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Prezygotic isolation, mating preferences, and the evolution of chromosomal inversions

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Chromosomal inversions are frequently implicated in isolating species. Models have shown how inversions can evolve in the context of postmating isolation. Inversions are also frequently associated with mating preferences, a topic that has not been studied theoretically. Here, we show how inversions can spread by capturing a mating preference locus and one or more loci involved with epistatic incompatibilities. Inversions can be established under broad conditions ranging from near panmixis to nearly complete speciation. These results provide a hypothesis to explain the growing number of examples of inversions associated with premating isolating mechanisms.

KEY WORDS: **Chromosomal evolution, inversions, mating preference, models and simulations.**

An outstanding question in evolutionary biology is how and why chromosomal rearrangements are fixed in populations. Many chromosomal inversions have been discovered that carry genes involved with nonrandom mating. Cases include the seaweed fly *Coelopa frigida* (Day and Butlin 1987; Gilburn and Day 1996), the house mouse *Mus musculus* (Hammer et al. 1991), the fruitfly *Drosophila melanogaster* (Noor et al. 2001a), the apple maggot *Rhagoletis pomonella* (Feder et al. 2003), the white-throated sparrow *Zonotrichia albicollis* (Tuttle 2003; Tuttle et al. 2016), the yellow monkeyflower *Mimulus guttatus* (Lowry and Willis 2010; Twyford and Friedman 2015; Lee et al. 2016), and the mosquito *Anopheles funestus* (Ayala et al. 2013). Perhaps the most dramatic example is found in the arctic ruff *Philomachus pugnax*, where inversions have been shown to separate three separate male morphs with alternate breeding strategies (Lamichhaney et al. 2016).

Chromosome inversions have also been associated with prezygotic isolation between populations and species. The carrion crow (*Corvus corone*) and hooded crow (*Corvus corax*) are congeners that hybridize. The genomic region that shows greatest differentiation between them corresponds to a putative inversion that is fixed for alternative arrangements in the two species. The inversion carries genes that are involved with vision and pigmentation, suggesting that it may mediate prezygotic isolation (Poelstra et al. 2014). An inversion causes partial isolation between two social forms of the fire ant (*Solenopsis invicta*) (Shoemaker and Ross 1996; Wang et al. 2013). Recent studies implicated two inversions in differences in the spawning habits of two types of Atlantic cod (Berg et al. 2016; Kirubakaran et al. 2016).

At first sight, these observations are puzzling. Inversions can spread because they decrease recombination between alternative arrangements (Fisher 1930, p. 103; Hoffmann and Rieseberg 2008; Kirkpatrick 2010). It is not immediately obvious, however, why an inversion that carries prezygotic isolation loci would benefit from decreased recombination. Linkage disequilibrium between a female mating preference locus and a male sexual trait locus, for example, depends entirely on the strength of preference and not on the recombination rate between the two loci (Kirkpatrick 1982). On the other hand, while speciation can be prevented by recombination (Felsenstein 1981), it is not clear how selection favoring speciation might drive the evolution of decreased recombination by the establishment of inversions.

Several hypotheses have been proposed for how inversions can act as isolating mechanisms between species. Underdominant inversions can be established in a species by drift, leading to

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decreased viability when that species hybridizes with another (White 1978; Walsh 1982; Lande 1985; King 1993). Inversions can also spread by capturing alleles that cause incompatibilities between hybridizing species (Charlesworth and Charlesworth 1973, 1979; Kirkpatrick and Barton 2006). Trickett and Butlin (1994) studied how an inversion can increase genetic divergence between incipient species. Their simulations show that an inversion can spread when it captures a locus that influences assortative mating and one or two loci that have epistatic effects on viability. They did not, however, develop analytic results or study the range of genetic architectures and parameters that favor the establishment of an inversion.

This article fills that gap. We model the evolution of inversions that capture loci involved in mate choice that operates either through assortative mating or in a preference-trait system in which one sex chooses mates of the opposite sex. We begin by developing a model that applies to both a single species and to a pair of hybridizing species. We then focus on the case of two hybridizing species that have strong pre- and postmating isolation. We develop a model in which two loci affect viability, then generalize the results to more loci. Our analyses are greatly simplified by two key assumptions: selection and mate choice act during the haploid phase of life cycle, and allele frequencies are equal to ½ at all loci. We use simulations to show that our major conclusions hold qualitatively when those assumptions are relaxed.

We find that an inversion will be favored by selection whenever it captures a mating preference locus and at least one locus involved in epistatic incompatibilities. The forces that favor its spread are often weak, however, and so direct fitness effects of the inversion and drift may often be more powerful. We conclude that selection can favor inversions that capture mating preference loci at any stage of speciation, but they are favored most strongly when they occur during intermediate stages.

Models and Results

The model is of a large, sexually reproducing haploid population. We use the term "population" here in a very general way. The model can describe the case of a single, nearly panmictic species. At the opposite extreme, the model also describes the case of two nearly isolated species that occasionally hybridize. In that case, the "population" is composed almost entirely of just two genotypes with very strong linkage disequilibrium between loci.

After birth, viability selection acts on two loci j and k. Each locus segregates for two alleles, denoted 0 and 1. Some form of frequency-dependent selection maintains these alleles at equal frequencies (= ½). In the case of strongly isolated species that we will develop below, this type of selection corresponds to density dependence that maintains both species at equal densities. The

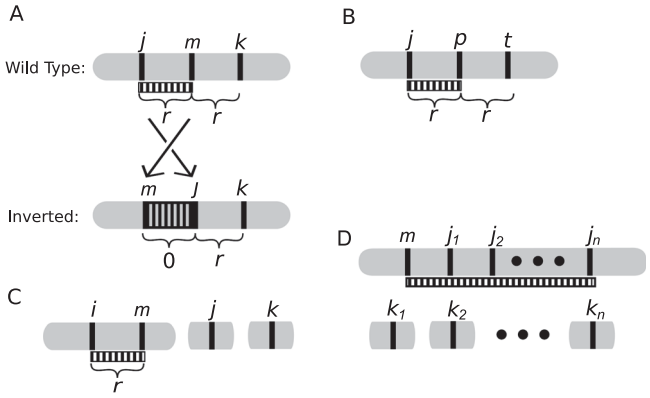

Figure 1. Three linkage maps used within the study with the span of the inversion shown in stripes. (A) Linkage map for the assortative mating model. Loci *m* and *j* are captured by the inversion, decreasing recombination between them to 0, but not changing the recombination rate outside of the inversion. (B) Linkage map for mating preference—trait model. (C) Linkage map for four locus model. Loci *j* and *k* are assumed to reside on separate chromosomes. (D) Linkage map for the general *n* epistatic pair model. The inversion captures all loci *j*, but none of the loci *k*, all of which are unlinked.

"pure" genotypes that carry only allele 0 or only allele 1 at both loci have equal fitness. Recombinant genotypes with mixtures of 0 and 1 alleles have a viability of S relative to the pure genotypes. With $S = 1$, all genotypes survive equally well, while with $S = 0$ there is complete postzygotic isolation between the pure genotypes.

Individuals choose their mates either through an assortative mating system or a preference-trait system. With assortment, mate choice is controlled by locus m. This locus segregates for two alleles, 0 and 1, that are at equal frequencies. Each individual has a probability H of mating with a partner that carries the opposite allele (and in this sense "hybridizes") at locus m. Thus $H = 0$ means perfect assortment, and $H = ½$ indicates random mating. The assumptions and notation for the preference-trait system are introduced in a later section.

Mating produces diploids, which then recombine to produce the haploid offspring of the next generation. The linkage map is $j - m - k$. When an individual is homozygous for either the ancestral or inverted chromosome, the recombination rate between loci j and m, and the rate between m and k, are both r (Fig. 1A). There is no interference, and so loci j and k recombine at a rate $2r(1 - r)$.

We assume that the inversion completely suppresses recombination between the loci that it carries in individuals that are heterozygous for the inversion. The inversion's fitness is determined by the alleles that it carries, and the inversion itself is assumed to have no direct effects on fertility or other fitness components.

SPREAD OF A RARE INVERSION

The fate of a new inversion is determined by its rate of spread while it is rare. We define s_e, the *effective selective coefficient*, as the fractional change in its frequency when rare. When s_e is negative, the inversion will be lost, while when s_e is positive it will spread. The effective selection coefficient is:

$$s_e = \lambda - 1 = \frac{\bar{W}_I}{\bar{W}} - 1, \quad (1)$$

where λ is the leading eigenvalue of the recursion equations for the genotype frequencies, $\bar{W}_I$ is the average fitness of individuals that carry the inversion when it is rare, and $\bar{W}$ is the mean fitness in the population before the inversion appears.

The mean fitness of the inversion (which appears as the numerator of (1)) depends on which loci are captured by the inversion. In the simplest case, the inversion captures the assortment locus but no viability loci. Then $\bar{W}_I = \bar{W}$, which shows that the inversion is selectively neutral. Therefore the inversion will not be established by selection.

Now consider an inversion that captures the assortment locus m and viability locus j. Assume that the inversion breakpoint lies immediately to the right of locus m, so that the recombination rate between m and k is unchanged by the inversion (Fig. 1A). An explicit expression for the effective selection coefficient is derived in Supporting Information 1, equation (A5). Crucially, the inversion will increase while rare whenever hybridization occurs, linkage between the loci is not complete, and hybrids are selected against. The inversion is therefore favored to spread under quite general conditions.

Figure 2 shows how the effective selection coefficient varies with the frequency of hybridization (H) and the survival of recombinants (S). It is maximized when H is large but less than ½, and when viability selection against recombinants is strong but not absolute. When H is close to 0, s_e varies little with r unless linkage is very tight. Likewise, when r is small, H has little effect except when it approaches 0. This is because the inversion has little effect on fitness when the recombination rate is already small or when hybridization is rare. Furthermore, if postzygotic selection is nearly complete, few hybrids survive until mating and so the inversion is not strongly favored. Due to closer linkage between j and k, the inversion is favored even when $H = 0.5$. If r is close to 0.5, assortative mating must be quite powerful (H small) to provide an advantage to the inversion.

The expression for the effective selection coefficient simplifies greatly when hybridization is weak ($H << ½$) and recombinants have decreased viability ($S < 1$). Strong linkage disequilibrium develops between all three loci. Biologically, this corresponds to two species with strong postmating isolation that occasionally hybridize. The population's mean fitness (which is the denominator of (1)) is:

$$\bar{W} = 1 - (P_{01} + P_{10})\ (1 - S) = 1 - Hr, \quad (2)$$

where P_{xy} is frequency of zygotes with allele x at locus j and allele y at locus k (see eq. A15 in Supporting Information 1). Interestingly, $\bar{W}$ does not depend on the strength of viability selection (S). This is reminiscent of classical results for mutation-selection balance, in which mean fitness is also independent of selection (Haldane 1937; Kimura and Maruyama 1966).

Because the population consists almost entirely of the pure (0,0,0) and (1,1,1) genotypes, an inversion will almost always capture one of those two. Its average fitness is therefore approximately 1. Using that observation, equations (1) and (2) show that the effective selection coefficient for the inversion is:

$$s_e = Hr \quad (3)$$

to leading order in H, S, and r. (A formal proof is given in Supporting Information 1, eq. A16.) This result shows that the inversion spreads whenever there is some positive rate of hybridization ($H > 0$). If assortment is perfect ($H = 0$), then there are no recombinant individuals, and therefore the inversion has no selective advantage. We also find that an inversion spreads if it captures the assortment locus and one of the viability loci, but does not change recombination between the viability loci. In this case, when isolation is strong, spread of the inversion is accelerated by stronger selection against hybrids and tighter initial linkage between the viability loci, but is unaffected by the strength of assortment (Supporting Information 1, eq. A20).

Next consider an inversion that captures both viability loci as well as the assortment locus. If the inversion captures a pure genotype, then $\bar{W}_I = 1$ and the inversion is favored whenever there is some selection against hybrids ($S < 1$, and therefore $\bar{W} < 1$), so long as there is at least some hybridization ($H > 0$). This result is consistent with earlier models of inversions that capture epistatic viability loci (Charlesworth and Charlesworth 1973).

MORE EPISTATIC VIABILITY LOCI

What if more than two loci affect viability? Assume now there are three viability loci (j,k,l). Again the pure genotypes have equal viability, and recombinant genotypes have relative viability S. The assortment locus m and viability locus j are linked, and viability loci k and l are unlinked (Fig. 1C). The inversion captures loci m and j. Although we were not able to find general analytical results for arbitrary values of S and H, we were again able to find an approximation for the case of weak hybridization between two strongly isolated species (H, $S << 1$). Equation (A37) in Supporting Information 1 shows that an inversion that captures

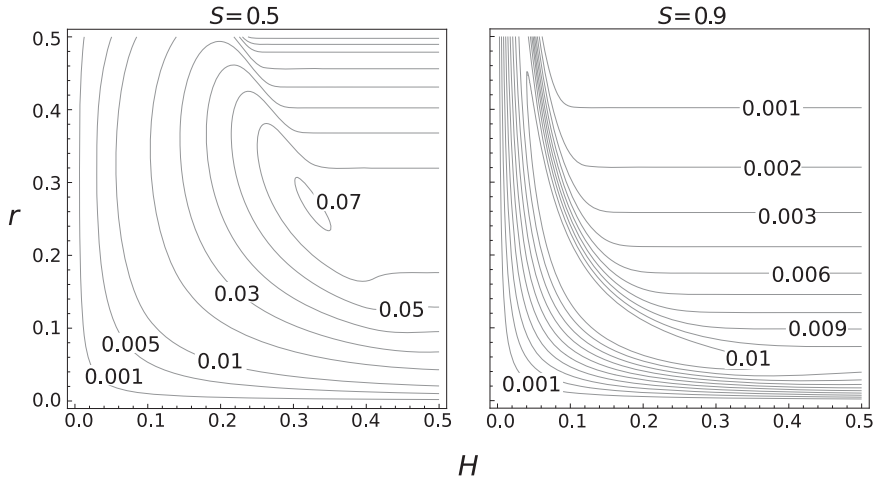

Figure 2. Contour plot of the effective selection coefficient for the inversion (s_e) versus the strength of assortment (*H*) and the recombination rate between *m* and *j* (*r*). Relative viability of hybrids (*S*) is 0.5 in the left panel and 0.9 in the right. Selection for inversions is strongest when hybrids are still relatively common (both *r* and *H* at intermediate values).

one out of three viability loci is again favored. We were unable to extend these results to epistatic interactions between larger numbers of loci, but we expect that the more loci are involved in an interaction, the smaller the benefit of capturing a single viability locus becomes.

We next see how our results extend when there is an arbitrary number n of epistatic pairs of loci. Locus j_i interacts with epistatic partner k_i. We assume that there are no epistatic interactions between pairs, and their viability effects are additive. Loci $j_1, j_2, \ldots, j_n$ are carried on the same chromosome as mating locus m, while none of the k loci are linked to the j loci or to each other (Fig. 1D). The inversion captures allele 1 at locus m and all of the j loci. Again recombination is completely suppressed in heterokaryotypes.

Supporting Information 2 (eq. B16) shows that when the inversion is still rare, its effective selection coefficient is:

$$s_e = \frac{(1-S)}{\bar{W}} \sum_{i=1}^{n} \left[\frac{P_{1k_i}}{2p_1} - P_{j_i k_i} \right], \qquad (4)$$

where P_{1k_i} is the frequency of individuals that carry the inversion and allele 1 at locus k_i, $P_{j_i k_i}$ is the frequency of individuals carrying alleles 1 at loci j_i and k_i, and p_1 is the frequency of the inversion. Supporting Information 2 proves that $s_e > 0$ and so the inversion spreads whenever there is at least some assortative mating and selection against recombinant individuals.

Equation (4) shows that the inversion spreads more quickly as the number of viability loci that it captures increases. How much of an effect the capture of an additional locus has depends on whether there are associations (linkage disequilibria) between different pairs of viability loci. Barton and de Cara (2009) found that when selection and assortment are sufficiently weak, there will be linkage disequilibrium between the loci within each pair but not between the pairs. In that case, each term of the summation in equation (4) is independent of the other terms. The effective selection coefficient for the inversion is then the sum of the selection coefficients we would find from considering each pair of epistatic loci in isolation (e.g., eq. (3)). The rate that the inversion spreads is therefore roughly proportional to the number of loci that it captures.

A different outcome occurs if selection and assortment are strong. In that case, associations will build up between different pairs of epistatic loci (Barton and de Cara 2009). The effect on the inversion of capturing an additional viability locus diminishes with the number of loci it has already captured. In the limiting case, all the epistatic pairs are perfectly associated. Then capturing an additional locus has no effect on the inversion since all pairs of loci act as one. The strength of selection favoring an inversion that captures a single j locus is equal to that for an inversion that captures all n loci.

In summary, we find that an inversion will generally spread if it captures a locus involved in assortative mating and one or more loci involved in epistatic hybrid inviability. We now proceed to see how these conclusions might extend to cases where mating is mediated by a female mating preference and male display trait.

A PREFERENCE-TRAIT MATING SYSTEM

We next consider the case of a preference-trait system. A female chooses between potential mates depending on her own allele at a preference locus p and the alleles carried by males at a trait locus t. A female mates with a male whose allele at t matches her allele at p with probability $1 - H$; conversely, with probability H she will hybridize with a male that has an allele that does not match. Thus mating is random when $H = 0.5$, while there is complete reproductive isolation between two species when $H = 0$.

We assume viability depends on an epistatic interaction between the trait locus t and a second viability locus j. Recombinant males with a mixture of 0 and 1 alleles at loci t and j have viability S relative to "pure" genotypes that carry only 0 alleles or only 1 alleles. The linkage map is $t - p - j$, and that the recombination rates between t and p and between p and j are both equal to r (Fig. 1B). This is similar to previous work that showed that an inversion that captures p and t may increase in frequency when it occurs in a population that has not reached neutral equilibrium (Trickett and Butlin 1994). An inversion that captures t and j is expected to follow much the same dynamics as an inversion capturing any pair of epistatic viability loci (Charlesworth and Charlesworth 1973).

We therefore consider the dynamics of an inversion that captures loci p and j but not the trait locus t. We were not able to find a general solution for when the inversion invades. However, when H and S are both much smaller than 1, Supporting Information 1 (eq. A49) shows that the effective selection coefficient is

$$s_e = \frac{1}{2} H (1 - S) \tag{5}$$

to leading order in H and S. We find again that the inversion invades whenever there is at least some hybridization ($H > 0$).

SELECTION IN DIPLOIDS

We used simulations to verify that our results extend to the case in which viability selection and mate choice occur during the diploid phase of the life cycle. We again consider two viability loci and a single assortative mating locus, with linkage map shown in Figure 1A. Again assume that pure genotypes carrying either all 0 alleles or all 1 alleles have equal viability, and all genotypes with mixtures of alleles have viability S relative to them. Each allele at the assortment locus has an independent effect on the probability of mating. For example, the probability that an individual with genotype (0,0) at locus m mates with an individual of genotype (0,1) equals the probability given by their first alleles ($= 1 - H$) times the probability given by their second alleles ($= H$). The inversion captures a "pure" genotype (i.e., with either allele 0 or allele 1 at both the assortment locus m and the viability locus j).

Figure 3 shows how the effective selection coefficient depends on S, H, and r for the diploid model. When assortment is strong ($H << 1$), the behavior of the diploid model follows the haploid model closely. The similarity results because in this situation, the inversion is almost always in a high viability diploid. With weaker assortment, however, values for s_e diverge somewhat between the haploid and diploid models. For example, with $S = 0.9$ and $H = 0.5$, the mean fitness of a haploid population is near 1, and so the inversion cannot benefit from a large fitness advantage. With selection on diploids, however, mean fitness is near 0.9, and so the inversions is more strongly favored. The inversion

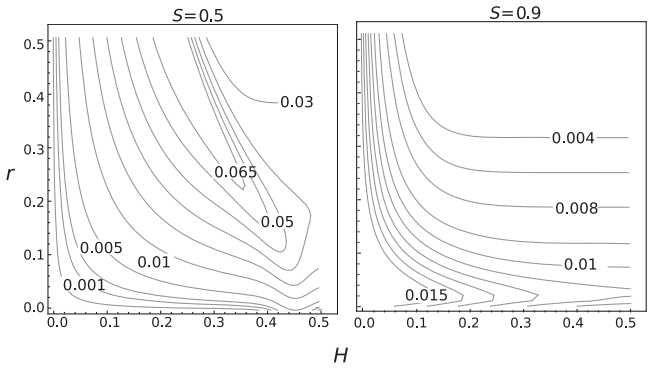

Figure 3. Contour plot of the effective selection coefficient s_e for the diploid model. The inversion is selected most strongly in similar circumstances as the haploid model. Selection for the inversion peaks at lower combinations of H and r, since stronger associations between loci are necessary to maintain higher fitness.

can spread when mating is random ($H = 0.5$) because it tightens linkage between j and k.

Finally, we tested the robustness of our results to the assumption of equal allele frequencies. We simulated cases in which frequency-dependent selection maintained alleles at the assortment and viability loci at frequencies different from ½. Again, the inversion spreads, and it is favored more strongly when hybrids are common (Fig. S1). If there is no frequency-dependent selection at all, polymorphism at the viability loci is expected to disappear, and so all fitness benefits of the inversion are lost.

In summary, an inversion is favored to spread if it captures a mating preference locus and at least one other locus that acts epistatically to determine viability. When species are strongly isolated, however, selective forces are very weak. The inversion is therefore likely to be lost due to drift when isolation between genotypes is strong. Thus inversions that capture mating preference loci may not often spread by the mechanism described by our model when species are strongly isolated.

Discussion

Our model shows that an inversion can spread if it captures a gene that affects mating preferences and also one or more genes that affect hybrid viability epistatically. Inversions that capture mating preference loci are most strongly favored when hybrids are common and have low fitness. An inversion that captures a mating preference locus gains a selective advantage because it decreases the frequency with which maladapted recombinant genotypes are produced. The advantage increases with the number of epistatically interacting viability loci that it captures. When pre- and postzygotic isolation are already strong, its advantage is weak because few recombinant genotypes are being produced. That simple observation suggests that inversions may not often

play an important role in strengthening barriers between species that already hybridize very rarely.

Three of our assumptions are worth revisiting. We assume that recombination is entirely suppressed by the inversion while in heterokaryotypes. Many inversions, however, have very low but positive levels of recombination when heterozygous. Intuitively, we expect recombination in heterokaryotypes will decrease the rate that the inversion invades, but that reduction will be very small so long as recombination in heterokaryotypes is rare. A second assumption in our models is that the inversion captures a "pure" (or high fitness) genotype. The fitness of an inversion that captures a low-fitness combination of alleles will be less than the population's mean fitness, and so it cannot invade. The probability that an inversion captures a high-fitness haplotype and spreads increases as the frequency of hybridization (H), the viability of hybrids (S), and the recombination rate (r) go down.

A third assumption in our models is that the inversion is free of direct selection. Many inversions are thought to be underdominant because they decrease fertility in heterokaryotypes (White 1978; King 1993). An underdominant inversion could still spread by the mechanism described in this article so long as its effective selection coefficient s_e is greater than the selection against heterokaryotypes. We expect s_e to be small, however, so inversions that are strongly underdominant cannot spread by our mechanism. On the other hand, recent research suggests that inversions may not be underdominant as often as was previously believed (Hoffmann and Rieseberg 2008). Stathos and Fishman (2014) used synthetic tetraploids to show that inversions fixed for alternative arrangements in *Mimulus lewisii* and *Mimulus cardinalis* are not underdominant. If these results can be extended to a broader range of taxa, selection for the inversion may not need to overcome selection against underdominance in heterokaryotypes.

The evolutionary advantage of the inversion depends on its mean fitness relative to that of the population as a whole. The inversion will have higher fitness whenever it keeps a larger number of coadapted genes together. It can do so in two ways. First, the inversion can reduce recombination between loci involved in epistatic incompatibilities that are captured within the inversion (Charlesworth and Charlesworth 1973). Second, an inversion that captures a mating preference locus and one or more epistatic viability loci will also increase linkage disequilibrium between the latter and the other incompatibility loci outside of the inversion that they interact with. When more than two loci interact epistatically, the fitness advantage to an inversion that captures just one of the loci declines as the number of interacting loci increases. We show this analytically for 2 and 3 viability loci, but we expect the results to extend to larger numbers of interacting loci. Capturing multiple loci involved in independent epistatic interactions increases selection for the inversion.

Random genetic drift can play two roles in the evolution of the inversions we have considered here. Even in a very large (effectively infinite) population, an inversion that appears as a unique mutation has a high probability of being lost by chance while still rare. A heuristic approximation for the probability that the inversion becomes established is $P_E = 2s_e$ (Charlesworth 1992). With a small value of s_e, there is a high probability that a new mutant inversion will be lost. Second, in populations that are not very large, the inversion will evolve nearly neutrally when $N_e\ s_e << 1$, and in this case it is at risk of loss by drift even when it is not rare. Our results show that selection for the inversion can be quite weak, for example when hybridization is rare. In these situations, the probability of loss is high. The most favorable situation is when inversions that capture mating loci occur recurrently, making it more likely that one of them will establish.

It has long been argued that inversions may also play a role in reinforcement (Rieseberg 2001; Ortiz-Barrientos et al. 2004; Kirkpatrick and Barton 2006). Our results show that inversions that capture mating preference loci may play a role in reinforcement during intermediate stages of speciation. They are unlikely to complete speciation through reinforcement, however, since the forces necessary to do so must be large (Bank et al. 2012), while the forces favoring the selection of inversions are quite weak when pre- and postzygotic isolation is strong (Fig. 2).

This model provides a novel hypothesis for why inversions are more frequently seen between sympatric species than allopatric ones (Noor et al. 2001b; Lowry and Willis 2010; Hooper and Price 2015). Quite simply, inversions are more likely to have higher relative fitness when there are unfit hybrids present. Taking the best case for the inversion, its fitness is 1 if it captures all of the loci in a fit combination. In nonhybridizing populations, this will be no different than $\bar{W}$, as there are no lower fitness hybrids. However, in hybridizing populations, the inversion is favored whenever $\bar{W} < 1$ that is always the case when there is at least some postzygotic selection.

Inversions linked to mating preference may be favored even early during the process of speciation. We found that the inversion is favored so long as there is viability selection against recombinant genotypes and some degree of nonrandom mating. This suggests inversions can be an important bridge in the speciation process. Inversions linked to mating preference that evolve early in the speciation process may serve as genomic islands of speciation (Noor et al. 2001b; Rieseberg 2001).

The forces driving the evolution of the inversions described in these models can act both early and late in the speciation process. These findings strengthen the plausibility that inversions contribute to adaptive differences between populations and species, but direct evidence is lacking. One possible way forward on this question would be to extend existing coalescent models for inversions (Guerrero et al. 2012) to include assortative mating, and use

them to analyze patterns of polymorphism in inversions sampled from natural populations.

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Supporting Information

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

Figure S1. Contour plot of the effective selection coefficient se when allele frequencies are not equal.
Supplemental Materials 1: Inversions That Capture Small Numbers of Loci.
Supplemental Materials 2: Multi-locus generalization.