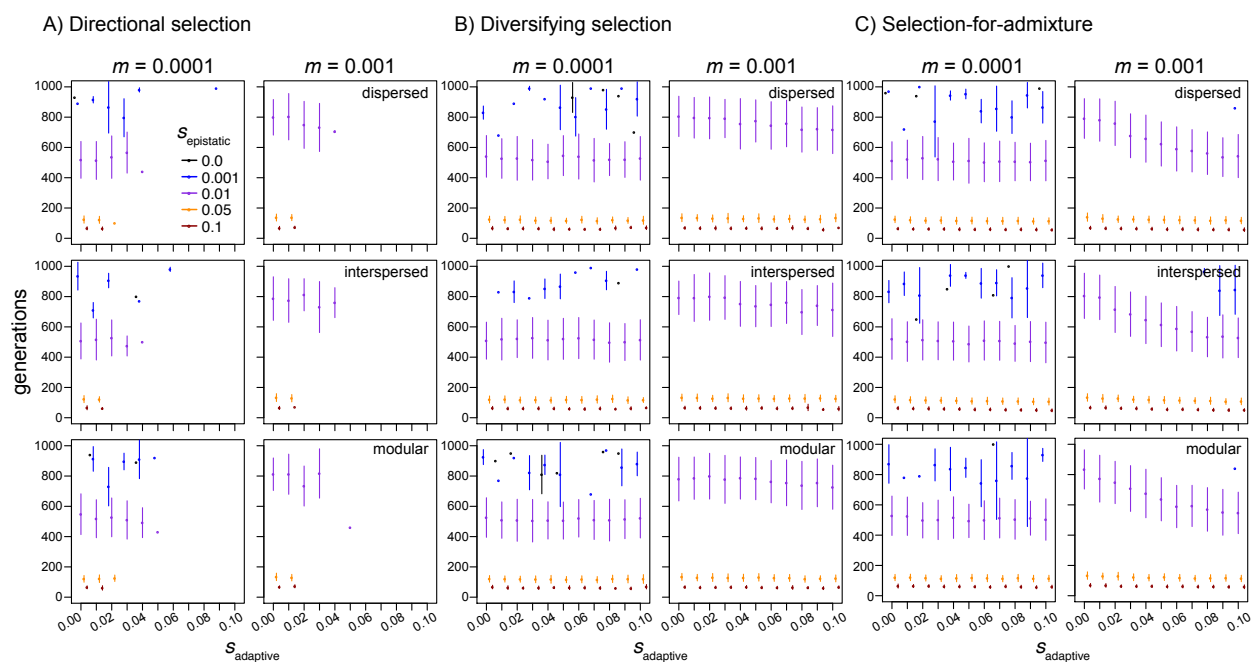
434 When the fitness of parental ancestries is not skewed towards one parent and
435 hybrids are less fit than their parental species (i.e. the diversifying selection model),
436 increasing selection against hybrids (and admixed genotypes) also tends to reduce the
437 probability of evolving symmetrical incompatibilities; however, the magnitude of this
438 effect is much less than for the directional selection model (compare panels between
439 Figure 2A and B). For example, when s_{adaptive} is greater than 0.03 and $s_{\text{epistatic}}$ is greater
440 than 0.001, an appreciable proportion (> 0.1) of admixed populations evolved
441 symmetrical incompatibilities under the diversifying selection model (Figure 2B), while
442 almost none evolved symmetrical incompatibilities under the directional selection model
443 (Figure 2A). Unlike under the directional selection model, the arrangement of loci along
444 the chromosome affected the magnitude of the reduction in the proportion of populations
445 that evolved RI with increasing s_{adaptive} under the diversifying selection model (compare

446 down panels in Figure 2A and B). For example, with moderate $s_{\text{epistatic}}$ (0.01), low
447 migration ($m = 0.0001$), weak linkage ($r = 0.2$), and diversifying selection, as s_{adaptive}
448 increases from 0.02 to 0.08 there is a 35%, 30%, and 17% reduction in the proportion of
449 simulated populations that evolve symmetrical incompatibilities for the dispersed,
450 interspersed, or modular genetic architectures, respectively. A modular architecture can
451 therefore facilitate the evolution of symmetrical incompatibilities relative to the dispersed
452 and interspersed architectures when s_{adaptive} is strong (yellow and red lines in Figure 2B),
453 migration rates are modest (right panels in Figure 2B), and parents do not differ in their
454 fitness (i.e. under the diversifying selection model).

455 The two models of selection summarized above both impose selection against
456 hybrid and admixed genotypes at adaptive loci. A third outcome of hybridization is that
457 there is transgressive segregation for fitness-associated traits, resulting in admixed
458 genotypes that are at a selective advantage relative to parental genotypes. Indeed,
459 previous work has shown how symmetrical incompatibilities are more likely to evolve
460 when hybrids have a fitness advantage in a novel environment (see Figure 2 of Buerkle
461 *et al.* 2000), and novel ecological traits in hybrids is a hallmark of one of the best
462 examples of homoploid hybrid speciation: sunflowers in the genus *Helianthus*
463 (Rieseberg *et al.* 1995, 2003). The simulations that I present here recapitulate this
464 result, with the primary difference being that I explicitly simulate linkage between the loci
465 subject to ecological selection (s_{adaptive}) and those that generate incompatibilities.

466 Linkage and the ordering of loci along the chromosome (genetic architecture) has
467 the opposite effect on the evolution of symmetrical incompatibilities under the selection-
468 for-admixture model when compared to the directional or diversifying selection models:
469 symmetrical incompatibilities were more likely to evolve under the dispersed and
470 interspersed architectures, on average, than the modular genetic architecture (compare
471 down panels of Figure 2C). (Note that selection-for-admixture only pertains to the
472 adaptive loci and selection acts on epistatic loci the same way in all three models of
473 'adaptive selection'.) This result is due to both selection favoring admixed genotypes (in
474 the case where $r = 0$) and linkage between adaptive and epistatic loci in the dispersed

475 and interspersed architectures (when $r > 0$; Figures 2 and 3). Consistent with previous
 476 work (Buerkle *et al.* 2000), symmetrical incompatibilities are therefore most likely to
 477 evolve when selection favors hybrids, with linkage and genetic architecture interacting to
 478 increase the probability that different pairs of epistatic loci evolve to fix different
 479 ancestries.
 480



481
 482
 483 Figure 5. The number of generations required for hybrid populations to evolve
 484 reproductive isolation from their parental species. Time is given in generations along the
 485 y-axis of each panel for different strengths of selection against alleles at loci affecting
 486 fitness in the environment (x-axis). Each colored point within the panels represents the
 487 mean time to speciation for hybrid swarms that evolved reproductive isolation from their
 488 parental species and points are staggered along the x-axis. Vertical lines are bounded
 489 by the 2.5% and 97.5% empirical quantiles of time to speciation for a given set of hybrid
 490 populations. Missing points occur for parameter combinations where no populations
 491 evolved RI. Results are shown for hybrid populations simulated with an inter-locus
 492 recombination rate of 0.2.
 493
 494

495 *Time to evolution of RI*

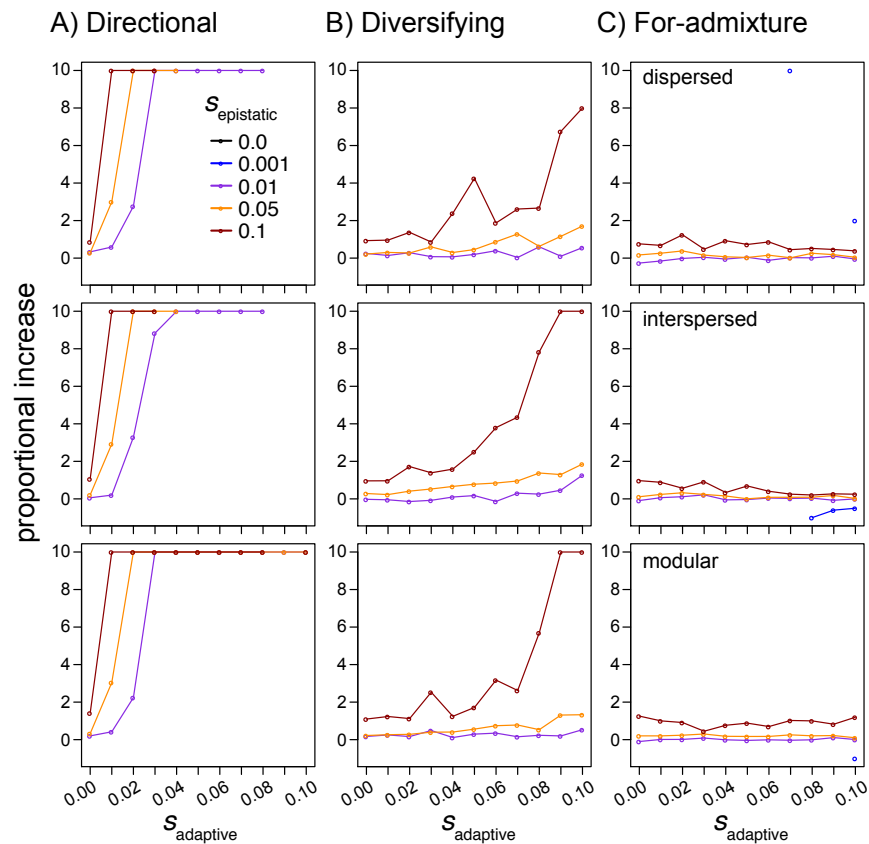
496 Because hybridization requires two species or their gametes to be present in the
497 same location (at least temporarily), the faster that incompatibilities are able to stabilize
498 within admixed populations, the more likely they will show meaningful RI from their
499 parental species in the face of ongoing hybridization. To determine how quickly RI
500 evolved due to symmetrical incompatibilities, I recorded the time (to the nearest 10
501 generations) it took novel hybrid genotypes to evolve a mean allele frequency difference
502 at the two epistatic pairs of loci greater than 0.9. As expected, the stronger $s_{\text{epistatic}}$ was,
503 the faster symmetrical incompatibilities tended to evolve (different colored points in
504 Figure 5). Relative to $s_{\text{epistatic}}$, both s_{adaptive} and genetic architecture had negligible effects
505 on the time it took to evolve RI (x-axis of panels and panel columns in Figure 5,
506 respectively). The one exception to this pattern was that increasing s_{adaptive} under the
507 selection-for-admixture model resulted in decreasing the time it took to evolve
508 symmetrical incompatibilities when $s_{\text{epistatic}}$ was moderate ($s_{\text{epistatic}} = 0.01$; purple points in
509 Figure 5C). This result highlights how once populations begin to evolve allele frequency
510 differences at epistatic pairs of loci, the primary factor affecting the speed that those
511 pairs fix alternate parental alleles is the strength of selection acting to maintain viable
512 epistatic interactions; however, increasing selection on linked loci can increase the
513 speed at which RI evolves in situations where $s_{\text{epistatic}}$ is not already very strong.

514

515 *The effect of initial conditions on the evolution of symmetrical incompatibilities*

516 When I forced a bout of hybridization by initiating simulations with a hybrid deme
517 composed of F_1 hybrids, symmetrical incompatibilities were, in general, more likely to
518 evolve than when simulations were initiated with randomly mating individuals of the
519 parental species (Figure 6). This was particularly true when s_{adaptive} was greater than
520 zero under the directional or diversifying selection models (Figure 6A and B,
521 respectively). Under directional selection, the relative enrichment in the proportion of
522 populations evolving symmetrical incompatibilities increased as both s_{adaptive} and as
523 $s_{\text{epistatic}}$ increased (compare increasing values on the x-axes and the purple, gold, and

524 red lines in Figure 6A, respectively). By contrast, with selection-for-admixture, an initial
 525 bout of hybridization had much less of an effect on increasing the proportion of
 526 populations that evolved symmetrical incompatibilities (Figure 6C). In this case, I only
 527 observed a modest ~ 1 -fold enrichment in the probability of evolving symmetrical
 528 incompatibilities when $s_{\text{epistatic}}$ was very strong (i.e. red lines in Figure 6C). An initial bout
 529 of admixture can therefore promote the evolution of symmetrical incompatibilities in
 530 scenarios where selection minimizes the probability that recombinant haplotypes will
 531 form: i.e. with increasing s_{adaptive} and $s_{\text{epistatic}}$ under the directional or diversifying selection
 532 models and with increasing $s_{\text{epistatic}}$ under the selection-for-admixture model.
 533



534
 535 Figure 6. The effect of a bout of forced hybridization on the fraction of populations
 536 evolving RI. Proportional change (y-axis) was calculated as the difference in the number
 537 of populations evolving RI when simulations were initiated with F_1 s versus randomly
 538 mating parental individuals over the number of populations that evolved RI when

539 simulations were initiated with randomly mating parental individuals. Symmetrical
540 incompatibilities, in general, evolved more frequently in simulations initiated with a
541 hybrid deme composed of F₁ hybrid individuals compared to when initiated with equal
542 proportions of randomly-mating parental genotypes. Results are shown for each of the
543 three simulated genetic architectures (panel rows) under the directional selection (A),
544 diversifying selection (B) and selection-for-admixture (C) models of selection acting on
545 ‘adaptive’ loci. Recombination rates and migration were held at 0.2 and 0.001,
546 respectively. In instances when there was a greater than 10-fold increase in the
547 proportion of populations that evolved RI, values were rounded down to 10. Missing
548 points occur for parameter combinations where no populations evolved RI across
549 simulations initiated under either initial condition.

550
551 When populations are subject to an initial bout of hybridization, genetic
552 architecture also has a larger effect on the probability of evolving RI. For example, a
553 more modular architecture with weaker linkage between epistatic and adaptive loci is
554 more permissive to symmetrical incompatibilities evolving under the directional and
555 diversifying selection models (Figures S5 and S6, respectively). This is because a high
556 frequency of F₁ individuals helps to facilitate the formation of recombinant haplotypes,
557 with the probability of a crossover events between different ‘types’ of loci being a
558 function of their position along a chromosome. Modular architectures where loci are not
559 in tight linkage are therefore the most conducive to the evolution of symmetrical
560 incompatibilities when selection on adaptive loci is directional or diversifying (Figures S5
561 and S6), while linkage between adaptive and epistatic loci is more conducive to the
562 evolution of symmetrical incompatibilities when selection favors admixture (Figures S7).

563

564 **Conclusions**

565

566 Genome-wide sequence data has led to an increased appreciation of the
567 prevalence of admixture and introgression between species (Payseur & Rieseberg
568 2016; Pease *et al.* 2016; Wallbank *et al.* 2016). While the consequences of hybridization
569 have historically been viewed as maladaptive (Fisher 1930), others have proposed that

570 hybridization can be a generative force that facilitates adaptive evolution and speciation
571 (Seehausen 2004; Mallet 2007; Hedrick 2013; Nieto Feliner *et al.* 2017). If this is the
572 case, hybridization may play a significant role in the production of biodiversity (Mallet
573 2007), and a few empirical examples have even linked the evolution of RI, without a
574 change in ploidy, to hybridization and admixture occurring between different species
575 (Rieseberg *et al.* 1995; Ungerer *et al.* 1998; Jiggins *et al.* 2008; Melo *et al.* 2009;
576 Lamichhaney *et al.* 2017). Ascribing a causative role to hybridization and admixture in
577 generating RI is however challenging, and the prevalence of HHS still remains largely
578 unknown (Schumer *et al.* 2014).

579 Here I have focused on one general mechanism that can lead to the evolution of
580 RI in hybrid populations: the fixation of different parental alleles at two or more groups of
581 ‘coadapted’ or interacting loci (Buerkle *et al.* 2000; Schumer *et al.* 2015). Through
582 simulation, I have shown that the evolution of RI due to symmetrical incompatibilities is
583 strongly affected by (1) the strength and form of selection acting on different types of
584 loci, (2) linkage relationships between adaptive and epistatic loci, (3) the arrangement of
585 those loci along a chromosome, (4) gene flow between populations of hybrids and their
586 parental species, and (5) the degree of hybridization occurring in a hybrid zone. These
587 results suggest that there will be ‘sweet-spots’ – both genetic and ecological – that will
588 be most conducive to the evolution of RI in hybrid populations. From a genetic
589 perspective, weak incompatibilities between parental genomes are only capable of
590 generating weak RI due to symmetrical incompatibilities. By contrast, strong and
591 pervasive (in terms of number) incompatibilities will reduce the probability that admixed
592 haplotypes will form and increase in frequency within a population. Therefore, the
593 evolution of symmetrical incompatibilities will be most likely when parental species
594 display an intermediate level of incompatibility; this will allow selection to maintain
595 linkage disequilibrium between ‘coadapted’ alleles but not severely limit the ability of
596 recombinant haplotypes to be present at an appreciable frequency within a population.

597 From an ecological perspective, the evolution of symmetrical incompatibilities is
598 most likely when selection favors hybrid and admixed genotypes. Previous empirical

599 work has shown that hybrid species tend to show novel ecologies or phenotypes when
600 compared to their parental species (e.g. *Helianthus* sunflowers: (Rieseberg *et al.* 1995)
601 *Heliconius* butterflies: (Melo *et al.* 2009; Salazar *et al.* 2010), *Geospiza* finches:
602 (Lamichhaney *et al.* 2017)). These novel ecologies and phenotypes may be required to
603 afford recombinant genotypes the opportunity to establish and evolve RI from their
604 parental species, especially in a situation where hybrid populations are not found in
605 geographic isolation.

606 Future work in speciation will benefit from continuing to quantify the extent of
607 admixture within regions of hybridization and ultimately measure the fitness of hybrids
608 relative to their parental species. Collecting these types of data across taxa that differ in
609 the nature of hybridization (e.g. the extent of genetic divergence between parental
610 species) and across a variety of environments are not trivial tasks. However, these data
611 are needed if we are to understand the consequences of hybridization between species
612 and populations in nature, and when and where we might expect to see admixed
613 genomes stabilize and hybrid species evolve.

614

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- 723

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730
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733 [acceptance](#). Files containing allele frequencies, recorded every 10 generations within
734 the simulated populations analyzed here, will be deposited on Dryad upon acceptance.

735
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737 manuscript.