

ADAPTIVE CHROMOSOMAL DIVERGENCE DRIVEN BY MIXED GEOGRAPHIC MODE OF EVOLUTION

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Chromosomal inversions are ubiquitous in nature and of great significance for understanding adaptation and speciation. Inversions were the first markers used to investigate the genetic structure of natural populations, leading to the concept of coadapted gene complexes and theories concerning founder effects and genetic drift in small populations. However, we still lack elements of a general theory accounting for the origins and distribution of inversions in nature. Here, we use computer simulations to show that a “mixed geographic mode” of evolution involving allopatric separation of populations followed by secondary contact and gene flow generates chromosomal divergence by natural selection under wider conditions than previous hypotheses. This occurs because inversions arising in allopatry contain a full complement of locally adapted genes. Once gene flow ensues, reduced recombination within inversions keeps these favorable genotypic combinations intact, resulting in inverted genomic regions being favored over collinear regions. This process allows inversions to establish to high frequencies. Our model can account for several classic patterns in the geographic distribution of inversions and highlights how selection on standing genetic variation allows rapid chromosomal evolution without the waiting time for new mutations. As inversion differences often separate closely related taxa, mixed modes of divergence could be common.

KEY WORDS: adaptation, allopatric speciation, chromosomal inversions, gene flow, secondary contact, sympatric.

Inversions have played a central role in evolutionary biology (Dobzhansky 1947; White 1978; Coluzzi 1982; Krimbas and Powell 1992; King 1993; Spirito 1998; Provine 2003; Ayala and Coluzzi 2005; Hoffmann and Rieseberg 2008). Inversions were the first markers used to investigate the genetic structure of natural populations, leading to the concept of coadapted gene complexes (Dobzhansky 1947). Inversions have also advanced theories concerning nonadaptive, stochastic processes in evolution (White 1978; King 1993). Because of the reduced fitness of heterokaryotype individuals carrying inverted and collinear chromosomes (Sites and Moritz 1987; Spirito 1998; Noor et al.

2001; Coyne and Orr 2004), and thus the presumed maladaptive nature of inversions, it was argued that the fixation of rearrangements generally required founder effects and/or pronounced genetic drift in small, isolated populations (Bush et al. 1977; White 1978; Lande 1985; King 1993).

In contrast to these “underdominance” models, more recent genic hypotheses based on the allelic content and reduced recombination of inversions have shown that inversions can establish in populations due to selection (Coluzzi 1982; Trickett and Butlin 1994; Noor et al. 2001; Rieseberg 2001; Navarro and Barton 2003; Kirkpatrick and Barton 2006). Published genic

Table 1. Summary of the three genic inversion models described in the main text.

	General description	Conditions under which the model works
1. Allopatric origins model	An inversion initially rises to high frequency in a geographically isolated population. On secondary contact, populations remain genetically differentiated for genes within inversions, whereas collinear regions homogenize.	Requires presumably maladaptive inversions to fix in allopatric populations. Thus, likely requires special conditions allowing for a period of nonadaptive evolution via genetic drift (e.g., small populations, founder effects).
2. Sympatric origins model	A newly formed inversion captures locally adapted genes in hybridizing populations and is favored over the ancestral, collinear arrangement because the inversion keeps well-adapted genotypes intact.	Does not require maladaptive evolution. However, conditions for inversion spread are somewhat restricted: (1) migration must be much lower than selection ($m \ll s$), but not so low that selection favoring reduced recombination for a new inversion is unimportant, (2) generally requires equal population sizes and selection coefficients. Modest, but not too high or low recombination favors inversion spread. Greater number of loci in inversion acts to decrease chances of inversion establishment.
3. Mixed geographic mode model	Low-frequency inversions persist in allopatric populations and contain the full complement of locally adapted genes due to lack of gene flow. Thus, following secondary contact, the selective advantage of reduced recombination overpowers the slightly deleterious meiotic effects in heterokaryotypes, resulting in the spread of the inversion.	Requires periods of both allopatry and sympatry. If such conditions occur, inversions can spread under quite general conditions, including a wide range of migration rates and unequal population sizes/selection coefficients. Inversions most likely to spread under high migration and recombination rates, and moderately strong divergent selection relative to migration. Greater numbers of prestanding copies of an inversion that exist in allopatry prior to secondary contact increase the efficacy of the mixed model. Number of loci in inversion has a small (but positive) effect on inversion establishment. The mixed model predicts that inversions in different regions of the genome can share similar estimated times of origins based on DNA sequence divergence.

models can be divided into two categories of “allopatric origins” and “sympatric origins” based on the geographic context in which the inversion arose and became established (see Table 1 for descriptive summaries of these models). In allopatric origins models, an inversion is assumed to be initially fixed or at high frequency in a geographically isolated population. On secondary contact, populations remain differentiated for inversions, whereas collinear regions homogenize via gene flow and recombination, due to differences in the effectiveness of selection in regions of low (inverted) versus high (collinear) recombination (Noor et al. 2001; Rieseberg 2001).

There are theoretical difficulties, however, with allopatric origins models (Kirkpatrick and Barton 2006; Feder and Nosil 2009). First, most inversions are likely deleterious, for example, due to alterations in gene expression patterns and/or meiotic

irregularities in heterokaryotypes (White 1978; Spirito 1998; Coyne and Orr 2004). Thus, it is hard to explain how inversions are initially fixed or rise to high frequency in allopatric populations experiencing homogenous environmental selection pressures (Kirkpatrick and Barton 2006), as assumed by the allopatric models, except perhaps by meiotic drive (White 1978; King 1993). Second, if inversions often fix in allopatry prior to secondary contact, then they should commonly distinguish allopatric populations. Although this is sometimes the case (White 1978; Coluzzi 1982; Krimbas and Powell 1992; King 1993; Spirito 1998; Noor et al. 2001; Hoffmann and Rieseberg 2008), there are glaring exceptions that are difficult to explain such as *Drosophila*, where five of six sympatric pairs of sister species display inversion differences, whereas eight of nine allopatric pairs do not (Noor et al. 2001).

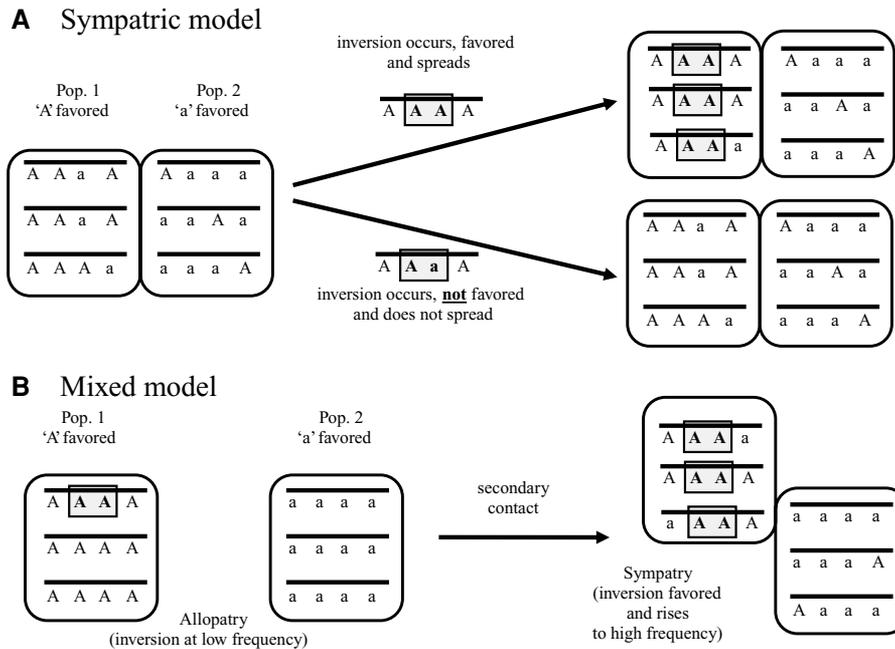


Figure 1. Schematic diagram of the (A) sympatric origins and (B) mixed mode models for the adaptive establishment of chromosomal inversions. Populations 1 and 2 are shown by boxes. When boxes touch the populations are exchanging genes, when they do not touch there is no gene flow (i.e., allopatry). Horizontal lines represent chromosomes and letters below the lines two alleles, “A” and “a,” differentially adapted to local conditions in populations 1 and 2, respectively. Light gray boxes surrounding chromosomal regions represent inversions.

In contrast to the allopatric models, sympatric origins genetic models involve newly formed rearrangements capturing locally adapted genes between hybridizing populations (Fig. 1A and Table 1). With gene flow in sympatry, a newly derived inversion can be favored over the ancestral, collinear arrangement by keeping well-adapted genotypes intact due to reduced recombination between loci in inversion heterokaryotypes. Sympatric origins models could potentially provide a general mechanism for adaptive inversion evolution and account for instances such as *Drosophila* where sympatric, but not allopatric, populations display chromosomal differences (Kirkpatrick and Barton 2006). The sympatric hypothesis is somewhat restricted, however, to conditions where migration between hybridizing populations is much lower than selection favoring locally adapted alleles ($m \ll s$) (Kirkpatrick and Barton 2006). Lower migration rates are needed to avoid locally favored genes being swamped out by gene flow, and to ensure that a new inversion captures all of the locally favorable alleles segregating in a population, a condition required for the inversion to establish (Kirkpatrick and Barton 2006). But if migration rates are too low, selection favoring a new inversion is low because well-adapted genotypes are already present at high frequencies in the collinear region. Consequently, new inversions will often be lost through stochastic processes, aided by selection against them due to any deleterious effects they have on meiosis in heterokaryotypes. The end result is that inversions have diffi-

culty establishing in populations. Thus, current genetic models have greatly advanced our understanding by providing a genes-based framework for the adaptive establishment of inversions. However, these models have limitations that can restrict the evolution of chromosomal differences.

Here, we propose a “mixed geographic mode” model involving a period of population divergence in allopatry followed by secondary contact and gene flow that extends current genetic theories to allow for the establishment of inversions under more general conditions (Fig. 1B and Table 1). The mixed mode model has potentially important evolutionary implications because inversions are predicted to harbor genes causing adaptive divergence and reproductive isolation. Thus, mechanisms that facilitate the establishment of inversions, such as the mixed mode model, likely also promote the creation of new species (Noor et al. 2001; Rieseberg 2001; Feder and Nosil 2009; Lowry and Willis 2010).

Materials and Methods

VERBAL OVERVIEW OF MIXED MODE MODEL

The basic premise of the mixed mode model for inversions is that speciation may often involve multiple geographic modes of divergence, for example, being initiated in allopatry and then completed with gene flow in sympatry following secondary contact, as documented in empirical cases (Feder et al. 2003; Coyne

and Orr 2004; Rundle and Nosil 2005). Under such a mixed geographic mode, the strengths of the allopatric and sympatric origin models complement, whereas their weaknesses can be alleviated. Although it is difficult for rearrangements to rise to high frequency in allopatry due to their aforementioned fitness costs (Kirkpatrick and Barton 2006), inversions are nonetheless often present at low frequencies in allopatric populations (Hoffmann and Rieseberg 2008; Pombi et al. 2008). These inversions may be retained due to mutation-purifying selection balance or be present due to genetic drift (see Results section below on the effects of prestanding copy number). However, these low-frequency inversions will often contain the full complement of locally adapted genes, because allopatric populations are well adapted across the genome due to lack of gene flow (Fig. 1B). Thus, once gene flow ensues following secondary contact, the selective advantage of reduced recombination within an inversion may overcome any slightly deleterious meiotic effects in heterokaryotypes, resulting in inverted regions being selectively favored over collinear regions. Ultimately, this can lead to the establishment of the inversion.

COMPUTER SIMULATIONS

The verbal argument above raises a number of quantitative questions. For example, what levels of migration and recombination are conducive to the establishment of inversions under a mixed model compared to a model with sympatric divergence? How many copies of inversions are required in allopatry for the mixed model to work effectively? How do population sizes and selection coefficients affect the establishment of inversions, and how might asymmetry in these parameters affect outcomes? Most critically, how well can the mixed model explain empirical patterns in nature?

To address these questions, we used computer simulations to estimate the probabilities that an inversion becomes established and differentiates populations under the mixed geographic mode and sympatric origins models. It would be ideal to eventually derive analytical solutions to complement these computer simulations. In the Supporting information, we examine an analytical approach suggested to us by S. Yeaman (pers. comm.) combining (Kirkpatrick and Barton's 2006) method for approximating for the increase in frequency of a rare inversion between generations (λ) with Kimura's diffusion equation to estimate the probabilities of establishment for new inversions (see Crow and Kimura 1970; Yeaman and Otto 2011). However, we found this analytical approximation did not perform particularly well, at least in a quantitative sense (although qualitatively similar patterns were, at times, observed; see Figs. S1 and S2). The approximation performed especially poorly under conditions of moderate-to-high migration rate, and strong selection. As these represent conditions particularly relevant to the mixed mode model, further work

will be necessary to derive useful analytical approximations to extend the simulation results we present in the current article.

We used discrete generation, two-deme population genetic computer simulations written in Matlab[®] for a diploid, hermaphroditically reproducing organism to estimate the probabilities of establishment of inversions (i.e., to determine how often the inversion would be retained by selection vs. lost by genetic drift). The stochastic simulations contained both frequency-based and individual-based elements (see below for details). The simulations initially assumed: (1) no gene flux between collinear and inverted regions (i.e., no effective recombination or gene conversion in heterokaryotypes, as in past models Noor et al. 2001; Kirkpatrick and Barton 2006; but see Feder and Nosil 2009), (2) multiplicative fitness interactions between loci with no epistasis, (3) a life cycle in which divergent selection followed migration between populations and occurred prior to mating, and (4) meiotic irregularities in heterokaryotypes due to single exchange events resulting in a baseline deleterious effect of 10^{-5} . We chose the value of 10^{-5} for meiotic irregularities as a very modest, yet still present, deleterious effect of single exchange events on heterokaryotype fitness. Deleterious meiotic irregularities in heterokaryotypes lessen the probability of initial establishment of inversions under both the mixed and sympatric model. This is because the deleterious consequences of a single exchange lessen the recombination suppressing effects of an inversion when it is the rarer karyotype in populations. Inversions having large negative meiotic effects will therefore be quickly eliminated by selection and be of little consequence for generating chromosomal divergence between populations. Thus, new inversions contributing to population differentiation will generally have low meiotic consequences in heterokaryotypes. Most models of inversions do not consider meiotic irregularities in the spread of an inversion. We therefore consider our inclusion of a low level meiotic effect to represent a more realistic and conservative scenario for estimating inversion establishment. Critically, however, we examined the consequences of relaxing this assumption and varying the deleterious effects of meiotic irregularities in heterokaryotypes in the Supporting information. Similarly, we also explored the effects of relaxing the assumptions of no gene flux between arrangements, no epistasis among loci, and divergent selection occurring after rather than before migration in the Supporting information. We report that relaxing these assumptions generally had minor, and certainly not qualitative, effects on the probability of establishment of inversions in the simulations.

MIXED MODE SIMULATIONS

For the mixed mode model, we considered the two populations to initially be geographically isolated and not exchanging genes. Thus, at the start of a simulation run populations 1 and 2 were alternately fixed for different locally adapted alleles A and a ,

respectively, at each locus under divergent selection. Recombination occurred at a rate of r between loci in homokaryotypes (inverted/inverted and collinear/collinear karyotypes). After secondary contact, individuals migrated from population 1 into population 2 at a rate m_{12} each generation and from population 2 into population 1 at a rate of m_{21} . Population densities were independently regulated in the two demes (i.e., soft selection), with a total of n_1 and n_2 zygotes (newborn offspring) produced in each population each generation. We considered a life cycle with selection following migration and preceding mating (newborn offspring > dispersal between populations > viability selection within populations > recombination/meiosis in parents > random mating and fusion of gametes within populations > next generation of zygotes in populations). We then followed the fate of the inversion until it was either lost or established as a polymorphism (see below for criteria used to determine inversion establishment).

STOCHASTIC SIMULATIONS

Stochastic processes affecting allele and inversion frequencies were present in the simulations in the migratory and reproductive (mating) phases of the life cycle. Following meiosis and recombination, gametes were randomly drawn from the gene pools of populations 1 and 2 and separately combined to form the n_1 and n_2 diploid zygotes in populations 1 and 2, respectively, constituting the next generation. This mating phase of the model therefore represented an individually based, stochastic element of the simulations. After this, a proportion of m_{12} of the newborn offspring in population 1 was randomly assigned to migrate to population 2 and $1-m_{12}$ to remain in population 1. The reverse was true for offspring in population 2, with relative proportions of migration and residency being m_{21} and $1 - m_{21}$, respectively. Again, the migratory phase of the simulations represented an individually based element of the model. Following migration, genotype frequencies were estimated for the two populations separately and viability selection occurred independently in the two populations based on the relative fitness values of genotypes. The selection phase of the model was therefore frequency-based. Following selection, meiosis and recombination also occurred in a frequency-based manner to generate the relative proportions of different inversion and collinear gametes in population 1 and population 2 gene pools. This was followed by the stochastic mating phase of the simulations where gametes were combined together at random in an individually based manner in demes 1 and 2 to generate the next generation of genotypes. Modeling selection and meiosis/recombination in a frequency-based manner greatly accelerated the computational running time of the simulations, while having individual-based mating and migration phases retained the critical stochastic elements for estimating probabilities of inversion loss and gain.

PARAMETER VALUES

The simulations were run varying the parameter values for migration probability (m), recombination rate (r), divergent selection strength (s), population size (n), and number of loci ($nloci$). A total of 100,000 trials were performed for each combination of parameter values. For comparative purposes, we performed most of the stochastic simulation runs considering the inversion to span four loci under divergent selection. For $nloci = 4$, we examined 10 different rates of recombination between genes in homokaryotypes (i.e., between loci in collinear/collinear or inversion/inversion karyotypes) ranging from very tight linkage to random assortment ($r = 0.001, 0.005, 0.01, 0.02, 0.05, 0.10, 0.20, 0.30, 0.40,$ and 0.50). Three different levels of migration probability were considered ($m = 0.001$ [low], 0.01 [moderate], and 0.1 [high]). Five different intensities of divergent selection affecting the fitness of alleles segregating at each locus differentially across habitats and interacting in a multiplicative manner were analyzed ($s = 0.01$ [weak], $0.05, 0.1$ [moderate], $0.20,$ and 0.50 [strong]). Segregating alleles under selection were considered to interact in a partially dominant manner ($h = 0.5$) such that the relative fitness of alternate homozygotes and the heterozygote at a locus in population 1 were $1, 1 - s_1$ and $1 - s_1/2$, respectively, and were $1 - s_2, 1,$ and $1 - s_2/2$ in population 2, where s_1 is the relative selection coefficient acting against disfavored aa homozygotes in population 1 and s_2 is the relative selection coefficient acting against disfavored AA homozygotes in population 2 (i.e., divergent selection generated performance trade-offs between the habitats occupied by populations 1 and 2). For the majority of runs, migration probabilities m_{12} and m_{21} , selection coefficients s_1 and s_2 , and population sizes n_1 and n_2 were equal (symmetric) between populations (Populations sizes for all of the simulation runs are given in the Table S1). However, we also performed a series of stochastic simulations using unequal migration probabilities, selection coefficients, and population sizes to assess the effects of nonsymmetric parameter values for inversion establishment.

INVERSION ESTABLISHMENT PROBABILITIES

An inversion was considered lost if its frequency dropped to zero in both populations to the limit of computational precision. An inversion was considered to become established in a stochastic simulation run if the inversion exceeded a predetermined threshold frequency in population 1. For a given set of parameter values, this threshold frequency for the inversion in population 1 was determined through analysis of a deterministic selection model without genetic drift (i.e., simulations conducted without individually based, random generation of genotypes from population 1 and population 2 gamete pools and without random assignment of genotypes for migration following zygote formation). Specifically, we set the threshold as the frequency when the ratio of the expected change in frequency of the inversion in

population 1 between generations under the deterministic model divided by the standard deviation for the expected change in frequency under a random sampling, drift process, as determined by a binomial distribution with population size n_1 , first became equal to 0.5. Through stochastic computer simulations and analytical approaches, we found that once a ratio of 0.5 was attained in population 1 where the inversion contained locally favored alleles, there was a low probability ($<0.5 \times 10^{-4}$) of the inversion decreasing in frequency in the next 100 generations in population 1. We therefore considered any inversion that reached the threshold frequency to be established as a polymorphism. The eventual expected equilibrium frequencies for the inversion polymorphism in populations 1 and 2 were determined through deterministic simulations by running the simulations until the change of frequency of the inversion between generations in the two populations became equal to zero (again, to the limit of computational precision). We consider how inversions might rise to complete fixation in the discussion.

VARIATION IN INVERSION NUMBER

In addition to performing the mixed mode stochastic simulations with just one initial copy of the inversion, runs were also conducted varying the copy number from 2 to 200 to reflect different levels of standing genetic variation present prior to contact. For these simulations, we assumed that the inversions were similar to one another in length and encompassed the same set of loci under divergent selection (see Results for discussion of when these conditions do not hold). This entailed that either the breakpoints for the inversions were relatively near one another (possibly due to recurrent mutation in rearrangement breakpoint “hot spots” in the genome) or at the exact same locations (due to the inversions sharing a common origin and being present in multiple copies due increases in frequency via genetic drift). As such, single exchange events between inverted chromosomes were considered to have no fitness consequences aside from the alleles that they contained. Under these conditions, we found that the analytical formula $1 - (1 - pr_{siml})^k$ for predicting inversion establishment accurately approximated the multicopy results from the simulations, where pr_{siml} = the simulation estimate of the probability of establishment for a single copy rearrangement, and k = the prestanding number of inversions in a population when multiple copies were present prior to secondary contact. We present further analytical formula and stochastic simulation outcomes in the Results section.

SYMPATRIC ORIGINS MODEL

The sympatric origins model was analyzed in a similar manner to the mixed mode model except for three differences. First, the stochastic simulations for the sympatric origins model were begun with the frequencies of the alleles at loci in selection–migration

balance between populations 1 and 2. This was accomplished by starting the simulations deterministically with the frequencies of the A and a alleles at all loci in populations 1 and 2 equal to 0.5 and in linkage equilibrium with one another and running the simulations until the change in allele frequencies between generations became equal to zero. Second, following attainment of selection–migration balance, an inversion was introduced as a single new mutation into a randomly chosen gamete in either population 1 or 2. The inversion gamete was then combined with a randomly chosen gamete in the population to form a diploid zygote and the fate of the new inversion followed until it was lost or retained. Third, the total probability for the establishment of a new inversion in population 1 was calculated as the mean of 100,000 simulation runs conducted introducing the new chromosomal rearrangement into populations 1 and 2. These values therefore represent the probability that a given new inversion occurring anywhere in the two diverging populations will become established in population 1 under the sympatric origins model.

Results

ESTABLISHMENT OF INVERSIONS UNDER THE MIXED MODEL

The parameter values most conducive to the establishment of an inversion by the mixed mode model were high migration rate (Fig. 2), high recombination rate among loci in collinear arrangements (Fig. 3), and moderately strong divergent selection relative to migration (Fig. 2). High migration and recombination rates (for homokaryotes) favored the establishment of an inversion under the mixed mode model by increasing the frequencies of locally maladapted alleles in the collinear arrangement following secondary contact and introgression. Total divergent selection in the range of one to 40 times the migration rate generally worked best for establishing a rearrangement under the mixed model. When selection was too weak, then locally adapted alleles were swamped out by gene flow. When selection was too strong, then locally favored alleles were present in a high frequency in collinear regions, lessening the advantage of reduced recombination for inversions (Fig. 2).

EFFECTS OF PRESTANDING COPY NUMBER

Greater existing numbers of prestanding copies of an inversion prior to secondary contact increased the efficacy of the mixed mode model. Figures 2 and 3 illustrate how the probability of establishment of an inversion in the mixed mode model increased with increasing copy number of standing inversions. The key consideration is that with multiple standing inversions, all copies must be lost for a rearrangement not to establish. Thus, under the assumption that a rearrangement does not greatly affect the

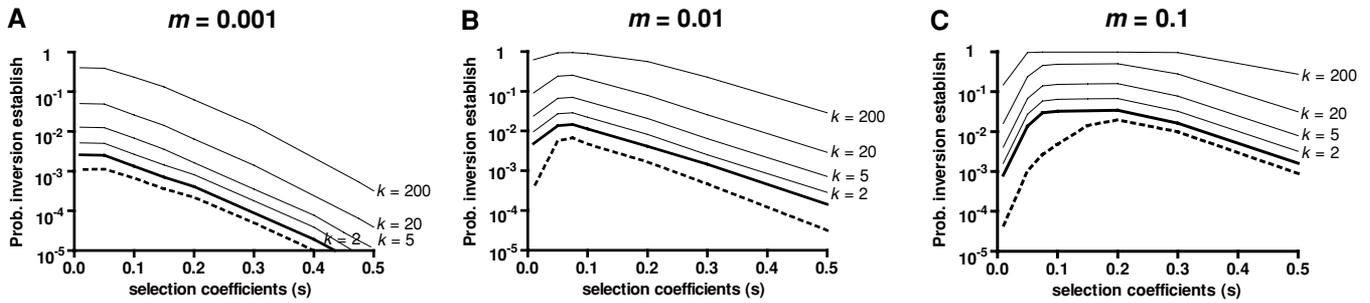


Figure 2. The conditions for the establishment of an inversion under the mixed mode (heavy solid lines) and sympatric origins (stippled lines) models when an inversion was initially present as a single copy ($k = 1$) in population 1. For the mixed mode model, probabilities of establishment are also given in light solid lines for different numbers of standing copies of the inversion in population 1 prior to secondary contact ranging from $k = 2$ to 200 based on the formula $1 - (1 - pr_{sim1})^k$, where pr_{sim1} = the simulation estimate of the probability of establishment for a single copy rearrangement (simulation runs gave near identical results and are not shown). Shown on a log base 10 scale are the probabilities of establishment for an inversion in population 1 derived from 100,000 simulation runs with (A) low 0.001, (B) moderate 0.01, and (C) high 0.1 migration rates (m) between equal-sized populations. The rearrangement contains four loci separated by recombination distances of 10 cM ($r = 0.1$) under varying strengths of divergent selection (s) ranging from 0.01 to 0.5 per locus.

chance that any other copy of the rearrangement is lost, the relative probabilities for establishment of an inversion under the mixed versus sympatry origins models are $\sim 1 - (1 - 2s)^k$ versus $2s$, where k = copy number of the inversion at time of contact, and s = selective advantage of an inversion heterokaryotype.

What is the expected frequency of standing inversion polymorphism in an allopatric population? Under mutation-purifying selection balance, the mean expected frequency of a dominant

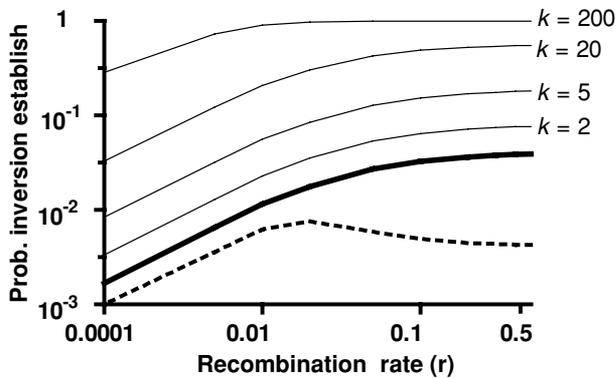


Figure 3. The effects of varying recombination rate on the establishment of an inversion. Shown on a log scale are the probabilities of establishment for an inversion in population 1 containing four loci experiencing moderately strong divergent selection ($s = 0.1$) under the mixed mode (heavy solid lines) and sympatric origins (stippled line) models estimated from 100,000 simulation runs ($m = 0.1$). For the mixed mode model, the probabilities of establishment are also given for different numbers of standing copies of the inversion in population 1 ranging from $k = 2$ to 200 based on the formula $1 - (1 - pr_{sim1})^k$, where pr_{sim1} = the simulation estimate of the probability of establishment for a single copy rearrangement (simulation runs gave near identical results and are not shown).

deleterious inversion is $\sim u/s$ (= mutation rate/selection coefficient against heterokaryotypes) (Haldane 1927). Thus, for example, if the mutation rate per gamete is 10^{-9} to generate slightly deleterious inversions across a region of the genome encompassing the set of loci experiencing divergent selection with s values in the range of 10^{-5} to 10^{-6} acting against the rearrangement, we would expect to see inversion frequencies from 0.001 to 0.0001 in allopatric populations. Such frequencies are observed in nature (Hoffmann and Rieseberg 2008; Pombi et al. 2008). For a population of $n = 100,000$ diploid individuals, this would translate into a copy number (k) of from 20 to 200, resulting in a much higher probability that an inversion is quickly established in the mixed mode than sympatric origins model (Figs. 2 and 3). We note that exact values of u and s are not critical for the standing variation argument. We chose $u = 10^{-9}$ and s values ranging from 10^{-5} to 10^{-6} for illustrative purposes. Rather, it is the ratio of u to s that is important. Hence, u/s ratios varying from 10^{-2} to 10^{-6} may be common and due to a wide range of differing u and s values, leading to appreciable prestanding copy numbers of inversions, depending upon population size. We also note that Figures 2 and 3 consider standing inversion polymorphism in just one of the two populations prior to secondary contact. However, it may often be the case that both populations 1 and 2 contain standing inversion variation prior to secondary contact. In the Supporting information, we show that this will generally increase the probability of establishment of an inversion further (Fig. S3).

It is also critical to realize that different prestanding copies of inversions need not be identical (i.e., share the same mutational origin and the exact same chromosomal breakpoints) for mutation–selection balance to operate under the mixed mode model. In the current simulations, the prestanding inversions must simply encompass the same set of selected genes and not have

major detrimental meiotic consequences in heterokaryotypes. This ensures that the inversions are not eliminated immediately from populations and may be retained as standing variation prior to secondary contact. Thus, it is the rearrangement rate for a particular chromosomal region and not necessarily for specific breakpoints that is the key when considering prestanding inversion copy number in mutation–selection balance. In the discussion, we consider how the dynamics of the mixed mode model can become more complex when the standing pool of inversion polymorphism contains rearrangements that do not share the same suite of locally adapted alleles.

In addition to mutation–selection balance, many slightly deleterious chromosomal rearrangements may also drift to modest frequency in allopatric populations (especially in small-sized populations where they may be very close to neutral), contributing to standing inversion variation prior to secondary contact and increasing their probabilities of establishment under the mixed mode model. Thus, the effects of standing inversions prior to contact can potentially be significant. We note that although slightly deleterious inversions may often be present at low to modest frequencies in allopatric populations, it will be rare for them to rise to high frequency or fix on their own in allopatry. For example, even in an allopatric population of size 10,000, the probability of a slightly deleterious new inversion fixing in a diploid gene pool is still less than 0.00005 or $1/2n$ (the probability that a new neutral mutation will fix). Thus, it is introgression following secondary contact that provides the driving selective force favoring inversions that greatly elevates their chances of establishing and differentiating populations. All these arguments aside, it should not be forgotten that, whatever the cause, multiple copies of inversions are observed in allopatric populations in nature, confirming the realism of treating such scenarios in our models (Hoffmann and Rieseberg 2008; Pombi et al. 2008).

SYMPATRIC VERSUS MIXED MODEL: INEQUALITIES AND ASYMMETRIES

The recombination suppressing effects of inversions were favored in a similar manner due to the maladapted nature of introgression under both the mixed mode and sympatric origins model of Kirkpatrick and Barton (2006). Thus, many of the results were qualitatively similar between the two models. However, the mixed mode model generally relaxed the conditions for an inversion to establish relative to those for the sympatric origins model. As noted above, low migration rates can constrain the establishment of an inversion, and this can be true for both the mixed mode and sympatric origins model. However, the constraint of low migration rate can be partly overcome by asymmetric migration rates, unequal population sizes (Fig. 4), and unequal divergent selection coefficients (data not shown). (Note: unequal selection and asymmetric migration rates were not as effective as unequal selection

because the maximal possible proportion of individuals migrating into a population is capped at close to m with unequal selection and asymmetric migration. In contrast, with unequal population sizes the larger of the two populations can send more than m proportion of migrants into the smaller population. As increased migration tends to favor inversion establishment, unequal population size was generally most effective at increasing the probability of a new inversion establishing). These inequalities in migration rate, population size, and selection coefficients had much greater effect for the mixed than for the sympatric origins model (Fig. 4). The mixed model therefore more strongly predicts that inversions will be preferentially established in smaller populations and can thus explain inversion fixation in peripheral (peripatric pattern) or centrally located (stasipatric pattern) isolates without the need to invoke special circumstances such as founder effects and drift. In addition, when central populations are larger and migration rates are modest, they can accumulate higher levels of inversion polymorphism due to gene flow from surrounding populations, helping explain why the centers of species ranges are often more variable for rearrangements (Soule 1973).

VARIATION IN RECOMBINATION RATE

Varying the rate of recombination between loci had different effects on the probabilities of establishment for inversions under the mixed mode versus sympatric origins models, further highlighting important differences between the models. Simulation results for an inversion containing four loci experiencing moderately strong divergent selection ($s = 0.1$ for each gene) and high migration rate ($m = 0.1$) are presented in Figure 3. For the mixed mode model, higher recombination rates among loci increased the probability of establishment for an inversion by increasingly favoring the recombination suppressing effects of the rearrangement in heterokaryotypes. In contrast, the highest probability for a new inversion establishing under the sympatric origins model was with modest recombination rates among loci ($r = 0.02$). High recombination rates under the sympatric origins model decreased the effectiveness of selection at maintaining allele frequency differences between populations, lowering the probability that a new inversion captured locally adapted alleles across all loci. Low recombination rates under the sympatric origins model increased the effectiveness of selection at maintaining adaptive allele frequency differences between populations. As a result, relatively well-adapted genotypes were already present at high frequencies in the collinear region prior to the origin of an inversion, decreasing the strength of selection favoring new rearrangements.

VARIATION IN NUMBER OF LOCI UNDER DIVERGENT SELECTION

We also investigated the effects of varying the number of loci under divergent selection within an inversion from two to six with

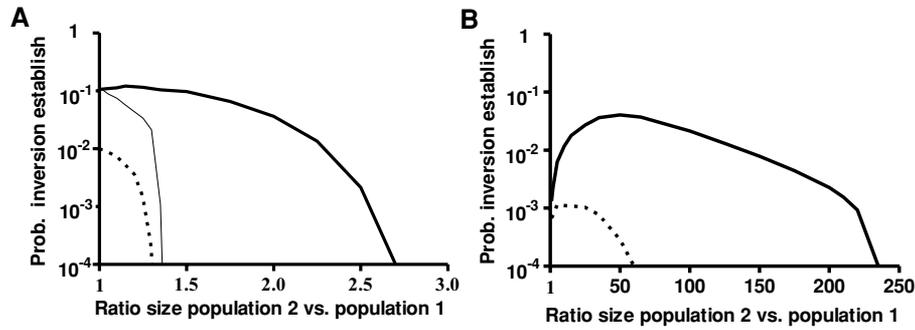


Figure 4. The effect of unequal population size on the establishment of an inversion with (A) high migration rate ($m = 0.1$) and (B) low migration rate ($m = 0.001$) between populations. Shown on a log scale are the probabilities of establishment for an inversion in the smaller population 1 (heavy solid line) and larger population 2 (thin solid line) for the mixed mode model and in population 1 or population 2 for the sympatric origins model (stippled line) estimated from 100,000 stochastic simulation runs. The rearrangement contained four loci, with a recombination rate of $r = 0.1$ between loci, and divergent selection of $s = 0.1$ per locus. With unequal population sizes and low migration, the probabilities of establishment of an inversion in the larger population 2 under the mixed mode model are low and are not shown in the figure.

migration rate $m = 0.1$ between equal-sized populations. To do this, we held the overall selective difference between alternate A and a homozygotes across all loci constant at $s = 0.3439$. Individual selection coefficients for a locus were therefore equal to $1 - (0.6561)^{1/nloci}$, where $nloci$ = the number of loci under divergent selection. The overall s value of 0.3439 was used because this equates with an individual locus s value of 0.1 for each gene in an inversion containing four loci under divergent selection, which we generally used as our standard comparison for selection strength in the simulations. Similarly, the size of the inversion with respect to its total recombination distance in homokaryotypes was also held constant at 30 cM. Thus, the recombination distance between loci was equal to $30\text{ cM}/(nloci - 1)$. The results showed that spreading the same overall amount of divergent selection over greater numbers of loci increasingly favored the establishment of an inversion polymorphism under the mixed mode model and had the opposite effect for the sympatric origins model (Fig. 5). Under the mixed mode model, distributing selection across a greater number of loci slightly, but increasingly, favored the recombination reducing effects of the inversion over the collinear gene arrangement. This was because introgression of maladapted alleles into the collinear region became more pronounced the more weakly selected each individual locus was, increasingly favoring the inversion. The same was also true for the sympatric origins model. However, this effect in the sympatric case was negated by increased introgression making it more difficult for a new inversion to initially capture the required combination of locally favored alleles across all loci for its establishment. As a consequence, probabilities of establishment under the sympatric origins model decreased with the inversion containing increasing numbers of loci. The mixed model thus predicts more strongly than the sympatric model that small inversions harboring few selected loci

will be rare in nature, again highlighting important differences between the two models.

Discussion

STANDING VARIATION AND THE RATE OF INVERSION ESTABLISHMENT

We have shown that a mixed geographic mode of divergence can enhance the opportunities for inversions to establish and

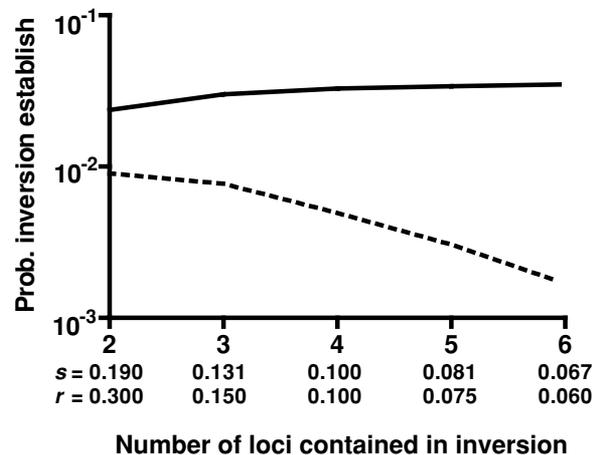


Figure 5. The effect of varying the number of loci contained within a rearrangement from two to six on the establishment of an inversion. Shown on a log scale are the probabilities of establishment for an inversion in population 1 for the mixed mode (solid line) and sympatric origins (stippled line) models estimated from 100,000 stochastic simulation runs with migration rate $m = 0.1$ between equal-sized populations. The overall selective difference between alternate a and A homozygotes across all loci was held constant at $s = 0.3439$, as was the total recombination distance among loci at 30 cM ($r = 0.3$).

differentiate taxa, providing a more general theory for chromosomal divergence between taxa than previous models. Our mixed mode model allows for selection to drive rapid chromosomal divergence from standing genetic variation (Barrett and Schluter 2008), as selection favoring the reduced recombination effect of an inversion would commence immediately following secondary contact and introgression. Thus, the waiting time under the mixed mode model is largely constrained only by when and how often cycles of allopatry and sympatry occur. Under the sympatric origins model in comparison, selection could not begin before a favorable new rearrangement occurred in the genome and the waiting time required for such a mutation can potentially be considerable. For example, given a mutation rate of 10^{-9} to generate rearrangements that are not disfavored during meiosis and 100,000 individuals in each of two sympatric populations, there would be an average 2500 generation waiting time for a de novo inversion to arise that would not be quickly eliminated from the population ($2500 \text{ generations} = 1/[(10^{-9} \text{ mutation rate per gamete}) \times (2 \times 10^5 \text{ gametes per diploid population per generation}) \times (2 \text{ populations})]$). Although inversions can arise at rates as high as 10^{-3} per gamete (Schaeffer and Anderson 2005; Kirkpatrick and Barton 2006; Navarro et al. 2007), most of these mutations are likely moderately to highly deleterious and quickly removed from populations, and therefore not germane to rearrangement establishment. To establish, new inversions in the sympatric model would also have to capture all locally favored alleles in one of the populations, a condition required for the inversion to be favored by selection and increase in frequency (Kirkpatrick and Barton 2006). If not, then recombination in the collinear region will generate a portion of haplotypes that contain all locally adapted alleles. These collinear haplotypes have higher fitness than the rearrangement, impeding the establishment of the new inversion. Moreover, the inversion also has to avoid stochastic loss. Thus, to determine the mean expected waiting time for establishment, we would have to multiply 2500 generations in our example by the probability of establishment for a new inversion under a given set of parameter values for the sympatric origins model in populations 1 and 2. For example, if $s = 0.1$ for each of four loci in an inversion under the sympatric model, this would result in an average waiting time of over 2.5×10^5 generations when $m = 0.1$, 2.6×10^5 generations when $m = 0.01$, and 1.8×10^6 generations when $m = 0.001$. We note that in our discussion of the longer waiting time for the sympatric model above, we did not consider the period of allopatry prior to secondary contact and introgression for the mixed mode model. Rather, we compared the mixed mode and sympatric origins models from a starting point of introgression occurring between populations. However, if the initial allopatric period is included for the mixed mode model, and this time period was substantial, it could make the net time for inversion divergence more equitable between the mixed mode and

sympatric models, or sometimes even longer for the mixed mode model. In addition, in very large populations, inversions with effectively neutral meiotic effects might arise more often reducing the waiting time for the sympatric model. Future work examining in greater detail the interaction of chromosome rearrangement rates (including probabilities of capturing favorable alleles) and population size could be useful for making predictions of when sympatric versus mixed model might be more important.

MULTIPLE DIFFERENT REARRANGEMENTS

The dynamics of the mixed mode model can become more complex when the standing pool of inversion polymorphism contains rearrangements that do not share the same suite of locally adapted alleles. Once again the recurrent mutation rate u for mutation–selection balance would reflect the rate that new inversions are generated across an entire chromosomal region and not for a specific pair of breakpoints. However, these rearrangements will experience varying degrees of divergent selection following secondary contact, depending upon their allelic content. Moreover, recombination between inversions of differing length can generate duplication and deletion gametes, implying that different prestanding rearrangements present in allopatric populations may often not pair properly with one another during meiosis, restricting exchange. Following secondary contact, the entire class of inversions will initially tend to rise in frequency compared to the corresponding collinear region due to selection favoring reduced recombination. However, individual inversions will rise to varying degrees, depending upon the locally favored alleles they possess, detrimental meiotic considerations, and stochastic chance. Eventually, if inversion differentiation is to occur, then a rearrangement or subset of rearrangements having similar and generally high(est) fitness will establish. The evolutionary dynamics of inversion establishment when different standing rearrangements exist could therefore have implications beyond our current simulations and warrant further future study.

FIXATION OF INVERSIONS

Many inversions establish themselves as a polymorphism rather than becoming differentially fixed between populations. This is true for both the mixed mode and sympatric origins models (Fig. 6). Fixation can occur following the establishment of a polymorphism by two means: (1) a second period of geographic isolation (Kirkpatrick and Barton 2006), or (2) the two alternate arrangements accumulating additional new substitutions differentially adapting them to habitats 1 and 2 (Navarro and Barton 2003; Kirkpatrick and Barton 2006). In Figure 7, we show an example of how “secondary” allopatry following secondary contact can lead to the rapid differential fixation of chromosomal arrangements in populations from a polymorphic state for an inversion containing four loci, with a recombination rate of

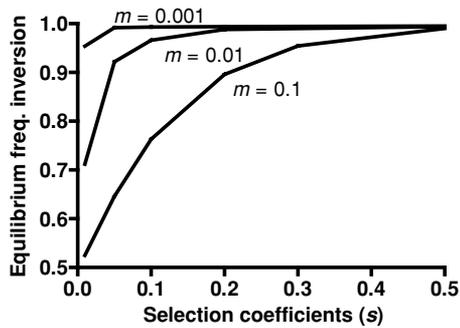


Figure 6. Equilibrium frequencies for an inversion established in population 1 under the mixed mode model for varying combinations of migration rate (m) and divergent selection (s) for equal-sized populations. The rearrangement contained four loci with a recombination rate of $r = 0.1$ between loci.

$r = 0.1$ between loci, divergent selection of $s = 0.1$ per locus, and migration rate $m = 0.1$ between equal-sized populations. Two factors contribute to fixation in allopatry. First, following the second period of allopatric separation between population 1 and 2 and the cessation of gene flow, an inversion containing a block of locally adapted genes will elevate further in frequency in

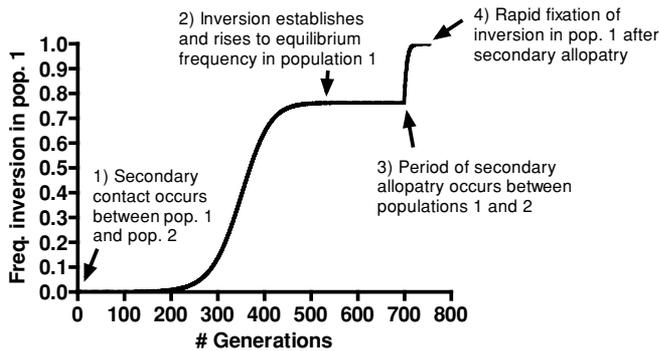


Figure 7. Illustrative example demonstrating how an inversion polymorphism can become established between populations and then differentially fixed from a cycle of allopatry, secondary contact and introgression, and then secondary allopatry. For the example, the frequencies of an inversion are shown through time (measured in generations) for a rearrangement containing four loci, with a recombination rate of $r = 0.1$ between loci, divergent selection of $s = 0.1$ per locus, and migration rate $m = 0.1$ between equal-sized populations. (1) Secondary contact of two previously isolated allopatric populations differentially adapted to alternative habitats. One of the populations contains an inversion held at low frequency in mutation-purifying selection balance; (2) Following secondary contact, the inversion increases in frequency to a high-frequency polymorphism in the population due to selection favoring reduced recombination among locally adapted alleles contained within the rearrangement; (3) Populations become separated during a second period of allopatry; (4) The inversion becomes alternately fixed and lost in the two allopatric populations.

population 1 (the population it is favored in) until all maladapted alleles in population 1 are purged from the corresponding collinear region. As a result, the inversion will generally be present at a higher frequency than the collinear arrangement in population 1. At this time, negative frequency dependent selection acting on the standard arrangement due to deleterious single exchange events in heterokaryotypes becomes important and helps to eliminate the standard arrangement from population 1. The process we describe will be reversed in the alternate geographic isolate (population 2) and favor the standard collinear arrangement, resulting in a fixed chromosomal difference between the populations. This argument predicts that multiple, re-iterated bouts of isolation and gene flow can be conducive to inversion fixation, and perhaps speciation. The mixed mode model can therefore provide a mechanism for evolving fixed inversion differences between populations, the assumed starting condition for previously postulated allopatric origins models (Noor et al. 2001; Rieseberg 2001; Navarro and Barton 2003). This would make arguments for the differential maintenance of genetic divergence between collinear and rearranged regions of the genome more plausible.

However, Feder and Nosil (2009) have shown that with gene flux, differences in the level of genetic divergence between inverted and collinear regions of the genome can be transient following secondary contact between populations for alleles at loci not generating fitness trade-offs (i.e., for genes that are not in some way differentially selected between populations). The results of Feder and Nosil (2009) do not negate an important role for chromosomal rearrangements in speciation, nor do they discount that inversions will sometimes display elevated levels of divergence compared to noninverted regions of the genome. Rather, they signify that the effects of chromosomal rearrangements can be transient and will be quantitative and not qualitative; there is no reason that loci contributing to reproductive isolation should not also exist in collinear regions of the genome outside inversions. Here, we establish conditions (cycles of allopatry followed by secondary contact and gene flow) under which the recombination suppressing effects of inversions will be most favored and selection acts to establish inversion differences between locally adapted populations. But in the absence of prestanding inversions, this does not mean that alleles causing fitness trade-offs will also not remain differentiated between populations following secondary contact and gene flow. Rather, collinear regions can remain differentiated according to the balance between selection and gene flow but with a lesser overall degree of divergence than inverted regions.

Allopatric isolation following a period of secondary contact and introgression is not the only way that an inversion containing locally adapted alleles and existing at equilibrium frequency as a polymorphism can become differentially fixed between populations. Fixation can essentially also occur in sympatry in the face of gene

flow if the inverted and standard arrangements continue to independently accumulate additional adaptive mutations contributing to reproductive isolation (Barton and Bengtsson 1986; Navarro and Barton 2003; Kirkpatrick and Barton 2006). Thus, inverted and collinear regions can become better and better adapted to alternate habitats, differentially rise to higher and higher frequencies, and, eventually reach near fixation between populations. The dynamics of this accumulation phase of divergence following initial chromosomal differentiation is another aspect of the mixed model warranting further future study.

PREDICTIONS AND CONCLUSIONS

As discussed above, the mixed mode and sympatric model differ in a number of ways such that they generate divergent predictions (Table 1). The mixed model also makes a prediction concerning the age of inversions that can help distinguish it from the sympatric origins model in some case. Specifically, the mixed model predicts that inversions in different regions of the genome can share similar estimated times of origins based on DNA sequence divergence, especially for sequences located near chromosomal breakpoints. This is because sequence divergence between taxa will tend to mark the time of original allopatric separation between populations (plus twice the effective size of the ancestral population prior to the split) for the mixed mode model, rather than the time of origin of the different chromosomal rearrangements themselves (Feder et al. 2003). Such patterns have been reported in *Rhagoletis* flies (Feder et al. 2003), *Drosophila* (Kulathinal et al. 2009), and *Anopheles* mosquitoes (White et al. 2009). In contrast, under the sympatric model, inversions should be relatively young and dispersed in their times of origin (presumably having arisen at different times during an ongoing period of gene flow). Indeed, coalescence times (divergence) of sequences near chromosomal break points under the sympatric model should reflect the sum of the time of origin of the inversion and twice the effective population size of the taxa.

The difficulty of fixing inversions solely in allopatry also means that the mixed model has implications for addressing a classic and ongoing debated in evolutionary biology: did a portion of population divergence occur in sympatry or strictly in allopatry (Coyne and Orr 2004)? Empirical data able to answer this question are notoriously difficult to obtain, yet patterns of inversion polymorphism for presently allopatric taxa might provide insight into the biogeography of divergence. Specifically, if allopatric populations differ by fixed inversion differences, then they may have gone through a cycle of initial separation, contact, and secondary isolation (i.e., some differentiation, at least chromosomally, occurred in sympatry and was even facilitated by gene flow). If inversion differences are not observed (as appears to be the case for several of the *Drosophila* species pairs discussed above), then populations may have been allopatric during their

entire history of divergence, because fixing inversions without gene flow can be difficult. We also note that inversion clines may also often characterize the mixed mode model when the contact zone between populations encompasses an ecological transition area between alternate habitats. The ancestral hawthorn-infesting race of *Rhagoletis pomonella* possesses latitudinal inversions cline that may have been established by such a process between Mexican and U.S. populations (Feder et al. 2003, 2005). Finally, the mixed mode model may be especially effective for facilitating chromosomal evolution in species with a metapopulation structure comprised of numerous small, fragmented subpopulations. In this case, allopatrically isolated demes may frequently form, differentiate locally, and then reestablish contact and gene flow among themselves, favoring inversion establishment.

In conclusion, the mixed mode model is not based on evolution occurring solely in sympatry or allopatry. Rather, it is the complementary combination of conditions occurring successively in allopatry and sympatry with temporal variation in migration rates that makes chromosomal divergence likely. In addition, our mixed mode model applies not only to inversions, but also to any structural or point mutation that alters (reduces) recombination for a chromosomal region. Moreover, spatial variation in migration rates could sometimes play a role analogous to our scenario of temporal variation. Finally, the establishment of an inversion polymorphism can not only serve as an immediate seed for speciation, but can also function as a reservoir of adaptive variation to foster the exploration of populations of novel ecological niches, leading to further differentiation (e.g., *Rhagoletis*) when different inverted/collinear regions are combined in novel combinations (Feder et al. 2003). Thus, inversion establishment via the mixed model could have similar consequences to hybridization during hybrid speciation (Rieseberg 2001; Seehausen 2004; Mallet 2007) if new resource opportunities become available that can be exploited by assembling diverged blocks of favorable alleles across the genome from different parental populations. As inversion differences often separate closely related taxa (Dobzhansky 1947; White 1978; Coluzzi 1982; Krimbas and Powell 1992; King 1993; Spirito 1998; Noor et al. 2001; Rieseberg 2001; Ayala and Coluzzi 2005; Hoffmann and Rieseberg 2008; Lowry and Willis 2010), mixed geographic modes of evolutionary divergence could be common.

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Supporting Information.

The following supporting information is available for this article:

Table S1. Population sizes (n_1 and for n_2) for computer simulation runs graphed in figures.

Figure S1: Simulation runs for comparison to analytical approximations with varying selection and migration rate were the same runs as those performed above in Figure 2.

Figure S2: Simulation runs for comparison to analytical approximations with varying recombination rate were the same runs as those performed above in Figure 3.

Figure S3: Simulation runs for assessing the effect of standing number of inversions with four loci in rearranged region of chromosome.

Figure S4: Simulation runs for assessing the effect of selection occurring before versus after mating with recombination rate constant at $r = 0.1$ between four loci in homokaryotypes for rearranged region of chromosome.

Figure S5 (A, B and C): The effects of fitness interactions between a pair of loci on the establishment of an inversion under different inversion models with positive epistasis and negative epistasis.

Supporting Information may be found in the online version of this article.

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